Author:
Steeds, Hannah G

Title:
Photochemistry and Catalysis

Synthetic Approaches to Complex Amine Scaffolds

Photochemistry and Catalysis: Synthetic Approaches to Complex Amine Scaffolds

Hannah Steeds

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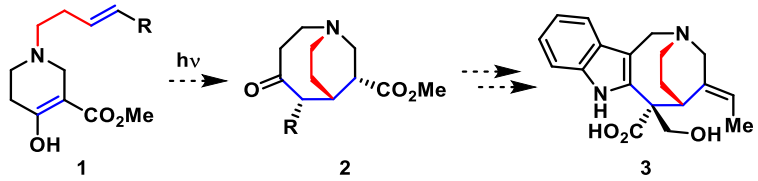
i. Abstract

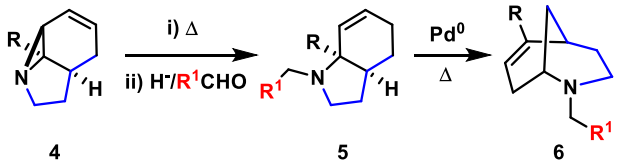
This thesis describes two main areas, natural product synthesis in Chapter 2, and palladium catalysis in Chapters 3 and 4. All three of which involve the use of synthetic organic photochemistry.

Chapter 2 outlines the studies towards the synthesis of the indole alkaloid alstoniascholarine A **3** (Scheme 1). The aim was to use the De Mayo reaction to synthesise the 6,8-fused bicyclic ring-system **2**, the core of the natural product. This however proved challenging, and so a variety of other photochemical methods were explored.



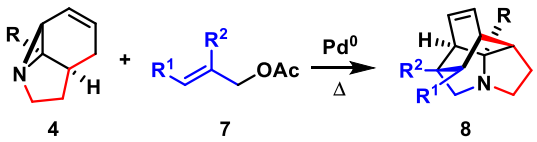
Scheme 1: Proposed synthetic route to alstoniascholarine A **3**.

Chapter 3 discusses the development and optimisation of a Pd-catalysed rearrangement reaction to form the medicinally relevant morphan scaffold **6** (Scheme 2). At the beginning, the reaction was limited to aryl iodide substrates **5**, but studies revealed that through the use of alternative activating agents, the scope of the reaction could be expanded, and indeed the rearrangement was shown to tolerate a wide range of substrates. Detailed mechanistic studies were carried out, including isotopic labelling experiments, which demonstrated that the process occurs *via* acid-assisted carbon-nitrogen bond cleavage, *β*-hydride elimination, and a terminal 1,6-conjugate addition step.



Scheme 2: The Pd-catalysed rearrangement of **5** to access the morphan ring system **6**. The photochemically derived tricyclic aziridine **4** undergoes an efficient 1,5-hydride shift/reductive amination sequence to afford **5**.

Chapter 4 describes the three-part cascade process, involving palladium catalysis and a thermal cycloaddition, to synthesise the tetracyclic amine **8** (Scheme 3). Reaction understanding allowed for the scope of such to be undertaken, which showed a number of aziridines **4** and allylated acetates **5** were transformed into the sp^3-rich product **8**. The thermodynamic activation parameters for the final stage of the cascade, the Diels-Alder reaction, were obtained from an Eyring plot, which highlighted the facile nature of the process.



Scheme 3: The cascade reaction of tricyclic aziridine **4** and allyl acetate **7** to form the tetracyclic amine **8**.

ii. Acknowledgements

I never imagined completing my PhD in the midst of a global pandemic. Nor did I imagine my supervisor would have retired during this time too. As Dan would say, ‘things can only get better’.

Although things often did not get better during my PhD, I would like to thank the people who supported me so much during those tough times. My supervisor, although now retired, Kev, was a huge boost of enthusiasm. His door was always open, and he was always full of encouragement. Jon, my unofficial supervisor, I do not think I can ever thank enough. You were at the end of Skype before video calling was the norm, constantly there answering my questions and pushing me to keep going when the chemistry was not co-operating. Thank you for all your motivation and support, I am sure your eagerness and hard-working attitude will take you far in academia!

Thanks of course to the legendary KBM group for making my time in the lab a lot of fun, even on the days (or more accurately months) when things did not work. Thanks for putting up with me giving out, swearing, my general pessimism and day-to-day stressing. I honestly feel very lucky to have spent this time with you all and I hope we can be reunited for a classic KBM session soon!

Katie Cooper, thanks for being a fabulous industrial supervisor. So supportive and willing to help whenever and wherever you could. Beth and I had a fantastic time at AZ on our CASE placement, we are both so grateful for our time spent there with you (and the free, unlimited heating).

Special thanks to Bristol & West Athletic Club for pushing me outside of the lab. I may not have achieved much in my PhD but a 1:25 half marathon and sub 18 5 K will suffice (Covid-19 put a stop championship entry at London Marathon, watch this space.) Thanks also to CRC for reigniting my passion for running and introducing me to so many of my wonderful friends.

Finally, a huge thanks to my parents, Mom and Eamon. It does not matter what I turn my hand to, you guys are always there as my No. 1 supporters. Thank you.

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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iii. Abbreviations

Ac	Acetyl
Ar	Aromatic
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Cbz	Carboxybenzyl
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
Cy	Cyclohexane
D	Dimensional
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,*N*-Diisopropylethylamine
DFT	Density functional theory
DMAP	4-Dimethylaminopyridine
DMP	Dess-Martin periodinane
DMPM	3,4-dimethoxybenzyl
DPEPhos	Bis[(2-diphenylphosphino)phenyl]ether
DPPF	1,1-Bis(diphenylphosphino)ferrocene
DPPB	1,4-Bis(diphenylphosphino)butane
EDG	Electron-donating group
EWG	Electron-withdrawing group
FDA	U.S. Food and Drug Administration
FEP	Fluorinated ethylene propylene
Fmoc	Fluorenylmethoxycarbonyl
FPT	Freeze-pump-thaw
g	Gram
h	Hour
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-trizolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HMBC	Heteronuclear multiple bond correlation
HMDS	Bis(trimethylsilyl)amine
HOMO	Highest unoccupied molecular orbital
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
IMDA	Intramolecular Diels-Alder
IC	Internal conversion
ISC	Intersystem crossing
J	Joule
KIE	Kinetic isotope effect
L	Litre
LDA	Lithium diisopropylamine
LUMO	Lowest unoccupied molecular orbital
m	*meta*
M	Molar
mes	Mesityl
min	Minute
mol	Mole
m.p.	Melting point
MS	Mass spectrometry
MSA	Methanesulfonic acid

m/z	Mass-charge ratio
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMI	1-Methylimidazole
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
NMP	1-Methyl-2-pyrrolidinone
Nu	Nucleophile
o	*ortho*
p	*para*
PMB	*p*-Methoxybenzyl
Py	Pyridine
Pyr	Pyrrolidine
P(*o*-toyl)$_3$	Tri(*o*-tolyl)phosphine
quant.	Quantitative
RT	Room temperature
S	Total spin angular momentum
S_0	Singlet ground state
S_1	Singlet excited state
T_1	Triplet excited sate
SM	Starting material
t	*tert*
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAI	Tetrabutylammonium iodide
TBDS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
TFP	Tri(2-furyl)phosphine
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Trost Ligand	(1*R*,2*R*)-(+)-1,2-Diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphino-1-naphthoyl)
Ts	4-Toluenesulfonyl
UV	Ultraviolet
VR	Vibrational relaxation
wt	Weight
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Δ	Heat
$\Delta^{\ddagger}H$	Enthalpy of activation
$\Delta^{\ddagger}S$	Entropy of activation

iv. Table of Contents

1. Introduction

1.1. The Importance of sp^3-Rich Heterocycles

Nitrogen-containing heterocycles are a prevalent structural motif within biologically active molecules (Figure 1). Indeed, they are found in 59% of all FDA approved small molecule drugs, highlighting both their prominence and their broad range of activity.[1] However, as the rate of success within clinical trials has fallen over the past two decades,[2,3,4] simple *N*-heterocycles are no longer sufficient. As such, there has been a growing demand within the pharmaceutical industry for molecules to be more three-dimensional in their shape, allowing expansion into a larger area of chemical space.[5,6] Compounds that have a high proportion of sp^3 hybridised carbon atoms and numerous stereogenic centres are hence desired, as these allow for increased protein-ligand interactions and specificity of binding, not generally accessible to flat, aromatic rings.[5] Ensuring the inclusion of such features in drug candidates enhances potency and selectivity, and in turn improves the likelihood of progression to market.[5] Furthermore, it has also been shown that this inherent complexity associated with enhanced sp^3 character, inhibits promiscuity of a drug candidate.[7] This is a key property that impacts toxicity, thus reducing the leading cause of attrition in the clinic.[7,8] The pharmaceutical company, GlaxoSmithKline, have published two key findings on this topic stating that 1) the fewer aromatic rings a drug molecule has, the more developable that candidate is and 2) carboaromatic (versus heteroaromatic) rings are the biggest (negative) contributor to these developability parameters.[9,10]

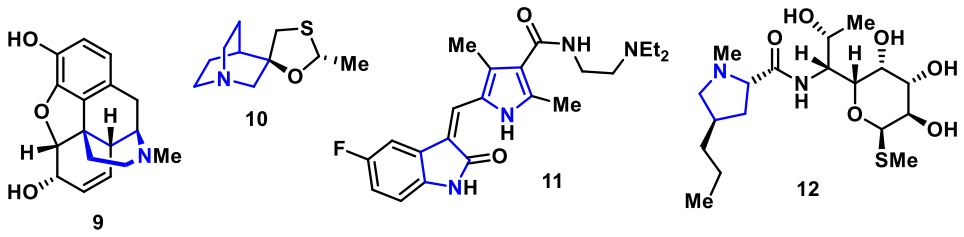


Figure 1: Drug molecules containing *N*-heterocycles. Morphine **9** is used for pain relief, cevimeline **10** is used for the treatment of a dry mouth, sunitinib **11** is an anti-cancer agent and lincomycin **12** is an antibiotic. Morphine and lincomycin are natural products.

However, despite this growing movement towards more saturated based heterocycles, sp^2-rich drug candidates remain dominant within the field due to the inherent challenges associated with the synthesis of their 3D counterparts.[11,12] In addition to this, a limited number of reactions are used within medicinal chemistry,[13,14] attributed to the need for such to be both reliable and robust. For example, palladium mediated sp^2-sp^2 cross-couplings are often selected for library synthesis as although they do not form products with the most desirable drug-like properties,[5] they have wide applicability, chemoselectivity and functional group tolerance.[15]

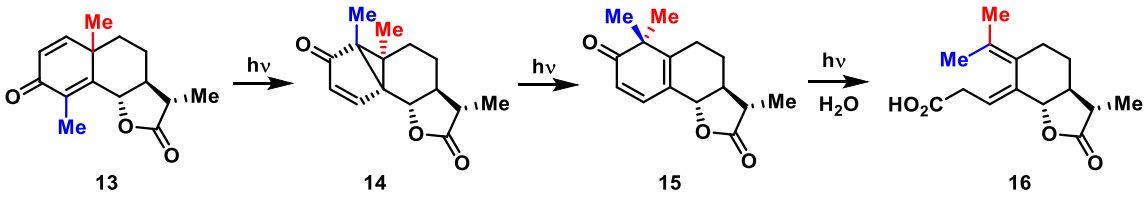
Natural products have long been a source of inspiration to the pharmaceutical industry,[16,17,18] but given the proceeding discussion, there is now even more emphasis on the natural world, with structurally

complex, diverse skeletons abundant within nature and hence inspiring medicinal chemists.[19,20] As such, there is still demand today for synthetic routes to lead into natural products, and derivatives of such, and for development of new methodologies that generate architecturally complex, non-planar heterocycles.

1.2. Photochemistry

Photochemistry, defined as *the branch of chemistry that deals with the effects on molecules and their reactions of the absorption of energy from light*,[21] is of utmost importance within nature; life ultimately depends on light. Light induced chemical reactions are far older than life itself.[22] The most obvious example of such is photosynthesis, a process where plants convert light energy into chemical energy, which began within the first billion years after the Earth's accretion phase.[23] Plants provided the Earth's atmosphere with oxygen,[24] which allowed for our existence and possibly even our development and evolution too.[25] Solar energy is thus vital for the survival of life.

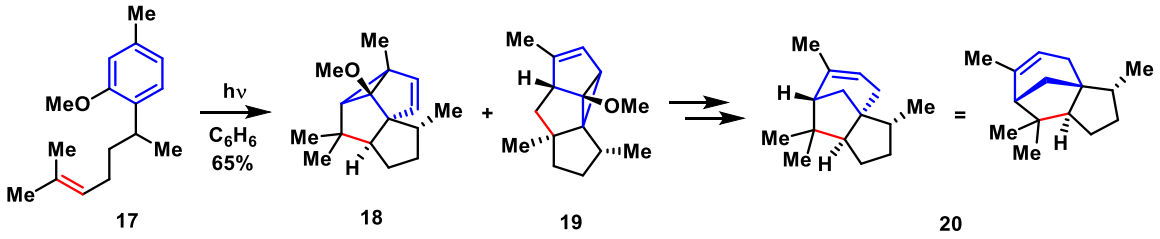
Photochemistry is perhaps unrivalled in its ability to generate molecular complexity from simple substrates in a single step. The first photochemical reactions of organic molecules were undoubtedly discovered serendipitously, accidental exposure to sunlight, for example, leading to a notable colour or solubility change. Perhaps the longest known photochemical reaction is that of santonin **13**,[23] which was reported in 1834 by Trommsdorff,[26] where he observed that upon exposure to sunlight the colourless solid **13** turned bright yellow and its crystals 'burst' (Scheme 4). Characterising santonin **13** and its photoproduct, photosantonic acid **16**, was however extremely difficult. Although realising that they were 'two isomeric modifications',[26] the exact structure was not determined until over hundred years later by van Tamblen.[27,28] It was a further five years, in 1963, when the intermediates were determined, [29,30] and as recently as 2007 when the crystal structural information was obtained.[31]



Scheme 4: The photorearrangement of santonin **13** reported by Trommsdorff.[23]

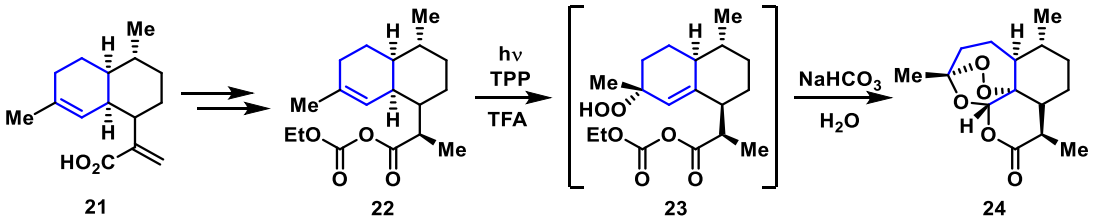
Chemists have always been interested in utilising light as an energy source to induce chemical reactions, and perhaps it is of even more relevance in today's world, where there is a strong emphasis on green and sustainable chemistry.[32] Using this interaction of light with matter as a synthetic tool however was not exploited within the laboratory until the 1900s. This likely reflects issues with the practicalities of using light and also a lack of understanding the theoretical concepts behind photochemical transformations.[33] Fortunately the application of photochemistry has nowadays become a valuable resource in synthetic chemistry, in both academia and industry alike. The admirable total synthesis of (±)-*α*-cedrene **20** by Wender *et al.* truly exemplifies how photochemistry can rapidly increase molecular

complexity (Scheme 5).[34] Employing the *meta*-photocycloaddition, the group were able to generate the tricyclic sesquiterpene, setting up all four stereogenic centres of the desired configuration in a single step. The remainder of the synthesis was completed in a further three steps, subsequent fragmentation of the cyclopropane ring, reductive dehalogenation and Wolff-Kishner reduction yielded (±)-*α*-cedrene **20**, in an impressive four steps.



Scheme 5: The key photochemical step in Wender *et al.*'s total synthesis of (±)-*α*-cedrene **20**.[34]

The large-scale production of artemisinin **24**, a natural product used in the treatment of malaria, showcases that photochemistry is indeed applicable for industrial usage.[35] Complex photochemically induced oxidations and rearrangements of dihydroartemisinic acid **22**, formed in two steps from artemisinic acid **21**, led to the active pharmaceutical ingredient **24** in a high 55% overall yield (Scheme 6).



Scheme 6: The pivotal photo-oxidation step in the manufacturing process to produce artemisinin **24** by Sanofi.[35]

A major advantage of photochemical processes is the ability to excite a molecule directly to the electronic state. To excite 1% of a population from the ground state to the first excited state *via* thermal means requires an energy of approximately 250 kJ mol^{-1}.[36] To do such, an approximate temperature of 6800 °C is needed, at which most molecular species would have long undergone decomposition.[36] Photochemistry thus also allows for the rapid construction of complex molecular architecture, which would be far more difficult, sometimes even impossible, to achieve using more conventional types of chemistry.

1.2.1. Principles of Photochemistry

Light is a form of energy, which possesses both wave-like and particle-like properties. It is a type of electromagnetic radiation, which travels in straight lines at a speed of 3 x 10^8 m s^{-1} within a vacuum. The frequency and wavelength of light can be related by the following equation:

$$c = \nu\lambda$$

where c is equal to the velocity of light (m s^{-1}), ν is the frequency (Hz) and λ is the wavelength (m).

If light is to be considered in the particle-like phase, the radiation behaves as if it consists of a stream of particles or light quanta. Each individual photon has a quantised amount of energy, which depends on the frequency of the radiation. This energy can be expressed as:

$$E = h\nu$$

where E is the energy (J) and h is Planck's constant (6.626 x 10^{-34} J s).

Combining these two equations relates both the wave-like and the particle-like properties of light:

$$E = \frac{h\nu}{\lambda}$$

There are two basic laws governing fundamental photochemical transformations, the first was formulated by Grotthuss and Draper at the beginning of the nineteenth century. The law states that *only light which is absorbed by a system can bring about a photochemical change*.[25] The evolution of quantum theory then led Stark and Einstein to develop the second law, known as the photo-equivalence law, stating that *for each photon absorbed only one molecule is excited*.[25] Hence the energy available to each reacting molecule, is equal to the energy possessed by the photon with which it interacts ($h\nu$). These laws can then allow the quantum yield, φ, of a system to be calculated, which is equal to the number of molecules of reactant consumed per photon of light absorbed.

Energy levels within atoms and indeed molecules are quantised. These defined, discrete energy levels result in chemical species having characteristic line spectra and band spectra. Species may possess internal energy such as rotational, vibrational and electronic energy, all of which are quantised. The electronic energy depends on the electron's location, its distance from the nucleus and type of orbital it occupies. It is these electronic transitions that are of concern within photochemistry. Absorption of quantum electromagnetic radiation by a chemical species results in it becoming excited. Which mode it assimilates that energy in, depends on the wavelength of the incident radiation. Longer wavelengths, and so lower energy radiation, usually only lead to transitions between rotational or vibrational states. Radiation in the visible to ultraviolet region, where $\lambda \approx$ 200-800 nm, are typically of the correct magnitude to induce electronic transitions. Such excitation can only happen if the photon is of the correct energy, that is equal to the difference in the energy levels where the transition occurs.

The excited state has very different reactivity compared to ground state, unsurprisingly it being the more reactive of the two. Hence, this difference allows the species to participate in new reactions that could not be completed in the ground state. Once an electron is promoted to the excited state, it has additional energy, which is of a similar magnitude to both typical bond energies and activation energies. Thus, the

excited state can often overcome reaction activation barriers, for which in the ground state it would be highly improbable to undergo. This altered reactivity is also due to the electron being excited to a new orbital, often of another type of orbital whereby its shape and symmetry would differ to that of the unexcited electron. As the spatial distributions of an electron control what reactions the species can undergo, this can have a major influence on reactivity.[25] Hence, why photochemistry can enable different modes of reactivity, allowing for new transformations to proceed.

Perhaps the most common way of describing electronic excited states is based on valence shell molecular orbitals (Figure 2). The ground state, or unexcited molecule is in the singlet state (S_0) where the lower bonding orbitals are fully occupied by pairs of electrons, with opposite spin. Upon excitation, an electron is promoted from this bonding orbital, also known as the highest occupied molecular orbital, to the upper anti-bonding orbital, or the lowest unoccupied molecular orbital. The electron conserves its spin, a spin allowed process in accordance with the spin selection rules (whereby electronic changes must occur with the conservation of spin, *i.e.* $\Delta S = 0$) and so the molecule is said to be in the singlet excited state (S_1). Alternatively, the spin state of the electron may be inverted and result in the formation of the triplet state (T_1). Direct excitation from $S_0 \rightarrow T_1$ is a spin forbidden process and so cannot be accessed directly from the ground state. It can however be accessed indirectly *via* intersystem crossing, ISC, from S_1 due to relaxation of the rule by spin-orbit coupling (whereby interactions between spin angular momentum and orbital angular momentum result in S no longer being a valid quantum number and hence the selection rules based upon it can fail).

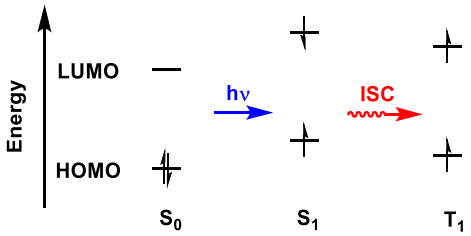


Figure 2: Molecular orbital diagram.

When a species is promoted to its electronic excited state, the spatial arrangement of the nuclei remains unchanged, since the time for the molecule to execute a vibration is much longer than that required for an electronic transition. This is a consequence of the Born-Oppenheimer approximation and is known as the Franck Condon principle (Figure 3). Hence, this results in the molecule occupying the most compatible vibrational energy level at the excited electronic level, that is one where the wavefunction of the initial vibrational state most closely resembles that of the wavefunction of the final vibrational state.

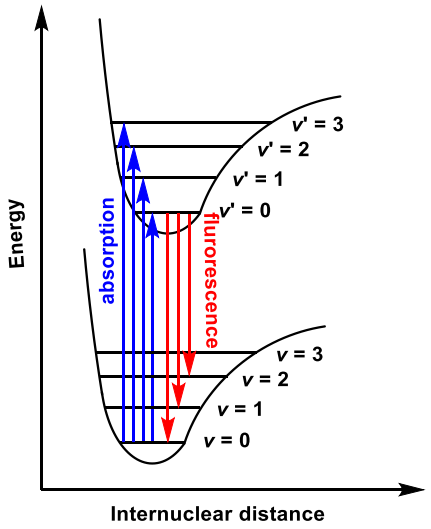


Figure 3: Diagram representing the Franck-Condon Principle, whereby an electronic transition occurs so rapidly the nuclei of a vibrating molecule can be assumed to be fixed during the transition, hence the vertical line.[25]

There are numerous processes, both physical and chemical, that govern the fate of the excited state. The lifetime of excited state is extremely short, typically for an organic molecule at room temperature it has a lifetime between 10^{-3} and 10^{-12} s.[37] Physical processes dominate this lifetime as they are much faster than the chemical alternatives, and are illustrated in the Jablonski diagram (Figure 4). Non-radiative transitions (whereby no light is emitted, represented by wavy arrows) occur when the energy is lost as vibrational energy, known as vibrational relaxation (VR). The electron can return to the ground state either by internal conversion (IC) for which it ends up in a higher vibrational state, or by emission of a photon, known as fluorescence (radiative decay). The excited singlet state may also undergo ISC, resulting in the excited triplet state. Upon VR, the molecule can then return to the singlet ground state by expulsion of a photon, called phosphorescence. Such a phenomenon is spin-forbidden, and so lifetimes of triplet states are generally much longer than those of singlet states. Thus, most photochemical reactions occur through the triplet excited state.[37]

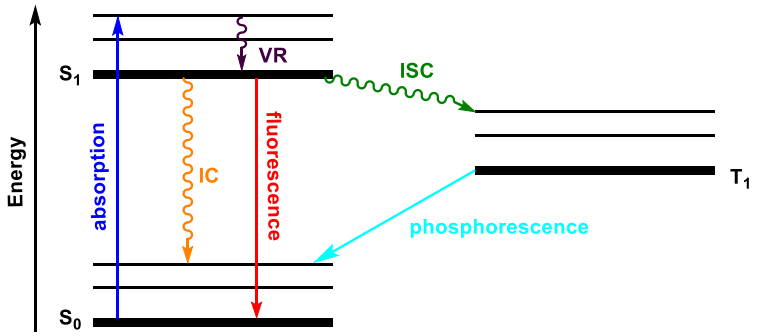


Figure 4: Jablonski diagram showing the absorption and the emission processes of fluorescence and phosphorescence.[38]

However, for many organic molecules the ISC from $S_1 \rightarrow T_1$ is not a very efficient process, and as such this can limit, or completely stop a photochemical reaction. The process of photosensitisation is

whereby another molecule is introduced into the reaction, and it is selectively excited to its triplet state, T_1, in a high quantum yield. This energy can then be transferred to the substrate molecule, and the sensitiser will return to the ground state. Hence this allows for the direct access of the triplet excited state of a photochemical substrate (Figure 5). Such a transfer is a spin allowed process as the total change in the spin state is equal to zero. This method also allows for access into the T_1 state of molecules that cannot be directly excited themselves, for instance perhaps due to being a poor chromophore or having poor ISC efficiency. The photosensitiser does need to meet certain requirements however; it must have a high extinction coefficient, *i.e.* absorb the light preferentially, have a triplet state energy higher than that of the substrate molecule and be able to efficiently transmit the energy to the substrate.

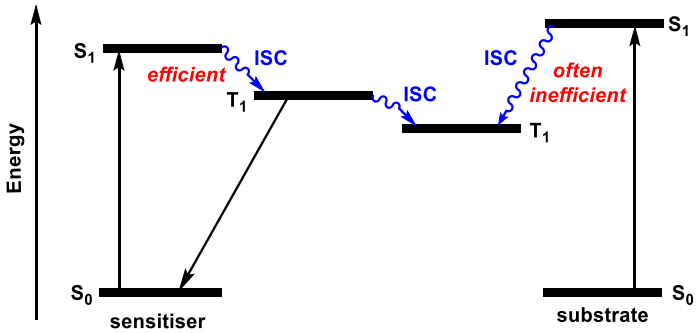


Figure 5: Mechanism of triplet photosensitisation.[39]

For such processes to occur, a chromophore must be present within the substrate molecule. A chromophore is defined as *a molecular moiety responsible for one or more electronic transitions, allied to absorption bands in the UV or visible range*.[40] They may be a specific functional group, such as a carbonyl, or often an extended π-electron system, such as a conjugated α, β-unsaturated carbonyl. As mentioned previously, the wavelength absorbed corresponds to the HOMO-LUMO band gap, which is dependent on the functional groups present. There are several possible electronic transitions, however in practice generally only the n $\rightarrow$ π^* and $\pi \rightarrow \pi^*$ transitions are exploited (Figure 6).

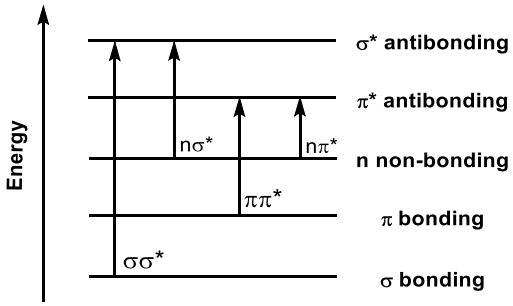


Figure 6: Characteristic types and energy ordering of electronic transitions in molecules.[38]

Saturated hydrocarbons have energy gaps between the $\sigma \rightarrow \sigma^*$ orbitals, corresponding to wavelengths of less than 200 nm (Table 1). Such wavelengths are difficult to achieve as organic solvents and glass reaction vessels strongly absorb at 200 nm and below. Unsaturated organic molecules however have

absorption bands in the more conventional photochemical region of the electromagnetic spectrum, the near UV region (200-400 nm) and thus can absorb such radiation.[41]

Entry	Chromophore	λ (nm)	Transition
1	C-C	<180	$\sigma \rightarrow \sigma^*$
2	C-H	<180	$\sigma \rightarrow \sigma^*$
3	C=C	180	$\pi \rightarrow \pi^*$
4	C=C-C=C	220	$\pi \rightarrow \pi^*$
5	C=O	280	n $\rightarrow \pi^*$
6	N=N	350	n $\rightarrow \pi^*$
7	C=C-C=O	350	n $\rightarrow \pi^*$
8	C=C-C=O	220	$\pi \rightarrow \pi^*$

Table 1: Absorption bands of some common organic chromophores.[41]

1.2.2. Practical Photochemistry

The irradiation apparatus used in preparative photochemistry most commonly uses mercury discharge lamps, which fall into three main categories: low, medium and high-pressure lamps. Such lamps have different output spectrums, which are dependent on the vapour pressure inside the lamp. They work by exciting the vaporised mercury atoms with an electric current, which emit photons upon returning to the ground state. Low-pressure lamps, or UVC lamps, operate at a temperature of 40-50 °C, with the mercury pressure around 10^{-5} atm. The majority of their radiation is emitted at wavelengths of 185 nm and 254 nm (Figure 7). As stated previously, the former is not accessible due to the reactor vessels filtering out these photons. Hence, these lamps can be seen as monochromatic. Commercially available filters for these lamps can however be used to access other wavelengths, for example phosphor coated UVB lamps emit at 312 nm and UVA lamps around 365 nm (Figure 7). Medium-pressure lamps operate at much higher temperatures, 600-800 °C, and so require a cooling system. They operate at higher power outputs than the low-pressure lamps, with a pressure of mercury covering the range of 1-10 atm. Medium-pressure lamps have a much broader spectral distribution, allowing for more chromophores to be targeted (Figure 7). However, this can also be a disadvantage, spreading the power output over a wide range of emission bands, which if exciting a chromophore with a narrow or specific absorption, much of the output is wasted. It can also lead to exciting other chromophores in the molecule, resulting in undesired photochemical reactions or photodegradation. High-pressure lamps are not used within this report and so will not be discussed further.

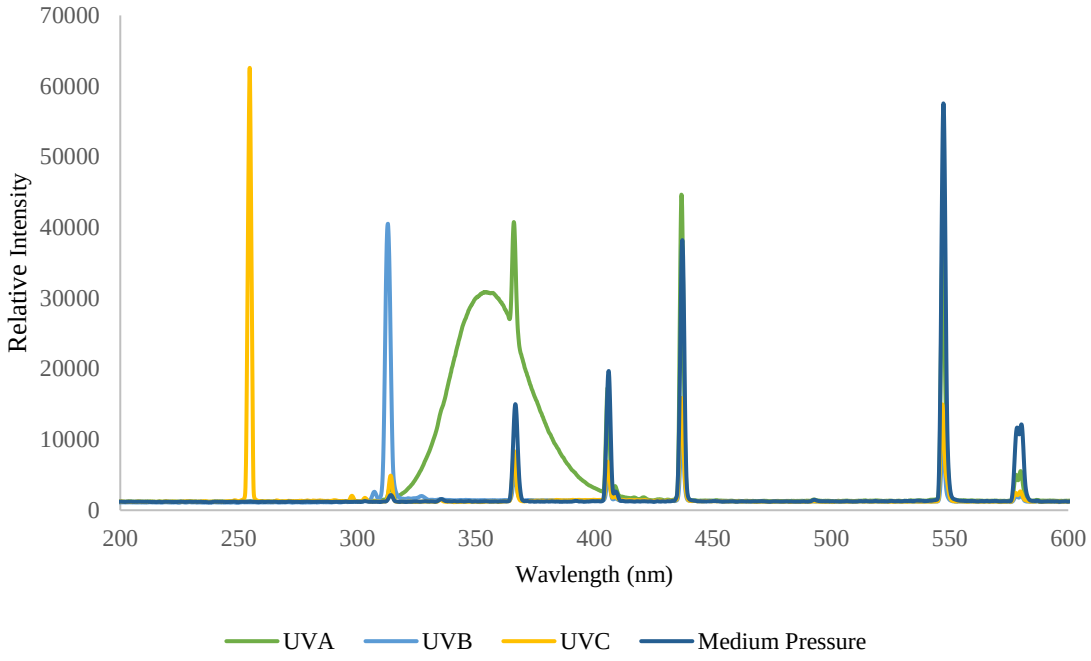


Figure 7: Emission spectra of low-pressure and medium-pressure mercury lamps.

Typically, photochemical reactions are carried out in batch reactors, where the lamp is fitted with a water-cooled jacket which is then immersed in a well containing the reaction mixture (Figure 8). These are fixed volume reactors, irradiated from within. The jacket surrounding the mercury lamp is usually quartz or pyrex, the former absorbing wavelengths below 170 nm and the latter below 275 nm. The reaction solution is degassed prior to irradiation to remove any dissolved oxygen, as it quenches excited states at a diffusion-controlled rate, and nitrogen is continuously bubbled through the system during the reaction.

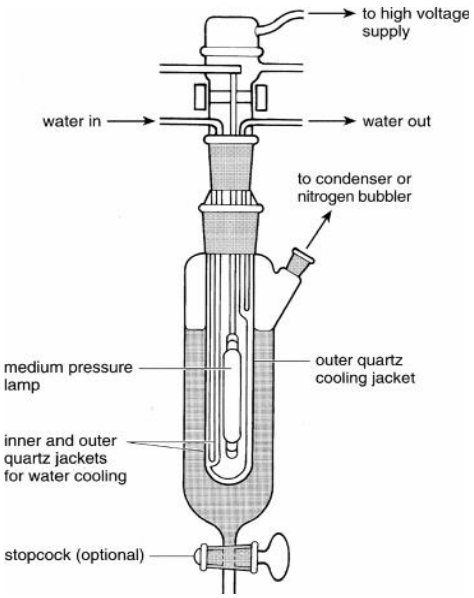


Figure 8: Diagram of an immersion well photochemical reactor.[42]

These reactor vessels offer an easy set-up for experimental screening, but the size of the lamp and reactor vessel limits the scale of the photochemical reaction. Increasing the reactor size (whilst maintaining the power of the UV source) does not solve this scale-up issue as this would require longer irradiation times, which is only suited for those reactions where photodegradation does not occur. This is a consequence of the Beer-Lambert law, which describes the distance of light transmitted through an absorbing solution:

$$A = \varepsilon c l$$

$$A = \log_{10}\left(\frac{I_o}{I_t}\right)$$

where A is the absorbance, ε is the molar extinction coefficient ($dm^3\ mol^{-1}\ cm^{-1}$), c is the concentration ($mol\ dm^{-3}$), l is the pathlength (cm), I_o is the incident intensity and I_t the transmitted intensity. Rearrangement of the equation shows that the intensity of light decreases exponentially with distance from the lamp, hence absorption becomes increasingly inefficient with increasing reactor volume. Consequently, high dilution or narrow reaction vessels are usually employed to improve light penetration.

$$I_t = I_o e^{-\varepsilon c l}$$

In an attempt to circumvent this issue, the use of continuous photochemical flow reactors have been established.[43] The Booker-Milburn group have developed their own such reactor, where the UV lamp is wrapped with UV transparent FEP tubing, thus minimising the pathlength of light, and the reaction solution is pumped through the tubing using a HPLC pump (Figure 9).[44] By controlling the flow rate, the length of exposure of the reaction mixture to irradiation, known as the residence time, can be used to optimise the yield. Such a reactor is advantageous for large scale photochemical reactions, which achieving the same in batch would require multiple experimental runs. Yet, a study by the group has shown that percentage yields and productivity of both the flow and batch reactors are largely similar.[45] Further development by the Booker-Milburn group has led to the construction of an even more efficient photochemical flow reactor than the FEP type system (as much as 30% more power efficiency). The Firefly reactor is capable of producing multi-kilogram quantities of photochemical products in a single day.[46]

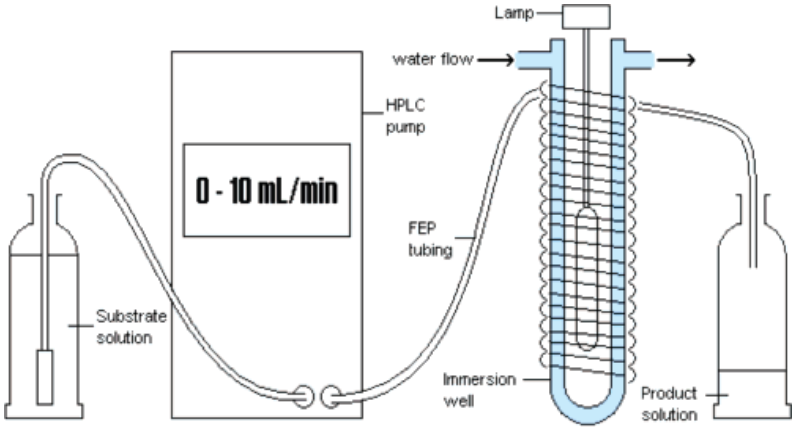
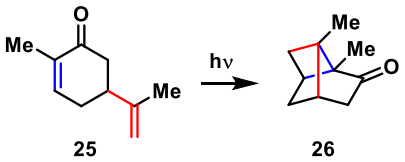


Figure 9: Diagram of the Booker-Milburn's FEP continuous photochemical flow reactor.[44]

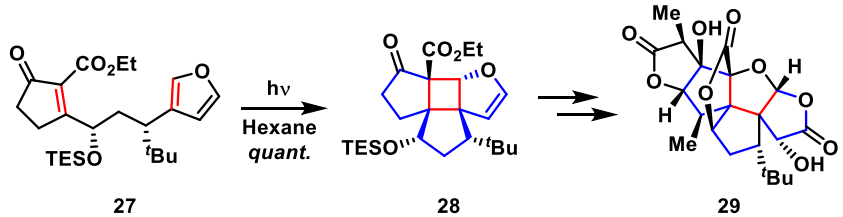
1.2.3. The [2+2] Photocycloaddition

Undisputedly the most well known and most applied photochemical reaction is the [2+2] photocycloaddition.[47,48] It involves the photoexcitation of a π system, followed by the reaction with another π system to form a cyclobutane ring and hence the formation of two new bonds. One of the earliest examples of a [2+2] photocycloaddition was reported in 1908 by Ciamican and Silber, where they noted the formation of carvone camphor **26** upon exposure of carvone **25** to sunlight for one year (Scheme 7).[49] Pleasingly nowadays, most [2+2] photocycloadditions do not require such a prolonged reaction time.



Scheme 7: The intramolecular [2+2] photocycloaddition of carvone **25** discovered by Ciamican and Silber.[49]

There are many hundreds of examples where this reaction has been exploited in natural product synthesis, both to afford the desired cyclobutane,[50,51,52,53] a common structural motif within nature,[54] and due to its usefulness as a synthetic precursor, for further chemical modifications.[55,56,57] One noteworthy example of the [2+2] photocycloaddition is that used in the synthesis of (±)-ginkgolide B **29** by Crimmins and co-workers (Scheme 8).[58] A stereoselective intramolecular photocycloaddition of the enone **27** was used to construct the congested core of the molecule, forming **28** in a quantitative yield and greater than 98% diastereoselectivity.



Scheme 8: [2+2] Photocycloaddition used as a key step in the synthesis of (±)-ginkgolide B **29** completed by Crimmins.[58]

The [2+2] photocycloaddition process is not thermally allowed due to the mismatched symmetries of the frontier molecular orbitals (Figure 10). Upon excitation, however, the electron is promoted to the new HOMO* orbital which does have the correct symmetry to allow for favourable overlap with the LUMO molecular orbital of the ground state species, and so the cycloaddition can take place.

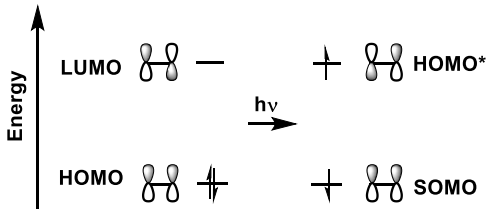


Figure 10: Frontier molecular orbitals involved in the [2+2] photocycloaddition reaction.

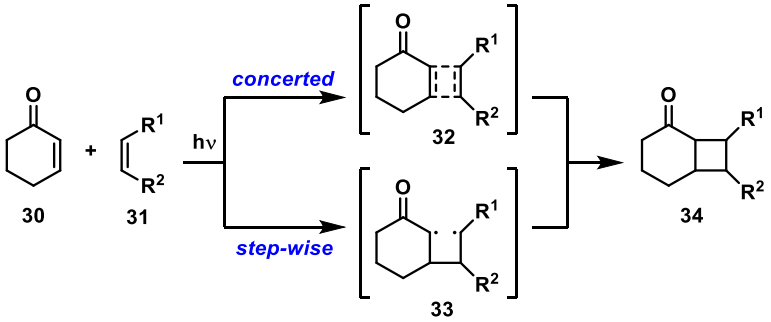
Examining the [2+2] photocycloaddition of an enone and alkene (Scheme 9), such proceeds by absorption of a photon by the enone **30**, resulting in the formation of an excited singlet state. This excited singlet enone can then undergo one of the following:[59]

1) Combination with the ground state alkene to form a singlet exciplex (an excited complex). The cyclobutane product **34** can then be generated directly, or *via* formation of a 1,4-diradical. The exciplex and diradical could however collapse back to the ground state.

2) Undergo ISC to an excited triplet state (which could also be accessed directly from a sensitized excitation). This too can combine with a ground state alkene to generate a triplet exciplex, whereby carbon-carbon bond formation can ensue and produce a triplet 1,4-diradical species. In this case however, ring-closure to the cyclobutane product **34** can only proceed after spin inversion to the singlet diradical has happened. Similarly, at any point, decay to the ground state can occur.

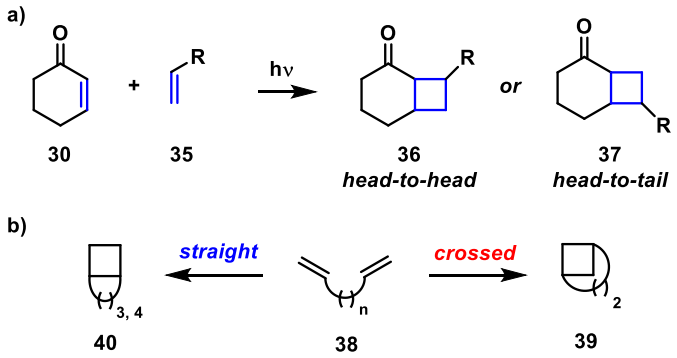
3) Relax back to the ground state.

Pathway two is generally the most productive pathway, as ISC to a triplet state is an efficient process, particularly when using five and six-membered cyclic enones. As such, the [2+2] photocycloaddition can be viewed as proceeding by either of the two possible mechanisms, in a concerted or step-wise manner (Scheme 9).[59] The former mechanism will proceed with stereochemical retention, whereas the stepwise process could proceed non-stereoselectively, due to the possible rotations of the 1,4-diradical **33** prior to combination. The mechanistic pathway followed depends on the reaction conditions and the substrates involved.



Scheme 9: Two possible mechanisms for the [2+2] photocycloadditions.[59]

As well as diastereomers, two regioisomers are also possible outcomes of this reaction (Scheme 10). The cyclobutane can form either the head-to-head or the head-to-tail regioisomeric product.[59] Typically, when the substituent is of electron-withdrawing nature, the head-to-head product **36** is observed, and when it is electron-donating, the head-to-tail product **37** is seen.[60] Intramolecular [2+2] photocycloadditions can also proceed one of two ways, in either a straight or crossed manner (Scheme 10).[61] In general, when the tether between the two reacting olefins is only two carbon atoms in length, the crossed regioisomer **39** will result to avoid the formation of a further strained four-membered ring. If the tether is longer than such, the straight regioisomer **40** will prevail.



Scheme 10: Regioselectivity in the [2+2] photocycloaddition, a) intermolecular products affording **36** the head-to-head product or **37** the head-to-tail product[59] and b) intramolecular products affording the crossed product **39** or the straight product **40**.[61]

2. Alstoniascholarine A

2.1. Introduction

2.1.1. Alstoniascholarine A

Alstoniascholarine A **3** is a member of a family of indole alkaloids (Figure 11), isolated from the *Alstonia scholaris* leaf (from the widespread genus Alstonia), an evergreen tree found in parts of Africa, Asia, Australia and Central America. The plant is rich in bioactivity and as such, it has been used extensively in traditional medicines within Asia.[62] Treatments include a wide range of ailments including malaria, cancer and jaundice.[63,64] The alkaloid family are structurally interesting, with alstoniascholarine A **3** consisting of an eight-membered nitrogen-containing heterocycle with a two-carbon bridge, fused to an indole. The monoterpenoid has only been isolated *via* leaf extraction.[63,64] As stated in Section 1.1., natural product synthesis has an important role in the development of new drug candidates, with almost half of all new chemical entities between 1981 and 2002 being either natural products themselves or synthetic analogues of such.[18,16,17,20]

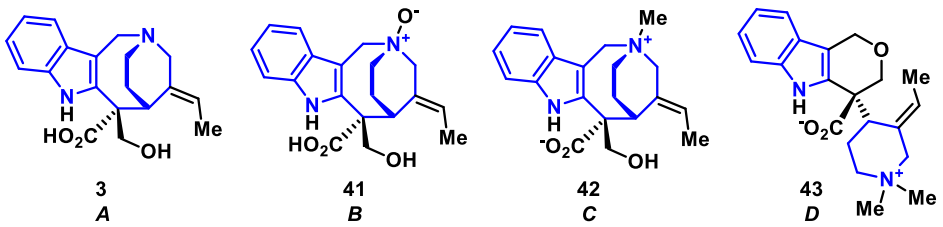


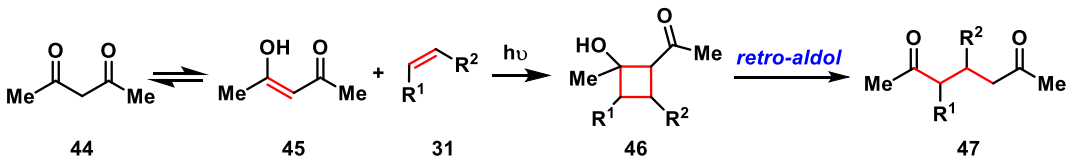
Figure 11: Four members of the alstoniascholarine family, alstoniascholarine A, B, C and D.[64]

2.1.2. The Formation of Medium-Sized Rings *via* the [2+2] Photocycloaddition

The [2+2] photocycloaddition has been exploited as an initial step to synthesise larger ring systems than the initial four-membered cyclobutane product, as alluded to in the previous section, *via* ring-fragmentation and then ring-expansion. Medium-sized rings (those containing between eight and twelve atoms) are more difficult to synthesise than their smaller and larger analogues, due to both entropic and enthalpic factors.[65] Entropically, there are less degrees of freedom of internal rotation around the bonds in the cyclic species compared to the disordered, acyclic equivalent. This eventually becomes negligible, as the ring-system gets larger and so can retain some flexibility even as the closed ring-system. Additionally, as the linear precursor's chain length increases, it is less likely for the terminal ends to meet and hence cyclise. Unfavourable enthalpic factors are also prevalent in the synthesis of medium-sized rings, due to Pitzer and transannular strain.[65] Medium-sized carbo- and heterocycles are however a common motif found in biologically active natural products. Such cyclic scaffolds have been shown to have enhanced binding affinities and cell permeabilities, as well as improved bioavailability.[66] This is thought to be due to their conformationally restricted core. Despite their often-inherent

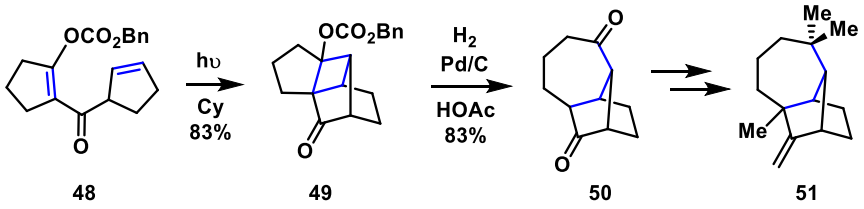
biological activity, such structures are scarce within approved pharmaceutical drugs,[67,68] and this is probably indicative of their challenging synthesis.

The De Mayo reaction involves a two-step process resulting in a two-carbon homologation (Scheme 11). Initially a tautomerisation of a 1,3-dicarbonyl species **44** to the corresponding enone **45**, which can then undergo a photochemical [2 + 2] cycloaddition with an olefin to form a cyclobutanol **46**. The second step involves a fragmentation of this cyclobutanol *via* a retro-aldol condensation to give the 1,5-dicarbonyl product **47**.[69,70]



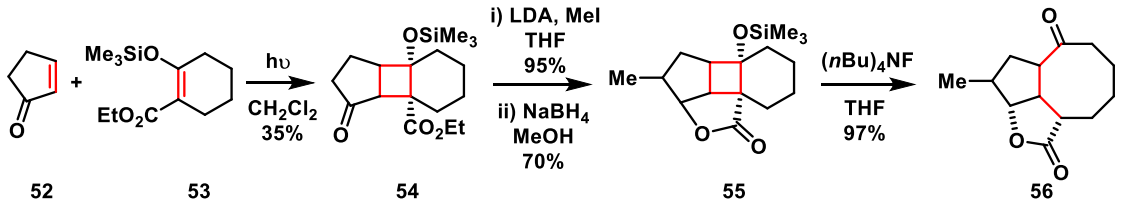
Scheme 11: The De Mayo reaction.[69,70]

Although initially the De Mayo fragmentation was concerned with acyclic 1,3-dicarbonyls, the reaction has since been expanded to ring systems.[71,72,73,56] Using a cyclic *β*-diketone as the precursor, ring-fragmentation of the corresponding fused cyclobutanol hence leads to ring-expansion, and so can be utilised in the synthesis of medium-sized rings.[73] This methodology exploits the strained bicyclic cyclobutane formed initially, and so ring-opening to afford the medium-sized ring relieves some degree of strain within the system. It also avoids the inherent difficulties of directly synthesising a medium-sized ring from a linear compound. The first example of such an intramolecular version was used by Oppolzer *et al*. in their total synthesis of (±)-longifolene **51** (Scheme 12).[74] Masking the diketone as the benzyloxycarbonyl derivative **48**, subsequent [2+2] photocycloaddition followed by hydrogenolysis, which triggered the retro-aldol reaction, and hence ring-expansion to form the norbornanone moiety **50**. An additional five steps completed the synthesis of the sesquiterpene, in an overall yield of 25%.



Scheme 12: The intramolecular De Mayo reaction utilised in Oppolzer *et al.*'s total synthesis of (±)-longifolene **51**.[74]

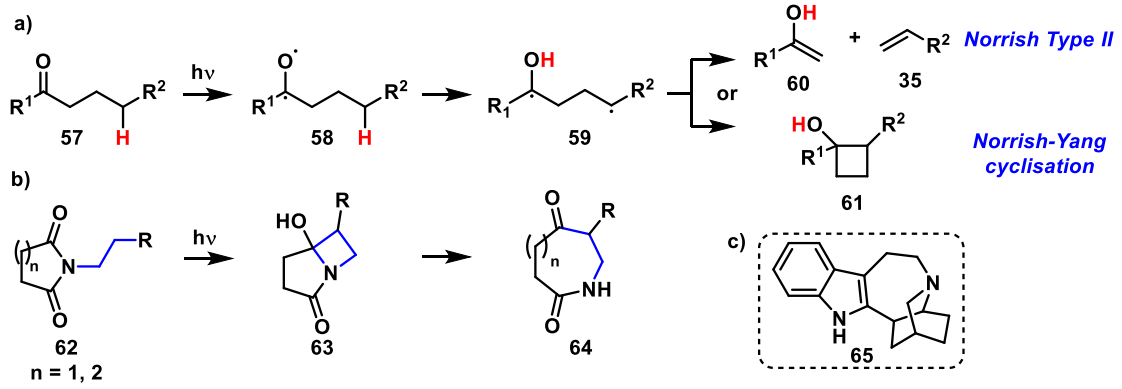
A further example, this time with a *β*-keto ester, was used by Lange *et al.* in the four-step synthesis of (±)-norasteriscanolide **56** (Scheme 13).[75] Upon excitation of 2-cyclopentenone **52**, [2+2] photocycloaddition occurred with the protected enol of the *β*-keto ester **53** in 35% yield. After methylation, reduction of the ketone and subsequent formation of the lactone, the silyl protecting group was cleaved and the molecule underwent a retro-aldol reaction to give the eight-membered tricyclic product **56**.



Scheme 13: Lange *et al.*'s synthesis (±)-norasteriscanolide **56** using the De Mayo reaction.[75]

2.1.3. The Norrish-Yang Cyclisation

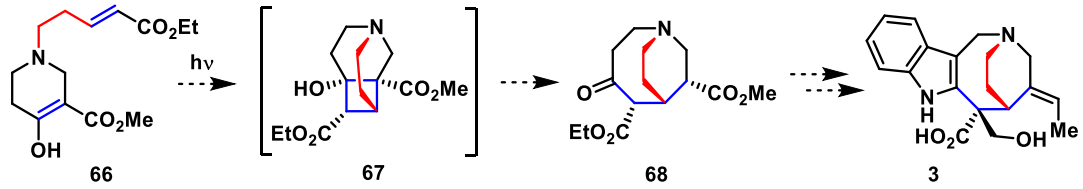
Upon irradiation of a *γ*-hydrogen bearing carbonyl, intramolecular hydrogen abstraction can ensue forming a diradical intermediate **59** (Scheme 14). This can then follow either two pathways: carbon-carbon bond fragmentation to form an enol **60** and olefin **35**, the Norrish Type II reaction,[76,77] or the diradicals can combine, forming a cyclobutanol **61**. The latter is the Norrish-Yang cyclisation which was reported in 1958 by Yang[78] and as seen in the De Mayo reaction, the formation of such a cyclobutanol can readily fragment and afford ring-expanded products. This was exploited by Kanaoka in the 1970s to photochemically form azepines from either succinimides or glutarimides with a variety of substituents (Scheme 14).[79,80] This methodology has also been used within the Booker-Milburn group, in the synthesis of (±)-desethylibogamine **65**, an analogue of the natural product (±)-ibogamine.[81,82]



Scheme 14: a) Norrish Type II versus Norrish-Yang cyclisation; b) formation of azepines in the Norrish-Yang cyclisation;[79] and c) (±)-desethylibogamine **65**.

2.2. Aim of Project

The aim of this project was to photochemically synthesise medium-sized rings and incorporate this as a key step within the natural product synthesis of alstoniascholarine A **3** (Scheme 15). After optimisation of this [2+2] photocycloaddition, it was envisaged to utilise photochemical flow reactors, allowing for scale-up of the reaction and hence enable large quantities of photochemically-derived intermediates to be synthesised, thus alleviating material mass problems often encountered in natural product synthesis. As discussed, alstoniascholarine A **3** has potential biological activity and at the time of writing, a synthetic route to the molecule had not been published.

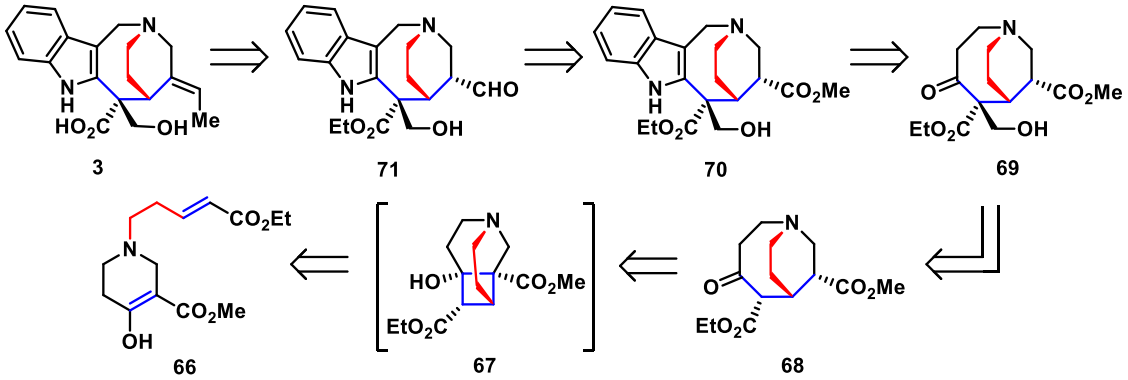


Scheme 15: Synthetic route to alstoniascholarine A **3** *via* the key De Mayo reaction.

2.3. Results and Discussion

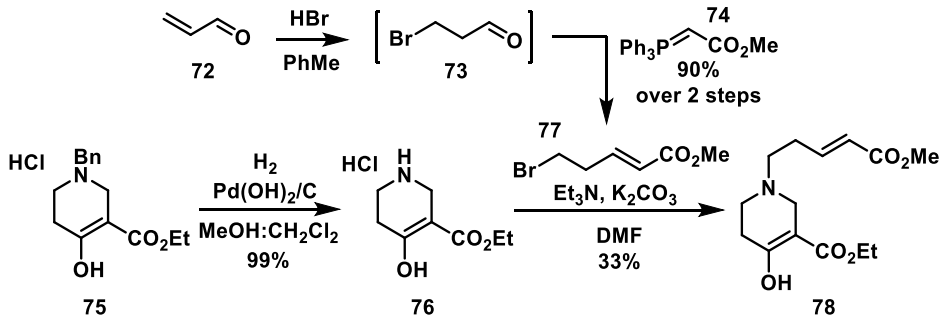
2.3.1. Synthetic Route to Alstoniascholarine A

The fundamental retrosynthetic route would lead to alstoniascholarine A in a mere six steps from the cyclisation precursor **66** (Scheme 16). The natural product was envisaged to be generated from **71**, by carbon-carbon bond formation/dehydration to form the olefin and subsequent hydrolysis of the ester to the carboxylic acid. Aldehyde **71** was reasoned to be obtained by reduction of the least hindered, and more reactive methyl ester on **70**, the core of the natural product, which was planned to be formed *via* a Fischer indole synthesis. Alkylation at the *α*-position would give **69** from the eight-membered ring **68**. Irradiation of enol ether **66** was proposed to induce a De Mayo reaction, which would spontaneously fragment and hence ring-expand, leading to **68**.



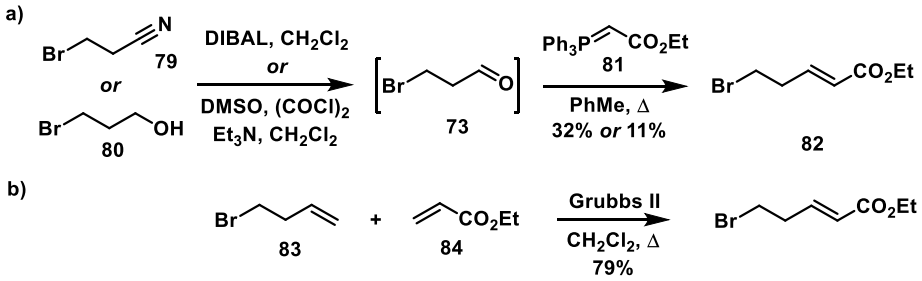
Scheme 16: Retrosynthetic route to alstoniascholarine A **3**.

Although the exact photochemical substrate **66** was not known in the literature, Joseph *et al.* have reported a very similar analogue **78**, whereby the methyl and ethyl esters are simply the opposite way round. The group used such to form 1-azabicyclic frames *via* tandem conjugative isomerisation-intramolecular Michael addition.[83] Their synthesis of **78** involved brominating acrolein using gaseous HBr followed by the Wittig olefination to form the bromopentanoate tether **77** (Scheme 17). The piperidone hydrochloric salt **76** was obtained by hydrogenation of the commercially available benzyl hydrochloric salt **75**. This was alkylated to afford the desired enol ether **78**, albeit in a poor yield of 33%, which took seven days to achieve. The paper reports the group's considerable efforts to increase the yield; however, this was unfortunately not successful.



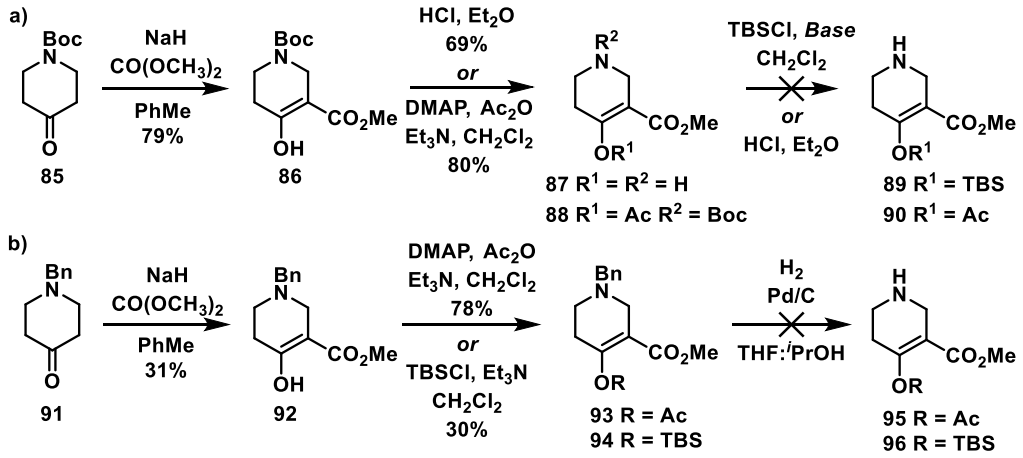
Scheme 17: Joseph *et al.*'s synthesis to **78**, closely related to the desired photochemical substrate **66**.[83]

Although it would have been possible to synthesise cyclisation precursor **66** *via* Joseph's synthetic route, due to the substandard alkylation step (both in terms of yield and timescale), the hazardous nature of acrolein and the handling of gaseous HBr, it was decided to modify this. Focusing on the synthesis of tether **82**, the initial route proceeded *via* the reduction and hydrolysis of 3-bromopropionitrile to afford the aldehyde **73**, which was then subjected to Wittig olefination conditions to form the desired bromopentanoate **82**, in preparation for alkylation studies (Scheme 18). Unsurprisingly however, the aldehyde intermediate **73** was unstable and readily underwent elimination to form HBr and acrolein. Completing the two steps within a single vessel did give the desired product **82**, albeit in a 32% yield (19:1, *E*:*Z* isomers). However, reproducing this yield consistently was not achievable, nor was improvement of such. Alternatively, oxidation of the corresponding bromopropanol substrate **80** was also examined but this resulted in a poorer overall yield of 11%, again with a similar reproducibility issues. Both the chloro-equivalents of **79** and **80** were tried under the same conditions but led to no product formation. Due to these limitations, other synthetic methods were sought and pleasingly, a cross metathesis reaction of 4-bromobutene **83** and ethyl acrylate **84** afforded the tether product **82** in a good yield of 79% (13:1, *E*:*Z* isomers).



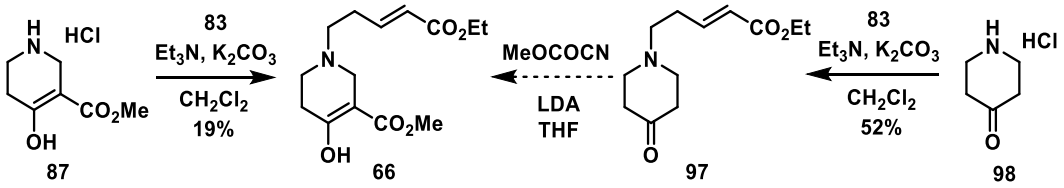
Scheme 18: a) Reduction, oxidation and b) cross-metathesis synthetic routes to synthesise bromopentanoate **82**.

The prospective route to the piperidone region of the molecule also differed from the literature precedence by starting with the commercially available Boc-protected piperidone **85** and forming the *β*-keto ester **86** with dimethyl carbonate (Scheme 19). In an effort to improve the subsequent alkylation, it was decided to protect the enol ether, hence only allowing for *N*-alkylation over *O*-alkylation (although estimation of pK_as would suggest *N*-alkylation is favoured, protection would eliminate any possibility of a competing reaction). However, despite various attempts this was proven unsuccessful. Although Boc removal of **86** proceeded in a 69% yield, TBS protection of which, with a range of bases, did not lead to any of the protected enol **89**. Acetyl protection did form the di-protected piperidone **88**, however upon exposure to acid, both protecting groups were cleaved. The benzyl protected analogue **91** was then synthesised, in the hope that it could be selectively removed *via* hydrogenation. Both the acetate and silyl protecting groups were installed successfully, however hydrogenation of compounds **93** and **94** led to degradation. In a final attempt to access the protected enol, trapping as the enol ether was tried, yet refluxing **92** with trimethyl orthoformate under acidic conditions for six days only recovered starting material.



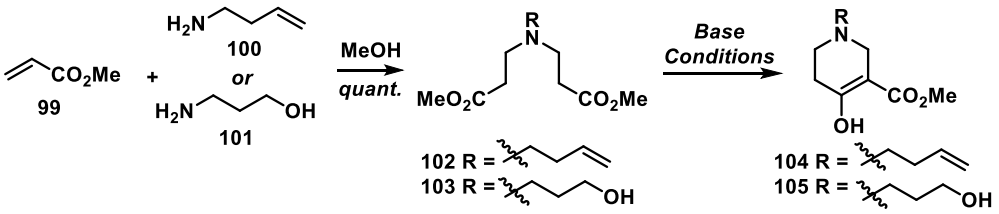
Scheme 19: Attempted routes to functionalised piperidones **89**, **90**, **95** and **96** for alkylation studies.

With limited success on forming the two protected precursors for the alkylation, the reaction was completed nonetheless on the unprotected enol **87** (Scheme 20), following the protocol of Joseph *et al.*[83] As expected, a low yield of 19% was achieved, which took seven days to reach. It was then thought that perhaps forming the carbon-nitrogen bond before the synthesis of *β*-keto-ester may be advantageous and would also eliminate any possible *O*-alkylation. An improved yield of 52% for such a reaction to piperidone **97** was obtained but unfortunately another prolonged reaction time of five days was required.



Scheme 20: Alkylation *via* Joseph's route and a possible alternative *β*-keto-ester synthesis to photochemical substrate **66**.

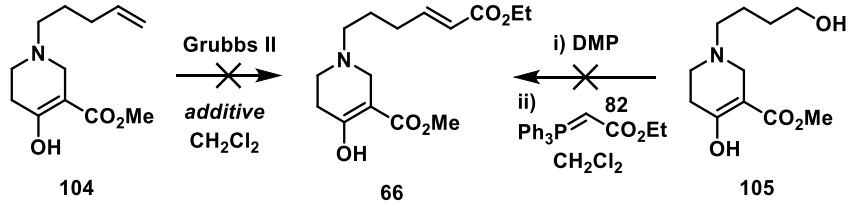
The decision was made to avoid such an alkylation step due to its challenging nature. The Dieckmann cyclisation was seen as a simplistic, but viable route into the photocycloaddition precursor **66** (Figure 12). Michael addition of the two amines, the terminal olefin **100** and the hydroxyl **101**, to methyl acrylate gave the tertiary amines **102** and **103** in quantitative yields. Yet the subsequent intramolecular cyclisation proved challenging; literature precedence of similar systems completed the reaction with NaOMe as the base,[84] yet with these two tethers only starting material was recovered (Entry 1), even with freshly synthesised NaOMe (Entry 2). Quenching the reaction with D_2O led to no incorporation of the deuterium isotope in the molecule, and so stronger bases were next investigated. NaH led to degradation and LDA also resulted in no reaction (Entries 3 and 4). Fortunately, the Dieckmann reaction did proceed with KHMDS and NaHMDS (Entries 5 and 6), in good yields of 75% for the terminal olefin product **104** and 92% for the terminal alcohol **105**.



Entry	*Base*	*Conditions*	*Time (hours)*	Result 104	Result 105
1	NaOMe	PhMe, Δ	24	-	SM
2	NaOMe[a]	PhMe, Δ	19	SM	SM
3	NaH	PhMe, Δ	48	Degradation	Degradation
4	LDA[a]	THF, -78 °C→ RT	2	-	SM
5	KHMDS	THF, RT	2	75%	-
6	NaHMDS	THF, RT	2	57%	92%

Figure 12: Base screen carried out for the Dieckmann cyclisation to afford terminal olefin **104** and alcohol **105**. [a]Freshly prepared base.

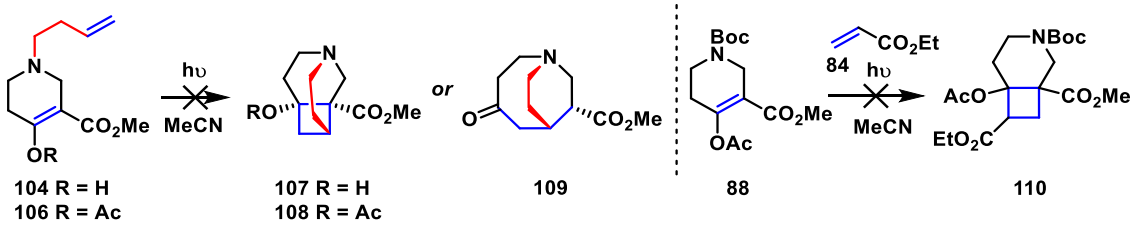
With the analogues **104** and **105** in hand, studies next began on converting to the desired ethyl ester photochemical substrate **66**. Cross metathesis of the alkene **104** with both Grubbs type II and Grubbs-Hoveyda catalyst resulted in no product formation (Scheme 21). Additives such as titanium isopropoxide and *p*-TsOH, envisaged to coordinate to the nitrogen and hence stop it from inhibiting the catalyst,[85,86] were also tried but yet again only starting material was isolated. Sequential oxidation and Wittig olefination of the alcohol **105** was also not successful, with recovery of only the substrate **105**. Due to these futile reactions, and the earlier failures, coupled with Joseph's similar synthetic difficulties on such analogues,[83] it was decided not to pursue this route any further.



Scheme 21: Unsuccessful reactions to form the desired photochemical substrate **66**.

2.3.2. Photochemical Investigations

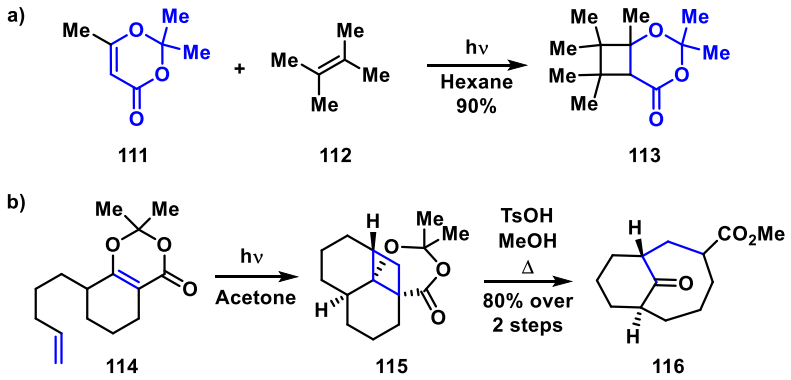
Despite the synthetic difficulties to reach **66**, photochemical studies of terminal alkene **104** were undertaken nonetheless. Irradiation of such did not form any of the desired De Mayo ring-expansion product **109**, nor the tricyclic species **107**, only recovered starting material was isolated. The reaction was repeated with the photosensitiser, isopropylthioxanthone (E_T = 266 kJ mol^{-1})[31], and also within a quartz well, but these too did not lead to any product formation. The free enol ether was then trapped as the acetate **106** (acetylation proceeded in a 24% yield), and the irradiation was repeated but unfortunately the same result was obtained, recovered substrate. Efforts next turned to the intermolecular analogue **88**, to ensure it was not due to intramolecular strain inhibiting the cyclisation. However, irradiation of the acetate protected piperidone **88** with ethyl acrylate **84** also did not undergo the desired [2+2] photocycloaddition.



Scheme 22: Attempted [2+2] photocycloadditions led to only recovered starting material in both intramolecular and intermolecular cases.

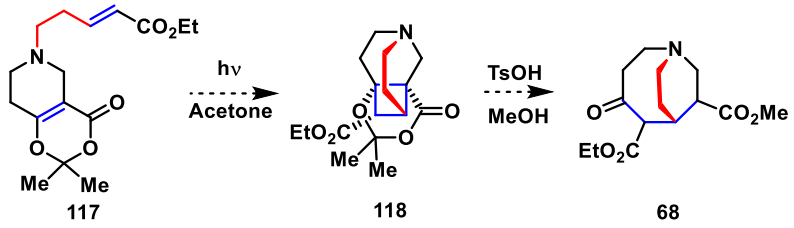
The De Mayo reaction of such *β*-keto esters was clearly ineffective and so led to a literature search of such systems and their apparent lack of reactivity in the [2+2] photocycloaddition. It was found that *β*-keto esters have indeed been shown to be poor coupling partners in the [2+2] photocycloaddition compared to their diketone analogues.[57,87] It is thought the moiety does absorb incident photons, but upon excitation is quickly returned to the ground state by some quenching effect, possibly due to the free rotation of the ester. This was also noted by Lange *et al*. in their synthesis of (±)-norasteriscanolide **56**,[75] see Section 2.1.2., Scheme 13, whereby they used various protected derivatives of the *β*-keto ester **53** to undergo the [2+2] photocycloaddition with cyclopentenone. It has also been reported that irradiation of these *β*-keto esters in the presence of an alkene can lead to the formation of an oxetane in some cases, *via* the [2+2] photocycloaddition with the carbonyl moiety as in the Paternò-Büchi reaction,[88] rather than with the enol of the keto ester.[89]

Baldwin *et al.* have managed to solve this problem by covalently restricting the enol tautomer, in the form of a dioxolenone **111**, which allows the moiety to complete the desired [2+2] photocycloaddition (Scheme 23).[87] Winkler *et al.* have taken this methodology one step further, and applied it to intramolecular systems, and so to synthesise medium-sized rings such **116** (Scheme 23).[90,91] The group have used this in numerous total synthesises, including that of (±)-ingenol and (±)-saudin.[92,93]



Scheme 23: a) Baldwin's use of the dioxolenone group in the intermolecular [2+2] photocycloaddition[87] and b) Winkler's use of such in the intramolecular [2+2] photocycloaddition, leading to the formation of the eight-membered ring **116**.[90]

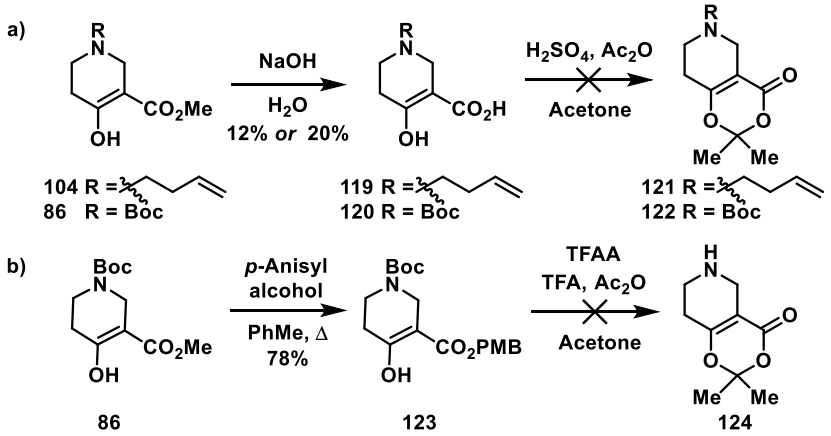
In accordance with this work, efforts moved onto conformationally restricting the *β*-keto ester in the form of a dioxolenone motif, in line with Winkler's work.[92] Irradiation would excite molecule **117** to its triplet state, in the presence of the sensitiser acetone (E_T = 332 kJ mol^{-1})[31], and undergo an intramolecular [2+2] photocycloaddition with the olefin tether to achieve the tricyclic species **118**. Subsequent fragmentation of the dioxolenone group under acid conditions would reveal the key 6, 8-fused bicyclic system **68** within alstoniascholarine A (Scheme 24).



Scheme 24: Proposed route from dioxolenone substrate **117** to the core alstoniascholarine A.

The synthesis of the dioxolenone moiety was initially attempted from two different substrates, the Dieckmann cyclic product **104** and the Boc-protected nitrogen variant **86**, *via* the carboxylic acid intermediate **119** and **120** (Scheme 25).[94] However, issues arose with the formation of which due to both the instability of the carboxylic acid intermediates **119** and **120**, and as such rapid decarboxylation occurred, and in cases where this could be halted, the highly polar nature of the acid. Due to these issues, low yields of the acid intermediates were obtained, 12% for the terminal alkene **119** and 20% for the Boc-protected moiety **120**. Subsequent formation of the dioxolenone was also proven unsuccessful, resulting in cleavage of the carboxylic acid group, returning piperidone for this reaction. Forming the carboxylic acid *in situ* and subjecting it to the dioxolenone conditions, and so avoiding isolation of which, was also tested, but again with little success. Alternatively, synthesis *via* a transesterification reaction was next examined, hence exchanging the methyl ester to afford the more labile *tert*-butyl or *p*-methoxybenzyl ester, which would then be subjected to strong acidic conditions to give the dioxolenone chromophore (Scheme 25). This route appeared to be the more popular synthesis adopted by Winkler himself.[90,92,95] The ester exchange was trialled on three analogues, **104**, **86** and the benzyl-

protected system **93**. A wide range of conditions were attempted, including basic conditions with *n*BuLi, DMAP catalysed conditions in cyclohexane,[96] using NMI as an additive,[97] and with either *tert*-butanol or *p*-anisyl alcohol. Simply refluxing the corresponding alcohol with the ester in PhMe using Dean-Stark apparatus was successful but only for the Boc-protected substrate **86**, which gave product **123** in a 78% yield (Scheme 25), with all other cases returning starting material.[92] It can be concluded from this lack of reactivity that an electron-withdrawing group on the nitrogen atom is required. This can be rationalised as it prevents protonation of the nitrogen as the lone pair is tied in conjugation. For the other systems, **86** and **93**, this is not viable and so protonation of the nitrogen inhibits the reaction. Unfortunately however, precursor **123** was unstable under the acidic dioxolenone formation conditions, and degradation was observed in the subsequent step.

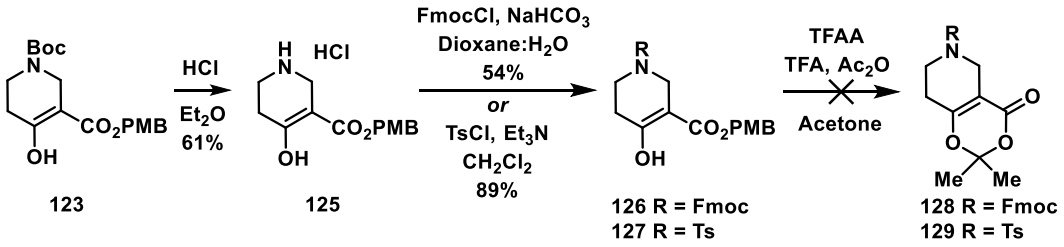


Scheme 25: Unsuccessful routes to the dioxolenones **121**, **122** and **124** a) *via* the carboxylic acid intermediates **119** and **120** and b) *via* the PMB ester **123**.

Hence alternating the Boc protecting group to an orthogonal group, that would be stable under these subsequent conditions was next investigated. Therefore, post-transesterification, Boc cleavage of *p*-methoxybenzyl ester **123** followed by Fmoc protection afforded the desired substrate **126** in 54% yield (Scheme 26). However, the successive dioxolenone formation was not straightforward, ^{1}H-NMR analysis of the crude material showed the geminal dimethyl peaks of the dioxolenone **128** were present and the Fmoc group had remained intact, indicating the reaction had indeed worked but the product could not be purified. Different column conditions and recrystallisation techniques were attempted but with no success, the product **128** could not be obtained cleanly. It was reasoned that this was due to the high aromaticity of the Fmoc group, and perhaps its greasy nature was hindering the purification. Removal of which was then attempted to solve this, but unfortunately this resulted in several degradation products which could not be identified.

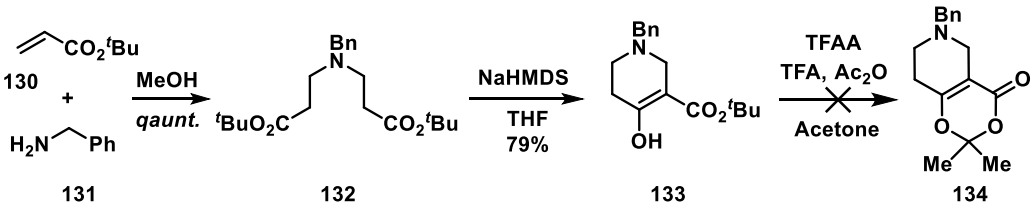
The synthesis was repeated with the tosyl protecting group instead but again, issues arose at forming the dioxolenone **129** (Scheme 26). Similarly, the dimethyl peaks could be seen in the ^{1}H-NMR but again with an accompanying, unidentified impurity, which by mass spectrometry was shown to be of high molecular weight. Although not confirmed, this was speculated to be some form of self-dimerisation of

the *p*-methoxybenzyl cation upon cleavage. It has been reported that using such acid conditions to remove this protecting group, without a cation scavenger, can form unwanted polymeric products.[98,99]



Scheme 26: Attempted synthesis of dioxolenones **128** and **129**.

In a final attempt to synthesise the desired dioxolenone, the Dieckmann cyclisation was completed on the amine substrate **133**, which importantly already had the *tert*-butyl ester installed and hence would avoid its previously troublesome formation (Scheme 27). The condensation proceeded in a good yield of 79% however, the generation of the chromophore **134** yet again proved difficult. Recovered starting material suggested that the nitrogen lone pair was hindering the reaction. As before with the transesterification reaction, the nitrogen atom was probably being protonated under the acidic conditions and thus stopping the desired reaction from proceeding. Similarly, positioning an electron-withdrawing substituent on such would presumably allow the dioxolenone formation to occur. However, due to the large number of issues encountered with this route into alstoniascholarine A, the decision was made to seek alternative syntheses.

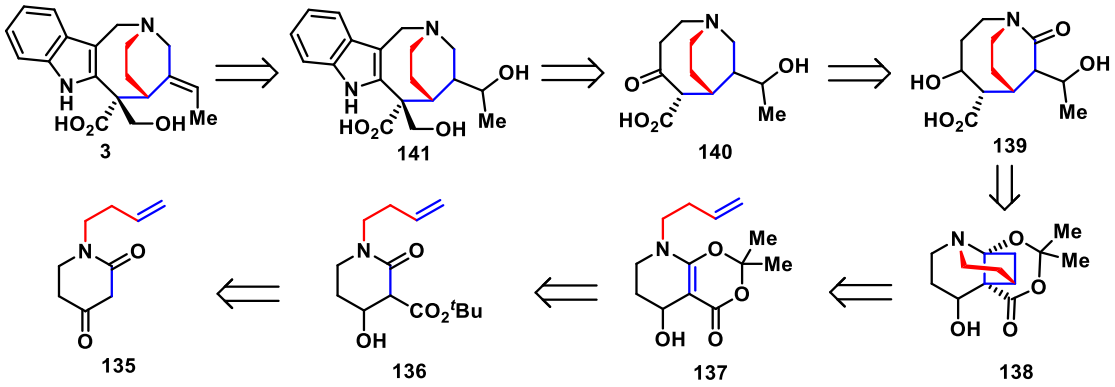


Scheme 27: Michael addition and Dieckmann cyclisation to install the *tert*-butyl *β*-keto ester **133** but was unsuccessful to form the dioxolanone **134**.

2.3.3. Amide Route to Alstoniascholarine A

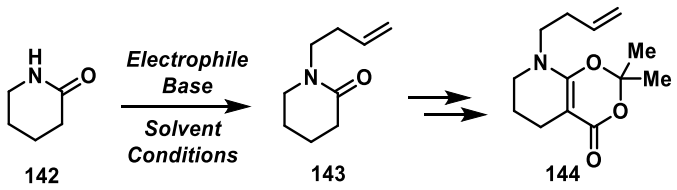
With the knowledge that the reaction to produce the dioxolenone required an electron-withdrawing group *α* to the nitrogen, it was considered that perhaps it did not have to be in the form of a protecting group, and rather incorporated directly within the six-membered ring. Situating a carbonyl group, and so having an amide functionality, would not alter the synthetic route to alstoniascholarine A significantly, and would still allow for the possibility of an intramolecular [2+2] photocycloaddition (Scheme 28). As in the original route, the final step would involve dehydration to yield the natural product from **141**, which would arise from Fischer indole synthesis of **140**. This would be synthesised by reduction of the amide to the amine, and oxidation of the alcohol from **139**. Note that under basic conditions the dioxolenone fragment can be cleaved to give the carboxylic acid functionality.[100] The

photochemical [2+2] cycloaddition of the dioxolenone chromophore would this time however, rely on such a reaction to proceed in a crossed manner. The *β*-keto-ester precursor to this, **136**, was envisaged to come from the commercially available 2,4-piperidinedione **135**.



Scheme 28: New retrosynthetic route to alstoniascholarine A using the amide functionality.

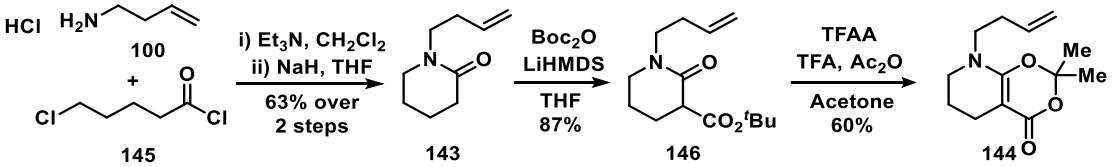
As a synthetically simpler alternative to **137**, substrate **144** which did not contain the 4-hydroxyl, was initially sought to test the photochemical step (Figure 13). Synthesis of which was planned to start with *δ*-valerolactam **142**, which upon alkylation, *β*-keto ester formation and dioxolenone installation would lead to **144**. However, issues arose immediately with the alkylation procedure, which gave a poor yield of 11% using the base NaH and electrophile 4-bromobutene. Studies attempted to improve this (Figure 13), but neither alternate solvents (Entries 2 and 3) nor bases (Entries 4 and 5) led to any improvement. Heating the reaction had a detrimental effect on yield (Entry 6). Other electrophiles were then tested as it was speculated 4-bromobutene was undergoing an elimination reaction to form butadiene, rather than the desired S_N2 reaction. Hence, the corresponding alcohol and iodo-alkenes were tried in the reaction, nonetheless, these too gave poor yields (Entries 7 and 8). The screen was therefore ineffective; with all entries either only recovering starting material or those that did allow the reaction to proceed, were of a lower yield than the preliminary conditions.



Entry	*Base*	*Solvent*	*Conditions*	*Electrophile*	Yield of 143
1	NaH	THF	0 °C → RT	Bromobutene	11%
2	NaH	DMF	0 °C → RT	Bromobutene	10%
3	NaH	THF:DMF[a]	RT	Bromobutene	10%
4	*n*BuLi	THF	RT	Bromobutene	SM
5	KOH	DMSO	RT	Bromobutene	SM
6	NaH	DMF	RT→ 65 °C	Bromobutene	2%
7	NaH	DMF	RT	Bromobutanol	SM
8	NaH	THF	RT	Iodobutene	6%

Figure 13: Conditions tried in the alkylation of δ-valerolactam. [a]Ratio 5:1.

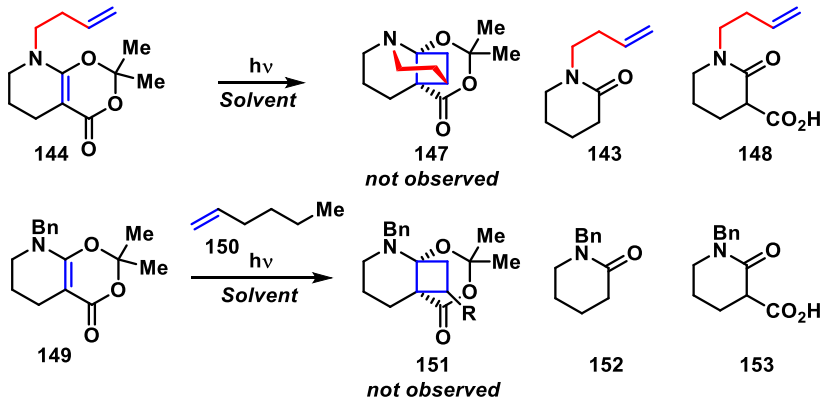
With the alkylation proceeding in poor yields at best, further research into the literature revealed a cyclisation procedure into the lactam **143**, thus avoiding such a problematic step (Scheme 29).[101] The ammonium hydrochloride salt **100** was deprotonated with Et_3N and reacted with the corresponding acyl chloride **145** to give the amide acyclic precursor. This was used without purification in the cyclisation reaction with NaH to afford the desired alkylated lactam **143** in 63% yield over the two steps. Pleasingly, the synthesis of the β-keto ester also proceeded in a good yield of 87% to give the *tert*-butyl ester, which avoided the troublesome transesterification previously encountered. It also avoided the unstable carboxylic acid intermediate. The dioxolenone framework was then installed successfully, affording **144** in a 60% yield. It was also found that anhydrous conditions were key to forming such in a good yield.



Scheme 29: Synthesis of the model system **144**, incorporating the amide functionality within the ring system.

Unfortunately, the subsequent photochemical step of dioxolenone **144** was not successful (Figure 14). Within 15 minutes of irradiation, TLC analysis showed the precursor had started undergoing degradation (Entries 1 and 2). Upon isolation, these degradation products were shown to be the preliminary amide **143** and the corresponding α-carboxylic acid **148**. In an attempt to prevent such decomposition, anhydrous MeCN was trailed as the reaction solvent but similar results were obtained (Entry 3). A UVA lamp was then used, as it emits a longer wavelength of light than the corresponding medium-pressure lamps, but again the same degradation occurred, albeit at a slower rate (Entry 4). The

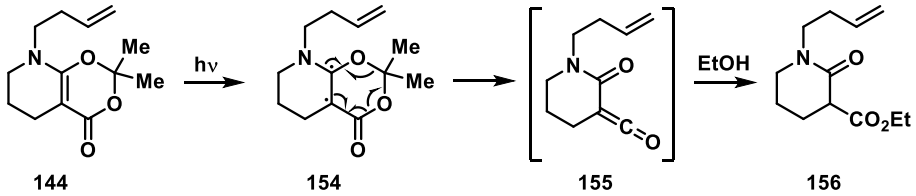
benzyl dioxolenone equivalent **149** was also irradiated with alkene **150**, but this too resulted in similar decomposition products (Entry 5).



Entry	*Lamp*	*Substrate*	*Solvent*	*Reaction Time (hours)*	Product
1	125 W	**144**	MeCN:Acetone[a]	2.5	**143**
2	125 W	**144**	MeCN:Acetone[a]	1.5	**143**, **148**
3	125 W	**144**	MeCN[b]	1	**143**
4	UVA	**144**	MeCN[b]	7	**148**
5	125 W	**149**	MeCN[b]	1.2	**152**, **153**

Figure 14: Unsuccessful photochemistry studies on dioxolenones **144** and **149**. [a]Ratio 9:1, [b]anhydrous MeCN.

Upon a literature search, dioxolenones are also well-known precursors in the synthesis of ketenes.[102,103] Thus, to prove that the above decomposition was going *via* a ketene, **144** was irradiated in anhydrous EtOH and confirming such, the resulting ethyl ester **156** was isolated (Scheme 30).

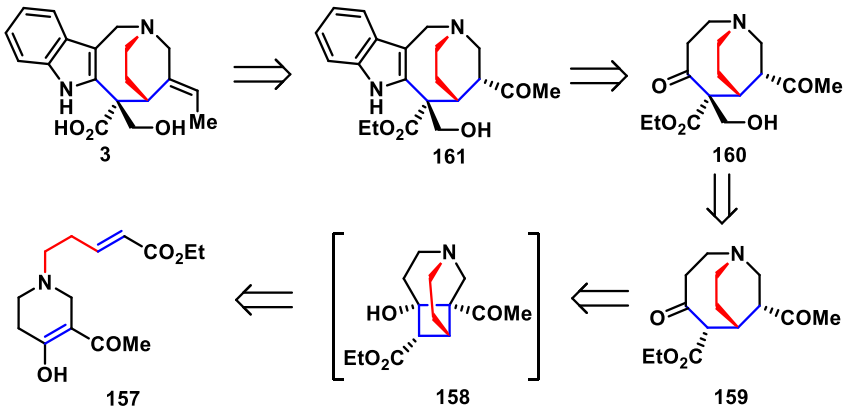


Scheme 30: Undesired photochemical pathway of dioxolenone **144** to form ethyl ester **156** *via* ketene **155**.

With this result in hand, the dioxolenone strategy was hence deemed as an unviable route to lead to alstoniascholarine A.

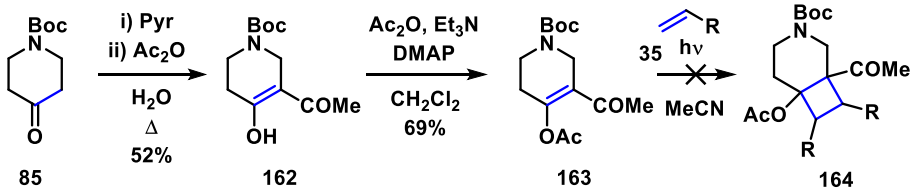
2.3.4. *β*-Diketone Route to Alstoniascholarine A

Upon revisiting the studies completed thus far, it became clear that the issues that arose were due to the *β*-keto ester, both in the synthesis of which and in the proceeding photochemistry. Inspecting the original synthetic route to reach alstoniascholarine A, such needs to be converted into an alkene, and hence does not necessarily have to stem from the ester (Scheme 31). As the original De Mayo reaction uses a 1,3-diketone, for which the photochemistry is known to work,[69,70] one could foresee forming such from a ketone **161** *via* reduction and dehydration (Scheme 31).



Scheme 31: Retrosynthetic route towards alstoniascholarine A **3** using the 1,3-diketone moiety **157**.

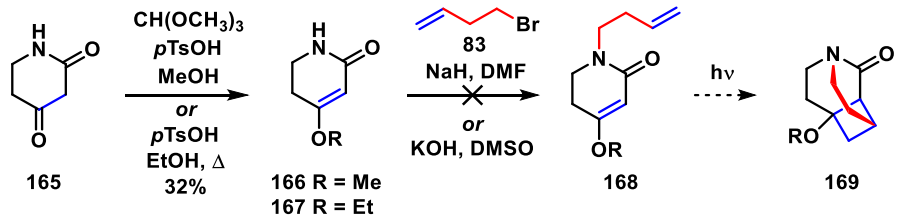
Again, a basic model system **162** was first inspected, whereby an intermolecular [2+2] photocycloaddition would ensue (Scheme 32). The 1,3-diketone **162** was literature known, and synthesised by simply refluxing Boc-piperidone and pyrrolidine using Dean stark apparatus to form the enamine and then refluxing with Ac_2O and H_2O.[100] This was trapped as the acetate enol **163** and irradiated with a number of olefin coupling partners (Scheme 32). Initially this was completed with ethyl acrylate, for which none of the desired [2+2] product was observed, only starting material and the free enol **162**, whereby the acetate had been cleaved, were isolated. As this would require two electron-deficient alkenes to cyclise, cyclopentene was next employed as the coupling partner but yet again, the same result was obtained. The lack of reactivity in this case was reasoned to be due to the difficulty in getting the molecular orbitals of two conformationally locked cyclic alkenes to overlap. Thus, the final alkene irradiated with **163** was an acyclic, electronically neutral species, allyl alcohol. Unfortunately, this neither led to the desired cyclobutane product **164**, again resulting in both recovered starting material **163** and deacetylated material **161**. As the acetate group was proven unsuitable in this photochemical reaction, installation of the silyl ethers TBS and TBDPS were tried instead. However, the protection of **162** with such would only lead only to a 1:1 mixture of starting material and protected product, and the two could not be separated.



Scheme 32: Simplified substrates **162** and **163** for photochemical studies, which proved unsuccessful.

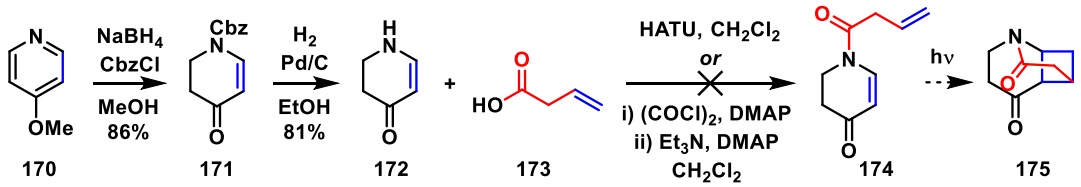
Due to such ineffective attempts, another model system was sought. The literature highlighted that *β*-diketone **165** could be protected as either the methyl or ethyl ether, trapping the enone **166** or **167** (Scheme 33),[104,105] a well-known chromophore.[59] Unfortunately, due to purification issues, the methyl

enone **166** could not be isolated. The ethyl analogue **167** could, but in a rather poor yield of 32%. The subsequent alkylation step however would not proceed, with neither base NaH nor KOH.



Scheme 33: Unsuccessful enone route to alkylated photochemical precursor **168**.[105]

Keeping in line with the enone photochemical precursor, Bach *et. al.* reported an analogous system to **174**, whereby the carbon chain on the nitrogen atom was one unit less (Scheme 34).[106] Inspired by their work, synthesis of **174** began with 4-methoxypyridine **170**, which was partially reduced and protected as the *N*-Cbz **171** in 86% yield. Cleavage of such under hydrogenation conditions afforded **172** in a good yield of 81%. Amide formation with the *in situ* generated acyl chloride however did not give the desired product **174**, instead afforded the isomerised alkene, in conjugation with the carbonyl. Under amide coupling conditions with HATU, the same undesired isomerisation occurred.

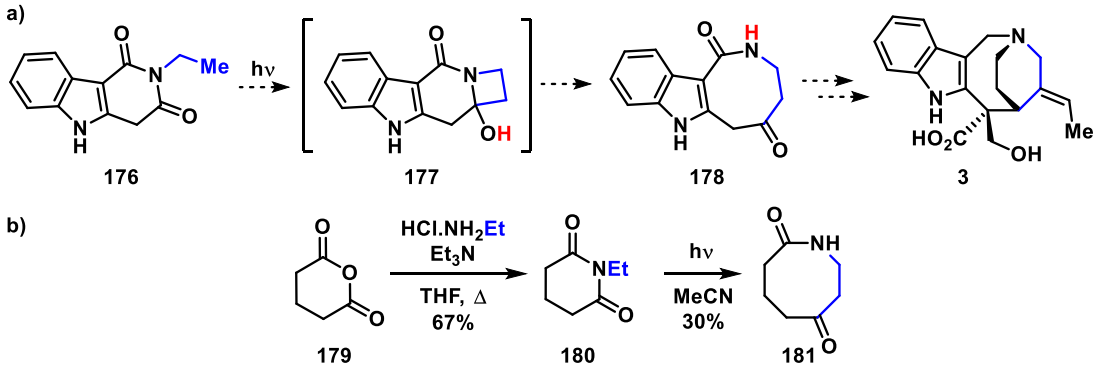


Scheme 34: Synthetic attempts to access enone **174**.[106]

With numerous futile attempts at accessing both photochemical precursors, be it dioxolenones or alkylated diketones, and [2+2] photochemical cycloadditions, it was clear a completely new synthetic route to alstoniascholarine A was required.

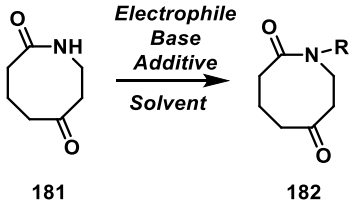
2.3.5. The Norrish-Yang Cyclisation Route to Alstoniascholarine A

With the previous work failing to address the key photochemical step within the alstoniascholarine A synthesis, it was hoped the Norrish-Yang cyclisation would enable generation of the medium-sized heterocycle **178** (Scheme 35). Ideally this reaction would proceed with the indole moiety already installed and both bridge formation and functionalisation at the two remaining sites would be completed post-cyclisation. Preliminary studies succeeded in forming the eight-membered ring **181** on a simplified system, from glutarimide **180** (Scheme 35).



Scheme 35: a) Proposed synthesis of alstoniascholarine A incorporating the Norrish-Yang cyclisation and b) a model system shown to undergo the Norrish-Yang cyclisation to form the eight-membered ring **181**.

The medium-sized heterocycle **181** was then subjected to a range of conditions to incorporate the bridge functionality within the molecule, initially alkylating the nitrogen atom, with the intention of Grignard formation followed by deoxygenation. However, a range of conditions were tried for the alkylation reaction, differing bases, solvents and electrophiles, and yet recovered starting material was only obtained (Entries 1-7, Figure 15), even when using methyl iodide as the alkylating agent (Entry 8).

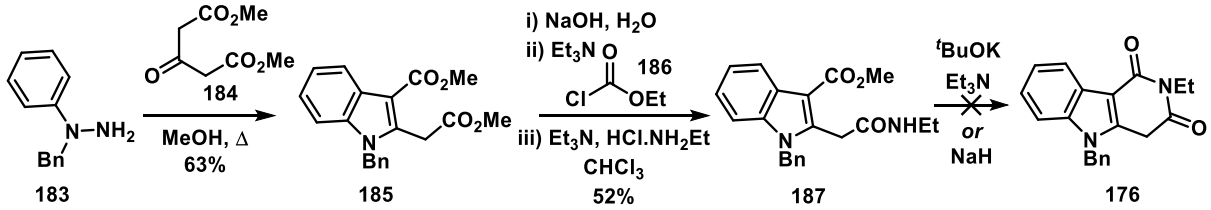


Entry	*Electrophile*	*Base*	*Additive*	*Solvent*	Result
1	1-Bromo-2-chloroethane	KOH	-	DMSO	SM
2	1,2-Dibromoethane	NaH	-	DMF	SM
3	1,2-Dibromoethane	K_2CO_3	-	Acetone	SM
4	2-Bromoethyl methanesulfonate	NaH	-	DMF	SM
5	1,2-Dibromoethane	Cs_2CO_3	TBAI	Butanone	SM
6	1,2-Dibromoethane	K_2CO_3	TBAI	Acetone	SM
7	1,2-Diiodoethane	NaH	-	DMF	SM
8	Methyl iodide	NaH	-	DMF	SM

Figure 15: Conditions tried in the alkylation of amide **181**.

A Mitsunobu reaction with **181** was also tested using either 2-bromoethanol or allyl alcohol, yet neither reactions yielded any product formation. A Wittig reaction on the ketone was then attempted but it too led to no reaction.

Simultaneously, work on synthesising the indole substrate **176** for photochemical studies was also undertaken (Scheme 36). Fischer indole synthesis of hydrazine **183** with dimethyl ester **184** afforded the indole **185** in good yield of 63%.[107] Notably, with the ethyl analogue of 1**84**, the reaction would not proceed. Cyclisation attempts of **185** initially began by simply heating with ethyl amine and Et_3N in THF. This did not lead to any of the desired cyclised product **176**, only recovered starting material. Refluxing in xylene also yielded started material. Completing such a cyclisation stepwise was then trialled, and the carboxylic acid derivative of **185** was formed, followed by *in situ* acyl chloride formation then amide synthesis with ethyl amine to afford **187**. Various bases were then tried in the intramolecular cyclisation but **176** could not be generated.



Scheme 36: Unsuccessful synthesis of indole photochemical precursor **176.**

Unfortunately, due to the numerous difficulties and synthetic challenges that lead to little progress towards the synthesis of alstoniascholarine A, the decision was made to focus on other heterocyclic methodology, which also incorporated a key photochemical synthetic step.

2.4. Conclusions

To conclude, the key [2+2] photochemical cycloaddition within the synthetic route to alstoniascholarine A proved challenging. The initial studies focused on irradiating the *β*-keto esters **104** and **106**, which unfortunately were shown to be poor coupling partners within the photochemical cyclisation (Figure 16). Thus, efforts turned to the synthesis of their dioxolenone containing derivatives, to enhance their photochemical reactivity. Several routes and analogues of such were investigated until eventually the dioxolenone containing moieties **144** and **149** were successfully synthesised (Figure 16). However, these did not undergo the desired [2+2] photocycloaddition to form the four-membered ring, they decomposed upon irradiation *via* a ketene formed *in situ*. This route was hence proven unviable in the formation of the medium-sized ring within alstoniascholarine A.

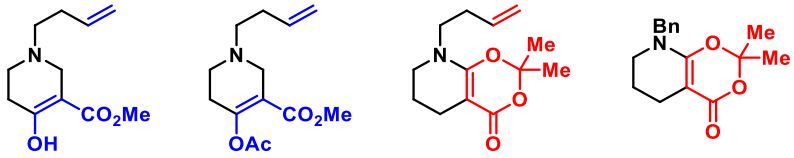
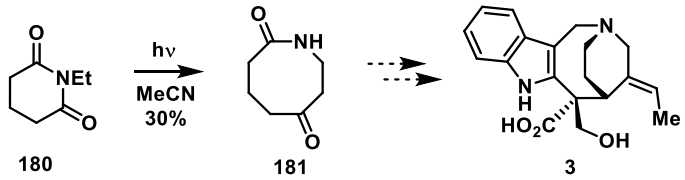


Figure 16: Precursors that were unsuccessful in the [2+2] photochemical cycloaddition.

1,3-Diketones and enones were also investigated as potential reactants within the De Mayo process. However, further synthetic and photochemical difficulties resulted in these routes also being disregarded. Finally, the Norrish-Yang cyclisation was briefly examined, and although this route did enable the formation of an eight-membered ring **181**, it did not include the bridged component of the natural product (Scheme 37). It was anticipated several further steps, manipulations and modifications would be required to complete the synthesis, and ultimately losing the elegant one-step synthesis of the nitrogen containing medium-sized ring and two-carbon bridge, deemed such as unworthy. Hence alstoniascholarine A **3** remains a novel synthetic target.



Scheme 37: The Norrish-Yang reaction was successful in affording the medium-sized ring **181**.

3. The Pd-Catalysed Rearrangement to Synthesise 2-Azabicyclo[3.3.1]nonane Scaffolds

3.1. Introduction

3.1.1. Aziridines

Aziridines are the smallest nitrogen-containing heterocycle. These three-membered saturated rings are often employed as versatile intermediates in synthesis,[108,109] as well as important synthetic targets in their own right.[110,111] Similarly to their carbon and oxygen counterparts, cyclopropanes and epoxides, due to their structure aziridines experience a high level of Baeyer strain, enabling facile ring-opening. Thus, this ability to undergo highly regio- and stereoselective ring-opening reactions renders them useful building blocks.[108] As synthetic targets, they are powerful alkylating agents and perhaps the most well-known, naturally occurring example is the mitomycin family (Figure 17). Such compounds possess anti-tumour and antibiotic activity, attributed to the aziridine ring.[112]

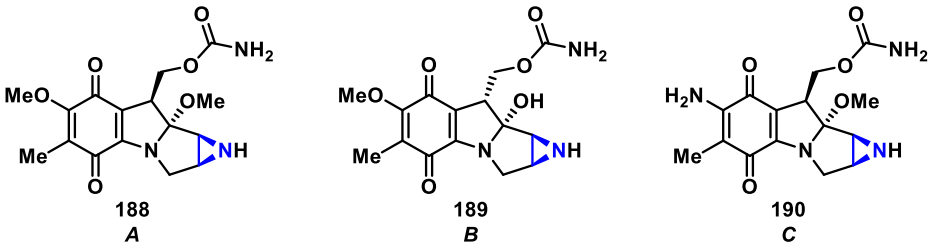
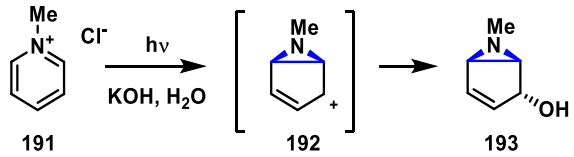


Figure 17: Structure of the natural products mitomycins A, B and C which contain an aziridine ring within their core.

Synthetic methodologies for the preparation of aziridines includes the nitrene addition to olefins, carbene and ylid addition to imines and cyclization of 1,2-amino alcohols, 1,2-aminohalides and 1,2-azido alcohols.[113,114] Photochemical approaches to the formation of aziridines are perhaps not as widespread, but will be a focus of this thesis.

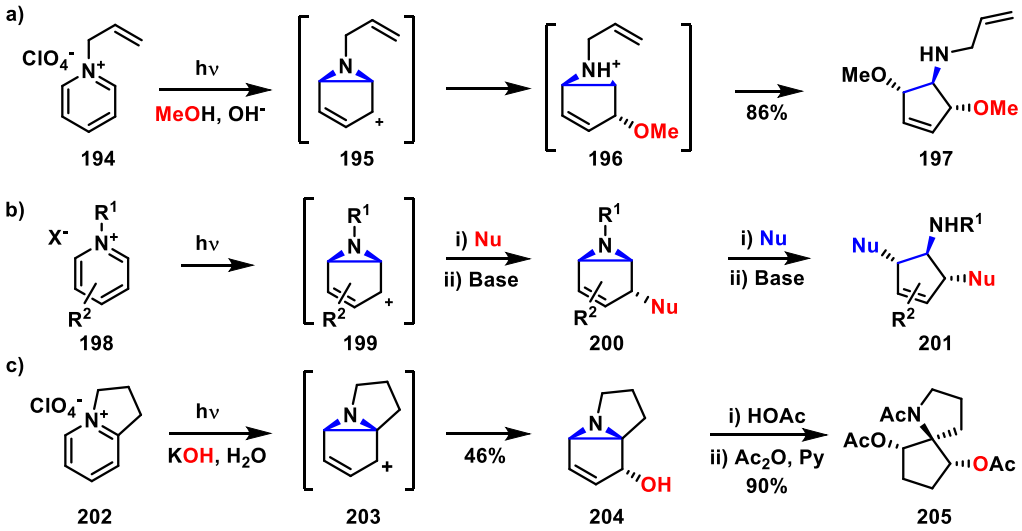
3.1.2. Photochemical Aziridine Formation

The first photochemical synthesis to form azacyclopropanes, or aziridines, was carried out in the early 1970s by Kaplan and co-workers (Scheme 38).[115] Irradiation of the simple *N*-methylpyridinium chloride salt **191** in aqueous KOH afforded the rather complex, bicyclic aziridine **193** stereoselectively. The mechanism was proposed to involve an excited state electrocyclisation *via* the azabicyclohexenyl cation **192**, which upon hydroxide addition from the *exo* face afforded the product **193**. Unfortunately, no yield was reported for the formation of the vinyl aziridine **193**. It was however, a further 30 years before the utility of this reaction was truly realised.



Scheme 38: Early photochemical studies on pyridinium salt **191** to form aziridine **193** by Kapan *et al.*[115]

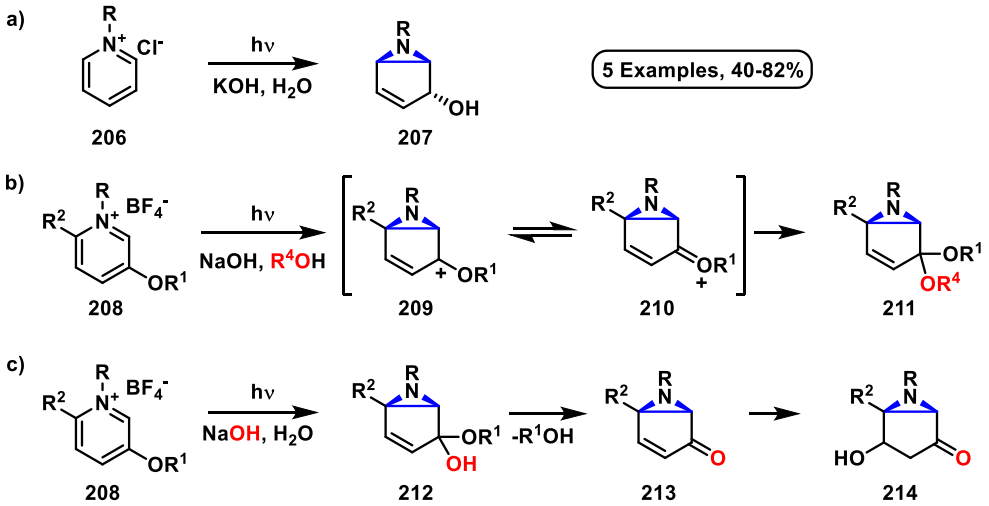
Ten years after this discovery, Mariano *et al.* briefly revisited the photochemistry.[116,117] They irradiated a pyridinium salt with an allyl tether **194** in MeOH, which followed by neutralisation gave the amino-cyclopentene **197** in a high yield of 86% (Scheme 39). Analogously to Kaplan, this was shown to go *via* the same mechanism, *i.e.* an allyl cationic bicyclic aziridine which then underwent ring cleavage. However, it was not until the mid-1990s when the group really exploited this reaction.[118] Expanding upon the pyridinium salts used, utilising other nucleophilic solvents to capture the cationic intermediate species, and reacting such with other nucleophiles in a highly regio- and stereocontrolled manner.[118] Mariano showcased the diversity of the methodology, and as such sparked a huge interest in the area.[119,120] They further elaborated upon this in 2005, irradiating the fused cyclopentapyridinium salt **202** which resulted in the tricyclic aziridine **201**.[121] Acetic acid ring-opening and peracetylation resulted in the spirocyclic diester **205**, an impressive two-step procedure from the simplified pyridinium salt **202**.



Scheme 39: Mariano's developments on the photochemical formation of aziridines. a) Initial photosolvation of *N*-allyl pyridinium perchlorates **194** in MeOH,[116,117] b) *N*-substituted pyridinium salts **198**[118] and c) bicyclic pyridinium salts **202** to gain access to tricyclic aziridines **205**.[121]

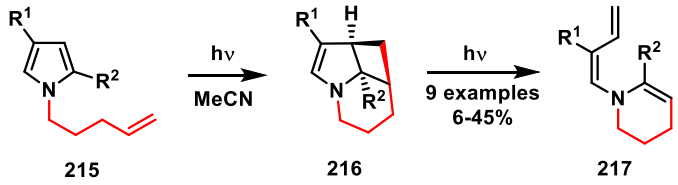
In 1998 Burger *et al.* similarly expanded upon the series of pyridinium salts **206** that undergo the transformation and also functionalised the bicyclic aziridine products, further highlighting their synthetic worth (Scheme 40).[122] The group then carried out extensive mechanistic studies, both theoretically and experimentally, on the photohydration.[123] Optimised geometries of the transition state structures were obtained *via* density functional theory, DFT, calculations which then led to in-depth

mechanistic studies, including deuterium labelling experiments and the effect of the substitution on the aromatic ring. The final notable example was done so by Penkett and co-workers, whereby the effect of an electron-donating substituent on the pyridinium ring was studied.[119,124] Using tetrafluoroborate salts **208** they formed the cyclopentenone ketal products **211** by diastereoselective incorporation of the alcoholic solvent and the cyclopentanone products **214** when in H_2O (Scheme 40).[124]



Scheme 40: a) Substrate scope carried out by Burger *et al.* in the photochemical transformation of pyridinium salts **206**[122] and b) Penkett's used of substituted pyridinium rings **208** in alcohols and c) in water.[119,124]

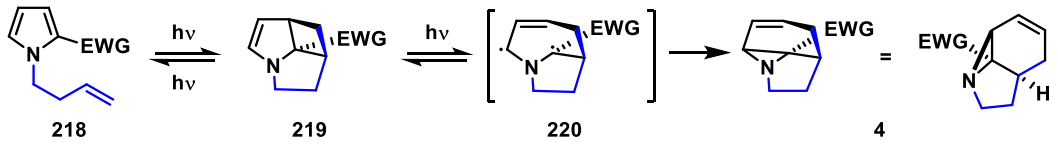
In 2007 the Booker-Milburn group published the intramolecular photometathesis of *N*-pentenylpyrroles (Scheme 41).[125] Upon UV irradiation, simple pyrroles such as **215** underwent a [2+2] photocycloaddition of the alkene tether to the C2-C3 aromatic bond, followed by *retro* [2+2] cycloaddition to give the triene **217**.



Scheme 41: The intramolecular photometathesis of simple pyrroles **217**.[125]

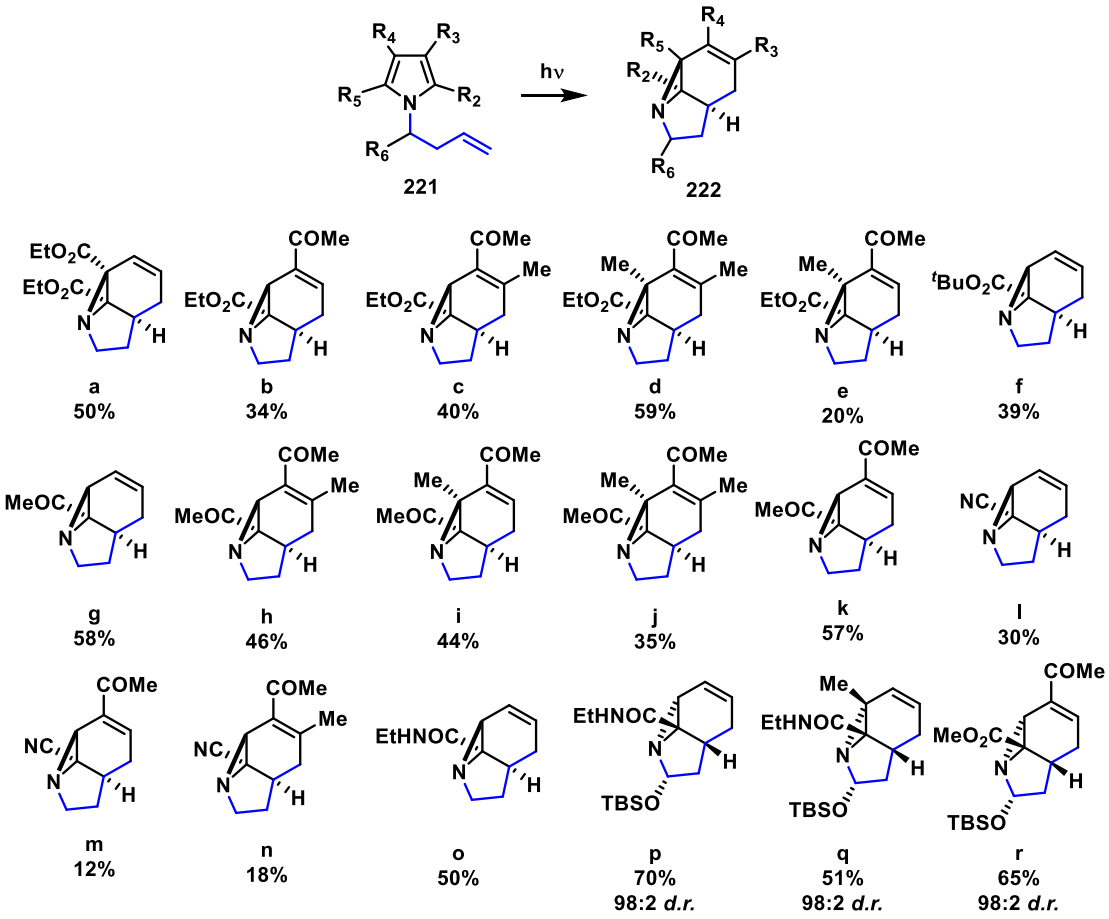
With the aim of further expanding the scope of this photometathesis reaction, *N*-butenylpyrroles were synthesised and subjected to irradiation. Surprisingly however, when shortening the length of the alkene tether by one carbon unit, none of the triene product **217** was observed, the major product isolated was the perhaps the more interesting, tricyclic, fused aziridine **4** (Scheme 42).[126] The first step of this unusual reaction proceeds as so in the original photometathesis reaction, with a [2+2] photocycloaddition to form the cyclobutene **219**. Further excitation then leads to the diradical **220**, which is likely to be a common intermediate in the two processes. In this case however, radical combination between C2 and C5 occurs, resulting in the aziridine ring **4**. This remarkable cycloaddition-rearrangement sequence

again highlights the synthetic power of photochemistry, generating four contiguous stereogenic centres and three fused rings, from a simple precursor in a single step.



Scheme 42: Mechanism of the photochemical sequence to form tricyclic aziridines **4**.[126]

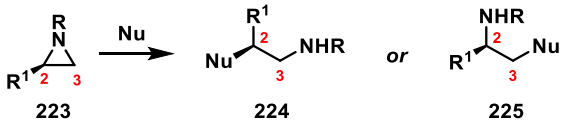
The reaction requires an electron-withdrawing group at the C2 position of the pyrrole, assumed to reduce the HOMO-LUMO gap to the required energy to facilitate the [2+2] photocycloaddition. Such electron-withdrawing groups tolerated by the reaction were esters **a**-**f**, ketones **g**-**k**, nitriles **l**-**n** and ethyl amides **o**-**q** (Scheme 43). The pyrrole starting material can be substituted, with the reaction proceeding with mono- to tetra-substituted pyrroles, as can the butenyl tether.[127] A diastereoselective variant of the photorearrangement can also proceed, by addition of an OTBS or alkyl group *α* to the nitrogen, allowing access to enantiopure material, **p**-**r**.[127] In addition, the chemistry could be completed in flow allowing for multi-gram quantities of the aziridines to be generated.[126]



Scheme 43: Examples of tricyclic aziridine products **222** generated upon irradiating simple pyrroles **221**.[126,127]

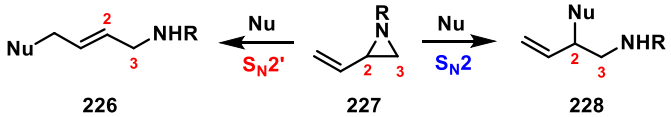
3.1.3. Ring-Opening Reactions of Vinyl Aziridines

Due to their geometric constraints, aziridines have a similar Baeyer strain of 111 kJ mol^{-1} to epoxides.[128] However, as nitrogen is less electronegative than oxygen, unlike epoxides, aziridines undergo ring-opening reactions less readily and generally require some activation to do so.[128] Such activated aziridines have an electron-withdrawing substituent on the nitrogen, which can stabilise the resulting anion, such as *N*-carbonyl, *N*-sulfonyl, and *N*-phosponyl groups.[128] In contrast, non-activated aziridines have neutral or electron-donating groups attached and generally require Lewis or Brønsted acid catalysis to initially form an aziridinium ion which can then fragment.[129] This concept was discussed briefly in the previous section, when detailing Mariano's derivatisation of aziridines (Section 3.1.2., Scheme 39). Although nucleophilic ring-opening has the potential to occur *via* a S_N1 or an S_N2 mechanism, it is generally the latter pathway that proceeds. As anticipated, the regioselectivity of nucleophilic attack normally favours that of the least hindered carbon.[128,130] However electronic and steric effects, such as the nature of the aziridine, the nucleophilic species and the substituents present, may perturb this preference.[130,131,132]



Scheme 44: Regioselectivity in the S_N2 ring-opening of aziridines, attack of least hindered C3 is usually favoured affording **225**, unless for example R^1 = aryl, then attack of C2 is preferential, affording **224**.[128]

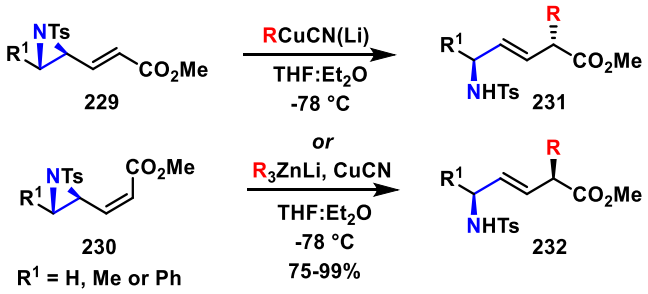
Vinyl aziridines possess a further manifold of activity, allowing for more versatile transformations and as such, introduce the possibility of S_N2' nucleophilic ring-opening reactions, in addition to the S_N2 pathway (Scheme 45).[133] Selectivity is dependent on the nucleophile employed, and generally soft nucleophiles, those with pK_a < 25, for instance organocuprates, preferentially follow the S_N2' pathway.[134] Hard nucleophiles, those with pK_a > 25, such as organolithiums proceed by the S_N2 mechanism.[135] Examples of S_N2 ring-opening of vinyl aziridines generally occur at the most substituted carbon atom, which has been rationalised due to resonance stabilisation of the developing carbenium ion.[130]



Scheme 45: Vinyl aziridines can undergo both S_N2 and S_N2' ring-opening.

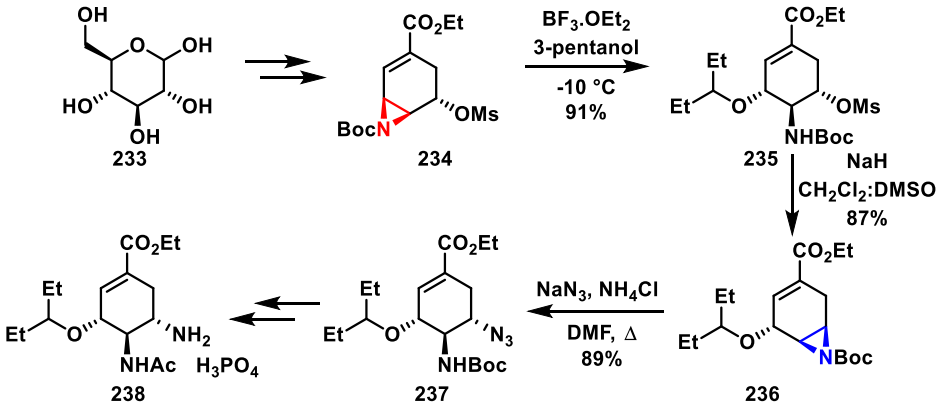
An early report of stereospecific S_N2' organocopper mediated ring-opening comes from Ibuka and co-workers, where aziridines bearing an *α*, *β*-unsaturated ester were transformed to *E*-alkene dipeptide isosteres (Scheme 46).[136,137] Despite the four possible positions of attack, (an additional mode of 1,4-addition in these substrates) lower order alkylcyanocuprates were shown to afford the alkene products

in a highly controlled regio- and stereoselective manner, generating the products **231** and **232** in excellent yields.



Scheme 46: S_N2' ring-opening of vinyl aziridines **229** and **230** with organocuprates.[136,137]

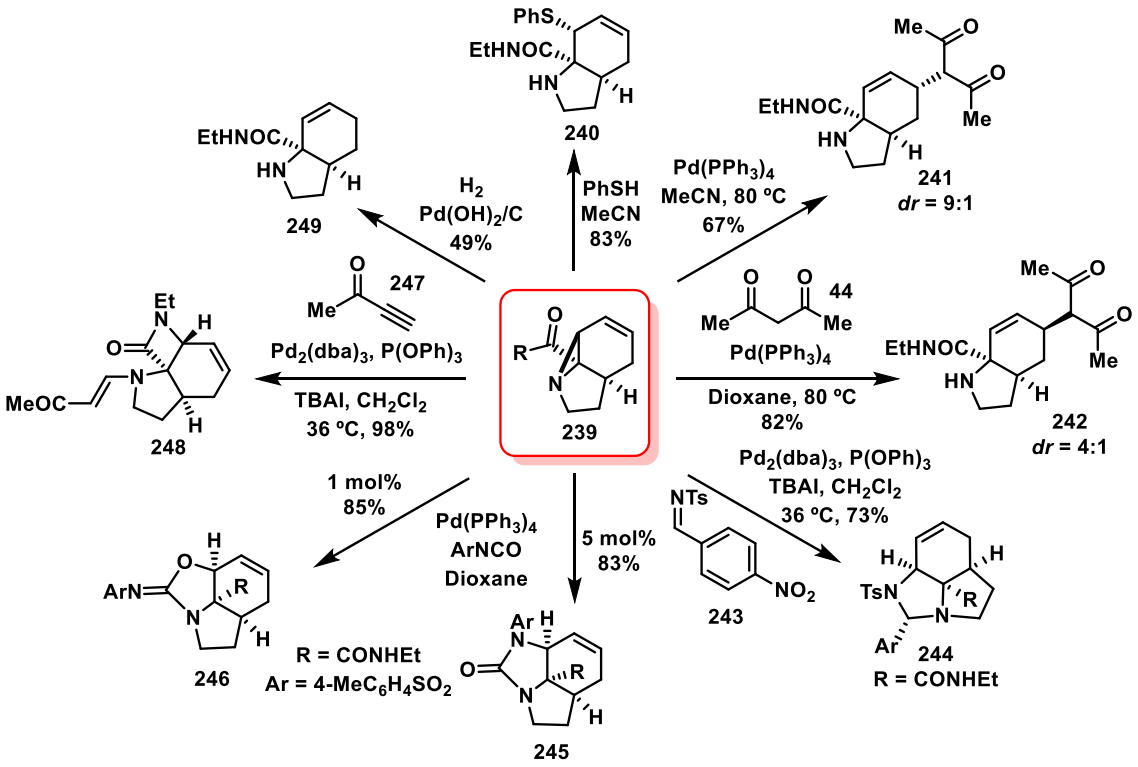
A straightforward example of S_N2 ring-opening of vinyl aziridines can be found in the synthetic route to oseltamivir phosphate, an anti-influenza drug (Scheme 47).[138] This simple, yet effective route utilises both oxygen and nitrogen nucleophiles to regio- and stereospecifically open two aziridines **234**, initially with the Lewis acid $BF_3{\cdot}OEt_2$ and 3-pentanol then after reformation of the aziridine **236**, with sodium azide. Three further steps afforded the bioactive molecule **238** in an overall yield of 7%.



Scheme 47: Double S_N2 ring-opening of *N*-Boc aziridines **234** and **236** in the synthesis of oseltamivir phosphate **238**.[138]

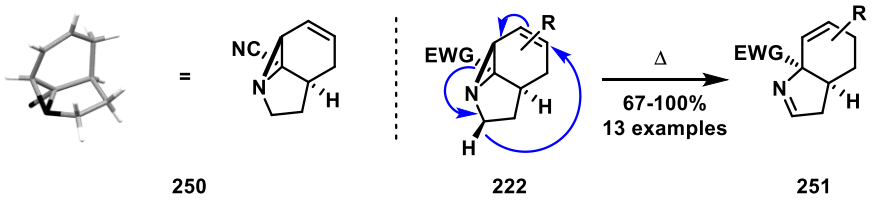
As described in Section 3.1.2., the Booker-Milburn group have photochemically synthesised numerous substituted tricyclic aziridines and they have subjected these reactive products to a range of ring-opening and cycloaddition reactions (Scheme 48).[139,140] Although the aziridines formed are not activated, they have been shown to undergo such processes readily under mild conditions. This has been attributed to the aziridines being under additional strain caused by their tricyclic system.[139] As such, the aziridines exemplified facile S_N2 ring-opening, with thiophenol to give **240**, without any additional additives (Scheme 48). Again, highlighting the tricyclic aziridines inherent reactivity, the Pd-catalysed Tsuji-Trost reaction proceeded on these vinyl aziridines, with facial selectivity depending on the solvent used to give either amine **241** or **242** (Scheme 48, this switch is likely caused by a change in mechanism, from an outer sphere mechanism favouring the *anti*-isomer, to the inner sphere favouring the *syn*-isomer. This will be covered in more depth in Section 4.1.1.). Pd-catalysed [3+2] cycloadditions with

imines and isocyanates provided access to tricyclic fused pyrrolidines such as **244** and cyclic ureas **245** (Scheme 48, similarly this will be revisited in Section 4.1.3.). Interestingly, when lowering the catalyst loading to 1 mol%, cyclic imidate **246** was observed instead of the urea product **245**. Generally, previous Pd-catalysed [3+2] reactions within the literature required activated aziridines,[141] emphasising the additional strain these heterocycles withstand. The formation of *β*-lactams was also possible *via* a novel Pd-catalysed addition/cyclisation sequence with alkynes giving products such as **248** (Scheme 48). Finally, selective reductive ring-opening to generate the secondary amine **249** can also be achieved.



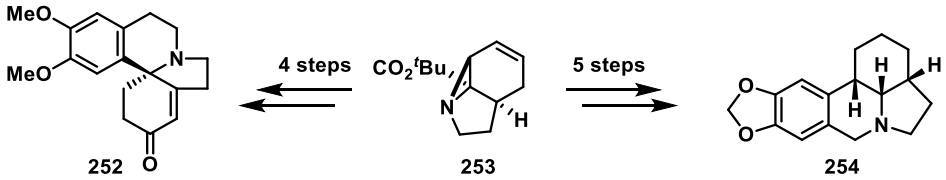
Scheme 48: Highlights of derivatisation of tricyclic, vinyl aziridines **239** completed by the Booker-Milburn group.[139]

During these studies a notable side-reaction often proceeded and this was identified as a thermal homodienyl-[1,5]-hydrogen shift to form the imine **251** (Scheme 49).[142] Its occurrence was thought to be due to the bowl-like confirmation of the starting aziridine, where the migrating *endo*-hydrogen is orientated in close proximity (3 Å) above the *π*-system of the alkene, enabling the hydrogen to readily shift and release the strain associated with the three-membered ring. This rearrangement was proven general in terms of scope, and as will be shown in Section 3.3., represents a synthetically useful process in its own right.



Scheme 49: Crystal structure of starting nitrile aziridine **250** and the thermal homodienyl-[1,5]-hydrogen shift to form imine **251**.[140]

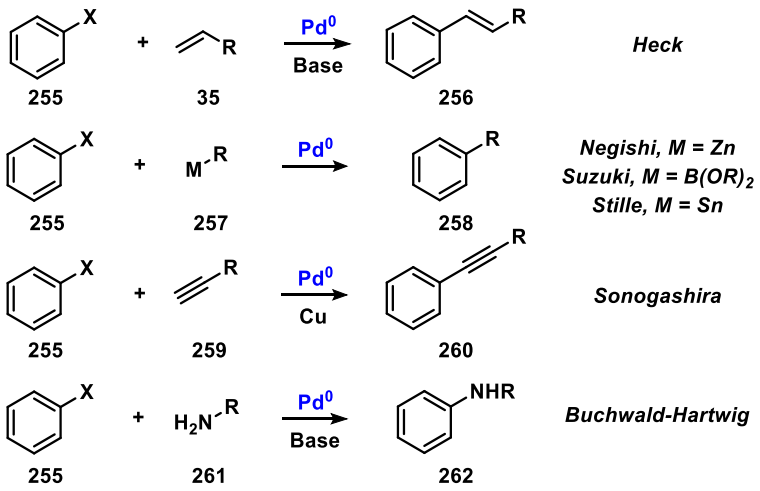
The Booker-Milburn group has also showcased this photochemical methodology within natural product synthesis, to form the erythrina alkaloid (±)-3-demethoxyerythratidinone **252**, in 15% overall yield from the starting pyrrole, and the amaryllidaceae alkaloid (±)-γ-lycorane **254**, in 13% overall yield (Scheme 50).[143,144]



Scheme 50: Tricyclic aziridine **253** used in the total synthesis of (±)-3-demethoxyerythratidinone **252** and (±)-γ-lycorane **254**.

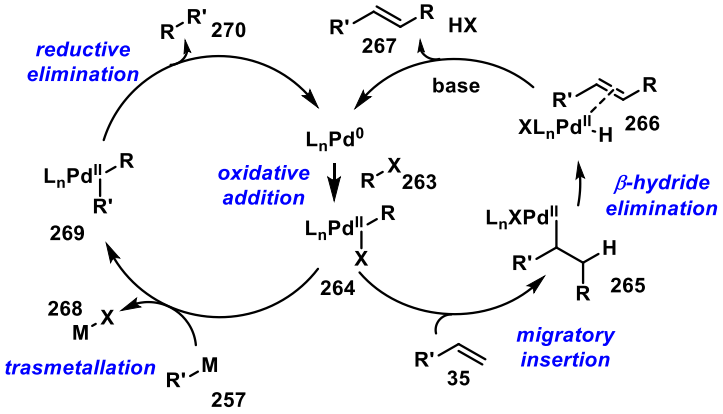
3.1.4. Pd^0-Catalysed Cross-Coupling Reactions

Cross-coupling reactions have revolutionised synthetic organic chemistry, drastically changing the way chemists conceptualise and construct molecules. This monumental work, that was initiated in the 1970s, has enabled previously impossible carbon-carbon bond formations achievable at a synthetically useful rate. The importance of such was highlighted in 2010 when Heck, Negishi and Suzuki were awarded the Nobel Prize.[145,146] Cross-coupling reactions rank amongst the most versatile and useful reactions, and as such are used as an indispensable tool across the industrial and academic community alike. This widespread usage within the pharmaceutical industry was noted in Section 1.1., despite these processes often being limited to sp^2-sp^2 coupling.[13,15] Although several transition metals are capable of catalysing these transformations, it is palladium that dominates the field. Notable Pd^0 cross-coupling reactions are the Heck,[147] Negishi,[148] Suzuki,[149] Stille,[150] Sonogashira[151] and Buchwald-Hartwig cross-couplings (Scheme 51).[152]



Scheme 51: Some of the most used Pd^0 cross-coupling reactions. Noteworthy that the reactions are not limited to aryl halide substrates.

Although these reaction mechanisms differ slightly, they all conform to a general catalytic cycle (Scheme 52).[153] Often Pd^{II} is used as a pre-catalyst, due to its higher stability, and this is reduced *in situ* to form the active catalyst, Pd^0, which undergoes oxidative addition to the halide or *pseudo* halide to form **264**. At this point the cycles diverge; in the Heck reaction, coordination of the alkene followed by *syn* migratory insertion results in organopalladium species **265**, which then undergoes *syn* β-hydride elimination to form the product **267**, and base assisted elimination regenerates the catalyst. In the Negishi, Suzuki, Stille, and Sonogashira cross-coupling transformations, transmetallation occurs instead generating the Pd^{II} species **269** followed by reductive elimination to afford the product **270** and the active catalyst.

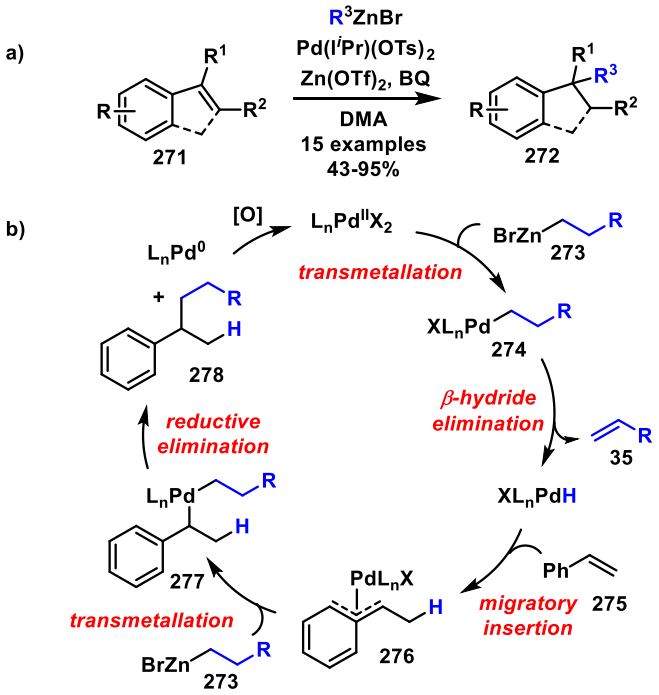


Scheme 52: General mechanism for Pd^0 cross-coupling reactions, the Heck reaction following the catalytic cycle on the right and the Negishi, Suzuki, Stille and Sonogashira the cycle on the left..[153]

This vital work has led to the development of numerous expansions of cross-coupling reactions, including carbon-heteroatom coupling,[152,154] α-arylation,[155] C-H activation[156] and decarboxylative coupling.[157]

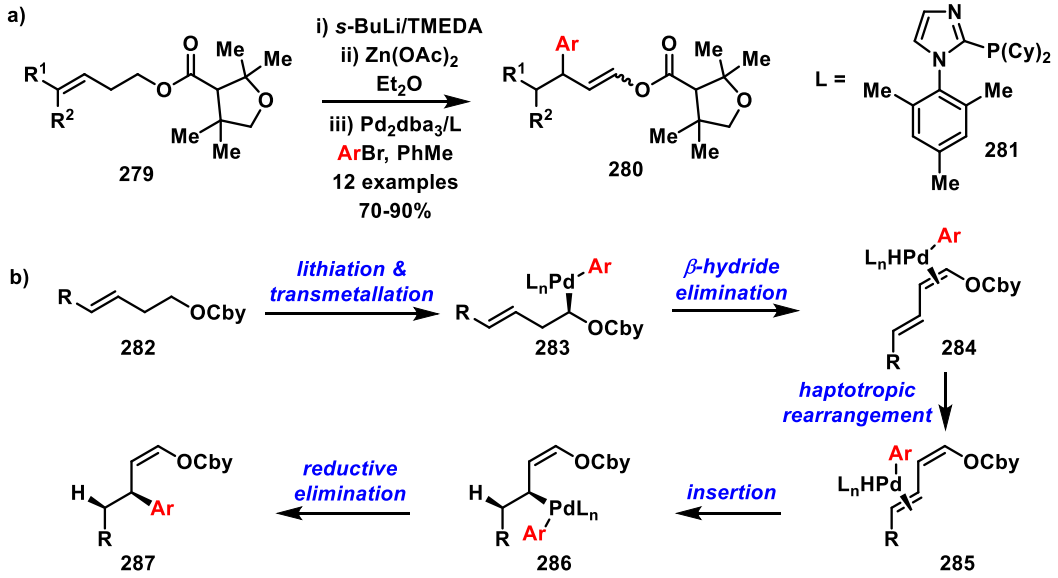
3.1.5. Utilising the *β*-Hydride Elimination Reaction

The *β*-hydride elimination reaction is a pivotal organometallic step which occurs due to the kinetic instability of numerous organo-transition metal complexes. Such is a key step within the Heck cross-coupling reaction, quenching the carbon-palladium bond to terminate the reaction and form the product (Scheme 52). The reaction can however become the origin of off-cycle processes and hence the formation of side-products, and thus controlling it is often a means of improving both the yield and selectivity of a reaction.[158] Three general approaches to inhibit the elimination are 1) rapid oxidation of the intermediate, enabling either substitution or reductive elimination of the Pd-complex[159] 2) ligand control[160,132] and/or 3) substrate control through the use of stabilising interactions, such as *π*-allyl intermediates.[161] Yet, in some cases, it can be a useful reaction to exploit, and Sigman and co-workers have used palladium's tendency to undergo facile *β*-hydride elimination to uncover new transformations.[162] For instance, the Pd-catalysed hydroalkylation of styrenes **271**, in the presence of an organozinc **273** and oxidant, enables formation of an sp^3-sp^3 carbon-carbon bond.[163] The reaction was shown to be highly tolerant of the styrene functionality, and able to form quaternary carbon centres. It was postulated that the mechanism initially undergoes transmetallation to form the Pd-alkyl intermediate **274**. This is prone to *β*-hydride elimination and indeed does such, which is then intercepted by styrene **275** to give a *π*-benzyl stabilised Pd-alkyl intermediate **276**. Finally, this undergoes transmetallation and reductive elimination to afford the hydroalkylation product **278**. This cross-coupling alternative methodology was also expanded to allyl amines[164] and protected alcohols.[165]



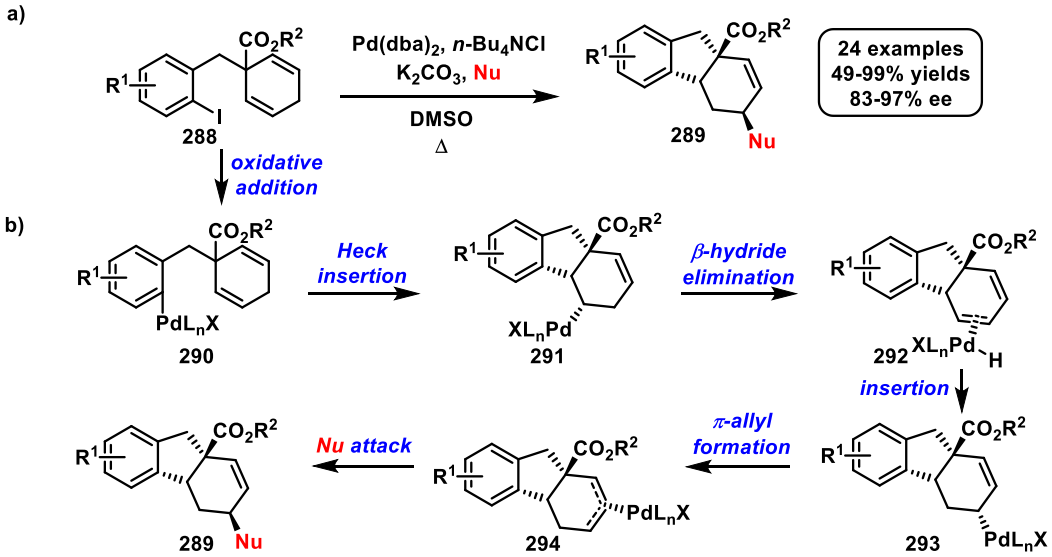
Scheme 53: Exploitation of facile *β*-hydride elimination by Sigman *et al.* a) Pd-catalysed hydroalkylation of styrenes **271** and b) the proposed mechanism.[163]

Dienes frequently serve as useful synthetic intermediates,[166,167] and hence introduces the possibility that their formation could become part of a productive catalytic cycle. Indeed, this has been verified in numerous cases,[162,168] including that by the Baudoin group where they showed unusual *γ*-arylation of *O*-carbamates **279** *via* directed lithiation, transmetallation to zinc and Negishi coupling, when using an *ortho*-substituted aryl electrophile and phosphine ligand (Scheme 54).[169] The proposed mechanism involved *β*-hydride elimination, a haptotropic rearrangement, further Pd-insertion and subsequent reductive elimination.



Scheme 54: a) Arylation of *γ*, *δ*-unsaturated *O*-carbamates **279** and b) the proposed mechanism, post-*α*-lithiation and transmetallation.[161]

A further example of using dienes within a catalytic cycle, and indeed as a synthetic precursor, was shown by Wu and co-workers, where they synthesised chiral tetrahydrofluorenes *via* a tandem intramolecular Heck/Tsuji-Trost process (Scheme 55).[170] The asymmetric coupling of 2,5-cyclohexadienyl-susbstitued aryl iodides **288** and nucleophiles afforded the products **289** as single diastereomers in good yields with excellent enantioselectivities. The mechanism was proposed to start with oxidative addition, followed by insertion and the inherent *β*-hydride elimination step. Alkene reinsertion succeeded, *π*-allyl formation to give **294** and the cycle concluded with nucleophilic attack to give the tetrahydrofluorene product **289**.



Scheme 55: a) The tandem Heck/Tsuji-Trost process by Wu *et al.* and b) the proposed mechanism.[170]

3.1.6. The 2-Azabicyclo[3.3.1]nonane Ring-System

The 2-azabicyclo[3.3.1]nonane scaffold is ubiquitous in natural products. More commonly known as morphan, perhaps the two-best known compounds containing such a bicyclic ring system are the alkaloids morphine **9**,[171] used for pain relief, and strychnine **295**,[172] a pesticide (Figure 18). Others include the cytotoxic alkaloids madangamine A **296** and daphniphyllum A **297**,[173,174] and the immunosuppressant FR9014834 **298**.[175] With this motif having such a broad spectrum of medicinal properties, analogues of such represent a highly desirable synthetic target.

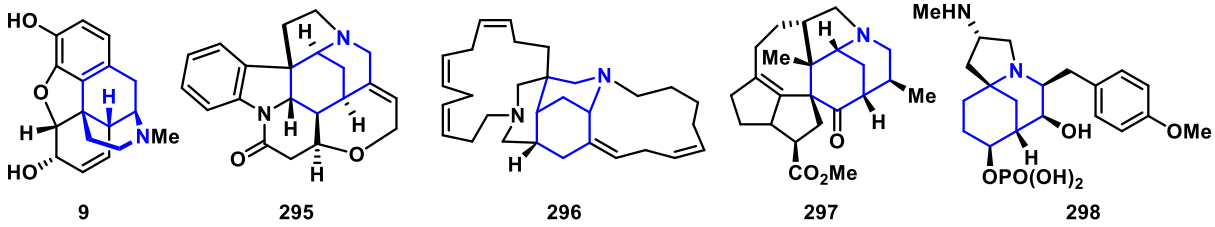
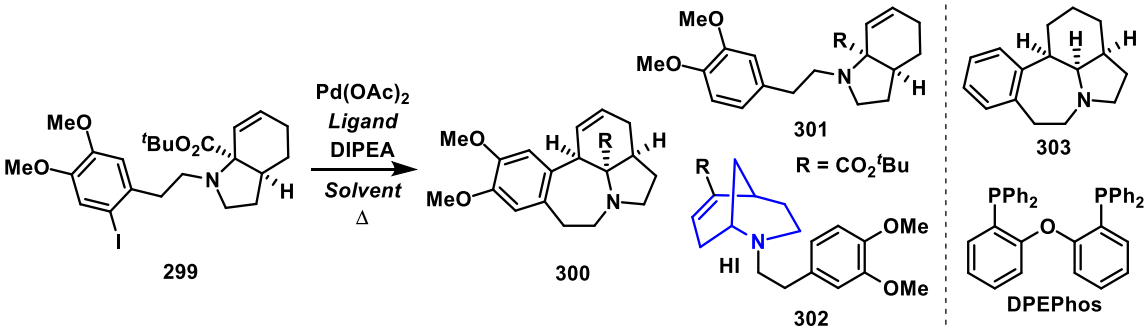


Figure 18: Natural products containing the morphan ring system.

3.1.7. Previous Preliminary Studies

Previous work within the Booker-Milburn group synthesised iodo-bicyclic compound **299** in two steps from the corresponding tricyclic aziridine **253** (Figure 19); a thermal 1,5-hydrogen shift gave the imine[142] which was subjected to reductive amination conditions with the appropriate aryl aldehyde.[39] It was envisaged that this compound **299** would undergo an intramolecular Heck reaction to access the seven-membered-tetracyclic product **300**, and analogues of such**,** to then lead to the natural product (±)-hexahydroapoerysopine **303**. A range of conditions were screened to try and optimise this reaction, which unfortunately were not successful, such generally returned starting material **299** or afforded the dehalogenated analogue **301** of which (Figure 19). Interestingly however, the morphan iodide salt **302**

was isolated in a reasonable yield of 76% in one set of conditions (Entry 6, 39% yield upon removal of the HI salt).[39]



Entry	*Ligand*	*Solvent*	*Temperature (°C)*	Product	Yield
1	P(*o*-tol)$_3$	MeCN	85	**301**	<5%
2	P(*o*-tol)$_3$	DMF	100	SM	-
3	P(*o*-tol)$_3$	PhMe	100	**301**	<5%
4	P(*o*-tol)$_3$	Dioxane	100	**301**	<5%
5	DPEPhos	MeCN	85	**302**	<5%
6	DPEPhos	Dioxane	100	**302**	76%
7	DPEPhos	DMF	100	SM	-
8	P(*o*-tol)$_3$	Dioxane	100	SM	-
9	XantPhos	Dioxane	100	**301**	55%

Figure 19: Previous conditions screened for attempted access to the seven-membered ring **300**.[39]

A crystal structure of the morphan HI salt **302** was also obtained.[39]

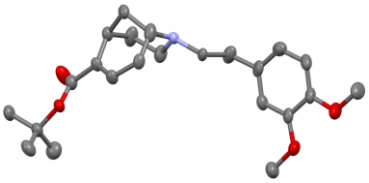
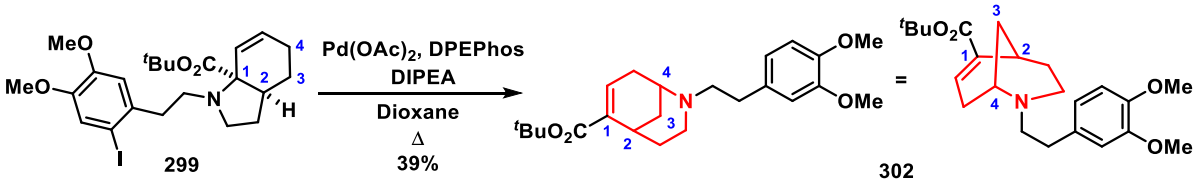


Figure 20: Crystal structure of **302**.

3.2. Aim of Project

As discussed in Section 3.1.7., under Pd catalysis iodo-bicycle **299** resulted in the formation of the dehalogenated 2-azabicyclo[3.3.1]nonane product **302** (Scheme 56).[39] This unusual reaction was hypothesised to result from an allylic type rearrangement process but with a *β*-hydride elimination/1,6 conjugate addition sequence as the termination step. Due to both the interesting nature of this reaction, and that such morphan products are biologically privileged scaffolds,[176,177,178,179] reaction optimisation and mechanistic understanding was sought. It was hoped that this dehalogenation-cyclisation process could then be applied to a broader set of substrates, leading to a range of substituted morphan ring systems.

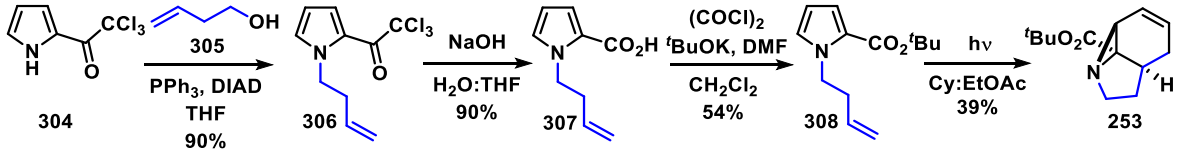


Scheme 56: The Pd-catalysed reaction to gain access to the morphan ring system **302**.[39]

3.3. Results and Discussion

3.3.1. Synthetic Route to Precursor

The synthetic route to lead to the iodo-substrate **299** for the Pd-catalysed reaction was relatively straight forward; however, it did consist of a rather lengthy six linear steps (Scheme 57). Commercially available trichloroacetyl pyrrole **304** was alkylated with 3-buten-1-ol **305** *via* a Mitsunobu reaction, hydrolysed to form the carboxylic acid **307** and then esterified to give **308**. All of which were completed on greater than 20 g scale, affording products in good to excellent yields. The pyrrole ester **308** was then irradiated to form the tricyclic aziridine **253**, in a relatively low yield of 39% (albeit expected, likely due to a low overall quantum yield of the two-photon process).[143]



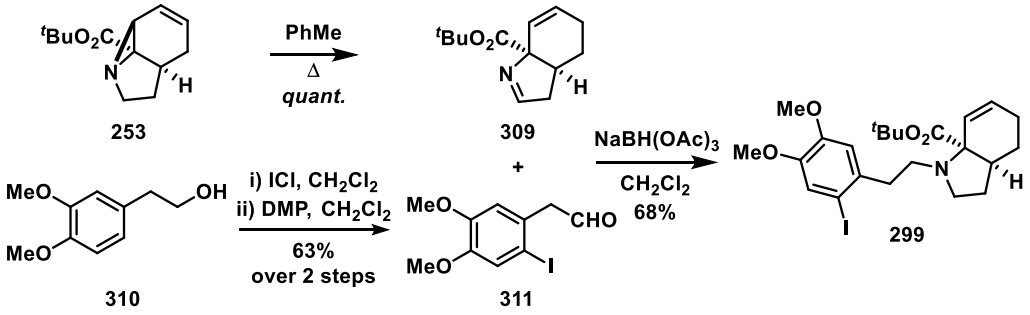
Scheme 57: Synthetic route to *tert*-butyl ester aziridine **253**.[143]

The *tert*-butyl aziridine **253** was generated in batch, irradiated using a 36 W UVC lamp for 15 hours and the photolysate was then concentrated *in vacuo* and purified. At the end of the reaction the reactor well was consistently stained yellow, an indication of photodegradation. Due to the limitation of batch reactions (Section 1.2.2.), especially in this instance where only ~400 mg of product could be synthesised overnight due the high dilution requirement of the reaction, completing the reaction in flow was investigated. Three 36 W UVC lamp sources were set up in parallel each wrapped in FEP tubing and the *tert*-butyl pyrrole substrate **308** was pumped through the system at a flow rate of 3 mL/min using a standard HPLC pump (see Section 1.2.2.).[180] In theory, this should have only taken ~3 hours to irradiate 2.5 g of substrate, compared to an overnight reaction for 1 g in when completed in batch. However, due to the *tert*-butyl pyrrole **308** continuously fowling the reactor, the FEP tubing had to be flushed with DMSO and MeCN regularly. This was therefore quite time-consuming as it required handling to continuously swap over the systems from pyrrole substrate to solvent flush and hence delayed the irradiation. Although there was a large increase in hourly productivity for the flow set-up, due to the need for regular solvent flushes and the fact there was a small deterioration in percentage yield, the batch photochemical process to synthesise the *tert*-butyl ester aziridine **253** was seen as a more reliable, easier method to carry out.

	Flow Rate (mL/min)	Time (hours)	Productivity [a] (g/h)	Productivity [b] (g/h)	Yield
Batch	-	15	0.03	0.03	39%
Flow	3	3.1	1.24	0.18	32%

Table 2: Comparison of batch versus flow photochemistry for pyrrole **308**. An additional 1 hour 40 minutes was required to flush the reactor with DMSO and MeCN. [a]Additional time not accounted for in this calculation; [b]additional 1 hour 40 minutes accounted for.

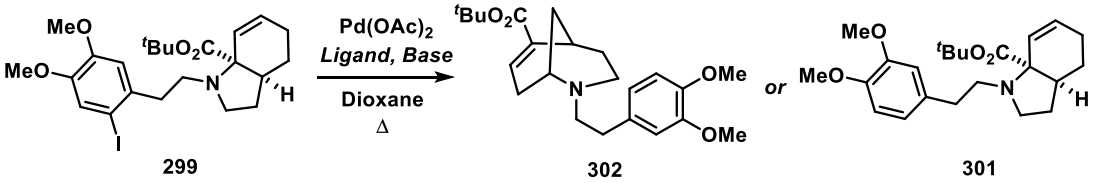
After aziridine formation, **253** was then heated in PhMe for 16 hours to give the imine **309**, *via* the [1,5]-hydrogen shift ring-opening reaction (Scheme 58).[140] To complete the synthetic route to substrate **299**, this then underwent reductive amination with aldehyde **311**, which was synthesised from alcohol **310** by iodination at the 2-position with ICl and oxidation with DMP.[39]



Scheme 58: Synthesis of iodo precursor **299**.[39]

3.3.2. Reaction Familiarisation

Early work began on understanding the fundamentals of the reaction (Figure 21). Without the presence of the amine base DIPEA or a ligand, the reaction did not proceed and staring material **299** was recovered (Entries 2 and 3). Wet dioxane also inhibited the reaction. Replacement of DIPEA with another tertiary amine base, Et_3N, gave the dehalogenated starting material **301** (Entry 4). A brief ligand screen was conducted focusing on bidenate ligands, for which the bite angles were considered (albeit not correlated in the results) yet none improved upon the result with DPEPhos (Entries 5-8). The monodenate ligand PPh_3 was also included in the screen but gave a modest yield of 39% (Entry 9). Other solvents, including MeCN, PhMe and DMF, had already been previously looked at for the original intramolecular Heck reaction (see Section 3.1.7.) but only MeCN led to a small amount of product formation, the others only yielding deiodinated substrate **301** or led to no reaction at all.[39]

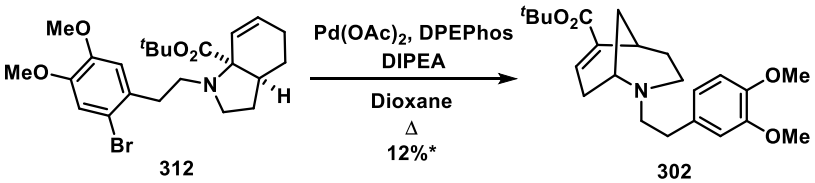


Entry	*Ligand*	*β*[181]	*Base*	Result	Yield
1	DPEPhos	103°	DIPEA	**302**	76%
2	DPEPhos	103°	-	SM	-
3	-	-	DIPEA	SM	-
4	DPEPhos	103°	Et_3N	**301**	42%
5	Xantphos	107°	DIPEA	SM	-
6	DPPF	96°	DIPEA	**302**	21%[a]
7	DPPB	98°	DIPEA	**302**	3%[a]
8	DCEPhos[b]	103°	DIPEA	**302**	6%[a]
9	PPh_3	-	DIPEA	**302**	39%

Figure 21: Familiarisation work for the Pd-catalysed synthesis of morphan **302**. [a]Percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard; [b]bis(dicylohexylphophinophenyl)ether. Note Entry 5 contradicts those results obtained previously, see Section 3.1.7.

The original conditions discovered appeared to be the optimal, although an improved yield of 76% was achieved (compared to 39%), assumed to be due to removing the HI salt by inclusion of a work-up and therefore easing purification. These conditions premixed $Pd(OAc)_2$ (0.1 equiv.) and DPEPhos (0.15 equiv.) in dioxane for 10 minutes, added the substrate **299** in dioxane and DIPEA, then heated for 17 hours. However, this premix would often form a yellow precipitate, and if the reaction was continued it would only lead to dehalogenated starting material **301**. Due to this, the amine base was included in this premix, which seemed to reduce the precipitate formation and hence increase subsequent successful reactions.

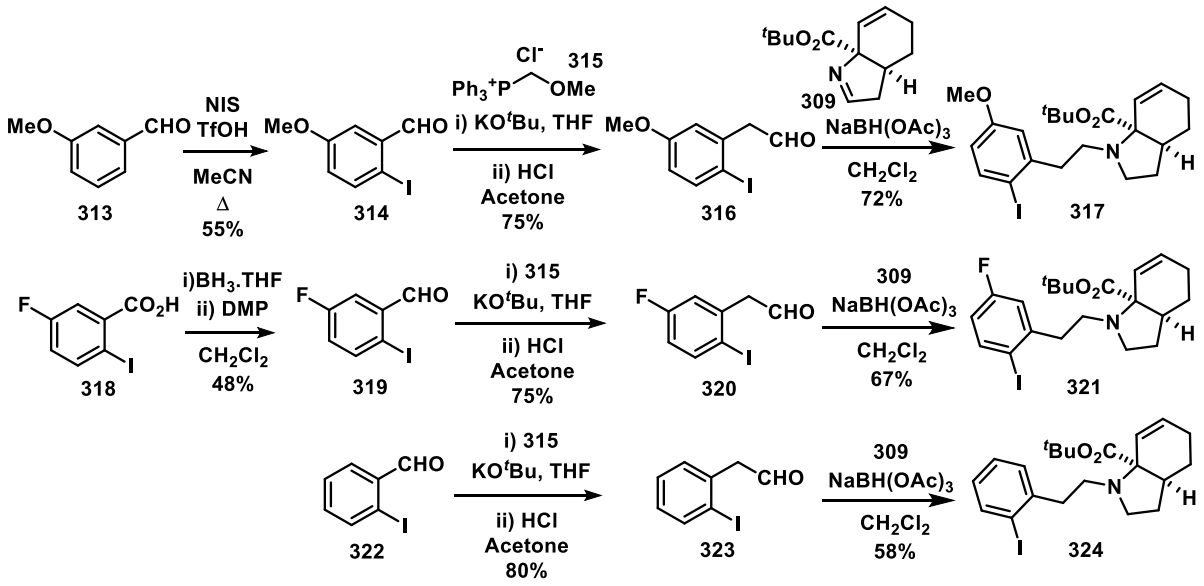
The bromo analogue **312** was also synthesised (as so in Section 3.3.1., Scheme 58, albeit brominating with NBS) and subjected to the reaction conditions (Scheme 59). However, this did not perform as well as its iodo counterpart in the reaction, only giving a mere 12% yield of product **302**. Although it can be assumed oxidative addition for this moiety would be less facile than that of the iodo moiety,[182] this would not explain such a decrease in the yield observed. Perhaps the subsequent protodepalladation has a reduced rate, or the catalyst system was simply more active with iodide.



Scheme 59: Product formation using the bromo analogue **312**. *Percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

3.3.3. Aryl Iodide Scope

A brief scope of similar aryl iodide substrates was next completed, subjecting three analogues to the reaction conditions: the monomethoxy aryl iodide **317**, the fluorinated aryl iodide **321** and the aryl iodide **324** (Scheme 60). The synthetic route to these systems, was similar to that of the original substrate **299**, the one half of the molecule stemming from the aziridine remained the same, and the aldehyde half was dependant on both commercially available materials and aromatic substitution patterns, which were then joined in a reductive amination. *m*-Anisaldehyde was iodinated with NIS, followed by a Wittig homologation to form the homoallylic ether, for which acidic cleavage and isomerisation gave aldehyde **316**, which upon reductive amination with imine **309**, afforded the first substrate **317** in a good yield of 72%. For the fluorinated precursor, due to regioselectivity issues with iodinating 3-fluorobenzaldehyde, the carboxylic acid **318** was initially reduced to the alcohol,[183] oxidised to the aldehyde **319**, which was then subjected to the same Wittig and acidic conditions as before, to afford the homologated aldehyde **320**. Reductive amination with $NaBH(OAc)_3$ furnished the desired precursor **321** in a 67% yield. Similarly, aldehyde **323** was obtained *via* this sequential route, albeit initiating with the commercially available 2-iodobenzaldehyde **322**.



Scheme 60: Synthetic route to precursors monomethoxy aryl iodide **317**, fluoro aryl iodide **321** and aryl iodide **324**. **317** and **324** were synthesised by another member of the group.[184]

Gratifyingly, all three of the aryl iodide substrates underwent the Pd-catalysed reaction to afford the morphan ring products **325**, **326** and **327** (Figure 22). The monomethoxy system **317** gave the lowest yield of 21% and the fluorinated moiety also gave a poor yield of 33%. However, the aryl iodide produced the morphan product **327** in a good yield of 74%. It can be rationalised that the slightly deactivating nature of the halide would be less reactive than the original dimethoxy substrate **300**, and hence the poorer yield. However why this system, and the aryl iodide **324** performed superior to the monomethoxy **317**, was not understood at this stage (see Section 3.3.6. for a potential explanation).

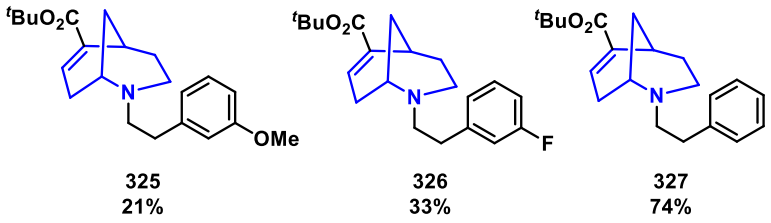
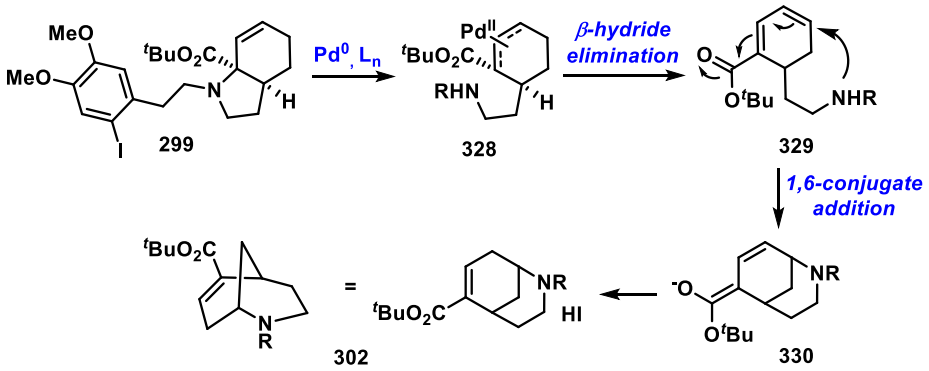


Figure 22: Initial scope generating morphan products **325**, **326** and **327**.

The substrate scope was particularly limited at this time. By shortening the two-methylene unit tether by one carbon atom, the competing intramolecular Heck reaction would occur instead, due to the formation of a favourable six-membered ring.[65] Another limitation was the requirement of the aryl iodide. If the equivalent substrate without the iodide substituent, **301**, was subjected to the Pd-catalysed reaction conditions, it would only be recovered with no product formation. The proposed rationale behind this requirement will be further discussed in the next section.

3.3.4. Proposed Mechanism

The below mechanism was hypothesised for the reaction. It was assumed a Pd-π-allyl species **328** was formed initially, which subsequently underwent β-hydride elimination to give the diene **329**. Intramolecular 1, 6-conjugate addition followed by proton shuffling yielded the morphan product **302**.



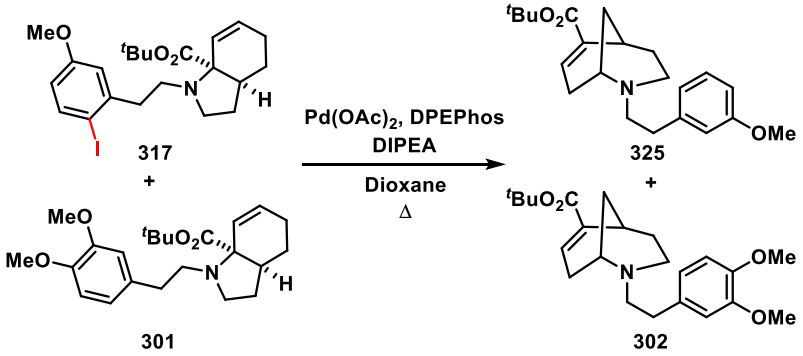
Scheme 61: Proposed mechanism for the formation of morphan scaffold **302** from aryl iodide **299**.

At some point throughout this process, dehalogenation occurred and as stated earlier, the iodide substituent was necessary for the reaction to proceed. It was curious to know its involvement in the reaction, and there were several hypotheses for its necessity:

1) Perhaps oxidative addition of Pd^0 occurred, for which the generated Pd^{II} species then acted as a Lewis acid coordinating to the nitrogen atom.[185,186] Hence this activated the nitrogen and facilitated the bond cleavage for when a another Pd^0 atom acted as a nucleophile to form the π-allyl species **328**. Two palladium atoms would therefore be involved in the mechanism.
2) Alternatively, after this oxidative addition, protodepalladation occurred and this modified the catalyst or formed by-products such that were essential for the reaction to occur.

3) Or the iodide was required simply for steric reasons, potentially forcing the molecule into a conformation that enabled the reaction to occur, and hence the reaction could be achieved by replacing the iodide with alternative bulky groups at the 2-position.

Differentiating between these mechanisms was essential to extend the scope of the reaction. It was also a requirement to enable optimisation. Investigating pathway two seemed the most straightforward, and this was completed by subjecting two different substrates in the same vessel to the reaction conditions (Scheme 62). Hence, the mixed reaction system consisted of the monomethoxy aryl iodide **317**, which was known to form morphan product **325** under such conditions, and the dimethoxy species **301**, without an iodide substituent on the aromatic ring, which was known not to undergo the reaction (the difference in substitution pattern was to help identification purposes). As such, when both of these were combined in one vessel, morphan products for both precursors were observed. This gave reasonable evidence that the reaction was proceeding *via* pathway two: post-protodepalladation, the catalyst was modified in such a way, or formed by-products which then enabled the reaction to proceed.



Scheme 62: Cross-over reaction affording both morphan products **325** and **302**, in a ratio of 0.3:1 respectively.

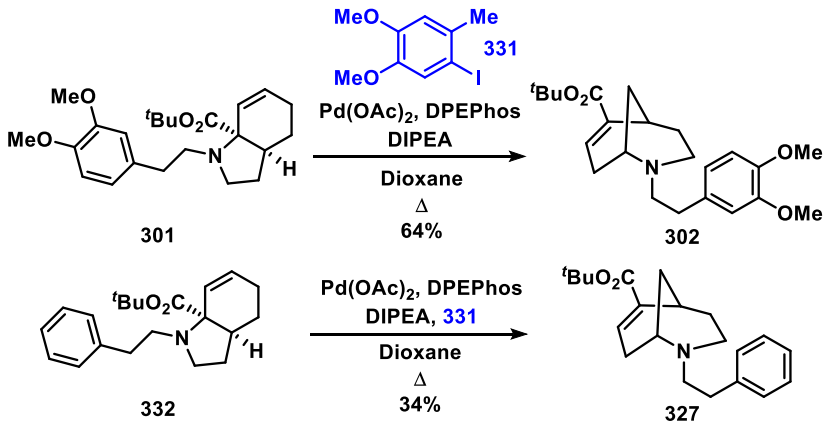
Crucially, this meant that the substrate itself no longer required an aryl iodide tether for the Pd-catalysed reaction to succeed.

3.3.5. Additives

3.3.5.1. Aryl Iodides

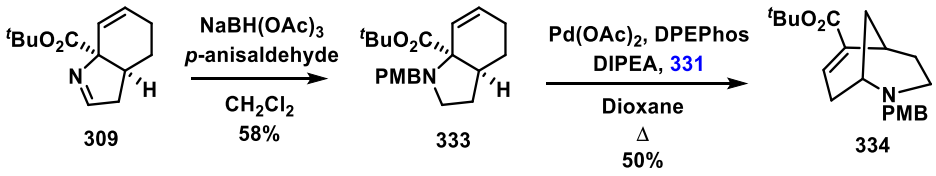
Results from the cross-over reaction indicated that a sacrificial additive could be used to turn over the reaction. The selected additive to test this hypothesis was dimethoxy-methyl aryl iodide **331**, as this was similar in both electronic and steric effects to the original system (Scheme 63). Such was synthesised *via* iodination of the commercially available material 3,4-dimethoxy toluene with NIS.[184] The two substrates, dimethoxy aryl **301** and aryl **332**, neither of which contained an aryl iodide, were synthesised as before by reductive amination of imine **309** with either 3,4-dimethoxyphenyl acetaldehyde or phenyl acetaldehyde. Each were subjected to the Pd-catalysed reaction conditions, with 1 equivalent of aryl iodide **331** and pleasingly afforded morphan products. However, such were obtained in a lower yield compared to the equivalent iodo substrates **299** and **324** (64% versus 76% for the

dimethoxy system **302** and 34% versus 74% for the phenyl system **327**). Despite this decrease, removing the requirement of the iodide substituent on the precursor was seen as an improvement.



Scheme 63: Product formation with aryl iodide additive **331**, crucially highlighting there was no longer a need for the iodide to be within the substrate itself.

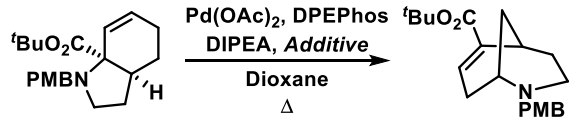
With this success in hand, investigations into changing the tether on nitrogen began. A cleavable protecting group was sought to continue optimisation studies and the PMB group was selected due to its similarities to the original substrate **299**. Again, standard reductive amination conditions with imine **309** and *p*-anisaldehyde yielded bicyclic **333** in a 58% yield (Scheme 64). This was then subjected to the Pd-catalysed reaction conditions and a 50% yield of the morphan PMB product **334** was isolated. Interestingly, the deiodinated analogue of **331** was also identified, by mass spectrometry, and hence a further indication that protodepalladation does occur. Successfully turning over a substrate with one methylene unit in the tether and hence enabling the potential for its removal, to leave the parent morphan system, was a sufficient development. The reaction could now be viewed as a true rearrangement process.



Scheme 64: Successful PMB morphan product **334** formation.

As the rearrangement proceeded in a 50% yield, further optimisation to improve this was undertaken (Figure 23). This began with studying other aryl iodides, as although **331** was only one step from a commercially available compound, it was desirable to have a readily available additive. Completing the reaction with an analogous additive without the methyl substituent, had quite a negative effect on the ^{1}H-NMR yield, dropping to 26% from 40% (Entry 2). Similarly, 4-iodoanisole gave a low ^{1}H-NMR yield of 23% (Entry 3) and this trend continued to decrease with iodobenzene (Entry 4). The difference in results were assumed to reflect either, or both, the steric or electronic influence on the rate of protodepalladation. TBAI did not lead to any reaction, only recovered starting material was observed

(Entry 5). Attempting to reduce the amount of the aryl iodide **331** used in the reaction was also explored, however the best results obtained were when one equivalent was used (Entries 6-8).



333 **334**

Entry	*Additive*	*Equivalents of Additive*	Yield of 334	Conversion[a]
1	**331**	0.5	40%	93%
2	1-Iodo-2,4-dimethoxybenzene	0.5	26%[b]	-
3	4-Iodoanisole	0.5	23%[b]	-
4	Iodobenzene	0.5	19%[b]	-
5	TBAI	0.5	SM	-
6	**331**	1	50%	96%
7	**331**	0.25	-	69%
8	**331**	0.1	-	43%

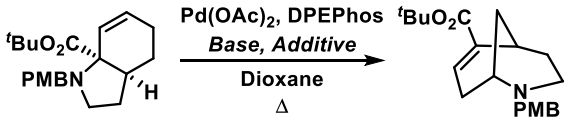
Figure 23: Iodide additives trialled in the Pd-catalysed rearrangement of PMB substrate **333**. [a]Percentage conversion based on level of SM and product in the crude ^{1}H-NMR; [b]percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

As the use of stoichiometric iodides was not particularly efficient, and as no improvement in yield was observed, other activating agents were sought after.

3.3.5.2. Brønsted Acids

Protodehalogenation of aryl halides is well documented within cross-coupling reactions,[187,188,189] potentially generating stoichiometric quantities of HX. Generation of which could perhaps activate the nitrogen atom, facilitating the observed cleavage of the carbon-nitrogen bond,[190] thus leading to the morphan product, and evidence for this was obtained in the cross-over reaction, Section 3.3.4., Scheme 62. Hence protonation using a Brønsted acid was next explored, envisaged to replace the requirement of an aryl iodide additive and ideally, be commercially available.

Based on the results thus far, formation of a DIPEA.HI salt seemed logical to test first, potentially enabling both the base and additive to be added as one (Figure 24). Pleasingly this was successful, and the PMB product **334** was observed in a 53% yield (Entry 1). Varying the equivalents of such and addition of DIPEA was also investigated to try and improve the percentage yields but with no success (Entries 2 and 3). As with the aryl iodide **331** however, DIPEA.HI was not commercially available. The equivalent HCl salt was, yet unfortunately this did not work in the reaction (Entry 4).

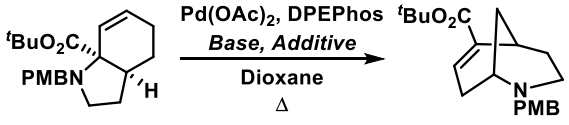


333 334

Entry	*Base*	*Additive*	*Equivalents of Additive*	Yield of 334
1	-	DIPEA.HI	1	53%
2	-	DIPEA.HI	2	46%[a]
3	DIPEA[b]	DIPEA.HI	1	39%[a]
4	-	DIPEA.HCl	1	SM

Figure 24: Screening results using DIPEA salts as an additive for the rearrangement of PMB substrate **333**. [a]Percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard; [b]0.15 equiv. of base used.

Although a slight increase in yield was observed upon addition of DIPEA.HI in comparison to the dimethoxy methyl aryl iodide **331** (53% versus 50%) due to the inherent hygroscopic properties associated with salts, and hence the potential for a variability in purity, the screen was continued (Figure 25). Acetic acid was tried in the reaction, but no product formation was observed (Entry 1). TBAI was then included too, in case an iodide source was necessary, but this also failed (Entry 2). Moving to a stronger acid, camphorsulfonic acid, with the exclusion of DIPEA, for which morphan product **334** was seen, albeit in a poor yield of 23% (Entry 3). This could however be increased on inclusion upon DIPEA (Entries 4 and 5). Methanesulfonic acid gave a slightly improved ^{1}H-NMR yield of 46% (Entry 6), although still not quite as good as the isolated yield obtained with aryl iodide **331** of 50%.



333 334

Entry	*Base*	*Additive*[a]	Yield of 334
1	DIPEA	AcOH	SM
2	DIPEA	AcOH and TBAI	SM
3	-	CSA	23%[c]
4	DIPEA	CSA	43%
5	DIPEA[b]	CSA	42%[c]
6	DIPEA	MSA	46%[c]

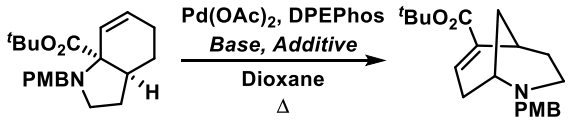
Figure 25: Screening results of acid additives for the Pd-catalysed rearrangement of PMB substrate **333**. Inclusion of the base within the premix and adding the acid after 10 minutes appeared to give the best results. [a]1 equiv. of additive used; [b]0.5 equiv. of base used, in all other cases 1 equiv. was used; [c]percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

Based on the above screening results with the addition of a Brønsted acid, it was speculated that Lewis acids could also allow the transformation to occur, coordinating to the nitrogen and facilitating bond cleavage. Although only triisopropyl borate was tested, this was not successful and only starting material was recovered from the reaction.

3.3.6. Reproducibility Issues

Optimisation of the reaction had still not led to any distinct improvements, although now enabling the use of a commercially available additive, the yield of morphan PMB product **334** remained moderate. Additionally, optimisation work was slowed due to issues with reproducibility (Figure 26). As mentioned previously (Section 3.3.2.), sometimes the catalyst premix would form a yellow precipitate and the reaction would fail, and although inclusion of DIPEA had helped to prevent its formation, it still occurred occasionally at what appeared to be sporadic instances. Tests were carried out to include the substrate within this premix, which did seem to stop the precipitation (Entry 1). However, the reaction would still occasionally fail, or at least give variable results, even now the precipitate no longer formed (Entries 2-7). There was no indication of why this occurred, and several factors were investigated to try and prevent this issue reoccurring.

Different sources of dioxane were tested in the reaction along with freeze-pump-thawing and degassing. The different batches of solvent did not highlight any obvious differences, nor did Karl-Fischer analysis. However sufficiently degassing the solvent did have a dramatic effect on the reaction, either reducing the ^{1}H-NMR yield to 16% or combined with the removal of the premix, inhibiting it completely (Entries 8-10). The ligand DPEPhos was analysed and recrystallised but this did not appear to affect the reaction. There has been much work conducted by Fairlamb *et al.* on the common impurities found in $Pd(OAc)_2$ and its and differing forms.[191,192,193,194] However, as two different bottles of the catalyst had been used (due to a move to industry), both from different suppliers and as both seemed to give inconsistent results, no studies of its quality were undertaken. Finally, DIPEA and methanesulfonic acid were distilled, and the sequence of additions and premixes were investigated yet frustratingly, the reaction was still not reproducible.

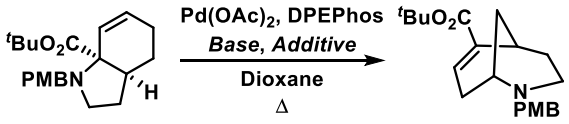


333 334

Entry	*Base*	*Additive*	*Additional Conditions*	Yield of 334	Repeat 1	Repeat 2
1	DIPEA	CSA	Substrate in premix	43%*	42%*	-
2	DIPEA	**331**	-	SM	50%	-
3	DIPEA	4-iodoanisole	-	62%*	23%*	-
4	-	DIPEA.HI	-	53%	28%*	SM
5	DIPEA	CSA	-	43%	24%*	-
6	DIPEA	MSA	-	46%	SM	-
7	DIPEA	MSA	Substrate in premix	SM	85%*	-
8	DIPEA	CSA	No premix, FPT	SM	-	-
9	DIPEA	CSA	No premix, N_2 sparge	SM	-	-
10	DIPEA	CSA	FPT	16%*	-	-
11	DIPEA	CSA	Dry solvent, open to air	SM	-	-

Figure 26: Repeat reactions of **333** to highlight reproducibility issues and different conditions tried to circumvent this. Premix of Pd, ligand and DIPEA in dioxane for 10 minutes unless stated otherwise. *Percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

Carrying out the reaction in a completely inert atmosphere was thought to give some indication about the lack of reproducibility. Although anticipating that completing the rearrangement process in a glovebox would halt the process altogether, as degassing and freeze-pump-thawing showed dramatic decreases in percentage yields, it would finalise that the reaction needed a small amount of oxygen to proceed. Surprisingly however, the reaction proceeded in a 65% ^{1}H-NMR yield, an increase of 15%, and importantly this was repeated a further four times, each affording similar ^{1}H-NMR yields (Figure 27, Entries 1-5). The reaction was clearly more sensitive to oxygen than first thought. This was reasoned to be due to catalyst decomposition with molecular oxygen.[195] Interestingly a decrease in nearly 20% yield occurred when a solution of the starting material in dioxane was added first to the Pd catalyst and ligand followed by dioxane and DIPEA (Entry 6), rather than adding dioxane and DIPEA to the catalyst system and then the solution of substrate.



333 334

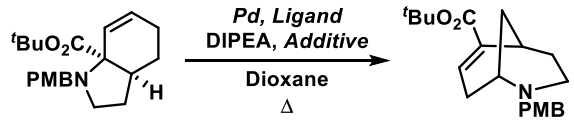
Entry	*Base*	*Additive*	Yield of 334[c]
1[a]	DIPEA	MSA	65%
2[a]	DIPEA	MSA	69%
3[a]	DIPEA	MSA	65%
4[a]	DIPEA	MSA	65%
5[a]	DIPEA	MSA	67%
6[b]	DIPEA	MSA	46%

Figure 27: Glovebox repeat reactions for the rearrangement of PMB substrate **333**. [a]Substrate **333** added as a solution in dioxane to Pd, L and DIPEA in dioxane, stirred for 10 minutes then MSA added; [b]dioxane and DIPEA added to Pd, ligand and substrate **333**, stirred for 10 minutes then MSA added; [c]all percentage yields based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

An oxygen sensor was installed in a reaction vessel within the fume-hood, to directly compare the oxygen levels in this set-up versus in the glovebox. The sensor detected 0.05 wt%, or 500 ppm, oxygen content, whereas the glovebox remained ~10 ppm during these studies (Figure 27). Hence, it was shown that at least with the current laboratory set-up (house vacuum and a Schlenk line under N_2), sufficiently low levels of oxygen could not be achieved, and could only be done so by utilising the glovebox. This variation in results was hence believed to be behind the unexplainable trend in yields observed in the aryl iodide substrate scope (see Section 3.3.3.).

With confidence that the rearrangement procedure was now reliable, the decision was made to conduct a further screen of conditions within the glovebox to try and increase the percentage yield for the PMB system **334**, which was isolated in a 70% yield (Figure 28, Entry 1). Hence a brief investigation into a variety of ligands, acids and Pd sources was conducted. A different selection of ligands, in comparison to the previous screen, was tested however, due to the good result obtained with PPh_3, 73% ^{1}H-NMR yield (Entry 2). Thus, focusing on altering the steric and electronic properties of PPh_3, initially changing the phenyl substituents to the more electron-withdrawing furyl group and hence making the phosphine a poorer σ-donor, stopped the reaction completely (Entry 3). As was also true with the bulkier tri(*o*-toyl)phosphine ligand (Entry 4). Although some product formation was observed for the more electron-donating methoxy aromatic (Entry 5), the result was poor compared to PPh_3, 39% versus 73% yield. Unsurprisingly, the fluorinated equivalent gave a similar yield to PPh_3 (Entry 6). Pd^0 sources were tried and both $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ afforded similar yields to $Pd(OAc)_2$ (Entries 7-9). This provided more evidence that it is indeed a Pd^0 species catalysing the rearrangement. Acetic and trifluoroacetic acid replaced methanesulfonic acid in two sets of conditions but afforded the morphan PMB product in lower

yield, correlating with pK_as (Entries 10 and 11). Finally, the Lewis acid triisopropyl borate was also tested again, but as seen before, resulted in recovered substrate (Entry 12).



333 334

Entry	*Pd Source*	*Ligand*	*Additive*	Yield of 334
1	$Pd(OAc)_2$	DPEPhos	MSA	70%
2	$Pd(OAc)_2$	PPh_3	MSA	73%*
3	$Pd(OAc)_2$	TFP	MSA	SM
4	$Pd(OAc)_2$	P(*o*-toyl)$_3$	MSA	SM
5	$Pd(OAc)_2$	Tris(4-methoxyphenyl) phosphine	MSA	39%*
6	$Pd(OAc)_2$	Tris(4-fluorophenyl) phosphine	MSA	65%*
7	$Pd(PPh_3)_4$	DPEPhos	MSA	60%*
8	$Pd(PPh_3)_4$	-	MSA	57%*
9	$Pd_2(dba)_3$	DPEPhos	MSA	65%*
10	$Pd(OAc)_2$	DPEPhos	AcOH	22%*
11	$Pd(OAc)_2$	DPEPhos	TFA	43%*
12	$Pd(OAc)_2$	DPEPhos	Triisopropyl borate	SM

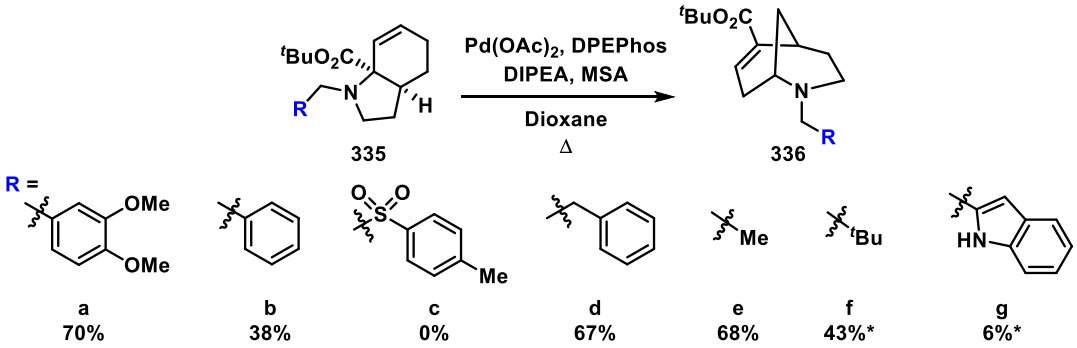
Figure 28: Optimisation screen conducted within the glovebox on model system, PMB substrate **333**. *Percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

Although a slight increase in yield was observed for the ligand PPh_3, this increase was not quantified by isolation nor was it confirmed as reliable. Hence, it was decided upon to remain with the same reaction conditions as those previous to the screen, $Pd(OAc)_2$, DPEPhos and methanesulfonic acid. As the yield for the PMB parent system had been increased from 50% to 70%, using a commercially available acid, without the requirement for a stoichiometric quantity of an aryl iodide, the optimisation and screening studies were hence viewed as an ultimate success.

3.3.7. Reaction Scope

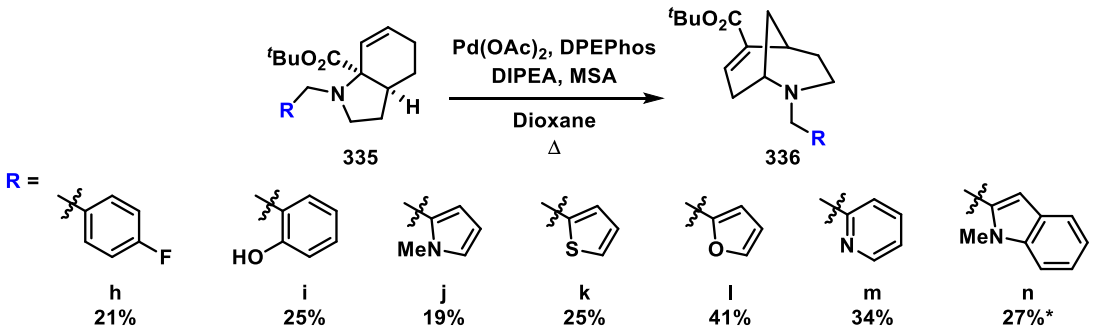
Keen to investigate the scope of this reaction, a range of substrates were synthesised and as seen before, these were differentiated simply by changing the aldehyde in the reductive amination reaction. Initially seven precursors were formed, three of such were alternative protecting groups on the nitrogen, the DMPM group **335a**, the benzyl group **335b** and the tosylate group **335c** (Scheme 64). The tether was lengthened in substrate **335d**, reverting to a two-methylene unit as seen in the original work. Two alkyl substituents, ethyl and *tert*-butyl **335e** and **335f** were also synthesised, and finally the indole substrate **335g**. Upon subjection to the reaction conditions pleasingly, six out of the seven gave some formation of morphan product. The DMPM group **336a** unsurprisingly gave the best yield, isolated at 70% yield. The benzyl substrate **336b** afforded a relatively poor 38% yield of product, its analogue with the extended chain giving a good yield of 67%. Interestingly the tosylate **336c** did not afford any morphan

ring product, despite enhancing the nitrogen's leaving group ability. Both the ethyl and *tert*-butyl systems turned over in reasonable yields, 68% and 43% respectively. Unfortunately, an isolated yield for the *tert*-butyl system could not be obtained, due to an inseparable, unidentified impurity. The indole containing substrate **335g** gave only a mere 6% ^{1}H-NMR yield of morphan product, possibly due to coordination of the free NH with the catalyst.



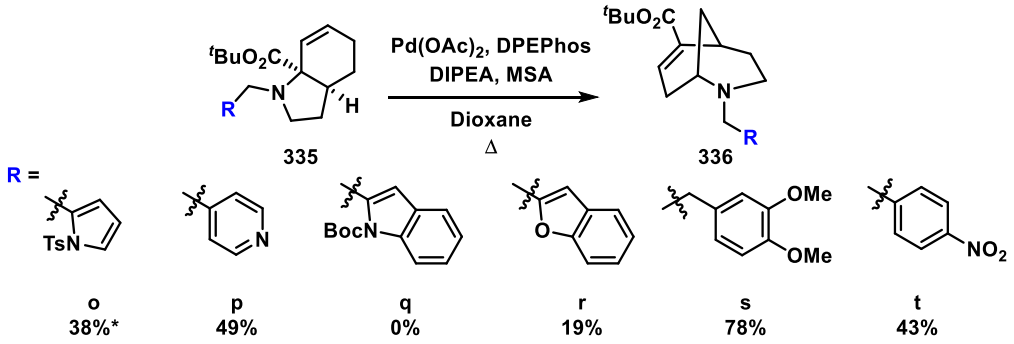
Scheme 64: Initial scope of the Pd-catalysed rearrangement to morphan systems **336a-g**. *Percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

The next set of substrates to be tested under the rearrangement conditions focused on aromatic systems (Scheme 65). Substituted aromatics, the fluorinated and the hydroxyl substrates **335h** and **335i** gave relatively poor yields of 21% and 25% respectively. The fluorinated result fitted nicely with previous results, the low yield speculated to be due to the slightly electron-withdrawing nature of the fluorine, contrasting the preference towards electron-donating substituents observed previously. Although the free hydroxyl group **336i** does not quite support this theory, it may have interfered in the reaction, *via* coordination of the oxygen or proton shuffling, and hence the low observed yield. Installing a protecting group may have improved product formation. Heteroaromatics methyl pyrrole **335j**, thiophene **335k** and furan **335l** all pleasingly turned over, giving poor to moderate yields of 19%, 41% and 25% respectively. Pyridine system **335m** gave morphan product **336m** in a 34% yield. Methylation of the indole substrate **335g** gave a distinct improvement in ^{1}H-NMR yield, increasing by 20% from the previous screen. Unfortunately however, despite the improvement in yield, issues with purification of **336n** prevented an isolated yield being obtained.



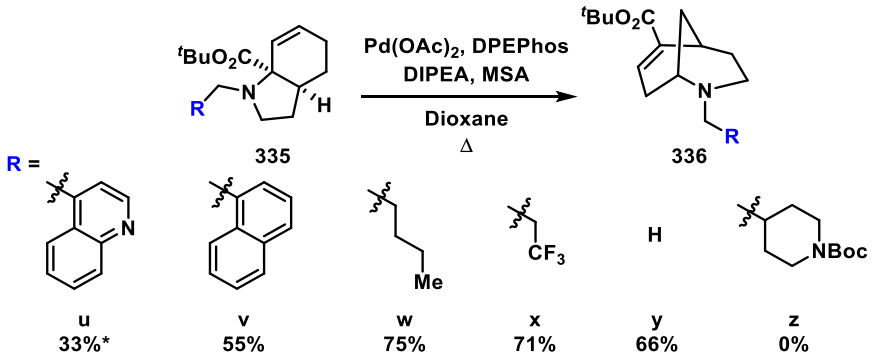
Scheme 65: Heteroaromatic scope of the Pd-catalysed rearrangement to morphan scaffolds **336h-n**. *Percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

Modifications of some of the substrates were completed in an attempt to improve the yields of the morphan products (Scheme 66). Altering the protecting group on the pyrrole system **335j** to an electron-withdrawing tosyl group **335o** did improve the ^{1}H-NMR yield to 38%, although a purified sample of **336o** could not be obtained. Moving the nitrogen to the 4-position from the 2-position within the pyridine precursor was also a success, which fortunately could be purified, and the isolated yield of 4-pyridine **336p** was 49% compared to 2-pyridine **336m** which was 34%. This difference has been attributed due the occurrence of coordination to the Pd catalyst, which can only occur in the 2-pyridine system **336m**, and hence inhibition of the reaction. Similarly, the indole substrate **335n** was protected with a Boc group instead, hoped to both improve the yield of the reaction and the purification. This however was unsuccessful, and no product formation was observed. Extending the aromaticity in the form of benzofuran system **335r** was also subjected to the Pd-catalysed conditions, which albeit gave a lower yield of 19% compared to the furan system **336l** of 41%. Two other aromatic precursors were also synthesised, again based on previous results. As the dimethoxy aromatic systems were known to work well under such conditions, **335s** was synthesised and gratifyingly afforded 78% yield of the morphan product **336s**. A further electron-poor aromatic system **335t** was tested, giving the nitro-morphan **336t** in 43% yield.



Scheme 66: Further scope of the Pd-catalysed rearrangement to morphan systems **336o-t**. *Percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

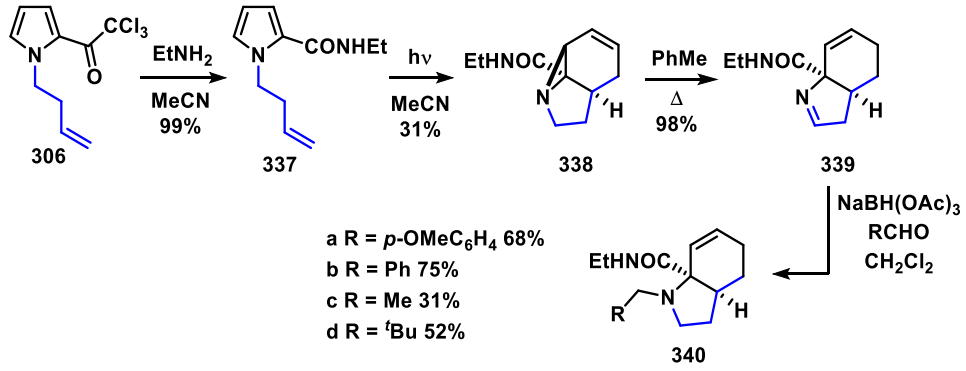
A final set of morphan substituted products were then synthesised (Scheme 67). The two extended planar aromatic precursors, quinoline **335u** and naphthalene **335v** were subjected to the reaction conditions. The naphthyl morphan **336v** was obtained in a 55% yield but the nitrogen variant of such, **336u**, gave a 33% ^{1}H-NMR yield which could not be separated from decomposition by-products. Moving away from aromatic systems, pentyl tether **335w**, CF_3 tether **335x** and *N*-methyl tether **335y** all underwent the rearrangement, in good yields. The concluding substrate explored was the sp^3 nitrogen precursor **335z**, which alas led only to degradation.



Scheme 67: Final scope of the Pd-catalysed rearrangement to morphan scaffolds **336u-z**. *Percentage yield based on ^{1}H-NMR, using 1,3,5-trimethoxybenzene as an internal standard.

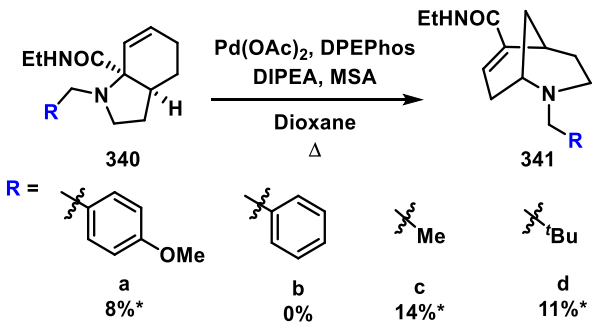
3.3.7.1. Amide Substituent

Keen to expand an already extensive scope, other points of derivatisation on the morphan scaffold were considered. Alternating the *tert*-butyl ester substituent seemed a viable method to increase the library of molecules and this would simply stem from a differing electron-withdrawing group on the starting pyrrole. The amide functional group was studied first, synthesis of which also began with the alkylated trichloroacetyl pyrrole **306** (Scheme 68). Amidation followed with ethylamine to give **337**, which as before was completed on a large scale, ~20 g. This too was irradiated in flow, at a flow rate of 3 mL/min, to afford the aziridine **338** in a yield of 61%. This was then heated in PhMe to form the imine **339** *via* the [1,5]-hydrogen shift.[126,142] As seen previously, the imine was then subjected to reductive amination conditions with four different aldehydes to afford four substrates: the PMB **340a**, the benzyl **340b**, the ethyl **340c** and the *tert*-butyl **340d**.



Scheme 68: Synthesis of amide precursor**s 340a-d**.[126,142]

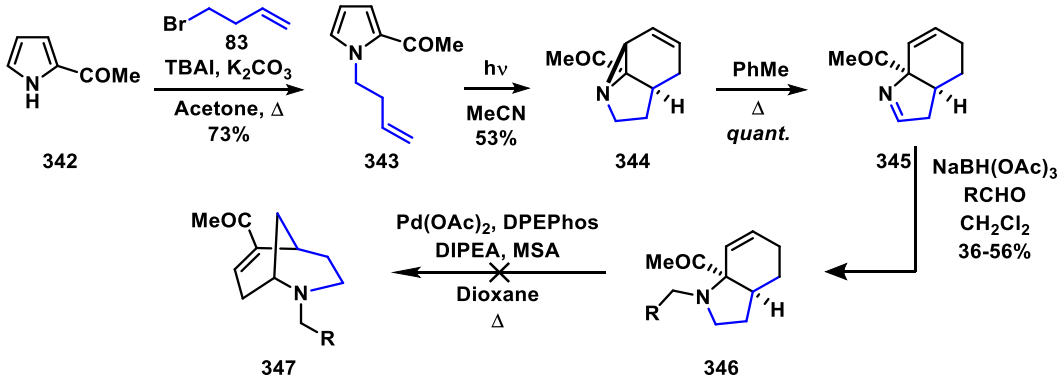
However, under the Pd-catalysed rearrangement conditions all four of these precursors gave low ^{1}H-NMR yields of the morphan products **341a-d** (Scheme 69). This was reasoned to be due to the poor ability of amides to act as Michael acceptors, which would be a requirement in the 1,6-conjugate addition step of the reaction.



Scheme 69: Poor results for amide system in Pd-catalysed rearrangement. *Percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

3.3.7.2. Ketone Substituent

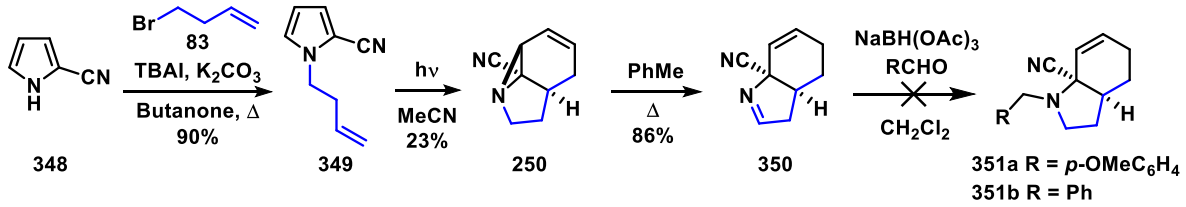
Due to the lack of success with the amide functional group, the corresponding ketone was next investigated, envisaged to enable the 1,6-conjugate addition that was thought to be inhibiting the amide system. Synthesis of which began with 2-acetyl pyrrole **342**, which was alkylated *via* a Filkenstein reaction with 4-bromobutene **83** and TBAI in a 73% yield (Scheme 70). This was irradiated in batch, affording aziridine **344** in 53% yield which was then quantitatively converted to the imine **345**. Again four substrates were synthesised by reductive amination of the imine with $NaBH(OAc)_3$ and either *p*-anisaldehyde, giving the bicyclic precursor in a 36% yield, benzaldehyde, a 56% yield, 3,4-dimethoxyaldehyde, 56%, or phenylacetaldehyde to afford bicycle in a 49% yield. Yet again however, upon refluxing under the Pd-catalysed rearrangement conditions no product formation was observed for any of the substrates.



Scheme 70: Synthesis of ketone precursors, which unfortunately did not undergo the rearrangement process to form morphan product **347**.

3.3.7.3. Nitrile Substituent

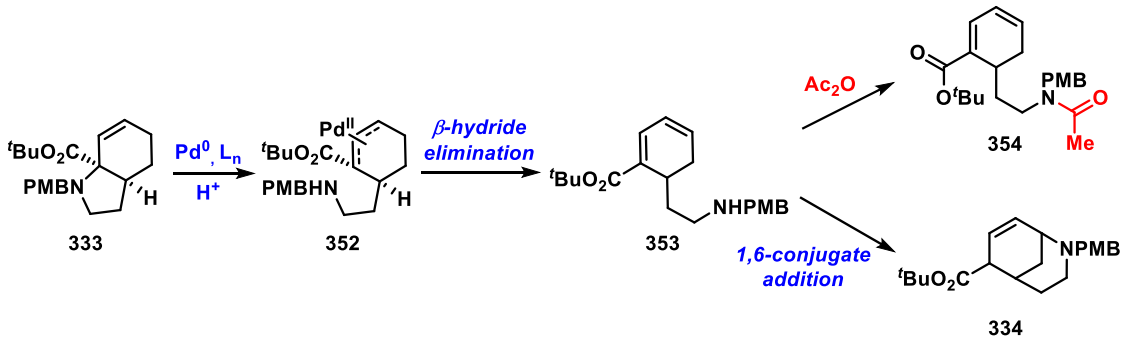
Finally, the nitrile analogue was briefly examined but the precursors for the Pd-catalysed step, PMB **351a** and benzyl **351b** could not be synthesised *via* the reductive amination conditions used previously (Scheme 71). Alkylation of pyrrole-2-carbonitrile led to **349** which again was irradiated to give the aziridine **250**.[196] The [1,5]-hydrogen shift rearrangement gave the imine **350** in 86% yield, but no product formation was observed in the following reductive amination reaction, nor was any starting material recovered, with either *p*-anisaldehyde or benzaldehyde.



Scheme 71: Unsuccessful route to nitrile precursors **351**. The alkylation step and aziridine formation were completed by a previous member of the group.[196]

3.3.8. Mechanistic Studies

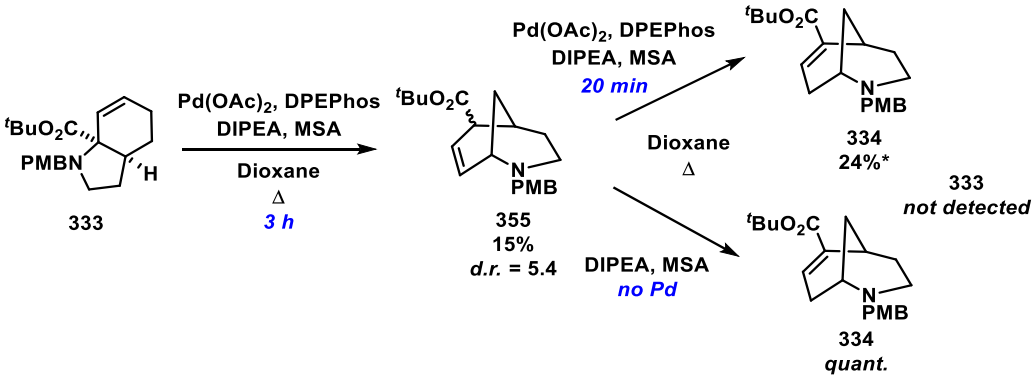
Although the mechanism has already been alluded to (Section 3.3.4.) further mechanistic insight was desired. Completing the reaction with the addition of Ac_2O, resulted in the isolation of the *N*-acetate diene **354**, in an excellent yield of 82% (Scheme 72). This addition thus trapped the intermediate diene, halting the subsequent cyclisation step, giving evidence in support of the proposed *β*-hydride elimination process. In the absence of Ac_2O, hence under standard reaction conditions, intramolecular 1,6-conjugate addition could ensue to generate the morphan product **334**.



Scheme 72: Addition of Ac_2O for nitrogen acetylation and hence trap the diene intermediate **353**.

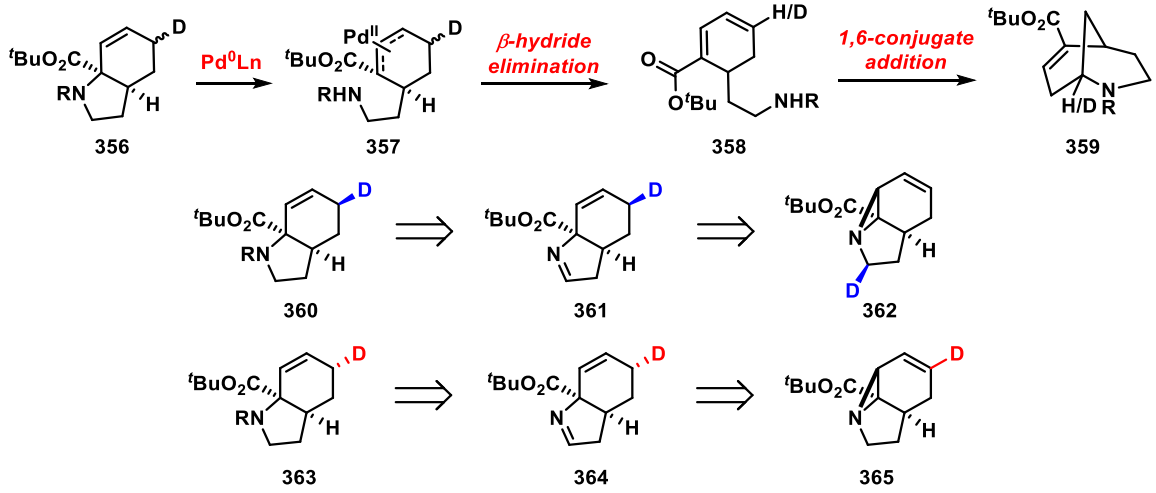
Upon stopping the Pd-catalysed rearrangement before completion, after 3 hours rather than 20 hours, reaction intermediates were observed in the crude ^{1}H-NMR spectrum (Scheme 73). Upon isolating, these were identified as the morphan diastereomers **355**. In agreement with the proposed mechanism for the iodinated substrate, Section 3.3.4., this was rationalised to be formed post-1,6-conjugate addition but prior to the system returning to conjugation. Two reactions of these diastereomers were then carried out: 1) re-subjecting such to the reaction conditions but for a shortened reaction time and 2) refluxing with acid and base (Scheme 73). Experiment 1 was completed to examine if there was an equilibrium

between these intermediates **355** and the starting material **333**, hence the brief reaction time. However, no starting material was observed, only morphan product **334** in a yield of 24%, the remaining were the unreacted diastereomers **355**. Experiment 2 showed that in the absence of palladium the morphan product **334** was formed quantitatively, thereby proving that only acid and base were required to isomerise diastereomers **355** to **334**. Starting material **333** was not detected in this case either.



Scheme 73: Quenching the reaction early led to the isolation of diastereomers **355** which were further subjected to the reaction conditions and acid/base. *Percentage yield determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

In addition to this, isotopic labelling studies were considered. By placing a deuterium label at the allyl position on substrate **356**, the selectivity of the *β*-hydride elimination could be determined (Scheme 74). This would also uncover if there was a kinetic isotope effect (KIE) in operation and hence potentially determine if this step was the rate-determining step. Due to the synthetic route to form precursor **356**, see Section 3.3.1., it was relatively straightforward to both incorporate a deuterium atom at this position and do so with facial selectivity, **360** and **363** (Scheme 74).



Scheme 74: Isotopic labelling studies to determine if *β*-hydride elimination was *endo* or *exo* selective and if there was a KIE in operation. The stereoselective 1,5-hydrogen shift reaction enables the deuterium label to be placed on either face with relative ease. Substrate **360** contains a second, remote deuterium label as a consequence of the synthetic route.

3.3.8.1. Synthetic Route to Deuterium Labelled Substrates

The synthetic route into deuterium substrate **360** began by using a deuterated reducing agent to prepare the di-deuterated alcohol **367** (Scheme 75), which would then undergo the Mitsunobu reaction with trichloroacetyl pyrrole **368** and hence follow the previous synthesis as for the non-labelled precursor (Section 3.3.1.). However, the extremely high cost of $LiAlD_4$ (£2556 for 5 g) which was the reducing agent of choice was prohibitive, and so a range of other alternatives were investigated:

1) $NaBD_4$ could be purchased at a reasonable price but reducing the ester, methyl 3-butenoate **366**, would require an additive or protic solvent to facilitate the reduction (Scheme 75).[197] An example of the latter is using PEG as the solvent, thought to enable complexation to inorganic salts and hence enhance the reactivity of the anion.[198] Although in this instance methyl-3-butenoate **366** was reduced to the alcohol, isomerisation to the internal alkene occurred during the reaction. Similarly, the reduction was also conducted in MeOH,[199] and although did give the desired alcohol product **366**, however due to the volatility of such, not all the residual solvent could be completely removed. As the subsequent step in the synthesis was the Mitsunobu reaction, and any remaining MeOH would be detrimental to the yield, and hence this route was deemed as unviable.

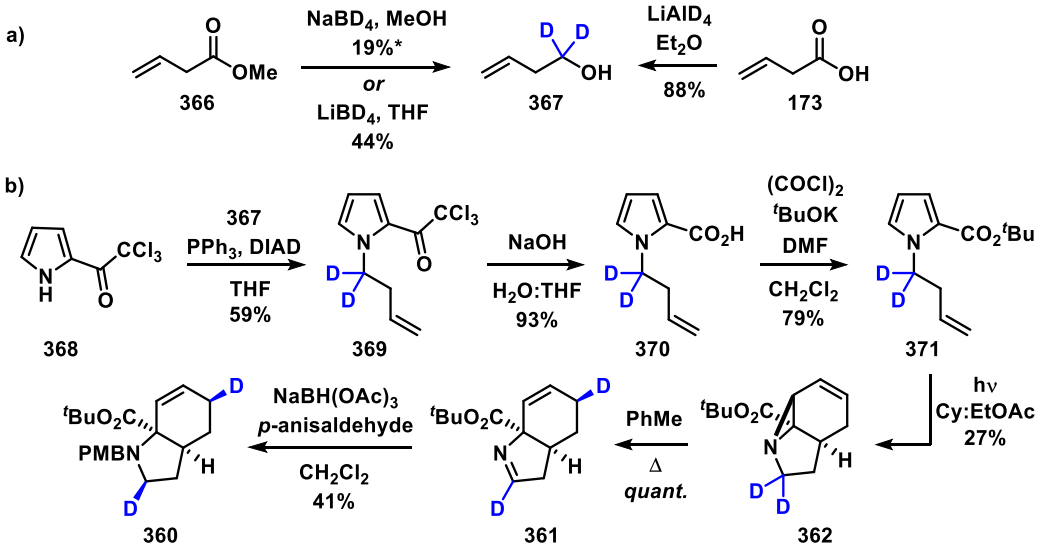
2) $LiBD_4$ is known to reduce esters,[200,201] yet it is not commercially available. Hence synthesis of which was completed by refluxing $NaBD_4$ and LiCl,[202] which was used immediately in the reduction of methyl-3-butenoate **366** (Scheme 75). The deuterated alcohol **367** was obtained, albeit in 44% yield, and due to its volatile nature used without purification in the Mitsunobu reaction. Unfortunately, this did not lead to any of the desired alkylated pyrrole **369**.

3) Lithium tri-*tert*-butoxyaluminum deuteride was also deemed too expensive (£2314 for 1 g of material).

4) DIBAL-D was unavailable to purchase.

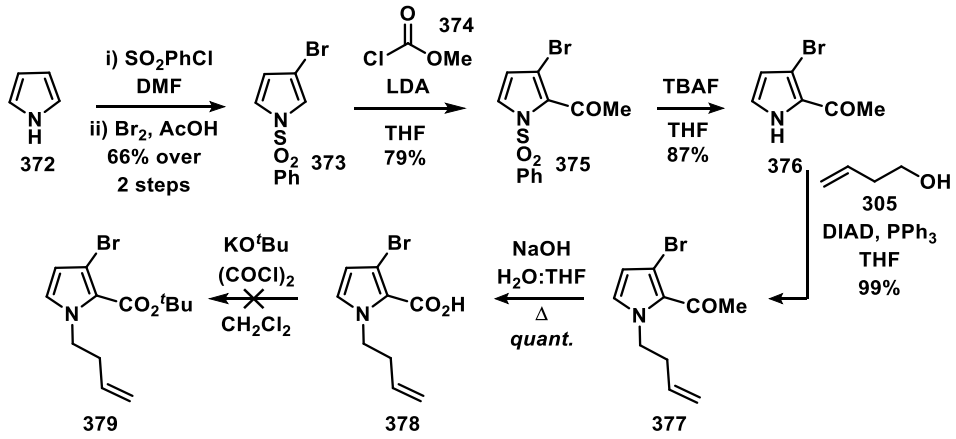
4) Although BD_3 was reasonably priced, due to the requirement of an alkene in the molecule, this route was also unsuitable.

Fortunately, after these unsuccessful studies, a sample of $LiAlD_4$ was discovered which allowed for 3-butenoic acid **173** to be reduced in an excellent yield of 88% (Scheme 75). The remainder of the route was completed as before (Section 3.3.1.).



Scheme 75: a) $LiAlD_4$ was shown to be the superior reducing agent to form deuterated alcohol **367** and b) the remainder of the synthetic route to deuterium labelled substrate **360**. *Yield based on non-deuterated equivalent.

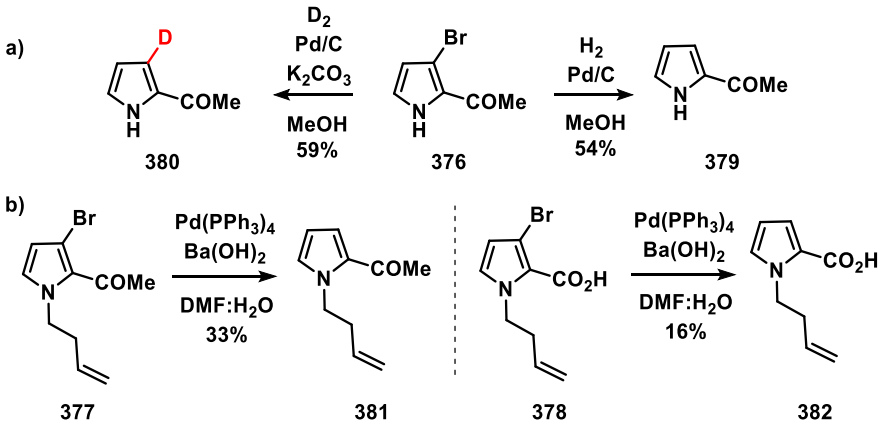
The synthesis of the second deuterium isomer **363** was also not as straightforward as initially thought. For this substrate, the isotopic label needed to be placed at the C3 position of the pyrrole, and this was thought to be incorporated by selectively brominating this position, then either Pd-catalysed dehalogenation or hydrogenation would ensue.[203,204] Pyrrole **372** was hence protected with a bulky phenyl sulfonyl group and bromination at the desired C3 position followed with Br_2 and AcOH (Scheme 76). Directed lithiation at the 2-position with LDA and subsequent trapping with the electrophile methyl chloroformate led to methyl ester **375**, from which sulfonyl deprotection afforded **376** in 87% yield.[205] Again, a Mitsunobu reaction with 3-buten-1-ol and hydrolysis to form the carboxylic acid **378** were completed in excellent yields. Yet the succeeding *tert*-butyl ester formation did not proceed, reasoned to be due to the steric clash with the bromine atom.



Scheme 76: Unsuccessful synthetic route to deuterated pyrrole **379**.

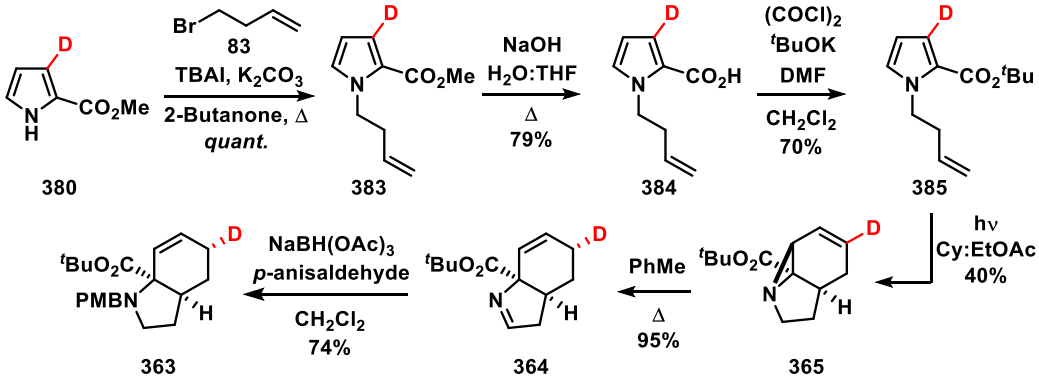
To alleviate such, incorporation of the deuterium atom before this step was investigated on each of the three pyrroles **376**, **377** and **378**, initially with a hydrogen source (Scheme 77). Hydrogenation of

pyrrole **376** led to the desired product **379** in a reasonable yield of 54%.[204] The two alkylated pyrroles **377** and **378** were subjected to cross-coupling conditions, due to the terminal olefin, which gave poor yields of 33% and 16% respectively.[203] Based on these results, the hydrogenation was chosen and so repeated with deuterium. Upon isolation of this crude reaction however, mono-, di- and tri-deuterated pyrroles were observed. During the course of the reaction, DBr was generated as a by-product and so under these acidic conditions, facile H-D exchange occurred on the pyrrole. Inclusion of 1.2 equivalents of K_2CO_3 neutralised the reaction medium and hence only mono-deuterated pyrrole **380** at the C3 position was obtained in a 59% yield.



Scheme 77: a) Hydrogenation and deuteration of pyrrole **376** and b) Pd-catalysed dehalogenation, DMF-d_7 would have been used as the deuterium source if this route was selected.[203]

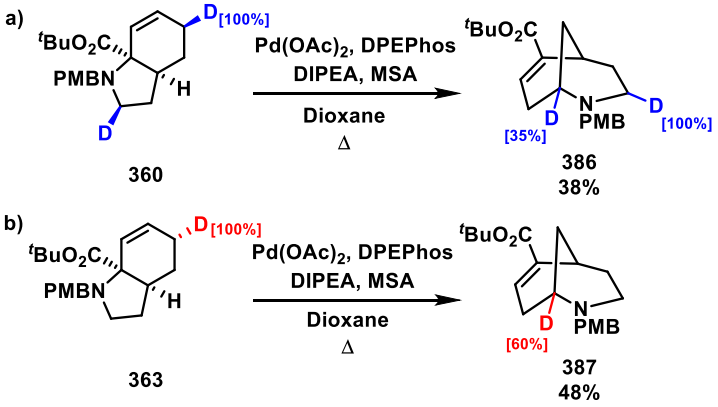
The remainder of the synthesis to precursor **363** was again very similar to previous work, the only major difference was the alkylation step, for which the best yield was obtained *via* an *in situ* Finkelstein reaction and alkylation rather than the Mitsunobu reaction.



Scheme 78: Continuation of the synthetic route to the deuterium labelled substrate **363**.

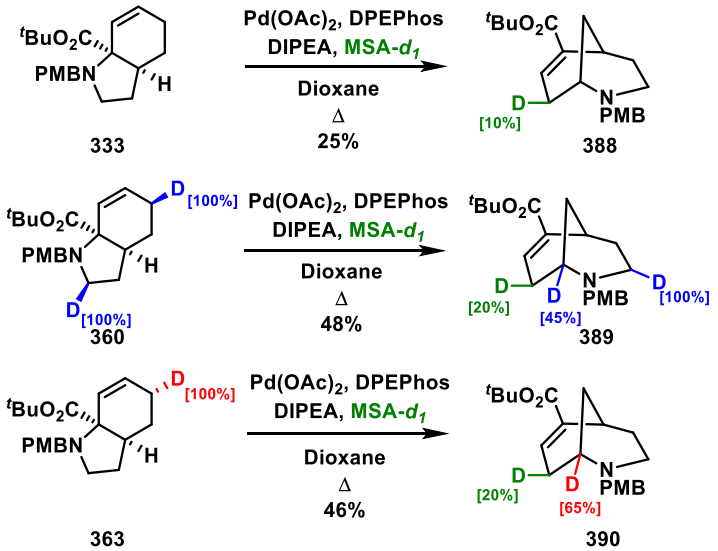
3.3.8.2. Deuterium Labelled Studies

With the two diastereomeric deuterium labelled substrates **360** and **363** in hand, both were individually subjected to the Pd-catalysed reaction conditions (Scheme 79). As previously stated, this was envisaged to conclude which hydrogen underwent *β*-hydride elimination, either that on the *endo* or *exo* face. Surprisingly however a similar level of deuterium labelling within the morphan product was observed in both cases, with the precursor with the deuterium atom on the *exo* face **363** showed a slightly higher level of deuterium incorporation, despite the C-D bond being expected to cleave *via syn β*-hydride elimination.



Scheme 79: Deuterium labelling studies of isomers a) **360** and b) **361**.

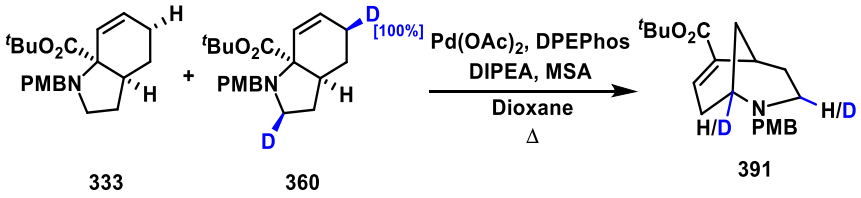
Given the loss of deuteration in both processes, the reactions were performed using deuterated methanesulfonic acid (Scheme 80). This was prepared by hydrolysing methanesulfonic anhydride with D_2O. However, although some deuteration of the *exo* hydrogen at the allylic position was seen, this did not lead to any significant change in the level of deuterium incorporation at the bridgehead on either isomer **389** or **390**. The allylic assignment was determined by ^{1}H-NMR NOE studies, as such hydrogen atoms have separate chemical shifts.



Scheme 80: MSA-d_1 reaction studies.

It is also note-worthy that during these MSA-d_1 studies, an increase in the intermediate diastereomers **355** were observed. This has been reasoned to be due to both the increase in acidity of MSA-d_1 compared to non-deuterated MSA and the stronger bond of O-D versus O-H, hence the observed slower rate of isomerisation to form the morphan product.

A brief investigation of the potential kinetic isotope effect was then performed, *via* an intermolecular competition experiment using an equimolar mixture of the non-deuterated and deuterated compounds **333** and **360** (Figure 29). Stopping the reaction at an early stage allowed the change in level of deuteration of starting material to be determined. As no significant change was observed, it can be deduced that a primary KIE is likely not operating within the catalytic cycle.

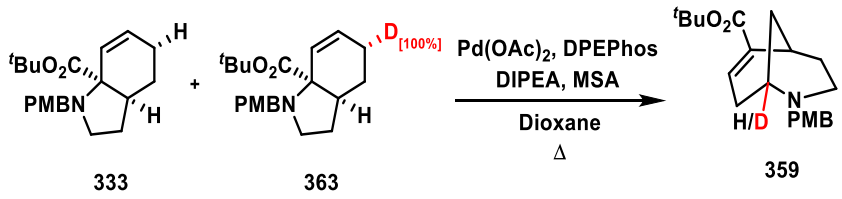


333 360 391

Entry	*Conversion*	H:D SM
1	43%	1:1
2	51%	1:1

Figure 29: Competition experiment of non-labelled and labelled substrates **333** and **360**. Percentage conversion was calculated from a determination of the level of starting material based on the crude ^{1}H-NMR.

In agreement with the first set of results, the competition experiment of the *exo* deuterated compound **363** and non-deuterated compound **333** gave similar levels of deuterated and non-deuterated recovered starting material and morphan product (Figure 30).



333 363 359

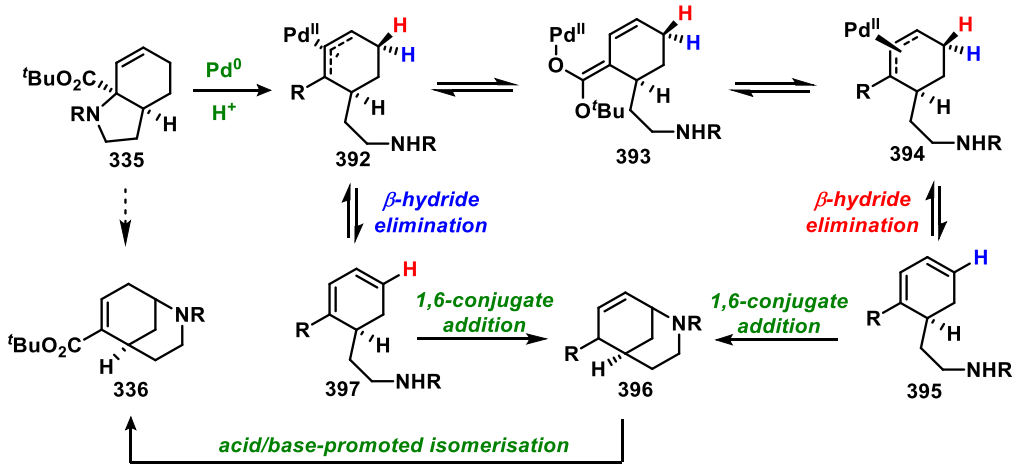
Entry	*Conversion*	H:D SM	H:D Product
1	41%	1:1	1:1
2	78%	1:1	1:1
3	84%	1:1	1:1

Figure 30: Competition experiment of non-labelled and labelled substrates **333** and **363**. Percentage conversion was calculated from a determination of the level of starting material based on the crude ^{1}H-NMR.

Due to the lack of a KIE in operation, it can be concluded from this work that the β-hydride elimination step is not the rate-determining step.[206] KIE values for β-hydride elimination within π-allyl palladium complexes have previously reported as being in the range of 2.2-2.6.[207]

3.3.9. Proposed Mechanism

Based on the experimental evidence acquired, the below mechanism for the Pd-catalysed rearrangement has been proposed (Scheme 81). Initial acid-promoted cleavage of the carbon-nitrogen bond by Pd^0 forms the π-allyl Pd^{II} species **392**, which based on the lack of KIE observed, is turn-over limiting. Due to the similar level of hydrogen and deuterium observed in the morphan products for the deuterated precursors **360** and **363** (Section 3.3.8.2., Scheme 79), this is thought to undergo equilibration between faces, presumably *via* a Pd-enolate **393**.[208,209,210,211,212] Thus, enabling β-hydride elimination to occur from either face, occurring somewhat preferentially from the *endo* face (*i.e.* from complex **394**). The exchange of Pd between either face of the π-allyl complex suggests that this does have a significant lifetime, combined with the absence of an appreciable primary KIE,[206] opens the possibility that this step to form the diene **395** and **397** may be reversible. Such an intermediate diene was isolated by inclusion of the electrophile acetic anhydride, see Section 3.3.8., Scheme 72. Otherwise, this undergoes irreversible 1,6-conjugate addition to form intermediate **396** as a mixture of diastereomers, again which have been isolated by stopping the reaction prematurely (Section 3.3.8., Scheme 73). Related conjugate addition processes have been shown to occur under Pd catalysis.[213] These diastereomers then undergo acid/base promoted isomerisation to the morphan product **336**.

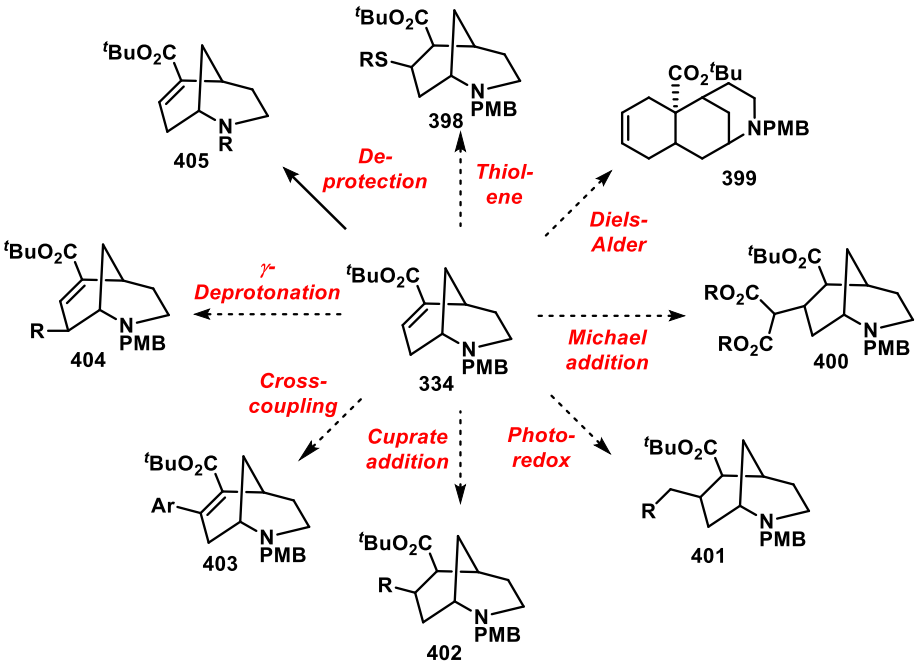


Scheme 81: Proposed mechanism to form the morphan ring system **336**.

3.3.10. Functionalisation of the 2-Azabicyclo[3.3.1]nonane Framework

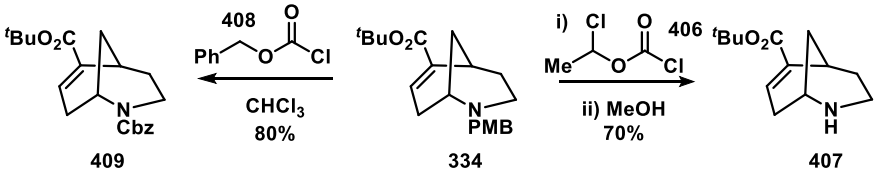
The concluding part of this work focused on derivatising the morphan scaffolds. The molecule has numerous points for further derivatisation, and the reactions below were achieved with varying degrees of success (Scheme 82). Initially a thiol-ene Michael addition reaction was attempted with thiophenol, under neutral, acidic and basic conditions but no product formation was observed. A Diels-Alder reaction with *O*-acetyl diene and the conformationally rigid, cyclopentadiene were also attempted, but even refluxing in PhMe in a sealed tube led to no reaction. Michael addition with NaOMe and dimethyl malonate also returned starting material. Radical decarboxylative 1,4-conjugate addition,[214] mediated by photoredox catalysis was tried but instead of forming the desired carbon-carbon bond, the PMB

protecting group was cleaved. Cuprate addition with the dimethyl Gilman reagent, Heck cross-coupling with aryl iodide and δ-deprotonation and trapping with an aldehyde all proved unsuccessful.



Scheme 82: Attempted reactions of morphan **334** to further functionalise the ring system.

Fortunately, *N*-deprotection with ace-Cl **406**, *via* a quaternary ammonium salt and carbamate followed by hydrolysis, afforded **407** in a 70% yield (Scheme 83). Surprisingly, this PMB group could not be cleaved under more traditional methods such as hydrogenation, oxidation or under strongly acidic conditions. In a similar fashion, the PMB protecting group could be exchanged to the orthogonal CBz group **409**, with benzoyl chloride **408**. Deprotection of such with KOH was however unsuccessful. Cleavage of the *tert*-butyl ester was also attempted but unfortunately was not achieved.

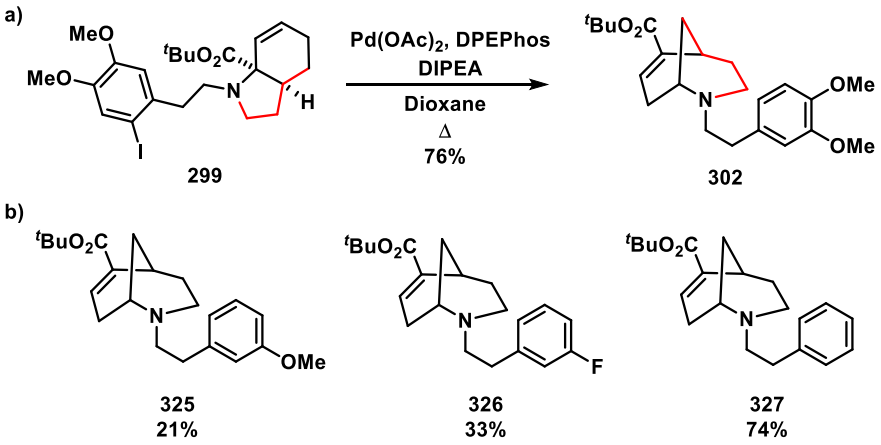


Scheme 83: *N*-deprotection and exchange for the more versatile CBz group.

3.4. Conclusions and Future Work

To conclude, a novel pathway to the medicinally relevant morphan scaffold has been developed and optimised, shown to tolerate a wide-range of nitrogen-substituents. Mechanistic studies demonstrated that the process occurs by acid-assisted carbon-nitrogen bond cleavage followed by *β*-hydride elimination to form a reactive diene, which then undergoes 1,6-conjugate addition to afford the morphan ring-system.

The original dehalogenation-cyclisation reaction was optimised to afford the morphan scaffold **302** in a good yield of 76%. Three other aryl iodide substrates were also converted into the morphan products **325**, **326** and **327** (Scheme 84). It would be preferential however to repeat these studies within the glovebox, as it could be foreseen that some of these yields may improve.



Scheme 84: a) Optimised Pd-catalysed dehalogenation reaction and b) scope of the reaction.

By combining both the aryl iodide **317**, and the non-iodinated molecule, **301**, within the same reaction vessel (Section 3.3.4., Scheme 62), it was realised that the process was not limited to substrates that contained an aryl iodide, and hence other activating agents were investigated. A further screen of such additives revealed the readily available Brønsted acid, methanesulfonic acid, provided the morphan PMB substituted product **334** in the best yield of 70%. This then enabled a scope of the reaction to be completed, where the reaction proved general, giving a wide-range of *N*-substituted morphan scaffolds (Figure 31). Inclusion of the medicinally relevant CF_3 is notable **336x**,[215,216] along with the *N*-methyl morphan **336y** due to its prevalence within natural products (see Scheme 88 for two examples of such). The heteroaromatic systems are also of interest **336j**, **k**, **l**, **m**, **p**, **r**,[10] despite their lower yields, given the importance of this scaffold within medicinal chemistry. [176,177,178,179]

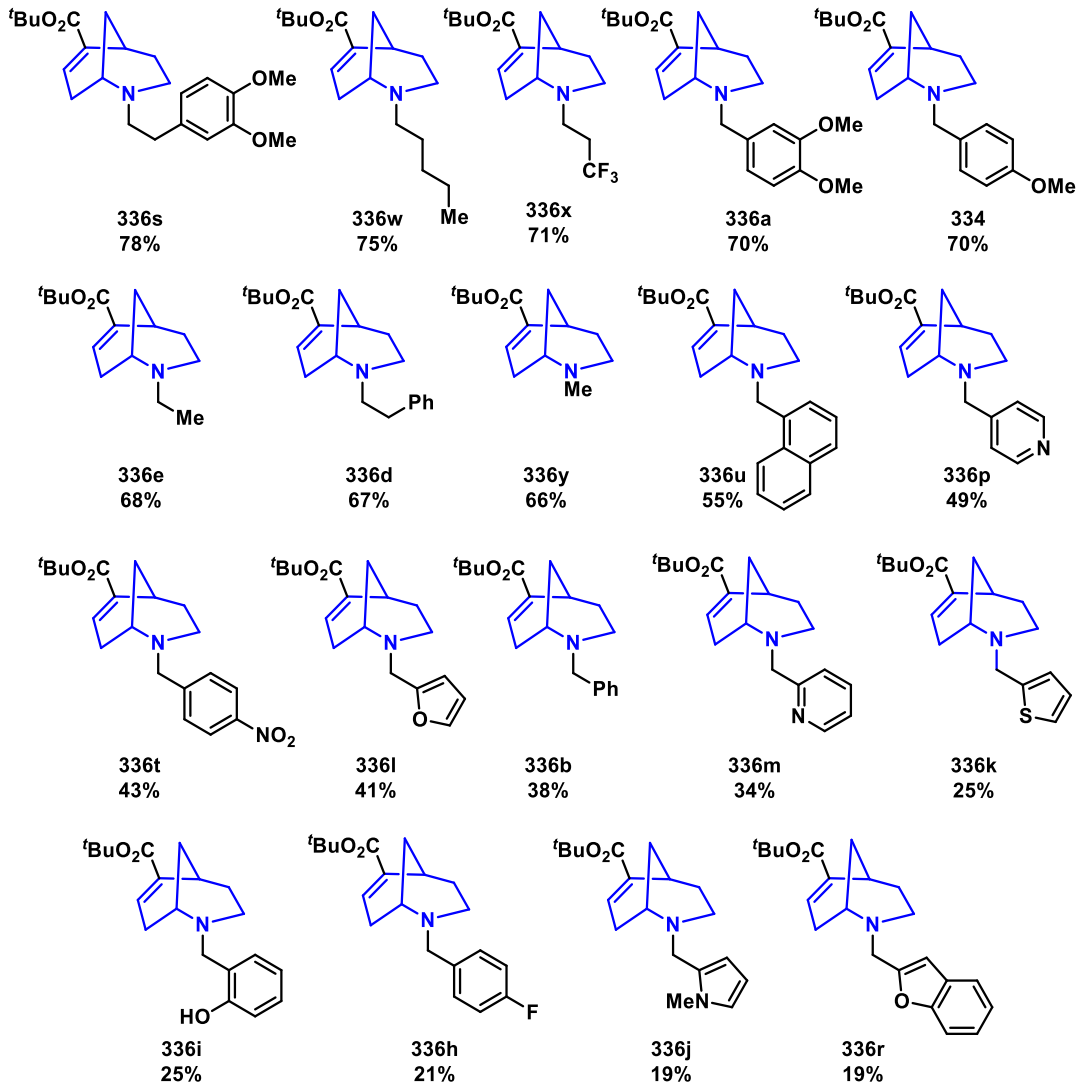
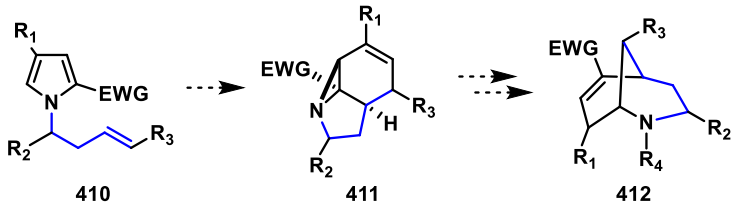


Figure 31: Scope of the Pd-catalysed rearrangement reaction.

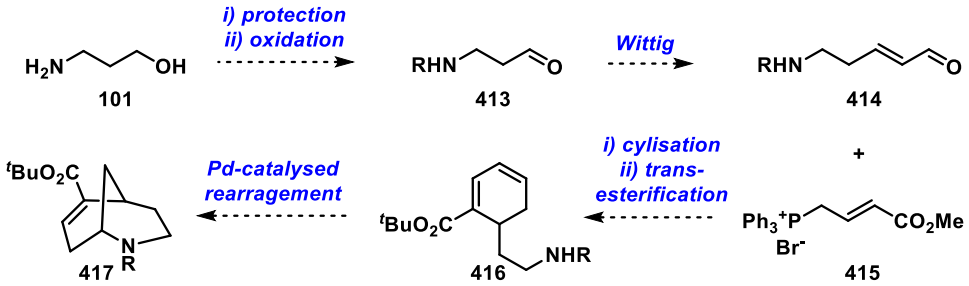
The mechanism of the reaction was also probed, and the results from deuterium labelling studies indicate that several reversible steps are involved, including that of facial equilibration *via* a Pd-enolate species. Two intermediates have also been successfully isolated, suggesting they are both true intermediates within the rearrangement.

Further work should start by continuing the scope of the reaction, however rather than simply changing the tether on nitrogen by the aldehyde in the reductive amination step, altering the substitution pattern of the pyrrole **410** would be beneficial (Scheme 85). Although the amide and methyl ketone did not undergo the rearrangement, other bulky electron-withdrawing groups could be investigated. As further functionalising the morphan product was relatively unsuccessful, including such before the cyclisation would enable diversification of the ring.



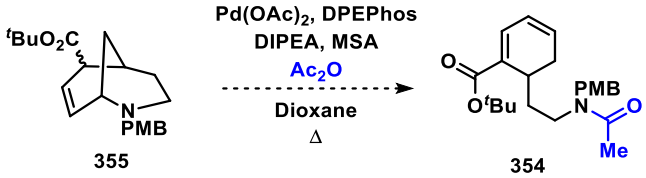
Scheme 85: Expanding the scope by changing the substituents on the starting pyrrole **410**.

Additional studies on the mechanism could also be investigated. Synthesising an analogue of the diene intermediate, rather than trapping as the *N*-acetate **354** as before, would allow for the cyclisation step to be further probed (Scheme 86). Synthesis of which would begin with 3-amino-1-propanol **101**, protection of the nitrogen, then oxidation and sequential Wittig reaction would lead to aldehyde **414**.[217] Similar aldehydes (and ketones) have been shown to undergo a tandem Michael addition/ylide olefination reaction with phosphorous ylides to form functionalised cyclohexadienes.[218] Hence, reaction of aldehyde **414** with ylide **415** and conversion to the *tert*-butyl ester would lead to the model system **416** for cyclisation studies. Simply heating this analogue in dioxane would examine if this step requires Pd to catalyse the 1,6-conjugate addition, for which there are related examples in the literature which do only proceed to cyclise under Pd catalysis.[213]



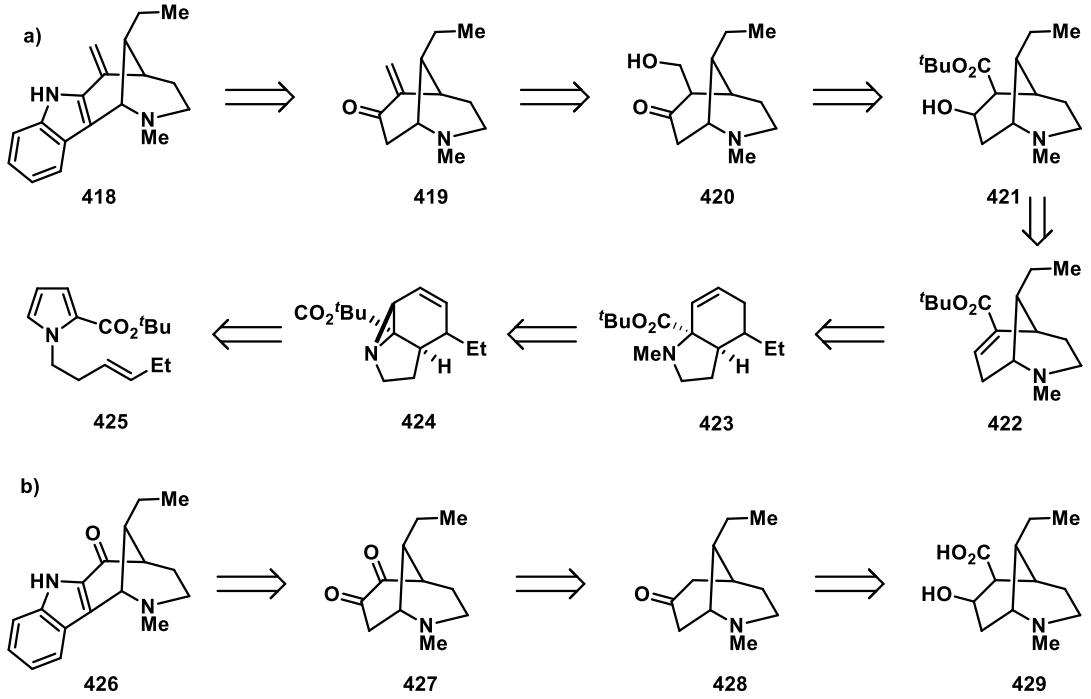
Scheme 86: Synthetic route to intermediate **416**[218] and further studies investigating if the 1,6-addition is Pd-catalysed.

Furthermore, the diastereomers could be subjected to the reaction conditions with the addition acetic anhydride (Scheme 87). Previously, submitting these to the reaction conditions tested if both the initial carbon-nitrogen cleavage step and 1,6-conjugate addition step was reversible. With the addition of Ac_2O, this would only test the latter, if diene **354** was observed, the conjugate addition step would be shown to be reversible.



Scheme 87: Subjecting **355** to the standard reaction conditions with the addition of Ac_2O would investigate if the 1,6-conjugate addition process is reversible.

There is also the opportunity to utilise this methodology within natural product synthesis. As stated earlier, the *N*-methyl morphan scaffold is contained within the two alkaloids (±)-uleine **418** and (±)-dasycarpidone **426** (Scheme 88).[219] A retrosynthetic route to uleine **418** could involve Fischer indole synthesis to return to the key morphan structure **419**, dehydration of **420** to form the terminal olefin, selective oxidation of the secondary alcohol **421** and reduction of the *tert*-butyl ester. The Pd-catalysed rearrangement would begin from bicycle **423**, again stemming from the pyrrole **425**, this time with the ethyl substituent on the end of the alkene. Dasycarpidone similarly would involve Fischer indole synthesis, this time from the diketone **427**. This would be generated *via* α-hydroxylation of **428** and subsequent oxidation, post-oxidation and decarboxylation of **429**. This would stem from the common intermediate **421**.



Scheme 88: Potential route to lead to natural products a) (±)-uleine **418** and b) (±)-dasycarpidone **426** *via* the Pd-catalysed rearrangement methodology.

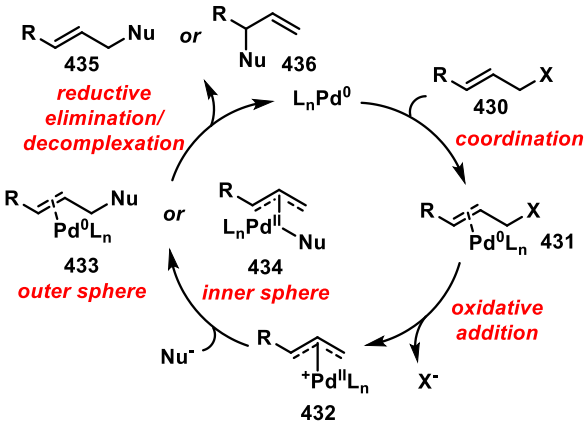
Methodologies to gain rapid access into sp^3-rich heterocycles remains a modern synthetic challenge,[5] and this process has not only exemplified such, but by also exploiting what are often viewed as side reactions within Pd catalysis has led to the discovery of a novel rearrangement process into the privileged morphan scaffold.[162,171]

4. The Diverted Tsuji-Trost/Tsuji-Trost/Diels-Alder Sequence into Complex Tetracyclic Amines

4.1. Introduction

4.1.1. The Tsuji-Trost Allylation

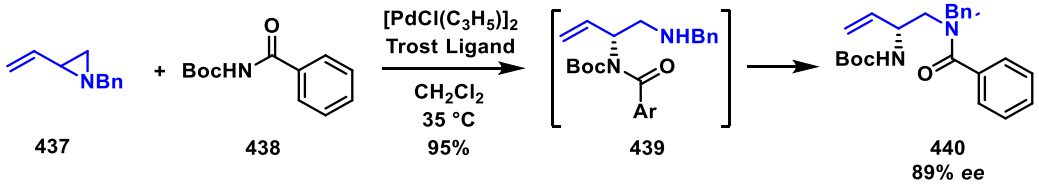
The Tsuji-Trost reaction is the palladium catalysed allylation of a nucleophile (Scheme 89). Developed independently in the late 1960s and early 1970s, Tsuji and Trost demonstrated a key carbon-carbon bond forming methodology,[220,221] which has since been expanded to carbon-heteroatom and enantioselective variants.[222,223] As the reaction typically connects fragments *via* sp^3 hybridised centres, inherently there is the potential to achieve more three-dimensional structures and the importance of such was highlighted in Section 1.1. The reaction essentially uses the olefin as an activator of an adjacent C-X bond and upon treatment of a Pd^0 source, forms a η^2-π-allyl species **431** (Scheme 89). Oxidative addition follows, expelling the leaving group resulting in a η^3-π-allyl complex **432**, a reactive carbon electrophile. At this point, the reaction mechanism can go *via* two alternative pathways, largely controlled by the basicity of the nucleophile. Soft nucleophiles, defined as those derived from conjugate acids with $pK_a < 25$,[222] generally attack the allyl moiety directly, outside the coordination sphere of the metal **433**, and successive decomplexation affords the allylated product **435** or **436**. On the other hand, hard nucleophiles, those derived from conjugate acids with $pK_a > 25$,[222] initially attack the metal centre **434**, and subsequent reductive elimination gives the product. Of which, it is generally the linear product **435** that is observed, with nucleophilic attack being more favourable at the less hindered, terminal position.[224] The regioselectivity can however be reversed to give the branched product **436**, through design of substrates, reagents and catalyst systems.[224]



Scheme 89: Catalytic cycle for the Tsuji-Trost allylation reaction.[225]

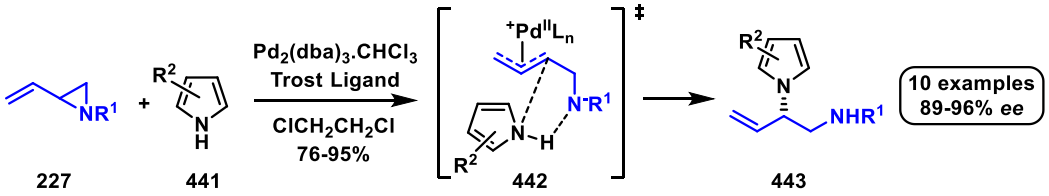
Surprisingly, there are limited examples of using vinyl aziridines in such Pd-catalysed allylic alkylations within the literature, although their epoxide analogues are far more prevalent.[226,227] In 2007 Trost *et al.* did expand their asymmetric addition work to such aziridines **437**, using imido-carboxylates **438** as

nucleophiles (Scheme 90).[228] An *in situ* migration of the acyl group occurred, giving chiral vicinal diamines **440** in good yields and excellent enantioselectivities. The branched regioselectivity was rationalised to be due to both hydrogen bonding, between the NH of the imide nucleophile and the amine of the η^3-π-allyl intermediate, and the directing effect of the ligand.



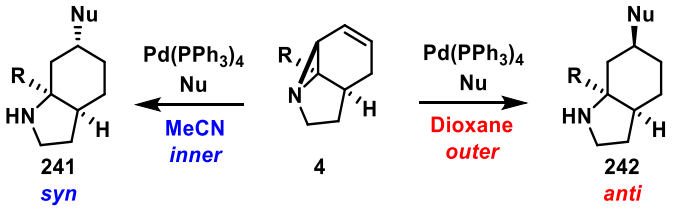
Scheme 90: Enantioselctive Tsuji-Trost reaction with vinyl aziridines **437** and benzoyl imido carboxylates **438** *via* the *in situ* migration of the benzoyl group.[228]

The group further expanded upon this methodology in 2010, this time using nitrogen heterocycles, indoles and pyrroles as the nucleophilic species (Scheme 91).[229] Again, the reaction was shown to be highly chemo-, regio- and enantioselective, affording *N*-alkylated products **443**. Similarly, the observed branched regioisomer was due to the vinyl aziridine anion directing the nucleophile by hydrogen bonding interactions, thus attacking through a five-membered transition state, as opposed to the linear product which would go *via* an unfavourable seven-membered transition state.



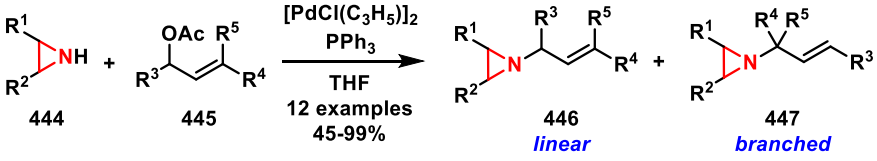
Scheme 91: Tsuji-Trost reaction giving chiral 1,2-diamines **443** with rationale for observed regiochemistry.[229]

As briefly mentioned in Section 3.1.3. the Booker-Milburn group subjected their photochemically generated tricyclic aziridines to Tsuji-Trost conditions for which the ratio of *syn* to *anti* allylated products could be switched based on the solvent used (Scheme 92).[139] This was likely due to a change in mechanism from outer sphere to inner sphere.[230] As stated at the beginning of this section, usually this is dependent on the pK_a of the nucleophile. In this case, it would appear that due to the decreasing stability of the anionic form of the nucleophile in more polar solvents, it attacks the metal centre, leading to overall inversion and the *syn* product **241**. In less polar solvents, the nucleophile attacks the η^3-π-allyl complex directly, thus retaining the configuration.



Scheme 92: Controlling the stereochemical outcome of the Tsuji-Trost reaction by solvent selection. The *syn* product **241** is obtained in polar solvents *via* an inner sphere mechanism, the *anti*-product **242** in non-polar solvents *via* an outer sphere mechanism.

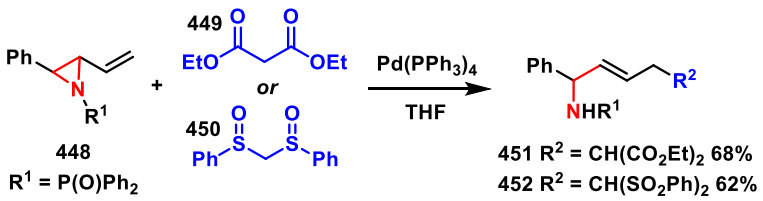
In contrast to the proceeding work reported thus far, in 2004 Yudin *et al.*, a notable contributor to the field of aziridine chemistry,[231,232,233,234] detailed the unusual behaviour of unprotected aziridines, undergoing Pd-catalysed allylic aminations to afford tertiary aziridine products.[235] Interestingly, rather than undergoing ring-opening, such aziridines were themselves acting as the nucleophilic species (Scheme 93). The reaction was shown to be extremely facile with allyl acetates **445**, affording the biologically active allylamine functionality in good to excellent yields.[236,237] The reaction could also be used to prepare enantiomerically enriched aziridines, by using a chiral ligand. The *N*-allyl aziridine products were then transformed into functionalised branched amines by using well-established ring-opening protocols, further highlighting their dual nucleophilic/electrophilic functionality.[235] The group additionally completed detailed mechanistic studies into the observed regioselectivity of the reaction, where the valuable branched products **447** were favoured in the case of aliphatic allyl acetates.[238] This selectively is opposite to that observed when other amines are used as nucleophiles, reasoned to be due to the allyl aziridines being more stable towards Pd-catalysed isomerisation due to their higher degree of s-character (branched amines undergo isomerisation to the thermodynamic linear product).[238]



Scheme 93: Synthesis of *N*-allyl aziridines **446** and **447** by Pd-catalysed allylic amination.[235]

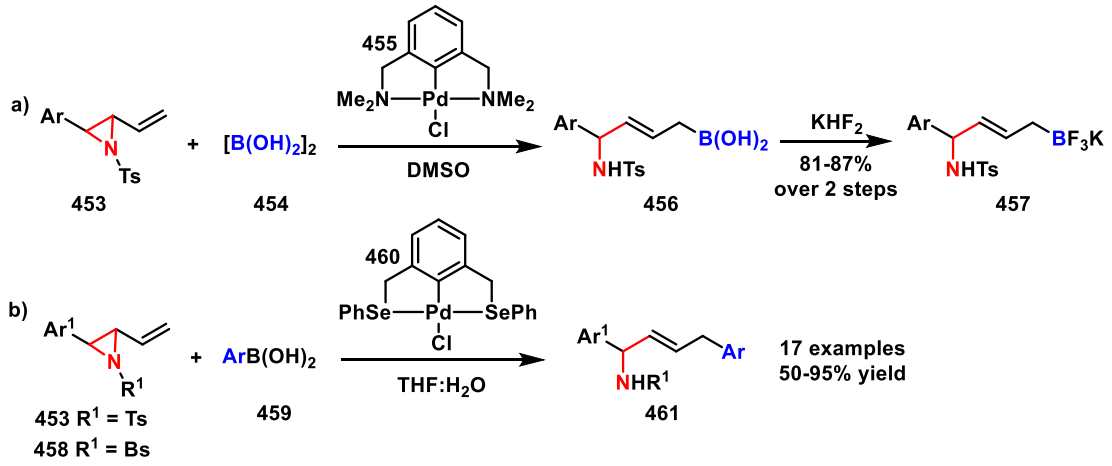
4.1.2. Pd-Catalysed Ring-Openings of Vinyl Aziridines

In the previous chapter ring-opening reactions of vinyl aziridines were discussed, see Section 3.1.3. Herein a few examples of those specifically catalysed by the Pd metal will be noted, as such are of relevance to this chapter. Pioneering work in this field was initially reported by Sweeney and co-workers in 1996.[134,239] The paper consisted of numerous examples of S_N2' ring-opening reactions of vinyl aziridines with organocuprates. Two additional examples, almost anomalies within the paper, used catalytic $Pd(PPh_3)_4$ in the presence of diethyl malonate **449** or bis(phenylsulfonyl)methane **450** to afford the allylic amines **451** and **452** regioselectively (Scheme 94).



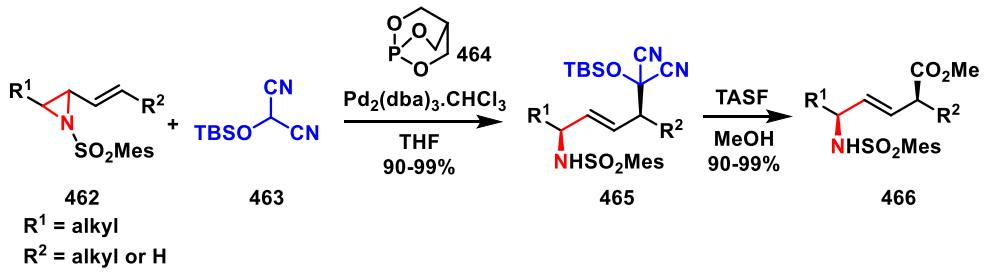
Scheme 94: Preliminary Pd^0-catalysed ring-opening of vinyl aziridines **448** by Sweeney *et al*.[134]

Szabó used the pincer complex catalyst **455** to readily synthesise functionalised allyl boronic acids from vinyl aziridines **453** and tetrahydroxydiboron **454** (Scheme 95).[240] Such pincer catalyst species were shown to be superior, both in activity and selectivity, compared to more conventional Pd^0 sources in the boronate transfer reaction. Due to the instability of the boronic acid products, they were quickly converted to potassium trifluoroborate derivatives **457**, which remain highly useful synthetic precursors.[241] The reactions were shown to proceed under mild conditions, tolerating several different functional groups and proceeding in excellent regioselectivity. The mechanism was believed to begin with formation of a boronate-coordinated pincer complex intermediate and subsequent transfer of the $B(OH)_2$ from the metal to the substrate. The group further expanded this methodology, showing such pincer complexes **460** catalyse cross-coupling reaction of vinyl aziridines **453** and **458** with organoboronic acids **459** to afford the ring-opened allyl amine products **461** (Scheme 95).[242]



Scheme 95: Pincer complex catalysed synthesis of a) allylborates **456**[240] and b) allylamines **461**.[242]

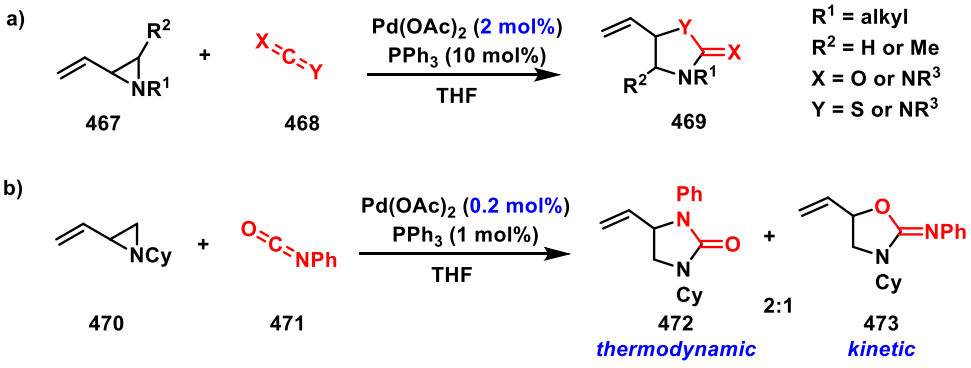
A more recent example is from the Nemoto group, whereby a highly regio- and stereoselective carbon-carbon bond formation of vinyl aziridines with a masked acyl cyanide reagent **463**, in the presence of catalytic Pd is reported (Scheme 96).[242] The reactions proceeded *via* a double inversion mechanism through a η^3-π-allyl palladium species. The nitrile products **465** were readily transformed to the corresponding methyl esters **466** using tris(dimethylamino)sulfonium difluorotrimethylsilicate.



Scheme 96: Regio- and stereoselective ring-opening of vinyl aziridines **462** with a masked acyl anion **463**.[242]

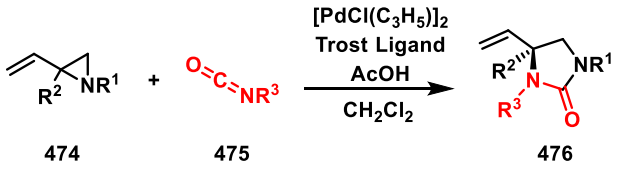
4.1.3. Pd-Catalysed Annulations of Vinyl Aziridines

As noted with Tsuji-Trost allylations, Pd-catalysed annulations of vinyl epoxides are far more common within the literature than with their aziridine analogues.[243,244,245] In 2000 however, Alper *et al.* expanded their Pd-catalysed cycloaddition methodology to such systems, affording five-membered heterocycles **469**, **472** and **473** (Scheme 97).[246] Treatment of the vinyl aziridines and the heterocumulenes, either isocyanates, isothiocyanates or carbodiimides, to $Pd(OAc)_2$ and PPh_3, afforded the imidazolidinone, imidazolidinethione or imidazolidineimine products **469**, in 34-97% yields. Rapid reaction times of 2 hours were reported for the isocyanate systems, but prolonged times of 20 hours were required for the isothiocyanates and carbodiimides, reasoned to be due to the comparatively reduced nucleophilicity of the sulphur and nitrogen atoms. Studies of the catalyst loading with isocyanates **471** revealed that lower concentrations of Pd formed inseparable mixtures of two structural isomers, both the cyclic urea **472** and imidate **473** (Scheme 97). The latter *O*-alkylated product was shown to isomerise under the reaction conditions to the desired thermodynamically product, the urea, and so avoidance of such could be achieved through sufficient catalyst quantities.



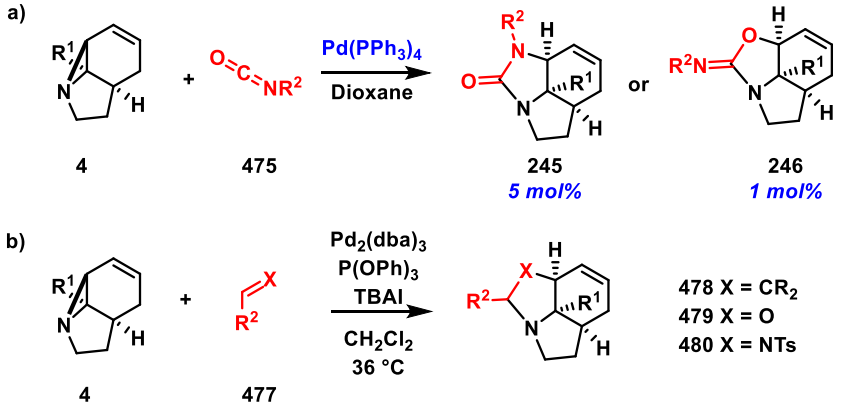
Scheme 97: a) Alper's Pd-catalysed [3+2]-cycloadditions of vinyl aziridines **467** with a range of heterocumulenes **468** and b) lowering the catalyst loading afforded a mixture of urea **472** and imidate **473** products.[246]

This work was further expanded upon by Trost *et al.* in 2003,[247] whereby the first asymmetric cycloaddition of isocyanates **475** to vinyl aziridines **474** was shown (Scheme 98). Utilising dynamic asymmetric transformations, the cyclic urea **476** could be generated in yields of up to 99% with an *ee* of 95%.



Scheme 98: Dynamic kinetic asymmetric cycloadditions of isocyanates **475** to vinyl aziridines **474** to afford cyclic ureas **476** by Trost.[247]

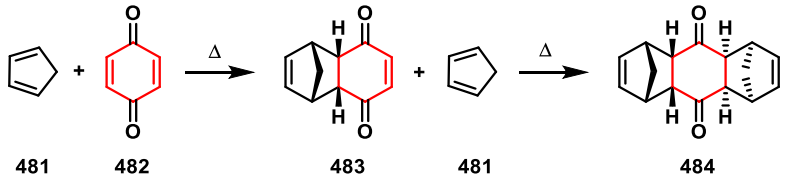
As briefly stated in Section 3.1.3., the Booker-Milburn group also developed this ring-opening, cycloaddition methodology with their photochemical tricyclic aziridines **239** as substrates (Scheme 99).[139] Under Pd^0 catalysis, a range of aryl and sulfonyl isocyanates gave the tricyclic urea products **245** in good to excellent yields. Similarly, as Alper observed,[246] when the catalyst loading was reduced, the cyclic imidates **246** were favoured, and in this case exclusively isolated. The cycloadditions were also shown to proceed with specific alkenes such as benzylidine malonitrile to afford pyrrolidines **478**. A range of aldehydes also underwent the [3+2] catalysed cycloadditions giving several oxazolidine products **479**. Finally, the group showed a novel mode of addition to vinyl aziridines, *via* a ring-opening and cyclisation with *N*-tosyl imines, accessing functionalised aminals **480**.



Scheme 99: Booker-Milburn *et al.* elaboration of Pd-catalysed cycloadditions of tricyclic aziridines **239**, forming a) ureas **245** and imidates **246** and b) pyrrolidines **478**, oxazolidines **479** and aminals **480**.[229]

4.1.4. The Diels-Alder Reaction

The most famous pericyclic reaction is undoubtedly the Diels-Alder reaction. Discovered by, as the name would suggest, Diels and Alder in 1928,[248] the cycloaddition between a conjugated diene **481** and dienophile **482** has truly transformed organic synthesis (Scheme 100).[249] As such the pair were awarded the Nobel prize in 1950 and although this was 70 years ago,[250] the reaction remains a fundamental transformation to generate six-membered rings. The stereo- and regioselective [4+2] cycloaddition can form up to four stereogenic centres in a single step, readily increasing molecular complexity, often by simply heating. This powerful reaction is certainly one of the most efficient and atom economical routes to synthesise highly functionalised six-membered rings.



Scheme 100: The discovery of the Diels-Alder reaction, whereby the products **483** and **484** were identified by Diels and Alder.[248]

As the Diels-Alder reaction is a pericyclic reaction, it hence proceeds in one-step without the formation of any intermediates. Such reactions are tightly controlled by orbitals, and the reaction proceeds due to the alignment in symmetry of the LUMO of the dienophile and the HOMO of the diene (Figure 32).[251] Notably if an electron-withdrawing group is placed on the dienophile, an activated dienophile, the LUMO is lowered in energy and as such, the two overlapping orbitals are closer in energy, hence making the reaction more favourable. The same principal applies for an electron-donating substituent on the HOMO of the diene, which would then be raised in energy. This is classified as a 'normal electron demand' Diels-Alder- if the cycloaddition was principally controlled by the energy gap separating the LUMO-HOMO between an electron-deficient diene and an electron-rich dienophile, then it would be termed 'inverse electron demand'.[252]

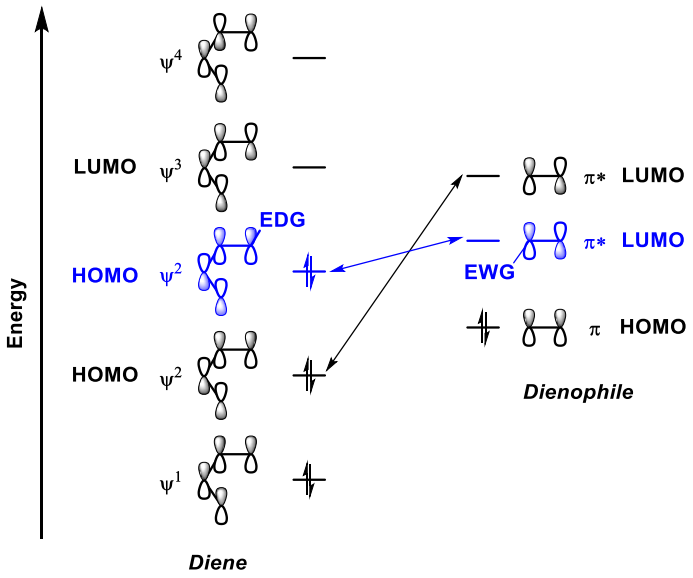
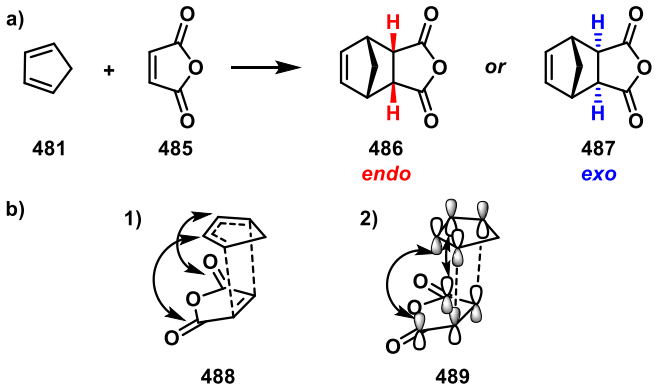


Figure 32: Molecular orbital diagram for the Diels-Alder reaction of a diene and a dienophile. Note the lowering and raising of energy with the addition of an electron-poor and electron-rich substituent, minimising the energy gap, shown in blue.[251]

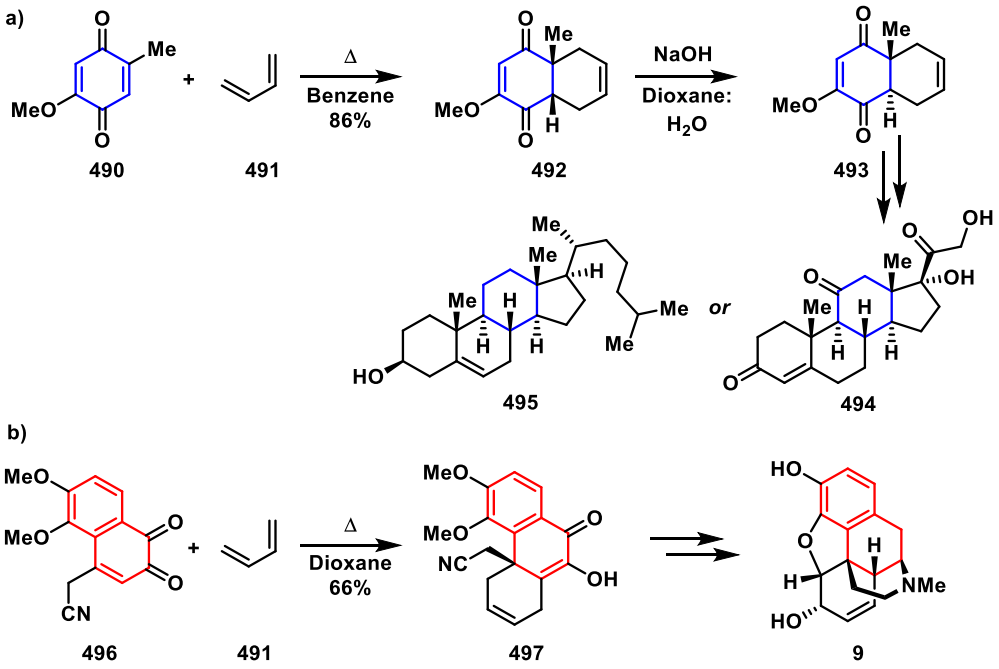
When predicting the stereochemistry of the Diels-Alder reaction, there are two ways in which the reactants can approach one another, leading to either the *endo* **486** or *exo* product **487** (Scheme 101). For the reaction of cyclopentadiene **481** and maleic anhydride **485**, it is the *endo* product **486** that is formed, even though there is more steric hinderance compared to the *exo* alternative **487** (Scheme 101).[251] This is the kinetic product, and its formation is due to two reasons: 1) there is a secondary

orbital interaction between the electron-deficient carbonyl groups of the dienophile and the π system of the diene, which lowers the energy of the transition state **488** and 2) the symmetry of the orbitals at the back of the diene are correct for a bonding interaction **489**, which although does not lead to the formation of a new bond, it does guide the reaction.[251] This has become known as the '*endo* rule'.



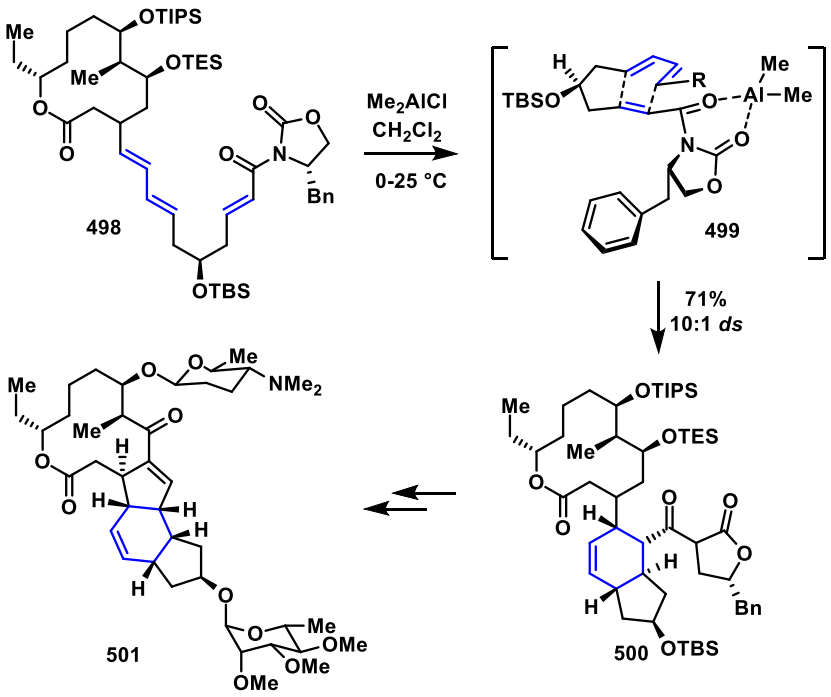
Scheme 101: a) Two possible diastereomers, the *endo* product **486** and the *exo* product **487** and b) *endo* selectivity observed due to 1) the bonding interactions in the transition state between C=O groups and back of diene **488** and 2) the secondary orbital overlap **489**.[251]

The Diels-Alder reaction has seen significant use in natural product synthesis,[253,254,255,256] one of the earliest examples is the total synthesis of the steroid hormones cortisone **494** and cholesterol **495**, completed by Woodward *et al.* in 1952 (Scheme 102).[257] The regioselectivity of the pericyclic reaction was controlled by installation of a methyl versus a methoxy substituent on the quinone nucleus **490**. Sequential base epimerisation led to the desired *trans* fused ring junction. Gates and group also used the Diels-Alder reaction as a key step in the first total synthesis of morphine **9** in 1956 (Scheme 102).[258] The reaction was implemented early in the synthetic route to generate the core of the alkaloid. Notably these early examples were still twenty years post-reaction discovery, the delay reasoned to be due to World War II.[253] However, since the 1950s the Diels-Alder cycloaddition has enabled, shaped, and dominated total synthesis.[253,259,260]



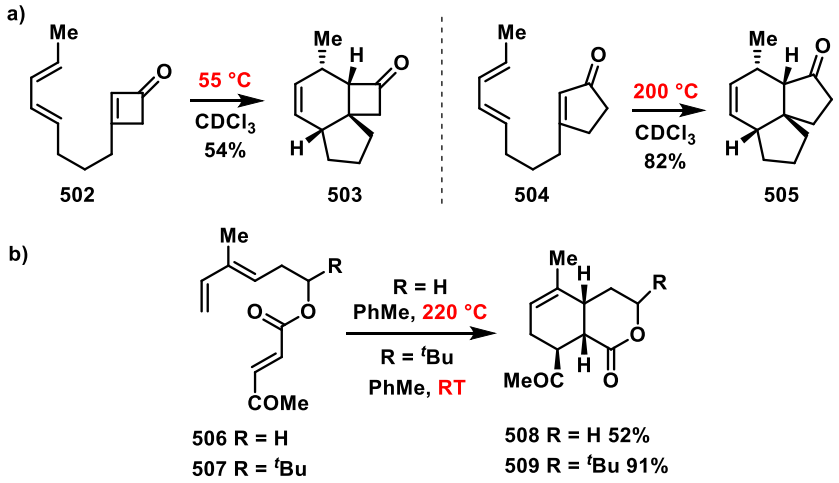
Scheme 102: The Diels-Alder reaction in the total synthesis of a) cortisone **494**, cholesterol **495** [257] and b) morphine **9**.[258]

There have been numerous developments to the reaction including hetero,[261,262] intramolecular,[259,260,263] Lewis-acid catalysed[264] and asymmetric Diels-Alder variants.[265,266] An example of the latter of these approaches can be found in Evans' total synthesis of (+)-lepicidin **501** (Scheme 103).[267] Using the Evans' chiral auxiliary installed on the intermediate **498**, the Lewis-acid mediated intramolecular Diels-Alder (IMDA) afforded the cyclised *endo* adduct **500** in a stereocontrolled 71% yield. The Lewis acid, Me_2AlCl, coordinated to both the carbonyl groups, aligning the dienophile in which the lowest energy conformation ensured the diene approached on the opposite face from the benzyl group **499**, resulting in the observed *endo* selectivity.



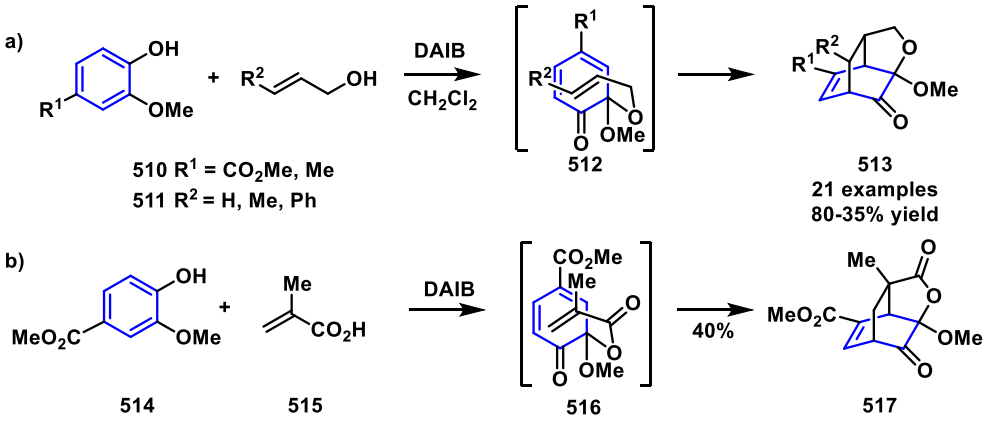
Scheme 103: Evan's stereocontrolled route to (+)-lepicidin A **501** using both a chiral auxiliary and a Lewis-acid for the IMDA.[267]

In general, most uncatalysed IMDA reactions require moderately forcing conditions to proceed,[268,269] unless they are conformationally restrained to begin with. For instance, Danishefsky *et al.* described, for the first time, the use of cyclobutenone **502** as a dienophile within an IMDA reaction, and it was shown to be far more reactive than its analogous, larger cycloalkenone dienophiles **504** (Scheme 104).[270,271] The four membered dienophile **502** underwent the [4+2] cycloaddition at 55 °C, whereas the corresponding five-membered system **504** required temperatures of 200 °C to proceed. Similarly, Kurth and co-workers noted that if a bulky substituent was placed on the starting decatrienoate **507**, the IMDA would occur at room temperature (Scheme 104).[272] Without the *tert*-butyl activating group, the reaction required a temperature of 220 °C in a sealed tube to reach completion.



Scheme 104: a) Danishefsky's observation that the cyclobutenone **502** was more reactive than the corresponding **504**[270] and b) addition of the ^{t}Bu group was shown to be a powerful IMDA activator.[272] Note **505** was the major product, *endo*:*exo* selectivity was 3.6:1 and **508** the major product, where *endo*:*exo* ratio was 6:4.

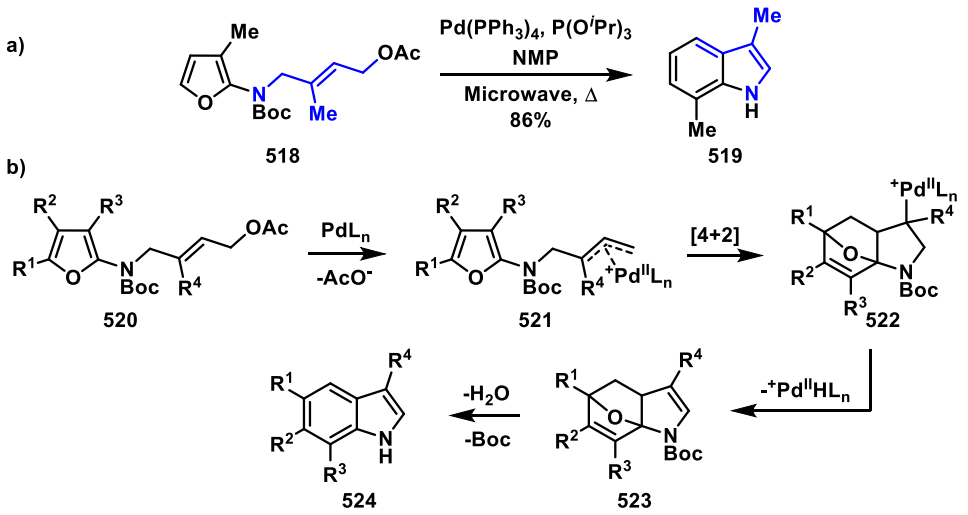
There have also been several reports of Diels-Alder reactions being used within a cascade process.[273,274] As the name suggests, such tandem, or domino, processes generate molecules of high complexity in a rapid and efficient manner.[275,276] An example of such by the Liao group used a tandem oxidative acetalization/intermolecular Diels-Alder reaction to synthesise bicyclo[2.2.2]octenone derivatives **513** (Scheme 105).[277] Oxidising analogues of 2-methoxyphenol **510** with (diacetoxy)iodobenzene in the presence of an allyl alcohol **511** resulted in the *in situ* formation of the masked *o*-benzoquinone **512**, which rapidly underwent an IMDA cyclisation at room temperature to form the tricyclic compound **513**. Replacing the alkenol **511** with alkenoic acid **515** also successfully underwent the domino reaction, furnishing the desired lactone **517** in a moderate yield of 40%.



Scheme 105: Liao *et al.*'s tandem synthesis of oxidation and IMDA to afford **513** and **517**.

A further example of an IMDA reaction within a tandem sequence is in the synthesis of indoles by Wipf and co-workers (Scheme 106).[278] Although affording a relatively straightforward product, an indole **519**, the mechanism under which they were generated is unusual. Commencing with a tethered allylic

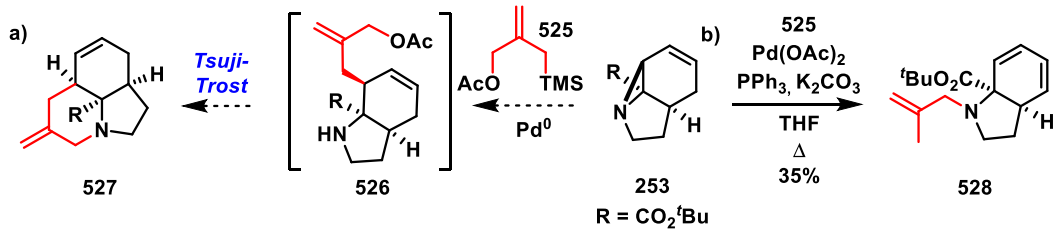
acetate on a furan **520**, a Pd-π-allyl complex **521** is formed which initiates the [4+2] cyclisation. Expulsion of H_2O and cleavage of the Boc group follows which gives the indole product **524**. This convergent process was shown to proceed in moderate to good yields with a relatively wide scope extending to 5-, 6- and 7-substituted indoles earing alkyl, alkenyl, aryl and heteroatom functionalised side chains.



Scheme 106: a) Indole synthesis by Pd-catalysed tandem allylic isomerisation/Diels-Alder reaction and b) possible reaction mechanism.[278]

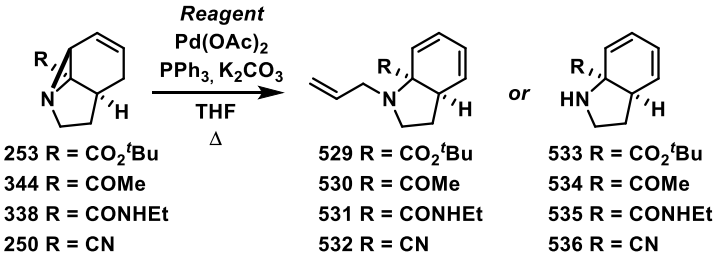
4.1.5. Previous Preliminary Studies

In an attempt to continue the Pd-catalysed [3+2] annulation work (Section 4.1.3.),[139] it was hoped that this methodology could be expanded to synthesise analogous six-membered rings such as **527** (Scheme 107). Using the dual functionality of TMS allyl acetate **525**, designed to act as both a nucleophilic and electrophilic source, initial nucleophilic ring-opening under Pd catalysis, and subsequent Tsuji-Trost of the aziridine, would furnish the all carbon ring **527**. However, reaction of tricyclic aziridine **253** with **525** afforded the 2,3,8,9-tetrhydroindole **528**, where apparent β-hydride elimination to form the diene and desilyation of the allyl component had occurred. This process was viewed as a diverted Tsuji-Trost reaction, forming the diene, followed by a conventional Tsuji-Trost reaction to form the carbon-nitrogen bond. Although not the desired outcome, due to dienes themselves being versatile intermediates (see Section 3.1.5. for further elaboration of this) more detailed studies on understanding the apparent change in mechanism was sought.



Scheme 107: a) Planned nucleophilic ring-opening and Tsuji-Trost allylation to tricyclic species **527** and b) the observed reaction forming diene **528**.[184]

Replacement of the TMS reagent **525** with allyl acetate afforded the *N*-alkylated diene product **529** in a much-improved yield of 87% (Figure 33, Entry 1). The ketone and amide aziridines **344** and **338** also underwent the ring-opening and elimination sequence successfully, albeit in slightly lower yields (Entries 2 and 3). The reaction could also be completed without any alkylating agent, affording the NH diene products (Entries 5-8). The nitrile aziridine **250** unfortunately did not undergo the sequence, instead gave the imine *via* the 1,5-hydrogen shift reaction (Entries 4 and 8, see Section 3.1.3.).[142] This was reasoned to be due to its lack of steric bulk compared to the other electron-withdrawing groups used, which likely reduces the reactivity of the aziridine ring.

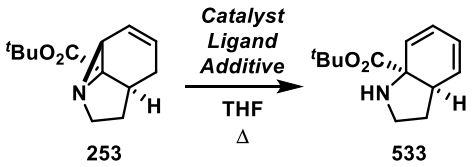


Entry	R	*Reagent*	*Temperature*	Product	Yield
1	$CO_2{}^tBu$	Allyl acetate	70	**529**	87%
2	COMe	Allyl acetate	30	**530**	56%[a]
3	CONHEt	Allyl acetate	70	**531**	60%[a,b]
4	CN	Allyl acetate	70	**532**	0%[c]
5[d]	$CO_2{}^tBu$	-	70	**533**	83%
6[d]	COMe	-	70	**534**	82%
7[d]	CONHEt	-	70	**535**	44%
8[d]	CN	-	70	**536**	0%[c]

Figure 33: Variation of aziridine and allyl component in the Pd-catalysed ring-opening/elimination reaction. [a]Percentage yields based on ^{1}H-NMR yield using 1,3,5-trimethoxybenzene as an internal standard; [b]two hour reaction time, [c]imine product was observed; [d]reaction carried out without K_2CO_3.

4.1.5.1. Mechanistic Studies

A preliminary screen of the catalyst and additive was also conducted, gaining important understanding of the necessities of the diene formation (Figure 34).[184] The reaction was shown to be rapid, both in the presence and absence of K_2CO_3 (Entries 1 and 2). Replacing $Pd(OAc)_2$ and PPh_3 with $Pd(PPh_3)_4$ led to no detectable product within the same time period (Entry 3). Simple addition of AcOH with $Pd(PPh_3)_4$ did afford product **533** (Entry 4), whereas the presence of $OPPh_3$ did not (Entry 5), suggesting that by-products of catalyst activation play a key role in generating an active catalytic system. Exploring this further, Ac_2O was added and the reaction reached completion (Entry 6), CsOAc led to a slower conversion (29%, Entry 7), and acetate Bu_4NOAc proved ineffective (Entry 8). Similar results were obtained using the $Pd_2(dba)_3/PPh_3$ catalytic system, where using alone resulted in no observed reaction (Entry 9), addition of $OPPh_3$ again failed to affect any reaction (Entry 10) and addition of AcOH led to a rapid reaction. These results are consistent with *N*-activation being key to the observed reactivity, with this being achieved by protonation (AcOH), reaction with an electrophile (Ac_2O) or complexation to a coordinating metal (CsOAc).



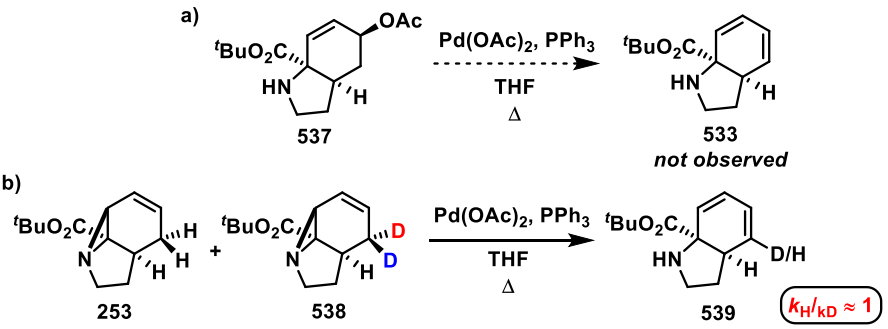
253 533

Entry	*Catalyst*[a]	*Ligand*	*Additive*[b]	Conversion[c]
1	$Pd(OAc)_2$	PPh_3	-	100%
2	$Pd(OAc)_2$	PPh_3	K_2CO_3	100%
3	$Pd(PPh_3)_4$	-	-	0%
4	$Pd(PPh_3)_4$	-	AcOH	100%
5	$Pd(PPh_3)_4$	-	$OPPh_3$	0%
6	$Pd(PPh_3)_4$	-	Ac_2O	100%[d]
7	$Pd(PPh_3)_4$	-	CsOAc	29%
8	$Pd(PPh_3)_4$	-	Bu_4NOAc	0%
9	$Pd_2(dba)_3$	PPh_3	-	0%
10	$Pd_2(dba)_3$	PPh_3	$OPPh_3$	<5%
11	$Pd_2(dba)_3$	PPh_3	AcOH	100%

Figure 34: Effect of catalyst and additives on the ring-opening/elimination sequence. [a]5 mol% catalyst loading; [b]added in an equimolar quantity to substrate; [c]determined by ^{1}H-NMR after 45 minutes at 70 °C; [d]a mixture of **533** and the corresponding acetamide was formed.

To further probe the reaction mechanism, acetate compound **537** was synthesised, and subjected to the reaction conditions to test if such was an intermediate within the reaction (Scheme 108). As no product formation was observed, it can be concluded that **537** is not an intermediate. To investigate if there was a KIE associated with the process, the deuterated aziridine **538** was also synthesised, and a competition experiment of it and its non-deuterated analogue was completed (Scheme 108). This showed the same

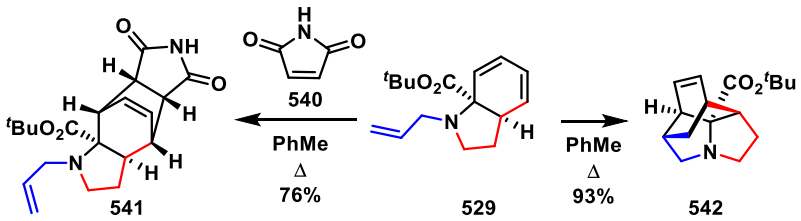
level of deuterated and non-deuterated starting material and product throughout the reaction. Hence there is no KIE associated with the *β*-hydride elimination process (although this low KIE value necessarily means that such a process may be reversible).[206]



Scheme 108: a) Mechanistic and b) isotopic labelling studies.[184]

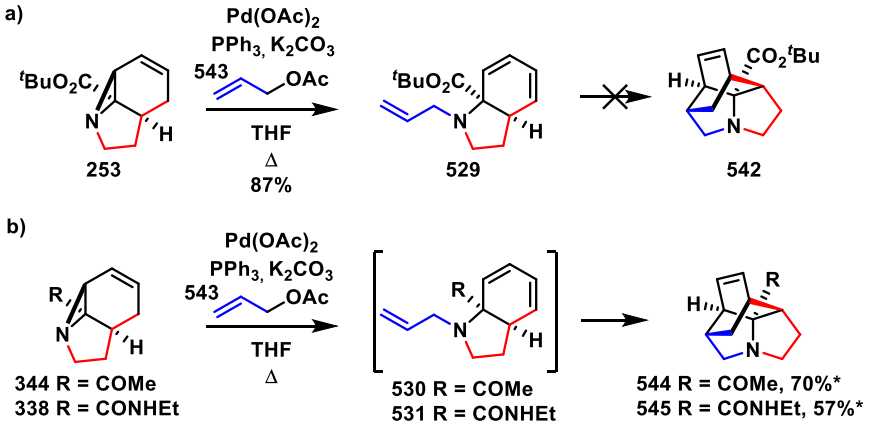
4.1.5.2. The Diels-Alder Cyclisation of 2,3,8,9-Tetrahydroindoles

Previous work also exploited the dienyl component of the tetrahydroindoles, initially heating **529** with the dienophile maleimide **540** in PhMe, which pleasingly afforded the [4+2] cycloaddition product **541** (Scheme 109). Interestingly a trace amount of the rather complex, intramolecular Diels-Alder product **542** was also observed. Due to the un-activated nature of the terminal dienophile, this result was somewhat surprising. Indeed, heating diene **529** for 24 hours afforded the tetracyclic amine **542** in an excellent yield of 93%. Given the degree of complexity generated, forming a previously unreported ring system, this led investigations to explore the generality of this process.



Scheme 109: Inter- and intramolecular Diels-Alder cyclisations of diene **529**.[184]

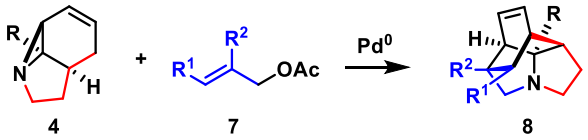
Performing the entire Tsuji-Trost/Diels-Alder sequence in a single vessel was desired, however upon refluxing *tert*-butyl ester aziridine **253** and allyl acetate **543** under the Pd-catalysed conditions in THF, only the allylated intermediate **529** was obtained (Scheme 110). However, taking the analogous ketone and amide aziridines, **344** and **338**, and subjecting them to the reaction conditions, Diels-Alder products **544** and **545** were gratifyingly observed, in ^{1}H-NMR yields of 70% and 57% respectively.[196] Unfortunately, these compounds could not be isolated due to their highly polar nature and co-elution with the side product $OPPh_3$. Although other allyl acetates were shown to be successful in the reaction, likewise the tetracyclic compounds could not be purified.



Scheme 110: a) Refluxing ^{t}Bu aziridine **253** in THF only led to intermediate **529** and b) one-pot conversion of COMe and CONHEt aziridines **344** and **338** did proceed, but isolation was unsuccessful.[196] *Percentage yield based on ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

4.2. Aim of Project

The aim of this project was thus to complete a substrate scope of the three-part process, optimising a one-pot synthetic route from aziridines to teracycles **8** and hence identifying conditions to obtain purified products. Additional studies on further understanding the mechanism were also desirable, along with derivatisation of the amine products to showcase their potential use in 3D-amine library synthesis.

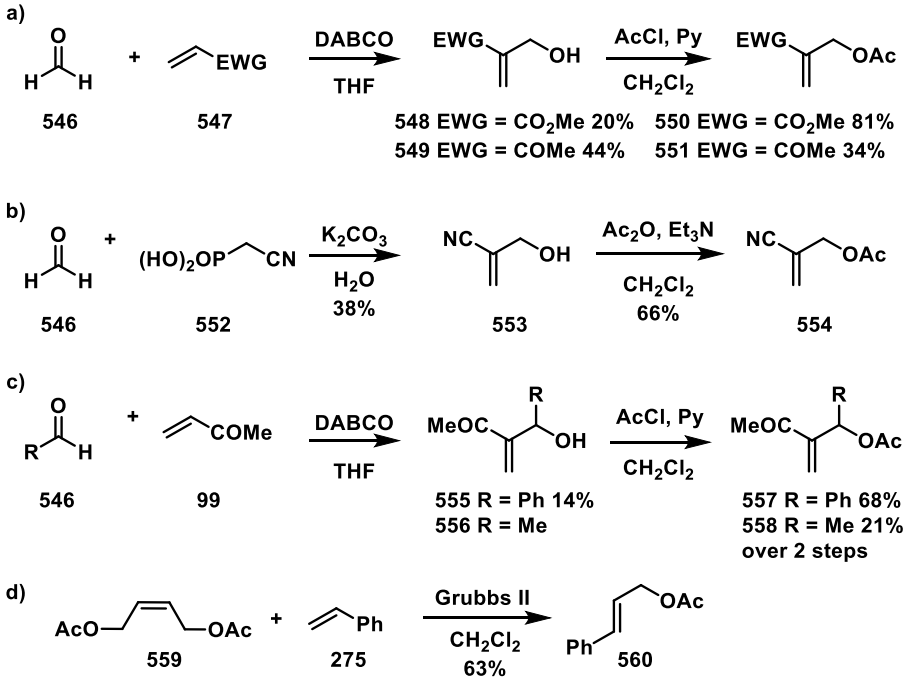


Scheme 111: Optimisation of the three-part cascade was required.

4.3. Results and Discussion

4.3.1. Reaction Scope

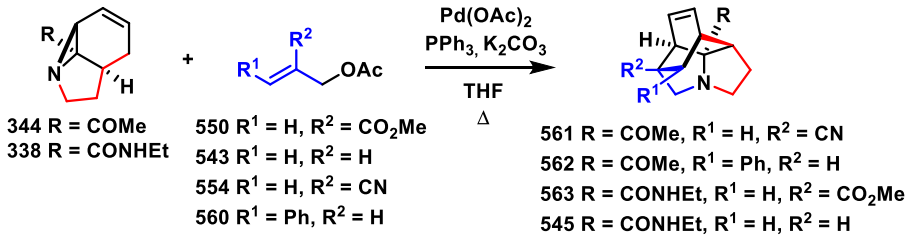
Initial results came from investigating the scope of the reaction. The three aziridines **253**, **344** and **338**, were synthesised as before, see Section 3.3.1. and 3.3.7., and a range of substituted allyl acetates were also synthesised, focusing on electron-poor systems to lower the energy of the LUMO orbital (Scheme 112). Thus, minimising the energy gap between it and the HOMO of the diene and in turn, lowering the energy needed for the IMDA to occur. Three allylic acetates substituted at the C2 position were synthesised **550**, **551** and **554**, the methyl ester **548** and the methyl ketone **549** using a Bayliss-Hillman reaction from the corresponding alkene and formaldehyde **546**, and the nitrile **553** *via* a Horner-Wadsworth-Emmons reaction with diethyl cyanomethylphosphonate **552** and formaldehyde **546** (Scheme 112). The hydroxyl group was simply protected using either acetyl chloride or acetic anhydride with a tertiary amine base. The two tethers with the additional phenyl or methyl substituent, **557** and **558**, were desired as this would enable the possibility of the IMDA product to contain a further functional group. Similarly, these were synthesised *via* a Bayliss-Hillman reaction and then acetylated. The C3 substituted phenyl tether **560**, which introduced the potential for two regioisomers to be formed, was obtained from a rather expensive method of cross-metathesis of 1,4-diacetoxy-2-butene **559** and styrene **275**.



Scheme 112: Synthetic routes to allylic acetates. All systems apart from **558** were synthesised by previous members of the group.[184,196]

To begin, the ketone and amide aziridines were first examined, as it was known that the diverted Tsuji-Trost/Tsuji-Trost/Diels-Alder cascade could be achieved in a single vessel using the one reaction solvent, THF. With issues known for the purification stage, several reactions were completed in

duplicate to trial a range of solvent systems for SiO_2 flash chromatography. However, it became apparent based on ^{1}H-NMR yields that the reaction gave variable results (Figure 35).

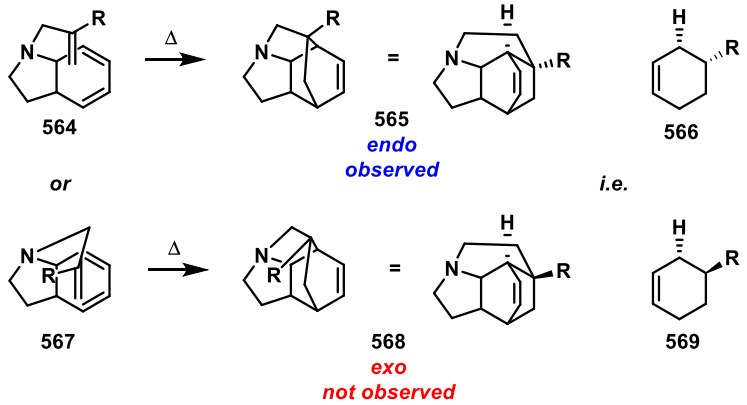


Entry	*R*	*R*^{1}	*R*^{2}	Yield	Repeat 1	Repeat 2	Repeat 3
1	COMe	H	CN	34%*	75%*	75%	-
2	COMe	Ph	H	76%*	37%*	24%*	64%*
3	CONHEt	H	CO_2Me	78%*	74%*	30%*	58%
4	CONHEt	H	H	63%*	67%*	52%	24%

Figure 35: Variability in the Pd-catalysed cascade. *^{1}H-NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

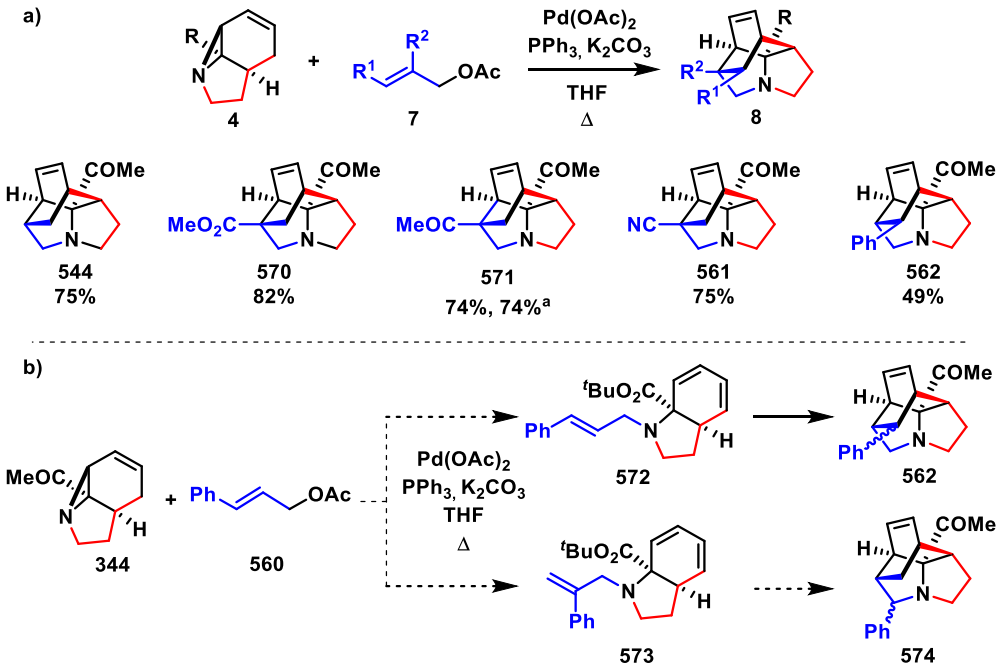
Further purification of the starting aziridines or differing the batches of base and ligand did not lead to any reduction in this variability. The reaction set-up included a premix of catalyst, ligand, and base for 5 minutes in THF before addition of the aziridine and allyl acetate. It was found that if this premix was extended to 10 minutes, and the reaction solvent was thoroughly degassed (by sparging with N_2) before use, the cascade was indeed reproducible for the ketone and amide starting materials. Fortunately, due to these issues several batches of crude material were available to investigate the purification stage. Suitable solvent systems to purify the highly polar products using SiO_2 flash chromatography were found to be solutions of aqueous NH_3:EtOH in Et_2O or CH_2Cl_2, or aqueous NH_3 in EtOAc/EtOH.

It should be noted that the IMDA reactions proceeded selectively, affording only the *endo* stereoisomer **565** in all cases (Scheme 113). Upon examining the transition states for each conformational isomer, it becomes apparent as to why this selectivity is observed. The *exo* isomer **568** requires an unfeasibly long carbon-nitrogen bond in order to position the electron-poor substituent on the dienophile into this conformation.



Scheme 113: *Endo* **565** and *exo* **568** transition states for the IMDA cyclisation. Note the electron-withdrawing group on the bridgehead carbon has been omitted for clarity.

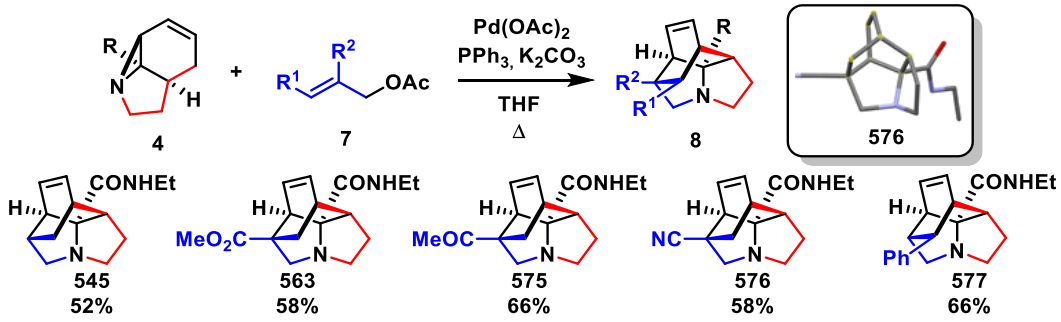
Thus, the scope of the reaction could now proceed (Scheme 114). Generally, the isolated yields for the ketone system **344** were good, and that with allyl acetate affording product **543** in a 75% yield. The highest yield of 82% was observed with the methyl ester allylic acetate **550**. The sequence with the methyl ketone allylic acetate to afford product **571**, was completed twice, the former at the standard 0.27 mmol scale and the latter at a 3 mmol scale, which pleasingly was shown to proceed in exactly the same yield of 74%.[279] As stated earlier, the C3 substituted phenyl tether **560** enables the possibility of two regioisomers (and indeed two stereoisomers for each regioisomer) to be formed, the linear Tsuji-Trost product **572** and the branched product **573**, which would translate into the tetracyclic product. Due to the preferential nucleophilic attack at the least hindered carbon in π-allyl complexes,[224] and the generality that Pd-catalysed allylic aminations proceed in a linear fashion,[280] it was anticipated regioisomer **572** would predominate. There is also precedence that the *E*-olefin is favoured in Tsuji-Trost reactions, regardless of the staring allylic acetate's geometry.[281] As the subsequent Diels-Alder reaction is concerted, this stereochemistry would hence be preserved. Indeed all of this was proven so, affording **562** as a single stereoisomer in a reasonable yield of 49% (the stereochemistry of which was confirmed by ^{1}H-NMR NOE studies).[196]



Scheme 114: a) Substrate scope of ketone aziridine **344** in the 3-part cascade process and b) potential regioisomers from the Tsuji-Trost reaction with allyl acetate **560**. [a]Reaction completed on a 3 mmol scale. The ketone systems (apart from **544**) were completed by another member of the group.[279]

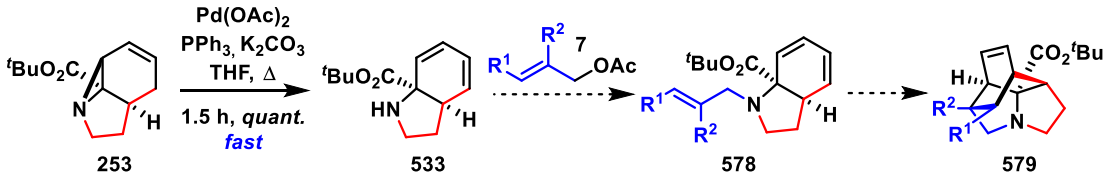
In almost all cases, the ketone aziridine **344** afforded higher yields than the corresponding amide starting material **338**, but perhaps gave more similar percentage yields across the allylic acetates **7** examined (Scheme 115). This could potentially be due to the nitrogen atom coordinating to the Pd catalyst and preventing the reaction from reaching completion.[282] Allylic acetate yielded the tetracyclic product **545** in 52% and the corresponding methyl ester gave **563** in 58% yield. The methyl ketone tether **551**

afforded the amide product **575** in the highest yield of 66% and the nitrile tether **554** in 58%. Interestingly the C3 acetate **560** also gave product in highest yield of 66%, again showing high regiocontrol for the linear isomer at the allylation stage combining with high *E*-selectivity to yield the product **577**. The *endo* stereoselectivity of the IMDA reaction was also proven by obtaining a crystal structure of **576**.



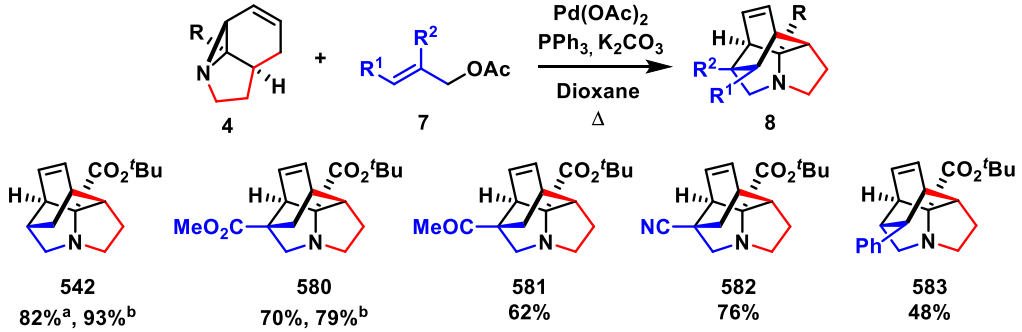
Scheme 115: Substrate scope of amide aziridine **338** in the 3-part cascade process and the crystal structure of **576**, which was obtained by a previous member of the group.[196]

Thus, efforts turned to the *tert*-butyl ester aziridine substrate **253**. Unfortunately, only the reaction with allyl acetate **543** proceeded, which still required a solvent swap to reach completion of the IMDA, from THF to PhMe, as seen in Section 4.1.5.2. The other reactions with the activated tethers generally gave complex mixtures of starting material **253**, ring-opened aziridine **533**, a small amount of the Tsuji-Trost intermediate and other unidentified side-products. The reactions were completed in THF but due to the crude reaction affording several intermediates, simply heating in another higher boiling point solvent, for example PhMe, did not result in the tetracyclic product, only further complicated the crude mixture. In order to understand why this failure for the ester system was occurring, the cascade was divided into its separate reaction components. Completion of the reaction in the absence of any allyl unit, showed that NH diene formation in refluxing THF (Scheme 116) was relatively quick and would reach full conversion in 1.5 hours, monitored by ^{1}H-NMR. Hence, it appeared that it was not the initial Pd-catalysed aziridine ring-opening and elimination step that was causing the issue. Therefore, it was either of the latter two steps of the cascade that appeared to be problematic, the carbon-nitrogen bond formation in the Tsuji-Trost reaction or the cyclisation in the IMDA reaction. A decrease in rate for both of which could be rationalised by the increased steric bulk of the *tert*-butyl ester compared to the ketone and amide aziridine systems. It was decided to change the solvent to dioxane, for which the temperature of the reaction could be increased, thought to drive either, or both, the Tsuji-Trost and the final IMDA reaction (see Section 4.3.2. for a conclusion on which of these was inhibiting the reaction). The timing of the addition of the allyl acetate was also changed, rather than addition with the aziridine after the premix, it was added after 1.5 hour of refluxing, post-premix and aziridine addition, to ensure the NH diene **533** had formed completely.



Scheme 116: The first step in the Pd-catalysed cascade forming the NH diene **533** was shown to be complete within 1.5 hour.

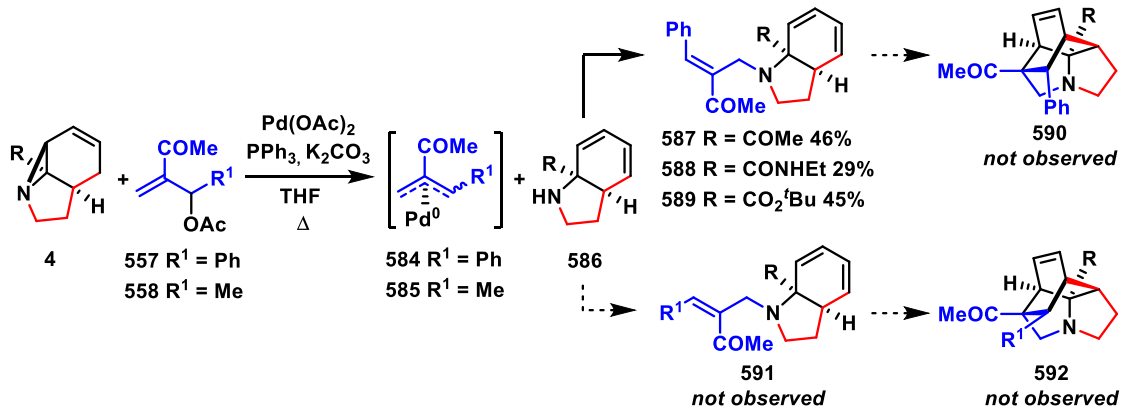
These two changes, switching to dioxane as the reaction solvent and delaying the addition of the allyl acetate, were indeed successful, and pleasingly the ester products could be isolated using similar solvent systems in their purification as with the analogous aziridines **344** and **338** (Scheme 117). Due to the increased temperature of the reaction, tetracyclic product **542** could now be obtained in the one-pot. However, it was noted that the percentage yield of this system had decreased, from 81% over the two steps to 70%. As allyl acetate **543** has a boiling point of 103 °C, and the reaction was completed at 100 °C it was assumed this decrease in yield was caused by loss of reagent. Indeed, increasing the equivalents of allyl acetate to three circumvented this issue and the yield returned to 82% (Scheme 117). Pleasingly, if this was carried out on a larger scale, 3 mmol, the yield of **542** improved further to an excellent 93%.[279] This correlation between increase in yield and scale was also observed in the formation of product **580**, with the methyl ester allylic acetate **550** from 70% to 79%.[279] The ketone and nitrile allylic acetates also afforded products **581** and **582** in good yields of 62% and 76% respectively. The lowest yield was observed for the more challenging C3 substituted tether **560**, although still in a modest yield of 48% as a single stereoisomer.



Scheme 117: Substrate scope of the *tert*-butyl ester aziridine **253** in the Pd-catalysed cascade process. [a]3 equivalents of allyl acetate used; [b]reaction completed on a 3 mmol scale. Synthesis of **582** and **583** and the 3 mmol reactions were completed by another member of the group.[279]

The final investigation into the scope of the reaction was with tethers **557** and **558**, which would enable two substituents to be included within the tetracyclic product (Scheme 118). Unfortunately, this was not successful with either tether or any of the three aziridines. The phenyl allylic acetate **557** afforded the Tsuji-Trost allylated intermediate for each aziridine, in yields of 46%, 29% and 45% for the ketone **587**, amide **588** and ester **589** respectively. These intermediates were then refluxed in high boiling point solvents including PhMe, xylene and dioxane but this did not lead to any of the desired [4+2] cyclisation

product **590**. Upon further analysis it was perhaps realised why this final step of the cascade would not proceed; ^{1}H-NMR NOE studies revealed the alkene to be of *E*-geometry. Surprisingly, reaction of the corresponding methyl tether **558** under the reaction conditions did not give any of the allylated intermediate **591**, nor IMDA product **521**. A complex mixture consisting of ring-opened aziridine, NH diene and other unidentified products were observed in all cases of aziridine.



Scheme 118: Unsuccessful routes with tethers **557** and **558** to afford the disubstituted tetracyclic products **590** and **592**. However only allylated products **587**, **588** and **589** were observed. **587** and **589** were isolated by another member of the group.[279]

4.3.2. Kinetics of the Diels-Alder Reaction

As mentioned earlier, in comparison to other literature examples, the IMDA cycloaddition appeared facile, readily occurring at 70 °C for the ketone and amide systems even for those without an activated dienophile component. Hence this prompted work to further probe this final part of the three-part cascade. Initially rate constants were obtained at 75 °C for the ester and amide intermediates **529** and **531**. These were synthesised either by halting the cascade early or by alkylating the NH diene intermediate. The rate constants were acquired by monitoring the IMDA reaction by ^{1}H-NMR, and simply plotting log$_c$ of the starting material concentration (using 1,3,5-trimethoxybenzene as an internal standard) versus time. As this was a unimolecular reaction, and hence first order, the rate constant is equal to the slope of this straight-line plot. As anticipated, the amide system was shown to be more reactive than the corresponding ester, by a significant eight-fold, where k = 5.5 x 10^{-5} s^{-1} compared to k = 6.8 x 10^{-6} s^{-1}.

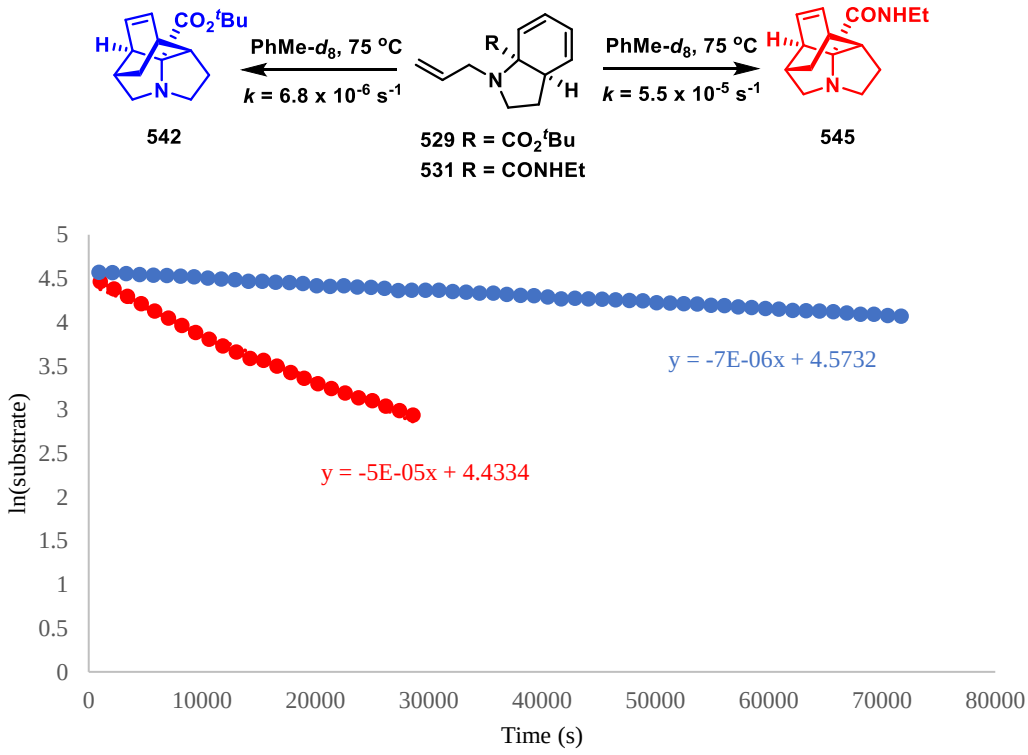


Figure 36: Plot of ln(substrate) versus time to obtain rate constants for the IMDA of ester **529** and amide **531**.

To obtain the thermodynamic activation parameters for both of these systems **529** and **531**, an Eyring graph was plotted. The Eyring equation describes the temperature dependence of a reaction rate,[283] as does the Arrhenius equation. However, the latter can only be applied to the kinetics of gas phase reactions, whereas the Eyring equation is based on the transition state model and can be used in solution phase reactions.[284] The Arrhenius equation also only yields the activation energy of a reaction. The Eyring equation is:

$$k = \kappa \times \frac{k_B \mathrm{T}}{h} \times K^{\ddagger}$$

where k is equal to the rate constant, κ the transmission coefficient, k_B is Boltzmann's constant, 1.381 x 10^{-23} J K^{-1}, T is the temperature measured in kelvin, h is Planck's constant, 6.626 x10^{-34} J s and $K^{\ddagger}$ is the equilibrium constant. As the calculation of the equilibrium constant is very difficult except in model cases, it is more useful to express the Eyring equation in terms of thermodynamic parameters. Hence as:

$$K^{\ddagger} = e^{-\Delta^{\ddagger}G/RT}$$

$$\Delta G^{\ddagger} = -RTlnK^{\ddagger}$$

$$\Delta^{\ddagger}G = \Delta^{\ddagger}H - T\Delta^{\ddagger}S$$

Then assuming $\kappa = 1$:

$$k = \frac{k_B T}{h} e^{-(\Delta^{\ddagger}H - T\Delta^{\ddagger}S)/RT}$$

For which the linear Eyring equation can then be obtained:

$$lnk = ln\frac{k_B}{h}.T - \frac{\Delta^{\ddagger}H}{R}.\frac{1}{T} + \frac{\Delta^{\ddagger}S}{R}$$

$$\ln\frac{k}{T} = -\frac{\Delta^{\ddagger}H}{R}.\frac{1}{T} + ln\frac{k_B}{h} + \frac{\Delta^{\ddagger}S}{R}$$

Hence plotting ln(k/T) versus (1/T), an Eyring plot, the values of $\Delta^{\ddagger}H$ and $\Delta^{\ddagger}S$ can be obtained, as the equation of the straight line with a negative slope is equal to:

$$m = -\frac{\Delta^{\ddagger}H}{R}$$

and the y-intercept:

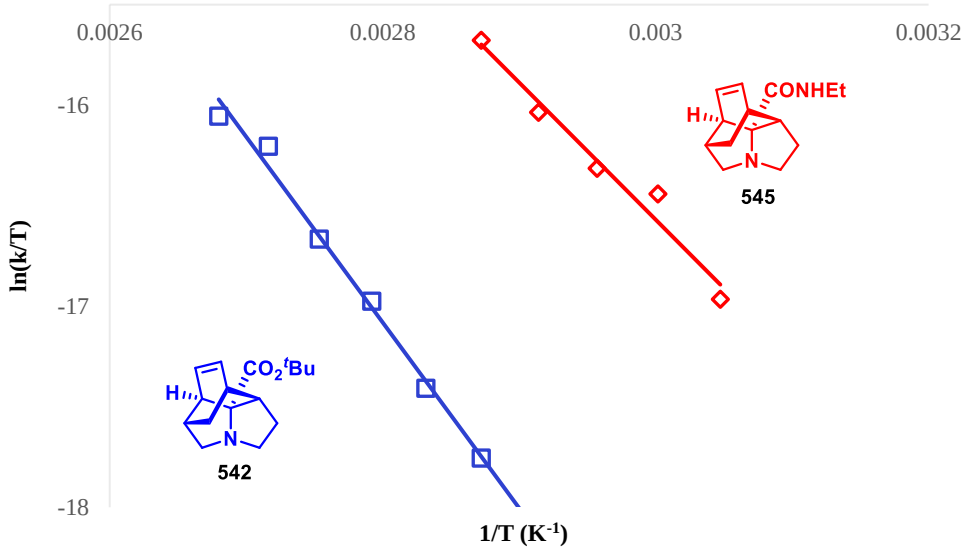
$$y(x=0) = \frac{\Delta^{\ddagger}S}{R} + ln\frac{k_B}{h}$$

Therefore, the IMDA reactions were completed at a range of different temperatures and monitored by ^{1}H-NMR, and the rate constants for each were extrapolated (Table 3).

Entry	*Temperature (°C)*	Ester *k* (s^{-1})	Amide *k* (s^{-1})
1	55	-	1.41 x 10^{-5}
2	60	-	2.41 x 10^{-5}
3	65	-	2.78 x 10^{-5}
4	70	-	3.73 x 10^{-5}
5	75	6.78 x 10^{-6}	5.41 x 10^{-5}
6	80	9.72 x 10^{-6}	-
7	85	1.52 x 10^{-5}	-
8	90	2.10 x 10^{-5}	-
9	95	3.38 x 10^{-5}	-
10	100	3.98 x 10^{-5}	-

Table 3: Rate constants for the IMDA reaction of ester **529** and amide **531**.

Thus, the ln/T values were plotted against 1/*T* to give the Eyring plot for which $\Delta^{\ddagger}H$ and $\Delta^{\ddagger}S$ were then abstracted and calculated (Figure 37).



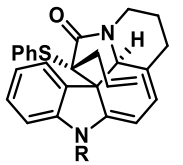
	$\Delta^{\ddagger}H$ (kJ mol^{-1})	Error (kJ mol^{-1})	$\Delta^{\ddagger}S$ (J K^{-1} mol^{-1})	Error (J K^{-1} mol^{-1})	$\Delta^{\ddagger}G$ (kJ mol^{-1})
Ester	77	±4	-125	±10	121
Amide	57	±6	-165	±17	114

Figure 37: Eyring plot for the IMDA cyclisation to form tetracycles **542** and **545** and calculated $\Delta^{\ddagger}H$, $\Delta^{\ddagger}S$ and $\Delta^{\ddagger}G$ values. $\Delta^{\ddagger}G$ values were calculated at 75 °C.

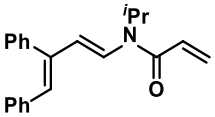
The difference in rate was seen to be largely due to the enthalpy of activation, which was higher for the *tert*-butyl ester system (77 ± 4 kJ mol^{-1} versus 57 ± 6 kJ mol^{-1}). As anticipated, both **529** and **531** gave positive $\Delta^{\ddagger}H$ values, indicating an endothermic reaction, and negative $\Delta^{\ddagger}S$ values, as they move into a more ordered product. The entropy of activation was less negative for the ester (-125 ± 10 J K^{-1} mol^{-1} versus -165 ± 17 J K^{-1} mol^{-1}). Initially, it was somewhat surprising that the entropy of activation was less negative for the ester (-125 ± 10 J K^{-1} mol^{-1} versus -165 ± 17 J K^{-1} mol^{-1}). Due to the *tert*-butyl ester being a larger functional group than the amide, it was imagined this would have more degrees of freedom, and hence a more negative $\Delta^{\ddagger}S$ value. To rationalise these values, it has been postulated that due to the *tert*-butyl ester's larger steric bulk, this may inhibit its freedom and conformationally restrict the molecule. Such was also exemplified in Section 4.1.4., Scheme 104, where the *tert*-butyl group activated the system to undergo a facile IMDA. The activation energy values at 75 °C were also calculated, that for the ester and amide found to be 121 kJ mol^{-1} and 114 kJ mol^{-1} respectively.

Although it is unclear whether the increased enthalpy of activation for the ester system compared to the amide is due to electronic factors (the diene in the former would be slightly more electron poor) or if it is due to the diene experiencing an increased barrier to attaining a reactive conformation due to steric demand, both enthalpies for each system are generally significantly lower than those reported in the literature (Figure 38). For instance, if these systems are converted into kcal mol^{-1} units, $\Delta^{\ddagger}H_{ester}$ = 18.4

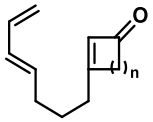
kcal mol^{-1} and $\Delta^{\ddagger}H_{amide}$ = 13.6 kcal mol^{-1}, comparing with a similarly un-activated dienophile component and a cyclic diene **593**, an Eyring plot revealed $\Delta^{\ddagger}H$ = 22.5 kcal mol^{-1}.[285] Experimental values are also known for pentadienylacrylamides (*i.e.* activated dienophiles), such as **594**, where $\Delta^{\ddagger}H$ = 20.4 kcal mol^{-1}, a difference of 6.8 kcal mol^{-1} and 2 kcal mol^{-1} increase compared to these systems.[286] Computed $\Delta^{\ddagger}H$ values for IMDA reactions involving activated dienophile cyclopentenone **596** (19.7 kcal mol^{-1}) and cyclohexanone systems **597** (21.5 kcal mol^{-1}) are also consistently larger, with only cyclobutenone **595** (15.6 kcal mol^{-1}) systems showing comparable reactivity.[287] Computed values for substituted vinylcyclohexadienes **598** and **599** are also available, which are in the range of 21.6 kcal mol^{-1} to 31.5 kcal mol^{-1} at 25 °C for activated dienophiles, rising as high as 37.1 kcal mol^{-1} for those lacking an activating group **600**.[288]



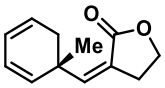
593
R = SO_2pOMeC_6H_4



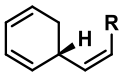
594



595 n = 1 15.6
596 n = 2 19.7
597 n = 3 21.5



598

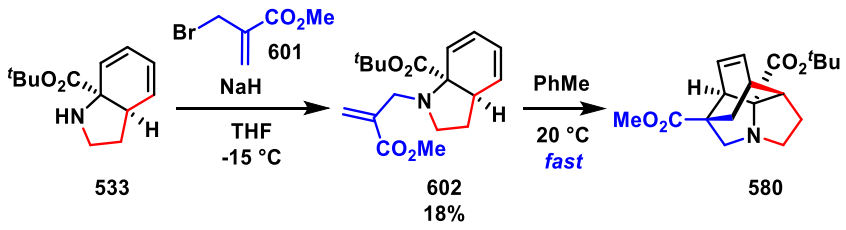


599 R = CO_2Me
600 R = Me

Entry	System	$\Delta^{\ddagger}H$ (kcal mol^{-1})
1	Ester **529**	18.4
2	Amide **531**	13.6
3	Un-activated dienophile **593**[285]	22.5
4	Pentadienylacrylamides **594** [286]	20.4
5	Cyclobutenone **595**[287]	15.6
6	Cyclopentenone **596**[287]	19.7
7	Cyclohexanone **597**[286]	21.5
8	Vinylcyclohexadiene **600**[288]	37.1

Figure 38: Comparison of experimental and computed $\Delta^{\ddagger}H$ values.

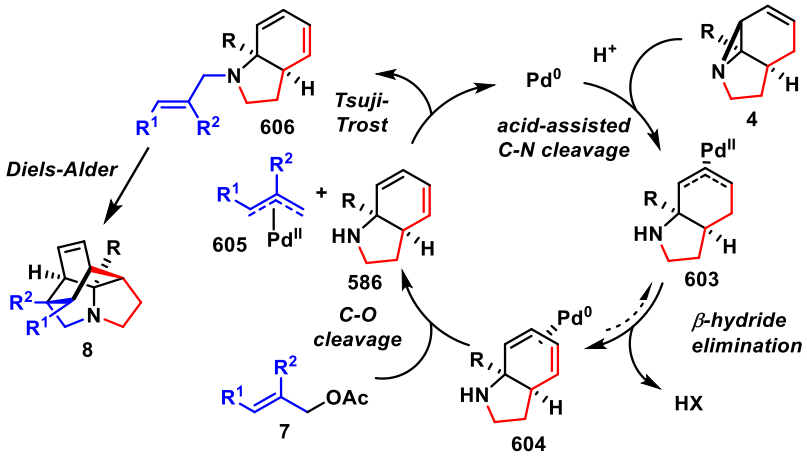
To explore the impact of the dienophile component, synthesis of the activated intermediate **602** was attempted (Scheme 119). Deprotonating the NH diene with NaH and subsequent reaction with the electrophile **601** resulted in rapid formation of **602**. However, upon purification, both the allylated intermediate **602** and the Diels-Alder product **580** were present (1:0.3 ratio respectively). After a further 48 hours at room temperature, all the intermediate **602** had undergone the [4+2] cyclisation and formed the tetracyclic product **580**. Thus, completing an Eyring study on this system proved not to be possible. However, this does highlight how facile these IMDA reactions are, and upon revisiting the previous section, it was clearly the Tsuji-Trost reaction of the *tert*-butyl ester diene that was inhibiting the sequence, as the Diels-Alder reaction has since been shown to proceed rapidly at room temperature with an activated dienophile.



Scheme 119: Rapid formation of tetracyclic product **580**. **602** was isolated in 18% yield, in 1:0.3 ratio of **602**:**580**. The remainder of the yield was shown to be IMDA product **580**.

4.3.3. Proposed Reaction Mechanism

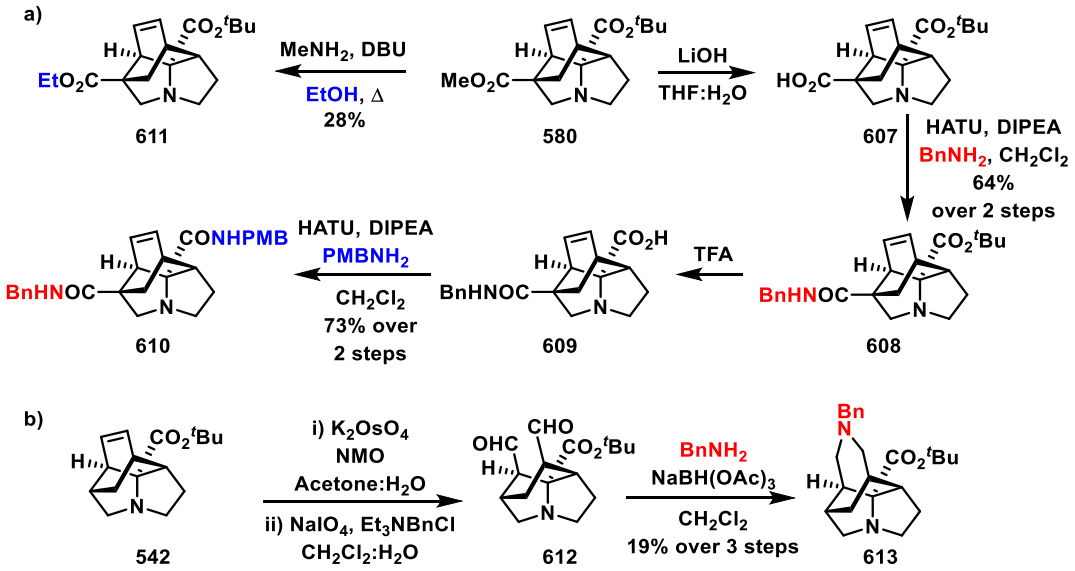
Teamed with the earlier mechanistic studies and the Eyring data, a mechanism for the three-part cascade was then be proposed (Scheme 120). Initial acid-assisted, Pd-catalysed carbon-nitrogen bond cleavage of **4** leads to the formation of the Pd π-allyl intermediate **603**. This species then undergoes direct β-hydride elimination, even in the absence of additional base (Section 4.1.5.1., Figure 34) to form the intermediate diene 604, which can be readily isolated. Following this, a standard Tsuji-Trost mechanism between 586 and the allyl acetate **7** is proposed,[220,221] with the added base serving to ensure sufficient levels of reactive free amine **586**. The lack of a significant KIE associated with this process, as determined by competition (*i.e.,* between **253** and **538**, Section 4.1.5.1., Scheme 108), is consistent with the first step (carbon-nitrogen bond cleavage) being turnover limiting. This low KIE value necessarily means that a reversible β-hydride elimination cannot be ruled out.[206] The resulting *N*-allylated product **606** then undergoes an IMDA cycloaddition to the product **8**, the rate of which is controlled by both the aziridine and allyl substituent. At the time of writing, this appears to be the first example of a sequential Tsuji-Trost/intramolecular Diels-Alder cascade.



Scheme 120: Proposed mechanism of the diverted Tsuji-Trost/Tsuji-Trost/Diels-Alder cascade to tetracyclic amine **8**.

4.3.4. Derivatisation of Tetracyclic Amines

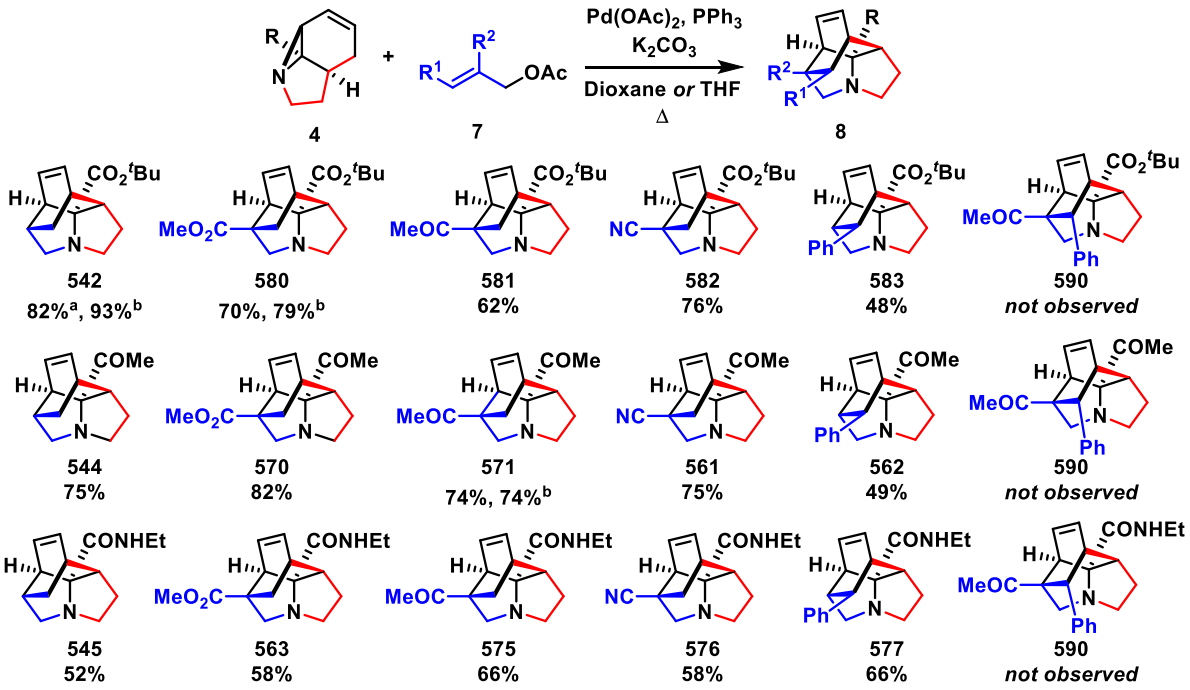
The final part of this project was focused on functionalising the tetracyclic products, ideally using routine transformations employed in medicinal chemistry. The di-ester product **580** was initially subjected to hydrolysis conditions, to selectively cleave the methyl ester forming the carboxylic acid **607** (Scheme 121). Although successful, further derivatisation of this product became problematic as it could not be extracted from the aqueous reaction mixture. The starting compounds were highly polar, and introduction of a carboxylic acid functional group only further increased this polarity. As such, a number of amide-coupling reactions were tried in aqueous solution, but these did not lead to any formation of **608**. *In situ* acid chloride synthesis was also attempted but only recovered starting material **580** was observed. Direct methyl amide formation *via* aminolysis was tried as this would avoid the highly polar acid intermediate. However, refluxing **580** with $MeNH_2$ in EtOH only led to transesterification of the ester to afford **611** and refluxing in MeOH recovered starting material **580**. It was then found that if the aqueous layer from the hydrolysis stage was concentrated *in vacuo*, and the crude carboxylic acid was dissolved in CH_2Cl_2, amide formation proceeded, affording **608** in 64% over the two steps. The *tert*-butyl ester could then be cleaved in TFA, which similarly underwent amide coupling in CH_2Cl_2 with HATU and DIPEA, to give di-amide **610** in 47% yield overall.[279] Diversification of the alkene was also proven possible, *via* a telescoped oxidative cleavage/reductive amination sequence forming the amino ester **613** (Scheme 121). Isolation of the intermediate diol nor aldehyde **612** was not possible due to instability.



Scheme 121: Functionalisation of tetracyclic products **580** and **542**. a) Transesterification and di-amidation to afford **610** and **611** and b) oxidative cleavage and reductive amination giving **613**. Formation of **610** was completed by another member of the group.[279]

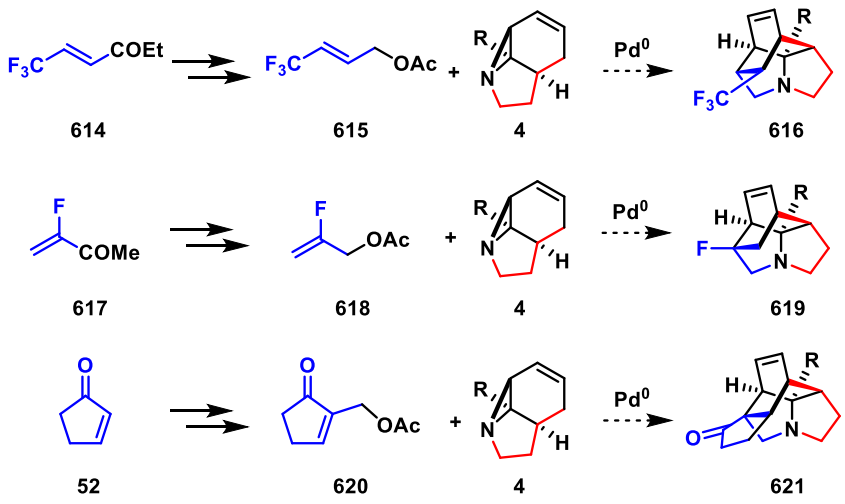
4.4. Conclusions and Future Work

In conclusion, the diverted Tsuji-Trost/Tsuji-Trost/Diels-Alder cascade to form highly three-dimensional, tetracyclic amines from aziridines has been optimised and further reaction understanding has been obtained. Purification issues have been solved such that a substrate scope could be completed and in the case of the *tert*-butyl ester aziridine **253**, the process has been telescoped allowing for a one-pot procedure. The three-part cascade was shown to be highly stereoselective and afforded the complex amine products in good to excellent yields (Scheme 122). Three reactions were also completed on a larger scale, which generally afforded the products in higher yields.[279] Limitations of the cascade were also highlighted, where a disubstituted alkene was shown not to undergo the Diels-Alder reaction. The ability of these compounds to readily undergo further transformations was also exemplified, highlighting their potential use in medicinal chemistry for drug library synthesis.



Scheme 122: Substrate scope of the three-part cascade. [a]3 equiv. of allyl acetate added; [b]completed on a 3 mmol scale.

Studies should continue to further expand upon the scope of this reaction (Scheme 123). For example, introducing a fluorine atom would increase the scaffold's lipophilicity and thus its medicinal relevance, **616** and **619**.[289,216] Two relatively simple ways to do so would be in the form of allyl acetates **615** and **618**, both obtained by reducing the commercially available esters **614** and **617**, followed by acetylation. A disubstituted allylated intermediate would improve the generality of the process and increase the complexity of the final product **621**. By doing so with cyclopentenone **52**, the ring system would restrict the alkene, thus keeping it in *cis* configuration. Earlier attempted studies were believed to be unsuccessful due to the *trans* conformation of the *N*-allylated intermediate. Thus, the *cis*-geometry should then enable the IMDA to proceed, affording the pentacyclic product **621**.



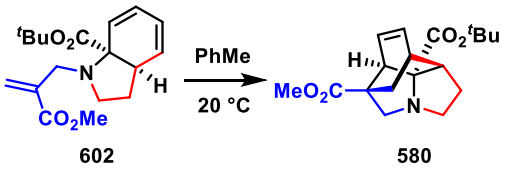
Scheme 123: Potential elaboration of substrate scope.

As the IMDA reaction appeared facile, Eyring analysis was completed and indeed the activation parameters corroborate this, with the enthalpy of activation values (77 ± 4 kJ mol^{-1} and 57 ± 6 kJ mol^{-1} for the ester and amide respectively) proving significantly lower than those in the literature.

Figure 39: Eyring plot for the Diels-Alder cyclisation of amide and ester.

An additional Eyring plot on an activated dienophile would complete this series. Then, quantitative analysis of both the aziridine substituent and the dienophile would highlight the importance of each in the Diels-Alder reaction. Although from the studies already completed, it can be assumed the dienophile component has an enormous effect on the rate of reaction. Low-temperature ^{1}H-NMR studies are possible, which should allow for the Eyring analysis to be finalised. As difficulties arose in isolating and purifying in the allylated diene intermediate **602**, due to rapid IMDA cyclisation, completing this on the crude solution may be an alternative. Additionally, it would be rewarding to use DFT to calculate the activation parameters and verify those obtained experimentally. This would also enable abstraction

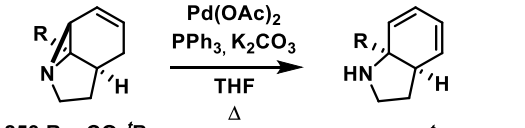
of $\Delta^{\ddagger}H$ and $\Delta^{\ddagger}S$ values for the activated dienophile system **602** if experimental ones are deemed too difficult to acquire. Furthermore, DFT modelling could be used to determine transition states for the reaction.



602 580

Scheme 124: Deriving an Eyring plot of the activated dienophile **602** would complete the series.

The intermediate dienes, as previously discussed are useful synthetic intermediates (Section 3.1.5.), and these 2,3,8,9-tetrahydroindole cores **533-535** are of particular interest. There are limited synthetic routes into such structures within the literature,[290,291] and this is believed to be due to their tendency towards aromatisation. The synthesis reported here was shown to be relatively broad, with a number of aziridines undergoing the reaction in good to excellent yields. Although this report only investigated their reactivity within the IMDA cyclisation, there is a plethora of reactions they could undergo.



253 R = $CO_2{}^tBu$
344 R = COMe
338 R = CONHEt

533 R = $CO_2{}^tBu$ 83%
534 R = COMe 82%
535 R = CONHEt 44%

Scheme 125: Synthesis of 2,3,8,9-tetrahydroindole cores **533**, **534**, **535**.

As stated at the beginning of this thesis, nitrogenated-heterocycles are hugely important structural motifs within bioactive molecules.[67] As such, innovative strategies for their efficient synthesis remains a fundamental objective for synthetic chemists to explore novel chemical space outside of 'flatland'.[5] These highly three-dimensional amine scaffolds truly epitomize this.

5. Experimental

5.1. General Information

Chemicals were purchased and used without further purification. Dry solvents were obtained by passage through a column of anhydrous alumina using equipment from Anhydrous Engineering (University of Bristol) based on the Grubbs' design. Straus flasks were used to collect anhydrous solvent. All other commercially available reagents were used as received. Reactions requiring anhydrous conditions were performed under N_2, glassware was flame dried immediately prior to use. Liquid reagents, solutions or solvents were added *via* syringe through rubber septa; solid reagents were added *via* Schlenk type adapters. Reaction mixtures were stirred magnetically, those carried out at RT varied between 16-24 ºC depending on the season. The Pd-catalysed rearrangement reactions were carried out in a glovebox.

Photochemical reactions carried out in flow used the 3 lamp FEP-flow reactor.[45] The reactor was constructed by wrapping FEP tubing (2.7 mm internal diameter, 3.1 mm external diameter) around a 360 mm length of quartz tube (44 mm internal diameter, 48 mm external diameter), which was capped at both ends with PTFE discs to act as a convenient stand and platform guides for the FEP tubing. Into this was inserted a 36 W single ended PL-L lamp at 365 nm (Philips TUV PL-L 36W UVC germicidal). Three reactors were connected together in series *via* FEP tubing and the reactor was wrapped in aluminium foil to reflect back light. The solution of pyrrole was passed through the reactor at the flow rate described.

Flash column chromatography was performed on Aldrich silica gel: 230-400 mesh (40-63 μm). Analytical thin layer chromatography was performed on aluminium backed 60 F_{254} silica plates. Visualisation was achieved by UV florescence (254 or 365 nm) and/or staining with $KMnO_4$ solution and heat. Extracts were concentrated *in vacuo* using both a Heidolph Hei-VAP Advantage rotary evaporator (bath temperatures up to 50 °C) at a pressure of 15 mmHg (diaphragm pump) and a high vacuum line at room temperature.

^{1}H-NMR and ^{13}C-NMR spectra were measured at 25 °C in the solvent specified with Varian, Jeol or Bruker spectrometers operating at field strengths listed. Chemical shifts (δ) are quoted in parts per million (ppm) with spectra referenced to the residual solvent peaks. Coupling constants (*J*) are reported in Hz and are reported to the nearest 0.1 Hz. Multiplicities are abbreviated as: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet), br (broad), app (apparent) or combinations thereof. Assignments of ^{1}H-NMR and ^{13}C-NMR signals were made where possible, using COSY, HSQC, HMBC and ^{1}H-NOE experiments.

Melting points were determined from a recrystallised material using Bibby Stuart SMP10 apparatus and are uncorrected.

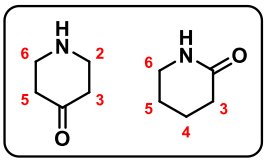
Infra-red spectra were recorded in the range 4000-650 cm^{-1} on a Perkin Elmer Spectrum either as neat films or solids compressed onto a diamond window.

Mass spectra were determined by the University of Bristol mass spectrometry service by electrospray ionisation (ESI) mode or electron ionisation (EI) mode.

5.2. Experimental Procedures and Compound Data

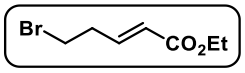
5.2.1. Alstoniascholarine A: Synthetic Procedures

Numbering nomenclature in piperidone systems are as shown below:



Ethyl-(*E*)-5-bromopent-2-enoate 82

Metathesis Procedure



4-Bromo-1-butene (0.09 mL, 0.92 mmol) and ethyl acrylate (0.10 mL, 0.92 mmol) were added sequentially to a stirred solution of Grubbs 2nd generation catalyst (2.5 mol%, 20 mg, 0.02 mmol) in CH_2Cl_2 (2.5 mL) and the reaction was heated under reflux. After 5 h, the reaction mixture was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-5% EtOAc/petrol to give a colourless oil (0.15 g, 79%). This was an inseparable 13:1 mixture of *E*:*Z* geometric isomers. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.89 (dt, 1H, *J* = 15.7, 6.8 Hz, CH_2CH), 5.90 (br d, 1H, *J* = 15.7 Hz, CH), 4.20 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 3.45 (t, *J* = 6.8 Hz, 2H, $BrCH_2$) 2.78 (q, 2H, *J* = 6.8 Hz, CH_2CH) 1.29 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.1 (CO), 144.5 (CH_2CH), 123.8 (CH), 60.5 (CH_2CH_3), 35.1 (CH_2CH), 29.9 ($BrCH_2$), 14.2 (CH_3); υ_{max}/cm^{-1} 2968.5, 1696.0, 1718.3, 1438.7, 1368.0, 1216.0, 1282.5, 1177.5, 1117.3, 1040.3; *m/z* LRMS (ESI$^+$) found $[M + Na]^+$ 229.0 and 231.0, $[C_7H_{11}{}^{79}BrO_2Na]^+$ requires 228.9840 and $[C_7H_{11}{}^{81}BrO_2Na]^+$ requires 230.9820. ^{1}H-NMR and ^{13}C-NMR are consistent with the literature.[83]

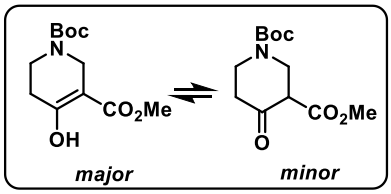
Reduction Procedure

DIBAL-H (1 M solution in hexane, 3.0 mL, 2.98 mmol) was added dropwise over 3 min to a stirred solution of 3-bromopropionitrile (0.12 mL, 1.49 mmol) in CH_2Cl_2 (13 mL) at -78 ˚C. The reaction mixture was stirred at -78 ºC for 2 h, warmed to RT and stirred for a further 2 h. The reaction mixture was cooled back to -78 ºC and quenched with methanol (6 mL) and HCl (3 M aqueous solution, 4 mL). The organic layer was then extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was dissolved in PhMe (2 mL) and added to a stirred solution of (carbethoxyethylidene)triphenylphosphorane (0.57 g, 1.64 mmol) in PhMe (4 mL). After 66.5 h, the reaction mixture was concentrated *in vacuo* to give the crude as an orange oil, which was purified by SiO_2 flash chromatography, 0-5% EtOAc/petrol to afford a colourless oil (0.1 g, 32%).

Oxidation Procedure

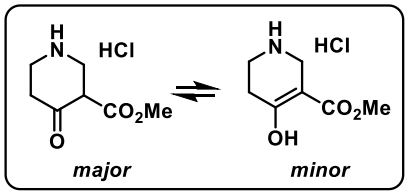
Dimethyl sulfoxide (0.28 mL, 3.98 mmol) was added to oxalyl chloride (2 M in CH_2Cl_2, 1.33 mL, 2.65 mmol) in CH_2Cl_2 (10 mL) at -78 ºC. After 5 min, 3-bromo-1-propanol (0.24 mL, 2.65 mmol) was added to the reaction mixture and after 10 min, $^{i}Pr_2NH$ (1.23 mL, 8.75 mmol) was added at -78 ºC. After 15 min the reaction was warmed to RT and stirred for 20 min. HCl (3 M aqueous solution, 4 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was dissolved in PhMe (5mL) and added to a stirred solution of (carbethoxyethylidene)triphenylphosphorane (1.02 g, 2.92 mmol) in PhMe (3mL) and heated under reflux. After 19 h, the reaction mixture was concentrated *in vacuo* to give the crude as an orange oil, which was purified by SiO_2 flash chromatography, 5-10% EtOAc/petrol to afford a colourless oil (62 mg, 11%).

tert-Butyl 4-oxopiperidine-1-carboxylate 86



Dimethyl carbonate (5.29 mL, 62.73 mmol) was added to a suspension of NaH (60% in mineral oil, 2.51 g, 62.73 mmol) in PhMe (50 mL) and heated under reflux. A solution of 1-boc-4-piperidone (5.0 g, 25.09 mmol) in PhMe (13 mL) was added dropwise to the refluxing solution over 45 min and gas evolution was observed. The reaction mixture was stirred for 18.5 h, cooled to 0 °C, quenched with H_2O (14 mL) and neutralised with HCl (1 M aqueous solution, 20 mL). The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude orange oil was purified by SiO_2 flash chromatography, eluting with 10-30% EtOAc/petrol, to give a colourless solid (4.52 g, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.84 (s, 1H, OH), 3.93 (s, 2H, 2-CH_2), 3.65 (s, 3H, OCH_3), 3.44 (t, 2H, J = 6.0 Hz, 6-CH_2), 2.24 (br t, 2H, J = 6.0 Hz, 5-CH_2), 1.35 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.2 (CO), 170.7 (CO), 154.3 (CO), 79.7 (C), 56.0 (3-CH), 51.2 (OCH_3), 40.0 (2-CH_2), 28.5 (5-CH_2), 28.1 (3 x CH_3) 28.0 (6-CH_2); υ_{max}/cm^{-1} 1689.7, 1665.5, 1420.3, 1365.9, 1309.5, 1232.9, 1164.6, 1064.3, 912.5, 731.9; *m/z* LRMS (ESI$^+$) found $[M + Na]^+$ 280.1, $[C_{12}H_{19}NO_5Na]^+$ requires 280.1161; m.p. 57-59 °C (EtOAc/petrol). ^{1}H-NMR and ^{13}C-NMR are consistent with the literature.[292]

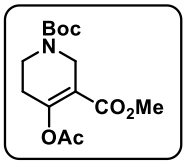
Methyl 4-oxopiperidine-3-carboxylate hydrochloride 87



HCl (2 M solution in Et_2O, 5 mL) was added to 1-*tert*-butyl 3-methyl 4-oxopiperidine-1,3-dicarboxylate (1.0 g, 3.89 mmol) at 0 ºC. The reaction mixture was warmed to RT and stirred for 18.5 h. The suspension was filtered and washed with cold Et_2O (10 mL) to give a colourless solid (0.52 g, 69%). ^{1}H-NMR (400 MHz, MeOH-d_4) δ 3.88 (br s, 2H, 2-CH_2), 3.84 (s, 3H, OCH_3), 3.46 (t, 2H, J = 6.5 Hz, 6-CH_2), 3.26 (br s, 1H, 3-CH), 2.71 (t, 2H, J = 6.5 Hz, 5-CH_2); ^{13}C-

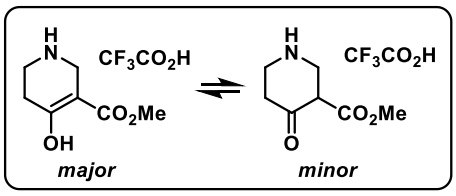
NMR (100 MHz, MeOH-d_4) δ 171.0 (CO), 169.3 (C), 93.5 (C), 52.6 (OCH_3), 41.5 (6-CH_2), 40.9 (2-CH_2), 26.3 (5-CH_2); υ_{max}/cm^{-1} 3374.2, 2493.9, 1670.9, 1446.3, 1327.1, 1298.6, 1214.0, 1116.4, 1097.6, 970.9; *m/z* LRMS (ESI^+) found $[M + H]^+$ 158.0, $[C_7H_{13}NO_3]^+$ requires 158.0817.

1-(*tert*-Butyl) 3-methyl 4-acetoxy-5, 6 dihydopyridine-1,3 (2*H*)-dicarboxylate 88



4-(Dimethylamino) pyridine (50 mg, 0.39 mmol) was added to a stirred solution of methyl 4-oxopiperidine-3-carboxylate trifluoroacetate (1.0 g, 3.89 mmol), Ac_2O (0.44 mL, 4.67 mmol) and Et_3N (2.70 mL, 19.45 mmol) in CH_2Cl_2 (5 mL). After 15 h, $NaHCO_3$ (saturated aqueous solution, 7 mL) was added to the reaction mixture and the organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude orange solution was purified by SiO_2 flash chromatography, eluting with 10-40% EtOAc/petrol, to give the *title compound* as a colourless oil (0.93 g, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.16 (br s, 2H, 2-CH_2), 3.68 (s, 3H, OCH_3), 3.54 (t, 2H, J = 5.7 Hz, 6-CH_2), 2.33-2.30 (m, 2H, 5-CH_2) 2.17 (s, 3H, CH_3) 1.43 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.2 (CO), 163.6 (CO), 155.0 (C), 154.2 (CO), 115.2 (C), 60.2 (C), 51.6 (OCH_3), 42.4 (2-CH_2), 38.9 (6-CH_2), 29.3 (5-CH_2), 28.2 (3 x CH_3), 20.8 (CH_3); υ_{max}/cm^{-1} 1695.3, 1219.1, 1418.8, 1365.3, 1294.3, 1238.8, 1209.6, 1163.7, 1118.8, 1057.5; *m/z* HRMS (ESI^+) found $[M + Na]^+$ 322.1271, $[C_{14}H_{21}NO_6Na]^+$ requires 322.1267.

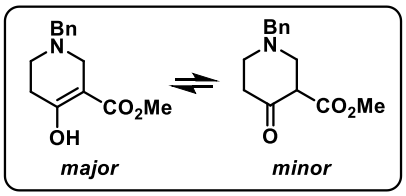
Methyl 4-oxopiperidine-3-carboxylate trifluoroacetate S1



Trifluoroacetic acid (9.0 mL) was added to *tert*-butyl 4-oxopiperidine-1-carboxylate (3.0 g, 11.67 mmol) in CH_2Cl_2 (7 mL) and stirred for 16 h, at which point it was concentrated *in vacuo* to give the crude material as a colourless oil which was used directly in the next step without further purification (0.84 g, *quant.*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.93 (br s, 1H, OH), 3.90 (br s, 2H, 2-CH_2), 3.79 (s, 3H, OCH_3), 3.43 (br s, 2H, 6-CH_2), 2.65 (t, 2H, J = 5.3 Hz, 5-CH_2); υ_{max}/cm^{-1} 2988.0, 1666.3, 1446.3, 1298.3, 1244.8, 1197.5, 1126.4, 833.9, 797.5, 721.3; *m/z* LRMS (ESI^+) found $[M + H]^+$ 158.1, $[C_7H_{12}NO_3]^+$ requires 158.0817.

Methyl 1-benzyl-4-oxopiperidine-3-carboxylate 92

β-Keto Ester Procedure



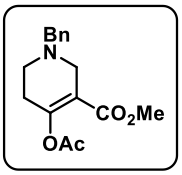
Dimethyl carbonate (4.90 mL, 66.05 mmol) was added to a suspension of NaH (60% in mineral oil, 2.65 g, 66.05 mmol) in PhMe (60 mL) and heated under reflux. A solution of 1-benzyl-4-piperidone (4.90 mL, 26.42 mmol) was added dropwise to the refluxing solution over 40 min and gas evolution was observed. The reaction mixture was stirred for 17 h, at which point it was cooled to 0 °C, quenched with H_2O (12 mL) and then neutralised with HCl (1

M aqueous solution, 30 mL). The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The crude orange oil was purified by SiO_2 flash chromatography eluting with 10-40% EtOAc/petrol, to afford a pale-yellow oil (2.01 g, 31%). ^{1}H-NMR δ 11.96 (s, 1H, OH), 7.34-7.27 (m, 5H, ArH), 3.71 (s, 3H, OCH_3), 3.63 (br s, 2H, NCH_2), 3.18 (br s, 2H, 2-CH_2), 2.61 (t, 2H, *J* = 5.5 Hz, 6-CH_2), 2.40 (t, 2H, *J* = 5.5 Hz, 5-CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.7 (CO), 170.3 (CO), 128.8 (ArCH), 128.6 (ArC), 128.2 (ArCH), 127.0 (ArCH), 61.4 (NCH_2), 56.3 (3-CH), 51.2 (OCH_3), 49.7 (2-CH_2), 48.6 (5-CH_2), 29.3 (6-CH_2); υ_{max}/cm^{-1} 1663.6, 1622.5, 1442.4, 1363.1, 1304.3, 1234.5, 1213.6, 1194.1, 1125.6; *m/z* LRMS (ESI$^+$) found $[M + H]^+$ 248.1 and $[M + Na]^+$ 270.1, $[C_{14}H_{18}NO_3]^+$ requires 248.1281 and $[C_{14}H_{17}NO_3Na]^+$ requires 270.1106. ^{1}H-NMR and ^{13}C-NMR are consistent with the literature.[84]

Dieckmann Procedure

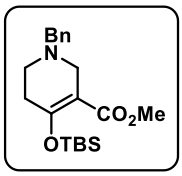
Potassium bis(trimethylsilylamide) (0.7 M in PhMe, 20 mL, 14.0 mmol) was added to a stirred solution of dimethyl 3,3'-(benzylazanediyl)dipropionate (2.61 g, 9.33 mmol) in PhMe (72 mL) at 0 ˚C. After 3 h, MeOH (20 mL) was added and the reaction mixture was concentrated *in vacuo*. The crude material was loaded purified by SiO_2 flash chromatography, eluting with 50-100% EtOAc/petrol, to give a yellow oil (1.38 g, 60%).

Methyl 4-acetoxy-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate 93



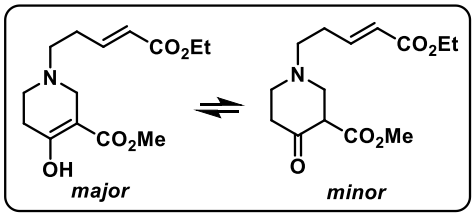
4-(Dimethylamino)pyridine (40 mg, 0.03 mmol) was added to a stirred solution of methyl 1-benzyl-4-oxopiperidine-3-carboxylate (0.75 g, 3.03 mmol), Ac_2O (0.34 mL, 3.64 mmol) and Et_3N (0.92 mL, 6.67 mmol) in CH_2Cl_2 (4 mL). After 17 h, additional Et_3N (1.18 mL, 8.48 mmol) and Ac_2O (0.09 mL, 0.91 mmol) were added to the reaction mixture. $NaHCO_3$ (saturated aqueous solution, 5 mL) was added to the reaction mixture after a further 26 h stirring, and the organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude orange solution was purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to give the *title compound* as a thick yellow oil (0.69 g, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H, ArH), 3.67 (s, 3H, OCH_3), 3.65 (s, 2H, NCH_2), 3.34 (t, 2H, *J* = 2.7 Hz, 2-CH_2), 2.66 (t, 2H, *J* = 5.9 Hz, 5-CH_2), 2.36 (app qn, 2H, 6-CH_2), 2.20 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.3 (CO), 164.2 (CO), 155.2 (C), 137.7 (ArC), 128.7 (ArCH), 128.3 (ArCH), 127.2 (ArCH), 115.7 (C), 61.3 (NCH_2), 51.5 (2-CH_2), 51.4 (OCH_3), 48.1 (5-CH_2), 29.5 (6-CH_2), 20.8 (CH_3); υ_{max}/cm^{-1} 1759.9, 1720.2, 1364.7, 1260.3, 1210.6, 1191.3, 1158.7, 1141.9, 1111.3, 1053.7; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 290.1396 and $[M + Na]^+$ 312.1210, $[C_{16}H_{20}NO_4]^+$ requires 290.1387 and $[C_{16}H_{19}NO_4Na]^+$ requires 312.1212.

Methyl 1-benzyl-4(*tert*-butyldimethylsilyl)oxy)-1,2,5,6-tetrahydropyridine-3-carboxylate 94



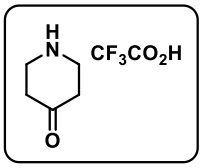
tert-Butyldimethylsilyl chloride (0.25 g, 1.65 mmol) was added to a stirred solution of methyl 1-benzyl-4-oxopiperidine-3-carboxylate (0.37 g, 1.50 mmol) and Et_3N (0.45 mL, 3.30 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 90.5 h, at which point additional Et_3N (0.58 mL, 4.20 mmol) and *tert*-butyldimethylsilyl chloride (90 mg, 0.60 mmol) were added. After 22 h, the reaction mixture was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to give the *title compound* as a colourless oil (0.16 g, 30%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, ArH, 5H), 3.68 (s, 3H, OCH_3), 3.62 (s, 2H, Ar-CH_2), 3.27 (br s, 2H, 2-CH_2), 2.56 (t, 2H, *J* = 6.0 Hz, 5-CH_2), 2.28 (br t, 2H, *J* = 6.0 Hz, 6-CH_2), 0.96 (s, 9H, 3 x CH_3), 0.19 (s, 6H, 2 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.5 (CO), 158.7 (C), 138.2 (ArC), 129.0 (ArCH), 128.2 (ArCH), 127.1 (ArCH), 106.6 (C), 61.9 (Ar-CH_2), 52.5 (2-CH_2), 50.8 (OCH_3), 49.0 (5-CH_2), 32.6 (6-CH_2), 25.6 (3 x CH_3), 18.3 ($\underline{C}(CH_3)$), -3.7 (2 x CH_3); υ_{max}/cm^{-1} 1721.8, 1689.1, 1635.0, 1382.5, 1254.0, 1208.2, 1120.0, 897.7, 837.9, 781.4; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 362.2156 and $[M + Na]^+$ 384.1977, $[C_{20}H_{32}NO_3]^+$ requires 362.2146 and $[C_{20}H_{31}NO_3Na]^+$ requires 384.1971.

Methyl (*E*)-1-(5-ethoxy-5-oxopent-3-en-1-yl)-4-oxopiperidine-3-carboxylate 66



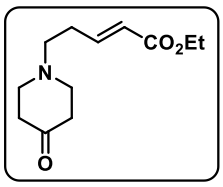
Et_3N (0.31 mL, 2.20 mmol) was added to a stirred solution of methyl 4-oxopiperidine-3-carboxylate hydrochloride (90 mg, 0.44 mmol), ethyl-(*E*)-5-bromopent-2-enoate (0.10 g, 0.48 mmol) and K_2CO_3 (0.91 g, 0.66 mmol) in CH_2Cl_2 (3 mL). After 7 days, the reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 20-60% EtOAc/cyclohexane, to afford the product as a colourless oil (0.24 g, 19%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.91 (s, 1H, OH), 5.79-5.58 (m, 2H, CHCH), 4.14 (q, 2H, *J* = 7.2 Hz, C$\underline{H}_2$CH$_3$), 3.74 (s, 3H, OCH_3), 3.13-3.08 (m, 4H, CHCHC$\underline{H}_2$ and 2-CH_2), 2.61 (t, 2H, *J* = 6.3 Hz, 6-CH_2), 2.41 (br t, 2H, *J* = 6.3 Hz, 5-CH_2), 1.76 (s, 2H, NCH_2), 1.25 (t, 3H, *J* = 7.2 Hz, $CH_2C\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.8 (CO), 171.6 (CO), 170.3 (CO), 130.5 (CH), 126.0 (CH), 60.7 ($\underline{C}H_2CH_3$), 56.4 (3-CH), 51.4 (OCH_3), 49.6 (2-CH_2), 48.7 (6-CH_2), 40.7 (NCH_2), 37.7 (CHCH$\underline{C}H_2$), 29.3 (5-CH_2), 14.2 (CH_3); υ_{max}/cm^{-1} 1731.9, 1663.8, 1442.59, 1305.9, 1216.7, 1233.8, 1192.8, 1162.8, 1127.6, 1027.8; *m/z* LRMS (ESI$^+$) found $[M + H]^+$ 284.1, $[C_{14}H_{22}NO_5]^+$ requires 284.1492.

Piperidin-4-one trifluoroacetate S2



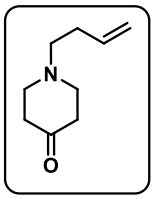
Trifluoroacetic acid (5.0 mL) was added in one portion to a stirred solution of 1-boc-4-piperidone (5.0 g, 25.09 mmol) in CH_2Cl_2 (15 mL). After 21 h, additional trifluoroacetic acid (5.0 mL) was added and the reaction mixture was stirred for 3 h then concentrated *in vacuo* to afford the crude material as a colourless solid which was used directly in the next step without further purification (5.35 g, *quant.*). ^{1}H-NMR (400 MHz, MeOH-d_4) δ 3.21 (t, 4H, J = 6.3 Hz, 2-CH_2 and 6-CH_2), 1.95 (app q, 4H, 3-CH_2 and 5-CH_2); ^{13}C-NMR (100 MHz, MeOH-d_4) δ 94.1 (CO), 48.1 (2-CH_2 and 6-CH_2), 33.4 (3-CH_2 and 5-CH_2); υ_{max}/cm^{-1} 3391.2, 2514.7, 1669.6, 1429.5, 979.4, 1184.6, 1130.2, 1100.6, 979.4, 838.2, 799.9, 722.2. ^{1}H-NMR data is consistent with the literature.[293]

Ethyl (*E*)-5-(4-oxopiperidin-1-yl)pent-2-enoate 97



Ethyl-(*E*)-5-bromopent-2-enoate (0.52 g, 2.52 mmol) was added to a stirred solution of piperidin-4-one hydrochloric acid (0.31 g, 2.52 mmol), K_2CO_3 (0.48 g, 3.44 mmol) and Et_3N (1.59 mL, 11.45 mmol) in CH_2Cl_2 (15 mL). The reaction was heated to 30 ˚C for 43 h, cooled to RT and stirred for 72 h, filtered through a bed of celite, washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 50% EtOAc/petrol then 10% MeOH/CH_2Cl_2, to give an orange oil (0.11g, 52%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.76-5.59 (m, 2H, CHCH), 4.10 (q, 2H, J = 7.2 Hz, C$\underline{H}_2$CH$_3$), 3.07-3.05 (m, 4H, NC$\underline{H}_2$C$\underline{H}_2$), 2.71 (t, 4H, J = 6.2 Hz, 3-CH_2 and 5-CH_2), 2.42 (t, 4H, J = 6.2 Hz, 2-CH_2 and 6-CH_2), 1.22 (t, 4H, J = 7.2 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.9 (CO), 171.5 (CO), 130.3 (CH), 126.1 (CH), 60.6 (C$\underline{H}_2$CH$_3$), 59.3 (NC$\underline{H}_2$), 52.7 (3-CH_2 and 5-CH_2), 42.0 (2-CH_2 and 6-CH_2), 37.7 (C$\underline{H}_2$CHCH), 14.1 (CH_3); υ_{max}/cm^{-1} 1731.8, 1715.8, 1671.1, 1400.3, 1326.3, 1198.9, 1176.4, 1159.1, 1011.2, 961.3; *m/z* HRMS (ESI$^+$) found [M + H]$^+$ 226.1453, [$C_{12}H_{21}NO_3$]$^+$ requires 226.1443.

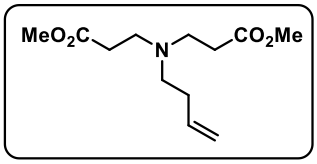
1-(But-3-en-1-yl)piperidine-4-one S3



4-Bromo-1-butene was added to a stirred solution of piperidin-4-one trifluoroacetate (0.20 g, 0.94 mmol), K_2CO_3 (0.19 g, 1.41 mmol) and Et_3N (0.65 mL, 4.70 mmol) in CH_2Cl_2 (3 mL). After 63.5 h, the reaction was diluted with CH_2Cl_2 (10 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 10-60% EtOAc/petrol, to give a colourless oil (72 mg, 36%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.87- 5.76 (m, 1H, CH), 5.10-5.00 (m, 2H, CHC$\underline{H}_2$), 2.75 (t, 4H, J = 6.2 Hz, 2-CH_2 and 6-CH_2), 2.54 (t, 2H, J = 7.7 Hz, NC$\underline{H}_2$), 2.45 (t, 4H, J = 6.2 Hz, 3-CH_2 and 5-CH_2), 2.29 (br q, 2H, J = 7.7 Hz, NCH$_2$C$\underline{H}_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.1 (CO), 136.2 (CH), 115.9 (CH$\underline{C}$H$_2$), 56.8 (NC$\underline{H}_2$), 53.0 (2-CH_2 and 6-CH_2), 41.1 (3-CH_2 and 5-CH_2), 31.8 (NCH$_2$$\underline{C}H_2$);

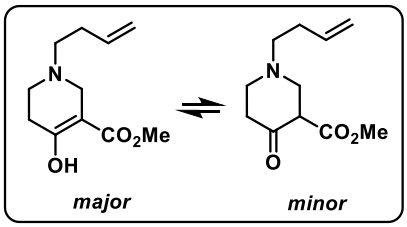
υ_{max}/cm^{-1} 2963.4, 2809.3, 1720.2, 1374.1, 1351.8, 1234.3, 1131.2, 1085.9, 914.2, 755.1; *m/z* LRMS (ESI$^+$) found $[M + H]^+$ 154.1, $[C_9H_{15}NO]^+$ requires 154.1232.

Dimethyl 3,3'-(but-3-en-1-ylazanediyl)dipropionate 102



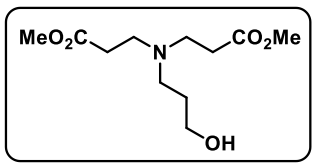
Methyl acrylate (3.80 mL, 42.18 mmol) was added dropwise over 5 min to a stirred solution of 3-butene-1-amine (1.30 mL, 14.06 mmol) in MeOH (15 mL). After 18.5 h, the reaction mixture was concentrated *in vacuo* to give the crude material as an orange oil which was used directly in the next step without further purification (3.47 g, *quant.*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.73-5.63 (m, 1H, CH), 4.98-4.88 (m, 2H, CHC$\underline{H}_2$), 3.59 (s, 6H, 2 x OCH_3), 2.71 (t, 4H, *J* = 7.2 Hz, 2 x C$\underline{H}_2CO_2CH_3$), 2.43 (t, 2H, *J* = 7.8 Hz, NC$\underline{H}_2$), 2.37 (t, 4H, *J* = 7.2 Hz, 2 x NC$\underline{H}_2$), 2.11 (app q, 2H, C$\underline{H}_2$CHCH$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.9 (2 x CO), 136.5 (CH), 115.6 (CH$\underline{C}H_2$), 53.2 (N$\underline{C}H_2$), 51.5 (2 x OCH_3), 49.1 (2 x $\underline{C}H_2CO_2CH_3$), 32.5 (2 x N$\underline{C}H_2$), 31.5 ($\underline{C}H_2$CHCH$_2$); υ_{max}/cm^{-1} 1734.5, 1436.1, 1356.4, 1253.1, 1194.4, 1172.9, 1126.8, 1047.7, 995.9, 913.4; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 244.1545, $[C_{12}H_{22}NO_4]^+$ requires 244.1549.

Methyl-1-(but-3-en-1-yl)-4-oxopiperdine-3-carboxylate 104



Potasssium bis(trimethylsilyl)amide (0.7 M in PhMe, 4.41 mL, 3.09 mmol) was added dropwise to a stirred solution of dimethyl 3,3'-(but-3-en-1-ylazanediyl)dipropionate (0.50 g, 2.06 mmol) in PhMe (20 mL) at 0 ˚C. After 1 h 45 min, MeOH (10 mL) was added and the reaction mixture was concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 25-50% EtOAc/petrol, to give the *title compound* as a pale-yellow oil (0.44 g, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.89 (s, 1H, OH), 5.86-5.75 (m, 1H, CH), 5.09-4.98 (m, 2H, CHC$\underline{H}_2$), 3.74 (s, 3H, OCH_3), 3.15 (t, 2H, *J* = 1.7 Hz, 5-CH_2), 2.63 (t, 2H, *J* = 5.7 Hz, 2-CH_2), 2.55-2.51 (m, 2H, NCH_2), 2.41 (tt, 2H, *J* = 5.7, 1.7 Hz, 6-CH_2), 2.32-2.24 (m, 2H, NCH$_2$C$\underline{H}_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.9 (CO), 170.3 (CO), 136.2 ($\underline{C}HCH_2$), 115.8 (CH$\underline{C}H_2$), 57.1 (NCH_2), 56.4 (3-CH), 51.3 (OCH_3), 49.6 (5-CH_2), 49.2 (2-CH_2), 31.7 (NCH$_2\underline{C}H_2$), 29.3 (6-CH_2); υ_{max}/cm^{-1} 1663.5, 1623.2, 1442.1, 1306.6, 1213.5, 1230.6, 1193.6, 1133.3, 914.0, 812.8; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 212.1298, $[C_{11}H_{18}NO_3]^+$ requires 212.1287.

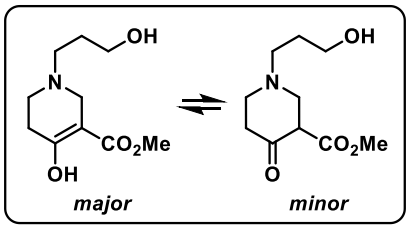
Dimethyl 3,3'-((hydroxypropyl)azanediyl)dipropionate 103



Methyl acrylate (2.88 mL, 31.94 mmol) was added dropwise over 5 min to a stirred solution of 3-amino-1-propanol (1.02 mL, 13.31 mmol) in MeOH (15 mL). The reaction mixture was stirred for 71 h and concentrated *in vacuo* to give the crude, material as a colourless oil which was used directly in the next step without further purification (3.29 g, *quant.*). ^{1}H-NMR (400 MHz,

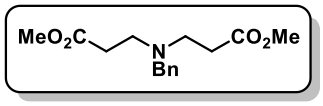
MeOH-d_4) δ 3.77 (br s, 1H, OH), 3.65 (t, 2H, J = 5.3 Hz, C$\underline{H}_2$OH), 3.63 (s, 6H, 2 x OCH_3), 2.73 (t, 4H, J = 6.9 Hz, 2 x C$\underline{H}_2CO_2CH_3$), 2.57 (t, 4H, J = 5.8 Hz, NCH_2), 2.44 (t, 4H, J = 7.0 Hz, 2 x NCH_2), 1.63 (app qn, 2H, $CH_2C\underline{H}_2CH_2$); ^{13}C-NMR (100 MHz, MeOH-d_4) δ 172.7 (2 x CO), 62.7 ($\underline{C}H_2OH$), 52.7 (NCH_2), 51.6 (2 x OCH_3), 49.2 (2 x $\underline{C}H_2CO_2CH_3$), 30.0 (2 x NCH_2), 28.4 ($CH_2\underline{C}H_2CH_2$); υ_{max}/cm^{-1} 3415.8, 2952.2, 2848.2, 1732.1, 1437.0, 1255.8, 1197.9, 1173.9, 1046.9, 842.6; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 248.1503, $[C_{11}H_{22}NO_5]^+$ requires 248.1492.

Methyl 1-(3-hydroxypropyl)-4-oxopiperidine-3-carboxylate 105



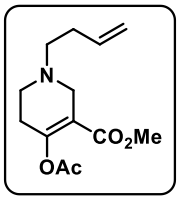
Sodium bis(trimethylsilyl)amide (2 M in THF, 3.0 mL, 6.0 mmol) was added dropwise to a stirred solution of dimethyl 3,3'-((hydroxypropyl)azanediyl)dipropionate (1.0 g, 4.05 mmol) in THF (40 mL). After 2 h, MeOH (20 mL) was added and the reaction mixture was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-10% MeOH/CH_2Cl_2, to give the *title compound* as a pale-yellow oil (0.80 g, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.75 (t, 2H, J = 5.2 Hz, NCH_2), 3.71 (s, 3H, OCH_3), 3.17 (br s, 2H, 2-CH_2), 2.66 (m, 4H, CH_2OH and 5-CH_2), 2.38 (br tt, J = 5.9, 1.5 Hz, 6-CH_2), 1.73 (app qn, 2H, $CH_2C\underline{H}_2CH_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.1 (CO), 169.9 (CO), 64.0 (NCH_2), 57.6 (CH_2OH), 56.4 (3-CH), 51.3 (OCH_3), 49.8 (2-CH_2), 49.2 (5-CH_2), 29.1 (6-CH_2), 27.7 ($CH_2\underline{C}H_2CH_2$); υ_{max}/cm^{-1} 2160.4, 1670.4, 1437.3, 1399.9, 1325.9, 1199.4, 1183.2, 1158.2, 959.9, 915.3; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 216.1243 and $[M + Na]^+$ 238.1054, $[C_{10}H_{18}NO_4]^+$ requires 216.1236 and $[C_{10}H_{17}NO_4Na]^+$ requires 238.1055.

Dimethyl 3,3'-(benzylazanediyl)dipropionate S4



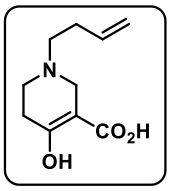
Methyl acrylate (4.94 mL, 54.87 mmol) was added to a stirred solution of benzylamine (2 mL, 18.29 mmol) in MeOH (65 mL). After 20.5 h, the reaction was concentrated *in vacuo* to give a colourless oil which was used directly in the next step without further purification (5.12 g, *quant.*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.19 (m, 5H, ArH), 3.62 (s, 6H, 2 x OCH_3), 3.57 (s, 2H, NCH_2), 2.78 (t, 4H, J = 7.2 Hz, 2 x NCH_2), 2.45 (t, 4H, J = 7.2 Hz, 2 x CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.8 (CO), 138.9 (ArC), 128.6 (ArCH), 128.1 (ArCH), 126.9 (ArCH), 58.3 (NCH_2), 51.4 (OCH_3), 49.1 (2 x NCH_2), 32.5 (2 x CH_2); υ_{max}/cm^{-1} 1732.5, 1436.2, 1247.4, 1193.9, 1170.7, 1129.1, 1039.9, 1027.7, 736.6, 698.2; *m/z* LRMS (ESI$^+$) found $[M + H]^+$ 280.2, $[C_{15}H_{22}NO_4]^+$ requires 280.1549. ^{1}H-NMR and ^{13}C-NMR are consistent with the literature.[294]

Methyl 4-acetoxy-1-(but-3-en-1-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate 106



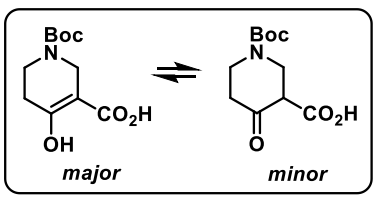
4-(Dimethylamino)pyridine (49 mg, 0.4 mmol) was added to a stirred solution of methyl-1-(but-3-en-1-yl)-4-oxopiperidine-3-carboxylate (0.33 g, 1.58 mmol), Ac_2O (0.37 mL, 3.95 mmol) and Et_3N (0.55 mL, 3.95 mmol) in CH_2Cl_2 (3 mL). After 16 h, $NaHCO_3$ (saturated aqueous solution, 5 mL) was added to the reaction mixture and the organic layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude orange solution was purified by SiO_2 flash chromatography, eluting with 10-50% EtOAc/petrol, to give the *title compound* as a yellow oil (96 mg, 24%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.86-5.75 (m, 1H, CH), 5.10-4.99 (m, 2H, CHC$\underline{H}_2$), 3.69 (s, 3H, OCH_3), 3.32 (t, 2H, *J* = 2.8 Hz, 2-CH_2), 2.70 (t, 2H, *J* = 5.8 Hz, 5-CH_2), 2.57 (t, 2H, *J* = 8.1 Hz, NC$\underline{H}_2$), 2.39-2.36 (m, 2H, 6-CH_2), 2.29 (br q, 2H, *J* = 7.2 Hz, $NCH_2C\underline{H}_2$), 2.19 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.4 (CO), 164.2 (CO), 155.2 (C), 136.2 (CH), 115.9 (CH_2), 115.6 (C), 56.5 (N$\underline{C}H_2$), 51.6 (OCH_3), 51.2 (2-CH_2), 48.8 (5-CH_2), 31.6 ($NCH_2\underline{C}H_2$), 29.5 (6-CH_2), 20.9 (CH_3); υ_{max}/cm^{-1} 1714.4, 1641.4, 1425.8, 1366.1, 1192.9, 1063.3, 1002.9, 913.6, 731.5; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 254.1400 and $[M + Na]^+$ 276.1214, $[C_{13}H_{20}NO_4]^+$ requires 254.1392 and $[C_{13}H_{19}NO_4Na]^+$ requires 276.1212.

1-(But-3-en-1-yl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid 119



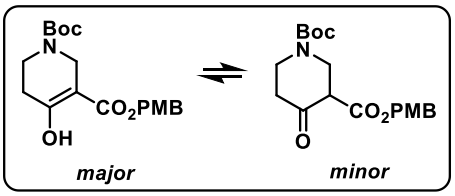
NaOH (1 M aqueous solution, 2 mL) was added to a stirred solution of methyl-1-(but-3-en-1-yl)-4-oxopiperdine-3-carboxylate, (0.40 g, 1.89 mmol) in H_2O (4 mL) at 0 ºC and stirred for 20 h at RT, at which point it was neutralised with HCl (1 M aqueous solution, 2 mL), extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the product (5 mg, 12%), which was used directly in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.76 (app t, 1H, CH), 5.11-5.04 (m, 2H, CHC$\underline{H}_2$), 3.68-3.55 (m, 2H, NCH_2), 3.50-3.43 (m, 2H, 2-CH_2), 2.90-2.85 (dd, 2H, *J* = 16.4, 7.0 Hz, 6-CH_2), 2.68-2.57 (m, 2H, $NCH_2C\underline{H}_2$), 2.34-2.32 (m, 2H, 5-CH_2).

1-(*tert*-Butoxycarbonyl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid 120



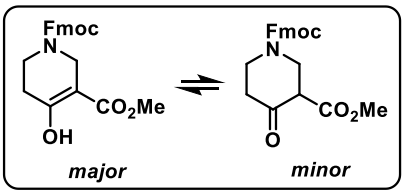
NaOH (1 M aqueous solution, 2 mL) was added to *tert*-butyl 4-oxopiperidine-1-carboxylate (0.38 g, 1.48 mmol) and stirred for 18 h, at which point it was neutralised with HCl (1 M aqueous solution, 2 mL), extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless solid (73 mg, 20%), which was used directly in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.75 (t, 2H, *J* = 6.4 Hz, 2-CH_2), 2.47 (t, 2H, *J* = 6.4 Hz, 6-CH_2), 1.71-1.69 (m, 2H, 5-CH_2), 1.49 (s, 9H, 3 x CH_3); *m/z* LRMS (ESI$^-$) found $[M - H]^-$ 242.2, $[C_{11}H_{16}NO_5]^+$ requires 242.1028.

1-(*tert*-Butyl)-3-(4-methoxybenzyl) 4-oxopiperidine-1,3-dicarboxylate 123



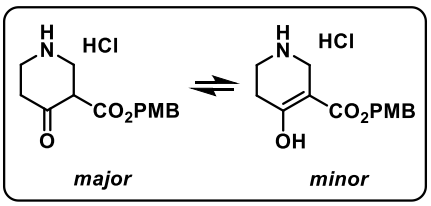
p-Methoxybenzyl alcohol (0.97 mL, 7.78 mmol) was added to a stirred solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (1.0 g, 3.89 mmol) in PhMe (29 mL) and heated under reflux using Dean-Stark apparatus for 21.5 h. The reaction mixture was cooled to RT, concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to give a colourless oil (1.41 g, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.99, (s, 1H, OH), 7.30 (d, 2H, *J* = 8.6 Hz, ArH) 6.88 (d, 2H, *J* = 8.6 Hz, ArH), 5.15 (s, 2H, $ArCH_2$), 4.07 (s, 2H, 2-CH_2), 3.81 (s, 3H, OCH_3), 3.55 (t, 2H, *J* = 5.7 Hz, 2H, 6-CH_2), 2.36 (t, 2H, *J* = 5.7 Hz, 2H, 5-CH_2), 1.46 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.6 (CO), 170.45 (CO), 159.7 (CO), 130.2 (ArC), 130.0 (ArCH), 129.4 (ArC), 113.8 (ArCH), 80.1 (3-CH), 65.9 ($ArCH_2$), 55.3 (OCH_3), 40.2 (2-CH_2), 39.2 (6-CH_2), 28.9 (5-CH_2), 28.4 (3 x CH_3); υ_{max}/cm^{-1} 1660.7, 1693.5, 1514.7, 1303.2, 1240.3, 1195.8, 1163.2, 1118.8, 820.9; *m/z* LRMS (ESI$^+$) found $[M + Na]^+$ 386.2, $[C_{19}H_{25}NO_6Na]^+$ requires 386.1580.

1-((9*H*-Fluoren-9-yl)methyl) 3-methyl 4-oxopiperidine-1,3-dicarboxylate S5



9-Fluororenylmethoxycarbonyl chloride (1.05 g, 4.06 mmol) was added to a stirred solution of methyl 4-oxopiperidine-3-carboxylate trifluoroacetate (1 g, 3.69 mmol), $NaHCO_3$ (0.47 g, 5.54 mmol) in dioxane:H_2O (3:2, 26:17 mL). After 18.5 h, the reaction mixture was diluted with EtOAc (10 mL), washed with H_2O (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 0-20% EtOAC/petrol, to give a colourless thick oil (0.86 g, 61%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H, OH), 7.78-7.74 (m, 2H, ArCH), 7.58-7.56 (m, 2H, ArCH), 7.42-7.38 (m, 2H, ArCH), 7.35-7.29 (m, 2H, ArCH), 4.50 (d, 2H, *J* = 6.6 Hz, CHC$\underline{H}_2$), 4.26 (t, 1H, *J* = 6.6 Hz, CH), 4.07 (m, 2H, 2-CH_2), 3.81 (br s, 3H, OCH_3), 3.57 (m, 2H, 6-CH_2), 2.31 (br s, 2H, 5-CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.5 (CO), 170.8 (CO), 170.1 (CO), 143.9 (ArC), 141.4 (ArCH), 127.7 (ArCH), 127.0 (ArCH), 124.9 (ArC), 119.9 (ArCH), 67.3 (CH$\underline{C}H_2$), 52.4 (3-CH), 51.6 (OCH_3), 47.4 (CH), 40.4 (2-CH_2), 39.9 (6-CH_2), 28.4 (5-CH_2); υ_{max}/cm^{-1} 1727.4, 1660.8, 1699.9, 1302.1, 1230.2, 1195.8, 1174.6, 1114.3, 753.0, 738.2; *m/z* LRMS (ESI$^+$) found $[M + Na]^+$ 402.11, $[C_{22}H_{21}NNaO_5]^+$ requires 402.1317.

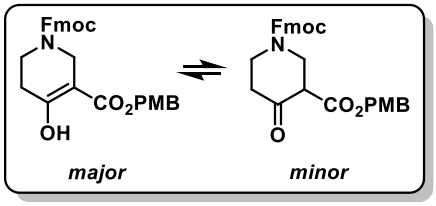
4-Methoxybenzyl 4-oxopiperidine-3-carboxylate hydrogen chloride 125



HCl (2 M solution in Et_2O, 4.0 mL) was added to 1-(*tert*-butyl) 3-(4-methoxybenzyl) 4-oxopiperidine-1,3 dicarboxylate (0.53 g, 1.46 mmol) and stirred for 19 h, at which point it was filtered and washed with cold Et_2O to give a colourless solid, which was used directly in the next step without further purification (0.44 g,

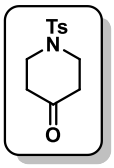
61%). ^{1}H-NMR (400 MHz, MeOH-d_4) δ 7.35 (d, 2H, J = 8.7 Hz, ArH), 6.93 (d, 2H, J = 8.7 Hz, ArH), 5.22 (s, 2H, $ArCH_2$), 3.84 (br s, 2H, 2-CH_2), 3.81 (s, 3H, OCH_3), 3.85 (br s, 1H, 3-CH), 3.42 (t, 2H, J = 6.4 Hz, 5-CH_2), 2.68 (tt, 2H, J = 6.4, 1.3 Hz, 6-CH_2); ^{13}C-NMR (100 MHz, MeOH-d_4) δ 169.0 (CO), 168.0 (CO), 160.0 (ArC), 130.4 (ArCH), 126.8 (ArC), 114.1 (ArCH), 92.1 (3-CH), 66.8 ($ArCH_2$), 55.3 (OCH_3), 39.9 (5-CH_2), 39.1 (2-CH_2), 25.3 (6-CH_2); υ_{max}/cm^{-1} 1664.4, 1612.7, 1514.6, 1411.3, 1292.3, 1237.3, 1215.9, 1084.5, 1164.2, 821.9; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 264.1231 and $[M + HCl + H]^+$ 300.1749, $[C_{14}H_{18}NO_4]^+$ requires 264.1236 and $[C_{14}H_{19}ClNO_4]^+$ requires 300.1003.

1-((9*H*-Fluoren-9-yl)methyl) 3-(4-methoxybenzyl) 4-oxopiperidine-1,3-dicarboxylate 126



9-Fluororenylmethoxycarbonyl chloride (0.26 g, 0.99 mmol) was added to a stirred solution of 4-methoxybenzyl 4-oxopiperidine-3-carboxylate hydrogen chloride (0.27 g, 0.90 mmol), $NaHCO_3$ (0.11 g, 1.35 mmol) in dioxane:H_2O (3:2, 7:5 mL). After 24 h, the reaction mixture was extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 10-50% EtOAC/petrol, to give a colourless oil (0.28 g, 64%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.02 (s, 1H, OH), 7.23 (br s, 2H, ArCH), 7.55 (d, 2H, J = 7.4 Hz, ArCH), 7.39 (br s, 2H, ArCH), 7.32 (d, 2H, J = 7.4 Hz, ArCH), 7.22 (br s, 2H, ArCH), 6.90 (d, 2H, J = 8.7 Hz, ArCH), 5.17 (br s, 2H, $ArCH_2$), 4.47 (d, 2H, J = 6.3 Hz, CHC$\underline{H}_2$), 4.24 (br t, 1H, J = 6.3 Hz, 6, C$\underline{H}CH_2$), 4.10 (br s, 2H, 2-CH_2), 3.80 (s, 3H, OCH_3), 3.55 (br m, 2H, 5-CH_2), 2.30 (br m, 2H, 6-CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.9 (CO), 170.3 (CO), 159.7 (CO), 143.8 (ArC), 141.3 ArCH), 130.2 (ArC), 130.2 (ArCH), 127.6 (ArCH), 127.0 (ArCH), 124.9 (ArC), 120.0 (ArCH), 114.0 (ArCH), 67.3 (CHC$\underline{H}_2$), 67.1 (3-CH), 66.1 ($ArCH_2$), 55.3 (OCH_3), 47.4 ($\underline{C}HCH_2$), 40.5 (2-CH_2), 39.9 (5-CH_2), 28.7 (6-CH_2); υ_{max}/cm^{-1} 1698.5, 1303.1, 1229.1, 1195.1, 1174.1, 1113.3, 908.1, 820.7, 757.8, 726.2; *m/z* HRMS (ESI$^+$) found $[M + Na]^+$ 508.1706, $[C_{29}H_{27}NNaO_6]^+$ requires 508.1736.

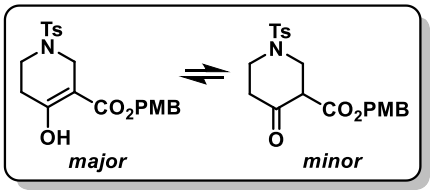
1-Tosylpiperidin-4-one S6



p-Toluenesulfonyl chloride (1.80 g, 9.46 mmol) was added to a stirred solution of piperidin-4-one trifluoroacetate (1.68 g, 7.88 mmol), Et_3N (2.20 mL, 15.76 mmol) and 4-(dimethylamino)pyridine (0.58 g, 4.73 mmol) in CH_2Cl_2 (16 mL) at 0 ˚C. After 16.5 h, H_2O (10 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with $NaHCO_3$ (saturated aqueous solution, 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 10-30% EtOAC/petrol, to give a colourless solid (1.78 g, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2H, J = 8.2 Hz, ArCH), 7.33 (d, 2H, J = 8.2 Hz, ArCH), 3.38 (t, 4H, J = 6.3 Hz, 3-CH_2 and 5-CH_2), 2.52 (t, 4H, J = 6.3 Hz, 2-CH_2 and 6-CH_2), 2.43 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 205.6 (CO), 144.1 (ArC), 133.3 (ArC), 129.9 (ArCH), 127.5 (ArCH), 45.9 (3-CH_2

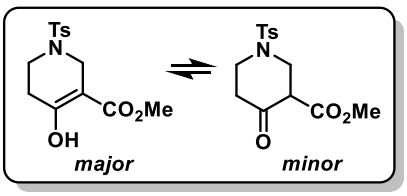
and 5-CH_2), 40.6 (2-CH_2 and 6-CH_2), 21.5 (CH_3); υ_{max}/cm^{-1} 1715.8, 1337.5, 1214.5, 1160.1, 917.3, 814.2, 729.4, 679.6, 564.5, 545.9; *m/z* LRMS (ESI^+) found $[M + H]^+$ 308.1 and $[M + Na]^+$ 276.1, $[C_{12}H_{16}NO_3S]^+$ requires 254.0670 and $[C_{12}H_{15}NNaO_3S]^+$ requires 254.0851; m.p. 129-131 °C (EtOAc/petrol), lit 134 °C.[295]

4-Methoxybenzyl 4-oxo-1-tosylpiperidine-3-carboxylate 127



4-(Dimethylamino)pyridine (32 mg, 0.26 mmol) was added to a stirred solution of 4-methoxybenzyl 4-oxopiperidine-3-carboxylate hydrogenchloride (0.13 g, 0.43 mmol), *p*-toluenesulfonyl chloride (0.10 g, 0.52 mmol) and Et_3N (0.12 mL, 0.86 mmol) in CH_2Cl_2 (1 mL). After 16.5 h, H_2O (5 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with $NaHCO_3$ (saturated aqueous solution, 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-5% MeOH/CH_2Cl_2, to give a yellow oil (0.16 g, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.97 (s, 1H, OH), 7.66 (d, 2H, *J* = 8.4 Hz, ArCH), 7.29 (m, 4H, ArCH), 6.89 (d, 2H, *J* = 8.4 Hz, ArCH), 5.14 (s, 2H, Ar-CH_2), 3.81 (s, 3H, OCH_3), 3.77 (br s, 2H, 2-CH_2), 3.24 (t, 2H, *J* = 5.8 Hz, 5-CH_2), 2.43 (br s, 2H, 6-CH_2), 2.41 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 205.5 (CO), 169.5 (CO), 159.7 (ArC), 143.8 (ArC), 133.5 (ArC), 130.1 (ArCH), 129.9 (ArC), 129.7 (ArCH), 127.5 (ArCH), 113.9 (ArCH), 95.0 (3-CH), 66.1 (Ar-CH_2), 55.2 (OCH_3), 42.2 (2 or 5-CH_2), 42.1 (2 or 5-CH_2) 28.8 (6-CH_2), 21.5 (CH_3); υ_{max}/cm^{-1} 1661.8, 1342.9, 1296.9, 1244.5, 1225.7, 1161.9, 1104.4, 816.1, 564.4, 548.9; *m/z* HRMS (ESI^+) found $[M + Na]^+$ 440.1141, $[C_{21}H_{23}NO_6SNa]^+$ requires 440.1140.

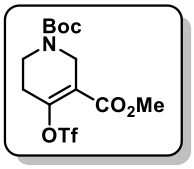
Methyl 4-oxo-1-tosylpiperidine-3 carboxylate S7



4-(Dimethylamino)pyridine (76 mg, 0.62 mmol) was added to a stirred solution of methyl 4-oxopiperidine-3-carboxylate hydrogenchloride (0.20 g, 1.03 mmol), *p*-toluenesulfonyl chloride (0.24 g, 1.24 mmol) and Et_3N (0.29 mL, 2.06 mmol) in CH_2Cl_2 (6 mL). After 23.5 h, H_2O (8 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with $NaHCO_3$ (saturated aqueous solution, 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to give a colourless oil (0.21 g, 66%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.92 (s, 1H, OH), 7.69 (d, 2H, *J* = 8.2 Hz, ArCH), 7.33 (d, 2H, *J* = 8.2 Hz, ArCH), 3.76 (s, 3H, OCH_3) superimposed on 3.76 (br s, 2H, 2-CH_2), 3.26 (t, 2H, *J* = 6.0 Hz, 5-CH_2), 2.46 (tt, 2H, *J* = 6.0, 5.4 Hz, 6-CH_2) superimposed on 2.43 (s, 3H, $ArCH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.5 (CO), 169.3 (C), 143.8 (ArC), 133.4 (ArC), 129.8 (ArCH), 127.6 (ArCH), 94.9 (C), 51.7 (OCH_3), 42.2 (2-CH_2), 42.2 (5-CH_2), 28.9 (6-CH_2), 21.5 ($ArCH_3$); υ_{max}/cm^{-1} 1667.8, 1444.1, 1350.9, 1311.8,

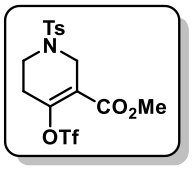
1247.3, 1229.1, 1163.9, 1106.8, 566.6, 549.7; *m/z* LRMS (ESI^+) found $[M + H]^+$ 312.1 and $[M + Na]^+$ 334.1, $[C_{14}H_{18}NO_5S]^+$ requires 312.0906 and $[C_{14}H_{17}NO_5SNa]^+$ requires 334.0906; m.p. 84-85 °C (EtOAc/petrol).

1-(*tert*-Butyl) 3-methyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihyrdopyridine-1,3(2*H*)-dicarboxylate S8



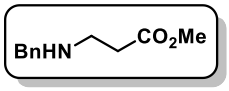
Sodium bis(trimethylsilyl)amide (1 M in THF, 0.65 mL, 0.65 mmol) was added dropwise over 2 min to a stirred solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (0.11 g, 0.43 mmol) in THF (2 mL) at -78 ˚C. After 1 h, *N*-phenyl-bis(trifluoromethanesulfonimide) (0.23 g, 0.65 mmol) was added in one portion at -78 ˚C. The reaction mixture was allowed to warm to RT over 30 min. After 24 h, the reaction was quenched with H_2O (5 mL), extracted with EtOAc (3 × 10 mL), washed with NH_4Cl (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with CH_2Cl_2, to give a yellow oil (91.3 mg, 55%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.27 (s, 2H, 2-CH_2), 3.83 (s, 3H, OCH_3), 3.62 (t, 2H, *J* = 5.8 Hz, 5-CH_2), 2.51 (br s, 2H, 6-CH_2), 1.48 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.1 (CO), 162.8 (CO), 153.9 (C), 150.9 (C), 119.9 (C), 118.3 (q, *J* = 324.0 Hz, CF_3), 81.0 (C), 52.4 (OCH_3), 43.0 (2-CH_2), 39.5 (5-CH_2), 28.9 (6-CH_2), 28.3 (3 x CH_3); ^{19}F-NMR (376 MHz, $CDCl_3$); -74.62; υ_{max}/cm^{-1} 1703.0, 1421.9, 1296.8, 1241.5, 1209.0, 1161.0, 1140.9, 1080.8, 1044.5, 823.7; *m/z* HRMS (ESI^+) found $[M + Na]^+$ 412.0654, $[C_{13}H_{18}F_3NNaO_7S]^+$ requires 412.0654

Methyl 1-tosyl-4-(((trifluoromethyl)sulfonyl)oxy)-1,2,5,6-tetrahydropyridine-3-carboxylate S9



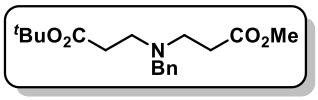
Sodium bis(trimethylsilyl)amide (1 M in THF, 12.34 mL, 12.24 mmol) was added dropwise to a stirred solution of methyl 4-oxo-1-tosylpiperidine-3-carboxylate (2.54 g, 8.16 mmol) in THF (42 mL) at -78 ˚C. After 1 h, *N*-phenyl-bis(trifluoromethanesulfonimide) (4.37 g, 12.24 mmol) was added in one portion at -78 ˚C. The reaction mixture was warmed slowly to RT. After 19 h, the reaction was poured into with brine (20 mL), extracted with EtOAc (3 × 10 mL), washed with NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-30% EtOAc/petrol, to give a colourless solid (1.21 g, 33%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 (d, 2H, *J* = 8.2 Hz, ArCH), 7.35 (d, 2H, *J* = 8.2 Hz, ArCH), 4.01 (t, 2H, *J* = 2.7 Hz, 2-CH_2), 3.81 (s, 3H, OCH_3), 3.35 (t, 2H, *J* = 5.9 Hz, 5-CH_2), 2.54 (m, 2H, 6-CH_2), 2.44 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.3 (CO), 150.2 (C), 144.4 (C), 133.1 (ArC), 130.0 (ArCH), 127.5 (ArCH), 119.3 (ArC), 118.2 (q, *J* = 320.1 Hz, CF_3), 52.5 (OCH_3), 44.5 (2-CH_2), 42.2 (5-CH_2), 28.8 (6-CH_2), 21.5 (CH_3); ^{19}F-NMR (376 MHz, $CDCl_3$); -74.50; υ_{max}/cm^{-1} 1424.5, 1206.4, 1163.3, 1137.9, 1104.7, 1079.1, 954.4, 886.0, 832.6, 619.3; *m/z* HRMS (ESI^+) found $[M + Na]^+$ 466.0211, $[C_{15}H_{16}F_3NO_7S_2Na]^+$ requires 466.0218

Methyl 3-(benzylamino)propanoate S10



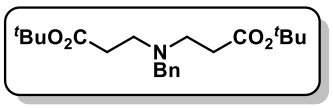
Methyl acrylate (0.08 mL, 0.93 mmol) was added to a stirred solution of benzyl amine (0.1 mL, 0.93 mmol) in MeOH (1 mL). The reaction mixture was concentrated *in vacuo* after 22 h to give a colourless oil which was used directly in the next step without further purification (0.18 g, *quant.*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32-7.31 (m, 5H, ArH), 3.81 (s, 2H, $ArCH_2$), 3.68 (s, 3H, OCH_3), 2.90 (t, 2H, *J* = 6.6 Hz, NCH_2), 2.54 (t, 2H, *J* = 6.6 Hz, $NCH_2C\underline{H}_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.2 (CO), 140.1 (ArC), 128.4 (ArCH), 128.0 (ArCH), 126.9 (ArCH), 53.7 ($ArCH_2$), 49.2 (OCH_3), 44.4 (NCH_2), 34.6 ($NCH_2\underline{C}H_2$); υ_{max}/cm^{-1} 2951.7, 1733.3, 1453.7, 1436.7, 1360.4, 1171.7, 1121.2, 1027.5, 736.8, 698.9; *m/z* LRMS (ESI$^+$) found $[M + H]^+$ 194.1, $[C_{11}H_{16}NO_2]^+$ requires 194.1181. ^{1}H-NMR and ^{13}C-NMR are consistent with the literature.[296]

***tert*-Butyl 3-(benzyl(3-methoxy-3-oxopropyl)amino)propanoate S11**



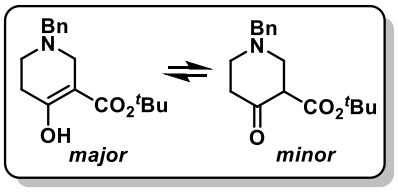
tert-Butyl acrylate (0.68 mL, 4.40 mmol) was added to a stirred solution of methyl 3-(benzylamino)propanoate (0.17 g, 0.88 mmol) in MeOH (1 mL). After 72 h, the reaction was concentrated *in vacuo* to give a colourless oil which was used directly in the next step without further purification (0.28 g, *quant.*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.28 (m, 5H, ArH), 3.64 (s, 3H, OCH_3), 3.58 (s, 2H, NCH_2), 2.81-2.74 (m, 4H, 2 x NCH_2), 2.47 (t, 2H, *J* = 7.1 Hz, $C\underline{H}_2CO_2CH_3$), 2.38 (t, 2H, *J* = 7.1 Hz, $C\underline{H}_2CO_2{}^t$Bu), 1.43 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.0 (CO), 171.9 (CO), 139.2 (C), 128.7 (ArCH), 128.2 (ArCH), 127.0 (ArCH), 80.3 (C), 58.3 ($ArCH_2$), 51.3 (OCH_3), 49.4 (NCH_2), 49.1 (NCH_2), 33.8 ($C\underline{H}_2CO_2{}^t$Bu), 32.6 ($\underline{C}H_2CO_2CH_3$), 28.1 (3 x CH_3); υ_{max}/cm^{-1} 1728.9, 1454.4, 1436.7, 1367.2, 1330.4, 1228.2, 1251.3, 1157.5, 736.3, 698.6; *m/z* LRMS (ESI$^+$) found $[M + H]^+$ 322.2, $[C_{18}H_{28}NO_4]^+$ requires 322.2018. ^{1}H-NMR and ^{13}C-NMR are consistent with the literature.[296]

Di-*tert*-butyl 3,3'-(benzylazanediyl)dipropionate 132



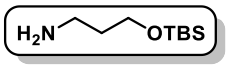
tert-Butyl acrylate (0.72 mL, 4.65 mmol) was added to a stirred solution of benzyl amine (0.10 g, 0.93 mmol) in MeOH (1 mL). After 72 h, the reaction was concentrated *in vacuo* to give a colourless oil which was used directly in the next step without further purification (0.34 g, *quant.*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.29 (m, 5H, ArH), 3.58 (s, 2H, NCH_2), 2.76 (t, 4H, *J* = 7.3 Hz, 2 x NCH_2), 2.38 (t, 4H, *J* = 7.3 Hz, 2 x $NCH_2C\underline{H}_2$), 1.43 (s, 18H, 6 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.0 (CO), 139.3 (ArC), 128.7 (ArCH), 128.2 (ArCH), 126.9 (ArCH), 80.3 (C), 58.2 (NCH_2), 49.3 (2 x NCH_2), 33.8 (2 x $NCH_2\underline{C}H_2$), 28.1 (6 x CH_3); υ_{max}/cm^{-1} 2977.5, 1725.8, 1454.4, 1392.2, 1366.7, 1253.0, 1153.1, 847.6, 737.2, 698.3; *m/z* LRMS (ESI$^+$) found $[M + H]^+$ 364.2, $[C_{21}H_{34}NO_4]^+$ requires 364.2488.

tert-Butyl 1-benzyl-4-oxopiperidine-3-carboxylate 133



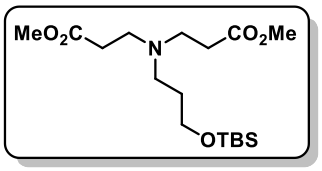
Sodium bis(trimethylsilyl)amide (1 M in THF, 1.5 mL, 1.49 mmol) was added to a stirred solution of di-*tert*-butyl 3,3'-(benzylazanediyl)dipropionate (0.36 g, 0.99 mmol) in THF (3 mL). After 4 h, MeOH (10 mL) was added and the reaction mixture was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to give the *title compound* as a colourless oil (0.23 g, 79%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.16 (s, 1H, OH), 7.34-7.33 (m, 5H, ArH), 3.62 (s, 2H, NCH_2), 3.17 (br t, 2H, *J* = 1.6 Hz, 2-CH_2), 2.56 (t, 2H, *J* = 6.1 Hz, 5-CH_2), 2.35 (tt, 2H, *J* = 6.1, 1.6 Hz, 6-CH_2), 1.48 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.7 (CO), 168.2 (CO), 129.0 (ArCH), 128.8 (ArCH), 128.3 (ArCH), 127.2 (ArC), 81.9 (3-CH), 61.7 (NCH_2), 50.6 (2-CH_2), 48.4 (5-CH_2), 29.4 (6-CH_2), 28.0 (3 x CH_3); υ_{max}/cm^{-1} 1718.9, 1658.8, 1393.3, 1336.9,1318.5, 1237.8, 1153.1, 847.2, 740.9, 698.7; *m/z* LRMS (ESI^+) found $[M + H]^+$ 290.2, $[C_{17}H_{24}NO_3]^+$ requires 290.1756.

3-((_tert_-Butyldimethylsilyl)oxy)prop-1-amine S12



tert-Butyldimethylsilyl chloride (4.33 g, 28.71 mmol) was added to a stirred solution of 3-aminopropanol (2 mL, 26.10 mmol) and imidazole (2.67 g, 39.15 mmol) in CH_2Cl_2 (65 mL). After 22.5 h, $NaHCO_3$ (saturated aqueous solution, 20 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a pale-yellow oil, which was used directly in the next step without further purification (4.94 g, *quant.*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.70 (t, 2H, *J* = 6.0 Hz, OCH_2), 2.83 (t, 2H, *J* = 6.8 Hz, NCH_2), 1.72-1.66 (m, 2H, $CH_2C\underline{H}_2CH_2$), 0.90 (s, 9H, 3 x CH_3), 0.05 (s, 6H, 2 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 61.2 (OCH_2), 39.2 (NCH_2), 35.4 ($CH_2C\underline{H}_2CH_2$), 25.9 (3 x CH_3), 18.3 (C), -5.4 (2 x CH_3); υ_{max}/cm^{-1} 2928.6, 2866.5, 1471.7, 1463.7, 1254.7, 1095.7, 1066.3, 833.8, 815.2, 774.7. ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[297]

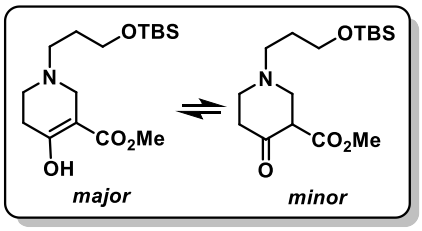
Dimethyl 3,3'-((3-((_tert_-butyldimethylsilyl)oxy)propyl)azandiyl)dipropionate S13



Methyl acrylate (7.05 mL, 78.27 mmol) was added to a stirred solution of 3-((*tert*-butyldimethylsilyl)oxy)prop-1-amine (4.94 g, 26.09 mmol) in methanol (25 mL). After 20.5 h, the reaction was concentrated *in vacuo* to give a colourless oil which was used directly in the next step without further purification (8.37 g, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 6H, 2 x OCH_3), 3.58 (t, 2H, *J* = 6.2 Hz, OCH_2), 2.74 (t, 2H, *J* = 7.3 Hz, 2 x NCH_2), 2.48 (t, 2H, *J* = 7.1 Hz, NCH_2), 2.42 (t, 2H, *J* = 7.3 Hz, 2 x $C\underline{H}_2CO_2Me$), 1.63-1.57 (m, 2H, $CH_2C\underline{H}_2CH_2$), 0.86 (s, 9H, 3 x CH_3), 0.02 (s, 6H, 2 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.0 (CO), 60.9 (OCH_2), 51.5 (OCH_3), 50.2 (NCH_2), 49.2 (2 x NCH_2), 32.5 (2 x $\underline{C}H_2CO_2Me$), 30.2 ($CH_2\underline{C}H_2CH_2$), 25.9 (3 x CH_3), 18.2 (C), -5.4 (2 x CH_3); υ_{max}/cm^{-1}

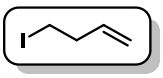
1737.8, 1436.3, 1251.9, 1193.8, 1172.7, 1094.2, 1006.1, 834.0, 814.0, 774.60; *m/z* LRMS (ESI^+) found $[M + H]^+$ 362.2, $[C_{17}H_{36}NO_5Si]^+$ requires 362.2363.

Methyl 1-(3-((*tert*-butyldimethysilyl)oxy)propyl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate S14



Potassium bis(triemthylsilylamide) (0.7 M in PhMe, 3.96 mL, 4.16 mmol) was added to a stirred solution of dimethyl 3,3'-((3-((*tert*-butyldimethylsilyl)oxy)propyl)azandiyl)dipropionate (1 g, 2.77 mmol) in PhMe (20 mL) at 0 ˚C. After 1 h, MeOH (10 mL) was added to the reaction mixture and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-30% EtOAc/petrol, to give a yellow oil (0.70 g, 63%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.96 (br s, 1H, OH), 3.73 (s, 3H, OCH_3), 3.66-3.63 (m, 2H, OCH_2), 3.11 (t, 2H, *J* = 1.7 Hz, 2-CH_2), 2.60 (t, 2H, *J* = 5.9 Hz, Z 5-CH_2), 2.51 (t, 2H, *J* = 7.7 Hz, NCH_2), 2.39 (tt, 2H, *J* = 5.9, 1.6 Hz, 6-CH_2), 1.76-1.66 (m, 2H, $CH_2C\underline{H}_2CH_2$), 0.87 (s, 9H, 3 x CH_3), 0.03 (s, 6H, 2 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.3 (CO), 170.3 (C), 96.6 (C), 61.3 (OCH_2), 54.5 (NCH_2), 52.2 (OCH_3), 49.7 (2-CH_2), 49.4 (5-CH_2), 30.5 ($CH_2\underline{C}H_2CH_2$), 29.4 (6-CH_2), 25.9 (3 x CH_3), 18.3 (C), -5.4 (2 x CH_3); υ_{max}/cm^{-1} 1665.6, 1308.4, 1232.7, 1211.9, 1194.0, 1095.7, 1073.5, 833.2, 813.3, 773.9; *m/z* LRMS (ESI^+) found $[M + H]^+$ 330.2, $[C_{16}H_{31}NO_4Si]^+$ requires 330.2101.

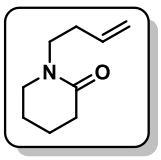
4-Iodobut-1-ene S15



4-Bromobut-1-ene (0.75 mL, 7.41 mmol) was added to a stirred solution of NaI (2.22 g, 14.82 mmol) in acetone (9 mL) and heated under reflux. After 1 h, the reaction mixture was cooled to RT and H_2O (10 mL) and Et_2O (10 mL) were added. The solution was extracted with Et_2O (3 x 10 mL), washed with H_2O (20 mL), Na_2SO_3 (1 M aqueous solution, 20 mL) and brine (20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material as a pale-yellow oil, which was used directly in the next step without further purification (0.96 g, 71%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.81-5.70 (m, 1H, CH), 5.14-5.09 (m, 2H, $CHC\underline{H}_2$), 3.18 (t, 2H, *J* = 7.8 Hz, ICH_2), 2.62 (app q, 2H, $C\underline{H}_2CH$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.8 ($\underline{C}HCH_2$), 117.0 ($CH\underline{C}H_2$), 37.6 ($CH\underline{C}H_2$), 4.7 (ICH_2). ^{1}H-NMR and ^{13}C-NMR are consistent with the literature [298]

1-(But-3-en-1-yl)piperidin-2-one 143

Cyclisation Procedure

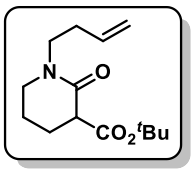


5-Chlorovaleroyl chloride (0.66 mL, 5.12 mmol) was added dropwise to a stirred solution of but-3-en-1-amine hydrochloride (0.50 g, 4.65 mmol) and Et_3N (0.97 mL, 6.98 mmol) in CH_2Cl_2 at 0 °C over 3 min. The reaction mixture was warmed to RT and after 4 h, HCl (1 M aqueous solution, 15 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was dissolved in THF (10 mL) added dropwise to a stirred solution of NaH (60% in mineral oil, 0.56 g, 13.95 mmol) in THF (37 mL). The reaction mixture was then heated under reflux for 17.5 h, cooled to 0 °C and quenched with H_2O (20 mL). The organic layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 0-5% MeOH/CH_2Cl_2, to afford an orange oil (0.45 g, 63%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.83-5.73 (m, 1H, CH), 5.09-5.00 (m, 2H, CHC$\underline{H}_2$), 3.41 (t, 2H, *J* = 7.4 Hz, NCH_2), 3.27 (br t, 2H, *J* = 5.8 Hz, 3-CH_2), 2.36 (br t, 2H, *J* = 5.8 Hz, 6-CH_2), superimposed on 2.31 (app q, 2H, C$\underline{H}_2$CH) 1.80-1.74 (m, 4H, 4-CH_2 and 5-CH_2CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.7 (CO), 135.4 (CH), 116.6 (CH$\underline{C}H_2$), 48.1 (3-CH_2), 46.5 (NCH_2), 32.3 (6-CH_2), 31.6 (C$\underline{H}_2$CH), 23.2 (4-CH_2 or 5-CH_2), 21.3 (4-CH_2 or 5-CH_2); υ_{max}/cm^{-1} 1621.6, 1494.0, 1466.8, 1447.3, 1417.4, 1328.5, 1178.7, 1166.4, 912.0; *m/z* LRMS (ESI$^+$) found $[M + H]^+$ 154.1 and $[M + Na]^+$ 176.1, $[C_9H_{16}NO]^+$ requires 154.1232 and $[C_9H_{15}NONa]^+$ requires 176.1051. ^{1}H-NMR and ^{13}C-NMR are consistent with the literature.[101]

Alkylation Procedure

NaH (60% mineral oil, 30 mg, 0.75 mmol) was added to a stirred solution of δ-valerolactam (50 mg, 0.50 mmol) in THF (4 mL). After 1 h, 4-iodobut-1-ene (0.46 g, 2.50 mmol) was added dropwise and the reaction was stirred for 16.5 h. After which, the reaction mixture was poured in H_2O and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 40-70% EtOAc/petrol, to give the product (4.3 mg, 6%).

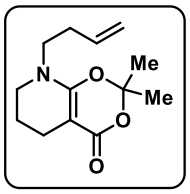
***tert*-Butyl 1-(but-3-en-1-yl)-2-oxopiperidine-3-carboxylate 146**



Lithium bis(trimethylsilyl)amide (0.9 M solution in hexane, 3.96 mL, 3.56 mmol) was added dropwise over 3 min to a stirred solution of 1-(but-3-en-1-yl)piperidin-2-one (0.33 g, 2.37 mmol) in THF (4 mL) at -78 °C. After 1 h, di-*tert*-butyl dicarbonate (0.52 g, 2.37 mmol) in THF (3 mL) was added dropwise over 2 min to the reaction mixture at -78 °C. The reaction was stirred at this temperature for 5 h and then slowly warmed to RT. After 16 h, the reaction was quenched with HCl (1 M aqueous solution, 10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$,

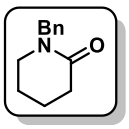
filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-5% MeOH/CH_2Cl_2, to give a yellow oil (0.52 g, 87 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.82-5.71 (m, 1H, CH), 5.09-4.99 (m, 2H, CHC<u>H</u>$_2$), 3.40 (t, 2H, *J* = 7.5 Hz, NCH_2), 3.36-3.30 (m, 1H, 3-CH), 3.25 (t, 2H, *J* = 6.35 Hz, 6-CH_2), 2.30 (q, 2H, *J* = 7.5 Hz, $NCH_2C\underline{H}_2$), 2.07-1.97 (m, 2H, 4-CH_2), 1.95-1.86 (m, 2H, 5-CH_2), 1.45 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4 (CO), 166.0 (CO), 135.2 (CH), 116.7 (CHC<u>H</u>$_2$), 81.3 (C), 50.1 (6-CH_2), 47.9 (3-CH), 46.8 (NCH_2), 31.5 ($NCH_2\underline{C}H_2$), 27.9 (3 x CH_3), 25.1 (4-CH_2), 20.9 (5-CH_2); υ_{max}/cm^{-1} 1728.7, 1640.9, 1492.6, 1366.6, 1277.4, 1254.9, 1207.9, 1147.1, 1092.9, 849.0; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 254.1757 and $[M + Na]^+$ 276.1588, $[C_{14}H_{24}NO_3]^+$ requires 254.1756 and $[C_{14}H_{23}NO_3Na]^+$ requires 276.1576.

8-(But-3-en-1-yl)-2,2-dimethyl-5,6,7,8-tetrahydro-4*H*-[1,3]dioxino[4,5-*b*]pyridine-4-one 144



Trifluoroacetic anhydride (0.94 mL, 6.74 mmol), Ac_2O (0.73 mL, 7.70 mmol) and trifluoroacetic acid (4.66 mL, 60.46 mmol) were all added sequentially dropwise to a stirred solution of *tert*-butyl-(but-3-en-1-yl)-2-oxopiperidine-3-carboxylate (0.27 g, 1.07 mmol) in acetone (4.66 mL, 63.45 mmol) at -78 °C over 15 min. The reaction mixture was stirred at this temperature for 4 h, then RT for 20 h. The reaction mixture was added dropwise to $NaHCO_3$ (saturated aqueous solution, 20 mL), and additional $NaHCO_3$ was added to maintain pH 7-8. The quenched mixture was extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 10-50% EtOAc/petrol, to give a yellow oil (0.15 g, 60%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.78-5.68 (ddt, 1H, *J* = 17.0, 10.1, 7.0 Hz, C<u>H</u>CH_2), 5.12-5.05 (m, 2H, CHC<u>H</u>$_2$), 3.31 (t, 2H, *J* = 7.1 Hz, NCH_2), 3.29-3.26 (m, 2H, 6-CH_2), 2.38 (t, 2H, *J* = 6.4 Hz, 4-CH_2), 2.28-2.26 (m, 2H, $NCH_2C\underline{H}_2CH$), 1.86-1.80 (m, 2H, 5-CH_2), 1.68 (s, 6H, 2 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.8 (CO), 162.9 (C), 159.1 (C), 134.6 (<u>C</u>HCH_2), 117.5 (CH<u>C</u>H$_2$), 104.4 (C), 48.1 (6-CH_2), 47.4 (NCH_2), 33.0 ($NCH_2\underline{C}H_2CH$), 25.3 (2 x CH_3), 21.6 (5-CH_2), 19.6 (4-CH_2); υ_{max}/cm^{-1} 1639.4, 1589.4, 1496.9, 1433.6, 1365.2, 1309.3, 1261.7, 1204.1, 1146.7, 1005.7; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 238.1448 and $[M + Na]^+$ 260.1269, $[C_{13}H_{20}NO_5]^+$ requires 238.1443 and $[C_{13}H_{19}NO_3Na]^+$ requires 260.1263.

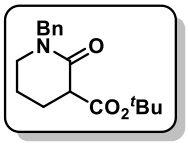
1-Benzylpiperidin-2-one 152



5-Chlorovaleroyl chloride (3.91 mL, 30.24 mmol) was added dropwise to a stirred solution of benzylamine (3.0 mL, 27.49 mmol) and trimethylamine (4.21 mL, 30.24 mmol) in CH_2Cl_2 (70 mL) at 0 °C over 3 min. The reaction mixture was warmed to RT. After 4.5 h, HCl (1 M aqueous solution, 50 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (saturated aqueous solution, 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was dissolved in THF (48 mL), to which NaH (60% in mineral oil, 1.21 g, 30.24 mmol) was added. The reaction mixture was then heated under reflux for 16 h, cooled to 0 °C and quenched with H_2O (30 mL). The organic layer was extracted

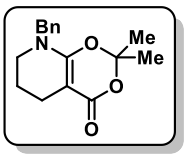
with Et_2O (3 x 20 mL and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 30-60% EtOAc/petrol, to afford a colourless oil (2.06 g, 40%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H, ArCH), 4.60 (s, 2H, $ArCH_2$), 3.19 (t, 2H, *J* = 6.2 Hz, 3-CH_2), 2.47 (t, 2H, *J* = 6.5 Hz, 6-CH_2), 1.82-1.72 (m, 4H, 4-CH_2 and 5-CH_2); 169.8 (CO), 137.3 (ArC), 128.5 (ArCH), 128.0 (ArCH), 127.3 (ArC), 50.1 ($ArCH_2$), 47.2 (3-CH_2), 32.4 (6-CH_2), 23.2 (4-CH_2 or 5-CH_2), 21.4 (4-CH_2 or 5-CH_2). ^{1}H-NMR and ^{13}C-NMR data is consistent with the literature.[299]

tert-Butyl 1-benzyl-2-oxopiperidine-3-carboxylate S16



Lithium bis(trimethylsilyl)amide (0.9 M solution in hexane, 17.6 mL, 15.86 mmol) was added dropwise over 3 min to a stirred solution of 1-benzylpiperidin-2-one (2.0 g, 10.57 mmol) in THF (16 mL) at -78 °C. After 1 h, di-*tert*-butyl dicarbonate (2.31 g, 10.57 mmol) in THF (16 mL) was added dropwise over 2 min to the reaction mixture at -78 °C. The reaction was slowly warmed to RT. After 20 h, the reaction was quenched with HCl (1 M aqueous solution, 30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 40-50% EtOAc/petrol, to give a yellow oil (2.57 g, 84 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H, ArCH), 4.61 (dd, 2H, *J* = 131.1, 14.8 Hz, $ArCH_2$), 3.38 (t, 1H, *J* = 7.0 Hz, CH), 3.28-3.15 (m, 2H, 6-CH_2), 2.15 (m, 2H, 4-CH_2), 1.94-1.65 (m, 2H, 5-CH_2), 1.50 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4 (CO), 166.3 (CO), 136.9 (ArC), 128.5 (ArCH), 127.9 (ArCH), 127.3 (ArCH), 81.5 (C), 50.2 ($ArCH_2$), 50.1 (CH), 47.0 (6-CH_2), 28.0 (3 x CH_3), 25.3 (4-CH_2), 20.8 (5-CH_2). ^{1}H-NMR and ^{13}C-NMR data is consistent with the literature.[300]

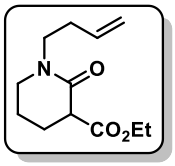
8-Benzyl-2,2-dimethyl-5,6,7,8-tetrahydro-4*H*-[1,3]dioxino[4,5-*b*]pyridine-4-one 149



Trifluoroacetic anhydride (4.50 mL, 32.63 mmol), Ac_2O (3.50 mL, 37.30 mmol) and trifluoroacetic acid (22.60 mL, 292.67 mmol) were all added sequentially dropwise to a stirred solution of *tert*-butyl-benzyl-2-oxopiperidine-3-carboxylate (1.50 g, 5.18 mmol) in acetone (22.60 mL, 307.17 mmol) at -78 °C over 20 min. The reaction mixture was stirred at this temperature for 3.5 h, then RT for 14.5 h. The reaction mixture was added dropwise to $NaHCO_3$ (saturated aqueous solution, 50 mL), and additional $NaHCO_3$ was added to maintain pH 7-8. The quenched mixture was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with $NaHCO_3$ (saturated aqueous solution, 50 mL) and brine (30 mL). The crude material was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 10-60% EtOAc/petrol, to give a yellow oil (0.63 g, 44%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 3H, ArCH), 7.20-7.18 (m, 2H, ArCH), 4.43 (s, 2H, $ArCH_2$), 3.22 (t, 2H, *J* = 5.6 Hz, 6-CH_2), 2.42 (t, 2H, *J* = 6.1 Hz, 4-CH_2), 1.86-1.80 (m, 1.86-1.80, 2H, 5-CH_2), 1.68 (s, 6H,

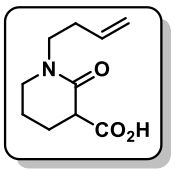
2 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.0 (CO), 159.0 (C), 136.7 (ArC), 128.8 (ArCH), 127.7 (ArCH), 127.3 (ArCH), 104.7 (C), 73.7 (C), 51.2 ($ArCH_2$), 47.7 (6-CH_2), 25.3 (4-CH_2), 21.6 (5-CH_2), 19.5 (2 x CH_3); υ_{max}/cm^{-1} 1589.9, 1578.9, 1495.6, 1434.7, 1387.8, 1263.9, 1203.44, 1142.3, 730.1, 689.9; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 274.1441 and $[M + Na]^+$ 296.1257, $[C_{16}H_{20}NO_3]^+$ requires 274.1443 and $[C_{16}H_{19}NO_3Na]^+$ requires 296.1263.

Ethyl 1-(but-3-en-1-yl)-2-oxopiperidine-3-carboxylate 156



Lithium bis(trimethylsilyl)amide (1 M in THF 13.1 mL, 13.06 mmol) was added dropwise to a stirred solution of 1-(but-3-en-1-yl)piperidin-2-one (1.0 g, 6.53 mmol) in THF (20 mL) at -78 °C. The reaction mixture was stirred for 1 h, and ethyl chloroformate (0.62 mL, 6.53 mmol) was added. The reaction mixture was stirred at RT for 17.5 h, poured into H_2O (20 mL) and exctracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude residue was purified by SiO_2 flash chromatography, eluting with 10-20% petrol/CH_2Cl_2, to give a yellow oil (1.23 g, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.83-5.73 (m, 1H, C<u>H</u>CH_2), 5.10-5.01 (m, 2H, CHC<u>H</u>$_2$), 4.26-4.15 (m, 2H, C<u>H</u>$_2$C$_3$), 3.42 (t, 2H, *J* = 7.2 Hz, NC<u>H</u>$_2$CH$_2$CH), 3.39-3.33 (m, 2H, 6-CH_2), 3.30-3.25 (m, 1H, CH), 2.32 (q, 2H, *J* = 7.2 Hz, NCH$_2$C<u>H</u>$_2$CH), 2.14-1.90 (m, 3H, 4-CH_2 and 5-CH_2), 1.80-1.70 (m, 1H, 5-CH_2), 1.28 (t, 3H, *J* = 7.3 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.1 (CO), 165.6 (CO), 135.2 (C<u>H</u>CH_2), 116.2 (CH<u>C</u>H_2), 61.2 (<u>C</u>H_2CH$_3$), 49.1 (6-CH_2), 47.9 (CH), 46.9 (N<u>C</u>H$_2$CH$_2$CH), 31.5 (NCH$_2$<u>C</u>H$_2$CH), 25.0 (4-CH_2), 21.0 (5-CH_2), 14.1 (CH$_2$C<u>H</u>$_3$); υ_{max}/cm^{-1} 1732.9, 1637.7, 1492.5, 1445.4, 1356.5, 1312.9, 1250.7, 1156.8, 1030.2, 912.7; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 226.1442 and $[M + Na]^+$ 248.1259, $[C_{12}H_{20}NO_3]^+$ requires 226.1443 and $[C_{12}H_{19}NO_3Na]^+$ requires 248.1263.

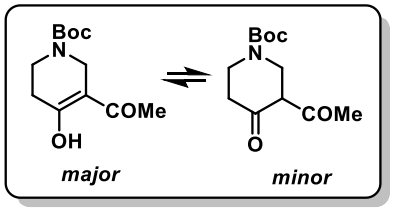
1-(But-3-en-1-yl)-2-oxopiperidine-3-carboxylic acid 148



NaOH (2 M aqueous solution, 2.68 mL) was added to a stirred solution of ethyl 1-(but-3-en-1-yl)-2-oxopiperidine-3-carboxylate (1.21 g, 5.37 mmol) in MeOH (15 mL) and H_2O (12 mL). After 20 h, the reaction mixture was quenched with HCl (1M aqueous solution, 30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo* to give the title compound as a yellow oil (1.03 g, 97%) which was used directly in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.66 (s, 1H, COOH), 5.73 (ddt, 1H, *J* = 17.2, 10.1, 7.0 Hz, C<u>H</u>CH_2), 5.09-5.03 (m, 2H, CHC<u>H</u>$_2$), 3.47 (t, 2H, *J* = 7.3 Hz, NC<u>H</u>$_2$CH$_2$CH), 3.41-3.30 (m, 2H, 6-CH_2), 3.21-3.17 (m, H, CH), 2.33 (app q, 3H, NCH$_2$C<u>H</u>$_2$CH and 5-CH_2), 2.02-1.92 (m, 2H, 4-CH_2), 1.86-1.75 (m, 1H, 5-CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.6 (CO), 134.3 (<u>C</u>HCH_2), 117.4 (CH<u>C</u>H_2), 48.6 (6-CH_2), 47.4 (N<u>C</u>H$_2$CH$_2$CH), 44.5 (CH), 31.3 (NCH$_2$<u>C</u>H$_2$CH), 23.1 (5-CH_2), 21.5 (4-CH_2); υ_{max}/cm^{-1} 1731.9, 1597.8, 1492.8, 1466.6, 1434.7, 1357.5, 1274.7, 1242.3, 1172.6, 913.2; *m/z*

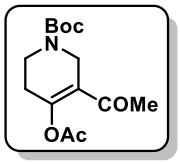
HRMS (ESI$^+$) found $[M + H]^+$ 198.1120 and $[M + Na]^+$ 220.0936, $[C_{10}H_{16}NO_3]^+$ requires 198.1130 and $[C_{10}H_{15}NO_3Na]^+$ requires 220.0950.

***tert*-Butyl 3-acetyl-4-oxopiperidine-1-carboxylate 162**



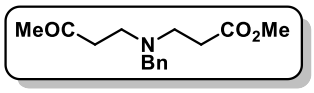
1-Boc-4-piperidone (2.0 g, 10.04 mmol) and pyrrolidine (1.68 mL, 20.08 mmol) in dioxane (5 mL) was heated under reflux using Dean-Stark apparatus for 3 h. The reaction was cooled to RT and concentrated *in vacuo* to afford an orange oil, which was dissolved in PhMe (5 mL) and treated with Ac_2O (1.90 mL, 22.09 mmol). The reaction mixture was stirred for 15 h, at which point H_2O (3 mL) was added and the reaction was heated under reflux for 25 h. The reaction mixture was cooled to RT diluted with H_2O (10 mL) and the organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with HCl (5% aqueous solution, 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 0-2.5% EtOAc/petrol, to afford a colourless oil (1.25 g, 52%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 15.62 (s, 1H, OH), 4.15 (br s, 2H, 2-CH_2), 3.55 (t, 2H, J = 5.6 Hz, 6-CH_2), 2.40 (br s, 2H, 5-CH_2), 2.10 (s, 3H, CH_3), 1.45 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.9 (CO), 180.4 (CO), 157.4 (CO), 105.2 (3-CH), 80.3 (C), 41.4 (2-CH_2), 39.9 (6-CH_2), 31.0 (5-CH_2), 28.3 (3 x CH_3), 24.3 (CH_3); υ_{max}/cm^{-1} 1693.4, 1601.4, 1412.2, 1364.6, 1336.1, 1316.1, 1237.4, 1160.3, 1111.7, 877.2; *m/z* LRMS (ESI$^+$) found $[M + Na]^+$ 264.1, $[C_{12}H_{19}NO_4Na]^+$ requires 264.1212. ^{1}H-NMR is consistent with the literature.[100]

***tert*-Butyl 4-acetoxy-5-acetyl-3,6-dihydropyridine-1(2*H*)-carboxylate 163**



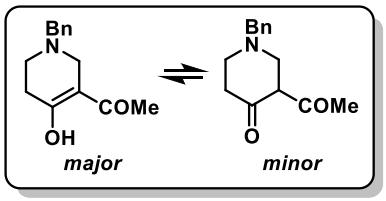
4-(Dimethylamino) pyridine (7 mg, 0.06 mmol) was added to a stirred solution of *tert*-butyl 3-acetyl-4-oxopiperidine-1-carboxylate (0.14 g, 0.58 mmol), Ac_2O (0.07 mL, 0.70 mmol), trimethylamine (0.12 mL, 0.87 mmol) in CH_2Cl_2 (1.5 mL). After 16 h, $NaHCO_3$ (saturated aqueous solution, 5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 10-30% EtOAc/petrol, to give a colourless oil (0.11 g, 69%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.15 (br s, 2H, 2-CH_2), 3.57 (t, 2H, J = 5.7 Hz, 6-CH_2), 2.42 (br s, 2H, 5-CH_2), 2.30 (s, 3H, $COCH_3$), 2.24 (s, 3H, $OCOCH_3$), 1.45 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.5 (CO), 168.0 (CO), 154.4 (CO), 140.6 (C), 123.7 (C), 80.4 (C), 42.3 (2-CH_2), 39.2 (6-CH_2), 31.0 ($CO\underline{C}H_3$), 28.8 (5-CH_2), 28.4 (3 x CH_3), 21.2 ($OCO\underline{C}H_3$); υ_{max}/cm^{-1} 1693.9, 1672.1, 1656.2, 1419.0, 1365.3, 1239.2, 1201.3, 1116.4, 1158.2, 1095.7; *m/z* HRMS (ESI$^+$) found $[M + Na]^+$ 306.1315, $[C_{14}H_{21}NO_5Na]^+$ requires 306.1317.

Methyl 3-(benzyl(3-oxobutyl)amino)propanoate S17



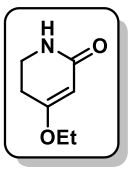
Methyl acrylate (0.80 mL, 9.33 mmol) was added to a stirred solution of benzylamine (1.0 mL, 9.33 mmol) in MeOH (10 mL). After stirring for 16 h, the reaction mixture was concentrated *in vacuo* and dissolved in MeOH (8 mL). 3-Buten-2-one (0.67 mL, 8.20 mmol) was added to this solution and the reaction was stirred for 15 h, at which point it was concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-30% EtOAc/petrol, to give a yellow oil (1.42 g, 72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.21 (m, 5 H, ArH), 3.64 (s, 3H, OCH_3), 3.56 (s, 2H, $ArCH_2$), 2.76 (m, 4H, 2 x NCH_2), 2.56 (t, 2H, *J* = 7.0 Hz, CH_3COCH_2), 2.46 (t, 2H, *J* = 7.1 Hz, NCH_2CH_2), 2.07 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.1 (CO), 173.0 (CO), 138.9 (ArC), 128.7 (ArCH), 128.2 (ArCH), 127.1 (ArCH), 58.5 ($ArCH_2$), 51.6 (OCH_3), 49.3 (NCH_2), 48.4 (NCH_2), 41.7 (CH_3COCH_2), 32.4 (NCH_2CH_2), 30.1 (CH_3); υ_{max}/cm^{-1} 1733.3, 1711.9, 1435.9, 1356.7, 1250.0, 1193.8, 1169.5, 1130.5, 736.0, 698.6; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 264.1593 and $[M + Na]^+$ 286.1423, $[C_{15}H_{22}NO_3]^+$ requires 264.1600 and $[C_{15}H_{21}NO_3Na]^+$ requires 286.1419.

1-(1-Benzyl-4-hydroxyl-1,2,5,6-tetrahydropyridin-3-yl)ethan-1-one S18



Sodium bis(trimethylsilylamide) (2 M solution in THF, 1.43 mL, 2.85 mmol) was added to a stirred solution of methyl 3-(benzyl(3-oxobutyl)amino)propanoate) (0.50 g, 1.90 mmol) in THF (6 mL). The reaction mixture turned deep red upon this addition. After 16 h, the reaction was quenched with MeOH (5 mL) and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 10-20% EtOAC/petrol, to give a yellow oil (0.24 g, 55%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 15.69 (s, 1H, OH), 7.35-7.25 (m, 5H, ArCH), 3.66 (s, 2H, $ArCH_2$), 3.26 (s, 2H, 2-CH_2), 2.63 (t, 2H, *J* = 6.0 Hz, 6-CH_2), 2.46 (t, 2H, *J* = 6.0 Hz, 5-CH_2), 2.04 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 190.1 (CO), 181.0 (C), 137.8 (ArC), 128.9 (ArCH), 128.4 (ArCH), 127.3 (ArCH), 106.2 (C), 62.4 ($ArCH_2$), 51.7 (2-CH_2), 48.6 (6-CH_2), 31.5 (5-CH_2), 24.2 (CH_3); υ_{max}/cm^{-1} 1601.8, 1494.9, 1453.76, 1411.2, 1362.7, 1319.6, 1249.6, 953.5, 742.3, 699.4; *m/z* LRMS (ESI$^+$) found $[M + H]^+$ 232.1338 and $[M + Na]^+$ 254.1160, $[C_{14}H_{18}NO_2]^+$ requires 232.1338 and $[C_{14}H_{17}NONa]^+$ requires 254.2848.

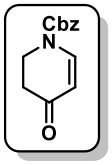
4-Ethoxy-5,6-dihydropridin-2(1*H*)-one 167



*p*TsOH.H_2O (17 mg, 0.09 mmol) was added in one portion to a stirred solution of 2,4-piperidinedione (0.10 g, 0.88 mmol) in EtOH (7 mL) and heated under reflux for 19.5 h. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-5% MeOH/CH_2Cl_2, to give a pale-yellow solid (86 mg, 72%). ^{1}H-NMR (400 MHz,

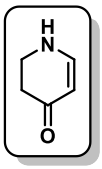
$CDCl_3$) δ 5.37 (br s, 1H, NH), 5.03 (s, 1H, 3-CH), 3.90 (q, 2H, *J* = 7.2 Hz, OCH_2), 3.42 (td, 2H, *J* = 7.0, 2.6 Hz, 6-CH_2), 2.45 (t, 2H, *J* = 7.0 Hz, 5-CH_2), 1.36 (t, 2H, *J* = 7.2 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.1 (CO), 169.5 (C), 93.7 (3-CH), 69.9 (OCH_2), 38.5 (6-CH_2), 27.8 (5-CH_2), 14.0 CH_3); υ_{max}/cm^{-1} 1648.4, 1606.6, 1482.99, 1451.7, 1379.7, 1337.9, 1223.2, 1187.7, 1032.6, 817.8; *m/z* LRMS (ESI^+) found $[M + H]^+$ 142.1 and $[M + Na]^+$ 164.1, $[C_7H_{12}NO_2]^+$ requires 142.0868 and $[C_7H_{11}NO_2Na]^+$ requires 164.0687. ^{1}H-NMR and ^{13}C-NMR data is consistent with the literature.[105]

Benzyl 4-oxo-3,4-dihydropyridine-1(2*H*) carboxylate 171



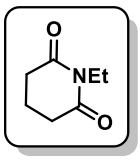
Sodium borohydride (0.56 g, 14.78 mmol) was added in one portion to a stirred solution of 4-methxoypiperidine (1.0 mL, 9.85 mmol) in MeOH (15 mL) at -78 ˚C. After 20 min, benzyl chloroformate (2.11 mL, 14.78 mmol) in Et_2O (2.5 mL) was added and the reaction mixture was stirred for 3 h at -78 ˚C. The reaction mixture was quenched with H_2O (30 mL) and warmed to RT, where it was stirred for 1 h. The organic layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 10-50% EtOAc/petrol, to give a colourless solid (1.97 g, 86%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85 (br s, 1H, 2-CH), 7.41-7.36 (m, 5H, ArH), 5.34 (br s, 1H, 3-CH), 5.26 (s, 2H, $ArCH_2$), 4.04 (t, 2H, *J* = 7.3 Hz, 6-CH_2), 2.56 (t, 2H, *J* = 7.3 Hz, 5-CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.3 (CO), 152.7 (2-CH), 143.4 (CO), 134.9 (C), 128.8 (ArCH), 128.7 ($ArCH_2$), 128.5 ($ArCH_2$), 107.7 (3-CH), 69.1 ($ArCH_2$), 42.6 (6-CH_2), 35.6 (5-CH_2); υ_{max}/cm^{-1} 1722.4, 1665.9, 1600.6, 1389.7, 13431.2, 1323.5, 1298.1, 1208.4, 1181.4, 1105.8; *m/z* LRMS (ESI^+) found $[M + H]^+$ 232.1 and $[M + Na]^+$ 254.1, $[C_{13}H_{14}NO_3]^+$ requires 232.0974 and $[C_{13}H_{13}NO_3Na]^+$ requires 254.0793; m.p. 71-72 ˚C (EtOAc/Petrol), lit. 71-72 ˚C.[301] ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[106]

2,3-Dihydropyridin-4(1*H*)-one 172



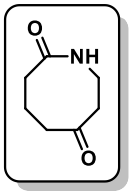
A hydrogen balloon was added to a stirred solution of benzyl 4-oxo-3,4-dihydropyrine-1(2*H*) carboxylate (1.0 g, 4.32 mmol) and Pd/C (10% mass, 100 mg, 0.09 mmol) in EtOH (20 mL). After 2h the reaction mixture was filtered through celite and concentrated *in vacuo* to give the crude martial as a colourless solid (0.34 g, 81%) which was used directly in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21 (app t, 1H, 2-CH), 5.98 (br s, 1H, NH), 4.96 (d, 1H, *J* = 7.6 Hz, 3-CH), 3.56 (td, 2H, *J* = 7.8, 2.5 Hz, 6-CH_2), 2.45 (t, 2H, *J* = 7.8 Hz, 5-CH_2);); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 192.8 (CO), 152.3 (2-CH), 98.6 (3-CH), 41.7 (6-CH_2), 35.9 (5-CH_2); υ_{max}/cm^{-1} 1550.2, 1350.1, 1244.8, 1172.2, 795.2, 750.9, 614.4, 508.6, 486.2, 449.5; *m/z* LRMS (ESI^+) found $[M + H]^+$ 98.1 and $[M + Na]^+$ 120.0, $[C_5H_8NO]^+$ requires 98.0606 and $[C_5H_7NONa]^+$ requires 120.0425. ^{1}H-NMR and ^{13}C-NMR data is consistent with the literature.[106]

1-Ethylpiperidine-2,6-dione 180



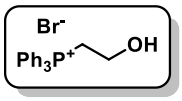
Et_3N (2 mL, 14.46 mmol) was added to a stirred solution of ethylamine hydrochloride (0.79 g, 9.64 mmol) in THF (5 mL) at 0 ˚C. After 10 min, glutaric anhydride (1.0 g, 8.76 mmol) was added at 0 ˚C and after 1 h, the reaction mixture was concentrated *in vacuo*. The crude material was heated to 175 ˚C for 15.5 h, which was purified by SiO_2 flash chromatography, eluting with 30-50% EtOAc/petrol, to give a yellow oil (0.83 g, 67%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.81 (q, 2H, *J* = 6.9 Hz, NCH_2), 2.63 (t, 4H, *J* = 6.8 Hz, 2 x $NCOCH_2$), 1.92 (qn, 2H, *J* = 6.8 Hz, $CH_2C\underline{H}_2CH_2$), 1.10 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.3 (CO), 34.7 (NCH_2), 32.8 (2 x $NCOCH_2$), 17.2 ($CH_2\underline{C}H_2CH_2$), 13.3 (CH_3); υ_{max}/cm^{-1} 1724.4, 1666.9, 1387.8, 1358.1, 1344.4, 1251.9, 1193.0, 1116.6, 1051.7, 565.5. ^{1}H-NMR is consistent with the literature.[297]

Azocane-2,6-dione 181



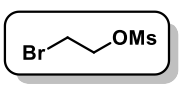
1-Ethylpiperidine-2,6-dione (0.82 g, 7.18 mmol) in degassed MeCN (450 mL, 0.02 M) was irradiated using a water cooled, 36 W low pressure Hg lamp. After 4 h, the reaction mixture was concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-4% MeOH/CH_2Cl_2, to give a yellow solid (0.30 g, 30%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.23 (s, 1H, NH), 3.63 (q, 2H, *J* = 5.9 Hz, NCH_2), 2.61 (app qn, 4H, $NCH_2C\underline{H}_2$ and $NCOC\underline{H}_2$), 2.46 (t, 2H, *J* = 6.2 Hz, $NCH_2CH_2COC\underline{H}_2$), 1.99-1.92 (m, 2H, $CH_2C\underline{H}_2CH_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 211.8 (CO), 175.7 (CO), 49.1 ($NCO\underline{C}H_2$), 40.2 ($NCH_2\underline{C}H_2$), 39.1 (NCH_2), 32.3 ($NCH_2CH_2CO\underline{C}H_2$), 22.6 ($CH_2\underline{C}H_2CH_2$); *m/z* LRMS (ESI$^+$) found $[M + H]^+$ 142.1 and $[M + Na]^+$ 164.1, $[C_7H_{12}NO_2]^+$ requires 142.0868 and $[C_7H_{11}NO_2Na]^+$ requires 164.0687; m.p. 113-115 ˚C (EtOH), lit. 117-118 ˚C.[79]

(2-Hydoxyethyl)triphenylphosphonium bromide S19



Bromoethanol (0.53 mL, 7.50 mmol) and PPh_3 (1.31 g, 5 mmol) in Et_2O (1.5 mL) were heated under reflux for 6 h. The solid was filtered and washed with Et_2O (50 mL) to give the crude material as a colourless solid which was used directly in the next step without further purification (1.76 g, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.91-7.72 (m, 15H, ArCH), 3.97 (dt, 2H, *J* = 20.7, 6.1 Hz, OCH_2), 3.69-3.63 (m, 2H, $C\underline{H}_2PPh_3$); ^{31}P-NMR (162 MHz, $CDCl_3$) δ 24.4. ^{1}H and ^{31}P-NMR data is consistent with the literature.[302]

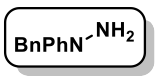
2-Bromoethyl methanesulfonate S20



Methanesulfonyl chloride (0.05 mL, 0.60 mmol) was added to a stirred solution of Et_3N (0.14 mL, 1.0 mmol) and bromoethanol (0.04 mL, 0.50 mmol) in CH_2Cl_2 (2 mL). After 24 h, the reaction mixture was quenched with H_2O (2 mL). The organic layer was extracted with CH_2Cl_2 (3 x 5 mL) and washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo* to give the crude material as a yellow oil which was used directly in the next step without

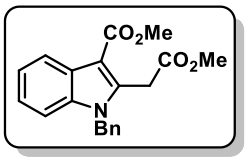
further purification (*quant.*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.49 (t, 2H, *J* = 6.3 Hz, C$\underline{H_2}$OMs), 3.58 (t, 2H, *J* = 6.3 Hz, $BrCH_2$), 3.09 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 68.2 ($\underline{C}H_2OMs$), 37.9 ($BrCH_2$), 27.8 (CH_3).

1-Benzyl-1-phenylhydrazine 182



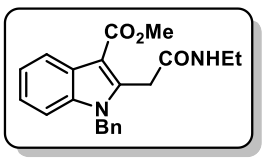
Benzylbromide (1.10 mL, 9.25 mmol) was added to a stirred solution of phenylhydrazine (0.93 mL, 9.25 mmol) and $NaHCO_3$ (1.87 g, 22.20 mmol) in H_2O (4 mL). The reaction mixture was heated under reflux for 3 h, extracted with Et_2O (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo* to give the crude material as a yellow oil which was used directly in the next step without further purification (1.34 g, 73%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.20 (m, 10H, ArCH), 4.55 (s, 2H, $ArCH_2$), 3.51 (s, 1H, NH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.7 (ArC), 137.5 (ArC), 129.1 (ArCH), 128.7 (ArCH), 127.9 (ArCH), 127.4 (ArCH), 118.6 (ArCH), 113.6 (ArCH), 60.4 ($ArCH_2$). ^{1}H-NMR is consistent with the literature.[303]

Methyl 1-benzyl-2-(2-(methoxy-2-oxoethyl)-1*H*-indole-3-carboxylate 185



Dimethyl-1,3-acetone dicarboxylate (0.06 mL, 0.43 mmol) was added to a stirred solution of 1-benzyl-1-phenylhydrazine hydrochloride (0.1 g, 0.43 mmol) in MeOH (10 mL) and the reaction mixture was heated under reflux for 44 h. The reaction mixture was cooled to RT, concentrated *in vacuo* and the crude material was purified by SiO_2 flash chromatography, eluting with 0-10% EtOAc/petrol, to give a yellow solid (88 mg, 63%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20-8.17 (m, 2H, ArCH), 7.30-7.21 (m, 5H, ArCH), 6.99-6.97 (m, 2H, ArCH), 5.42 (s, 2H, $ArCH_2$), 4.32 (s, 2H, CH_2), 3.95 (s, 3H, OCH_3), 3.60 (OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.5 (CO), 166.1 (CO), 140.2 (ArC), 136.6 (ArC), 136.0 (ArC), 128.9 (ArCH), 127.8 (ArCH), 126.2 (ArC), 125.9 (ArCH), 123.1 (ArCH), 122.1 (ArCH), 121.9 (ArCH), 110.0 (ArCH), 106.1 (ArC), 52.4 (OCH_3), 51.0 (OCH_3), 46.9 ($ArCH_2$), 31.6 (CH_2); υ_{max}/cm^{-1} 1725.3, 1682.9, 1440.6, 1206.9, 1181.0, 1133.9, 1113.9, 741.7, 725.8, 695.9; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 338.1402 and $[M + Na]^+$ 360.1240, $[C_{20}H_{20}NO_4]^+$ requires 338.1392 and $[C_{20}H_{19}NO_4Na]^+$ requires 360.1212; m.p. 117-118 ˚C (EtOAc/petrol).

Methyl 1-benzyl-2-(2-(ethylamino)-2-oxoethyl)-1*H*-indole-3-carboxylate 187

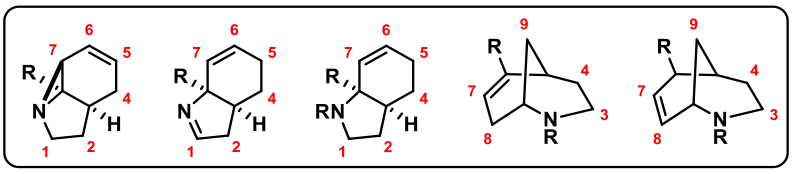


NaOH (24 mg, 0.59 mmol) was added to a stirred solution of methyl 1-benzyl-2-(2-(methoxy-2-oxoethyl)-1*H*-indole-3-carboxylate (0.20 g, 0.59 mmol) in EtOH:H_2O (10:1, 11 mL) and stirred for 23 h. The crude material was concentrated *in vacuo* and partitioned between Et_2O and H_2O (10:1, 11 mL). The aqueous phase was acidified to pH 3 with HCl (37% in H_2O) and extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated i*n vacuo*. Et_3N (0.10 mL, 0.68 mmol) and ethyl chloroformate (0.05 mL, 0.52 mmol) were added to a stirred solution of the crude material in $CHCl_3$ (5

mL) at 0 ˚C. In a separate flask, Et_3N (0.2 mL, 1.44 mmol) was added to a stirred solution of ethylamine hydrochloride (98 mg, 1.20 mmol) in $CHCl_3$ (1 mL). After 1 h, the amine solution was added to the acid and stirred for 16 h. H_2O (5 mL) was added and the crude material was extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-30% EtOAc/petrol, to give the title compound as a yellow solid (0.11 g, 52% over 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19-8.17 (m, 1H, ArCH), 7.30-7.21 (m, 6H, ArCH), 6.99-6.97 (m, 2H, ArCH), 5.42 (s, 2H, $ArCH_2$), 4.29 (s, 2H, CH_2), 4.08 (q, 2H, *J* = 7.0 Hz, $C\underline{H}_2CH_3$), 3.94 (s, 3H, OCH_3), 1.19 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.1 (CO), 166.0 (CO), 140.3 (ArC), 136.6 (ArC), 136.1 (ArC), 128.9 (ArCH), 127.8 (ArCH), 126.3 (ArCH), 125.9 (ArCH), 123.0 (ArCH), 122.1 (ArCH), 121.9 (ArCH), 110.0 (ArC), 106.1 (ArC), 61.3 ($\underline{C}H_2CH_3$), 50.9 (OCH_3), 46.9 ($ArCH_2$), 31.9 (CH_2), 14.1 (CH_3); υ_{max}/cm^{-1} 1722.5, 1692.3, 1435.1, 1210.9, 1133.9, 1116.4, 1025.9, 739.8, 730.2, 696.8; *m/z* HRMS (ESI$^+$) found $[M + Na]^+$ 373.1578, $[C_{21}H_{22}N_2O_3Na]^+$ requires 373.1528; m.p. 123-125 ˚C (EtOAc/petrol).

5.2.2. The Pd-Catalysed Rearrangement: Synthetic Procedures

Numbering nomenclature in aziridine, imine, bicycle substrate and morphan systems are as shown below:



5.2.2.1. General Procedures*:*

General Procedure A: Reductive Amination

Sodium triacetoxyborohydride (3 equiv.) was added in one portion to a stirred solution of crude imine (1 equiv.) and aldehyde (1 equiv.) in CH_2Cl_2 (0.3 M) at 0 °C. The reaction was warmed to RT and stirred for 17 h, quenched with $NaHCO_3$ (saturated aqueous solution) and stirred for 10 min. The organic layer was extracted with CH_2Cl_2 (x 3) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography.

General Procedure B: Reductive Amination with Oligomer Aldehydes (paraformaldehyde and 3,3,3-trifluoropropanal)

Sodium triacetoxyborohydride (3 equiv.) was added in one portion to a stirred solution of crude imine (1 equiv.) and aldehyde (3 equiv. paraformaldehyde, 1 equiv. 3,3,3-trifluoropropanal) in CH_2Cl_2 (0.3 M) at 0 °C. The reaction was warmed to 35 ºC and stirred for 17 h, quenched with $NaHCO_3$ (saturated aqueous solution) and stirred for 10 min. The organic layer was extracted with CH_2Cl_2 (x 3) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography.

General Procedure C: Pd catalysed 1,4-Rearrangement of Aryl Iodide Substrates

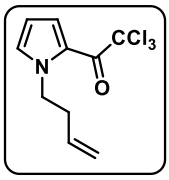
Dioxane (0.06 M) and *N*,*N*-diisopropylethylamine (1 equiv.) were added to $Pd(OAc)_2$ (0.10 equiv.) and DPEPhos (0.15 equiv.) and stirred for 10 min. The aryl iodide substrate (1 equiv.) in dioxane (0.06 M) was added and the reaction was heated under reflux. After 17 h, the reaction mixture was cooled to RT and $NaHCO_3$ (saturated aqueous solution) was added. The organic layer was extracted with CH_2Cl_2 (x 3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography.

General Procedure D: Pd catalysed 1,4-Rearrangement

Dioxane (0.06 M) and *N*,*N*-diisopropylethylamine (1 equiv.) were added to $Pd(OAc)_2$ (0.10 equiv.) and DPEPhos (0.15 equiv.), followed by the substrate (1 equiv.) in dioxane (0.06 M). The reaction mixture was stirred for 10 min, methanesulfonic acid was added (1 equiv.) and the reaction was heated under

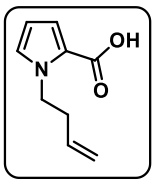
reflux. After 20 h, the reaction mixture was cooled to RT and $NaHCO_3$ (saturated aqueous solution) was added. The organic layer was extracted with CH_2Cl_2 (x 3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography.

1-(1-(But-3-en-1-yl)-1*H*-pyrrol-2-yl)-2,2,2-trichloroethan-1-one 306



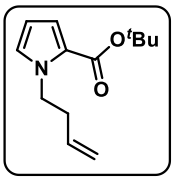
Diisopropyl azodicarboxylate (40.0 mL, 203.16 mmol) was added dropwise over 15 min to a stirred solution of triphenylphosphine (52.0 g, 198.25 mmol) in THF (600 mL) at -78 °C. The reaction mixture turned bright yellow after this addition. The mixture was stirred for 40 min and 3-buten-1-ol (19.0 mL, 220.80 mmol) was added dropwise over 5 min. After a further 1 h, 2-(trichloroacetyl)pyrrole (41.40 g, 194.86 mmol) was added in one portion and the reaction mixture was warmed to RT. After 20 h, the reaction mixture was concentrated *in vacuo* and the residue triturated in Et_2O/petrol (2:3, 500 mL) at -10 °C and filtered. The residue was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with petrol, to give the product as a light-yellow oil (46.87 g, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, 1H, *J* = 4.4, 1.4 Hz, ArCH), 7.00 (app t, 1H, ArCH), 6.22 (dd, 1H, *J* = 4.4, 2.1 Hz, ArCH), 5.82-5.71 (m, 1H, C<u>H</u>CH_2), 5.07-5.03 (m, 2H, CHC<u>H</u>$_2$), 4.39 (t, 2H, *J* = 7.1 Hz, NCH_2), 2.51 (app q, 2H, NCH_2C<u>H</u>$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.6 (CO), 134.0 (<u>C</u>HCH_2), 133.2 (ArCH), 124.7 (ArCH), 121.0 (ArC), 117.8 (CH<u>C</u>H_2), 108.9 (ArCH), 96.5 (C), 50.1 (NCH_2), 35.4 (NCH_2<u>C</u>H_2). ^{1}H-NMR an ^{13}C-NMR data is consistent with the literature.[126]

1-(Buten-3-en-1-yl)-1*H*-pyrrole-2-carboxylic acid 307



NaOH (2 M aqueous solution, 190 mL) was added to a stirred solution of 1-(1-(but-3-en-1-yl)-1*H*-pyrrol-2-yl)-2,2,2-trichloroethan-1-one (31.59 g, 119.41 mmol) in THF (104 mL). After 17 the reaction mixture was cooled to 0 °C and quenched with HCl (3 M aqueous solution, 150 mL). The mixture was extracted with Et_2O (2 x 150 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was recrystallized from petrol to give a yellow solid (17.79 g, 90%). ^{1}H-NMR (400 MHz, MeOH-d_4) δ 6.93-6.92 (m, 2H, ArCH), 6.07-6.05 (m, 1H, ArCH), 5.81-5.71 (m, 1H, C<u>H</u>CH_2), 5.02-4.96 (m, 2H, CHC<u>H</u>$_2$), 4.89 (br s, 1H, OH), 4.36 (t, 2H, *J* = 7.1 Hz, NCH_2), 2.47 (app q, 2H, CH_2C<u>H</u>$_2$); ^{13}C-NMR (100 MHz, MeOH-d_4) δ 164.2 (CO), 136.0 (<u>C</u>HCH_2), 130.4 (ArCH), 122.8 (ArC), 119.9 (ArCH), 117.4 (CH<u>C</u>H_2), 108.7 (ArCH), 49.5 (NCH_2), 37.2 (NCH_2<u>C</u>H_2) υ_{max}/cm^{-1} 2919.4, 1659.8, 1532.8, 1428.4, 1326.1, 1256.8, 1107.8, 1073.6, 917.2, 739.5; *m/z* HRMS (Nanospray) found $[M - H]^-$ 164.0711 and $[M - 2H + Na]^-$ 186.1150, $[C_9H_{10}NO_2]^+$ requires 164.0712 and $[C_9H_9NO_2Na]^+$ requires 186.0530; m.p. 48 - 49 ˚C (petrol).

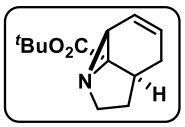
tert-Butyl 1-(but-3-en-1-yl)-1_H_-pyrrole-2-carboxylate 308



Oxalyl chloride (10.90 mL, 128.94 mmol) was added dropwise over 55 min to a stirred solution of 1-(buten-3-en-1-yl)-1*H*-pyrrole-2-carboxylic acid (17.75 g, 107.45 mmol) and DMF (6 drops) in CH_2Cl_2 (245 mL) at -10 °C. The reaction mixture was warmed to RT for 40 min then cooled to 0 °C and potassium *tert*-butoxide (35.17 g, 322.35 mmol) was added portion wise over 20 min. The reaction was warmed to RT, stirred for 2.5 h and quenched with H_2O (200 mL). The mixture was separated, extracted with CH_2Cl_2 (2 x 200 mL), washed with brine (400 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography, eluting with 0-5% EtOAc/petrol, to give the product as a light-yellow oil (12.94 g, 54%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.89-6.87 (m, 1H, ArCH), 6.77 (br s, 1H, ArCH), 6.08-6.06 (m, 1H, ArCH), 5.81-5.71 (m, 1H, C<u>H</u>CH$_2$), 5.06-5.01 (m, 2H, CHC<u>H</u>$_2$), 4.34 (t, 2H, *J* = 7.0 Hz, NCH$_2$), 2.51 (app q, 2H, NCH$_2$C<u>H</u>$_2$), 1.55 (s, 9H, CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.6 (CO), 134.7 (<u>C</u>HCH$_2$), 128.1 (ArCH), 123.2 (ArC), 117.9 (CH<u>C</u>H$_2$), 117.1 (ArCH), 107.4 (ArCH), 80.2 (C), 48.7 (NCH$_2$), 36.0 (NCH$_2$<u>C</u>H$_2$), 28.4 (CH$_3$). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[143]

(±)-_tert_-Butyl (3^1_R_,3a_S_,6a_S_)-1,3a,6,6a-terahydroazirino[2,3,1-_hi_]indole-3^1(2H)-carboxylate 253

Batch Procedure

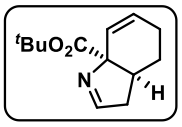


tert-Butyl 1-(but-3-en-1-yl)-1*H*-pyrrole-2-carboxylate (1.00 g, 4.52 mmol) in degassed cyclohexane:EtOAc (5.7:1, 470 mL) was irradiated using a water cooled 36 W low pressure Hg lamp. After 15 h, the reaction mixture was concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 20-50% EtOAc/petrol, to give a yellow oil (0.39 g, 39%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.24-6.19 (m, 1H, 5-CH), 5.78 (dt, 1H, *J* = 10.0, 3.5 Hz, 6-CH) 3.24-3.16 (m, 2H, 1-CH and 3-CH), 2.84 (d, *J* = 3.5 Hz, 1H, 7-CH), 2.60-2.47 (m, 2H, 1-CH and 2-CH), 2.30 (br d, *J* = 18.1 Hz, 1H, 4-CH), 1.91 (dd, *J* = 18.1, 6.1 Hz, 1H, 4-CH), 1.52 (m, 1H, 2-CH), 1.47 (s, 9 H, CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.6 (CO), 135.0 (6-CH), 120.7 (5-CH), 81.2 (C), 52.4 (C), 49.8 (1-CH$_2$), 43.5 (7-CH), 41.2 (2-CH$_2$), 33.5 (3-CH), 29.5 (4-CH$_2$), 28.0 (CH$_3$). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[143]

Flow Procedure

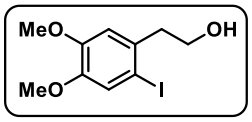
tert-Butyl 1-(but-3-en-1-yl)-1*H*-pyrrole-2-carboxylate (2.50 g 11.30 mmol) in degassed cyclohexane: EtOAc (5.7:1, 560 mL) was irradiated using 3 36 W low pressure Hg lamps whilst being passed through a flow reactor (flow rate 3 mL min^{-1}). The crude material was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 20-50% EtOAc/petrol, to give an orange oil (0.80 g, 32%).

(±)-*tert*-Butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate 309



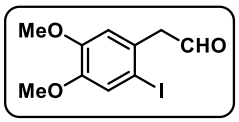
(±)-*tert*-Butyl (3^1*S*,3a*R*,6a*R*)-1,3a,6,6a-tetrahydoazirino [2,3,1-*hi*] indole-3^1(2*H*) carboxylate (0.70 g, 3.16 mmol) was stirred in PhMe (30 mL) at 100 °C for 15 h. The reaction mixture was concentrated *in vacuo* to give the crude product as a brown oil (0.70 g, *quant.*) which was used directly in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H, 1-CH), 6.04 (dt, 1H, *J* = 10.7, 1.7 Hz, 6-CH), 5.98 (dt, 1H, *J* = 10.1, 3.6 Hz, 7-CH), 2.86- 2.79 (m, 1H, 2-CH), 2.77-2.70 (m, 1H, 3-CH), 2.43-2.36 (m, 1H, 2-CH), 2.03-1.97 (m, 2H, 5-CH_2), 1.88-1.81 (m, 1H, 4-CH) 1.46 (s, 9H, CH_3), 1.40-1.37 (m, 1H, 4-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.0 (CO), 167.8 (1-CH), 130.0 (6-CH), 126.8 (7-CH), 81.4 ($\underline{C}(CH_3)_3$), 80.9 (C), 42.8 (2-CH_2), 37.2 (3-CH), 27.9 (CH_3), 24.8 (4-CH_2), 21.6 (5-CH_2). ^{1}H-NMR data is consistent with the literature.[144]

(2-Iodo-4,5-dimethoxyphenyl)ethanol 310



Iodomonochloride (2.50 g, 15.37 mmol) in CH_2Cl_2 (8 mL) was added dropwise over 10 min to a stirred solution of 2-(3,4-dimethoxyphenyl)ethanol (2.0 g, 10.98 mmol) in CH_2Cl_2 (34 mL). After 26.5 h, the reaction mixture was quenched with $Na_2S_2O_3$ (1 M aqueous solution, 30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 10-40% EtOAc/petrol, which was recrystallised from Et_2O to give the product as a light pink solid (1.81 g, 54%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.22 (s, 1H, ArCH), 6.78 (s, 1H, ArCH), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.82 (m, 2H, $C\underline{H}_2OH$), 2.94 (t, 2H, *J* = 6.7 Hz, $ArCH_2$), 1.48 (br s, 1H, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.3 (ArC), 148.2 (ArC), 133.4 (ArCH), 121.8 (ArC), 113.0 (ArCH), 88.2 (ArC), 62.5 (CH_2OH), 56.1 (OCH_3), 55.9 (OCH_3) 43.2 ($ArCH_2$); m.p. 58-59 ˚C (Et_2O), lit. 53-54˚C.[143] ^{1}H-NMR and ^{13}C-NMR data is consistent with the literature.[143]

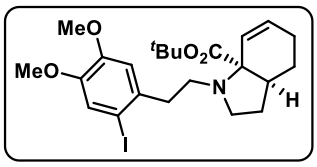
2-(2-Iodo-4,5-dimethoxyphenyl)acetaldehyde 311



Dess martin periodinane (2.94 g, 6.94 mmol) was added in one portion to a stirred solution of (2-iodo-4,5-dimethoxphenyl)methanol (1.78 g, 5.78 mmol) in CH_2Cl_2 (24 mL). After 16.5 h, the reaction was quenched with $Na_2S_2O_3$ (1 M aqueous solution, 30 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with $NaHCO_3$ (saturated aqueous solution, 30 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to yield the product as a yellow solid (1.26 g, 72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H, CHO), 7.26 (s, 1H, ArCH), 6.70 (s, 1H, ArCH), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.81 (m, 2H, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.7 (CHO), 149.6 (ArC), 148.9 (ArC), 128.2 (ArC),

121.7 (ArCH), 113.3 (ArCH), 88.9 (ArC), 56.2 (OCH_3), 55.9 (OCH_3), 54.3 (CH_2); m.p. 70-71 ˚C (EtOAc/petrol), lit. 53-56 ˚C.[304] ^{1}H-NMR data is consistent with the literature.[304]

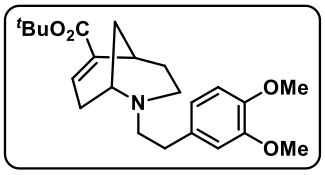
(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(2-iodo-4,5-dimethoxyphenethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 299



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.65 g, 2.92 mmol) and 2-(2-iodo-4,5-dimethoxyphenyl)acetaldehyde (0.89 g, 2.92 mmol) were stirred with sodium triacetoxyborohydride (1.86 g, 8.76 mmol) in CH_2Cl_2 (11 mL). The crude material was purified by SiO_2 flash chromatography, 0-30% EtOAc/petrol, to give a yellow oil (1.02 g, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H, ArCH), 6.79 (s, 1H, ArCH), 5.93 (dt, 1H, *J* = 10.3, 3.8 Hz, 6-CH), 5.76 (br dt, 1H, *J* = 10.3, 1.8 Hz, 7-CH), 3.83 (s, 6H, 2 x OCH_3), 3.07 (m, 1H, 1-CH), 2.91-2.80 (m, 4H, 1-CH, NCH<u>H</u>, $NCH_2C\underline{H}_2$), 2.72-2.66 (m, 1H, NC<u>H</u>H), 2.57-2.50 (m, 1H, 3-CH), 2.14-1.93 (m, 3H, 2-CH and 4-CH_2), 1.75-1.68 (m, 1H, 5-CH), 1.62-1.54 (m, 2H, 2-CH and 5-CH), 1.45 (s, 9H, CH_3); υ_{max}/cm^{-1} 2930.0, 2970.7, 1715.4, 1503.6, 1454.9, 1367.2, 1217.2, 1252.7, 1159.4, 1029.2. ^{1}H-NMR data is consistent with the literature.[39]

(±)-*tert*-Butyl (1*R*)-2-(3,4-dimethoxyphenethyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 302/336s

Aryl Iodide Substrate Procedure

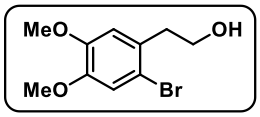


According to general procedure C, $Pd(OAc)_2$ (2 mg, 0.01 mmol) and DPEPhos (8 mg, 0.02 mmol) were stirred in dioxane (0.50 mL) for 10 min and the reaction mixture turned bright yellow. (±)-*tert*-Butyl (3*R*,7a*S*)-1-iodo-4, 5-dimethoxyphenethyl)-1,2,3,3a,4,5-hexhydro-7a*H*-indole-7a-carboxylate (50 mg, 0.10 mmol) in dioxane (0.50 mL) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.19 mmol) were added to the stirred reaction solution and heated under reflux. The crude material was purified by SiO_2 flash chromatography, 30-50% EtOAc/petrol, to give a yellow oil (29 mg, 76%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.04 (t, 1H, *J* = 3.9 Hz, 7-CH), 6.79-6.73 (m, 3H, ArCH), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.13 (br s, 1H, 1-CH), 2.89 (br s, 1H, 5-CH), 2.75-2.56 (m, 5H, 3-CH, NCH_2 and $NCH_2C\underline{H}_2$), 2.41 (dd, 1H, *J* = 20.9, 3.9 Hz, 8-CH), 2.25 (td, 1H, *J* = 12.2, 3.8 Hz, 3-CH), 2.09-2.02 (m, 1H, 8-CH), 1.96 (br d, 1H, *J* = 12.4 Hz, 9-CH), 1.88 (tt, 1H, *J* = 12.8, 3.8 Hz, 4-CH), 1.64-1.60 (m, 1H, 9-CH), 1.52 (br s, 1H, 4-CH), 1.47 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.8 (CO), 148.7 (ArC), 147.3 (ArC), 139.9 (7-CH), 134.2 (6-C), 133.1 (ArC), 120.5 (ArCH), 79.9 (C), 57.6 ($NCH_2\underline{C}H_2$), 55.7 (OCH_3), 50.3 (1-CH), 44.4 (3-CH), 34.0 (NCH_2), 31.8 (9-CH), 28.8 (4-CH), 28.1 (CH_3), 26.7 (5-CH), 24.8 (8-CH). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[39]

MSA Additive Procedure

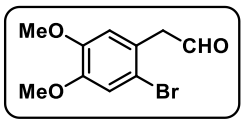
According to general procedure D, (±)-*tert*-butyl (3a*S*, 7a*R*)-1-(3,4-dimethoxyphenethyl)-1, 2, 3, 3a, 4, 5-hexahydro-7a*H*-indole-7a-carboxylate (58 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-60% EtOAc/petrol, to give a yellow oil (45 mg, 78%).

(2-Bromo-4,5-dimethoxyphenyl)ethanol S21



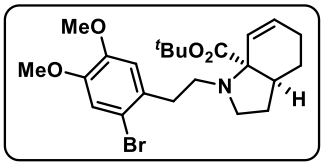
N-Bromo-succinimide (2.15 g, 12.08 mmol) was added in one portion to a stirred solution of 2-(3,4-dimethoxyphenyl)ethanol (2.0 g, 10.98 mmol) in CH_3Cl (70 mL) and heated under reflux. After 5.5 h, the reaction mixture was cooled to RT, quenched with $Na_2S_2O_3$ (1 M aqueous solution, 80 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 10-50% EtOAc/petrol, to give the product as an orange oil (2.18 g, 76%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H, ArCH), 6.78 (s, 1H, ArCH), 3.87-3.84 (m, 8H, C$\underline{H}_2$OH and 2 x OCH_3), 2.95 (t, 2H, *J* = 6.7 Hz, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.4 (ArC), 148.3 (ArC), 129.7 (ArC), 115.7 (ArCH), 114.4 (ArC), 113.8 (ArCH), 62.3 (OCH_2), 56.1 (OCH_3), 56.1 (OCH_3), 39.0 (CH_2). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[305]

2-(2-Bromo-4,5-dimethoxyphenyl)acetaldehyde S22



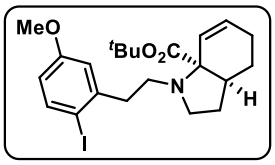
Dess Martin periodinane (3.84 g, 9.05 mmol) was added in one portion to a stirred solution of (2-bromo-4,5-dimethoxphenyl)methanol (2.15 g, 8.23 mmol) in CH_2Cl_2 (35 mL). After 2 h, the reaction was quenched with $Na_2S_2O_3$ (1 M aqueous solution, 20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with $NaHCO_3$ (saturated aqueous solution, 20 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to yield the product as a yellow oil (1.26 g, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.73 (br s, 1H, CHO), 7.07 (s, 1H, ArCH), 6.70 (s, 1H, ArCH), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.78 (d, 2H, *J* = 1.6 Hz, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.5 (CO), 149.1 (ArC), 148.7 (ArC), 124.2 (ArC), 115.7 (ArCH), 115.0 (ArC), 114.0 (ArCH), 56.2 (OCH_3), 56.1 (OCH_3), 50.1 (CH_2); m.p. 59-62 ˚C (EtOAc/petrol), lit. 64-65 ˚C.[306] ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[307]

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 312



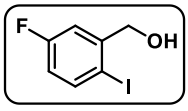
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.25 g, 0.95 mmol) and 2-(2-bromo-4,5-dimethoxyphenyl)acetaldehyde (0.25 g, 0.95 mmol) were stirred with sodium triacetoxyborohydride (0.60 g, 2.85 mmol) in CH_2Cl_2 (4 mL). The crude material was purified by SiO_2 flash chromatography, 0-30% EtOAc/petrol, to give a yellow oil (0.39 g, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1H, ArCH), 6.78 (s, 1H, ArCH), 5.93 (td, 1H, *J* = 10.3, 3.7 Hz, 6-CH), 5.75 (br d, 1H, *J* = 10.3 Hz, 7-CH), 3.84 (s, 3H, OCH_3), 3.06-2.99 (m, 1H, 1-CH), 2.94-2.78 (m, 4H, 1-CH, NCH<u>H</u> and $NCH_2C\underline{H}_2$), 2.78-2.67 (m, 1H, NC<u>H</u>H), 2.58-2.50 (m, 1H, 3-CH), 2.13-1.92 (m, 3H, 4-CH_2 and 5-CH), 1.75-1.68 (m, 1H, 2-CH), 1.61-1.53 (m, 2H, 2-CH and 5-CH), 1.45 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.6 (CO), 148.2 (ArC), 147.8 (ArC), 131.9 (ArC), 130.4 (6-CH), 124.4 (7-CH), 115.3 (ArCH), 114.0 (ArC), 113.4 (ArCH), 80.8 (C), 69.0 ($\underline{C}CH_3$), 56.1 (OCH_3), 56.0 (NCH_2), 50.3 (1-CH), 40.3 (3-CH), 35.7 ($NCH_2\underline{C}H_2$), 28.1 (5-CH_2), 27.3 (CH_3), 25.2 (2-CH), 22.1 (4-CH_2); υ_{max}/cm^{-1} 1715.3, 1505.6, 1455.5, 1439.6, 1382.4, 1366.8, 1256.4, 1219.7, 1161.9, 1033.2; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 466.1574 and 468.1555, $[C_{23}H_{33}{}^{79}BrNO_4]^+$ requires 466.1593 and $[C_{23}H_{33}{}^{81}BrNO_4]^+$ requires 468.1572.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(2-iodo-5-methoxyphenethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 317



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.20 g, 0.90 mmol) and 2-(2-iodo-5-methoxyphenyl)acetaldehyde (0.22 g, 0.80 mmol) were stirred with sodium triacetoxyborohydride (0.57 g, 2.70 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, to give a yellow oil (0.28 g, 72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (d, 1H, *J* = 9.0 Hz, ArCH), 6.83 (br s, 1H, ArCH), 6.50 (dd, 1H, *J* = 9.0, 3.2 Hz, ArCH), 5.93 (br s, 1H, 6-CH), 5.75 (d, 1H, *J* = 10.5 Hz, 7-CH), 3.76 (s, 3H, OCH_3), 3.07 (br s, 1H, 1-CH), 2.90-2.83 (m, 4H, 1-CH, NC<u>H</u>H and $NCH_2C\underline{H}_2$), 2.75-2.71 (m, 1H, NCH<u>H</u>), 2.54 (br s, 1H, 3-CH), 2.14-1.94 (m, 3H, 2-CH and 4-CH_2), 1.74-1.68 (m, 1H, 5-CH), 1.62-1.53 (m, 2H, 2-CH and 5-CH), 1.46 (s, 9H, CH_3); υ_{max}/cm^{-1} 2930.9, 1715.9, 1465.9, 1366.6, 1289.3, 1236.7, 1157.5, 1048.5, 1004.9, 846.9. ^{1}H-NMR data is consistent with the literature.[184]

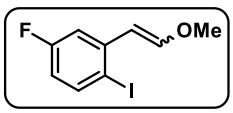
(5-Fluoro-2-iodophenyl)methanol S23



Borane tetrahydrofuran complex (1 M solution in THF, 11.3 mL, 11.28 mmol) was added dropwise over 20 min to a stirred solution of 5-fluoro-2-iodobenzoic acid (2.0 g, 7.52 mmol) in THF (15 mL) at 0 ˚C. The reaction mixture was warmed to RT, stirred for 6 h then quenched with H_2O:THF (1:1, 15 mL) and solid K_2CO_3. The reaction was extracted

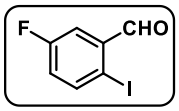
with Et_2O (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 20-40% EtOAc/petrol, to give a colourless solid (0.58 g, 31%). ^{1}H-NMR (400 MHz, MeOH-d_4) δ 7.83 (dd, 1H, *J* = 8.5, 5.5 Hz, ArCH), 7.31 (dd, 1H, *J* = 9.9, 3.0 Hz, ArCH), 6.85 (td, 1H, *J* = 8.5, 3.0 Hz, ArCH), 4.55 (s, 2H, CH_2); ^{13}C-NMR (100 MHz, MeOH-d_4) δ 164.9 (d, *J* = 246.7 Hz, ArCF), 147.5 (d, *J* = 6.9 Hz, Ar<u>C</u>CH_2), 141.4 (d, *J* = 7.8 Hz, ArCH), 116.8 (d, *J* = 22.5 Hz, ArCH), 115.7 (d, *J* = 24.1 Hz, ArCH), 89.3 (ArCI), 68.9 (CH_2); ^{19}F-NMR (377 MHz, MeOH-d_4) δ -113.4; m.p. 106-108 ˚C (EtOAc/petrol), lit. 107-108 ˚C.[183] ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[183]

4-Fluoro-1-iodo-2-(methoxyvinyl)benzene S24



Potassium *tert*-butoxide (0.33 g, 2.90 mmol) was added portion wise to a stirred solution of (methoxymethyl)triphenylphosphonium chloride (1.04 g, 1.32 mmol) in THF (6 mL) at 0 ˚C. The reaction mixture turned bright orange upon this addition. After 15 min, 5-fluoro-2-iodobenzaldehyde (0.33 g, 1.32 mmol) in THF (3 mL) was added dropwise over 10 min to the reaction mixture at 0 ˚C. Upon this addition the reaction mixture turned pale yellow and was warmed to RT. After 21 h, the reaction was quenched with H_2O (6 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 100% petrol, to give a colourless oil as a 1:1 mixture of *E*:*Z* geometric isomers (0.30 g, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81-7.72 (m, 3H, ArCH), 7.03 (dd, 1H, *J* = 10.4, 2.8 Hz, ArCH), 6.93 (d, 1H, *J* = 12.9 Hz, ArC<u>H</u>CH), 6.65-6.59 (m, 2H, 2 x ArCH), 6.27 (d, 1H, *J* = 7.2 Hz, ArC<u>H</u>CH), 5.93 (d, 1H, *J* = 12.9 Hz, ArCHC<u>H</u>), 5.44 (d, 1H, *J* = 7.2 Hz, ArCHC<u>H</u>), 3.81 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.2 (d, *J* = 247.4 Hz, ArCF), 162.8 (d, *J* = 248.7 Hz, ArCF), 151.4, (Ar<u>C</u>HCH) 150.1 (Ar<u>C</u>HCH), 141.6 (d, *J* = 8.5 Hz, ArC), 140.4 (d, *J* = 8.4 Hz, ArCH), 139.9 (d, *J* = 7.8 Hz, ArCH), 116.4 (d, *J* = 23.2 Hz, ArCH), 114.8 (ArCH), 114.6 (ArCH) 111.8 (d, *J* = 24.0 Hz, ArCH), 108.9 (d, *J* = 2.5 Hz, ArCH<u>C</u>H), 108.4 (d, *J* = 2.5 Hz, ArCH<u>C</u>H), 93.9 (ArCI), 92.3 (ArCI), 61.0 (OCH_3), 56.8 (OCH_3); ^{19}F-NMR (377 MHz, $CDCl_3$) δ -114.24, -114.40.

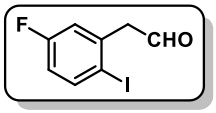
5-Fluoro-2-iodobenzaldehyde 319



Dess Martin periodinane (0.64 g, 1.51 mmol) was added in one portion to a stirred solution of (5-fluoro-2-iodophenyl)methanol (0.57 g, 1.26 mmol) in CH_2Cl_2 (15 mL). After 18 h, the reaction was quenched with $Na_2S_2O_3$ (1 M aqueous solution, 15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with $NaHCO_3$ (saturated aqueous solution, 30 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-5% EtOAc/petrol, to yield the product as a yellow solid (0.36 g, 64%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.02 (d, 1H, *J* = 3.2 Hz, CHO), 7.93 (dd, 1H, *J* = 8.5, 5.0 Hz, ArCH), 7.61 (dd, 1H, *J* = 8.5, 3.0 Hz, ArCH), 7.08 (td, 1H , *J* = 8.5, 3.2

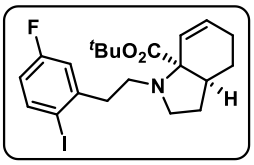
Hz, ArCH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.6 (d, *J* = 1.4 Hz, CO), 163.2 (d, *J* = 250.8 Hz, ArCF), 141.9 (d, *J* = 6.8 Hz, ArCH), 136.6 (d, *J* = 6.0 Hz, ArC), 123.0 (d, *J* = 22.1 Hz, ArCH), 116.9 (d, *J* = 23.3 Hz, ArCH), 93.3 (ArCI); ^{19}F-NMR (377 MHz, $CDCl_3$) δ -111.73; m.p. 93-95 ˚C (EtOAc/petrol).

2-(5-Fluoro-2-iodophenyl)acetaldehyde 320



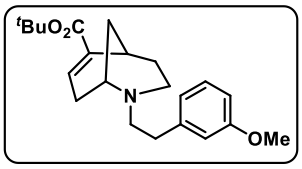
HCl (1 M aqueous solution, 0.6 mL, 0.55 mmol) was added to a stirred solution of 4-fluoro-1-iodo-2-(methoxyvinyl)benzene (0.26 g, 0.94 mmol) in acetone (4 mL) and the reaction mixture was heated to 60 ˚C. After 2 h, the reaction was cooled to RT and concentrated *in vacuo*. The crude material was partitioned between CH_2Cl_2 (10 mL) and $NaHCO_3$ (saturated aqueous solution, 10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-5% EtOAc/petrol, to give a yellow oil (0.17 g, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.78 (br t, 1H, *J* = 1.3 Hz, CHO), 7.82 (dd, 1H, *J* = 8.6, 5.6 Hz, ArCH), 6.99 (dd, 1H , *J* = 9.1, 2.5 Hz, ArCH), 6.79 (td, 1H, *J* = 8.6, 2.5 Hz, ArCH), 3.89 (d, 2H, *J* = 1.3 Hz, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.4 (CO), 163.0 (d, *J* = 249.3 Hz, ArCF), 140.8 (d, *J* = 8.0 Hz, ArCH), 138.3 (d, *J* = 8.0 Hz, ArC), 118.2 (d, *J* = 22.3 Hz, ArCH), 116.7 (d, *J* = 22.3 Hz, ArCH), 93.8 (d, *J* = 3.4 Hz, ArCI), 54.5 (CH_2); ^{19}F-NMR (377 MHz, $CDCl_3$) δ -113.4; υ_{max}/cm^{-1} 1715.6, 1692.6, 1575.4, 1465.6, 1405.0, 1274.7, 1232.6, 1155.4, 1018.8, 811.6.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(5-fluoro-2-iodophenethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 321



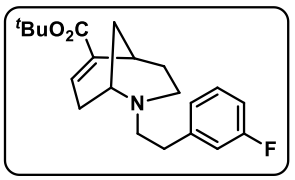
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.10 g, 0.45 mmol) and 2-(5-fluoro-2-iodophenyl)acetaldehyde (0.12 g, 0.45 mmol) were stirred with sodium triacetoxyborohydride (0.29 g, 1.35 mmol) in CH_2Cl_2 (2 mL). The crude material was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, to give a yellow oil (0.14 g, 67%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, 1H, *J* = 8.6, 5.8 Hz, ArCH), 7.00 (dd, 1H, *J* = 9.8, 2.9 Hz, ArCH), 6.65 (td, 1H, *J* = 8.6, 2.9 Hz, ArCH), 5.92 (dt, 1H, *J* = 10.3, 3.8 Hz, 6-CH), 5.72 (br d, 1H, *J* = 10.3 Hz, 7-CH), 3.04-2.99 (m, 1H, 1-CH), 2.95-2.83 (m, 4H, 1-CH, NC<u>H</u>H, NCH_2), 2.77-2.71 (m, 1H, NCH<u>H</u>), 2.56-2.49 (m, 1H, 3-CH), 2.13-1.92 (m, 3H, 2-CH and 5-CH_2), 1.74-1.66 (m, 1H, 4-CH), 1.60-1.54 (m, 2H, 2-CH and 4-CH), 1.45 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.7 (CO), 163.0 (d, *J* = 247.7 Hz, ArCF), 145.7 (d, *J* = 7.1 Hz, ArC) 140.2 (d, *J* = 7.9 Hz, ArCH), 130.5 (6-CH), 124.4 (7-CH), 117.1 (d, *J* = 22.2 Hz, ArCH), 115.1 (d, *J* = 21.6 Hz, ArCH), 93.3 (d, *J* = 2.8 Hz, ArCI), 80.8 (C), 69.1 (<u>C</u>CH_3), 50.2 (1-CH), 50.0 (NCH_2), 40.6 ($NCH_2C\underline{H}_2$), 40.4 (3-CH), 28.2 (CH_3), 27.4 (5-CH_2), 25.3 (4-CH_2), 22.3 (2-CH_2); ^{19}F-NMR (377 MHz, $CDCl_3$) δ -114.82; υ_{max}/cm^{-1} 2928.7, 1716.7, 1461.3, 1366.9, 1250.9, 1230.8, 1155.6, 1048.1, 1014.8, 806.6; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 472.1130, $[C_{21}H_{28}FINO_2]^+$ requires 472.1149.

(±)-*tert*-Butyl (1*R*)-2-(4-methoxyphenethyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 325



According to general procedure C, $Pd(OAc)_2$ (2 mg, 0.01 mmol), DPEPhos (9 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.04 mL, 0.22 mmol) were stirred in dioxane (0.5 mL) for 10 min. The reaction mixture turned bright yellow. (±)-*tert*-Butyl (3*R*,7a*S*)-1-(2-iodo-5-methoxyphenethyl)-1,2,3,3a,4,5-hexhydro-7a*H*-indole-7a-carboxylate (52 mg, 0.11 mmol) in dioxane (0.5 mL) was added to the stirred reaction and heated under reflux. The crude material was purified by SiO_2 flash chromatography, 30-50% EtOAc/petrol, to give a yellow oil (39 mg, 21%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20 (t, 1H, *J* = 7.8 Hz, ArCH), 7.04 (t, 1H, *J* = 3.7 Hz, 7-CH), 6.81-6.73 (m, 3H, ArCH), 3.80 (s, 3H, OCH_3), 3.14 (br s, 1H, 1-CH), 2.89 (br s, 1H, 5-CH), 2.79-2.74 (m, 2H, NCH_2), 2.71-2.68 (m, 1H, 3-CH), 2.65-2.60 (m, 2H, $NCH_2C\underline{H}_2$), 2.43-2.39 (m, 1H, 8-CH), 2.25 (br t, 1H, *J* = 12.3 Hz, 3-CH), 2.09-2.03 (m, 1H, 8-CH), 1.98-1.85 (m, 1H, 9-CH), 1.92-1.85 (m, 1H, 4-CH), 1.65-1.61 (m, 1H, 9-CH), 1.53 (br s, 1H, 4-CH), 1.48 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.8 (CO), 159.6 (ArC), 142.2 (6-C), 140.0 (7-CH), 134.3 (ArC), 129.3 (ArCH), 121.1 (ArCH), 114.5 (ArCH), 111.3 (ArCH), 80.0 (C), 57.3 ($NCH_2\underline{C}H_2$), 55.1 (OCH_3), 50.4 (1-CH), 44.5 (3-CH), 34.5 (NCH_2), 31.8 (9-CH), 28.9 (4-CH), 28.0 (CH_3), 26.8 (5-CH), 24.8 (8-CH). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[184]

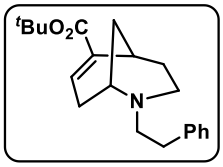
(±)-*tert*-Butyl (1*R*)-2-(3-fluorophenethyl)2-azabicylo[3.3.1]non-6-ene-6-carboxylate 326



According to general procedure C, $Pd(OAc)_2$ (3 mg, 0.01 mmol), DPEPhos (11 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.05 mL, 0.28 mmol) were stirred in dioxane (0.6 mL) for 10 min. The reaction mixture turned orange. (±)-*tert*-Butyl (3*aS*,7a*R*)-1-(5-fluoro-2-iodophenethyl)-1,2,3,3a,4,5-hexhydro-7a*H*-indole-7a-carboxylate (65 mg, 0.14 mmol) in dioxane (0.7 mL) was added to the stirred reaction and heated under reflux. The crude material was purified by SiO_2 flash chromatography, 30-40% EtOAc/petrol, to give a brown oil (16 mg, 33%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 1H, ArCH), 7.04 (br s, 1H, 7-CH), 6.98 (d, 1H, *J* = 7.5 Hz, ArCH), 6.93-6.87 (m, 2H, ArCH), 3.11 (s, 1H, 1-CH), 2.89 (s, 1H, 5-CH), 2.81-2.76 (m, 2H, NCH_2), 2.69-2.60 (m, 3H, 3-CH and $NCH_2C\underline{H}_2$), 2.40 (br d, 1H, *J* = 20.4 Hz, 8-CH), 2.26 (t, 1H, *J* = 12.1 Hz, 3-CH), 2.07 (br d, 1H, *J* = 20.4 Hz, 8-CH), 1.95 (br d, 1H, *J* = 12.4 Hz, 9-CH), 1.87 (br t, 1H, *J* = 12.1 Hz, 4-CH), 1.63 (br d, 1H, *J* = 12.4 Hz, 9-CH), 1.52 (s, 1H, 4-CH), 1.48 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.8 (CO), 162.8 (d, *J* = 245.0 Hz, ArCF), 143.2 (ArC), 139.9 (7-CH), 134.3 (6-CH), 129.7 (d, *J* = 8.3 Hz, ArCH), 124.4 (d, *J* = 2.8 Hz, ArCH), 115.5 (d, *J* = 20.9, ArCH), 112.8 (d, *J* = 21.1 Hz, ArCH), 80.0 (C), 57.0 ($NCH_2\underline{C}H_2$), 50.5 (1-CH), 44.4 (3-CH_2), 34.2 (NCH_2), 31.8 (9-CH_2), 28.8 (4-CH_2), 28.2 (CH_3), 26.8 (5-CH), 24.9 (8-CH_2); ^{19}F-NMR (377 MHz, $CDCl_3$) δ -133.81; υ_{max}/cm^{-1} 2930.2, 1701.7, 1588.9, 1448.2, 1367.0, 1284.5, 1251.2, 1167.7, 1137.7, 1077.1; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 346.2177, $[C_{21}H_{29}FNO_2]^+$ requires 346.2182.

(±)-*tert*-Butyl (1*R*)-2-phenethyl-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 327/336d

Aryl Iodide Substrate Procedure

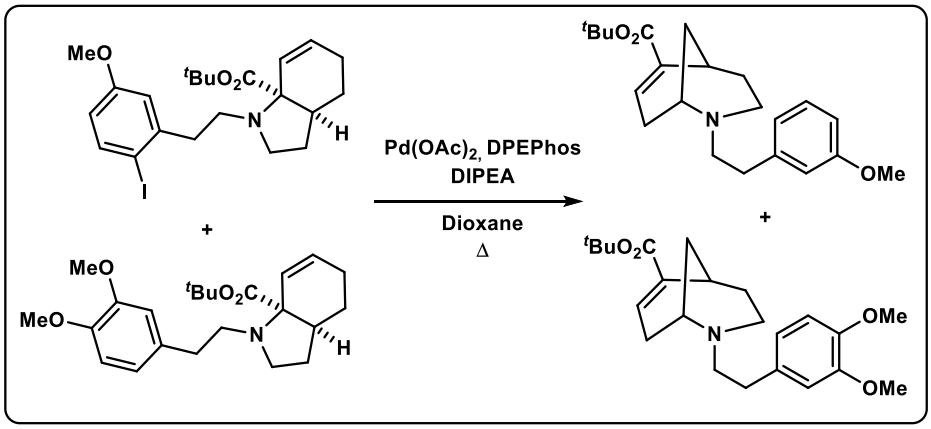


According to general procedure C, $Pd(OAc)_2$ (3 mg, 0.01 mmol), DPEPhos (10 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.04 mL, 0.24 mmol) were stirred in dioxane (0.5 mL) for 10 min. The reaction mixture turned bright yellow then turned orange. (±)-*tert*-Butyl (3a*R*,7a*S*)-1-(2-iodophenethyl)- 1,2,3,3a,4,5-hexhydro-7a*H*-indole-7a-carboxylate (53 mg, 0.12 mmol) in dioxane (0.5 mL) was added to the stirred reaction solution and heated under reflux. The crude material was purified by SiO_2 flash chromatography, 10-50% EtOAc/petrol, to give a yellow oil (29 mg, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H, ArCH), 7.26-7.22 (m, 3H, ArCH), 7.09 (t, 1H, *J* = 3.9 Hz, 7-CH), 3.19 (br s, 1H, 1-CH), 2.94 (br s, 1H, 5-CH), 2.85-2.81 (m, 2H, NCH_2), 2.76-2.73 (m, 1H, 3-CH), 2.70-2.63 (m, 2H, $NCH_2C\underline{H}_2$), 2.46 (dd, 1H, *J* = 20.7, 3.9 Hz, 8-CH), 2.30 (td, 1H, *J* = 12.4, 3.3 Hz, 3-CH), 2.13-2.07 (m, 1H, 8-CH), 2.01 (br dt, *J* = 12.3, 2.8 Hz, 1H, 9-CH), 1.93 (tt, 1H, *J* = 12.9, 4.3 Hz, 4-CH), 1.69-1.65 (m, 1H, 9-CH), 1.58-1.57 (m, 1H, 4-CH), 1.53 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.8 (CO), 140.5 (6-CH), 140.0 (7-CH), 134.3 (ArC), 128.7 (ArCH), 128.3 (ArCH), 126.0 (ArCH), 79.9 (C), 57.5 ($NCH_2\underline{C}H_2$), 50.3 (1-CH), 44.5 (3-CH), 34.5 (NCH_2), 31.8 (9-CH), 28.9 (4-CH), 28.2 (CH_3), 26.8 (5-CH), 24.8 (8-CH). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[184]

MSA Additive Procedure

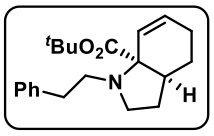
According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-phenethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (45 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmoL) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-40% EtOAc/isohexane, to give a yellow oil (30 mg, 67%).

Cross-over Reaction



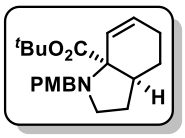
N,*N*-Diisopropylethylamine (0.07 mL, 0.4 mmol) was added to a stirred solution of $Pd(OAc)_2$ (5 mg, 0.02 mmol) and DPEPhos (19 mg, 0.04 mmol) in dioxane (0.5 mL). After 10 min, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(2-iodo-5-methoxyphenethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (69 mg, 0.14 mmol) and (±)-*tert*-butyl (3a*S*,7a*R*)-1-(3,4-dimethoxyphenethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (53 mg, 0.14 mmol) as a solution in dioxane (1 mL) were added and the reaction mixture was heated under reflux for 17 h. The reaction was cooled to RT, $NaHCO_3$ (saturated aqueous solution, 5 mL), was added and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 30-60% EtOAc/petrol, to give the products as an inseparable mixture (47 mg, 1:0.3, dimethoxy **302**: monomethoxy **325**).

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-phenethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 332



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.20 g, 0.90 mmol) and phenyl acetaldehyde (0.11 mL, 0.90 mmol) were stirred with sodium triacetoxyborohydride (0.57 g, 2.70 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, to give a yellow oil (0.26 g, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.16 (m, 5H, ArCH), 5.97-5.92 (m, 1H, 6-CH), 5.74 (br d, *J* = 10.3 Hz, 1H, 7-CH), 3.03-2.94 (m, 2H, 1-CH and NC<u>H</u>H), 2.82-2.69 (m, 4H, 1-CH, NCH<u>H</u> and $NCH_2C\underline{H}_2$), 2.56 (br s, 1H, 3-CH), 2.10-2.03 (m, 2H, 2-CH and 5-CH), 1.99-1.92 (m, 1H, 5-CH), 1.78-1.70 (m, 1H, 4-CH), 1.62-1.54 (m, 2H, 2-CH and 4-CH), 1.45 (s, 9H CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.6 (CO), 140.8 (ArC), 130.4 (6-CH), 128.7 (ArCH), 128.2 (ArCH), 125.8 (ArCH), 124.4 (7-CH), 80.7 (C), 69.1 (C), 52.3 (NCH_2), 50.5 (1-CH_2), 40.4 (3-CH), 36.3 ($NCH_2\underline{C}H_2$), 28.2 (CH_3), 27.2 (2-CH_2), 25.0 (4-CH_2), 22.0 (5-CH_2); υ_{max}/cm^{-1} 2928.9, 1715.9, 1453.9, 1366.6, 1248.9, 1154.7, 1047.3, 1029.9, 749.0, 698.5; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 328.2308, $[C_{21}H_{30}NO_2]^+$ requires 328.2277.

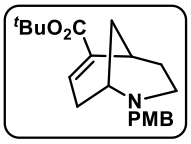
(±)- *tert*-Butyl (3a*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 333



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.25 g, 0.95 mmol) and *p*-anisaldehyde (0.12 mL, 0.95 mmol) were stirred with sodium triacetoxyborohydride (0.60 g, 2.85 mmol) in CH_2Cl_2 (4 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/petrol, to give the product as a colourless oil (0.19 g, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 2H, *J* = 8.40 Hz, ArCH), 6.83 (d, 2H, *J* = 8.40 Hz, ArCH), 6.01 (dt, 1H, *J* = 10.3, 3.9 Hz, 6-CH), 5.85 (br d, 1H, *J* = 10.3 Hz, 7-CH), 3.82 (s, 1H, ArC<u>H</u>H), 3.79 (s, 3H, OCH_3), 3.60 (d, 1H, *J* = 13.2 Hz, ArCH<u>H</u>), 2.69 (td, 1H, *J* = 9.0, 4.9 Hz, 1-CH), 2.62-2.53 (m, 2H, 1-CH and 3-CH), 2.14-1.94 (m, 3H, 5-CH_2 and 2-CH), 1.77-1.69 (m, 1H, 4-CH), 1.65-1.59 (m, 1H, 4-CH), 1.56-1.53 (m, 1H, 2-CH), 1.50 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.8 (CO), 158.4 (ArC), 132.8 (ArC), 130.7 (6-CH), 129.4 (ArCH), 124.7 (7-CH), 113.5 (ArCH), 80.8 (C), 69.0 (<u>C</u>CH_3), 55.2 (OCH_3), 53.4 ($ArCH_2$), 49.7 (1-CH_2), 40.4 (3-CH), 28.2 (CH_3), 27.3 (2-CH_2), 25.4, (4-CH_2), 22.4 (5-CH_2). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[184]

(±)-*tert*-Butyl (1*R*)-2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 334

Aryl Iodide Additive Procedure



N,*N*-Diisopropylethylamine (0.06 mL, 0.34 mmol) in dioxane (0.80 mL) was added to $Pd(OAc)_2$ (4 mg, 0.02 mmol) and DPEPhos (14 mg, 0.03 mmol) and stirred for 10 min. (±)-*tert*-Butyl (3a*S*,7a*R*)- 1- (4-methoxybenzyl) - 1, 2, 3, 3a, 4, 5-hexahydro-7a*H*-indole-7a-carboxylate (60 mg, 0.17 mmol) in dioxane (0.8 mL) and 1-iodo-4,5-dimethoxy-2-methylbenzene (47 mg, 0.17 mmol) was added to the stirred reaction solution and heated under reflux. After 17 h, the reaction mixture was cooled to RT, quenched with $NaHCO_3$ (saturated aqueous solution, 5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 10-30% EtOAc/petrol, to give a yellow oil (30 mg, 50%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.28 (m, 2H, ArCH), 7.10 (t, 1H, *J* = 3.6 Hz, 7-CH), 6.88-6.86 (m, 2H, ArCH), 3.82 (s, 3H, OCH_3), 3.52 (d, 2H, *J* = 6.5 Hz, $ArCH_2$), 3.01 (br s, 1H, 1-CH), 2.90 (br s, 1H, 5-CH), 2.56-2.42 (m, 2H, 3-CH and 8-CH), 2.26 (td, 1H, *J* = 12.5, 3.4 Hz, 3-CH), 2.07-2.00 (m, 1H, 8-CH), 1.94 (br d, 1H, *J* = 12.2 Hz, 9-CH), 1.85 (tt, 1H, *J* = 12.5, 4.3 Hz, 4-CH), 1.59 (br dq, 1H, *J* = 12.2, 2.7 Hz, 9-CH), 1.51 (s, 9H, CH_3) superimposed on 1.49 (m, 1H, 4-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9 (CO), 158.5 (ArC), 140.2 (7-CH), 134.4 (6-C), 131.3 (ArC), 129.9 (ArCH), 113.6 (ArCH), 79.9 (C), 58.9 ($ArCH_2$), 55.2 (OCH_3), 49.5 (1-CH), 44.2 (3-CH_2), 31.9 (9-CH_2), 28.9 (4-CH_2), 28.2 (CH_3), 26.9 (5-CH), 24.8 (8-CH_2); υ_{max}/cm^{-1} 1700.7, 1511.3, 1366.2, 1284.5, 1245.5, 1166.9, 1071.8, 1131.7, 1036.5, 1025.8; *m/z* HRMS (ESI^+) found $[M + H]^+$ 344.2232, $[C_{21}H_{30}NO_3]^+$ requires 344.2226.

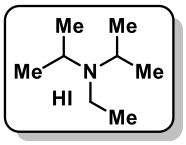
DIPEA HI Additive Procedure

N,*N*-Diisopropylethylamine hydroiodide (44 mg, 0.17 mmol) was added to a stirred solution of $Pd(OAc)_2$ (4 mg, 0.02 mmol) and DPEPhos (14 mg, 0.03 mmol) in dioxane (0.8 mL) and stirred for 10 min. The reaction mixture turned black. (±)-*tert*-Butyl (3a*S*,7a*R*)- 1- (4-methoxybenzyl) - 1, 2, 3, 3a, 4, 5-hexahydro-7a*H*-indole-7a-carboxylate (60 mg, 0.17 mmol) in dioxane (0.8 mL) was added to the stirred reaction solution and heated under reflux. After 17 h, the reaction mixture was cooled to RT, quenched with $NaHCO_3$ (saturated aqueous solution, 5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 10-25% EtOAc/petrol, to give a yellow oil (32 mg, 53%).

MSA Additive Procedure

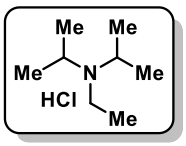
According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)- 1- (4-methoxybenzyl) - 1, 2, 3, 3a, 4, 5-hexahydro-7a*H*-indole-7a-carboxylate (62 mg, 0.18 mmol) in dioxane (0.8 mL) was added to a stirred solution of $Pd(OAc)_2$, DPEPhos and *N*,*N*-diisopropylethylamine in dioxane (0.8 mL). After 10 min methanesulfonic acid was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-20% EtOAc/isohexane, to give a yellow oil (43 mg, 70%).

_N_,_N_-Diisopropylethylamine hydroiodide S25



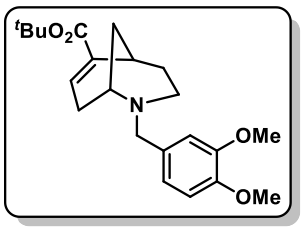
Hydriodic acid (56% aqueous solution, 0.77 mL, 5.74 mmol) was added dropwise to a stirred solution of *N*,*N*-diisopropylethylamine (1.0 mL, 5.74 mmol) in CH_2Cl_2 (10 mL) at 0 ˚C. The reaction mixture was warmed to RT and stirred for 10 min, extracted with CH_2Cl_2 (4 x 10 mL) and concentrated *in vacuo*. The crude material was recrystallised from Et_2O to give a pale-yellow solid (1.26 g, 85%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.35 (br s, 1H, HI), 3.82-3.76 (m, 2H, 2 x NCH), 3.20 (q, 2H, *J* = 6.7 Hz, 2 x NCH_2), 1.66-1.61 (m, 9H, CH_3), 1.51-1.50 (d, 6H, *J* = 6.7 Hz, $CH_2C\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 54.6 (NCH), 42.7 (NCH_2), 18.6 (CH_3), 17.4 (CH_3), 12.1 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[308]

_N_,_N_-Diisopropylethylamine hydrochloride S26



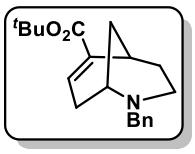
Hydrochloric acid (2 M sol in Et_2O, 2.87 mL, 5.74 mmol) added dropwise to a stirred solution of *N*,*N*-diisopropylethylamine (1.0 mL, 5.74 mmol) in CH_2Cl_2 (15 mL) and stirred for 15 min. The reaction mixture was concentrated *in vacuo* and the solid washed with Et_2O to give a colourless solid which was used directly in the next step without further purification (0.91 g, 96%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.19 (br s, 1H, HCl), 3.64 (qn, 2H, *J* = 6.4 Hz, 2 x NCH), 3.07 (q, 2H, *J* = 7.4 Hz, NCH_2), 1.55-1.42 (m, 15H, 5 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 53.6 (NCH), 41.9 (NCH_2), 15.6 (CH_3), 17.3 (CH_3), 12.0 (CH_3).

(±)-*tert*-Butyl (1*R*)-2-(3,4-dimethoxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336a



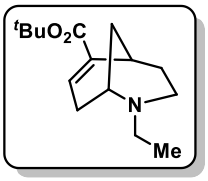
According to general procedure D, *tert*-butyl (±)-(3a*S*,7a*R*)-1-(3,4-dimethoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (56 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-30% EtOAc/isohexane, to give a yellow oil (39 mg, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.06 (t, 1H, *J* = 3.6 Hz, 7-CH), 6.93 (br s, 1H, ArCH), 6.84-6.78 (m, 2H, ArCH), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.49 (d, 2H, *J* = 6.4 Hz, $ArCH_2$), 2.98 (br s, 1H, 1-CH), 2.87 (br s, 1H, 5-CH), 2.54-2.51 (m, 1H, 3-CH), 2.48-2.44 (m, 1H, 8-CH), 2.24 (td, 1H, *J* = 12.3, 3.2 Hz, 3-CH), 2.05-1.99 (m, 1H, 8-CH), 1.95-1.92 (m, 1H, 9-CH), 1.87-1.80 (m, 1H, 4-CH), 1.59-1.55 (m, 1H, 9-CH), 1.48 (s, 9H, 3 x CH_3) superimposed on 1.48-1.46 (m, 1H, 4-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.9 (CO), 148.9 (ArC), 147.9 (ArC), 140.1 (7-CH), 134.4 (6-CH), 131.8 (ArC), 120.7 (ArCH), 111.9 (ArCH), 110.7 (ArCH), 79.9 (C), 59.2 ($ArCH_2$), 55.9 (OCH_3), 55.8 (OCH_3), 49.5 (1-CH), 44.2 (3-CH_2), 31.8 (9-CH_2), 28.9 (4-CH_2), 28.2 (3 x CH_3), 26.9 (5-CH), 24.9 (8-CH_2); υ_{max}/cm^{-1} 1700.5, 1512.9, 1463.8, 1366.0, 1252.9, 1233.4, 1156.4, 1138.5, 1072.8, 1027.2; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 374.2315, $[C_{22}H_{32}NO_4]^+$ requires 374.2331.

(±)-*tert*-Butyl (1*R*)-2-benzyl-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336b



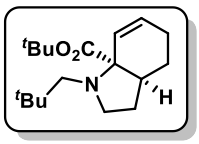
According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-benzyl-2-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (47 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-20% EtOAc/isohexane, to give a colourless oil (18 mg, 38%). ^{1}H-NMR (400 MHz, $CDCl_3$) 7.35-7.29 (m, 4H, ArCH), 7.24-7.22 (m, 1H, ArCH), 7.08 (t, 1H, *J* = 3.6 Hz, 7-CH), 3.56 (app q, 2H, $ArCH_2$), 3.00 (br s, 1H, 1-CH), 2.88 (br s, 1H, 5-CH), 2.54-2.46 (m, 2H, 3-CH and 8-CH), 2.27 (td, 1H, *J* = 12.0, 3.6 Hz, 3-CH), 2.06-2.00 (m, 1H, 8-CH), 1.95 (br d, 1H, *J* = 12.0 Hz, 9-CH), 1.84 (tt, 1H, *J* = 12.8, 4.5 Hz, 4-CH), 1.59-1.57 (m, 1H, 9-CH), 1.48 (s, 9H, 3 x CH_3) 1.47-1.46 (m, 1H, 4-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9 (CO), 140.2 (7-CH), 139.4 (ArC), 134.4 (6-C), 128.8 (ArCH), 128.2 (ArCH), 126.8 (ArCH), 79.9 (C), 59.6 ($ArCH_2$), 49.8 (1-CH), 44.3 (3-CH_2), 31.9 (9-CH_2), 28.9 (4-CH_2), 28.2 (3 x CH_3), 26.9 (5-CH), 24.9 (8-CH_2); υ_{max}/cm^{-1} 2930.4, 1701.9, 1366.5, 1284.2, 1251.3, 1166.9, 1135.8, 1070.2, 1024.8, 697.9; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 314.2109, $[C_{20}H_{28}NO_2]^+$ requires 314.2120.

(±)-*tert*-Butyl (1*R*)-2-ethyl-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336e



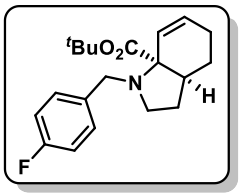
According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-ethyl- 1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (38 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-50% EtOAc/isohexane then 10% MeOH/CH_2Cl_2, to give a brown oil (26 mg, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.00 (t, 1H, *J* = 3.7 Hz, 7-CH), 3.53 (br s, 1H, 1-CH), 3.03 (br d, 1H, *J* = 12.4 Hz, 3-CH), 2.98 (br t, 1H, *J* = 3.1 Hz, 5-CH), 2.91-2.84 (m, 1H, NC<u>H</u>H), 2.80-2.74 (m, 1H, NCH<u>H</u>), 2.55-2.47 (m, 2H, 3-CH and 8-CH), 2.38-2.29 (m, 2H, 8-CH and 9-CH), 2.17-2.14 (br t, 1H, *J* = 13.1 Hz, 4-CH), 1.67 (app dq, 1H, 9-CH), 1.59 (br d, 1H, *J* = 13.1 Hz, 4-CH), 1.48 (s, 9H, 3 x CH_3), 1.27 (t, 3H, *J* = 7.5 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.6 (CO), 138.6 (7-CH), 134.2 (6-C), 80.7 (C), 49.8 (1-CH), 48.2 (NCH_2), 43.9 (3-CH_2), 29.0 (9-CH_2), 28.1 (3 x CH_3), 26.7 (4-CH_2), 25.6 (5-CH), 25.0 (8-CH_2), 10.5 (CH_3); υ_{max}/cm^{-1} 2974.1, 1702.1, 1646.3, 1436.9, 1392.5, 1367.4, 1253.6, 1166.9, 1082.6, 758.0; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 252.1955, $[C_{15}H_{25}NO_2]^+$ requires 252.1964.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-neopentyl- 1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335f



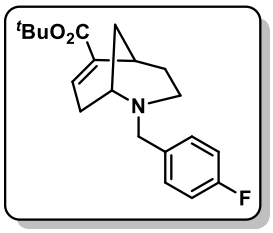
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.15 g, 0.68 mmol) and trimethylacetaldehyde (0.07 mL, 0.68 mmol) were stirred with sodium triacetoxyborohydride (0.43 g, 2.04 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a colourless oil (0.14 g, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88-5.84 (m, 1H, 6-CH), 5.73 (dt, 1H, *J* = 10.2, 1.9 Hz, 7-CH), 3.08 (dt, 1H, *J* = 8.9, 5.1 Hz, 1-CH), 2.87-2.82 (m, 1H, 1-CH), 2.43-2.34 (m, 3H, 3-CH and NCH_2), 2.14-2.07 (m, 1H, 2-CH), 2.02-1.97 (m, 2H, 5-CH_2), 1.61-1.57 (m, 2H, 4-CH_2), 1.52-1.46 (m, 1H, 2-CH), 1.45 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.7 (CO), 128.7 (6-CH), 126.7 (7-CH), 80.5 (C), 70.6 (C), 63.3 (NCH_2), 54.0 (1-CH_2), 40.5 (3-CH), 32.9 (C), 29.0 (4-CH_2), 28.7 (3 x CH_3), 28.3 (3 x CH_3), 26.6 (2-CH_2), 23.7 (5-CH_2); υ_{max}/cm^{-1} 2972.0, 2904.4, 1408.6, 1393.8, 1380.3, 1250.4, 1077.7, 1066.2, 1056.8, 1028.5; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 294.2427, $[C_{18}H_{31}NO_2]^+$ requires 294.2433.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(4-fluorobenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335h



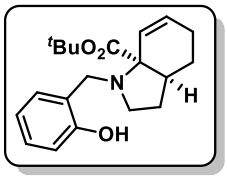
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.10 g, 0.45 mmol) and 4-fluorobenzaldehyde (0.05 mL, 0.45 mmol) were stirred with sodium triacetoxyborohydride (0.29 g, 1.35 mmol) in CH_2Cl_2 (2 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a colourless oil (71 mg, 47%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H, ArCH), 6.98-6.94 (m, 2H, ArCH), 6.02 (dt, 1H, *J* = 10.2, 3.9 Hz, 6-CH), 5.82 (dt, *J* = 10.2, 2.0 Hz, 7-CH), 3.84 (d, 1H, *J* = 13.2 Hz, ArC<u>H</u>H), 3.62 (d, 1H, *J* = 13.2 Hz, ArCH<u>H</u>), 2.67 (td, 1H, *J* = 8.8, 4.6 Hz, 1-CH), 2.61-2.53 (m, 2H, 1-CH and 3-CH), 2.13-2.06 (m, 1H, 2-CH), 2.04-1.96 (m, 2H, 2-CH and 5-CH), 1.77-1.71 (m, 1H, 4-CH), 1.65-1.58 (m, 1H, 4-CH), 1.54-1.50 (m, 1H, 5-CH), 1.49 (s, 9H, 3 x CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.7 (CO), 161.8 (d, *J* = 246.6 Hz, ArCF), 136.3 (ArC), 130.9 (6-CH), 129.1 (d, *J* = 8.2 Hz, ArCH), 124.5 (7-CH), 114.7 (d, *J* = 21.2 Hz, ArCH), 80.8 (C), 67.0 (C), 53.3 ($ArCH_2$), 49.7 (1-CH_2), 40.3 (3-CH), 28.2 (3 x CH_3), 27.3 (5-CH_2), 25.4 (4-CH_2), 22.4 (2-CH_2); ^{19}F-NMR (377 MHz, $CDCl_3$) δ -116.69; υ_{max}/cm^{-1} 2930.3, 1717.7, 1603.0, 1508.1, 1367.0, 1247.2, 1220.6, 1151.6, 848.4, 825.7; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 332.2014, $[C_{20}H_{27}FNO_2]^+$ requires 332.2026.

(±)-*tert*-Butyl (1*R*)-2-(4-fluorobenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336h



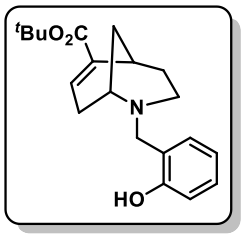
According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(4-fluorobenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (52 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 5-20% EtOAc/isohexane, to give a colourless oil (11 mg, 21%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H, ArCH), 7.07 (t, 1H, *J* = 3.7 Hz, 7-CH), 7.00-6.96 (m, 2H, ArCH), 3.51 (app q, 2H, $ArCH_2$), 2.98 (m, 1H, 1-CH), 2.88 (br t, 1H, *J* = 3.2 Hz, 5-CH), 2.49 (m, 2H, 3-CH and 8-CH), 2.25 (td, 1H, *J* = 12.3, 3.4 Hz, 3-CH), 2.07-2.01 (m, 1H, 8-CH), 1.93 (br d, 1H, *J* = 11.6 Hz, 9-CH), 1.82 (tt, 1H, *J* = 12.9, 4.2 Hz, 4-CH), 1.60-1.50 (m, 2H, 4-CH and 9-CH), 1.48 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9 (CO), 161.9 (d, *J* = 2.44.5 Hz, ArCF), 140.0 (7-CH), 134.9 (ArC), 134.4 (6-C), 130.1 (d, *J* = 7.7 Hz, ArCH), 115.0 (d, *J* = 22.2 Hz, ArCH), 79.9 (C), 58.8 ($ArCH_2$), 49.8 (1-CH), 44.2 (3-CH_2), 31.9 (9-CH_2), 28.9 (3 x CH_3), 28.2 (4-CH_2), 26.8 (5-CH), 25.0 (8-CH_2); ^{19}F-NMR (377 MHz, $CDCl_3$) δ -116.19; υ_{max}/cm^{-1} 1702.3, 1508.7, 1366.8, 1285.1, 1252.2, 1220.6, 1166.5, 1072.6, 832.0, 760.1; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 332.2014, $[C_{20}H_{27}FNO_2]^+$ requires 332.2026.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(2-hyroxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335i



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.10 g, 0.45 mmol) and salicyaldehyde (0.05 mL, 0.45 mmol) were stirred with sodium triacetoxyborohydride (0.29 g, 1.35 mmol) in CH_2Cl_2 (2 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a colourless oil (78 mg, 52%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.15 (td, 1H, *J* = 7.4, 1.5 Hz, ArCH), 6.96 (br d, 1H, *J* = 7.4 Hz, ArCH), 6.81 (d, 1H, *J* = 7.4 Hz, ArCH), 6.75 (td, 1H, *J* = 7.4, 1.5 Hz, ArCH), 6.15 (dt, 1H, *J* = 10.4, 3.7 Hz, 6-CH), 5.81 (br t, 1H, *J* = 10.4 Hz, 7-CH), 4.13 (d, 1H, *J* = 13.4 Hz, ArC<u>H</u>H), 3.64 (d, 1H, *J* = 13.4 Hz, ArCH<u>H</u>), 2.85 (dt, 1H, *J* = 9.4, 3.9 Hz, 1-CH), 2.66-2.62 (m, 1H, 3-CH), 2.51 (m, 1H, 1-CH), 2.17-2.10 (m, 1H, 5-CH), 2.07-1.99 (m, 2H, 2-CH and 5-CH), 1.85-1.78 (m, 1H, 4-CH), 1.63-1.57 (m, 2H, 2-CH and 4-CH), 1.51 (s, 9H, 3 x CH_3); 4.08 (d, 1H, *J* = 14.3 Hz, ArC<u>H</u>H), 3.89 (d, 1H, *J* = 14.3 Hz, ArCH<u>H</u>), 2.81 (dt, 1H, *J* = 8.6, 4.9 Hz, CH), 2.73-2.69 (m, 1H, CH), 2.62-2.57 (m, 1H, CH), 2.13-2.06 (m, 1H, CH), 2.05-1.97 (m, 2H, CH), 1.75-1.69 (m, 1H, CH), 1.66-1.59 (m, 1H, CH), 1.52-1.51 (m, 1H, CH), 1.49 (s, 9H, 3 x CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.2 (CO), 157.8 (ArC), 132.8 (6-CH), 128.6 (ArCH), 128.5 (ArCH), 122.3 (7-CH), 122.1 (ArC), 118.8 (ArCH), 115.9 (ArCH), 82.0 (C), 69.1 (C), 53.3 ($ArCH_2$), 49.8 (1-CH_2), 40.8 (3-CH), 28.0 (3 x CH_3), 26.5 (2-CH_2), 24.2 (4-CH_2), 21.5 (5-CH_2); υ_{max}/cm^{-1} 2972.6, 2928.5, 1721.5, 1588.3, 1489.4, 1367.8, 1252.7, 1160.2, 1036.7, 753.3; *m/z* HRMS (ESI$^+$) found [M + H]$^+$ 330.2061, $[C_{20}H_{27}NO_3]^+$ requires 320.2069.

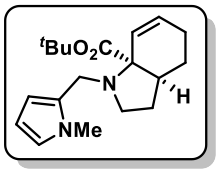
(±)-*tert*-Butyl (1*R*)-2-(2-hydroxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336i



According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(2-hyroxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (49 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude product was purified by SiO_2 flash chromatography, eluting with 10-20% EtOAc/isohexane, to give a yellow oil (13 mg, 27%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 1H, ArCH), 7.05 (t, 1H, *J* = 3.5 Hz, 7-CH), 6.95 (br d, 1H, *J* = 7.6 Hz, ArCH), 6.80 (d, 1H, *J* = 7.6 Hz, ArCH), 6.75 (m, 1H, ArCH), 3.77 (app q, 2H, $ArCH_2$), 3.17 (br s, 1H, 1-CH), 2.94 (br t, 1H, *J* = 3.0 Hz, 5-CH), 2.68 (dd, 1H, *J* = 12.7, 4.3 Hz, 3-CH), 2.46 (dd, 1H, *J* = 20.7, 3.5 Hz, 8-CH), 2.36 (br t, 1H, *J* = 12.7 Hz, 3-CH), 2.15 (br d, 1H, *J* = 20.7 Hz, 8-CH), 1.97 (br d, 1H, *J* = 12.6 Hz, 9-CH), 1.89 (tt, 1H, *J* = 12.7, 4.5 Hz, 4-CH) 1.67 (br d, 1H, *J* = 12.6 Hz, 9-CH),1.58-1.51 (m, 1H, 4-CH), 1.48 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.5 (CO), 158.4 (ArC), 139.1 (7-CH), 134.4 (6-C), 128.7 (ArCH), 128.5 (ArCH), 121.2 (ArC), 118.9 (ArCH), 116.0 (ArCH), 80.3 (C), 58.4 ($ArCH_2$), 49.6 (1-CH_2), 43.7 (3-CH_2), 31.7 (9-CH_2), 28.6 (4-CH_2), 28.2

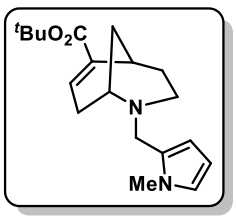
(3 x CH_3), 26.5 (5-CH), 24.6 (8-CH_2); υ_{max}/cm^{-1} 2930.2, 1703.6, 1477.8, 1367.2, 1255.7, 1167.5, 1103.5, 1073.0, 1020.4, 753.7; *m/z* HRMS (ESI^+) found $[M + H]^+$ 330.2056 $[C_{20}H_{28}NO_3]^+$ requires 330.2069.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-((1-methyl-1*H*-pyrol-2-yl)methyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335j



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.15 g, 0.68 mmol) and *N*-methyl-2-pyrrolecarboxylaldehyde (75 mg, 0.68 mmol) were stirred with sodium triacetoxyborohydride (0.43 g, 2.04 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a yellow oil (91 mg, 41%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.55 (app t, 1H, ArCH), 5.99-5.98 (m, 1H, ArCH) superimposed on 5.98-5.96 (m, 1H, 6-CH), superimposed on 5.95-5.94 (m, 1H, ArCH), 5.87 (dt, 1H, *J* = 10.2, 2.1 Hz, 7-CH), 3.73 (d, 2H, *J* = 2.5 Hz, $ArCH_2$), 3.62 (s, 3H, NCH_3), 2.64-2.61 (m, 2H, 1-CH_2), 2.55-2.54 (m, 1H, 3-CH), 2.05-1.97 (m, 3H, 2-CH and 5-CH_2), 1.69-1.61 (m, 1H, 4-CH), 1.59-1.56 (m, 2H, 2-CH and 4-CH), 1.49 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 179.6 (CO), 173.4 (ArC), 130.7 (6-CH), 124.6 (7-CH), 122.2 (ArCH), 108.3 (ArCH), 105.9 (ArCH), 80.9 (C), 68.4 (C), 49.7 (1-CH), 45.4 ($ArCH_2$), 40.6 (3-CH), 34.0 (NCH_3), 28.3 (3 x CH_3), 27.5 (5-CH_2), 26.2 (2-CH_2), 23.1 (5-CH_2); υ_{max}/cm^{-1} 2979.9, 2928.7, 1715.8, 1392.4, 1368.1, 1250.9, 1158.5, 1073.3, 1048.8, 1028.5; *m/z* HRMS (ESI^+) found $[M + H]^+$ 317.2220, $[C_{19}H_{29}N_2O_2]^+$ requires 317.2229.

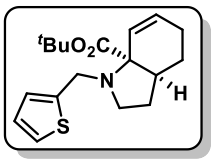
(±)-*tert*-Butyl (1*R*)-2-((1-methyl-1*H*-pyrrol-2-yl)methyl)-2-azabicyclo[3.3.1]non-6-ene-carboxylate 336j



According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-((1-methyl-1*H*-pyrol-2-yl)methyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (47 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-30% EtOAc/isohexane, to give a yellow oil (9 mg, 19%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.06 (br t, 1H, *J* = 3.6 Hz, 7-CH), 6.58 (br s, 1H, ArCH), 6.01-5.95 (m, 2H, ArCH), 3.65 (s, 3H, CH_3), 3.49 (s, 2H, $ArCH_2$), 2.90-2.86 (m, 2H, 1-CH and 5-CH), 2.53-2.40 (m, 2H, 3-CH and 8-CH), 2.25-2.18 (m, 1H, 3-CH), 2.05-1.97 (m, 1H, 8-CH), 1.85-1.72 (m, 2H, 4-CH and 9-CH), 1.56-1.54 (m, 2H, 4-CH and 9-CH), 1.48 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9 (CO), 140.3 (7-CH), 134.3 (6-C), 129.4 (ArC), 122.4 (ArCH), 108.9 (ArCH), 106.0 (ArCH), 79.9 (C), 51.2 ($ArCH_2$), 48.9 (1-CH), 44.0 (3-CH_2), 33.8 (NCH_3), 32.0 (9-CH_2), 29.0 (4-CH_2), 28.2 (3 x CH_3), 27.0 (5-CH), 24.5 (8-CH_2); υ_{max}/cm^{-1} 2927.0, 1702.8, 1454.9, 1366.8, 1251.7, 1168.2,

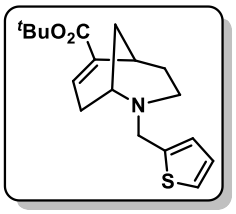
1072.4, 1024.7, 912.0, 708.0; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 317.2223 $[C_{19}H_{29}N_2O_2]^+$ requires 317.2229.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(thiophen-2-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a carboxylate 335k



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.10 g, 0.45 mmol) and 2-thiphenecarboxaldehyde (0.04 mL, 0.45 mmol) were stirred with sodium triacetoxyborohydride (0.29 g, 1.35 mmol) in CH_2Cl_2 (2 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a colourless oil (75 mg, 54%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, 1H, *J* = 4.9, 1.3 Hz, ArCH), 6.91-6.88 (m, 2H, ArCH), 6.02 (dt, 1H, *J* = 10.2, 3.8 Hz, 6-CH), 5.81 (dt, 1H, *J* = 10.2, 2.1 Hz, 7-CH), 4.08 (d, 1H, *J* = 14.2 Hz, ArCHH), 3.90 (d, 1H, *J* = 14.2 Hz, ArCHH), 2.81 (td, 1H, *J* = 8.8, 5.0 Hz, 1-CH), 2.73-2.69 (m, 1H, 1-CH), 2.62-2.57 (m, 1H, 3-CH), 2.13-2.06 (m, 1H, 5-CH), 2.05-1.97 (m, 2H, 2-CH and 5-CH), 1.75-1.69 (m, 1H, 4-CH), 1.66-1.59 (m, 1H, 4-CH), 1.52-1.51 (m, 1H, 2-CH), 1.49 (s, 9H, 3 x CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.6 (CO), 145.7 (ArC), 131.3 (6-CH), 126.2 (ArCH), 124.3 (7-CH), 124.2 (ArCH), 124.0 (ArCH), 80.9 (C), 68.9 (C), 50.0 (1-CH_2) 48.9 ($ArCH_2$), 40.2 (3-CH), 28.2 (3 x CH_3), 27.3 (2-CH_2), 25.4 (4-CH_2), 22.6 (5-CH_2); υ_{max}/cm^{-1} 2971.8, 2904.4, 1703.7, 1393.7, 1384.3, 1251.0, 1166.0, 1066.3, 1056.8, 1020.5; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 320.1678, $[C_{18}H_{26}NO_2S]^+$ requires 320.1684.

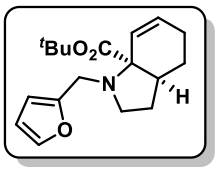
(±)-*tert*-Butyl (1*R*)-2-(thiophen-2-ylmethyl)-2-azabicyclo[3.3.1]non-6-ene-6- carboxylate 336k



According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(thiophen-2-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (48 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/isohexane, to give a colourless oil (12 mg, 12%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21-7.20 (m, 1H, ArCH), 7.06 (t, 1H, *J* = 3.6 Hz, 7-CH), 6.93-6.91 (m, 2H, ArCH), 3.76 (d, 2H, *J* = 6.5 Hz, $ArCH_2$), 3.08 (br s, 1H, 1-CH), 2.88 (br s, 1H, 5-CH), 2.74-2.60 (m, 2H, 3-CH and 8-CH), 2.41 (br dd, 1H, *J* = 20.8, 4.2 Hz, 8-CH), 2.28 (br t, 1H, *J* = 12.1 Hz, 3-CH), 2.09-2.02 (m, 1H, 8-CH), 1.94 (br d, 1H, *J* = 12.3 Hz, 9-CH), 1.90-1.81 (m, 1H, 4-CH), 1.59-1.55 (m, 2H, 4-CH and 9-CH), 1.48 (s, 9 H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9 (CO), 143.9 (ArC), 140.0 (7-CH), 134.4 (6-C), 126.3 (ArCH), 125.0 (ArCH), 124.7 (ArCH), 79.9 (C), 54.1 ($ArCH_2$), 49.6 (1-CH), 44.3 (3-CH_2), 31.7 (9-CH_2), 28.2 (3 x CH_3), 27.9 (4-CH_2), 26.8 (5-CH), 25.0 (8-

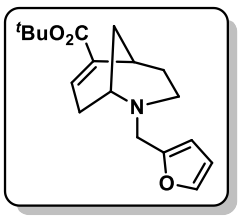
CH_2); υ_{max}/cm^{-1} 2927.2, 1724.7, 1702.8, 1366.7, 1285.1, 1251.7, 1164.0, 1073.3, 731.7, 696.3; *m/z* HRMS (ESI^+) found $[M + H]^+$ 320.1672, $[C_{18}H_{26}NO_2S]^+$ requires 320.1684.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(furan-2-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335l



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.10 g, 0.45 mmol) and furfural (0.04 mL, 0.45 mmol) were stirred with sodium triacetoxyborohydride (0.29 g, 1.35 mmol) in CH_2Cl_2 (2 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a colourless oil (94 mg, 67%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.34 (m, 1H, ArCH), 6.28-6.27 (m, 1H, ArCH), 6.15-6.14 (m, 1H, ArCH), 6.01 (dt, 1H, *J* = 10.3, 4.0 Hz, 6-CH), 5.75 (dt, 1H, *J* = 10.3, 1.9 Hz, 7-CH), 3.96 (d, 1H, *J* = 13.6 Hz, ArC<u>H</u>H), 3.63 (d, 1H, *J* = 13.6 Hz, ArCH<u>H</u>), 2.88 (td, 1H, *J* = 8.6, 4.6 Hz, 1-CH), 2.68-2.60 (m, 2H, 1-CH and 3-CH), 2.12- 2.04 (m, 1H, 5-CH), 2.03-1.94 (m, 2H, 5-CH and 2-CH), 1.80-1.73 (m, 1H, 4-CH), 1.63-1.58 (m, 1H, 4-CH), 1.56-1.51 (m, 1H, 2-CH), 1.49 (s, 9H, 3 x CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.3 (CO), 153.8 (ArC), 141.7 (ArCH), 131.2 (6-CH), 124.0 (7-CH), 110.0 (ArCH), 109.2 (ArCH), 80.9 (C), 68.5 (C), 50.7 (1-CH_2), 46.8 (ArCH_2), 40.3 (3-CH), 28.2 (CH_3), 27.0 (2-CH_2), 25.1 (4-CH_2), 21.9 (5-CH_2); υ_{max}/cm^{-1} 2926.8, 2852.3, 1717.2, 1456.6, 1366.9, 1248.4, 1156.2, 1012.7, 847.2, 729.9; *m/z* HRMS (ESI^+) found $[M + H]^+$ 304.1907, $[C_{18}H_{26}NO_3]^+$ requires 304.1913.

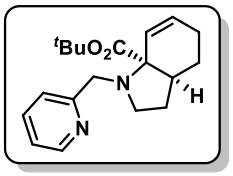
(±)-*tert*-Butyl (1*R*)-2-(furan-2-ylmethyl)-2-azabicyclo[3.3.1]non-6-ene-6- carboxylate 336l



According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(furan-2-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (46 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min methanesulfonic acid was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-20% EtOAc/isohexane, to give a yellow oil (19 mg, 41%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.37 (m, 1H, ArCH), 7.05 (t, 1H, *J* = 3.8 Hz, 7-CH), 6.30-6.29 (m, 1H, ArCH), 6.19-6.18 (m, 1H, ArCH), 3.58 (s, 2H, ArCH_2), 2.99-2.98 (m, 1H, 1-CH), 2.87 (br s, 1H, 5-CH), 2.60-2.56 (m, 1H, 3-CH), 2.43 (dd, 1H, *J* = 20.7, 4.3 Hz, 8-CH), 2.27 (td, 1H, *J* = 12.8, 3.5 Hz, 3-CH), 2.07-2.03 (m, 1H, 8-CH), 1.97 (br d, 1H, *J* = 13.0 Hz, 9-CH), 1.89 (tt, 1H, *J* = 12.6, 4.5 Hz, 4-CH), 1.58 (app dq, 1H, 9-CH), 1.48 (s, 9 H, 3 x CH_3), superimposed on 1.46-1.45 (m, 1H, 4-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.8 (CO), 152.4 (ArC), 142.1 (ArCH), 139.9 (7-CH), 134.4 (6-C), 110.0 (ArCH), 108.3 (ArCH), 79.9 (C), 51.9 (ArCH_2), 49.6 (1-CH), 44.5 (3-CH_2), 31.6 (9-CH_2), 28.6 (4-CH_2), 28.2 (3 x CH_3), 26.7 (5-CH), 24.7 (8-CH_2); υ_{max}/cm^{-1} 2927.7, 1702.3, 1366.6, 1285.2, 1251.4, 1167.6,

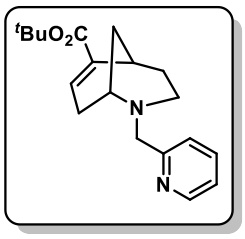
1149.6, 1124.2, 1072.1, 731.6; *m/z* HRMS (ESI^+) found $[M + H]^+$ 304.1906, $[C_{18}H_{26}NO_3]^+$ requires 304.1913.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(pyridine-2-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335m



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.15 g, 0.68 mmol) and 2-pyridinecarboxyladehyde (0.06 mL, 0.68 mmol) were stirred with sodium triacetoxyborohydride (0.43 g, 2.04 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a yellow oil (0.13 g, 62%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49-8.48 (m, 1H, ArCH), 7.63 (td, 1H, *J* = 7.7, 2.0 Hz, ArCH), 7.55 (br d, 1H, *J* = 7.7 Hz, ArCH), 7.12-7.10 (m, 1H, ArCH), 6.01 (dt, 1H, *J* = 10.3, 3.8 Hz, 6-CH), 5.84 (dt, 1H, *J* = 10.3, 2.1 Hz, 7-CH), 4.04 (d, 1H, *J* = 15.3 Hz, ArCHH), 3.87 (d, 1H, *J* = 15.3 Hz, ArCHH), 2.80 (td, 1H, *J* = 8.9, 5.0 Hz, 1-CH), 2.73-2.68 (m, 1H, 1-CH), 2.63-2.57 (m, 1H, 3-CH), 2.13-1.98 (m, 3H, 5-CH_2 and 2-CH), 1.80-1.74 (m, 1H, 4-CH), 1.67-1.60 (m, 1H, 4-CH), 1.52-1.48 (m, 1H, 2-CH), 1.48 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.7 (CO), 161.2 (ArC), 148.6 (ArCH), 136.4 (ArCH), 130.9 (6-CH), 124.6 (7-CH), 122.4 (ArCH), 121.6 (ArCH), 80.9 (C), 69.1 (C), 56.1 ($ArCH_2$), 50.3 (1-CH_2), 40.3 (3-CH), 28.2 (3 x CH_3), 27.7 (2-CH_2), 25.6 (4-CH_2), 22.5 (5-CH_2); υ_{max}/cm^{-1} 2972.8, 2929.0, 1716.7, 1432.2, 1366.8, 1248.6, 1156.0, 1046.7, 846.6, 757.0; *m/z* HRMS (ESI^+) found $[M + H]^+$ 315.2061, $[C_{19}H_{27}N_2O_2]^+$ requires 315.2073.

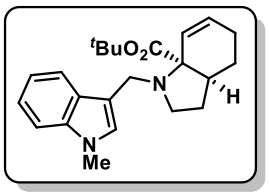
(±)-*tert*-Butyl (1*R*)-2-(pyridine-2-ylmethyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336m



According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(pyridine-2-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (47 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-30% EtOAc/isohexane to give a yellow oil (16 mg, 34%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.52 (br d, 1H, *J* = 5.3 Hz, ArCH), 7.64 (m, 1H, ArCH), 7.48 (br d, 1H, *J* = 7.8 Hz, ArCH), 7.13 (m, 1H, ArCH), 7.08 (t, 1H, *J* = 3.6 Hz, 7-CH), 3.72 (app q, 1H, $ArCH_2$), 3.02-3.01 (m, 1H, 1-CH), 2.89 (br t, 1H, *J* = 2.9 Hz, 5-CH), 2.54-2.50 (m, 2H, 3-CH and 8-CH), 2.36 (td, 1H, *J* = 12.2, 3.5 Hz, 3-CH), 2.08 (br d, 1H, *J* = 20.3 Hz, 8-CH), 2.00 (t, 1H, *J* = 12.2 Hz, 9-CH), 1.87 (tt, 1H, *J* = 12.5, 4.1 Hz, 4-CH), 1.60-1.51 (m, 2H, 4-CH and 9-CH), 1.48 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9 (CO), 159.8 (C), 149.0 (ArCH), 140.2 (7-CH), 136.4 (ArCH), 134.3 (6-C), 122.7 (ArCH), 121.8 (ArCH), 79.9 (C), 61.5 ($ArCH_2$), 50.5 (1-CH), 44.5 (3-CH_2), 31.9 (9-CH_2), 28.9 (4-CH_2), 28.2 (3 x CH_3), 26.7 (5-CH), 25.5 (8-CH_2); υ_{max}/cm^{-1} 2928.6, 1702.0,

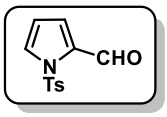
1473.6, 1432.5, 1366.9, 1284.9, 1251.8, 1166.9, 1072.7, 755.7; *m/z* HRMS (ESI^+) found $[M + H]^+$ 315.2060, $[C_{19}H_{27}N_2O_2]^+$ requires 315.2073.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-((1-methyl-1*H*-indol-3-yl)methyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335n



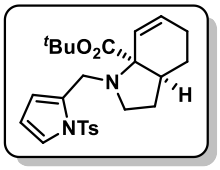
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.15 g, 0.68 mmol) and 1-methylindole-3-carboxyaldehyde (0.11 g, 0.68 mmol) were stirred with sodium triacetoxyborohydride (0.43 g, 2.04 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a colourless oil (0.14 g, 67%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (br d, 1H, *J* = 8.0 Hz, ArCH), 7.27-7.26 (m, 1H, ArCH), 7.21-7.18 (m, 1H, ArCH), 7.09-7.06 (m, 1H, ArCH), 6.97 (br s, 1H, ArCH), 6.08-6.00 (m, 2H, 6-CH and 7-CH), 3.99 (d, 1H, *J* = 13.0 Hz, ArC<u>H</u>H), 3.90 (d, 1H, *J* = 13.0 Hz, ArCH<u>H</u>), 3.74 (s, 3H, CH_3), 2.76 (td, 1H, *J* = 8.6, 5.0 Hz, 1-CH), 2.68-2.64 (m, 1H, 1-CH), 2.63-2.58 (m, 1H, 3-CH), 2.15-2.08 (m, 1H, 5-CH), 2.05-2.01 (m, 1H, 5-CH), 2.01-1.94 (m, 1H, 2-CH), 1.75-1.69 (m, 1H, 4-CH), 1.66-1.59 (m, 1H, 4-CH), 1.52 (s, 9H, 3 x CH_3), 1.50-1.43 (m, 1H, 2-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.8 (CO), 137.1 (ArC), 130.6 (6-CH), 128.0 (ArC), 127.5 (ArCH), 124.8 (7-CH), 121.3 (ArCH), 119.9 (ArCH), 118.6 (ArCH), 113.5 (ArC), 108.9 (ArCH); 80.7 (C), 68.9 (C), 50.2 (1-CH_2), 44.9 ($ArCH_2$), 40.6 (3-CH), 32.6 (CH_3), 28.3 (3 x CH_3), 27.3 (2-CH_2), 25.6 (4-CH_2), 22.5 (5-CH_2); υ_{max}/cm^{-1} 2971.7, 2929.0, 1714.9, 1473.2, 1366.6, 1327.3, 1246.8, 1155.8, 1047.7, 739.4; *m/z* HRMS (ESI^+) found $[M + H]^+$ 367.2374, $[C_{23}H_{31}N_2O_2]^+$ requires 367.2386.

1-Tosyl-1*H*-pyrrole-2-carbaldehyde S27



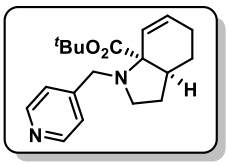
Pyrrole-2-carboxaldehyde (0.30 g, 3.15 mmol) in THF (5 mL) was added dropwise over 3 min to a stirred solution of NaH (60% in mineral oil, 0.16 g, 4.41 mmol) in THF (10 mL). Upon this addition effervescence was observed and the reaction mixture turned orange. After 40 min *p*-toluenesulfonyl chloride (0.84 g, 4.41 mmol) was added dropwise over 2 min and the reaction was stirred for 5.5 h. At which point the reaction mixture was concentrated *in vacuo* and partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was separated and further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to give a pale-yellow solid (0.67 g, 85%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H, CHO), 7.80 (d, 2H, *J* = 8.4 Hz, ArCH), 7.62 (dd, 1H, *J* = 3.2, 1.8 Hz, ArCH), 7.32 (d, 2H, *J* = 8.4 Hz, ArCH), 7.16 (dd, 1H, *J* = 3.9, 1.8 Hz, ArCH), 6.40 (t, 1H, *J* = 3.2 Hz, ArCH), 2.42 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 179.0 (CO), 145.9 (ArC), 135.2 (ArC), 133.5 (ArC), 130.1 (ArCH), 129.4 (ArCH), 127.5 (ArCH), 124.5 (ArCH), 112.4 (ArCH), 21.7 (CH_3); m.p. 95-96 ˚C (EtOAc/petrol), lit. 91-93 ˚C.[309] ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[310]

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-((1-tosyl-1*H*-pyrrol-2-yl)methyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335o



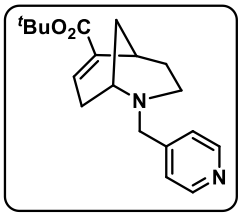
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.12 g, 0.52 mmol) and 1-tosyl-1*H*-pyrrole-2-carbaldehyde (0.13 g, 0.52 mmol) were stirred with sodium triacetoxyborohydride (0.33 g, 1.56 mmol) in CH_2Cl_2 (2 mL). The crude material was purified by SiO_2 flash chromatography, 0-4% EtOAc/petrol, to give the product as a colourless oil (0.13 g, 54%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 2H, *J* = 8.6 Hz, ArCH), 7.26-7.23 (m, 3H, ArCH), 6.21-6.18 (m, 2H, ArCH), 5.90 (dt, 1H, *J* = 10.2, 3.8 Hz, 6-CH), 5.75 (dt, 1H, *J* = 10.2, 21. Hz, 7-CH), 3.94 (d, 2H, *J* = 2.74 Hz, NCH_2), 2.65-2.59 (m, 1H, 1-CH), 2.55-2.49 (m, 2H, 1-CH and 3-CH), 2.39 (s, 3H, CH_3), 1.99-1.96 (m, 2H, 5-CH_2), 1.93-1.86 (m, 1H, 2-CH), 1.69-1.61 (m, 1H, 4-CH), 1.54-1.48 (m, 1H, 4-CH), 1.46 (s, 9H, 3 x CH_3), 1.42-1.35 (m, 1H, 2-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.3 (CO), 144.4 (ArC), 136.7 (ArC), 134.2 (ArC), 130.1 (6-CH), 129.6 (ArCH), 127.0 (ArCH), 124.9 (7-CH), 122.6 (ArCH), 113.8 (ArCH), 111.3 (ArCH), 81.0 (C(CH_3)), 68.8 (C), 50.4 (1-CH_2), 46.5 (NCH_2), 40.3 (3-CH), 28.2 (3 x CH_3), 27.6 (2-CH_2), 25.8 (4-CH_2), 22.7 (5-CH_2), 21.6 (CH_3); υ_{max}/cm^{-1} 1716.5, 1367.6, 1247.8, 1175.1, 1153.1, 1189.6, 1117.1, 1046.8, 1091.2, 671.3; *m/z* HRMS (ESI$^+$) found [M + H]$^+$ 457.2151, $[C_{25}H_{33}N_2O_4S]^+$ requires 457.2161.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(pyridine-4-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335p



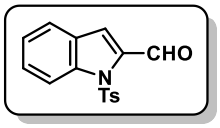
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.12 g, 0.52 mmol) and 4-pyridinecarboxaldehyde (0.05 mL, 0.52 mmol) were stirred with sodium triacetoxyborohydride (0.33 g, 1.56 mmol) in CH_2Cl_2 (2 mL). The crude product was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, to give the product as a yellow oil (89 mg, 56%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.51 (d, 2H, *J* = 5.8 Hz, ArCH), 7.31 (d, 2H, *J* = 5.8 Hz, ArCH), 6.03 (dt, 1H, *J* = 10.4, 3.8 Hz, 6-CH), 5.79 (dt, 1H, *J* = 10.4, 1.8 Hz, 7-CH), 3.80 (d, 1H, *J* = 15.2 Hz, NC<u>H</u>H), 3.70 (d, 1H, *J* = 15.2 Hz, NCH<u>H</u>), 2.73-2.67 (m, 1H, 1-CH), 2.64-2.57 (m, 2H, 1-CH and 3-CH), 2.11-1.99 (m, 3H, 2-CH and 5-CH_2), 1.80-1.72 (m, 1H, 4-CH), 1.67-1.61 (m, 1H, 4-CH), 1.58-1.51 (m, 1H, 2-CH), 1.48 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.6 (CO), 150.3 (ArC), 149.5 (ArCH), 131.3 (6-CH), 124.3 (7-CH), 123.3 (ArCH), 81.0 (C(CH_3)), 69.0 (C), 53.0 (NCH_2), 50.0 (1-CH_2), 40.2 (3-CH), 28.2 (3 x CH_3), 27.5 (5-CH_2), 25.5 (4-CH_2), 22.6 (2-CH_2); υ_{max}/cm^{-1} 2972.8, 2929.1, 1717.8, 1601.6, 1413.6, 1367.1, 1250.1, 1155.8, 1047.6, 846.3; *m/z* HRMS (ESI$^+$) found [M + H]$^+$ 315.2065, $[C_{19}H_{27}N_2O_2]^+$ requires 315.2073.

(±)-*tert*-Butyl (1*R*)-2-(pyridine-4-ylmethyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336p



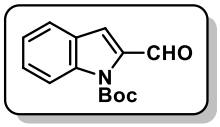
According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(pyridine-4-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (47 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-100% EtOAc/petrol, to give a yellow oil (23 mg, 49%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.53-8.51 (m, 2H, ArCH), 7.29-7.28 (m, 2H, ArCH), 7.07 (t, 1H, *J* = 3.3 Hz, 7-CH), 3.56 (app q, 2H, $ArCH_2$), 2.99 (br s, 1H, 1-CH), 2.89 (br t, 1H, *J* = 3.5 Hz, 5-CH), 2.48-2.40 (m, 2H, 3-CH and 8-CH), 2.30 (td, 1H, *J* = 12.8, 3.3 Hz, 3-CH), 2.12-2.05 (m, 1H, 8-CH), 1.98 (dt, 1H, *J* = 12.1, 3.3 Hz, 9-CH), 1.80-1.89 (m, 1H, 4-CH), 1.63-1.54 (m, 2H, 4-CH and 9-CH), 1.48 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.8 (CO), 149.8 (ArCH), 139.7 (7-CH), 134.4 (6-CH), 132.0 (ArC), 123.6 (ArCH), 80.0 (C), 58.5 ($ArCH_2$), 50.5 (1-CH), 44.3 (3-CH_2), 31.8 (9-CH_2), 28.2 (CH_3), 27.9 (4-CH_2), 26.6 (5-CH), 25.3 (8-CH_2); υ_{max}/cm^{-1} 2930.2, 1701.9, 1601.4, 1419.5, 1367.1, 1252.6, 1164.7, 1071.4, 1033.0, 800.5; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 315.2053, $[C_{19}H_{27}N_2O_2]^+$ requires 315.2073.

1-Tosyl-1*H*-indole-2-carbaldehyde S28



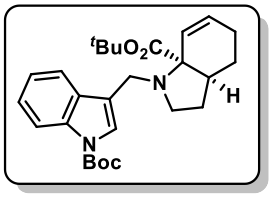
Indole-2-carboxaldehyde (0.46 g, 3.15 mmol) in THF (5 mL) was added dropwise over 3 min to a stirred solution of NaH (60% in mineral oil, 0.16 g, 4.41 mmol) in THF (10 mL). Upon this addition effervescence was observed and the reaction mixture turned orange. After 40 min *p*-toluenesulfonyl chloride (0.84 g, 4.41 mmol) was added dropwise over 2 min and the reaction was stirred for 5 h. At which point the reaction mixture was concentrated *in vacuo* and partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was separated and further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-10% EtOAc/petrol, to give a colourless solid (72 mg, 8%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H, CHO), 8.24 (br d, 1H, *J* = 8.6 Hz, ArCH), 7.66 (d, 2H, *J* = 8.6 Hz, ArCH), 7.62 (dt, 1H, *J* = 7.9, 1.0 Hz, ArCH), 7.55-7.50 (m, 1H, ArCH), 7.47 (d, 1H, *J* = 1.0 Hz, ArCH), 2.33 (s, 3H, CH_3); υ_{max}/cm^{-1} 1675.2, 1529.9, 1371.3, 1195.3, 1188.7, 1174.9, 1152.7, 1090.0, 751.05, 671.0; m.p. 133-134 ˚C (EtOAc/petrol), lit. 138-139 ˚C.[309] ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[311]

***tert*-Butyl 2-formyl-1*H*-indole-1-carboxylate S29**



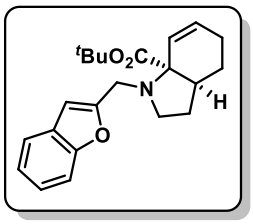
Di-*tert*-butyl-di-carbonate (0.27 g, 1.24 mmol) was added in one portion to a stirred solution of indole-2-carboxaldehyde (0.15g, 1.03 mmol), Et_3N (0.17 mL, 1.24 mmol), 4-(dimethylamino)pyridine (12 mg, 0.10 mmol) in THF (10 mL). The reaction mixture was stirred for 16 h, concentrated *in vacuo* and partitioned between EtOAc (5 mL) and H_2O (10 mL). The organic layer was separated and further extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-10% EtOAc/petrol, to give a yellow oil (0.25 g, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H, CHO), 8.17 (d, 1H, *J* = 8.6 Hz, ArCH), 7.68 (d, 1H, *J* = 7.7 Hz, ArCH), 7.51-7.47 (m, 1H, ArCH), 7.44 (s, 1H, ArCH), 7.30 (t, 1H, *J* = 7.7 Hz, ArCH), 1.72 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 184.2 (CO), 149.9 (ArC), 137.9 (ArC), 128.2 (ArCH), 127.5 (ArC), 123.8 (ArCH), 123.2 (ArCH), 116.4 (ArCH), 116.1 (ArCH), 85.6 (C), 28.2 (CH_3); m.p. 71-72 ˚C (EtOAc/petrol), lit. 74-75 ˚C.[312] ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[313]

(±)-*tert*-Butyl 3-(((3a*S*,7a*R*)-7a-(*tert*-butoxycarbonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indol-1-yl)methyl)-1*H*-indole-1-carboxylate 335q



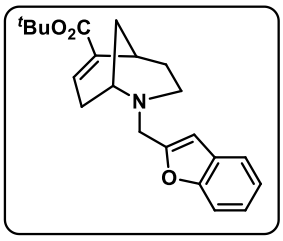
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.12 g, 0.52 mmol) and *tert*-butyl 2-formyl-1*H*-indole-1-carboxylate (0.13 g, 0.52 mmol) were stirred with sodium triacetoxyborohydride (0.33 g, 1.56 mmol) in CH_2Cl_2 (2 mL). The crude material was purified by SiO_2 flash chromatography, 0-4% EtOAc/petrol to give the product as a yellow oil (0.13 g, 54%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.03 (d, 1H, *J* = 7.4 Hz, ArCH), 7.43 (d, 1H, *J* = 7.4 Hz, ArCH), 7.20-7.13 (m, 2H, ArCH), 6.64 (br s, 1H, ArCH), 5.95 (dt, 1H, *J* = 10.2, 3.7 Hz, 6-CH), 5.81 (br d, 1H, *J* = 10.2 Hz, 7-CH), 4.19 (app q, 2H, NCH_2), 2.98-2.83 (m, 2H, 1-CH_2), 2.59-2.53 (m, 1H, 3-CH), 2.13-1.99 (m, 3H, 2-CH and 5-CH_2), 1.77-1.71 (m, 2H, 4-CH_2), 1.65 (s, 9H, 3 x CH_3), 1.61-1.57 (m, 1H, 2-CH), 1.43 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.9 (CO), 141.5 (ArC), 136.8 (ArC), 130.4 (6-CH), 129.5 (ArC), 125.0 (7-CH), 123.0 (ArCH), 122.4 (ArCH), 119.9 (ArCH), 115.2 (ArCH), 107.6 (ArCH), 83.6 (C), 80.8 (C), 69.2 (C), 50.9 (1-CH_2), 49.8 (NCH_2), 40.4 (3-CH), 28.3 (3 x CH_3), 28.1 (3 x CH_3), 27.8 (2-CH_2), 25.8 (4-CH_2), 22.8 (5-CH_2); υ_{max}/cm^{-1} 1730.6, 1454.3, 1368.3, 1326.3, 1305.9, 1250.6, 1116.9, 1159.5, 1082.6, 744.7; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 453.2741, $[C_{27}H_{37}N_2O_2]^+$ requires 453.2753.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(benzofuran-2-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335r



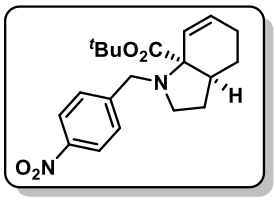
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.12 g, 0.52 mmol) and 2-benzofurancarboxaldehyde (0.06 mL, 0.52 mmol) were stirred with sodium triacetoxyborohydride (0.33 g, 1.56 mmol) in CH_2Cl_2 (2 mL). The crude product was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, to give the product as a yellow oil (0.12 g, 67%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48-7.42 (m, 2H, ArCH), 7.21-7.13 (m, 3H, ArCH), 6.54 (br s, 1H, ArCH), 6.03 (dt, 1H, *J* = 10.2, 3.7 Hz, 6-CH), 5.78 (dt, 1H, *J* = 10.2, 2.1 Hz, CH), 4.10 (d, 1H, *J* = 15.0 Hz, NCHH), 3.78 (d, 1H, *J* = 15.0 Hz, NCHH), 2.93 (td, 1H, *J* = 8.7, 4.5 Hz, 1-CH), 2.73 (td, 1H, *J* = 8.7, 9.1 Hz, 1-CH), 2.67-2.60 (m, 1H, 3-CH), 2.12-1.97 (m, 3H, 2-CH and 5-CH_2), 1.80-1.73 (m, 1H, 4-CH), 1.65-1.60 (m, 1H, 4-CH), 1.58-1.53 (m, 1H, 2-CH), 1.47 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.3 (CO), 157.1 (ArC), 155.0 (ArC), 131.5 (6-CH), 128.6 (ArC), 123.9 (7-CH), 123.4 (ArCH), 122.4 (ArCH), 120.5 (ArCH), 111.2 (ArCH), 103.9 (ArCH), 81.1 (C(CH_3)), 68.7 (C), 50.8 (1-CH_2), 47.4 (NCH_2), 40.2 (3-CH), 28.2 (3 x CH_3), 27.1 (2-CH_2), 25.2 (4-CH_2), 22.1 (5-CH_2); υ_{max}/cm^{-1} 2928.7, 1717.6, 1454.5, 1367.4, 1253.9, 1155.8, 1049.5, 1032.9, 751.3, 742.1; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 354.2061, $[C_{22}H_{28}NO_3]^+$ requires 354.2069.

(±)-*tert*-Butyl (1*R*)-2-(benzofuran-2-ylmethyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336r



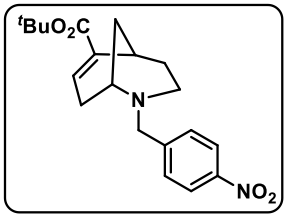
According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(benzofuran-2-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (53 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 0-30% EtOAc/petrol, to give a yellow oil (10 mg, 19%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52-7.46 (m, 2H, ArCH), 7.24-7.17 (m, 2H, ArCH), 7.07 (t, 1H, *J* = 3.5 Hz, 7-CH), 6.59 (s, 1H, ArCH), 3.74 (s, 2H, $ArCH_2$), 3.08 (br s, 1H, 1-CH), 2.90 (br t, 1H, *J* = 3.0 Hz, 5-CH), 2.69-2.63 (m, 1H, 3-CH), 2.48 (dd, 1H, *J* = 20.7, 4.0 Hz, 8-CH), 2.36 (td, 1H, *J* = 12.0, 3.5 Hz, 3-CH), 2.12-2.04 (m, 1H, 8-CH), 2.01 (td, 1H, *J* = 12.3, 3.0 Hz, 9-CH), 1.93 (tt, 1H, *J* = 12.6, 4.1 Hz, 4-CH), 1.62-1.57 (m, 2H, 4-CH and 9-CH), 1.48 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.8 (CO), 155.5 (ArC), 155.1 (ArC), 139.8 (7-CH), 134.4 (6-CH), 128.4 (ArC), 123.8 (ArCH), 122.6 (ArCH), 120.6 (ArCH), 111.3 (ArCH), 105.1 (ArCH), 80.0 (C), 52.5 ($ArCH_2$), 49.8 (1-CH), 44.7 (3-CH), 31.6 (9-CH_2), 28.6 (4-CH_2), 28.2 (CH_3), 26.7 (5-CH), 24.8 (8-CH_2); υ_{max}/cm^{-1} 2928.5, 1701.4, 1454.3, 1366.8, 1284.2, 1252.7, 1165.8, 1072.6, 1025.3, 750.9; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 354.2058, $[C_{22}H_{28}NO_3]^+$ requires 354.2069.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(4-nitrobenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335t



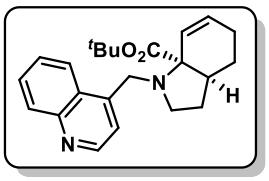
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.12 g, 0.52 mmol) and 4-nitrobenzaldehyde (79 mg, 0.52 mmol) were stirred with sodium triacetoxyborohydride (0.33 g, 1.56 mmol) in CH_2Cl_2 (2 mL). The crude material was purified by SiO_2 flash chromatography, 0-2.5% EtOAc/petrol, to give a yellow oil (0.13 g, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 2H, *J* = 8.6 Hz, $ArCH_2$), 7.53 (d, 2H, *J* = 8.6 Hz, ArCH), 6.05 (dt, 1H, *J* = 10.1, 4.0 Hz, 6-CH), 5.79 (br dt, 1H, *J* = 10.1, 1.8 Hz, 7-CH), 4.00 (d, 1H, *J* = 14.3 Hz, NCH<u>H</u>), 3.77 (d, 1H, *J* = 14.3 Hz, NC<u>H</u>H), 2.72-2.66 (m, 1H, 1-CH), 2.61-2.55 (m, 2H, 1-CH and 3-CH), 2.12-1.98 (m, 3H, 2-CH and 5-CH_2), 1.81-1.73 (m, 1H, 4-CH), 1.67-1.60 (m, 1H, 2-CH), 1.55-1.53 (m, 1H, 4-CH), 1.49 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.6 (CO), 148.9 (ArC), 146.9 (ArC), 131.5 (6-CH), 128.8 (ArCH), 124.1 (7-CH), 123.4 (ArCH), 81.1 ($C(CH_3)$), 69.0 (C), 53.5 (NCH_2), 49.9 (1-CH_2), 40.2 (3-CH), 28.2 (CH_3), 27.4 (2-CH_2), 25.4 (4-CH_2), 22.5 (5-CH_2); υ_{max}/cm^{-1} 2929.9, 1717.7, 1519.7, 1367.2, 1344.0, 1250.1, 1155.0, 1108.9, 1047.6, 847.3; *m/z* HRMS (ESI^+) found $[M + H]^+$ 359.1960, $[C_{20}H_{27}N_2O_4]^+$ requires 359.1971.

(±)-*tert*-Butyl (1*R*)-2-(4-nitrobenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336t



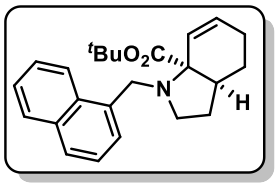
According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(4-nitrobenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (54 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux for 26 h. The crude material was purified by SiO_2 flash chromatography, eluting with 0-25% EtOAc/petrol, to give a yellow oil (23 mg, 43%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 2H, *J* = 8.7 Hz, ArCH), 7.53 (d, 2H, *J* = 8.7 Hz, ArCH), 7.07 (t, 1H, *J* = 3.7 Hz, 7-CH), 3.72-3.58 (m, 2H, $ArCH_2$), 3.00 (br s, 1H, 1-CH), 2.90 (br s, 1H. 5-CH), 2.48-2.42 (m, 2H, 3-CH and 8-CH), 2.31 (br t, 1H, *J* = 12.3 Hz, 3-CH), 2.14-2.06 (m, 1H , 8-CH), 1.98 (d, 1H, *J* = 11.6 Hz, 9-CH), 1.84 (br t, 1H, *J* = 12.5 Hz, 4-CH), 1.61 (dq, 1H, *J* = 12.2, 2.6 Hz, 9-CH), 1.48 (s, 9H, CH_3) superimposed on (m, 1H, 4-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.7 (CO), 147.6 (6-C), 147.1 (7-CH), 139.7 (ArC), 134.4 (ArC), 129.1 (ArCH), 123.5 (ArCH), 80.1 (C), 59.0 ($ArCH_2$), 50.6 (1-CH), 44.3 (3-CH_2), 31.8 (9-CH_2), 28.8 (4-CH_2), 28.2 (3 x CH_3), 26.6 (5-CH), 25.4 (8-CH_2); υ_{max}/cm^{-1} 1699.4, 1518.5, 1343.1, 1366.5, 1284.3, 1251.8, 1155.7, 1084.9, 1073.1, 852.8; *m/z* HRMS (ESI^+) found $[M + H]^+$ 359.1958, $[C_{20}H_{27}N_2O_4]^+$ requires 224.1651.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(quinoline-4-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335u



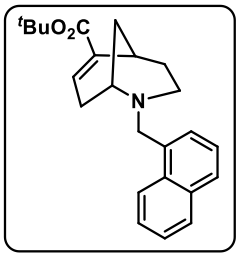
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.12 g, 0.52 mmol) and 4-quinolinecarboxaldehyde (82 mg, 0.52 mmol) were stirred with sodium triacetoxyborohydride (0.33 g, 1.56 mmol) in CH_2Cl_2 (2 mL). The crude material was purified by SiO_2 flash chromatography, 0-15% EtOAc/petrol, to give a yellow oil (0.13 g, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.84 (d, 1H, *J* = 4.4 Hz, ArCH) 8.29 (d, 1H, *J* = 8.5 Hz, ArCH), 8.10 (d, 1H, *J* = 8.5 Hz, ArCH), 7.69 (t, 1H, *J* = 7.4 Hz, ArCH), 7.54-7.49 (m, 2H, ArCH), 6.11 (dt, 1H, *J* = 10.3, 3.7 Hz, 6-CH), 5.98 (br dt, 1H, *J* = 10.3, 2.1 Hz, 7-CH), 4.29 (app q, 2H, NCH_2), 2.73-2.58 (m, 3H, 1-CH_2 and 3-CH), 2.14-2.01 (m, 3H, 2-CH and 5-CH_2), 1.77-1.60 (m, 3H, 2-CH and 4-CH_2), 1.51 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.5 (CO), 150.3 (ArCH), 148.1 (ArC), 146.1 (ArC), 131.8 (6-CH), 129.8 (ArCH), 128.9 (ArCH), 127.5 (ArC), 126.0 (ArCH), 124.2 (7-CH), 124.1 (ArCH), 120.6 (ArCH), 81.1 (C(CH_3)), 69.2 (C), 50.8 (NCH_2), 50.0 (1-CH_2), 40.2 (3-CH), 28.3 (CH_3), 27.7 (2-CH_2), 25.9 (4-CH_2), 23.1 (5-CH_2); υ_{max}/cm^{-1} 2929.4, 2971.9, 1716.7, 1366.7, 1248.0, 1154.4, 1117.8, 1048.8, 845.8, 756.6; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 365.2223, $[C_{23}H_{29}N_2O_2]^+$ requires 365.2229.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1-(naphthalen-1-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335v



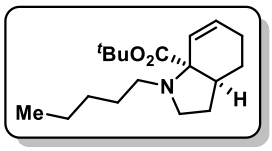
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.25 g, 1.13 mmol) and 1-naphthaldehyde (0.15 mL, 1.13 mmol) were stirred with sodium triacetoxyborohydride (0.72 g, 3.39 mmol) in CH_2Cl_2 (5 mL). The crude product was purified by SiO_2 flash chromatography, 0-5% EtOAc/petrol, which was contaminated with 1-naphthaldehyde. The crude material was left open to air for 3 weeks, dissolved in MeOH (10 mL) and $NaHSO_3$ (saturated aqueous solution, 10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo* to give the pure product as a yellow oil (0.12 g, 29%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38-8.36 (m, 1H, ArCH), 7.82-7.80 (m, 1H, ArCH), 7.72 (d, 1H, *J* = 8.2 Hz, ArCH), 7.47-7.43 (m, 3H, ArCH), 7.36 (t, 1H, *J* = 8.2 Hz, ArCH), 6.08 (br s, 2H, 6-CH and 7-CH), 4.22 (app q, 2H, NCH_2), 2.65-2.54 (m, 3H, 1-CH_2 and 3-CH), 2.12-1.95 (m, 3H, 2-CH and 5-CH_2), 1.69-1.58 (m, 2H, 4-CH_2), 1.52 (s, 9H, 3 x CH_3), 1.45-1.37 (m, 1H, 2-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ; 173.6 (CO), 136.7 (ArC), 135.9 (ArC), 133.7 (ArCH), 132.4 (ArC), 131.3 (6-CH), 128.3 (ArCH), 127.3 (ArCH), 126.4 (ArCH), 125.4 (ArCH), 125.2 (ArCH), 124.8 (7-CH), 124.6 (ArCH), 81.0 (C(CH_3)), 69.2 (C), 52.0 (NCH_2), 49.7 (1-CH_2), 40.4 (3-CH), 28.3 (3 x CH_3), 27.6 (2-CH_2), 26.1 (4-CH_2), 23.2 (5-CH_2); υ_{max}/cm^{-1} 1716.4, 1692.9, 1367.0, 1249.0, 1154.6, 1118.2, 1048.9, 801.0, 792.2, 778.7; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 364.2269, $[C_{24}H_{30}NO_2]^+$ requires 364.227.

(±)-*tert*-Butyl (1*R*)-2-(naphthalen-1-ylmethyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336v



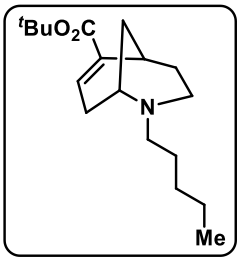
According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(naphthalen-1-ylmethyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (55 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 0-10% EtOAc/petrol, to give a yellow oil (30 mg, 55%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (d, 1H, *J* = 7.9 Hz, ArCH), 7.84 (d, 1H, *J* = 6.8 Hz, ArCH), 7.76 (d, 1H, *J* = 7.4 Hz, ArCH), 7.51-7.47 (m, 2H, ArCH), 7.42-7.37 (m, 2H, ArCH), 7.11 (t, 1H, *J* = 3.5 Hz, 7-CH), 3.98 (d, 2H, *J* = 6.0 Hz, $ArCH_2$), 3.05 (br s, 1H, 1-CH), 2.88 (br s, 1H, 5-CH), 2.60 (br dd, 2H, *J* = 21.0, 3.9 Hz, 3-CH and 8-CH), 2.36 (br t, 1H, *J* = 12.5 Hz, 3-CH), 2.10 (br s, 1H, 8-CH), 1.92 (d, 1H, *J* = 12.9 Hz, 9-CH), 1.86-1.76 (m, 2H, 4-CH_2), 1.57-15.4 (m, 1H, 9-CH), 1.49 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.3 (CO), 140.2 (7-CH), 133.9 (6-C), 133.6 (ArC), 133.4 (ArC), 132.7 (ArC), 128.3 (ArCH), 127.7 (ArCH), 126.8 (ArCH), 126.8 (ArCH), 125.6 (ArCH), 125.5 (ArCH), 125.1 (ArCH), 79.9 (C), 57.9 ($ArCH_2$), 49.8 (1-CH), 44.4 (3-CH_2), 30.9 (9-CH_2), 28.2 (CH_3), 28.0 (4-CH_2), 26.9 (5-CH), 25.0 (8-CH_2); υ_{max}/cm^{-1} 2929.7, 1723.4, 1701.8, 1366.6, 1284.9, 1252.0, 1163.9, 1073.5, 791.7, 779.7; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 364.2263, $[C_{24}H_{29}NO_2]^+$ requires 364.2277.

(±)-*tert*-Butyl (3a*R*,7a*R*)-1-pentyl-)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335w



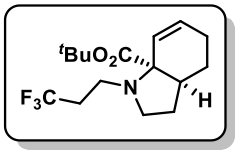
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.15 g, 0.68 mmol) and valeraldehyde (0.07 mL, 0.68 mmol) were stirred with sodium triacetoxyborohydride (0.43 g, 2.04 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, to give the product as a yellow oil (0.11 g, 55%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.95 (dt, 1H, *J* = 10.3, 3.8 Hz, 6-CH), 5.78 (br d, 1H, *J* = 10.3 Hz, 7-CH), 2.89 (td, 1H, *J* = 8.9, 4.8 Hz, 1-CH), 2.69-2.59 (m, 2H, 1-CH and NC<u>H</u>H), 2.57-2.50 (m, 1H, 3-CH), 2.48-2.41 (m, 1H, NCH<u>H</u>), 2.08-2.01 (m, 2H, 2-CH and 5-CH), 1.99-1.91 (m, 1H, 2-CH), 1.75-1.67 (m, 1H, 4-CH), 1.61-1.53 (m, 4H, 4-CH, 5-CH and CH_2), 1.46 (s, 9H, 3 x CH_3), 1.34-1.25 (m, 4H, CH_2 and CH_2), 0.88 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.8 (CO), 130.0 (6-CH), 124.8 (7-CH), 80.6 (C(CH_3)), 69.0 (C), 50.4 (1-CH_2), 50.3 (NCH_2), 40.5 (3-CH), 29.8 (CH_2), 29.1 (CH_2), 28.2 (3 x CH_3), 27.3 (5-CH_2), 25.2 (4-CH_2), 22.6 (CH_2), 22.1 (2-CH_2), 14.1 (CH_3); υ_{max}/cm^{-1} 2957.3, 2930.3, 2859.8, 1718.3, 1456.2, 1392.2, 1367.3, 1250.1, 1156.8, 1048.3; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 294.2428, $[C_{18}H_{32}NO_2]^+$ requires 294.2433.

(±)-*tert*-Butyl (1*R*)-2-pentyl-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336w



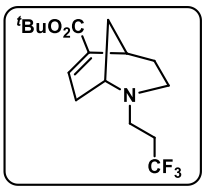
According to general procedure A, (±)-*tert*-butyl (3a*R*,7a*R*)-1-pentyl-)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (44 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-40% EtOAc/petrol, to give a yellow oil (33 mg, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.04 (t, 1H, *J* = 3.5 Hz, 7-CH), 3.07 (br s, 1H, 1-CH), 2.87 (t, 1H, *J* = 2.9 Hz, 5-CH), 2.59 (dd, 1H, *J* = 11.8, 4.9 Hz, 3-CH), 2.42-2.33 (m, 3H, 8-CH and NCH_2), 2.17 (td, 1H, *J* = 12.3, 3.4 Hz, 3-CH), 2.05-1.98 (m, 1H, 8-CH), 1.92 (br d, 1H, *J* = 12.5 Hz, 4-CH), 1.85 (tt, 1H, *J* = 12.6, 4.5 Hz, 9-CH), 1.63-1.57 (m, 1H, 9-CH), 1.48 (s, 9H, 3 x CH_3) superimposed on 1.47-1.44 (m, 3H, 4-CH and CH_2), 1.35-1.25 (m, 4H, CH_2 and CH_2), 0.89 (t, 3H, *J* = 7.8 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9 (CO), 140.2 (7-CH), 134.3 (6-C), 79.9 (C), 55.3 (NCH_2), 49.8 (1-CH), 44.6 (3-CH_2), 31.9 (9-CH_2), 29.9 (CH_2), 28.9 (4-CH_2), 28.2 (3 x CH_3), 27.3 (CH_2), 26.9 (5-CH), 24.5 (8-CH_2), 22.7 (CH_2), 14.1 (CH_3); υ_{max}/cm^{-1} 2931.1, 2860.0, 1703.9, 1645.7, 1367.1, 1334.9, 1284.5, 1251.4, 1169.9, 1080.2; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 294.2435, $[C_{18}H_{32}NO_4]^+$ requires 294.2433.

(±)-*tert*-Butyl (3a*R*,7a*R*)-1-(3,3,3-trifluoropropyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335x



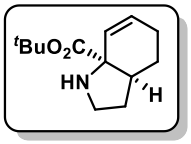
According to general procedure B, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.15 g, 0.68 mmol) and 3,3,3-trifluoropropanal (0.06 mL, 0.68 mmol) were stirred with sodium triacetoxyborohydride (0.43 g, 2.04 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-3% EtOAc/petrol, to give the product as a yellow oil (0.17 g, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.99 (dt, 1H, *J* = 10.7, 4.1 Hz, 6-CH), 5.72 (dt, 1H, *J* = 10.1, 2.0 Hz, 7-CH), 3.03-2.96 (m, 1H, NC<u>H</u>HCH_2), 2.91 (td, 1H, *J* = 8.6, 4.6 Hz, 1-CH), 2.78-2.66 (m, 2H, 1-CH and NCH<u>H</u>), 2.57-2.50 (m, 1H, 3-CH), 2.31-2.24 (m, 2H, CH_2CF_3), 2.09-1.98 (m, 3H, 2-CH and 5-CH_2), 1.77-1.69 (m, 1H, 4-CH), 1.62-1.52 (m, 2H, 2-CH and 4-CH), 1.46 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 73.3 (CO), 131.2 (6-CH), 126.5 (q, *J* = 278.1 Hz, CF_3), 123.8 (7-CH), 81.1 ($C(CH_3)$), 69.0 (C), 50.1 (1-CH_2), 43.0 (N<u>C</u>H_2CH_2), 34.2 (q, *J* = 27.2 Hz, <u>C</u>H_2CF_3), 28.1 (CH_3), 27.1 (2-CH_2), 25.0 (4-CH_2), 22.2 (5-CH_2); ^{19}F-NMR (377 MHz, $CDCl_3$) δ -65.43; υ_{max}/cm^{-1} 1718.1, 1393.2, 1368.4, 1342.2, 1250.2, 1155.5, 1128.1, 1046.6, 1007.2, 847.2; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 320.1820, $[C_{16}H_{25}F_3NO_2]^+$ requires 320.1837.

(±)-*tert*-Butyl (1*R*)-2-(3,3,3-trifluoropropyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336x



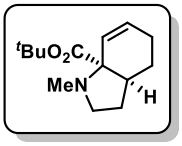
According to general procedure D, (±)-*tert*-butyl (3a*R*,7a*R*)-1-(3,3,3-trifluoropropyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (48 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 5-50% EtOAc/petrol, to give a yellow oil (34 mg, 71%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.05 (t, 1H, *J* = 3.5 Hz, 7-CH), 3.02 (br s, 1H, 1-CH), 2.87 (br s, 1H, 5-CH), 2.69-2.53 (m, 3H, NCH_2 and 3-CH), 2.38-2.21 (m, 4H, 3-CH, 8-CH and CH_2CF_3), 2.13-2.05 (m, 1H, 8-CH), 1.90 (br d, 1H, *J* = 12.2 Hz, 9-CH), 1.82 (tt, 1H, *J* = 12.9, 4.3 Hz, 4-CH), 1.64-1.60 (m, 2H, 4-CH and 9-CH), 1.48 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.7 (CO), 139.7 (7-CH), 134.3 (6-C), 126.7 (q, *J* = 280.5 Hz, CF_3), 80.0 (C), 50.9 (1-CH), 48.0 (NCH_2), 44.2 (3-CH_2), 32.9 (q, *J* = 27.3 Hz, $\underline{C}H_2CF_3$), 31.8 (9-CH_2), 28.8 (4-CH_2), 28.2 (CH_3), 26.6 (5-CH), 25.2 (8-CH_2); υ_{max}/cm^{-1} 1703.1, 1367.7, 1336.3, 1285.7, 1251.6, 1222.5, 1145.1, 1122.4, 1080.9, 996.0; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 320.1831, $[C_{16}H_{25}F_3NO_2]^+$ requires 320.1837.

(±)-*tert*-Butyl (3a*S*,7a*R*)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate S30



Sodium triacetoxyborohydride (0.29 g, 1.35 mmol) was added to a stirred solution of (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.20 g, 0.90 mmol) in CH_2Cl_2 (4 mL). After 16 h, the reaction mixture was quenched with $NaHCO_3$ (saturated aqueous solution) and stirred for 10 min. The organic layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 0-5% MeOH/CH_2Cl_2 to give the product as a yellow oil (0.17 g, 85%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.90 (dt, 1H, *J* = 10.0, 3.9 Hz, 6-CH), 5.53 (dt, 1H, *J* = 10.0, 2.0 Hz, 7-CH), 2.99-2.95 (m, 2H, 1-CH_2), 2.49-2.42 (m, 1H, 3-CH), 2.06-1.99 (m, 2H, 5-CH_2), 1.93-1.82 (m, 2H, 2-CH and 4-CH), 1.66-1.53 (m, 2H, 2-CH and 4-CH), 1.45 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.0 (CO), 129.7 (6-CH), 128.3 (7-CH), 81.1 (C(CH_3)), 67.1 (C), 44.4 (1-CH_2), 40.0 (3-CH), 30.2 (2-CH_2), 27.9 (CH_3), 24.4 (4-CH_2), 21.7 (5-CH_2); υ_{max}/cm^{-1} 2974.6, 2928.8, 1717.22, 1454.9, 1367.5, 1254.2, 1158.7, 1123.1, 1052.1, 847.5; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 224.1644, $[C_{13}H_{22}NO_2]^+$ requires 224.1651.

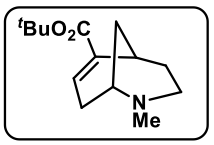
(±)-*tert*-Butyl (3a*R*,7a*R*)-1-methyl-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335y



According to general procedure B, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.13 g, 0.59 mmol) and paraformaldehyde (53 mg, 1.77 mmol) were stirred with sodium triacetoxyborohydride (0.38 g, 1.77 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 10-40%

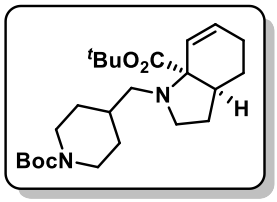
EtOAc/petrol, to give the product as a yellow oil (49 mg, 35%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.01 (dt, 1H, *J* = 10.2, 4.0 Hz, 6-CH), 5.82 (dt, 1H, *J* = 10.2, 1.9 Hz, 7-CH), 2.90-2.84 (m, 1H, 1-CH), 2.77-2.71 (m, 1H, 1-CH), 2.61-2.54 (m, 1H, 3-CH), 2.41 (s, 3H, NCH_3), 2.13-2.02 (m, 2H, 5-CH and 2-CH), 2.00-1.92 (m, 1H, 5-CH), 1.79-1.71 (m, 1H, 4-CH), 1.63-1.52 (m, 2H, 4-CH and 2-CH), 1.47 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.1 (CO), 130.7 (6-CH), 124.0 (7-CH), 80.1 ($C(CH_3)$), 63.3 (C), 53.1 (1-CH_2), 40.4 (3-CH), 35.7 (NCH_3), 28.2 (3 x CH_3), 27.5 (2-CH_2), 25.6 (4-CH_2), 22.1 (5-CH_2); υ_{max}/cm^{-1} 2972.6, 2929.9, 1716.1, 1454.2, 1367.3, 1250.8, 1156.2, 1049.5, 1033.3, 846.2; *m/z* HRMS (ESI^+) found $[M + H]^+$ 238.1795, $[C_{14}H_{24}NO_2]^+$ requires 238.1807.

(±)-*tert*-Butyl (1*R*)-2-methyl-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate 336y



According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-methyl-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (36 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 0-10% MeOH/CH_2Cl_2, to give a yellow oil (24 mg, 67%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.02 (t, 1H, *J* = 3.7 Hz, 7-CH), 3.12 (br s, 1H, 1-CH), 2.90 (br t, 1H, *J* = 2.9 Hz, 5-CH), 2.65 (dd, 1H, *J* = 12.0, 3.6 Hz, 3-CH), 2.49 (dd, 1H, *J* = 20.9, 3.5 Hz, 8-CH), 2.41 (s, 3H, CH_3) superimposed on 2.34 (br d, 1H, *J* = 12.2 Hz, 3-CH), (2.15 (br d, 1H, *J* = 20.6 Hz, 8-CH), 2.08 (br d, 1H, *J* = 12.9 Hz, 9-CH), 1.97 (tt, 1H, *J* = 13.1, 4.0 Hz, 4-CH), 1.65 (br d, 1H, *J* = 12.4 Hz, 9-CH), 1.54 (br d, 1H, *J* = 13.5 Hz, 4-CH) 1.48 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.5, (CO) 139.1 (7-CH), 134.2 (6-C), 80.3 (C), 52.5 (1-CH), 46.1 (3-CH_2), 42.4 (CH_3), 30.9 (9-CH_2), 29.7 (4-CH_2), 28.1 (CH_3), 25.8 (5-CH), 24.3 (8-CH_2); υ_{max}/cm^{-1} 2928.7, 1703.5, 1367.9, 1286.1, 1253.1, 1168.9, 1077.0, 1042.1, 1020.1, 732.5; *m/z* HRMS (ESI^+) found $[M + H]^+$ 238.1792, $[C_{14}H_{24}NO_2]^+$ requires 238.1807.

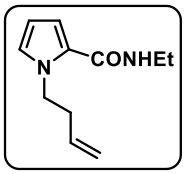
***tert*-Butyl (3a*S*,7a*R*)-1((1-*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate 335z**



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate (0.12 g, 0.52 mmol) and *N*-boc-4-piperidinecarboxaldehyde (0.11 g, 0.52 mmol) were stirred with sodium triacetoxyborohydride (0.33 g, 1.56 mmol) in CH_2Cl_2 (2 mL). The crude product was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, to give a pale-yellow oil (0.13 g, 59%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.90 (dt, 1H, *J* = 10.2, 3.8 Hz, 6-CH), 5.72 (br dt, 1H, *J* = 10.2, 1.7 Hz, 7-CH), 2.82-2.72 (m, 2H, 1-CH_2), 2.52-2.43 (m, 2H, NC<u>H</u>H and 3-CH), 2.38-2.33 (m, 1H, NCH<u>H</u>), 2.08-1.94 (m, 3H, 2-CH and 5-CH_2), 1.75-1.59 (m, 5H, 4-CH and 2 x CH_2), 1.57-1.48 (m, 6H, 2-CH, 4-CH and 2 x NBocC<u>H</u>$_2$), 1.43 (s, 18H, 6 x CH_3) superimposed on

(m, 1H, CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.9 (CO), 129.9 (6-CH), 125.1 (7-CH), 80.7 ($C(CH_3)$), 79.1 (C), 69.1 (C), 55.9 (NCH_2), 50.6 (1-CH_2), 40.4 (3-CH), 35.5 (2 x NBoc$\underline{C}H_2$), 30.7 (CH), 28.5 (CH_3), 28.2 (CH_3), 27.8 (2-CH_2), 25.7 (4-CH_2), 23.8 (2 x CH_2), 22.8 (5-CH_2), 20.8; υ_{max}/cm^{-1} 2927.3, 1716.0, 1693.6, 1450.4, 1422.3, 1365.5, 1392.1, 1270.8, 1245.0, 1154.1; *m/z* HRMS (ESI$^+$) found [M + H]$^+$ 421.3053, $[C_{24}H_{41}N_2O_4]^+$ requires 421.6020.

1-(But-3-en-1-yl)-*N*-ethyl-1*H*-pyrrole-2-carboxamide 337

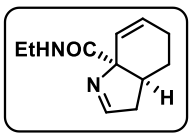


Ethylamine (2 M in THF, 49.0 mL, 98.0 mmol) was added dropwise over 20 min to a stirred solution of 1-(1-(but-3-en-1-yl)-1*H*-pyrrol-2-yl)-2,2,2-trichloroethan-1-one (15.17 g, 57.33 mmol) in MeCN (150 mL) at 0 °C. After 16 h, the reaction mixture was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 10-40% EtOAc/petrol, to give the product as a yellow oil (10.96 g, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.75 (app t, 1H, ArCH), 6.50 (dd, 1H, *J* = 3.9, 1.7 Hz, ArCH), 6.07-6.05 (m, 1H, ArCH), 5.84 (br s, 1H, NH), 5.82-5.72 (m, 1H, C$\underline{H}$$CH_2$), 5.06-4.99 (m, 2H, $CHC\underline{H}_2$), 4.39 (t, 2H, *J* = 7.1 Hz, NCH_2), 3.44-3.37 (m, 2H, $NCH_2C\underline{H}_2$), 2.53 (q, 2H, *J* = 7.3 Hz, $C\underline{H}_2CH_3$), 1.21 (t, 3H, *J* = 7.3 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.8 (CO), 135.0 ($\underline{C}HCH_2$), 126.8 (ArCH), 125.2 (ArC), 116.9 ($CH\underline{C}H_2$), 115.4 (ArCH), 107.0 (ArCH), 48.5 (NCH_2), 36.2 ($NCH_2\underline{C}H_2$), 34.1 ($\underline{C}H_2CH_3$), 15.1 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[126]

(±)-(3^1*R*,3a*S*,6a*S*)-*N*-Ethyl-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*]indole-3^1(2*H*-carboxamide 338

1-(But-3-en-1-yl)-*N*-ethyl-1*H*-pyrrole-2-carboxamide (5.0 g, 26.0 mmol) in degassed MeCN (1300 mL) was irradiated using 3 36 W low pressure Hg lamp whilst being passed through a flow reactor (flow rate 5.56 mL min^{-1}). The crude material was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 10-100%, EtOAc/petrol, to give a yellow oil (1.54 g, 31%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.54 (br s, 1H, NH), 6.26-6.22 (m, 1H, 6-CH), 5.76-5.72 (m, 1H, 5-CH), 3.28-3.19 (m, 2H, $C\underline{H}_2CH_3$), 3.11-306 (m, 2H, 1-CH and 4-CH), 2.57-2.41 (m, 4H, 1-CH, 2-CH, 4-CH and 7-CH), 1.98-1.91 (m, 1H, 3-CH), 1.51-1.46 (m, 1H, 2-CH), 1.11 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.3 (CO), 135.6 (6-CH), 119.9 (5-CH), 53.0 (C), 49.1 (1-CH_2), 44.4 (7-CH), 41.0 (2-CH_2), 33.9 (4-CH_2), 33.8 ($C\underline{H}_2CH_3$), 30.0 (3-CH), 14.8 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[126]

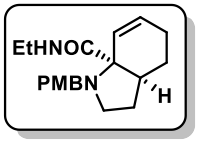
(±)-(3a*S*,7a*R*)-*N*-Ethyl-3,3a,4,5-tetrahydro-7a*H*-indole-7a*H*-carboxamide 339



(±)-(3^1*S*,3a*R*,6a*R*)-*N*-Ethyl-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*] in-dole-3^1(2*H*-carboxamide (1.50 g, 7.80 mmol) was stirred in PhMe (80 mL) at 100 °C for 15 h. The reaction mixture was concentrated *in vacuo* to give the crude material as a brown oil (1.47 g, 98%) which was used directly in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H, 1-CH), 6.61 (br s, 1H, NH), 6.00 (dt, 1H, *J* = 9.9, 3.9 Hz, 7-CH), 5.72 (dt,

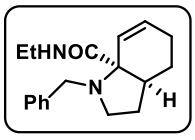
1H, *J* = 9.9, 1.8 Hz, 6-CH), 3.36-3.19 (m, 2H, C<u>H</u>$_2$CH$_3$), 2.74-2.65 (m, 2H, 2-CH and 3-CH), 2.47-2.39 (m, 1H, 2-CH), 2.21-2.14 (m, 1H, 5-CH), 2.08-2.08 (m, 2H, 4-CH and 5-CH), 1.57-1.50 (m, 1H, 4-CH), 1.13 (t, 3H, *J* = 7.4 Hz, CH$_2$C<u>H</u>$_3$). ^{1}H-NMR data is consistent with the literature.[142]

(±)-(3a*S*,7a*R*)-*N*-Ethyl-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxamide 340a



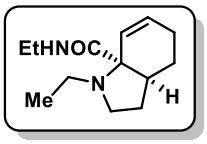
According to general procedure A, crude (±)-(3a*S*,7a*R*)-*N*-ethyl-3,3a,4,5-tetrahydro-7a*H*-indole-7a*H*-carboxamide (0.15 g, 0.78 mmol) and *p*-anisaldehyde (0.09 mL, 0.78 mmol) were stirred with sodium triacetoxyborohydride (0.50 g, 2.34 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a colourless oil (0.17 g, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (br s, 1H, NH), 7.19 (d, 2H, *J* = 9.0 Hz, ArCH), 6.88 (d, 2H, *J* = 9.0 Hz, ArCH), 6.23 (dt, 1H, *J* = 10.1, 3.4 Hz, 6-CH), 5.68 (br d, 1H, *J* = 10.1 Hz, 7-CH), 3.91 (d, 1H, *J* = 12.7 Hz, ArC<u>H</u>H), 3.81 (s, 3 H, OCH$_3$), 3.41-3.34 (m, 1H, NC<u>H</u>H), 3.30-3.24 (m, 2H, ArCH<u>H</u> and NCH<u>H</u>), 2.91 (td, 1H, *J* = 9.0, 2.8 Hz, 1-CH), 2.47-2.42 (m, 1H, 3-CH), 2.34 (app q, 1H, 1-CH), 2.10-2.06 (m, 2H, 5-CH$_2$), 1.90-1.82 (m, 2H, 2-CH and 4-CH), 1.63-1.52 (m, 2H, 2-CH and 4-CH), 1.16 (t, 3H, *J* = 7.2 Hz, CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.1 (CO), 158.7 (ArC), 133.4 (6-CH), 131.7 (ArC), 129.3 (ArCH), 122.8 (7-CH), 113.9 (ArCH), 70.0 (C), 55.3 (OCH$_3$), 54.6 (ArCH$_2$), 50.4 (1-CH$_2$), 42.3 (3-CH), 34.0 (NCH$_2$), 26.5 (2-CH$_2$), 23.8 (4-CH$_2$), 20.9 (5-CH$_2$), 15.0 (CH$_3$); υ_{max}/cm^{-1} 2974.6, 2921.3, 2850.4, 1729.5, 1704.9, 1512.8, 1366.5, 1321.0, 1249.9, 1146.2; *m/z* HRMS (ESI$^+$) found [M + H]$^+$ 315.2066, [$C_{19}H_{27}N_2O_2$]$^+$ requires 315.2073.

(±)-(3a*S*,7a*R*)-1-Benzyl-*N*-ethyl-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxamide 340b



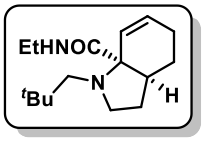
According to general procedure A, crude (±)-(3a*S*,7a*R*)-*N*-ethyl-3,3a,4,5-tetrahydro-7a*H*-indole-7a*H*-carboxamide (0.30 g, 1.56 mmol) and benzaldehyde (0.16 mL, 1.56 mmol) were stirred with sodium triacetoxyborohydride (0.99 g, 4.68 mmol) in CH_2Cl_2 (6 mL). The crude material was purified by SiO_2 flash chromatography, 0-40% EtOAc/petrol, to give a yellow oil (0.33 g, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (br s, 1H, NH), 7.37-7.26 (m, 5H, ArCH), 6.24 (dt, 1H, *J* = 10.6, 3.8 Hz, 7-CH), 5.69 (br d, 1H, *J* = 10.6 Hz, 6-CH), 3.97 (d, 1H, *J* = 13.5 Hz, NC<u>H</u>H), 3.40-3.23 (m, 3H, NCH<u>H</u> and C<u>H</u>$_2$CH$_3$), 2.93 (td, 1H, *J* = 9.0, 2.7 Hz, 1-CH), 2.49-2.42 (m, 1H, 3-CH), 2.39-2.32 (app q, 1H, 1-CH), 2.12-2.06 (m, 2H, 5-CH$_2$), 1.92-1.82 (m, 2H, 2-CH and 4-CH), 1.62-1.51 (m, 2H, 2-CH and 4-CH), 1.15 (t, 3H, *J* = 7.2 Hz, CH$_3$), ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.0 (CO), 139.6 (ArC), 133.5 (7-CH), 128.5 (ArCH), 128.2 (ArCH), 127.0 (ArCH), 122.7 (6-CH), 70.1 (C), 55.3 (NCH$_2$), 50.5 (1-CH), 42.3 (3-CH), 34.0 (<u>C</u>H$_2$CH$_3$), 26.5 (2-CH), 23.8 (4-CH), 20.9 (5-CH$_2$), 15.0 (CH$_2$<u>C</u>H$_3$); υ_{max}/cm^{-1} 3368.4, 3025.6, 2926.5, 1667.3, 1504.9, 1452.9, 1149.8, 1072.4, 741.1, 697.2; *m/z* HRMS (ESI$^+$) found [M + H]$^+$ 285.1975 and [M + Na]$^+$ 307.1794, [$C_{18}H_{25}N_2O$]$^+$ requires 285.1967 and [$C_{18}H_{24}N_2NaO$]$^+$ requires 307.1786.

(±)-(3a*S*,7a*R*)-*N*-Ethyl-1-diethyl-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxamide 340c



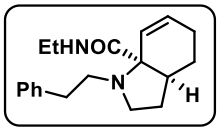
According to general procedure A, crude (±)-(3a*S*,7a*R*)-*N*-ethyl-3,3a,4,5-tetrahydro-7a*H*-indole-7a*H*-carboxamide (0.15 g, 0.78 mmol) and acetaldehyde (0.04 mL, 0.78 mmol) were stirred with sodium triacetoxyborohydride (0.50 g, 2.34 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a colourless oil (53 mg, 31%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52 (br s, 1H, NH), 6.15 (dt, 1H, *J* = 10.2, 3.8 Hz, 6-CH), 5.55 (br d, 1H, *J* = 10.2 Hz, 7-CH), 3.37-3.28 (m, 1H, CONHC<u>H</u>H), 3.27-3.21 (m, 1H, CONHCH<u>H</u>), 3.19-3.15 (m, 1H, 1-CH), 2.75-2.68 (m, 1H, NC<u>H</u>H), 2.40-2.35 (m, 1H, 3-CH), 2.33-2.27 (m, 2H, NCH<u>H</u> and 1-CH), 2.07-2.02 (m, 2H, 5-CH_2), 1.93-1.79 (m, 2H, 2-CH and 4-CH), 1.63-1.57 (m, 1H, 2-CH), 1.52-1.47 (m, 1H, 4-CH), 1.13 (t, 3H, *J* = 7.2 Hz, CH_3), 1.08 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.3 (CO), 132.9 (6-CH), 122.8 (7-CH), 69.9 (C), 50.0 (1-CH_2), 45.0 (NCH_2), 42.2 (3-CH), 33.8 (CONH<u>C</u>H_2), 26.4 (2-CH_2), 23.6 (4-CH_2), 20.9 (CH_3), 15.0 (CH_3); υ_{max}/cm^{-1} 2965.1, 2928.8, 2815.5, 1660.7, 1505.1, 1451.1, 1380.8, 1187.3, 1166.4, 693.0; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 223.1801, $[C_{13}H_{23}N_2O]^+$ requires 223.1810.

(±)-(3a*S*,7a*R*)-*N*-Ethyl-1-neopentyl-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxamide 340d



According to general procedure A, crude (±)-(3a*S*,7a*R*)-*N*-ethyl-3,3a,4,5-tetrahydro-7a*H*-indole-7a*H*-carboxamide (0.15 g, 0.78 mmol) and trimethylacetaldehyde (0.08 mL, 0.78 mmol), were stirred with sodium triacetoxyborohydride (0.50 g, 2.34 mmol) in CH_2Cl_2 (3 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/isohexane, to give a colourless oil (0.11 g, 52%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (br s, 1H, NH), 6.11 (dt, 1H, *J* = 10.2, 3.9 Hz, 6-CH), 5.55 (dt, 1H, *J* = 10.2, 2.0 Hz, 7-CH), 3.30-3.23 (m, 3H, 1-CH and CONHC<u>H</u>$_2$), 2.65 (d, 1H, *J* = 12.9 Hz, NC<u>H</u>H), 2.49-2.37 (m, 2H, 1-CH and 3-CH), 2.10-2.04 (m, 3H, 5-CH_2 and NCH<u>H</u>), 1.92-1.84 (m, 1H, 2-CH), 1.80-1.74 (m, 1H, 4-CH), 1.65-1.58 (m, 1H, 2-CH), 1.41-1.35 (m, 1H, 4-CH), 1.13 (t, *J* = 7.3 Hz, CH_3), 0.94 (s, 9H, 3 x CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.6 (CO), 132.6 (6-CH), 123.7 (7-CH), 72.6 (C), 65.2 (NCH_2), 54.1 (1-CH_2), 41.2 (3-CH), 33.9 (CONH<u>C</u>H_2), 32.8 (C), 29.0 (3 x CH_3), 27.8 (2-CH_2), 23.7 (4-CH_2), 22.0 (5-CH_2), 14.9 (CH_3); υ_{max}/cm^{-1} 2920.1, 2850.4, 1735.5, 1675.5, 1505.2, 1463.5, 1365.6, 1244.0, 1146.5, 1023.8; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 265.2274, $[C_{16}H_{29}N_2O]^+$ requires 265.2280.

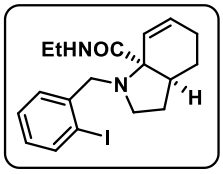
(±)-(3a*S*,7a*R*)-*N*-Ethyl-1-phenyethyl-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboaamide S31



According to general procedure A, crude (±)-(3a*S*,7a*R*)-*N*-ethyl-3,3a,4,5-tetrahydro-7a*H*-indole-7a*H*-carboxamide (0.30 g, 1.56 mmol) and phenyl acetaldehyde (0.18 mL, 1.56 mmol) were stirred with sodium triacetoxyborohydride (0.99 g, 4.68 mmol) in CH_2Cl_2 (6 mL). The crude material was purified by SiO_2 flash chromatography, 20-40% EtOAc/petrol, to give a yellow oil (0.32 g, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.20 (m, 5H, ArCH), 6.81 (br s, 1H, NH), 6.12 (dt, 1H, *J* = 10.5, 3.7 Hz, 7-CH), 5.51

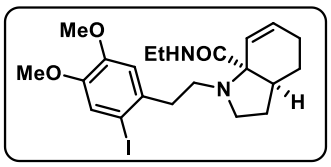
(br d, 1H, 6-CH), 3.33 (td, 1H, *J* = 8.9, 2.9 Hz, 1-CH), 3.05-2.98 (m, 1H, CH<u>H</u>CH$_3$), 2.93-2.86 (m, 1H, NC<u>H</u>H), 2.82-2.59 (m, 4H, NCH<u>H</u>, NCH$_2$C<u>H</u>$_2$ and C<u>H</u>HCH$_3$), 2.42 (app q, 1H, 1-CH), 2.33-2.27 (m, 1H, 3-CH), 2.04 (br s, 2H, 5-CH$_2$), 1.93-1.77 (m, 2H, 2-CH and 4-CH), 1.67-1.58 (m, 1H, 2-CH), 1.51-1.43 (m, 1H, 4-CH), 0.81 (t, 3H, *J* = 7.1 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 174.9 (CO), 140.5 (ArC), 132.8 (7-CH), 128.9 (ArCH), 128.4 (ArCH), 126.2 (ArCH), 122.9 (6-CH), 89.9 (C), 52.9 (NCH$_2$), 50.2 (1-CH$_2$), 42.1 (3-CH), 35.4 (NCH$_2$<u>C</u>H$_2$), 33.6 (<u>C</u>H$_2$CH$_3$), 26.6 (2-CH$_2$), 23.5 (4-CH$_2$), 21.1 (5-CH$_2$), 14.8 (CH$_2$<u>C</u>H$_3$); υ_{max}/cm^{-1} 3357.7, 2927.5, 1667.0, 1505.5, 1452.5, 1375.9, 1126.8, 1066.5, 751.5, 701.0; *m/z* HRMS (ESI$^+$) found [M + H]$^+$ 299.2120, [C$_{19}$H$_{27}$N$_2$O]$^+$ requires 299.2123.

(±)-(3a*S*,7a*R*)-*N*-Ethyl-1-(2-iodobenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxamide S32



According to general procedure A, crude (±)-(3a*S*,7a*R*)-*N*-ethyl-3,3a,4,5-tetrahydro-7a*H*-indole-7a*H*-carboxamide (0.30 g, 1.56 mmol) and 2-iodobenzaldehyde (0.12 g, 0.52 mmol) were stirred with sodium triacetoxyborohydride (0.33 g, 1.56 mmol) in CH$_2$Cl$_2$ (2 mL). The crude material was purified by SiO$_2$ flash chromatography, 10-30% EtOAc/petrol, to give a yellow oil (0.33 g, 75%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.84 (m, 2H, ArCH), 7.50 (br s, 1H, NH), 7.44-7.34 (m, 2H, ArCH), 6.99-6.94 (m, 1H, ArCH), 6.27 (dt, 1H, *J* = 10.5, 3.4 Hz, 7-CH), 5.75 (br d, 1H, *J* = 10.5 Hz, 6-CH), 3.91 (br d, 1H, *J* = 14.7 Hz, NCH<u>H</u>), 3.52 (br d, 1H, *J* = 14.7 Hz, NC<u>H</u>H), 3.26-3.18 (m, 2H, C<u>H</u>$_2$CH$_3$), 3.02 (td, 1H, *J* = 8.5, 2.8 Hz, 1-CH), 2.54-2.46 (m, 2H, 1-CH and 3-CH), 2.14-2.10 (m, 2H, 5-CH$_2$), 1.99-1.83 (m, 2H, 2-CH and 4-CH), 1.64-1.59 (m, 1H, 2-CH), 1.59-1.50 (m, 1H, 4-CH), 1.03 (t, 3H, *J* = 7.3 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 174.8 (CO), 143.3 (ArCH), 139.7 (ArCH), 133.7 (7-CH), 129.1 (ArC) , 128.7 (ArCH), 128.2 (ArCH), 123.1 (6-CH), 99.8 (ArC), 70.5 (C), 59.7 (NCH$_2$), 51.1 (1-CH), 42.1 (3-CH), 34.0 (<u>C</u>H$_2$CH$_3$), 27.0 (2-CH), 24.1(4-CH), 21.5 (5-CH$_2$), 14.8 (CH$_2$<u>C</u>H$_3$); υ_{max}/cm^{-1} 2925.8, 1663.2, 1506.4, 1435.7, 1355.6, 1203.2, 1152.3, 1012.3, 751.6, 649.4; *m/z* HRMS (ESI$^+$) found [M + H]$^+$ 411.0912, [C$_{18}$H$_{24}$IN$_2$O]$^+$ requires 411.0933.

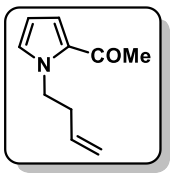
(±)-(3a*S*,7a*R*)-*N*-Ethyl-1-(2-iodo-4,5-dimethoxyphenethyl0-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxamide S33



According to general procedure A, crude (±)-(3a*S*,7a*R*)-*N*-ethyl-3,3a,4,5-tetrahydro-7a*H*-indole-7a*H*-carboxamide (0.15 g, 0.78 mmol) and 2-(2-iodo-4,5-dimethoxyphenl)acetaldehyde (0.24 g, 0.78 mmol) were stirred with sodium triacetoxyborohydride (0.50 g, 2.34 mmol) in CH$_2$Cl$_2$ (3 mL). The crude material was purified by SiO$_2$ flash chromatography, 0-50% EtOAc/petrol, to give a yellow oil (0.22 g, 58%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.22 (s, 1H, ArCH), 7.02 (br s, 1H, NH), 6.72 (s, 1H, ArCH) 6.14 (dt, 1H, *J* = 10.2, 3.4 Hz, 6-CH), 5.53 (br d, 1H, *J* = 10.2 Hz, 7-CH), 3.85 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 3.37 (td, 1H, *J* = 8.6, 2.9 Hz, 1-CH), 3.22-3.11 (m, 1H, NHC<u>H</u>HCH$_3$), 2.99-2.74 (m, 4H, NC<u>H</u>H, NHCH<u>H</u>CH$_3$ and NCH$_2$C<u>H</u>$_2$), 2.50-2.43 (m, 2H, 1-CH and

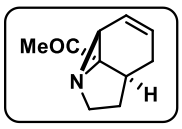
3-CH), 2.38-2.32 (m, 1H, NCHH), 2.07-2.02 (m, 2H, 5-CH_2) 1.97-1.87 (m, 1H, 2-CH), 1.86-1.79 (m, 1H, 4-CH), 1.69-1.63 (m, 1H, 2-CH), 1.53-1.46 (m, 1H, 4-CH), 0.96 (t, 3H, *J* = 7.2 Hz, CH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.9 (CO), 149.2 (ArC), 148.1 (ArC), 135.3 (ArC), 133.0 (6-CH), 122.7 (7-CH), 121.7 (ArCH), 112.7 (ArCH), 88.1 (ArC), 70.0 (C), 56.2 (OCH_3), 56.0 (OCH_3), 51.7 (NCH_2), 50.7 (1-CH), 42.1 (3-CH), 39.9 (NCH_2CH_2), 33.8 (CH_2CH_3), 26.6 (2-CH), 23.6 (4-CH), 21.0 (5-CH_2), 14.9 (CH_3); υ_{max}/cm^{-1} 2928.9, 1665.2, 1504.7, 1440.0, 1377.5, 1254.8, 1218.0, 1161.9, 1028.6, 785.1; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 485.1299, $[C_{21}H_{30}IN_2O_3]^+$ requires 485.1301.

1-(1-(But-3-en-1-yl)-1*H*-pyrrol-2-yl)ethan-1-one 343



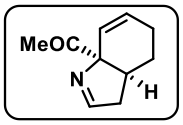
K_2CO_3 (19.0 g, 137.45 mmol) was added to a stirred solution of 2-acetyl pyrrole (5.0 g, 45.82 mmol), 4-bromo-1-butene (15.35 mL, 151.19 mmol) and tetrabutylammonium iodide (1.69 g, 4.58 mmol) in acetone (125 mL) and the reaction mixture was heated under reflux for 48 h. The reaction mixture was cooled to RT, concentrated *in vacuo* and partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The organic layer was separated and further extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-5% EtOAc/petrol, to afford a yellow oil (5.47 g, 73%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, 1H, *J* = 4.1, 1.8 Hz, ArCH), 6.84 (t, 1H, *J* = 2.4 Hz, ArCH), 6.11 (dd, 1H, *J* = 4.1, 2.4 Hz, ArCH), 5.80-5.70 (m, 1H, CH), 5.06-5.00 (m, 2H, $CHCH_2$), 4.37 (t, 2H, *J* = 7.0 Hz, NCH_2), 2.51-2.45 (m, 2H, CH_2), 2.44 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 188.2 (CO), 134.7 (CH), 130.3 (ArCH), 130.1 (ArC), 120.3 (ArCH), 117.1 ($CHCH_2$), 107.8, 49.3 (NCH_2), 35.7 (CH_2), 27.3 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[126]

(±)-1-((3^1*R*,3a*S*,6a*S*)-1,3a,6,6a-Tetrahydroazirino[2,3,1-*hi*]indol-3^1(2*H*)-yl)ethan-1-one 344



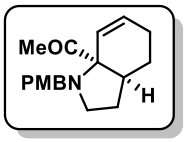
1-(1-(But-3-en-1-yl)-1*H*-pyrrole-2-yl)ethan-1-one (1.0 g, 6.13 mmol) in degassed MeCN (450 mL) was irradiated using a water cooled 36 W low pressure Hg lamp. After 6 h, the reaction mixture was concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 20-40% EtOAc/petrol, to give a yellow oil (0.53 g, 53%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.23-6.18 (m, 1H, 5-CH), 5.77 (app dt, 1H, 6-CH), 3.26-3.23 (m, 1H, 3-CH), 3.14 (td, 1H, *J* = 11.0, 2.3 Hz, 1-CH), 2.83 (d, 1H, *J* = 3.9 Hz, 7-CH), 2.58-2.51 (m, 1H, 1-CH), 2.47-2.37 (m, 1H, 2-CH), 2.29-2.21 (m, 1H, 4-CH), 2.06 (s, 3H, CH_3), 1.91 (br dd, 1H, *J* = 17.4, 2.1 Hz, 4-CH), 1.51-1.45 (m, 1H, 2-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.4 (CO), 135.5 (6-CH), 119.9 (5-CH), 59.3 (C), 49.8 (1-CH_2), 43.8 (7-CH), 40.9 (2-CH_2), 31.7 (3-CH), 29.6 (4-CH_2), 24.1 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[126]

(±)-1-((3a*S*,7a*R*)-3,3a,4,5-Tetrahydro-7a*H*-indol-7a-yl)ethan-1-one 345



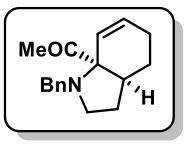
(±)-1-((3^1*R*,3a*S*,6a*S*)-1,3a,6,6a- Tetrahydroazirino[2,3,1-*hi*]indol-3^1(2*H*)-yl)ethan-1-one (1.0 g, 6.13 mmol) was stirred in PhMe (50 mL) at 100 °C for 15 h. The reaction mixture was concentrated *in vacuo* to give the crude product as a dark orange oil which was used directly in the next step without further purification (1.0 g, *quant*.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H, NCH), 6.08-6.03 (m, 1H, 6-CH), 5.98 (dt, 1H, *J* = 10.1, 1.8 Hz, 7-CH), 2.79-2.67 (m, 2H, 2-CH and 3-CH), 2.41-2.35 (m, 1H, 2-CH), 2.30 (s, 3H, CH_3), 2.08-1.97 (m, 2H, 5-CH_2), 1.90-1.83 (m, 1H, 4-CH), 1.42-1.33 (m, 1H, 4-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 207.6 (CO), 167.4 (NCH), 131.8 (6-CH), 125.8 (7-CH), 86.6 (C), 42.5 (2-CH_2), 35.0 (3-CH), 26.3 (CH_3), 24.8 (4-CH_2), 21.9 (5-CH_2). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[142]

(±)-1-((3a*S*,7a*R*)-1-(4-Methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indol-7a-yl)ethan-1-one 346a



According to general procedure A, crude (±)-1-((3a*S*,7a*R*)-3,3a,4,5-tetrahydro-7a*H*-indol-7a-yl)ethan-1-one (0.25 g, 1.53 mmol) and *p*-anisaldehyde (0.19 mL, 1.53 mmol) were stirred with sodium triacetoxyborohydride (0.68 g, 3.21 mmol) in CH_2Cl_2 (6 mL). The crude material was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, which was contaminated with residual *p*-anisaldehyde. This was dissolved in MeOH and washed with $NaHSO_3$ (saturated aqueous solution, 10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo* to give the pure product as a yellow oil (0.16 g, 36%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H, *J* = 8.8 Hz, ArCH), 6.86 (d, 2H, *J* = 8.8 Hz, ArCH), 6.21-6.17 (m, 1H, 6-CH), 5.70 (d, 2H, *J* = 10.4 Hz, 7-CH), 3.80 (s, 3H, OCH_3) superimposed on 3.78 (d, 1H, *J* = 13.4 Hz, NC<u>H</u>H), 3.37 (d, 1H, *J* = 13.4 Hz, NCH<u>H</u>), 2.92 (td, 1H, *J* = 8.8, 2.8 Hz, 1-CH), 2.55-2.49 (m, 1H, 3-CH), 2.35 (s, 3H, CH_3) superimposed on 2.35-2.28 (m, 1H, 1-CH), 2.16-2.07 (m, 1H, 5-CH), 2.04-1.91 (m, 2H, and 5-CH), 1.69-1.59 (m, 3H, 2-CH and 4-CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 206.9 (CO), 158.6 (ArC), 132.7 (6-CH), 131.6 (ArC), 129.2 (ArCH), 122.9 (7-CH), 113.7 (ArCH), 74.5 (C), 55.3 (OCH_3), 54.1 (NCH_2), 50.4 (1-CH_2), 39.6 (3-CH), 26.4 (2-CH_2), 24.5 (CH_3), 23.2 (4-CH_2), 20.8 (5-CH_2); υ_{max}/cm^{-1} 2920.8, 2765.5, 1702.9, 1611.5, 1511.2, 1349.5, 1301.8, 1244.7, 1174.1, 1034.7; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 286.1805, $[C_{18}H_{24}NO_2]^+$ requires 286.1807.

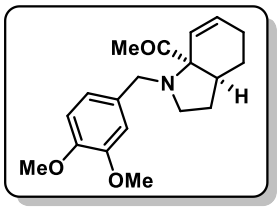
(±)-1-((3a*S*,7a*R*)-1-Benzyl-1,2,3,3a,4,5-hexahydro-7a*H*-indol-7a-yl)ethan-1-one 346b



According to general procedure A, crude (±)-1-((3a*S*,7a*R*)-3,3a,4,5-tetrahydro-7a*H*-indol-7a-yl)ethan-1-one (0.25 g, 1.53 mmol) and benzaldehyde (0.16 mL, 1.53 mmol) were stirred with sodium triacetoxyborohydride (0.68 g, 3.21 mmol) in CH_2Cl_2 (6 mL). The crude material was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, to give the product as a yellow oil (0.22 g, 56%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 4H, ArCH), 7.23-7.20 (m, 1H, ArCH), 6.20-6.16 (m, 1H, 6-CH), 5.70-5.67 (m, 1H, 7-CH), 3.83 (d, 1H, *J* =

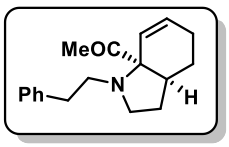
13.6 Hz, NCHH), 3.41 (d, 1H, *J* = 13.6 Hz, NCHH), 2.92 (td, 1H, *J* = 9.0, 3.0 Hz, Hz, 1-CH), 2.55-2.49 (m, 1H, 3-CH), 2.34 (s, 3H, CH_3) superimposed on 2.34-2.28 (m, 1H, 1-CH), 2.15-2.05 (m, 1H, 5-CH), 2.03-1.93 (m, 2H, 2-CH and 5-CH), 1.68-1.57 (m, 3H, 2-CH and 4-CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 213.2 (CO), 139.6 (ArC), 132.7 (6-CH), 128.3 (ArCH), 128.1 (ArCH), 126.9 (ArCH), 122.9 (7-CH), 74.6 (C), 54.7 (NCH_2), 50.4 (1-CH_2), 39.6 (3-CH), 26.5 (2-CH_2), 24.5 (CH_3), 23.2 (4-CH_2), 20.8 (5-CH_2); υ_{max}/cm^{-1} 2921.8, 1703.5, 1494.7, 1453.5, 1349.2, 1189.8, 1177.0, 1150.4, 738.7, 698.1; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 256.1692, $[C_{17}H_{22}NO]^+$ requires 256.1701.

(±)-1-((3a*S*,7a*R*)-1-(3,4-Dimethoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indol-7a-yl)ethan-1-one 346c



According to general procedure A, crude (±)-1-((3a*S*,7a*R*)-3,3a,4,5-tetrahydro-7a*H*-indol-7a-yl)ethan-1-one (0.25 g, 1.53 mmol) and 3,4-dimethoxybenzaldehyde (0.25 g, 1.53 mmol) were stirred with sodium triacetoxyborohydride (0.68 g, 3.21 mmol) in CH_2Cl_2 (6 mL). The crude material was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol which was contaminated with residual aldehyde. This was dissolved in MeOH and washed with $NaHSO_3$ (saturated aqueous solution, 10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo* to give the pure product as a yellow oil (0.27 g, 56%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.90-6.78 (m, 3H, ArCH), 6.20-6.16 (m, 1H, 6-CH), 5.65 (br s, 1H, 7-CH), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3) superimposed on 3.81-3.80 (m, 1H, NCHH), 3.38 (br s, 1H, NCHH), 2.99-2.94 (m, 1H, 1-CH), 2.53-2.50 (m, 1H, 3-CH), 2.31 (s, 3H, CH_3) superimposed on 2.31 (m, 1H, 1-CH), 2.15-2.06 (m, 1H, 5-CH), 2.03-1.95 (m, 2H, 2-CH and 5-CH), 1.68-1.58 (m, 3H, 2-CH and 4-CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 190.9 (CO), 154.5 (ArC), 148.9 (ArC), 132.9 (6-CH), 126.9 (ArC), 122.8 (7-CH), 120.2 (ArCH), 111.5 (ArCH), 111.0 (ArCH), 74.6 (C), 55.9 (OCH_3), 55.8 (OCH_3), 54.5 (NCH_2), 50.5 (1-CH_2), 39.6 (3-CH), 26.5 (2-CH_2), 24.6 (CH_3), 23.2 (4-CH_2), 20.9 (5-CH_2); υ_{max}/cm^{-1} 1701.6, 1512.3, 1454.2, 1418.0, 1349.2, 1264.36, 1233.0, 1188.8, 1136.5, 1027.2; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 316.1916, $[C_{19}H_{26}NO_3]^+$ requires 316.4210.

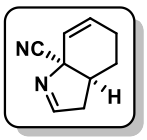
(±)-1-((3a*S*,7a*R*)-1-Phenethyl-1,2,3,3a,4,5-hexahydro-7a*H*-indol-7a-yl)ethan-1-one 346d



According to general procedure A, crude (±)-1-((3a*S*,7a*R*)-3,3a,4,5-tetrahydro-7a*H*-indol-7a-yl)ethan-1-one (0.25 g, 1.53 mmol) and phenylacetaldehyde (0.18 mL, 1.53 mmol) was stirred with sodium triacetoxyborohydride (0.68 g, 3.21 mmol) in CH_2Cl_2 (6 mL). The crude material was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, which was contaminated with residual aldehyde. This was dissolved in MeOH and washed with $NaHSO_3$ (saturated aqueous solution, 10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo* to give the pure product as a brown oil (0.20 g, 49%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27-7.23 (m, 2H, ArCH), 7.19-

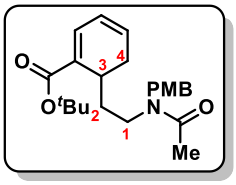
7.15 (m, 3H, ArCH), 6.13-6.09 (m, 1H, 6-CH), 5.55 (br d, *J* = 10.5 Hz, 7-CH), 3.32 (td, 1H, *J* = 8.9, 3.5 Hz, 1-CH), 2.82-2.72 (m, 3H, NCHH and $ArCH_2$), 2.67-2.61 (m, 1H, NCHH), 2.45-2.41 (m, 2H, 1-CH and 3-CH), 2.10-2.05 (m, 2H, 2-CH and 5-CH) superimposed on 2.02 (s, 3H, CH_3), 2.00-1.96 (m, 1H, 5-CH), 1.73-1.65 (m, 1H, 2-CH), 1.58-1.53 (m, 2H, 4-CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 180.3 (CO), 140.2 (ArC), 132.8 (6-CH), 128.8 (ArCH), 128.3 (ArCH), 126.1 (ArCH), 122.5 (7-CH), 75.0 (C), 53.1 (NCH_2), 50.6 (1-CH_2), 39.3 (3-CH), 35.6 ($ArCH_2$), 26.4 (2-CH_2), 24.2 (CH_3), 23.0 (4-CH_2), 20.8 (5-CH_2); υ_{max}/cm^{-1} 2922.2, 1702.3, 1495.5, 1453.7, 1350.2, 1188.6, 1124.3, 1029.6, 750.2, 699.3; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 270.1847, $[C_{18}H_{24}NO]^+$ requires 270.1858.

(±)-(3a*S*,7a*R*)-3-3a,4,5-Tetrahydro-7a*H*-indole-7a-carbonitrile 250



(±)-(3^1*R*,3a*S*,6a*S*)-1,3a,6,6a-Tetrahydoazirino[2,3,1-*hi*]indole-3^1(2*H*) carbonitrile (0.44 g, 3.01 mmol) was stirred in PhMe (20 mL) at 100 °C for 16 h. The reaction mixture was concentrated *in vacuo* to give the crude material as a brown oil which was used directly in the next step without purification (0.38 g, 86%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H, 1-CH), 6.11 (dt, 1H, *J* = 10.0, 4.1 Hz, 6-CH), 5.99 (dt, 1H, *J* = 10.0, 2.0 Hz, 7-CH), 2.98-2.93 (m, 1H, 2-CH), 2.85-2.80 (m, 1H, 3-CH), 2.55 (dd, 1H, *J* = 17.9, 5.1 Hz, 2-CH), 2.08 (m, 2H, 5-CH_2), 1.92-1.86 (m, 1H, 4-CH) 1.44-1.37 (m, 1H, 4-CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.3 (1-CH), 132.4 (6-CH), 123.6 (7-CH), 120.5 (CN), 69.7 (C), 42.4 (2-CH_2), 40.1 (3-CH), 23.3 (4-CH_2), 21.4 (5-CH_2). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[142]

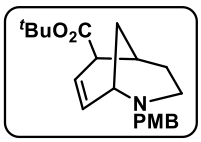
***tert*-Butyl 6-(2-(*N*-(4-methoxybenzyl)acetamido)ethyl)cyclohexa-1,3-diene-1-caboxylate 354**



N,*N*-Diisopropylethylamine (0.02 mL, 0.13 mmol) in dioxane (0.60 mL) was added to $Pd(OAc)_2$ (3 mg, 0.01 mmol) and DPEPhos (9 mg, 0.02 mmol) and stirred for 10 min. The reaction mixture turned bright yellow. (±)-*tert*-Butyl (3a*S*,7a*R*)- 1- (4-methoxybenzyl) - 1, 2, 3, 3a, 4, 5-hexahydro-7a*H*-indole-7a-carboxylate (44 mg, 0.13 mmol) in dioxane (0.6 mL), camphorsulfonic acid (30 mg, 0.13 mmol) and Ac_2O (0.01 mL, 0.13mmol) were added sequentially and the reaction mixture was heated under reflux. After 17 h, the reaction was cooled to RT, quenched with $NaHCO_3$ (saturated aqueous solution, 5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 10-30% EtOAc/petrol, to give a yellow oil (41 mg, 82%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.16-7.06 (m, 2H, ArCH), 6.93-6.89 (m, 1H, CH), 6.88-6.81 (m, 2H, ArCH), 6.05-5.95 (m, 2H, 2 x CH), 4.57-4.42 (m, 2H, $ArCH_2$), 3.78 (s, 3H, OCH_3), 3.49-3.37 (m, 1H, 3-CH), 3.31-3.05 (m, 2H, 1-CH_2), 2.67-2.58 (m, 1H, 2-CH), 2.49-2.38 (m, 1 H, 2-CH), 2.19-2.13 (m, 1H, 4-CH), 2.11 (s, 3H, CH_3), 1.65-1.60 (m, 1H, 4-CH), 1.46 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.2 (CO), 166.5 (CO), 158.9 (C), 132.1 (7-CH), 132.0 (ArC), 130.9 (CH), 129.5 (ArCH), 128.7 (ArC), 123.8 (CH), 113.9 (ArCH), 80.3 (C), 55.2 (OCH_3), 50.8 ($ArCH_2$), 45.4 (1-CH_2), 42.6 (3-CH), 28.2 (4-CH_2), 28.1 (3 x CH_3), 27.4 (2-CH_2), 21.4

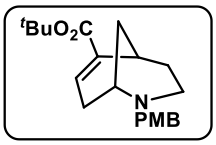
($COCH_3$); υ_{max}/cm^{-1} 2931.9, 1696.5, 1645.2, 1512.9, 1411.9, 1366.8, 1279.6, 1247.0, 1161.8, 1033.7; *m/z* HRMS (ESI^+) found $[M + H]^+$ 386.2329 and $[M + Na]^+$ 408.2146, $[C_{23}H_{32}NO_4]^+$ requires 386.2331 and $[C_{23}H_{31}NO_4Na]^+$ requires 408.2151.

(±)-*tert*-Butyl (1*S*,6*S*)-2-(4-Methoxybenzyl)-2-azabicyclo[3.3.1]non-7-ene-6-carboxylate 355



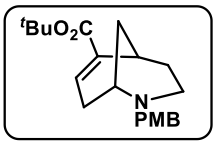
(±)-*tert*-Butyl (3a*S*,7a*R*)- 1- (4-methoxybenzyl) - 1, 2, 3, 3a, 4, 5-hexahydro-7a*H*-indole-7a-carboxylate (104 mg, 0.30 mmol) in dioxane (1.2 mL) was added to a stirred solution of *N*, *N*-diisopropylethylamine (0.06 mL, 0.30 mmol), $Pd(OAc)_2$ (6 mg, 0.03 mmol) and DPEPhos (24 mg, 0.05 mmol) in dioxane (1.2 mL). The reaction mixture was stirred for 10 min, methanesulfonic acid (0.02 mL, 0.30 mmol) was added and the reaction was heated to 100 °C. After 3 h, the reaction mixture was cooled to RT, quenched with $NaHCO_3$ (saturated aqueous solution, 5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, 5-50% EtOAc/petrol, to give the conjugated morphan product (29 mg, 28%) and the unconjugated morphan intermediate (16 mg, 15%) as a 1:0.7 inseparable mixture of diastereomers. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H, ArCH), 6.85 (d, 2H, *J* = 8.9 Hz, ArCH), 6.22-6.13 (m, 1H, 7-CH), 5.87-5.72 (m, 1H, 8-CH), 3.79 (s, 3H, OCH_3), 3.51-3.47 (m, 1H, $ArCH_2$), 3.36 (app t, 1H, $ArCH_2$), 3.24-3.17 (m, 1H, 1-CH), 2.74 (app t, 1H, 6-CH), 2.58-2.52 (m, 1H, 3-CH), 2.45-2.25 (m, 2H, 3-CH and 4-CH), 2.02-1.71 (m, 3H, 5-CH and 9-CH_2), 1.59-1.53 (m, 1H, 4-CH), 1.44 (s, 9H, CH_3); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 172.5 (CO), 158.7 (ArC), 132.0 (ArC), 130.2 (7-CH), 130.1 (ArCH), 125.2 (8-CH), 113.6 (ArCH), 80.5 (C), 59.5 ($ArCH_2$), 55.2 (OCH_3), 49.5 (1-CH), 48.1 (6-CH), 44.9 (3-CH_2), 32.3 (9-CH_2), 29.3 (5-CH), 28.0 (CH_3), 27.8 (4-CH_2); υ_{max}/cm^{-1} 2929.4, 1724.7, 1512.2, 1367.3, 1301.7, 1244.3, 1151.4, 1105.3, 1037.3, 835.8; *m/z* HRMS (ESI^+) found $[M + H]^+$ 344.2234, $[C_{21}H_{30}NO_3]^+$ requires 344.2226.

Subjecting (±)-*tert*-butyl (1*S*,6*S*)-2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-7-ene-6-carboxylate to Standard Conditions



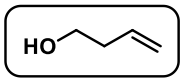
(±)-*tert*-Butyl (1*S*,6*S*)-2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-7-ene-6-carboxylate (29 mg, 0.08 mmol) in dioxane (0.35 mL) was added to a stirred solution of *N*,*N*-diisopropylethylamine (0.02 mL, 0.08 mmol), $Pd(OAc)_2$ (1 mg, 0.008 mmol) and DPEPhos (7 mg, 0.01 mmol) in dioxane (0.35 mL). The reaction mixture was stirred for 10 min, methanesulfonic acid (0.005 mL, 0.08 mmol) was added and the reaction was heated under reflux. After 20 min, the reaction mixture was cooled to RT, quenched with $NaHCO_3$ (saturated aqueous solution, 5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*, to give crude (±)-*tert*-butyl (1*R*)-2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (24% based on ^{1}H-NMR) and unreacted (±)-*tert*-butyl (1*S*,6*S*)-2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-7-ene-6-carboxylate (76% based on ^{1}H-NMR).

Subjecting (±)-*tert*-butyl (1*S*,6*S*)-2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-7-ene-6-carboxylate to Acid and Base



N,*N*-Diisopropylethylamine (0.01 mL, 0.05 mmol) was added to a stirred solution of (±)-*tert*-butyl (1*S*,6*S*)-2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-7-ene-6-carboxylate (16 mg, 0.05 mmol) in dioxane (0.4 mL). The reaction mixture was stirred for 10 min, methanesulfonic acid (0.003 mL, 0.05 mmol) was added and the reaction was heated under reflux. After 20 h, the reaction mixture was cooled to RT, quenched with $NaHCO_3$ (saturated aqueous solution, 5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*, to give crude (±)-*tert*-butyl (1*R*)-2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (*quant.* based on ^{1}H-NMR).

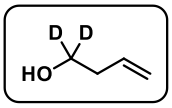
But-3-en-1-ol 305



Sodium borohydride (0.33 g, 8.82 mmol) was added in one portion to a stirred solution of methyl but-3-enoate (5.88 mmol) in MeOH (5 mL) at 0 °C and the reaction mixturewas gradually warmed to RT. After 16.5 h, the reaction mixture was quenched with H_2O, extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude material as a light brown oil (80 mg, 19% accounting for 15.07 equiv. MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.87-5.77 (m, 1H, CH), 5.17-5.11 (m, 2H, CHC$\underline{H}_2$), 3.69 (q, 2H, *J* = 5.7 Hz, C$\underline{H}_2$OH), 2.36-2.33 (m, 2H, CH_2). ^{1}H-NMR data is consistent with the literature.[314]

But-3-en-1,1-*d*$_2$-1-ol 367

Reduction of Ester Procedure



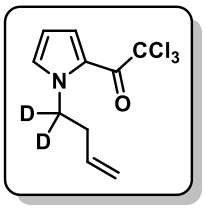
Lithium borodeuteride (1.54 g, 59.67 mmol) was added in one portion to a stirred solution of methyl but-3-enoate (2.99 g, 29.84 mmol) in THF (60 mL), the reaction turned cloudy upon this addition. The reaction mixture was stirred for 16 h, quenched with H_2O, extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude material which was used directly in the next step without further purification (0.97 g, 44% accounting for 3.88 equiv. THF).

Reduction of Acid Procedure

3-Butenoic acid (3.39 mL, 39.91 mmol) was added dropwise over 10 min to a stirred solution of lithium aluminium deuteride (1.91 g, 45.50 mmol) in Et_2O (68 mL) at 0 °C. Significant effervescence was observed during this addition. The reaction mixture was stirred at 0 °C for 20 min, heated under reflux for 2 h then cooled to RT and stirred for a further 4 h. The reaction mixture was quenched with H_2O (1 mL), NaOH (15% aqueous solution, 3.3 mL) and H_2O (1 mL). After 15 min the solution was filtered through celite, the filtrate dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material as a yellow oil which was used directly in the next step without further purification (2.61 g,

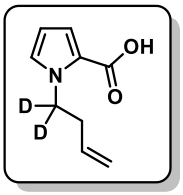
88% accounting for 0.22 equiv. Et_2O). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.86-5.75 (m, 1H, CH), 5.18-5.11 (m, 2H, CHC<u>H</u>$_2$), 2.32 (br d, 2H, *J* = 6.8 Hz, CH_2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 134.8 (CH), 117.7 (CH<u>C</u>H$_2$), 60.9 (qn, *J* = 21.9 Hz, CD_2), 36.9 (CH_2). ^{1}H-NMR data is consistent with the literature.[315]

1-(1-(But-3-en-1-yl-1,1-*d*$_2$)-1*H*-pyrrol-2-yl)-2,2,2-trichloroethan-1-one 369



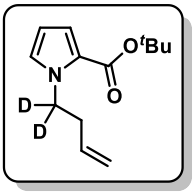
Diisopropyl azodicarboxylate (0.12 mL, 0.61 mmol) was added dropwise to a stirred solution of triphenylphosphine (0.16 g, 0.60 mmol) in THF (1.5 mL) at -78 °C. The mixture was stirred for 50 min and but-3-en-1,1-*d*$_2$-1-ol (81% solution in Et_2O, 61 mg, 0.67 mmol) was added dropwise. After a further 1 h, 2-(trichloroacetyl)pyrrole (0.13 g, 0.59 mmol) was added in one portion and the reaction mixture was warmed to RT. After 21 h, the reaction mixture was concentrated *in vacuo* and the residue triturated in Et_2O/petrol (2:3, 5 mL) at -10 °C and filtered. The residue was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-2% Et_2O/petrol, to give the product as a light-yellow oil (94 mg, 59%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, 1H, *J* = 4.4, 1.6 Hz, ArCH), 7.00-6.99 (m, 1H, ArCH), 6.23-6.21 (m, 1H, ArCH), 5.82-5.71 (m, 1H, CH), 5.08-5.02 (m, 2H, CHC<u>H</u>$_2$), 2.50 (d, 1H, *J* = 6.9 Hz, NCD_2CH_2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.6 (CO), 134.0 (CH), 133.1 (ArCH), 124.7 (ArCH), 121.0 (ArC), 117.8 (CH<u>C</u>H$_2$), 108.9 (ArCH), 96.4 (C), 49.5 (qn, *J* = 21.8 Hz, CD_2), 35.2 (NCD_2<u>C</u>H$_2$); υ_{max}/cm^{-1} 1666.7, 1458.8, 1408.6, 1354.5, 1319.3, 1057.5, 842.7, 802.2, 741.3, 686.1; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 267.9948, $[C_{10}H_9D_2ClNO]^+$ requires 268.0032.

1-(But-3-en-1-yl-1,1-*d*$_2$)-1*H*-pyrrole-2-carboxylic acid 370



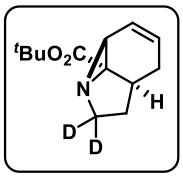
NaOH (2 M aqueous solution, 26 mL) was added to a stirred solution of 1-(1-(but-3-en-1-yl-1,1-*d*$_2$)-1*H*-pyrrol-2-yl)-2,2,2-trichloroethan-1-one (3.93 g, mmol) in THF (14 mL) and the reaction mixture was heated to 60 °C for 16 h. The reaction was neutralised with HCl (3 M aqueous solution), extracted with EtOAc (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was used directly in the next step without further purification (2.29 g, 93 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, 1H, *J* = 4.2, 1.8 Hz, ArCH), 6.88 (app t, 1H, ArCH), 6.16-6.14 (m, 1H, ArCH), 5.81-5.71 (m, 1H, CH), 5.07-5.02 (m, 2H, CHC<u>H</u>$_2$), 2.52 (d, 2H, *J* = 7.1 Hz, NCD_2CH_2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.9 (CO), 134.4 (CH), 130.0 (ArCH), 122.2 (ArC), 120.4 (ArCH), 117.4 (CH<u>C</u>H$_2$), 108.3 (ArCH), 48.3 (qn, *J* = 21.2 Hz, CD_2), 35.7 (NCD_2<u>C</u>H$_2$); υ_{max}/cm^{-1} 2973.1, 1664.2, 1462.9, 1428.7, 1312.93, 1256.2, 1098.5, 1079.6, 1054.7, 740.5; *m/z* HRMS (ES$^-$) found $[M - H]^-$ 166.0837, $[C_9H_9DNO_2]^+$ requires 166.0843.

***tert*-Butyl 1-(but-3-en-1-yl-1,1-d_2)-1*H*-pyrrole-2-carboxylate 371**



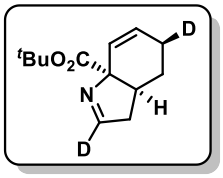
Oxalyl chloride (0.90 mL, 10.66 mmol) was added dropwise over 5 min to a stirred solution of 1-(but-3-en-1-yl)-1*H*-pyrrole-2-carboxylic-3-*d* acid (1.72 g, 10.35 mmol) and DMF (1 drop) in CH_2Cl_2 (24 mL) at -10 °C. The reaction mixture was warmed to RT for 45 min then cooled to 0 °C and potassium *tert*-butoxide (3.48 g, 31.05 mmol) was added portion wise over 5 min. The reaction was warmed to RT, stirred for 2.5 h and quenched with H_2O (20 mL). The mixture was separated, extracted with CH_2Cl_2 (2 x 30 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-4% EtOAc/petrol, to give the product as a yellow oil (1.81 g, 79%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.89-6.87 (m, 1H, ArCH), 6.78-6.76 (m, 1H, CH), 6.07 (dd, 1H, *J* = 3.9, 2.6 Hz, ArCH), 5.81-5.71 (m, 1H, C<u>H</u>CH_2), 5.07-5.01 (m, 2H, CHC<u>H</u>$_2$), 2.49 (d, 2H, *J* = 6.8 Hz, NCD_2CH_2), 1.55 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.6 (CO), 134.7 (<u>C</u>HCH_2), 128.1 (ArCH), 123.2 (ArC), 117.9 (ArCH), 117.1 (CH<u>C</u>H_2), 107.4 (ArCH), 80.2 (C), 48.1 (qn, *J* = 21.7 Hz, CD_2), 35.8 (NCD_2<u>C</u>H_2), 28.4 (CH_3); υ_{max}/cm^{-1} 1696.9, 1413.3, 1367.7, 1315.9, 1250.8, 1178.1, 1144.6, 1121.8, 1097.4, 735.6; *m/z* HRMS (ESI$^+$) found $[M + Na]^+$ 246.1444, $[C_{13}H_{17}D_2NNaO_2]^+$ requires 246.1439.

(±)-*tert*-Butyl (3^1*R*,3a*S*,6a*S*)-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*]indole-3^1(2*H*)-carboxylate-2,2-d_2 362



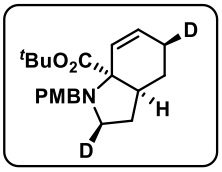
tert-Butyl 1-(but-3-en-1-yl-1,1-d_2)-1*H*-pyrrole-2-carboxylate (1.00 g, 4.48 mmol) in degassed cyclohexane:EtOAc (5.7:1, 470 mL) was irradiated using a water cooled 36 W low pressure Hg lamp. After 14 h, the reaction mixture was concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 5-40% EtOAc/petrol, to give a yellow oil (0.27 g, 27%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.24-6.19 (m, 1H, 5-CH), 5.79 (dt, 1H, *J* = 10.1, 3.4 Hz, 6-CH), 3.22-3.19 (m, 1H, 3-CH), 2.85 (d, 1H, *J* = 3.8 Hz, 7-CH), 2.53 (t, 1H, *J* = 11.2 Hz, 2-CH), 2.30 (br d, *J* = 17.6 Hz, 4-CH), 1.92 (dd, 1H, *J* = 17.6, 6.3 Hz, 4-CH), 1.51 (br s, 1H, 2-CH) superimposed on 1.48 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 171.6 (CO), 135.0 (5-CH), 120.7 (6-CH), 81.2 (<u>C</u>$(CH_3)_3$), 52.4 (C), 49.2 (qn, *J* = 21.2 Hz, CD_2), 43.4 (7-CH), 41.0 (2-CH_2), 33.5 (3-CH), 29.5 (4-CH_2), 28.0 (CH_3); υ_{max}/cm^{-1} 2975.9, 2932.9, 1714.2, 1367.7, 1324.0, 1303.7, 1276.2, 1252.9, 1149.6, 1057.6; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 224.1614, $[C_{13}H_{18}D_2NO_2]^+$ requires 224.1620.

(±)-*tert*-Butyl (3a*S*,5*S*,7a*S*)-3,3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate-2,5-d_2 361



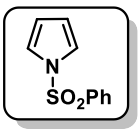
(±)-*tert*-Butyl (3^1*R*,3a*S*,6a*S*)-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*]indole-3^1(2*H*)-carboxylate-2,2-d_2 (0.25 g, 1.12 mmol) was stirred in PhMe (10 mL) at 100 °C for 16 h. The reaction mixture was concentrated *in vacuo* to give the crude material as a brown oil which was used directly in the next step without further purification (0.25 g, *quant.*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, 1H, *J* = 10.2, 2.0 Hz, 7-CH), 5.97 (dd, 1H, *J* = 10.2, 3.3 Hz, 6-CH), 2.86-2.79 (m, 1H, 2-CH), 2.76-2.70 (m, 1H, 3-CH), 2.39 (dd, 1H, *J* = 17.1, 5.2 Hz, 2-CH), 1.95 (br s, 1H, 5-CH), 1.84 (dt, 1H, *J* = 13.2, 4.9 Hz, 4-CH), 1.44 (s, 9H, CH_3), 1.41-1.34 (m, 1H, 4-CH), 1.46 (s, 9H, CH_3), 1.39-1.34 (m, 1H, 4-CH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.0 (CO), 167.4 (t, *J* = 28.1 Hz, NCD), 130.0 (6-CH), 126.8 (7-CH), 81.4 ($\underline{C}(CH_3)_3$), 80.9 (C), 42.7 (2-CH_2), 37.2 (3-CH), 27.9 (CH_3), 24.8 (4-CH_2), 21.2 (t, *J* = 19.3 Hz, CD); υ_{max}/cm^{-1} 2976.7, 2930.2, 1722.8, 1392.5, 1367.7, 1254.5, 1162.8, 1092.5, 1064.7, 847.8; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 224.1615, $[C_{13}H_{18}D_2NO_2]^+$ requires 224.1620.

(±)-*tert*-Butyl (2*R*,3a*S*,5*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate-2,5-d_2 360



According to general procedure A, crude (±)-*tert*-butyl (3a*S*,5*S*,7a*S*)-3,3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate-2,5-d_2 (0.24 g, 1.07 mmol) and *p*-anisaldehyde (0.13 mL, 1.07 mmol) were stirred with sodium triacetoxyborohydride (0.68 g, 3.21 mmol) in CH_2Cl_2 (5 mL). The crude material was purified by SiO_2 flash chromatography, 0-10% EtOAc/petrol, to give the product as a yellow oil (0.15 g, 41%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 2H, *J* = 8.8 Hz, ArCH), 6.83 (d, 2H, *J* = 8.8 Hz, ArCH), 6.01 (dd, 1H, *J* = 10.4, 4.0 Hz, 7-CH), 5.85 (dd, 1H, *J* = 10.4, 1.9 Hz, 6-CH), 3.79 (dd, 1H, *J* = 13.0 Hz, $ArCH_2$), superimposed on 3.79 (s, 3H, OCH_3), 3.60 (dd, 1H, *J* = 13.0 Hz, $ArCH_2$), 2.67 (dd, 1H, *J* = 9.1, 4.8 Hz, 1-CHD), 2.61-2.55 (m, 1H, 3-CH), 2.02-1.94 (m, 2H, 2-CH and 5-CHD), 1.72 (dt, 1H, *J* = 13.2, 4.7 Hz, 4-CH), 1.62 (app qn, 1H, 4-CH), 1.50 (s, 9H, CH_3), 1.47-1.46 (m, 1H, 2-CH);^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.8 (CO), 158.4 (ArC), 132.8 (ArC), 130.6 (7-CH), 129.4 (ArCH), 124.8 (6-CH), 113.5 (ArCH), 80.8 ($\underline{C}(CH_3)_3$), 69.0 (C), 55.2 (OCH_3), 53.4 ($ArCH_2$), 49.4 (t, *J* = 20.6 Hz, 2-CDH), 40.4 (3-CH), 28.2 (CH_3), 27.3 (2-CH_2), 25.4 (4-CH_2), 22.1 (t, *J* = 19.2 Hz, 5-CDH); υ_{max}/cm^{-1} 2932.6, 1716.8, 1612.3, 1511.2, 1366.9, 1244.7, 1163.9, 1038.8, 845.9, 821.1; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 346.2352, $[C_{21}H_{28}D_2NO_3]^+$ requires 346.2351.

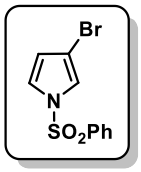
1-(Phenylsulfonyl)-1*H*-pyrrole 372



Pyrrole (8.0 mL, 0.12 mol) was added dropwise over 20 min to a stirred solution of NaH (60% in mineral oil, 5.60 g, 0.14 mol) in DMF (100 mL) at 0 ºC. The reaction was warmed to RT, stirred for 5 min then cooled back to 0 ºC, at which point benzenesulfonyl chloride (15.50 mL, 0.12 mol) was added dropwise over 8 min. The reaction was warmed to RT and

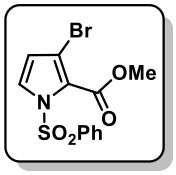
stirred for 17 h, quenched with H_2O (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated i*n vacuo*. The crude product was purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to give a yellow solid. This was further purified by trituration (5% Et_2O/hexane, 100 mL) to give the product as a yellow solid (15.28 g, 61%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H, ArCH), 7.60 (app tt, 1H, ArCH), 7.52-7.48 (m, 2H, ArCH), 7.17 (t, 2H, *J* = 2.3 Hz, NCH), 6.30 (t, 2H, *J* = 2.3 Hz, NCHC<u>H</u>); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.1 (ArC), 133.8 (ArCH), 129.4 (ArCH), 126.8 (ArCH), 120.8 (NCH), 113.7 (NCH<u>C</u>H); m.p. ˚C (EtOAc/petrol) 88-89 ˚C, lit. 88.5-89.3 ˚C.[316] ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[316]

3-Bromo-1-(phenylsulfonyl)-1*H*-pyrrole 373



A solution of bromine (3.0 mL, 57.90 mmol) in AcOH (20 mL) was added to a stirred solution of 1-(phenylsulfonyl)-1*H*-pyrrole (10.0 g, 48.25 mmol) in AcOH (120 mL) and the reaction mixture was heated under reflux. After 2 h, the reaction was cooled to RT, concentrated *in vacuo* and dissolved in EtOAc (100 mL) and $Na_2S_2O_3$ (1M aqueous solution, 50 mL). The organic layer was extracted with EtOAc (2 x 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated i*n vacuo*. The crude product was purified by SiO_2 flash chromatography, eluting with 0-5% EtOAc/petrol, to give a pink solid (9.71 g, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87-7.86 (d, 2H, *J* = 7.6 Hz, ArCH), 7.63 (t, 1H, *J* = 7.5 Hz, ArCH), 7.57-7.50 (m, 2H, ArCH), 7.20-7.17 (m, 1H, NCHCBr), 7.09 (t, 2H, *J* = 2.7 Hz, NCH), 6.30 (br s, 1H, NCHC<u>H</u>); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.4 (ArC), 134.2 (ArCH), 129.6 (ArCH), 127.0 (ArCH), 121.3 (NCH), 119.7 (N<u>C</u>HCBr), 116.4 (NCH<u>C</u>H) 102.2 (CBr); m.p. 73-75 ˚C (EtOAc/petrol), lit. 66.5-67 ˚C.[317] ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[317]

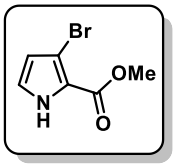
Methyl 3-bromo-1-(phenylsulfonyl)-1*H*-pyrrole-2-carboxylate 375



n-BuLi (2.5 M solution in hexanes, 16.40 mL, 41.0 mmol) was added dropwise over 10 min to a stirred solution of diisopropylamine (7.20 mL, 51.26 mmol) in THF (120 mL) at -78 ºC. The reaction mixture was stirred for 15 min, warmed to 0 ºC for 5 min then cooled to -78 ºC, at which point 3-bromo-1-(phenylsulfonyl)-1H-pyrrole (9.71 g, 34.17 mmol) in THF (33 mL) was added dropwise over 10 min. The reaction mixture was stirred for 1 h at -78 ºC and methyl chloroformate (5.80 mL, 75.17 mmol) in THF (33 mL) was added dropwise over 10 min. After stirring for a further hour, the reaction mixture was warmed to RT, quenched with NH_4Cl (saturated aqueous solution, 300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated i*n vacuo*. The crude product was purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to give an orange liquid (9.34 g, 79%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H, ArCH), 7.68-7.63 (m, 1H, ArCH), 7.58-7.54 (m, 3H, ArCH and NCH), 6.41 (d, 1H, *J* = 3.4 Hz, NCHC<u>H</u>), 3.80 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$)

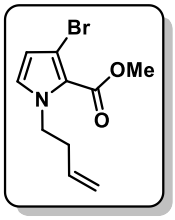
δ 159.3 (CO), 138.7 (ArC), 134.1 (ArCH), 129.0 (ArCH), 127.9 (ArCH), 126.8 (NCH), 115.3 (NCHCH), 109.7 (CBr), 52.1 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[316]

Methyl 3-bromo-1*H*-pyrrole-2-carboxylate 376



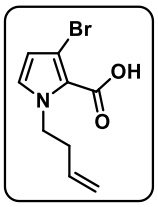
Tetrabutylammonium fluoride (1 M solution in THF, 52.0 mL) was added to a stirred solution of methyl 3-bromo-1-(phenylsulfonyl)-1*H*-pyrrole-2-carboxylate (9.30 g, 27.02 mmol) in THF (27 mL) and the reaction was heated to 65 ºC for 5 h. The reaction mixture was cooled to RT, concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-100% EtOAc/petrol, to afford a pink solid (4.79 g, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.20 (br s, 1H, NH), 6.87 (t, 1H, *J* = 3.1 Hz, NCH), 6.34 (t, 1H, *J* = 3.1 Hz, NCHCH), 3.89 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.5 (CO), 122.4 (NCH), 116.9 (C), 114.9 (NCHCH), 103.6 (CBr), 51.7 (CH_3); m.p. 197-198 ˚C (EtOAc/petrol), lit. 202-204 ˚C.[318] ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[318]

Methyl 3-bromo-1-(but-3-en-1-yl)-1*H*-pyrrole-2-carboxylate 377



Diisopropyl azodicarboxylate (4.80 mL, 24.42 mmol) was added dropwise over 5 min to a stirred solution of triphenylphosphine (6.28 g, 23.95 mmol) in THF (70 mL) at -78 °C. The mixture was stirred for 50 min and 3-buten-1-ol (2.28 mL, 26.53 mmol) was added dropwise over 5 min. After a further 1 h, methyl 3-bromo-1H-pyrrole-2-carboxylate (4.79 g, 23.48 mmol) was added in one portion and the reaction mixture was warmed to RT. After 17 h, the reaction mixture was concentrated *in vacuo* and the residue triturated in Et_2O/petrol (2:3, 70 mL) at -10 °C and filtered. The residue was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-10% EtOAc/petrol, to give the product as a yellow oil (5.97 g, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.74 (d, 1H, *J* = 2.8 Hz, ArCH), 6.22 (d, 1H, *J* = 2.8 Hz, ArCH), 5.78-5.67 (m, 1H, C<u>H</u>CH_2), 5.08-5.02 (m, 2H, CHC<u>H</u>$_2$), 4.39 (t, 2H, *J* = 7.2 Hz, NCH_2), 3.87 (s, 3H, CH_3), 2.50-2.45 (m, 2H, NCH_2C<u>H</u>$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.9 (CO), 134.1 (<u>C</u>HCH_2), 128.1 (ArCH), 117.6 (CH<u>C</u>H_2), 112.7 (ArCH), 105.1 (CBr), 95.2 (C), 51.2 (OCH_3), 50.3 (NCH_2), 35.8 (NCH_2<u>C</u>H_2); υ_{max}/cm^{-1} 1702.7, 1436.0, 1403.8, 1326.2, 1249.2, 1205.0, 1106.4, 1127.5, 923.3, 775.7; *m/z* HRMS (ESI$^+$) found $[M + Na]^+$ 279.9944, $[C_{10}H_{12}{}^{79}BrNO_2Na]^+$ requires 279.9949.

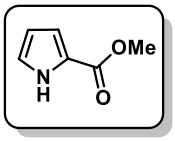
3-Bromo-1-(but-3-en-1yl)-1*H*-pyrrole-2-carboxylic acid 378



NaOH (2 M aqueous solution, 35 mL) was added to a stirred solution of methyl 3-bromo-1-but-3-en-1-yl)-1*H*-pyrrole carboxylate (5.60 g, 21.70 mmol) in THF (20 mL). After 16 h, the reaction mixture was heated under reflux for 24 h, cooled to 0 °C and quenched with HCl (3 M aqueous solution, 40 mL). The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was used directly in the next step without further

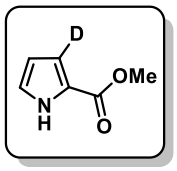
purification (4.73 g, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.82 (d, 2H, *J* = 2.7 Hz, ArCH), 6.29 (d, 2H, *J* = 2.7 Hz, ArCH), 5.79-5.68 (m, 1H, C<u>H</u>CH_2), 5.08-5.02 (m, 2H, CHC<u>H</u>$_2$), 4.37 (t, 2H, *J* = 7.3 Hz, NCH_2), 2.54-2.48 (m, 2H, CH_2C<u>H</u>$_2$).

Methyl 1*H*-pyrrole-2-carboxylate 379



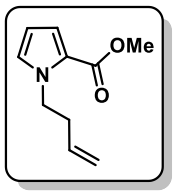
Pd/C (5% wt., 40 mg) was added to a stirred solution of methyl 3-bromo-1*H*-pyrrole-2-carboxylate (0.10 g, 0.49 mmol) in MeOH (49 mL) and the reaction mixture was hydrogenated for 16 h at 50 ºC. The reaction mixture was cooled to RT, filtered through celite and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 10% EtOAc/petrol, to afford a colourless solid (33 mg, 54%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.37 (br s, 1H, NH), 6.97-6.95 (m, 1H, NCH), 6.93-6.91 (m, 1H, NCHCHC<u>H</u>), 6.26 (app dt, 1H, NCHC<u>H</u>), 3.86 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.7 (CO), 122.9 (NCH), 122.6 (C), 115.3 (NCHCH<u>C</u>H), 110.41 (NCH<u>C</u>H), 51.4 (CH_3) m.p. 66-68 ˚C (EtOAc/petrol), lit. 72-73 ˚C.[319] ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[319]

Methyl 1*H*-pyrrole-2-carboxylate-3-*d* 380



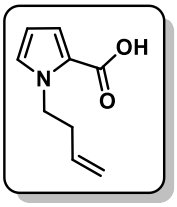
Pd/C (5% wt., 4.71 g) and K_2CO_3 (4.71 g, 34.09 mmol) were added to a stirred solution of methyl 3-bromo-1*H*-pyrrole-2-carboxylate (5.74 g, 28.41 mmol) in MeOH-d_4 (145 mL) and the reaction mixture was hydrogenated with deuterium for 5.5 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude material was dissolved in Et_2O (20 mL), washed with H_2O (20 mL) and extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used directly in the next step without further purification (37 mg, 59%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.30 (br s, 1H, NH), 6.94 (t, 1H, *J* = 2.7 Hz, ArCH), 6.24 (t, 1H, *J* = 2.7 Hz, ArCH) 3.84 (s, 3H, OCH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 161.7 (CO), 122.9 (ArCH), 122.5 (ArC), 115.0 (t, *J* = 26.7 Hz, ArCD), 110.3 (ArCH), 51.4 (OCH_3).

Methyl 1-(but-3-en-1-yl)-1*H*-pyrrole-2-craboxylate 381



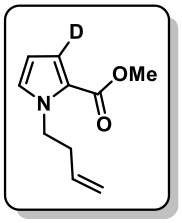
$Ba(OH)_2$ (61 mg, 0.36 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added to a stirred solution of methyl 3-bromo-1-(but-3-en-1-yl)-1*H*-pyrrole-2-carboxylate (61 mg, 0.24 mmol) in DMF:H_2O (5:1, 10 mL) and heated to 120 °C for 8 h. The reaction mixture was filtered through celite, washed with EtOAc (4 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography, eluting with 0-30% EtOAc/petrol, to give the product as a colourless oil (14 mg, 33%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.05-6.94 (m, 1H, ArCH), 6.83 (app t, 1H, ArCH), 6.11-6.10 (m, 1H, ArCH), 5.81-5.71 (m, 1H, C<u>H</u>CH_2), 5.07-5.02 (m, 2H, CHC<u>H</u>$_2$), 4.37 (t, 1H, *J* = 7.0 Hz, NCH_2), 3.81 (s, 3H, OCH_3), 2.51 (app q, 1H, NCH_2C<u>H</u>$_2$). ^{1}H-NMR data is consistent with the literature.[204]

1-(But-3-en-1-yl)-1*H*-pyrrole-2-carboxylic acid 382



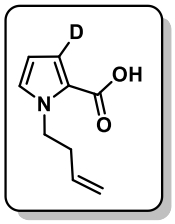
$Ba(OH)_2$ (57 mg, 0.33 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added to a stirred solution of 3-bromo-1-(but-3-en-1-yl)-1*H*-pyrrole-2-carboxylic acid (54 mg, 0.22 mmol) in DMF:H_2O (5:1, 10 mL) and heated to 120 °C for 4.5 h. The reaction mixture was filtered through celite, washed with EtOAc (4 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by SiO_2 flash chromatography, eluting with 0-30% EtOAc/petrol, to give the product as a yellow oil (6 mg, 16%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, 1H, *J* = 4.1, 1.9 Hz, ArCH), 6.88 (app t, 1H, ArCH), 6.15 (dd, 1H, *J* = 3.8, 2.8 Hz, ArCH), 5.81-5.71 (m, 1H, C<u>H</u>CH_2), 5.07-5.02 (m, 2H, CHC<u>H</u>$_2$), 4.37 (t, 1H, *J* = 6.7 Hz, NCH_2), 3.48 (app q, 1H, $NCH_2C\underline{H}_2$).

Methyl 1(but-3-en-1yl)-1*H*-pyrrole-2-carboxylate-3-*d* 383



K_2CO_3 (0.15 g, 1.11 mmol), tetrabutylammonium iodide (29 mg, 0.08 mmol) and 4-bromo-1-butene (0.16 mL, 1.58 mmol) was added to a stirred solution of methyl 1*H*-pyrrole-2-carboxylate-3-*d* (0.1 g, 0.79 mmol) in 2-butanone (1.5 mL) and the reaction mixture was heated under reflux. After 24 h, the reaction mixture was cooled to RT, filtered, concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-5% EtOAc/petrol, to give the product as a yellow solid (0.14 g, *quant.*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.83 (d, 1H, *J* = 2.7 Hz, ArCH), 6.11 (d, 1H, *J* = 2.7 Hz, ArCH), 5.81-5.71 (m, 1H, CH), 5.07-5.02 (m, 2H, CHCH), 4.36 (d, 2H, *J* = 7.4 Hz, NCH_2), 3.81 (s, 3H, CH_3), 2.51 (app q, 2H, $NCH_2C\underline{H}_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 161.5 (CO), 134.6 (<u>C</u>HCH_2), 128.8 (ArCH), 121.3 (ArC), 118.0 (t, *J* = 25.9 Hz, ArCD), 117.21 (CH<u>C</u>H_2), 107.7 (ArCH), 51.0 (OCH_3), 48.7 (NCH_2), 35.9 ($NCH_2\underline{C}H_2$); υ_{max}/cm^{-1} 1703.4, 1512.9, 1436.6, 1409.6, 1332.2, 1247.3, 1108.1, 1089.8, 786.6, 678.2; *m/z* HRMS (APCI$^+$) found $[M + H]^+$ 181.1078, $[C_{10}H_{13}DNO_2]^+$ requires 181.1087.

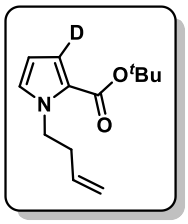
1-(But-3-en-1-yl)-1*H*-pyrrole-2-carboxylic-3-*d* acid 384



NaOH (2 M aqueous solution, 21 mL) was added to a stirred solution of methyl 1(but-3-en-1yl)-1*H*-pyrrole-2-carboxylate-3-*d* (2.36 g, 13.09 mmol) in THF (11 mL) and the reaction mixture was heated under reflux for 18 h. The reaction mixture was neutralised with HCl (3 M aqueous solution), extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was used directly in the next step without further purification (1.72 g, 79%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.88 (d, 1H, *J* = 2.5 Hz, ArCH), 6.15 (d, 1H, *J* = 2.5 Hz, ArCH), 5.81-5.71 (m, 1H, C<u>H</u>CH_2), 5.07-5.02 (m, 2H, CHC<u>H</u>$_2$), 4.37 (t, 2H, *J* = 7.2 Hz, NCH_2), 2.56-2.51 (m, 2H, $NCH_2C\underline{H}_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.6 (CO), 134.5 (<u>C</u>HCH_2), 130.0 (ArCH), 120.6 (C), 120.19 (t, *J* = 25.0 Hz, ArCD), 117.4 (CH<u>C</u>H_2), 108.2 (ArCH), 48.9 (NCH_2), 35.9 ($NCH_2C\underline{H}_2$); υ_{max}/cm^{-1}

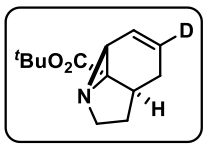
1664.9, 1517.1, 1429.6, 1324.4, 1254.4, 1107.7, 904.0, 727.6, 680.7, 649.9; *m/z* HRMS (ES^-) found $[M - H]^-$ 165.0770, $[C_9H_9DNO_2]^+$ requires 165.0774.

tert-Butyl 1-(but-3-en-1-yl)-1*H*-pyrrole-2-carboxylate-3-*d* 385



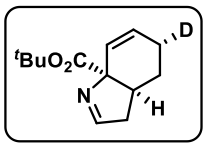
Oxalyl chloride (0.90 mL, 10.66 mmol) was added dropwise over 5 min to a stirred solution of 1-(but-3-en-1-yl)-1*H*-pyrrole-2-carboxylic-3-*d* acid (1.72 g, 10.35 mmol) and DMF (1 drop) in CH_2Cl_2 (24 mL) at -10 °C. The reaction mixture was warmed to RT for 45 min then cooled to 0 °C and potassium *tert*-butoxide (3.48 g, 31.05 mmol) was added portion wise over 5 min. The reaction was warmed to RT, stirred for 2.5 h and quenched with H_2O (20 mL). The mixture was separated, extracted with CH_2Cl_2 (2 x 30 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-4% EtOAc/petrol, to give the product as a yellow oil (1.81 g, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.77 (d, 1H, *J* = 2.6 Hz, ArCH), 6.07 (d, 1H, *J* = 2.5 Hz, ArCH), 5.81-5.71 (m, 1H, C<u>H</u>CH_2), 5.07-5.01 (m, 2H, CHC<u>H</u>$_2$), 4.34 (t, 2H, *J* = 7.1 Hz, NCH_2), 2.54-2.48 (m, 2H, NCH_2C<u>H</u>$_2$), 1.55 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.6 (CO), 134.7 (<u>C</u>HCH_2), 128.1 (ArCH), 123.1 (ArC), 117.7 (t, *J* = 26.6 Hz, ArCD), 117.1 (CH<u>C</u>H_2), 107.3 (ArCH), 80.2 ($C(CH_3)$), 48.6 (NCH_2), 36.0 (NCH_2CH_2), 28.4 (CH_3); υ_{max}/cm^{-1} 1696.0, 1409.2, 1247.4, 1167.2, 1126.2, 1103.2, 904.1, 726.8, 678.3, 649.6; *m/z* HRMS (ESI^+) found $[M + Na]^+$ 245.1369, $[C_{13}H_{18}DNO_2Na]^+$ requires 245.1376.

(±)-_tert_-Butyl (3^1*R*,3a*S*,6a*S*)-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*]indole-3^1(2*H*)-carboxylate-5-*d* 365



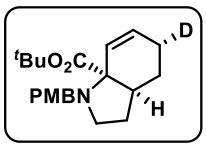
tert-Butyl 1-(but-3-en-1-yl)-1*H*-pyrrole-2-carboxylate-3-*d* (1.00 g, 4.50 mmol) in degassed cyclohexane:EtOAc (5.7:1, 470 mL) was irradiated using a water cooled 36 W low pressure Hg lamp. After 14 h, the reaction mixture was concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-30% EtOAc/petrol, to give a yellow oil (0.40 g, 40%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.76 (br t, 1H, *J* = 3.1 Hz, 6-CH), 3.22-3.14 (m, 2H, 1-CH and 3-CH), 2.81 (d, 1H, *J* = 3.8 Hz, 7-CH), 2.57-2.45 (m, 2H, 1-CH and 2-CH), 2.27 (dt, 1H, *J* = 17.8, 3.6 Hz, 4-CH), 1.89 (d, 1H, *J* = 17.8 Hz, 4-CH), 1.52-1.49 (m, 1H, 2-CH), 1.45 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 171.6 (CO), 134.6 (t, *J* = 24.4 Hz, CD), 120.5 (6-CH), 81.2 ($C(CH_3)$), 52.4 (C), 49.8 (1-CH_2), 43.5 (7-CH), 41.2 (2-CH_2), 33.4 (3-CH), 29.4 (4-CH_2), 28.0 (CH_3); υ_{max}/cm^{-1} 2973.1, 2894.9, 1713.4, 1392.6, 1367.1, 1302.2, 1250.6, 1150.8, 1072.9, 1051.1; *m/z* HRMS (ESI^+) found $[M + H]^+$ 223.1553, $[C_{13}H_{19}DNO_2]^+$ requires 223.1557.

(±)-*tert*-Butyl (3a*S*,5*R*,7a*S*)-3,3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate-5-*d* 364



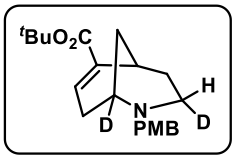
(±)-*tert*-Butyl (3[1]*S*,3a*R*,6a*R*)-1,3a,6,6a-tetrahydoazirino[2,3,1-*hi*]indole-3[1](2*H*) carboxylate-5-*d* (0.38 g, 1.71 mmol) was stirred in PhMe (16 mL) at 100 °C for 16 h. The reaction mixture was concentrated *in vacuo* to give the crude material as a brown oil which was used directly in the next step without further purification (0.36 g, 95%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H, 1-CH), 6.01 (dd, 1H, *J* = 10.1, 1.5 Hz, 6-CH), 5.94 (dd, 1H, *J* = 10.1, 4.3 Hz, 7-CH), 2.83-2.76 (m, 1H, 2-CH), 2.74-2.67 (m, 1H, 3-CH), 2.40-2.33 (m, 1H, 2-CH), 1.98 (br s, 1H, 5-CH), 1.85-1.78 (m, 1H, 4-CH), 1.44 (s, 9H, CH_3), 1.41-1.34 (m, 1H, 4-CH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.1 (CO), 167.8 (1-CH), 129.9 (6-CH), 126.8 (7-CH), 81.3 (C), 80.9 (C), 42.7 (2-CH_2), 37.2 (3-CH), 27.9 (CH_3), 24.6 (4-CH_2), 21.1 (t, *J* = 19.6 Hz, 5-CDH); υ_{max}/cm^{-1} 2975.4, 2927.6, 1722.0, 1367.4, 1248.6, 1159.5, 1126.9, 1079.2, 1055.6, 846.6; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 223.1554, $[C_{13}H_{19}DNO_2]^+$ requires 223.1557.

(±)-*tert*-Butyl (3a*S*,5*R*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate-5-*d* 363



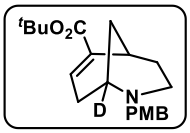
According to general procedure A, crude (±)-*tert*-butyl (3a*S*,7a*R*)-3-3a,4,5-tetrahydro-7a*H*-indole-7a-carboxylate-5-*d* (0.34 g, 1.53 mmol) and *p*-anisaldehyde (0.19 mL, 1.53 mmol) were stirred with sodium triacetoxyborohydride (0.97 g, 4.86 mmol) in CH_2Cl_2 (7 mL). The crude material was purified by SiO_2 flash chromatography, 0-5% EtOAc/petrol, to give the product as a yellow oil (0.39 g, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 2H, *J* = 8.7 Hz, ArCH), 6.83 (d, 2H, *J* = 8.7 Hz, ArCH), 6.01 (dd, 1H, *J* = 10.5, 3.4 Hz, 6-CH), 5.84 (dd, 1H, *J* = 10.5, 2.04 Hz, 7-CH), 3.81 (d, 1H, *J* = 13.6 Hz, ArC<u>H</u>H), superimposed on 3.79 (s, 3H, OCH_3), 3.58 (d, 1H, *J* = 13.6 Hz, ArCH<u>H</u>), 2.69 (td, 1H, *J* = 9.2, 4.8 Hz, 1-CH), 2.63-2.51 (m, 2H, 1-CH and 3-CH), 2.07 (br s, 1H, 5-CH), 2.03-1.93 (m, 1H, 2-CH), 1.76-1.69 (m, 1H, 4-CH), 1.65-1.59 (m, 1H, 4-CH), 1.54-1.50 (m, 1H, 2-CH) superimposed on 1.50 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.8 (CO), 158.4 (ArC), 132.8 (ArC), 130.6 (6-CH), 129.4 (ArCH), 124.7 (7-CH), 113.5 (ArCH), 80.7 (C(CH_3)), 69.0 (C), 55.2 (OCH_3), 53.4 ($ArCH_2$), 49.8 (1-CH_2), 40.4 (3-CH), 28.2 (CH_3), 27.3 (2-CH_2), 25.3 (4-CH_2), 22.0 (t, *J* = 17.9 Hz, CDH); υ_{max}/cm^{-1} 29712.0, 2929.5, 1716.4, 1510.8, 1366.6, 1243.4, 1161.4, 1074.8, 1065.6, 1042.4; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 345.2278, $[C_{21}H_{29}DNO_3]^+$ requires 345.2288.

(±)-*tert*-Butyl 2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate-1,3-d_2 386



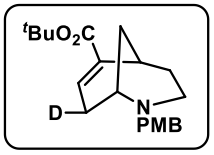
According to general procedure D, (±)-*tert*-butyl (2*R*,3a*S*,5*S*,7a*R*)-1-(4-methoxybenzyl) -1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate-2,5-d_2 (52 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 10-25% EtOAc/petrol, to give a yellow oil (20 mg, 38%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H, *J* = 9.0 Hz, ArCH), 7.07 (t, 1H, *J* = 3.8 Hz, 7-CH), 6.85 (d, 2H, *J* = 9.0 Hz, ArCH), 3.79 (s, 3H, OCH_3), 3.50 (d, 2H, *J* = 3.4 Hz, $ArCH_2$), 3.00 (br s, 0.7H, 1-CH), 2.88 (t, 1H, *J* = 3.2 Hz, 5-CH), 2.48 (br dd, 1H, *J* = 20.0, 4.5 Hz, 8-CH), 2.23 (dd, 1H, *J* = 12.8, 3.0 Hz, 3-CHD), 2.06-1.99 (m, 1H, 8-CH), 1.95-1.92 (m, 1H, 9-CH), 1.83 (td, 1H, *J* = 12.9, 4.4 Hz, 4-CH) 1.59-1.53 (m, 1H, 9-CH), 1.48 (s, 9H, CH_3), 1.43-1.42 (m, 1H, 4-CH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.9 (CO), 158.6 (ArC), 140.1 (7-CH), 134.4 (6-C), 131.0 (ArC), 129.9 (ArCH), 113.6 (ArCH), 79.9 (C), 58.8 ($ArCH_2$), 55.2 (OCH_3), 49.5 (1-CH), 49.0 (t, *J* = 21.1 Hz, 1-CD), 43.8 (t, *J* = 20.5 Hz, 3-CDH), 31.8 (9-CH_2), 28.7 (4-CH_2), 28.2 (CH_3), 26.9 (5-CH), 24.8 (8-CH_2); υ_{max}/cm^{-1} 2929.4, 1724.7, 1512.2, 1367.3, 1301.7, 1244.3, 11551.4, 1105.3, 1037.3, 835.8; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 346.2330, $[C_{21}H_{28}D_2NO_3]^+$ requires 345.2288.

(±)-*tert*-Butyl 2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate-1-*d* 387



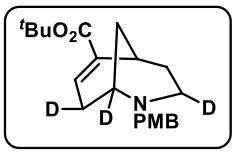
According to general procedure D, (±)-*tert*-butyl (3a*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate-5-*d* (52 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. The crude material was purified by SiO_2 flash chromatography, eluting with 5-50% EtOAc/petrol to give a yellow oil (25 mg, 48%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H, *J* = 8.7 Hz, ArCH), 7.07 (t, 1H, *J* = 3.6 Hz, 7-CH), 6.85 (d, 2H, *J* = 8.7 Hz, ArCH), 3.80 (s, 3H, OCH_3), 3.50 (d, 2H, *J* = 5.1 Hz, $ArCH_2$), 2.98 (br s, 0.4H, 1-CH), 2.87 (br s, 1H, 5-CH), 2.54-2.43 (m, 2H, 3-CH and 8-CH), 2.24 (td, 1H, *J* = 12.2, 3.1 Hz, 3-CH), 2.05-1.90 (m, 2H, 8-CH and 9-CH), 1.87-1.79 (m, 1H, 4-CH), 1.58-1.53 (m, 1H, 9-CH), 1.48 (s, 9H, CH_3) superimposed on 1.48-1.46 (m, 1H, 4-CH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.9 (CO), 158.6 (ArC), 140.2 (7-CH), 134.4 (6-C), 131.3 (ArC), 129.9 (ArCH), 113.6 (ArCH), 79.9 (C), 58.8 ($ArCH_2$), 55.2 (OCH_3), 49.5 (1-CH), 49.0 (t, *J* = 20.8 Hz, 1-CD), 44.2 (3-CH_2), 31.7 (9-CH_2), 28.9 (4-CH_2), 28.2 (CH_3), 26.9 (5-CH), 24.7 (8-CH_2); υ_{max}/cm^{-1} 2931.6, 1702.2, 1512.1, 1367.0, 1247.2, 1168.5, 1072.4, 903.2, 724.3, 649.9; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 345.2280, $[C_{21}H_{29}DNO_3]^+$ requires 345.2288.

(±)-*tert*-Butyl 2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate-8-d_1 388



(±)-*tert*-Butyl (3a*S*,7a*R*) -1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (52 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid-*d* (0.6 M solution in dioxane, 0.25 mL, 0.15 mmol) was added and the reaction was heated under reflux for 20 h. The reaction mixture was cooled to RT and $NaHCO_3$ (saturated aqueous solution, 5 mL) was added. The organic layer was extracted with CH_2Cl_2 (3 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 5-25% EtOAc/petrol, to give the deuterated product as a yellow oil (13 mg, 25%) and the unconjugated morphan product (24 mg, 46%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 2H, *J* = 9.0 Hz, ArCH), 7.07 (t, 1H, *J* = 3.9 Hz, 7-CH), 6.85 (d, 2H, *J* = 9.0 Hz, ArCH), 3.79 (s, 3H, OCH_3), 3.49 (d, 2H, *J* = 7.1 Hz, $ArCH_2$), 2.98 (br s, 1H, 1-CH), 2.87 (app t, 1H, 5-CH), 2.54-2.44 (m, 2H, 3-CH and 8-CH), 2.24 (td, 1H, *J* = 11.7, 3.8 Hz, 3-CH), 2.05-1.98 (m, 0.9 H, 8-CH), 1.93 (dt, 1H, *J* = 11.7, 3.4 Hz, 9-CH), 1.83 (tt, 1H, *J* = 12.1, 4.6 Hz, 4-CH) 1.59-1.53 (m, 1H, 9-CH), 1.49 (s, 9H, CH_3) superimposed on 1.48 (m, 1H, 4-CH); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 171.3 (CO), 158.5 (ArC), 140.0 (7-CH), 134.4 (6-C), 131.2 (ArC), 129.8 (ArCH), 113.6 (ArCH), 79.9 (C), 58.9 ($ArCH_2$), 55.2 (OCH_3), 49.5 (1-CH), 44.2 (3-CH_2), 31.8 (9-CH_2), 28.8 (4-CH_2), 28.2 (CH_3), 26.9 (5-CH), 24.3 (t, *J* = 19.2 Hz, 8-CH_2); *m/z* HRMS (ESI^+) found $[M + H]^+$ 344.2226 and 345.2288, $[C_{21}H_{30}NO_3]^+$ requires 344.2226 and $[C_{21}H_{29}DNO_3]^+$ requires 345.2288.

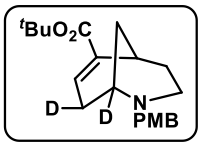
(±)-*tert*-Butyl 2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate-1,3,8-d_3 389



(±)-*tert*-Butyl (2*R*,3a*S*,5*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate-2,5-d_2 (52 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid-*d* (0.6 M solution in dioxane, 0.25 mL, 0.15 mmol) was added and the reaction was heated under reflux for 20 h. The reaction mixture was cooled to RT and $NaHCO_3$ (saturated aqueous solution, 5 mL) was added. The organic layer was extracted with CH_2Cl_2 (3 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 10-50% EtOAc/petrol, to give the deuterated product as a yellow oil (25 mg, 48%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 2H, *J* = 8.6 Hz, ArCH), 7.07 (t, 1H, *J* = 3.5 Hz, 7-CH), 6.84 (d, 2H, *J* = 8.6 Hz, ArCH), 3.79 (s, 3H, OCH_3), 3.49 (d, 2H, *J* = 5.2 Hz, $ArCH_2$), 2.98 (br s, 0.54 H, 1-CH), 2.87 (app t, 1H, 5-CH), 2.50-2.44 (m, 1H, 8-CH), 2.21 (dd, 1H, *J* = 12.5, 3.1 Hz, 3-CH), 2.05-1.98 (m, 0.8 H, 8-CH), 1.94-1.90 (m, 1H, 9-CH), 1.82 (td, 1H, *J* = 12.8, 4.0 Hz, 4-CH), 1.59-1.52 (m, 1H, 9-CH), 1.48 (s, 9H, CH_3) superimposed 1.47-1.45 (m, 1H, 4-CH); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 165.1 (CO), 158.5 (ArC), 140.2 (7-CH), 134.4 (6-C), 131.2 (ArC), 129.9 (ArCH),

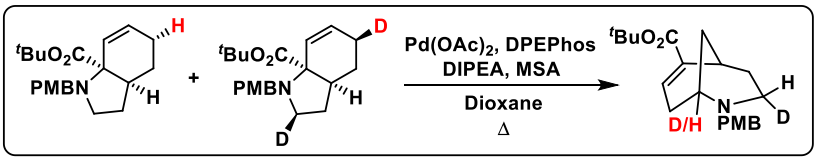
113.6 (ArCH), 79.8 (C), 58.8 ($ArCH_2$), 55.2 (OCH_3), 49.0 (t, *J* = 22.0 Hz, 1-CH), 43.8 (t, *J* = 21.0 Hz, 3-CH_2), 31.9 (9-CH_2), 28.7 (4-CH_2), 28.2 (CH_3), 26.8 (5-CH), 24.4 (t, *J* = 19.0 Hz, 8-CH_2); *m/z* HRMS (ESI^+) found $[M + H]^+$ 345.2296, 346.2357 and 347.2411, $[C_{21}H_{29}DNO_3]^+$ requires 345.2288, $[C_{21}H_{28}D_2NO_3]^+$ requires 346.2351 and $[C_{21}H_{27}D_3NO_3]^+$ requires 347.2411.

(±)-*tert*-Butyl 2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate-1,8-d_2 390



(±)-*tert*-Butyl 2-(4-methoxybenzyl)-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate-1-*d* (52 mg, 0.15 mmol) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid-*d* (0.6 M solution in dioxane, 0.25 mL, 0.15 mmol) was added and the reaction was heated under reflux for 20 h. The reaction mixture was cooled to RT and $NaHCO_3$ (saturated aqueous solution, 5 mL) was added. The organic layer was extracted with CH_2Cl_2 (3 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 5-30% EtOAc/petrol, to give the deuterated product as a yellow oil (24 mg, 46%) and the unconjugated morphan product (9 mg, 17%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H, *J* = 8.6 Hz, ArCH), 7.07 (t, 1H, *J* = 3.84 Hz, 7-CH), 6.85 (d, 2H, *J* = 8.6 Hz, ArCH), 3.79 (s, 3H, OCH_3), 3.49 (d, 2H, *J* = 5.6 Hz, $ArCH_2$), 2.98 (br s, 0.3H, 1-CH), 2.88 (t, 1H, *J* = 3.2 Hz, 5-CH), 2.54-2.43 (m, 2H, 3-CH and 8-CH), 2.24 (td, 1H, *J* = 12.0, 3.0 Hz, 3-CH), 2.01 (dd, 0.8 H, *J* = 20.4, 3.2 Hz, 8-CH), 1.92 (br d, 1H, *J* = 12.3 Hz, 9-CH), 1.83 (tt, 1H, *J* = 13.0, 4.6 Hz, 4-CH), 1.57-1.53 (m, 1H, 9-CH), 1.48 (s, 9H, CH_3) superimposed on 1.47 (m, 1H, 4-CH); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 165.9 (CO), 158.5 (ArC), 140.2 (7-CH), 134.4 (6-C), 131.2 (ArC), 129.9 (ArCH), 113.6 (ArCH), 79.9 (C), 58.8 ($ArCH_2$), 55.2 (OCH_3), 49.0 (t, *J* = 21 Hz, 1-CH), 44.2 (3-CH_2), 31.7 (9-CH_2), 28.9 (4-CH_2), 28.2 (CH_3), 26.9 (5-CH), 24.3 (t, *J* = 18 Hz, 8-CH_2); *m/z* HRMS (ESI^+) found $[M + H]^+$ 344.2213, 345.2280 and 346.2336, $[C_{21}H_{30}NO_3]^+$ requires 344.2226, $[C_{21}H_{29}DNO_3]^+$ requires 345.2288 and $[C_{21}H_{28}D_2NO_3]^+$ requires 346.2351.

Competition Experiment of (±)-*tert*-butyl (2*R*,3a*S*,5*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate-2,5-d_2 and (±)-*tert*-butyl (3a*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate



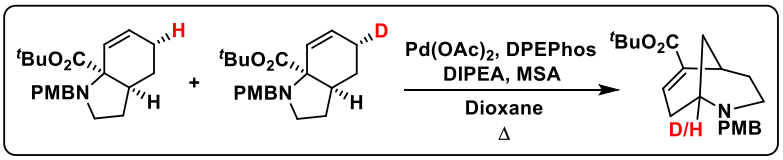
An equimolar solution of (±)-*tert*-butyl (3a*S*,5*R*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro- 7a*H* -indole-7a-carboxylate-2,5-d_2 and (±)-*tert*-butyl (3a*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (0.075 mmol of each) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added

and the reaction was heated under reflux. After 60 min and 6 h, the reaction mixture was cooled to RT and $NaHCO_3$ (saturated aqueous solution, 2 mL) was added. The organic layer was extracted with CH_2Cl_2 (3 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude products were purified by SiO_2 flash chromatography, eluting with 5-20% EtOAc/petrol, to separate the unreacted starting material.

Conversion	H:D SM
43%	1:1
51%	1:1

Table S1: Competition experiment of non-labelled and labelled substrates **333** and **360**. Percentage conversion was calculated from a determination of the level of starting material based on the crude ^{1}H-NMR.

Competition Experiment of (±)-*tert*-butyl (3a*S*,5*R*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate-5-*d* and (±)-*tert*-butyl (3a*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate

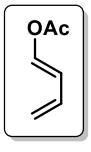


An equimolar solution of (±)-*tert*-butyl (3a*S*,5*R*,7a*R*) - 1-(4-methoxybenzyl) -1,2,3,3a,4,5-hexahydro- 7a*H* -indole-7a-carboxylate-5-*d* and (±)-*tert*-butyl (3a*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carboxylate (0.075 mmol of each) in dioxane (0.6 mL) was added to a stirred solution of $Pd(OAc)_2$ (3 mg, 0.02 mmol), DPEPhos (12 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (0.03 mL, 0.15 mmol) in dioxane (0.6 mL). After 10 min, methanesulfonic acid (0.01 mL, 0.15 mmol) was added and the reaction was heated under reflux. After 30 mins, 60 min and 120 min the reaction mixture was cooled to RT and $NaHCO_3$ (saturated aqueous solution, 2 mL) was added. The organic layer was extracted with CH_2Cl_2 (3 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude products were purified by SiO_2 flash chromatography, eluting with 10-20% EtOAc/petrol, to separate the unreacted starting material and the morphan product.

Conversion	H:D SM	H:D product
41%	1:1	1:1
78%	1:1	1:1
84%	1:1	1:1

Table S2: Competition experiment of non-labelled and labelled substrates **333** and **363**. Percentage conversion was calculated from a determination of the level of starting material based on the crude ^{1}H-NMR.

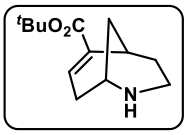
(*E*)-Buta-1,3-dien-1-yl acetate S34



4-(Dimethylamino)pyridine (0.15 g, 1.22 mmol) was added to a stirred solution of crotonaldehyde (0.50 mL, 6.09 mmol), and Et_3N (1.78 mL, 12.79 mmol) in Ac_2O (2.94 mL, 31.06 mmol). After 17.5 h, the reaction mixture was diluted with Et_2O (10 mL) and washed

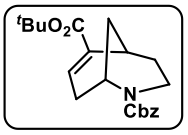
H_2O (2 x 10 mL), then $NaHCO_3$ (saturated aqueous solution, 3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material as a brown oil which was used directly in the next step without further purification (0.40 g, 59%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, *J* = 12.3 Hz, AcOC<u>H</u>), 6.27 (dt, 1H, *J* = 16.9, 10.7 Hz, C<u>H</u>CH_2), 6.04 (app t, 1H, AcOCHC<u>H</u>), 5.21 (d, 1H, *J* = 16.9 Hz, C<u>H</u>H), 5.09 (d, 1H, *J* = 10.3 Hz, CH<u>H</u>), 2.18 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.8 (CO), 138.7 (AcO<u>C</u>H), 131.7 (<u>C</u>HCH_2), 117.3 (CH_2), 116.0 (AcOCH<u>C</u>H) 20.1 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[320]

(±)-*tert*-Butyl) (1*R*)-2-azabicyclo [3.3.1]non-6-ene-6-carboxylate 407



1-Chloroethyl chloroformate (0.02 mL, 0.23 mmol) was added to a stirred solution of (±)-*tert*-butyl (3a*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexhydro-7a*H*-indole-7a-carboxylate (50 mg, 0.15 mmol) in $CHCl_3$ (1 mL). After 5 h, the reaction mixture was concentrated *in vacuo*, dissolved in MeOH (1.5 mL) and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 10-20% EtOAc/petrol then 0-10% MeOH/CH_2Cl_2, to give the product as a brown solid (23 mg, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.56 (br s, 1H, NH), 7.02 (t, 1H, *J* = 3.6 Hz, 7-CH), 3.88 (br s, 1H, 1-CH), 3.22 (dd, 1H, *J* = 13.2, 4.2 Hz, 3-CH), 3.05 (br s, 1H, 5-CH), 2.97 (td, 1H, *J* = 13.2, 3.4 Hz, 3-CH), 2.83 (dd, 1H, *J* = 21.4, 3.6 Hz, 8-CH), 2.69-2.61 (m, 1H, 8-CH), 2.35 (br d, 1H, *J* = 13.3 Hz, 9-CH), 2.16 (tt, 1H, *J* = 13.7, 4.2 Hz, 4-CH), 1.75-1.66 (m, 2H, 4-CH and 9-CH), 1.48 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.6 (CO), 137.2 (7-CH), 133.7 (6-C), 81.0 (C), 45.8 (1-CH), 36.3 (3-CH_2), 28.9 (8-CH_2), 28.1 (CH_3), 27.9 (9-CH_2), 26.0 (4-CH_2), 25.0 (5-CH); υ_{max}/cm^{-1} 2933.5, 2791.8, 2706.8, 2758.3, 1699.8, 1369.8, 1289.0, 1253.1, 1165.8, 1081.0; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 224.1648, $[C_{13}H_{22}NO_2]^+$ requires 224.1651; m.p. 216-218 ˚C (MeOH/CH_2Cl_2).

(±)-2-Benzyl 6-(*tert*-butyl) (1*R*)-2-azabicyclo [3.3.1]non-6-ene-2,6-dicarboxylate 409

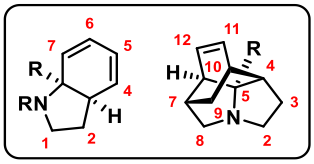


Benzyl chloroformate (0.03 mL, 0.23 mmol) was added to a stirred solution of (±)-*tert*-butyl (3a*S*,7a*R*)-1-(4-methoxybenzyl)-1,2,3,3a,4,5-hexhydro-7a*H*-indole-7a-carboxylate (50 mg, 0.15 mmol) in $CHCl_3$ (1 mL). The reaction mixture was stirred for 17.5 h, concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-20% EtOAc/petrol, to afford the product as a yellow oil (43 mg, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 (br s, 5H, ArCH), 7.06-7.04 (m, 1H, 7-CH), 5.14-5.12 (m, 2H, ArCH_2), 4.50 (d, 1H, *J* = 29.6 Hz, 1-CH), 3.97 (dd, 1H, *J* = 31.2, 4.0 Hz, 3-CH), 2.96-2.85 (m, 2H, 3-CH and 5-CH), 2.60-2.49 (m, 1H, 8-CH), 2.24-2.14 (m, 1H, 8-CH), 1.85-1.70 (m, 2H, 4-CH and 9-CH), 1.65-1.58 (m, 2H, 4-CH and 9-CH), 1.48 (s, 9H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.5 (CO), 139.0 (7-CH), 136.9 (6-C), 128.5 (ArCH), 127.9 (ArCH) 127.8 (ArCH), 113.9 (ArC), 80.3 (C), 66.9 (ArCH_2), 44.3 (1-CH), 37.2 (3-CH_2), 32.6 (8-CH_2), 30.5 (9-CH_2), 28.1 (CH_3), 27.9 (4-CH_2), 26.5 (5-CH); υ_{max}/cm^{-1} 1694.4, 1366.4, 1410.7,

1275.4, 1250.9, 1215.2, 1163.6, 1088.2, 1067.3, 697.4; *m/z* HRMS (ESI^+) found $[M + H]^+$ 358.2001 and $[M + Na]^+$ 380.1808, $[C_{21}H_{28}NO_4]^+$ requires 358.2018 and $[C_{21}H_{27}NNaO_4]^+$ requires 380.1838.

5.2.3. Complex Tetracyclic Amines: Synthetic Procedures

Numbering nomenclature in diene and tricyclic systems are as shown below:



5.2.3.1. General Procedures:

General Procedure E: Ring-opening/Tsuji-Trost/Diels-Alder Sequence in THF

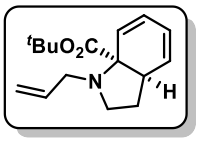
$Pd(OAc)_2$ (0.1 equiv.), PPh_3 (0.42 equiv.) and K_2CO_3 (1.3 equiv.) were stirred in degassed THF (0.03 M) for 10 min. The appropriate aziridine (1 equiv.) in THF (0.01 M) followed by the desired allyl acetate (1.2 equiv.) in THF (0.01 M) were added to the stirred solution and the reaction was heated under reflux for 16 h. The reaction mixture was cooled to RT, filtered, concentrated *in vacuo* and purified by SiO_2 flash chromatography.

General Procedure F: Ring-opening/Tsuji-Trost/Diels Alder Sequence in Dioxane

$Pd(OAc)_2$ (0.1 equiv.), PPh_3 (0.42 equiv.) and K_2CO_3 (1.3 equiv.) were stirred in degassed dioxane, (0.03 M) for 10 min. The appropriate aziridine (1 equiv.) in dioxane (0.01 M) was added and the reaction was heated under reflux for 1.5 h. The appropriate allyl acetate (1.2 equiv.) in dioxane (0.01 M) was added and the reaction was heated under reflux for a further 16 h. The reaction mixture was cooled to RT, filtered, concentrated *in vacuo* and purified by SiO_2 flash chromatography.

(±)-*tert*-Butyl (3a*R*,7a*S*)-1-allyl-1,2,3,3a-tetrahydro-7a*H*-indole-7a-carboxylate 529

Standard Procedure



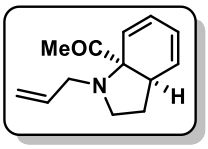
According to general procedure E, K_2CO_3 (48 mg, 0.35 mmol) was added to a stirred solution of $Pd(OAc)_2$ (7 mg, 0.03 mmol) and PPh_3 (29 mg, 0.11 mmol) in THF (2.5 mL). After 10 min, (±)-*tert*-butyl (3^1*R*,3a*S*,6a*S*)-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*]indol-3^1(2*H*)-carboxylate (60 mg, 0.27 mmol) in THF (2.5 mL) and allyl acetate (0.04 mg, 0.33 mmol) were added to the stirred solution and the reaction was heated to 70 °C for 16 h. The reaction mixture was cooled to RT, filtered, concentrated *in vacuo* to afford the intermediate allylated diene which was used directly in the next step without further purification.

Alkylation Procedure

Allyl bromide (0.04 mL, 0.50 mmol) was added to a stirred solution of (±)-*tert*-butyl (3a*R*,7a*S*)-1,2,3,3a-tetrahydro-7a*H*-indole-7a-carboxylate (74 mg, 0.33 mmol), K_2CO_3 (69 mg, 0.50 mmol) and TBAI (11 mg, 0.03 mmol) in acetone (2 mL). After 16 h, the reaction was quenched with $NaHCO_3$ (saturated aqueous solution, 2 mL) and extracted with CH_2Cl_2 (3 x 3 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO_2 flash chromatography, eluting with 0-

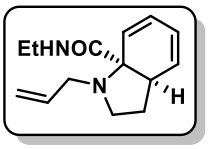
10% EtOAc/petrol, to give the product as a colourless oil (58 mg, 67%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.01-5.97 (m, 1H, 6-CH), 5.90-5.82 (m, 3H, 5-CH, 7-CH and C<u>H</u>CH_2), 5.73 (dd, 1H, *J* = 9.6, 4.2 Hz, 4-CH), 5.17 (d, 1H, *J* = 16.9 Hz, CHC<u>H</u>H), 5.05 (d, 1H, *J* = 10.0 Hz, CHCH<u>H</u>), 3.41 (dd, 1H, *J* = 13.4, 5.9 Hz, NC<u>H</u>H), 3.22-3.16 (m, 2H, NCH<u>H</u> and 3-CH), 2.70 (td, 1H, *J* = 7.9, 3.2 Hz, 1-CH), 2.55 (q, 1H, *J* = 8.2 Hz, 1-CH), 2.38-2.30 (m, 1H, 2-CH), 1.68-1.59 (m, 1H, 2-CH), 1.47 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.2 (CO), 137.1 (5-CH, 7-CH or <u>C</u>HCH_2), 129.7 (4-CH), 123.6 (6-CH), 122.3 (5-CH, 7-CH or <u>C</u>HCH_2), 119.4 (5-CH, 7-CH or <u>C</u>HCH_2), 116.2 (CH<u>C</u>H_2), 81.3 (C), 67.4 (C), 52.9 (NCH_2), 47.2 (1-CH_2), 42.0 (3-CH), 32.7 (2-CH_2), 28.2 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[184]

(±)-1-((3a*R*,7a*S*)-1-Allyl-1,2,3,3a-tetrahydro-7a*H*-indol-7a-yl)ethan-1-one 530



K_2CO_3 (48 mg, 0.35 mmol) was added to a stirred solution of $Pd(OAc)_2$ (7 mg, 0.03 mmol) and PPh_3 (29 mg, 0.11 mmol) in THF (2.5 mL). After 10 min, (±)-1((3^{1}*R*,3a*S*,6a*S*)-1,3a,6,6a-tetrahydroazirino [2,3,1-*hi*]indol-3^{1}(2*H*)-yl)ethan-1-one (44 mg, 0.27 mmol) in THF (2.5 mL) and allyl acetate (0.034 mL, 0.33 mmol) were added to the stirred solution and the reaction was heated to 30 °C for 5 h. The crude material was cooled to RT, filtered, concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-50% EtOAc/petrol, to give a yellow oil (17 mg, 31%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.17 (ddd, 1H, *J* = 10.1, 5.3, 0.9 Hz, 7-CH), 5.90-5.81 (m, 2H, C<u>H</u>CH_2 and 5-CH), 5.75 (ddt, 1H, *J* = 9.6, 4.9, 1.0 Hz, 4-CH), 5.65 (dt, 1H, *J* = 10.0, 0.8 Hz, 6-CH), 5.18 (dq, 1H, *J* = 16.9, 1.8 Hz, CHC<u>H</u>H), 5.07 (dq, 1H, *J* = 10.0, 1.4 Hz, CHCH<u>H</u>) 3.36 (ddt, 1H, *J* = 13.7, 5.6, 1.6 Hz, NC<u>H</u>H), 3.06 (ttt, 1H, *J* = 6.8, 1.2 Hz, NCH<u>H</u>), 3.03-2.96 (m, 2H, 1-CH and 3-CH), 2.41 (app q, 1H, 1-CH), 2.28-2.23 (m, 1H, 2-CH) superimposed on 2.22 (s, 3H, CH_3), 1.70-1.62 (m, 1H, 2-CH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.0 (CO), 136.6 (<u>C</u>HCH_2 or 5-CH), 129.8 (4-CH), 125.9 (7-CH), 122.1 (6-CH), 120.8 (<u>C</u>HCH_2 or 5-CH), 116.3 (CH<u>C</u>H_2), 73.1 (C), 53.0 (NCH_2), 50.4 (1-CH_2), 41.4 (3-CH), 33.3 (2-CH_2), 25.3 (CH_3); υ_{max}/cm^{-1} 2937.9, 2866.4, 1702.7, 1349.8, 1205.3, 1152.4, 1176.9, 1051.3, 713.5, 691.1, *m/z* HRMS (ESI^{+}) found $[M + H]^{+}$ 204.1382, $[C_{13}H_{17}NO]^{+}$ requires 204.1388.

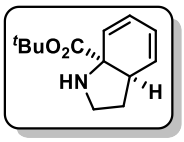
(±)-(3a*R*,7a*S*)-1-Allyl-*N*-ethyl-1,2,3,3a-tetrahydro-7a*H*-indole-7a-carboxamide 531



K_2CO_3 (48 mg, 0.35 mmol) was added to a stirred solution of $Pd(OAc)_2$ (7 mg, 0.03 mmol) and PPh_3 (29 mg, 0.11 mmol) in THF (2.5 mL). After 10 min, (±)-(3^{1}*R*,3a*S*,6a*S*)-*N*-ethyl-1,3a,6,6a-tetrahydroazirino [2,3,1-*hi*] indol-3^{1}(2*H*)-carboxamide (52 mg, 0.27 mmol) in THF (2.5 mL) and allyl acetate (0.034 mL, 0.33 mmol) were added to the stirred solution and the reaction was heated to 70 °C for 2 h. The crude material was cooled to RT, filtered, concentrated *in vacuo* and purified by SiO_2 flash chromatography., eluting with 5-60% EtOAc/petrol, to give a yellow oil (21 mg, 33%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (br s, 1H, NH), 6.17 (dd, 1H, *J* = 9.6, 5.7 Hz, 7-CH), 5.90-5.80 (m, 2H, C<u>H</u>CH_2 and 5-CH), 5.59

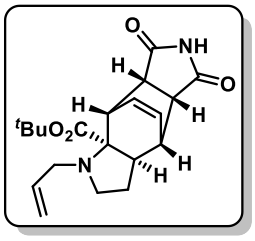
(dd, 1H, *J* = 9.7, 3.9 Hz, 4-CH), 5.51 (d, 1H, *J* = 9.7 Hz, 6-CH), 5.18 (dq, 1H, *J* = 17.1, 1.7 Hz, CHC<u>H</u>H), 5.08 (br d, 1H, *J* = 10.3 Hz, CHCH<u>H</u>), 3.35 (ddt, 1H, *J* = 13.6, 5.5, 1.7 Hz, NC<u>H</u>H), 3.31-3.20 (m, 3H, 3-CH and CONHC<u>H</u>$_2$), 3.07-3.02 (m, 1H, 1-CH), 2.94 (br dd, 1H, *J* = 14.0, 7.2 Hz, NCH<u>H</u>), 2.46-2.39 (m, 1H, 1-CH), 2.18-2.08 (m, 1H, 2-CH), 1.70-1.67 (m, 1H, 2-CH), 1.12 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 175.7 (CO), 136.8 (<u>C</u>HCH$_2$ or 5-CH), 130.0 (4-CH), 126.2 (7-CH), 122.0 (6-CH), 121.4 (<u>C</u>HCH$_2$ or 5-CH), 116.4 (CH<u>C</u>H$_2$), 69.1 (C), 53.2 (NCH$_2$), 51.4 (1-CH$_2$), 43.4 (CONH<u>C</u>H$_2$), 34.0 (3-CH), 32.1 (2-CH$_2$), 14.9 (CH_3); υ_{max}/cm^{-1} 2932.7, 2869.9, 1657.8, 1504.9, 1449.3, 1150.0, 1106.9, 1050.8, 914.3, 691.1; *m/z* HRMS (ESI$^+$) found $[M + H]^+$ 233.1639, $[C_{14}H_{20}N_2O]^+$ requires 233.1654.

(±)-*tert*-Butyl (3a*R*,7a*S*)-1,2,3,3a-tetrahydro-7a*H*-indole-7a-carboxylate 533



K_2CO_3 (48 mg, 0.35 mmol) was added to a stirred solution of $Pd(OAc)_2$ (7 mg, 0.03 mmol) and PPh_3 (29 mg, 0.11 mmol) in THF (2.5 mL) for 10 min. After 10 min, (±)-*tert*-butyl (3^1*R*,3a*S*,6a*S*)-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*]indol-3^1(2*H*)-carboxylate (60 mg, 0.27 mmol) in THF (2.5 mL) was added to the stirred solution and the reaction was heated to 70 °C for 16 h. The crude material was cooled to RT, filtered, concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 20-40% EtOAc/petrol, to afford a yellow oil (55 mg, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.95 (dd, 1H, *J* = 10.6, 5.7 Hz, 5-CH or 6-CH), 5.83 (dd, 1H, *J* = 9.6, 5.7 Hz, 7-CH), 5.76 (ddt, 1H, *J* = 9.5, 4.1, 1.0 Hz, 4-CH), 5.58 (d, 1H, *J* = 9.6Hz, 5-CH or 6-CH), 3.13-3.08 (m, 1H, 3-CH), 2.78-2.65 (m, 2H, 1-CH$_2$), 2.27-2.19 (m, 1H, 2-CH), 1.99 (br s, 1H, NH), 1.66-1.57 (m, 1H, 2-CH), 1.43 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.7 (CO), 129.5 (4-CH), 126.0 (5-CH or 6-CH), 122.5 (5-CH or 6-CH), 119.5 (7-CH), 81.4 (C), 61.2 (C), 42.0 (1-CH$_2$), 40.9 (3-CH), 35.1 (2-CH$_2$), 27.9 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[184]

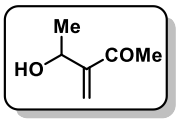
(±)-*tert*-Butyl (3a*R*,4*S*,4a*S*,7a*R*,8*S*,8a*R*)-1-allyl-5,7-dioxo-2,3,3a,4,4a,5,6,7,7a,8-decahydro-4,8-ethenopyrrolo[3,4-*f*]indole-8a(1*H*)-carboxyalte 541



Maleimide (14 mg, 0.14 mmol) was added to a stirred solution of (±)-*tert*-butyl (3a*R*,7a*S*)-1-allyl-1,2,3,3a-tetrahydro-7a*H*-indole-7a-carboxylate (27 mg, 0.10 mmol) in PhMe (5mL) and the reaction mixture was heated under reflux for 2 h. The crude solution was cooled to RT, concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 10-30% EtOAc/petrol, to afford the product as a colourless oil (19 mg, 53%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H, NH), 6.13 (dt, 2H, *J* = 22.5, 7.5 Hz, 5-CH and 6-CH), 5.78-5.68 (m, 1H, C<u>H</u>CH$_2$), 5.12 (d, 1H, *J* = 17.3 Hz, CHC<u>H</u>H), 5.03 (d, 1H, *J* = 10.0 Hz, CHCH<u>H</u>), 3.58 (br d, 1H, *J* = 6.0 Hz, 7-CH), 3.38 (dd, 1H, *J* = 14.0, 5.3 Hz, NC<u>H</u>H), 3.10 (br s, 1H, 4-CH), 3.01-2.95 (m, 2H, NCH<u>H</u> and NCOCH), 2.83-2.79 (m, 2H, 1-CH and NCOCH), 2.74-2.69 (m, 1H, 3-CH), 2.54 (q, 1H, *J* = 7.2 Hz, 1-CH), 2.02-1.95 (m, 1H, 2-CH), 1.50 (s, 9H, CH_3), 1.40-1.31 (m, 1H, 2-CH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 178.4 (CO), 178.3 (CO), 171.4

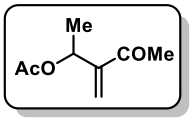
(CO), 136.4 (<u>C</u>HCH$_2$), 132.9 (5 or 6-CH), 124.5 (5 or 6-CH), 116.0 (CH<u>C</u>H$_2$), 81.9 (C), 74.8 (C), 52.1 (NCH$_2$), 51.0 (1-CH$_2$), 47.0 (3-CH), 45.2 (CH), 41.9 (CH), 37.5 (4-CH), 36.9 (7-CH), 28.9 (2-CH$_2$), 28.3 (CH$_3$). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[184]

4-Hydroxy-3-methylenepentan-2-one 556



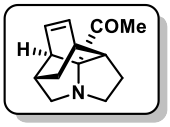
Methyl vinyl ketone (0.90 mL, 10.95 mmol) was added dropwise over 2 min to a stirred solution of acetaldehyde (0.61 mL, 10.95 mmol) and 1,4-diazobicylo[2.2.2]octane (0.11 g, 1.01 mmol) at 0 °C. The reaction mixture turned orange upon this addition and was warmed to RT. After 18 h, the reaction mixture was poured into HCl (1 M aqueous solution, 5 mL) and extracted with Et$_2$O (3 x 5 mL). The combined organic layers were washed with NaHCO$_3$ (saturated aqueous solution, 15 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo* to give a colourless oil which was used directly in the next step without further purification. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 6.09 (s, 1H, CH), 6.03 (s, 1H, CH), 4.64 (br s, 3H, CH), 2.78 (br s, 1H, OH), 2.36 (s, 3H, COCH$_3$), 1.34 (d, 3H, *J* = 6.5 Hz, CH$_3$); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 200.1 (CO), 151.2 (C), 125.0 (CH), 66.8 (CO<u>C</u>H$_3$), 26.4 (CH), 22.0 (CH$_3$). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[321]

3-Methylene-4-oxopentan-2-yl acetate 558



Acetyl chloride (1 mL, 14.24 mmol) was added dropwise over 5 min to a stirred solution of 4-hydroxy-3-methylenepentan-2-one (10.95 mmol) and pyridine (1.15 mL, 14.24 mmol) in CH$_2$Cl$_2$ (19 mL) at 0 °C. The reaction was warmed to RT, stirred for 18 h and quenched with HCl (1 M aqueous solution, 15 mL). The organic layer was extracted with in CH$_2$Cl$_2$ (2 x 10 mL) and the combined layers were washed with NaHCO$_3$ (saturated aqueous solution, 15 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO$_2$ flash chromatography, eluting with 10-20% EtOAc/petrol, to give the product as a colourless oil (0.35 g, 21% over 2 steps). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 6.10 (s, 1H, CH), 5.99 (d, 1H, *J* = 1.3 Hz, CH), 5.72 (qd, 1H, *J* = 6.5, 0.9 Hz, C<u>H</u>CH$_3$), 2.34 (s, 3H, COCH$_3$), 2.06 (s, 3H, COCH$_3$), 1.34 (d, 3H *J* = 6.9 Hz, CH$_3$); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 197.7 (CO), 169.9 (CO), 143.4 (C), 124.2 (CH), 67.7 (CH), 26.1 (CH$_3$), 21.2 (CH$_3$), 20.4 (CH$_3$).

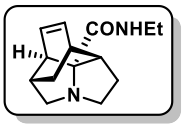
(±)-((1*S*,3^1*R*,5a*R*,6*S*,8a*R*)-1,4,5,5a,6,8a-Hexahydro-1,6-methanopyrrolo[3,2,1-*hi*]indol-3^1(2*H*)-yl)ethan-1-one 544



According to general procedure E, Pd(OAc)$_2$ (7 mg, 0.03 mmol), PPh$_3$ (29 mg, 0.11 mmol) and K$_2$CO$_3$ (48 mg, 0.35 mmol) were stirred in THF (2.5 mL) for 5 min. (±)-1-((3^1*R*,3a*S*,6a*S*)-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*]indol-3^1(2*H*)-yl)ethan-1-one (44 mg, 0.27 mmol) in THF (2.5 mL) and allyl acetate (0.03 mL, 0.33 mmol) were added to the stirred solution and the reaction was heated to 70 °C. The crude material was purified by SiO$_2$ flash

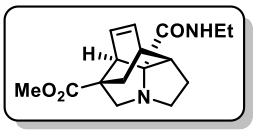
chromatography, eluting with 0-8% 1:8 NH_3:EtOH/CH_2Cl_2, to give a brown oil (41 mg, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.56-6.52 (m, 1H, 11-CH), 6.02-5.98 (m, 1H, 12-CH), 3.64 (dd, 1H, *J* = 11.7, 4.5 Hz, 8-CH), 3.13-3.10 (m, 1H, 6-CH), 3.04-2.90 (m, 2H, 2-CH_2), 2.62-2.57 (m, 1H, 4-CH), 2.43-2.39 (m, 1H, 10-CH), 2.32 (d, 1H, *J* = 11.7 Hz, 8-CH), 2.24 (s, 3H, CH_3), 2.02-1.97 (m, 1H, 7-CH), 1.93-1.85 (m, 1H, 3-CH), 1.58-1.48 (m, 1H, 3-CH), 1.45-1.37 (m, 2H, 9-CH_2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.2 (CO), 139.2 (11-CH), 127.2 (12-CH), 85.7 (C), 63.6 (8-CH_2), 57.3 (2-CH_2), 46.2 (6-CH), 45.2 (4-CH), 35.4 (7-CH), 33.9 (10-CH), 31.2 (9-CH_2), 27.7, (3-CH_2), 25.0 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[196]

(±)-(1*S*,3^1*R*,5a*R*,6*S*,8a*R*)-*N*-Ethyl-1,4,5,5a,6,8a-hexahydro-1,6-methanopyrrolo[3,2,1-*hi*]indole-3^1(2*H*)-carboxamide 545



According to general procedure E, $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (29 mg, 0.11 mmol) and K_2CO_3 (48 mg, 0.35 mmol) were stirred in THF (2.5 mL) for 5 min. (±)-(3^1*R*,3a*S*,6a*S*)-*N*-ethyl-1,3a,6,6a-tetrahydroazirino [2,3,1-*hi*] indol-3^1(2*H*)-carboxamide (52 mg, 0.27 mmol) in THF (2.5 mL) and allyl acetate (0.03 mL, 0.33 mmol) were added to the stirred solution and the reaction was heated to 70 °C. The crude material was purified by SiO_2 flash chromatography, eluting with 0-1% 1:8 NH_3:EtOH/Et_2O, to give a colourless oil (33 mg, 52%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (br s, 1H, NH), 6.55-6.51 (m, 1H, 11-CH), 6.14-6.10 (m, 1H, 12-CH), 3.46 (dd, 1H, *J* = 11.4, 4.4 Hz, 8-CH), 3.24-3.17 (m, 2H, C$\underline{H}_2$CH$_3$), 3.02-2.94 (m, 2H, 2-CH_2), 2.86-2.83 (app t, 1H, 6-CH), 2.61 (dqn, 1H, *J* = 9.3, 2.0 Hz, 4-CH), 2.41-2.38 (m, 1H, 10-CH), 2.26 (d, 1H, *J* = 11.4 Hz, 8-CH), 1.92-1.83 (m, 2H, 3-CH and 7-CH), 1.57-1.48 (m, 1H, 3-CH), 1.46-1.35 (m, 2H, 9-CH_2), 1.10 (t, 3H, *J* = 7.4 Hz, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.8 (CO), 137.7 (11-CH), 128.0 (12-CH), 80.9 (C), 62.8 (8-CH_2), 56.9 (2-CH_2), 47.7 (6-CH), 47.0 (4-CH), 36.0 (7-CH), 34.2 (10-CH), 33.7 ($\underline{C}H_2CH_3$), 31.3 (9-CH_2), 27.9 (3-CH_2), 14.9 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[196]

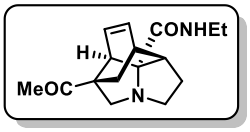
(±)-Methyl (1*S*,3^1*R*,5a*R*,6*S*,8a*R*)-3^1-(ethylcarbamoyl)-3^1,4,5,5a,6,8a-hexahydro-1,6-methano pyrrolo[3,2,1-*hi*]indole-1(2*H*)-carboxylate 563



According to general procedure E, $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (29 mg, 0.11 mmol) and K_2CO_3 (48 mg, 0.35 mmol) were stirred in THF (2.5 mL) for 5 min. (±)-(3^1*R*,3a*S*,6a*S*)-*N*-ethyl-1,3a,6,6a-tetrahydroazirino [2,3,1-*hi*]indol-3^1(2*H*)-carboxamide (52 mg, 0.27 mmol) in THF (2.5 mL) and methyl 2-(acetoxymethyl)acrylate (52 mg, 0.33 mmol) were added to the stirred solution and the reaction was heated to 70 °C. The crude material was purified by SiO_2 flash chromatography, eluting with 0-1% 1:8 NH_3:EtOH/Et_2O, to give a colourless oil (45 mg, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70 (br s, 1H, NH), 6.55 (app t, 1H, 11-CH), 6.10 (app t, 1H, 12-CH), 3.70-3.66 (m, 1H, 8-CH), superimposed on 3.62 (s, 3H, OCH_3), 3.24-3.17 (m, 3H, 6-CH and C$\underline{H}_2$CH$_3$), 3.09-2.94 (m, 2H, 2-CH_2), 2.61 (br d, 1H, *J* = 7.8 Hz, 4-CH), 2.50 (d,

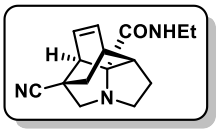
2H, *J* = 11.5 Hz, 8-CH), 1.97-1.89 (m, 1H, 3-CH), 1.83-1.69 (m, 2H, 9-CH_2), 1.60-1.51 (m, 1H, 3-CH), 1.10 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.3 (CO), 173.3 (CO), 137.7 (11-CH), 127.0 (12-CH), 81.1 (C), 65.6 (8-CH_2), 56.9 (2-CH_2), 52.1 (OCH_3), 51.7 (C), 49.9 (6-CH), 46.6 (4-CH), 35.2 (10-CH) 34.0 ($\underline{C}H_2CH_3$), 33.9 (9-CH_2), 27.9 (3-CH_2), 14.8 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[196]

(±)-(1*S*,3^1*R*,5a*R*,6*S*,8a*R*)-1-Acetyl-*N*-ethyl-1,4,5,5a,6,8a-hexahydro-1,6-methanopyrrolo[3,2,1-*hi*]indole-3^1(2*H*)-carboxamide 575



According to general procedure E, $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (29 mg, 0.11 mmol) and K_2CO_3 (48 mg, 0.35 mmol) were stirred in THF (2.5 mL) for 5 min. (±)-(3^1*R*,3a*S*,6a*S*)-*N*-ethyl-1,3a,6,6a-tetrahydroazirino [2,3,1-*hi*]indol-3^1(2*H*)-carboxamide (52 mg, 0.27 mmol) in THF (2.5 mL) and 2-methylene-3-oxo butyl acetate (47 mg, 0.33 mmol) were added to the stirred solution and the reaction was heated to 70 °C. The crude material was purified by SiO_2 flash chromatography, eluting with 0-1% 1:8 NH_3:EtOH/Et_2O, to give a yellow oil (49 mg, 66%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (br s, 1H, NH), 6.57-6.53 (m, 1H, 11-CH), 6.17-6.13 (m, 1H, 12-CH), 3.61 (d, 1H, *J* = 11.5 Hz, 8-CH), 3.25-3.18 (m, 2H, $C\underline{H}_2CH_3$), 3.13 (d, 1H, *J* = 6.7 Hz, 6-CH), 3.05-2.95 (m, 2H, 2-CH_2), 2.64 (m, 1H, 4-CH), 2.56-2.53 (m, 1H, 10-CH), 2.47 (d, 1H, *J* = 11.5 Hz, 8-CH), 2.05 (s, 3H, CH_3), 1.99-1.91 (m, 1H, 3-CH), 1.76-1.62 (m, 2H, 9-CH_2), 1.64-1.53 (m, 1H, 3-CH), 1.11 (t, 3H, *J* = 7.4 Hz, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 208.5 (CO), 173.8 (CO), 137.4 (11-CH), 127.0 (12-CH), 81.1 (C), 64.7 (8-CH_2), 58.5 (C), 56.9 (2-CH_2), 49.0 (6-CH), 46.8 (4-CH), 35.3 (10-CH), 33.9 ($\underline{C}H_2CH_3$), 28.0 (3-CH_2), 26.8 (CH_3), 14.8 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[196]

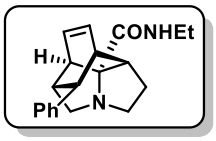
(±)-(1*R*, 3^1*R*,5a*R*,6*S*,8a*R*)-1-Cyano-*N*-ethyl-1,4,5,5a,6,8a-hexahydro-1,6-methanopyrrolo[3,2,1-*hi*]indole-3^1(2*H*)-carboxamide 576



According to general procedure E, $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (29 mg, 0.11 mmol) and K_2CO_3 (48 mg, 0.35 mmol) were stirred in THF (2.5 mL) for 5 min. (±)-(3^1*R*,3a*S*,6a*S*)-*N*-ethyl-1,3a,6,6a-tetrahydroazirino [2,3,1-*hi*] indol-3^1(2*H*)-carboxamide (52 mg, 0.27 mmol) in THF (2.5 mL) and 2-cyanoallylacetate (41 mg, 0.33 mmol) were added to the stirred solution and the reaction was heated to 70 °C. The crude material was purified by SiO_2 flash chromatography, eluting with Et_2O, to give a pale-yellow oil (40 mg, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.59 (br s, 1H, NH), 6.71-6.67 (m, 1H, 11-CH), 6.23-6.19 (m, 1H, 12-CH), 3.71 (d, 1H, *J* = 11.4 Hz, 8-CH), 3.26-3.15 (m, 3H, 6-CH and CH_2CH_3), 3.13-2.98 (m, 2H, 2-CH_2), 2.69 (d, 1H, *J* = 11.4 Hz, 8-CH), 2.62 (br d, 1H, *J* = 8.8 Hz, 4-CH), 2.56-2.53 (m, 1H, 10-CH), 2.00-1.91 (m, 1H, 3-CH), 1.88-1.84 (m, 1H, 9-CH), 1.77-1.73 (m, 1H, 9-CH), 1.57-1.48 (m, 1H, 3-CH), 1.11 (t, 3H, *J* = 7.6 Hz, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.5 (CO), 138.9 (11-CH), 125.8 (12-CH), 121.9 (CN), 80.3

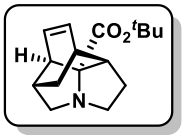
(C), 65.4 (8-CH_2), 57.1 (2-CH_2), 50.9 (6-CH), 46.5 (4-CH), 38.0 (C), 35.8 (9-CH_2), 34.5 (10-CH), 34.0 ($\underline{C}H_2CH_3$), 27.6 (3-CH_2), 14.8 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[196]

(±)-(1*S*, 3^1*R*,5a*R*,6*R*,8a*R*,9*R*)-*N*-Ethyl-9-phenyl-1,4,5,5a,6,8a-hexahydro-1,6-methanopyrrolo [3,2,1-*hi*]indole-3^1(2*H*)-carboxamide 577



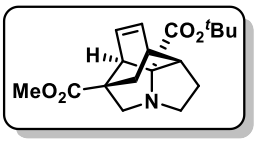
According to general procedure E, $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (29 mg, 0.11 mmol) and K_2CO_3 (48 mg, 0.35 mmol) were stirred in THF (2.5 mL) for 5 min. (±)-(3^1*R*,3a*S*,6a*S*)-*N*-ethyl-1,3a,6,6a-tetrahydroazirino [2,3,1-*hi*] indol-3^1(2*H*)-carboxamide (52 mg, 0.27 mmol) in THF (2.5 mL) and cinnamyl acetate (58 mg, 0.33 mmol) were added to the stirred solution and the reaction was heated to 70 °C. The crude material was purified by SiO_2 flash chromatography, eluting with Et_2O, to give a colourless oil (55 mg, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81 (br s,1H, NH), 7.25-7.15 (m, 2H, ArCH), 7.17-7.13 (m, 1H, ArCH), 7.08-7.06 (m, 2H, ArCH), 6.36-6.32 (m, 1H, 12-CH), 6.25-6.21 (m, 1H, 11-CH), 3.54 (dd, 1H, *J* = 11.6, 3.4 Hz, 8-CH), 3.29-3.23 (m, 2H, $C\underline{H}_2CH_3$), 3.20-3.07 (m, 2H, 2-CH_2), 3.01-2.98 (m, 1H, 6- CH), 2.80 (br s, 1H, 9-CH), 2.66 (dt, 1H, *J* = 9.5, 3.1 Hz, 4-CH), 2.61-2.59 (m, 1H, 10-CH), 2.43 (d, 1H, *J* = 11.6 Hz, 8-CH), 2.33-2.31 (m, 1H, 7-CH), 2.06-1.97 (m, 1H, 3-CH), 1.84-1.75 (m, 1H, 3-CH), 1.13 (t, 3H, *J* = 7.3 Hz, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.7 (CO), 145.3 (ArC), 134.6 (11-CH), 129.3 (12-CH), 128.4 (ArCH), 127.8 (ArCH), 125.8 (ArCH), 80.6 (C), 63.4 (8-CH_2), 57.4 (2-CH_2), 48.4 (6-CH), 47.6 (4-CH), 47.0 (9-CH), 45.0 (7-CH), 43.0 (10-CH), 33.8 ($\underline{C}H_2CH_3$), 28.0 (3-CH_2), 14.9 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[196]

(±)-*tert*-Butyl (1*S*, 3^1*R*,5a*R*,6*S*,8a*R*,9*R*)-1,4,5,5a,6,8a-hexahydro-1,6-methanopyrrolo[3,2,1-*hi*]indole-3^1(2*H*)-carboxylate 542



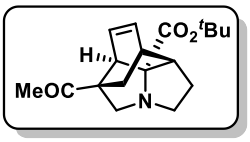
Crude (±)-*tert*-butyl (3a*R*,7a*S*)-1-allyl-1,2,3,3a-tetrahydro-7a*H*-indole-7a-carboxylate (1.35 mmol) was dissolved in PhMe (20 mL) and heated to 100 °C for 24 h. The reaction mixture RT, concentrated *in vacuo* and purified by SiO_2 flash chromatography, 0-5% 1:8 NH_3:EtOH/CH_2Cl_2, to give a brown oil (0.22 g, 63%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.47-6.43 (m, 1H, 11-CH), 6.18-6.14 (m, 1H, 12-CH), 3.50 (dd, 1H, *J* = 10.4, 4.4 Hz, 8-CH), 3.42-3.34 (m, 1H, 2-CH), 3.25-3.22 (m, 1H, 6-CH), 3.06-3.00 (m, 1H, 2-CH), 2.34-2.28 (m, 2H, 4-CH and 10-CH), 2.24 (d, 1H, *J* = 10.9 Hz, 8-CH), 2.04-1.95 (m, 1H, 3-CH), 1.89-1.83 (m, 1H, 7-CH), 1.59-1.51 (m, 1H, 3-CH), 1.43 (s, 9H, CH), superimposed on 1.41-1.38 (m, 1H, 9-CH_2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 200.5 (CO), 137.5 (11-CH), 129.2 (12-CH), 80.9 (C), 80.4 (C), 64.1 (8-CH_2), 58.6 (2-CH_2), 49.7 (4-CH), 45.0 (6-CH), 34.8 (7-CH), 34.4 (10-CH), 31.4 (9-CH_2), 28.1 (3-CH_2), 28.0 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[184]

(±)-3^1-(*tert*-Butyl) 1-methyl (1*R*, 3^1*R*,5a*R*,6*S*,8a*R*)-5,5a,6,8a-tetrahydro-1,6-methanopyrrolo [3,2,1-*hi*]indole-1,3^1(2*H*,4*H*)-dicarboxylate 580



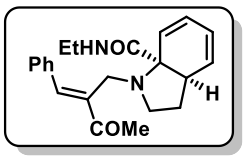
According to general procedure F, $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (29 mg, 0.11 mmol) and K_2CO_3 (48 mg, 0.35 mmol) were stirred in dioxane (2.5 mL) for 10 min. (±)-*tert*-butyl (3^1*R*,3a*S*,6a*S*)-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*]indol-3^1(2*H*)-carboxylate (60 mg, 0.27 mmol) in dioxane (2.5 mL) and methyl 2-(acetoxymethyl)acrylate (52 mg, 0.33 mmol) were added to the stirred solution and the reaction was heated to 100 °C. The crude material was purified by SiO_2 flash chromatography, eluting with Et_2O, to give a yellow oil (44 mg, 51%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.48-6.44 (m, 1H, 11-CH), 6.16-6.12 (m, 1H, 12-CH), 3.67 (d, 1H, *J* = 11.4 Hz, 8-CH) superimposed on 3.63 (s, 3H, CH_3), 3.58 (d, 1H, *J* = 6.6 Hz, 6-CH), 3.44-3.37 (m, 1H, 2-CH), 3.05-2.99 (m, 1H, 2-CH), 2.46 (d, 1H, *J* = 10.8 Hz, 8-CH) superimposed on 2.43-2.41 (m, 1H, 10-CH), 2.27-2.23 (m, 1H, 4-CH), 2.10-2.01 (m, 1H, 3-CH), 1.79 (dq, 1H, *J* = 13.6, 1.6 Hz, 9-CH), 1.68 (dd, 1H, *J* = 13.6, 3.1 Hz, 9-CH), 1.62-1.53 (m, 1H, 3-CH), 1.41 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.5 (CO), 173.2 (CO), 137.3 (11-CH), 128.3 (12-CH), 80.9 (C), 80.7 (C), 66.6 (8-CH_2), 58.6 (2-CH_2), 52.0 (CH_3), 49.4 (4-CH), 47.1 (6-CH), 35.3 (10-CH), 33.9 (9-CH_2), 28.3 (3-CH_2), 27.9 (CH_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[196]

(±)-*tert*-Butyl (1*S*, 3^1*R*,5a*R*,6*S*,8a*R*,9*R*)-1-acetyl-1,4,5,5a,6,8a-hexahydro-1,6-methanopyrrolo [3,2,1-*hi*]indole-3^1(2*H*)-carboxylate 581



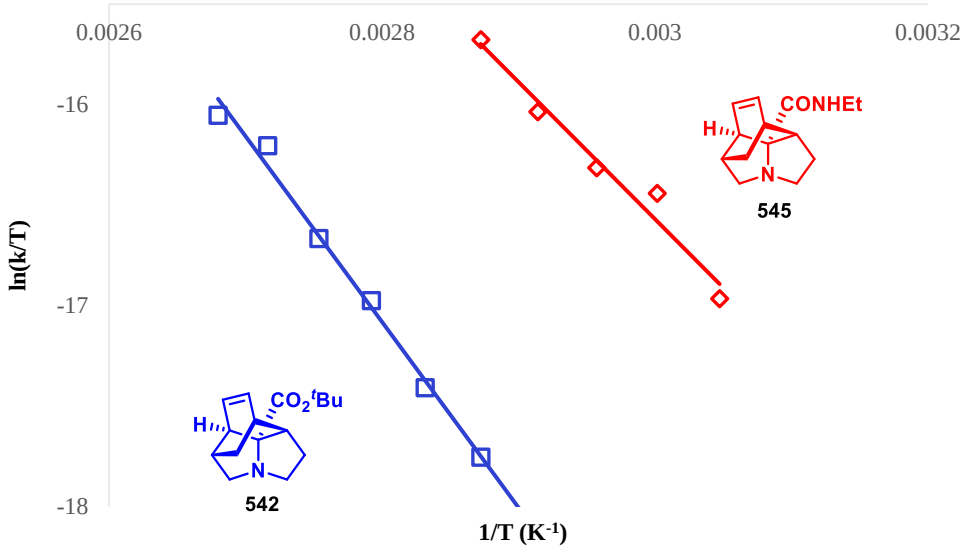
According to general procedure E, $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (29 mg, 0.11 mmol) and K_2CO_3 (48 mg, 0.35 mmol) were stirred in THF (2.5 mL) for 10 min. (±)-*tert*-butyl (3^1*R*,3a*S*,6a*S*)-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*]indol-3^1(2*H*)-carboxylate (60 mg, 0.27 mmol) in THF (2.5 mL) and 2-methylene-3-oxobutyl acetate (47 mg, 0.33 mmol) were added to the stirred solution and the reaction was heated to 70 °C. The crude material was purified by SiO_2 flash chromatography, eluting with 0-1% 1:8 NH_3:EtOH/Et_2O, to give a yellow oil (46 mg, 56%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.47-6.43 (m, 1H, 11-CH), 6.18-6.14 (m, 1H, 12-CH), 3.62 (d, 1H, *J* = 11.4 Hz, 8-CH), 3.53 (d, 1H, *J* = 6.6 Hz, 6-CH), 3.44-3.36 (m, 1H, 2-CH), 3.07-3.00 (m, 1H, 2-CH), 2.48-2.45 (m, 1H, 10-CH), 2.42 (d, 1H, *J* = 11.4 Hz, 8-CH), 2.31-2.27 (m, 1H, 4-CH), 2.11-2.05 (m, 1H, 3-CH) superimposed on 2.02 (s, 3H, CH_3), 1.68-1.67 (m, 2H, 9-CH_2), 1.64-1.55 (m, 1H, 3-CH), 1.42 (s, 9H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 208.6 (CO), 173.2 (CO), 137.3 (11-CH), 128.4 (12-CH), 81.1 (C), 80.8 (C), 65.9 (8-CH_2), 58.5 (2-CH_2), 57.6 (C), 49.5 (4-CH), 46.4 (6-CH), 35.3 (10-CH), 33.4 (9-CH_2), 28.2 (3-CH_2), 27.9 (CH_3), 26.7 (CO$\underline{C}H_3$). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[196]

(±)-(3a*R*,7a*S*)-1-(2-((*E*)-Benzylidene)-3-oxobutyl)-*N*-ethyl-1,2,3,3a-tetrahydro-7a*H*-indole-7a-carboxamide 588



According to general procedure E, $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (29 mg, 0.11 mmol) and K_2CO_3 (48 mg, 0.35 mmol) were stirred in THF (2.5 mL) for 10 min. (±)-(3^1*R*,3a*S*,6a*S*)-*N*-ethyl-1,3a,6,6a-tetrahydroazirino[2,3,1-*hi*]indol-3^1(2*H*)-carboxamide (52 mg, 0.27 mmol) in THF (2.5 mL) and 2-methylene-3-oxo-1-phenylbutyl acetate (72 mg, 0.33 mmol) were added to the stirred solution and the reaction was heated to 70 °C for 16 h. The crude material was purified by SiO_2 flash chromatography, eluting with 0-1% 1:8 NH_3:EtOH/Et_2O, to give a yellow oil (26 mg, 27%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H, NCH), 7.63 (s, 1H, CC<u>H</u>), 7.43-7.30 (m, 5H, ArCH), 6.03 (dd, 1H, *J* = 9.5, 5.5 Hz, CH), 5.80-5.76 (m, 1H, CH), 5.48 (dd, 1H, *J* = 9.8, 3.6 Hz, CH), 5.43 (d, 1H, *J* = 9.8 Hz, CH), 3.66-3.55 (m, 2H, NCH_2), 3.34-3.27 (m, 3H, N<u>C</u>H_2CH_3 and 3-CH), 2.78-2.74 (m, 1H, 1-CH), 2.50 (s, 3H, CH_3), 2.26-2.19 (m, 1H, 1-CH), 2.00-1.94 (m, 1H, 2-CH), 1.60-1.54 (m, 1H, 2-CH), 1.20 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 200.9 (CO), 175.8 (CO), 142.3 (C<u>C</u>H), 140.4 (C), 134.9 (C), 130.3 (CH), 129.3 (ArCH), 128.8 (ArCH), 128.5 (ArCH), 126.1 (CH), 122.2 (CH), 121.5 (CH), 69.2 (C), 51.3 (1-CH_2), 44.6 (NCH_2), 43.0 (N<u>C</u>H_2CH_3), 34.2 (3-CH), 31.6 (2-CH_2), 26.6 (CH_3), 14.7 (NCH_2<u>C</u>H_3). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[279]

Eyring Plot



	Δ‡H (kJ mol^{-1})	Error (kJ mol^{-1})	*Δ‡S* (J K^{-1} mol^{-1})	Error (J K^{-1} mol^{-1})	*Δ‡G* (kJ mol^{-1})
Ester	77	±4	-125	±10	121
Amide	57	±6	-165	±17	114

Figure S1: Eyring plot for the IMDA cyclisation to form tetracycles **542** and **545** and calculated *Δ‡H*, *Δ‡S* and *Δ‡G* values. *Δ‡G* values were calculated at 75 °C.

Entry	Temperature (°C)	Ester k (s^{-1})	Amide k (s^{-1})
1	55	-	1.41×10^{-5}
2	60	-	2.41×10^{-5}
3	65	-	2.78×10^{-5}
4	70	-	3.73×10^{-5}
5	75	6.78×10^{-6}	5.41×10^{-5}
6	80	9.72×10^{-6}	-
7	85	1.52×10^{-5}	-
8	90	2.10×10^{-5}	-
9	95	3.38×10^{-5}	-
10	100	3.98×10^{-5}	-

Table S3: Rate constants for the IMDA reaction of ester **529** and amide **531**.

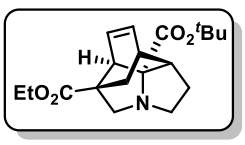
General Considerations for Kinetic Experiments

Rate constants were obtained using ^{1}H-NMR spectroscopy, acquired on a 500 MHz Varian spectrometer. A solution of substrate and standard, 1,3,5-trimethoxybenzene, were dissolved in PhMe-d_8 (0.7 mL) and a RT ^{1}H-NMR was obtained. The instrument was then heated to the required temperature, and another spectrum was obtained. Spectra were obtained every 20 min for between 12 to 20 h and the ^{1}H-NMR array data was processed using MestReNova. Errors were calculated in Microsoft Excel *via* the least squares analysis method.

Representative Kinetic Experiment

A standard solution of allylated diene **529** (10.4 mg, 0.04 mmol), 1,3,5-trimethoxybenzene (1 mg, 0.006 mmol) in PhMe-d_8 (0.7 mL) was added into an NMR tube, which was manually loaded into the NMR spectrometer with the probe temperature set at 25 °C. A spectrum was obtained at this temperature, the probe was heated to 85 °C with the sample loaded within the magnet. The time taken to reach this temperature was recorded (generally ~15 min for the instrument to reach the desired temperature), and then an array of experiments was started, without further tuning or shimming, collecting spectra every 20 min for 20 h.

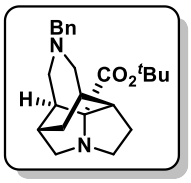
(±)-3^1-(*tert*-Butyl) 1-ethyl (1*R*, 3^1*R*,5a*R*,6*S*,8a*R*)-5,5a,6,8a-tetrahydro-1,6-methanopyrrolo [3,2,1-*hi*]indole-1,3^1(2*H*,4*H*)-dicarboxylate 611



1,8-Diazabcyclo[5.4.0]undec-7-ene (0.01 mL, 0.01 mmol) was added to a stirred solution of (±)-3^1-(*tert*-butyl) 1-methyl (1*R*, 3^1*R*,5a*R*,6*S*,8a*R*)-5,5a,6,8a-tetrahydro-1,6-methanopyrrolo [3,2,1-*hi*]indole-1,3^1(2*H*,4*H*)-dicarboxylate (44 mg, 0.14 mmol) in methylamine (33% wt. solution in EtOH, 1 mL) and stirred in a sealed tube at 90 ºC for 24 h. The reaction mixture was cooled to RT, concentrated *in vacuo* and purified by SiO_2 flash chromatography, eluting with 0-40% EtOAc/petrol, to afford the title product as a yellow oil (13 mg, 28%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.47 (t, 1H, J = 7.3 Hz, 11-CH), 6.16 (t, 1H, J = 7.3 Hz, 12-CH),

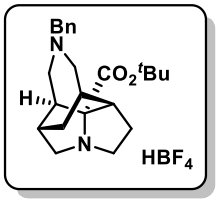
4.09 (q, 2H, *J* = 6.9 Hz, C<u>H</u>$_2$CH$_3$), 3.72 (d, 1H, *J* = 11.1 Hz, 8-CH), 3.61 (d, 1H, *J* = 6.6 Hz, 6-CH), 3.48-3.40 (m, 1H, 2-CH), 3.08-3.02 (m, 1H, 2-CH), 2.48 (d, 1H, *J* = 11.4 Hz, 8-CH) superimposed on 2.45-2.44 (m, 1H, 10-CH), 2.29-2.26 (m, 1H, 4-CH), 2.12-2.03 (m, 1H, 3-CH), 1.82 (br d, 1H, *J* = 13.9 Hz, 9-CH), 1.70 (dd, 1H, *J* = 13.9, 2.7 Hz, 9-CH), 1.65-1.56 (m, 1H, 3-CH), 1.43 (s, 9H, CH), 1.22 (t, 3H, *J* = 7.6 Hz, CH$_3$); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 174.0 (CO), 173.0 (CO), 137.27 (11-CH), 128.3 (12-CH), 81.0 (C), 66.5 (C), 60.8 (<u>C</u>H$_2$CH$_3$), 58.5 (2-CH$_2$), 50.7 (C), 49.4 (4-CH), 47.1 (6-CH), 35.3 (10-CH), 34.0 (9-CH$_2$), 30.9 (C), 28.2 (3-CH$_2$), 27.9 (CH$_3$), 14.1 (CH$_3$); υ_{max}/cm^{-1} 1724.1, 1367.4, 1303.8, 1283.3, 1234.7, 1160.4, 1104.9, 1085.7, 1054.4, 1026.9; *m/z* HRMS (ESI$^+$) found [M + H]$^+$ 334.2024, [C$_{19}$H$_{28}$NO$_4$]$^+$ requires 334.2018.

(±)-*tert*-Butyl (4*R*,4a*R*,4a^1*R*,9*S*,9a*S*)-2-benzyldecahydro-4a^1 *H*-4,9-methanoazepino[3,4,5-*gh*]pyrrolizine-4a^1-carboxylate 613



4-Methylmorpholine *N*-oxide (70 mg, 0.60 mmol) and K$_2$OsO$_4$.2H$_2$O (3 mg, 0.01 mmol) were added to a stirred solution of (±)-*tert*-butyl (1*S*, 3^1*R*,5a*R*,6*S*,8a*R*,9*R*)-1,4,5,5a,6,8a-hexahydro-1,6-methanopyrrolo [3,2,1-*hi*] indole-3^1(2*H*)-carboxylate (0.10 g, 0.38 mmol) in acetone:H$_2$O (10:1, 4.4 mL). After 16 h of vigorous stirring, the reaction mixture was quenched with Na$_2$SO$_4$ (saturated aqueous solution, 5 mL) and concentrated *in vacuo*. The organics were extracted with CH$_2$Cl$_2$ (3 x 5 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude material was dissolved in H$_2$O:CH$_2$Cl$_2$ (2.5:1, 2.8 mL) and NaOI$_4$ (90 mg, 0.42 mmol) and Et$_3$BnNCl (5 mg, 0.02 mmol) was added. The reaction mixture was stirred for an hour, at which point the organic layer was extracted with CH$_2$Cl$_2$ (3 x 3 mL), dried over MgsO$_4$ and concentrated *in vacuo* to approx. 5 mL volume. To which benzylamine (0.05 mL, 0.48 mmol) and sodium triacetoxyborohydride (0.27 g, 1.27 mmol) were added and the reaction mixture was stirred for 2 h. The reaction was quenched with NaHCO$_3$ (saturated aqueous solution, 5 mL) and stirred for 10 min. The organic layer was extracted with CH$_2$Cl$_2$ (3 x 5 mL) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude material was purified by SiO$_2$ flash chromatography, eluting with 1-4% NH$_3$:EtOH, 1:8/CH$_2$Cl$_2$, to afford the title compound as a brown oil (27 mg, 19%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.27-7.25 (m, 5H, ArCH), 3.65 (d, 1H, *J* = 13.4 Hz, ArC<u>H</u>H), 3.56 (dd, 1H, *J* = 11.3, 5.3 Hz, NC<u>H</u>H), 3.31 (d, 1H, *J* = 13.4 Hz, ArCH<u>H</u>), 3.10-2.99 (m, 3H, 2-CH, 6-CH and 8-CH), 2.90-2.83 (m, 2H, 4-CH and 8-CH), 2.78 (br dd, 1H, *J* = 11.4, 5.6 Hz, C<u>H</u>HN), 2.50 (d, 1H, *J* = 12.2 Hz, 2-CH), 2.20-2.13 (m, 2H, 3-CH and 7-CH), 2.09 (d, 1H, *J* = 11.3 Hz, NCH<u>H</u>), 2.03-1.97 (m, 1H, 9-CH), 1.89 (d, 1H, *J* = 11.4 Hz, CH<u>H</u>N), 1.74-1.66 (m, 2H, 9-CH and 10-CH), 1.64-1.56 (m, 1H, 3-CH), 1.49 (s, 9H, CH$_3$); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 174.9 (CO), 139.3 (ArC), 128.6 (ArCH), 128.2 (ArCH), 126.8 (ArCH), 80.6 (C), 78.6 (C), 64.3 (NCH$_2$), 63.6 (NCH$_2$), 62.0 (ArCH$_2$), 54.2 (8-CH$_2$), 53.2 (2-CH$_2$), 45.8 (4-CH), 43.8 (6-CH), 36.6 (7-CH), 34.8 (9-CH$_2$), 34.1 (10-CH), 31.3 (3-CH$_2$), 28.0 (CH$_3$). ^{1}H-NMR and ^{13}C-NMR data are consistent with the literature.[279]

(±)-*tert*-Butyl (4*R*,4a*R*,4a^1*R*,9*S*,9a*S*)-2-benzyldecahydro-4a^1 *H*-4,9-methanoazepino[3,4,5-*gh*]pyrrolizine-4a^1-carboxylate tetrafluoroboric salt S35



To a solution of (±)-*tert*-butyl (4*R*,4a*R*,4a^1*R*,9*S*,9a*S*)-2-benzyldecahydro-4a^1 *H*-4,9-methanoazepino[3,4,5-*gh*]pyrrolizine-4a^1-carboxylate (42 mg, 0.11 mmol) in H_2O (0.1 mL) was added HBF_4 (50% w/w aqueous solution, 0.02 mL) at 0 °C and left for 3 h. The slurry was concentrated *in vacuo*, recrystallised from MeCN to afford the title compound (50 mg, *quant*.).

v. References

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Catalysis

Rapid Access to Azabicyclo[3.3.1]nonanes by a Tandem Diverted Tsuji–Trost Process

Hannah G. Steeds,[a] Jonathan P. Knowles,*[b] Wai L. Yu,[a] Jeffery Richardson,[c] Katie G. Cooper,[d] and Kevin I. Booker-Milburn*[a]

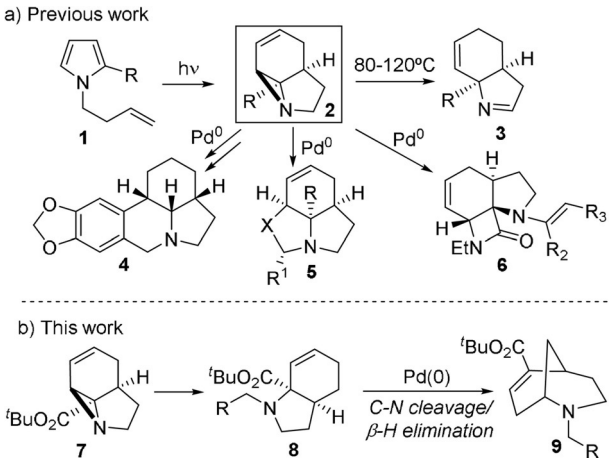
Abstract: A three-step synthesis of the 2-azabicyclo[3.3.1]-nonane ring system from simple pyrroles, employing a combined photochemical/palladium-catalysed approach is reported. Substrate scope is broad, allowing the incorporation of a wide range of functionality relevant to medicinal chemistry. Mechanistic studies demonstrate that the process occurs by acid-assisted C–N bond cleavage followed by β-hydride elimination to form a reactive diene, demonstrating that efficient control of what might be considered off-cycle reactions can result in productive tandem catalytic processes. This represents a short and versatile route to the biologically important morphan scaffold.

Since their discovery, palladium-catalysed cross-coupling reactions have seen increasing use in the synthesis of bioactive molecules.[1] In particular, due to its reliability, the Suzuki cross-coupling has become a key C–C bond forming reaction within medicinal chemistry.[2] However, the resulting compounds are often relatively planar in nature, despite evidence that increased bioactivity might result from increased levels of sp^3-hybridized carbon.[3] The Tsuji–Trost allylation represents a palladium-catalysed process with potential to achieve more three-dimensional molecules, necessarily connecting fragments via sp^3-hybridized centres.[4] Recent work has added to this potential with increasingly effective systems for performing enantioselective Tsuji–Trost reactions.[5] The power of such reactions within tandem processes has also been demonstrated, particularly in combination with photochemistry to create complex, three-dimensional molecules from simple substrates (Scheme 1 a).[6]

Tsuji–Trost reactions are also potentially less prone to side reactions, such as competing protodehalogenation encountered in Suzuki cross-couplings.[7] While competing β-hydride elimination from intermediate π-allyl Pd complexes to form dienes is known,[8] this process is less reported and potentially reversible.[9] However, dienes themselves frequently serve as useful synthetic intermediates,[11] raising the possibility that their formation could form part of a productive catalytic cycle.[11] Herein, we report a diverted Tsuji–Trost process, where β-hydride elimination to form a reactive diene results in a novel tandem process, forming complex tertiary amines that represent the core of the biologically significant morphan ring-system (Scheme 1 b).

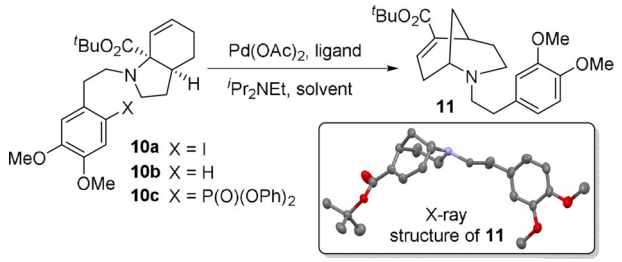
Following our recently reported synthesis of lycorane alkaloid **4**,[12] employing a key Heck cyclisation on a photochemically-derived substrate, we were led to consider whether simple homologation of the carbon tether might lead directly to the homologated alkaloid series. However, initial investigation of the Heck reaction of iodide **10a** in fact yielded deiodinated material **10b** under the majority of conditions (Table 1). In no case was the desired Heck product detected, with use of previously successful phosphite ligands[13] leading to the unex-

[a] H. G. Steeds, Dr. W. L. Yu, Prof. K. I. Booker-Milburn
School of Chemistry, University of Bristol
Cantock' Close, Bristol, BS8 1TS (UK)
E-mail: k.booker-milburn@bristol.ac.uk
[b] Dr. J. P. Knowles
Northumbria University, Newcastle upon Tyne, NE1 8ST (UK)
E-mail: jonathan.p.knowles@northumbria.ac.uk
[c] Dr. J. Richardson
DCRT European Innovation Hub
Lilly Erl Wood Manor, Windlesham, GU20 6PH (UK)
[d] Dr. K. G. Cooper
Pharmaceutical Technology & Development, AstraZeneca
Macclesfield Campus, Cheshire, SK10 2NA (UK)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.202003762.



Scheme 1. Previous synthetic utility of photochemically synthesized vinyl aziridines and their formation of azabicyclo[3.3.1]nonanes in a diverted Tsuji–Trost process.[6]

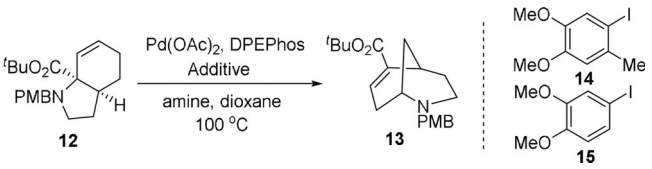
Table 1. Initial reaction screening.



Entry	Ligand	Solvent[a]	**10b** [%]	**11** [%]
1	P(*o*-tol)$_3$	MeCN	<5	0
2	P(*o*-tol)$_3$	toluene	<5	0
3	P(*o*-tol)$_3$	dioxane	<5	0
4	P(OPh)$_3$	MeCN	89[b]	0
5	XantPhos	dioxane	55	0
6	dppb	dioxane	0	3[c]
7	dppf	dioxane	0	21[c]
8	PPh$_3$	dioxane	0	36[c]
9	DPEPhos	dioxane	0	76
10[d]	DPEPhos	dioxane	42	0
11[e]	DPEPhos	dioxane	0	0
12	CyDPEPhos	dioxane	0	6[c]

[a] All reactions were performed at reflux for 20 h. [b] Yield for phosphonate ester **10c**, based on P(OPh)$_3$. [c] Based on ^{1}H NMR using 1,3,5-trimethoxybenezene as an internal standard. [d] Et$_3$N used instead of *i*Pr$_2$NEt. [e] No amine added.

Table 2. Optimization study of reaction additives.



Entry[a]	Amine (equiv)	Additive (equiv[b])	**13** [%]
1	None	None	0
2	*i*Pr$_2$NEt (2)	**14** (1)	50
3	*i*Pr$_2$NEt (2)	**14** (0.5)	40
4	*i*Pr$_2$NEt (2)	**15** (0.5)	26[c]
5	*i*Pr$_2$NEt (2)	4-iodoanisole (0.5)	23[c]
6	*i*Pr$_2$NEt (2)	PhI (0.5)	19[c]
7	*i*Pr$_2$NEt (2)	TBAI (1)	0
8	*i*Pr$_2$NEt (2)	AcOH/TBAI (1)	0
9	none	*i*Pr$_2$NEt.HI (1)	53
10	*i*Pr$_2$NEt (0.2)	*i*Pr$_2$NEt.HI (1)	39[c]
11	*i*Pr$_2$NEt (1)	CSA (1)	43
12	*i*Pr$_2$NEt (1)	MSA (1)	70

[a] All reactions were performed at reflux for 20 h. [b] Equivalents relate to molar quantity of starting material **12**. [c] Yield based on ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. TBAI = tetrabutylammonium iodide. CSA = camphorsulfonic acid. MSA = methanesulfonic acid.

pected phosphonate ester **10c** (Entry 4), presumably via reductive elimination to a phosphonium salt intermediate.[14] However, the use of triphenylphosphine and dppf (Entries 7 and 8) led to the formation of bicyclic amine **11**. This process appeared to result from C–N bond cleavage with concurrent amine migration and reduction of the iodide moiety. Further screening of reaction conditions demonstrated that bicyclic amine **11** was formed in good yield through the use of DPEPhos (Entry 9), and that *i*Pr$_2$NEt was required for this process to occur, with either no base or Et$_3$N proving unsuccessful (Entries 10 and 11).

While this process was found to be relatively tolerant of variation of the aryl group (see SI for details), the inclusion of a sacrificial iodide moiety (i.e. X = I) proved essential for reactivity.[15] As noted previously, the protodehalogenation of aryl halides is well documented within cross coupling reactions. Such a process has the potential to generate stoichiometric quantities of HX, which might then facilitate the observed cleavage of the C–N bond.[16] Further evidence for this was obtained from a cross-over reaction where a mixture of iodinated and non-iodinated substrates led to product formation from both (see SI for details). We therefore investigated various additives (Table 2).

It can be seen that the use of an external electron-rich aryl iodide led to efficient reaction (Entry 2). However stoichiometric quantities were required (Entry 3), and the use of simpler, less electron-rich species was less effective (Entries 4–6). Use of iodide anion itself, either alone or in the presence of a weak acid proved ineffective (Entries 7 and 8). However, the use of the HI salt of *i*Pr$_2$NEt proved a real breakthrough, obviating the need for a sacrificial aryl iodide (Entry 9). Exploring the required acid and amine stoichiometry led to further refinement, with a buffered system of 1 equiv. each of methanesulfonic acid and *i*Pr$_2$NEt (Entry 12) proving optimal (see SI for complete acid study).

With these conditions in hand, we explored the scope of this reaction (Figure 1), the substrates being easily accessible via a simple two-step process from pyrrole **1** (R = CO$_2$*t*Bu), involving photochemical conversion to tricyclic aziridine **7** followed by a one pot retro-ene reaction/reductive amination sequence (see SI for details).[6a,c]

The reaction proved very general, with a range of *N*-alkyl, *N*-benzyl and *N*-homobenzyl substrates proceeding in good to moderate yield (**17a–i**). Of particular note is the potential to include a simple methyl group (**17h**), permitting access to *N*-methyl morphan structures, and the medicinally important CF$_3$ group (**17c**).[17] Given the importance of the morphan scaffold to medicinal chemistry,[18] we also explored heterocyclic substituents. The reaction proved to tolerate a range of electron-rich (**17l**, **o**, **r**) and electron-poor (**17j**, **n**) heterocycles, albeit in reduced yield. *N*-tosyl system (**17t**) was also explored but proved unreactive.

The rapidity with which such complex, sp^3-rich aza-systems can be reached from a single parent pyrrole is a significant highlight of the methodology, as is the ability to include reactive functional groups as in **17p**. Importantly, *N*-deprotection can be readily achieved to form **19**, permitting the installation of additional functionality on nitrogen in only two further steps. This could allow a practical approach to further expand the range of R groups in **17**. Exchange of PMB for the more versatile Cbz protecting group is conveniently achieved in a single step, as shown in the formation of **18**. This could be a significant advantage for a medicinal chemist wishing to pre-

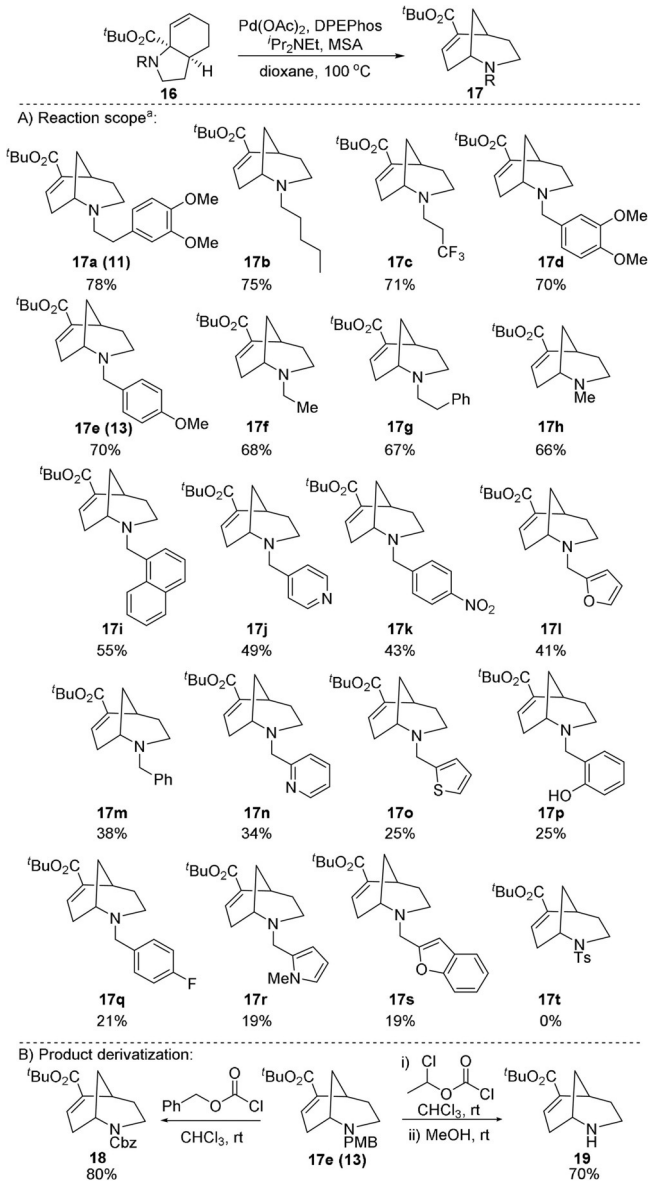
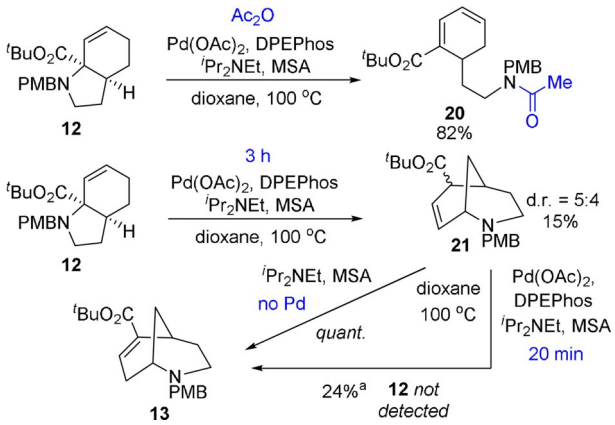


Figure 1. Reaction scope and product derivatization. [a] Pd-catalysed reactions were performed using 10 mol% $Pd(OAc)_2$, 20 mol% DPEPhos at 0.2 M concentration for 20 h. Amine to acid stoichiometry was 1:1.

pare a 2D-library of compounds by dual functionalization of the ester and amine moieties in **17**.

Having established the scope to be relatively broad, we turned our attention to the reaction mechanism. Formally a rearrangement, we considered that the process most likely involved acid-assisted cleavage of the C–N bond forming a π-allyl Pd intermediate, from which β-hydride elimination formed a diene. This was tested by the addition of acetic anhydride to a reaction of substrate **12**, where uncyclized acetamide **20** was formed in good yield (Scheme 2). Stopping the reaction at an early stage also showed the presence of intermediate **21**, consistent with intramolecular 1,6-addition to this diene. Re-subjection of **21** to the reaction conditions showed conversion to **13** even in the absence of palladium. Furthermore, brief treatment of **21** to the optimized reaction conditions gave only **13**

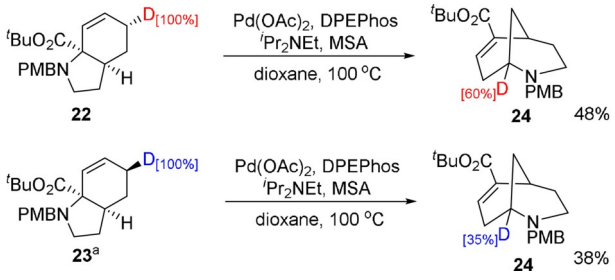


Scheme 2. Investigation of trapping and intermediates. [a] Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. Reaction time of 20 h unless stated otherwise.

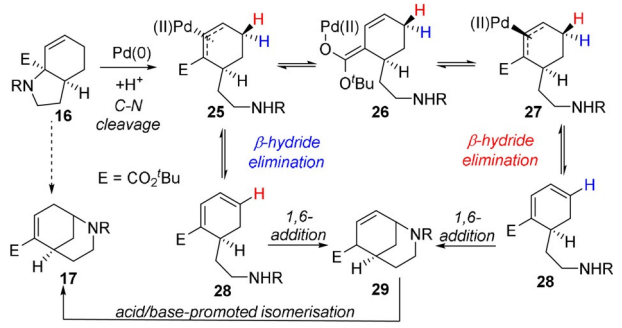
and no starting material **12** was detected. This latter experiment likely indicates that 1,6-addition is not reversible.

We then prepared deuterated compounds **22** and **23** and subjected these to the reaction conditions (Scheme 3). This led to a somewhat surprising results, with both compounds showing deuterium incorporation within the product; in fact, compound **24** showed a higher level of deuterium incorporation at the bridgehead (60% vs. 35%), despite an *anti*-addition[19]/*syn*-elimination[20] mechanism being expected to result in selective cleavage of the C–D bond of **22** and the C–H bond of **23**. Assuming addition of palladium occurs *anti* to nitrogen, such behaviour suggests that facile equilibration of palladium between the *endo* and *exo* faces occurs within the π-allyl Pd complex (vide infra). Further, a competition reaction between **22** and **12** (see Supporting Information for details) suggested no significant kinetic isotope effect was operating, although a secondary KIE, for instance during rate limiting π-allyl complex formation, cannot be excluded.[21]

Based on these results, a mechanism is proposed in Scheme 4. Initial acid-promoted cleavage of the C–N bond by Pd^0 forms π-allyl Pd complex **25**. Based on the similar H/D ratios in the products of deuterated compounds **22** and **23**, this undergoes equilibration between faces, presumably by palladium *O*-enolate **26**,[22] with β-hydride elimination thus



Scheme 3. Deuterium-labelling studies. [a] Substrate **24** contains a second remote deuterium atom ($NCH_{endo}D_{exo}$) as a consequence of the synthetic route, which remained unchanged in the reaction (see the Supporting Information for full details).



Scheme 4. Proposed mechanism.

being possible from either face to form diene **28**, and occurring somewhat preferentially from the *endo* face (i.e. from complex **27**). The exchange of Pd between the faces of the π-allyl complex suggests this species has a significant lifetime, and this combined with the absence of the appreciable primary KIE generally associated with β-hydride elimination,[23] leaves open the possibility that this step to form diene **28** may be reversible. Trapping of this diene is possible through the inclusion of an electrophile such as acetic anhydride (Scheme 2), and otherwise this diene then undergoes irreversible 1,6-conjugate addition to form intermediate **29** as a mixture of diastereomers. These species undergo acid/base-promoted isomerization to the observed product. Related conjugated addition processes have been observed to occur under palladium catalysis.[24]

In conclusion, we have demonstrated that a diverted Tsuji–Trost process provides rapid access to biologically important ring systems. This occurs via an unusual Pd-catalysed mechanism, exploiting processes often regarded as unwanted side reactions that is, proto-dehalogenation, β-hydride elimination and Pd *O*-enolate equilibration. Overall, this methodology provides three-step access to complex, biologically significant molecules from simple aromatic starting materials. The versatility of this chemistry could prove useful for medicinal chemists in the construction of 2D-libraries based on the morphan scaffold, and once again highlights the power of combining photochemical synthesis with palladium catalysis.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: heterocycles · morphan · Pd catalysis · rearrangements · Tsuji–Trost

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Pd-Catalyzed Cascade Reactions of Aziridines: One-Step Access to Complex Tetracyclic Amines

Jonathan P. Knowles,*[,§] Hannah G. Steeds,[§] Maria Schwarz, Francesca Latter, and Kevin I. Booker-Milburn*

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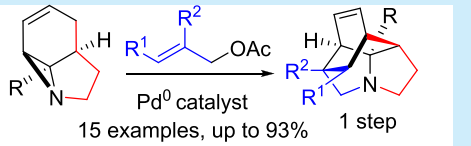
ABSTRACT: The combination of palladium catalysis and thermal cycloaddition is shown to transform tricyclic aziridines into complex, stereodefined tetracyclic products in a single step. This highly unusual cascade process involves a diverted Tsuji–Trost sequence leading to a surprisingly facile intramolecular Diels–Alder reaction. The starting materials are accessible on multigram scales from the photochemical rearrangement of simple pyrroles. The tetracyclic amine products can be further elaborated through routine transformations, highlighting their potential as scaffolds for medicinal chemistry.



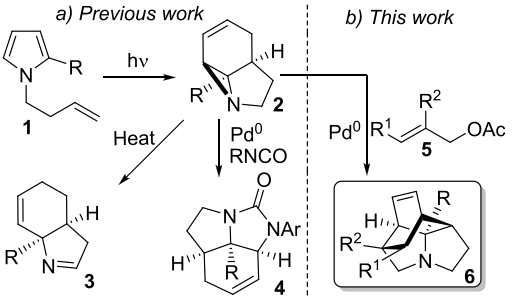
- Stereoselective access to tetracyclic amines
- Diverted Tsuji-Trost/Diels-Alder cascade
- Selective diversification to sp^3-rich scaffolds
- Simple & scalable access to starting materials

Nitrogen-containing heterocycles are among the most prominent structural motifs within bioactive molecules, showing a wide range of activity, including anticancer, antibacterial, and antiviral activity, and some acting on the central nervous system (CNS).[1,2] Compounds rich in sp^3 character are known to perform favorably within the clinic, where their enhanced three-dimensionality leads to improved selectivity.[3] Methodologies for accessing N-containing, complex three-dimensional scaffolds are therefore a key objective for synthetic chemists, potentially allowing rapid access to high-value lead compounds.[4] Cascade reactions represent an ideal route to such compounds, necessarily adding significant complexity in a single transformation.[5]

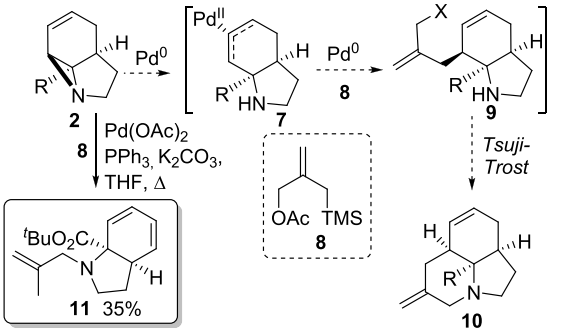
Synthetic photochemistry has a long history of creating highly complex molecules.[6] These products are frequently reactive, thus proving to be versatile intermediates in synthesis.[6,7] Catalytic modification of such products continues to harbor interest, forming conformationally constrained, saturated heterocycles. We have previously shown tricyclic aziridines **2**, formed directly from pyrroles **1**,[8] are particularly versatile intermediates in this respect (Scheme 1a).[9,10] Herein, we report an efficient single-step approach to the hitherto unreported ring system **6** via a novel three-part cascade process.

Previous Pd^0-mediated ring expansion/cycloaddition of **2** with dipolarophiles gave access to five-membered rings such as **4**,[10] and we were interested in determining whether extension to six-membered rings was possible. We therefore considered whether bifunctional reagent **8** could function as both a mild nucleophile and an electrophile, enabling formation of **10** (Scheme 2). Surprisingly, however, reaction of **2** (R = $CO_2{}^tBu$) gave N-alkylated product **11**, where diene formation and

Scheme 1. Previous and Current Photochemical/Catalytic Sequences to Form Complex Structures[9,10]



Scheme 2. Planned Tsuji–Trost Pathway



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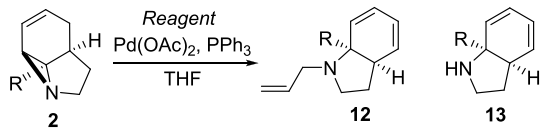
desilylation had occurred. As dienes are key synthetic building blocks,[11] we decided to investigate the scope of this reaction.

Replacing **8** with allyl acetate converted **2** (R = $CO_2{}^tBu$) to allylated product **12a** in a much-improved 87% yield (Table 1). These conditions also proved to be applicable to aziridines

Table 1. Effect of the Variation of the Aziridine and Allyl Reagent



entry	R	reagent	product	yield (%)
1[a,b]	$CO_2{}^tBu$	allyl acetate	**12a**	87
2[b,c]	COMe	allyl acetate	**12b**	56[d]
3[b,c]	CONHEt	allyl acetate	**12c**	60[d]
4[a,b]	CN	allyl acetate	**12d**	0[e]
5[d]	$CO_2{}^tBu$	none	**13a**	83
6[a]	COMe	none	**13b**	82
7[a]	CONHEt	none	**13c**	44
8[a]	CN	none	**13d**	0[e]
9[a,f]	$CO_2{}^tBu$	none	**13a**	0
10[a,g]	$CO_2{}^tBu$	none	**13a**	0

[a]Reaction performed at 70 °C. [b]Performed in the presence of 1.3 equiv of K_2CO_3. [c]Reaction performed at 30 °C. [d]Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [e]Slow conversion to retro-ene product **3** was observed.[9] [f]Performed using $Pd(PPh_3)_4$. [g]Performed using $Pd_2(dba)_3/PPh_3$.

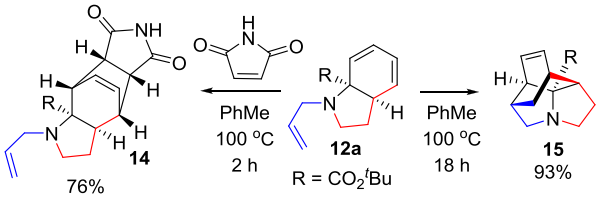
2b (R = COMe) and **2c** (R = CONHEt). Nitrile **2d** proved to be unsuccessful, possibly due to a decreased level of steric crowding of the aziridine ring.[12] Use of allylic bromides rather than allylic acetates also proved to be possible but gave reduced yields and did not remove the requirement for Pd catalysis.

Reaction in the absence of an allylating reagent also proved to be successful, forming secondary amino-dienes **13a–c** in good yield (entries 5–7, respectively). This was found to proceed most efficiently in the absence of K_2CO_3, and again nitrile **2d** proved to be unreactive. Interestingly, these reactions proved to be unsuccessful when other $Pd(0)/PPh_3$-based systems were employed (entries 9 and 10), suggesting a byproduct of catalyst activation might play a key role in aziridine N activation. Consistent with this, the presence of a mild Lewis or Brønsted acid was found to be essential for the reaction to occur (see the Supporting Information for full details).

We then turned our attention to exploiting the dienyl component of these cyclic dienes **12**. Diels–Alder reaction of N-allyl derivative **12a** with maleimide formed the expected adduct **14** (Scheme 3). However, we were intrigued to isolate trace amounts of the intramolecular Diels–Alder (IMDA) reaction product **15**, which was unexpected given the unactivated nature of the dienophile. Simply heating **12a** led to formation of **15** in an excellent 93% yield, demonstrating rapid access to a complex unreported, ring system (three steps from pyrrole **1a**[13]).

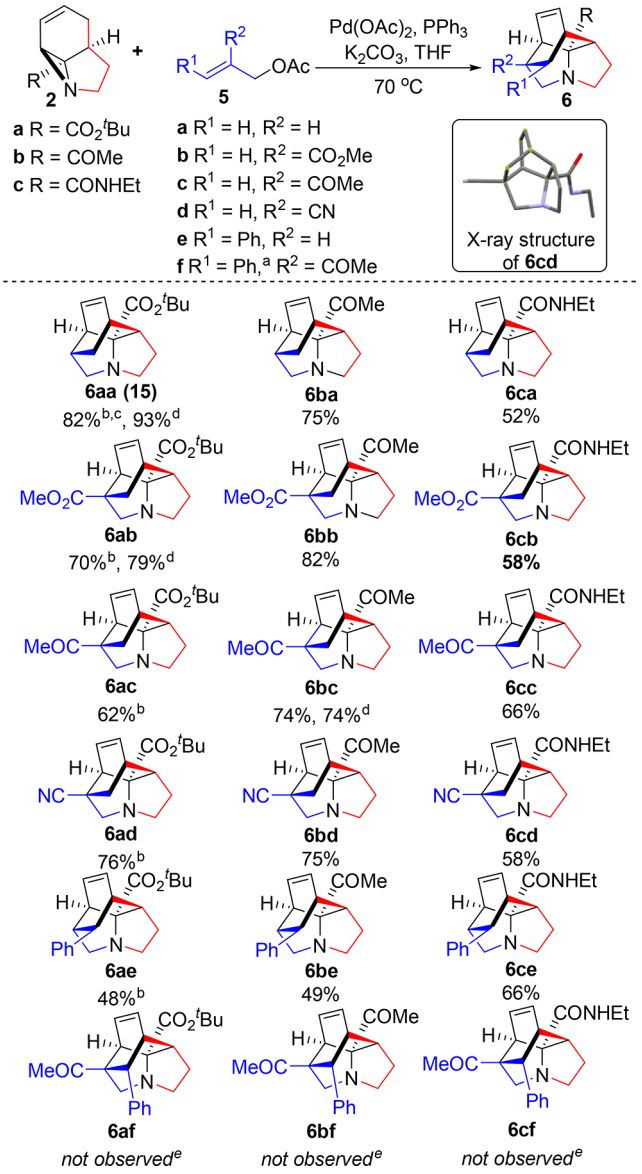
To explore this further, we expanded the range of allylating reagents and moved to performing the ring-opening/cyclo-addition sequence in a single step. This proved to be highly successful, with use of an electron-withdrawing functionality at position 2 of component **5** being well tolerated and

Scheme 3. Inter- and Intramolecular Diels–Alder Reactions of 12a



accelerating the Diels–Alder reaction (Scheme 4). One-pot reaction of **2a** required refluxing in dioxane to effect full conversion in the Tsuji–Trost reaction; however, the less sterically hindered aziridines **2b** and **2c** were found to react

Scheme 4. Scope and Limitations of the Tandem Ring-Opening/Diels–Alder Process



[a]Substituted with R^1 at the methylene rather than the alkenyl position. [b]Performed in dioxane at 100 °C. [c]With 3 equiv of allyl acetate. [d]On a 3 mmol scale. [e]Intermediates **12af–cf** were isolated in 45%, 46%, and 29% yields, respectively.

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fully in THF. Importantly, scale-up of these reactions proved to be facile, with **6aa**, **6ab**, and **6bc** being formed in equal or increased yield on a 3 mmol scale.

Reactions of 3-substituted tether **5e** also proved to be successful, with high regiocontrol for the linear allylated intermediate combining with high *E* selectivity to yield a single stereoisomer. However, attempted reactions of disubstituted allyl acetate **5f** were less successful, with only the allylated diene intermediate being obtained. This likely reflects increased steric demand, where the phenyl substituent of the *E*-alkene would need to adopt an unfavorable *endo*-cyclic position in the transition state.

The cycloaddition step was seen to occur under conditions substantially milder than those of similar IMDA reactions.[14] Indeed, substrates lacking an activated dienophile (i.e., **12a−c**) reacted at 70 °C, and we chose to investigate this further. As observed above, ^{t}Bu system **12a** proved to be less reactive than amide **12c** ($k = 6.8 \times 10^{-6}$ s^{-1} vs $k = 5.5 \times 10^{-5}$ s^{-1} at 75 °C). An Eyring study (Figure 1) demonstrated this variation to be

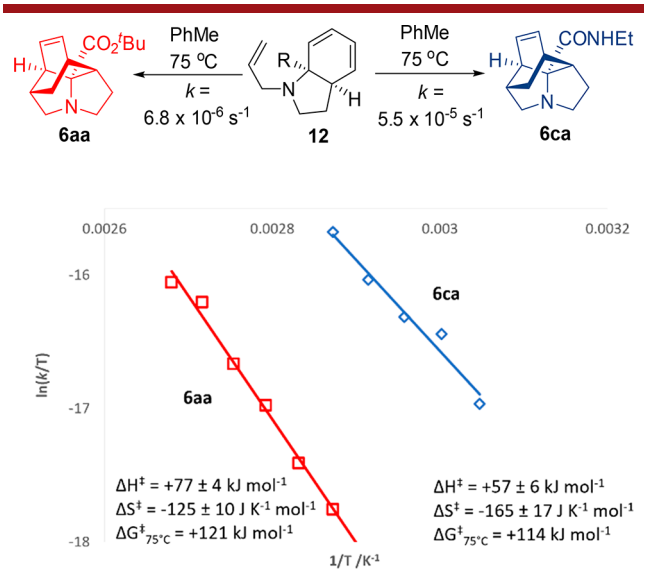
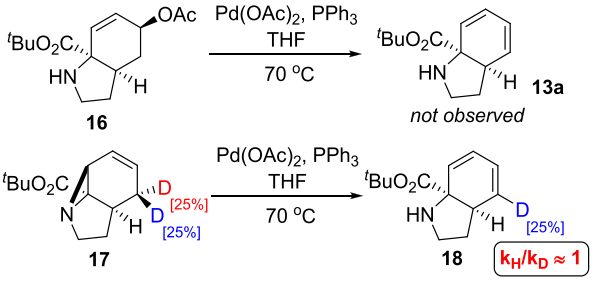


Figure 1. Eyring plots and thermodynamic parameters for the Diels−Alder cyclization to form **6aa** and **6ca**.

largely controlled by the enthalpy of activation, with a 20 kJ mol^{-1} difference between **12a** and **12c**. While it is unclear whether this increase is due entirely to electronic factors or includes an additional conformational element, both values appear to be low when compared with those known for other IMDA reactions.[15] Further attempts to explore the impact of the dienophile activation proved not to be possible due to appreciable formation of **6ab** even at 20 °C, again emphasizing the facile nature of this IMDA process.

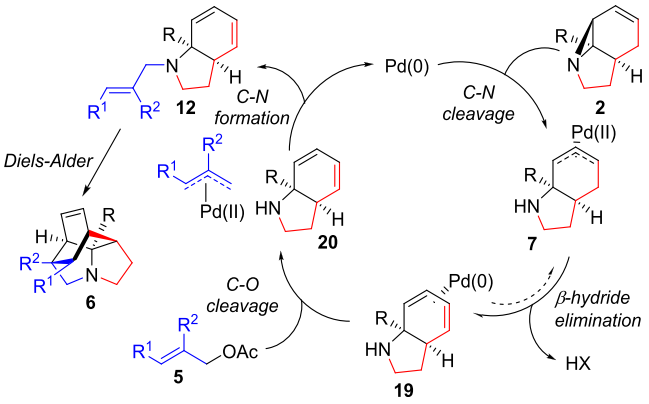
To explore the role of acetate observed in Table 1 [entries 9 and 10 (see also the Supporting Information)], compound **16** was prepared and subjected to the reaction conditions;[13] however, diene **13a** was not observed, ruling this out as a potential intermediate (Scheme 5). Deuterated substrate **17** was also subjected to the reaction conditions, leading to the formation of **18** by cleavage of a single C−D bond. The kinetic isotope effect associated with this process was investigated through a competition reaction with **17** and **2a**, which showed essentially no difference in reaction rate (see the Supporting Information for details).

Scheme 5. Mechanistic and Isotopic Labeling Studies



On the basis of this and the preceding results, the mechanism can be proposed (Scheme 6). Initial additive-

Scheme 6. Proposed Mechanism



assisted, Pd-catalyzed C−N cleavage of **2** leads to the formation of a π-allyl Pd intermediate **7**. This species then undergoes direct β-hydride elimination, even in the absence of additional base, to form intermediate diene **20**. What follows is likely to be a standard Tsuji−Trost mechanism between **20** and allyl acetate **5**, with the added base present serving to ensure sufficient levels of reactive free amine **20**. The lack of a significant KIE associated with this process, as determined by competition (i.e., between **17** and **2a**), is consistent with the first step (C−N cleavage) being turnover-limiting. This low KIE value necessarily means that a reversible β-hydride elimination cannot be ruled out.[16] The resulting N-allylated product **12** then undergoes cycloaddition to form product **6**, the rate of which is controlled by the aziridine and allyl substituents. Although a Pd-catalyzed elimination/intermolecular DA process has been reported previously,[17] to the best of our knowledge, this is the first example of a sequential Tsuji−Trost/IMDA cascade.[18,19]

Given our previous discussion of the importance of a high sp^3 content within drug discovery programs,[3] we undertook a short study to diversify products **6** using routine transformations (Scheme 7). For example, in a telescoped oxidative cleavage/reductive amination sequence, compound **6aa** was efficiently transformed into tetracyclic amino ester **21**, possessing orthogonal protection for further functionalization. Alternatively, selective and sequential ester hydrolysis/amide formation gave **22** in a 47% yield overall, demonstrating potential for efficient two-dimensional amide library formation.

In conclusion, we have shown that stereodefined tetracycles **6** can be formed in only two steps from simple pyrroles, through initial photochemical conversion to aziridines **2**. These

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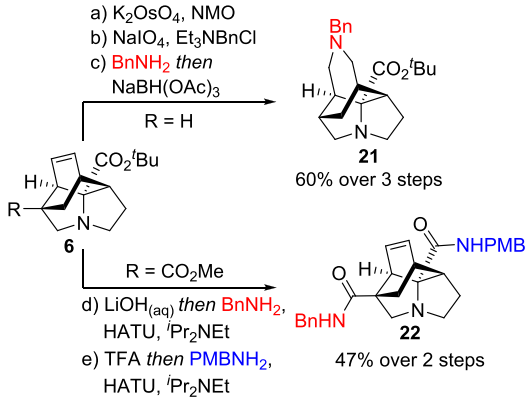
Scheme 7. Functionalization of Tetracyclic Scaffolds



undergo a one-pot diverted Tsuji–Trost reaction, followed by a standard Tsuji–Trost reaction affording the allylated diene, which itself undergoes a direct IMDA reaction. The mechanism of diene formation likely involves rate-limiting acid-assisted C–N cleavage, followed by direct β-hydride elimination. These results underline the power of photochemical/catalytic sequences in preparing complex ring systems. Finally, we have shown that the tetracyclic amines formed from this cascade process undergo further functionalization reactions, highlighting their potential as sp^3-rich scaffolds in drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01403.

Experimental procedures, spectral and analytical data, copies of ^1H and ^{13}C NMR spectra for new compounds, and crystallographic data of **6cd** (PDF)

Accession Codes

CCDC 2047771 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Jonathan P. Knowles − *Department of Applied Sciences, Northumbria University, Newcastle upon Tyne NE1 8ST, U.K.*; orcid.org/0000-0001-5110-4131; Email: jonathan.p.knowles@northumbria.ac.uk

Kevin I. Booker-Milburn − *School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.*; orcid.org/0000-0001-6789-6882; Email: K.Booker-Milburn@bristol.ac.uk

Authors

Hannah G. Steeds − *School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.*

Maria Schwarz − *School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.*

Francesca Latter − *School of Chemistry, University of Bristol, Bristol BS8 1TS, U.K.*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01403

Author Contributions

[§]J.P.K. and H.G.S. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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