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Palladium-catalysed [2+3] cycloaddition routes to the tricyclic core of the stenine group of Stemona alkaloids

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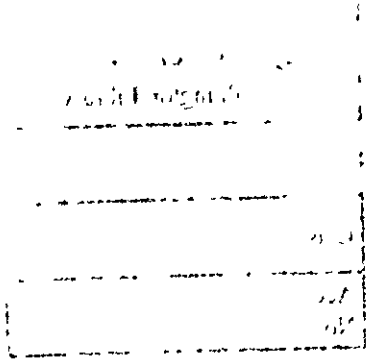
Palladium Catalysed [2+3] Cycloaddition Routes to the Tricyclic Core of the Stenine group of *Stemona* Alkaloids

By Vincent John Neary

A Doctoral Thesis 2007

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



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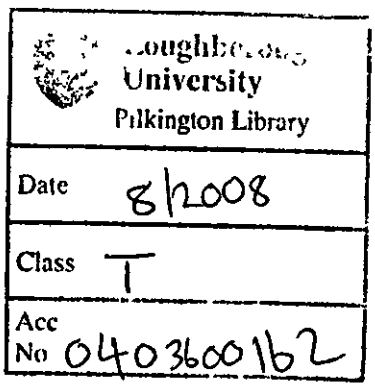
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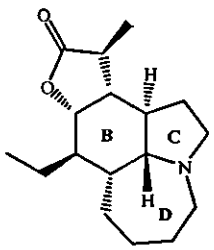
Contents

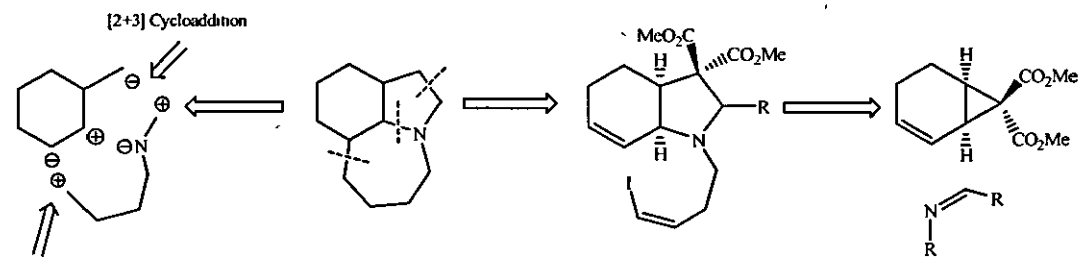
Palladium Catalysed [2+3] Cycloaddition Routes to the Tricyclic Core of the Stenine group of *Stemona* Alkaloids

The stemona alkaloids have generated considerable interest in recent years. They are from the *Stemonacae* family, which has two genera, *Stemona* and *Croomia* and are a structurally interesting class of alkaloids isolated from the roots and rhizomes of the *Stemonacae* plant family. Common to all of the stemona alkaloids is the central azapinoindole, (B, C, D system) shown in stenine below.

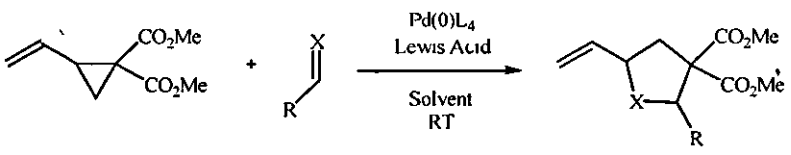


Stenine

The route, to the stenine core which we wished to look at, envisaged using a Pd(0) catalysed [2+3] cycloaddition between an activated vinylcyclopropane substrate and a suitable imine to give the hydroindole core. A subsequent intramolecular Heck reaction could then be carried out to construct the 7-membered azepine ring of the tricylic core.



We have already established Pd(0) catalysed [2+3] cycloaddition routes to five membered heterocylces *via* the trapping of various imines with vinylcyclopropanes and we hope that using this methodology we can access the tricyclic core of stenine.



X = O or NR

Acknowledgements

Firstly I would like the thank Dr Gareth Pritchard (Dr P, Gaz, the Big Boss man) throughout the whole of this research. His patience, understanding and ideas helped me immensely throughout the three years of this work and the four years of my undergraduate degree. His genuine concern and care when times were tough was also a great help, he is a real top bloke!

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I want to thank my old house mates Dr Toby Stein and Dave Foley for their reassurance and general good banter through our times living together. Also Lithuanian-Scandinavian FC (Sean, Stanny, Wozza, Mikel) for telling me I was good

enough to step up 15 levels to play for Shepshed Dynamo FC. Especially Jaime Cummins and Gareth Wyn Jones for their constant praise of me on my journey into non-league football, knowing that they fully supported me, gave me a great amount of comfort when I was sat in the Shepshed dug out. Dr Mark "The Hulk" Landon (he finally got there) and Dr Ciaran "Steve" O'Connor (he shouldn't have got there) for their work outs down the gym, it was always a pleasure that someone my size could "flick" heavier weights than them.

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I would also like to thank Dr Mark Edgar for all his nOe's and time he took with me going through some of my ^{1}H NMR data, he was also a great help.

One more mention must go to my A-level teachers at Trinity school who gave me the enthusiasm and inspiration for science (and sport), Mr John Dexter and Miss Tracy Sturrock my chemistry teachers who always gave me the confidence to believe in myself that I could perform well in the subject. Mr Gerry McMahon and Mr Raymond "Raymundo" Gayne for their entertaining biology lessons and also the eventful biology field trip to Wales in 1998.

Two other teachers must also get a mention, Mr Richard Stevens and Mr Rupert Bennett of the DT department, I just hope their rashes have cleared up by now!

Abbreviations

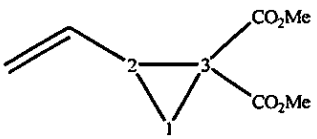
AIBN	azobisiosobutyronitrile
aq.	aqueous
Bn	benzyl
Br	bromine
C	carbon
cat.	catalytic
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
d	doublet
dba	dibenzylidenacetone
DBU	1,8-diazabicyclo[5.4 0]undecene-7
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
DCC	dicyclohexylcarbodiimide
DEAD	diethylazocarboxylate
DIBAL	diisobutylaluminiumhydride
DIEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenlylphosphorylazide
EI	electron ionisation
eq	equivalent
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
HATU	*N*-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridine-1-ylmethylene]*N*-methylmethanminium hexafluorophosphate *N*-oxide

HCl	hydrochloric acid
HMPA	hexamethylphosporamide
hr	hour
Hz	hertz
i	*ipso*
J	coupling constant
Jones reagent	conditions: sodium dichromate, sulphuric acid, acetone.
K_2SO_3	potassium carbonate
LDA	lithium diisopropylamide
m	*meta*
***m*-CPBA**	*meta*-chloroperoxybenzoic acid
MeOH	methanol
$MgSO_4$	magnesium sulphate
mins	minutes
mp	melting point
Ms	mesyl
MS	molecular sieves
m/z	mass to charge ratio
$NaHCO_3$	sodium hydrogen carbonate
NaOH	sodium hydroxide
Na_2SO_4	sodium sulphate
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
o	*ortho*
p	*para*
***p*-TSA**	*para-toluenesulphonic acid*
Pd	palladium
$Pd(OAc)_2$	palladium acetate
$Pd(PPh_3)_4$	tetrakistriphenylphospinepalladium(0)
PPh_3	triphenylphosphine
ppm	parts per million
q	quartet
RT	room temperature

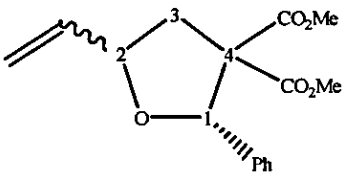
s	singlet
SiO_2	silica dioxide
SM	starting material
$SnCl_2$	tin(II)chloride
str	stretch
Swern	conditions: DMSO, oxalyl chloride, Et_3N, -78°C.
t	tertiary
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Ts	*para*-toluenesulfonyl
$ZnBr_2$	zinc bromide

Compound Numbering

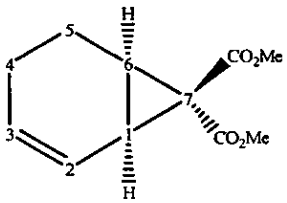
Vinylcyclopropanes



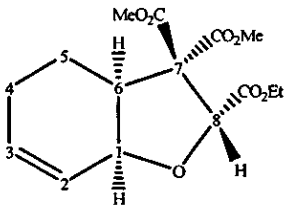
Tetrahydrofurans/pyrrolidines



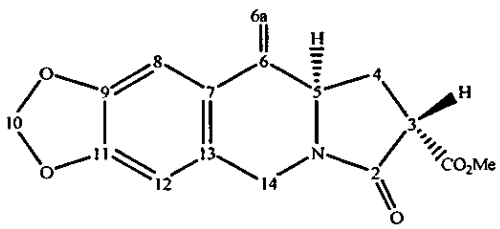
Fused vinylcyclopropanes



Fused bicyclic heterocycles



Fused polycyclic heterocylces



Chapter 1: Synthesis of the Tricyclic Core of the Stenine group of *Stemona* Alkaloids

The *Stemona* alkaloids have generated considerable interest in recent years they represent a class of polycyclic alkaloids with relatively complex structures.[1] They are isolated from the *Stemonacae* family, which has two genera, *Stemona* and *Croomia*.[2] They are a structurally interesting class of alkaloids isolated from the roots and rhizomes of the *Stemonacae* plant family. The roots of the *stemona tuberosa* and *stemona japonica* have long been used in Chinese folk medicine as insecticidal, anti-parasitic (in both humans and animals) and anti-tussive agents.[3] Approximately 50 structurally novel polycyclic metabolites have been isolated to date.

The alkaloids of the *stemona* family have interesting polycyclic structures and so have been classified into groups based on their core, at the centre of five of these groups is the pyrrolo[1,2-α]azepine skeleton, also named perhydroazulene and 4-azaazulene which characterises the *stemona* alkaloids (figure 1).[1]

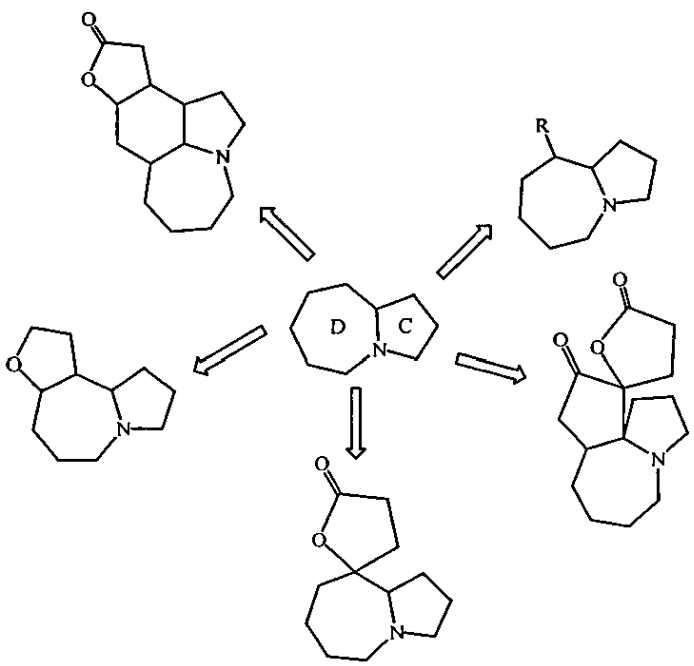


Figure 1: The pyrrolo[1,2-α]azepine core.[1]

Although the stemonacae family encompasses more than 30 species, the phytochemical studies have been restricted to only 8 of them, most belonging to the genus *Stemona*.[1] Due to their complex nature, most of the *Stemona* alkaloids had their structure characterised by crystallographic analyses.[1]

Some examples of members of the *stemona* alkaloids containing this core structure are shown in figure 2. Their respective stereochemistry and additional functional groups are also shown below; stenine (**1**), stemoamide (**2**), tuberostemospironine (**3**), stemonamine (**4**) and parvistemoline (**5**).

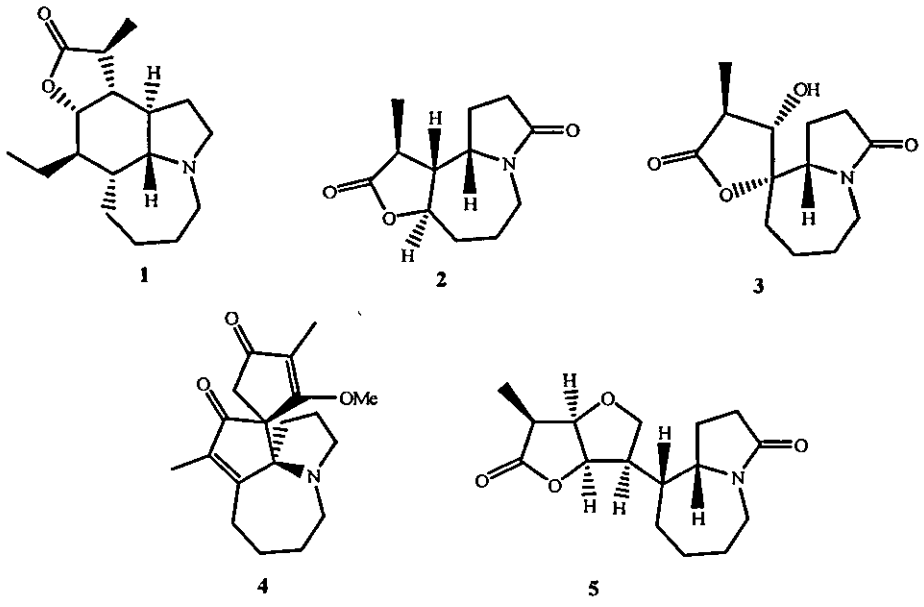


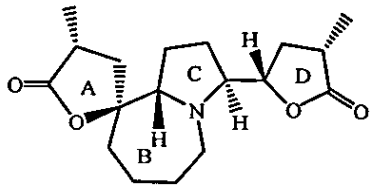
Figure 2: *Stemona* alkaloids with the pyrrolo[1,2-α]azepine core.[1]

The stenine group, where stenine **1** is the parent compound, has 7 members and is a subclass of the *Stemona* alkaloids. Stemoamide **2** represents 9 alkaloids, tuberostemospironine **3** comprises 7 members, stemonamine **4** has 5 and parvistemoline **5** has 3 members.

Their unusual structures have intrigued chemists and inspired several total syntheses of the *Stemona* alkaloids.[2] To date there is no general, facile route to these compounds though a number of long, demanding total syntheses to stenine do exist.[5]

1.1 Syntheses of the stemona alkaloids

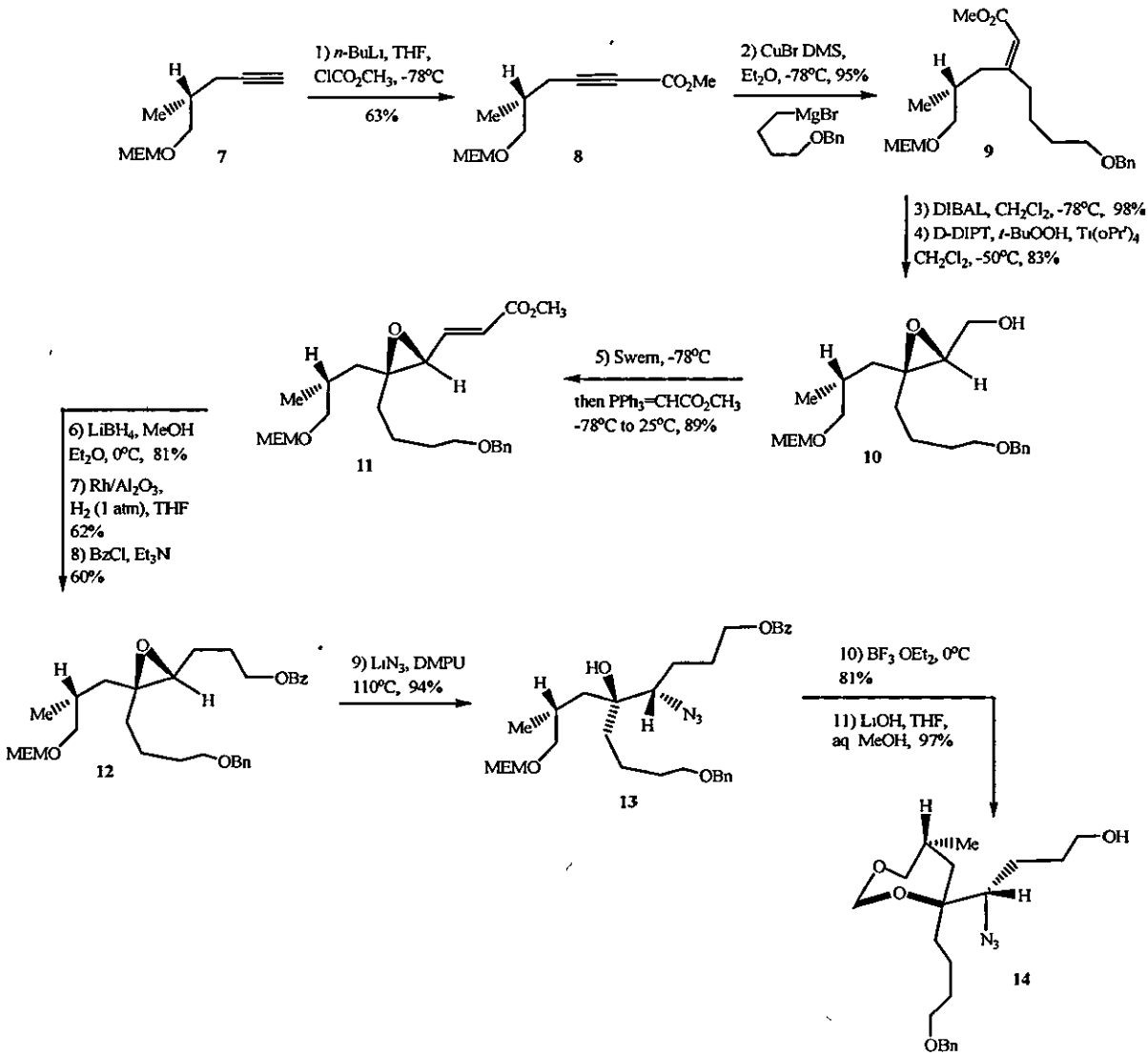
The first total synthesis of a *stemona* alkaloid was reported in 1989 by Williams *et al.* who prepared (+)-croomine **6** (figure 3). [4]



6

Figure 3: (+)-croomine.

Their intentions were to develop a strategy involving firstly the construction of a branched acyclic carbon chain then ring closure of each heterocycle, in the order A-B-C-D. Acylation of the acetylene **7** with methyl chloroformate yielded the chiral ester **8**, which was then mixed with the Gilman type reagent ((4-benzyloxy)butylmagnesium bromide in ether then addition to an ethereal solution of cuprous bromide-dimethyl sulphide complex). The conjugate *syn* addition to the acetylenic ester was optimised by using a methanol quench, giving both high yields and stereoselectivity. Reduction with DIBAL of **9** afforded the allylic alcohol in preparation for the Sharpless epoxidation to afford **10** (scheme 1).[4]

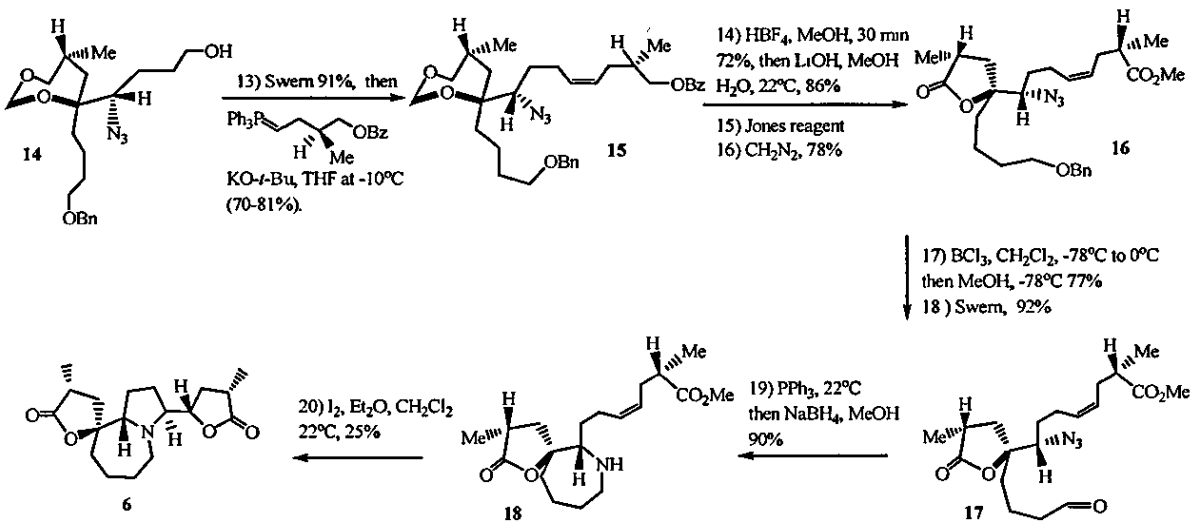


Scheme 1: William's synthesis of (+)-croomine[4]

Swern oxidation of **10** gave the corresponding aldehyde, which in some instances was not isolated, and was allowed to warm to 0°C before the addition of the (carbomethoxymethylene) triphenyl phosphorane substrate to produce the α,β-unsaturated ester **11** in an 89% yield. Lithium borohydride reduction resulted in a mixture of the desired alcohol and also its corresponding (*E*/*Z*) allylic alcohol due to both conjugate and carbonyl reduction taking place. The mixture was then hydrogenated to complete the conversion to the primary alcohol (scheme 1) [4]

Esterification then followed to afford the benzoate **12** in 97% yield, ring opening of the epoxide was carried out using lithium azide, providing the β-azido alcohol **13**, which was converted into the dioxepine **14** so as to protect the hindered tertiary alcohol. Saponification

was followed by a Swern oxidation to give an unstable aldehyde, which was then subjected to Wittig olefination conditions with the chiral phosphorane yielding only the (*Z*)-alkene **15**. The butyrolactone **16** was formed by acetal hydrolysis of **15**, then basic saponification gave the triol Addition of Jones reagent then followed. Further concentration of solvents followed by esterification with ethereal diazomethane afforded **16** in a 78% yield (scheme 2).[4]



Scheme 2: Williams synthesis of (+)-croomine.[4]

Removal of the benzyl ether and then subsequent oxidation gave the aldehyde, which was treated with triphenylphosphine to give the aza ylide, then the subsequent intramolecular Wittig afforded a 7-membered imine. This was reduced with sodium borohydride to afford the perhydroazepine **18** in a 90% yield. The final closing of the C and D rings to give (+)-croomine **6** was achieved in one step by treatment with iodide, initial iodoamination closed the C ring and the D ring closure followed by nucleophilic anchimeric assistance by the terminal amine.[4]

1.2 Syntheses of stenine

Hart and Chen *et al.* described the first synthesis of racemic stenine in 1990, using a strategy that could be extended to the synthesis of tuberostemonine shown in figure 4.[6]

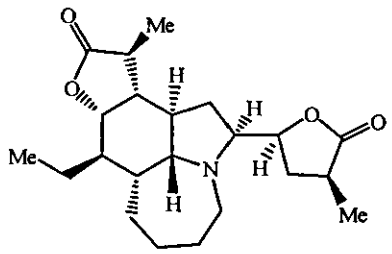


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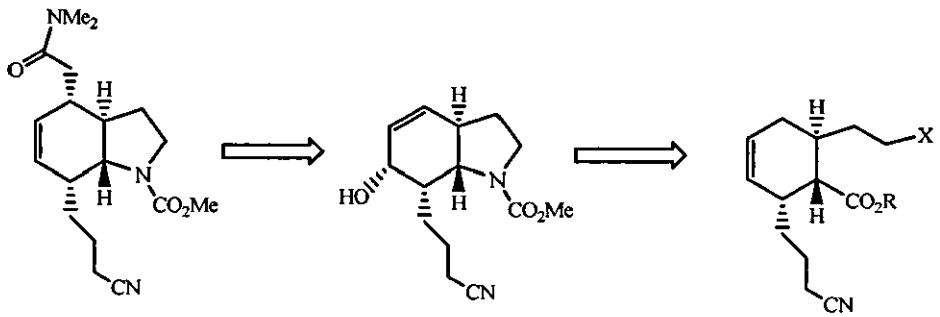
Figure 4: Tuberostemonine

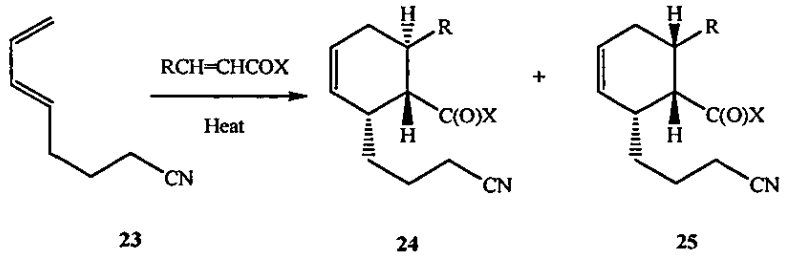
The synthesis was accomplished in 25 steps in a 5% overall yield. It was felt that the amido nitrile **22** contained the appropriate functionality for completion of the synthesis and it was imagined that it could be prepared from the allylic alcohol **21** using a Claisen rearrangement (scheme 3).



22 21 20

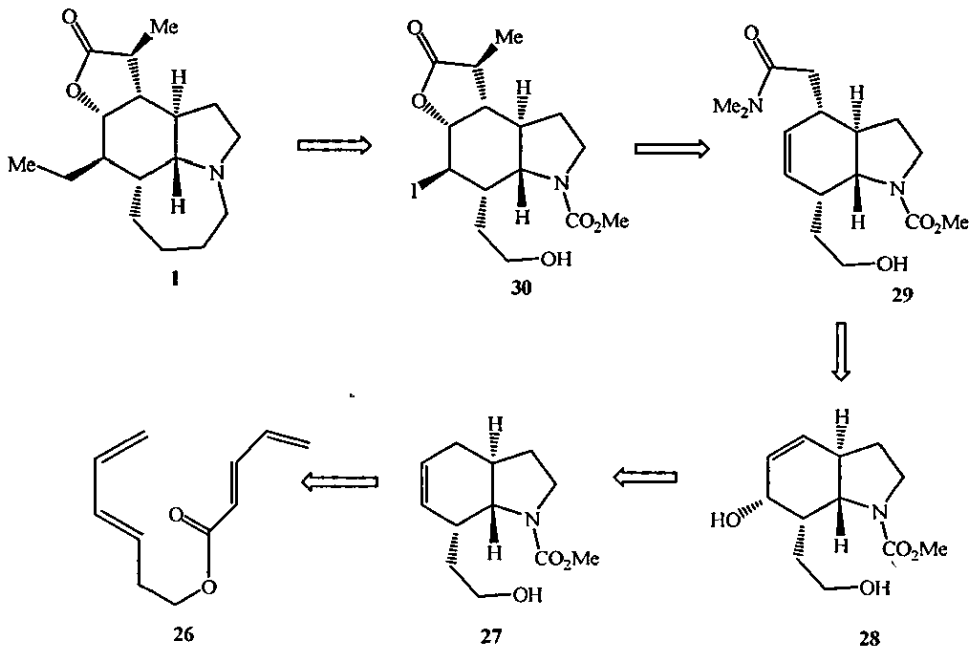
Scheme 3: Initial Plan for synthesis of stenine.[6]

The ester was proposed as a suitable handle for introducing the nitrogen and could also be used to install the allylic alcohol using a halolactonisation-dehydrohalogenation sequence. The ester was prepared by a cycloaddition reaction between (*E*)-octa-5,7-dienenitrile and an appropriate β-substituted acrylate [6]



Scheme 4: Cycloadditions with selected thioesters and acid chlorides[6]

On the whole their initial studies were discouraging, polymerisation of the diene was observed under thermal conditions and also the dienophile was destroyed when Lewis acid catalysis was attempted. There was also poor stereoselectivity in the cycloaddition reactions and after investigating several unsuccessful intermolecular routes using an intermolecular Diels-Alder reaction they turned their attentions to an intramolecular cycloaddition variant.[6, 7]

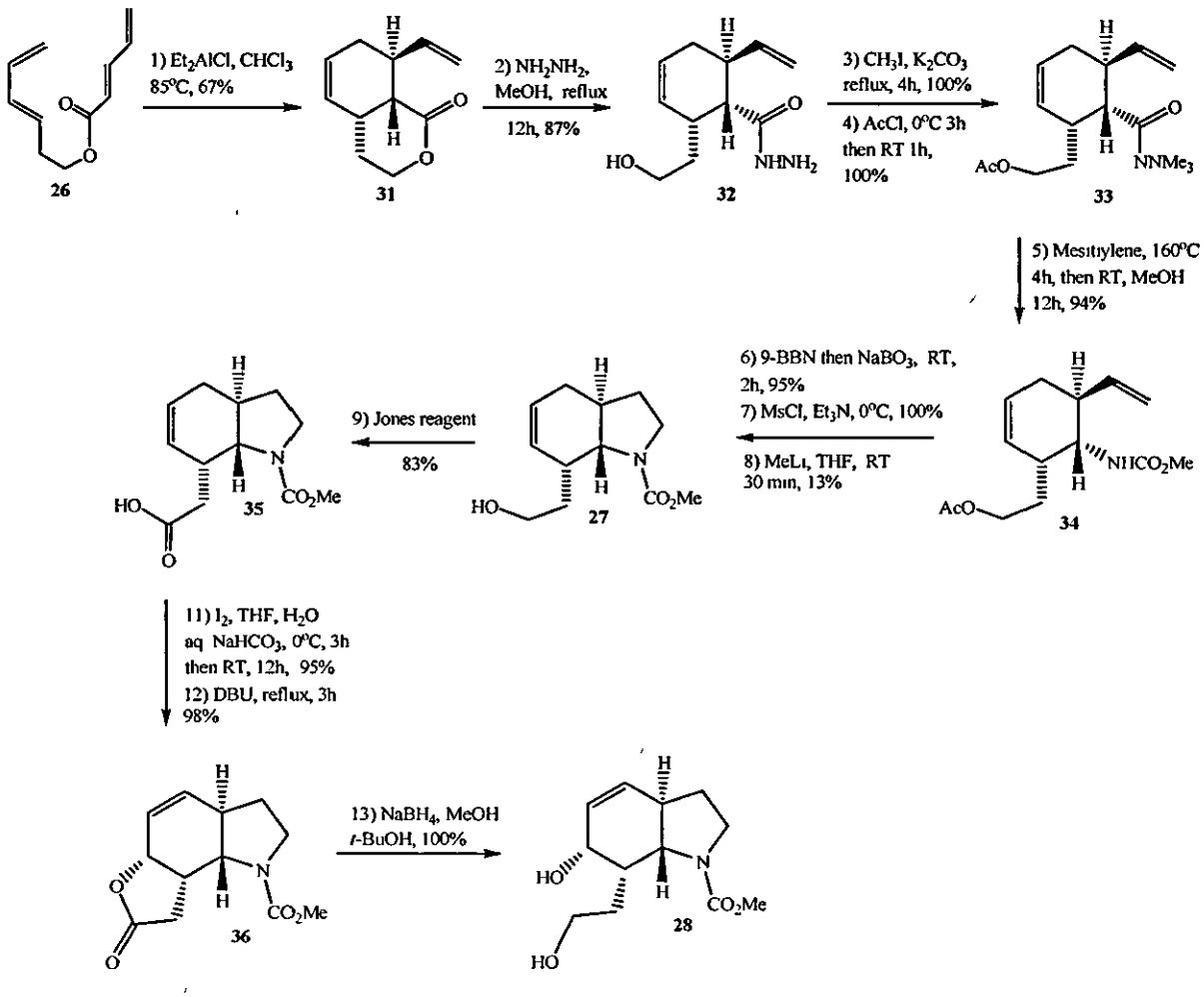


Scheme 5: Hart and Chen's Retrosynthetic route to Stenine[6]

The seven membered ring would be formed in the later stages of the synthesis. It was felt that the iodo lactone **30** would be a reasonable precursor to stenine **1**. The C (14) methyl group could be introduced by alkylation, while the ethyl group was to be introduced using an intermolecular free radical carbon-carbon bond forming reaction. It was anticipated that the iodo lactone **30** would be prepared from the tertiary amide **29** which in turn would be

prepared *via* an Eschenmoser-Claisen rearrangement. The cyclohexane ring was constructed using a Diels-Alder reaction using **26**.[6]

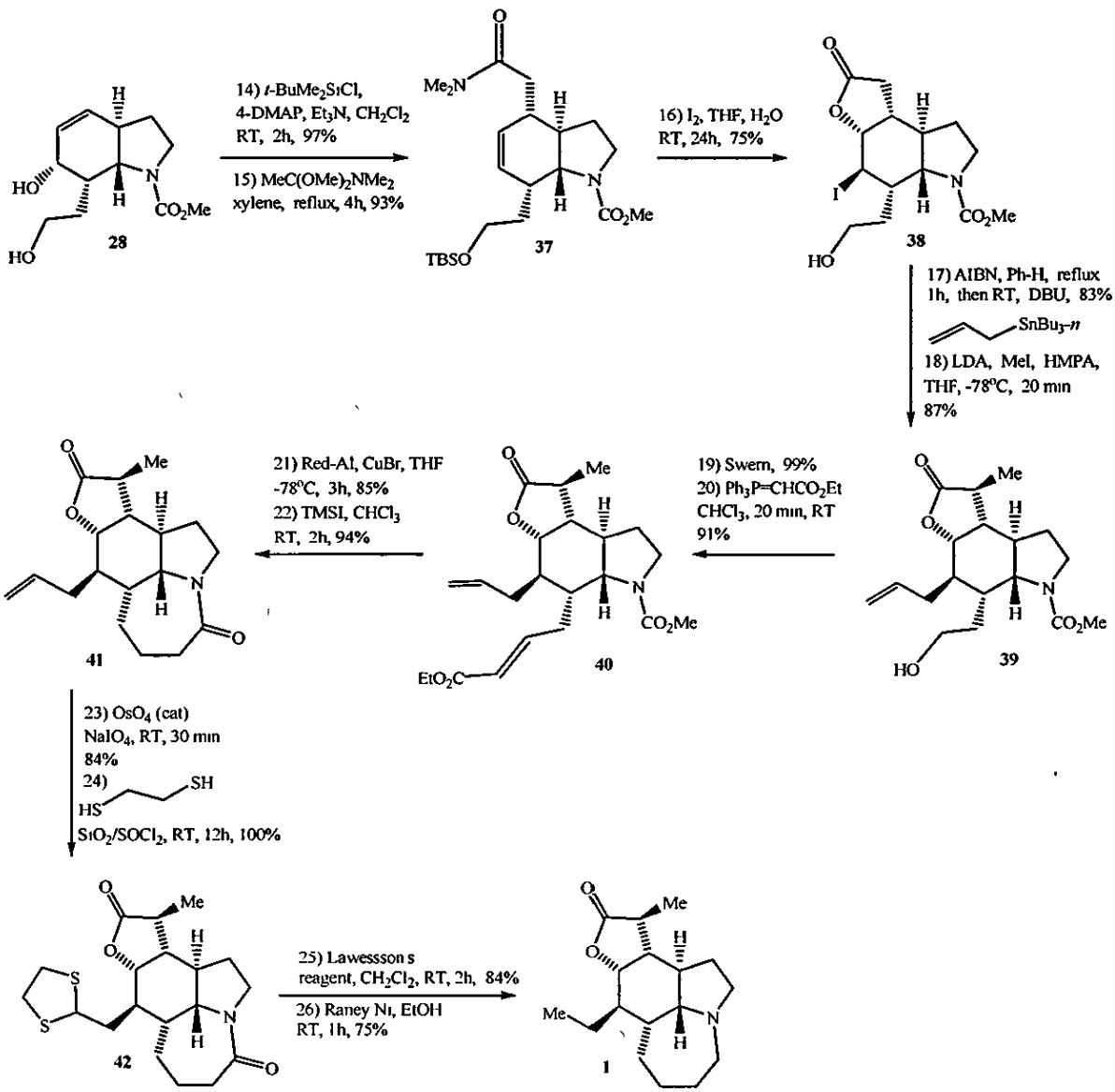
The Diels-Alder reaction of **26** yielded **31**, which was then treated with hydrazine to afford the acyl hydrazide **32** in an 87% yield. Exhaustive methylation followed by acylation yielding **33**, thermolysis of this then followed which was carried out in mesitylene, followed by addition of MeOH yielded the carbamate **34** Hydroboration then oxidation followed by mesylation of the alcohol which then formed the B and C rings of stenine after treatment with methyllithuim (scheme 6).[6, 7]



Scheme 6: Hart and Chen's synthesis of stenine.[6, 7]

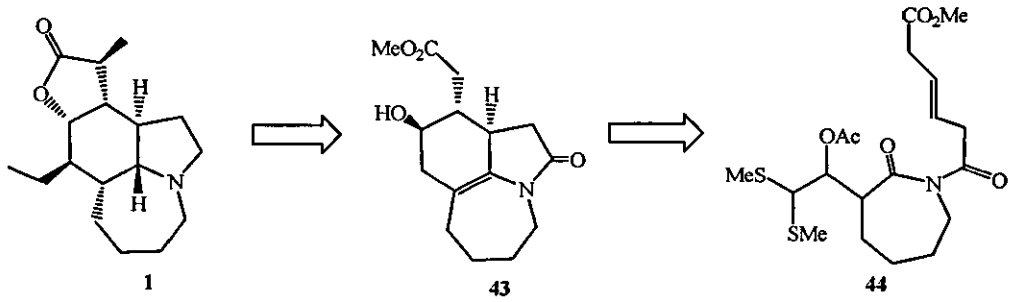
The addition of Jones' reagent provided the corresponding carboxylic acid **35**, the lactone was introduced *via* iodo-lactonisation, which was then ring opened using sodium borohydride to afford the diol **28** in 100% yield. The primary alcohol in **28** was protected as *tert*-

butyldimethylsilyl ether before being treated to form the appropriate amide acetal yielding **37** in 93% yield. Iodolactonisation was again used to furnish **38**, which was then followed by Keck allylation and alkylation of the enolate to give **39**.[6, 7] Swern oxidation gave the aldehyde which *via* a Wittig olefination furnished the α,β-unsaturated ester **40**, conjugate reduction of the ester followed by removal of the carbamate group allowed for azepine construction. A Johnson-Lemieux oxidation of **41** followed by protection with 1,2-ethanedithiol gave **42**. The total synthesis was then completed using Lawesson's reagent giving the thiolactam, then Raney-nickel desulfurisation afforded the racemic stenine in a 75% yield (scheme 7).[6, 7]



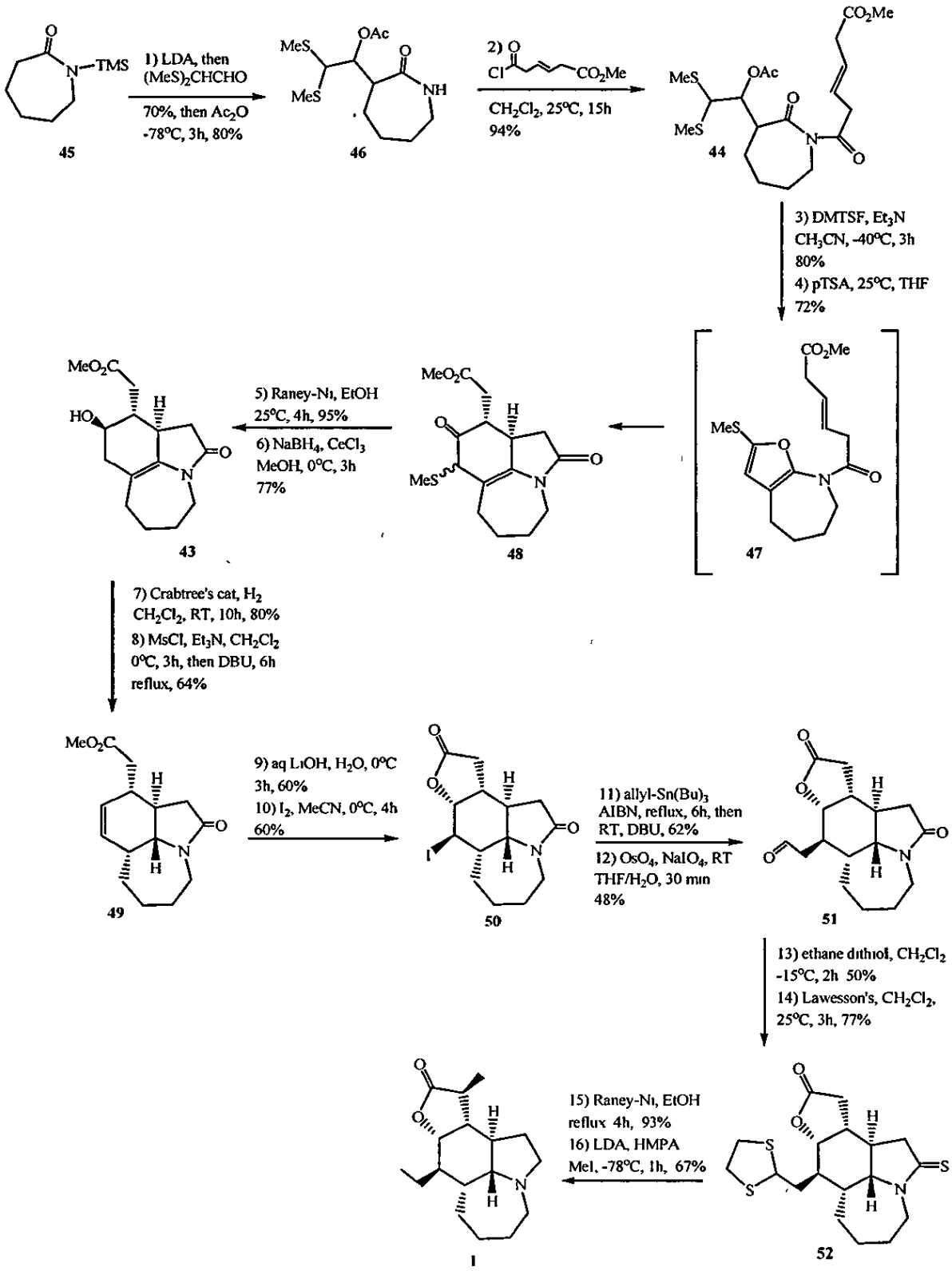
Scheme 7: Hart and Chen's synthesis of stenine.[6, 7]

Padwa *et al.* has also described a short, elegant synthesis of racemic stenine *via* an intramolecular Diels-Alder reaction of a 2-amido-5-alkylthio-substituted furan Their approach was based on construction around the 7-membered azepine ring present from the onset and the use it to as a template set the required stereochemistry (scheme 8).[8]



Scheme 8: Padwa's proposed route to stenine.[8]

The synthesis of the amide **46** began from the mixed aldol reaction of the *N*-trimethylsilyl ε-caprolactam with bis(methylsulfanylacetaldehyde) followed by an acetic anhydride quench. This was followed by acylation of **46** to afford **44** in a 94% yield. Methylsulfenylation of one of the methylthio groups of **44** induced the thionium-promoted cyclisation to furnish the desired furan **44** after loss of acetic acid. However it could not be isolated and underwent a [4+2] cycloaddition/methyl thio rearranegement rapidly at room temperature to furnish the azepinoindole **47** in a 72% yield. The methylthio group was removed with Raney-nickel yielding one diastereoisomer, reduction of the ketone using Luché conditions afforded the alcohol **43** as a single diastereoisomer in a 77% yield.[8]

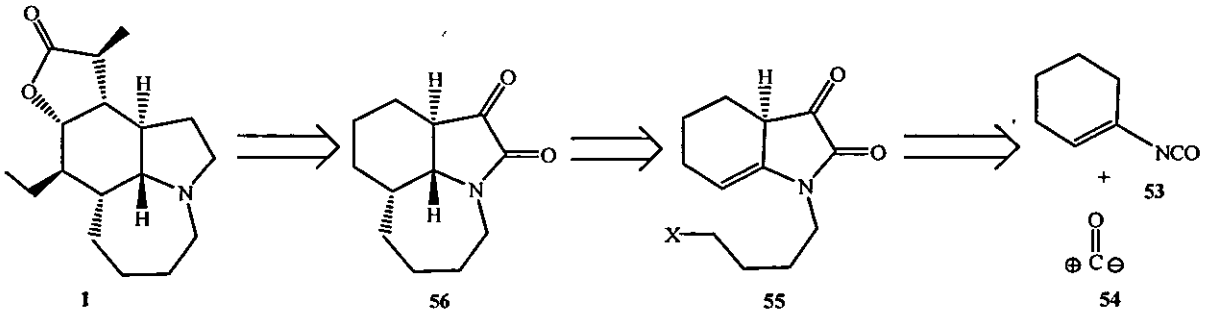


Scheme 9: Padwa's synthesis of stenine.[8]

Controlled hydrogenation of the enamide π-bond in **43** was carried out using Crabtree's catalyst ([Ir(cod)pyr(Pcy_3)]PF_6/CH_2Cl) in an 80% yield, setting up the required syn-anti

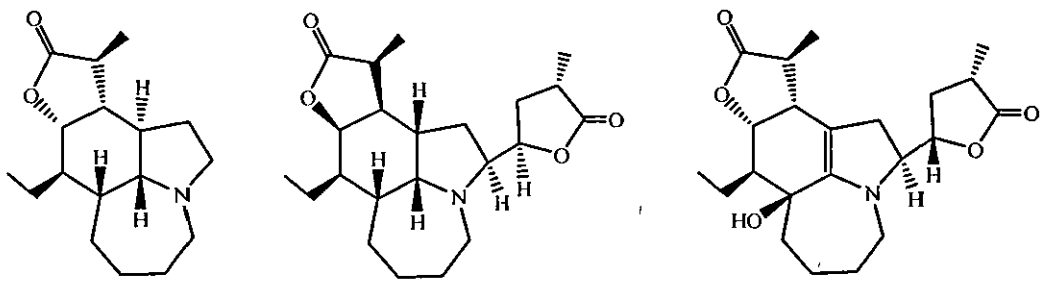
stereochemistry at the ring fusion sites. Removal of the alcohol set the stage for construction of the butyrolactone ring, where the lactone was formed *via* iodo-lactonisation of the unsaturated ester. The conversion of **50** to stenine was achieved based on the Hart/Wipf protocol using Keck allylation, then the Johnson-Lemieux oxidation of the allyl group yielding the aldehyde **51.** This was further manipulated using Raney-nickel to remove the dithiol group and then methylation using MeI and LDA to furnish stenine in a 2.1% overall yield in a 16 step sequence from ε-caprolactam (scheme 9).[8]

Rigby *et al.* reported a route to the tricyclic core of stenine by employing a 7-endo radical cyclisation of an N-alkylated hydroindolone substrate.[9]



Scheme 10: Rigby's retrosynthetic route to the tricyclic core of stenine.[9]

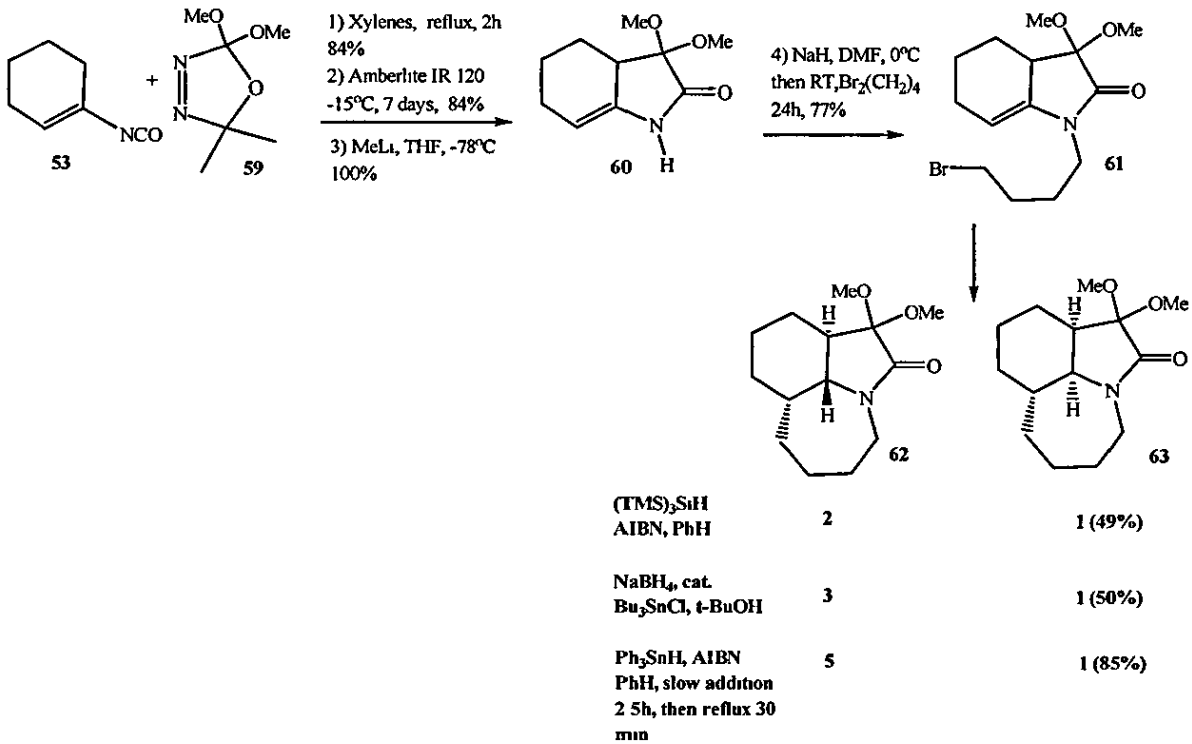
The hydroindole building block **55** could be synthesised by a [1+4] cycloaddition between an appropriate vinyl isocyanate **53** and one of several nucleophilic 1,1-dipole **54** equivalents already developed by them, followed by N-alkylation of the enamide and then a 7-*endo-trig* radical cyclisation to produce the azepine ring **56** (scheme 10).[9]



Stenine **1** neotubereostemonine **57** tuberostemonol **58**

Figure 5: Structurally related stemona alkaloids.

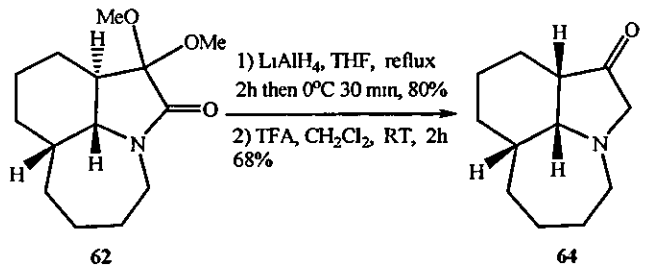
They hoped that the synthesis would deliver a route into the tricyclic core so that by careful manipulation the ring fusion stereochemistry of the 3 compounds in figure 5 could be achieved. The preliminary study began with the synthesis of the hydroindolone substrate **60** which was produced in a 71% yield (scheme 11).[9]



Scheme 11: Rigby's synthesis of the tricyclic core of stenine.[9]

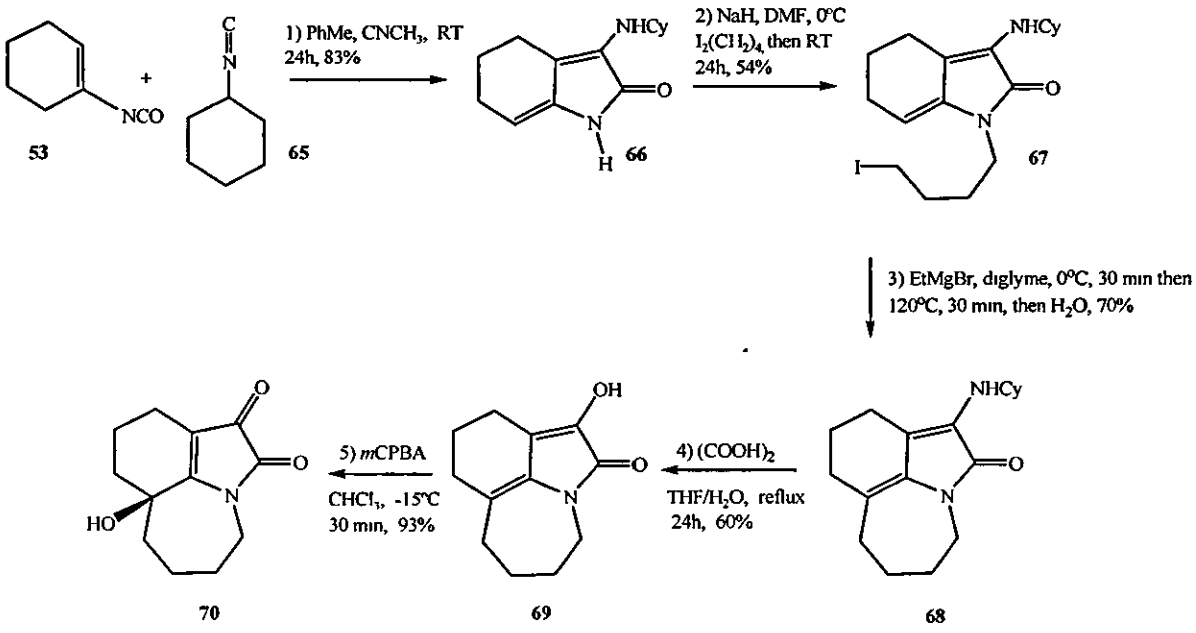
Several radical cyclisations were performed which led to various mixtures of isomeric azepinoindoles **62** and **63**. The best yield and product ratio was obtained using Ph_3SnH in refluxing benzene under slow addition conditions.[9]

With the *syn-anti* stereochemistry established, which showed that rapid access to stenine and related *stemona* alkaloids could be achieved, efforts to produce the *syn-syn* isomer were carried out; a characteristic of neotuberostemonine.[9]



Scheme 12: Rigby's synthesis of the tricyclic core of stenine.[9]

Heating lactam **62** with $LiAlH_4$ followed by hydrolysis of the dimethoxy acetal afforded the new azepinoindole **64**. A route into the third ring-fusion type displayed in tuberostemonol was also attempted where unsaturation is retained in the hydroindolone core.[9]

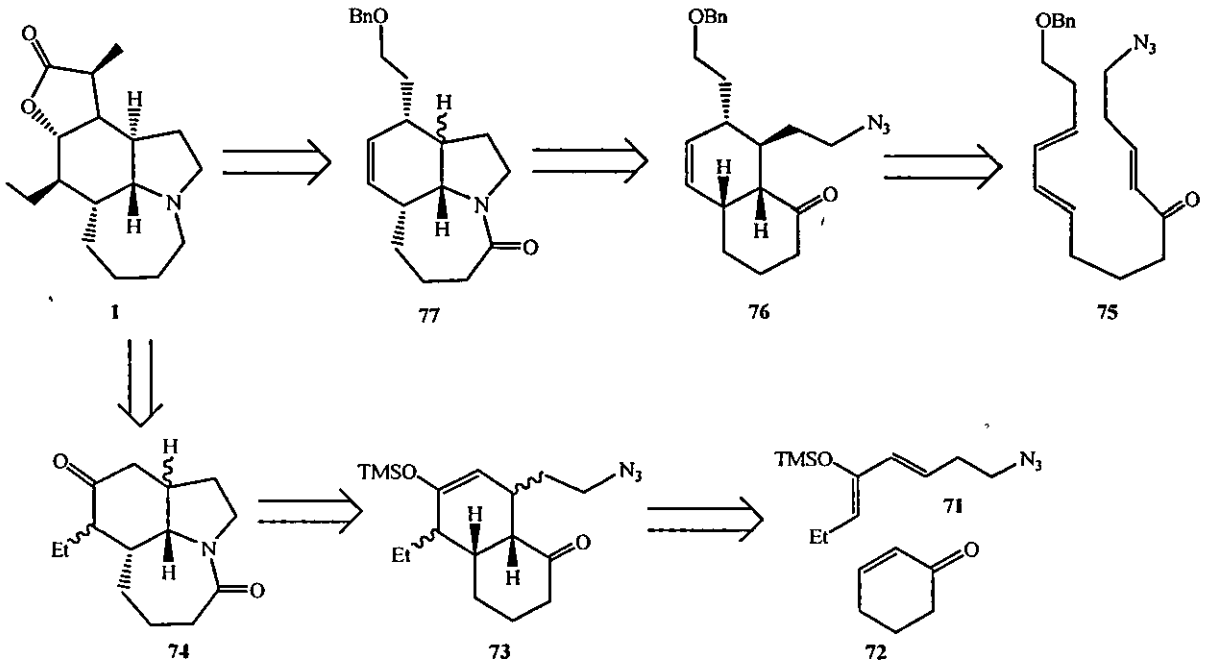


Scheme 13: Rigby's synthesis of the tricyclic core of stenine [9]

The functionalised hydroindolone intermediate was derived from a [1+4] cycloaddition between a vinyl isocycanate **53** and an alkyl isocyanide **65** acting as the 1,1-dipole equivalent. The hydroindole **66** was produced after room temperature cycloaddition of **53** and **65**, enamide N-alkylation with 1,4-diiodobutane afforded **67** in a 56% yield. The cyclisation to furnish final azepine ring thus to complete the tricyclic core **68** was carried out in diglyme *via* a metalloenamine intermediate, subsequent hydrolysis of the enamine then gave the

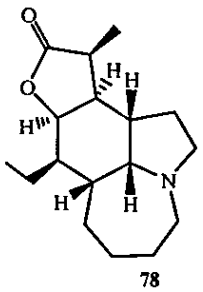
hydroisatin derivative **69** Treatment with *m*-CPBA gave the oxidation product **70** in a 93% yield to give the ring fusion pattern found in tuberostemonol (scheme 13).[9]

Aubé *et al.* described a recent facile synthesis of stenine in only 8 steps in a 14% overall yield, an excellent feature of this synthesis was that the tricyclic core was introduced early in the route. They envisioned that the B, C, D ring could be formed from an intramolecular Schmidt reaction on the ketone **76** prepared from the Diels-Alder reaction of the triene **75**. Initial work showed that the Schmidt and the Diels-Alder reactions could be carried out in one pot; however the reaction was poorly regio- and stereoselective. Their alternative route using a different disconnection was *via* **74** which would only require the butyrolactone attachment. This was a more facile route as the diene involved could be prepared more quickly and the ethyl group is incorporated early in the synthesis also (scheme 14).[10]



Scheme 14: Aubé's retrosynthetic route to stenine.[10]

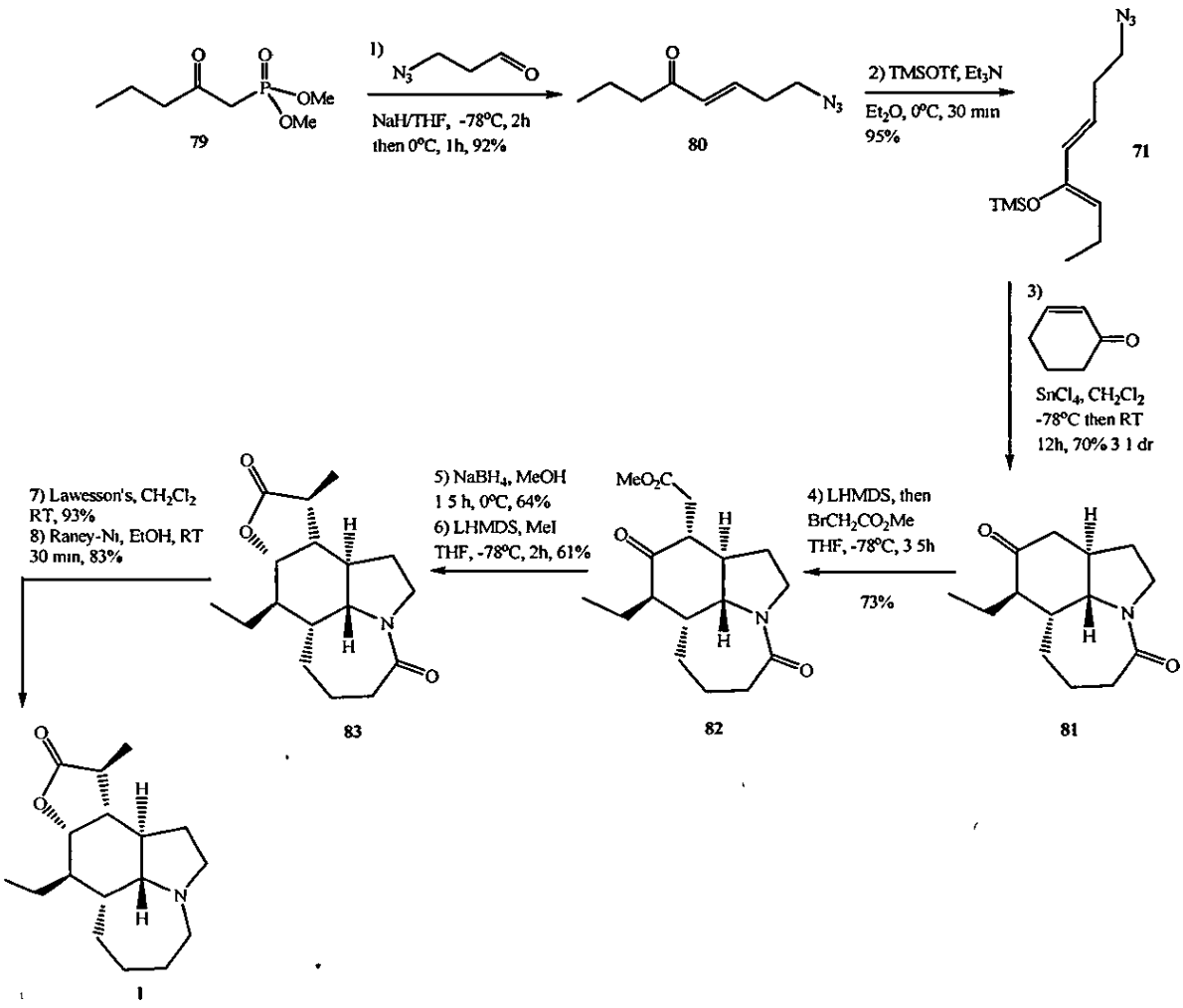
However the stereochemical outcome was uncertain, if the *exo*-Diels-Alder reaction occurred this would lead to natural stenine, whereas the *endo* route would yield the *epi*-ethyl version of neostenine.[10]



78

Figure 6: neostenine

The known Horner-Wadsworth-Emmons reagent **79** was stirred with the appropriate azido aldehyde to afford the enone **80** in a 92% yield, which was then converted into the diene **71** (scheme 15).



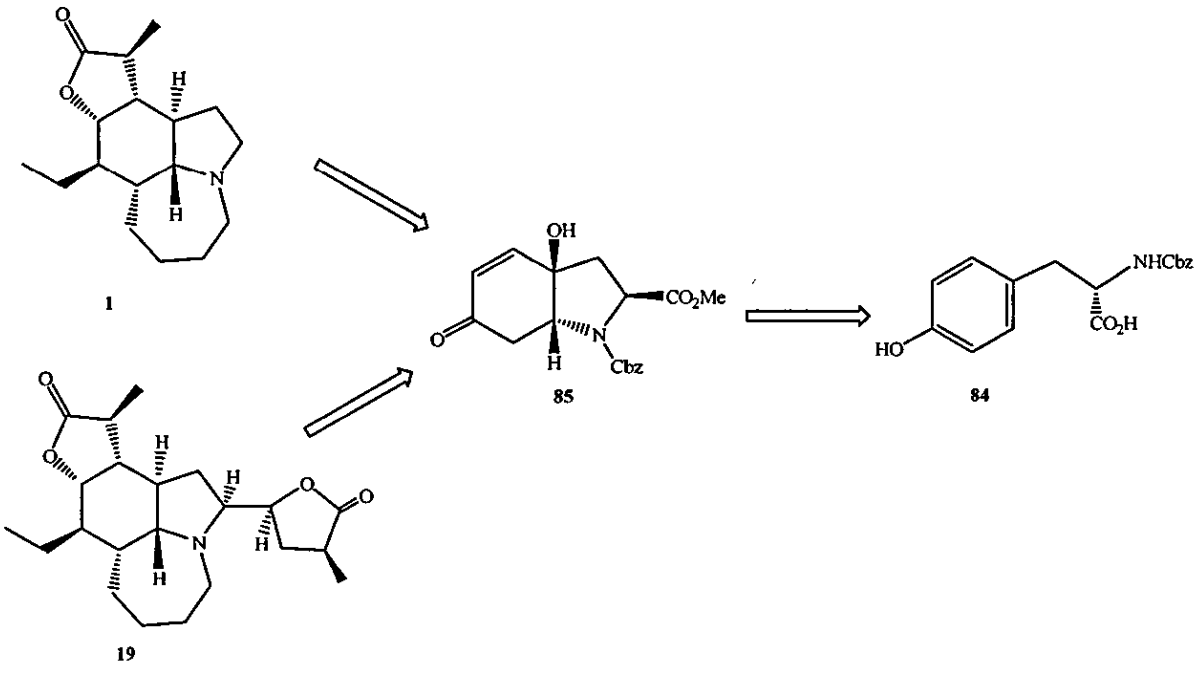
Scheme 15: Aubé's synthesis of stenine.[10]

Treatment with $SnCl_2$ and cyclohexanone gave the Diels-Alder/ Schmidt adduct *via* the *exo* pathway. The synthesis was then completed by an axially directed alkylation and reduction

yielding **81** and **82** respectively. The final steps were completed using known conditions with the total synthesis completed in only 8 steps in a 14% overall yield (scheme 15).[10]

1.3 Asymmetric sytheses of stenine

Wipf *et al.* described the first asymmetric synthesis of (–)-stenine from L-tyrosine **84**, scheme 16 outlines their retrosynthetic strategy. [11]

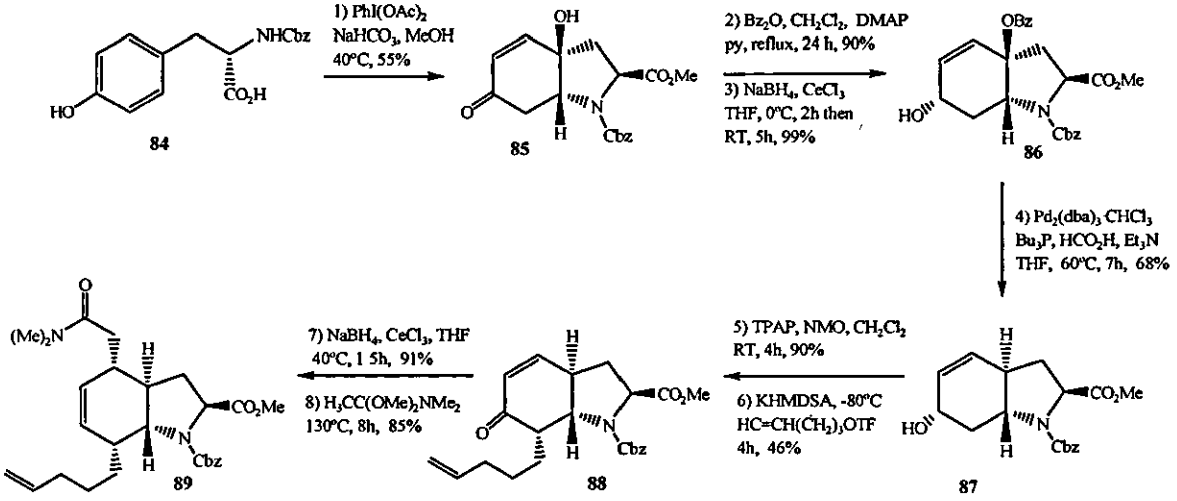


Scheme 16: Wipf's retrosynthetic route to Stenine from L-Tyrosine[11]

It was envisioned that a concise entry towards the perhydroindole ring system by means of the bicycle in scheme 16, which was obtained enantio- and diastereomerically pure in a single step from L-tyrosine **84**.[21] The major challenge of converting the *cis*-hydroxyindole ring system to the trans-fused perhydroindole present in *Stenine* and *Tuberostemonine* was solved by π-allyl-palladium chemistry.[21]

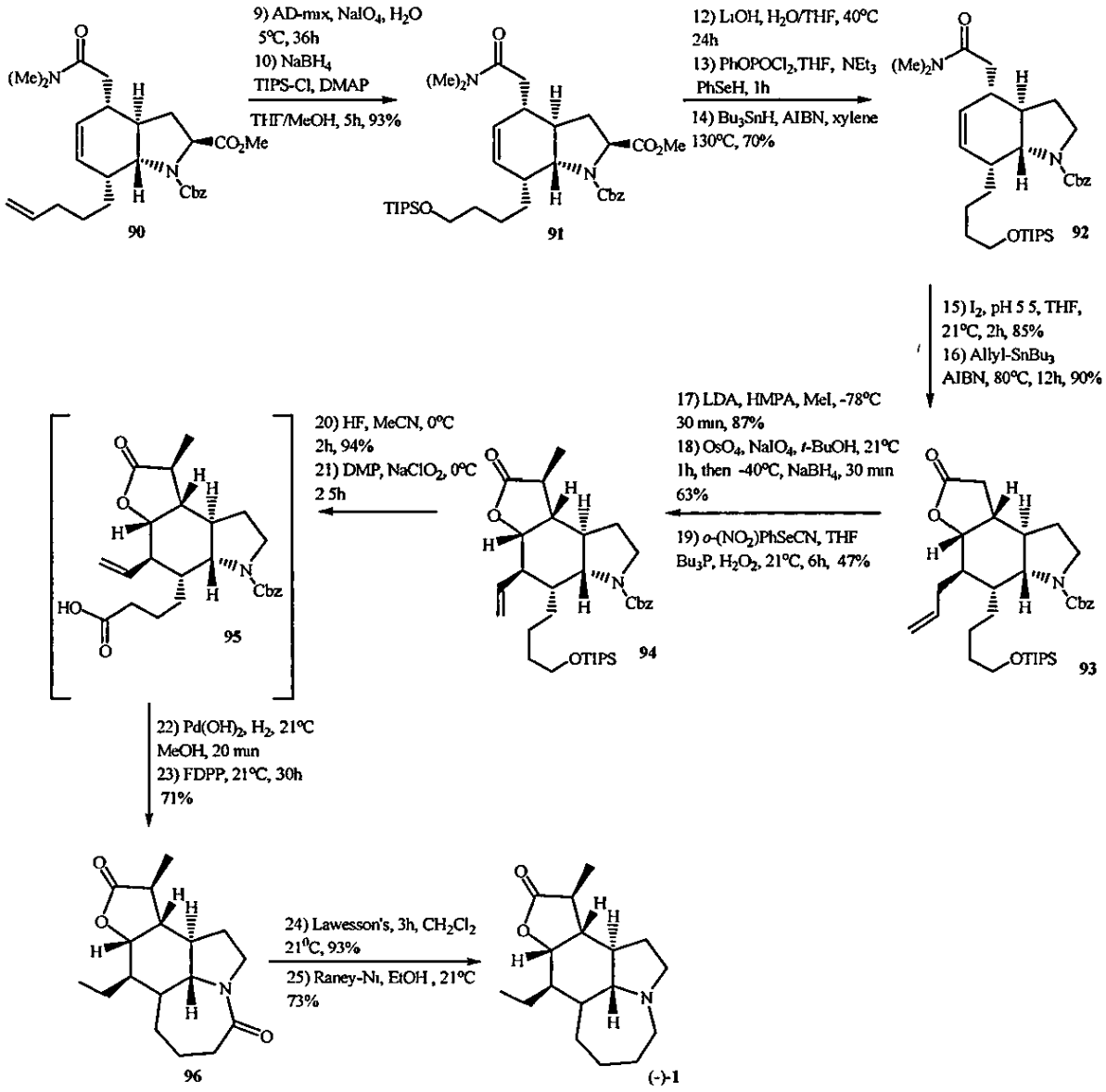
By stereoselective introduction of four additional stereocentres, a butyrolactone and an azepine ring were attached to this alkaloid building block.[11] Benzoylation of the tertiary alcohol in **85** and reduction of the enone with sodium borohydride, in the prescence of $CeCl_3$ gave the equatorial alcohol **86** as a single diastereoisomer in a 99% yield. The *trans*-

hexahydroindole **87** was afforded after some optimisation of the conditions in a modest 68% yield. Oxidation of **87** with TPAP regenerated the enone, which was subsequently deprotonated with KHMDS then alkylated with pentenyl triflate. A 1,2-reduction of the enone **88** furnished the equatorial alcohol which then would allow for the introduction of the butyrolactone (scheme 17).[11]



Scheme 17: Wipf's synthesis of stenine.[11]

Cleavage of the monosubstituted alkene over the cyclohexene ring was achieved using AD-mix-β followed by cleavage of the diol with sodium periodate, subsequent reduction of the aldehyde then silylation of the primary alcohol gave **91** in a 93% yield [11]

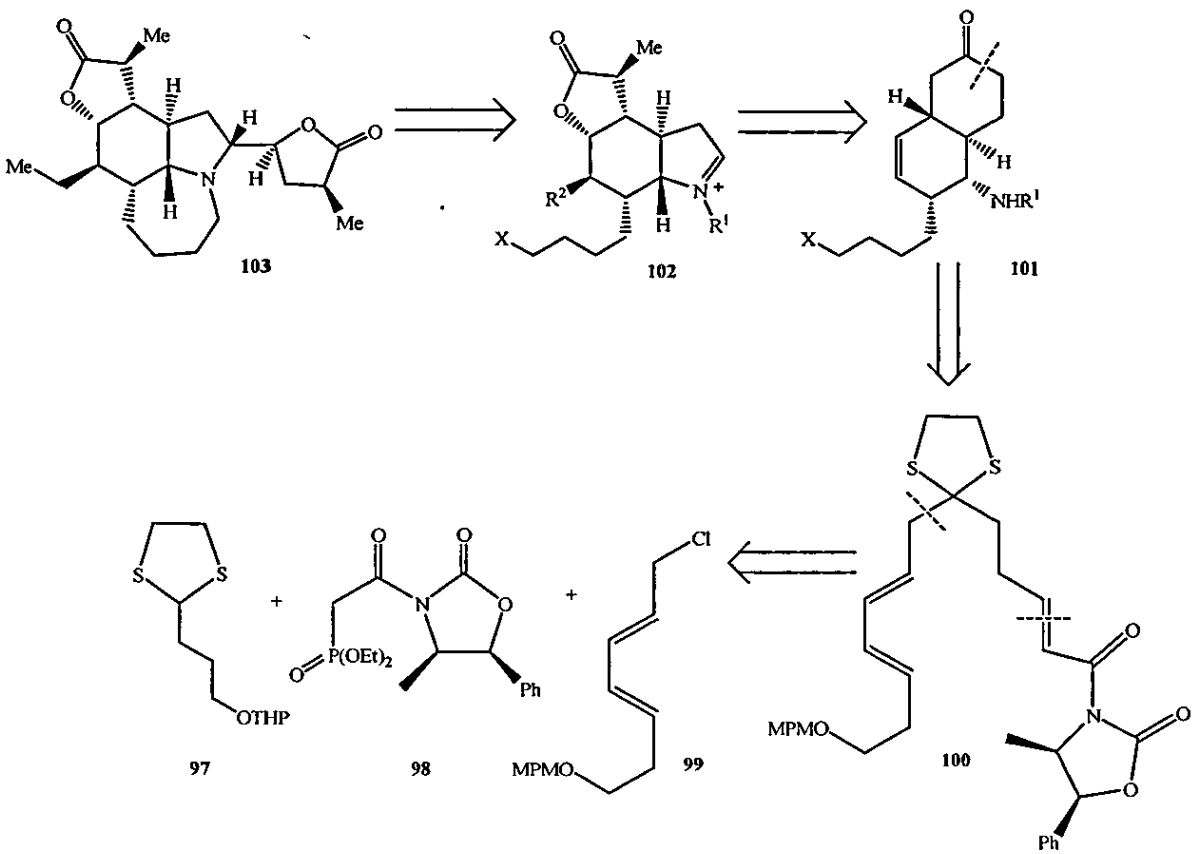


Scheme 18: Wipf's synthesis of stenine [11]

The carboxylic acid was removed *via* radical decarbonylation in a 70% yield, this was then followed by iodolactonisation carried out at a pH of 5.5 to minimise the hydrolysis of the silyl ether and then a Keck allylation to furnish **93**. Methylation was then carried out on the lactone and the allyl group was converted to a vinyl group utilising the Johnson-Lemieux oxidation, reduction and Grieco- elimination afforded **94** in a modest 47% yield. Formation of the last ring, the azepine was initiated by desilylation and oxidation of the primary alcohol to the acid using Dess-Martin periodinane. The acid **95** was hydrogenated and then cyclised using pentafluorophenyl diphenylphosphinate (FDPP) to give the lactam **96** in a 71% yield. Final conversion to stenine was accomplished using previously used conditions with

Lawesson's reagent used to furnish the thioamide then desulfurisation with Raney-nickel to provide (-)-stenine in an overall yield of 2% from 25 steps (scheme 18).[11]

Morimoto *et al.* also described an asymmetric synthesis of (–)-stenine, the retro-synthetic analysis is outlined in scheme 19 where tuberostemonine A **103** could also be achieved by this route.[12]

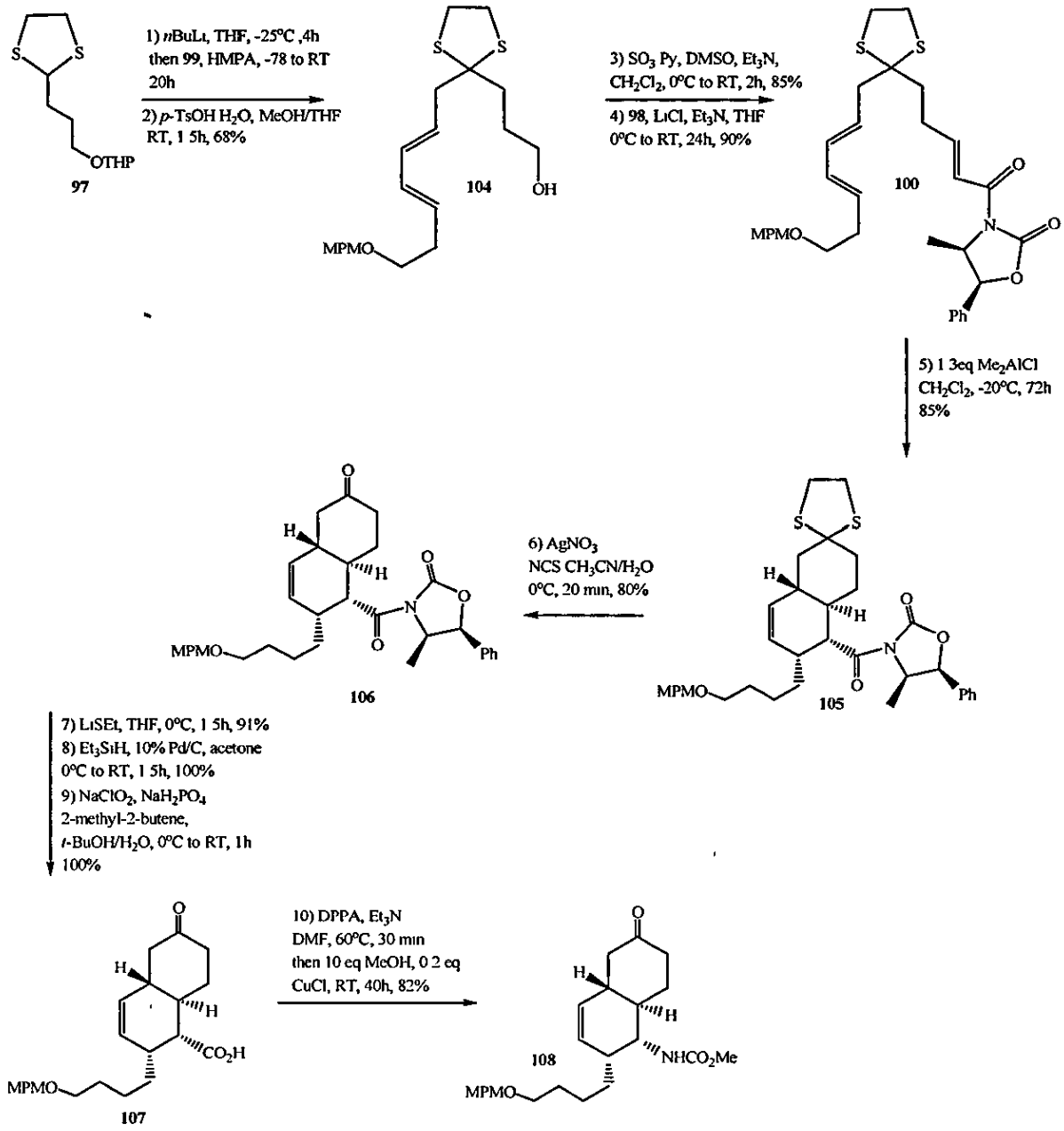


Scheme 19: Morimoto's retrosynthetic analysis of Stenine.[12]

The key step of the synthesis was the intramolecular asymmetric Diels-Alder reaction of the triene **100** prepared in a convergent fashion from the three readily available components giving the complete *endo* product (scheme 19).[12]

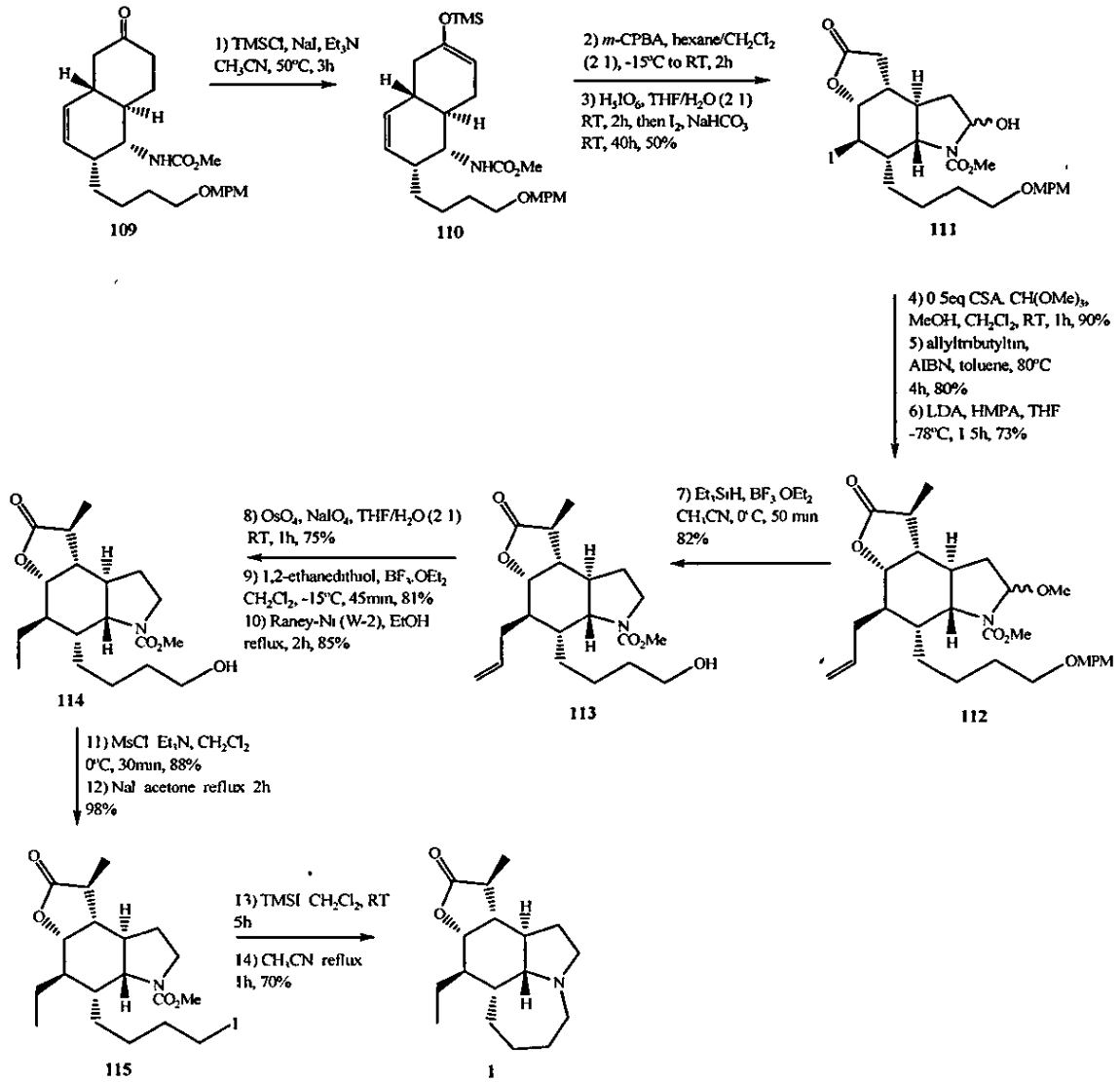
The synthesis began with the alkylation of the dithiane **97** with the dienyl chloride **99**; removal of the THP group provided the alcohol which was oxidised with SO_3.Py. The resulting aldehyde was subjected to a modified Horner-Emmons reaction with the chiral phosphonate **98**. The triene was afforded in good yields and then the key asymmetric Diels-

Alder reaction was carried out in the prescence of a Lewis acid to produce **105** in complete *endo* selectivity. Manipulation of **105**, hydrolysis of the 1,3-dithiane, removal of the chiral oxazolidinone, reduction of the resulting thiol ester to the aldehyde and oxidation of the aldehyde furnished the carboxylic acid **107** in high yields. The nitrogen functionality was introduced by the modified Curtius rearrangement using Shioiri's method (scheme 20).[12]



Scheme 20: Morimoto's synthesis of stenine.[12]

The next step was the oxidative cleavage of the alkene bond next to the TMS protected ketone in **110**, this was performed using *m*-CPBA followed by cleavage using orthoperiodic acid. An *in-situ* iodo-lactonisation then took place which stereoselectively formed the A, B, D ring system in **111**. The hemi-acetal in **111** was then protected, then using Hart's procedure the appropriate α-alkoxycarbamate **112** was constructed by stereocontrolled allylation and methylation. Reduction of the acetal group and of the *p*-methoxy-benzyl ether afforded the alcohol **113** in good yield, the Lemieux-Johnson oxidation was once again utilised by this group to convert the allylic group to an ethyl group. The formation of the dithiolane and desulfurisation with Raney-Ni furnished **114** (scheme 21).[12]

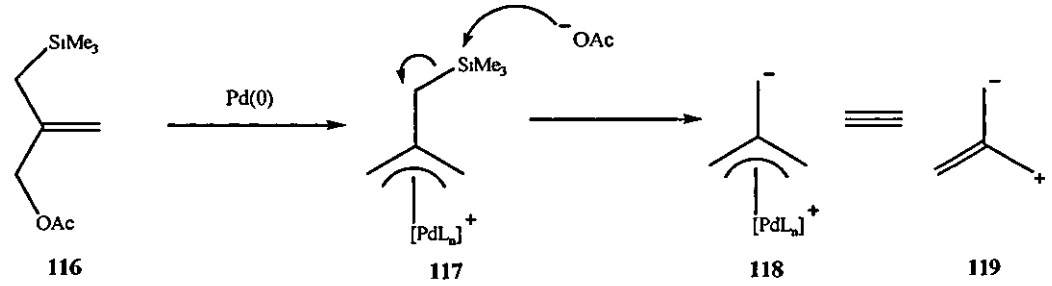


Scheme 21: Morimoto's synthesis of stenine.[12]

The iodide was set in place using a common method used for azepine ring formation, the C ring was constructed by removal of the methoxy carbonyl group with TMSI followed by subsequent intramolecular *N*-alkylation of the corresponding amine to yield (-)-stenine.[12]

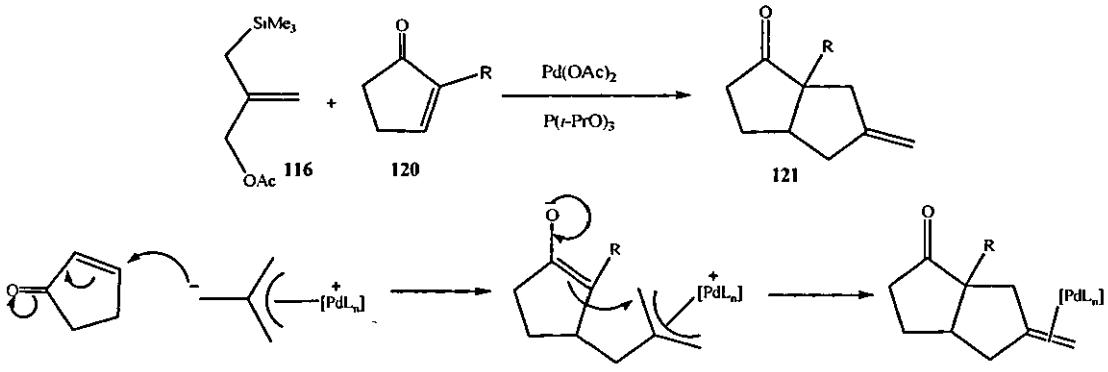
1.4 [2+3] Intramolecular Cycloadditions

Five membered rings are present in many structures of biological and chemical significance and this has led to research into a variety of methods for their preparation. One of the most successful is the Pd(0) catalysed [3+2] cycloaddition of trimethylenemethane. This unit will behave as a weak nucleophile and electrophile in the presence of palladium(0).[13, 14]



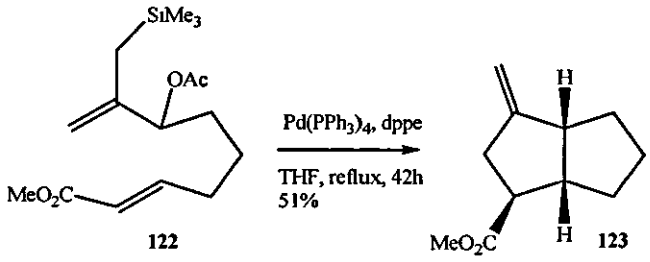
Scheme 22: Palladium complex of trimethylenemethane (TMM).

Formation of the palladium π-allyl complex **117** is followed by removal of the trimethylsilyl group by nucleophilic attack, producing a zwitterionic palladium complex **118** that can undergo cycloaddition reactions.[13, 14a]



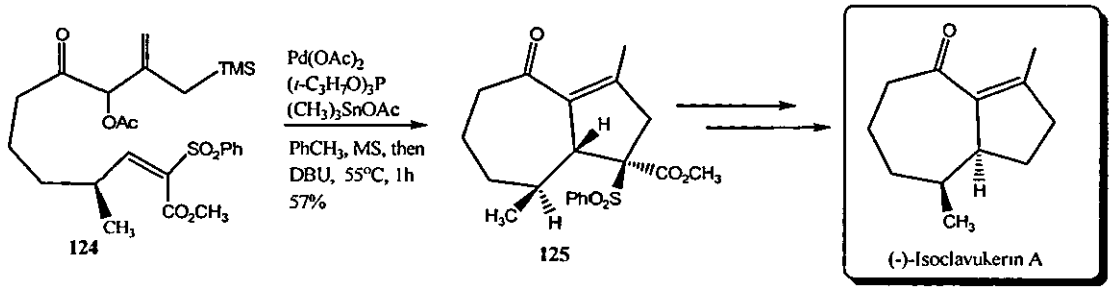
Scheme 23: [2+3] Pd(0) catalysed cycloaddition.

Of the few studies that had been performed in 80's and the early 90's was the intramolecular cycloadditions of methylenecyclopropanes which stood out. Initial studies carried out by Trost *et al.* looked at the development of [3+2] cycloadditions *via* the intermediacy of trimethylenemethane palladium complexes (TMM-PdL_2) carried out intramolecularly. Trost reported the synthesis of the cyclopentenoid **123** using the intramolecular version of this reaction (scheme 24).[13, 14a]



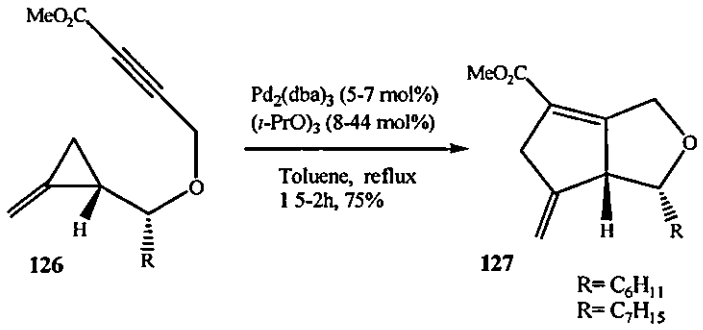
Scheme 24: Intramolecular Pd(0) catalysed cycloaddition. [13, 14]

Using this type of chemistry Trost reported an asymmetric synthesis of the perhdyroazulene (–)-isoclavukerin A using an intramolecular Pd-catlysed TMM cycloaddition of substrate **124** (scheme 25).[14b]



Scheme 25: Trost's synthesis of (–)-Isoclavukerin A.[14b]

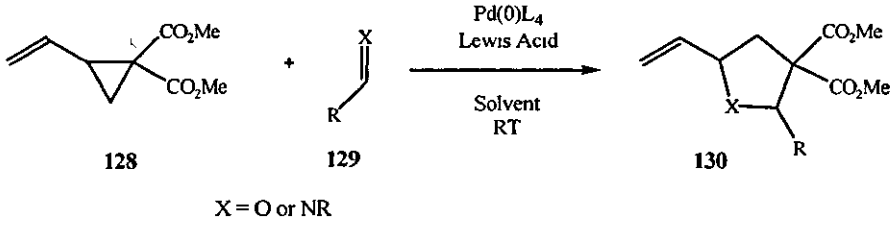
Palladium catalysed TMM cycloadditions have received considerable attention from various groups with intramolecular methylenecyclopropane reactions also being described by Noyori, Motherwell and Lautens respectively.[15, 16, 17]



Scheme 26: Intramolecular Pd(0) catalysed cycloaddition.[17]

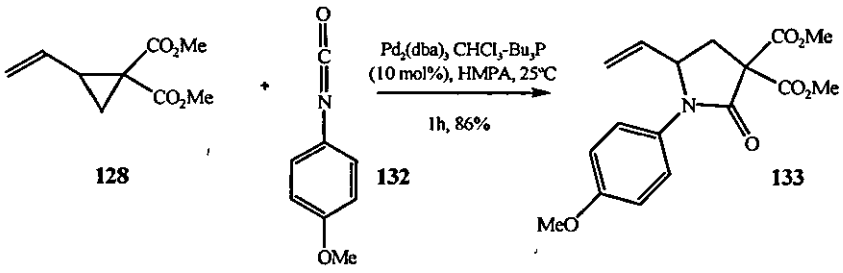
1.5 Intermolecular [2+3] Cycloadditions

Within the group work has centred on the Pd(0) catalysed [2+3] cycloadditions of imines **129** with vinyl cyclopropanes **128** work originally described by Tsuji *et al.* to access five membered heterocycles **130** (scheme 27).[18]



Scheme 27: General Pd(0) catalysed [2+3] cycloaddition [18]

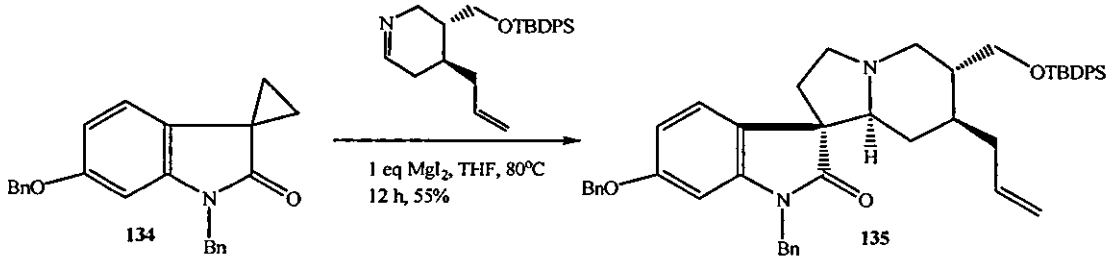
Tsuji generated the heterocyclic compound vinylbutyrolactam **133** by trapping *p*-methoxy-phenyl-isocycanate **132** with the vinyl cyclopropane **131.** It was a novel route into the construction of 5-membered heterocycles and importantly an avenue into compounds with pharmaceutical interest. However, the drawback with cycloaddition reaction conditions was that it required the use of HMPA as the solvent (scheme 28).[18]



Scheme 28: Tsuji's synthesis of vinylbutyrolactam.[18]

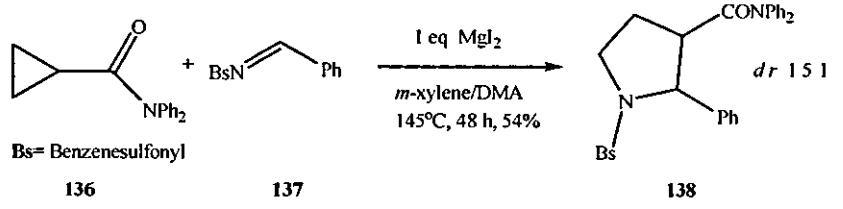
The reaction of an imine with a cyclopropyl moiety to form five-membered nitrogen heterocycles has also been exploited by a number of research groups using solely Lewis acid mediated methods also.

Carriera *et al.* in their synthesis of (±)-Strychnofoline, a spirotryprostatin alkaloid, and the related horsfiline showed that 3-spirocyclopropyl-2-oxindoles undergo reaction with imines under the influence of MgI_2 (scheme 29).[19]



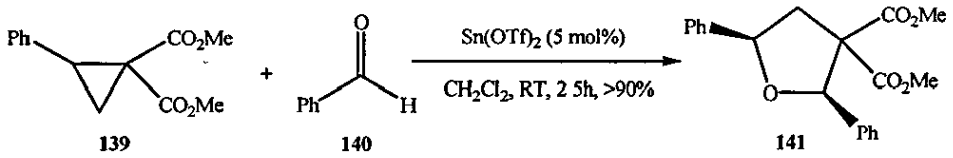
Scheme 29: Carriera *et al.* synthesis of (±)-Strychnofoline [19]

Lautens has also shown that MgI_2 catalyses the reaction of methylene cyclopropanes with imines to give pyrrolidines as the major product (scheme 30).[20]



Scheme 30: Lautens MgI_2 mediated ring expansion.[20]

Recently Johnson has shown that 1,1-cyclopropanediesters **139** and aldehydes **140** in the presence of $Sn(OTf)_2$ furnish tetrahydrofurans **141,** where the Lewis acid chelates to the electron withdrawing ester groups which subsequently ring opens the cyclopropane moiety and then traps the respective aldehyde to deliver the tetrahydrofuran **141** (scheme 31).[21]



Scheme 31: Johnson's Lewis acid mediated [2+3] cycloaddition.

Kerr *et al.* has very recently employed a nitrone/cyclopropane cycloaddition in his synthesis of the manazmine alkaloid Nakadomarin A, the only manzamine alkaloid to contain a furan ring (figure 7).[22]

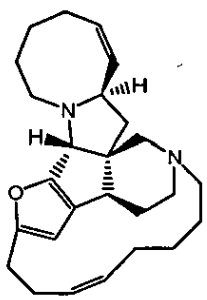
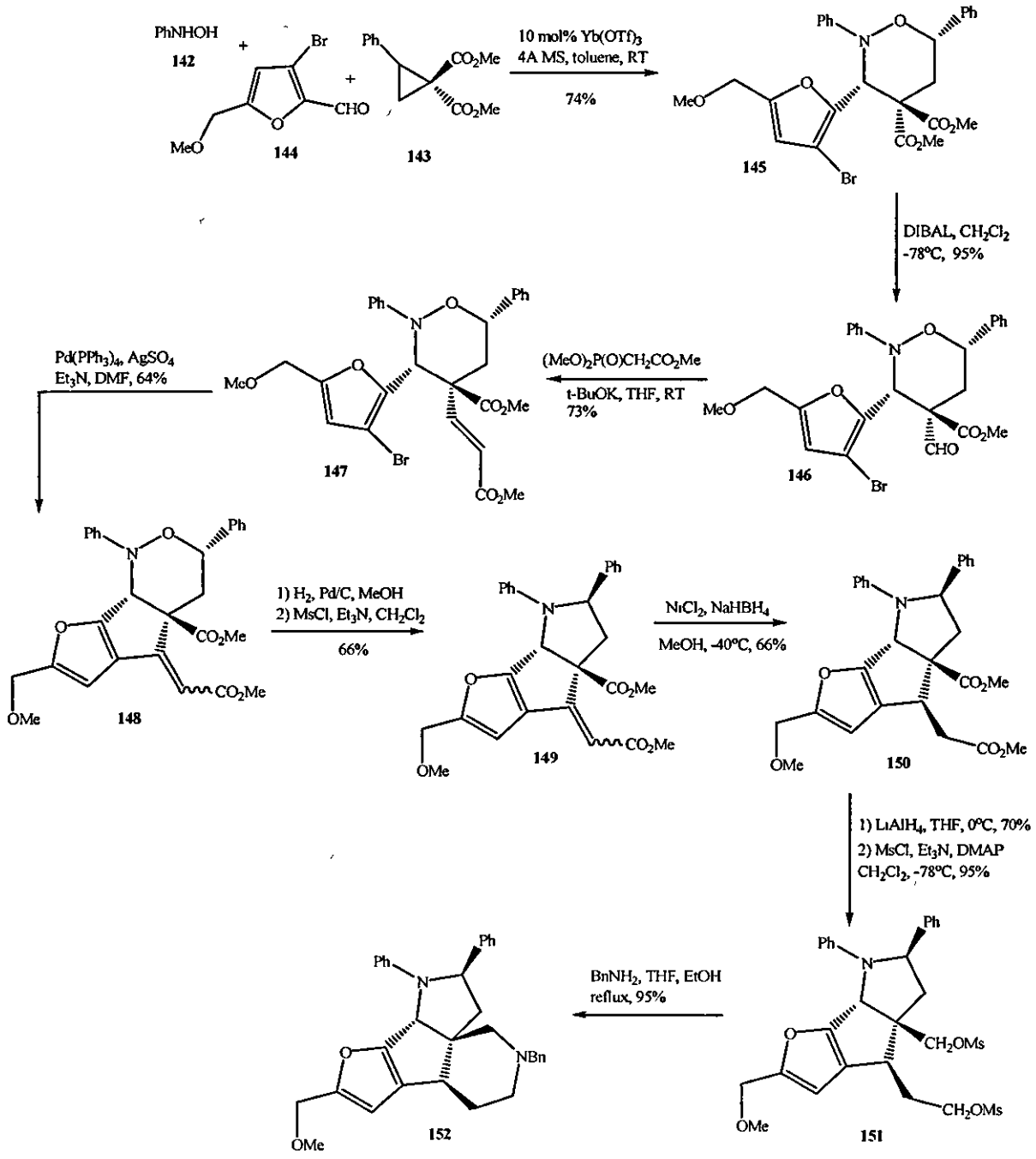


Figure 7: Nakadomarin A[22b]

Kerr reported the synthesis of pyrrolidines could be achieved *via* the manipulation of tetrahydrooxazines **145.** The oxazines were prepared from a cycloaddition of nitrones with 1,1-cyclopropanediesters **143** [22a]



Scheme 32: Kerr's synthesis of pyrrolidines.[22]

The synthesis of the nakodomarin A core began with the coupling of phenylhydroxylamine, furfural **144** and the cyclopropane **143** This afforded the adduct **145** in an 74 % yield. A selective reduction with of the equatorial ester with DIBAL gave the aldehyde **146** and a Horner-Emmons olefination gave the enoate **147**. This underwent a Heck reaction to give **148** in a 64% yield (scheme 32).[22]

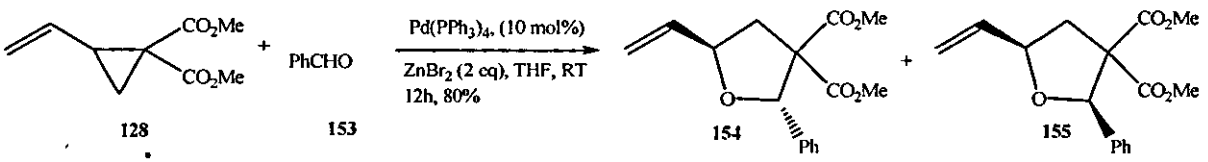
Cleavage of the N-O bond and recyclisation to the pyrrolidine furnished the tricyclic compound **149** in a 66% overall yield. The diester **150** was formed *via* reduction of the enolate double bond with nickel boride. Formation of the piperidine ring was achieved by ester reduction to the diol, formation of the dimesylate **151** and displacement with benzylamine producing the nakadomarin A tetracyclic core in 10 steps. [22]

1.6 Previous research

The Pritchard group has developed mild conditions and have generated a range of heterocyclic compounds using this Pd(0) catalysed [2+3] cycloaddition chemistry.

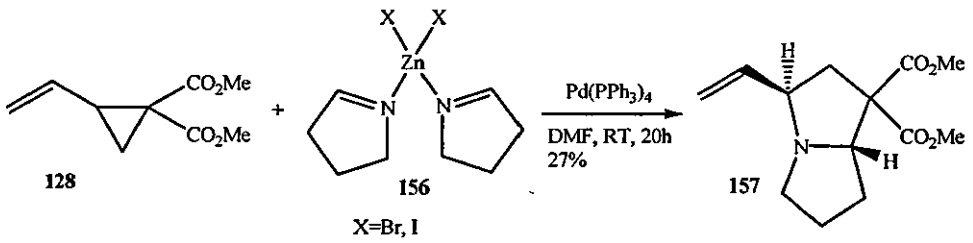
Thus far the conditions employed in the trapping of simple imines with the vinyl cyclopropane have employed the use of the solvent THF and palladium tetrakistriphenylphosphine ($Pd(PPh_3)_4$) (10 mol%) as the catalyst. Lewis acids have also been used to activate the vinylcyclopropane by co-ordinating to the two ester groups.

Tang has shown that a variety of imines and aldehydes can successfully be trapped with a vinylcyclopropane substrate in the presence of Pd(0) and Lewis acids giving pyrrolidines and tetrahydrofurans in good yields as a pair of diastereoisomers (scheme 33).



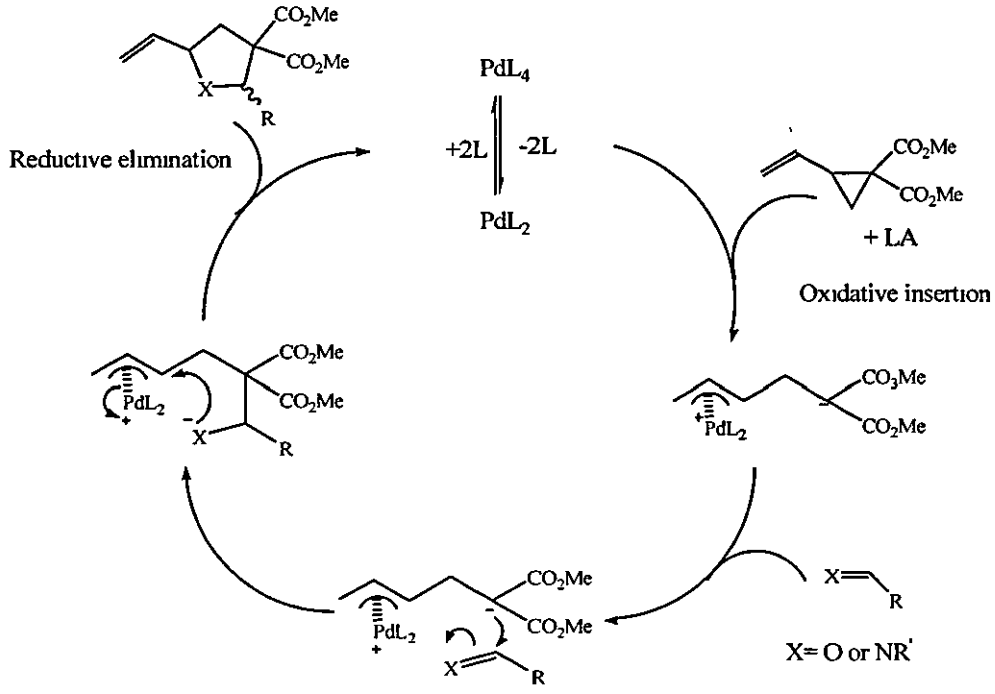
Scheme 33: Pd(0) catalysed [2+3] cycloadditions.

The tetrahydrofurans **154** and **155** were produced as a 1:1 mixture of diastereoisomers. Tang has also developed conditions for the successful trapping of cyclic imines **156** from the 1-pyrroline zinc iodide complex giving access to the pyrrolizidine derivative **157** in one step (scheme 34).



Scheme 34: Pd(0) catalysed [2+3] cycloadditon with cyclic imines.

The mechanism for the generation of these heterocyclic substrates is shown in the cycle in scheme 35.

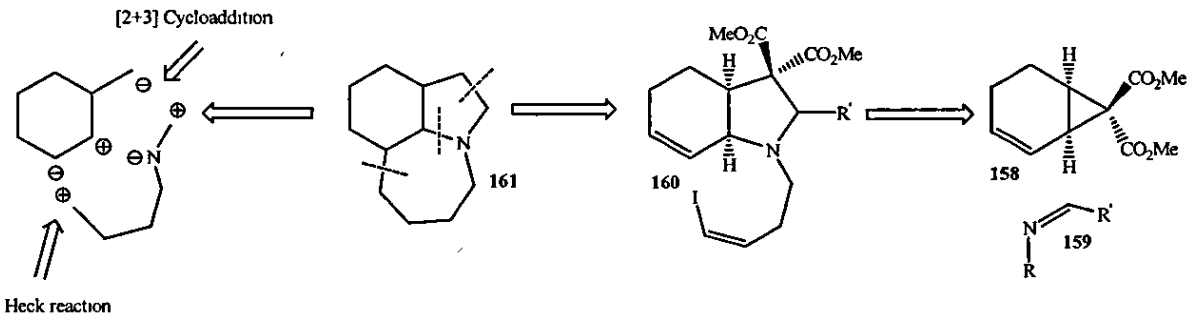


Scheme 35: General Pd(0) catalysed cycloaddition with the vinylcyclopropane.

It is hoped that using [2+3] cycloaddition chemistry the tricyclic core of stenine can be accessed.

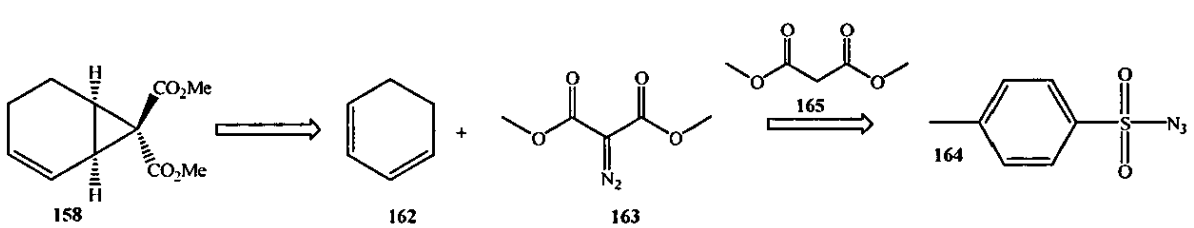
Chapter 2: Pd(0) Catalysed [2+3] Cycloaddition route to the tricylic core of the stenine group of stemona alkaloids

The route, to the stenine core which we wished to look at, envisaged using a Pd(0) catalysed [2+3] cycloaddition between an activated vinylcyclopropane substrate **158** and a suitable imine **159** to give the hydroindole core **160**. A subsequent intramolecular Heck reaction on **160** could then be carried out to construct the 7-membered azepine ring of the tricylic core **161** (scheme 36).[5]



Scheme 36: Retrosynthetic route to the tricyclic core of stenine.[5]

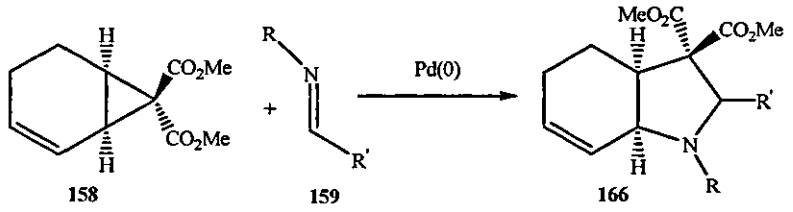
The synthesis of **158** was going to be approached *via* the Rh(II) acetate dimer catalysed cyclopropanation of 1,3-cyclohexadiene **162** with dimethyl diazomalonate **163**, which in turn would be synthesised using a diazo transfer from the tosyl azide **164** with dimethyl malonate **165** (scheme 37).[24]



Scheme 37: Intermolecular route to the tricyclic core.

2.1 Synthesis of the Imine

When constructing the hydroindole core **166**, the group R' must be open to further manipulation so that stenine related targets can be accessed. Therefore the imine must contain a synthetically versatile group so extra functionality can be added later in the syntheses in that position (scheme 38).



Scheme 38: Proposed Pd(0) catalysed [2+3] cycloaddition.

The carbon in the R' position is very important as it contains a lactone in the natural products neotuberostemonine and tuberostemonol as shown in figure 5.

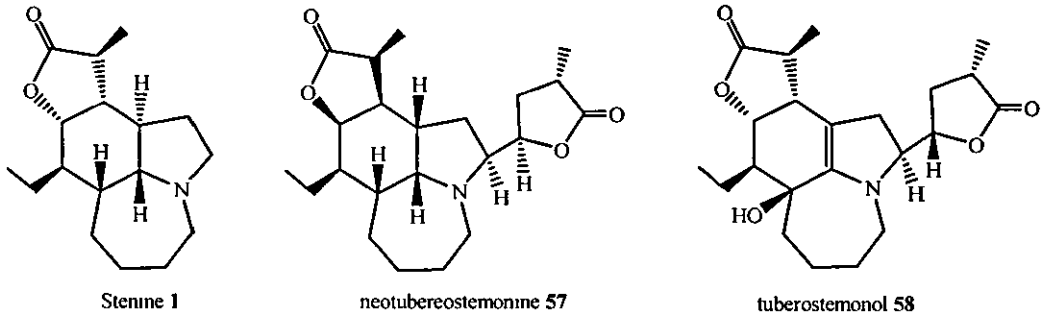
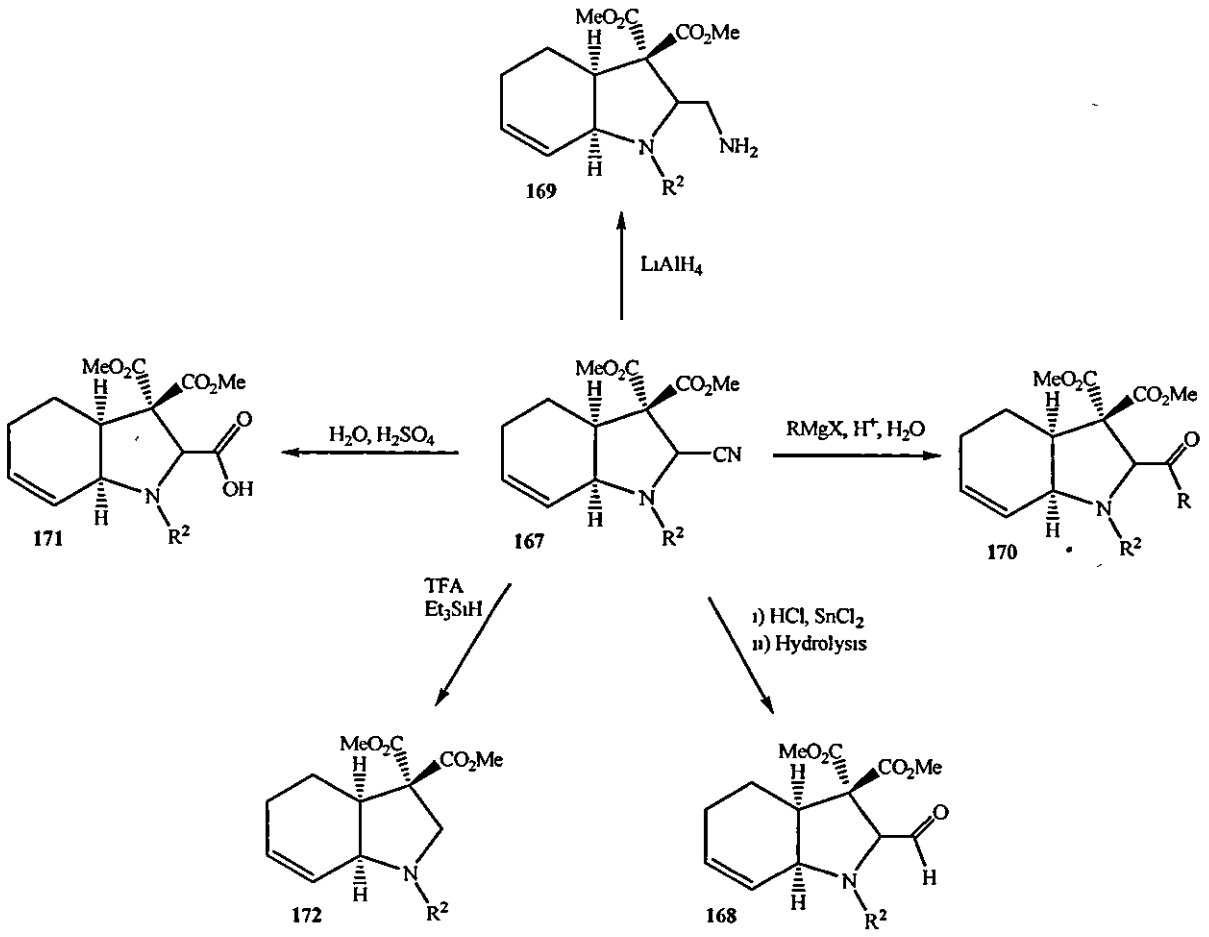


Figure 5: Stenine and related alkaloids.

So by incorporating a chemically versatile group *via* the trapping of an imine here in this position this can serve as a handle by which other targets in the stemona family can be accessed also The imine we wished to synthesise contained the nitrile functionality, this functional group can be converted for example to the aldehyde **168**, reduced to the corresponding amine **169** using $LiAlH_4$ or to the ketone **170** using a Grignard reagent (scheme 39)



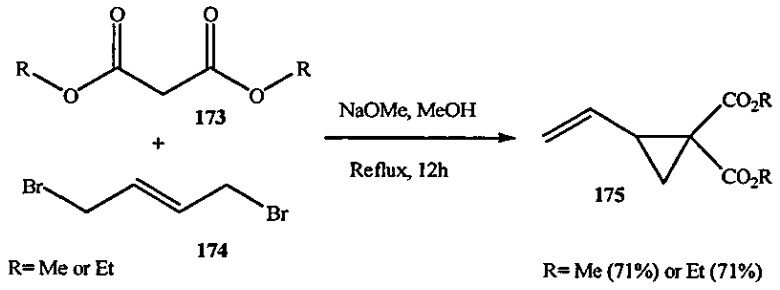
Scheme 39: Nitrile group interconversions.

The conversion to the aldehyde **168** can be performed using the Stephen reduction, treatment with HCl then reduction with $SnCl_2$ and hydrolysis would give the aldehyde. This can also be carried out using a metal hydride reducing agent where 1 mol of hydrogen and hydrolysis can be performed *in situ*, DIBAL can also be a reagent used for this. The many functional group conversions that can be performed on the nitrile functionality made it ideal for it to be incorporated into the imine (scheme 39).

2.2 Preparation of activated vinylcyclopropanes

Previous work within the group utilised the reactive nature of activated vinylcyclopropanes to access five-membered heterocycles. The most successful methods of synthesising these activated vinylcyclopropane substrates have been *via* the double displacement of a di-substituted but-2-ene precursor with an activated methylene component. This method has

been adopted by the group, and a range of activated vinylcyclopropane derivatives have been prepared (scheme 40).[24, 25]



Scheme 40: General preparation of activated vinylcyclopropanes.[24, 25]

For the synthesis of stenine, the activated cyclopropane which was required was the fused vinylcyclopropane **158** shown in figure 6.

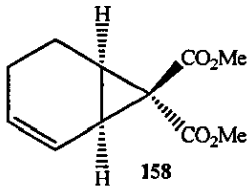
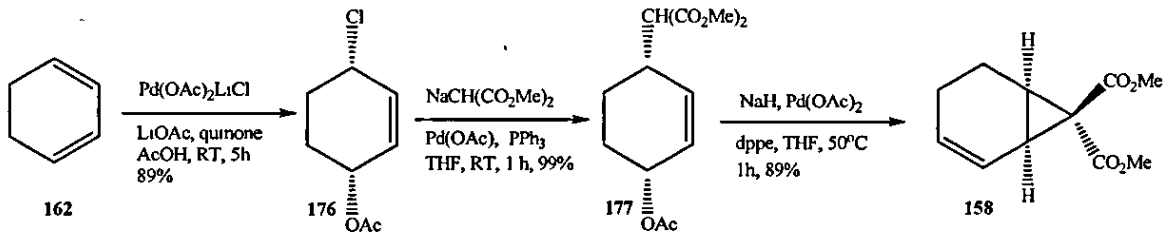


Figure 6: 7,7-Dicarbomethoxybicyclo[4.1.0]hept-2-ene.

With this activated bicyclic cyclopropane we could then carry out a Pd(0) catalysed [2+3] cycloaddition with an imine to furnish the hydroindole core. There have been various routes to 7,7-dicarbomethoxybicyclo[4 1.0]hept-2-ene **158** already reported, these were investigated and are described.

2.3 Routes to 7,7-dicarbomethoxybicyclo[4.1.0]hept-2-ene

Access to this activated bicyclic vinylcyclopropane had already been investigated previously within the group, following a number of syntheses already reported. Backvall *et al.* had described a synthesis of **158** using a palladium catalysed route shown in scheme 41.[26, 27]

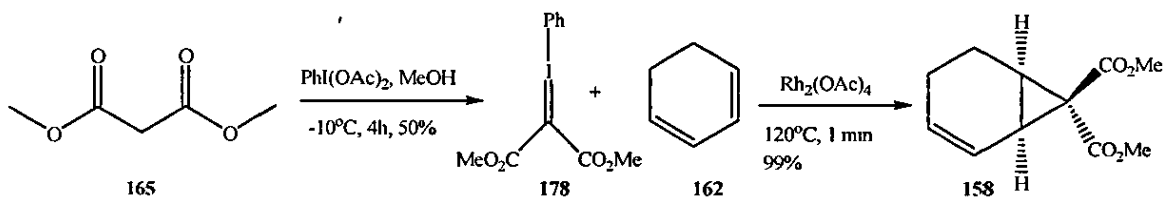


Scheme 41: Backvall synthesis of 7,7-dicarbomethoxybicyclo[4 1.0]hept-3-ene.[26, 27]

This route was very appealing for our approach as it would furnish the hydroindole core and then the tricylic core in an entirely palladium catalysed route. The work involved a palladium catalysed oxidation of **162** in the presence of LiCl and LiOAc to give the chloro derivative **176**. Substitution of the chloro group by the dimethyl malonate anion and subsequent palladium catalysed cyclisation furnished the fused cyclopropane **158** in an 89% (scheme 41).[26, 27]

Due to the nature of the chemistry involved in the above synthesis it could also open up the avenue of developing a number of 'one-pot' procedures. A draw-back of Backvall's route, however is that it required two sources of Pd(0), whereas we hope to develop a route using only one source

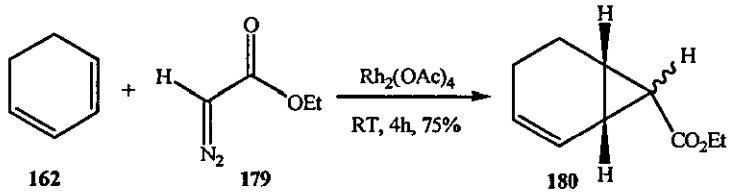
Another route investigated had been described by Georgakopoulou *et al.* based on the use of an iodonium ylide **178** derived from dimethyl malonate **165** and 1,3-cyclohexadiene **162** (scheme 42).[28]



Scheme 42: Georgakopoulou's synthesis of 7,7-dicarbomethoxybicyclo[4.1.0]hept-3-ene.[28]

This route incorporated a rhodium(II) acetate dimer catalysed cycloaddition to form the bicyclic activated vinylcyclopropane **158** in near quantitative yields.

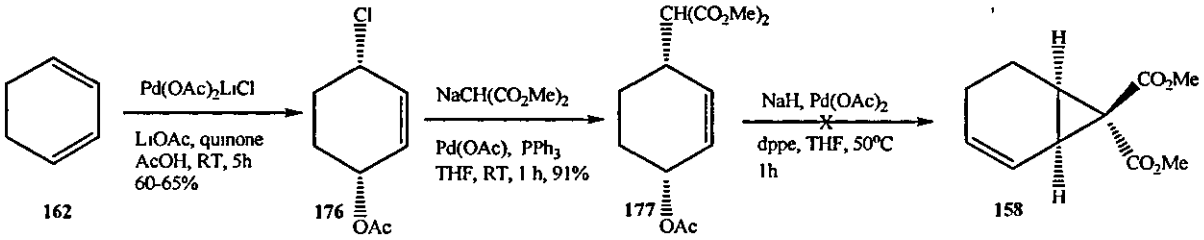
The use of rhodium stabilised carbenoid chemistry with diazo carbonyl compounds has already been reported using ethyl-diazoacetate **179** in excellent yields, the attractiveness of this chemistry has been further reinforced due to the number of asymmetric routes which have also been described using this substrate (scheme 43).[29]



162 **179** **180**

Scheme 43: Cyclopropanation of 1,3-cyclohexadiene with ethyl diazoacetate.[29]

Previously within the group attempts to synthesise **158** had already been investigated, initial work followed that described by Backvall *et al.* [24, 26, 27]



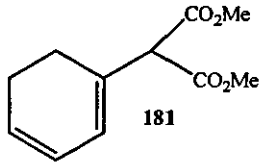
162 **176** **177** **158**

Scheme 44: Backvall *et al* cyclopropanation.[26, 27]

This synthesis was followed by a co-worker and initially the work looked promising, the oxidation of 1,3-cyclohexadiene **162** to the chloro-acetate **176** proceeded in a 60-65% yield, lower than the reported yield of Backvall (89%). Displacement of the chloride by sodium dimethylmalonate using Pd(0) was problematic, the reaction was successful but isolation and purification of the desired compound **177** was difficult due to un-reacted starting materials The work was also not reproducible on a large scale, when the work was performed on >200 mg the yields fell.[24, 26, 27]

Substrate **177** was isolated firstly in a modest 60% yield, though optimisation of the work-up conditions raised this to a high 91% yield. The final step though was the stumbling block **158** was not isolated in the reaction. The conditions in the final step were repeated and modified,

longer reaction times were used however only the starting material **168** was isolated along with **181** shown in figure 7.[24]

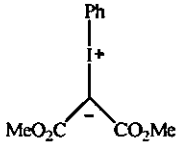


181

Figure 7: Isolated bi-product.[24]

No explanation could be provided as to why the reaction failed therefore it was felt that following work by Georgakopoulou could prove more fruitful.[28]

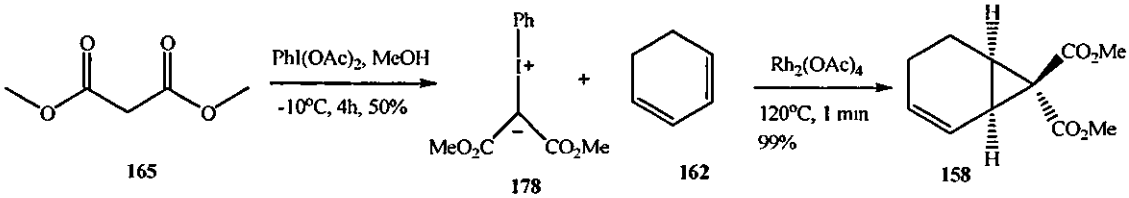
Georgakopoulou *et al.* reported the cyclopropanation of dienes including **162** with an iodonium ylide **178** derived from dimethyl malonate **165** and diacetoxyiodobenzene. Iodonium ylides have been used as reactive alternatives to diazo compounds without the drawbacks of being explosive or having associated health hazards.[28]



178

Figure 8: Iodonium ylide.[28]

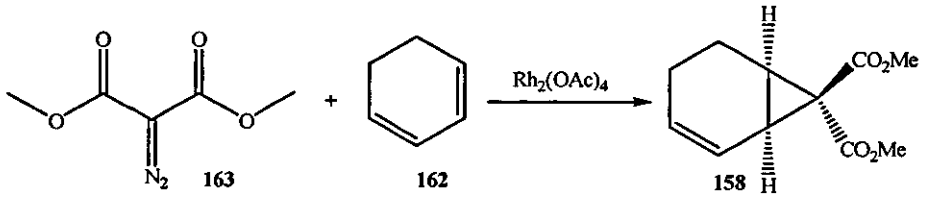
They reported a 99% yield of **158** when cyclopropanating excess 1,3-cyclohexadiene **162** with this ylide in 1 minute. Unfortunately this synthesis could not be replicated; even when longer reaction times were used only starting materials were recovered (scheme 45).[24, 28]



165 **178** **162** **158**

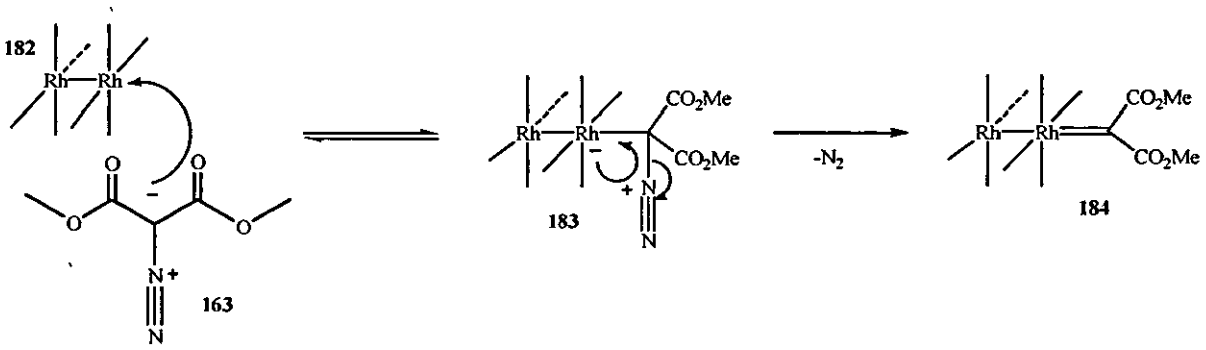
Scheme 45: Georgakopoulou's cyclopropanation.[28]

The final route to **158** which was investigated was the Rh(II) acetate dimer catalysed cyclopropanation of a diazo-carbonyl substrate with a diene (scheme 46).[24, 29]



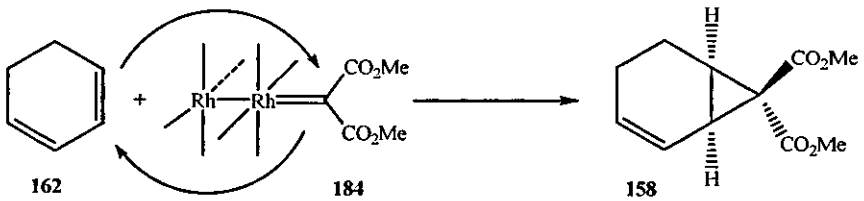
Scheme 46: Rh(II) acetate dimer catalysed cyclopropanation.

The Rh(II)-catalysed reaction of α-diazo carbonyl compounds has been established as a powerful approach to generate Rh(II) carbenes.[29, 30] The mechanism of the Rh(II) catalysed diazo decomposition has not been fully understood with a vast amount of research being carried out, the generally accepted mechanism is shown in scheme 47.[29, 30, 31]



Scheme 47: Proposed mechanism for Rh(II) carbene generation.[29, 30, 31]

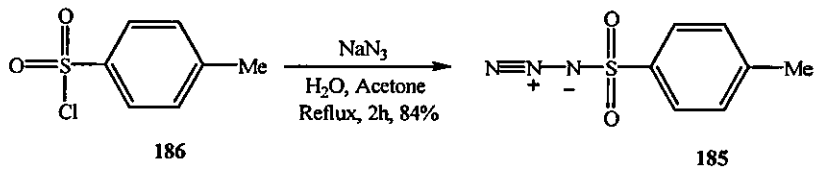
The carbene is generated by the initial complexation of the negatively polarised carbon of the diazo compound **163** to the axial site of the Rh(II) catalyst **182**. Subsequent extrusion of N_2 then generates the Rh(II) carbene **183** which then cyclopropanates the required diene.[30]



Scheme 48: Cyclopropanation.

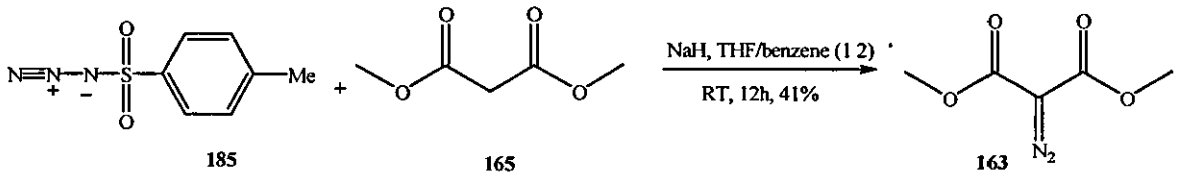
Work by Berson *et al.* on the properties of 7,7-dicarbomethoxycycloheptatriene described a synthetic route to 7,7-dicarbomethoxybicyclo[4.1.0] hepten-2-ene from dimethyl diazomalonate **163** and 1,3-cyclohexadiene **162**.[32]

The synthesis of the dimethyl diazomalonate **163** was achieved *via* a diazo transfer from the tosyl azide **185** and dimethyl malonate **165**. The tosyl azide was synthesised from tosyl chloride **186** and sodium azide in an 84% yield (scheme 49).[24]



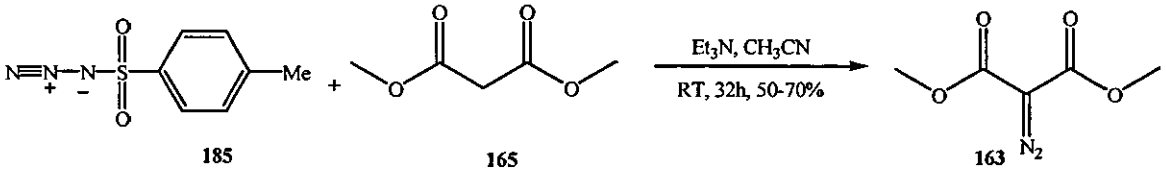
Scheme 49: Synthesis of the tosyl azide.

This reaction was simple and could be performed on a large scale and the tosyl azide **185** could be used without further purification. The synthesis of the dimethyl diazomalonate **163** was initially based on work carried out by Vandewalle *et al.* the diazo transfer was complete in 12 hours in a low yield of 41% (scheme 50).[33]



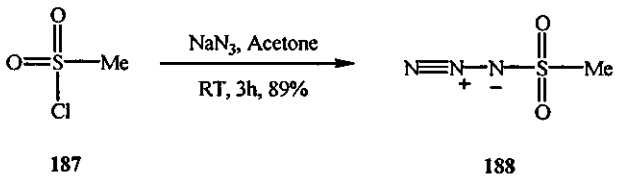
Scheme 50: Synthesis of dimethyl diazomalonate.[24]

Long reaction times were needed and poor yields were obtained using this method, therefore to increase the yield of the dimethyl diazomalonate, work described by Regitz *et al.* was followed. In this method Et_3N was used as the base and acetonitrile as the solvent but more worrying was that longer reaction times were required, up to 32 hours in this instance (scheme 51).[34]



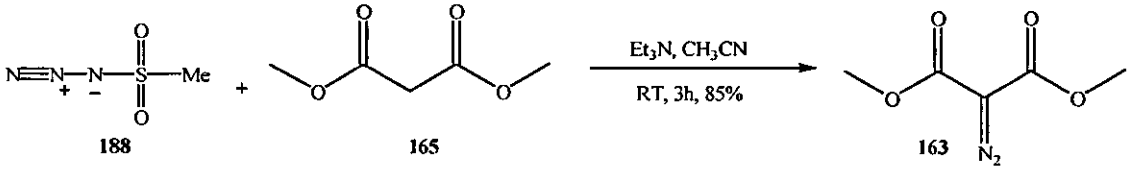
Scheme 51: Synthesis of dimethyl diazomalonate.

An alternative to the tosyl azide was to use the mesyl azide variant **188.** Work by Danheiser *et al.* had shown the synthesis of the mesyl azide to be a relatively straightforward procedure (scheme 52).[35]



Scheme 52: Synthesis of mesyl azide.[35]

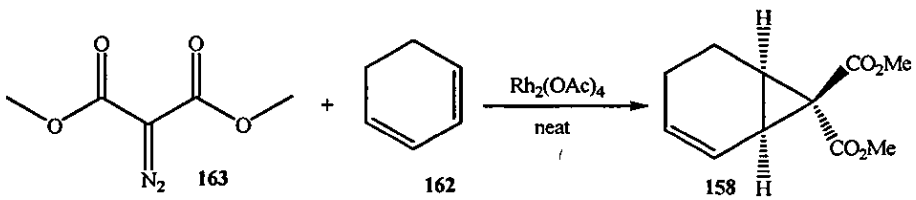
Short reaction times were required affording the azide **188** in a high 89% yield which was reproducible when the reaction was performed on a large scale. Work by Taber *et al.* had shown a very successful procedure for the diazo transfer *via* the mesyl azide intermediate. Using tosyl azide for the diazo transfer process is a very common method however work by Taber has shown that the mesyl azide **188** is also an excellent reagent for this.[36]



Scheme 53: Synthesis of diazo dimethylmalonate.[36]

An excellent reproducible yield was obtained using mild conditions giving access to the dimethyl diazomalonate **163** on large scales in a short reaction time. With the synthesis of the dimethyl diazomalonate now optimised the next step was to perform the cyclopropanation with the diene **162.**

Initially the cyclopropanation was performed neat based on work within the group, however poor yields were obtained using this method.[24] The conditions were then altered, different solvents were investigated and also the use of a syringe pump to introduce **163** into the mixture was explored.



Diene	Diazomalonate	Solvent	Yield 158 (%)
1 0 eq.	1 0 eq.	Neat	7
1 0 eq.	1 0 eq.	Neat	26
1 0 eq.	1 0 eq.	Neat	34
1 0 eq	1.1 eq	Neat	26
1 0 eq	1.1 eq	Neat	32
1 0 eq	2 0 eq	Neat	12

Table 1: Cyclopropanation results.

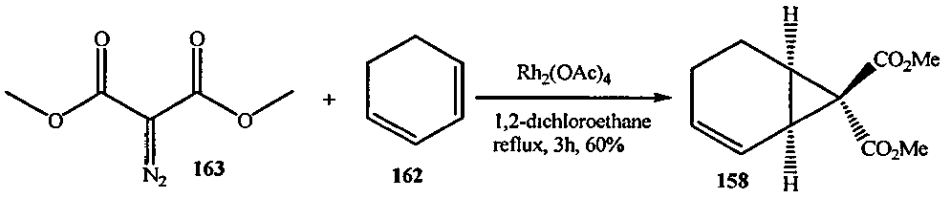
Previously within the group the work had been carried out in neat conditions, so that the concentration of the reacting substrates was high.[24] The reaction yields were not reproducible and they fluctuated greatly, even when changing the equivalents of the respective reacting materials the yields varied and were very low.

When performed neat the reaction also became very viscous so stirring was difficult therefore thorough mixing of the diene, diazo compound and catalyst was not maximised The next step was to investigate conditions suitable for the reaction

Diene	Diazomalonate	Solvent	Product 158 (%)
1 0 eq	2 0 eq	DCM	6
1 0 eq	1.1 eq	1,2-dichloroethane	49
1 0 eq	1.1 eq	Toluene	33
1 0 eq	1 1 eq	1,2-dichloroethane	60
1 1 eq	1.0 eq	1,2-dichloroethane	54
1.1 eq	1 0 eq	1,2-dichloroethane	56

Table 2: Cyclopropanation results.

Initially DCM was used as the solvent and there was a dramatic decrease in yield which could not be explained, however upon the use of 1,2-dichloroethane, a higher boiling point solvent, the yields increased dramatically. Switching to toluene caused the yield to fall again so it appeared that 1,2-dichloroethane was the solvent of choice.

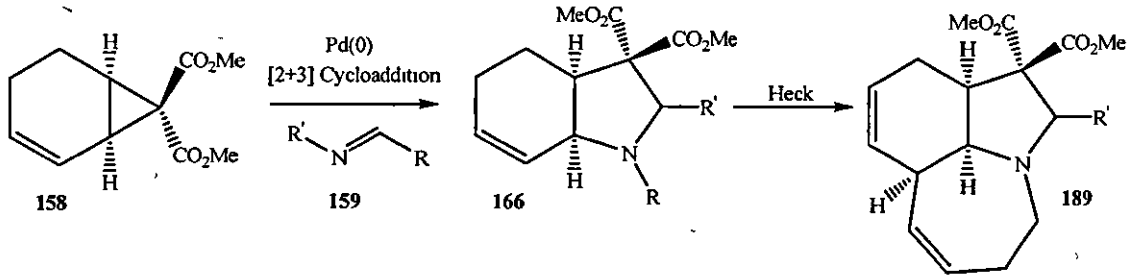


Scheme 54: Cyclopropanation.

As diazo compounds are explosive in nature upon scale up of the reaction the dimethyl diazomalonate was introduced into the reaction mixture *via* a syringe pump. This did not appear to affect the reaction and the yield was reproducible at 60% meaning that **158** could be produced on a relatively large scale (scheme 54).

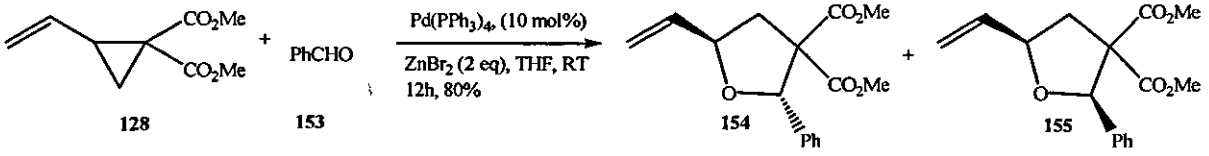
2.4 Pd(0) Catalysed [2+3] Cycloaddition

With the route to the precursor **158** now established in a 60% yield, the next step was to perform a trial Pd(0) catalysed [2+3] cycloaddition with a suitable substrate as it is proposed that the hydroindole core **166** will be synthesised utilising this chemistry (scheme 55).



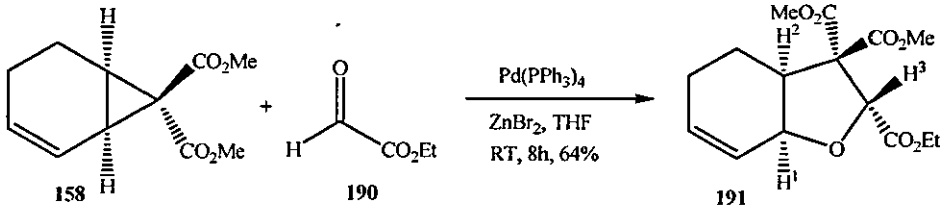
Scheme 55: Route to the tricyclic core.

The Pd(0) catalysed [2+3] cycloaddition had already been established within the group using simple vinylcyclopropanes which has furnished various heterocyclic compounds (scheme 56).[23, 24, 25, 37, 38]



Scheme 56: Pd(0) catalysed [2+3] cycloaddition.

The Pd(0) catalysed [2+3] cycloaddition with benzaldehyde gave the furan as a mixture of diastereoisomers in an inseparable 1:1 ratio. These conditions were applied to the fused cyclopropane **158** and ethyl glyoxylate **190** was used as the trapping agent (scheme 57).



Scheme 57: Pd(0) catalysed [2+3] cycloaddition

The reaction was successful in a modest 64% yield, a singlet peak at 4.74 ppm was characteristic for H^1, 4.18 ppm for H^2 and a singlet at 5.28 ppm H^3 and the stereochemistry was assigned using nOe analysis. There was no nOe between proton H^3 and H^4.

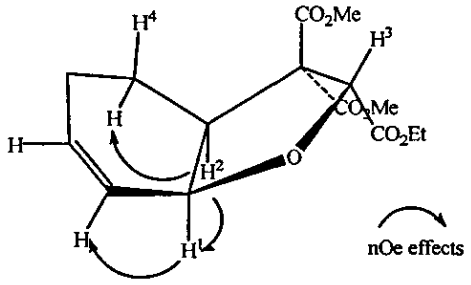
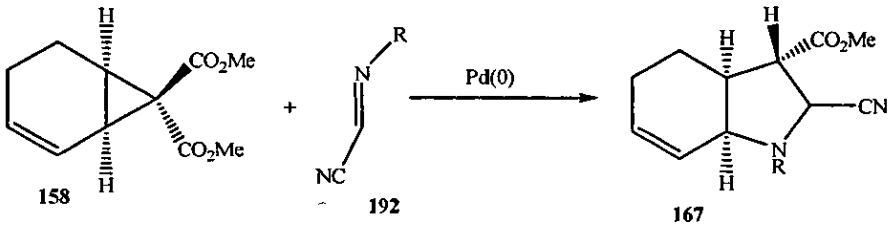


Figure 9: nOe effects.

As the cycloaddition was successful the next stage was to synthesise the imine precursor that could be used to synthesise the hydroindole core of stenine.

2.5 Synthesis of the Imine precursor

Once the imine precursor was synthesised the cycloaddition shown in the scheme 58 could be carried out, the use of a Lewis acid would also be investigated.

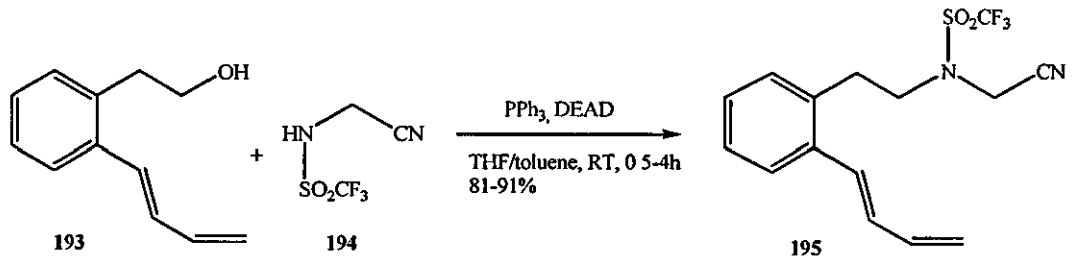


Scheme 58: Pd(0) catalysed [2+3] cycloaddition.[5]

As the aim was to provide a route to the total synthesis of the stenine group of the stemona alkaloids, the group introduced *via* the imine must be converted to the lactone which is present in many of the stemona alkaloids.

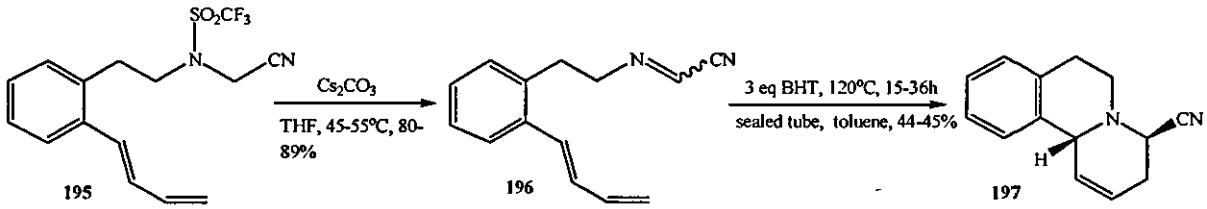
Therefore the nitrile group is a synthetically versatile agent as the group is small and linear so no foreseeable steric effects could occur, also further chemistry may be carried out on the nitrile group so that different functionalities may be introduced onto the ring in that position.

Danheiser *et al.* had shown a very elegant route to the synthesis of various cyano imines and from these a range of [4+2] intramolecular cycloadditions of iminoacetonitriles producing cyclic α-amino nitriles had been performed (scheme 59).[39]



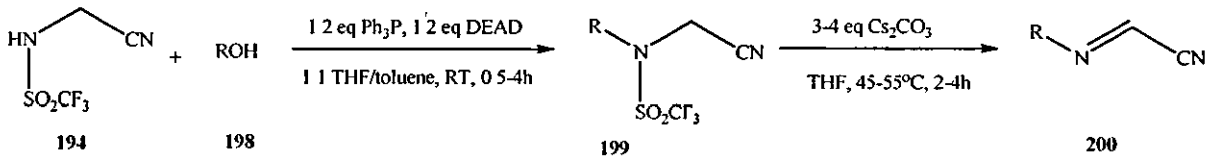
Scheme 59: Danheiser's [4+2] intramolecular cycloaddition.[39]

They employed a Mitsunobu reaction with the reagent **194** and the alcohol **193** then a base-promoted elimination of the trifluoromethanesulfinate group furnished the desired iminoacetonitrile **196** as a mixture of *E* and *Z* isomers in a 77:23 ratio (scheme 60).[39]



Scheme 60: Imine generation then [4+2] cycloaddition.[39]

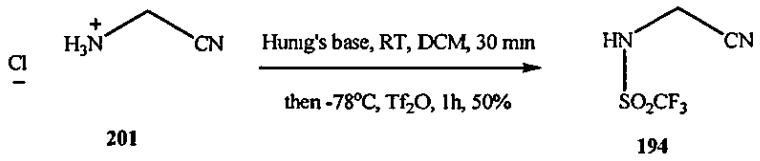
These then underwent an intramolecular [4+2] cycloaddition to yield the tricyclic product **197** in a 44-45% yield in a ratio of 79:21, *cis trans* isomers.



Scheme 61: Danheiser's preparative route to the cyanoimine.

Undertaking the synthesis of the imine precursor required three steps, the synthesis of *N*-(cyanomethyl)trifluoromethanesulfonamide **194**, a Mitsunobu reaction with a suitable alcohol and then base-catalysed elimination to give the imine **200** (scheme 61).[39]

Work began with the synthesis of *N*-(cyanomethyl)trifluoromethanesulfonamide **194** which furnished by treating **201** with diisopropylethylamine (Hunig's base) at room temperature, the solution was then cooled to -78°C before trifluoromethanesulfonic anhydride was added giving **194** in a 50% yield (scheme 62).[39]

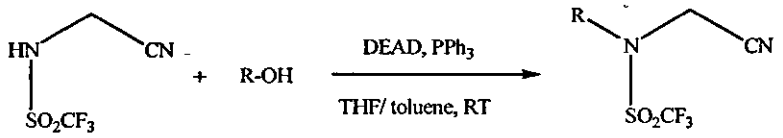


201 **194**

Scheme 62

Purification of the sulphonamide was difficult as it was a very viscous material and applying the compound to the chromatography column proved problematic which may account for the low yield after purification. Initially we were unsure if the reaction had been unsuccessful as there was no presence of a stretch corresponding to a nitrile group at 2300 cm^{-1} in the IR data. Mass spectral analysis showed the presence of the parent ion in an abundance of 2% and the ^1H NMR data agreed with that provided by Danheiser. With this data the sulphonamide was brought forward to the Mitsunobu stage.[39]

Although using different alcohols, Danheiser reported yields ranging from 64-93% of his desired iminoacetonitriles, however we were unfortunately unable to reproduce any such yields when applied to our work.[39] Initially we carried out the Mitsunobu reaction using simple alcohols, such as ethyl and benzyl alcohol. The desired products were not isolated upon work up in each case and we were unable to deduce what had occurred in the reaction



194 199

194	R-OH (1 eq)	Solvent	DEAD	PPh_3	Time	Temp °C	Product 199
1 05 eq	Benzyl	THF/Toluene	1 2 eq	1 2 eq	2 h	RT	Complex mixture by ^{1}H NMR
1.05 eq	Ethyl	THF/Toluene	1 2 eq.	1 2 eq	2 h	RT	"
1.05 eq	Benzyl	THF/Toluene	1 2 eq.	1 2 eq	2 h	RT	"
1 05 eq	Benzyl	THF/Toluene	1 2 eq.	1 2 eq	4 h	RT	"
1 05 eq	Benzyl	THF/Toluene	2 eq	2 eq	4 h	RT	"

Table 3: Mitsunobu results.

This was frustrating even when the equivalents of the reagents and reaction time were increased not even starting materials were isolated. Due to this it was decided to use an alcohol similar to that used by Danheiser, in this case phenethyl alcohol was used.[39]

194	R-OH (1 eq)	Solvent	DEAD	PPh_3	Time	Temp °C	Product 199
1 05 eq	Phenethyl	THF/Toluene	1 2 eq.	1 2 eq	2 h	RT	Complex mixture by ^{1}H NNR
1.05 eq	Phenethyl	THF/Toluene	1 6 eq	1 6 eq	8 h	RT	"
1 05 eq	Phenethyl	THF/Toluene	1 6 eq	1 6 eq	24 h	RT	"

Table 4: Mitsunobu results.

Again the reaction was unsuccessful, increasing the equivalents of the DEAD and triphenylphosphine had no effect, increasing the reaction time to 24 hours was also fruitless. The next step was to investigate the reagents as to whether or not they were hampering the reaction, fresh DEAD was used and the triphenylphosphine was re-crystallised also hopefully improving its purity.

The Mitsunobu reaction was then repeated this time using 5-hexen-1-ol, DEAD and the re-crystallised triphenylphospine. The 5-hexen-1-ol was used as we felt with the presence of the extra double bond in the substrate it would be easier to identify the product in the ^{1}H NMR.

194	R-OH (1 eq)	Solvent	DEAD	PPh_3	Time	Temp °C	Product 199
1 05 eq	5-Hexen-1-ol	THF/Toluene	1 6 eq	1 6 eq	24 h	50	Complex mixture by ^{1}H NMR
1.05 eq	5-Hexen-1-ol	THF/Toluene	1 6 eq	1 6 eq	24 h	50	"
1.05 eq	5-Hexen-1-ol	THF	1 6 eq	1 6 eq	24 h	50	"
1 05 eq	5-Hexen-1-ol	Toluene	1 6 eq	1 6 eq	24 h	50	"
1 05 eq.	5-Hexen-1-ol	THF/Toluene	1.6 eq	1 6 eq.	24 h	50	"
1 05 eq.	5-Hexen-1-ol	THF	1 6 eq	1 6 eq.	24 h	Reflux	"
1.05 eq.	5-Hexen-1-ol	Toluene	1 6 eq	1 6 eq	24 h	Reflux	"
1.05 eq.	5-Hexen-1-ol	THF/Toluene	2 0 eq	2 0 eq	24 h	50	"
1.05 eq.	5-Hexen-1-ol	DCM	1 6 eq	1 6 eq	24 h	50	"

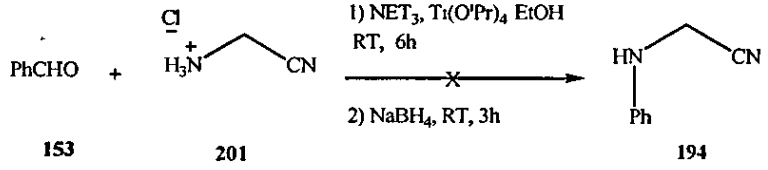
Table 5: Mitsunobu results.

This time the reaction was heated between 50°C up to reflux the solvent conditions were varied and the equivalents of the reagents were varied again we were unable to deduce what had occurred in the reaction as no recognisable materials were isolated. At this point it was decided that because a considerable amount of time and effort had been spent on this synthesis a new route to the cyanoimine was needed.

2.6 Synthesis of the cyanoimine *via* a Reductive alkylation

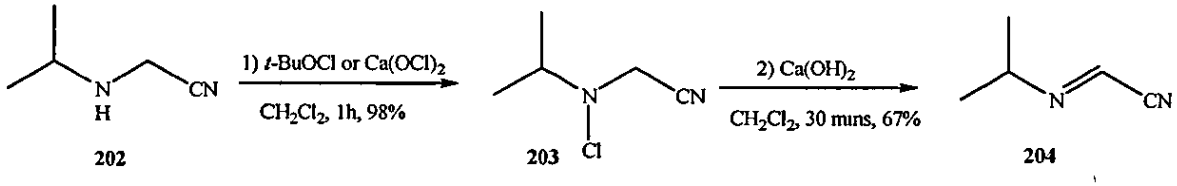
A second route to the imine precursor that would still incorporate the nitrile group was a reductive alkylation onto the readily available starting material aminoacetonitrile hydrochloride **201** with benzaldehyde **153** This would produce the secondary amine **194** *via* a reductive amination, from here the triflate group could be incorporated then eliminated to obtain the imine.

Work by Miriyala *et al.* had produced symmetrical secondary amines from aldehydes *via* reductive alkylation of ammonia.[40] It was envisaged that this work could be incorporated here It was hoped that the treatment of the aldehyde **153** in ethanol with **201** and titanium isopropoxide followed by an *in-situ* sodium borohydride reduction would yield the amine **194** (scheme 63).[40]



Scheme 63: Reductive alkylation.[40]

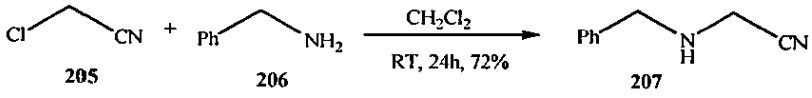
Unfortunately this reaction was also unsuccessful and the amine **194** was not isolated, however Perosa *et al.* had described an efficient synthesis of *N*-alkylformidoyl cyanides (RRCHN=CHCN), *via* an oxidation/ elimination using aqueous NaOCl on various amines.[41] Previous work on their synthesis was achieved in a two step sequence, *N*-chlorination followed by dehydrochlorination with a base. An example is shown in scheme 64.[41]



Scheme 64: Synthesis of *N*-alkylformidoyl cyanides.[41]

Long reaction times were required for this chemistry which appeared to be the major disadvantage to this route. The *N*-chloro derivatives of the amines needed to be isolated and the reaction temperature needed to be controlled as to optimize the yields. Perosa reported a one-pot reaction under mild conditions using commercial aqueous solution of NaOCl.[41]

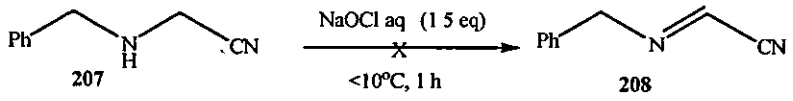
The cyanoamine **205** was prepared in a high 72% yield by stirring chloroacetonitrile with benzylamine in DCM at room temperature for 24 hours (scheme 65).



Scheme 65: Preparation of the cyanoamine.

Unfortunately the reaction using Perosa's conditions was unsuccessful; the cyanoimine **208** was not isolated only starting material **207** was recovered on work up.[41] The cyanoamine **207**

was stirred with an aqueous NaOCl solution for 1 hour monitoring the temperature so that it remained below 10°C. Unfortunately the reaction was not successful as only starting material was recovered (scheme 66).

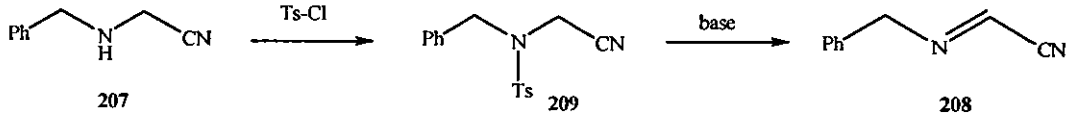


Scheme 66: Preparation of the cyanoimine.[41]

When the amine was added to the aqueous NaOCl solution the mixture became very viscous and stirring would sometimes cease, this could be a reason for the reaction not working as the reagents were not mixing thoroughly for them to react. This problem could not be overcome and a modification to the route was decided.

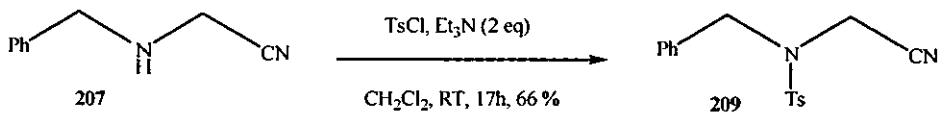
2.7 Tosylation of the cyanoamine

Due to problems with the previous chlorination method the use of a tosyl leaving group was envisaged. The amine **207** could be tosylated using tosyl chloride which in turn could be eliminated *via* a base promoted elimination to yield the subsequent imine **208.**



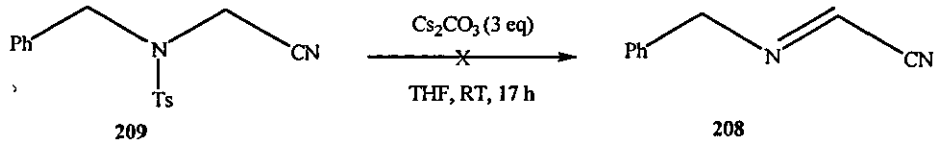
Scheme 67: Tosylation then elimination of the tosylate to afford the cyanoimine.

The amine **207** was tosylated in a reasonable 66% yield and the next step then was to eliminate the tosyl group using Cs_2CO_3 as the base



Scheme 68: Tosylation of the cyanoamine.

The tosylamine was stirred at room temperature and under reflux however the tosyl group was not eliminated and only starting material was isolated on work up.



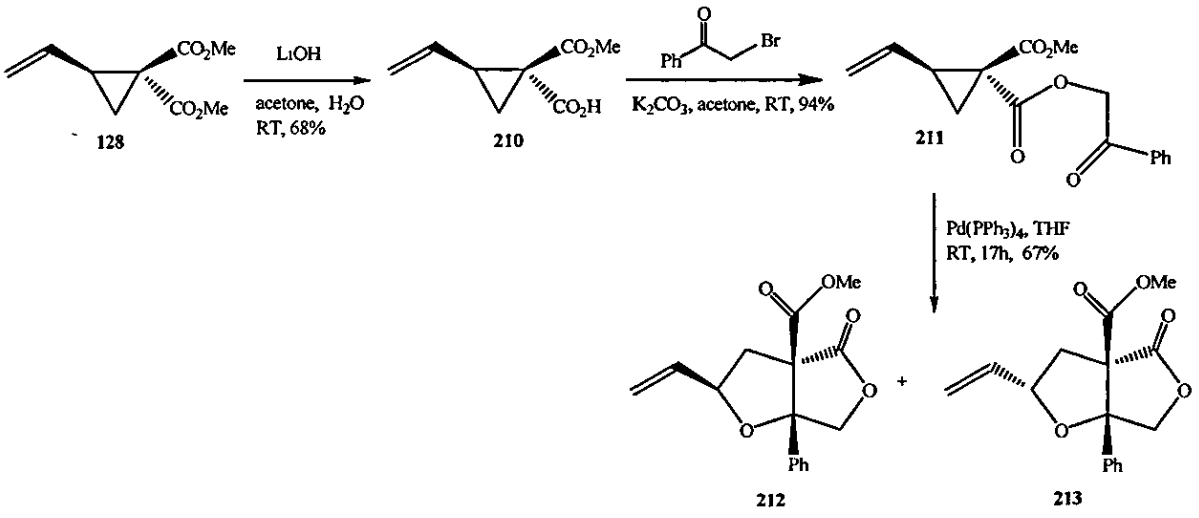
Scheme 69: Imine formation.

The next option was to probe a suitable intramolecular route to the construction of the tricyclic core as the intermolecular route was proving to be elusive.

Chapter 3: Intramolecular Routes to the hydroindole core

3 Previous work

Research within the group had been carried out where alkylations were carried out onto activated vinylcyclopropane substrates **210** and then subsequent Pd(0) catalysed intramolecular cyclisations had been carried out producing bicyclic ring systems (scheme 70).[25]



Scheme 70: Bicyclic heterocycle synthesis

Using this route a mixture of diastereoisomers were produced in a ratio of 5:1 in favour of the *trans* isomer, the Pd(0) rearrangement was performed in the absence of a Lewis acid. The above scheme outlines the importance of the route as the bicyclic structures **212** and **213** were produced with three chiral centres from a simple starting material in two steps. The nOe data showed that the vinyl, methyl ester and the phenyl group were all on the same face; X-ray crystallography also showed this stereochemistry.[25]

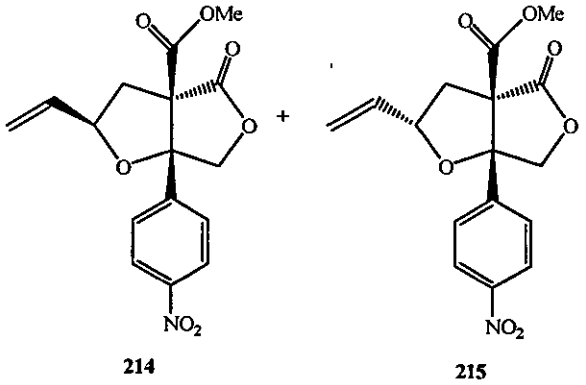
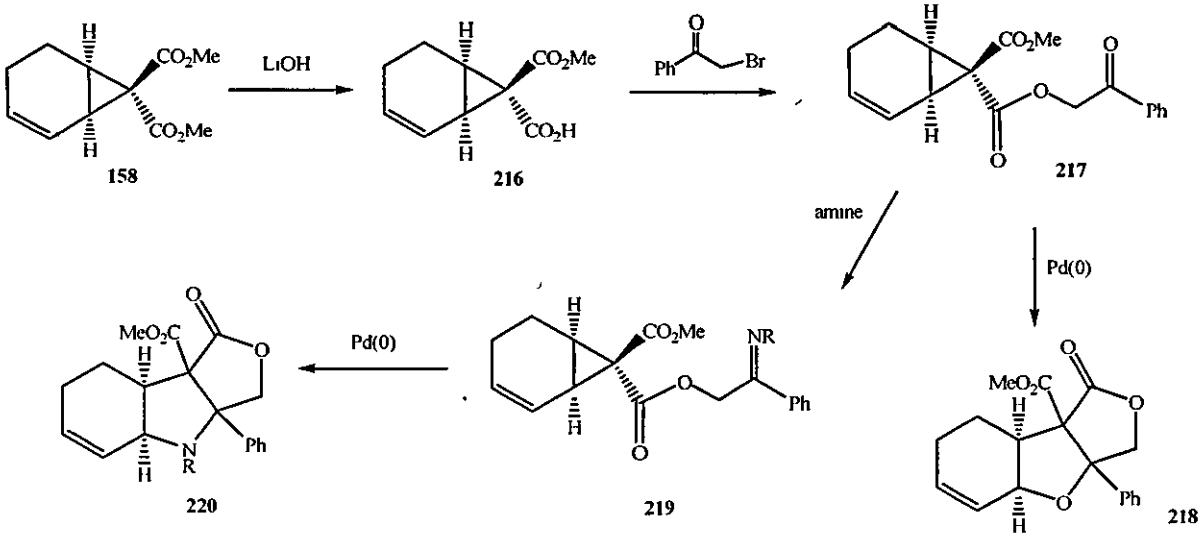


Figure 10: Relative sterochemistry

This work was also repeated using *p*-nitro-phenacyl bromide as the alkylating agent yielding the bicyclic structures shown in figure 10.[25] This work was performed to determine whether the rearrangement would also be successful with the electron deficient *p*-nitro carbon tether. By repeating the tethered work on the fused vinylcyclopropane **158** this could lead to the hydroindole **220**.

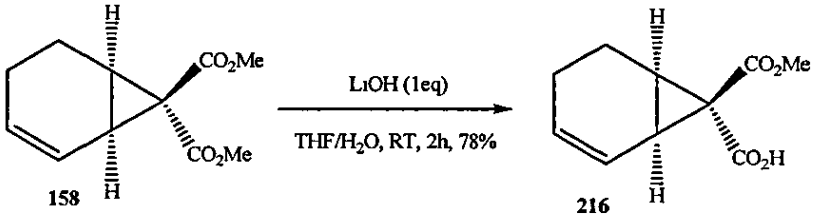


Scheme 71: Intramolecular route.

Upon hydrolysis of the ester to the mono acid **216** alkylation with phenacyl bromide would furnish the ketone **217**. Using the conditions employed by Wyatt, the substrate will be subjected to Pd(0) conditions to invoke the rearrangement.[25] If the rearrangement is

successful then a suitable amine could be introduced to the ketone to give the imine and then the subsequent rearrangement would furnish the hydroindole core.

The ester was firstly hydrolysed to the mono acid **216** using LiOH in a THF/water solution in a 78% yield this was then carried forward un-purified and alkylated with phenacyl bromide.[25]



Scheme 72: Ester hydrolysis.

It was proposed that the carboxylic acid group is *exo* to the ring, as the hydroxide molecule would attack *via* the least hindered route, see figure 11 for its arrangement in space.

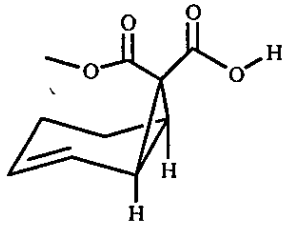
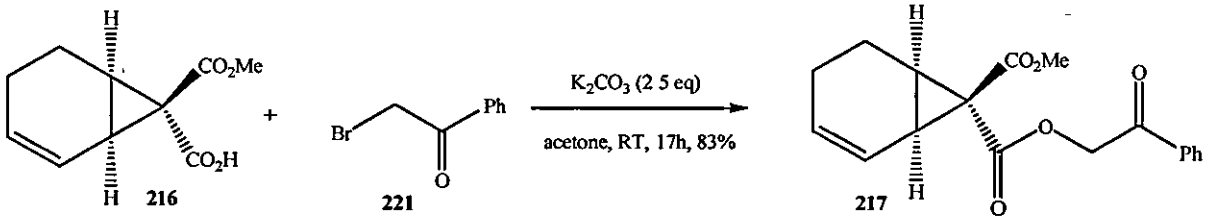


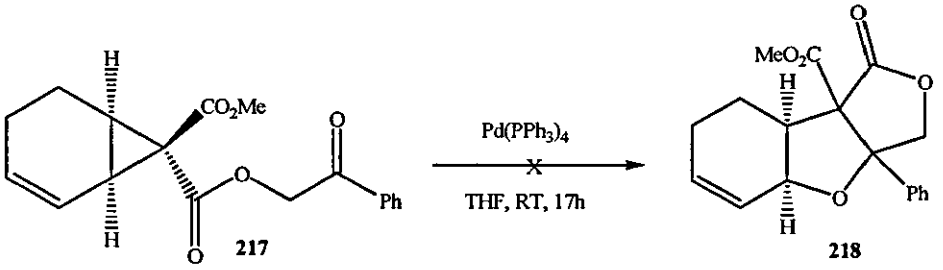
Figure 11

The alkylation with phenacyl bromide was carried out in acetone at room temperature and was successful in 17 hours furnishing the ketone **217** in an 83% yield The structure was characterised by ^{1}H/ ^{13}C NMR, IR and mass spectroscopy. The presence of a singlet corresponding to the CH_2 next to the ketone at 5.27 ppm was visible in the ^{1}H NMR. Along with a multiplet seen between 7-8 ppm corresponded to the phenyl group.



Scheme 73: Alkylation with phenacyl bromide.[25]

The aromatic ketone **217** was then subjected to a variety of Pd(0) conditions.

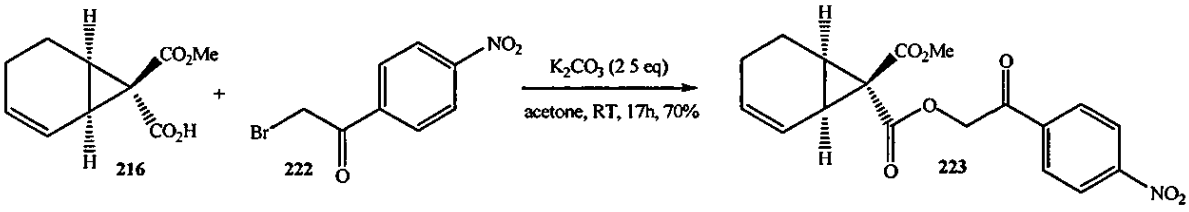


Structure	Lewis acid	Temp (°C)	Time (h)	Product 218
217	-	35	17	Complex mixture by ^{1}H NMR
217	$ZnBr_2$	35	17	"
217	$ZnBr_2$	RT	17	"
217	-	RT	17	"
217	$ZnBr_2$	-20	17	"
217	-	-20	17	"

Table 6

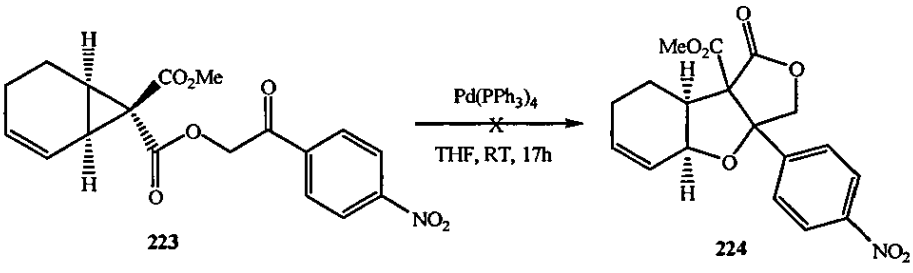
Unfortunately the reaction was unsuccessful, it was thought that the aromatic ketone **217** was not reactive enough for the rearrangement to occur, however there was something taking place in the reaction, the tricylic product **218** was not isolated but there appeared to be another related compound in the mixture.

Due to the failure of the phenacyl bromide tether rearranging the *p*-nitro version was explored, the electron withdrawing nature of the nitro group would hopefully activate the carbonyl group closest to the phenyl ring towards nucleophillic attack, after the oxidative addition of the Pd(0) catalyst.



Scheme 74: Alkylation with *p*-nitro phenacyl bromide.[25]

The reaction was successful using the previous alkylation conditions in a high 70% yield and again the substrate **223** was subjected to the Pd(0) conditions (scheme 74).

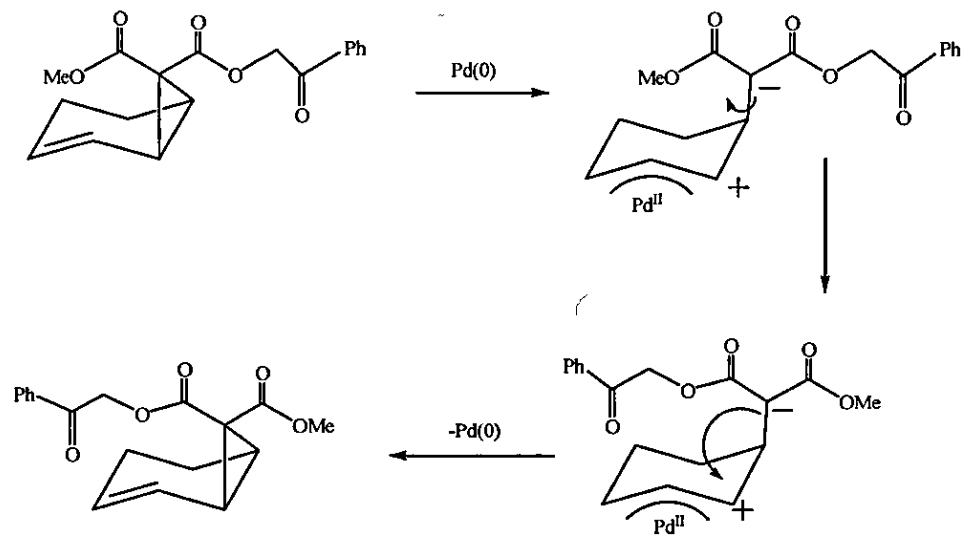


Structure	Lewis acid	Temp (°C)	Time (h)	Product 224
223	$ZnBr_2$	35	17	Complex mixture by ^1H NMR
223	-	35	17	"
223	$ZnBr_2$	RT	17	"
223	-	RT	17	"
223	$ZnBr_2$	-20	17	"
223	-	-20	17	"

Table 7

Again the rearrangement was proving to be problematic, the tricyclic product was not observed in the ^1H NMR, however there appeared to be isomers in the reaction mixture as before.

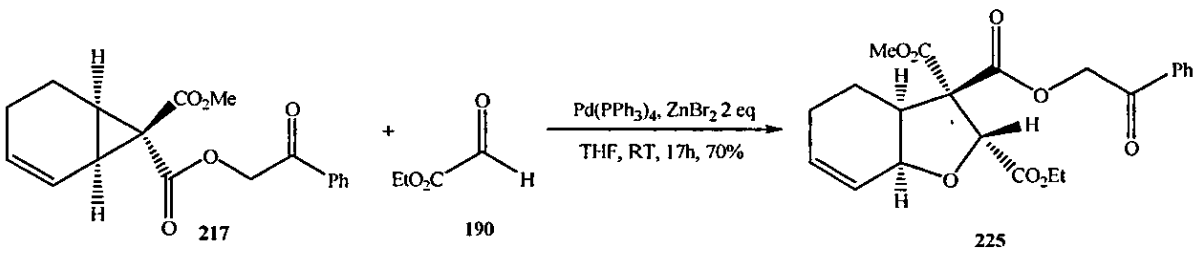
It was proposed that the Pd(0) catalyst had oxidatively inserted into the alkene double bond thus ring opening the cyclopropane moiety, but before the cyclisation could occur it appeared the bond had rotated and re-closed.



Scheme 75: Proposed mechanism.

Work by Wyatt showed the rearrangement occurred at high temperatures in the case of cyclisation of the tethered vinylcyclopropanes, however this was not the case here.[25] When zinc bromide was employed in the reaction mixture the substrate was destroyed and no identifiable material was recovered.

The aromatic ketone tether **217** was probably not reactive enough to invoke the intramolecular cyclisation; therefore substrate **217** was stirred with ethyl glyoxylate **190** a successful trapping agent as this had successfully undergone a [2+3] cycloaddition with **158**, and 10 mol % $Pd(PPh_3)_4$ with $ZnBr_2$ in THF at room temperature. By performing this reaction it was possible to determine if the Pd(0) was oxidatively inserting into the double bond and producing the palladium π-allyl complex (scheme 76).



Scheme 76: Pd(0) catalysed [2+3] cycloaddition with ethyl glyoxylate.

As predicted, the ethyl glyoxlate under went the [2+3] cycloaddition rather than the tether rearranging and **225** was isolated in a 70% yield. Therefore the use of a different tether was required. The presence of a singlet at 4.75 ppm was indicative of H^1 next to the oxygen of the furan as was a singlet at 5.23 ppm corresponding to H^2 adjacent to the ethyl ester.

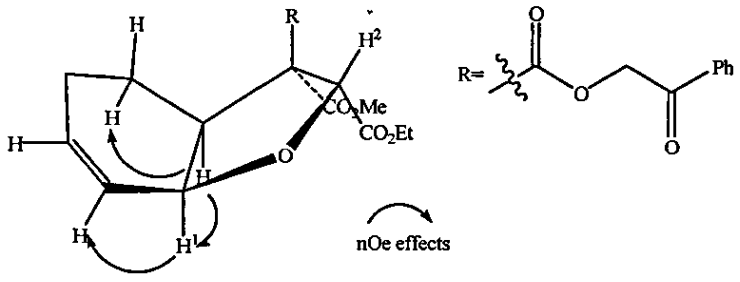


Figure 12: nOe analysis.

Mass spectral data also confirmed the presence of the product and nOe analysis showed the above stereochemistry.

3.1 Synthesis of bicyclohept-2-ene-7,7-dicarboxylic acid methyl ester 2-oxo-ethyl ester

As the Pd(0) catalysed [2+3] cycloaddition route was proving to be problematic another route leading to the tricyclic core structure of stenine was envisaged *via* an alkylation of a suitable acetal **226**, then subsequent deprotection to yield the corresponding aldehyde **228**.

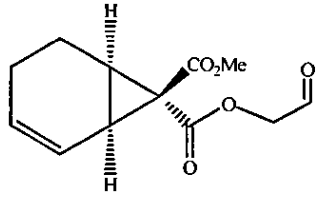
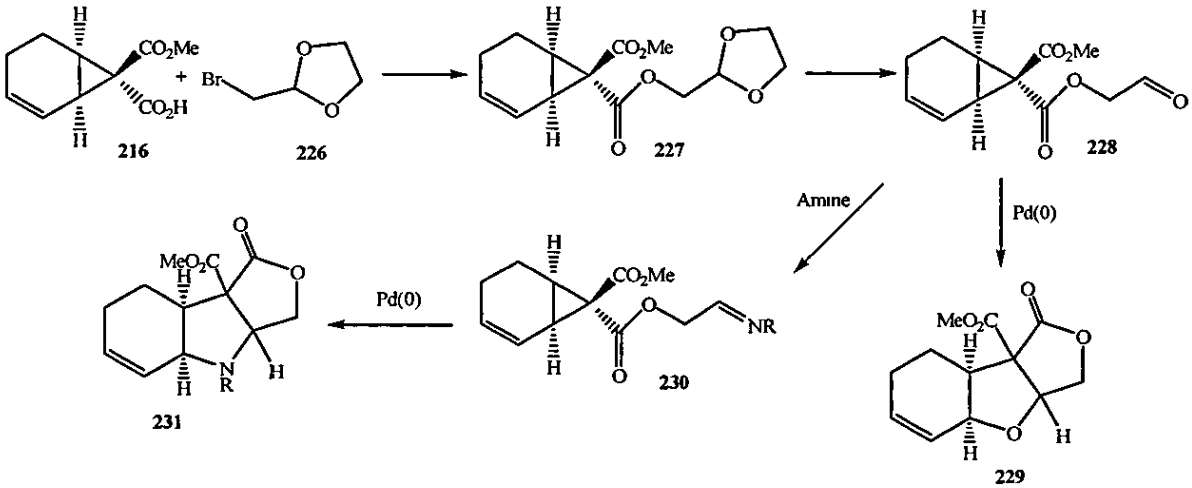


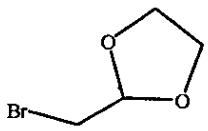
Figure 13: bicyclohept-2-ene-7,7-dicarboxylic acid methyl ester 2-oxo-ethyl ester.

From here a Pd(0) catalysed rearrangement could be carried out, if this is successful the aldehyde could be converted to the imine **230**, then cyclisation to yield **231** in scheme 77.



Scheme 77: Intramolecular route.

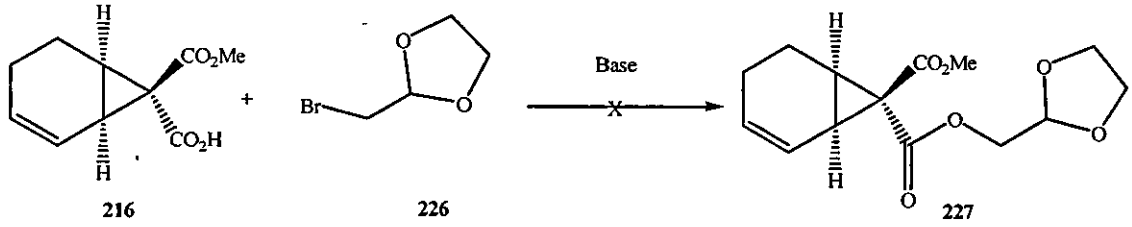
Commercially available 2-(bromomethyl)-1,3-dioxolane **226** was used as the acetal in this route shown in figure 14.



226

Figure 14: 2-(bromomethyl)-1,3-dioxolane.

Firstly the mono acid **216** was alkylated with 2-(bromomethyl)-1,3-dioxolane **226** to yield **227**, a range of alkylation conditions were investigated for this.

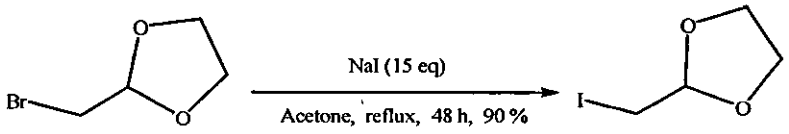


216 226 227

Solvent	Base	Temperature	Time (h)	Product 227
Acetone	K_2CO_3	RT	17	SM
Acetone	K_2CO_3	Reflux	17	SM
DMF	NEt_3	100	3	SM
DMF	Cs_2CO_3	100	3	SM

Table 8

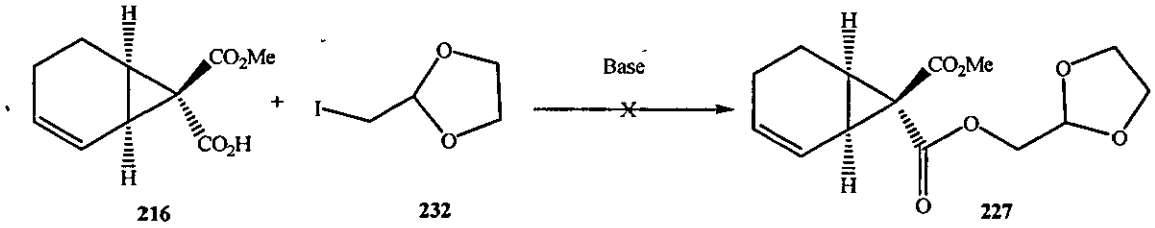
Using a variety of conditions the acetal **227** was not isolated, a Finkelstein reaction was conducted, it was hoped that having the iodide a better leaving group than the bromide might improve the possibility of alkylation.



226 232

Scheme 78: Finkelstein reaction.

The Finkelstein was carried out refluxing **226** with sodium iodide in acetone for two days furnishing the iodide **232** in a 90% yield. Taking the dioxolane **232** a series of alkylations were performed.



Solvent	Base	Temperature	Time (h)	Product 227
Acetone	K_2CO_3	RT	17	SM
Acetone	K_2CO_3	Reflux	17	SM
DMF	NEt_3	100	3	SM
DMF	Cs_2CO_3	100	3	SM

Table 9

Again the desired acetal **227** was not furnished, there were two plausible explanations as to the failure of this reaction. One could be the sterics involved with alkylating onto the acid; the other could be due to the interaction of the lone pairs on the oxygen of the acetal with the pathway of the approaching acidic nucleophile.

As the nucleophilic substrate **216** approaches at 180° to the leaving group, the pathway of the nucleophile is repelled by the lone pairs on the oxygen atoms therefore preventing the nucleophile from approaching successfully (figure 15).

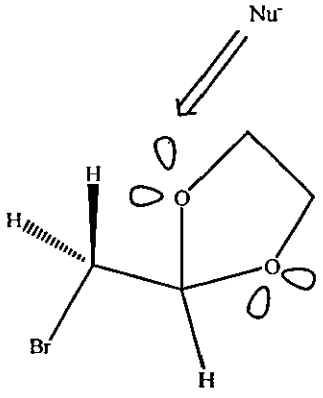
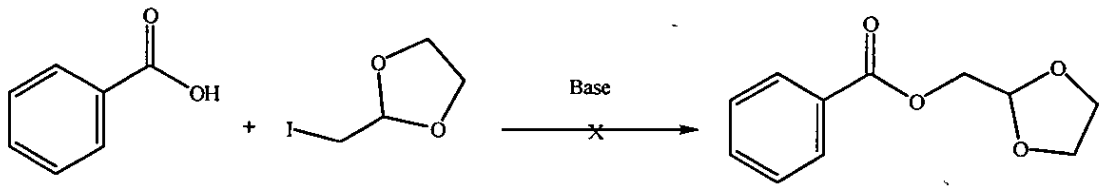


Figure 15: Path of approaching nucleophile.

To explore these theories, the alkylating conditions were performed again using benzoic acid **233** as the nucleophile. This could possibly rule out some of the possible steric affects of **216**.

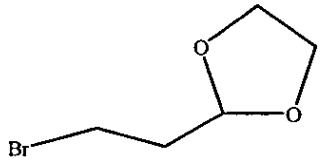


233 232 234

Solvent	Base	Temperature	Time (h)	Product 234
Acetone	K_2CO_3	RT	17	SM
Acetone	K_2CO_3	Reflux	17	SM
Acetone	Cs_2CO_3	RT	17	SM
Acetone	Cs_2CO_3	Reflux	17	SM
DMF	NEt_3	100	3	SM
DMF	Cs_2CO_3	100	3	SM

Table 10

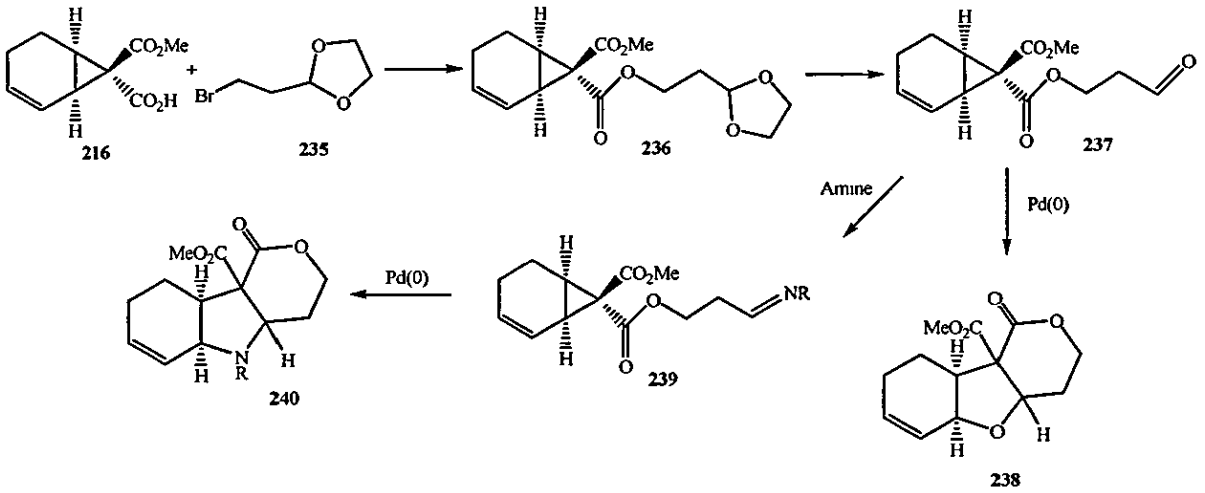
Another possibility was the addition of an extra CH_2 group onto the protected acetal to act as a carbon spacer group. Therefore giving more distance between the leaving group and the lone pair of electrons on the oxygen.



235

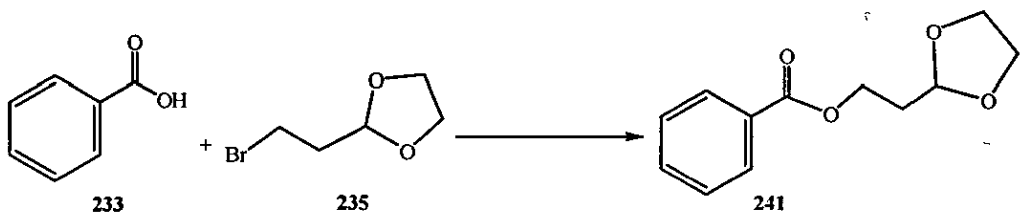
Figure 16: Bromoethyl-1,3-dioxolane.

The extra CH_2 spacer group will not affect the proposed synthetic route, as the 5 and the 6-membered bicyclic ring will be produced



Scheme 79: Alkylation with Bromoethyl 1,3-dioxolane.

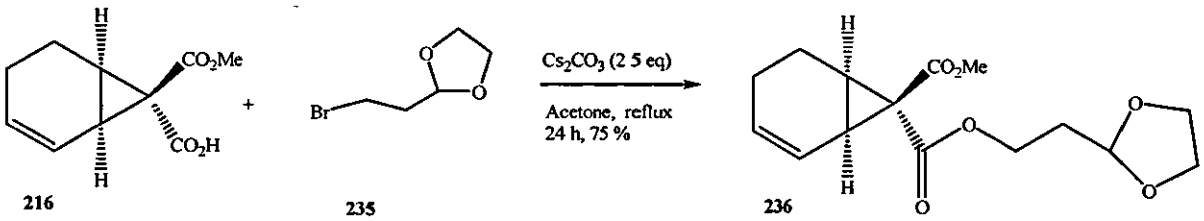
Commercially available bromoethyl-1,3-dioxolane **235** was reacted in a variety of conditions with benzoic acid **233** as the test substrate.



Solvent	Base	Temperature	Time (h)	Product 241
Acetone	K_2CO_3	RT	17	SM
Acetone	K_2CO_3	Reflux	17	47 %
Acetone	Cs_2CO_3	RT	17	SM
Acetone	Cs_2CO_3	Reflux	17	60 %

Table 11

Although the yields were not good, the presence of the extra CH_2 did appear to be beneficial to the reaction we think this may be because the path of the approaching nucleophile was not obstructed. The greatest yields for the reaction were obtained using caesium carbonate as the base, these conditions were applied to **216** (scheme 80).

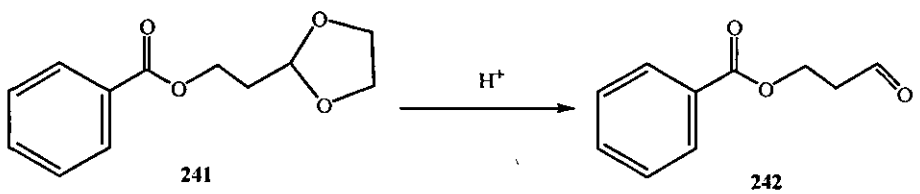


Scheme 80: Alkylation onto 7-[(methyloxy)carbon]bicycle[4.1.0]hept-2-ene-7-carboxylic acid.

The above alkylation was carried out in acetone under reflux for 24 hours with cesium carbonate as the base. It was successful and gave **236** in a high 75% yield, purification was *via* flash chromatography and the dioxolane ring was stable to the silica column, therefore problems of deprotection were not seen during purification.

3.2 Acetal deprotection-Synthesis of the aldehyde

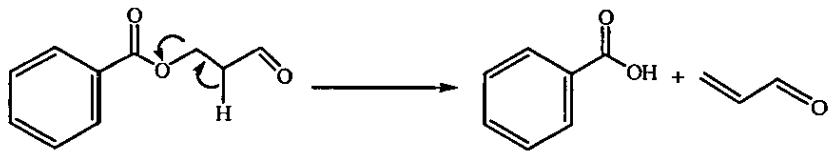
The next stage in the synthesis was to perform the acetal deprotection, there were a variety of methods available for this and the table below shows the conditions applied using benzoic acid [1,3]dioxolan-2-yl ethyl ester (**241**) as the test substrate.



Acid	Solvent	Time (h)	Temperature	Product 242
1 M HCl	THF	3	RT	7%
1 M HCl	THF	24	RT	~50%
5 M HCl	THF	3	RT	~50%
p-TSA	MeOH	3	RT	~5%
p-TSA	MeOH	24	RT	~10%
p-TSA/ 5 M HCL	MeOH	48	RT	~90%

Table 12

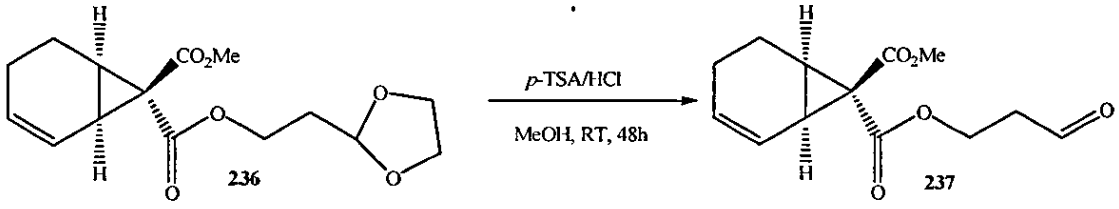
There were problems encountered in the acetal deprotection; acetal **241** was stable to the acidic conditions used and in the majority of cases only starting material was isolated. When the reaction mixture was purified by flash chromatography, any aldehyde present was destroyed on the column. The first entry in table 12 was only 7% which was obtained after a chromatography column, therefore the remaining entries are approximations as the reaction mixtures were left crude. Scheme 81 suggests what could be occurring.



Scheme 81: Aldehyde decomposition.

In each case ^{1}H NMR data of the reaction mixture had suggested that the aldehyde **242** was present, however on the column the aldehyde product was not isolated and only the starting material **241** was recovered.

When a combination of *p*-TSA and 5 *M* HCl were used, the deprotection was more successful and the aldehyde was produced as the major product, characterisation was again difficult as flash chromatography destroyed the unstable aldehyde product The conditions were applied to **236** and the aldehyde **237** was recovered on work up along with starting material in 48 hours at room temperature, due to the difficulty of isolating and purifying the aldehyde no yields could be recorded

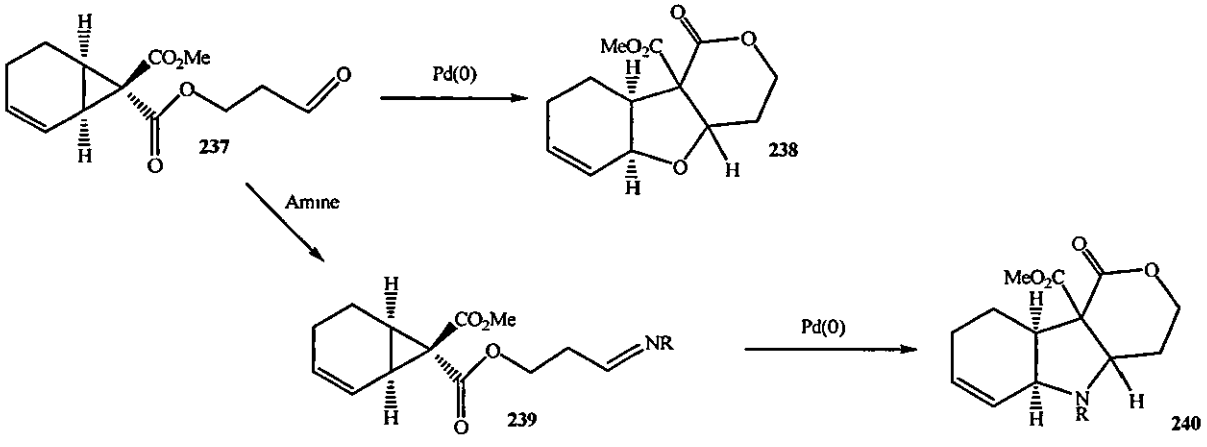


Scheme 82: Acetal deprotection

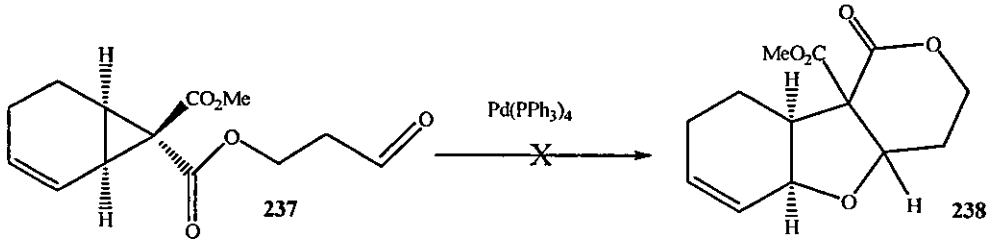
Due to the problems encountered with purification, i.e. the instability of the aldehyde product, the Pd(0) catalysed rearrangement was immediately performed after the acetal deprotection.

3.3 Palladium(0) Catalysed Rearrangement

The next step after the arrangement would be to add a suitable amine to the aldehyde under Dean Stark conditions to form the imine **239** could which could then be subsequently rearranged to give the tricyclic product **240**.



Scheme 83: Alkylation with bromoethyl-1,3-dioxolane.



Catalyst	Lewis acid	Solvent	Temperature	Time (h)	Product 238
$Pd(PPh_3)_4$	$ZnBr_2$	THF	RT	17	SM
$Pd(PPh_3)_4$	-	THF	RT	17	SM

Table 13

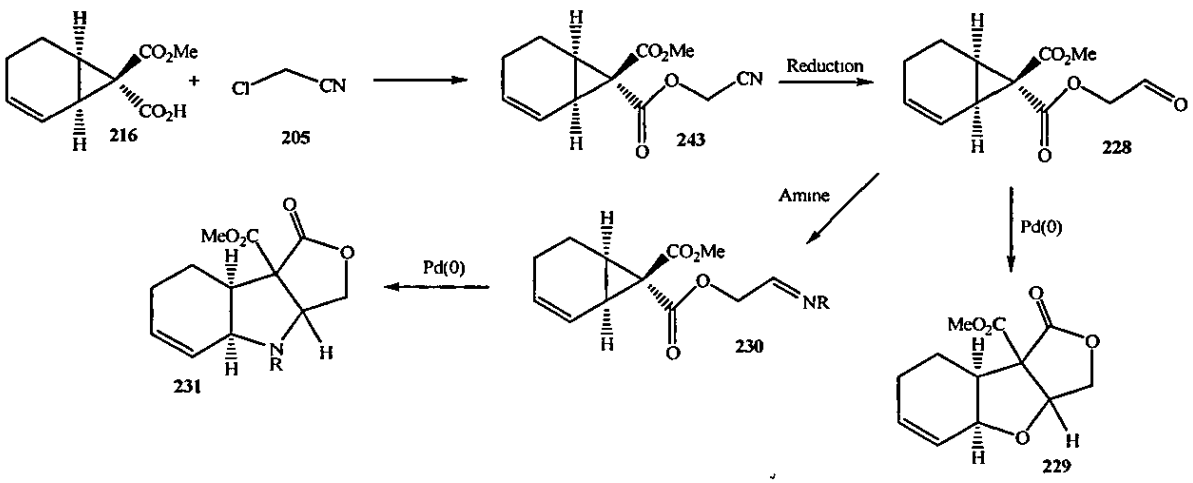
Unfortunately the rearrangement was unsuccessful using 10 mol % $Pd(PPh_3)_4$ in THF at room temperature with and without the Lewis acid. The tricyclic product was not isolated on workup. The rearrangement was monitored by TLC, during the reaction a new spot appeared by TLC but after work up only the acetal **236** was recovered and isolated The unknown spot

appeared to be a complex mixture which could not been determined by ^1H NMR, there were no characteristic peaks of any of the materials associated with the reaction.

The problem with this reaction was the unstable nature of the aldehyde. Because of this the rearrangement was performed as a crude mixture so this was the most likely cause of the reaction failing.

3.4 Synthesis of the Cyanomethyl ester tether

In another attempt to synthesise the aldehyde, a different approach was sought. It was envisaged that the cyanomethyl ester of 7-[(methyloxy)carbon]bicycle[4.1.0]hept-2-ene-7-carboxylic acid **243** could be selectively reduced to the aldehyde using a modified lithuim aluminium hydride reagent.

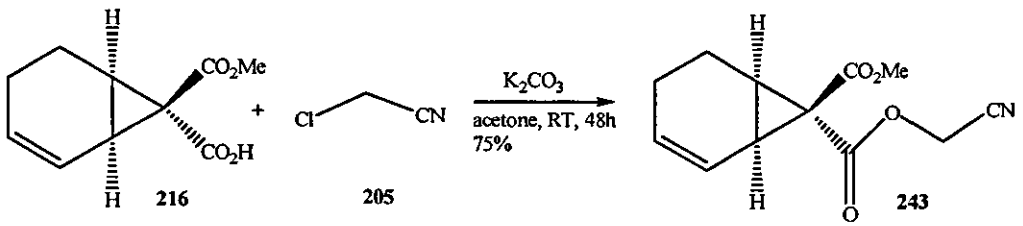


Scheme 84: Intramolecular route.

The subsequent aldehyde **228** could then be subjected to a palladium(0) catalysed rearrangement as before, if this is successful the imine **230** could be synthesised and subjected to the same conditions to induce the rearrangement giving the indole type structure **231**.

3.5 Synthesis of bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid cyanomethyl ester methyl ester

A variety of conditions were studied using benzoic acid as the test substrate, all were successful, therefore the conditions were applied to **216**.



Base	Solvent	Temperature	Time (h)	Product 243 (%)
Et_3N	DCM	RT	48	75
Et_3N	Ethyl Acetate	RT	48	60
K_2CO_3	Acetone	RT	48	75

Table 14

The yields were reasonable but long reaction times were required, the reactions were monitored by TLC and it appeared that the reaction required at least 24 hours before product formation was observed The cyanomethyl ester **243** was stable and was purified by flash chromatography.

3.6 Selective reduction of the bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid cyanomethyl ester methyl ester

The next step involved the selective reduction of the nitrile group, where the two ester groups would remain. The conversion of nitriles to aldehydes is an important synthetic route,[42] the Stephen procedure and the partial reduction with $LiAlH_4$ are usually adequate for the conversion of aromatic nitriles but less so for aliphatic nitriles.[42, 43, 44]

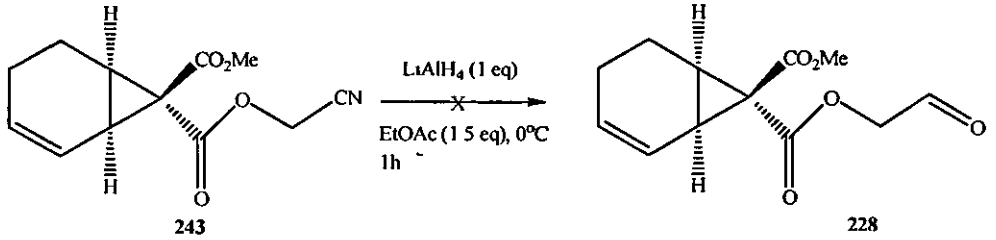
Due to the sterically hindered nature of the methyl and the cyanomethyl ester it is hoped that these would remain intact and only the nitrile group would be selectively reduced.

Brown *et al.* has shown that a modified $LiAlH_4$ reagent such as lithium triethoxyaluminohydride was a convenient reagent for the conversion of nitriles to aldehydes.[45]

Nitrile	Aldehyde yield (%)
n-butyronitrile	68
n-capronitrile	69
cyclopropancarbonitrile	69
o-toluonitrile	87
cinnamonitrile	61

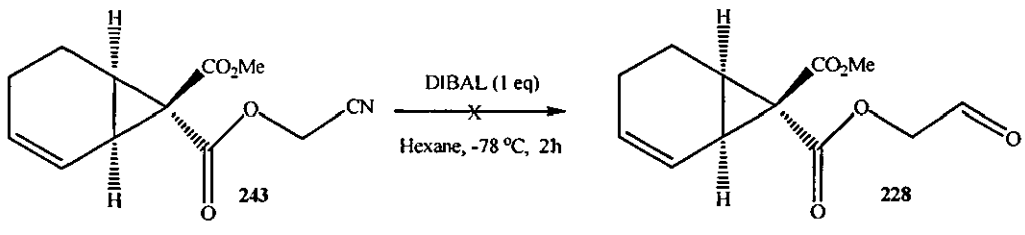
Table 15: Yield of aldehydes in the reduction of nitriles by lithium triethoxyaluminohydride.[45]

The modified $LiAlH_4$ reagent was synthesised *in situ* by treating a standard solution of lithium aluminium hydride in diethyl ether with 1.5 equivalents of ethyl acetate, then the cyanomethyl ester **243** was added and the reaction was stirred for 1h at 0°C (scheme 85).



Scheme 85: Reduction with lithium triethoxyaluminohydride.[45]

The reaction was unsuccessful, only a trace of the aldehyde was evident in the crude ^1H NMR indicating that the nitrile group had not been fully reduced.

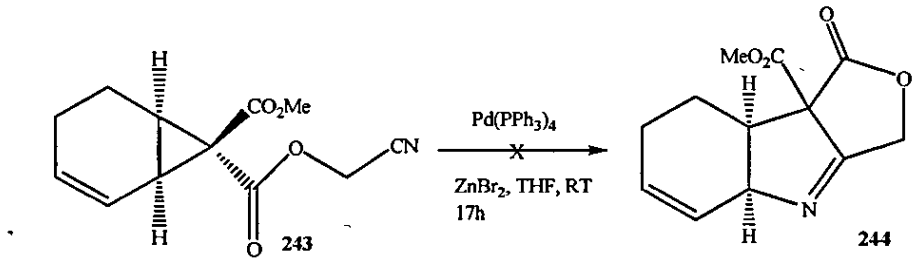


Scheme 86: Reduction with DIBAL.

A reduction with DIBAL was then performed; again no reaction occurred, only the starting material was recovered. The reaction was repeated, this time the reaction was allowed to warm to room temperature before the reaction was quenched with methanol. Again the reduction did not take place and only staring material was isolated on work up.

3.7 Pd(0) Catalysed Rearrangement of bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid cyanomethyl ester methyl ester

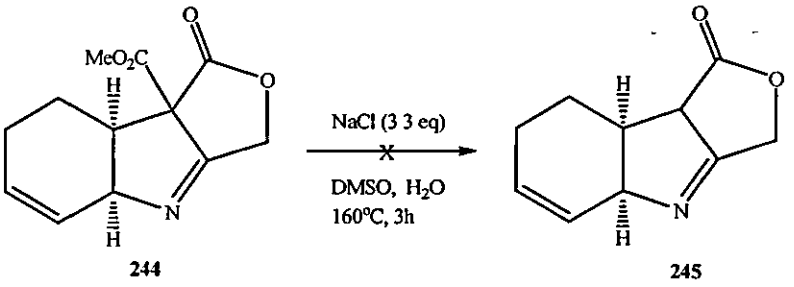
As the reduction of the nitrile group was somewhat problematic, an alternative approach was attempted *via* a palladium catalysed rearrangement of the cyano group.



Scheme 87: Pd(0) catalysed rearrangement.

The cyclisation was performed in the presence and absence of Lewis acid and analysis of the crude reaction mixture was inconclusive. There appeared to be many diasteroisomers in the mixture which could not be separated, making assignment impossible.

The reaction was not reproducible, each time the outcome was different, the ^{1}H and ^{13}C NMR varied from reaction to reaction. A Krapcho decarboxylation was performed on the product from one of the reactions in an attempt to remove the methyl ester group thus reducing the amount of diastereoisomers in the mixture, therefore making assignment of the compound easier.



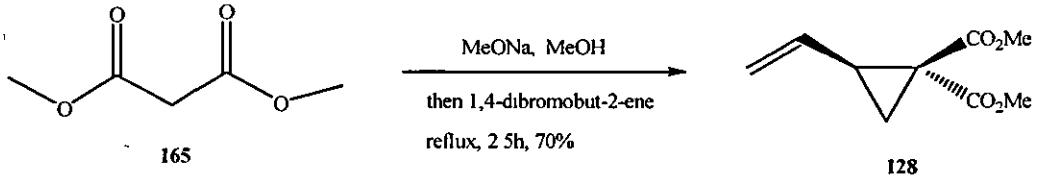
Scheme 88: Krapcho decarboxylation.

The outcome of the reaction was disappointing and no recognisable structure was seen in the crude NMR data as it was a complex mixture.

3.8 Synthesis of the vinylcyclopropane cyanomethyl ester tether

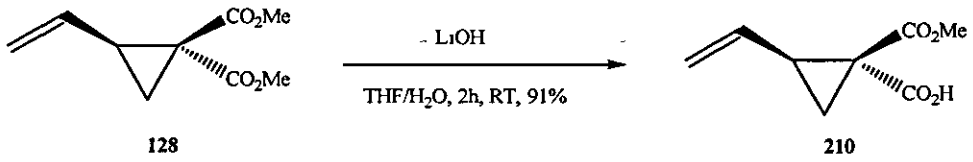
As the intramolecular rearrangement on **216** was failing it was decided that in parallel to this work the vinylcyclopropane substrate **128** could also be alkylated with chloroacetonitrile and subjected to the cyclisation conditions. The rearrangement using vinylcyclopropane substrates had already been shown to be a promising route to interesting bicyclic products where various five-membered heterocycles have been synthesised incorporating oxygen and nitrogen in the ring.

The vinylcyclopropane **128** was synthesised from dimethyl malonate **165** and 1,4-dibromobut-2-ene, in refluxing methanol with sodium methoxide (scheme 89).



Scheme 89: Synthesis of the vinylcyclopropane.

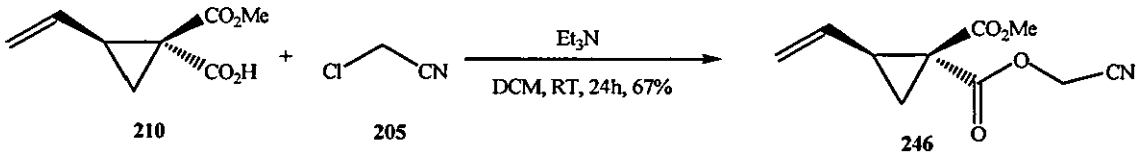
The vinycyclopropane **128** was then hydrolysed to the mono acid **210** using LiOH and a THF/H_2O mix in a ratio of 5:1 at room temperature and was complete in 2 hours to furnish the mono acid in an approximately 9:1 ratio in favour of the *trans* isomer. An acid base wash was carried out to obtain the *trans* isomer in a 91% yield



128 210

Scheme 90: Ester hydrolysis.

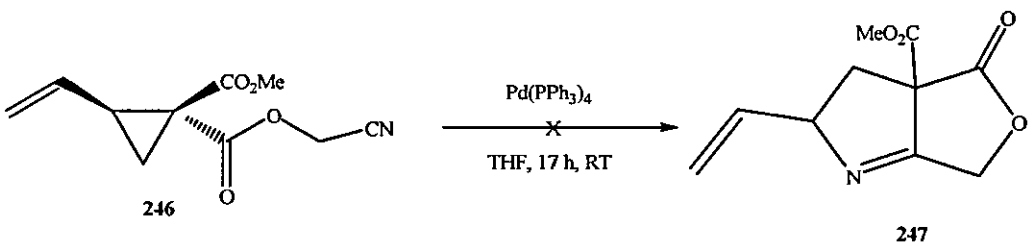
The mono acid **210** was then alkylated with chloroacetonitrile **205** to afford the cyanomethyl ester **246** in a modest 67% yield.



210 205 246

Scheme 91: Alkylation with chloroacetonitrile.

The cyano methyl ester **246** was then subjected to Pd(0) rearrangement conditions.



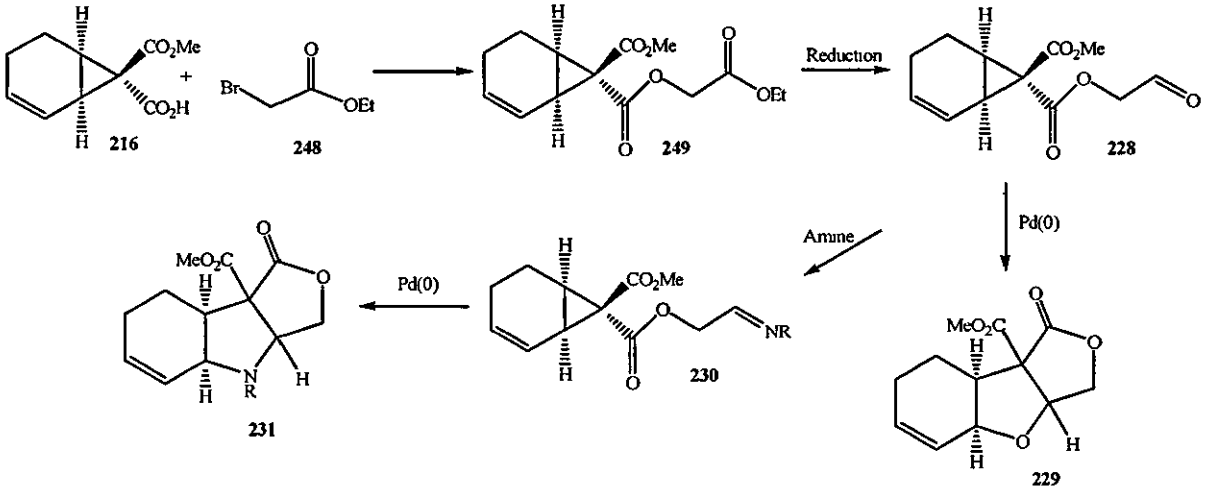
246 247

Scheme 92: Pd(0) catalysed rearrangement.

Again the reaction mixture appeared complex, the product was purified by flash chromatography and the ^{1}H NMR data was different to that of the starting material, indicating the presence of an unknown mixture which could not be separated and isolated. Due to the problems encountered in both routes it was decided to pursue another avenue to the hydroindole core.

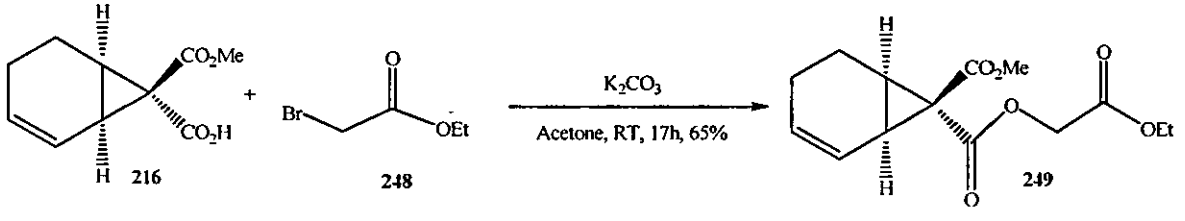
3.9 Synthesis of bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid ethoxycarbonylmethyl ester methyl ester

To conclude this chapter one more intramolecular approach that could possibly lead to the tricyclic core of stenine was *via* bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid ethoxycarbonylmethyl ester methyl ester **249**.



Scheme 93: Intramolecular route.

Again a similar route was proposed to that of the cyanomethyl ester and the protected acetal tether, **216** was alkylated with ethyl bromoacetate **248** to give the ethyl ester **249**.



Scheme 94: Alkylation with ethyl bromoacetate.

Once successful it is hoped that a selective reduction would be carried out on the ethyl ester to furnish the aldehyde shown in figure 17.

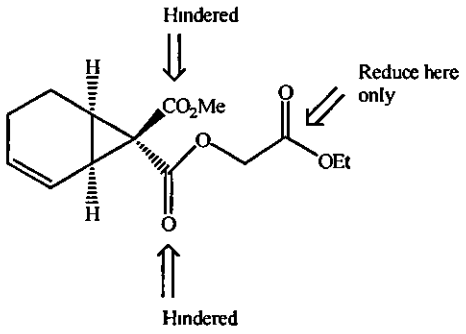
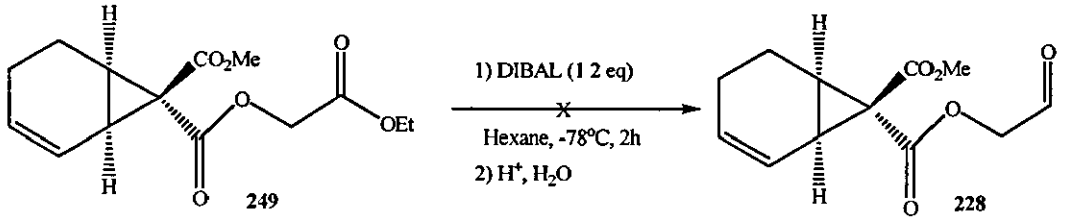


Figure 17: Selective reduction.

The ethyl ester was afforded a modest 65% yield after stirring **216** and **248** in acetone with potassium carbonate for 17 hours at room temperature. The selective reduction reaction was then performed using standard reduction conditions, where DIBAL was used as the reducing agent



Scheme 95: Reduction with DIBAL.

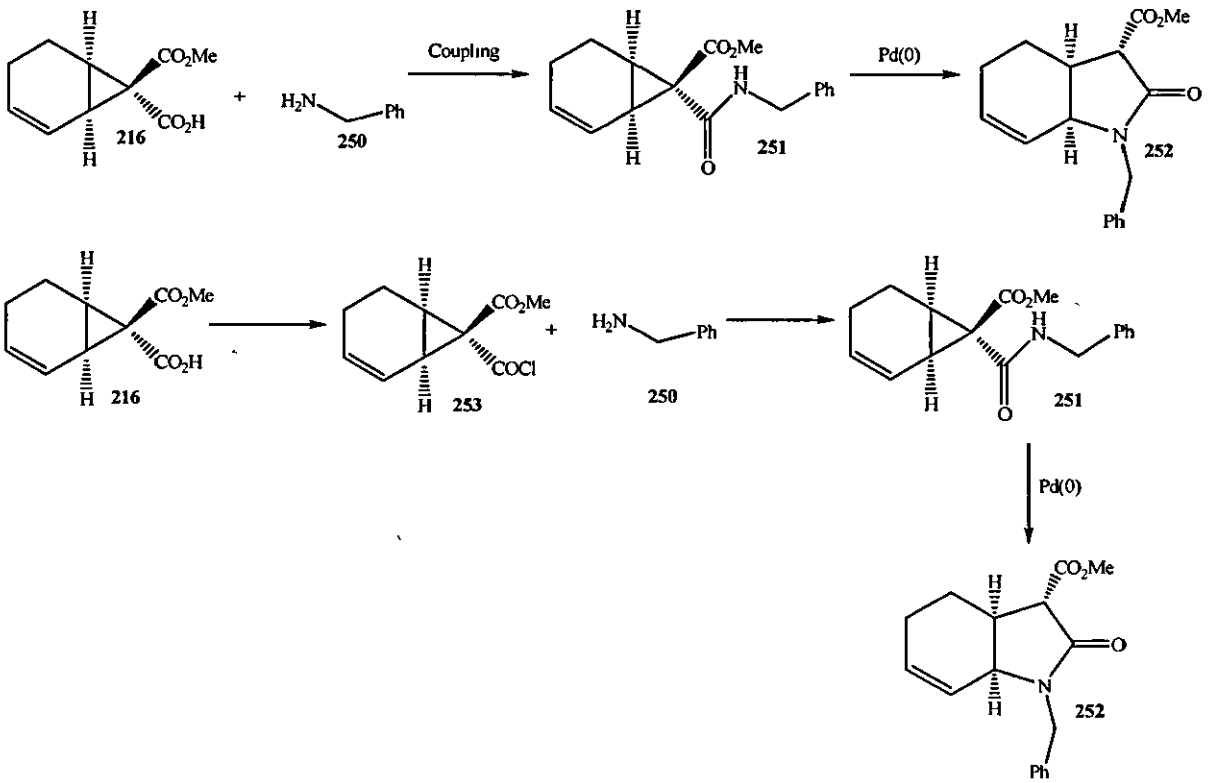
Unfortunately the aldehyde **228** was not isolated in the reaction, no characteristic peak was visible in the 9-10 ppm area of the ^{1}H NMR and only the starting material **249** was recovered and identified.

Every route involving the synthesis of an aldehyde tether was proving fruitless. The intramolecular rearrangement was still a very attractive route to the hydroindole core and was still very much worth investigating due to the synthesis of bicyclic ring products on the vinylcyclopropane system.

Another route was envisaged where by it was hoped that an amide tether could provide the answer to the rearrangement problems.

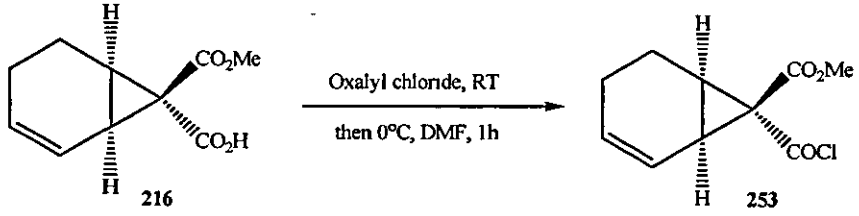
Chapter 4: Synthesis of the amide tether

The route was envisaged with two alternatives, one incorporating the use of an intermolecular peptide coupling of the acid **216** and benzylamine **250** and then a subsequent novel Pd(0) catalysed rearrangement of the resulting amide **251**. The other route involved the synthesis of the more reactive acid chloride **253** then stirring with benzylamine **250** to produce the desired amide **251**.



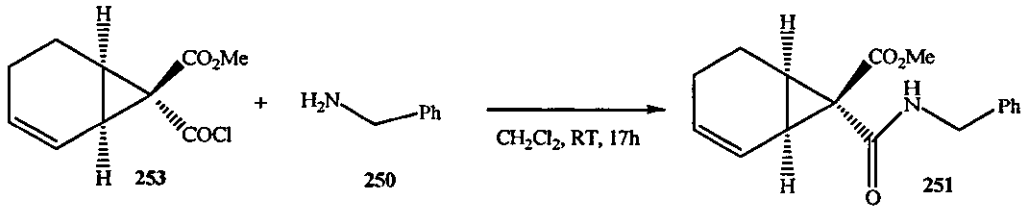
Scheme 96: Synthesis of the hydroindole core.

The acid chloride **253** was synthesised using oxalyl chloride in DMF, due to the stability of the acid chloride, the product was tentatively assigned using IR analysis and assuming 100% conversion it was carried forward to the amide bond forming reaction unpurified (scheme 97)



Scheme 97: Synthesis of the acid chloride.

The amide bond forming reaction was carried out in DCM at room temperature for 1 hour with one and a half equivalents of benzylamine then added upon formation of the acid chloride, no base was used in the reaction.



Scheme 98: Synthesis of the amide.

The benzyl amide **251** was not isolated, however when the crude reaction mixture was analysed two interesting products had been formed according to ^{1}H NMR. The crude mixture was purified by flash chromatography, two compounds **252** and **254** were isolated in a 42 and 11 % yield resepectively.

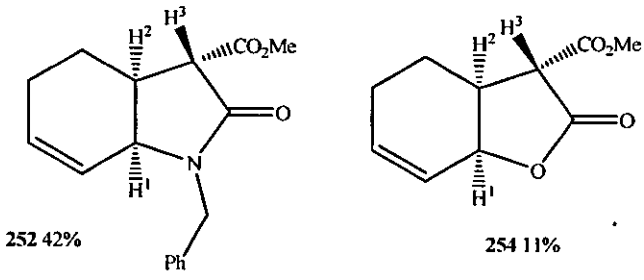


Figure 18

In the hydroindole **252** a singlet at 4.93, a mulitplet at 2.68-2.70 and a doublet at 3.25 ppm were indicative of the protons 1, 2 and 3 in the ^{1}H NMR. In the lactone **254** a singlet at 4.95,

a multiplet at 2.94-2.97 and a doublet at 3.33 ppm were again characteristic for the protons 1, 2 and 3. The stereochemistry at the ester centre was determined using nOe analysis.

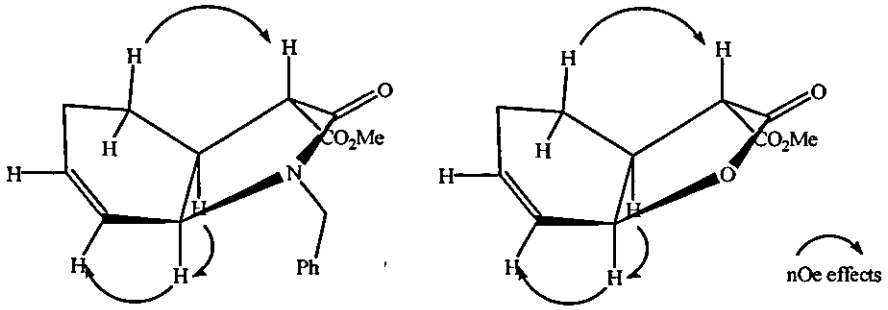
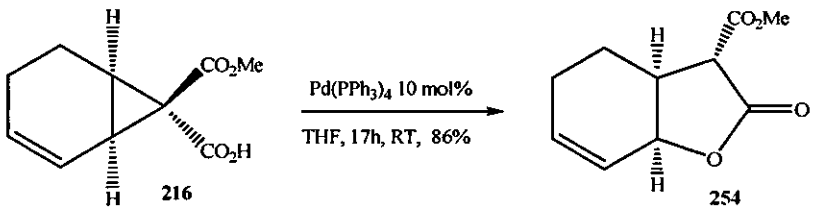


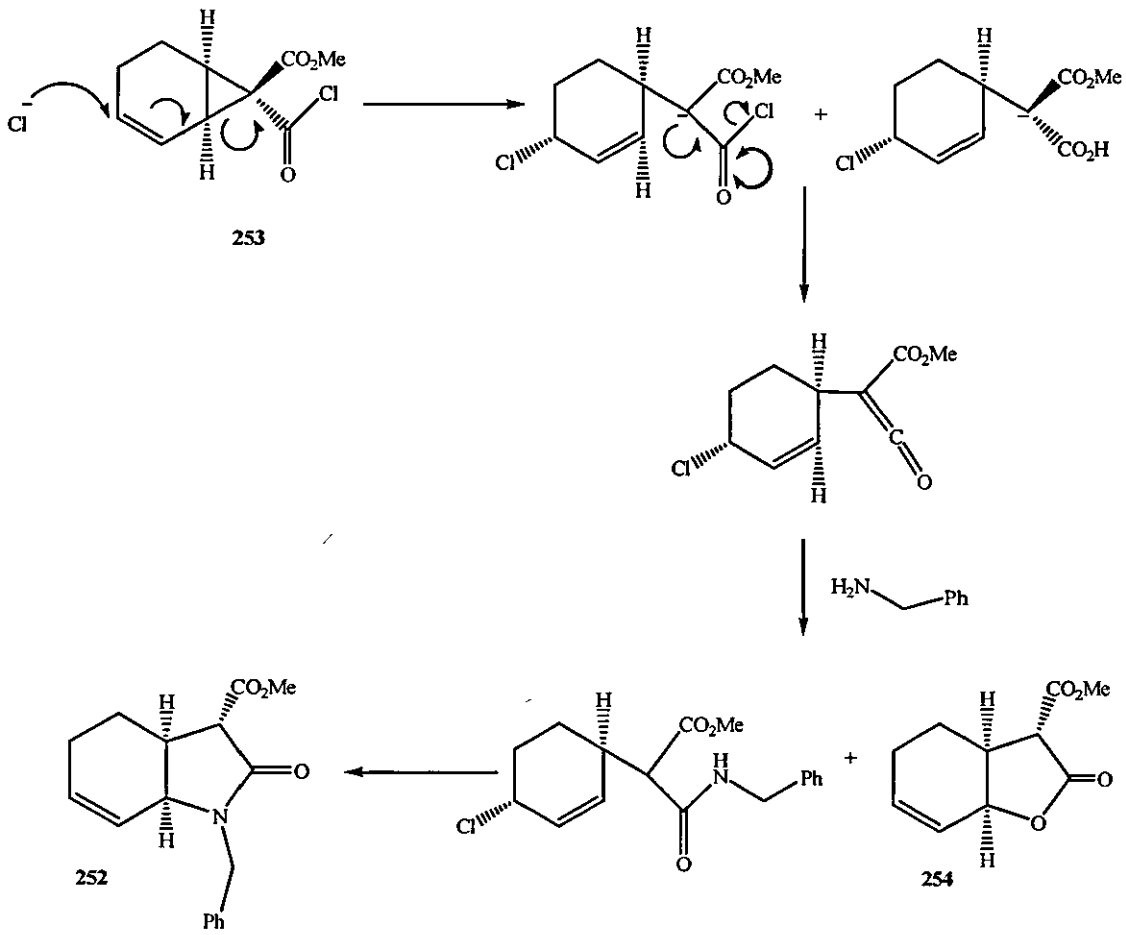
Figure 19: nOe effects

Due to the isolation of these compounds it was clear that the amide **251** was synthesised *in situ* and then the intramolecular rearrangement had occurred on the amide **251** and the remaining un-reacted mono acid **216** starting material. To prove this theory the mono acid starting material was rearranged in the presence of a Pd(0) catalyst with and without Lewis acid giving the bicyclic furan to provide comparative evidence of the isolation of compound.



Scheme 99: Pd(0) catalysed rearrangement of the mono acid.

The route to the amide using the acid chloride intermediate **253** was not reproducible, only once was the rearrangement products isolated A possible explanation to the mechanism of the reaction is shown in scheme 100.



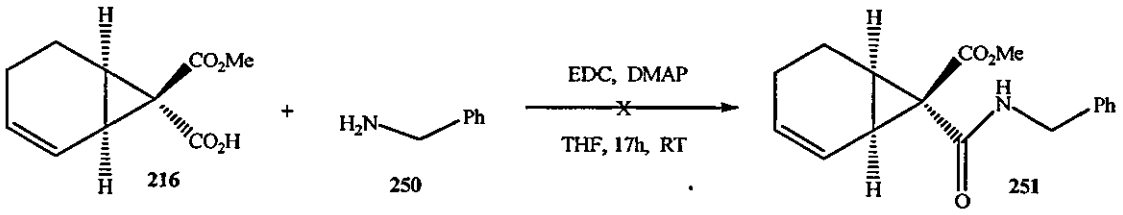
Scheme 100: Formation of bicyclic products.

It is proposed that free chloride generated in the reaction may attack the alkene double bond causing the cyclopropane to ring open (it is unknown whether ring opening occurs at the acid chloride or the amide stage). The ketene would then be generated which could then react with benzylamine to give the amide which would ring close to give **252**. We were not sure when this reaction occurred, this could have been during the addition of the amine or on work up at the end of the reaction.

The reaction was repeated but it was not reproducible, products corresponding to **252** and **254** were never isolated again following this method. Though frustrating, the isolation of these structures proved that the rearrangement of the amide **251** was possible but more importantly furnished the hydroindole core, therefore the peptide coupling route was investigated.

The amide coupling was performed using EDC as the coupling reagent due to its solubility in water so that it can be easily removed. With a catalytic amount of DMAP the reaction was

stirred in THF for 17 hours, unfortunately the reaction was unsuccessful. Using DCC as the coupling reagent had no affect either, this may be due to the fact that the mono acid is fairly sterically hindered.



Scheme 101: Peptide coupling.

One of the most common peptide coupling additives is 1-hydroxy-benzotriazole **255** (HOBt) which can be used either in conjunction with a carbodiimide or another coupling agent or built into a reagent such as 1-benzotriazolyoxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) **256.**[46]

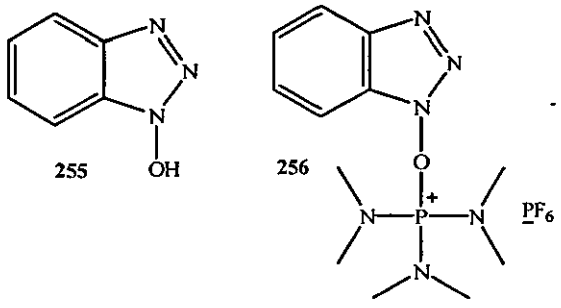


Figure 20: HOBt **255** and BOP **256.**

This salt derived from 7-aza-1-hydroxybenzotriazole has been shown to be superior to its benzotriazole analogs in terms of coupling efficiency,[47, 48] racemisation,[49] and cyclisation,[46] in solution and solid phase strategies. If an excess of HOBt is present the HOBt intercepts the activated ester first therefore it does not have time to racemise, then the amine attacks the HOBt ester and gives the peptide in a very fast reaction.

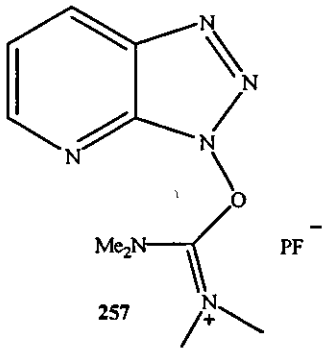
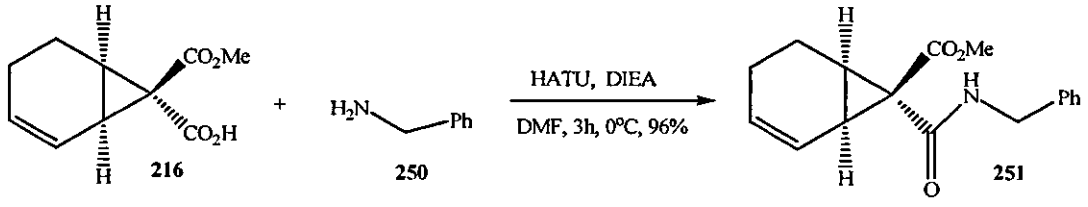


Figure 21: HATU (**257**) coupling reagent.[46]

Another peptide coupling reagent used when sterically demanding substrates are involved is *N*-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridine-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide **257** (HATU).

Due to the sterically demanding nature of the mono acid **216**, HATU was employed as the coupling agent in the reaction.[46]

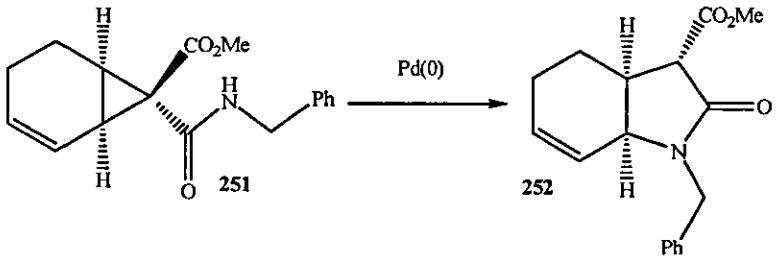


Scheme 102: Amide coupling [46]

The coupling reactions were carried out in DMF solution with benzyl amine **250** and the HATU coupling reagent and DIEA as the base. The reaction proceeded cleanly at 0°C in 3 hours yielding the corresponding activated amide **251** in an excellent 96% yield. The reaction could also be performed at room temperature affording the same results (scheme 102)

4.1 The Pd(0) Catalysed Rearrangement-Preliminary studies

The activated amide **250** was then subjected to a variety of Pd(0) conditions outlined in table 16.



Catalyst	Lewis Acid	Solvent	Temp (°C)	Time (h)	Product (252)
$Pd(PPh_3)_4$	$ZnBr_2$	THF	RT	17	SM (100%)
$Pd(PPh_3)_4$	-	THF	RT	17	SM (100%)
$Pd(PPh_3)_4$	$ZnBr_2$	THF	Reflux	17	SM (100%)
$Pd(PPh_3)_4$	-	THF	Reflux	17	**258/259** (10%) + SM (90%)
$Pd(PPh_3)_4$	$ZnBr_2$	THF	Reflux	17	SM (100%)

Table 16: Rearrangement conditions.

The initial conditions used for the rearrangement were those developed by the group for the trapping of various imines and intramolecular rearrangements onto vinyl cyclopropanes (THF, $ZnBr_2$, $Pd(PPh_3)_4$).[23, 24, 25, 36, 37] The Lewis acid $ZnBr_2$ was used to help facilitate the opening of the cyclopropane ring by co-ordinating to the methyl ester group. When applied to this system only the amide **251** was isolated. The reaction was then refluxed, however no reaction took place and only starting material was recovered. An interesting product was however isolated on one occasion along with starting material when heating in THF at reflux with no Lewis acid present. It was not the desired rearranged product but was none the less interesting and was tentatively assigned as one of the two structures (**258/259**) shown in figure 22.

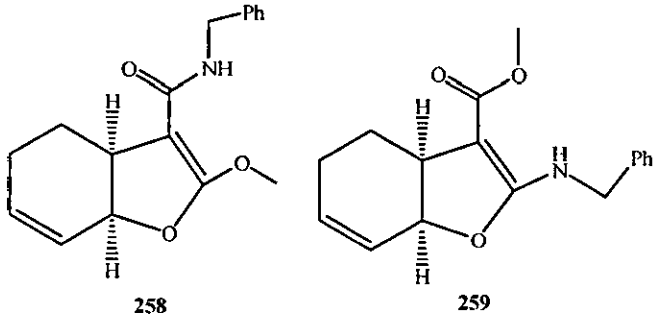


Figure 22

The other rearrangement product was isolated in trace amounts alongside the starting material **251**. Infra-red analysis indicated that **259** was the structure as a stretch at 1730 cm^{-1} indicates the presence of a methyl ester group, which is not present in **258**. A fragment ion corresponding to a methyl ester group was also seen in the fragment pattern.

The solvent was then changed to DMF and the reaction was repeated again at a higher temperature this time, disappointingly only starting material was recovered. Microwave conditions were also employed using DMF and THF as the solvent but again this failed to promote the rearrangement also.

Catalyst	Lewis Acid	Solvent	Temp (°C)	Time (h)	Product (252)
$Pd(PPh_3)_4$	-	DMF	RT	17	SM
$Pd(PPh_3)_4$	$ZnBr_2$	DMF	RT	17	SM
$Pd(PPh_3)_4$	-	DMF	100	17	SM
$Pd(PPh_3)_4$	$ZnBr_2$	DMF	100	17	SM

Table 17: Rearrangement conditions.

Success eventually came when the solvents were switched to DCM and finally to methanol. Methanol had previously been used in Pd(0) catalysed [2+3] cycloadditions with the vinylcyclopropane substrate and was thought it could be effective here. When using Pd(0) without Lewis acid in DCM at room temperature the rearranged product was formed in a 50% yield along with **258/259**.

Catalyst	Lewis Acid	Solvent	Temp (°C)	Time (h)	Product (252)
$Pd(PPh_3)_4$	-	DCM	RT	17	50% + **258** or **259** (50%)
$Pd(PPh_3)_4$	$ZnCl_2$	DCM	RT	17	SM
-	$ZnCl_2$	DCM	RT	3	SM
$Pd(PPh_3)_4$	-	MeOH	RT	3	50%+ **258** or **259** (50%)
$Pd(PPh_3)_4$	-	MeOH	RT	17	99%
-	$ZnCl_2$	MeOH	RT	17	SM
$Pd(PPh_3)_4$	$ZnCl_2$	MeOH	RT	17 h	SM

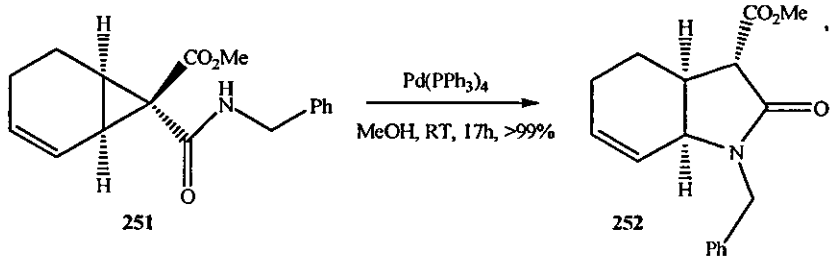
Table 18: Rearrangement conditions

When using methanol as the solvent the rearrangement was shown by monitoring *via* TLC to occur around 3 hours to give two compounds. The desired compound was isolated as one diastereoisomer in addition with the other rearranged product **258/259**.

However when the reaction was left stirring for 17 hours the sole thermodynamic product **252** was isolated exclusively in a quantitative yield. On repeating the reaction using methanol as the solvent, in the absence of Lewis acid and increasing the reaction time to 17 hours at room temperature structures **258** and **259** were not isolated from the reaction mixture, therefore methanol was used as the solvent of choice for the rearrangement.

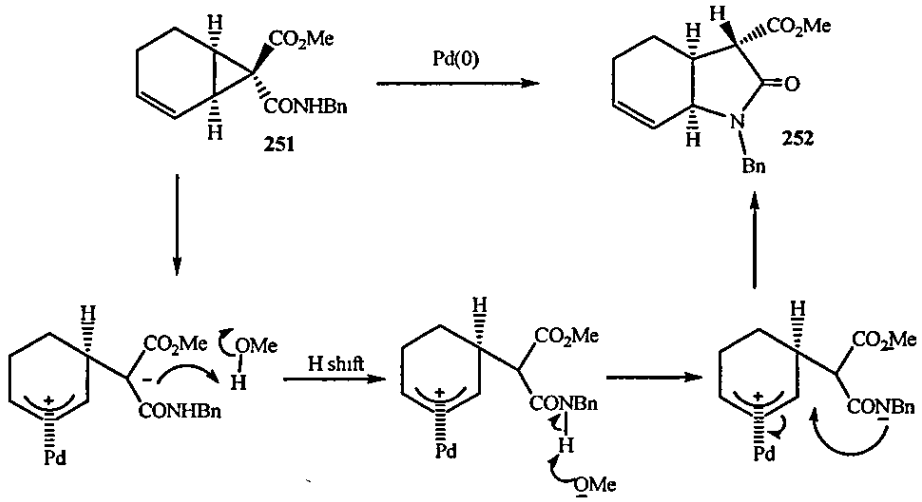
4.2 Solvent Effects

The solvent it appeared played a very important role in the reaction. Only when methanol was used as the solvent the rearrangement occurred and went to completion, DCM was successful but starting material was also present in the reaction.



Scheme 103: Pd(0) catalysed rearrangement.

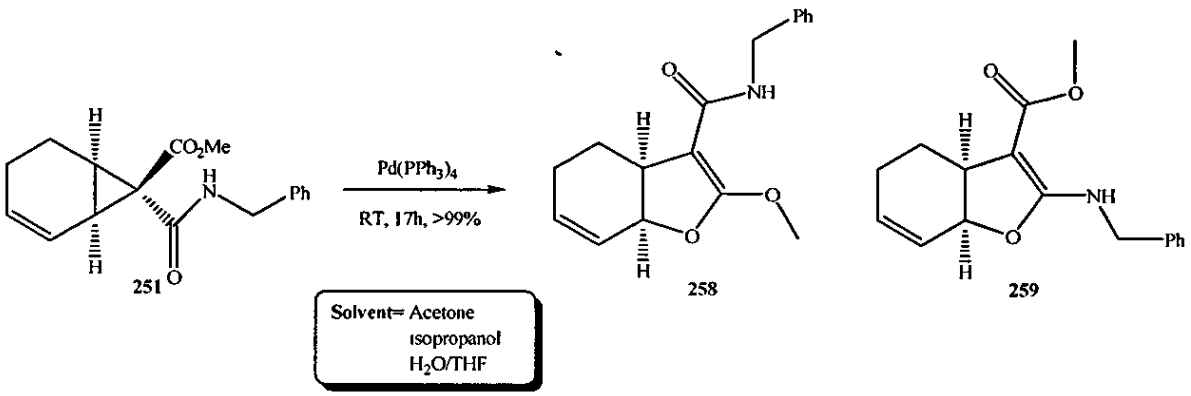
It was hypothesised that the methanol could be hydrogen bonding with the malonate intermediate and assisting with the H-shift and then abstracting the hydrogen from the amide thus placing the negative charge onto the nitrogen which subsequently then eliminates the Pd species to form the five-membered ring.



Scheme 104: Solvent effects.

Other solvents were then used in the reaction to determine if the rearrangement was specific for methanol. Other polar protic solvents such as a H_2O/THF mix and iso-propanol and the dipolar aprotic solvent acetone were all used in the rearrangement

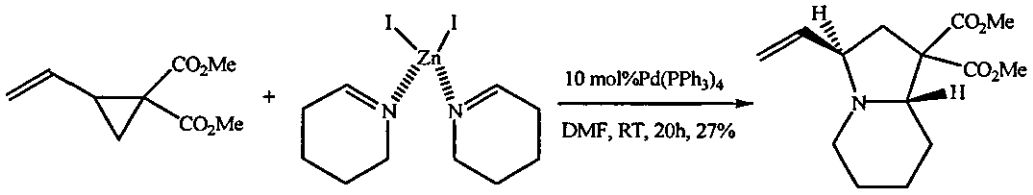
The desired hydroindole product **252** was not isolated but the other rearranged structure was isolated in all three cases in a >90% yield. No starting material was isolated. The structure was tentatively assigned to that in scheme 105.



Scheme 105: Pd(0) catalysed rearrangement.

The solvent could also be causing the rearrangement and that the Pd(0) might not be needed at all. This solvent effect has been seen in some instances with the vinylcyclopropane system

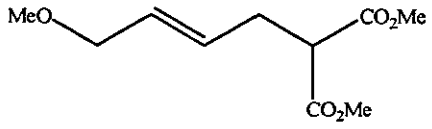
when trapping imines in methanol, the methanol had attacked the vinyl group and ring opened the cyclopropane ring.[50]



128 260 261

Scheme 106: Pd(0) catalysed [2+3] cycloaddition.[50]

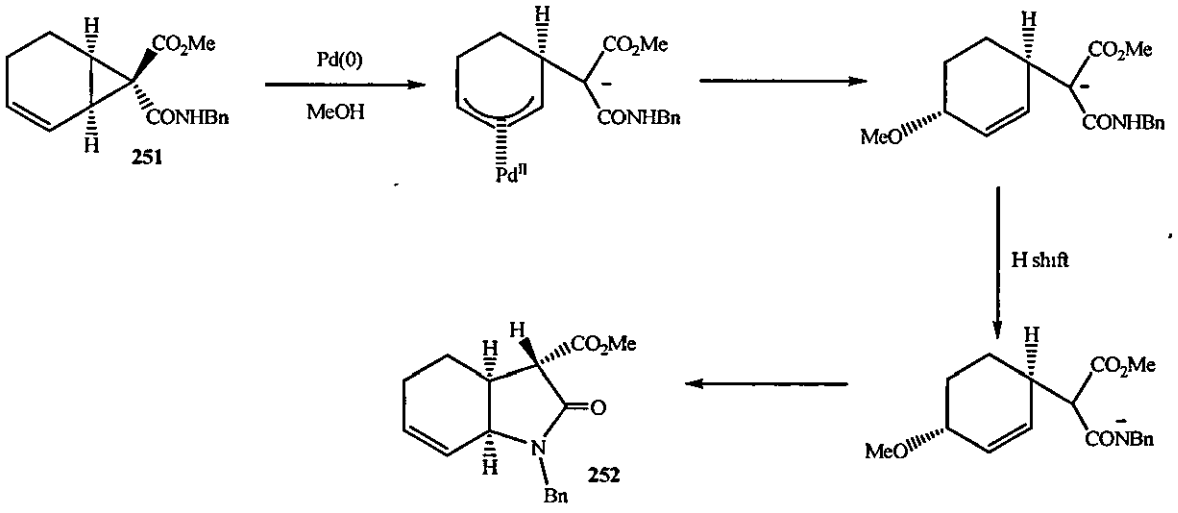
In the synthesis of **261** when using methanol as the solvent a major bi-product of the reaction was the alkene **262** shown in figure 23.[50]



262

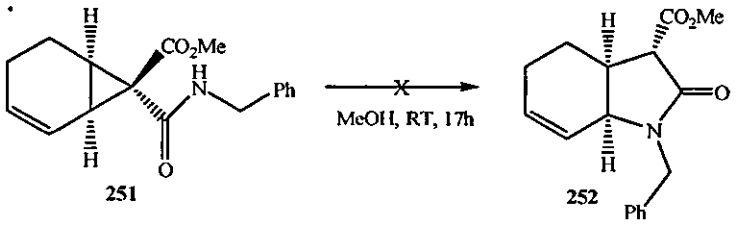
Figure 23: Bi-product.[50]

This could be produced by the methanol acting as a nucleophile towards the zwitterionic species after palladium insertion into the alkene.



Scheme 107: Methanol catalysed rearrangement.

The benzyl amide **251** was stirred in methanol overnight without the presence of the Pd(0) catalyst to determine if the methanol is acting alone and is causing the ring opening of the cyclopropane moiety.



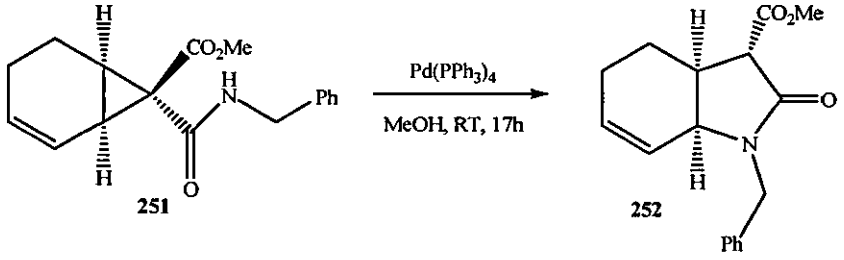
Scheme 108: Methanol catalysed rearrangement.

No reaction was seen and only the starting material was isolated, thus proving that the rearrangement needs the Pd(0) catalyst to initiate the reaction. It appears at this time that this rearrangement using these conditions is novel, examples of this work is not evident at this time.

4.3 Pd(0): Catalyst Loadings

Following on from the work on the solvent effects, work on determining the optimum mol % of the catalyst which could be used was also investigated. In any synthesis the need to be

economic and environmentally friendly is crucial so to minimise the amounts of reagents used in a synthesis is important.



Catalyst	Loading (%)	Yield 252 (%)
$Pd(PPh_3)_4$	5	90
$Pd(PPh_3)_4$	2.5	78
$Pd(PPh_3)_4$	1	60
$Pd(PPh_3)_4$	0 5	50

Table 19: Catalyst loadings.

Upon loading the catalyst to 5, 2.5 and 1 mol % the reaction was successful in high yields on all occasions on the test system. When the loading was reduced to 0.5 mol % the product was seen in an approximately 1.1 ratio with the rearranged dihydrofuran shown in figure 23.

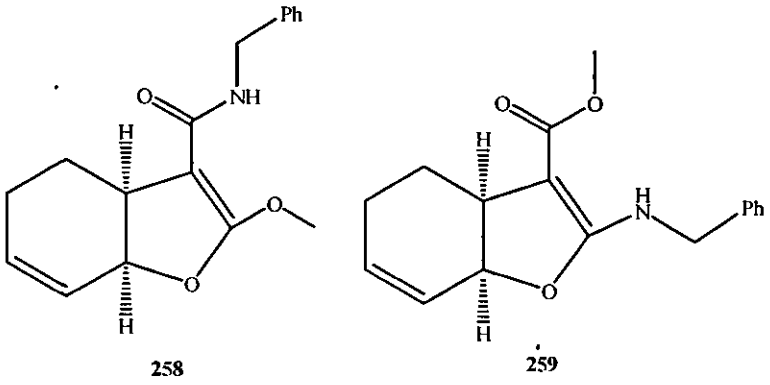


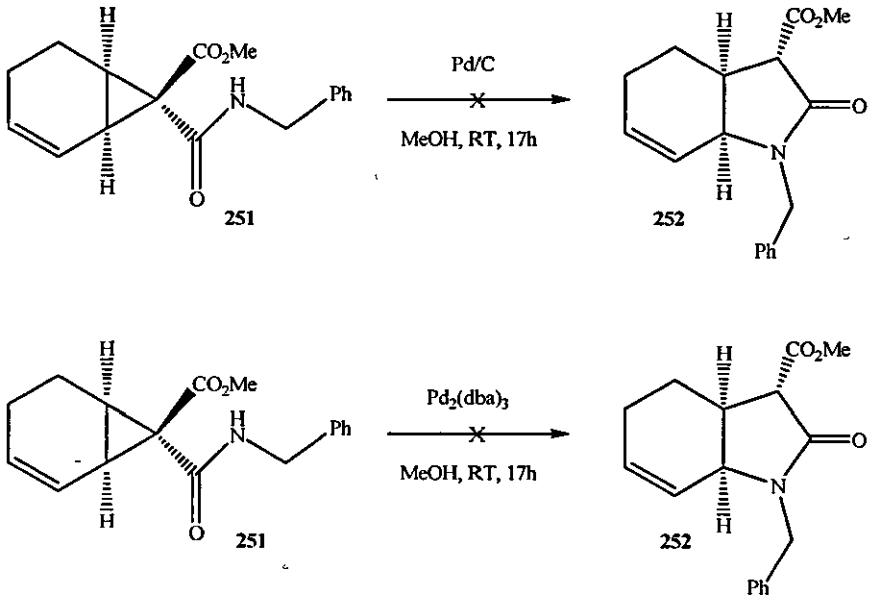
Figure 23

Although not ideal, no product was lost in the reaction as the dihydrofuran was ring opened and driven to the hydroindole product when re-subjected to the Pd(0) conditions and stirred for a further 17 hours at room temperature.

With the optimum catalyst loadings between 0.5 and 1 %, other sources of the Pd catalyst were researched.

4.4 Sources of Palladium

The rearrangement was also performed using other sources of palladium, the reaction was performed on the benzyl amide in methanol at room temperature with both Pd/C and $Pd_2(dba)_3$ (scheme 109).



Scheme 109: Pd(0) catalysed rearrangement.

Both rearrangements were unsuccessful and only the starting material amide was recovered on work up.

4.5 Scope of the Rearrangement

The scope of the rearrangement was assessed to determine whether it could be successfully applied to a number of amide tethers on various sized fused vinyl cyclopropane substrates to synthesis various novel compounds and also identify any conformational problems.

The peptide coupling, using a range of amines and subsequent rearrangement conditions was applied to the systems shown in figure 24.

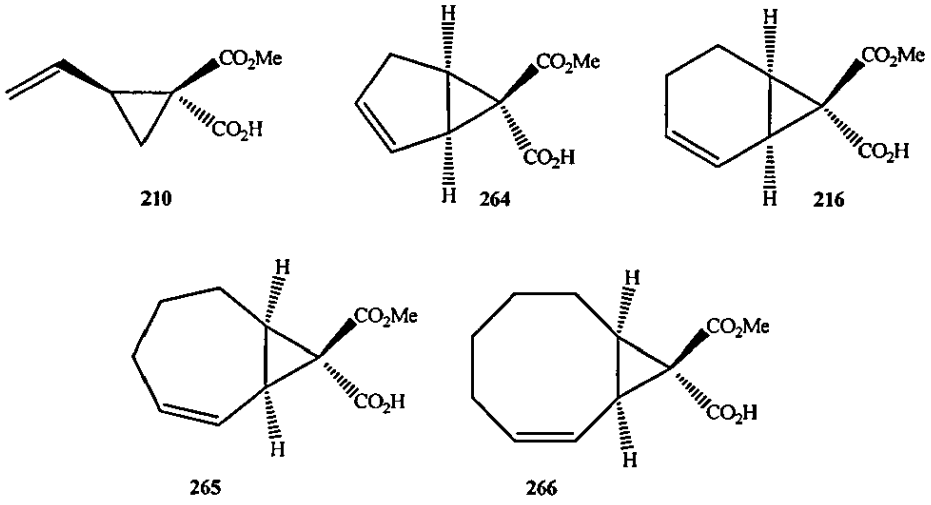


Figure 24: Cyclopropane systems.

The coupling and rearrangements were carried out on alkyl, benzyl, aromatic and electron deficient amines. The amine **268** containing a C-Br sp^2 bond is an interesting amine, with the bromide in the 2-position it was interesting to discover if the Pd(0) would insert here also in the rearrangement stage.

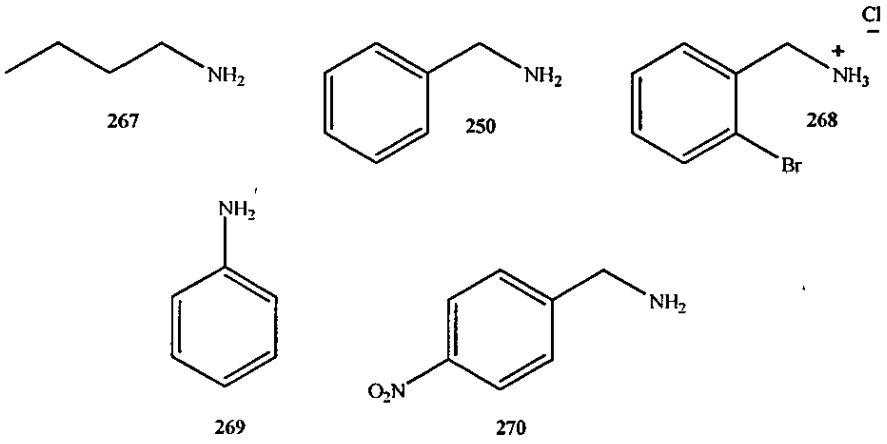
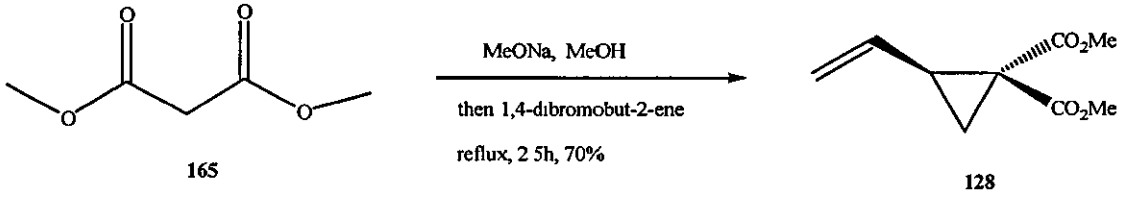


Figure 25: Amines to be used for peptide coupling.

If the couplings and rearrangements are successful this would be an attractive novel route to a variety of bicyclic compounds.

4.6 Applications on the vinylcyclopropane system

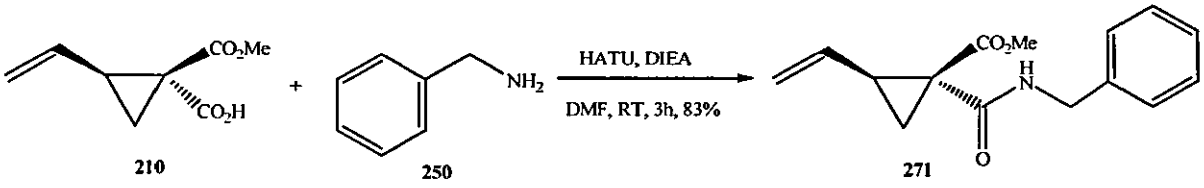
The vinylcyclopropane **128** was synthesised using an S_N2' reaction of dimethyl malonate **165** and 1,4-dibromo-but-2-ene with sodium methoxide, generated *in situ* from sodium in methanol, as before.



165 128

Scheme 110: Synthesis of the vinylcyclopropane.

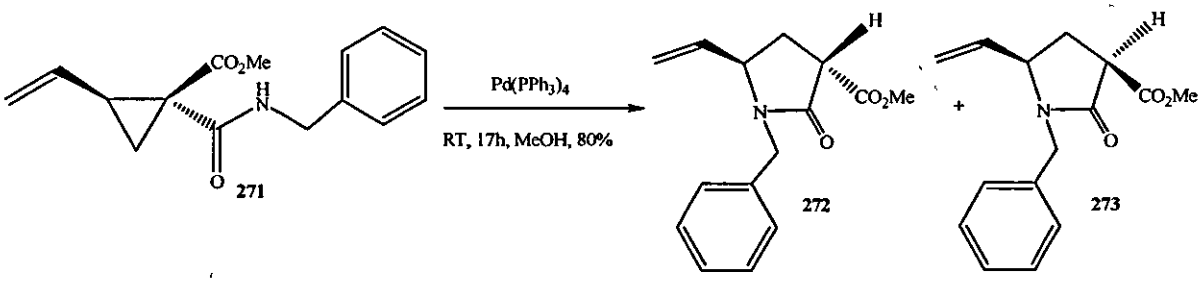
The vinylcyclopropane **128** was then hydrolysed to the mono acid **210** using LiOH in THF/water in a 91% yield and used unpurified in the amide bond forming reaction. The standard amide coupling conditions were performed, benzylamine **250** was coupled as the model test substrate as before (scheme 111).



210 250 271

Scheme 111: Amide coupling

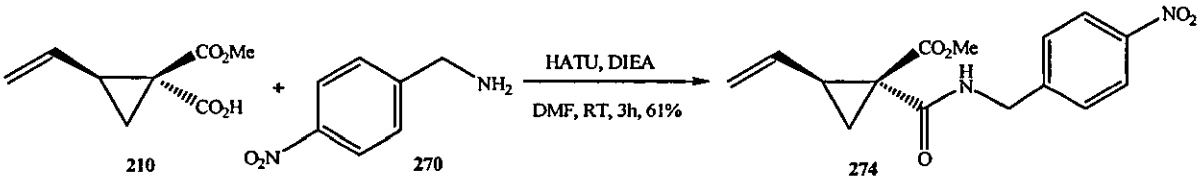
The coupling with benzylamine was successful in a high, reproducible 83% yield, the amide **271** was then purified and was carried forward to the Pd(0) catalysed rearrangement conditions.



Scheme 112: Pd(0) catalysed rearrangement.

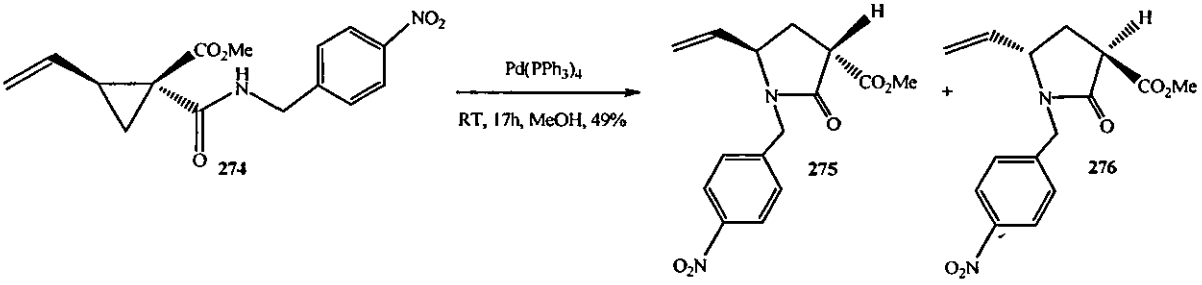
The rearrangement was successful in a high 80% yield and gave approximately a 1:1 to mixture of inseparable *cis* and *trans* diastereoisomers.

The electron with drawing natue of *p*-nitrobenzylamine was also investigated, **270** was also coupled to the mono acid **210** in a modest 61% yield (scheme 113).



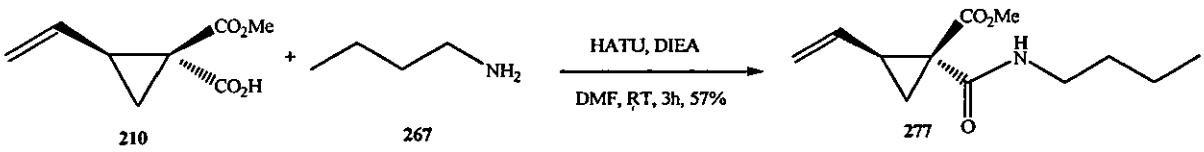
Scheme 113: Coupling with *p*-nitrobenzylamine.

The amide **274** was subjected to the Pd(0) conditions to give a 1:1 mixture of the diastereoisomers **275** and **276** in a low 49% yield again the diastereoisomers could not be separated and isolated.



Scheme 114: Pd(0) catalysed rearrangement.

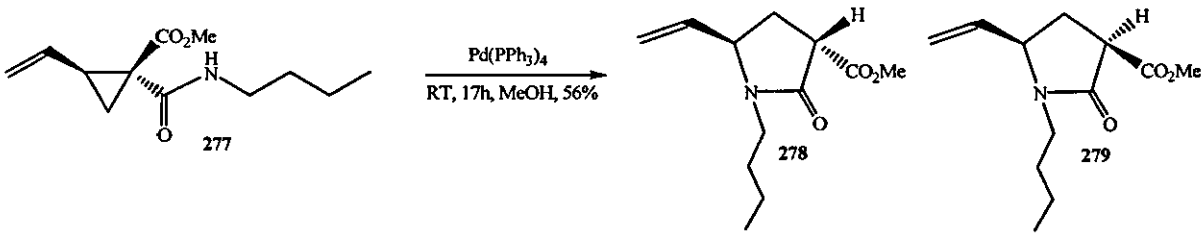
The next amine that was successfully coupled was butyl amine in a modest 57% yield again the coupling yield was quite low.



210 267 277

Scheme 115: Amide coupling with butyl amine.

The amide **277** was then subjected to the rearrangement conditions and 1-butyl-2-oxo-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester was afforded in a 56% yield as a 1:1 mixture of diastereoisomers.

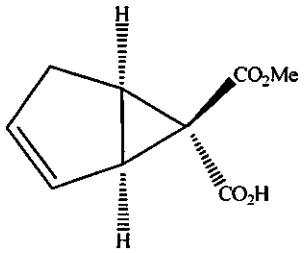


277 278 279

Scheme 116: Pd(0) catalysed rearrangement.

4.7 Applications on the 5-membered system

The next system to be investigated was the 5-membered system, bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester.

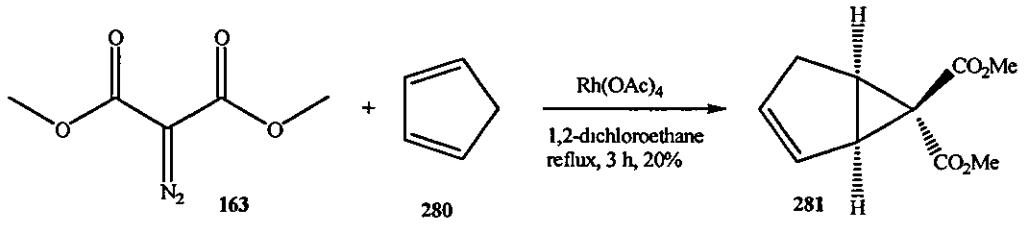


264

Figure 25: Bicyclo[3 1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester.

Amide couplings and the subsequent rearrangements on this substrate would lead to a variety of novel compounds and work within the group had already been carried out on the synthesis of bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester **281** which would then be hydrolysed to the mono acid **264** shown in figure 13.[24, 52]

Due to the dimersiation of cyclopentadiene it was cracked and separated into the monomer by distillation at atmospheric pressure.

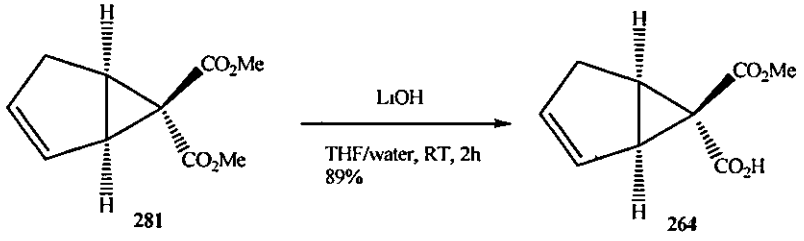


Scheme 117: Cyclopropanation of cyclopentadiene.

The yield was low (20%) as in the high temperature of the cyclopropanation conditions the cyclopentadiene was dimerising back to dicyclopentadiene.

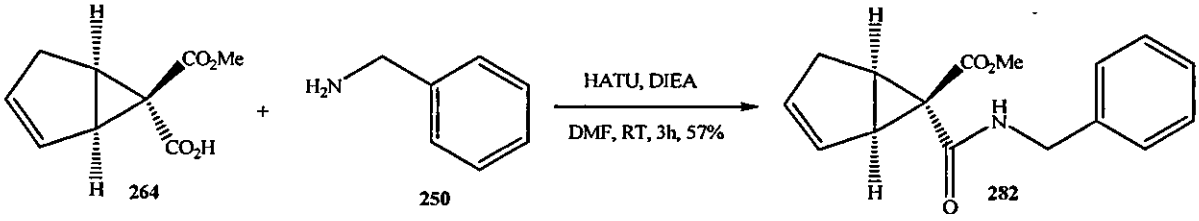
Although a low yield the reaction could be performed on a relatively large scale to provide enough of the starting material for the next steps in the synthesis.

Once the diester **281** was purified it was hydrolysed using LiOH in THF/ water to yield the corresponding mono acid **264** in an 89% yield in 2 hours The stereochemistry shown in **264** is based on the theory that the ester hydrolysis was more likely to occur on the methyl ester *exo* to the ring (scheme 118).



Scheme 118: Ester hydrolysis.

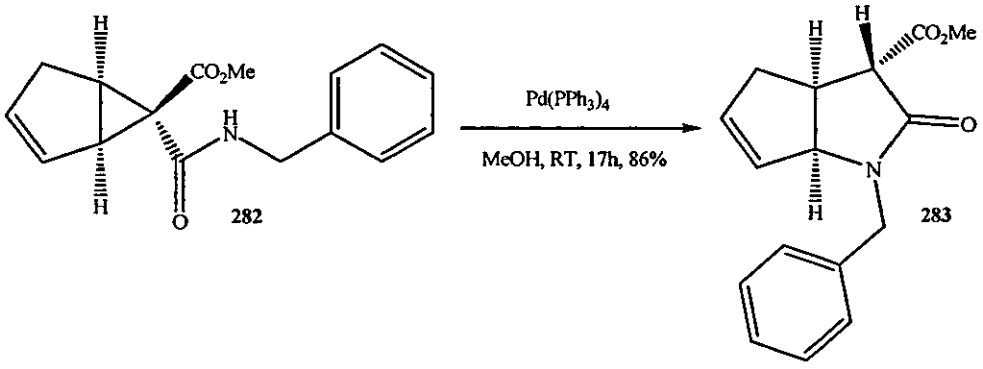
Using the standard amide coupling conditions, benzyl amine was coupled with the un-purified mono-acid in 3 hours to afford the benzyl amide **275** in a respectable 57% yield.



Scheme 119: Amide coupling with benzyl amine.

The yield was lower than anticipated and the mono acid **264** and diester **281** were also isolated, which was why the yield was low as the mono acid was probably not as pure as desired. Again the reaction could be performed on a reasonable scale as to furnish the amide in large quantities.

The amide **282** was then subjected to the Pd(0) conditions as before and yielded the pyrrole substrate **283** in an excellent 86% yield (scheme 120).



Scheme 120: Pd(0) catalysed rearrangement.

Only one diastereoisomer was isolated and the stereochemistry at the ester centre was assigned using nOe analysis.

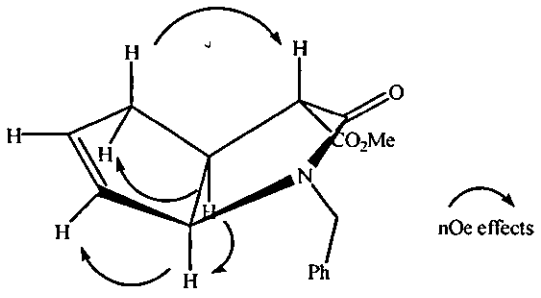
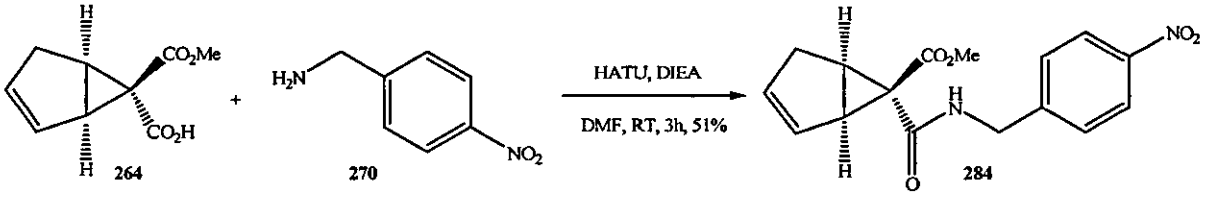


Figure 26: nOe analysis.

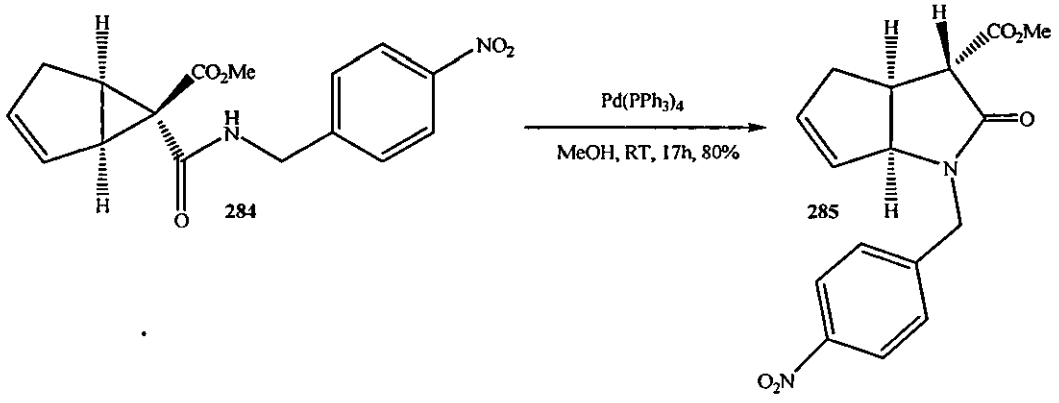
In relation to the work performed on the vinylcyclopropane substrate the electron deficient amine, *p*-nitrobenzylamine was also coupled to **264** to see whether the nitro group had an affect on the amide coupling/ Pd(0) catalysed rearrangement (scheme 121)



Scheme 121: Amide coupling with *p*-nitrobenzylamine

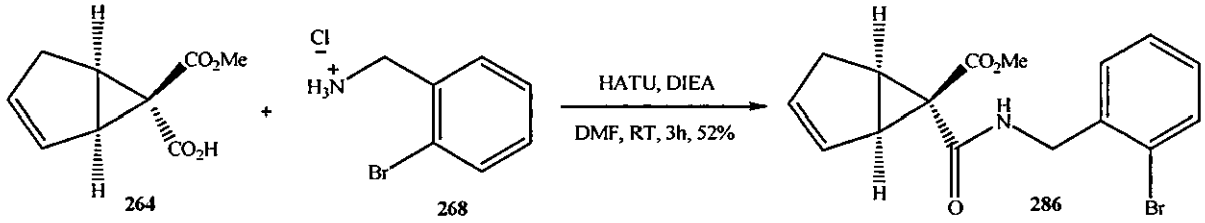
Again the amide coupling was achieved in 3 hours at a reasonable 51% yield, the low yield could also be due to the impurities associated with the mono acid, however the reaction could be performed on a relatively large scale.

The rearrangement was carried out as before and was successful in an impressive 80% yield yielding one diasteroisomer (scheme 122).



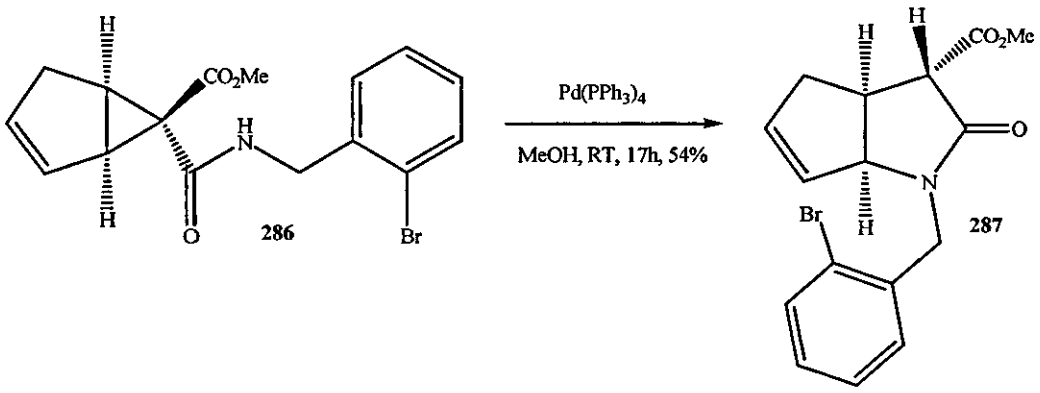
Scheme 122: Pd(0) catalysed rearrangement.

The next amine to be coupled was **268** which had a bromide in the 2-position on the aromatic ring (scheme 123)



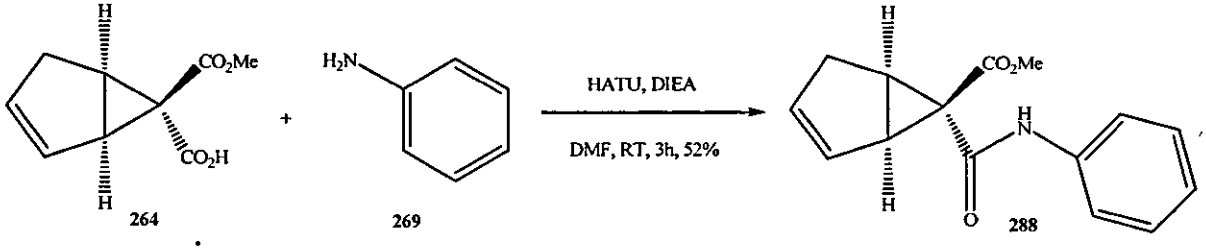
Scheme 123: Amide coupling with 2-bromo-benzylamine.

The coupling was successful in a 52 % yield and the Pd(0) catalysed rearrangement was performed. With the bromide in the 2-position it was thought the Pd(0) would insert here also and maybe inhibit the rearrangement from occurring but the reaction was successful in a 54% yield (scheme 124).



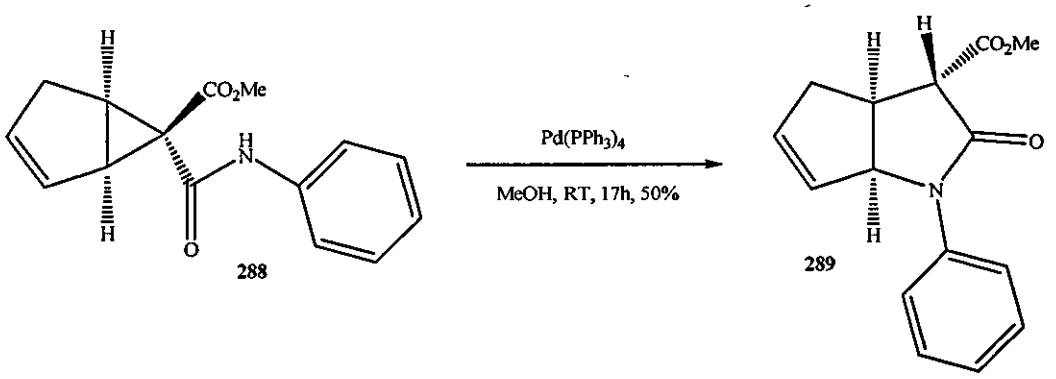
Scheme 124: Pd(0) catalysed rearrangement conditions.

To identify any problems with the amide coupling and rearrangement it was investigated whether an aromatic amine such as aniline could be coupled and if the lack of the CH_2 could pose any problems as the amines thus far had been benzylic in nature (scheme 125).



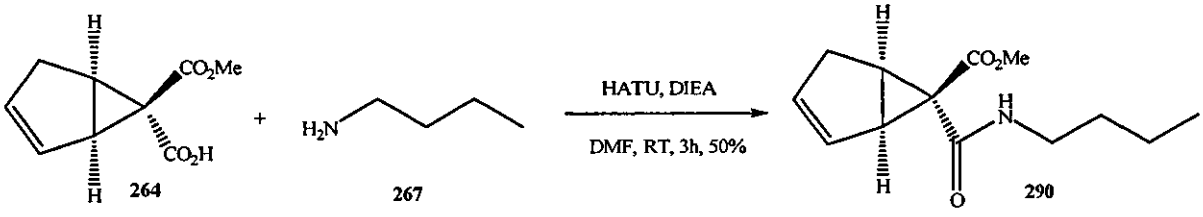
Scheme 125: Amide coupling with aniline.

Aniline **269** was coupled to **264** in a reasonable 52% yield.



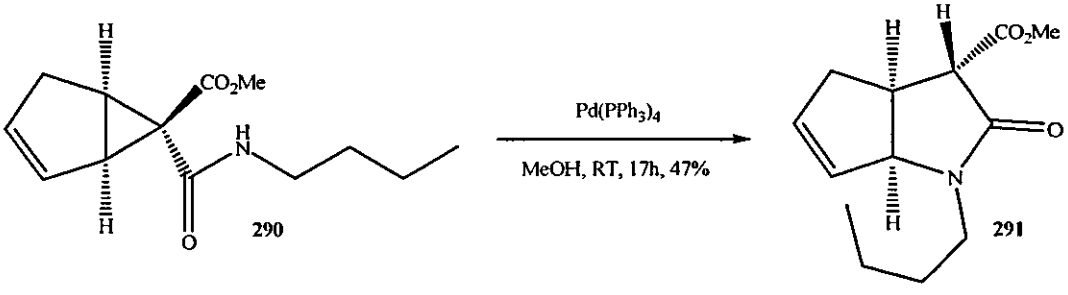
Scheme 126: Pd(0) catalysed rearrangement.

The rearrangement occurred in a 50% yield and another unknown material isolated in the reaction which could not be identified. Following on from this the aliphatic amine, butyl amine was coupled with the fused cyclopropane substrate (scheme 127).



Scheme 127: Amide coupling with butylamine.

The amide coupling occurred in a 50% yield and the amide **290** was rearranged as before to give the bicyclic product **291** in a 47% yield.

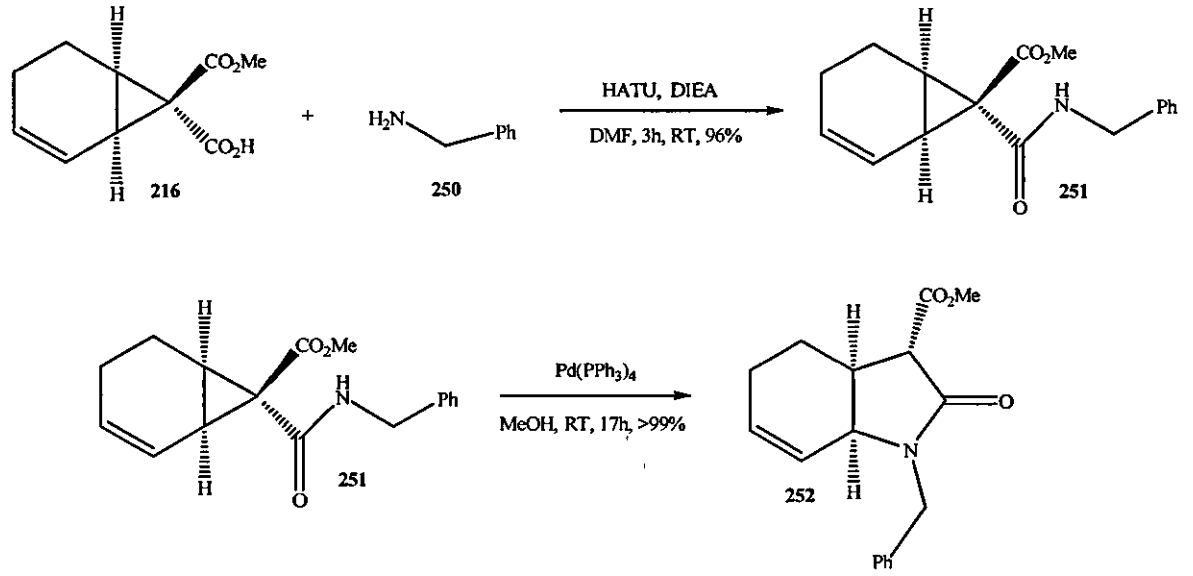


Scheme 128: Pd(0) catalysed rearrangement.

Although the yields were fairly low on this system it was still a promising method by which a variety of bicyclic products can be synthesised in reasonable yields. Thus far we have shown that the coupling and rearrangement can be applied to the vinylcylopropane and the 5-membered system yielding interesting compounds.

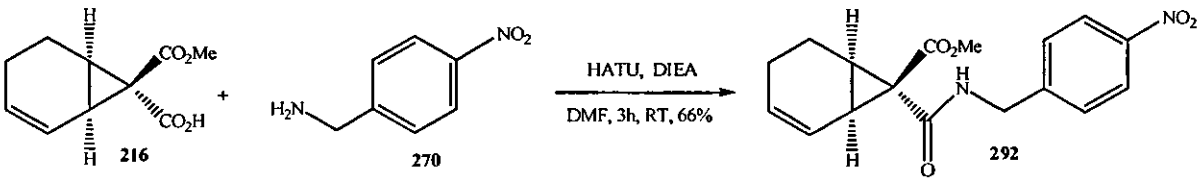
4.8 Applications on the 6-membered system

It was hoped that the previous amines coupled to the vinylcyclopropane and 5-membered systems could be applied on the [4.1.0] system where this research began (scheme 129).



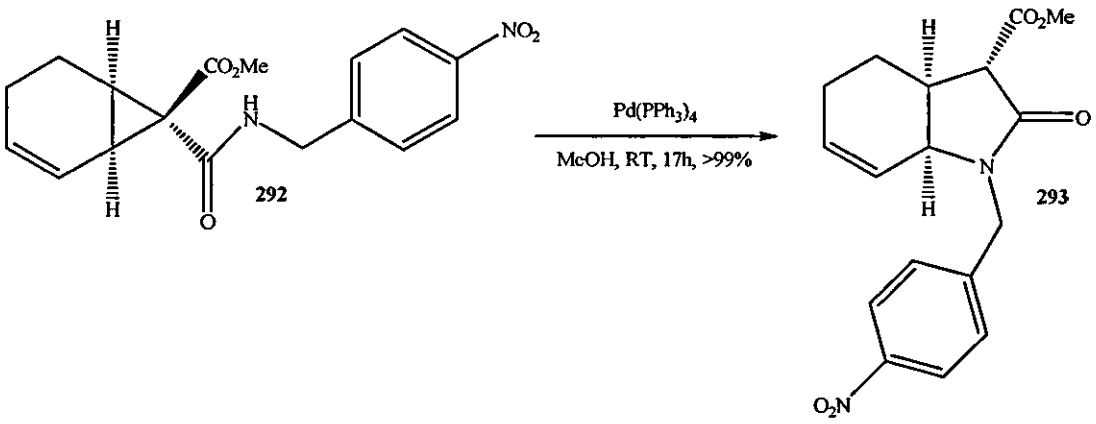
Scheme 129: Amide coupling and Pd(0) catalysed rearrangement.

The *p*-nitrobenzylamine was used as it was hoped that by having the nitro group incorporated the product could be crystalline and an X-ray crystal could be obtained. From this the stereochemistry at the ester centre could be positively assigned.



Scheme 130: Amide coupling.

The amide coupling was performed and the product **292** was isolated in a 66% yield, the reaction was left to stir for longer but this did not affect the overall yield, the reaction was also reproducible on a large scale. The amide was then stirred with the Pd(0) catalyst and the rearranged product was isolated in a quantitative yield (scheme 131)



Scheme 131: Pd(0) catalysed rearrangement.

An nOe was obtained and it was evident that the H^2 was not on the same face as the protons on the bridge of the rings, there also appeared to be a weak nOe between H^1 and H^2 but it was not conclusive.

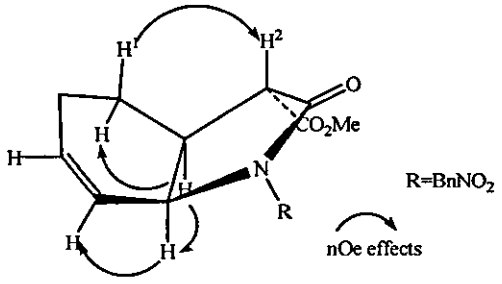


Figure 27: nOe analysis.

The product was crystalline and an X-ray of **293** was obtained, supported with the nOe data the stereochemistry was determined that the methyl ester and the protons at the bridge of the rings were all on the same face as shown in scheme 131.

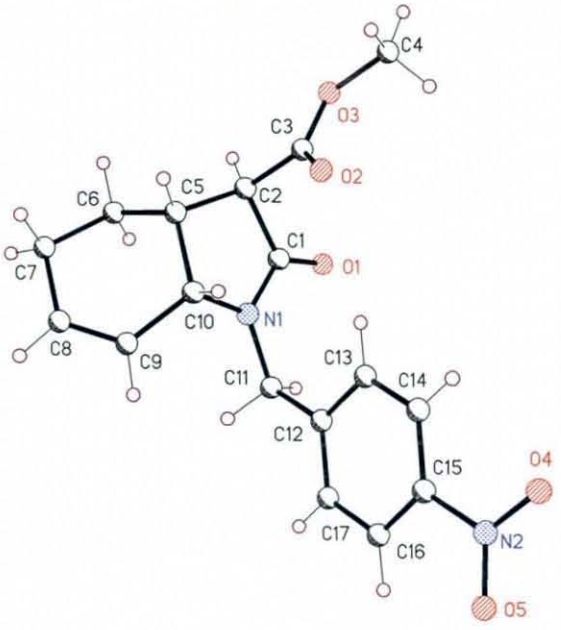
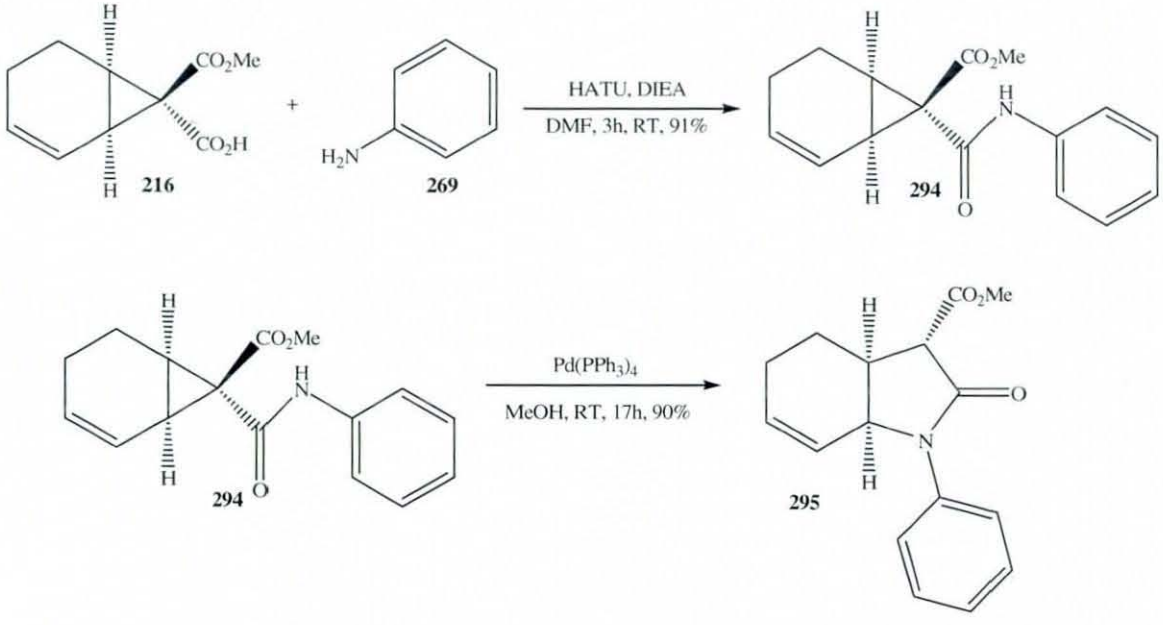


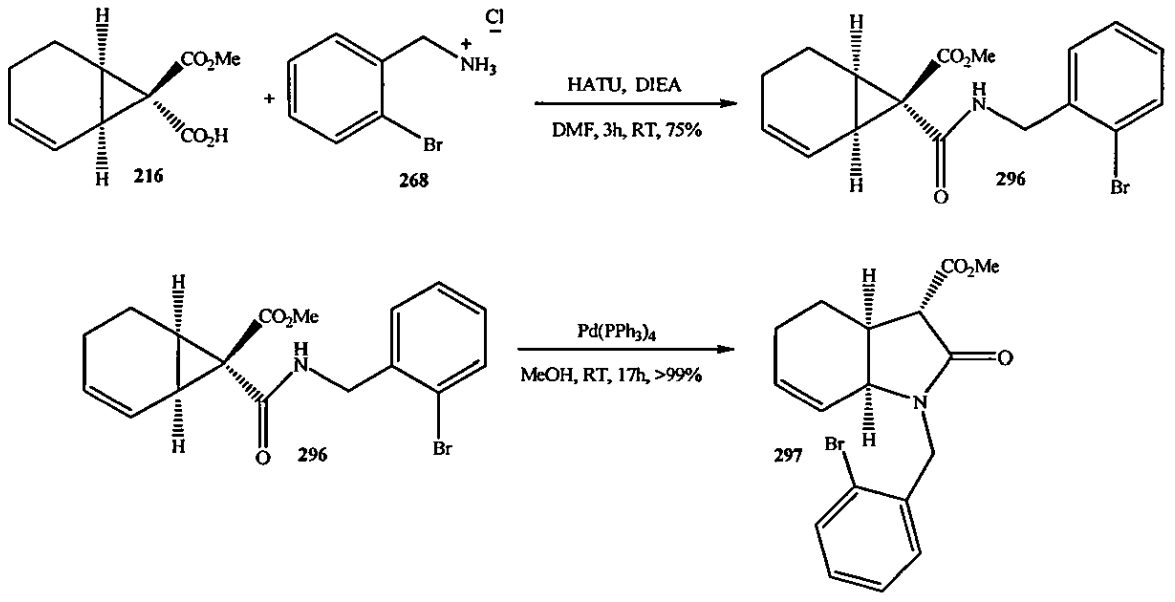
Figure 28: X-ray of **293**.

Following on from this aniline, 2-bromobenzylamine and the aliphatic butylamine were all coupled and rearranged successfully.



Scheme 132: Amide coupling and Pd(0) catalysed rearrangement.

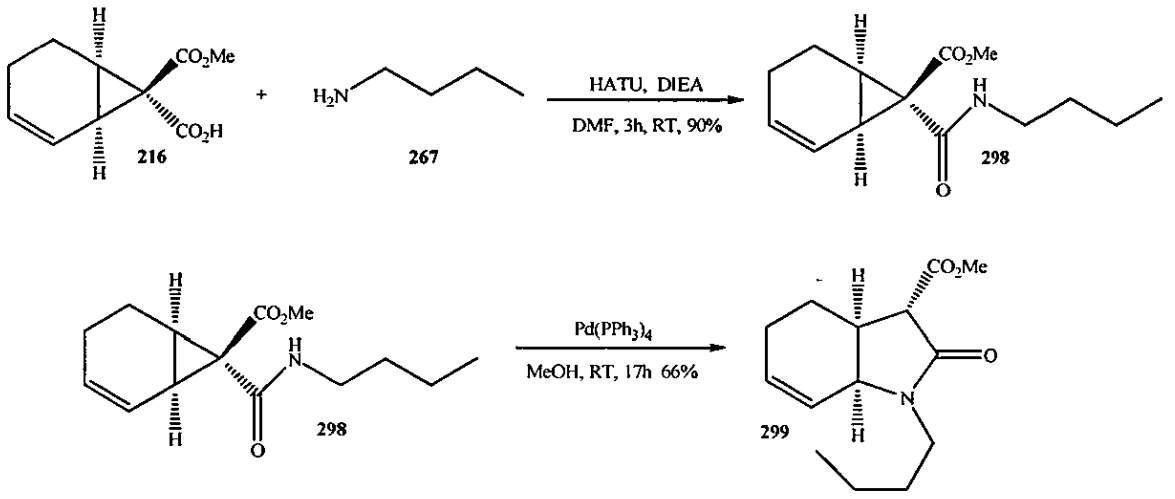
Both the coupling of aniline and 2-bromobenzylamine along with the rearrangements of both amide substrates occurred in excellent yields.



Scheme 133: Amide coupling and Pd(0) catalysed rearrangement.

The hydroindole type structure containing the 2-bromobenzyl moiety again offered the opportunity for an intramolecular Heck reaction to be carried out.

Coupling with butylamine **267** proceeded in a high 90% yield but the rearrangement product **298** was only isolated in a 66% yield, no other material was isolated from the mixture (scheme 134).

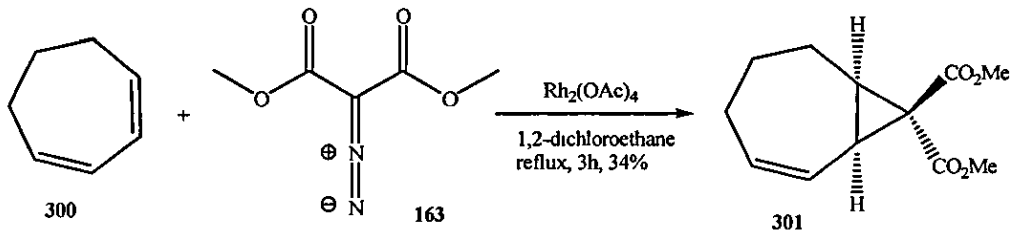


Scheme 134: Amide coupling and Pd(0) catalysed rearrangement.

All of the applications on the 6-membered system again yielded one diastereoisomer, overall the yields of both the amide coupling and rearrangement were encouraging.

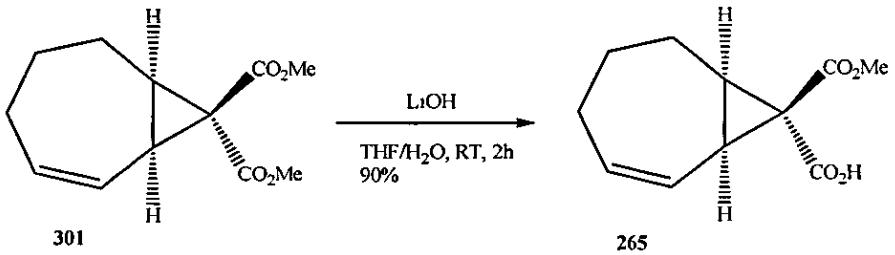
4.9 Applications on the 7-membered system

The ring sizes were increased so that we could synthesise more novel heterocyclic compounds and also to discover if the ring size has any affect on the coupling and rearrangement reactions.



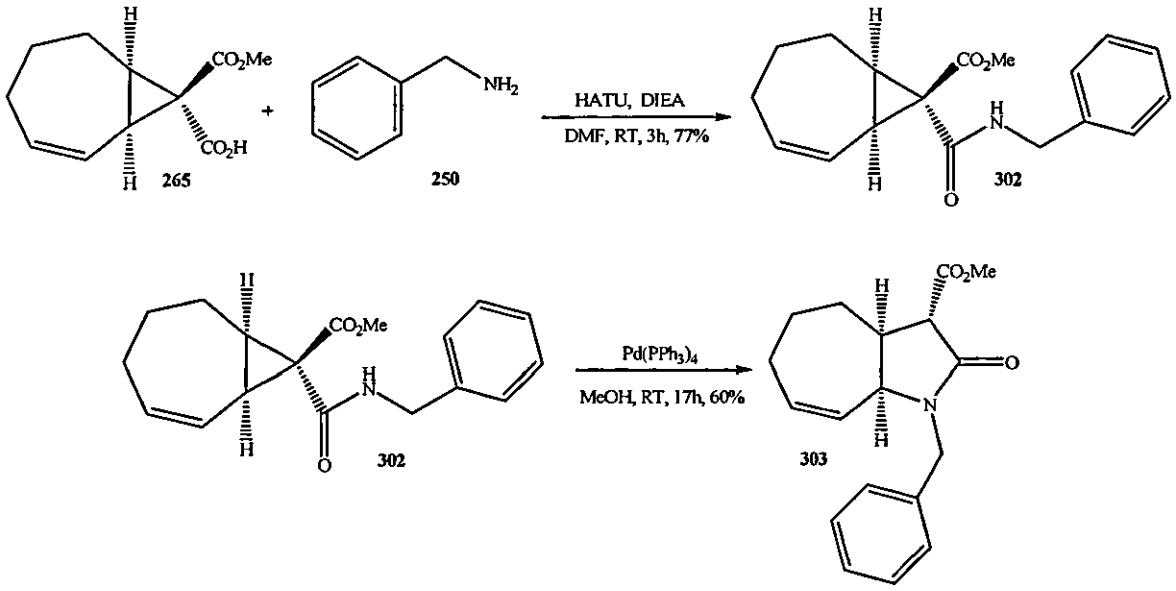
Scheme 135: Rhodium(II) acetate dimer catalysed cyclopropanation.

The rhodium(II) acetate dimers catalysed cyclopropanation of 1,3-cycloheptadiene **300** with dimethyl diazomalonate **163** gave the corresponding activated cyclopropane **301** in a low 34% yield, the reaction though could be performed on a sufficient enough scale so as to produce a significant amount of the diester starting material (scheme 135).



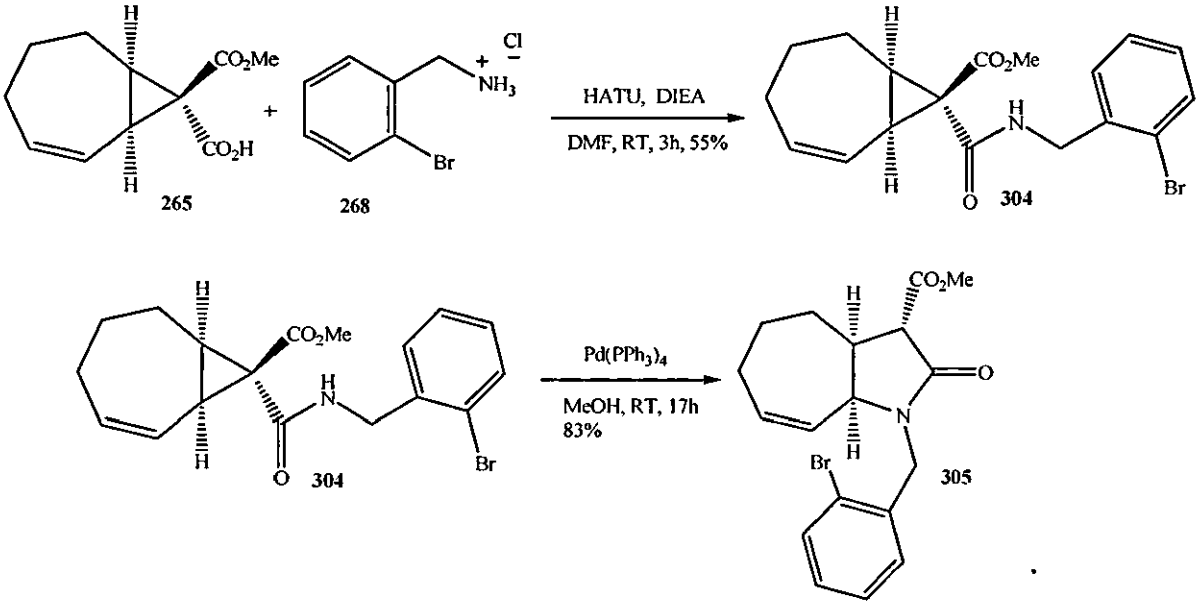
Scheme 136: Ester hydrolysis.

With the mono acid **265** now synthesised benzyl, 2-bromobenzyl, *p*-nitrobenzyl, butylamine and aniline were all coupled using the standard amide coupling conditions and rearranged to give a variety of interesting bi-cyclic products.



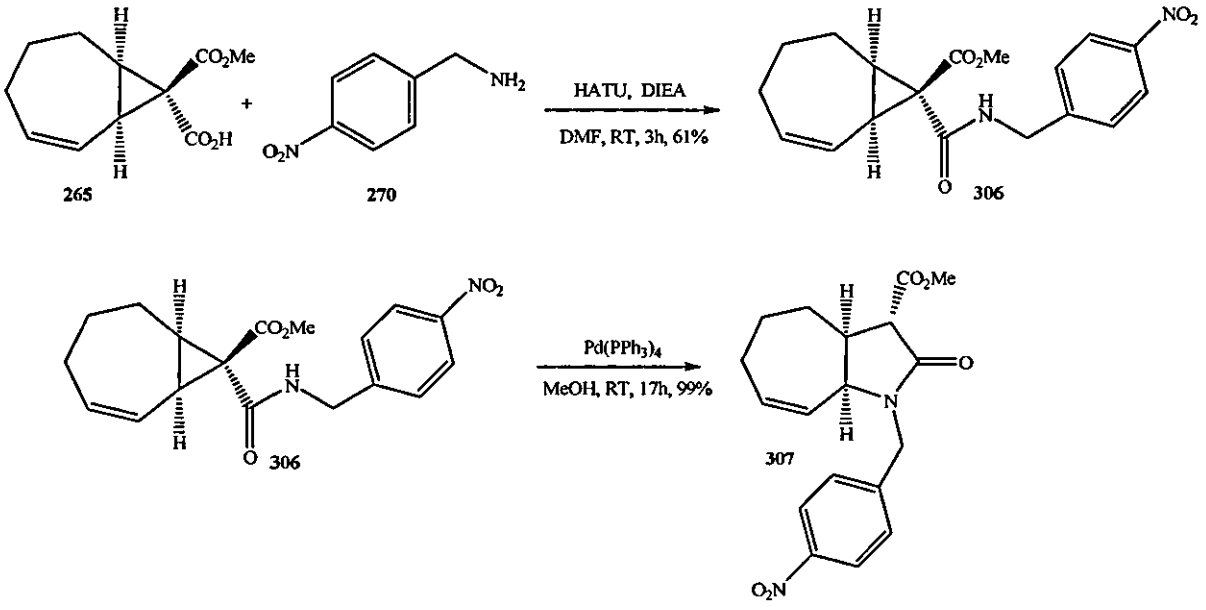
Scheme 137: Amide coupling and Pd(0) catalysed rearrangement.

The amide coupling with benzylamine was successful in a high 77% yield in 3 hours, the subsequent Pd(0) rearrangement of the amide **302** occurred in a 60% yield, in relation to the work on the 5 and 6-membered rings only one diastereoisomer was isolated in the reaction (scheme 137).



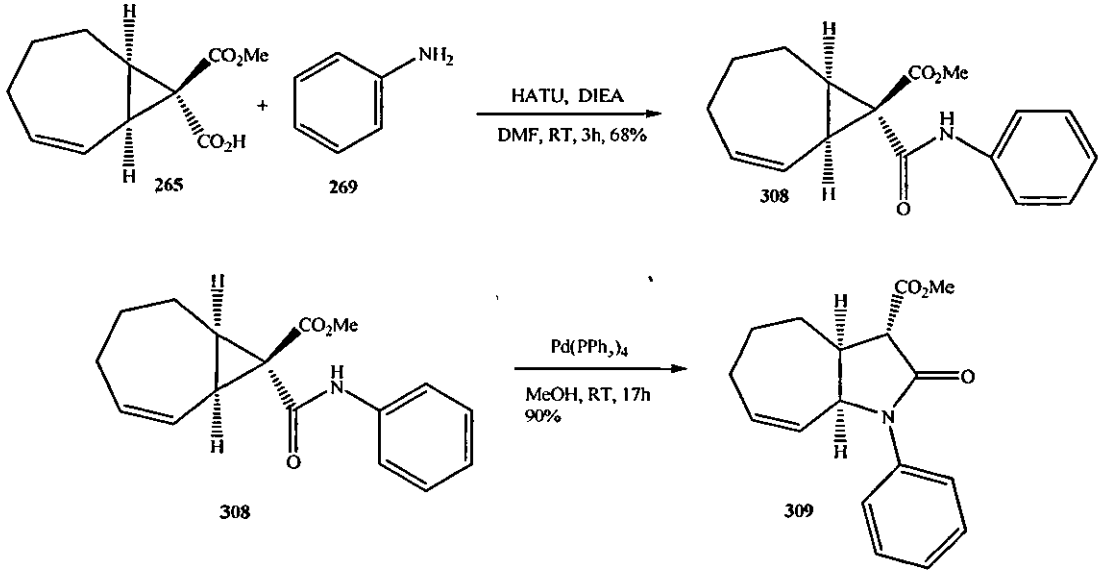
Scheme 138: Amide coupling and Pd(0) rearrangement.

The coupling of the 2-bromobenzylamine **268** occurred in a low yield, the amine was coupled as the hydrochloride salt, so it might have been worth coupling the amine as the free base to determine if this had any affect on the yield. Regardless the rearrangement was carried out and the bicyclic product **305** was isolated in a high 83% yield (scheme 138).



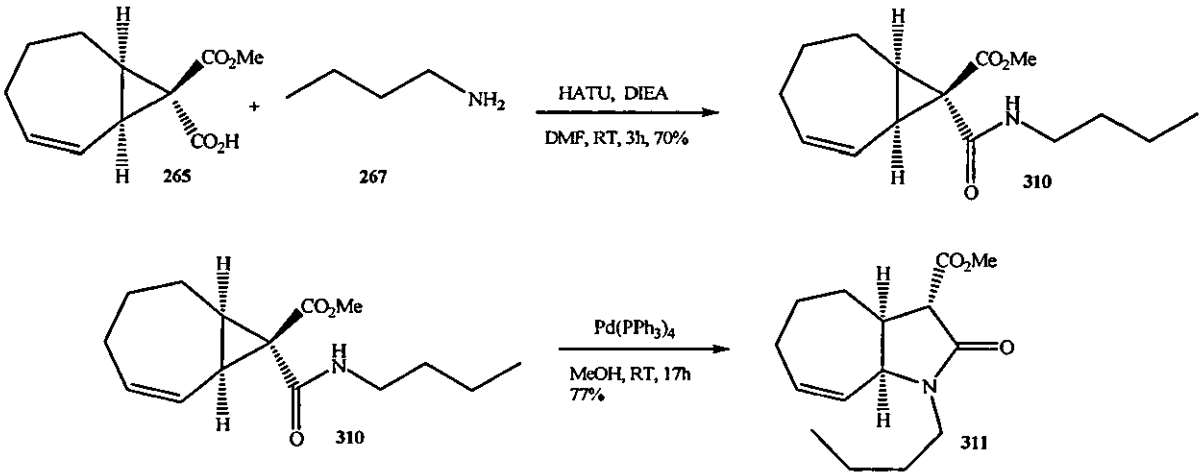
Scheme 139: Amide coupling and Pd(0) catalysed rearrangement

The *p*-nitrobenzylamine **270** coupled in a reasonable 61% yield and **306** was rearranged in a quantitative yield with only one diastereoisomer produced (scheme 139).



Scheme 140: Amide coupling and Pd(0) catalysed rearrangement.

The coupling with aniline **269** was also very promising, the amide coupling occurred in a respectable 68% yield and again there was no such problems with the rearrangement as this occurred in a 90% yield (scheme 140).



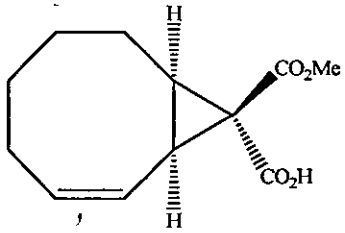
Scheme 141: Amide coupling and Pd(0) catalysed rearrangement.

Both the coupling with **267** and rearrangement of this activated amide occurred in excellent yields. All the work thus far had been excellent on the 5, 6 and 7-membered systems with only one diastereoisomer produced in each respective rearrangement reaction. All the yields in both the coupling and rearrangement were also respectable and reproducible.

Work on the vinylcyclopropane system had also been very fruitful where a number of heterocyclic compounds had been synthesised, over all the rearrangement appears to be a very versatile method of synthesising a variety of interesting heterocyclic products and tolerates a range of amines and cyclopropane substrates

4.91 Applications on the 8-membered system

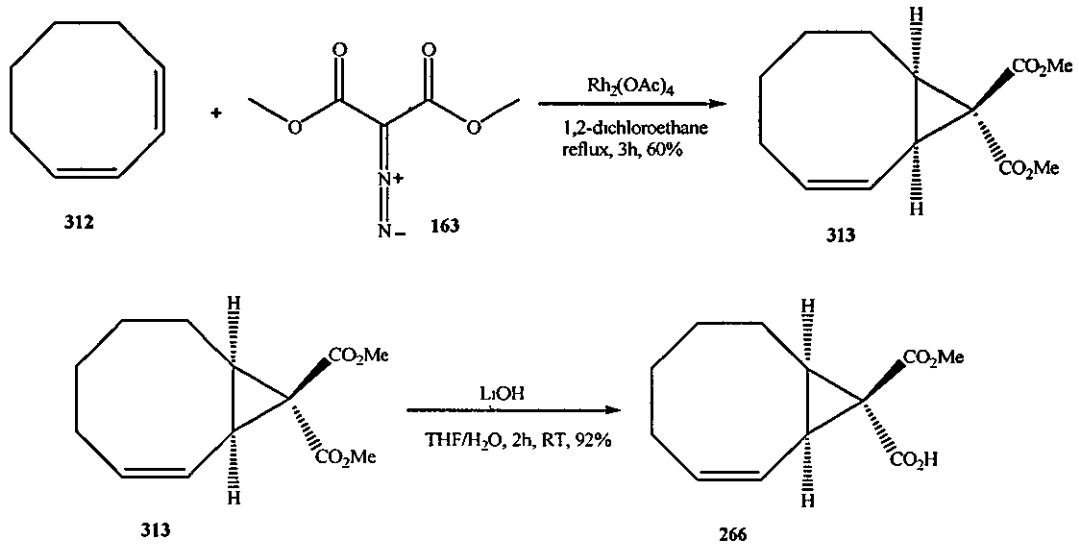
The last system which was investigated was the bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid methyl ester.



266

Figure 29: bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid methyl ester.

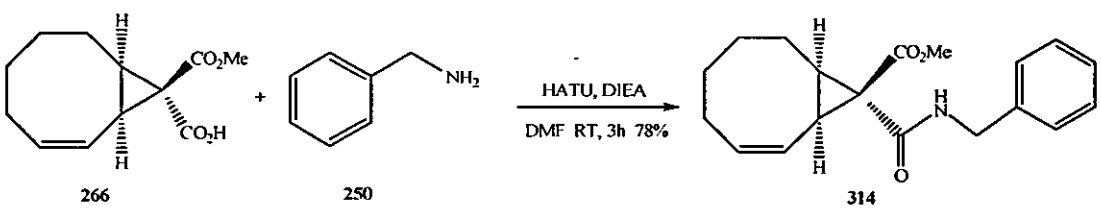
In this instance 1,3-cyclooctadiene **312** was cyclopropanated with dimethyl diazo malonate **163** in a high 60% yield, from here the ester was then hydrolysed to the mono **266** acid using the standard hydrolysis conditions (figure 29).



312 163 313 313 266

Scheme 142: Cyclopropanation and ester hydrolysis.

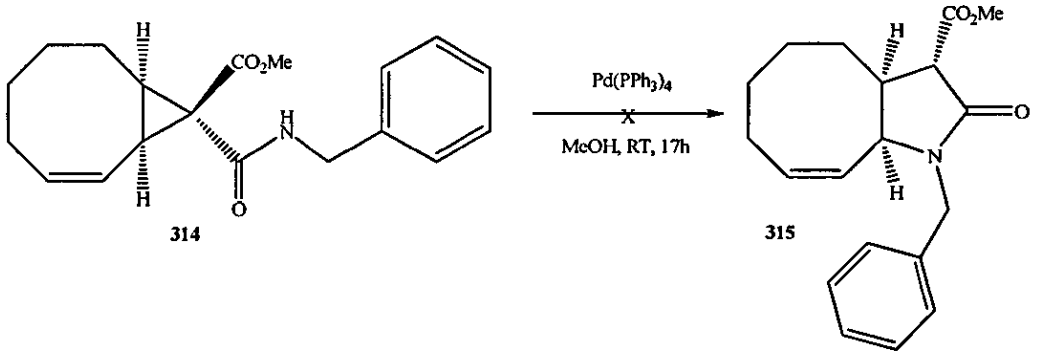
Benzylamine **250** was coupled to the mono acid **266** affording the amide **314** in a high 78% yield using the standard conditions.



266 250 314

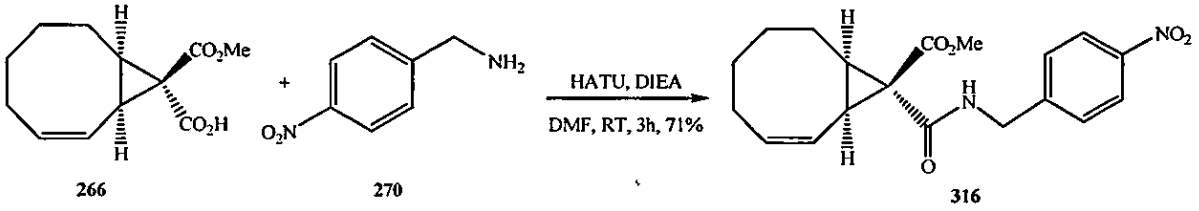
Scheme 143: Amide coupling.

When the amide **314** was subjected to the Pd(0) conditions no reaction was observed, even when the reaction was refluxed the rearrangement still did not occur.



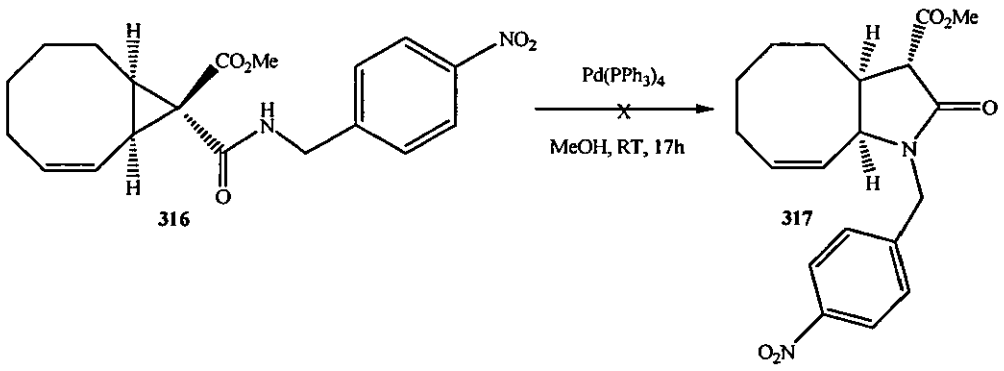
Scheme 144: Pd(0) catalysed rearrangement.

The problem could have been due to the stereoelectronics of the bicyclic product so the rearrangement might not be favourable. With this in mind the *p*-nitrobenzylamine was also coupled to see whether the rearrangement would be successful with the electron withdrawing nature of the nitro group.



Scheme 145: Amide coupling.

The *p*-nitrobenzylamine **270** coupled in a high 71% yield and the amide **316** was subjected to the Pd(0) conditions



Scheme 146: Pd(0) catalysed rearrangement.

Again the reaction was unsuccessful, even under reflux no rearrangement was observed only the amide **316** was isolated. The 8-membered ring appeared to be the limit of the rearrangement at this time.

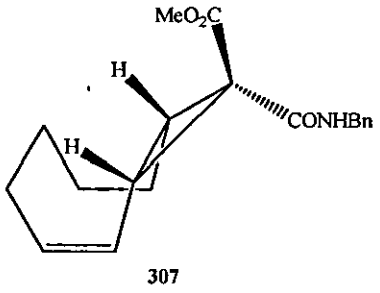


Figure 30: 8-membered conformation.

The substrate **314** could possibly adopt this conformation where the alkene double bond is not aligned with the cyclopropane ring, therefore when the Pd(0) inserts the cyclopropane does not ring open.

4.92 Synthesis of bicyclic lactones

To conclude work on the each fused vinylcyclopropane the mono acid substrate was also rearranged on the 5, 6 and 7-membered ring systems in near quantitative yields using the standard rearrangement conditions.

The lactone **319** shown in figure 31 is an intermediate used by Corey *et al.* in their synthesis of prostaglandins E_2 and $F_2\alpha$.[51, 52] The lactone **318** is similar to **319** and can be synthesised in

an excellent yield using our novel Pd(0) catalysed rearrangement thus showing the wide applicability of this rearrangement.

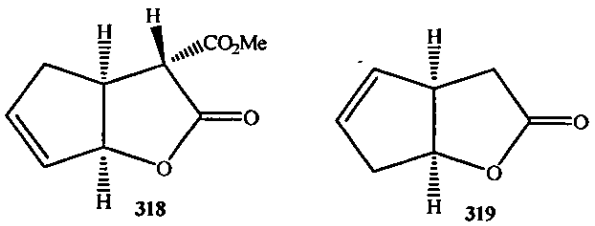
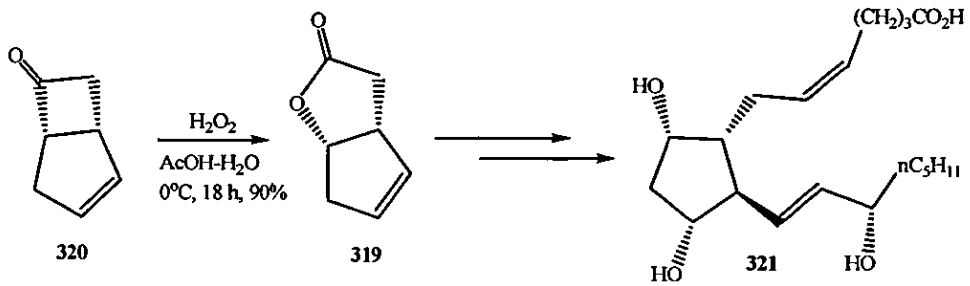
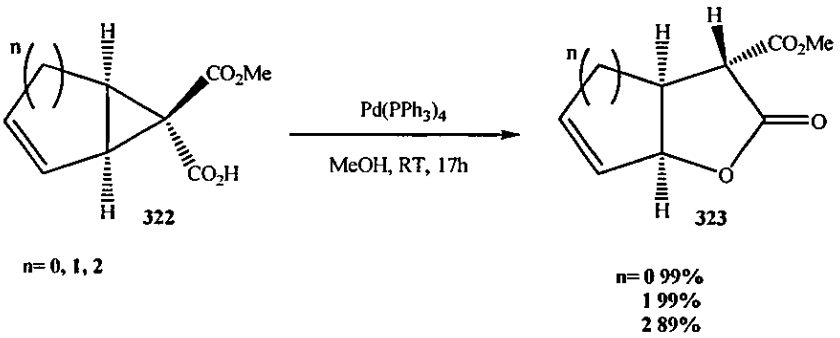


Figure 31: lactones.



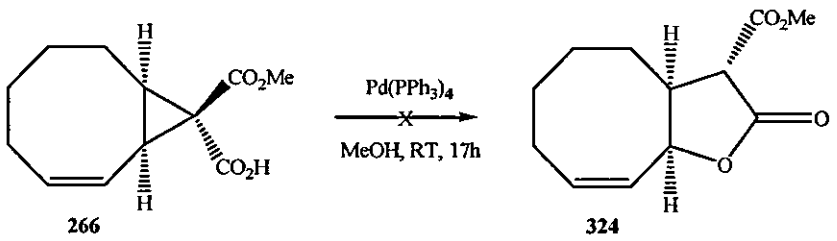
Scheme 147: Corey's synthesis prostaglandin E_2 **321**.[51, 52]

Corey's synthesis was *via* the lactone **319**, showing how versatile this novel rearrangement is as hopefully it could be applied in the syntheses of other important heterocyclic compounds.[51, 52]



Scheme 148: Pd(0) catalysed rearrangement.

Again the lactones were furnished as one diastereoisomer, and the stereochemistry was confirmed by nOe analysis. The only mono acid which did not undergo rearrangement was that of the 8-membered system, the mono acid **266** was subjected to the Pd(0) conditions.

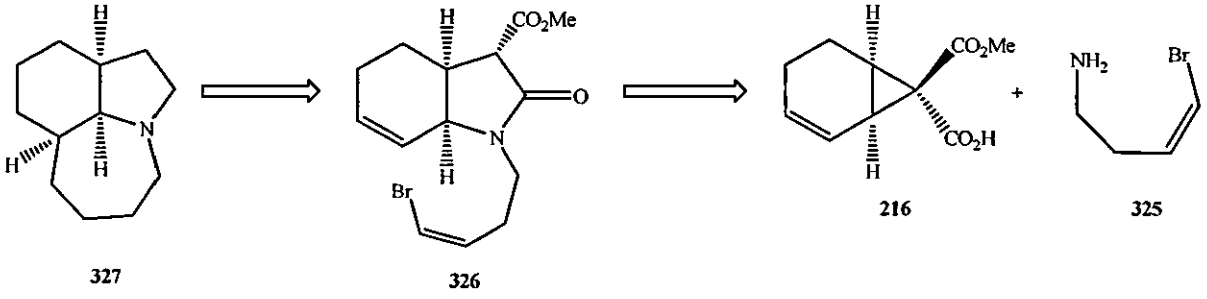


Scheme 149: Pd(0) catalysed rearrangement.

Again the rearrangement was unsuccessful thus maybe proving that the conformation **266** adopts prevents the alkene and the cyclopropane are not aligned, the reaction was further stirred for 17 hours at reflux but again no reaction was observed.

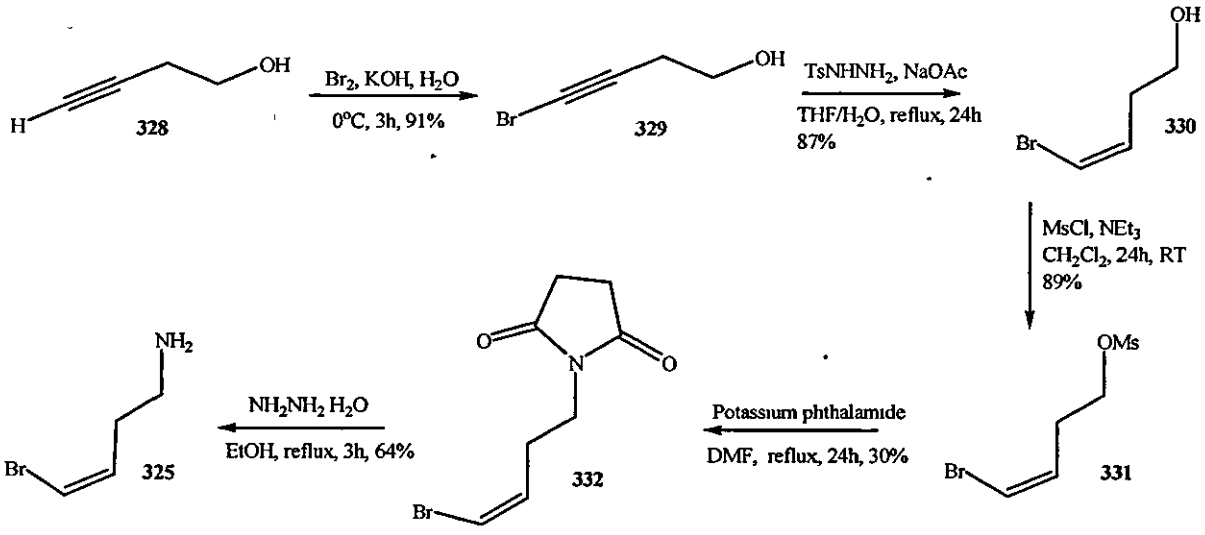
4.93 Intramolecular Route to the tricylic core of Stenine

With the peptide couplings and rearrangements successful on a variety of substrates a revised intramolecular route to the tricyclic core of stenine and related stemona alkaloids was devised.



Scheme 150: Retrosynthetic route to the tricyclic core.

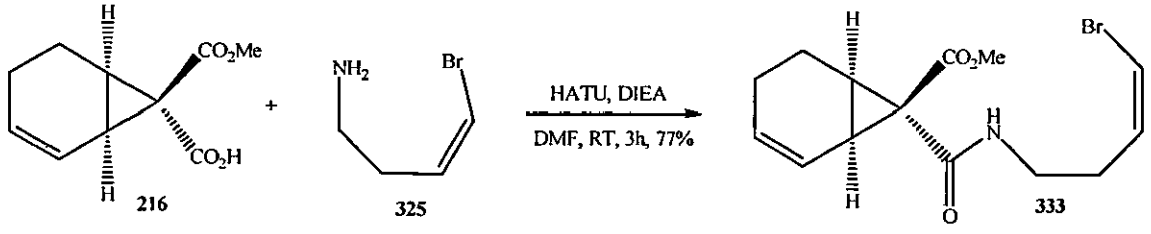
The azepine ring of the tricyclic product **327** could be synthesised from the intramolecular Heck reaction of the hydroindole **326** which in turn could be synthesised from the coupling of the amine **325** with the mono acid **216** and the subsequent rearrangement (scheme 150).



Scheme 151: Synthesis of the bromo amine.[53]

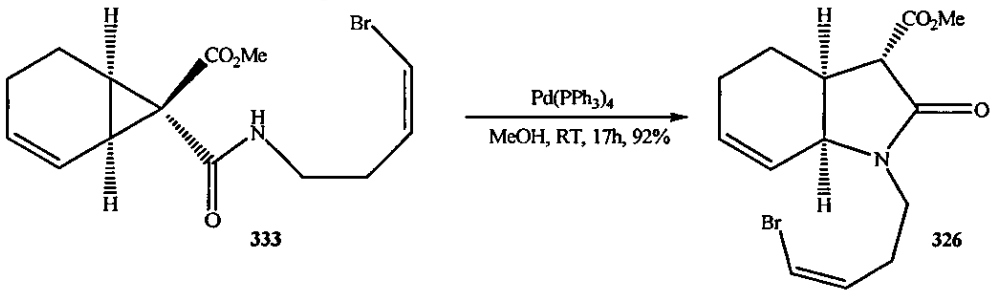
The amine **325** was synthesised by a co-worker by the following route, bromination of 3-butyn-1-ol **328** occurred in a 91% yield. The alkyne **329** was then reduced to the alkene **330** in an 87% yield using tosyl hydrazine and then mesylation of the alcohol afforded compound **331** in an 89% yield. Elimination of the mesylate with the phthalamide gave **332** in a low 30% yield. Finally the amine **325** was furnished by treating **332** with hydrazine monohydrate to yield the amine in a 64% yield (scheme 151).[53]

Due to difficulties involved in the synthesis, only a small quantity of the amine was obtained and coupled to the mono acid as the bromo amine **325** was only synthesised on a small scale.[53]



Scheme 152: Amide coupling.

The amide **333** was isolated in a high 77% yield using the standard conditions, the activated amide was then stirred overnight in methanol with $Pd(PPh_3)_4$.

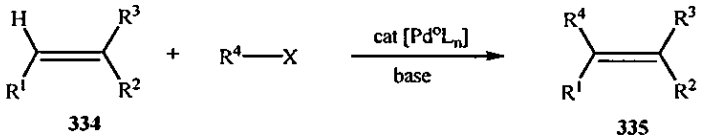


Scheme 153: Pd(0) catalysed rearrangement.

We were delighted to isolate the hydroindole core **326** in an excellent 92% yield as one diastereoisomer. The final step was the decisive intramolecular Heck reaction to form the azepine ring.

4.94 The Intramolecular Heck reaction

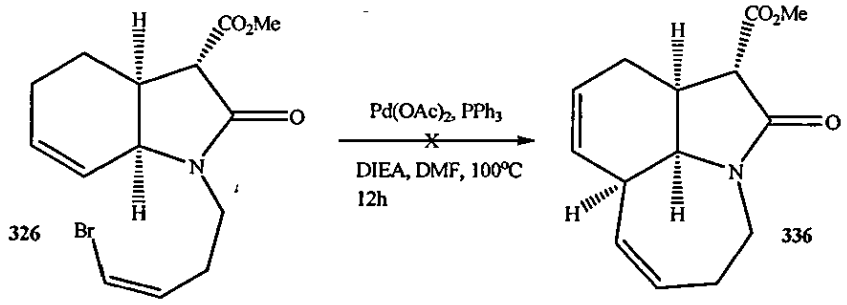
The Heck reaction has been widely applied in total synthesis it is a remarkable robust method for carbon-carbon bond formation especially in the generation of tertiary and quaternary stereocentres and also intramolecular ring formation.[54] The Heck reaction can broadly be defined as the palladium-catalysed coupling of alkenyl or aryl (sp^2) halides or triflates with alkenes yielding products which result in the substitution of a hydrogen atom in the alkene coupling partner.



R^4= aryl, benzyl, vinyl
X = Cl, Br, I, OTf

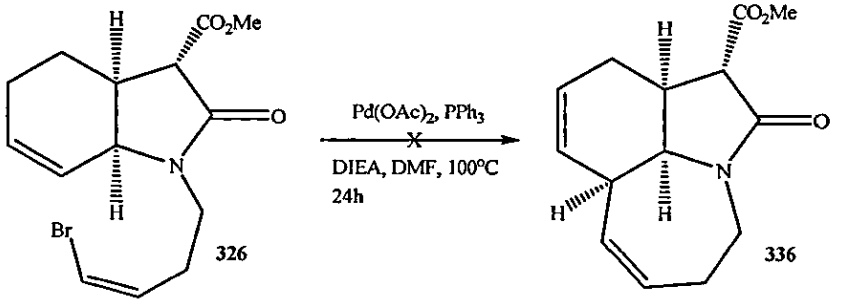
Scheme 154: General Heck Reaction.[54]

Due to the problems encountered in the synthesis of the bromo amine only a small amount was furnished for the amide coupling. Due to this the Heck reaction was only attempted twice.



Scheme 155: Intramolecular Heck reaction.

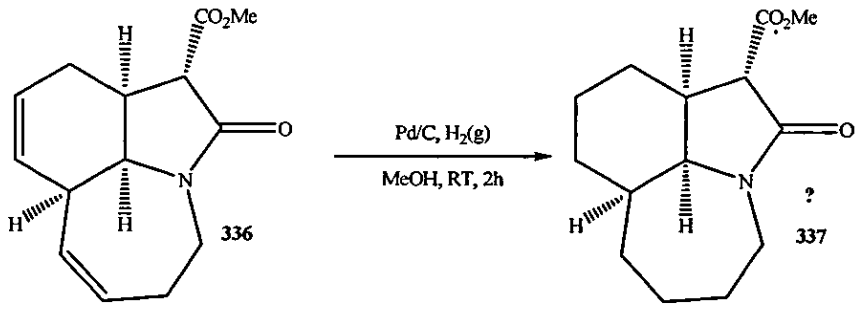
The reaction was stirred for 12h at 100°C in DMF with palladium acetate and triphenyl phosphine, on work up of the reaction approximately 50% of the starting material was isolated, the remaining material could not be accounted for. The reaction was repeated again the time the reaction was stirred for 24 hours.



Scheme 156: Intramolecular Heck reaction.

Again it was difficult to determine what was occurring in the reaction, starting material was again isolated but another compound was isolated from the mixture. Removing the DMF was difficult which was swamping the ^{1}H NMR, TLC analysis was also difficult as in polar solvents the compound did not elute from the base line.

A hydrogenation reaction was carried out on the product from the reaction in the hope that this would simplify the structure making assignment easier.



Scheme 157: Catalytic hydrogenation.

Unfortunately it appeared that the structure was lost in these conditions and no structure resembling that of **337** was isolated. With these disappointing results we turned our attention to the synthesis of γ-lycorane, a pentacyclic alkaloid and a member of the lycorine type alkaloids.

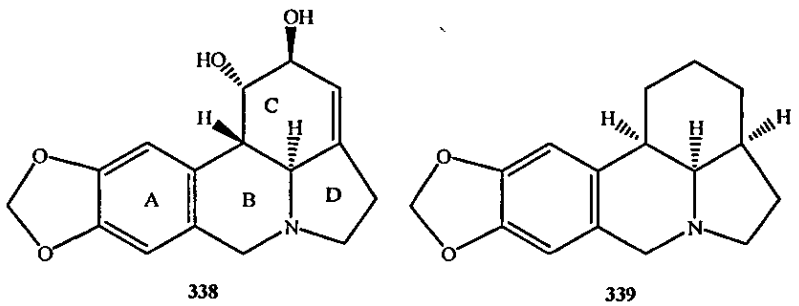


Figure 32: Lycorine (**338**) and γ-lycorane (**339**).

Chapter 5 Lycorines- An Introduction

The alkaloids of the *Amaryllidaceae* family are composed of over 100 architecturally interesting natural bases and have been classified into various skeletally homogeneous sub-groups.[55]

The lycorine type alkaloids; characterised by the presence of the galanthan ring system, constitutes one of the eight classes within this large family of natural products and has captured interest among a number of synthetic groups as targets for total synthesis.[55, 56]

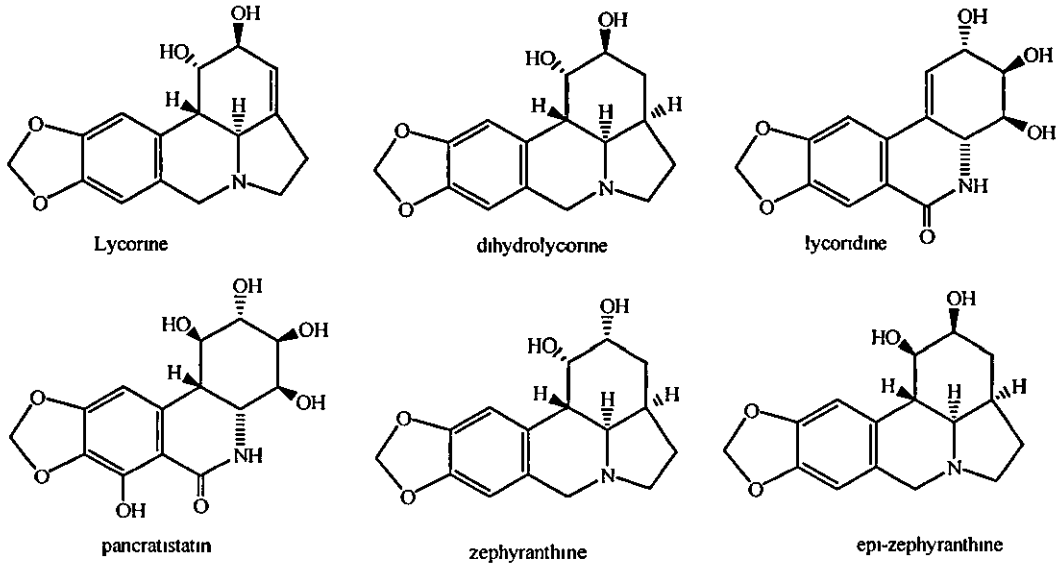
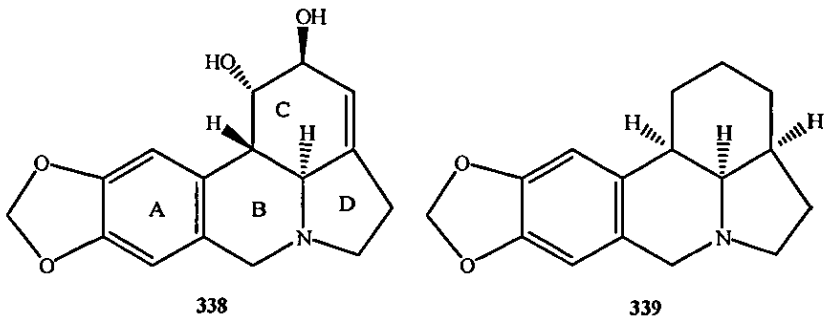


Figure 33: The lycorine type alkaloids

The lycorine type alkaloids display useful biological properties including antiviral, insect anti-feedant and antineoplastic activity.[55] Lycorine was first isolated in 1877 and has shown to be a powerful inhibitor of growth and cell division in higher plants [56] The structure of lycorine **338** (figure 34) was established by Uyeo and Wildman in 1955.[56]



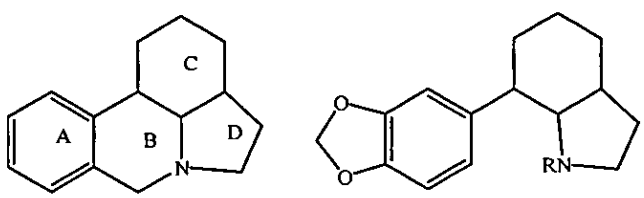
338 339

Figure 34: Lycorine **338** and lycorane **339**.

5.1 Syntheses of lycorane

There have been many syntheses of lycorane over the years, ranging from radical based stategies through to intramolecular Diels-Alder, palladium mediated and photochemical based routes. Of the various syntheses of the core structure of the lycorine alkaloids the Diels-Alder cycloaddition has played a key role in the preparation of the C-ring of these natural products.[55]

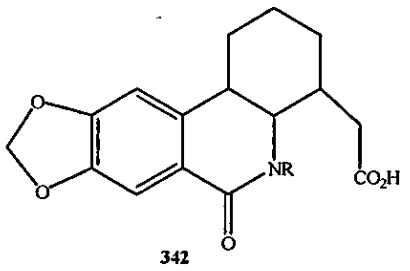
Among the numerous strategies used for constructing the pentacyclic structure, closure of the B-ring at a late stage in the synthesis is a historically important method, as shown by Banwell *et al.*[59, 60]



340 341

Figure 35: B-ring closure.[59]

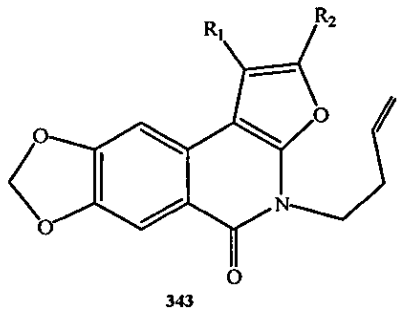
Late stage formation of the D-ring using phenanthridinone derivatives has also been shown by Uyeo *et al.*[59]



342

Figure 36: D-ring closure.[59]

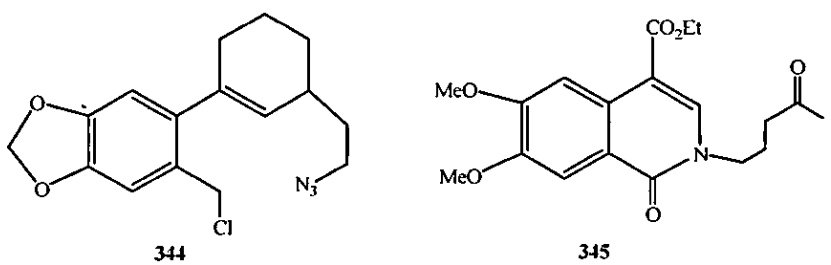
The simultaneous formation of two rings, C and D has been demonstrated effectively by the intramolecular Diels-Alder reaction. Padwa *et al* utilised this method in his approach to lycorane and has also shown its versatility in his synthesis of stenine.[55, 56, 59]



343

Figure 37: C and D-ring closure.[55, 56, 59]

Multiple ring closure using tandem reactions using substrates such as the azide **344** shown by Pearson's *et al* and the isocarbostyril **345** have been reported.[59, 60]



344 345

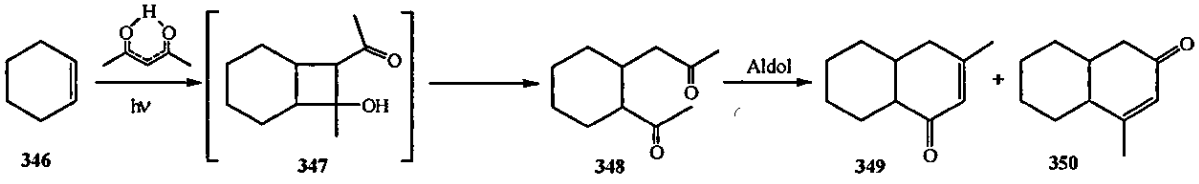
Figure 38: Multiple ring cloure.[59]

Approaches to B-ring construction using radical and photochemical cyclisations have been also described.[59]

5.2 Syntheses of the galanthan core

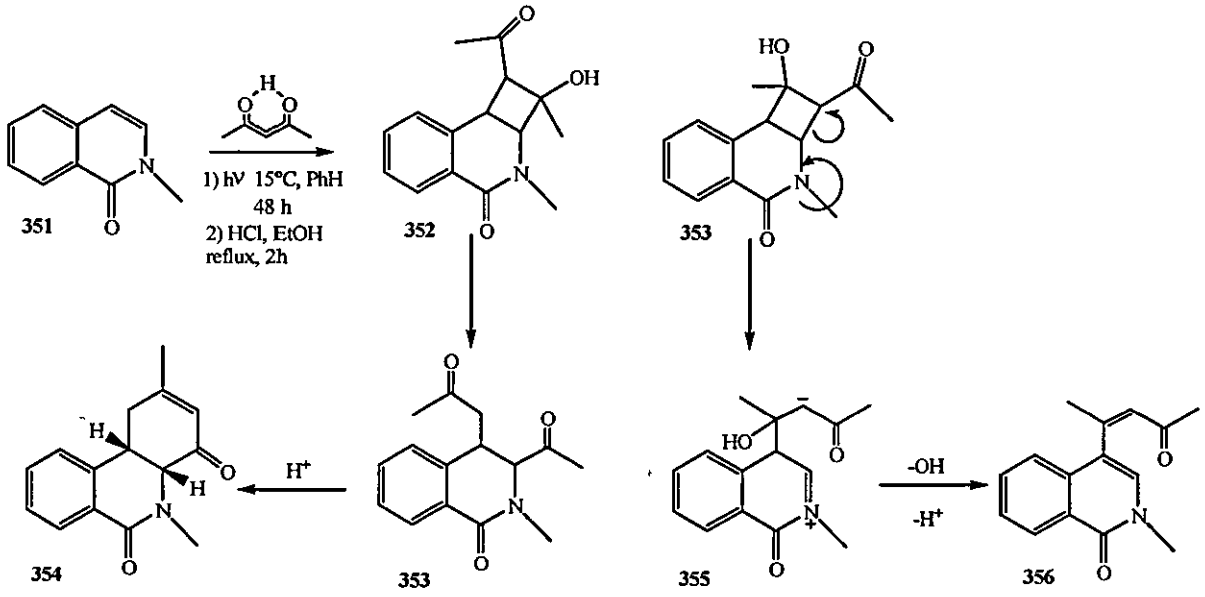
Minter and Winslow reported a strategy to the galanthan core where the key step was an unusual intramolecular de Mayo reaction using an isocarbostyril substrate with a functionalised tether on nitrogen.[59]

The de Mayo reaction involves a [2+2] photocycloaddition of the alkene **346** to the H-bonded enol tautomer of a β-dicarbonyl compound. The resulting cyclobutanol **347** ring opens spontaneously to a δ-dicarbonyl product which cyclises under aldol conditions to give cyclohexenones.[59]



Scheme 158: Minter and Winslow's synthesis of the galanthan core.[59]

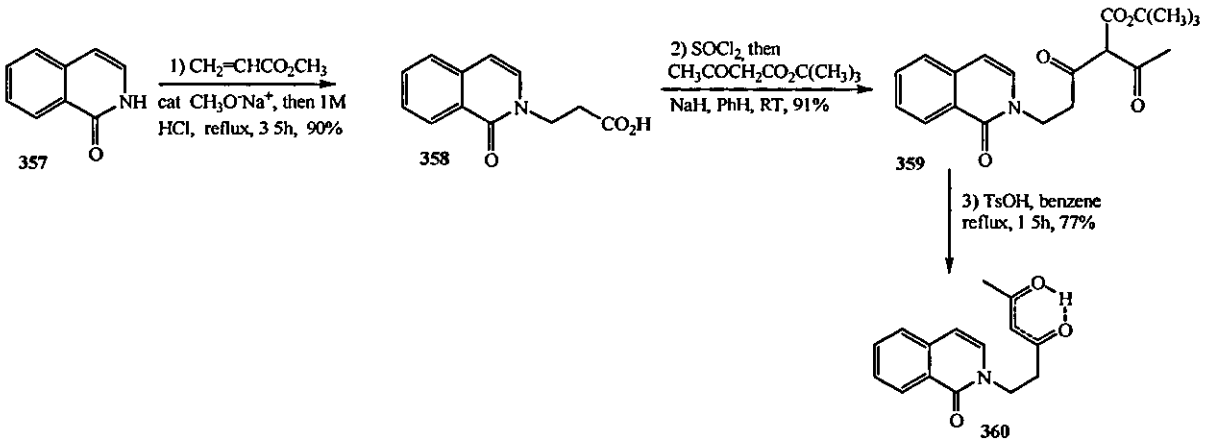
The isocarbostyril **351** was evaluated as a possible de Mayo substrate as a route using an isocarbostyril had not yet been reported. The substrate **351** was irradiated with an excess of 2,4-pentanedione and the resulting ketones were treated with alcoholic HCl under aldol conditions. The two major products **354** and **356** were isolated in 38 and 46% yields respectively.[59]



Scheme 159: Minter and Winslow's synthesis of the galanthan core.[59]

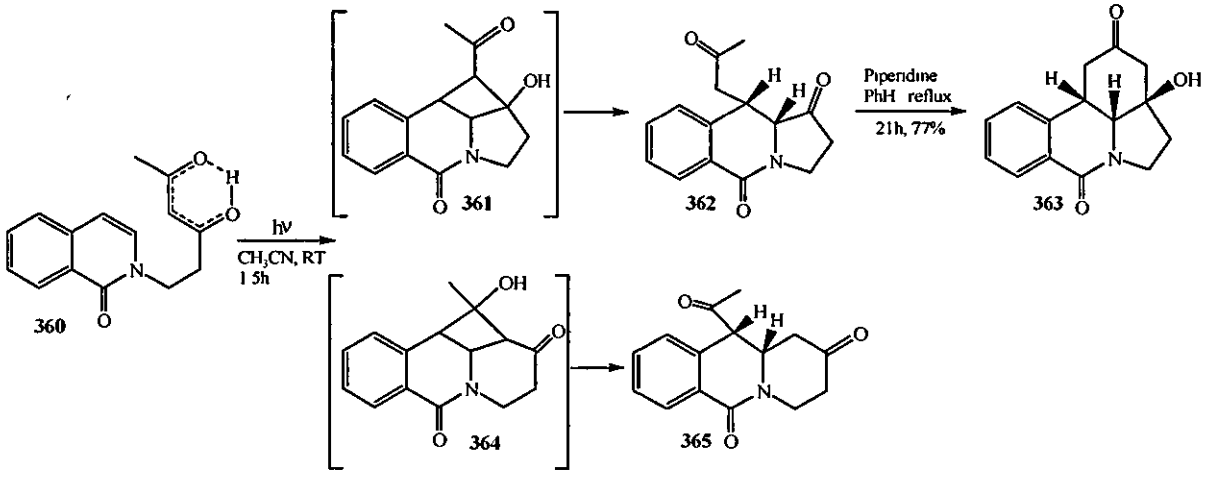
The ketone **354** is one of two possible products of the photoannelation occurring from a "head-to-tail" approach of the enol to **351** and subsequent aldol condensation. Ketone **356** is not an annelation product, resulting from the reversal of the regiochemistry in the photocycloaddition step.[59]

By incorporating a β-diketone into the six carbon tether on nitrogen, the isocarbostyril **360** becomes a precursor to the basic galanthan skeleton.[3] Substrate **360** was synthesised firstly by Michael addition of the isocarbostyril anion with methyl acrylate followed by hydrolysis of the resulting ester, to afford **358** in a 90% yield. The acid chloride of **358** was then used to acylate sodium-*tert*-butyl acetoacetate; furnishing **359** in an excellent yield. The synthesis was complete *via* cleavage of the ester then decarboxylation giving **360** in an overall 63% yield.[59]



Scheme 160: Minter and Winslow's synthesis of the galanthan core.[59]

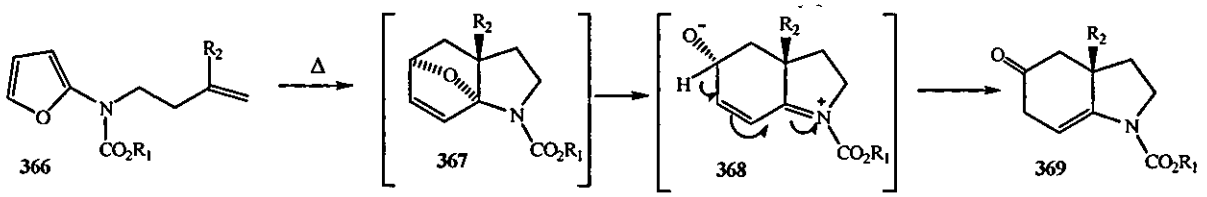
Irradiation of **360** in acetonitrile for 1.5 hours gave the single product **362** in >70% yield, ring closure of **362** to give the galanthan derivative **363** was carried out in basic conditions with piperidine in benzene at reflux. This afforded **363** in a 77% yield as a single diastereoisomer, overall the synthesis was complete in a 35% yield in a 5 step sequence which provided an alternative route to the tetracyclic core found in these alkaloids.[59]



Scheme 161: Minter and Winslow's synthesis of the galanthan core [59]

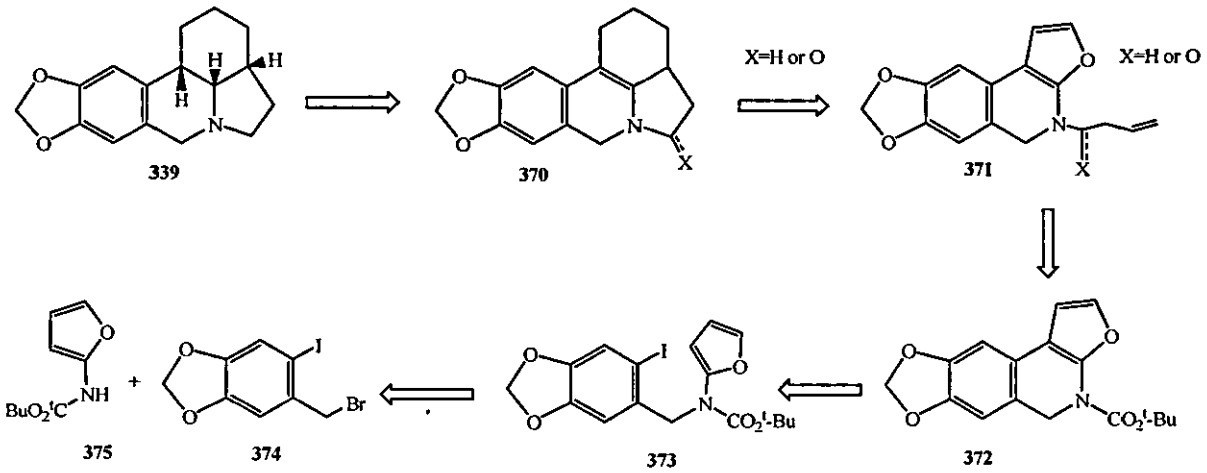
5.3 Syntheses of (±)-γ-lycorane

Padwa *et al* showed how the application of the Diels-Alder reaction could be used in the synthesis of stenine and has also applied it to the total synthesis of (±)-γ-lycorane and (±)-1-deoxylycorine *via* a [4+2] cycloaddition/rearrangement of furanyl carbamates [56]



Scheme 162: Padwa's synthesis of (±)-γ-lycorane.[56]

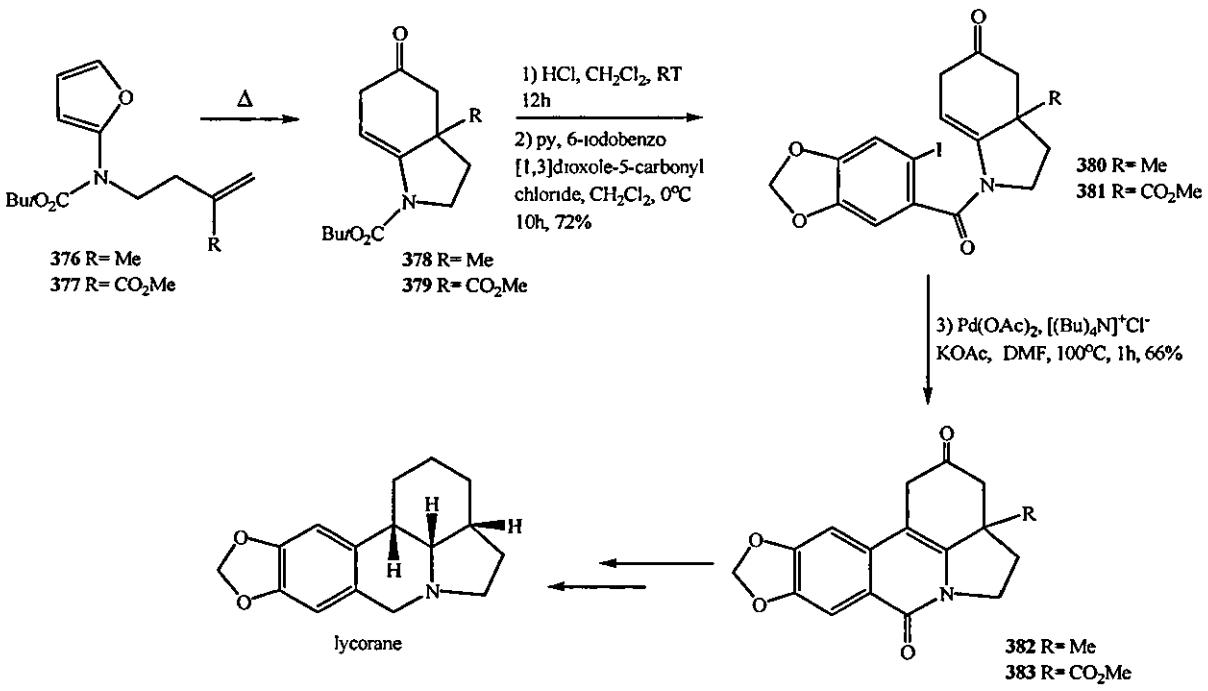
Heterocycles, such as the furan ring have shown the ability to undergo Diels-Alder reactions.[57] They found that the [4+2] adduct from the IMDAF of **366** underwent a nitrogen assisted ring opening followed by the subsequent hydrogen shift gave the hexahydroindole ring system **369**.[56]



Scheme 163: Padwa's retrosynthetic route to (±)-γ-lycorane.[56]

The furanyl carbamate **372** was prepared in a good yield (75%) by treating carbamate **375** with the iodo-substituted benzyl bromide **374** in the presence of base. Heck cyclisation of the resulting aryl iodide **373** occurred smoothly and **372** was afforded in a 75% yield However all attempts to convert **372** to **371** failed.[56]

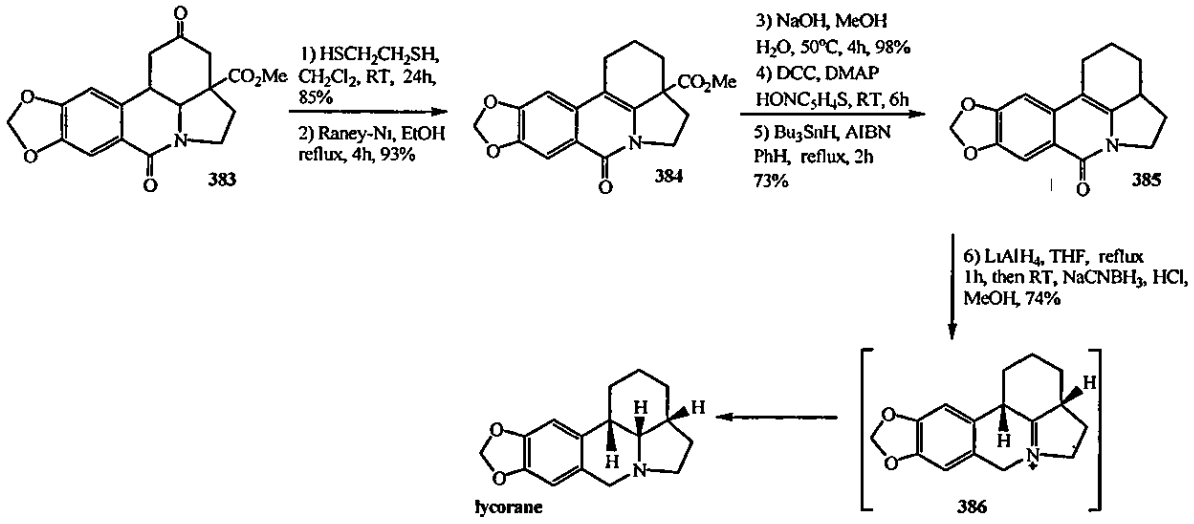
Due to the failure to isolate **357** using the previous conditions, the synthesis was approached *via* an alternative strategy. Their attentions turned to a Pd(0) catalysed cyclisation of an iodo-aryl amide which would become the key B-ring assembly step



Scheme 164: Padwa's synthesis of (±)-γ-lycorane.[56]

The desired hexahydroindolinone **378** was isolated on thermolysis of **376**. It was subsequently hydrolysed under acidic conditions to afford the desired imine, which was converted to the desired enamide **380** isolated in 72% overall yield. Using the Rigby protocol, **380** was treated with the Jeffrey palladium catalyst and **382** was exclusively isolated as the sole *endo* product in 66% yield. The synthesis of lycorane from **383** was complete by conversion to its thioketal derivative; then subsequent reduction using Raney-nickel afforded **384** in an overall 78% yield.[56]

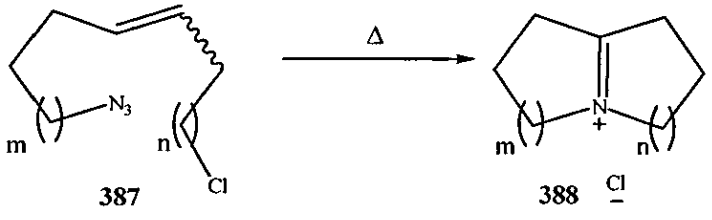
The initial studies were carried out using the substrate where R was a methyl group, once successful the *endo*-selective cyclisation was applied to the more functionalised hexahydroindolinone where R was the methyl ester group (**381**) [56]



Scheme 165: Padwa's synthesis of (±)-γ-lycorane.[56]

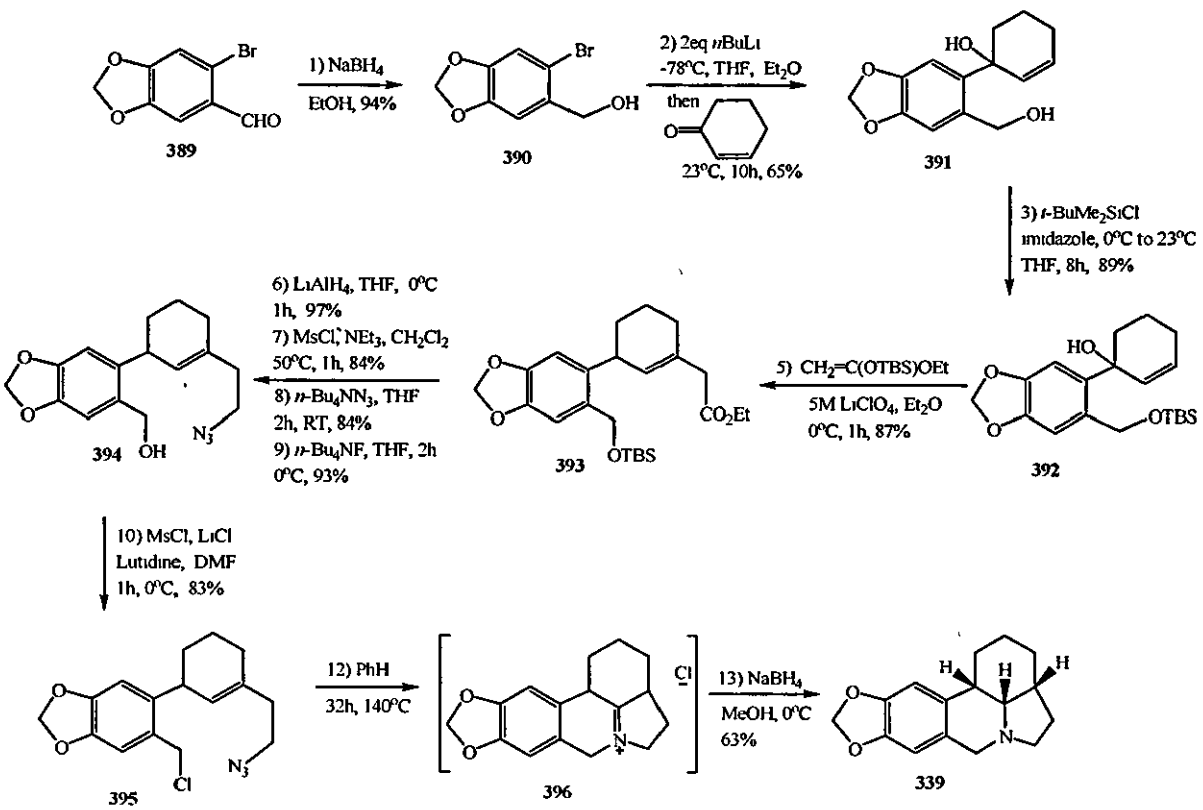
The substrate was then hydrolysed to the carboxylic acid which was subsequently decarboxylated using a modification of the Barton-McCombie deoxygenation.[58] This was achieved by converting the acid to the corresponding thione ester *via* a DCC/DMAP coupling. The ester was then heated followed by addition of AIBN affording **385** in a 71% overall yield. One of the main difficulties encountered in the synthesis was controlling the stereochemistry at the B, C ring juncture, initial hydrogenation conditions of the enamide bond only produced low yields. Therefore the amido carbonyl group was reduced first then subsequent reduction of the enamine followed affording (±)-γ-lycorane in a high 74% yield.[56]

Pearson *et al* described a racemic synthesis of γ-lycorane by an intramolecular cycloaddition of an azide with a ω-chloroalkene. They had already described a method for the generation of bycyclic iminium ions (**388**) in a one pot operation from azides (**387**) shown in scheme 165.[60]



Scheme 166: Pearson's synthesis of lycorane.[60]

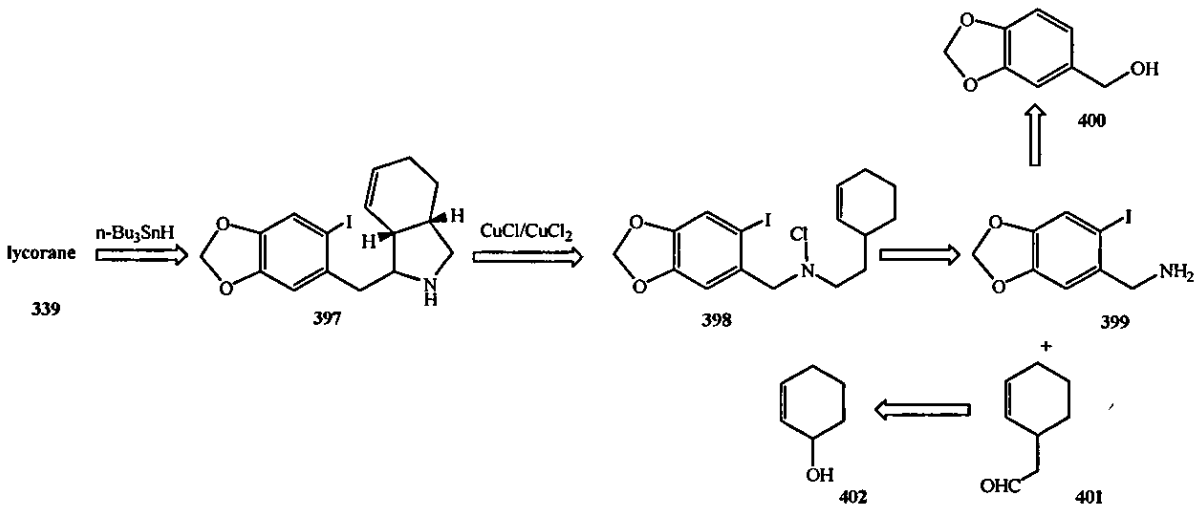
Reduction of the bromopiperonal **389** afforded the alcohol **390** which was converted to the dianion then quenched with 2-cyclohexen-1-one. The diol **391** was then silylated to yield **392**; initially the transformation of **392** to **393** was envisaged by a Claisen rearrangement or a Pd catalysed akylation with an appropriate carbon nuceleophile Both methods were successful however they gave poor yields. Following the work of Grieco, **391** could be ionised to an allylic carbocation in the presence of a soft nucleophile and could maybe furnish the desired product. Lithuim perchlorate promoted the substitution of **392** with a silyl ketene acetal furnishing **393** in a good yield.[60]



Scheme 167: Pearson's synthesis of lycorane.[60]

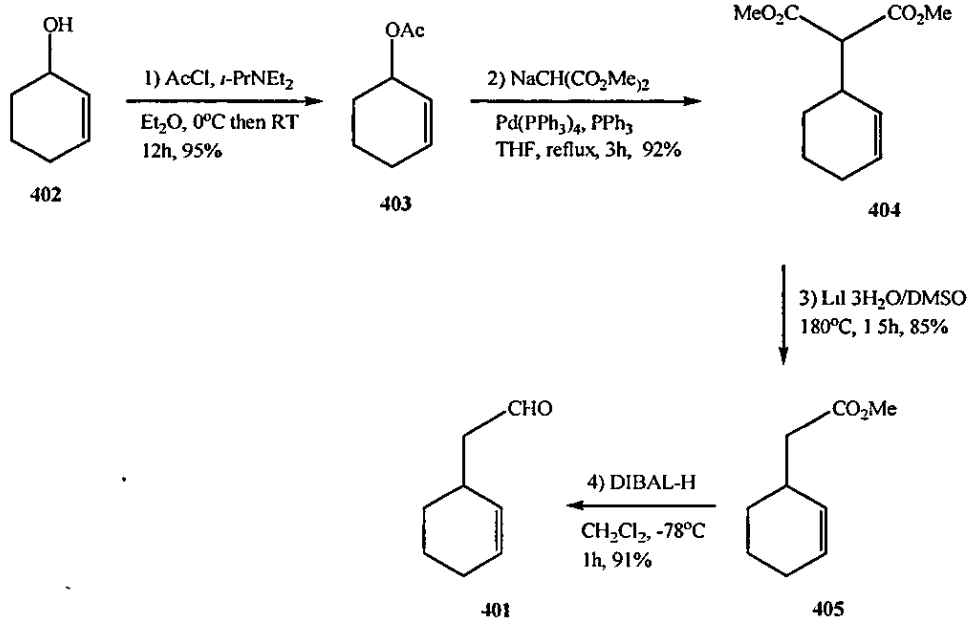
Reduction of **393** then mesylation of the alcohol, subsequent displacement with azide and desilylation gave **394**. Conversion to the desired chloroazide was then carried out; heating of **395** in a sealed tube gave the iminium ion **396** which was reduced using sodium borohydride to furnish (±)-γ-lycorane in a 63% yield as a single diastereoismer.[60]

Cossy *et al* reported that the D and B rings of (±)-γ-lycorane could be achieved by using two consecutive radical cyclisations as the key steps.[7]



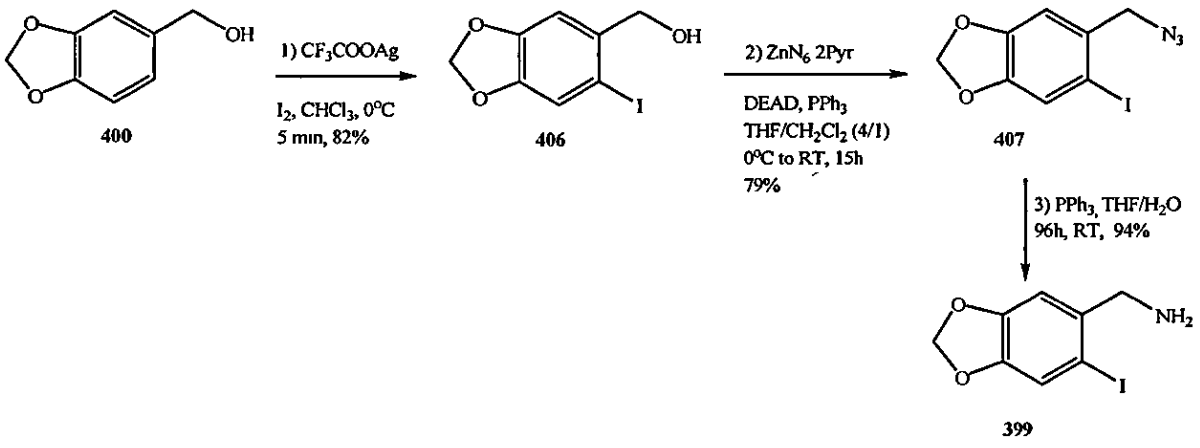
Scheme 168: Cossy's retrosynthetic route to γ-lycorane.[61]

The precursor **397** of (±)-γ-lycorane was synthesised in a convergent manner from cyclohexen-2-ol **402** and piperonol **400**. Cyclohexen-2-ol was converted into the corresponding acetate using AcCl and Hunig's base, which was then transformed into a diester. The diester was then decarboxylated and the unsaturated ester was then reduced to the aldehyde **401**.



Scheme 169: Cossy's synthesis of γ-lycorane.[61]

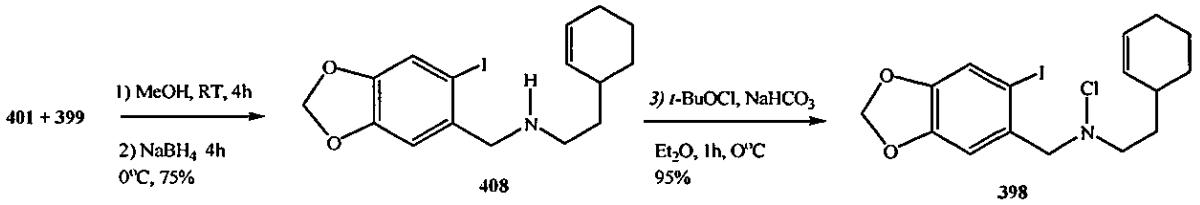
The iodoamine **399** was synthesised from piperonyl alcohol **400**, the iodination was achieved with I_2 in the presence of silver trifluoroacetate in chloroform. A Mitsunobu reaction was subsequently performed producing the corresponding azide which on reduction using Staudinger conditions the amine **399** was isolated in a high 94% yield.[61]



400 406 407 399

Scheme 170: Synthesis of 6-iodo-benzo[1,3]dioxol-5-yl-methylamine.[61]

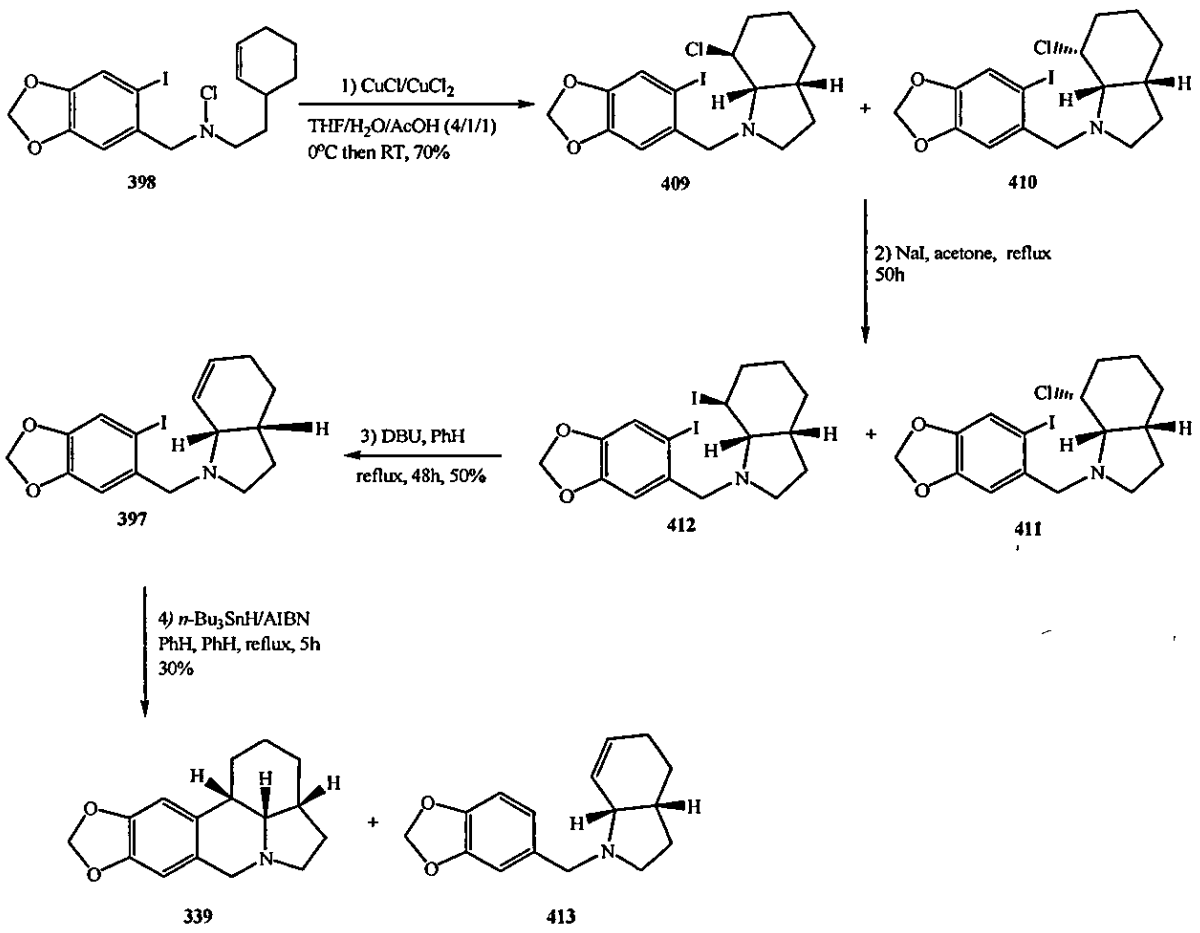
The coupling product **408** was achieved by reductive amination of **401** by **399** using $NaBH_4$ in MeOH which was then subsequently chlorinated using *t*-BuOCl in the presence of $NaHCO_3$ affording the chlorinated product **398** in a 95% yield.[61]



408 398

Scheme 171: Cossy's synthesis of γ-lycorane.[61]

The D ring of the (±)-γ-lycorane was produced *via* the formation of an aminyl radical which attacked the olefinic system according to a 5-*exo*-trig process to give two inseparable isomeric products **409** and **410** obtained in a 60/40 ratio in a 70% yield. Formation of the B ring from intermediates **409** and **410** using different conditions did not produce (±)-γ-lycorane.

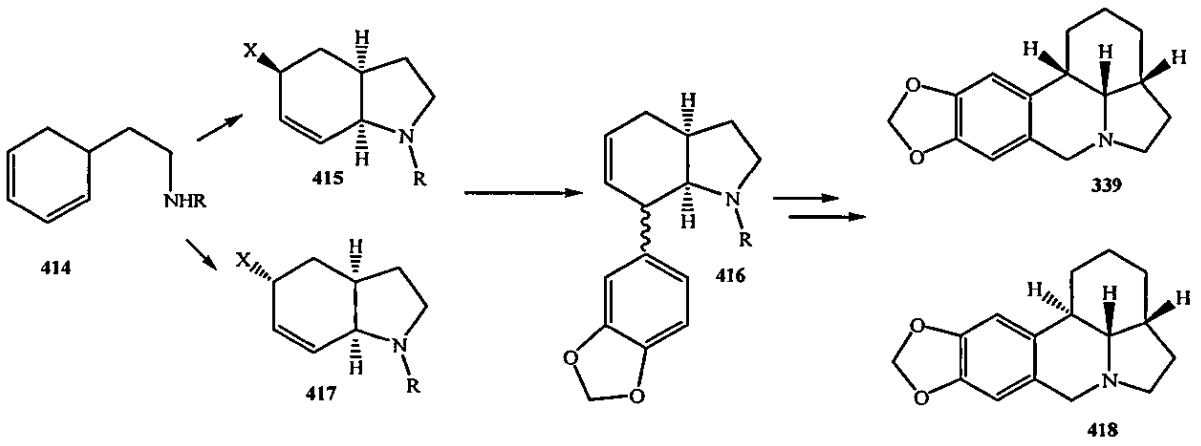


Scheme 172: Cossy's synthesis of γ-lycorane.[61]

It was decided to attempt a second radical cyclisation *via* a halogen exchange reaction as the treatment of **411** and **412** with various bases did not yield the unsaturated product **397**. Treatment of **409** and **410** with NaI in acetone allowed a stereoselective halogen exchange because **412** was the only iodo compound formed The iodoinated compound **412** was treated with DBU and the unsaturated **397** was isolated in 50% overall yield from **409**, 25% of **410** was also recovered. Treatment of **397** with *n*-Bu_3SnH in the presence of AIBN furnished (±)-γ-lycorane **339** in 30% and the dehalogenated product **413** in 25% yield.[61]

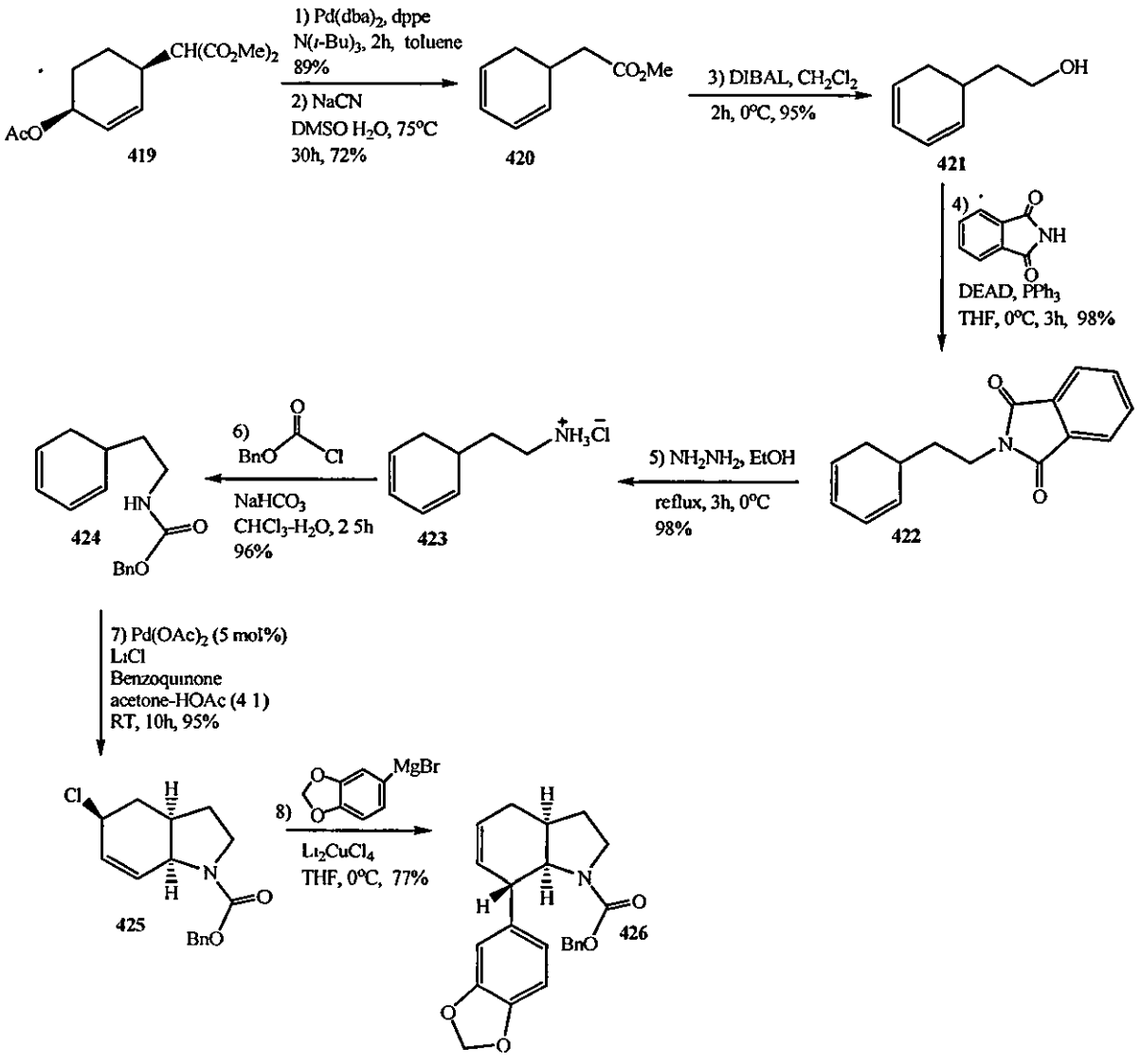
The synthesis of (±)-γ-lycorane was achieved in 10 steps from piperonyl alcohol by using two consecutive radical cyclisations that allow the formation of the D and B rings of this alkaloid.[61]

Bäckwall *et al.* described an elegant synthesis of (±)-α-lycorane and (±)-γ-lycorane *via* a stereocontrolled organopalladium route. Bäckwall had already developed a Pd catalysed intramolecular 1,4-addition to cyclic dienes **414** using amides as nuceleophiles, yielding hexahydroindoles **415** and **417**. Then the use of a S_N2' displacement of the allylic leaving group X by the appropriate aryl group would provide the useful intermediate **416** for further manipulation to access both α and γ-lycorane.[62]



Scheme 173: Backwall's proposed synthetic route to (±)-α-lycorane and (±)-γ-lycorane.[62]

The intermediate **416** could then be cyclised *via* a Bischler-Napieralski reaction Reduction of the diene ester **420** with DIBAL afforded the alcohol **421** where a Mitsunobu reaction was then carried out giving the phthalimide **422** in 98% yield. Cleavage of the phthalimide was carried out using hydrazine hydrate giving the hydrochloride **423**, which on treatment with bezyl chloroformate and $NaHCO_3$ afforded the carbamate **424** in a 96% yield. Palladium catalysed 1,4-chloroamidation of **424** proceeded smoothly with high regio- and stereoselectivity to give the chlorocarbamate **425**. The next step required the 3,4-(methylenedioxy)phenyl group should be introduced *via* γ-attack They found that Li_2CuCl_4 in combination with a slow addition of the Grignard reagent favoured γ-attack and **426** was isolated in a 77% yield.[62]

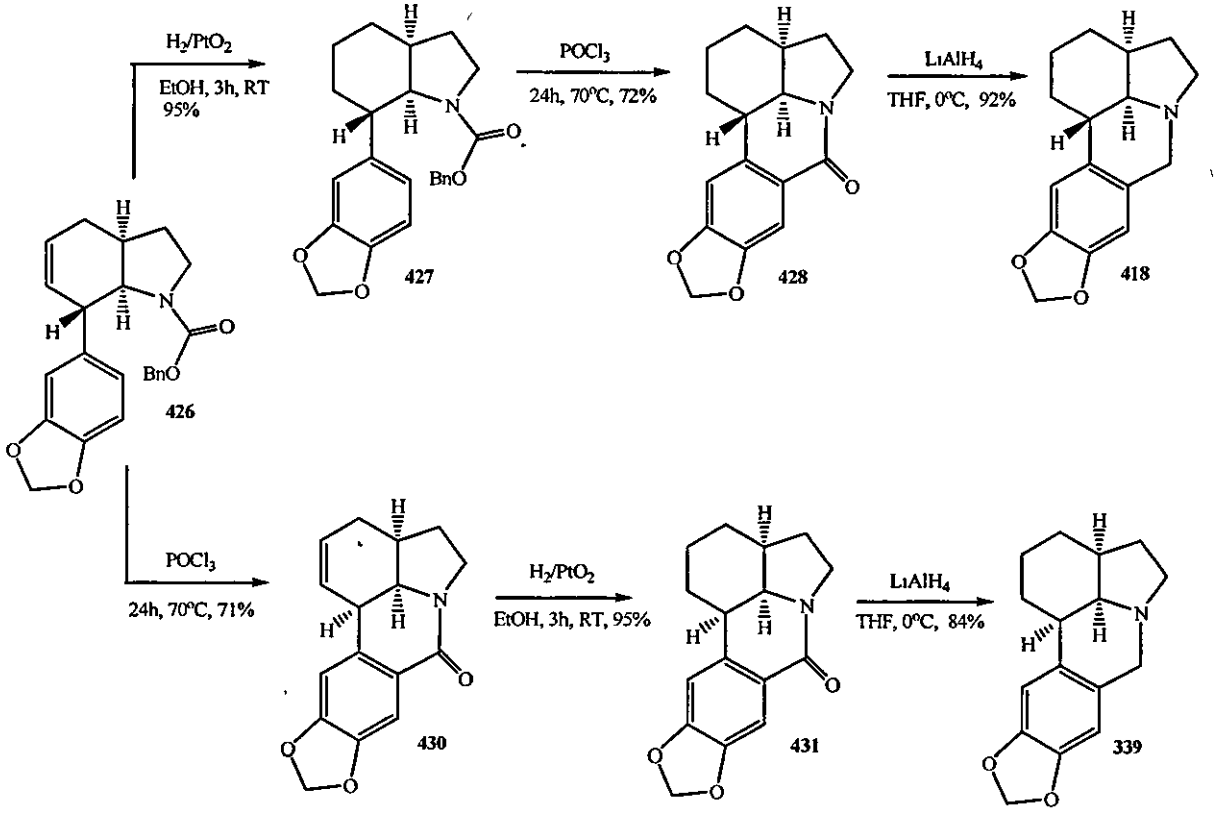


Scheme 174: Bäckwall's synthetic route to (±)-α-lycorane and (±)-γ-lycorane.[62]

The double bond in **426** was selectively hydrogenated without cleavage of the benzyloxy bond by using PtO_2 giving **427**. Subsequent cyclisation to **428** followed using a Bischler-Napieralski type cyclisation in a 72% yield, this was further transformed into α-lycorane *via* a $LiAlH_4$ reduction. It was then discovered that if the order of hydrogenation and cyclisation was reversed a highly stereoselective isomeristion took place in the Bischler-Napieralski cyclisation.[62]

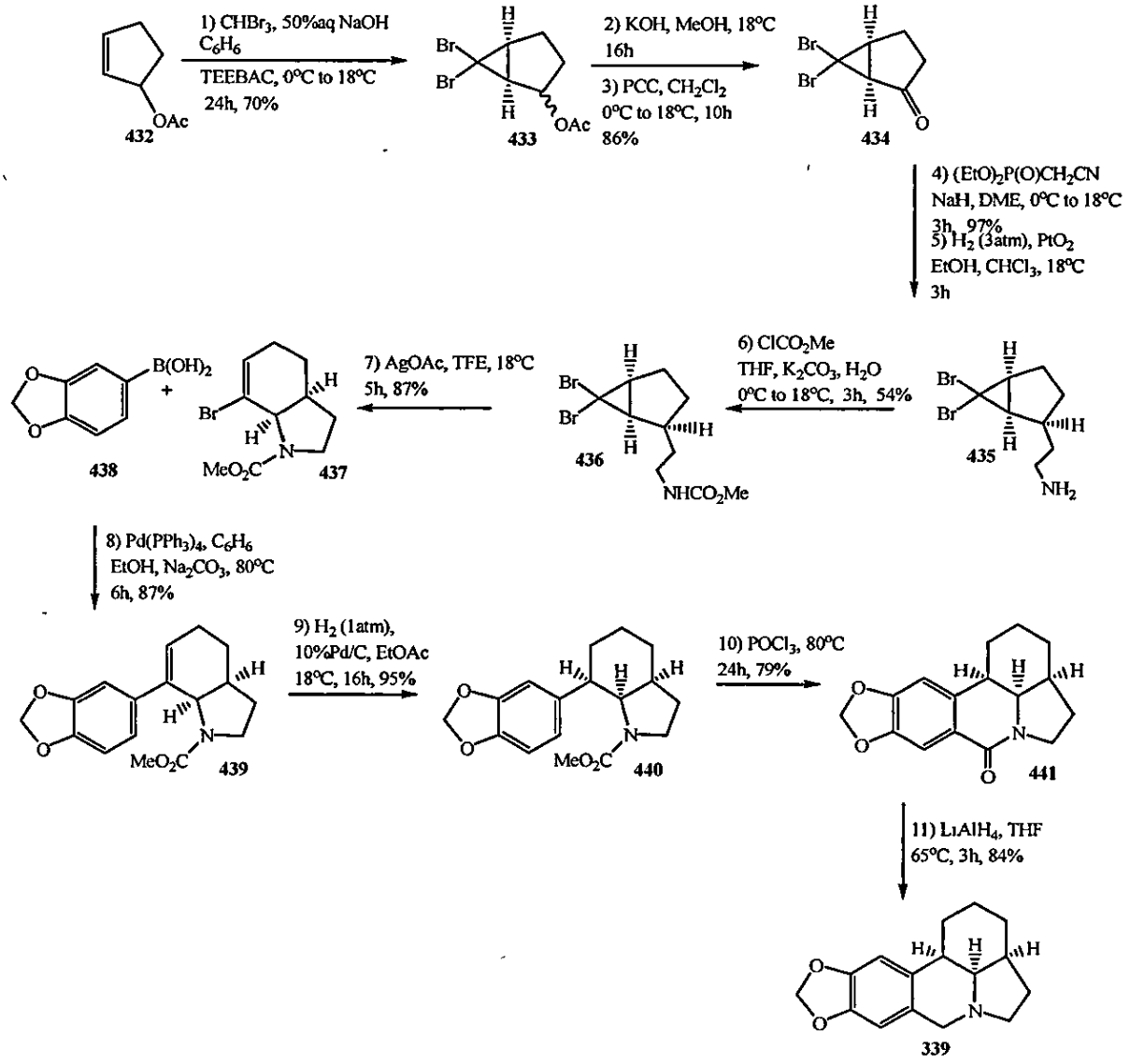
Thus treatment of **426** with $POCl_3$ afforded **430** in a 71 % yield with the transformation to γ-lycorane being achieved in two more steps in an overall 82% yield. Firstly hydrogenation of

the double bond followed by $LiAlH_4$ reduction. The overall yields of (±)-α-lycorane **418** and (±)-γ-lycorane **339** were 40 and 36% resepectively.[62]



Scheme 175: Bäckwall's synthetic route to (±)-α-lycorane and (±)-γ-lycorane.[62]

Wu and Banwell described a short stereoselective total synthesis of (±)-γ-lycorane starting from the allylic acetate in scheme 175. The dibromocarbene addition to the allylic acetate **432** was achieved using Makosa conditions using TEBAC as a phase transfer catalyst This was then converted to its corresponding alcohol and oxidised to the ketone **434** using PCC in an 86% yield. A Wadsworth-Emmons reaction was then performed on **434** giving a mixture of *E*- and *Z*-isomers which were then reduced to afford the amine **435**. Addition of methyl chloroformate gave the corresponding carbamate **436** in a 54% yield. A TFE solution of compound **436** with silver acetate gave hexahydroindole derivative **437** in an 87% yield. A Suzuki cross-coupling between **437** and the boronic acid **438** resulted in the formation of **439** which was then hydrogenated to give the saturated carbamate **440** in a 95% yield.[63]

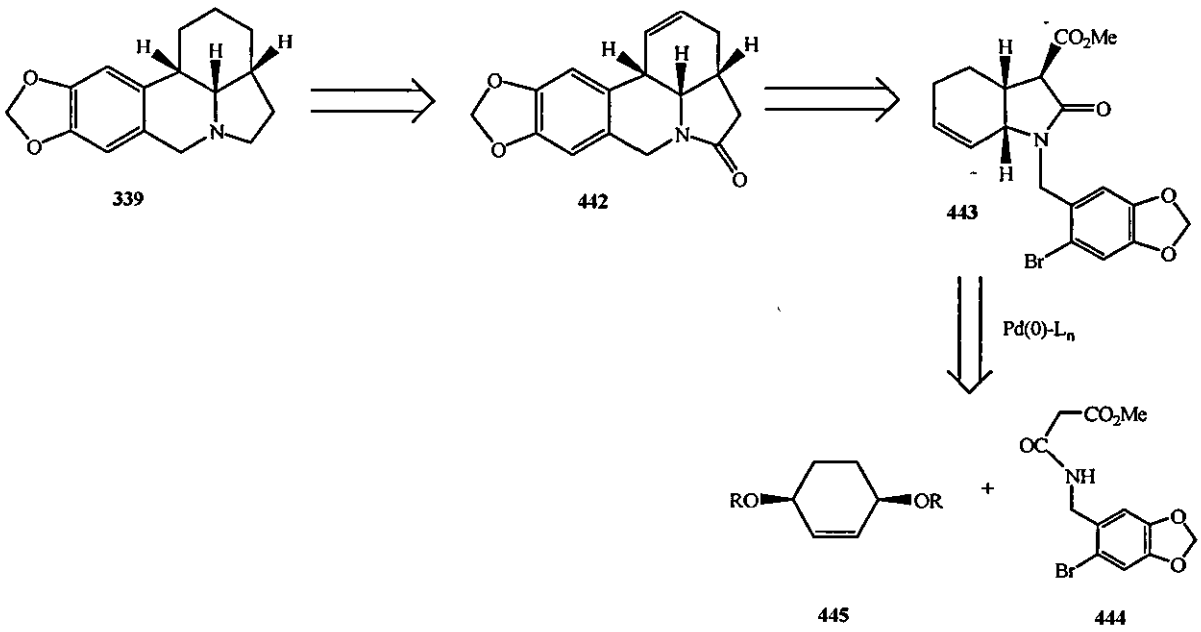


Scheme 176: Wu and Banwell's synthesis of (±)-γ-lycorane. [63]

By utilising a Bischler-Napieralski cyclisation the lactam **441** was established with the correct stereochemistry, which was then reduced using Bäckvall *et al* conditions to give (±)-γ-lycorane **339** in an 84% yield.[62, 63]

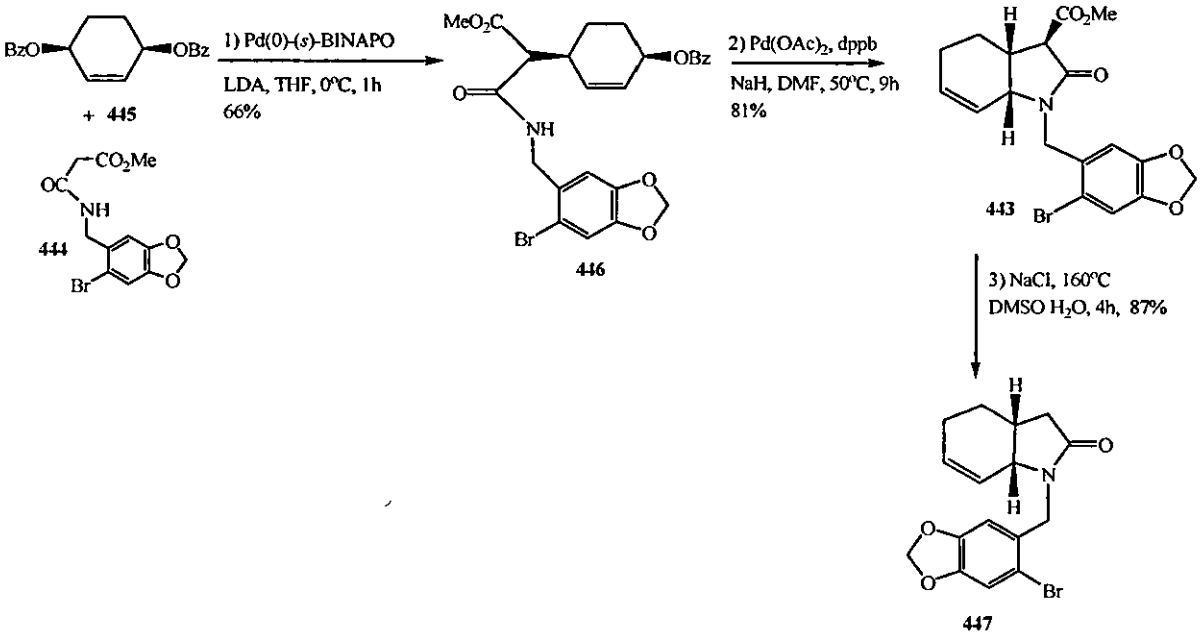
5.4 Asymmetric syntheses of γ-lycorane

Mori *et al* described the first asymmetric route to lycorane **339** using a palladium mediated synthesis. It was envisioned that cyclohexenediol **445** when treated with **444** in the presence of a Pd(0) catalyst with a chiral phosphene ligand would furnish the oxindole substrate **443**. From here the total synthesis of (+)-γ-lycorane could be achieved.[64]



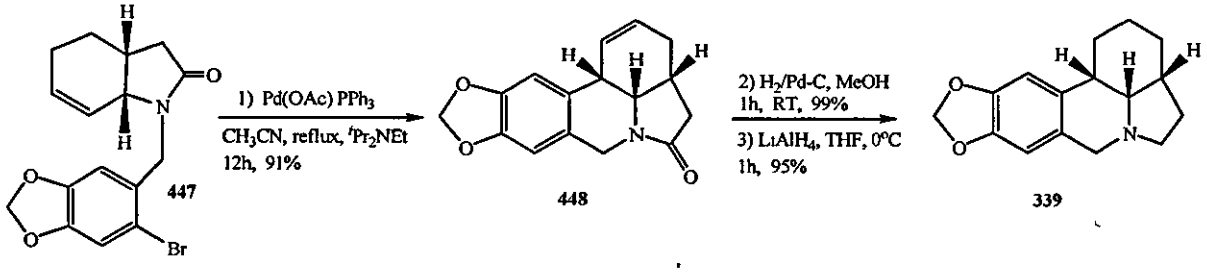
Scheme 177: Mori's retrosynthetic route to (+)-γ-lycorane.[64]

To achieve the total synthesis of optically active γ-lycorane, **444** was reacted with **445** in the presence of $Pd(OAc)_2$ and (*S*)-BINAPO with LDA to afford the monoalkylated product **446** in a 66% yield and a 40% ee. This was subsequently treated with Pd(0) to afford **443** which, using Krapcho conditions, was converted into **447** in an 87% yield.[64]



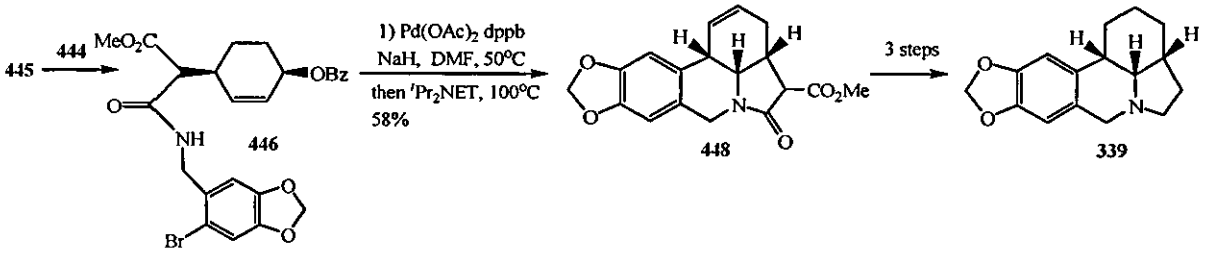
Scheme 178: Mori's asymmetric route to (+)-γ-lycorane [64]

The final phase of the synthesis was then carried out, an intramolecular Heck reaction was then performed using a catalytic amount of $Pd(OAc)_2$ and PPh_3 to give the tetracyclic core **448** in a 91% yield. Subsequent hydrogenation and $LiAlH_4$ reduction of the amido carbonyl gave (+)-γ-lycorane in an overall 17% from **445**.[64]



Scheme 179: Mori's asymmetric route to(+)-γ-lycorane.[10]

Mori also developed a shorter total synthesis of (+)-γ-lycorane *via* a tandem allylic amination-intramolecular Heck reaction. A solution of **446** was warmed with NaH, $Pd(OAc)_2$ and dppb in DMF for 2 hours and then Hunig's base was added. The solution was then warmed for 4 h at 100°C to yield **448** in a 58% yield.[64]



Scheme 180: Mori's asymmetric route to(+)-γ-lycorane.[64]

The remaining three steps had been carried out previously, decarboxymethoxylation, hydrogenation and finally reduction of the carbonyl gave (+)-γ-lycorane **339** in 5 steps in 23% overall yield.[64]

Mori's synthesis was re-visited by Ojima *et al.* very recently, where they improved the synthesis by using their new chiral monodentate phosphoramidite ligands so as to optimize the enantioselectivity and chemical yield.[65]

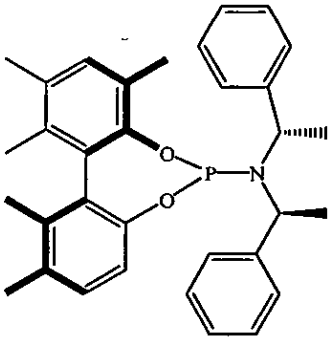
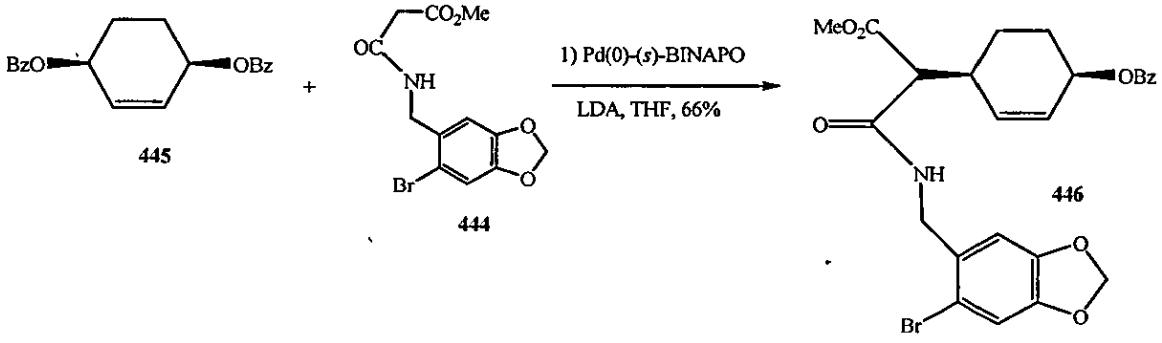


Figure 39: An example of a Phosphoramidite ligand.[65]

In Mori's synthesis the key step in scheme 181, the best enantioselecivity achieved using (*S*)-BINAPO was 54% ee giving **446** in 30% yield using 2.6 equivalents of **444** and LDA. This changed when using 1.1 equivalents of LDA and **444** to a 66% yield and 40% ee.[64, 65]



Scheme 181: Mori's asymmetric route to (+)-γ-lycorane [64, 65]

After screening a library of ligands it was discovered that the best enantioselectivities were achieved using the ligands in figure 40. These non-symmetrical moieties furnished **446** with a 99 7% ee (76% yield, **A**) and 99.4% ee (83% yield, **B**) respectively.[65]

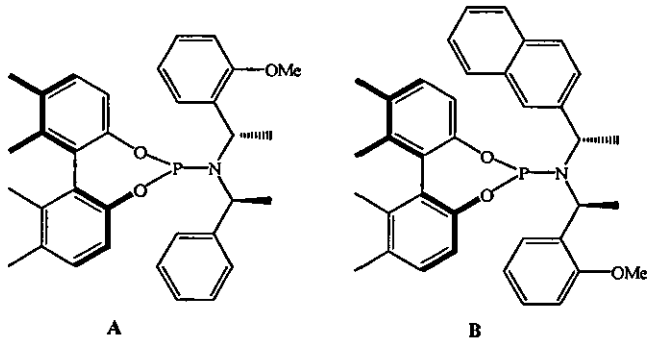
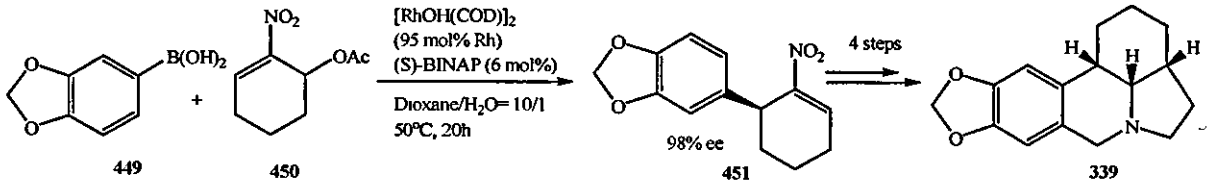


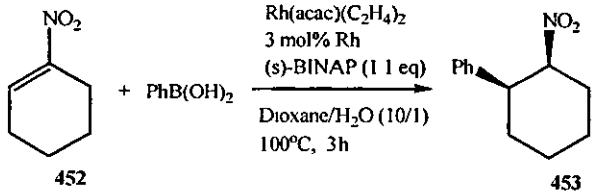
Figure 40: Non-symmetrical Phosphoramidite ligands.[65]

Dong *et al* has described a recent synthesis of (+)-γ-lycorane **339** *via* an asymmetric nitroallylation of an arylboronic acid **449** with nitroallyl acetates **450** using a rhodium catalyst.[66]



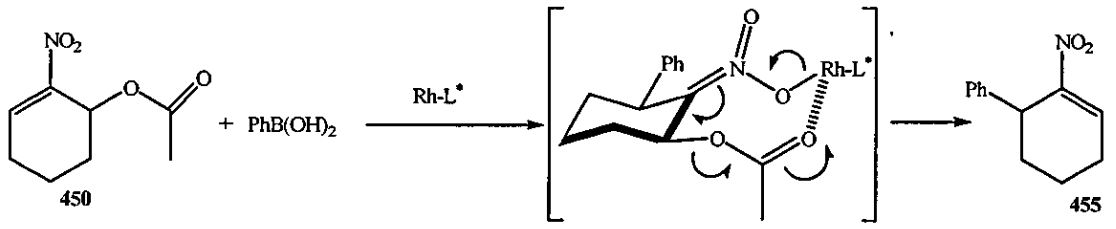
Scheme 182: Dong's asymmetric synthesis of (+)-γ-lycorane.[66]

Hayashi *et al* had reported that the 1,4-addition of 1-nitrocyclohexane **452** with phenylboronic acid in the presence of a rhodium complex of (*S*)-binap gave 2-phenyl-1-nitrocyclohexane **453** in high yield and good enantioselectivity.[66, 67]



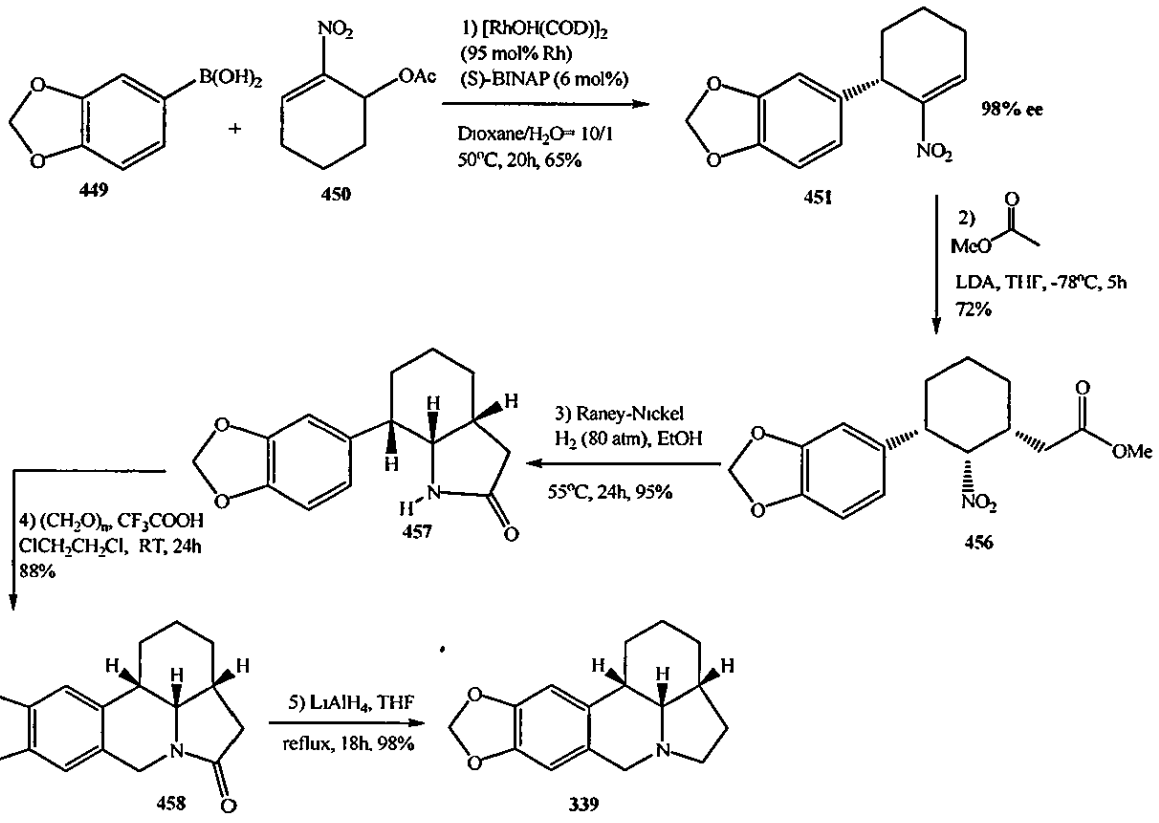
Scheme 183: Dong's asymmetric 1,4-addition.[66, 67]

However it was unclear if having an ester group on the nitrocyclohexene would affect the outcome of the reaction and if the 1,4-addition of the phenylboronic acid would occur with subsequent elimination of the ester group to give **455** shown in scheme 183.[67]



Scheme 184: Dong's 1,4-addition.[66]

The reaction was successful in a 94% ee but only a 30% yield, therefore the conditions were optimised, low temperatures were required as decomposition took place at 100°C. Screening of the transition-metal source showed that $[Rh(OH)(COD)]_2$ and (*R*)- or (*S*)-BINAP catalysed the reaction in a good yield with 97% ee at 50°C. From here they hoped their newly developed nitroallylation of acetic acid 2-nitrocyclohex-2-enyl ester **450** could be used to synthesise (+)-γ-lycorane **339**.[67]

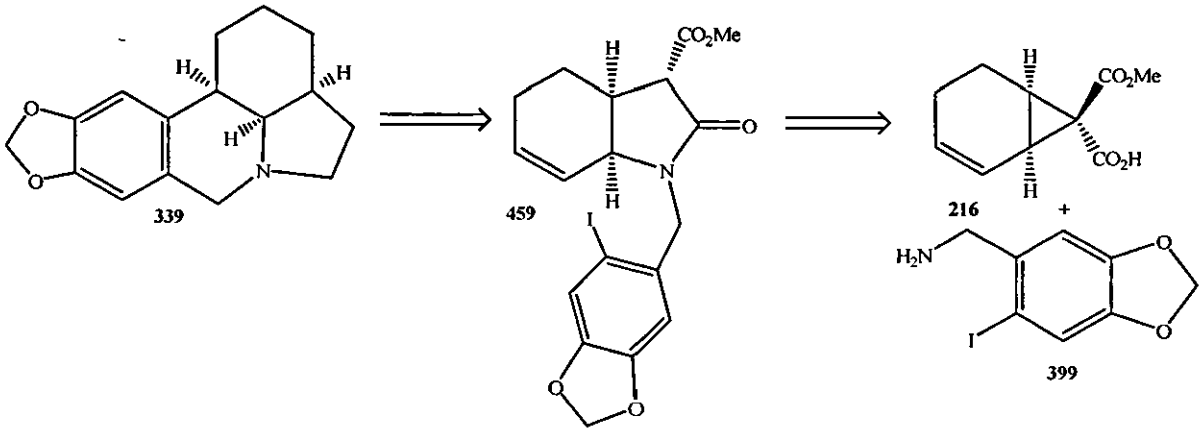


Scheme 185: Dong's asymmetric synthesis of (+)-γ-lycorane.[66]

The nitroallylation of the acetate **450** with **449** in the presence of the rhodium catalyst gave the product **451** in a 65% yield and a 98% ee. Treatment of **451** with LDA and methyl acetate furnished **456** in favour of the *cis,cis*-diastereoisomer in a 7:1 ratio. The chiral ester **456** was then hydrogenated using Raney-nickel which gave the lactam **457** in a 95% yield. This was then ring-closed using a modified Pictet-Spengler reaction affording **458** in an 88% yield. The total synthesis was complete *via* reduction using $LiAlH_4$ giving (+)-γ-lycorane **339** in an overall yield of 38%.[67]

5.5 Retrosynthesis of γ- Lycorane

The route to which the synthesis of γ-lycorane was envisaged utilised the novel Pd(0) catalysed rearrangement which have been established, of the activated amide synthesised from an amide coupling between iodo-amine **399** and the carboxylic acid **216**, followed by an intramolecular Heck reaction of the hydroindole **459**.

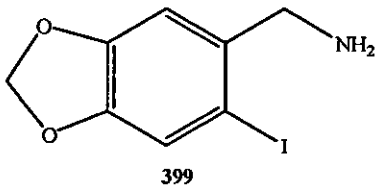


Scheme 186: Proposed retrosynthetic route to γ- Lycorane.

From here removal of the methyl ester, hydrogenation of the alkene double bond and reduction of the amide carbonyl would furnish lycorane in a very short, facile route

5.6 Synthesis of 6-Iodo-benzo[1,3]dioxol-5-yl-methylamine

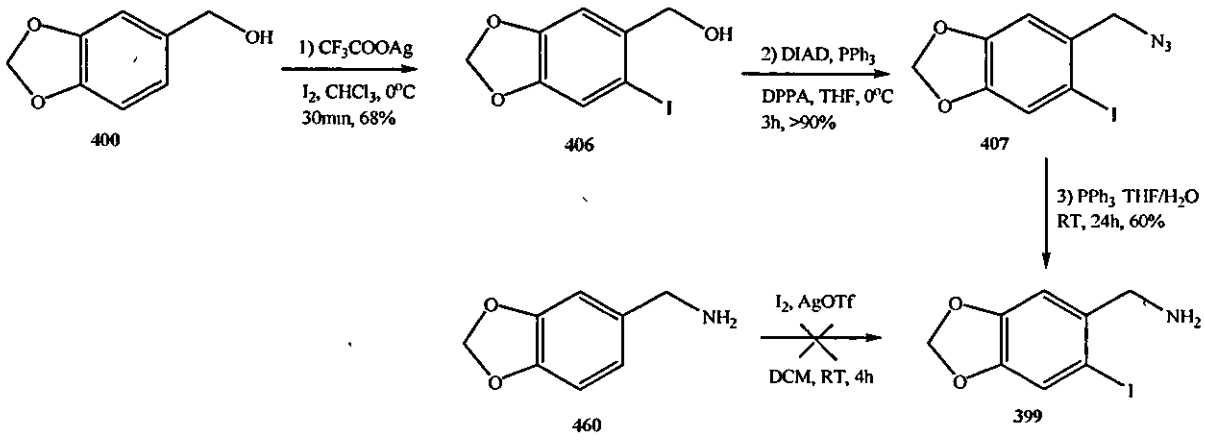
The amine **399** in figure 41 that was required for the total synthesis had been synthesised previously by Cossy *et al.* and was used in their radical mediated total synthesis of γ-lycorane.[61]



399

Figure 41: 6-Iodo-benzo[1,3]dioxol-5-yl-methylamine.[61]

The amine was synthesised in three steps from the commercially available piperonyl alcohol **400**, following the procedure described by Cossy, with a few minor adjustments the amine was synthesised in a reasonable 60% yield.[61]



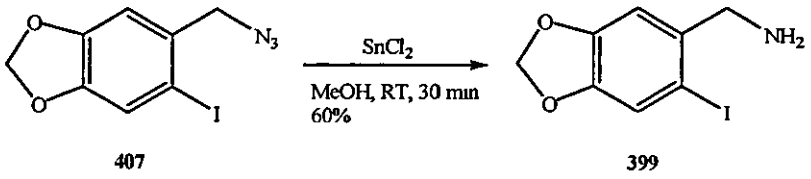
Scheme 187: Synthesis of 6-iodo-benzo[1,3]dioxol-5-yl-methylamine.

Cossy *et al.* reported that the iodination proceeded in 5 minutes with an 82% yield unfortunately this could not be repeated and the greatest yield (68%) was observed after stirring for 30 minutes. The Mitsunobu reaction peroformed on **406** proceeded in 3 hours in an excellent 90% yield, the reduction of the azide **407** using Staudinger conditions was problematic, again Cossy reported a yield of 94% however the highest achieved was 60%.[61]

Purification of the amine was problematic as it was difficult to isolate the amine from the triphenylphosphine oxide produced in the azide reduction. This was achieved by using acidic

silica cartridges where the amine is bound to the column and the excess triphenyl phosphine oxide is washed through. The amine was then eluted from the column using a 2 *M* ammonia in methanol solution.

Reduction of the azide **407** was also performed using $SnCl_2$ affording the amine in a 60% yield, where the isolation of the amine was easier and was achieved by filtering off the $SnCl_2$.



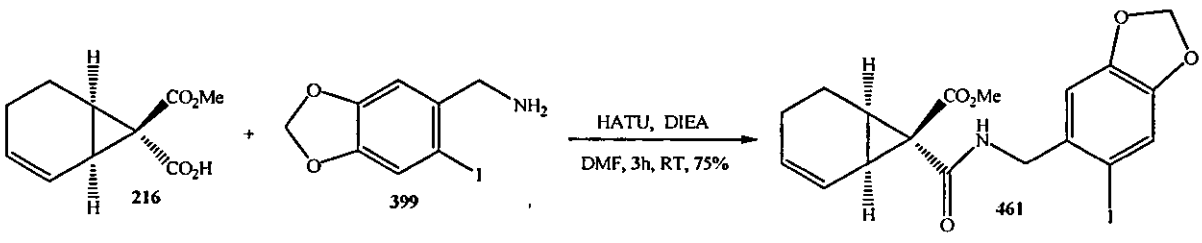
407 **399**

Scheme 188: Azide reduction.

Direct iodination of piperonyl amine **460** was also performed in an attempt to reduce the total number of steps in the synthesis, unfortunately the reaction was unsuccessful.

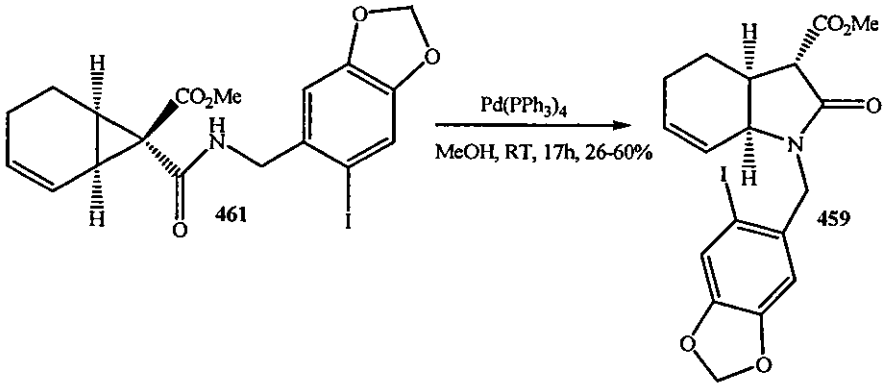
5.7 Synthesis of 7-(1-[6-iodo-benzo[1,3] dioxol-5-yl methyl)-amino]-vinyl)-bicyclo [4.1.0]hept-2-ene-7 carboxylic acid methyl ester

The amide coupling was performed using the standard conditions and we were pleased to isolate the amide **461** in a high 75% yield, again the reaction could be performed on a scale up to 500 mg with reproducible yields.



Scheme 189: Amide coupling.

The rearrangement was then carried out using the standard conditions and the reaction was complete in 17 hours.



Scheme 190: Pd(0) catalysed rearrangement.

Initially the reaction was worrying as it appeared the reaction was dependant on the scale. On a 100mg scale the desired rearranged structure **459** was isolated exclusively, however on scale up to 500mg another rearranged product was observed and isolated in the mixture. The other product was tentatively assigned to have one of the two structures shown in figure 42.

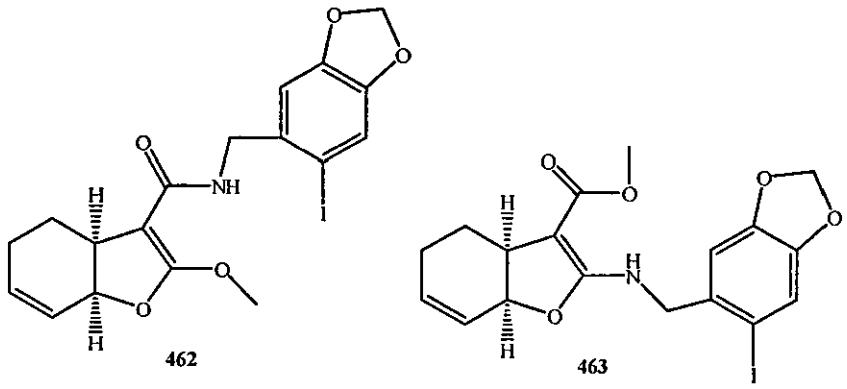
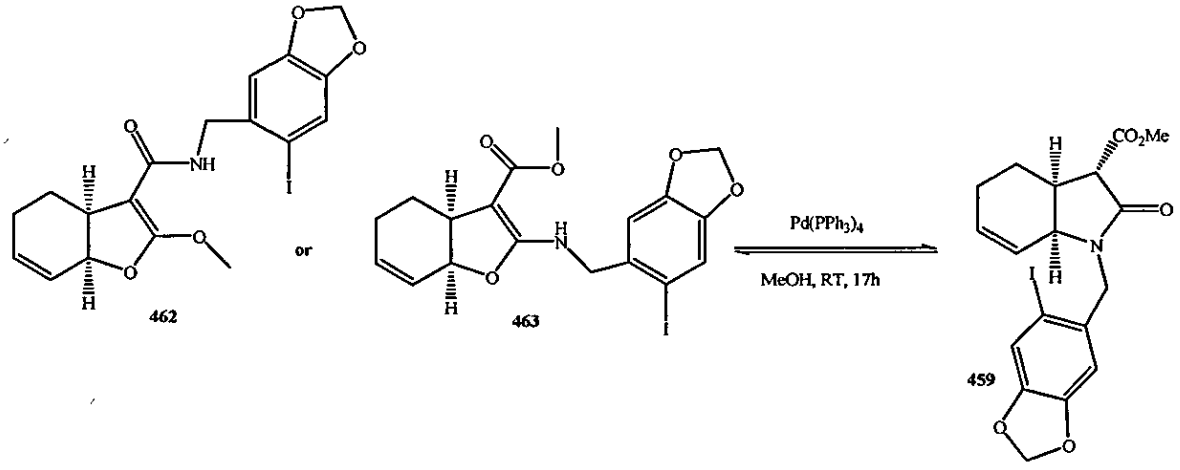


Figure 42: Rearrangement products.

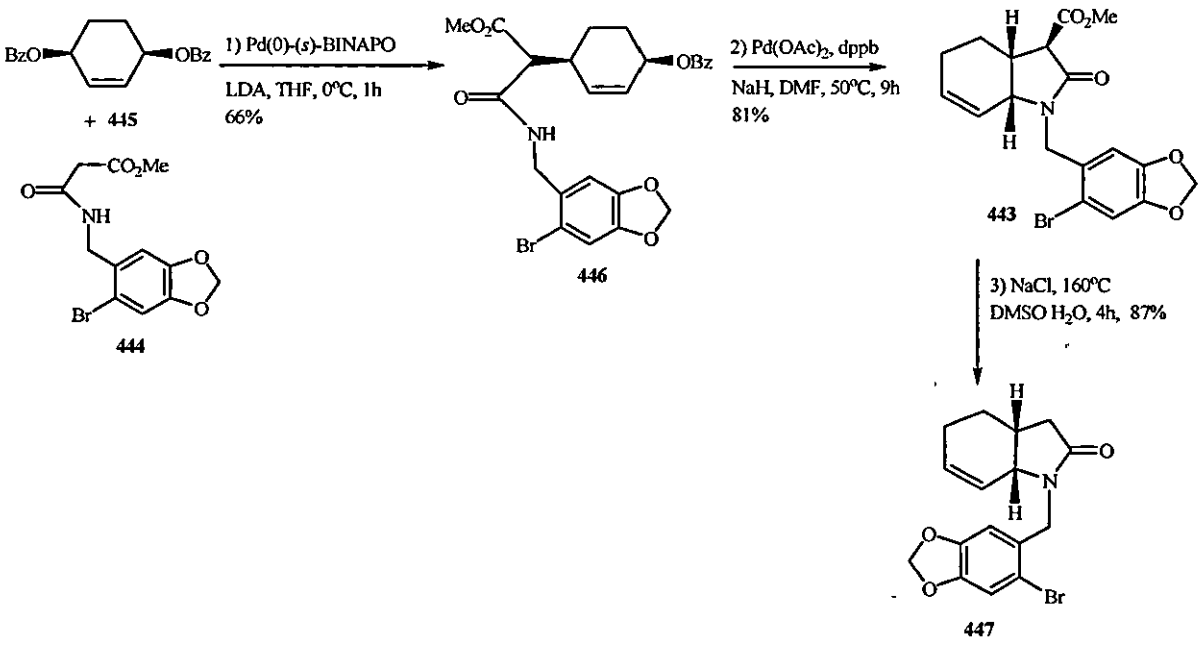
This type of rearrangement product had been seen before, when using benzyl amine as the test substrate. This other rearranged product was again subjected to the Pd(0) conditions to assess whether the structure would ring open again and rearrange to the desired product.



Scheme 191: Pd(0) catalysed rearrangement.

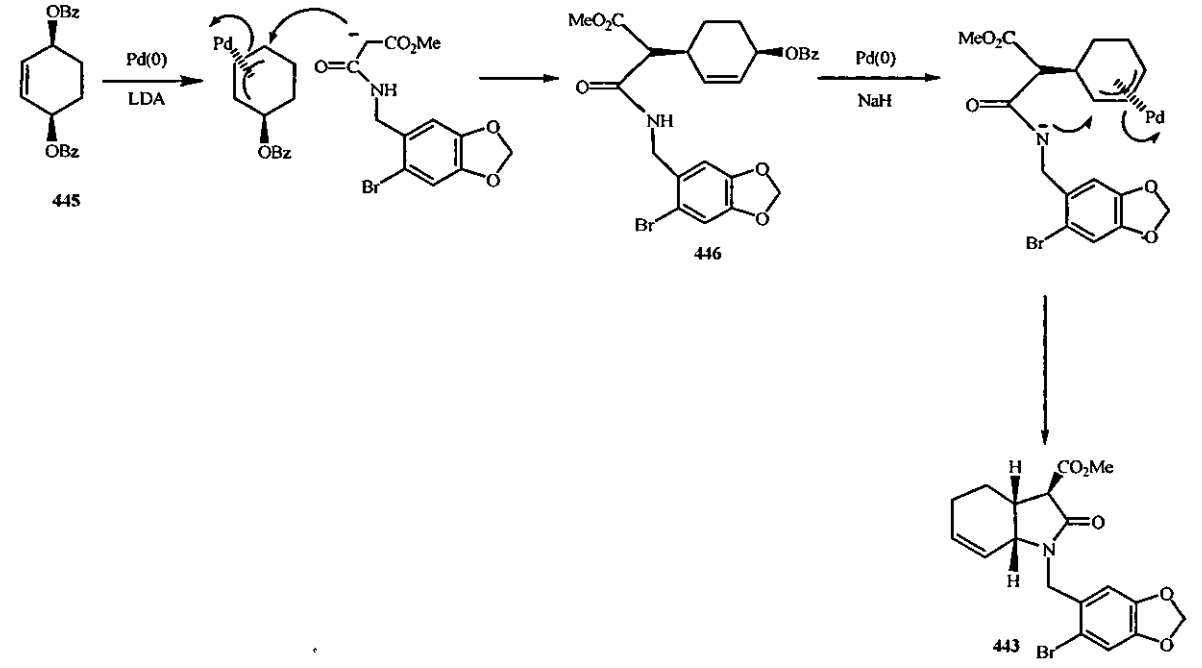
This was indeed the case, it seemed that the two products were in equilibrium with one another, when the desired product **459** was removed from the mixture and the other rearranged product **462/463** was again subjected to the same Pd(0) conditions, the ring opening occurred again, leading to the isolation of **462/463** in an approximately 1:1 ratio. So although the initial yields of **459** appear low, the product can be obtained by subjecting **462/463** to the Pd(0) conditions. So the amide **461** can be rearranged in near quantitative yields by 'recycling' **462/463**.

Work by Mori *et al.* involved a similar intermediate to **459**, it involved an asymmetric alkylation of the cyclohexenediol derivative **445** with structure **444** using a catalytic amount of $Pd(OAc)_2$ in the presence of (*S*)-BINAPO, with further manipulation to afford **447**.[64]



Scheme 192: Mori's total synthesis of γ-lycorane.[64]

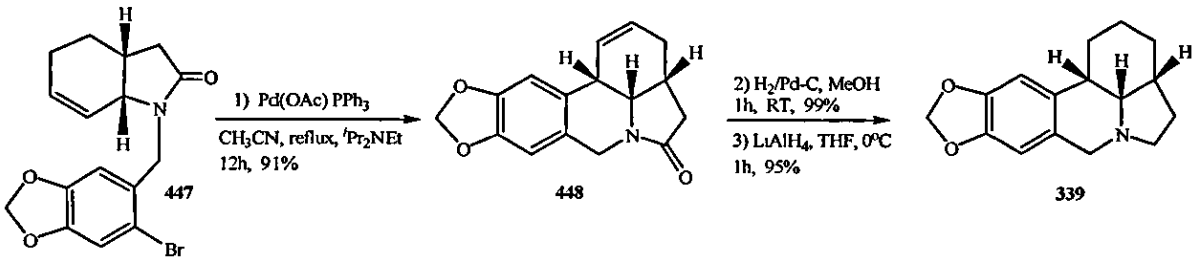
A drawback of Mori's work, like Backvall's, was the fact Mori required two sources of Pd(0) to access the hydroindole **443** where in our novel method we require only one source.[26, 27, 64]



Scheme 193: Mori's total synthesis of γ-lycorane.[64]

Oxidative insertion of the Pd(0) into the double bond of **445**, results in the displacement of the leaving group (OBz) by the nucleophile with retention of configuration. A second oxidative addition of the second source Pd(0) and subsequent nucleophilic attack on the π-allyl complex results in the synthesis of **443** with overall retention of configuration.

Mori *et al* constructed the penta cyclic core using Heck conditions, to yield the desired product **448** in 91%.[64]

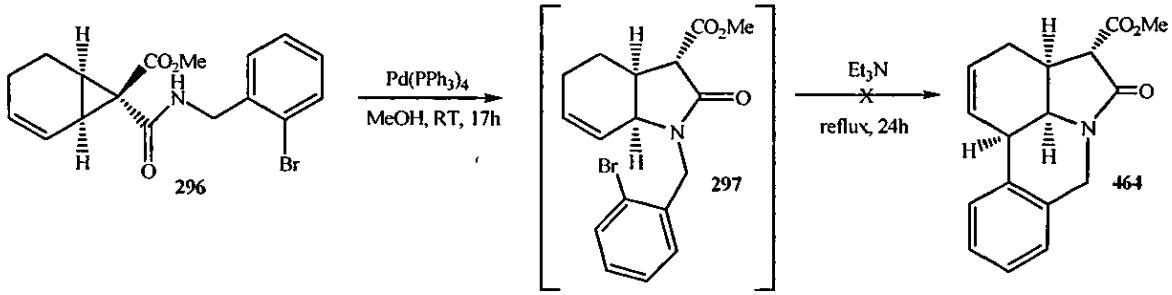


Scheme 194: Mori's total synthesis of γ-lycorane.[64]

The total synthesis of γ-lycorane was then achieved by Mori *et al.* in 2 more steps in an overall yield of 23% *via* a hydrogenation and reduction using $LiAlH_4$.[64]

5.8 Preliminary Heck work-Cascade rearrangement/Heck reaction

We felt an initial preliminary cascade rearrangement/ Heck reaction could be performed on the amide **296**, which would furnish the tetracyclic product **464** in one step.



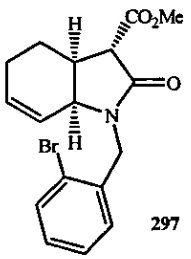
Scheme 195: Cascade rearrangement/ Heck reaction.

Once the rearrangement was complete *via* TLC analysis, triethylamine was added and the reaction was refluxed for 24 hours Unfortunately the cascade reaction was unsuccessful, only

the rearrangement product **297** was recovered on work up. The cascade reaction was not fully explored here, but will be returned to later during the total synthesis of (+)-γ-lycorane.

5.9 The Heck reaction-Model Studies

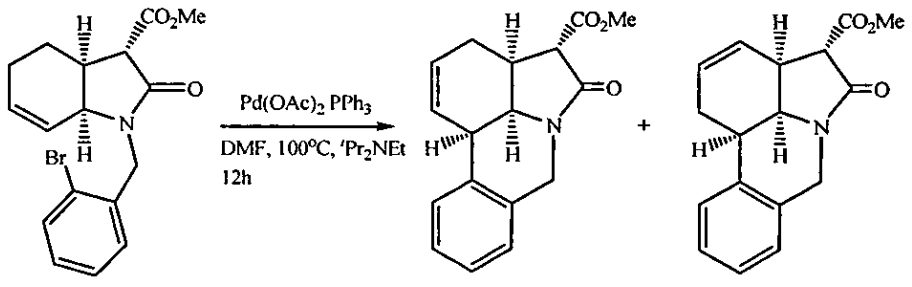
Since the amide **297** was structurally related to that used by Mori, we tried to reproduce their Heck conditions using this substrate.[64]



297

Figure 43: 1-(2-Bromo-benzyl)-2-oxo-2,3,3a,4,5,7a-hexahydro-1H-indole-3-carboxylic acid methyl ester.

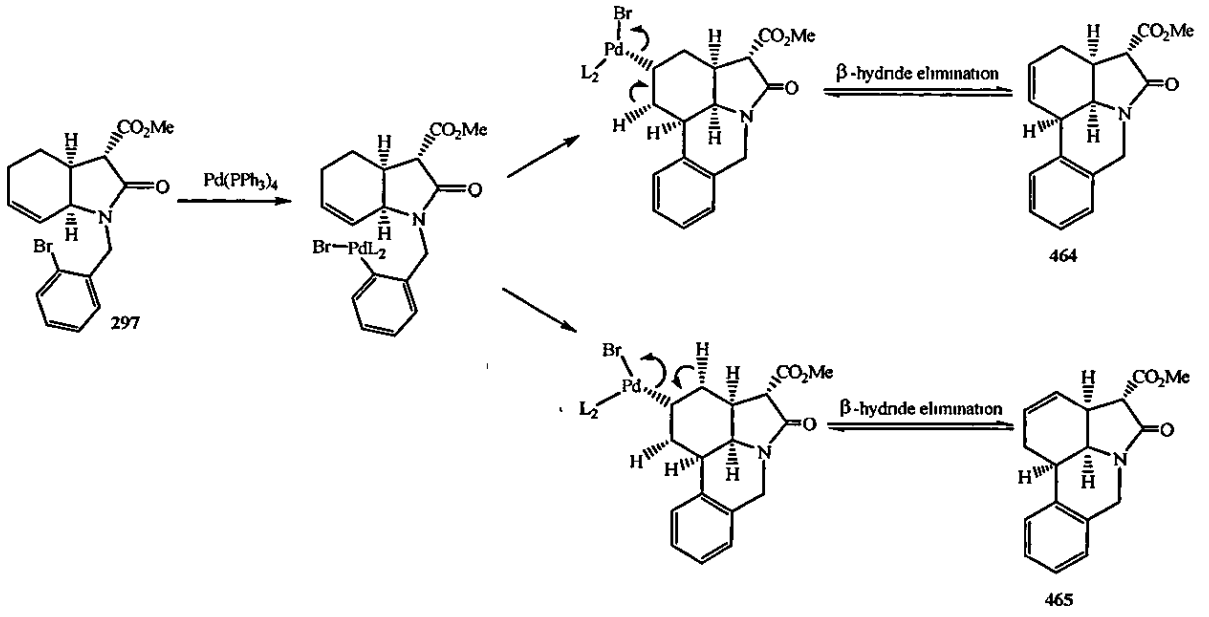
The active Pd(0) catalyst was formed by stirring palladium acetate with the triphenyl phosphine in DMF for 20 minutes at room temperature before the hydroindole **297** was added. Hunigs base was then added and the reaction was stirred for 12 hours at 100°C.



297 464 465

Scheme 196: Intramolecular Heck reaction.[64]

It was difficult to determine if the reaction was successful as there was an inseparable mixture of products isolated at the end of the reaction. Analysis of the reaction mixture by ^{1}H NMR showed that starting material was present but also peaks corresponding to products **464** and **465** where regioisomerisation of the alkene double bond had occurred.

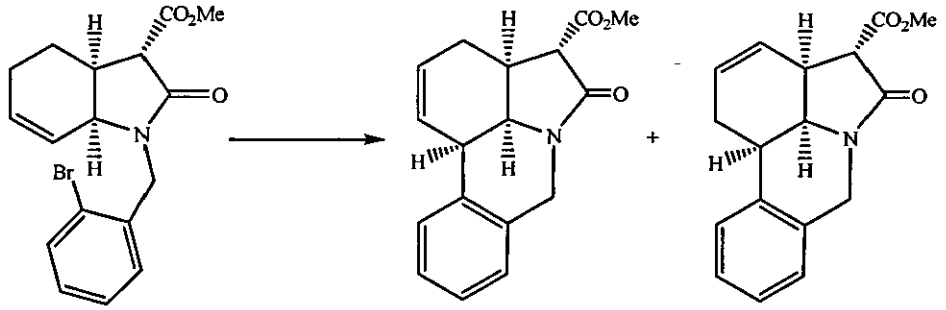


Scheme 197: Alkene isomerisation.

After the Pd(0) oxidative insertion into the C-Br bond and insertion into the alknene, *β*-hydride elimination can have two possible outcomes giving the two regio isomers **464** and **465** shown in scheme 197.

Unfortunately it appeared that the Heck reaction had occurred in only trace amounts and could not be isolated from the starting material so we were unable to determine if the reaction was a success.

We were disappointed that the reaction had not worked especially as we were applying Mori's conditions to a very similar substrate, inspite of this the conditions were changed and the following table outlines the work carried out.[64]



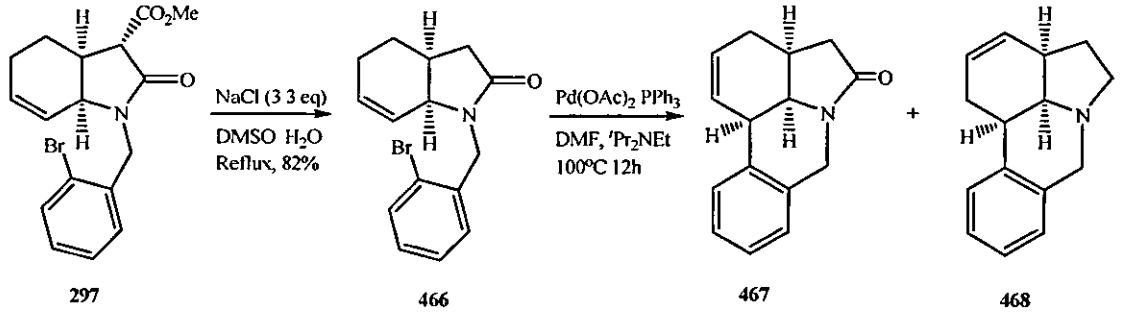
297 464 465

Catalyst	Solvent	Base	Temperature	Time (h)	Product
$Pd(PPh_3)_4$	Et_3N	Et_3N	Reflux	24	SM (90%), **464/465** (10%, 1:1)
$Pd(PPh_3)_4$	Et_3N	Et_3N	Reflux	48	SM (90%), **464/465** (20%, 1.1)
$Pd(OAc)_2$, PPh_3	Et_3N	Et_3N	Reflux	24	SM (90%), **464/465** (10%, 1·1)
$Pd(OAc)_2$, PPh_3	Et_3N	Et_3N	Reflux	48	SM (80%), **464/465** (20%, 1.1)
$Pd(OAc)_2$, PPh_3	Et_3N	Et_3N	Reflux	96	SM (85%), **464/465** (15%, 1·1)
$Pd(OAc)_2$, PPh_3	Et_3N	Et_3N	Microwave	0 2	SM (35%), **464/465** (65%, 1·1)
$Pd(OAc)_2$, PPh_3	DMF	DIEA	100	12	SM
$Pd(OAc)_2$, PPh_3	DMF	DIEA	100	17	SM (76%), (**464/465** (24%, 1·1)

Table 20: Heck conditions.

Again varying the conditions were fruitless, it was noted that on leaving the Heck reaction for longer than 24 hours, the concentration of the products **464** and **465** in which the double bond had isomerised was also increasing but again both products could not be isolated.

Mori *et al.* had also performed the Heck reaction on the substrate in which the methyl ester had been previously removed under Krapcho conditions, although it was unlikely that the methyl ester would be affecting the Heck reaction, it was removed and the Heck was performed again.[64]



297 466 467 468

Scheme 198: Krapcho decarboxylation and Heck reaction.[64]

The reactions were monitored by TLC and on work up starting material was recovered along with another two other products. Again it appeared that the double bond maybe isomerising but only in trace amounts according to the ^{1}H NMR to yield **467** and **468**. Again the reaction conditions were varied, table 21 outlines the conditions used.

Catalyst	Solvent	Base	Temperature	Time (h)	Product
$Pd(PPh_3)_4$	Et_3N	Et_3N	Microwave	0.2	SM (90%), 467/468 10%, 1:1)
$Pd(PPh_3)_4$	Et_3N	Et_3N	Reflux	48	SM (90%), 467/468 10%, 1.1)
$Pd(OAc)_2$, PPh_3	Et_3N	Et_3N	Reflux	72	SM (90%), 467k468 10%, 1:1)

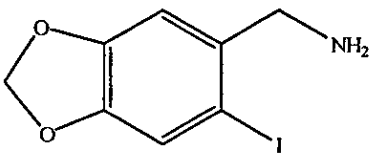
Table 21: Heck conditions.

Even changing the conditions yielded the same results, the reaction would only work in trace amounts affording a mixture of regio isomers and the starting material.

Chapter 6: A Total Formal Synthesis of γ-lycorane

The model system for the Heck reaction was proving problematic and we believed that the Heck reaction was working but only in trace amounts. This may be due to the fact that the lesser reactive aryl bromide was being used.

The amine **399** in figure 44 had the iodine at the 2-position instead of the bromide so the insertion of the Pd catalyst should be more favourable than with bromide analogue.

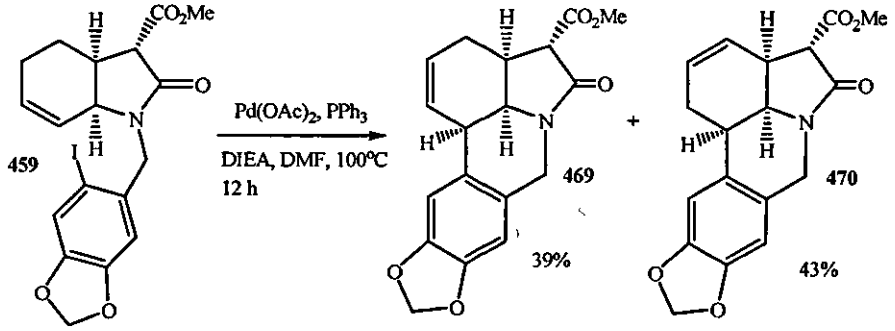


399

Figure 44: 6-Iodo-benzo[1,3]dioxol-5-yl-methylamine.[61]

Rather than waste any more time on the model route the conditions Mori applied in his synthesis were performed on the system shown in scheme 198. It was believed that the

reaction would be more successful due to the iodine being present in the 2-position on the benzyl group.

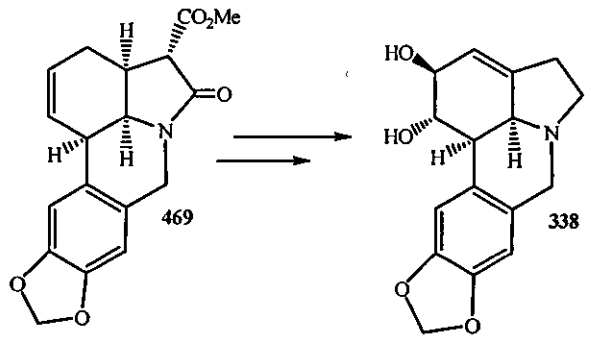


Scheme 199: The Heck reaction.[64]

The intramolecular Heck reaction was successful in an overall yield of 82% with the rest of the material recovered being that of the starting material **459**, even though regio isomerisation of the double bond had occurred it was not a major problem as the double bond would be removed *via* a hydrogenation reaction later in the total synthesis.

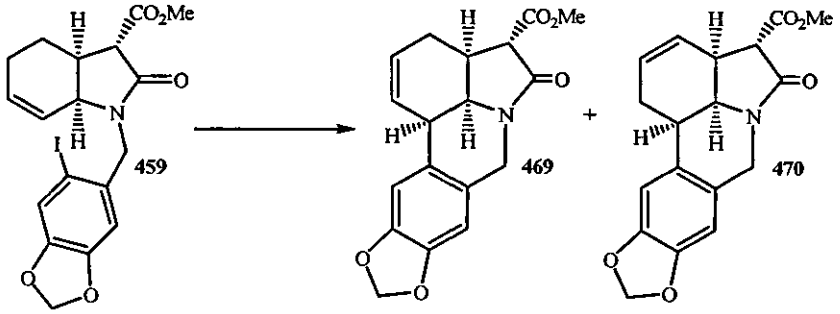
Separation of the two isomers was difficult but was achieved after two flash chromatography columns in significant purity to obtain full characterisation. Mori *et al.* only obtained **469** as the single product and did not mention any isomerisation of the double bond after β-hydride elimination.

To make the Heck reaction more selective would be beneficial if lycorine **338** was chosen as the target, so other catalysts and conditions were investigated wether we could control the regiochemistry of the reaction



Scheme 200: Lycorine synthesis.

The Heck reaction was repeated this time varying the catalyst, solvent and base in the reaction.



Catalyst	Solvent	Base	Temp (°C)	Time (h)	469 (%)	470 (%)
$Pd_2(dba)_3$, P(*t*-Bu)$_3$	1,4-dioxane	Cy_2NMe	RT-100	17	27%	56%
$Pd(OAc)_2$, PPh_3	DMF	DIEA	RT-100	17	41%	44%
$Pd(OAc)_2$, $(CH_3C_6H_4)_3P$	DMF	DIEA	RT-100	72	Trace	81%

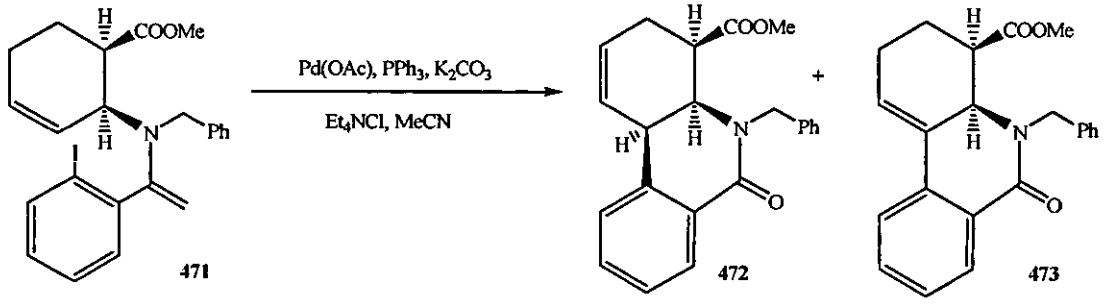
Table 22: Heck conditions

The Heck reactions were working well with an average yield of greater than 80%. In all three cases the reactions were initially performed at room temperature After 1 hour in all instances only starting material was present by LC-MS so the temperature was increased to 50°C. Again there was no change after 1 hour so the temperature was increased to 70°C. After 2 hours at 70°C again no product was visible by LC-MS so the reaction was eventually stirred at 100°C where product formation was eventually seen.

On employing the catalyst ($Pd_2(dba)_3$, P(*t*-Bu)$_3$) as used by Fu *et al.* the product was isolated in an approximate 1:2 ratio of **469**:**470**.[68] When the tolyl phosphine ligands were used this gave great regio selectivity as **470** was isolated as the major product in a 81% yield.

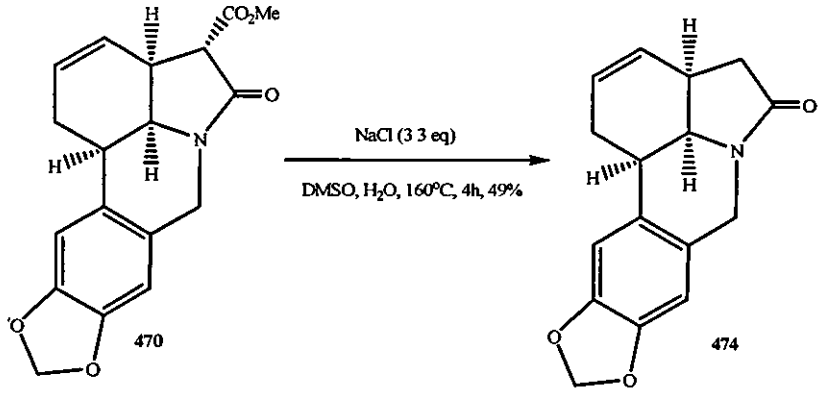
Work by Grigg *et al.* on the synthesis of fused ring nitrogen heterocycles *via* intramolecular Heck reactions described the addition of tetraethylammonium chloride to $Pd(OAc)_2$ resulting in cyclisation of **471** occurring at reduced temperature and with reduced isomerisation.[69] Double bond isomerisation is always a potential problem in Heck type reactions and addition of either tetraalkylammonium chloride or silver salts (nitrate, carbonate) suppresses this with the latter claimed to be more efficient.

Addition of silver salts in place of tetraethylammonium chloride resulted in a slower reaction but the reaction was now selective for the synthesis of **472** (scheme 201).[69]



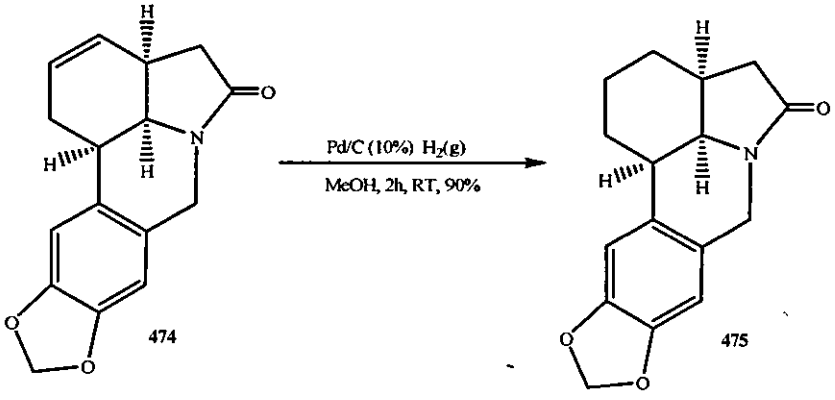
Scheme 201: Grigg *et al.*[69]

In this instance no silver salts were added as the double bond was removed later in the synthesis. The next step in the total synthesis was the removal of the methyl ester group using a Krapcho decarboxylation, scheme 202.



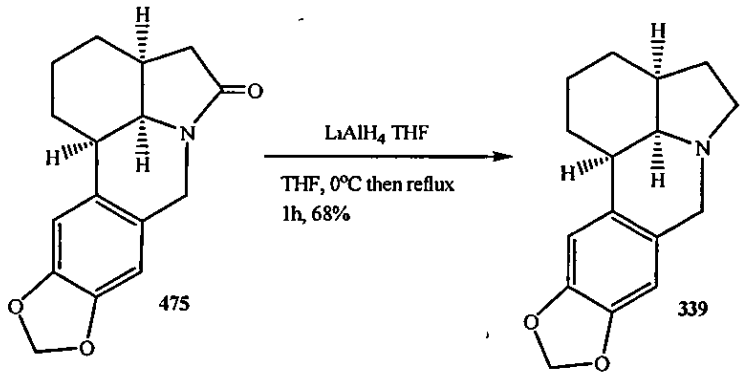
Scheme 202: Krapcho decarboxylation.

The Krapcho decarboxylation was problematic as the decarboxylation only proceeded in a 49% yield where the remainder of the material isolated was that of the starting material **470,** so that at least the starting material could be isolated and re-cycled. Leaving the reaction to heat for longer had no affect along with adding more equivalents of NaCl and H_2O. Another problem was the removal of DMSO from the product **474,** however this was achieved after multiple water washes. The next step was then the removal of the double bond by hydrogenation using 10% Pd/C in MeOH (scheme 203).[64]



Scheme 203: Hydrogenation.

The catalytic hydrogenation was successful in a 90% yield, Mori reported a yield of 99% but this was never matched and 90% was the highest yield of **475** obtained.[64]

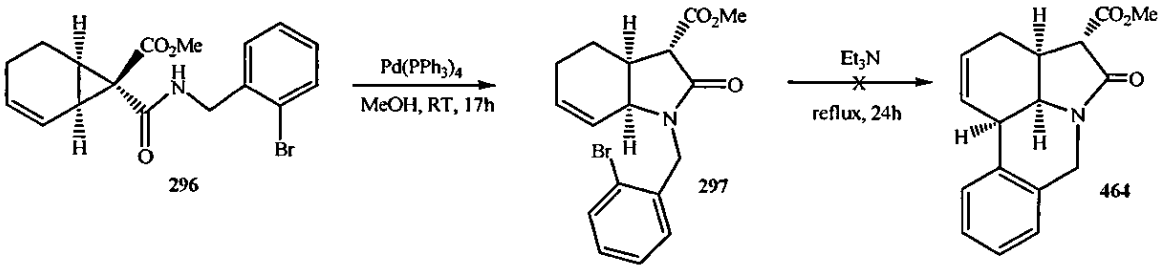


Scheme 204: $LiAlH_4$ reduction.[64]

The total synthesis was finished in 9 steps from 1,3-cyclohexadiene *via* the reduction of the amide carbonyl group of **475** with $LiAlH_4$ afforded γ-lycorane in an overall yield of 18% based on recovered starting material.

6.1 Cascade Rearrangement/Heck Reaction

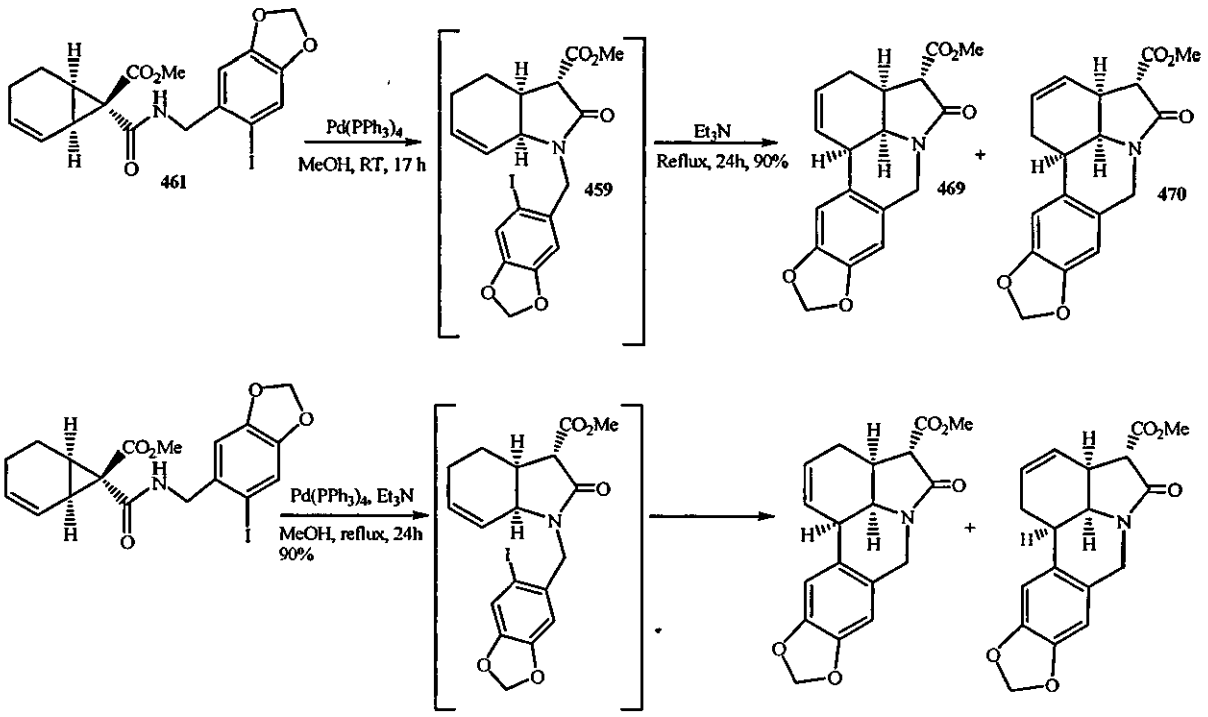
To improve on the total synthesis the initial work carried out on the 2-bromobenzyl system **296** was revisited, it was envisaged that the rearrangement and Heck reaction could be carried out in 'one pot.'



Scheme 205: Cascade rearrangement/Heck reaction.

Previous work was not promising on the system shown in scheme 204, but as we proved this was due to the poor reactivity of the aryl bromide to the Pd(0) insertion, with the iodine now in the 2-position the cascade reaction could now be feasible.

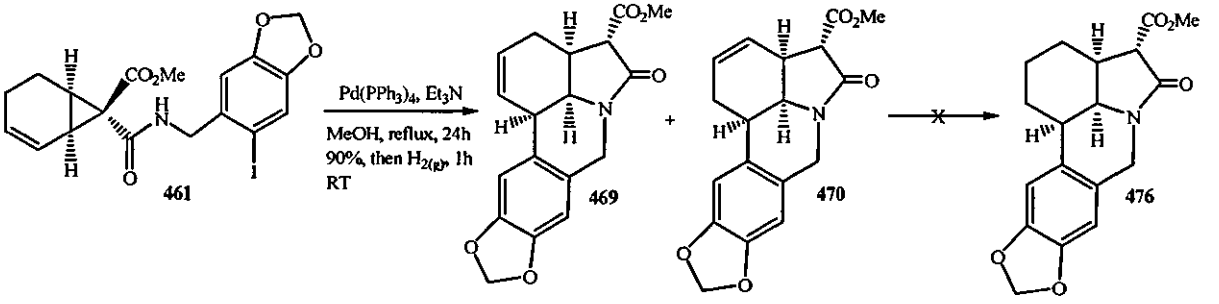
Two cascade reactions were performed, for comparative purposes. The first rearrangement was carried out in which the base was added sequentially. The other rearrangement was carried out where the base was present from the onset. There appears to be no literature precendent for the Heck reactions to be carried out in MeOH.



Scheme 206: Cascade rearrangement/Heck reaction.

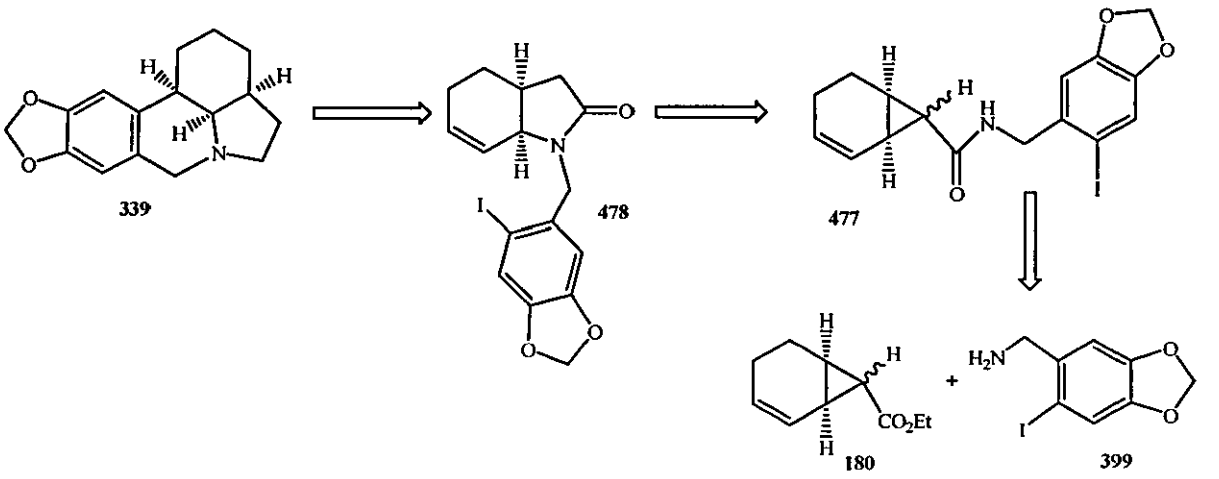
The cascade reactions were both very successful on small scales (90%) and **469**:**470** were isolated in approximately a 1:1 ratio. When the reactions were repeated on a larger scale the rearrangement product was isolated exclusively along with **461** and a trace of the Heck product.

A variant of the above reaction was also performed, in an attempt to further reduce the total number of steps in the synthesis by one the cascade rearrangement/Heck reaction was performed and then hydrogen gas was introduced at atmospheric pressure in an act to reduce the double bond.



Scheme 207: Cascade rearrangement/Heck/hydrogenation reaction.

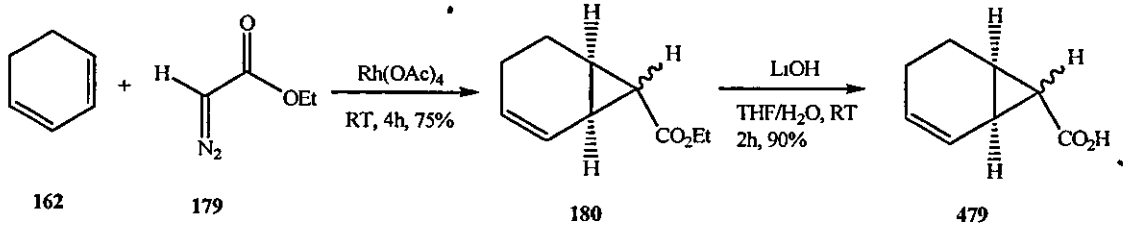
The hydrogenation did not occur and only the hydroindole **459** and the Heck products **469** and **470** were isolated on work up. In another attempt to further reduce the number of steps in the total synthesis, the following route was considered.



Scheme 208: Synthesis of lycorane.

With the methyl ester group absent from the onset it would reduce the synthesis by one step as the Krapcho decarboxylation would not be required. The mono acid **479** can be obtained from the ester hydrolysis of the ethyl ester **180** which was synthesised from the cyclopropanation of 1,3-cyclohexadiene **162** with the commercially available ethyl diazoacetate **179**.

Using ethyl diazoacetate, also opened up the opportunity of an asymmetric route. There are examples of asymmetric cyclopropanations with this substrate using various catalysts in the literature.[29]

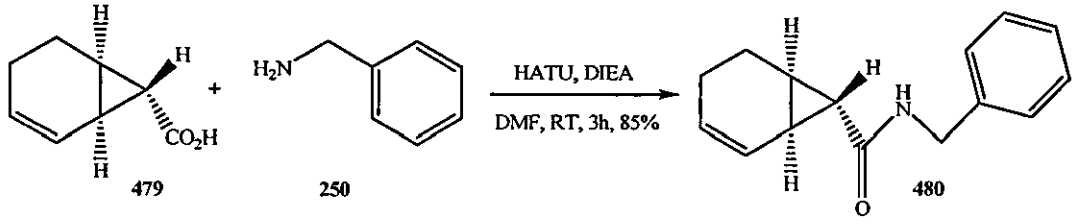


162 179 180 479

Scheme 209: Cyclopropanation and ester hydrolysis.

This route was promising as the initial cyclopropanation proceeded in a very high 75% yield and there was no need for preparation of the starting materials. The ester hydrolysis proceeded in a quantitative yield.

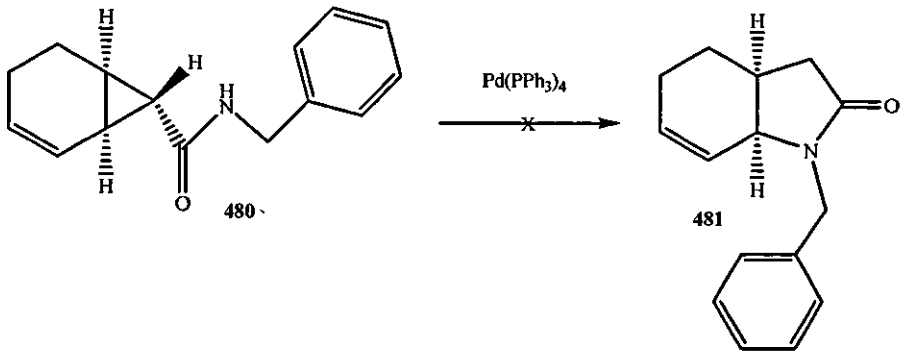
The amide coupling was performed using benzyl amine **250** in the standard conditions and the desired amide **480** was isolated in an excellent 85% yield.



479 250 480

Scheme 210: Amide coupling.

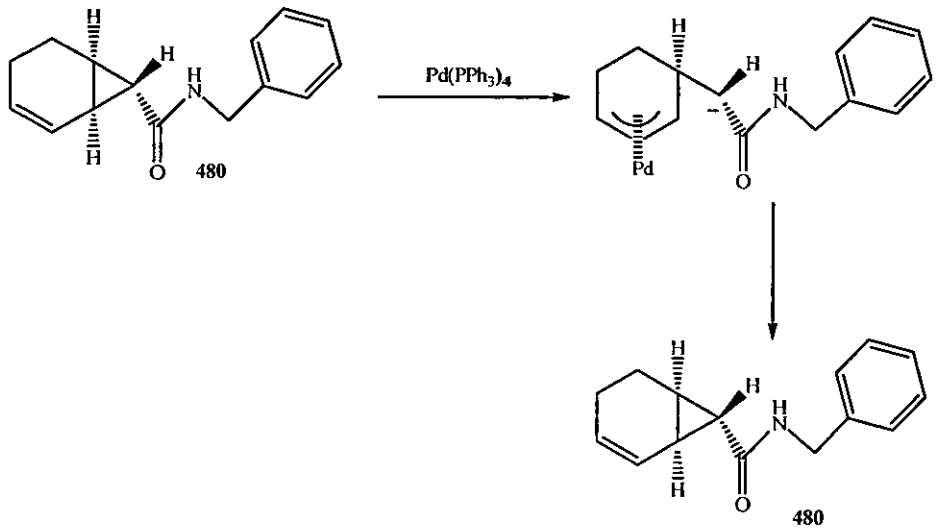
With the amide in hand the rearrangement was performed, the amide was stirred in methanol over night at room temperature with the Pd(0) catalyst.



Time (h)	Temperature (°C)	Solvent	Lewis Acid	Yield 481 (%)
17	RT	MeOH	-	SM
24	RT	MeOH	-	SM
24	RT	MeOH	$ZnBr_2$	SM
24	Reflux	*t*-BuOH	-	SM
0 2	Microwave	DMSO	-	SM

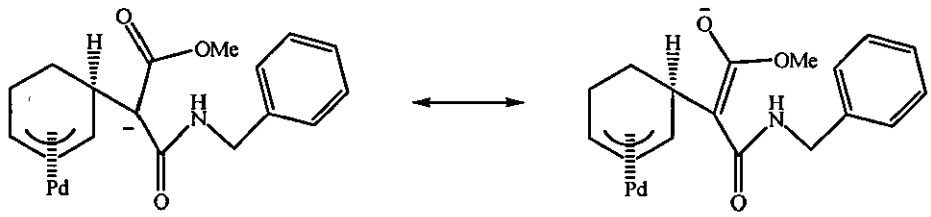
Table 23: Rearrangement results.

Unfortunately the rearrangement failed even when supplying more energy to the system the reaction would not work. With the methyl ester group not being present the negative charge cannot be stabilised by the intermediate so if the cyclopropyl ring does ring open after addition of the Pd(0), the intermediate might not be stable and therefore ring close again.



Scheme 211: Pd(0) catalysed rearrangement.

With the methyl ester present the negative charge can be stabilised by the methyl ester group thus making the intermediate stable.

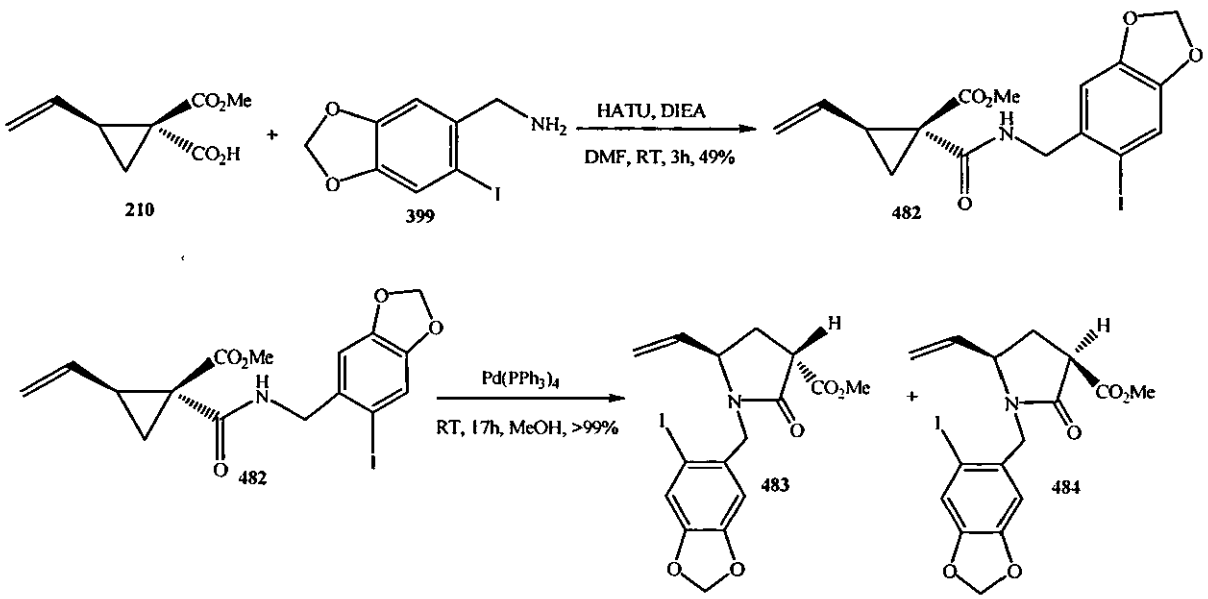


Scheme 212

After the hydrogen shift the nitrogen can then attack and eliminate the Pd catalyst, the π-allyl intermediate of **208** cannot stabilise the negative charge so ring closes to give the starting material.

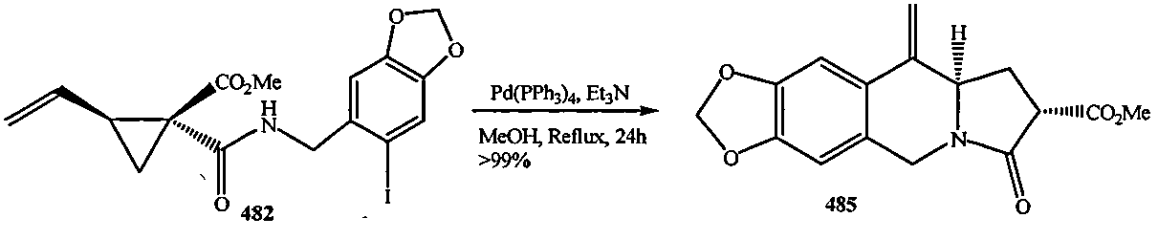
6.2 Applications of the Cascade Rearrangement/Heck Reaction

The intramolecular Heck and the 'one-pot' cascade rearrangement/Heck reaction with its elegant success on the 6-membered system was also applied to the vinylcyclopropane, 5 and 7-membered ring systems in an attempt to how applicable the conditions were.



Scheme 213: Amide coupling and Pd(0) catalysed rearrangement.

The iodo-amine **399** was coupled in a low 49% yield which appears to be standard for the vinylcyclopropane system but was rearranged in a near quantitative yield of 99% to give the pyrrolidine product as a 1:1 mixture of diastereoisomers. The cascade rearrangement/ Heck was then carried out.



Scheme 214: Cascade rearrangement/Heck reaction.

The cascade reaction was a success and the polycyclic alkaloid **485** was afforded in a remarkable 99% yield as one diastereoisomer, showing the excellent versatility of this work.

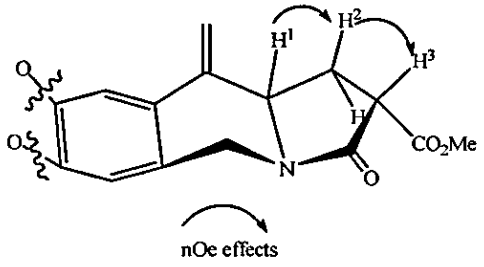
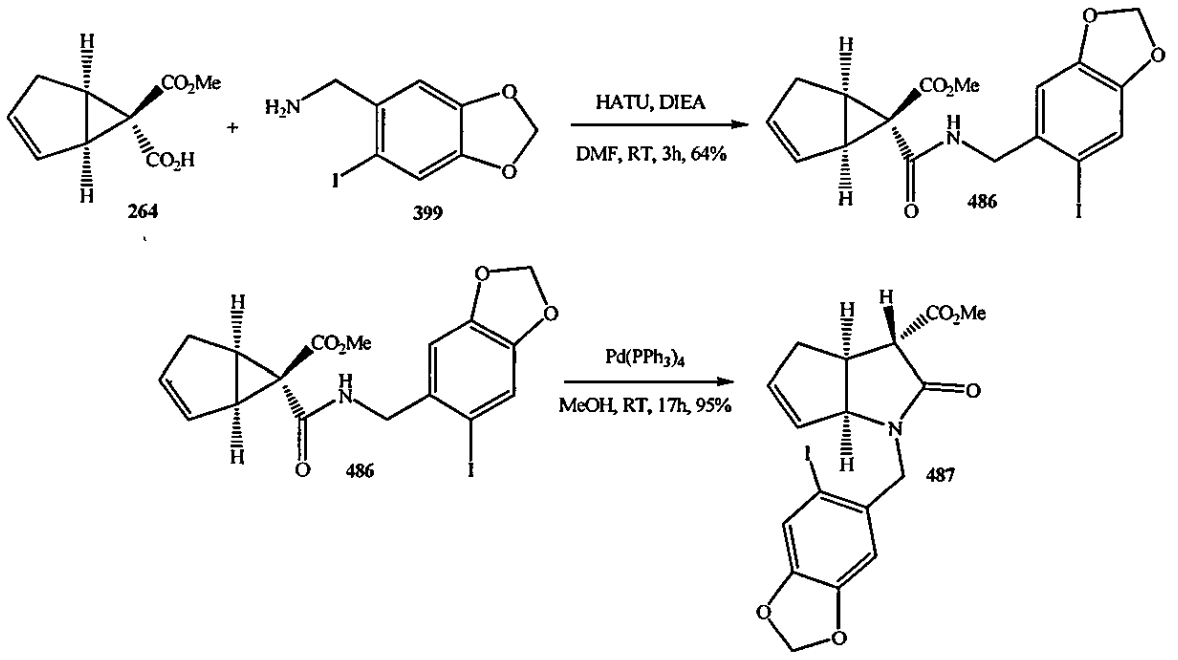


Figure 45: nOe effects.

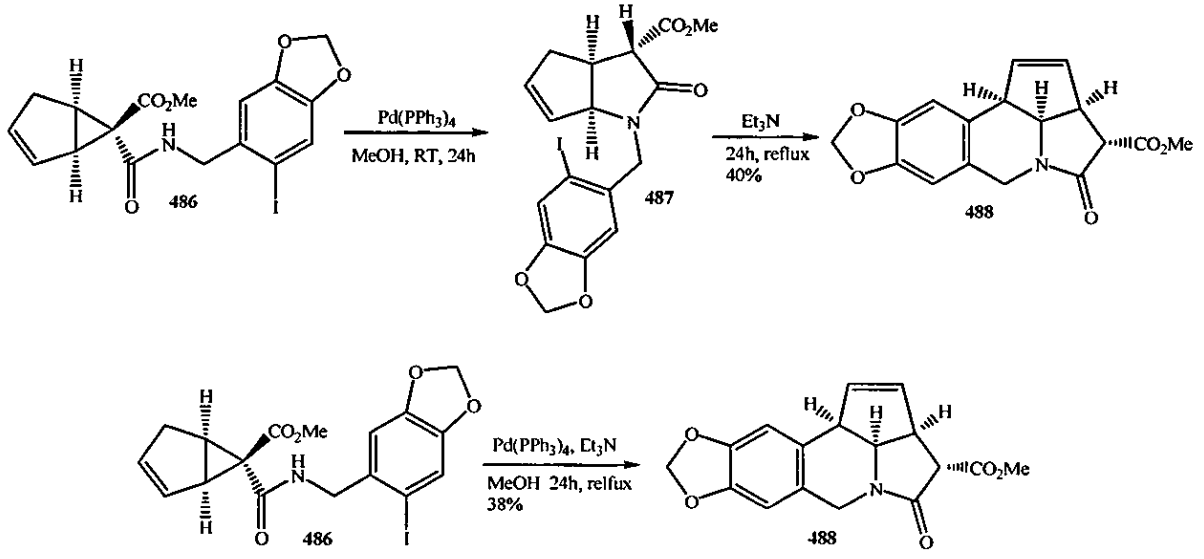
The stereochemistry shown in the scheme was based on that determined by nOe analysis. There was a nOe between proton 1 and 2 and between 2 and 3. However there was no positive nOe between proton 1 and 3.

Application of the 5-membered system was also carried out, both the coupling and rearrangement occurred in excellent yields with only one diastereoisomer produced.



Scheme 215: Amide coupling and Pd(0) rearrangement.

Again two cascade reactions were performed, for comparative purposes.



Scheme 216: Cascade rearrangement/Heck reaction.

Both cascade reactions were successful albeit in low yields but considering that the system **488** is strained and the fact that the rearrangement and Heck reaction worked in tandem using unoptimised conditions was very promising. The rearrangement product **487** was also

isolated in the reaction, so even though the yield was low no material was lost in the conditions. The low yield could be due to the strained nature of the product **488**.

Due to the nature of the reaction occurring in a low yield, isolation of a pure product was difficult making the assignment of the stereochemistry problematic. The stereochemistry displayed was assigned using nOe analysis.

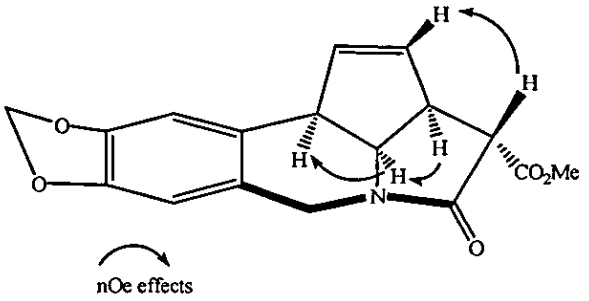
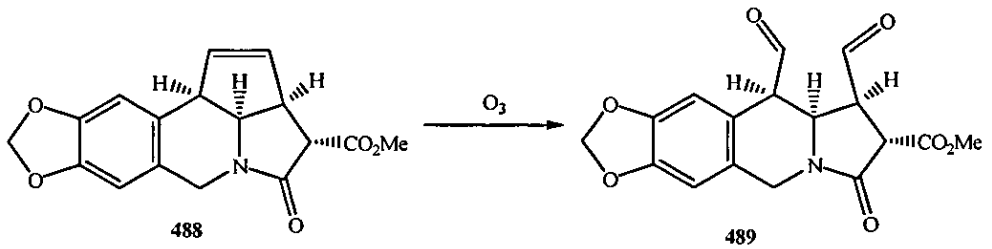


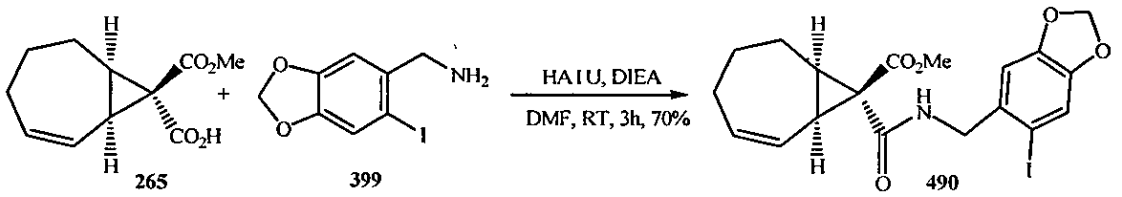
Figure 45: nOe effects.

The alkaloid **488** was interesting as further chemistry could be performed on this structure for example, dihydroxylation or ozonlysis could be carried out on the alkene to give the structure below, which then could be further manipulated.



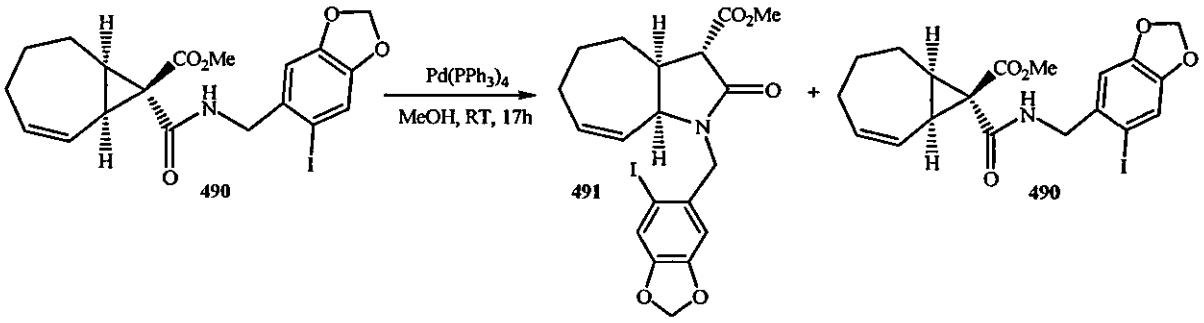
Scheme 217: Ozonolysis.

The last system to perform this work on was the 7-membered system which proved the most difficult in this instance. Work on the 8-membered ring system was not attempted due to the failure of any previous rearrangements to occur on that substrate.



Scheme 218: Amide coupling.

The coupling on the 7-membered system proceeded in a high 70% yield using the standard conditions. Problems were encountered in the rearrangement stage as when the amide **490** was subjected to the Pd(0) conditions the rearrangement product **491** could not be isolated exclusively.



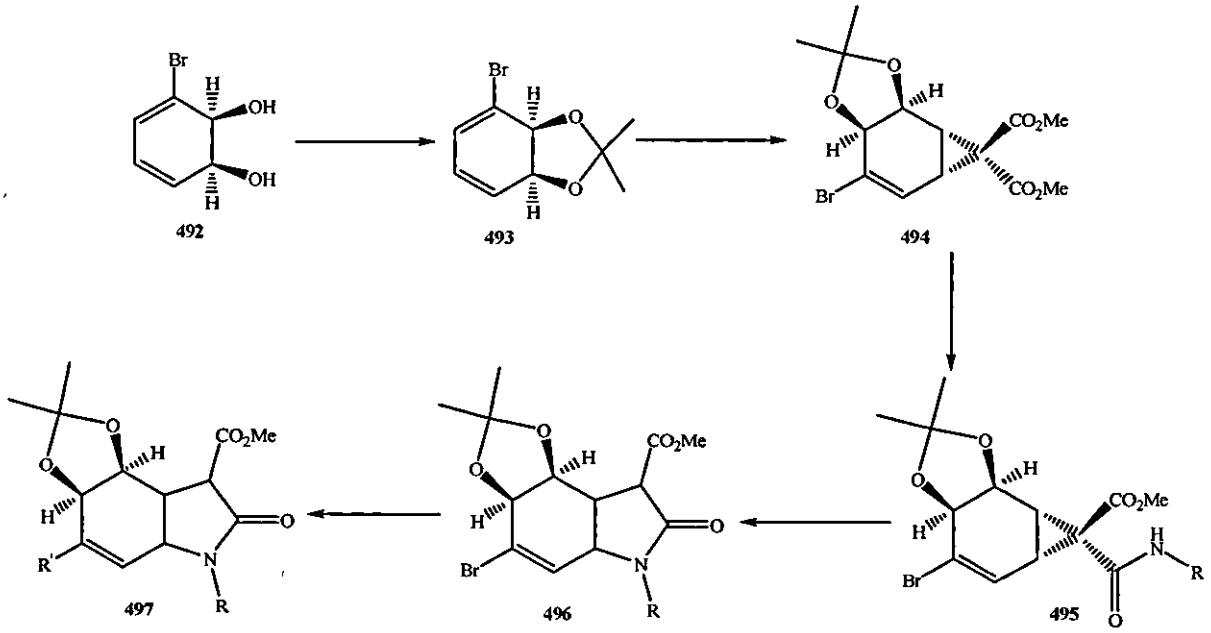
Scheme 219: Pd(0) catalysed rearrangement.

The reaction was left for 17 hours and the bicyclic product **491** was evident in the ^{1}H NMR along with the starting material amide **490.** An extra 10 mol% of the Pd(0) catalyst was added to the mixture and the reaction was left to stir once more for 17 hours. Upon analysis the product and starting material were still apparent as a 1:1 mixture.

The reaction was purified by column chromatography however the bicyclic product could not be separated and isolated from the starting material amide, because of this and time constraints the tandem rearrangement/Heck reaction was not pursued on this substrate.

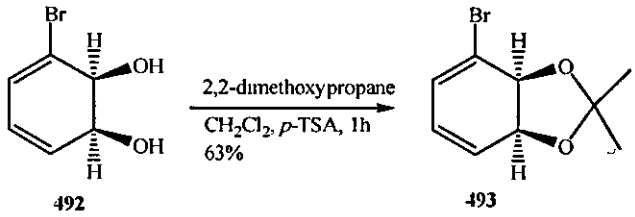
6.3 Asymmetric applications

Towards the end of the research we decided to approach an asymmetric route to these bicyclic compounds incorporating the carbene cyclopropanation, amide coupling and subsequent Pd(0) rearrangement.



Scheme 220: Proposed route.

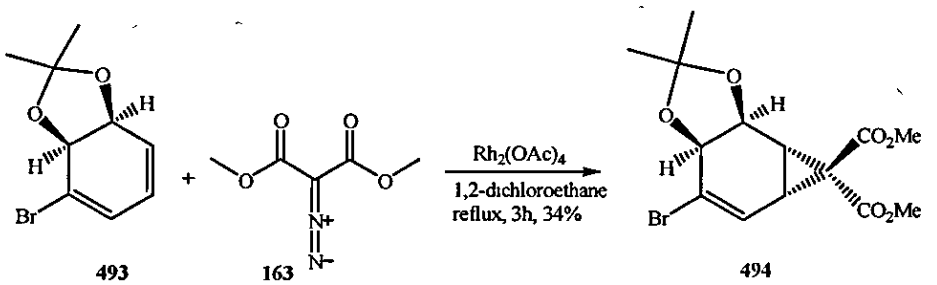
We hoped that we could take the diol **492** and protect the alcohols and perform a selective cyclopropantion to give the fused cyclopropane **494**. From here an amide coupling could be performed and then subsequent rearrangement to give the hydroindole **496** With the presence of the bromide we could also perform various couplings at this centre and introduce more functionality onto the ring.



Scheme 221: Diol protection [70]

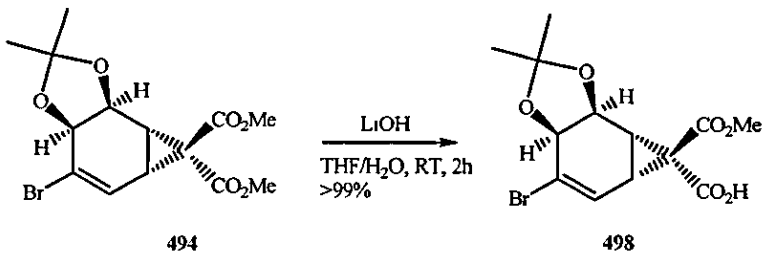
The commercially available enantiomerically pure diol **492** was protected using 2,2-dimethoxypropane in DCM with a catalytic amount of *p*-TSA in 1 hour furnishing **493** in a 63% yield.[70]

The dioxole **493** was then cyclopropanated using dimethyl diazomalonate **163** with the rhodium(II) acetate dimer catalyst as used previously.



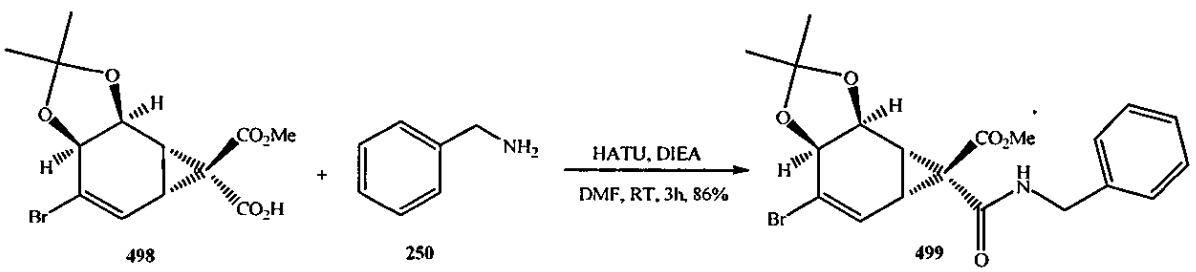
Scheme 222: Rhodium catalysed cyclopropanation.

The cyclopropanation conditions were un-optimised at this time and the cyclopropanation occurred in a low 34% yield which was still promising. It was proposed that with the presence of the bromide substituted on the other alkene bond, the cyclopropanation would predominate on the other and give us the exclusive product shown in scheme 222.



Scheme 223: Ester hydrolysis.

The mono acid **498** was synthesised in a quantitative yield and the amide coupling was carried out using benzylamine once more.

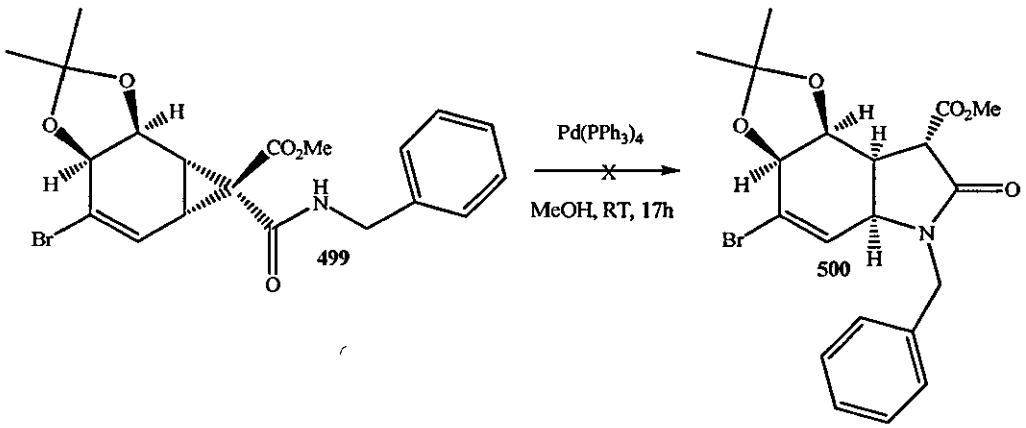


Scheme 224: Amide coupling.

The amide coupling was successful in an excellent 86% yield, the route was starting to look promising with the only drawback being the low yield of the cyclopropanation stage but this

has been an underlying theme of the whole project as further work is needed on the cyclopropanation step.

Doubts were raised as to whether the rearrangement on the amide would occur due to the presence of the bromide adjacent to the double bond where the Pd(0) will oxidatively insert, the deactivating nature of the bromine could be problematic.



Scheme 225: Pd(0) catalysed rearrangement.

As we thought the reaction did not occur and only the amide **499** was recovered on work-up, even when using forcing conditions (reflux) the reaction failed to work. The deactivating nature of the bromide could be preventing the Pd(0) from inserting into the alkene double bond.

Due to time constraints this was as far as we got on this area, it is hoped that this work will be carried on in the group as it is an intriguing route to research. With the bromide in that position of the cyclohexane ring a series of Pd catalysed cross couplings could be performed. If these were successful the Pd(0) catalysed rearrangement could be performed once more. Extra functionality is also present on the ring due to the protection of the *cis* alcohols, this could lead to a route to the synthesis of lycorine.

6.4 Summary

In summary we have synthesised a range of fused cyclopropanes using a Rh(II) acetate catalysed cyclopropanation of various dienes (figure 49).

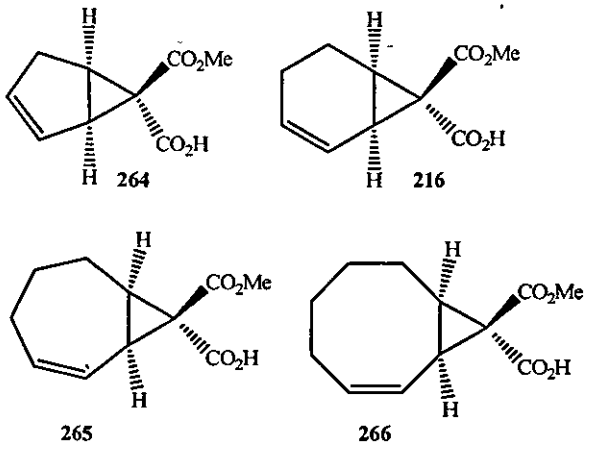
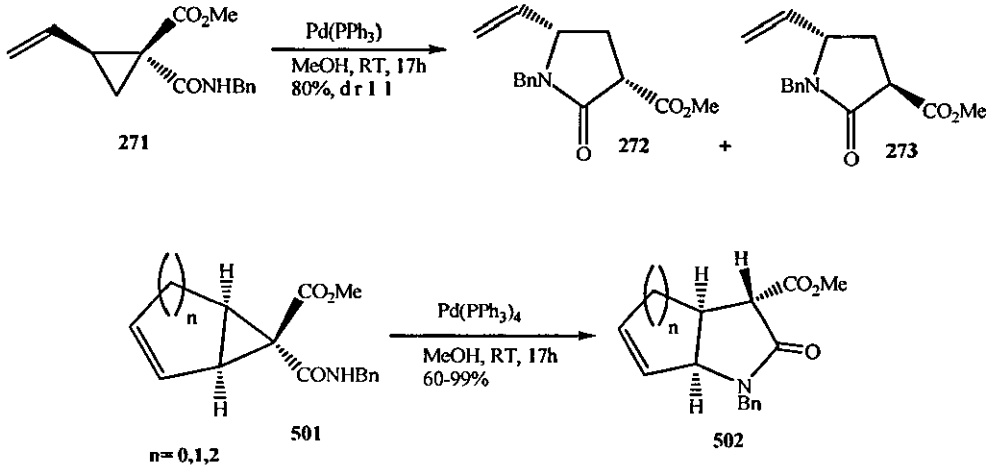


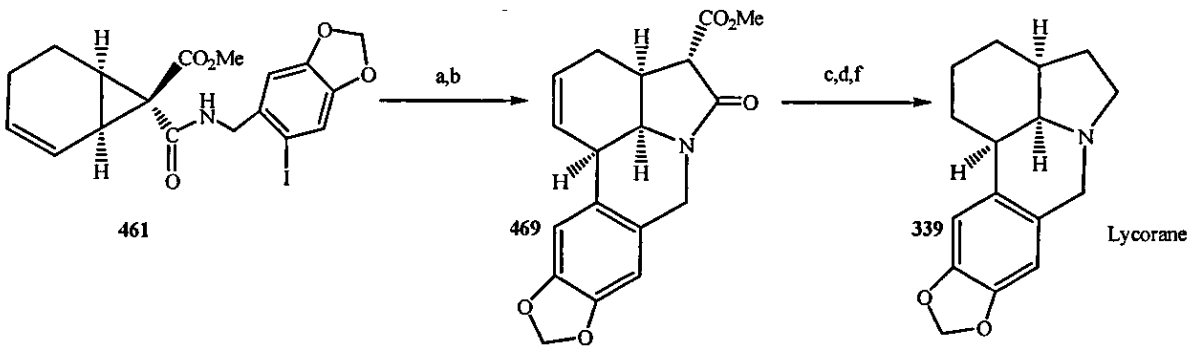
Figure 49: Fused cyclopropanes.

From this cyclopropanation a range of amide couplings and subsequent rearrangements were developed which were applied to various activated amide tethers on various sized fused cyclopropanes leading to the synthesis of over 20 novel heterocyclic compounds in good yields.



Scheme 226: General Pd(0) catalysed rearrangement.

This chemistry was then applied in the total formal synthesis of γ-lycorane *via* one of the shortest known routes to date in an overall yield of 18% from 1,3-cyclohexadiene.



Scheme 227: a) $Pd(PPh_3)_4$, MeOH, RT, 17h, >60%; b) $Pd(Oac)_2$, PPh_3, DIEA, DMF, 100°C, 12h, 82%; c) NaCl, DMSO, 4h, 160°C, 65%; d) $H_{2(g)}$, Pd/C, MeOH, RT, 2h, 90%; f) $LiAlH_4$, THF, reflux, 1h, 86%

This synthesis was further improved by the development of a cascade rearrangement/ Heck reaction reducing the total synthesis by one step and was also applied to other substrates, furnishing strained polycyclic systems in good yields.

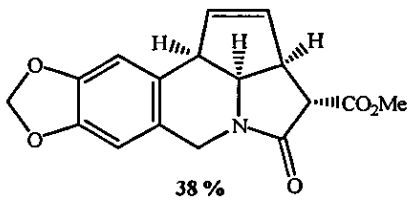
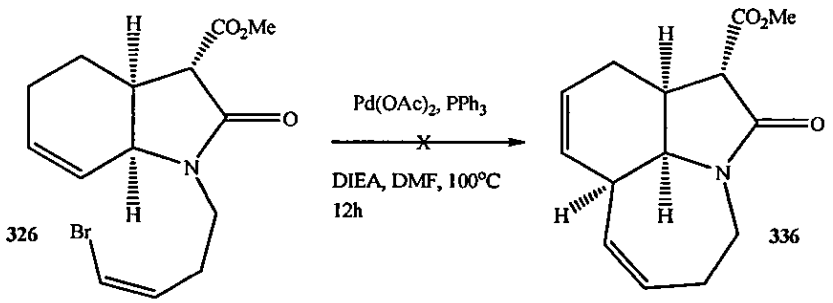


Figure 50: Pentacyclic product from cascade rearranegement/ Heck.

In short we have demonstrated that this novel Pd(0) catalysed rearrangement can be applied to a variety of activated amide tethers on a range of various sized fused cyclopropane furnishing heterocyclic compounds in high yields using mild conditions. This rearrangement has been successfully apllied in a total synthesis of a natural product and has the capability to be applied to other polycyclic compounds.

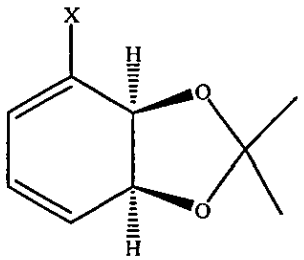
6.5 Future work

Having only been one step away from the synthesis of the tricyclic core of stenine, future work would begin here.



Scheme 228: Intramolecular Heck reaction.

The initial studies on the Heck reaction were discouraging as **336** was not isolated, more research on the Heck reaction is needed here. If work here proved to be successful then attention would be turned to the work on the protected enantiomerically pure protected diol **493.**



493 X=Br, Me

Figure 51: Diol.

With the rearrangement of the amide **499** being unsuccessful Pd(0) couplings could be performed utilising the presence of the halide to determine of the presence of other groups in that position will allow the rearrangement to occur.

7 Experimental

General experimental

All solvents were purified by standard distillation before use. Reagents were supplied from commercial sources as appropriate. 40-60 Petroleum ether (40-60 P E) refers to the fraction of light petroleum ether, which boils between 40 and 60°C. DCM, Et_2O and MeOH refer to dichloromethane, diethyl ether and methanol respectively. Solvents were removed under reduced pressure using a Buchi R114 rotavapour.

Infrared spectra were recorded using a Perkin-Elmer Paragon 1000 spectrometer with major absorbances only being quoted.

^1H NMR spectra were recorded at 250 and 400MHz using Bruker AC-250 and Bruker AM-400 instruments with COSY editing to assist assignment of diastereoisomeric ratios. For ^1H spectra recorded in $CDCl_3$ chemical shifts are quoted in parts per million (ppm) and are referred to TMS. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Where

^{13}C NMR spectra were recorded at 100MHz using a Bruker AM-400 instrument with DEPT editing to assist assignment Chemical shifts are quoted in ppm and are referenced to $CDCl_3$.

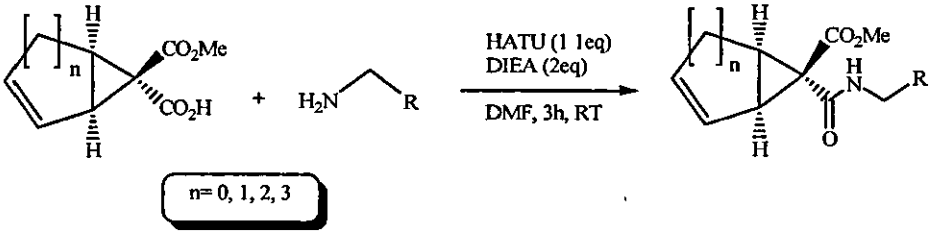
Mass spectra were recorded using a JEOL-SX102 spectrometer as EI and FAB with molecular ion, molecular ion fragments and major peakd being reported, Accurate masses were also recorded.

Flash chromatography was carried out on silica gel Thin layer chromatography was carried out on alumina backed plates pre-coated with silica gel, which were visualised by quenching of UV fluorescence or by staining with 10% w/v potassium permanganate (followed by heat) or I_2/SiO_2 as appropriate.

Unless otherwise stated, all reactions were carried out under anhydrous conditions and a nitrogen atmosphere. Experimental procedures are reported for those reactions that were successful in producing a product.

General conditions:

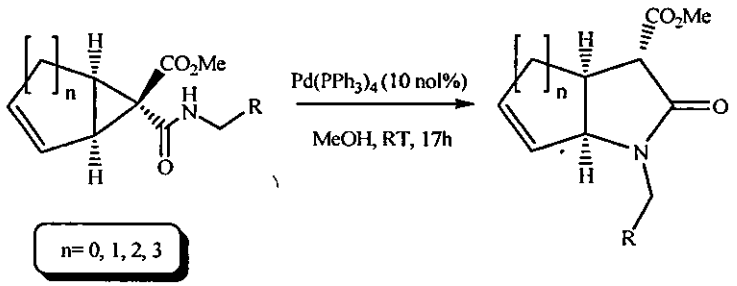
Amide Coupling Conditions



Procedure:

To a stirred solution of the acid (1 eq.), in DMF at room temperature was added DIEA (2 eq.), along with HATU (1.1 eq.) and the mixture was left stirring for 10 min. Then the amine (1.1 eq.) was added and the reaction was left stirring for 3 h. The reaction was then diluted with DCM (15 ml), washed with 2 *M* HCl (10 ml), aqueous $NaHCO_3$ (20 ml) and re-extracted into DCM (3x 20 ml), the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (silica gel, light petroleum: EtOAc) to yield the desired amide product.

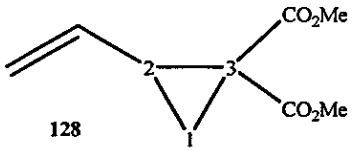
Pd(0) Catalysed Rearrangement



To a stirred solution of the amide (1 eq.) in MeOH under N_2 was added $Pd(PPh_3)_4$ (10 mol%) and the reaction was left stirring at room temperature for 17 h. The solvent was removed *in*

vacuo and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, light petroleum: EtOAc) to afford the desired heterocyclic product.

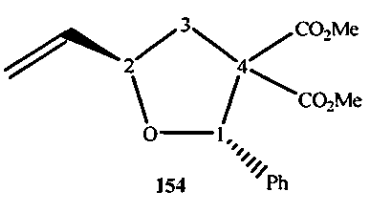
2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester[23]



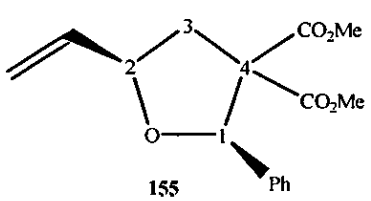
128

To a stirred solution of sodium methoxide prepared from sodium (1.15 g, 500 mmol) and methanol (20 ml), dimethylmalonate (5.89 ml, 51.5 mmol) was added followed by a solution of *trans*-1,4-dibromobut-2-ene (5.35 g, 25.0 mmol) in MeOH (20 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*. The crude mixture was partitioned between Et_2O (30 ml) and distilled H_2O (30 ml) The layers were separated and the organics were washed with H_2O (2x 30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow oil (3.15 g). The product was purified by flash chromatography (Silica gel, Et_2O: light petroleum 1:4) to afford the desired cyclopropane as a colourless oil (2.40 g, 13.0 mmol, 52 %); ν_{max} (thin film)cm^{-1} 2950m (C-H str), 1735 (C=O str), 1637, 1330, 1275, 1210 and 1132 (C-O str); δ_H (400MHz; $CDCl_3$) 1.57 (1H, dd, *J* 5 0 and 9.0 Hz, 1-C*H*H), 1.71 (1H, dd, *J* 5.0, 9.0 Hz, 1-CH*H*), 2 57 (1H, q, *J* 8.5 Hz, 2-C*H*), 3.73 (6H, s, 2x CH_3), 5.13 (1H, d, *J* 10.5 Hz, CH_2=CH), 5 16 (1H, d, *J* 17 Hz, CH_2=CH), 5 37 (1H, m, CH_2=C*H*); δ_c (100 MHz; $CDCl_3$) 20 61 (1-CH_2), 31.49 (2-CH), 35.72 (3-*C*), 52 61 (2x CH_3), 118.72 (CH_2=CH), 132.47 (CH_2=CH), 167.79 (*C*O) and 170.01 (*C*O); ms (EI): *m/z* 184 (M^+, 24%), 152 (84), 124 (72), 113 (12), 96 (35), 93 (58), 79 (49), 71 (74), 65 (62) and 59 (100). HRMS calc. for $C_9H_{12}O_4$ requires 184.0735, observed 184.0733.

2-Phenyl-5-vinyldihydrofuran-3,3-dicarboxylic acid dimethylester[23]



154

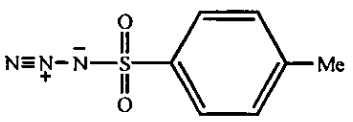


155

To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (0.18 g, 1.00 mmol) in anhydrous MeOH (5 ml) was added benzaldehyde (0.11 g, 1.00 mmol) at room temperature. This mixture was left to stir for 10 min under nitrogen before $Pd(PPh_3)_4$

(0.12 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 48 h. The solvent was then 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 water (2x 30 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo*. This crude material was purified by column chromatography (Silica gel, 4.6 Et_2O: light petroleum) to afford 2-phenyl-5-vinyldihydrofuran-3,3-dicarboxylic acid dimethylester as a colourless oil (0.12 g, 0.41 mmol, 41 %); υ_{max} (thin film)cm^{-1} 2951 (C-H str), 1733 (C=O str), 1271, 1229, 1206, 1155, 1135, 1091, 1051 and 1028 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.12 (1H, dd, *J* 7 and 13 Hz, 3-C(*H*)H), 2.41 (1H, dd, *J* 7 and 13 Hz, 3'-C(*H*)H), 2 69 (1H, dd, *J* 10 and 13 Hz, 3'-C(H)*H*), 2.96 (1H, dd, *J* 7 and 13 Hz, 3-C(H)*H*), 3.03 (3H, s, OC'H_3), 3.10 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.73 (3H, s, OC'H_3), 4.33-4.36 (1H, m, 2-C'*H*), 4.90-5.09 (1H, m, 2-C*H*), 5.12 (1H, m, CH_2=CH), 5.19 (1H, m, C'H_2=CH), 5.22 (1H, m, CH_2=CH), 5.36 (1H, m, C'H_2=CH), 5.61 (1H, s, 1-C'*H*-Ar), 5.72 (1H, s,1-C*H*-Ar), 5.84 (1H, m, CH_2=C*H*), 6.00 (1H, m, CH_2=CH), 7.15-7.34 (10H, m, 2x Ar-*H*); δ_c (100 MHz; $CDCl_3$) 40 33 (3-*C*'H_2-C-CO_2Me), 40.51 (3-*C*H_2-C-CO_2Me), 52.21 (*C*'H_3), 52.86 (2x *C*H_3), 53.02 (*C*'H_3), 66.18 (2x 4-*C*), 77.98 (2-*C*H), 79.26 (2-*C*'H), 83.49 (1-*C*H), 84.21 (1-*C*'H), 116.17 (*C*H_2=CH), 117.77 (*C*'H_2=CH), 126.50 (2x Ar), 126.95 (2x Ar), 127.82 (2x Ar), 127.89 (2x Ar), 128.01 (Ar), 128.14 (Ar), 136.44 (*C*'H), 137.75 (*C*H), 148.11 (*C* and *C*'), 168.98 (*C*O and *C*'O) and 171.23 (*C*O and *C*'O); ms (EI): *m/z* 290 [M^+ 22%], 236 (76), 230 (20), 184 (65), 153 (40), 152 (81), 124 (51), 115 (34), 105 (100), 71 (39) and 59 (36). HRMS calc. for $C_{16}H_{18}O_5$ requires 290.3132, observed 290.3130.

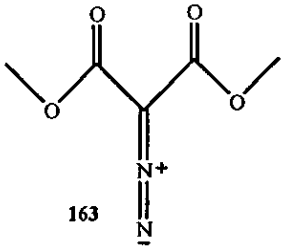
Tosyl-azide[24]



164

To a stirred solution of sodium azide (5.00 g, 77.0 mmol) in acetone (60 ml) and H_2O (40 ml) was added tosyl chloride (7.00 g, 36.8 mmol). The reaction was left to reflux for 2 h. H_2O (40 ml) was added and the organic layer was extracted with DCM (2x 100 ml), dried over $MgSO_4$ and concentrated *in vacuo* to afford the tosyl azide as a colourless oil (6 12 g, 31.1 mmol, 84 %); υ_{max} (thin film)cm^{-1} 2354 (N_3 str),1369, 1307, 1296, 1166 and 1120 (SO_2 str); δ_H (400 MHz; $CDCl_3$) 2.48 (3H, s, CH_3), 7.39 (2H, d, *J* 8 Hz, Ar*H*-CH_3), 7.82 (2H, d, *J* 8 Hz, Ar*H*-SO_2).

Dimethyl diazomalonate[24, 34]



163

Method A

To a solution of dimethyl malonate (1.57 g, 11.9 mmol) and triethylamine (1.24 g, 12.2 mmol) was added tosyl azide (2.39 g, 12.1 mmol) and were left to stand in anhydrous acetonitrile (20 ml) at room temperature for 22 h. The solvent was reduced *in vacuo* to furnish a white solid. The solid was triturated with Et_2O (150 ml) and the ether extract was washed with KOH (2.70 g) in H_2O (100 ml). The aqueous layer was saturated with Na_2SO_4 and extracted with Et_2O (100 ml). The combined ethereal extracts were acidified with 6 *M* HCl, dried (Na_2SO_4) and concentrated *in vacuo* to afford the dimethyl diazomalonate as a yellow viscous oil (0.42 g, 2.65 mmol, 26 %); υ_{max} (thin film)cm^{-1} 2956 (C-H str), 2138 ($R_2C=N^+=N^-$), 1757, 1739 (C=O str), 1437, 1334, 1276, 1190, 1164 and 1097 (C-O str); δ_H (400 MHz; $CDCl_3$) 3.84 (6H, s, 2x OCH_3).

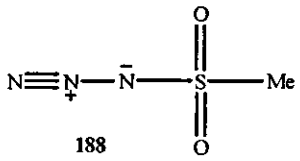
Method B[33]

To a solution of dimethyl malonate (3.01 g, 22 8 mmol) and triethylamine (2.38 g, 23.5 mmol) was added tosyl azide (4.43 g, 22 4 mmol) and were left to stand in dry benzene (20 ml) at room temperature for 18 h. 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 (3.09 g, 19.5 mmol, 87 %) See previous data.

Method C[36]

To a stirred solution of dimethyl malonate (5.00 g, 37.9 mmol), mesyl azide (5.04 g, 41.7 mmol) in acetonitrile (25 ml) was added triethylamine (7.65 g, 75.6 mmol, 10.5 ml). The reaction was followed by TLC but complete in 3 h. The mixture was diluted with 10% aqueous NaOH and extracted with DCM (3x 30 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the dimethyl diazomalonate as a yellow oil (5.12 g, 32.4 mmol, 85 %). See previous data.

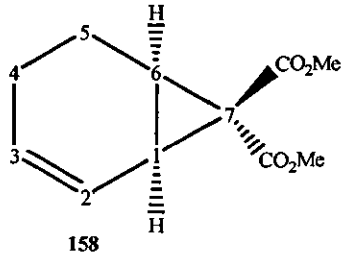
Mesyl Azide[24, 35]



188

To a stirred solution of methanesulfonyl chloride (4.50 ml, 6 66 g, 58.1 mmol) in acetone (30 ml) was added sodium azide (5.67 g, 87.2 mmol) over 30 min *via* the powder addition funnel. The resulting mixture was stirred for an additional 1.5 h at 25 °C. The reaction mixture was then filtered through a sintered glass funnel and the salts which were separated were washed with acetone and concentrated with stirring at 25°C (51mmHg) for 1.5 h to afford the mesyl azide as a colourless oil (6.27 g, 51.8 mmol, 89 %); υ_{max} (thin film)cm^{-1} 2141 (N=N=N str), 1357, 1328, 1199 and 1166 (SN str); δ_H (400 MHz; $CDCl_3$) 3 26 (3H, s, CH_3).

Bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester[24]



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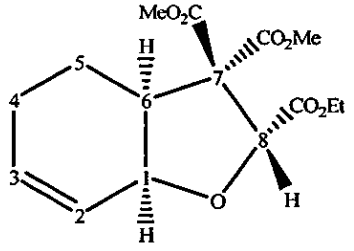
Method A

To a solution of 1,3-cyclohexadiene (1.01 g, 12.6 mmol), and $Rh_2(OAc)_4$ (0.05 g, 0.11 mmol) was added dimethyl diazomalonate (2 00 g, 12 6 mmol) which were stirred under reflux for 3 h. The oil was purified by flash chromatography (Silica gel, hexane: EtOAc, 2:1) to afford the bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester as a colourless viscous oil (0.69 g, 3.26 mmol, 34 %); υ_{max} (thin film)cm^{-1} 3034, 2950 (C-H str), 1726 (C=O str), 1435, 1333, 1254, 1199, 1174 and 1107 (C-O str), δ_H (400 MHz; $CDCl_3$) 1.65-2.19 (6H, m, 4-CH_2, 5-CH_2, 1-C*H* and 6-C*H*), 3 73 (6H, s, 2x CH_3), 5 69-5.74 (1H, m, 2-C*H*=CH), 5.89-5.93 (1H, m, 3-CH=C*H*); δ_c (100 MHz; $CDCl_3$) 16.05 (5-CH_2), 21.65 (4-CH_2), 24 61 (6-*C*H), 25 40 (1-*C*H), 37.63 (7-*C*), 52.75 (2x CH_3), 121 83 (2-*C*H=CH), 127 92 (3-CH=*C*H), 167.78 (*C*O), 170.19 (*C*O); ms (EI): *m/z* 210 [M^+ 16%], 178 (100), 146 (74), 132 (14), 118 (44), 100 (29), 91 (65), 79 (45), 69 (19), and 59 (15). HRMS calc. for $C_{11}H_{14}O_4$ requires 210 0892, observed 210.0889.

Method B

To a stirred solution of 1,3-cyclohexadiene (1.11 g, 13.9 mmol) and $Rh_2(OAc)_4$ (0.06 g, 0.14 mmol) in 1,2-dichloroethane (3 ml), was added dimethyl diazomalonate (2.00 g, 12 6 mmol) diluted in 1,2-dichloroethane (13 ml) *via* syringe pump over 30 min. The reaction was then stirred under reflux for 3 h, where then it was allowed to cool, concentrated *in vacuo* and purified by flash chromatography (Silica gel, hexane: EtOAc, 2:1) to afford the bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester as a colourless viscous oil (1.74 g , 8.29 mmol, 60 %); see previous data.

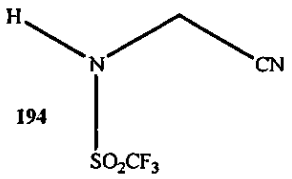
Dimethyl, 2-(ethoxy)-2, 3-dihydrobenzo[b] furan-3,3-dicarboxylate[24]



191

To a stirred solution of 7,7-dicarbomethoxybicyclo[4.1.0] hept-2-ene (0.10 g, 0.48 mmol), ethyl glyoxylate (0 05 g, 0.48 mmol) in THF (3 ml) was added $Pd(PPh_3)_4$ (0.06 g, 0 05 mmol) and $ZnBr_2$ (0.22 g, 0.98 mmol). The reaction mixture was stirred at room temperature for 8 h The solvent was removed *in vacuo* to yield a viscous yellow oil, which was dissolved in EtOAc (10 ml), washed with H_2O (10 ml) and dried ($MgSO_4$). The product was purified by flash chromatography (Silica gel, EtOAc : Petroleum ether, 1:5) and then concentrated *in vacuo* to afford the desired dimethyl, 2-(ethoxy)-2, 3-dihydrobenzo[b] furan-3,3-dicarboxylate (0.09 g, 64 %); υ_{max} (thin film)cm^{-1} 2953 (CH), 1743 (CO), 1279, 1254, 1225, 1200, 1111 and 1063 (CO); δ_H (400 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.90-2.10 (2H, m, 5-CH_2), 2.14- 2.25 (2H, m, 4-CH_2), 2.98-3.00 (1H, dt, *J* 4.8 and 14 Hz, 6-C*H*), 3.70 (3H, s, CH_3), 3.80 (3H, s, CH_3), 4.18 (2H, m, CH_2CH_3), 4.74 (1H, s, 1-C*H*O), 5.24 (1H, s, 8-C*H*CO_2Et), 5.90 (1H, m, 2-C*H*=CH), 6.00 (1H, m, 3-CH=C*H*); δ_c (100 MHz; $CDCl_3$) 14 10 (5-CH_2), 20.44 (4-CH_2), 24 25 (6-*C*H), 42.84 (6-*C*H), 52 89 (CH_3), 53.07 (CH_3), 61 39 (CH_2CH_3), 68 59 (7-*C*), 75.85 (1-*C*H), 79.95 (8-*C*H), 124.10 (2-*C*H), 132.44 (3-*C*H), 167 59 (*C*O), 168.87 (*C*O), 170.85 (*C*O); ms (EI): *m/z* 312 [M^+ 1%], 253 (8) , 239 (14), 193 (6), 179 (56), 161 (22), 119 (13), 96 (100), 80 (21) and 59 (8). HRMS calc. for $C_{15}H_{20}O_7$ requires 312.1209, observed 312.1215.

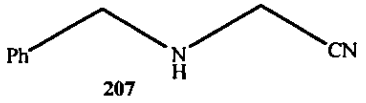
N-(Cyanomethyl) trifluoromethanesulfonamide[39]



194

To a stirred solution of aminoacetonitrile hydrochloride (1.50 g, 16.2 mmol) in DCM (25 ml) was added diisopropylethylamine (6.20 ml, 35.6 ml) in one portion. The pale yellow solution was next cooled to -78°C while trifluoromethanesulfonic anhydride (2.85 ml, 4.80 g, 17.0 mmol) was added by syringe over 6 min. The resulting red-brown solution was stirred at -78°C for 1 h. Then aqueous 1*M* HCl (15 ml) was then added and the reaction mixture was allowed to warm to room temperature. The aqueous layer was separated and extracted with 3x 30 ml portions of DCM and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give (8.90 g, 46.6 mmol) of the crude brown product. This material was then deposited onto 16.5 g of silica gel and purified on 55.0 g of silica gel (gradient elution with 20-50% EtOAc: hexane) to afford N-(cyanomethyl) trifluoromethanesulfonamide as a pale yellow oil (1.52 g, 8.13 mmol, 50 %); υ_{max} (thin film)cm^{-1} 3311 (N-H str), 2999 (C-H str), 2272 (CN str), 1423, 1382 (SO_2-N), 1200; 1146, 1092, 995, 909 and 841 (C-F str); δ_H (400 MHz; $CDCl_3$) 4.23 (2H, d, *J* 7.5 Hz, CH_2), 6 03 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 31.81 (CH_2), 114.37 (*C*N), 120.81 (C-F, q, *J* 318 Hz); ms (EI): *m/z* 188 [M^+ 2%], 162 (6), 133 (27), 119 (100), 96 (100), 69 (100) and 53 (99) HRMS calc. for $C_3H_3SO_2F_3N_2$ requires 187.9867, observed 187.9863.

Benzylamino-acetonitrile

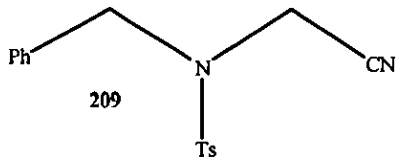


207

To a stirred solution of chloroacetonitrile (0 20 g, 2.65 mmol) in anhydrous DCM (4 ml) was added benzylamine (0.17 g, 5.30 mmol) and left stirring at room temperature for 24 h. The solution was then washed with aqueous $NaHCO_3$ (20 ml) and extracted into DCM (3x 20 ml), dried ($MgSO_4$), and concentrated *in vacuo* The crude mixture was purified by flash chromatography (silica gel, gradient elution 4:1-2:1-1:1, light petroleum· EtOAc) to afford the benzylamino-acetonitrile as an orange oil (0.28 g, 1.89 mmol, 72 %); υ_{max} (thin film)cm^{-1} 3331 (N-H str), 2232 (CN str); δ_H (400 MHz; $CDCl_3$) 1.67 (1H, s, N*H*), 3.55 (2H, s, CH_2), 3.92 (2H, s, CH_2), 7.25-7.35 (5H, m, *Ar*-H); δ_c (100 MHz; $CDCl_3$) 36 25 (CH_2), 52.29 (CH_2), 117.68 (*C*), 127 69 (*Ar*-H), 128.43 (2x *Ar*-H), 128.64 (2x *Ar*-H), 137.78 (*C*N); ms (EI): *m/z*

146 [$M^{+\cdot}$ 56%], 119 (13), 118 (10), 91 (100) and 69 (16). HRMS calc. for $C_9H_{10}N_2$ requires 146.0844, observed 146.0846.

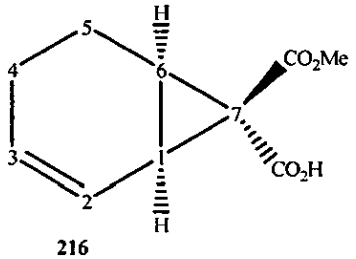
_N_-Benzyl-_N_-cyanomethyl-4-methyl-benzenesulfonamide



209

To a stirred solution of benzylamino-acetonitrile (0.19 g, 1.15 mmol), in anhydrous DCM (10 ml) was added triethylamine (0.40 g, 2.88 mmol) and was left to stir at room temperature for 10 mins, before tosyl chloride (0.26 g, 1.38 mmol) was added and left stirring overnight. The reaction was then washed with aqueous $NaHCO_3$ (20 ml) and extracted into DCM (3x 20 ml), combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (silica gel, gradient elution 4:1 to 2:1, light petroleum: EtOAc) to afford the *N*-benzyl-*N*-cyanomethyl-4-methyl-benzenesulfonamide as an orange brown solid (0.231 g, 0.770 mmol, 66 %); υ_{max} (thin film)cm^{-1} 2983 (C-H str), 1596, 1454, 1353 and 1164 (SO_2 str); δ_H (400 MHz; $CDCl_3$) 2.48 (3H, s, C*H*$_3$), 4.04 (2H, s, C*H*$_2$), 4 33 (2H, s, C*H*$_2$), 7.34-7.37 (5H, m, Ar-*H*), 7.40-7.43 (2H, d, *J* 8.5 Hz, 2x Ar-*H*), 7.79-7.81 (2H, d, *J* 8.5 Hz, 2x Ar-*H*); δ_c (100 MHz, $CDCl_3$) 21.70 (*C*H$_3$), 34.24 (*C*H$_2$), 51.02 (*C*H$_2$), 113 14 (*C*), 127.68 (2x *Ar*-H), 128.84 (2x *Ar*-H), 129.13 (2x *Ar*-H), 130.20 (3x *Ar*-H), 133.26 (*C*), 134.07 (C) and 144.89 (*C*N).

Bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid methyl ester[25]

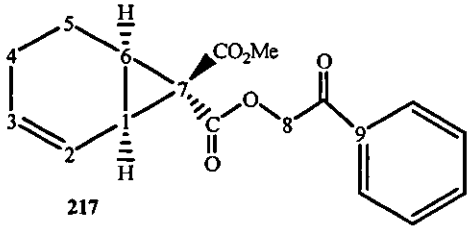


216

To a stirred solution of 7,7-dicarbomethoxybicyclo[4.1.0] hept-2-ene (0 53 g, 2 53 mmol) in THF (6 ml), H_2O (6 ml), LiOH (0.06 g, 2.54 mmol) was then added and the reaction was left stirring for 2 h. The resulting mixture was then acidified to pH 2 with 1*M* HCl and extracted with Et_2O (2x 30 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid methyl ester as a white solid

(0.39 g, 1.98 mmol, 78%); mp range 114.5-123.1 °C; υ_{max} (thin film)cm^{-1} 3454, 3036 (OH), 2950 (C-H str), 1733 (C=O str) and 1694 (C=O str), 1437, 1324, 1256 and 1199 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.95-2.19 (6H, m, 4-C*H*$_2$, 5-C*H*$_2$, 1-C*H* and 6-C*H*), 3 69 (3H, s, C*H*$_3$), 5.71-5.72 (1H, m, 2-C*H*=CH), 5.86-5.88 (1H, m, 3-CH=C*H*), 8.10 (1H, s, O*H*); δ_c (100 MHz; $CDCl_3$) 16.04 (5-*C*H$_2$), 20.74 (4-*C*H$_2$), 25.52 (6-*C*H), 27.35 (1-*C*H), 40.79 (7-*C*), 52.69 (*C*H$_3$), 121.82 (2-*C*H), 128.41 (3-*C*H), 170.22 (*C*O), 174.97 (*C*O); ms (EI): *m/z* 196 [M$^+$ 2%], 178 (31), 164 (20), 146 (48), 118 (43), 91 (100) and 79 (47). HRMS calc. for $C_{10}H_{12}O_4$ requires 196.0735, observed 196.0737.

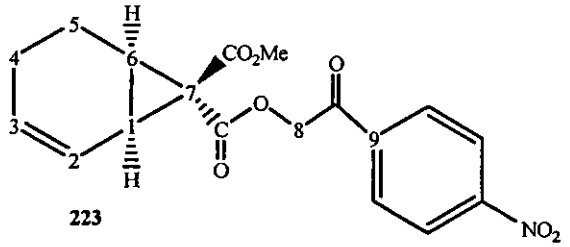
7-Methyl 7-(2-oxo-2-phenethyl)bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylate[25]



217

To a stirred solution of 7,7-dicarbomethoxybicyclo[4.1.0]hept-2-ene (0.39 g, 1.98 mmol), was added K_2CO_3 (0.68 g, 4.95 mmol) in acetone (10 ml) for 10 mins before 2-bromoacetophenone (0 39 g, 1.98 mmol) was added. This mixture was then stirred at room temperature for 17 h. The solvent was removed *in vacuo* to afford a yellow oil which was partitioned between DCM (30 ml) and 1 *M* HCl (30 ml). The organic layer was then washed with aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. This was purified by flash chromatography (Silica gel, 1: 4, EtOAc: Hexane) to afford 7-methyl 7-(2-oxo-2-phenethyl)bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylate as a yellow oil (0.52 g, 1.67 mmol, 83%); υ_{max} (thin film)cm^{-1} 2944 (C-H str), 1734 and 1703 (CO_2Me), 1596, 1449, 1434, 1370, 1333, 1252, 1225, 1200, 1178 and 1109 (C-O); δ_H (400 MHz; $CDCl_3$) 1 64-2.20 (6H, m, C*H*$_2$-C*H*$_2$-C*H*-C*H*), 3 66 (3H, s, C*H*$_3$), 5.27 (2H, s, 8-C*H*$_2$), 5 64-5 69 (1H, m, 2-C*H*=CH), 5.81-5 90 (1H, m, 3-CH=C*H*), 7.39-7.43 (2H, m, Ar-*H*), 7.52-7 53 (2H, m, Ar-*H*), 7 80-7.83 (1H, m, Ar-*H*); δ_c (400 MHz; $CDCl_3$) 16.09 (5-*C*H$_2$), 20 55 (4-*C*H$_2$), 24 87 (6-*C*H), 27 01 (7-*C*H), 37.62 (7-*C*), 40.78 (9-*C*), 52.71 (*C*H$_3$), 66 74 (*C*H$_2$), 121.75 (2-*C*H), 127 81 (2x *Ar*-H), 128.17 (3-*C*H), 128.89 (2x *Ar*-H), 134 08 (*Ar*), 167 48 (*C*O), 169.25 (*C*O) and 191.50 (*C*O); ms (EI): *m/z* 314 (M$^+$ 1 %), 282 (14), 195 (15), 178 (56), 146 (47), 118 (35), 91 (67) and 77 (100). HRMS calc. for $C_{18}H_{18}O_5$ requires 314 1154, observed 314.1160.

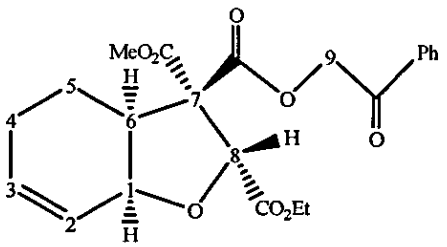
Bicyclo[4.1.0]hept-2-ene-7,7-carboxylic acid methyl ester 2-(4-nitro-phenyl)-2-oxo-ethyl ester[25]



223

To a stirred solution of 7-[(methyloxy)carbonyl]bicyclo[4 1.0]hept-2-ene-7-carboxylic acid (0.30 g, 1.40 mmol), K_2CO_3 (0.48 g, 3.47 mmol) in acetone (6 ml) for 20 mins Then 2-bromo-4'-nitroacetophenone (0.34 g, 1.40 mmol) was added and the solution was stirred at room temperature for 17 h. The solvent was then removed *in vacuo* to afford a brown/red oil which was partitioned between DCM (30 ml) and 1 *M* HCl (30 ml). The organic layer was washed with aqueous $NaHCO_3$ (2x 30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford bicyclo[4.1.0]hept-2-ene-7,7-carboxylic acid methyl ester 2-(4-nitro-phenyl)-2-oxo-ethyl ester as a yellow oil which was purified by flash chromatography (Silica gel, 1:1 Petroleum ether. Et_2O) to afford a yellow solid (0.35 g, 0.98 mmol, 70%); mp range 116.2-121.3 °C υ_{max} (thin film)cm^{-1} 2945 (C-H str), 1736 (C=O str), 1712 (C-O str), 1526 and 1345 (NO_2 str); δ_H (400 MHz; $CDCl_3$) 1.36-2.18 (6H, m, C*H*-C*H*-CH_2-CH_2), 3.66 (3H, s, CH_3), 5.26 (2H, s, 8-CH_2), 5.65-5.84 (1H, m, 2-C*H*=CH), 5.84 (1H, m, 3-CH=C*H*), 7.97-8 00 (2H, m, Ar-*H*), 8.26-8.29 (2H, m, Ar-*H*); δ_c (400 MHz; $CDCl_3$) 16 06 (5-CH_2), 20 51 (4-CH_2), 25.11 (6-*C*H), 27.19 (1-*C*H), 30 26 (7-*C*), 52.68 (CH_3), 66.81 (8-CH_2), 121.50 (2-*C*H), 124.09 (2x *Ar*-H), 128.38 (3-*C*H), 128.99 (2x *Ar*-H), 138.57 (9-*C*), 150.75 (*C*-NO_2), 167 21 (*C*O), 169.16 (*C*O) and 190.56 (*C*O); ms (EI): *m/z* 359 [M^+ 2%], 327 (17), 195 (22), 178 (78), 163 (44), 146 (72), 135 (12), 118 (62), 104 (32), 91 (100) and 59 (20). HRMS calc. for $C_{18}H_{17}O_7N$ requires 359.1005, observed 359.1010.

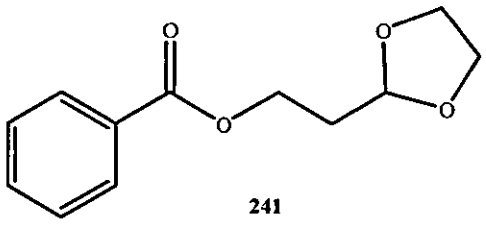
2-Ethyl 3-methyl 3-(2-oxo-2-phenylethyl)2,3,3a,4,5,7a-hexahydrobenzo[*b*]-2,3,3-tricarboxylate



225

To a stirred solution of 7-methyl 7-(2-oxo-2-phenethyl)bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylate (0.14 g, 0.45 mmol) in anhydrous THF (8 ml) was added ethyl glyoxylate (0.05 g, 0.45 mmol) and was left to stir for 10 min. To this $ZnBr_2$ was added (0.10 g, 0.45 mmol) and left to stir at room temperature. This mixture was left to stir for 15 min under nitrogen before $Pd(PPh_3)_4$ (0.05 g, 0 05 mmol) was added and left stirring for 17h at room temperature. The solvent was removed *in vacuo* and re-dissolved in EtOAc (20 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, 1:1 Et_2O: light petroleum, to afford 2-ethyl 3-methyl 3-(2-oxo-2-phenylethyl)2,3,3a,4,5,7a-hexahydrobenzo[*b*]-2,3,3-tricarboxylate as a yellow oil (0.13 g, 0.32 mmol, 70 %); υ_{max} (thin film)cm^{-1} 2950 (C-H str), 1743 (C=O), 1705 (C=O str), 1597, 1448, 1433, 1395, 1373, 1280, 1225, 1222 and 1196 (C-O); δ_H (400 MHz; $CDCl_3$) 1.22 (3H, t, *J* 7.2 Hz, C*H*$_3$), 1.40-1 60 (2H, m, 5-C*H*$_2$), 1 97-2.20 (2H, m, 4-C*H*$_2$), 3.04 (1H, dt, *J* 4.8 and 13 Hz, C*H*), 3.81 (3H, s, C*H*$_3$), 4.11-4.19 (2H, m, C*H*$_2$), 4.75 (1H, s, 1-C*H*O), 5 01 (1H, d, *J* 16 Hz, 9-C*H*H), 5.23 (1H, s, 8-C*H*), 5.46-5.50 (1H, d, *J* 16 Hz, 9-C*H*), 5.80 (1H, m, 2-C*H*=CH), 5.95 (1H, m, 3-CH=C*H*), 7 42 (2H, m, Ar-*H*), 7.54 (2H, m, Ar-*H*), 7.81 (1H, m, Ar-*H*), δ_c (100 MHz; $CDCl_3$) 14.10 (*C*H$_3$), 20 63 (5-*C*H$_2$), 24 24 (4-*C*H$_2$), 44.12 (6-*C*H), 52.96 (*C*H$_3$), 61.49 (*C*H$_2$CH$_3$), 66.98 (9-*C*H$_2$), 68 54 (7-*C*), 75.87 (1-*C*H), 80.63 (8-*C*H), 122.99 (2-*C*H), 127.79 (2x *Ar*-H), 128.91 (2x *Ar*-H), 132.24 (3-*C*H), 133.98 (*Ar*-H), 134.13 (*C*), 166.68 (*C*O), 167.33 (*C*O), 170.82 (*C*O) and 190.98 (*C*O), ms (FAB): *m/z* [M^+ 14%], 253 (14), 233 (12), 179 (18), 154 (50), 137 (60), 105 (76), 91 (90) and 55 (100) HRMS calc. for $C_{22}H_{24}O_8$ requires 417.1549, observed 417.1542

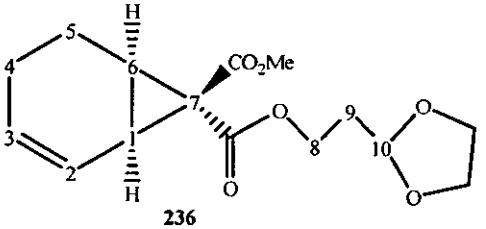
Benzoic acid [1,3]dioxolan-2-yl ethyl ester



241

To a stirred solution of benzoic acid (0.10 g, 0.82 mmol) dissolved in DCM (4 ml) and Cs_2CO_3 (0.66 g, 2 04 mmol) was added bromoethyl-1,3-dıoxolane (0.15 g, 0.82 mmol) and the mixture was stirred at reflux for 17 h. The reaction mixture was then extracted into DCM (3x 20 ml) and washed with aqueous $NaHCO_3$ (3x 15 ml). The organic fractions were then combined, dried ($MgSO_4$) and concentrated *in vacuo.* The resulting mixture was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford the benzoic acid [1,3]dioxolan-2-yl ethyl ester as a colourless oıl (0.18 g, 0.80 mmol, 98 %); υ_{max} (thin film)cm^{-1} 2964 (C-H str), 1717 (C=O str, 1601 (C=O str), 1451, 1314, 1276, 1140, 1116, 1070 and 1026 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.12 (2H, dt, *J* 4.5 and 6.5 Hz, C*H*$_2$), 3.85 (4H, m, 2x C*H*$_2$), 4.46 (2H, t, *J* 6.5 Hz, C*H*$_2$), 5.06 (1H, t, *J* 4.5 Hz, C*H*), 7.41 (2H, m, Ar-*H*), 7.53 (1H, m, Ar-*H*), 8.03-8.05 (2H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 33.29 (*C*H$_2$), 60.75 (*C*H$_2$), 64.99 (2x *C*H$_2$), 102.02 (*C*H), 128.35 (2x *C*H), 129.59 (2x *C*H), 130.23 (*C*), 132.93 (*C*H) and 166.47 (*C*O).

Bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid 2-[1,3]dioxolan-2-yl-ethyl ester methyl ester

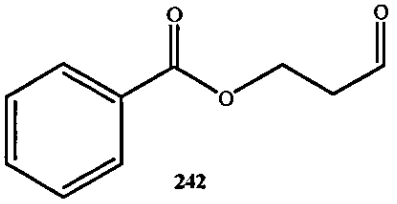


236

To a stirred solution of 7-[(methyloxy)carbon]bıcycle[4.1.0]hept-2-ene-7-carboxylıc acid (0 14 g, 0.71 mmol) and Cs_2CO_3 (0.58 g, 1.79 mmol) in acetone (8 ml) was added bromoethyl 1,3-dioxolane (0.16 g, 0 86 mmol) was added and stirred under reflux for 24 h. The mixture was then cooled and extracted into DCM (3x 20 ml), washed with aqueous $NaHCO_3$ (20 ml), the organic fractions were then combıned, dried ($MgSO_4$) and concentrated *in vacuo.* The mixture was then purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford the bicyclo[4 1 0]hept-2-ene-7,7-dicarboxylic acıd 2-

[1,3]dioxolan-2-yl-ethyl ester methyl ester as a colourless oil (0.16 g, 0.54 mmol, 75 %); υ_{max} (thin film)cm^{-1} 2925 (C-H str), 1725 (C=O str), 1324, 1247, 1197, 1106, 1066 and 1024 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.68-1.75 (4H, m, 5-CH_2 and 4-CH_2), 1.94-2.00 (2H, m, 8-CH_2), 2.12-2.15 (2H, m, 1-C*H* and 6-C*H*), 3.71 (3H, s, CH_3), 3.83-3.87 (2H, m, CH_2), 3.95-3.98 (2H, m, CH_2), 4.23-4.26 (2H, t, *J* 6.5 Hz, 9-CH_2), 4.94 (1H, t, *J* 5 Hz, 10-C*H*), 5.68-5.73 (1H, m, 2-C*H*=CH), 5.89-5.95 (1H, m, 3-CH=C*H*); δ_c (100 MHz; $CDCl_3$) 16 05 (5-*C*H_2), 20.53 (4-*C*H_2), 24.51 (6-*C*H), 26.65 (1-*C*H), 33.04 (8-*C*H_2), 40.88 (7-*C*), 52.53 (*C*H_3), 61.38 (9-*C*H_2), 64.92 (2x *C*H_2), 101.75 (10-*C*H), 121.82 (2-*C*H), 127.94 (3-*C*H), 167.69 (*C*O) and 169.54 (*C*O); ms (EI): *m/z* 296 [M^+ 4%], 264 (8), 208 (4), 178 (55), 163 (7), 146 (31), 135 (4), 118 (18), 101 (38), 91 (32), 79 (21), 73 (100), 57 (29) and 45 (24). HRMS calc. for $C_{15}H_{20}O_6$ requires 296.1259, observed 296.1262.

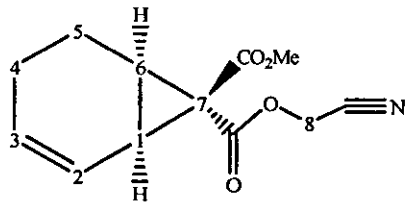
Benzoic acid 3-oxo-propyl ester



242

To a stirred solution of benzoic acid [1,3]dioxolan-2-yl ethyl ester (0.05 g, 0.23 mmol) in THF (1 ml) was added aqueous 5 *M* HCl (1 ml) at room temperature for 3 h. The reaction was then washed with aqueous $NaHCO_3$ (10 ml) and extracted into DCM (20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a mixture of benzoic acid 3-oxo-propyl ester and starting material as a colourless oil. Due to the unstable nature of the compound the assignment of the structure is tentative; δ_H (400 MHz; $CDCl_3$) 2.90-2.99 (2H, dt, *J* 1 and 6 Hz, CH_2), 4.67 (2H, t, *J* 6 Hz, CH_2), 7.26-7.45 (2H, m, Ar-*H*), 7.55-7.57 (1H, m, Ar-*H*), 7.99-8.02 (2H, m, Ar-*H*), 9 87 (1H, s, C*H*O); δ_c (100 MHz; $CDCl_3$) 42.83 (*C*H_2), 58 49 (*C*H_2), 128.34 (2x *C*H), 129.63 (2x *C*H), 130.17 (*C*), 133.20 (*C*H), 166.38 (*C*O) and 199 40 (*C*HO); m/z (EI): *m/z* 178 [M^+ 0.16%], 162 (4), 149 (9), 129 (22), 122 (100), 105 (100), 100 (27), 94 (25), 86 (26) and 77 (100). HRMS calc. for $C_{10}H_{10}O_3$ requires 178 06300, observed 178 06253.

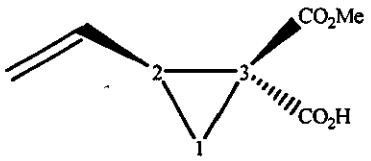
Bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid cyanomethyl ester methyl ester



243

To a stirred solution of 7-[(methyloxy)carbon]bicycle[4.1.0]hept-2-ene-7-carboxylic acid (0.15 g, 0.77 mmol) in DCM (8 ml) and triethylamine (0.15 g, 1.53 mmol) was added chloroacetonitrile (0.07 g, 0.92 mmol) and the mixture was stirred at room temperature for 17 h. The reaction mixture was washed with 2M HCl (15 ml), aqueous $NaHCO_3$ (3x 15 ml), and extracted into DCM (3x 20 ml). The organic phase was then dried ($MgSO_4$). The resulting mixture was concentrated *in vacuo* and purified by flash chromatography (silica gel, gradient elution 4:1 to 2:1, light petroleum: EtOAc) to afford the bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid cyanomethyl ester methyl ester as a yellow oil (0.14 g, 0.57 mmol, 75 %); υ_{max} (thin film)cm^{-1} 2949 (C-H str), 2359 (CN), 1736 (C=O str), 1435, 1331, 1233, 1201, 1176, 1108 and 1068 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.53-1.62 (1H, m, 5-C*H*H) 1.91- 1.97 (2H, m, 5-CH*H* and 4-C*H*H), 2.10-2.17 (3H, m, 4-CH*H*, 6-C*H* and 1-C*H*), 3.69 (3H, s, CH_3), 4.67 (2H, s, 8-CH_2), 5.68 (1H, m, 2-C*H*=CH), 5 80 (1H, m, 3-CH=C*H*); δ_c (100 MHz; $CDCl_3$) 15.93 (5-CH_2), 20 43 (4-CH_2), 25.88 (6-*C*H), 27 94 (1-*C*H), 37.62 (7-*C*), 49.14 (8-CH_2), 53.15 (CH_3), 113.95 (*C*N), 121.07 (2-*C*H), 128.73 (3-*C*H), 166.66 (*C*O), 168.36 (*C*O); ms (EI): *m/z* 235 [M^+ 9%], 203 (54), 178 (76), 163 (34), 146 (92), 135 (19), 118 (65), 100 (30), 91 (100), 79 (77), 65 (26), 59 (14), 51 (10) and 41 (10). HRMS calc. for $C_{12}H_{13}O_4N$ requires 235.0844, observed 235 0843.

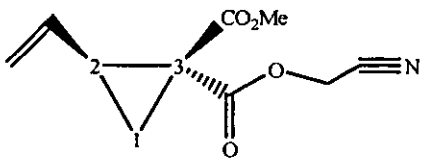
2-Vinyl-cyclopropane-1,1-dicarboxylic acid methyl ester[25, 71]



210

To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (1.00 g, 5.43 mmol) in THF (20 ml) and H_2O (20 ml) was added LiOH (0.13 g, 5.43 mmol) at room temperature. The reaction was stirred for 2 h, then acidified to pH 2 with 2 *M* HCl, extracted in Et_2O (3x 15 ml), washed with brine (3x 15 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford 2-vinyl-cyclopropane-1,1-dicarboxylic acid methyl ester as a colourless oil (0.85 g, 4.94 mmol, 91 %); υ_{max} (thin film)cm^{-1} 3088 (O-H str), 2955 (C-H str), 1732 (C=O str), 1439, 1333, 1208 and 1145 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.97-2.11 (2H, m, 1-C*H*$_2$), 2.72 (1H, q, *J* 8.8 Hz, 2-C*H*), 3 82 (3H, s, C*H*$_3$), 5.23 (1H, d, *J* 10.0 Hz, C*H*H), 5.38 (1H, d, *J* 16.8 Hz, CH*H*), 5.57-5.66 (1H, m, CH_2=C*H*), 10.40 (1H, s, O*H*); δ_c (100 MHz; $CDCl_3$) 23.46 (*C*H_2), 33.41 (*C*H), 38.83 (*C*H), 53.17 (*C*H_3), 120.92 (*C*H_2), 132.05 (*C*H), 171.52 (*C*O) and 172.93 (*C*O); ms (EI): *m/z* 188 [M^+ 40 %], 170 (100), 152 (70) and 120 (5). HMRS calc. for $C_8H_{10}O_4$ $[M^+NH_4]^+$ requires 188.0917, observed 188.0919.

2-Vinyl-cyclopropane-1,1-dicarboxylic acid cyanomethyl ester methyl ester

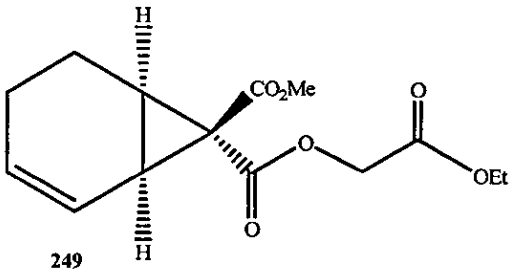


246

To a stirred solution of 2-vinyl-cyclopropane-1,1-dicarboxylic acid methyl ester (0.12 g, 0 68 mmol) in DCM (5 ml) was added triethylamine (0.14 g, 1.35 mmol) and stirred at room temperature for 10 min. Chloroacetonitrile (0.06 g, 0 81 mmol) was then added and left to stir for 24 h at room temperature. The reaction mixture was washed with 2 *M* HCl (15 ml), aqueous $NaHCO_3$ (3x 15 ml), and extracted into DCM (3x 20 ml). The organic phase was then dried ($MgSO_4$) The resulting mixture was then purified by flash chromatography (silica gel, gradient elution 4.1 to 2:1, light petroleum: EtOAc) to afford the 2-vinyl-cyclopropane-1,1-dicarboxylic acid cyanomethyl ester methyl ester (0.09 g, 0.46 mmol, 67 %); υ_{max} (thin film)cm^{-1} 2955 (C-H str), 2344 (CN str), 1734 (C=O str), 1437, 1374, 1329, 1264, 1207, 1181

and 1124 (C-O str); δ_H (400 MHz, $CDCl_3$) 1.68 (1H, dd, *J* 5.0 and 9.0 Hz, 1-C*H*H), 1.87 (1H, dd, *J* 5.0 and 7.5 Hz, 1-CH*H*), 2.66 (1H, q, *J* 8 0 Hz, 2-C*H*), 3.76 (3H, s, CH_3), 4.78 (2H, s, CH_2), 5.19 (1H, dd, *J* 9.0 and 12.0 Hz, C*H*), 5.36 (1H, d, *J* 17.0 Hz, CH_2=CH), 5.41 (1H, m, CH_2=C*H*), δ_c (100 MHz; $CDCl_3$) 21.50 (2-*C*H), 32.65 (1-CH_2), 35.17 (3-*C*), 49.19 (CH_3), 52.90 (CH_2), 113.94 (*C*N), 119.80 (*C*H), 131.71 (CH_2), 166.73 (*C*O) and 168.27 (*C*O).

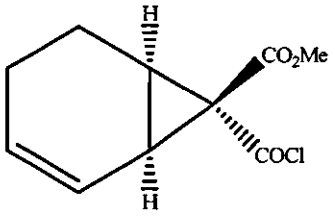
Bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid ethoxycarbonylmethyl ester methyl ester



249

To a stirred solution of 7-[(methyloxy)carbon]bicyclo[4.1.0]hept-2-ene-7-carboxylic acid (0.14 g, 0 69 mmol) in acetone (8 ml) was added K_2CO_3 (0.24 g, 1.73 mmol) and left stirring at room temperature for 10 minutes before bromoethyl acetate (0.13 g, 0.76 mmol) was added. The reaction was left stirring overnight at room temperature. The reaction mixture was then washed with 2 *M* HCl (10 ml), aqueous $NaHCO_3$ (10 ml) and extracted into DCM (3x 20 ml). The fractions were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (silica gel, gradient elution 4:1-2:1, light petroleum: EtOAc) to afford the bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid ethoxycarbonylmethyl ester methyl ester as a colourless oil (0.13 g, 0.46 mmol, 65 %); υ_{max} (thin film)cm^{-1} 2983 (C-H str), 1761 (C=O str), 1734 (C=O str), 1436, 1331, 1254, 1204, 1177 and 1107 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.26 (3H, t, *J* 7.0 Hz, CH_3), 1.72-1 80 (2H, m, CH_2), 1.96-1.99 (2H, m, CH_2), 2.18-2.23 (2H, m, 2x C*H*), 3.74 (3H, s, CH_3), 4.19-4.24 (2H, q, *J* 7.0 Hz, CH_2), 4.61 (2H, s, CH_2), 5.73 (1H, m, CH=C*H*), 5 89 (1H, m, C*H*=CH); δ_c (100 MHz; $CDCl_3$) 14 08 (CH_3), 16.03 (CH_2), 20.51 (CH_2), 24.81 (*C*H), 26.94 (*C*H), 40.64 (*C*), 52 68 (CH_3), 61.40 (CH_2), 62.47 (CH_2), 121.62 (*C*H), 128 21 (*C*H), 167.22 (*C*O), 167.31 (*C*O) and 169.16 (*C*O); ms (EI) *m/z* 282 [M^+ 5%], 250 (76), 178 (95), 146 (100), 118 (74), 91 (50) and 79 (36) HRMS calc. for $C_{14}H_{18}O_6$ requires 282.1103, observed 282.1107.

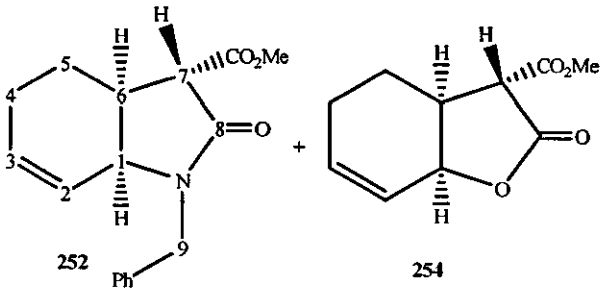
Methyl 7-chloro bicycle[4.1.0]hept-2-ene-7-carboxylate



253

To a stirred solution of bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid methyl ester (0.20 g, 1.00 mmol) in anhydrous DCM (5 ml) was added oxallyl chloride (0.13 g, 0.09 mmol) and stirred at room temperature for 15 min. The reaction mixture was then cooled to O° C as 1 drop of DMF was added and the reaction was then allowed to reach room temperature and was stirred for 1 h. The solvent was then removed and the resulting product was carried forward to the next reaction without purification.

Methyl 2-oxo-1-(phenylmethyl)-2,3,3a,4,5,7a-hexahydro-1H-indole-3-carboxylate and methyl 2-oxo-2,3,3a,4,5,7a-hexahydrobenzo[b]furan-3-carboxylate

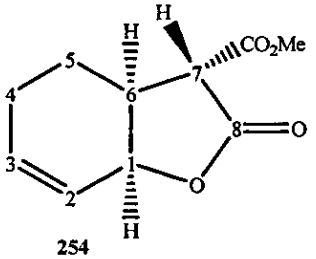


252 254

To a stirred solution of methyl 7-chloro bicycle[4.1.0]hept-2-ene-7-carboxylate in anhydrous DCM (5 ml) was added benzylamine (0.16 g, 0.16 mmol) and the solution was stirred at room temperature for 24 h. The resulting mixture was concentrated *in vacuo* and purified by flash chromatography (silica gel, 4:1, light petroleum: EtOAc) to afford methyl 2-oxo-1-(phenylmethyl)-2,3,3a,4,5,7a-hexahydro-1H-indole-3-carboxylate (0.09 g, 0 32 mmol, 42 %) and methyl 2-oxo-2,3,3a,4,5,7a-hexahydrobenzo[b]furan-3-carboxylate (0 02 g, 0.12 mmol, 11 %), see following data for methyl 2-oxo-2,3,3a,4,5,7a-hexahydrobenzo[b]furan-3-carboxylate **252**; υ_{max} (thin film)cm^{-1} 3364 (N-R str), 2925 (C-H str), 1738 (C=O str), 1694 (C=O str), 1435, 1395, 1267, 1195 and 1165 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.45-1.67 (2H, m, 5-C*H*$_2$), 1.97-1.98 (2H, m, 4-C*H*$_2$), 2 68-2.70 (1H, m, 6-C*H*), 3.25 (1H, d, *J* 7.0 Hz, 7-C*H*), 3.72 (3H, s, C*H*$_3$), 3 88 (1H, m, 1-C*H*), 3.91 (1H, d, *J* 15.0 Hz, 9-C*H*H), 4.93 (1H, d, *J* 15.0 Hz, 9-CH*H*), 5 57-5.61 (1H, m, 2-CH=C*H*), 5.87-5.90 (1H, m, 3-C*H*=CH), 7.24-7.28 (5H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 22.10 (*C*H$_2$), 23.44 (*C*H$_2$), 35.79 (*C*H), 44.52 (*C*H$_2$),

52.63 (*C*H), 52.85 (*C*H$_3$), 53.11 (*C*H), 122.69 (2-CH=*C*H), 127 62 (*Ar*-H), 127.93 (2x *Ar*-H), 128.71 (2x *Ar*-H), 131.83 (3-*C*H=CH), 136.04 (*C*), 169.26 (*C*O), 170.33 (*C*O); ms (EI): *m/z* 285 [M$^+$ 60%], 254 (9), 226 (22), 206 (10), 194 (22), 174 (14), 162 (16), 146 (44) and 91 (100). HRMS calc. for $C_{17}H_{19}NO_3$ requires 285.1364, observed 285.1360.

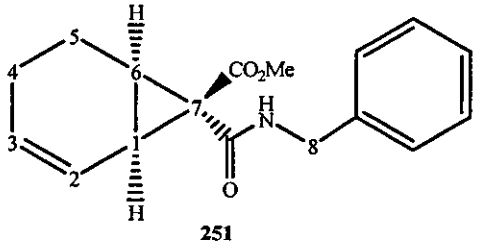
Methyl 2-oxo-2,3,3a,4,5,7a-hexahydrobenzo[b]furan-3-carboxylate



254

To a stirred solution of bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid methyl ester (0.05 g, 0.26 mmol) in anhydrous THF (4 ml) was added $ZnBr_2$ (0.01 g, 0.005 mmol) and was left to stir at room temperature. This mixture was left to stir under nitrogen for 15 min before $Pd(PPh_3)_4$ (0 03 g, 10 mol %) was added and was further stirred for 24 h. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, 4:1, light petroleum: EtOAc) to afford methyl 2-oxo-2,3,3a,4,5,7a-hexahydrobenzo[b]furan-3-carboxylate as a yellow oil (0.04 g, 0.22 mmol, 86 %); υ_{max} (thin film)cm^{-1} 2928 (C-H str), 1776 (C=O str), 1736 (C=O str), 1437, 1396, 1329, 1268, 1194, 1167 and 1142 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.57-1.61 (1H, m, 5-C*H*), 1.77-1.78 (1H, m, 5-C*H*), 2.03-2.08 (2H, m, 4-C*H*$_2$), 2.94-2.97 (1H, m, 6-C*H*), 3.33 (1H, d, *J* 6 0 Hz, 7-C*H*), 3.74 (3H, s, C*H*$_3$), 4.95 (1H, s, 1-C*H*O), 5.75-5.78 (1H, m, 2-CH=C*H*), 6.02-6.05 (1H, m, 3-C*H*=CH); δ_c (100 MHz; $CDCl_3$) 21 62 (5-*C*H$_2$), 23.49 (4-*C*H$_2$), 37 63 (6-*C*H), 51.34 (7-*C*H), 55.89 (*C*H$_3$), 75 17 (1-*C*HO), 123 33 (2-*C*H=CH), 133 60 (3-CH=*C*H), 167.95 (*C*O) and 171.36 (*C*O); ms (EI): *m/z* 196 [M$^+$ 1%], 168 (5), 137 (100), 118 (7), 109 (6), 100 (3), 96 (27), 91 (40), 77 (24), 68 (10) and 59 (7). HRMS calc for $C_{10}H_{12}O_4$ requires 196.0735, observed 196 0731.

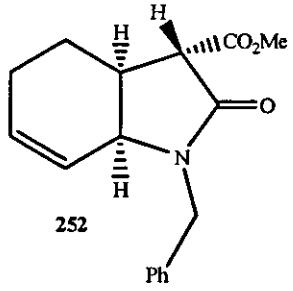
7-Benzylcarbamoyl-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester[46]



251

To a stirred solution of 7-[(methyloxy)carbon]bicycle[4.1.0]hept-2-ene-7-carboxylic acid (0.05 g, 0.26 mmol), DIEA (0.09 ml, 0.51 mmol), HATU (0.12 g, 0.31 mmol) in anhydrous DMF (2 ml) at room temperature was added benzylamine (0.06 g, 0.51 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for a further 3 h before being diluted with DCM (15 ml). The mixture was then washed with 2 *M* HCl (10 ml), aqueous $NaHCO_3$ (2x 10 ml) and extracted into DCM (3x 15 ml). The organic extracts were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by flash chromatography using gradient elution (silica gel, 4:1 to 2:1, light petroleum: EtOAc) to afford the 7-benzylcarbamoyl-bicyclo[4.1 0]hept-2-ene-7-carboxylic acid methyl ester as a colourless oil (0.07 g, 0 25 mmol, 96 %); υ_{max} (thin film)cm^{-1} 3359 (N-H str), 1731 (C=O str), 1651 (C=O str), 1523, 1454, 1434, 1321, 1256, 1197 and 1115 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.98-2.06 (4H, m, 4 and 5-C*H*$_2$), 2.20-2.27 (2H, m, 1-C*H* and 6-C*H*), 3.71 (3H, s, C*H*$_3$), 4.43 (2H, d, *J* 5 0 Hz, 8-C*H*$_2$), 5.72 (1H, m, 2-C*H*=CH), 5.87 (1H, m, 3-CH=C*H*), 6.83 (1H, s, N*H*), 7.28 (5H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 16.07 (5-*C*H$_2$), 20 80 (4-*C*H$_2$), 24.21 (6-*C*H), 24.87 (1-*C*H), 42.44 (7-*C*), 44.10 (8-*C*H$_2$), 52.62 (*C*H$_3$), 121.86 (3-*C*H), 127.45 (2x *Ar*-H), 127.57 (*Ar*-H), 127.92 (*Ar*-H), 128.19 (2-*C*H), 128.69 (*Ar*-H), 138 10 (*C*), 167.45 (*C*O), 170.75 (*C*O); ms (EI): *m/z* 285 (M^+ 4 %), 253 (15), 224 (2), 207 (2), 178 (65), 146 (22), 118 (15), 106 (18), 91 (100), 79 (18) and 65 (17). HRMS calc. for $C_{17}H_{19}O_3N$ requires 285. 1364, observed 285.1367.

1-Benzyl-2-oxo-2,3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester



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Method A

To a stirred solution of 7-benzylcarbamoyl-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester (0.02 g, 0 07 mmol) in methanol (2 ml) was added $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol). This solution was stirred for 3 h at room temperature. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford the 1-benzyl-2-oxo-2,3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester as a yellow oil (0.01 g, 0.05 mmol, 70 %); υ_{max} (thin film)cm^{-1} 3364 (N-R str), 2925 (C-H str), 1738 (C=O str), 1694 (C=O str), 1435, 1395, 1267, 1195 and 1165 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.45-1.67 (2H, m, C*H*$_2$), 1.97-1.98 (2H, m, C*H*$_2$), 2.69 (1H, m, C*H*), 3 25 (1H, d, *J* 7.0 Hz, C*H*), 3.72 (3H, s, C*H*$_3$), 3.88 (1H, m, C*H*), 3.93 (1H, d, *J* 15.0 Hz, C*H*), 4.93-4.97 (1H, d, *J* 15.0 Hz, C*H*), 5.59 (1H, m, CH=C*H*), 5.89 (1H, m, C*H*=CH), 7.24-7.28 (5H, m, Ph); δ_c (100 MHz; $CDCl_3$) 22.10 (*C*H$_2$), 23.44 (*C*H$_2$), 35.79 (*C*H), 44 52 (*C*H$_2$), 52.63 (*C*H), 52.85 (*C*H$_3$), 53.11 (*C*H), 122.69 (CH=*C*H), 127.62 (*C*H), 127.93 (2x *C*H), 128.71 (2x *C*H), 131.83 (*C*H=CH), 136.04 (*C*), 169.26 (*C*O) and 170.33 (*C*O); ms (EI): *m/z* 285 [M^+ 60%], 254 (9), 226 (22), 206 (10),194 (22), 174 (14), 162 (16), 146 (44) and 91 (100). HRMS calc. for $C_{17}H_{19}NO_3$ requires 285.1364, observed 285.1360.

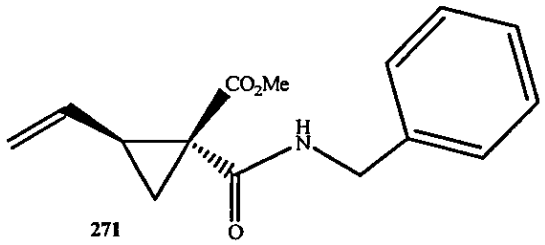
Method B

To a stirred solution 7-benzylcarbamoyl-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester (0.06 g, 0.22 mmol) in MeOH (2 ml) was added $Pd(PPh_3)_4$ (0.03 g, 0 02 mmol). This solution was stirred for 17 h at room temperature. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-benzyl-2-oxo-2,3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester as a yellow oil (0.06 g, 0 22 mmol, 99 %); data as above.

Method C

To a stirred solution of 7-benzylcarbamoyl-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester (0 02 g, 0.07 mmol) in anhydrous DCM (2 ml) was added $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol). This solution was stirred for 24 h at room temperature. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-benzyl-2-oxo-2,3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester as a yellow oil (0 03 g, 0.12 mmol, 53 %): data as above.

1-Benzylcarbamoyl-2-vinyl-cyclopropanecarboxylic acid methyl ester



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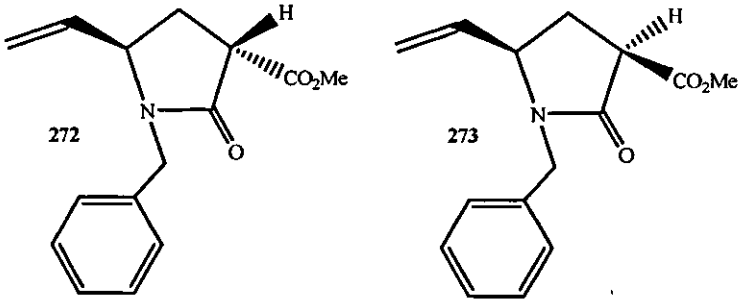
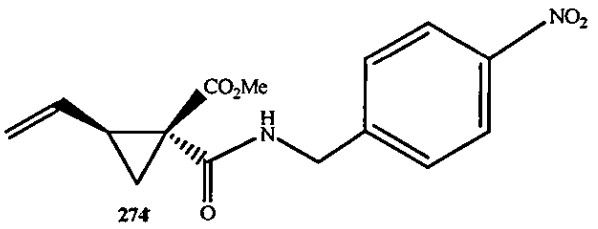
After subjecting 2-vinyl-cyclopropane-1,1-dicarboxylic acid methyl ester and benzylamine to the standard amide coupling and work-up conditions the crude material was purified by flash chromatography (silica gel, 4:1, light petroleum: EtOAc) to afford 1-benzylcarbamoyl-2-vinyl-cyclopropanecarboxylic acid methyl ester as a yellow oil (0.41 g, 1.58 mmol, 83 %); υ_{max} (thin film)cm^{-1} 3357 (N-H str), 2961 (C-H str), 1711 (C=O str), 1653 (C=O str), 1523, 1438, 1200 and 1143 (C-O str); δ_H (400 MHz, $CDCl_3$) 1.80-1.83 (1H, dd, *J* 4.0 and 8.0 Hz, C*H*), 2.02-2.05 (1H, dd, *J* 4.0 and 8.0 Hz, C*H*), 2 49-2.56 (1H, q, *J* 8 5 Hz, C*H*), 3.63 (3H, s, CH_3), 4.36 (1H, dd, J_{AB} 5.6 and 14.8 Hz, C*H*H), 4.46 (1H, dd, J_{AB} 5 6 and 14.8 Hz, CH*H*), 5.09 (1H, d, *J* 10.4 Hz, C*H*H), 5.11 (1H, d, *J* 16.8 Hz, CH*H*), 5.51-5.60 (1H, m, CH_2=C*H*), 7.19-7.27 (5H, m, Ar-*H*), 8.60 (1H, br s, N*H*); δ_c (100 MHz; $CDCl_3$) 21.55 (CH_2), 34.46 (*C*), 37.14 (*C*H), 44.03 (CH_2), 52 08 (CH_3), 119.70 (CH_2), 127.35 (*C*H), 127.67 (2x *C*H), 128.67 (2x *C*H), 133.24 (*C*H), 138.29 (*C*), 167 84 (*C*O) and 171.83 (*C*O); ms (EI): *m/z* 277 [M^+ 5%], 260 (10), 200 (18), 130 (38), 106 (71), 91 (100), 77 (27) and 65 (66). HRMS calc. for $C_{15}H_{17}NO_3$ $[M^+NH_4]^+$ requires 277.1547, observed 277.1547.

1-Benzyl-2-oxo-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester



After subjecting 1-benzylcarbamoyl-2-vinyl-cyclopropanecarboxylic acid methyl ester to the standard rearrangement conditions the crude mixture was purified by flash chromatography (silica gel, gradient elution 2:1 to 1:1 light petroleum: EtOAc) to afford 1-benzyl-2-oxo-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester (0.09 g, 0.37 mmol, 80 %) as an inseparable 1:1 mixture of diastereoisomers as a yellow oil. Due to the nature of the inseparable mixture ' denotes one diastereoisomer from the other, unfortunately it was not possible to deduce the *cis* from the *trans* isomer; υ_{max} (thin film)cm^{-1} 2950 (C-H str), 1740 (C=O str), 1685 (C=O str), 1495, 1419, 1335, 1249 and 1166 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.89-1.96 (1H, m, 'C*H*H), 2 07-2.15 (1H, m, C*H*H), 2.30-2.37 (1H, m, CH*H*), 2.41-2.48 (1H, m, 'CH*H*), 3.39-3.44 (1H, m, C*H*), 3.47-3.51 (1H, m, 'C*H*), 3.71 (3H, s, 'CH_3), 3.73 (3H, s, CH_3), 3.76-3 80 (1H, m, C*H*), 3.78 (2H, t, *J* 14.8 Hz, 'CH_2), 3.92-3.97 (1H, m, 'C*H*), 4 88 (2H, dd, *J* 14.8 and 22.0 Hz, CH_2), 5.05-5.10 (2H, m, 'CH_2), 5.14-5.22 (2H, m, CH_2), 5.48-5.57 (1H, m, 'C*H*), 5 60-5 69 (1H, m, C*H*), 7.12-7.24 (10H, m, 'Ar-*H* and Ar-*H*); δ_c (100 MHz; $CDCl_3$) 29.06 (*C*H_2), 29.60 ('*C*H_2), 44.61 (*C*H_2), 44.67 ('*C*H_2), 47.59 ('*C*H), 48.00 (*C*H), 52.73 (*C*H_3), 52.80 ('*C*H_3), 59 09 ('*C*H), 59.28 (*C*H), 119.23 (*C*H_2), 119.77 ('*C*H_2), 127.56 (*C*H), 127.63 (2x *C*H), 128.18 (2x *C*H), 128.52 (2x '*C*H), 128 62 (2x '*C*H), 128.65 ('*C*H), 135.90 (*C*), 136.18 ('*C*), 136 66 ('*C*H), 137.41 (*C*H), 169 66 (*C*O), 169.85 ('*C*O), 170.55 ('*C*O) and 170.69 (*C*O).

1-(4-Nitro-benzylcarbamoyl)-2-vinyl-cyclopropanecarboxylic acid methyl ester



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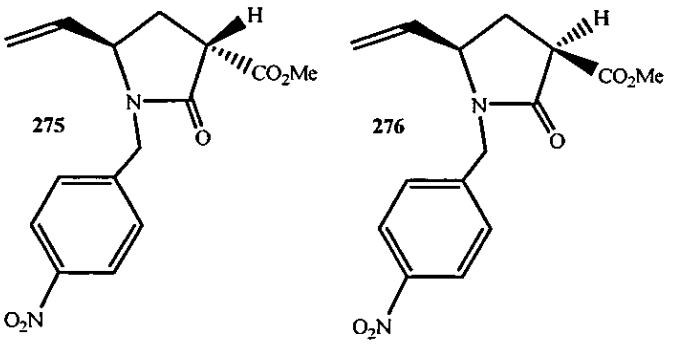
After subjecting 2-vinyl-cyclopropane-1,1-dicarboxylic acid methyl ester and *p*-nitro benzylamine to the standard amide coupling conditions the crude material was purified by flash chromatography (silica gel, 4:1, light petroleum: EtOAc) to afford the 1-(4-Nitro-benzylcarbamoyl)-2-vinyl-cyclopropanecarboxylic acid methyl ester as a pale yellow oil (0.23 g, 0.74 mmol, 61 %); υ_{max} (thin film)cm^{-1} 3352 (N-H str), 2952 (C-H str), 1707 (C=O str), 1657 (C=O str), 1519 (NO_2), 1439, 1344 and 1199 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.93 (1H, dd, *J* 4.4 and 8.0 Hz, C*H*H), 2.10 (1H, dd, *J* 4 4 and 8.0 Hz, CH*H*), 2.58 (1H, q, *J* 17.2 Hz, C*H*), 3.74 (3H, s, CH_3), 4.57 (1H, dd, J_{AB} 6.0 and 15.6 Hz, C*H*H), 4 63 (1H, dd, J_{AB} 6.0 and 15.6 Hz, CH*H*), 5.19 (1H, d, *J* 10.0 Hz, C*H*), 5.38 (1H, d, *J* 16.8 Hz, C*H*), 5.60-5.67 (1H, m, CH_2=C*H*), 7.45 (2H, d, *J* 8.8 Hz, Ar-*H*), 8.19 (2H, d, *J* 8.8 Hz, Ar-*H*), 9.00 (1H, t, *J* 8 0 Hz, N*H*); δ_c (100 MHz; $CDCl_3$) 21.82 (*C*H_2), 34.47 (*C*), 37 66 (*C*H), 43.24 (*C*H_2), 52.23 (*C*H_3), 120.05 (*C*H_2), 123.88 (*C*H), 127.93 (*C*H), 128.13 (*C*H), 132.13 (*C*H), 146.05 (*C*), 147.18 (*C*), 168.40 (*C*O) and 171.97 (*C*O); ms (EI): *m/z* 327 [M^+ 78%], 262 (12), 192 (53), 102 (100) and 88 (40). HRMS calc. for $C_{15}H_{16}N_2O_5$ $[M^+Na]^+$ requires 327.0951, observed 327.0954.

1-(4-Nitro-benzyl)-2-oxo-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester

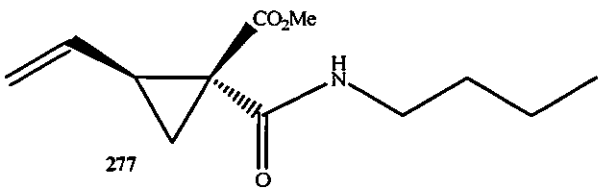


275 276

After subjecting 1-(4-nitro-benzylcarbamoyl)-2-vinyl-cyclopropanecarboxylic acid methyl ester to the standard rearrangement conditions the crude mixture was purified by flash chromatography (silica gel, gradient elution 4:1-1:1, light petroleum: EtOAc) to afford 1-(4-nitro-benzyl)-2-oxo-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester as an inseparable 1:1 mixture of diastereoisomers as a yellow oil (0.04 g, 0 15 mmol, 49 %). Due to the nature of

the inseparable mixture 'denotes one diastereoisomer from the other, unfortunately it was not possible to deduce the *cis* from the *trans* isomer, υ_{max} (thin film)cm^{-1} 2952 (C-H str), 1740 (C=O str), 1696 (C=O str), 1605, 1517 (NO_2), 1432, 1345, 1257 and 1168 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.01-2.08 (1H, m, 'C*H*H), 2.20-2.27 (1H, m, C*H*H), 2.44-2.49 (1H, m, CH*H*), 2.52-2.59 (1H, m, 'CH*H*), 3.53 (1H, t, *J* 9.2 Hz, C*H*), 3.57-3.60 (1H, m, 'C*H*), 3.80 (3H, s, 'CH_3), 3.82 (3H, s, CH_3), 3.84-3.90 (1H, m, C*H*), 4.03 (1H, s, 'C*H*), 4.05 (1H, d, *J* 15.6 Hz, 'C*H*H), 4.20 (1H, d, *J* 15.2 Hz, C*H*H), 4.98 (1H, d, *J* 15.6 Hz, 'CH*H*), 5.02 (1H, d, *J* 15.6 Hz, CH*H*), 5.20 (2H, t, *J* 17.6 Hz, 'C*H*H), 5.26-5.30 (2H, m, CH_2), 5.54-5.61 (1H, m, 'C*H*), 5.68-5.74 (1H, m, C*H*), 7.38 (2H, d, *J* 8.4 Hz, 'Ar-*H*), 7.38 (2H, d, *J* 8.4 Hz, Ar-*H*), 8.16 (2H, d, *J* 8.0 Hz, 'Ar-*H*), 8.16 (2H, d, *J* 8.0 Hz, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 29.26 ('CH_2), 29 87 (CH_2), 44.11 ('CH_2), 44.33 (CH_2), 47.44 ('*C*H and *C*H), 52.87 ('CH_3), 52.92 (CH_3), 59.83 ('*C*H), 60.06 (*C*H), 120 05 ('CH_2), 120.32 (CH_2), 123.93 (2x '*C*H and 2x *C*H), 128.80 (2x *C*H), 129.12 (2x '*C*H), 136.42 (*C*H), 137.36 ('*C*H), 143.34 (*C*), 143.79 ('*C*), 147.45 ('*C* and *C*), 170 04 ('*C*O), 170.23 (*C*O) and 170.59 ('*C*O and *C*O); ms (EI): *m/z* 305 [M^+ 20%], 245 (22), 191 (35), 136 (38), 101 (45), 89 (98), 78 (60) and 59 (100). HRMS calc for $C_{15}H_{16}N_2O_5$ $[M^+H]^+$ requires 305 1132, observed 305.1130.

1-Butylcarbamoyl-2-vinyl-cyclopropanecarboxylic acid methyl ester



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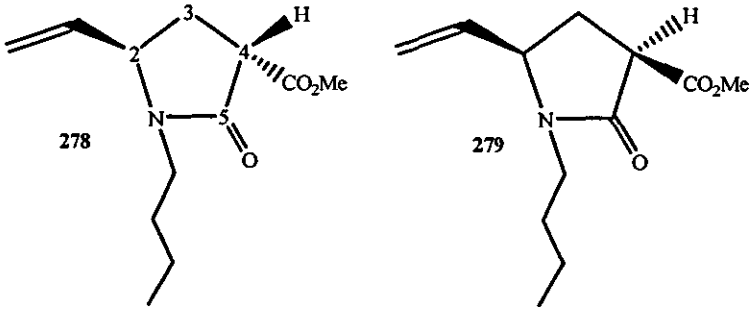
To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid methyl ester (0.21 g, 1.23 mmol), in DMF (3 ml) at room temperature was added DIEA (0 33 ml, 1 48 mmol), along with HATU (0.56 g, 1.48 mmol) and the mixture was left stirring for 10 min. Then butylamine (0 09 g, 1.23 mmol) was added and the reaction was left stirring for 3 h. The reaction was then diluted with DCM (15 ml), washed with 2M HCl (10 ml), aqueous $NaHCO_3$ (20 ml) and re-extracted into DCM (3x 20 ml), the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (silica gel, 4·1, light petroleum: EtOAc) to afford the 1-butylcarbamoyl-2-vinyl-cyclopropanecarboxylic acid methyl ester as a pale yellow oil (0.16 g, 0.70 mmol, 57 %); υ_{max} (thin film)cm^{-1} 3364 (N-H str), 2955 (C-H str), 1709 (C=O str), 1653 (C=O str), 1534, 1437, 1344, 1319 and 1141 (C-O str); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7 6 Hz, CH_3), 1.31-1.56 (4H, m, CH_2CH_2), 1.85 (1H, dd, *J* 4.0 and 8.5 Hz, C*H*), 2.06 (1H, dd, *J* 4 0

and 8.5 Hz, C*H*), 2.50 (1H, q, *J* 8.0 Hz, C*H*), 3 24-3.34 (2H, m, CH_2), 3.74 (3H, s, CH_3), 5.14 (1H, d, *J* 10.0 Hz, C*H*H), 5.30 (1H, d, *J* 17.2 Hz, CH*H*), 5.57-5.63 (1H, m, CH_2=C*H*), 8.37 (1H, br s, N*H*); δ_c (100 MHz; $CDCl_3$) 13.78 (CH_3), 20 19 (CH_2), 21.28 (CH_2), 31.48 (CH_2), 34.35 (*C*), 36.46 (*C*H), 39.71 (CH_2), 52 03 (CH_3), 119.59 (CH_2), 133.37 (*C*H), 171.97 (*C*O) and 172.71 (*C*O); ms (EI): *m/z* 248 [M^+ 40%], 219 (12), 153 (10), 130 (32) and 88 (100). HRMS calc. for $C_{12}H_{19}NO_3$ $[M^+Na]^+$ requires 248.1258, observed 248.1257.

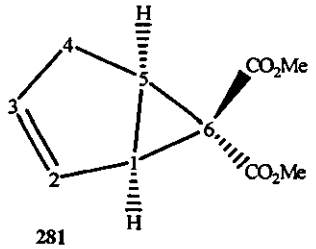
1-Butyl-2-oxo-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester



To a stirred solution of the 1-butylcarbamoyl-2-vinyl-cyclopropanecarboxylic acid methyl ester (0 08 g, 0.36 mmol) in MeOH (2 ml) under N_2 was added $Pd(PPh_3)_4$ (0 04 g, 0.04 mmol) and the reaction was left stirring at room temperature for 17 h. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, gradient elution 2:1 to 1:1, light petroleum: EtOAc) to afford 1-butyl-2-oxo-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester as a yellow oil in a 1:1 mixture of inseparable diastereoisomers (0.05 g, 0.20 mmol, 56 %). Due to the nature of the inseparable mixture ' denotes one diastereoisomer from the other, unfortunately it was not possible to deduce the *cis* from the *trans* isomer, υ_{max} (thin film)cm^{-1} 3405 (N-R str), 2957 (C-H str), 1741 (C=O str), 1682 (C=O str), 1454, 1426, 1257 and 1168 (C-O str), δ_H (400 MHz; $CDCl_3$) 0.81 (6H, t, *J* 7.2 Hz, 'CH_3 and CH_3), 1.16-1 23 (4H, m, 'CH_2 and CH_2), 1.34-1.45 (2H, m, 'CH_2 and CH_2), 1.83-1.93 (1H, m, 'C*H*H), 2.01-2.13 (1H, m, C*H*H), 2 34-2.40 (1H, m, CH*H*), 2.48-2.53 (1H, m, 'CH*H*), 2.81-2.88 (2H, m, 'C*H*H and C*H*H), 3 42-3.47 (2H, m, 'C*H* and C*H*), 3.49-4 56 (2H, m, 'CH*H* and CH*H*), 3.70 (3H, s, 'CH_3), 3.71 (3H, s, CH_3), 3.90 (1H, q, *J* 16.0 Hz, C*H*), 4.11-4 17 (1H, m, 'C*H*), 5.17-5 26 (4H, m, 'CH_2 and CH_2), 5.51-5.57 (1H, m, 'C*H*); 5.60-5 69 (1H, m, C*H*); δ_c (100 MHz; $CDCl_3$) 13.74 (CH_3), 13.76 (CH_3), 19.91 (CH_2), 20.02 (CH_2), 29.10 (CH_2), 29.13 (CH_2), 29.30 (CH_3), 29.83 (CH_2), 40.78 (CH_2), 40.81 (CH_2), 47.74 (*C*H), 48.00 (*C*H), 52 70 (CH_3), 52.76 (CH_3), 60.01 (*C*H), 60.18 (*C*H), 118.77 (CH_2), 119.14 (CH_2), 137.23 (*C*H), 137.87 (*C*H), 169.47 (*C*O), 169.59 (*C*O), 170.70 (*C*O) and 170.84 (*C*O);

ms (EI): *m/z* 226 [M^+ 13%] 196 (12), 182 (14), 166 (20), 150 (22), 59 (48) and 41 (100). HRMS calc. for $C_{12}H_{19}NO_3$ $[M^+H]^+$ requires 226.1438, observed 226.1438.

Bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester[24]



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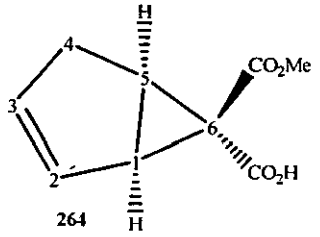
To a stirred solution of 1,3-cyclopentatadiene (0.92 g, 13.9 mmol), and $Rh_2(OAc)_4$ (0.06 g, 0.14 mmol) in 1,2-dichloroethane (2 ml) was added dimethyl diazomalonate (2.00 g, 12.7 mmol) *via* syringe pump diluted in 1,2-dichloroethane (4 ml). The mixture was stirred under reflux for 3 h. The mixture was allowed to cool to room temperature before being concentrated *in vacuo*. The resulting oil was purified by flash chromatography (Silica gel, hexane: EtOAc, 2.1) to afford as a colourless viscous oil (0.48 g, 2.44 mmol, 20 %); υ_{max} (thin film)cm^{-1} 2952 (C-H str), 1728 (C=O str), 1436, 1254, 1162 and 1083 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.34-2.39 (1H, m, 5-C*H*), 2.63-2.71 (3H, m, 1-C*H* and 4-CH_2), 3.56 (3H, s, CH_3), 3.65 (3H, s, CH_3), 5.52-5.57 (1H, m, 3-C*H*=CH), 5.72-5.75 (1H, m, 2-CH=C*H*); δ_c (100 MHz; $CDCl_3$) 31.61 (5-*C*H), 34.62 (4-*C*H_2), 38.61 (6-*C*), 39.36 (1-*C*H), 52.21 (*C*H_3), 52.37 (*C*H_3), 129 49 (3-*C*H), 132.18 (2-*C*H), 166 92 (*C*O) and 170.16 (*C*O); m/z: (EI) 196 (M+, 36%) 164 (100), 136 (27), 105 (38) and 77 (31); HRMS Found 196 0737 $C_{10}H_{12}O_4$ requires 196.0735.

Bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester



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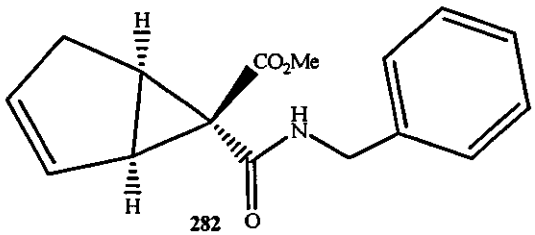
To a stirred solution of bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester(1 46 g, 7.45 mmol) in THF/H_2O (1:1, 2ml) was added LiOH (0 31 g, 7.45 mmol) and stirred at room temperature for 2 h. The mixture was then acidified to pH 2 with 2 *M* HCl, extracted into Et_2O (3x 10 ml), washed with brine (3x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester as an impure orange solid

(1.20 g, 6.59 mmol, 89 %); mp range 106 8-117.3 °C; υ_{max} (thin film)cm^{-1} 2953 (C-H str), 1734 (C=O str), 1436, 1317, 1264, 1198 and 1162 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.60-2.83 (4H, m, 4-C*H*$_2$, 5-C*H* and 1-C*H*), 3.57 (3H, s, C*H*$_3$), 5.58-5.59 (1H, m, 2-C*H*=CH), 5.73-5.75 (1H, m, 3-CH=C*H*), 9.10 (1H, s, O*H*), δ_c (100 MHz; $CDCl_3$) 28.67 (5-*C*H), 37.80 (4-*C*H$_2$), 38.49 (6-*C*), 40.26 (1-*C*H), 52.54 (*C*H$_3$), 129.30 (2-*C*H), 132.63 (3-*C*H), 166.09 (*C*O) and 176.11 (*C*O).

6-Benzylcarbamoyl-bicyclo[3.1.0]hex-2-ene-6-carboylic acid methyl ester



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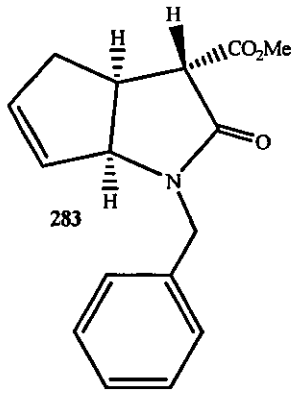
To a stirred solution of bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester (0.24 g, 1.30 mmol), in DMF (3 ml) at room temperature was added DIEA (0.450 ml, 2.60 mmol), along with HATU (0.59 g, 1.56 mmol) and the mixture was left stirring for 10 min. Then benzylamine (0.17g, 1.56 mmol) was added and the reaction was left stirring for 3 h. The reaction was then diluted with DCM (15 ml), washed with 2 *M* HCl (10 ml), aqueous $NaHCO_3$ (20 ml) and re-extracted into DCM (3x 20 ml), the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 2:1, light petroleum: EtOAc) to afford 6-benzylcarbamoyl-bicyclo[3 1.0]hex-2-ene-6-carboylic acid methyl ester as a white solid (0.20 g, 0.74 mmol, 57 %); mp range 137.1-139.4 °C; υ_{max} (thin film)cm^{-1} 3298 (N-H str), 1727 (C=O str), 1640 (C=O str), 1535, 1432, 1300 and 1158 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.53-2.54 (1H, m, C*H*), 2 64-2.67 (2H, m, C*H*$_2$), 2.67-2.74 (1H, m, C*H*), 3.55 (3H, s, C*H*$_3$), 4.37 (2H, d, *J* 5.7 Hz, C*H*$_2$), 5 58-5.59 (1H, m, C*H*=CH), 5.70-5.71 (1H, m, CH=C*H*), 6.50 (1H, s, N*H*), 7.17-7.26 (5H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 29.53 (*C*H), 34.51 (*C*H$_2$), 39.23 (*C*H), 39.55 (*C*), 44.01 (*C*H$_2$), 52.35 (*C*H$_3$), 127.50 (2x *C*H), 127.57 (2x *C*H), 128.73 (*C*H), 129.25 (*C*H), 132.72 (*C*H), 138.05 (*C*), 167.46 (*C*O) and 169.37 (*C*O); ms (FAB): *m/z* 272 [M$^+$ 100%], 240 (21), 165 (76), 136 (34), 106 (27) and 91 (82). HRMS calc. for $C_{17}H_{17}NO_5$ requires 272 21623, observed 272.21660

1-Benzyl-2-oxo-1,2,3,3a,4,6a-hexahydeocyclopenta[*b*]pyrrole-3-carboxylic acid methyl ester



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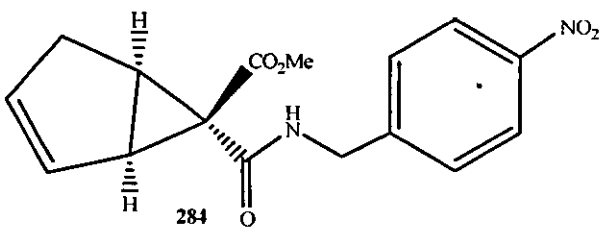
After subjecting 6-benzylcarbamoyl-bicyclo[3.1.0]hex-2-ene-6-carboylic acid methyl ester to the standard rearrangement conditions the crude mixture was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford **1**-Benzyl-2-oxo-1,2,3,3a,4,6a-hexahydeocyclopenta[*b*]pyrrole-3-carboxylic acid methyl ester as a yellow oil (0.04 g, 0.16 mmol, 86%); υ_{max} (thin film)cm^{-1} 2950 (C-H str), 1738 (C=O str), 1687 (C=O str), 1431, 1356, 1267 and 1161 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.24 (1H, m, C*H*H), 2.64 (1H, m, CH*H*), 3.15-3.17 (1H, m, C*H*), 3.25 (1H, d, *J* 6.0 Hz, C*H*), 3.74 (3H, s, CH_3), 4.12 (1H, d, *J* 15.0 Hz, C*H*H), 4.37 (1H, m, C*H*), 4.79 (1H, d, *J* 15.0 Hz, CH*H*), 5.55-5.57 (1H, m, C*H*=CH), 5.80-5.82 (1H, m, CH=C*H*), 7.18-7.29 (5H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 37.69 (*C*H), 38.39 (CH_2), 46 00 (CH_2), 52.79 (CH_3), 55.99 (*C*H), 67.07 (*C*H), 127.72 (*C*H), 128.14 (*C*H), 128 30 (2x *C*H), 128.76 (2x *C*H), 134.30 (*C*H), 136 07 (*C*), 168.87 (*C*O) and 170.88 (*C*O); ms (EI): *m/z* 272 [M^+ 5%], 146 (70), 101 (27), 91 (100), 77 (40), 65 (50) and 59 (15). HRMS calc. for $C_{16}H_{17}NO_2$ requires 272.1281, observed 272.1282.

6-(4-nitro-benzylcarbamoyl)-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester



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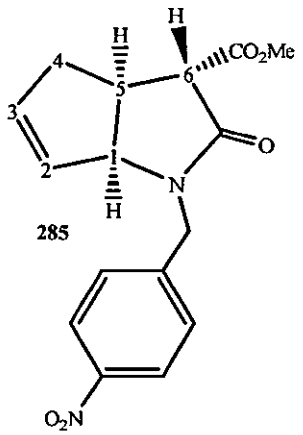
After subjecting bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester and *p*-nitro benzylamine to the standard amide coupling and work-up conditions the crude mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 2:1, light petroleum:

EtOAc) to afford 6-(4-nitro-benzylcarbamoyl)-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester as a white solid (0.14 g, 0.39 mmol, 51 %); mp range 150.8-152.4 °C; υ_{max} (thin film)cm^{-1} 3362 (N-H str), 2925 (C-H str), 1732 (C=O str), 1652 (C=O str), 1519 (NO_2), 1345, 1159 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.62-2.81 (4H, s, C*H*$_2$-C*H*-C*H*), 3.66 (3H, s, C*H*$_3$), 4.53-4.55 (2H, m, C*H*$_2$), 5.69-5.71 (1H, m, C*H*=CH), 5.77-5.79 (1H, m, CH=C*H*), 6.90 (1H, s, N*H*), 7.41 (2H, m, Ar-*H*), 8.19 (2H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 29.80 (*C*H), 34.58 (*C*H$_2$), 39.22 (*C*), 39.86 (*C*H), 43.23 (*C*H$_2$), 52.43 (*C*H$_3$), 123.93 (2x *Ar*-H), 128.03 (2x *Ar*-H), 128.88 (*C*H), 133.15 (*C*H), 145.79 (*C*), 147.25 (*C*-NO_2), 167.93 (*C*O) and 169.60 (*C*O); m/z (EI): *m/z* 317 [M^+, 10 %] 284 (100), 255 (80), 227 (22), and 209 (20). HRMS calc. for $C_{16}H_{16}NO_4$ requires 317.1132, observed 317.1131.

1-(4-Nitro-benzyl)-2-oxo-1,2,3,3a,4,6a-hexahydrocyclopenta[*b*]pyrrole-3-carboxylic acid methyl ester



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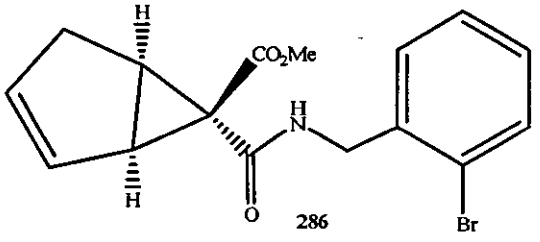
To a stirred solution of the 6-(4-nitro-benzylcarbamoyl)-bicyclo[3.1 0]hex-2-ene-6-carboxylic acid methyl ester (0 06 g, 0.16 mmol) in MeOH (2 ml) under N_2 was added $Pd(PPh_3)_4$ (0.03 g, 0 02 mmol) and the reaction was left stirring at room temperature for 17 h. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica The crude material was purified by flash chromatography (silica gel, 2:1, light petroleum:EtOAc) to afford 1-(4-nitro-benzyl)-2-oxo-1,2,3,3a,4,6a-hexahydeocyclopenta[*b*]pyrrole-3-carboxylic acid methyl ester as a yellow oil (0 04 g, 0.14 mmol, 80 %); υ_{max} (thin film)cm^{-1} 2922 (C-H str), 1734 (C=O str), 1684 (C=O str), 1521 (NO_2), 1432, 1345, 1260 (C-O str), δ_H (400 MHz; $CDCl_3$) 2.30-2.36 (1H, m, 4-C*H*H), 2.75-2 82 (1H, m, 4-CH*H*), 3.24-3.31 (1H, m, 5-C*H*), 3.37 (1H, d, *J* 5 6 Hz, 6-C*H*), 3.81 (3H, s, C*H*$_3$), 4.30 (1H, d, *J* 16.0 Hz, C*H*H), 4.49 (1H, m, 1-C*H*), 4.86 (1H, d, *J* 16 0 Hz, CH*H*), 5.64-5.67 (1H, m, 2-C*H*=CH), 5.94-5.97 (1H, m, 3-CH=C*H*), 7.43-746 (2H, m, Ar-

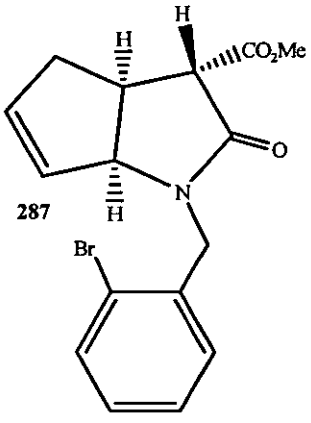
H), 8.19-8.23 (2H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 37.91 (5-*C*H), 38.50 (4-*C*H_2), 47.48 (*C*H_2), 52.92 (*C*H_3), 55.60 (6-*C*H), 67.36 (1-*C*H), 124.03 (2x *Ar*-H), 127.67 (2-*C*H), 128.62 (2x *Ar*-H), 135.32 (3-*C*H), 143.74 (*C*), 147.52 (*C*), 169.35 (*C*O) and 170.67 (*C*O); ms (EI): *m/z* 317 [M^+ 12 %] 190 (22), 149 (32), 106 (38), 101 (72), 89 (85) and 77 (100). HRMS calc. for $C_{16}H_{16}N_2O_5$ requires 317.1132, observed 317.1132.

6-(2-Bromo-benzylcarbamoyl)-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester



After subjecting bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester and 2-bromobenzylamine hydrochloride to the standard amide coupling conditions the crude mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 2:1, light petroleum: EtOAc) to afford 6-(2-bromo-benzylcarbamoyl)-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester as a yellow solid (0.23 g, 0.59 mmol, 52 %); mp range 81.0-84.3 °C; υ_{max} (thin film)cm^{-1} 3353 (N-H str), 2949 (C-H str), 1732 (C=O str), 1651 (C=O str), 1520, 1424, 1303, 1159 and 1026 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.48-2.70 (4H, m, C*H*$_2$-C*H*-C*H*), 3.59 (3H, s, C*H*$_3$), 4.41-4.43 (2H, m, C*H*$_2$), 5.57-5.59 (1H, m, C*H*=CH), 5.67-5.70 (1H, m, CH=C*H*), 6.77 (1H, s, N*H*), 7.07 (1H, td, *J* 1.6 and 7.6 Hz, Ar-*H*), 7.20 (1H, td, *J* 1.2 and 7.6 Hz, Ar-*H*), 7.26 (1H, dd, *J* 2.0 and 7.6 Hz, Ar-*H*), 7.46 (1H, dd, *J* 1.2 and 7.6 Hz, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 29.51 (*C*H), 34 48 (*C*H_2), 39.33 (*C*H), 39.46 (*C*), 44.28 (*C*H_2), 52.37 (*C*H_3), 123.67 (*C*), 127.73 (*C*H), 129 14 (*C*H), 129.18 (*C*H), 130.17 (*C*H), 132 81 (2x *C*H), 137.05 (*C*), 167.44 (*C*O) and 169.10 (*C*O); ms (EI): *m/z* 352 [M^+, 98%, ^{81}Br], 350 [M^+, 100%, ^{79}Br], 319 (70), 316 (62), 290 (50), 270 (22), 238 (20), 185 (100), 163 (100), 105 (55) and 77 (60). HRMS calc. for $C_{16}H_{16}NO_3{}^{79}Br$ requires 350 0368, observed 350.0384.

1-(2-Bromo-benzyl)-2-oxo-1,2,3,3a,4,6a-hexahydeocyclopenta[*b*]pyrrole-3-carboxylic acid methyl ester



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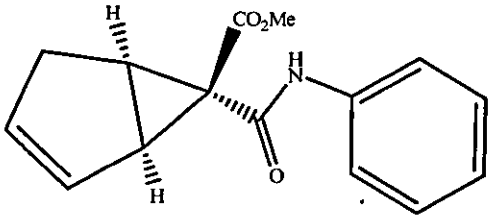
After subjecting 6-(2-bromo-benzylcarbamoyl)-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester to the standard rearrangement conditions the crude mixture was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-(2-bromo-benzyl)-2-oxo-1,2,3,3a,4,6a-hexahydeocyclopenta[*b*]pyrrole-3-carboxylic acid methyl ester as a yellow oil (0.04 g, 0 11 mmol, 54 %); υ_{max} (thin film)cm^{-1} 2949 (C-H str), 1739 (C=O str), 1690 (C=O str), 1433, 1266, 1160 and 1024 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.28-2.34 (1H, m, C*H*H), 2.70-2.80 (1H, m, CH*H*), 3.26-3.28 (1H, m, C*H*), 3.33 (1H, d, *J* 5.6 Hz, C*H*), 3.81 (3H, s, CH_3), 4.40 (1H, d, *J* 15.6 Hz, C*H*H), 4.50-4.52 (1H, m, C*H*), 4.85 (1H, d, *J* 15.6 Hz, CH*H*), 5.71-5.73 (1H, m, C*H*=CH), 5.90-5.92 (1H, m, CH=C*H*), 7.13-7.18 (1H, m, Ar-*H*), 7.29-7.31 (2H, m, Ar-*H*), 7.55-7.31 (1H, d, *J* 8.0 Hz, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 37.73 (*C*H), 38.44 (*C*H_2), 45.67 (*C*H_2), 52.80 (*C*H_3), 55.79 (*C*H), 67.27 (*C*H), 123 61 (*C*), 127.94 (*Ar*-H), 128.47 (*C*H), 129.28 (*Ar*-H), 129.85 (*Ar*-H), 132.87 (*Ar*-H), 134.46 (*C*H), 135.22 (*C*-Br), 169 06 (*C*O) and 170.79 (*C*O); ms (EI): *m/z* 352 [M^+, 96%, ^{81}Br], 350 [M^+, 100%, ^{79}Br], 289 (20), 270 (55), 170 (40), 107 (78), 89 (38), 77 (40) and 59 (38). HRMS calc. for $C_{16}H_{19}NO_3{}^{79}Br$ requires 350 0386, observed 350.0386.

6-Phenylcarbamoyl-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester



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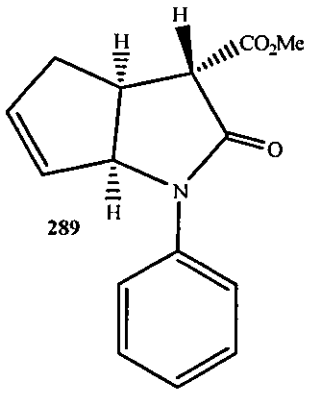
After subjecting bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester and aniline to the standard amide coupling and work-up conditions the crude mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 2:1, light petroleum: EtOAc) to afford 6-phenylcarbamoyl-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester as a yellow oil (0.14 g, 0.55 mmol, 52 %); υ_{max} (thin film)cm^{-1} 3339 (N-H str), 2949 (C-H str), 1734 (C=O str), 1684 (C=O str), 1598, 1533, 1499, 1441, 1314 and 1157 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.63-2.78 (4H, m, C*H*$_2$-C*H*-C*H*), 3.62 (3H, s, C*H*$_3$), 5.63-5.65 (1H, m, C*H*=CH), 5.72-5.74 (1H, m, CH=C*H*), 7 00-7.04 (1H, m, Ar-*H*), 7.21-7.25 (2H, m, 2x Ar-*H*), 7.38-7.40 (2H, m, 2x Ar-*H*), 8.28 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 29.53 (*C*H), 34.67 (*C*H$_2$), 39.89 (*C*), 40.05 (*C*H), 54.80 (*C*H$_3$), 119.80 (*Ar*-H), 120.14 (*Ar*-H), 124.44 (*Ar*-H), 128.93 (*C*H), 128.98 (*Ar*-H), 133.02 (*Ar*-H), 133.29 (*C*H), 137.61 (*C*), 165 30 (*C*O) and 169.90 (*C*O); ms (EI): *m/z* 258 [M^+ 13 %], 225 (19), 191 (20), 163 (100), 133 (38), 104 (93), 93 (72), 76 (81) and 64 (71) HRMS calc. for $C_{15}H_{15}NO_3$ requires 258.1125, observed 258.1125.

2-Oxo-1,2,3,3a,4,6a-hexahydeocyclopenta[*b*]pyrrole-3-carboxylic acid methyl ester



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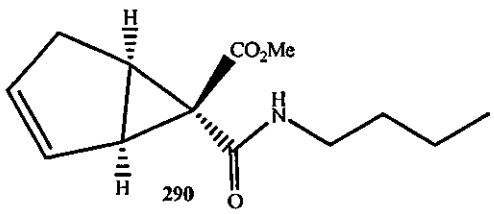
After subjecting 6-phenylcarbamoyl-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester to the standard rearrangement and work-up conditions the crude mixture was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 2-oxo-1,2,3,3a,4,6a-hexahydeocyclopenta[*b*]pyrrole-3-carboxylic acid methyl ester as a orange oil (0.03 g, 0.13

mmol, 50 %); υ_{max} (thin film)cm^{-1} 2950 (C-H str), 1738 (C=O str), 1694 (C=O str), 1595, 1495, 1386, 1271 and 1160 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.30-2.35 (1H, m, C*H*H), 2.72-2.78 (1H, m, CH*H*), 3.34-3.38 (1H, m, C*H*), 3.41 (1H, d, *J* 6.8 Hz, C*H*), 3.74 (3H, s, CH_3), 5.12-5.15 (1H, m, C*H*), 5.82-5.85 (1H, m, C*H*=CH), 5.92-5.94 (1H, m, CH=C*H*), 7.10-7.19 (1H, m, Ar-*H*), 7.29-7.33 (2H, m, Ar-*H*), 7.52-7.55 (2H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 37.29 (*C*H), 38.20 (CH_2), 52.87 (CH_3), 56.96 (*C*H), 69.11 (*C*H), 121.16 (2x *C*H), 125.51 (*C*H), 128.74 (2x *C*H), 129.09 (*C*H), 134.76 (*C*H), 138.28 (*C*), 168.13 (*C*O) and 170.39 (*C*O); *m/z* 258 [M^+ 100%], 226 (8), 196 (7), 154 (10), 139 (20), 107 (28) and 77 (19). HRMS calc. for $C_{15}H_{15}NO_3$ $[M^+H]^+$ requires 258.11302, observed 258.11302.

6-Butylcarbamoyl-bicyclo[3.1.0]hex-2-ene-6-carboylic acid methyl ester



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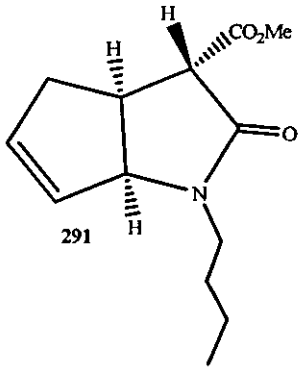
After subjecting bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester and butylamine to the standard amide coupling and work-up conditions the crude mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 2:1, light petroleum: EtOAc) to afford 6-butylcarbamoyl-bicyclo[3.1 0]hex-2-ene-6-carboylic acid methyl ester as a yellow oil (0.130 g, 0.54 mmol, 50 %); υ_{max} (thin film)cm^{-1} 3349 (N-H str), 2954 (C-H str), 1734 (C=O str), 1647 (C=O str), 1528, 1434, 1306, 1196 and 1158 (C-O str); δ_H (400 MHz; $CDCl_3$) 0 82 (3H, t, *J* 7.3 Hz, CH_3), 1.18-1 26 (2H, m, CH_2), 1.39-1.43 (2H, m, CH_2), 2.47 (1H, m, C*H*), 2.62-2.68 (3H, m, CH_2-C*H*-C*H*), 3.15-3.17 (2H, m, CH_2), 3.57 (3H, s, CH_3), 5.56-5.57 (1H, m, C*H*=CH), 5.68-5.70 (1H, m, CH=C*H*), 6.18 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 13 73 (CH_3), 22.01 (CH_2), 28 99 (*C*H), 31.50 (CH_2), 34.41 (CH_2), 38 80 (*C*H), 39.60 (*C*), 39 80 (CH_2), 52.21 (CH_3), 129.36 (*C*H), 134.74 (*C*H), 167.23 (*C*O) and 169.48 (*C*O); ms (EI) *m/z* 238 [M^+ 5%], 205 (18), 164 (100), 131 (30), 105 (75), 77 (90), 66 (40) and 41 (69). HRMS calc. for $C_{13}H_{19}NO_3$ requires 238.1438, observed 238 1440.

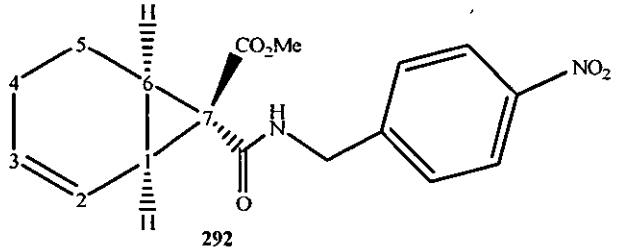
1-Butyl-2-oxo-1,2,3,3a,4,6a-hexahydeocyclopenta[*b*]pyrrole-3-carboxylic acid methyl ester



291

After subjecting 6-butylcarbamoyl-bicyclo[3.1.0]hex-2-ene-6-carboylic acid methyl ester to the standard rearrangement and work-up conditions the crude mixture was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-butyl-2-oxo-1,2,3,3a,4,6a-hexahydeocyclopenta[*b*]pyrrole-3-carboxylic acid methyl ester as a orange oil (0.03 g, 0.13 mmol, 47 %); υ_{max} (thin film)cm^{-1} 2955 (C-H str), 1739 (C=O str), 1688 (C=O str), 1431, 1356, 1266 and 1163 (C-O str); δ_H (400 MHz; $CDCl_3$) 0.84 (3H, t, *J* 7.2 Hz, C*H*$_3$), 1.23-1.29 (1H, m, C*H*H), 1.44-1.54 (1H, m, CH*H*), 2.18-2.24 (1H, m, CH*H*), 2.66-2.72 (1H, m, C*H*H), 2.96-3.01 (1H, m, C*H*), 3 20-3.45 (2H, m, C*HH*), 3.47-3.52 (1H, m, C*H*), 3.73 (3H, s, C*H*$_3$), 4.53-4.55 (1H, m, C*H*), 5.78-5.80 (1H, m, CH=C*H*), 5.87-5.90 (1H, m, C*H*=CH), δ_c (100 MHz; $CDCl_3$) 13.75 (*C*H$_3$), 19.99 (*C*H$_2$), 29.54 (*C*H$_2$), 37.67 (*C*H), 38.45 (*C*H$_2$), 41.85 (*C*H$_2$), 52 69 (*CH*$_3$), 56.11 (*C*H), 67.42 (*C*H), 128.48 (*C*H), 134.58 (*C*H), 168.59 (*C*O) and 170.95 (*C*O); ms (FAB): *m/z* 238 [M^+ 50%], 207 (25), 147 (47), 136 (24), 107 (15), 91 (12) and 73 (100). HRMS calc. for $C_{13}H_{19}NO_3$ $[M^+H]^+$ requires 238.1443, observed 238 1437

7-(4-Nitro-benzylcarbamoyl)-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester

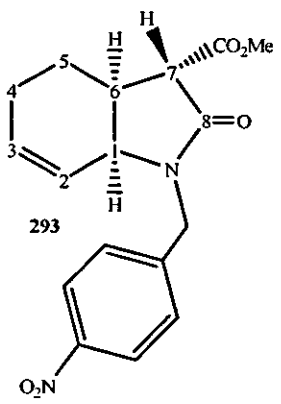


292

To a stirred solution of 7-[(methyloxy)carbon]bicycle[4.1.0]hept-2-ene-7-carboxylic acid (0 22 g, 1.10 mmol), in DMF (5 ml) at room temperature was added DIEA (0 38 ml, 2.20 mmol), along with HATU (0.50 g, 1.32 mmol) and the mixture was left stirring for 10 min.

Then *p*-nitro-benzylamine (0.21 g, 1.10 mmol) was added and the reaction was left stirring for 3 h. The reaction was then diluted with DCM (15 ml), washed with 2 *M* HCl (10 ml), aqueous $NaHCO_3$ (20 ml) and re-extracted into DCM (3x 20 ml), the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 1:1, light petroleum: EtOAc) to afford 7-(4-nitro-benzylcarbamoyl)-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester as a white solid (0.24 g, 0.73 mmol, 66 %); mp range 128.3-130 0 °C; υ_{max} (thin film)cm^{-1} 3319 (N-H str), 2908 (C-H str), 1734 (C=O str), 1653 (C=O str), 1539 (NO_2), 1516, 1457, 1436 and 1349 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.69-2.25 (6H, m, 4-C*H*$_2$, 5-C*H*$_2$, 1-C*H* and 6-C*H*), 3.72 (3H, s, C*H*$_3$), 4.54 (2H, d, *J* 6.0 Hz, C*H*$_2$), 5.73 (1H, m, 2-C*H*=CH), 5.84 (1H, m, 3-CH=C*H*), 7.22 (1H, s, N*H*), 7.41 (2H, d, *J* 9.0 Hz, 2x Ar-*H*), 8.17 (2H, d, *J* 9.0 Hz, 2x Ar-*H*); δ_c (100 MHz; $CDCl_3$) 16.00 (5-*C*H$_2$), 20.89 (4-*C*H$_2$), 25.02 (6-*C*H), 25.36 (1-*C*H), 42.37 (7-*C*), 43.38 (*C*H$_2$), 52.52 (*C*H$_3$), 121.43 (2-*C*H), 123.96 (2x *Ar*-H), 128.15 (3-*C*H), 128.73 (2x *Ar*-H), 145.91 (*C*), 147.30 (*C*), 168.06 (*C*O) and 171.08 (*C*O); ms (EI): *m/z* 331 [M^+ 100%)], 301 (30) and 106 (20). HRMS calc. for $C_{17}H_{18}N_2O_5$ requires 331.1288, observed 331.1290.

1-(4-Nitro-benzyl)-2-oxo-2-3-3a,4,5,7a-hexahydro-1*H*-indole-3-carboxyl acid methyl ester

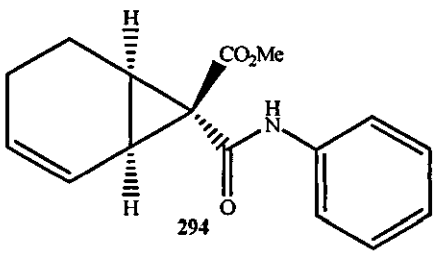


293

To a stirred solution of 7-(4-nitro-benzylcarbamoyl)-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester (0.10 g, 0.30 mmol) in MeOH (4 ml) under N_2 was added $Pd(PPh_3)_4$ (0 05 g, 0.03 mmol) and the reaction was left stirring at room temperature for 17 h. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica The crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-(4-nitro-benzyl)-2-oxo-2-3-3a,4,5,7a-hexahydro-1*H*-indole-3-carboxyl acid methyl ester as a white solid (0.10 g, 0.30 mmol, 99 %); mp range

89.0-93.0 °C; υ_{max} (thin film)cm^{-1} 2928 (C-H str), 1738 (C=O str), 1693 (C=O str), 1519 (NO_2), 1434, 1345 and 1267 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.59 (2H, m, 5-C*H*$_2$), 2 07 (2H, m, 4-C*H*$_2$), 2.80 (1H, m, 6-C*H*), 3.32 (1H, d, *J* 6.0 Hz, 7-C*H*), 3.81 (3H, s, C*H*$_3$), 4.01 (1H, m, 1-C*H*), 4 21 (1H, d, *J* 16.0 Hz, C*H*H), 5.02 (1H, d, *J* 16.0 Hz, CH*H*), 5.60 (1H, m, 2-C*H*=CH), 6.03 (1H, m, 3-CH=C*H*), 7.44 (2H, d, *J* 12 0 Hz, Ar-*H*), 8.20 (2H, d, *J* 12.0 Hz, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 22.37 (5-*C*H$_2$), 23.61 (4-*C*H$_2$), 36.01 (6-*C*H), 44.03 (*C*H$_2$), 52.75 (7-*C*H), 53.04 (*C*H$_3$), 53.56 (1-*C*H), 121.99 (2-*C*H), 123.99 (2x *Ar*-H), 128.52 (2x *Ar*-H), 132 88 (3-*C*H), 143 83 (*C*), 147.48 (*C*), 169.71 (*C*O) and 170.15 (*C*O); ms (ES): *m/z* 331 [M^+ 100 %], 271 (80), 194 (52), 162 (45), 106 (28), 91 (70), and 77 (89). HRMS calc. for $C_{17}H_{18}N_2O_5$ requires 331.1288, observed 331.1288.

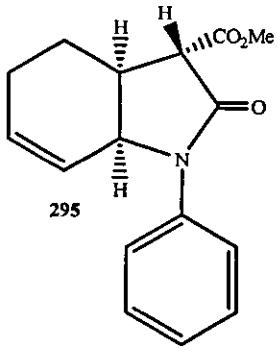
7-Phenylcarbamoyl-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester



294

After subjecting 7-[(methyloxy)carbon]bicycle[4.1.0]hept-2-ene-7-carboxylic acid and aniline to the standard amide coupling and work-up conditions the crude mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 2:1, light petroleum: EtOAc) to afford 7-phenylcarbamoyl-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester as a yellow solid (0.13 g, 0.47 mmol, 91 %); mp range 122 0-123.5 °C; υ_{max} (thin film)cm^{-1} 3340 (N-H str), 2946 (C-H str), 1730 (C=O str), 1597 (C=O str), 1479, 1441 and 1313 (C-O str), δ_H (400 MHz; $CDCl_3$) 1.91-2.21 (6H, m, C*H*$_2$-C*H*$_2$-C*H*-C*H*), 3.68 (3H, s, C*H*$_3$), 5 67-5.71 (1H, m, C*H*=CH), 5.80-5 82 (1H, m, CH=C*H*), 7.01-7.04 (2H, m, Ar-*H*), 7.22-7.26 (1H, m, Ar-*H*), 7.39-7.42 (2H, m, Ar-*H*), 8 65 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 16.09 (*C*H$_2$), 20.85 (*C*H$_2$), 25.12 (*C*H), 25.16 (*C*H), 43.02 (*C*), 52 61 (*C*H$_3$), 120.13 (2x *C*H), 121.52 (*C*H), 124.35 (2x *C*H), 128 71 (*C*H), 128.97 (*C*H), 137.74 (*C*), 165.37 (*C*O) and 171.37 (*C*O); ms (EI) *m/z* 272 [M^+ 100%], 238 (28), 191 (12), 178 (100), 146 (30), 118 (18), 91 (60) and 79 (62). HRMS calc. for $C_{16}H_{17}NO_3$ requires 272.1281, observed 272.1279.

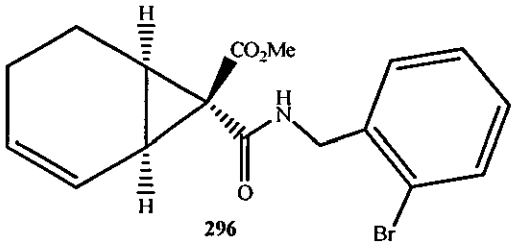
2-Oxo-1-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester



295

After subjecting 7-phenylcarbamoyl-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester to the standard rearrangement and work-up conditions the crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 2-oxo-1-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester as a yellow oil (0.05 g, 0.17 mmol, 90 %); υ_{max} (thin film)cm^{-1} 2923 (C-H str), 1740 (C=O str), 1696 (C=O str), 1596, 1496, 1383, 1274 and 1158 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.71-2.07 (4H, m, 2x C*H*$_2$), 2.90 (1H, m, C*H*), 3.44 (1H, d, *J* 8.4 Hz, C*H*), 3.74 (3H, s, C*H*$_3$), 4.65-4.66 (1H, m, C*H*), 5.61-5.64 (1H, m, C*H*=CH), 5.86-5.89 (1H, m, CH=C*H*), 7.14 (1H, m, Ar-*H*), 7.29-7.34 (2H, m, 2x Ar-*H*), 7.39-7.43 (2H, m, 2x Ar-*H*); δ_c (100 MHz; $CDCl_3$) 21.47 (*C*H$_2$), 22 68 (*C*H$_2$), 35.31 (*C*H), 52.74 (*C*H), 52.88 (*C*H$_3$), 56.10 (*C*H), 123.16 (*C*H), 123.26 (*C*H), 125.92 (*C*H), 128.29 (*C*H), 129 13 (*C*H), 130.07 (*C*H), 131.25 (*C*H), 137.40 (*C*), 168.53 (*C*O) and 169.93 (*C*O); ms (EI): *m/z* 272 [M^+ 60%], 212 (100), 184 (28), 156 (13), 118 (20), 91 (40) and 77 (55). HRMS calc for $C_{16}H_{17}NO_3$ requires 272.1281, observed 272.1282

7-(2-Bromo-benzylcarbamoyl)-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester

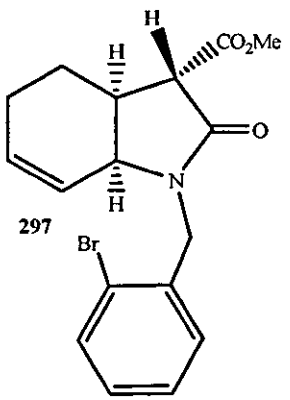


296

To a stirred solution of 7-[(methyloxy)carbonyl]bicyclo[4 1.0]hept-2-ene-7-carboxylic acid (0 22 g, 1.10 mmol), DIEA (0.38 ml, 2 20 mmol), HATU (0.46 g, 1.21 mmol) in anhydrous DMF (5 ml) at room temperature was added 2-bromobenzylamine hydrochloride (0.49 g, 2.20 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for a further 3 h before being diluted with DCM (15 ml). The mixture was then washed with

2 *M* HCl (10 ml), aqueous $NaHCO_3$ (2x 10 ml) and extracted into DCM (3x 15 ml). The organic extracts were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by flash chromatography using (silica gel, gradient elution 4:1 to 2.1, light petroleum: EtOAc) to afford the 7-(2-bromo-benzylcarbamoyl)-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester as a yellow oil (0.30 g, 0.82 mmol, 75 %); υ_{max} (thin film)cm^{-1} 3347 (N-H str), 2925 (C-H str), 1733 (C=O str), 1653 (C=O str), 1521, 1436, 1320, 1254, 1197 and 1113 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.97-2.02 (4H, m, 2x C*H*$_2$), 2.02-2.24 (2H, m, 2x C*H*), 3.72 (3H, s, C*H*$_3$), 4.49 (2H, d, *J* 6.0 Hz, C*H*$_2$), 5.71 (1H, m, CH=C*H*), 5.84 (1H, m, C*H*=CH), 7.08 (1H, s, N*H*), 7.14 (1H, td, *J* 2.0 and 8 0 Hz, Ar-*H*), 7.23 (1H, dd, *J* 2.0 and 8.0 Hz, Ar-*H*), 7.32 (1H, dd, *J* 2.0 and 8.0 Hz, Ar-*H*), 7.54 (1H, dd, *J* 2.0 and 8.0 Hz, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 16.03 (*C*H$_2$), 20.79 (*C*H$_2$), 24.27 (*C*H), 24.61 (*C*H), 42.36 (*C*), 44.36 (*C*H$_2$), 52.63 (*C*H$_3$), 121.79 (*C*H), 123.71 (*C*), 127.70 (*C*H), 128.26 (*C*H), 129.14 (*C*H), 130.21 (*C*H), 132.79 (*C*H), 137.11 (*C*), 167.40 (*C*O) and 170.54 (*C*O). ms (EI): *m/z* 366 [M^+, 98%, ^{81}Br], 364 [M^+, 100%, ^{79}Br], 303 (80), 284 (100), 224 (12), 170 (50), 107 (38) and 91 (73). HRMS calc. for $C_{17}H_{18}NO_3{}^{79}Br$ requires 364.0543, found 364.0543.

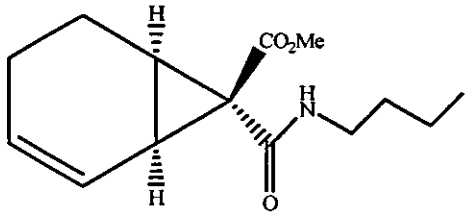
1-(2-Bromo-benzyl)-2-oxo-3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester[65]



To a stirred solution 7-(2-bromo-benzylcarbamoyl)-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester (0.05 g, 0.13 mmol) in MeOH (2 ml) was added $Pd(PPh_3)_4$ (0.02 g, 0.01 mmol). This solution was stirred for 24 h at room temperature. The solvent was removed *in vacuo* and the material dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica The crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-(2-bromo-benzyl)-2-oxo-3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester as a yellow oil (0.05 g, 0.13 mmol, 99 %); υ_{max} (thin film)cm^{-1} 2921 (C-H str), 1738 (C=O str), 1695 (C=O str), 1434, 1319, 1269 and 1174 (C-O

str); δ_H (400 MHz; $CDCl_3$) 1.66-1.85 (2H, m, C*H*$_2$), 2.04-2 09 (2H, m, C*H*$_2$), 2.85-2.88 (1H, m, C*H*), 3 36 (1H, d, *J* 7.0 Hz, C*H*), 3.81 (3H, s, C*H*$_3$), 4.02 (1H, s, C*H*), 4 36 (1H, d, *J* 16 0 Hz, CH*H*), 4.92 (1H, d, *J* 16 0 Hz, C*H*H), 5.71 (1H, m, C*H*), 5 95 (1H, m, C*H*), 7.14 (1H, m, C*H*), 7.26-7.31 (2H, m, C*H*), 7.54 (1H, d, *J* 8.0 Hz, C*H*); δ_c (100 MHz; $CDCl_3$) 21.82 (*C*H$_2$), 23.22 (*C*H$_2$), 35.87 (*C*H), 44.38 (*C*H$_2$), 52.29 (*C*H$_3$), 52.69 (*C*H), 53.55 (*C*H), 122.86 (*C*H), 123.29 (*C*), 127.87 (*C*H), 129.12 (*C*H), 129 45 (*C*H), 131.70 (*C*H), 132.89 (*C*H), 135.26 (*C*), 169.46 (*C*O) and 170.31 (*C*O).

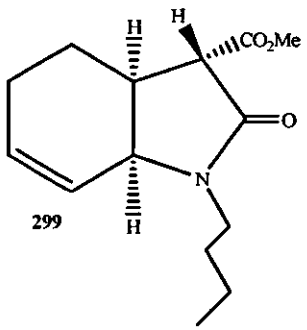
7-Butylcarbamoyl-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester



298

After subjecting 7-[(methyloxy)carbon]bicycle[4.1.0]hept-2-ene-7-carboxylic acid and butylamine to the standard amide coupling using and work-up conditions the crude reaction mixture was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 7-butylcarbamoyl-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester as a pale yellow solid (0 09 g, 0.37 mmol, 90 %); mp range 42.7-27.2 °C; υ_{max} (thin film)cm^{-1} 3352 (N-H str), 2930 (C-H str), 1731 (C=O str), 1656 (C=O str), 1530, 1434, 1320, 1277 and 1198 (C-O str); δ_H (400 MHz; $CDCl_3$) 0.84 (3H, t, *J* 7.3 Hz, C*H*$_3$), 1.23-1.28 (2H, m, C*H*$_2$), 1.39-1 43 (2H, m, C*H*$_2$), 1.89-2.14 (4H, m, 2x C*H*$_2$), 3.13 (2H, ddd, *J* 5 6, 6 8 and 12.8 Hz, C*H*$_2$), 3.65 (3H, s, C*H*$_3$), 5.61-5.66 (1H, m, C*H*=CH), 5.78-5.82 (1H, m, CH=C*H*), 6 39 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 13.76 (*C*H$_3$), 16 06 (*C*H$_2$), 20.05 (*C*H$_2$), 20.79 (*C*H$_2$), 23.78 (*C*H), 24.56 (*C*H), 31.48 (*C*H$_2$), 39.90 (*C*H$_2$), 42.43 (*C*), 52.46 (*C*H$_3$), 122.05 (*C*H), 127.92 (*C*H), 167 21 (*C*O) and 170.92 (*C*O); ms (EI): *m/z* 252 [M$^+$ 100 %], 218 (25), 178 (88), 146 (80), 118 (52), 91 (100) and 79 (65). HRMS calc. for $C_{14}H_{21}NO_3$ requires 252.1594, observed 252 1595.

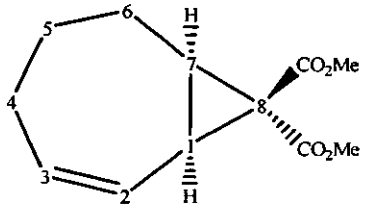
1-Butyl-2-oxo-2,3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester



299

After subjecting 7-butylcarbamoyl-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester to the standard rearrangement and work-up condtions the crude reaction mixture was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-butyl-2-oxo-2,3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester as a yellow oil (0.03 g, 0.12 mmol, 66 %); υ_{max} (thin film)cm^{-1} 2929 (C-H str), 1741 (C=O str), 1692 (C=O str), 1434, 1267, 1195 and 1161 (C-O str); δ_H (400 MHz; $CDCl_3$) 0.86 (3H, t, *J* 7.0 Hz, C*H*$_3$), 1.24-1.27 (2H, m, C*H*$_2$) 1.43-1 49 (2H, m, C*H*$_2$), 1.65-1.70 (2H, m, C*H*$_2$), 1.99-2.02 (1H, m, C*H*), 2.65-2.78 (2H, m, C*H*$_2$), 2.92-2.98 (1H, m, C*H*H), 3.15 (1H, d, *J* 5.7 Hz, C*H*), 3.52-3.56 (1H, m, CH*H*), 3.69 (3H, s, C*H*$_3$), 4.05 (1H, m, C*H*), 5.69-5.73 (1H, m, C*H*=CH), 5.73-5.95 (1H, m, CH=C*H*); δ_c (100 MHz; $CDCl_3$) 13.80 (*C*H$_3$), 20.01 (*C*H$_2$), 22.21 (*C*H$_2$), 23.40 (*C*), 29.56 (*C*H$_2$), 35.73 (*C*H), 40.44 (*C*H$_2$), 52.57 (*C*H), 53.04 (*C*H), 53.63 (*C*H$_3$), 122.93 (*C*H), 131.88 (*C*H), 168.85 (*C*O) and 170.44 (*C*O); ms (EI). *m/z* 274 [M^+ 0.8%], 191 (30), 148 (20), 118 (15), 91 (55), 79 (50), 59 (38) and 41 (100). HRMS calc. for $C_{14}H_{21}NO_3$ $[M^+Na]^+$ requires 274.1414, observed 274.1415.

Bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic dimethyl ester[24]

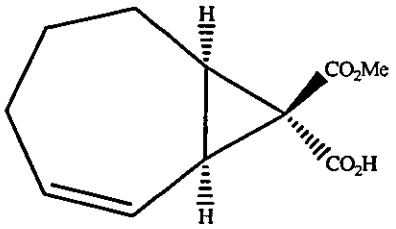


301

To a stirred solution of 1,3-cycloheptadiene (1.01 g, 12.7 mmol), and $Rh_2(OAc)_4$ (0.05 g, 0.10 mmol) in 1,2-dichloroethane (2 ml) was added dimethyl diazomalonate (2 00 g, 12.7 mmol) *via* syringe pump diluted in 1,2-dichloroethane (4 ml). The mixture was stirred under reflux for 3 h. The mixture was allowed to cool to room temperature before being

concentrated *in vacuo*. The resulting oil was purified by flash chromatography (Silica gel, hexane: EtOAc, 2:1) to afford bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic dimethyl ester as a colourless viscous oil (0.69 g, 3.26 mmol, 34 %); υ_{max} (thin film)cm^{-1} 2949 (C-H str), 1727 (C=O str), 1435, 1323, 1260 and 1215 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.18-2.36 (8H, m, 4-C*H*$_2$, 5-C*H*$_2$, 6-C*H*$_2$, 1-C*H* and 7-C*H*), 3.65 (3H, s, C*H*$_3$), 3.66 (3H, s, C*H*$_3$), 5.49-5.55 (1H, m, 2-C*H*=CH), 5.63-5.64 (1H, m, 3-CH=C*H*); δ_c (100 MHz; $CDCl_3$) 23.24 (6-*C*H$_2$), 23.79 (5-*C*H$_2$), 28.49 (4-*C*H$_2$), 29.96 (7-*C*H), 30.91 (1-*C*H), 38.35 (8-*C*), 52.20 (*C*H$_3$), 52 69 (*C*H$_3$), 123.53 (2-*C*H), 131.25 (3-*C*H), 167.26 (*C*O) and 171.00 (*C*O); ms (EI): *m/z* 225 [M^+ 100%], 224 (48) and 150 (12). HRMS calc. for $C_{12}H_{16}O_4$ requires 225.1121, found 225.1119.

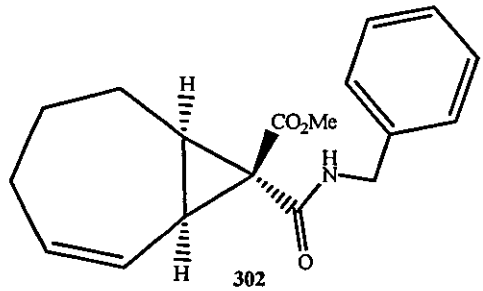
Bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic methyl ester



267

To a stirred solution of bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic dimethyl ester (1.04 g, 4.64 mmol) in THF/H_2O (1:1, 2ml) was added LiOH (0 20 g, 4 64 mmol) and stirred at room temperature for 2 h. The mixture was then acidified to pH2 with 2 *M* HCl, extracted into Et_2O (3x 10 ml), washed with brine (3x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic methyl ester as a yellow oil (0.88 g, 4.17 mmol, 90 %);υ_{max} (thin film)cm^{-1} 3008 (O-H str), 2948 (C-H str), 1731 (C=O str), 1693 (C=O str), 1434, 1325, 1266, 1196 and 1123 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.62-1.69 (2H, m, C*H*$_2$), 1.79-1.81 (1H, m, C*H*), 1 93-2.21 (3H, m, C*H*-C*H*$_2$), 2 35-2.40 (2H, m, C*H*$_2$), 3.68 (3H, s, C*H*$_3$), 5.52-5.64 (2H, m, C*H*=C*H*),. 7.50 (1H, s, O*H*); δ_c (100 MHz, $CDCl_3$) 15.18 (*C*H), 23.55 (*C*H$_2$), 28.95 (*C*H$_2$), 30.01 (*C*H), 37.76 (*C*), 52.27 (*C*H$_3$), 67.92 (*C*H$_2$), 123.03 (*C*H), 131.83 (*C*H), 171.08 (*C*O and 175.13 (*C*O).

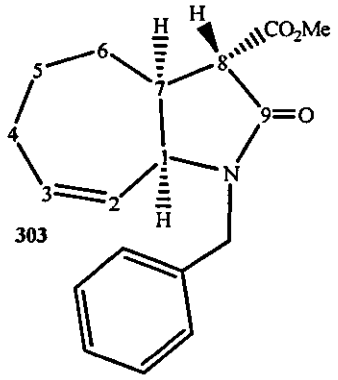
8-Benzylcarbamoyl-bicyclo[5.1.0]oct-2-ene-8-carboxyl acid methyl ester



302

To a stirred solution of bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic methyl ester (0.08 g, 0.36 mmol), in DMF (3 ml) was added DIEA (0.09 g, 0.72 mmol), HATU (0.17 g, 0.43 mmol) and the mixture was left to stir for 10 min. Then benzylamine (0.05 g, 0.43 mmol) was then added and the reaction mixture was allowed to warm to room temperature and was stirred for a further 3 h before being diluted with DCM (15 ml). The mixture was then washed with 2 *M* HCl (10 ml), aqueous $NaHCO_3$ (2x 10 ml) and extracted into DCM (3x 15 ml). The organic extracts were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 8-benzylcarbamoyl-bicyclo[5.1.0]oct-2-ene-8-carboxyl acid methyl ester as a pale yellow solid (0.70 g, 1.54 mmol, 77 %); mp range 99.3-103 3 °C; υ_{max} (thin film)cm^{-1} 3342 (N-H str), 2930 (C-H str), 1731 (C=O str), 1650 (C=O str), 1534, 1454, 1131, 1195 and 1126 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.44-2.56 (8H, m, CH_2-CH_2-CH_2-CH-CH), 3.62 (3H, s, CH_3), 4.39 (2H, d, *J* 5.6 Hz, CH_2), 5.51-5.59 (2H, m, CH=CH), 7.19-7.29 (5H, m, Ar-*H*) 7.68 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 23.00 (CH_2), 24.08 (CH_2), 29.25 (CH_2), 31.32 (*C*H), 33 22 (*C*H), 38.22 (*C*), 44.17 (CH_2), 51.86 (CH_3), 123.94 (*C*H), 127.39 (*C*H), 127.66 (2x *C*H), 128 69 (*C*H), 130.99 (2x *C*H), 138 29 (*C*), 168.56 (*C*O) and 171.36 (*C*O), ms (EI): *m/z* 300 [M^+ 100%], 267 (15), 192 (52), 159 (18), 106 (28), 91 (100) and 77 (22). HRMS calc. for $C_{18}H_{21}NO_3$ requires 300.1594, observed 300 1591.

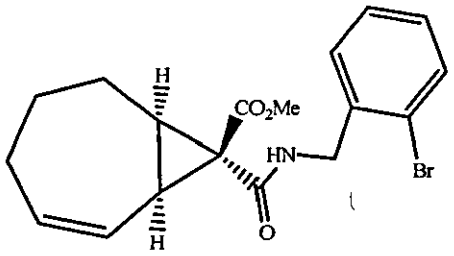
1-Benzyl-2-oxo-1,2,3,3a,4,5,6,8a-octahydrocyclohepta[b]pyrrole-3-carboxyl acid methyl ester



303

To a stirred solution of 8-benzylcarbamoyl-bicyclo[5.1.0]oct-2-ene-8-carboxyl acid methyl ester (0.05 g, 0.19 mmol) in MeOH (2 ml) under N_2 was added $Pd(PPh_3)_4$ (0.030 g, 0.02 mmol) and the reaction was left stirring at room temperature for 17 h. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-benzyl-2-oxo-1,2,3,3a,4,5,6,8a-octahydrocyclohepta[b]pyrrole-3-carboxyl acid methyl ester as a yellow oil (0.03 g, 0.10 mmol, 60 %); υ_{max} (thin film)cm^{-1} 3385 (N-R str), 2925 (C-H str), 1740 (C=O str), 1690 (C=O str), 1434, 1266, and 1163 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.40-1.45 (4H, m, 6-C*H*$_2$ and 5-C*H*$_2$), 2.08-2.10 (2H, m, 4-C*H*$_2$), 2.70-2.75 (1H, m, 7-C*H*), 3.19 (1H, d, *J* 11.0 Hz, 8-C*H*), 3 75 (3H, s, C*H*$_3$), 3.93 (1H, d, *J* 15.0 Hz, C*H*H), 4 26 (1H, m, 1-C*H*), 5.00 (1H, d, *J* 15.0 Hz, CH*H*), 5.33-5.37 (1H, m, 2-C*H*=CH), 5.60-5.65 (1H, m, 3-CH=C*H*), 7.16-7.28 (5H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 20.59 (6-*C*H$_2$), 27.65 (5-*C*H$_2$), 27.90 (4-*C*H$_2$), 40.17 (7-*C*H), 44.91 (*C*H$_2$), 52.70 (*C*H$_3$), 54.81 (8-*C*H), 56.77 (1-*C*H), 126.07 (2-*C*H), 127.69 (*C*H), 128.10 (2x *C*H), 128 22 (2x *C*H), 130.22 (3-*C*H), 135.84 (*C*), 169.33 (*C*O) and 170.49 (*C*O).

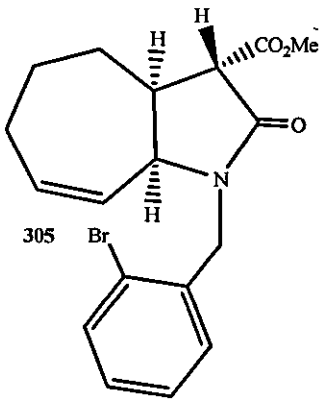
8-(2-Bromo-benzylcarbamoyl)-bicyclo[5.1.0]oct-2-ene-8-carboxyl acid methyl ester



304

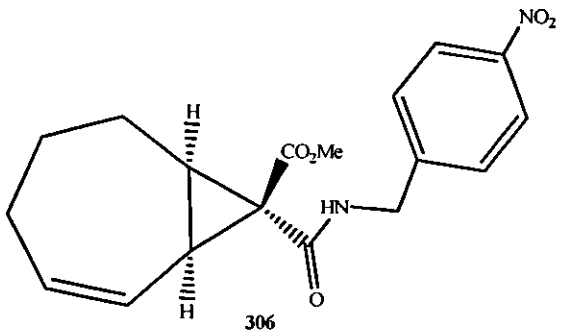
After subjecting bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic methyl ester and -2-bromo-benzylamine hydrochloride to the standard amide coupling and work-up conditions the resulting oil was purified by flash chromatography (Silica gel, gradient elution, 4:1-2:1, hexane: EtOAc) to afford 8-(2-bromo-benzylcarbamoyl)-bicyclo[5.1.0]oct-2-ene-8-carboxyl acid methyl ester as a colourless oil (0.17 g, 55 %); υ_{max} (thin film)cm^{-1} 3340 (N-H str), 2928 (C-H str), 1731 (C=O str), 1697 (C=O str), 1523, 1438, 1316, 1195 and 1195 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.48-1.63 (2H, m, C*HH*), 1.96-1.99 (3H, m, C*HHH*), 2.00-2.16 (1H, m, C*H*), 2.36-2.37 (1H, m, C*H*), 2.51-2.53 (1H, m, C*H*), 3.65 (3H, s, CH_3), 4.46 (2H, d, *J* 6.0 Hz, CH_2), 5.52-5.55 (2H, m, C*H*=C*H*), 7.07 (1H, td, *J* 1 6 and 8.0 Hz, Ar-*H*), 7.23 (1H, td, *J* 1.2 and 7.2 Hz, Ar-*H*), 7.31 (1H, dd, *J* 1.6 and 7.6 Hz, Ar-*H*), 7.49 (1H, dd, *J* 1.2 and 8.0 Hz, Ar-*H*), 7.89 (1H, t, *J* 6 0 Hz, N*H*); δ_c (100 MHz; $CDCl_3$) 22.95 (CH_2), 24.07 (CH_2), 29.25 (CH_2), 31.38 (*C*H), 33.24 (*C*H), 38.20 (*C*), 44 39 (CH_2), 51.91 (CH_3), 123.78 (*C*), 123 88 (*C*H), 127.68 (*C*H), 129.06 (*C*H), 130 20 (*C*H), 131.04 (*C*H), 132.78 (*C*H), 137 37 (*C*), 168.56 (*C*O) and 171.11 (*C*O); ms (FAB)· *m/z* 380 [M^+, Br^{81}, 74%] 378 [M^+, Br^{79}, 80 %], 346 (56), 281 (48), 221 (35), 207 (48), 193 (78), 169 (100), 147 (84), 136 (76) and 73 (82). HRMS calc. for $C_{18}H_{20}NO_3{}^{79}Br$ requires 378.0748, observed 378 07086.

1-(2-Bromo-benzyl)-2-oxo-1,2,3,3a,4,5,6,8a-octahydrocyclohepta[b]pyrrole-3-carboxyl acid methyl ester



After subjecting 8-(2-bromo-benzylcarbamoyl)-bicyclo[5.1.0]oct-2-ene-8-carboxyl acid methyl ester to the standard rearrangement and work-up conditions the crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-(2-bromo-benzyl)-2-oxo-1,2,3,3a,4,5,6,8a-octahydrocyclohepta[b]pyrrole-3-carboxyl acid methyl ester as a yellow oil (0.06 g, 0.17 mmol, 83 %); υ_{max} (thin film)cm^{-1} 3385 (N-R str), 2931 (C-H str), 1738 (C=O str), 1698 (C=O str), 1433, 1349, 1261 and 1154 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.42-1 60 (3H, m, C*H*$_2$ and C*H*H), 1.78-1.83 (1H, m, CH*H*), 2.09-2.14 (2H, m, C*H*$_2$), 2.82-2.86 (1H, m, C*H*), 3.18 (1H, d, *J* 10.4 Hz, C*H*), 3.75 (3H, s, C*H*$_3$), 4 21 (1H, d, *J* 15 6 Hz, C*H*H), 4.34-4.25 (1H, m, C*H*), 4.89 (1H, d, *J* 16.0 Hz, CH*H*), 5.35-5.39 (1H, m, C*H*=CH), 5.59-5.63 (1H, m, CH=C*H*), 7.06-7.10 (1H, m, Ar-*H*), 7.17-7.25 (2H, m, Ar-*H*), 7.47-7.49 (1H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 19.57 (*C*H$_2$), 26.66 (*C*H$_2$), 26.86 (*C*H$_2$), 39.28 (*C*H), 43 81 (*C*H$_2$), 51 68 (*C*H$_3$), 53.56 (*C*H), 56.21 (*C*H), 122 56 (*C*), 125.11 (*C*H), 126.91 (*C*H), 128.16 (*C*H), 128.40 (*C*H), 129.17 (*C*H), 131.90 (*C*H), 133.97 (*C*), 168.49 (*C*O) and 169.39 (*C*O).

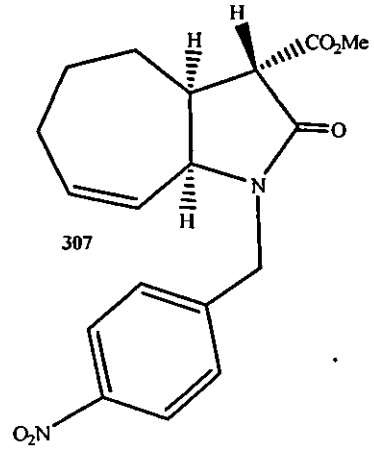
8-(4-Nitro-benzylcarbamoyl)-bicyclo[5.1.0]oct-2-ene-8-carboxyl acid methyl ester



After subjecting bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic methyl ester and *p*-nitro benzylamine to the standard amide coupling and work-up conditions the resulting oil was

purified by flash chromatography (Silica gel, 4:1, hexane: EtOAc) to afford 8-(4-nitro-benzylcarbamoyl)-bicyclo[5.1.0]oct-2-ene-8-carboxyl acid methyl ester as a colourless oil (0 12 g, 0.34 mmol, 61 %); υ_{max} (thin film)cm^{-1} 3344 (N-H str), 2932 (C-H str), 1731 (C=O str), 1697 (C=O str), 1659, 1604, 1518 (N-O) and1431 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.66-1.71 (3H, m, C*H*-C*HH*), 1.95-2.05 (2H, m, C*H*-C*H*), 2.18-2.24 (1H, m, C*H*), 2 36-2.42 (1H, m, C*H*), 2.56-2.58 (1H, m, C*H*), 3.66 (3H, s, CH_3), 4.50 (2H, d, *J* 6.0 Hz, CH_2), 5.54-5.56 (2H, m, C*H*=C*H*), 7.36 (2H, d, *J* 8.4 Hz, Ar-*H*), 8.10 (2H, d, *J* 8.4 Hz, Ar-*H*), 8.12 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 22.91 (CH_2), 24.16 (CH_2), 29.38 (CH_2), 32.12 (*C*H), 34.01 (*C*H), 37.96 (*C*), 43.38 (CH_2), 51.87 (CH_3), 123.59 (*C*H), 123.87 (2x *C*H), 128.11 (2x *C*H), 131.31 (*C*H), 146.10 (*C*), 147.22 (*C*), 169.30 (*C*O), 171.73 (*C*O); ms (FAB): *m/z* 345 [M$^+$ 4%], 327 (18), 221 (44), 191 (31), 161 (32), 136 (70), 91 (38) and 73 (100). HRMS calc. for $C_{18}H_{20}N_2O_5$ requires 345.1450, observed 345.1457.

1-(4-Nitro-benzyl)-2-oxo-1,2,3,3a,4,5,6,8a-octahydro-cyclohepta[b]pyrrole-3-carboxylic acid methyl ester

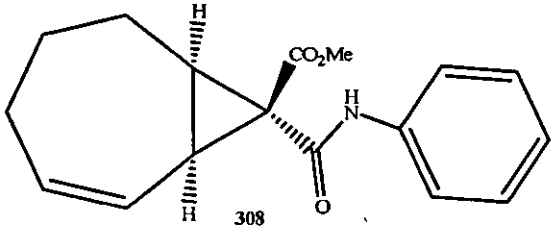


307

After subjecting 8-(4-nitro-benzylcarbamoyl)-bicyclo[5.1.0]oct-2-ene-8-carboxyl acid methyl ester to the standard rearrangement and work-up conditions the crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-(4-nitro-benzyl)-2-oxo-1,2,3,3a,4,5,6,8a-octahydro-cyclohepta[b]pyrrole-3-carboxylic acid methyl ester as a yellow oil (0.04 g, 0 11 mmol, 99 %); υ_{max} (thin film)cm^{-1} 2932 (C-H str), 1738 (C=O str), 1694 (C=O str), 1520 (NO_2), 1434, 1345 and 1264 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.42-1.59 (3H, m, CH_2 and C*H*H), 1.78-1.83 (1H, m, CH*H*), 2.08-2.14 (2H, m, CH_2), 2.78-2.81 (1H, m, C*H*), 3.18 (1H, d, *J* 10.0 Hz, C*H*), 3.76 (3H, s, CH_3), 4.06 (1H, d, *J* 16 0 Hz, C*H*H), 4 28-4 30 (1H, m, C*H*), 4.97 (1H, d, *J* 16.0 Hz, CH*H*), 5.29-5 33 (1H, m, C*H*=CH), 5.62-5.68 (1H, m, CH=C*H*), 7.35 (2H, d, *J* 8.4 Hz, Ar-*H*), 8.12 (2H, d, *J* 8 4 Hz,

Ar-*H*); δ_c (100 MHz; $CDCl_3$) 20.54 (*C*H_2), 27.55 (*C*H_2), 27.94 (*C*H_2), 40.24 (*C*H), 44.50 (*C*H_2), 52 83 (*C*H), 54.35 (*C*H_3), 57.30 (*C*H), 124.08 (2x *C*H), 125.49 (*C*H), 128.76 (2x *C*H), 131.09 (*C*H), 143.53 (*C*), 147.56 (*C*), 169.71 (*C*O) and 170.28 (*C*O); ms (FAB): *m/z* 345 [M^+ 57%], 281 (15), 207 (20), 136 (43), 91 (28), and 73 (100). HRMS calc. for $C_{18}H_{20}N_2O_5$ requires 345.1450, observed 345.1455.

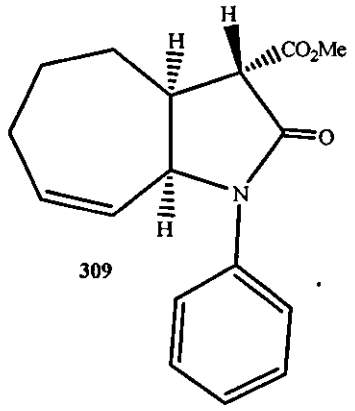
8-Phenylcarbamoyl-bicyclo[5.1.0]oct-2-ene-8-carboxylic acid methyl ester



308

After subjecting bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic methyl ester and aniline to the standard amide coupling and work-up conditions the resulting oil was purified by flash chromatography (Silica gel, 4:1, hexane: EtOAc) to afford 8-phenylcarbamoyl-bicyclo[5.1.0]oct-2-ene-8-carboxylic acid methyl ester as white solid (0.13 g, 0.45 mmol, 68 %); mp range 99.3-103.3 °C; υ_{max} (thin film)cm^{-1} 3315 (N-H str), 2930 (C-H str), 1734 (C=O str), 1695 (C=O str), 1596, 1539, 1499, 1441, 1344 and 1257 (C-O str); δ_H (400 MHz, $CDCl_3$) 1.53-1.71 (4H, m, C*H*$_2$C*H*$_2$), 1.97-2.06 (1H, m, C*H*H), 2.28-2.33 (1H, m, C*H*), 2.39-2.40 (1H, m, CH*H*), 2.65-2.66 (1H, m, C*H*), 3.71 (3H, s, C*H*$_3$), 5 56-5 61 (2H, m, C*H*$_2$), 7.00 (1H, t, *J* 7.6 Hz, Ar-*H*), 7.22 (2H, t, *J* 7.6 Hz, Ar-*H*), 7.46 (2H, d, *J* 7.6 Hz, Ar-*H*), 9.72 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 23.02 (*C*H_2), 24 28 (*C*H_2), 29.50 (*C*H_2), 32.39 (*C*H), 34 46 (*C*H), 38.54 (*C*), 51 97 (*C*H_3), 120.17 (2x *Ar*-H), 123.75 (*C*H), 124.17 (*Ar*-H), 128.93 (2x *Ar*-H), 131.29 (*C*H), 138 04 (*C*), 166.60 (*C*O) and 172.10 (*C*O); ms (EI): *m/z* 286 [M^+ 51%], 254 (18), 207 (27), 193 (88), 161 (61), 149 (81), 136 (27), 105 (50), 93 (100) and 73 (75) HRMS calc. for $C_{17}H_{19}NO_3$ $[M^+H]^+$ requires 286 14332, observed 286.14402.

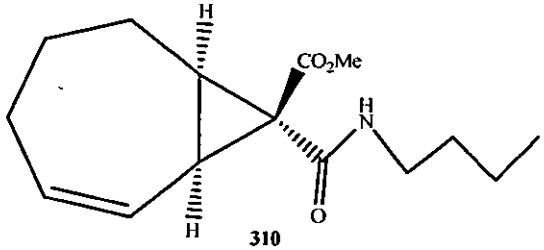
2-Oxo-1-phenyl-1,2,3,3a,4,5,6,8a-octahydrocyclohepta[b]pyrrole-3-carboxyl acid methyl ester



309

After subjecting 8-phenylcarbamoyl-bicyclo[5.1.0]oct-2-ene-8-carboxylic acid methyl ester to the standard rearrangement and work-up contitions the crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: ethyl acetate) to afford 2-oxo-1-phenyl-1,2,3,3a,4,5,6,8a-octahydrocyclohepta[b]pyrrole-3-carboxyl acid methyl ester as a yellow oil (0.04 g, 0.15 mmol, 90 %); υ_{max} (thin film)cm^{-1} 3378 (N-R str), 2928 (C-H str), 1740 (C=O str), 1696 (C=O str), 1596, 1496, 1437 and 1379 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.48-1.66 (3H, m, C*H*$_2$ and C*H*H), 1.88-1.92 (1H, m, CH*H*), 2.18-2.20 (1H, m, C*H*H), 2.31-2.40 (1H, m, CH*H*), 2.99-3.03 (1H, m, C*H*), 3.38 (1H, d, *J* 11.2 Hz, C*H*), 3.75 (3H, s, C*H*$_3$), 5.06-5.08 (1H, m, C*H*), 5.34-5.38 (1H, m, C*H*=CH), 5.62-5.65 (1H, m, CH=C*H*), 7.07 (1H, t, *J* 7.6 Hz, Ar-*H*), 7.26 (2H, t, *J* 8.4 Hz, Ar-*H*), 7.53 (2H, d, *J* 7.6 Hz, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 19.60 (*C*H$_2$), 26.68 (*C*H$_2$), 27.16 (*C*H$_2$), 39.01 (*C*H), 51.68 (*C*H$_3$), 55.19 (*C*H), 58.22 (*C*H), 120.21 (2x *C*H), 124.09 (*C*H), 126.21 (*C*H), 127.97 (*C*H), 129.15 (2x *C*H), 136.99 (*C*), 167.44 (*C*O) and 168.86 (*C*O); ms (FAB): *m/z* 286 [M^+ 22%], 267 (11), 221 (15), 207 (25), 154 (28), 147 (54), 136 (64) and 73 (100). HRMS calc. for $C_{17}H_{19}NO_3$ requires 286.1443, observed 286.1449.

8-Butylcarbamoyl-bicyclo[5.1.0]oct-2-ene-8-carboxylic acid methyl ester

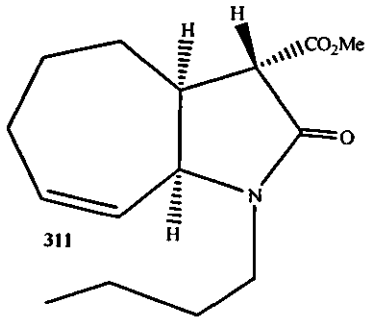


310

After subjecting bicyclo[5 1 0]oct-2-ene-8,8-dicarboxylic methyl ester and butylamine to the standard amide coupling and work-up conditions the resulting oil was purified by flash

chromatography (Silica gel, 4:1, hexane EtOAc) to afford 8-butylcarbamoyl-bicyclo[5.1.0]oct-2-ene-8-carboxylic acid methyl ester as a yellow oil (0.12 g, 0.46 mmol, 70 %); υ_{max} (thin film)cm^{-1} 3345 (N-H str), 2930 (C-H str), 1734 (C=O str), 1653 (C=O str), 1533, 1436, 1313 and 1194 (C-O str); δ_H (400 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7.6 Hz, C*H*$_3$), 1.30-1.41 (2H, m, C*H*$_2$), 1.42-1.45 (3H, m, C*H*$_2$-C*H*), 1.62-1.69 (2H, m, C*H*$_2$), 1.95-1.99 (2H, m, C*H*-C*H*H), 2.07-2.12 (1H, m, C*H*), 2 47-2.49 (1H, m, C*H*), 2.50 (1H, m, C*H*), 3.16 (2H, ddd, *J* 5.6, 7.2 and 12.4 Hz, C*H*$_2$), 3.67 (3H, s, C*H*$_3$), 5.51-5.56 (2H, m, C*H*=C*H*), 7.20 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 12.76 (*C*H$_3$), 19.12 (*C*H$_2$), 22.05 (*C*H$_2$), 23.01 (*C*H$_2$), 28.13 (*C*H$_2$), 29.77 (*C*H), 30.48 (*C*H$_2$), 31.63 (*C*H), 37.24 (*C*), 38.88 (*C*H$_2$), 50.77 (*C*H$_3$), 123.09 (*C*H), 129.75 (*C*H), 167.26 (*C*O) and 170.45 (*C*O); ms (FAB): *m/z* 266 [M^+ 100 %], 234 (50), 193 (25), 161 (22), 136 (11), 105 (11), and 73 (14). HRMS calc. for $C_{15}H_{23}NO_3$ requires 265.1756, observed 266.1758.

1-Butyl-2-oxo-1,2,3,3a,4,5,6,8a-octahydro-cyclohepta[b]pyrrole-3-carboxylic acid methyl ester

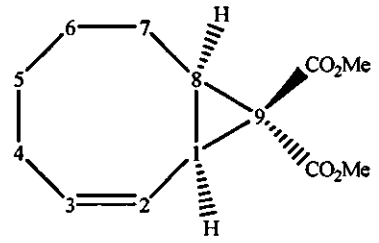


311

After subjecting 8-butylcarbamoyl-bicyclo[5.1.0]oct-2-ene-8-carboxylic acid methyl ester to the standard rearrangement and work-up conditions the crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-butyl-2-oxo-1,2,3,3a,4,5,6,8a-octahydro-cyclohepta[b]pyrrole-3-carboxylic acid methyl ester as a yellow oil (0.03 g, 0.09 mmol, 79 %);υ_{max} (thin film)cm^{-1} 2929 (C-H str), 1737 (C=O str), 1692 (C=O str), 1433 and 1264 (C-O str); δ_H (400 MHz, $CDCl_3$) 0 53 (3H, t, *J* 4 Hz, C*H*$_3$), 1.22-1.28 (2H, m, C*H*$_2$), 1.66 (5H, m, C*H*$_2$-C*H*$_2$ and C*H*), 1.77-1.80 (1H, m, C*H*H), 2.13-2 21 (2H, m, C*H*$_2$), 2.78-2.88 (2H, m, CH*H* and C*H*H), 3.12 (1H, d, *J* 10.4 Hz, C*H*), 3.58-3.60 (1H, m, CH*H*), 3.63 (3H, s, C*H*$_3$), 4.46 (1H, s, C*H*), 5 23-5 34 (1H, m, C*H*=CH), 5.62-5 64 (1H, m, CH=C*H*); δ_c (100 MHz, $CDCl_3$) 13.79 (*C*H), 20.10 (*C*H$_2$), 20 65 (*C*H$_2$), 27.55 (*C*H$_2$), 27.87 (*C*H$_2$), 29.22 (*C*H$_2$), 40 05 (*C*H), 41.08 (*C*H$_2$), 52 69 (*C*H), 54.95 (*C*H$_3$), 57 32 (*C*H), 126.60 (*C*H), 130 04 (*C*H), 169.09 (*C*O) and 170 67 (*C*O); ms (FAB): *m/z* 266 [M^+ 100 %], 234 (14),

206 (11), 154 (23), 136 (28), 107 (13), and 73 (11). HRMS calc. for $C_{15}H_{23}NO_3$ requires 266.1756, observed 266.1754.

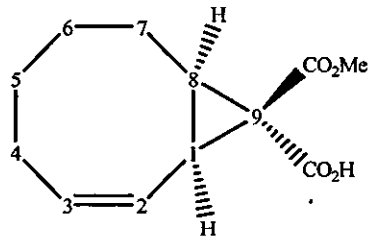
Bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid dimethyl ester[24]



313

To a stirred solution of 1,3-cyclooctadiene (0.75 g, 6.96 mmol), and $Rh_2(OAc)_4$ (0.03 g, 0.07 mmol) in 1,2-dichloroethane (2 ml) was added dimethyl diazomalonate (1.00 g, 6.33 mmol) *via* syringe pump diluted in 1,2-dichloroethane (4 ml). The mixture was stirred under reflux for 3 h. The mixture was allowed to cool to room temperature before being concentrated *in vacuo*. The resulting oil was purified by flash chromatography (Silica gel, hexane: EtOAc, 2:1) to afford bicyclo[6 1.0]non-2-ene-9,9-dicarboxylic acid dimethyl ester as a colourless viscous oil (0.96 g, 3.99 mmol, 60 %); υ_{max} (thin film)cm^{-1} 2950 (C-H str), 1726 (C=O str), 1435, 1333, 1254, 1199, 1174 and 1107 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.02-1.06 (1H, m, 7-C*H*H), 1.36-1.39 (1H, m, 8-C*H*), 1.52-1 67 (3H, m, 1-C*H*, 5-C*H*H and 7-CH*H*), 1.70-1.98 (3H, m, 6-CH_2 and 4-C*H*H), 2.28-2.37 (2H, m, 4-CH*H* and 5-CH*H*) 3.71 (3H, s, CH_3), 3.73 (3H, s, CH_3), 5.53-5.56 (1H, m, 2-C*H*=CH), 5.75-5.79 (1H, m, 3-CH=C*H*); δ_c (100 MHz; $CDCl_3$) 24.01 (7-*C*H_2), 24.73 (5-*C*H_2), 29.15 (4-*C*H_2), 29.74 (6-*C*H_2), 30.22 (1-*C*H), 32.92 (8-*C*H), 36.11 (9-*C*), 52.14 (*C*H_3), 52.45 (*C*H_3), 120.58 (2-*C*H), 136.33 (3-*C*H), 167.14 (*C*O) and 171.28 (*C*O); ms (FAB): *m/z* 239 [M^+ 100%], 207 (93), 175 (54), 119 (26), 107 (34), 91 (21) and 79 (16). HRMS calc. for $C_{13}H_{18}O_4$ $[M^+H]^+$ requires 239.1283, observed 239.1279.

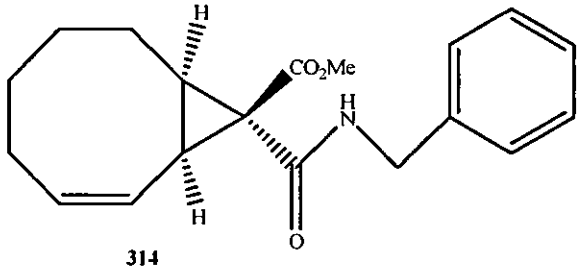
Bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid methyl ester



266

To a stirred solution of ester (0.20 g, 0.82 mmol) in THF/H_2O (1:1, 6ml) was added LiOH (0.16 g, 0 82 mmol) and stirred at room temperature for 2 h. The mixture was then acidified to pH 2 with 2 *M* HCl, extracted into Et_2O (3x 10 ml), washed with brine (3x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid methyl ester as a colourless oil (0.17 g, 0.76 mmol, 92 %); υ_{max} (thin film)cm^{-1} 3500 (O-H str), 2981 (C-H str), 1734 (C=O str), 1436, 1326, 1249, 1212 and 1118 (C-O str); 1.25-2.63 (10H, m, *CH*$_2$*CH*$_2$*CH*$_2$*CH*$_2$*CHCH*), 3.72 (3H, s, *CH*$_3$), 5.50-5.56 (1H, m, *CH*=CH), 5.75-5.81 (1H, m, CH=*CH*), 9.40 (1H, s, *OH*); δ_c (100 MHz; $CDCl_3$) 22.05 (*CH*$_2$), 23.62 (*CH*$_2$), 24.04 (*CH*$_2$), 24 74 (*CH*$_2$), 30 26 (*CH*), 35.42 (*CH*), 38.08 (*CH*), 52.38 (*CH*$_3$), 120.33 (*CH*), 136.15 (*CH*), 171.35 (*CO*) and 175.65 (*CO*); ms (FAB): *m/z* 239 [M^+ 50%], 207 (86), 175 (72), 136 (100), 119 (56), 107 (80), 91 (89) and 79 (31). HRMS calc. for $C_{12}H_{16}O_4$ $[M^+H]^+$ requires 225.1126, observed 225.1131.

9-Phenylcarbamoyl-bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid methyl ester

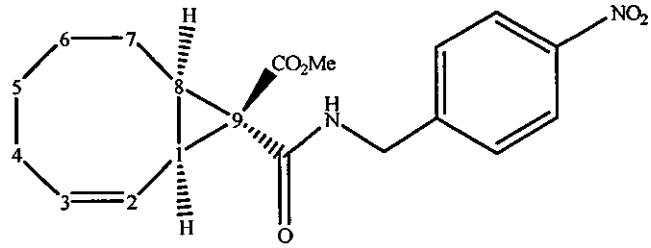


314

After subjecting bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid methyl ester and benzylamine to the standard amide coupling and work-up conditions the mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 2:1, light petroleum: EtOAc) to afford 9-phenylcarbamoyl-bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid methyl ester as a yellow oil (0.09 g, 0.28 mmol, 78 %); υ_{max} (thin film)cm^{-1} 3338 (N-H str), 2924 (C-H str), 1731 (C=O str), 1697 (C=O str), 1650, 1531, 1454, 1316 and 1163 (C-O str); δ_H (400 MHz;

$CDCl_3$) 1.44-2.56 (8H, m, CH_2-CH_2-CH_2-CH_2), 2 04.2 07 (1H, m, C*H*), 2.75- 2.77 (1H, m, C*H*), 3.73 (3H, s, CH_3), 4.47 (2H, d, *J* 5.6 Hz, CH_2), 5.44-5.46 (1H, m, C*H*=CH), 5.75 (1H, m, CH=C*H*), 7.26-7.36 (5H, m, Ar-*H*), 7.90 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 22 34 (CH_2), 25.25 (CH_2), 29.25 (CH_2), 29.73 (CH_2), 31.94 (*C*H), 35.41 (CH), 36.13 (*C*), 44.17 (CH_2), 51.79 (CH_3), 121.71 (*C*H), 127.35 (*C*H), 127.67 (2x *C*H), 128.66 (2x *C*H), 134.63 (*C*H), 138.33 (*C*), 168.80 (*C*O) and 171.63 (*C*O); *m/z* 214 [M^+ 82%], 282 (41), 221 (24), 207 (24), 175 (24), 147 (60), 109 (37) and 91 (100). HRMS calc. for $C_{19}H_{23}NO_3$ $[M^+H]^+$ requires 314.1756, observed 314.1758.

9-(4-Nitro-phenylcarbamoyl)-bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid methyl ester

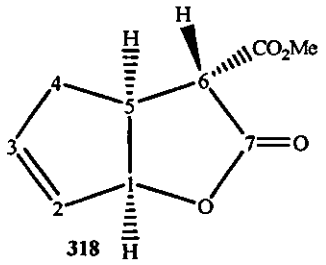


316

To a stirred solution of bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid methyl ester (0 06 g, 0.29 mmol), in DMF (3 ml) at room temperature was added DIEA (0.10 ml, 0 57 mmol), HATU (0 13 g, 0.34 mmol) and the mixture was left stirring for 10 min. Then *p*-nitro-benzylamine (0.07 g, 0.34 mmol) was added and the reaction was left stirring for 3 h The reaction was then diluted with DCM (15 ml), washed with 2 *M* HCl (10 ml), aqueous $NaHCO_3$ (20 ml) and re-extracted into DCM (3x 20 ml), the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 2 1, light petroleum: ethyl EtOAc) to afford 9-(4-nitro-phenylcarbamoyl)-bicyclo[6 1.0]non-2-ene-9,9-dicarboxylic acid methyl ester as a colourless oil (0 08 g, 0 20 mmol, 71 %); υ_{max} (thin film)cm^{-1} 3335 (N-H str), 2924 (C-H str), 1733 (C=O str), 1653 (C=O str), 1521, 1344, 1317 and 1163 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.81-2 01 (8H, m, 4-C*H*H, 5-CH_2, 6-CH_2, 7-CH_2 and 8-C*H*), 2 27-2 29 (1H, m, 4-CH*H*), 2.70-2.73 (1H, m, 1-C*H*), 3.65 (3H, s, CH_3), 4 49 (2H, d, *J* 5 6 Hz, CH_2), 5 53-5 38 (1H, m, 3-C*H*=CH), 5.66-5.69 (1H, m, 2-CH=C*H*), 7 37 (2H, d, *J* 8 8 Hz, Ar-*H*), 8.12 (2H, d, *J* 8.8 Hz, Ar-*H*) 8.33 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 22.76 (7-CH_2), 25.24 (6-CH_2), 29.23 (5-CH_2), 29.66 (4-CH_2), 32.74 (1-*C*H), 35.92 (9-*C*), 36.31 (8-*C*H) 43.40 (CH_2), 51.79 (CH_3), 121 47 (3-*C*H), 123.88 (2x *C*H), 128.16 (2x *C*H), 134.73 (2-*C*H), 146 16 (*C*), 147.17 (*C*), 169.41 (*C*O) and

172.08 (*C*O); ms (FAB): *m/z* 359 [M^+ 4%], 279 (100), 233 (13), 201 (14), 136 (6), 91 (5) and 77 (9). HRMS calc. for $C_{19}H_{22}N_2O_5$ requires 359.2607, observed 359.2600.

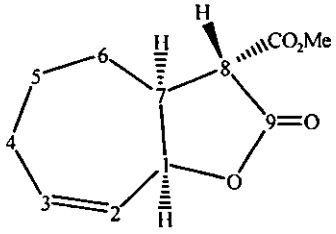
2-Oxo-3,3a,4,6a-tetrahydro-2-*H*-cyclopenta[b]furan-3-carboxylic acid methyl ester



318

After subjecting bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester to the standard rearrangement conditions on bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester as the substrate the crude mixture was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 2-oxo-3,3a,4,6a-tetrahydro-2-*H*-cyclopenta[b]furan-3-carboxylic acid methyl ester as a yellow oil (0.05 g, 0.28 mmol, 99 %); υ_{max} (thin film)cm^{-1} 2953 (C-H str), 1772 (C=O str), 1733, 1616, 1436, 1362, 1333, 1269 and 1146 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.37-2.42 (1H, m, 4-C*H*H), 2.79-2.85 (1H, m, 4-CH*H*), 3.39 (1H, d, *J* 6.4 Hz, 6-C*H*), 3.48-3.53 (1H, m, 5-C*H*), 3.82 (3H, s, CH_3), 5.58-5 61 (1H, m, 1-C*H*), 5.89-5.92 (1H, m, 2-C*H*=CH) 6.10-6.12 (1H, m, 3-CH=C*H*); δ_c (100 MHz; $CDCl_3$) 34.40 (4-CH_2), 39.10 (6-*C*H), 53.20 (CH_3), 53.90 (6-*C*H), 88.66 (1-*C*H), 127.99 (2-*C*H), 136.85 (3-*C*H), 168.37 (*C*O) and 171.71 (7-*C*O); *m/z* 183 [M^+ 100%], 137 (98), 107 (32), 95 (36), 79 (35), 69 (44) and 55 (60) HRMS calc. for $C_9H_{10}O_4$ $[M^+H]^+$ requires 183 06574, observed 183.06598.

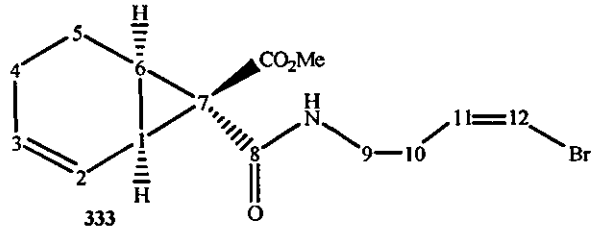
2-Oxo-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[b]furan-3-carboxylic acid methyl ester



After subjecting bicyclo[5 1 0]oct-2-ene-8,8-dicarboxylic methyl ester to the standard rearrangement and work-up conditions the crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 2-oxo-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[b]furan-3-carboxylic acid methyl ester as a colourless oil (0 09 g,

0.43 mmol, 88 %); υ_{max} (thin film)cm^{-1} 2932 (C-H str), 1778 (C=O str), 1738 (C=O str), 1436, 1345, 1273 and 1147 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.53-1.68 (3H, s, 6-C*H*$_2$ and 4-C*H*H), 1.81-1.85 (1H, m, 5-C*H*H), 2.14-2.20 (2H, m, 4-CH*H* and 5-CH*H*), 3.09-3.12 (1H, m, 7-C*H*), 3.28 (1H, d, *J* 19.6 Hz, 8-C*H*), 3.69 (3H, s, C*H*$_3$), 5.39-5.42 (1H, m, 1-C*H*), 5.46-5.50 (1H, m, 2-C*H*=CH), 5.62 -5.67 (1H, m, 3-CH=C*H*); δ_c (100 MHz; $CDCl_3$) 21.83 (6-*C*H$_2$), 27.25 (5-*C*H$_2$), 28.61 (4-*C*H$_2$), 42.91 (7-*C*H), 53.06 (*C*H$_3$), 53.06 (8-*C*H), 86.33 (1-*C*H), 126.20 (2-*C*H), 130.19 (3-*C*H), 167.99 (*C*O) and 171.27 (*C*O).

7-(4-Bromo-but-3-enylcarbamoyl)-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester[53]

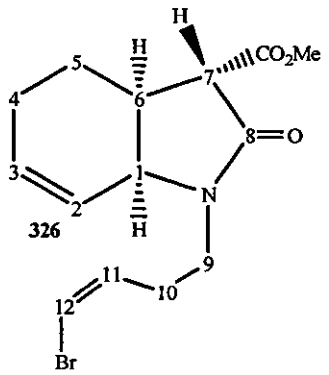


333

To a stirred solution of bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid methyl ester (0 20 g, 1.03 mmol), in anhydrous DMF (2 ml) was added DIEA (0.36 ml, 2.06 mmol), HATU (0.47 g, 1.24 mmol). Then 4-bromo-but-3-enylamine (0.15 g, 0.10 mmol) was added and was stirred for a further 3 h before being diluted with DCM (15 ml). The mixture was then washed with 2 *M* HCl (10 ml), aqueous $NaHCO_3$ (2x 10 ml) and extracted into DCM (3x 15 ml). The organic extracts were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. The product was then purified by flash chromatography using gradient elution (silica gel, 4:1-2:1, light petroleum: EtOAc) to yield 7-(4-bromo-but-3-enylcarbamoyl)-bicyclo[4.1 0]hept-2-ene-7-carboxylic acid methyl ester as a yellow oil (0.26 g, 0.80 mmol, 77 %); υ_{max} (thin film)cm^{-1} 3357 (N-H str), 2988 (C-H str), 1731 (C=O str), 1650 (C=O str), 1529, 1434, 1319, 1198 (C-O str) and 698 (C-Br str); δ_H (400 MHz, $CDCl_3$) 1.60-1.68 (1H, m, 5-C*H*H), 1.89-2.15 (5H, m, 4-C*H*$_2$, 1-C*H*, 6-C*H* and 5-CH*H*), 2.33 (2H, q, *J* 6.8 Hz, 10-C*H*$_2$), 3.29 (2H, q, *J* 6.8 Hz, 9-C*H*$_2$), 3 65 (3H, s, C*H*$_3$), 5 61-5 66 (1H, m, 2-C*H*=CH), 5.78-5.81 (1H, m, 3-CH=C*H*), 5.99 (1H, q, *J* 7.2 Hz, 11-C*H*=CH), 6.21-6.23 (1H, m, 12-CH=C*H*), 6 51 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 16.03 (5-*C*H$_2$), 20.77 (4-*C*H$_2$), 23.94 (6-*C*H), 24 72 (1-*C*H), 29.88 (10-*C*H$_2$), 38.34 (9-*C*H$_2$), 42.40 (7-*C*), 52.54 (*C*H$_3$), 110.25 (12-*C*H), 121.94 (3-*C*H), 128 01 (2-*C*H), 131.37 (11-*C*H), 167.53 (*C*O) and 170.61 (*C*O); ms (EI) 330 [M^+, 4%, ^{81}Br],

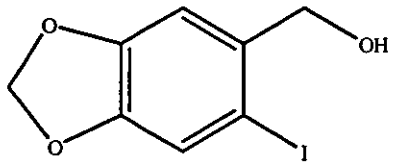
328 [M^+, 7%, ^{79}Br], 294 (35), 178 (88), 146 (30), 119 (40), 91 (100), 79 (98), 65 (55), 53 (69) and 39 (96). HRMS calc. for $C_{14}H_{18}NO_3{}^{79}Br$ $[M^+H]^+$ requires 328 0543, observed 328 0542.

1-(4-Bromo-but-3-enyl)-2-oxo-2,3,3a,4,5,7a-hexahydro-*1H*-indole-3-carboxylic acid methyl estert



To a stirred solution of 7-(4-bromo-but-3-enylcarbamoyl)-bicyclo[4.1.0]hept-2-ene-7-carboxylic acid methyl ester (0.11 g, 0.33 mmol) in MeOH (2 ml) under N_2 was added $Pd(PPh_3)_4$ (0.04 g, 0.03 mmol) and the reaction was left stirring at room temperature for 17 h. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-(4-bromo-but-3-enyl)-2-oxo-2,3,3a,4,5,7a-hexahydro-*1H*-indole-3-carboxylic acid methyl ester as a yellow oil (0.10 g, 0.30 mmol, 92 %); υ_{max} (thin film)cm^{-1} 2927 (C-H str), 1737 (C=O str), 1692 (C=O str), 1434, 1288, 1269, 1165 (C-O str) and 667 (C-Br str); δ_H (400 MHz; $CDCl_3$) 1.51-1.54 (1H, m, 5-C*H*H), 1.68-1.70 (1H, m, 5-CH*H*), 2.00-2.05 (2H, m, 4-CH_2), 2.38 (2H, q, *J* 7.2 Hz, 10-CH_2), 2.73-2.76 (1H, m, 6-C*H*), 3.03 (1H, m, 9-C*H*H), 3.15 (1H, d, *J* 6.0 Hz, 7-C*H*), 3.60-3.69 (1H, m, 9-CH*H*), 3.70 (3H, s, CH_3), 4.10 (1H, s, 1-C*H*), 5.73-5 77 (1H, m, 2-C*H*=CH), 5.94-5.99 (1H, m, 3-CH=C*H*), 6.03 (1H, q, *J* 7.2 Hz, 11-C*H*), 6.16-6.19 (1H, m, 12-C*H*); δ_c (100 MHz; $CDCl_3$) 22.24 (4-*C*H_2), 23 36 (5-*C*H_2), 28.38 (10-*C*H_2), 35.78 (6-*C*H), 38.78 (9-*C*H_2), 52.59 (*C*H_3), 52.95 (7-*C*H), 53.73 (1-*C*H), 110.12 (12-*C*H), 122.68 (2-*C*H), 131.11 (11-*C*H), 132.22 (3-*C*H), 169.21 (*C*O) and 170.15 (*C*O); ms (EI) 330 [M^+, 4%, ^{81}Br], 328 [M^+, 9%, ^{79}Br], 296 (35), 208 (100), 148 (26), 118 (46), 91 (45), 77 (40), 59 (45) and 39 (79). HRMS calc. for $C_{14}H_{18}NO_3{}^{79}Br$ requires 328.0543, observed 328.0546.

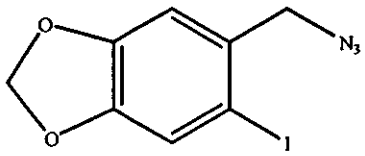
6-Iodo-benzo[1,3]dioxol-5-yl methanol[61]



406

To a stirred solution of piperonyl alcohol (3.00 g, 19.7 mmol), CF_3CO_2Ag (5.66 g, 25.6 mmol) in anhydrous $CHCl_3$ (90 ml) at 0 °C in a 250ml 3-necked flask was added I_2 (6.51 g, 25.6 mmol) in one portion. The resulting mixture was maintained at 0°C for 30 min; whereupon it was filtered. The filtrate was washed with Na_2SO_3 (3x 20ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow solid. Recrystallisation from $CHCl_3$ afforded 6-iodo-benzo[1,3]dioxol-5-yl methanol (3.73 g, 13.4 mmol, 68%) as white needles; mp range 109-111 °C, lit mp 106-107 °C; υ_{max} (thin film)cm^{-1} 3170 (O-H str), 2906 (C-H str), 1498, 1476, 1448, 1242, 1225, 1100, 1029, 1037 (C-O str) and 857 (C-I str); δ_H (400 MHz; $CDCl_3$) 1.58 (1H, s, O*H*), 4.58 (2H, s, CH_2), 5.98 (2H, s, CH_2O_2), 6.99 (1H, s, Ar-*H*), 7.24, s, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 6.93 (*C*H_2), 85.4 (*C*), 101.7 (*C*H_2), 109.1 (*C*H), 118.5 (*C*H), 136.2 (*C*), 147.9 (*C*) and 148.6 (*C*).

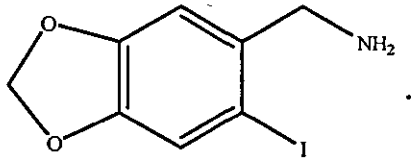
6-Iodo-benzo[1,3]dioxol-5-yl-methylazide[61]



407

To a stirred solution of 6-iodo-benzo[1,3]dioxol-5-yl methanol (0.50 g, 1.80 mmol), in anhydrous THF (20 ml) at 0°C was added PPh_3 (0.71 g, 2.70 mmol) and diphenyl phosphoryl azide (0.74 g, 2.70 mmol) and the mixture was left stirring for 10 min DIAD (0 74 g, 2.70 mmol) was then added dropwise over 15 mins and after addition was complete the reaction was left stirring for 2 h. The reaction mixture was then washed with H_2O (3x 20ml) and extracted with DCM (3x 20ml), the organics were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 2:1, light petroleum: EtOAc) to afford the 6-iodo-benzo[1,3]dioxol-5-yl-methylazide as a yellow oil (0 55 g, 1.81 mmol, 99 %); υ_{max} (thin film)cm^{-1} 2981 (C-H str), 2101 (N_3 str), 1718, 1501, 1477 and 1236 (C-O str); δ_H (400 MHz; $CDCl_3$) 4.36 (2H, s, CH_2), 5.99 (2H, s, CH_2), 6 88 (1H, s, C*H*), 7.27 (1H, s, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 58.9 (*C*H_2), 87 4 (*C*), 102.0 (*C*H_2), 109.7 (*C*H), 118.9 (*C*H), 131.4 (*C*), 148.4 (*C*) and 148.7 (*C*).

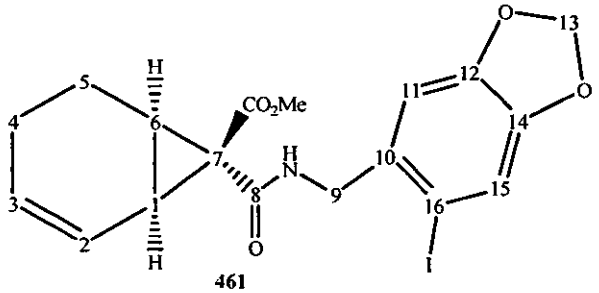
6-Iodo-benzo[1,3]dioxol-5-yl-methylamine[61]



399

To a stirred solution of the 6-iodo-benzo[1,3]dioxol-5-yl-methylazide (0.86 g, 2.85 mmol) in THF/ H_2O (1:5, 30 ml) at room temperature was added PPh_3 (1.12 g, 4.28 mmol) and the reaction was stirred at room temperature for 72 h The reaction was then washed with Na_2SO_3 (3x 20 ml), brine (15 ml) and extracted into DCM (3x 20 ml). The organics were combined, dried (Na_2SO_4) and concentrated *in vacuo* to yield a pale yellow residue. The reaction mixture was then purified on an SCX cartridge using a vacuum filtration box, elution of the desired amine was completed using 2*M* NH_3 in MeOH. The resulting fractions were concentrated *in vacuo* to afford the 6-iodo-benzo[1,3]dioxol-5-yl-methylamine as a pale yellow residue (0.550 g, 2.000 mmol, 70 %); υ_{max} (thin film)cm^{-1} 3368 (N-H str), 2976 (C-H str), 1498, 1475, 1405 and 1385 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.56 (2H, s, N*H*$_2$), 3.79 (2H, s, C*H*$_2$), 5.96 (2H, s, C*H*$_2$), 6.90 (1H, s, Ar-*H*), 7.22 (1H, s, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 51.2 (*C*H$_2$), 86.4 (*C*), 101.6 (*C*H$_2$), 108.8 (*C*H), 118.6 (*C*H), 138.8 (*C*), 147.3 (*C*) and 148.6 (*C*).

7-(1-[6-iodo-benzo[1,3] dioxol-5-yl methyl)-amino]-vinyl)-bicyclo [4.1.0]hept-2-ene-7 carboxylic acid methyl ester

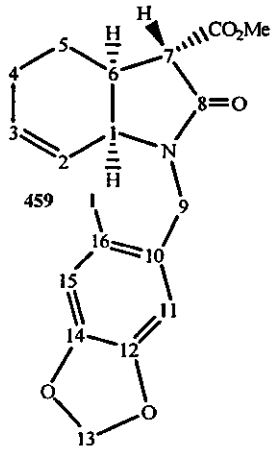


461

To a stirred solution of 7-[(methyloxy)carbon]bicycle[4.1.0]hept-2-ene-7-carboxylic acid (0 39 g, 2 00 mmol), in DMF (7 ml) under N_2 at room temprature was added DIEA (0 49 ml, 2 84 mmol), along with HATU (0.65 g, 1.70 mmol) and the mixture was left stirring for 10 min Then 6-iodo-benzo[1,3]dioxol-5-yl-methylamine (0.55 g, 2 00 mmol) was added and the reaction was left stirring for 3 h. The reaction was then diluted with DCM (15 ml), washed with 2 *M* HCl (10 ml), aqueous $NaHCO_3$ (20 ml) and re-extracted into DCM (3x 20 ml), the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was

purified by flash chromatography (silica gel, gradient elution, 4:1 to 1:1, light petroleum: EtOAc) to afford the 7-(1-[6-iodo-benzo[1,3] dioxol-5-yl methyl)-amino]-vinyl)-bicyclo[4.1.0]hept-2-ene-7 carboxylic acid methyl ester as a pale yellow oil (0.70 g, 1.54 mmol, 77 %); υ_{max} (thin film)cm^{-1} 3351 (N-H str), 2920 (C-H str), 1730 (C=O str), 1659 (C=O str), 1518, 1433, 1386 and 1320 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.69-2.25 (6H, m, 5-C*H*$_2$, 4-C*H*$_2$, 1-C*H* and 6-C*H*), 3.72 (3H, s, C*H*$_3$), 4.34 (2H, d, *J* 6.0 Hz, 9-C*H*$_2$), 5.69-5 74 (1H, m, 2-CH=C*H*), 5.84-5.87 (1H, m, 3-C*H*=CH), 5.95 (2H, s, 13-CH$_2$), 6.86 (1H, s, 11-Ar-*H*), 7.04 (1H, s, N*H*), 7.21 (1H, s, 15-Ar-*H*); δ_c (100 MHz; $CDCl_3$) 16.0 (5-*C*H$_2$), 20.8 (4-*C*H$_2$), 24.2 (6-*C*H), 24.9 (1-*C*H), 42.4 (7-*C*), 48.5 (9-*C*H$_2$), 52.6 (*C*H$_3$), 86.8 (16-*C*), 101.7 (13-*C*H$_2$), 110.0 (11-*C*H), 118 6 (15-*C*H), 121.8 (2-*C*H), 128.3 (3-*C*H), 133.8 (10-*C*), 147.9 (12-*C*), 148.5 (14-*C*) 167.3 (*C*O) and 167.3 (*C*O); ms (EI): *m/z* 456 [M$^+$ 77%], 330 (100), 269 (10), 150 (68), 135 (49), 98 (19) and 77 (10). HRMS calc. for $C_{18}H_{18}NO_5I$ requires 456.0302, observed 456.0308.

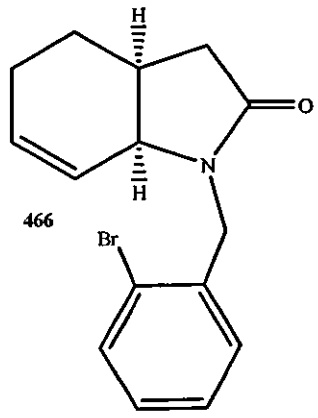
1-(6-Iodo-benzo[1,3]dioxol-5-yl methyl)2-oxo-2,3,3a,4,5,7a-hexahydro-1*H* indole



To a stirred solution of 7-(1-[6-iodo-benzo[1,3] dioxol-5-yl methyl)-amino]-vinyl)-bicyclo[4.1.0]hept-2-ene-7 carboxylic acid methyl ester (0.53 g, 1.12 mmol) in MeOH (4 ml) under N_2 was added $Pd(PPh_3)_4$ (0.17 g, 0.11 mmol) and the reaction was left stirring at room temprature for 17 h The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford the 1-(6-iodo-benzo[1,3]dioxol-5-yl methyl)2-oxo-2,3,3a,4,5,7a-hexahydro-1*H* indole as a yellow oil (0.32 g, 0.71 mmol, 64 %) and another unknown rearrangement product as a white residue (0.158 g); υ_{max} (thin film)cm^{-1} 2921 (C-H str), 1740 (C=O str), 1692 (C=O str), 1500, 1478, 1433 and 1384 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.66 (2H, m, 5-C*H*$_2$), 2.08 (2H, m, 4-C*H*$_2$),

2.83 (1H, m, 6-C*H*), 3.34 (1H, d, *J* 6.8 Hz, 7-C*H*), 3.81 (3H, s, CH_3), 4.01 (1H, s, 1-C*H*), 4.20 (1H, d, *J* 16 0 Hz, CH*H*), 4.83 (1H, d, *J* 16.0 Hz, C*H*H), 5 71 (1H, m, 2-CH=C*H*), 5.97 (2H, s, CH_2), 5.98 (1H, m, 3-C*H*=CH), 6.83 (1H, s, 11-Ar-*H*) 7.22 (1H, s, 15-Ar-*H*); δ_c (100 MHz; $CDCl_3$) 21.9 (5-*C*H_2), 23.3 (4-*C*H_2), 36.0 (6-*C*H), 49.2 (9-*C*H_2), 52.4 (7-C*H*), 52.6 (*C*H_3), 53.4 (1-*C*H), 86.3 (16-*C*), 101.8 (13-*C*H_2), 108.9 (11-*C*H), 118.4 (15-*C*H), 123.0 (2-*C*H), 131.7 (3-*C*H), 131.7 (10-*C*), 148.5 (12-*C*), 147.9 (14-*C*), 169.2 (*C*O) and 170.7 (*C*O); ms (EI): *m/z* 456 [M^+ 100%], 330 (80), 263 (90), 151 (30), 135 (12), 98 (16) and 58 (25). HRMS calc. for $C_{18}H_{18}NO_5I$ requires 456.0305, observed 456 0302.

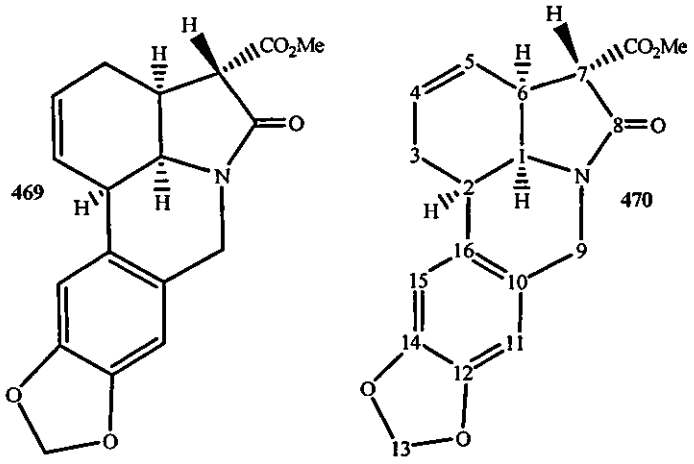
1-(2-Bromo-benzyl)-1,3,3a,4,5,7a-hexahydro-indol-2-one[64]



To a stirred solution of 1-(2-bromo-benzyl)-2-oxo-3,3a,4,5,7a-hexahydro-1*H*-indole-3-carboxylic acid methyl ester (0.09 g, 0.26 mmol) in DMSO (2 ml) was added NaCl (0.05 g, 0.85 mmol) and H_2O (1 drop). The reaction was stirred at reflux for 4 h. The reaction was then allowed to cool to room temperature before being diluted with EtOAc (10 ml). The organic phase was washed with H_2O (3x 10 ml), brine (3x 10 ml) and re-extracted into EtOAc (3x 10 ml) and dried ($MgSO_4$). The reaction mixture was then purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-(2-bromo-benzyl)-1,3,3a,4,5,7a-hexahydro-indol-2-one as a yellow oil (0 06 g, 0.21 mmol, 82 %); υ_{max} (thin film)cm^{-1} 2921 (C-H str), 1687 (C=O str), 1434, 1319, 1269 and 1174 (C-O str); δ_H (400 MHz; $CDCl_3$) 1 58 (1H, m C*H*H), 1.69 (1H, m, CH*H*), 2 02 (2H, m, CH_2), 2.27 (1H, m, C*H*), 2.49 (2H, m, CH_2), 3.88 (1H, m, C*H*), 4.32 (1H, d, *J* 16 0 Hz, C*H*H), 4 85 (1H, d, *J* 16 0 Hz, CH*H*), 5 69 (1H, m, C*H*=CH), 5 93 (1H, m, CH=C*H*), 7.10 (1H, m, Ar-*H*), 7.22 (2H, m, Ar-*H*), 7.53 (1H, m, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 22.30 (*C*H_2), 24 16 (*C*H_2), 31.06 (*C*H), 35.82 (*C*H_2), 44.19 (*C*H_2), 54.85 (*C*H), 123.11 (*C*H), 123.24 (*C*H), 127 66 (*C*H), 128 46 (*C*H), 128.93 (*C*H), 132.14 (*C*H), 132.89 (*C*H), 135.92 (*C*) and 174 92 (*C*O).

5-oxo-3a,4,5,12b,12c-hexahydro-3*H*[1,3]dioxolo[4,5]pyrrolo[3,2,1-de]phenanthridine-4-carboxylic acid methyl ester

and 5-oxo-1,3a,4,5,12b,12c-hexahydro-7*H*[1,3]dioxolo[4,5]pyrrolo[3,2,1-de]phenanthridine-4-carboxylic acid methyl ester[64]



Method A

To a stirred solution of $Pd(OAc)_2$ (0.07 g, 0.03 mmol), PPh_3 (0.03 g, 0.12 mmol) in DMF (1 ml) under N_2 for 10 min before 1-(6-iodo-benzo[1,3]dioxol-5-yl methyl)2-oxo-2,3,3a,4,5,7a-hexahydro-1*H* indole (0.15 g, 0.33 mmol) was added in a DMF solution (2 ml) followed by the addition of DIEA (0.12 ml, 0 67 mmol). The reaction was then stirred at 100 °C for 12 h. After the reaction was finished it was allowed to cool to room temperature and H_2O (1 ml) was added to the mixture and the aqueous layer was extracted with EtOAc (3x 15 ml). The organics were combined and washed with brine (15 ml), combined and dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (silica gel, 100 0 to 0.100, light petroleum: Et_2O) to afford the 5-oxo-3a,4,5,12b,12c-hexahydro-3*H*[1,3]dioxolo[4,5]pyrrolo[3,2,1-de]phenanthridine-4-carboxylic acid methyl ester and 5-oxo-1,3a,4,5,12b,12c-hexahydro-7*H*[1,3]dioxolo[4,5]pyrrolo[3,2,1-de]phenanthridine-4-carboxylic acid methyl ester (0.04 g, 0 13 mmol, 39 %) and (0.050 g, 0.14 mmol, 43 %) respectively, υ_{max} (thin film)cm^{-1} 3445 (N-R str), 2909 (C-H str), 1730 (C=O str), 1692 (C=O str), 1506, 1485, 1457 and 1361 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.81-1.85 (1H, m, 3-C*H*H), 2.13-2.19 (1H, m, 3-CH*H*), 2.87 (1H, m 2-C*H*), 3.24 (1H, s, 7-C*H*), 3.41 (1H, s, 6-C*H*), 3.78 (3H, m, CH_3), 4.23 (1H, s, 1-C*H*), 4.37 (1H, d, *J* 14.0 Hz, 9-CH*H*), 4 67 (1H, d, *J* 14 0 Hz, 9-C*H*H), 5 58-5 61 (1H, m, 5-C*H*=CH), 5.84-5.86 (1H, m, 4-CH=C*H*), 5.94 (2H, d, *J* 6 8 Hz, 13-CH_2), 6.63 (2H, s, 2x Ar-*H*); δ_c (100 MHz, $CDCl_3$) 27.90 (3-CH_2), 37.10 (6-*C*H), 37.40 (2-*C*H), 43.40 (9-CH_2), 52.80 (CH_3), 54 80 (1-*C*H), 56 10 (7-*C*H), 101.10 (13-CH_2), 107.00 (11-*C*H), 108.20 (15-*C*H), 123.20 (16-*C*), 126.30 (5-*C*H), 127.10 (4-*C*H), 131.70 (10-*C*),

146.90 (12-*C* and 14-*C*), 169.30 (*C*O) and 170.00 (*C*O); υ_{max} (thin film)cm^{-1} 3445 (N-R str), 2909 (C-H str), 1730 (C=O str), 1692 (C=O str), 1506, 1485, 1457 and 1361 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.24-2.27 (2H, m, 5-CH_2), 3 19 (1H, d, *J* 4.0 Hz, 7-C*H*), 3.27 (1H, s, 2-C*H*), 3.27 (1H, s, 6-C*H*), 3.79 (3H, s, CH_3), 4.15 (1H, d, *J* 13.5 Hz, 9-CH*H*), 4.19-4.22 (1H, m, 1-C*H*), 4.84 (1H, d, *J* 13.5 Hz, 9-C*H*H), 5.69-5.71 (1H, m, 3-CH=C*H*), 5.90-5.92 (1H, m, 4-C*H*=CH), 5.94 (2H, s, 13-CH_2), 6.58 (1H, s, 11-C*H*), 6.66 (1H, s, 15-C*H*); δ_c (100 MHz; $CDCl_3$) 26.9 (5-*C*H_2), 34.3 (6-*C*H), 38.3 (2-*C*H), 42.4 (9-*C*H_2), 52.7 (*C*H_3), 55.6 (7-*C*H), 55.7 (1-*C*H), 101.2 (13-*C*H_2), 106.0 (11-*Ar*-H), 108.9 (15-*Ar*-H), 124.1 (10-*C*), 126.7 (4-*C*H), 129.4 (16-*C*), 133.7 (3-*C*H), 146.7 (14-*C*), 147.0 (12-*C*), 168.7 (*C*O) and 170.7 (*C*O); ms (FAB): *m/z* 328 [M^+ 24%], 268 (15), 149 (50), 136 (35), 105 (72), 91 (45), 57 (91) and 55 (100). HRMS calc. for $C_{18}H_{17}NO_5$ requires 328.11850, observed 328.1183.

Method B

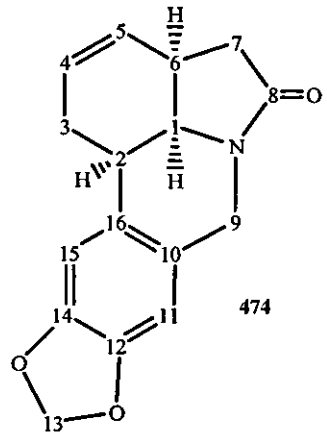
To a stirred solution of 7-(1-[6-iodo-benzo[1,3] dioxol-5-yl methyl)-amino]-vinyl)-bicyclo [4.1.0]hept-2-ene-7 carboxylic acid methyl ester (0.050 g, 0.110 mmol) in MeOH (2 ml) was added $Pd(PPh_3)_4$ (0.017 g, 0.015 mmol) and stirred under N_2 for 10 min at room temperature. Et_3N (0 017 ml, 0.290 mmol) was then added and the reaction stirred under reflux for 24 h. The reaction was allowed to cool to room temperature. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, gradient elution, 100 % to 100%, light petroleum· Et_2O) to afford 5-oxo-1,3a,4,5,12b,12c-hexahydro-7*H*[1,3]dioxolo[4,5]pyrrolo[3,2,1-de]phenanthridine-4-carboxylic acid methyl ester and 5-oxo-3a,4,5,12b,12c-hexahydro-3*H*[1,3]dioxolo[4,5]pyrrolo[3,2,1-de]phenanthridine-4-carboxylic acid methyl ester as a mixture (> 99 %); see previous data.

Method C

To a stirred solution of 7-(1-[6-iodo-benzo[1,3] dioxol-5-yl methyl)-amino]-vinyl)-bicyclo[4.1.0]hept-2-ene-7 carboxylic acid methyl ester (0.05 g, 0.11 mmol) in MeOH (2 ml) was added $Pd(PPh_3)_4$ (0.02 g, 0.02 mmol) and stirred under N_2 for 24 h at room temperature. The reaction was monitored *via* TLC and LC-MS once 1-(6-iodo-benzo[1,3]dioxol-5-yl methyl)2-oxo-2,3,3a,4,5,7a-hexahydro-1*H* indole was observed Et_3N (0.017 ml, 0.290 mmol) was then added and the reaction stirred under reflux for 24 h. The reaction was allowed to cool to room temperature The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was

purified by flash chromatography (silica gel, gradient elution, 100.0 to 0:100, light petroleum: Et_2O) to afford 5-oxo-1,3a,4,5,12b,12c-hexahydro-7*H*[1,3]dioxolo[4,5]pyrrolo[3,2,1-de]phenanthridine-4-carboxylic acid methyl ester and 5-oxo-3a,4,5,12b,12c-hexahydro-3*H*[1,3]dioxolo[4,5]pyrrolo[3,2,1-de]phenanthridine-4-carboxylic acid methyl ester as a mixture (99 %); see previous data.

3a,4,12b,12c-Tetrahydro-1*H*,7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-5-one[64]

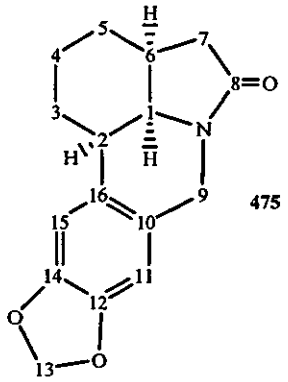


474

To a stirred solution of 5-oxo-1,3a,4,5,12b,12c-hexahydro-7*H*[1,3]dioxolo[4,5]pyrrolo[3,2,1-de]phenanthridine-4-carboxylic acid methyl ester (0.11 g, 0.33 mmol) in DMSO (2 ml) was added H_2O (1 drop) and NaCl (0.06 g, 1.089 mmol). The reaction was heated at 160 °C for 4 h before being allowed to cool to room temperature before being diluted with EtOAc (10 ml). The organic phase was washed with H_2O (3x 10ml, brine (3x 10ml) and re-extracted into EtOAc (10 ml). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford 3a,4,12b,12c-tetrahydro-1*H*,7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-5-one as a pale yellow oil (0 04 g, 0.16 mmol, 49 %);υ_{max} (thin film)cm^{-1} 2924 (C-H str), 1684 (C=O str), 1483, 1259, 1036 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.78-1.87 (1H, m, 3-C*H*H), 2.09-2.18 (1H, m, 3-CH*H*), 2.21 (1H, d, *J* 16.8 Hz, 7-C*H*H), 2.77 (1H, d, *J* 9 6 Hz, 7-CH*H*), 2.81-2.91 (1H, m, 2-C*H*) 3.10 (1H, s, 6-C*H*), 4.00 (1H, m, 1-C*H*), 4.29 (1H, d, *J* 14 0 Hz, 9-C*H*H), 4.62 (1H, d, *J* 14.0 Hz, 9-CH*H*), 5.57-5.59 (1H, m, 5-C*H*=CH), 5.77-5.79 (1H, m, 4-CH=C*H*), 5.93 (2H, d, *J* 6.8 Hz, 13-CH_2), 6.63 (2H, s, 2x Ar-*H*); δ_c (100 MHz; $CDCl_3$) 28.19 (3-CH_2), 31.88 (6-*C*H), 37 46 (2-*C*H), 38.53 (9-CH_2), 42.98 (7-CH_2), 55 64 (1-*C*H), 101.12 (13-CH_2), 106.97 (11-*C*H), 108.37 (15-*C*H), 123.45 (16-*C*), 125 69 (5-*C*H), 128.17 (4-*C*H), 132 09 (10-*C*), 146.55 (12-*C*), 146.88 (14-*C*) and 174.63 (*C*O); ms (EI): *m/z* 270 [M^+ 100%], 188 (28),

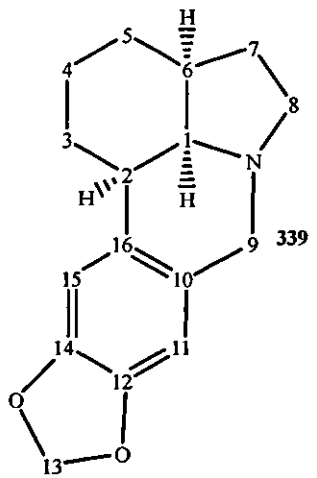
173 (85), 116 (18), 89 (15), 67 (32) and 51 (13). HRMS calc. for $C_{16}H_{15}NO_3$ requires 270.1125, observed 270.1126.

2,3,3a,4,12b,12c-hexahydro-1*H*,7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-5-one[64]



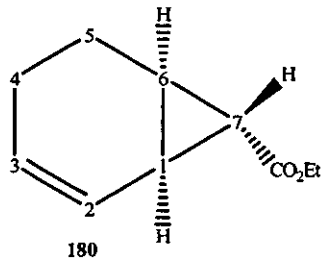
To a stirred solution of 3a,4,12b,12c-tetrahydro-1*H*,7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-5-one (0.02 g, 0.09 mmol) was added Pd/C (10 %) and was stirred in MeOH (2 ml) under an atmosphere of H_2 for 2 h at room temperature. The reaction was then concentrated *in vacuo* re-dissolved in EtOAc (5 ml) and the catalyst removed through a plug of silica to afford the 2,3,3a,4,12b,12c-hexahydro-1*H*,7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-5-one as a pale yellow oil (0.02 g, 0 08 mmol, 90 %); υ_{max} (thin film)cm^{-1} 2926 (C-H str), 1693 (C=O str), 1504, 1484, 1416, 1210 and 1036 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.11-1 41 (3H, m, 4-C*H*$_2$ and 3-C*H*H), 1.68-1.76 (3H, m, 5-CH_2 and 3-CH*H*), 2 08 (1H, d, *J* 16 Hz, 7-C*H*H), 2.38 (1H, m, 6-CH), 2 56 (1H, dd, *J* 6.8 Hz, 7-CH*H*), 2.75 (1H, dt, *J* 4.4 and 12.8 Hz, 2-C*H*), 3.71 (1H, t, *J* 4 8 Hz, 1-C*H*), 4.35 (1H, d, *J* 17.6 Hz, 9-C*H*H), 4.52 (1H, d, *J* 17.6 Hz, 9-CH*H*), 5 92 (2H, dd, *J* 1.6 Hz, 13-C*H*$_2$), 6.59 (1H, s, 15-C*H*), 6 61 (1H, s, 11-C*H*); δ_c (100 MHz; $CDCl_3$) 23.68 (3-*C*H_2), 27.99 (4-*C*H_2), 30 30 (5-*C*H_2), 33 11 (6-*C*H), 39.86 (7-*C*H_2), 40 34 (2-*C*H), 42.74 (9-*C*H_2), 55.78 (1-*C*H), 101.11 (13-*C*H_2), 106 71 (11-*C*H), 108.32 (15-*C*H), 123.33 (16-*C*), 131 63 (10-*C*), 146 68 (12-*C*), 146 87 (14-*C*) and 175.75 (*C*O); ms (EI). *m/z* 271 [M^+ 100%], 242 (7), 228 (8), 174 (15), 149 (12) and 84 (10). HRMS calc. for $C_{16}H_{17}NO_3$ requires 271.12084, observed 271.12098.

1,2,3a,4,5,7,12b,12c-Octahydro-3H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridine[64]



To a stirred solution of 2,3,3a,4,12b,12c-hexahydro-1*H*,7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-5-one (0.02 g, 0.08 mmol) in THF (1 ml) was added a THF suspension of $LiAlH_4$ (0.02 g, 0.39 mmol) at O°C. The reaction was then refluxed for 1 hr before $Na_2SO_4.10H_2O$ was added and the mixture was stirred overnight at room temperature. The resulting precipitate was removed by filtration and the mixture concentrated *in vacuo* to afford 1,2,3a,4,5,7,12b,12c-Octahydro-3H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridine as a pale yellow oil (0.01 g, 0.05 mmol, 68 %); υ_{max} (thin film)cm^{-1} 2923 (C-H str), 1502, 1481, 1444, 1317, 1229 and 1039 (C- strO); δ_H (400 MHz; $CDCl_3$) 1.18-1.44 (6H, m, 3-C*H*$_2$, 4-C*H*$_2$ and 5-C*H*$_2$), 1.61-1.62 (1H, m, 7-C*H*H), 1.67-1.71 (1H, m, 6-C*H*), 1.93-1.96 (1H, m, 7-CH*H*), 2.09-2.11 (1H, m, 8-C*H*H), 2.29-2.32 (1H, m, 2-C*H*), 2.66-2.69 (1H, m, 1-C*H*), 3.12 (1H, d, *J* 14.4 Hz, 9-C*H*H), 3.28-3 33 (1H, ddd, *J* 4.0, 9.2 and 13.2 Hz, 8-CH*H*), 3.93 (1H, d, *J* 14 4 Hz, 9-CH*H*), 5.82 (2H, dd, *J* 2.4 and 4.0 Hz, 13-C*H*$_2$), 6.42 (1H, s, 15-Ar-*H*), 6.54 (1H, s, 11-Ar-*H*); δ_c (100 MHz; $CDCl_3$) 24.78 (3-*C*H_2), 28.57 (4-*C*H_2), 29.39 (5-*C*H_2), 30.69 (7-*C*H_2), 36.33 (6-*C*H), 38.43 (2-*C*H), 52.73 (8-*C*H_2), 56.12 (9-*C*H_2), 61.88 (6-*C*H), 99.63 (13-*C*H_2), 105.23 (11-*C*H), 107.31 (15-*C*H), 126.27 (16-*C*), 132.15 (10-*C*), 144.61 (12-*C*) and 145.01 (14-*C*), ms (EI): *m/z* 258 (M^+ 29%), 256 (25), 207 (17), 147 (46), 136 (37), 73 (100) and 55 (19). HRMS $C_{16}H_{19}NO_2$ requires 258.14940, observed 258 14919

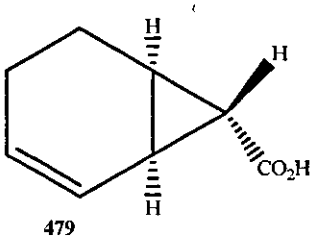
Bicyclo[4.1.0]hept-2-ene-7-carboxylic acid ethyl ester[29]



180

To a stirred solution of 1,3-hexadiene (0.39 g, 4.82 mmol), and $Rh_2(OAc)_4$ (0 02 g, 0.04 mmol) in 1,2-dichloroethane (1 ml) was added ethyl diazoacetate (0.50 g, 4.38 mmol) diluted in 1,2-dichloroethane (2 ml) *via* syringe over 30 min. The reaction was stirred under reflux for 3 hr under an atmosphere of N_2. The reaction was then allowed to cool to room temperature and the solvent was removed *in vacuo*. The mixture was purified by column chromatography (silica gel, 4:1, light petroleum: EtOAc) to afford bicyclo[4.1.0]hept-2-ene-7-carboxylic acid ethyl ester as a mixture of isomers as a pale yellow oil (0.62 g, 3.70 mmol, 75 %); υ_{max} (thin film)cm^{-1} 2930 (C-H str), 1721 (C=O str), 1443, 1366, 1294 and 1157 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.15 (3H, t, *J* 7.2 Hz, C*H*$_3$), 1.56-1.99 (7H, m, 4-C*H*$_2$, 5-C*H*$_2$, 1-C*H*, 6-C*H* and 7-C*H*), 4.01 (2H, q, *J* 14 4 Hz, C*H*$_2$), 5 45-5.49 (1H, m, 2-C*H*=CH), 5.90-5.93 (1H, m, 3-CH=C*H*); δ_c (100 MHz; $CDCl_3$) 14.26 (*C*H$_3$), 17.50 (5-*C*H$_2$), 20 53 (4-*C*H$_2$), 20.92 (6-*C*H), 24.02 (1-*C*H), 24.99 (7-*C*H), 60.36 (*C*H$_2$), 125.15 (2-*C*H), 125.46 (3-*C*H) and 170.75 (*C*O).

Bicyclo[4.1.0]hept-2-ene-7-carboxylic acid

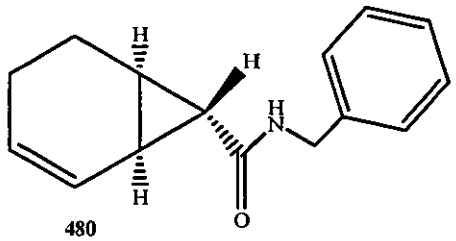


479

To a stirred solution of bicyclo[4.1.0]hept-2-ene-7-carboxylic acid ethyl ester (0 241 g, 1.45 mmol) in aqueous EtOH (5 ml) was added KOH (0.244 g, 4.5 mmol) and stirred overnight at room temperature. The mixture was then acidified to pH 2 using 2 *M* HCl, extracted into Et_2O (3x 20 ml), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was re-dissolved in EtOAc (20 ml) and extracted with $NaHCO_3$ (20 ml). The aqueous layer was acidified to pH 2 with 1 *M* HCl and extracted with Et_2O (2 x 20 ml). The combined

Et_2O layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford the bicyclo[4.1 0]hept-2-ene-7-carboxylic acid as a colourless oily residue (0.17 g, 1.23 mmol, 85%); υ_{max} (thin film)cm^{-1} 3032 (O-H str), 2927 (C-H str), 1688 (C=O str), 1445, 1298 and 1216 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.56-1.99 (7H, m, C*H*$_2$-C*H*$_2$-C*H*-C*H*-C*H*), 5.49-5.52 (1H, m, C*H*), 5.88-5.93 (1H, m, C*H*), 10.39 (1H, s, O*H*); δ_c (100 MHz; $CDCl_3$) 18.06 (*C*H$_2$), 20.44 (*C*H$_2$), 21.90 (*C*H), 24.94 (*C*H), 24.95 (*C*H), 125.03 (*C*H), 125.61 (*C*H) and 180.01 (*C*O); ms (EI): *m/z* 156 [M^+ 100 %], 138 (10), 120 (8), 108 (6), 91 (12), and 52 (13). HRMS calc. for $C_8H_{10}O_2$ $[M^+NH_4]^+$ requires 156.1019, observed 156.1019.

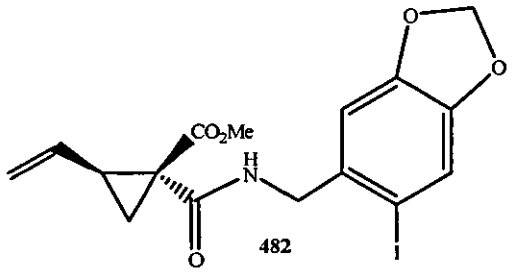
Bicyclo[4.1.0]hept-2-ene-7-carboxylic acid benzylamide



480

After subjecting 7-[(methyloxy)carbon]bicycle[4.1.0]hept-2-ene-7-carboxylic acid and benzylamine (0.09 g, 0.87 mmol) to the standard amide coupling and work-up conditions the crude mixture was purified by flash chromatography (silica gel, gradient elution, 4:1 to 2:1, light petroleum: EtOAc) to afford bicyclo[4.1 0]hept-2-ene-7-carboxylic acid benzylamide as a white solid (0.14 g, 0.62 mmol, 85 %); mp range 152.4-154.6 °C; υ_{max} (thin film)cm^{-1} 3283 (N-H str), 1623 (C=O str); δ_H (400 MHz; $CDCl_3$) 1.52-1.89 (7H, m, C*H*$_2$-C*H*$_2$-C*H*-C*H*-C*H*), 4.41 (2H, d, *J* 6.0 Hz, C*H*$_2$), 5.48-5.52 (1H, m, C*H*=CH), 5.97-6.01 (1H, m, CH=C*H*), 6.13 (1H, s, N*H*), 7.24-7.34 (5H, m, Ar-*H*), δ_c (100 MHz; $CDCl_3$) 17 44 (*C*H$_2$), 19 95 (*C*H), 20 75 (*C*H$_2$), 22 82 (*C*H), 27.23 (*C*H), 43.91 (*C*H$_2$), 124.71 (*C*H), 126.21 (*C*H), 127.53 (2x *C*H), 127.96 (*C*H), 128 72 (2x *C*H), 138 39 (*C*) and 171.91 (*C*O); ms (EI): *m/z* 228 [M^+ 12%], 149 (30), 135 (8), 117 (10), 106 (40), 91 (100), 77 (32), 65 (22) and 51 (38) HRMS calc for $C_{15}H_{17}NO$ requires 228.1383, observed 228.1387.

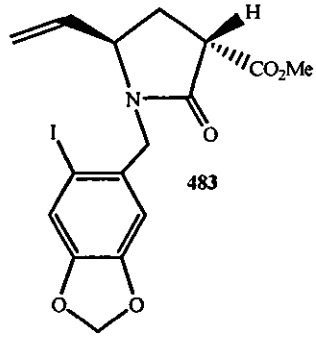
1-[(6-Iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-2-vinyl-cyclopropanecarboxylic acid methyl ester



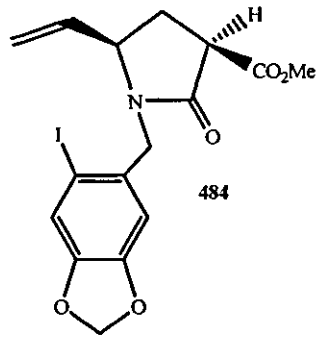
482

After subjecting 2-vinyl-cyclopropane-1,1-dicarboxylic acid methyl ester and 6-Iodo-benzo[1,3]dioxol-5-yl-methylamine to the standard amide coupling conditions the crude mixture was purified by flash chromatography (silica gel, 4:1, light petroleum: EtOAc) to afford 1-[(6-iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-2-vinyl-cyclopropanecarboxylic acid methyl ester as a yellow oil (0.16 g, 0.36 mmol, 48 %); υ_{max} (thin film)cm^{-1} 3354 (N-H str), 1706 (C=O str), 1653 (C=O str), 1527, 1477, 1231, 1142, 1037 and 929 (C-I str); δ_H (400 MHz; $CDCl_3$) 1.80 (1H, dd, *J* 4.4 and 8.0 Hz, C*H*), 1.98 (1H, dd, *J* 4.4 and 8.0 Hz, C*H*), 2.49 (1H, q, *J* 8.5 Hz, C*H*), 3.66 (3H, s, CH_3), 4.29 (1H, dd, J_{AB} 6.0 and 14.8 Hz, C*H*H), 4.37 (1H, dd, J_{AB} 6.0 and 14 8 Hz, CH*H*), 5.08 (1H, dd, *J* 1.6 and 8 8 Hz, C*H*H), 5.25 (1H, dd, *J* 1.6 and 15 6 Hz, CH*H*), 5.51-5.60 (1H, m, CH_2=C*H*), 5.88 (2H, s, CH_2), 6.83 (1H, s, Ar-*H*), 7.16 (1H, s, Ar-*H*), 8.77 (1H, t, *J* 4 8 Hz, N*H*), δ_c (100 MHz; $CDCl_3$) 21 63 (CH_2), 34.46 (*C*), 37 27 (*C*H), 48.52 (CH_2), 52.21 (CH_3), 86.98 (*C*), 101 71 (CH_2), 109.91 (*C*H), 118.61 (*C*H), 119.80 (CH_2), 133.17 (*C*H), 134 04 (*C*), 147.83 (*C*O), 148.53 (*C*O), 167.84 (*C*O) and 171.67 (*C*O); ms (EI): *m/z* 451 [M^+ 100%], 446 (10), 322 (16), 308 (19), 260 (22) and 254 (42). HRMS calc. for $C_{16}H_{16}NO_5I$ $[M^+Na]^+$ requires 451.9965, observed 451.9963.

1-(6-Iodo-benzo[1,3]dioxol-5-ylmethyl)-2-oxo-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester



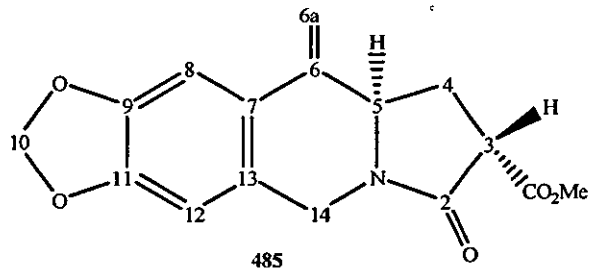
483



484

After subjecting 1-[(6-iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-2-vinyl-cyclopropanecarboxylic acid methyl ester to the standard rearrangement and work-up conditions the crude mixture was purified by flash chromatography (silica gel, gradient elution 4:1 to 2:1, light petroleum: EtOAc) to afford 1-(6-iodo-benzo[1,3]dioxol-5-ylmethyl)-2-oxo-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester in an inseparable 1:1 mixture of diastereoisomers as an orange oil (0.05 g, 0.13 mmol, 99 %). Due to the nature of the inseparable mixture ' denotes one diastereoisomer from the other, unfortunately it was not possible to deduce the *cis* from the *trans* isomer; υ_{max} (thin film)cm^{-1} 2915 (C-H str), 1740 (C=O str), 1692 (C=O str), 1501, 1478, 1426, 1235, 1165 (C-O str) and 929 (C-I); δ_H (400 MHz; $CDCl_3$) 1.94-2.01 (1H, m, '*CH*H), 2.12-2.21 (1H, m, *CH*H), 2.39-2.45 (1H, m, CH*H*), 2 48-2.55 (1H, m, 'CH*H*), 3.46-3.53 (1H, m, '*CH*), 3.46-3.53 (1H, m, *CH*), 3.74 (3H, s, 'CH_3), 3.74 (3H, s, CH_3), 3.84-3.86 (1H, m, *CH*), 3.98-4 01 (2H, m, '*CH*-*CH*H), 4.07 (1H, d, *J* 15.6 Hz, *CH*H), 4.38 (1H, d, *J* 15.2 Hz, CH*H*), 4.68 (1H, d, *J* 15.6 Hz, '*CH*H), 5 09-5.19 (2H, m, 'CH_2), 5 09-5.19 (2H, m, CH_2), 5.49-5.56 (1H, m, *CH*), 5.59-5.68 (1H, m, '*CH*), 5 89 (2H, s, 'CH_2), 5.89 (2H, s, CH_2), 6 62 (1H, s, 'Ar-*H*), 6.89 (1H, s, Ar-*H*), 7.14 (1H, s, 'Ar-*H*), 7 14 (1H, s, Ar-*H*), δ_c (100 MHz; $CDCl_3$) 28.08 (CH_2), 28.76 ('CH_2), 46.43 ('*C*H), 46 82 (*C*H), 48.31 ('CH_2), 48.60 (CH_2), 51.78 ('CH_3), 51.82 (CH_3), 58.31 ('*C*H), 59 02 (*C*H), 85.12 ('*C*), 85.12 (*C*), 100 34 ('CH_2), 100.73 (CH_2), 107.63 ('*C*H), 107.97 (*C*H), 117.56 ('*C*H), 117.61 (*C*H), 118 43 ('CH_2), 118 81 (CH_2), 130 42 ('*C*), 130 62 (*C*), 135.10 ('*C*H), 135 82 (*C*H), 146.86 ('*C*O), 146.86 (*C*O), 147.67 (*C*O), 147 83 ('*C*O), 168.92 ('*C*O), 169 04 (*C*O), 169.45 ('*C*O) and 169 59 (*C*O); ms (FAB): *m/z* 430 [M^+ 10%], 302 (10), 261 (19), 207 (13), 136 (20), 91 (11) and 73 (100). HRMS calc. for $C_{16}H_{16}NO_5I$ $[M^+H]^+$ requires 430.0151, observed 430 0159.

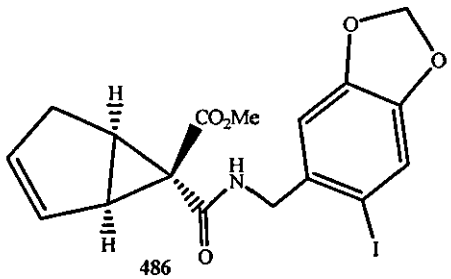
9-Methylene-6-oxo-5,6,7,8,8a,9-hexahydro-1,3-dioxa-5a-aza-dicyclopenta[b,g]naphthalene-7-carboxylic acid methyl ester



485

To a stirred solution of 1-[(6-iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-2-vinyl-cyclopropanecarboxylic acid methyl ester (0.05 g, 0.12 mmol) in MeOH (2 ml) was added $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol) and stirred under N_2 for 10 min at room temperature. Et_3N (0.03 ml, 0.23 mmol) was then added and the reaction stirred under reflux for 24 h. The reaction was allowed to cool to room temperature. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, gradient elution, 2:1 to 0:100, light petroleum: EtOAc) to afford 9-methylene-6-oxo-5,6,7,8,8a,9-hexahydro-1,3-dioxa-5a-aza-dicyclopenta[b,g]naphthalene-7-carboxylic acid methyl ester as a yellow oil (0.04 g, 0.11 mmol, 99 %); υ_{max} (thin film)cm^{-1} 1734 (C=O str), 1695 (C=O str), 1485, 1436, 1218 and 1036 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.50-2.58 (1H, m, 4-C*H*H), 2.72-2.79 (1H, m, 4-CH*H*), 3.49 (1H, t, *J* 12 0 Hz, 3-C*H*), 3.76 (3H, s, CH_3), 4.15 (1H, d, *J* 16.0 Hz, 14-C*H*H), 4.29 (1H, t, *J* 8 0 Hz, 8-C*H*), 4.82 (1H, d, *J* 16 0 Hz, 14-CH*H*), 5.05 (1H, s, 6a-C*H*H), 5.56 (1H, s, 6a-CH*H*), 5 93 (2H, s, 10-CH_2), 6 60 (1H, s, 8-Ar-*H*), 7.08 (1H, s, 12-Ar-*H*); δ_c (100 MHz; $CDCl_3$) 29.80 (4-CH_2), 42.69 (14-CH_2), 48.50 (3-*C*H), 52.75 (CH_3), 54.95 (5-*C*H), 101 38 (10-CH_2), 104 29 (12-*C*H), 106 10 (8-*C*H), 107.45 (6-CH_2), 125.50 (6-*C*), 125.71 (7-*C*), 141.50 (13-*C*), 147.49 (9-*C*), 148.36 (11-*C*), 168.55 (*C*O) and 170.02 (*C*O); ms (FAB): *m/z* 302 [M^+ 9%], 207 (20), 154 (43), 136 (78), 120 (17), 95 (34), 91 (48), 73 (100), 69 (51) and 55 (65) HRMS calc. for $C_{16}H_{15}NO_5$ $[M^+H]^+$ requires 302.1028, observed 302 10218.

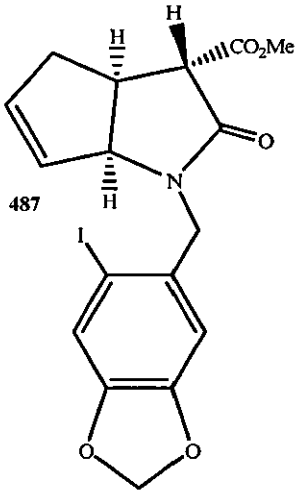
6-[(6-Iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester



486

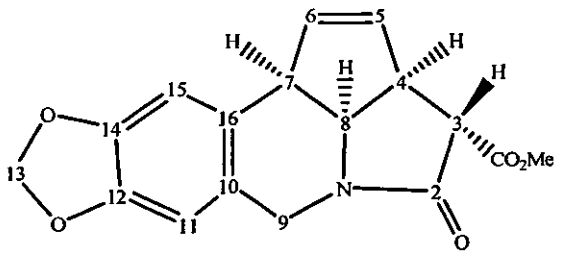
After subjecting bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid methyl ester and 6-iodo-benzo[1,3]dioxol-5-yl-methylamine to the standard amide coupling and work-up conditions the crude mixture was purified by flash chromatography (silica gel, 4:1, light petroleum: EtOAc) to afford 6-[(6-Iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester as a yellow oil (0.22 g, 0.49 mmol, 64 %); υ_{max} (thin film)cm^{-1} 3351 (N-H str), 2949 (C-H str), 1730 (C=O str), 1658 (C=O str), 1518, 1502, 1477, 1239, 1138 and 1037 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.48-2.52 (1H, m, C*H*), 2.62-2.70 (3H, m, C*H*-CH_2), 3.59 (3H, s, CH_3), 4.23-4.33 (2H, m, CH_2), 5.58-5.59 (1H, m, C*H*=CH), 5 68-5.70 (1H, m, CH=C*H*), 5.88 (2H, s, CH_2), 6.71 (1H, s, N*H*), 6.78 (1H, s, Ar-*H*), 7.14 (1H, s, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 29.52 (*C*H), 34.49 (*C*H_2), 39.34 (*C*H), 39.44 (*C*), 48.39 (*C*H_2), 52.40 (*C*H_3), 86.87 (*C*), 101.77 (*C*H_2), 110.13 (*C*H), 118.60 (*C*H), 129.14 (*C*H), 132.81 (*C*H), 133.71 (*C*), 147.95 (*C*), 148.55 (*C*), 167.36 (*C*O) and 169 06 (*C*O); ms (EI): *m/z* 442 [M^+, 20%], 335 (20), 314 (14), 261 (100), 207 (18), 165 (25), 154 (40), 136 (59), and 73 (47). HRMS calc. for $C_{17}H_{14}NO_5I$ requires 442 0151, observed 442 0159.

1-(4-Iodo-benzo[1,3]dioxol-5-ylmethyl)-2-oxo-1,2,3,3a,4,6a-hexahydro-cyclopenta[b]pyrrole-3-carboxylic acid methyl ester



After subjecting 6-[(6-iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester to the standard rearrangement and work-up conditions the crude mixture was purified by flash chromatography (silica gel, 2:1, light petroleum: EtOAc) to afford 1-(4-iodo-benzo[1,3]dioxol-5-ylmethyl)-2-oxo-1,2,3,3a,4,6a-hexahydro-cyclopenta[b]pyrrole-3-carboxylic acid methyl ester as a brown oil (0.04 g, 0.09 mmol, 95 %); υ_{max} (thin film)cm^{-1} 2914 (C-H str), 1734 (C=O str), 1684 (C=O str), 1476, 1431, 1232, 1160 and 1035 (C-O str); δ_H (400 MHz; $CDCl_3$) 2.20-2.22 (1H, m, C*H*), 2.64-2.67 (1H, m, CH_2), 3.16-3.27 (1H, m, C*H*), 3.24 (1H, d, *J* 6.0 Hz, C*H*), 3.74 (3H, s, CH_3), 4.21 (1H, d, *J* 15.2 Hz, C*H*H), 4.42 (1H, d, *J* 7.6 Hz, C*H*), 4.67 (1H, d, *J* 15.2 Hz, CH*H*), 5 67-5.70 (1H, m, C*H*=CH), 5.83-5 86 (1H, m, CH=C*H*), 5 89-5.90 (2H, m, CH_2), 6.76 (1H, s, Ar-*H*), 7.16 (1H, s, Ar-*H*); δ_c (100 MHz; $CDCl_3$) 37 77 (*C*H), 38 45 (*C*H_2), 50.38 (*C*H_2), 52 82 (*C*H_3), 55.84 (*C*H), 64 50 (C), 67 16 (*C*H), 101.84 (*C*H_2), 109.23 (*C*H), 118.44 (*C*H), 128 69 (*C*H), 131.91 (*C*), 134.40 (*C*H), 147.95 (*C*), 148.55 (*C*), 167 36 (*C*O) and 170.72 (*C*O); ms (FAB): *m/z* 442 [M^+ 68%], 314 (42), 261 (94), 207 (23), 136 (70), 119 (2), 91 (44) and 73 (100). HRMS calc. for $C_{17}H_{16}NO_5I$ $[M^+H]^+$ requires 442 0151, observed 442.0144.

9-Pentene-6-Oxo-5,6,7,8,8a,9-hexahydro-1,3-dioxa-5a-azadicyclopenta[b,g]naphthalene-7-carboxylic acid methyl ester



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Method A

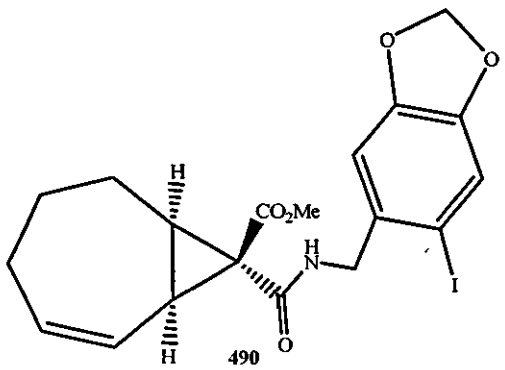
To a stirred solution of 6-[(6-iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester (0.06 g, 0.15 mmol) in MeOH (2 ml) was added $Pd(PPh_3)_4$ (0 08 g, 0.02 mmol) and stirred under N_2 for 10 min at room temperature. Et_3N (0.04 ml, 0.29 mmol) was then added and the reaction stirred under reflux for 24 h. The reaction was allowed to cool to room temperature. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, gradient elution, 2:1 to 1:1, light petroleum: EtOAc) to afford as a orange oil (0.02 g, 0 05 mmol, 38 %); υ_{max} (thin film)cm^{-1} 2919 (C-H str), 1734 (C=O str), 1689 (C=O str), 1482, 1436, 1193 and 1036 (C-O str); δ_H (400 MHz; $CDCl_3$) 3.34 (1H, s, 3-C*H*), 3.74 (1H, s, 4-C*H*), 3 77 (3H, s, CH_3), 3.93 (1H, s, 7-C*H*), 3.99 (1H, d, *J* 16.8 Hz, 9-C*H*H), 4.49 (1H, t, *J* 6.0 Hz, 8-C*H*), 4 87 (1H, d, *J* 16 8 Hz, 9-CH*H*), 5.56-5 59 (1H, m, 5-C*H*=CH), 5.75-5.77 (1H, m, 6-CH=C*H*), 5.93 (2H, d, *J* 1.6 and 5.2 Hz, 13-CH_2), 6.57 (1H, s, 15-Ar-*H*), 6 71 (1H, s, 11-Ar-*H*); δ_c (100 MHz, $CDCl_3$) 41.01 (9-*C*H_2), 48 09 (4-*C*H), 48.51 (7-*C*H), 52 89 (*C*H_3), 53.53 (3-*C*H), 58.68 (8-*C*H), 101.13 (13-*C*H_2), 106.19 (15-*C*H), 108.48 (11-*C*H), 124 68 (16-*C*), 126.69 (10-*C*), 129.64 (5-*C*H), 135.37 (6-*C*H), 146.58 (12-*C*O), 146.94 (14-*C*O), 166.66 (2-*C*O) and 170 07 (*C*O); ms (FAB): *m/z* 314 [M^+ 21%), 279 (13), 207 (28), 153 (31), 136 (43), 107 (27), 91 (32) and 73 (100). HRMS calc. for $C_{17}H_{15}NO_5$ $[M^+H]^+$ requires 314.1028, observed 314.1020.

Method B

To a stirred solution of 6-[(6-iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid methyl ester (0.06 g, 0.13 mmol) in MeOH (2 ml)

was added $Pd(PPh_3)_4$ (0.02 g, 0.01 mmol) and stirred under N_2 for 24 h at room temperature. Once 1-(4-iodo-benzo[1,3]dioxol-5-ylmethyl)-2-oxo-1,2,3,3a,4,6a-hexahydro-cyclopenta[b]pyrrole-3-carboxylic acid methyl ester was observed *via* TLC. Et_3N (0.04 ml, 0.27 mmol) was then added and the reaction stirred under reflux for 24 h. The reaction was allowed to cool to room temperature. The solvent was removed *in vacuo* and re-dissolved in EtOAc (15 ml) and the palladium catalyst was removed through a plug of silica. The crude material was purified by flash chromatography (silica gel, gradient elution, 2:1 to 1:1, light petroleum: EtOAc) to afford as an orange oil (0.017 g, 0.054 mmol, 40 %); data as above.

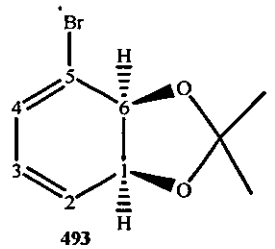
8-[(6-Iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-bicyclo[5.1.0]oct-2-ene-8-carboxylic acid methyl ester



490

After subjecting bicyclo[5.1 0]oct-2-ene-8,8-dicarboxylic methyl ester and 6-iodo-benzo[1,3]dioxol-5-yl-methylamine to the standard amide coupling and work-up conditions the resulting oil was purified by flash chromatography (Silica gel, 4:1, hexane: EtOAc) to afford 8-[(6-iodo-benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-bicyclo[5.1.0]oct-2-ene-8-carboxylic acid methyl ester as a colourless oil (0.33 g, 0.70 mmol, 70 %); υ_{max} (thin film)cm^{-1} 3334 (N-H str), 2926 (C-H str), 1731 (C=O str), 1695, 1652 (C=O str), 1520, 1476, 1315 and 1240 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.71-1.20 (1H, m, C*H*), 1.44-1.51 (1H, m, C*H*), 1.60-1.69 (1H, m, C*H*), 1.93-2.03 (2H, m, CH_2), 2.11-2.21 (1H, m, C*H*), 2 36-2.42 (1H, m, C*H*), 2.50-2.53 (1H, m, C*H*), 3.66 (3H, s, CH_3), 4 04 (2H, d, *J* 7.2 Hz, CH_2), 5 50-5.58 (2H, m, C*H*=C*H*), 5 88 (2H, s, CH_2), 6 83 (1H, s, Ar-*H*), 7.19 (1H, s, Ar-*H*), 7.84 (1H, s, N*H*); δ_c (100 MHz, $CDCl_3$) 22.93 (CH_2), 24 07 (CH_2), 29.26 (*C*H), 31.39 (*C*H), 33.26 (*C*H), 38.18 (*C*), 48.59 (CH_2), 51.97 (CH_3), 86.94 (*C*), 101.73 (CH_2), 110.06 (*C*H), 118 58 (*C*H), 123.86 (*C*H), 131 06 (*C*H), 134.03 (*C*), 147.86 (*C*O), 148.52 (*C*O), 168.49 (*C*O) and 171.06 (*C*O); ms (FAB): *m/z* 469 [M^+ 22%], 342 (15), 261 (100), 193 (9), 136 (12), 91 (10) and 79 (7). HRMS calc. for $C_{19}H_{20}NO_5I$ $[M^+H]^+$ requires 470.0464, observed 470.0467

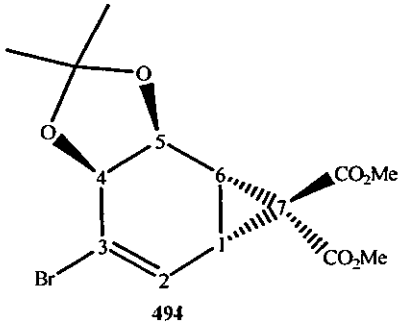
4-Bromo-2,2-dimethyl-3a,7a-dihydro-benzo[1,3]dioxole[69]



493

To a stirred solution of 3-bromo-cyclohexa-3,5-diene-1,2-diol (1.18 g, 6.24 mmol) in anhydrous DCM was added 2,2-dimethoxypropane (0.71 g, 6.85 mmol), and a catalytic amount of *p*-TSA. The reaction was stirred at room temperature for 1 hr then was quenched by addition of aqueous $NaHCO_3$ (40 ml), extracted into DCM (3x 15 ml), the organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield 4-bromo-2,2-dimethyl-3a,7a-dihydro-benzo[1,3]dioxole as a brown oil (0.93 g, 4.08 mmol, 63 %); $[\alpha]_D$ +123.6 [0.1 CH_3Cl]; υ_{max} (thin film)cm^{-1} 2984 (C-H str), 1580, 1371, 1210, 1157, 1034 (C-O str) and 871 (CBr); δ_H (400 MHz; $CDCl_3$) 1.37 (3H, s, C*H*$_3$), 1.39 (3H, s, C*H*$_3$), 4.66 (2H, s, 1-C*H* and 6-C*H*), 5.79 (1H, dd, *J* 6 0 and 9.6 Hz, 3-C*H*=CH), 5.89-5.92 (1H, m, 2-C*H*=CH), 6.27 (1H, d, *J* 6.0 Hz, 4-C*H*); δ_c (100 MHz; $CDCl_3$) 24.95 (*C*H$_3$), 26.72 (*C*H$_3$), 72.44 (1-*C*H), 76 76 (6-*C*H), 106.19 (*C*), 124.12 (3-*C*H), 124.36(2-*C*H), 124.61 (5-*C*Br) and 125.78 (4-*C*H).

3-Bromo-5,5,-dimethyl-1a,3a,6a,6b-tetrahydro-4,6-dioxacycloprop[e]indene-1,1-dicarboxylic acid dimethyl ester

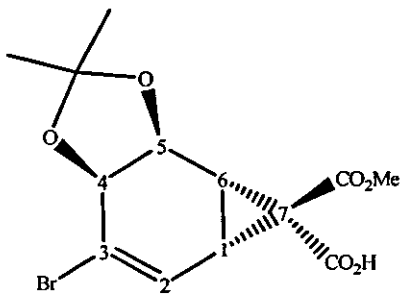


494

To a solution of 4-bromo-2,2-dimethyl-3a,7a-dihydro-benzo[1,3]dioxole (0 93 g, 4.08 mmol), and $Rh_2(OAc)_4$ (0 01 g, 0.03 mmol) in 1,2-dichloroethane (2 ml) was added dimethyl diazomalonate (0 44 g, 2 81 mmol) diluted in 1,2-dichloroethane (6 ml) *via* syringe pump over 30 min and was then stirred under reflux for 3 h. The oil was purified by flash chromatography (Silica gel, hexane: EtOAc, 2:1) to afford 3-bromo-v5,5,-dimethyl-1a,3a,6a,6b-tetrahydro-4,6-dioxacycloprop[e]indene-1,1-dicarboxylic acid dimethyl ester as a

yellow oil (0.69 g, 3.26 mmol, 34 %); $[\alpha]_D$ -46 [0.1 CH_3Cl]; υ_{max} (thin film)cm^{-1} 2988 (C-H str), 1731 (C=O str), 1437, 1381, 1324, 1205, 1164, 1110, 1065 (C-O str) and 869; δ_H (400 MHz; $CDCl_3$) 1.34 (3H, s, C*H*$_3$), 1.39 (3H, s, C*H*$_3$), 2.24 (1H, d, *J* 8.4 Hz, 6-C*H*), 2.37-2 40 (1H, m, 1-C*H*), 3.67 (3H, s, CH_3), 3.68 (3H, s, C*H*$_3$), 4.21 (1H, d, *J* 6.8 Hz, 5-C*H*), 5.02 (1H, d, *J* 6 8 Hz, 4-C*H*), 6.21-6.23 (1H, m, 2-C*H*); δ_c (100 MHz; $CDCl_3$) 24.81 (6-*C*H), 25.65 (*C*H$_3$), 25.91 (1-*C*H), 27.43 (*C*H$_3$), 39.76 (7-*C*), 53.07 (*C*H$_3$), 53.13 (*C*H$_3$), 71.24 (4-*C*H), 73.76 (5-*C*H), 110.06 (*C*), 124.69 (3-*C*), 124.93 (2-*C*H), 166.82 (*C*O) and 168.76 (*C*O); ms (EI) 363 [M^+, 7 %, ^{81}Br], 361 [M^+, 70%, ^{79}Br], 303 (41), 283 (21), 225 (45), 150 (100), 135 (21) and 98 (25). HRMS calc. for $C_{14}H_{17}O_6{}^{79}Br$ requires 361.0281, observed 361.0285.

3-Bromo-5,5,-dimethyl-1a,3a,6a,6b-tetrahydro-4,6-dioxacycloprop[e]indene-1,1-dicarboxylic acid methyl ester

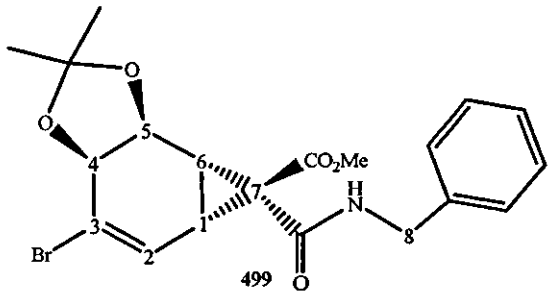


498

To a stirred solution of 3-bromo-5,5,-dimethyl-1a,3a,6a,6b-tetrahydro-4,6-dioxacycloprop[e]indene-1,1-dicarboxylic acid dimethyl ester (0.40 g, 1.11 mmol) in THF (6 ml), H_2O (6 ml), was added LiOH (0.05 g, 1.11 mmol) and the reaction was left stirring for 2 h at room temperature The resulting mixture was then acidified to pH 2 with 1 *M* HCl and extracted with diethyl ether (2x 30 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford 3-bromo-5,5,-dimethyl-1a,3a,6a,6b-tetrahydro-4,6-dioxacycloprop[e]indene-1,1-dicarboxylic acid methyl ester as a pale yellow oil (0.38 g, 1.10 mmol, >99 %); $[\alpha]_D$ -39.3 [0.12 CH_3Cl]; υ_{max} (thin film)cm^{-1} 3467 (O-H str), 2988 (C-H str), 1733 (C=O str), 1641 (C=O str), 1437, 1332, 1163 and 1062 (C-O str); δ_H (400 MHz; $CDCl_3$) 1.35 (3H, s, C*H*$_3$), 1 40 (3H, s, C*H*$_3$), 2 32-2.34 (1H, m, 6-C*H*), 2.40-2.44 (1H, m, 1-C*H*), 3.70 (3H, s, C*H*$_3$), 4 23 (1H, d, *J* 7 2 Hz, 5-C*H*), 5.02 (1H, d, *J* 7.2 Hz, 4-C*H*), 6 22 (1H, d, *J* 5 6 Hz, 3-C*H*), 7 20-7.50 (1H, s, O*H*); δ_c (100 MHz; $CDCl_3$) 25.67 (*C*H$_3$), 25.60 (*C*H$_3$), 27.41 (6-*C*H), 27.46 (1-*C*H), 39.47 (7-*C*), 53.14 (*C*H$_3$), 71.26 (4-*C*H), 73.87 (5-*C*H), 110.18 (*C*), 124.65 (2-*C*H), 125.06 (3-*C*Br), 166.94 (*C*O) and 172.39 (*C*O); ms (EI) 366 [M^+, 45%, ^{81}Br],

364 [M^+, 51%, ^{79}Br], 347 (30), 302 (25), 288 (10), 95 (39) and 79 (100). HRMS calc. for $C_{13}H_{15}O_6{}^{79}Br$ $[M^+NH_4]^+$ requires 364.0390, observed 364.0389.

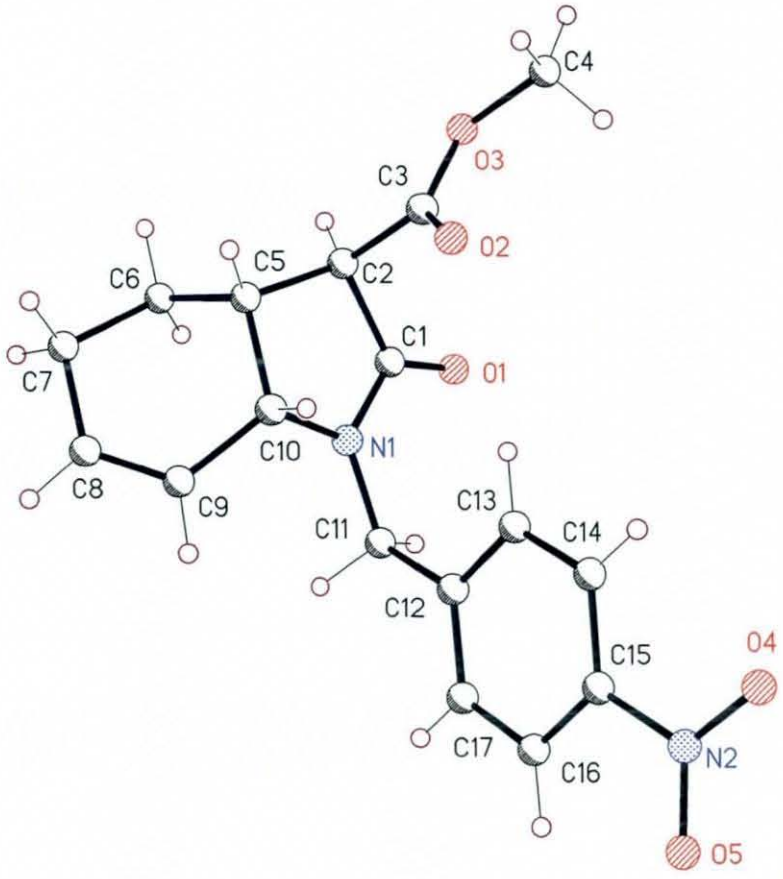
1-Benzylcarbamoyl-3-bromo-5,5-dimethyl-1a,3a,6a,6b-tetrahydro-1*H*-4,6-dioxa-cyclopropa[e]indene-1-carboxylic acid methyl ester



To a stirred solution of 3-bromo-5,5,-dimethyl-1a,3a,6a,6b-tetrahydro-4,6-dioxacycloprop[e]indene-1,1-dicarboxylic acid methyl ester (0.12 g, 0.34 mmol) in anhydrous DMF (2 ml) was added DIEA (0.07 ml, 0.39 mmol), HATU (0.16 g, 0.41 mmol)) and was left stirring for 10 min at room temperature. Then benzyl amine (0 04 g, 0.34 mmol) was added and the reaction stirred at room temperature for 3 h before being diluted with DCM (15 ml). The mixture was then washed with 2M HCl (10 ml), aqueous $NaHCO_3$ (2x 10 ml) and extracted into DCM (3x 15 ml). The organic extracts were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. The product was then purified by flash chromatography (silica gel, 4:1, light petroleum: EtOAc) to afford 1-benzylcarbamoyl-3-bromo-5,5-dimethyl-1a,3a,6a,6b-tetrahydro-1*H*-4,6-dioxa-cyclopropa[e]indene-1-carboxylic acid methyl ester as a yellow oil (0.13 g, 0.30 mmol, 86 %); $[\alpha]_D$ -91.2 [0.1 CH_3Cl]; υ_{max} (thin film)cm^{-1} 3329 (N-H str), 2985 (C-H str), 1731 (C=O str), 1656 (C=O str), 1536, 1317, 1259, 1163, 1044 (C-O str), 698; δ_H (400 MHz; $CDCl_3$) 1 39 (3H, s, C*H*$_3$), 1.46 (3H, s, C*H*$_3$), 2.37-2.40 (1H, dd, *J* 5.2 and 8 4 Hz, 1-C*H*H), 2 63 (1H, d, *J* 8.4 Hz, 6-CH*H*), 3.66 (3H, s, C*H*$_3$), 4.30 (1H, d, *J* 7.2 Hz, 5-C*H*), 4.38 (2H, d, *J* 5.6 Hz, 8-C*H*$_2$), 4.96 (1H, d, *J* 5.2 Hz, 4-C*H*), 6.17 (1H, d, *J* 5.2 Hz, 2-C*H*), 7.19-7.29 (5H, m, Ar-*H*), 7.40 (1H, s, N*H*); δ_c (100 MHz; $CDCl_3$) 24.39 (*C*H$_3$), 25 29 (*C*H$_3$), 27.26 (6-CH), 29 06 (1-*C*H), 39.75 (7-*C*), 44.31 (8-*C*H$_2$), 52.98 (*C*H$_3$), 72.12 (4-CH), 74.80 (5-*C*H), 110 04 (*C*), 124.16 (2-*C*H), 125.75 (3-*C*Br), 127.62 (2x *C*H), 127.65 (*C*H), 128.78 (2x *C*H), 137.78 (*C*), 165.87 (*C*O) and 169.29 (*C*O); ms (EI) 438 [M^+, 100%, ^{81}Br], 436 [M^+, 90%, ^{79}Br], 358 (20), 225 (32), 208 (50), 135 (30) 106 (100) and 52 (62). HRMS calc for $C_{20}H_{22}NO_5{}^{79}Br$ $[M^+ H]^+$requires 436.0754, observed 437.0759.

X-Ray data:

1-(4-Nitro-benzyl)-2-oxo-2-3-3a,4,5,7a-hexahydro-1*H*-indole-3-carboxyl acid methyl ester



The data were collected at 150(2)K on a Bruker Apex II CCD diffractometer. The structure was solved by direct methods and refined on F^2 using all the reflections*. All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model. Parameters for data collection and refinement are summarised in Table 1.

There are π–π stacking interactions between the nitrated rings – more details if you want them.

* G.M. Sheldrick, SHELXTL Version 6.12, Bruker AXS, Madison WI, 2001.

Table 1. Crystal data and structure refinement for gp6.

Identification code	gp6
Empirical formula	C17 H18 N2 O5
Formula weight	330 33
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 15 2209(5) Å α= 90°.
b = 8 2083(3) Å	β= 102 1410(10)°.
c = 13.2338(5) Å	γ = 90°.
Volume	1616 42(10) $Å^3$
Z	4
Density (calculated)	1 357 Mg/m^3
Absorption coefficient	0 101 mm^{-1}
F(000)	696
Crystal size	0.33 x 0 23 x 0 08 mm^3
Crystal description	Colourless plate
Theta range for data collection	2 74 to 26 41°.
Index ranges	-19<=h<=19, -10<=k<=10, -16<=l<=16
Reflections collected	14095
Independent reflections	3325 [R(int) = 0 0259]
Completeness to theta = 26 41°	99 9 %
Absorption correction	Semi-empirical from equivalents
Max and min. transmission	0 9920 and 0 9674
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3325 / 0 / 217
Goodness-of-fit on F^2	1 024
Final R indices [I>2sigma(I)]	R1 = 0 0357, wR2 = 0 0855
R indices (all data)	R1 = 0 0459, wR2 = 0 0917
Largest diff peak and hole	0 244 and -0 201 e $Å^{-3}$

Table 2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for gp6 U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

x	y	z	U(eq)	
O(1)	4259(1)	1486(1)	5969(1)	32(1)
C(1)	3744(1)	1143(1)	5157(1)	24(1)
C(2)	3986(1)	1054(2)	4092(1)	26(1)
C(3)	4098(1)	2784(2)	3751(1)	27(1)
O(2)	3484(1)	3730(1)	3508(1)	42(1)
O(3)	4953(1)	3149(1)	3776(1)	36(1)
C(4)	5121(1)	4817(2)	3506(1)	45(1)
C(5)	3180(1)	165(2)	3425(1)	25(1)
C(6)	3372(1)	-1666(2)	3434(1)	33(1)
C(7)	2544(1)	-2627(2)	2923(1)	39(1)
C(8)	1746(1)	-2148(2)	3344(1)	37(1)
C(9)	1685(1)	-759(2)	3835(1)	33(1)
C(10)	2393(1)	544(2)	3957(1)	25(1)
N(1)	2861(1)	809(1)	5038(1)	25(1)
C(11)	2405(1)	897(2)	5890(1)	27(1)
C(12)	1861(1)	2434(2)	5913(1)	25(1)
C(13)	2042(1)	3868(2)	5432(1)	27(1)
C(14)	1556(1)	5274(2)	5506(1)	28(1)
C(15)	885(1)	5220(2)	6065(1)	27(1)
N(2)	370(1)	6706(2)	6160(1)	33(1)
O(4)	627(1)	7997(1)	5852(1)	46(1)
O(5)	-289(1)	6591(1)	6550(1)	45(1)
C(16)	692(1)	3820(2)	6553(1)	33(1)
C(17)	1180(1)	2428(2)	6468(1)	31(1)

Table 3 Bond lengths [Å] and angles [°] for gp6

O(1)-C(1)	1 2224(15)	C(9)-C(10)	1.5035(18)
C(1)-N(1)	1 3468(16)	C(10)-N(1)	1.4745(16)
C(1)-C(2)	1 5315(18)	N(1)-C(11)	1.4453(16)
C(2)-C(3)	1 5105(18)	C(11)-C(12)	1.5127(18)
C(2)-C(5)	1.5368(17)	C(12)-C(17)	1 3905(18)
C(3)-O(2)	1 2048(16)	C(12)-C(13)	1.3928(18)
C(3)-O(3)	1.3286(16)	C(13)-C(14)	1 3853(18)
O(3)-C(4)	1.4522(18)	C(14)-C(15)	1 3806(18)
C(5)-C(6)	1 5304(18)	C(15)-C(16)	1 3797(19)
C(5)-C(10)	1 5428(17)	C(15)-N(2)	1.4697(17)
C(6)-C(7)	1 5194(19)	N(2)-O(5)	1 2253(15)
C(7)-C(8)	1 491(2)	N(2)-O(4)	1 2275(16)
C(8)-C(9)	1.325(2)	C(16)-C(17)	1.380(2)

O(1)-C(1)-N(1)	126 06(12)	C(9)-C(10)-C(5)	114.54(11)
O(1)-C(1)-C(2)	125 83(12)	C(1)-N(1)-C(11)	122 02(10)
N(1)-C(1)-C(2)	108 10(10)	C(1)-N(1)-C(10)	114.16(10)
C(3)-C(2)-C(1)	107 09(10)	C(11)-N(1)-C(10)	123 44(10)
C(3)-C(2)-C(5)	113 67(10)	N(1)-C(11)-C(12)	114 31(10)
C(1)-C(2)-C(5)	103 49(10)	C(17)-C(12)-C(13)	119 02(12)
O(2)-C(3)-O(3)	124 14(13)	C(17)-C(12)-C(11)	118 64(12)
O(2)-C(3)-C(2)	123 79(12)	C(13)-C(12)-C(11)	122 29(11)
O(3)-C(3)-C(2)	112 05(11)	C(14)-C(13)-C(12)	120 76(12)
C(3)-O(3)-C(4)	115 42(11)	C(15)-C(14)-C(13)	118 53(12)
C(6)-C(5)-C(2)	109 51(10)	C(16)-C(15)-C(14)	122.09(12)
C(6)-C(5)-C(10)	111 07(11)	C(16)-C(15)-N(2)	118.76(12)
C(2)-C(5)-C(10)	104 16(10)	C(14)-C(15)-N(2)	119.14(12)
C(7)-C(6)-C(5)	111 53(11)	O(5)-N(2)-O(4)	123 50(13)
C(8)-C(7)-C(6)	111 22(12)	O(5)-N(2)-C(15)	118 09(12)
C(9)-C(8)-C(7)	123 79(13)	O(4)-N(2)-C(15)	118 40(11)
C(8)-C(9)-C(10)	122.85(13)	C(15)-C(16)-C(17)	118 69(12)
N(1)-C(10)-C(9)	113 51(10)	C(16)-C(17)-C(12)	120.91(13)
N(1)-C(10)-C(5)	102 10(10)		

Symmetry transformations used to generate equivalent atoms:

Table 4 Anisotropic displacement parameters ($Å^2 x 10^3$) for gp6. The anisotropic displacement factor exponent takes the form. $-2\pi^2[h^2 a^{*2} U^{11} + \ldots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	29(1)	34(1)	29(1)	-2(1)	-3(1)	-1(1)
C(1)	25(1)	19(1)	28(1)	2(1)	2(1)	3(1)
C(2)	23(1)	24(1)	29(1)	1(1)	5(1)	5(1)
C(3)	29(1)	29(1)	26(1)	-1(1)	8(1)	1(1)
O(2)	36(1)	31(1)	60(1)	14(1)	13(1)	8(1)
O(3)	30(1)	32(1)	47(1)	-1(1)	11(1)	-5(1)
C(4)	47(1)	37(1)	54(1)	0(1)	17(1)	-13(1)
C(5)	26(1)	25(1)	23(1)	1(1)	3(1)	4(1)
C(6)	36(1)	26(1)	34(1)	-2(1)	-1(1)	6(1)
C(7)	49(1)	24(1)	38(1)	-2(1)	-8(1)	3(1)
C(8)	40(1)	35(1)	30(1)	7(1)	-9(1)	-11(1)
C(9)	27(1)	44(1)	25(1)	6(1)	-1(1)	-5(1)
C(10)	24(1)	27(1)	23(1)	2(1)	1(1)	3(1)
N(1)	25(1)	27(1)	22(1)	1(1)	2(1)	2(1)
C(11)	29(1)	29(1)	23(1)	3(1)	5(1)	-2(1)
C(12)	25(1)	30(1)	18(1)	-2(1)	2(1)	-4(1)
C(13)	28(1)	32(1)	25(1)	0(1)	9(1)	-1(1)
C(14)	32(1)	29(1)	24(1)	0(1)	7(1)	-1(1)
C(15)	25(1)	32(1)	23(1)	-6(1)	1(1)	0(1)
N(2)	29(1)	41(1)	28(1)	-10(1)	2(1)	3(1)
O(4)	50(1)	35(1)	54(1)	-1(1)	13(1)	7(1)
O(5)	32(1)	57(1)	46(1)	-14(1)	13(1)	5(1)
C(16)	27(1)	43(1)	31(1)	-5(1)	13(1)	-6(1)
C(17)	33(1)	33(1)	28(1)	1(1)	10(1)	-7(1)

Table 5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 x 10^3$) for gp6

x	y	z	U(eq)
H(2)	4552	418	4127	31

H(4A)	5766	4967	3544	67
H(4B)	4921	5564	3989	67
H(4C)	4790	5046	2801	67
H(5)	3053	595	2702	30
H(6A)	3862	-1878	3065	40
H(6B)	3575	-2038	4157	40
H(7A)	2416	-2430	2169	47
H(7B)	2660	-3805	3041	47
H(8)	1252	-2882	3255	45
H(9)	1171	-579	4122	40
H(10)	2105	1589	3673	30
H(11A)	2858	818	6546	33
H(11B)	2000	-54	5855	33
H(13)	2504	3882	5048	33
H(14)	1681	6253	5181	34
H(16)	232	3815	6939	39
H(17)	1049	1453	6793	37

Table 6 Torsion angles [°] for gp6

O(1)-C(1)-C(2)-C(3)	-73 68(15)	C(6)-C(7)-C(8)-C(9)	19 86(19)
N(1)-C(1)-C(2)-C(3)	105 13(11)	C(7)-C(8)-C(9)-C(10)	4 4(2)
O(1)-C(1)-C(2)-C(5)	165.95(12)	C(8)-C(9)-C(10)-N(1)	-114 31(14)
N(1)-C(1)-C(2)-C(5)	-15 24(12)	C(8)-C(9)-C(10)-C(5)	2 43(18)
C(1)-C(2)-C(3)-O(2)	-70 00(16)	C(6)-C(5)-C(10)-N(1)	90 61(12)
C(5)-C(2)-C(3)-O(2)	43 64(18)	C(2)-C(5)-C(10)-N(1)	-27 18(12)
C(1)-C(2)-C(3)-O(3)	108 43(12)	C(6)-C(5)-C(10)-C(9)	-32 50(15)
C(5)-C(2)-C(3)-O(3)	-137 92(11)	C(2)-C(5)-C(10)-C(9)	-150 30(10)
O(2)-C(3)-O(3)-C(4)	1 2(2)	O(1)-C(1)-N(1)-C(11)	2 92(19)
C(2)-C(3)-O(3)-C(4)	-177 23(11)	C(2)-C(1)-N(1)-C(11)	-175 89(11)
C(3)-C(2)-C(5)-C(6)	151.44(11)	O(1)-C(1)-N(1)-C(10)	176 11(12)
C(1)-C(2)-C(5)-C(6)	-92 77(12)	C(2)-C(1)-N(1)-C(10)	-2 70(14)
C(3)-C(2)-C(5)-C(10)	-89 69(12)	C(9)-C(10)-N(1)-C(1)	143 08(11)
C(1)-C(2)-C(5)-C(10)	26 10(12)	C(5)-C(10)-N(1)-C(1)	19 28(13)
C(2)-C(5)-C(6)-C(7)	171 30(11)	C(9)-C(10)-N(1)-C(11)	-43 83(16)
C(10)-C(5)-C(6)-C(7)	56 81(15)	C(5)-C(10)-N(1)-C(11)	-167 64(11)
C(5)-C(6)-C(7)-C(8)	-49 99(16)	C(1)-N(1)-C(11)-C(12)	100 92(13)

C(10)-N(1)-C(11)-C(12)	-71 63(15)
N(1)-C(11)-C(12)-C(17)	159 39(11)
N(1)-C(11)-C(12)-C(13)	-23 22(17)
C(17)-C(12)-C(13)-C(14)	0 30(19)
C(11)-C(12)-C(13)-C(14)	-177 09(12)
C(12)-C(13)-C(14)-C(15)	-0 28(19)
C(13)-C(14)-C(15)-C(16)	0.50(19)
C(13)-C(14)-C(15)-N(2)	179 39(11)
C(16)-C(15)-N(2)-O(5)	-9 61(18)
C(14)-C(15)-N(2)-O(5)	171.46(12)
C(16)-C(15)-N(2)-O(4)	169 77(12)
C(14)-C(15)-N(2)-O(4)	-9.16(18)
C(14)-C(15)-C(16)-C(17)	-0.7(2)
N(2)-C(15)-C(16)-C(17)	-179 62(12)
C(15)-C(16)-C(17)-C(12)	0.7(2)
C(13)-C(12)-C(17)-C(16)	-0 53(19)
C(11)-C(12)-C(17)-C(16)	176 95(12)

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