SYNTHESIS OF PYRROLOBENZOTHIADIAZEPINES, PYRROLIZIDINES AND INDOLES

By

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A thesis submitted to the University of Huddersfield in partial fulfilment of the requirements for the degree of Doctor of Philosophy

University of Huddersfield

July 2014

I dedicate this thesis to my mother Mavis and my sister Hannah,

without them, getting this far would have not been possible.

We did it together!

x

Acknowledgements

I would like to express my deepest gratitude to my advisor Dr. Karl Hemming for taking a chance on an eager student from across the globe. His technical knowledge, guidance, his adventures of diving and being a triathlete has taught me that being a well-rounded individual is just as important as being a good researcher.

My best friends - my mom Mavis and sister Hannah with a combination of hugs, sacrifice and tough love have supported me through the sweat and tears.

My dearest Shaun for saying I could do this, thank you for being my sounding board especially through my stressful, snappy writing up phase.

My dear friend Alexander, whose kindness and support has been monumental in achieving my dream of a doctorate.

I would like to thank Prof. Craig Rice for his encouragement to apply for the TA position, it made me realise I would like to become a lecturer someday. Our Big Bang theory banter will be some of my fondest memories.

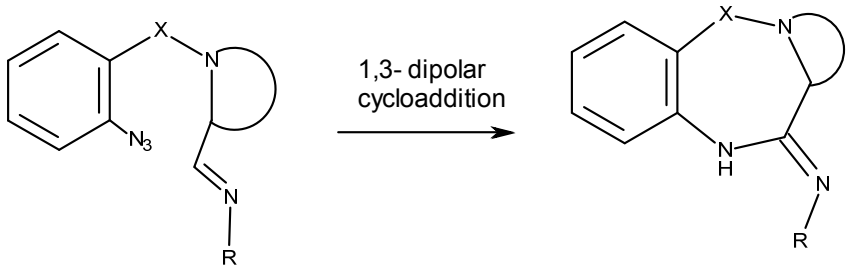
My chemistry and biology teachers at Dhempe College in Goa, Prof. S.P.Kamat and Dr. Savia Torres have inspired me and told me they could see potential to pursue research even when I didn't.

I am fortunate for my friends, for their understanding and love inspite of all the missed weddings, birthdays, engagements and births. My dearest friends Puja, Sam, Amy and Luke I cannot begin to tell you how important you have been on this journey as well as the many others like Charlotte W, Jack, Dharmit, Joe, Lucy, Michael, and Deborah C.

I would also like to thank Dr. Neil Mclay for his NMR and mass spec support, all the members of the IPOS team for their mass spec support and constant smiles, all the technicians and administrative staff in the research office and resource center, have been wonderful and contributed to this experience. Lastly, I would like to thank the University of Huddersfield for their fee-waiver scholarship.

Abstract

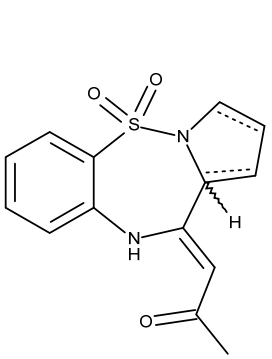
In this thesis, novel syntheses of analogues of pyrrolobenzodiazepines (PBDs) are described. These compounds are of great interest as synthetic targets due to their potential medical properties. The first process involved is the intramolecular 1,3-dipolar cycloaddition between the azide and imine present to form the PBD core, a process that occurs *via* cycloaddition and extrusion of nitrogen. An azide to nitrile cycloaddition was also explored.



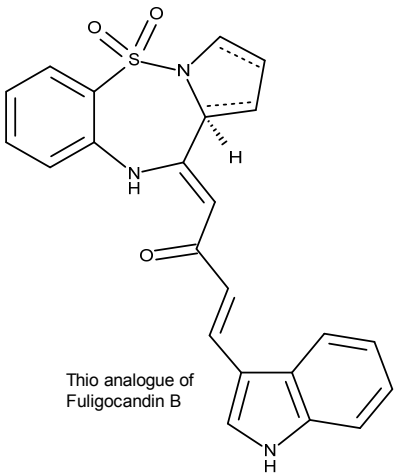
X= SO_2 or CO_2

As an extension to azide work, a series of 2-azidobenzenesulfonamides with homoallylic substituents were investigated as precursors in aza-Prins reactions. Although this was unsuccessful, it led to the observation of an interesting transamination type process.

The attempted synthesis of the sulfur analogues of Fuligocandins A and B are also discussed. Fuligocandin B is known to sensitise leukaemia cells to apoptosis and thus analogues are worthy targets. Synthetic ease drove us to apply the Eschenmoser episulfide contraction to the synthesis of analogues.



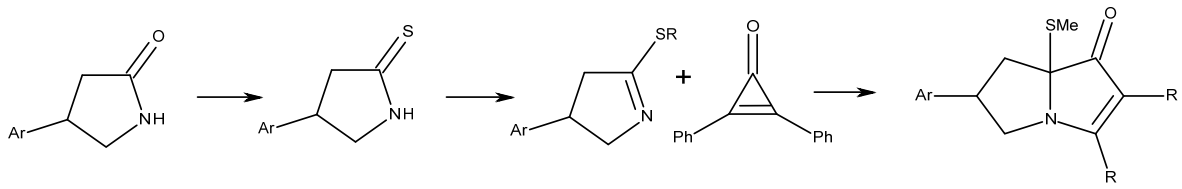
Thio analogue of
Fuligocandin A



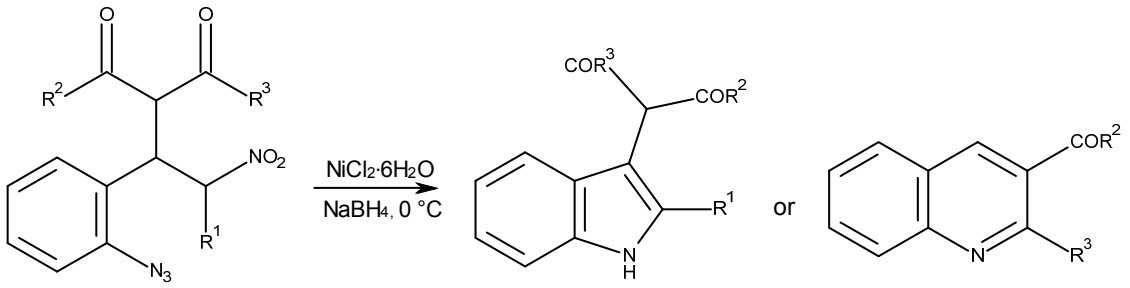
Thio analogue of
Fuligocandin B

The thesis includes the synthesis of other pyrrolo-fused systems with a focus on the indolizidines and pyrrolizidines. These were prepared from the reaction of a cyclic imine

with diphenylcyclopropenone (DPP) as illustrated in the Scheme. The imines were reacted with DPP to study the effect of a large substituent at position 3 to investigate its effect on the stereochemical outcome of the reaction.



While accessing these indolizidines we serendipitously synthesised several examples of indoles and quinoline systems.



Abbreviations

$[M + H]^+$	Molecular ion with hydrogen (MS)
$[M + Na]^+$	Molecular ion with sodium (MS)
~	Approximately
Δ	Reflux
° C	Degree Celsius (Temperature)
MeCN	Acetonitrile
AcOH	Acetic acid
bd	broad doublet
bm	broad multiplet
br	broad (IR)
brs	broad singlet
CNS	Central Nervous System
COSY	Correlation spectroscopy
Cbz	Carboxybenzyl
d	Doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	Dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
Dept	Distortionless Enhancement by Polarization Transfer
DIBAL-*H*	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMF-DMA	*N*,*N*-Dimethylformamide dimethyl acetal
DMSO	Dimethyl sulfoxide
DPP	Diphenylcyclopropenone
DPPE	1,2-Bis(diphenylphosphino)ethane
dt	doublet of a triplet
eq	Equivalents
ESI+	Electron spray ionisation
g	Gram
H	Hydrogen/proton
HIV	Human immunodeficiency virus
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectra
HSQC	Heteronuclear Single Quantum Coherence

Hz	Hertz
IBX	2-iodoxybenzoic acid
iPrOH	Isopropanol
IR	Infra-red
J	Coupling constant (NMR)
M	Molar (unit of concentration, moles per liter)
m.p	Melting point
*m*CPBA	*meta*-chloro perbenzoicacid
mg	Milligram
min	minute(s)
mmol	Millimole
mol	Mole
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Mass spectroscopy
N_2	Nitrogen gas
NMR	Nuclear magnetic resonance spectroscopy
o.n	Overnight
PBD	pyrrolobenzodiazepine
PBTD	pyrrolobenzothiadiazepine
PCC	pyridinium chlorochromate
Pd/C	palladium-carbon
ppm	parts per million
QCS	quinolinium camphorsulfonate
q	quartet
r.t.	room temperature
s	singlet (NMR)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
vs	very strong (IR)
w	weak (IR)
δ	Chemical shift (NMR)
µL	Micro litres (1×10^{-6})
ν_{max}	Frequency of vibration (IR)

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Chapter 1: Literature review

This literature review introduces the pyrrolobenzodiazepines (Section 1.1), pyrrolobenzothiadiazepines (Section 1.2), indolizidines and pyrrolizidines (Section 1.3) and indoles (Section 1.4).

Each section will introduce the topics, focus on selected published syntheses and provide insight into the molecules that form the discussion of this thesis.

1.1 An Introduction to Pyrrolobenzodiazepines (PBDs)

Discovered in the 1960s[1, 2] the pyrrolobenzodiazepines (PBDs) are an important class of sequence selective DNA-interactive agents that bind covalently to guanine bases within the minor groove of DNA[3]. With extensive research being carried out over the last 5 decades, there are now two recognised sub groups of pyrrolobenzodiazepines - the monomers and the dimers (Figure 1.0).

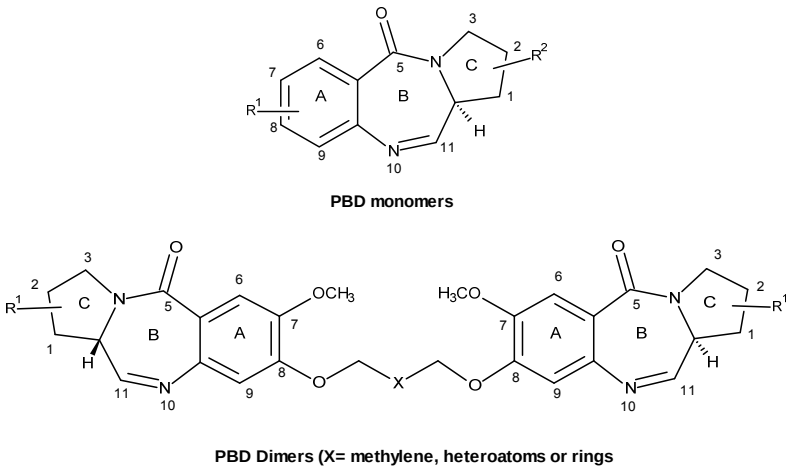


Figure 1.0 Structure of PBD monomer and dimer sub families.

The PBD monomer sub family consists of the compounds originally discovered in the cultures of *Streptomyces* species (eg. anthramycin and tomaymycin) and most recently from *Micrococcus* (i.e. the limazepines[4]) along with a wealth of more recently synthesised analogues.

Their importance lies in their ability to possess a 3D shape[3] which allows them to fit perfectly in the minor groove of the DNA with a right handed twist brought about by the *S* configuration at the C11a position. Chirality is the essential factor that endows biological activity to these compounds.

The mechanism of action of the PBDs is derived from their ability to bind covalently within the minor groove, thus interfering with DNA function. After insertion in the minor groove, an aminal bond is formed through nucleophilic attack of the exocyclic N2 of a guanine at the electrophilic C11-position (Figure 1.1)[5].

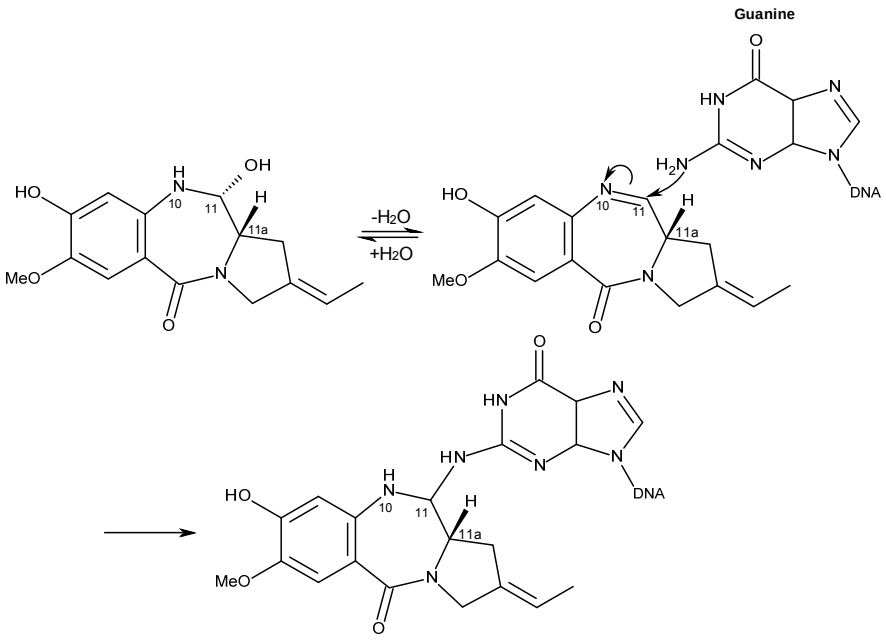


Figure 1.1 shows how PBDs interact with guanine residue of DNA.

The PBD monomers have antibacterial properties and selective cytotoxicity towards tumour cells and their production by *Streptomyces* and *Micrococcus* species has presumably evolved as a means of chemical attack or defence. In addition to the naturally occurring PBD monomers a wide range of analogues has been produced synthetically over the last 50 years. The second sub group, PBD dimers, are not naturally occurring and the first examples[6, 7] were designed to span greater lengths of DNA than the PBD monomers. Their significance arises from their ability to form inter- and intra- strand crosslinks in DNA and be used as chemical probes[8, 9] to study DNA structure and function. More recently pyrrolobenzodiazepine (PBD) dimers have been used as warheads[10] in antibody drug conjugates and have also exhibited significant biological activity against MRSA strains of bacteria[11]. Although the PBD monomers and dimers are of continuing interest, our main focus in this thesis will be directed to PBD monomers and will not cover PBD dimers or conjugates.

All PBDs contain the tricyclic ring system formed by an anthranilate (A), a diazepine (B), and hydropyrrole (C) moieties, shown in Figure 1.0. Different degrees and types of substituents at the A- and C- rings provide chemical diversity among PBDs, for example, PBDs such as sibiromycin and sibanomicin are glycosylated at C7 of the A-ring (Figure 1.2). In addition, the ring C can be fully saturated, unsaturated at the C2–C3 bond, or exocyclically unsaturated at C2 as in neothramycin, anthramycin, and tomaymycin, respectively.

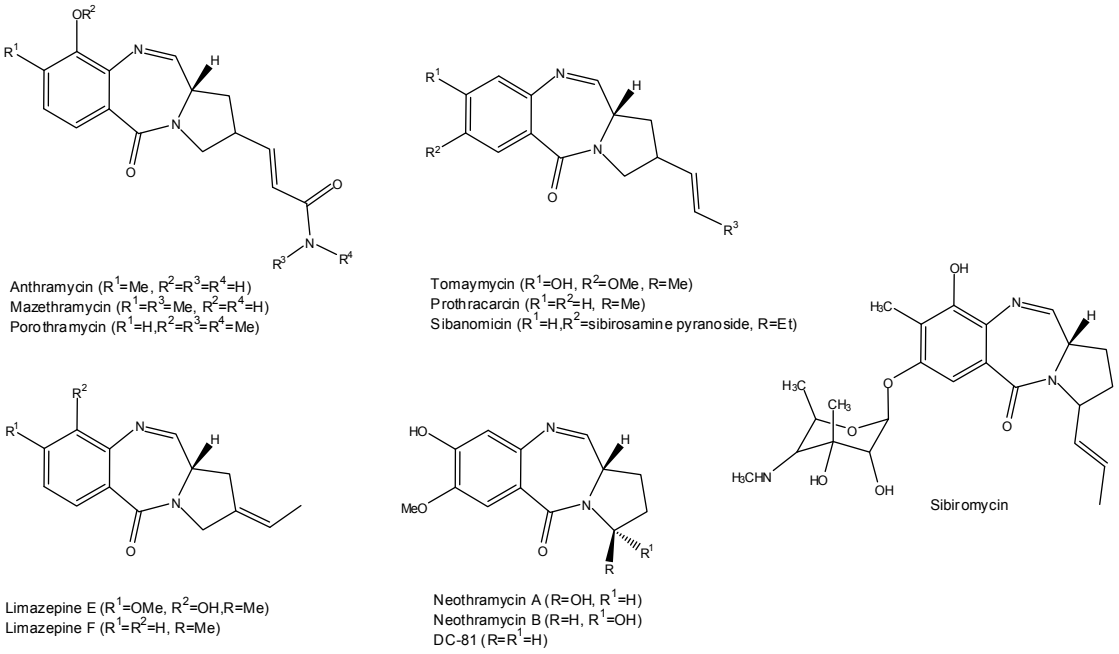


Figure 1.2 shows naturally produced pyrrolobenzodiazepines (taken from a review by Gerratana[12]).

The N10-C11 imine moiety may exist in the hydrated form depending upon precise structure of the compound and the method of isolation or synthetic workup. The imine and methyl ether forms are interconvertible by dissolution of imine in methanol or by heating at reflux the methyl ether at reflux in chloroform followed by evaporation of the solvent in vacuum (Figure 1.3).

Although all three forms are chemically distinct and can be individually characterised by analytical techniques like HPLC, NMR and MS they are generally considered to be chemically equivalent together to represent the parent compound. It is worth noting that for biological reactions the PBDs are always dissolved in aqueous solutions, sometimes containing small amounts of organic solvents (methanol, ethanol, chloroform) depending upon the solubility characteristics of the PBD being studied. In the aqueous environment, the imine **1** and the carbinolamine methyl ether forms **3** are usually converted to the carbinol form **2** as depicted in Figure 1.3. Although the N10-C11 carbinolamine or its chemical equivalent is a prerequisite for antitumour activity, the exact steps of alkylation at the cellular level are not fully known[13].

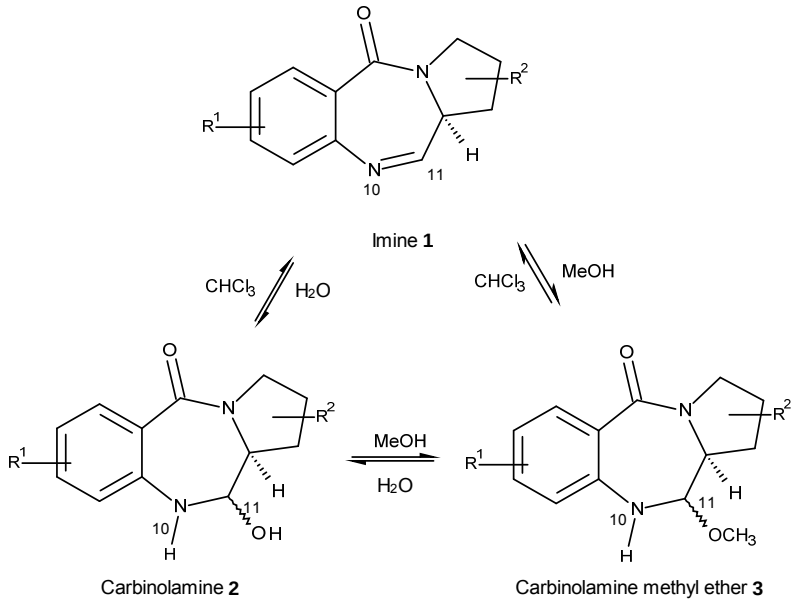
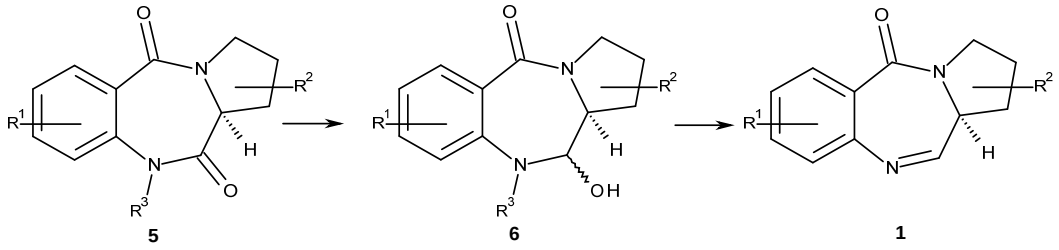


Figure 1.3: Three interconvertible forms of PBDs (imine, carbinolamine and carbinolamine methyl ether) considered to be biologically equivalent.

Leimgruber and co-workers elucidated the structure of anthramycin in 1965 and reported the first total synthesis 3 years later[1, 2, 13]. Their synthetic strategy was based on the reduction of the N10-C11 amide functionality of a PBD dilactam intermediate of type **5** using lithium borohydride which ultimately provided the carbinolamine intermediate of type **6**, which on elimination of water provided the N10-C11 imine **1** (Scheme 1.1).



Scheme 1.1: General approach of the hydride reduction to synthesise PBD imines from PBD lactams.

1.1.1 Synthetic strategies

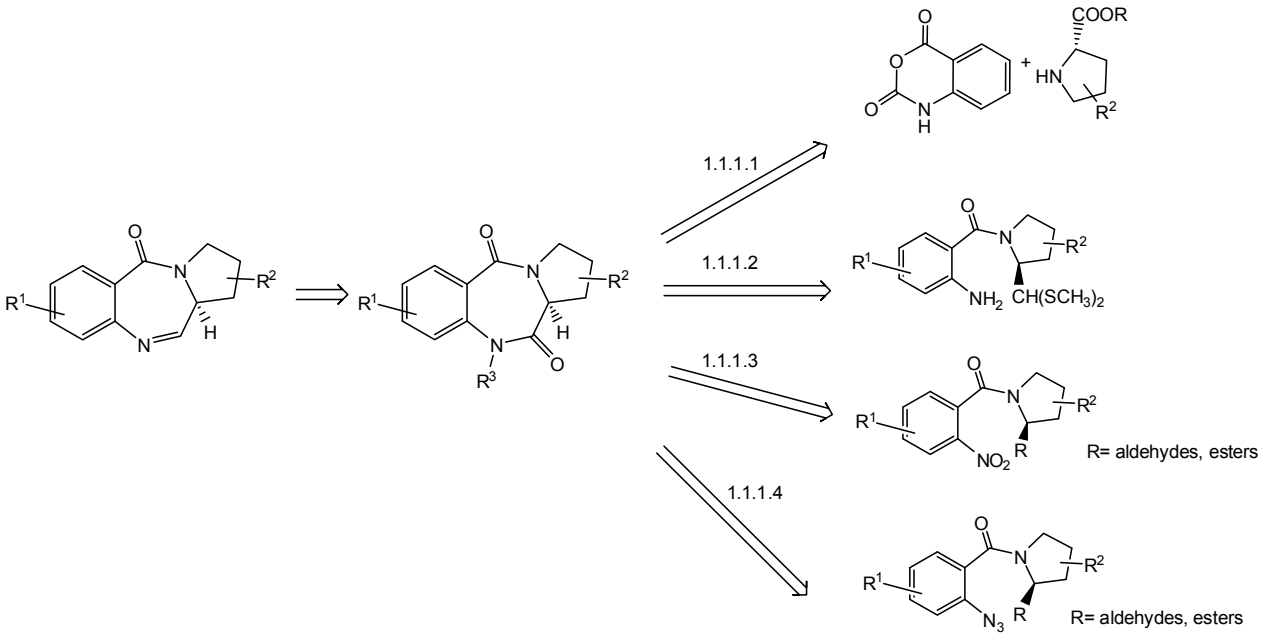
Most of the work we are interested in is based around the crucial B ring cyclisation reaction that allows formation of the PBD skeleton as it is a major focus in our ongoing research projects.

Many synthetic methods for synthesising the PBD core structure have been published and the most up to date review by Thurston and Antonow[13] has broadly summarised the synthetic chemistry literature relating to PBDs. Five decades' worth of synthetic strategies

are available in this review and a full description of all synthetic routes is therefore not necessary in this thesis. Hence, this literature review will focus only on the most commonly encountered synthetic routes with little or no emphasis on side chain manipulations and PBD dimers.

The more common routes to preparing PBDs are represented in Scheme 1.2. They include condensation of isatoic anhydride and *L*-proline derivatives (Scheme 1.2, 1.1.1.1), cyclisation of aminothioacetals (Scheme 1.2, 1.1.1.2), reductive cyclisation of acyclic nitroaldehydes/nitroesters, (Scheme 1.2, 1.1.1.3) and finally cyclisations of azido aldehydes/esters (Scheme 1.2, 1.1.1.4).

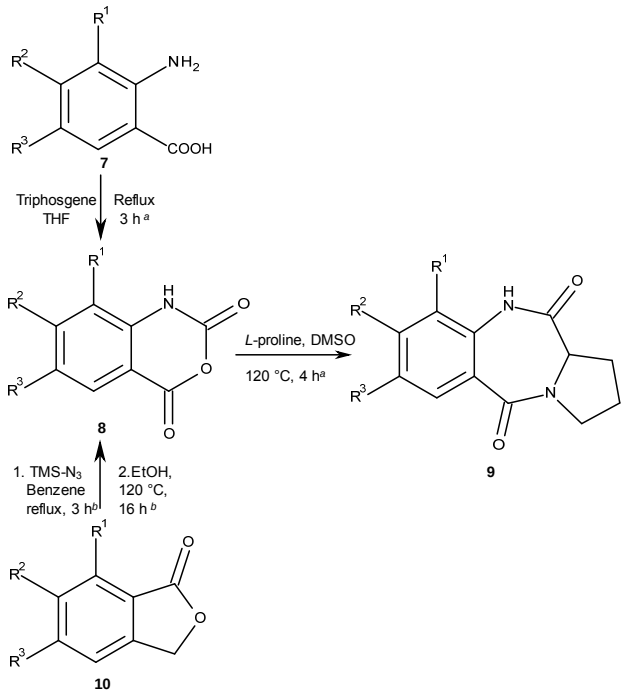
Retrosynthetically, PBDs are often made from their dilactams as shown in Scheme 1.2. Traditionally, the reduction of the amide to imine /carbinolamine is carried out using covalent hydrides[5, 14]. The main protocol in use is hydride reduction in the presence of excess sodium borohydride in ethanol/THF mixture[15] at r.t. to give the imine/carbinolamine.



Scheme 1.2: Retrosynthetic analysis of some of the methods used in the synthesis of PBD systems mentioned in this thesis.

1.1.1.1 Cyclocondensation of isatoic anhydride and substituted prolines

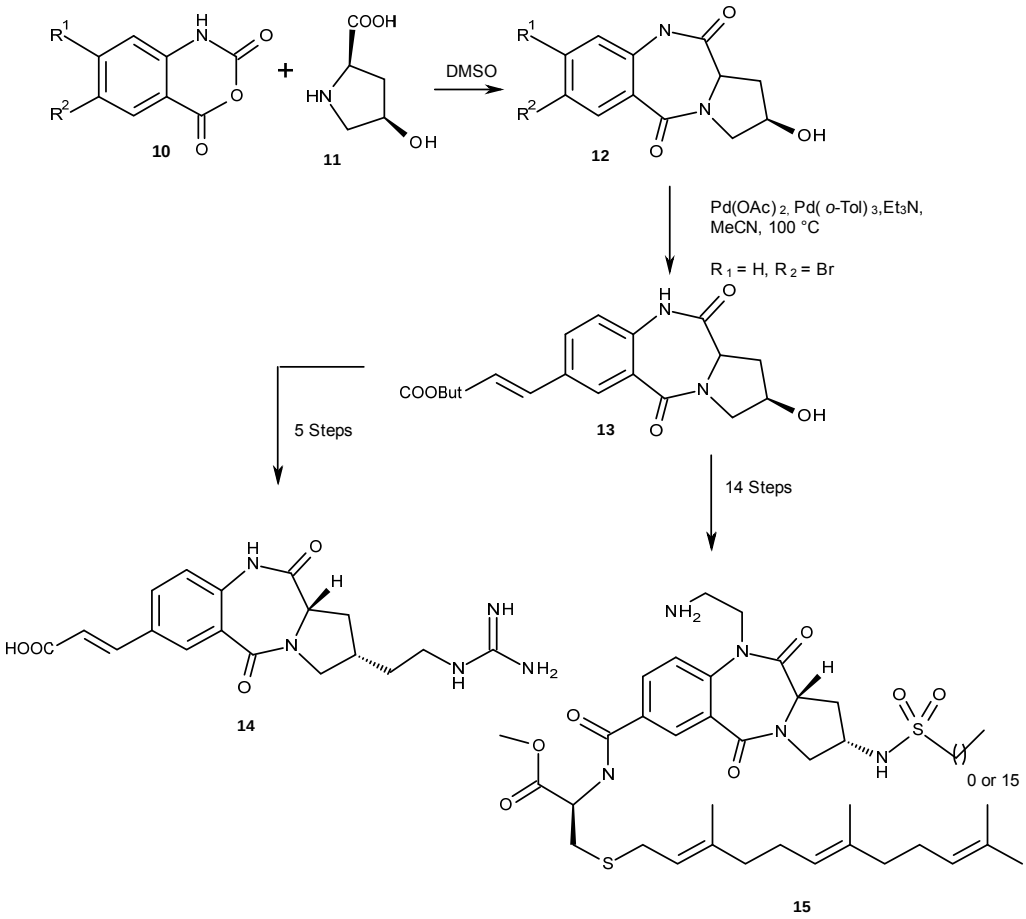
Cyclocondensation of isatoic anhydride and proline has been used as an avenue to synthesise PBDs and analogues to bring about variation in the A and C ring of PBD dilactams.



Where R^1=H, R^2 =OBn, R^3=OCH_3 [a] *reaction conditions according to Wang and co-workers[16].*
R^1=H, OBn,R^2= R^3=H [b] *reaction conditions according to Nagasaka and Koseki[18].*

Scheme 1.3: Isatoic anhydride route for PBD dilactam synthesis.

Isatoic anhydrides **8** are commercially available but can also be prepared in excellent yield by heating at reflux the corresponding anthranilic acid derivative **7** with triphosgene in THF[16, 17]. Alternatively, they can be synthesised *via* a modified Curtius rearrangement by treating phthalic anhydrides **10** with trimethylsilyl azide as stipulated by Nagasaka and Koseki[18] in their synthesis of Tilivalline[19], a naturally occurring PBD isolated from *Klebsiella pneumonia* var. *oxytoca*. Simplicity of the coupling procedure combined with ease of purification, work up and high yields obtained make it a preferred route to PBD dilactam core **9**. The condensation step is not restricted to *L*-proline; 4-hydroxy-*L*-proline and *L*-glutamic acid have also been used to build the PBD scaffold. For example, Jolivet-Fouchet and co-workers[20] synthesised PBD dilactams after reacting 4-hydroxy-*L*-proline **11** with isatoic anhydride **10** in DMSO under microwave radiation for 30 mins (Scheme 1.4). Giannis and co-workers[21, 22] then used this as the initial step towards preparing acyl protein thioesterase (APT1) inhibitors[22] of type **14** and **15**, a process that involved the intermediate **13**.



Scheme 1.4: Cyclocondensation of isatoic anhydride and 4-hydroxy-*L*-proline for the synthesis of PBD dilactam analogues.

In 2004, Nakatani and his co-workers[23] investigated the extract of the fruiting bodies of the myxomycete *Fuligo candida* and isolated cycloanthraniloproline derivatives of the type **16** and **17.** The structures were elucidated using NMR and MS studies and were termed Fuligocandin A and Fuligocandin B respectively.

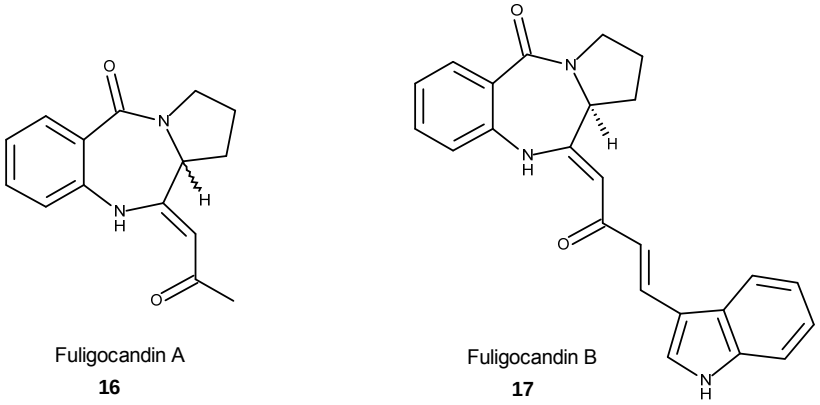
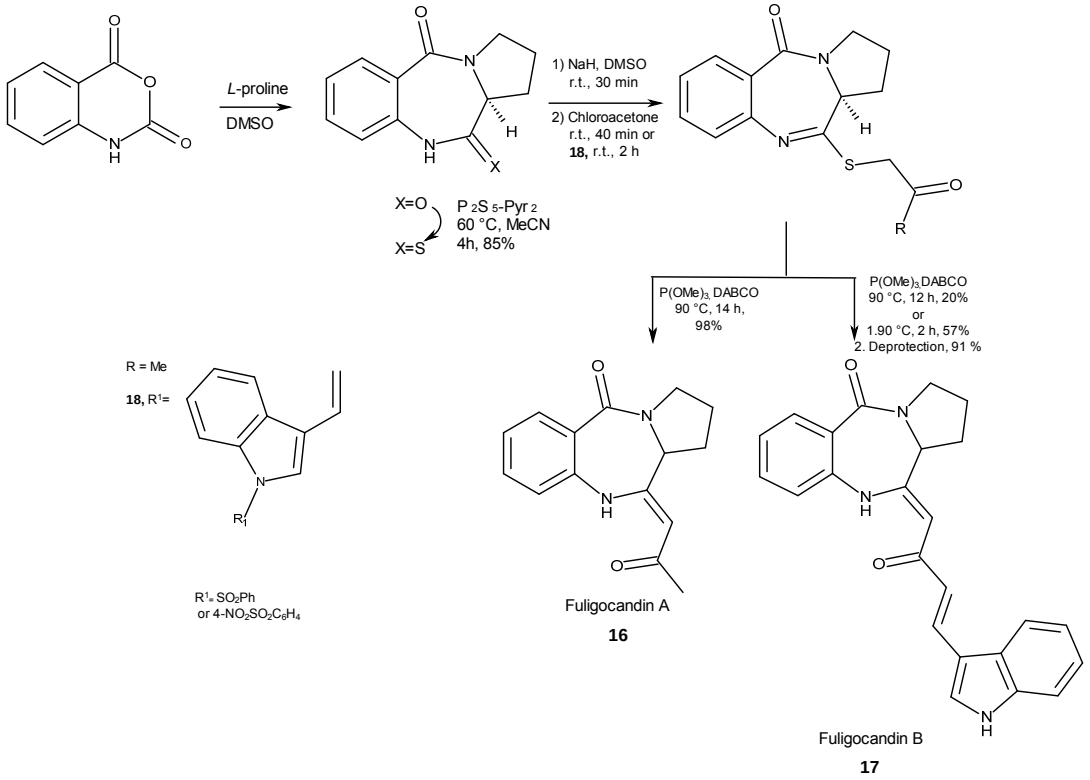


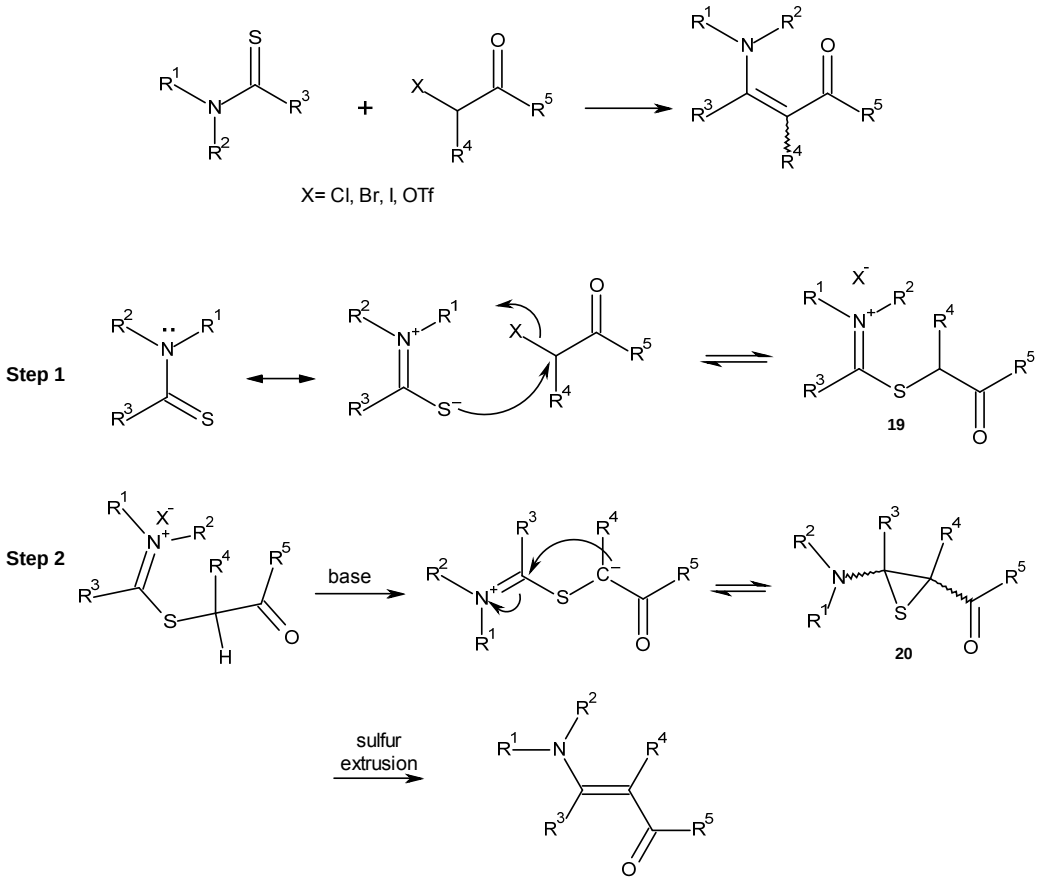
Figure 1.4

A recent study by Hasegawa and his group[24] has shown that fuligocandin B has the ability to sensitize leukaemia cells to apoptosis caused by the tumour necrosis factor related apoptosis inducing ligand (TRAIL)[25]. This biological discovery prompted chemists Bergman and Pettersson to develop a practical total synthesis[26] of Fuligocandin A and B utilising Eschenmoser episulfide contraction as the key method in their synthesis as shown in Scheme 1.5.



Scheme 1.5: Total synthesis of Fuligocandin A and B by Bergman and Pettersson.

The Eschenmoser coupling reaction[27] (sulfide contraction/sulfur extrusion reaction) is a general distinct method for the preparations of β-enaminocarbonyls **18** upon treatment of a thioamide with a suitable α-halocarbonyl component[28] normally a *α*-bromocarbonyl system (sometimes chlorocarbonyl system). Sulfur extrusion as a method to effect carbon-carbon bond formation was first observed by Knott[29] in his investigation of sulfur containing chromophores. Later, a mechanism proceeding through an episulfide intermediate, followed by the extrusion of a sulfur atom was proposed to explain his observation[30, 31] (See Scheme 1.6). Later, the sulfide contraction became more prominent as a synthetic tool when it was implemented by Albert Eschenmoser and applied in the synthesis of vitamin B12[32, 33]. Since these early days the Eschenmoser coupling step has been applied as a successful reaction step in various synthetic strategies for natural products such as sedamine alkaloids[30], sparteine[34] and vitamin B12 derivatives[35].



Scheme 1.6: Mechanism showing the Eschenmoser episulfide contraction.

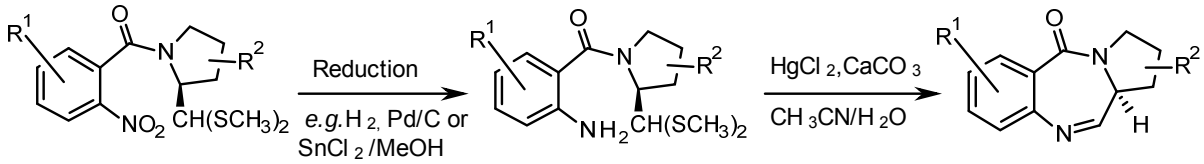
The reaction mechanism consists of two distinct steps (Scheme 1.6): Step 1 is the reversible S-alkylation of the thioamide with an electrophile to form a thioiminium cation **19** and Step 2 is the deprotonation of the proton α to the C=O by a base followed by sulfur extrusion from the episulfide **20** to produce the alkene bond.

The new carbon-carbon bond formation occurs during the construction of the episulfide intermediate which requires base catalysis. Episulfide contraction from the episulfide yields the β-enaminocarbonyl derivative. However the detailed mechanism for the sulfur extraction step has not fully been elucidated[36].

1.1.1.2 Amino thioacetal ring closure

This approach is widely used for PBD synthesis and based on the concept of protecting a pre C-11 position aldehyde group as a diethyl thioacetal functionality. Protection can either be carried out after A- to C- ring coupling (as seen in Scheme 1.7) or a C building

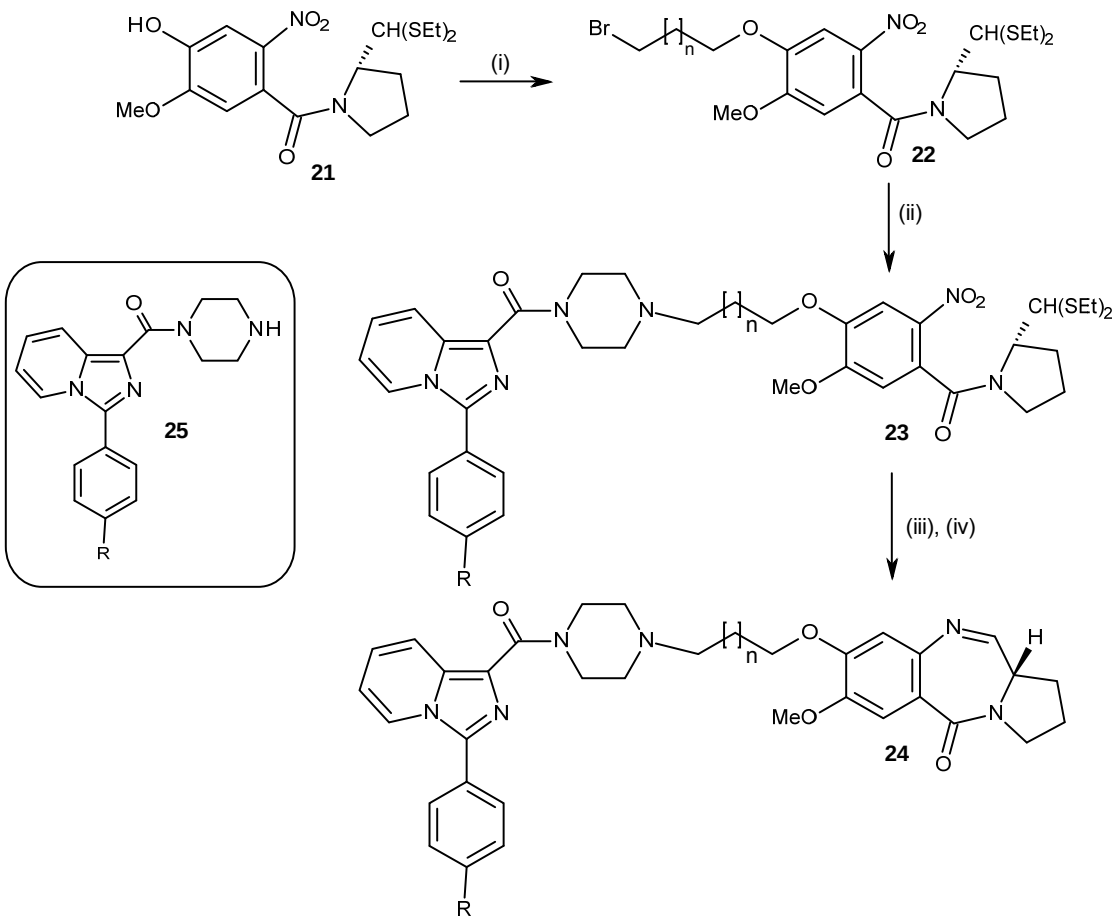
block already carrying the diethyl thioacetal group can be coupled to an A ring. Apart from the ability to introduce the thioacetal group pre- or post- A-/C- ring coupling, the other main advantage is that there have been no reported racemisations at the C11a position of the final PBD structures[5].



Scheme 1.7: Cyclisation of the *N*-(2-aminobenzoyl) pyrrolidine-2-carboxaldehyde diethyl thioacetals to provide PBD imines.

Mercury (II) chloride has been the reagent of choice for the removal of the thioacetal group and to effect ring closure but this brings with it the disadvantage of mercuric salt formation that reportedly makes isolation of the PBD product difficult with reduced yields[37]. The stench of the alkylmercaptan released in the protection-deprotection step and the toxic nature of $HgCl_2$ were other major disadvantages to this approach. In recent reports ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$)[38] and bismuth triflate[39] have been used in the deprotection step of the thioacetal to overcome these problems. Similar thioacetal approaches to the PBD core have also been reported[40-47] for PBD dimers as well as PBD trimer[42] cross linking agents.

Kamal and his group have carried out extensive studies into synthesising and studying mechanistic pathways involved in the synthesis of PBD systems. Recently they extended their methodology to synthesise imidazo[1,5-pyridine]-PBD conjugates[48] as potential DNA alkylating agents. The synthesis of the imidazopyridine PBD conjugates **24** (Scheme 1.8) was carried out by employing the carboxaldehyde thioacetal **21** and imidazo precursors **25** which were synthesised using a previously reported synthesis[49]. The nitro thioacetal **21** was synthesised from its corresponding nitro aldehyde while the imidazopyridine precursor **25** was derived from a 6 step reaction sequence starting with ethyl-2-(2-pyridyl)acetate. Scheme 1.8 shows the nitro group was reduced using $SnCl_2 \cdot 2H_2O$ to provide the amino thioacetals which underwent deprotection and cyclisation using $HgCl_2$ and $CaCO_3$ to provide the desired PBD conjugates in excellent yields.



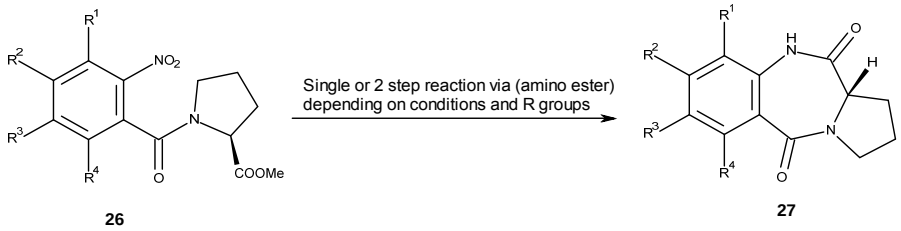
Reagents and conditions: (i) dibromoalkane, K_2CO_3, acetone, reflux, 24 h, 90-96%; (ii) using **25**, K_2CO_3, acetone, reflux, 24 h, 70-80%; (iii) $SnCl_2 \cdot 2H_2O$, MeOH, reflux, 6 h; (iv) $HgCl_2$, $CaCO_3$, CH_3CN:H_2O (4:1), r.t., overnight, 52-60%.

Scheme 1.8: Application of thioacetal approach to prepare PBD conjugates.

1.1.1.3 Nitro based reductive cyclisations

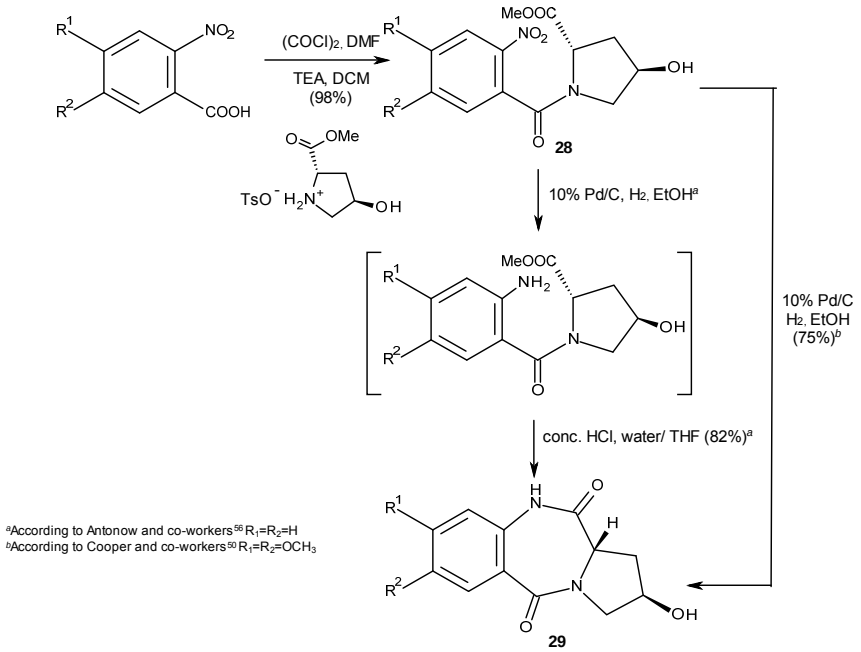
1.1.3a Reductive cyclisation of methyl and ethyl N-(2-nitrobenzoyl)pyrrolidine-2-carboxylates.

Methyl and ethyl *N*-(2-nitrobenzoyl)pyrrolidine carboxylates can be synthesised easily by condensing 2-nitrobenzoic acid derivatives with pyrrolidine derived building blocks. The nitro group undergoes reduction to a nucleophilic aniline which then reacts with the electrophilic pre C11a carbon (i.e. ester carbon) attached to the pyrrolidine ring as shown in Scheme 1.9.



Scheme 1.9: Reductive cyclisation.

Occasionally the reduction-cyclisation step is achieved *in situ* in a single direct step[50, 51] while in other cases, small amounts of HCl or heating at reflux were required to promote cyclisation[52]. Heating nitro esters **26** with $FeSO_4/NH_4OH$ in an EtOH-water mixture[53] (1:1) yielded the desired dilactams **27** in good yields of 86%. Alternatively, other methods[54, 55] for reduction and cyclisation include using elemental iron with glacial acetic acid at 110 °C to afford the PBD dilactams. Catalytic hydrogenation in the presence of palladium on charcoal[50] has also been used for the reduction of nitro groups[56, 57] within *N*-(2-nitrobenzoyl)pyrrolidine derivatives **28** as seen in Scheme 1.10.



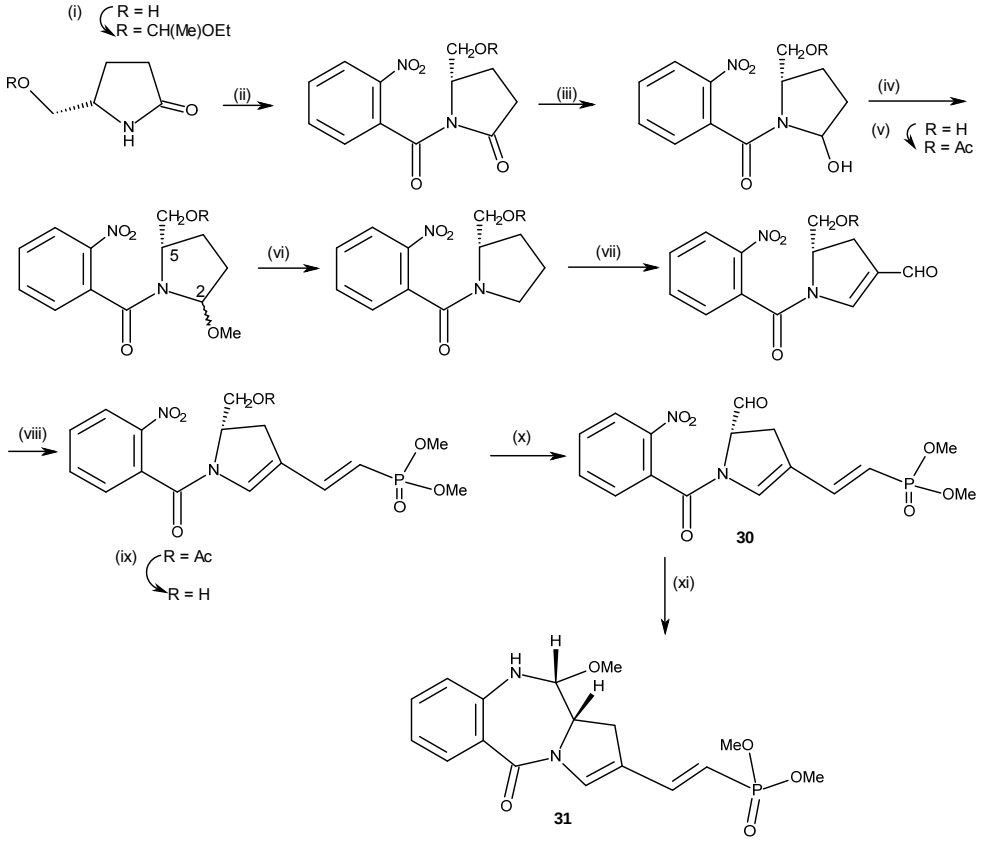
Scheme 1.10 depicts how catalytic hydrogenation yields PBD dilactams.

The disadvantage of employing Pd/C catalyst for hydrogenation in the B-ring cyclisation is that any unsaturated sites in the building blocks would undergo reduction as well. This problem was overcome by chemoselective reduction that was described by Kitamura and his co-workers[58]. They subjected an unsaturated pyrrolidinone derivative of compound **28** to

zinc dust in dichloromethane for 30 mins in the presence of acetic acid to give the PBD without affecting the sites of unsaturation in the pyrrolidine ring.

1.1.1.3b Reductive cyclisation of N-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehydes.

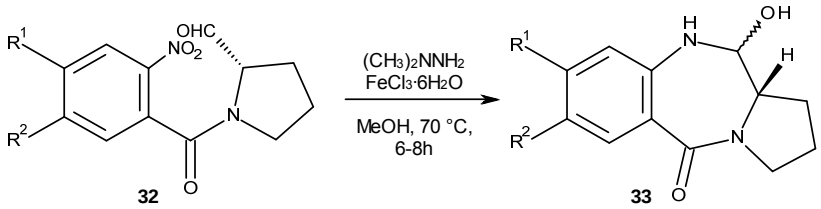
In this approach the pre-C11a is an unprotected aldehyde that undergoes cyclisation to result in a PBD system from reduction of the A-ring nitro group. This strategy has similarities to the cyclisation of the *N*-(2-nitrobenzoyl)pyrrolidine carboxylates discussed previously. Reductive cyclisation was initially reported using palladium catalysed hydrogenation on charcoal[59] of the nitro moiety on the aromatic ring. Thurston and Langley used this approach[60] and found problems of over reduction of the N10-C11 imine bond to produce the biologically inactive secondary amine instead. Langlois and co-workers used the reductive cyclisation approach in the synthesis of (+)-porothramycin[61] **31** and anthramycin analogues as shown in Scheme 1.11. The PBD system was obtained by selectively reducing the nitro aldehyde **30** with Raney-Ni catalyst.



Reagents: (i) Ethylvinyl ether in $CHCl_3$, cat. trichloroacetic acid (97%); (ii) NaH, KI, *o*-NO_2 benzoyl chloride (95%); (iii) DIBAL–*H*, Tol (80%); (iv) MeOH, TsOH (100%); (v) Ac_2O, Py (98%); (vi) 15 mol% QCS, Tol (94%); (vii) $POCl_3$–DMF (100%); (viii) $CH_2[P(O)(OMe)_2]_2$, *n*BuLi (87%); (ix) $Ba(OH)_2$, then CO_2 (86%); (x) DMSO, $COCl_2$, iPr_2NEt (99%); (xi) Raney-Ni, then MeOH, H^+ (36%).

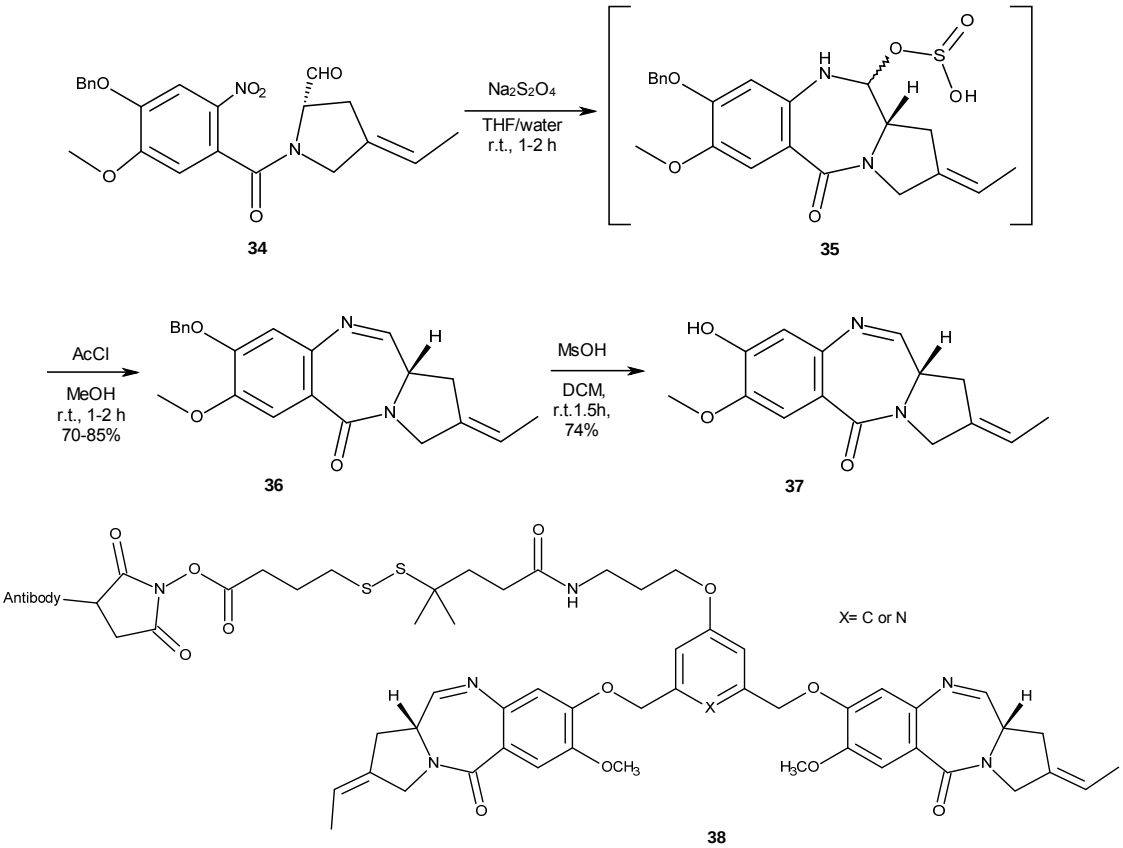
Scheme 1.11 shows the synthesis of Porothramycin analogues according to Langlois et al.

A one pot synthesis approach devised by Kamal and his colleagues using *N,N*-dimethylhydrazine with $FeCl_3 \cdot 6H_2O$[62] to synthesise the N10-C11 carbinolamine **33** from nitro aldehydes **32** is noteworthy because it did not lead to problems of racemisation at C11a, as shown in Scheme 1.12.



Scheme 1.12 shows cyclisation according to Kamal.

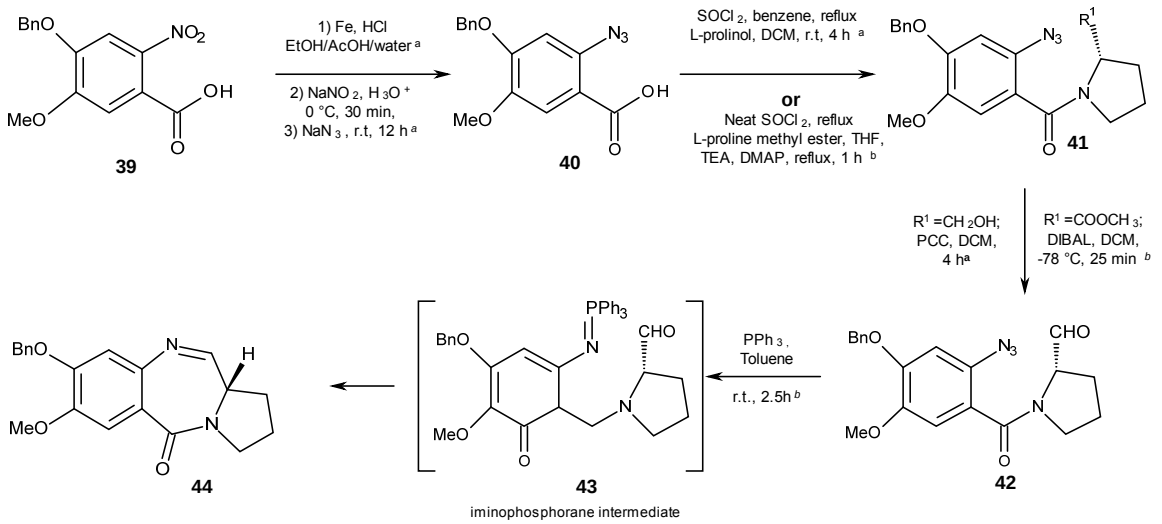
Another approach towards reductive cyclisation reported the use of disodium dithionite[63] ($Na_2S_2O_4$) in THF-water at r.t. gave a C11 hydrogen sulfite intermediate **35** that consequently underwent treatment with acetyl chloride (CH_3COCl) in MeOH to give the imine product **36** in excellent yields (> 85%). This route was applied to the synthesis of PBD "warheads" for use in antibody drug conjugates **38** after coupling with the deprotected **37**[63].



Scheme 1.13: PBD intermediates used in synthesising immunoconjugates.

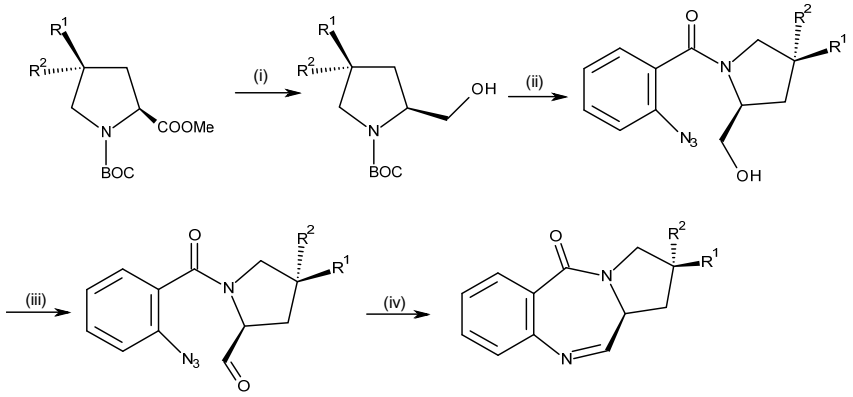
1.1.1.4 Azide based cyclisations:

In 1995, two research groups, Eguchi and co-workers[64] and Molina and co-workers[65] independently described a new method for PBD synthesis involving consecutive Staudinger / intramolecular aza-Wittig reactions of *N*-(2-azidobenzoyl)-pyrrolidine-2-carboxaldehydes **42** (Scheme 1.14). Using this approach both groups synthesised C8-OBn protected DC-81 with minor differences in the reagents used.



Scheme 1.14: The Staudinger and aza-Wittig approach to PBDs.

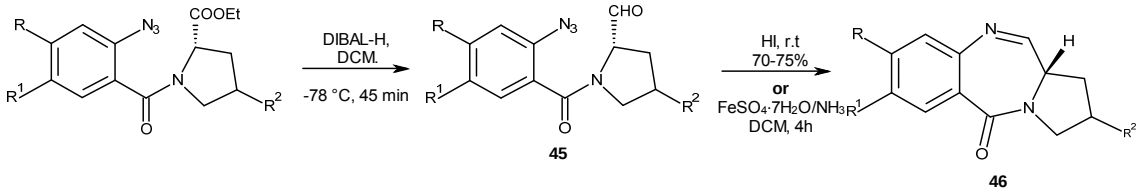
Scheme 1.14 shows the treatment of the azido aldehyde derivative **42** with triphenylphosphine to form the iminophosphorane intermediate **43** (Staudinger reaction) followed by spontaneous aza-Wittig[66] reaction at r.t. to arrive at the PBD ring system **44**. O'Neil later reported difficulties with the separation of triphenylphosphine oxide (Ph_3PO) from the PBD by column chromatography and found a better alternative was 1,2-bis(diphenylphosphino)ethane (DPPE)[67] shown in Scheme 1.15.



Reagents and conditions: (i) DIBAL-H, THF, -78 °C to r.t., o.n., then 4M HCl in 1, 4-dioxane, o.n. (ii) 2-azidobenzoyl chloride, Et_3N, DCM, -78 °C to r.t., o.n. (iii) Dess-Martin periodinane, DCM, r.t., o.n., (iv) DPPE, THF, 2 h.

Scheme 1.15: Staudinger/aza-Wittig cyclisation with DPPE.

Kamal and his co-workers have pioneered many successful synthetic methodologies that involve the reduction of the azide group to an amine succeeded by effective cyclisation that result in PBD imines. For example, the reduction of the azido functionality **45** with HI to initiate ring closure[68] in the formation of the corresponding imine **46** in yields of 70-75% as shown in Scheme 1.16.



Scheme 1.16: HI used as a tool in reductive cyclisation.

The same group also developed a route to PBDs by employing ferrous sulfate heptahydrate with ammonia ($FeSO_4{\cdot}7H_2O/NH_3$)[38] to effectively produce PBD imine systems in good yields ranging from 68 - 72%. They have also employed dialkyl boron triflates[69] as reducing agents as well as carried out extensive research on PBD dimers and conjugates incorporating various heterocyclic functionalities[43, 45, 47, 70].

1.2 Introduction to Pyrrolobenzothiadiazepines (PBTDs)

While the synthesis and biological application of pyrrolobenzodiazepines (PBDs) continue to be investigated and attract enormous attention in the literature, the corresponding sulfur analogue, the pyrrolobenzothiadiazepines (PBTDs) have been under less scrutiny. The PBTDs (see Figure 1.5) are pyrrolobenzodiazepines that possess a sulfonyl group (SO_2) at what was position 5 in the 7 membered 1,4-diazepine ring. These sulfur analogues have

exhibited potential apoptotic activity in K562 leukaemia cells[71-74] and act as potent non-nucleoside reverse transcriptase inhibitors of HIV[73, 75, 76].

A general review by Hemming and Loukou in 2005 covers the synthesis of PBTDs and other benzothiadiazepines[77].

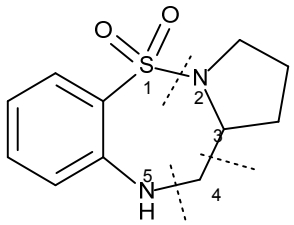


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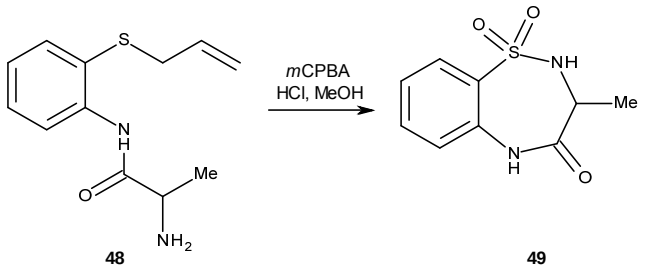
Figure 1.5 shows synthetic strategies *via* different bond formations.

1.2.1 Synthetic strategies

Here the synthetic strategies for the PBTDs are discussed according to the last bond formed. The possibilities are shown in Figure 1.5. Synthesis *via* 1, 2-bond formation and 2, 3-bond formation are not used to synthesise pyrrolobenzothiazdiazepines, while the route that is most commonly used to prepare benzothiadiazepines is *via* 4, 5-bond construction.

1.2.1.1 Synthesis *via* 1, 2- bond formation

Intramolecular sulfonamide bond formation i.e. forming the S-N bond as the approach to synthesising PBTDs is not used. However, benzothiadiazepines can be made in this way. In Scheme 1.18, allyl phenyl sulfide **48** was treated with *m*-chloroperbenzoic acid in concentrated hydrochloric acid and methanol to generate 1, 2, 5-benzothiadiazepine-4-one **49**. The synthesis[78, 79] can be explained by initial oxidation of the sulfur, epoxidation of the alkene and cyclisation where the 1,2- bond formation is accompanied by the loss of the three carbon leaving group.

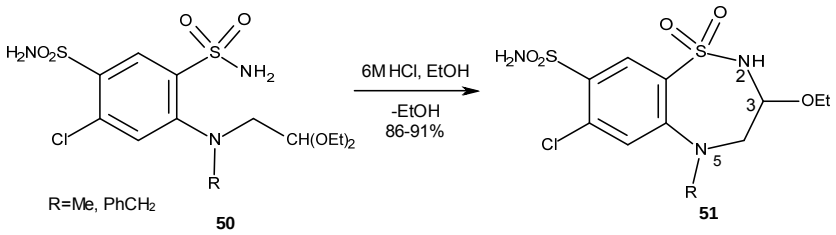


48 **49**

Scheme 1.18: 1, 2- bond formation in benzothiadiazepine systems.

1.2.1.1 Synthesis *via* 2, 3- bond formation

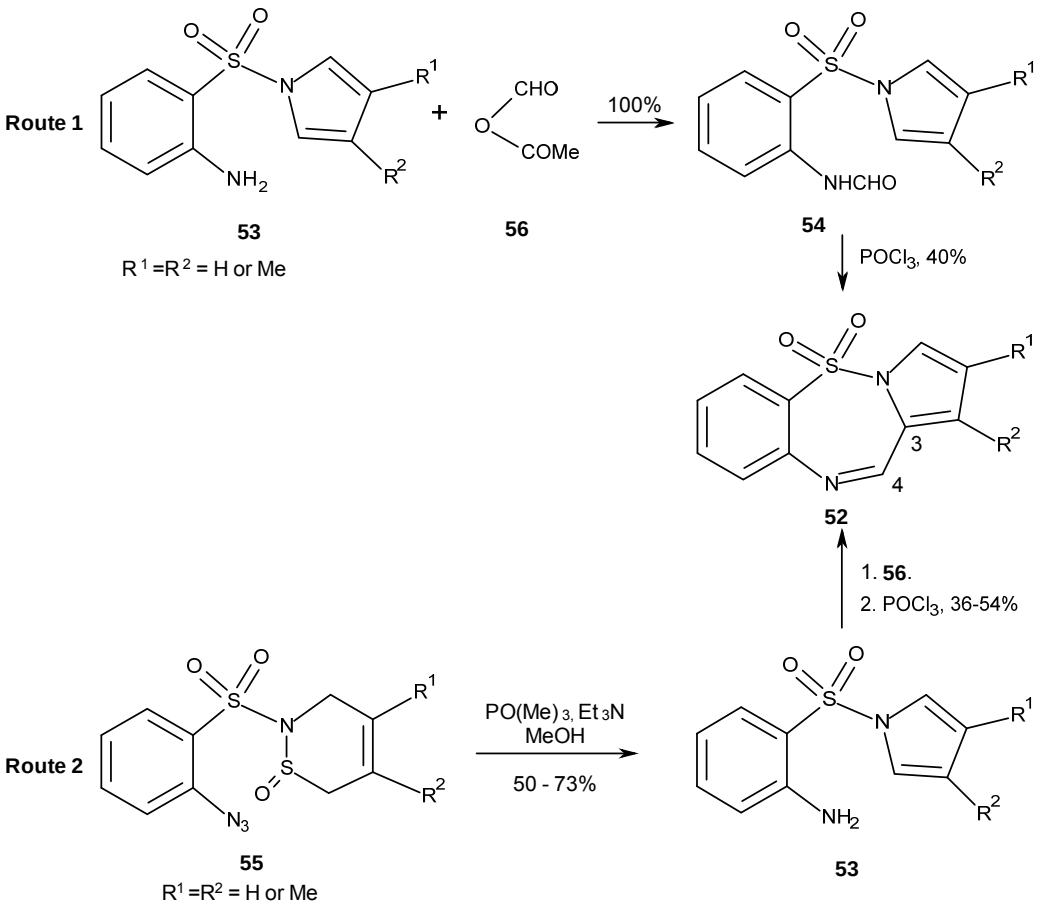
Again, PBTDs aren't made by this route but benzothiadiazepines have been constructed using 2, 3-bond formation. Ring closure effected by nucleophilic attack of the sulfonamide nitrogen on an electrophilic carbon has been utilised. Scheme 1.19 depicts treatment of *N*-β,β-diethoxyethyl-N-methyl- and *N*-benzylanilines **50** with acid which resulted in the elimination of ethanol and therefore produced the corresponding 1,2,5-benzothiadiazepines **51** in high yields[80].



Scheme 1.19: 2, 3- bond formation in benzothiadiazepine systems.

1.2.1.3 Synthesis *via* 3,4- bond formation

This synthetic strategy works well by virtue of the pyrrole ring which possesses the necessary reactive carbon that becomes position 3 of the benzothiadiazepine ring system. Artico and co-workers constructed pyrrole[1,2-b]benzothiadiazepine-1,1-dioxide **52** by a phosphorus oxychloride mediated Bischler-Napieralski cyclisation reaction of the formylated pyrrole precursor **54** (Scheme 1.20). The starting material **53** was derived from the reaction of acetic formic anhydride with 2-aminobenzenesulfonyl chloride[81] which in turn was synthesised in a fairly straightforward reaction between the corresponding sulfonyl chloride and pyrrole.

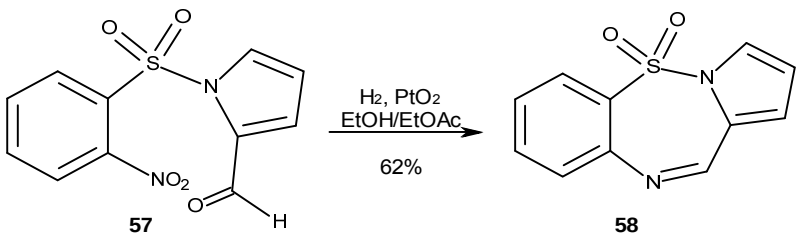


Scheme 1.20 shows routes developed by Artico et al. (Route 1) and Hemming et al. (Route 2).

This *N*-formylation ring closure methodology was then utilised by Hemming and Patel to provide an alternative route to PBTD **52** *via* the 2-(*o*-azidobenzenesulfonyl)pyrroles **53** which were derived from the 2-(*o*-azidobenzenesulfonyl)-1,2-thioxides **55** as shown in Scheme 1.20[82]. The key transformation proceeds *via* a trimethylphosphite mediated ring contraction and desulfurisation of the 1,2-thiazine-1-oxide and is accompanied by the concomitant conversion of an azide to an amine *via* Staudinger reaction and hydrolysis[83].

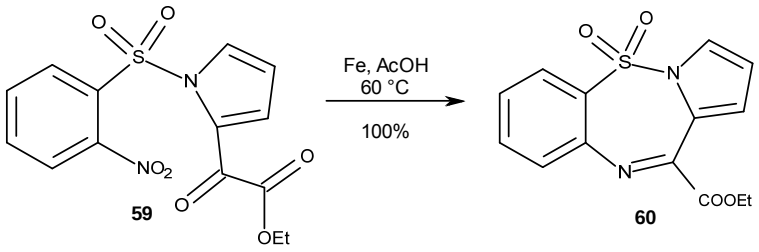
1.2.1.4 Synthesis *via* 4, 5- bond formation

The popularity and ease with which the 4, 5 C-N bond can be constructed makes this by far the most common approach for synthesising PBTDs. The nitro-carbonyl cyclisation approach to tricyclic pyrrolobenzothiadiazepines **58** was first described by Chimenti et al[84].



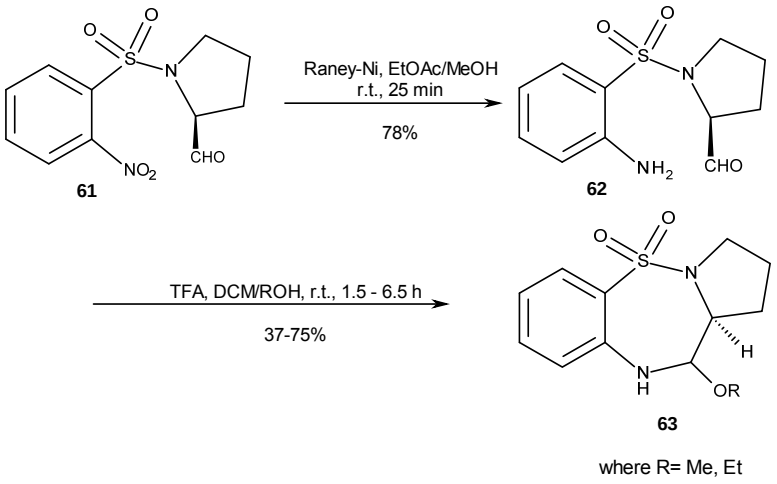
Scheme 1.21: Chimenti's approach using platinum catalyst.

Later, Artico[81] and co-workers improved the yield to 92% when iron and acetic acid were used for the reductive cyclisation step on the same substrates. The same group then extended this approach to nitropyrroles with a glyoxylic ester group[85] **59** in place of the pendant carbonyl functionality Scheme 1.22. Here the glyoxic ester was treated with iron powder in acetic acid to produce the pyrrolobenzothiadiazepine **60** quantitatively with the newly formed imine bond intact in a single step.



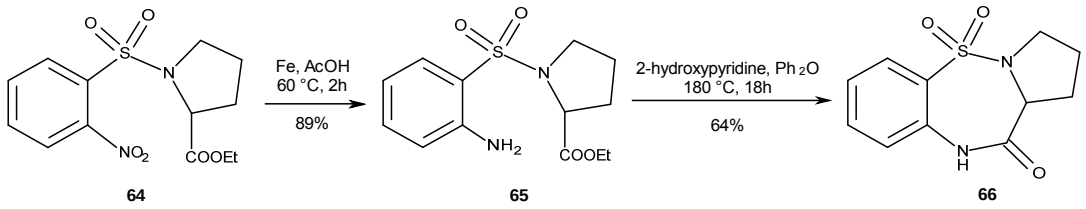
Scheme 1.22: Synthesis of PBTDs *via* nitro hydroxamates reductive cyclisation.

Another group found that reduction with zinc and acetic acid lead to complete over reduction of the imine bond[86]. It is often seen that when reductive conditions are employed with nitro derivatives, the amine intermediate (of type **62**, Scheme 1.23) and the carbonyl undergo immediate spontaneous intramolecular cyclisation. However, Langlois et al.[87] showed that the amino derivative **62** could be isolated when Raney Nickel is used as the reducing agent with the nitro precursor **61** and subsequent cyclisation yielded the desired compound **63** i.e. the sulfur analogue of the natural anti-tumour antibiotic PBD abbeymycin.



Scheme 1.23: Langlois' approach using Raney-Nickel.

Artico et al.[85] later reported that if the carbonyl group used was an ester the amino group derivative was isolatable as illustrated in Scheme 1.24. Intramolecular cyclisation of the aniline **65** was achieved when heating was carried out in the presence of 2-hydroxypyridine as the catalyst which afforded the target molecule in moderate yields (Scheme 1.24).

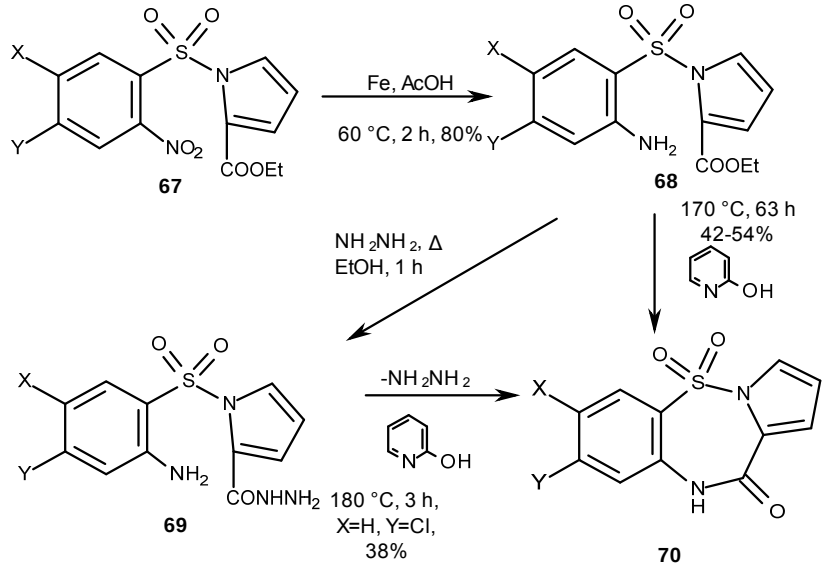


Scheme 1.24 shows Artico's approach using 2-hydroxypyridine.

Reviews[5, 13] have extensively described that the pyrrolobenzodiazepine (PBD) natural products are thought to require a saturated pyrrolidine ring to be present for the compound to exhibit biological activity[5]. However, pyrrolobenzothiadiazepines with intact pyrrole rings have enjoyed considerable attention in the exploration of non-nucleosidic reverse transcriptase inhibitors[79, 88].

Thus, the synthesis of pyrrolo[1,2-b][1,2,5]benzothiadiazepine-4-one-1,2,-dioxides in 42-54% yields was achieved *via* intramolecular cyclisation of the ester[88] **68** using 2-hydroxypyridine to facilitate amide bond formation (Scheme 1.25). Heating the nitro ester **67** in the presence of iron/acetic acid for 2 h delivered the amino ester **68** in high yields (>80%). Alternatively, when the precursor 1-(2-amino-5-chlorobenzenensulfonyl)pyrrole-2-carbohydrazide **69** was heated with 2-hydroxypyridine it formed the desired pyrrolobenzothiadiazepine-4-one **70** in moderate yields after elimination of hydrazine. The

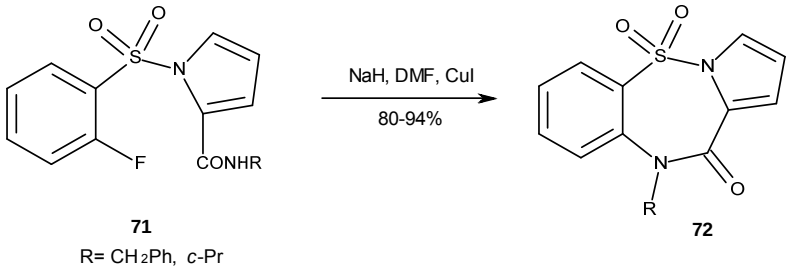
carbohydrazide precursor was prepared by reacting the ester **68** with hydrazine and ethanol[79].



Scheme 1.25: Formation of PBDs with an unsaturated pyrrole ring.

1.2.1.5 Synthesis *via* 5, 6- bond formation

Substituted 5-benzyl (R= CH_2Ph) and 5-cyclopropyl (R= *c*-Pr) pyrrolobenzothiadiazepine-4-ones **72** were obtained in high yields by intramolecular cyclisation mediated by nucleophilic aromatic substitution in the presence of sodium hydride and cuprous iodide as investigated by Artico et al[88] as shown in Scheme 1.26.

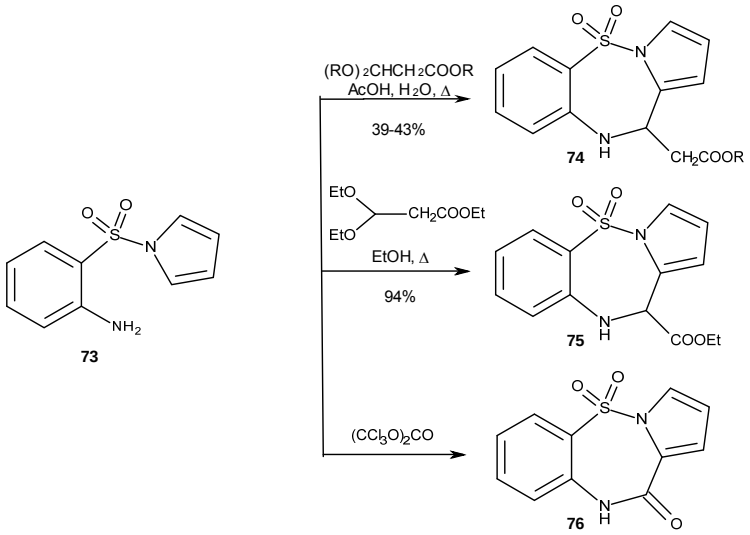


Scheme 1.26: Ring closure by 5, 6- bond formation.

1.2.1.6 Synthesis by other methods

Another method that describes access to PBTDs is the simultaneous formation of the 3, 4 C-C and 4, 5 C-N bond. Scheme 1.27 shows that the reaction with several different substrates can

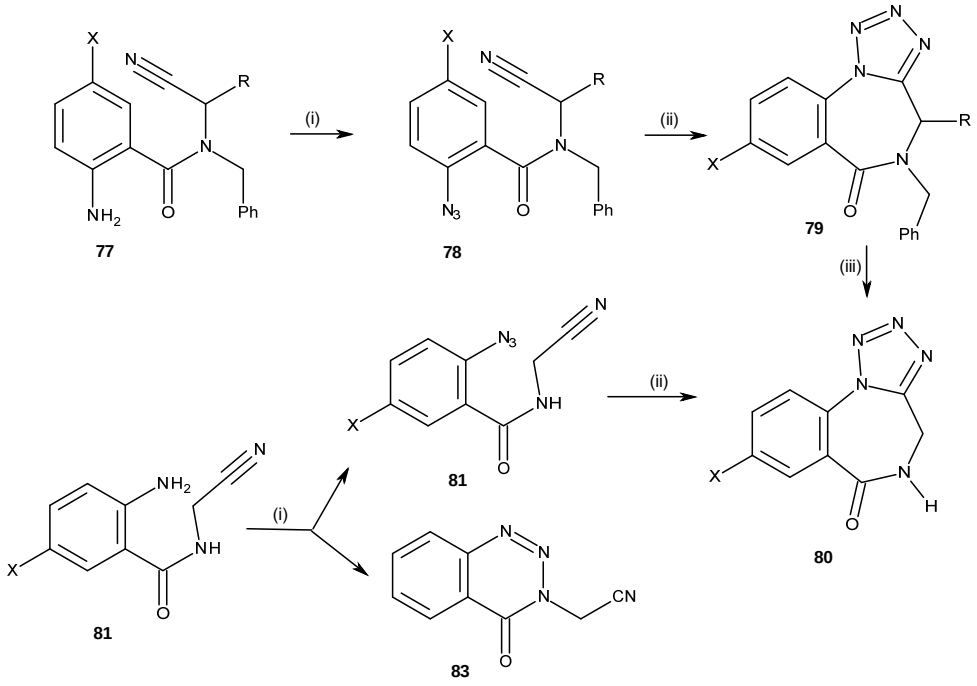
lead to the PBTD motif. The reaction of 1-(2-aminobenzenesulfonyl)pyrrole with alkyl 3,3-dimethoxy propionates (R= OCH_3) afforded **74** while with ethyl glyoxylate hemiacetal furnished **75** in high yields of 94% whilst reaction with triphosgene provided access to pyrrolobenzothiadiazepinones **76**[89].



Scheme 1.27 depicts other available routes to PBTD synthesis.

1.2.2 Other tetra- and tricyclic benzodiazepines, PBDs and PBTDs

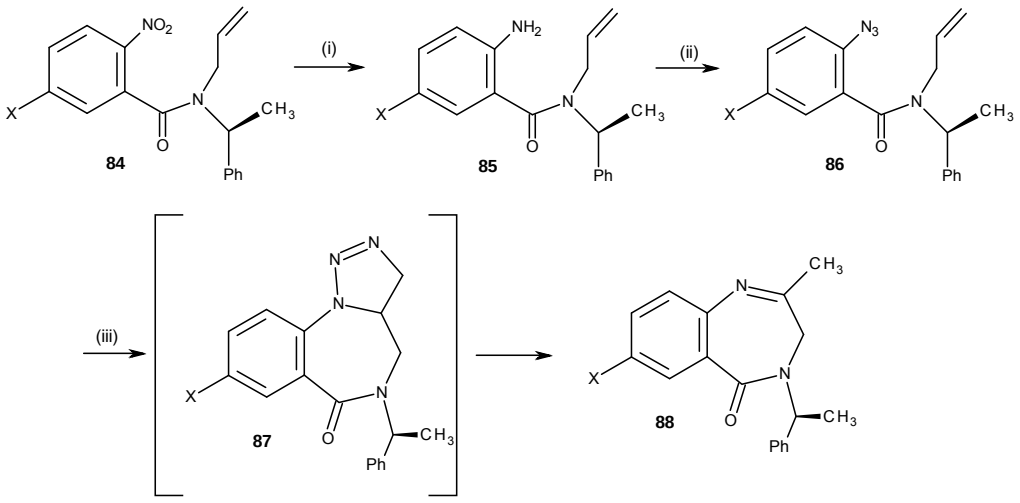
Broggini et al.[90] developed a route to benzodiazepines *via* intramolecular cyclisation between a nitrile moiety and a dipolar azide group. 2-Aminocarbonylanilines **77** on treatment with nitrous acid followed by sodium azide produced 2-substituted aryl azides **78**. The cyclisation step was carried out by heating in toluene to afford the desired target **79** in variable yields (30-95%). The unsubstituted product **80** was deemed a valuable target and hence 2-amino-*N*-cyanomethylbenzamide **81** was converted to the corresponding azide derivative **82**. The reaction yields were low, due to the formation of an undesired side product **83**. Alternatively, **79** afforded **80** by benzylic cleavage with 95% formic acid.



Reaction conditions: (i) $NaNO_2$, HCl, then NaN_3, (ii) Toluene, reflux, (iii) 95% formic acid

Scheme 1.28 shows Broggini's approach to benzodiazepine formation.

The same group[91] then extended their approach to include alkenes and alkynes. The intramolecular cyclisation reaction between an alkene and an azide as shown in Scheme 1.29 proceeded by initial reduction of **84** to give amine compound **85** which on diazotisation followed by azidation with NaN_3 produced **86**. Intramolecular cyclisation brought upon by heating at reflux gave a triazoline product which decomposed to afford the imine **88**.



Reaction conditions: (i) Fe, EtOH, AcOH;(ii) $NaNO_2$, HCl, 0 °C then NaN_3; (iii) toluene, reflux; (X=H/Cl/F).

Scheme 1.29 Broggini and Beccalli's approach to BDs with alkenes.

It is known that intramolecular cycloaddition between an alkene and azide results in the formation of a triazoline **89** which spontaneously collapses to lose molecular nitrogen to provide either an aziridine **90** or methyl imine **91** as shown below (Figure 1.6)[91, 92].

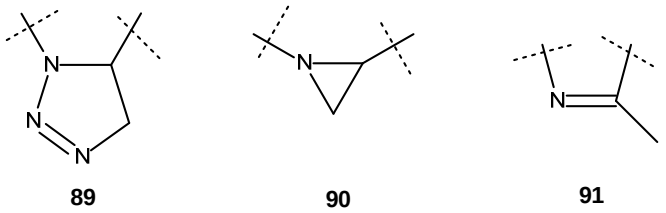
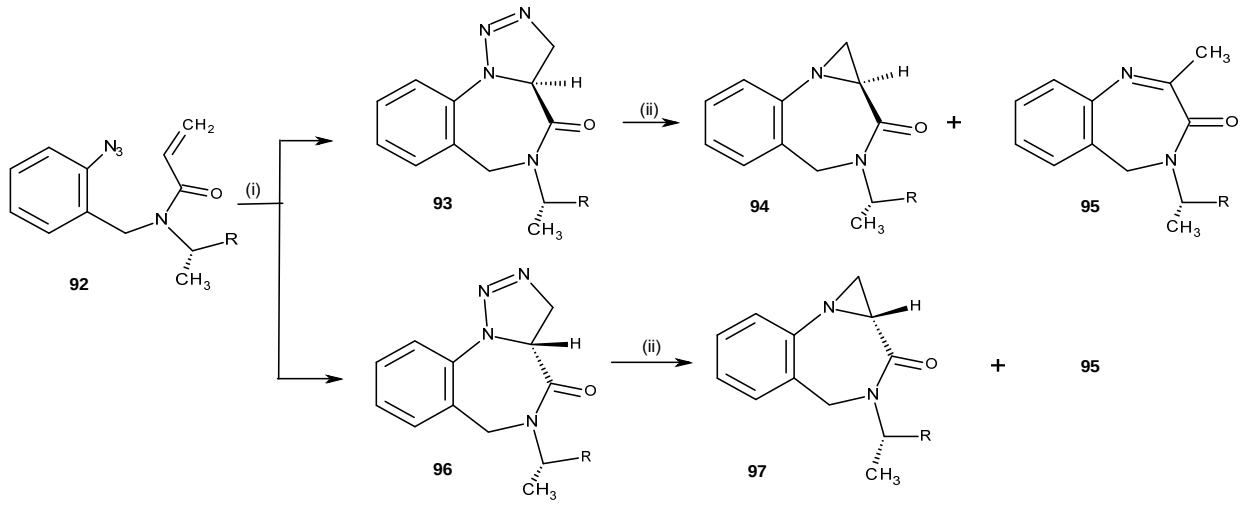


Figure 1.6: Decomposition products of triazoline

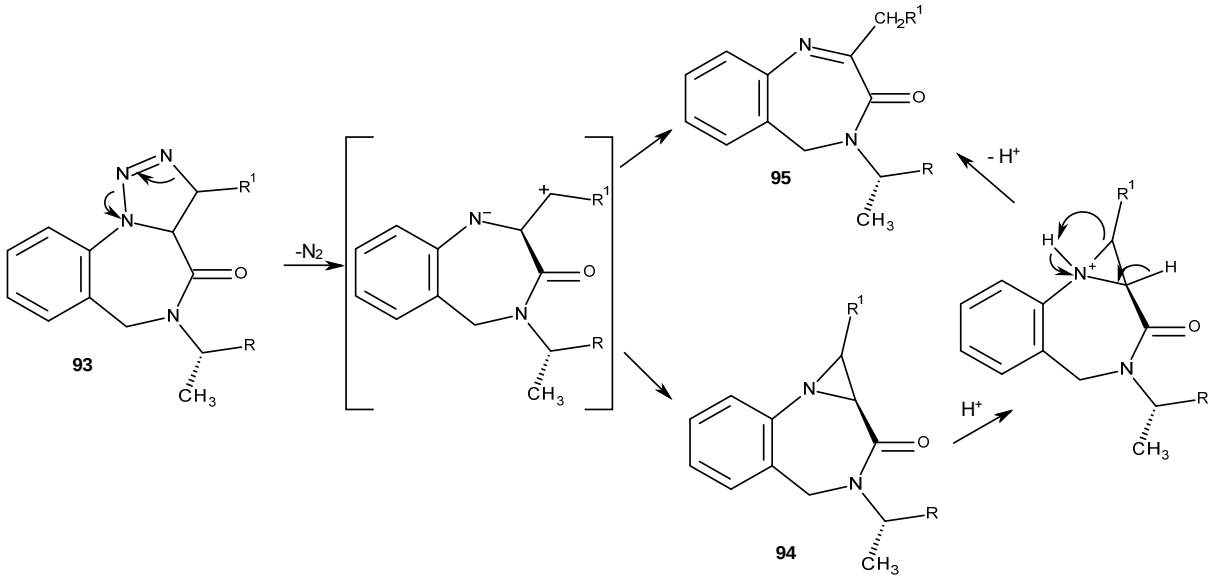
An example of triazoline formation was seen when unsubstituted alkenes underwent immediate intramolecular cycloaddition to give a crude mixture of diastereomeric 1,2,2-triazolo[1,5-*a*]benzodiazepinones **93** and **96**. On heating to reflux in toluene these triazole derivatives gave the corresponding aziridines **94**, **97** and methyl imine **95** *via* nitrogen extrusion[91].



Reaction conditions (i) Et_2O, r.t. (ii) toluene, reflux

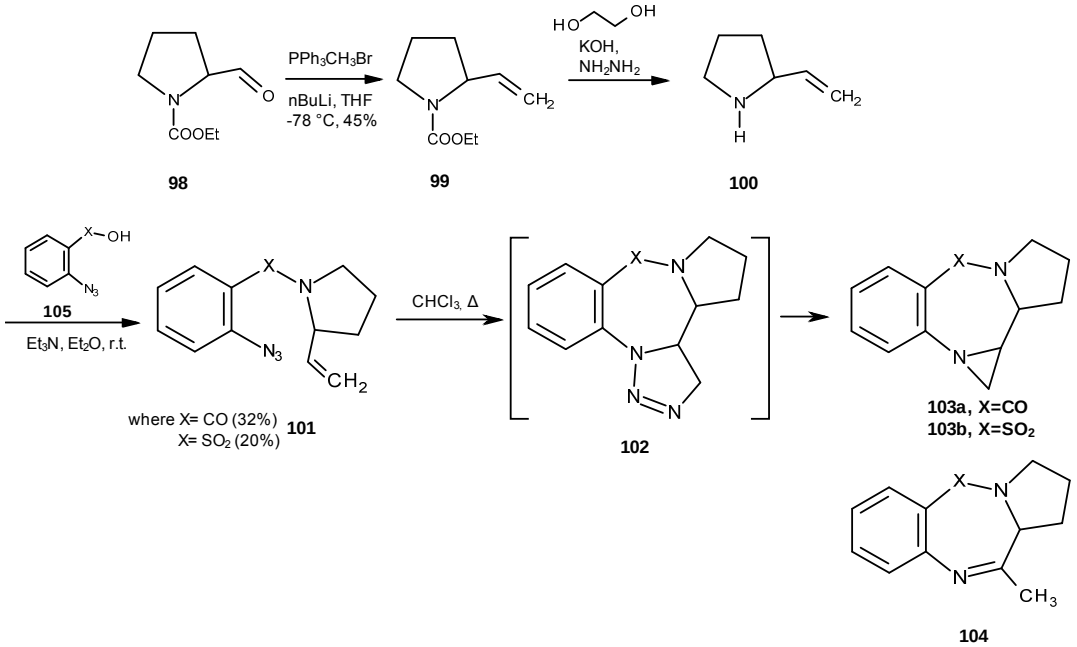
Scheme 1.30 shows intramolecular cyclisation between and alkene and azide.

It has been proposed that the loss of molecular nitrogen is possible by two routes[93] as depicted in Scheme 1.31.



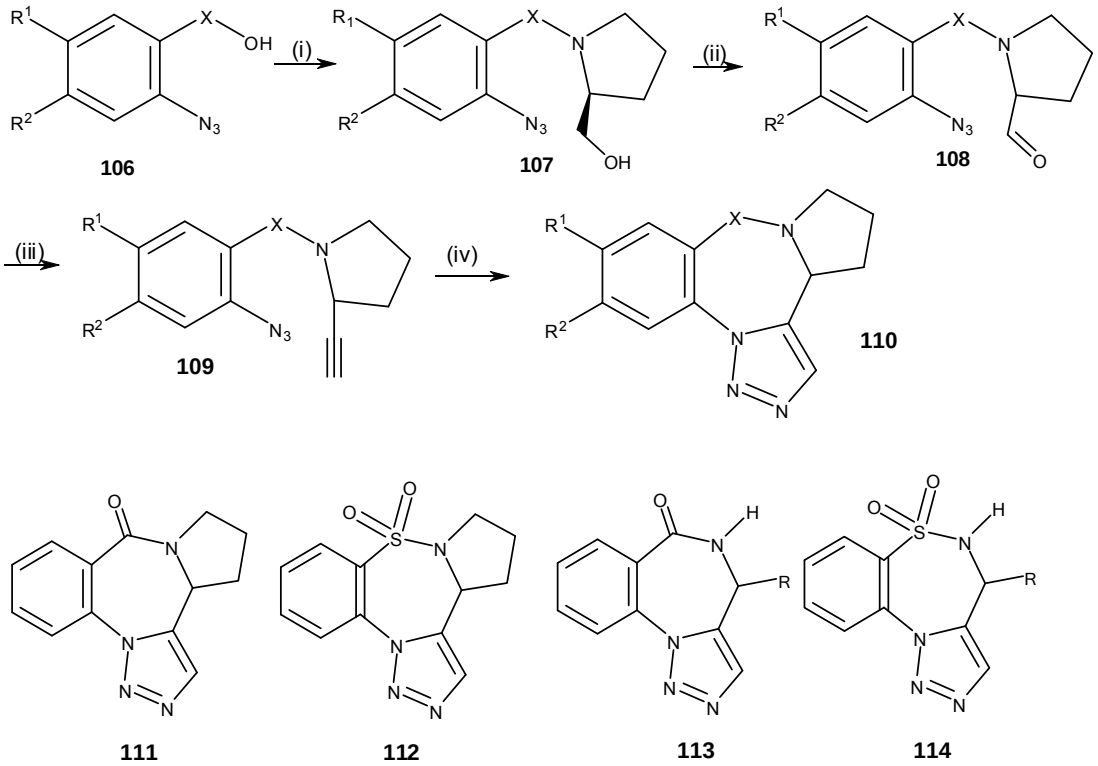
Scheme 1.31. Possible mechanisms for the loss of N_2.

Hemming and his co-workers have also explored the intramolecular cycloaddition based approach towards pyrrolobenzodiazepines (PBDs) and pyrrolobenzothiadiazepines (PBTDs). They have shown that 1,3-dipolar cycloaddition between alkenes[94] and azide moieties present in compound **101** allow access to aziridinopyrrolobenzodiazepine **103a** and the corresponding sulfur analogues, the aziridinopyrrolobenzothiadiazepine **103b**. Broggini et al. reported a similar investigation but isolated the triazolo-PBD (Type **102**) and not the aziridine[91].



Scheme 1.32 displays the intramolecular cycloaddition between an alkene and an azide.

Intramolecular reactions between the azide and alkynes[95] have also provided an interesting route to tetra- and tri- cyclic PBD and PBTD ring systems **110**. Scheme 1.33 begins by reacting the azido carboxylic acid **106** with *L*-prolinol. The resulting alcohol **107** is oxidised to the corresponding aldehyde in good yields (65-75%) utilising Swern's conditions. The aldehyde **108** is converted to the alkyne **109** in a single step using Bestmann-Ohira reagent. The alkynes could not be isolated, as they readily underwent cyclisation to form the triazoles **111** and **112**. When **106** was coupled to other amino acid derivatives, this strategy gave rise to tricyclic benzodiazepines of the type **113** and **114**. Using this strategy a variety of PBDs and their thio analogues were synthesised including systems with the DC-81 and neothramycin substitution pattern. 7



Reagents and conditions: (i)$(COCl)_2$, DCM, r.t. then *L*-prolinol, K_2CO_3, DCM, r.t; (ii) $(COCl)_2$, DMSO, EtN_3, -78 °C; (iii)Bestmann–Ohira reagent, K_2CO_3, MeOH, r.t, (iv)$CHCl_3$, reflux.

Scheme 1.33: Utilising alkenes as a route to PBDs and PBTDs

1.3. Introduction to indolizidines and pyrrolizidines

These heterocyclic systems have attracted interest due to their biological importance and structural complexity. This section provides a general introduction to the indolizidine and pyrrolizidine alkaloids followed by a typical synthesis and a short review specifically on the

cycloaddition approaches involving thioimidates developed in our group prior to the work carried out in this thesis.

The indolizidine[96] and pyrrolizidine[96, 97] heterocycles have attracted attention due to their biological activity. A significant sub-class is commonly known as the 'aza-sugars' or imino sugars since they are bicyclic structural analogues of traditional carbohydrates in which the oxygen is replaced by a nitrogen atom with the nitrogen in the bridgehead position of a bicylic system.

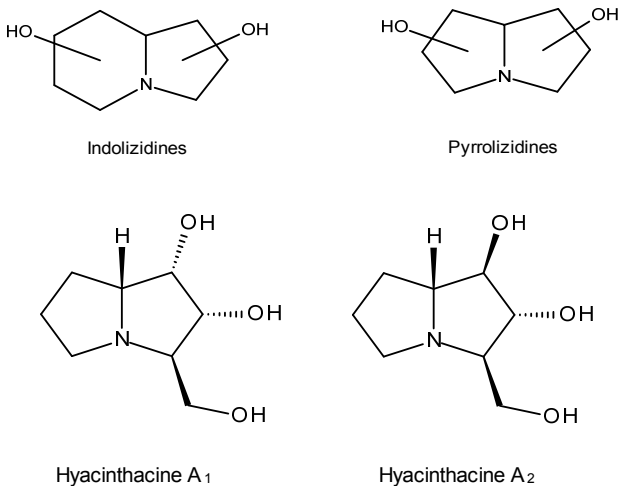


Figure 1.7 Structures and examples of indolizidines and pyrrolizidines.

Typical compounds shown in Figure 1.7 and Figure 1.8 are naturally occurring imino sugars such as hyacinthacines A_1/A_2[98-100], hyacinthacines B_1/B_2[101-103], australine[104-108] and castanospermine[106, 109-112] which have attracted significant attention as glycosidase inhibitors.

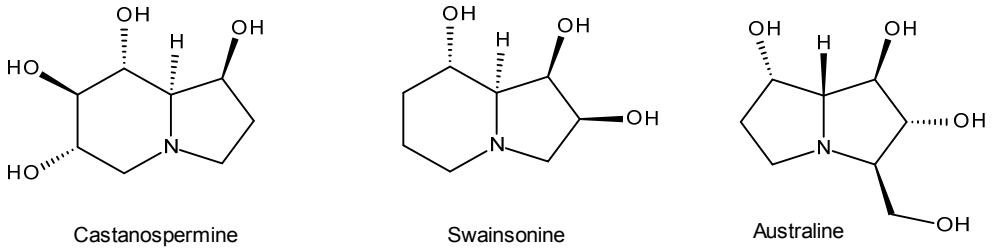


Figure 1.8 Examples of biologically active indolizidines and pyrrolizidines.

Glycosidases play important roles in a number of diseases including cancers, lysomal storage disorders such as Gaucher's disease and type 2 diabetes. Type 2 diabetes can be controlled by administering glycosidase inhibitors that prevent the breakdown of polysaccharides and thus regulate blood sugar levels[113]. Iminosugars have also gained interest as antiviral compounds and antibiotics[114-119]. Hyacinthacine A_1, for example has

attracted interest as a lead in the possible treatment of various cancers, diabetes and viral infections[120].

Also of importance are indolizidine alkaloids with alkyl substituents such as the amphibian derived indolizidine 195B[121] and related systems such as indolizidines 209D, 167B, 223AB and 235B secreted by the skin of a specific species of frog *dendrobatidae.* These compounds function as analgesics and as potential leads in the search for the treatment of Alzheimers and other neurological diseases[96, 122-125].

The pyrrolizidine core is also embedded in natural mitomycins A and C which are potent antitumour antibiotics. Another non-polyhydroxylated pyrrolizidines class is the jenamidines one of which is known to inhibit proliferation of leukaemia cells belonging to K-562 cell line[126]. The jenamidines are of importance in this thesis and are shown below in Figure 1.9.

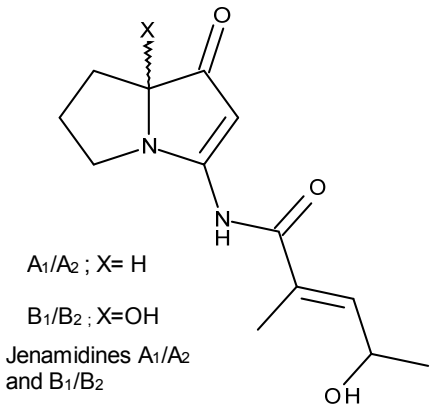
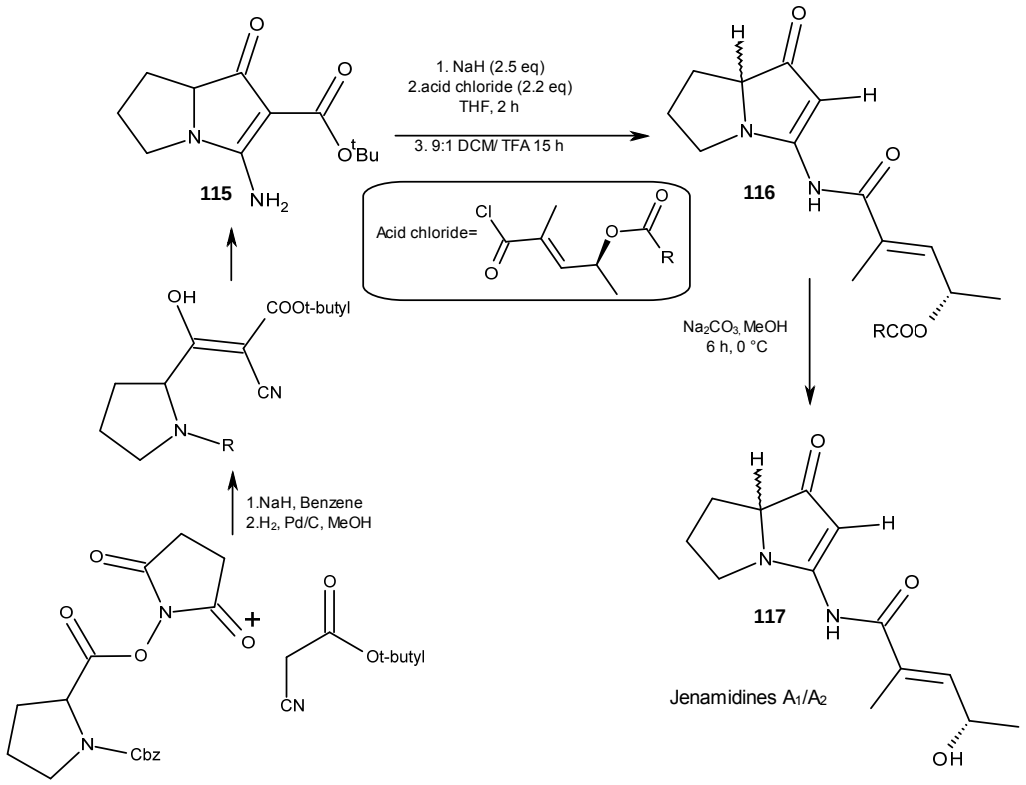


Figure 1.9: Structure of jenamidines

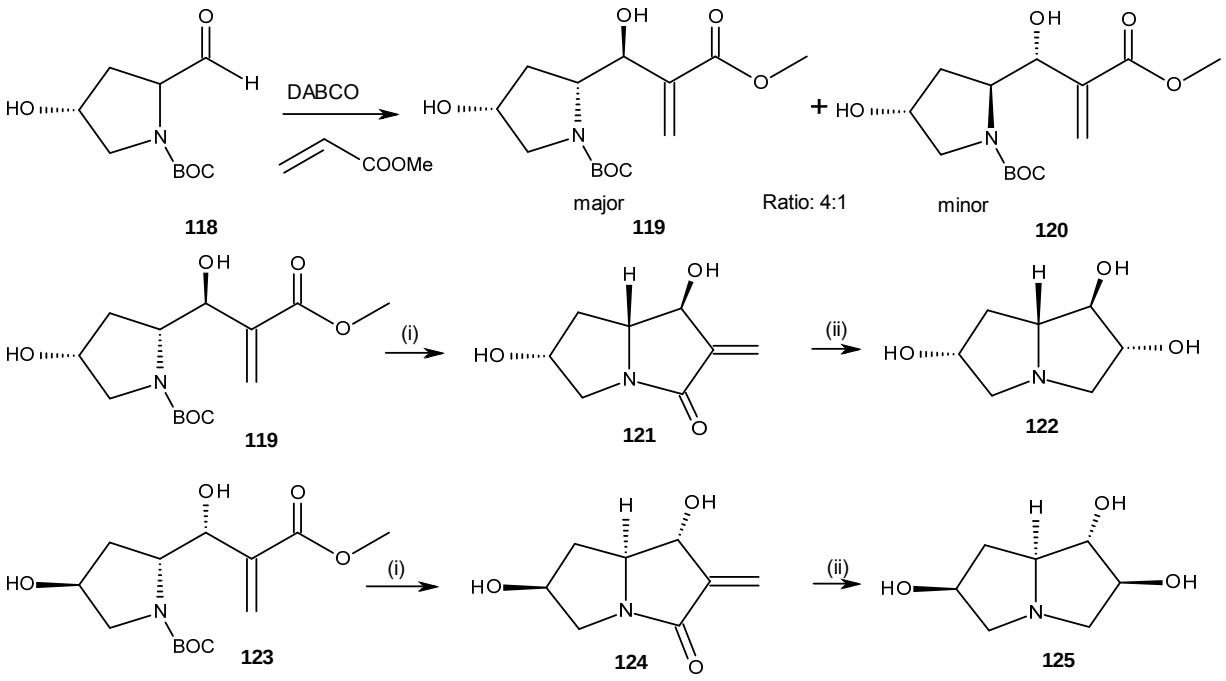
1.3.1 Synthetic strategies

Snider et al.[127] successfully confirmed the structure of the jenamidines A_1/A_2 and synthesised them from activated proline derivatives in a 3 step sequence from **115** to the target molecule **117.** The synthesis began with the acylation of the vinylogous urea **115** with NaH and the acid chloride followed by hydrolysis and decarboxylation to give the jenamidine acetate ($R=CH_3$) **116** in 84% yield. On further mild hydrolysis, jenamidines A_1/A_2 were synthesised in an overall satisfactory yield of 45% considering the amide was in a base labile environment. The key starting pyrrolizidine **115** was synthesised by reacting Cbz-proline *N*-hydroxysuccinimide ester with the enolate of *tert*-butyl cyanoacetate and NaH in benzene which gave an intermediate that was hydrogenated with Pd/C and underwent cyclisation[127].



Scheme 1.34: Jenamidine A_1/A_2 synthesis by Snider et al.

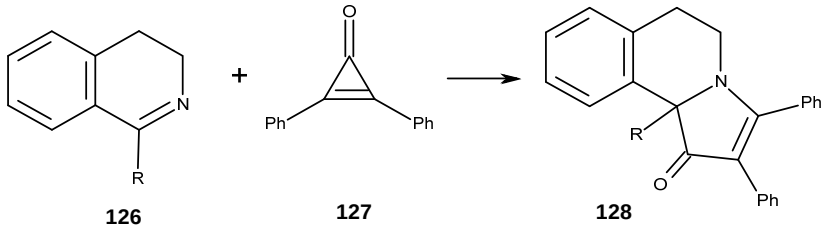
Recently, Luna-Freire and his co-workers[128] developed a novel approach to synthesising pyrrolizidines and pyrrolizidones which involved the Morita-Baylis-Hillman (MBH) reaction. Starting with a substituted prolinal **118** and submitting it to MBH conditions with methyl acrylate and DABCO as the *tert*-amine catalyst produced the diastereomers **119** and **120** whereby the hydroxyl group at C3 influenced the process to a large extent (Scheme 1.35). Compound **119** was later converted to the pyrrolizidine **122** after treatment of intermediate **121** with ozone. The enantiomer **125** could be obtained in the same manner from isomer **123**.



Reagents and conditions: (i) conc. HCl, toluene, 0 °C, 5 min, then NaOH, 0 °C, 30 min; (ii) O_3, CH_2Cl_2/MeOH (8:2), −78 °C, 10 min; $NaBH_4$, −78 °C to r.t., 4 h.

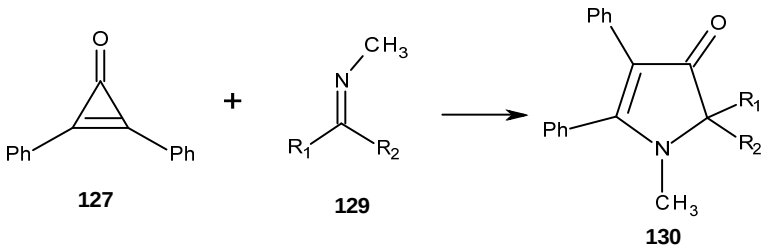
Scheme 1.35: Synthesis of pyrrolizidinones and pyrrolizidines.

Eicher developed a study focussed on the reactivity of diphenylcyclopropenone (DPP) **127** with cyclic imines **126** and showed that these gave a tricyclic indolizidine[127] type product **128** in the mechanism as shown in Scheme 1.36.



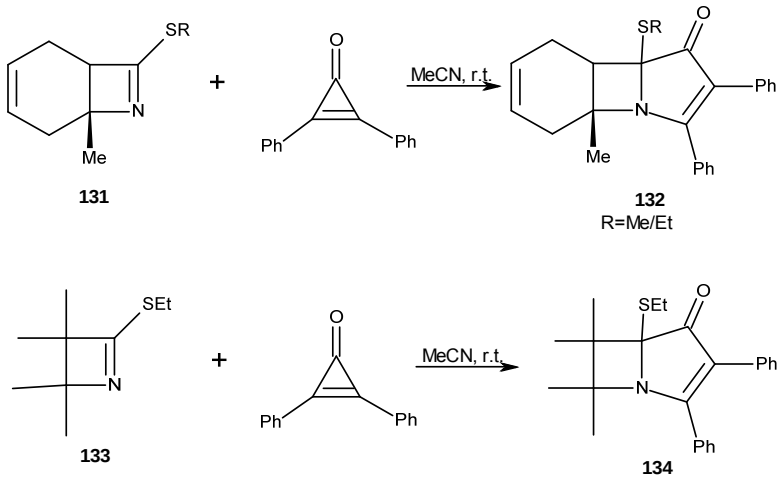
Scheme 1.36: Eicher's work with cyclic imines.

This work built upon Eicher's earlier research[129, 130] on the reactivity of imines with DPP. An acyclic ketamine **129** was reacted with DPP **127** and resulted in the formation of substituted pyrrolidinones **128** in good yields. The reaction mechanism was presumed to be an overall [3+2] cycloaddition type process which will be discussed in detail later.



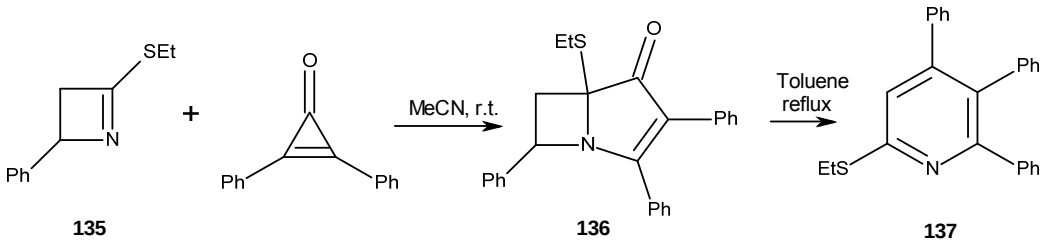
Scheme 1.37: Eicher's initial work with DPP.

Work by Yoshida also showed pyrrolidinones can be accessed from the reaction of acyclic imines with DPP[131, 132]. In later work reported by Hemming and Luheshi a bicyclic imino thioether **131** undergoes a formal cycloaddition with diphenylcyclopropenone (DPP) to yield cycloadducts **132** in good yield. The reaction was successful in producing a cycloadduct **134** when monocyclic imino thioether **133** was utilised.



Scheme 1.38: Cycloaddition route according to Hemming and Luheshi.

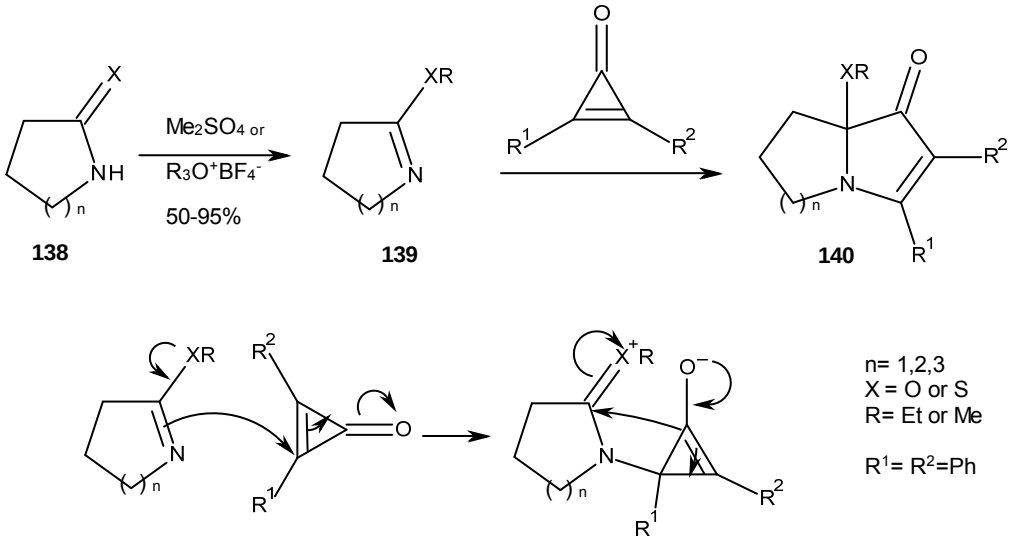
This reaction also works with aryl substituted cyclic imines[133] **135** although it is interesting to note that the products **136** rearranged and reacted further to give pyridines **137**.



Scheme 1.39: Synthesis of pyridines from cyclic imines.

The Hemming group accessed highly sought after pyrrolizidine, indolizidine and pyrroloazepine nuclei[134] by reacting 5-, 6-, 7- membered cyclic thioimidates (X=S) with

cyclopropenones. The alkylation of the amides and thioamides **138** gave the alkylated imine **139** which afforded the pyrrolizidines **140** after reacting with cyclopropenones. The suggested mechanism, shown in Scheme 1.40 is a Michael–type addition followed by cyclopropene ring opening.

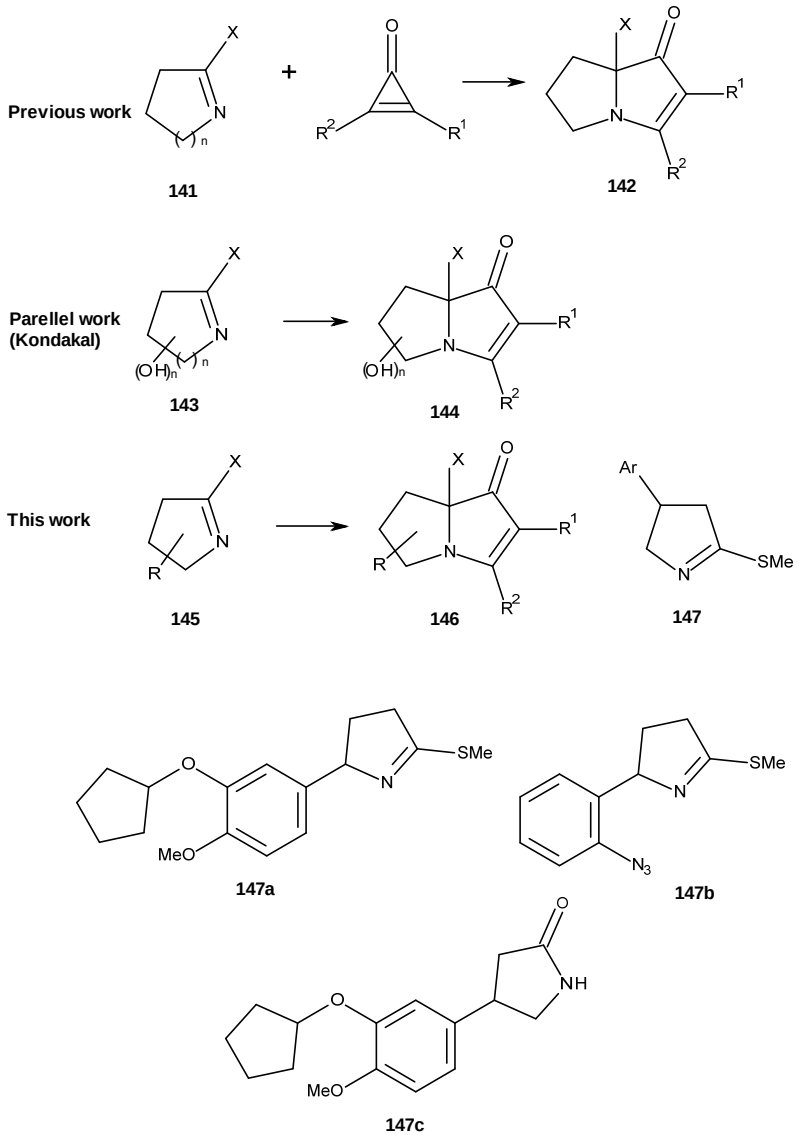


Scheme 1.40: Synthesis of indolizidnes and pyrrolizidines using DPP

The same research group later applied their synthetic idea to other cyclic imines and varied the substituted cyclopropenones to generate polyhydroxylated indolizidines and pyrrolizidines systems[135] with OH at the bridgehead. It is this work upon which the work described in this thesis was originally based.

1.3.2 Our aim

This work began as part of an ongoing project concerned with the reaction of cyclopropenones with cyclic imine systems. Past members of our group have worked with these processes (mentioned above in Scheme 1.38 - 1.40) and have investigated the reactions of a variety of 5-, 6-, 7- membered cyclic thioimidates with a range of cyclopropenones (mono-, diphenyl, mono-phenyl etc., see Scheme 1.40). Our aim was to investigate the outcome with substituted cyclic imines as shown in Scheme 1.41..

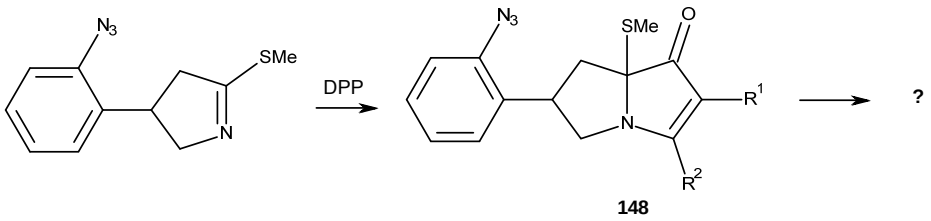


Scheme 1.41: Summary of our research work.

Our interest lies in investigating the stereochemical outcome of reactions involving cyclopropenenones and cyclic imines **145**. Research carried out by a previous member showed the presence of a small R group (Me) at positions 2 and 3 of a cyclic pyrroline was found to have no significant effect on the stereochemical outcome and produced a mixture of diastereomers **146**. This project investigates the effect of a larger sized R group on the stereochemical outcome.

The system chosen for the study due to the ready availability of precursors in literature was the aryl substituted pyrroline, **147**. The aryl groups chosen for study were those shown in structures **147a** and **147b**. **147a** was chosen due to its anticipated availability from Rolipram **147c**, discussed later. The azide **147b** was chosen as azides are a recurring theme within our research group and we decided to introduce the azide functionality in order to

study the reactivity of the anticipated highly functionalised adduct **148** as seen in Scheme 1.42.



148

Scheme 1.42: Synthesis of azido aryl substituted indolizidines.

This project then evolved as new work came to light that had to be pursued as will be explained in the discussion of this thesis. This resulted in the generation of a series of interesting results that lead to a series of unexpected indoles. Hence, a condensed review on indoles follows, discussing their biological importance with selected approaches to their synthesis.

1.4 Introduction to Indoles

The indole scaffold represents one of the most important structural subunits in Nature. The wide variety of important biological activities that are exhibited by indole-based natural products and this has made them attractive synthetic targets over the years. Found in a hugely diverse array of biologically significant natural compounds from simple derivatives such as the neurotransmitter serotonin to complex alkaloids such as clinically used anticancer agents like vinblastine and mitomycin C and the hypertensive alkaloid reserpine (Figure 1.10), the importance of indoles to biological chemistry cannot be overstated [136-138].

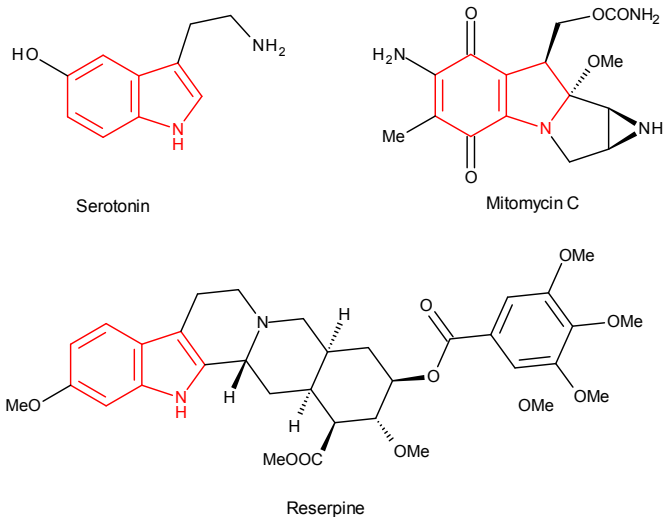


Figure 1.10: Some naturally occurring indoles.

Additionally a number of important synthetic drugs contain the indole motif including sumatripan[139], rizatriptan[140, 141] and fluvastatin[142].

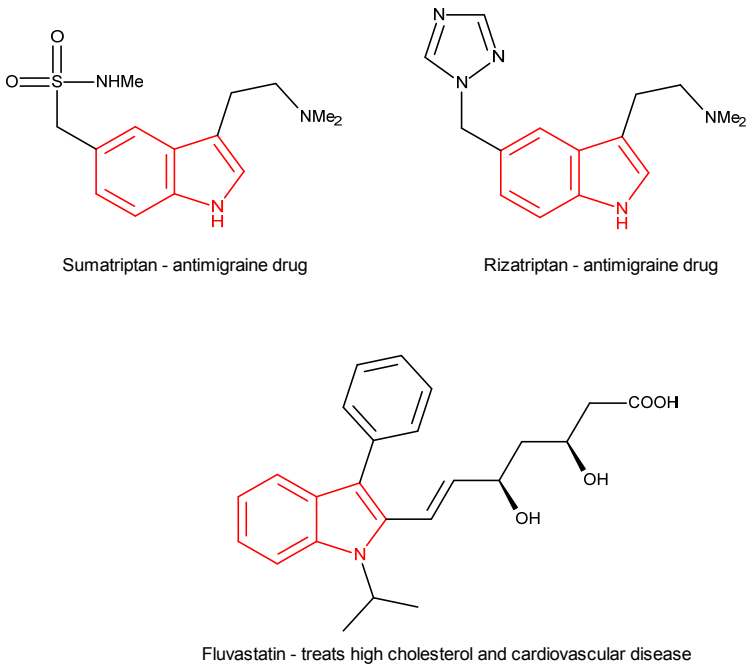
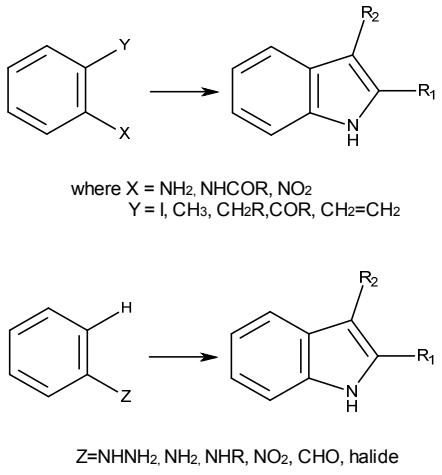


Figure 1.11: Clinically used indoles

Indole synthesis almost universally involves annelation of the five membered pyrrole ring to an existing benzene ring with the appropriate attached functionalities. This approach can be divided into those reactions in which there are two substituents sharing an *ortho* relationship to each other and those in which a single attachment on the aromatic ring can be cyclised onto the ring itself in Scheme 1.43.

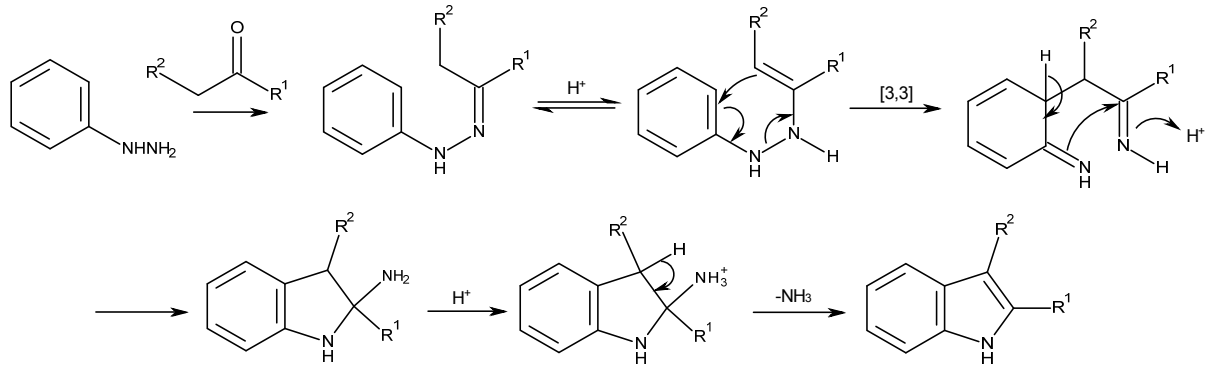


Scheme 1.43: One substituent and two substituent approach to indoles.

Many reviews on indole synthesis are in circulation[137, 138, 143] and a full discussion is not provided in this thesis. In this section a few key reactions will be considered with a focus on reductive cyclisation, as will be seen later in this thesis, was how indoles were serendipitously synthesised using a reducing agent.

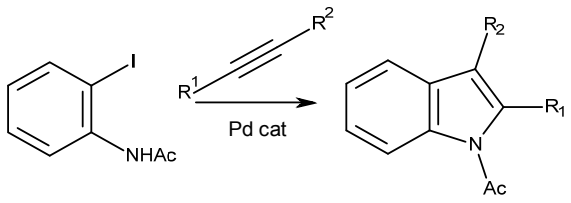
1.4.1 Synthetic strategies in indole synthesis

The Fischer indole synthesis represents the most general synthetic route (Scheme 1.44). However, the common instability and toxicity of hydrazines has led to the development of alternative syntheses starting from less expensive and more available reagents, such as anilines.



Scheme 1.44: The Fischer indole synthesis.

For example, Larock's procedure makes use of modified aniline derivatives, such as *ortho*-haloanilines, in the presence of palladium catalysts[143] as seen in Scheme 1.45.

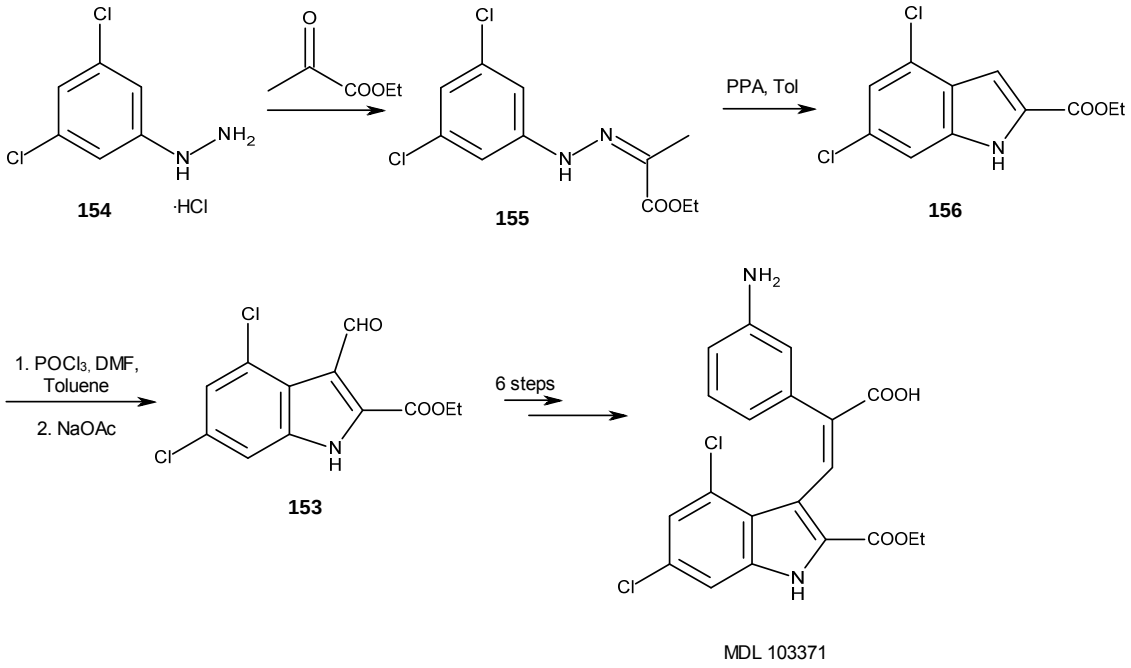


Scheme 1.45: Larock's synthesis of indoles.

1.4.1.1 Typical Fischer indole synthesis

Many applications[144, 145] of the Fischer indole synthesis are available in the literature, the synthesis of MDL 103371, a *N*-methyl-D-aspartate (NMDA) type glycine receptor antagonist

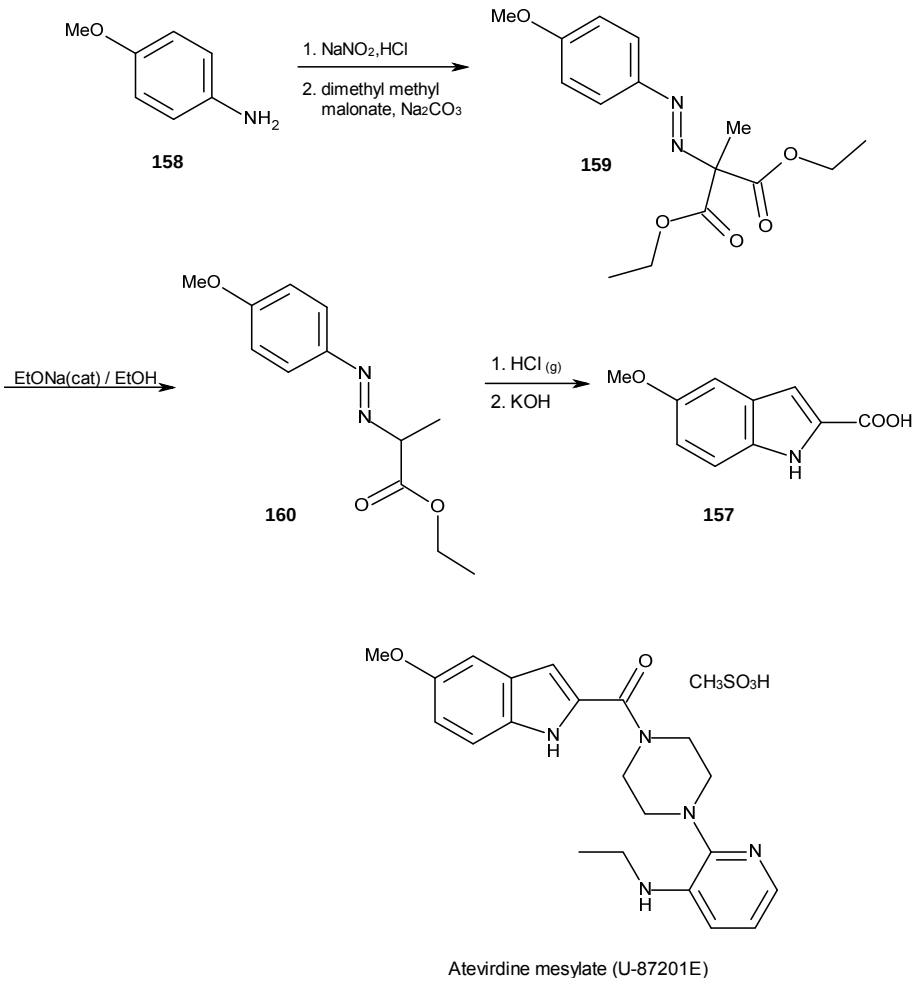
for the potential treatment of stroke was reported by Watson and co-workers[146]. Treatment of commercially available 3,5-dichlorophenylhydrazine hydrochloride **154** with ethyl pyruvate gave the hydrazone product **155** as a mixture of E/Z isomers. Fischer cyclisation using PPA (polyphosphoric acid) in toluene at 95 - 100 °C synthesised the indole ethylcarboxylate precursor **156**. Vilsmeier-Haack formylation synthesised the indole **153** which was then used to synthesis MDL 103371.



Scheme 1.46: Synthesis of MDL 103371 *via* indole intermediates.

1.4.1.2 Japp-Klingemann

The Japp-Klingemann route is a useful alternative to the arylhydrazones used in the Fischer indole synthetic process. An aryldiazonium salt is treated directly with *β*-ketoesters. Deacylation gives rise to substituted indole esters. As an example, Bessard[147] described an efficient process for the preparation of **157** *via* Japp-Klingemann using readily available malonate substrates (see Scheme 1.47). *p*-Anisidine **158** was diazotised to give the diazonium salt which was directly treated with 2-methylmalonate to give the azo intermediate **159**. Catalytic sodium ethoxide in ethanol afforded the hydrazone **160**, which underwent Fischer cyclisation on treatment with gaseous HCl in boiling ethanol. Subsequent hydrolysis provided 2-indole carboxylic acid **157**. This indole is used as an intermediate in the synthesis of the non-nucleosidic reverse transcriptase inhibitor ateviridine mesylate (U-87201E).



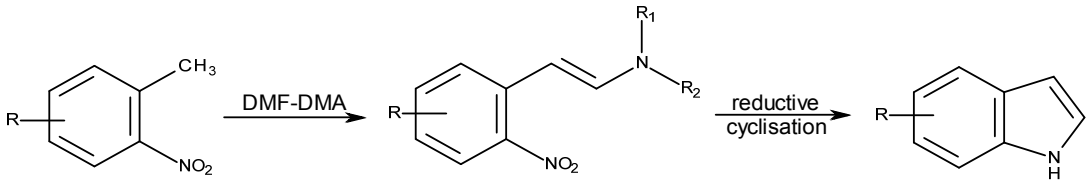
Scheme 1.47: Indoles are used as intermediates in the synthesis of biologically important molecules.

Japp-Klingemann has also been used in the synthesis of indole derivatives which have been used in the total synthesis natural products such as (+) majvinine[148], keramamide A[149], and jaspamide[150].

1.4.1.3 Reductive cyclisations

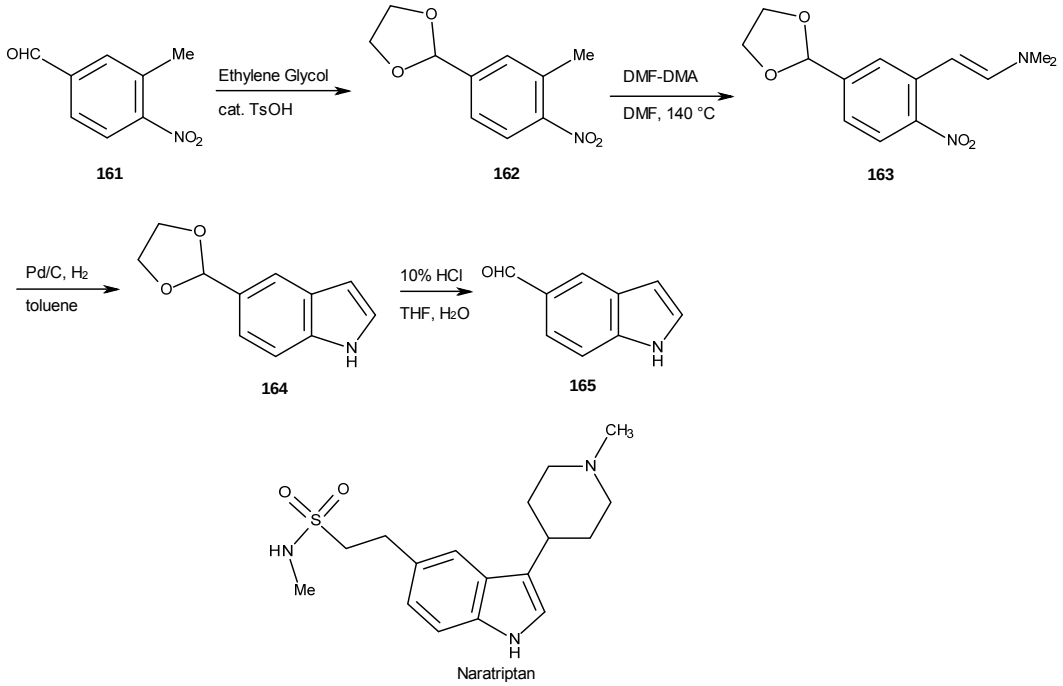
The reductive cyclisation of aromatic nitro compounds is a powerful method in the synthesis of the indole ring and has been reviewed in the past [151, 152]. Reductive cyclisation has been accomplished by catalytic hydrogenation using Pt/C, Pd/C[153] or a combination of Raney-Ni and hydrazine[154], sodium dithionite[155]. Other reactants that have proved suitable are iron/zinc in acetic acid[156] and nickel boride[157]. Leimgruber and Batcho[158] indole synthesis and the reductive cyclisation of *o*-nitrobenzylcarbonyl, *o*-nitrostyrenes and *o*-dinitrostyrenes are routes that provide access to the indole motif with relative ease.

The well-known Leimgruber indole synthesis[152, 158] involves the condensation of *o*-nitrotoluene with dimethylformamide dimethyl acetal (DMF-DMA) to give an intermediate *β*-(dimethylamino)-2-nitrostyrene. This then undergoes reductive cyclisation which leads to indoles.



Scheme 1.48: Leimgruber indole synthesis.

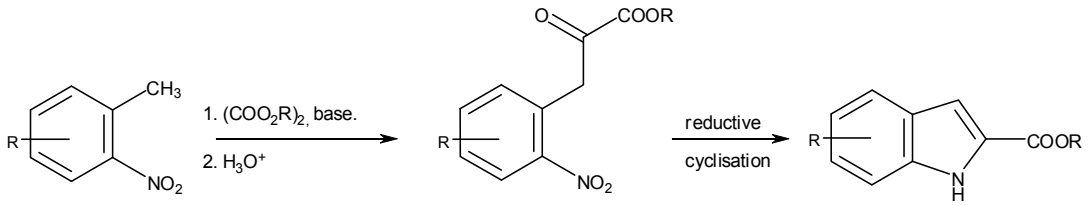
An example of this process is the synthesis of the anti-migraine drug naratriptan[159] by Simig and his co-workers. The synthesis began by reacting 3-methyl-4-nitrobenzaldehyde **161** with ethylene glycol in the presence of catalytic TsOH to give the acetal **162** in excellent yield (82%). Treatment of the acetal with DMF-DMA in DMF at 140 °C and subsequent catalytic hydrogenation of the nitro group with Pd/C afforded the indole **164** in excellent yield. Hydrolysis of the acetal with aqueous HCl furnished the 5-formylindole **165** which is used to synthesis the drug Naratriptan.



Scheme 1.49: Naratriptan synthesis *via* Leimgruber reaction.

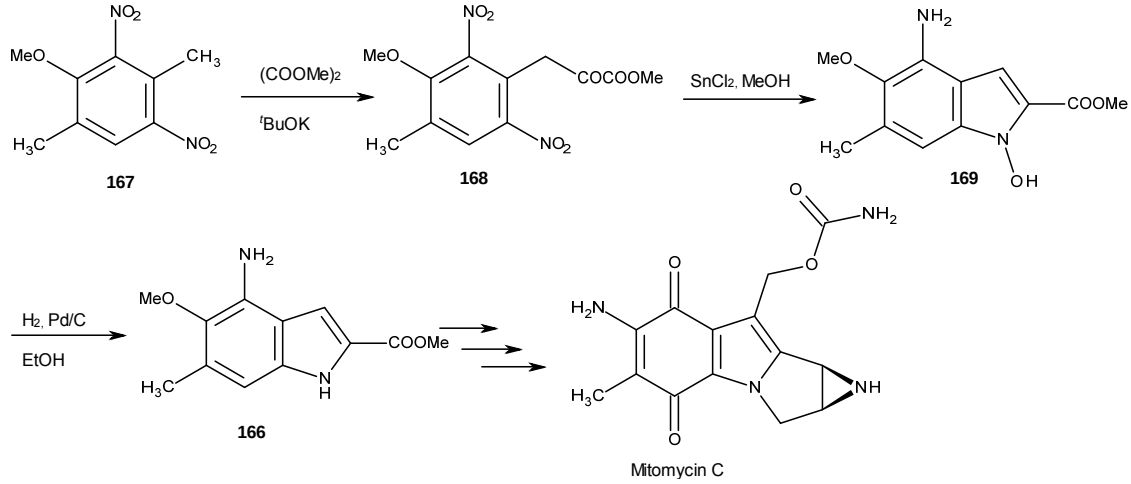
Another reductive cyclisation is seen in the classic Reissert synthesis[160, 161] shown in Scheme 1.50. This reaction involves condensation of a *o*-nitrotoluene with an oxalic ester to give a *o*-

nitrophenyl pyruvate derivative followed by reductive cyclisation to indole-2-carboxylic acid derivatives[162].



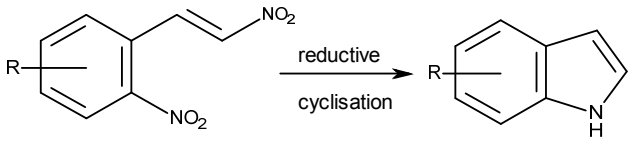
Scheme 1.50: Classic Reissert reaction.

Jimenez et al. reported the synthesis of the indole **166** *via* Reissert reaction in the synthesis of mitomycin C and derivatives[163, 164] as shown in Scheme 1.51. They reacted 3,6-dimethyl-2,4-dinitroanisole with dimethyl oxalate in the presence KO*t*-Bu to give ketoester **168**. Reductive cyclisation with stannous chloride in MeOH gave the *N*-hydroxyindole **169** exclusively. Catalytic hydrogenation followed to provide the indole **166** in quantitative yield which was further elaborated to synthesise mitomycin C.



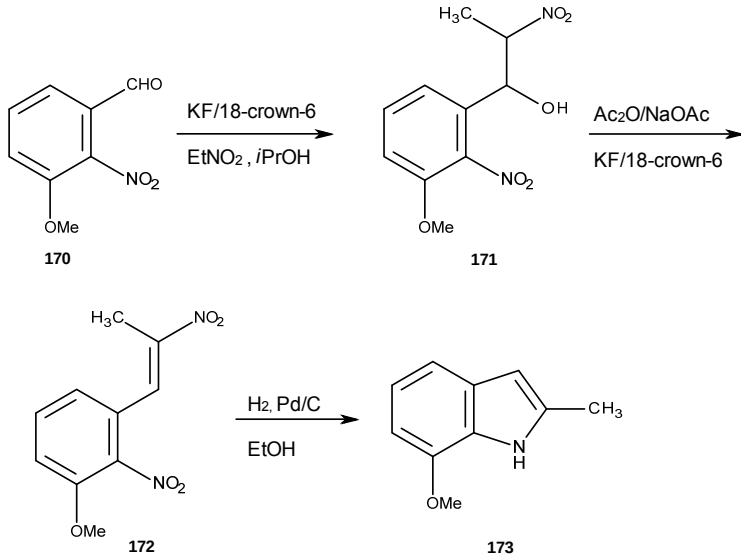
Scheme 1.51: Reissert reaction in the synthesis of mitomycin C.

The reductive cyclisation of *o*-*β*-nitrostyrenes is an effective method for the construction of indoles. The *o*-*β*-nitrostyrenes are usually prepared by the condensation of an *o*-nitrobenzaldehyde with a nitroalkane or nitration of a benzaldehyde precursor[155].



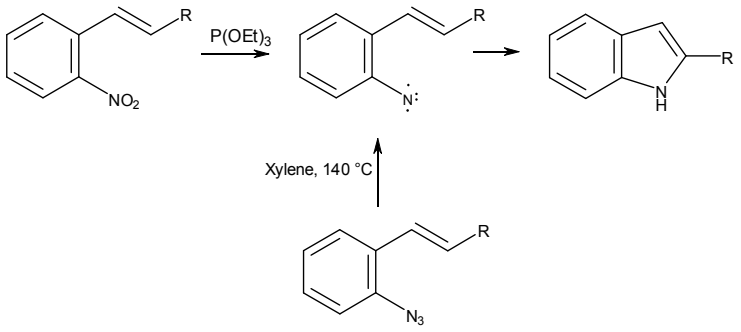
Scheme 1.52: Reductive cyclisation of nitrostyrenes.

Chen et al.[153] reported the synthesis of 2-methyl-7-methoxyindole **173**, a structural unit embedded in a number of biologically active molecules. Initial attempts to synthesise the nitro olefin **172** in a single direct step from corresponding aldehyde **170** afforded the nitro olefin in low yields (<45%) but the two-step reaction to the olefin proved advantageous as the yield of the indole improved to 96%.



Scheme 1.53: Synthesis of important indole derivatives using reductive cyclisation.

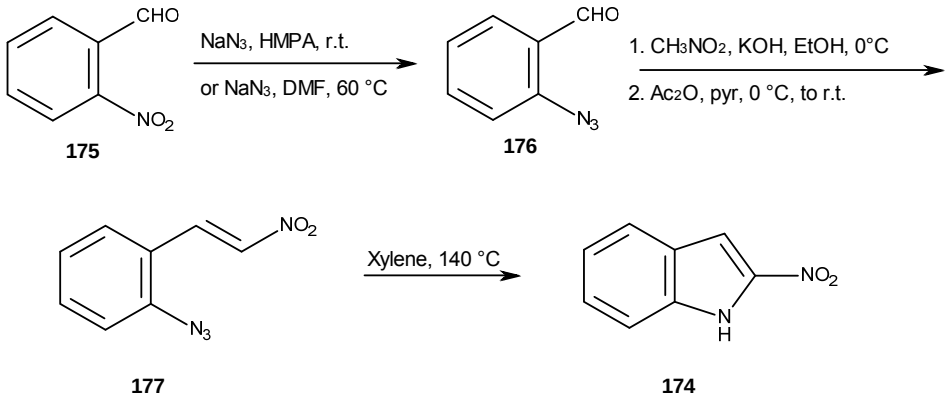
Azides have commonly been used as a route to indoles. Sundberg reported that *ortho*-azido styrenes can be utilised as indole precursors and were converted to the corresponding indoles on thermolysis[165]. The Cadogan[166]–Sundberg[167] indole synthesis is a related indole ring formation method which involves the deoxygenation of *o*-nitrostyrenes or *o*-nitrostilbenes with triethylphosphite and cyclisation of the resulting nitrene to form the indole. Both methods are shown in Scheme 1.54.



Scheme 1.54: Cadogan's and Sundberg's approach to indole synthesis.

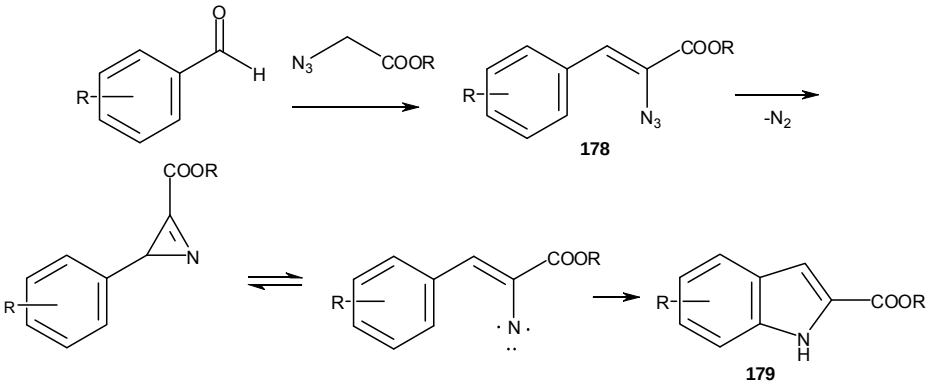
Pelkey and Gribble[168] later discovered a 3-step sequence using Sundberg's protocol starting with 2-nitrobenzaldehyde to synthesise the nitro indole **174**. The process starts with the

conversion of readily available 2-nitroaldehyde **175** into 2-azidobenzaldehyde **176** with sodium azide in HMPA[169] at ambient temperature or alternatively using the DMF procedure developed by Molina[170], to refrain from using carcinogenic HMPA. This was then converted to the nitrostyrene **177** which on thermolysis gave 2-nitroindole **174** in moderate yield (54%).



Scheme 1.55: Thermolysis of azides leads to indoles.

The Hemetsberger indole synthesis[143] is related to Sundberg's indole synthesis whereby the azido group is on the side chain (i.e. an α-azidocinnamate **178**) rather than on the benzene ring. β-Styrylazides readily undergo thermal decomposition to 2*H*-azirines which exist in equilibrium with the vinyl nitrene isomer. Electrocyclisation onto the aromatic ring then gives the indole **179** (Scheme 1.56).



Scheme 1.56: Hemetsberger's indole synthesis.

Chapter 2: Results and Discussion

This chapter describes in detail the results and findings of our experiments to synthesise PBDs (Section 2.1 - 2.2), the thio analogues of the fuligocandins (Section 2.3 - 2.5), pyrrolizidines (Section 2.6 - 2.7), indoles (Section 2.8 - 2.9) and also describes exploration of some aza-Prins chemistry (Section 2.10).

2.1 Synthesis of triazolopyrrolobenzodiazepines

Pyrrolobenzodiazepines and pyrrolobenzothiadiazepines, as discussed in the introduction section of this thesis, are highly valued synthetic targets due to their potential biological activity.

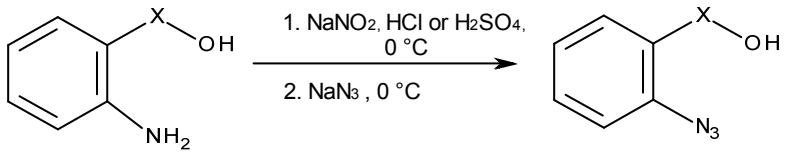
Extensive work has been carried out on PBDs and PBTDs within the Hemming group. As part of an ongoing project, our research group have investigated the synthesis of benzodiazepines *via* cycloaddition between an azide group and alkenes, alkynes and nitriles. To extend this work further, the aim of this part of the thesis is to investigate the result of an intramolecular cycloaddition between an azide and the imine moiety i.e. C=N-R.

Knowing the outcome of the 1, 3-dipolar cycloaddition reaction between the alkene and azide (see Chapter 1, Scheme 1.32, Section 1.22) we were interested in studying the result of the intramolecular 1, 3-dipolar cycloaddition of the imine and the azide group.

This work focussed on 2 amino acid derivatives – *L*-prolinol and *L*-valinol: the first having the aim of producing PBD analogues and the second having the aim of checking possible applications with other simple amino acids. In order to gain familiarity with the chemistry the project began by repeating an investigation of nitrile work developed previously in the group in order to arrive at a tetrazolo PBD system as described by Chambers[171].

2.1.1 Synthesis of 2-azidobenzoic acid and 2-azidobenzenesulfonic acid

The scheme below depicts the synthesis of 2-azidobenzoic acid **181a** and 2-azidobenzenesulfonic acid **181b** which are the synthetic precursors to the PBD and PBTDs we aim to synthesise. The diazonium was formed and then displaced by the nucleophilic azide anion which afforded the products in high yields.



180a, X = CO
180b, X = SO2

181a, X = CO
181b, X = SO2

Scheme 2.1: Synthesis of azides from the corresponding amine.

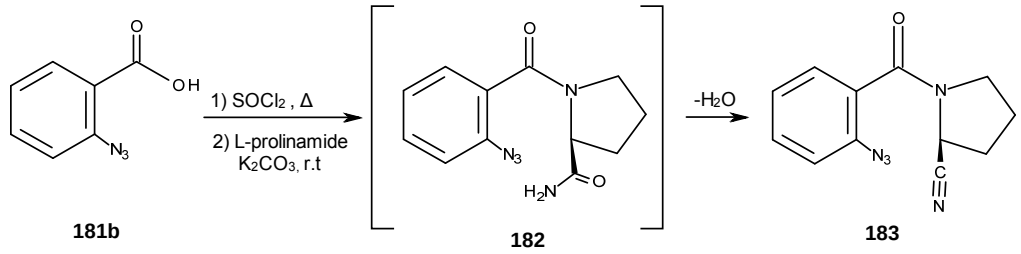
The structure of 2-azidobenzoic acid was confirmed by the strong absorption peak at 2122 cm^{-1} in the IR spectrum which indicated the presence of the azide group. ^1H NMR

analysis further confirmed four aromatic protons with a 1, 2-substitution pattern on the benzene ring, i.e. doublets at 7.20 ppm and 7.67 ppm and doublets of doublets at 7.15 ppm and 7.67 ppm.

The structure of 2-azidobenzenesulfonic acid was confirmed using IR and spectroscopic analysis. The infra-red spectrum showed the azide functionality at 2123 cm^{-1} and the data was consistent with that reported in literature[171].

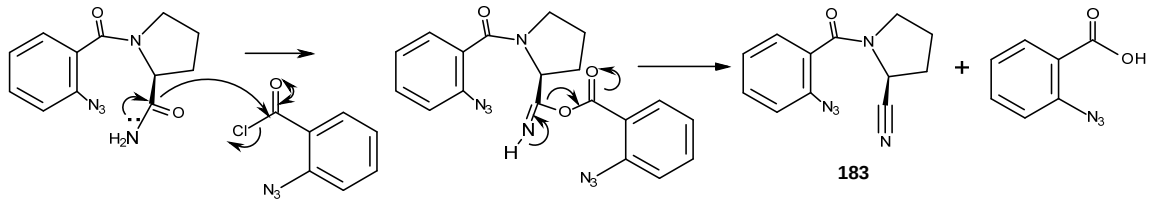
2.1.2 Coupling of the acid chlorides with prolinamide

With the azide group at the desired position, the next step involved the coupling of the acid to *L*-prolinamide *via* acid chloride formation. The carboxylic acid was heated in thionyl chloride to produce the acid chloride following which was immediately coupled with the *L*-prolinamide in a mixed phase reaction pot containing K_2CO_3 as the base. The coupled product **182** was not isolated but underwent *in situ* dehydration to give the nitrile **183**. The nitrile product was isolated as a mixture of rotamers in 31% yield.



Scheme 2.2: Single step synthesis of the nitrile.

The mechanism in Scheme 2.3 explains the formation of the nitrile *in situ* by dehydration of the amide which uses the excess acyl chloride in the reaction to initiate the dehydration process.



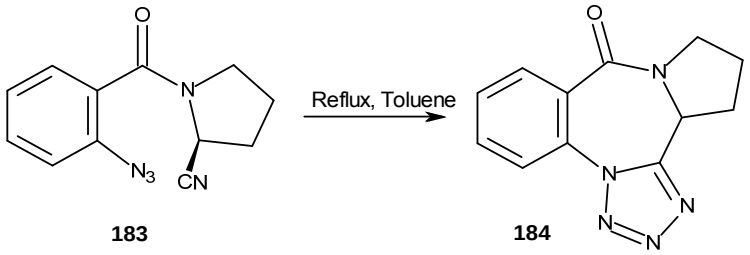
Scheme 2.3: Mechanism showing dehydration of the coupled amide.

The structural assignment of **183** was determined by NMR analysis. In the ^1H NMR spectrum, the aromatic protons appeared as a multiplet at 7.23 ppm integrating to 2 aromatic CHs, a doublet of doublets at 7.35 ppm integrating to 1 proton and a doublet of doublet of doublets (ddd) at 7.48 ppm integrating to one aromatic CH which showed the 1,2-

substitution pattern on the aromatic ring. The IR spectrum confirmed the absence of broad NH peaks that would have been seen if the amide group was present. The ^{13}C spectrum was highly complex due to the rotameric doubling of peaks. The quarternary carbon at 118.0/118.1 ppm was confirmative of the CN moiety. Further confirmation was arrived at through IR which showed the CN peak at 2241 cm^{-1} and the diagnostic peak of the azide at 2122 cm^{-1}. The data was consistent with reported values[95, 171].

2.1.3 Synthesis of tetrazolo[1,5-a] pyrrolo[2,1-c][1,4]-benzodiazepine -5-one

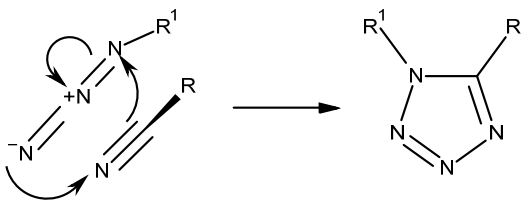
This next step involves a Huisgen 1,3-dipolar cycloaddition between the nitrile and the azide to give the tetrazolo ring (Scheme 2.4). Upon heating in toluene for 7 h the nitrile underwent cyclisation affording the PBD in 40% yield.



183 **184**

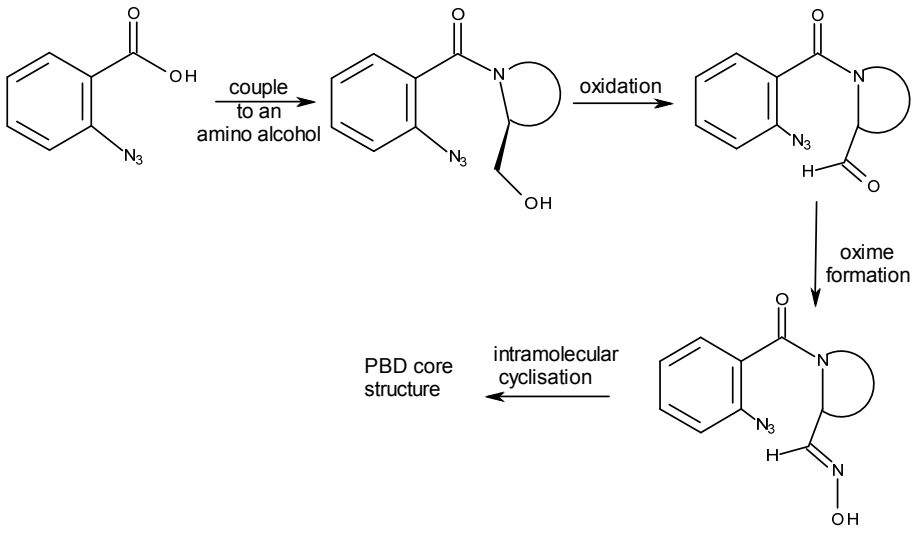
Scheme 2.4

The loss of the azide and nitrile peak signals in the IR spectrum at ν_{max} ~2100 cm^{-1} and 2305 cm^{-1} respectively suggested successful occurrence of the cycloaddition step. The evidence of the PBD structure was further confirmed using NMR spectroscopic data. All 7 alkyl protons of the pyrrolidine ring appeared as multiplets while the aromatic protons appeared in the classic 1,2-disubstitution pattern as a doublet of doublet of doublets (ddd) at 7.64 and 7.76 ppm and as a doublet of doublets at 7.95 and 8.18 ppm. The loss of the rotamer signals was another indication that cyclisation occurred and had 'locked' the molecule synthesising the desired tetracyclic compound. This data was consistent with previously reported data from a member within our research group[171] and provided important information of the robustness of the chemistry.



Scheme 2.5: Mechanistic pathway of 1,3-dipolar cycloaddition between the azide and nitrile.

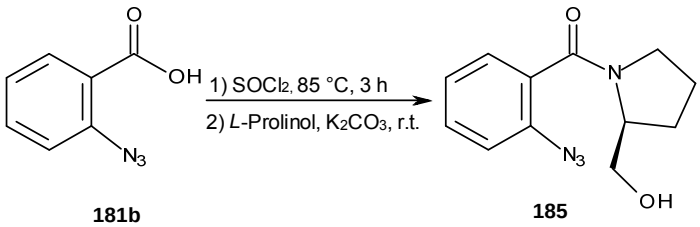
Moving on to imines, the methodology envisaged is depicted below in Scheme 2.6. We wanted to investigate the result of the intramolecular cycloaddition between an azide functionality and an imine. The imine is to be synthesised from the alcohol by oxidation to an aldehyde and subsequent oxime formation with hydroxylamine hydrochloride.



Scheme 2.6: Intramolecular cyclisation between the azide and imine functionalities.

2.1.4 Prolinol coupling reaction

The chemistry begins with the coupling of the amino acid derivative, *L*-prolinol to the acid chloride. The *L*-isomer was chosen in order to maintain the same stereochemistry as the natural products mentioned in the introduction. The acid **181b** was converted to the acid chloride which was then immediately coupled to *L*-prolinol in an aqueous solution of potassium carbonate to yield the coupled product as a mixture of rotamers in 53% yield.



Scheme 2.7

The structure of the coupled product **185** was confirmed by the appearance of the broad OH singlet at 4.69 ppm. The 7 protons of the pyrrolidine ring were seen at 1.63 - 1.83 ppm, 2.13 - 2.19 ppm, 3.15 - 3.26 ppm and 4.31 - 4.36 ppm. The four aromatic CHs appeared in the

deshielded region as a multiplet (m), doublet (d) and doublet of doublets (dd) at 7.14 - 7.20 ppm, 7.31 ppm and 7.43 ppm respectively.

The ^{13}C spectrum showed the carbons of the pyrrolidine ring in the region spanning from 24.4 - 66.1 ppm and the carbonyl C at 168.0 ppm. The presence of 'shadow peaks' for each peak indicated the compound existed as a mixture of rotamers in the ratio 3:1. The IR spectrum contained the expected broad OH peak at 3300 - 3200 cm^{-1} and the azide peak at 2125 cm^{-1}. The data matched literature values[171].

2.1.5 Synthesis of (2*S*)-*N*-(2'-azidobenzoyl)-2-prolinal

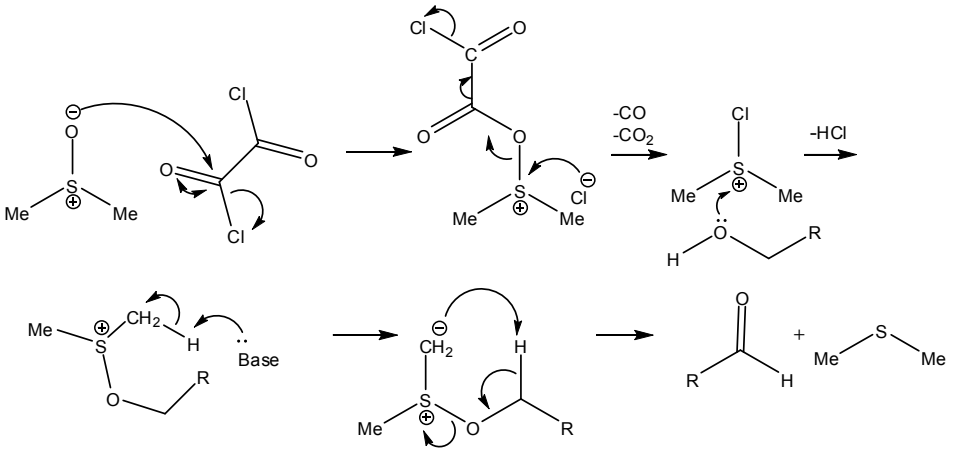
Oxidation of the alcohol moiety to an aldehyde was the next step in the sequence towards synthesising the oxime. Although many oxidation methods are known and available, our initial attempt was to oxidise the alcohol using Dess-Martin periodinane[75, 168] which gave extremely low yields (~20%). It was then decided to follow Swern oxidation conditions which use $(COCl)_2$ and DMSO with Et_3N as a base at -78 °C. This successfully furnished the aldehyde **186** in 83% yield.

185 **186**

Scheme 2.8: Swern oxidation process using $(COCl)_2$ and DMSO.

The main evidence for successful conversion to the aldehyde was the presence of the aldehydic proton signal as doublets at 9.29 and 9.70 ppm while absence of the primary alkyl chain (CH_2OH) alongside the loss of the broad OH peak gave further proof of successful conversion. The doubling of peaks in the ^{13}C NMR spectrum showed that this compound also existed as a mixture of rotamers. The data was consistent with previously reported values[171].

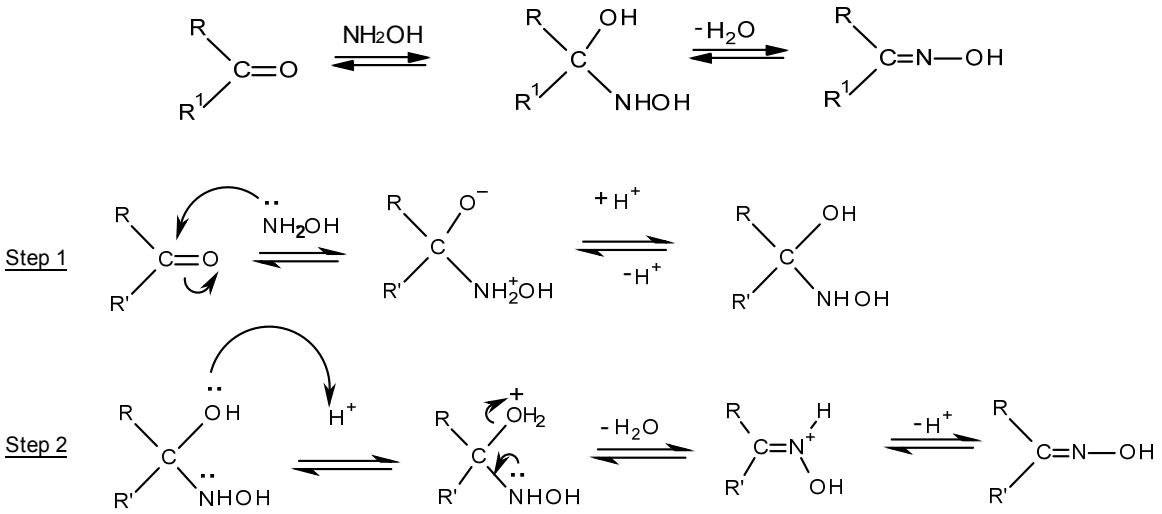
The mechanism for the Swern oxidation process is illustrated in Scheme 2.9.



Scheme 2.9: Mechanism of Swern oxidation.

2.1.6 Conversion of the aldehyde to the oxime.

Oximes are synthesised by the condensation reaction of carbonyl compounds with hydroxylamines[172] (see Scheme 2.10 below). The mechanism involves initial addition of the hydroxylamine to the carbonyl compound to form an unstable intermediate (Step 1), which decomposes losing H_2O to afford the oxime[173] (Step 2 of Scheme 2.10).



Scheme 2.10: Mechanism in the oxime formation.

When a carbonyl component like an aldehyde or ketone forms an oxime, there is a possibility of forming alternative *syn* and *anti* geometrical isomers as illustrated below (Figure 2.1).

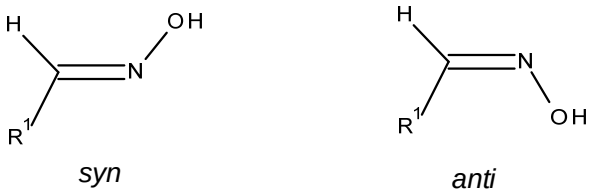
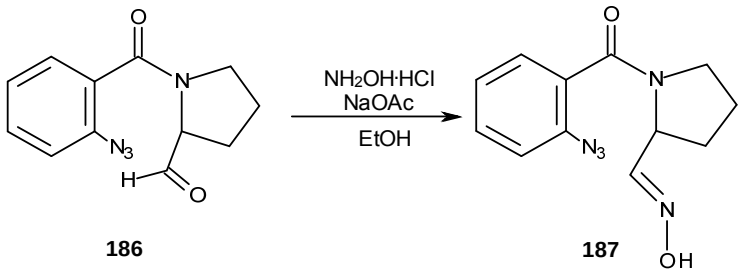


Figure 2.1

In our work, the conversion of the aldehyde to an oxime was carried out by heating to reflux the aldehyde **186** with hydroxylamine hydrochloride and sodium acetate as a base in ethanol for 4 h to give the oxime **187** in 29% yield. Attempts were made to optimise reaction conditions to improve the yield of the oxime product, but to no avail.



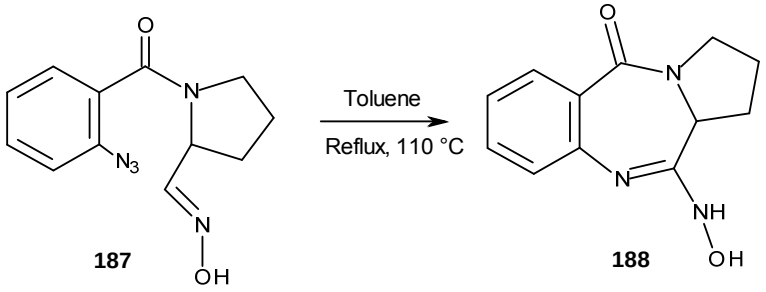
Scheme 2.11

Oxime **187** showed a number of peak signals in the ^{1}H and ^{13}C spectra, which indicated the existence of the compound as a mixture of rotamers along with the *syn* and *anti* isomers of the oxime. The ^{1}H spectrum was highly complex where most of the signals coalesced due to the overlapping of peaks. The oxime structure was confirmed by the presence of the characteristic highly deshielded broad OH singlet which appeared at 9.14 and 9.15 ppm along with the absence of the characteristic aldehyde doublet signal.

The ^{13}C spectrum was equally complex with quadruple signals for each C in the compound i.e. the pyrrolidine, aromatic and the imine carbons implying geometrical isomers as well as rotamers. The carbon spectrum showed a cluster of signals at 149 - 152 ppm indicative of the imine carbon (and its rotamers) which was not present in the spectrum of the aldehyde. The reappearance of the broad OH stretch at 3246 cm^{-1} and loss of the aldehyde CHO stretch in the IR spectrum gave additional evidence to the formation of the oxime. HSQC and COSY analysis confirmed connectivity and the structure of compound **187** was confirmed by HRMS analysis with an accurate measured mass of 282.0959 when the required mass for the $[M+Na]^{+}$ was 282.0961. This data has not been previously reported.

2.1.7 Reactivity of the oxime

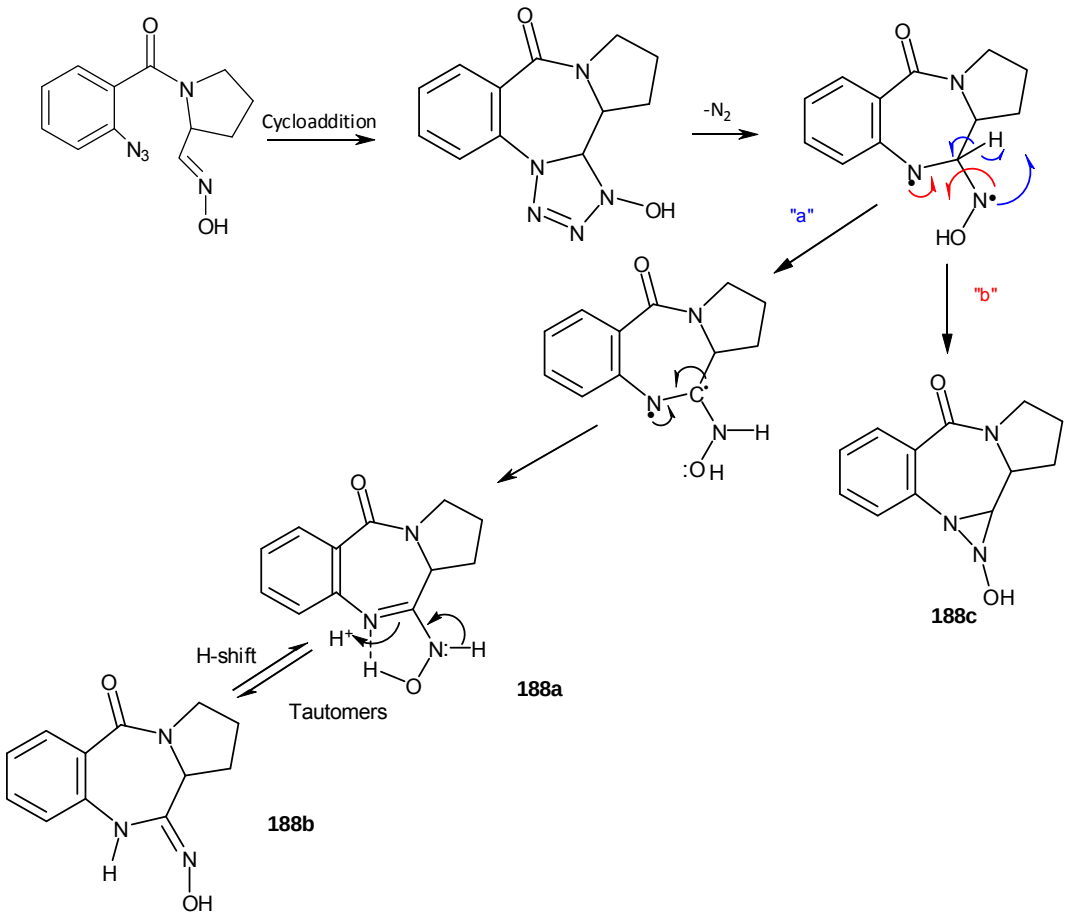
The intramolecular cyclisation between the azide and the imine was investigated by heating compound **187** to reflux in toluene for 72 h, a process which was found to afford the oxime pyrrolobenzodiazepine **188** as a yellow oil in 30% yield.



Scheme 2.12

Spectroscopic analysis confirmed the structure as compound **188**. The infra-red spectrum showed the absence of the azide stretch at (2122 cm^{-1}) implying the possibility that it reacted with the imine. The characteristic hydroxyl was seen at 9.60 ppm while the NH appeared at 7.52 ppm in the ^{1}H NMR spectrum. An imine peak (C=N) and a carbonyl peak (C=O) were seen at 149.9 ppm and 165.8 ppm respectively in the ^{13}C NMR spectrum. The structure was confirmed by HRMS mass spectroscopy which gave $[M+Na]^{+}$ at 254.0888 when $C_{12}H_{13}N_3O_2$ required 254.0899.

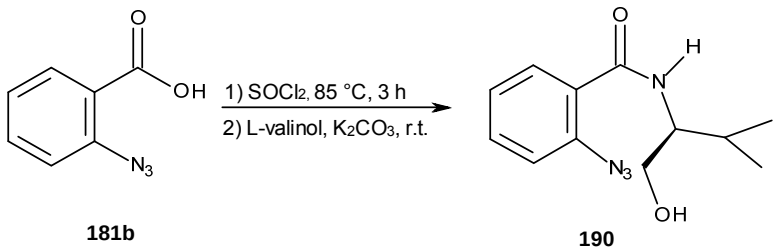
Scheme 2.13 shows one possible mechanism to explain the formation of **188**. The 1, 3-dipolar intramolecular cycloaddition forms a tetrazolo ring which collapses leading to the expulsion of N_2 to give **188** shown in Scheme 2.13 as a mixture of tautomers **188a/b**. Our compound was a single product but we were unable to distinguish between the two tautomers. The alternative product **188c** could be discounted on the basis of $^{1}H/^{13}C$ evidence.



Scheme 2.13: Proposed mechanism for the synthesis of the cycloaddition product.

2.1.8 Coupling to *L*-valinol

The same strategy was next applied to another amino acid derivative, *L*-valinol. The synthesis of the aldehyde was previously carried out by a member of the Hemming group and no problems with its synthesis were anticipated. The acid chloride was once again prepared using thionyl chloride and then coupled *in situ* to *L*-valinol to give the corresponding coupled product **190**.

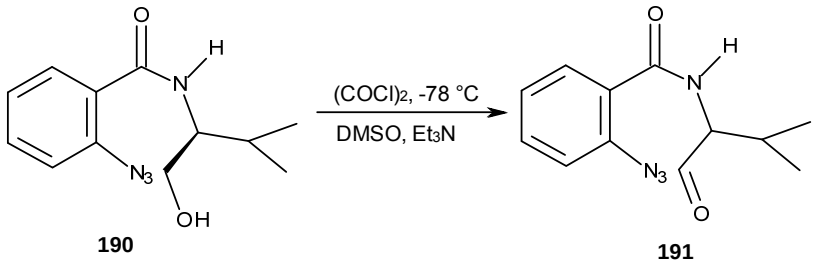


Scheme 2.14

The valinol derivative **190** was characterised by ^{1}H spectroscopy which showed the two methyl units in the isopropyl group occurred as a doublet at 1.03 ppm which integrated to 6H while the OH proton was observed as a broad singlet at 3.36 ppm. The methylene protons of the alkanol chain (CH_2OH) appeared at 3.72 - 3.80 ppm as a multiplet and the NH peak which occurred as a broad doublet at 7.64 ppm supported the structure of the coupled product. The data for **190** was identical to previously reported values[171].

2.1.9 Oxidation of the alcohol

The valinol coupled product **190** underwent oxidation under Swern conditions to yield the corresponding valinal derivative **191** in 58% yield.



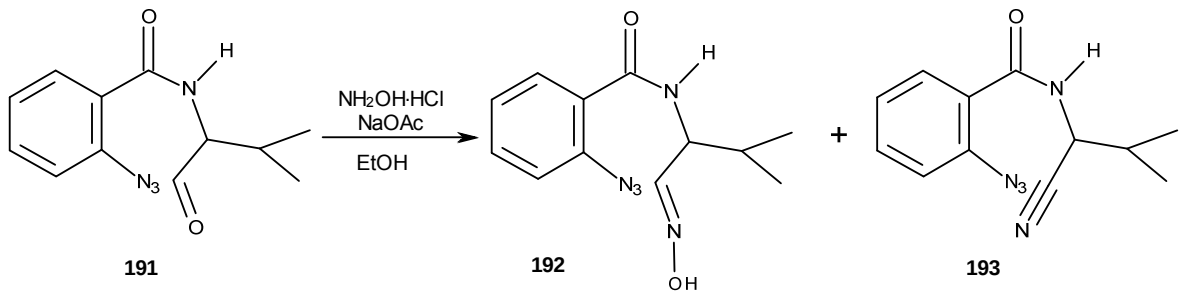
190 **191**

Scheme 2.15

In the ^{1}H spectrum the structure was indicated by the absence of the OH broad singlet and appearance of the aldehyde peak as a singlet at 9.73 ppm. The isopropyl unit was seen at 1.02 ppm as a doublet (d) integrating to 6H and the CH at 2.45 ppm appeared as an apparent septet. The structure was confirmed by the ^{13}C spectrum that showed the aldehyde signal at 200.0 ppm as well as the two CH_3 units at 18.0 and 19.2 ppm with the CH of the isopropyl unit at 29.0 ppm. The data closely matched previously reported values[171].

2.1.10 Synthesis of the oxime

The oxime was synthesised in 22% yield by heating to reflux a reaction mixture containing hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$), ethanol and sodium acetate with the valinal derivative **191**. The reaction was monitored *via* TLC and it was observed that a side product had been formed along with the oxime **192.** Along with some amount of unreacted starting material a side product isolated was found to be the nitrile **193** which was formed due to dehydration of the oxime during the course of the reaction.

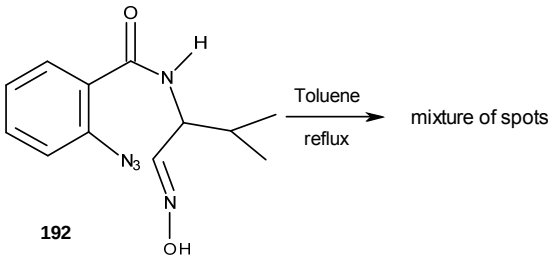


Scheme 2.16: Synthesis of oxime

With regard to the nitrile **193**, this compound has already been studied within the Hemming group[95, 171]. Hence our focus was on optimising the reaction conditions in an effort to improve the yield of the oxime **192**. The yield could not be improved upon in spite of repeated attempts with different conditions.

The ^{1}H NMR spectrum of the oxime **192** showed a broad doublet at 7.94 ppm corresponding to the NH along with a highly deshielded singlet at 8.81 ppm which is indicative of an oxime OH. The ^{13}C spectrum showed the imine CH at 149.4 ppm. The structure of the oxime product was further confirmed by HRMS analysis with an accurate measured mass (m/z) for $[M+Na]^{+}$ of 284.1122 for a required mass of 284.1118.

2.1.11 Attempted cyclisation of the valinol based oxime



Scheme 2.17

When the oxime **192** was heated at reflux in toluene to initiate intramolecular cyclisation between the oxime and azide, a complex mixture of spots formed as seen on TLC and no significant or identifiable products were isolated.

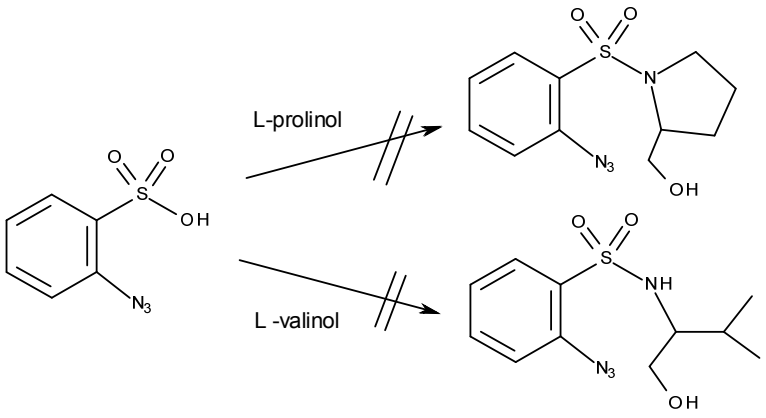
2.12 Summary

1,3-Dipolar cycloaddition between an azide and an imine successfully synthesised a pyrrolobenzodiazepine system when *L*-prolinol was used but when *L*-valinol was used, such

a system was not isolated. Future work could include application to other amino acid imine derivatives.

2.2. Attempted synthesis of pyrrolobenzothiadiazepines

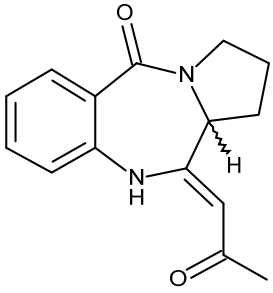
Pyrrolobenzothiadiazepines are the lesser explored sulfonamide analogues of the PBDs. The chemistry to be explored was similar to that of the carbon analogues discussed in Section 2.1 but starting with 2-azidobenzenesulfonic acid as shown in Scheme 2.18. Although the synthesis of 2-azidobenzenesulfonic acid had proceeded smoothly the ensuing couplings of the acid to *L*-prolinol and *L*-valinol were unsuccessful despite repeated attempts and modifications.



Scheme 2.18: Attempted synthesis of PBTDs.

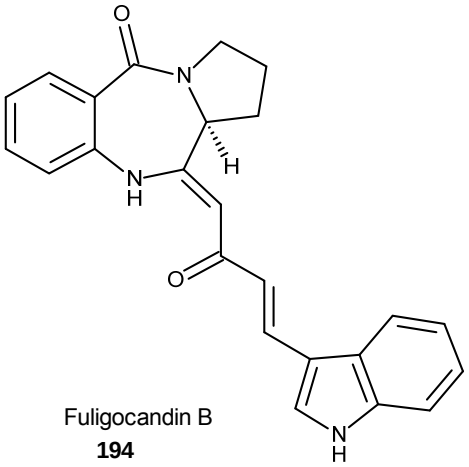
2.3 Synthesis of sulfur analogues of Fuligocandin A and Fuligocandin B

Fuligocandins A and B are examples of pyrrolobenzodiazepines that were extracted from the fruit bodies of the myxomycete *Fuligo candida* by Nakatani et al.[23] in 2004. The discovery of Fuliogocandin B's biological activity against leukaemia cells[24] and their recent total synthesis by Bergman[26] propelled us to synthesise the corresponding PBTD motifs.



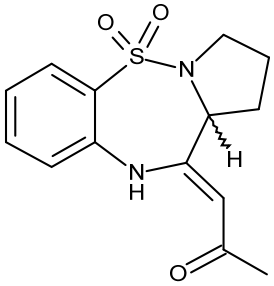
Fuligocandin A

193



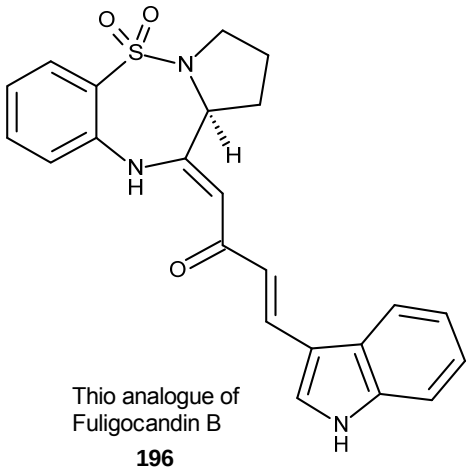
Fuligocandin B

194



Thio analogue of Fuligocandin A

195

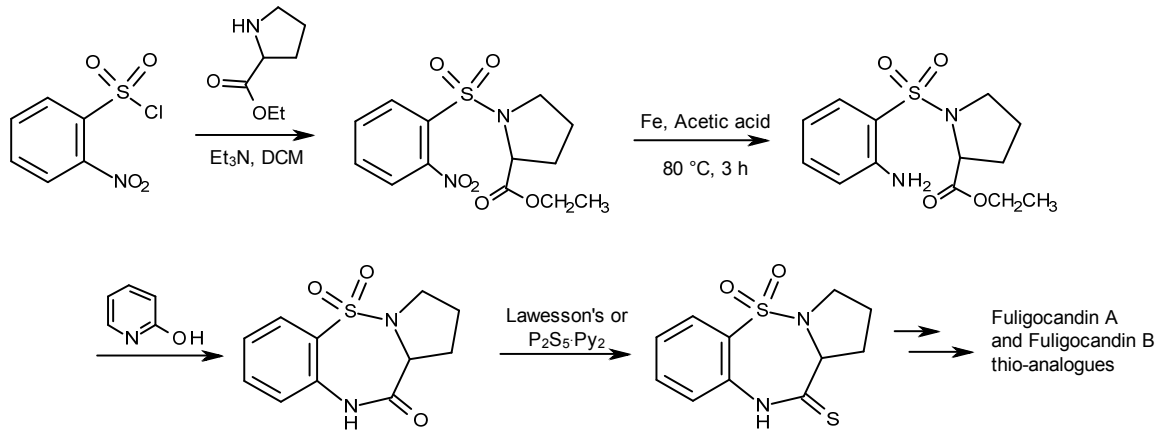


Thio analogue of Fuligocandin B

196

Figure 2.2

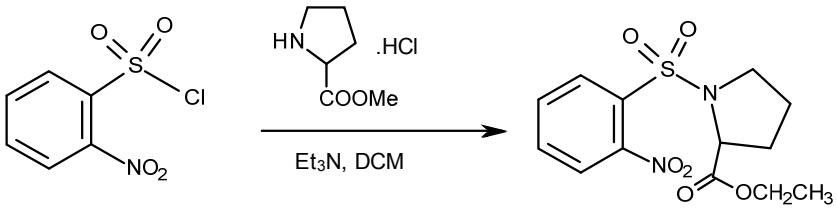
To arrive at the thioamide, we decided to first start with 2-nitrobenzenesulfonyl chloride and couple with an *L*-proline ester, followed by reduction of the nitro group to an amine and then cyclisation. Thionation using either Lawesson's or Bergman's reagent would produce the thioamide precursor to the Fuligocandins (Scheme 2.19). We then anticipated that the thioamide would be easily converted into the Fuligocandin analogues as per Scheme 1.5 in the introduction.



Scheme 2.19: Proposed route to synthesise the Fuligocandin thio analogues.

2.3.1. Attempted synthesis of 2-nitrobenzenesulfonylpyrrolidine-2-ethyl ester

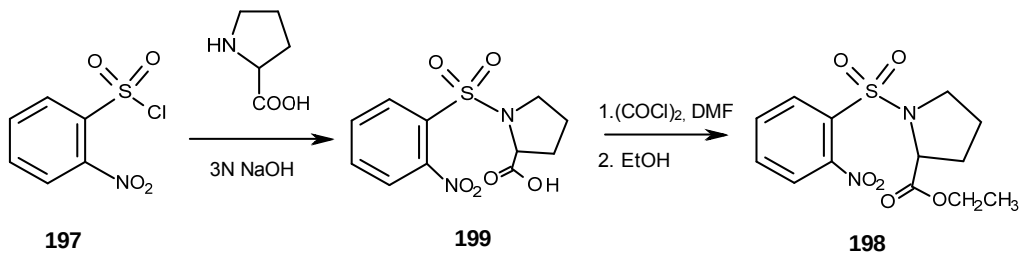
We attempted the synthesis of 2-nitrobenzenesulfonylpyrrolidine-2-ethyl ester **198** by coupling 2-nitrobenzenesulfonylchloride to the *L*-proline ester in the presence of triethylamine as a base. The reaction proceeded to give the desired product but always in low yields (<10%), meaning that a different route was required.



197 **198**

Scheme 2.20

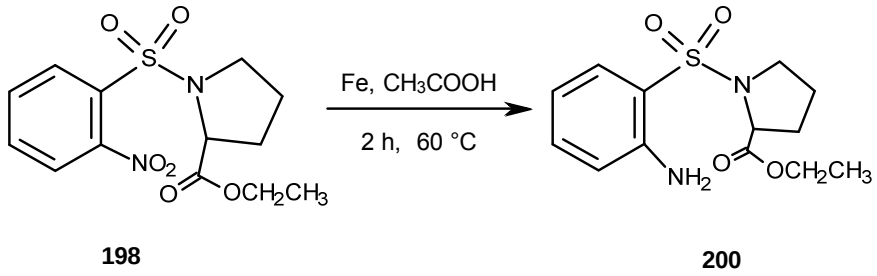
To improve the yield we used a route developed by Artico[174]. Thus, commercially available 2-nitrobenzenesulfonylchloride **197** was coupled to the amino acid *L*-proline in a base catalysed reaction the product of which was in turn chlorinated with oxalyl chloride under anhydrous conditions to furnish the chloride intermediate to which ethanol was immediately added to synthesise the desired nitro ester **198** (Scheme 2.21). The overall yield of this route was an acceptable 76% and this route was consistent and reliable.



Scheme 2.21: Artico's route to the nitro ester.

2.3.2 Synthesis of the 2-ethoxycarbonyl-1-(aminobenzenesulfonyl)pyrrolidine

Reduction of the aromatic nitro group to an amine occurred by heating to reflux compound **198** with Fe using acetic acid as the proton source. The successful conversion was confirmed by ^{1}H NMR spectroscopy.

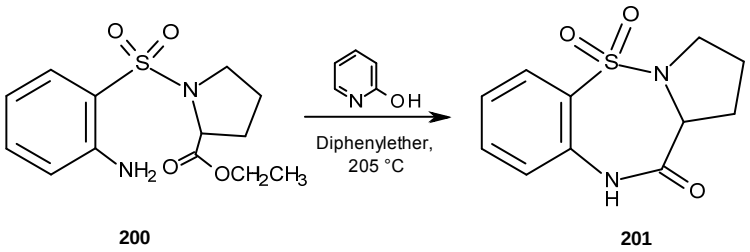


Scheme 2.22

In the ^{1}H spectrum, a new broad singlet appeared at 5.21 ppm corresponded to the 2H of the NH_2. A triplet at 1.24 ppm and a multiplet at 4.02 - 4.19 ppm corresponded to the CH_3 and CH_2 of the ethyl group respectively confirmed the structure of the amino ester **200**. The data matched the values reported in literature[79].

2.3.3 Cyclisation of the aminoester derivative

The next step was the cyclisation of the amino ester **200** to form pyrrolobenzothiadiazepine **201**. The procedure according to Artico et al.[79] seemed straightforward wherein the reaction was carried out in diphenylether with 2-hydroxypyridine and heated at 180 °C. The reaction proceeded to give the desired cyclised product in extremely low yields (~5%). Several attempts were made to improve the yield by varying reaction temperature, reaction time and the amount of 2-hydroxypyridine.



200 **201**

Scheme 2.23

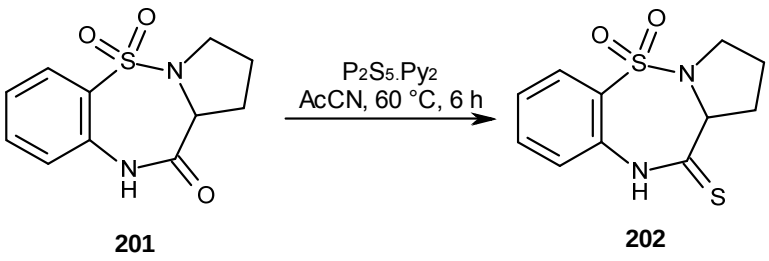
The best yield (40%) was obtained on heating the reaction to 205 °C for 15 h, which gave the cyclised product together with some unreacted starting material. Shorter reaction times and temperatures lower than 180 °C did not promote the cyclisation step while increased reaction times led to charring of the starting material and the product with low recovery of both. Attempted microwave reactions were unsuccessful.

Spectroscopic analysis determined the structure of **201**. ^{1}H NMR analysis depicted the 7 pyrrolidine protons as multiplets in the 1.77 - 4.65 ppm region. The aromatic protons were observed as a doublet at 7.12 ppm, a doublet of doublets (dd) at 7.19 ppm, a doublet of doublets of doublets (ddd) at 7.50 ppm and a doublet of doublets (dd) at 7.88 ppm while the NH exhibited a singlet at 8.96 ppm. The data closely matched the values available in literature[79].

2.3.4 Thionation of the amide

The most well-known route to thioamides is the thionation of the corresponding amide. A broad range of thionating agents is known and used for the thionation of carbonyl compounds[175], including Lawesson's reagent[176, 177], Davy's reagent[178, 179] or Heimgartner's reagent[180]. High yields, convenient handling, easy work-up, commercial availability, and use of mild conditions make Lawesson's reagent a very attractive thionating reagent. Furthermore, it has been reported in many successful thionations of amides, and lactams[181-183].

Lawesson's reagent was thus our first method of choice. The yields were found to be low (35%) and inconsistent when repeated. We looked at alternatives such as $P_2S_5.py_2$ as used by Bergman in his work on the parent (non-SO_2) Fuligocandins[26]. When Bergman's thionating reagent was freshly prepared and utilised, the yield of the thioamide **202** improved to 60%.

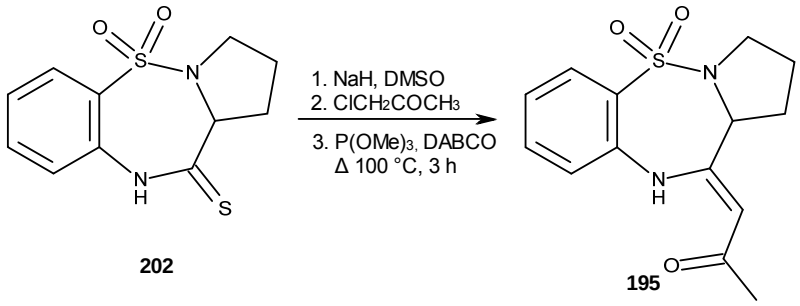


201 **202**

Scheme 2.24

The structural assignment of compound **202** was supported by NMR analysis as well as infra-red and mass spectroscopy. The infra-red spectrum showed the broad NH at ν_{max} 3140 cm^{-1} . The ^{1}H spectrum revealed the NH shift from 8.96 ppm [N*H*-CO] to 12.35 ppm [N*H*-CS] while the ^{13}C NMR spectrum showed the shift from 174.9 ppm (C=O) to 206.3 ppm (C=S) which were indicators of a successful conversion. The high resolution mass spectrum confirmed the product with the $[M+Na]^{+}$ found at 291.0236 when $C_{11}H_{12}N_2O_2S_2Na$ required 291.0232.

2.3.5. Attempted synthesis of the thio analogue of Fuligocandin A



202 **195**

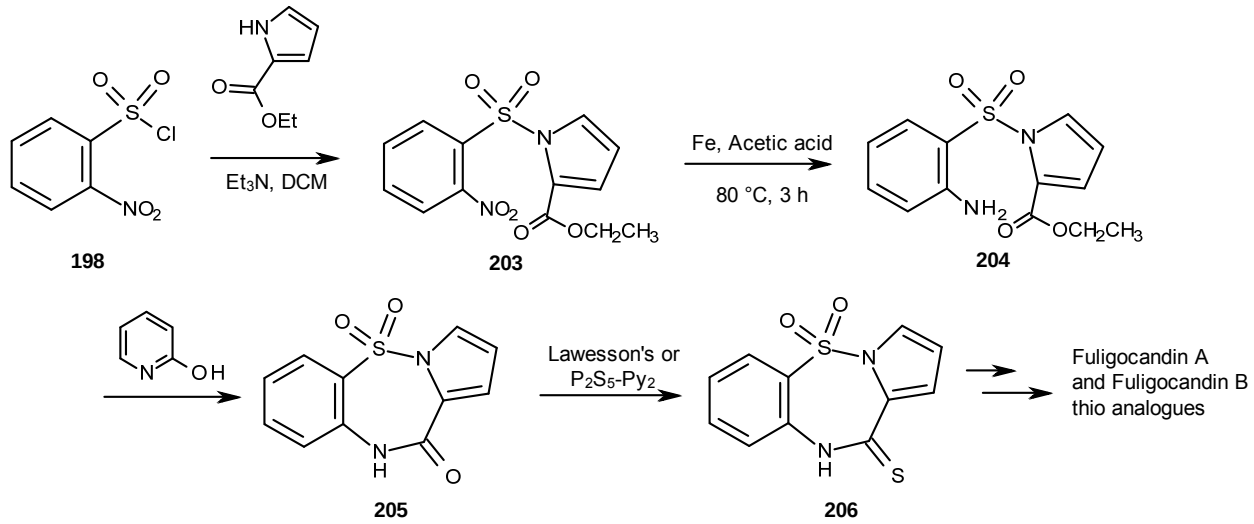
Scheme 2.25

When the thioamide **202** in a solution of DMSO was treated with sodium hydride followed by the addition of chloroacetone and subsequent addition of trimethyl phosphite and DABCO the process did not yield any identifiable products despite the same conditions having been successful for fuligocandin itself[26].

We also decided to apply the same strategy to the synthesis of the unsaturated (aromatic) pyrrole ring compound in order to provide a sample of this compound and hopefully, later allow us to compare the biological activity of the two systems - saturated and unsaturated (Scheme 2.26).

2.4 Synthesis of fuligocandin A with an unsaturated pyrrole ring

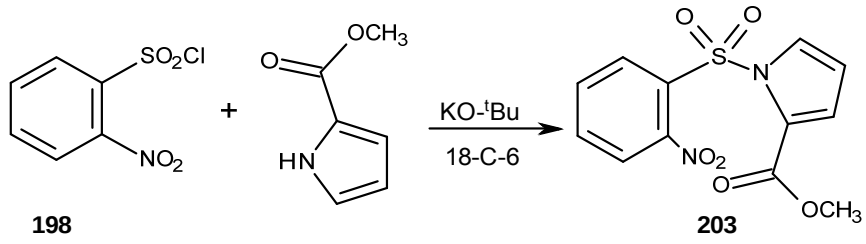
The same strategy was applied to the aromatic pyrrole system as depicted below in Scheme 2.26.



Scheme 2.26: Fuligocandin analogues with an unsaturated pyrrole moiety

2.4.1. Synthesis of 2-methoxycarbonyl-1-(2-nitrobenzenesulfonyl)-1*H*-pyrrole

The nitro ester **203** was synthesised as a white solid in 65% yield by coupling 2-methoxycarbonyl-1H-pyrrole with commercially available 2-nitrobenzenesulfonyl chloride **198** in the presence of 18-crown-6 and potassium *tert*-butoxide[79].

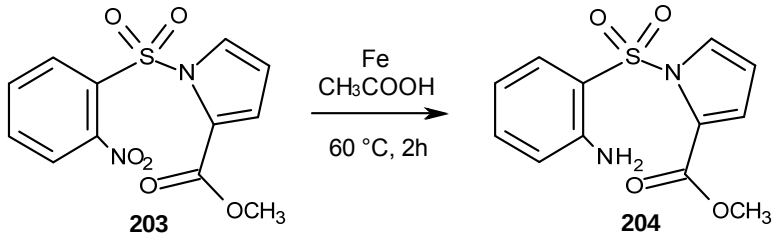


Scheme 2.27

The ^{1}H NMR spectrum of the product showed the methoxy protons at 3.69 ppm and the 3 pyrrole CHs at 6.34 ppm, 7.10 and 7.16 ppm each as a doublet of doublets. The benzene protons appeared as multiplets at 7.75 - 7.83 ppm (3H) and 8.32 - 8.36 ppm (1H). The data was identical to that in literature[79].

2.4.2. Synthesis of 2-methoxycarbonyl-1-(2-aminobenzenesulfonyl)-1*H*-pyrrole

Although there are many known methods for reduction of the NO_2 group attached to the aromatic ring, powdered iron in glacial acetic acid was the method of choice as it was found to give exceptional yields according to Artico et al[79]. Reduction of the NO_2 group was carried out by heating compound **203** to 60 °C for 2 h with Fe powder in glacial acetic acid which acted as the proton source to afford the aminoester **204** in 80% yield.



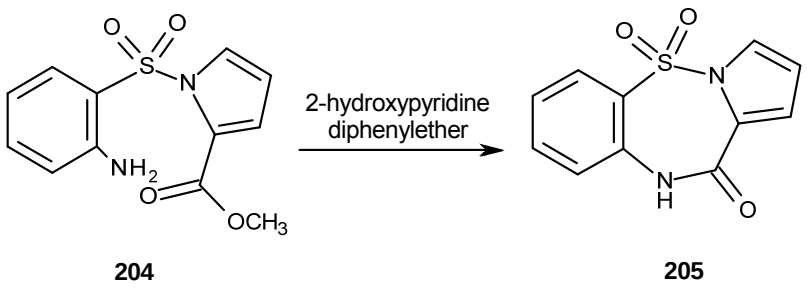
203 **204**

Scheme 2.28

The structure of the amino ester **204** was confirmed by the ^{1}H NMR spectrum which showed the characteristic broad singlet at 5.12 ppm which integrated to two protons indicating the reduction to the amine was successful. The data matched the values specified in the literature report[79].

2.4.3. Synthesis of 11-oxo(10H)-pyrrolo-[2,1-c][1,2,5]benzothiadiazepine 5,5-dioxide

The next step was to cyclise the amino ester to afford the pyrrolobenzodiazepine core **205**. We attempted the synthesis using the literature procedure by Artico et al.[79] which claimed that the pyrrolobenzodiazepine nucleus is formed in 64% yield by treating the amino ester **204** with a bifunctional catalyst 2-hydroxypyridine in a solventless reaction. But when carried out in our laboratory the reaction did not yield any cyclised product with only partial recovery of the starting material. Attempts to modify the conditions and use diphenyl ether as the solvent proved to be fruitful and gave the amide albeit in a low yield of 39% when carried out on a small scale (approx. 400mg of starting material). Several attempts were made to optimise the reaction in order to improve the yield but to no avail. It was established that when carried out on a larger scale, the yield dropped leading to a bigger loss of the starting material and ergo the reaction had to be repeated numerous times on a small scale (~300 – 400 mg scale) to arrive at suitable quantities of the desired amide **205**.



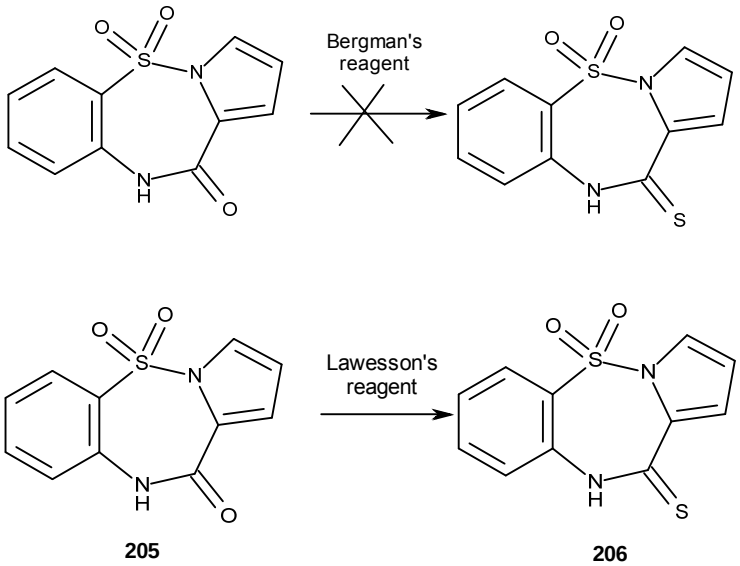
204 **205**

Scheme 2.29

Spectroscopic analysis by ^{1}H NMR confirmed the structure of the amide **205**. The two key aspects noted were the appearance of a deshielded NH singlet at 11.14 ppm and disappearance of the ester which led us to believe that compound **205** was successfully synthesised. The data was consistent with reported values[79].

2.4.4. Synthesis of the thioamide

Lawesson's reagent was our reagent of choice. The amide **205** was first stirred at r.t. with Lawesson's reagent and heated at reflux for 12 h to yield the thionated product in 37% yield. Attempts to optimise the reaction and improve the yield were made but longer reaction times did not prove successful.



205 **206**

Scheme 2.30

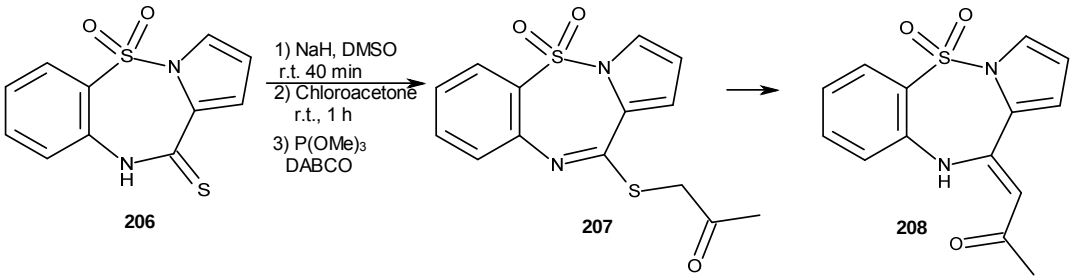
According to Bergman et al.[184] similar compounds were thionated using freshly made P_2S_5-Py_2 but the reaction when attempted with P_2S_5-Py_2 did not go as planned and we recovered

the starting material unchanged, meaning on this occasion that Lawesson's reagent remained our reagent of choice.

Spectroscopic analysis by ^{1}H NMR confirmed the structure of the thionated product **206**. The aromatic and pyrrole ring protons appeared as expected and the NH shift from 11.1 to 12.8 ppm as well as a shift in the ^{13}C spectrum from 159.3 ppm (C=O) to 194.7 ppm (C=S) were important indicators of a new product being formed. The high resolution mass spectral data then confirmed the structure as the thionated amide with 286.9910 $[M+Na]^{+}$ when $C_{11}H_8N_2O_2S_2Na$ required 286.9919.

2.4.5. Synthesis of thio analogue using episulfide contraction

The route followed again was that reported by Bergman[26] and started with the formation of the thioimidate which then undergoes an Eschenmoser type episulfide contraction.



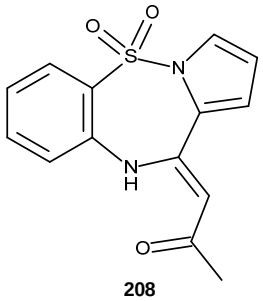
Scheme 2.31

Isolation (64% yield) and spectroscopic analysis of the thioimidate **207** revealed the NH signal was absent in the ^{1}H NMR spectrum, instead two new signals were seen; a singlet integrating to 3 protons appeared at 2.31 ppm which signifies the methyl group attached to the carbonyl, and a broad doublet which integrated to 2 protons observed at 4.01 ppm which is the deshielded methylene group flanked by sulfur on one side and the methyl ketone on the other.

In the ^{13}C spectrum of **207** the chemical shifts of the CH_3 group appeared at 28.6 ppm, while that of the deshielded methylene group was seen at 41.3 ppm. The 7 CHs appeared at 111.4, 117.7, 122.5, 125.4, 125.6, 128.1, 134.8 ppm and the carbonyl signal appeared as expected at 202.7 ppm.

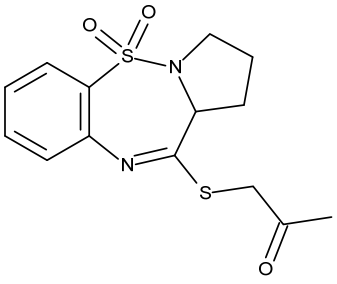
The IR spectrum further confirmed the structure of the thioimidate with the absence of the NH stretch in the 3300 – 3000 cm^{-1} region together with the presence of a carbonyl at 1710 cm^{-1}.

Heating of compound **207** to 100 °C for 2 h produced the thio analogue of Fuligocandin A with an unsaturated pyrrole ring **208** as a yellow oil in 52% yield.

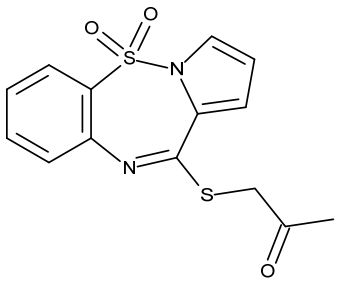


208

Analysis of the ^{1}H NMR spectrum revealed the distinct peaks of the methyl ketone as a singlet at 2.18 ppm. The appearance of the newly formed alkene CH as a singlet at 5.69 ppm and the emergence of a NH singlet at 13.5 ppm were strong indications that the Fuligocandin A analogue had been formed. The ^{13}C spectrum confirmed the appearance of an alkenic CH at 98.3 ppm while a signal at 198.2 ppm was indicative of a conjugated ketone. Furthermore, the IR spectrum displayed a strong broad NH peak at 3355 cm^{-1} (ν_{max}) while a sharp peak at 1680 cm^{-1} confirmed the carbonyl as a conjugated ketone as it had shifted from the original 1710 cm^{-1} of the thioimidate. The high resolution mass spectral data found the sodiated cation $[M+Na]^{+}$ at 311.0461 when 311.0468 was required for $C_{14}H_{12}N_2O_3SNa$.



202b



207

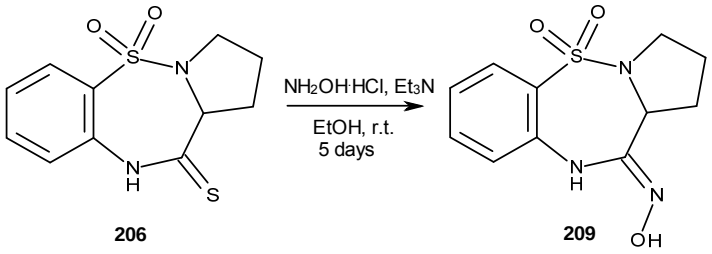
Returning now to the saturated system **202** (See Scheme 2.25, pg 62), it should be noted that the intermediate **202b** could be isolated but that its proton NMR looked similar to the ^{1}H NMR of the intermediate of the unsaturated ring **207**. This could be due to chemical transformation involving aromatisation of the ring or a human error such as a mix up of samples. Repetition would be necessary to replicate these results and further work is needed as it would be interesting to see if under these conditions the saturated ring was indeed

being aromatised. The possibility that compound **202** produces compound **207** under these conditions is an interesting one. Unfortunately time restrictions prevented a more thorough investigation.

2.4.6. Towards an oxadiazole analogue

There is a clear possibility that Fuligocandin A exists in a H-bonded conformation that mimics a 6-membered ring and hence acts as a tetracyclic analogue of a PBD. This led us to wonder if an oxadiazolo fused PBTD might be of interest. The oxadiazole was chosen because of the group's interest in this heterocycle[185] and because an easy route was available through to it *via* the oxime. Tetracyclic PBD and PBTDs are of interest for reasons detailed earlier in this thesis. The standard process is conversion of the amide to the thioamide, then conversion to the oxime and a final reaction with a phosgene equivalent.

To synthesise the oxime **209** the thioamide was reacted with hydroxylamine hydrochloride at r.t. in ethanol over 5 days. Being a relatively slow reaction, **209** was formed in 20 % yield as the minor product along with another compound which when analysed was established to be the amide (major product). The oxime **209** was found to be hydrolytically sensitive and decomposed to the amide over time. However, we are still unsure whether the thioamide gave the amide or if the oxime formed first and then produced the amide.



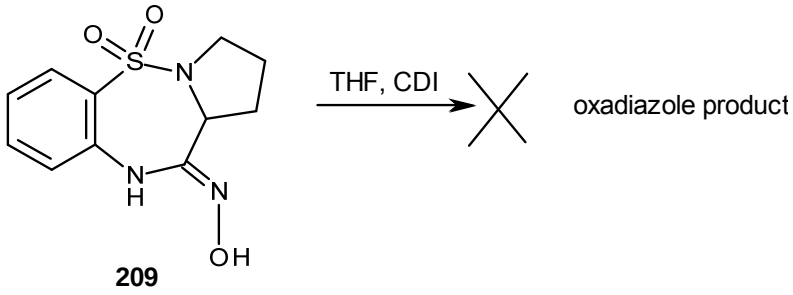
206 **209**

Scheme 2.32

Spectroscopic analysis gave evidence for the successful formation of the product **209**. Infra-red studies showed a broad OH stretch between 3600 - 3500 cm^{-1} and a signal at 3309 cm^{-1} suggested an NH stretch while a medium stretch at 1662 cm^{-1} for C=N offered further evidence for oxime formation. The ^{1}H NMR spectrum showed multiplets at 1.73 - 1.95 ppm, 2.01 - 2.16 ppm, 2.89 - 3.02 ppm and 3.36 - 3.49 ppm corresponding to the 7 protons of the pyrrolidine ring. Two of the aromatic CHs were observed as overlapping multiplets at 6.99 - 7.08 ppm. Another aromatic CH appeared at 7.42 ppm split as a doublet of doublets and the remaining CH appeared as a doublet at 7.75 ppm. Two broad singlets, one at 7.55 ppm for the NH proton and the other at 9.15 ppm for the OH proton were characteristic of an oxime.

DEPT, COSY and HSQC were used in confirming the structural framework. The ^{13}C NMR spectrum gives strong evidence that the quarternary C at 150.0 ppm corresponds to the oxime carbon C=N-OH while mass spectroscopy gave strong evidence for the oxime with $[M+Na]^+$ at 290.0563 when $C_{11}H_{13}N_3O_3SNa$ required 290.0569.

2.4.7 Attempted reaction of the oxime with CDI



209

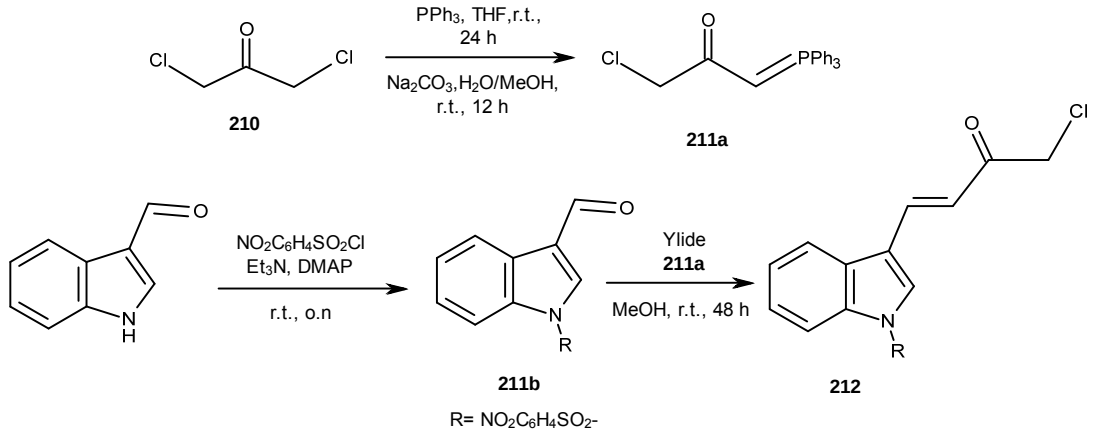
Scheme 2.33

All attempts to convert the oxime **209** into an oxadiazole were unsuccessful.

2.5 Synthesis of the Fuligocandin B analogues

2.5.1 Synthesis of the indole fragment of Fuligocandin B

This analogue required that the indole fragment (see Figure 2.2) be made first, ready for subsequent Eschenmoser reaction.



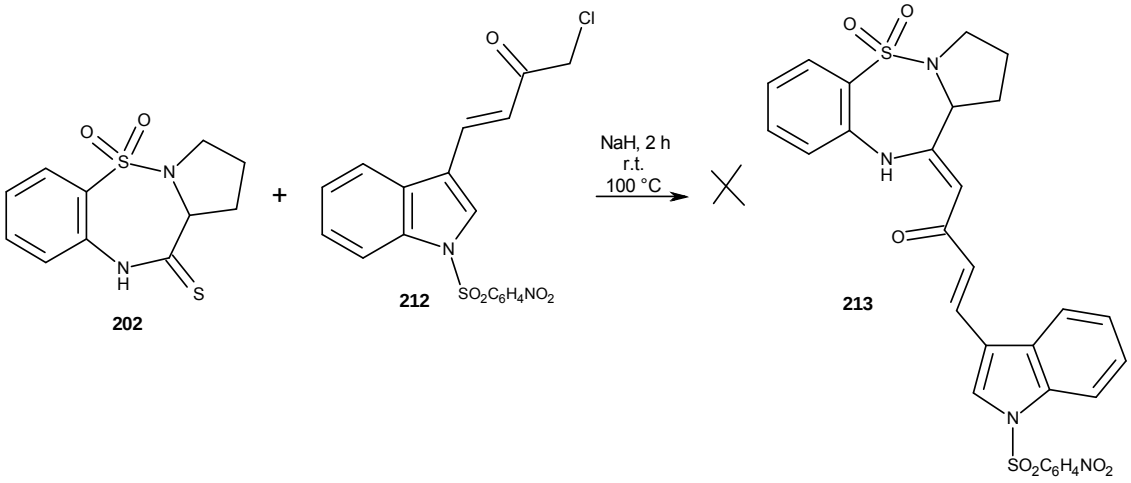
Scheme 2.34

Synthesis of the indole fragment **212** was carried out as shown in Scheme 2.34. The ylide **211a** was synthesised by reacting 1, 3-dichloroacetone **210** with triphenylphosphine

followed by a sodium carbonate work up to give **211a** in 89% yield. Alongside, indole-3-carbaldehyde was protected by treatment with DMAP and 4-nitrophenylsulfonyl chloride to afford a beige solid **211b.** This protected indole was reacted with the previously synthesised ylide **211a** over 24 h to access the indole fragment **212** in excellent yield.

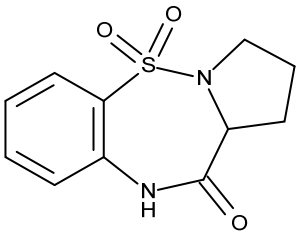
When fuligocandin B was synthesised according to Bergman and Pettersson[26], they claimed trimethyl phosphite and DABCO were not necessary for the episulfide contraction step and that in fact the reaction proceeded in their absence to give the Fuligocandin B in better yields. So it was decided to attempt to synthesise the sulfur analogue of Fuligocandin B under the same conditions.

2.5.2 Attempted synthesis of the Fuligocandin B analogue



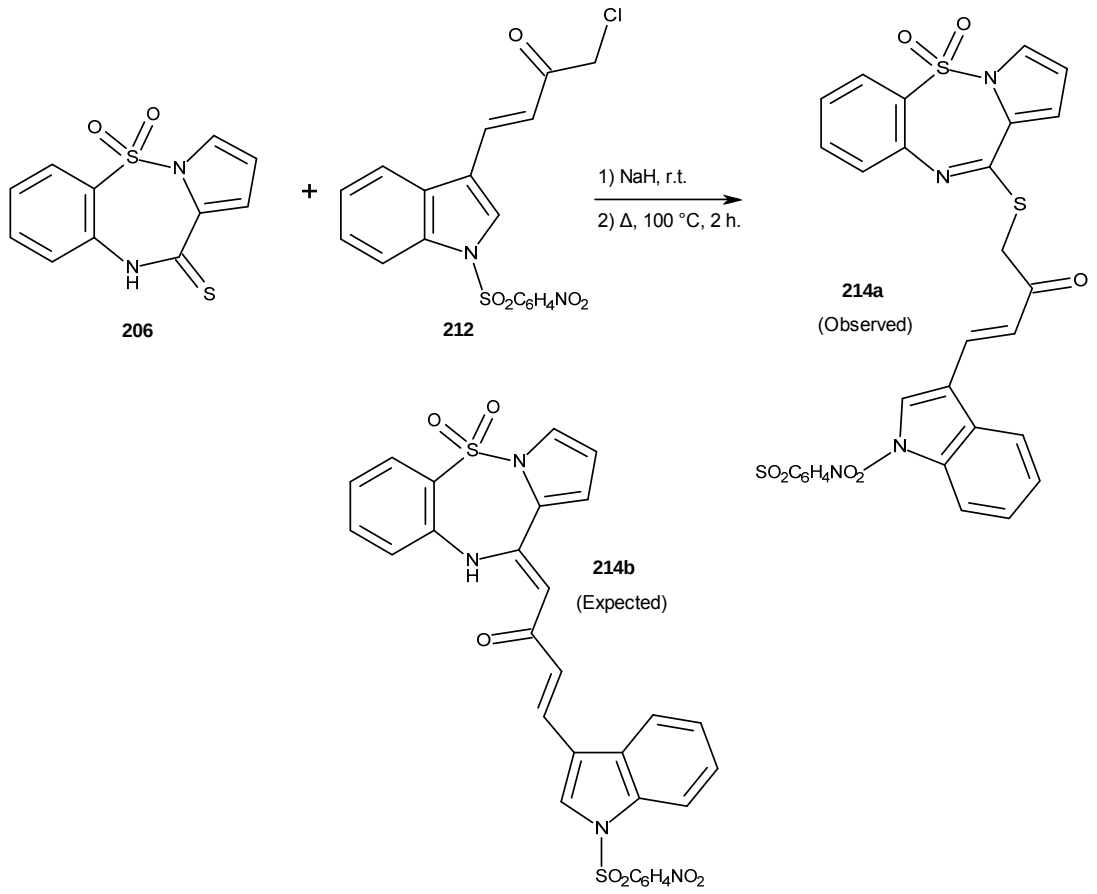
Scheme 2.35

On reacting the thioamide **202** with the prepared indole fragment **212** in the presence of sodium hydride at r.t., the reaction did not yield the desired compound **213.** The only compound that could be isolated was the amide **201**. Attempts to deprotect the protected fuligocandin B analogue without isolation were similarly unsuccessful and led only to the amide **201**. The failure of this process again led us to explore the synthesis of the corresponding aromatised pyrrole system due to ready availability of the thioamide **206**.



201

2.5.3 Attempted synthesis of a Fuligocandin B thio analogue with an unsaturated (aromatic) pyrrole ring



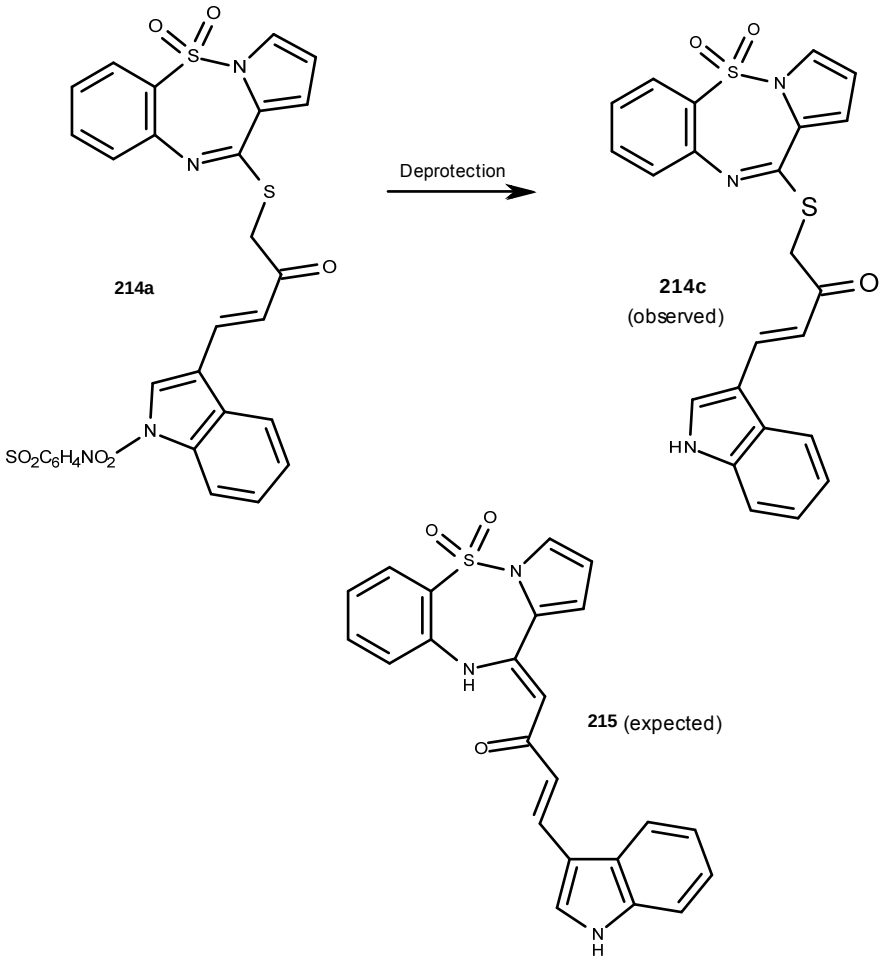
Scheme 2.36

A reaction pot containing the thioamide **206** with sodium hydride in DMSO was treated with the neat addition of the indole fragment at r.t.; it was then heated for 2 h at 100 °C. Bergman and Pettersson claimed that the episulfide contraction step occurred without the use of trimethyl phosphite and DABCO in much better yields than when they were used. Purification and isolation using silica gel chromatography was carried out to confirm the structure of the product as the protected intermediate **214a**. Analysis by ^{1}H NMR revealed a complex aromatic region as expected due to the presence of 18 proton signals overlapping in the aromatic/alkenic regions spanning from 6.42 - 8.38 ppm as multiplets. The ^{13}C NMR spectrum showed a quarternary carbon at 193.8 ppm which indicated the presence of a carbonyl in conjugation. HSQC and DEPT were used to account for all the sp^2 and quarternary carbons in the spectrum. A broad singlet (corresponding to two protons) at 4.02 ppm in the ^{1}H NMR spectrum correlated to a CH_2 at 39.5 ppm in the ^{13}C spectrum implied that the intermediate **214a** had formed rather than the episulfide contraction product **214b.** High

resolution mass spectroscopy confirmed the product as **214a** with an accurate mass of 632.0494 for a required value of 632.0491 for $C_{29}H_{20}N_4O_7S_3$.

2.5.4 Attempted deprotection

The nosyl protected intermediate **214a** was pushed through to the deprotection step with the possibility that the deprotected and contracted product would possibly form. Thiophenol was selected as it was readily available and is the standard method for nosyl deprotection.



Scheme 2.37

When the deprotection was attempted a complex mixture was obtained. ^{1}H NMR analysis revealed fragmentation products as the major products. One of the minor products isolated gave too little material to obtain complete characterised data but the ^{1}H NMR did show a singlet at 14.2 ppm (indole NH) indicating possible deprotection. HSQC showed the presence of 14 CHs which implied deprotection but not desulfurisation had occurred. Mass

spectral analysis of the same indicated it was indeed the deprotected **214c** with a $[M]^+$ of 447.0708 for a required value of 447.0711 with a formula of $C_{23}H_{17}N_3O_3S_2$.

2.5.5 Summary

Eschenmoser episulfide contraction allowed the successful synthesis of a sulfur analogue of Fuligocandin A, albeit with an aromatic pyrrole. Attempts to prepare the saturated pyrrolidine system were unsuccessful. With Fuligocandin B, attempts to make the saturated pyrrolo system were also unsuccessful. The corresponding aromatic pyrrolo Fuligocandin B thio analogue intermediate appears to have been successfully made but this requires confirmation and optimisation. Further attempts are being made to synthesise Fuligocandin B by other reserachers within the group by using trimethyl phosphite and DABCO to bring about contraction with simultaneous desulfurisation.

2.6 Cyclopropenones as a route to synthesising indolizidines and pyrrolizidines

This section deals with the synthesis of indolizidines and pyrrolizidines, a class of molecules linked to the PBDs and PBTDs by having a fused pyrrole ring at the centre. In our group, the pyrrole ring is constructed by reacting a cyclic imine with a cyclopropenone. Cyclopropenones were discovered in 1965[129] and were highly sought after as the smallest Hückel aromatic system with a reactive nature explained by the strained 3-membered ring. It is known to react with both nucleophilic and electrophilic reagents as well as molecules with an electron rich π system[186]. The unsubstituted ring itself is known to be highly unstable yet the mono-substituted and di-substituted derivatives are known to be stable.

As discussed in the introduction, our group has shown that cyclic imines react with cyclopropenones to give fused pyrrolidinones. Previous work in the group has indicated that a simple indolizidine derived from the parent δ-lactam underwent an unexpected (and unconfirmed) thermal rearrangement. Thus, we started by repeating this previous synthesis in order to see if a rearrangement occurred.

2.6.1 Synthesis of 2-piperidinthione

Lawesson's reagent was used to convert the amide **216** to the corresponding sulfur compound. The reaction was carried out in anhydrous THF stirred at r.t. and heated at reflux under a nitrogen atmosphere for 2 h to yield the product **217** as white crystals in 90% yield.

216 **217**

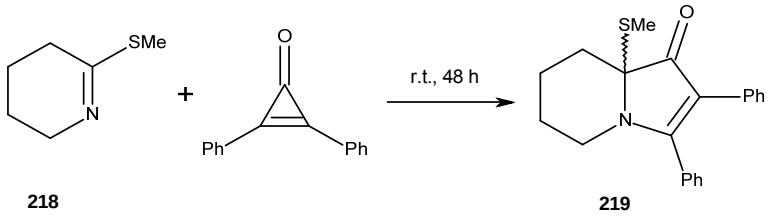
Scheme 2.38

The structure of the thioamide **217** was confirmed by ^{1}H NMR spectrum where the protons of the saturated ring appeared in the upfield region between 1.71 - 1.85 ppm, 2.89 ppm and 3.33 - 3.37 ppm while the N-H peak appeared as a singlet at 9.19 ppm. The ^{13}C spectrum showed the CH_2 protons between 20.1 and 44.6 ppm while the quaternary C appeared at 202.1 ppm. Infra-red spectroscopy confirmed the thioamide by the presence of the thiocarbonyl stretch [C=S] at 1138 cm^{-1} and the N-H stretch appeared at 3155 cm^{-1}. The data closely matched previously reported values[187].

The thioamide was alkylated with dimethyl sulfate (DMS) to give rise to the alkylated product **218** which due to instability was used directly in the next step.

2.6.2 Synthesis of 2,3-diphenyl-5-methylthio-1-azabicyclo[4.3.0]non-2-en-4-one

The alkylated product **218** was made to react with diphenylcyclopropenone (DPP) and the bicyclic adduct **219** was formed in 65% yield.



218 **219**

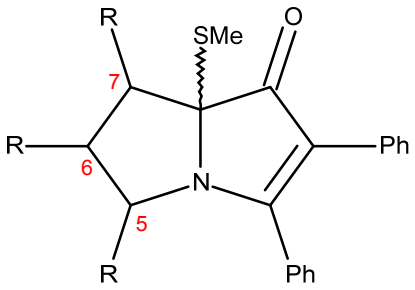
Scheme 2.39

Evidence for the formation of compound **219** was given by the isolation of a new product on TLC whose spectroscopic data was fully consistent with the expected structure. In the ^{1}H spectrum all the protons of the piperidine ring were present in the 1.71 to 3.55 ppm region as overlapping multiplets while the 10 aromatic protons were accounted for in the region spanning from 6.96 - 7.44 ppm. The key singlet corresponding to the thiomethyl (SMe) group appeared at 1.95 ppm. This data was consistent with previously reported data[187].

Compound **219** was found to be stable when heated in a variety of solvents**.** Thus, the project moved on to other areas, the first of which was to investigate the stereo-chemical outcome of the reaction of cyclic pyrrolines with cyclopropenones. This project has been ongoing in the group for some time and is closely related to an ongoing interest in the synthesis of jenamidines analogues (see Schemes 1.40 - 1.42).

2.7 Synthesis of Jenamidine-type indolizidine compounds

Jenamidines, as discussed previously, are a class of non-polyhydroxylated pyrrolizidines that are known to have anticancer activity against K-562 cell lines. Therefore, as part of our ongoing study on the jenamidines we decided to study issues of stereoselectivity in the reaction of imines towards cyclopropenones, starting with diphenylcyclopropenone. Previous work within our group investigated the stereochemical outcome of R groups (R= COOMe, Me, $CH_2OSiMe_2{}^tBu_)$ at position 5 of the ring **220** and found no selectivity. In this thesis we started to look at the C6 substituents.

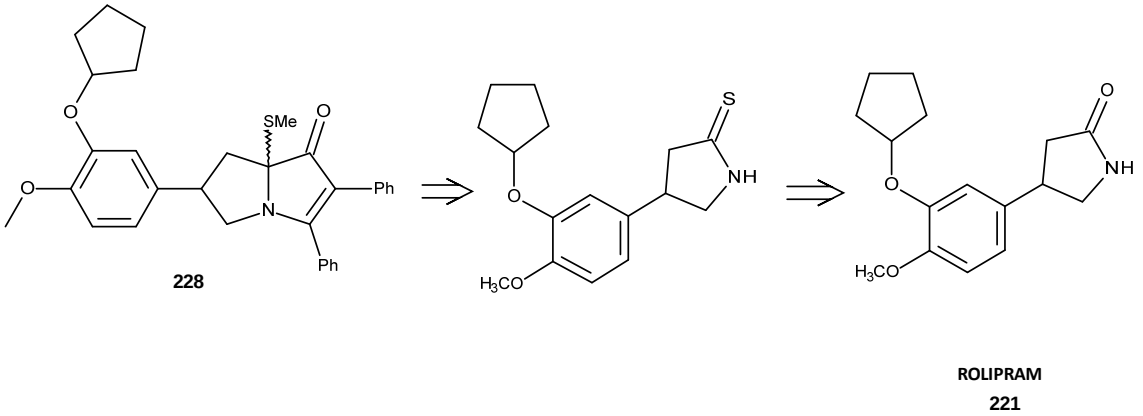


220

Figure 2.3

To synthesise this type of system, we looked at Rolipram as a readily available cyclic imine precursor. Rolipram **221** is an inhibitor of (PDE)-IV, a cyclic adenosine phosphodiesterase, and is employed in the treatment of depression[188, 189]. Barnes et al., have already shown how Rolipram was synthesised relatively easily and in excellent overall yields of 76% using conjugate addition of malonate esters to nitroolefins[190] and hence no problems were anticipated with its synthesis. Once Rolipram was synthesised, the next step would be conversion to its thioamide and thence to the cyclic imine. Scheme 2.40 summarises the

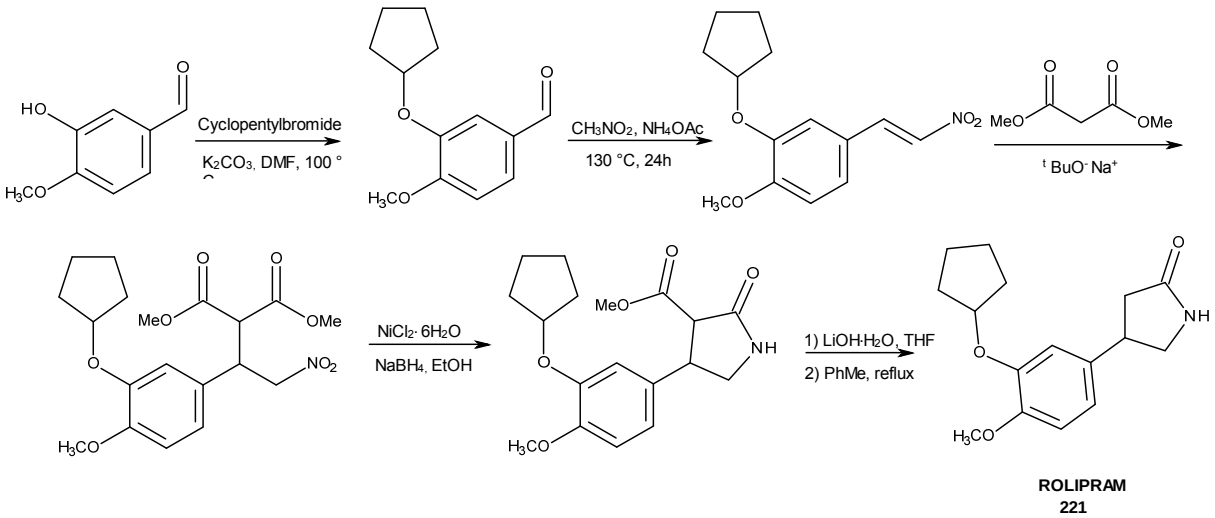
retrosynthetic strategy involved from the target indolizidine **228** to Rolipram **221**.



Scheme 2.40: Retrosynthetic strategy of the proposed indolizidine **228.**

Although Barnes et al.[190] carried out an asymmetric synthesis to access enantiomers of rolipram; we substituted the catalyst involved in the asymmetric process for a simple base triethylamine (Et_3N) since our initial study did not focus on enantioselectivity. The availability of single enantiomers, however, offers the possibility of future asymmetric studies.

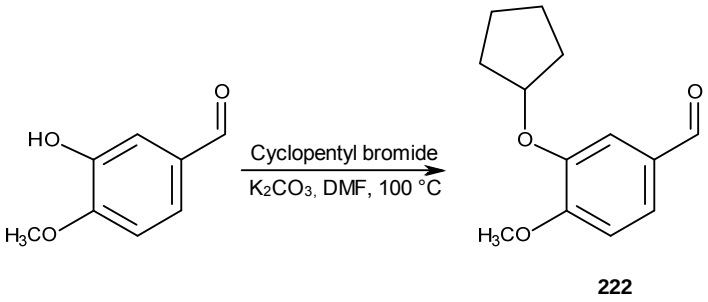
Scheme 2.41 depicts the 5 step conversion from commercially available isovanillin to rolipram. The hydrolysis that occurs as the last step offers a lactam precursor on which the indolizidine could be prepared and stereochemistry of the bridged substituent investigated.



Scheme 2.41: Synthesis of Rolipram according to Barnes et al.

2.7.1 Synthesis of 3-(cyclopentyloxy)-4-methoxybenzaldehyde

We first needed to protect the hydroxyl group of isovanillin as an ether moiety which was carried out by heating at reflux a mixture of commercially available isovanillin, K_2CO_3 and cyclopentyl bromide in DMF for 24 h. The reaction proceeded affording the desired product **222** quantitatively in excellent purity that did not require further purification.



222

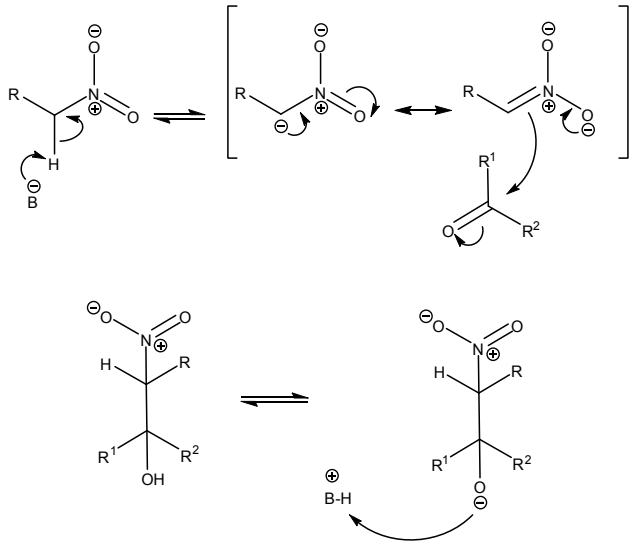
Scheme 2.42

The structure of compound **222** was confirmed by the ^{1}H NMR assignment of the protons. The characteristic aldehyde singlet was seen downfield at 9.79 ppm and the methoxy group appeared as a singlet at 3.88 ppm showing that the isovanillin core was present. The presence of the ether fragment was confirmed by the presence of the protons of the cyclopentyloxy group. 4 CH_2 signals were observed as multiplets in the region spanning from 1.50 - 2.11 ppm and the CH proton appeared as a multiplet between 4.76 - 4.85 ppm. The data was consistent with that found in literature[190].

2.7.2 Synthesis of 2-(cyclopentyloxy)-1-methoxy-4-[2-nitroethenyl]benzene

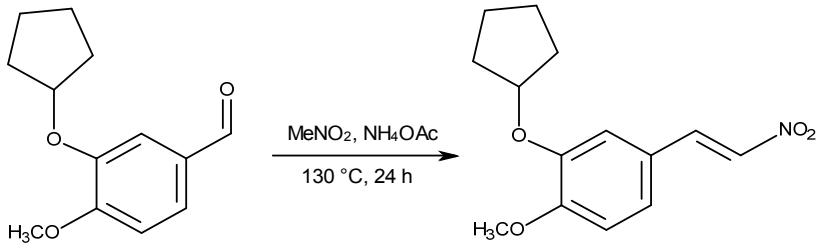
The next step involved the chemical transformation of the aldehyde to a nitroalkene using Henry condensation. The Henry reaction[191] is a classic carbon – carbon bond formation reaction in which a nitroalkane reacts with a aldehyde or ketone in the presence of a base. It is also sometimes referred to as the nitro aldol reaction[192, 193].

Scheme 2.43 shows the initial product formed would be the nitro aldol product followed by subsequent dehydration to give the nitroalkene.



Scheme 2.43 Mechanism of the Henry reaction.

Here the aldehyde **222** is subjected to the Henry condensation conditions to give the nitro olefin **223** in a single step in 88% yield. The reaction was carried out by heating at reflux compound **222** in nitromethane overnight using ammonium acetate as a base to furnish the desired olefin as a yellow solid.



222 **223**

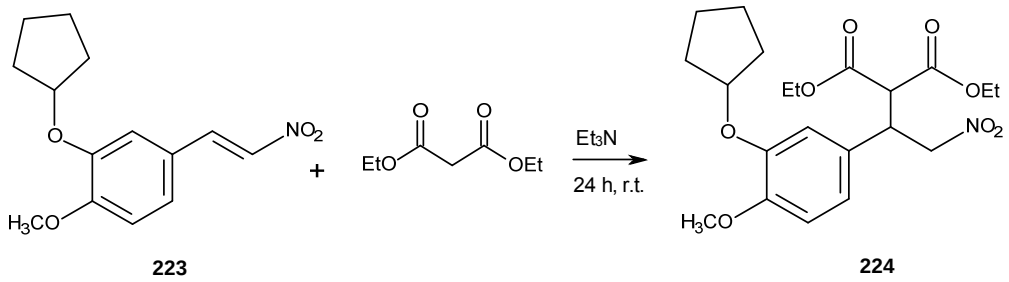
Scheme 2.44

Spectroscopic analysis was consistent with the formation of compound **223**. In the ^{1}H spectrum the loss of the aldehyde singlet at 9.79 ppm and the concurrent appearance of 2 new signals corresponding to the alkenyl protons implied the alkene product had been synthesised. The new alkene peaks at 7.48 ppm and 7.93 ppm were split into doublets with a coupling constant value of 13.3 Hz which indicates the alkene protons are aligned *trans* to one another.

2.7.3 Synthesis of diethyl-[3-cyclopentyloxy)-4-methoxyphenyl)-2-nitroethyl]propanedioate

Next we used a conjugate addition process between a Michael donor (nucleophilic species) and Michael acceptor in a base catalysed reaction to furnish the Michael adduct. Many examples have surfaced where asymmetric Michael reactions of malonates with nitroolefins in the presence of organocatalysts are known[194-197] and can be used to generate single enantiomers if required.

Barnes et al.[190] used dimethyl malonate but we decided to use diethyl malonate as it was available at hand and should not affect the overall scheme because in the later steps the diethoxy carbonyl function is removed. Using triethylamine as the base, the conjugate addition of the nucleophilic diethyl malonate carbanion yielded the Michael adduct **224** in 65% yield (Scheme 2.45).

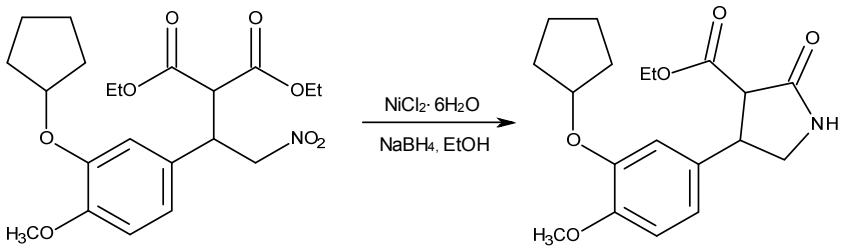


Scheme 2.45: Michael reaction.

Evidence of the formation of the Michael adduct **224** was given by ^{1}H NMR spectroscopy. The alkenyl proton signals had disappeared and were met with the appearance of a new set of proton signals. A multiplet was observed at 3.73 ppm corresponding to the acidic CH flanked by the 2 ester groups on either side. The proton attached to the chiral carbon at 4.03 ppm also emerged as a multiplet while the deshielded CH_2 protons attached to the nitro group (CH_2-NO_2) were split into two doublets of doublets (dd) that appeared at 4.73 and 4.80 ppm. ^{13}C NMR spectroscopy supported the information supplied by the ^{1}H spectrum. The chiral carbon appeared at 42.4 ppm, the acidic CH appeared at 54.7 ppm while the carbonyls were seen at 166.6 ppm and 167.3 ppm which were indicative of a successful reaction.

2.7.4 Synthesis of ethyl-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-oxopyrrolidine-3-carboxylate

The next step was the reduction of the nitro group to an amine using $NiCl_2 \cdot 6H_2O$ with $NaBH_4$ which further reacts *in situ* to form the lactam as shown below.



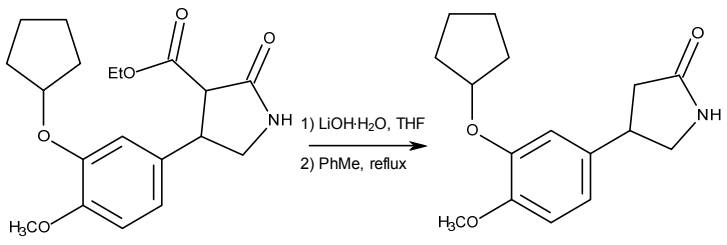
224 **225**

Scheme 2.46

Structural determination of compound **225** was on the basis on NMR and comparison with literature values. The loss of an ethoxy group (OCH_2CH_3) was obvious in the ^1H NMR due to a missing set of ethoxy peaks. The formation of the pyrrolidine ring was confirmed mainly by the appearance of an NH as a broad singlet at 7.06 ppm and the pair of protons at 3.68 and 3.96 ppm bordering the NH that emerged as a multiplet / doublet of doublets (dd). A doublet at 3.46 ppm integrated to 1H was the CH next to the carbonyls and a multiplet between 4.66 - 4.76 ppm which also integrated to one proton was the CH adjacent to the aromatic ring. The data was consistent with the reported values[190].

2.7.5 Synthesis of 4-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidin-2-one

To remove the unwanted ethoxy moiety, the lactam **221** would have to be decarboxylated in a 2 stage base hydrolysis and thermolysis process[190].



225 **221**

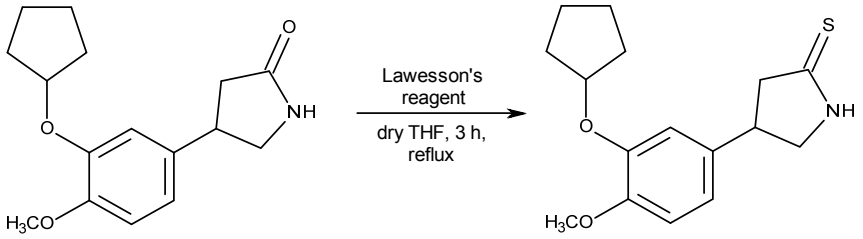
Scheme 2.47

$LiOH{\cdot}H_2O$ hydrolyzed the ester to give the acid which was in turn heated at reflux to promote the decarboxylation step that afforded the rolipram **221** as a mixture of enantiomers in 93% yield.

Spectroscopic analysis was consistent with the reported data[190]. The loss of the ethoxy group and appearance of the additional proton bordering the carbonyl implied the unsubstituted pyrrolidine ring had formed. Thus, in the ^1H NMR spectrum, the 2 sets of doublets of doublets (dd) at 2.43 ppm and 2.67 ppm belonged to the pair of protons neighbouring the carbonyl. A broad singlet at 7.03 ppm that corresponds to NH confirmed the pyrrolidinone ring. In the ^{13}C spectrum the appearance of an additional CH_2 at 38.1 ppm along with the C=O peak at 178.0 ppm were the key indicators that rolipram **221** was synthesised. The data obtained was fully consistent with published values for rolipram[190].

2.7.6 Synthesis of the thioamide

The thionation step was carried out with Lawesson's reagent and resulted in the formation of the thioamide **226** in 96% yield.



221 **226**

Scheme 2.48

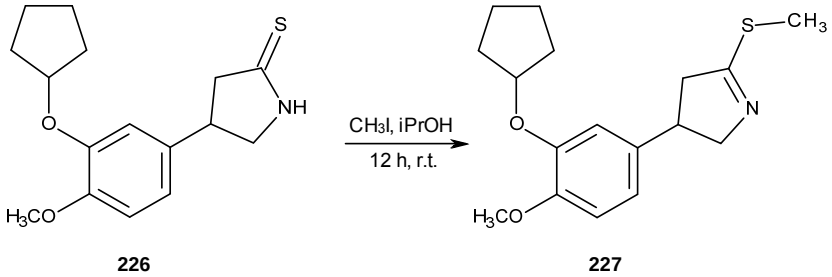
Spectroscopic analysis confirmed the structure of the thionated product **226**. The evidence of successful thionation was the chemical shift in the ^{13}C NMR spectrum from 178 ppm (C=O) to 205.2 ppm (C=S), as well as the absence of a carbonyl stretch and a presence of C=S absorption at 1120 cm^{-1} in the infrared spectrum.

The ^1H NMR spectrum confirmed the presence of the protons of the cyclopentyl ring as multiplets in the 1.53 - 1.96 ppm range, the methoxy on the aromatic ring appeared as a singlet at 3.80 ppm and the CH of the cyclopentyl ring emerged as a multiplet at 4.71 ppm. More importantly, the pair of protons adjacent to the thiocarbonyl appeared as doublets of doublets at 2.99 ppm and 3.28 ppm while the pair of protons neighbouring the NH appeared as multiplets at 3.57 - 3.61 ppm and 3.94 - 4.01 ppm with the NH singlet at 8.34 ppm. Further

validation for $C_{16}H_{21}N_1O_2NaS$ was given by the correct mass measurement of 314.1185 for the ion $[M+Na]^+$.

2.7.7 Synthesis of the thioimidate

Initial efforts to alkylate the thioamide with alkylating agents like dimethyl sulfate (DMS)[198] and Meerwein's reagent[187,199] were inefficient. DMS proved difficult to remove and separate from the reaction product while Meerwein's regent and Meerwein's salt caused the molecule to degrade. Using methyl iodide in isopropanol[200] was successful giving the thioimidate **227** as a yellow oil in 37% yield.

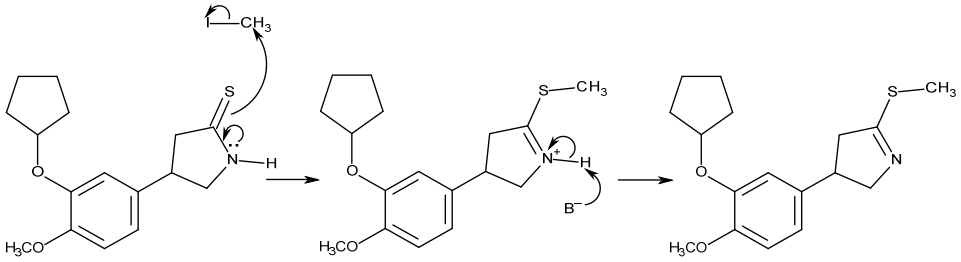


226 **227**

Scheme 2.49

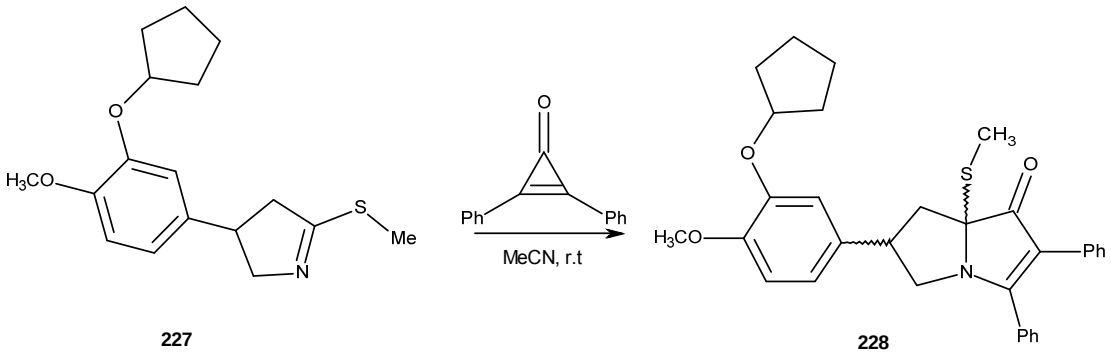
The evidence of the presence of the methyl group was provided by the ^1H NMR spectrum with the appearance of a singlet at 2.37 ppm integrating to 3H. The evidence of S-alkylation was provided by ^{13}C NMR data with the S-CH_3 peak at 68.3 ppm, a shift from 205.2 ppm (C=S) to 173.2 ppm (C=N) whilst the IR data showed the C=N absorption stretch at 1655 cm^{-1} along with the disappearance of the NH broad absorption at 3136 cm^{-1}. This data confirmed the outcome of S-alkylation and disclaimed N-alkylation. Further confirmation for $C_{17}H_{24}NO_2S$ was provided by the correct mass measurement of 306.1523 for the ion $[M+H]^+$.

Once the intermediate was characterised it was immediately carried forward to react with diphenylcyclopropenone (DPP). The mechanism for the alkylation step is depicted below in Scheme 2.50.



Scheme 2.50 Mechanism of the alkylation step

2.7.8 Reaction of the thioimidate with cyclopropenone



Scheme 2.51

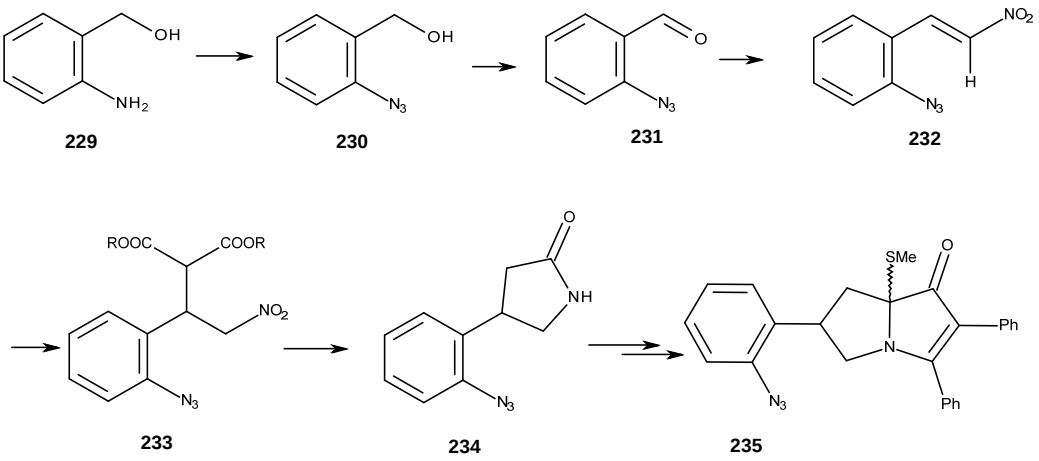
The reaction of the imine **227** with DPP was carried out at r.t. whilst stirring for 3 days in MeCN. Purification by chromatography afforded the target indolizidine product **228** as a mixture of diastereoisomers in a 1:1 ratio, indicating there was no stereocontrol induced by the 3-cyclopentyloxy-2-methoxybenzene ring and that this substituent at C6 had no effect in controlling the spatial arrangement of SMe and therefore the stereochemical outcome.

Formation of the indolizidine ring **228** was confirmed by NMR, infra-red and mass spectroscopy. The appearance of a singlet at 1.98 ppm integrating to 3H was indicative of the S-CH_3. Multiplets between 1.49 - 1.93 ppm and 4.52 - 4.85 ppm [O*CH*$(CH_2)_4$] corresponded to the protons of the cyclopentyl ring and all were accounted for. The pair of protons attached to the carbon next to N appeared at 3.34 and 3.78 - 3.84 ppm as multiplets while the other CH_2 protons appeared at 2.59 - 2.73 ppm. The aromatic region was noisy due to overlapping multiplets between 6.50 - 6.77 ppm for 3 aromatic CHs and a cluster of multiplets in the region spanning 6.97 - 7.56 ppm for 10 aromatic CHs.

The ^{13}C NMR spectrum showed the doubling of all the carbon signals wherein S-CH_3 was observed at 11.2 ppm and 11.3 ppm, all the CH_2 signals were accounted for at 23.9/24.0 ppm, 32.71/32.75 ppm, 37.91/37.93 ppm and 41.82/41.84 ppm, the 2 CHs were seen at 43.41/43.43 ppm and 80.4/80.5 ppm [OCH$(CH_2)_4$]. The carbonyl peaks were confirmed at 199.5/200.9 ppm (C=O). Further evidence was provided by IR data showing a shift in absorption from 1655 cm^{-1} (C=N) to 1697 cm^{-1} (C=O) and HRMS confirmed $C_{32}H_{33}NO_3SNa$ by the accurate and consistent mass measurement of 534.2011 $[M+Na]^+$ when 534.2013 was required.

In order to verify that an aryl group at C6 was unable to control the stereochemistry of the SMe group after cycloaddition, a second example was explored. The group's interest in azide

chemistry led us to explore the *o*-azidobenzene substituted system shown below. We envisaged that this would enable us to explore not only the stereochemical outcome of the reaction, but also the azido chemistry of compounds **233**, **234** and **235**. For example, the intramolecular aza Wittig reaction of **233** and **234** (Scheme 2.52).



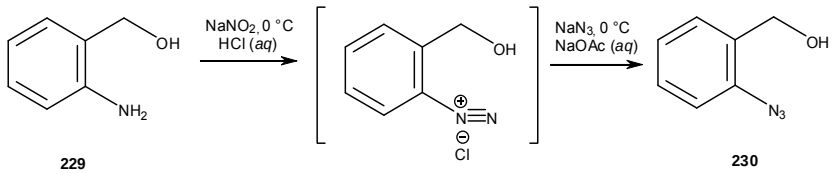
Scheme 2.52

To arrive at the nitroalkene **232**, a fairly simple 3 step reaction sequence starting with commercially available *o*-aminobenzyl alcohol **229** was used as outlined above.

2.8 Attempted synthesis of the azide substituted pyrrolizidine

2.8.1 Synthesis of *o*-azidobenzyl alcohol

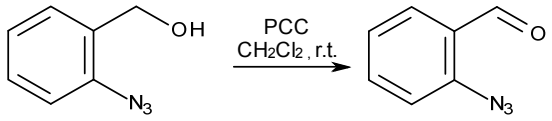
Amino groups can be conveniently converted to the corresponding azide by diazotisation followed by azidation of the amine functionality. Readily available *o*-aminobenzyl alcohol **229** was treated with sodium nitrite ($NaNO_2$) in an acidified aqueous solution containing hydrochloric acid at 0 °C to form the corresponding diazonium salt. After an hour, the diazonium salt solution was added dropwise to a mixture of sodium azide and sodium acetate in water to arrive at *o*-azidobenzyl alcohol **230** in quantitative yield.



Scheme 2.53: Diazotisation followed by azidation.

The data was found to be consistent with that reported in literature[201]. The IR spectrum and the melting point were paramount in confirming the structure as 2-azidobenzyl alcohol. The infra-red spectra exhibited a broad peak at 3346 cm^{-1} which was indicative of an alcohol and a peak at 2129 cm^{-1} which is characteristic of an azide moiety.

2.8.2 Synthesis of *o*-azidobenzaldehyde

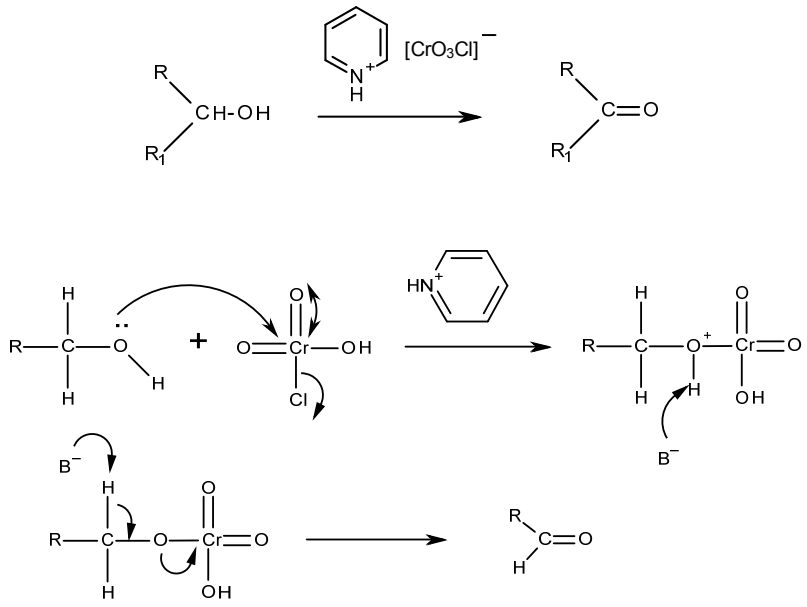


230 **231**

Scheme 2.54

Oxidation using PCC[201] gave the aldehyde product **231** in quantitative yield and excellent purity. The loss of the broad OH peak in the infra-red spectrum and appearance of the peak at 1710 cm^{-1} suggested a carbonyl group was present and a functional group conversion had occurred. The 2123 cm^{-1} peak diagnostic for the azide group indicated that the azide was still in place.

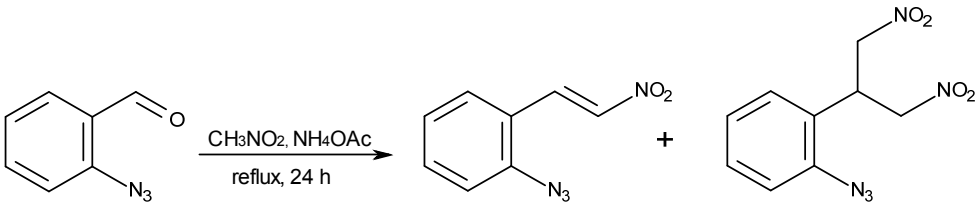
The ^1H spectrum confirmed the structure of *o*-azidobenzaldehyde **231** by the presence of the expected aldehyde proton downfield at 10.37 ppm and the absence of the CH_2 protons of the primary alkanol chain. The mechanistic pathway is shown in Scheme 2.55.



Scheme 2.55: Mechanism for the conversion of OH to CHO using PCC.

2.8.3 Synthesis of the corresponding nitro olefin (Henry reaction)

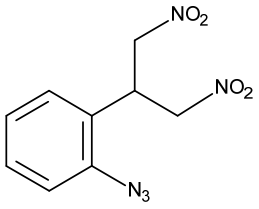
The reaction of the aldehyde with nitromethane was used to access the required nitro olefin **232a**.



231 **232a**, 65% **232b**, 6%

Scheme 2.56

The structure of the nitro olefin **232a** was established by NMR, infra-red and mass spectroscopy. The ^{1}H spectrum indicated the absence of the aldehyde proton (CHO) singlet and appearance of alkenyl protons (-CH=CH-) at 7.75 ppm and 8.14 ppm each split into a doublet with a coupling constant of 13.8 Hz suggesting *trans* geometry in the alkene. The infra-red spectrum suggested loss of the aldehyde carbonyl peak and appearance of NO_2 stretches at 1537 and 1377 cm^{-1}. Analysis by mass spectroscopy found accurate mass measurements of $[M+Na]^+$ 213.0381 when $C_8H_6N_4O_2Na$ required 213.0382.



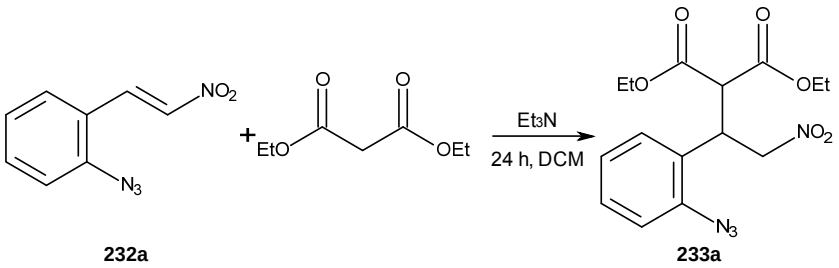
232b

Chromatographic purification of the reaction also yielded a side product corresponding to a di-nitro product **232b** that resulted from a Michael addition to the Henry product. This reaction was later optimised to allow one product to form over the other. Thus, the dinitro addition product dominated when a large excess of nitromethane was used with longer reaction times. Spectroscopic analysis of the dinitro adduct **232b** was confirmed using NMR, IR and mass spectroscopy. The ^{1}H NMR spectrum showed the highly acidic CH proton at 4.53 ppm split into a multiplet [$CH(CH_2NO_2)_2$] and the 4H of the two CH_2 groups were observed as a doublet at 4.85 ppm. The aromatic protons resonated at 7.21 and 7.41 ppm, the former as a multiplet integrating to 2 protons while the latter appeared as a doublet of doublets of doublets at 7.41 ppm. The ^{13}C NMR spectrum confirmed the presence of the

acidic CH at 37.6 ppm, the CH_2 at 74.5 ppm whilst the aromatic carbons (C-H) appeared at 118.4, 124.8, 129.1 and 130.0 ppm. A consistent and accurate MS ($[M+Na]^+$ 274.0557 found where $C_9H_9N_5O_4Na$ required 274.0547) established the structure of the double Henry adduct.

2.8.4 Michael addition to the nitroalkene

Following the successful formation of the nitroalkene, it was made to react with the enolate of diethyl malonate at r.t. with constant stirring over 24 h. The reaction yielded the Michael adduct in 58% yield.



232a **233a**

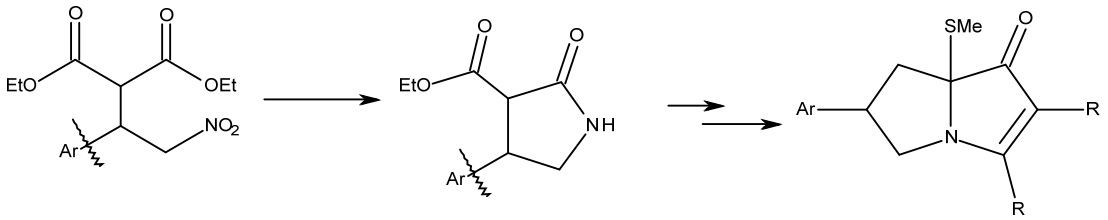
Scheme 2.57

The structural assignment of the adduct **233a** was given by NMR analysis. The reaction generated a chiral center which resulted in a diastereotopic splitting pattern. The ^1H (500 MHz) spectrum showed two sets of triplets at 0.98 and 1.18 ppm and two sets of quartets at 3.93 and 4.15 ppm that correspond to the CH_3 and OCH_2 of the ethoxy units respectively. The CH between the ester groups appeared at 4.07 ppm as a doublet while the CH_2 protons appeared as doublets of doublets at 4.85 and 4.98 ppm. The chiral CH was observed at 4.38 ppm and split into a doublet of triplets. The aromatic ring protons appeared at 7.01 (dd), 7.10 (d), 7.15 (d) and 7.26 (dd) displaying the classic 1, 2- substitution pattern. The data from the ^{13}C spectrum supported the structural assignment as the CH_3s were seen at 13.5 and 13.7 ppm. The CHs appeared at 39.2 ppm and 52.9 ppm – the former value corresponded to the chiral CH and the latter to the CH-CO. The OCH_2 signals were seen at 61.6 and 61.8 ppm while the CH_2 attached to NO_2 was seen at 75.8 ppm. Mass spectroscopy found $[M+Na]^+$ at 373.1119 for $C_{15}H_{18}N_4O_6Na$ (required 373.1122) giving further evidence for the structure of the compound **233a**. Infra-red spectral data proved that the azide was still present (2125 cm^{-1}) and the ester carbonyl stretch occurred at 1729 cm^{-1} as expected.

2.8.5 Attempted reductive cyclisation of the Michael adduct

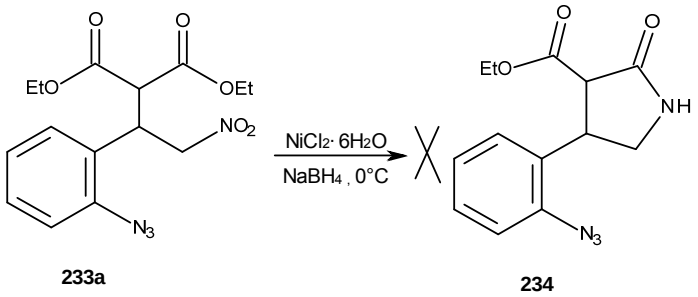
In a bid to repeat the success seen in synthesising an indolizidine from rolipram **221** the next step in the synthetic strategy was the reductive cyclisation using nickel chloride

hexahydrate ($NiCl_2 \cdot 6H_2O$) and sodium borohydride ($NaBH_4$) at 0 °C to form the amide ring as a stepping stone towards building the indolizidine core (see Scheme 2.58).



Scheme 2.58: Synthetic strategy towards synthesising the indolizidine system

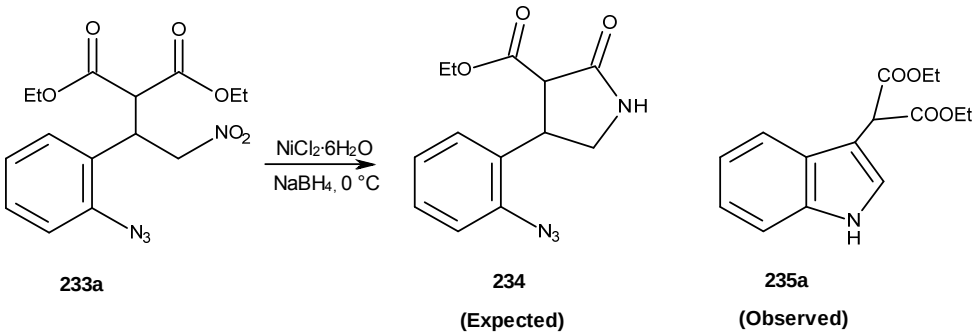
When the reaction was carried out, a white solid was isolated. The data did not match that required of the amide ring. We expected the data to show the amide ring with a single ester group. However, two sets of ethoxy peaks were seen in the ^1H NMR spectrum. The aromatic CHs were observed at 7.13 and 7.19 ppm split as a doublet of doublet of doublets (ddd) and the remaining 2 CHs were seen at 7.34 and 7.64 ppm each as a doublet. An unexpected doublet at 7.34 with a *J* value of 2.5 Hz was seen while the alkyl protons of the expected lactam were missing. An additional CH existed as a singlet at 4.92 ppm. The infra-red spectrum showed the azide group was not present in the compound as the diagnostic azide peak (2122 cm^{-1}) was missing. Using all this information it was concluded that the amide ring **234** as shown in Scheme 2.59 was not formed.



233a **234**

Scheme 2.59

Using ^{13}C NMR and HSQC analysis we arrived at the conclusion that the product was not the amide ring **234** but indole **235a**. This was further attested by the accurate mass measurement of the compound that found $[M+Na]^+$ as 298.1050 when $C_{15}H_{17}NO_4Na$ required 298.1050. The yield of the indole **235a** was 99%.

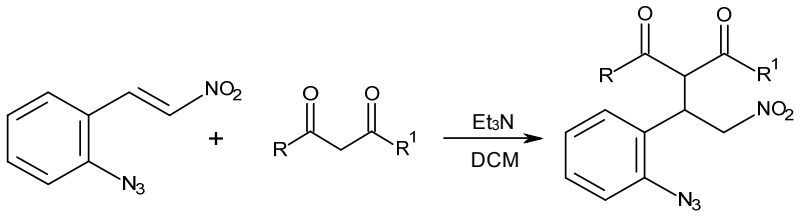


233a **234** **(Expected)** **235a** **(Observed)**

Scheme 2.60

This fascinating find piqued our interest and prompted us to examine more closely if this result was reproducible and consistent if the substituent groups were varied. Success with diethyl malonate caused us to first look at other malonates in the series.

We initially began reacting the nitro olefin **232a** with malonate esters which proceeded readily generating the Michael adducts in good yields (~55-60%). The results are tabulated and presented in Table 2.1. The table indicates that the *tert*-butyl malonates (**233e and f**) did not react to form the Michael adduct possibly due to the steric hindrance.



232a **233a-d**

Scheme 2.61: General Michael reaction

Table 2.1 shows the % yields for Michael adducts derived from malonic esters.

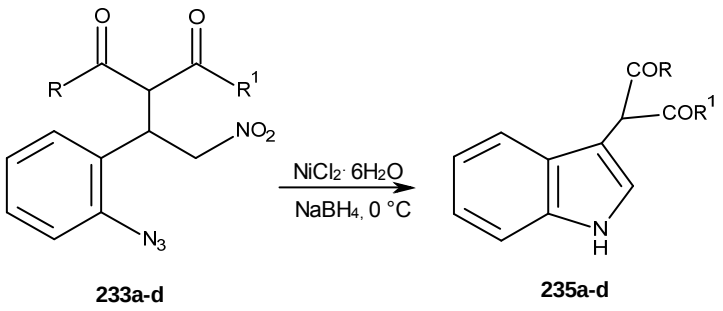
Entry	R	R^1	Yield (%)
a	OEt	OEt	58
b	OMe	OMe	61
c	OPr	OPr	60
d	OCH_2Ph	OCH_2Ph	55

e	O-*tert* butyl	O-*tert* butyl	Unreacted
f	O-*tert* butyl	OEt	Unreacted

*Yield obtained after chromatography

The structure of the Michael adducts **233** (Table 2.1 Entries **a-d**) was confirmed using NMR analysis as well as accurate mass measurement.

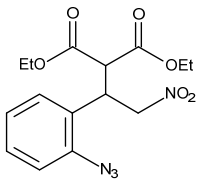
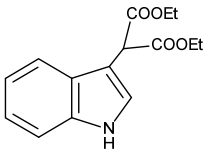
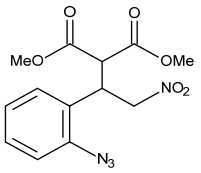
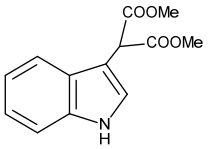
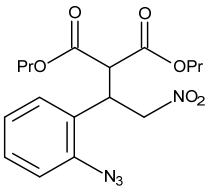
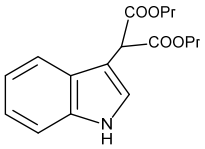
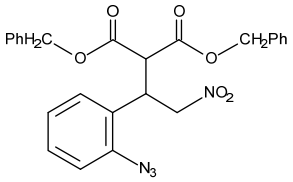
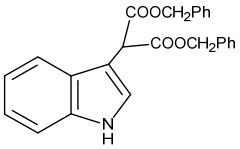
Reductive cyclisation using $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ at 0 °C of these Michael adducts gave the indole unit with the side chain at position 3 (Scheme 2.62).



Scheme 2.62: Reductive cyclisation step reaction

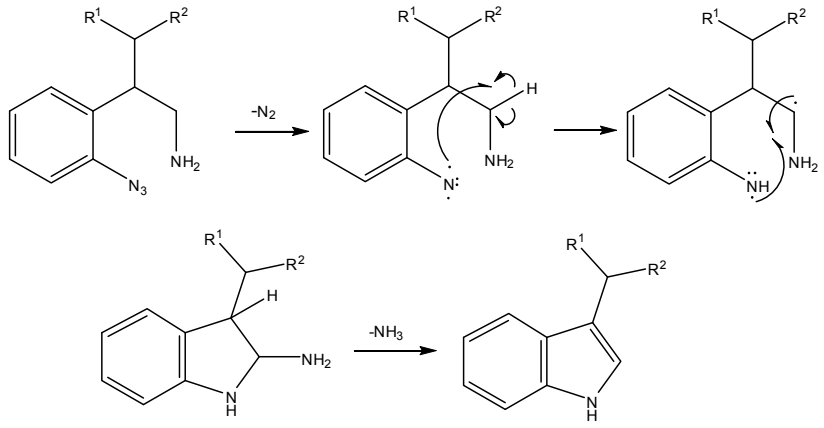
The dimethyl **233b** and dipropyl adducts **233c** gave the expected indoles (**235b** and **235c** respectively) in good yields whilst the dibenzyl adduct **233d** adduct gave the indole **235d** in below 10% yield in spite of repeated attempts to improve the yield. All spectroscopic data were fully consistent with the assigned structures. In each case ^{1}H (400 MHz) NMR spectroscopy showed the disappearance of the CH_2 and the appearance of the NH signal above 8 ppm as well as an additional indole CH. All of the ^{13}C (100 MHz) NMR spectra showed the presence of an extra CH in the aromatic region and the disappearance of the aliphatic CH_2 of the nitro alkyl chain. All the infra-red spectra showed the disappearance of the azide moiety and the appearance of a broad NH stretch. The correct accurate masses were observed by high resolution mass spectrometry for all the examples. Table 2.2 summarises the yields of the different analogues.

Table 2.2 shows the % yields for indoles derived from the Michael adducts.

Entry	Michael adducts (233)	Indoles (235)	Yield (%)*
a			99
b			93
c			89
d			8

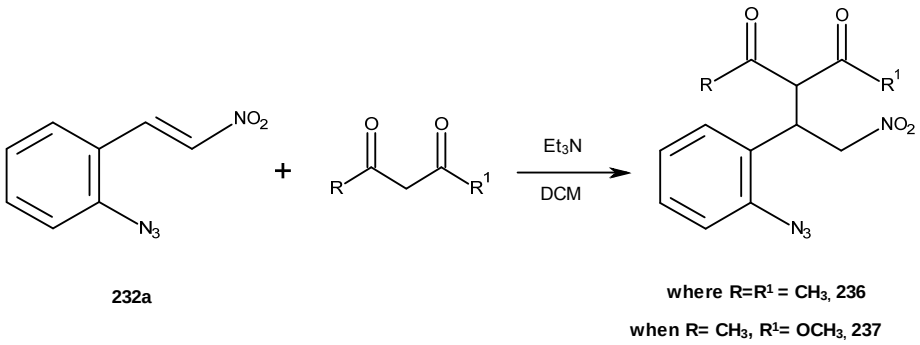
*Yield obtained after chromatography

By examining precedent set by Cadogan and Sundberg's formation of indoles *via* nitrenes (Scheme 1.54), we also know that azides are precursors to nitrenes. This led to the suggested mechanism in Scheme 2.63. Alternatively, no previous syntheses are known where indoles have formed from azide precursors under reductive conditions using nickel chloride hexahydrate in ethanol at low temperatures.



Scheme 2.63: Possible mechanism for indole formation.

Seeing a pattern emerge amongst the esters, we decided to explore this process further with other carbonyl compounds namely 2, 4-pentadione and ethylacetoacetate.



232a

where R=R¹ = CH_3, 236

when R= CH_3, R¹= OCH_3, 237

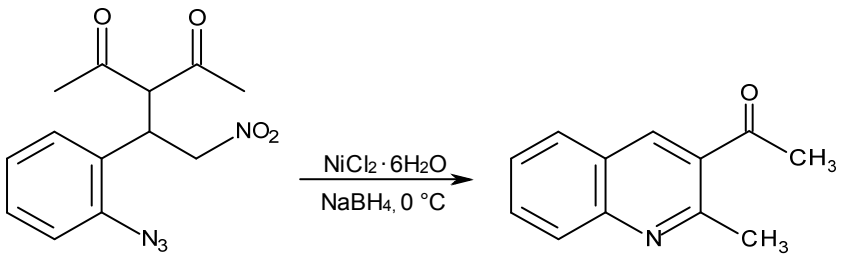
Scheme 2.64: Michael addition of a nitro olefin with ketones

The pentadione Michael adduct **236** and the acetoacetate adduct **237** were successfully synthesised in 65% and 61% yield respectively. Spectroscopic analysis confirmed the structure of both compounds. It was also found that the Michael reaction with cyclic ketones did not give the expected Michael adducts.

The diketo adduct **236** was isolated as a yellow oil after reacting with the azido nitrostyrene **232a** at r.t. for 4 h. The 2 methyl groups were seen as singlets at 1.94 and 2.22 ppm, the CH between the two carbonyl groups occurred as a multiplet between 4.40 - 4.49 ppm and the CH_2 protons adjacent to the nitro group appeared as a multiplet between 4.51 - 4.59 ppm. All 4 aromatic protons were accounted for at 6.99 - 7.28 ppm proving the Michael reaction was a success. The ^{13}C NMR spectrum further supported the ^{1}H data and showed the 2 CH_3 groups at 29.1 and 30.8 ppm. The CH attached to the carbonyls was observed at 69.2 ppm, the chiral carbon was seen at 38.6 ppm, the CH_2 attached to the nitro group occurred at 76.1 ppm and the carbonyls were seen at 201.3 and 202.2 ppm.

The diketo Michael adduct **236** was then subjected to reduction with $NiCl_2 \cdot 6H_2O$ and $NaBH_4$. The ^1H NMR data indicated 2 CH_3 groups were present as singlets at 2.70 and 2.90 ppm and no alkyl protons were observed. Two of the aromatic protons that coupled together were observed as individual sets of doublets of doublets (dd) at 7.54 and 8.03 ppm and the other two aromatic CHs were observed each as doublets at 7.77 and 7.85 ppm. Additionally, a singlet at 8.48 ppm integrating to a CH was detected. The lack of a NH signal (^1H and IR) indicated that the indole had not been formed at all. The ^{13}C NMR spectrum revealed a CH_3 at 26.1 and 29.7 ppm with the aromatic CHs at 126.0, 127.1, 129.1, 132.2 ppm. An extra CH was observed at 138.7 ppm and only a single carbonyl was seen present at 199.8 (C=O).

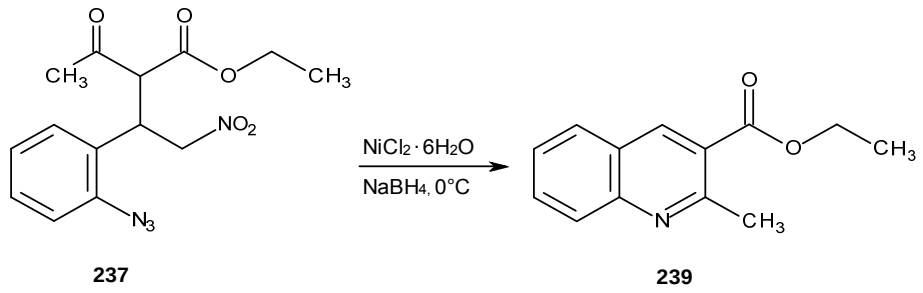
Using HSQC, COSY and mass spectroscopy it was established the structure to be a quinoline **238** and this was isolated as a brown oil in 11% yield.



236 **238**

Scheme 2.65

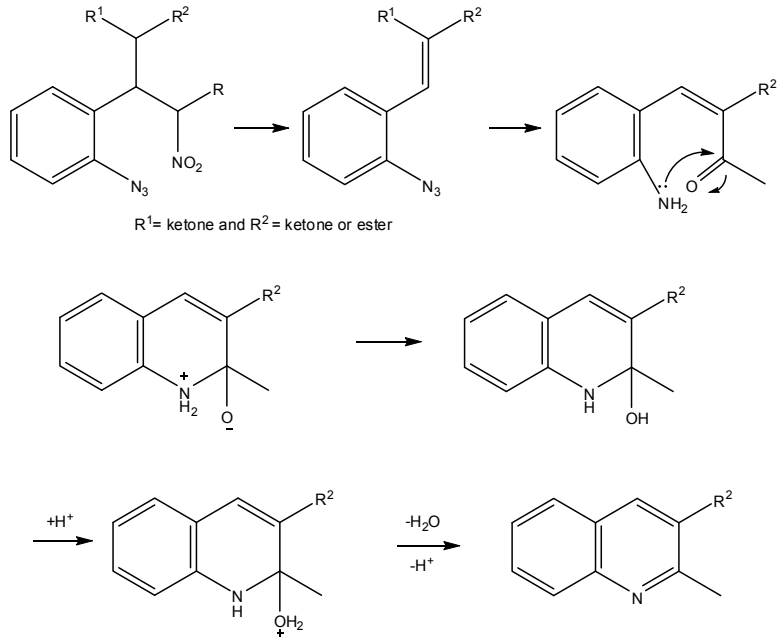
Next, the keto ester adduct **237** was reduced with $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ and afforded a yellow solid. The ^1H spectrum revealed 2 CH_3 groups were present one as a triplet at 1.43 ppm and the other as a singlet at 2.97 ppm. A quartet at 4.42 ppm integrating to 2 protons suggested OCH_2 of the ethoxy moiety was present. In the aromatic region two sets of doublets of doublets at 7.51 and 7.75 ppm, two sets of doublets at 7.84 and 8.02 ppm and a singlet at 8.71 ppm integrating to a CH again showed the quinoline (9% yield) compound **239** as the most likely structure. The ^{13}C NMR spectrum displayed a CH_3 at 14.3 and 25.6 ppm while the CH_2 appeared at 61.4 ppm. The aromatic CHs were observed at 126.5, 128.4, 128.5, 131.7, 139.9 ppm and the ester carbonyl at 166.5 ppm. The high resolution mass spectrum found $[M+H]^+$ 216.1019 for $C_{13}H_{14}NO_2$ which required 216.1019.



237 **239**

Scheme 2.66

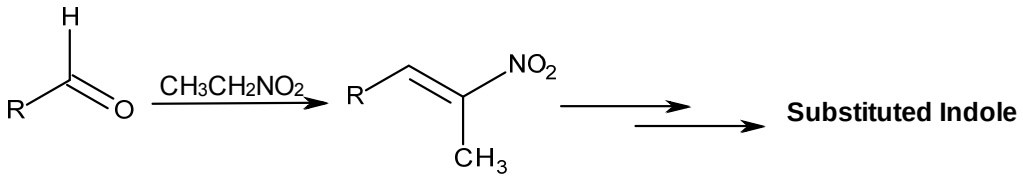
The suggested mechanism of quinoline formation is depicted in Scheme 2.67. The mechanism may involve a retro-aldol reaction to arrive at the quinoline structure. Conversion of the azide to the amine and cyclisation of the amine onto the ketone then gives the quinoline. There is no literature precedent on which this mechanism is based, other than azides being a precursor to nitrenes (according to Sundberg) and the strong possibility of a retro-aldol.



Scheme 2.67 shows the possible mechanism for the formation of quinolines.

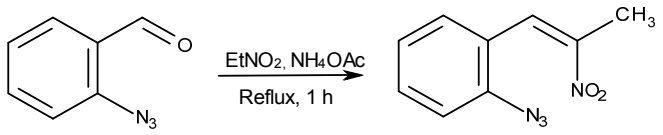
2.8.6 Variation in the nitro olefin

The production of indoles and quinoline systems from a nitro olefin were interesting finds. To explore and understand this chemistry further we decided to synthesise a substituted nitro olefin (Scheme 2.68) and repeat the sequence of reactions.



Scheme 2.68

2.8.6.1 Synthesis of the nitroethane derivative



231 **240**

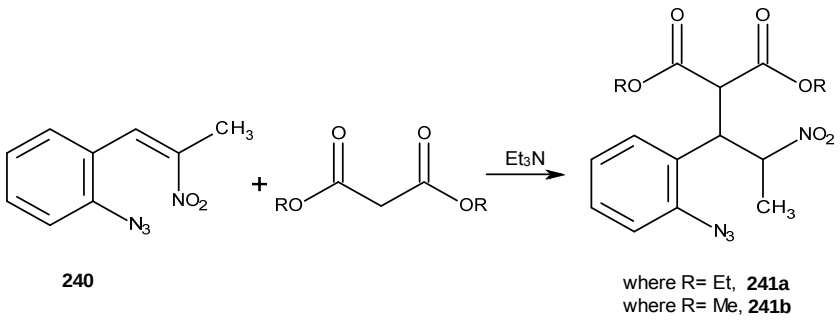
Scheme 2.69

The azido aldehyde **231** was heated at reflux in nitroethane using ammonium acetate as the base to furnish the desired product **240** as an orange solid in 98% yield after purification by chromatography.

In the ^{1}H NMR spectrum, all four aromatic CHs were seen between 7.25 - 7.50 ppm as expected with a singlet corresponding to CH_3 at 2.40 ppm and a singlet integrating to one CH at 8.10 ppm which made it evident that the substituted nitro olefin **240** had been successfully synthesised. HSQC and ^{13}C NMR confirmed the signal at 13.9 ppm as the CH_3 and a signal at 124.6 ppm as the alkenic CH. Infra-red data indicated the azide functionality was present due to the appearance of the sharp azide stretch at 2121 cm^{-1} andT high resolution mass spectroscopy found $[M+Na]^+$ at 227.0540 when $C_9H_8N_4O_2Na$ required 227.0539 confirming the structure.

We decided to react **240** with diethyl malonate and dimethyl malonate to synthesise the Michael adducts and in turn reduce them to learn if the substituted indole could be synthesised.

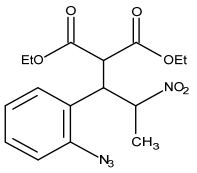
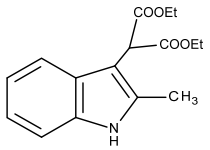
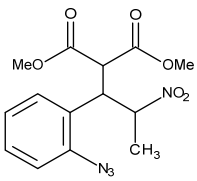
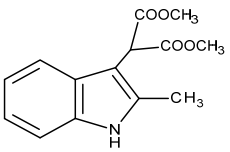
2.8.6.2 Synthesis of Michael adducts



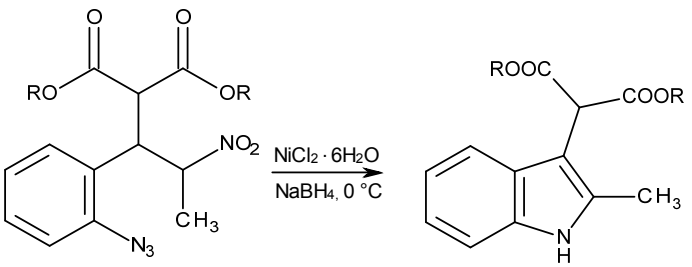
Scheme 2.70

Compounds **241a** and **241b** were synthesised successfully in 55% and 61% yield. Evidence for the successful formation of the dimethyl adduct **241b** (R= CH_3) was given by the ^{1}H NMR spectrum which showed a doublet at 1.37 ppm corresponding to the CH_3 on the methine (CH) that is also attached to the nitro group. 2 singlets were observed at 3.67 and 3.74 ppm corresponding to the OCH_3 methyl groups, multiplets at 4.08 - 4.21 ppm and 5.06 - 5.20 ppm were seen for the three CH groups. Due to the presence of stereocenters, diastereomers were formed and were found in the ratio 3:1. For the sake of convenience only the peaks belonging to the major isomer have been discussed above. In the next step, the reduction of both the isomers would arrive at the same product so the presence of diastereomers was not a problem and the stereochemical outcome was not analysed further.

Table 2.3 Shows the substituted Michael adducts and their indoles.

Entry	Michael adducts (241)	Yield %	Reduction products (242)	Yield %
a		55		13
b		61		8

2.8.6.3 Reduction of the substituted Michael adducts



241(a-b) **242 (a-b)**

Scheme 2.71

When the dimethyl and diethyl adducts **241a/b** were reduced with $NiCl_2 \cdot 6H_2O$ and $NaBH_4$, they gave rise to the corresponding substituted indoles **242a/b** (See Table 2.3). The structural assignments were allocated by NMR, IR and MS. For instance, identity of the indole derived from the dimethyl substituted adduct **242b** was confirmed by the ^1H NMR spectrum which showed a methyl group slightly downfield at 2.44 ppm which can be explained by its attachment at position 2 on the indole. The methoxy groups appeared as a singlet at 3.75 ppm integrating to 6H and the acidic CH appeared further downfield at 4.91 while the distinct NH singlet appeared at 7.91 ppm. The ^{13}C spectrum and mass spectral data further confirmed the structure with the carbonyl peak at 169.1 ppm and the accurate mass of 284.0896 for $[M+Na]^+$ when $C_{14}H_{15}NO_4Na$ required 284.0893. The IR spectrum showed the NH at 3327 cm^{-1} and the C=O at 1734 cm^{-1}. The yields of these processes are lower than those seen previously and these reactions are currently being optimised by other researchers in the group.

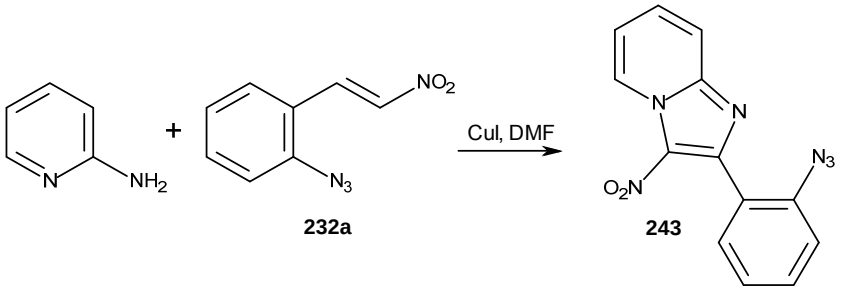
2.8.6.4 Summary

This study led us to a novel route for the formation of indoles and quinolines *via* a nitrene mechanism similar to that suggested by Sundberg and Cadogan but with a nitrene insertion into a sp^3 centre and the loss of the NO_2 group probably *via* reduction and loss of ammonia.

2.9 Amino pyridines

2.9.1 Reaction of the nitro-olefin with amino pyridine

At this point it was thought useful to explore the utility of compound **232a** further. A recent literature report[202] showed that *β*-nitrostyrene reacts with 2-aminopyridine to give an imidazopyridine. If **232a** underwent the same reaction, it would yield compound **243** and we were intrigued to see how this might behave under $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ conditions that were explored above.



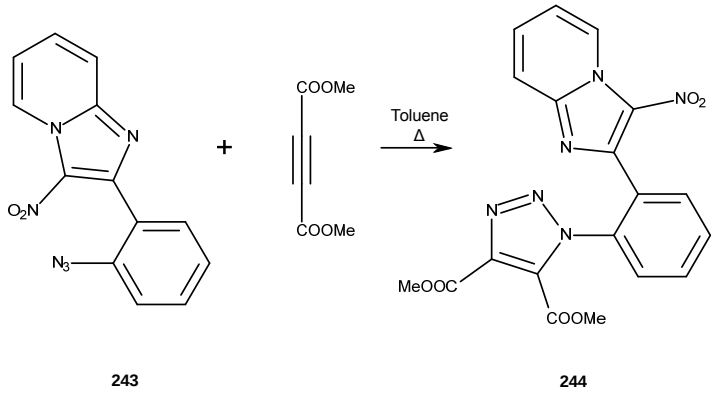
Scheme 2.72

The nitro olefin **232a** was reacted with 2-aminopyridine in the presence of copper(I) iodide using DMF as the solvent. It was heated to 80 °C for 6.5 h which resulted in the formation of the adduct **243** as a brown oil in 19% yield after purification. Spectroscopic analysis confirmed the structure of the adduct as **243**. In the ^1H NMR spectrum, three of the aromatic protons appeared at 7.22 - 7.30 ppm as multiplets whilst two other protons corresponded to a multiplet between 7.48 - 7.56 ppm. Two protons at 7.62 and 7.81 ppm each appeared as doublet of doublets which were coupled to each other (*J* 8.5 Hz) whilst the remaining proton appeared as a doublet at 9.45 ppm. The ^{13}C data supported the ^1H spectral data and accounted for all 8 CHs and 5 quarternary carbon signals. The infra-red spectrum indicated the azide group was present due to the appearance of the distinct peak at 2122 cm^{-1}.

Accurate and consistent mass spectral data further confirmed the structure with 303.0605 for the $[M+Na]^+$ ion when $C_{13}H_8N_6O_2Na$ required 303.0600.

2.9.2 Cycloaddition of the azido adduct with DMAD

DMAD is known to be an excellent dipolarophile. With cycloadduct **243** in hand, we decided to investigate the reactivity of its azide moiety towards DMAD. The reaction was performed by heating at reflux in toluene over 3 days (~90 h) to afford a brown solid.



243 **244**

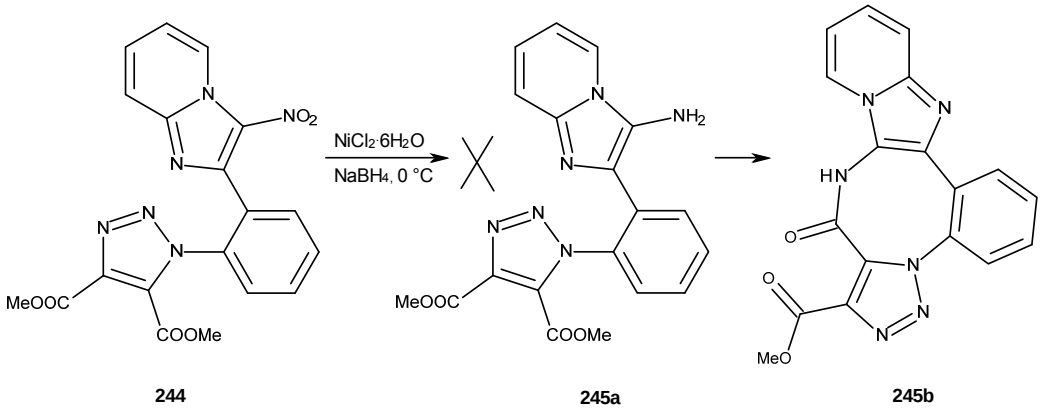
Scheme 2.73

The structure of the proposed product **244** was confirmed by spectroscopic analysis. The ^{1}H NMR spectrum was consistent with the structure in which three aromatic protons were observed as multiplets between 7.26 – 7.65 and 7.76 – 7.82 ppm. Another multiplet integrated to four protons between 7.66 - 7.74 whilst a doublet appeared at 9.37 ppm corresponded to an aromatic proton. Two singlets each integrated to three protons at 3.81 and 3.91 ppm indicating the presence of the two methyl esters in the molecule.

^{13}C NMR and HSQC analysis further confirmed the proposed structure with the two carbonyls as quaternary carbons at 158.4 and 160.1 ppm, the quaternary carbons of the triazole ring at 133.3 and 134.5 ppm, whilst the sp^3 methyl carbons were seen at 52.6 and 53.6 ppm. All the CHs and other quarternary carbons were all accounted for. In addition, the IR spectrum provided evidence of successful cycloaddition by the loss of the azide stretch at 2122 cm^{-1} with the added appearance of a strong absorption peak at 1720 cm^{-1} for the presence of the two methyl ester groups. HRMS data confirmed the proposed structure with a measured accurate mass (m/z) of 445.0870 for a required mass of 445.0867 as expected for the sodiated ion $C_{19}H_{14}N_6O_6Na$. Compound **244** was formed in 54% yield *via* a 1,3-dipolar cycloaddition between the azide and DMAD (Scheme 2.73).

2.9.3 Attempted reduction and cyclisation of the triazole adduct

We also decided to explore the reactivity of cycloadduct **244** towards $NiCl_2{\cdot}6H_2O/NaBH_4$, system with the possibility that the product **245a** might undergo further reaction to give, for example the diazocine **245b**.

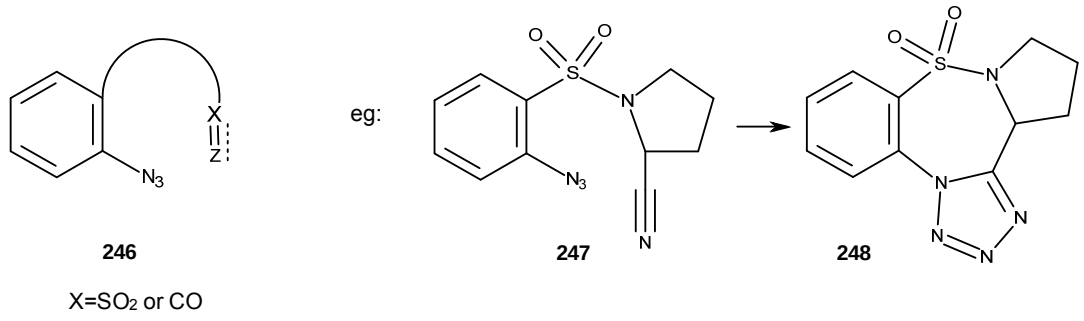


Scheme 2.74

The substituted triazole **244** was treated with nickel chloride hexahydrate and sodium borohydride in ethanol at 0 °C to in an attempt to bring about the reduction of the nitro functionality and consequently allow for intramolecular cyclisation to occur. Unfortunately this did not materialise under a variety of reaction times and the starting material was recovered unchanged.

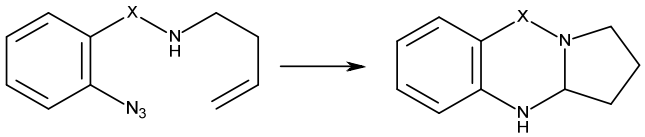
2.10. Aza-Prins series

As discussed earlier in this thesis, one of the original aims was to investigate cycloadditions of molecules of general structure **246** as exemplified by the cyclisation of **247** to **248** shown below.



Scheme 2.75

Earlier workers in the group[94] had explored homoallylic amide and sulfonamide precursors of the type **249** shown below and had observed an unexpected reaction giving **250**.

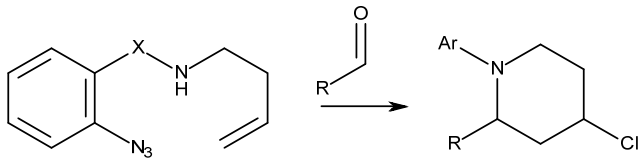


249 **250**

X=SO_2 or CO

Scheme 2.76

As part of this project it was decided to explore the chemistry of **249** in more detail to specifically look at the possible use of **249** in the aza-Prins reaction shown in Scheme 2.77.



249

X=SO_2 or CO

Scheme 2.77

The aza-Prins reaction is an example of an iminium cyclisation method used in the construction of nitrogen heterocycles[203] (Figure 2.4). The reaction substrates are a homoallylic amine, an aldehyde and a Lewis acid, wherein the homoallylic amines can be easily accessed using the chemistry devised in our group for the synthesis of compounds **249**, above.

Condensation of an aldehyde onto the amine nitrogen would furnish the iminium ion, which then undergoes nucleophilic attack by the alkene. Interception of the developing carbocation by either the solvent or nucleophile would furnish the 6-membered ring or the loss of an adjacent proton from the ring would lead to olefin formation.

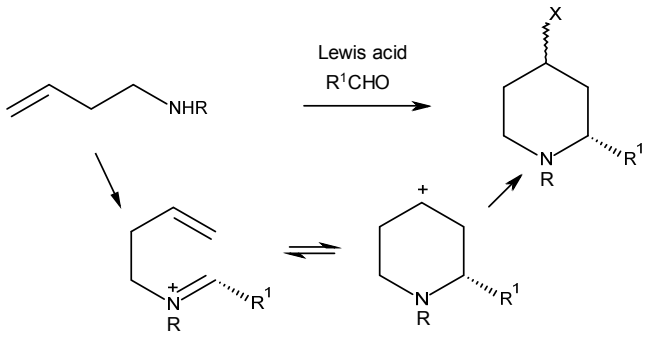
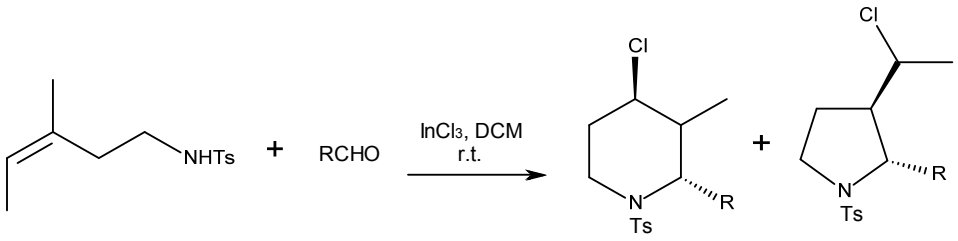


Figure 2.4

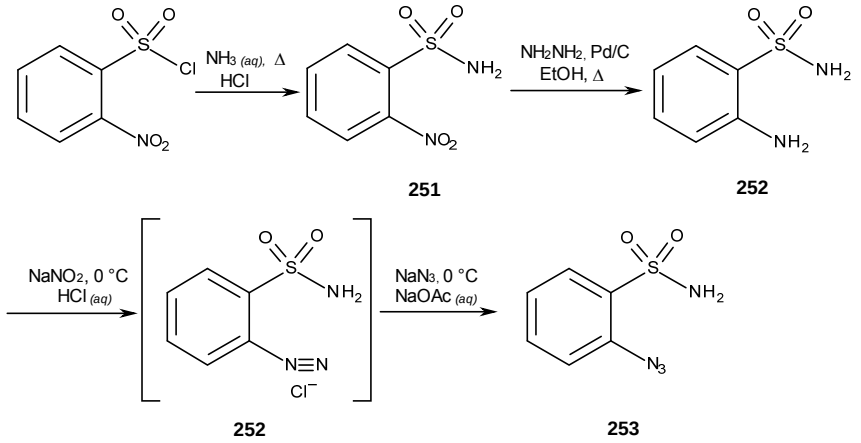
Several groups have employed aza-Prins cyclisations in total syntheses; Frank and Aube[204] reported a titanium tetrachloride-promoted aza-Prins type reaction in synthesis the of martinellines; Hanessian et al[205] used tin tetrabromide to promote *N*-acyliminium ion aza-Prins cyclisation to form octahydroindoles and Shair et al. used an aza-Prins bicyclisation approach to the synthesis of the endothelial cell proliferation inhibitor (+)-Cortistatin[206].

Lewis acids such as iron (III) chloride[207], tin tetrachloride[208] as well as acid catalysts eg. PTSA (*para*-toluenesulfonic acid)[209] have been used to promote the synthesis of aza-cycles. Dobbs et al.[203] found success in using indium trichloride with homoallyl tosylamines to synthesise of 5- and 6- membered ring products as shown in Scheme 2.78. They found that the proportion of 5- and 6-membered rings formed, varied based on the R group. Due to the readily available indium chloride and relative ease in reaction conditions at r.t. and its success with tosyl based systems, this was the route selected in our attempt of the aza-Prins reaction.



Scheme 2.78 Dobbs' investigation of tosylated amines in the aza-Prins approach.

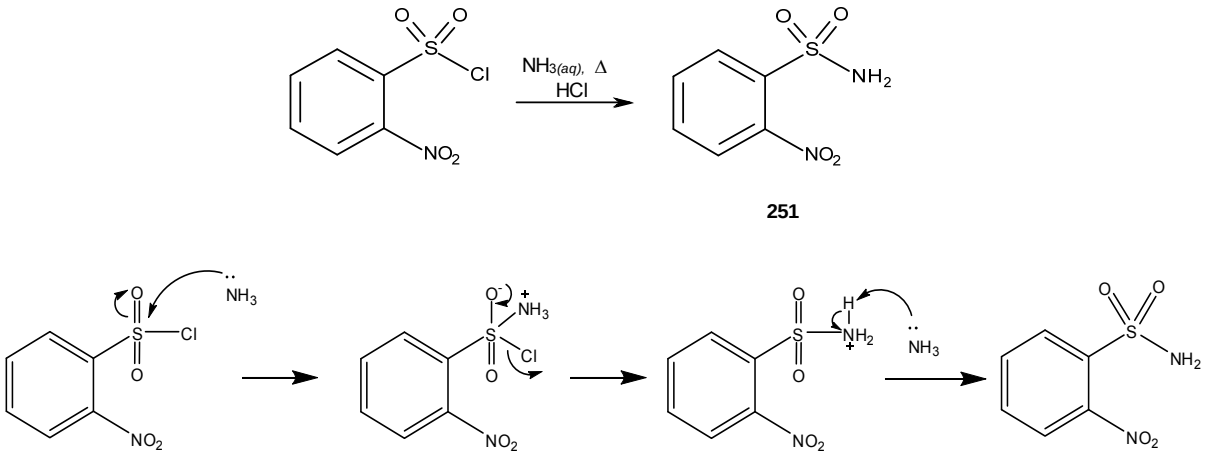
To begin this study, the nitro **251** and azido **253** precursors to **249** were readily prepared from commercially available 2-nitrobenzenesulfonyl chloride as shown in Scheme 2.79. The nitrobenzene sulfonamide **251** was prepared in a single step starting from 2-nitrobenzenesulfonyl chloride whilst the aryl azide **253** was obtained by diazotisation of the corresponding amine **252**, followed by azidation of the resulting diazonium chloride.



Scheme 2.79: Synthesis of the azide precursor from *o*-nitrobenzenesulfonyl chloride

2.10.1 Synthesis of *o*-nitrobenzenesulfonamide

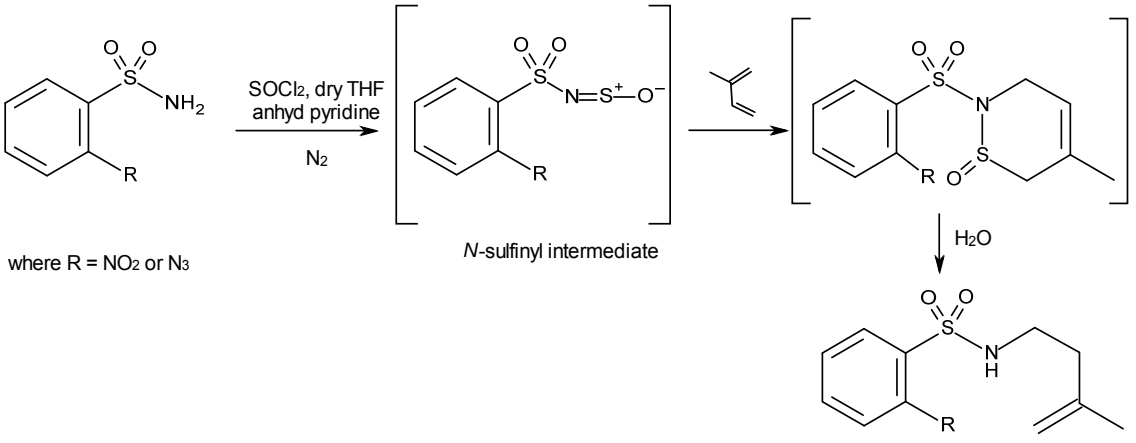
o-Nitrobenzenesulfonamide **251** was obtained in 94% yield and its structure was confirmed with melting point and spectroscopic data as recorded in the literature[201]. The mechanism[173] is thought to proceed *via* nucleophilic substitution as depicted in Scheme 2.80.



Scheme 2.80: Mechanism of sulfonamide formation

2.10.2 Synthesis of *N*-sulfinyl-*o*-substituted benzenesulfonamide

The method employed for the synthesis of the homoallylic sulfonamide derivatives needed for this work was previously used in the group by Patel and Chambers[95] as illustrated in the outline below (Scheme 2.81).

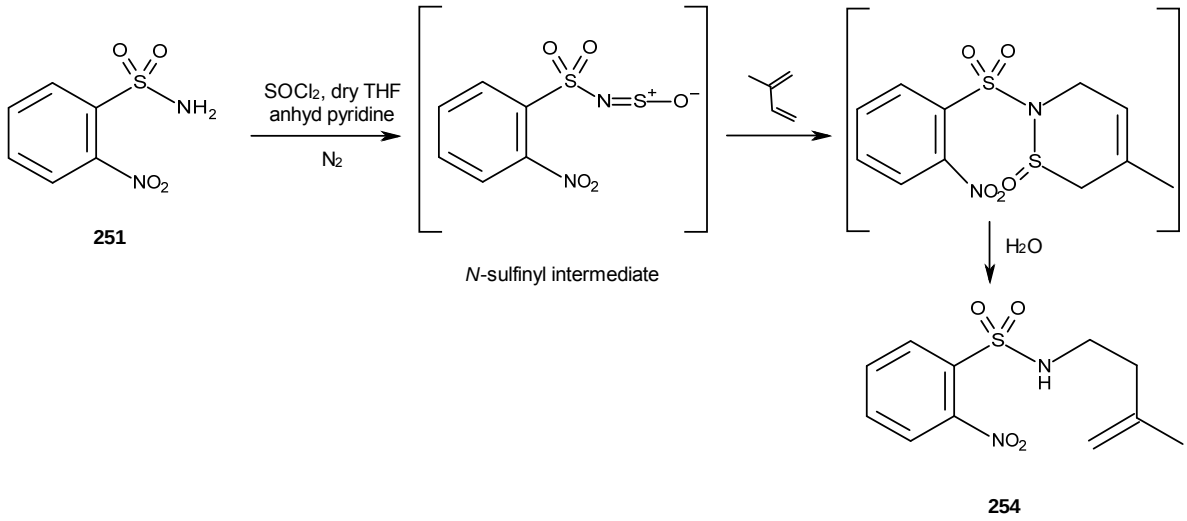


Scheme 2.81

This process generates an *N*-sulfinyl intermediate that then undergoes Diels-Alder reaction with a diene followed by hydrolytic extrusion of sulfur. Due to the fact that that *N*-sulfinyl compounds are prone to hydrolysis in the presence of atmospheric moisture[210] the reactions

the first two reactions were performed under dry conditions and the products were directly used in the next step without purification. This reaction was performed first with the nitro system **251** as described below.

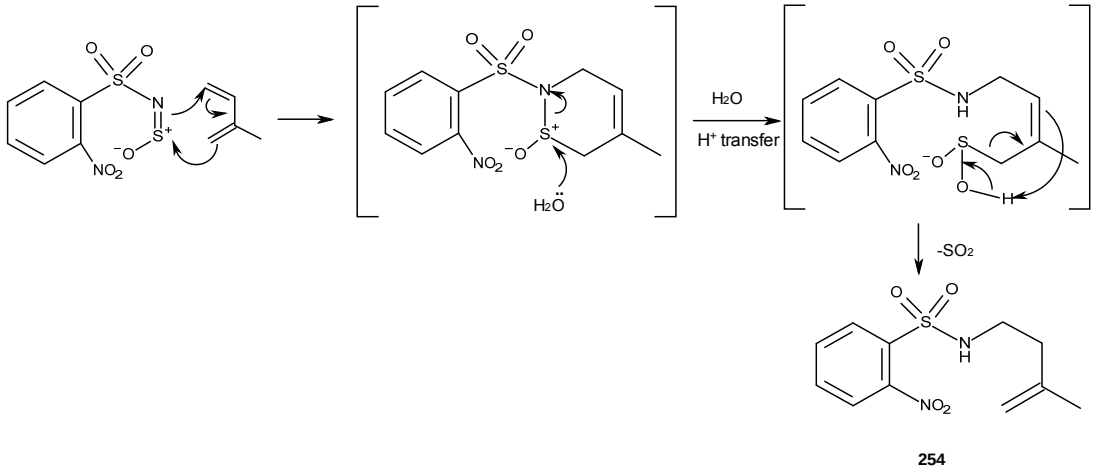
2.10.3 Reaction of the *N*-sulfinyl compound with isoprene



Scheme 2.82

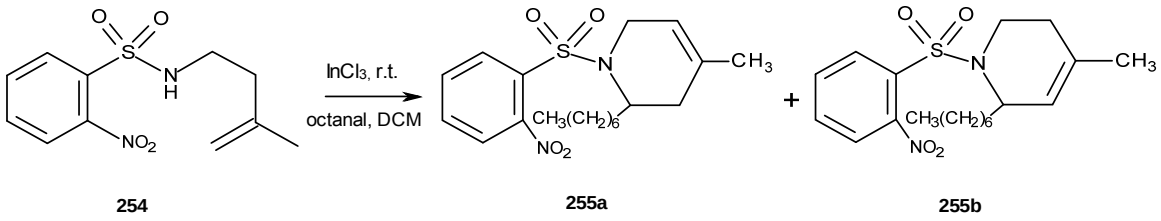
Here, the nitro *N*-sulfinyl intermediate once synthesised was trapped immediately with isoprene and further converted into the desired compound **254** isolated after hydrolysis of the intermediate as a yellow oil in 81% yield. The structure of compound **254** was confirmed using spectroscopic analysis. The infrared spectrum distinctly captured the broad NH peak at 3301 cm^{-1} whilst in the ^{1}H NMR the methyl group appeared as a singlet at 1.59 ppm, the neighbouring CH_2 protons coupled together (J 6.7Hz) and appeared as an apparent triplet and quartet at 2.20 and 3.19 ppm respectively. The alkenic protons appeared at 4.64 and 4.72 as singlets, the NH proton was seen at 5.29 ppm as a broad singlet and the aromatic protons were observed as multiplets at 7.70 - 7.67, 7.81 - 7.86 and 8.08 - 8.15 ppm. The ^{13}C NMR spectrum and high resolution mass spectroscopy supported the ^{1}H data and revealed the methyl protons at 21.7 ppm, the alkene CH_2 carbon at 113.4 ppm. An accurate consistent mass of 271.0747 for $C_{11}H_{14}N_2O_4$ which required 271.0750 was also consistent with the proposed structure.

This reaction proceeds through a Diels-Alder reaction to give an adduct which very readily hydrolyses (on chromatographic workup) to give the required homoallylic sulfonamide **254**. In the hydrolytic step, water attacks the sulfur atom of the 1,2-thiazine ring to generate an intermediate that undergoes spontaneous loss of SO_2 as shown below.



Scheme 2.83

2.10.3 Attempted aza-Prins reaction



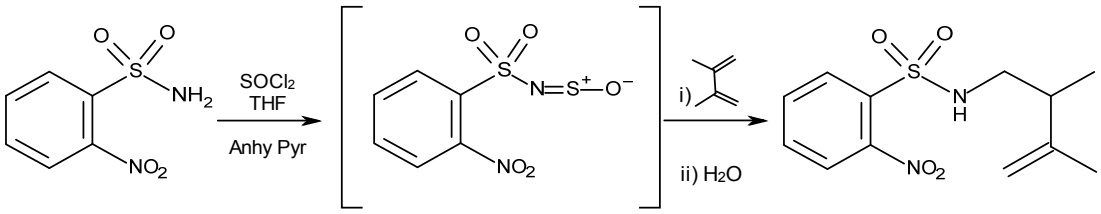
Scheme 2.84

When compound **254** was treated with indium chloride at r.t. for 24 h, the majority of the starting material was consumed and column chromatography gave a white solid in low yield (13%). Spectroscopic analysis indicated that a successful aza-Prins reaction occurred by the loss of the NH peak and CH_2 alkene signals. The octanal unit's alkyl protons were present in the 1.22 - 1.71 ppm region but the product appeared to be mixture of alkene products (**255a/ 255b**) and could not be purified further. This attempt indicated that the reaction may be of interest and therefore further unsuccessful attempts were made in an attempt to optimise the process. The process was also repeated with another diene (2,3-dimethyl butadiene) to see if better results could be obtained as discussed below.

2.10.4 Synthesis

o-Nitrobenzenesulfonamide was treated with a solution of thionyl chloride in THF in the presence of anhydrous pyridine under dry conditions and consequently with 2,3-dimethylbutadiene to yield the derivative **256** as a yellow oil in 23% yield after hydrolytic workup. Spectroscopic analysis confirmed the structure as compound **256**. The ^{1}H NMR

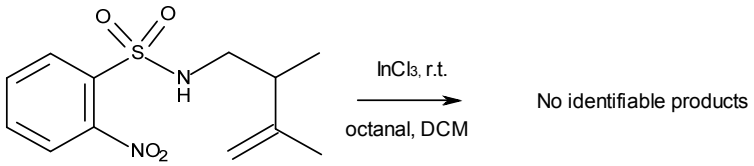
spectrum showed a doublet at 0.98 ppm corresponding to the methyl group adjacent to the alkene functionality with a singlet at 1.53 ppm integrating to 3H indicative of a methyl attached directly to the alkene moiety. The ^{13}C spectrum showed the two methyls were present at 16.8 and 18.7 ppm whilst the sp^2 CH_2 appeared at 112.7 ppm. The high resolution mass spectrum was consistent when 307.0723 was required for $C_{12}H_{16}N_2O_4SNa$, 307.0732 was found.



251 **256**

Scheme 2.85

2.10.5 Attempted aza-Prins reaction



256

Scheme 2.86

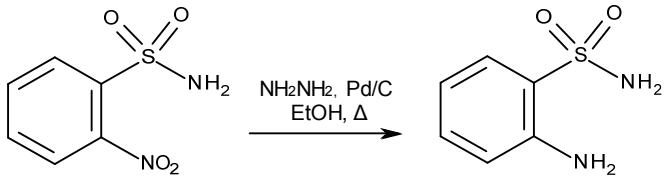
On subjecting the nitro alkene derivative **256** to aza-Prins reaction conditions with indium chloride, the reaction was unsuccessful and did not produce any identifiable products. The isoprene reaction had hinted that the reaction may be possible but could not be repeated.

Next we decided to look at the isoprene again with a different aromatic substituent. We moved on to prepare the corresponding azides, a species that as discussed before in this thesis, has always been of interest due to our focus on the azide group. To synthesise the azide ortho to the sulfonyl group, 2-nitro sulfonamine **251** was reduced to an aryl amine **257** which then underwent diazotisation and azidation to synthesise the azide precursor.

2.10.6 Synthesis of *o*-amino benzenesulfonamide

There are many known synthetic methods for the reduction of aromatic nitro compounds to their corresponding anilines. The commonly investigated routes include using Zn, Sn, Fe as well as catalytic hydrogenations with hydrazine in the presence of a catalyst[211]. Catalytic

reduction using hydrazine is an efficient method and the yields are often found to be superior to using direct catalytic reduction and other hydrogenation methods[212].

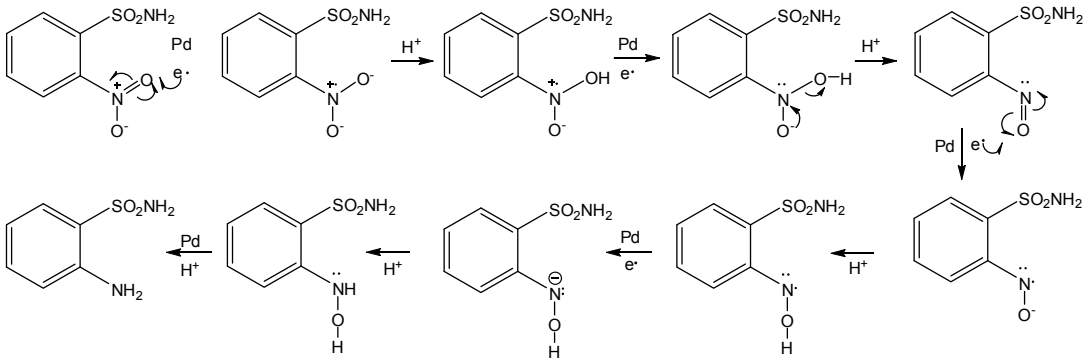


251 **257**

Scheme 2.87

When *o*-nitrobenzenesulfonamide **251** was heated at reflux with hydrazine in the presence of a palladium-carbon catalyst in ethanol, *o*-aminobenzenesulfonamide was synthesised as a white crystalline solid in 77% yield. The melting point and spectroscopic data were consistent with reported values in literature[201].

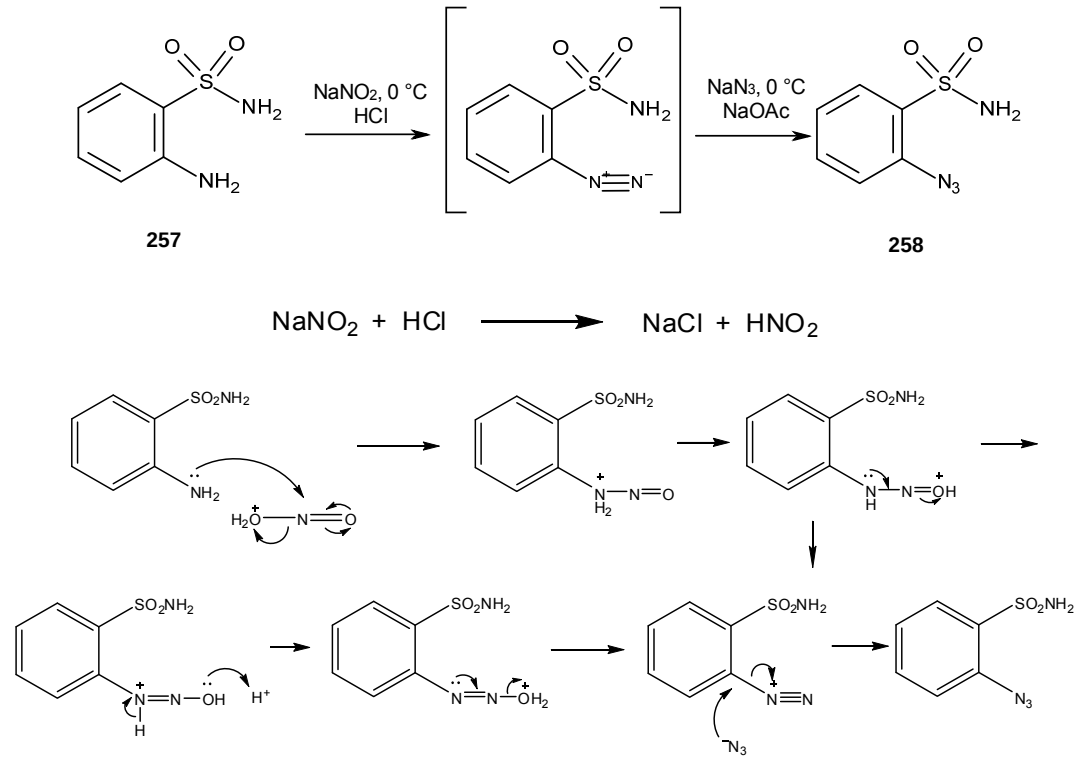
The mechanism, as illustrated in Scheme 2.88 is proposed to follow a single electron transfer from the metal surface where hydrazine is the proton source.



Scheme 2.88: Proposed mechanism in reduction with hydrazine and Pd/C.

2.10.7 Synthesis of *o*-azidobenzenesulfonamide

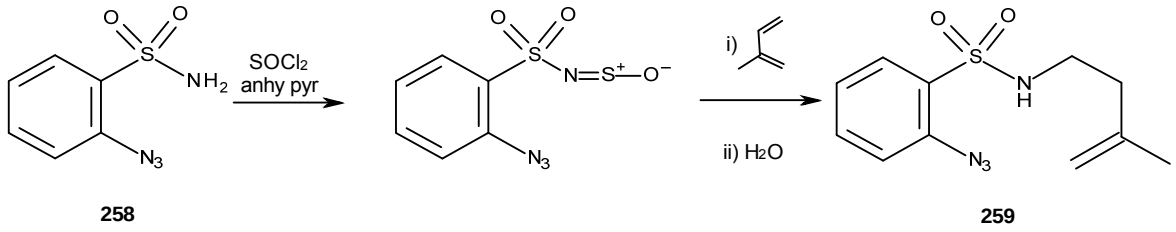
The commonly exploited route to azides is *via* azidation of the diazonium salts using sodium azide in sodium acetate[201, 213]. Here, *o*-aminobenzenesulfonamide **257** was treated with sodium nitrite and hydrochloric acid at 0 °C in an ice bath and immediately treated with sodium azide and sodium acetate to furnish the azido compound **258** as a fawn coloured solid in 80% yield *via* the process shown in Scheme 2.89.



Scheme 2.89 shows diazotoisation followed by azidation.

Matching melting point data and the presence of the azide functionality (2122 cm^{-1}) in the infra-red data confirmed the compound as **258**. These data values matched reported values[201].

2.10.8 Reaction with isoprene

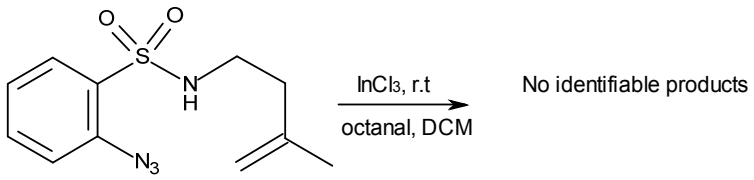


Scheme 2.90

2-Azidosulfonamide **258** was reacted with thionyl chloride solution in THF in the presence of anhydrous pyridine under an inert atmosphere followed by the addition of isoprene dropwise to synthesise the homoallylic sulfonamide derivative **259** as a pale yellow oil in extremely low yield (7%) after chromatographic workup. In the ^{1}H NMR spectrum the methyl group appeared as a singlet at 1.54 ppm indicative of a methyl attached directly to the alkene moiety. The alkene protons appeared as singlets at 4.65 and 4.80 ppm. The ^{13}C

spectrum showed the methyl was present at 21.6 ppm whilst the sp^2 CH_2 appeared at 113.0 ppm. The high resolution mass spectrum was consistent and accurate with the 2M sodiated ion at 555.1538 when 555.1540 was required for $C_{22}H_{28}N_8O_4S_2Na$.

2.10.9 Attempted aza-Prins reaction

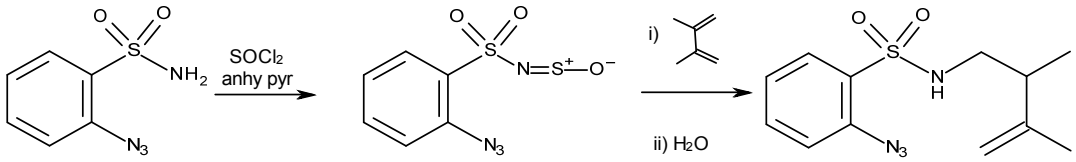


259

Scheme 2.91

When **259** was subjected to the aza-Prins conditions using indium chloride as the Lewis acid, the reaction was unsuccessful and no significant products were obtained.

2.10.10 Reaction with 2,3-dimethylbutadiene

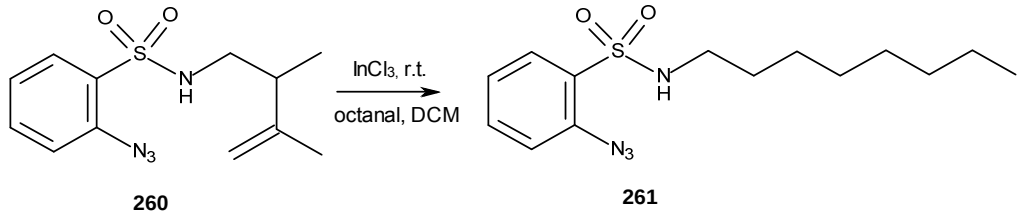


258 **260**

Scheme 2.92

When *o*-azidobenzenesulfonamide **258** was treated with a solution of thionyl chloride and dry THF in the presence of anhydrous pyridine, followed by the addition of 2,3-dimethylbutadiene, chromatographic workup gave the homoallylic sulfonamide **260.** Spectroscopic analysis confirmed the structure. ^1H NMR showed the presence of the two methyl groups, one as a doublet at 0.97 ppm and the other a singlet at 1.53 ppm. The alkenic protons appeared as singlets at 4.73 and 4.86 ppm and the vinylic CH_2 was present in the ^{13}C spectrum. This data matched previously reported values[94].

2.10.11 Attempted aza-Prins reaction



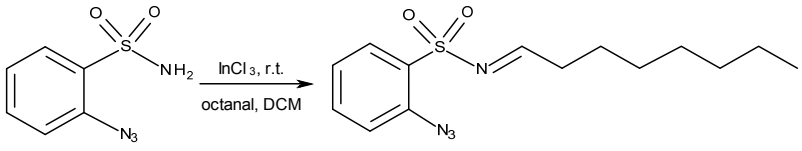
260 **261**

Scheme 2.93

When the azido butadiene derivative was subjected to aza-Prins conditions, it gave a white solid in good yield. Spectroscopic analysis by ^{1}H NMR and ^{13}C spectra showed the structure as **261**. Infra-red spectroscopy showed the presence of NH as a broad peak at 3291 cm^{-1} while the azide functionality appeared as a sharp stretch at 2132 cm^{-1}. The ^{1}H NMR spectrum showed the protons of the alkyl chain as overlapping multiplets in the region spanning from 0.82 - 2.90 ppm. The NH peak appeared at 4.88 ppm as a broad singlet. High resolution mass spectroscopy provided a consistent and accurate mass for the sodiated mass ion at 333.1364 for a required value of 333.1356. Compound **261** was formed in 54% and its formation was unexpected meaning that the process required further investigation.

2.10.12 Reaction of 2-azidobenzenesulfonamide with octanal

In order to gain some insight to the mechanism of this process, it was decided to react the sulfonamide **248** with octanal and indium chloride to investigate the outcome and ascertain whether or not compound **261** would form under these conditions.

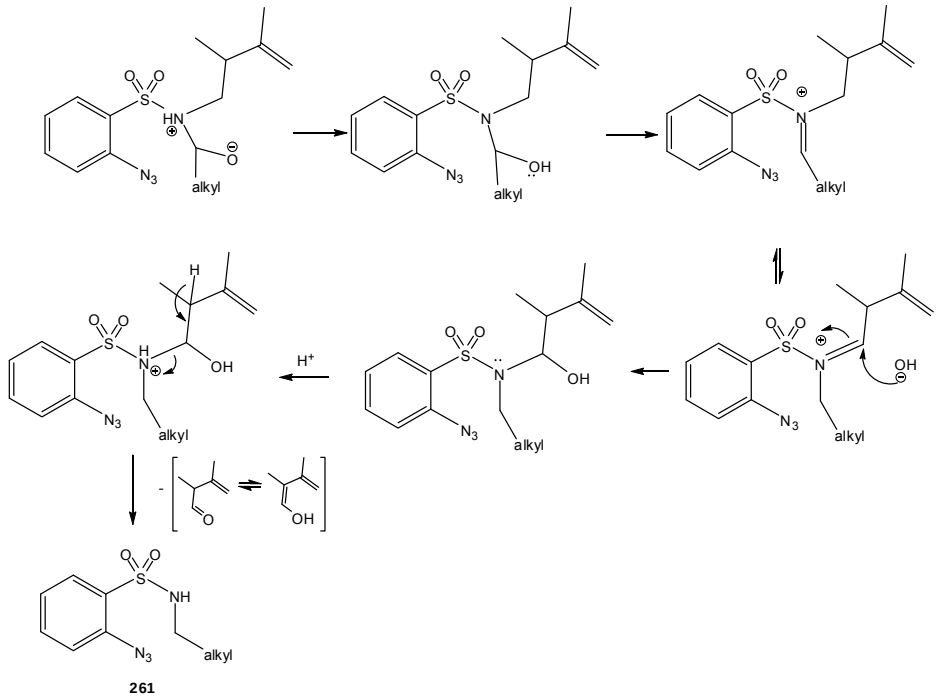


258 **262**

Scheme 2.94

When 2-azidosulfonamide **258** was reacted under aza-Prins reaction conditions, it gave the corresponding imine **262** as a pale yellow oil in 26% yield and no saturated amine of the type **261** was isolated. This indicates that the imine **262** is not a precursor to the amine **261** which implies the reformation of **258** under these reaction conditions is unlikely to be a valid mechanism. A suggested mechanism is shown in Scheme 2.95 below. Thus, the nucleophilic nitrogen attacks the aldehyde, loses OH to form an iminium (as per the expected Prins

mechanism in Figure 2.4), tautomerises and and then picks up the hydroxide to give the aminol. Protonation of nitrogen and loss of a proton from the homoallylic side chain then releases a dienol along with the observed product **261**.



Scheme 2.95 Plausible mechanism for the synthesis of the imine.

2.10.13 Summary

Based on various successful literature reports, we attempted to use aza-Prins chemistry to form nitrogen heterocycles. Aza-Prins processes on homo allylic sulfonamides derived from *o*-nitro and *o*-azidobenzene sulfonamides were unsuccessful. The system derived from *o*-azidobenzene sulfonamide and dimethyl butadiene appeared to undergo an interesting transformation upon treatment with octanal, whereby the homoallylic substituent was replaced by the octyl chain. Future work could focus on using other aldehydes in order to ascertain if this process is peculiar to octanal.

Chapter 3: Experimental

This chapter concludes this thesis with specific details of the experimental procedures and complete characterisation data for the compounds synthesised throughout the results and discussion chapter of this thesis.

General Techniques

For all reactions conducted under anhydrous conditions, the glassware was oven dried and the reaction was carried out under a nitrogen atmosphere, unless otherwise stated.

Solvents and Reagents

Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Reagents and solvents used were obtained from commercial suppliers or purified according to standard procedures. Pet ether refers to distilled light petroleum of fraction (40–60 °C). THF was distilled over sodium wires (1-2%, w/v) with benzophenone as the indicator. Dichloromethane and toluene were distilled over calcium hydride (5% w/v) for ~5 h. All other anhydrous solvents and commercially available starting materials were purchased from the following suppliers Acros, Fisher Scientific and Sigma Aldrich. Deuterated solvents were purchased from Goss Scientific.

All reactions were monitored by thin layer chromatography (TLC) which was carried out on 0.20 mm Macherey-Nagel Alugram® Sil G/UV_{254} silica gel-60 precoated aluminum plates; analysis was achieved using ultraviolet light and/or vanillin stain. Flash silica gel column chromatography was performed with commercial solvents using Merck silica gel (0.063-0.200, 60Å). Where necessary, 60Å, 50-200 μm, basic alumina gel was used after activation with water over 24 h (3 mL/100g).

Melting Points

Melting points were recorded on a Stuart SMP 10 digital melting point apparatus with the sample contained in a thin glass tube at ambient pressure and are uncorrected.

Infra-Red Spectroscopy

Infrared spectra were recorded on a Nicolet 380 FT-IR instrument as a thin film for oils and neat for solids.

NMR Spectroscopy

^{1}H, ^{13}C, DEPT, COSY and HSQC NMR spectra were recorded on Bruker Avance 500 MHz or 400 MHz spectrometers wherever stated. Chemical shifts (δ_H) are quoted in parts per million relative to the residual protiosolvent (δ_H ($CHCl_3$) = 7.24 ppm) against an internal deuterium lock. Coupling constants (J) are given in Hertz.

The ^{1}H NMR spectra are reported as follows: δ / ppm (number of protons, multiplicity, coupling constants J /Hz, assignment). DEPT and two-dimensional NMR spectroscopy (COSY, HSQC) were used where appropriate to assist the assignment of the signals in the ^{1}H NMR and ^{13}C NMR spectra.

Mass Spectrometry

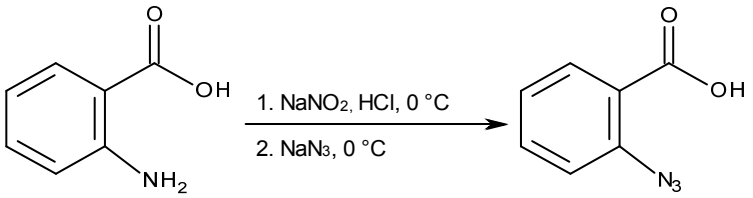
High resolution mass spectra (accurate mass) were recorded on a Bruker Daltonics micrOTOF-Q mass spectrometer.

Literature References

If a literature procedure was followed, this is indicated explicitly in the method text.

3.1 Synthesis of pyrrolobenzodiazepines and pyrrolobenzothiadiazepines

3.1.1 Synthesis of 2-azidobenzoic acid



180a **181b**

To a suspension of anthranilic acid (2.00 g, 14.58 mmol, 1.0 eq) in water (6 mL), a solution of $NaNO_2$ (1.21 g, 17.49 mmol, 1.2 eq) in water (6 mL) was added dropwise and the mixture was stirred at 0 °C for 30 min. This resultant solution was then added dropwise to a solution of sodium acetate (14.95 g, 182.25 mmol, 12.5 eq), sodium azide (1.14 g, 17.49 mmol, 12.5 eq) in water (22 mL) and the mixture was stirred for 2 h at 0 °C. The precipitate was collected by vacuum filtration to afford 2-azidobenzoic acid as a tan coloured solid (1.95 g, 89%).

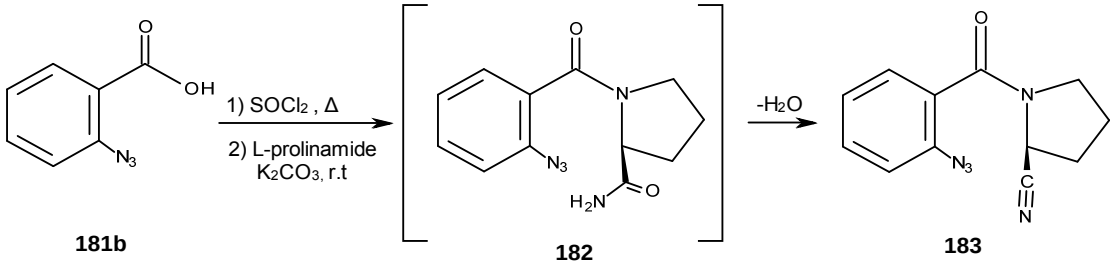
δ_H (500 MHz, $CDCl_3$): 7.15 (1H, dd, *J* 8.0, 8.0, Ar*H*), 7.20 (1H, d, *J* 8.0, Ar*H*), 7.49 (1H, dd, *J* 7.9, 7.9, Ar*H*), 7.67 (1H, d, *J* 7.9, Ar*H*).

δ_C (125 MHz, $CDCl_3$): 121.2 (*C*H), 124.0 (*qC*), 125.7 (*C*H), 132.2 (*C*H), 134.4 (*C*H), 139.9 (*qC*), 168.4 (*qC*).

ν_{max} (cm^{-1}): 3006 - 2615 (br), 2122 [N_3] (m), 1689 [C=O] (s), 1596 (s), 1575 (s), 1484 (s), 749 (s).

The data was consistent with previously reported data[171].

3.1.2 Synthesis of (2S)-*N*-(2'-azidobenzoyl)-2-(hydroxymethyl)-pyrrolidine-2-carbonitrile



181b **182** **183**

2-Azidobenzoic acid (0.710 g, 4.36 mmol, 2.49 eq) in thionyl chloride (5 mL) was heated at 85 °C under a N_2 atmosphere for 3 h. The reaction mixture was allowed to cool to r.t. and then the excess thionyl chloride was removed *in vacuo* and the residue was washed with DCM (2 x 10 mL) and evaporated to yield the 2-azidobenzoyl chloride as a dark coloured solid which was dissolved in DCM (10 mL). *L*-Prolinamide (0.200 g, 1.75 mmol, 1 eq) was dissolved in DCM (5 mL) and to this K_2CO_3 (1.00 g, 7.23 mmol, 4.14 eq) in water (5 mL) was added in one portion. The acid chloride in DCM (10 mL) was added dropwise to the above reaction mixture and the whole was stirred overnight. The organic phase was separated, and the aqueous phase was extracted with DCM (3 x 10 mL). The organic phases were combined, dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (66% EtOAc: Pet) to give the nitrile product as a brown oil (0.130 g, 31%).

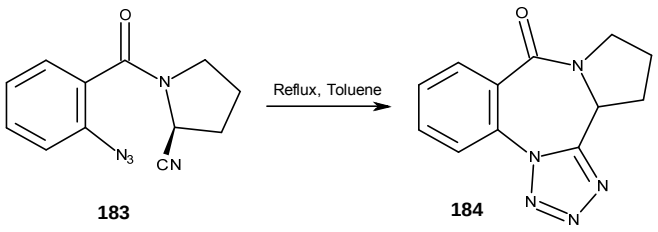
δ_H (400 MHz, $CDCl_3$) rotamers: 1.98 - 2.08 (1H, m, C*H*H), 2.10 - 2.24 (1H, m, C*H*H), 2.27 - 2.40 (1H, m, C*H*H), 3.26 - 3.31 (1H, m, C*H*H), 3.37 - 3.44 (1H, m, NCH*H*), 3.69 - 3.80 (1H, m, NC*H*H), 4.92 (1H, dd, *J* 7.8, 3.8, C*H*CN), 7.23 (2H, m, Ar*H*), 7.34 (1H, dd, *J* 7.8, 1.6, Ar*H*), 7.48 (1H, ddd, *J* 7.8, 7.8, 1.6, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 23.1/24.9 (CH_2), 30.4/32.2 (CH_2), 45.6/46.1 (*C*H), 47.5/48.7 (CH_2), 118.0/118.1 (*qC*), 118.5/118.6 (*C*H), 125.1/125.4 (*C*H), 127.7/127.8 (*qC*), 128.1 (*C*H), 131.1/131.3 (*C*H), 136.4 (*qC*), 167.0 (*qC*).

ν_{max} (thin film cm^{-1}): 3012 (m), 2992 (m), 2225[CN] (w), 2112 (s), 1642 (s), 1578 (m), 1450 (s), 1094 (w).

The data was consistent with previously reported data[171].

3.1.3 Synthesis of tetrazolo[1,5-a] pyrrolo[2,1-c][1,4]-benzodiazepine-5-one



183 **184**

(2*S*)-*N*-(2'-azidobenzoyl)-2-(hydroxymethyl)-pyrrolidine-2-carbonitrile (0.100 g, 0.415 mmol) was heated to reflux in anhydrous toluene (5 mL) under a nitrogen atmosphere for 7 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in*

vacuo to yield a pale yellow oil, which was purified by flash silica gel chromatography (66% EtOAc: Pet) to afford the tetrazolo product as a white solid (0.040 g, 40%).

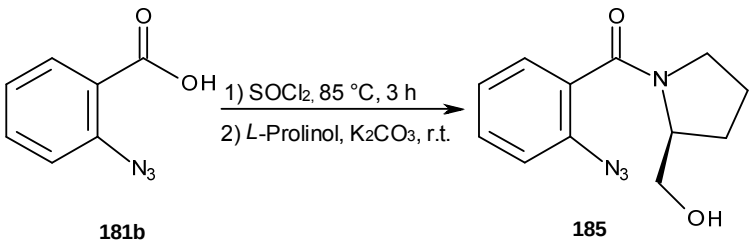
δ_H (400 MHz, $CDCl_3$): 2.16 - 2.24 (2H, m, NCH_2CH_2), 2.54 - 2.63 (1H, m, CH*H*), 3.16 - 3.23 (1H, m, CHC*H*H), 3.70 - 3.77 (1H, m, NCH*H*), 3.84 - 3.90 (1H, m, NC*H*H), 4.83 (1H, dd, *J* 8.4, 3.2, C*H*CN), 7.64 (1H, ddd, *J* 7.6, 7.6, 1.3, Ar*H*), 7.76 (1H, ddd, *J* 7.6, 7.6, 1.3, Ar*H*), 7.95 (1H, dd, *J* 8.0, 1.3, Ar*H*), 8.18 (1H, dd, *J* 8.0, 1.3, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 23.5 (CH_2), 28.2 (CH_2), 48.2 (CH_2), 49.7 (*C*H), 122.5 (*C*H), 127.2 (*qC*), 129.8 (*C*H), 130.3 (*qC*), 132.3 (*C*H), 133.1 (*C*H), 154.5 (*qC*), 163.4 (*qC*).

ν_{max} (thin film cm^{-1}): 2923 (m), 1644 [C=O] (s), 1470 (s), 1409 (s), 1241 (m), 1151 (m), 1125 (m), 1095 (m), 832 (m).

The data was consistent with previously reported data[171].

3.1.4 Synthesis of (2S)- *N*- (2'-azidobenzoyl)-2-(hydroxymethyl)-pyrrolidine



181b **185**

Thionyl chloride (5 mL) was added to 2-azidobenzoic acid (0.77 g, 4.72 mmol, 1 eq) and was heated to reflux under a nitrogen atmosphere at 85 °C for 3 h. The reaction mixture was allowed to cool to r.t., and the excess thionyl chloride was removed *in vacuo* and the residue was washed with DCM (2 x 10 mL) and evaporated to yield the acid chloride as a dark coloured liquid which was dissolved in DCM (10 mL).

To a stirring solution of *S*-prolinol (0.78 g, 7.71 mmol, 1.6 eq) in DCM (15 mL), was added a solution of potassium carbonate (2.07 g, 14.97 mmol, 3.2 eq) in one portion. After stirring for 15 min, the 2-azidobenzoyl chloride in 10 mL DCM was added dropwise to the reaction mixture, and the whole was stirred at r.t. overnight. The organic phase was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated to yield a dark coloured oil. Purification by silica chromatography (50% EtOAc: Hex) yielded the desired alcohol as a yellow solid (0.610 g, 53%).

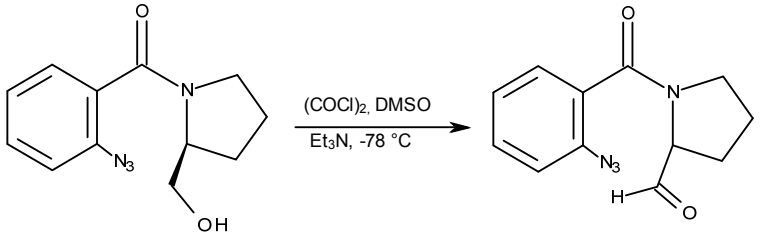
δ_H (400 MHz, $CDCl_3$): 1.68 - 1.83 (3H, m, CH*H*+CH_2), 2.13 - 2.19 (1H, m, C*H*H), 3.15 - 3.26 (2H, m, NCH_2), 3.72 (1H, dd, *J* 7.0, 11.5, C*H*HOH), 3.75 - 3.78 (1H, m, C*H*HOH), 4.31 - 4.36 (1H, m, NC*H*CH_2), 4.69 (1H, brs, O*H*), 7.14 - 7.20 (2H, m, Ar*H*), 7.31 (1H, d, *J* 7.5, Ar*H),* 7.43 (1H, dd, *J* 7.5, 1.5, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 24.4 (*C*H_2), 28.4 (*C*H_2), 49.4 (*C*H_2), 61.0 (*C*H), 66.1 (*C*H_2), 118.4 (*C*H), 125.1 (*C*H), 128.1 (*C*H), 129.3 (*qC*), 130.7 (*C*H), 135.9 (*qC*), 168.0 (*qC*).

ν_{max} (thin film cm^{-1}): 3300 - 3200 (br), 3059 (w), 2902 (w), 2870 (w), 2125 [N_3](s), 1597 (s), 1494 (s), 1455 (s), 1428 (s), 1290 (m), 1260 (s), 752 (s).

The data was consistent with previously reported data[171].

3.1.5 Synthesis of *N*-(2'-azidobenzoyl)-2-prolinal



185 **186**

A solution of oxalyl chloride in DCM (1.80 mL, 3.66 mmol, 1.2 eq) was cooled to -78 °C and diluted with dry DCM (4 mL). To it, DMSO (0.63 mL, 0.693 g, 8.87 mmol, 2.9 eq) in dry DCM (5 mL) and the alcohol (0.750 g, 3.05 mmol, 1 eq) in dry DCM (5 mL) were added dropwise. After stirring the resultant solution for 15 min at -78 °C, Et_3N (1.12 mL, 0.813 g, 8.04 mmol, 2.6 eq) was added dropwise and the mixture was allowed to reach r.t. over an hour. The reaction mixture was then quenched with Et_2O (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the product as a brown oil. The crude oil was then chromatographed over silica; 75% EtOAc: Hex to yield the desired aldehyde as a yellow oil as a mixture of rotamers (0.62 g, 83%).

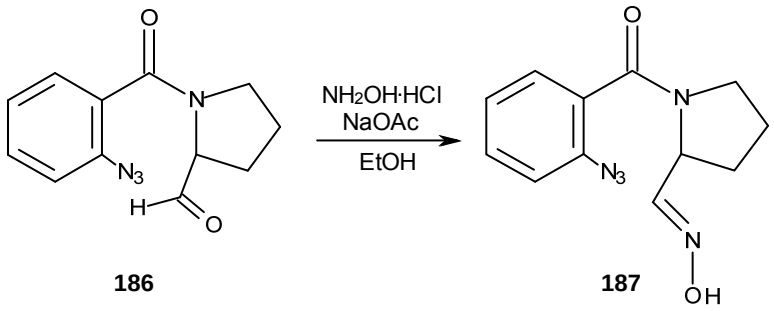
δ_H (400 MHz, $CDCl_3$) rotamers: 1.84 - 1.96 (2H, m, CH_2), 2.04 - 2.12 (1H, m, C*H*H), 2.14 - 2.21 (1H, m, C*H*H), 3.22 - 3.43 & 3.71 - 3.88 (2H, m, CH_2), 4.15 - 4.17 & 4.62 - 4.65 (1H, m , C*H*CHO), 7.12 - 7.23 (2H, m, Ar*H*), 7.26 (1H, dd, *J* 7.7, 1.4, Ar*H*), 7.35 (1H, dd, *J* 7.7, 1.4, Ar*H*), 7.40 & 7.45 (1H, ddd, *J* 7.7, 7.7, 1.4, Ar*H*), 9.29 & 9.70 (1H, d, *J* 1.9, C*H*O).

δ_C (100 MHz, $CDCl_3$) rotamers: 22.7/24.6 (*C*H_2), 26.2/27.8 (*C*H_2), 46.5/48.6 (*C*H_2), 64.5/66.3 (*C*H), 118.4 (*C*H), 125.1/125.2 (*C*H), 127.8/128.0 (*C*H), 128.4/128.8 (*qC*), 130.7/130.8 (*C*H), 136.0/136.2 (*qC*), 167.2/167.4 (*qC)*, 197.8/199.1 (*C*H).

ν_{max} (thin film cm^{-1}): 3052 (m), 2987 (m), 2820 (m), 2722 (m), 2130 (s), 1735 [CHO](m), 1635[C=O] (s), 1450 (m), 1266 (s), 890 (m).

The data was consistent with previously reported data[171].

3.1.6 Synthesis of the oxime



186 **187**

The aldehyde (0.600 g, 2.54 mmol, 1 eq), hydroxylamine HCl (0.265 g, 3.81 mmol, 1.5 eq) and sodium acetate (0.254 g, 3.10 mmol, 1.22 eq) were dissolved in 2.5 mL of ethanol and 3 mL of water. The resultant solution was heated at reflux for 3.5 h, cooled to r.t. and the solvent was removed *in vacuo* to yield a honey coloured solid. It was then purified using silica chromatography (65% EtOAc: Pet) to produce the desired compound as a yellow solid (0.190 g, 29%), m.p (133-134 °C).

δ_H (400 MHz, $CDCl_3$) E/Z isomers/rotamers: 1.77 - 1.99 (2H, m, C*H*$_2$), 2.09 - 2.17 (1H, m, C*H*H), 2.19 - 2.28 (1H, m, CH*H*), 2.35 - 2.46 (2H, m, C*HH*), 3.19 - 3.34 & 3.61 - 3.85 (2H, m, C*H*$_2$), 4.84 - 4.90 (1H, m, NC*H*), 5.15 - 5.20 (1H, m, C*H*NOH), 6.52 & 6.87 (1H, d, *J* 5.1, Ar*H*), 7.10 - 7.22 & 7.28 - 7.51 (2H, m, Ar*H*), 7.55 (1H, d, *J* 4.6, Ar*H*), 9.14 & 9.15 (1H, s, O*H*).

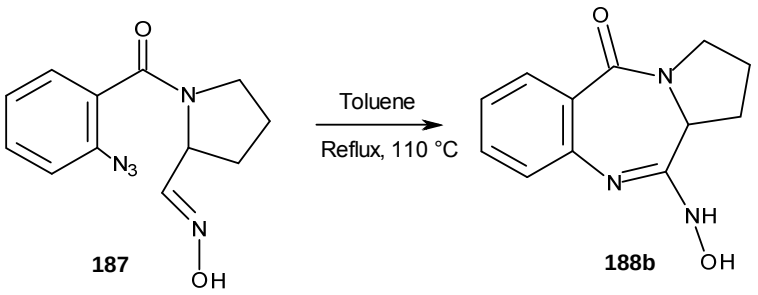
δ_C (100 MHz, $CDCl_3$) E/Z isomers/ rotamers: 21.0/22.5/23.5/24.2 (*C*H_2), 28.9/29.6/30.9/31.1 (*C*H_2), 46.2/46.4/48.3/48.6 (*C*H_2), 53.4/53.7/55.8/57.7 (*C*H), 118.5 (*C*H), 124.9/125.0/125.1/ 125.2 (*C*H), 128.01/128.07/128.4/128.7/129.0/129.1 (*qC*), 130.6/130.7 (*C*H), 136.1/ 136.2 *(qC*), 149.2/149.9/151.2/152.9 (*C*H), 167.2/ 167.4/ 167.6/ 167.8 (*qC*).

ν_{max} (thin film) cm^{-1}: 3246 [OH] (br s), 3081 (m), 2124 [N_3] (s), 1678 (m), 1596 (s), 1489 (s), 952 (m), 750 (s).

HRMS (ESI+): Found 282.0959 $[M+Na]^+$, $C_{12}H_{13}N_5O_2Na$ requires 282.0961.

This data is previously unreported.

3.1.7 Thermolysis of the oxime



The oxime (0.155 g, 0.59 mmol, 1 eq) was heated to reflux in dry toluene for 72 h, the solvent was then removed *in vacuo* and purified by column chromatography [30% EtOAc: Pet] to afford the product as a white solid (0.040 g, 30%), m.p (106-107 °C).

δ_H (500 MHz, $CDCl_3$) : 1.72 - 1.99 (2H, m, CH_2), 2.65 - 2.75 (2H, m, CH_2), 2.56 - 2.63 (1H, m, CHH), 3.46 - 3.65 (2H, m, CH_2), 6.70 (1H, d, J 8.0, ArH), 6.92 (1H, dd, J 8.0, 8.0, ArH), 7.21 (1H, dd, J 7.8, 7.8, ArH), 7.52 (1H, m, NH), 7.70 (1H, d, J 7.8, ArH), 9.60 (1H, s, OH).

δ_C (125 MHz, $CDCl_3$): 22.9 (CH$_2$), 25.4 (CH$_2$), 46.9 (CH$_2$), 54.0 (CH), 120.5 (CH), 122.3 (CH), 124.9 (qC), 130.8 (CH), 132.0 (CH), 137.1 (qC), 149.9 (C=N), 165.8 (C=O).

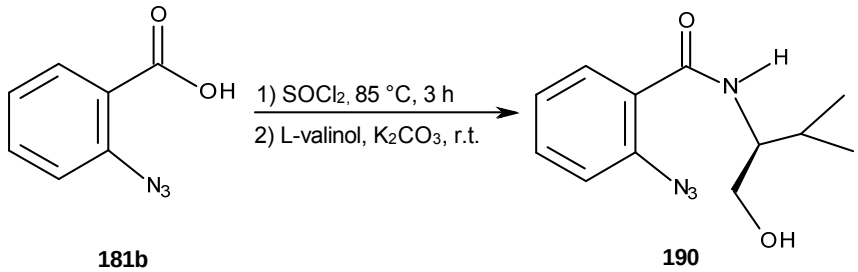
ν_{max} (thin film) cm^{-1}: 3273 (br), 2359 (s), 2341 (s), 1660 (m), 1610 (m), 1594 (s), 1485 (s), 1242.9 (m), 1164 (m), 728 (s).

HRMS (ESI+) : Found 254.0888 $[M+Na]^+$ $C_{12}H_{13}N_3O_2Na$ requires 254.0899

This compound is previously unreported.

3.2 Synthesis of valinol derivatives

3.2.1 Synthesis of (*S*)-*N*-(2'-azidobenzoyl) valinol



181b **190**

A solution of 2-azidobenzoic acid (0.295 g, 1.81 mmol, 1 eq) in $SOCl_2$ (5 mL) was heated at reflux under nitrogen at 85 °C for 3 h. It was then allowed to cool to r.t. and the excess $SOCl_2$ was removed *in vacuo* to yield the acid chloride as a crude oil which was redissolved in DCM (2 x 10 mL) concentrated under reduced pressure and finally dissolved in DCM (5 mL).

(*S*)-Valinol (0.285 g, 2.71 mmol, 1.5 eq) was dissolved in DCM (10 mL) and to this K_2CO_3 (1.00 g, 7.24 mmol, 4 eq) in water (5 mL) was added in one portion. The acid chloride in DCM (5 mL) was added dropwise to the above solution and the whole was stirred overnight. The organic phase was separated, and the aqueous phase was extracted with DCM (3 x 10 mL). The organic phases were combined, dried ($MgSO_4$), concentrated under reduced pressure and purified by silica column chromatography (40% EtOAc: Pet) to give the product as a yellow solid (0.435 g, 88%).

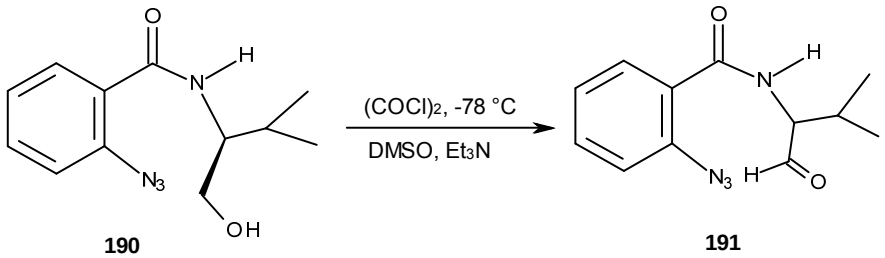
δ_H (400 MHz, $CDCl_3$): 1.03 (6H, d, *J* 6.8, (C*H*$_3$)$_2$CH), 2.03 (1H, app oct, *J* 6.8, C*H*(CH$_3$)$_2$), 3.36 (1H, br s, O*H*), 3.72 - 3.80 (2H, m, C*H*$_2$OH), 3.95 - 4.01 (1H, m, C*H*NH), 7.18 (1H, d, *J* 8.0, Ar*H*), 7.22 , (1H, d, *J* 8.0, Ar*H*), 7.49 (1H, dd, *J* 7.8, 1.6, Ar*H*), 7.64, (1H, bd, *J* 7.8, N*H*), 8.09 (1H, dd, *J* 7.8, 1.6, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 18.7 (*C*H$_3$), 19.7 (*C*H$_3$), 29.1 (*C*H), 58.0 (*C*H), 64.1 (*C*H$_2$), 118.3 (*C*H), 124.9 (*qC*), 125.2 (*C*H), 132.2 (*C*H), 132.4 (*C*H), 137.0 (*qC*), 165.6 (*qC*).

ν_{max} (thin film cm^{-1}): 3200 - 3350 (br), 2959 (m), 2871 (m), 2114 (s), 1612 (s), 1544 (m), 1480 (s), 1288 (m), 1072 (m), 751 (m).

The data was consistent with previously reported data[171].

3.2.2 Synthesis of *N*-(2'-azidobenzoyl) valinal



190 **191**

A solution of 2M oxalyl chloride in DCM (1.7 mL, 3.46 mmol, 1.2 eq) was cooled to -78 °C and diluted with dry DCM (6 mL). DMSO (0.57 mL, 0.628 g, 8.03 mmol, 2.4 eq) in dry DCM (6 mL) and the alcohol (0.754 g, 3.04 mmol, 1 eq) in dry DCM (6 mL) were added dropwise. The resultant solution was stirred for 15 min at -78 °C. Et_3N (1.01 mL, 0.799 g, 7.90 mmol, 2.6 eq) was added dropwise and the whole was allowed to reach r.t. over an hour. The reaction mixture was then quenched with Et_2O (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the product as brown oil. The oil was then chromatographed over silica (30% EtOAc: Pet) and yielded the desired product as a yellow solid (0.497g, 58%).

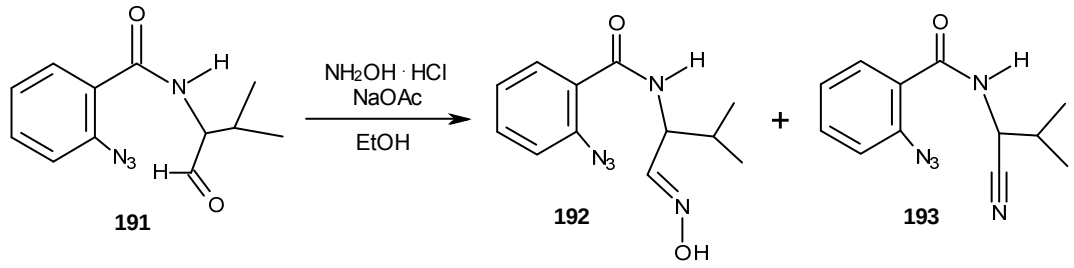
δ_H (400 MHz, $CDCl_3$): 1.02 (6H, d, *J* 7.0, (C*H*$_3$)$_2$CH), 2.45 (1H, app sept, *J* 7.0, C*H*(CH$_3$)$_2$), 4.67 - 4.69 (1H, m, NHC*H*), 7.18 (2H, m, Ar*H*), 7.45 (1H, ddd, *J* 7.6, 7.6, 1.6, Ar*H*), 8.07 (1H, bd, *J* 7.6, N*H*), 8.15 (1H, dd, *J* 7.6, 1.6, Ar*H*), 9.73 (1H, s, C*H*O).

δ_C (100 MHz, $CDCl_3$): 18.0 (*C*H$_3$), 19.2 (*C*H$_3$), 29.0 (*C*H), 64.2 (*C*H), 118.4 (*C*H), 124.2 (*C*H), 125.2 (*C*H), 132.3 (*C*H), 132.7 (*C*H), 137.3 (*qC*), 164.8 (*qC*), 200.0 (*C*H).

ν_{max} (thin film cm^{-1}): 3318 (br), 2961 (m), 2822 (w), 2725 (w), 2123 [N_3] (s), 1725 (s), 1624 (s), 1586 (m), 1472 (s), 759 (s)

The data was identical to that reported previously[171].

3.2.3 Synthesis of the valinal oxime



Ethanol (5 mL) was added to the aldehyde (0.375 g, 1.52 mmol, 1 eq) until it dissolved. Consequently $NH_2OH{\cdot}HCl$ (0.211 g, 3.04 mmol, 2 eq) and sodium acetate (0.174 g, 2.12 mmol, 1.4 eq) were added and the mixture was stirred to give a cloudy solution. 1.5 – 2 mL of water was added until the cloudiness disappeared to yield a clear yellow solution which was heated at reflux for 24 h. The mixture was extracted into DCM (3 x 10 mL), all organic washings were collected and dried ($MgSO_4$). The solvent was evaporated to dryness and purified by silica chromatography (30% EtOAc: Pet) to yield the oxime in 23% yield (0.070 g) and the nitrile in 7% yield (0.020 g).

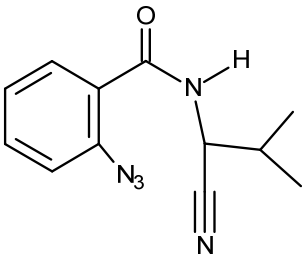
δ_H (400 MHz, $CDCl_3$): 0.96 (3H, d, *J* 6.8 (CH_3)$_2$CH), 1.00 (3H, d, *J* 6.8, (CH_3)$_2$CH), 2.09 - 2.18 (1H, m, C*H*(CH_3)$_2$), 4.72 - 4.80 (1H, m, C*H*NH), 7.11 - 7.21 (2H, m, Ar*H*), 7.42 - 7.50 (2H, m, Ar*H*), 7.94 (1H, br d, *J* 8.0, N*H*), 8.11 (1H, dd, *J* 8.0, 1.6, Ar*H*), 8.81 (1H, s, O*H*).

δ_C (100 MHz, $CDCl_3$): 18.3 (*C*H_3), 18.4 (*C*H_3), 31.3 (*C*H), 54.4 (*C*H), 118.3 (*C*H), 124.5 (*qC*), 125.1 (*C*H), 132.4 (*C*H), 132.5 (*C*H), 137.1 (*qC*), 149.4 (*C*H=N), 199.3 (*C*=O).

ν_{max} (thin film cm^{-1}): 3500 - 3200 (br), 3010 (m), 2964 (s), 2875 (m), 2130 (s), 1641 (s), 1598 (m), 1536 (s), 1480 (s), 1277 (m), 1216 (m), 908 (s), 755 (s)

HRMS (ESI+): Found 284.1122 $[M+Na]^+$ $C_{12}H_{15}N_5O_2Na$ requires 284.1118.

This data is previously unreported.



193

N-(2'-azidobenzoyl)-2-amino-3-methyl-butanonitrile, **193**:

δ_H (400 MHz, $CDCl_3$): 1.11 (3H, d, *J* 6.8, CH_3CH), 1.15 (3H, d, *J* 6.8, CH_3CH), 2.12 - 2.22 (1H, m, C*H*[CH_3]$_2$), 4.99 (1H, dd, *J* 8.7, 6.0, C*H*CN), 7.18 - 7.27 (2H, m, ArH), 7.53 (1H, ddd, *J* 7.8, 7.8, 1.7, ArH), 8.02 (1H, bd, *J* 8.3, N*H*), 8.17 (1H, dd, *J* 7.8, 1.7, ArH).

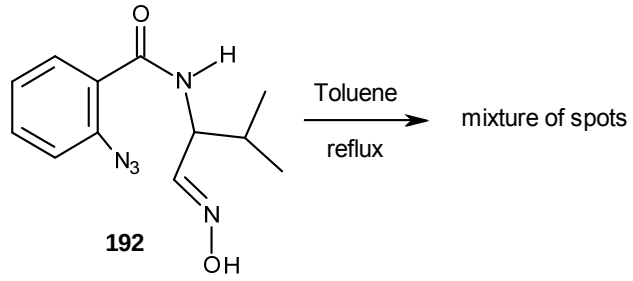
δ_C (100 MHz, $CDCl_3$): 18.2 (*C*H_3), 18.7 (*C*H_3), 31.6 (*C*H), 47.0 (*C*H), 117.8 (*qC*), 118.4 (*C*H), 123.0 (*qC*), 125.4 (*C*H), 132.8 (*C*H), 133.3 (*C*H), 137.2 (*qC*), 163.9 (*qC*).

ν_{max} (thin film cm^{-1}): 2967 (s), 2127 (s), 1656 (s), 1485 (s), 1597 (s), 754 (s).

HRMS (ESI+): Found 266.1012 $[M+Na]^+$, $C_{12}H_{13}N_5ONa$ requires 266.1012.

The data was consistent with previously reported values[171].

3.2.4 Thermolysis of the oxime

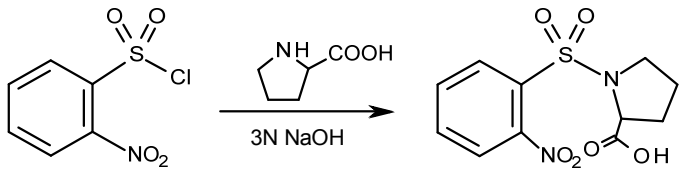


192

When the oxime was heated at reflux in toluene, the reaction did not give any single identifiable product.

3.3 Synthesis of sulfur analogues of Fuligocandin A and B

3.3.1 Synthesis of 1-(2-nitrobenzenesulfonyl)pyrrolidine-2-carboxylic acid



197 **198**

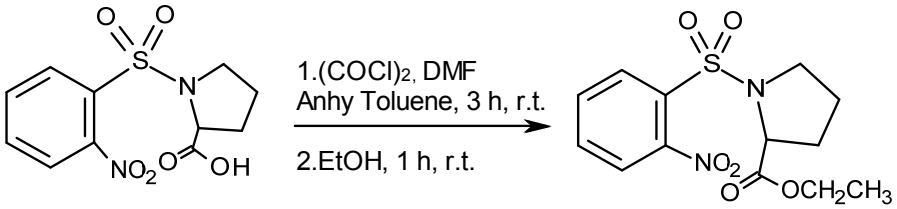
2-Nitrobenzenesulfonyl chloride (2.00 g, 9.02 mmol, 1 eq) was added portionwise over a period of 5 min to a well stirred and ice-cooled solution of pyrrolidine-2-carboxylic acid (1.04 g, 9.02 mmol, 1 eq) in 3N NaOH (7 mL). 30 min of vigorous stirring resulted in a

clear yellow solution which was acidified with conc. HCl dropwise then extracted into ethylacetate (3 x 15 mL). The organic extracts were combined, dried and evaporated to give a pale yellow oil (2.06 g) in 76% yield and excellent purity which was directly carried forward without any purification.

δ_H (400 MHz, $CDCl_3$): 1.91 - 2.07 (2H, m, pyrrolidine *H*), 2.09 - 2.18 (1H, m, pyrrolidine *H*), 2.21 - 2.33 (1H, m, pyrrolidine *H*), 3.44 - 3.66 (2H, m pyrrolidine *H*), 4.57 (1H, dd, *J* 3.0, 8.7, pyrrolidine *H*), 7.59 - 7.65 (1H, m, Ar*H*), 7.66 - 7.74 (2H, m, Ar*H*), 8.01 - 8.08 (1H, m, Ar*H*), 11.06 (1H, s, O*H*).

The data closely matched values found in literature[174].

3.3.2 Synthesis of 2-ethoxycarbonyl-1-(2-nitrobenzenesulfonyl)pyrrolidine



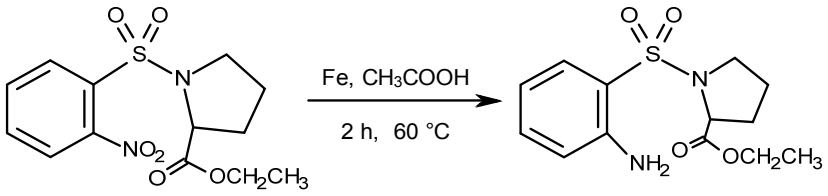
199 **198**

Oxalyl chloride (0.6 mL, 0.85 g, 6.66 mmol) and anhydrous *N,N*-dimethylformamide (40 µL) were sequentially added into a suspension of the nitro acid (2.00 g, 6.66 mmol, 1 eq) in dry toluene (15 mL). The resulting mixture was stirred at r.t. under N_2 atmosphere for 3 h. Absolute ethanol (14 mL) was then added and stirring was maintained for 1 h. After concentration, ethyl acetate (3 x 15 mL) was added and the organic layers were separated, washed with sodium bicarbonate (10 mL), brine and dried ($MgSO_4$). Removal of the solvent afforded the desired nitroester in 82% (1.80 g).

δ_H (400 MHz, $CDCl_3$): 1.21 (3H, t, *J* 7.1, CH_2CH_3), 1.92 - 2.12 (3H, m, pyrrolidine *H*), 2.21 - 2.34 (1H, m, pyrrolidine *H*), 3.51 - 3.69 (2H, m, pyrrolidine H), 4.06 - 4.19 (2H, m, OCH_2), 4.59 (1H, dd, *J* 8.6, 2.8, pyrr *H*), 7.60 - 7.66 (1H, m, Ar*H*), 7.67 - 7.73 (2H, m, Ar*H*), 8.08 - 8.14 (1H, m, Ar*H*).

The data for the compound closely matched that available in literature[174].

3.3.3 Synthesis of 2-methoxycarbonyl-1-(2-aminobenznenesulfonyl) pyrrolidine



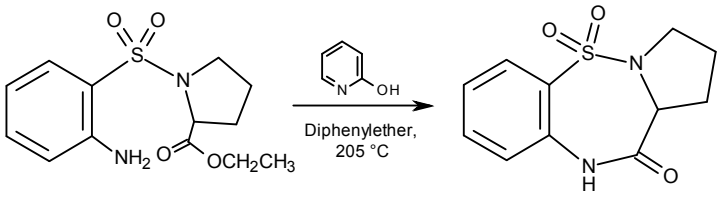
198 **200**

To a solution of the nitroester (2.05 g, 6.25mmol, 1 eq) in glacial acetic acid (25 mL), iron powder (1.80 g) was added over 30 min. The reaction mixture was stirred and heated at 60 °C for 2 h. Removal of the solvent gave a gummy residue which was extracted with ethyl acetate (4 x 30 mL). The organic extracts were combined, washed with sodium bicarbonate, brine and dried. Concentration *in vacuo* afforded the amino ester as a brown solid in 73% yield (1.36 g).

δ_H (400 MHz, $CDCl_3$): 1.24 (3H, t, *J* 7.1, CH_2CH_3), 1.78 - 2.03 (3H, m, pyrrolidine *H*), 2.11 - 2.23 (1H, m, pyrrolidine *H*), 3.28 - 3.39 (2H, m, pyrrolidine *H*), 4.09 - 4.19 (2H, m, OCH_2), 4.47 (1H, dd, *J* 8.6, 4.3, pyrrolidine *H*), 5.21 (2H, br s , NH_2), 6.67 - 6.72 (2H, m, Ar*H*), 7.25 - 7.30 (1H, m, Ar*H*), 7.68 (1H, d, *J* 8.0, Ar*H*).

The above data closely matched that available in literature[174].

3.3.4 Intramolecular cyclisation of the amino ester



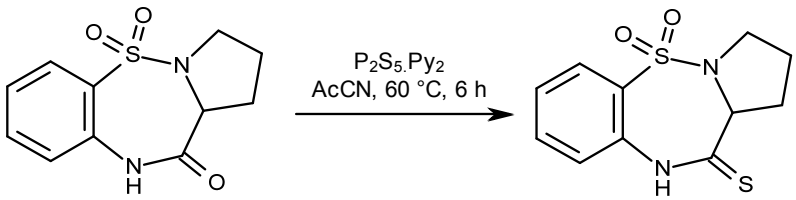
200 **201**

A mixture of the aminoester (1.77 g, 5.94 mmol, 1 eq), 2-hydroxypyridine (0.56 g, 5.94 mmol, 1 eq) in diphenyl ether (10 mL) was heated at 205 °C while monitoring *via* TLC overnight for 15 h. On cooling the crude reaction mixture was poured over *n*-hexane (10 mL) and allowed to stand for 10 min. The clear supernatant was discarded and the solid was dissolved in $CHCl_3$ (2 mL) and purified on an alumina column ($CHCl_3$) to afford the cyclised compound as a brown solid (0.450 g) in 34% yield.

δ_H (400 MHz, $CDCl_3$): 1.77 - 1.83 (1H, m, pyrrolidine *H*), 1.93 - 2.02 (1H, m, pyrrolidine *H*), 2.11 - 2.14 (1H, m, pyrrolidine *H*), 2.40 - 2.52 (1H, m, pyrrolidine H), 2.93 - 3.01 (1H, m, pyrrolidine *H*), 3.44 - 3.54 (1H, m, pyrrolidine *H*), 4.61 - 4.65 (1H, m, pyrrolidine *H*), 7.12 (1H, d, *J* 7.8, Ar*H*), 7.19 (1H, d, *J* 7.8, Ar*H*), 7.50 (1H, dd, *J* 7.8, 1.4, Ar*H*), 7.88 (1H, dd, *J* 7.8, 1.4, Ar*H*), 8.96 (1H, s, N*H*).

The data closely matched literature values[79].

3.3.5 Synthesis of the thioamide



201 **202**

The thionating agent P_2S_5-py_2[184] (0.190 g, 0.49 mmol, 1 eq) was added to the amide (0.38 g, 1.49 mmol, 3 eq) in dry MeCN (7 mL) and heated at reflux for 6 h. The reaction was then concentrated *in vacuo,* dissolved in DCM and purified *via* silica flash chromatography to yield the thioamide as a yellow solid in 60% yield (0.240 g).

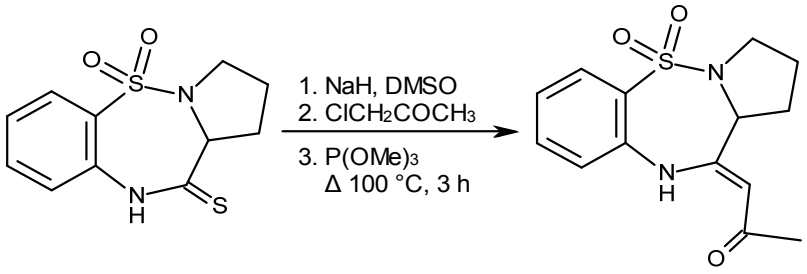
δ_H (400 MHz, d_6-DMSO): 1.74 - 2.04 (4H, m, pyrrolidine *H*), 2.29 - 2.39 (1H, m, pyrrolidine *H*), 2.85 - 2.95 (1H, m, pyrrolidine *H*), 4.80 (1H, app t, *J* 7.1, pyrrolidine *H*), 7.39 (1H, ddd, *J* 1.1, 7.6, 7.6, Ar*H*), 7.44 (1H, dd, *J* 7.6, 7.6, Ar*H*), 7.71 (1H, ddd, *J* 7.8, 7.8, 1.1, Ar*H*), 7.77 (1H, dd, *J* 7.8, 1.4, Ar*H*), 12.35 (1H, s, N*H*).

δ_C (100 MHz, d_6-DMSO): 24.1 (*C*H_2), 35.2 (*C*H_2), 49.6 (*C*H_2), 70.8 (*C*H), 124.0 (*C*H), 125.7 (*C*H), 128.2 (*C*H), 130.6 (*qC*), 134.9 (*C*H), 135.2 (*q*C), 206.3 (*C*=S).

ν_{max} (cm^{-1}): 3140 (br), 3020 (w), 2979 (w), 1537 (m), 1295 (m) 1188 (m), 714 (s).

HRMS (ESI^+): Found 291.0236 $[M+Na]^+$, $C_{11}H_{12}N_2O_2S_2Na$ requires 291.0232.

3.3.6 Attempted synthesis of the Fuligocandin A thio analogue

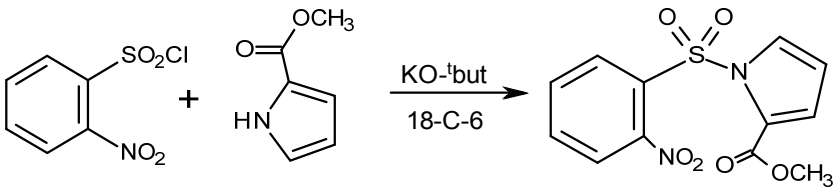


202 **195**

To a solution of the thioamide (0.098 g, 0.366 mmol, 1 eq) in DMSO (5 mL) was added sodium hydride (60%, 0.018 g, 0.732 mmol, 2 eq) over 5 min and the mixture was stirred at r.t. for 30 min under N_2. The reaction mixture was then treated with chloroacetone (0.07 mL, 0.085 g, 0.915 mmol, 2.5 eq) and after an hour of stirring at r.t., trimethyl phosphite (0.13 mL, 0.136 g, 1.10 mmol, 3 eq) and DABCO (0.124 g, 1.10 mmol, 3 eq) were added and the whole reaction mixture was allowed to stir at 100 °C and the reaction was monitored by TLC until all the alkylated species was consumed. After 3 h, the reaction mixture was poured into distilled water (15 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with water (3 x 20 mL) dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was isolated and purified by column chromatography eluting with 20% EtOAc: Pet to give no distinct or identifiable products.

3.4 Fuligocandin A analogue with an unsaturated pyrrole ring

3.4.1 Synthesis of 2-methoxycarbonyl-1-(2-nitrobenzenesulfonyl)-1H-pyrrole



198 **203**

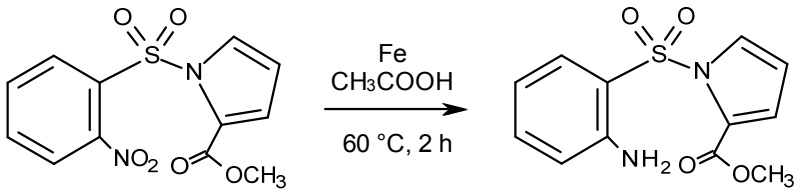
A solution of 2-methoxycarbonyl-1H-pyrrole (2.00 g, 16.00 mmol, 1 eq) in dry THF (32 mL) was added dropwise to a well stirred mixture of 18-crown-6 (0.423 g, 1.60 mmol, 0.1 eq) and potassium *tert* butoxide (1.80 g, 16.00 mmol, 1 eq) in dry THF (32 mL) which was cooled in an ice bath and allowed to stir for 15 min. A solution of the 2-nitrobenzenesulfonyl

chloride (3.55 g, 16.00 mmol, 1 eq) in dry THF (32 mL) was slowly dropped onto the ice-cooled suspension and stirring was then continued at r.t. for 2.5 h. After concentrating the solution under reduced pressure, the resulting residue was extracted in dichloromethane (3 x 40 mL). The organic extracts were washed with brine (1 x 20 mL) and dried over $MgSO_4$. On removal of the solvent the residue was purified on an alumina column with $CHCl_3$ as the eluent to afford the product as a white solid in 65% yield (3.01 g).

δ_H (400 MHz, $CDCl_3$): 3.69 (3H, s, C*H*$_3$), 6.34 (1H, dd, *J* 3.6, 3.6, pyrrole *H*), 7.10 (1H, dd, *J* 3.6, 1.8, pyrrole *H*), 7.66 (1H, dd, *J* 3.6, 1.8, pyrrole *H*), 7.75 - 7.83 (3H, m, Ar*H*), 8.32 - 8.36 (1H, m, Ar*H*).

The data was identical to that reported in literature[79].

3.4.2 Synthesis of 2-methoxycarbonyl-1-(2-aminobenzenesulfonyl)-1H-pyrrole



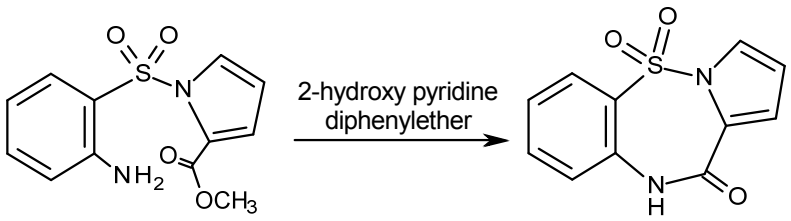
203 **204**

Iron powder (1.50 g) was added over 30 min to a solution of the nitroester (1.62 g, 5.23 mmol, 1 eq) in glacial acetic acid (20 mL). The reaction mixture was stirred and heated at 60 °C for 2 h. After concentration *in vacuo* the residue was extracted with ethyl acetate (5 x 30 mL), the organic washings were combined, washed with $NaHCO_3$ to remove traces of acetic acid and dried with $MgSO_4$. Evaporation of the solvent gave the desired amino ester as a brown solid (1.06 g) in 80% yield.

δ_H (400 MHz, $CDCl_3$): 3.71 (3H, s, C*H*$_3$), 5.12 (2H, br s, N*H*$_2$), 6.27 (1H, dd, *J* 3.5, 3.5, pyrrole *H*), 6.65 - 6.75 (2H, m, pyrrole *H* + Ar*H*), 7.05 (1H, dd, *J* 3.5, 1.8, pyrrole *H*), 7.28 (1H, ddd, *J* 7.7, 7.7, 1.8, Ar*H*), 7.60 (1H, d, *J* 7.7, Ar*H*), 7.68 (1H, m, Ar*H*).

The data closely matched the literature data[79].

3.4.3 Synthesis of 11-oxo(10H)-pyrrolo-[2,1-c][1,2,5]benzothiadiazepine 5,5-dioxide



204 **205**

A well stirred reaction mixture of the aminoester (0.488 g, 1.74 mmol, 1 eq), 2-hydroxy pyridine (0.083 g, 1.74 mmol, 1 eq) and diphenyl ether (5 mL) was heated at 205 °C under a nitrogen stream while monitoring *via* TLC. After 5 h the crude residue was cooled and poured over *n*-hexane (20 mL) and allowed to stand for 10 min. The clear supernatant was discarded and the remaining residue was dissolved in $CHCl_3$ and purified on an alumina column and yielded a brown solid (0.170 g) in 39% yield. M.p. 292-293 °C (Lit 292-293 °C).

δ_H (400MHz, d_6-DMSO): 6.51 (1H, dd, *J* 3.3, 3.3, pyrrole *H*), 7.14 (1H, dd, *J* 3.3, 1.7, pyrrole *H*), 7.43 (1H, dd, *J* 7.4, 7.4, Ar*H*), 7.49 (1H, d, *J* 8.0, Ar*H*), 7.58-7.60 (1H, dd, *J* 3.3, 1.7, Ar*H*), 7.79 (1H, ddd, 8.0, 8.0, 1.3, Ar*H*), 8.01 (1H, dd, *J* 8.0, 1.3, Ar*H*), 11.15 (1H, s, N*H*).

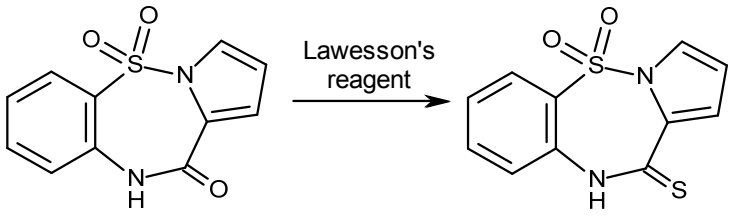
δ_C (100 MHz, $CDCl_3$): 112.3 (*C*H), 121.9 (*C*H), 123.1 (*C*H), 123.9 (*C*H), 125.1 (*C*H), 125.4 (*qC*), 126.3 (*C*H), 128.0 (*qC)*, 135.8 (*qC*), 136.5 (*C*H), 159.3 (*C*=O).

ν_{max} (cm^{-1}): 3133 (br), 3045 (w), 2990 (w), 1640 (s), 1550 (s), 1305 (s), 1145 (m).

HRMS (ESI^+): Found 271.0149 $[M+Na]^+$ $C_{11}H_8N_2O_3SNa$ requires 271.0148.

The data matched values reported in literature[79].

3.4.4 Synthesis of the thioamide



205 **206**

Lawesson's reagent (0.63 g, 1.55 mmol, 0.5eq) was added to a solution of the amide (0.770 g, 3.10 mmol, 1 eq) in dry THF (15 mL). It was then stirred at r.t. for an hour followed by heating at reflux for 12 h. The solvent was evaporated and purified by silica chromatography (0.5% MeOH: $CHCl_3$) to afford the thioamide as a yellow solid (0.305 g, 37%).

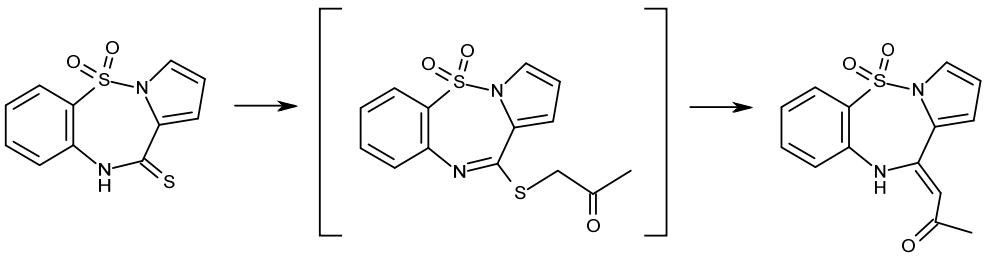
δ_H (400 MHz, $CDCl_3$) : 6.52 (1H, dd, *J* 3.3, 3.3, pyrrole *H*), 7.29-7.34 (2H, m, pyrrole *H*), 7.56 (1H, dd, *J* 7.6, 7.6, Ar *H*), 7.61 (1H, d, *J* 8.1, Ar *H*), 7.87 (1H, d, *J* 8.1, Ar *H*), 8.04 (1H, d, *J* 7.6, Ar *H*), 12.83 (1H, s, N*H*).

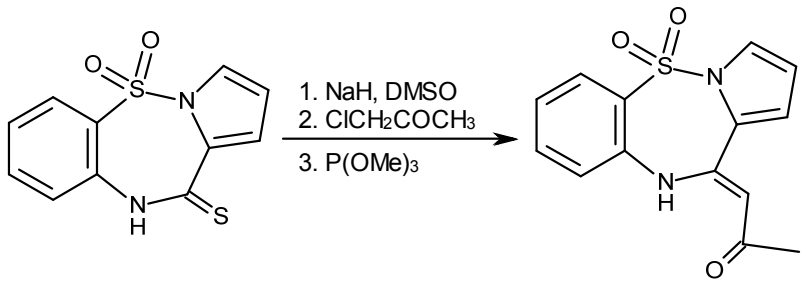
δ_C (100 MHz, $CDCl_3$): 112.6 (*C*H), 120.5 (*C*H), 122.7 (*C*H), 123.6 (*C*H), 124.7 (*C*H), 126.0 (*qC*), 126.3 (*C*H), 126.9 (*qC*), 135.8 (*qC*), 137.0 (*C*H), 186.5 (*C*=S).

ν_{max} (cm^{-1}): 3136 (br), 2974 (w), 1587 (s), 1497 (m), 1368 (m), 1296 (s), 1152 (m).

HRMS (ESI^+): Found 286.9910 $[M+Na]^+$ $C_{11}H_8N_2O_2S_2Na$ requires 286.9919.

3.4.5 Synthesis of the Fuligocandin A analogue, **208**





206 **208**

To a solution of the thioamide (0.240 g, 0.91 mmol, 1 eq) in DMSO (5 mL) was added sodium hydride (60%, 0.050 g, 1.00 mmol, 1.1 eq) over 5 min and the mixture was stirred at r.t. for 30 min under a N_2 stream. The reaction was then treated with chloroacetone (0.19 mL, 0.208 g, 2.25 mmol, 2.5 eq) and after an hour of stirring at r.t., trimethyl phosphite (0.32 mL, 0.318 g, 2.7 mmol, 3 eq) and DABCO (0.302 g, 2.70 mmol, 3 eq) were added and the solution was allowed to stir at 100 °C and monitored by TLC until all the alkylated species was

consumed. After 2 h, the reaction mixture was poured into distilled water (10 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were washed with water (40 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was isolated and purified by column chromatography eluting with 20% EtOAc: Pet to give the desired analogue of fuligocandin A as a yellow oil (0.136 g, 52%).

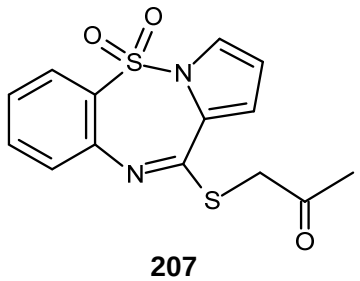
δ_H (400 MHz, $CDCl_3$): 2.18 (3H, s, C*H*$_3$), 5.69 (1H, s, C*H*), 6.28 (1H, dd, *J* 3.3, 3.3, pyrrole *H*), 6.70 (1H, dd, *J* 3.3, 1.6, pyrrole *H*), 7.14 - 7.21 (2H, m, Ar*H*), 7.35 (1H, dd, *J* 3.3, 1.6, pyrrole *H*), 7.53 (1H, ddd, *J* 8.0, 8.0, 1.6, Ar*H*), 7.88 (1H, dd, *J* 8.0,1.6, Ar*H*), 13.5 (1H, s, N*H*).

δ_C (100 MHz, $CDCl_3$): 24.2 (*C*H_3), 98.3 (*C*H), 111.4 (*C*H), 117.7 (*C*H), 122.7 (*C*H), 123.9 (*C*H), 124.0 (*C*H), 125.4 (*qC*), 126.5 (*C*H), 129.7 (*qC*), 135.4 (*C*H), 137.3 (*qC*), 148.9 (*qC*), 198.2 (*C*=O).

ν_{max} (cm^{-1}): 3355 [NH] (br), 1680 [C=O](s), 1603 (s), 1446 (m), 1575 (s), 1371 (vs) 761 (s).

HRMS (ESI^+): Found 311.0461 $[M+Na]^+$, $C_{14}H_{12}N_2O_3SNa$ requires 311.0468.

3.4.6 Isolation of the thioimidate intermediate:



207

The compound was isolated before the heating step to confirm the structure as the proposed intermediate; it was immediately carried on to the next step i.e. the episulfide contraction.

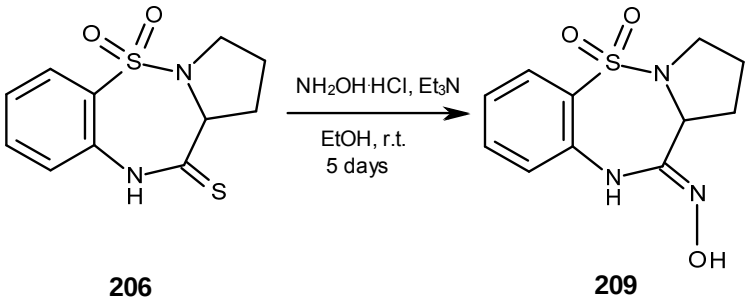
δ_H (400 MHz, $CDCl_3$): 2.31 (3H, s, C*H*$_3$), 4.01 (2H, br d, C*H*$_2$), 6.36 (1H, dd, *J* 3.3, 3.3, pyrrole), 6.97 (1H, dd, *J* 3.3, 1.6, pyrrole *H*), 7.25 - 7.30 (2H, m, pyrrole *H* + Ar *H*), 7.43 - 7.46 (1H, m, Ar*H*), 7.60 (1H, ddd, *J* 8.0, 8.0, 1.6, Ar*H*), 7.93 (1H, dd, *J* 8.0, 1.6, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 28.6 (*C*H_3), 41.3 (*C*H_2), 111.4 (*C*H), 117.7 (*C*H), 122.5 (*C*H), 125.3 (*qC*), 125.4 (*C*H), 125.6 (*C*H), 128.1 (*C*H), 129.5 (*qC*), 134.8 (*C*H), 143.4 (*qC*), 157.7 (*qC*), 202.7 (*C*=O).

ν_{max} (cm^{-1}): 2924 (m), 2853 (w), 1710 [C=O](s), 1670 [C=N](m), 1597 (m), 1573 (s), 1368 (vs) 762 (s).

The compound was found to be unstable hence no mass spectral data was acquired.

3.5.1 Synthesis of the oxime



206 **209**

The thiolactam (0.140 g, 0.522 mmol, 1 eq) was dissolved in EtOH (2 mL) and $NH_2OH{\cdot}HCl$ (0.073g, 1.045 mmol, 2 eq) was added. Triethylamine (0.15 mL) was added dropwise over 5 min and the light yellow suspension was stirred at r.t. for 24 h. The solvent was removed *in vacuo* and the residue was washed with $CHCl_3$ (20 mL) and water (10 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* and purified using silica chromatography ($CHCl_3$: 0.5% MeOH) to arrive at the desired target (0.030 g, 20 %).

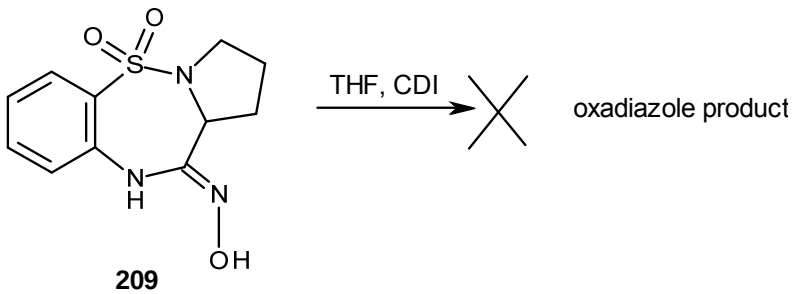
δ_H (400 MHz, $CDCl_3$): 1.73 - 1.95 (3H, m, pyrrolidine C*H*), 2.01 - 2.16 (1H, m, pyrrolidine C*H*), 2.89 - 3.02 (1H, m, pyrrolidine C*H*), 3.36 - 3.49 (1H, m, pyrrolidine C*H*), 4.26 - 4.39 (1H, m, pyrrolidine C*H*), 6.99 - 7.08 (2H, m, Ar*H*), 7.42 (1H, dd, *J* 7.8, 7.8, Ar*H*), 7.55 (1H, br s, N*H*), 7.75 (1H, d, *J* 7.8, Ar*H*), 9.15 (1H, br s, O*H*).

δ_C (100 MHz, $CDCl_3$): 24.3 (CH_2), 31.7 (CH_2), 49.5 (CH_2), 61.8 (CH), 121.2 (CH), 121.7 (CH), 126.8 (*qC*), 129.0 (CH), 134.2 (CH), 136.5 (*qC*), 150.0 (*C*=N-OH).

ν_{max} (cm^{-1}): 3309 (br), 2975 (m), 1662 (s), 1593 (s), 1336 (vs), 1134 (vs), 691 (s).

HRMS (ESI^+): Found 290.0563 $[M+Na]^+$, $C_{11}H_{13}N_3NaO_3S$ requires 290.0569.

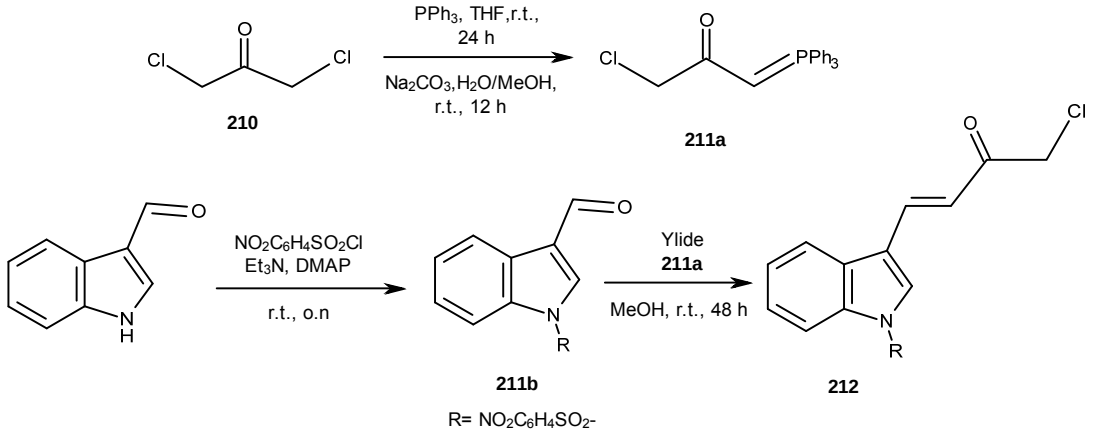
3.5.2 Attempted reaction of oxime with CDI



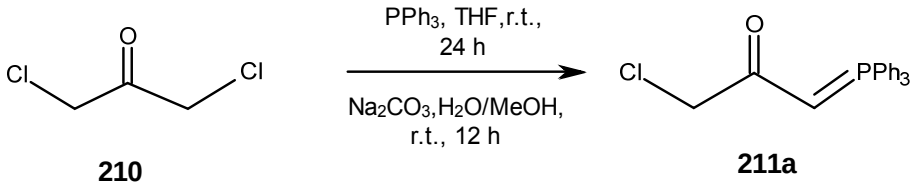
209

In a nitrogen atmosphere, the oxime (0.035 g, 0.131 mmol, 1 eq) was dissolved in dry THF (4 mL) and subsequently treated with 1, 1'-carbonyl diimidazole (0.024 g, 0.145 mmol, 1.1 eq). The reaction was heated at reflux for 24 h. The solvent was then removed *in vacuo*, the residue was extracted with dichloromethane and water (3 x 10 mL). The organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The major product was found to be the corresponding amide **201**.

3.6.1 Synthesis of the indole fragment of Fuligocandin B

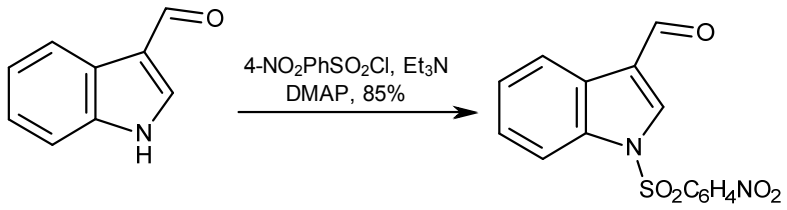


3.6.1a Synthesis of 1-chloro-3-(triphenylphosphanylidene)-propan-2-one



To a THF-solution (15 mL) of 1, 3-dichloroacetone (2.80 g, 22 mmol, 1 eq), a solution of triphenylphosphine (5.24 g, 20 mmol, 0.9 eq) in THF (10 mL) was added and the mixture was heated at reflux for 24 h. A white solid was collected by filtration and then dissolved in methanol (10 mL), consequently to which a solution of Na_2CO_3 (1.16 g, 11 mmol, 0.5 eq) in water (10 mL) was added which immediately led to the formation of a white precipitate. After 1 h of stirring at r.t., the phosphorus ylide was filtered, dissolved in DCM (20 mL), dried ($MgSO_4$) and evaporated to give a pure white solid (6.9 g, 89 %). M.p 179-180 °C (Lit 178-180 °C)[26].

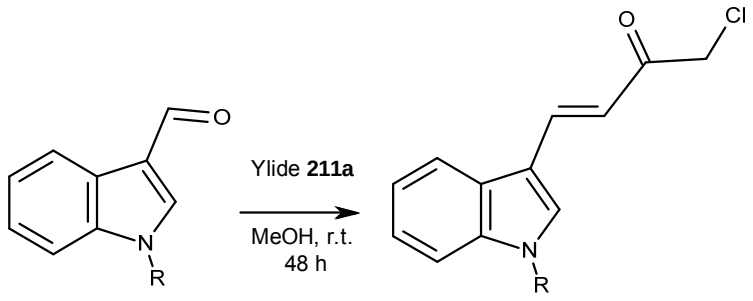
3.6.1b Synthesis of 1-(4-nitrophenylsulfonyl)-3-carbaldehyde



211b

A DCM suspension (10 mL) of indole-3-carbaldehyde (0.900 g, 6.2 mmol, 1 eq), DMAP (0.061 g, 0.5 mmol, 0.08 eq) and triethylamine (1.3 mL, 9.3 mmol, 1.5 eq) was stirred for 10 min at r.t., and then a solution of 4-nitrophenylsulfonyl chloride (1.50 g, 6.8 mmol, 1.1 eq) in 12 mL of CH_2Cl_2 was added dropwise over 10 min. After stirring at r.t. overnight, the reaction mixture was quenched with 5% HCl solution. The phases were separated and extracted with DCM (3 x 20 mL), the organic phases were combined and dried (Na_2SO_4). The red solution was flushed through a short silica plug. On evaporation the yellow filtrate gave an off-white solid in excellent yield (1.73 g, 85%) m.p 178-179 °C (lit 178-180 °C). Data was found to be identical to reported literature values[26].

3.6.2 Synthesis of the indole fragment in Fuligocandin B



211b **212**

R= $SO_2C_6H_4NO_2$

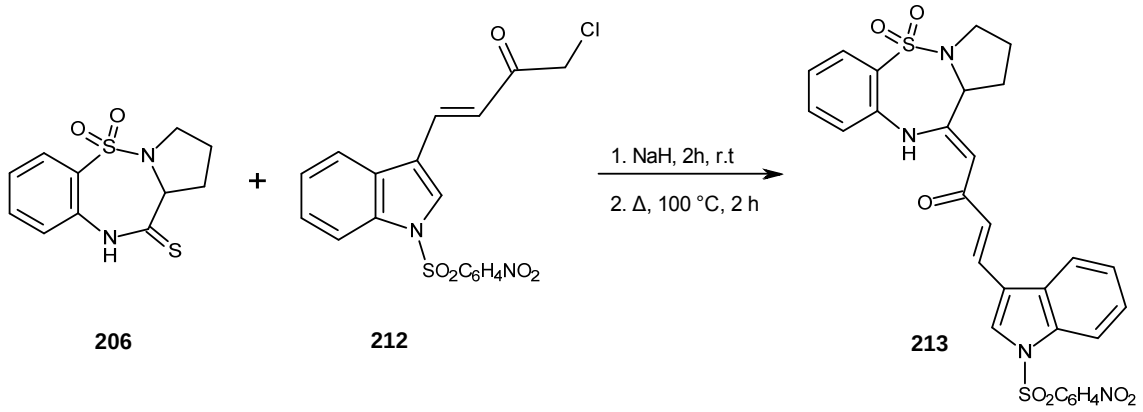
A suspension of the protected indole-3-carbaldehyde (0.710 g, 2.15 mmol, 1 eq) in MeOH (10 mL) was heated for 30 min and then the phosphorus ylide (0.910 g, 2.58 mmol, 1.2 eq) was added (neat). After 3 days of gentle reflux, the yellow suspension turned to an orange solution while an orange precipitate continued to form for 2 h on cooling to r.t. The crude product was collected by filtration and then stirred in MeOH for a few min and filtered to give the *E*-1-chloro-4-(1,4-nitrophenylsulfonyl)-1*H*-indol-3-yl)but-3-en-2-one as an orange solid in 80% yield (0.690 g), m.p 174-175 °C (lit 174-175 °C).

δ_H (400 MHz, d_6-DMSO): 4.76 (2H, s, CH_2-Cl), 7.15 (1H, d, *J* 16.0, =C*H*), 7.40 - 7.51 (2H, m, ArH), 7.85 (1H, d, *J* 16.0, =C*H*), 8.04 (2H, dd, *J* 7.7, 7.7, Ar*H*), 8.33 (2H, m, Ar*H*), 8.38 (2H, m, Ar*H*), 8.58 (1H, s, indole *H*).

ν_{max} (cm^{-1}): 3106 (m), 1698 (m), 1606 (s), 1524 (s), 1177 (s), 984 (s), 734 (s).

This data was consistent with reported values[190].

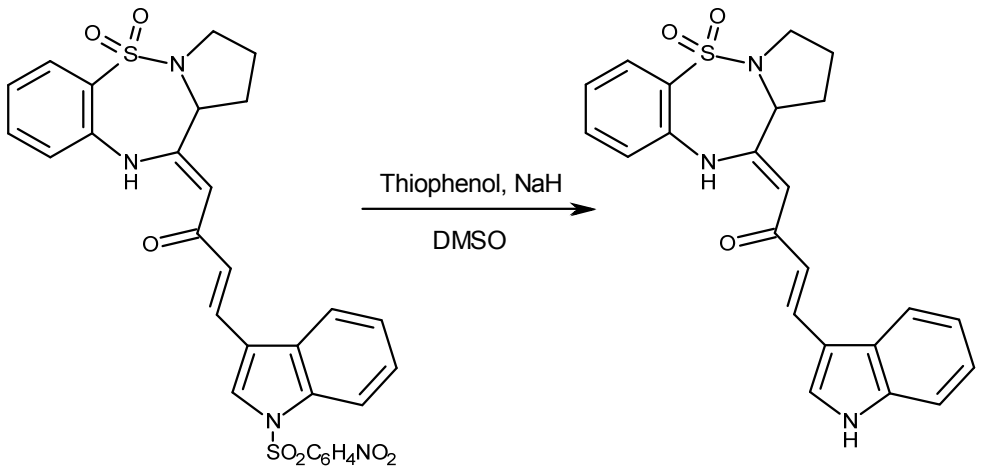
3.6.3 Attempted synthesis of the thio analogue of Fuligocandin B



206 **212** **213**

To a solution of the thioamide (0.088 g, 0.328 mmol, 1 eq) in DMSO (3 mL) was added sodium hydride (60%, 0.008 g, 0.328 mmol, 1 eq) and the mixture was stirred at r.t. After 2 h, the indole derivative (0.133 g, 0.328 mmol, 1 eq) was added. After 2 h at r.t., TLC analysis showed traces of starting material, and so the reaction mixture was heated at 100 °C for 1 h. The product was not isolated but carried forward to the next step directly for deprotection of the indole fragment.

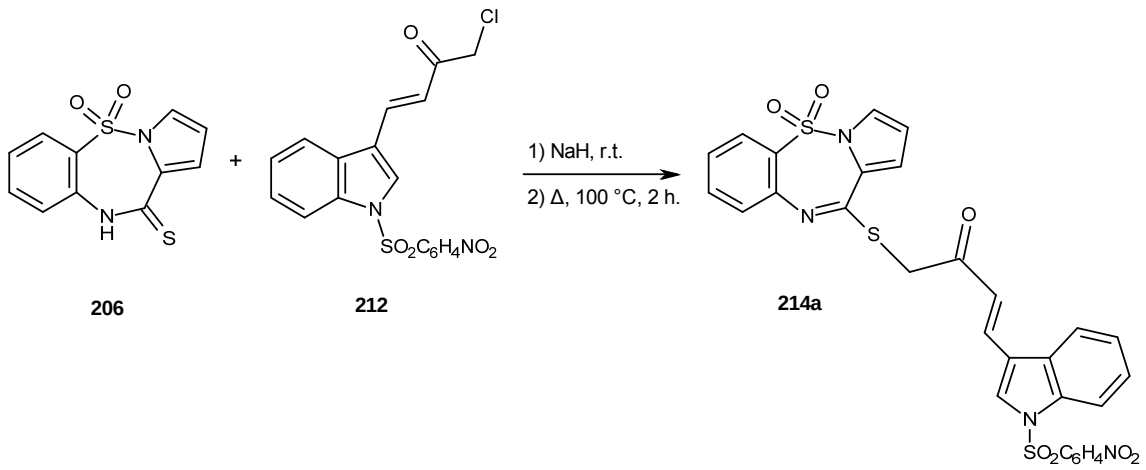
3.6.4 Deprotection of the protected thio analogue using thiophenol



213 **196**

Sodium hydride (60%, 0.027 g, 1.1 mmol, 1 eq) was added to a solution of thiophenol (0.23 mL, 0.22 g, 2.2 mmol, 2 eq) in DMSO (1 mL) and after being stirred for 3 min, 0.33 mL of this mixture, was added to a solution of **213** at r.t. After monitoring *via* TLC, distilled water (15 mL) was added to the dark red mixture and the organic product was extracted into DCM (3 x 10 mL). The combined organic fractions were washed with water (5 x 10 mL), dried over Na_2SO_4. and evaporated under reduced pressure. The crude material was purified using column chromatography EtOAc/ Hexane (50%) and yielded fragmented products from which only the amide **201** was isolated.

3.6.5 Synthesis of the protected Fuligocandin B analogue intermediate



206 **212** **214a**

To a solution of the thioamide (0.085 g, 0.322 mmol, 1 eq) in DMSO (5 mL) was added sodium hydride (60%, 0.016 g, 0.644 mmol, 2 eq) and the mixture was stirred at r.t. for 1 h.

The indole derivative (0.130 g, 0.322 mmol, 1 eq) was then added and this reaction mixture was allowed to stir at r.t. for 3 h. TLC analysis showed only traces of starting material hence the reaction mixture was heated at 100 °C for 2 h. The product was isolated using column chromatography (EtOAc/ Hexane, 40%) and shown to be the sulfide **214a**.

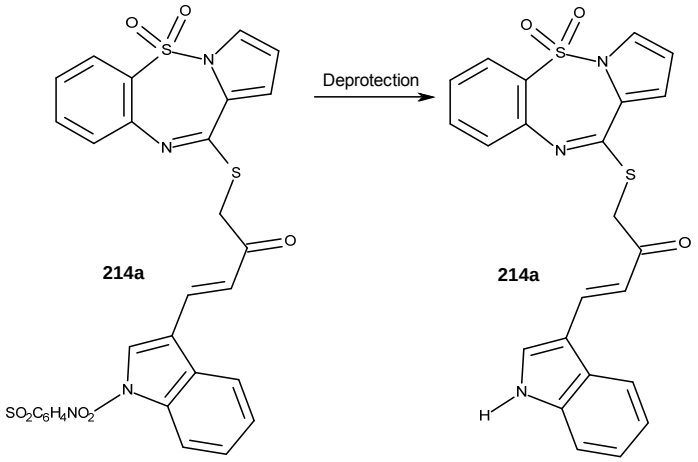
δ_H (400 MHz, $CDCl_3$): 4.03 (2H, br s, CH_2) 6.42 - 6.46 (1H, m, Ar*H*), 7.00 - 7.07 (1H, m, Ar*H*), 7.19 - 7.47 (4H, m, Ar*H*), 7.48 - 7.56 (2H, m, Ar*H*), 7.57 - 7.73 (2H, m, Ar*H*), 7.74 - 7.83 (2H, m, Ar*H*), 7.90 - 7.95 (1H, m, Ar*H*), 7.97 - 8.05 (2H, m, Ar*H*), 8.08 - 8.17 (2H, m, Ar*H*), 8.24 - 8.38 (1H, m, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 39.5 (*C*H_2), 111.6 (*C*H), 113.5 (*C*H), 117.7 (*C*H), 119.6 (*qC*), 120.9 (*C*H), 122.6 (*C*H), 123.7 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.3 (*qC*), 125.5 (*C*H), 125.6 (*C*H), 126.0 (*C*H), 127.9 (*C*H), 128.1 (*C*H), 128.4 (*C*H), 129.4 (*qC*), 134.9 (*C*H), 135.3 (*qC*), 135.6 (*C*H), 142.8 (*qC*) 143.0 (*qC*), 151.1 (*qC*), 164.9 (*qC*), 174.5 (*qC*), 193.8 (*C=O*).

ν_{max} (cm^{-1}): 3100 (m), 1697 (m), 1603 (s), 1552 (s), 734 (s).

HRMS (ESI^+): Found 632.0494 $[M]^+$, $C_{29}H_{20}N_4O_7S_3$ requires 632.0491.

3.6.6 Attempted deprotection using thiophenol



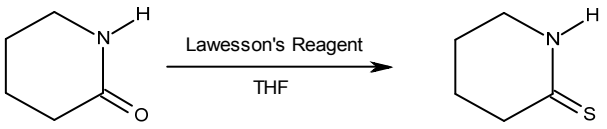
Sodium hydride (0.027 g, 1.1 mmol, 1 eq) was added to a solution of thiophenol (0.23 mL, 0.22 g, 2.2 mmol, 2 eq) in DMSO (1 mL) and after being stirred for 3 min, 0.33 mL was added to the reaction mixture from above. After monitoring via TLC, distilled water (15 mL) was added to the dark red mixture which was extracted into DCM (3 x 10 mL). The organic extracts were dried over Na_2SO_4 and removed *in vacuo*. The crude material was purified using column chromatography EtOAc/ Hexane (50%) and yielded fragmented products and

no quantifiable deprotected fuligocandin B analogue was isolated or characterised (See discussion 2.5.4).

HRMS (ESI$^+$): Found 447.0708 $[M]^+$, $C_{23}H_{17}N_3O_3S_2$.requires 447.0711 (See discussion 2.5.4).

3.7 Synthesis of indolizidines and pyrrolizidines

3.7.1 Synthesis of 2-piperidinthione



216 **217**

Lawesson's reagent (1.01 g, 2.50 mmol, 1eq) was added to a solution of 2-piperidone (0.545 g, 5.0 mmoL, 2 eq) in anhydrous THF (15 mL) and the reaction mixture was stirred gently at r.t. under a nitrogen atmosphere for 1h and then heated at reflux under N_2 for 2 h.

The reaction was checked for completion by TLC in a fume cupboard and once complete it was allowed to cool to r.t., concentrated and purified by silica chromatography (65% EtOAc: Hex) to yield the product as white crystals (0.525 g, 91%).

δ_H (400 MHz, $CDCl_3$): 1.71 - 1.85 (4H, m, C*H*$_2$C*H*$_2$), 2.89 (2H, t, *J* 6.3, C*H*$_2$), 3.33 - 3.37 (2H, m, C*H*$_2$CH$_2$), 9.19 (1H, s, N*H*).

δ_C (100 MHz, $CDCl_3$): 20.7 (*C*H$_2$), 39.1 (*C*H$_2$), 44.62 (*C*H$_2$), 44.6 (*C*H$_2$), 202.17 (*qC*).

ν_{max} (thin film cm^{-1}): 3155 (m), 3080 (m), 2996 (m), 1563 (m), 1449 (s), 1347 (m), 1318 (s), 1138 (s), 819 (m), 737 (m).

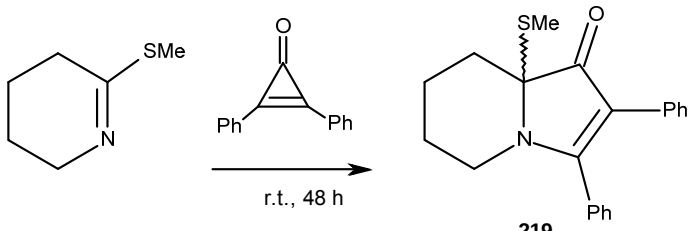
The data closely resembled that of literature values[187].

3.7.2 Synthesis of the 6-methylsulfanyl-2,3,4,5-tetrahydropyridine

217 **218**

Dimethyl sulfate (0.32 mL, 0.421 g, 3.74 mmol, 1.1 eq) was added to the thioamide **217** (0.350 g, 3.4 mmol, 1 eq) and the mixture was stirred gently overnight under a nitrogen atmosphere. It was then washed with ether (10 mL) and 10% K_2CO_3 (20 mL). The aqueous phase was extracted with DCM (3 x 20 mL), dried ($MgSO_4$) and filtered. Most of the solvent was removed *in vacuo* at r.t. leaving 2 mL of the reaction mixture, as the compound was found to be volatile. This solution was used directly in the next step.

3.7.3 Synthesis of 2, 3-diphenyl-5-methylthio-1-azabicyclo[4.3.0] non-2-en-4-one



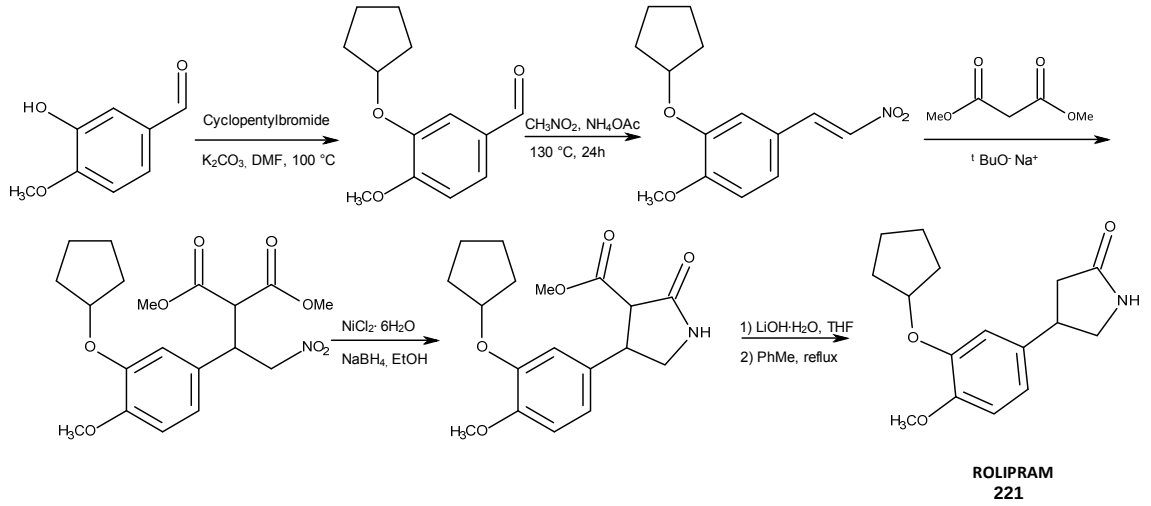
218 **219**

Anhydrous MeCN (10 mL) was added to the crude solution from the above reaction and DPP was added to it in one portion (0.627 g, 3.04 mmol, 1 eq) under an inert N_2 atmosphere. The resultant solution was stirred at r.t. for 48 h and checked for completion by TLC. The solvent was removed *in vacuo* and purified under silica column chromatography (30% EtOAc: Pet) to give the indolizidine product **219** as yellow oil (0.240 g, 24%).

δ_H (400 MHz, $CDCl_3$): 1.05 - 1.34 (2H, m, CH_2), 1.62 - 1.88 (3H, m, CH_2 + C*H*H), 1.95 (3H, s, SC*H*$_3$), 2.11 - 2.16 (1H, m, CH*H*), 3.39 (1H, m, NC*H*H), 3.55 (1H, m, NCH*H*), 6.96 - 6.99 (1H, m, Ar*H*), 7.02 - 7.08 (4H, m, Ar), 7.18 - 7.22 (2H, m, Ar*H*), 7.36-7.44 (3H, m, Ar*H*).

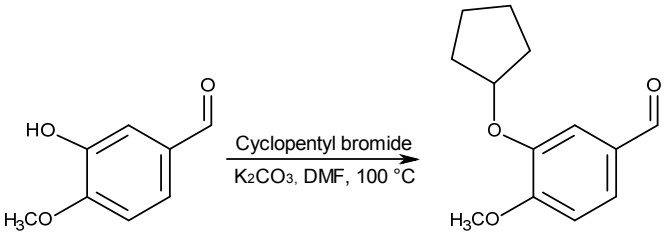
The data closely resembled that of literature values[187].

3.8 Synthesis of Rolipram



ROLIPRAM
221

3.8.1 Synthesis of 3-(cyclopentyloxy)-4-methoxybenzaldehyde



222

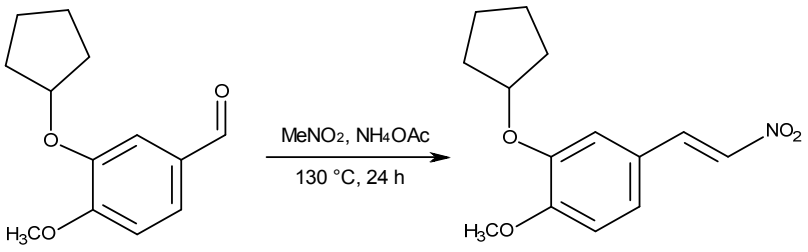
Cyclopentyl bromide (4.60 mL, 6.37 g, 42.71 mmol, 1.3 eq) and potassium carbonate (6.80 g, 49.35 mmol, 1.5 eq) were added to a stirred solution of isovanillin (5.19 g, 32.85 mmol, 1 eq) in DMF (35 mL) and heated at 100 °C for 30 h. The reaction mixture was cooled to r.t. and quenched with saturated aqueous ammonium chloride (130 mL). The mixture was then stirred for 10 min at r.t., the layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The organic extracts were combined, washed with water (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was isolated as a brown oil (6.70 g, 93%) and carried forward to the next step without further purification.

δ_H (400 MHz, $CDCl_3$): 1.50 - 1.65 (2H, m, cyclopentyl *H*), 1.70 - 2.11 (6H, m, cyclopentyl *H*), 3.88 (3H, s, Ar-OC*H*$_3$), 4.76 - 4.85 (1H, m, OC*H*$(CH_2)_4$), 6.89 (1H, d, *J* 8.1, Ar*H*), 7.32 (1H, d, *J* 1.9, Ar*H*), 7.35 (1 H, dd, *J* 8.1, 1.9, Ar*H*), 9.79 (1H, s, C*H*O).

δ_C (100 MHz, $CDCl_3$): 23.9 (2 x *C*H_2), 32.5 (2 x *C*H_2), 55.9 (O*C*H_3), 80.2 (O*C*H$(CH_2)_4$), 110.5 (*C*H), 111.7 (*C*H), 126.2 (*C*H), 130.1 (*qC*), 148.3 (*q*C), 150.2 (*qC*), 190.9 (*C*HO).

The data was found to be consistent with that reported in literature[190].

3.8.2 2-(Cyclopentoxy)-1-methoxy-4-[2-nitroethenyl]benzene]



222 **223**

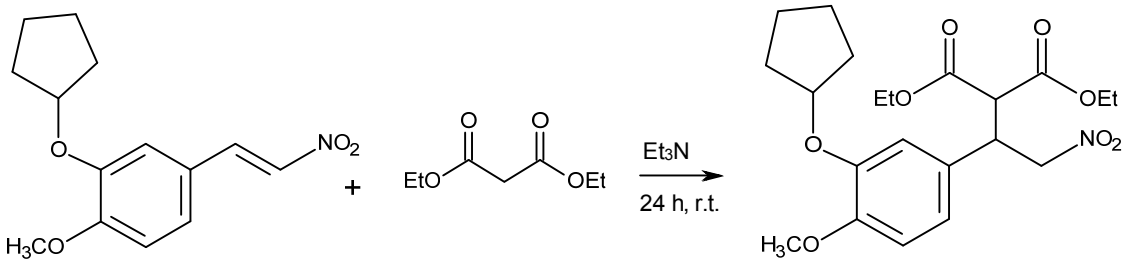
To a stirring solution of the crude aryl aldehyde (6.50 g, 29.50 mmol, 1 eq) and nitromethane (150 mL) was added ammonium acetate (2.50 g, 32.50 mmol, 1.1 eq). The solution was heated to reflux for 24 h. The reaction mixture was concentrated *in vacuo* and then dissolved in DCM: H_2O (20 mL; 1:1), the organics were extracted into DCM (3 x 100 mL), then washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by silica gel chromatography [EtOAc/Pet, 20% graduated to 50%] afforded the title compound as a canary yellow solid (6.50 g, 88%). M.pt 138-139 °C (Lit 138-140 °C).

δ_H (400 MHz, $CDCl_3$): 1.56 - 1.68 (2H, m, cyclopentyl *H*), 1.77 - 2.01 (6H, m, cyclopentyl *H*), 3.88 (3H, s, OCH_3), 4.72 - 4.82 (1H, m, $OCH(CH_2)_4$), 6.87 (1H, d, *J* 8.2, Ar*H*), 6.98 (1H, d, *J* 1.9, Ar*H*), 7.12 (1H, dd, *J* 8.2, 1.9, Ar*H*), 7.48 (1H, d, *J* 13.3, CH=C*H*NO_2), 7.93 (1 H, d, *J* 13.3, C*H*=CH-NO_2).

δ_C (100 MHz, $CDCl_3$): 24.0 (2 x CH_2), 32.7 (2 x CH_2), 56.0 (OCH_3), 80.6 ($OCH(CH_2)_4$), 111.6 (CH), 113.6 (CH), 122.5 (*qC*), 124.2 (*qC*), 134.9 (CH), 139.6 (CH), 148.1 (*qC*), 153.7 (*qC*).

The data was found to be consistent with that reported in literature[190].

3.8.3 Synthesis of the Michael addition product



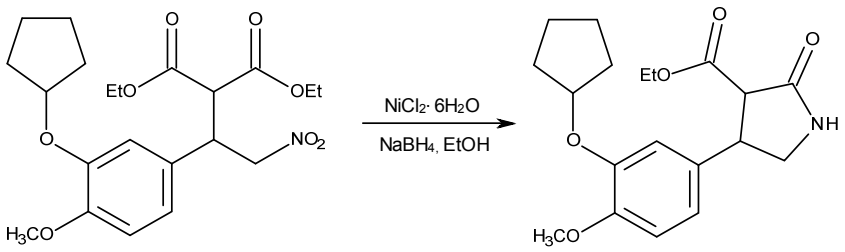
223 **224**

Triethylamine (0.6 mL) was added dropwise to a stirring solution of the nitro olefin (1.00 g, 3.80 mmol, 1 eq) and the diethyl malonate (2 mL, 11.4 mmol, 3 eq) in DCM (4 mL), The reaction mixture was allowed to stir at r.t. under a nitrogen atmosphere for 24 h until analysis by TLC indicated that all the nitro olefin had been consumed. The murky brown reaction mixture was quenched with ether and water (20 mL, 1:1) and extracted into DCM (3 x 15 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography with a solvent system of 10% EtOAc/Pet graduated to 20% afforded the title compound as a colourless solid (1.05 g, 65%) with data consistent to that reported in literature[190].

δ_H (400 MHz, $CDCl_3$): 0.97 (3H, t, *J* 7.1, C*H*$_3$), 1.17 (3H, t, *J* 7.1, C*H*$_3$), 1.46 - 1.60 (2H, m, cyclopentyl *H*), 1.68 - 1.90 (6H, m, cyclopentyl *H*), 3.71 (3H, s, OC*H*$_3$), 3.73 (1H, d, *J* 9.0, C*H*-C), 3.92 (2H, q, *J* 7.1, OC*H*$_2$), 4.03 - 4.09 (3H, m, Ar-C*H* and OC*H*$_2$), 4.67 - 4.69 (1H, m, OC*H*$(CH_2)_4$), 4.73 (1H, dd, *J* 12.9, 9.0, CH_ACH_BNO$_2$), 4.80 (1H, dd, *J* 12.9, 4.9, CH_ACH_BNO$_2$), 6.64 - 6.68 (2H, m, Ar*H*), 6.68 - 6.72 (1H, m, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 13.5 (*C*H_3), 13.7 (*C*H_3), 23.7 (2 x *C*H_2), 32.4 (2 x *C*H_2), 42.4 (Ar- *C),* 54.7 (*C*H=CO), 55.6 (Ar-O*C*H_3), 61.5 (O*C*H_2), 61.8 (O*C*H_2), 77.7 (*C*-NO_2), 80.1 [O*C*H$(CH_2)_4$], 111.6 (*qC*), 114.5 (*C*H), 119.9 (*C*H), 128.0 (*C*H), 147.3 (*qC*), 149.5 (*qC*), 166.6 (*C*=O), 167.3 (*C*=O).

3.8.4 Synthesis of ethyl-[3-cyclopentyloxy)-4-methoxyphenyl]-2-oxopyrrolidine-3-carboxylate



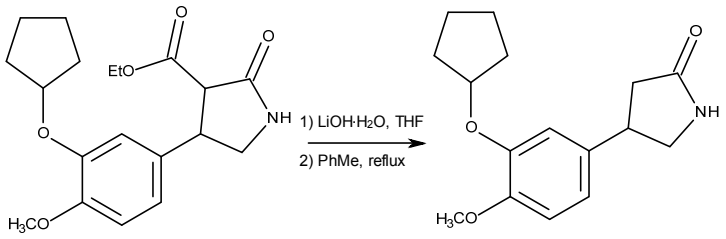
224 **225**

A stirred solution of the Michael adduct (0.400 g, 0.925 mmol, 1 eq) in ethanol (5 mL) was cooled to 0 °C before $NiCl_2{\cdot}6H_2O$ (0.220 g, 0.925 mmol, 1 eq) and sodium borohydride (0.385 g, 10.18 mmol, 11 eq) was added. The reaction mixture was then stirred for 2 h before being quenched with saturated aqueous ammonium chloride (20 mL). The solution was diluted with chloroform (20 mL), dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo* to obtain the title compound (0.315 g, 98%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 1.21 (3H, t, *J* 7.0, C*H*$_3$), 1.49 - 1.62 (2H, m, cyclopentyl *H*), 1.69 - 1.94 (6H, m, cyclopentyl *H*), 3.34 (1H, d, *J* 9.1, OC*H*$(CH_2)_4$), 3.46 (1H, d, *J* 9.8, C*H*-C), 3.68 - 3.78 (4H, m, Ar-OC*H*$_3$ and C*H*$_A$CH$_B$-NH), 3.96 (1H, dd, *J* 18.1, 8.6, CH$_A$C*H*$_B$-NH), 4.17 (2H, q, *J* 7.0, OC*H*$_2$), 4.66 - 4.76 (1H, m, Ar -C*H*), 6.67 - 6.80 (3H, m, Ar*H*), 7.66 (1H, brs, N*H*).

The data was found to be consistent with that reported in literature[190].

3.8.5 Synthesis of 3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidine-2-one



225 **221**

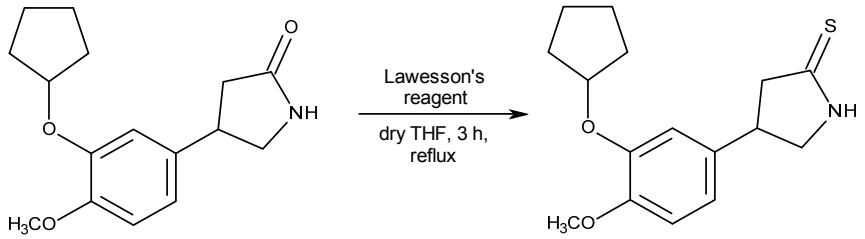
A stirred solution of the substituted pyrrolidinone (0.120 g, 0.345 mmol, 1 eq) in THF (5 mL) was treated with a solution of aqueous LiOH until pH 14. The reaction was allowed to stir at r.t. for 2 h and then acidified to pH 1 with HCl (1N). The aqueous layer was extracted with $CHCl_3$/IPA (3:1, 3 x 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was dissolved in toluene (10 mL) and refluxed overnight. Purification by flash silica gel chromatography (EtOAc) afforded the title compound, Rolipram, as a colourless solid (0.088 g, 93%), m.p 132-133 °C (Lit. 132-134°C).

δ_H (400 MHz, $CDCl_3$): 1.50 - 1.64 (2H, m, cyclopentyl *H*), 1.73 - 1.95 (6H, m, cyclopentyl *H*), 2.43 (1H, dd, *J* 16.9, 9.0, C*H*$_A$H$_B$CO), 2.67 (1H, dd, *J* 16.9, 9.0, CH$_A$*H*$_B$CO), 3.34 (1H, dd, *J* 9.0, 7.7, C*H*$_A$H$_B$NH), 3.53-3.61 (1H, m, ArC*H*), 3.71-3.74 (1H, m, CH$_A$*H*$_B$NH), 3.78 (3H, s, OC*H*$_3$), 4.65-4.81 (1H, m, OC*H*$(CH_2)_4$), 6.68 - 6.80 (3H, m, Ar*H*), 7.03 (1H, s, N*H*).

δ_C (100MHz, $CDCl_3$): 23.9 (2 x *C*H_2), 32.6 (2 x *C*H_2), 38.1 (*C*H_2), 39. 8 (Ar- *CH*), 49.7 (*C*H_2-CO), 56.0 (OC*H*$_3$), 80.4 (OC*H*$(CH_2)_4$), 111.9 (*qC*), 113.6 (*C*H), 118.6 (*C*H), 134.4 (*C*H), 147.7 (Ar-*C*O), 148.9 (Ar-*C*O), 178.0 (*C*=O).

The data was found to be consistent with that reported in literature[190].

3.8.6 Synthesis of the thioamide



221 **226**

Lawesson's reagent (0.162 g, 0.4 mmol, 0.5 eq) was added to a stirring solution of Rolipram (0.220 g, 0.800 mmol, 1 eq) in dry THF (8 mL), the reaction was allowed to stir at r.t. for 1 h and then heated to reflux for 2 h. It was then allowed to cool to r.t. and the solvent was removed *in vacuo*. Purification using flash silica gel chromatography (40% EtOAc: Pet) yielded the thioamide as a yellow oil (0.225, 97%).

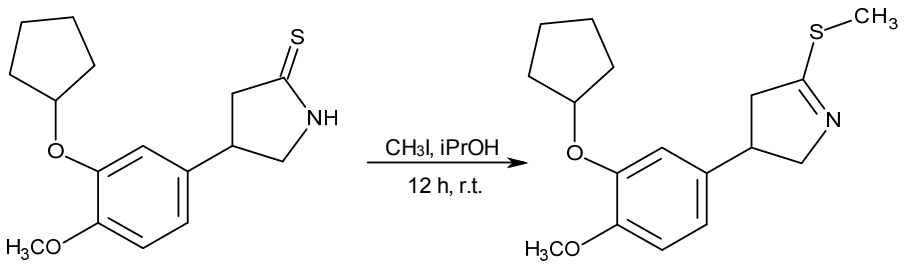
δ_H (400 MHz, $CDCl_3$): 1.53 - 1.64 (2H, m, cyclopentyl *H*), 1.74 - 1.96 (6H, m, cyclopentyl *H*), 2.99 (1H, dd, *J* 7.9, 17.9, C$H_A$$CH_B$CS), 3.28 (1H, dd, *J* 8.0, 17.9, CH_ACH_BCS), 3.57-3.61 (1H, m, C$H_A$$CH_B$NH), 3.70 (1H, m, ArC*H*), 3.80 (3H, s, OCH_3), 3.94 - 4.01 (1H, m, CH_ACH_BNH), 4.69- 4.71 (1H, m, OC*H*$(CH_2)_4$), 6.68 - 6.73 (2H, m, Ar*H*), 6.79 (1H, d, *J* 7.9, Ar*H*), 8.34 (1H, s, N*H*).

δ_C (100MHz, $CDCl_3$): 23.9 (2 x *C*H_2), 32.7 (2 x *C*H_2), 42.2 (Ar-*C*H), 50.6 (*C*H_2), 56.0 (O*C*H_3), 56.6 (*C*H_2), 80.6 (O*C*H$(CH_2)_4$), 112.1 (*qC*), 113.4 (*C*H), 118.7 (*C*H), 133.3 (*C*H), 147.9 (Ar-*C*O), 149.2 (Ar-*C*O), 205.2 (*C*=S).

ν_{max} (cm^{-1}): 3145 (br), 3033 (w), 2921 (w), 1687 (s), 1480 (m) 1120 (s).

HRMS (ESI^+): Found 314.1185 $[M+Na]^+$, $C_{16}H_{21}N_1O_2NaS$ requires 314.1185.

3.8.7 Synthesis of thioimidate



226 **227**

Iodomethane (6 mL) was added to a solution of thiolactam (0.275 g, 0.945 mmol, 1 eq) and 2-propanol (3 mL). The mixture was stirred under nitrogen for 12 h and the solvent

was removed *in vacuo.* The residue was treated with water (10 mL) and a solution of saturated potassium carbonate and extracted into ether (3 x 15 mL). The organic layers were combined, dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the mixture was then purified using silica gel chromatography (20% EtOAc: Pet) to give **227** as a yellow oil (0.101 g, 37%).

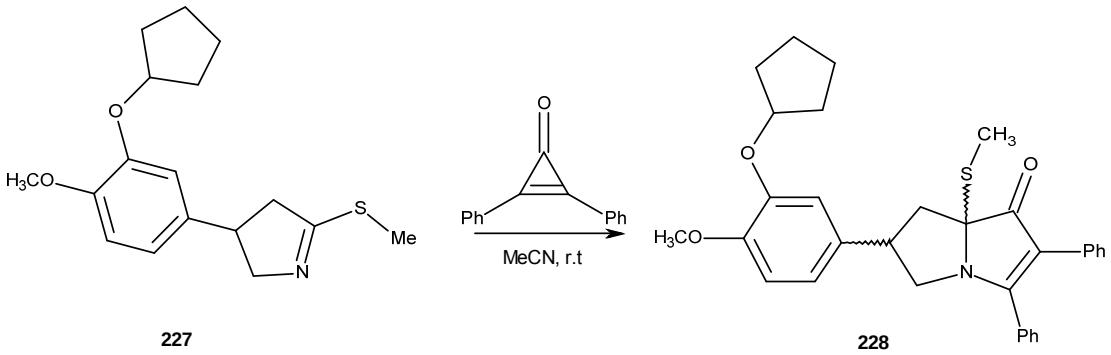
δ_H (400 MHz, $CDCl_3$): 1.51-1.68 (2H, m, cyclopentyl *H*), 1.70 - 2.01 (6H, m, cyclopentyl *H*), 2.37 (3H, s, SC*H*$_3$), 2.62 - 3.01 (1H, m, C*H*$_A$CH$_B$CS), 3.00 - 3.09 (1H, m, CH$_A$*CH*$_B$CS), 3.45 - 3.51 (2H, m, C*H*$_A$CH$_B$NH + Ar-C*H*), 3.83 (3H, s, OC*H*$_3$), 4.17 - 4.20 (1H, m, CH$_A$C*H*$_B$NH), 4.68 - 4.72 (1H, m, O*CH*$(CH_2)_4$), 6.45 - 6.68 (2H, m, Ar*H*), 6.70 - 6.76 (2H, m, Ar*H*).

δ_C (100MHz, $CDCl_3$): 24.0 (2 x *C*H_2), 32.8 (2 x *C*H_2), 43.6 (Ar-*CH*), 47.0 (*C*H_2-CS), 56.1 (O*C*H_3), 56.6 (*C*H_2N), 68.3 (S-*C*H_3), 80.4 (O*C*H$(CH_2)_4$), 112.1 (*C*H), 113.4 (*C*H), 118.7 (*C*H), 136.2 (*qC*), 147.7 (Ar-*C*O), 148.7 (Ar-*C*O), 173.2 (*C*=N).

ν_{max} (cm^{-1}): 2921 (w), 1655 [C=N] (s), 1590 (m), 1495 (m), 1152 (w).

HRMS (ESI^+): Found 306.1523 $[M+H]^+$, $C_{17}H_{24}NO_2S$ requires 306.1522.

3.8.8 Cycloaddition reaction of the thioimidate with DPP



Diphenylcyclopropenone (0.062 g, 0.301 mmol, 1 eq) was added to a solution of the thioimidate (0.092 g, 0.301 mmol, 1 eq) in dry MeCN (5 mL). The reaction was stirred at r.t. for 3 days. On completion of the reaction, the solvent was removed by rotary evaporation and subsequently purified by silica gel chromatography (20% EtOAc: Pet) to afford the indolizidine product as a yellow oil as a mixture of stereoisomers in a 1:1 ratio (0.021 g, 14%).

δ_H (400 MHz, $CDCl_3$): 1.49 - 1.63 (2H, m, cyclopentyl *H*), 1.72 - 1.93 (6H, m, cyclopentyl *H*), 1.98 (3H, s, SC*H*$_3$), 2.59 - 2.73 (2H, m, C*H*$_2$), 3.34 (1H, dd, *J* 9.2, 7.7, C*H*$_A$CH$_B$N), 3.53 - 3.61 (1H,

m, ArC*H*), 3.71 - 3.74 (1H, m, $CH_AC\mathit{H}_BN$), 3.78 (3H, s, $OC\mathit{H}_3$), 4.52 - 4.85 (1H, m, $OC\mathit{H}(CH_2)_4$), 6.50 - 6.77 (3H, m, Ar*H*), 6.97 - 7.56 (10H, m, Ar*H*).

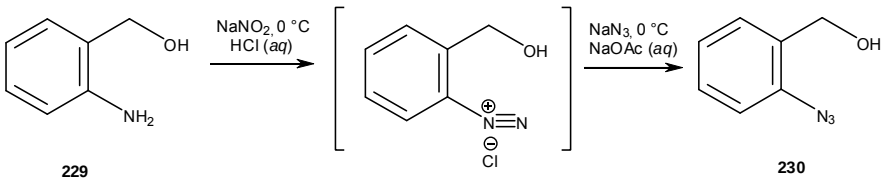
δ_C (100MHz, $CDCl_3$): 11.2/11.3 (S-Me), 23.9/24.0 ($\mathit{C}H_2$), 32.71/32.75 ($\mathit{C}H_2$), 37.91/37.93 ($\mathit{C}H_2$), 41.82/41.84 ($\mathit{C}H_2$), 43.41/43.43 ($\mathit{C}H$), 56.0/56.1 ($O\mathit{C}H_3$), 80.4/80.5 (OCH), 111.81/111.83 ($\mathit{C}H$), 114.0/114.2 ($\mathit{C}H$), 116.1/116.4 (*qC*), 117.80/117.84 (*qC*), 118.7/119.0 ($\mathit{C}H$), 126.2/126.3 ($\mathit{C}H$), 128.00/128.07 ($\mathit{C}H$), 128.6/128.7 ($\mathit{C}H$), 128.73/128.75 ($\mathit{C}H$), 129.56/129.57 ($\mathit{C}H$), 130.6/130.7 (*qC*), 130.9/131.1 (*qC*), 131.1/131.2 ($\mathit{C}H$), 131.3/132.1 (*qC*), 147.5/147.6 (*qC)*, 149.0/149.1 (*qC*), 174.8/175.8 (*qC*), 199.5/200.9 (C=O).

ν_{max} (cm^{-1}): 2931 (w), 1697 [C=O] (s), 1587 (m), 1491 (m), 1150 (w), 701 (w).

HRMS (ESI^+): Found 534.2011 $[M+Na]^+$, $C_{32}H_{33}NO_3SNa$ requires 534.2013.

3.9 Attempted synthesis of azido-substituted pyrrolizidine

3.9.1 Synthesis of *o*-azidobenzoyl alcohol



229 **230**

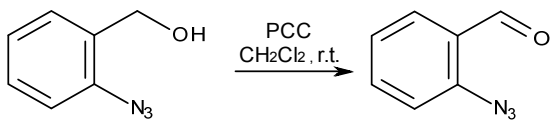
To a solution of *o*-aminobenzyl alcohol (1.00 g, 8.12 mmol, 1.0 eq) in concentrated hydrochloric acid (8 mL) and water (8 mL) at 0 °C, a solution of sodium nitrite (0.57 g, 8.20 mmol, 1.01 eq) in water (2 mL) was added dropwise over 10 min. The resulting reaction mixture was allowed to stir for an hour at 0 °C. It was then added dropwise (over an hour) to an ice cold solution of sodium azide (0.53 g, 8.12 mmol, 1.0 eq) and sodium acetate (7.50 g) in water (15 mL). The white precipitate so formed was filtered, washed with water and dried *in vacuo* to give the *o*-azidobenzyl alcohol as a fawn coloured crystalline solid (0.940 g, 78%). M.p: 50-51 °C (Lit m.p: 50-52 °C).

δ_H (400 MHz, $CDCl_3$): 2.14 (1H, br s, O*H*), 4.61 (2H, s, $C\mathit{H}_2OH$), 7.09 - 7.17 (2H, m, Ar*H*), 7.29 - 7.38 (2H, m, Ar*H*).

ν_{max} (cm^{-1}): 3346 (br), 2916 (m), 2815 (m), 2129 (s), 1582 (s), 1482 (m), 749 (s).

The data collected closely matched that reported in literature[201].

3.9.2 Synthesis of *o*-azidobenzaldehyde



230 **231**

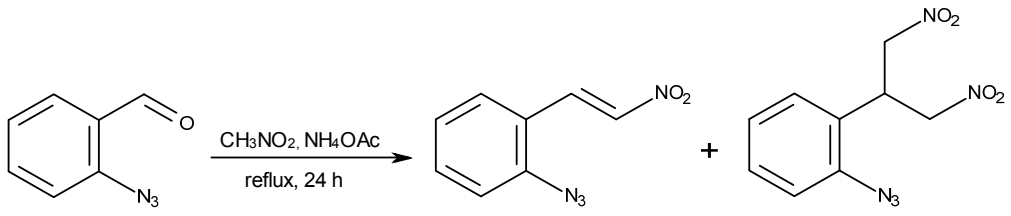
Pyridinium chlorochromate (7.37 g, 34.18 mmol, 1.7 eq) was added to a solution of o-azidobenzyl alcohol (3.00 g, 20.11 mmol, 1 eq) in anhydrous dichloromethane (25 mL) and the whole was stirred vigorously for 3 h at r.t. with occasional cooling in a water bath. The dark reaction mixture was washed thoroughly with ether (30 mL) and the supernatant liquid was removed by decantation. The black tar residue was washed thoroughly with EtOAc (5 x 20 mL) and the combined organic layers were collected, dried ($MgSO_4$), and filtered. The solvent was removed *in vacuo* and yielded *o*-azidobenzaldehyde as a brown oil (2.89 g, 98%).

δ_H (400 MHz, $CDCl_3$): 7.09 - 7.31 (2H, m, Ar*H*), 7.64 (1H, dd, *J* 7.3, 7.3, Ar*H*), 7.90 (1H, d, *J* 7.3, Ar*H*), 10.37 (1H, s, C*H*O).

δ_C (100 MHz, $CDCl_3$): 119.0 (*C*H), 124.9 (*qC*), 126.9 (*C*H), 129.0 (*C*H), 135.4 (*C*H), 142.9 (*qC*), 188.6 (*C*=O) .

ν_{max} (cm^{-1}): 3068 (m), 2858 (w), 2752 (w), 2123 (s), 1710 (s), 1686 (vs), 1593 (s), 1477 (m), 752 (s).

3.9.3 Synthesis of the corresponding nitro olefin (Henry reaction)



231 **232a**, 65% **232b**, 6%

To a stirred solution of the crude aryl aldehyde (0.51 g, 3.46 mmol, 1 eq) and nitromethane (30 mL) was added ammonium acetate (0.29 g, 3.80 mmol, 1.1 eq). The solution was heated to reflux for 20 h. The reaction mixture was concentrated *in vacuo* and then dissolved in CH_2Cl_2/H_2O (20 mL; 1:1). The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The resulting oil was purified using silica gel chromatography

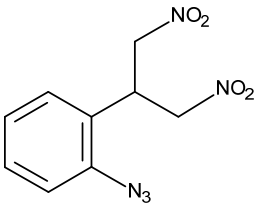
(5% - 10% EtOAc: Pet) which afforded the nitro olefin as a bright yellow solid (0.43 g, 65%) and the double addition product (minor product) was isolated as an orange oil (0.05 g, 6%).

δ_H (400 MHz, $CDCl_3$): 7.18 (1H, dd, *J* 8.2, 8.2, Ar*H*), 7.22 (1H, d, *J* 8.2, Ar*H*), 7.47 - 7.52 (2H, m, Ar*H*), 7.75 (1H, d, *J* 13.8, C*H*=CH), 8.14 (1H, d, *J* 13.8, CH=C*H*).

δ_C (100 MHz, $CDCl_3$) : 119.1 (*C*H), 121.4 (*qC*), 125.1 (*C*H), 130.6 (*C*H), 133.0 (*C*H), 134.1 (*C*H), 138.5 (*C*H), 140.4 (*qC*).

ν_{max} (cm^{-1}): 2124 [N_3](s), 1631 (w), 1556 (m), 1537 (m), 1495 (m), 1377 (m), 756 (s).

HRMS (ESI^+): Found 213.0381 $[M+Na]^+$, $C_8H_6N_4O_2Na$ requires 213.0382.



232b

Spectroscopic data of the double Henry product, **232b**:

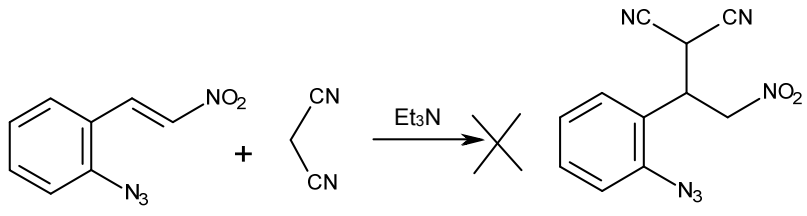
δ_H (400 MHz, $CDCl_3$): 4.53 (1H, m, C*H*(CH_2NO_2)$_2$, 4.85 (4H, d, *J* 6.9, CH(C*H*$_2$$NO_2$)$_2$, 7.11 (1H, dd, *J* 7.6, 7.6, ArH), 7.21 (2H, m, Ar*H*), 7.41 (1H, ddd, *J* 7.6, 7.6, 1.6, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 37.6 (*C*H), 74.5 (*C*H_2), 118.3 (*C*H), 124.2 (*qC*), 124.8 (*C*H), 129.8 (*C*H), 130.4 (*C*H), 138.1 (*qC*).

ν_{max} (cm^{-1}): 2123[N_3] (s), 1635 (w), 1543 (m), 1340 (m), 759 (s).

HRMS (ESI^+): Found 274.0557 $[M+Na]^+$, $C_9H_9N_5O_4Na$ requires 274.0547.

3.9.4 Attempted Michael reaction with malanonitrile

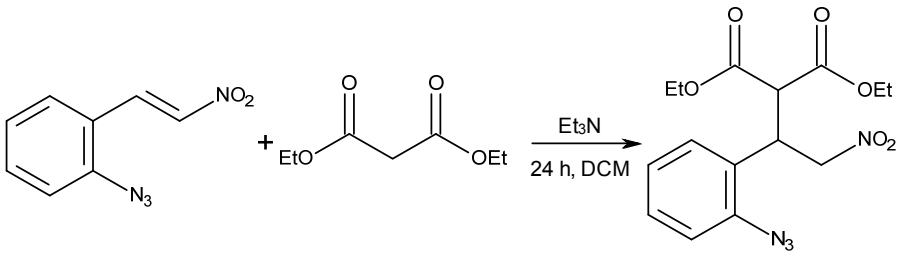


232a

To a stirring solution of the nitro olefin (0.27 g, 1.41 mmol, 1 eq) in DCM (8 mL), malanonitrile (0.1 mL, 0.10 g, 1.55 mmol, 1.1 eq) and triethylamine (0.5 mL) were added dropwise. The reaction mixture was stirred at r.t. for 2 h and monitored by TLC. The reaction was purified by silica gel chromatography (10% EtOAc: Pet) but the products isolated were the decomposed starting material.

3.10. Reaction with malonic esters

3.10.1 Synthesis of the Michael addition product



232a **233a**

To a stirred solution of the nitro olefin (0.360 g, 1.89 mmol, 1 eq) in DCM (8 mL), diethyl malonate (0.86 mL, 0.90 g, 5.67 mmol, 3 eq) and triethylamine (0.5 mL) were added dropwise. The reaction mixture was allowed to stir at r.t. for 24 h until analysis by TLC indicated all the nitro olefin had been consumed. The murky brown reaction mixture was quenched with ether and water (1:1, 50 mL) and extracted into DCM (3 x 15 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography [10% EtOAc: Pet graduated to 20%] afforded the Michael adduct as a pale yellow oil (0.385 g, 58%).

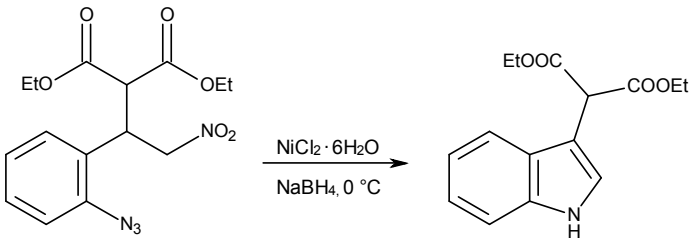
δ_H (500 MHz, $CDCl_3$): 0.98 (3H, t, *J* 7.1, C*H*$_3$), 1.18 (3H, t, *J* 7.1, C*H*$_3$), 3.93 (2H, q, *J* 7.1, OC*H*$_2$), 4.07 (1H, d, *J* 9.4, *CH*-CO), 4.15 (2H, q, *J* 7.1, OC*H*$_2$), 4.38 (1H, dt, *J* 9.4, 4.5, C*H*-Ar), 4.85 (1H, dd, *J* 13.2, 4.5, CH_AH$_B$NO$_2$), 4.98 (1H, dd, *J* 13.2, 4.5, CH$_A$$H_BNO_2$), 7.01 (1H, dd, *J* 7.8, 1.2, Ar*H*), 7.10 (1H, d, *J* 7.7, Ar*H*), 7.15 (1H, d, *J* 7.7, ArH), 7.26 (1H, dd, *J* 7.8, 1.2, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 13.5 (*C*H$_3$), 13.7 (*C*H$_3$), 39.2 (*C*H), 52.9 (*C*H), 61.6 (*C*H$_2$), 61.8 (*C*H$_2$), 75.8 (*C*H$_2$), 118.5 (*C*H), 124.8 (*C*H), 126.9 (*qC*), 129.5 (*C*H), 130.3 (*C*H), 138.1 (*qC*), 166.6 (*C*=O), 167.3 (*C*=O).

ν_{max} (cm^{-1}): 2984 (w), 2125 (s), 1729 (s), 1282 (w), 1553 (s), 1491 (m), 1491 (m), 1369 (m), 754 (s).

HRMS (ESI$^+$): Found 373.1119 $[M+Na]^+$, $C_{15}H_{18}N_4O_6Na$ requires 373.1122.

3.10.2 Synthesis of the substituted indole



233a **235a**

To a stirred solution of adduct **233a** (0.200 g, 0.57 mmol, 1 eq) and $NiCl_2{\cdot}6H_2O$ (0.136 g, 0.57 mmol, 1 eq) in EtOH (5 mL) was added $NaBH_4$ (0.238 g, 6.28 mmol, 11 eq) at 0 °C. The reaction was stirred at 0 °C for 2 h before being quenched with saturated aqueous NH_4Cl (20 mL). The solution was diluted with $CHCl_3$ (20 mL) and extracted into $CHCl_3$ (3 x 10 mL), dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo.* The crude mixture was purified by chromatography to afford the indole product as an off white solid (0.155 g, 99%).

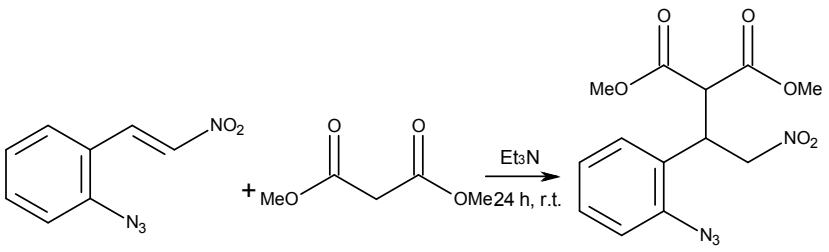
δ_H (400 MHz, $CDCl_3$): 1.25 (6H, t, *J* 7.1, CH_3CH_2), 4.16 - 4.25 (4H, m, CH_2CH_3), 4.92 (1H, s, *CH*-CO), 7.13 (1H, ddd, *J* 7.3, 7.3, 1.2, Ar*H*), 7.19 (1H, ddd, *J* 7.3, 7.3, 1.2, Ar*H*), 7.34 (1H, d, *J* 8.0, Ar*H*), 7.36 (1H, d, *J* 2.5, indole C*H*), 7.64 (1H, d, *J* 8.0, Ar*H*), 8.23 (1H, s, N*H*).

δ_C (100 MHz, $CDCl_3$): 14.0 (CH_3), 49.7 (*C*H), 61.7 (CH_2), 107.6 (*q*C), 111.5 (*C*H), 119.5 (*C*H), 120.4 (*C*H), 122.6 (*C*H), 124.2 (Indole *C*H), 126.6 (*qC*), 135.9 (*qC*), 167.9 (*C*=O).

ν_{max} (cm^{-1}): 3391 (br), 2980 (w), 1726 (s), 1620 (w), 1458 (w), 1298 (m), 1026 (m).

HRMS (ESI$^+$): Found 298.1050 $[M+Na]^+$, $C_{15}H_{17}NO_4Na$ requires 298.1050.

3.10.3 Synthesis of the dimethyl derivative



232a **235b**

To a stirring solution of the nitro olefin (0.360 g, 1.89 mmol, 1 eq) in DCM (8 mL) dimethyl malonate (0.65 mL, 0.747 g, 5.67 mmol, 3 eq) and triethylamine (0.5 mL) were added dropwise. The reaction mixture was allowed to stir at r.t. for 24 h until analysis by TLC indicated that all the nitro olefin had been consumed. The murky brown reaction mixture was quenched with ether (5 mL) and water (30 mL) and was extracted into DCM (3 x 15 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude mixture was purified using silica gel column chromatography [10% EtOAc: Pet graduated to 20%] to yield the Michael adduct as a white solid (0.370 g, 61%).

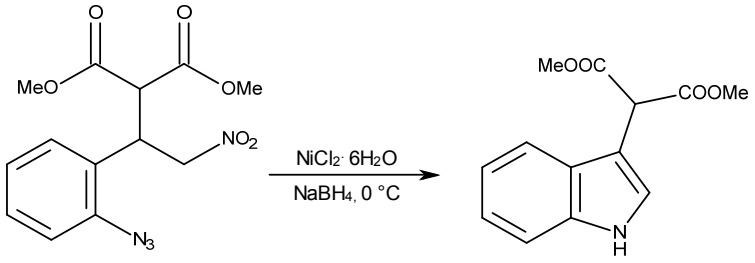
δ_H (400 MHz, $CDCl_3$): 3.55 (3H, s, O*CH₃*), 3.72 (3H, s, O*CH₃*), 4.13 (1H, d, *J* 9.4, *CH*-CO), 4.38 - 4.46 (1H, m, C*H*-Ar), 4.86 (1H, dd, *J* 4.6, 13.2, CH_AH_B), 5.00 - 5.08 (1H, m, CH_AH_B), 7.05 (1H, dd, *J* 7.7, 7.7, Ar*H*), 7.11 - 7.20 (2H, m, Ar*H*), 7.31 (1H, dd, *J* 7.7, 7.7, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 39.2 (*C*H), 52.6 (*C*H), 52.8 (*C*H_3), 52.9 (*C*H_3), 75.6 (*C*H_2), 118.7 (*C*H), 124.8 (Ar*C*H), 126.6 (*qC*), 129.7 (*C*H), 130.1 (*C*H), 138.0 (*qC*), 167.2 (*C*=O), 167.8 (*C*=O).

ν_{max} (cm^{-1}): 3371 (br), 2965 (w), 1731 (s), 1622 (w), 1540 (w), 1345 (m), 735 (s)

HRMS (ESI^+): Found 345.0811 $[M+Na]^+$, $C_{13}H_{14}N_4O_6Na$ requires 345.0806.

3.10.4 Synthesis of the dimethyl derivative indole



233b **235b**

To the solution of the Michael adduct **233b** (0.20 g, 0.62 mmol, 1 eq) in EtOH (10 mL), $NiCl_2 \cdot 6H_2O$ (0.15 g, 0.62 mmol, 1 eq) and $NaBH_4$ (0.260 g, 6.83 mmol, 11 eq) were added. The reaction temperature was maintained at 0 °C and allowed to stir for 2 h. It was then quenched with saturated NH_4Cl (20 mL), diluted with $CHCl_3$ (20 mL) and extracted into $CHCl_3$ (3 x 20 mL), dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo* to afford an indole product as a white solid (0.142 g, 93%).

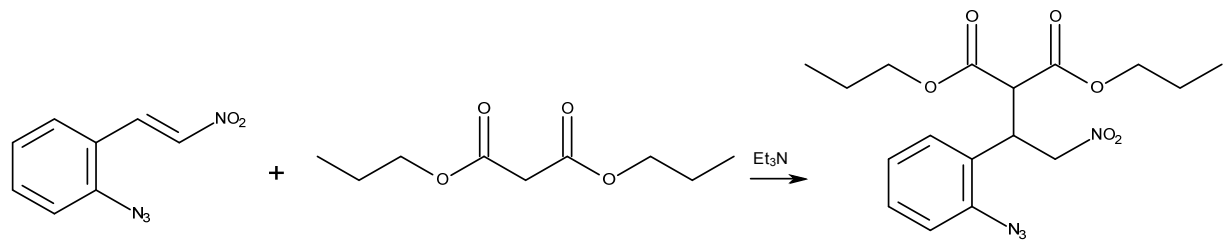
δ_H (400 MHz, $CDCl_3$): 3.76 (6H, s, O*CH₃*), 4.96 (1H, s, C*H*), 7.13 (1H, ddd, *J* 7.6, 7.6, 1.0, Ar*H*), 7.19 (1H, ddd, *J* 7.6, 7.6, 1.0, Ar*H*), 7.34 (1H, d, *J* 8.0, Ar*H*), 7.36 (1H, d, *J* 2.5, Indole C*H*), 7.61 (1H, d, *J* 8.0, Ar*H*), 8.25 (1H, s, N*H*).

δ_C (100 MHz, $CDCl_3$): 49.7 (*C*H), 52.7 (*C*H_3), 52.8 (*C*H_3), 107.4 (*qC*), 111.3 (*C*H), 119.0 (*C*H), 120.1 (*C*H), 122.4 (*C*H), 124.0 (Indole *C*H), 126.5 (*qC*), 135.9 (*qC*), 169.0 (*C*=O).

ν_{max} (cm^{-1}): 3370 (br), 1742 (s), 1511 (w), 1434 (w), 1315 (w), 1250 (m), 1198 (m), 745 (s).

HRMS (ESI^+): Found 270.0767 $[M+Na]^+$, $C_{13}H_{13}NO_4Na$ requires 270.0770.

3.10.5. Synthesis of the dipropyl adduct



232a **233c**

The dipropyl Michael adduct was successfully synthesised as a pale yellow solid (0.480 g, 60%) from the azidonitro styrene (0.405 g, 2.13 mmol, 1 eq), dipropyl malonate (0.4 mL, 0.401 g, 2.13 mmol, 1 eq) and triethylamine (0.6 mL) after stirring at r.t. for 5 days in DCM (10 mL) and was purified with 10% EtOAc: Pet as the eluent using silica gel chromatography.

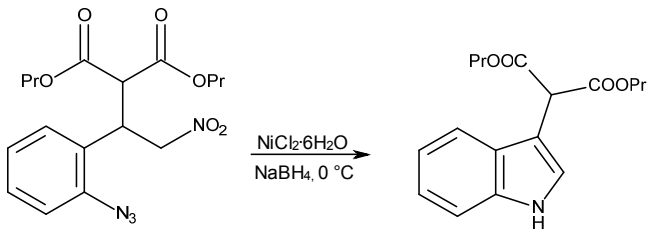
δ_H (400 MHz, $CDCl_3$): 0.76 (3H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.36 - 1.47 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 3.85 (2H, q, *J* 7.1, OC*H*$_2$), 4.11 (1H, m, C*H*-CO), 4.39 (1H, dd, *J* 9.4, 4.4, C*H*-Ar), 4.84 (1H, dd, *J* 13.2, 4.4, C*H*$_A$H$_B$NO$_2$), 5.01 (1H, dd, *J* 13.2, 9.4, CH$_A$*H*$_B$NO$_2$), 7.01 (1H, dd, *J* 7.7, 1.2, Ar*H*), 7.10 (1H, ddd, *J* 8.0, 8.0, 1.3, Ar*H*), 7.16 (1H, dd, *J* 7.7, 1.2, Ar*H*), 7.27 (1H, ddd, *J* 8.0, 8.0, 1.3, Ar*H*).

δ_C (100 MHz, $CDCl_3$) : 10.13 (*C*H_3), 10.18 (*C*H_3), 21.3 (*C*H_2), 21.7 (*C*H_2), 39.3 (*C*H), 52.9 (*C*H), 67.3 (O*C*H_2), 67.6 (O*C*H_2), 75.9 (*C*H_2), 118.7 (*C*H), 125.0 (*C*H), 126.8 (*qC*), 129.6 (*C*H), 130.3 (*C*H), 138.1 (*qC*), 167.0 (*C*=O), 167.6 (*C*=O).

ν_{max} (cm^{-1}): 2969 (w), 2127 [N_3] (s), 1731 (vs), 1592 (m), 1556 (m), 1378 (w), 756 (s).

HRMS (ESI^+): Found $[M+Na]^+$ 401.1442, $C_{17}H_{22}N_4O_6Na$ requires 401.1431.

3.10.6 Reduction of the dipropyl Michael adduct using $NiCl_2 \cdot 6H_2O$



233c **235c**

Following its successful formation, the dipropyl Michael adduct (0.233 g, 0.60 mmol, 1 eq) was reduced with $NiCl_2 \cdot 6H_2O$ (0.144 g, 0.60 mmol, 1 eq) and $NaBH_4$ (0.251 g, 6.63 mmol, 11 eq) in EtOH (10 mL) at 0 °C for 2 h to afford an indole product as a yellow oil (0.162 g, 89%) purified with silica chromatography eluted by 15% EtOAc: Pet.

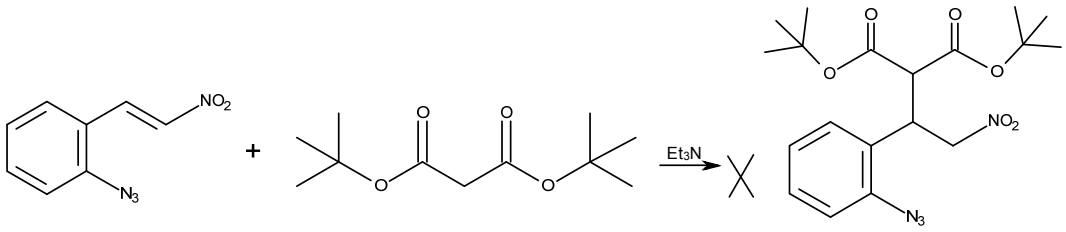
δ_H (400 MHz, $CDCl_3$): 0.88 (6H, t, *J* 7.1, 2 x OC*H*$_3$), 1.62 - 1.64 (4H, m, 2 x C*H*$_2$), 4.09 - 4.11 (4H, m, OC*H*$_2$), 4.94 (1H, s, C*H*-CO), 7.12 (1H, dd, *J* 7.4, 7.4, Ar*H*), 7.18 (1H, dd, *J* 7.4, 7.4, Ar*H*), 7.33 (1H, d, *J* 7.9, Ar*H*), 7.38 (1H, d, *J* 2.3, Indole C*H*), 7.63 (1H, d, *J* 7.9, Ar*H*), 8.21 (1H, s, N*H*).

δ_C (100 MHz, $CDCl_3$): 10.3 (*C*H_3), 21.8 (*C*H_2), 49.7 (*C*H), 67.2 (*C*H_2), 107.6 (*qC*), 111.2 (*C*H), 119.1 (*C*H), 119.9 (*C*H), 122.3 (CH), 124.0 (*C*H), 126.6 (*qC*), 135.8 (*qC*), 168.7 (*C*=O).

ν_{max} (cm^{-1}): 3372 (br), 2929 (m), 1739 (s), 1619 (w), 1456 (w), 1315 (w), 1250 (m).

HRMS (ESI^+): Found 326.1361 $[M+Na]^+$, $C_{17}H_{21}NO_4Na$ requires 326.1363.

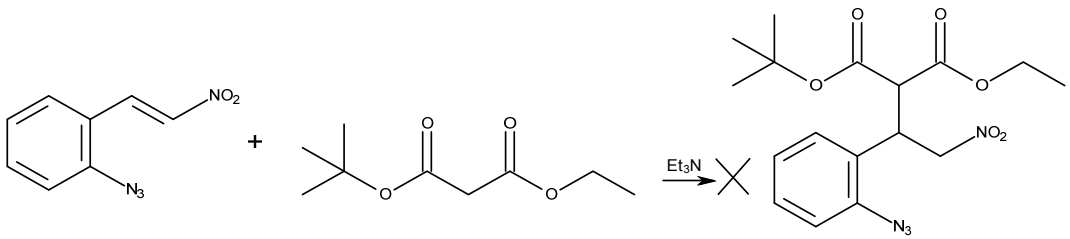
3.10.7 Attempted Michael reaction with di-*tert*-butyl malonate



232a

To a stirring solution of the nitro olefin (0.500 g, 2.63 mmol, 1 eq) in DCM (10 mL), di-*tert*-butyl malonate (1.1 mL, 1.13 g, 5.26 mmol, 2 eq) and triethylamine (0.5 mL) were added dropwise. The reaction mixture was allowed to stir at r.t. for 5 days. It was then heated gently yet the reaction mixture remained unchanged and yielded both the starting materials unreacted and unchanged.

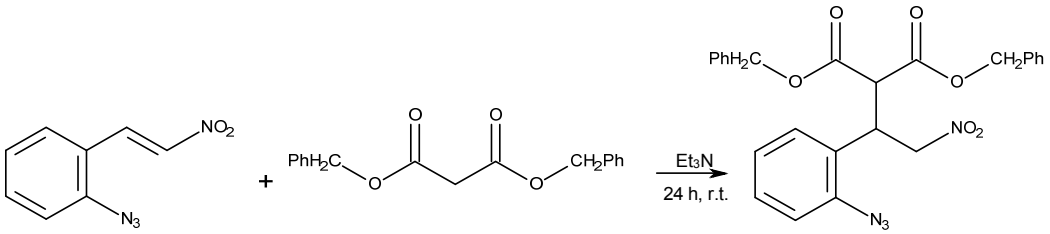
3.10.8 Attempted Michael reaction with *tert*-butyl ethyl malonate



232a

To a stirring solution of the nitro olefin (0.470 g, 2.47 mmol, 1 eq) in DCM (10 mL), *tert*-butyl ethyl malonate (0.42 mL, 0.434 g, 2.50 mmol, 1.05 eq) and triethylamine (0.50 mL) were added dropwise. The reaction mixture was allowed to stir at r.t. for 5 days. It was then heated gently but the mixture remained unchanged as seen on TLC.

3.10.9 Synthesis of the dibenzyl Michael adduct



232a **233d**

The dibenzyl Michael adduct was successfully synthesised as a brown oil (0.365 g, 55%) from azido nitrostyrene (0.265 g, 1.39 mmol, 1 eq), dibenzyl malonate (0.35 mL, 0.396 g, 1.39 mmol, 1 eq) and triethylamine (0.5 mL) after stirring at r.t. for 7 days in DCM and purified by silica gel chromatography with 15% EtOAc: Pet solvent system (graduated to 20%).

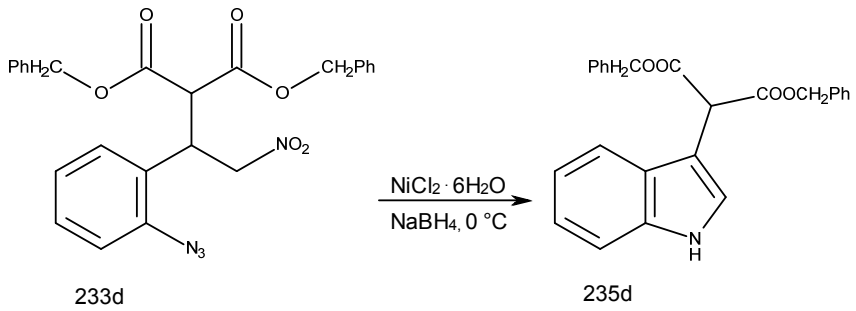
δ_H (400 MHz, $CDCl_3$): 3.47 (2H, s, OCH_2), 4.24 (1H, m, C*H*-C), 4.44 (1H, dt, *J* 9.4, 4.4, C*H*-Ar), 4.80 (1H, dd, *J* 13.2, 4.4, CH_ACH_B), 4.98 (1H, dd, *J* 13.2, 9.4, CH_ACH_B), 6.97 (1H, dd, *J* 7.6, 7.6, Ar*H*), 7.05 - 7.10 (4H, m, Ar*H*), 7.24 - 7.29 (5H, m, Ar*H*), 7.30 - 7.36 (4H, m, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 39.3 (*C*H), 52.9 (*C*H), 67.5 (O*C*H_2), 67.7 (O*C*H_2), 75.8 (*C*H_2), 118.7 (*C*H), 125.0 (*C*H), 126.4 (*qC*), 127.49 (*C*H), 127.51 (*C*H), 128.52 (*C*H), 128.58 (*C*H), 128.65 (*C*H), 128.68 (*C*H), 129.6 (*C*H), 130.3 (*C*H), 136.1 (*qC*), 138.0 (*qC*), 166.5 (*C*O), 167.2 (*C*O).

ν_{max} (cm^{-1}): 3033 (w), 2956 (w), 2127 (s), 1731 (vs), 1582 (m), 1553 (m), 1327 (m), 748 (s).

HRMS (ESI^+): Found 497.1445 $[M+Na]^+$, $C_{25}H_{22}N_4O_6Na$ requires 497.1432.

3.10.10 Synthesis of the dibenzyl indole



233d 235d

The dibenzyl Michael adduct (0.305 g, 0.64 mmol, 1 eq) was reduced with $NiCl_2 \cdot 6H_2O$ (0.153 g, 0.64 mmol, 1 eq) and $NaBH_4$ (0.268 g, 7.07 mmol, 11 eq) in EtOH (20 mL) at 0 °C for 2 h to afford an indole product as a brown oil (0.020 g, 8%) purified with silica chromatography eluted with 15% EtOAc: Pet.

δ_H (400 MHz, $CDCl_3$): 4.15 - 4.25 (2H, m, OCH_2), 4.92 (1H, s, C*H*), 7.06 - 7.21 (3H, m, Ar*H*), 7.26 - 7.31 (3H, m, Ar*H*), 7.33 - 7.40 (3H, m, Ar*H*), 7.56 - 7.65 (1H, m, Ar*H*), 8.19 (1H, s, N*H*).

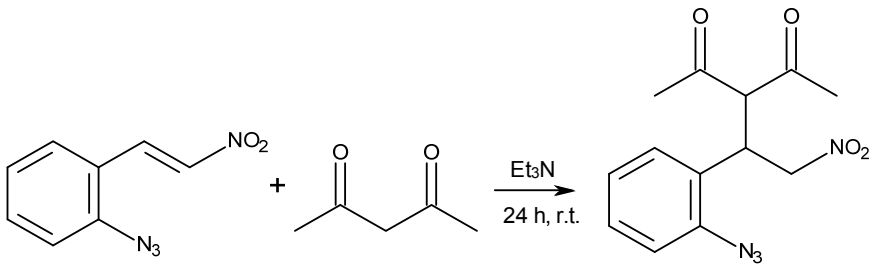
δ_C (100 MHz, $CDCl_3$): 49.7 (*C*H), 67.4 (*C*H_2), 107.6 (*qC*), 111.2 (*C*H), 119.1 (*C*H), 120.1 (*C*H), 122.4 (*C*H), 124.1 (Indole *C*H), 126.4 (*qC*), 128.1 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 135.3 (*q*C), 136.2 (*q*C), 168.2 (*C*=O).

ν_{max} (cm^{-1}): 3370 (br), 2932 (m), 1740 (s), 1615 (m), 1501 (m).

HRMS (ESI^+): Found 422.1362 $[M+Na]^+$, $C_{25}H_{21}NO_4Na$ requires 422.1378.

3.11 Reactions with diketones

3.11.1 Synthesis of the diketo Michael adduct



232a **236**

The diketo Michael adduct was obtained as a yellow oil (0.395 g, 65%) from azido nitrostyrene (0.400 g, 2.10 mmol, 1 eq), 2, 4-pentadione (0.5 mL, 0.42 g, 4.21 mmol, 2 eq) and

triethylamine (0.5 mL) after stirring at r.t. for 4 h. The crude mixture was purified by silica gel chromatography eluting with 20% EtOAc: Pet graduated to 25%.

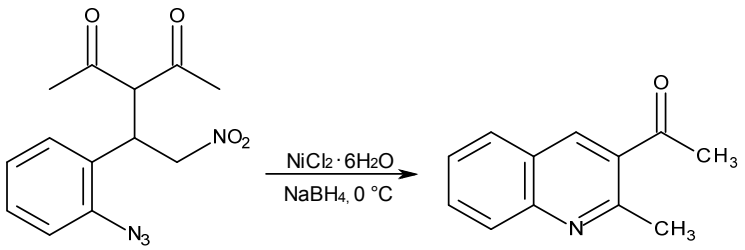
δ_H (400 MHz, $CDCl_3$): 1.94 (3H, s, C*H*$_3$), 2.22 (3H, s, C*H*$_3$), 4.40 - 4.49 (1H, m, C*H*-CO), 4.51 - 4.59 (2H, m, C*H*$_2$NO$_2$), 4.72 - 4.74 (1H, m, C*H*-Ar), 6.99 - 7.15 (3H, m, Ar*H*), 7.28 (1H, dd, *J* 7.7, 7.7, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 29.1 (*C*H$_3$), 30.8 (*C*H$_3$), 38.6 (*C*H), 69.2 (*C*H), 76.4 (*C*H$_2$), 119.0 (*C*H), 125.6 (*C*H), 126.7 (*qC*), 129.8 (*C*H), 130.0 (*C*H), 138.2 (*qC*), 201.3 (*C*=O), 202.2 (*C*=O).

ν_{max} (cm^{-1}): 2124 (s), 1698 (m), 1550 (m), 1489 (m), 1149 (m), 1356 (m), 754 (s).

HRMS (ESI$^+$): Found 313.0920 $[M+Na]^+$, $C_{13}H_{14}N_4O_4Na$ requires 313.0907.

3.11.2 Reduction of the diketone Michael adduct



236 **238**

The diketo Michael adduct (0.350 g, 1.21 mmol, 1 eq) in ethanol (5 mL) was cooled to 0 °C after which $NiCl_2 \cdot 6H_2O$ (0.290 g, 1.21 mmol, 1 eq) and $NaBH_4$ (0.505 g, 6.83 mmol, 11 eq) were added. The reaction mixture was stirred for 2 h at 0 °C and was then quenched with saturated aqueous NH_4Cl (20 mL), diluted with $CHCl_3$ (20mL) and extracted into $CHCl_3$ (3 x 20 mL), dried ($MgSO_4$), filtered through Celite and concentrated *in* vacuo. The crude mixture was purified by column chromatography (30% EtOAc: Pet; graduated to 35%) to afford the quinoline product as a brown oil (0.025 g, 11%)[214].

δ_H (400 MHz, $CDCl_3$): 2.70 (3H, s, C*H*$_3$), 2.90 (3H, s, C*H*$_3$), 7.54 (1H, dd, *J* 7.4, 7.4, Ar*H*), 7.77 (1H, d, *J* 7.4, Ar*H*), 7.85 (1H, d, *J* 8.1, Ar*H*), 8.03 (1H, dd, *J* 8.1, 8.1, Ar*H*), 8.48 (1H, s, C*H*).

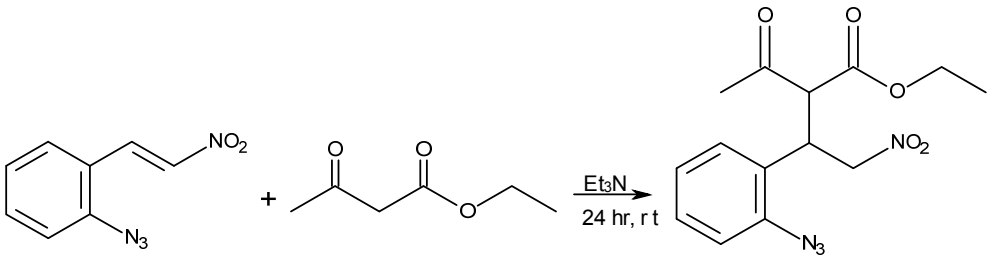
δ_C (100 MHz, $CDCl_3$): 26.1 (*C*H$_3$), 29.7 (*C*H$_3$), 126.0 (*C*H), 127.1 (*C*H), 128.8 (*q*C), 129.1 (CH), 131.4 (*q*C), 132.2 (*C*H), 138.7 (*C*H), 148.7 (*qC*), 158.0 (*qC*), 199.8 (*C*=O).

ν_{max} (cm^{-1}): 3101 (w), 2921 (w), 1730 (s), 1592 (w), 1495 (w), 744 (s).

HRMS (ESI$^+$): Found 186.0920 $[M + H]^+$, $C_{12}H_{12}NO$ requires 186.0916.

3.12 Reaction with a mixed substrate i.e. keto ester

3.12.1 Michael reaction with ethylacetoacetate



232 **237**

The adduct was obtained as a yellow oil (0.205 g, 61%) from azidonitro styrene (0.200 g, 1.05 mmol, 1eq), ethylacetoacetate (0.14 mL, 0.137 g, 1.05 mmol, 1 eq) and triethylamine (0.4 mL) after stirring at r.t. for 4 h in DCM (8 mL). The crude mixture was purified by silica gel chromatography eluting with 10% EtOAc: Pet solvent system. The Michael adduct was isolated as a mixture of diasteroisomers in 1:1 ratio.

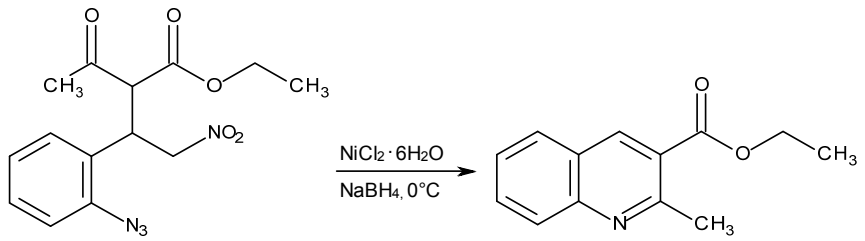
δ_H (500 MHz, $CDCl_3$): 0.99 / 1.24 (3H, t, *J* 7.1, C*H*$_3$), 2.12 / 2.27 (3H, s, C*H*$_3$), 3.95 / 4.19 (2H, q, *J* 7.1, C*H*$_2$), 4.32 (1H, d, *J* 9.2, C*H*-CO), 4.41 - 4.47 (2H, m, C*H*+C*H*), 4.51 (1H, dt, *J* 9.2, 4.3, C*H*-Ar), 4.74 (1H, dd, *J* 13.2, 4.3, CH_ACH$_B$), 4.83 - 4.95 (2H, m, CH_ACH_B), 5.05 (1H, m, CH$_A$CH_B), 7.07 - 7.14 (2H, m, Ar*H*), 7.17 - 7.22 (4H, m, Ar*H*), 7.32 - 7.39 (2H, m, Ar*H*).

δ_C (125 MHz, $CDCl_3$): 13.4/13.7 (*C*H$_3$), 29.6/29.7 (*C*H$_3$), 38.0/38.3 (*C*H), 59.6/59.8 (*C*H), 61.6/61.9 (*C*H$_2$), 75.7/76.0 (*C*H$_2$), 118.4/118.5 (*C*H), 124.8/124.9 (*C*H), 126.8/126.9 (*qC*), 129.5/129.6 (*C*H), 129.9/130.2 (*C*H), 137.9/138.1 (*qC*), 167.3/167.6 (*C*=O), 200.3/200.7 (*C*=O).

ν_{max} (cm^{-1}): 2980 (m), 2126 (s), 1736 (s), 1715 (s), 1581 (m), 1551 (m), 1490 (m), 1375 (w), 753 (s).

HRMS (ESI$^+$): Found 343.0998 $[M+Na]^+$, $C_{14}H_{16}N_4O_5Na$ requires 343.1013.

3.12.2 Reduction of the keto-ester Michael adduct



237 **239**

The Michael adduct (0.200 g, 0.62 mmol, 1 eq) in EtOH (5 mL) was cooled to 0 °C after which $NiCl_2{\cdot}6H_2O$ (0.150 g, 0.62 mmol, 1 eq) and $NaBH_4$ (0.260 g, 0.68 mmol, 11 eq) were added. The reaction mixture was stirred for 2 h at 0 °C and was then quenched with saturated aqueous NH_4Cl (20 mL), diluted with $CHCl_3$ (20mL) and extracted into $CHCl_3$ (3 x 20 mL), dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo.* The crude mixture was purified by column chromatography (30% EtOAc: Pet) to afford the quinoline product, ethyl 2-methylquinoline-3-carboxylate as a dark yellow solid (0.012 g, 9%). M.p 68-70 °C (Lit values, 69-70 °C)[214].

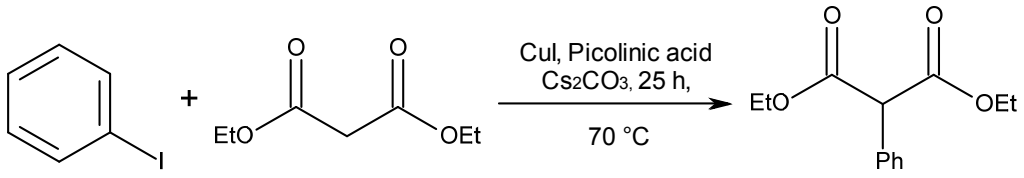
δ_H (400 MHz, $CDCl_3$): 1.43 (3H, t, *J* 7.1, C*H*$_3$-CH_2), 2.97 (3H, s, C*H*$_3$), 4.42 (2H, q, *J* 7.1, OC*H*$_2$), 7.51 (1H, dd, *J* 7.6, 7.6, Ar*H*), 7.75 (1H, dd, *J* 7.6, 7.6, Ar*H*), 7.84 (1H, d, *J* 8.0, Ar*H*), 8.02 (1H, d, *J* 8.0, Ar*H*), 8.71 (1H, s, C*H*).

δ_C (100 MHz, $CDCl_3$): 14.3 (*C*H_3), 25.6 (*C*H_3), 61.4 (*C*H_2), 123.9 (*qC*), 125.7 (*qC*), 126.5 (*C*H), 128.4 (*C*H), 128.5 (*C*H), 131.7 (*C*H), 139.9 (*C*H), 148.5 (*qC*), 158.5 (*qC)*, 166.5 (C=O).

ν_{max} (cm^{-1}): 3050 (w), 2927 (w), 1711 (s), 1594 (w), 1492 (w), 747 (s).

HRMS (ESI^+): Found 216.1019 $[M+H]^+$, $C_{13}H_{14}NO_2$ requires 216.1019.

3.12.3 Synthesis of diethyl phenyl malonate



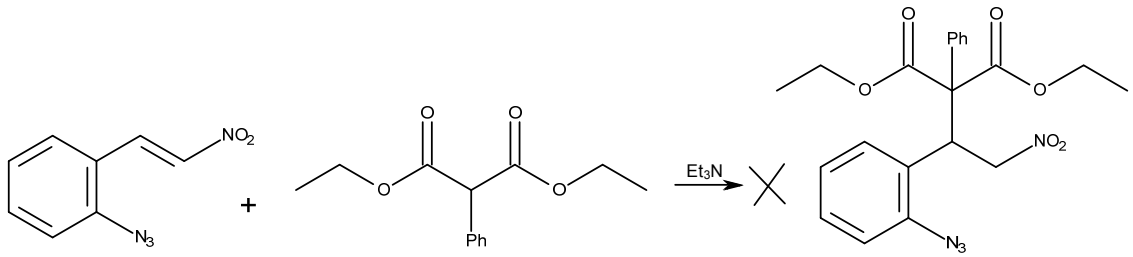
To a solution of iodobenzene (1.11 mL, 2.04 g, 10 mmol, 1 eq) in anhydrous dioxane (10 mL) was added diethyl malonate (3.04 mL, 20 mmol, 2 eq), 2-picolinic acid (0.123 g, 1 mmol, 10 mol%), CuI (0.095 g, 0.5 mmol, 5 mol%) and Cs_2CO_3 (9.8 g, 30 mmol, 3 eq). The reaction was

stirred at 70 °C for 25 h. It was then cooled to ambient temperature and quenched with saturated aqueous NH_4Cl and extracted into EtOAc (2 x 30 mL). Purification by silica gel chromatography (8% EtOAc: Pet) gave the substituted diethyl phenyl malonate as a pale yellow oil (1.21 g, 51%).

δ_H (400 MHz, $CDCl_3$): 1.24 (6H, dt, *J* 7.2, 2.0, 2 x C*H*$_3$-CH_2), 4.42 (4H, dq, *J* 7.2, 2.0, OC*H*$_2$), 4.64 (1H, s, C*H*), 7.29 - 7.38 (3H, m, Ar*H*), 7.41 (2H, d, *J* 7.6, Ar*H*),

The data matched the reported values[215].

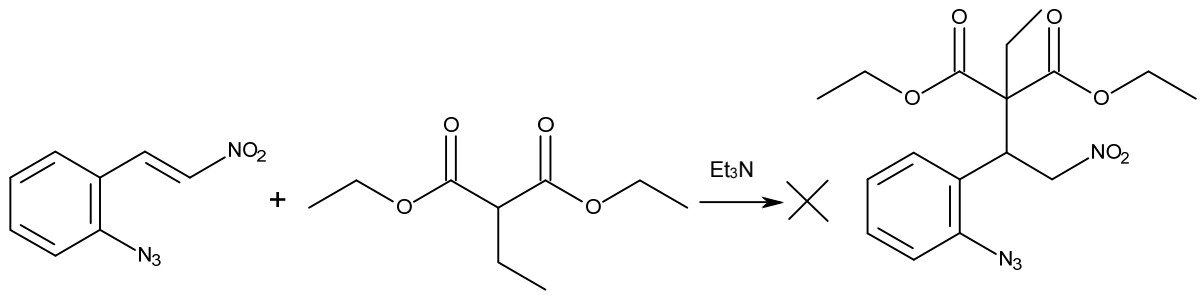
3.12.4 Attempted Michael reaction with diethyl phenyl malonate



232a

To a stirred solution of the nitro olefin (0.360 g, 1.89 mmol, 1 eq) in DCM (8 mL) diethyl phenyl malonate (0.67 g, 2.83 mmol, 1.5 eq) and triethylamine (0.5 mL) were added dropwise. The reaction mixture was stirred at r.t. for 24 h. The reaction mixture remained unchanged and gave the starting materials unreacted.

3.12.5 Attempted Michael reaction with diethyl ethylmalonate

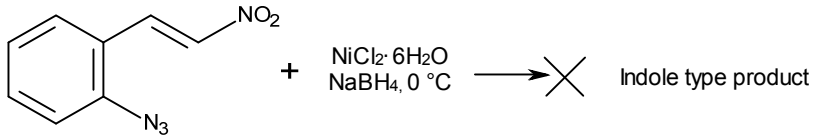


232a

To a stirring solution of the nitro olefin (0.400 g, 2.10 mmol, 1 eq) in DCM (10 mL) diethyl ethyl malonate (0.6 mL, 0.594 g, 3.16 mmol, 1.5 eq) and triethylamine (0.5 mL) were

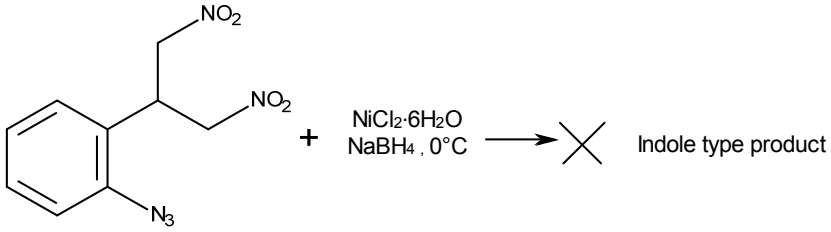
added dropwise. The reaction mixture was allowed to stir at r.t. for 6 days. The reaction mixture remained unchanged and gave the starting materials unreacted.

3.13 Attempted reduction of the nitro olefin



To an ice-cooled solution of the azidonitroalkene (0.603 g, 2.40 mmol, 1 eq) in EtOH (20 mL), $NiCl_2 \cdot 6H_2O$ (0.571 g, 2.40 mmol, 1 eq) and $NaBH_4$ (0.900 g, 24.0 mmol, 10 eq) were added. The reaction was stirred for 2 h at 0 °C, it was then quenched with saturated aqueous NH_4Cl (20 mL), diluted with $CHCl_3$ (20 mL) and extracted into $CHCl_3$ (3 x 20 mL). It was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo.* The crude mixture was isolated as a complex mixture of spots and on purification did not yield any significant or identifiable products.

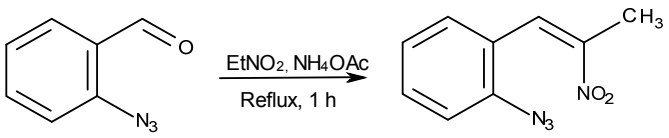
3.14 Attempted reduction of the double Michael adduct



$NiCl_2 \cdot 6H_2O$ (0.571 g, 2.40 mmol, 1 eq) and $NaBH_4$ (0.900 g, 24.00 mmol, 10 eq) were added in one portion to an ice cooled solution of the double Michael adduct (0.603 g, 2.40 mmol, 1 eq) in EtOH (20 mL). The reaction temperature was maintained at 0 °C and stirred for 2 h and was then quenched with saturated aqueous NH_4Cl (20 mL), diluted with $CHCl_3$ (20mL) and extracted into $CHCl_3$ (3 x 20 mL). It was dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo*. The crude product gave a complex mixture and on purification did not yield any significant or identifiable products.

3.15 Synthesis of the nitroethane derivatives

3.15.1 Synthesis of the nitroethane derivative



231 **240**

A mixture of the aldehyde (1.00 g, 6.80 mmol, 1 eq) and ammonium acetate (0.577 g, 7.48 mmol, 1.1 eq) was heated to reflux in nitroethane (20 mL) for an hour till TLC analysis showed complete consumption of the aldehyde. The mixture was then evaporated under reduced pressure and the resulting mixture was extracted into DCM, dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the crude product as a brown oil. The crude olefin mixture was subjected to silica chromatography (5% EtOAc: Pet) to give an orange solid in 98% yield (1.36 g).

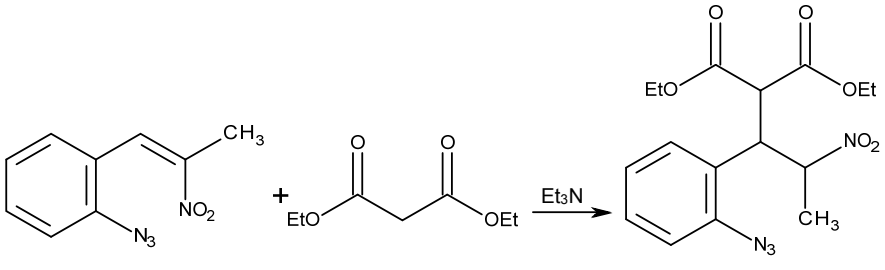
δ_H (400 MHz, $CDCl_3$): 2.40 (3H, s, C*H*$_3$), 7.25 - 7.30 (2H, m, Ar*H*), 7.37 (1H, d, *J* 7.7, Ar*H*), 7.50 (1H, dd, *J* 7.7, 7.7, Ar*H*), 8.1 (1H, s, C*H*).

δ_C (100 MHz, $CDCl_3$): 13.9 (*C*H_3), 118.0 (*C*H), 123.7 (*qC*), 124.6 (=*C*H), 128.8 (*C*H), 130.0 (*C*H), 131.3 (*C*H), 139.5 (*qC*), 148.5 (*qC*).

ν_{max} (cm^{-1}): 3069 (w), 2121 (s), 1594 (m), 1573 (s), 1506 (w), 1481 (w), 1388 (s), 758 (s).

HRMS (ESI^+): Found 227.0540 $[M+Na]^+$, $C_9H_8N_4O_2Na$ requires 227.0539.

3.15.2 Synthesis of the Michael adduct



240 **241a**

To a stirred solution of the substituted nitro olefin (0.297 g, 1.45 mmol, 1 eq) in DCM (10 mL), diethyl malonate (0.44 mL, 0.466 g, 2.91 mmol, 2 eq) and triethylamine (0.5 mL) were added dropwise. The reaction mixture was allowed to stir at r.t. for 4 days until analysis

by TLC indicated all the nitro olefin had been consumed. The reaction mixture was quenched with ether and water (20 mL, 1:1) and extracted into DCM (3 x 10 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography [5% EtOAc/Pet] afforded the Michael adduct as a mixture of stereoisomers in the ratio 3:1 as a yellow oil (0.292 g, 55%).

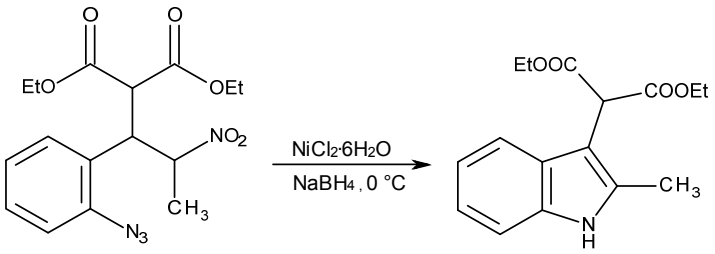
δ_H (400 MHz, $CDCl_3$): 0.91 (3H, t, *J* 7.1, *CH₃*), 1.28 (3H, t, *J* 7.1, *CH₃*), 1.41 (3H, d, *J* 6.7, C*H₃*), 3.82 - 3.93 (2H, m, O*CH₂*), 4.14 - 4.38 (4H, m, C*H*-CO+ OC*H₂* + C*H*-Ar), 5.12 - 5.22 (1H, m, C*H*NO_2), 6.97 (1H, d, *J* 7.6, Ar*H*), 7.03 (1H, dd, *J* 7.6, 7.6, Ar*H*), 7.13 (1H, d, *J* 8.0, Ar*H*), 7.30 (1H, dd, *J* 8.0, 8.0, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 13.5 (*C*H_3), 13.9 (*C*H_3), 16.5 (*C*H_3), 41.6 (*C*H), 53.6 (*C*H), 61.6 (*C*H_2), 62.1 (*C*H_2), 83.0 (*C*H), 118.2 (*C*H), 124.9 (*C*H), 125.8 (*qC*), 129.5 (*C*H), 130.1 (*C*H), 139.1 (*qC*), 166.5 (*C*=O), 166.9 (*C*=O).

ν_{max} (cm^{-1}): 2973 (w), 2127 (s), 1730 (s), 1539 (s), 1497 (m), 1369 (m), 749 (s).

HRMS (ESI^+): Found 387.1279 $[M+Na]^+$, $C_{16}H_{20}N_4O_6Na$ requires 387.1275.

3.15.3 Reduction using nickel chloride hexahydrate and sodium borohydride



241a **242a**

The adduct (0.200 g, 0.55 mmol, 1 eq) in EtOH (5 mL) was cooled to 0 °C after which $NiCl_2{\cdot}6H_2O$ (0.131 g, 0.55 mmol, 1 eq) and $NaBH_4$ (0.229 g, 6.05 mmol, 11 eq) were added. The reaction mixture was stirred for 2 h at 0 °C and was then quenched with saturated NH_4Cl (20 mL), diluted with $CHCl_3$ (20 mL) and extracted into $CHCl_3$ (3 x 20 mL), dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo.* The crude mixture was purified by silica gel chromatography eluted with 15% EtOAc: Pet solvent system to afford the indole **242a** as a brown oil (0.021 g, 13%).

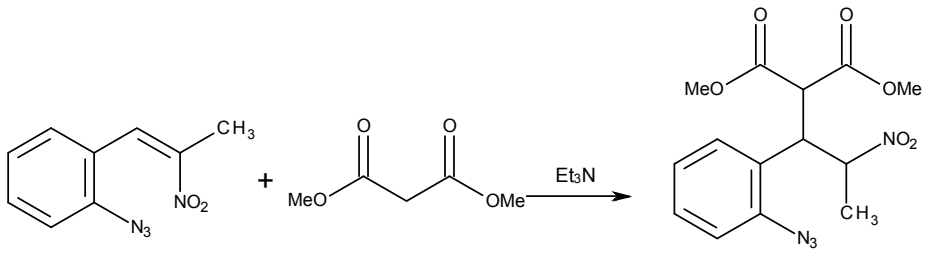
δ_H (400 MHz, $CDCl_3$): 1.24 (6H, t, *J* 7.3, C*H₃* x 2), 2.41 (3H, s, C*H₃*), 4.21 (4H, q, *J* 7.3, OC*H₂* x2), 4.84 (1H, s, C*H*), 7.04 - 7.13 (2H, m, Ar*H*), 7.25 (1H, m, Ar*H*), 7.57 (1H, d, *J* 7.3, Ar*H*), 7.94 (1H, s, N*H*).

δ_C (100 MHz, $CDCl_3$): 12.2 (*C*H_3), 14.1 (*C*H_3), 48.3 (*C*H), 60.5 (*C*H_2), 102.9 (*qC*), 109.2 (*C*H), 118.1 (*C*H), 118.7 (*C*H), 120.3 (*C*H), 126.6 (*qC*), 132.6 (*qC*), 133.9 (*qC*), 167.7 (*qC*).

ν_{max} (cm^{-1}): 3322 (br), 2992 (w), 2851 (m), 1732 (s), 1587 (w), 1494 (m), 1367 (m), 747 (s).

HRMS (ESI^+): Found 312.1205 $[M+Na]^+$, $C_{16}H_{19}NO_4Na$ requires 312.1206.

3.15.4 Synthesis of the dimethyl malonate Michael adduct



240 **241b**

The dimethyl adduct **241b** was successfully synthesised as a pale yellow oil (0.322 g, 61 %) from the substituted nitrostyrene (0.320 g, 1.56 mmol, 1 eq), dimethyl malonate (0.36 mL, 0.414 g, 3.137 mmol, 2 eq) and triethylamine (0.5 mL) in DCM (8 mL) after stirring at r.t. for 4 days and purified by silica gel chromatography with 10% EtOAc: Pet solvent system.

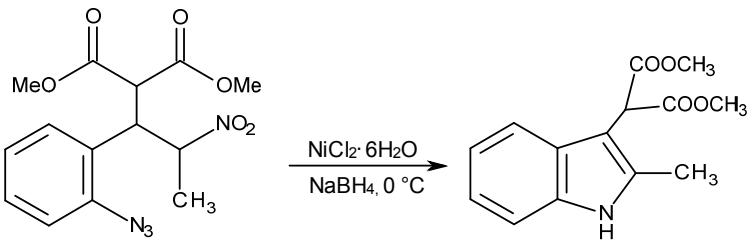
δ_H (400 MHz, $CDCl_3$): 1.37 (3H, d, *J* 6.3, C*H*$_3$), 3.67 (3H, s, OC*H*$_3$), 3.74 (3H, s, OC*H*$_3$), 4.08 - 4.21 (2H, m, C*H*-CO+ C*H*-Ar), 5.06 - 5.20 (1H, m, C*H*NO_2), 6.93 (1H, d, *J* 7.6, Ar*H*), 6.99 (1H, dd, *J* 7.6, 7.6, Ar*H*), 7.10 (1H, d, *J* 7.7, ArH), 7.30 (1H, dd, *J* 7.7, 7.7, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 16.3 (*C*H_3), 41.2 (*C*H), 52.5 (*C*H_3), 52.6 (*C*H_3), 53.3 (*C*H), 83.0 (*C*H), 118.4 (*C*H), 125.0 (*C*H), 125.9 (*qC*), 129.6 (*C*H), 130.1 (*C*H), 139.1 (*qC*), 166.9 (*C*=O), 167.4 (*C*=O).

ν_{max} (cm^{-1}): 2992 (m), 2125 (s), 1729 (s), 1535 (s), 1492 (m), 1375 (m), 752 (s).

HRMS (ESI^+): Found 359.0963 $[M+Na]^+$, $C_{14}H_{16}N_4O_6Na$ requires 359.0962.

3.15.5 Synthesis of the indole dimethyl malonate adduct with $NiCl_2 \cdot 6H_2O$



241b **242b**

The Michael adduct (0.193 g, 0.57 mmol, 1 eq) was reduced with $NiCl_2 \cdot 6H_2O$ (0.137 g, 0.57 mmol, 1 eq) and $NaBH_4$ (0.239 g, 6.32 mmol, 11 eq) in EtOH (10 mL) at 0 °C for 2 h to afford the indole product as a yellow oil (0.020 g, 8%) purified with silica chromatography eluted with 10% EtOAc: Pet solvent system.

δ_H (400 MHz, $CDCl_3$): 2.44 (3H, s, C*H*$_3$), 3.75 (6H, s, OC*H*$_3$ x2), 4.91 (1H, s, C*H*), 7.03 - 7.12 (2H, m, ArC*H*), 7.22 (1H, m, ArC*H*), 7.56 (1H, d, *J*7.2, ArC*H*), 7.91 (1H, s, N*H*).

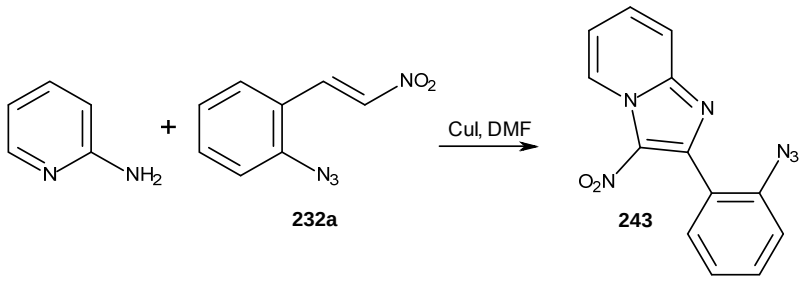
δ_C (100 MHz, $CDCl_3$): 12.1 (*C*H$_3$), 48.8 (*C*H), 52.6 (*C*H$_3$), 102.9 (*q*C), 110.3 (*C*H), 118.9 (*C*H), 119.9 (*C*H), 121.5 (*C*H), 126.4 (*q*C), 132.2 (*q*C), 133.7 (*q*C), 169.1 (*C*=O).

ν_{max} (cm^{-1}): 3327 (br), 2999 (w), 2857 (m), 1734 (s), 1592 (w), 1491 (m), 752 (s).

HRMS (ESI^+): Found 284.0896 $[M+Na]^+$, $C_{14}H_{15}NO_4Na$ requires 284.0893.

3.16 Reaction with aminopyridines

3.16.1 Synthesis of the imidazo [1,2-*a*] pyridine from aminopyridine and the nitro olefin



232a **243**

To a round bottom flask containing the nitro olefin (0.400 g, 2.11 mmol, 1.2 eq), amino pyridine (0.166 g, 1.76 mmol, 1 eq), and CuI (0.036 g, 0.176 mmol, 0.1 eq, 10 mol %),

DMF (4 mL) was added to the reaction system. The reaction mixture was then stirred at 80 °C for 6.5 h. When the reaction was complete it was allowed to cool to r.t. and diluted with ethyl acetate (50 mL). It was then washed with brine (25 mL), ice cold water (20 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* and the resulting brown oil was purified by column chromatography, eluting with 50% EtOAc: Pet to afford the imidazo-[1,2-*a*] pyridine product **243** as a brown oil (0.110 g, 19%).

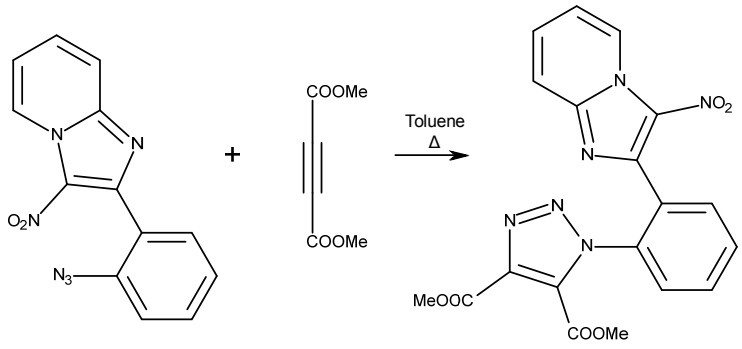
δ_H (400 MHz, $CDCl_3$): 7.22 - 7.30 (3H, m, aromatic *H*), 7.48 - 7.56 (2H, m, aromatic *H*), 7.62 (1H, dd, *J* 8.5, 8.5, aromatic *H*), 7.81 (1H, dd, *J* 8.5, 8.5, aromatic *H*), 9.45 (1H, d, *J* 6.5, aromatic *H*).

δ_C (100 MHz, $CDCl_3$): 116.5 (*C*H), 118.2 (*C*H), 118.3 (*C*H), 124.3 (*qC*), 124.7 (*C*H), 127.8 (*C*H), 130.0 (*qC*), 130.6 (*C*H), 130.9 (*C*H), 131.0 (*C*H), 133.7 (*qC*), 145.0 (*qC*), 146.4 (*qC*).

ν_{max} (cm^{-1}): 3003 (w), 2122 (s), 1601 (w), 1536 (m), 1480 (m), 1363 (m), 745 (m).

HRMS (ESI^+): Found 303.0605 $[M+Na]^+$, $C_{13}H_8N_6O_2Na$ requires 303.0600.

3.16.2 Synthesis of cycloaddition product



243 **244**

The azido addduct (0.10 g, 0.361 mmol, 1 eq) was dissolved in toluene (5 mL) and DMAD (0.005 mL, 0.055 g, 0.368 mmol, 1.02 eq) was added dropwise to the solution. The reaction mixture was then heated to reflux at 115 °C for 90 h whilst being monitored by TLC. The crude product was purified by column chromatography (50% EtOAc: Pet) to afford the cycloaddition product as a brown solid (0.082 g) in 54% yield.

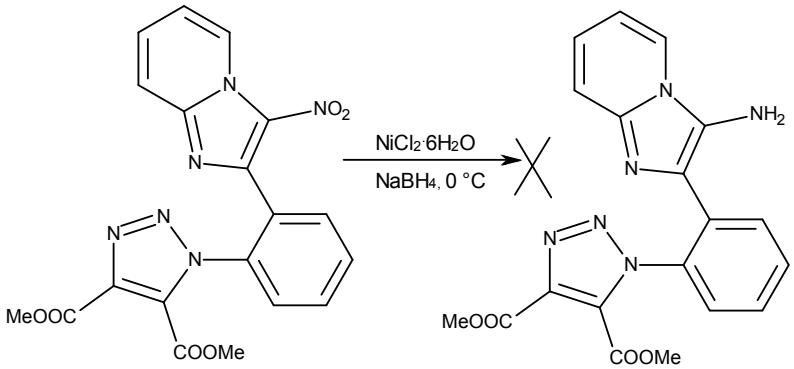
δ_H (400 MHz, $CDCl_3$): 3.81 (3H, s, C*H*$_3$), 3.91 (3H, s, C*H*$_3$), 7.26 - 7.33 (1H, m, aromatic *H*), 7.58 - 7.65 (1H, m, aromatic *H*), 7.66 - 7.74 (4H, m, aromatic *H*), 7.76 - 7.82 (1H, m, aromatic *H*), 9.37 (1H, d, *J* 7.0, C*H*).

δ_C (100 MHz, $CDCl_3$): 52.6 (*C*H_3), 53.6 (*C*H_3), 117.0 (*C*H), 118.5 (*C*H), 127.3 (*C*H), 127.9 (*C*H), 129.6 (*q*C), 130.5 (*C*H), 130.6 (*C*H), 131.5 (*C*H), 131.9 (*C*H), 133.3 (*q*C), 134.5 (*q*C), 138.6 (*q*C), 140.8 (*q*C), 145.0 (*q*C), 145.4 (*q*C), 158.4 (*q*C), 160.1 (*q*C).

ν_{max} (cm-1): 2954 (w), 1720 (s), 1630 (m), 1542 (s), 1481 (s), 1365 (s), 764 (s).

HRMS (ESI+): Found 445.0870 $[M+Na]^+$, $C_{19}H_{14}N_6O_6Na$ requires 445.0867.

3.16.3 Attempted cyclisation of reduced product

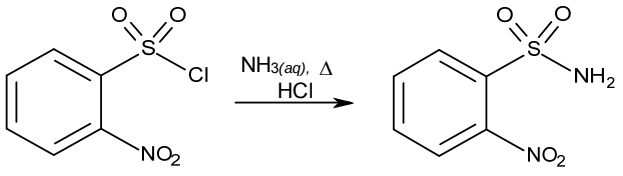


244 **245**

To a stirred solution of adduct **244** (0.075 g, 0.177 mmol, 1 eq) and $NiCl_2{\cdot}6H_2O$ (0.043 g, 0.57 mmol, 1 eq) in EtOH (5 mL) was added $NaBH_4$ (0.074 g, 1.95 mmol, 11 eq) at 0 °C. The reaction was stirred at 0 °C for 2 h before being quenched with saturated NH_4Cl (20 mL). The solution was diluted with $CHCl_3$ (20 mL) and extracted into $CHCl_3$ (3 x 10 mL), dried ($MgSO_4$), filtered through Celite and concentrated *in vacuo.* The crude mixture was purified by silica chromatography (40% EtOAc: Pet) to afford the starting material quantitatively.

3.17 Attempted aza-Prins reactions

3.17.1. Synthesis of *o*-nitrobenzenesulfonamide

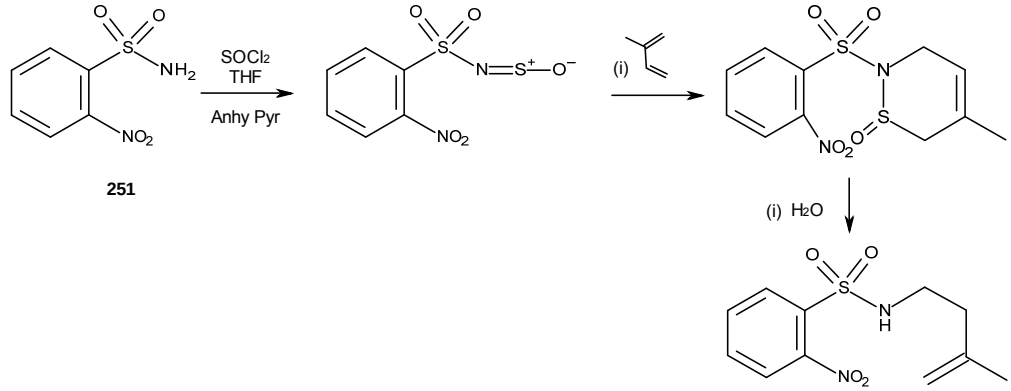


251

To a suspension of *o*-nitrobenzene sulfonyl chloride (12.5 g, 56.4 mmol, 1 eq) in water (70 mL) was added concentrated ammonia solution (50 mL) and the whole was heated

to reflux for 4 h. The mixture was allowed to cool to ambient temperature and was acidified with hydrochloric acid (2M, 0.5 mL) to form a pale yellow precipitate. This precipitate was filtered under vacuum and dried to yield *o*-nitrobenzenesulfonamide as a pale yellow solid (10.75 g, 94%). M.p: (190 - 192 °C),(Lit m.p 191 °C)[201].

3.17.2 Reaction of the *N*-sulfinyl compound with isoprene



251 **254**

A solution of thionyl chloride (0.50 mL, 0.763 g, 6.18 mmol, 1 eq) in dry THF (5 mL) was added dropwise over 3h to a stirring solution of the nitroarylamide (1.24 g, 6.18 mmol, 1 eq) and anhydrous pyridine (1 mL, 0.979 g, 12.38 mmol, 2 eq) in dry THF (20 mL) under a nitrogen atmosphere. The crude mixture was allowed to stir for a further 30 min followed by the dropwise addition of the isoprene (1.0 mL, 0.6744 g, 9.90 mmol, 1.6 eq) and the whole reaction mixture was allowed to stir at r.t. for 30 h whilst being monitored by TLC. After the reaction was complete the solvent was removed *in vacuo* and the crude oil was purified using column chromatography (30% EtOAc: Hex) to obtain the desired product **254** as a pale yellow oil in 81% yield (1.35 g).

δ_H (400MHz, $CDCl_3$): 1.59 (3H, s, C*H*$_3$), 2.20 (2H, t, *J* 6.7, C*H*$_2$), 3.19 (2H, q, *J* 6.7, NC*H*$_2$), 4.64 (1H, s, CH*H*=), 4.72 (1H, s, C*H*H=), 5.29 (1H, br s, NH), 7.70 - 7.67 (2H, m, Ar*H*), 7.81 - 7.86 (1H, m, Ar*H*), 8.08 - 8.15 (1H, m, Ar*H*).

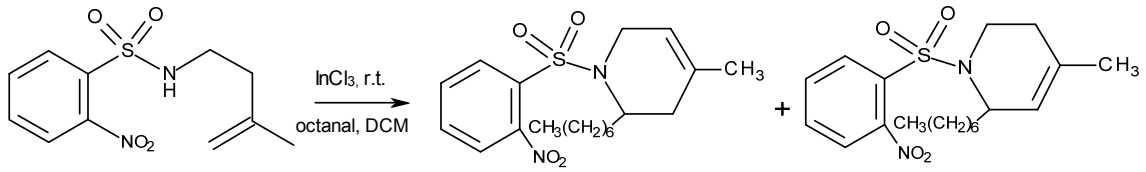
δ_C (100MHz, $CDCl_3$): 21.7 (*C*H_3), 37.2 (*C*H_2), 41.3 (*C*H_2), 113.4 (*C*H_2), 125.4 (*C*H), 131.0 (*C*H), 132.8 (*qC*), 132.9 (*C*H), 133.6 (*C*H), 141.0 (*qC*), 148.0 (*qC*).

ν_{max} (cm^{-1}): 3301 (br), 3022 (w), 2928 (w), 1537 (m), 1342 (m), 757 (s).

HRMS (ESI^+): Found 271.0750 $[M+H]^+$, $C_{11}H_{15}N_2O_4S$ requires 271.0747.

The data was found to be consistent with that reported in the group previously[201].

3.17.3 Attempted aza-Prins reaction



254 **255a** **255b**

To a suspension of $InCl_3$ (0.308 g, 1.39 mmol, 1.5 eq), in dry DCM (5 mL), octanal (0.22 mL, 0.178 g, 1.39 mmol, 1.5 eq) in 2 mL DCM was added. The mixture was stirred at r.t. for 15 min, after which the nitroalkene **254** (0.250 g, 0.926 mmol, 1 eq) was added. The resulting mixture was stirred till the TLC showed the starting material was consumed. On consequent purification, a colourless solid was obtained in low yield (0.045 g, 13%) and as a mixture of compounds **255a** & **255b**. (see discussion 2.10.3).

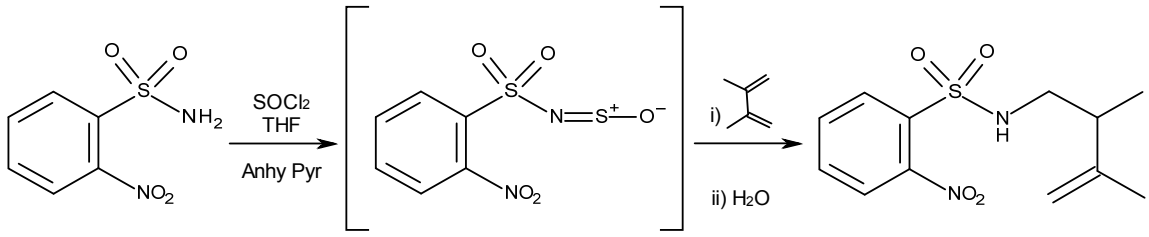
δ_H (400 MHz, $CDCl_3$): 0.80 (3H, m, CH_3), 1.22 - 1.71 (15H, m, octanal unit + CH_3-C=), 2.97 - 3.27 (2H, m, NCH_2), 3.54 - 3.70 (1H, m, C*H*-N), 4.58 - 4.63 (1H, m, C*H*=C), 7.62 - 7.71 (2H, m, ArC*H*), 7.74 - 7.84 (1H, m, ArC*H*), 8.01 - 8.10 (1H, m, ArC*H*),

δ_C (100 MHz, $CDCl_3$): 14.3 (CH_3), 20.9 (CH_3), 22.0 (CH_2), 22.5 (CH_2), 25.9 (CH_2), 27.2 (CH_2), 29.0 (CH_2), 31.5 (CH_2), 38.9 (CH_2), 40.2 (C*H*), 46.8 (NCH_2), 112.7 (=C*H*), 125.3 (C*H*), 131.0 (C*H*), 132.5 (*q*C), 132.7 (C*H*), 133.5 (C*H*), 138.1 (*q*C), 145.4 (*q*C).

ν_{max} (cm^{-1}): 3026 (w), 2932 (w), 1550 (m), 1360 (m), 749 (s).

HRMS (ESI^+): Found 381.1848 $[M+H]^+$, $C_{19}H_{29}N_2O_4S$ requires 381.1843.

3.17.4 Synthesis of a coupled benzenesulfonamide using 3,4-dimethylbutadiene



251 **256**

To a stirring solution of 2-nitrobenzenesulfonylamide **251** (1.00 g, 4.95 mmol, 1 eq), and anhydrous pyridine (0.8 mL, 0.783 g, 9.90 mmol, 2 eq) in dry THF (5 mL) under a

nitrogen stream, was added a solution of thionyl chloride (1.00 mL, 1.47 g, 1 eq) in dry THF (5 mL) dropwise over 3 h. The crude mixture was stirred for 30 min at ambient temperature followed by the dropwise addition of the 2,3-dimethylbutadiene (0.90 mL, 0.650 g, 7.92 mmol, 1.6 eq) and the whole reaction mixture was stirred at r.t. for 24 h whilst being monitored by TLC. After the reaction was complete the solvent was removed *in vacuo* and the crude oil was purified using column chromatography (30% EtOAc: Hex) to obtain **256** as a yellow oil in 23% yield (0.320 g).

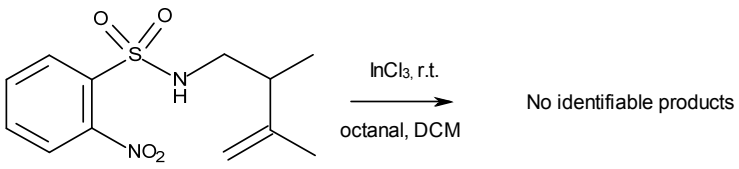
δ_H (400 MHz, $CDCl_3$): 0.98 (3H, d, *J* 6.8, C*H*$_3$), 1.53 (3H, s, C*H*$_3$), 2.26 - 2.40 (1H, m, C*H*CH_3), 2.88 - 2.99 (1H, m, N-CH*H*), 3.04 - 3.15 (1H, m, N-C*H*H), 4.61 (1H, s,=C*H*H), 4.80 (1H, s, =CH*H*), 5.24 (1H, br s, N*H*), 7.66 - 7.76 (2H, m, Ar*H*), 7.88 - 7.92 (1H, m, Ar*H*), 8.02 - 8.14 (1H, m, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 16.8 (*C*H_3), 18.7 (*C*H_3), 40.7 (*C*H), 46.8 (*C*H_2), 112.7 (=*C*H_2), 125.3 (*C*H), 131.0 (*C*H), 132.7 (*C*H),132.5 (*qC*), 133.5 (*C*H), 145.4 (*qC*), 148.0 (*qC*).

ν_{max} (cm^{-1}): 3331 (br), 3015 (w), 2947 (w), 1542 (m), 1367 (m), 743 (s).

HRMS (ESI^+): Found 307.0732 $[M+Na]^+$, $C_{12}H_{16}N_2O_4SNa$ requires 307.0723.

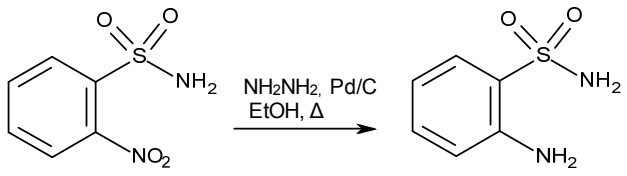
3.17.5 Attempted aza-Prins reaction



256

To a suspension of $InCl_3$ (0.330 g, 1.49 mmol, 1.5 eq), in dry DCM (5 mL), octanal (0.23 mL, 0.191 g, 1.49 mmol, 1.5 eq) in 2 mL DCM was added. The mixture was stirred at r.t. for 15 min, after which the nitroalkene **256** (0.286 g, 0.99 mmol, 1 eq) was added. The resulting mixture was stirred till the TLC showed the starting material was consumed. On TLC and consequent purification, no product was identified.

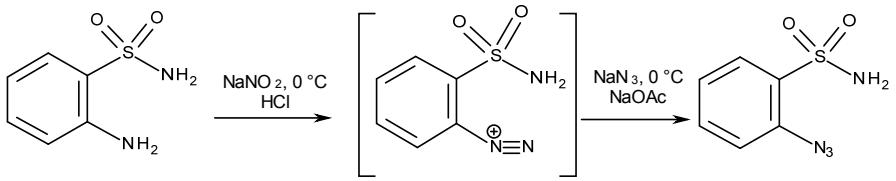
3.17.6 Synthesis of *o*-aminobenzenesulfonamide



251 **257**

A solution of *o*-nitrobenzenesulfonamide (5.00 g, 24.73 mmol, 1 eq) in ethanol (75 mL) at r.t. was treated with palladium on charcoal (10%, 0.250 g) followed by the addition of hydrazine hydrate (10 mL) and the whole was heated to reflux for 4 h. The mixture was filtered whilst hot, washed with cold ethanol, reduced to half the bulk *in vacuo* and cooled to 0 °C. The white crystalline precipitate formed was filtered off and dried *in vacuo* to yield *o*-aminobenzenesulfonamide (3.26 g, 77%) as a white crystalline solid. Mpt. 150 °C - 151 °C (Lit m.p 150 °C)[201].

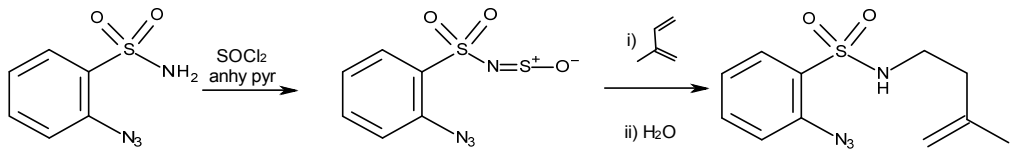
3.17.7 Synthesis of *o*-azidobenzenesulfonamide



257 **258**

To a suspension of *o*-aminobenzenesulfonamide (1.60 g, 9.29 mmol, 1 eq) in concentrated hydrochloric acid (15 mL) and water (15 mL) at 0 °C was added with stirring, a solution of sodium nitrite (0.70 g, 10.22 mmol, 1.1 eq) in water (10 mL), dropwise over 10 min. Stirring was continued for a further hour and the resulting mixture, maintaining its temperature at 0 °C, was added dropwise over an hour to an ice cooled solution of sodium azide (0.620 g, 9.29 mmol, 1 eq) and sodium acetate (60 g) in water (100 mL). The precipitate formed was filtered, washed thoroughly with water (50 mL) and dried in the oven overnight to give as a fawn coloured solid in 80% yield (1.47 g). M.p. 189 - 190 °C (Lit m.p. 191 °C)[201].

3.17.8 Synthesis of the azido isoprene derivative



258 **259**

To a stirring solution of the azidoarylsulfonamide (0.76 g, 4.57 mmol, 1 eq) and anhydrous pyridine (0.74 mL, 0.724 g, 9.15 mmol, 2 eq) in dry THF (40 mL) under a N_2 stream was added a solution of thionyl chloride (0.33 mL, 0.543 g, 4.57 mmol, 1 eq) in dry THF (5 mL) dropwise over a 3 h period. The crude mixture was allowed to stir for a further 30 min followed by the dropwise addition of the isoprene (0.73 mL, 0.498 g, 7.31 mmol, 1.6 eq) and the whole reaction mixture was allowed to stir at r.t. for 20 h whilst being monitored by TLC. After the reaction was complete the solvent was removed *in vacuo* and the crude oil was purified using column chromatography (30% EtOAc: Hex) to obtain the desired product **259** as a pale yellow oil in 7% yield (0.085 g).

δ_H (400 MHz, $CDCl_3$): 1.54 (3H, s, C*H*$_3$), 2.12 (2H, t, *J* 6.8, C*H*$_2$), 2.94 (2H, q, *J* 6.8, NC*H*$_2$), 4.65 (1H, s, CH*H*=), 4.80 (1H, s, C*H*H=), 4.93 (1H, s, N*H*), 7.18 - 7.24 (2H, m, Ar*H*), 7.54 (1H, dd, *J* 7.6, 7.6, Ar*H*), 7.92 (1H, d, *J* 7.6, Ar*H*).

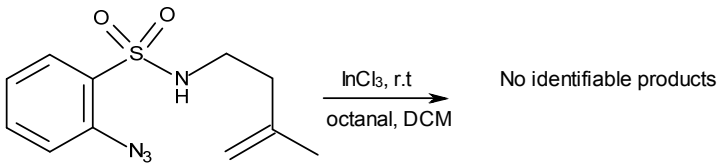
δ_C (100 MHz, $CDCl_3$): 21.6 (*C*H$_3$), 37.0 (*C*H$_2$), 40.7 (*C*H$_2$), 113.0 (*C*H$_2$), 119.4 (*C*H), 124.8 (*C*H), 129.7 (*q*C), 130.8 (*C*H), 134.1 (*C*H), 137.4 (*q*C), 141.6 (*q*C).

ν_{max} (cm^{-1}): 3308 (br), 3022 (w), 2921 (m), 2131 (s), 1537 (m), 1327 m), 1160 (s), 758 (s).

HRMS (ESI^+): Found 555.1538 $[2M+Na]^+$, $C_{22}H_{28}N_8O_4S_2Na$ requires 555.1540.

This data matches those reported in the group previously[94].

3.17.9 Attempted aza-Prins reaction

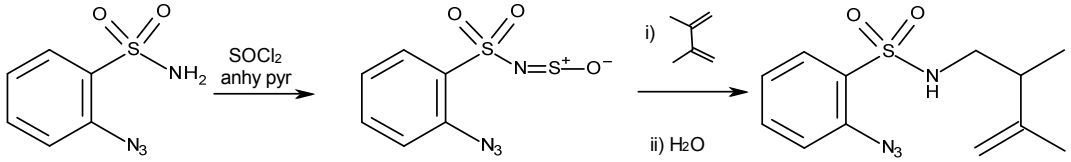


259

To a suspension of $InCl_3$ (0.308 g, 1.39 mmol, 1.5 eq), in dry DCM (3 mL), octanal (0.22 mL, 0.178 g, 1.39 mmol, 1.5 eq) in 2 mL DCM was added. The mixture was stirred at r.t.

for 15 min, after which the azidoalkene **259** (0.260 g, 0926 mmol, 1 eq) in dry DCM (3mL) was added dropwise. The resulting mixture was stirred till the TLC showed the starting material was consumed. On TLC and consequent purification, no product was identified.

3.17.10 Reaction of azido *N*-sulfinyl derivative with 2, 3-dimethyl butadiene



258 **260**

To a suspension of *o*-azidobenzenesulfonamide **258** (0.410 g, 2.47 mmol, 1 eq) and anhydrous pyridine (0.40 mL, 0.390g, 4.94 mmol, 2 eq) in dry THF (5 mL) under a N_2 atmosphere was added a solution of thionyl chloride (0.18 mL, 0.294 g, 2.47 mmol, 1 eq) in dry THF (5 mL) dropwise over a period of 3 h with continuous stirring which yielded the crude intermediate. Dropwise addition of (neat) 2,3-dimethyl butadiene (0.45 mL, 0.324 g, 3.95 mmol, 1.6 eq) to the reaction mixture was followed by stirring at r.t. for 20 h till TLC indicated most of the starting material was consumed. The solvent was removed *in vacuo* and the crude mixture was purified using column chromatography (8% EtOAc: Hex) to obtain **260** as a pale yellow oil in 64% yield (0.450 g).

δ_H (400 MHz, $CDCl_3$): 0.97 (3H, d, *J* 6.8, C*H*$_3$), 1.53 (3H, s, C*H*$_3$), 2.33 (1H, sextet, *J* 6.8, C*H*CH_3), 2.65 - 2.80 (1H, m, N-C*H*H), 2.86 - 3.01 (1H, m, N-CH*H*), 4.73 (1H, s, =C*H*H), 4.86 (1H, s, =CH*H*), 4.97 (1H, br s, N*H*), 7.26 - 7.34 (2H, m, Ar*H*), 7.60 (1H, d, *J* 7.9, Ar*H*), 7.95 (1H, d, *J* 7.9, Ar*H*).

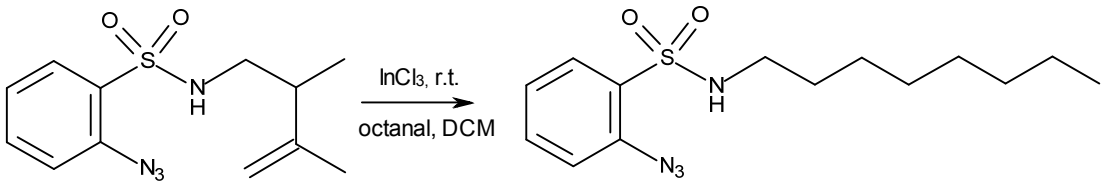
δ_C (100 MHz, $CDCl_3$): 16.9 (*C*H_3), 18.6 (*C*H_3), 40.6 (*C*H), 46.4 (*C*H_2), 112.3 (=*C*H_2), 119.3 (*C*H), 124.8 (*C*H), 129.5 (*q*C), 130.7 (*C*H), 134.0 (*C*H), 137.5 (*q*C), 146.1 (*q*C).

ν_{max} (cm^{-1}): 3312 (br), 3011 (w), 2916 (w), 2128 (s), 1532 (m), 1357 (m), 752 (s).

HRMS (ESI^+): Found 303.0894 $[M+Na]^+$, $C_{12}H_{16}N_4O_2SNa$ requires 303.0886.

This data matches previously reported values [94].

3.17.11 Attempted synthesis of the aza-Prins product



260 **261**

To a suspension of $InCl_3$ (0.308 g, 1.39 mmol, 1.5 eq), in dry DCM (3 mL), octanal (0.22 mL, 0.178 g, 1.39 mmol, 1.5 eq) in 2 mL DCM was added. The mixture was stirred for 15 min at r.t., after which the azidoalkene **260** (0.260 g, 0.92 mmol, 1 eq) in dry DCM (3mL) was added through dropwise addition. The resulting mixture was stirred till the TLC showed the majority of the starting material was consumed. The solvent was removed by rotary evaporation and purified with 6% EtOAc: Hex to give a white solid (0.101 g, 57%).

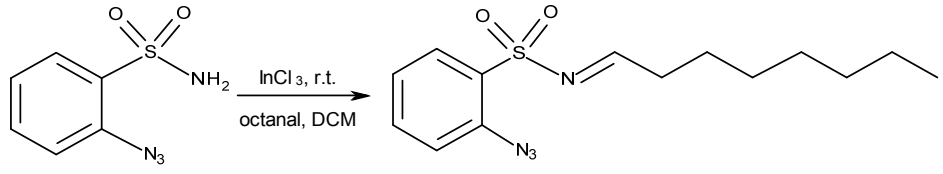
δ_H (500 MHz, $CDCl_3$): 0.82 - 0.93 (3H, m, alkyl chain), 1.17 - 1.34 (8H, m, alkyl chain), 1.43 - 1.51 (2H, m, alkyl), 1.53 - 1.63 (2H, m, C*H*$_2$), 2.73 - 2.90 (2H, m, NC*H*$_2$), 4.88 (1H, s, N*H*), 7.14 - 7.30 (2H, m, Ar*H*), 7.46 - 7.60 (1H, d, *J* 7.8, Ar*H*), 7.84 - 8.01 (1H, d, *J* 7.8, Ar*H*).

δ_C (125 MHz, $CDCl_3$): 14.1 (*C*H_3), 22.6 (*C*H_2), 26.5 (*C*H_2), 27.3 (*C*H_2), 29.1 (*C*H_2), 29.4 (*C*H_2), 31.7 (*C*H_2), 43.4 (*C*H_2), 119.3 (*C*H), 124.9 (*C*H), 130.0 (*qC*), 130.7 (*C*H), 133.8 (*C*H), 137.4 (*qC*).

ν_{max} (cm^{-1}): 3291 (br), 2923 (m), 2854 (w), 2132 (s), 1575 (m), 1329 (m), 1160 (s), 756 (s).

HRMS (ESI^+): Found 333.1364 $[M+Na]^+$, $C_{14}H_{22}N_4O_2SNa$ requires 333.1356.

3.17.12 Synthesis of the sulfonyl imine under aza-Prins conditions



258 **262**

To a suspension of $InCl_3$ (0.553 g, 2.50 mmol, 1.5 eq), in dry DCM (5 mL), octanal (0.39 mL, 0.320 g, 2.50 mmol, 1.5 eq) in 2 mL DCM solution was added. The mixture was stirred for 15 min at r.t., after which azido sulfonamide **258** (0.300 g, 1.60 mmol, 1 eq) in dry DCM (3mL) was added dropwise. The resulting mixture was stirred till the TLC showed the

majority of the starting material was consumed. The solvent was removed by rotary evaporation and purified with 6% EtOAc: Hex to give a pale yellow oil (0.130 g, 26%).

δ_H (400 MHz, $CDCl_3$): 0.75 - 0.84 (4H, m, alkyl chain), 0.97 - 1.38 (7H, m, alkyl chain), 1.26 - 1.39 (2H, m, alkyl chain), 2.18 - 2.27 (1H, m, alkyl chain), 3.38 - 3.51 (1H, m, alkyl chain), 5.26 (1H, d, *J* 8.8, =C*H*), 7.14 - 7.25 (2H, m, Ar*H*), 7.52 (1H, dd, *J* 7.8, Ar*H*), 7.88 (1H, dd, *J* 7.8, Ar*H*).

δ_C (100 MHz, $CDCl_3$): 14.0 (CH_3), 22.5 (CH_2), 25.9 (CH_2), 27.3 (CH_2), 29.0 (CH_2), 31.6 (CH_2), 54.6 (CH_2), 119.3 (*C*H), 124.9 (*C*H), 129.8 (*C*H), 131.3 (*qC*), 133.7 (*C*H), 137.7 (*qC*), 162.2 (*C*H).

ν_{max} (cm^{-1}): 2924 (m), 2132 (s), 1575 (m), 1470 (m), 1162 (s), 756 (s).

HRMS (ESI^+): Found 309.1376 $[M+H]^+$, $C_{14}H_{21}N_4O_2S$ required 309.1376.

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