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# **Synthetic Applications of the Meta Photocycloaddition Reaction**

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Submitted to the University of Sussex in part fulfilment of the requirements of the  
degree of Doctor of Philosophy, December 2008.

**Declaration**

I hereby declare that this thesis has not been submitted in whole or in part form for the award of another degree.

Signed

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Finally I must thank my family for support over the last three years.

## Abstract

The meta photocycloaddition between a substituted aryl ring and alkene affords architecturally complex tricyclic intermediates that have been utilised to investigate three different areas of synthetic organic chemistry.

Firstly, a novel palladium catalysed oxidative fragmentation/cyclisation of the *Z*-but-2-ene-1,4-diol and anisole derived meta photocycloadduct **30** was investigated. It was proposed that a *meso*  $\pi$ -allyl palladium intermediate was generated during the course of the oxidative cyclisation process and it was hoped that a desymmetrisation reaction could be achieved by attaching a homochiral ligand to the palladium core and result in the enantioenrichment of the cyclised product. Unfortunately under the conditions used only a racemic mixture of products was obtained.

Secondly, the use of nitrogen in exchange for oxygen in the oxidative cyclisation procedure was investigated with a view to preparing a conformationally constrained bicyclic amino acid. Installation of the amino group at the photocycloaddition stage failed and derivatisation of the hydroxyl group of the allyl alcohol/anisole derived photoadduct resulted in an undesired fragmentation. Acid induced fragmentation of the allyl alcohol/anisole derived photoadduct **25** and subsequent triflation of the hydroxyl followed by displacement with azide, reduction with Lindlar's catalyst and protection, afforded the requisite amide. Cyclisation with phenylselenenylchloride and concomitant oxidation furnished the cyclised amide.

Finally, the total synthesis of gelsemine was investigated. Building on the results of a previous researcher in the group an advanced intermediate derived from the meta photocycloaddition of allyl alcohol/anisole failed to undergo the desired palladium catalysed alkoxycarbonylation to assemble the key quaternary centre of the oxindole group. Reaction of the allyl alcohol/anisole photoadduct with *N*-chlorosulfonyl isocyanate afforded an alternative route forward and subsequent synthetic modifications led to an attempted intramolecular Heck spirocyclisation reaction, which led to the formation of a spirooxindole centre that was epimeric to gelsemine. Utilisation of the diol photoadduct afforded functionality which would allow construction of the pyrrolidine ring prior to forming the spirooxindole centre. The same synthetic route

was applied to afford the hydroxyl group, where epimerisation of the oxidised product, a further oxidation and Curtius rearrangement furnished the *exo* carbamate **154**. The system now had the requisite functionality present to complete the total synthesis of gelsemine.



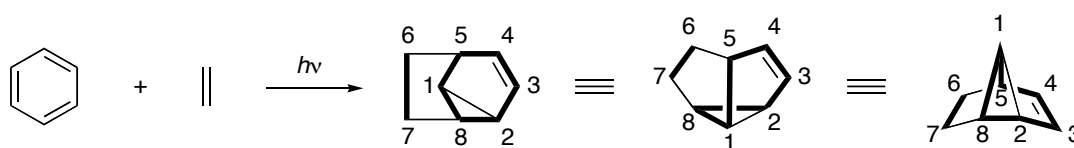
## Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	Acetyl
AIBN	2,2'-azobisisobutyronitrile
Alloc	Allyloxycarbonyl
Bn	Benzyl
BOC	<i>tertiary</i> -butyloxycarbonyl
Bu	Butyl
Cat.	Catalytic
CNS	Central Nervous System
d	Day
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DIBALH	Diisobutylaluminum hydride
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DMDO	Dimethylsulfoxide
DME	Dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMS	Dimethyl sulfide
dppe	<i>bis</i> -(diphenylphosphino)ethane
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
EDCI	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
Et	Ethyl
HMDS	Hexamethyldisilazide
HPMA	Hexamethylphosphorousamide
Hr	Hours
Hz	Hertz
IBX	<i>o</i> -Iodoxybenzoic acid
<i>i</i> Pr	<i>iso</i> Propyl
LDA	Lithium diisopropylamide
L-Selectride	Lithium tri- <i>sec</i> -butylborohydride
MAD	bis(2,6-di- <i>tert</i> -butyl-4-methylphenoxide)methylaluminum
<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic acid
Me	Methyl
mins	Minutes
MMPP	Magnesium monoperoxyphthalic acid
MOM	Methoxymethyl
Ms	Methanesulfonyl
NBS	<i>N</i> -bromosuccinimide
nm	nano metre
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser effect

Oxone	Potassium peroxomonosulfate
PCC	Pyridinium chlorochromate
Ph	Phenyl
Piv	2,2,2-Trimethylacetyl
PMP	4-Methoxyphenol
PPTS	pyridinium <i>p</i> -toluenesulfonate
RT	Room Temperature
SEM	2-(Trimethylsilyl)ethoxymethyl
TBAF	Tetrabutylammoniumfluoride
<i>t</i> Bu	<i>tertiary</i> -Butyl
TES	Triethylsilyl
TDS	Thexyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
Ts	<i>p</i> -Toluene sulfonyl
UV	Ultra violet

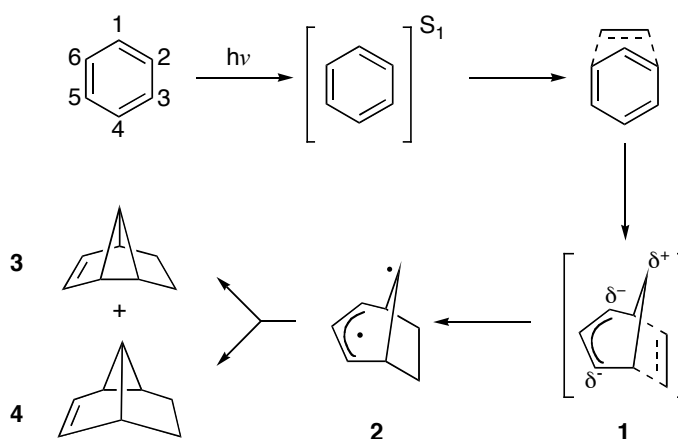
## 1. The meta photocycloaddition reaction

The meta photocycloaddition reaction was initially reported by Wilzbach and Kaplan<sup>1</sup> and Bryce-Smith, Gilbert and Orger<sup>2</sup> in 1966. The reaction is a photochemically induced cycloaddition of an alkene across a benzene derivative, the simplest being ethene and benzene. The reaction gives rise to a complex tricyclic fused ring system containing a vinylcyclopropane subunit. The meta photocycloaddition between ethene and benzene can be represented in three different forms as shown in scheme 1.



Scheme 1. Meta photocycloaddition of benzene and ethene.

The mechanism of the meta photocycloaddition has still not been fully elucidated despite much experimentation,<sup>3</sup> but generally it is thought that the reaction proceeds *via* the excitation of the benzene ring to its first singlet state ( $s_1$ ) by irradiation with 254 nm UV light which in turn forms an arene-alkene exciplex (scheme 1.1).

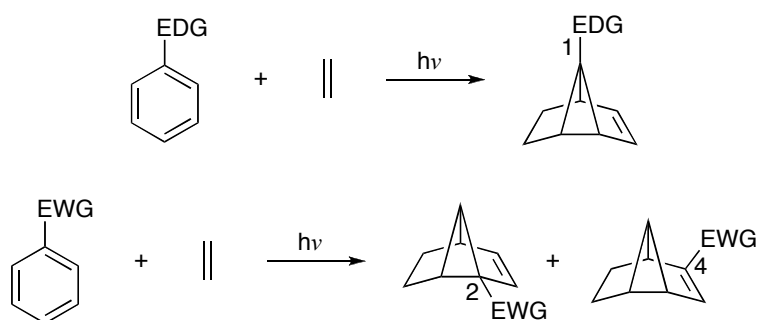


Scheme 1.1. General mechanism of meta photocycloaddition.

As the reaction proceeds, the complex **1** is polarised with a small positive charge at position 1, with an allylically distributed small negative charge between positions 3 and 5 if the alkene is undergoing 2,6-addition. As the alkene-arene bonds are formed a

biradical intermediate **2** has been proposed which precedes the cyclopropane ring closure to give species **3** or **4**.

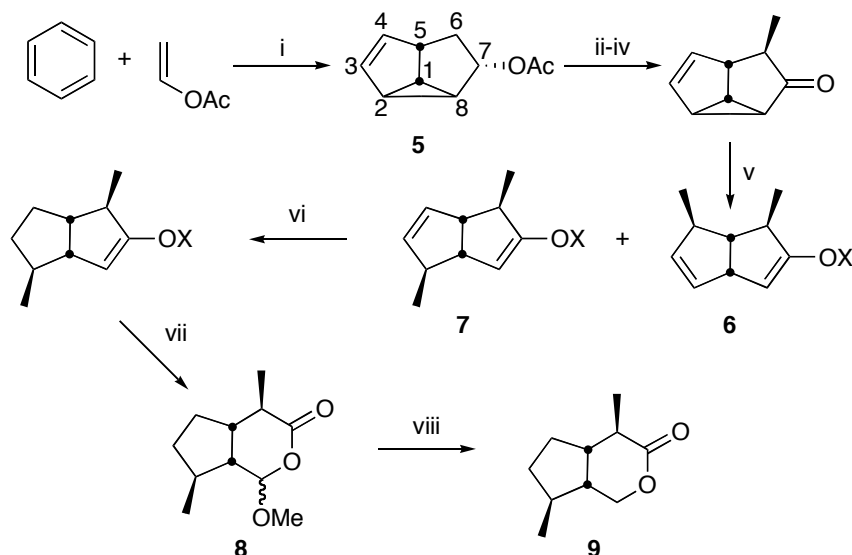
The regiochemistry of the photocycloaddition is controlled mainly by the electronic nature of the substituents on the aryl ring. Electron donating groups (EDG) (e.g. methyl, methoxy) will stabilize the build up of positive charge and are hence found at the bridgehead (position 1) of the product. Electron withdrawing groups (EWG) (e.g. cyano, trifluoromethyl) will stabilize the allylically distributed negative charge, and hence are found at either the 2 or 4 positions of the product (scheme 1.2).



Scheme 1.2. Regiochemical control *via* the use of differing substituents on the aryl ring.

The stereocontrol of the intermolecular meta photocycloaddition gives predominately *endo* selectivity particularly with small ring alkenes such as cyclopentene. Work by Houk<sup>4</sup> has shown that the *endo* selectivity between *cis*-2-butene and benzene is favoured by secondary orbital interactions between the S and A\* of the alkene with the  $\pi$  and  $\pi^*$  of benzene, which stabilize the *endo*-alkene-arene complex while destabilizing the *exo*-complex.

An interesting synthetic use of the intermolecular meta photocycloaddition was reported by Wender<sup>5</sup> in the total synthesis of isoiridomyrecin (Scheme 1.3).



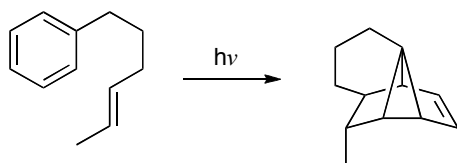
*Reagents & Conditions:* (i)  $h\nu$  (Vycor filter); (ii)  $\text{LiAlH}_4$ , 89%; (iii)  $\text{MnO}_2$ , 95%; (iv)  $\text{LDA}$ ,  $-78^\circ\text{C}$ ,  $\text{MeI}$ , 75%; (v)  $\text{Me}_2\text{CuLi}$ ,  $\text{THF}$ ,  $-78^\circ\text{C}$  then  $\text{Cl}_2\text{PO}(\text{NMe}_2)$  then  $\text{Me}_2\text{NH}$ , 100%; (vi)  $\text{H}_2$ ,  $\text{PtO}_2$ , 90%; (vii)  $\text{O}_3$ ,  $\text{MeOH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  then  $\text{NaBH}_4$ , 92% 1:1 epimers; (viii)  $\text{NaBH}_3\text{CN}$ ,  $\text{H}_2\text{O}$ ,  $\text{THF}$ ,  $\text{H}_2\text{SO}_4$  68%.

Scheme 1.3. Wender's total synthesis of isoiridomyrecin.

Meta photocycloaddition of vinyl acetate and benzene provided the meta photocycloadduct **5** as a starting point. The concave ring system allowed for regioselective enolate formation to give *exo*-alkylation at the 6 position. The cyclopropane ring was fragmented followed by addition of a methyl group *via* a Gilman cuprate addition, to afford a mixture of regioisomers **6** and **7**, with the correct regioisomer in the majority. Selective hydrogenation with Adams catalyst and then ozonolysis gave the diastereoisomeric pseudolactone **8**. Completion of the synthesis was achieved with a sodium cyanoborohydride mediated reduction to afford isoiridomyrecin **9** in 68% yield.

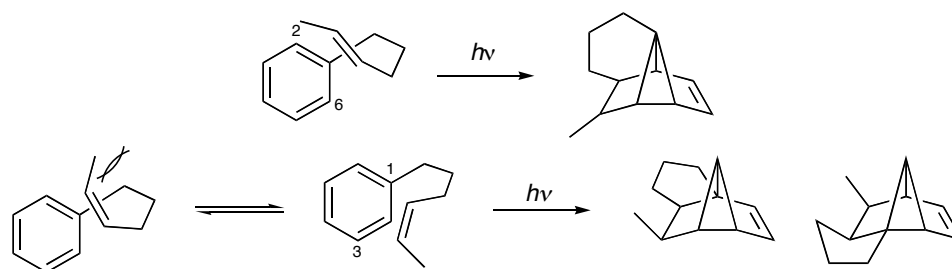
### 1.1 Intramolecular meta photocycloaddition

The intramolecular variant of the meta photocycloaddition reaction was discovered by Morrison and Ferree<sup>6</sup> whilst investigating the light induced *cis/trans* isomerisation of 6-phenyl-hex-2-ene (Scheme 1.4).



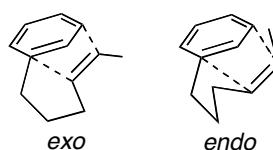
Scheme 1.4. Intramolecular meta photocycloaddition of 6-phenyl-hex-2-ene.

The intramolecular variant has been widely utilised within synthetic organic chemistry compared to the intermolecular variant, mainly due to the increased regio and stereo control it affords. The majority of studies have used a three-atom tether connecting the alkene to the aryl ring. Terminal and *E*-disubstituted double bonds almost exclusively give rise to 2,6-addition across the aryl ring. When the geometry of the double bond is *Z*, the meta photocycloaddition reaction gives rise to 1,3-addition across the aryl ring (Scheme 1.5).



Scheme 1.5. 2-6 & 1-3 meta photocycloaddition.

In the case of 1,3-addition, the steric interactions of the vinyl methyl group with hydrogens on the linking tether dictate the addition of the alkene to arene. The *exo*-isomer is the major product formed during the meta photocycloaddition reaction. Wender<sup>7</sup> rationalised this outcome by the need to minimise strain in the tether caused by the *endo* configuration, whilst maximising orbital overlap of the alkene-arene complex (Scheme 1.6).



Scheme 1.6. Minimisation of steric interactions to favour the *exo*-isomer.

The utility of the intramolecular meta photocycloaddition was perhaps best illustrated by the synthesis of  $\alpha$ -cedrene by Wender *et al.*<sup>8</sup> The presence of the *Z*-double bond gives rise to the more stable *exo*-exciplex with 1,3-addition and the methyl group adjacent to the aryl ring forces the tether to adopt a distorted *syn*-pentane conformation (Figure 1).

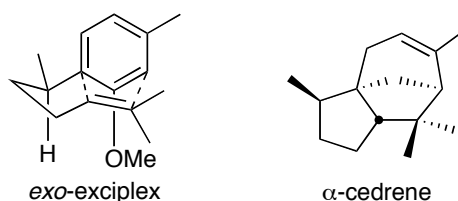


Figure 1. Stereocontrol of the intramolecular meta photocycloaddition towards the synthesis of  $\alpha$ -cedrene.

Essentially the methyl group gives rise to  $\pi$ -facial selectivity giving stereochemical control to the proceeding meta photocycloaddition reaction. The photocycloaddition afforded Wender two regioisomeric cyclopropanes in a 1:1 ratio. Further chemical manipulations provided  $\alpha$ -cedrene in 58% yield in an overall total synthesis consisting of just four steps.

Work by Penkett *et al.*<sup>9</sup> also utilised an intramolecular meta photocycloaddition towards the assembly of the core skeletons of the natural products gymnomitrol and gelsemine (Figure 1.1).

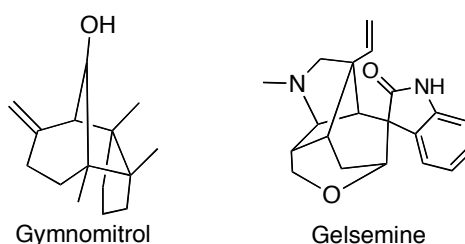
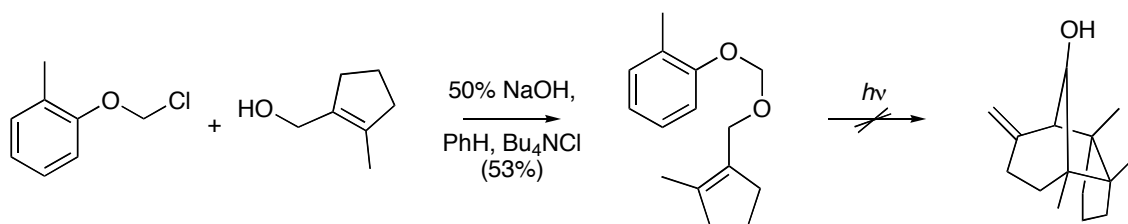


Figure 1.1.

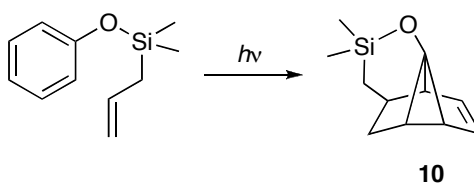
Instead of the standard three-atom tether utilised by other groups, Penkett used a four-atom ‘temporary’ tether with the intention of selectively cleaving the tether from the final product. In the case of gymnomitrol, (2-methylcyclopent-1-enyl)methanol was tethered to 2-methylphenyl chloromethyl ether to form a methylene acetal tether and irradiated with 254 nm UV light (Scheme 1.7).



Scheme 1.7. Penkett's studies towards gymnomitrol.

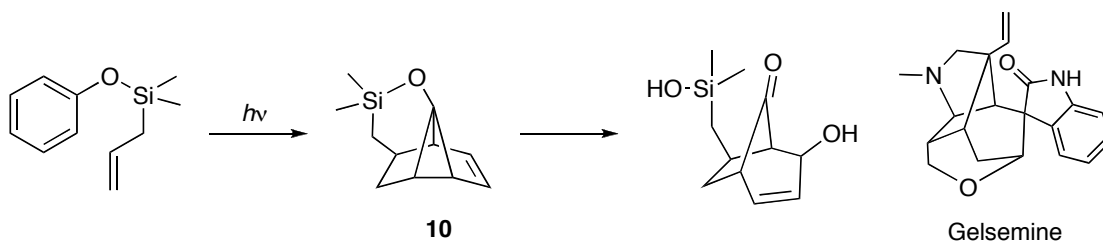
Unfortunately, the steric encumbrance of a tetra-substituted alkene reacting with a di-substituted aryl ring proved too much to allow the meta photocycloaddition to occur. Although the photocycloaddition did not occur with the tetra-substituted alkene, a simple di-substituted alkene was found to undergo meta photocycloaddition illustrating the effect of steric encumbrance on the previous synthesis.

In the case of gelsemine, Penkett utilised a silicon tethered alkene-arene meta photocycloaddition<sup>10</sup>, based on previous work by Fleming<sup>11</sup> and Gilbert<sup>12</sup> to afford the 2,6-cycloadduct **9** (Scheme 1.8).



Scheme 1.8. Penkett's use of a silicon tether with the intramolecular meta photocycloaddition reaction.

In an elegant synthetic operation, the cycloadduct **10** was then subjected to epoxidation and concomitant fragmentation to give the bicyclo[3.2.1]octane skeleton found in gelsemine (Scheme 1.9).



Scheme 1.9. Penkett's studies towards gelsemine.

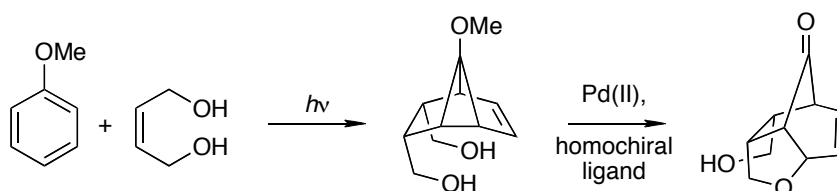


Although the meta photocycloaddition reaction is not widely used within synthetic organic chemistry, it still represents a powerful tool that can access targets of high geometric complexity in one synthetic operation, as illustrated by the above examples.

## Overview of thesis

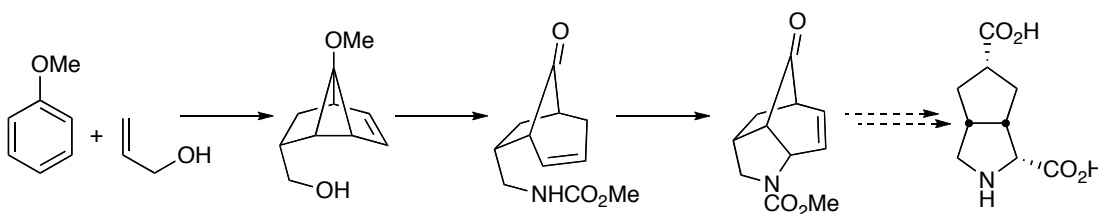
This thesis is divided into three main topics of research, which are linked in the sense that a meta photocycloaddition reaction is involved in forming a key intermediate. The propensity of the meta photocycloadduct to undergo electrophile induced fragmentation to afford a fused bicyclic framework, provides an expedient route to complex synthons.

The first area of research reported in chapter 2, is an oxidative cyclisation reaction that attempted to induce desymmetrisation, *via* a *meso*  $\pi$ -allyl palladium intermediate of a meta photocycloadduct derived from *Z*-but-2-ene-1,4-diol and anisole. The intention was to afford enantioenrichment of the product *via* the use of a homochiral ligand (Scheme 1).



Scheme 1. Investigations toward palladium catalysed enantioselective cyclisation.

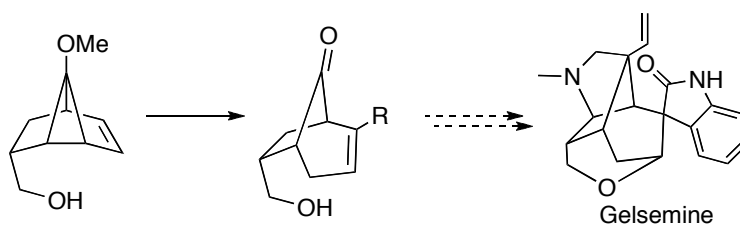
The realisation that palladium could be used to catalyse oxidative cyclisation to afford a tetrahydrofuran ring, led us to investigate the use of another heteroatom, in particular nitrogen, to provide access to an amine analogue as the pyrrolidine ring, which is reported in chapter 3. This would lead to the possibility of forming a conformationally constrained bicyclic amino acid (Scheme 2).



Scheme 2. Investigations toward the formation of the amino analogue.

The meta photocycloaddition reaction also provided a synthetic starting point toward the total synthesis of the alkaloid gelsemine, which is discussed in chapter 4, the third

and main body of work. The intention was to use different electrophiles to induce fragmentation of the meta photocycloadduct to provide the core bicyclo[3.2.1]octane skeleton of gelsemine, with functionality present to provide a route that could be utilised to complete the total synthesis of gelsemine (Scheme 3).



Scheme 3. Investigations toward the total synthesis of gelsemine.

## 2. Palladium-mediated fragmentation of meta photocycloadducts

### 2.1 Development of Pd based catalysis

One of the most important reactions in organic chemistry is the formation of new carbon-carbon bonds; one method of achieving this is the 'cross-coupling' reaction of a metal alkyl and alkyl halide (Scheme 2).



Scheme 2.

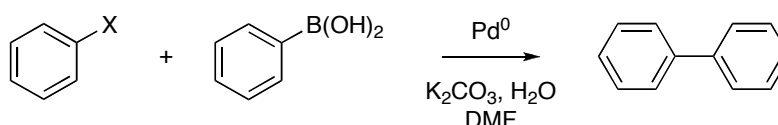
The formation of new carbon-carbon bonds *via* cross-coupling before the 1960s was largely carried out with Mg and Li, which in turn limited the synthetic usefulness of the reaction, as generally only unhindered alkyl halides could undergo a cross-coupling reaction. The application of Grignard or organolithium cross-coupling reactions also gives rise to various side reactions such as non-selective metal-halogen exchange,  $\alpha$  and  $\beta$  elimination and reaction with other functional groups present within the substrate. One main problem associated with organometallic reagents containing Mg or Li is their low chemoselectivity. It was not until 1972<sup>12</sup> that transition metals were first utilised in the cross-coupling reaction, the first of which was based on a Ni catalysed cross-coupling of Grignard reagents<sup>13</sup>. The use of phosphine ligands made the catalysis by Ni a dependable synthetic methodology, with the catalytic cycle of oxidative addition, transmetalation and reductive elimination being widely adaptable.

By 1975 several groups<sup>14</sup> had published independent studies of some Pd-catalysed cross-coupling reactions such as the alkyne variant of the Heck reaction<sup>15</sup> and the Sonogashira Pd catalysed reaction<sup>16</sup>. Over the next four years the use of Pd as a catalyst, was largely superseded by Ni based catalysis as the various products formed could easily be obtained from the latter. Further experimentation eventually led to the realisation of the importance of Pd within synthetic chemistry, in particular Negishi<sup>17</sup> found that Ni catalysed synthesis of conjugated diene systems gave low stereospecificity (90-95%) whereas Pd catalysed synthesis of *E, E* and *E, Z* dienes gave nearly 100% stereoselectivity. Pd mediated cross-coupling reactions were developed substantially during the period after the discovery, with seminal work carried out by

Suzuki and Miyaura<sup>18</sup>, Stille<sup>19</sup>, Sonogashira<sup>20</sup> and Heck<sup>21</sup> to name but a few. A brief overview of each of these reactions will now be presented.

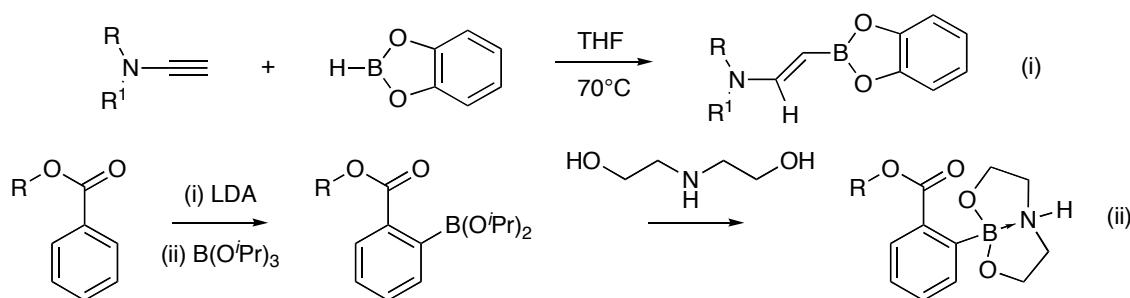
### 2.1.1 The Suzuki-Miyaura coupling reaction

The Suzuki-Miyaura cross-coupling reaction is perhaps one of the most widely used cross-coupling reactions within organic synthesis. The reaction is based on the coupling of an aryl halide with a boronic acid (Scheme 2.1).



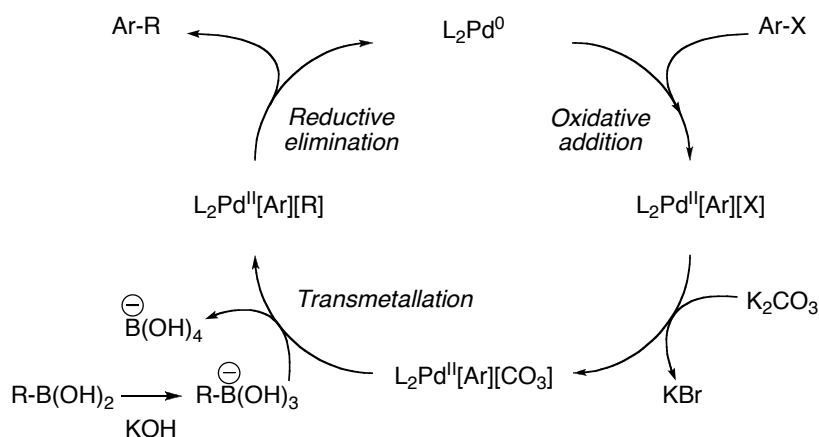
Scheme 2.1. Example of the Suzuki-Miyuara coupling reaction.

The applicability of this reaction rests on the use of boronic acids, in general, which are non toxic, stable to heat, air and moisture. There also exist a wide variety of boronic acid derivatives that are commercially available or can easily be prepared in the laboratory. A variety of methods exists in forming organoboron compounds, two such methods are hydroboration (i) and *ortho*-metallation-borylation (ii) (Scheme 2.2).



Scheme 2.2. Hydroboration and ortho-metallation.

The catalytic cycle proceeds with three main mechanistic steps, oxidative addition, transmetallation and reductive elimination and is shown in scheme 2.3.



Scheme 2.3. Suzuki catalytic cycle.

The reaction is carried out with a source of Pd(0) such as  $Pd(PPh_3)_4$ , which loses two ligands to generate the catalytically active species  $L_2Pd(0)$ . Oxidative insertion between the carbon-halide bond then occurs to generate a Pd(II) species. The Pd(II) complex then undergoes transmetalation with the base activated boronate. Reductive elimination then occurs to give the coupled product whilst regenerating the catalytically active Pd(0) species. It should be noted that the rate of oxidative addition of aryl halides is in the order of  $Ar-I > Ar-Br > Ar-Cl$ . Aryl iodides and bromides are generally more expensive and less available than the chlorides, thus this presented a problem with the number of aryl halides that could be utilised. To circumvent this problem, the use of mono-ligated palladium complexes that contain bulky electron-rich ligands was developed<sup>22</sup>. The ligands shown in figure 2 have the ability to stabilize low-coordination Pd complexes and by the virtue of being mono-ligated, the Pd(0) complex becomes a highly active species in oxidative insertion due to the low electron count.

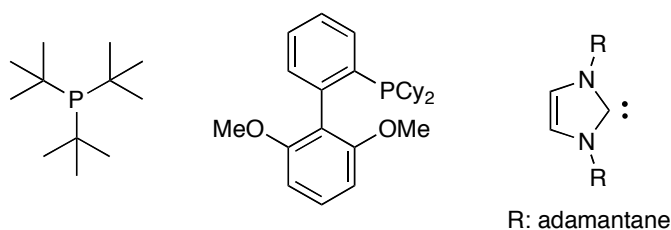
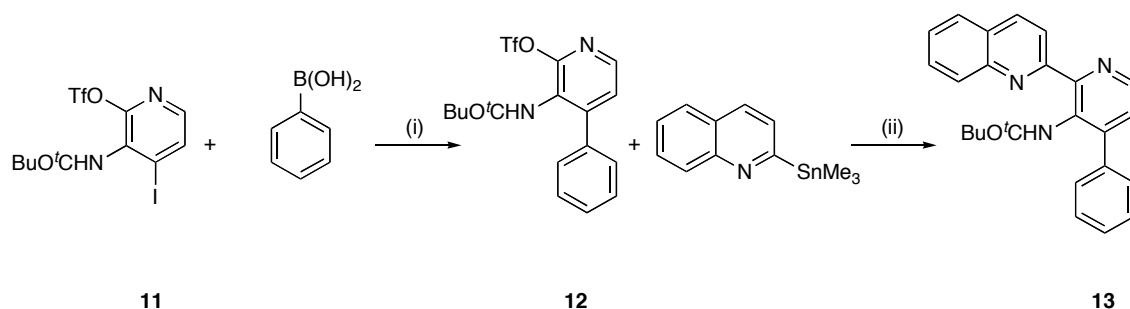


Figure 2. Fu, Buchwald &amp; Herrmann ligands.

The synthetic utility of the Suzuki-Miyaura cross-coupling reaction is exemplified by the convergent synthesis of the streptonigrin alkaloid skeleton by Godard<sup>23</sup>. The

synthetic route began with the readily available 2-methoxy-3-pivaloylaminopyridine, which after three synthetic transformations afforded the precursor to the Pd mediated cross-coupling reaction. The 2-(4-iodo-3-pivaloylamino)pyridyl triflate **11** was reacted with various phenylboronic acids, for simplicity, only phenylboronic acid is shown (Scheme 2.4).



*Reagents & conditions:* (i)  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Na}_2\text{CO}_3$  (2M), toluene, reflux, 12 hr, 95%; (ii)  $\text{Pd}(\text{PPh}_3)_4$ , xylene, reflux, 12 hr, 40%

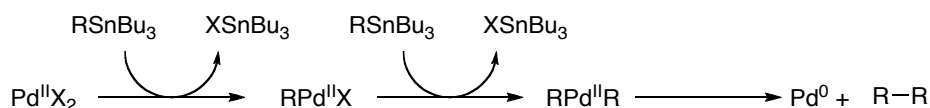
Scheme 2.4. Synthesis of the streptonigrin alkaloid skeleton.

Thus, treatment of **11** under standard Suzuki conditions afforded the cross-coupled product **12** in 98% yield. With the cross-coupled triflate in hand, it was then reacted with (2-quinolyl)trimethylstannane in the presence of  $\text{Pd}(\text{PPh}_3)_4$  which underwent a Stille cross-coupling reaction to afford the streptonigrin skeleton **13** in 84% yield.

The above synthesis perhaps best illustrates the usefulness of palladium as a synthetic organic tool with two separate palladium catalysed steps within the same synthetic route.

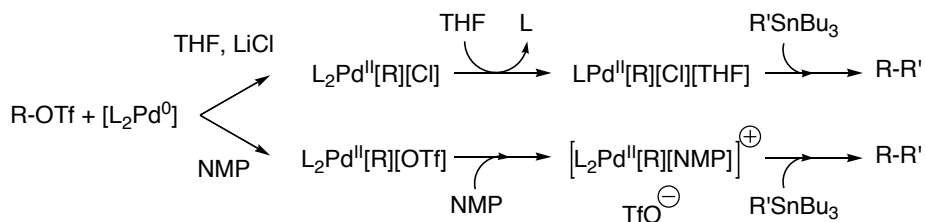
### 2.1.2 The Stille cross-coupling reaction

The Stille cross-coupling reaction<sup>19</sup> is characterised by the use of organotin reagents (as seen in the synthesis of the streptonigrin skeleton) as the coupling partner with aryl triflates. Organotin reagents are generally air and moisture stable that have the advantage of not reacting with other functional group present within the substrate. The catalytic cycle follows that of the Suzuki-Miyaura, with oxidative insertion, transmetallation and reductive elimination. The active Pd species is  $\text{Pd}(0)$  which can either be accessed directly from  $\text{Pd}(\text{PPh}_3)_4$  or by treatment of a  $\text{Pd}(\text{II})$  salt such as  $\text{PdCl}_2$  with two equivalents of the organostannane being used in the reaction (Scheme 2.5).

Scheme 2.5. Generation of Pd(0) *via* organostannanes.

The rate determining step in the Stille coupling reaction is often transmetallation. It is thought to occur after ligand dissociation from the Pd complex, thus the rate of transmetallation can be increased by the use of low donicity ligating species<sup>19</sup> towards Pd(II) such as AsPh<sub>3</sub> or trifuran-2-ylphosphine. A marked increase in rate is seen with very slow Stille couplings even at room temperature with the use of these ligands.

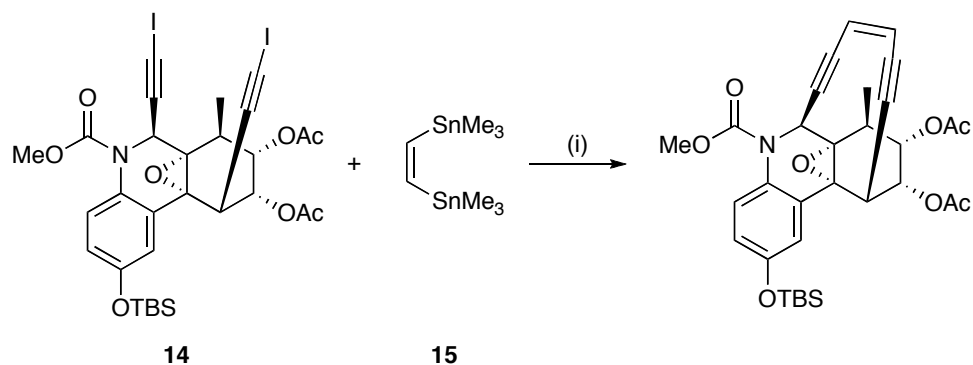
The use of different solvents gives rise to two separate mechanistic pathways. The addition of LiCl to the Stille coupling of aryl triflates in THF is necessary as it facilitates the transmetallation step by causing ligand exchange to occur, whereas in a more polar solvent such as N-methylpyrrolidone, LiCl can be omitted, as the triflate will de-ligate from the Pd core to give a cationic species. A solvent molecule then occupies the vacant site on Pd that aids transmetallation. The two mechanistic pathways can be seen in Scheme 2.6.



Scheme 2.6. THF or NMP as solvents and differing mechanistic pathways.

The Stille reaction was elegantly utilised in Danishefsky's total synthesis of (±)-dynemicin A<sup>24</sup>, a metabolite from *Micromonospora chersina* that demonstrates *in vitro* antitumor properties. The construction of the enediyne ring system was achieved by the cross-coupling of a *Z*-distannylethene **14** with the bis-iodoalkyne **15** to afford the enediyne linkage (Scheme 2.7).





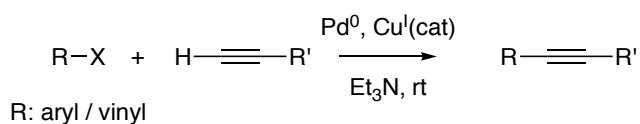
*Reagents & conditions:* (i)  $\text{Pd}(\text{PPh}_3)_4$  (10 mol %), DMF,  $60^\circ\text{C}$ , 1 hr, 80%

Scheme 2.7. Danishefsky's construction of the enediyne ring system.

The only drawback to the Stille cross-coupling reaction is in the use of tin reagents, which are highly toxic and often difficult to separate from the product mixture using conventional chromatographic methods.

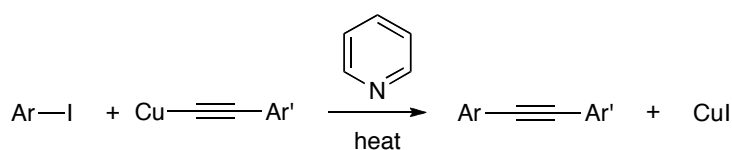
### 2.1.3 The Sonogashira cross-coupling reaction

The Sonogashira reaction presents an excellent method of coupling aryl or vinyl halides, with terminal alkynes in the presence of a base and a Cu(I) co-catalyst (Scheme 2.8).



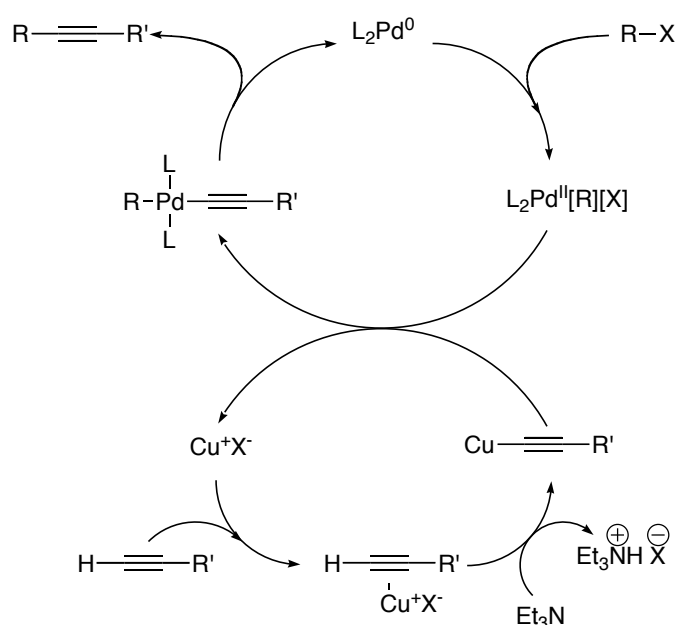
Scheme 2.8. General coupling of aryl/vinyl halide with acetylide.

As seen before with Danishefsky's total synthesis of dynemicin, enediyne systems are present within a wide range of antibiotics and anticancer agents<sup>25</sup>. The Sonogashira coupling reaction was first observed by Stephens and Castro<sup>26</sup> with the coupling of copper acetylides and aryl iodides (Scheme 2.9).



Scheme 2.9. Stephens-Castro coupling.

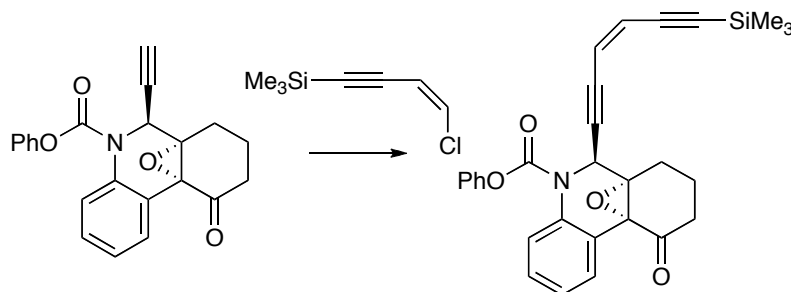
The Stephens-Castro coupling method has undesirable reaction conditions, particularly high temperatures, whereas the Sonogashira reaction is carried out at room temperature. The catalytic cycle differs from that of the Suzuki and Stille with the inclusion of two separate cycles, one involving Pd and the other Cu. The exact mechanism of the Cu-cocatalysed Sonogashira reaction is still unknown as it is very difficult at present to isolate and characterise the various organometallic intermediates from the homogenous mixture. The generally accepted catalytic cycle is shown in scheme 2.1.0<sup>27</sup>.



Scheme 2.1.0. Sonogashira catalytic cycle.

The active Pd(0) species is generated by the reduction of a source of Pd(II) under the employed reaction conditions, as it is known that amines and phosphanes can reduce Pd(II) species<sup>27</sup>. Oxidative addition then occurs which is followed by the introduction of the Cu-co-catalyst cycle as the transmetalation step which is usually rate determining. The Pd complex then undergoes *cis/trans* isomerisation and reductive elimination to give the coupled alkyne with regeneration of the Pd(0) catalyst. The Cu-cycle is poorly understood, though it is thought that the Cu(I) halide forms a  $\pi$ -alkyne complex that facilitates the deprotonation of the alkyne by the aminos base, which then enters the Pd-cycle.

Work carried out by Nicolaou *et al.*<sup>28</sup> on the synthesis of dynemicin A models, utilised the Sonogashira Cu-cocatalysed coupling reaction, to introduce the enediyne subunit (scheme 2.1.1).



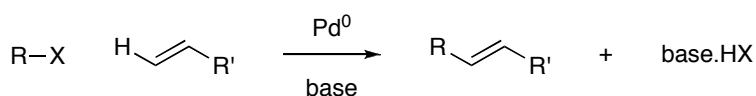
Reagents & conditions: *n*BuNH<sub>2</sub>, PPh<sub>3</sub>, Pd(OAc)<sub>2</sub>, CuI, PhH, 25°C, 4 hr, 88%

Scheme 2.1.1. Nicolaou's synthesis towards the enediyne ring system.

The utility of the Sonogashira reaction can be seen when compared to Danishefsky's synthesis of the enediyne ring. Danishefsky's Stille protocol necessitated the use of increased reaction temperatures in DMF, whereas Nicolaou's Sonogashira coupling reaction was carried out at room temperature in toluene.

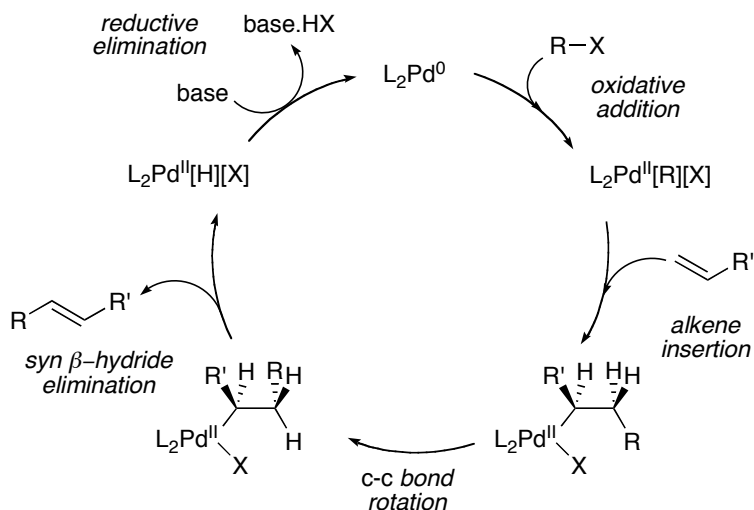
#### 2.1.4 The Heck cross-coupling reaction

The Heck reaction couples an aryl or vinyl halide with an alkene (Scheme 2.1.2).



Scheme 2.1.2. General Heck reaction.

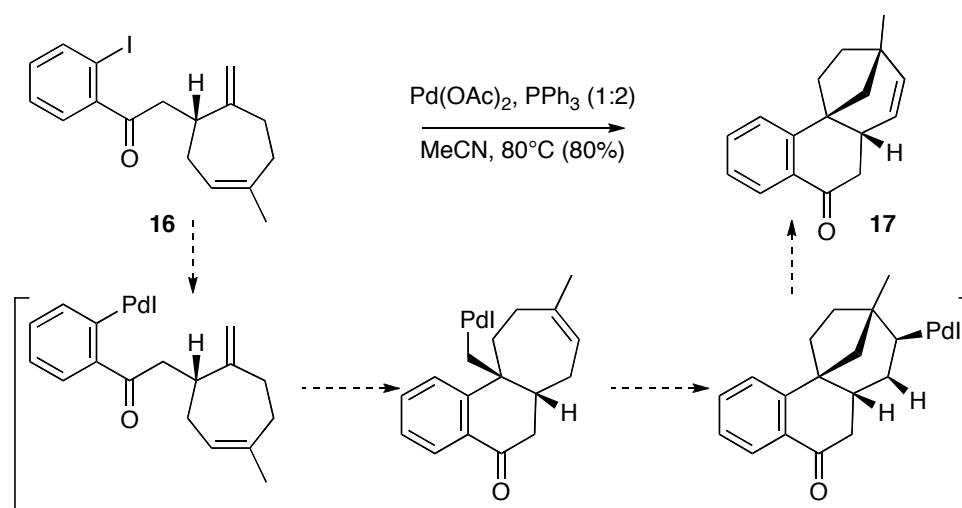
The reaction was first discovered in the 1960's but it was not until the 1980's that the Heck reaction's potential was developed. The active catalytic species is Pd(0)L<sub>2</sub>, which in the first instance undergoes oxidative addition with the aryl or vinyl halide. The overall catalytic cycle is shown in scheme 2.1.3.



Scheme 2.1.3. Heck catalytic cycle.

The process of oxidative addition results in the highly reactive Pd-R  $\sigma$  bond. Alkene coordination to the Pd(II) core is then immediately proceeded by migratory insertion into the Pd-R  $\sigma$  bond, a process also known as carbopalladation. Internal rotation of the carbon-carbon bond now takes place for one proton to align *syn* to palladium in order for  $\beta$ -hydride elimination to occur. The Pd(II) species is then reduced to the catalytically active Pd(0) by base induced reductive elimination.

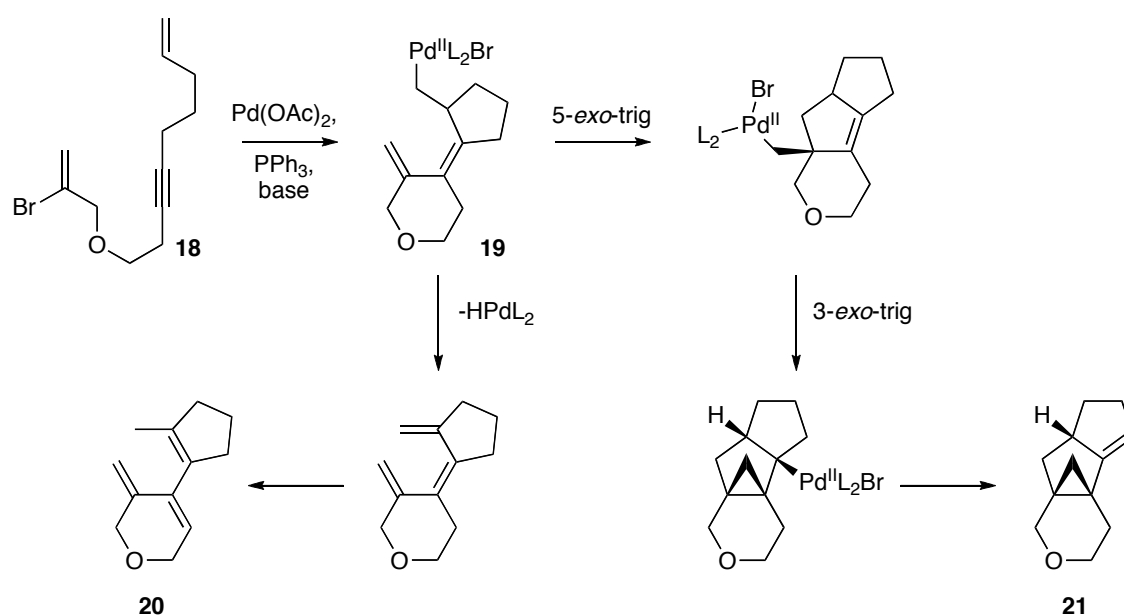
The Heck reaction has the ability to carry out multiple transformations in one synthetic operation, which was elegantly shown by Overman's synthesis of scopadulcic acid A<sup>29</sup> (Scheme 2.1.4).



The dienyl iodide **16** precursor to the key bis-intramolecular Heck was set up in eight steps, from the readily available starting material 2-iodobenzaldehyde. The tandem

reaction proceeded with the Pd(0) species oxidatively inserting into the carbon-iodine bond, which then underwent cyclisation onto the *exo* methylene group to generate one of the key quaternary centres. The resultant organopalladium species could not undergo  $\beta$ -hydride elimination but instead performed a second cyclisation onto the remaining olefin to give the second key quaternary centre, from which in this case  $\beta$ -hydride elimination could occur, to give the bis-cyclised product **17** in 80% yield.

Another Heck catalysed tandem cyclisation was also shown by Parsons *et al.*<sup>30</sup> in the synthesis of novel tetracyclic systems (Scheme 2.1.5).

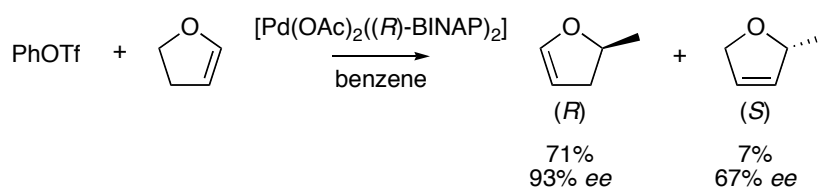


Scheme 2.1.5. Parsons' synthesis of novel tetracyclic systems.

The tandem cyclisation was carried out with treatment of 2-bromo-4-oxa dienyne **18** with a source of Pd(0) that afforded an unexpected cross-conjugated triene **20**. Interestingly, along with the cross-conjugated triene, the geometrically complex tetracyclic product **21** was also formed. Parsons rationalised this novel transformation in terms of the relatively slow  $\beta$ -hydride elimination of the alkylpalladium species **19** after the first 6-*exo-dig* and subsequent 5-*exo-trig* Pd catalysed cyclisations. The alkylpalladium species then underwent another 5-*exo-trig* ring closure which cannot  $\beta$ -hydride eliminate, thus the alkylpalladium performs a final 3-*exo-trig* ring closure to afford the cyclopropane moiety **21** in 5 - 10% yield.

### 2.1.5 Asymmetric Heck cross-coupling

The Heck reaction also provides a route to asymmetric induction in organic synthesis both intermolecularly and intramolecularly *via* the use of chiral auxiliaries attached to the metal centre. Hayashi<sup>31</sup> first reported the use of chiral ligands in the asymmetric intermolecular arylation of dihydrofurans. During the course of the study, Hayashi observed that with standard iodoarenes and the chiral ligand ((*R*)-BINAP), the enantiomeric excess was low. It was only with the use of phenyl triflates that high enantioselectivity and yields were observed (Scheme 2.1.6).



Scheme 2.1.6. Hayashi's asymmetric synthesis of furans.

The increase in enantiomeric excess was attributed to the dissociation of the labile triflate ligand from the metal core (compared with halides that are more strongly bound), generating a cationic complex, which in turn allows the BINAP ligand to be more tightly bound, thus upon migratory insertion, asymmetric induction is possible.

Although intermolecular asymmetric Heck reactions are a valuable tool in the organic chemists arsenal, the intramolecular variant has perhaps received more attention. In 1989, Shibasaki<sup>31</sup> and Overman<sup>32</sup> reported independently the first examples of asymmetric intramolecular Heck reactions. The reaction can proceed either *via* a cationic pathway, with unsaturated triflates or halides in the presence of a halide scavenger such as Ag(I), or it can proceed *via* a neutral pathway where ligand dissociation occurs to give rise to poor enantioselectivity. A variety of chiral phosphine ligands can be used to affect asymmetric Heck reactions, where as seen previously, BINAP has been used extensively, though other ligands are utilised as well as BINAP and are shown in Figure 2.1.

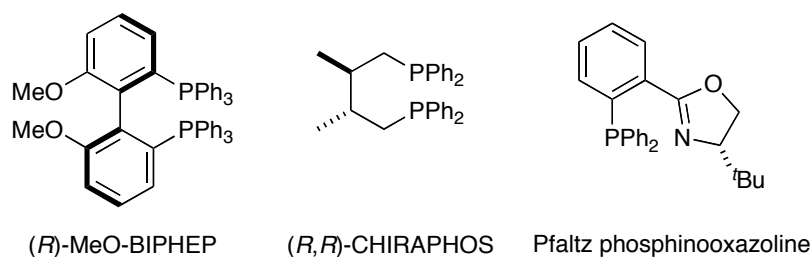
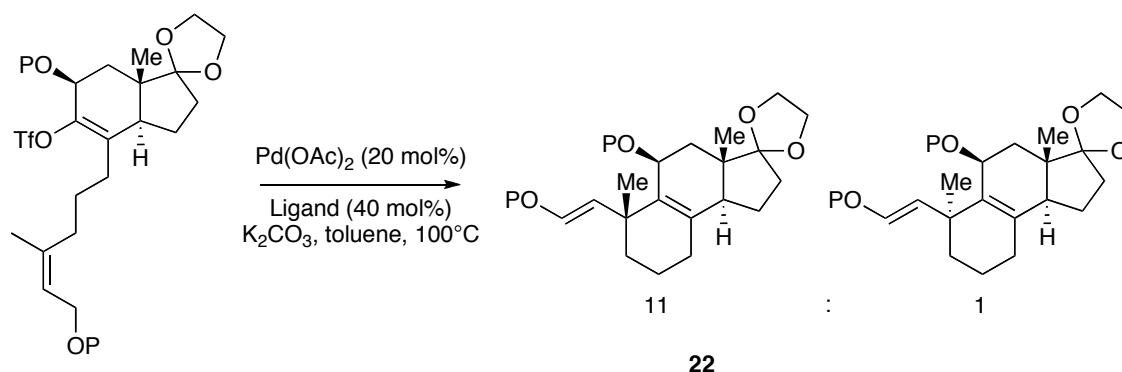


Figure 2.1. Other phosphine ligands.

As previously shown with Overman's synthesis of scopadulcic acid A, the intramolecular Heck reaction can readily give access to key quaternary centres. When the asymmetric intramolecular Heck reaction is invoked, it presents a formidable synthetic tool in the construction of complex polycyclic natural products. Shibasaki *et al.*<sup>33</sup> demonstrated this with an asymmetric Heck cyclisation to install a key allylic quaternary carbon stereocentre of the polyketide, wortmannin (Scheme 2.1.7).

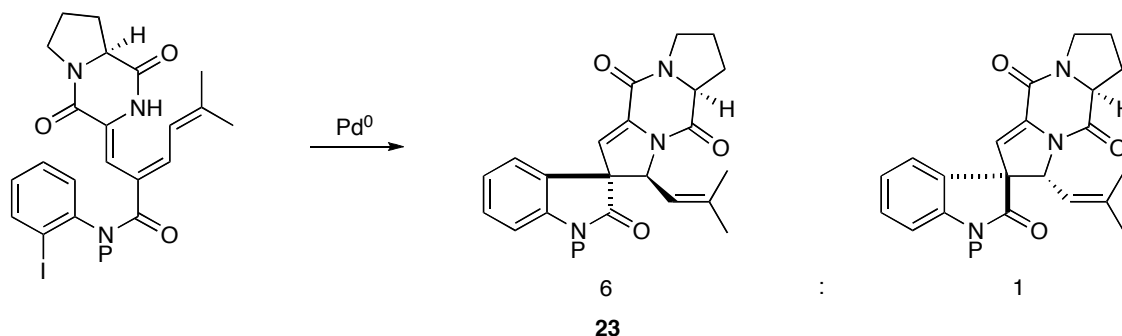


Scheme 2.1.7. Shibasaki's synthesis of key allylic quaternary centre of wortmannin.

A series of chiral bidentate phosphine ligands were screened, with (*R*)-tol-BINAP giving **22** in a highly diastereoselective (11:1) and enantioselective (96% ee) fashion.

An elegant use of the asymmetric intramolecular Heck was realised by Overman and Rosen<sup>34</sup> in the studies toward the synthesis of (-)-spirotryprostatin B. Overman's strategy was to correlate the relative configuration of the quaternary stereocentre and the adjacent tertiary stereocentre, to the geometry of the internal double bond (*E*) of the triene. The key step relied on the stereochemical outcome of two distinct Pd catalysed reactions; firstly the intramolecular asymmetric Heck favoured 5-*exo* cyclisation, to set

in place the quaternary centre, then concomitant trapping of the newly generated  $\eta^3$ -allylpalladium intermediate, by an internal nitrogen nucleophile (Scheme 2.1.8).



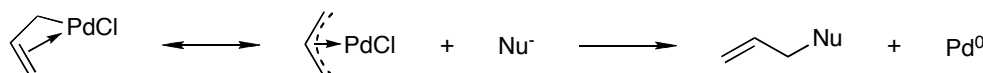
Scheme 2.1.8. Overman & Rosen's studies towards (-)-spirotryprostatin B.

Overman utilised  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ , (*R*)-BINAP and PMP in DMA at 100 °C, to afford a 6:1 mixture of the major pentacyclic product **23** in 26% yield.

As seen with the above examples, the catalytic asymmetric Heck cyclisation has been employed as a central strategic step in the total synthesis of a variety of natural products. The allure of the asymmetric Heck lies within three major factors: the high functional group tolerance of the Pd catalyst, the ability to construct carbon-carbon bonds in sterically congested situations, and the catalysis of cascade processes that form multiple ring systems.

### 2.1.6 Palladium catalysed allylic alkylation reactions

In 1965 Tsuji<sup>35</sup> reported a novel carbon-carbon bond forming reaction involving a  $\pi$ -allylpalladium species and a carbon nucleophile (Scheme 2.1.9).

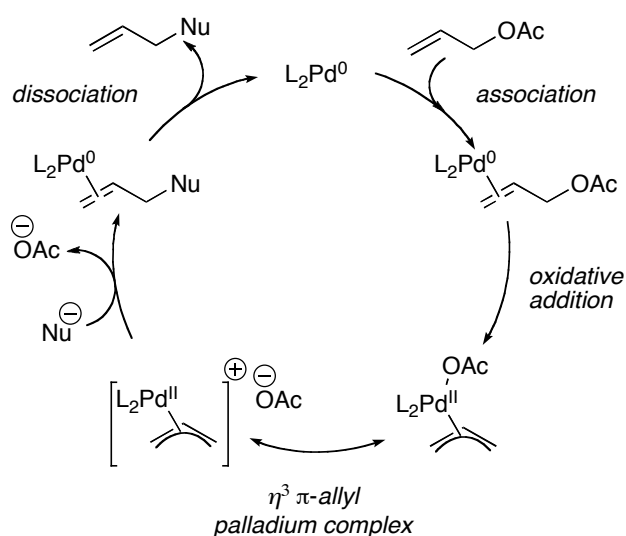


Scheme 2.1.9. General  $\pi$ -allyl palladium reaction.

$\pi$ -Allylpalladium complexes are formed by the reaction of various allylic compounds, and a source of  $\text{Pd}(0)$ . This was elegantly utilised by Overman in the synthesis of (-)-spirotryprostatin B (*vide supra*). In general, many allylic compounds can be used, such as allyl halides, amides, esters and phosphonates, which upon complexation with the

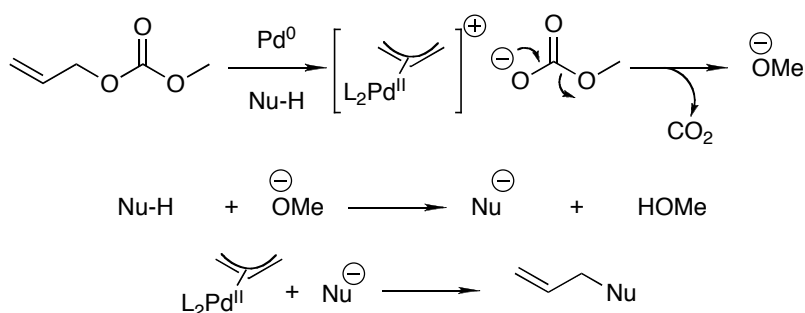


electron-rich Pd(0) and oxidative elimination, gives rise to the Pd(II) allyl cation complex. The general catalytic cycle with an allylic ester is shown in scheme 2.2.0.



Scheme 2.2.0. Palladium catalysed allylic alkylation catalytic cycle.

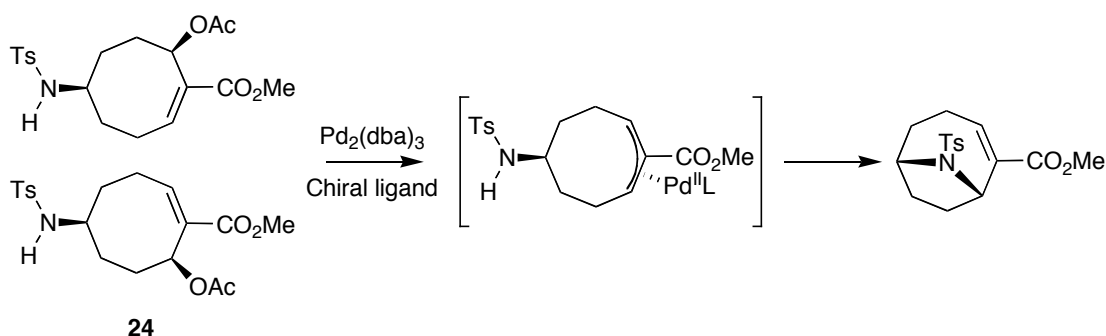
Soft nucleophiles generally give the best results for this reaction. The reaction occurs with an overall retention of configuration, thus the associated problems with allylation *via* conventional methods i.e. loss of regiochemical control, are not found. The different allylic compounds that can be used have varying reactivities toward Pd(0). Allylic chlorides are more reactive than allylic acetates and allylic alcohols and alkyl ethers are relatively non-reactive. Allylic acetates are the most widely used, although a base must be added for the reaction to proceed. The formation of a base *in situ* allows for the reaction to be carried out at room temperature under essentially neutral conditions, which can be useful when base sensitive functionality exists in the substrate. Allylic carbonates<sup>35</sup> are one such example where the base is formed *in situ* (Scheme 2.2.1).



Scheme 2.2.1. Allylic carbonates.

The palladium catalysed allylic alkylation reaction can also provide a route to enantiocontrol within organic synthesis. Asymmetric allylic alkylation has the ability to transform achiral, prochiral, or chiral racemic material to an enantiopure product with the use of chiral ligands ligated to the Pd core. The catalytic cycle is generally the same as with the non-asymmetric allylic alkylation. Enantio-discrimination can be determined out at various stages within the cycle, the first of which being the olefin complexation to the Pd catalyst. In essence, if one complex leads to oxidative elimination at a rate faster than the other, and nucleophilic trapping of the diastereoisomer is fast relative to a  $\pi$ - $\sigma$ - $\pi$  equilibration, then complexation becomes the enantiodetermining step<sup>36</sup>. Where the substrate has two potential leaving groups in a *meso* or gem-disubstituted manner, then enantiotopic ionisation of one of the leaving groups gives rise to enantio-discrimination. If the oxidative elimination step leads to a *meso*  $\pi$ -allylpalladium complex, then there exist two possible enantiotopic locations for nucleophilic addition to occur. With judicious use of a chiral ligand, the regioselectivity of nucleophilic addition can be controlled and hence it can be used to determine the enantioselectivity of the final product.

The asymmetric allylic alkylation was utilised by Trost *et al.*<sup>37</sup> in the enantioselective total synthesis of (-)-anatoxin-A. Trost subjected the chiral racemic amido carbonate **24** to palladium catalysed allylic alkylation, with the intention of using the amido functionality as the internal nucleophile to form the 9-azabicyclo[4.2.1]nonane skeleton. Upon reaction with  $\text{Pd}_2(\text{dba})_3$  and a chiral ligand developed by Trost<sup>37</sup>, the cyclisation of the *cis* amido carbonate proceeded smoothly at 0 °C in 90% yield and 88% ee (Scheme 2.2.2).

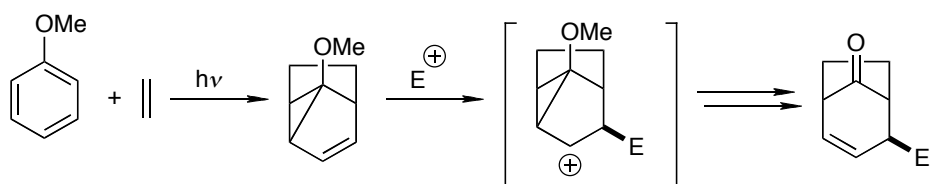


Scheme 2.2.2. Trost's palladium catalysed key step towards (-)-anatoxin-A.

Further synthetic transformations led to the total synthesis of (-)-anatoxin-A in 15% overall yield.

### 2.1.7 Applications of palladium catalysed reactions with meta photocycloadducts

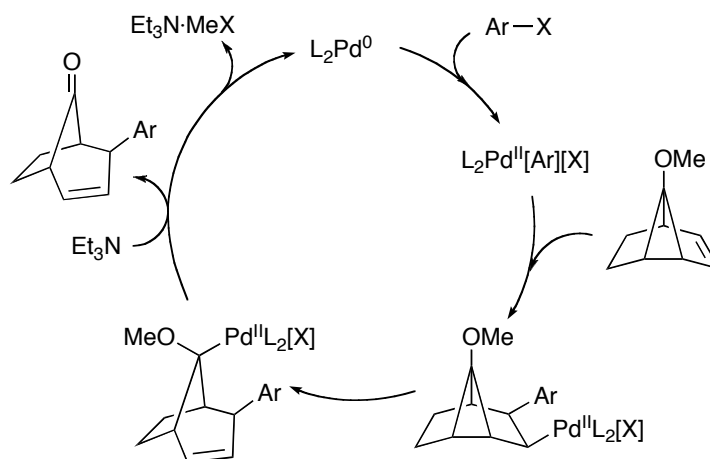
Palladium catalysed cross-coupling reactions can also be applied to the anisole and alkene derived meta photocycloaddition adduct. It is known that the photocycloaddition adduct can undergo electrophilic<sup>38</sup> addition to the electron rich olefin, to induce fragmentation of the highly strained cyclopropane ring, which affords a [3.2.1] bridged bicyclic ketone (Scheme 2.2.3).



Scheme 2.2.3. Electrophilic fragmentation of the anisole/alkene derived metaphotocyclo adduct.

Work by Penkett *et al.*<sup>39</sup> developed the electrophilic induced fragmentation reaction to include a carbocation equivalent as the electrophile. They reasoned that an aryl halide would act as the electrophile in the presence of a Pd catalyst to give rise to a fragmentation/arylation reaction that is analogous to the Heck cross-coupling reaction.

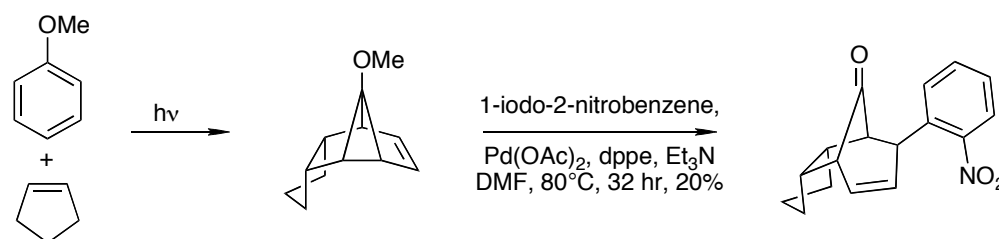
Penkett proposed a modified version of the generally accepted Heck catalytic cycle, with the inclusion of cyclopropane ring fragmentation after carbopalladation (Scheme 2.2.4).



Scheme 2.2.4. Penkett's modified Heck catalytic cycle.

The initial steps involving oxidative addition of the aryl halide to the Pd(0), followed by carbopalladation are comparable to that of the classic cycle, although the rigid structure of the meta photocycloadduct does not allow the carbon-palladium  $\sigma$ -bond to align *syn* to a  $\beta$ -hydrogen in order for  $\beta$ -hydride elimination to occur. As a consequence of this, cyclopropane ring fragmentation occurs, and the Pd(II) species is then reductively eliminated to Pd(0) with the assistance of a base, to afford an arylated bicyclic ketone.

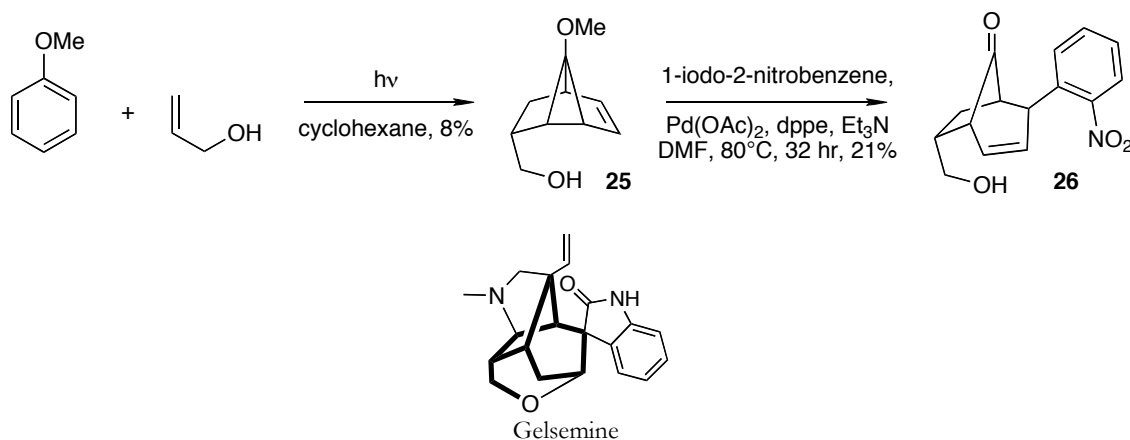
The mechanism was verified by reacting the cyclopentene/anisole derived meta photocycloadduct with 1-iodo-2-nitrobenzene in the presence of Pd(OAc)<sub>2</sub> and dppe ligand as the catalyst and Et<sub>3</sub>N as the base, to afford the arylated product in 20% yield (Scheme 2.2.5).



Scheme 2.2.5. Palladium catalysed arylation/fragmentation of the anisole/cyclopentene derived metaphotocyclo adduct.

The palladium induced arylation/fragmentation reaction was also carried out with the anisole/allyl alcohol meta photocycloadduct<sup>40</sup>, with the intention of constructing the

core skeleton of the natural product gelsemine in one synthetic operation (Scheme 2.2.6).



Scheme 2.2.6. Palladium catalysed arylation/fragmentation of the anisole/allyl alcohol derived metaphotocyclo adduct & the alkaloid gelsemine with core skeleton in bold.

The same reaction conditions were employed as before to afford the arylated product in 21% yield. Interestingly, upon using higher reaction temperatures, another isomeric product was produced (Figure 2.3).

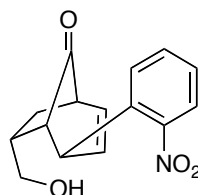


Figure 2.3. Other isomeric product.

The presence of this novel product led Penkett to propose that a new catalytic pathway existed that went *via* an  $\pi$ -allyl palladium intermediate after the initial fragmentation of the vinyl-cyclopropane ring (Figure 2.4).

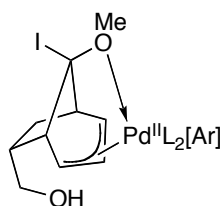
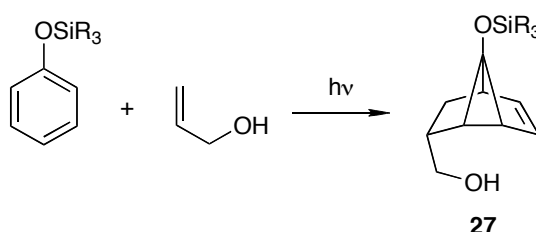


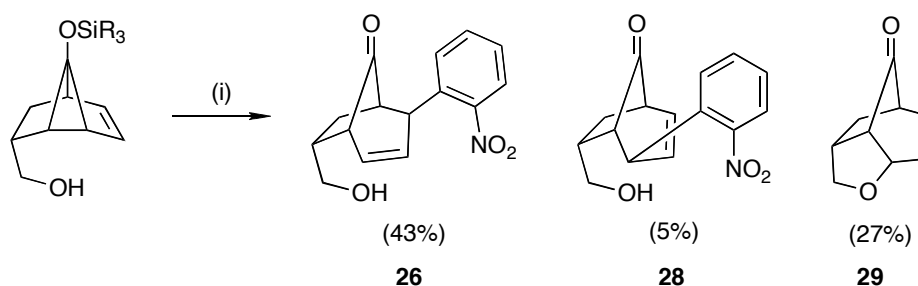
Figure 2.4. Proposed  $\pi$ -allyl intermediate.

This novel reaction was further optimised<sup>40</sup> by replacing the methoxy group of anisole with a alkylsiloxy group to aid in cyclopropane ring fragmentation, and subjecting it to the meta photocycloaddition reaction with allyl alcohol, afforded the bridgehead trimethylsiloxy moiety **27** (Scheme 2.2.7).



Scheme 2.2.7. Meta photocycloaddition of trimethyl(phenoxy)silane & allyl alcohol.

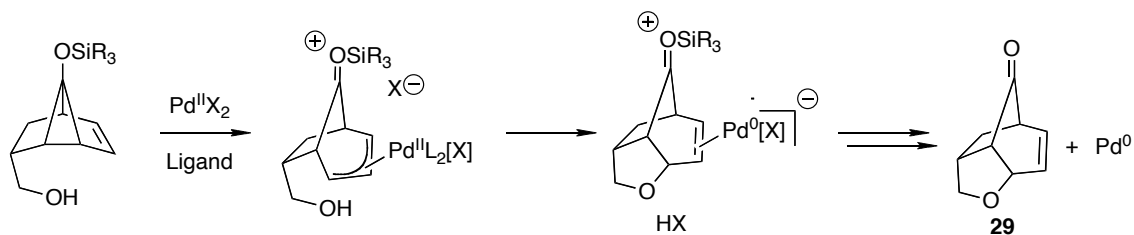
The Pd catalysed fragmentation/arylation of the meta photocycloadduct **27** was again carried out using the standard conditions, to afford the two isomeric products **26** and **28** along with another unique product **29** (Scheme 2.2.8).



Reagents & conditions: (i) 1-iodo-2-nitrobenzene, Pd(OAc)<sub>2</sub> (5 mol %), P(*o*-Tol)<sub>3</sub> (10 mol %), Et<sub>3</sub>N, DMF, 120 °C, 12 hr.

Scheme 2.2.8. Palladium catalysed arylation/fragmentation & cyclised product.

The formation of the tricyclic ether **29** was attributed to a formal oxidation process *via* an internal nucleophilic displacement reaction<sup>40</sup>. It was found that the 1-iodo-2-nitrobenzene was the reoxidation source of the Pd(0) species, replacing this with copper(II) chloride as the reoxidant increased the yield of the tricyclic ester obtained. The presence of the cyclised compound **29** gave credibility to the theory of the  $\pi$ -allyl palladium species formed after initial fragmentation of the vinyl-cyclopropane ring, and an oxidative cyclisation mechanism was proposed (Scheme 2.2.9).

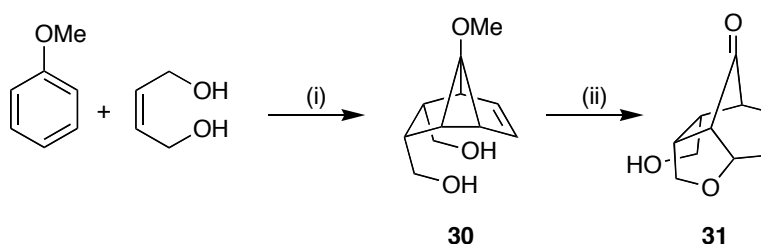


Scheme 2.2.9. Proposed oxidative cyclisation mechanism.

As previously seen,  $\pi$ -allyl palladium complexes have the ability to transform achiral, prochiral, or chiral racemic material to enantiopure products. It was postulated that if an analogue of the  $\pi$ -allyl palladium intermediate that displayed *meso* symmetry could be generated, then attachment of a homochiral ligand to the Pd core, could cause desymmetrisation. This in turn would kinetically favour a stereoselective displacement process and result in the formation of an enantioenriched product.

## 2.2 Results & Discussion

The meta photocycloadduct derived from anisole and *Z*-but-2-ene-1,4-diol was deemed a suitable substrate to undergo Pd catalysed oxidative desymmetrisation (Scheme 2.3.0), with the same conditions used to form the tricyclic ether **31**.

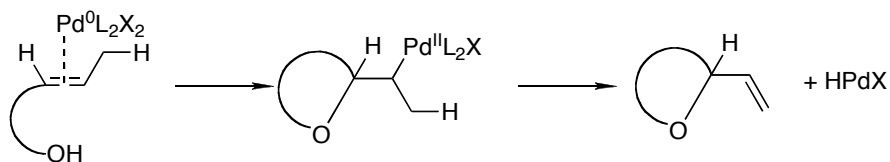


*Reagents & conditions:* (i) hv, MeOH, 14%; (ii) PdCl<sub>2</sub>, (5 mol %), P(*o*-Tol)<sub>3</sub> (10 mol %), CuCl<sub>2</sub>, Et<sub>3</sub>N, DMF, 20 °C, 48 hrs, 11%.

Scheme 2.3.0. Meta photocycloaddition and palladium catalysed oxidative cyclisation.

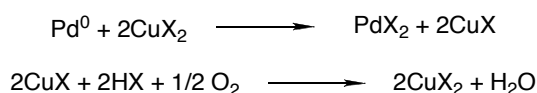
A solution of anisole and *Z*-but-2-ene-1,4-diol in methanol was irradiated with 254 nm UV light in a quartz immersion well reactor to afford the meta photocycloadduct **30** in 14% yield.

The palladium catalysed oxidative cyclisation of the meta photocycloadduct **25** or **30** is comparable to that of the intramolecular Wacker oxypalladation of alkenes<sup>41</sup> (Scheme 2.3.1).



Scheme 31. Wacker intramolecular oxidative cyclisation.

The Wacker process operates as a redox catalyst, with the catalytically active Pd(II) species being regenerated by sub-stoichiometric amounts of copper(II) chloride. The resultant copper(I) chloride is oxidised to copper(II) chloride in the presence of oxygen within its own cycle (Scheme 2.3.2).



Scheme 2.3.2. Redox catalytic reaction.

To achieve enantioenrichment a range of chiral ligands were chosen (Figure 2.5). The BINAP and Trost ligands were chosen as they were both good, standard, commercially available ligands for the use in allylic alkylation reactions<sup>42</sup>. The QUINAP ligand was chosen as it had two different ligating atoms (N and P)<sup>43</sup>. Finally sparteine<sup>44</sup> was chosen, as it was less prone to oxidation.

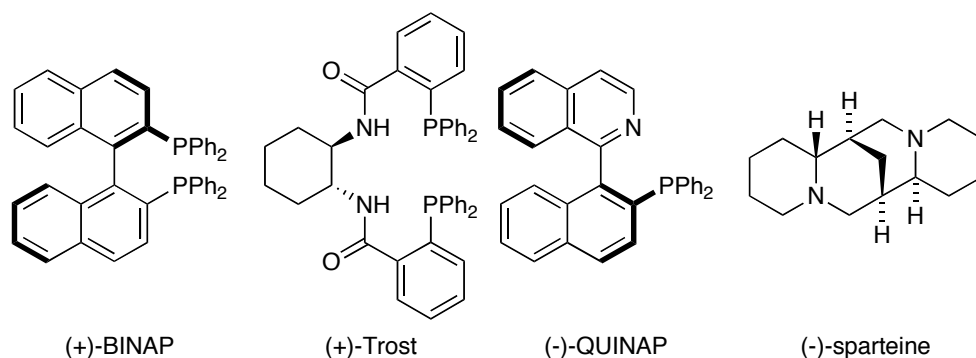
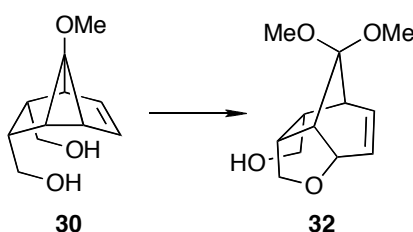


Figure 2.5. Chiral ligands.



The palladium catalyst was preformed prior to reaction by stirring palladium chloride with the ligand in methanol overnight under an atmosphere of nitrogen. The solvent was removed *in vacuo* to afford the various palladium complexes as yellow solids.

A series of experiments (Table 1) were carried out with the diol substrate **30** and the various palladium complexes (5 mol %) and a catalytic amount of copper(II) chloride (5 mol %). The stoichiometric re-oxidant was a balloon of oxygen gas. After previous studies by Rupert Sims<sup>84</sup>, it was found that MeOH was the solvent of choice for the reaction.



Entry	Ligand	Stoichiometric reoxidant	Time (hr)	Yield (%)
1	(+)-BINAP	O <sub>2</sub>	72	16
2	(+)-Trost	O <sub>2</sub>	72	16
3	(-)-QUINAP	O <sub>2</sub>	72	10
4	(-)-Sparteine	O <sub>2</sub>	48	35

Table 1.

To establish if enantioenrichment had occurred, the free hydroxy group of the cyclised product **32** was derivatised to the benzoate ester and each was submitted for chiral HPLC analysis. Unfortunately, no evidence of enantioenrichment was observed of the cyclised product. Generally, the Wacker conditions required long reaction times and resulted in low yields of the cyclised product with the exception of entry 4, where the sparteine ligand was employed. In retrospect, it was not surprising the yields for entries 1-3 are lower than that of entry 4, as phosphine ligands are prone to oxidation under the aerobic conditions<sup>44</sup>. Work by Stoltz *et al.*<sup>45</sup> had shown that sparteine could be used to induce enantioenrichment in the Wacker oxidative cyclisation reactions. The reaction involved heating the substrate in toluene at 80 °C under an oxygen atmosphere with palladium bis(trifluoroacetate), 40 mol % sparteine and molecular sieves. The reaction was carried out on the diol moiety **30**, which disappointingly failed to produce any of the cyclised ketone **31**. Work by Hosokawa *et al.*<sup>41</sup> utilised a palladium(II) complex

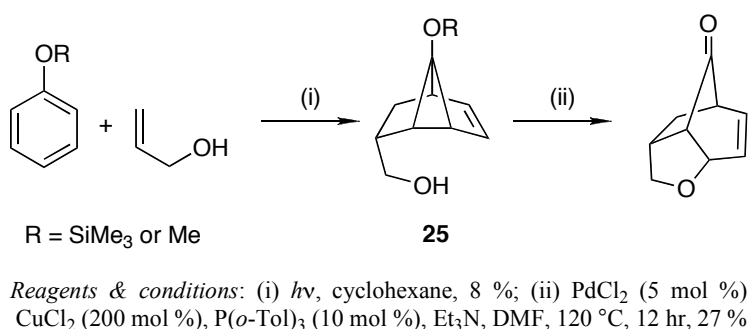
bearing a chiral hydrocarbon  $\pi$ -allyl ligand to induce enantioselectivity in the cyclisation of *trans*-2-(2-butenyl)phenols with efficacious results. The studies presented by Stoltz and Hosokawa would suggest that the palladium catalysed asymmetric cyclisation of **30** has not fully been investigated, and a greater survey of chiral ligands would be advantageous.

### 2.3 Conclusion

The discovery of the unique tricyclic ether **29** gave validity to the proposed novel  $\pi$ -allyl palladium intermediate within the Heck cross-coupling of an aryl-halide to a meta photocycloadduct. This in turn led to the realisation that this novel  $\pi$ -allyl palladium intermediate could be exploited *via* a *meso*  $\pi$ -allyl palladium species to induce enantioenrichment of the cyclised product. Unfortunately attempts to bring about enantioenrichment with homochiral ligands have failed thus far.

### 3. Towards the synthesis of a conformationally constrained bicyclic amino acid.

The novel palladium catalysed fragmentation/cyclisation of the meta photocycloadduct **25** as discussed in chapter 2, gave rise to an architecturally complex tricyclic intermediate in just two synthetic operations (Scheme 3.0).



Scheme 3.1. Palladium catalysed fragmentation/cyclisation.

This important result led us to speculate whether a heteroatom other than oxygen could be used to affect the same result. We postulated that the use of nitrogen as the heteroatom in the meta photocycloaddition reaction could lead to the formation of a pyrrolidine ring upon palladium induced cyclisation, reductive removal of the ketone moiety and oxidative olefin cleavage, would ultimately afford a bicyclic amino acid shown in Figure 3.0. The power of the meta photocycloaddition reaction would be demonstrated in this process as a highly complex and potentially very useful molecule could be prepared in a very efficient manner, which could then be converted into a conformationally constrained amino acid in an expedient manner.

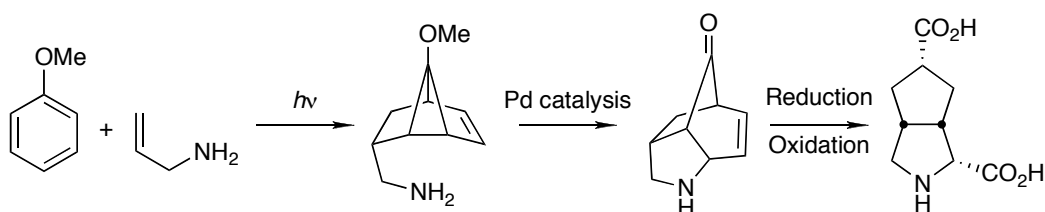
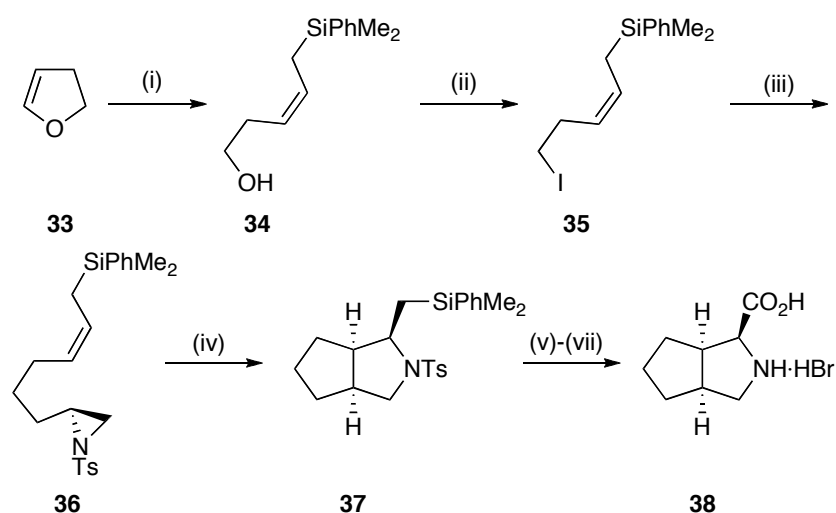


Figure 3.0. Proposed synthesis of amino acid.

Conformationally constrained amino acids are an important class of organic compounds, both natural and unnatural. The use of unnatural amino acids in the synthesis of drug-like targets and peptidomimetics has risen exponentially over the last ten years<sup>46,47</sup>. The conformational constraint of such amino acids, especially bicyclic analogues where the nitrogen is incorporated within the ring system, often gives rise to increased biological activity and metabolic stability<sup>48</sup> and as such, find an important role within pharmacological assays<sup>48</sup>.

A multitude of synthetic methods exist in constructing bicyclic conformationally constrained amino acids, one such example which closely resembles our own synthetic target was demonstrated by Bergmeier *et al.*<sup>49</sup> with the synthesis of bicyclic proline analogues *via* an intramolecular 3 + 2 aziridine-allylsilane cycloaddition reaction (Scheme 3.1).



*Reagents & conditions:* (i)  $\text{PhMe}_2\text{SiCH}_2\text{MgCl}$ , then [1,2-bis( $\text{Ph}_2\text{P}$ )ethane]  $\text{NiCl}_2$  (10 mol %), benzene, reflux, 10 hrs, 77%; (ii) *p*-toluenesulfonyl chloride,  $\text{Et}_3\text{N}$ , DMAP (cat.), 0 °C, then NaI, acetone, reflux, 2hrs, 81 % over two steps; (iii) *t*BuLi,  $\text{Et}_2\text{O}$ , -78 °C to RT, 1 hr, then CuI/*n*-Bu<sub>3</sub>P, -78 °C to -40 °C, 40 mins, then (*R*)-(1-tosylaziridin-2-yl)methyl 4-methylbenzenesulfonate, -78 °C, 1 hr, 70 %; (iv)  $\text{BF}_3 \cdot \text{OEt}_2$  (15 mol %),  $\text{CH}_2\text{Cl}_2$ , 0 °C, 1 hr, 65 %; (v)  $\text{Hg}(\text{OAc})_2$ , AcOH, EtOH,  $\text{CH}_3\text{CO}_3\text{H}$ , 0 °C, 3 hrs, 79 %; (vi)  $\text{NaIO}_4$ ,  $\text{CCl}_4$ , MeCN,  $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ , RT, 18 hrs, 69 %; (vii) HBr/AcOH, phenol, RT, 24 hrs, 100%.

Scheme 3.1. Bergmeier aziridine-allylsilane cycloaddition.

The requisite aziridine was synthesised from the readily available dihydrofuran **33** *via* ring opening of the furan with dimethylphenylsilyl magnesium chloride in the presence of a nickel catalyst to afford the alcohol **34** in 77% yield. Tosylation and subsequent treatment of the tosylated product with NaI gave the precursor to aziridine formation, **35**

in 81% yield. The resulting iodide underwent metal halogen exchange to give an organolithium which was in turn converted to an organo cuprate. This was reacted with an aziridiny methyl tosylate to afford the required aziridine-allylsilane **36** in 70% yield. The system was now set to perform the intramolecular 3 + 2 aziridine-allylsilane cycloaddition reaction, which commenced with the treatment of **36** with  $\text{BF}_3 \cdot \text{OEt}_2$  in dichloromethane to obtain the diastereomerically pure bicyclic amine **37** in a respectable 65% yield. Oxidation of the silyl group with mercuric(II) acetate<sup>1</sup>, afforded the alcohol, which was oxidised further and deprotected, to give the amino acid salt **38** in 100% yield.

The structural motif of the pyrrolidine moiety is also found in the important neuronal excitatory amino acids, kainic acid **39** and domoic acid **40** (Figure 3.1).

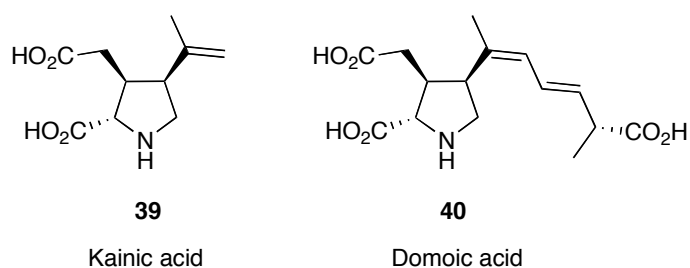
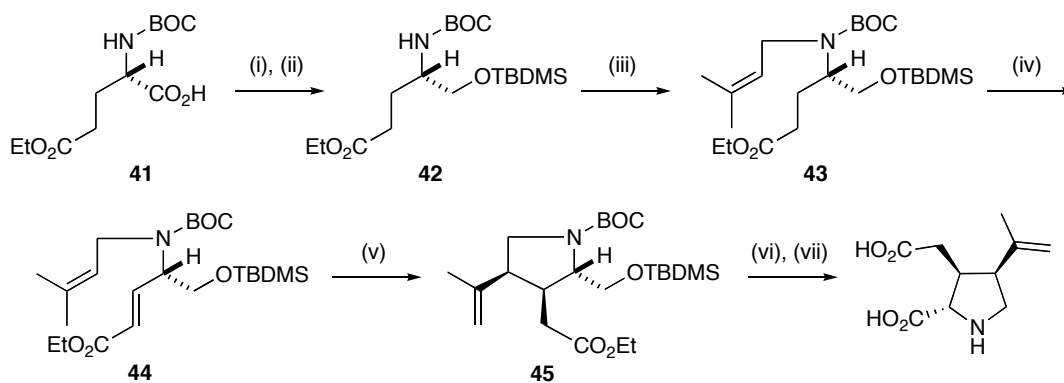


Figure 3.1. kainic acid and domoic acid.

The biological activity rests in the stereochemical configuration of the acids, and to that end, enantioselective syntheses are required to achieve the desired stereochemical outcome. The first enantioselective synthesis of (-)- $\alpha$ -kainic acid was reported by Oppolzer and Thirring<sup>50</sup> utilising an intramolecular thermal type I ene reaction of the 1,6 diene **44** to afford the ring closed product **45**. The synthesis of the 1,6 diene commenced from the optically pure carbamate **41** (Scheme 3.2).

<sup>1</sup> Fleming-Tamao oxidation. Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc. Perkin Trans.* **1995**, *1*, 317.



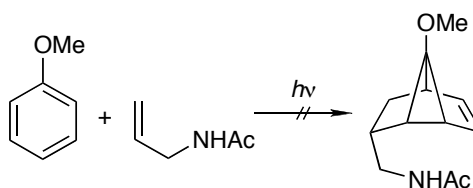
*Reagents & conditions:* (i)  $\text{BH}_3$ , THF,  $-15\text{ }^\circ\text{C}$ , 13 hrs, 57 %; (ii)  $t\text{-Bu}(\text{Me})_2\text{SiCl}$ ,  $\text{Et}_3\text{N}$ , DMAP (cat.),  $\text{CH}_2\text{Cl}_2$ , RT, 3 d, 92 %; (iii)  $\text{NaH}$ , 1-bromo-3-methyl-2-butene, HMPA,  $0\text{ }^\circ\text{C}$ , 1 hr, then RT, 16 hrs, 77 %; (iv) a. lithium 2,2,6,6-tetramethyl-piperidide, THF,  $-78\text{ }^\circ\text{C}$ , 45 mins; b.  $\text{PhSeCl}$ ,  $-78\text{ }^\circ\text{C}$  to RT; c. 30 % aq.  $\text{H}_2\text{O}_2$ , pyridine,  $\text{CH}_2\text{Cl}_2$ , RT, 15 mins, 48 %; (v) toluene,  $130\text{ }^\circ\text{C}$ , 40 hrs, 70 %; (vi) a. TBAF, THF, RT, 1 hr; b. Jones' reagent, acetone,  $0\text{ }^\circ\text{C}$ , 20 mins, 60 %; (vii) a.  $\text{LiOH}$ ,  $\text{MeOH}/\text{H}_2\text{O}$  (3:1), RT, 40 hrs; b. pH 2, evaporation; c.  $\text{CF}_3\text{CO}_2\text{H}/\text{CHCl}_3$  (1:1),  $0\text{ }^\circ\text{C}$ , 1 hr; d. ion-exchange resin, 56 %.

Scheme 3.2. Enantioselective synthesis of (-)- $\alpha$ -kainic acid.

Selective reduction of the carboxylic acid with diborane, and subsequent silylation of the primary alcohol, prevented thermal olefin migration as observed previously by the group. The amide **42** was alkylated with 1-bromo-3-methyl-2-butene to afford the saturated ester **43** in 77% yield. Deprotonation of the ester with lithium TMP, selenation of the enolate and subsequent oxidation of the selenide species, afforded the  $\alpha$ - $\beta$ -unsaturated ester in 48% yield. With the precursor **44** to the intramolecular thermal ene reaction in hand, heating a 5% solution in toluene at  $130\text{ }^\circ\text{C}$  for 40 hrs gave the pyrrolidine moiety **45** in 75% yield. Removal of the silicon protecting group and oxidation with Jones' reagent gave the acid and final saponification of the ester gave (-)- $\alpha$ -Kainic acid in 56% yield.

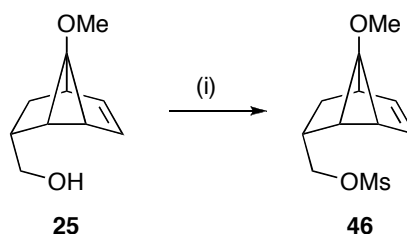
The important biological attributes of conformationally constrained amino acids and the natural products, kainic acid and domoic acid, led us to postulate the possibility of our own analogue exhibiting similar traits. With this in mind studies<sup>51</sup> within our group commenced towards the meta photocycloaddition between allyl amine and anisole. Previous work reported by Gilbert *et al.*<sup>52</sup>, showed that an intramolecular meta photocycloaddition of a tethered allyl amine to an aryl ring generally failed due to single electron transfer from the free amine to the arene exciplex, effectively quenching the reaction. The solution was to protect the nitrogen as the *N*-acetyl or *N*-carbomethoxy derivative that afforded the meta photocycloaddition product. This

important piece of data led to the use of *N*-allylethanamide as the photocycloaddition partner with anisole (Scheme 3.3).



Scheme 3.3. Meta photocycloaddition reaction between allylamine and anisole.

Unfortunately all attempts at photolysis to gain the nitrogen analogue of the meta photocycloadduct resulted in failure. Attentions were then focused on the meta photocycloadduct **25** derived from allyl alcohol and anisole. The decision to use the 7-*endo* meta photocycloadduct lay with the presence of the hydroxyl group, which could be derivatised to the required amine functionality. It was proposed that conversion of the alcohol to a leaving group and subsequent displacement with a suitable aminos nucleophile would provide the amine. Thus, mesylation of the 7-*endo* meta photocycloadduct using diisopropylethylamine and methanesulfonylchloride afforded the mesylate **46** in good yield (Scheme 3.4).

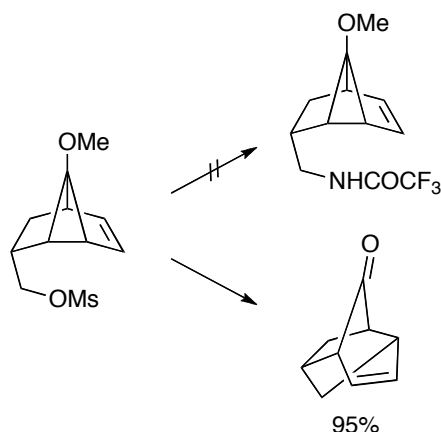


Reagents & conditions: (i) MsCl, EtN(*i*Pr)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 75%.

Scheme 3.4.

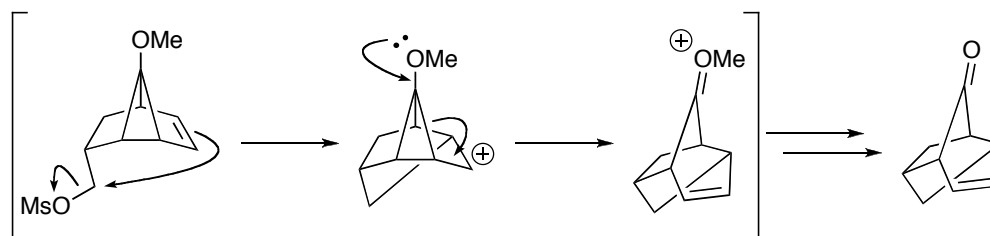
Initially trifluoroacetamide was chosen as the nucleophile in order to provide a protected amide before carrying out the palladium catalysed fragmentation/cyclisation reaction, as it was felt the free amine would coordinate with the catalyst, and interfere with the reaction. Deprotonation of the acetamide with NaH and addition of the mesylate unfortunately did not result in the desired acetamide. Instead an internal

displacement of the mesylate had taken place to afford the intramolecular fragmentation/cyclisation product (Scheme 3.5).



Scheme 3.5. Novel intramolecular displacement/fragmentation.

The explanation for this result lay in the close proximity of the highly electron rich alkene with the carbon atom bearing the mesylate group. Hence displacement of the leaving group generated a cyclopropyl carbinyl cation, which then underwent fragmentation to give the tricyclic ketone shown in scheme 3.6.



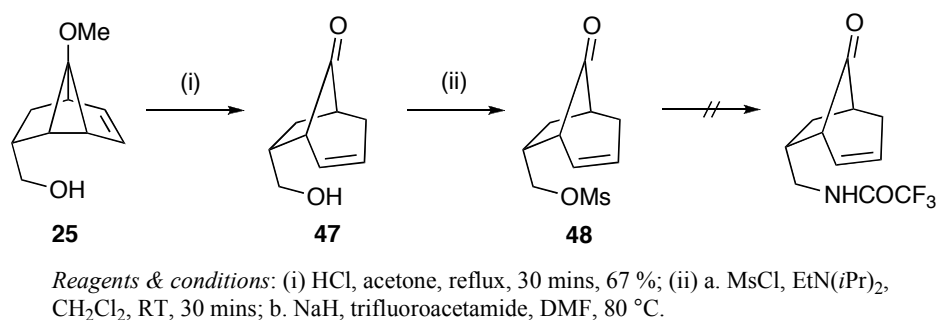
Scheme 3.6. Mechanism of displacement / fragmentation reaction.

Although the intramolecular fragmentation/cyclisation reaction was very intriguing, it did not provide the requisite amine functionality to push forward with the synthetic route and hence an alternative strategy was sought.



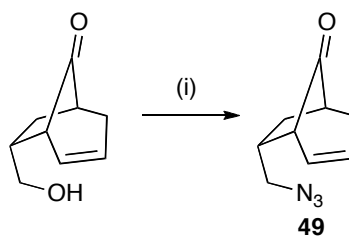
### 3.1 Results and discussion

Reviewing the unwanted fragmentation pathway, it was clear that the presence of the highly strained cyclopropane ring of the 7-*endo* metaphotocycloadduct **25** was causing the undesired side reaction. The ability of the meta photocycloadducts to undergo electrophilic induced fragmentation has been well documented<sup>38</sup> with a variety of electrophiles, such as  $H^+$ ,  $Br^+$  and carbon based electrophiles, as seen within our own groups research<sup>39</sup>. Fragmentation of the cyclopropane ring would effectively remove the intramolecular displacement pathway, and hence allow derivatisation of the hydroxyl group to the amine. Treatment of the 7-*endo* metaphotocycloadduct **25** with HCl in refluxing acetone cleanly gave the hydroxy ketone **47** in 67% yield and subsequent treatment with mesyl chloride with Hünig's base afforded the mesylate compound **48** that was reacted with the sodium salt of trifluoroacetamide (Scheme 3.9).



Scheme 3.9. Acid induced fragmentation and subsequent steps towards the amide.

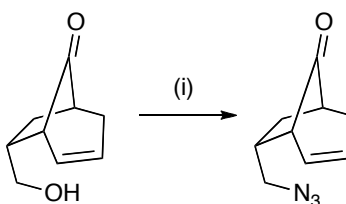
Displacement of the mesylate with the sodium salt of trifluoroacetamide only resulted in hydrolysis of the mesylate to reform the alcohol. As an alternative sodium azide was chosen as the nucleophile as it would allow for the installation of an amine functionality after reduction of the azide intermediate. This was achieved by reacting the resulting mesylate of the alcohol with sodium azide in DMF (Scheme 3.1.0).



*Reagents & conditions:* (i) a.  $\text{MsCl}$ ,  $\text{EtN}(\text{iPr})_2$ ,  $\text{CH}_2\text{Cl}_2$ ; b.  $\text{NaN}_3$ , DMF,  $80^\circ\text{C}$ , 30 %.

Scheme 3.1.0. Mesylation and displacement with  $\text{NaN}_3$ .

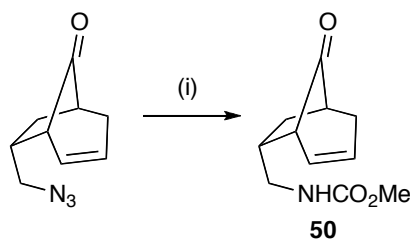
The formation of the mesylate proceeded smoothly at room temperature in 30 mins, though subsequent displacement with sodium azide was sluggish and poor yielding even at elevated temperatures. The disappointing yields of the displacement step were improved by replacing the mesylate with the more reactive trifluoromethanesulfonate and utilising 15-crown-5 ether<sup>53</sup> to complex the sodium ion and thereby greatly increase the reactivity of the azide anion. These modifications allowed for the formation of the azide **49** in a far more efficient 62% yield (Scheme 3.1.1).



*Reagents & conditions:* (i) a.  $\text{Tf}_2\text{O}$ , pyridine,  $\text{CH}_2\text{Cl}_2$ ; b.  $\text{NaN}_3$ , 15-crown-5, DMF, RT, 62 %.

Scheme 3.1.1. Triflation and displacement with  $\text{NaN}_3$ .

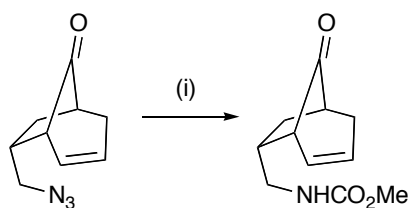
The reduction of the azide was less trivial than expected. The standard Staudinger<sup>54</sup> reaction failed on all accounts, the use of trimethylphosphine<sup>55</sup> and concomitant quenching of the reaction with methyl chloroformate (Scheme 3.1.2), furnished the required carbamate **50**, although the result was irreproducible.



*Reagents & conditions:* (i)  $\text{PMe}_3$ , THF, RT, 30 mins, then methylchloroformate, 30 mins, 27 %.

Scheme 3.1.2. Reduction of the azide with  $\text{PMe}_3$ .

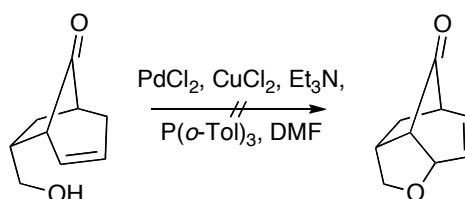
Attempted reduction of the azide using  $\text{NaBH}_4$ , zinc- $\text{NH}_4\text{Cl}$ <sup>56</sup> and  $\text{SnCl}_2$ <sup>57</sup>, all resulted in the recovery of starting material. However, the azide was finally reduced to the carbamate by the use of Lindlar's catalyst<sup>58</sup> in EtOH and treatment of the crude material with methylchloroformate (Scheme 3.1.3).



*Reagents & conditions:* (i) Lindlar's catalyst, EtOH,  $\text{H}_2$  (1 atm), RT, 12 hrs, then methylchloroformate, 30 mins, 51%.

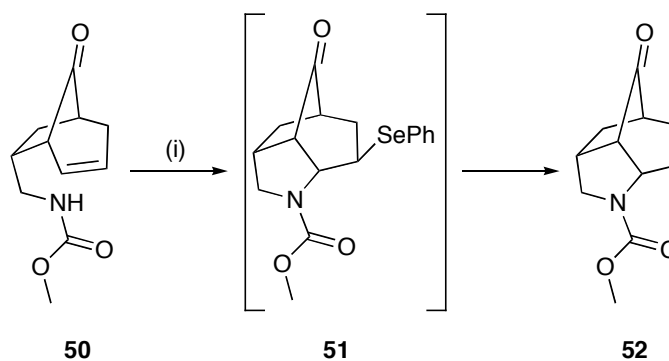
Scheme 3.1.3. Reduction of the azide with Lindlars catalyst & carbamate formation.

The palladium catalysed cyclisation to form the pyrrolidine ring, was initially attempted on the alcohol analogue as a model system. The alcohol **47** was treated with palladium(II) chloride, copper(II) chloride,  $\text{Et}_3\text{N}$  and tri-*ortho*-tolylphosphine in DMF, however only starting material was recovered (Scheme 3.1.4).



Scheme 3.1.4. Failed palladium catalysed cyclisation.

The reaction was also carried out on the real system, as it was known that cyclisation of urethanes could be achieved with the use of a palladium catalyst<sup>59</sup>, utilising the conditions *vida supra* and also aerobic oxidative conditions (PdCl<sub>2</sub>[MeCN]<sub>2</sub>, O<sub>2</sub>, Et<sub>3</sub>N, CuCl<sub>2</sub>) but again, only starting material was recovered. With this disappointing result, our strategy turned toward the use of selenium to induce cyclisation, in particular Nicolau's<sup>60</sup> *N*-(phenylseleno)phthalimide (NPSP) was chosen as a mild alternative to phenylselenenyl chloride and shown to be effective in urethane cyclisation. Thus treatment of the carbamate **50** with NPSP and catalytic CSA in dichloromethane afforded the cyclised selenide **51**, which was oxidised *in situ* to afford the alkene **52** (Scheme 3.1.5).



*Reagents & conditions:* (i) *N*-(phenylseleno)phthalimide, CSA (cat.), CH<sub>2</sub>Cl<sub>2</sub>, 30 mins, then MMPP, 30 mins, 67 %.

Scheme 3.1.5. Selenium induced cyclisation.

The reaction proceeded well on a small scale, though upon scale up of the chemistry, the yield dropped to such an extent that we had to recourse to the use of phenylselenenyl chloride to effect cyclisation. Treatment of the carbamate **50** with phenylselenenyl chloride in the presence of base and catalytic SiO<sub>2</sub> afforded the cyclised product, which again was oxidised *in situ* to give the alkene **52** in 71% yield.

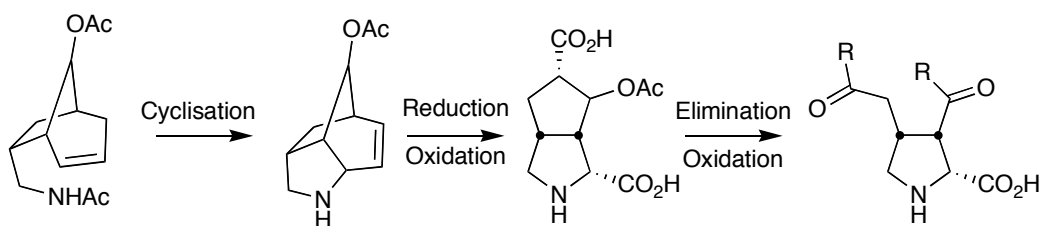
The removal of the bridgehead ketone utilising the Huang-Minlon modified Wolff-Kishner<sup>61</sup> reduction disappointingly led to decomposition of starting material. Performing the Wolff-Kishner reduction, prior to manipulation of the alcohol within the synthesis, also resulted in decomposition of starting material. The Wolff-Kishner reaction is generally the most effective method for reducing ketones to a methylene group, although it would seem with our synthetic route, the strong basic conditions

proved too harsh for the system. Due to time restrictions, the oxidative cleavage of the olefin was sadly not investigated, although the use of  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$  and  $\text{NaIO}_4$  to effect oxidative cleavage to the diacid is well documented<sup>62</sup> and hopefully would not pose a problem to the synthetic route.

In conclusion, the synthesis towards a conformationally constrained amino acid *via* the meta photocycloaddition reaction did not prove to be a trivial task. Instead an alternative route utilising proven standard chemical techniques was utilised which afforded the pyrrolidine ring in good yield.

### 3.2 Future scope

The removal of the ketone prior to oxidative ring closure could be achieved *via* reduction using a hydride source such as  $\text{LiAlH}_4$ . This could in theory be utilised to reduce both the azide and ketone to the amine and alcohol groups respectively in one step, with concomitant protection of both as the acetamide and acetate. The inclusion of the protected alcohol would provide extra synthetic potential after oxidative cleavage to provide access to analogues of the conformationally constrained amino acid, for example elimination of the  $\beta$ -acetoxy acid would afford the alkene that could be oxidatively cleaved to provide a route to kainic acid analogues.

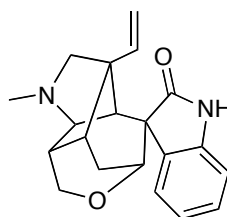


Scheme 14. Synthetic potential towards analogues of kainic acid.

#### 4. Studies towards the total synthesis of (±) Gelsemine.

The alkaloid gelsemine was first isolated from *gelsemium sempervirens* in 1870.<sup>63</sup> Although the molecular formula was known by 1910, it was not until 1959 that the structure of gelsemine was elucidated by Conroy and Chakrabati<sup>64</sup> through degradative and spectroscopic studies available at that time. Simultaneously, Lovell *et al.*<sup>65</sup> had proven the structure of gelsemine *via* crystallographic methods, which verified Conroy and Charkrabarti's findings.

The structure of gelsemine (Figure 4.0.) has attracted the attention of synthetic organic chemists ever since the complex molecular architecture was resolved in 1959. In essence, gelsemine consists of a fused hexacyclic skeleton containing a core bicyclo[3.2.1]octane substructure with two key quaternary centres, and a pyrrolidine and tetrahydropyran ring.



Gelsemine

Figure 4.0.

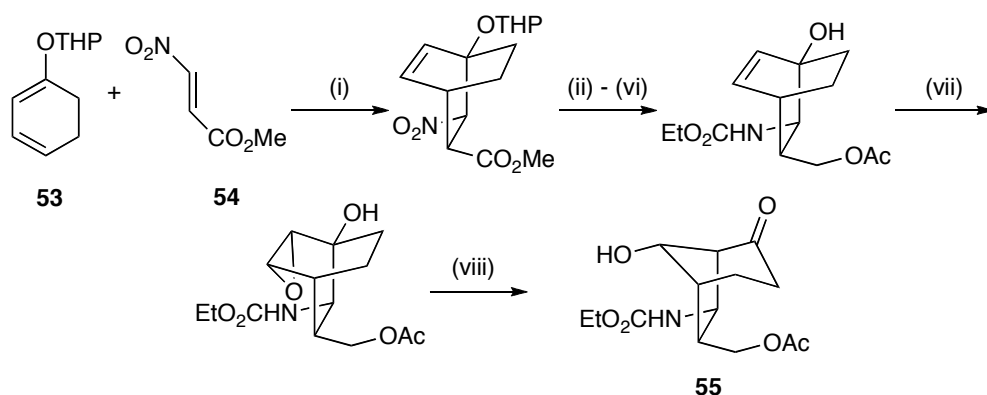
Gelsemine's biological activity is primarily CNS depression,<sup>66</sup> although it has found little use within the pharmaceutical industry. The attraction to the total synthesis of gelsemine relies on the fascinating three-dimensional structure, with seven total syntheses completed to date.<sup>67</sup> From these seven total syntheses a wealth of novel chemical techniques has arisen that have been utilised in other complex natural product syntheses.

The total synthesis of gelsemine can be divided into four main strategic areas, with each representing the different functionalities present within the molecule. The four areas are: construction of the bicyclo[3.2.1]octane skeleton, formation of the pyrrolidine ring

with key quaternary centre, introduction of the spirooxindole moiety and finally the construction of the tetrahydropyran ring. A summary of the main synthetic strategies by various groups will now be presented.

#### 4.1 Formation of the bicyclo[3.2.1]octane skeleton.

The approach by Fleming *et al.*<sup>68</sup> utilised a Diels-Alder reaction to access a functionalised bicyclo[2.2.2]octane skeleton, whereupon epoxidation and concurrent ring expansion gave the bicyclo[3.2.1]octane structure (Scheme 4.0).

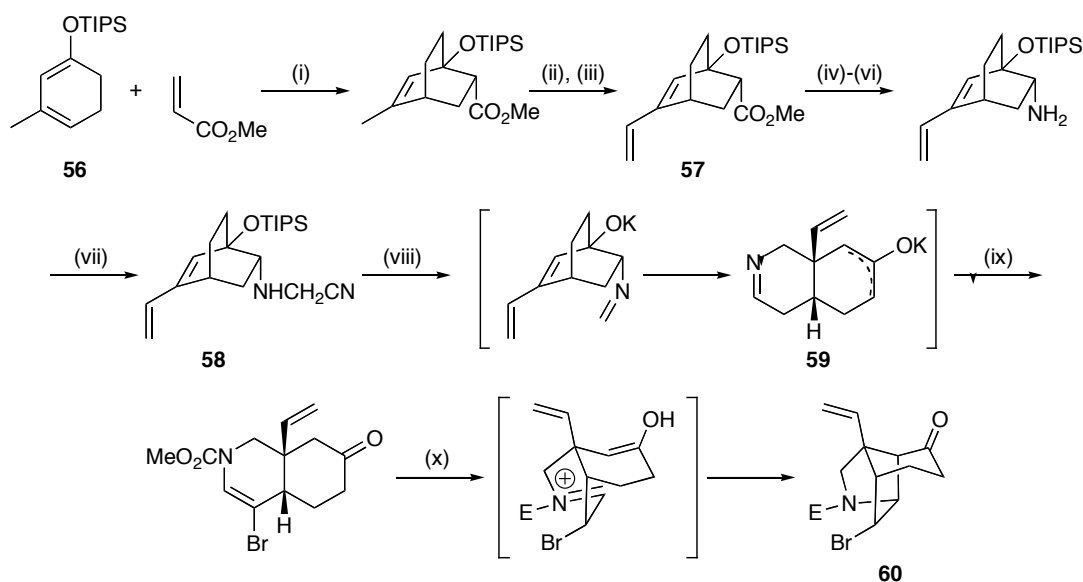


*Reagents & conditions:* (i) pyrogallol (cat.), benzene, 0 °C-RT, 43%; (ii) Al/Hg, MeOH; (iii) EtO<sub>2</sub>CCl, Et<sub>3</sub>N; (iv) LiAlH<sub>4</sub>; (v) AcCl, Et<sub>3</sub>N; (vi) PPTS, EtOH, 81% over 5 steps; (vii) *p*-nitro-perbenzoic acid, CH<sub>2</sub>Cl<sub>2</sub>, 85%; (viii) MgBr<sub>2</sub>, Et<sub>2</sub>O, benzene/THF, 78%.

Scheme 4.0. Fleming's approach to the bicyclo[3.2.1]octane skeleton.

The Diels-Alder reaction was carried out with the diene **53** and  $\beta$ -nitroacrylate **54**, to afford the bicyclo[2.2.2]octane along with an isomer in which the nitro group had the *exo* configuration. Reduction of the nitro group to the amine, and protection as the ethyl carbamate was conducted to rule out the possibility of a retro-Henry reaction. The ester function was reduced to the alcohol and protected as the acetate and the tetrahydropyranyl group was removed under acid-catalysed conditions. Epoxidation was carried out to obtain the *endo* epoxide, which was treated with MgBr<sub>2</sub> to afford the bicyclo[3.2.1]octane skeleton **55**, with the stereochemistry and functionality present required for further elaboration.

The strategy employed by Overman *et al.*<sup>69</sup> also utilised a Diels-Alder approach to form a bicyclo[2.2.2]octane skeleton, though the key step was an *N*-acyliminium Mannich cyclisation which led to the azatricyclo[4.4.0.0<sup>2,8</sup>]decane **60** substructure of gelsemine (Scheme 4.1).



*Reagents & conditions:* (i)  $\text{AlCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 80%; (ii)  $\text{SeO}_2$ , dioxane,  $100^\circ\text{C}$ ; (iii)  $\text{Ph}_3\text{P}=\text{CH}_2$ , THF,  $-78^\circ\text{C}$  -  $0^\circ\text{C}$ , 62-90% over two steps; (iv)  $\text{KOH}$ ,  $\text{EtOH}/\text{H}_2\text{O}$ ,  $90^\circ\text{C}$ ; (v) a.  $(\text{ClCO})_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; b.  $\text{NaN}_3$ , acetone/ $\text{H}_2\text{O}$ ; c. toluene, reflux; (vi)  $\text{KOH}$ , dioxane/ $\text{H}_2\text{O}$ ,  $23^\circ\text{C}$ , 64% over three steps; (vii) a.  $\text{ClCH}_2\text{CN}$ ,  $\text{Bu}_4\text{NI}$  (2 mol%),  $i\text{Pr}_2\text{NEt}$ , THF,  $67^\circ\text{C}$ ; b.  $\text{Bu}_4\text{NF}$ , THF,  $0^\circ\text{C}$ , 90%; (viii) a.  $\text{KH}$ , 18-crown-6, THF, RT; b.  $\text{ClCO}_2\text{Me}$ , DTBMP,  $-78^\circ\text{C}$  - RT; c.  $\text{KOH}$ ,  $\text{MeOH}$ ,  $\text{H}_2\text{O}$ , RT, 81%; (ix)  $\text{Br}_2$ , 1,2,2,6,6-pentamethylpiperidine,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; (x) TFA, reflux, 67% over two steps.

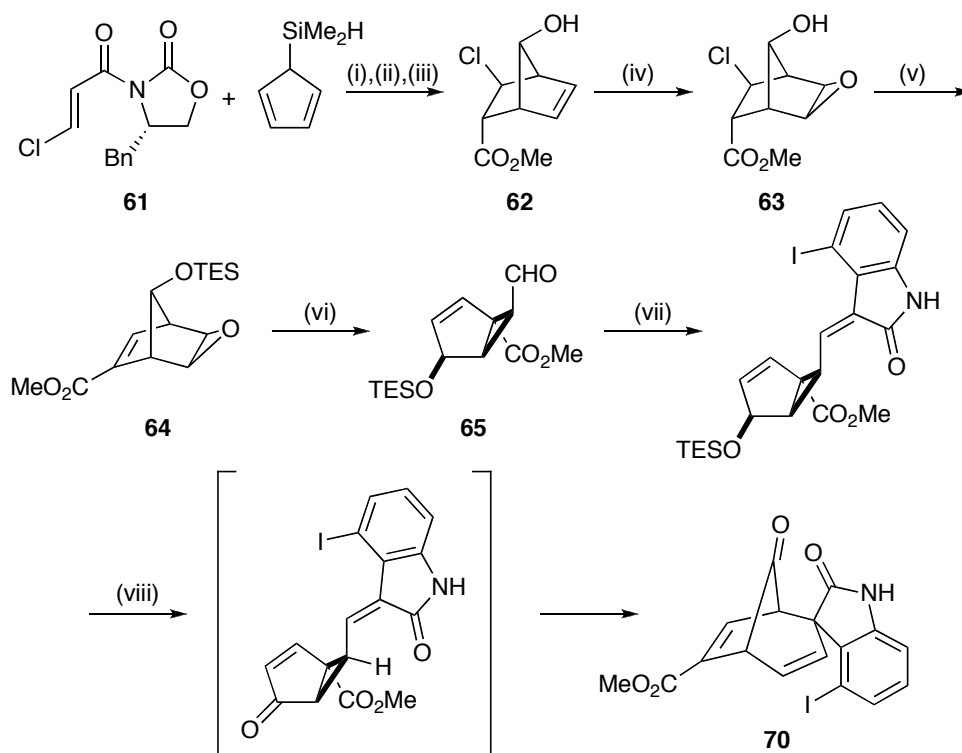
Scheme 4.1. Overman's synthesis of the azabicyclo skeleton.

A simple Diels-Alder reaction of 1-alkoxy-1,3-cyclohexadiene **56** and methyl acrylate provided the bicyclo[2.2.2]octane skeleton with high stereoselectivity (*endo exo* 10:1). Allylic oxidation of the methyl group with selenium dioxide followed by Wittig methylenation, afforded the terminal alkene **57**. A Curtius rearrangement gave the amine which was alkylated to the cyanomethylamine **58**. Desilylation was then carried out followed by the key anionic [3,3]-sigmatropic hydroxy-aza-Cope rearrangement catalysed with excess  $\text{KH}$ . The imine enolate **59** was then alkoxy-carbonylated at both heteroatoms by quenching with excess methyl chloroformate, followed by selective cleavage of the carbonate to afford the bicyclic keto enecarbamate in 81% yield. With the *cis*-hydroisoquinoline in hand, the enecarbamate was selectively brominated and the resulting bromide heated at reflux to elegantly provide the azatricyclo[4.4.0.0<sup>2,8</sup>]decane skeleton **60** as a single diastereoisomer in 67% yield.



The formation of the azatricyclo[4.4.0.0<sup>2,8</sup>]decane ring system was achieved from the readily available 3-methylanisole in 12 steps and 16% overall yield.

A different approach to the bicyclo[3.2.1]octane skeleton was reported by the groups of Fukuyama<sup>70</sup> and Danishefsky<sup>71</sup> via the use of a divinylcyclopropane rearrangement. Fukuyama's work was also the first enantioselective total synthesis of gelsemine. The enantioselective route began with an asymmetric Diels-Alder reaction of the dienophile **61** and 5-dimethylsilylcyclopentadiene (Scheme 4.2).



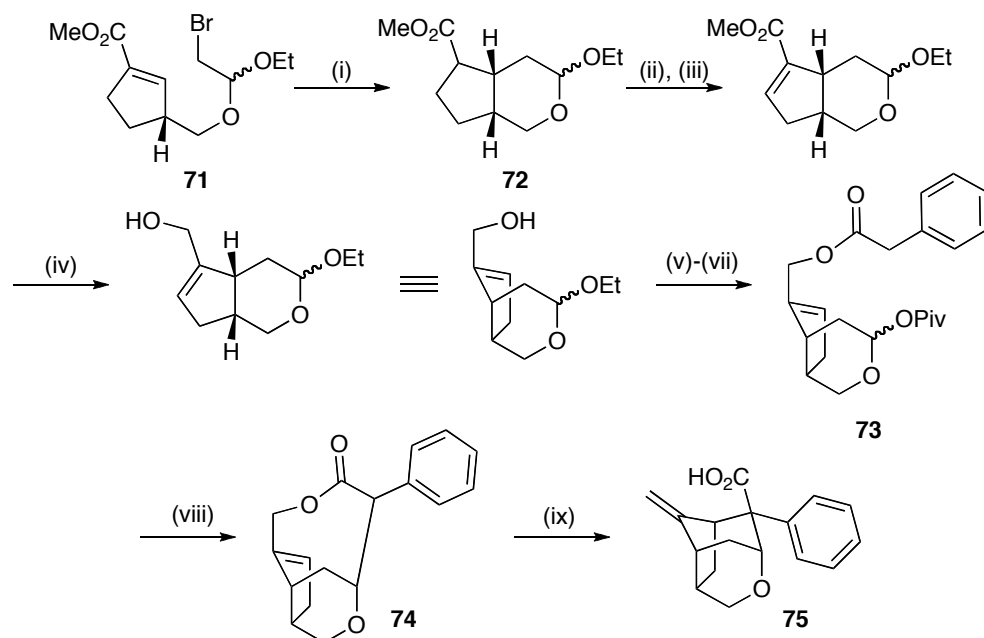
*Reagents & conditions:* (i)  $\text{Et}_2\text{AlCl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 88%; (ii)  $\text{Sm}(\text{OTf})_3$  (cat.), MeOH, 99%; (iii) 30%  $\text{H}_2\text{O}_2$ , KF,  $\text{KHCO}_3$ , THF/MeOH, 53%; (iv)  $\text{VO}(\text{acac})_2$ ,  $t\text{BuOOH}$ , benzene, 100%; (v) a.  $\text{TESOTf}$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ , 97%; b.  $t\text{BuOK}$ , benzene, 98%; (vi) MAD, toluene,  $-20^\circ\text{C}$ ; (vii) 4-iodooxindole, piperidine (cat.), MeOH, 60% (over two steps); (viii) TBAF, THF, 87%;  $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ , acetone, then toluene/MeCN, 83% (over two steps).

Scheme 4.2. Fukuyama's enantioselective synthesis of bicyclo[3.2.1]octane skeleton.

The asymmetric Diels-Alder was carried out in the presence of  $\text{Et}_2\text{AlCl}$  to afford the bicyclo[2.1.2]heptane **62**, with the relative and absolute configurations confirmed *via* X-ray crystallography. The chiral auxiliary was removed with  $\text{Sm}(\text{OTf})_3$  in MeOH and the dimethylsilyl group was oxidised to the alcohol, before stereoselective epoxidation of the olefin with  $t\text{BuOOH}$  and  $\text{VO}(\text{acac})_2$  to afford the *exo* epoxide **63**. Treatment of

the epoxide with *t*BuOK gave the  $\alpha,\beta$ -unsaturated ester **64** in 98% yield. Then, Lewis acid catalysed rearrangement to the ester, afforded exclusively the  $\alpha$ -methyl ester cyclopropane moiety **65**. Stereoselective condensation of the aldehyde **65** and 4-iodooxindole gave the desired (*Z*)-alkylidene indolinone in 60% yield. The system was now set up to carry out the key divinylcyclopropane rearrangement. This was achieved *via* desilylation and concurrent Jones oxidation of the resulting alcohol to afford the bicyclo[3.2.1]octane skeleton, along with a isomeric *trans* pre-cursor. Fukuyama reported that the *cis-trans* isomerisation was of no consequence<sup>70</sup> as it was a key intermediate in their racemic approach to gelsemine. Heating the mixture of isomers at 90 °C afforded the enantiomerically pure key bicyclo[3.2.1]octane with spirooxindole substructure **70** in 83% yield.

Two different approaches to the bicyclo[3.2.1] core were reported by Stork *et al.*<sup>72</sup> and (as previously written in chapter 1), Penkett *et al.*<sup>9</sup>. The approach by Stork utilised two key transformations: a mixed acetal radical cyclisation and a sequential transannular alkylation – Claisen rearrangement (Scheme 4.3).

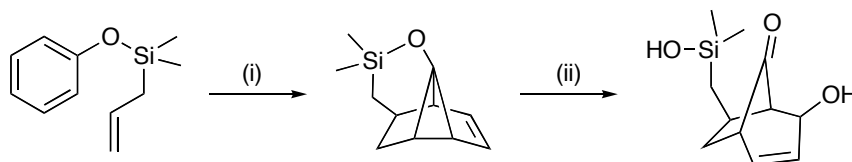


*Reagents & conditions:* (i) Bu<sub>3</sub>SnH, AIBN (cat. 0.02 M in benzene), reflux, 3 hrs, 95%; (ii) a. LDA, THF, -78 °C to -30 °C; b. -78 °C, PhSe-SePh, 93%; (iii) a. *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>, -40 °C, 1hr; b. Et<sub>3</sub>N, RT, 98%; (iv) DIBAL, Et<sub>2</sub>O, 0 °C, 1hr, 95%; (v) phenylacetic acid, DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, RT, 30 mins, 79%; (vi) Amberlite-H<sup>+</sup>, THF/H<sub>2</sub>O, (20:1), 1-2 hrs, 65 °C, 90%; (vii) PivCl, DMAP, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, RT, 1 hr, 85%; (viii) a. LDA, TMSCl, THF, -78 °C; b. diluted with CH<sub>2</sub>Cl<sub>2</sub>/THF (1:1) to 0.002 M, TMSOTf, -78 °C to -20 °C, 67%; (ix) LDA, TMSCl, THF -78 °C to RT, 24 hrs, 96%.

Scheme 4.3. Stork's synthesis of bicyclo[3.2.1]octane core.

The mixed acetal radical cyclisation on the bromide **71** provided the bicyclic ester **72** in 95% yield, which was transformed to the unsaturated ester *via* selenation and oxidative elimination. Reduction of the ester with DIBAL-H gave the allylic alcohol, which was converted to the phenylacetate **73**. The displacement potential of the ethoxy group was increased by conversion to the pivaloate ester. The precursor to the Claisen rearrangement was achieved *via* forming the trimethylsilyl ketene acetal, then inducing cyclisation with trimethylsilyl triflate, to afford the strained lactone **74**. Reaction of the lactone with LDA and TMSCl gave the silyl enol ether, which readily underwent the desired Claisen rearrangement to afford the acid **75** in 96% yield. This elegant route resulted in the formation of the key bicyclo[3.2.1]octane skeleton and the tetrahydropyran ring, with functionality present to construct the spirooxindole ring.

Penkett devised a novel route to the bicyclo[3.2.1]octane skeleton through the use of a silicon tethered alkene-arene meta photocycloaddition reaction as seen in chapter 2. Subsequent epoxidation and concomitant acid catalysed fragmentation, afforded the desired bicyclo ring system in 56% yield (Scheme 4.4).

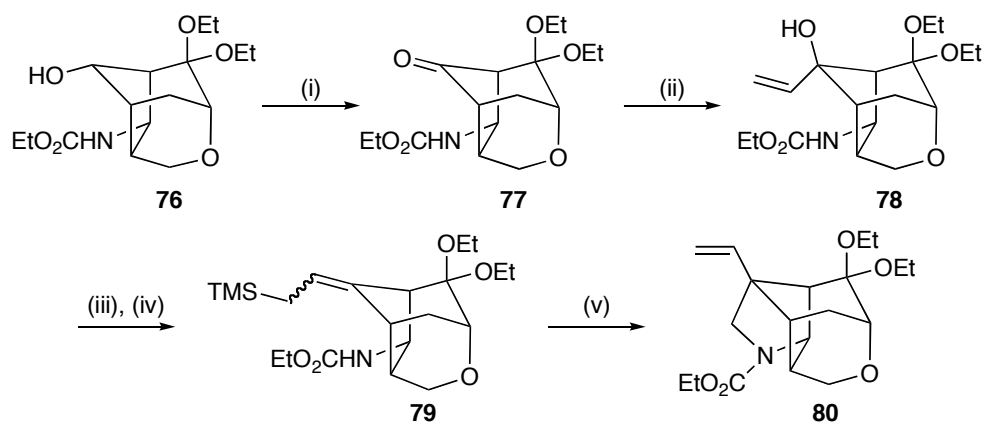


Reagents & conditions: (i)  $h\nu$ , 254 nm, hexane, 38%; (ii) *m*CPBA, 56%.

Scheme 4.4. Penkett's route to bicyclo[3.2.1]octane skeleton.

#### 4.1.2 Formation of the pyrrolidine ring & quaternary centre.

The formation of the pyrrolidine ring and quaternary centre has in the main been achieved as a consequence of a Diels-Alder approach to the bicyclo[3.2.1]octane skeleton, as exemplified by the work of Overman<sup>69</sup>, Speckamp<sup>73</sup>, Hart<sup>74</sup> and Cha<sup>75</sup>. It was only the work of Fleming, Danishefsky and Fukayama that the pyrrolidine ring had to be constructed at a latter stage in the synthesis. The approach by Fleming *et al.*<sup>68</sup> utilised an intramolecular 5-*endo-trig* cyclisation of an allylsilane with an acyliminium species (Scheme 4.5) based on a similar reaction by Hiemstra and Speckamp<sup>76</sup>.

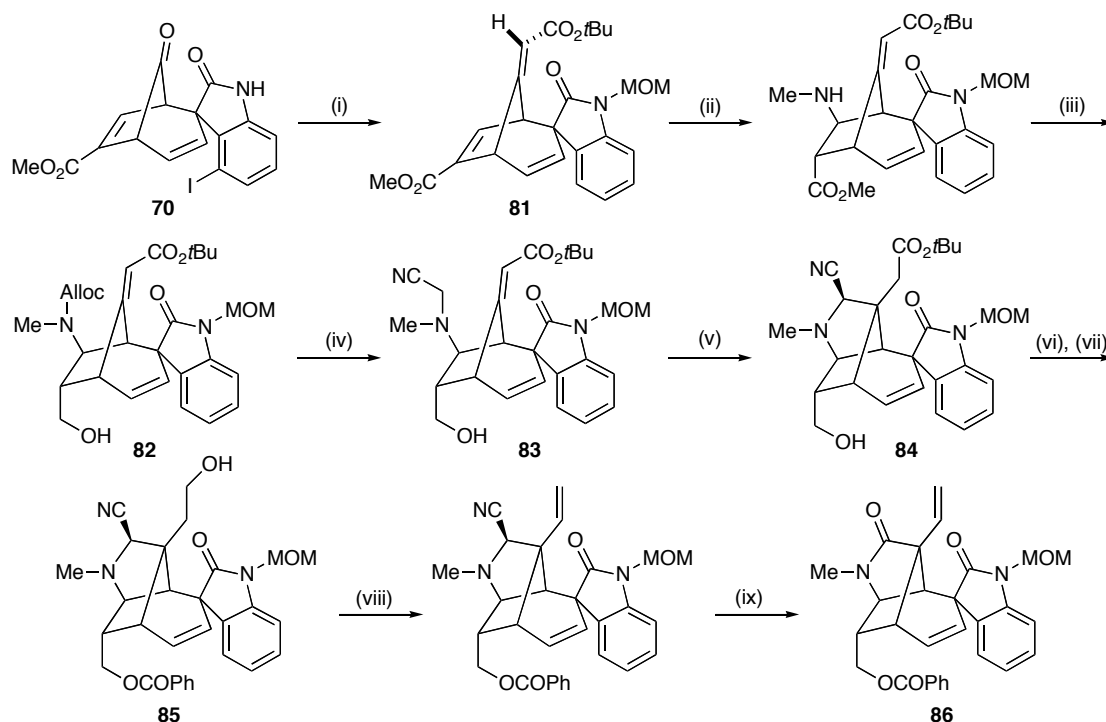


*Reagents & conditions:* (i) PCC, Al<sub>2</sub>O<sub>3</sub>, 91%; (ii) CH<sub>2</sub>=CHMgBr, 90%; (iii) SOCl<sub>2</sub>, 97%; (iv) (Me<sub>3</sub>Si)<sub>2</sub>CuLi, 84%; (v) (CH<sub>2</sub>O)<sub>3</sub>, HCO<sub>2</sub>H, 85%.

Scheme 4.5. Fleming's synthesis of the pyrrolidine ring.

The alcohol of **76** was oxidised with PCC, which was then subjected to a Grignard reaction with vinyl magnesium bromide to afford the allylic alcohol **78**. Treatment of the allylic alcohol with thionyl chloride gave the allylic chloride, which was transformed to the allylsilane **79** via silyl-cuprate addition in 84% yield. With the precursor to intramolecular cyclisation in hand, reaction with formaldehyde under acidic conditions afforded the pyrrolidine ring **80** with the vinyl group present at the crucial quaternary centre in 85% yield. Interestingly, Fleming had tried to access the allylsilane directly from the ketone **77** via a Wittig reaction, unfortunately without success.

Work by Fukuyama *et al.*<sup>70</sup> on their asymmetric approach to gelsemine focused on the optically pure ketone **70** (Scheme 4.6).



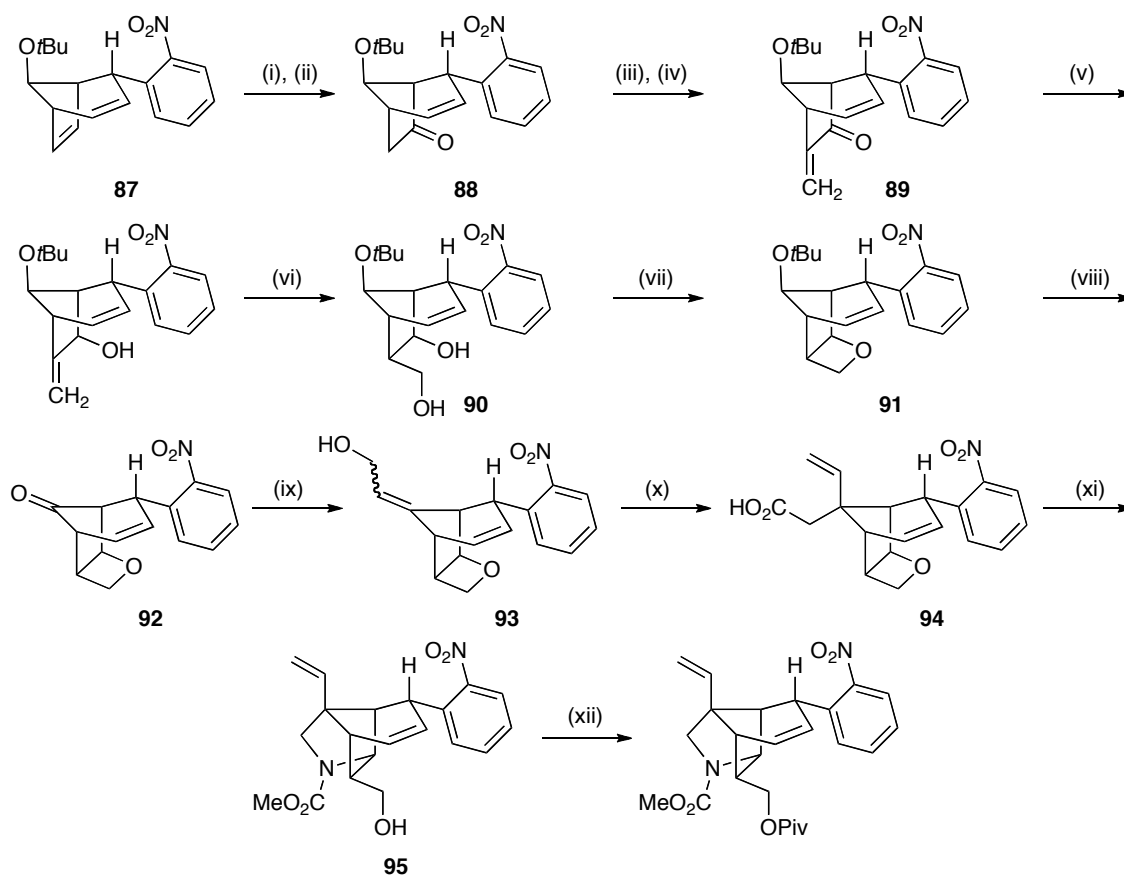
**Reagents & conditions:** (i) a.  $(\text{EtO})_2\text{POCH}_2\text{CO}_2t\text{Bu}$ ,  $n\text{BuLi}$ , THF, 65%; b. MOMCl,  $t\text{BuOK}$ , 72%; c.  $n\text{Bu}_3\text{SnH}$ , AIBN, benzene, reflux, 75%; (ii)  $\text{MeNH}_2$ ,  $\text{MeOH}$ , 100%; (iii) a. AllocCl, pyridine, DMAP (cat.),  $\text{CH}_2\text{Cl}_2$ , 94%; b.  $\text{LiBH}_4$ ,  $\text{LiBEt}_3\text{H}$  (cat.), THF, 94%; (iv) a.  $\text{Pd}(\text{PPh}_3)_4$ , pyrrolidine, THF;  $\text{ICH}_2\text{CN}$ ,  $i\text{Pr}_2\text{NEt}$ , MeCN, 78% over two steps; (v) KHMDS, THF,  $-78^\circ\text{C}$  to  $0^\circ\text{C}$ , 62%; (vi)  $\text{PhCOCl}$ , pyridine, DMAP (cat.),  $\text{CH}_2\text{Cl}_2$ , 92%; (vii)  $\text{HCO}_2\text{H}$ , 96%;  $\text{ClCO}_2\text{Et}$ ,  $\text{NEt}_3$ , THF, then  $\text{NaBH}_4$ ,  $\text{H}_2\text{O}$ , 80%; (viii) a.  $o\text{-NO}_2\text{C}_6\text{H}_4\text{SeCN}$ ,  $\text{PBu}_3$ , THF; b.  $m\text{CPBA}$ , then  $\text{Et}_3\text{N}$ , 97%; (ix)  $m\text{CPBA}$ , THF/ $\text{H}_2\text{O}$ , then  $\text{Et}_3\text{N}$ , 83%.

Scheme 4.6. Fukuyama's synthesis towards the pyrrolidine ring.

The formation of the pyrrolidine ring commenced with reaction of the ketone with lithiated *t*-butyl 2-(diethoxyphosphoryl)ethanoate, then subsequent protection of the oxindole amide and replacement of the iodide with a hydrogen afforded the *t*-butyl ester **81** in 70% yield. Michael addition of methylamine to the  $\alpha$ - $\beta$  unsaturated methyl ester, gave the amine functionality needed for the closure of the pyrrolidine ring system. Protection of the amine as the allyl carbamate and selective reduction of the methyl ester afforded the alcohol **82**. Removal of the Alloc group and concurrent cyanomethylation with 2-iodoacetonitrile provided the aminonitrile **83**, which upon treatment with KHMDS closed the pyrrolidine ring in an intramolecular Michael fashion to afford the single isomer **84** in 62% yield. Attention was then turned to the quaternary vinyl functionality, which was accessed *via* hydrolysis of the *t*-butyl ester and subsequent reduction to the alcohol **85**, after protection of the hydroxyl functionality as the benzoate. The alcohol was then converted to the vinyl moiety utilising Grieco's procedure<sup>77</sup> in 97% yield. Removal of the cyano functionality with

*m*CPBA afforded the  $\gamma$ -lactam ring **86** in 83% yield which was reduced at a later stage in the synthesis to give (+)-gelsemine.

The approach to the pyrrolidine ring and quaternary centre by Danishefsky *et al.*<sup>71</sup> made use of a Lewis acid catalysed intramolecular ring opening of an oxetane ring as the key step (Scheme 4.7).



**Reagents & conditions:** (i)  $\text{BH}_3\text{Cl}\cdot\text{DMS}$ ,  $\text{Et}_2\text{O}$ ,  $0\text{ }^\circ\text{C}$  then  $\text{NaOH}/\text{H}_2\text{O}_2$ , 77%; (ii)  $(\text{COCl})_2$ ,  $\text{DMSO}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 98%; (iii)  $\text{LiHMDS}$ ,  $\text{TESCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{THF}$ ,  $-78\text{ }^\circ\text{C}$  to  $0\text{ }^\circ\text{C}$  then  $(\text{CH}_3)_2\text{N}=\text{CH}_2\text{I}$ ,  $\text{CH}_2\text{Cl}_2$ , 91%; (iv)  $\text{MeI}$ ,  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$  then  $\text{Al}_2\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 95%; (v)  $\text{NaBH}_4$ ,  $\text{CeCl}_3\cdot 7\text{H}_2\text{O}$ ,  $\text{MeOH}$ , 99%; (vi) 9-BBN dimer,  $\text{THF}$ ,  $\text{NaOH}/\text{H}_2\text{O}_2$ , 88%; (vii)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$  then  $\text{NaHMDS}$ ,  $\text{THF}$ ,  $-78\text{ }^\circ\text{C}$ , 91%; (viii) a.  $\text{TFA}/\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^\circ\text{C}$ , 81%; b.  $(\text{COCl})_2$ ,  $\text{DMSO}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ , 81%; (ix) a. triethylphosphonoacetate,  $\text{NaH}$ ,  $\text{THF}$ ,  $0\text{ }^\circ\text{C}$ , d.r. 3:2, 92%; b.  $\text{DIBAL}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ , 88%; (x) a. propionic acid (cat.),  $\text{H}_3\text{CC}(\text{OEt})_3$ , toluene, reflux, 64%; b.  $\text{NaOH}/\text{THF}/\text{EtOH}$ , 86%; (xi) a.  $\text{PhO}_2\text{PON}_3$ ,  $\text{Et}_3\text{N}$ , benzene,  $25\text{ }^\circ\text{C}$  to reflux then  $\text{MeOH}$ , reflux, 89%; b.  $\text{BF}_3\cdot\text{Et}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$  to  $12\text{ }^\circ\text{C}$ , 64%; (xii)  $\text{PivCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{DMAP}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^\circ\text{C}$  to  $25\text{ }^\circ\text{C}$ , 92%.

Scheme 4.7. Danishefsky's route to the pyrrolidine ring.

The stereospecific Claisen rearrangement product **87**, began the synthesis towards the key pyrrolidine ring system. Hydroboration of **87** with BH<sub>2</sub>Cl·DMS and oxidative workup gave the secondary alcohol, which was further oxidised to the ketone **88**.

Formation of the silyl enol ether and trapping with Eschenmoser's salt provided the dimethylaminomethyl species, whereupon methylation of the nitrogen, and base induced elimination afforded the  $\alpha$ -methyleneketone **89**. Luche reduction of the ketone, and a second hydroboration gave the *cis* diol moiety **90** in 88% yield. Mesylation of the primary alcohol, then deprotonation of the secondary alcohol with NaHMDS at -78°C, afforded the key oxetane ring **91** in 91% yield. With the oxetane ring in hand, functionalisation at the quaternary centre commenced with the formation of the ketone **92**. A Wadsworth Emmons-type condensation afforded the unsaturated ester in a 3:2 mixture of isomers, where both isomeric forms were reduced to the allylic alcohol **93**. Separate treatment of the isomeric allylic alcohols with triethylorthoacetate gave rise to a [3,3] Claisen rearrangement which resulted in a single and identical  $\gamma,\delta$ -unsaturated ester **94** from the two starting materials in 64% yield. Conversion to the acid allowed for a Curtius rearrangement in the presence of MeOH to provide the methoxy carbamate in 89% yield. Finally, with the required urethane nitrogen in place, the oxetane ring was opened *via* Lewis acid activated intramolecular cyclisation, to afford the pyrrolidine ring **95** in 64% yield.

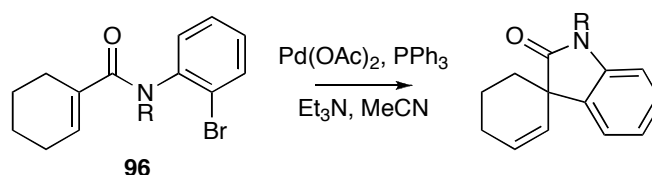
The synthetic route to the pyrrolidine ring functionality of all three groups relied on ring closing methodology, with judicious use of organosilicon chemistry to facilitate addition to an *N*-acyliminium species, as demonstrated by Fleming, to the utilisation of a Michael addition of an aminonitrile by Fukuyama. Danishefsky made use of an oxetane ring to store molecular functionality in a compact setting.

#### 4.1.3 Formation of the spirooxindole ring system.

The strategies towards the formation of the spirooxindole subsystem, as with the formation of the pyrrolidine ring, depended on the strategy utilised to form the bicyclo[3.2.1]octane skeleton. Work by Fukuyama *et al.*<sup>70</sup> utilising the divinylcyclopropane rearrangement, set in place the spirooxindole moiety at an early stage within the synthesis, which will be discussed shortly. Generally, the construction of the spirooxindole occurred after the pyrrolidine ring and quaternary vinylic group were set in place.

Two main areas of chemistry have been applied to access the spirooxindole moiety; the first being a palladium catalysed intramolecular Heck reaction, as utilised by Overman *et al.* and Speckamp *et al.*, and the second area utilising a radical based cyclisation to achieve the same goal, as seen by the work of Hart *et al.* and Johnson *et al.*<sup>79</sup>

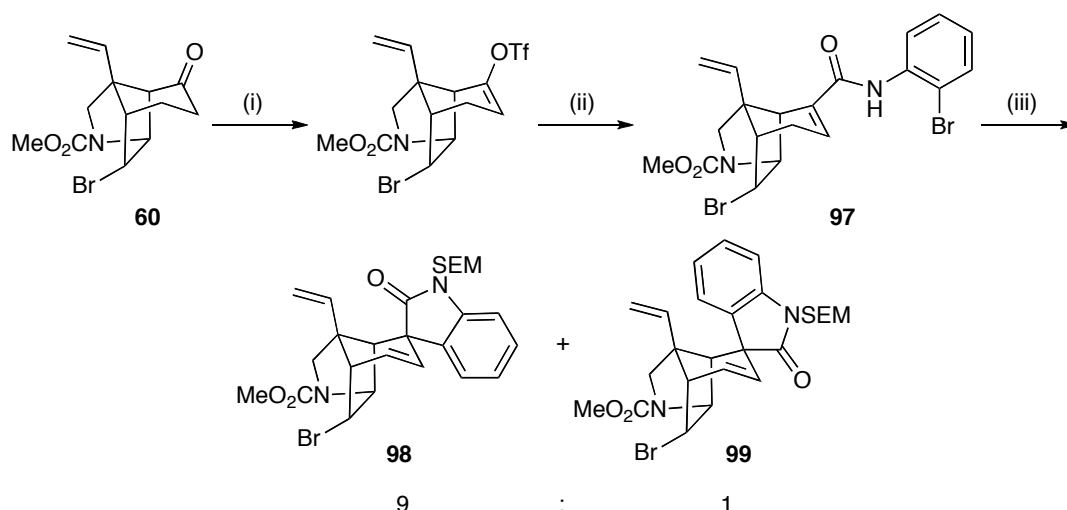
The pioneering work by Overman *et al.*<sup>78</sup> on the palladium catalysed intramolecular arylation of alkenes, otherwise known as the Heck arylation, in the synthesis of 3-spiro-2-oxindoles, gave a route to the formation of the key spirooxindole moiety of gelsemine. Initial studies with the reaction of *N*-(2-bromophenyl)cyclohexenecarboxamide and Pd(OAc)<sub>2</sub>, gave rise to the desired 3-spiro-2-oxindole (Scheme 4.8).



Scheme 4.8. Overman's initial studies of spirocyclisation.

Thus treatment of the cyclohexenecarboxamide **96** with Pd(OAc)<sub>2</sub>, PPh<sub>3</sub> and Et<sub>3</sub>N in boiling acetonitrile, afforded the cyclised product. It was found that the secondary anilide, where R = H, cyclised in moderate to low yields, whereupon treatment of the tertiary anilide, where R = CH<sub>3</sub>, Benzyl, or SEM, provided the cyclised products in yields of 85%, 68% and 70% respectively. With these results in hand, the route to the crucial intramolecular Heck cyclisation was commenced beginning on the advanced intermediate **60** (Scheme 4.9).





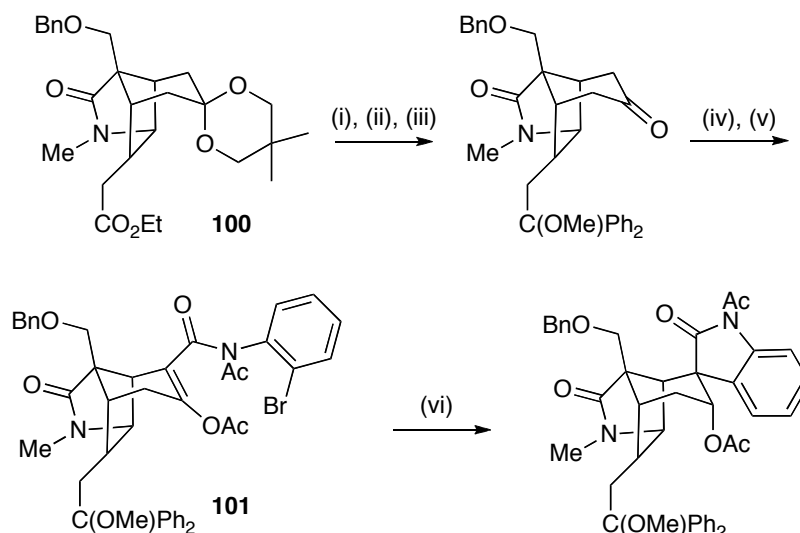
*Reagents & conditions:* (i) LDA, PhNTf<sub>2</sub>, THF, -78 °C to 0 °C, 100%; (ii) a. Pd(PPh<sub>3</sub>)<sub>4</sub> (1 mol %), 2-bromoaniline, CO, 1 atm, DMF, 80 °C, 79%; b. NaH, SEMCl, THF, 23 °C; (iii) Pd<sub>2</sub>(dba)<sub>3</sub> (10 - 20 mol %), Et<sub>3</sub>N, toluene, 110 °C, 92%.

Scheme 4.9. Intramolecular Heck spirocyclisation.

The ketone **60** was converted to the enol triflate by treatment with LDA and *N*-phenyltrifluoromethanesulfonimide, which was then proceeded with palladium catalysed carbonylation in the presence of 2-bromoaniline and carbon monoxide gas, to afford the cyclisation precursor **97** in 79% yield. The resulting amide was alkylated with SEMCl to give the crucial tertiary anilide. With the tertiary anilide in hand, a ‘ligandless’<sup>80</sup> Heck reaction with Pd<sub>2</sub>(dba)<sub>3</sub>, Et<sub>3</sub>N in boiling toluene gave the stereoisomeric spirooxindole moieties **98** and **99** in a 9:1 ratio in 92% yield.

The work by Speckamp *et al.*<sup>73</sup> to introduce the spirooxindole centre, closely followed that of Overman *et al.* with formation of the enol triflate, then palladium catalysed carbonylation in the presence of 2-bromoaniline. After protection of the amide with SEMCl, standard Heck arylation conditions (Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, Et<sub>3</sub>N, MeCN, reflux) gave a single spirooxindole product that unfortunately possessed the opposite spiro stereochemistry to that of gelsemine. Upon utilising the conditions reported by Overman (*vide supra*), the required spiro stereochemistry was gained in 60% yield, along with the epimeric product in 30% yield.

The radical cyclisation approach by Hart *et al.*<sup>74</sup> to assemble the spirooxindole ring system was achieved from the ester **100** (Scheme 4.1.0).

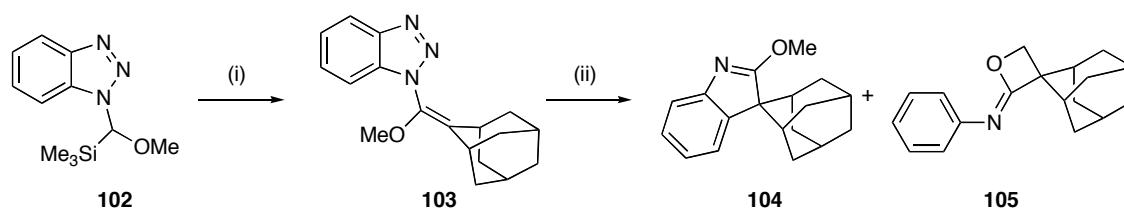


*Reagents & conditions:* (i) PhMgBr, 87%; (ii) NaH, DMSO, CH<sub>3</sub>I, 100%; (iii) TsOH, acetone, 94%; (iv) NaH, KH, *o*-BrC<sub>6</sub>H<sub>4</sub>N=C=O, THF, 80%; (v) Ac<sub>2</sub>O, DMAP, Et<sub>3</sub>N, DMF, 98%; (vi) Bn<sub>3</sub>SnH, AIBN (cat.), toluene, *hν*, 40%.

Scheme 4.1.0. Hart's radical cyclisation.

The ester **100** was treated with phenylmagnesium bromide to afford the tertiary alcohol, which was then further alkylated with iodomethane to give the methoxyl moiety. Deprotection of the ketal provided the ketone in 81% yield and treatment of the ketone with *o*-bromophenylisocyanate, NaH and catalytic KH, then acetylation of the enol and amide functionality, afforded the radical cyclisation precursor **101**. The radical initiated cyclisation was achieved by reaction of the aryl bromide species with Bu<sub>3</sub>SnH under photochemical conditions, to afford the spirooxindole substructure with the correct stereochemistry in 40% yield, along with the epimeric product in 15% yield.

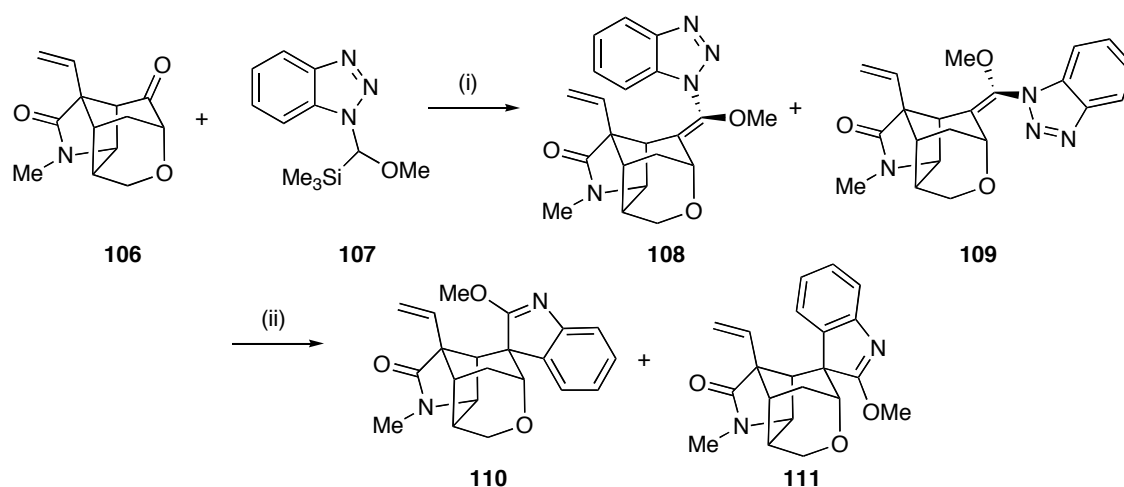
The other radical cyclisation method used towards the spirooxindole system by Johnson *et al.*<sup>79</sup> was developed from a model system based on the condensation of sterically demanding adamantane and the benzotriazole moiety **102** (Scheme 4.1.1).



*Reagents & conditions:* (i) LDA, adamantane; (ii) *hν*, MeCN.

Scheme 4.1.1. Condensation then UV induced cyclisation.

Thus an LDA mediated Petersen olefination gave the coupled product **103** in 80% yield, which was then subjected to irradiation with UV light in MeCN to afford the cyclised product **104** in 40% yield. They also observed the formation of the oxetan-2-imine moiety **105** in equal amounts, which Johnson attributed to initial proton transfer from the methoxy group, followed by cyclisation. With these results in hand, the formation of the key spirooxindole functionality proceeded *via* the condensation of the advanced ketone intermediate **106** and the lithiated 1-(methoxytrimethylsilylmethyl)benzotriazole **107** (Scheme 4.1.2).



Reagents & conditions: (i) LDA, 65%; (ii) *hν*, MeCN, pyrex, (ratio of 1:2, combined yield of 36%).

Scheme 4.1.2. Condensation of ketone and benzotriazole.

The condensation reaction gave a mixture of the (*E*) and (*Z*) methoxymethylene isomers **108** and **109** in 65% yield, with the (*E*) isomer in the majority. Irradiation of the two isomers separately with UV light in MeCN afforded the two cyclised isomers **110** and **111** in a 1:2 ratio and overall yield of 36%, with the minor isomer **110** bearing the correct stereochemistry to that of gelsemine. Hydrolysis of the minor isomer with HCl in aqueous THF and further reduction of the tertiary amide with DIBALH afforded gelsemine.

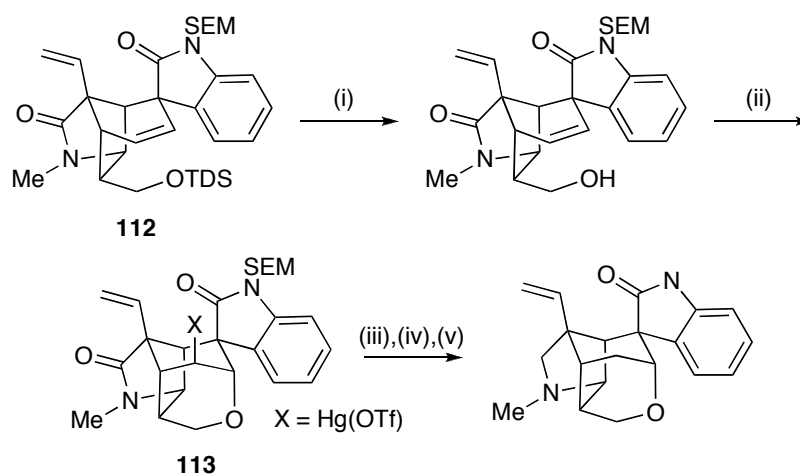
With each of the approaches to the formation of the spirooxindole system presented here, stereoselectivity issues were evident throughout, with the epimeric spiro centre present in considerable quantities. Fukuyama's approach to the construction of the bicyclo[3.2.1]octane skeleton and *in situ* spirooxindole formation (Scheme 4.2),

overcame the issue of stereochemical control with use of a bulky iodide in the oxindole framework. Upon the key divinylcyclopropane rearrangement to form the bicyclo[3.2.1]octane moiety, a single isomer was obtained, which *via* single crystal X-ray analysis of the corresponding bromide rearrangement precursor, confirmed the correct stereochemistry of the spiro centre.

#### 4.1.4 Formation of the tetrahydropyran ring system.

The attempts to construct the tetrahydropyran ring system relied on two main strategies: oxymercuration as shown in the work by the groups of Fukuyama, Danishefsky<sup>71b</sup> and Speckamp; the second consisting of lactone or hemiacetal formation with concurrent reduction to the tetrahydropyran ring, as exemplified by the work of Hart *et al.* and Overman *et al.*

The first reported use of oxymercuration to form the tetrahydropyran ring was by Speckamp *et al.*, where the advanced intermediate **112** was first deprotected and then subjected to mercurial induced intramolecular cyclisation (Scheme 4.1.3).



*Reagents & conditions:* (i)  $\text{Bu}_4\text{NF}$ , THF, RT, 2 hrs; (ii)  $\text{HgO}$ ,  $\text{Tf}_2\text{O}$ , *N,N*-dimethylaniline,  $\text{MeNO}_2$ , RT, 3 d, 60%; (iii)  $\text{NaBH}_4$ ,  $\text{NaOH}$ ,  $\text{CH}_2\text{Cl}_2$ , EtOH, 80%; (iv)  $\text{Bu}_4\text{NF}$ , THF, 4 Å sieves, reflux, 4 hrs, 90%; (v)  $\text{AlH}_3$ , THF,  $-65^\circ\text{C}$  to  $0^\circ\text{C}$ , 4 hrs, 50%.

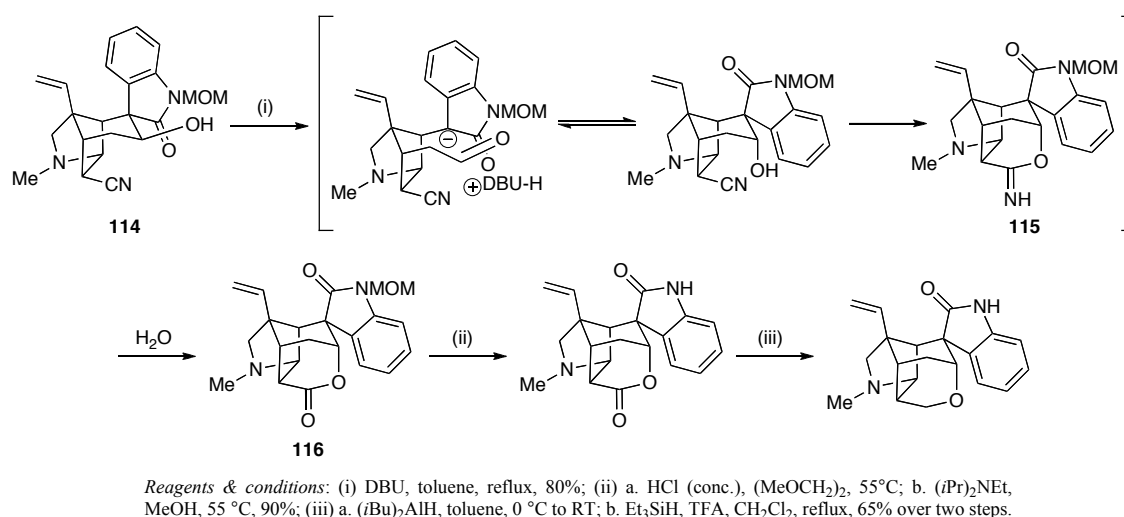
Scheme 4.1.3. Speckamp's formation of the tetrahydropyran ring.

The thexyldimethylsilyl (TDS) ether **112** was removed with TBAF to afford the hydroxyl moiety, which was then reacted with mercury(II) triflate, in the presence of

*N,N*-dimethylaniline, to give the organomercury species **113** in 60% yield. Reduction of the organomercury compound with an alkaline sodium borohydride solution gave 21-oxogelsemine, which with removal of the SEM protecting group and reduction of the tertiary amide with aluminium hydride, afforded ( $\pm$ )-gelsemine.

The other routes utilised by Fukuyama and Danishefsky, followed closely that of Speckamp, with the exception of functional group protection: MOM instead of SEM, in the case of Fukuyama's synthesis, and the methyl carbamate of the pyrrolidine ring in Danishefsky's route.

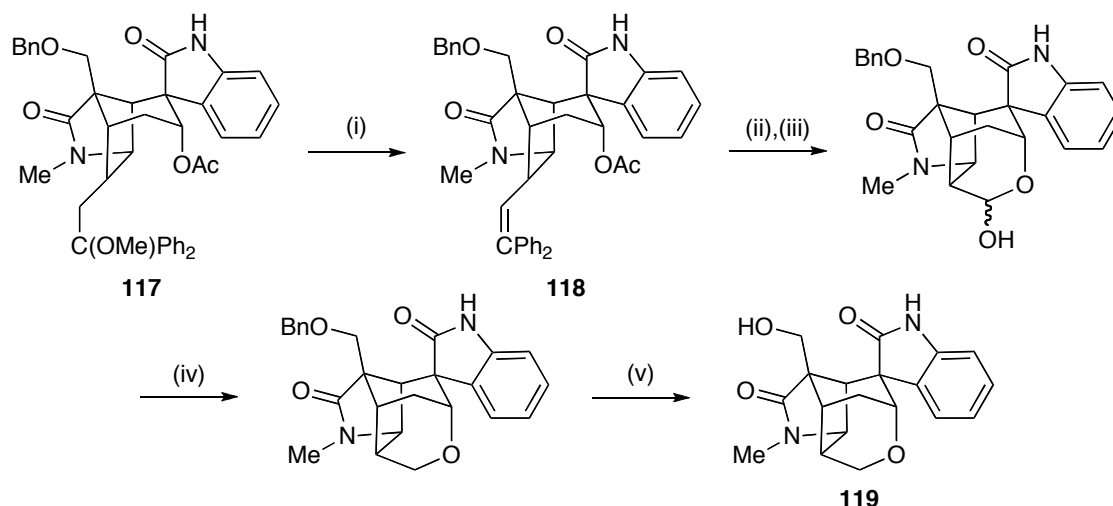
Overman *et al.* first reported the second strategic route to the ether bridge whilst epimerising the undesired spiro stereoisomer to the correct configuration *via* a retro-aldol cleavage of the alcohol moiety **114** (Scheme 4.1.4).



Scheme 4.1.4. Overman's retro-Aldol approach to tetrahydropyran ring.

Treatment of the alcohol with DBU afforded the correct stereochemistry at the spiro centre, whilst elegantly giving the *endo* alcohol after aldol closure, which in turn cyclised to form the imide **115**, that upon aqueous workup afforded the lactone **116** in 80% yield. The resultant lactone was reduced to the tetrahydropyran ring with diisobutylaluminium hydride and Et<sub>3</sub>SiH and the MOM protecting group cleaved with triethylsilane to afford ( $\pm$ )-gelsemine.

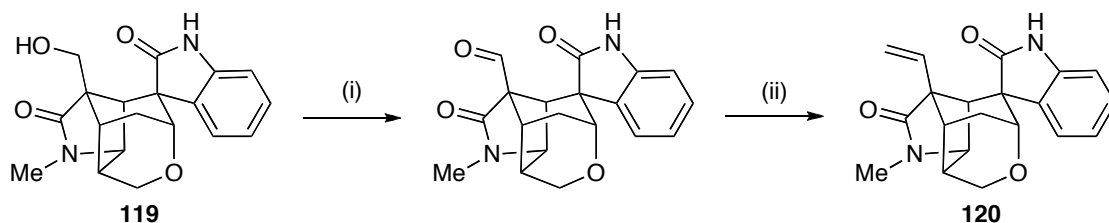
Hart's synthetic strategy to the tetrahydropyran ring began with the tertiary methyl ether **117** which was reacted with TsOH in dichloromethane and then MeOH to effect conversion to the diphenyl alkene moiety **118** (Scheme 4.1.5).



*Reagents & conditions:* (i) TsOH, CH<sub>2</sub>Cl<sub>2</sub>, then MeOH, 93%; (ii) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, MeOH, then Me<sub>2</sub>S, 65%; (iii) HCl, H<sub>2</sub>O, DME, 48 °C, 16 hrs, 65%; (iv) Et<sub>3</sub>SiH, TFA, CH<sub>2</sub>Cl<sub>2</sub>, 83%; (v) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 95%.

Scheme 4.1.5. Hart's synthesis of the tetrahydropyran ring.

Ozonolysis of the olefin **118** afforded the aldehyde, which was then treated with HCl in DME to effect epimerisation and subsequent hemiacetal formation in one synthetic operation. The lactol was then reduced with triethylsilane and trifluoroacetic acid to provide the tetrahydropyran ring in 83% yield. The total synthesis of (±)-21-oxogelsemine was accomplished *via* treatment of the benzyl ether with boron tribromide to afford the alcohol **119** (Scheme 4.1.6).



*Reagents & conditions:* (i) Dess-Martin periodinane, 71%; (ii) [Cp<sub>2</sub>TiMe<sub>2</sub>], 87%.

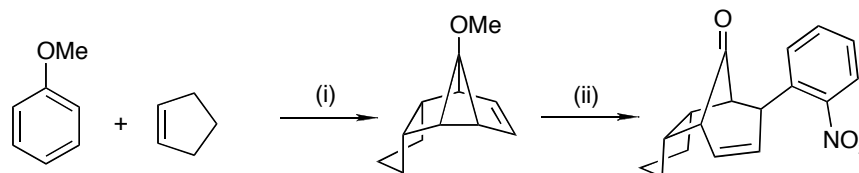
Scheme 4.1.6. Hart's completion of (±)-21-oxogelsemine.

A Dess-Martin oxidation and concurrent reaction with Petasis' reagent gave the quaternary vinylic group and hence (±)-21-oxogelsemine **120**.

The strategies presented here by all groups, represent an overwhelming wealth of excellence in organic synthesis, with the complex natural product gelsemine, providing a fascinating target that leads to the discovery of novel reactions and insights into complex molecular architecture. The total synthesis of gelsemine is still a challenging target, as exemplified by the use of similar routes to achieve the same goal, although the individual strategies employed are still uniquely fascinating.

#### 4.1.5 A photochemical route to the total synthesis of gelsemine.

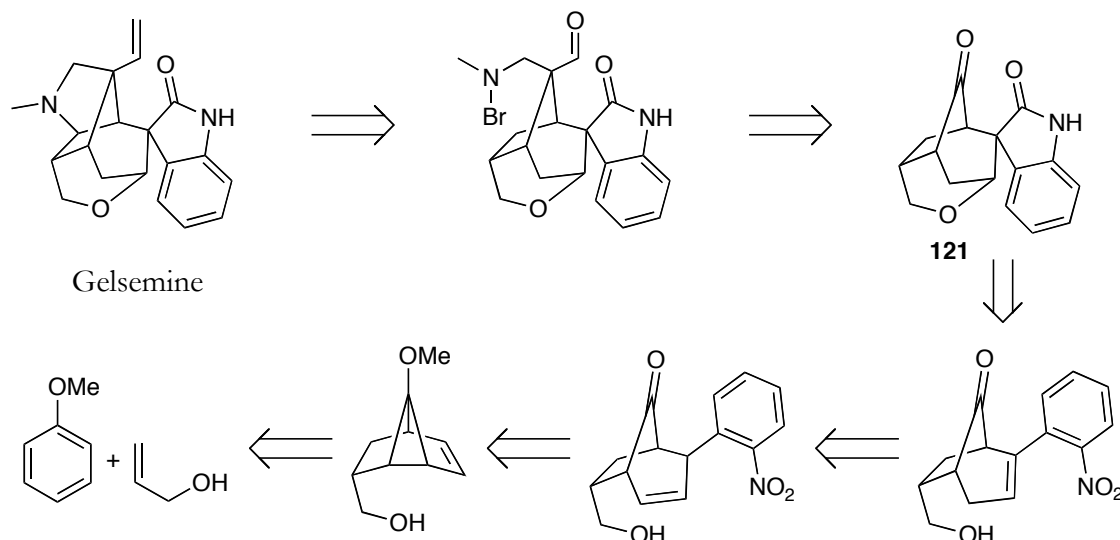
Studies towards the total synthesis of gelsemine by Penkett *et al.*<sup>9</sup> began with the investigation into the silicon tethered alkene-arene meta photocycloaddition reactions as mentioned in section 4.1 (Scheme 4.4). Further investigations utilising the propensity of the meta photocycloadduct to undergo fragmentation led to the discovery of the palladium catalysed arylation/fragmentation reaction as discussed in chapter 2, which afforded an advanced intermediate towards the total synthesis of gelsemine (Scheme 4.1.7).



Reagents & conditions: (i)  $h\nu$ , cyclohexane, 8%; (ii)  $\text{Pd}(\text{OAc})_2$ , dppe,  $\text{Et}_3\text{N}$ , DMF,  $80^\circ\text{C}$ , 32 hrs 20%.

Scheme 4.1.7. Palladium catalysed arylation fragmentation.

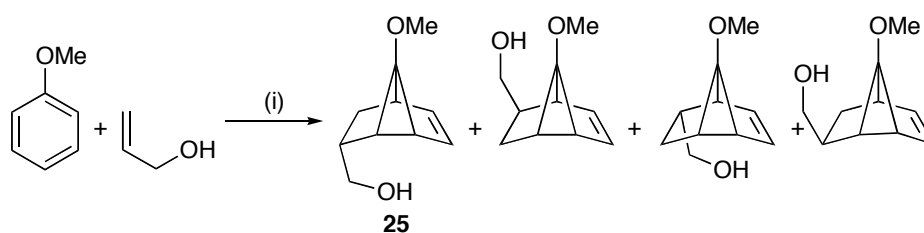
The realisation that in two synthetic operations, the bicyclo[3.2.1]octane skeleton along with suitable functionality to allow the construction of the crucial spiro centre, gave the possibility of achieving the total synthesis of gelsemine *via* photochemical means. As the origins of this work provide the basis to the current synthetic extension towards the total synthesis of gelsemine, a more in depth analysis will be given, beginning with the original retrosynthetic plan (Scheme 4.1.8).



Scheme 4.1.8. Original retrosynthetic analysis.

From gelsemine, it was proposed that the pyrrolidine ring of gelsemine could be formed *via* a nitrogen radical based Hoffman Loeffler-Freitag<sup>81</sup> reaction, and the formation of the key quaternary centre by a Mannich<sup>82</sup> reaction on an aldehyde, which in turn derived from the Wittig product of the ketone **121**. An intramolecular alkoxypalladation/carbonylation<sup>83</sup> reaction would furnish both the crucial quaternary spiro centre and tetrahydropyran ring system in a single tandem process. The core bicyclo[3.2.1]octane skeleton of gelsemine, was to be prepared utilising palladium mediated arylation/fragmentation methodology of the meta photocycloaddition product derived from anisole and allyl alcohol, as previously discussed.

The sequence began with the irradiation of anisole and allyl alcohol in cyclohexane using UV light to afford the desired meta photoadduct **25** in 8% yield along with three other isomers (Scheme 4.1.9).

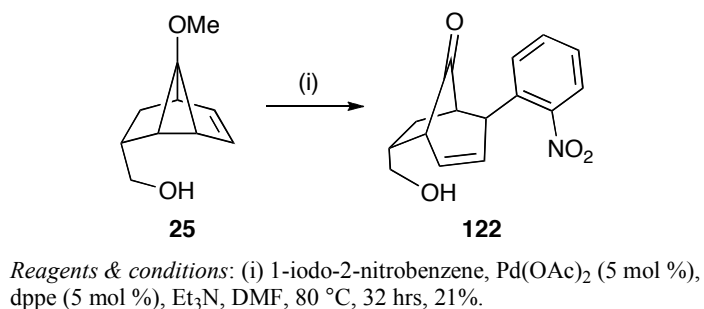


*Reagents & conditions:* (i)  $h\nu$ , cyclohexane, 8%.

Scheme 4.1.9. Metaphotocycloaddition of anisole and allyl alcohol.



With the 7-*endo* meta photocycloadduct **25** in hand, it was then subjected to the palladium catalysed arylation/fragmentation reaction<sup>39</sup> (Scheme 4.2.0).



Scheme 4.2.0. Palladium catalysed arylation/fragmentation reaction.

Thus treatment of **25** with Pd(0) afforded the arylated product **122** in 21% yield. Further optimisation studies revealed that changing the bidentate ligand dppe to the monodentate ligand PPh<sub>3</sub>, increased the yield further still. Upon utilisation of tri-*ortho*-tolylphosphine as the ligand, the yield was further improved and this was attributed to the palladium complex's thermal stability at elevated temperatures.

With the aryl-nitro functionality in place, attention turned towards conjugation of the olefin with respect to the alkoxypalladation/carbonylation step. It was thought that treatment of the unconjugated species **122** with a base, such as NaOMe would effect conjugation<sup>84</sup> (Figure 4.1), the assumption being that the proton to be removed had a similar  $pK_a$  to that of *p*-nitrotoluene ( $pK_a = 22$ ).

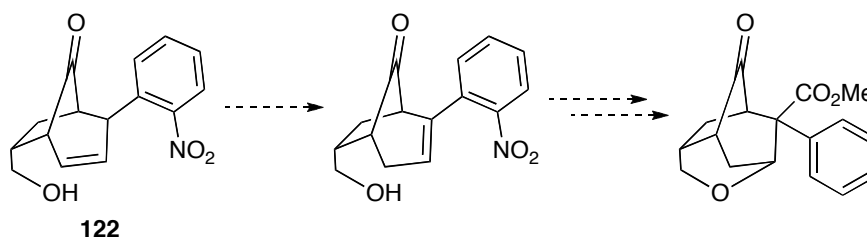
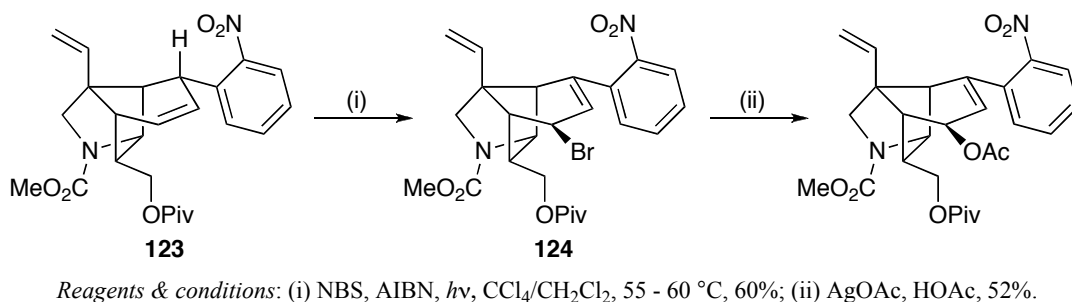


Figure 4.1. Attempts at conjugation.

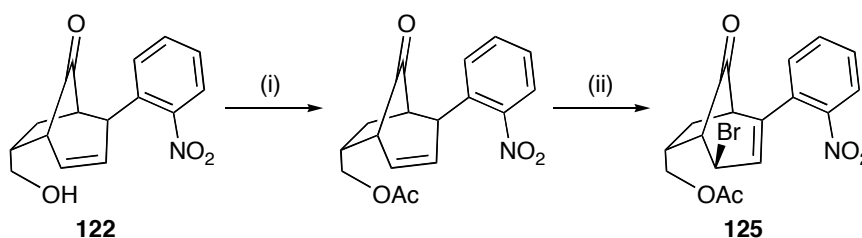
Treatment of **122** with NaOMe in MeOH afforded only starting material after 120 hrs at room temperature or 2.5 hrs at reflux temperature. A series of bases and acids were screened, with varying reaction conditions (temperature, time, solvent) to result in either

reclamation or decomposition of starting material. The use of allylic bromination to effect conjugation of the olefin was also investigated, as demonstrated by Danishefsky *et al.*<sup>71b</sup> in the construction of the spirooxindole moiety (Scheme 4.2.1).



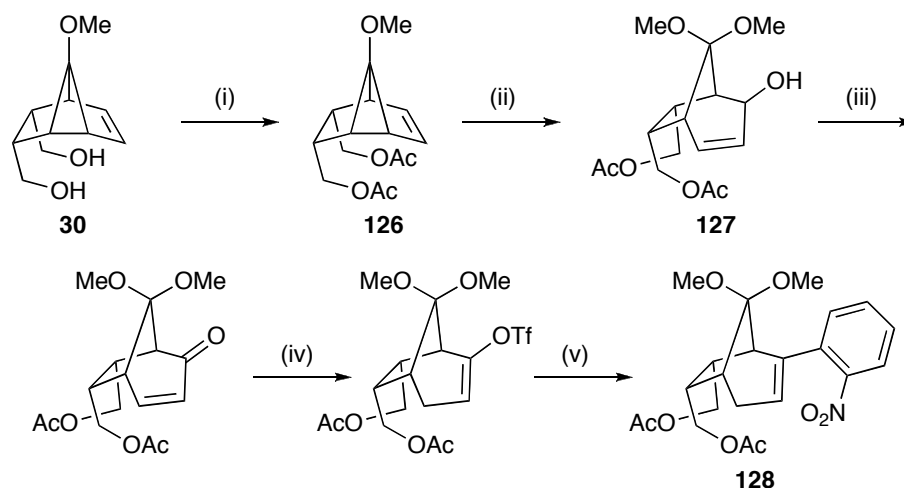
Scheme 4.2.1. Danishefsky's allylic Bromination.

Photochemical induced bromination of the pivaloate **123** afforded the allyl bromide **124**, which was subsequently debrominated with AgOAc to give the allylic acetate in 52% yield. Thus in Rupert Sims<sup>84</sup> work, acetate protection of the alcohol **122** to prevent halogen mediated tetrahydrofuran ring formation, and photolytic bromination using NBS and AIBN, afforded the allyl bromide **125** (Scheme 4.2.2).



Scheme 4.2.2. Rupert Sims' attempts at allylic bromination.

Unfortunately, attempts to remove the resultant bromide with  $(\text{Me}_3\text{Si})_3\text{SiH}$  or  $\text{Bu}_3\text{SnH}$  gave a complex mixture of products, with no evidence of the desired material. Penkett *et al.*<sup>84</sup> then devised a new route (Scheme 4.2.3) to the conjugated species based on a fragmentation route previously reported by the group.

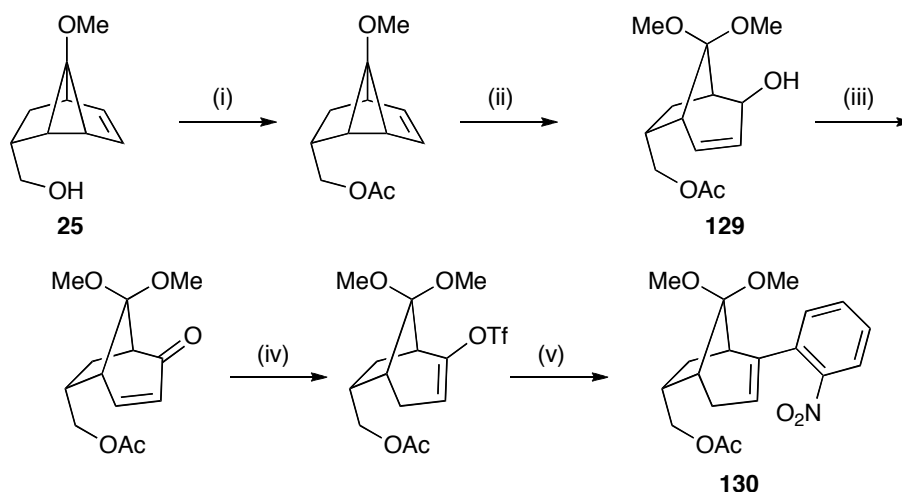


*Reagents & conditions:* (i)  $\text{Ac}_2\text{O}$ , pyridine, 0 °C - 20 °C, 24 hrs, 88%; (ii) Oxone®,  $\text{NaHCO}_3$ , EtOAc, acetone, then HCl, MeOH, 50%; (iii) IBX, DMSO, RT, 24 hrs, 77%; (iv) L-Selectride®,  $\text{PhNTf}_2$ , THF, -78 °C to -20 °C, 24 hrs, 62%; (v) 2-nitrophenylboronic acid,  $\text{Pd(PPh}_3)_4$ ,  $\text{K}_2\text{CO}_3$  (2 M), KBr, DME, 90 °C, 4 hrs, 93%.

Scheme 4.2.3. Alternative route to conjugated species.

The *endo*-bis-diol meta photocycloadduct **30** was used as a model system, which was first diacetylated to afford the protected diol **126** in 88% yield. Treatment of **126** with *in situ* formed DMDO and subsequent acid catalysed hydrolysis in MeOH of the epoxide gave the allylic alcohol **127** in 50% yield. Conversion of the allylic alcohol to the ketone with IBX, then formation of the enol triflate, as described by Crisp *et al.*<sup>85</sup> afforded the precursor to a Suzuki-Miyaura cross-coupling reaction. Reaction conditions based on work by Wustrow *et al.*<sup>86</sup> utilising an aqueous solution of  $\text{K}_2\text{CO}_3$  and 2-nitrophenylboronic acid as the coupling partner, afforded the conjugated product **128** in 93% yield.

The proven synthetic route was also applied<sup>87</sup> to the 7-endo metaphotocycloadduct **25** derived from allyl alcohol and anisole, following closely the experimental procedure as with the diol meta photocycloadduct **30** (Scheme 4.2.4).



*Reagents & conditions:* (i)  $\text{Ac}_2\text{O}$ , pyridine,  $0\text{ }^\circ\text{C}$  to  $20\text{ }^\circ\text{C}$ , 48 hrs, 79%; (ii)  $m\text{CPBA}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^\circ\text{C}$ , then MeOH, 50%; (iii) IBX, acetone,  $60\text{ }^\circ\text{C}$ , 12 hrs, 99%; (iv) L-Selectride®,  $\text{PhNTf}_2$ , THF,  $-78\text{ }^\circ\text{C}$  to  $-20\text{ }^\circ\text{C}$ , 45 mins, 61%; (v) 2-nitrophenylboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{K}_2\text{CO}_3$  (2 M), KBr, DME,  $90\text{ }^\circ\text{C}$ , 12 hrs, 70%.

Scheme 4.2.4. Penkett's photochemical approach to gelsemine on the real system.

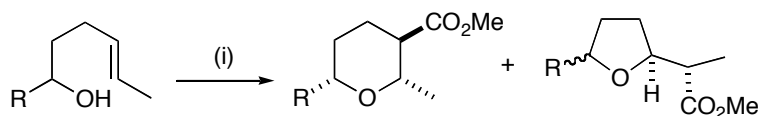
The standard photochemical conditions (*vide supra*) were employed to afford the starting material **25**. The hydroxyl group was protected as the acetate, and the resultant product subjected to the epoxidation/acid catalysed fragmentation reaction to provide the allylic alcohol **129** in 26% yield. Oxidation of the alcohol with IBX gave the ketone that was then converted to the enol triflate *via* the conditions used on the model system. The Suzuki-Miyaura cross-coupling reaction proceeded smoothly to afford the aryl-nitro species **130** in 80% yield. Removal of the dimethoxy acetal and acetate under acid conditions gave the ketone moiety **131** in 97% yield, which is shown in the next section.

With the crucial conjugated arylated species in hand, the alkoxypalladation/carbonylation reaction was attempted which will be discussed in the next section.

## 4.2 Results and discussion.

The use of the palladium catalysed oxycarbonylation reaction of alkenes is an efficient method to access pyran and furan ring systems. The general reaction utilises a source of Pd(II) such as  $\text{PdCl}_2$ , with copper(II) chloride as the reoxidant in an atmosphere of carbon monoxide. A protic solvent, normally methanol, is used to displace the

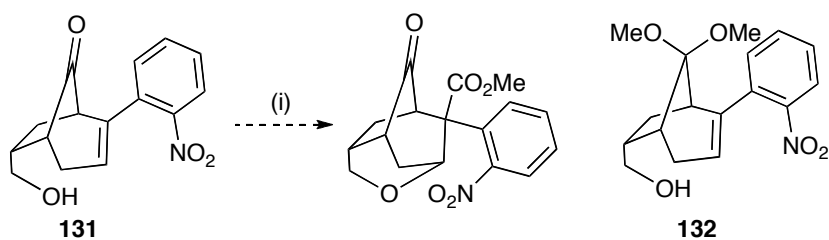
palladium to give either the tetrahydropyran or tetrahydrofuran methylcarboxylate<sup>88</sup> (Scheme 4.2.5).



*Reagents & conditions:* (i) PdCl<sub>2</sub>, CuCl<sub>2</sub>, CO (1.1 atm), MeOH, 25°C, 17 hrs, 84%.

Scheme 4.2.5. Semmelhack's tetrahydropyran and tetrahydrofuran ring formation.

Thus the ketone moiety **131** (previously synthesised by Jason Lai<sup>87</sup>) was subjected to the same alkoxypalladation/carbonylation conditions as set out above, however analysis of the <sup>1</sup>H NMR spectrum of the crude mixture revealed that no oxycarbonylation had taken place and only the dimethoxyacetal **132** had formed (Scheme 4.2.6).



*Reagents & conditions:* (i) PdCl<sub>2</sub>, CuCl<sub>2</sub>, CO (1 atm), MeOH.

Scheme 4.2.6. Attempts at palladium catalysed alkoxycarbonylation.

A series of experiments with varying reaction conditions (temperature, solvent, additive) were performed and these are summarised in Table 1.

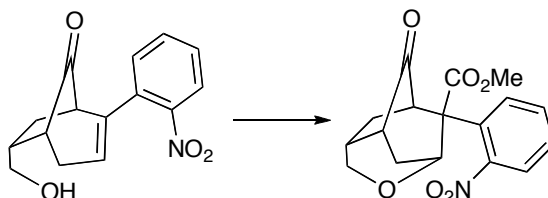


Table 2. Attempts at palladium catalysed alkoxycarbonylation utilising PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub>, a source of Cu(II) and a balloon of CO gas.

Entry	Catalyst	Solvent	Oxidant	Additives	Time	Temp°C	Product
1	PdCl <sub>2</sub>	MeOH	CuCl <sub>2</sub>	-	12hrs	RT	<b>132</b>
2	PdCl <sub>2</sub>	MeOH/MeCN	CuCl <sub>2</sub>	Propylene Oxide	12hrs	RT	<b>132</b>
3	PdCl <sub>2</sub>	MeOH/MeCN	CuCl <sub>2</sub>	Propylene Oxide	12hrs	80°C	<b>132</b>
4	Pd(OAc) <sub>2</sub>	MeOH/MeCN	Cu(OAc) <sub>2</sub>	-	12hrs	RT	<b>132</b>

Table 2.

Propylene oxide (entries 2 and 3) was utilised as a proton-sequestering reagent. Unfortunately, in all cases only the protection of the ketone as the dimethoxyacetal was observed *via* proton NMR with no detection of the desired product. With this disappointing result a new synthetic route was developed based around the fragmentation pathway of the meta photocycloadduct **25**.

With the palladium catalysed arylation/fragmentation route, the core structure of gelsemine could be accessed within two synthetic operations, although all attempts at conjugation of the double bond failed as previously discussed. We instead looked toward the introduction of suitable functionality at the critical C4 centre so that conjugation of the olefin could occur and subsequent synthetic modifications would lead to an intramolecular Heck arylation, as exemplified by Overman *et al.* The use of a Lewis acid catalysed electrophilic addition of an acyl chloride, in particular methyl chloroformate, was carried out with the view to introducing an ester at the C4 position whilst causing fragmentation of the cyclopropane ring. The ester could then be saponified to the acid, and then coupled with 2-iodoaniline utilising EDCI, to afford a precursor to the intramolecular Heck spirocyclisation (Figure 4.2).

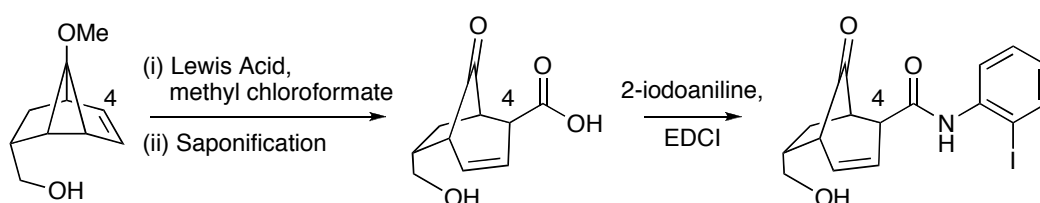


Figure 4.2. Introduction of functionality at the C4 position.

To prevent esterification of the hydroxy group it was protected as the TIPS ether **133**. The TIPS ether was then reacted with methyl chloroformate in the presence of 10 mol%  $\text{BF}_3 \cdot \text{OEt}_2$  in THF at  $-70\text{ }^\circ\text{C}$  and allowed to warm to  $0\text{ }^\circ\text{C}$ . Unfortunately all that was observed *via* TLC was starting material. Upon heating the reaction to reflux temperature, fragmentation of the cyclopropane ring did indeed occur but only afforded a protonated product.

This negative result led us to consider the use of isocyanates, which are known to undergo  $2 + 2$  cycloaddition reactions with alkenes<sup>89</sup> to afford  $\beta$ -lactam rings. The application of isocyanate addition to the meta photocycloadduct olefin to produce the highly strained  $\beta$ -lactam ring, could be utilised to afford a similar fragmentation of the cyclopropane ring and concomitant  $\beta$ -lactam ring opening with a suitable Lewis acid, to give the crucial bicyclo[3.2.1]octane substructure with functionality at the C4 position (Figure 4.3).

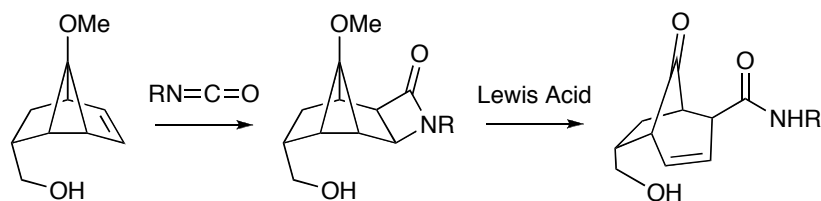


Figure 4.3. Postulated reaction of the 7-endo metaphotocycloadduct with an isocyanate.

Phenyl isocyanate was chosen first, with the intention of installing the anilide moiety in one synthetic operation. No reaction occurred when the TIPS protected metaphotocycloadduct was heated at reflux temperature in toluene with phenyl isocyanate, hence the more reactive *N*-chlorosulfonyl isocyanate was utilised. In this case a new product was revealed to have formed by TLC analysis of the reaction mixture after 30 minutes of combining **133** with *N*-chlorosulfonyl isocyanate and a substoichiometric amount of  $\text{Na}_2\text{CO}_3$  in dichloromethane at  $-20\text{ }^\circ\text{C}$ , subsequent removal of the volatiles *in vacuo* afforded a yellow solid. Analysis of the proton NMR spectrum of the crude residue revealed the presence of a methoxy function within the structure, which was quite unexpected, as we assumed the mechanism would proceed *via* cyclopropane ring fragmentation, to give the bridgehead ketone and amide.

Further investigations led us to postulate that the mechanism did proceed *via* cyclopropane ring fragmentation with concomitant  $\beta$ -lactam ring fracture, to result in the amide anion, which then ring closed to quench the oxy-cation giving the  $\gamma$ -lactam ring (Figure 4.4).

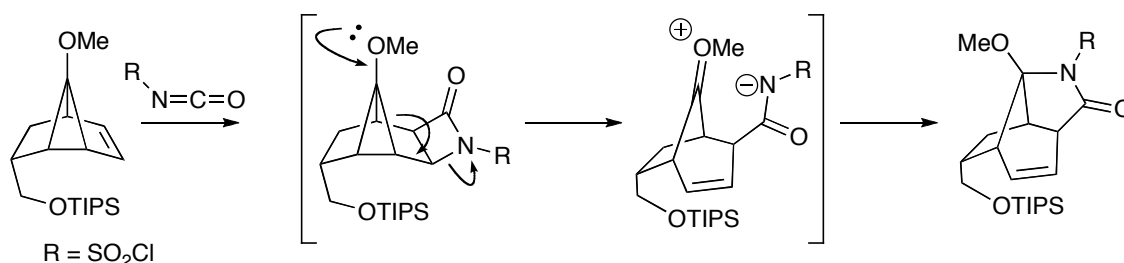
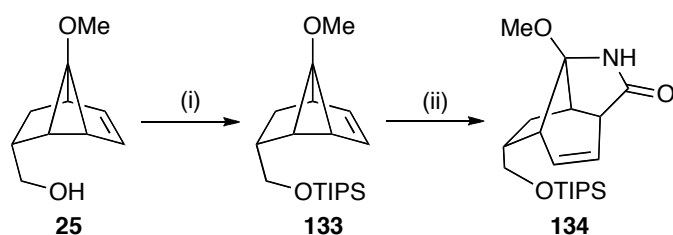
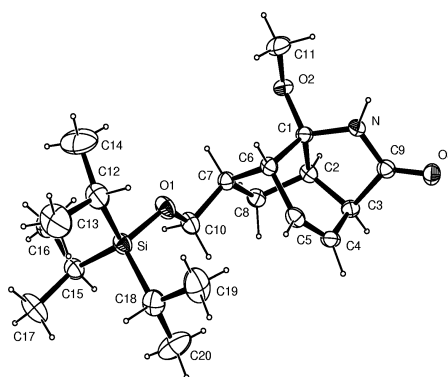


Figure 4.4. Postulation of reaction mechanism.

The intriguing reaction was repeated utilising the procedure set out above. Upon completion of the reaction, the sulfonyl chloride was reduced with catalytic KI<sup>90</sup> in a H<sub>2</sub>O/Et<sub>2</sub>O biphasic solution to afford the amide **134**. Silica chromatography of the crude product afforded a crystalline solid in 40% yield (Scheme 4.2.7).



*Reagents & conditions:* (i) TIPSCl, imidazole, DMAP (cat.), CH<sub>2</sub>Cl<sub>2</sub>, RT, 95%  
(ii) *N*-chlorosulfonyl isocyanate, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 30 mins, then KI, Et<sub>2</sub>O/H<sub>2</sub>O (2:1), 40%.



Scheme 4.2.7. Reaction with NCSI and ORTEP representation.



The crystallographic data did indeed support our hypothesis, although on closer inspection of the literature the transformation was unfortunately already known<sup>91</sup>. However the result still led to the development of a new strategy towards the total synthesis of gelsemine (Figure 4.5).

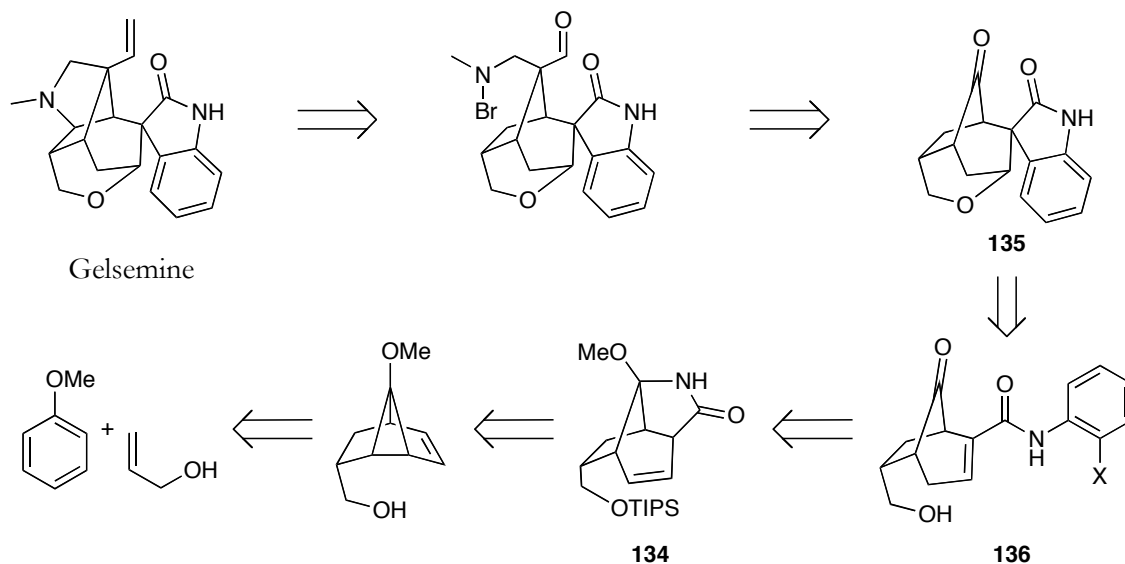
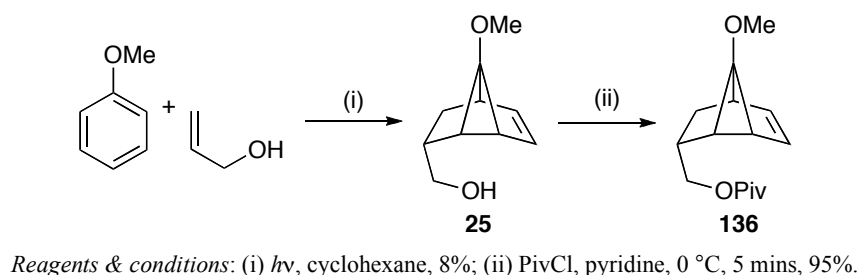


Figure 4.5. Retrosynthetic analysis of new route.

Thus the pyrrolidine ring of gelsemine would be prepared *via* a Hoffman Loeffler-Freitag reaction. The *N*-bromo amine functionality could be introduced *via* a Mannich type reaction of an enol ether derived from the bridgehead ketone **135** *via* a Wittig olefination using methoxymethylenetriphenylphosphine. The key oxindole spirocentre and tetrahydropyran ring could be installed using the intramolecular Heck type cyclisation developed by Overman from the unsaturated amide **136**. This could be prepared from the  $\gamma$ -lactam **134**, which would ultimately be gained from the construction of the core structure *via* the meta photocycloaddition reaction of anisole and allyl alcohol.

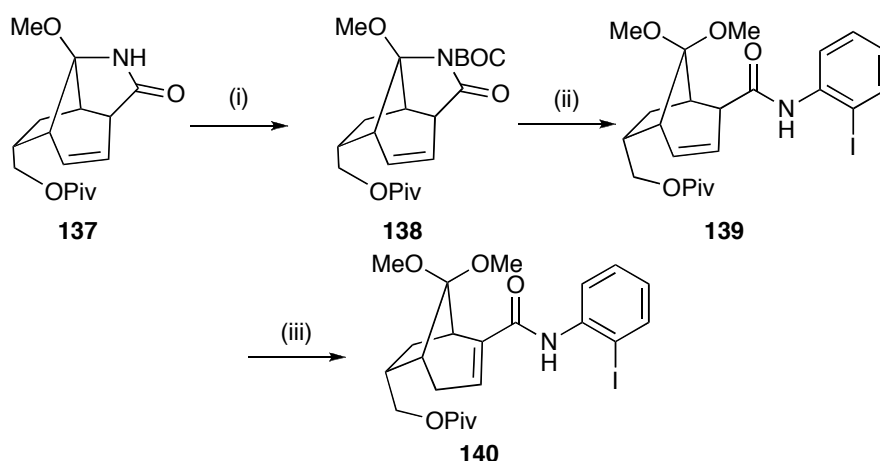
The light induced meta photocycloaddition reaction of anisole and allyl alcohol to afford the 7-endo meta photocycloadduct as the major product began the new synthetic route. A more robust protecting group in the form of the pivaloate ester was chosen for the oxygen functionality, as it was thought the triisopropylsilyl ether would not withstand the acidic conditions utilised during the synthetic route. Thus treatment of

the meta photocycloadduct **25** with trimethylacetyl chloride in pyridine at 0 °C, afforded the pivalate ester **136** in 95% yield (Scheme 4.2.8).



Scheme 4.2.8. Meta photocycloaddition then protection of the alcohol.

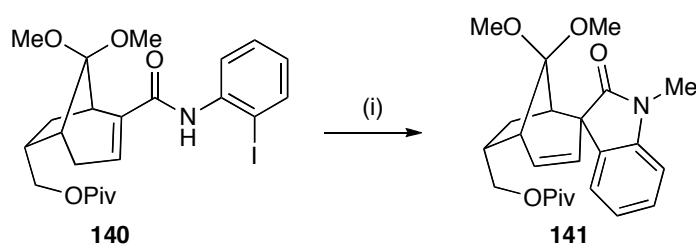
The resultant ester was converted to the  $\gamma$ -lactam **137** via reaction with *N*-chlorosulfonyl isocyanate (*vide supra*). The use of 1.5 equivalents of the isocyanate, as opposed to 5 equivalents in the original investigation, afforded the  $\gamma$ -lactam ring in 95% yield. Our attentions then turned towards opening the  $\gamma$ -lactam ring to afford the anilide functionality. A brief literature survey<sup>92</sup> revealed that tertiary amides such as *N*-BOC or *N*-Ts readily undergo nucleophilic addition to the carbonyl group, in this instance causing rupture of the  $\gamma$ -lactam ring. The nucleophile chosen was 2-iodoaniline, as this would provide the crucial iodo functionality needed to perform the intramolecular Heck spirocyclisation. The synthesis towards the precursor of the Heck intramolecular spirocyclisation can be seen in scheme 4.2.9.



Scheme 4.2.9. Ring opening & conjugation of alkene.

The  $\gamma$ -lactam nitrogen **137** was protected as the *t*-butyl carbamate and subsequently treated with lithiated 2-iodoaniline at  $-78\text{ }^{\circ}\text{C}$  to cleanly afford the ring open product **139**. The *t*-butyl carbamate was now no longer required, and hence was replaced by a methoxy group by treatment with a methanolic solution of HCl. The yield was a rather disappointing 25% as some amide hydrolysis had occurred, which was to be expected under these conditions. The crucial conjugation of the double bond, which was unsuccessful in the previous route, was successfully achieved by reaction of the unconjugated species with one equivalent of DBU in THF at room temperature. DBU was chosen as the base due to its inherent non-nucleophilic nature imparted by the steric hindrance of the bicyclo[5.4.0]undecane ring system. With the conjugated species **140** in hand, our focus moved to the crucial palladium induced spirocyclisation as utilised by Overman *et al.*<sup>69</sup> and Speckamp *et al.*<sup>73</sup>. As previously shown by Overman *et al.*<sup>78</sup> in their model studies towards the installation of the spirooxindole moiety (section 4.1.3), the tertiary amide gave superior yields when subjected to palladium catalysed arylation. Thus the secondary amide **140** was protected as the *N*-methyl amide *via* reaction of the amide with NaH and iodomethane and used without further isolation. The methyl group was chosen to simplify NMR analysis, whereas in the ‘real’ system a cleavable protecting group would need to be utilised.

The system was now setup to undergo the crucial intramolecular Heck spirocyclisation. Following in the same vein as Overman and Speckamp,  $\text{Pd}_2(\text{dba})_3$  was used as the source of palladium(0) (Scheme 4.3.0).



Reagents & conditions: (i) a. NaH, MeI, THF, RT, 1hr; b.  $\text{Pd}_2(\text{dba})_3$ ,  $\text{Et}_3\text{N}$ , MeCN,  $80\text{ }^{\circ}\text{C}$ , 5 hrs, 56%.

Scheme 4.3.0. Methylation and spirocyclisation.

In preliminary studies the iodide was treated with 20 mol %  $\text{Pd}_2(\text{dba})_3$ ,  $\text{Et}_3\text{N}$  in MeCN at reflux temperature in a sealed pressure tube. Gratifyingly, TLC analysis of the

reaction mixture revealed the formation of a new product and complete consumption of starting material had occurred after approximately 5 hrs, although the actual yield of the product was very low. After purification of the crude material, NMR analysis revealed the palladium catalysed spirocyclisation had indeed occurred to give a single compound. Changing the catalyst to  $\text{Pd}(\text{PPh}_3)_4$  in boiling MeCN gave the spirooxindole in 82 % yield after 1.5 hrs. The increased yield was attributed to the greater stability of the catalyst at elevated temperatures. Unfortunately the correct stereochemistry of the spirooxindole could not be assigned at this stage due to an inability to perform nOe experiments. The synthetic route was carried forward in the hope that an intermediate would exist as a crystalline solid and therefore enable assignment of the spirocentre stereochemistry.

The next major synthetic challenge was the formation of the pyrrolidine ring *via* the nitrogen radical based Hoffman Loeffler-Freitag reaction. The precursor to this reaction would stem ultimately from the bridgehead ketone, as discussed in the retrosynthetic analysis, thus transketalisation of the dimethoxyacetal with TsOH in acetone at reflux temperature, afforded the ketone **142** in 54% yield. Fortuitously after purification, the ketone was a crystalline solid, thus single crystal X-ray diffraction gave a definitive answer to the spirooxindole stereochemistry at the C7 position as represented in the ORTEP diagram (Figure 4.6).

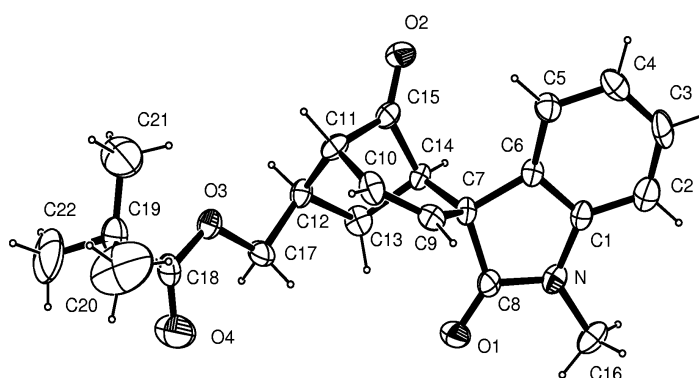


Figure 4.6. ORTEP representation of epimeric spirooxindole (**142**).

As one can quite clearly see, we had solely the epimeric spirooxindole moiety to that of gelsemine. As it was known<sup>80</sup> that the bulky  $\text{Pd}(\text{PPh}_3)_4$  catalyst gave rise to predominantly the wrong epimer and  $\text{Pd}_2(\text{dba})_3$  was also utilised although to only result in the same outcome, it was evident that carbopalladation exclusively occurred on the *exo* face (Figure 4.7).

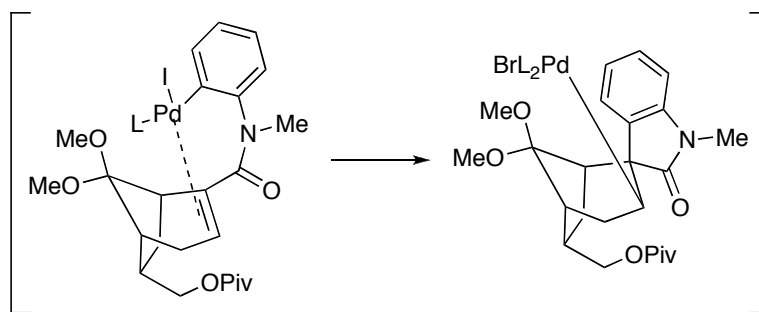


Figure 4.7. *exo*-facial carbopalladation.

This would suggest that carbopalladation of the sterically demanding *endo*-face of the bicyclo[3.2.1]octane skeleton was severely hindered, particularly with the presence of the methylene pivalate ester. Though the argument for the singular formation of the wrong epimer is contradicted by the work of Speckamp *et al.* where a methylene *t*-butyldimethylsilyl ether (**144**) was in place of the methylene pivalate ester as in our system (**143**) (Figure 4.8).

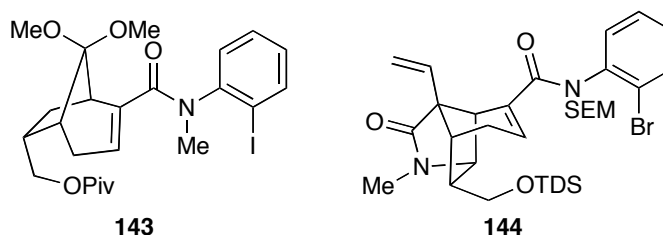


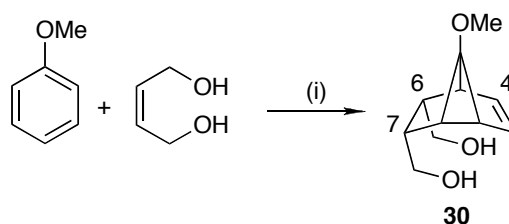
Figure 4.8. Comparison of our own system and Speckamp's precursor to spirocyclisation.

Upon utilising the same conditions to effect spirocyclisation ( $\text{Pd}_2(\text{dba})_3$ ,  $\text{Et}_3\text{N}$ , toluene, reflux) Speckamp observed a mixture of diastereoisomers in the ratio of 2:1 with the correct epimer in the majority, whereas with our own work, only a single isomer was observed. One common aspect to all the syntheses that utilised the intramolecular Heck

spirocyclisation, apart from our own, was the presence of the pyrrolidine ring substructure. It would seem that the incorporation of the pyrrolidine ring, distorts the geometry of the bicyclo[3.2.1]octane to such an extent as to allow *endo*-facial carbopalladation, and hence the correct epimeric product. With this in mind, our attentions focused toward the construction of the pyrrolidine ring.

What appeared to be a straightforward strategy: Wittig reaction to give the enol ether, Mannich reaction to install the secondary amine, bromination of the amine and concurrent subjection of the bromide to the Hofmann Loeffler-Freitag radical based cyclisation reaction, suddenly seemed less trivial than first envisaged. Unfortunately the strategy was underpinned by the formation of the spirooxindole ring and tetrahydropyran ring first. It was assumed that the presence of the tetrahydropyran ring would distort the bicyclo[3.2.1]octane skeleton, to favour abstraction of the C6 proton giving the correct pyrrolidine moiety. A three dimensional model of the system without the tetrahydropyran ring, suggested there would be little differentiation between either the C6 or C7 protons for abstraction. Also, the formation of the tetrahydropyran ring before the spirooxindole, quite clearly would not allow for the installation of the crucial spirocentre. The realisation that the synthetic route would not be successful led us to develop a new strategy based on the meta photocycloaddition adduct derived from anisole and but-2-ene-1,4-diol. It was known from previous studies within the group<sup>8</sup> that no meta photocycloaddition could be achieved between *E*-but-2-ene-1,4-diol and anisole, although reaction of *Z*-but-2-ene-1,4-diol and anisole did occur.

The utility of the anisole and *Z*-but-2-ene-1,4-diol derived meta photocycloaddition adduct **30**, lies with the existence of functionality at the C6 position (Scheme 4.3.1), which could then be further functionalised in order to construct the pyrrolidine ring.

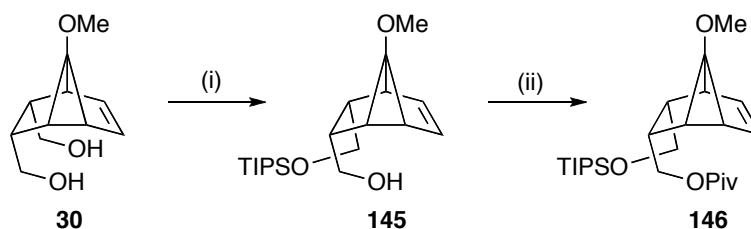


Reagents & conditions: (i) *hν*, MeOH, 14%.

Scheme 4.3.1. Meta photocycloaddition reaction of *Z*-but-2-ene-1,4-diol and anisole.

Monoprotection of the diol and subsequent protection of the remaining hydroxyl functionality with a different protecting group, would allow for selective deprotection of the desired C6 methylene hydroxy group. The strategies in the previous synthetic route could also be utilised to afford functionality at the C4 position.

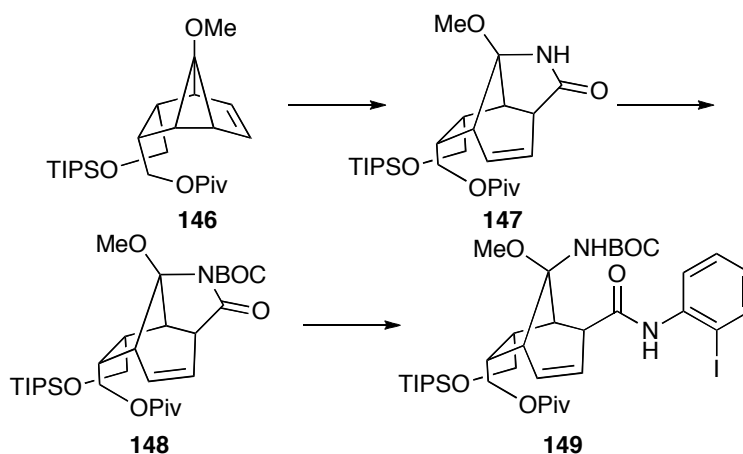
The diol meta photocycloadduct **30** was synthesised as previously mentioned (chapter 2, section 2.2) and treated with NaH in THF to form the alkoxide anion, which was then quenched with TIPSCl to afford the monoprotected triisopropylsilyl ether **145** in a 1:1 mixture of diastereoisomers, which were separable by flash silica chromatography. The resultant free hydroxyl group **145** was then protected as the pivaloate ester to afford the bis protected species **146** in 87% yield over two steps (Scheme 4.3.2).



Reagents & conditions: (i) NaH, TIPSCl, THF; (ii) PivCl, pyridine, 87% over two steps.

Scheme 4.3.2. Monoprotection and subsequent pivaloate protection.

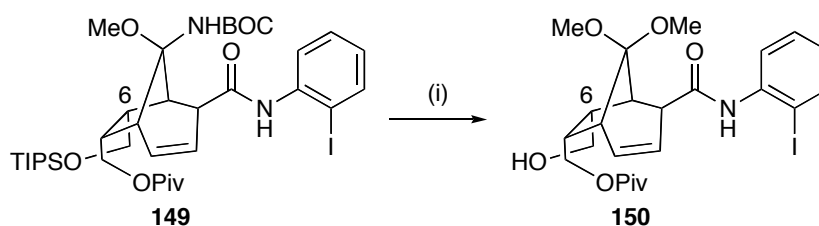
The bis protected species **146** was then reacted with *N*-chlorosulfonyl isocyanate, as before, to afford the  $\gamma$ -lactam ring **147** as a yellow oil in 98% yield. BOC protection of the  $\gamma$ -lactam ring and subsequent treatment of **148** with lithiated 2-iodoaniline at  $-78\text{ }^{\circ}\text{C}$  gave the ring opened product **149** in good yield (Scheme 4.3.3).



*Reagents & conditions:* (i) *N*-chlorosulfonyl isocyanate,  $\text{Na}_2\text{CO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-20^\circ\text{C}$ , 30 mins, 98%; (ii)  $\text{BOC}_2\text{O}$ , pyridine, DMAP (cat.),  $\text{Et}_2\text{O}$ , 87%; (iii) 2-iodoaniline,  $n\text{BuLi}$ , THF,  $-78^\circ\text{C}$  to  $-70^\circ\text{C}$ , 30 mins, 92%.

Scheme 4.3.3. Formation of  $\gamma$ -lactam ring and concurrent ring opening.

Gratifyingly, the conditions utilised in the previous synthetic route were proving to be applicable to the current route, with good yields and reproducible results. Acid catalysed hydrolysis of the bridgehead *t*-butyl carbamate in MeOH afforded the dimethoxyacetal, whilst also cleaving the acid labile triisopropylsilyl group to give the alcohol **150** in reasonable yield with some hydrolysis of the anilide functionality (Scheme 4.3.4).



*Reagents & conditions:* (i)  $\text{HCl}$  (cat.), MeOH, RT, 5 hrs, 68%.

Scheme 4.3.4. Acid catalysed hydrolysis of *t*-butyl carbamate and TIPS removal.

We were now at a point to address the construction of the pyrrolidine ring. Our strategy was based on utilising an intramolecular Mannich reaction; thus installation of an amino group *exo* at the C6 position and then transformation of the bridgehead ketone to the enol ether or aldehyde, would provide the necessary framework to carry out the Mannich reaction (Figure 4.9).



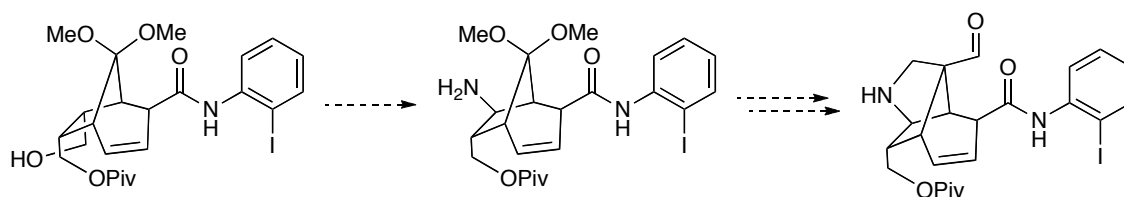
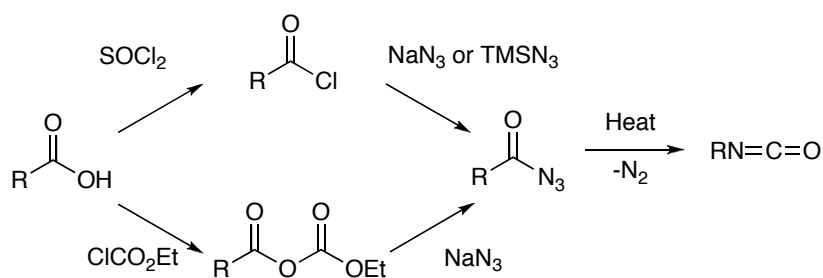


Figure 4.9. Strategy towards the pyrrolidine ring.

The first strategy was based on the use of the Barton modified Hunsdiecker halodecarboxylation<sup>93</sup> of a carboxylic acid, to install a halide at the critical C6 position and displace with an aminos nucleophile. This method was ruled out on the basis that the alkyl radical-halide recombination would commence with no control of the direction of attack of the halide radical.

The next strategy to construct the pyrrolidine ring focused on the use of a Curtius rearrangement<sup>94</sup>. The Curtius rearrangement is essentially the thermal decomposition of an acyl azide (formed from the acyl halide or mixed anhydride) to the isocyanate (Scheme 4.3.5), which can be isolated if the reaction is conducted in non-protic conditions. If the pyrolysis is carried out in protic solvents such as alcohols, amines or water, the reaction will afford carbamates, ureas and primary amines respectively.

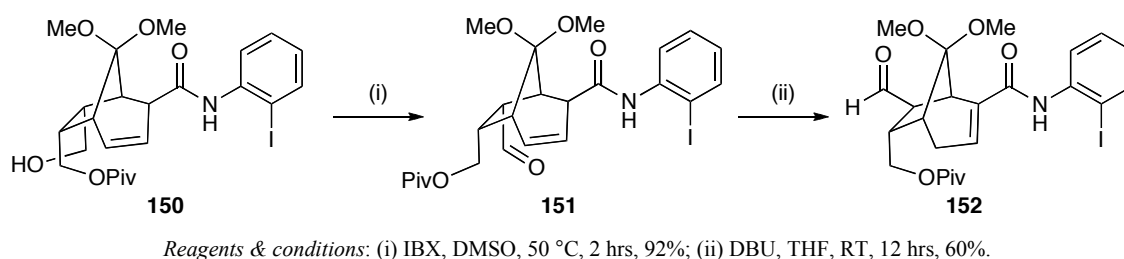


Scheme 4.3.5. Curtius rearrangement.

The use of diphenylphosphoryl azide<sup>95</sup> in the Curtius rearrangement avoids the formation of the acyl halide with the acyl azide being formed *in situ* from the base activated carboxylic acid and diphenylphosphoryl azide, which then undergoes rearrangement to the isocyanate.

The problem of installing amino functionality on the C6 *exo* facial position prior to undergoing the crucial intramolecular Mannich reaction was solved *via* the use of epimerisation. To afford the carboxylic acid precursor to the Curtius rearrangement, the alcohol functionality would have to be oxidised twice: once to the aldehyde and again to the acid. It was theorised that whilst at the aldehyde oxidation level, treatment with a suitable base would affect epimerisation at the C6 centre, with the aldehyde preferring to sit away from the sterically bulky pivaloate ester.

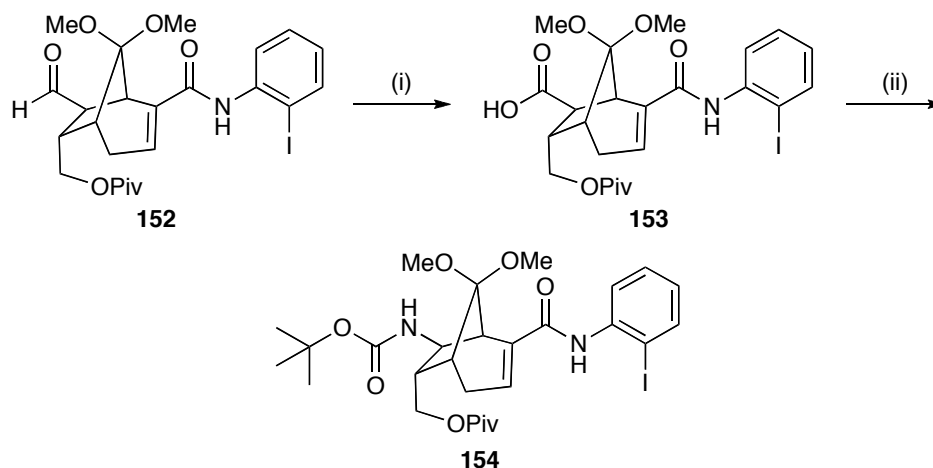
It was also reasoned that upon base induced epimerisation, conjugation of the double bond might also occur at the same time. Thus reaction of the alcohol **150** with IBX in DMSO at 50 °C afforded the aldehyde **151** in good yield. The base selected to affect epimerisation was DBU as it had successfully conjugated the double bond in the previous synthetic route. Treatment of the aldehyde with one equivalent of DBU in THF at room temperature for 12 hrs afforded a new compound (Scheme 4.3.6), which after purification *via* silica chromatography, was deduced to have contained a conjugated double bond. This was confirmed by the presence of a single alkenic peak in its NMR spectrum.



Scheme 4.3.6. Oxidation to aldehyde and epimerisation.

Epimerisation of the aldehyde was less straightforward to confirm. The two vicinal protons if *trans* to one another would have a *J* coupling value of approximately 7 Hz, although in a rigid ring structure the angle between the two protons could be negligible. Further analysis of the proton NMR did reveal a *J* value of around 7 Hz between the two protons, although without nOe experiments, epimerisation of the aldehyde *exo*, could not be fully ascertained.

The synthetic route was continued with the assumption that the aldehyde was now in the *exo* position, with oxidation to the acid and subsequent Curtius rearrangement (Scheme 4.3.7).



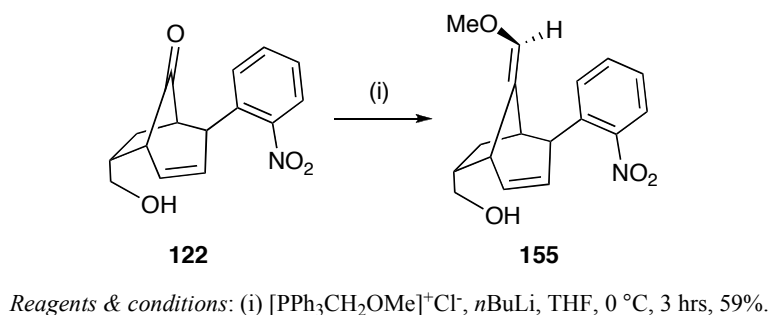
*Reagents & conditions:* (i)  $\text{NaClO}_2$ , 2-methyl-2-butene,  $\text{KH}_2\text{PO}_4$ , *t*BuOH,  $\text{H}_2\text{O}$ , RT, 1hr, 70%; (ii) diphenylphosphoryl azide,  $\text{Et}_3\text{N}$ , *t*BuOH, reflux, 5 hrs, 40%.

Scheme 4.3.7. Oxidation to acid and subsequent Curtius rearrangement.

The aldehyde **152** was oxidised with  $\text{NaClO}_2$ ,<sup>96</sup> in a solution of *t*-butanol and  $\text{H}_2\text{O}$  at room temperature to afford the acid **153** in 70% yield. With the acid in hand, the Curtius rearrangement was attempted utilising diphenylphosphoryl azide and  $\text{Et}_3\text{N}$  as the base. The solvent of choice was *t*-butanol to afford the carbamate as the product. A solution of the acid, diphenylphosphoryl azide,  $\text{Et}_3\text{N}$  in *t*-butanol was heated at reflux temperature for approximately 5 hrs under a nitrogen atmosphere. TLC analysis of the reaction mixture indicated the formation of a less polar compound, which was to be expected. After silica chromatographic purification of the new product, proton NMR analysis revealed the presence of the amidic carbamate proton in its rotameric form, confirming the Curtius rearrangement to afford **154** had been successful. The carbamate fortunately existed as a semi-crystalline solid, from which a partial X-ray crystallographic structure was obtained. This crucial piece of data was of paramount importance for two reasons, firstly it revealed the location of the pivaloate ester functionality because monoprotection of the diol **30** afforded a 1:1 mixture of structural isomers, which could not be fully characterised without nOe experiments. Secondly, the crystal structure revealed the stereochemistry at the C6 position. To our delight, epimerisation had occurred to give the *exo* aldehyde, which was subsequently converted

to the carbamate (*vide supra*). Unfortunately the crystallographic data was of a low quality, thus only the structure could be reasonably determined without any publishable data.

With this exceptional result in hand, we then turned our attention to functionalisation at the bridgehead position in order to affect the intramolecular Mannich reaction. Time restraints meant that only preliminary studies could begin towards the intramolecular Mannich cyclisation. As previously mentioned, the installation of the enol ether *via* Wittig reaction could feasibly be utilised to instigate the intramolecular Mannich reaction. The conversion of the bridgehead ketone to the enol ether on a different system was shown by previous work in our group<sup>84</sup>. The Wittig salt derived from methoxymethyl chloride and triphenylphosphine provided the necessary reagent to afford the enol ether moiety **155** (Scheme 4.3.8).



Scheme 4.3.8. Wittig reaction on the bridgehead ketone.

The ketone **122** was reacted with the Wittig ylide formed *via* the treatment of the Wittig salt with  $n\text{BuLi}$  at 0 °C to afford the enol ether in 59% yield. With this encouraging result, we began our investigation with the acid catalysed transketalisation of the bridgehead dimethoxyacetal to the ketone under conditions previously utilised. The ketone was taken forward without further purification and subjected to the Wittig reaction with the same conditions as used previously. TLC analysis of the reaction mixture indicated the complete consumption of starting material and the formation of a new product, although analysis of the crude material revealed complete decomposition of starting material and only the presence of triphenylphosphine oxide *via* proton NMR. At this point, sadly due to time restrictions, the project had to be put on hold and the Mannich reaction was not further investigated. In retrospect, the utilisation of the non-

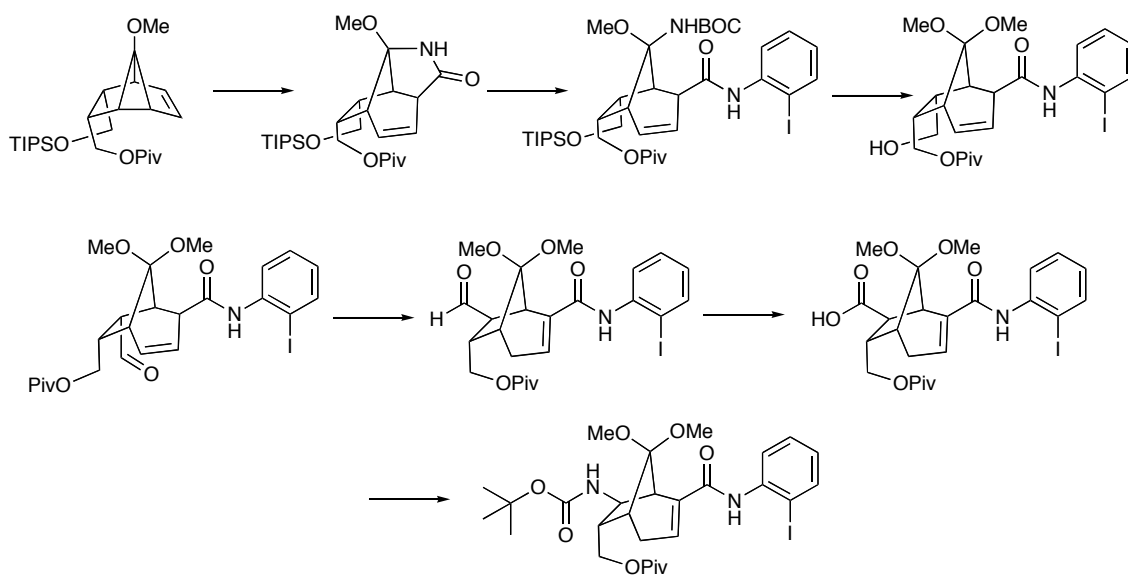
stabilised (methoxymethyl)triphenylphosphonium ylide on such a congested system was perhaps too adventurous, functionalisation of the bridgehead ketone by other groups such as Fukuyama *et al.* utilised the Horner-Wadsworth-Emmons<sup>97</sup> modified Wittig reaction, where the ylide is stabilised by the  $\beta$ -ester. This method had the added benefit of two ethoxy groups on the phosphorus, instead of the bulky triphenylphosphines.

In conclusion, a thorough investigation into the total synthesis of gelsemine realised *via* the meta photocycloaddition reaction has been accomplished. The atom efficient construction of a complex fused tricyclic system, along with the propensity for the anisole/allyl alcohol derived meta photocycloadduct to fragment, gives credence to the choice of starting material. The original synthetic plan, although elegant in design, failed with what seemed a trivial synthetic operation of conjugating the double bond. This unfortunate failure exemplified the non-triviality of the total synthesis, which was quite evident with the synthetic strategies presented at the beginning of this chapter.

Although the original synthetic plan failed, strategies to circumvent this were sought, again based on the fragmentation route but directed towards installation of the crucial conjugated double bond. The route successfully achieved the goal of conjugation, with the nitro aryl ring present in order to construct the spirooxindole moiety, although attempts at palladium catalysed alkoxycarbonylation on the congested quaternary centre to furnish the required carbonate were unsuccessful. The formation of the  $\gamma$ -lactam ring *via* isocyanate addition was a welcome breakthrough, although not a novel reaction as previously thought, that allowed access to the precursor of the intramolecular Heck cyclisation. The formation of the epimeric spirocentre was a disappointment, but the synthetic potential of the meta photocycloadduct had not yet been exhausted. The mere fact that work by previous groups into the total synthesis of gelsemine has produced an impressive amount of research, allows one to devise a more robust synthetic plan based around the findings.

The utility of the meta photocycloaddition reaction was again demonstrated, with the application of the diol moiety **30**. This ultimately led to the Curtius product **154**, the precursor to an intramolecular Mannich reaction, which unfortunately, due to time restrictions, was never thoroughly investigated. An analysis of the current system (**154**)

reveals that all the functionality is present in order to complete, with proven concurrent synthetic steps, the total synthesis of gelsemine.



Overview of current route

### 4.3 Future scope

The first task to be undertaken is to construct the pyrrolidine ring system. The Horner-Wadsworth-Emmons reaction on the bridgehead ketone, would afford the vinyl ester, which, with the *exo* carbamate in place could undergo Michael addition as exemplified by Fukuyama *et al.* to give the lactam ring. Further elaboration would give rise to a formal synthesis of gelsemine.

An intriguing reaction to investigate would be to have the bridgehead enol ether in place before the Curtius rearrangement. Treatment of the *exo* carboxylic acid with diphenylphosphoryl azide in non-protic conditions would afford the isocyanate, which could lead to *in situ* ring closure to give the lactam ring in one synthetic operation.

## 5. Experimental

### 5.1 General procedures

$^1\text{H}$  NMR spectra were recorded on Bruker DPX300 or Bruker AMX500 Fourier transform spectrometers at 300 or 500 MHz. Chemical shifts ( $\delta$ ) are quoted in ppm using tetramethylsilane or residual chloroform as internal reference ( $\delta = 0.00$  ppm), and coupling constants ( $J$ ) are quoted in Hz.  $^{13}\text{C}$  NMR spectra were recorded using the same instruments, and chemical shifts ( $\delta$ ) are quoted in ppm using  $\text{CDCl}_3$  as internal reference ( $\delta = 77.0$  ppm).

IR spectra were recorded on Perkin-Elmer Spectrum One Fourier transform instruments and frequencies ( $\nu_{\text{max}}$ ) are quoted in wavenumbers ( $\text{cm}^{-1}$ ).

Low- and high-resolution electron impact (EI) mass spectra were recorded using a Fisons Autospec instrument. High-resolution electrospray ionization (ESI) mass spectra were recorded using a Bruker Daltonics APEXIII instrument.

The starting materials for the synthesis of the compounds were obtained from the usual suppliers (Sigma – Aldrich – Fluka, Lancaster, Fisher etc.) unless otherwise stated. The anhydrous solvents were obtained from Aldrich Chemicals in Sure/Seale bottles and were used without further purification. Petroleum ether used with a boiling range of 40 – 60 °C. Flash column chromatography was performed using Fisher Matrex 60 (35–70 mm) silica. Analytical thin-layer chromatography (TLC) was performed using Whatman K6F silica gel plates (60 Å porosity) developed with UV light or an alkaline solution of potassium permanganate followed by heating to give yellow spots.

Irradiations were carried out in quartz immersion-well reactors fitted with 6 or 16 W low-pressure mercury vapour lamps or 125 or 400 W medium-pressure mercury vapour lamps as supplied by Photochemical Reactors Ltd, Reading, UK. Oxygen free solvent for the irradiation experiments was simply obtained by passing a vigorous stream of nitrogen gas through sintered glass tube into the solvent for 15 min at RT. Experiments

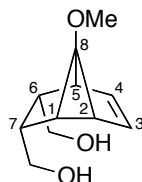
were conducted with gentle stirring of the reaction solution under an atmosphere of nitrogen and with cold-water cooling of the lamp and vessel contents throughout.

## 5.2 Experimental data

### 5.2.1 Palladium-mediated fragmentation of meta photocycloadducts

#### ***rac*-(1*S*,2*R*,5*S*,6*S*,7*R*,8*S*)-6,7-Dihydroxymethyl-8-methoxytricyclo[3.2.1.0<sup>2,8</sup>]oct-3-ene **30**.**

A solution of anisole (43.2 g, 400 mmol) and *Z*-but-2-ene-1,4-diol (70.4 g, 800 mmol) in methanol (350 mL) was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 20 mins. This solution was then irradiated with 254 nm UV light for 120 h using a 16 W low pressure mercury vapour lamp. The unreacted starting materials and solvent were removed by distillation and the residue was subjected to column chromatography (silica, Et<sub>2</sub>O/MeOH, 100:1, then CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 20:1) to obtain the *endo* isomer **30** (11.3 g, 14%) as a viscous, pale green oil.



<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

δ: 2.06 (1H, ddd, *J* = 1.2, 2.4, 8.4 Hz, H-2), 2.26 (1H, dd, *J* = 6.7, 8.4 Hz, H-1), 2.80–2.88 (1H, br s, –OH), 2.87–2.94 (1H, m, H-7), 3.03–3.09 (1H, m, H-6), 3.14 (1H, ddd, *J* = 1.3, 2.6, 5.7 Hz, H-5), 3.38 (3H, s, –OCH<sub>3</sub>), 3.48–3.60 (1H, br s, –OH), 3.50 (1H, dd, *J* = 4.3, 10.7 Hz, –CHHOH), 3.57 (1H, dd, *J* = 4.5, 11.4 Hz, –CHHOH), 3.67 (1H, t, *J* = 11.2 Hz, –CHHOH), 3.98 (1H, t, *J* = 10.3 Hz, –CHHOH), 5.63 (1H, ddd, *J* = 1.2, 2.6, 5.8 Hz, H-4), 5.73 (1H, dd, *J* = 2.4, 5.8 Hz, H-3).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)

δ: 35.2, 39.0, 44.7, 53.4, 55.4, 56.4, 60.9, 62.8, 90.6, 131.3, 133.0.



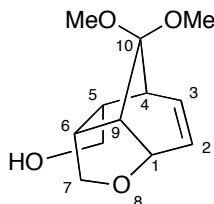
HRMS (ESI)  $m/z$  calcd for  $C_{11}H_{16}NaO_3 [M+Na]^+$  219.0997, found 219.0998.

FTIR /  $cm^{-1}$ : 1592, 1656, 3306.

**rac-(1*S*,4*S*,5*S*,6*R*,9*S*)-8-Oxa-5-hydroxymethyltricyclo-10,10-dimethoxy[4.2.1.1<sup>4,9</sup>]dec-2-ene **32**.**

The catalyst was preformed by mixing equimolar amounts of palladium(II) chloride and the ligand of choice (+)-Binap, (+)-Trosc, (-)-Quinap, (-)-Sparteine in MeOH (2 mL) overnight. The solvent was removed *in vacuo* and the pre-formed catalyst was used without further purification.

A mixture of the diol photoadduct **30** (0.52 mmol), preformed catalyst (5 mol %) and MeOH (2 mL) was added to a round bottom flask with a balloon of dioxygen attached. The solution was stirred for 72 hrs. The reaction mixture was passed through Celite and the MeOH was removed *in vacuo*. The resultant oil was dissolved in dichloromethane (25 mL) and washed with brine (2 x 10 mL) and dried over  $MgSO_4$ . The solvent was removed *in vacuo* and the residue subjected to column chromatography (silica, petroleum ether/EtOAc, 4:1) to afford **32** (0.02 g, 19 %) as a white solid, mp 90.4 – 91.8°C.



$^1H$  NMR (500 MHz,  $CDCl_3$ )

$\delta$ : 1.53 (1H, br s, -OH), 2.63 (1H, ddd,  $J = 2.1, 5.1, 7.0$  Hz, H-4), 2.76 (1H, dddd,  $J = 5.1, 7.9, 7.9, 9.0$  Hz, H-5), 2.82 – 2.88 (1H, m, H-6), 2.89 – 2.92 (1H, m, H-9), 3.18 (3H, s, -OCH<sub>3</sub>), 3.27 (3H, s, -OCH<sub>3</sub>), 3.66 (1H, dd,  $J = 3.8, 9.3$  Hz, H-7), 3.67 (1H, dd,  $J = 8.0, 10.4$  Hz, -CHHOH), 3.74 (1H, dd,  $J = 8.0, 10.4$  Hz, -CHHOH), 3.91 (1H, dd,  $J = 8.0, 9.4$  Hz, H-7'), 4.70 (1H, dd,  $J = 3.6, 6.2$  Hz, H-1), 5.73 (1H, ddd,  $J = 1.0, 3.6, 9.4$  Hz, H-2), 5.89 (1H, dd,  $J = 7.0, 9.4$  Hz, H-3).

$^{13}C$  NMR (125MHz,  $CDCl_3$ )

$\delta$ : 40.3, 41.3, 47.0, 48.3, 49.2, 51.0, 61.2, 67.0, 79.1, 110.0, 128.5, 129.3.

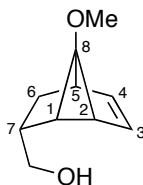
HRMS (ESI)  $m/z$  calcd for  $C_{12}H_{18}NaO_4$   $[M+Na]^+$  249.1103, found 249.1101.

FTIR /  $cm^{-1}$ : 1641, 3400.

## 5.2.2 Studies towards a conformationally constrained amino acid

### **rac-(1S,2R,5R,7R,8S)-7-Hydroxymethyl-8-methoxytricyclo[3.2.1.0<sup>2,8</sup>]oct-3-ene **25**.**

A solution of anisole (43.2 g, 400 mmol) and allyl alcohol (46.4 g, 800 mmol) in cyclohexane (302 mL) was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 20 mins. This solution was then irradiated with 254 nm UV light for 120 hrs using a 16 W low-pressure mercury vapour lamp. The unreacted starting materials were removed *in vacuo* and the residue subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether, 2:1) to afford the 7-*endo* metaphotocycloadduct **25** (5.8 g, 8%) as a yellow oil.



<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

$\delta$ : 1.52 (1H, dd,  $J$  = 1.3, 12.9 Hz, H-6a), 2.05 (1H, br s, -OH), 2.09 (1H, ddd,  $J$  = 0.6, 2.2, 8.5 Hz, H-2), 2.15 (1H, dd,  $J$  = 6.2, 8.5 Hz, H-1), 2.43 (1H, ddd,  $J$  = 6.6, 11.4, 12.9 Hz, H-6b), 2.75 (1H, m, H-7), 3.18 (1H, ddd,  $J$  = 1.3, 2.7, 6.8 Hz, H-5), 3.37 (3H, s, -OCH<sub>3</sub>), 3.51 (1H, dd,  $J$  = 7.2, 10.3 Hz, -CHHOH), 3.59 (1H, dd,  $J$  = 8.4, 10.3 Hz, -CHHOH), 5.57 (1H, dddd,  $J$  = 0.6, 1.3, 2.7, 5.6 Hz, H-4), 5.65 (1H, dd,  $J$  = 2.2, 5.6 Hz, H-3).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)

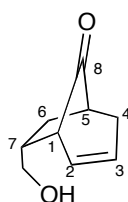
$\delta$ : 36.7, 38.9, 40.0, 44.9, 51.2, 56.2, 65.7, 91.4, 129.1, 136.5.

HRMS (EI)  $m/z$  calcd for  $C_{10}H_{14}O_2$   $[M]^+$  166.0994, found 166.0996.

FTIR /  $cm^{-1}$ : 1645, 2933, 3403.

**rac-(1*S*,5*S*,7*R*)-7-(Hydroxymethyl)bicyclo[3.2.1]oct-2-en-8-one 47.**

A mixture of the 7 *endo* metaphotocyclo adduct **25** (3.0 mmol) and concentrated hydrochloric acid (6.0 mmol) in an acetone/water mix (15 mL, 1:1) was heated at 75 °C for approximately 0.5 hrs. After this time the mixture was allowed to cool to RT and the reaction quenched with a saturated solution of NaHCO<sub>3</sub> (25 mL). The aqueous layer was extracted with dichloromethane (3 x 25 mL) and the organic layer washed with brine (1 x 50 mL) and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica, Et<sub>2</sub>O/petroleum ether 3:1) to afford the hydroxy ketone **47** (1.31 g, 67%) as a yellow oil.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.14 (1H, ddd, *J* = 1.5, 9.5, 13.2 Hz, H-6), 1.75 (1H, br, -OH), 1.99 - 2.09 (1H, m, H-6'), 2.17 - 2.20 (1H, m, H-5), 2.33 (1H, dd, *J* = 2.5, 2.8 Hz, H-4), 2.38 - 2.40 (1H, m, H-7), 2.47 - 2.50 (1H, m, H-1), 2.74 (1H, ddt, *J* = 2.1, 6.1, 17.2 Hz, H-4'), 3.55 (1H, dd, *J* = 6.0, 10.4 Hz, -CHH-OH), 3.64 (1H, dd, *J* = 8.9, 10.4 Hz, -CHH-OH), 5.49 - 5.60 (2H, m, H-2, H-3).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

δ: 29.1, 43.0, 43.1, 44.6, 47.3, 63.4, 76.7, 77.0, 77.2, 127.4, 128.4, 216.4.

HRMS (ESI) *m/z* calcd for C<sub>9</sub>H<sub>12</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup> 175.0735 found 175.0729.

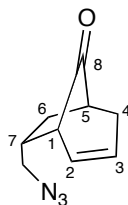
FTIR / cm<sup>-1</sup>: 1630, 1752, 3399.

**rac-(1*S*,5*S*,7*R*)-7-(Azidomethyl)bicyclo[3.2.1]oct-2-en-8-one 49.**

A stirred mixture of the hydroxy ketone **47** (0.6 g, 3.9 mmol), pyridine (0.47 mL, 5.9 mmol) and dichloromethane (2 mL) was cooled to 0 °C. To the solution, trifluoromethanesulfonate anhydride (0.73 mL, 4.3 mmol) was added drop wise *via* syringe and the mixture allowed to stir for approximately 30 mins. The crude reaction mixture was diluted with dichloromethane (20 mL) and washed with water (3 x 20 mL)

and brine (20 mL). The aqueous fractions were back extracted once with dichloromethane (30 mL). The combined organic layers were dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The crude triflate was used without further purification.

A stirred solution of the triflate (0.81 g, 2.8 mmol) in DMF (3 mL) was cooled to 10 °C and to this was added sodium azide (0.27 g, 4.2 mmol) and 15-crown-5 ether (3.1 mmol). After approximately 1 hr the reaction mixture was poured into water (25 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The residue was subjected to column chromatography (silica,  $\text{Et}_2\text{O}$ /petroleum ether, 1:3) to afford the azide **49** (0.25 g, 50%) as a pale yellow oil.



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 1.34 (1H, dd,  $J = 7.6, 13.4$ , H-6), 2.22 – 2.30 (1H, m, H-6'), 2.33 – 2.39 (1H, m, H-4), 2.52 (1H, dd,  $J = 2.9, 5.7$  Hz, H-5), 2.56 (1H, dd,  $J = 2.8, 5.5$  Hz, H-1), 2.59 – 2.63 (1H, m, H-7), 2.93 (1H, dm, H-4'), 3.42 (1H, ddd,  $J = 2.9, 6.3, 12.2$  Hz, -CHH-), 3.50 (1H, ddd,  $J = 2.9, 8.8, 12.0$  Hz, -CHH-), 5.69 (1H, dt,  $J = 2.8, 9.3$  Hz, H-3), 5.67 – 5.75 (1H, m, H-2).

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )

$\delta$ : 15.6, 30.8, 42.3, 43.6, 47.9, 52.8, 128.4, 128.5, 215.9.

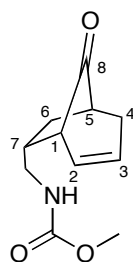
HRMS (EI) calcd for  $\text{C}_9\text{H}_{11}\text{N}_3\text{O}$   $[\text{M}]^+$  177.0900, found 177.0902.

FTIR /  $\text{cm}^{-1}$ : 1647, 1756, 2099.

**rac-((1*S*,5*R*,7*R*)-8-Oxobicyclo[3.2.1]oct-3-en-7-yl)-7-methylcarbamate **50**.**

A mixture of the azide **49** (0.58 g, 3.3 mmol), Lindlar's catalyst (0.35 g, 6.6 mmol) and ethanol (3 mL) was vigorously stirred under a hydrogen atmosphere for 12 hrs. The palladium catalyst was removed *via* filtration and the solid rinsed with ethanol (25 mL). The filtrate was reduced *in vacuo* and the resultant residue dissolved in dichloromethane (25 mL) and dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. A solution of the

crude amine (0.45 g, 2.9 mmol), Et<sub>3</sub>N (0.45 g, 4.4 mmol) in THF (2 mL) was cooled to 0 °C and methylchloroformate (0.39 g, 4.1 mmol) was added drop wise *via* syringe. The resultant solution was stirred for 1 hr at 0 °C and the reaction quenched with a saturated solution of NH<sub>4</sub>Cl (5 mL). The resultant mixture was extracted with DCM (3 x 20 mL) and the organic fractions were dried over MgSO<sub>4</sub> and reduced *in vacuo*. The residue was subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether, 2:1) to afford the carbamate **50** (0.27 g, 40%) as a yellow oil.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.48 (1H, dd, *J* = 8.4, 12.3 Hz, H-6a), 2.34 - 2.39 (1H, m, H-6b), 2.46 – 2.50 (1H, m, H-4a), 2.58 – 2.69 (3H, m, H-1, H-5, H-7), 3.02 (1H, dd, *J* = 3.2, 17.2 Hz, H-4b), 3.43 – 3.60 (2H, m, -CH<sub>2</sub>-N-), 3.78 (3H, s, -NHCOOCH<sub>3</sub>), 4.95 (1H, br s -NH), 5.83 (2H, m, H-2, H-3).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

δ: 30.8, 31.2, 43.0, 43.5, 43.7, 47.9, 57.5, 128.1, 128.7, 157.3, 207.4.

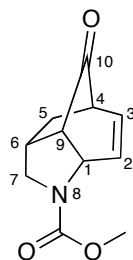
HRMS (ESI) *m/z* calcd for C<sub>11</sub>H<sub>15</sub>NNaO<sub>3</sub> 232.0949, found 232.0944.

FTIR / cm<sup>-1</sup>: 1704, 1753, 3337.

**rac-((6*R*,9*R*,1*S*,4*R*)-8-(Methoxycarbonylamino))-10-oxotricyclo[5.4.3.0<sup>1,9</sup>]non-2-ene **52**.**

A mixture of the carbamate **51** (0.21 g, 1.0 mmol), PhSeCl (0.20 g, 1.0 mmol), K<sub>2</sub>CO<sub>3</sub> (0.13 g, 1.0 mmol), silica (10 wt. %) in DCM (2 mL) was stirred for approximately 2 hrs. The reaction mixture was filtered, dried over MgSO<sub>4</sub> and the solvent removed *in vacuo*. The crude pyrrolidine (0.46 g, 1.2 mmol) was dissolved in THF (2 mL) and MMPP (0.63 g, 2.5 mmol) was added and the resultant mixture stirred for 1 hr. The reaction mixture was filtered through celite and the solvent removed *in vacuo*. The

residue was subjected to column chromatography (silica, Et<sub>2</sub>O/petrol 4:1) to afford the cyclised methyl carbamate **52** as a yellow oil (0.15 g, 71%).



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.65 (1H, dd, *J* = 2.9, 13.1 Hz, H-5), 2.47 (1H, ddd, *J* = 6.6, 13.0, 17.1 Hz, H-5'), 2.59 (1H, dt, *J* = 6.7, 16 Hz, H-4), 2.73 – 2.78 (1H, m, H-9), 2.83 – 2.88 (1H, m, H-6), 3.26 (1H, t, *J* = 9.4 Hz, H-7a), 3.64 (3H, d, *J* = 5.3 Hz, -NCOOCH<sub>3</sub>), 3.82 (1H, m, H-7b), 4.97 (1H, dd, *J* = 4.0, 6.7 Hz, H-1), 5.83 (1H, dd, *J* = 3.7, 8.7 Hz, H-3), 6.09 (1H, dd, *J* = 7.7, 8.8 Hz, H-2).

(Proton H-7b exists in its rotameric form).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

δ: 34.8, 35.8, 39.1, 44.5, 50.8, 51.7, 54.4, 126.5, 134.6, 154.1, 210.5.

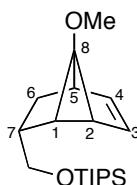
HRMS (ESI) *m/z* calcd for C<sub>11</sub>H<sub>13</sub>NNaO<sub>3</sub> 230.0793, found 230.0787.

FTIR / cm<sup>-1</sup>: 1388, 1451, 1696, 1759.

### 5.2.3 Studies toward the total synthesis of gelsemine.

#### *rac*-(1*S*,2*R*,5*R*,7*R*,8*S*)-7-Trisopropylsilylmethylether-8-methoxy-tricyclo[3.2.1.0<sup>2,8</sup>]oct-3-ene **133**.

A mixture of the 7-*endo* metaphotocycloadduct **25** (2 g, 12 mmol), imidazole (1.63 g, 24 mmol), DMAP (0.073 g, 0.6 mmol, 5 mol %) in dichloromethane (2 mL) was cooled to 0 °C and triisopropylsilyl chloride (2.5 g, 13 mmol) was added drop wise *via* syringe over 5 mins. The resultant mixture was stirred for approximately 12 hrs and diluted with dichloromethane (30 mL). The organic layer was washed with brine (2 x 20 mL), dried over MgSO<sub>4</sub> and reduced *in vacuo*. The residue was subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether, 1:10) to afford the triisopropylsilyl ether **133** (3.7 g, 95%) as a yellow oil.



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 0.87 (3H, m,  $-\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$ ), 1.03 (18H, s,  $-\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$ ), 1.59 (1H, dd,  $J = 1.5, 12.8$  Hz, H-6a), 2.05 (1H, ddd,  $J = 1.8, 3.6, 8.5$  Hz, H-2), 2.16 (1H, dd,  $J = 6.2, 8.5$  Hz, H-1), 2.39 (1H, ddd,  $J = 6.5, 11.4, 12.9$  Hz, H-6b), 2.72 – 2.84 (1H, m, H-7), 3.15 (1H, ddd,  $J = 1.0, 2.7, 6.4$  Hz, H-5), 3.37 (3H, s,  $-\text{OCH}_3$ ), 3.61 (1H, d,  $J = 2.8$  Hz,  $-\text{CHHOTIPS}$ ), 3.63 (1H, d,  $J = 3.2$  Hz,  $-\text{CHHOTIPS}$ ), 5.57 (1H, dddd,  $J = 0.6, 1.9, 2.6, 5.5$  Hz, H-4), 5.63 (1H, dd,  $J = 2.2, 5.5$  Hz, H-3).

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )

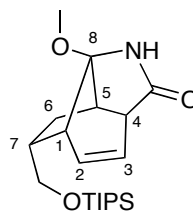
$\delta$ : 12.3, 18.7, 36.4, 39.9, 40.3, 45.7, 51.6, 56.5, 66.9, 91.9, 129.5, 136.9.

HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{34}\text{NaO}_2\text{Si}$   $[\text{M}+\text{Na}]^+$  345.2225, found 345.2220.

FTIR /  $\text{cm}^{-1}$ : 1097, 1592.

**rac-((1*S*,3*R*,4*R*,7*R*)-8-Oxo-9-aza-10-methoxytricyclo[5.3.2.0<sup>1,7</sup>]dec-5-en-1-yl)methyl 2,2-dimethylpropanoate **134**.**

A mixture of the triisopropylsilyl ether **133** (1 g, 3.0 mmol),  $\text{Na}_2\text{CO}_3$  (0.049 g, 0.4 mmol) in dichloromethane (5 mL) was cooled to 0 °C and *N*-chlorosulfonyl isocyanate (2.2 g, 15 mmol) was added drop wise *via* syringe over 5 mins. The resultant mixture was stirred for 1 hr and quenched with  $\text{H}_2\text{O}$  (1 mL). The yellow residue was dissolved in  $\text{Et}_2\text{O}$  (50 mL) and water (50 mL) and a sub stoichiometric amount of KI was added and the biphasic solution was stirred for 5 hrs. The organic layer was partitioned and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (2 x 20 mL). The organic layers were dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The residue was subjected to column chromatography (silica,  $\text{Et}_2\text{O}$ /petroleum ether 3:1) to afford the  $\gamma$ -lactam ring **134** (0.45 g, 40%) as a white crystalline solid, mp 83.5 – 85.5 °C (for crystallographic data see appendix I).



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 0.80 (3H, m,  $-\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$ ), 0.98 (18H, s,  $-\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$ ), 1.66 (2H, m, H-6a, H-6b), 2.63 (1H, ddd,  $J = 1.4, 5.0, 6.0$  Hz, H-4), 2.76 (1H, ddd,  $J = 1.4, 7.4, 8.9$  Hz, H-5), 2.84 – 2.93 (2H, m, H-1, H-7), 3.30 (3H, s,  $-\text{OCH}_3$ ), 3.59 (1H, d,  $J = 1.5$  Hz,  $-\text{CHHOTIPS}$ ), 3.62 (1H, d,  $J = 3.3$  Hz,  $-\text{CHHOTIPS}$ ), 5.76 (1H, br s,  $-\text{NH}-$ ), 5.81 (1H, ddd,  $J = 1.1, 5.5, 9.1$  Hz, H-3), 5.89 (1H, ddd,  $J = 1.2, 5.5, 9.1$  Hz, H-2).

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )

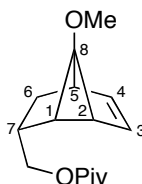
$\delta$ : 12.3, 24.2, 18.4, 44.7, 46.2, 49.9, 50.2, 52.5, 64.3, 99.3, 126.7, 132.5, 178.6.

HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{35}\text{NNaO}_3\text{Si}$  388.2283, found 388.2278.

FTIR /  $\text{cm}^{-1}$ : 1459, 1622, 1711, 3178.

**rac-(1*S*,2*R*,5*S*,6*S*,7*R*,8*S*)-7-Methyl 2,2-dimethylpropanoate-8-methoxytricyclo[3.2.1.0<sup>2,8</sup>]oct-3-ene **136**.**

A stirred solution of the 7-*endo* alcohol **25** (2.78 g, 16 mmol) in pyridine (5 mL) was cooled to 0 °C. To this solution was added trimethylacetyl chloride (4 g, 33 mmol) drop wise *via* syringe over 5 mins. The reaction was allowed to stir for approximately 5 mins and then diluted with  $\text{Et}_2\text{O}$  (30 mL) and washed with 2 M HCl (20 mL) and brine (2 x 20 mL). The organic layer was dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The residue was subjected to flash chromatography (silica,  $\text{Et}_2\text{O}$ /petroleum ether, 1:5) to afford the 7-*endo* pivaloate ester **136** (4 g, 95%) as a yellow oil.



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 1.09 (9H, s,  $-\text{OCOC}(\text{CH}_3)_3$ ), 1.53 (1H, dd,  $J = 0.9, 12.9$  Hz, H-6a), 2.04 – 2.14 (2H, m, H-1, H-2), 2.40 (1H, ddd,  $J = 6.4, 11.2, 12.8$  Hz, H-6b), 2.74 – 2.86 (1H, m, H-7),



3.15 (1H, ddd,  $J = 0.8, 2.4, 6.1$  Hz, H-5), 3.34 (3H, s, -OCH<sub>3</sub>), 3.98 (2H, ddd,  $J = 8.0, 10.5, 18.6$  Hz, CH<sub>2</sub>OPiv), 5.57 (1H, dddd,  $J = 0.8, 1.9, 3.5, 5.6$  Hz, H-4), 5.65 (1H, dd,  $J = 2.0, 5.5$  Hz, H-3).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

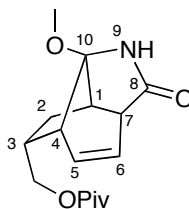
δ: 26.1, 37.0, 39.0, 39.3, 40.6, 41.3, 51.6, 56.5, 67.6, 91.3, 129.7, 136.7, 178.6.

HRMS (ESI)  $m/z$  calcd for C<sub>15</sub>H<sub>22</sub>NaO<sub>3</sub> 273.1466, found 273.1460.

FTIR / cm<sup>-1</sup>: 1397, 1481, 1729.

**rac-((1*S*,3*R*,4*R*,7*R*)-8-Oxo-9-aza-10-methoxytricyclo[5.3.2.0<sup>1,7</sup>]dec-5-en-1-yl)methyl 2,2-dimethylpropanoate **137**.**

A mixture of sodium carbonate (0.13 g, 1.2 mmol), 7-*endo* pivaloate ester **136** (2 g, 7.9 mmol) and dichloromethane (10 mL) was cooled to -20 °C. To the cooled solution was added *N*-chlorosulfonyl isocyanate (1.69 g, 11 mmol) drop wise *via* syringe and the reaction allowed to stir for 30 mins. After this time, the reaction was quenched with a saturated solution of ammonium chloride (1 mL) and the solvent removed *in vacuo*. The yellow residue was dissolved in Et<sub>2</sub>O (50 mL) and water (50 mL) and KI (0.5 mol %) was added and the biphasic solution stirred for 5 hrs. The organic layer was partitioned and the aqueous layer was extracted with Et<sub>2</sub>O (2 x 20 mL). The organic layers were dried over MgSO<sub>4</sub> and the solvent removed *in vacuo*. The residue was subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether, 6:1) to afford the γ-lactam ring **137** (1.52 g, 64%) as a white solid, mp 102.7-103.8 °C.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.13 (9H, s, -OCOC(CH<sub>3</sub>)<sub>3</sub>), 1.31 (1H, dd,  $J = 1.2, 4.8$  Hz, H-2a), 1.75 (1H, ddd,  $J = 1.6, 7.8, 13.6$  Hz, H-2b), 2.56 (1H, ddd,  $J = 1.6, 5.9, 10.2$  Hz, H-7), 2.72 (1H, ddd,  $J = 1.5, 7.4, 13.1$  Hz, H-1), 2.90 (1H, t,  $J = 5.5$  Hz, H-4), 2.94 – 3.02 (1H, m, H-3), 3.30 (3H, s, -OCH<sub>3</sub>), 4.00 (1H, d,  $J = 2.0$  Hz, -CHHOPiv), 4.02 (1H, s, -CHHOPiv), 5.77

(1H, ddd,  $J = 0.7, 5.6, 9.1$  Hz, H-6), 5.92 (1H, ddd,  $J = 1.4, 5.6, 9.1$  Hz, H-5), 6.79 (1H, br s, -NH-).

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )

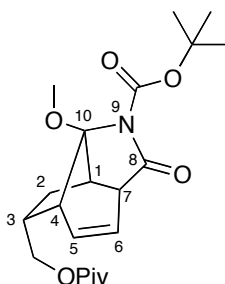
$\delta$ : 24.4, 27.5, 39.1, 44.2, 45.9, 46.4, 50.2, 52.4, 65.0, 66.2, 99.2, 127.5, 131.7, 178.7.

HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{23}\text{NNaO}_4$   $[\text{M}+\text{Na}]^+$  316.1525, found 316.1519.

FTIR /  $\text{cm}^{-1}$ : 1536, 1695, 1719, 3181.

**rac-((1*S*,3*R*,4*R*,7*R*)-8-Oxo-9-*tert*-butoxycarbonylamino-10-methoxytricyclo[5.3.2.0<sup>1,7</sup>]dec-5-en-1-yl)methyl 2,2-dimethylpropanoate **138**.**

A mixture of the  $\gamma$ -lactam **137** (1.52 g, 5.2 mmol), pyridine (0.5 g, 6.2 mmol) and dimethoxyaminopyridine (0.06 g, 0.5 mmol) in dry  $\text{Et}_2\text{O}$  (5 mL) was stirred as  $\text{BOC}_2\text{O}$  (1.35 g, 6.2 mmol) was added drop wise *via* syringe. After approximately 1.5 hrs the reaction mixture was diluted with  $\text{Et}_2\text{O}$  (20 mL) and washed with brine (2 x 20 mL). The aqueous layer was back extracted once with  $\text{Et}_2\text{O}$  (20 mL). The organic fractions were dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The residue was subjected to flash chromatography (silica,  $\text{Et}_2\text{O}$ /petroleum ether, 1:3) to afford the BOC protected  $\gamma$ -lactam **138** (1.9 g, 89%) as a yellow oil.



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 1.12 (9H, s,  $-\text{OCOC}(\text{CH}_3)_3$ ), 1.45 (9H, s,  $-\text{NCOO}t\text{Bu}$ ), 1.32 (1H, d,  $J = 4.9$  Hz, H-2a), 1.77 (1H, ddd,  $J = 0.6, 8.5, 13.7$  Hz, H-2b), 2.76 (1H, ddd,  $J = 0.7, 6.8, 12.4$  Hz, H-7), 2.92 (1H, ddd,  $J = 0.7, 4.7, 8.7$  Hz, H-1), 2.98 – 3.04 (2H, m, H-4, H-3), 3.24 (3H, s,  $-\text{OCH}_3$ ), 3.99 (2H, dd,  $J = 6.9, 10.1$  Hz,  $-\text{CH}_2\text{OPiv}$ ), 5.77 – 5.87 (2H, m, H-6, H-5).

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )

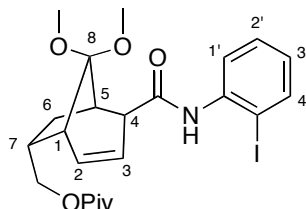
$\delta$ : 24.0, 27.5, 28.3, 39.1, 39.9, 45.5, 45.8, 49.9, 52.0, 64.8, 83.3, 101.3, 125.5, 132.9, 173.8, 178.2.

HRMS (ESI)  $m/z$  calcd for  $C_{21}H_{31}NNaO_6$   $[M+Na]^+$  416.2049, found 416.2044.

FTIR /  $cm^{-1}$ : 1728, 1789, 2969.

**rac-((1*S*,4*R*,5*R*,7*R*)-4-(2-Iodophenylcarbamoyl)-8,8-dimethoxybicyclo[3.2.1]oct-2-en-5-yl)methyl 2,2-dimethylpropanoate **139**.**

A solution of 2-iodoaniline (1.98 g, 9.3 mmol) in dry THF (5 mL) was cooled to  $-78\text{ }^{\circ}\text{C}$  in a round bottom flask equipped with nitrogen inlet. To the cooled reaction mixture *n*-butyl lithium (2.8 mL 6.9 mmol, 2.3 M solution in THF) was added drop wise *via* syringe. A solution of the BOC protected  $\gamma$ -lactam **138** (1.89 g, 4.6 mmol) in dry THF (5 mL) was cooled to  $-78\text{ }^{\circ}\text{C}$  in a separate round bottom flask equipped with nitrogen inlet. The lithium salt of 2-iodoaniline was added drop wise *via* cannula to the solution of the BOC protected  $\gamma$ -lactam. The resultant mixture was allowed to stir for 45 mins. After this time, a saturated solution of ammonium chloride (1 mL) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (25 mL) and washed with brine (2 x 20 mL) and the aqueous fraction was washed once with  $\text{Et}_2\text{O}$  (25 mL). The organic fraction was dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The residue was dissolved in MeOH (5 mL) and concentrated HCl (10 mol %) was added and the resultant solution stirred for 12 hrs. The reaction was neutralised with  $\text{NaHCO}_3$  and the aqueous layer extracted with dichloromethane. The organic fractions were dried over  $\text{MgSO}_4$  and reduced *in vacuo*. The residue was subjected to column chromatography (silica,  $\text{Et}_2\text{O}$ /petroleum ether, 1:1) to afford the dimethoxyacetal **139** (0.62 g, 25%) as a yellow oil.



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 0.96 (1H, dd,  $J = 6.2, 13.7$  Hz, H-6a), 1.13 (9H, s,  $-\text{OCOC}(\text{CH}_3)_3$ ), 2.17 (1H, ddd,  $J = 1.9, 5.7, 13.6$ , H-6b), 2.58 (1H, ddd,  $J = 1.0, 6.9, 12.0$  Hz, H-4), 2.63 – 2.73 (1H, m, H-

7), 2.93 (1H, dd,  $J = 0.9, 6.9$  Hz, H-5), 3.02 (1H, m, H-1), 3.08 (3H, s, -OCH<sub>3</sub>), 3.17 (3H, s, -OCH<sub>3</sub>), 3.92 (1H, dd,  $J = 9.9, 10.8$  Hz, -CHHOPiv), 4.01 (1H, dd,  $J = 6.7, 10.8$  Hz, -CHHOPiv), 5.98 – 6.03 (2H, m, H-2, H-3), 6.82 (1H, ddd,  $J = 1.6, 7.2, 8.9$  Hz, H-3'), 7.33 (1H, dt,  $J = 1.4, 7.4$  Hz, H-2'), 7.77 (1H, dd,  $J = 1.4, 7.9$ , H-4'), 8.01 (1H, br s, -NH-Ar), 8.35 (1H, dd,  $J = 1.5, 8.2$  Hz, H-1').

<sup>13</sup>C NMR (75.5MHz, CDCl<sub>3</sub>)

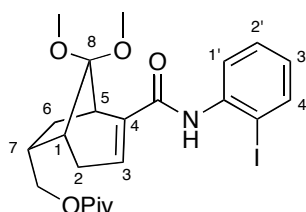
δ: 27.5, 28.6, 32.1, 39.1, 42.2, 42.6, 48.6, 51.5, 56.3, 66.1, 99.0, 108.1, 115.4, 121.7, 124.8, 126.0, 129.6, 132.9, 139.2, 162.7, 170.7.

HRMS (ESI)  $m/z$  calcd for C<sub>23</sub>H<sub>30</sub>INaNO [M+Na]<sup>+</sup> 550.1066, found 550.1060.

FTIR / cm<sup>-1</sup>: 1518, 1584, 1726.

**rac-(1*S*,5*R*,7*R*)-4-(2-Iodophenylcarbamoyl)-8,8-dimethoxybicyclo[3.2.1]oct-3-en-5-yl)methyl 2,2-dimethylpropanoate **140**.**

A solution of the dimethoxyacetal **139** (0.62 g, 1.4 mmol), DBU (0.43 g, 2.8 mmol) in THF (5 mL) was stirred for approximately 12 hrs at RT. The solution was neutralised with 2 M HCl and extracted with Et<sub>2</sub>O (3 x 25 mL) and the organic fractions combined and washed once with brine (20 mL). The organic fractions were dried over MgSO<sub>4</sub> and the solvent removed *in vacuo*. The residue was subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether, 1:1.5) to afford the conjugated alkene **140** (0.52 g, 83 %) as a yellow oil.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.20 (9H, s, -OCOC(CH<sub>3</sub>)<sub>3</sub>), 1.84 (1H, dd,  $J = 4.8, 13.4$  Hz, H-6a), 2.43 (1H, ddd,  $J = 6.6, 11.2, 13.4$  Hz, H-6b), 2.53 (1H, dd,  $J = 5.1, 6.9$  Hz, H-1), 2.72 – 2.80 (1H, m, H-7), 2.88 (1H, ddd,  $J = 1.9, 4.0, 19.6$  Hz, H-2a), 2.99 (1H, ddd,  $J = 3.2, 4.8, 19.8$  Hz, H-2b), 3.15 (1H, dd,  $J = 1.0, 7.0$  Hz, H-5), 3.19 (3H, s, -OCH<sub>3</sub>), 3.22 (3H, s, -OCH<sub>3</sub>), 4.14 (1H, t,  $J = 10.4$  Hz, -CHHOPiv), 4.29 (1H, dd,  $J = 6.2, 11.2$  Hz, -CHHOPiv), 6.59 (1H, t,  $J =$

3.5 Hz, H-3), 6.87 (1H, ddd,  $J = 1.5, 7.6, 9.2$  Hz, H-3'), 7.36 (1H, ddd,  $J = 1.4, 7.5, 8.5$  Hz, H-2'), 7.78 (1H, dd,  $J = 1.4, 7.9$  Hz, H-4'), 7.79 (1H, br s, -NH-), 8.27 (1H, dd,  $J = 1.5, 8.2$  Hz, H-1').

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )

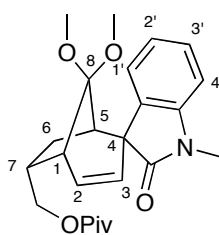
$\delta$ : 27.2, 32.9, 33.7, 42.0, 43.9, 44.3, 44.6, 46.5, 64.8, 87.5, 93.0, 108.9, 121.7, 126.0, 129.1, 130.8, 134.0, 138.2, 138.7, 169.3, 178.0.

HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{30}\text{INaNO}$   $[\text{M}+\text{Na}]^+$  550.1066, found 550.1060.

FTIR /  $\text{cm}^{-1}$ : 1515, 1679, 1726, 1761, 3309.

**rac-((1*R*,5*R*,7*R*)-8,8-Dimethoxy-1'-methyl-2'-oxospiro[bicyclo[3.2.1]oct[2]ene-2,3'-indoline]-5-yl)methyl 2,2-dimethylpropanoate **141**.**

To a solution of the enamide **140** (0.52 g, 0.9 mmol) in THF (2 mL) was added NaH (0.05 g, 1.9 mmol) and the resultant suspension stirred for 10 mins at 0 °C under a nitrogen atmosphere. After this time iodomethane (0.2 g, 1.4 mmol) was added drop wise *via* syringe and the mixture stirred for a further 30 mins. After this time, a saturated solution of  $\text{NH}_4\text{Cl}$  (1 mL) was added and the crude reaction mixture extracted with dichloromethane (2 x 20 mL). The combined organic fractions were dried over  $\text{MgSO}_4$  and reduced *in vacuo* and the resultant *N*-methyl amide used without further purification. A mixture of the *N*-methyl amide (0.4 g, 0.8 mmol),  $\text{Et}_3\text{N}$  (0.8 g, 8.1 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (0.09 g, 0.081 mmol) in MeCN (5 mL) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and the mixture heated at 90 °C for 1.5 hrs. The reaction was diluted with  $\text{Et}_2\text{O}$  (25 mL) and washed with  $\text{H}_2\text{O}$  (2 x 20 mL) and the organic layer dried over  $\text{MgSO}_4$  and reduced *in vacuo*. The residue was subjected to column chromatography (silica,  $\text{Et}_2\text{O}$ /petroleum ether, 1:3) to afford the spirooxindole **141** (0.32 g, 82 %) as a yellow oil.



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 1.13 (9H, s,  $-\text{OCOC}(\text{CH}_3)_3$ ), 1.59 (1H, ddd,  $J = 2.7, 6.2, 9.8$  Hz, H-6), 2.15 (1H, dd,  $J = 0.7, 7.8$  Hz, H-6'), 2.33 (1H, dd  $J = 3.4, 13.6$  Hz, H-5), 2.57 – 2.70 (2H, m, H-1, H-7), 3.07 (3H, s,  $-\text{OCH}_3$ ), 3.09 (3H, s,  $-\text{OCH}_3$ ), 3.22 (3H, s,  $-\text{N-CH}_3$ ), 4.29 (2H, d,  $J = 8.0$  Hz,  $\text{CH}_2\text{OPiv}$ ), 5.36 (1H, d,  $J = 10.8$  Hz, H-3), 5.92 (1H, dd,  $J = 6.9, 10.7$  Hz, H-2), 6.72 (1H, dd,  $J = 0.6, 7.8$  Hz, H-1'), 6.93 (1H, ddd,  $J = 1.0, 7.7, 8.8$  Hz, H-2'), 7.18 (1H, ddd,  $J = 1.2, 7.1, 8.6$  Hz, H-3'), 7.67 (1H, dd,  $J = 1.0, 7.5$  Hz, H-4').

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )

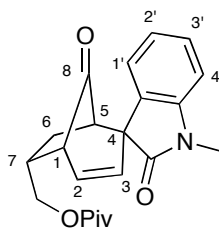
$\delta$ : 24.3, 26.8, 27.6, 39.1, 40.7, 41.4, 43.7, 48.3, 50.3, 58.8, 65.9, 107.7, 110.8, 122.4, 128.3, 128.6, 129.0, 130.0, 133.9, 143.3, 178.5, 178.6.

HRMS (ESI)  $m/z$  calcd for  $\text{C}_{24}\text{H}_{31}\text{NNaO}_5$   $[\text{M}+\text{Na}]^+$  436.2099, found 436.2094.

FTIR /  $\text{cm}^{-1}$ : 1470, 1680, 1711.

**rac-((1*R*,5*R*,7*R*)-1'-Methyl-2',8-dioxospiro[bicyclo[3.2.1]oct[2]ene-2,3'-indoline]-5-yl)methyl 2,2-dimethylpropanoate **142**.**

A solution of the spirooxindole **141** (0.32 g, 0.77 mmol), *p*-toluenesulfonic acid (10 mol %) in acetone (5 mL) was heated at reflux temperature for 30 mins. The reaction was allowed to cool to RT and neutralised with  $\text{NaHCO}_3$ . The aqueous solution was extracted with dichloromethane (3 x 20 mL) and the combined organic fractions dried over  $\text{MgSO}_4$  and reduced *in vacuo*. The residue was subjected to column chromatography (silica,  $\text{Et}_2\text{O}$ /petroleum ether, 2:1) to afford the ketone **142** (0.15 g, 54 %) as a crystalline solid, mp 82.2 – 83.5 °C (for crystallographic data see appendix I).



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 1.21 (9H, s,  $-\text{OCOC}(\text{CH}_3)_3$ ), 1.91 (1H, ddd,  $J = 7.6, 9.7, 14.0$  Hz, H-6), 2.25 (1H, dd,  $J = 1.3, 7.9$  Hz, H-6b), 2.59 – 2.69 (1H, m, H-7), 2.83 (1H, t,  $J = 5.7$  Hz, H-1), 3.03 (1H, ddd,  $J = 1.0, 7.7, 13.8$  Hz, H-5), 3.20 (3H, s,  $-\text{NCH}_3$ ), 4.31 (2H, dd,  $J = 7.6, 9.7$  Hz,  $-\text{CH}_2\text{OPiv}$ ), 5.49 (1H, dd,  $J = 1.6, 9.3$  Hz, H-3), 6.13 (1H, dd,  $J = 6.6, 9.2$  Hz, H-2), 6.83 (1H, d,  $J = 7.8$  Hz, H-1'), 7.01 – 7.09 (2H, m, H-2', H-3'), 7.30 (1H, ddd,  $J = 3.6, 7.8, 9.5$  Hz, H-4').

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )

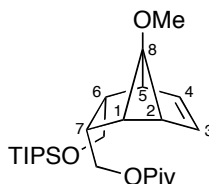
$\delta$ : 21.6, 28.3, 28.7, 31.0, 39.0, 42.7, 55.4, 67.3, 108.1, 111.0, 120.2, 128.3, 128.5, 129.1, 130.0, 134.0, 144.5, 177.2, 178.8, 213.1.

FTIR /  $\text{cm}^{-1}$ : 1504, 1607, 1731, 1756, 1809.

**rac-((1S,2R,5S,6S,7R,8S)-6-Methyl-2,2-dimethylpropanoate-7-(triisopropylsilyloxy))methyl-8-methoxytricyclo[3.2.1.0<sup>2,8</sup>]oct-3-ene 146.**

A suspension of sodium hydride (0.243 g, 10.1 mmol) and THF (3 mL) was cooled to 0 °C. The diol metaphotoadduct **30** (2 g, 10.1 mmol) was dissolved in THF (2 mL) and added drop wise *via* syringe to the vigorously stirred solution. After 45 mins a black precipitate had formed and triisopropylsilyl chloride (1.94 g, 10.1 mmol) in THF (2 mL) was added drop wise *via* syringe to the reaction mixture. The solution was stirred for a further 30 mins. After this time, the reaction was quenched with saturated ammonium chloride (2 mL) and extracted with diethyl ether (3 x 50 mL). The organic layer was washed once with brine (20 mL) and dried over  $\text{MgSO}_4$ . The solvent was removed *in vacuo* and the residue was subjected to flash chromatography (silica,  $\text{Et}_2\text{O}$ /petroleum ether, 1:1.5), to afford the monoprotected 6-*endo* triisopropylsilyl methyl ether as a pale yellow oil (1.02 g, 57%), and the monoprotected 7-*endo* triisopropylsilyl methyl ether as a pale yellow oil (1.21 g, 67%). A stirred solution of the 6-*endo* triisopropylsilyl methyl ether (1.02 g, 2.8 mmol) and pyridine (1 mL) was cooled to 0 °C. To this solution, trimethylacetyl chloride (0.52 g, 4.3 mmol) was added drop wise *via* syringe. The reaction was allowed to stir for approximately 5 mins and then poured into  $\text{Et}_2\text{O}$  (30 mL) and washed with 2 M HCl (5 mL) and brine (20 mL). The organic layer was dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The residue was subjected to

flash chromatography (silica, Et<sub>2</sub>O/petroleum ether, 1:8) to afford the bis protected metaphotocycloadduct **146** (1.13 g, 89%) as a golden yellow oil.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.02 (21H, m, -OSi(CH<sub>3</sub>)<sub>2</sub>)<sub>3</sub>), 1.19 (9H, s, -OCOC(CH<sub>3</sub>)<sub>3</sub>), 2.08 (1H, ddd, *J* = 1.2, 2.3, 8.5 Hz, H-2), 2.27 (1H, dd, *J* = 6.3, 8.5 Hz, H-1), 2.80 (1H, m, H-7), 3.10 (1H, m, H-6), 3.22 (1H, ddd, *J* = 1.3, 2.5, 5.9 Hz, H-5), 3.38 (3H, s, -OCH<sub>3</sub>), 3.58 (1H, dd, *J* = 8.0, 9.4 Hz, -CHHOTIPS), 3.71 (1H, dd, *J* = 6.8, 9.4 Hz, -CHHOTIPS), 3.95 (1H, dd, *J* = 9.6, 11.2 Hz, -CHHOPiv), 4.07 (1H, dd, *J* = 6.9, 11.2 Hz, -CHHOPiv), 5.65 (1H, ddd, *J* = 1.2, 2.6, 5.7 Hz, H-4), 5.75 (1H, dd, *J* = 2.3, 5.7 Hz, H-5).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

δ: 12.3, 18.3, 27.5, 35.9, 39.1, 39.3, 45.8, 52.2, 52.8, 56.6, 63.5, 63.7, 91.1, 132.1, 133.1, 178.7.

HRMS (ESI) *m/z* calcd for C<sub>25</sub>H<sub>44</sub>NaO<sub>4</sub>Si [M+Na]<sup>+</sup> 459.2907, found 459.2901.

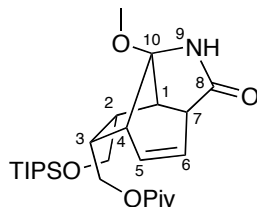
FTIR / cm<sup>-1</sup>: 1157, 1462, 1731.

**rac-(1*S*,2*S*,3*R*,4*R*,7*R*)-8-Oxo-9-aza-10-methoxy-2-((triisopropylsilyloxy)methyl)tricyclo[5.3.2.0<sup>7,1</sup>]dec-5-en-1-yl)methyl 2,2-propanoate **147**.**

A mixture of sodium carbonate (0.06 g, 0.059 mmol), bis-protected metaphotocycloadduct **146** (1.73 g, 3.9 mmol) and dichloromethane (4 mL) was cooled to -20 °C. To the cooled solution was added *N*-chlorosulfonyl isocyanate (0.84 g, 5.9 mmol) drop wise *via* syringe and the reaction allowed to stir for 30 mins. After this time, the reaction was quenched with saturated ammonium chloride (1 mL) and the solvent removed *in vacuo*. The resultant crude material was dissolved in Et<sub>2</sub>O/H<sub>2</sub>O (50 mL 1:1) and KI (0.5 mol %) was added and the biphasic mixture stirred under a nitrogen atmosphere for 5 hrs. The crude mixture was partitioned and the aqueous layer



extracted with Et<sub>2</sub>O (2 x 25 mL). The organic fractions were dried over MgSO<sub>4</sub> and reduced *in vacuo*. The resultant crude material was subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether, 3:1) to afford the  $\gamma$ -lactam **147** (1.9 g, 98 %) as a yellow glass.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

$\delta$ : 0.98 (18H, s, -OSi(CH-(CH<sub>3</sub>)<sub>2</sub>)<sub>3</sub>), 1.04 (3H, m, -OSi(CH-(CH<sub>3</sub>)<sub>2</sub>)<sub>3</sub>), 1.10 (9H, s, -OCOC(CH<sub>3</sub>)<sub>3</sub>), 2.48 (1H, m, H-3), 2.62 (1H, t,  $J$  = 5.9 Hz, H-7), 2.93 (2H, m, H-4, H-1), 3.00 (1H, m, H-2), 3.33 (3H, s, -OCH<sub>3</sub>), 3.74 (2H, dt,  $J$  = 9.7, 17.6 Hz, -CH<sub>2</sub>OTIPS), 4.06 (1H, t,  $J$  = 10.5 Hz, -CHHOPiv), 4.22 (1H, dd,  $J$  = 6.4, 10.7 Hz, -CHHOPiv), 5.80 (1H, br s, -NH-), 5.87 (1H, dd,  $J$  = 6.2, 9.0 Hz, H-6), 5.93 (1H, ddd,  $J$  = 2.1, 4.5, 8.9 Hz, H-5).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

$\delta$ : 12.2, 18.4, 27.5, 35.7, 39.0, 46.3, 48.7, 49.6, 50.2, 50.9, 61.1, 64.0, 98.1, 127.4, 133.4, 177.8, 178.5.

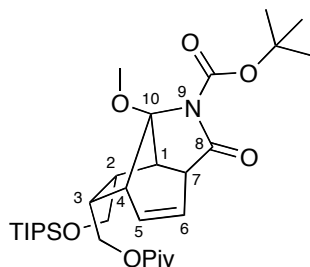
HRMS (ESI)  $m/z$  calcd for C<sub>26</sub>H<sub>45</sub>NNaO<sub>5</sub>Si [M+Na]<sup>+</sup> 502.2965, found 502.2959.

FTIR / cm<sup>-1</sup>: 1156, 1462, 1717, 3232.

**rac-(1*S*,2*S*,3*R*,4*R*,7*R*)-8-Oxo-9-*tert*-butoxycarbonylamino-10-methoxy-2-((triisopropylsilyloxy)methyl)tricyclo[5.3.2.0<sup>7,1</sup>]dec-5-en-1-yl)methyl 2,2-propanoate **148**.**

A mixture of the  $\gamma$ -lactam **147** (1.9 g, 4.0 mmol), pyridine (0.48 g, 6.1 mmol) and dimethoxyaminopyridine (0.05 g, 0.4 mmol) in dry Et<sub>2</sub>O (5 mL) was stirred as BOC<sub>2</sub>O (1.3 g, 6.1 mmol) was added drop wise *via* syringe. After approximately 1.5 hrs the reaction mixture was diluted with Et<sub>2</sub>O (20 mL) and washed with brine (2 x 20 mL). The aqueous layer was back extracted once with Et<sub>2</sub>O (20 mL). The organic fractions

were dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo*. The residue was subjected to flash chromatography (silica,  $\text{Et}_2\text{O}$ /petroleum ether, 1:2) to afford the BOC protected  $\gamma$ -lactam ring **148** (1.6 g, 69%) as a yellow oil.



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$ : 0.93 (18H, s,  $-\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$ ), 1.04 (3H, m,  $-\text{OSi}(\text{CH}(\text{CH}_3)_2)_3$ ), 1.05 (9H, s,  $-\text{OCOC}(\text{CH}_3)_3$ ), 2.44 (1H, ddt,  $J = 10.1, 17.1$  Hz, H-3), 2.84 (1H, m, H-2), 2.92 (1H, m, H-4), 2.97 (1H, ddd,  $J = 0.77, 5.9, 10.5$  Hz, H-7), 3.22 (3H, s,  $-\text{OCH}_3$ ), 3.50 (1H, m, H-1), 3.67 (2H, m,  $-\text{CH}_2\text{OTIPS}$ ), 3.98 (1H, t,  $J = 10.7$  Hz,  $-\text{CHHOPiv}$ ), 4.21 (1H, dd,  $J = 6.2, 10.8$  Hz,  $-\text{CHHOPiv}$ ), 5.77 (1H, dd,  $J = 5.2, 9.1$  Hz, H-6), 5.90 (1H, dd,  $J = 5.6, 9.0$  Hz, H-5).

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )

$\delta$ : 12.2, 15.6, 18.3, 27.4, 28.2, 35.4, 39.0, 44.3, 45.9, 49.3, 50.2, 66.7, 83.2, 100.3, 125.4, 134.5, 150.1, 173.4, 178.4.

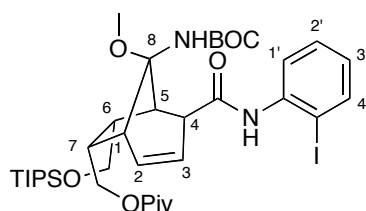
HRMS (ESI)  $m/z$  calcd for  $\text{C}_{31}\text{H}_{53}\text{NNaO}_7\text{Si}$   $[\text{M}+\text{Na}]^+$  602.3489, found 602.3483.

FTIR /  $\text{cm}^{-1}$ : 1731, 1763, 1790.

**rac-((1*S*,4*S*,5*R*,6*S*,7*R*)-8-(*tert*-Butoxycarbonylamino)-4-(2-iodophenylcarbamoyl)-8-methoxy-7-((triisopropylsilyloxy)methyl)bicyclo[3.2.1]oct-2-en-5-yl)methyl 2,2-dimethylpropanoate **149**.**

A solution of 2-iodoaniline (1.12 g, 5.2 mmol) in dry THF (5 mL) was cooled to  $-78^\circ\text{C}$  in a round bottom flask equipped with nitrogen inlet. To the cooled reaction mixture *n*-butyl lithium (2.15 mL, 4.9 mmol, 2.3 M solution in THF) was added drop wise *via* syringe. A solution of the BOC protected  $\gamma$ -lactam ring **148** (1.69 g, 2.9 mmol) in dry THF (5 mL) was cooled to  $-78^\circ\text{C}$  in a separate round bottom flask equipped with nitrogen inlet. The lithium salt of 2-iodoaniline was added drop wise *via* cannula to the

solution of the BOC protected  $\gamma$ -lactam. The resultant mixture was allowed to stir for 45 mins. After this time, a saturated solution of ammonium chloride (1 mL) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with Et<sub>2</sub>O (25 mL) and washed with brine (2 x 20 mL) and the aqueous fraction extracted once with Et<sub>2</sub>O (25 mL). The organic fraction was dried over MgSO<sub>4</sub> and the solvent removed *in vacuo*. The residue was subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether, 1:8 then Et<sub>2</sub>O/petroleum ether, 2:1) to afford the iodophenylcarbamoyl **149** (2.29 g, 98%) as a dark orange oil.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.05 (21H, m, -OSi(CH<sub>3</sub>)<sub>3</sub>), 1.14 (9H, br s, -NHCOOC(CH<sub>3</sub>)<sub>3</sub>), 1.18 (9H, s, -OCOC(CH<sub>3</sub>)<sub>3</sub>), 2.71 (1H, m, H-6), 2.90 (1H, ddt, *J* = 11.2, 17.6 Hz, H-7) 2.96 – 3.20 (2H, m, H-1, H-4), 3.23 (3H, s, -OCH<sub>3</sub>), 3.54 (1H, m, H-5), 3.73 (2H, dd, *J* = 2.79, 7.66 Hz, -CH<sub>2</sub>OTIPS), 3.98 (1H, t, *J* = 11.2, -CHHOPiv), 4.35 (1H, m, -CHHOPiv), 5.46 (1H, s, -NHBOC), 5.93 (1H, dd, *J* = 3.7, 10.6 Hz, H-3), 6.18 (1H, ddd, *J* = 1.7, 6.7, 9.1 Hz, H-2), 6.83 (1H, dt, *J* = 1.5, 7.6, H-3'), 7.32 (1H, ddd, *J* = 1.5, 7.3, 8.6 Hz, H-2'), 7.75 (1H, dd, *J* = 1.4, 7.9 Hz, H-4'), 7.75 (1H, s, -NH-), 8.28 (1H, dd, *J* = 1.5, 8.2 Hz, H-1').

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

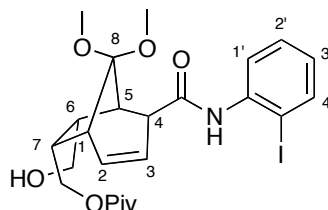
δ: 12.3, 18.7, 27.4, 28.4, 37.6, 39.4, 42.4, 46.2, 47.3, 47.5, 49.2, 61.5, 63.1, 90.3, 90.8, 121.7, 122.0, 126.6, 129.7, 135.7, 138.4, 139.2, 154.5, 172.0, 179.1.

HRMS (ESI) *m/z* calcd for C<sub>37</sub>H<sub>59</sub>IN<sub>2</sub>NaO<sub>7</sub>Si 821.3034, found 821.3028.

FTIR / cm<sup>-1</sup>: 1520, 1584, 1683, 1730, 3360.

**rac-((1*S*,4*S*,5*R*,6*S*,7*R*)-6-(Hydroxymethyl)-4-(2-iodophenylcarbamoyl)-8,8-dimethoxybicyclo[3.2.1]oct-2-en-5-yl)methyl 2,2-dimethylpropanoate **150**.**

A solution of the iodophenylcarbamoyl **149** (0.8 g, 1.4 mmol) in MeOH (10 mL) was divided into ten portions and HCl (0.01 mL, 0.12 mmol, 12 M) was added to each portion. The resultant solutions were stirred overnight and each neutralised with saturated aqueous solution of NaHCO<sub>3</sub>. The combined crude reaction mixtures were extracted with Et<sub>2</sub>O (3 x 25 mL) and the organic layer was dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the residue subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether, 3:1) to afford the bridgehead dimethoxyacetal **150** (0.38 g, 68%) as a yellow oil.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.18 (9H, s, -OCOC(CH<sub>3</sub>)<sub>3</sub>), 1.57 (1H, br s, -OH), 2.68 (3H, m, H-1, H-5, H-7), 3.06 (3H, s, -OCH<sub>3</sub>), 3.10 (2H, m, H-4, H-6), 3.18 (3H, s, -OCH<sub>3</sub>), 3.64 (2H, m, -CH<sub>2</sub>OH), 3.94 (1H, dd, *J* = 10.1, 11.0 Hz, -CHHOPiv), 4.21 (1H, dd, *J* = 6.0, 11.0 Hz, -CHHOPiv), 5.95 (1H, ddd, *J* = 1.5, 3.6, 9.5 Hz, H-3), 6.10 (1H, ddd, *J* = 1.5, 6.4, 9.9 Hz, H-2), 6.74 (1H, dt, *J* = 1.6, 7.3, 15.3 Hz, H-3'), 7.25 (1H, ddd, *J* = 1.5, 7.4, 15.6 Hz, H-2'), 7.69 (1H, dd, *J* = 1.5, 7.9 Hz, H-4'), 7.82 (1H, br s, NH), 8.25 (1H, dd, *J* = 1.6, 8.2 Hz, H-1').

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

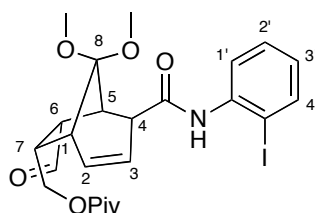
δ: 27.5, 37.7, 39.2, 42.5, 42.7, 46.2, 48.3, 48.5, 51.2, 60.9, 62.7, 89.5, 107.0, 121.6, 124.4, 125.8, 129.6, 133.9, 139.2, 177.0, 178.8.

HRMS (ESI) *m/z* calcd for C<sub>24</sub>H<sub>32</sub>INNaO<sub>6</sub> [M+Na]<sup>+</sup> 580.1172, found 580.1166.

FTIR / cm<sup>-1</sup>: 1520, 1584, 1688, 1725, 3360.

**rac-((1*S*,4*S*,5*R*,6*S*,7*R*)-6-Formyl-4-(2-iodophenylcarbamoyl)-8,8-dimethoxybicyclo[3.2.1]oct-2-en-5-yl)methyl 2,2-dimethylpropanoate **151**.**

A mixture of the dimethoxyacetal **150** (0.49 g, 0.89 mmol), IBX (0.56 g, 1.3 mmol) in DMSO (3 mL) was stirred for 3 hrs at 50 °C. After this time, water (10 mL) was added and the crude reaction mixture was passed through Celite. The crude solution was diluted with Et<sub>2</sub>O (25 mL) and washed with water (3 x 10 mL) and the organic layer was dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the residue subjected to column chromatography (silica, Et<sub>2</sub>O) to afford the 6-*endo* aldehyde **151** (0.45 g, 92%) as a white foam.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.15 (9H, s, -OCOC(CH<sub>3</sub>)<sub>3</sub>), 2.82 (1H, ddd, *J* = 1.4, 7.3, 7.6 Hz, H-1), 2.96 (1H, dd, *J* = 1.8, 7.1 Hz, H-4), 2.97 – 3.03 (1H, m, H-7), 3.07 (3H, s, -OCH<sub>3</sub>), 3.17 (3H, s, -OCH<sub>3</sub>), 3.20 (2H, m, H-5, H-6), 4.18 (1H, dd, *J* = 8.7, 11.3 Hz, -CHHOPiv), 4.35 (1H, dd, *J* = 7.3, 11.4 Hz, -CHHOPiv), 5.94 (1H, dd, *J* = 4.4, 9.5 Hz, H-3), 6.28 (1H, ddd, *J* = 1.2, 7.9, 9.4 Hz, H-2), 6.75 (1H, ddd, *J* = 1.5, 7.5, 9.1 Hz, H-3'), 7.26 (1H, ddd, *J* = 1.5, 8.6, 8.6 Hz, H-2'), 7.70 (1H, dd, *J* = 1.3, 7.9 Hz, H-4'), 7.77 (1H, br s, -NH-), 8.25 (1H, dd, *J* = 1.5, 8.2 Hz, H-1'), 9.73 (1H, s, -CHO).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

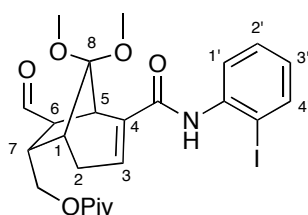
δ: 27.1, 34.2, 38.7, 39.5, 42.2, 48.3, 49.1, 51.7, 57.3, 66.3, 91.8, 93.1, 106.9, 121.5, 126.0, 129.7, 133.9, 139.2, 158.8, 161.7, 184.9, 202.9.

HRMS (ESI) *m/z* calcd for C<sub>24</sub>H<sub>30</sub>INNaO<sub>6</sub> [M+Na]<sup>+</sup> 578.1016, found 578.1010.

FTIR / cm<sup>-1</sup>: 1584, 1727, 3356.

**rac-((1*S*,5*R*,6*S*,7*R*)-6-Formyl-4-(2-iodophenylcarbamoyl)-8,8-dimethoxybicyclo[3.2.1]oct-3-en-5-yl)methyl 2,2-dimethylpropanoate **152**.**

A solution of the aldehyde **151** (0.32 g, 0.58 mmol), DBU (0.17 g, 1.16 mmol) in THF (8 mL) was stirred for approximately 12 hrs. The solution was neutralised with 2M HCl and extracted with Et<sub>2</sub>O (3 x 25 mL) and the organic fractions combined and washed once with brine (20 mL). The organic layer was dried over MgSO<sub>4</sub> and the solvent removed *in vacuo*. The residue was subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether 1:1) to afford the epimerised aldehyde **152** (0.19 g, 60%) as a yellow gum.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.01 (9H, s, -OCOC(CH<sub>3</sub>)<sub>3</sub>), 2.08 (1H, d, *J* = 6.8 Hz, H-6), 2.24 (1H, dd, *J* = 3.0, 18.3 Hz, H-2), 2.69 (1H, dd, *J* = 3.0, 4.7 Hz, H-5), 2.78 (1H, m, H-2b), 2.98 (1H, m, H-7), 3.11 (3H, s, -OCH<sub>3</sub>), 3.17 (3H, s, -OCH<sub>3</sub>), 3.38 (1H, dd, *J* = 1.6, 5.8 Hz, H-1) 4.10 (2H, dddd, *J* = 7.4, 11.0, 18.3, -CH<sub>2</sub>OPiv), 6.60 (1H, t, *J* = 3.5, 6.3 Hz, H-3), 6.76 (1H, ddd, *J* = 1.5, 7.4, 15.3 Hz, H-3'), 7.25 (1H, ddd, *J* = 1.5, 7.5, 15.6 Hz, H-2'), 7.69 (1H, dd, *J* = 1.4, 7.9, 15.6 Hz, H-4'), 7.85 (1H, br s, -NH-), 8.15 (1H, dd, *J* = 1.5, 8.2 Hz, H-1'), 9.54 (1H, s, -CHO).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

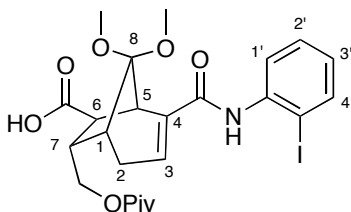
δ: 27.4, 35.6, 37.5, 39.0, 41.5, 44.7, 48.5, 51.4, 58.8, 65.8, 90.7, 94.9, 107.6, 122.2, 126.4, 129.6, 133.3, 135.8, 139.0, 165.0, 178.6, 201.6.

HRMS (ESI) *m/z* calcd for C<sub>24</sub>H<sub>30</sub>INNaO<sub>6</sub> [M+Na]<sup>+</sup> 578.1016, found 578.1010.

FTIR / cm<sup>-1</sup>: 1584, 1727, 3356.

**rac-((1*S*,5*R*,6*S*,7*R*)-7-((2,2-Dimethylpropanoyloxy)methyl)-4-(2-iodophenylcarbamoyl)-8,8-dimethoxybicyclo[3.2.1]oct-3-ene-6-carboxylic acid **153**.**

A solution of the 6-*exo* aldehyde **152** (0.23 g, 0.41 mmol) and 2-methyl-2-butene (0.3 mL, 0.62 mmol, 2 M solution in THF) in *t*-BuOH/water (2 mL, 5:1) was buffered with KH<sub>2</sub>PO<sub>4</sub> to approximately pH 5. To the mixture was added sodium chlorite (0.06 g, 0.62 mmol) and the reaction stirred for 2 hrs. The crude reaction mixture was diluted with Et<sub>2</sub>O (25 mL) and washed with water (2 x 10 mL). The organic layer was dried over MgSO<sub>4</sub> and the solvent removed *in vacuo*. The residue was subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether, 3:1) to afford the 6-*exo* acid **153** (0.16 g, 70%) as a white foam.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 0.98 (9H, s, -OCOC(CH<sub>3</sub>)<sub>3</sub>), 2.23 (1H, s, H-1), 2.29 (1H, dd, *J* = 1.8, 3.7 Hz, H-2a), 2.71 (1H, dt, *J* = 3.0, 7.6, H-2b), 2.82 (1H, m, H-5), 3.11 (1H, m, H-7), 3.20 (6H, s, -OCH<sub>3</sub>), 3.40 (1H, m, H-6), 3.99 (1H, dd, *J* = 9.4, 11.0 Hz, -CHHOPiv), 4.26 (1H, dd, *J* = 6.2, 11.0 Hz, -CHHOPiv), 6.57 (1H, t, *J* = 3.3, 6.8 Hz, H-3), 6.76 (1H, ddd, *J* = 1.5, 7.4, 15.3 Hz, H-3'), 7.24 (1H, ddd, *J* = 1.5, 7.4, 15.6 Hz, H-2'), 7.69 (1H, dd, *J* = 1.4, 7.9 Hz, H-4'), 7.82 (1H, s, -NH-), 8.15 (1H, dd, *J* = 1.5, 8.2 Hz, H-1'), 10.0 (1H, br s, -COOH).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

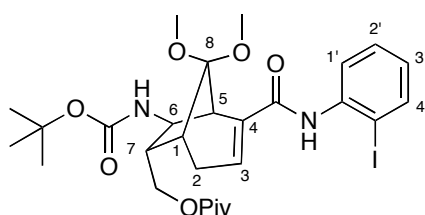
δ: 27.5, 37.6, 42.0, 42.8, 47.9, 48.5, 48.6, 51.2, 63.2, 89.5, 106.4, 121.6, 123.7, 125.9, 129.6, 133.7, 138.8, 139.2, 141.8, 171.9, 177.6, 178.7.

HRMS (ESI) *m/z* calcd for C<sub>24</sub>H<sub>30</sub>INNaO<sub>7</sub> [M+Na]<sup>+</sup> 594.0965, found 594.0959.

FTIR / cm<sup>-1</sup>: 1584, 1724, 2594, 3355.

**rac-((1*S*,5*R*,6*S*,7*R*)-6-(*tert*-Butoxycarbonylamino)-4-(2-iodophenylcarbamoyl)-8,8-dimethoxybicyclo[3.2.1]oct-3-en-5-yl)methyl 2,2-dimethylpropanoate **154**.**

A solution of acid **143** (0.21 g, 0.37 mmol), Et<sub>3</sub>N (37 mg, 0.37 mmol) and diphenylphosphoryl azide (0.10 g, 0.37 mmol) in *t*BuOH (2 mL) was heated at 100 °C for approximately 5 hrs. After this time the reaction mixture was allowed to cool and diluted with Et<sub>2</sub>O (10 mL) and washed with H<sub>2</sub>O (2 x 10 mL). The organic fraction was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was subjected to column chromatography (silica, Et<sub>2</sub>O/petroleum ether, 1.5:1) to afford the carbamate **154** (0.11 g, 47%) a yellow gum.



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)

δ: 1.02 (9H, s, -OCOC(CH<sub>3</sub>)<sub>3</sub>), 1.18 (9H, s, -NHCOO*t*Bu), 2.20 (1H, m, H-5), 2.40 – 2.47 (2H, m, H-1, H-7), 2.63 (2H, dt, *J* = 4.6, 19.5 Hz, H-2a, H-2b), 3.18 (3H, s, -OCH<sub>3</sub>), 3.23 (3H, s, -OCH<sub>3</sub>), 3.62 (1H, dd, *J* = 5.8, 8.9 Hz, H-5), 4.08 (2H, dd, *J* = 5.3, 7.9 Hz, -CH<sub>2</sub>OPiv), 5.37 (1H, d, *J* = 8.8 Hz, -NHBOC), 6.54 (1H, t, *J* = 3.4 Hz, H-3), 6.77 (1H, ddd, *J* = 1.5, 7.4, 8.5 Hz, H-3'), 7.25 (1H, ddd, *J* = 1.4, 7.4, 8.5 Hz, H-2'), 7.70 (1H, dd, *J* = 1.4, 7.9 Hz, H-4'), 7.82 (1H, br s, -NH-Ar), 8.16 (1H, d, *J* = 1.5, 8.2 Hz, H-1').

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)

δ: 27.5, 31.3, 34.0, 39.0, 41.4, 44.5, 48.5, 51.1, 52.0, 58.6, 66.2, 90.5, 107.8, 122.0, 126.3, 129.6, 132.1, 135.1, 135.7, 138.3, 139.7, 156.0, 164.9, 178.6.

HRMS (ESI) *m/z* calcd for C<sub>28</sub>H<sub>39</sub>IN<sub>2</sub>NaO<sub>7</sub> [M+Na]<sup>+</sup> 665.1700, found 665.1694.

FTIR / cm<sup>-1</sup>: 1520, 1682, 1728, 3271.



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**Appendix I**

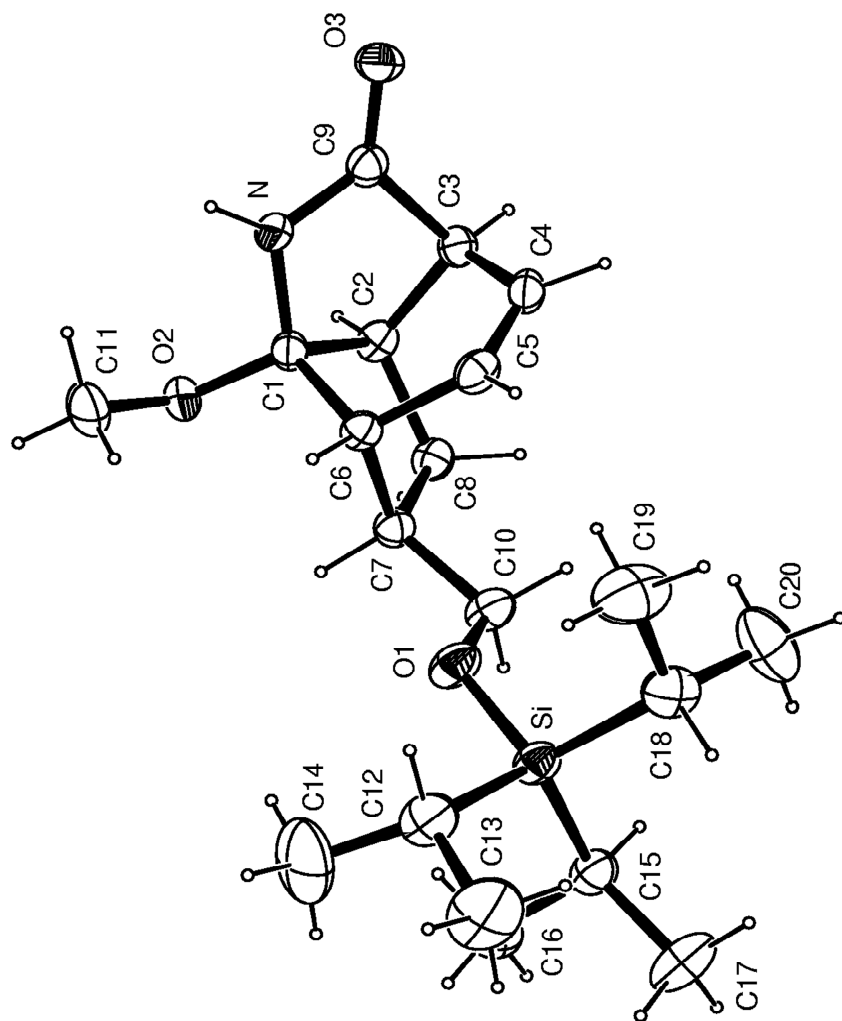


Figure 1. ORTEP representation of compound **134**.

Crystal data and structure refinement for compound **137**.

Identification code	sep1506	
Empirical formula	C <sub>20</sub> H <sub>35</sub> N O <sub>3</sub> Si	
Formula weight	365.58	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2 <sub>1</sub> /c (No.14)	
Unit cell dimensions	a = 22.3887(7) Å	α = 90°.
	b = 8.3804(2) Å	β = 104.938(1)°.
	c = 11.6714(4) Å	γ = 90°.
Volume	2115.85(11) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.15 Mg/m <sup>3</sup>	
Absorption coefficient	0.13 mm <sup>-1</sup>	
F(000)	800	
Crystal size	0.20 x 0.20 x 0.02 mm <sup>3</sup>	
Theta range for data collection	3.49 to 26.04°.	
Index ranges	-27 ≤ h ≤ 27, -10 ≤ k ≤ 9, -14 ≤ l ≤ 14	
Reflections collected	25811	
Independent reflections	4175 [R(int) = 0.070]	
Reflections with I > 2σ(I)	3019	
Completeness to theta = 26.04°	99.5 %	
Tmax. and Tmin.	0.9974 and 0.9748	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	4175 / 0 / 226	
Goodness-of-fit on F <sup>2</sup>	1.024	
Final R indices [I > 2σ(I)]	R1 = 0.053, wR2 = 0.111	
R indices (all data)	R1 = 0.083, wR2 = 0.124	
Largest diff. peak and hole	0.27 and -0.26 e.Å <sup>-3</sup>	

Data collection KappaCCD , Program package WinGX , Abs correction not applied ,

Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows



Table 1. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for sepi506.  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U^{ij}$  tensor.

	x	y	z	$U(\text{eq})$
Si	8367(1)	5207(1)	2823(1)	26(1)
O(1)	7758(1)	6226(2)	2965(1)	31(1)
O(2)	6115(1)	9793(2)	3261(1)	26(1)
O(3)	4596(1)	8064(2)	92(1)	31(1)
N	5467(1)	9122(2)	1370(2)	23(1)
C(1)	5949(1)	8591(2)	2394(2)	20(1)
C(2)	5645(1)	7200(2)	2880(2)	22(1)
C(3)	5282(1)	6476(2)	1690(2)	23(1)
C(4)	5735(1)	5780(2)	1048(2)	25(1)
C(5)	6283(1)	6446(2)	1200(2)	25(1)
C(6)	6510(1)	7719(2)	2132(2)	21(1)
C(7)	6774(1)	6871(2)	3333(2)	22(1)
C(8)	6184(1)	6201(2)	3630(2)	24(1)
C(9)	5048(1)	7965(2)	951(2)	24(1)
C(10)	7245(1)	5578(3)	3333(2)	29(1)
C(11)	6383(1)	11195(3)	2912(2)	42(1)
C(12)	8903(1)	6794(3)	2552(2)	39(1)
C(13)	9509(1)	6156(4)	2352(3)	66(1)
C(14)	9030(2)	8153(3)	3450(3)	69(1)
C(15)	8658(1)	3959(3)	4192(2)	29(1)
C(16)	8832(1)	4956(3)	5329(2)	45(1)
C(17)	9184(1)	2808(3)	4142(3)	51(1)
C(18)	8162(1)	3872(3)	1484(2)	37(1)
C(19)	7889(1)	4806(4)	337(2)	59(1)
C(20)	7736(1)	2470(4)	1585(3)	59(1)

Table 2. Bond lengths [ $\text{\AA}$ ] and angles [ $^\circ$ ] for sep1506.

Si-O(1)	1.653(2)
Si-C(12)	1.873(2)
Si-C(15)	1.880(2)
Si-C(18)	1.881(2)
O(1)-C(10)	1.433(3)
O(2)-C(1)	1.408(2)
O(2)-C(11)	1.427(3)
O(3)-C(9)	1.229(3)
N-C(9)	1.351(3)
N-C(1)	1.458(3)
C(1)-C(2)	1.531(3)
C(1)-C(6)	1.550(3)
C(2)-C(3)	1.541(3)
C(2)-C(8)	1.543(3)
C(3)-C(4)	1.523(3)
C(3)-C(9)	1.531(3)
C(4)-C(5)	1.319(3)
C(5)-C(6)	1.515(3)
C(6)-C(7)	1.547(3)
C(7)-C(10)	1.512(3)
C(7)-C(8)	1.554(3)
C(12)-C(14)	1.524(4)
C(12)-C(13)	1.531(4)
C(15)-C(16)	1.531(3)
C(15)-C(17)	1.534(3)
C(18)-C(19)	1.535(4)
C(18)-C(20)	1.537(4)
O(1)-Si-C(12)	103.37(10)
O(1)-Si-C(15)	108.49(9)
C(12)-Si-C(15)	116.19(11)
O(1)-Si-C(18)	111.15(10)
C(12)-Si-C(18)	108.12(12)
C(15)-Si-C(18)	109.39(11)
C(10)-O(1)-Si	125.43(13)
C(1)-O(2)-C(11)	115.82(17)

C(9)-N-C(1)	112.15(16)
O(2)-C(1)-N	111.86(15)
O(2)-C(1)-C(2)	109.74(16)
N-C(1)-C(2)	103.26(16)
O(2)-C(1)-C(6)	113.77(16)
N-C(1)-C(6)	116.66(17)
C(2)-C(1)-C(6)	100.08(15)
C(1)-C(2)-C(3)	98.47(16)
C(1)-C(2)-C(8)	105.39(16)
C(3)-C(2)-C(8)	116.80(17)
C(4)-C(3)-C(9)	102.08(16)
C(4)-C(3)-C(2)	109.37(17)
C(9)-C(3)-C(2)	102.21(16)
C(5)-C(4)-C(3)	119.11(19)
C(4)-C(5)-C(6)	121.55(19)
C(5)-C(6)-C(7)	107.83(16)
C(5)-C(6)-C(1)	109.56(16)
C(7)-C(6)-C(1)	100.17(16)
C(10)-C(7)-C(6)	115.59(17)
C(10)-C(7)-C(8)	111.96(17)
C(6)-C(7)-C(8)	102.78(16)
C(2)-C(8)-C(7)	105.23(16)
O(3)-C(9)-N	126.59(19)
O(3)-C(9)-C(3)	127.23(19)
N-C(9)-C(3)	105.97(17)
O(1)-C(10)-C(7)	109.98(17)
C(14)-C(12)-C(13)	110.5(2)
C(14)-C(12)-Si	115.35(19)
C(13)-C(12)-Si	114.20(18)
C(16)-C(15)-C(17)	110.5(2)
C(16)-C(15)-Si	112.85(16)
C(17)-C(15)-Si	114.79(17)
C(19)-C(18)-C(20)	109.9(2)
C(19)-C(18)-Si	112.20(19)
C(20)-C(18)-Si	114.44(17)

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Hydrogen bonds with  $H\cdots A < r(A) + 2.000$  Angstroms and  $\angle DHA > 110$  deg. D-H  $d(D-H)$   $d(H\cdots A)$   
 $\angle DHA$   $d(D\cdots A)$  N-H0 0.88 2.04 163 2.893 O3 [ -x+1, -y+2, -z ]

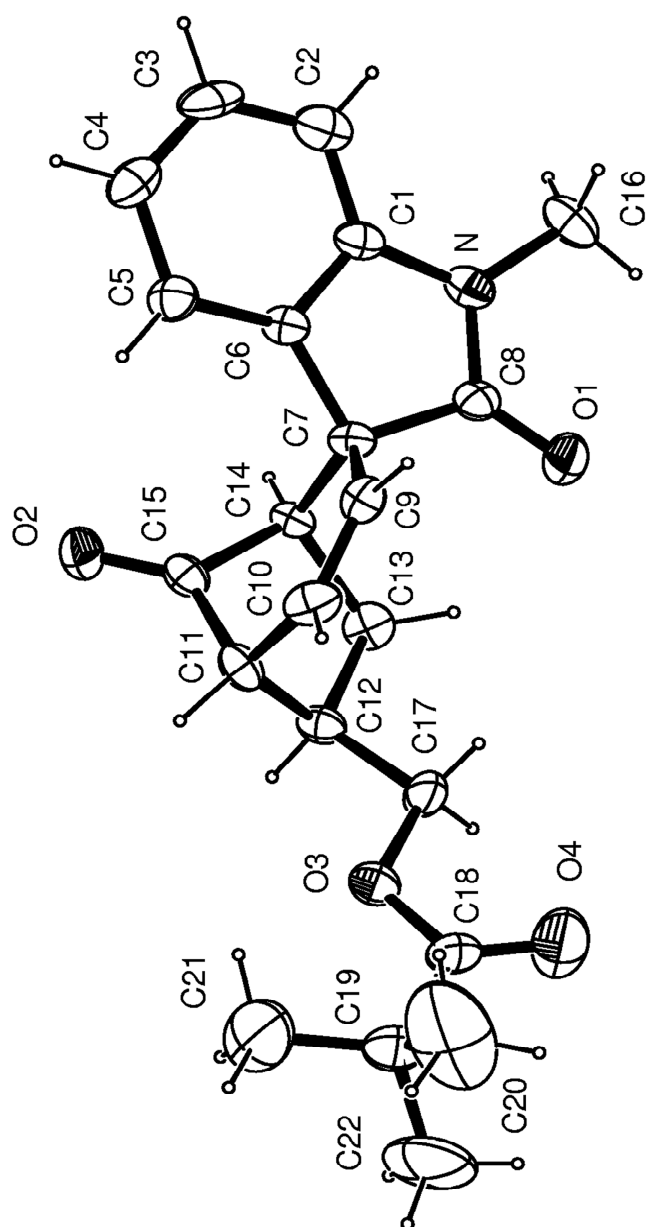


Figure 2. ORTEP representation of Compound **142**.

Crystal data and structure refinement for compound **142**.

Identification code	dec806	
Empirical formula	C <sub>22</sub> H <sub>25</sub> N O <sub>4</sub>	
Formula weight	367.43	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	Cc (No.9)	
Unit cell dimensions	a = 6.0119(3) Å	$\alpha = 90^\circ$ .
	b = 28.654(3) Å	$\beta = 93.066(5)^\circ$ .
	c = 11.1384(9) Å	$\gamma = 90^\circ$ .
Volume	1916.0(3) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.27 Mg/m <sup>3</sup>	
Absorption coefficient	0.09 mm <sup>-1</sup>	
F(000)	784	
Crystal size	0.40 x 0.25 x 0.05 mm <sup>3</sup>	
Theta range for data collection	3.47 to 26.03°.	
Index ranges	-7 ≤ h ≤ 5, -29 ≤ k ≤ 35, -13 ≤ l ≤ 13	
Reflections collected	6323	
Independent reflections	1874 [R(int) = 0.091]	
Reflections with I > 2σ(I)	1594	
Completeness to theta = 26.03°	98.7 %	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	1874 / 2 / 248	
Goodness-of-fit on F <sup>2</sup>	1.038	
Final R indices [I > 2σ(I)]	R1 = 0.105, wR2 = 0.285	
R indices (all data)	R1 = 0.118, wR2 = 0.294	
Absolute structure parameter	0(5)	
Largest diff. peak and hole	0.60 and -0.33 e.Å <sup>-3</sup>	

Although diffraction was measured to 26° in theta, there was essentially nothing observable above 23° .

Data collection KappaCCD , Program package WinGX , Abs correction not applied ,

Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 3. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for dec806.  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U^{ij}$  tensor.

	x	y	z	$U(\text{eq})$
O(1)	3146(11)	5032(2)	5764(6)	37(2)
O(2)	-1990(11)	4312(2)	1917(6)	35(2)
O(3)	1051(12)	3140(2)	5251(6)	37(2)
O(4)	2820(20)	3016(3)	7017(10)	82(4)
N	1530(12)	5659(3)	4775(7)	28(2)
C(1)	-431(15)	5742(3)	4067(8)	28(2)
C(2)	-1253(18)	6167(4)	3654(10)	39(2)
C(3)	-3278(18)	6164(4)	3001(9)	39(2)
C(4)	-4438(16)	5749(4)	2731(9)	35(2)
C(5)	-3528(14)	5316(3)	3137(8)	29(2)
C(6)	-1509(12)	5321(3)	3788(8)	22(2)
C(7)	-68(13)	4922(3)	4323(8)	22(2)
C(8)	1756(14)	5196(3)	5059(8)	25(2)
C(9)	-1358(12)	4617(3)	5172(8)	26(2)
C(10)	-1737(15)	4165(3)	4944(9)	31(2)
C(11)	-926(14)	3919(3)	3833(8)	27(2)
C(12)	1530(14)	3800(3)	3962(8)	25(2)
C(13)	2742(15)	4274(3)	3806(8)	28(2)
C(14)	920(13)	4625(3)	3325(8)	23(2)
C(15)	-891(15)	4290(3)	2866(8)	26(2)
C(16)	2943(17)	6019(4)	5331(10)	39(2)
C(17)	2297(16)	3571(3)	5153(10)	36(2)
C(18)	1470(20)	2892(4)	6260(11)	45(3)
C(19)	120(20)	2444(4)	6296(12)	48(3)
C(20)	-1100(40)	2471(8)	7498(19)	119(9)
C(21)	-1620(30)	2393(6)	5290(20)	96(7)
C(22)	1660(30)	2045(5)	6390(30)	122(10)

Table 4. Bond lengths [ $\text{\AA}$ ] and angles [ $^\circ$ ] for dec806.

O(1)-C(8)	1.211(11)
O(2)-C(15)	1.217(11)
O(3)-C(18)	1.342(13)
O(3)-C(17)	1.450(11)
O(4)-C(18)	1.193(14)
N-C(8)	1.368(11)
N-C(1)	1.404(13)
N-C(16)	1.455(12)
C(1)-C(2)	1.382(14)
C(1)-C(6)	1.396(12)
C(2)-C(3)	1.384(16)
C(3)-C(4)	1.404(16)
C(4)-C(5)	1.419(13)
C(5)-C(6)	1.380(12)
C(6)-C(7)	1.537(12)
C(7)-C(9)	1.529(11)
C(7)-C(14)	1.545(11)
C(7)-C(8)	1.547(12)
C(9)-C(10)	1.336(14)
C(10)-C(11)	1.527(13)
C(11)-C(15)	1.514(13)
C(11)-C(12)	1.514(12)
C(12)-C(17)	1.530(13)
C(12)-C(13)	1.556(12)
C(13)-C(14)	1.559(12)
C(14)-C(15)	1.519(12)
C(18)-C(19)	1.522(15)
C(19)-C(22)	1.47(2)
C(19)-C(21)	1.50(2)
C(19)-C(20)	1.56(2)
C(18)-O(3)-C(17)	116.0(8)
C(8)-N-C(1)	111.4(7)
C(8)-N-C(16)	122.8(8)
C(1)-N-C(16)	124.9(8)
C(2)-C(1)-C(6)	122.2(8)

C(2)-C(1)-N	127.7(9)
C(6)-C(1)-N	110.1(7)
C(1)-C(2)-C(3)	117.3(10)
C(2)-C(3)-C(4)	122.0(9)
C(3)-C(4)-C(5)	119.6(9)
C(6)-C(5)-C(4)	118.1(9)
C(5)-C(6)-C(1)	120.7(8)
C(5)-C(6)-C(7)	131.1(8)
C(1)-C(6)-C(7)	108.1(7)
C(9)-C(7)-C(6)	111.8(6)
C(9)-C(7)-C(14)	111.0(7)
C(6)-C(7)-C(14)	111.2(7)
C(9)-C(7)-C(8)	109.3(7)
C(6)-C(7)-C(8)	101.4(7)
C(14)-C(7)-C(8)	111.8(6)
O(1)-C(8)-N	125.6(9)
O(1)-C(8)-C(7)	126.3(8)
N-C(8)-C(7)	108.1(7)
C(10)-C(9)-C(7)	121.5(8)
C(9)-C(10)-C(11)	122.9(8)
C(15)-C(11)-C(12)	100.0(7)
C(15)-C(11)-C(10)	105.7(7)
C(12)-C(11)-C(10)	112.3(7)
C(11)-C(12)-C(17)	115.2(7)
C(11)-C(12)-C(13)	104.7(7)
C(17)-C(12)-C(13)	110.5(7)
C(12)-C(13)-C(14)	106.0(7)
C(15)-C(14)-C(7)	107.1(6)
C(15)-C(14)-C(13)	100.8(7)
C(7)-C(14)-C(13)	113.4(7)
O(2)-C(15)-C(11)	128.8(8)
O(2)-C(15)-C(14)	127.2(8)
C(11)-C(15)-C(14)	103.9(7)
O(3)-C(17)-C(12)	107.3(7)
O(4)-C(18)-O(3)	121.7(10)
O(4)-C(18)-C(19)	125.2(10)
O(3)-C(18)-C(19)	113.1(9)
C(22)-C(19)-C(21)	112.8(15)



C(22)-C(19)-C(18)	108.8(11)
C(21)-C(19)-C(18)	114.5(10)
C(22)-C(19)-C(20)	107.6(18)
C(21)-C(19)-C(20)	107.8(15)
C(18)-C(19)-C(20)	104.8(11)

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