Biomimetic approaches to tryptophan-derived alkaloids

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Thesis submitted to the University of Nottingham
for the degree of Doctor of Philosophy

September 2016

Contents

Acknowledgments

Firstly, I would like to thank Professor Chris Moody for the opportunity to study for my PhD under his guidance and for his enthusiasm and support. I would also like to thank members of the Moody group past and present for their friendship, advice and support through difficult times, particularly Martin, Chris, Hannah, Simon, Andy, Alpa and Maxime. I would also like to thank Adam for his friendship and always being willing to provide help and advice at the beginning of my PhD studies.

I would like to thank the technical and stores staff for their help and Dr William Lewis for the X-ray crystallographic data contained in this thesis.

I would also like to thank my friends outside of chemistry for always being there to listen and to my parents and family for their constant support throughout my education. Finally I would like to thank George for his endless patience, love, support and encouragement.

Abbreviations

App	Apparent
Br	Broad
BOC	*t*-Butoxycarbonyl
Cbz	Carboxybenzyl
COSY	Correlation spectroscopy
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
ESI	Electrospray ionisation
HSQC	Heteronuclear single-quantum correlation spectroscopy
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HPLC	High-performance liquid chromatography
HRESIMS	High resolution electrospray ionisation mass spectrometry
HRFABMS	High resolution fast atom bombardment mass spectrometry
KHMDS	Potassium bis(trimethylsilyl) amide
LiHMDS	Lithium bis(trimethylsilyl) amide
mCPBA	meta-Chloroperoxybenzoic acid
NOESY	Nuclear overhauser spectroscopy
Pg	Protecting group
ROESY	Rotating-frame nuclear overhauser effect spectroscopy
TFA	Trifluoroacetyl
TFAA	Trifluoroacetic anhydride
TLC	Thin layer spectroscopy
TMSCl	Trimethylsilyl chloride
TOCSY	Total correlation spectroscopy

Abstract

Chapter One describes several natural products derived from the amino acid tryptophan including the structures of the new natural products hyrtioseragamine A and B and tintamine.

Chapter Two describes the work towards hyrtioseragamine A and B. It was intended that the unknown furo[2,3-*b*]pyrazine-2(1*H*)-one core would be synthesised from a 1,4-dicarbonyl and this has been synthesised from the amino acid ornithine and the tryptophan derivative kynurenine. Cyclisation of this material to give the 2,3-amino-furan was unsuccessful and thus a number of model systems were synthesised to examine the barrier to furan formation. These models suggest formation of a furan with nitrogen at its 2- and 3-positions was not possible by this route, and further attempts to install a nitrogen to a 2-amino-furan also proved unsuccessful.

Chapter Three describes work on the synthesis of the marine natural product tintamine. This novel compound contains a unique tropo-1,2-dihydro-3,6-phenanthroline core and our synthesis was based on biomimetic principles. A Friedländer reaction allowed successful formation of the quinoline and the attached seven-membered ring was further functionalised to a tropolone. Formation of the dihydro-phenanthroline was successful; it was also possible to separately functionalise the tropolone-quinoline with the sulfur side chain present in tintamine. Unfortunately several of the key intermediates of this route proved unstable, and at this point a final deprotection to form the natural product has not been successful.

Chapter Four contains the synthetic details for the preparation of the novel compounds described in Chapters Two and Three.

Chapter 1: Introduction

1.1 Natural products

Molecules obtained from nature have been used in medicine for thousands of years, long before their structures or mechanisms of action were understood. Less than 10% of the planet's biodiversity has been examined for biological activity, leaving a large untapped source of potential drug molecules.[1]

Natural products provide privileged scaffolds, as they have evolved to interact with proteins. Many successful drugs are natural product derived; the anti-cancer compounds taxol and camptothecin are derived from plant sources. The anti-hypertensive drug mevastatin and antibiotics, including cyclosporine and ciprofloxin, are also derived from natural products.[1] In total between 60 and 80% of antibiotics and anti-cancer compounds are derived from natural products.[2]

Pharmaceutical companies had moved away from natural products to combinatorial libraries as sources of lead compounds in drug discovery, but more recently a trend towards smaller libraries where small molecules are derived from natural product scaffolds have become popular.[3] An advantage of natural product based libraries is that the compounds are more drug-like and are better suited to absorption and metabolism than compounds from conventional small molecule libraries.[1]

Natural products have also been used as chemical probes to examine biological systems.[4] As biologically active and structurally complex molecules they can be used to probe biological pathways. In 2005 Waldmann *et al.* classified the structural components of natural products in an attempt to examine biologically relevant chemical space and identify the molecules that control protein function; nitrogen containing heterocycles feature heavily on this scaffold tree.[5]

Whilst natural products are known to be biologically important, it is imperative that enough of the compound can be isolated to examine its activity. This has led to the vast chemical area of natural product synthesis.[6]

Whilst many of the more well-known natural products come from plants, the marine environment provides a wealth of novel chemical structures.[7-9] The marine environment can often be harsh and has resulted in a number of unusual structures, which are markedly different to those isolated from a terrestrial environment. The vast array of natural products is broken down into groups that are divided based on their structural features or by the biosynthetic pathways that forms them. One such group is the alkaloids, a large group of nitrogen containing natural products that is further broken down according to their biogenesis.

1.2 Alkaloids

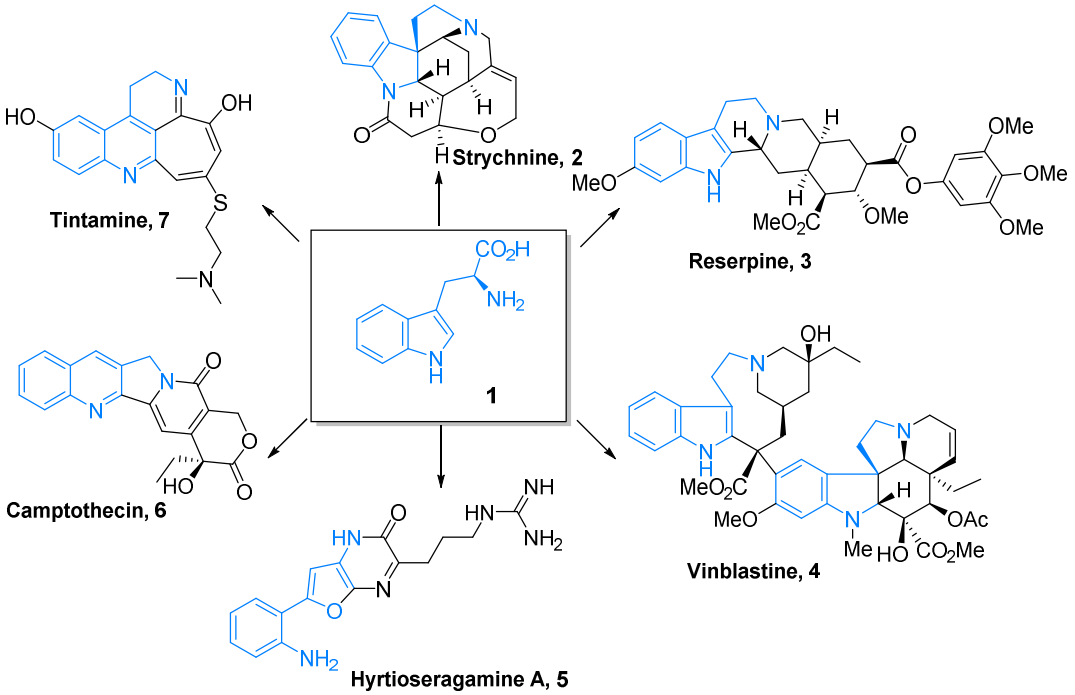
Alkaloids are a diverse group of nitrogen containing compounds that are isolated from the natural environment. They are biologically active and many alkaloids are highly toxic. The definition of alkaloid is fluid, with many groups believing that they are amino acid-derived and need to contain a basic nitrogen. However, there is some dispute about if the nitrogen needs to be basic, or if alkaloids can possess only neutral nitrogen.[10]

The alkaloids can be classified by their biological activity, their structure, or their biosynthetic origin. They can also be classified by the amino acid from which the basic nitrogen is derived, with lysine, ornithine, tyrosine, histidine, phenylalanine and tryptophan all being possible precursors.

More than 25% of higher plants contain alkaloids, and they can also come from animals, fungi, bacteria or the marine environment.[10, 11] Amino acids, antibiotics, nucleotides and peptides are not typically considered to be alkaloids.[10]

Alkaloids are formed either from amino acids or by transamination.[10] Tryptophan is the precursor for many alkaloids including indoles, terpenoid indoles, pyrroloindoles, ergots and

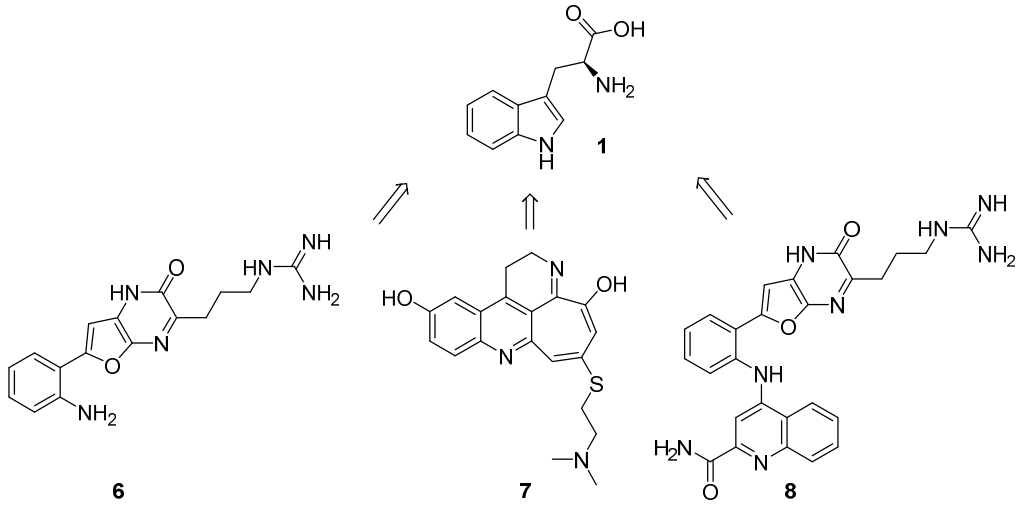
quinoline alkaloids. In many tryptophan-derived alkaloids the indole motif is directly incorporated and is obvious within the structure of the natural product; however, in some, where oxidation of the indole has occurred, it may be less apparent (Scheme 1).



Scheme 1: Tryptophan (1) derived natural products; 2 strychnine, 3: reserpine; 4: vinblastine; 5: hytrioseragamine A; 6 camptothecin; 7: tintamine.

The terpene indole alkaloid strychnine (**2)** is isolated from the plant family S*trychnos* and is highly toxic.[10, 12] Reserpine (**3)** is an anti- hypertensive and anti-psychotic drug isolated from the root of *Rauwolfia serpentina* that has traditionally been used as a treatment for insanity.[13] Vinblastine (**4)** was isolated from *Catharanthus roseus* and is used in the treatment of cancer.[14, 15] Incorporation of tryptophan is less obvious in hyrtioseragamine A (**5)**, camptothecin (**6)** and tintamine (**7)** although it has been shown that quinolines can be biosynthesised from tryptophan. In the biosynthesis of these natural products the indole has undergone an oxidation reaction, resulting in opening of the pyrrole ring. This reaction of tryptophan will be discussed later.

Hyrtioseragamines A and B **(8)** contain a novel furo[2,3-*b*]pyrazine-2(1*H*)-one core with hyrtioseragamine B differing from A by the presence of a quinoline moiety. Tintamine contains a previously unseen tropo-1,2-dihydro-3,6-phenanthroline core. The common features of these natural products are the use of tryptophan as a biosynthetic precursor, and in the case of tintamine and hyrtioseragamine B, the use of tryptophan as a precursor for the quinolines. These complex marine derived heterocycles have yet to be synthesised and their novel cores provide interesting targets for biomimetic total synthesis.

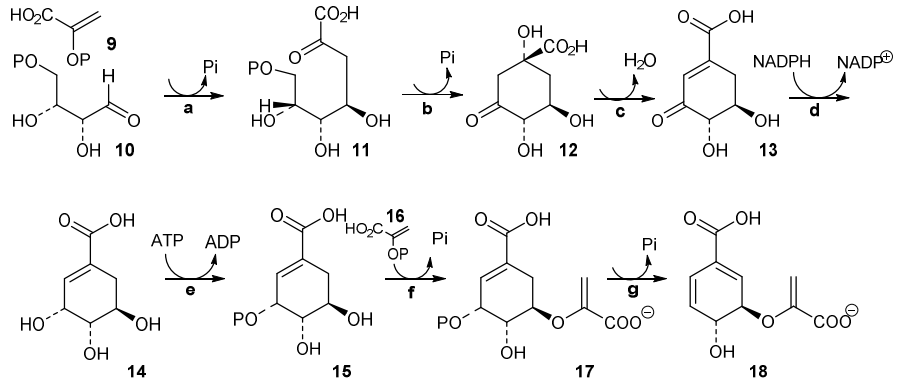


Scheme 2: Tryptophan 1 derived hyrtioseragamine A 5, hyrtioseragamine B 8,[16] tintamine 7.[17]

1.3 Tryptophan biosynthesis: The shikimate pathway

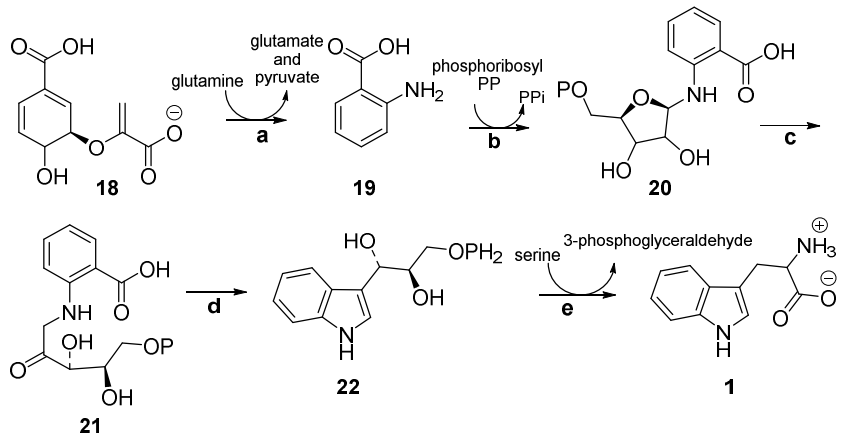
Tryptophan, alongside the amino acids tyrosine and phenylalanine, is known to be biosynthesised *via* the shikimate pathway and the intermediate chorismic acid is common to all three aromatic amino acids. This pathway features in microorganisms and plants but does

not occur in animals and thus tryptophan, phenylalanine and tyrosine are essential amino acids.[18, 19]



Scheme 3: Shikimate pathway; chorismic acid (18) biosynthesis from *D*-erythrose-4-phosphate (10); a: DAHP synthase, b: 3-dehydroquinate synthase, c: 3-dehydroquinase, d: shikimate dehydrogenase, e: shikimate kinase, f: enolpyruvylshikimic acid 3-phosphate synthase, g: $FMNH_2$, chorismate synthase.

Coupling of the phosphate containing intermediates **9** and **10**, which come from the glycolytic pathway and the pentose phosphate cycle, gives **11**. An aldol reaction follows elimination of the phosphate group to give 3-dehydroquinic acid **12**. Dehydration gives 3-dehydroshikimic acid (**13)** and a reduction gives shikimic acid (**14)**. Incorporation of phosphoenolpyruvate **16** as a side chain and elimination of phosphoric acid allows formation of the chorismic acid intermediate **18** common to the biosynthesis of the aromatic amino acids.[18] Variation occurs from chorismic acid, with both tyrosine and phenylalanine undergoing conversion *via* prephenic acid and tryptophan synthesis going *via* an anthranilic acid intermediate.

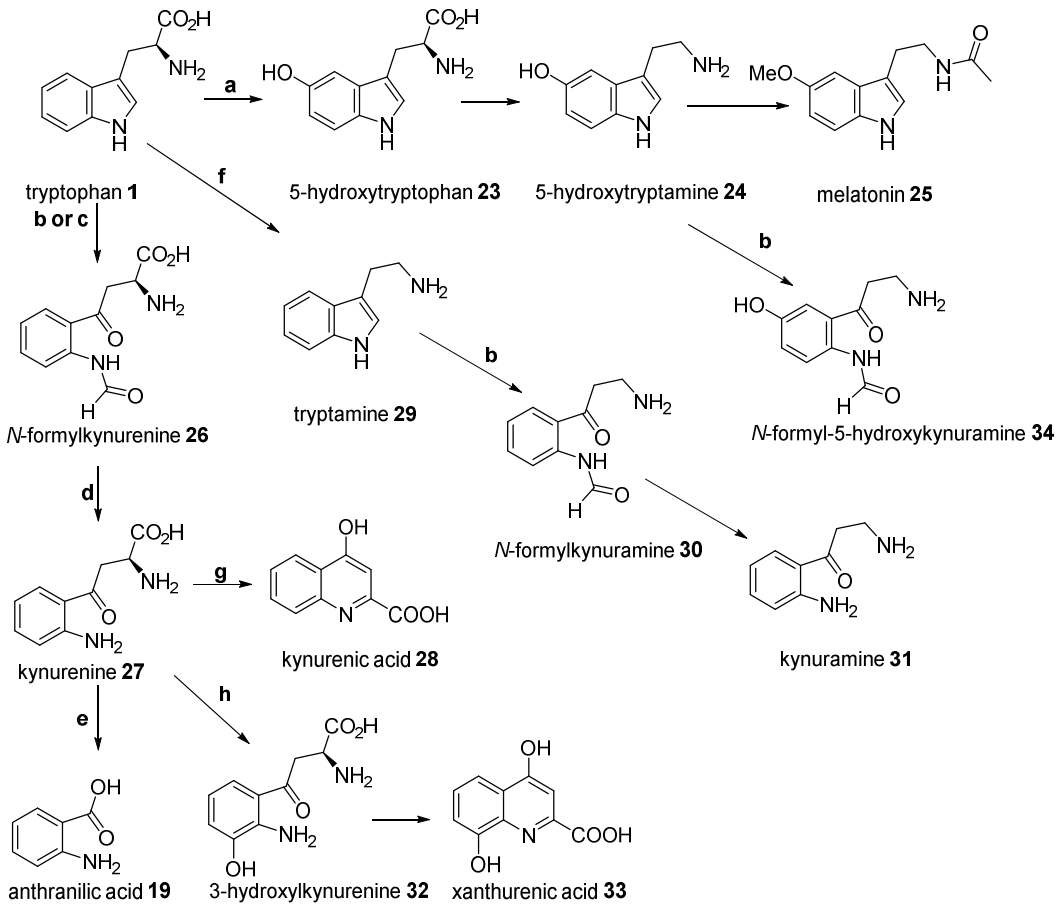


Scheme 4: Tryptophan synthesis from chorisimic acid 18; a: anthranilate synthase, b: anthranilate phosphoribosyl transferase, c: phosphoribosylanthranilate isomerase, d: indole-3-glycerol phosphate synthase, e: tryptophan synthase.[18, 20]

Chorismic acid is converted into anthranilic acid (**19)** using ammonia generated from glutamine. Anthranilic acid then attacks phosphoribosyl PP in an S_N2 reaction to give phosphoribosylanthranalic acid **20**. Ring opening, followed by imine-enamine tautomerisation and keto-enol tautomerisation gives the precursor to tryptophan. A retro aldol reaction and addition of serine gives *L*-tryptophan.

1.4 Tryptophan oxidation pathways

Tryptophan is known to undergo reactions to form several important secondary metabolites. Decarboxylation gives tryptamine (**29)**, which is found within several natural products.[18] 5-Hydroxytryptamine, also known as serotonin (**24)**, is found in the body as a neurotransmitter and its metabolite melatonin is implicated in control of circadian rhythm and is active against oxidative stress.[21] Many tryptophan metabolites have biological activity and this has resulted in the oxidation pathways being examined in detail (Scheme 5).[22, 23]

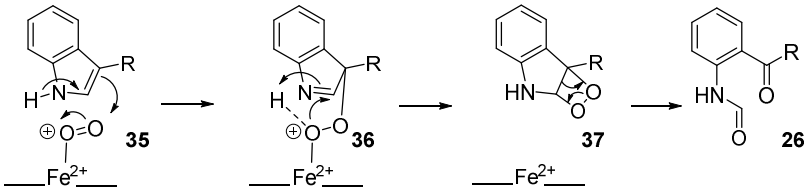


Scheme 5: Biological metabolism of tryptophan: a: Tryptophan hydroxylase, b: indoleamine-2,3-dioxygenase, c: tryptophan-2,3-dioxygenase, d: kynurenine formamidase, e: kynureninease, f: tryptophan decarboxylase, g: kynurenine amino transferase, h: kynurenine-3-hydroxylase, i: kynurenine-3-hydroxylase.[24]

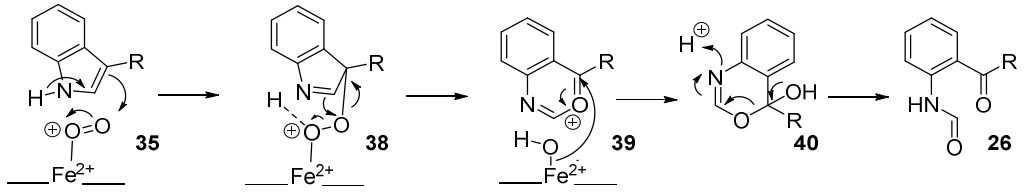
The enzymes indole-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) are implicated in the oxidation of tryptophan (Scheme 5) and act as the rate limiting step in the kynurenine pathway.[25] The implication of these enzymes in a number of diseases mean they have been studied in detail and their mechanism of action probed. Both are haem centred enzymes where iron(II) is known to be key for catalytic activity.[26]

Several different mechanisms have been proposed as to how oxidation of the indole occurs in the enzyme active site, all of which rely on a dioxygen molecule binding.[25] It has been proposed that the substrate binds and that this then causes the oxygen to bind to the iron. Both the dioxetane (Scheme 6) and Criegee mechanism (Scheme 7) have the same first step, but whilst one mechanism goes *via* a dioxetane intermediate **37**, which then ring opens to give *N*-

formylkynurenine (**26)**, the Criegee mechanism relies on a six-membered intermediate **40** before ring opening occurs. An alternative mechanism that has also been proposed is a diradical mechanism, whereby the binding of the oxygen relies on radicals.[25] Whilst there is still discussion about which mechanism is the most favourable, each uses dioxygen to open the pyrrole ring and this can be harnessed in a biomimetic synthesis of *N*-formylkynurenine (**26)** or *N*-formylkynuramine (**30)**.



Scheme 6: Proposed dioxetane mechanism of IDO/TDO catalysed tryptophan oxidation to *N*-formylkynurenine.[25]



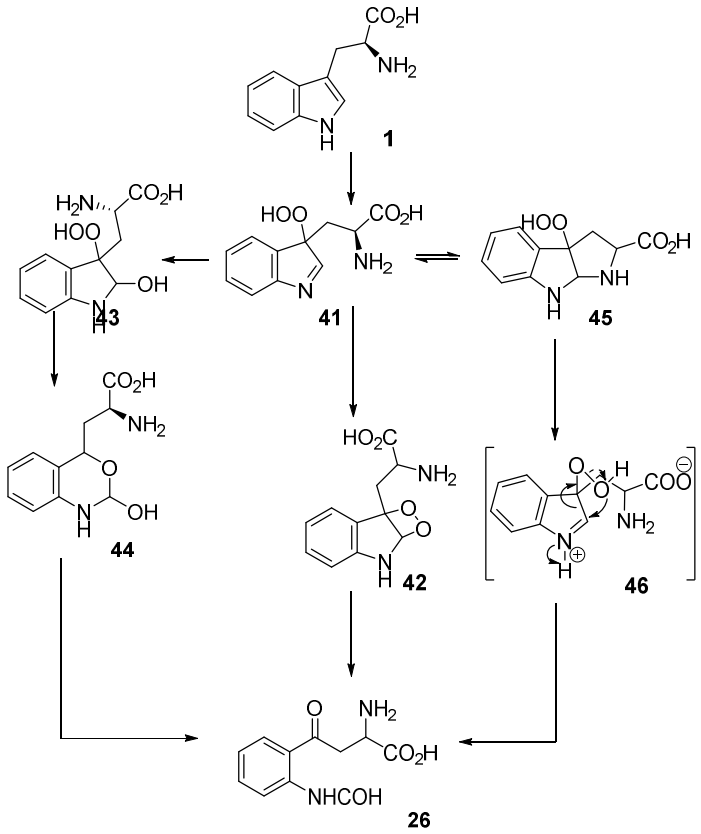
Scheme 7: Alternative mechanism of IDO/TDO catalysed tryptophan oxidation; Criegee mechanism.[25]

Kynurenine (**27**) is implicated in several diseases and both its biosynthesis and the enzymes that catalyse tryptophan's oxidation to kynurenine have been examined in a number of studies.[25, 26] In humans the kynurenine pathway is responsible for 95% of the metabolism of dietary tryptophan.[22, 27] The pathway is implicated in neurological conditions such as Huntington's, Alzheimer's and Parkinson's disease as well as cancer and HIV.[28-31]

The biological importance of this pathway means that tryptophan metabolism has also been probed chemically. Steinhart looked at the oxidation pathways of tryptophan using hydrogen peroxide and observed that the 2-postion of the pyrrole ring was the part of the molecule most prone to oxidation.[32]

The photochemical mechanism of oxidation was examined by Witkop *et al*.[33] Oxidation of the indole ring in tryptophan was thought to proceed *via* 3-hydroperoxyindolenine (**41)**, which

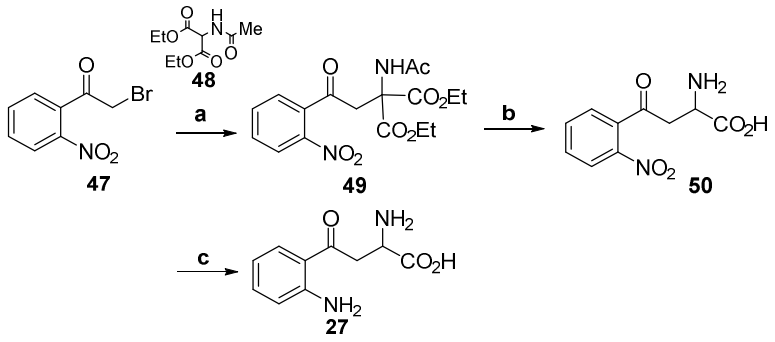
could then react *via* two possible pathways to reach *N*-formylkynurenine (**26)** (Scheme 8). Of these two routes one, *via* a dioxetane intermediate **42**, was seen as being energetically unfavourable with the other going *via* a hydrated intermediate **43/44**. Examination of these possible routes by Witkop *et al.* using dye-sensitised photooxygenation led to the suggestion of a new pathway *via* a hydroperoxypyrrolidinoindole intermediate **45**.[33] They conclude that **43** and **44** are not likely intermediates and that the mechanism proceeds by either **45** or dioxetane **42**. The equilibrium between **41** and **45** disfavours **45** being formed at low temperatures; however upon heating the reaction mixture post irradiation the formation of **45** was observed. The authors postulate that transition state **46** is the most likely intermediate in the formation of **26** when heat is applied.



Scheme 8: Proposed photochemical routes to *N*-formylkynurenine 26.[33]

Traditional synthetic routes to tryptophan metabolites are often long, with various aromatic starting materials being used. An early method for kynurenine formation involved the reaction

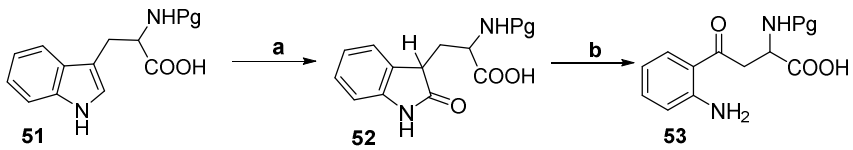
of the sodium salt of diethyl acetamidomalonate (**48)** with *o*-nitrophenacyl bromide **(47)** (Scheme 9); hydrolysis, decarboxylation and reduction allows access to the desired kynurenine **27**.[34]



Scheme 9: Formation of kynurenine; a: 48, Sodium, EtOH, 41%: b: AcOH, HCl; ii: pyridine, H_2O, 94%; c: Pd/C, H_2SO_4, 71%.[34]

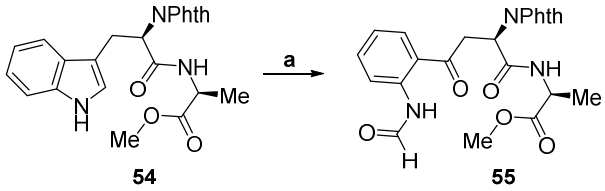
Routes to kynurenine following biomimetic principles tend to be more direct. Ozonolysis of tryptophan provides a direct route to *N*-formylkynurenine;[35] however, this method is known to result in a number of impurities and tends to have variable yields.[36] It has also been reported that tryptophan absorbs sunlight and decomposes to kynurenine; this has been harnessed by Sanders *et al.* who showed that kynurenine can be accessed photochemically from tryptophan, but this work does not appear to be scalable.[37]

Several groups have devised routes that go *via* the non-physiological tryptophan metabolite oxindolylalanine (**52)**, where tryptophan is treated with acetic acid, DMSO and concentrated hydrochloric acid.[38, 39] Oxindolylalanine is then treated with oxygen under basic conditions to mediate formation of kynurenine.



Scheme 10: Oxidation of tryptophan to give kynurenine *via* oxidolylalanine; a: AcOH, DMSO, HCl, 62% b: O_2, NaOH, H_2O, 52%.[23 39]

Evano *et al.* discovered that treatment of **54** with *meta*-chloroperoxybenzoic acid (*m*CPBA) resulted in oxidation of the pyrrole ring to give **55**; however when Martin *et al*. attempted to apply these conditions to a Cbz protected tryptophan methyl ester they found that treatment with *m*CPBA resulted in a number of unwanted side products.[40,39]



Scheme 11: Evano group oxidation; a: *m*CPBA, CH_2Cl_2, -40 °C, 85%.[40]

The decarboxylated kynurenine derivative kynuramine (**31)** is an oxidation product of tryptamine; however in contrast to the plethora of literature on the synthesis of kynurenine, [33, 35-37, 39, 40] the synthesis of kynuramine is rarely examined. It can be synthesised by oxidation of the indole ring of tryptamine and cleavage of the formyl group, or by decarboxylation of kynurenine.[41] Kynuramine is known to have biological activity and is a precursor for melatonin.[42] Kynuramine is present in natural products where tryptamine is oxidised and is believed to be a precursor to tintamine (see Section 3.1).[17]

1.5 Quinolines in nature

The quinoline motif is present in both hyrtioseragamine B and in tintamine. Quinoline was first isolated from coal tar in 1834[43] and since then this functionality has been observed in many natural products.[43-46] Quinine (**56)** is a centuries old treatment for malaria and the drug chloroquinine (**57)** is based on its structure.[43] A large number of quinolines are biologically active; skimmianine (**58)** is known to be a sedative and anticonvulsant.[43] Sanguinarine (**59)** is an antibacterial compound[47] and camptothecin (**6)** has anti-cancer properties as a topoisomerase I inhibtor.[48]

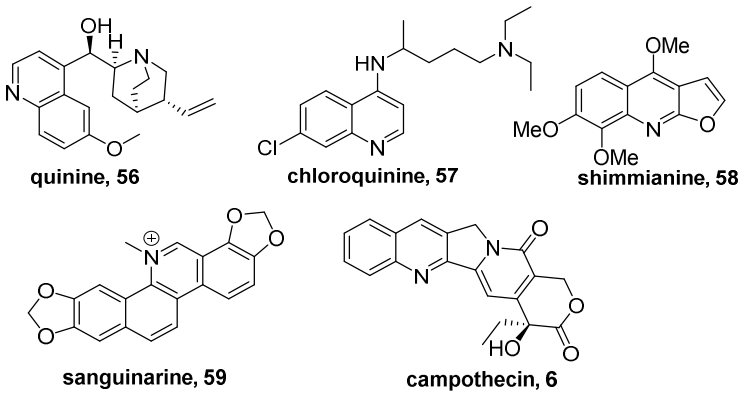
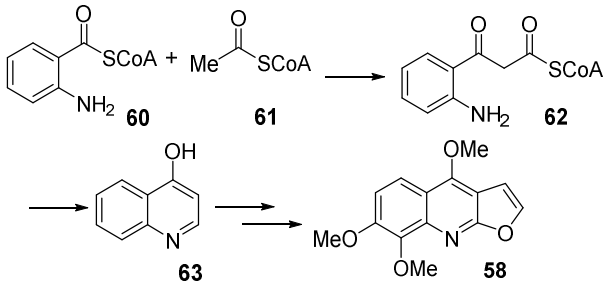


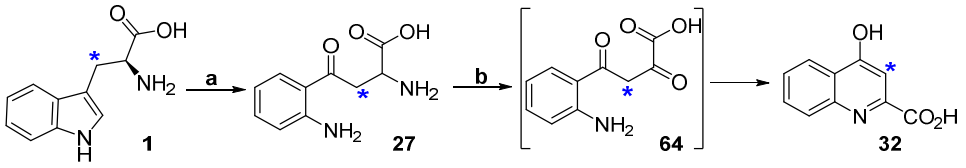
Figure 1: Quinoline containing compounds with medicinal properties: quinine 56, chloroquinine 57, skimmianine 58, sanguinarine 59 and camptothecin 6.

Quinolines are mostly found in flowering plants, but have also been isolated from animal and microbial sources.[44] It has been shown that quinolines are biosynthesised from tryptophan, with oxidation to the *o*-aryl amino ketone required to make the heterocycle. Skimmianine's biosynthesis was examined using radiolabelling in 1966.[49] Analysis of the degradation products of radiolabelled skimmianine showed that it is biosynthesised from anthranilic acid and acetic acid (Scheme 12); radiolabelled tryptophan is also incorporated into the molecule. Anthranilic acid (**18)** is a precursor to tryptophan in the shikimate pathway and is also a metabolite of the kynurenine pathway.[18, 24]



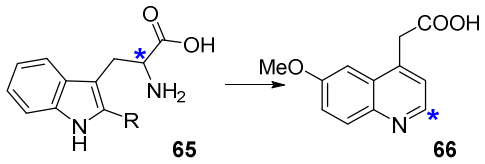
Scheme 12: Proposed biosynthesis of skimmianine 58 from anthranilic acid and acetic acid.[49]

In 1960 Tanaka and Behrman used enzymes to probe the hypothesis that in *pseudomonas* the quinoline pathway uses tryptophan oxidation.[46] From radiolabelled tryptophan they carried out an oxidation with tryptophan pyrrolase formamidase to form *L*-kynurenine. Further treatment with *L*-amino acid oxidase and spontaneous cyclisation gave kynurenic acid (Scheme 13).



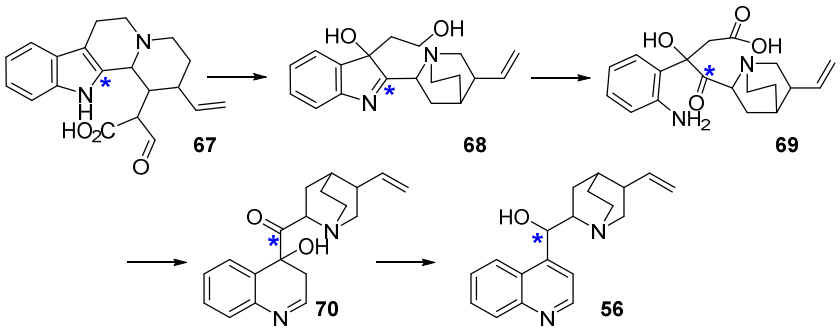
Scheme 13: The synthesis of kynurenic acid from tryptophan; a: Tryptophan pyrrolase formamidase; b: *L*-amino acid oxidase.[46]

In 1962 Leete examined the incorporation of tryptophan into the cinchona alkaloids. *DL*-tryptophan-2-C^{14} was fed to the alkaloid producing plant and it was observed that the radio label was incorporated into the 2' carbon of the alkaloid extracted from the plant (Scheme 14).[50]



Scheme 14: Examination of the biosynthesis of quinoline in the cinchona alkaloids using radiolabelling.[50]

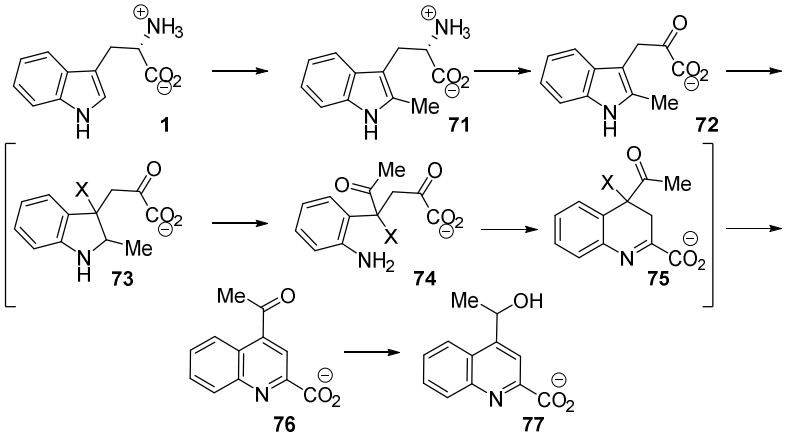
Further work on the biosynthesis of quinine resulted in the proposal of the biosynthetic route seen in Scheme 15, with this again showing the quinoline moiety is biologically synthesised from tryptophan.[51]



Scheme 15: Proposed biosynthesis of quinine.[51]

The biosynthesis of the quinoline motif observed in thiostrepton has also been examined, leading to the pathway shown in Scheme 16.[52, 53] It is described that the quinaldic acid moiety is derived almost exclusively from tryptophan, with the methyl group coming from methionine. *D,L*-2-Methyl-[3'-^{13}C]tryptophan was used in radiolabelling studies and it was

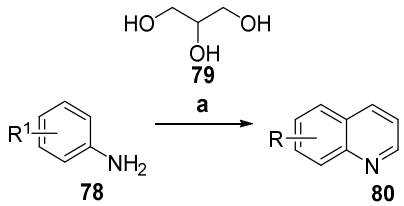
observed that the thiostrepton formed contained 40% ^{13}C at the 3-position of the quinoline. The ring expansion to convert the indole to quinoline was proved to proceed *via* cleavage of the N-1/C-2 bond and connection of C-2' to N-1 (Scheme 16).[52]



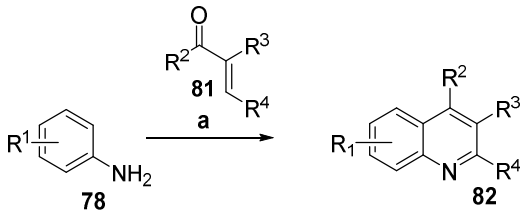
Scheme 16: Proposed pathway for the conversion of tryptophan into quinaldic acid 77 in thiostrepton.[52, 53]

1.5.1 Synthesis of quinolines

Alongside work on biosynthesis, the frequent appearance of quinolines in natural product synthesis has resulted in a wide number of chemical routes to quinolines being described.[54] The Skraup quinoline synthesis was first described in 1880 from glycerol, aniline, inorganic acid and an oxidising agent (Scheme 17).[54, 55] This method allows only substitution of the benzene ring as only the aniline starting material can be modified. An alternative method is the Doebner-Miller quinoline synthesis that uses α, β-unsaturated aldehydes, ketones or diols alongside aniline to give access to the quinoline core.[56] This allows substitution of the pyridine ring as well as the aniline, as the carbonyl component of the starting material can be substituted.

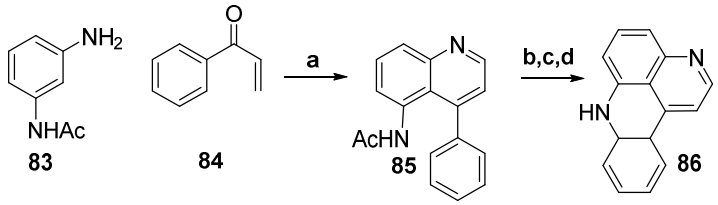


Scheme 17: Skraup quinoline synthesis; a: 79, H_2SO_4, oxidising agent.



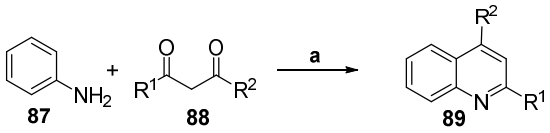
Scheme 18: Doebner-Miller modification: a: 81, HCl (aq), Zn.[56]

This method has been applied to give a pyrido[2,3,4-*kl*]acridine core **86** similar to that seen in tintamine **7**.[17, 57] The synthetic route uses the Doebner-Miller method to give phenylquinoline **85**. The acetoamido group is then converted into the azide and nitrene insertion gives the pyridoacridine core.



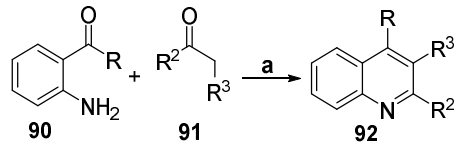
Scheme 19: Kashman synthesis of the pyridoacridine core; a: AcOH, Δ, *m*-nitrobenzene sulfonic acid Na-salt; b: H_2SO_4 (aq), 130 °C; c: i) $NaNO_2$, H^+, 0 °C, ii) NaN_3; d: durene, 200 °C, Ar.[57, 58]

The Combes quinoline synthesis uses a condensation reaction and Schiff base chemistry to allow access to the quinoline core.[59] This method typically involves heating the substrates in acid; it can give access to a substituted quinoline and has been used to form a number of complex quinoline containing motifs.



Scheme 20: Combes quinoline synthesis, H^+, Δ.

The Friedländer reaction allows access to substituted quinoline derivatives using an *o*-amino aryl ketone or aldehyde, alongside a ketone.[60] Two possible mechanisms exist; an aldol condensation is followed by a cyclisation reaction to give the quinoline or a Schiff base is formed and is followed by an aldol and elimination reaction to form the quinoline.

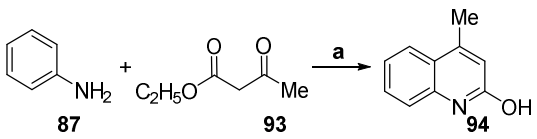


Scheme 21: Friedländer quinoline synthesis; a: H+ or base. R= H or CH_2.

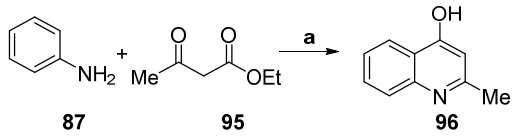
Whilst this reaction is typically catalysed by an acid or base, there are a number of modified reactions that use alternative methods to achieve the cyclisation reaction. Efforts have been made towards carrying out this reaction in the absence of a catalyst.

Work by Wang *et al.* examined the use of microwave reactions to carry out a practical, green Friedländer reaction.[61] Irradiation of the substrate in water at 70 °C was applied successfully to a range of substrates in good yield, with the only notable exception being cyclohexanone, which they attribute to low nucleophilicity of its enol. Microwave irradiation has also been applied to Friedländer substrates with *p*-toluenesulfonic acid using solvent free conditions, allowing access to a range of quinoline derivatives in excellent yield after a number of seconds.[62] The use of a Lewis acid as a catalyst for this reaction is also common. Adapa *et al*. screened a range of Lewis acids and found that neodymium(III) nitrate hexahydrate was most effective in carrying out the transformation. They then went on to optimise this reaction to give conditions that could be applied to a range of substrates in good yields.[63]

Both the Knorr and Conrad-Limpach quinoline synthesis use the same style of chemistry where a Schiff base mechanism is employed; the Knorr synthesis forms a 2-hydroxyquinoline and the Conrad-Limpach synthesis gives the 4-hydroxyquinoline.[54, 64-67] The Camp quinoline synthesis is an example of an intramolecular reaction where the *o*-acylaminoacetopheonone is converted into give two hydroxyquinoline isomers in a base catalysed reaction.[66]

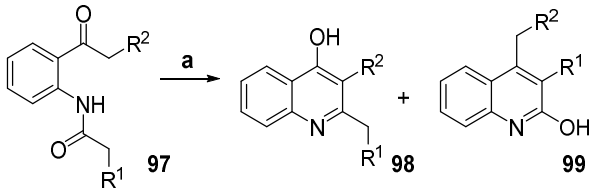


Scheme 22: Knorr quinoline synthesis; a: H_2SO_4.[67]



87 95 96

Scheme 23: Conrad-Limpach quinoline synthesis; a: Ph_2O, Δ.[60]



97 98 99

Scheme 24: Camp quinoline synthesis; a: NaOR, ROH.[60, 66]

Whilst this is not an exhaustive survey of all the reactions available to synthesise quinolines, with many modern routes also being available,[68] the number described gives an idea as to the importance of quinolines as targets for organic synthesis.

Chapter 2: Hyrtioseragamines A and B

2.1. Introduction

Hyrtioseragamines A and B were isolated from the *Hyrtios* sponge in 2011 by Kobayashi *et al*.[16] These novel alkaloids contain a unique furo[2,3-*b*]pyrazine-2(1*H*)-one core and a guanidine functionality. Hyrtioseragamine A contains an aniline and in hyrtioseragamines B this aniline is further functionalised with a quinoline derivative.

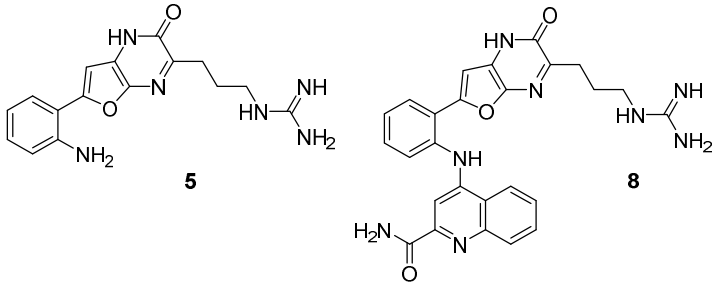


Figure 2: Hyrtioseragamine A (5) and B (8).[16]

2.1.1 Isolation and structural elucidation

The compounds were isolated from *Hyrtios* sp. (SS-985) found off the Japanese island of Okinawa. The sponge was extracted with methanol and the extract partitioned between water and *n*-hexane. The aqueous layer was then washed with chloroform, ethyl acetate and *n*-butanol. The material collected from the chloroform and butanol layers were subjected to C18 chromatography and HPLC to give hyrtioseragamine A and B alongside three known β-carbolines.[16]

Characterisation of hyrtioseragamine A by high resolution electrospray ionisation mass spectrometry (HRESIMS) gave a mass (M+H) of 327.1570 corresponding to $C_{16}H_{18}N_6O_2$ and infrared spectroscopy gave peaks indicative of a carbonyl and a NH_2 or OH functionality. UV-vis spectroscopy suggested an extended conjugated system. Analysis of the ^{1}H NMR spectrum (in CD_3OD) showed eight proton signals and the ^{13}C NMR spectrum showed three sp^3 environments in the aliphatic region and five sp^2 carbons in the aromatic region. Eight

additional sp^2 quaternary carbons were observed in the aromatic and carbonyl regions. The observation of a sp^2 quaternary carbon at δ_C 159.6 ppm alongside a positive Sakaguchi test suggested the presence of a guanidine moiety.[69]

The 2D NMR spectra suggested the presence of a 1,2-disubstituted benzene ring with the 2D NMR correlations being shown in Figure 3.

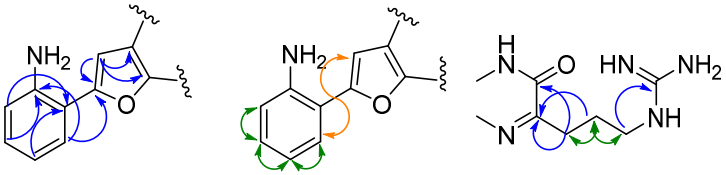


Figure 3: 2D NMR correlations of hyrtioseragamine A (green denotes COSY, blue denotes HMBC and orange denotes ROESY correlation.)

Hyrtioseragamine A was methylated using methyl iodide to probe the position of the nitrogen atoms and this resulted in the formation of compounds which were mono and dimethylated at the aniline nitrogen. Analysis of the HMBC and NOESY spectra of the most substituted version gave the results depicted in Figure 4.

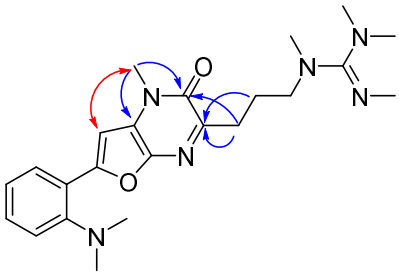
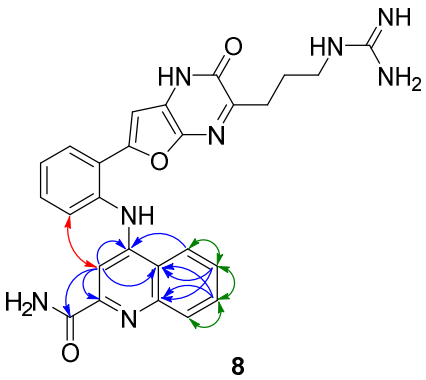


Figure 4: 2D NMR correlation over the methylated hyrtioseragamines A (blue denotes HMBC and red denotes NOESY correlation).

Hyrtioseragamine B exhibited similar UV-vis and infrared data, the HRESIMS gave a (M+H) peak at 497.2047 corresponding to $C_{26}H_{24}N_8O_3$. ^1H NMR showed ten sp^2 and three sp^3 hydrogen environments and ^{13}C NMR showed an additional 13 sp^2 quaternary carbons. This data suggested the presence of an additional aromatic system within the molecule. Analysis of the 2D NMR spectra suggested that a large part of the molecule was the same as hyrtioseragamine A with an additional 1,2-disubstituted benzene also being present. The

additional ring was deduced to be a 2,4-disubstiuted quinoline with the 2D NMR correlations seen in Figure 5.



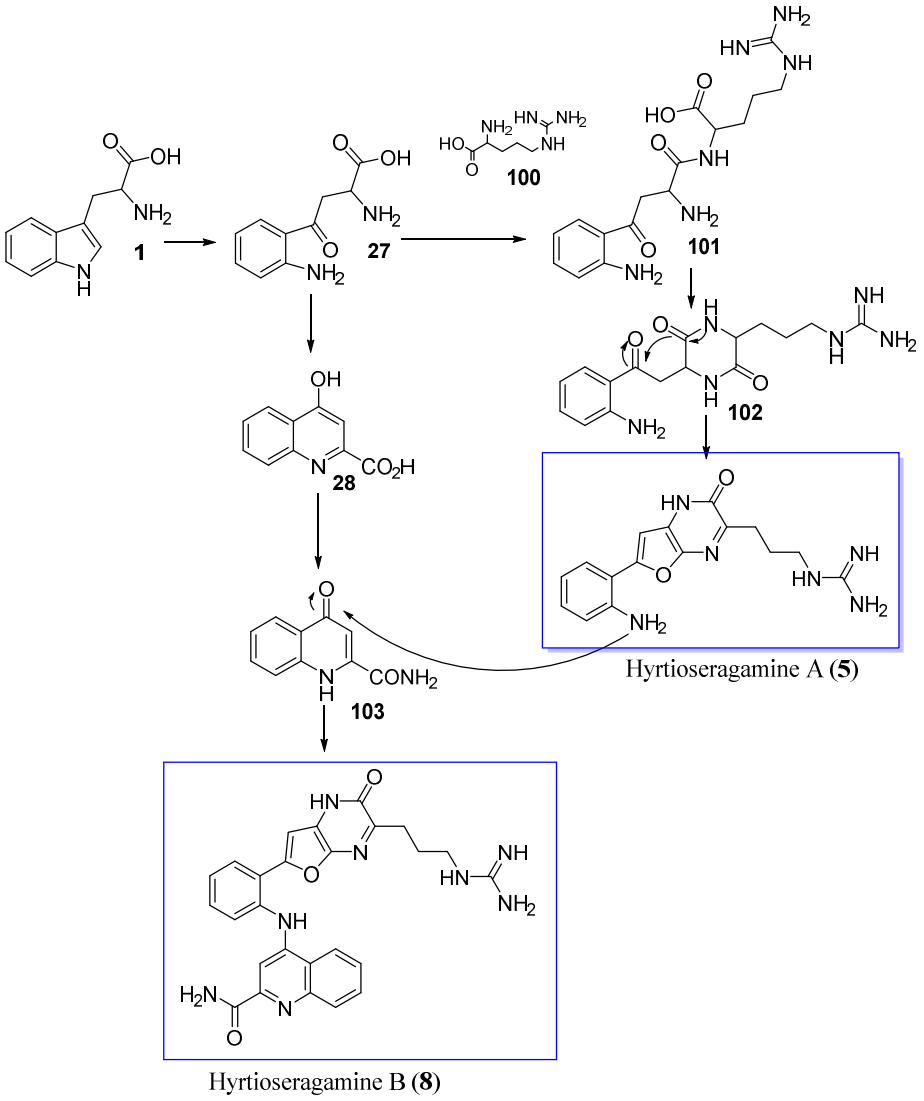
8

Figure 5: 2D NMR spectrum correlations of hyrtioseragamine B (green denotes COSY, blue denotes HMBC and red denotes ROSEY correlation).

This substituted quinoline is a rare functional group within marine organisms and this, alongside the novel furo-[2,3-*b*]pyrazine-2(1*H*)-one core means hyrtioseragamines A and B are interesting structures for total synthesis. The molecules showed anti-microbial activity against *Aspergillus niger* and *Crypticoccus neoformans,* but did not show anti-cancer activity against the tested cell lines.

2.1.2 Proposed biosynthesis of Hyrtioseragamine A and B.

Kobayashi *et al.* propose that hyrtioseragamine A and B are biosynthesised from arginine **100** and tryptophan **1**, as shown in Scheme 25.[16] They propose that tryptophan is oxidised to kynurenine and that this is coupled to arginine. From the dipeptide diketopiperazine **102** is formed and this intermediate is then cyclised to form hyrtioseragamine A **5**. It is known that quinolines are biosynthesised from tryptophan[46, 49-53] and cyclisation of kynurenine to form kynurenic acid **28**, followed by modification to **103** would give the additional moiety needed to form hyrtioseragamine B.



Scheme 25: Proposed biosynthesis of hyrtioseragamine A and B.[16]

2.1.3 Key structural features

The novel furo-[2,3-*b*]pyrazine-2(1*H*)-one core present in both members of the hyrtioseragamine family provides several interesting features for a total synthesis. The molecule contains a 2,3,5-trisubstituted furan with nitrogen atoms at the 2- and 3-position, and these are rarely seen. The molecules also contains a basic guanidine group that are known to prove challenging where they are featured in total syntheses. A number of routes to diketopiperazines are known[70] and a brief review of quinoline structures, as observed in hyrtioseragamine B, is discussed in the introduction of this Thesis.

2.1.3.1 2,3,5-Trisubstiuted furans

Furans are found in a range of natural products and many of these are polysubstituted. Furan containing compounds are often biologically active; Bhimamycin B (**104)** has antibacterial activity[71] and fungal derived furoscrobiculin B (**105)** is used as a defensive chemical in nature.[72] Furans are rarely found attached to diketopiperazines, and are more commonly seen joined to aromatic systems.[73, 74] In the hyrtioseragamine core the substitution pattern of the furan, with a nitrogen at the 2- and 3-positions, makes it challenging synthetically. Nitrogen containing furans tend to be prepared from molecules which have the nitrogen atoms as part of a wider aromatic system prior to cyclisation in order to increase the furans stability.[73, 74]

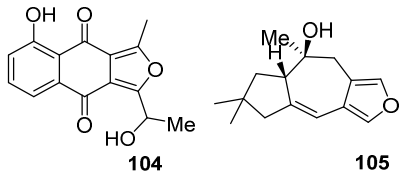
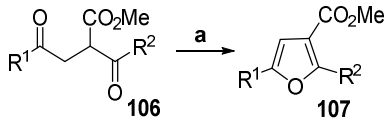


Figure 6: Bhimamycin B 104[71] and furoscrobiculin B 105.[72]

2.1.3.1.1 Established routes to comparable structures

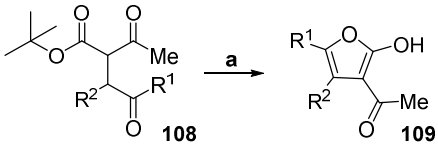
A number of methods to synthesise furans exist; furans can by synthesised by ring closing metathesis, Feist-Benary furan synthesis and the Paal-Knorr furan synthesis, amongst others.[75] In the biosynthetic route to the hyrtioseragamine core proposed by Kobayashi it is suggested that a 1,4-dicarbonyl undergoes a cyclisation to access the furan from the diketopiperazine intermediate **120** (Scheme 25).[16]

A microwave assisted Paal-Knorr synthesis of furan is described by Taddei *et al.* as a route to polysubstiuted furans from a 1,4-diketone (Scheme 26).[76] Treatment of **106**, where the R groups are a range of hydrocarbons, with ethanol and hydrochloric acid at 100 °C with microwave irradiation gave access to 2,3,5-trisubstiuted furans in good yields.[76]



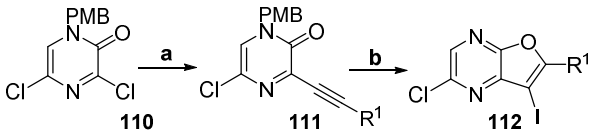
Scheme 26: Microwave assisted furan formation; a: EtOH/HCl, 100 °C, MW irradiation, 86-91%.[76]

Formation of a furan from a 1,4-diketone is often catalysed by Brønsted or Lewis acids. Neier *et al.* formed a range of polysubstituted furans from 1,4-ketoester in the presence of trifluoroacetic acid; however none of their examples contain a nitrogen at the 2- or 3-position.[78]



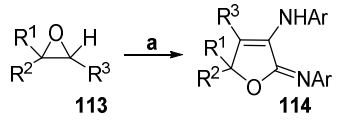
Scheme 27: Synthesis of polysubstiruted furans; a: TFA or TFA/CH_2Cl_2 (1:10).[78]

Examination of the literature provides routes to the furo[2,3-*b*]pyrazine; however few use biomimetic principles. In 2012 Van der Eycken *et al.*[79] published a route to these polysubstituted furans (Scheme 28). From a halogen substituted protected pyrazine-2(1*H*)one (**110**) Sonagashira coupling is carried out to install an alkyne, this then undergoes iodine mediated cyclisation reaction to form furan **112**. The group then use palladium chemistry to install a range of functionalities in place of the halogens.



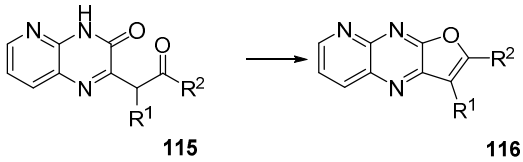
Scheme 28: Synthesis of a 2,3-dinitrogen substituted furan; a: $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (5 mol%), acetylene, Et_3N/DMF, 90 °C, MW conditions, 70-81%; b: I_2, CH_2Cl_2, 70-86%.[79]

It has also been shown that 2,3-dinitrogen substituted dihydrofurans can be synthesised from epoxides and isocyanides in the presence of gallium(III) chloride.[80] Gallium(III) chloride is known to open epoxides to the carbocation; double insertion of isocyanide followed by a 1,3-hydrogen shift gives access to the desired product.



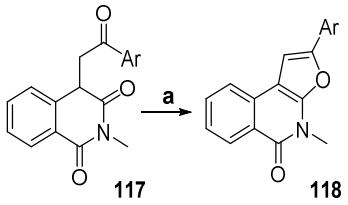
Scheme 29: 2,3-Nitrogen substituted 2,5-dihydofuran synthesis; a: Ar-NC, $GaCl_3$, CH_2Cl_2.[80]

One example of a 2,3-dinitrogen substituted furan being formed from a 1,4-dicarbonyl was described by Zimmer *et al.*[73] Sulfuric acid was used to initiate formation of the furan from a 1,4-ketoamide to form the polysubstituted furan (Scheme 30). These conditions were applied to several substrates, each of which contain a halogen as the R^1 group.



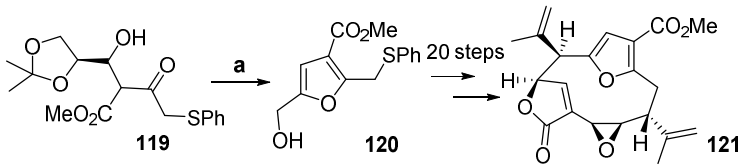
Scheme 30: Sulfuric acid-catalysed cyclisation as described by Zimmer *et al.* where R_1 is a halogen; a: H_2SO_4.[73]

Onda *et al.* has described the use of *p*-toluenesulfonic acid in ethylene glycol and benzene to aid cyclisation of a 1,4-dicarbonyl with nitrogen at the 2-position (Scheme 31).[74]



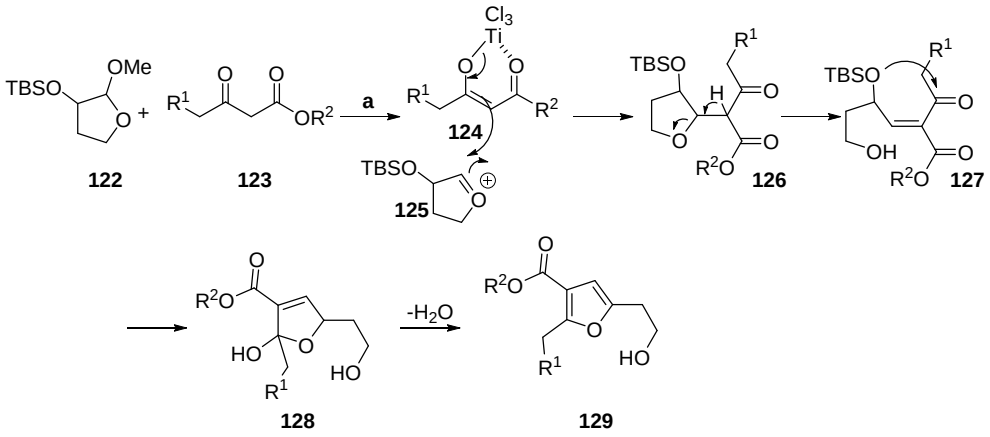
Scheme 31: Onda *et al.* cyclisation; a: *p*-TsOH, ethylene glycol, PhMe.[74]

In the synthesis of furanocembranolide natural products, such as pseudopterolide (**121**), a 3,4-dioxygented ketone was treated with acetic acid, water and ethanol at 80 °C to initiate cyclisation.[81]



Scheme 32: Synthesis of the furan moiety in furanocembranolides; a: AcOH, H_2O, EtOH, 80 °C.[81]

Lewis acids, such as titanium tetrachloride, and β-ketoesters **123** with cyclic acetal groups **122** can be employed as an alternative route to furans. A titanium enolate **124** attacks the oxonium ion **125** on the acetal, followed by acetal ring opening and cyclisation giving the trisubstituted furan (Scheme 33).[82]



Scheme 33: Lewis acid-catalysed furan formation: a: $TiCl_4$.[82]

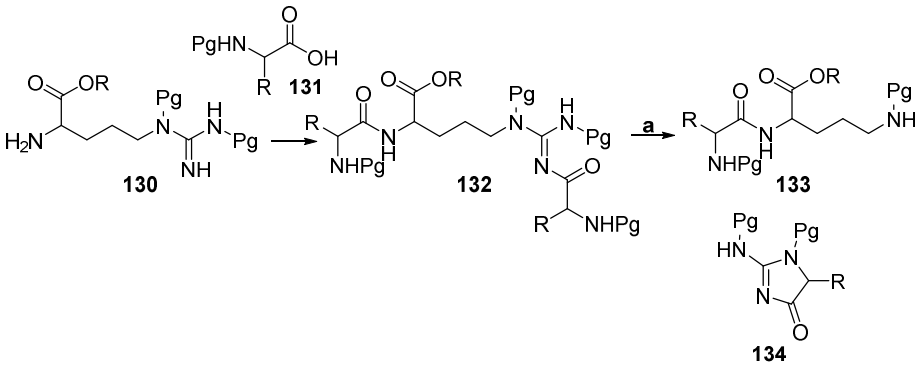
Many of these examples illustrate formation of furans that are stabilised by electron-withdrawing groups, and these will not be present in the synthesis of the hyrtioseragamine core. The limited literature precedent for the synthesis of furans with nitrogen atoms at the 2- and 3-positions means the use of acid-catalysed cyclisation based on a biomimetic Paal-Knorr approach will be investigated in the synthesis of the furo[2,3-*b*]pyrazine-2(1*H*)-one core of the hyrtioseragamines.

2.1.3.2 Arginine containing peptides

The reactive guanidine group of the amino acid arginine is both basic and nucleophilic and is known to be problematic during synthetic sequences; it is often masked to prevent side reactions occurring during synthesis.[83]

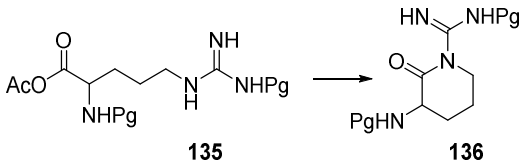
The use of protecting groups to mask the guanidine is common; whilst protecting all of the guanidine nitrogens is desirable, this is not always possible and the use of bulky protecting groups allow mono and di-protected guanidine to be employed. Whilst a range of protecting groups are available, a number of problems are still associated with the use of guanidine

groups. For example, when carrying out amino acid coupling under basic conditions it has been observed that the reactive nature of the guanidine group can result in acetylation of the guanidine nitrogen. This can then result in the guanidine group being lost to give the non-proteinogenic amino acid ornithine, despite the presence of protecting groups (Scheme 34).[84]



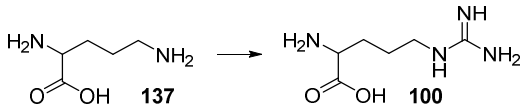
Scheme 34: Deguanidation process of arginine in basic conditions; a: basic conditions.[84]

Activation of the carboxylic acid group of the arginine, for example as a mixed anhydride, often results in formation of the δ-lactam, as shown in Scheme 35, despite the presence of a protecting group on the guanidine.[83]



Scheme 35: Formation of the δ-lactam of arginine, 48-88%.[83]

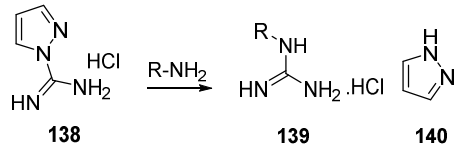
In a synthesis containing arginine, it is possible to avoid the problems associated with guanidine by instead using non-proteinogenic amino acid ornithine in its place. The ornithine δ-amine can be converted into a guanidine group at a late stage of the synthesis (Scheme 36).



Scheme 36: Conversion of ornithine 137 to arginine 100.

A wide number of reagents exist for guanylating the ornithine, with these providing the opportunity to install the guanidine with protecting groups.[85] Bernatowicz *et al.* found that

conventional guanylating reagents were not able to convert ornithine into arginine in solid phase peptide synthesis. Instead they used the 1*H*-pyrazole-1-carboxamidine (**138)** to carry out the guanylation reaction. This strategy has been developed by a number of groups to form reagents with a range of protecting groups; it has been found that Boc and Cbz-protected derivatives are more reactive than the unprotected **138**.[86] Work in the Moody group on the arginine containing peptide plantazolicin resulted in the development of a Teoc protected pyrazole derivative to guanylate ornithine.[87]



138 **139** **140**

Scheme 37: Guanylation of a primary amine with 1*H*-pyrazole-1-carboxamidine; a: DIPEA, DMF, 48-88%.[88]

The use of an ornithine derivative and late stage installation of the guanidine group has been shown to prevent side reactions from occurring, and this strategy will be employed in the synthesis of the hyrtioseragamines.

2.1.3.3 2,5-Diketopiperazines

The 2,5-diketopiperazine motif present in the hyrtioseragamines is also seen in many other natural products.[89-91] They are structurally rigid, chiral molecules that can bind to receptors with high affinity and have a number of biological applications.[92] The motif consists of two amides and thus has four possible hydrogen bond sites. Diketopiperazines are also stable to proteolysis. Diketopiperazines are believed to be either secondary functional metabolites or side products from terminal peptide cleavage and are typically isolated from a marine environment or from microorganisms.[93]

Biologically, diketopiperazine derivatives have been seen to inhibit plasminogen-activator inhibitor-1, control cardiovascular function and effect blood clotting factors.[92] They are also known to have anti-bacterial,[93] anti-viral,[94] cytotoxic[95] and immunosuppressive properties.[96]

The privileged scaffolds of diketopiperazines mean they appear in drug molecules; one example is Retosilban (Figure 7) that is being developed as an oxytocin antagonist.[97]

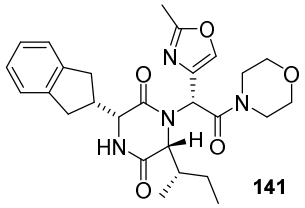


Figure 7: Oxytocin inhibitor Retosilban.

Diketopiperazines are biosynthesised from amino acids,[92] and Figure 8 shows several tryptophan derived diketopiperazines. They were thought to be synthesised by non-ribosomal peptide synthetases, but in 2002 it was shown the cyclodipeptide synthatases formed a *L*-leucine-*L*-phenylalanine diketopiperazine[98] and it has been accepted that this family of enzymes is also responsible for diketopiperazine biosynthesis.[99] Gypesetin (**142)** is an indole containing diketopiperazine that has been shown to inhibit the enzyme acyl-CoA:cholesterol acyltransferase, which is implicated in the uptake of cholesterol.[91] Tryprostatin (**143)** was isolated from *Aspergillus fumigatus* and is known to inhibit the cell cycle. Notamide C (**144)** was synthesised by Williams *et al*. in 2007 and is believed to be biosynthesised from a gramine derivative, proline and a glycine.[90] Brevianamide E (**145)** is a tryptophan and proline derived diketopiperazine isolated from *Penicillium brevicompactum*.[91, 100]

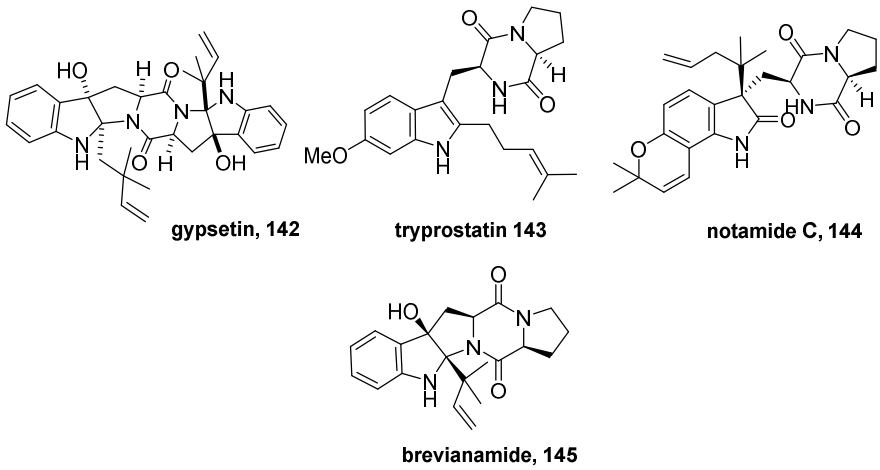
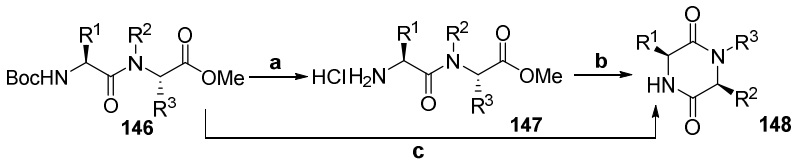


Figure 8: Tryptophan derived diketopiperazines; 142 gypsetin, [91] tryprostatin 143,[89] notoamide C 144[90] and brevianamide E 145.[95]

2.1.3.3.1 Established routes to comparable structures

Methods such as the Ugi-reaction, Diels Alder reaction and aza-Michael addition reactions have all been employed in diketopiperazine synthesis;[70] however, these methods do not use a dipeptide intermediate and so will not be considered here as they are not appropriate for the biomimetic route described by Kobayashi.[16]

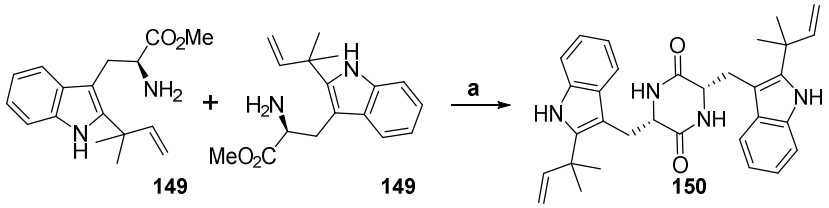
Luthman *et al.* used microwave conditions at 200 °C with water as a solvent to induce cyclisation of dipeptide **146** to the diketopiperazine.[77] From hydrochloride salt **147** cyclisation occurs in water in the presence of triethylamine under microwave irradiation. Alternatively, they observe that the Boc-protected material can be cyclised directly in water, heating with microwave irradiation at 200 °C (Scheme 38).



Scheme 38: Microwave induced diketopiperazine formation; a: HCl, MeOH, 52-88%; b: Et_3N, H_2O, MW heating, 140 °C, 60-88%; c: H_2O, 200 °C, MW irradiation 40-73%.[77]

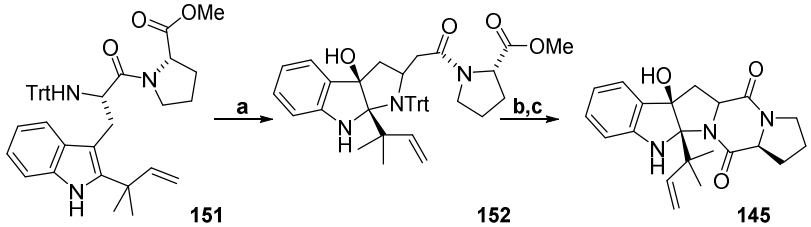
The total synthesis of the acyl-CoA:cholesterol acyltransferase inhibitor gypsetin (**142**) by Danishefsky *et. al.* originally used Bop-Cl to couple indole **149** with a Boc-protected version of **149**; removal of the Boc protecting group and ammonia mediated cyclisation formed

diketopiperazine **150**.[91] However, when reconsidering this route they found that heating **149** at 140 °C resulted in formation of the diketopiperazine in a 30% yield in one step.



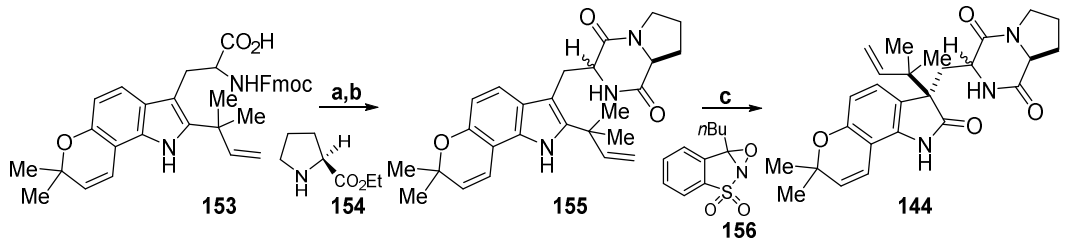
Scheme 39: Diketopiperazine formation in gypsetin synthesis; a: 140 °C, 30%.[91]

A route to the diketopiperazine brevianamide E has been developed by Perrin *et. al.*, where a tryptophan proline derivative (**151**) was treated with dimethyldioxirane (DMDO) to carry out an oxidative cyclisation to give the precursor to diketopiperazine formation **152**.[100] This substrate was treated with hexafluoro-2-propanol (HFIP) to remove the protecting group and addition of *N*,*N*-diisopropylethylamine resulted in diketopiperazine formation (Scheme 40).



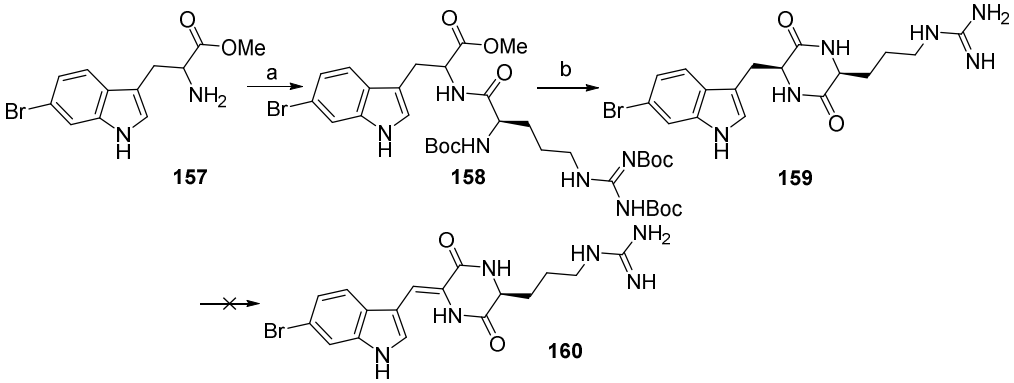
Scheme 40: Brevianamide E synthesis; a: DMDO, CH_2Cl_2/acetone, -78 °C; b: HFIP/CH_2Cl_2; c: *N*,*N*-diisopropylethylamine, MeOH, 80 °C.[100]

The biomimetic synthesis of notoamide C was carried out by Williams in 2007, with the diketopiperazine again being formed from a proline and tryptophan derived dipeptide.[90] On this occasion the dipeptide is treated with morpholine in THF to give the precursor to the natural product. Oxidation of the indole ring using an oxaziridine and migration of the prenyl group gave access to notoamide C **144**.



Scheme 41: Synthesis of notoamide C: a: BopCl, *N*,*N*-diisopropylethylamine, ; b: morpholine, THF; c: CH_2Cl_2.[90]

In work towards the synthesis of natural product barettin, a diketopiperazine was formed from a tryptophan derivative **157** and arginine, forming a diketopiperazine similar to that seen in the hyrtioseragamines.[101] To overcome the known problems with the guanidine moiety of arginine a Boc-protected derivative was employed and coupled to the methyl ester of 6-bromo-tryptophan. Acidic conditions removed the Boc protecting group and treatment with *N*-methylmorpholine induced cyclisation to diketopiperazine **159**. Unfortunately, from this molecule they were unable to access the natural product.



Scheme 42: Work towards the total synthesis of barettin; (a) EDC, HOBt, N,N-diisopropylethylamine, CH_2Cl_2, (b) i) TFA, CH_2Cl_2, ii) AcOH/BuOH, *N*-methylmorpholine.[101]

Whilst the furo[2,3-*b*]pyrazine-2(1*H*)-one core of the hyrtioseragamines is novel and no known route to this type of molecule exists, similar diketopiperazines formed from arginine and tryptophan are known within the literature. A number of routes to oxidise tryptophan to its metabolite kynurenine are also known (Section 1.4). The formation of the furan is likely to be the most challenging part of this synthesis; acidic conditions are frequently used to cyclise 1,4-diketones to furans and have also been used in the limited examples of furan synthesis

from a ketoamide. The principles of these acid mediated cyclisations will be applied to the synthesis of hyrtioseragamine A and B.

2.2 Aims and objectives

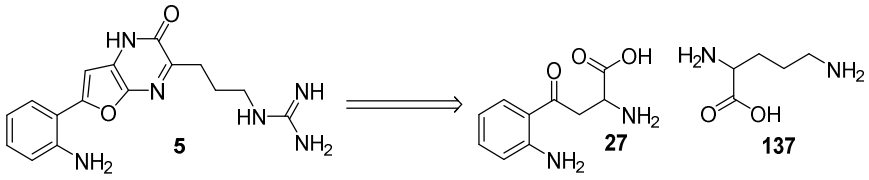
When the structures of hyrtioseragamine A and B were published, it was proposed that the novel furo[2,3-*b*]pyrazine-2(1*H*)-one core is biosynthesised from tryptophan metabolite kynurenine and arginine.[16] The formation of a diketopiperazine core from these two compounds is not described within the literature and a route to this key intermediate will need to be established.

The formation of the 2,5-diketopiperazine will give a molecule that contains a 1,4-ketoamide and it is proposed that this compound can be cyclised to form a furan and give access to the core of these natural products, and this hypothesis will be probed synthetically.

The natural products have biological activity and synthesis of more material would allow this to be investigated further. The novel core of these two natural products provide an interesting target for total synthesis and a synthetic route towards this challenging core will be investigated based on the biomimetic route described by Kobayashi *et al*.[16]

2.3 Results and discussion

Kobayashi *et al.* proposed that the hyrtioseragamine core is synthesised from arginine and the tryptophan derivative kynurenine.[16] The novel nature of the furo[2,3-*b*]pyrazine-2-(1*H*)-one core featured in these natural products means synthetic routes are not reported within the literature, and as a result of this, a route following the principles outlined when the hyrtioseragamine core was published were adopted (Scheme 43). Kobayashi proposes that the novel core is biosynthesised from tryptophan metabolite kynurenine **27** and arginine **137**.[16]



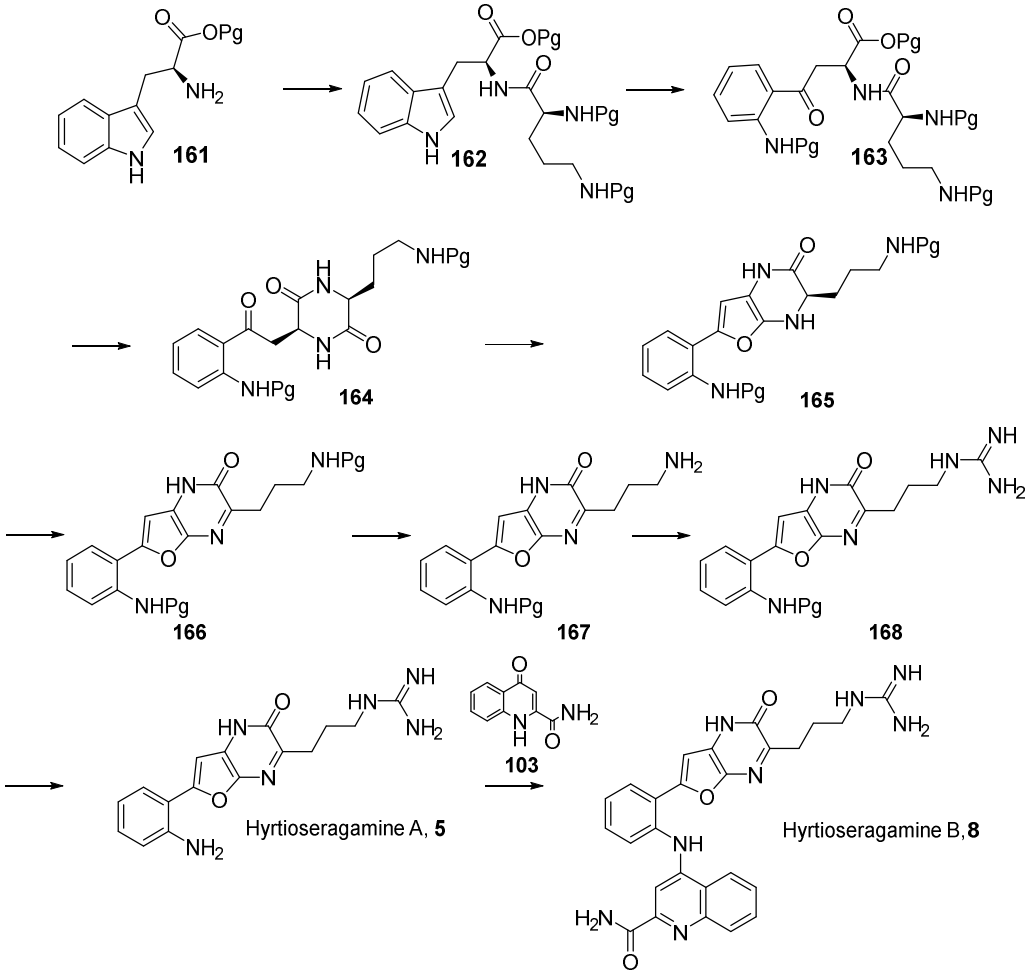
Scheme 43: Retrosynthetic analysis of hyrtioseragamine A.[16]

2.3.1 Biomimetic route and synthesis plan

Based on the biogenetic pathway described by Kobayashi *et al.* a route from tryptophan and arginine was designed (Scheme 44). Tryptophan is coupled to the non-proteinogenic amino acid ornithine. In Section 2.1.3.2 the problems with working with arginine were described; in this synthetic route a protected ornithine derivative is used and the guanidine motif installed at a late stage of the synthesis.

Oxidation of tryptophan to kynurenine has been described in section 1.4 and these principles can be applied to the synthesis of the hyrtioseragamine core. Exposure of the dipeptide to oxidising conditions gives the precursor **163** required for diketopiperazine formation. Diketopiperazine **164** contains a 1,4-dicarbonyl that is set up for furan formation; from the furan dehydrogenation of the diketopiperazine will give the furo[2,3-*b*]pyrazine-2-(1*H*)-one core **165** common to both natural products. From **166**, removal of the protecting group on the δ amine and installation of a guanidine will allow formation of the arginine. Removal of the

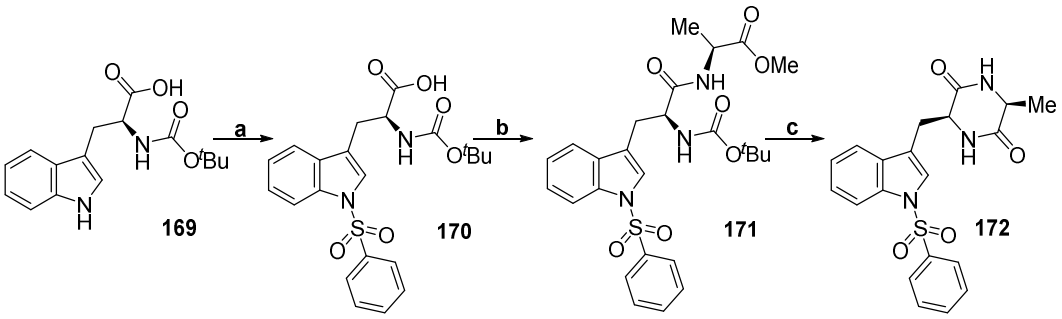
protecting group from the aniline will give hyrtioseragamine A (**5**) and installation of the quinoline group to the aniline nitrogen will allow access to hyrtioseragamine B (**8**).



Scheme 44: Proposed synthesis of hyrtioseragamine A and B.

2.3.2 Diketopiperazine formation

Whilst a number of methods to form diketopiperazines exist, formation of a dipeptide and subsequent cyclisation allows diketopiperazine formation to occur following biomimetic principles. Diketopiperazines containing tryptophan as one of the amino acids are common; in the total synthesis of (+)-11,11'-dideoxyverticillin A a diketopiperazine was formed from tryptophan biomimetically (Scheme 45),[102] and initially this route was explored.

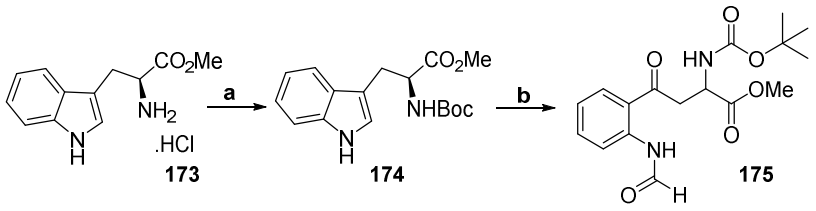


Scheme 45: Initial investigation of diketopiperazine formation based on the work of Movassaghi;[102] a: i) LiHMDS, THF, ii) benzene sulfonyl chloride, 52%; b:i) 1-hydroxybenzotriazole hydrate, *L*-alanine methyl ester hydrochloride, *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride, CH_2Cl_2, ii) Et_3N, $KHSO_4$, 90%; c: i) TFA, CH_2Cl_2, ii) morpholine, butanol, 53%.

Boc-protected *L*-tryptophan **165** was protected with a benzenesulfonyl group and *N*-sulfonated tryptophan **170** was then coupled to *L*-alanine methyl ester to form **171**. In our hands, treatment of **171** with trifluoroacetic acid removed the Boc group and treatment with morpholine allowed formation of diketopiperazine **172** in a 53% yield, which was slightly lower than the 84% reported by Movassaghi.[102] From **172** it was attempted to remove the protecting group from the indole nitrogen, but problems with solubility of the diketopiperazine meant this was problematic and it was concluded that this protecting group may not be appropriate for the synthesis of the hyrtioseragamine core.

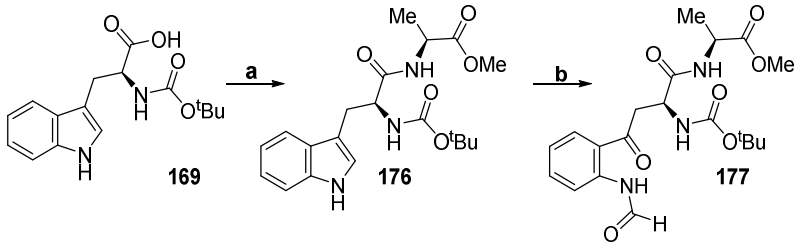
2.3.3. Tryptophan oxidation

Following the successful formation of diketopiperazine **172** on a model using tryptophan and alanine, efforts now turned to oxidation of the indole ring. It has been described by Evano that it was possible to use *m*-chloroperoxybenzoic acid (*m*CPBA) to oxidise the pyrrole ring.[40] *L*-Tryptophan methyl ester **173** was protected at the amino-nitrogen with a Boc group and tryptophan **174** was treated with *m*CPBA to cleave the 2,3-indole bond and give the desired *N*-formylkynurenine **175** in a 31% yield (Scheme 46).



Scheme 46: Oxidation of tryptophan; a: di-*tert*-butyl dicarbonate, Et_3N, CH_2Cl_2, 88%; b: *m*CPBA, CH_2Cl_2, 31%.

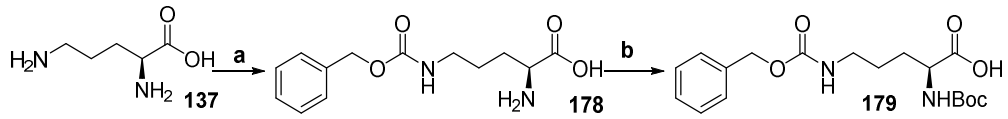
Martin *et al*. showed this methodology worked better on dipeptides than amino acids and these conditions were applied to intermediate **176**, which had been synthesised from Boc-protected tryptophan and *L*-alanine methyl ester in an 80% yield. Oxidation with *m*CPBA gave **177** in a 48% yield, with the formyl group on the aniline conveniently acting as a protecting group (Scheme 47).



Scheme 47: Oxidation of the dipeptide; a: *L*-alanine methyl ester hydrochloride, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, *N*,*N*-diisopropylethylamine, DMF, 97%; b: *m*CPBA, CH_2Cl_2, 48%.

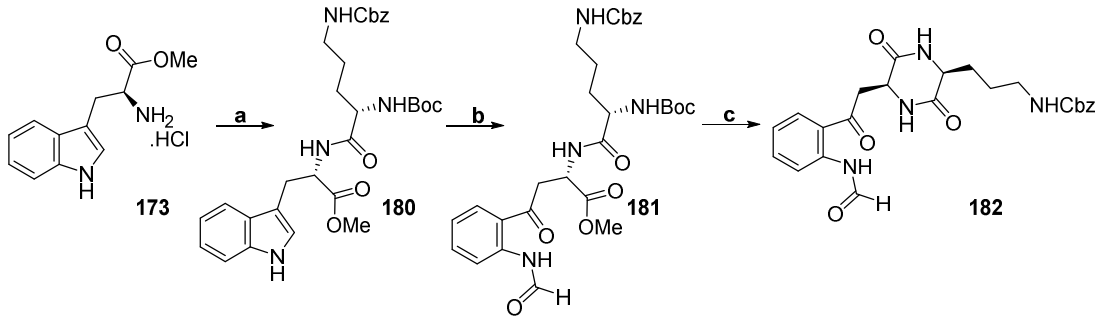
2.3.4 Attempts to form the furo [2,3-*b*]pyrazine-2(1*H*)-one core

With a route to oxidise tryptophan as a dipeptide established, attention turned to the real system. Protecting ornithine with a Boc group on the α-amine and a Cbz group on the δ-amine will allow the Boc group to be removed to form the diketopiperazine whilst the δ-amine protecting group remains in place until it is removed at a late stage of the synthesis. Formation of an ornithine with such protecting groups had been carried out by Pattenden *at al*. and these conditions were investigated (Scheme 48).[103]



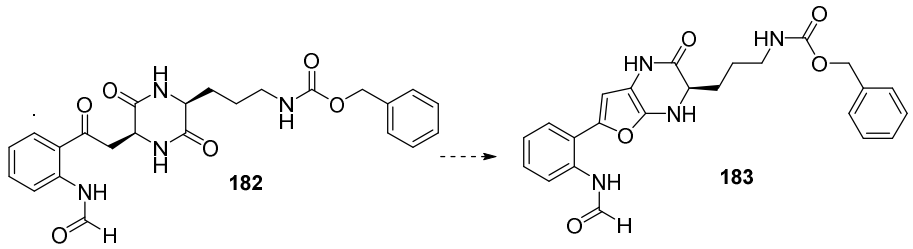
Scheme 48: Selective protection of ornithine[103]: (a): i) $CuCO_3 \cdot Cu(OH)_2$, water, 110 °C; ii) MgO, benzyl chloroformate; iii) EDTA, $NaHCO_3$, Δ; (b):K_2CO_3, di-*tert*-butyl dicarbonate, 1,4-dioxane; 36% over 2 setps.

Ornithine was treated with copper(II) carbonate and this allowed selective Cbz protection of δ-amine. Treatment with EDTA was followed by Boc-protection to allow formation of *N*α-*t*-Boc-*N*δ-Cbz-*L*-ornithine. Coupling of the protected ornithine to tryptophan methyl ester **173** occurred in quantitative yield and dipeptide **180** was then treated with *m*CPBA to oxidise the pyrrole in a pleasing 66% yield. Treatment of **181** with trifluoroacetic acid and morpholine resulted in formation of diketopiperazine **182** with the kynurenine side chain at the 2-position and ornithine at the 5-position in a 40% yield over three steps (Scheme 49). A brief examination of conditions to improve formation of the diketopiperazine using microwave conditions proved unsuccessful.[77]



Scheme 49: Route to the ornithine-*N*-formyl-kynurenine diketopiperazine; a; Nα-Boc-Nδ-Cbz-*L*-ornithine, *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate, *N,N*-diisopropylethylamine, DMF, 98%; b: *m*CPBA CH_2Cl_2, 66%; c: i) TFA, CH_2Cl_2; ii) morpholine, *t*-butanol, 60%.

With a route to key intermediate **182** established, it was now necessary to attempt to cyclise the 1,4-dicarbonyl to form the furan and establish the novel furo[2,3-*b*]pyrazine-2-(1*H*)-one core (Scheme 50).



Scheme 50: Proposed cyclisation to form the core furo[2,3-*b*]pyrazine-2(1*H*)-one structure.

Conditions	Result
H_2SO_4, 21 °C[73]	No reaction
H_2SO_4, reflux	Starting material with loss of formyl group
***p*-TsOH,**[74] **ethylene glycol, benzene, reflux.**	No reaction
***p*-TsOH, DMF, 21 °C**	No reaction
Camphorsulfonic acid, PhMe, 21 °C	No reaction
Polyphosphoric acid,[104] **160 °C**	Decomposition
Eaton's reagent, 140 °C	No reaction
TFA, 21 °C [78]	Starting material with loss of formyl group
$BF_3(OEt)_2$, PhMe, 21 °C **$BF_3(OEt)_2$, PhMe, 110 °C**	No reaction
$Sc(OTf)_3$, PhMe, 21 °C **$Sc(OTf)_3$, PhMe, 110 °C**	No reaction
$TiCl_4$, PhMe, 21 °C	No reaction
$AlCl_3$, PhMe, 21 °C	No reaction

Table 1: Conditions examined to form the furo[2,3-*b*]pyrazine-2(1*H*)-one core from 182 (Scheme 50).

Whilst there is a strong precedent for converting 1,4-diketones into furans using the Paal-Knorr synthesis, few furans have been reported with nitrogen at the 2- and 3-position and these compounds are rarely synthesised from 1,4-dicarbonyls.[79, 80] As a result of this it was decided to investigate acidic conditions to initiate furan formation, in an effort to mimic conditions used in Paal-Knorr furan synthesis (Table 1).

Application of the sulfuric acid conditions described by Zimmer (Section 2.1.3.1.1, Scheme 30)[73] to our substrate were unfortunately unsuccessful; at room temperature no reaction occurred and when **182** was heated in the presence of sulfuric acid the protecting groups were

lost, but no cyclisation was observed. Onda *et al*. also use acidic conditions to initiate cyclisation (Scheme 31).[74] On our system only starting material was isolated after treatment with *p*-toluenesulfonic acid and ethylene glycol, heating at reflux for 24 hours. The application of *p*-toluenesulfonic acid to this substrate in anhydrous DMF again resulted in only starting material being obtained. Camphorsulfonic acid in anhydrous toluene and DMF resulted in no reaction and subsequent heating of the reaction mixture again returned only starting material.

The use of polyphosphoric acid as a reagent to form furans from a 1,4-diketone is well documented since Snyder and Werber reported its use for cyclodehydration in 1950.[104-106] The difficulties documented with working with polyphosphoric acid resulted in Eaton *et al.* developing phosphorus pentoxide in a 1:10 mixture with methanesulfonic acid as an alternative.[107] Eaton's reagent was unsuccessful in initiating cyclodehydration on substrate **182** and reverting to polyphosphoric acid also resulted in decomposition.

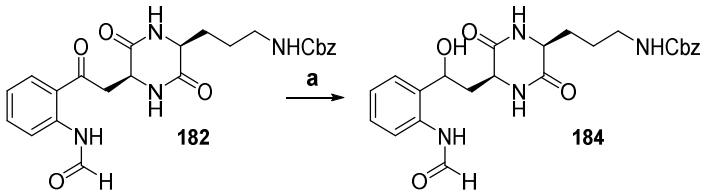
A final attempt at acid-catalysed furan formation from the 1,4-dicarbonyl was investigated with trifluoroacetic acid, as its use has been described in the synthesis of a range of tetra and trisubstituted furans from the corresponding 1,4-diketones;[78] unfortunately this resulted only in deprotection of the starting material.

A range of Lewis acids was also explored as possible conditions for cyclisation (Table 1); however in each of these cases cyclisation did not occur and only starting material was observed.

The use of microwave irradiation to aid cyclisation has also been described.[76] Application of microwave heating in acetic acid again resulted in only starting material being isolated.

Furan has also been synthesised from 1,4-diketones in dimethylsulfoxide (DMSO). Both the simple diketone acetonylacetone and its substituted derivatives were cyclised to the corresponding furans in good yield, with the avoidance of side reactions caused by the acid in other cyclisation reactions.[108] The diketopiperazine was heated at 190 °C for 5 days in DMSO, but only starting material was isolated.

The use of mesyl chloride as a dehydrating reagent to drive the reaction was also explored; sodium borohydride was able to successfully reduce the *N*-formylkynurenine ketone but the addition of mesyl chloride and triethylamine resulted in decomposition, with no cyclisation being observed.



Scheme 51: Reduction of the ketone to allow dehydration to occur; a: $NaBH_4$, MeOH, 28%, mixture of diastereoisomers (2:3).

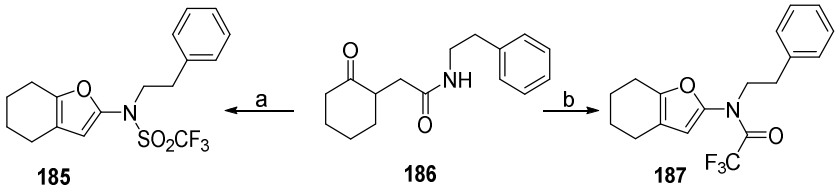
Despite a lack of literature precedent for base catalysed cyclisation of 1,4-dicarbonyls, this was investigated briefly since it was suggested that deprotonation of the diketopiperazine nitrogen initiates cyclisation in the biogenetic pathway (Section 2.1.2, Scheme 25).[16] Heating diketopiperazine **182** in either pyridine, triethylamine or morpholine was unsuccessful with starting material, or starting material without the formyl group being isolated after three days.

2.3.5 Alanine-kynurenine model and cyclisation attempts

A problem observed with many of these reactions was the lack of solubility of the diketopiperazine; as a result of this a simpler model system was examined using the alanine-kynurenine precursor to the diketopiperazine synthesised to examine tryptophan oxidation (Scheme 47). The soluble dipeptide was subjected to the range of acidic conditions previously employed in an attempt to initiate cyclisation on the diketopiperazine; however only starting material or starting material without the protecting groups were observed on each occasion. Conditions where **177** was treated with phosphorus pentoxide were also employed; **177** was heated with the drying agent and separately glacial acetic acid and concentrated sulfuric acid for 24 hours. The product of both of these reactions differed only from the starting material in the loss of the formyl group.

Trifluromethanesulfonic (triflic) anhydride is described as a useful reagent for the conversion of cyclic ketoamides to α-trifluoromethylsulfonylamido furans by Padwa *et al*.[109] (Scheme 52). However, application of this method to both the alanine *N*-formylkynurenine dipeptide **177** and the ornithine-*N*-formylkynurenine diketopiperazine **182** resulted in only starting material being isolated.

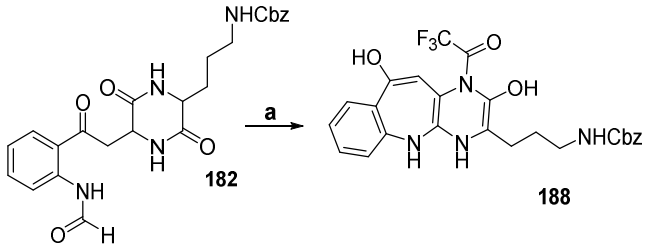
Padwa *et al*.[109] also experimented with the use of trifluoroacetic anhydride (TFAA) as a method for cyclisation of a γ-ketoamide, finding that cyclisation gave 2,4,5-substituted furans in good yields (Scheme 52).



Scheme 52: Padwa *et al.* formation of a nitrogen substituted furan; a: Tf_2O, Py, CH_2Cl_2, b: TFAA, pyridine, CH_2Cl_2.[109]

Application of this method, using TFAA in anhydrous dichloromethane with pyridine, to the alanine-*N*'-formylkynurenine dipeptide **177** provided an interesting result. Loss of the methylene protons of the *N*'-formylkynurenine part of the molecule, alongside the loss of the adjacent ketone was observed. It was decided to apply this methodology to the real system but a large range of products were formed in this reaction. One product, that could be isolated in reasonable purity, had the same mass as the desired product **183** after loss of its formyl group. This molecule was observed to undergo the same loss of the methylene protons and ketone as observed on the model system, alongside loss of the methine proton adjacent to the ornithine side chain. An additional methine proton was seen in the aromatic region and loss of the formyl group from the aniline had also occurred. This product could only be isolated in an approximately 19% yield and attempts to isolate the other products were met with limited success.

In an attempt to improve the outcome of this reaction, closer monitoring was carried out. Following the reaction by mass spectrometry showed initial addition of the trifluoroacetate group in up to three positions. However, cyclisation did not occur until the formyl group had been removed and the loss of the formyl group appears to coincide with the rearrangement taking place, perhaps with the aniline nitrogen taking part in ring formation. Whilst the molecular weight obtained from the ESI spectrum correlates with the desired furan product, the ^{1}H NMR shows the loss of the methine proton adjacent to the ornithine side chain. The appearance of a new quaternary carbonyl peak suggests the formation of an enol at this position, with the keto form not being evident in the NMR spectrum. The data seen in the HMBC NMR spectra shows that the nitrogen protons are not in the positions expected for the desired product, meaning an alternative cyclisation reaction must have occurred, with the structure shown in Scheme 53 fitting the data obtained.



Scheme 53: Potential product of cyclisation reaction; a: TFAA, pyridine, CH_2Cl_2, 19%.

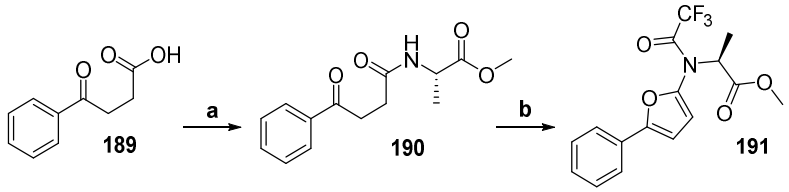
Whilst there is no literature precedent for formation of a benzazepine in this way, it is possible that loss of the formyl group allows the amine to attack the diketopiperazine amide, forming the seven membered ring. Dehydration followed by keto-enol tautomerisation could allow formation of the benzazepine.

2.3.6 Model systems

Cyclisation of the 1,4-dicarbonyl had proven problematic, with the molecule not undergoing the desired reaction to form the furan under a range of conditions. It was thought that the

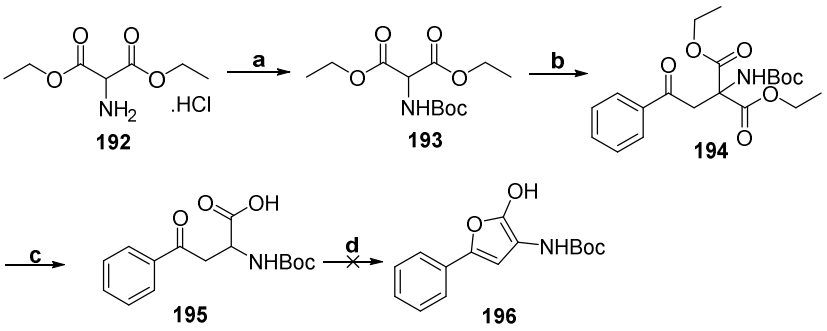
presence of nitrogen atoms in **177** and **182** might provide a barrier to cyclisation, and it was decided to investigate if this additional functionality was preventing access to the furan.

A simple model, with a nitrogen substituent at the 2-position and an aromatic group at the 5-position of the furan was developed. 3-Benzoylpropionic acid was coupled to *L*-alanine methyl ester in an 83% yield; from **190**, Padwa's trifluoroacetic anhydride and pyridine conditions allowed cyclisation to occur in a 66% yield in 30 minutes, proving that Padwa's conditions could be applied to a system containing an aromatic group (Scheme 54).[109]



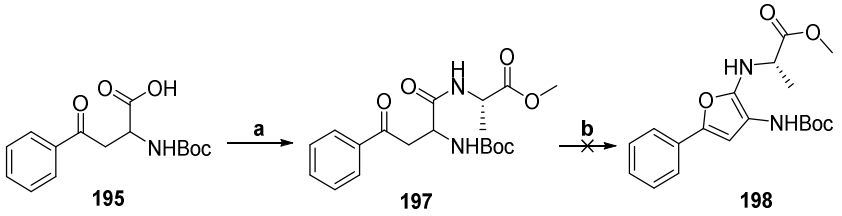
Scheme 54: Successful cyclisation to form a 2,5-disubstituted furan.; a: L-alanine methyl ester. HCl, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, *N*,*N*-diisopropylethylamine, DMF, 83%; b: TFAA, Pyridine, CH_2Cl_2, -78 °C, 66%.

After ascertaining that the presence of the aromatic group did not hinder this synthetic route, a simple model containing a nitrogen at the 3-position as well as the aromatic group at the 5-position was synthesised. Diethyl aminomalonate hydrochloride was protected with a Boc-group and then reacted with bromoacetophenone to give **194** in a 65% yield. Base catalysed hydrolysis and decarboxylation gave the precursor to the furan; however application of Padwa's conditions returned only starting material.



Scheme 55: Attempted synthesis of a 2,3,5 trisubstituted furan.; a: Di-*tert*-butyl-dicarbonate, Et_3N, THF, 82%; b: Bromoacetophenone, NaH, DMF, 65%; c: NaOH, MeOH, 90 °C, 31%; d: TFAA, pyridine, CH_2Cl_2.

To confirm that the absence of the amine at the 2-position was not hindering this cyclisation, **195** was coupled to *L*-alanine methyl ester to give an intermediate that would allow the formation of a furan with nitrogen at the 2- and 3-position and a benzene ring at the 5-position (Scheme 56). Again, application of Padwa's conditions did not induce cyclisation.

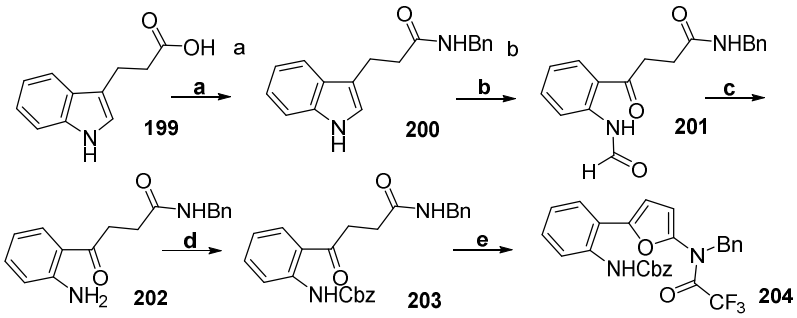


195 197 198

Scheme 56: Synthesis of the modified simple 2,5-disubstituted furan; a; *L*-alanine methyl ester. HCl, *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, *N*,*N*-diisopropylethylamine, DMF, 47%; b: TFAA, pyridine, CH_2Cl_2.

As it had been observed that application of Padwa's conditions to the real system, **182**, resulted in the aniline nitrogen taking part in the cyclisation to give benzazepine **188** (Scheme 53) it was decided to investigate if the cyclisation could be carried out on a model with a more robust aniline protecting group. A model was synthesised without nitrogen at the 3-position, as this appeared to be hindering cyclisation.

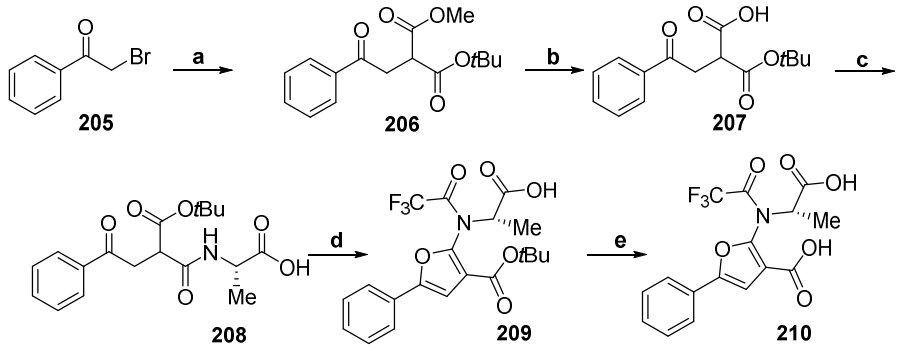
From indole propionic acid the benzyl amide was formed using benzyl amine, EDC and *N*,*N*-diisopropylethylamine. Oxidation of the indole ring and acid-catalysed removal of the formyl group gave **202**. A Cbz group was selected for the aniline nitrogen, as this robust group should be stable to acidic conditions. Protection with benzyl chloroformate gave substrate **203** required to investigate the trifluoroacetic anhydride conditions. It was seen that on this protected substrate cyclisation of the 1,4-dicarbonyl proceeded as expected, giving the furan in a 48% yield (Scheme 57).



Scheme 57: Successful cyclisation to form the aniline 2,5 disubstituted furan.; a: Benzylamine, EDC, *N,N*-diisopropylethylamine, CH_2Cl_2, 0 °C, 28%; b: *m*CPBA, CH_2Cl_2, -50 °C, 26%; c: HCl (aq), MeOH/1,4-dioxane, 99%; d: Benzyl chloroformate, $NaHCO_3$, THF, 0 °C, 38%; e: TFAA, pyridine, CH_2Cl_2, -78 °C, 48%.

As it had now been established that the nitrogen at the 3-position provided a barrier to cyclisation of the 1,4-dicarbonyl, it was decided to install the nitrogen at the 3-position of the furan after cyclisation.

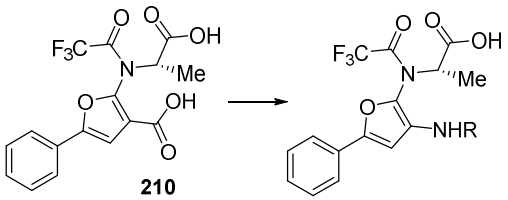
The first route investigated to install this nitrogen involved the use of a Curtius rearrangement, and this required synthesis of a furan with a carboxylic acid at the 3-position. A reaction of bromoacetophenone with *tert*-butyl methyl malonate gave intermediate **206**. Hydrolysis of the methyl ester gave the intermediate required for amino acid coupling with *L*-alanine methyl ester. From **208** it was possible to apply Padwa's conditions[109] to give the desired furan; from **209** hydrolysis of the methyl ester gave intermediate **210** required for investigation of the Curtius rearrangement.



Scheme 58: a: NaH, DMF, *tert*-butyl methyl malonate, 52%; b: i) $LiOH{\cdot}H_2O$, THF, 84%; c: *L*-alanine methyl ester. HCl, *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium

hexafluorophosphate, *N*,*N*-diisopropylethylamine, DMF, 79%; d: TFAA, pyridine, CH_2Cl_2, -78 °C, 28%; e: TFA, CH_2Cl_2, 57%.

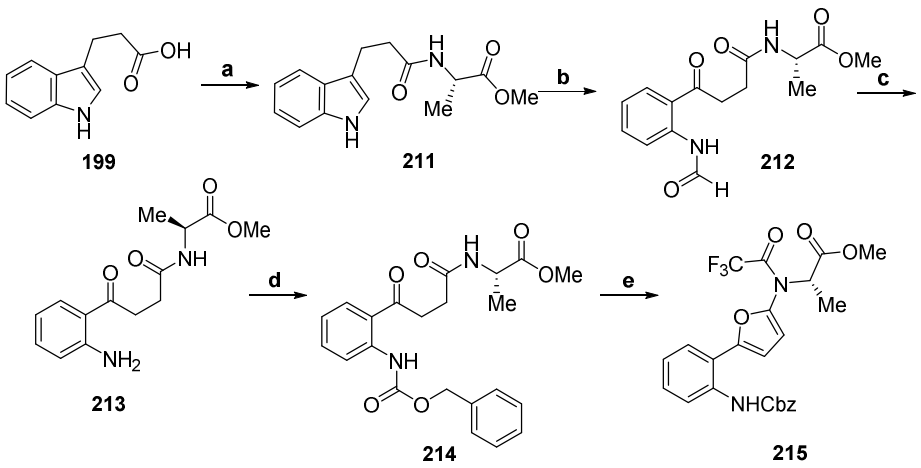
A range of conditions were investigated to carry out a Curtius rearrangement (Table 2). However, in each of these cases installation of the azide did not occur, with the first set of conditions resulting in formation of the mixed anhydride and no further reaction occurring. The use of diphenylphosphoryl azide (DPPA) with *tert*-butanol resulted in no reaction occurring.



Conditions	Result
i) N-methyl morpholine, ethyl chloroformate ii) Sodium azide, THF iii) *p*TSOH, *t*BuOH, PhMe	Mixed anhydride
DPPA, triethylamine, *t*BuOH, PhMe	No reaction
DPPA, triethylamine, *t*BuOH	No reaction

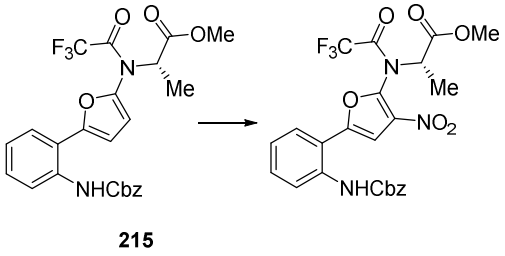
Table 2: Conditions examined to carry out a Curtius rearrangement on 210.

As installation of the final nitrogen using a Curtius rearrangement had been unsuccessful, installation of a nitrogen directly was investigated. A substrate with nitrogen at the 2-position and a protected aniline at the 5-position was readily synthesised; indolepropionic acid was coupled to *L*-alanine methyl ester and the indole ring was then subjected to oxidising conditions using *m*CPBA. The formyl group was exchanged for a more robust Cbz protecting group and this intermediate was treated with trifluoroacetic anhydride and pyridine to induce formation of the furan to give **215** required for investigation of nitrogen addition.



Scheme 59: a: *L*-alanine methyl ester. HCl, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, *N*,*N*-diisopropylethylamine, DMF, 1 h, 90%; b: *m*CPBA, CH_2Cl_2, -50 °C, 29%; c: HCl (aq), MeOH/1,4-dioxane, 71%; d: Benzyl chloroformate, $NaHCO_3$, THF, 0 °C, 65%; e: TFAA, Pyridine, CH_2Cl_2, -78 °C, 15%.

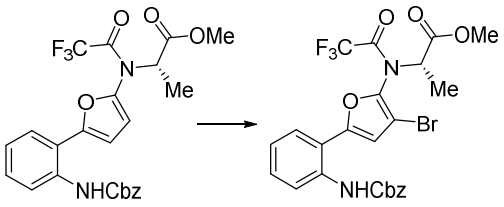
Unfortunately treating the molecule with nitric acid and acetic anhydride at 0 °C resulted only in decomposition and treatment with nitric acid and sulfuric acid resulted in no reaction occurring.



Conditions	Result
Fuming HNO_3, acetic anhydride, 0 °C	Decomposition
HNO_3, H_2SO_4	No reaction

Table 3: Conditions examined to install nitrogen at the 3-position of 215.

As this had been unsuccessful, it was instead decided to investigate installation of a bromine, with it being intended that the bromine could undergo Buchwald-Hartwig amination to install the missing nitrogen. Mild conditions were initially applied, using *N*-bromosuccinimide with *p*-toluenesulfonic acid, but no reaction occurred. The use of bromine with both acetic acid and sodium acetate and bromine with aluminium chloride resulted in decomposition (Table 4).



215

Conditions	Result
N-Bromosuccinimide, *p*-TsOH, THF	No reaction
Bromine, AcOH, sodium acetate	Decomposition
Bromine, $AlCl_3$, chloroform	Decomposition

Table 4: Conditions examined to install a bromine at the 3-position of 215.

The six model systems examined suggest that it is possible to synthesise a furan containing a nitrogen atom at the 2-position and an aniline substituent at the 5-position from a 1,4-ketoamide, but synthesis of a furan with a nitrogen at the 3-position is not possible using this methodology. All reasonable approaches to the biomimetic synthesis of the hyrtioseragamine core had been explored without any promising leads being identified.

2.4 Conclusion

A key intermediate towards the furo[2,3-*b*]pyrazine-2-(1*H*)one core has been synthesised with diketopiperazine **182** containing *N*-formylkynurenine and ornithine side chains. A range of conditions have been screened to cyclise the 1,4-dicarbonyl to give the required furan, but these were unsuccessful.

A more soluble model **177** was synthesised; again it was not possible to cyclise this 1,4-dicarbonyl to form the furan. Application of conditions described by Padwa in synthesising aminofurans from 1,4-ketoamides gave an interesting result on **177** and these conditions were applied to the ornithine-kynurenine diketopiperazine **182**.[109] Whilst a reaction occurred, it is believed that the product is an isomer of the desired furan proposed to be benzazepine **188**.

The limited number of known 2,3-aminofurans meant that the nitrogen substituents were examined as possible barriers to cyclisation,. A model system that contained nitrogen at the 2-position and a benzene ring at the 5-position was able to successfully undergo cyclisation to the furan under Padwa's conditions.[109] The same principles were applied to a different model containing a nitrogen at the 2-position and a protected aniline at the 5-position and this was also able to successfully undergo cyclisation giving furan **204**. Application of these conditions to a molecule containing a nitrogen at the 3-position was unsuccessful.

As it had been established that the nitrogen at the 3-position proved a barrier to cyclisation, synthetic routes to install this nitrogen after formation of the furan was explored. Unfortunately, neither a Curtius rearrangement on furan **210** nor installation of a halogen on furan **215** were successful.

Using model systems it had been concluded that it was not possible to synthesise the 2,3,5-trisubstituted furan present in the core of the hyrtioseragamines from 1,4-dicarbonyl **182**. To take this synthesis forward it will be necessary to design a non-biomimetic route to the novel hyrtioseragamine core.

Chapter 3: Tintamine

3.1 Introduction

Tintamine **7** is one of six natural products isolated from the marine tunicate *Cystodytes violatinctus* by the Kashman group in 1998.[17] Tintamine contains a unique core; the two other novel compounds (**216** and **217**) isolated alongside tintamine are members of the shermilamine family and contain a core structure common to this family.

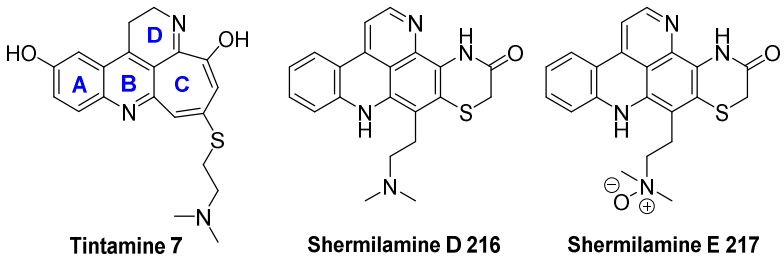


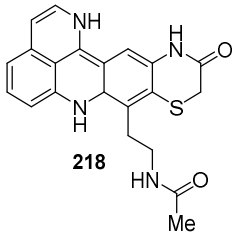
Figure 9: Novel compounds isolated from *Cystodytes violatinctus*; tintamine 7, shermilamine D 216and shermilamine E 217.[17]

3.1.1 Isolation and structural elucidation

These three novel natural products were isolated from a tunicate harvested in the Mayotte lagoon in the Comoros Islands, and were initially extracted with a mixture of methanol and chloroform. The gum isolated from this solvent mixture was partitioned between aqueous methanol and carbon tetrachloride, chloroform and *n*-butanol. The products of these extractions were subjected to column chromatography, initially on Sephadex L-20 with methanol, chloroform and hexane (1:1:2), and then using silica gel with chloroform and up to 30% methanol, to give shermilamine D as 4.5% of the crude mixture, shermilamine E as 0.4% and tintamine as 0.4% of the crude material.[17]

The structures of **7**, **216** and **217** were elucidated through NMR spectroscopic studies; all three compounds are described as amorphous powders and thus X-ray crystallographic studies could not be carried out. Analysis of the NMR spectra of shermilime D and E showed that they

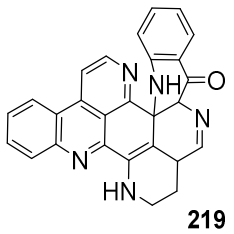
contained the shermilamine core and differed from the previously isolated shermilamine B (**218**) only by the side chain nitrogen substituents.[110]



218

Figure 10: Shermilamine B (218).[110]

Deducing the structure of tintamine proved more complex, with it not comparing to other structures previously isolated from a marine environment and it only being isolated in minute amounts. High resolution fast atom bombardment mass spectrometry (HRFABMS) revealed the molecular formula as $C_{20}H_{22}N_3O_2S_1$ ($M+H^+$). ^{13}C NMR spectroscopy showed 19 distinct carbon peaks, with nine quaternary carbon environments, five CH's, four CH_2's and one CH_3 environment being observed by DEPT experiments, with the CH_3 representing two equivalent carbons. This accounted for a total of 19 hydrogens and led the authors to conclude that the two remaining hydrogens must be attached to heteroatoms. They assigned ten of the hydrogens to a (dimethylamino)ethyl functionality, mirroring what had been observed in shermilamine D. The two remaining methylene carbons were assigned to a $=NCH_2CH_2C=$ structure, with the authors corroborating this assumption by comparison to the NMR spectroscopy data of eudistone A (**219**) which contains a similar motif.[111]



219

Figure 11: Eudistone A (219).[111]

Figure 12 illustrates the HMBC and NOESY spectroscopic cross-peaks that the authors use to assign the structure of the D ring of tintamine.

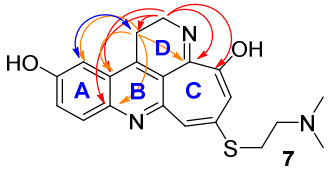


Figure 12: 2D NMR correlations seen in tintamine; red and orange arrows show HMBC correlations and the blue arrow corresponds to NOESY correlation.

Of the five aromatic protons, three were assigned to ring A with the NMR spectroscopic interactions shown in Figure 13.

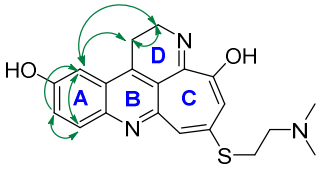


Figure 13: COSY and TOCSY correlation seen in tintamine.

The two remaining protons have a *meta* relationship, with a coupling of 1.9 Hz being observed for both peaks, and these two protons were assigned to a tropone ring system. It was concluded that the side chain must contain the sulfur and be attached to the C ring at the C-7 position, with HMBC correlations corroborating this (Figure 14). NOE analysis of this material resulted in correlations being observed between the protons on the tropone ring and the methylene protons in the sulfur side chain.

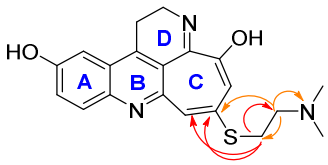
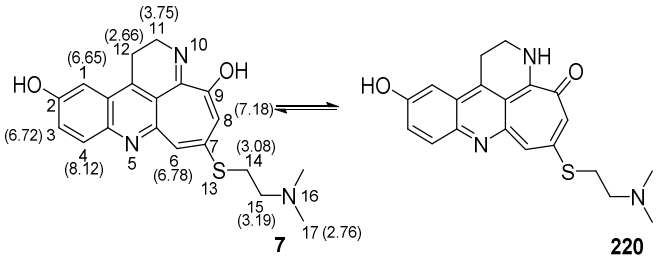


Figure 14: HMBC correlations seen in tintamine.

The authors proposed that the structure of tintamine exists as a rapidly interconverting mixture of tautomers **7** and **220** as evidenced by the slight broadening of the peak corresponding to the proton attached to C-8 (Scheme 60).



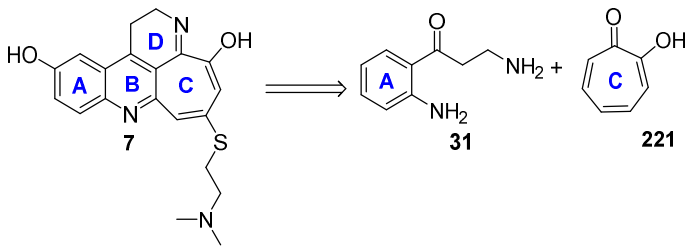
Scheme 60: Keto-enol tautomerisation observed in tintamine. Chemical shifts from proton NMR spectrum shown in brackets (ppm).

The quinoline chemical shifts obtained by proton NMR spectroscopy are as expected at the 4-position, but the hydrogens at the 1- and 2-positions occur at a lower field than would typically be expected for a substituted quinoline.[112-115]

To further confirm the structure of tintamine the authors treated the isolated material with acetic anhydride and pyridine. The structure of the resulting material contained two additional acetyl groups believed to be at the phenolic positions of tintamine. The proposed structure of tintamine is believed to exist as a keto-enol tautomer (Scheme 60) and contains a previously unknown tropono-1,2-dihydro-3,6-phenanthroline core.[17]

3.1.2 Proposed biosynthesis

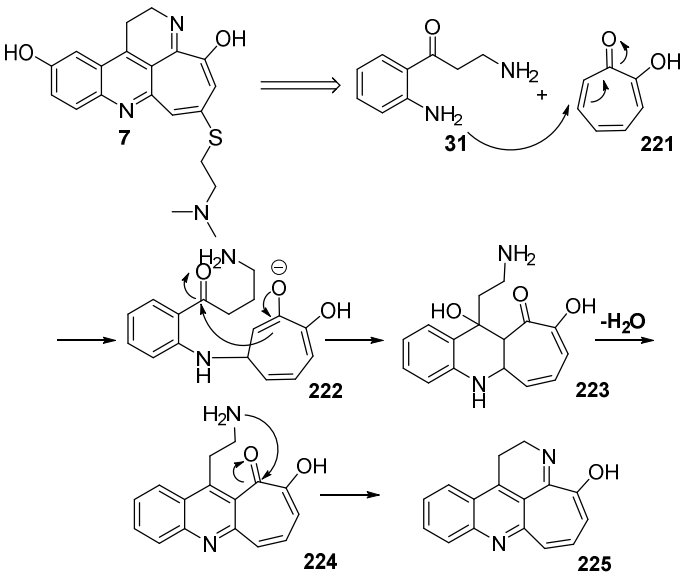
Kashman *et al.* proposed that **7**, **216** and **217** are biosynthesised from kynuramine (**31**), with the coupling partner of the shermilamines being a benzoquinone derivative, and tintamine formation requiring a tropolone substrate to couple with the kynuramine (Scheme 61).[17]



Scheme 61: Proposed biosynthesis of tintamine 7 from tropolone 221 and kynuramine 31.

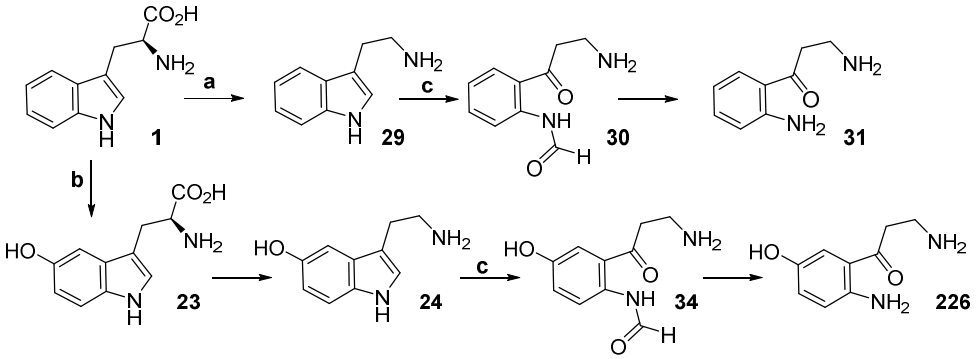
A route for the proposed biosynthesis of tintamine is shown in Scheme 62. A conjugate addition of the aniline derived from the indole ring would give enolate **222**, which can carry out an aldol reaction with the ketone to give tricycle **223**. Aromatisation of this intermediate

would form the quinoline and attack of the second amine and subsequent elimination would form the imine. The side chain could be introduced to the molecule by nucleophilic addition at several possible stage to give tintamine.



Scheme 62: Proposed biomimetic route to tintamine based on Kashman's biosynthetic plan.[17]

As discussed in Chapter One, it is known that kynuramine **31** is a metabolite of tryptophan; enzymatic decarboxylation, oxidation of the indole ring and removal of the formyl group allow the formation of kynuramine (**31**) in Nature (Scheme 63). In an alternative pathway serotonin **24**, or 5-hydroxytryptamine, can be formed by hydroxylation of tryptophan by the enzyme tryptophan-5-monooxygenase followed by decarboxylation, as seen in Scheme 63. Serotonin can also be oxidised and cleavage of the 2,3-indole bond gives access to 5-hydroxykynuramine **226**. It is possible that the serotonin derivative **226** is the coupling partner for tropolone in the biosynthesis of tintamine.



Scheme 63: Tryptophan metabolism to serotonin; a: tryptophan decarboxylase; b: tryptophan hydroxylase; c: indoleamine-3-hydroxylase.[24, 116]

3.1.3 Key structural features

3.1.3.1 Pyridoacridines

The main structural motif in tintamine is similar to the pyridoacridine aromatic system in many other natural products.[111, 117-120] However, in tintamine the pyridine ring is not fully oxidised and one of the rings contains an additional carbon atom. Whilst pyridoacridines are well known within marine natural products, this modified system containing a seven-membered-ring is previously unseen.

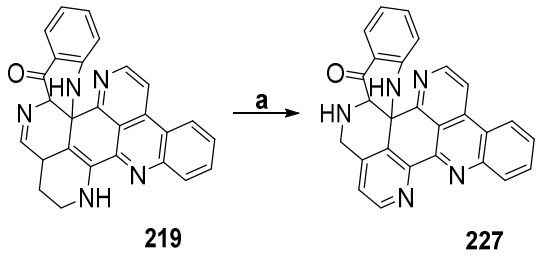
The pyridoacridines are a large family of highly coloured marine natural products that contain a common pyrido[4,3,2-*mn*]acridine core structure. They were described by Molinski as having uses as pH indicators as they contain several basic nitrogen atoms and an extended chromophore.[121] The pyridoacridine family's biosynthetic origin has been subject to debate. It is a widely distributed core leading to the proposal that it may be formed by a symbiotic microorganism, rather than the tunicates themselves.[122]

Almost all pyridoacridines are biologically active and this makes them an important target for total synthesis. Structural variation comes from the presence of additional rings, side chains and variations in oxidation state and it has been observed that a small variation in in the structure results in a large change in their pharmacological activity.[120] Whilst tintamine contains a tropolone ring in place of one of the benzene rings typically seen in this family, the

knowledge that the biological activity of the pyridoacridines can be tuned by structural variation makes tintamine an interesting target for total synthesis.

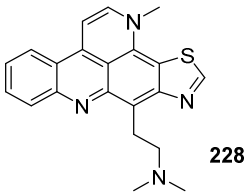
Pyridoacridines have been observed to have anticancer activity, alongside anti-HIV, anti-microbial, anti-parasitic and insecticidal properties. Biologically, they have been associated with: variations in calcium release, neuronal differentiation and metal chelation. They are also known to have an affinity towards GABA receptors.[120, 123]

Eudistone A and B are variants of this family that do not show a complete extended aromatic system.[111] Eudistone A **219** can be converted into eudistone B **227** by bubbling air through the solution at 60 °C for 48 hours (Scheme 64). Interestingly they are both described as being colourless, as opposed to other pyridoacridine derivatives that are highly coloured.



Scheme 64: Eudistone A 219 and eudistone B 227; a: air, DMSO, 60 °C.

The sulfur containing natural product dercitin (**228**),[124] a pyridoacridine containing a dimethyl aminoethyl functionality similar to that seen in tintamine, also contains four basic nitrogen atoms and it was found when examining the molecules biological activity that these nitrogen atoms bind to acidic residues.[120] Reducing the number of nitrogen atoms lowered the cytotoxic effect of the molecule, and it was also noted that the sulfur was essential for anti-viral activity. The molecule contains an extended planar system and a flexible side chain similar to that of tintamine and it is believed that the compound exerts its activity by intercalating with nucleic acids.[117] This information again suggests that tintamine is a relevant synthetic target as a similar sulfur containing planar system.

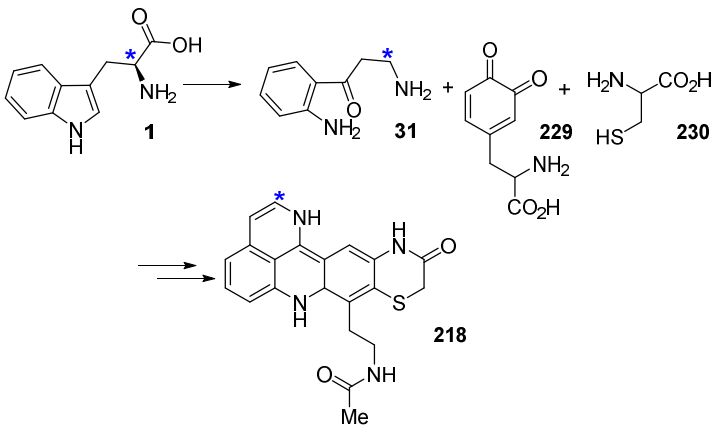


228

Figure 15: Dercitin 228, a pyridoacridine isolated from *Dercitus* sp. in 1988.[124]

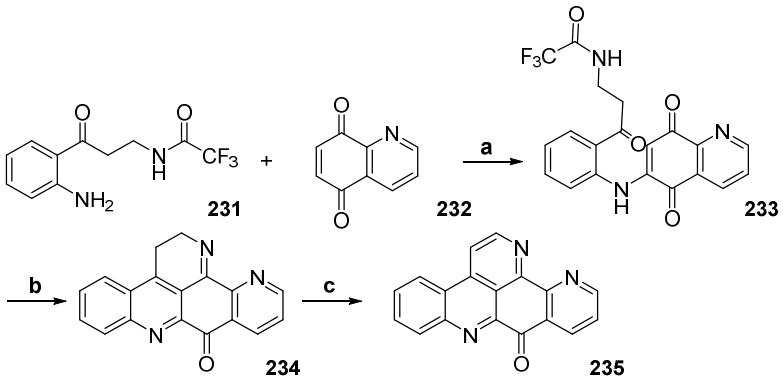
3.1.3.1.1 Biosynthesis of pyridoacridines

It has been proven experimentally that a number of pyridoacridine containing natural products are biosynthesised from kynuramine.[58, 118, 125, 126] Work on the biosynthesis of shermilamine B **218** by Pütz in 1993 used radiolabelling to illustrate the molecules biosynthetic origin.[125] Shermilamine B has been isolated from *Cystodytes dellechiajei* and upon keeping this tunicate in water containing *L*-[5-^{3}H] tryptophan and [7,8-^{3}H] dopamine both *L*-[5-^{3}H] tryptophan and [7,8-^{3}H] dopamine were incorporated into shermilamine B, but only at a low concentrations. It is known that primary metabolites are taken up slowly by marine tunicates and sponges[127] and whilst it was possible to conclude that both tryptophan and dopamine are used in the synthesis of shermilamine B, this method did not show how they are incorporated. An alternative test where *DL*-[α-^{13}C]tryptophan was incorporated into the molecule allowed ^{13}C NMR studies to show the radiolabelled carbon at the 2-position (Scheme 65). This result allowed the authors to conclude that in the synthesis of shermilamine B, tryptophan is converted into kynuramine and combined with dopa and cysteine. It is possible to apply the same principles to the biosynthesis of other pyridoacridine containing natural products.



Scheme 65: Proposed biosynthesis of shermilamine B (218) based on the radiolabel study by Pütz.[125]

Ascididemin **235** is a pyridoacridine natural product that has been synthesised by a number of groups.[118, 128] In Kashman's total synthesis a biomimetic route was undertaken, with kynuramine being coupled to quinolonequinone. From **233** it was possible to carry out deprotection of the amine and formation of 5,6-dihydroascididemin (Scheme 66).[118]



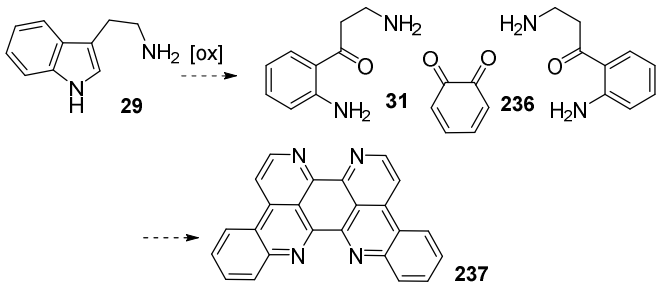
Scheme 66: Biomimetic synthesis of ascididemin; a: $CeCl_3 \cdot 7H_2O$, EtOH, b: NH_4OH, MeOH or 4 M HCl, c: air, methanol.[118]

It was observed that the dihydropyridoacridine intermediate **234** underwent oxidation in air to give the pyridoacridine **235**. The readiness of this oxidation to occur is slightly surprising based on the structure of tintamine, where the authors do not observe such an oxidation.

3.1.3.1.2 Synthesis of pyridoacridine containing natural products.

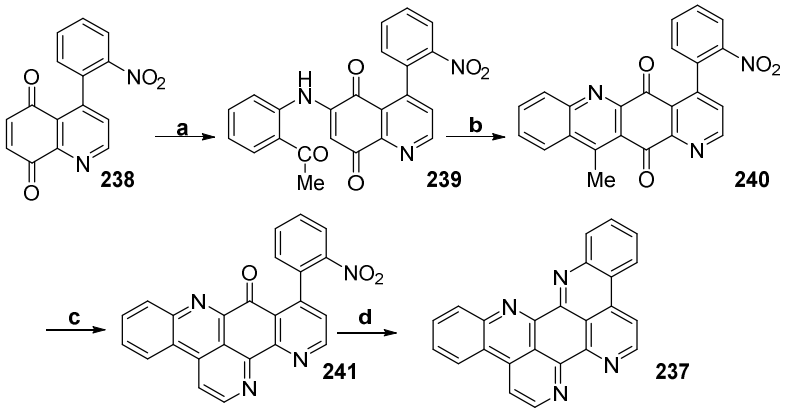
The diverse nature of the pyridoacridine core means that considerable effort has gone into its synthesis, by both biomimetic and more standard synthetic routes. The Kashman synthesis of

the similar natural product ascididemin *via* a biomimetic route, provides a strong starting point for the biomimetic synthesis of tintamine.[118] Kashman has worked on the synthesis of several other pyridoacridines and pyrroloacridines by biomimetic routes. They proposed that the natural product eilatin **237** is biosynthesised from kynuramine and **236**, and it has also been demonstrated that this route can be mimicked in the laboratory.[126]



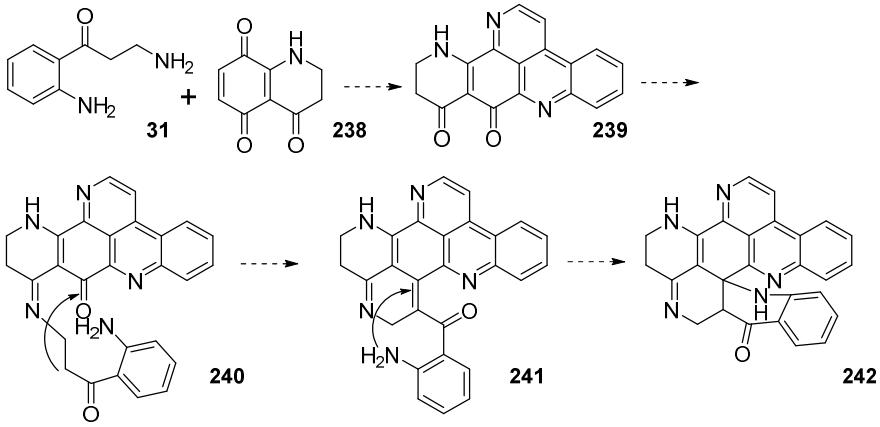
Scheme 67: Proposed biosynthesis of eilatin.[58]

Prior to this, eilatin was synthesised by Kubo *et al.* by reaction of quinolinequinone **238** with 2-aminoacetophenone in the presence of cerium(III) chloride to give **239**.[119] Further reaction to form the tetracyclic quinone was carried out under acidic conditions and treatment with *N*,*N*-dimethylformamide diethyl acetal followed by ammonium chloride in acetic acid formed the penultimate ring. Hydrogenation reduced the nitro group to the amine and this immediately cyclised to form the final ring of eilatin (Scheme 68). This route provides the possibility to modify the route proposed by Kashman and use a nitro group, rather than a protected amine, in the synthesis of tintamine.



Scheme 68: Kubo's route to eilatin; a: 2-aminoacetophenone, $CeCl_3.7H_2O$, EtOH; b: 10% H_2SO_4-AcOH; c: i) *N,N*-dimethylformamide diethyl acetal, ii) Ammonium chloride, AcOH; d: H_2, Pd/C (10%), EtOH.[119]

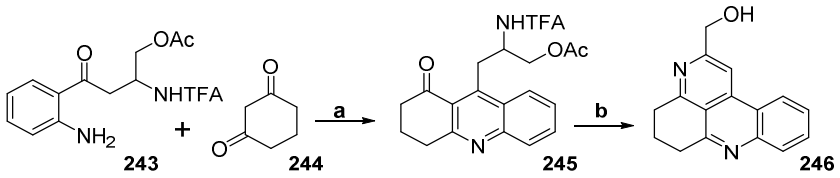
Kashman goes on to propose that biemnadin **242** is biosynthesised *via* a similar route, where quinolinequinone **238** and kynuramine are reacted to give **239** and this undergoes a further reaction with a second molecule of kynuramine.[58] In Nature an aldol condensation and aza-conjugate addition reaction could provide access to the natural product (Scheme 69). This concept has been investigated by Menendez *et al.*;[129] however, total synthesis of this compound has not been achieved.



Scheme 69: Proposed biosynthesis of biemnadin.[58]

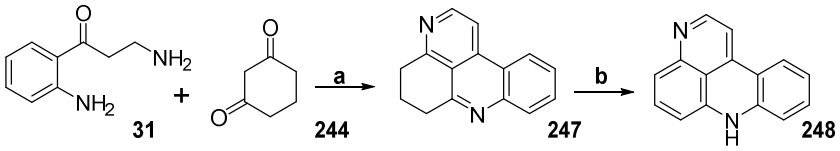
The Kashman group go on to show that cyclohexane-1,3-dione can be reacted with derivatives of kynurenine, the precursor to kynuramine used in the work towards hyrtioseragamines described in Chapter 2.[58] **243** and **244** undergo an acid mediated Friedländer reaction to give **245** in one pot. They then follow this up with ammonia mediated removal of the trifluoroacetyl

protecting group, observing complete oxidation of the pyridine ring despite the molecule not being a fully aromatic system.



Scheme 70: Acid mediated Friedländer reaction, followed by removal of the protecting groups to give 246; a: AcOH, HCl; b: NH_3 (28% aq), MeOH.[58]

Kashman *et al*. also observed that this reaction can be carried out with kynuramine, and that upon treatment with sodium *m*-nitrophenyl sulfonate under acidic conditions the molecule is oxidised to give the aromatic pyridine **247**. Imine **247** is then treated with DDQ to give access to the fully aromatic species **248**.

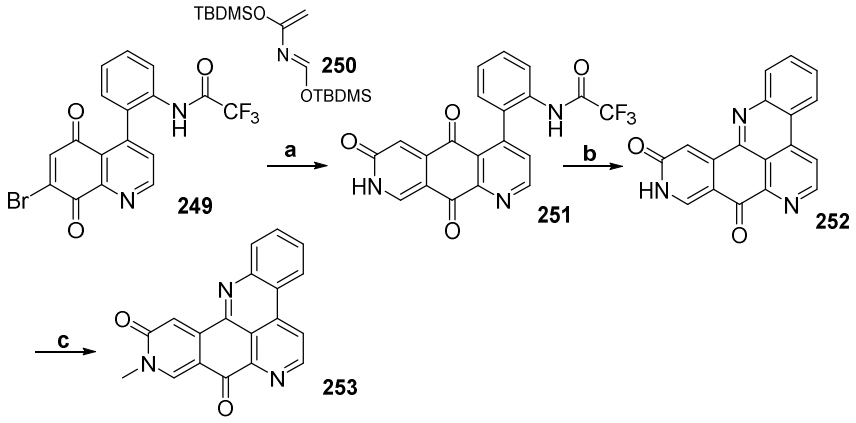


Scheme 71:Friedländer reaction on cyclohexane-1,3-dione and kynuramine; a: AcOH, HCl, sodium *m*-nitrophenyl sulfonate; b: DDQ.[58]

The ease of aromatisation of the final pyridine ring of these pyridoacridine derivatives, alongside the observation that ascididemin undergoes oxidation of its pyridine ring in air (Scheme 66), suggests avoiding this oxidation during the synthesis of tintamine may not prove trivial.

The total synthesis of the cytotoxic pyridoacridine amphimedine **253** has been accomplished using a hetero-Diels-Alder reaction between quinoline **249** and diene **250** and this provides access to **251** (Scheme 72).[130] Deprotection of the nitrogen allows formation of the final ring seen in amphimedine, with this being comparable to the other biomimetic routes discussed.

The final step of this route involves methylation of the nitrogen to give access to amphimedine **253**.



Scheme 72: Total synthesis of amphimedine; a: 250; b: HCl, THF; c: Me_2SO_4, K_2CO_3, DMF.[130]

Despite the route to amphimedine not following the biomimetic principles outlined by Kashman to give the first three rings, the formation of the final ring by a similar route to that described in the biomimetic synthesis of ascididemin and eilatin helps to corroborate the final part of the biosynthesis of the pyridoacridines.

The work of Kashman *et al.* and other groups on other similar pyridoacridine structures provides inspiration for the initial steps of the synthesis of tintamine; however, a reaction between kynurenine or kynuramine and a seven-membered 1,3-dione has not been investigated. Following the isolation of tintamine, the authors propose that tintamine is biosynthesised from kynuramine and tropolone and the literature provides few starting points for this type of reaction.

3.1.3.2 Tropolones

Tropolones are conjugated seven-membered rings containing a carbonyl group and an α-hydroxyl group; they are found in natural products isolated from a range of environments. Stipitatic acid **254** was first isolated in 1942; however, assignment of its structure did not prove trivial and it was eventually assigned by Dewar in 1945.[131] It was described as resembling a hydroxy acid and the structure was assigned as a seven-membered ring structure **254**. The core

became known as tropolone **221**.[131] The field advanced rapidly and over 200 of these 'non-benzenoid aromatic' natural products have been described from various origins, including plants and bacteria as well as fungi.[132]

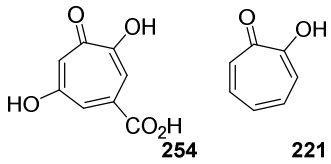
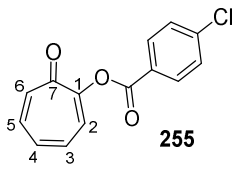


Figure 16: Stipitatic acid (254) and tropolone (221).

Dewar described stipitatic acid as being an aromatic system,[131] and several groups have gone on to analyse the aromatic properties of tropolones through X-ray structures. It was observed that copper(II) tropolone is an almost planar structure with an average bond length of 1.4 Å and Monteath described the compound as having a strong aromatic character.[133] Analysis of data from tropolonyl *p*-chlorobenzoate obtained by X-ray crystallography also showed that the tropolone ring is planar; however, they found that it shows alternation of bond character, shown in Table 5.[134]



Bond	Bond length Å
C1-C2	1.336 (6)
C2-C3	1.403 (7)
C3-C4	1.341 (7)
C4-C5	1.417 (7)
C5-C6	1.336 (6)
C6-C7	1.446 (6)
C7-C1	1.459 (6)

Table 5: Bond lengths observed in tropolonyl *p*-chlorobenzoate 255 (numbers in brackets denote estimated standard deviation).[134]

From these data the authors concluded that the tropolone is non-aromatic; however, it does show some aromatic character and can undergo aromatic electrophilic substitution reactions. Tropolone reacts with electrophilic reagents such as bromine in water and nitric acid. It is activated to electrophilic attack at the 3,5 and 7 position as the intermediate is stabilised by resonance of the positive charge. A reaction of tropolone with bromine in water gives the 3,5,7 trisubstiuted tropolone.[135]

Tropolones can be isolated from the cupresseaeae family of trees, and the tropolone is believed to act to prevent fungal decay in these plants. It has believed that the tropolones mediate this effect by protecting the cells from oxidative stress. Tropolone and some of its derivatives have been observed to possess both metal chelation and anti-oxidant properties.[136]

Simple tropolones such as stipitatic acid (**254**) and puberulic acid (**256**) contain just one ring but bicycles such as cordytropolone (**257**), and large heterocyclic systems such as diterpene hainanolidol (**258**) are also found as natural products.

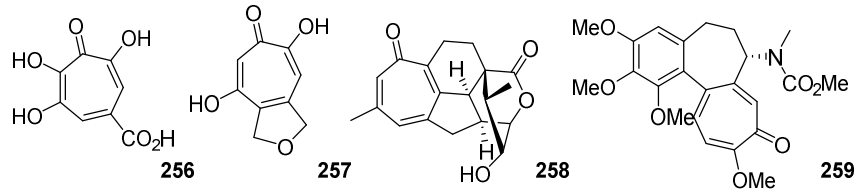


Figure 17: Puberulic acid (256), cordytropolone (257), hainanolidol (258), colchicine (259).

Colchicine (**259**) is one of the best known tropolone structures. The alkaloid, which comes from the meadow saffron, was first isolated in 1820 by Pelletier and Caventou. Its biological properties were known prior to this and it has been used as a treatment for gout for 2000 years.[137] The assignment of its structure was not completed until after the structure of stipitatic acid had been assigned, with Dewar suggesting that colchicine's structure could be solved as a tropolone.[132]

Tetracyclic natural products containing one tropolone unit, such as tintamine, are rare, with one example being the unnamed **260** which contains an 11-membered ring.[138]

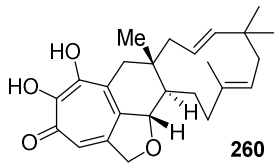


Figure 18: Unnamed tetracyclic heterocycle isolated from fungus *Acreminium strictum* (260).[138]

Whilst a bioactive family of tropoisoquinolines and tropoloisoquinolines have been isolated from the plants *Cissampelos pareira* and *Abuta granifolia*,[139] tropoloquinolines are not known within the literature.

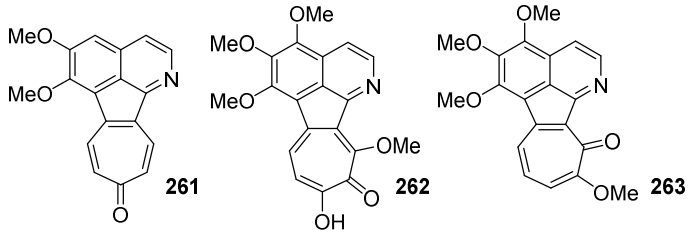


Figure 19: Tropisoquinoline pareitropone 261[140]; tropoloisoquinoline pareitrubrine A[141] 262 and imerbrine 263.[139]

Benzotropolones are common, with a number of these being examined in detail. Goupiolone A **264** and B **265** were isolated from the leaves of *Goupia glabra,* with **265** believed to be formed by a Diels Alder reaction between tropolone and a benzyne formed from naphthalene-1,2,3,4-tetraol.[142]

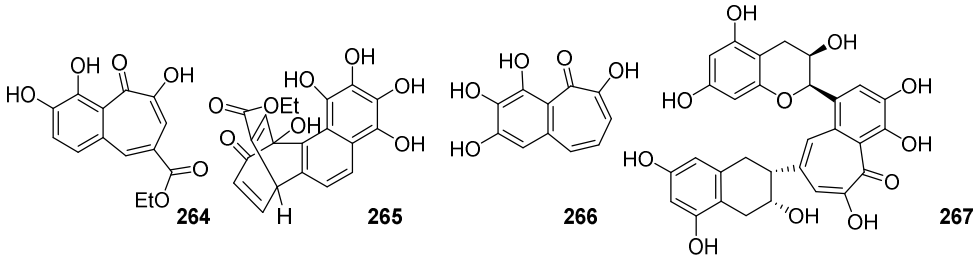


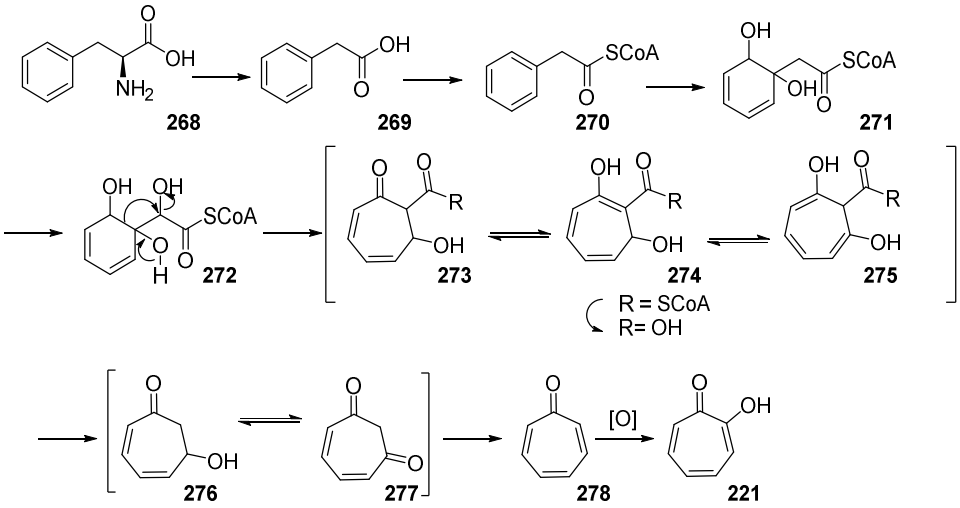
Figure 20: Goupiolone A 264 and B 265,[142] purpurogallin 266 and theaflavin 267.

Benzotropolones are biologically active and are known to inhibit the methylation of oestrogen derivatives implicated in cancer.[132] It is not fully understood whether this process is beneficial, but the mechanism of inhibition has been examined. With purpurogallin (**266)** the benzene ring is inserted into the active site of the methyl transferase enzyme, and with theaflavin (**267)** it is the galloyl ester that is inserted.[143]

3.1.3.2.1 Biosynthesis of tropolones

Tropolones are commonly described as being fungal metabolites,[132] but are also isolated from plants[137] and bacteria.[144] Biosynthesis of the tropolone varies, depending on the organism. As it is not known how tropolones are synthesised in marine tunicates, each biosynthetic route will be briefly considered.

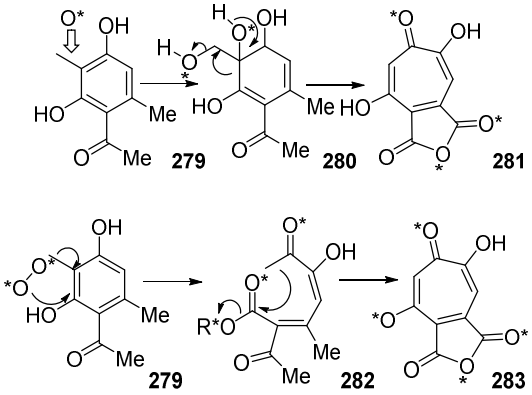
Schulz *et al*. examined the biosynthesis of tropolone in marine bacteria, observing that tropone and tropolone were synthesised from phenylalanine.[144] The use of radiolabelled phenylalanine allowed the biosynthetic route to be established. The authors describe *L*-phenylalanine undergoing transamination and oxidative decarboxylation to give **269**, which is converted into phenylacetyl-Co A. Two oxidations allow access to **272** and this then undergoes a ring expansion to the seven-membered ring. Hydrolysis gives the acid **274**, subsequently decarboxyalation and the elimination of water give tropone **278**, which can be oxidised to tropolone **221** (Scheme 73).



Scheme 73: Biosynthesis of tropone and tropolone using radiolabelled phenylalanine.[144]

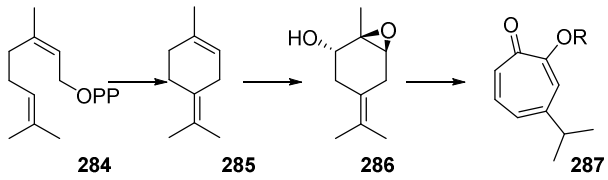
Stipitatic acid biosynthesis has been probed using [1-^{14}C]-*D*-glucose and the degradation products examined.[145] It was observed that its synthesis occurs from a polyketide route and ring expansion. Two possible mechanisms for ring enlargement were proposed (Scheme 74); incorporation of $^{18}O_2$ into stipitatic acid was examined with the use of ^{13}C NMR and this led

to the authors to conclude that the monooxygenase mechanism, seen in Scheme 74, is likely for the ring enlargement.[132, 145]



Scheme 74: Possible ring enlargement mechanisms for the biosynthesis of stipitatic acid. Top line: monooxygenase mechanism, bottom line: dioxygenase mechanism. [132, 145]

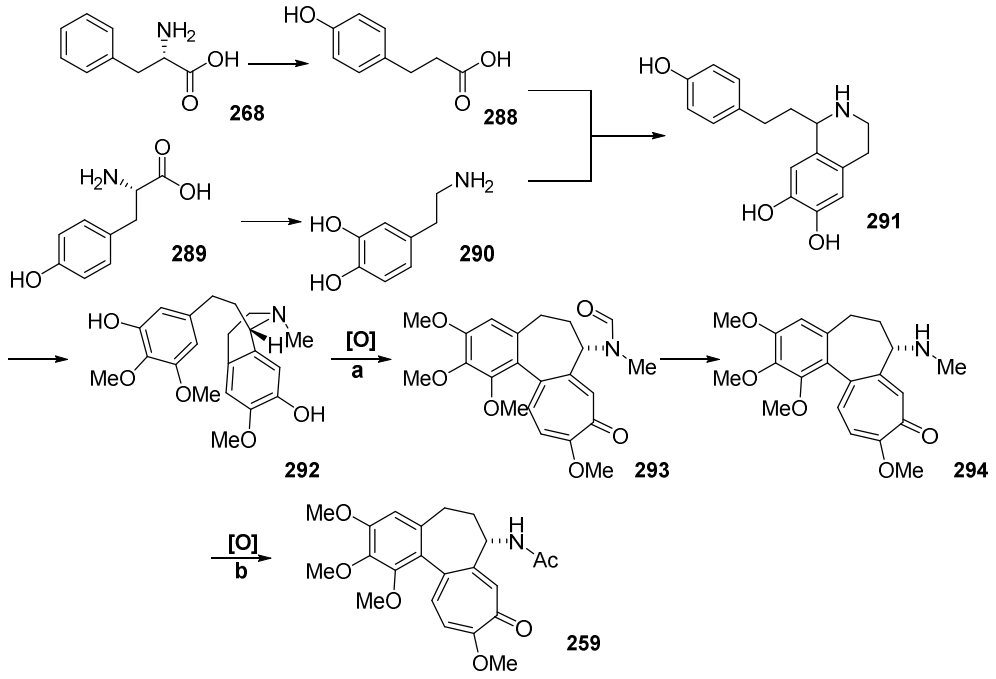
It has been shown that the 10-carbon β-thujaplicin **287** is biosynthesised in plants using terpene intermediates. The use of feeding experiments to trace its origin was employed by Sakai *et al.*,[146] where cell suspensions from *Cupresous lisitanica* were treated with organic acids present in the mevalonate pathway. The results provided evidence for the mevalonate pathway being involved in the biosynthesis of β-thujaplicin. Further work using radiolabelled glucose suggested that the geranyl pyrophosphate was largely derived from the non-mevalonate pathway[147, 148] and it was concluded that both the mevalonate and non-mevalonate pathway are involved in the biosynthesis of β-thujaplicin. The monoterpene **286** has been isolated from *Cupresous lisitanica* cultures and this has led Scheme 75 to be proposed as a possible route to β-thujaplicin.[148] It is not currently known how **286** is converted into tropolone.



Scheme 75: Proposed biosynthesis of β-thujaplicin.[148]

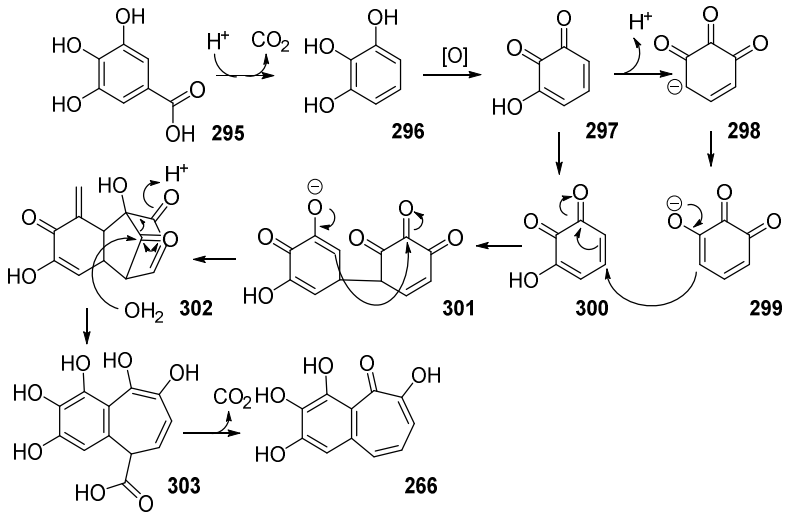
Biosynthesis of the tropolone containing natural product colchicine (259) has been probed through extensive biolabelling. It has been shown to be synthesised from *L*-phenylalanine and

L-tyrosine. The phenylalanine is modified by the cinnamic acid pathway to give **288**, and the tyrosine is converted into dopamine **290** to give the two starting materials required for colchicine synthesis. Labelling of the tyrosine has shown that its aromatic ring undergoes a ring expansion to form the tropolone (Scheme 76).[132]



Scheme 76: Biosynthesis of colchicine; a: i) autumnaline oxidase, O_2, NADPH, ii) SAM; b: acetyl-Co A.[18]

The biosynthesis of benzotropolones often involves the action of plant oxidases. Purpurogallin (**266**) can be obtained from pyrogallol by oxidation; its biosynthesis is shown in Scheme 77 and it is derived from the shikimate pathway.[132] Gallic acid **295** undergoes decarboxylation followed by oxidation to give the two intermediates required for this biosynthesis. Conjugate addition gives **301** and an aldol reaction; aromatisation and decarboxylation gives access to purpurogallin.



Scheme 77: Biosynthesis of benzotropolone purpurogallin 266.[132]

Only four naturally occurring sulfur containing tropones are known within the literature (Figure 21), each of these contain two sulfur atoms. Most of these molecules have been isolated from bacterial sources, and **304**, **305** and **306** are tautomeric.[132]

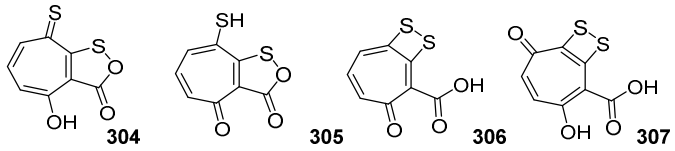
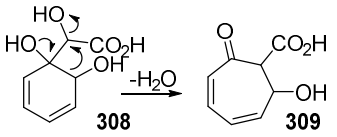


Figure 21: Sulfur containing tropolones; 305: thiotropocin, 306: troposulfenin; 307: tropodithietic acid; 308: hydroxytropodithietic acid.

Thiotropocin **305** was isolated in 1984 by Ono and Okazaki from the bacteria *Pseudomonas* sp. CB-104 and was the first example of a sulfur containing tropolone structure.[149] It is described to have antibacterial, antifungal and antiprotozoal activity.[150] Its biosynthesis was examined by Cane *et al.*, and through radiolabelling they were able to establish that the molecule was formed *via* the shikimate pathway.[150] The use of radiolabelled glucose allowed them to conclude that the molecule was likely to be formed through an oxidative ring expansion (Scheme 78). Further oxidation followed by sulfur-oxygen exchange and lactonisation would give access to thiotropocin **304**.



Scheme 78: Oxidative ring expansion to form the tropolone ring.[150]

Tropolone biosynthesis varies significantly depending on the organism, a marine tunicate synthesis of tropolone is not currently described and so an examination of the biosynthetic route to the tropolone in tintamine cannot be carried out.

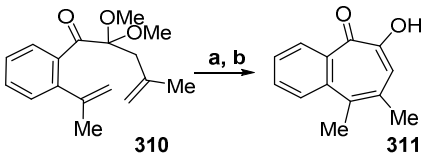
Whilst the biosynthetic origin of tintamine is not known, the work of the Kashman group on pyridoacridine biosynthesis and Pütz's work on the biosynthesis of shermilamine B help to provide justification for the original proposal.[17, 58, 118, 125, 126] The biological precursor tryptophan is known to be formed by the shikimate pathway and it has been described that some tropolones are also synthesised by this route.[132, 150]

Whilst tintamine has been extracted from a marine tunicate, it is possible that the molecule is actually produced by a symbiotic microorganism as it has been hypothesised that pyridoacridines could be made in this way. The known sulfur containing tropolones (**305**, **306** and **307**) have been synthesised by bacteria and both tropone and tropolones are released as volatiles from a member of the *Roseobacter* clade, a commonly found family of marine bacteria.[144] The combination of the suggestion that pyridoacridines could be formed by microorganisms, and the knowledge that sulfur containing tropolones can also be formed by marine bacteria means that the possibility that tintamine is formed by bacteria, rather than the marine tunicate itself, must be considered.

3.1.3.2.2 Synthesis of tropolone containing natural products.

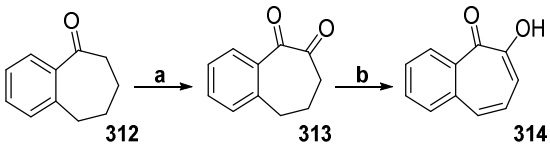
The simple tropolone puberulic acid (**256**) has been synthesised several times, twice using a ring expansion,[151, 152] and once using a ring closing metathesis.[153] Ring closing metathesis was also used in a synthesis of colchicine (**257**) that will be considered later.[154] Work on 2,3-

benzotropolone formation used Grubbs' second generation catalyst followed by *p*-toluenesulfonic acid to form the tropolone **311** (Scheme 79).[155]



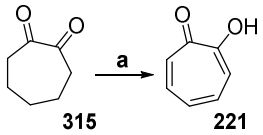
Scheme 79: Grubbs' catalysed ring closing metathesis; Grubbs' II catalyst, CH_2Cl_2; b: *p*-TsOH, H_2O, MeCN, 75 °C.[155]

In other systems a wide range of routes to tropolones have been employed; functionalisation of cycloheptanones is common, with this route being developed by Cook *et al.* in 1949.[156] 2,3-Benzocycloheptane-1-one **312** was oxidised to diketone **313** with selenium dioxide in ethanol. This was then converted into benzotropolone **314** using bromine in acetic acid (Scheme 80).



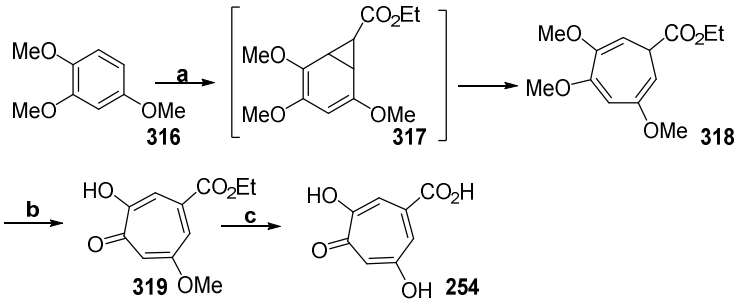
Scheme 80: Cook's synthesis of benzotropolone; a: Selenium dioxide, EtOH; b: Br_2, AcOH.[156]

The work of Cook provides a template for many syntheses of tropolone, with a modification by Knight *et al*. treating 2-hydroxy-cycloheptane-1-one **315** with bromine to give tropolone **221**.[157] Treatment of cycloheptane-1,2-diol with NBS, and elimination of the bromine gives tropolone directly, albeit in low yields (Scheme 81).[158]



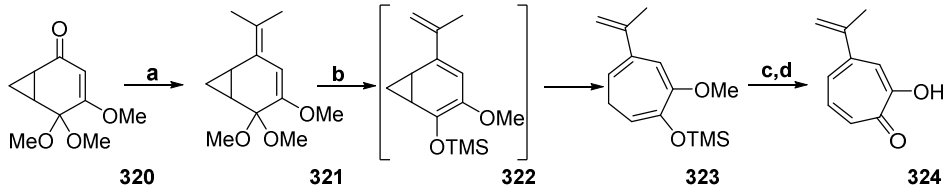
Scheme 81: a: i) NBS, $CHCl_3$, ii) 90-100 °C.[158]

Ring expansion has been employed in the synthesis of stipitatic acid where the Buchner reaction was used to form the seven-membered ring **318**.[159] This intermediate was then treated with bromine and the ester hydrolysed to give stipitatic acid (Scheme 82).



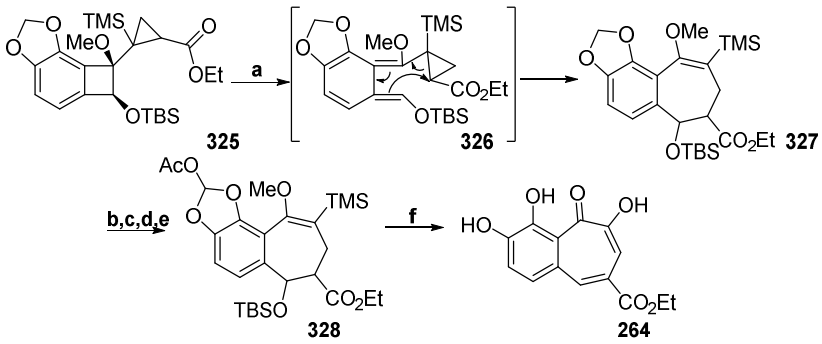
Scheme 82: Synthesis of stipitatic acid: a: N_2CHCO_2Et, hv; b: Br_2, $CHCl_3$ c: i) KOH, ii) HBr.[159]

Cyclopropanation and ring expansion is common in the synthesis of tropolone,[151, 160-162] and it was employed in the synthesis of β-dolabrin **324** by Evans (Scheme 83).[163] Ring expansion proceeds by electrocyclic ring opening of the enol **322**; subsequent oxidation with chloroanil and treatment with boron tribromide gave β-dolabrin (**324**).



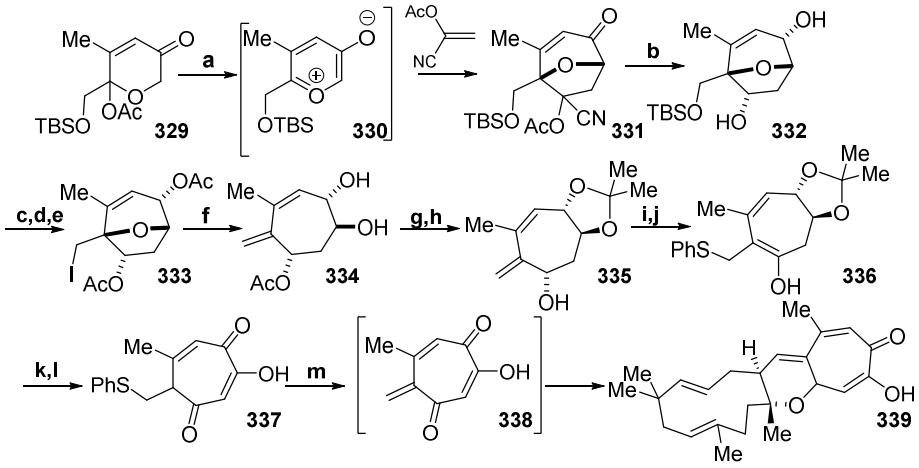
Scheme 83: Evans synthesis of β-dolabrin; a: i) *i*PrMgBr, ii) BF_3/Et_2O, CH_3NO_2; b: i) KH, THF, ii) TMSCl; c: chloroanil; d: BBr_3.[163]

Benzotropolones have also been synthesised by ring expansion. Suzuki *et al.* showed that cyclopropane and cyclobutane moieties could be combined to give **327** by heating in *p*-xylene with catalytic 2,6-di-(*tert*-butyl)-4-methoxyphenol (BHT) (Scheme 84).[164, 165] Subsequent oxidation, treatment with DBU and removal of the protecting groups gave access to the benzotropolone **264**.



Scheme 84: Suzuki synthesis of goupiolone A using a sigmatropic rearrangement;[165] a: BHT, *p*-xylene, reflux 82%, dr 1:1; b: i) *m*CPBA, Na_2CO_3, CH_2Cl_2, -78-0 °C; ii) HCl (2 M); c: DBU, MeCN; d: AcCl, Et_3N, CH_2Cl_2, 0 °C; e: $Pb(OAc)_4$, benzene, reflux, 48% from 327; f: conc. HCl, CH_2Cl_2, EtOH, reflux, 90%.

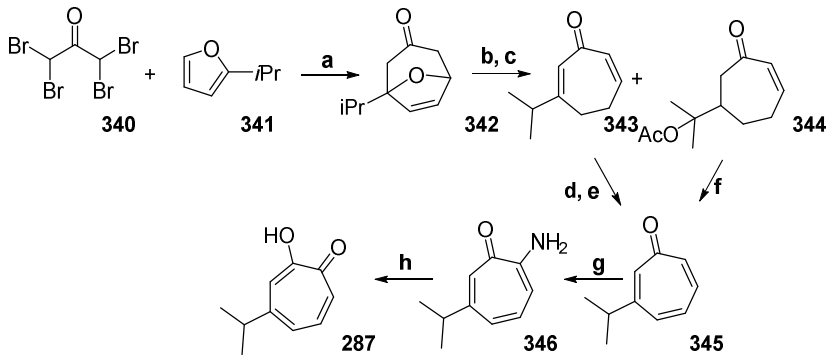
Cycloaddition reactions have also been employed in the synthesis of tropolones; [2+2]-cycloadditions have been used several times. Kato *et al*. used one in the formal synthesis of colchicine and this will be discussed later in this Thesis.[166] [5+2]-Cycloadditions have also been employed; whilst a number of different [5+2]-cycloadditions have been used, only Baldwin's synthesis of (±)-deoxyepolone B retains biomimetic principles.[167] Cyclisation gives bridged oxygen species **331** and this was followed by extensive functionalisation to give the intermediate **338** required for a hetero-Diels-Alder reaction with the terpene humulene to give the natural product (±)-deoxyepolone B **339**.



Scheme 85: Baldwin's synthesis of (±)-deoxyepolone B; a: PhMe, 120 °C, 54%; b: i) $NaBH_4$, $CeCl_3.7H_2O$, MeOH; ii) $NaBH_4$, 83%; c: Ac_2O, DMAP, Pyridine, 96%; d: HF, MeCN, 96%; e i) Tf_2O, Et_3N, CH_2Cl_2, -20 °C; *t*Butyl ammonium iodide, MeCN, 92%; f: Zn, EtOH, 78%; g: 2-methoxypropene, PPTS, 0°C, 88%; h: K_2CO_3, MeOH, 98%; i: $(COCl)_2$, DMSO, -65 °C then

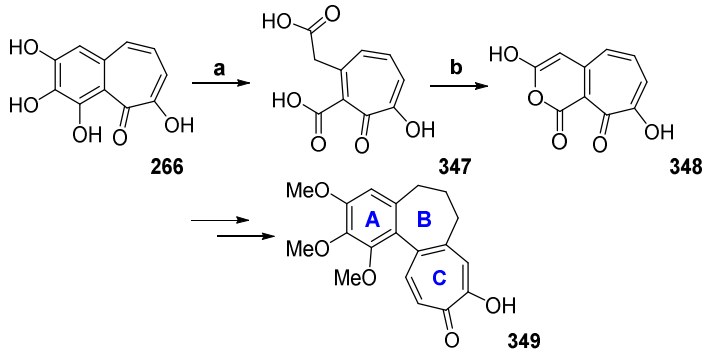
iPr$_2$NEt, -20 °C, 94%; j: NaSPh, EtOH, 0°C to rt, 92%; k: 70% AcOH (aq); l: TFAA, DMSO, Et$_3$N, 64%; m: humulene, *p*-xylene, 150 °C, sealed tube, 22%.[167]

A [4+3]-cycloaddition reaction was used by Noyori *et al.* in the synthesis of β-thujaplicin **345**, with the cycloaddition reaction giving **342** with an oxygen bridge.[168] Hydrogenation and acid-catalysed elimination gave **343** and **344** as a mixture and these can both be converted into tropone **345**. This was then functionalised to the tropolone using hydrazine monohydrate and potassium hydroxide.



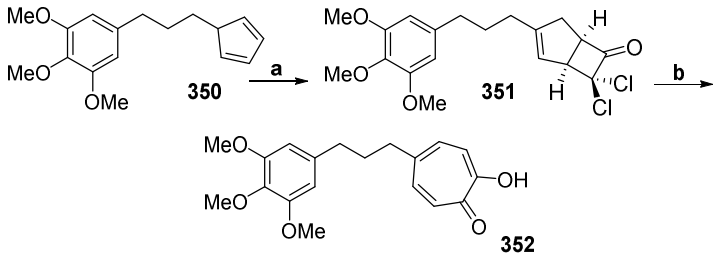
Scheme 86: Noyori's synthesis of β-thujaplicin using a formal [4+3] cycloaddition; a: i) Fe$_2$(CO)$_9$, benzene; ii) Zn-Cu; b: H$_2$ Pd/C, EtOH, NaHCO$_3$; c: i) BF$_3$.Et$_2$O, AcOH; ii) Al$_2$O$_3$; d: NBS, AIBN, CCl$_4$; e: LiCl-Li$_2$CO$_3$, DMF; f: DDQ; g: NH$_2$NH$_2$.H$_2$O, EtOH; h: KOH (aq), EtOH.[168]

As colchicine is one of the best known tropolone containing natural products, having been synthesised multiple times, examination as to how the tropolone is incorporated should provide inspiration for the synthesis of other tropolone containing natural products. Of the 15 syntheses of colchicine only three use a tropolone containing starting material, with the others synthesising it later in the synthesis. Scott *et al.*[169] and Kaneko *et al.*[170] used a similar route based on the work of Scott, where the tropolone comes from purpurogallin (**266**). Oxidative degradation of the benzene ring followed by dehydration gave intermediate **347** required for the coupling reaction to form the A and C ring of colchicine (Scheme 87).



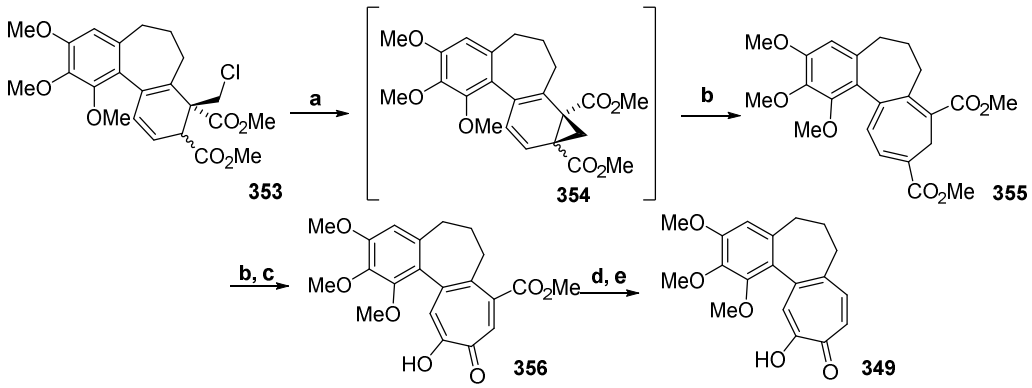
Scheme 87: Tropolone incorporation in Scott's formal synthesis of colchicine; a: H_2O_2, OH^-, 90-95 °C, b: H_2SO_4.[169]

Kato *et al.*[166] had an alternative approach to the installation of tropolone, where a ring expansion was used to install the fully oxidised seven-membered ring as seen in Scheme 88. A [2+2]-cycloaddition of cyclopentadione with the ketene derived from dichloroacetyl chloride gave intermediate **351** and treatment with potassium acetate and acetic acid at reflux installed the tropolone in a 66% yield.



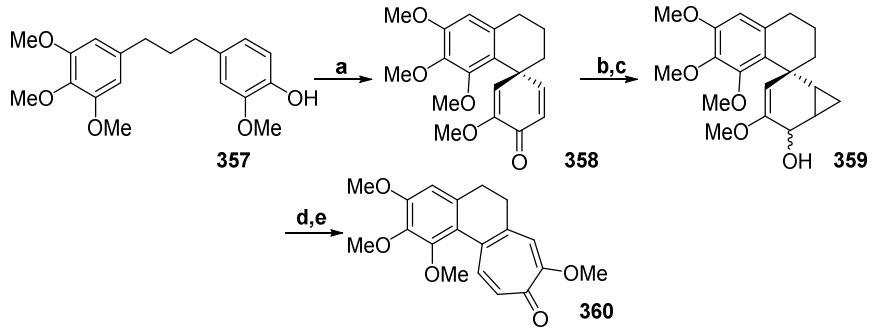
Scheme 88: Kato *et al.* installation of tropolone in the synthesis of colchicine; a: dichloroacetyl chloride, Et_3N, hexane; b: KOAc, H_2O, AcOH.[166]

Eschenmoser began the total synthesis of colchicine with purpurogallin; however, on this occasion purpurogallin was required for the A and B ring of colchicine, with the tropolone C ring being formed by a ring expansion (Scheme 89).[161]



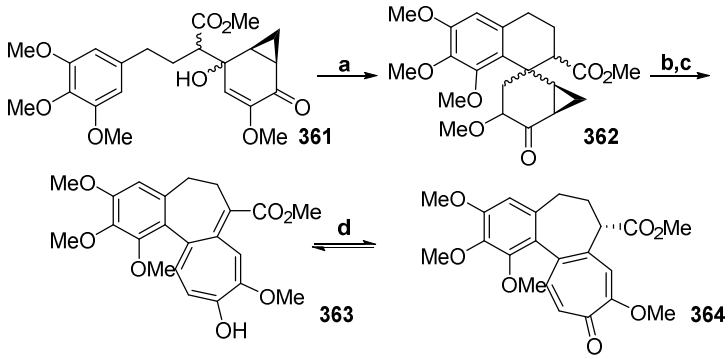
Scheme 89: Eschenmoser installation of tropolone using a ring expansion in the synthesis of colchicine precursor desacetamidocolchicine;[161] a: KO*t*Bu, tBuOH, benzene; b: NaOH, H_2O, MeOH, reflux; c: i) OsO_4, pyridine, Et_2O, ii) $KClO_3$, $NaHCO_3$, MeOH, 100 °C; d: NaOH, MeOH, reflux; e: powdered quartz glass, 260-270 °C.

A similar ring expansion has also been used by Tobinaga *et al.*,[160] Evans *et al.*,[163] and Banwell *et al.*[171] to form intermediates in the synthesis of the tropolone moiety of colchicine. Tobinaga treats intermediate **359** with acetic anhydride and sulfuric acid to give the methoxy-tropolone in a 90% yield (Scheme 90).



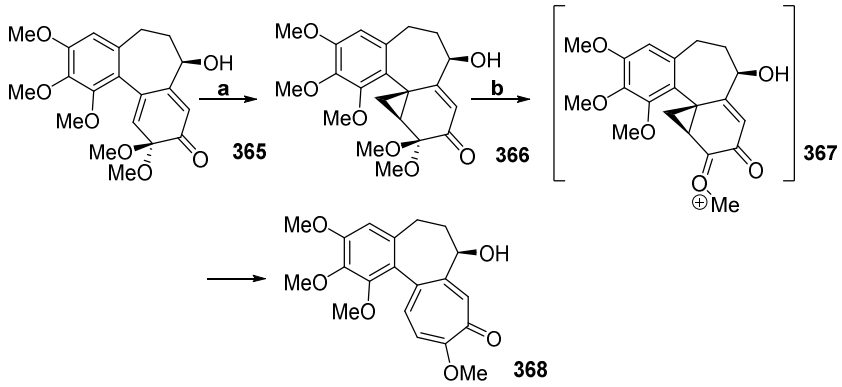
Scheme 90: Tobinaga synthesis of a key intermediate towards colchicine; a: anodic oxidation, HBF_4, MeCN; b: $NaBH_4$; c: CH_2I_2, Zn/Cu couple; d: Jones oxidation; e: Ac_2O, H_2SO_4.[160]

Evans treated intermediate **362** with trifluoroacetic acid, then DDQ to give the methoxy-tropolone in a 48% yield as two isomers that readily interconvert in deuterated chloroform (Scheme 91).[163]



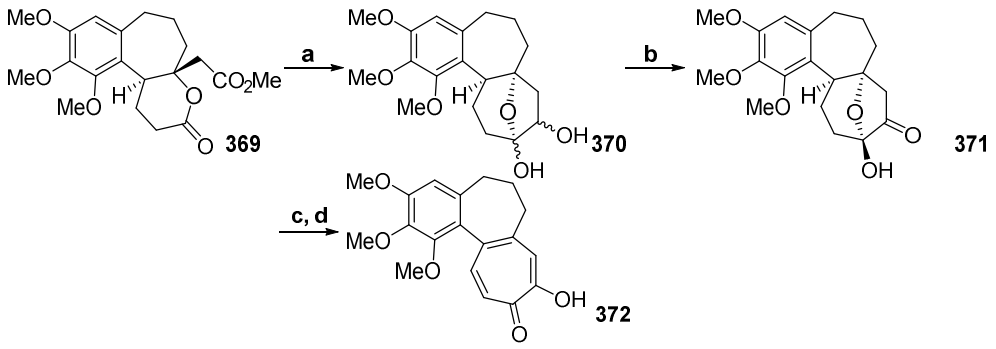
Scheme 91: Evans tropolone synthesis; a: CF_3CO_2H; b: CF_3CO_2H, reflux; c: DDQ, benzene, reflux; d: $CDCl_3$.[163]

Banwell also used trifluoroacetic acid to mediate expansion of the cyclopropane ring to the methoxy-tropolone in a 48% yield, with this route following the proposed biosynthesis of colchicine.[137, 171]



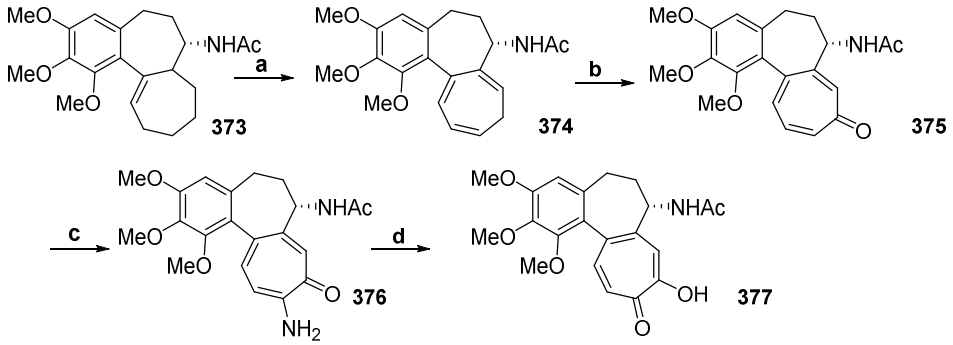
Scheme 92: Banwell acid mediated ring expansion to form methoxytropolone 368; a: $Me_3S(O)I$, NaH, DMSO, 15 °C; b: CH_3CO_2H, CH_2Cl_2, 15 °C.

In the Van Tamelen synthesis of colchicine treatment of **369** with sodium and liquid ammonia gives a mixture of diastereoisomers in a 9% yield; this mixture then underwent oxidation to **371**. Opening of the oxygen bridge and further oxidation gave the key tropolone structure **372** (Scheme 93).[172]



Scheme 93: Van Tamelen synthesis of the tropolone intermediate in colchicine; a: Na, liquid NH_3; b: $Cu(OAc)_2$, MeOH, reflux; c: $TsOH.H_2O$, benzene; d: NBS, $CHCl_3$, reflux.[172]

Other routes to install tropolone in the synthesis of colchicine exist; Nakamura has the C ring installed from the start as a non-functionalised cycloheptene and this is brominated and debrominated to give the tropilidene. **374** was oxidised to the tropone, treated with hydrazine mono hydrate and potassium hydroxide to give tropolone **377**. Several steps in this route proved to be low yielding with both steps a and b having 7% yields.[173]



Scheme 94: Nakamura functionalisation of the seven-membered ring to the tropolone; a: i) NBS, CCl_4, reflux; ii) collidine, 160-180 °C, 7%; b: PCl_5, CCl_4, 7%; c: i) NaOH (aq), ii) conc HCl; d: NH_2NH_2. H_2O, EtOH, reflux; e: NaOH (aq).[173]

The remaining routes carry out a cyclisation reaction to form the seven-membered ring, with both Woodward[174] and Martel[175] carrying out a Dieckmann cyclisation and Graening and Schmalz[176] carrying out a rhodium mediated cascade reaction to form the seven-membered rings. Whilst each of these routes has its own merit they would not be useful in a biomimetic synthesis and so will not be considered in more detail.

Despite the wealth of information about the synthesis of tropolone containing natural products, the literature does not provide any clues to the functionalisation of the tropolone ring system and a synthetic route to a tropolone adjacent to a quinoline is currently unknown. Many options to install tropolones at a late stage of a total synthesis exist, but to employ the biomimetic principles outlined in the paper describing the isolation of tintamine it will be necessary to use tropolone as one of the precursors.[17] The work of Kashman on the synthesis of pyridoacridines provides a strong starting point for our synthesis, and it is this work that will guide our approach to tintamine.[58]

3.2 Aims and objectives

Tintamine provides an interesting synthesis target as it contains a novel tropono-1,2-dihydro-3,6-phenanthroline core. It should be possible to develop a strategy to enable the synthesis of this previously unknown heterocycle, based on the synthesis of similar compounds in the literature.[58, 118, 126]

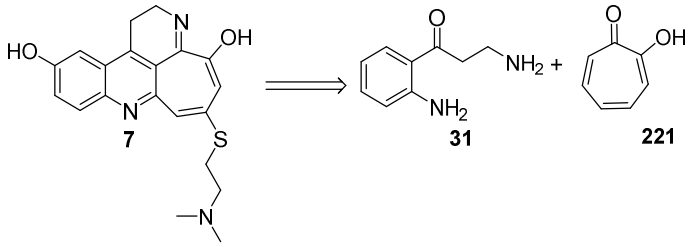
The original authors propose a route for the molecules biosynthetic origins,[17] and by developing a biomimetic route it will be possible to probe this hypothesis, examining the synthesis of tintamine in nature. Functionalisation of the seven-membered ring will prove the challenging part of this synthesis, with limited literature precedent for such systems.

As discussed in Sections 3.1.3.1 and 3.1.3.2, it has been seen that both pyridoacridines and tropolone derivatives have interesting biological properties. Investigation of the biological properties of tintamine have been hindered by the extremely small quantities isolated, and synthesis of more material would allow this to be probed.

3.3 Results and discussion

3.3.1 Biomimetic route and synthetic plan

The authors of the paper detailing the isolation of tintamine (**7**) propose that kynuramine (**31**) and tropolone (**221**) are starting materials for the biosynthesis of tintamine.[17] This is based on knowledge that the other novel natural products isolated alongside tintamine are produced using a similar route from kynuramine and a benzoquinone derivative.[17, 125]



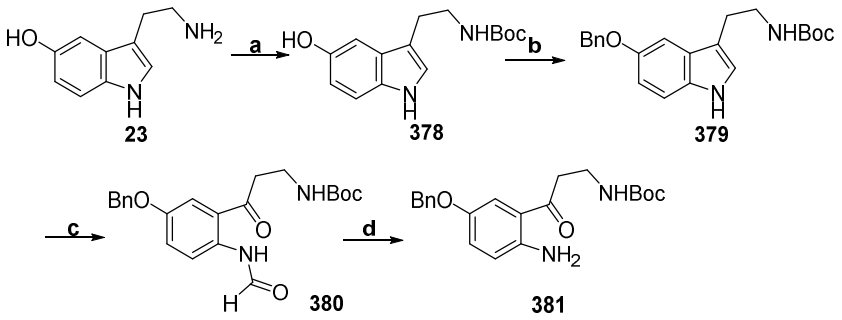
Scheme 95: Proposed biosynthesis of tintamine 7 from kynuramine 31 and tropolone 221.

Our initial investigations into the synthesis of tintamine were guided by this concept; however, we decided to work on a hydroxylated derivative of kynuramine, rather than attempt to install the hydroxyl group at the end of the synthesis. The introduction of this Thesis describes the extensive work that has been carried out on the modification of tryptophan to its metabolites. One of these is serotonin, that contains a hydroxyl group at the 5-position of tryptamine, with this providing a starting material for this synthesis.

3.3.2 Synthesis of protected 5-hydroxykynuramine

Whilst oxidation of tryptophan has been studied extensively, this is not true for serotonin (**23**). It was decided to apply conditions that had been used to oxidise the indole of tryptophan in the work on the hyrtioseragamines, where dipeptide **176** was treated with *m*CPBA (Section 2.3.3, Scheme 46). Protection of both the free amine and the hydroxyl group was necessary to allow control of subsequent reactions. The decision was taken to protect the amine with a Boc group using Schotten-Baumann conditions[177] to give **378** in a 92% yield (Scheme 96). The hydroxyl group was protected with a benzyl group, as it was intended that this could be

removed by hydrogenation as the final step of the synthesis. An initial set of conditions using benzyl bromide and caesium carbonate in DMF, described for benzyl protection of Boc-protected serotonin by Meng, proved to be low yielding in our hands.[177] Using benzyl bromide, potassium hydroxide and acetone reduced the number of side products, giving **379** in a 66% yield.

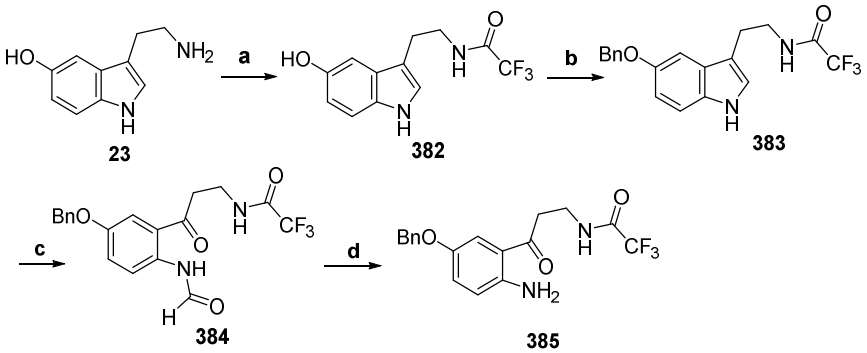


Scheme 96: a: Di-*tert*-butyl dicarbonate, $NaHCO_3$, NaCl, CH_2Cl_2/water, Δ 92%; b: benzyl bromide, KOH, acetone, Δ, 66%; c: *m*CPBA, CH_2Cl_2, -50 °C, 41%; d: 3 M hydrochloric acid, MeOH/1,4-dioxane, quantitative.

Oxidation of the indole did not prove trivial. The use of *m*CPBA as described in Chapter Two resulted in a low yield and a number of side-products. It was found that using 3 equivalents of *m*CPBA and quenching the reaction at -50 °C reduced the number of side reactions and the desired product **380** was isolated in a 41% yield. The formyl group was cleaved using mild acidic conditions with 3 M hydrochloric acid added to **380** in a solution of methanol and 1,4-dioxane to give aniline **381** in a quantitative yield, with no loss of the Boc group from the amine.

3.3.3 Trifluoroacetyl protected serotonin derivative

It was also decided to investigate the synthesis of material with an alternative protecting group on the amine. We decided to protect the amine with a trifluoroacetyl group and to achieve selective protection of the amine in the presence of the hydroxyl group conditions with ethyl trifluoroacetate were developed, with the protection occurring in a 93% yield (Scheme 97).

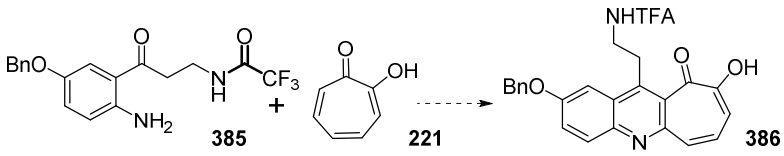


Scheme 97: Ethyl trifluoroacetate, Et_3N, MeOH/CH_2Cl_2 93%; b: benzyl bromide, KOH, acetone, 89% Δ; c: *m*CPBA, CH_2Cl_2, -50 °C, 30%; d: 3 M hydrochloric acid, MeOH/1,4-dioxane, 93%.

From **382** the route described for the Boc-protected material was applied, with an improved 89% yield being observed for the benzyl protection and the other steps occurring in comparable yield to the original route. It was hoped that the addition of the trifluoroacetyl group would improve the yield of the indole oxidation, as it was believed that some of the side-products were being formed due to loss of the Boc group, but unfortunately this was not the case with a slightly worse yield being obtained after the change in protecting group.

3.3.4 Investigation of Kashman's proposed biosynthesis

We decided to investigate Kashman's biosynthetic proposal using the trifluoroacetyl protected molecule, as this contained a more robust protecting group. Treatment of **385** and commercially available tropolone with a range of Brønsted and Lewis acid-catalysed conditions, seen in Table 6, was unsuccessful.



Scheme 98: Biomimetic synthesis of tintamine, conditions screened shown in Table 6.

Conditions	Result
EtOH, 18 h, 70 °C.	No reaction
EtOH, aq. HCl, 18 h, 70 °C.	No reaction
$FeBr_3$, EtOH, 18 h, 70 °C.	No reaction
$Sc(OTf)_3$, EtOH, 18 h, 70 °C.	No reaction
$CeCl_3 \cdot 7H_2O$, EtOH, 18 h, 70 °C.	No reaction
$ZnBr_2$, EtOH, 18 h, 70 °C.	No reaction

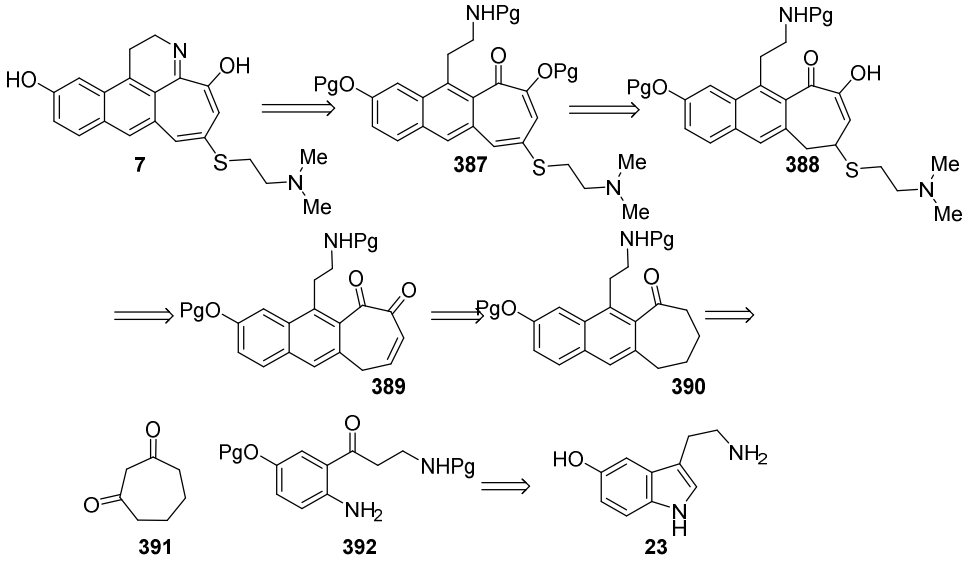
Table 6: Conditions screened for quinoline formation from tropolone and protected hydroxyl-kynuramine (Scheme 98).

Each of these conditions resulted in no reaction occurring, with only starting materials being observed after the reaction mixture was stirred overnight. As it seemed that tropolone was unreactive using these conditions an alternative cycloheptane derivative was instead investigated.

3.3.5 Development of an alternative strategy to form the ABC ring system

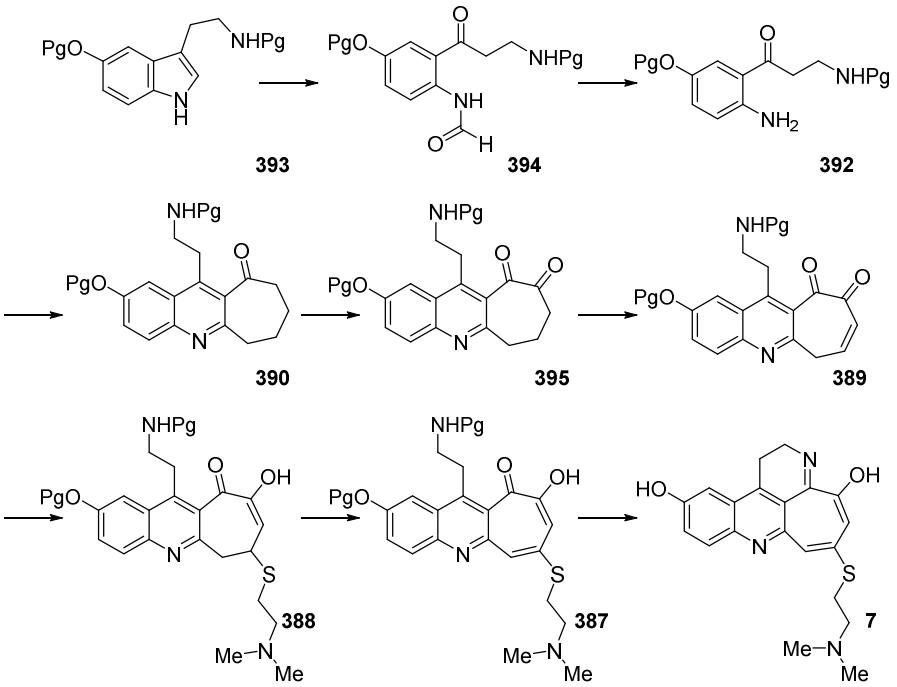
It was necessary to develop an alternative route to tintamine, retaining the principles described in the paper that details the isolation of tintamine.[17] Whilst it is highly likely that a kynuramine derivative is a biological precursor of tintamine, as it has been shown that several pyridoacridines are biosynthesised this way, the evidence for its coupling partner is less definitive. Cycloheptane-1,3-diones have been observed as volatiles released from the *Roseobacter* clade family of marine bacteria,[144] a family that is also known to be a marine source of tropone and tropolone. This dione could provide an alternative coupling partner for 5-hydroxykynuramine, allowing a route to tintamine with more options to control subsequent

reactions. It has been described in the synthesis of pyridoacridine analogues by Kashman that kynuramine can be reacted with cyclohexane-1,3-dione and this provided an initial starting point for this synthesis.[57] Whilst it would be possible to carry out the Friedländer reaction with cyclohexane-1,3-dione and then carry out a ring expansion to the seven-membered ring, it would be more elegant to install the seven-membered ring directly. Based on this knowledge an alternative forward synthesis was designed which retains biosynthetic principles.



Scheme 99: Retrosynthetic analysis for Tintamine.

This route uses cycloheptane-1,3-dione (**391**) in place of tropolone, with this being expected to undergo a Friedländer reaction with hydroxykynuramine **392**. From the Friedländer product **390** it will be necessary to oxidise the molecule to the diketone, and Saegusa-Ito oxidation should allow installation of a double bond (**389**), with the molecule now being set up for a conjugate addition to install the sulfur containing side chain. From **388** a Pummerer oxidation should allow access to the functionalised tropolone; deprotection of the amine would allow formation of the D ring of tintamine and the removal of the protecting group from the hydroxyl group would give access to the structure proposed by Kashman (Scheme 100).[17]



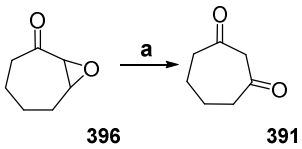
Scheme 100: Proposed synthesis of tintamine.

3.3.6 Cycloheptane-1,3-dione synthesis

Whilst cycloheptane-1,3-dione is available commercially, the cost of £263 per gram (Sigma-Aldrich, 20/04/2014) was problematic for an early stage of a total synthesis and so it was decided to make the compound. Cyclohexane-1,3-dione is a relatively common reagent for which many synthetic routes exist, but the seven-membered homologue is more difficult to synthesise with synthesis from a straight chain being known to be difficult and many routes relying on a ring expansion.[178]

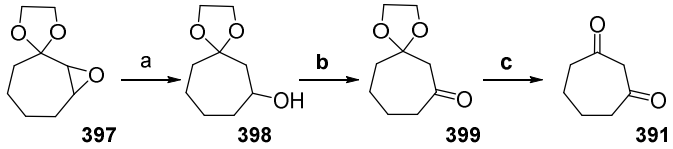
The synthesis of cycloheptane-1,3-dione from an enone starting material was explored by Noyori *et al*. A number of 1,3-diketones were formed from α,β-epoxy ketones using 1,2-

bis(diphenylphosphino)ethane (dppe) and $Pd(PPh_3)$ at 80-140 °C, including cycloheptane-1,3-dione in a 52% yield.[179]



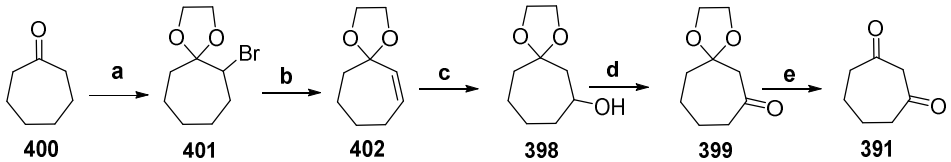
Scheme 101: Noyori formation of cycloheptane-1,3-dione; a: $Pd(PPh_3)_4$, dppe, 100 °C, 52%.[179]

Vankar also used an α,β-epoxy acetal (**397)**, where the epoxide was opened using lithium aluminium hydride; oxidation of the alcohol and removal of the protecting group gave the desired diketone over three steps (Scheme 102).[180]



Scheme 102: Vankar's work on cyclic 1,3 diones; a: $LiAlH_4$, THF, 81%; b: CrO_3, pyridine, CH_2Cl_2, 78%; c: H_2SO_4, CH_2Cl_2, silica gel, 71%.[180]

The synthesis of cycloheptane-1,3-dione was described by Bhushan *et al.* from the cheap commercial cycloheptanone (**400)** in 5 steps *via* the brominated acetal and elimination to alkene **402**. From **402** oxymercuration, oxidation and deprotection gave the dione **391** (Scheme 103).[181] The authors report a 66% yield over 4 steps from the bromoacetal **401** with no purification required. As the route appeared to be high yielding without purification this proved an appealing route to investigate.

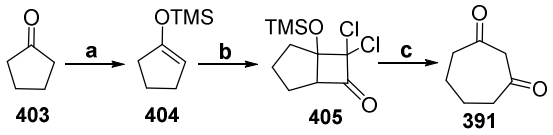


Scheme 103: Formation of cycloheptane-1,3-dione. a:ethylene glycol, Br_2, 61 %; b: KOtBu, DMSO, 40 °C, 50%; c:i) $Hg(OAc)_2$, THF/H_2O; ii) NaOH, $NaBH_4$, 0 °C, 65%; d) CrO_3, py, CH_2Cl_2, 13%; e) HCl (aq) 41%.

Investigation of this route resulted in the yields seen in Scheme 103, with several steps having yields lower than those described in the paper. Cycloheptanone was treated with bromine in ethylene glycol to protect the ketone and install the bromine. Potassium *tert*-butoxide

facilitated elimination of the bromine to give the alkene. Oxymercuration gave **398** and this was oxidised to **399** using chromium trioxide. Removal of the protecting group gave cycloheptane-1,3-dione. We carried out this reaction on an 89 mmol scale and observed that purification was necessary. Over the 5 steps a 1% yield was obtained, alongside a large amount of heavy metal salt by-products.

Further investigation of the literature led to the route described by Ragan *et al.*, using cyclopentanone as the starting material, being adopted (Scheme 104).[182] Cyclopentanone is converted into its silyl enol ether and dichloroacetyl chloride is treated with triethylamine to form the ketene, and this can undergo a [2+2]-cycloaddition with the silyl enol ether to give **405**. This intermediate is then treated with zinc under reducing conditions to give cycloheptane-1,3-dione. Ragan *et al.* obtained cycloheptane-1,3-dione in a 38% yield after distillation and a comparable 31% yield over the three steps was observed, with this route providing a practical and reproducible synthesis of the second intermediate required for the Friedländer reaction.

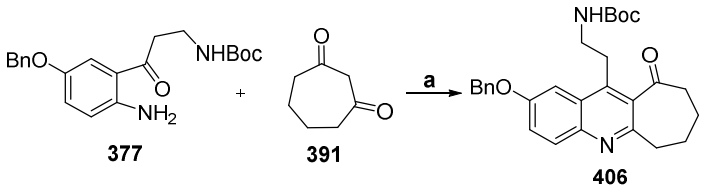


Scheme 104: Cycloheptane-1,3-dione synthesis.[182] a: TMSCl, Et_3N, DMF, 79%; b: dichloroacetyl chloride, Et_3N, hexane, 50%; c: i) Zn, H_2O, 2-propanol; ii) AcOH, H_2O, 77%

3.3.7 Formation of tricyclic ring system

From the protected hydroxykynuramine **377** and cycloheptane-1,3-dione it was now possible to investigate the Friedländer reaction. It was decided to investigate this with the Boc-protected material initially as this route had a slightly higher yield. Typical conditions for Friedländer annulation include both acid and base catalysed reactions; however, both of these conditions are associated with side reactions.[183] Concerns about the stability of the Boc group to Brønsted acid conditions meant that Lewis acids were studied as a mild way to form the quinoline. Whilst a number of Lewis acids have been described for this transformation, many of them are

associated with difficulties in work-up. In 2005 Wu described the use of molecular iodine as a mild Lewis acid catalyst for the Friedländer reaction, with these conditions being screened on a range of substrates, including cyclohexane-1,3-dione.[183] With the knowledge that these conditions could be applied to similar substrates it was decided to apply these mild conditions to our system. Pleasingly treatment with 10% catalytic iodine in ethanol over 24 hours allowed access to the desired tricyclic ring system in a 64% yield (Scheme 105).



Scheme 105: Iodine catalysed Friedländer annulation; a: Iodine (10 mol%), ethanol, 64%.

Recrystallisation of the purified material from ethanol gave crystals suitable for X-ray crystallography, shown in Figure 22.

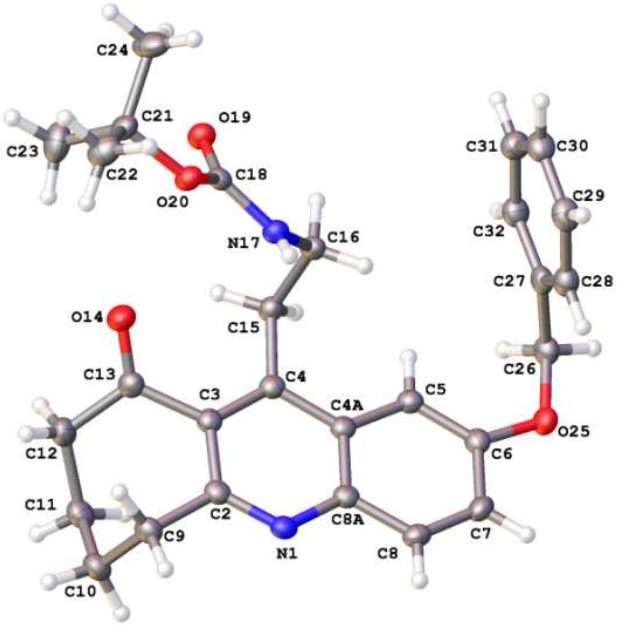
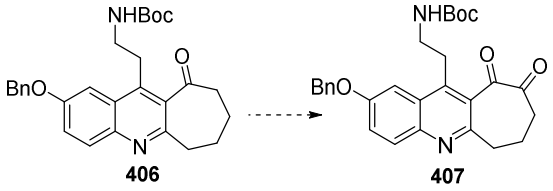


Figure 22: Crystal structure of the ABC ring system. Displacement ellipsoids are set at 40%.

The crystal structure of the ABC ring system confirmed that it was possible to carry out a Friedländer reaction and to form the first key intermediate in this synthesis of tintamine.

3.3.8 α-Oxidation of the ABC ring system.



Scheme 106: Proposed alpha oxidation of the ABC ring system.

Conditions	Results
SeO_2, EtOH, 50 °C	No reaction
SeO_2, Ac_2O, reflux	Some decomposition
SeO_2, AcOH, reflux	Decomposition
SeO_2, 1,4-dioxane, 90 °C	No reaction

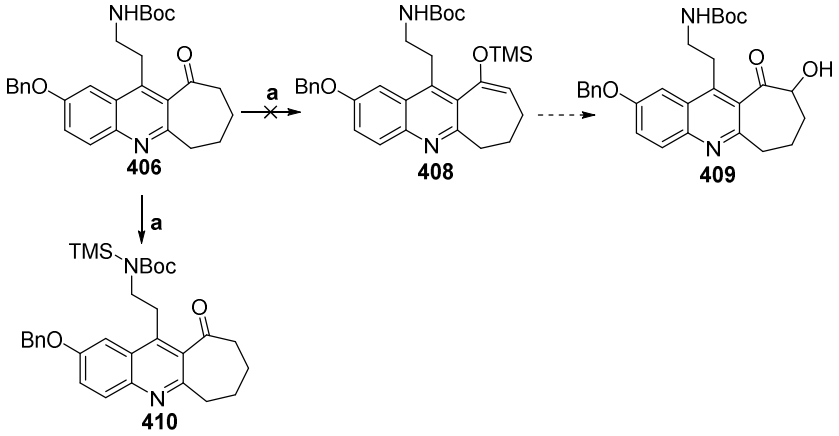
Table 7: Selenium dioxide conditions for alpha oxidation (Scheme 106).

The next step in our proposed synthesis of tintamine involved α-oxidation to provide a functional handle for further substitution of the seven-membered ring (Scheme 106). It has been described that sodium nitrite and hydrochloric acid can be used as mild conditions for the formation of 1,2-diketones from α-methylene ketones,[184] avoiding the use of selenium reagents that can be difficult to remove from products and have associated toxicity. Development of this methodology by Ruedi *et al.* increased the scope of this reaction to a range of other substrates.[185] Unfortunately in our hands this reaction returned only starting material. In a move back to more conventional methods, selenium dioxide was then investigated (Table 7).

Mild conditions, using selenium dioxide in ethanol with heating, are described by Majetich *et al*. as conditions to install a ketone in a complex ring system, but on substrate **406** only starting material was returned.[186] The use of acetic anhydride alongside selenium dioxide was described as high yielding by Zhang in the conversion of a ketone on a seven-membered ring to the 1,2-diketone; however, in our hands a combination of starting material and

decomposition products were observed.[187] The use of selenium dioxide in acetic acid at reflux, as described by Voss *et al.*,[188] resulted in loss of the Boc group and decomposition of the starting material without formation of the desired 1,2-diketone. Reverting to milder conditions, it was seen that heating **406** with selenium dioxide in 1,4-dioxane again returned only starting material.[189]

Previously within the group, a Rubottom oxidation on a cyclohexanone attached to a quinoline had been investigated, but this work indicated that the silyl group reacted with a trifluoroacetyl protected amine rather than making the desired silyl enol ether.[190] As our substrate had a different protecting group on the amine it was decided to investigate if formation of the silyl enol ether was possible.



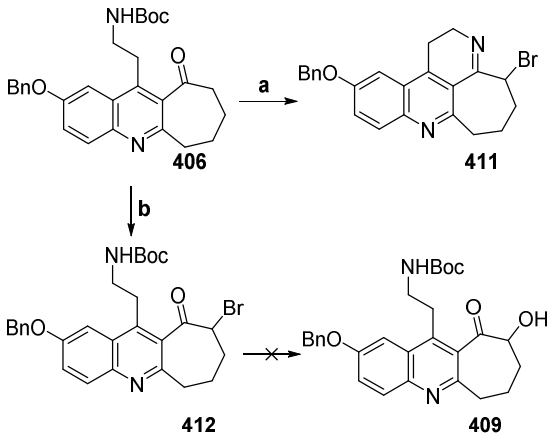
Scheme 107: Attempted work towards α-hydroxy-ketone 409; a: TMSCl, Et_3N, DMF.

On substrate **406** the same result was observed, with the protecting group reacting with the amine. A brief attempt to methylate the amine was made in order to prevent the silyl group reacting at this position, but this did not prove trivial. At this point it was decided that Rubottom oxidation was not possible without manipulation of the protecting groups, and this route was abandoned.

As an alternative method of α-hydroxylation, **406** was treated with Davis oxaziridine and Lithium bis(trimethylsilyl)amide (LiHMDS) but this resulted in no reaction, with this potentially being due to the reactive nature of the proton on the protected amine.

Oxone® has been used to install hydroxyl group adjacent to ketones, and this methodology was applied to substrate **406**.[191] Oxone®, trifluoroacetic anhydride (TFAA) and iodobenzene in an acetonitrile/water solvent system had been applied to a range of ketones adjacent to aromatic systems by Huang *et al.*[191] However, unfortunately these conditions were unsuccessful when applied to our system

Treatment of **406** with bromine in acetic acid resulted in a product being observed in the ESI spectrum that would corresponded to addition of the bromine; however, loss of the Boc group was also observed with the free amine going on to form the D ring seen in tintamine (Scheme 108). Milder conditions using bromine in chloroform were able to give access to the brominated material, albeit in low yields. Attempts to use even milder conditions using *N*-bromosuccinimide and *p*-toluenesulfonic acid in dichloromethane resulted in no reaction occurring, and installation of the bromine in basic conditions using LiHMDS resulted in decomposition.



Scheme 108: α-Bromination of 406; a: Br_2, AcOH (not isolated) b: Br_2, $CHCl_3$, 32%.

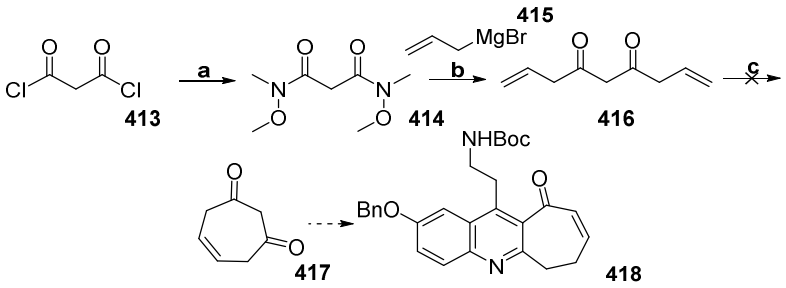
To investigate if optimisation of the bromine addition was worthwhile, conversion of the bromine to a ketone was investigated. Sodium iodide is commonly used for this reaction; for example, when improving the synthesis of camphorquinone it was found that 3-bromocamphor could be oxidised using sodium iodide in DMSO by bubbling air through the solution.[192] However on substrate **402** only starting material and material showing loss of the bromine was

observed after 24 h. Similar conditions were used by Macomber, where sodium iodide was used to displace the bromine and DMSO was used to carry out oxidation to the 1,2-diketone on a range of substrates.[193] Unfortunately, on our substrate this returned only starting material. In 2006 it was described by Horiuchi that microwave conditions could be used to convert α-bromoketones to the α-hydroxyketone in water,[194] but again on our substrate only starting material was isolated.

3.3.9 Functionalised cycloheptane-1,3-dione synthesis

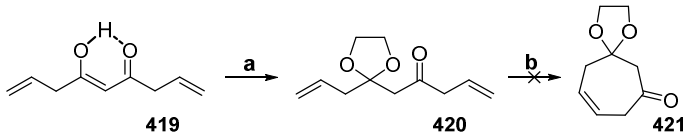
As a reaction of kynuramine with tropolone had been unsuccessful and α-oxidation of tricyclic **396** had not proven trivial, attention was turned an earlier stage functionalisation of the seven-membered ring so that the molecule would maintain a functional handle after the Friedländer reaction. To allow control of the Friedländer reaction and prevent the formation of by-products the seven-membered ring would need to remain symmetrical, and so it was decided to investigate the synthesis of cyclohept-5-ene-1,3-dione (**417)** using ring-closing metathesis.

Conversion of malonyl chloride to the bis-Weinreb amide[195] did not prove trivial. Bis-Weinreb amides are unusual within the literature and initial conditions resulted in a number of side-products, which we attributed to formation of a ketene. The use of triethylamine and dichloromethane under an argon atmosphere resulted in the bis-amide being formed in a 51% yield. Reaction of **414** with allylmagnesium bromide in THF resulted in the desired product **416** in an unoptimised 11% yield. Few examples exist within the literature of using a ring closing metathesis to form a seven-membered ring, with those which do using Grubbs' 2nd generation catalyst in dichloromethane.[153, 196, 197] Application of these conditions to our substrate resulted in no reaction occurring after heating at reflux for 24 h, in both dichloromethane and toluene.



Scheme 109: Attempted formation of cyclohept-5-ene-1,3-dione by ring closing metathesis; a: Weinreb amine.HCl, Et_3N, CH_2Cl_2, 0 °C, 51%; b: 415, THF, -20 °C, 11%; c: Grubbs' 2nd generation catalyst (30 mol%), CH_2Cl_2.

Analysis of the NMR data for **416** showed that the molecule appeared to exist in the hydrogen-bonded enol form (**419**) at room temperature, with this geometry providing a barrier to the ring closure. Protection of one of the ketones as the acetal was applied in an attempt to overcome this problem, refluxing **419** with ethylene glycol and *p*-toluenesulfonic acid under Dean-Stark conditions gave **420** as a solution in toluene. Addition of Grubbs 2nd generation catalyst to **420** as a solution in toluene did not result in any reaction, with only starting material observed after 24 hours.



Scheme 110: Protection of 419 to overcome the enol-keto tautomerisation as an aid to cyclisation; a: ethylene glycol, *p*TsOH, toluene, 140 °C; b: Grubbs' (II) catalyst (30 mol%), toluene.

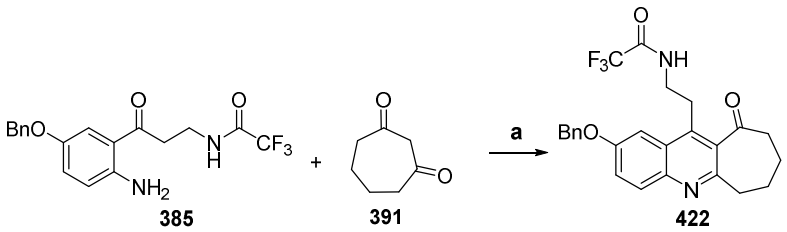
It is described in the literature that formation of a seven-membered ring from a straight chain molecule is known to be problematic,[178] and so at this point it was decided to make further attempts to functionalise the seven-membered ring after the Friedländer reaction had occurred.

3.3.10 Acid-catalysed Friedländer reaction.

Despite attempts to optimise the iodine catalysed Friedländer reaction, increasing the catalyst loading and applying heat, it was not possible to drive the reaction to completion and improve the yield. This, alongside the lability of the Boc protecting group, meant that it was necessary

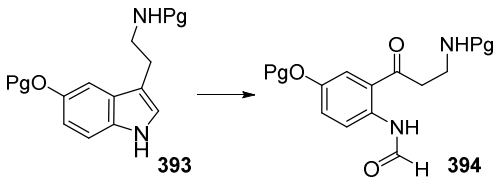
to look for a new route to the tricyclic ring system, turning to the trifluoroacetyl protected molecule (**385**) for its likely increased stability.

From intermediate **385** an acid mediated Friedländer annulation was investigated with trifluoroacetic acid-catalysed formation of the tricyclic system occurring in an improved 87% yield.



Scheme 111: Acid-catalysed Friedländer reaction; a: TFA (10 mol%), EtOH, 87%.

With the knowledge that the reaction to form the quinoline from cyclohepta-1,3-dione and 5-hydroxykynuramine was successful, allowing a biomimetic approach to the first 3 rings of tintamine, interest turned to scaling up this sequence. The addition of protecting groups and removal of the formyl group were all relatively high yielding; however, oxidation of the indole 2,3-bond was not. Attention was turned to improving this reaction.



Scheme 112: Oxidation of the indole 2,3-bond of protected serotonin to protected 5-hydroxy kynurenine.

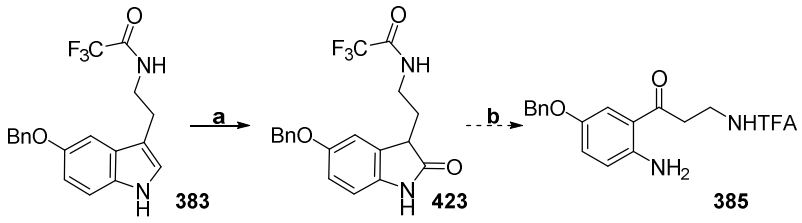
Conditions	Results
*m*CPBA, CH_2Cl_2, -50 °C	30%
Methylene blue, red LED, air, 21 °C	No reaction
Conc. HCl, phenol, acetic acid, DMSO, air, 21 °C	28% (oxindole **423**)
Ozonolysis, 21 °C	26%
MnTPP, DMSO, oxygen, 21 °C MnTPP, THF, oxygen, 21 °C	No reaction No reaction
$RuCl_3.H_2O$, $NaIO_4$, H_2SO_4, EtOAc, MeCN, 21 °C	Decomposition
$NaIO_4$, H_2O, MeOH, 21 °C	30-60%

Table 8: Conditions screened for oxidation of the indole (383).

A search of the literature provides a wealth of options for carrying out oxidation of the 2,3-bond of tryptophan derivatives, but it provides far fewer options for serotonin derived compounds. Reactions that are high yielding on tryptophan proved in our hands to be low yielding, or entirely unsuccessful on serotonin, possibly because of the changed electronics of the ring caused by the oxygen at the 5-position. In Nature the oxidation of tryptophan relies on an enzyme catalysed dioxygenase mechanism, and conditions that mimicked this approach were screened.

As had been previously seen, *m*CPBA in dichloromethane gave the desired product in a 30% yield with a large amount of an unidentifiable side-product being observed. The use of the photosensitiser methylene blue in the presence of red light and air had been described to cleanly oxidise the indole ring in the synthesis of melohenine B,[198] but with substrate **383** no

reaction was observed. The more traditional conditions applied by Hoffmann (Scheme 113) gave the first intermediate in the oxidation in a disappointing yield and therefore further oxidation to give 5-hydroxy *N*-formylkynuramine was not carried out.[23]



Scheme 113: Oxygen catalysed indole oxidation; a: Conc. HCl, phenol, AcOH, DMSO, air, 28%.[23]

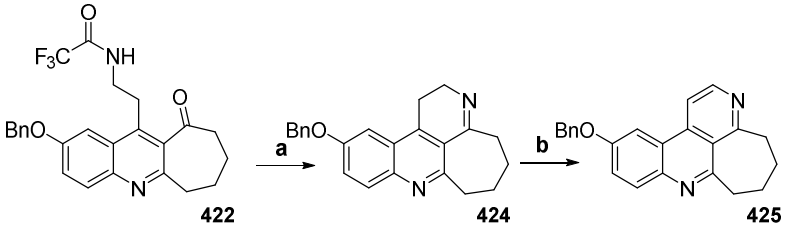
Ozonolysis is frequently described as a method for the oxidation of the 2,3-bond of indoles;[36, 58, 199, 200] on substrate **383** the reaction initially appeared to be clean but after purification the desired product was isolated in a disappointing 28% yield. Generation of the highly reactive ruthenium tetroxide species from ruthenium (III) chloride in the presence of sodium periodate was described as an oxidation method for an unreactive indole moiety; however, on our substrate only decomposition was observed.[198]

In Nature the enzymes IDO and TDO catalyse tryptophan oxidation using a haem centred mechanism and so a manganese porphyrin (MnTPP) was investigated based on the work of Ohkubo *et al.* and Gaudemer *et al.*[201, 202] They describe a stereoselective oxidation of tryptophan in THF, but when this reaction was investigated using the literature conditions, as well as using DMSO as a solvent, no reaction occurred.

Sodium periodate in methanol and water gave the desired product in a reasonable 30-60% yield, with large amounts of starting material also being isolated. Allowing the reaction to go to completion resulted in an increased return of the degradation products and a lower overall yield. Attempts to further optimise this reaction were unsuccessful; the reaction was found to work best with 4 equivalents of sodium periodate, with attempts to reduce this to limit degradation resulting in the reaction being very slow.

3.3.11 Formation of the D ring.

It had been seen in the biomimetic synthesis of a similar substrate that deprotection of the amine in either acidic or basic conditions resulted in spontaneous formation of the final ring (Section 3.1.3.1.1, Scheme 66).[118] Application of this principle to **422** was successful, using sodium hydroxide to deprotect the amine and form the D ring to give **424**, with a small amount of over-oxidised material **425** also being formed.

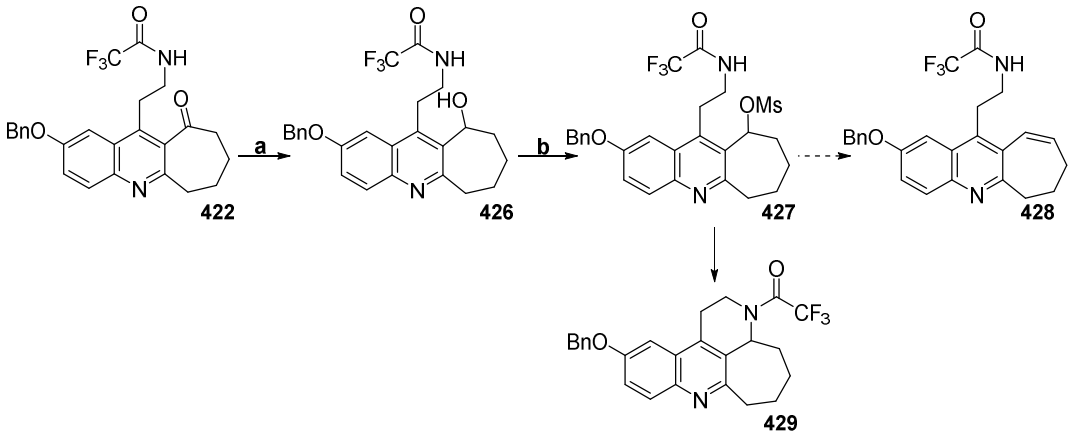


Scheme 114: Formation of the D ring: a: NaOH, MeOH, 55%; b: $CDCl_3$, air.

If the purified material was left as a solution in deuterated chloroform, gradual oxidation of the D ring occurred. After one week at room temperature 26% of the material had been converted into **425**, which was isolated as a colourless solid. This result was not entirely surprising, as in the synthesis of ascididemin the dihydropyridine undergoes oxidation in air to give the natural product.[118] When investigating the biosynthesis of pyridoacridines, Kashman also observed the oxidation of the dihydropyridine ring, despite it not being attached to a fully aromatic system (Section 3.1.3.1.1, Scheme 70).[58] As the D ring is not aromatic in the natural product, it was hoped that further substitution of the tropolone will act to stabilise the D ring in the correct oxidation state.

3.3.12 Functionalisation of the trifluoroacetyl protected Friedländer product

As it was now possible to access the tricyclic ring system in good yield, a brief investigation into α-oxidation *via* a bromination route was again made; however, difficulties carrying out a clean bromination were seen once again and an alternative route where the diol could be formed from an alkene was instead investigated (Scheme 115).



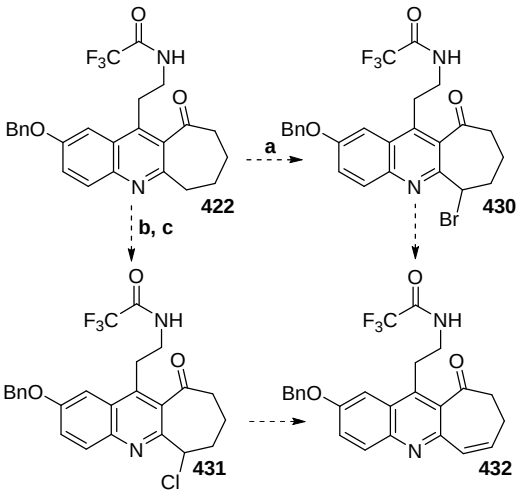
Scheme 115: Attempted formation of the diol; a: $NaBH_4$, MeOH, 65%; b: MsCl, Et_3N, CH_2Cl_2, 29%.

Whilst it was possible to reduce the ketone to alcohol **426** in good yield, elimination to the diol proved more difficult. The use of polyphosphoric acid to induce elimination was unsuccessful, with no reaction occurring. Mesyl chloride and triethylamine initially appeared to give access to the desired product, but on further analysis it was seen that an unexpected isomer of the desired product had been formed due to the reactive nature of the proton on the nitrogen, with compound **429** being tentatively assigned as the product of this reaction.

3.3.12.1 Functionalisation of the seven-membered ring adjacent to the nitrogen

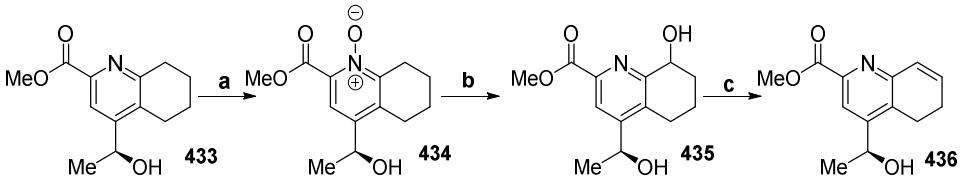
Owing to problems carrying out an α-hydroxylation to form the 1,2-diketone, a new route was designed to install functionality adjacent to the nitrogen. Investigations into installation of a bromine were carried out, with the idea that this could then be eliminated to access olefin **432**. Radical conditions using *N*-bromosuccinimide in carbon tetrachloride with either azobisisobutyronitrile (AIBN) or benzoyl peroxide were both unsuccessful, despite literature precedent for equivalent reactions of pyridines.[203, 204]

As this had proven problematic, we decided to investigate using the quinoline nitrogen as a handle to install functionality into the seven-membered ring. An alternative route to olefin formation involved installation of chlorine; whilst it was observed that chlorine added into the molecule (Scheme 116), it appeared to add to the side chain rather than at the desired position.



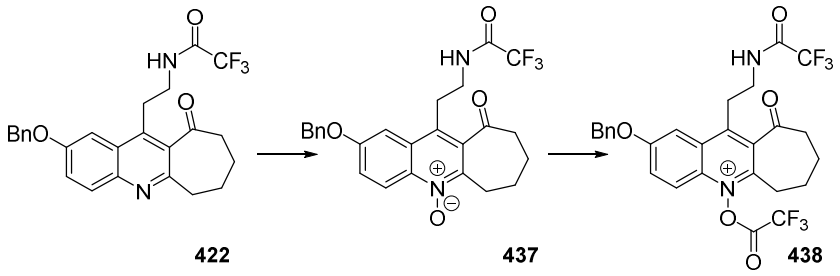
Scheme 116: a: AIBN, NBS; b: *m*CPBA, CH_2Cl_2; c: $POCl_3$, 80 °C.

Nicolaou's synthesis of thiostrepton provided further inspiration for this step; in this synthesis a double bond is installed adjacent to a pyridine using a Böckelheide type sequence (Scheme 117).[205]



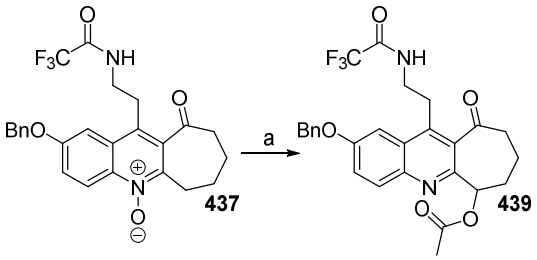
Scheme 117: Böckelheide-type reaction in the synthesis of thiostrepton, with elimination to give olefin 436; a: *m*CPBA, CH_2Cl_2, 0-25 °C; b: TFAA, CH_2Cl_2, 0-25 °C; c: Burgess reagent, THF then benzene.[205]

Application of these conditions to substrate **422** was not immediately successful. Whilst it was possible to form the *N*-oxide with *m*CPBA without the occurrence of by-products, attempts to carry out the Böckelheide reaction with TFAA resulted in a reaction with the *N*-oxide but no rearrangement occurred (Scheme 118).



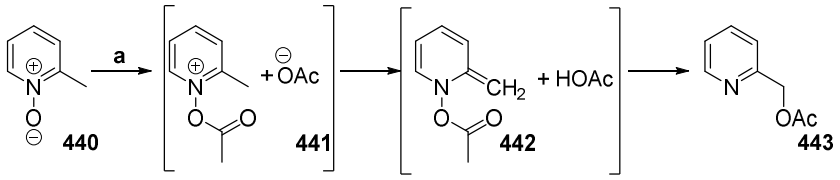
Scheme 118: Attempted Böckelheide rearrangement; a: *m*CPBA, CH_2Cl_2, quant. b: TFAA, CH_2Cl_2.

The Böckelheide reaction is traditionally described using acetic anhydride,[206] and happily it was found that under these conditions the rearrangement reaction occurred in a 53% yield with the application of heat increasing the yield to 85% (Scheme 119).



Scheme 119: Successful Böckelheide rearrangement and removal of the acetate; a: Acetic anhydride, CH_2Cl_2, 50 °C, 85%.

It has been described by Andreotti *et al.* that when the Böckelheide rearrangement is applied to pyridines with a substituent at the 4-position, that the reaction can occur on this substituent.[207] Pleasingly on our substrate this competing reaction was not observed. The mechanism of the Böckelheide reaction has been extensively examined but despite this it has still not been confirmed, with the general mechanism shown in Scheme 120.



Scheme 120: Overall scheme of Böckelheide reaction; a: Ac_2O.

It was initially proposed by Böckelheide and Harrington that the reaction relied on a free radical chain mechanism and homolytic cleavage of the nitrogen oxygen bond.[208] The

experimental evidence for this mechanism included the exothermic nature of the reaction, the rate of reaction not being affected by a change in solvent and that polystyrene was formed when styrene was added to the reaction. Work by Traynelis and Martello built on this concept by showing that addition of a free radical scavenger to the reaction reduced the rate of styrene polymerisation, but not the rate of the Böckelheide rearrangement.[209] They explain this result by suggesting that the reaction proceeds *via* a sigmatropic rearrangement.

Oae *et al*. examined the Böckelheide reaction using acetic anhydride containing three oxygen-18 atoms.[210] They found that scrambling of the oxygens occurred and from this they proposed that the reaction must occur either by a free radical chain mechanism, where the acetoxy radical acts to propagate the next step, or a radical-pair, with homolytic cleavage of the nitrogen-oxygen bond followed by recombination of the radicals in a solvent cage. The fact that the acetoxy radical is known to be short lived resulted in them discounting the first option. The solvent cage hypothesis was backed up by experiments showing the rate was unaffected by changes in solvent concentration or addition of a radical scavenger. In contrast to this, their studies on the 4-substituted pyridine showed that this reaction proceeds by a intermolecular rearrangement and nucleophilic attack.[211]

Work by Katritzky and Bodalski[212] confirmed Oae's work on the oxygen scrambling, but they drew different conclusions from this work. This led them to propose that the reaction occurs by an ion-pair intermediate, with the two possible options being shown in Figure 23.

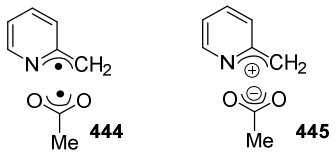
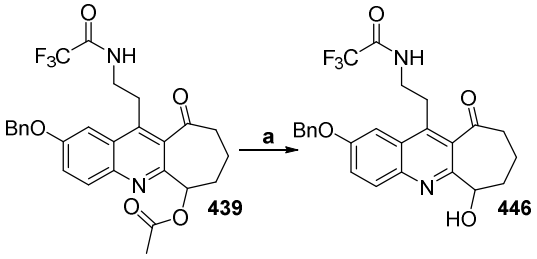


Figure 23: Suggested intermediates in the Böckelheide reaction. Radical-pair mechanism 444 proposed by Oae[210] and ion-pair mechanism 445 proposed by Katritzky and Bodalski.[212]

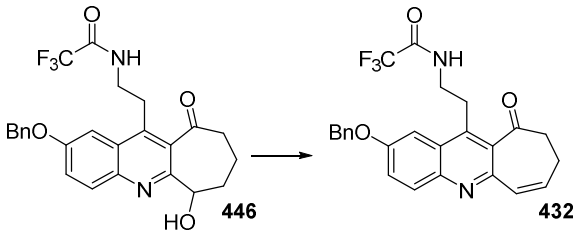
Even with the volume of research into this reaction, it is still described as an inconclusive mechanism.

Following our successful use of a Böckelheide rearrangement to give **439**, there were initial concerns that it would be difficult to remove the acetate group whilst retaining the trifluoroacetyl group. It was found that the amine protecting group was stable to potassium carbonate in methanol, giving access to alcohol **446** in a 79% yield.



Scheme 121: Selective removal of the acetate group in the presence of the trifluoroacetyl group; a: b: K_2CO_3, MeOH, 79%.

The next step was elimination of the alcohol to give the double bond; Burgess reagent (methyl *N*-(triethylammoniumsulfonyl)carbamate) in THF, followed by the removal of THF and the addition of benzene with heating to reflux, as described by Nicolaou,[205] gave the desired product in a 21% yield.



Scheme 122: Elimination of the alcohol to give alkene 432.

Conditions	Results
Burgess reagent, THF 21 °C then benzene, 80 °C.	21%
Martin's sulfurane, toluene. Martin's sulfurane, CH_2Cl_2.	No reaction
PPA.	No reaction
Mesyl chloride, Et_3N, CH_2Cl_2.	Mesyl addition occurs but no elimination
pTsOH.H_2O, PhMe, 110 °C.	Decomposition
2,6 Di-*tert*-butylpyridine, triflic anhydride, CH_2Cl_2.	No reaction
Methyl triphenoxyphosphonium iodide, 1,3 –dimethyl-2-imidazolidinone, 60 °C.	No reaction
Burgess reagent, benzene, 80 °C.	44%

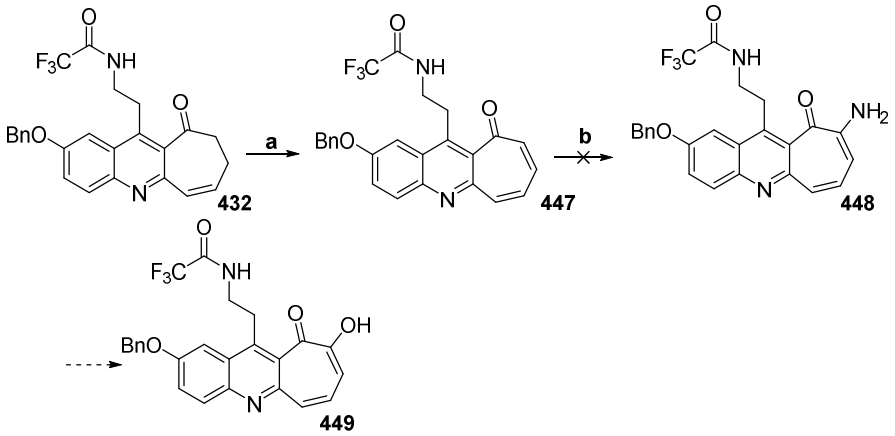
Table 9: Conditions screened for elimination of the alcohol to give olefin 432.

Work to optimise this reaction was initially unsuccessful; treatment with Martin's sulfurane[213] resulted in no reaction occurring (Table 9), as did treatment with polyphosphoric acid. Reacting the alcohol with mesyl chloride and triethylamine allowed formation of the mesylate but no elimination was seen. Subsequent treatment of the mesylate with DBU also did not aid elimination and treatment of the mesylate with LiHMDS in THF[214] resulted in loss of the mesyl group to return the alcohol. Heating with *p*-toluenesulfonic acid monohydrate in toluene

resulted in complete decomposition. Both 2,6-di-*tert*-butylpyridine with triflic anhydride and methyl triphenoxyphosphonium iodide also resulted in no reaction.[215]

As the other conditions had been entirely unsuccessful it was decided to move back to Burgess reagent and try to optimise this reaction. It was found that the large number of side-products observed could be reduced by carrying out the reaction entirely in benzene at reflux, resulting in a reproducible 44% yield.

With **432** in hand the next step was to further functionalise the molecule; it was found that heating the substrate in 1,4-dioxane with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) allowed formation of tropone **447** (Scheme 123).



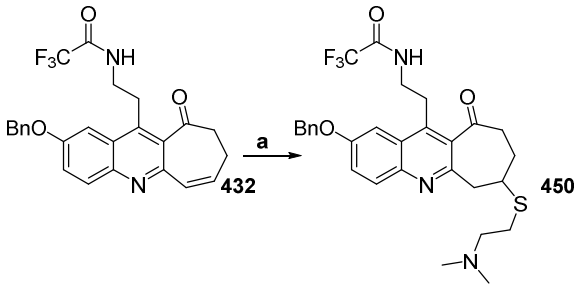
Scheme 123: Formation of tropone 447 and attempted formation of tropolone 449; [216]a: DDQ, 1,4-dioxane, 95 °C, 37%; b: $NH_2NH_2 \cdot H_2O$, EtOH.

It has been described that it is possible to oxidise tropones to the corresponding tropolone using hydrazine monohydrate in ethanol, followed by treatment with potassium hydroxide. These conditions have been applied to form a range of α-substituted tropolones by Wright *et al.*, based on Noyori's work on the synthesis of the well-known tropolone β-thujaplicin (Section 3.1.3.2.2, Scheme 86).[216, 217] Unfortunately when these conditions were applied to our substrate there was no reaction with it not being possible to form the amino-tropone.

3.3.12.2 Side chain addition to the alkene

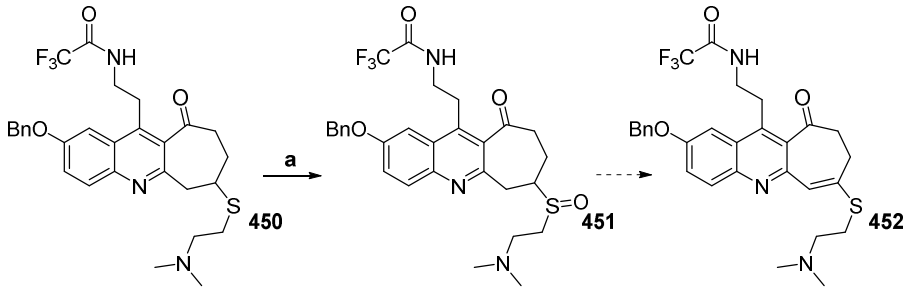
From **432** it was decided to investigate installation of the sulfur side chain; it was hoped that the sulfur would carry out a 1,4-conjugate addition, to add in in the correct position. Heating

the alkene with commercially available 2-(dimethylamino)ethanethiol hydrochloride at 80 °C for 2 hours gave access to **450** in a good yield, with this structure being confirmed by 2D NMR spectroscopy.



Scheme 124: Installation of the sulfur side chain; a: 2-(dimethylamino)ethanethiol·HCl, EtOH, 80 °C, 72%.

The Pummerer reaction has been described in the literature to install double bonds next to a sulfur atom.[218] This was investigated with the intention that from **450** it would be possible to reinstall the double bond to give **452**.



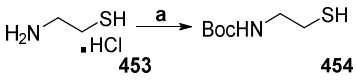
Scheme 125: Proposed Pummerer oxidation to form the vinyl sulfide; a: $NaIO_4$, MeOH.

Unfortunately oxidation of the sulfur to the sulfoxide proved problematic with this reaction appearing not to be reproducible, and decomposition being a problem. It has been described that treatment with *N*-chlorosuccinimide in benzene allows chlorination next to a sulfur, with treatment with triethylamine resulting in elimination of the chlorine and formation of a double bond.[219] On our substrate this resulted in decomposition of the starting material.

To avoid the need to reinstall the double bond, it was decided to attempt to install a leaving group so that it would be possible to carry out conjugate addition and elimination to form **452**

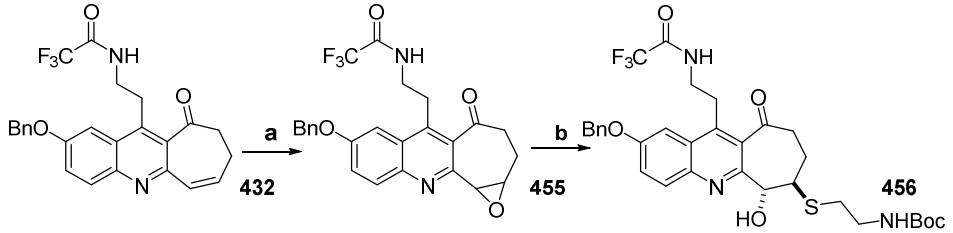
in one step. Direct installation of bromine did not prove trivial, as decomposition occurred before the reaction could go to completion using bromine in THF or chloroform.

It was found that it was possible to form the epoxide from the alkene using *m*CPBA without any unwanted side reactions occurring (Scheme 126). As the polar nature of the material with the dimethyl amino side chain had resulted in problems in purification of **450**, it was decided to instead use the Boc-protected amine, *tert* butyl (mercaptoethyl) carbamate **454**, which was synthesised using a modification of literature procedure (Scheme 126).[220]



Scheme 126: Synthesis of Boc protected 2-mercaptoethylamine; a: Boc_2O, Et_3N, CH_2Cl_2, argon, 81%.[220]

Treatment of the epoxide with the Boc-protected amino thiol in ethanol at 80 °C was unsuccessful, but it was found that **454** was able to add in at room temperature in methanol in the presence of triethylamine. Unfortunately it was not possible to purify this material, despite numerous attempts.



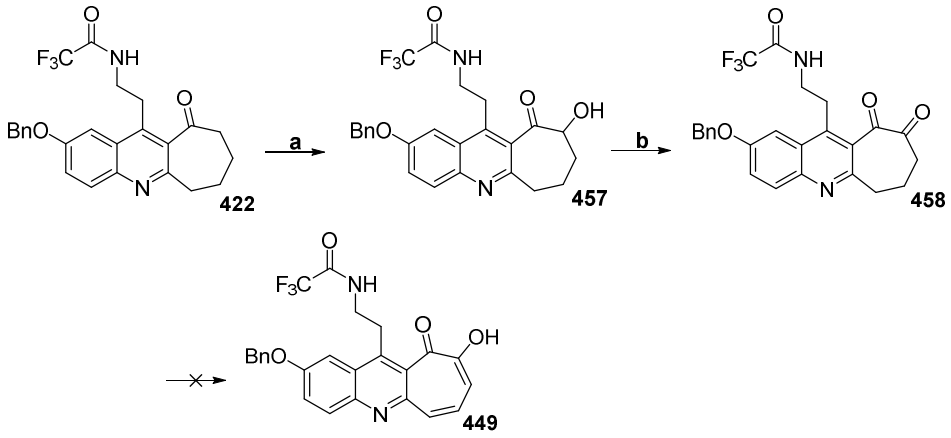
Scheme 127: Successful epoxide formation followed by attempted sulfur installation; a: *m*CPBA, CH_2Cl_2, 53%; b: *tert*-butyl (mercaptoethyl)carbamate, Et_3N, MeOH.

Treatment of the crude alcohol **456** with Burgess reagent in benzene resulted in loss of the hydroxyl group without elimination.

3.3.12.3 α-Hydroxylation

Due to the problems functionalising the seven-membered ring after installation of the sulfur, α-oxidation was again briefly investigated. Whilst Davis' oxaziridine had been tried previously with LiHMDS as a base, it was decided to try the same conditions using 2 equivalents of potassium bis(trimethylsilyl)amide (KHMDS) with the idea that whilst

deprotonation of the amine would occur, this would remain stable and allow a second deprotonation next to the oxygen. Pleasingly this theory proved successful and it was possible to form the desired α-hydroxylated ketone **457** in a good yield.



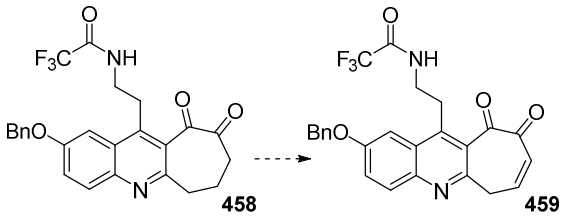
Scheme 128: Successful α-hydroxylation of ketone 442, followed by oxidation to give diketone 448 a: i) KHMDS, THF; ii) Davis oxaziridine, THF, -78 °C, 75%, b: Dess-Martin periodinane, CH_2Cl_2, 82%

From the α-hydroxy-ketone oxidation proceeded smoothly, with Dess-Martin periodinane being used to cleanly oxidise the alcohol to give the diketone in an 82% yield.

Whilst in five and six-membered rings 1,2-diketones exist almost entirely in the enol form, in larger rings the di-keto form also exists.[221] NMR analysis shows the molecule as the diketone, with the enol not being visible. Despite this, the diketone was treated with DDQ, with the idea being that this could aid oxidation to the tropolone but unfortunately this was unsuccessful with only starting material being returned.

3.3.12.4 Formation of the Michael acceptor.

From the diketone **458** it was possible to return to the original planned route, where it had been intended to form the enone to allow the molecule to undergo a conjugate addition to install the sulfur side chain (Scheme 129). The first route investigated was Saegusa-Ito oxidation; conditions described by She were investigated, but these returned only starting material.[222] Once again problems with the formation of the silyl enol ether appear to inhibit this reaction.

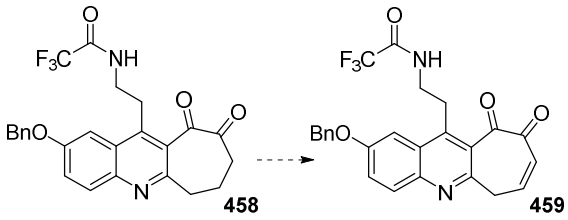


Scheme 129: Attempted Saegusa-Ito oxidation

To try to overcome this problem trimethylsilyl trifluroromethanesulfonate with 2,6-lutidine was investigated; an NMR of the crude material appeared to show formation of the silyl enol ether, but treatment of this material with palladium(II) acetate did not give the desired product. It has been described by Stahl *et al.* that it is possible to dehydrogenate cyclic ketones using catalytic palladium[223, 224] and that using palladium(II) trifluoroacetate in DMSO in an oxygen atmosphere can result in enone formation. Unfortunately despite the mild conditions of this reaction decomposition was still observed.

3.3.12.5 Selenoxide elimination

Selenoxide elimination is commonly used to form α,β-unsaturated carbonyls from their corresponding ketones. We briefly investigated selenium driven elimination to form the enone, but these conditions were unsuccessful with either no reaction or decomposition being observed (Table 10).



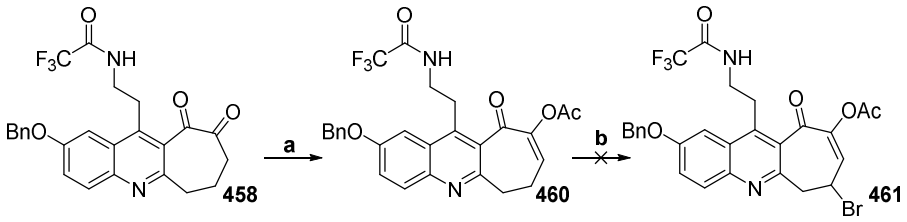
Conditions	Result
i) PhSeBr, EtOAc, 0 °C **ii) *m*CPBA, EtOAc**	No reaction
$(PhSeO)_2O$, PhCl, 80 °C **$(PhSeO)_2O$, PhCl, 50 °C**	Decomposition

Table 10: Conditions screened to form enone 459.

3.3.12.6 Bromine substitution

Treatment of diketone **458** with *N*-bromosuccinimide and benzoyl peroxide in carbon tetrachloride was unsuccessful in initiating the addition of a bromine, which could have been eliminated to give the desired enone. Direct bromination using bromine in either carbon tetrachloride or chloroform was also unsuccessful.

At this point it was then decided to convert the diketone to enol acetate **460**. From this intermediate it could be possible to install an adjacent bromine and then substitute the bromine with the sulfur side chain as described by Confalone on cycloheptane.[225] Unfortunately despite conversion to **460** it was not possible to install the bromine.

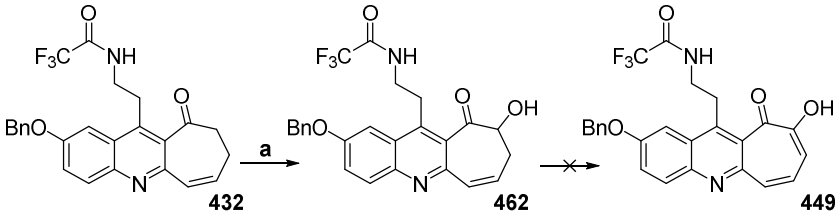


Scheme 130: Attempt to install sulfur side chain after radical bromination. a: Ac_2O, pyridine, CH_2Cl_2, 48%, b: NBS, benzoyl peroxide, CCl_4.

3.3.12.7 Further functionalisation of the α-hydroxylated species

As further functionalisation of the diketone to the enone had not proven as trivial as first anticipated, it was decided to investigate installation of the alkene adjacent to the nitrogen in diketone **458** using the Böckelheide type rearrangement described earlier. Whilst it was possible to form the *N*-oxide of the diketone, it was not possible to carry out the Böckelheide rearrangement to provide a leaving group for olefin formation.

Pleasingly it was found that rearranging these steps worked well. From alkene **432** it was possible to carry out the α-hydroxylation with an oxaziridine and KHMDS in good yield, and a single crystal of **462** was grown for analysis by X-ray crystallography (Figure 24), confirming the compounds structure.



Scheme 131: α-Oxidation of alkene 432; a: i) KHMDS, THF, ii) (1R)-(−)-(10-Camphorsulfonyl)oxaziridine, THF, -78 °C, 77%.

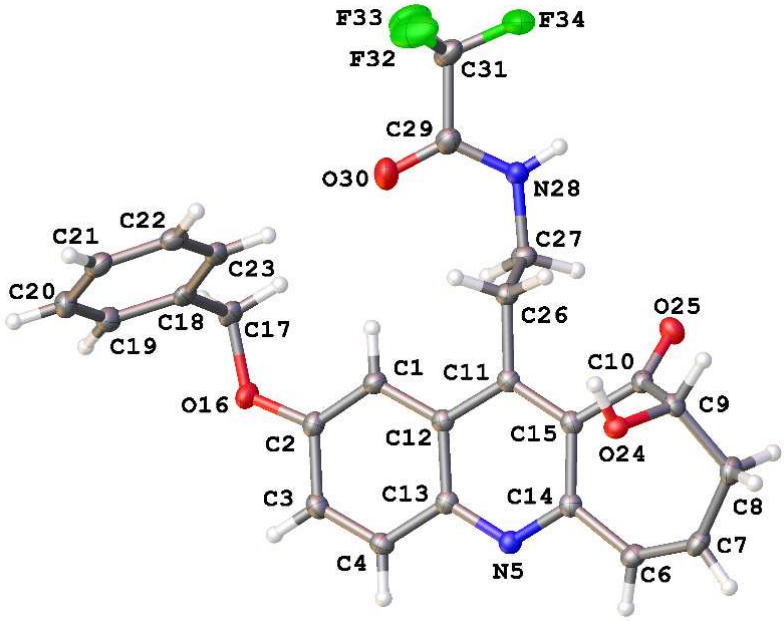
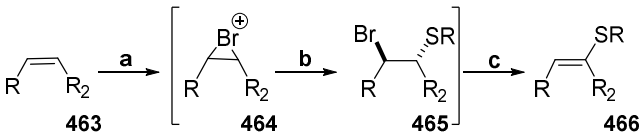


Figure 24: X-ray structure obtained of 462. Displacement ellipsoids are set at 40 %

Unfortunately it was not possible to oxidise alcohol **462** to give tropolone **449** using either Dess-Martin periodinane, pyridinium chlorochromate or Swern oxidation. DDQ at reflux in a range of solvents was also unable to oxidise the ring to give access to the tropolone oxidation state.

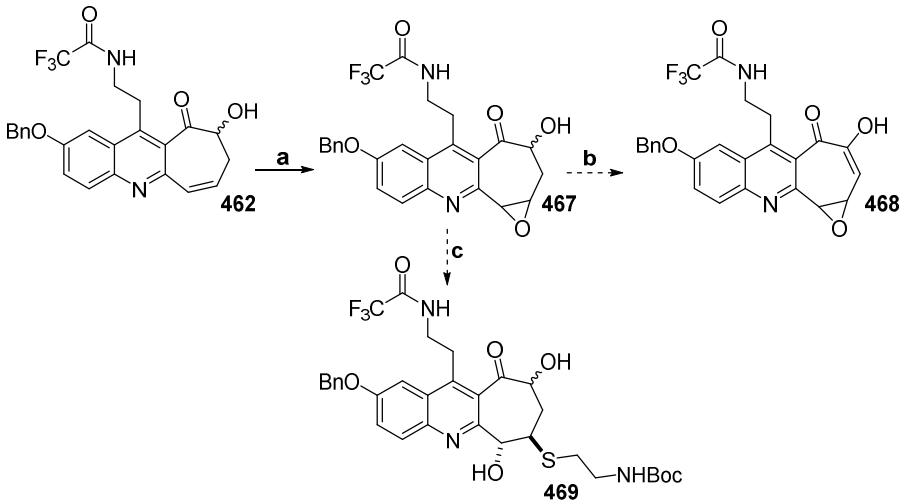
Addition of the sulfur side chain to **452** initially appeared to be successful, with consumption of the starting material being observed alongside observation of the correct mass, but no other evidence of the product was obtained.

N-Bromosuccinimide mediated bromination of alkenes, followed by attack of a thiol and elimination of the bromine to reform the alkene has been described by Zoghlami *et al.* on cyclic alkenes. The reaction proceeds by an *in situ* addition/base mediated elimination pathway (Scheme 132).[226] Application of these mild conditions to our alkene unfortunately resulted in no reaction occurring.



Scheme 132: *In situ* addition base catalysed elimination reaction; a: NBS, THF; b: RSH c: DBU.[226]

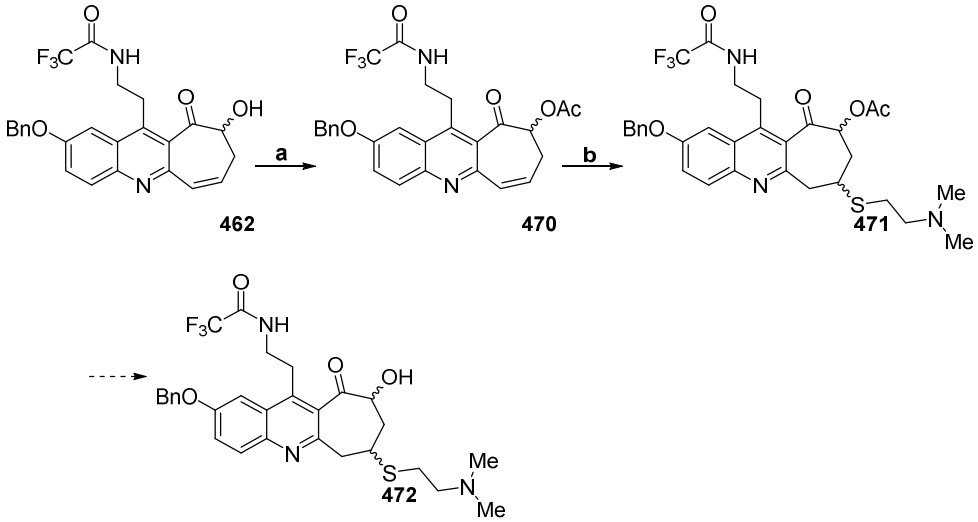
Due to problems in re-oxidising the molecule after addition of the sulfur side chain, epoxide formation was again investigated. Application of these conditions to alcohol **462** were again successful (Scheme 133). The epoxide is believed to form on the same side as the hydroxyl group, but this was not investigated as the chirality would be removed in subsequent steps. Unfortunately, intermediate **467** proved unreactive and it was not to be possible to install the sulfur side chain or oxidise the alcohol to the ketone.



Scheme 133: Epoxide formation of alcohol 462; a: *m*CPBA, CH_2Cl_2; b: Dess-Martin Periodinane, CH_2Cl_2; c: *tert*-butyl-(mercaptoethyl)carbamate, Et_3N, MeOH.

3.3.12.8 Formation of the protected tropolone

As isolation of the sulfur addition product of **462** had proven problematic, we decided to protect the alcohol of **462** to make isolation easier. Protection with an acetate group was chosen as this would mean removal could be carried out in the same step as removal of the trifluoroacetyl group. Formation of acetate **470** was carried out in a 90% yield upon treating the alcohol with acetic anhydride and pyridine (Scheme 134).



Scheme 134: Formation of acetate 470 followed by sulfur side chain addition; a: Ac_2O, pyridine, CH_2Cl_2, 90%; b: 2-(dimethylamino)ethane thiol·HCl, EtOH, 80 °C, 67%.

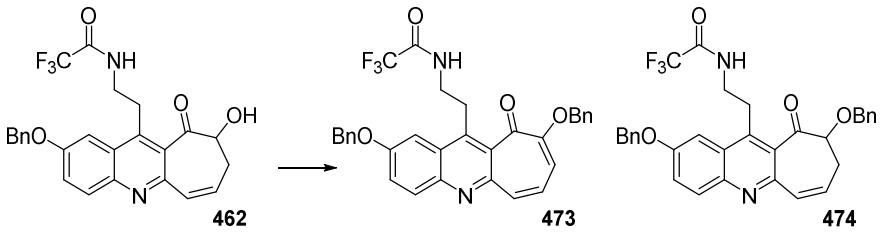
Addition of the side chain was again investigated and pleasingly it was possible to isolate **471** in a 67% yield as an inconsequential mixture of diastereoisomers. From the diastereoisomeric mixture it was hoped that it would be possible to remove the acetate and oxidise the molecule to the tropolone oxidation state. Treatment with potassium carbonate in methanol resulted in a compound with a mass corresponding to elimination of the sulfur side chain alongside the deprotection of the acetate being observed in the ESI spectrum.

As removal of the acetate had proven problematic, another protecting group was required. A benzyl group was selected, as it would be possible to deprotect both the alcohol and phenol simultaneously at the end of the synthesis. Surprisingly, it was observed that when **462** was treated with benzyl bromide and potassium hydroxide in air the molecule underwent an oxidation reaction in addition to the benzyl protection giving **473**. This pleasing result meant that it was possible to access the protected benzotropolone from the alcohol **462** in one pot, albeit in low yields.

It was found that even in the absence of a protecting group, treatment under basic conditions gave a mass that would correspond to the tropolone in the ESI spectrum. This was a surprising result as conventional oxidation had not been successful on alcohol **462**. Unfortunately, attempts to purify this compound were unsuccessful using silica gel, alumina or basified silica.

Benzotropolones are rarely purified by column chromatography and instead recrystallisation is often used. We were unable to isolate any material using this method.

As formation of the deprotected tropolone had been unsuccessful it was decided to persevere with protection of the hydroxyl group and attempt to improve the yield of the reaction. Conditions to optimise the benzyl protection were explored (Table 11).



Scheme 135: Optimisation of formation of the protected benzotropolone 473 and 474.

Conditions	Result
Benzyl bromide, K_2CO_3, MeCN, air.	Decomposition
Benzyl bromide, NaH, DMF, air.	10%
Benzyl bromide, Et_3N, MeOH, air.	No desired product, loss of TFA protecting group
Benzyl bromide, $CsCO_3$, MeCN, air.	15%
Benzyl bromide, KOH, DMSO, air.	No reaction
Benzyl bromide, K_2CO_3, DMF, Bu_4NI, air.	20% product and 20% non-oxidised species **474**
Benzyl bromide, KOH, acetone, air.	30%

Table 11: Optimisation of combined benzyl protection and tropolone formation.

It was found that a range of basic conditions resulted in oxidation in air and application of the same conditions under argon resulting in reduced oxidation. In an attempt to exploit the spontaneous oxidation it was decided to investigate carrying out the reaction under an oxygen atmosphere, but no marked improvement was seen and the use of DMSO as a solvent resulted in no reaction. Conditions using benzyl bromide and tetrabutylammonium iodide to form a

more reactive benzyl iodide species, as described by Boger *et al.*,[227] resulted in the isolation of both the oxidised and non-oxidised species. Reproducible synthesis of tropolone **473**, albeit in low yield, was accomplished using benzyl bromide, potassium hydroxide and acetone in air, giving the product as a vivid yellow solid. Crystals suitable for X-ray crystallography could be obtained by recrystallisation from ethanol, allowing confirmation of the assigned structure as shown in Figure 25.

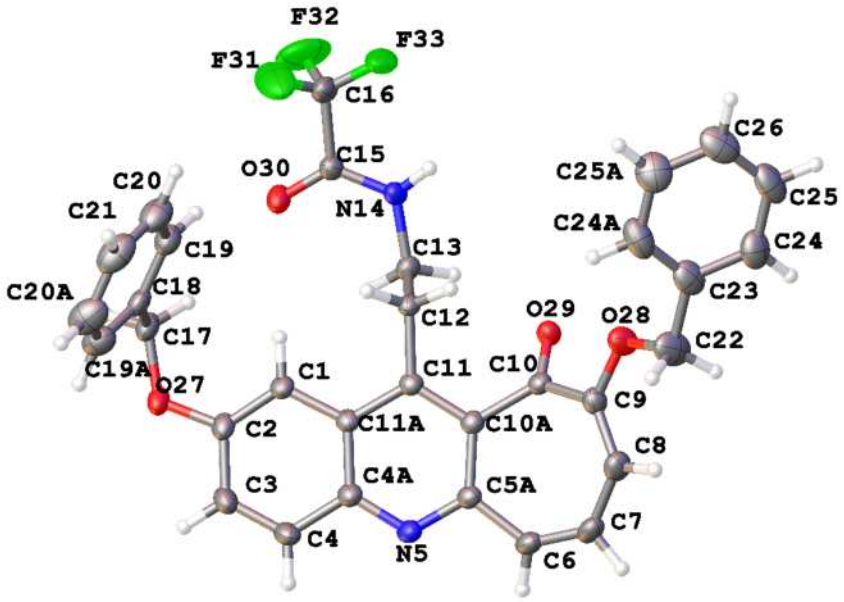


Figure 25: X-ray crystal of the benzyl protected tropolone 473. Displacement ellipsoids are set at 40 %.

Tropolone rings are described in the literature to have alternating bond lengths and that is the case with this molecule, with the exception of the bond at the ring junction that is longer than the comparable bond in tropolone (bond lengths shown in Appendix 1). The couplings observed in the ^{1}H NMR of this structure correlate with the alternating pattern obtained by X-ray crystallography. Tropolones are also described as almost planar molecules; an examination of the distance the atoms of the tropolone in **473** lie from the mean plane showed that this is mostly the case. It can be seen that C-10 is the furthest from the mean plane and C-5a and 8 also lie some distance from the plane (Appendix 1).

Comparison of the ^{1}H NMR chemical shifts of **463** with those reported for tintamine provided interesting results; in **463**, H-1 had a chemical shift of 7.73 ppm, H-3 was observed at 7.61 and H-4 had a shift of 8.09 ppm and in tintamine they were seen at 6.65, 6.72 and 8.12 ppm respectively.[17]

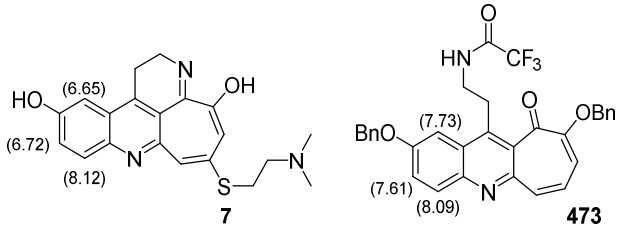


Figure 26: Comparison of ^{1}H NMR chemical shifts in tintamine (7) and 473.[17]

An examination of other similar quinoline containing molecules show the shifts reported for tintamine are significantly lower than expected, with the ^{1}H NMR shifts of quinolines **475**, **476**, **477** and **478** being more similar to those observed in our compound **473**. It is worth noting that there is a significant change in the chemical shifts at the 1-position between these similar molecules, with **477** in particular having a much lower shift than the other three molecules.[112-115]

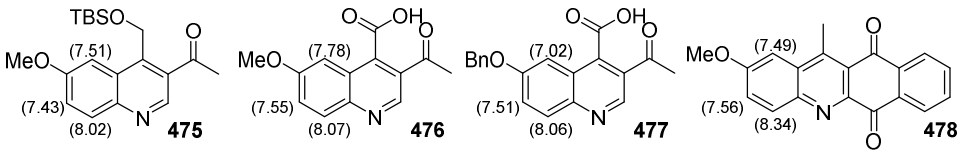
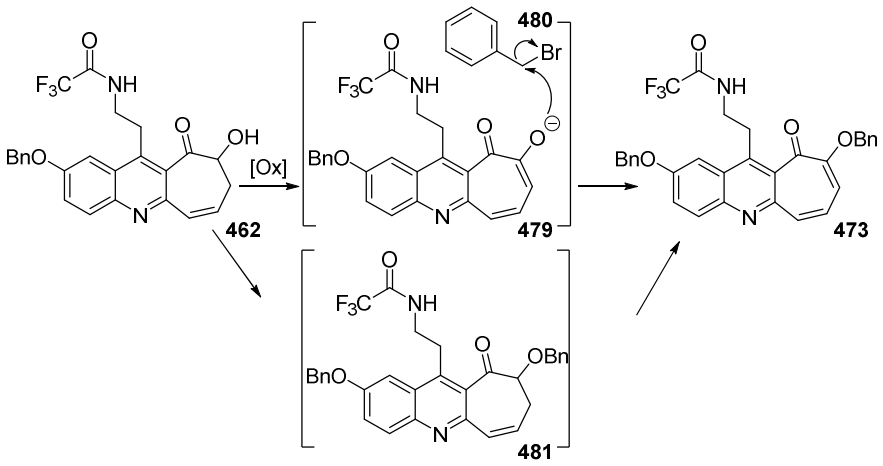


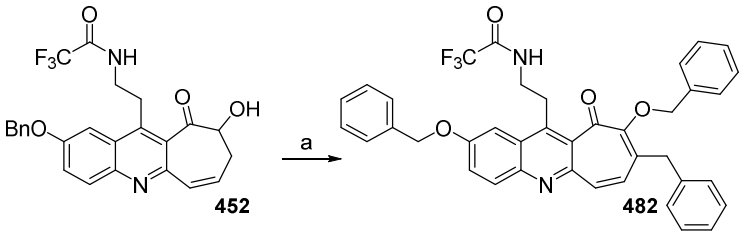
Figure 27: ^{1}H NMR chemical shifts seen in quinolines 475,[113] 476, 477[114] and 478.[115]

The reaction mechanism for the reaction of alcohol **462** to tropolone **473** could go *via* two possible routes; it is possible that benzylation occurs prior to the formation of the additional bond (Scheme 136) or the molecule could undergo oxidation in air to the tropolone, and this then reacts with the benzyl bromide. The reaction with benzyl bromide in the presence of tetrabutylammonium iodide allows isolation of **464** that has not undergone the oxidation reaction, suggesting that under these conditions benzylation occurs prior to oxidation.



Scheme 136: Possible routes for the formation of benzotropolone 473.

This reaction has several side-products, explaining its low yield. One of these products that could be isolated cleanly contained an additional benzyl group which is, unusually, attached to a carbon atom (**482**). The isolation of **482** suggests that alongside being reactive at the alcohol, **452** is also reactive at the β-carbon. It was not possible to reduce formation of this particular by-product.

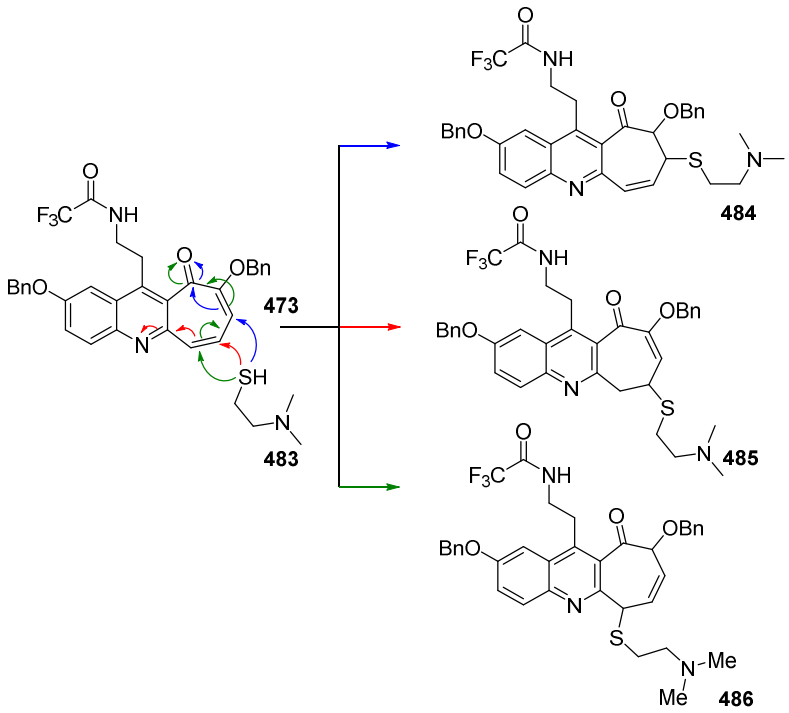


Scheme 137: Side product formation in the benzyl protection/tropolone formation reaction; a: benzyl bromide, KOH, acetone, 6%.

3.3.12.9 Side chain addition

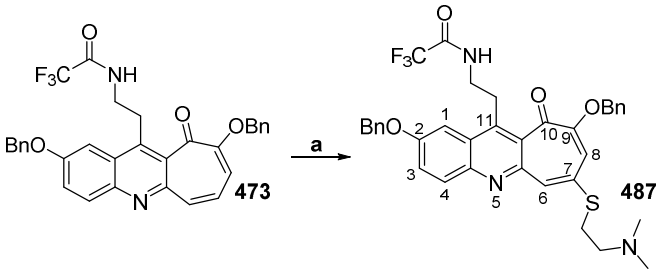
After the pleasing result of the benzyl protected material oxidising in air to give the desired tropolone oxidation state, it was decided to investigate if this molecule could undergo a conjugate addition to install the side chain present in the natural product. Whilst it had been seen previously that reacting 2-(dimethylamino)ethanethiol hydrochloride with **432** had been successful, it was now possible that the sulfur side chain could carry out a conjugate addition

at the enone, the alkylpyridine or undergo a 1,6 addition resulting in substitution at the 6, 7 or 8 position (Scheme 138).



Scheme 138: Possible products of the reaction of 2-(dimethylamino)ethanethiol.HCl with 473.

Application of previously described conditions, using ethanol as the solvent and heating the reaction mixture at 80 °C, pleasingly gave product **487**; auto-oxidation of the molecule to the tropolone oxidation occurred in air after the addition reaction (Scheme 139).



Scheme 139: 1,4-Conjugate addition of the side chain with spontaneous oxidation; a: 2-(dimethylamino)ethanethiol.HCl, ethanol, 80 °C, 45%.

These conditions allowed the reaction to proceed at a much slower rate than had been observed on the previous system (**432**). Heating the reaction mixture overnight allowed addition of the sulfur side chain and the molecule was able to spontaneously re-oxidise to

return to the tropolone oxidation state. NMR analysis showed that the side chain had undergone a 1,4-conjugate addition in the desired position; the molecule observed had two distinct singlet peaks, rather than the doublets that would be present in the oxidised forms of alternative products **484** and **486**.

Whilst the addition of the side chain in the correct position with spontaneous re-oxidation was a pleasing result, this only occurred in a 30% yield with a number of by-products being observed by TLC. The reaction was monitored using mass spectrometry to examine the reaction path and identify the additional products.

It was observed at 50 °C that conjugate addition occurred but oxidation back to the tropolone occurred slowly and this resulted in addition of a second molecule of 2-(dimethylamino)ethanethiol, presumably in the 8-position. This could be reduced by heating to 80 °C; however no improvements were observed by further increasing the temperature. Reducing the concentration of the reaction mixture meant it was possible to slightly increase the yield of the reaction to 45% at 80 °C.

After column chromatography it was possible to isolate the desired product as one isomer, but when the compound was left as a solution in deuterated chloroform it was seen that a rearrangement occurred. After 72 h it was observed by NMR (Figure 28) that complete conversion had occurred from the desired material to a new compound, which had the same Rf and had the same molecular weight.

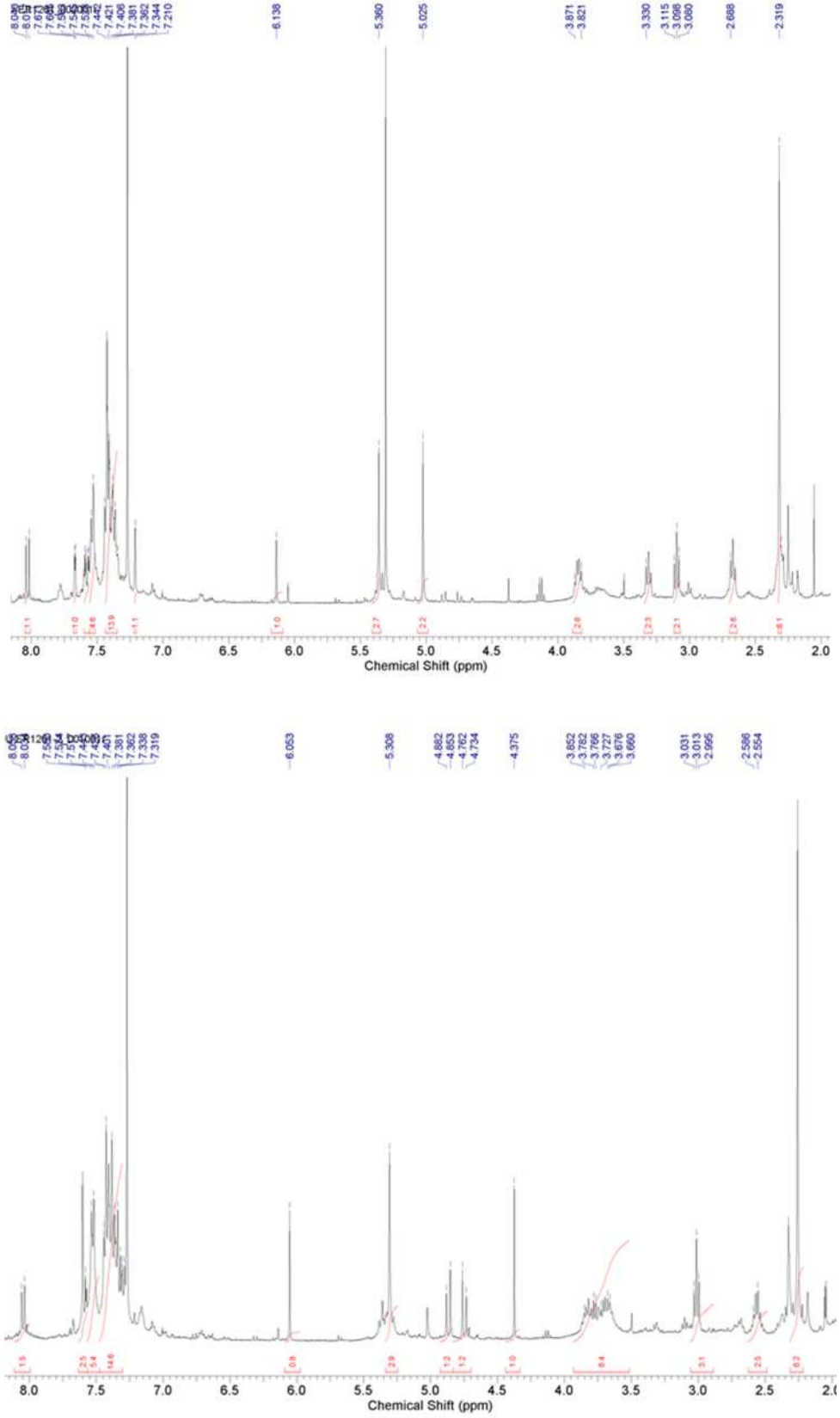
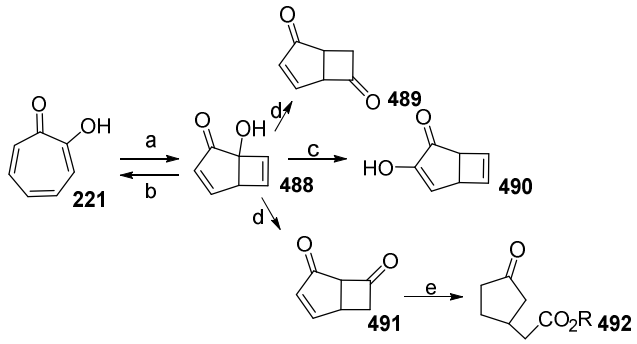


Figure 28: NMR showing rearrangement occurring on 487.

The NMR shows significant changes at 7.21 ppm where a peak is lost, 6.14 ppm where a further peak is lost and at 6.05 and 4.38 ppm where two new singlets appear. It can also be seen that the benzyl singlet at 5.03 is lost and is replaced by two doublets at 4.86 and 4.75 ppm, suggesting that the benzyl CH_2 is next to a chiral centre in the new product.

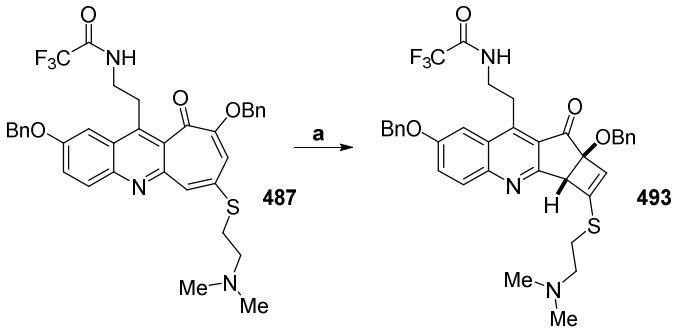
Searching the literature for similar reactions it was noted that it is possible for tropolone to undergo a photocatalysed electrocyclic rearrangment.[228, 229] It was described by Day in 1970 that α-tropolone undergoes photo-isomerisation in hexane or in water and methanol (Scheme 140).[230]



Scheme 140: Photo-isomerisation of α-tropolone; a: hν, water, methanol; b: aqueous base or Δ (> 150 °C); c: Δ (> 150 °C); d: hν; e: ROH.[230]

It is known that tropolone photo-isomerises to give **488** and that in the presence of aqueous base the molecule rearranges back to the tropolone. It was also observed that above 150 °C the molecule rearranges back to the tropolone or undergoes a further rearrangement reaction to give **490**.

Whilst it seemed unlikely that the rearrangement of compound **487** was photomediated, as the reaction still occurred when the solution was stored in the dark, the knowledge that this type of reaction was possible meant that these principles were applied to our system. It was hypothesised that the small amount of acid present in chloroform was catalysing a similar reaction to give a cyclobutene, with the NMR data for the rearranged compound being similar to that observed in the photocatalysed literature compounds.[229] With this knowledge a possible structure for the rearranged material was proposed, shown in Scheme 141.



Scheme 141: Proposed structure for rearrangement of the substituted tropolone; a: deuterated chloroform.

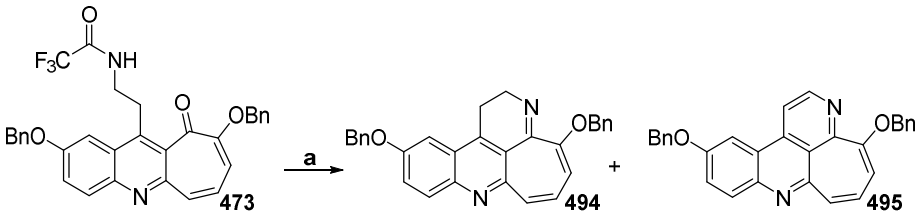
The proposed structure for the material is in agreement with the 2D NMR data obtained for this material, with the diastereotopic CH_2 fitting the benzyl protons on the tropolone and the newly observed singlet at 4.38 ppm corresponding to the proton on the ring junction.

It was observed that by changing the NMR solvent to methanol this rearrangement could be prevented, and full data for the tropolone **487** was obtained.

3.3.13 Deprotection

Notwithstanding the above rearrangement reaction, the route provides access to tropolone **473** and its thiol addition product **487** and the structure of **473** has been unambiguously assigned by X-ray crystallography. With the fully substituted tropolone in hand, two deprotection reactions remain before formation of the natural product.

Treatment of model system **473** with aqueous sodium hydroxide in methanol was able to remove the trifluoroacetyl group, forming the final ring in 3 hours in a 38% yield. Some over oxidised-material **495** (23%) was also observed, but pleasingly it was possible to separate this material from the desired product by column chromatography. NMR analysis of **494** was carried out in basified chloroform, with the material being kept in solution for the minimal amount of time.

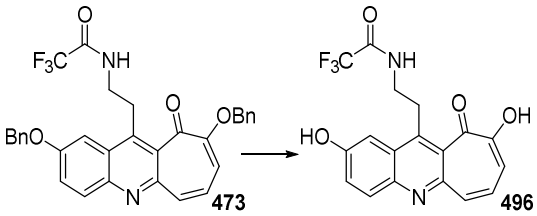


Scheme 142: Deprotection of 473 to form the final D ring and its analogue; a: NaOH (aq), MeOH, 38% 494 and 23% 495.

It was expected that the over oxidised material **495** would be stable and no precautions were taken to prevent other reactions from occurring. However, it was seen once again that the molecule was able to rearrange in solution to give a currently unidentified product. Lithium hydroxide was also able to carry out the deprotection, facilitating formation of the D ring, but still resulted in a mixture of **494** and **495**.

As the D ring of model **494** was prone to over oxidation, we decided to remove the benzyl protecting groups prior to formation of the final ring, with the hope that the keto-enol tautomerisation described by Kashman would provide stabilisation for this ring.[17]

Conditions screened for removal of the benzyl groups on model **473** are shown in Table 12.



Scheme 143: Removal of the benzyl protecting group to form alcohol 496.

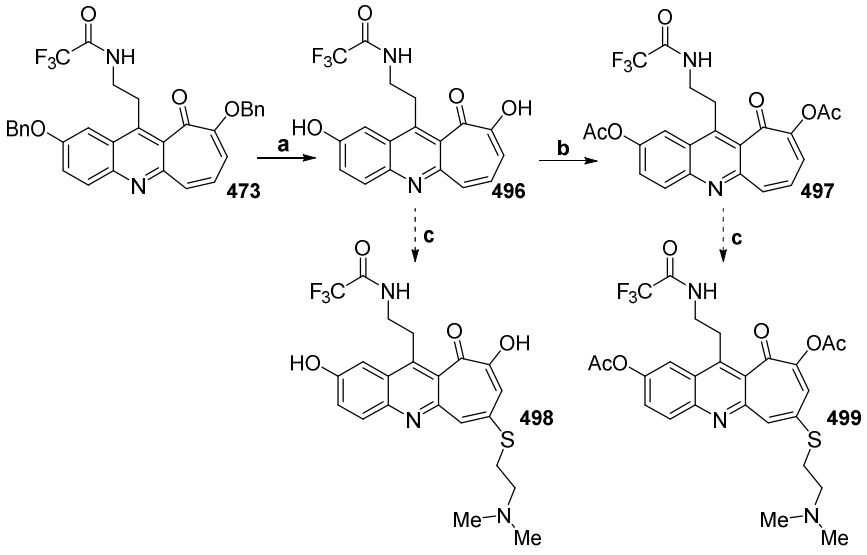
Conditions	Result
Hydrogenation (10% Pd/C), EtOH	Benzyl groups unaffected, hydrogenation of 2 double bonds
HBr (30% in AcOH)	Decomposition
BBr_3 (1.0 M in CH_2Cl_2), CH_2Cl_2	73%

Table 12: Benzyl group removal to the dihydroxy species 496

On model system **473** hydrogenation did not remove the benzyl groups and the ESI spectrum showed loss of four protons, potentially corresponding to reduction of the tropolone. Other

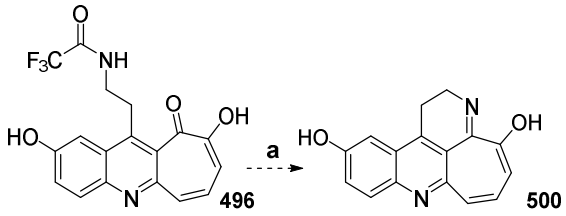
conditions for hydrogenation were not investigated at this point, as it is known that tropolone is prone to hydrogenation.[135] Treating **473** with hydrogen bromide (30%) in acetic acid for ten minutes resulted in a small amount of the desired deprotected material, but a large amount of decomposition also occurred. Boron tribromide as a 1 M solution in dichloromethane allowed access to the desired product **496.** It was found that **496** was unstable to column chromatography but the crude product was fully characterised by NMR spectroscopy and **496** was obtained in a 73% yield.

It was then decided to investigate installation of the sulfur side chain on the deprotected material; however results of this were inconclusive and it was not possible to isolate the product of this reaction. Protection of the material with acetate groups was instead investigated, as if the side chain could successfully be installed it should be possible to remove the trifluoroacetyl and acetate groups in one pot to leave the desired natural product. Whilst it was possible to access the diacetate protected material **497** in 25% on a small scale, it was found that treating this material with 2-(dimethylamino)ethane thiol hydrochloride resulted in the thiol addition occurring twice, as the material did not spontaneously re-oxidise and underwent a second conjugate addition at the alkyl pyridine.



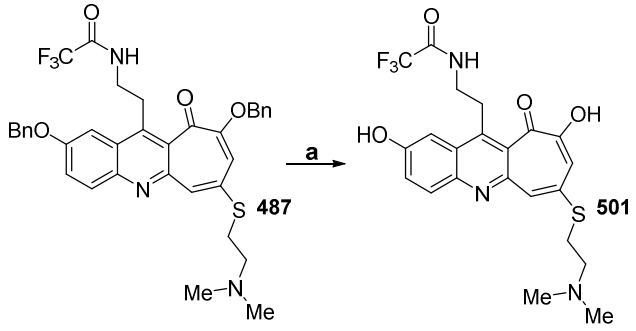
Scheme 144: Deprotection of the model system: a: BBr_3 (1.0 M in CH_2Cl_2), CH_2Cl_2, 73%; b: acetic anhydride, pyridine, CH_2Cl_2, 25%; c: 2-(dimethylamino)ethanethiol·HCl, ethanol, 80 °C.

The final deprotection of model system **496**, removing the benzyl groups to give an analogue of tintamine without the sulfur side chain, was investigated in spite of model **494** being prone to oxidation. Using the previously described boron tribromide conditions, a mass corresponding of the desired product was observed by ESI spectrometry (Scheme 145). However, unfortunately it proved difficult to isolate the product, potentially due to its zwitterionic nature, thus focus was shifted to the material containing the sulfur **487**.



Scheme 145: Attempted formation of tintamine analogue 496; a: BBr_3 (1 M in CH_2Cl_2), CH_2Cl_2.

Pleasingly, application of the benzyl deprotection conditions to **487** proved simple; boron tribromide (1.0 M in dichloromethane) was again successful with chloroform as a co-solvent to aid solubility. In the presence of the sulfur side chain the molecule **501** proved to be stable to column chromatography, with the material being isolated in a quantitative yield.



Scheme 146: Deprotection of the benzyl groups to give access to the sulfur substituted tropolone; a: BBr_3 (1.0 M in CH_2Cl_2), $CHCl_3$, quant.

Unfortunately, it was once again observed by NMR spectroscopy that the material was unstable as a solution, this time in deuterated methanol. The spectra shown in Figure 29 trace the decomposition of **501**, with almost complete consumption of the starting material occurring over 48 hours. The absence of a new peak around 4.4 ppm indicates that the 4π

electrocyclisation seen previously is not the cause of this change. The first spectrum shows only one compound; however, it does contain ethyl acetate and as a result of this the material was dried for 16 hours and a second NMR was run. This NMR shows a new peak at 7.0 ppm with the peak at 6.53 ppm decreasing in height. New peaks at 7.70, 7.73 and 8.24 ppm were also observed. Whilst the peak at 6.53 is eventually replaced entirely by the peak at 7.00 ppm the aromatic peaks are not replaced by the new peaks, with them existing in an approximately 1:1 ratio. It was not possible to explain or prevent this reaction.

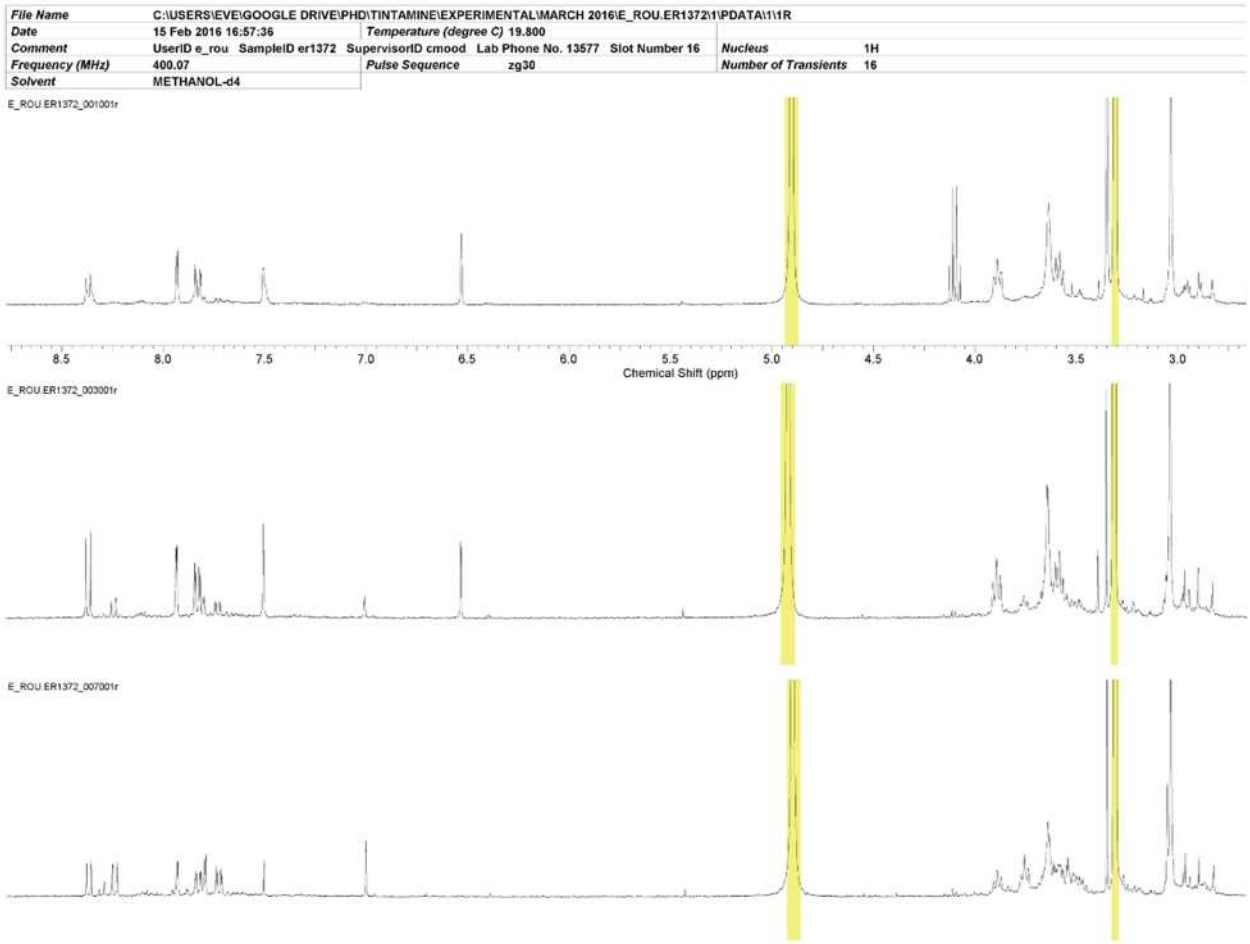


Figure 29: Spectra showing decomposition of 491: Top spectrum – 501 0 h after isolation; Middle spectrum – 501 after 16 h; Bottom spectrum 501 after 48 h.

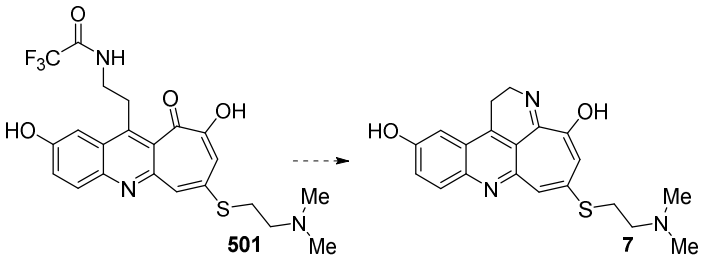
Comparison of the data obtained from the first NMR spectrum and the data reported for tintamine still show that the aromatic protons are downfield of those observed in tintamine;[17] however, it is expected that formation of the final D ring will result in significant change. As

the deprotected material **501** is unstable, it was decided to investigate reversing the order of deprotection steps, forming the final ring prior to removal of the benzyl groups.

Application of the basic deprotection conditions investigated on **473** in the absence of the sulfur side chain to the benzylated **487** containing the sulfur side chain at first appeared promising; treatment with sodium hydroxide initially appeared successful in forming the final ring with the ESI spectrum showing a mass corresponding to formation of the final ring and a small amount of over-oxidised material. An inconclusive proton NMR spectrum was obtained, this appeared to show both the over-oxidised material and decomposition products.

At this point, formation of the final ring as the last step in the synthesis appeared the most logical approach; attempts were made regardless of the observed instability of debenzylated **501**, as it was hoped that the D ring would provide stability.

Basic conditions were selected, due to the previously discussed stability problems seen in the presence of non-basified chloroform on the dibenzyl protected system **487**. Subjecting **501** to a range of basic conditions resulted in an immediate colour change from a vivid yellow solution, to dark red with the colour change possibly being due to the extended chromophore of the ring system.



Scheme 147: Attempted formation of the D ring of tintamine 7.

Conditions	Result
NaOH (40% aq), MeOH	Mass of product seen in ESI spectrum, unable to isolate product.
LiOH (aq), MeOH	Slow reaction, with degradation before reaction could go to completion.
K_2CO_3, MeOH, water	No reaction.
NH_4OH, MeOH	No reaction.
NaOMe, MeOH	No reaction.

Table 13: Conditions applied to 501 to remove the trifluoroacetyl protecting group to give tintamine 7.

A solution of aqueous sodium hydroxide in methanol was able to remove the trifluoroacetyl group and the correct mass was observed in the ESI spectrum, but severe problems were encountered in isolation of the natural product. Concerns about the zwitterionic nature of the compound meant extraction was carried out at a range of pH's but was unsuccessful, and the use of a pH 7 buffer to attempt to overcome these problems was also unsuccessful. An NMR spectrum of the crude material proved inconclusive and the compound was not suitable for chromatography on either silica gel or alumina.

A range of other basic conditions were also investigated. The starting material was not soluble in THF meaning that methanol was used to screen conditions. Whilst aqueous lithium hydroxide had worked well on a previous model, application of the same conditions to **501** resulted in a very slow reaction and decomposition occurring. Potassium carbonate was unable

to remove the trifluoroacetyl group. In the synthesis of ascididemin (Section 3.1.3.1.1, Scheme 66) it was seen that using aqueous ammonia on a similar system removed the trifluoroacetyl and allowed cyclisation to occur, but on our molecule the protecting group was stable to these conditions.

Investigation of anhydrous basic conditions was carried out in an attempt to allow isolation of product **7**. Freshly prepared sodium methoxide resulted in no reaction with approximately 10 equivalents of base and increasing the concentration of the sodium methoxide solution eventually resulted in decomposition of the starting material.

It was decided to probe the reaction of **501** with sodium hydroxide in deuterated methanol by proton and fluorine NMR, monitoring the reaction at hourly intervals. An initial shift downfield was noted after addition of the base. The fluorine NMR spectrum went from containing two peaks in the first NMR to one peak over the space of 3 hours; however, the proton NMR showed significant decomposition alongside main peaks.

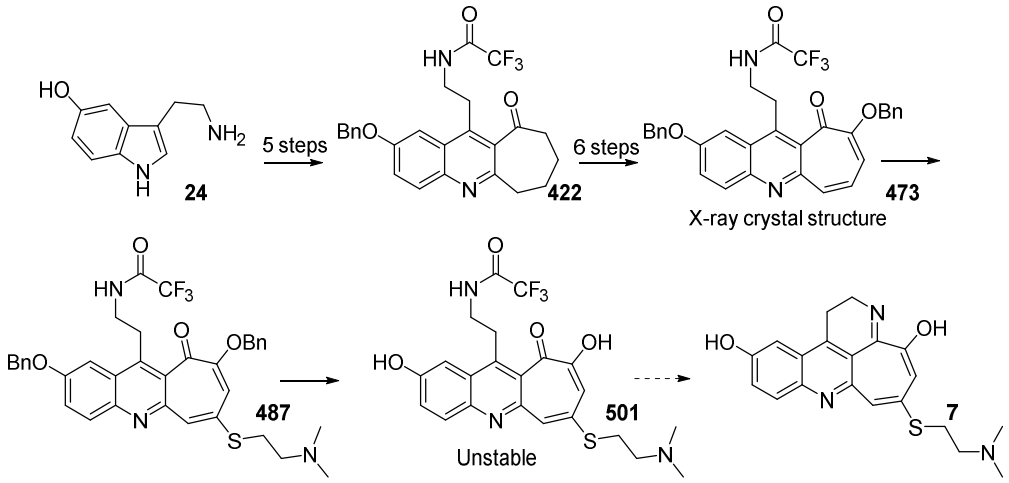
In an attempt to purify the product of this reaction, a prepacked Oasis HLB column was used as its hydrophilic system meant water could wash away the base before the organic products are eluted with increasing percentages of methanol. Whilst several species were separated, and a mass corresponding to the desired product was observed in the ESI spectrum, it did not correspond to a major component and the corresponding ^{1}H NMR spectrum showed significant degradation.

Due to time constraints, further attempts to isolate the product of these reactions were not made. A route to remove the final protecting group and isolate a compound with the structure proposed for tintamine by Kashman therefore requires either an improved isolation procedure or the use of alternative protecting groups.

3.4 Conclusion and future work

Although a total synthesis of tintamine has not been achieved, a successful route to the core structure of tintamine has been established. A Friedländer reaction gives access to tricylic quinoline **422** and this is oxidised to give the first synthesis of a tropolone-quinoline, with the structure of **473** having been confirmed by X-ray crystallography.

From tropolone-quinoline **473** it was possible to install the sulfur side chain present in tintamine at the correct position to give a precursor to tintamine **487** that requires only removal of the benzyl and trifluoroacetyl groups. This deprotection will allow formation of the final ring and give access to the natural product. On intermediate **473**, the trifluoroacetyl group has been successfully removed allowing formation of this final D ring. However, it has also been observed that this ring is prone to over oxidation in air. It is also possible to remove the benzyl groups from **473**, illustrating removal of both protecting groups from this tintamine analogue.



Scheme 148: Successful route to tintamine precursor.

In the case of the precursor to tintamine **487**, it has been observed that removal of the benzyl group is possible, but the product **501** is not stable and appears to readily decompose in solution (Section 3.1.13; Figure 29). Removal of the trifluoroacetyl protecting group from **487** also proved problematic as it was not possible to isolate the product of this reaction. Removal of the trifluoroacetyl group from the debenzylated material **501** to give access to tintamine

again did not prove trivial; monitoring this reaction by NMR spectroscopy showed decomposition.

Improvement of the final deprotection step is now crucial to allow isolation of material with the structure proposed by Kashman and allow comparison of the NMR spectroscopic data obtained from this product with that of the isolated natural product.

Chapter 4: Experimental details

4.1 General Procedure

Unless otherwise stated starting materials were obtained from suppliers and used without any further purification. THF was freshly distilled from sodium/benzophenone according to standard procedures. Triethylamine was distilled over calcium hydride and stored over activated 4 Å molecular sieves. Dichloromethane was distilled from calcium hydride and used immediately. Trifluoroacetic anhydride was distilled over phosphorus pentoxide and used immediately. All water used was previously deionised.

Microwave reactions were carried out using a CEM Discover S-class (300 W) with an IR temperature sensor. Melting points were measured using an Electrothermal IA92000 Digital melting point apparatus and are uncorrected. Thin layer chromatography was carried out using Merck silica gel pre-coated sheets SIL G/$UV_{254,}$ which were developed using either an acidic solution of vanillin in ethanol or basic potassium permanganate solution. Column chromatography was carried out using Merck silica gel 60, 35-70 µm particles.

Infrared spectra were recorded as dilute solutions in chloroform using a Perkin-Elmer 1600 FT spectrometer or in the solid state using a Nicolet Avatar 320 TTIR with an OMIVI sampler smart accessory HATR_IR (Ge, DTGS). Mass spectra were recorded on a MicroTOF 61 spectrometer using electrospray techniques with positive ion detection. UV/vis spectra were recorded on a Perkin Elmer Lambda 18 UV/vis spectrometer. Optical rotations were recorded on an ADP440 polarimeter, with an average reading, temperature, concentration and solvent being specified for each compound.

^{1}H and ^{13}C NMR spectra were obtained at 298 K using dilute solutions of $CDCl_{3,}$ $(CD_3)_2SO$ or CD_3OD. The spectra were recorded variously on a Brucker AV 400 MHz, AV (III) 400 MHz, AV (III) 500 and a DPX 300 MHz or a DPX 400 MHz spectrometer. The spectra were recorded on a δ scale in parts per million (ppm), relative to tetramethylsilane. The multiplicity of each

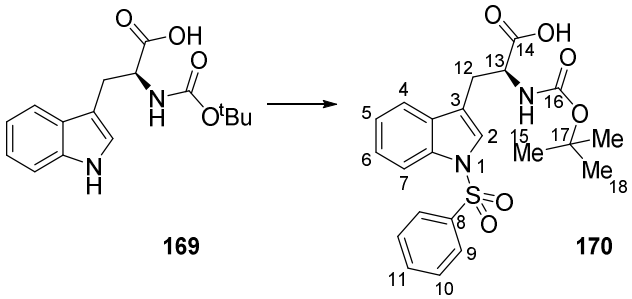
signal is given as the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. Assignments were made with the use of DEPT spectra as well as correlation techniques such as COSY, HMBC and HMQC spectra. J values are reported in Hertz (Hz) to one decimal place.

Crystals of **406**, **462** and **473** were mounted on MicroMounts (MiTeGen) using YR-1800 perfluoropolyether oil and cooled rapidly to 120 K in a stream of cold nitrogen using an Oxford Cryosystems low-temperature device. Data for compounds **406**, **462** and **473** were collected on an Oxford Diffraction SuperNova diffractometer equipped with a mirror-monochromated Cu *K*α source (λ = 1.5418 Å). Gaussian grid face-indexed absorption corrections with a beam profile correction were applied in CrysAlisPro[231]. All structures were solved via charge flipping using olex2.solve[232] and refined by full matrix least-squares using SHELXL.[233, 234]

4.2 Compounds discussed in Chapter 2

(*S*)-2-(*tert*-Butoxycarbonyl)amino)-3-(1-phenylsulfonyl-1*H*-indol-3-yl)]propanoic acid

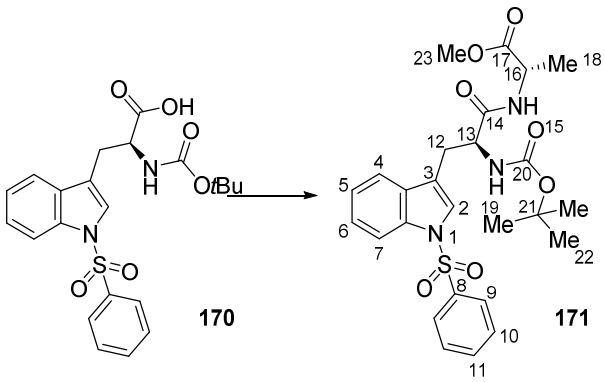
170



N-α-Boc-*L*-Tryptophan **169** (2.50 g, 8.20 mmol) was azeotropically dried with toluene (3 x 50.0 mL), and was dissolved in THF (17.0 mL) and the stirring solution cooled to -78 °C. Lithium bis(trimethyl)silyl amide (24.6 mL, 26.6 mmol of a 1 M solution in THF) was diluted with THF (6.00 mL) and added to the solution over 5 min and the solution stirred at -78 °C for 1 h. Benzenesulfonyl chloride (1.29 mL, 9.84 mmol) was added and the mixture was stirred at -78 °C for a further 2 h. The reaction mixture was quenched by the addition of a mixture of

acetic acid (1 mL) and ethyl acetate (1 mL) before hydrochloric acid (1 M; 50 mL) was added. The mixture was extracted with ethyl acetate (3 x 50 mL), the combined organic layers dried over Na_2SO_4 and the solvent removed *in vacuo* to give a colourless oil. Column chromatography on silica gel (acetic acid: light petroleum: dichloromethane; 5:45:50) gave the title compound **170** as a colourless solid (1.90 g, 52 %); mp 162-163 °C; $[\alpha]_D^{24}$ -20 (c = 0.38, $CHCl_3$); (Found C, 59.44; H, 5.51; N, 6.18; $C_{22}H_{24}N_2O_6S$ requires C, 59.45; H, 5.51; N, 6.30%); (Found M+Na^+, 467.1248. $C_{22}H_{24}N_2O_6S$ + Na^+ requires 467.1247); ν_{max} ($CHCl_3$)/cm^{-1} 3463, 2982, 1759, 1711, 1603, 1503, 1448, 1370, 1280, 1175; δ_H (400 MHz; $(CD_3)_2SO$) 12.72 (1 H, s, OH), 7.95-7.87 (3 H, m, H-9, 7), 7.69 (1 H, t, *J* 7.7, H-11), 7.64-7.53 (4 H, m, H-2, 4, 10), 7.35 (1 H, t, *J* 7.1, H-6), 7.30 (1 H, t, *J* 7.1, H-5), 7.15 (1 H, d, *J* 7.2, NH-15), 4.23-4.16 (1 H, m, H-13), 3.13 (1 H, dd, *J* 14.8, 4.5, H-12a), 2.96 (1 H, dd, *J* 14.8, 10.0, H-12b), 1.35 (9 H, s, H-18); δ_C (100 MHz; $(CD_3)_2SO$) 173.3 (C), 155.4 (C), 137.0 (C), 134.5 (CH), 134.3 (C), 130.5 (CH), 129.8 (C), 126.5 (CH), 124.8 (CH), 124.5 (CH), 123.4 (CH), 119.7 (CH), 119.0 (C), 113.1 (CH), 78.1 (C), 53.2 (CH), 28.1 (CH_3), 26.2 (CH_2). Data consistent with literature.[102]

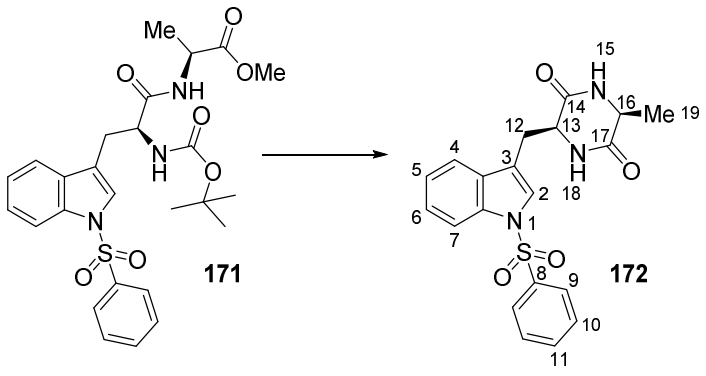
(*S*)-Methyl 2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1-phenylsulfonyl-1*H*-indol-3-yl)propanamido)propanoate 171



(S)-2-((*tert*-Butoxycarbonyl)amino)-3-(1-phenylsulfonyl-1H-indol-3-yl)propanoic acid **170** (200 mg, 0.45 mmol), hydroxybenzotriazole (101 mg, 0.67 mmol), *L*-alanine methyl ester

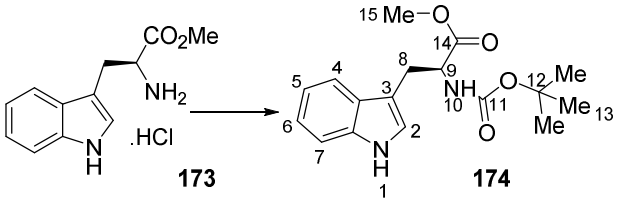
hydrochloride (93.6 mg, 0.67 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (160 mg, 0.83 mmol) and powdered 4 Å molecular sieves (1.00 g) were mixed with dichloromethane (5.00 mL), the mixture cooled to 0 °C and stirred for 1 h. Triethylamine (0.28 mL, 2.01 mmol) was added to the stirring mixture and this was allowed to warm to room temperature and stirred for 16 h before aqueous potassium hydrogen sulfate (1 M; 5 mL) was added. The sieves were removed by filtration and the organic layer washed with saturated sodium hydrogen carbonate solution (5 mL), before being washed with water (5 mL). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification by column chromatography (ethyl acetate: light petroleum; 2:3) gave the title compound **171** as a colourless foam (287 mg, 90 %); (Found: M+Na^+, 552.1774. $C_{26}H_{31}N_3O_7S$ + Na^+ requires 552.1774); ν_{max} ($CHCl_3$)/cm^{-1} 3425, 2982, 1741, 1707, 1678, 1490, 1450, 1370, 1175; δ_H (400 MHz; $CDCl_3$) 8.00 (1 H, d, *J* 7.7, H-7), 7.89 (2 H, d, *J* 7.0, H-9), 7.61-7.52 (2 H, m, H-4, 11), 7.51-7.36 (3 H, m, H-2, 10), 7.35 (1 H, dd, *J* 7.7, 7.7, H-6), 7.27 (1 H, t, *J* 7.7, H-5), 6.43 (1 H, d, *J* 7.7, NH-19), 5.08 (1 H, br s, NH-15), 4.56-4.40 (2 H, m, H-13, 16), 3.73 (3 H, s, H-23), 3.27-3.12 (2 H, m, H-12), 1.45 (9 H, s, H-22), 1.32 (3 H, d, *J* 7.2, H-18); δ_C (100 MHz, $CDCl_3$) 172.7 (C), 170.4 (C), 153.9 (C), 139.2 (C), 138.0 (C), 133.1 (CH), 129.0 (C), 129.3 (CH,), 126.8 (CH), 125.1 (CH), 124.6 (CH), 123.4 (CH), 119.6 (CH), 118.0 (C), 113.7 (CH), 81.6 (C), 63.2 (CH_3), 52.6 (CH), 48.2 (CH), 28.3 (CH_3), 28.3 (CH_2), 18.3 (CH_3). Data consistent with literature.[102]

(*S*)-(*S*)-3-Methyl-6-((1-phenylsulfonyl-1*H*-indol-3-yl)methyl)piperazine-2,5-dione 172



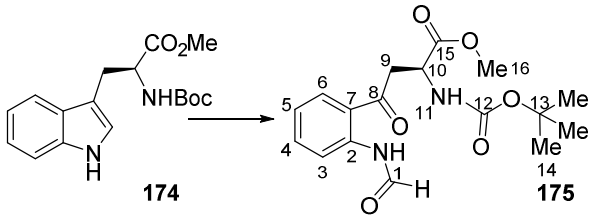
Trifluoroacetic acid (1.25 mL) was added to a stirring solution of (*S*)-methyl 2-(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(1-phenylsulfonyl-1*H*-indol-3-yl)propanamido)proponate **171** (250 mg, 0.47 mmol) in anhydrous dichloromethane (4.00 mL) and the mixture stirred at 0 °C for 4 h. The mixture was concentrated *in vacuo* to give an orange oil. The oil was dissolved in *tert*-butanol (10.0 mL), morpholine (1.96 mL) was added and the solution stirred for 44 h. A colourless precipitate formed and the solvent was removed *in vacuo* to give an orange residue. The residue was dissolved in DMF (5 mL) at 65 °C and the solution poured slowly into water (5 mL). The product precipitated as a colourless solid over 16 h, the solid was collected by vacuum filtration and dried at 50 °C for 24 h to give the title compound **172** as a colourless solid (100 mg, 53 %); mp 260-261 °C (lit. mp 260 °C); $[\alpha]_D^{24}$ -12 (c = 0.10, DMF); (Found C, 60.39; H, 4.95; N, 10.13; $C_{20}H_{19}N_3O_4S$ requires C, 60.44; H, 4.82; N, 10.57%); (Found: M+H$^+$, 398.1162. $C_{20}H_{19}N_3O_4S$ + H$^+$ requires 398.1160); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 3012, 2989, 2857, 1678, 1657, 1602, 1449, 1368, 1327, 1185, 1121; δ_H (400 MHz; $(CD_3)_2SO$) 8.18 (1 H, s, H-18), 8.06 (1 H, s, H-15), 7.92 (2 H, d, *J* 7.5, H-9), 7.87 (1 H, d, *J* 7.5, H-7), 7.74-7.63 (2 H, m, H-4, 11), 7.63-7.53 (3 H, m, H-2, 10), 7.32 (1 H, dd, *J* 7.5, 7.5, H-6), 7.25 (1 H, dd, *J* 7.5, 7.5, H-5), 4.27-4.23 (1 H, m, H-13), 3.68 (1 H, q, *J* 6.8, H-16), 3.23 (1 H, dd, *J* 14.2, 3.6, H-12a,), 3.02 (1 H, dd, *J* 14.2, 3.6, H-12b), 0.42 (3 H, d, *J* 6.8, H-19); δ_c (100 MHz; $(CD_3)_2SO$) 168.3 (C), 167.0 (C), 137.5 (C), 135.0 (CH), 134.4 (C), 131.4 (C), 130.3 (CH), 127.1 (CH), 125.9 (CH), 125.2 (CH), 123.7 (CH), 121.0 (CH), 117.9 (C), 113.3 (CH), 54.8 (CH), 50.1 (CH), 28.3 (CH_2), 19.8 (CH_3). Data consistent with literature.[102]

(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanoate 174



L-tryptophan methyl ester hydrochloride **173** (0.49 g, 1.95 mmol) was dissolved in anhydrous dichloromethane (7.80 mL) and triethylamine (0.27 mL, 1.96 mmol) was added to the stirring solution. Di-*tert*-butyl dicarbonate (0.51 g, 2.34 mmol) was dissolved in dichloromethane (0.80 mL) and added to the solution which was stirred at room temperature for 2 h. The solution was washed with brine (10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography (light petroleum: ethyl acetate; 4:1-2:1) gave the *title compound* **174** as a colourless powder (550 mg, 88%); m.p 145-146 °C; (Found M+Na^+ 341.1454. $C_{17}H_{22}N_2O_4$ + Na^+ requires 341.1472); ν_{max} ($CHCl_3$)/cm^{-1} 3480, 2928, 2854, 1742, 1708, 1500, 1458, 1440, 1368, 1167; δ_H (400 MHz; $CDCl_3$) 8.14 (1 H, s, br, NH-1), 7.58 (1 H, d, *J* 7.8, H-4), 7.38 (1 H, d, *J* 7.8, H-7), 7.22 (1 H, dd, *J* 7.8, 7.8, H-5), 7.15 (1 H, dd, *J* 7.8, 7.8, H-6), 7.03 (1 H, d, *J* 2.2, H-2), 5.11 (1 H, d, *J* 7.6, NH-10), 4.68 (1 H, m, H-9), 3.71 (3 H, s, H-15), 3.32 (2 H, m, H-8), 1.46 (9 H, s, H-13); δ_C (100 MHz; ($CDCl_3$) 172.8 (C), 155.2 (C), 136.2 (C), 127.8 (C), 122.8 (CH), 122.2 (CH), 119.6 (CH), 118.7 (CH), 111.2 (CH), 110.1 (C), 79.9 (C), 54.2 (CH), 52.3 (CH_3), 28.4 (CH_2), 28.0 (CH_3).

Methyl 4-(2-aminophenyl)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoate 175

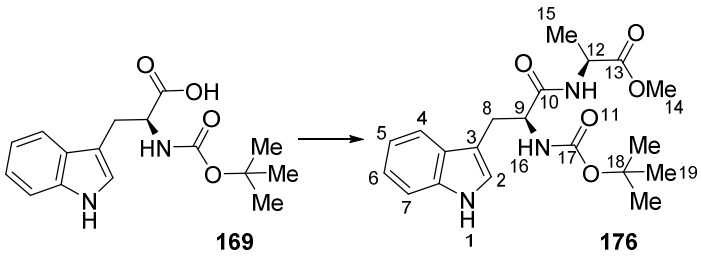


Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(1H-indol-3-yl)propanoate **174** (250 mg, 0.70 mmol) was dissolved in dichloromethane (14.0 mL) and the solution cooled to -50 °C; *m*-chloroperoxybenzoic acid (77%; 0.71 g, 3.10 mmol) was added and the mixture stirred at -50 °C for 1.5 h, before warming to room temperature over 30 min to form an orange solution. The orange solution was quenched with sodium thiosulfate solution (10 %; 10 mL) before saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture. The mixture was extracted with dichloromethane (3 x 20 mL) and the combined organic layers washed with

brine (30 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to give a brown foam. Column chromatography (light petroleum: ethyl acetate; 1:1) yielded the *title compound* **175** as a cream foam which was used without further purification (80.0 mg, 31 %); $[\alpha]_D^{25}$ 54 (c = 0.10 $CHCl_3$); (Found M+Na^+, 373.1368. $C_{17}H_{22}N_2O_6$ + Na^+ requires 373.1376); ν_{max} ($CHCl_3$)/cm^{-1} 3683, 3445, 3009, 2983, 1792, 1705, 1657, 1604, 1585, 1500, 1453, 1370, 1300, 1164; δ_H (400 MHz; $CDCl_3$) 11.40 (1 H, br s, H-1a), 8.75 (1 H, d, *J* 8.0, H-6), 8.48 (1 H, s, NH-1), 7.92 (1 H, d, *J* 8.0, H-3), 7.60 (1 H, dd, *J* 8.0, 8.0, H-5), 7.19 (1 H, dd, *J* 8.0, 8.0, H-4), 5.53 (1 H, br d, *J* 7.7, NH-11), 4.73-4.65 (1 H, m, H-10), 3.83-3.53 (5 H, m, H-9, 16), 1.45 (9 H, s, H-14); δ_C (100 MHz; ($CDCl_3$) 201.9 (C), 172.6 (C), 159.6 (CH), 143.7 (C), 140.0 (C), 136.1 (CH), 128.5 (CH), 123.2 (CH), 121.0 (C), 106.0 (CH), 80.2 (C), 56.4 (CH), 52.7 (CH_3), 42.2 (CH_2), 28.3 (CH_3).

Methyl 2-(2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)propanoate

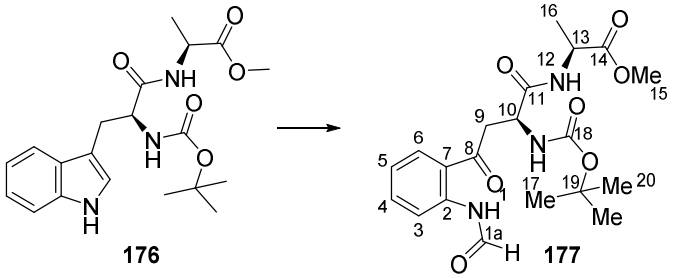
176



L-Alanine methyl ester hydrochloride (1.00 g, 7.16 mmol) was dissolved in DMF (71.0 mL) at room temperature with stirring. *N*-*α*-(*tert*-*B*utoxycarbonyl)-*L*-tryptophan **169** (3.23 g, 10.5 mmol), *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (4.06 g, 10.7 mmol) and *N,N*-diisopropylethylamine (3.70 mL, 25.0 mmol) were added to the solution and this was stirred for 1 h at room temperature. The resulting light yellow solution was diluted with ethyl acetate (100 mL) and washed with hydrochloric acid solution (1 M; 100 mL), saturated sodium hydrogen carbonate solution (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to give a cream foam. Purification

by column chromatography (ethyl acetate: light petroleum; 1:1 to 2:1) gave the *title compound* **176** as colourless solid (2.71 g, 97 %); mp 71-73 °C$[\alpha]_D^{25}$ 330 (c = 0.2 $CHCl_3$); (Found M+Na^+, 412.1852. $C_{20}H_{27}N_3O_5$ + Na^+ requires 412.1848); ν_{max} ($CHCl_3$)/cm^{-1} 3479, 3422, 3007, 2983, 1790, 1740, 1706, 1675, 1490, 1455, 1393, 1286, 1162; δ_H (400 MHz; $CDCl_3$) 8.21 (1 H, s, NH), 7.65 (1 H, d, *J* 7.5, H-4), 7.36 (1 H, d, *J* 7.5 H-7), 7.25-7.01 (3 H, m, H-2, 5, 6), 6.37 (1 H, br d, *J* 6.1, NH), 4.46-4.39 (2 H, m, H-9, 12), 3.66 (3 H, s, H-14), 3.40-3.26 (1 H, m, H-8a), 3.18-3.09 (1 H, m, H-8b), 1.44 (9 H, s, H-19), 1.26 (3 H, d, *J* 6.7, H-15); δ_C (100 MHz; ($CDCl_3$) 172.8 (C), 171.7 (C), 155.4 (C), 136.2 (C), 127.5 (C), 123.2 (CH), 122.2 (CH), 119.7 (CH), 118.9 (CH), 111.1 (CH), 110.6 (C), 80.8 (C), 55.0 (CH), 52.4 (CH_3), 48.1 (CH), 28.3 (CH_2), 28.3 (CH_3), 18.4 (CH_3).

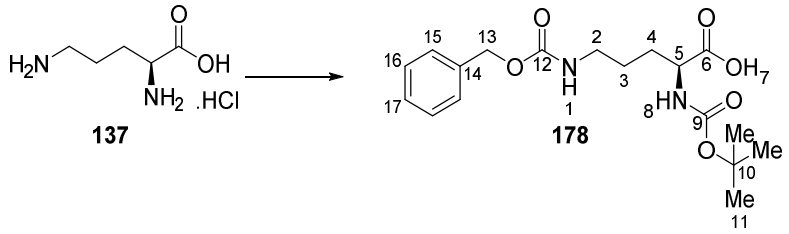
Methyl 2-(2-((*tert*-butoxycarbonyl)amino)-4-(2-formamidophenyl)-4-oxobutanamido)propanoate 66 177



Methyl 2-(2-((*tert*-butoxycarbonyl)amino)-3-(1H-indol-3-yl)propanamido)propanoate **176** (2.09 g, 5.37 mmol) was dissolved in dichloromethane (71.0 mL) and the solution cooled to –50 °C. *m*-Chloroperoxybenzoic acid (77%; 4.32 g, 20.5 mmol) was added to the stirring solution and the mixture allowed to warm to -10 °C over 1.5 h before the cool bath was removed and the stirring solution allowed to warm to room temperature over 30 min. Sodium thiosulfate solution (10 %, 40.0 mL) and saturated sodium hydrogen carbonate (40.0 mL) was added to the stirring solution and the mixture extracted with dichloromethane (3 x 100 mL) before being washed with brine (100 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification by column chromatography (ethyl acetate: light petroleum; 1:1) yielded

the *title compound* **177** as a light orange foam (1.09 g, 48 %); $[\alpha]_D^{25}$ 56.8 (c = 0.38 $CHCl_3$); (Found M+Na^+, 444.1742. $C_{20}H_{27}N_3O_7$ + Na^+ requires 444.1741); ν_{max} ($CHCl_3$)/cm^{-1} 3427, 2983, 1742, 1705, 1584, 1525, 1487, 1454, 1369, 1302, 1242, 1160; δ_H (400 MHz; $(CD_3)_2SO$) 10.82 (1 H, s, H-1a), 8.36 (1 H, d, *J* 7.0, NH-17), 7.64 (1 H, d, *J* 7.9, H-6), 7.35 (1 H, d, *J* 7.9, H-3), 7.15 (1 H, s, NH-1), 7.07 (1 H, dd, *J* 7.9, 7.9, H-4), 7.03 (1 H, dd, *J* 7.9, 7.9, H-5), 6.71 (1 H, d, *J* 8.4, NH-12), 4.33 (1 H, t, J 7.4, H-10), 4.28-4.21 (1 H, m, H-13), 3.64 (3 H, s, H-15), 3.09 (1 H, dd, *J* 14.6, 4.3, H-9a), 2.89 (1 H, dd, *J* 14.6, 9.6, H-9b) 1.34-1.29 (12 H, m, H-16, 20); δ_C (100 MHz; $(CD_3)_2SO$) 200.4 (C), 173.0 (C), 171.4 (C), 161.2 (CH), 155.2 (C), 138.0 (C), 134.1 (CH), 130.7 (CH), 128.8 (C), 127.9 (CH), 121.1 (CH), 78.2 (C), 51.9 (CH), 50.2 (CH), 47.6 (CH), 41.5 (CH_2) 28.1 (CH_3), 27.4 (CH_3), 16.9 (CH_3).

***Nα*-Boc-*Nδ*-*Z*-*L*-ornithine 178**

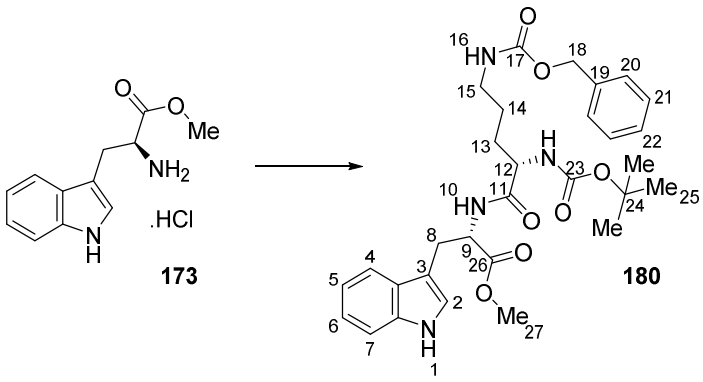


L-Ornithine hydrochloride **137** (303 mg, 1.78mmol) was dissolved in water (2.00 mL); copper carbonate basic (530 mg, 2.40 mmol) was added and the resulting mixture heated at reflux for 30 min. The hot solution was filtered to give a blue solution which was washed with water (3 x 3.00 mL) and allowed to cool to room temperature. The solution was basified with magnesium oxide (100 mg, 2.48 mmol) and the mixture cooled to 0 °C. A solution of benzyl chloroformate (0.50 mL, 3.23 mmol) in THF (10.0 ml) was added over 30 min, the mixture allowed to warm to room temperature and stirred for 22 h to give a blue precipitate which was collected by vacuum filtration and washed with water (10 ml), ethanol (10 ml) and diethyl ether (10 mL) to give a blue powder. Ethylenediaminetetraacetic acid (2.53 g, 8.67 mmol) was added to a solution of sodium hydrogen carbonate (4.42 g, 46.9 mmol in 20.0 mL of water) and the blue powder added to the stirring solution which was heated at reflux for 2 h. The

solution was cooled and a white precipitate formed which was filtered and washed with water to yield the protected ornithine species (177 mg, 37 %).

Potassium carbonate solution (0.12 g, 0.88 mmol, in 2 mL of water) was added to the protected ornithine and 1,4-dioxane (2.00 mL) and the mixture stirred for 30 min. Di-*tert*-butyl dicarbonate (0.15 g, 0.70 mmol) in 1,4-dioxane (1.00 mL) was added dropwise over 30 min. Additional 1,4-dioxane (2.00 mL) was added to improve the solubility of the protected ornithine, but precipitation remained. The mixture was stirred for 16 h and the volume reduced to 1 mL: before water (0.50 mL) was added and the mixture acidified to pH 2 with 1 M hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 5 mL) and the organic layers washed with hydrochloric acid solution (1 M; 2 mL), saturated ammonium chloride solution (2 mL), water (2 mL) and brine (2 mL) before being dried over Na_2SO_4 and the solvent removed *in vacuo* to yield the title compound as a colourless oil **178** which solidified on drying (248 mg, 98 %); $[\alpha]_D^{24}$ 12.0 (c = 1.0, $CHCl_3$); (Found C, 59.20; H, 7.29; N; 7.43; $C_{22}H_{24}N_2O_6S$ requires C, 59.00; H, 7.15; N, 7.43%); (Found M+Na^+, 389.1690. $C_{18}H_{26}N_2O_6$ + Na^+ requires 389.1689); ν_{max} ($CHCl_3$)/cm^{-1} 3674, 3477, 3011, 2982, 2953, 1714, 1509, 1369, 1243, 1161; δ_H (400 MHz; $(CD_3)_2SO$) 7.40-7.29 (5 H, m, H-15, 16, 17), 7.24 (1 H, t, *J* 5.4, NH-1), 7.06 (1 H, d, *J* 8.8, NH-8), 5.01 (2 H, s, H-13), 3.88-3.81 (1 H, m, H-5), 2.99 (2 H, dt, *J* 6.2, 5.4, H-2), 1.73-1.61 (1 H, m, H-3/4), 1.61-1.42 (3 H, m, H-3/4), 1.39 (9 H, s, H-11); δ_C (100 MHz; $(CD_3)_2SO$) 174.6 (C), 156.6 (C), 156.0 (C), 137.7 (C), 128.4 (CH), 127.8 (CH), 127.7 (CH), 78.4 (C), 65.6 (CH_2), 53.7 (CH), 40.5 (CH_2), 28.7 (CH_3), 28.7 (CH_2), 26.6 (CH_2). Data as literature compound.[235,236]

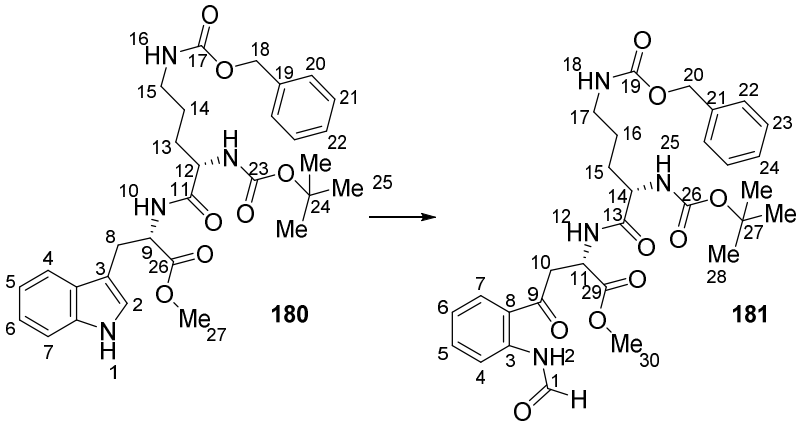
Methyl 5-((benzyloxycarbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)pentanoyl) tryptophanate 180



L-Tryptophan methyl ester hydrochloride **173** (303 mg, 1.19 mmol) was dissolved in DMF (9.00 mL) and *N*α-*t*-Boc-*N*δ-Cbz-*L*-ornithine (300 mg, 0.82 mmol) was added. *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (470 mg, 1.23 mmol) and *N, N*-diisopropylethylamine (0.43 ml, 2.46 mmol) were added to the solution which was stirred for 1 h at room temperature. The reaction mixture was diluted with hydrochloric acid (1 M; 20 mL), extracted with ethyl acetate (10 mL), washed with saturated sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to give the crude product as a cream foam. The product was purified by column chromatography (ethyl acetate: light petroleum; 1:1) to give the *title compound* **180** as a colourless foam (470 mg, 98 %); mp 61-63 °C; $[\alpha]_D^{25}$ 20 (c = 0.1, $CHCl_3$); (Found M+Na^+, 589.2636. $C_{30}H_{38}N_4O_7$ + Na^+ requires 589.2633); ν_{max} ($CHCl_3$)/cm^{-1} 3478, 3448, 3010, 1711, 1678, 1514, 1368, 1242, 1168; δ_H (400 MHz; $CDCl_3$) 8.13 (1 H, s, NH), 7.55 (1 H, d, *J* 7.4, H-7), 7.40-7.31 (6 H, m, H-4, 20, 21, 22), 7.17 (1 H, dt J 7.4, 1.1, H-5/6), 7.11 (1 H, dt J 7.4, 1.1, H-5/6), 7.07 (1 H, br s, H-2), 6.77 (1 H, s, NH), 5.12-4.18 (5H, m, NH, H-9, 12, 18), 4.22 (1 H, br s, NH), 3.70 (3H, s, H-27), 3.33 (3H, m, H-8a, 14), 3.19-3.13 (1 H, m, H-8b), 1.84-1.73 (1 H, m, H-15a), 1.67-1.40 (12 H, m, H-13, 15b, 25); δ_C (100 MHz, $CDCl_3$) 172.1 (C) 150.4 (C), 149.9 (C), 139.0 (C), 136.6 (C), 136.1 (C), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.5 (C), 123.3 (CH), 123.1 (C), 122.2 (CH), 119.7 (CH), 118.5 (CH),

111.3 (CH), 77.5 (CH), 70.1 (C), 66.7 (CH_2), 52.7 (CH), 52.4 (CH_3), 39.8 (CH_2), 30.2 (CH_2), 28.2 (CH_3), 27.5 (CH_2) 26.0 (CH_2).

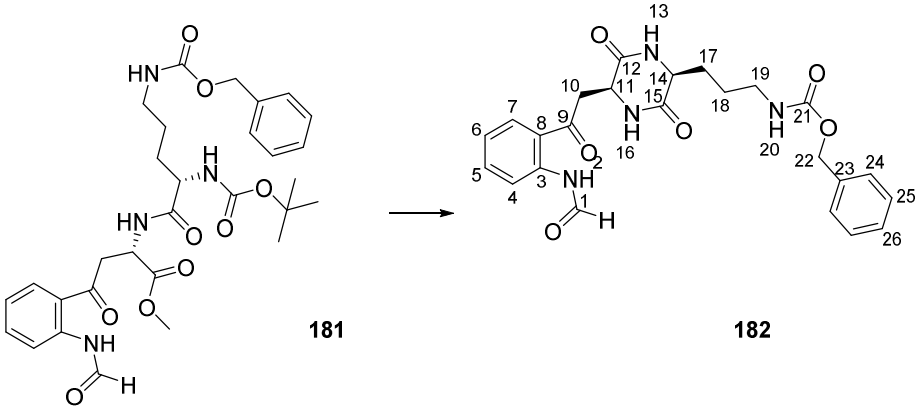
Methyl 2-(5-((benzyloxycarbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)pentamido)-4-(2-formamidophenyl)-4-oxobutanoate 181



Methyl 5-((benzyloxycarbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)pentanoyl) tryptophanate **180** (100 mg, 0.17 mmol) was dissolved in anhydrous dichloromethane (3.40 mL) and the solution cooled to -50 °C before *m*-chloroperoxybenzoic acid (66%; 158 mg, 0.71 mmol) was added. The light orange mixture was stirred at -50 °C for 1.5 h and warmed to room temperature over 30 min to form an orange solution. Sodium thiosulfate solution (10 %, 10 mL) and saturated sodium hydrogen carbonate solution (10 mL) were added to the stirring solution and the mixture extracted with dichloromethane (3 x 10 mL) and the combined organic layers washed with brine (20 mL) and dried over $MgSO_4$ and the solvent removed *in vacuo* to give **70** as an orange foam. Purification by column chromatography (ether: light petroleum; 1:1) yielded the *title compound* **181** as a colourless foam (67 mg, 66 %); $[\alpha]_D^{25}$ 65.5 (c = 0.52, $CHCl_3$); (Found M+Na^+, 621.2546. $C_{30}H_{38}N_4O_9$ + Na^+ requires 621.2536); ν_{max} ($CHCl_3$)/cm^{-1} 3045, 1661, 1451, 1365, 1326, 1171, 1107; δ_H (400 MHz; $CDCl_3$) 11.32 (1 H, s, H-1), 8.78 (1 H, d, *J* 8.3, H-4), 8.37 (1 H, s, NH-2), 7.91 (1 H, d, *J* 8.3, H-7), 7.61 (1 H, dd, *J* 8.3, 8.3, H-5), 7.45-7.15 (5 H, m, H-22, 23, 24), 7.27 (1 H, s, NH-25), 7.19 (1 H, dd, *J* 8.3, 8.3, H-6), 5.22 (1 H, d, *J* 12.3, H-20a), 5.18 (1 H, s, NH-12), 5.13 (1 H, d, *J* 12.3, H-20b),

5.07-4.96 (2 H, m, H-11, NH-18), 4.36-4.29 (1 H, m, H-14), 3.82 (1 H, dd, *J* 18.0, 4.6, H-10a), 3.76 (3 H, s, H-30), 3.64 (1 H, dd, *J* 18.0, 4.6, H-10b), 3.47-3.33 (1 H, m, H-17a), 3.26-3.14 (1 H, m, H-17b), 1.98-1.85 (1 H, m, H-15a), 1.71-1.54 (3 H, m, H-15b, H-16), 1.41 (9 H, s, H-28); δ_C (100 MHz; $CDCl_3$) 201.5 (C), 172.2 (C), 171.4 (C), 159.9 (CH), 156.9 (C), 155.6 (C), 140.0 (C), 136.6 (C), 135.8 (CH), 130.9 (CH), 128.54 (CH), 128.5 (CH), 128.1 (CH), 123.2 (CH), 121.7 (CH), 121.0 (C), 79.9 (C), 66.7 (CH_2), 53.2 (CH), 52.8 (CH_3), 48.0 (CH), 41.7 (CH_2), 39.9 (CH_2), 30.0 (CH_2), 28.2 (CH_3), 26.1 (CH_2).

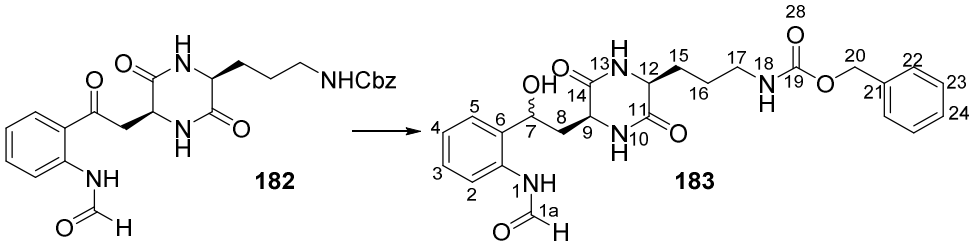
Benzyl (3-(5-(2-(2-formamidophenyl)-2-oxoethyl)-3,6-dioxopiperazin-2-yl)propyl)carbamate 182



Trifluoroacetic acid (4.67 mL) was added to a solution of methyl 2-(5-((benzyloxycarbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)pentamido)-4-(2-formamidophenyl)-4-oxobutanoate **181** (0.99 g, 1.68 mmol) in dichloromethane (12.0 mL) at 0 °C and the resulting solution stirred for 4 h. The solvent was removed *in vacuo*, the orange residue dissolved in *t*-butanol (37.0 mL) and morpholine (7.00 mL) was added to the resulting solution which was stirred for 16 h. The solvent was removed *in vacuo* and the orange residue dissolved in DMF (20 mL) at 65 °C before being poured slowly into water (20 mL). The product precipitated as a cream solid over 48 h which was collected by vacuum filtration and dried at 50 °C over 24 h to give the *title compound* as a colourless powder **182** (467 mg, 60 %); mp 189-192 °C; $[\alpha]_D^{25}$ 4.0 (c =1.0, DMF); (Found C, 61.64; H, 5.62; N, 11.94; $C_{24}H_{26}N_4O_6$

requires C, 61.79; H, 5.62; N, 12.01%); (Found M+Na^+, 489.1770. $C_{24}H_{26}N_4O_6$ + Na^+ requires 489.1750); ν_{max} (ATR)/cm^{-1} 1677, 1645, 1532, 1259; δ_H (400 MHz; $(CD_3)_2SO$) 11.01 (1 H, s, H-1), 8.45 (1 H, s, NH-16), 8.41 (1 H, dd, *J* 8.2, 0.9, H-4), 8.22 (1 H, s, NH-13), 8.02 (1 H, s, NH-2), 8.03 (1 H, d, *J* 8.2, H-7), 7.61 (1 H, dd, *J* 8.2, 8,2, H-5), 7.41-7.25 (6 H, m, H-24, 25, 26, NH-20), 7.23 (1 H, dd, *J* 8.2, 8,2, H-6), 5.02 (2 H, s, H-22), 4.48 (1 H, dd, *J* 6.0, 4.8, H-11), 4.00 (1 H, t, *J* 4.6, H-14), 3.61 (1 H, dd, *J* 17.6, 4.8, H-10a), 3.36 (1 H, dd, *J* 17.6, 6.0, H-10b), 3.03 (2 H, q, *J* 6.6, H-19), 1.79-1.75 (2 H, m, H-17), 1.64-1.44 (2 H, m, H-18); δ_C (100 MHz, $(CD_3)_2SO$) 200.1 (C), 168.1 (C), 168.1 (C), 160.9 (CH), 156.0 (C), 138.1 (C), 137.7 (C), 137.2 (CH), 133.9 (CH), 130.6 (CH), 128.2 (CH), 127.6 (CH), 124.2 (C), 123.3 (CH), 121.1 (CH), 65.0 (CH_2), 53.5 (CH) 50.5 (CH), 41.9 (CH_2), 40.1 (CH_2), 28.6 (CH_2), 24.7 (CH_2).

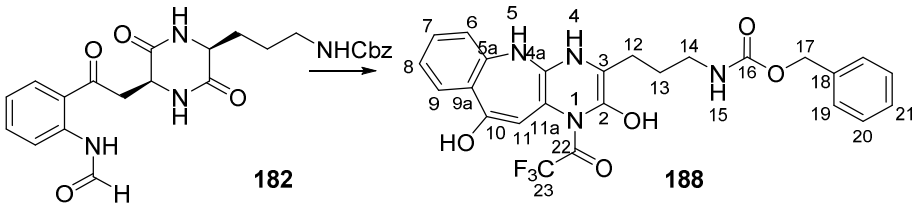
Benzyl (3-(5(2-(2-formamidophenyl)-2-hydroxyethyl)-3,6-dioxopiperazin-2-yl)propyl)carbamate 183



Benzyl (3-(5-(2-(2-formamidophenyl)-2-oxoethyl)-3,6-dioxopiperazin-2-yl-propyl)carbamate **182** (100 mg, 0.21 mmol) was dissolved in methanol (1.25 mL) at room temperature. Sodium borohydride (43 mg, 1.14 mmol) was added and the solution stirred for 16 h at room temperature. The solution was washed with hydrochloric acid (1 M, 1 mL) before being washed with dichloromethane (3 x 5 mL) and the combined organic layers dried over Na_2SO_4 before the solvent was removed *in vacuo*. Column chromatography (methanol: dichloromethane; 5:95) gave the *title compound* **183** as a colourless oil (28 mg, 28 %, mixture of diastereoisomers 2:3); (Found M+Na^+ 491.1919. $C_{24}H_{28}N_4O_6$ + Na^+ requires 491.1901); ν_{max} ($CHCl_3$)/cm^{-1} 3377, 3040, 2983, 2956, 2934, 1728, 1644, 1590, 1536, 1516; δ_H (400 MHz;

CD_3OD) 8.55 (0.4 H, d, *J* 8.5, H-5), 8.38 (0.6 H, d, *J* 8.5, H-5), 7.90 (04 H, d, *J* 7.5, H-2), 7.84 (0.6 H, d, *J* 7.5, H-2), 7.50 (0.6 H, t, *J* 7.9, H-3), 7.43 (0.4 H, t, *J* 7.9, H-3), 7.38-7.18 (6 H, m, H-4, 22, 23, 24), 5.06 (3 H, m, H-7, 20), 4.27 (0.4 H, dd, *J* 31.5, 5.5, H-12), 4.15 (0.6 H, dd, *J* 31.5, 5.5, H-12), 4.07 (0.4 H, dd, *J* 31.5, 5.5, H-9), 3.99 (0.6 H, dd, *J* 31.5, 5.5, H-9), 3.17 (2 H, t, *J* 6.3, H-17), 2.45-2.13 (1 H, m, H-8a), 2.09-1.77 (3 H, m, H-8b, 15), 1.64 (2 H, m, H-16); δ_C (100 MHz; CD_3OD) 169.9 (C), 161.0 (CH), 157.6 (C), 137.00 (C), 135.9 (C), 135.2 (C), 134.6 (C), 134.0 (C), 133.7 (C), 132.0 (C), 128.4 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 126.7 (CH), 126.6 (CH), 125.7 (CH), 125.2 (CH), 124.3 (CH), 123.8 (CH), 121.3 (CH), 69.6 (CH), 66.9 (CH), 66.6 (CH), 66.0 (CH_2), 54.4 (CH), 54.1 (CH), 53.0 (CH), 52.2 (CH), 41.9 (CH_2), 39.8 (CH_2), 31.1 (CH_2), 30.6 (CH_2), 25.1 (CH_2), 24.8 (CH_2).

Benzyl (3-(2,10-dihydro-1-(2,2,2-trifluoroacetyl)-4,5-dihydro-1*H*-benzo[b]pyrazino[2,3-*f*]azapin-3-yl)propyl)carbamate 188

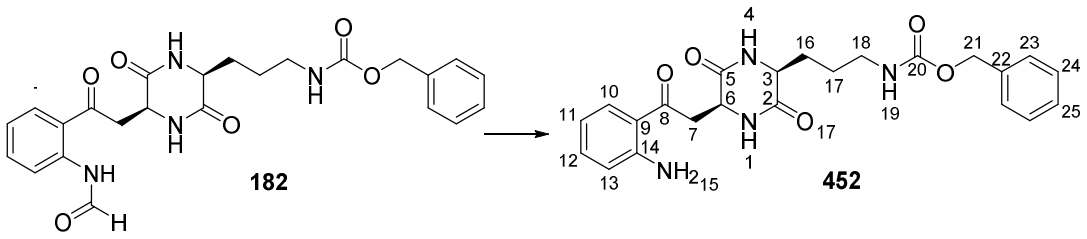


Benzyl (3-(5-(2-(2-formamidophenyl)-2-oxoethyl)-3,6-dioxopiperazin-2-yl-propyl)carbamate **182** (100 mg, 0.21 mmol) was dissolved in anhydrous dichloromethane (2.10 mL) under an argon atmosphere. Anhydrous pyridine (0.17 mL, 2.14 mmol) was added and the reaction cooled to -78 °C before anhydrous trifluoroacetic anhydride (0.31 mL, 1.07 mmol) was added. The suspension was allowed to warm to room temperature and stirred for 16 h to give a red solution. The solution was quenched with water (5 mL) and washed with dichloromethane (3 x 5 mL) before the combined organic layers were washed with saturated copper sulfate solution (3 x 5 mL) and brine (10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to give a brown oil. The oil was dissolved in methanol and left for 16 h giving the *title compound* **188** as a pale yellow powder and further product was collected by

filtration after the dropwise addition of water (21 mg, 19 %); decomposition above 210 °C ; *(*Found M+Na^+, 539.1514. $C_{25}H_{23}N_4F_3O_5$ + Na^+ requires 539.1518); ν_{max} ($CHCl_3$)/cm^{-1} 3632, 3450, 3381, 3011, 2942, 1703, 1588, 1417, 1455, 1263, 1192; δ_H (400 MHz; $(CD_3)_2SO$) 12.46 (1 H, s, OH-10), 9.68 (1 H, s, NH-4), 8.98 (1 H, s, NH-5), 7.54 (1 H, d, *J* 7.8, H-6/9) 7.52 (1 H, d, *J* 7.8, H-6/9), 7.42-7.23 (7 H, m, NH-15, H-20, 19, 7, 21), 7.18 (1 H, t, *J* 7.8, H-8), 6.84 (1 H, br s, H-11), 6.79 (1 H, s, OH-2), 5.02 (2 H, s, H-17), 3.01 (2 H, m, H-14), 2.00 (1 H, dt, *J* 12.8, 4.6, H-12a) 1.68 (1 H, dt, *J* 12.8, 4.6, H-12b), 1.50-1.32 (2 H, m, H-13); δ_C (100 MHz; $(CD_3)_2SO$) 165.5 (C), 160.4 (C), 160.3 (C, q, *J* 32.5), 156.0 (C), 137.2 (C), 136.6 (C), 135.9 (C), 128.3 (CH), 127.6 (CH), 127.6 (CH), 124.8 (C), 124.3 (CH), 121.4 (CH), 120.6 (CH), 115.7 (C, q, *J* 286), 112.6 (CH), 109.8 (C), 104.9 (CH), 81.5 (C), 65.1 (CH_2), 39.6 (CH_2), 35.1 (CH_2), 24.4 (CH_2).

Benzyl (3-(5-(2-(2-aminophenyl)-2-oxoethyl)-3,6-dioxopiperazin-2-yl)propyl)carbamate

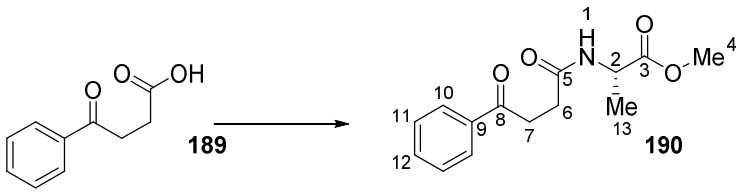
182



Benzyl (3-(5-(2-(2-formamidophenyl)-2-oxoethyl)-3,6-dioxopiperazin-2-yl-propyl)carbamate **182** (50.0 mg, 0.10 mmol) was dissolved in methanol (5.00 mL) and hydrochloric acid (3 M; 0.50 mL) was added. 1,4-Dioxane (1.60 mL) was added to the stirring solution. The reaction mixture was stirred at room temperature for 1 h before being poured into aqueous sodium carbonate solution (5 mL), extracted with ethyl acetate (3 x 10 mL) and the organic layers washed with brine (20 mL) before being dried over Na_2SO_4 and the solvent removed *in vacuo* to give a white powder. Column chromatography (dichloromethane: methanol; 95:5) gave the *title compound* **452** as a colourless powder (43 mg, 98%); mp 172-174 °C; (Found M+Na^+, 461.1790. $C_{23}H_{26}N_4O_5$ + Na^+ requires 461.1801); ν_{max} ($CHCl_3$)/cm^{-1}

3454, 3385, 3011, 1685, 1681, 1643, 1550, 1516, 1256; δ_H (400 MHz; CD_3OD) 7.72 (1 H, d, *J* 7.8, H-10), 7.37-7.27 (5 H, m, H-23, 24, 25), 7.24 (1 H, t, *J* 7.8, H-11), 6.73 (1 H, d, *J* 7.8, H-13), 6.58 (1 H, t, *J* 7.8, H-12), 5.06 (2 H, s, H-21), 4.53-4.48 (1 H, m, H-6), 4.06 (1 H, t, *J* 5.6, H-3), 3.66 (1 H, dd, *J* 17.8, 3.6, H-7a), 3.43 (1 H, dd, *J* 17.8, 3.6, H-7b), 3.18 (2 H, t, *J* 6.8, H-18), 2.00-1.85 (2 H, m, H-16), 1.78-1.59 (2 H, m, H-17); δ_C (100 MHz, CD_3OD) 199.0 (C), 171.9 (C), 171.8 (C), 156.7 (C), 155.5 (C), 150.5 (C), 135.0 (CH), 130.9 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 117.4 (CH), 117.0 (C), 116.0 (CH), 66.7 (CH_2), 53.4 (CH), 48.9 (CH), 40.8 (CH_2), 40.1 (CH_2), 30.3 (CH_2), 25.8 (CH_2).

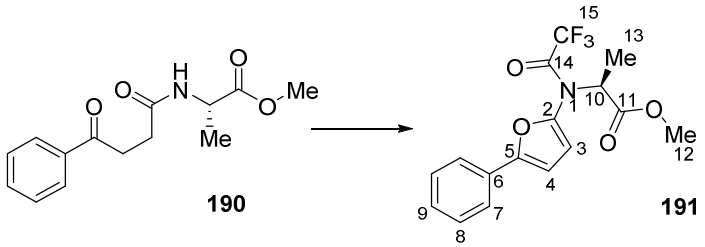
Methyl (4-oxo-4-phenylbutanoyl)-*L*-alaninate 190



3-Benzoyl propanoic acid **189** (500 mg, 2.80 mmol) was dissolved in DMF (28.0 mL) at room temperature. *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (1.63 g, 4.20 mmol), *N*,*N*-diisopropylethylamine (1.44 mL, 8.40 mmol) and *L*-alanine methyl ester hydrochloride (586 mg, 4.20 mmol) were added to the stirring solution. The solution was stirred for 1 h then diluted with hydrochloric acid (1 M; 30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with lithium chloride solution (5 %; 2 x 20 mL) and brine (30 mL) before being dried over Na_2SO_4. The solvent was removed *in vacuo* to give a colourless powder which was purified by column chromatography (ethyl acetate: light petroleum; 1:8) to give the *title compound* **190** as a colourless solid (614 mg, 83%); mp 77-79 °C; $[\alpha]_D^{25}$ 22.4 (*c* 0.20, $CHCl_3$); (Found M+Na^+, 286.1041. $C_{14}H_{17}NO_4$ + Na^+ requires 286.1055); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 3006, 2956, 1741, 1681, 1512, 1450, 1241, 1171, 985; δ_H (400 MHz; $CDCl_3$) 7.98 (2 H, d, *J* 7.6, H-10), 7.56 (1 H, td, *J* 7.6, 1.1, H-12), 7.45 (2 H, t, *J* 7.6, H-11), 6.42 (1 H, s br, NH-1), 4.59 (1 H, quin, *J* 7.3, H-2), 3.73 (3 H, s, H-4), 3.46-

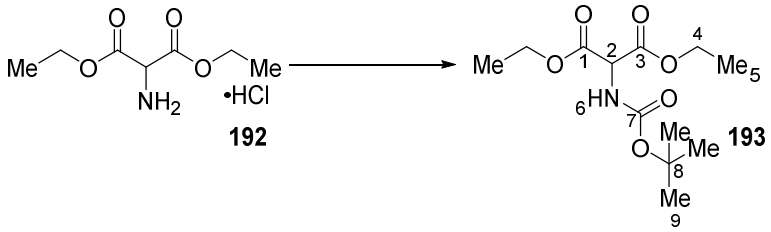
3.27 (2 H, m, H-7), 2.68 (2 H, t, *J* 6.6, H-6), 1.41 (3 H, d, *J* 7.0, H-13); δ_C (100 MHz; $CDCl_3$) 199.8 (C), 173.4 (C), 171.6 (C), 136.5 (C), 133.2 (CH), 128.5 (CH), 128.0 (CH), 52.4 (CH_3), 48.0 (CH), 33.8 (CH_2), 29.9 (CH_2), 18.3 (CH_3).

Methyl *N*-(5-phenylfuran-2-yl)-*N*-(2,2,2-trifluoroacetyl)-*L*-alaninate 191



Methyl (4-oxo-4-phenylbutanoyl)-*L*-alaninate **190** (164 mg, 0.62 mmol) was dissolved in anhydrous dichloromethane (6.25 mL) and cooled to -50 °C under an atmosphere of argon. Anhydrous pyridine (0.50 mL, 6.2 mmol) and trifluoroacetic anhydride (0.36 mL, 1.24 mmol) were added. The reaction mixture was stirred for 30 min whilst warming to room temperature to give a red solution. The solution was diluted carefully with water (5 mL) before being extracted into dichloromethane (3 x 10 mL) and the combined organic layers washed with saturated copper sulfate solution (20 mL) and brine (20 mL) before being dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 1: 9) gave the *title compound* **191** as a colourless oil (139 mg, 66%); $[\alpha]_D^{25}$ 13.8 (*c* 0.50, $CHCl_3$); (Found M+Na^+, 364.0769. $C_{16}H_{14}F_3NO_4$ + Na^+ requires 364.0767); ν_{max} ($CHCl_3$)/cm^{-1} 3012, 2956, 2928, 2854, 1748, 1719, 1617, 1549, 1437, 1404, 1192, 1168, 1123, 910; δ_H (400 MHz; $CDCl_3$) 7.64 (2 H, dd, *J* 7.5, 1.3, H-7), 7.42 (2 H, t, *J* 7.5, H-8), 7.33 (1 H, tt, *J* 7.5, 1.3, H-9), 6.67 (1 H, d, *J* 3.5, H-3/4), 6.52 (1 H, d, *J* 3.5, H-3/4), 5.05 (1 H, q, *J* 7.5, H-10), 3.81 (3 H, s, H-12), 1.42 (3 H, d, *J* 7.5, H-13); δ_C (100 MHz; $CDCl_3$) 170.5 (C), 158.0 (C, q, *J* 36.6), 152.8 (C), 140.7 (C), 129.8 (C), 128.8 (CH), 128.3 (CH), 123.9 (CH), 115.7 (C, q, *J* 287.6), 111.7 (CH), 105.9 (CH), 56.3 (CH), 52.7 (CH_3), 14.4 (CH_3).

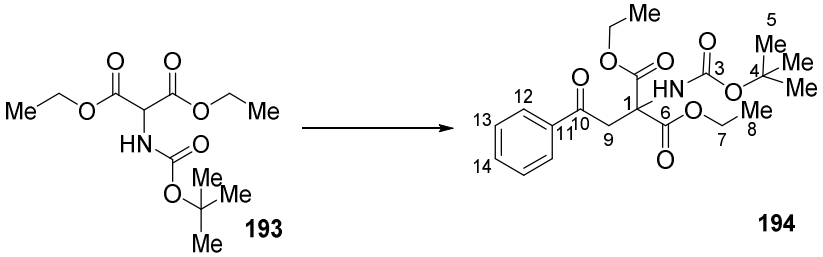
Diethyl 2-((*tert*-butoxycarbonyl)amino) malonate 193



Diethyl aminomalonate hydrochloride **192** (2.03 g, 9.46 mmol) was dissolved in THF (4.00 mL) at room temperature and triethylamine (4.80 mL, 47.2 mmol) was added to the solution. Di-*tert*-butyl dicarbonate (4.12 g, 18.9 mmol) dissolved in THF (2.00 mL) was added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was then poured into water (20 mL), extracted with ethyl acetate (3 x 20 mL) and the combined organic layers washed with brine (30 mL) before being dried over Na_2SO_4 and solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 1:4) gave the *title compound* **193** as a colourless oil (2.02 g, 82%); (Found M+Na^+, 298.1266. $C_{12}H_{21}NO_6$ + Na^+ requires 298.1261); ν_{max} ($CHCl_3$)/cm^{-1} 3438, 2984, 2939, 1758, 1739, 1715, 1498, 1394, 1371, 1336, 1161, 1063, 1026, 859; δ_H (400 MHz; $CDCl_3$) 5.58 (1 H, d br, *J* 8.1, NH-6), 4.96 (1 H, d, *J* 8.1, H-2), 4.36-4.21 (4 H, m, H-4), 1.47 (9 H, s, H-9), 1.32 (6 H, t, *J* 7.0, H-5); δ_C (100 MHz; $CDCl_3$) 166.6 (C), 154.8 (C), 80.6 (C), 62.5 (CH_2), 57.6 (CH), 28.2 (CH_3), 14.0 (CH_3).

Data matches literature.[237]

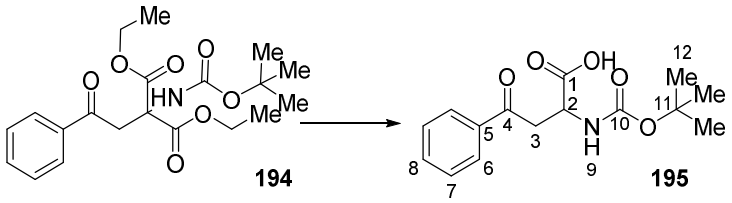
Diethyl 2-(*tert*-butoxycarbonyl amino)-2-(2-oxo-2-phenylethyl) malonate 194



Diethyl 2-(*tert*-butoxycarbonyl amino) malonate **193** (923 mg, 3.52 mmol) was dissolved in anhydrous DMF (2.90 mL) under argon with stirring. Sodium hydride (121 mg; 60 % in

mineral oil) was added and the solution stirred for 3 h. Bromoacetophenone (635 mg, 3.17 mmol) in anhydrous DMF (2.50 mL) was added dropwise and the resulting solution stirred for 16 h to form an orange solution. The reaction mixture was poured into water (20 mL), acidified to pH 3 using hydrochloric acid (1 M) and extracted into ethyl acetate (2 x 20 mL). The combined organic layers were washed with aqueous lithium chloride solution (5%, 2 x 30 mL), brine (30 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to give a colourless solid which was purified by column chromatography (ethyl acetate: light petroleum; 1: 9) to give the *title compound* **194** as a colourless solid (899 mg, 65%); mp 79-81 °C; (Found C, 61.05; H, 7.07; N, 3.47. $C_{20}H_{27}NO_7$ requires C, 61.06; H, 6.92; N, 3.58%); (Found M+Na^+, 416.1710. $C_{20}H_{27}NO_7 + Na^+$ requires 416.1685); ν_{max} ($CHCl_3$)/cm^{-1} 3666, 3423, 2984, 2933, 2873, 2856, 1743, 1705, 1487, 1406, 1369, 1240, 1163, 1003, 862; δ_H (400 MHz; $CDCl_3$) 7.98 (2 H, dd, *J* 7.6, 1.3, H-12), 7.59 (1 H, tt, *J* 7.6, 1.3, H-14), 7.47 (2 H, t, *J* 7.6, H-13), 6.25 (1 H, br s, NH-2), 4.35-4.12 (4 H, m, H-7), 4.20 (2 H, s, H-9), 1.38 (9 H, s, H-5), 1.26 (6 H, t, *J* 7.2, H-8); δ_C (100 MHz; $CDCl_3$) 196.9 (C), 167.6 (C), 154.4 (C), 136.4 (C), 133.6 (CH), 128.7 (CH), 128.3 (CH), 80.3 (C), 64.7 (C), 62.8 (CH_2), 42.4 (CH_2), 28.2 (CH_3), 13.9 (CH_3).

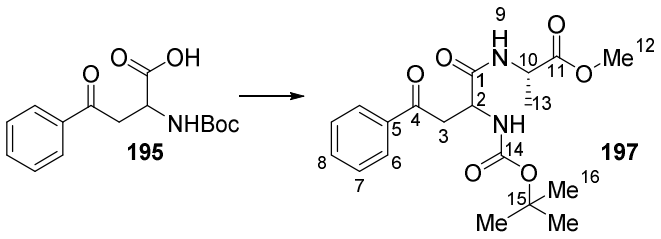
2-(((tert-Butoxycarbonyl)amino)-4-oxo-4-phenylbutanoic acid 195



Diethyl 2-(*tert*-butoxycarbonyl amino)-2-(2-oxo-2-phenylethyl) malonate **194** (300 mg, 0.76 mmol) was dissolved in methanol (4.00 mL) at room temperature. To the stirring solution sodium hydroxide solution (2 M; 0.90 mL) was added and the mixture heated to 90 °C. The solution was stirred at 90 °C for 16 h. The volatiles were removed *in vacuo* and the mixture re-dissolved in water (5 mL) before being acidified to pH 5/6 with 1 M hydrochloric acid. The product was extracted into ethyl acetate (3 x 10 mL) and the combined organic layers washed

with brine (20 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the *title compound* **195** as a colourless gum (70.0 mg, 31%); (Found M+Na^+, 316.1146. $C_{15}H_{19}NO_5$ + Na^+ requires 316.1155); ν_{max} ($CHCl_3$)/cm^{-1} 3670, 3442, 3009, 2982, 2933, 1704, 1598, 1501, 1445, 1393, 1369, 1323, 1284, 1164, 1062; δ_H (400 MHz; CD_3OD) 8.01 (2 H, d, *J* 7.5, H-6), 7.63 (1 H, t, *J* 7.5, H-8), 7.52 (2 H, t, *J* 7.5, H-7), 4.65 (1 H, app br d, *J* 5.3, H-2), 3.63-3.48 (2 H, m, H-3), 1.45 (9 H, s, H-12); δ_C (100 MHz; CD_3OD) 199.5 (C), 193.0 (C), 157.9 (C), 138.1 (C), 134.7 (CH), 129.9 (CH), 129.4 (CH), 80.7 (C), 49.6 (CH), 40.4 (CH_2), 28.8 (CH_3).

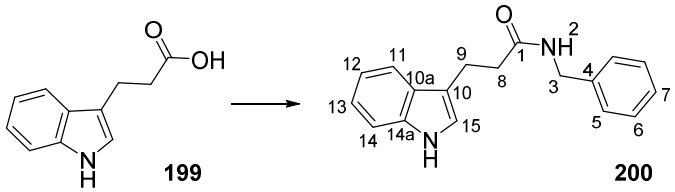
Methyl 2-(2-(*tert*-butoxycarbonyl amino)-4-oxo-4-phenylbutanamido) propanoate 197



2-*(tert*-Butoxycarbonylamino)-4-oxo-4-phenylbutanoic acid **195** (50.0 mg, 0.17 mmol) was dissolved in DMF (1.7 mL), to the stirring solution *L*-alanine methyl ester hydrochloride (35.0 mg, 0.25 mmol), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (96.0 mg, 0.25 mmol) and *N*,*N*-diisopropylethylamine (0.09 mL, 0.51 mmol) were added and the yellow solution stirred for 1 h at room temperature. The reaction was quenched with hydrochloric acid (1 M; 5 mL) and washed with ethyl acetate (3 x 10 mL) before the combined organic layers were washed with lithium chloride solution (5%; 10 mL) and brine (10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 2: 3) gave the *title compound* **197** as a colourless oil as a mixture of diastereoisomers (1:1) (30 mg, 47%); $[\alpha]_D^{22}$ -57.2 (*c* 0.20, $CHCl_3$); (Found M+Na^+, 401.1690. $C_{19}H_{26}N_2O_6$ + Na^+ requires 401.1689); ν_{max} ($CHCl_3$)/cm^{-1} 2690, 3424, 3010, 2983, 2956, 1742, 1711, 1681, 1518, 1451, 1240, 1162; δ_H (400 MHz;

$CDCl_3$) 7.95 (2 H, dd, *J* 7.5, 1.4, H-6), 7.59 (1 H, td, *J* 7.5, 1.4, H-8) , 7.47 (2 H, td, *J* 7.5, 1.4, H-7), 7.13 (1 H, s br, NH-9), 6.78 (1 H, br d, *J* 5.1, NH-14), 4.77-4.68 (1 H, m, H-2), 4.55 (1 H, qd, *J* 7.1, 2.4, H-10), 3.89-3.77 (1 H, m, H-3a), 3.75 (1.5 H, s, H-12), 3.71 (1.5 H, s, H-12), 3.38-3.24 (1 H, m, H-3b), 1.49 (4.5 H, s, H-16), 1.45 (4.5 H, s, H-16), 1.42 (3 H, app t, *J* 7.2, H-13); δ_C (100 MHz; $CDCl_3$) 204.1 (C), 173.0 (C), 170.8 (C), 170.7 (C), 136.3 (C), 133.7 (CH), 133.6 (CH), 128.7 (CH), 128.2 (CH), 78.2 (C), 52.42 (CH_3), 52.37 (CH_3), 48.3 (CH), 48.2 (CH), 39.8 (CH_2), 28.3 (CH_3), 18.21 (CH_3), 18.18 (CH_3).

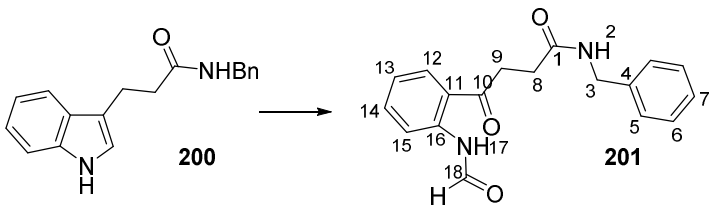
_N_-Benzyl-3-(1*H*-indol-3-yl)propanamide 200



Indol-3-propionic acid **199** (1.97 g, 10.5 mmol) was dissolved in anhydrous dichloromethane (80.0 mL) and the solution was cooled to 0 °C. Benzylamine (1.26 mL, 11.6 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.04 mL, 11.6 mmol) and *N*,*N*-diisopropylethylamine (4.00 mL, 23.1 mmol) were added to the stirring solution and the reaction mixture was allowed to warm to room temperature and stirred for 21 hours. The reaction mixture was quenched with hydrochloric acid (1 M; 40 mL) before being washed with saturated sodium hydrogen carbonate solution (40 mL) and extracted with dichloromethane (3 x 40 mL) before being dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (ethyl acetate: light petroleum; 3:7) gave the *title compound* **200** as colourless crystals (800 mg, 28%); mp 121-123 °C; (Found $M+H^+$, 279.1496. $C_{18}H_{18}N_2O$ + H^+ requires 279.1482); ν_{max} ($CHCl_3$)/cm^{-1} 3480, 3294, 3004, 2977, 1698, 1666, 1520, 1456, 1240, 909; δ_H (400 MHz; $(CD_3)_2SO$) 10.77 (1 H, s, NH-15), 8.33 (1 H, t, *J* 5.9, NH-2), 7.54 (1 H, d, *J* 7.9, H-14), 7.34 (1 H, d, *J* 7.9, H-11), 7.28 (2 H, tt, *J* 6.5, 1.1, H-6), 7.24-7.18 (1 H, m, H-7), 7.16 (2 H, br d, *J* 6.5, H-5), 7.09 (1 H, d, *J* 2.1, H-15), 7.06 (1 H, td, *J* 7.9, 0.9, H-12),

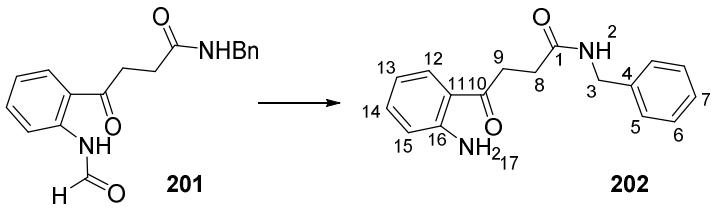
6.97 (1 H, td, *J* 7.9, 0.9, H-13), 4.25 (2 H, d, *J* 5.9, H-3), 2.96 (2 H, t, *J* 8.0, H-8/9), 2.52 (2 H, t, *J* 8.0, H-8/9); δ_C (100 MHz; $(CD_3)_2SO$) 171.9 (C), 139.6 (C), 136.2 (C), 128.2 (CH), 127.1 (CH), 127.0 (C), 126.6 (CH), 122.2 (CH), 120.9 (CH), 118.4 (CH), 118.1 (CH), 113.8 (C), 111.3 (CH), 42.0 (CH_2), 36.3 (CH_2), 21.0 (CH_2).

_N_-Benzyl-4-(2-formamidophenyl)-4-oxobutanamide 201



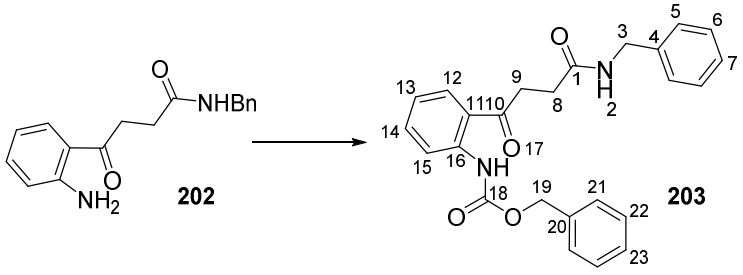
N-Benzyl-3-(1*H*-indol-3-yl)propanamide **200** (800 mg, 2.87 mmol) was dissolved in dichloromethane (29.0 mL) and the solution was cooled to -50 °C. To the stirring solution *m*-chloroperoxybenzoic acid (77%; 2.37 g, 11.5 mmol) was added and the reaction mixture was stirred at -50 °C for 2 h. The reaction was quenched with sodium thiosulfate solution (10%; 30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (30 mL) and brine (30 mL) before being dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 7:3) gave the *title compound* **201** as a pale yellow powder (230 mg, 26 %); mp 143-145 °C; (Found $M+Na^+$, 333.1203. $C_{18}H_{18}N_2O_3 + Na^+$ requires 333.1210); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3444, 3260, 2923, 1701, 1690, 1661, 1605, 1584, 1522, 1454; δ_H (400 MHz; $CDCl_3$) 11.47 (1 H, br s, H-18), 8.74 (1 H, d, *J* 8.0, H-15), 8.45 (1 H, s, NH-17), 8.02 (1 H, dd, *J* 8.0, 1.0, H-12), 7.57 (1 H, t, *J* 8.0, H-13), 7.38-7.28 (5 H, m, H-5, 6, 14), 7.18 (1 H, t, *J* 7.6, H-7), 6.02 (1 H, br s, NH-2), 4.47 (2 H, d, *J* 5.5, H-3), 3.46 (2 H, t, *J* 6.3, H-8/9), 2.56 (2 H, t, *J* 6.3, H-8/9); δ_C (100 MHz; $CDCl_3$) 203.2 (C), 171.5 (C), 159.7 (CH), 139.7 (C), 138.1 (C), 135.1 (CH), 130.7 (CH), 128.7 (CH), 127.8 (CH), 127.6 (CH), 123.2 (C), 121.7 (CH), 121.6 (CH), 43.8 (CH_2), 35.1 (CH_2), 30.1 (CH_2).

4-(2-Aminophenyl)-*N*-benzyl-4-oxobutanamide 202



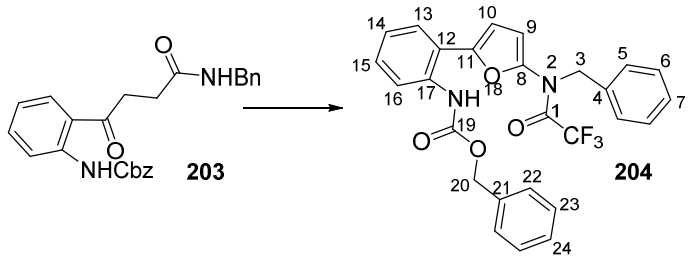
N-Benzyl-4-(2-formamidophenyl)-4-oxobutanamide **201** (100 mg, 0.32 mmol) was suspended in methanol (12.0 mL), 1,4-dioxane (3.00 mL) and hydrochloric acid (3 M; 1.50 mL) was added. The reaction mixture was stirred for 2 h at room temperature to give an orange solution which was quenched with saturated sodium hydrogen carbonate (3 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the *title compound* **202** as a pale orange foam which was used without further purification (90 mg, 99%); (Found $M+H^+$, 283.1439. $C_{17}H_{18}N_2O_2 + H^+$ requires 283.1441); ν_{max} ($CHCl_3$)/cm^{-1} 3503, 3445, 3361, 3002, 1651, 1615, 1584, 1550, 1515; δ_H (400 MHz; $CDCl_3$) 7.81 (1 H, d, *J* 8.0, H-12), 7.37-7.25 (8 H, m, H-5, 6, 7, 15, NH-17), 6.67 (2 H, t, *J* 8.0, H-13,14), 6.09 (1 H, br s, NH-2), 4.47 (2 H, d, *J* 5.7, H-3), 3.39 (2 H, t, *J* 6.5, H-8/9), 2.64 (2 H, t, *J* 6.5, H-8/9); δ_C (100 MHz; $CDCl_3$) 200.9 (C), 172.2 (C), 150.2 (C), 138.3 (C), 134.5 (CH), 131.0 (CH), 128.6 (CH), 127.7 (CH), 127.4 (CH), 117.7 (C), 117.3 (CH), 116.0 (CH), 43.7 (CH_2), 34.6 (CH_2), 30.6 (CH_2).

Benzyl (2-4-(benzylamino)-4-oxobutanoyl)phenyl)carbamate 203



4-(2-Aminophenyl)-*N*-benzyl-4-oxobutanamide **202** (90.0 mg, 0.32 mmol) was suspended in THF (0.70 mL), sodium hydrogen carbonate (54.0 mg, 0.64 mmol) was added and the solution was cooled to 0 °C. Benzyl chloroformate (0.05 ml, 0.35 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was then diluted with water (3 mL) and extracted with ethyl acetate (3 x 5 mL) before being washed with brine (10 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (ethyl acetate: light petroleum; 3:7) gave the *title compound* **203** as a colourless powder (50 mg, 38%); mp 108-110 °C; (Found M+H$^+$, 417.1807. $C_{25}H_{24}N_2O_4$ + H^+ requires 417.1809); ν_{max} ($CHCl_3$)/cm^{-1} 3262, 2928, 1732, 1659, 1605, 1585, 1537, 1453; δ_H (400 MHz; $CDCl_3$) 11.21 (1 H, s, NH-17), 8.50 (1 H, dd, *J* 8.1, 1.1, H-15), 7.94 (1 H, dd, *J* 8.1, 1.1, H-12), 7.54 (1 H, td, *J* 8.1, 1.1, H-14), 7.46-7.33 (5 H, m, H-5, 6, 7), 7.29-7.26 (4 H, m, H-21, 22), 7.24-7.18 (1 H, m, H-23), 7.06 (1H, td, *J* 8.1, 1.1, H-13), 6.22 (1 H, br t, *J* 5.4, NH-2), 5.21 (2 H, s, H-19), 4.43 (2 H, d, *J* 5.4, H-3), 3.40 (2 H, t, *J* 6.5, H-8/9), 2.58 (2 H, t, J 6.5, H-8/9); δ_C (100 MHz; $CDCl_3$) 202.6 (C), 171.7 (C), 153.6 (C), 141.1 (C), 138.2 (C), 136.6 (C), 135.0 (CH), 130.8 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.3 (CH), 121.5 (CH), 120.9 (C), 119.2 (CH), 66.8 (CH_2), 43.5 (CH_2), 34.9 (CH_2), 30.0 (CH_2).

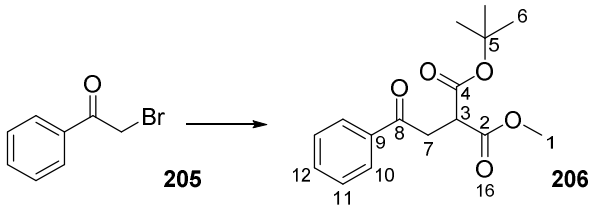
Benzyl (2-(5-(N-benzyl-2,2,2-trifluoroacetamido)furan-2-yl)phenyl)carbamate 204



Benzyl (2-4-(benzylamino)-4-oxobutanoyl)phenyl)carbamate **203** (38.0 mg, 0.09 mmol) was dissolved in anhydrous dichloromethane (1.00 mL) and the solution was cooled to -78 °C under an atmosphere of argon. Anhydrous pyridine (0.07 mL, 0.90 mmol) and anhydrous

trifluoroacetic anhydride (0.07 ml, 0.27 mmol) were added and the reaction stirred under argon for 4 h. The reaction was diluted with water (5 mL) and extracted with ethyl acetate (3 x 10 mL) and the combined organic layers washed with brine. The solution was dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (ethyl acetate: light petroleum; 3:7) gave the *title compound* **204** as a brown oil (21 mg, 48%); (Found $M+Na^+$, 517.1337. $C_{27}H_{21}F_3N_2O_4 + Na^+$ requires 517.1351); ν_{max} ($CHCl_3$)/cm^{-1} 3443, 3012, 1719, 1589, 1522, 1451, 1168; δ_H (400 MHz: $CDCl_3$) 8.09 (1 H, d, *J* 8.1, Ar-H), 7.51-7.33 (8 H, m, Ar-H, NH-18), 7.33-7.28 (3 H, m, Ar-H), 7.26-7.19 (2 H, m, Ar-H), 7.14 (1 H, dt, *J* 7.7, 1.0, Ar-H), 6.49 (1 H, d, *J* 3.4, H-9/10), 6.12 (1 H, d, *J* 3.4, H-9/10), 5.22 (2 H, s, H-20), 4.89 (2 H, s, H-3); δ_C (100 MHz: $CDCl_3$) 157.4 (C, q, *J* 36.0), 153.6 (C), 150.5 (C), 142.9 (C), 135.9 (C), 134.4 (C), 134.3 (C), 129.6 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 124.0 (CH), 121.7 (CH), 117.3 (C), 116.0 (C, q, *J* 288), 109.6 (CH), 109.2 (CH), 67.1 (CH_2), 53.7 (CH_2).

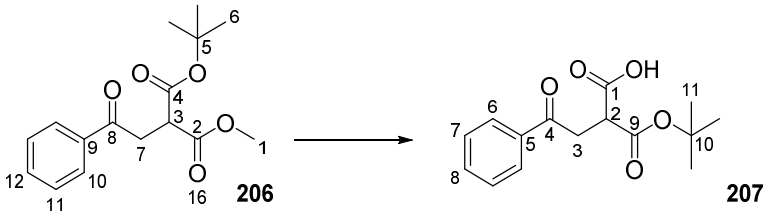
1-*tert*-Butyl 3-methyl 2-(2-oxo-2-phenylethyl) malonate 206



tert-Butyl methyl malonate (2.0 mL, 11.8 mmol) was dissolved in anhydrous DMF (9.60 mL); sodium hydride (303 mg, 12.4 mmol) was added and the solution stirred under argon for 3.75 h. To the stirring solution bromoacetophenone **205** (1.98 g, 10.2 mmol) in anhydrous DMF (7.00 mL) was added dropwise and the resulting yellow solution allowed to stir under argon for 15 h. The reaction mixture was poured into water (30 mL) and acidified to pH 3/4 using 1 M hydrochloric acid. The reaction mixture was extracted with ethyl acetate (2 x 20 mL), the combined organic layers were washed with lithium chloride solution (2 x 10 mL, 5% solution) and brine (20 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and column

chromatography (ethyl acetate: light petroleum; 3:97 to 1:4) gave the *title compound* **206** as a colourless oil (1.78 g, 52 %); (Found M+Na^+, 315.1206. $C_{16}H_{20}O_5$ + Na^+ requires 315.1208); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2983, 2955, 2933, 1744, 1727, 1688, 1450, 1438, 1287, 1257, 1149; δ_H (400 MHz; $CDCl_3$) 7.99 (2 H, d, *J* 7.5, H-10), 7.59 (1 H, t, *J* 7.5, H-12), 7.48 (2 H, t, *J* 7.5, H-11), 4.00 (1 H, t, *J* 7.0, H-3), 3.78 (3 H, s, H-1), 3.59 (2 H, d, *J* 7.0, H-7), 1.48 (9 H, s, H-6); δ_C (100 MHz; $CDCl_3$) 196.9 (C), 167.6 (C), 154.4 (C), 136.4 (C), 133.6 (CH), 128.7 (CH), 128.2 (CH), 80.4 (C), 64.2 (CH), 62.8 (CH_2), 28.3 (CH_3), 13.9 (CH_3).

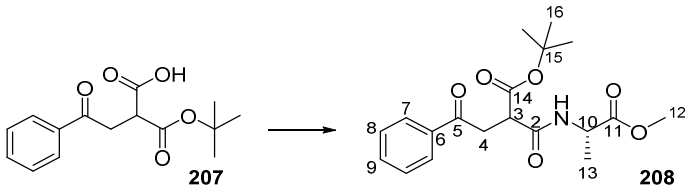
2-(*tert*-Butoxycarbonyl)-4-oxo-4-phenylbutanoic acid 207



1-*tert*-Butyl 3-methyl 2-(2-oxo-2-phenylethyl) malonate **206** (520 mg, 1.80 mmol) was dissolved in THF (16.0 mL) and to the stirring solution water (2.00 mL) was added. Lithium hydroxide monohydrate (215 mg, 5.13 mmol) was added and the reaction mixture heated to 60 °C for 4 h. The reaction mixture was poured into hydrochloric acid (1 M; 10 mL) and extracted with ethyl acetate (3 x 20 mL) before the combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and column chromatography (ethyl acetate: light petroleum; 1:4) gave the *title compound* **207** as a pale yellow oil (423 mg, 84%); (Found M+Na^+, 301.1048. $C_{15}H_{18}O_5$ + Na^+ requires 301.1046); ν_{max} ($CHCl_3$)/cm^{-1} 3660, 3510, 2984, 2935, 1759, 1731, 1688, 1450, 1371, 1246, 1153, 842; δ_H (400 MHz; $CDCl_3$) 8.01 (2 H, dd, *J* 7.3, 1.5, H-6), 7.62 (1H, t, *J* 7.3, H-8), 7.51 (1 H, t, *J* 7.3, H-7), 3.92 (1 H, q, *J* 5.6, H-2), 3.80-3.59 (2 H, m, H-3), 1.50 (9 H, s, H-11); δ_C (100 MHz; $CDCl_3$) 196.7 (C), 172.0 (C), 169.4 (C), 136.0 (C), 133.6 (CH), 128.7 (CH), 128.2 (CH), 88.7 (C), 46.7 (CH), 37.7 (CH_2), 27.8 (CH_3).

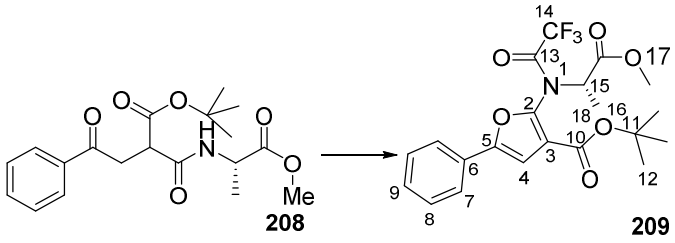
***tert*-Butyl 2-(((1S)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-4-oxo-4-phenylbutanoate**

208



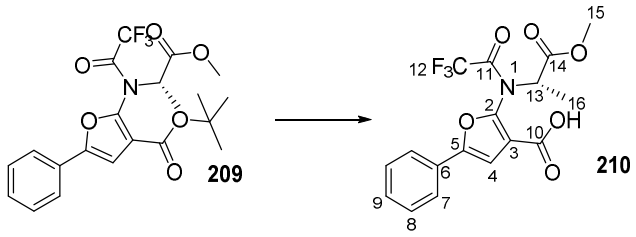
2-(*tert*-Butoxycarbonyl)-4-oxo-4-phenylbutanoic acid **207** (110 mg, 0.40 mmol) was dissolved in DMF (3.50 mmol) and to the stirring solution *L*-alanine methyl ester hydrochloride (75.0 mg, 0.54 mmol), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (204 mg, 0.54 mmol) and *N*,*N*-diisopropylethylamine (0.18 mL, 1.07 mmol) were added. The solution was stirred for 1 h before the reaction mixture was quenched with hydrochloric acid (5 mL, 1 M) and washed with ethyl acetate (3 x 10 mL). The combined organic layers were washed with lithium chloride solution (10 mL, 5%), brine (10 mL) and dried over $MgSO_4$. The volatiles were removed *in vacuo* and column chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **208** as a mixture of diastereoisomers (1:1) yellow oil (115 mg, 79%); $[\alpha]_D^{25}$ 99 (*c* 0.5, $CHCl_3$); (Found M+Na^+, 386.1588. $C_{19}H_{25}NO_6$ + Na^+ requires 386.1580); ν_{max} ($CHCl_3$)/cm^{-1} 3671, 3413, 3011, 2983, 2957, 2953, 1737, 1682, 1518, 1450, 1396, 1150; δ_H (400 MHz; $CDCl_3$) 7.99 (2 H, dt, *J* 7.5, 1.3, H-7), 7.55 (1 H, tt, *J* 7.5, 1.3, H-9), 7.45 (2 H, t, *J* 7.5, H-8), 7.17 (0.5 H, br d, *J* 7.4, NH), 7.12 (0.5 H, br d, *J* 7.4, NH), 4.61-4.52 (1 H, m, H-3), 3.95-3.86 (1 H, m, H-10), 3.74 (3 H, s, H-12), 3.71-3.51 (2 H, m, H-4), 1.46 (4.5 H, s, H-16), 1.44 (4.5 H, s, H-16), 1.42 (1.5 H, s, H-13), 1.40 (1.5 H, s, H-13); δ_C (100 MHz; $CDCl_3$) 197.6 (C), 197.5 (C), 191.6 (C), 173.1 (C), 173.0 (C), 168.8 (C), 168.6 (C), 136.4 (C), 136.3 (C), 133.3 (CH), 128.6 (CH), 128.1 (CH), 82.8 (C), 82.6 (C), 52.5 (CH_3), 52.3 (CH_3), 48.5 (CH), 48.4 (CH), 48.4 (CH), 48.3 (CH), 37.0 (CH_2), 36.9 (CH_2), 27.9 (CH_3), 27.8 (CH_3), 18.3 (CH_3), 18.2 (CH_3).

(1S)-*tert*-Butyl 5-phenyl-2-(2,2,2-trifluro-N-(1-methoxy-1-oxopropan-2-yl)acetamido) furan-3-carboxylate 209



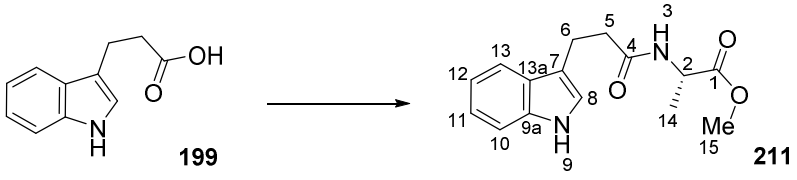
tert-Butyl 2-(((1S)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-4-oxo-4-phenylbutanoate **208** (269 mg, 0.70 mmol) was dissolved in anhydrous dichloromethane (7 mL) and the solution was cooled to – 50 °C. Anhydrous pyridine (0.56 mL, 7.01 mmol) and anhydrous trifluoroacetic anhydride (0.42 mL, 1.46 mmol) were added to the solution which was stirred for 16 h under argon. The reaction mixture was quenched with water and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$ before the solvent was removed *in vacuo*. Purification by column chromatography (ethyl acetate: light petroleum; 1:3) gave the *title compound* **209** as a colourless oil (90 mg, 28%); $[\alpha]_D^{24}$ 54.6 (*c* 1.10, $CHCl_3$); (Found M+Na^+, 464.1280. $C_{21}H_{22}F_3NO_6$ + Na^+ requires 464.1297); ν_{max} ($CHCl_3$)/cm^{-1}; 2983, 2928, 2856, 1715, 1624, 1560, 1455, 1426, 1395, 1371, 1252, 1192, 1167, 909; δ_H (400 MHz; $CDCl_3$) 7.68 (2 H, d, *J* 7.3, H-7), 7.45 (2 H, t, *J* 7.3, H-8), 7.38 (1 H, t, *J* 7.3, H-9), 7.00 (1 H, s, H-4), 5.05 (1 H, s br, H-15), 3.86 (3 H, s, H-17), 1.55 (9 H, s, H-12), 1.40 (3 H, s br, H-18); δ_C (100 MHz; $CDCl_3$) 160.5 (C), 157.8 (C, q, *J* 38.0), 152.3 (C), 129.5 (C), 128.9 (CH), 128.9 (CH), 128.7 (C), 128.5 (C), 128.1 (C), 124.2 (CH), 116.0 (C, q, *J* 268), 105.9 (CH), 82.5 (C), 52.8 (CH_3), 28.0 (CH_3), 27.3 (CH), 13.8 (CH_3).

(S)-5-Phenyl-2-(2,2,2-trifluoro-*N*-(1-methoxy-1-oxopropan-2-yl) acetamido) furan-3-carboxylic acid 210



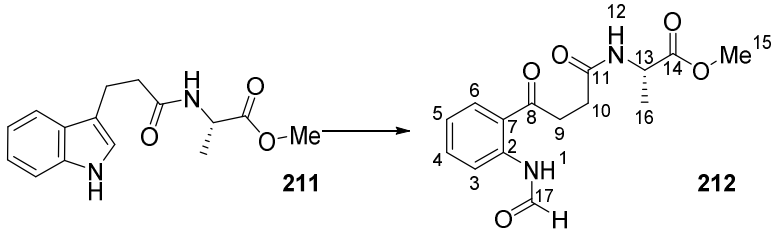
(S)-*tert*-Butyl 5-phenyl-2-(2,2,2-trifluro-N-(1-methoxy-1-oxopropan-2-yl)acetamido) furan-3-carboxylate **209** (40.0 mg, 0.09 mmol) was dissolved in dichloromethane (0.90 mL) and trifluoroacetic acid (0.50 mL) was added to the stirring solution. The solution was stirred for 2 h at room temperature before being quenched with water (5 mL), extracted with dichloromethane (3 x 5 mL) and the organic phases washed with brine (10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **210** as a colourless gum (20 mg, 57 %); $[\alpha]_D^{23}$ 57.6 (*c* 0.6, $CHCl_3$); (Found M+Na^+, 408.0673. $C_{17}H_{14}F_3NO_6$ + Na^+ requires 408.0665); ν_{max} ($CHCl_3$)/cm^{-1} 3030, 1743, 1687, 1450, 1242, 1222, 1214, 1202; δ_H (400 MHz; $CDCl_3$) 7.70 (2 H, d, *J* 7.4, H-7), 7.47 (2H, t, *J* 7.4, H-8), 7.41 (1 H, t, *J* 7.4, H-9), 7.06 (1 H, s, H-4), 5.09 (1H, s br, H-13), 3.87 (3 H, s, H-15), 1.45 (3 H, s br, H-16); δ_C (100 MHz; $CDCl_3$) 170.2 (C), 166.0 (C), 157.8 (C, q, *J* 38.0), 152.9 (C), 144.2 (C), 129.2 (CH), 129.0 (CH), 128.5 (C), 124.3 (CH), 116.9 (C, q, *J* 268), 114.0 (C), 105.6 (CH), 52.9 (CH_3), 29.7 (CH), 13.9 (CH_3).

(S)-Methyl 2-(3-(1*H*-indol-3-yl)propanamido) propanoate 211



Indolepropanoic acid **199** (1.00 g, 5.30 mmol) was dissolved in DMF (49.0 mL) at room temperature; *L*-alanine methyl ester hydrochloride (1.11 g, 7.90 mmol), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (3.00 g, 15.9 mmol) and *N*,*N*-diisopropylethylamine (2.82 mL, 7.90 mmol) were added and the solution stirred at room temperature for 1 h. The reaction mixture was quenched with hydrochloric acid (1 M: 30 mL), extracted with ethyl acetate (3 x 30 mL) and the combined organic layers washed with lithium chloride solution (50 mL, 5%) and brine (50 mL) before being dried over $MgSO_4$. The solvent was removed *in vacuo* and column chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **211** as a cream foam (1.30 g, 90%); $[\alpha]_D^{25}$2.77 (*c* 0.20, $CHCl_3$); (Found M+Na^+, 297.1202. $C_{15}H_{18}N_2O_3$ + Na^+ requires 297.1215); ν_{max} ($CHCl_3$)/cm^{-1} 3673, 3481, 3432, 3011, 2956, 1740, 1670, 1510, 1455, 1338, 1240, 1168, 909; δ_H (400 MHz; $CDCl_3$) 8.40 (1H, br s, NH-9), 7.58 (1 H, d, *J* 7.8, H-10), 7.34 (1 H, d, *J* 7.8, H-13), 7.17 (1 H, dd, *J* 7.8, 7.8, H-11/12), 7.10 (1 H, dd, *J* 7.8, 7.8, H-11/12), 6.97 (1 H, s, H-8), 6.20 (1H, br s, NH-3), 4.55 (1 H, q, *J* 7.2, H-2), 3.69 (3 H, s, H-15), 3.10 (2 H, t, *J* 7.5, H-6), 2.60 (2 H, t, *J* 7.5, H-5), 1.29 (3 H, d, *J* 7.2, H-14); δ_C (100 MHz; $CDCl_3$) 173.4, (C), 172.7 (C), 136.2 (C), 127.0 (C), 121.82 (CH), 121.79 (CH), 119.1 (CH), 118.5 (CH), 114.4 (C), 111.2 (CH), 52.3 (CH_3), 48.0 (CH), 36.9 (CH_2), 21.0 (CH_2), 18.1 (CH_3).

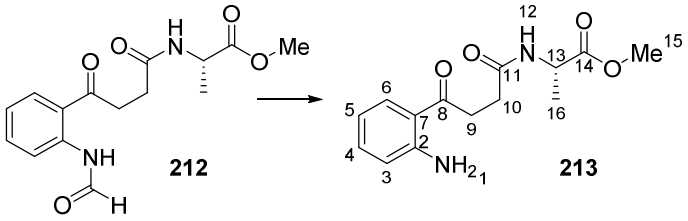
(S)-Methyl 2-(4-(2-formamidophenyl)-4-oxobutanamido)propanoate 212



(S)-Methyl 2-(3-(1*H*-indol-3-yl)propanamido) propanoate **211** (1.38 mg, 5.30 mmol) was dissolved in dichloromethane (53.0 mL) and the solution cooled to -50 °C. To the stirring solution *m*-chloroperoxybenzoic acid (77%; 4.50 g, 21.2 mmol) was added and the reaction stirred at -50 °C for 2 h, before being warmed to room temperature over 30 min. The reaction

mixture was quenched with sodium thiosulfate solution (10%; 20 mL) and saturated sodium hydrogen carbonate solution (20 mL) was added. The mixture was washed with dichloromethane (3 x 30 mL) and the combined organic layers washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum: 1:1) gave the *title compound* **212** as colourless powder (469 mg, 29%); mp 123-124 °C; $[\alpha]_D^{25}$ 5.26 (*c* 0.20, $CHCl_3$); (Found M+Na^+, 329.1096. $C_{15}H_{18}N_2O_5$ + Na^+ requires 329.1113); ν_{max} ($CHCl_3$)/cm^{-1} 3432, 3260, 3008, 2957, 1739, 1662, 1605, 1584, 1517, 1434, 1302, 1240, 1116, 923; δ_H (400 MHz; $CDCl_3$) 11.47 (1 H, s br, H-17), 8.74 (1 H, d, *J* 8.0, H-3), 8.49 (1 H, s, NH-1), 8.00 (1 H, d, *J* 8.0, H-6), 7.57 (1 H, t, *J* 8.0, H-5), 7.18 (1 H, t, *J* 8.0, H-4), 6.26 (1 H, d br, *J* 6.7, NH-12), 4.61 (1 H, app quin, *J* 7.3, H-13), 3.76 (3 H, s, H-15), 3.52-3.35 (2 H, m, H-9), 2.67 (2 H, t, *J* 6.3, H-10), 1.44 (3 H, d, *J* 7.2, H-16); δ_C (100 MHz; $CDCl_3$) 201.9 (C), 173.5 (C), 171.1 (C), 159.8 (CH), 139.7 (C), 135.1 (CH), 130.7 (CH), 123.2 (CH), 121.7 (C), 121.6 (CH), 52.5 (CH_3), 48.1 (CH), 34.9 (CH_2), 29.8 (CH_2), 18.5 (CH_3).

(S)-Methyl 2-(4-(2-aminophenyl)-4 oxobutanamido) propanoate 213

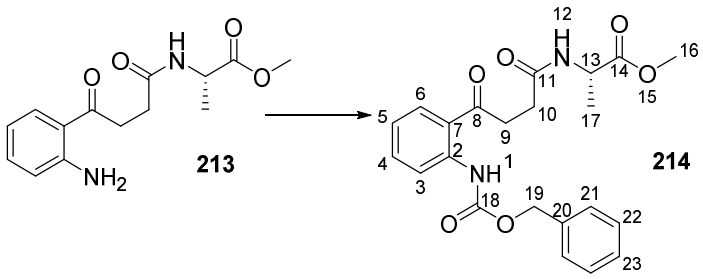


(S)-Methyl 2-(4-(2-formamidophenyl)-4-oxobutanamido)propanoate **212** (100 mg, 0.33 mmol) was dissolved in methanol (16.0 mL) and 1,4 dioxane (5.00 mL) was added to the solution. Hydrochloric acid (2.00 mL; 3 M) was added with stirring and the mixture was stirred at room temperature for 1.2 h. The mixture was poured into saturated sodium hydrogen carbonate solution (20 mL) and the mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with brine (20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* to give the *title compound* **213** (65 mg, 71%) as yellow crystals; mp 85-86 °C; $[\alpha]_D^{25}$ 37.7 (*c* 0.14, $CHCl_3$); ν_{max} (ATR)/cm^{-1}

3467, 3354, 3293, 2987, 1743, 1653, 1639, 1613, 1551, 1488, 1450, 1383, 1204,, 1181, 1147, 943, 763; (Found M+Na^+, 301.1140. $C_{14}H_{18}N_2O_4$ + Na^+ requires 301.1164); δ_H (400 MHz; $CDCl_3$) 7.79 (1 H, dd, *J* 8.0, 1.5, H-6), 7.27 (1 H, dt, *J* 8.0, 1.5, H-5), 6.67-6.63 (2 H, m, H-3, 4), 6.37 (1 H, br d, *J* 6.4, NH-12), 4.60 (1 H, q, *J* 7.4, H-13), 3.75 (3 H, s, H-15), 3.43-3.47 (2 H, m, H-10), 2.64 (2 H, t, *J* 6.7, H-9), 1.42 (3 H, d, *J* 7.4, H-16) ; δ_C (100 MHz; $CDCl_3$) 200.7 (C), 173.6 (C), 171.9 (C), 134.5 (CH), 133.7 (C), 131.0 (CH), 117.8 (C), 117.4 (CH), 116.0 (CH), 52.4 (CH_3), 48.1 (CH), 34.3 (CH_2), 30.4 (CH_2), 18.5 (CH_3).

(S)-Methyl 2-(4-(2-((benzyloxycarbonyl)amino)phenyl-4-oxobutanamido) propanoate

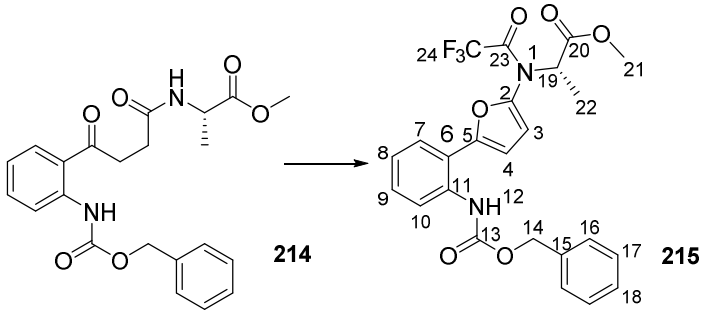
214



(S)-Methyl 2-(4-(2-aminophenyl)-4 oxobutanamido) propanoate **213** (71.0 mg, 0.26 mmol) was dissolved in THF (0.60 mL) and sodium hydrogen carbonate (53.0 mg, 0.56 mmol) was added. The solution was cooled to 0 °C and benzyl chloroformate (0.04 mL, 0.28 mmol) was added. The solution was allowed to warm to room temperature over 2 h. The reaction mixture was diluted with water (5 mL), washed with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with brine (20 mL) before being dried over $MgSO_4$ and the solvent removed *in vacuo* to give an orange oil. Column chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **214** as a pale yellow oil (70 mg, 65%); $[\alpha]_D^{25}$ 7.42 (*c* 0.70, $CHCl_3$); (Found M+Na^+, 435.1523. $C_{22}H_{24}N_2O_6$ + Na^+ requires 435.1532); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 3430, 3265, 3007, 2957, 2929, 1735, 1660, 1585, 1526, 1454, 1375, 1356, 1242, 1167, 1047, 984; δ_H (400 MHz; $CDCl_3$) 11.15 (1 H, s, NH-1), 8.49 (1 H, dd, *J* 8.3, 1.1, H-3,6), 7.96 (1 H, dd, *J* 8.3, 1.1, H-3/6), 7.54 (1 H, td, *J* 8.3, 1.1, H-4/5), 7.46-7.30

(5 H, m, H-21, 22, 23), 7.07 (1 H, td, *J* 8.3, 1.1, H-4/5) 6.23 (1 H, d, *J* 7.1, NH-12), 5.21 (2 H, s, H-19), 4.59 (1 H, quin, *J* 7.1, H-13), 3.74 (3 H, s, H-16), 3.48-3.32 (2 H, m, H-9), 2.63 (2 H, t, *J* 6.5, H-10), 1.42 (3 H, d, *J* 7.1, H-17); δ_C (100 MHz; $CDCl_3$) 202.4 (C), 173.4 (C), 171.3 (C), 153.6 (C), 141.2 (C), 136.3 (C), 135.0 (CH), 130.58 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 121.6 (CH), 121.1 (C), 119.3 (CH), 66.8 (CH_2), 52.4 (CH_3), 48.2 (CH), 34.9 (CH_2), 29.8 (CH_2), 18.4 (CH_3).

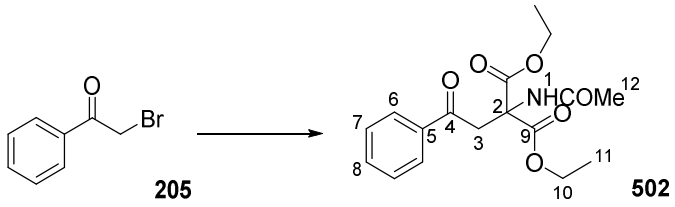
(S)-Methyl 2-(*N*-(5-(2-((benzyloxycarbonyl)amino)phenyl)furan-2-yl)-2,2,2-trifluoroacetamido) propanoate 215



(S)-Methyl 2-(4-(2-(((benzyloxy)carbonyl)amino)phenyl-4-oxobutanamido) propanoate **214** (64 mg, 0.15 mmol) was dissolved in anhydrous dichloromethane (1.50 mL) and cooled to -50 °C under argon. To the stirring solution anhydrous pyridine (0.12 mL, 1.56 mmol) and anhydrous trifluoroacetic anhydride (0.13 mL, 0.46 mmol) were added. The solution was stirred for 16 h under argon before being quenched with water (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo*. Purification by column chromatography (ethyl acetate: light petroleum; 1:5) gave the *title compound* **215** as a colourless oil (11 mg, 15 %); $[\alpha]_D^{25}$ 16.35 (*c* 0.85, $CHCl_3$); (Found M+Na^+, 513.1244. $C_{24}H_{21}F_3N_2O_6$ + Na^+ requires 513.1230); ν_{max} ($CHCl_3$)/cm^{-1}; 3691, 3606, 3442, 3052, 3005, 2957, 2855, 1728, 1603, 1588, 1521, 1450, 1307, 1190, 1167, 1120, 1045, 910; δ_H (400 MHz; $CDCl_3$) 8.11 (1 H, d, *J* 8.0, H-7/10), 7.68 (1 H, s br, NH-12), 7.48 (1 H, dd, *J* 8.0, 1.1, H-

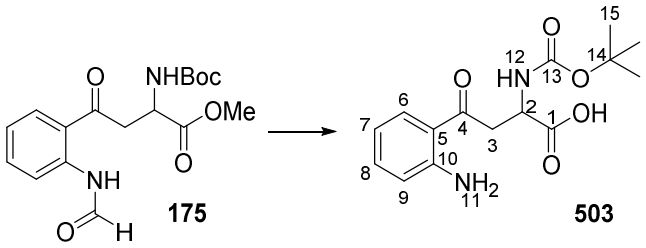
7/10), 7.42-7.30 (6 H, m, H-16, 17, 18, 8/9), 7.15 (1 H, t, *J* 8.0, H-8/9), 6.61 (1 H, d, *J* 3.4, H-3/4), 6.58 (1 H, d, *J* 3.4, H-3/4), 5.21 (2 H, s, H-14), 5.01 (1 H, q, *J* 7.4, H-19), 3.75 (3 H, s, H-21), 1.35 (3 H, d, *J* 7.4, H-22); δ_C (100 MHz; $CDCl_3$) 170.3 (C), 157.7 (C, q, *J* 36.8), 153.5 (C), 151.4 (C), 141.1 (C), 135.9 (C), 134.6 (C), 129.8 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 123.8 (CH), 121.6 (CH), 119.5 (C), 115.7 (C, q, *J* 286.4), 112.0 (CH), 109.7 (CH), 67.1 (CH_2), 56.3 (CH), 52.8 (CH_3), 14.3 (CH_3).

Diethyl 2-acetamido-2-(2-oxo-2-phenylethyl)malonate 502



Diethyl acetamidomalonate (2.03 g, 9.20 mmol) was dissolved in anhydrous DMF (7.60 mL) under an argon atmosphere and sodium hydride (60 % in mineral oil, 320 mg, 13.3 mmol) was added with stirring. The reaction was cooled to 0 °C, stirred for 1 h and bromoacetophenone **205** (1.64 g, 8.28 mmol) in anhydrous DMF (5.71 mL) was added to the solution, which was stirred at room temperature under argon for 16 h. The reaction mixture was poured into hydrochloric acid (3M; 10 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4 to give the crude product as a colourless powder. Column chromatography (light petroleum; ethyl acetate; 1:1) gave the title compound **502** as a colourless powder (1.73 g, 63%); mp 118-120 ° C; (lit., 117-120 °C)[67]; (Found M+Na^+ 358.1270. $C_{17}H_{21}NO_6$ + Na^+ requires 358.1261); ν_{max} ($CHCl_3$)/cm^{-1} 3415, 3011, 2939, 1743, 1685, 1599, 1581, 1497, 1449, 1301, 1239; δ_H (400 MHz; $CDCl_3$) 7.98-7.94 (2 H, d, *J* 7.6, H-6), 7.59 (1 H, t, *J* 7.6, H-8), 7.46 (2H, t, *J* 7.6, H-7), 7.14 (1 H, br s, NH-1), 4.30-4.23 (6 H, m, H-3, 10), 1.98 (3 H, s, H-12), 1.24 (6 H, t, *J* 7.1, H-11); δ_C (100 MHz, $CDCl_3$) 196.9 (C), 169.5 (C), 167.3 (C), 136.0 (C), 133.7 (CH), 128.7 (CH), 128.2 (CH), 64.0 (C), 62.9 (CH_2), 42.3 (CH_2), 22.9 (CH_3), 14.0 (CH_3). Data matches literature.[238]

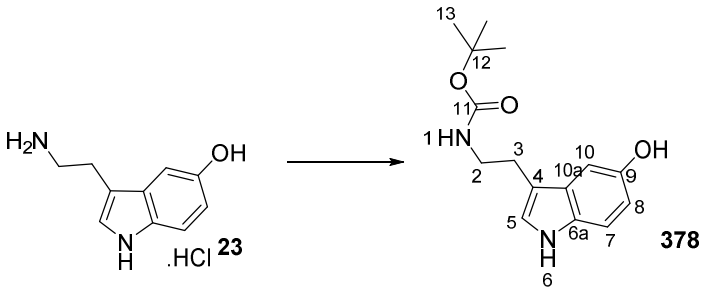
4-(2-Aminophenyl)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoic acid 503



Methyl 4-(2-aminophenyl)-2-((tert-butoxycarbonyl)amino)-4-oxobutanoate **175** (80.0 mg, 0.23 mmol) was dissolved in a 1:1 mixture of THF and water (3.80 mL), lithium hydroxide monohydrate (31.6 mg, 0.64 mmol) was added to the solution. The solution was heated at 70 °C for 4 h before being poured into hydrochloric acid (1 M; 3 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed the brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to give a yellow oil. Column chromatography (light petroleum: ethyl acetate; 1:1) yielded the *title compound* **503** as a yellow oil (66,0 mg, 93 %); (Found M+Na^+ 331.1285. $C_{15}H_{20}N_2O_5$ + Na^+ requires 331.1270); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3009, 2981, 1701, 1644, 1616, 1697, 1392, 1163; δ_H (400 MHz; $CDCl_3$) 7.77 (1 H, d, *J* 7.7, H-6), 7.26 (1 H, t, *J* 7.7, H-8), 6.65 (1 H, t, *J* 7.7, H-7), 6.62 (1 H, d, *J* 7.7, H-9), 6.48 (2 H, s br, H-11), 5.77 (1H, d, *J* 7.4, H-12), 4.42 (1H, br t, H-2), 3.71 (1H, dd, *J* 17.2, 4.3, H-3a), 3.47 (1H, dd, *J* 17.2, 4.3, H-3b), 1.45 (9H, s, H-15); δ_C (100 MHz; $CDCl_3$) 201.3 (C), 150.4 (C), 134.6 (CH), 131.4 (CH), 128.6 (C), 120.9 (C), 117.9 (C), 117.3 (CH), 116.0 (CH), 79.5 (C), 51.8 (CH), 43.6 (CH_2), 28.4 (CH_3).

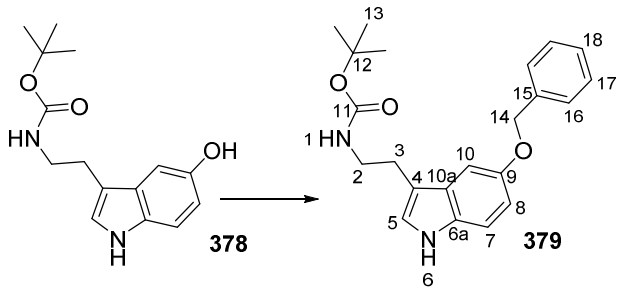
4.3 Compounds discussed in Chapter 3:

***tert*-Butyl (2-(5-hydroxy-1*H*-indol-3-yl)ethyl)carbamate 378**



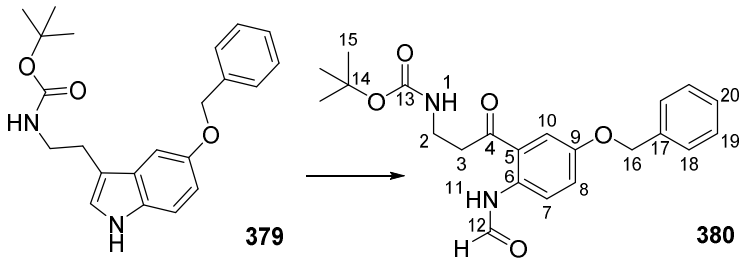
Serotonin hydrochloride **23** (4.00 g, 18.7 mmol) was suspended in dichloromethane (37.0 mL) and to the stirring mixture sodium chloride (4.01 g, 68.9 mmol), sodium hydrogen carbonate (3.14 g, 37.4 mmol) and water (9.00 mL) were added. Di-*tert*-butyl dicarbonate (4.13 g, 18.7 mmol) was added to the stirring mixture which was heated at 90 °C for 7 h. The solution was poured into water (30 mL) and extracted with dichloromethane (3 x 30 mL) before the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography (ethyl acetate; light petroleum: 1:1) gave the *title compound* **378** as a colourless foam (4.73 g, 92 %); (Found M+Na^+, 299.1348. $C_{15}H_{20}N_2O_3 + Na^+$ requires 299.1372); ν_{max} ($CHCl_3$)/cm^{-1} 3604, 3481, 3011, 2981, 2935, 1707, 1515, 1488, 1367, 1170, 909; δ_H (400 MHz; $CDCl_3$) 8.08 (1 H, br s, NH-6), 7.21 (1 H, d, *J* 8.4, H-7), 7.03 (1 H, d, *J* 2.3, H-10), 6.95 (1 H, s, H-5), 6.81 (1 H, dd, *J* 8.4, 2.3, H-8), 5.95 (1 H, br s, OH), 4.72 (1 H, br s, NH-1), 3.51-3.22 (2 H, m, H-2), 2.85 (2 H, t, *J* 6.1, H-3), 1.45 (9 H, s, H-13); δ_C (100 MHz; $CDCl_3$) 156.2 (C), 149.7 (C), 131.5 (C), 128.0 (C), 123.1 (CH), 112.2 (C), 112.0 (CH), 111.8 (CH), 103.3 (CH), 79.4 (C), 40.7 (CH_2), 28.4 (CH_3), 25.8 (CH_2).

tert-Butyl (2-(5-benzyloxy-1*H*-indol-3-yl)ethyl)carbamate 379



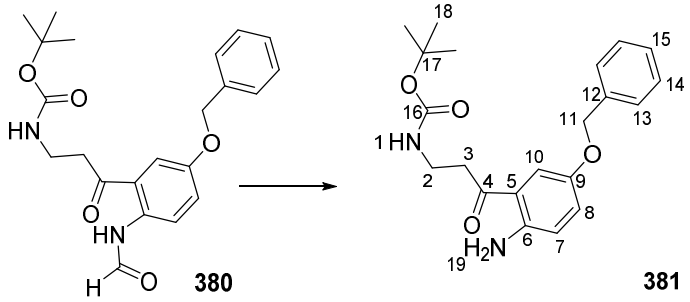
tert-Butyl (2-(5-hydroxy-1*H*-indol-3-yl)ethyl)carbamate **378** (5.16 g, 18.7 mmol) was dissolved in acetone (62 mL) and potassium hydroxide (1.25 g, 22.4 mmol) was added. Benzyl bromide (1.90 mL, 20.6 mmol) was added and the solution was heated at 60 °C for 4 h. The solution was diluted with hydrochloric acid (1 M; 60 mL) and extracted with ethyl acetate (3 x 100 mL) and washed with brine (100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (light petroleum; ethyl acetate: 4:1 then 1:1) gave the *title compound* **379** as a colourless solid (5.11 g, 75 %); mp: 125-126 °C; (Found: C, 72.08; H, 7.12; N, 7.63. $C_{22}H_{26}N_2O_3$ requires C, 72.11; H, 7.15; N, 7.64%); (Found M+Na^+, 389.1840. $C_{22}H_{26}N_2O_3$ + Na^+ requires 389.1841); ν_{max} ($CHCl_3$)/cm^{-1} 3841, 3009, 2981, 2934, 1706, 1504, 1482, 1367, 1170; δ_H (400 MHz; $CDCl_3$) 8.10 (1 H, s, NH-6), 7.50 (2 H, d, *J* 7.3, H-16), 7.41 (2 H, t, *J* 7.3, H-17), 7.34 (1 H, t, *J* 7.3, H-18), 7.26 (1H, d, *J* 8.7, H-7), 7.15 (1 H, d, *J* 2.3, H-10), 7.00 (1 H, br s, H-5), 6.96 (1 H, dd, *J* 8.7, 2.3, H-8), 5.15 (2 H, s, H-14), 4.67 (1 H, s br, NH-1), 3.57-3.37 (2 H, m, H-2), 2.92 (2 H, t, *J* 6.7, H-3), 1.46 (9 H, s, H-13); δ_C (100 MHz; $CDCl_3$) 156.0 (C), 153.2 (C), 137.6 (C), 131.7 (C), 128.5 (CH), 127.76 (CH), 127.73 (C), 127.61 (CH), 127.56 (C), 122.9 (CH), 112.9 (CH), 111.8 (CH), 102.4 (CH), 79.2 (C), 71.1 (CH_2), 30.9 (CH_2), 28.4 (CH_3), 25.8 (CH_2).

tert-Butyl (3-(5-(benzyloxy)-2-formamidophenyl)-3-oxopropyl)carbamate 380



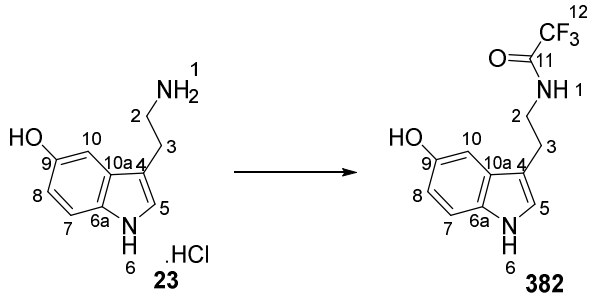
tert-Butyl (2-(5-(benzyloxy)-1*H*-indol-3-yl)ethyl)carbamate **379** (1.90 g, 5.25 mmol) was dissolved in dichloromethane (52.0 mL) and the solution cooled to -50 °C. To the stirring solution *m*-chloroperoxybenzoic acid (77%, 4.72 g, 21.0 mmol) was added and the solution stirred at -50 °C for 2 h. The solution was quenched with sodium thiosulfate solution (10%, 50 mL) and sodium hydrogen carbonate (30 mL) and warmed to room temperature before being extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum: 1:2) gave the *title compound* **380** as a cream solid (673 mg, 41%); mp 157-159 °C; (Found M+Na^+, 421.1741. $C_{22}H_{26}N_2O_5$ + Na^+ requires 421.1739); ν_{max} ($CHCl_3$)/cm^{-1} 3461, 3011, 2982, 1695, 1660, 1520, 1258, 1240, 1182; δ_H (400 MHz; $CDCl_3$) 11.30 (1 H, br s, H-12), 8.70 (1 H, d, *J* 9.2, H-7), 8.46 (1 H, d, *J* 1.9, NH-11), 7.51-7.35 (6 H, m, H-10, 18, 19, 20), 7.23 (1 H, dd, *J* 9.2, 3.0, H-8), 5.12 (2 H, s, H-16), 5.10-4.89 (1 H, m, NH-1), 3.60-3.49 (2 H, m, H-3), 3.26-3.18 (2 H, m, H-2), 1.46 (9 H, s, H-15); δ_C (100 MHz; $CDCl_3$) 203.3 (C), 159.4 (CH), 155.8 (C), 153.9 (C), 136.2 (C), 133.5 (C), 128.7 (CH), 128.3 (CH), 127.5 (CH), 123.1 (CH), 122.7 (C), 121.6 (CH), 116.9 (CH), 79.5 (C), 70.6 (CH_2), 40.1 (CH_2), 35.5 (CH_2), 28.4 (CH_3).

tert-Butyl (3-(2-amino-5-(benzoxy)phenyl)-3-oxopropyl)carbamate 381



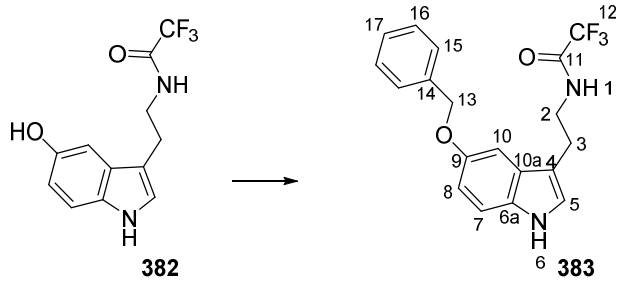
tert-Butyl (3-(5-(benzyloxy)-2-formamidophenyl)-3-oxopropyl)carbamate **380** (100 mg, 0.25 mmol) was suspended in methanol (12.0 mL) and 1,4-dioxane (3.00 mL) was added. Hydrochloric acid (3 M; 1.50 mL) was added and the solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated sodium hydrogen carbonate solution (10 mL) and extracted with ethyl acetate (3 x 10 mL) before being dried over $MgSO_4$ and the solvent removed *in vacuo* to give the *title compound* **381** as a yellow oil which was used without further purification (88.0 mg, 93 %); (Found $M+H^+$, 371.1978. $C_{21}H_{26}N_2O_4 + H^+$ requires 371.1971); ν_{max} ($CHCl_3$)/cm^{-1} 3460, 3360, 2982, 2933, 1705, 1650, 1553, 1503, 1240, 1168; δ_H (400 MHz; $CDCl_3$) 7.47-7.36 (4 H, m, H-13, 14), 7.33 (1 H, tt, *J* 6.9, 2.6, H-15), 7.25 (1 H, d, *J* 2.7, H-10), 7.05 (1 H, dd, *J* 9.0, 2.7, H-8), 6.63 (1 H, d, *J* 9.0, H-7), 6.00 (2 H, s, br, NH-19), 5.19-5.10 (1 H, m, NH-1), 5.02 (2 H, s, H-11), 3.56-3.48 (2 H, m, H-2), 3.10 (2 H, t, *J* 5.6, H-3), 1.44 (9 H, s, H-18); δ_C (100 MHz; $CDCl_3$) 200.8 (C), 155.9 (C), 149.7 (C), 145.3 (C), 137.0 (C), 128.6 (CH), 128.0 (CH), 127.5 (CH), 124.65 (CH), 118.7 (CH), 117.5 (C), 115.2 (CH), 79.2 (C), 71.2 (CH_2), 39.3 (CH_2), 35.6 (CH_2), 28.4 (CH_3).

2,2,2-Trifluoro-N-(2-(5-hydroxy-1H-indol-3-yl)ethyl)acetamide 382



Serotonin hydrochloride **23** (5.00 g, 23.5 mmol) was added to dichloromethane (78.0 mL) and to the stirring suspension methanol (20.0 mL), triethylamine (20.0 mL) and ethyl trifluoroacetate (3.40 mL, 28.2 mmol) were added. The solution was heated to 60 °C and stirred for 18 h before being acidified to pH 6 and extracted with dichloromethane (3 x 50 mL), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and purification by column chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **382** as a colourless foam (5.95 g, 93%); *m/z* (ESI): (Found $M+Na^+$ 295.0646. $C_{12}H_{11}O_2N_2F_3 + Na^+$ requires 295.0670); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 3480, 3008, 2927, 1724, 1602, 1544, 1488, 1170; δ_H (400 MHz; $CDCl_3$) 7.98 (1 H, s, NH-6), 7.26 (1 H, d, *J* 8.7, H-7), 7.03 (1 H, d, *J* 2.4, H-5), 6.99 (1 H, d, *J* 2.4, H-10), 6.82 (1 H, dd, *J* 8.7, 2.4, H-8), 6.40 (1 H, br s, NH-1) 4.81 (1 H, br s, OH), 3.67 (2 H, app q, *J* 6.7, 6.7, H-2), 3.00 (2 H, t, *J* 6.7, H-3); δ_c (100 MHz; $CDCl_3$) 157.1 (C, q, J 36.8), 149.7 (C), 131.7 (C), 127.7 (C), 123.3 (CH), 115.9 (C, q, *J* 288.1), 112.4 (CH), 112.1 (CH), 111.1 (C), 103.0 (CH), 40.0 (CH_2), 24.8 (CH_2).

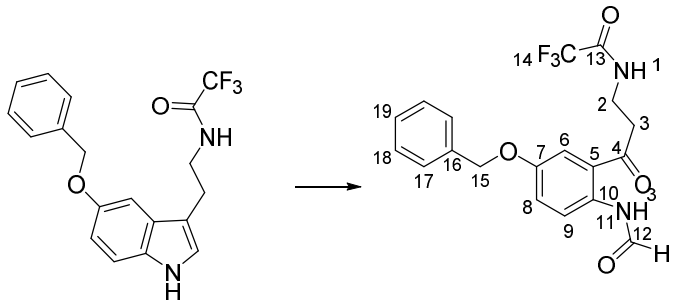
***N-(*2-(5-Benzyloxy-1 H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide 383**



2,2,2-Trifluoro-*N*-(2-(5-hydroxy-1H-indol-3-yl)ethyl)acetamide **382** (5.50 g, 20.2 mmol) was dissolved in acetone (67.0 mL) and to the stirring solution potassium hydroxide (1.35 g, 24.2 mmol) was added. Benzyl bromide (2.63 mL, 22.2 mmol) was added and the solution heated to 60 °C and stirred for 3 h. The reaction mixture was acidified to pH 6 and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (30 mL). The solution was dried over $MgSO_4$ and the solvent removed *in vacuo* and column chromatography

(light petroleum: ethyl acetate; 4:1) gave the *title compound* **383** as a colourless gum (6.50 g, 89%); *m/z* (ESI): (Found M+Na$^+$ 385.1123. $C_{19}H_{17}O_2N_2F_3$ + Na$^+$ requires 385.1134); ν_{max} ($CHCl_3$)/cm^{-1} 3692, 3607, 3480, 3436, 3066, 3008, 2929, 1724, 1602, 1544, 1482, 1171; δ_H (400 MHz; $CDCl_3$) 8.00 (1 H, br s, NH-6), 7.49 (2 H, d, *J* 7.3, H-15), 7.40 (2 H, tt, *J* 7.3, 1.6, H-16), 7.36-7.28 (2 H, m, H-7, 17), 7.12 (2 H, d, *J* 2.3, H-10), 7.04 (2 H, d, *J* 2.3, H-5), 6.99 (1 H, dd, *J* 8.8, 2.3, H-8), 6.34 (1 H, br s, NH-1), 5.12 (2 H, s, H-13), 3.68 (2 H, app q, *J* 6.4, 6.4, H-2), 3.02 (2 H, t, *J* 6.4, H-3); δ_c (100 MHz; $CDCl_3$) 157.1 (C, q, *J* 36.8), 153.4 (C), 137.5 (C), 131.7 (C), 128.5 (CH), 127.8 (CH), 127.6 (CH), 127.3 (C), 123.0 (CH), 115.7 (C, q, *J* 287), 113.4 (CH), 112.1 (CH), 111.5 (C), 101.9 (CH), 70.8 (CH_2), 39.9 (CH_2), 24.7 (CH_2).

***N*-(3-(5-(Benzyloxy)-2-formamidophenyl)-3-oxopropyl)-2,2,2-trifluoroacetamide 384**

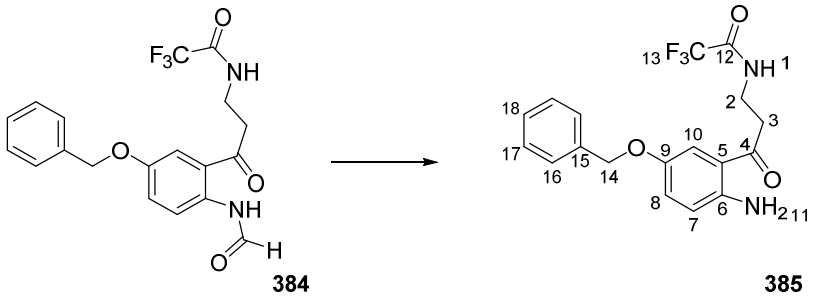


383 **384**

N-(2-(5-(Benzyloxy)-1 H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **383** (1.00 g, 2.76 mmol) was dissolved in anhydrous dichloromethane (27.0 mL) and the stirring solution cooled to -50 °C. To the cooled solution *m*-chloroperoxybenzoic acid (77%; 1.76 g, 8.30 mmol) was added and the solution was stirred for 2.5 h whilst warming to room temperature. Sodium thiosulfate solution (10%; 45 mL) was added to the reaction mixture before the addition of sodium hydrogen carbonate solution (45 mL, saturated). The reaction mixture was extracted with dichloromethane (3 x 30 mL) and the combined organic layers washed with brine (50 mL) before the combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (light petroleum: ethyl acetate; 3:7) gave the *title compound* **384** as a colourless powder (320 mg, 30%); mp: 151-152 °C; (Found: C, 57.76; H, 4.46; N, 6.90.

$C_{19}H_{17}O_4N_2F_3$ requires C, 57.87; H, 4.35; N, 7.10%); (Found M+Na^+ 417.1030. $C_{19}H_{17}O_4N_2F_3$ + Na^+ requires 417.1033); ν_{max} ($CHCl_3$)/cm^{-1} 3438, 3005, 2967, 2880, 1728, 1698, 1568, 1522, 1181; δ_H (400 MHz; $CDCl_3$) 11.11 (1 H, s br, H-12), 8.69 (1 H, d, *J* 9.2, H-9), 8.46 (1 H, d, *J* 1.7, NH-11), 7.46-7.33 (6 H, m, H-6, 17, 18, 19), 7.39-7.20 (1 H, m, H-8), 7.04 (1 H, br s, NH-1), 5.11 (2 H, s, H-15), 3.77 (2 H, app q, *J* 5.6, 5.6, H-2), 3.30 (2 H, t, *J* 5.6, H-3); δ_c (100 MHz; $CDCl_3$) 202.5 (C), 159.5 (CH), 156.9 (C, q, *J* 37.6), 154.0 (C), 136.1 (C), 133.6 (C), 128.7 (CH), 128.4 (CH), 127.5 (CH), 123.4 (CH), 122.2 (C), 122.2 (CH), 116.9 (CH), 115.7 (C, q, *J* 288), 70.7 (CH_2), 38.6 (CH_2), 34.7 (CH_2).

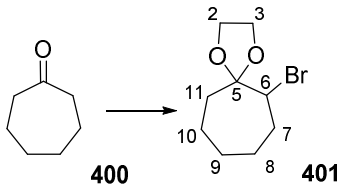
***N*-(3-(2-Amino-5-(benzyloxy)phenyl)-3-oxopropyl)-2,2,2-trifluoroacetamide 385**



N-(3-(5-(Benzyloxy)-2-formamidophenyl)-3-oxopropyl)-2,2,2-trifluoroacetamide **384** (100 mg, 0.25 mmol) was dissolved in methanol (12.0 mL) and 1,4-dioxane (1.60 mL) and to the stirring solution hydrochloric acid (3 M, 1.60 mL) was added and the solution was stirred for 2 h. The reaction was diluted with saturated sodium hydrogen carbonate (20 mL) and extracted with ethyl acetate (3 x 20 mL) and the combined organic layers washed with brine (10 mL). The solution was dried over $MgSO_4$ and the solvent removed *in vacuo* to give the *title compound* **385** as a yellow solid which was used without further purification (85 mg, 93%); mp 134-135 °C; (Found: C, 59.0; H, 4.5; N, 7.5. $C_{18}H_{17}F_3N_2O_3$ requires C, 59.0; H, 4.7; N, 7.7 %); (Found M+Na^+ 389.1083. $C_{18}H_{17}F_3N_2O_3$ + Na^+ requires 389.1089); ν_{max} ($CHCl_3$)/cm^{-1} 3432, 3361, 3011, 1723, 1649, 1172; δ_H (400 MHz; $CDCl_3$) 7.46-7.37 (4 H, m, H-16, 17), 7.37-7.31 (1 H, m, H-18), 7.23 (1 H, br s, NH-1), 7.16 (1 H, d, *J* 2.9, H-10), 7.07 (1 H, dd, *J*

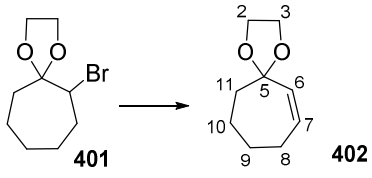
9.0, 2.9, H-8), 6.65 (1 H, d, *J* 9.0, H-7), 6.06 (2 H, s br, NH-11), 5.01 (2 H, s, H-14), 3.74 (2 H, app q, *J* 5.7, 5.7, H-2), 3.17 (2 H, t, *J* 5.6, H-3); δ_c (100 MHz; $CDCl_3$) 199.9 (C), 157.1 (C, q, *J* 36.6), 149.1 (C), 145.6 (C), 136.9 (C), 128.6 (CH), 128.1 (CH), 127.5 (CH), 125.3 (CH), 118.8 (CH), 116.8 (C), 115.8 (C, q, *J* 288), 114.8 (CH), 71.2 (CH_2), 37.6 (CH_2), 34.9 (CH_2).

6-Bromo-1,4-dioxaspiro[4.6]undecane 401



Cycloheptanone **400** (2.10 mL, 17.8 mmol) was dissolved in ethane-1,2-diol (24.0 mL) at 20 °C and to the stirring solution bromine (0.90 mL, 35.6 mmol) was added. The solution was stirred at room temperature for 1 h. The solution was poured into saturated sodium thiosulfate solution (50 mL), extracted with pentane (3 x 50 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo*. Column chromatography (light petroleum) gave the *title compound* **401** as a colourless oil (2.53 g, 61%); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2938, 2891, 2867, 1457, 1239, 1176, 1101, 1081, 1043, 950; δ_H (400 MHz; $CDCl_3$) 4.25 (1 H, ddd, *J* 8.6, 2.7, 0.8, H-6), 4.14-4.06 (2 H, m, H-2/3), 4.0.-3.93 (2 H, m, H-2/3), 2.30-2.20 (1 H, m, H-7), 2.15-2.00 (2 H, m, H-7/11), 1.92-1.52 (7 H, m, H-8, 9, 10, 11); δ_C (100 MHz; $CDCl_3$) 111.0 (C), 65.5 (CH_2), 65.0 (CH_2), 60.7 (CH), 35.0 (CH_2), 32.8 (CH_2), 26.0 (CH_2), 24.7 (CH_2), 20.5 (CH_2). Data consistent with literature.[239]

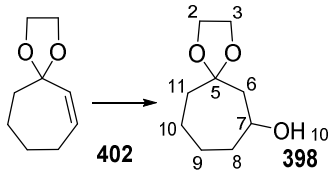
1,4-Dioxaspiro[4.6]undec-6-ene 402



Potassium *t*-butoxide (11.51 g, 94.2 mmol) was dissolved in anhydrous DMSO (62.8 mL) and stirred for 30 min at 40 °C. To the stirring solution 6-bromo-1,4-dioxaspiro[4.6]undecane

(14.7 g, 64.8 mmol), **401** was added and the solution stirred for 4 h at 20 °C. The reaction mixture was poured into water (100 mL) before being extracted with light petroleum (3 x 50 mL). The combined organic layers were washed with water (3 x 50 mL) and brine (100 mL) before being dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 5:95) gave the *title compound* **402** as a colourless oil (4.97 g, 50 %); ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2937, 2886, 1147, 1110, 1061; δ_H (400 MHz; $CDCl_3$) 5.90 (1 H, dt, *J* 11.8, 5.9, H-7), 5.66 (1 H, br d, *J* 11.8, H-6), 4.02-3.92 (4 H, m, H-2,3), 2.26-2.17 (2 H, m, H-11), 1.91 -1.85 (2 H, m, H-8), 1.84-1.76 (2 H, m, H-10), 1.71-1.63 (2 H, m, H-9); δ_C (100 MHz; $CDCl_3$) 171.2 (C), 133.8 (CH), 133.7 (CH), 64.3 (CH_2), 64.3 (CH_2), 36.0 (CH_2), 27.7 (CH_2), 26.8 (CH_2), 23.6 (CH_2). Data consistent with literature.[181]

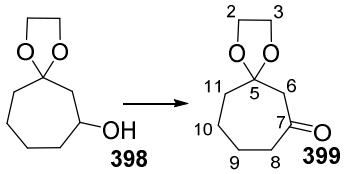
1,4-Dioxaspiro[4.6]undec-7-ol 398



1,4-Dioxaspiro[4.6]undec-6-ene **402** (4.97 g, 31.3 mmol) was added to a suspension of mercuric acetate (9.95 g, 31.3 mmol) in THF (15.0 mL) and water (15.0 mL) at room temperature and the reaction mixture was stirred at room temperature for 3 h. The solution was cooled to 0 °C and sodium hydroxide solution (10 %; 30.0 mL) was added. Sodium borohydride (591 mg, 15.63 mmol) was added and the suspension stirred for 30 min. The solution was extracted with ethyl acetate (3 x 30 mL), the combined organic layers washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to give a pale yellow oil **398** which was used without further purification (3.50 g, 65%); (Found M+Na^+, 195.0993. $C_9H_{16}O_3$ + Na^+ requires 195.0997); ν_{max} ($CHCl_3$)/cm^{-1} 3610, 3495, 3008, 2936, 1697, 1603, 1456, 1369, 1240, 1083, 1027, 947; δ_H (400 MHz; $CDCl_3$) 4.02-3.90 (5 H, m, H-2, 3, 7), 2.10-

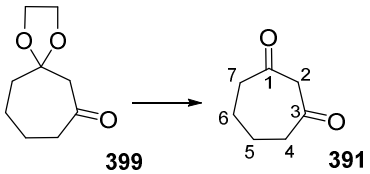
1.47 (10 H, m, H-6, 8, 9, 10, 11); δ_C (100 MHz; $CDCl_3$) 110.9 (C), 68.0 (CH), 64.2 (CH_2), 64.0 (CH_2), 46.0 (CH_2), 38.6 (CH_2), 35.6 (CH_2), 24.0 (CH_2), 22.8 (CH_2).

1,4-Dioxaspiro[4.6]undec-7-one 399



Pyridine (19.6 mL, 244 mmol) was added to a flask containing dichloromethane (220 mL), celite (15.0 g) and chromium trioxide (12.7 g, 121 mmol) and the solution stirred at 0 °C for 15 min. 1,4-Dioxaspiro[4.6]undec-7-ol **398** (3.50 g, 20.3 mmol) was dissolved in dichloromethane (7 mL) and this was added to the pyridine mixture. The mixture was stirred at 0 °C for 45 min before being filtered through celite and $MgSO_4$. The filter pad was washed with ether (200 mL) and the filtrate combined before the solvent was removed *in vacuo*. Column chromatography (ethyl acetate; light petroleum: 1:1) gave the title compound **399** as a pale yellow oil (447 mg, 13%); (Found M+Na^+, 193.0851. $C_9H_{14}O_3Na$ requires 193.0841); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2942, 2891, 1698, 1282, 1240, 1083, 1017, 948; δ_H (400 MHz; $CDCl_3$) 4.03-3.93 (4 H, m, H-2,3), 2.90 (2 H, s, H-6), 2.53 (2 H, t, *J* 6.5, H-8), 1.98-1.93 (2 H, m, H-11), 1.88-1.76 (4 H, m, H-9, 10); δ_C (100 MHz; $CDCl_3$) 209.2 (C), 107.4 (C), 64.5 (CH_2), 55.2 (CH_2), 43.6 (CH_2), 40.5 (CH_2), 24.5 (CH_2), 23.6 (CH_2).

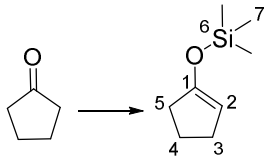
Cycloheptane-1,3-dione 391



1,4-Dioxaspiro[4.6]undec-7-one **399** (443 mg, 2.5 mmol) was dissolved in hydrochloric acid (6 M; 3.00 mL) and the solution was stirred at room temperature for 3 h. The reaction mixture was poured into water (5 mL) and extracted with chloroform (3 x 10 mL). The combined

organic layers were washed with water (20 mL) and brine (20 mL) before being dried over $MgSO_4$. The solvent was removed *in vacuo* to give a pale yellow oil **391** which was used without further purification (120 mg, 41%); (Found M+Na^+, 149.0565. $C_7H_{10}O_2$ + Na^+ requires 149.0578); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2945, 2868, 1722, 1698; δ_H (400 MHz; $CDCl_3$) 3.59 (2 H, s, H-2), 2.61-2.54 (4 H, m, H-4, 7), 2.03-1.94 (4 H, m, H-5, 6); δ_C (100 MHz; $CDCl_3$) 204.7 (C), 59.7 (CH_2), 44.1 (CH_2), 24.9 (CH_2). Data consistent with literature.[181]

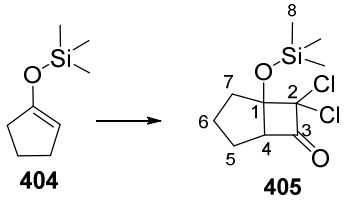
1-(Trimethylsiloxy)cyclopentene 404



403 **404**

Cyclopentanone **403** (1.00 g, 11.9 mmol) was dissolved in anhydrous DMF (5.00 mL) under an atmosphere of argon. Triethylamine (3.70 mL, 28.6 mmol) was added to the solution before trimethylsilyl chloride (1.80 mL, 14.3 mmol) was added dropwise. The reaction was heated to 90 °C for 3 h and stirred at room temperature for 18 h. The reaction mixture was diluted with water (60 mL) and extracted with light petroleum (3 x 30 mL) and the combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the title compound **404** as an orange oil which was used without further purification (1.46 g, 79%); ν_{max} ($CHCl_3$)/cm^{-1} 3632, 3009, 2944, 2839, 1334. 1240, 1016; δ_H (400 MHz: $CDCl_3$) 4.65-4.61 (1 H, m, H-2), 2.32-2.23 (4 H, m, H-3, 5), 1.90-1.81 (2 H, m, H-4); δ_c (100 MHz; $CDCl_3$) 155.0 (C), 102.1 (CH), 33.5 (CH_2), 28.7 (CH_2), 21.3 (CH_2), 0.0 (CH_3).

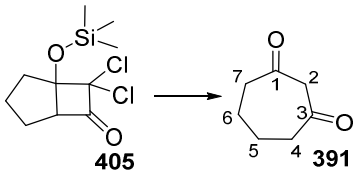
7,7-Dichloro-1-(trimethylsiloxy)bicyclo[3.2.0]heptan-6-one 405



404 **405**

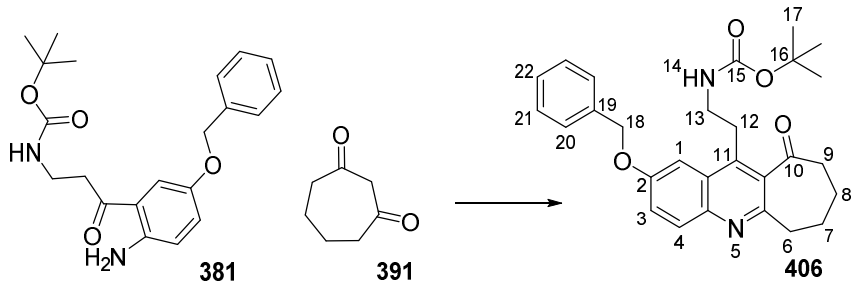
1-(Trimethylsiloxy)cyclopentene **404** (1.06 g, 6.79 mmol) was dissolved in hexane (10.0 mL). Triethylamine (1.10 mL, 8.14 mmol) was added to the solution followed by dropwise addition of dichloroacetyl chloride (0.65 mL, 6.79 mmol) in hexane (5.00 mL). The solution was stirred overnight and the resulting brown suspension was removed by filtration before the solvent was removed *in vacuo.* The resulting brown oil was purified by column chromatography (ethyl acetate: light petroleum; 1:9) to give the title compound **405** as a yellow oil (900 mg, 50 %); (Found M+Na^+, 289.0194. $C_{10}H_{16}O_2{}^{35}Cl_2Si + Na^+$ requires 289.0188); ν_{max} ($CHCl_3$)/cm^{-1} 2966, 2254, 1802, 1324, 1255, 1105, 909; δ_H (400 MHz: $CDCl_3$) 3.68-3.64 (1 H, m, H-4), 2.58-2.50 (1 H, m, H-7a), 2.11-1.84 (4 H, m, H-7b, 5, 6), 1.64-1.49 (1 H, m, H-5), 0.25 (9 H, s, H-8); δ_c (100 MHz: $CDCl_3$) 199.2 (C), 92.8 (C), 87.7 (C), 67.8 (CH), 38.1 (CH_2), 29.1 (CH_2), 26.2 (CH_2), 1.57 (CH_3). Data consistant with literature.[182]

Cyclohepta-1,3-dione 391



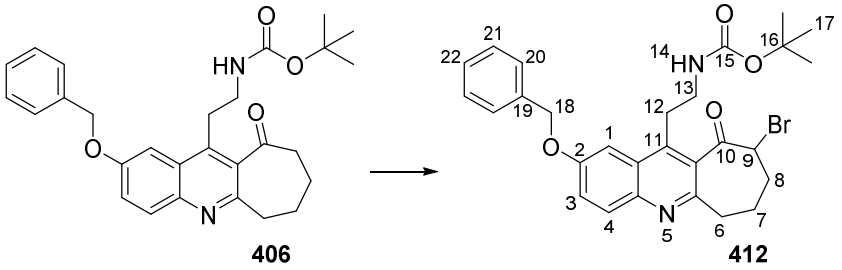
7,7-Dichloro-1-(trimethylsiloxy)bicyclo[3.2.0]heptan-6-one **405** (900 mg, 3.38 mmol) was dissolved in 2-propanol (2.00 mL) and water (2.00 mL) under an atmosphere of argon. Zinc powder (890 mg, 13.6 mmol) was added and the solution stirred at room temperature for 1 h. A solution of acetic acid (1.00 mL) in water (2.00 mL) was added dropwise over 10 min. The solution was stirred for 20 h before being the liquid was decanted and the zinc washed with acetic acid (20 mL) and combined, before the mixture was extracted with toluene (5 x 10 mL) and concentrated to give a brown oil. Purification by column chromatography (ethyl acetate: light petroleum; 3:7) gave the title compound **391** as a colourless oil (330 mg, 77 %). Data consistent with that obtained from Bhushan route.[181]

tert-Butyl (2-(2-(benzyloxy)-10-oxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)carbamate 406



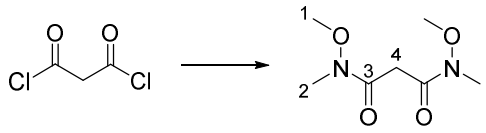
Cycloheptane-1,3-dione **391** (50.0 mg, 0.40 mmol) was dissolved in ethanol (2.00 mL) and added to *tert*-butyl (3-(2-amino-5-(benzoxy)phenyl)-3-oxopropyl)carbamate **381** (73.0 mg, 0.20 mmol). Iodine (7.00 mg, 0.05 mmol) was added and the solution was stirred at 20 °C for 24 h. The solution was poured into water (5 mL) and extracted with ethyl acetate (3 x 10 mL) before being washed with brine and dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography (light petroleum: ethyl acetate; 1:1) gave the *title compound* **406** as a cream powder (59 mg, 64 %), crystals suitable for X-ray crystallography were grown from a saturated solution of the *title compound* in hot ethanol; mp 144-146 °C; (Found $M+H^+$, 461.1422. $C_{28}H_{32}N_2O_4 + H^+$ requires 461.2440); ν_{max} ($CHCl_3$)/cm^{-1}; 3461, 3006, 2977, 1708, 1687, 1619, 1573, 1503, 1248, 1163; δ_H (400 MHz; $CDCl_3$) 7.97 (1 H, d, *J* 9.1, H-4), 7.83 (1H, br s, H-1), 7.55 (2 H, d, *J* 7.4, H-20), 7.47 (1 H, dd, *J* 9.1, 2.6, H-3), 7.41 (2 H, t, *J* 7.4, H-21), 7.34 (1 H, t, *J* 7.4, H-22), 5.35 (2 H, s, H-18), 5.20-5.13 (1 H, m, NH-14), 3.52-3.42 (2 H, m, H-13) , 3.17-3.05 (4 H, m, H-12, 9), 2.78-2.70 (2 H, m, H-6/7), 2.03-1.94 (2 H, m, H-6/7), 1.88-1.80 (2 H, m, H-8), 1.45 (9 H, s, H-17); δ_C (100 MHz; $CDCl_3$) 209.6 (C), 157.1 (C), 156.1 (C), 154.2 (C), 143.9 (C), 141.5 (C), 136.9 (C), 133.9 (C), 130.2 (CH), 128.0 (CH), 128.6 (CH), 127.6 (CH), 127.0 (C), 123.8 (CH), 104.6 (CH), 79.3 (C), 70.4 (CH_2), 42.8 (CH_2), 41.2 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 28.4 (CH_3), 24.9 (CH_2), 23.0 (CH_2).

tert-Butyl (2-(2-(benzyloxy)-9-bromo-10-oxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[b]quinolin-11-yl)ethyl)carbamate 412



Bromine (0.20 mL, 0.40 mmol) was dissolved in chloroform (5.00 mL) and 0.50 mL of this solution was added to *tert*-butyl (2-(2-(benzyloxy)-10-oxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)carbamate **406** (20.0 mg, 0.04 mmol) and the solution was stirred at room temperature for 4 h. The reaction mixture was poured into saturated sodium thiosulfate solution (3 mL) and extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine before being dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (ethyl acetate: light petroleum; 1:4) gave the *title compound* **412** as a brown oil (7.20 mg, 32%); (Found $M+H^+$, 541.1523. $C_{28}H_{32}O_4N_2{}^{79}Br + H^+$ requires 540.1525); ν_{max} ($CHCl_3$)/cm^{-1} 2928, 2856, 1724, 1718, 1466; δ_H (400 MHz; $CDCl_3$) 8.01-7.93 (2 H, m, H-1, 4), 7.61-7.47 (2 H, m, H-20), 7.45-7.31 (4 H, m, H-3, 21, 22), 5.41 (2 H, s, H-18), 5.06 (1 H, br s, NH-14), 4.84-4.79 (1 H, m, H-9), 3.62-3.12 (5 H, m, H-12, 13, 8a), 3.04-2.94 (2 H, m, H-6/7), 2.51-2.40 (1 H, m, H-8b), 2.34-2.14 (2 H, m, H-6/7), 1.46 (9 H, s, H-17); δ_C (100 MHz; $CDCl_3$) 202.7 (C), 157.5 (C), 156.2 (C), 152.5 (C), 136.9 (C), 131.9 (C), 130.6 (CH), 131.0 (C), 128.7 (C), 128.5 (CH), 127.9 (CH), 127.6 (CH), 126.8 (C), 124.0 (CH), 104.4 (CH), 79.4 (C), 70.4 (CH_2), 59.9 (CH), 41.3 (CH_2), 37.0 (CH_2), 35.0 (CH_2), 31.0 (CH_2), 28.4 (CH_3), 22.7 (CH_2).

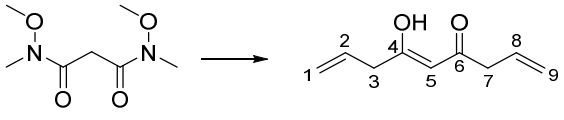
_N_, _N_-Dimethoxy-_N_, _N_-dimethylmalonamide 414



413 **414**

_N,O_-Dimethylhydroxylamine hydrochloride **413** (2.76 g, 28.4 mmol) was dissolved in dichloromethane (150 mL) and the solution cooled to 0 °C. Triethylamine (3.60 mL, 28.4 mmol) was added to the solution at 0 °C before malonyl dichloride (2.00 mL, 14.0 mmol) was added and the solution stirred at 0 °C for 1 h. The solution was quenched with hydrochloric acid (1 M; 30 mL) and extracted with dichloromethane (3 x 100 mL) before being washed with brine (100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed in *vacuo*. Column chromatography (light petroleum: ethyl acetate; 1:1) gave the *title compound* **414** as a yellow oil (1.36 g, 51%); *m/z* (ESI): (Found $M+Na^+$ 213.0853. $C_7H_{14}N_2O_4 + Na^+$ requires 213.0846); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3009, 2941, 1653, 1463, 1421, 1387, 1008; δ_H (400 MHz; $CDCl_3$) 3.72 (6 H, s, H-1), 3.64 (2 H, s, H-4), 3.22 (6 H, s, H-2); δ_c (100 MHz; $CDCl_3$) 168.3 (C), 61.2 (CH_3), 38.3 (CH_2), 32.2 (CH_3).

6-Hydroxynona-1,5,8-trien-4-one 416

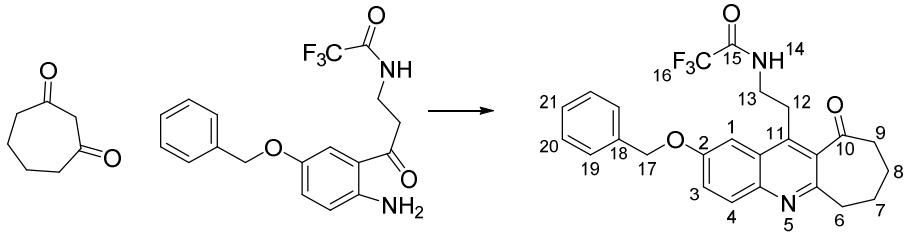


414 **416**

Allylmagnesium bromide (1.0 M in Et_2O, 1.16 mL, 1.16 mmol) was dissolved in THF (1.25 mL) and the solution cooled to 0 °C. _N_, _N_-dimethoxy-_N_, _N_-dimethylmalonamide **414** (100 mg, 0.52 mmol) was dissolved in THF (1.45 mL) and the solution stirred at 0 °C for 1 h. The reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (2 x 20 mL) and the combined organic layers washed with brine. The solution was dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum: 1:1) gave the *title compound* **416** as a light brown oil (20.0 mg, 11%);

m/z (ESI): (Found M+Na$^+$ 175.0728. $C_9H_{12}O_2$ + Na$^+$ requires 175.0730); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 2928, 2855, 1602, 1188, 994, 965, 924, 909; δ_H (400 MHz; $CDCl_3$) 15.27 (1 H, s, OH), 5.96-5.83 (2 H, m, H-2, 8), 5.54 (1 H, s, H-5), 5.28-5.13 (4 H, m, H-1, 9), 3.08 (4 H, m, H-3, 7); δ_c (100 MHz; $CDCl_3$) 192.1 (C), 171.0 (C), 131.1 (CH), 131.1 (CH), 119.0 (CH_2), 98.7 (CH), 65.8 (CH_2), 60.4 (CH_2), 43.0 (CH_2).

***N*-(2-(2-Benzyloxy-10-oxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 422**

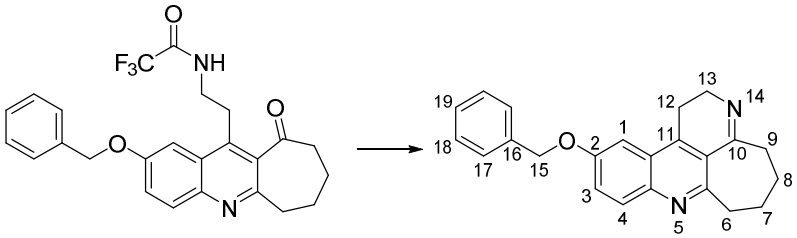


391 **385** **422**

To *N*-(3-(2-Amino-5-(benzyloxy)phenyl)-3-oxopropyl)-2,2,2-trifluoroacetamide **385** (126 mg, 0.30 mmol) cycloheptane-1,3-dione **391** (76.0 mg, 0.60 mmol) in ethanol (0.50 mL) was added. To the stirring solution trifluoroacetic acid (0.01 mL 0.15 mmol) was added and the solution heated to 70 °C for 0.5 h. The solution was quenched with saturated sodium hydrogen carbonate solution (2 mL) and extracted with ethyl acetate (3 x 5 mL) before being dried over $MgSO_4$. The solvent was removed *in vacuo* to give a brown foam which was purified by column chromatography (light petroleum: ethyl acetate; 3:7) to give the *title compound* **422** as a cream powder (119 mg, 87%); mp 142-144 °C; (Found C, 66.2; H, 5.08, N, 6.13; $C_{25}H_{23}F_3N_2O_3$ requires C, 65.78, H, 5.08, N, 6.14); (Found M+H$^+$ 457.1753. $C_{25}H_{23}F_3N_2O_3$ + H$^+$ requires 457.1739); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3275, 2947, 1720, 1678, 1620, 1602, 1562, 1503, 1455, 1455, 1168, 1025; δ_H (400 MHz; $CDCl_3$) 8.38 (1 H, s br, NH-14), 8.02 (1 H, d, *J* 8.8, H-4), 7.56-7.49 (3 H, m, H-3, H-19), 7.46-7.34 (4 H, m, H-1, H-21, H-20), 5.28 (2 H, s, H-17), 3.70 (2 H, m, H-13), 3.18 (2 H, t, *J* 6.4, H-12), 3.12 (2 H, t, *J* 6.5, H-9), 2.79 (2 H, t, *J* 6.0, H-9), 2.07-1.97 (2 H, m, H-7), 1.90-1.81 (2 H, m, H-6); δ_c (100 MHz; $CDCl_3$) 211.6

(C), 157.7 (C, q, *J* 37.5), 157.4 (C), 154.4 (C), 144.2 (C), 140.3 (C), 136.3 (C), 133.7 (C), 131.4 (CH), 128.8 (CH), 128.3 (CH), 127.6 (CH), 126.3 (C), 123.5 (CH), 115.7 (C, q, *J* 287.4), 104.1 (CH), 70.5 (CH_2), 42.6 (CH_2), 39.9 (CH_2), 35.9 (CH_2), 27.6 (CH_2), 24.8 (CH_2), 22.5 (CH_2).

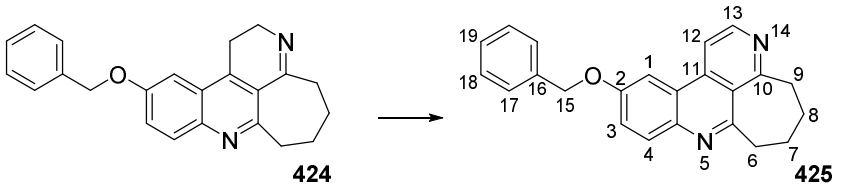
11-Benzyloxy-1,2,4,5,6,7-hexahydrobenzo[*c*]cyclohept[*ij*]naphthyridine 424



422 **424**

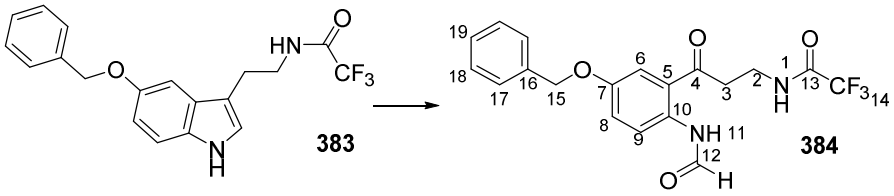
N-(2-(2-Benzyloxy-10-oxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **422** (72.0 mg, 0.15 mmol) was dissolved in methanol (0.30 mL) and to the stirring solution aqueous sodium hydroxide (40%, 0.17 mL) was added. The solution was stirred for 3 h before being neutralised to pH 7 with hydrochloric acid (1 M). The reaction mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (light petroleum: ethyl acetate; 1:1 then ethyl acetate) gave the *title compound* **424** as a colourless powder (30 mg, 58%); mp 134-136 °C; (Found $M+H^+$ 343.1792. $C_{23}H_{22}N_2O + H^+$ requires 343.1810); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2948, 2872, 1560, 1499, 1240; δ_H (400 MHz; $CDCl_3$) 7.96 (1 H, d, *J* 9.0, H-4), 7.55-7.47 (3 H, m, H-3, H-17), 7.46-7.40 (2 H, m, H-18), 7.37 (1 H, tt, *J* 7.1, 4, H-19), 7.28 (1 H, d, *J* 2.7, H-1), 5.22 (2 H, s, H-15), 3.79 (2 H, t, *J* 7.6, H-13), 3.32-3.25 (2 H, m, H-6), 3.04 (2 H, t, *J* 7.6, H-12), 2.96 (2 H, t, *J* 5.9, H-9), 2.04-1.96 (2 H, m, H-7), 1.96-1.87 (2 H, m, H-8); δ_c (100 MHz; $CDCl_3$) 173.2 (C), 157.8 (C), 157.2 (C), 145.4 (C), 144.1 (C), 136.0 (C), 130.9 (CH), 128.7 (CH), 128.3 (CH), 127.5 (CH), 124.8 (CH), 124.7 (C), 121.6 (C), 103.3 (CH), 70.4 (CH_2), 43.1 (CH_2), 36.2 (CH_2), 34.8 (CH_2), 28.1 (CH_2), 23.2 (CH_2), 22.1 (CH_2).

11- Benzyloxy-4,5,6,7-tetrahydrobenzo[*c*]cyclohepta[*ij*][2,7]naphthyridine 425



11-Benzyloxy-1,2,4,5,6,7-hexahydrobenzo[*c*]cyclohept[*ij*]naphthyridine **424** was left as a solution in deuterated chloroform for seven days at room temperature, resulting in a 26% conversion to the *title compound* **425**; mp 134-136 °C; (Found $M+H^+$, 341.1649. $C_{23}H_{20}N_2O$ + H^+ requires 341. 1648); ν_{max} ($CHCl_3$)/cm^{-1}; 3040, 3030, 3021, 2948, 1618, 1593, 1561, 1477, 1232, 1215, 1194; δ_H (400 MHz; $CDCl_3$) 8.72 (1 H, d, *J* 5.8, H-13), 8.13 (1 H, d, *J* 5.8, H-12), 8.05 (1 H, d, *J* 9.0, H-4), 7.91 (1 H, d, *J* 2.8, H-1), 7.57-7.51 (3 H, m, H-3, 17), 7.46 (2 H, t, *J* 7.3, H-18), 7.39 (1 H, t, *J* 7.3, H-19), 5.30 (2 H, s, H-15), 3.60-3.46 (4 H, m, H-6, 9), 2.18-2.07 (4 H, m, H-7, 8); δ_C (100 MHz; $CDCl_3$) 164.7 (C), 160.7 (C), 157.3 (C), 146.4 (CH), 139.9 (C), 138.9 (C), 136.5 (C), 130.7 (CH), 128.8 (CH), 128.3 (CH), 127.6 (CH), 122.8 (C), 121.5 (C), 121.1 (CH), 113.8 (CH), 104.8 (CH), 70.6 (CH_2), 40.6 (CH_2), 37.8 (CH_2), 24.4 (CH_2), 23.8 (CH_2).

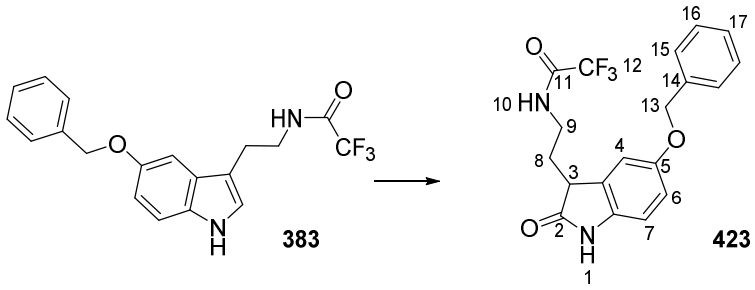
***N*-(3-(5-Benzyloxy-2-formamidophenyl)-3-oxopropyl)-2,2,2-trifluoroacetamide 384**



N-(2-(5-Benzyloxy-1*H*-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **383** (1.49 g, 4.25 mmol) was dissolved in methanol (43.0 mL) and water (43.0 mL) was added. To the stirring suspension sodium periodate (3.73 g, 17.4 mmol) was added and the reaction mixture stirred at room temperature for 28 h. The reaction mixture was poured into saturated sodium hydrogen carbonate solution (30 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo.* Column chromatography (ethyl acetate: light petroleum; 3:7)

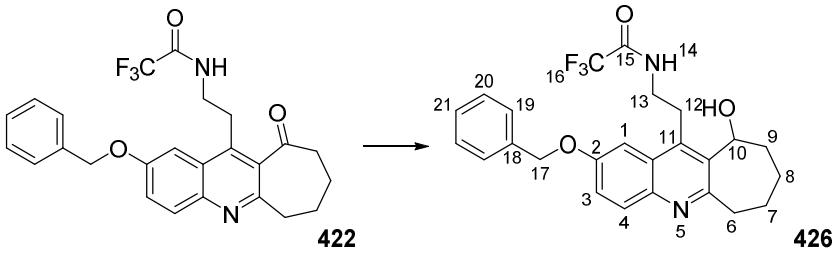
gave the *title compound* **384** as a colourless powder (1.03 g, 60 %); data consistent with previous route to **384**.

N-(2-(5-Benzyloxy-2-oxoindolin-3-yl)ethyl)-2,2,2-trifluoroacetamide 423



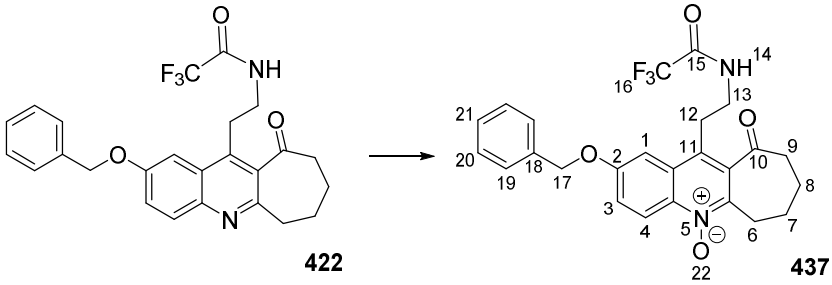
DMSO (12 mg, 0.15 mmol) was dissolved in concentrated hydrochloric acid (0.14 mL) and to the stirring solution phenol (3.10 mg, 0.03 mmol) was added and the solution stirred for 5 min. *N*-(2-(5-Benzyloxy-1*H*-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **383** (49.0 mg, 0.14 mmol) in acetic acid (0.80 mL) was added to give a dark green solution which was stirred at room temperature for 5 h before the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (2 mL), poured into water (5 mL) and neutralised with 1 M hydrochloric acid before being extracted with ethyl acetate (3 x 5 mL) and the combined organic layers washed with brine (10 mL) and dried over $MgSO_4$. Column chromatography (ethyl acetate: light petroleum; 1:1) gave the product **423** as a colourless powder (15 mg, 27%); m.p 166-168 °C; (Found: M+Na^+, 401.1077. $C_{19}H_{17}F_3N_2O_3$ + Na^+ requires 401.1089); ν_{max} ($CHCl_3$)/cm^{-1} 3437, 3011, 1719, 1603, 1490, 1454, 1189; δ_H (400 MHz: $CDCl_3$) 8.55 (1 H, br s, NH-1), 8.31 (1 H, br s, NH-10), 7.57-7.31 (5 H, m, H-15, 16, 17), 6.94 (1 H, br s, H-4), 6.87 (1 H, dd, *J* 12.0, 4.0, H-6), 6.82 (1 H, d, *J* 12.0, H-7), 5.05 (2 H, s, H-13), 3.84-3.72 (1 H, m, H-3), 3.57-3.44 (2 H, m, H-9), 2.40-2.30 (1 H, m, H-8a), 2.11-1.96 (1 H, m, H-8b); δ_C (100 MHz: $CDCl_3$) 180.5 (C), 157.4 (C, q, *J* 37.6), 155.4 (C), 136.7 (C), 134.3 (C), 129.9 (C), 128.6 (CH), 128.1 (CH), 127.5 (CH), 115.8 (C, q, *J* 288.4), 114.3 (CH), 112.2 (CH), 110.5 (CH), 70.7 (CH_2), 45.7 (CH), 38.5 (CH_2), 29.0 (CH_2).

_N_-(2-(2-Benzyloxy-10-hydroxy-7,8,9,10-tetrahydro-6_H_-cyclohepta[b]quinolin-11-yl)ethyl-2,2,2-trifluoroacetamide 426



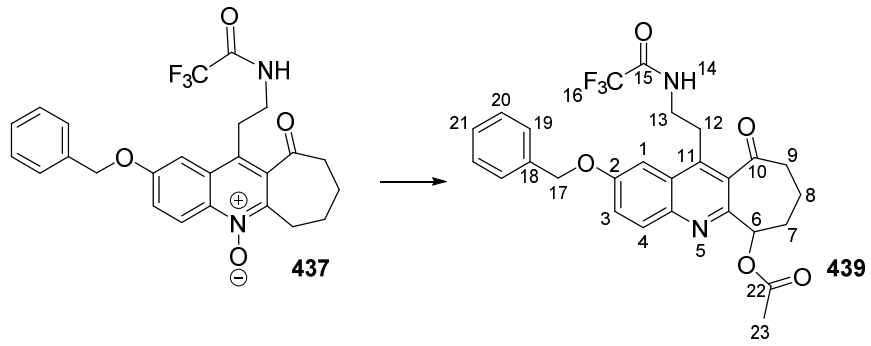
_N_-(2-(2-Benzyloxy)-10-oxo-7,8,9,10-tetrahydro-6_H_-cyclohepta[_b_]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **422** (100 mg, 0.21 mmol) was dissolved in anhydrous methanol (1.40 mL) under an atmosphere of argon and the solution cooled to 0 °C. To the stirring solution sodium borohydride (16.0 mg, 0.42 mmol) was added and the solution was allowed to warm to room temperature over 2 h. The reaction mixture was quenched with hydrochloric acid (1 M, 2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and purification by column chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **426** as a colourless solid (63 mg, 65%); mp 85-86 °C; (Found M+H^+, 459.1897. $C_{25}H_{25}F_3N_2O_3$ + H^+ requires 459.1896); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 3039, 3011, 2934, 2934, 1723, 1620, 1505, 1232, 1188; δ_H (400 MH; $CDCl_3$) 7.91 (1 H, d, *J* 10.0, H-4), 7.51 (2 H, d, *J* 8.5, H-19), 7.45-7.39 (3 H, m, H-3, 20), 7.36-7.33 (2 H, m, H-1, 21), 6.91 (1 H, br s, NH-14), 5.53 (1 H, br d, *J* 6.4, H-10), 5.28 (2 H, s, H-17), 3.58 (2 H, br t, J 11.4, H-13) 3.51-3.30 (3 H, m, H-6, 12a), 3.14 (1 H, dd, *J* 13.6, 6.7, H-12b), 2.41-2.28 (1 H, m, H-9a), 2.27-2.12 (1 H, m, 7a), 2.12-2.02 (1 H, m, 8a), 1.87-1.52 (3 H, m, H-7b, 9b, 8b); δ_C (100 MHz; $CDCl_3$) 161.0 (C), 157.8 (C, q, J 36.9), 157.0 (C), 142.1 (C), 139.0 (C), 136.8 (C), 134.3 (C), 130.7 (CH), 128.6 (CH), 128.0 (CH), 127.5 (CH), 126.7 (C), 121.7 (CH), 115.8 (C, q, J 287.6), 103.9 (CH), 70.3 (CH_2), 68.0 (CH), 39.9 (CH_2), 39.1 (CH_2), 34.0 (CH_2), 26.9 (CH_2), 26.6 (CH_2), 24.2 (CH_2).

2-Benzyloxy-10-oxo-11-(2-(2,2,2-trifluoroacetamido)ethyl)-7,8,9,10-tetrahydro-6*H*-cyclohepta[b]quinolone-5-oxide 437



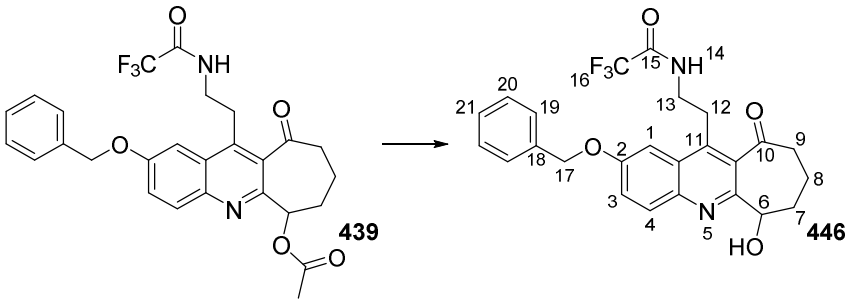
N-(2-(2-Benzyloxy-10-oxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **422** (800 mg, 1.73 mmol) was dissolved in dichloromethane (17.3 mL) and *m*-chloroperoxybenzoic acid (77%; 535 mg, 2.60 mmol) was added to the stirring solution. The solution was stirred at 50 °C for 18 h before being poured into saturated sodium hydrogen carbonate solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the *title compound* **437** as an orange foam which was used without further purification (810 mg, quantitative); (Found: $M+H^+$, 473.1712. $C_{25}H_{23}F_3N_2O_4 + H^+$ requires 473.1688); ν_{max} ($CHCl_3$)/cm^{-1} 3649, 3440, 3011, 2952, 1721, 1687, 1616, 1559, 1448, 1383, 1299, 1172; δ_H (400 MHz; $CDCl_3$) 8.73 (1 H, d, *J* 9.4, H-4), 7.88 (1 H, br s, NH-14), 7.66 (1 H, d, *J* 2.4, H-1), 7.61 (1 H, dd, *J* 9.4, 2.4, H-3), 7.55-7.48 (2 H, m, H-19), 7.46-7.34 (3 H, m, H-20, 21), 5.33 (2 H, s, H-17), 3.69 (2 H, m, H-13), 3.48 (2 H, t, *J* 6.3, H-6), 3.18 (2 H, t, *J* 7.1, H-12), 2.79 (2 H, dd, *J* 6.4, 6.2, H-9), 2.07-1.97 (2 H, m, H-7), 1.93-1.84 (2 H, m, H-8); δ_C (100 MHz; $CDCl_3$) 206.6 (C), 159.2 (C), 157.9 (C, q, *J* 37.7), 145.1 (C), 136.5 (C), 135.7 (C), 134.9 (C), 129.4 (C), 128.8 (CH), 128.7 (C), 128.5 (CH), 127.6 (CH), 125.5 (CH), 122.1 (CH), 115.6 (C, q, *J* 287.5), 105.3 (CH), 70.8 (CH_2), 42.1 (CH_2), 40.2 (CH_2), 28.2 (CH_2), 26.2 (CH_2), 22.8 (CH_2), 22.5 (CH_2).

2-Benzyloxy-10-oxo-11-(2-(2,2,2-trifluoroacetamido)ethyl)-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-6-yl acetate 439



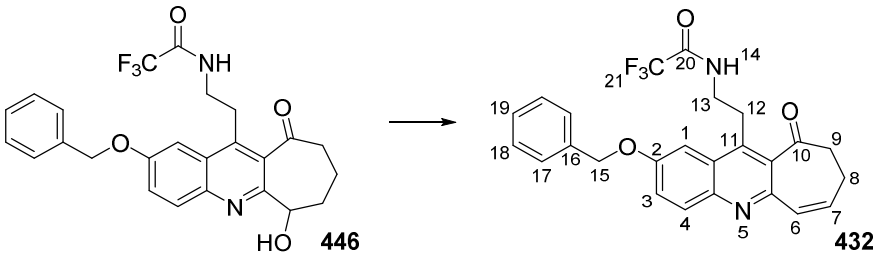
N-(2-(2-Benzyloxy-10-oxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-yl oxide)ethyl)-2,2,2-trifluoroacetamide **437** (879 mg, 1.86 mmol) was dissolved in dichloromethane (19.0 mL) and acetic anhydride (1.75 mL, 18.6 mmol) was added to the stirring solution. The solution was stirred at 50 °C for 36 h, diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **439** as a colourless foam (812 mg, 85 %); (Found: M+H$^+$, 515.1801. $C_{27}H_{25}F_3N_2O_5$ + H$^+$ requires 515.1788); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 2388, 2950, 1721, 1688, 1615, 1560, 1454, 1442, 1343, 1239, 1171; δ_H (400 MHz; $CDCl_3$) 8.62 (1 H, br s, NH-14), 8.07 (1 H, d, *J* 9.0, H-4), 7.54 (1 H, dd, *J* 9.0, 2.6, H-3), 7.50 (2 H, d, *J* 7.1, H-19), 7.46-7.40 (3 H, m, H-1, 20), 7.37 (1 H, tt, *J* 7.1, 2.5, H-21), 6.15 (1 H, dd, *J* 4.6, 2.9, H-6), 5.28 (2 H, s, H-17), 3.75-3.59 (2 H, m, H-13), 3.39 (1 H, dt, *J* 13.4, 5.1, H-12a), 3.07-2.95 (2 H, m, H-12b, H-9a), 2.69 (1 H, ddd, *J* 18.4, 5.8, 3.4, H-9b), 2.38-2.28 (1 H, m, H-7a), 2.26-2.14 (1 H, m, H-7b), 2.26-1.91 (4 H, m, H-23, H-8a), 1.75-1.61 (1 H, m, H-8b); δ_C (100 MHz; $CDCl_3$) 209.4 (C), 169.3 (C), 158.0 (C), 157.6 (C, q, *J* 37.6), 152.5 (C), 143.4 (C), 141.1 (C), 136.0 (C), 132.0 (CH), 131.2 (C), 128.8 (CH), 128.3 (CH), 127.5 (CH), 127.2 (CH), 123.8 (C), 115.6 (C, q, *J* 287.2), 104.0 (CH), 77.7 (CH), 70.5 (CH_2), 42.6 (CH_2), 39.8 (CH_2), 30.1 (CH_2), 27.2 (CH_2), 20.7 (CH_3), 20.0 (CH_2).

_N_-(2-(2-Benzyloxy-6-hydro-10-oxo-7,8,9,10-tetrahydro-6_H_-cyclohepta[_b_]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 446



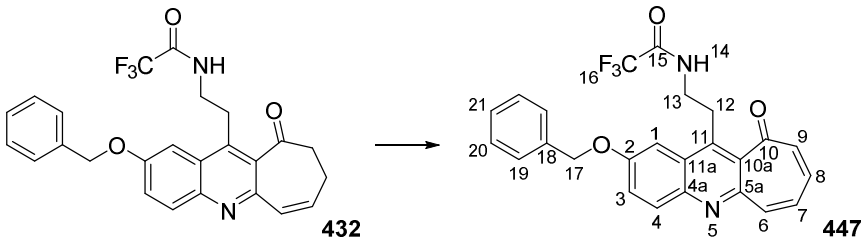
2-Benzyloxy-10-oxo-11-(2-(2,2,2-trifluoroacetamido)ethyl)-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-6-yl acetate **439** (592 mg, 1.15 mmol) was dissolved in methanol (7.00 mL), potassium carbonate (632 mg, 4.61 mmol) was added and the reaction mixture stirred for 20 min. The reaction mixture was diluted with water (10 mL) and the solution was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 3:7) gave the *title compound* **446** as colourless solid (427 mg, 79 %); mp 92-94 °C; (Found: $M+H^+$, 455.1594. $C_{25}H_{23}F_3N_2O_4 + H^+$ requires 455.1577); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3440, 3286, 3011, 2950, 1720, 1683, 1620, 1574, 1505, 1171; δ_H (400 MHz; $CDCl_3$) 8.18 (1 H, br s, NH-14), 8.04 (1 H, d, *J* 9.1, H-4), 7.58-7.46 (4 H, m, H-1, H-3, H-19), 7.43 (2 H, t, *J* 7.5, H-20), 7.37 (1 H, t, *J* 7.5, H-21), 5.30 (2 H, s, H-17), 4.90 (1 H, m H-6), 3.80-3.70 (1 H, m, H-13a), 3.70-3.59 (1 H, m, H-13b), 3.40 (1 H, dt, *J* 13.7, 5.7, H-12a), 3.05-2.95 (1 H, m, H-12b), 2.81 (2 H, t, *J* 2.8, H-9), 2.52-2.41 (1 H, m, H-8a), 2.11-1.77 (3 H, m, H-8b, 7); δ_C (100 MHz; $CDCl_3$) 210.1 (C), 157.7 (C, q, *J* 37.3), 157.9 (C), 154.3 (C), 142.4 (C), 141.1 (C), 136.2 (C), 131.6 (C), 131.2 (CH), 128.7 (CH), 128.3 (CH), 127.6 (CH), 127.2 (C), 124.0 (CH), 115.7 (C, q, *J* 286.8), 104.1 (CH), 71.7 (CH_2), 70.6 (CH), 42.3 (CH_2), 40.6 (CH_2), 34.6 (CH_2), 27.9 (CH_2), 21.4 (CH_2).

_N_-(2-(2-Benzyloxy-10-oxo-9-10-dihydro-8_H_-cyclohepta[_b_]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 432



N-(2-(2-Benzyloxy-6-hydro-10-oxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **446** (256 mg, 0.54 mmol) was dissolved in benzene (10.8 mL). Burgess reagent (380 mg, 1.62 mmol) was added and the solution was stirred at 80 °C for 16 h. The reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 3:7) gave the *title compound* **432** as a colourless solid (108 mg, 44 %); mp 187-188 °C; (Found: C, 66.34; H, 4.42; N, 5.97; $C_{25}H_{21}F_3N_2O_3$ requires C, 66.07; H, 4.66; N, 6.16%); (Found: $M+H^+$, 455.1579. $C_{25}H_{21}F_3N_2O_3 + H^+$ requires 455.1583); ν_{max} ($CHCl_3$)/cm^{-1} 3449, 2986, 2941, 2907, 2875, 1734 1478, 1466, 1446, 1375, 1248 1097, 1046; δ_H (400 MHz: $CDCl_3$) 8.24 (1 H, br s, NH-14), 8.00 (1 H, d, *J* 9.2, H-4), 7.56-7.48 (3 H, m, H-3, 17), 7.47-7.33 (4 H, m, H-1, 18, 19), 6.84 (1 H, d, *J* 12.3, H-6), 6.28 (1 H, dt, *J* 12.3, 4.9, H-7), 5.29 (2 H, s, H-15), 3.76-3.66 (2 H, m, H-13), 3.23 (2 H, t, *J* 6.7, H-12), 3.08 (2 H, t, *J* 6.7, H-9), 2.78-2.67 (2 H, m, H-8); δ_C (100 MHz: $CDCl_3$) 207.8 (C), 157.9 (C), 157.7 (C, q, *J* 37.2), 149.0 (C), 144.1 (C), 140.0 (C), 136.2 (C), 134.1 (CH), 133.6 (C), 133.1 (CH), 131.8 (CH), 128.7 (CH), 128.3 (CH), 127.6 (CH), 125.9 (C), 124.0 (CH), 115.7 (C, q, *J* 287.2), 103.9 (CH), 70.5 (CH_2), 43.1 (CH_2), 40.0 (CH_2), 28.6 (CH_2), 27.9 (CH_2).

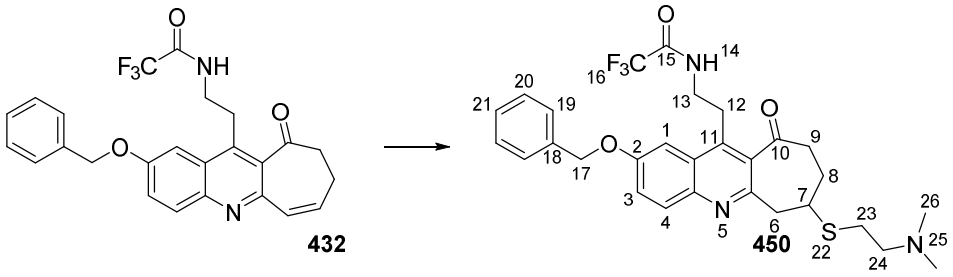
N-(2-(2-(Benzyloxy)-10-oxo-10*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 447



432 **447**

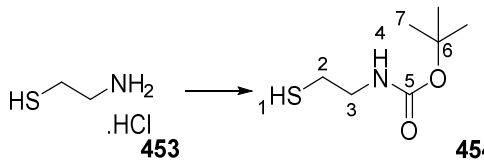
N-(2-(2-(Benzyloxy)-10-oxo-9-10-dihydro-8*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **432** (25 mg, 0.06 mmol) was dissolved in 1,4-dioxane (1.50 mL). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (26 mg, 0.11 mmol) was added and the solution was heated to 100 °C for 2 h. The reaction mixture was filtered through a neutral alumina pad before being concentrated *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 3:7) gave the *title compound* **447** as a yellow oil (8.10 mg, 29%); (Found: M+H$^+$, 453.1438. $C_{25}H_{19}N_2O_3F_3 + H^+$ requires 453.1421); ν_{max} ($CHCl_3$)/cm^{-1} 3439, 3011, 1720, 1645, 1620, 1492, 1456, 1434, 1378, 1193, 1172; δ_H (400 MHz; $CDCl_3$) 8.28 (1 H, br s, NH-14), 8.12 (1 H, d, *J* 9.2, H-4), 7.73-7.66 (3 H, m, H-3, 1, 6), 7.54 (2 H, d, *J* 7.6, H-19), 7.48-7.34 (3 H, m, H-20, 21) , 6.97 (1 H, ddd *J* 11.6, 7.2, 1.0, H-7), 6.86-6.76 (2 H, m, H-8, 9), 5.39 (2 H, s, H-17), 3.96-3.86 (2 H, m, H-12), 3.43 (2 H, t, *J* 7.1, H-13); δ_C (100 MHz; $CDCl_3$) 194.6 (C), 158.2 (C), 157.7 (C, q, *J* 37.1), 148.8 (C), 145.2 (C), 143.8 (C), 139.6 (CH), 136.1 (C), 134.0 (CH), 133.4 (CH), 132.9 (C), 132.2 (CH), 128.7 (CH), 128.3 (CH), 128.0 (C), 127.7 (CH), 127.1 (CH), 126.0 (CH), 115.0 (C, q, *J* 289), 103.6 (CH), 70.6 (CH_2), 40.4 (CH_2), 28.8 (CH_2).

_N_-(2-(2-Benzyloxy-7-((2-(dimethylamino)ethyl)thio)-10-oxo-7,8,9,10-tetrahydro-6_H_-cyclohepta[_b_]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 450



N-(2-(2-(Benzyloxy)-10-oxo-9-10-dihydro-8H-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **432** (11.0 mg, 0.02 mmol) was dissolved in ethanol (0.10 ml) and to the stirring solution 2-dimethylaminoethanethiol hydrochloride (7.00 mg, 0.05 mmol) was added. The solution was stirred at 80 °C for 2 h before sodium hydroxide solution (1 M in ethanol, 0.10 mL) was added. The reaction mixture was filtered and the residue washed with ethyl acetate (5 mL). The filtrate was poured into water (5 mL) and extracted with ethyl acetate (3 x 10 mL) and the combined organic layers washed with brine (10 mL). The solution was dried over $MgSO_4$ and the solvent removed *in vacuo* to give a brown oil. Column chromatography (ethyl acetate: light petroleum; 1:1 to 1:0) gave the *title compound* **450** as a colourless solid (8 mg, 72%); mp 123-125 °C; (Found: $M+H^+$, 560.2200. $C_{29}H_{32}N_3O_3F_3S + H^+$ requires 560.2195); ν_{max} ($CHCl_3$)/cm^{-1} 3012, 1716, 1675, 1619, 1561, 1503, 1193; δ_H (400 MHz; $CDCl_3$) 8.28 (1 H, br t, *J* 4.3, NH-14), 8.02 (1 H, d, *J* 9.2, H-4), 7.56-7.48 (3 H, m, H-3, 19), 7.46-7.34 (4 H, m, H-1, 20, 21), 5.29 (2 H, s, H-17), 3.75-3.62 (2 H, m, H-12), 3.58-3.40 (2 H, m, H-7, 6a), 3.36-2.98 (8 H, m, H-13, 23, 24, 6b, 9a), 2.82 (6 H, s, H-26), 2.74 (1 H, dd, H-9b), 2.26-2.15 (1 H, m, H-8a), 2.03-1.94 (1 H, m, H-8b); δ_C (100 MHz; $CDCl_3$) 210.0 (C), 158.0 (C, q, *J* 37.6), 157.9 (C), 151.9 (C), 144.3 (C), 141.1 (C), 138.8 (C), 136.2 (CH), 132.8 (C), 128.8 (CH), 128.3 (CH), 127.6 (CH), 126.6 (C), 123.8 (CH), 115.7 (C, q, *J* 288), 104.0 (CH), 70.5 (CH_2), 59.0 (CH_2), 45.2 (CH_3), 41.8 (CH_2), 41.1 (CH), 40.6 (CH_2), 39.1 (CH_2), 29.7 (CH_2), 28.9 (CH_2), 27.7 (CH_2).

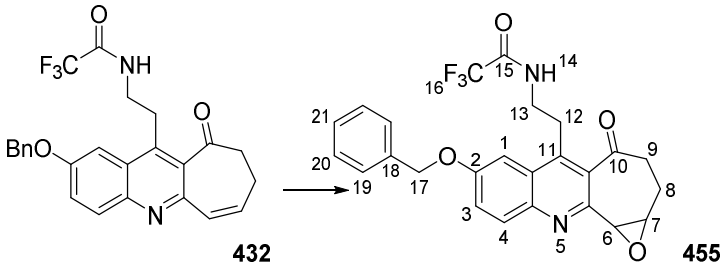
tert-Butyl (2-mercaptoethyl)carbamate 454



453 **454**

2-Mercaptoethylamine hydrochloride **453** (1.00 g, 8.8 mmol) was dissolved in dichloromethane (100 mL) under argon. Di-*tert*-butyl dicarbonate (1.73 g, 7.92 mmol) and triethylamine (3.7 mL, 26.4 mmol) were added and the solution stirred at room temperature under argon for 15 h. The reaction mixture was diluted with water (50 mL) and extracted with dichoromethane (3 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 1:1) gave the title compound **454** as a colourless oil which was stored under argon (1.26 g, 81%); (Found M+Na^+, 200.0721. $C_7H_{15}NO_2S + Na^+$ requires 200.0721); δ_H (400 MHz; $CDCl_3$) 5.03 (1 H, br s, NH-4), 3.46 (2 H, td, *J* 6.2, 6.3, H-3), 2.80 (2 H, t, *J* 6.3, H-2), 1.50 (1 H, s, SH-1), 1.45 (9 H, s, H-7); δ_C (100 MHz: $CDCl_3$) 155.7 (C), 79.4 (C), 39.2 (CH_2), 38.3 (CH_2), 28.3 (CH_3). Data consistent with literature.[220]

_N_-(2-(7-Benzyloxy-4-oxo-1a,3,4,10b-tetrahydro-2_H_-oxireno[2',3',6,7]cyclohepta[_b_]quinolin-5-yl)ethyl)-2,2,2-trifluoroacetamide 455

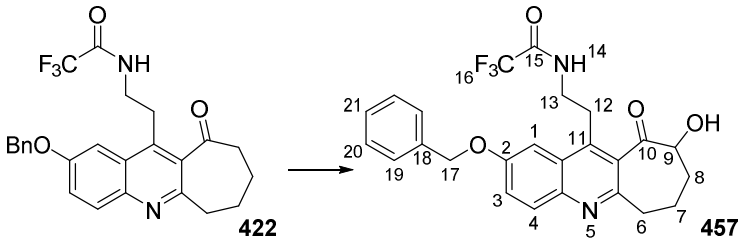


432 **455**

N-(2-(2-Benzyloxy-10-oxo-9-10-dihydro-8*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **432** (20.0 mg, 0.04 mmol) was dissolved in dichloromethane (0.40 mL) and to the stirring solution *m*-chloroperoxybenzoic acid (77%; 14 mg, 0.06 mmol) was added. The reaction mixture was stirred for 4.5 h before saturated sodium thiosulfate (1 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 5 mL). The combined

organic phases were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 7:3) gave the *title compound* **455** as a pale yellow powder (10 mg, 53%); mp 138-140 °C; (Found $M+H^+$, 471.1534. $C_{25}H_{21}F_3N_2O_4 + H^+$ requires 471.1532); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3607, 3010, 1721, 1602, 1549, 1235, 1171; δ_H (400 MHz; $CDCl_3$) 8.75 (1 H, d, *J* 9.5, H-4), 7.89 (1H, br s, NH-14), 7.59-7.50 (4 H, m, H-3, 1, 19), 7.48-7.37 (4 H, m, H-6, 20, 21), 6.45 (1 H, dt, *J* 12.1, 5.4, H-7), 5.34 (2 H, s, H-17), 3.71 (2 H, q, *J* 6.9, 5.4, H-13), 3.15 (2 H, dt, *J* 6.9, H-12), 3.08 (2 H, t, *J* 6.7, H-9), 2.79-2.72 (2 H, m, H-8); δ_C (100 MHz: $CDCl_3$) 204.6 (C), 159.2 (C), 157.8 (C, q, *J* 37.8), 137.8 (C), 137.2 (C), 136.2 (CH), 135.9 (C), 135.6 (C), 129.0 (C), 128.8 (CH), 128.4 (CH), 127.6 (CH), 127.5 (C), 123.9 (CH), 122.9 (CH), 122.8 (CH), 115.7 (C, q, *J* 287.5), 105.5 (CH), 70.7 (CH_2), 44.4 (CH_2), 40.1 (CH_2), 28.0 (CH_2), 27.9 (CH_2).

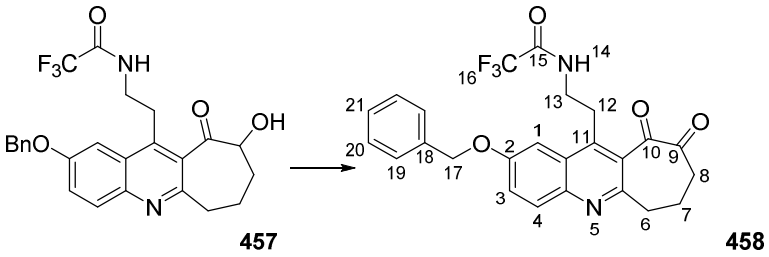
_N_-(2-(2-(Benzyloxy)-9-hydroxy-10-oxo-7,8,9,10-tetrahydrohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 457



N-(2-(2-(Benzyloxy)-10-oxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **422** (200 mg, 0.43 mmol) was dissolved in anhydrous THF (21.5 mL) under an atmosphere of argon and the solution was cooled to -78 °C. Potassium bis(trimethylsilyl)amide (2.15 mL, 1.29 mmol, 0.6 M in toluene) was added to the solution and the reaction mixture was stirred at -78 °C for 30 min then (1*R*)-(−)-(10-camphorsulfonyl) oxaziridine (150 mg, 0.65 mmol) in anhydrous THF (4.70 mL) was added. The reaction mixture was stirred at -78 °C for 1.5 h, before saturated ammonium chloride solution 10 mL was added and the reaction warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were washed with brine and

dried over Na_2SO_4 before the solvent was removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **457** as a colourless solid (131 mg, 65%); mp 74-76 °C; (Found $M+H^+$, 473.1704. $C_{25}H_{23}F_3N_2O_4$ + H^+ requires 473.1688); ν_{max} ($CHCl_3$)/cm^{-1}; 3441, 3310, 3011, 2947, 1721, 1688, 1620, 1566, 1428, 1378, 1337,1122; δ_H (400 MHz; $CDCl_3$) 7.99 (1 H, d, *J* 9.8, H-4), 7.76 (1 H, br s, NH-14), 7.57-7.49 (4 H, m, H-1, 3, 19), 7.47-7.40 (2 H, m, H-20), 7.40-7.34 (1 H, m, H-21), 5.32 (2 H, s, H-17), 4.50 (1 H, dd, *J* 9.3, 5.2, H-9), 3.81-3.71 (1 H, m H-13a), 3.69-3.58 (1 H, m, H-13b), 3.46-3.37 (1 H, m, H-12a), 3.36-3.21 (1 H, m, H-6a), 3.04-2.86 (1 H, m, H-6b), 2.86-2.76 (1 H, m, H-12b), 2.46-2.36 (1 H, m, H-8a), 2.32-2.15 (1 H, m, H-7a), 2.05-1.91 (2 H, m, H-7b, 8b); δ_C (100 MHz; $CDCl_3$) 212.1 (C), 157.7 (C, q, *J* 37.6), 157.6 (C), 154.0 (C), 143.9 (C), 140.6 (C), 136.3 (C), 132.2 (C), 131.3 (CH), 128.7 (CH), 128.2 (CH), 127.6 (CH), 126.0 (C), 124.0 (CH), 115.8 (C, q, *J* 288.3), 103.7 (CH), 78.0 (CH), 70.4 (CH_2), 40.0 (CH_2), 39.0 (CH_2), 37.4 (CH_2), 28.5 (CH_2), 23.4 (CH_2).

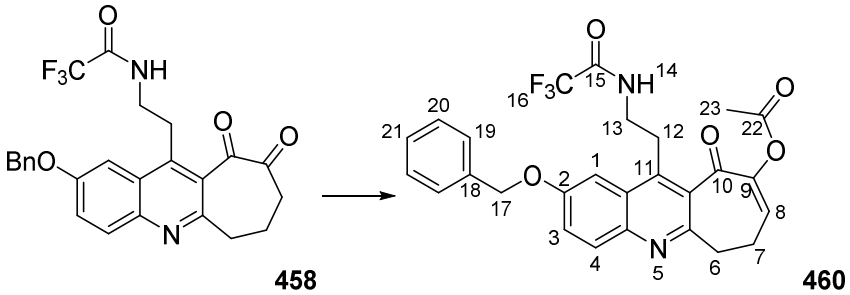
_N_-(2-(2-Benzyloxy)-9,10-dioxo-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 458



N-(2-(2-Benzyloxy-9-hydroxy-10-oxo-7,8,9,10-tetrahydrohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **457** (124 mg, 0.26 mmol) was dissolved in DMSO/THF (3.3 mL, 8:1) and to the stirring solution Dess-Martin periodinane (165 mg, 0.39 mmol) was added and the reaction mixture strirred for 2 h. The reaction mixture was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were washed with saturated sodium thiosulfate, saturated sodium hydrogen carbonate and brine. The combined organic phases were dried over Na_2SO_4

and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **458** as a colourless solid (100 mg, 82%); mp 97-98°C; (Found M+MeOH+H^+ 503.1788; $C_{25}H_{21}F_3N_2O_4$ + MeOH+H^+ requires 503.1788); ν_{max} ($CHCl_3$)/cm^{-1} 2962, 1722, 1619, 1566, 1502, 1380, 1239, 1171; δ_H (400 MHz; $CDCl_3$) 8.04 (1 H, d, *J* 9.2, H-4), 7.69 (1 H, d, *J* 2.6, H-1), 7.60 (1 H, dd, *J* 9.2, 2.6, H-3), 7.58-7.47 (3 H, m, H-19, NH-14), 7.45 (2 H, t, *J* 7.4, H-20), 7.38 (1 H, t, *J* 7.4, H-21), 5.37 (2 H, s, H-17), 3.79 (2 H, app q, *J* 6.8, 6.8, H-13), 3.36-3.29 (4 H, m, H-6, 12), 2.90 (2 H, t, *J* 6.9, H-8), 2.29 (2 H, dt, *J* 6.9, 13.5, H-7); δ_C (100 MHz; $CDCl_3$) 198.5 (C), 195.8 (C), 157.9 (C), 157.8 (C, q, *J* 37.7), 154.8 (C), 144.88 (C), 144.85 (C), 136.2 (C), 131.4 (CH), 128.9 (C), 128..7 (CH), 128.3 (CH), 127.7 (CH), 126.8 (C), 125.4 (CH), 115.7 (C, q, *J* 288), 104.0 (CH), 70.5 (CH_2), 40.2 (CH_2), 39.0 (CH_2), 36.2 (CH_2), 28.4 (CH_2), 22.2 (CH_2).

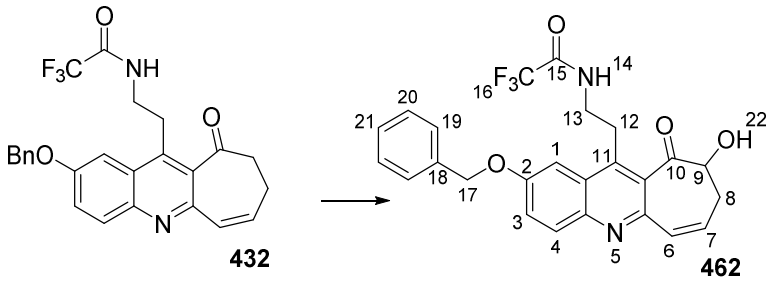
2-Benzyloxy-10-oxo-11-(2,2,2-trifluoroacetamido)ethyl)-7,10-dihydro-6*H*-cyclohepta[*b*]quinolin-9-yl acetate 460



N-(2-(2-Benzyloxy)-9,10-dioxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **458** (63.0 mg, 0.13 mmol) was dissolved in dichloromethane (2.00 mL) and to the stirring solution acetic anhydride (0.13 mL, 1.34 mmol) and pyridine (0.13 mL, 1.34 mmol) was added at room temperature. The reaction mixture was stirred for 48 h before being diluted with water (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with saturated copper sulfate solution (5 mL) and brine (10 mL) before being dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum: 1:1) gave the *title compound* **460** as a colourless film (32 mg,

48%); *m/z* (ESI); (Found M+H$^+$ 513.1624. $C_{27}H_{23}F_3N_2O_5$+H$^+$ requires 513.1624); ν $_{max}$ ($CHCl_3$)/cm^{-1} 3440, 3040, 3020, 3011, 2928, 2400, 1750, 1721, 1502, 1237, 1221; δ_H (400 MHz; $CDCl_3$) 8.04 (1 H, br t, *J* 5.4, NH-14), 7.97 (1 H, d, *J* 10.1, H-4), 7.55-7.49 (4 H, m, H-1, 3, 19), 7.44-7.39 (2 H, m, H-20), 7.38-7.33 (1 H, m, H-21), 6.47 (1 H, t, *J* 5.1, H-8), 5.30 (2 H, s, H-17), 3.71 (2 H, td, *J* 6.9, 5.4, H-13), 3.36 (2 H, dd, *J* 6.5, 5.1, H-6), 3.26 (2 H, t, *J* 6.9, H-12), 2.77-2.71 (2 H, m, H-7), 2.29 (3 H, s, H-21); δ_C (100 MHz; $CDCl_3$) 192.6 (C), 170.0 (C), 157.5 (C, q, *J* 36.6), 157.5 (C), 153.8 (C), 145.4 (C), 144.2 (C), 143.4 (C), 136.3 (C), 132.7 (CH), 132.6 (CH), 131.2 (C), 128.7 (CH), 128.2 (CH), 127.6 (CH), 126.8 (C), 124.1 (CH), 115.6 (C, q, *J* 288.3), 104.3 (CH), 70.5 (CH_2), 40.0 (CH_2), 37.3 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 20.4 (CH_3).

_N_-(2-(2-(Benzyloxy)-9-hydroxy-10-oxo-9,10-dihydro-8_H_-cyclohepta[b]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 462

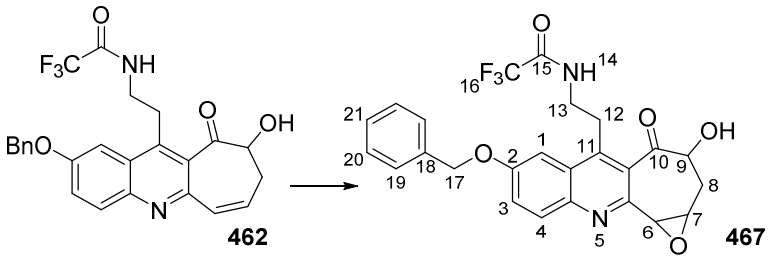


432 **462**

N-(2-(2-(Benzyloxy)-10-oxo-9-10-dihydro-8*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **432** (205 mg, 0.45 mmol) was dissolved in anhydrous THF (23.0 mL) under an atmosphere of argon and the solution was cooled to -78 °C. Potassium bis(trimethylsilyl)amide (1.55 mL, 0.99 mmol, 0.7 M in toluene) was added to the solution and the reaction mixture was stirred at -78 °C for 30 min before (1*R*)-(−)-(10-camphorsulfonyl) oxaziridine (154 mg, 0.68 mmol) in anhydrous THF (7.50 mL) was added. The reaction mixture was stirred at -78 °C for 1.5 h before saturated ammonium chloride solution (10 mL) was added and the reaction warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were

washed with brine and dried over Na_2SO_4 before the solvent was removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **462** as a colourless solid (165 mg, 78%); mp 175-177 °C; (Found C 64.10; H 4.21; N 5.72. $C_{25}H_{21}F_3N_2O_4$ requires C 63.83; H 4.56; 5.95%); (Found $M+H^+$, 471.1543. $C_{25}H_{21}F_3N_2O_4 + H^+$ requires 471.1526); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 3307, 3010, 2982, 1725, 1687, 1651, 1618, 1550, 1498, 1455, 1421, 1375, 1248, 1169; δ_H (400 MHz; $CDCl_3$) 7.98 (1 H, d, *J* 10.0, H-4), 7.73 (1 H, m, NH-14), 7.56-7.49 (4 H, m, H-1, 3, 19), 7.42 (2 H, t, *J* 7.3, H-20), 7.36 (1 H, t, *J* 7.3, H-21), 6.84 (1 H, br d, *J* 12.0, H-6), 6.19-6.11 (1 H, m, H-7), 5.32 (2 H, s, H-17), 4.90-4.85 (1 H, m, H-9), 3.83-3.73 (1 H, m, H-13a), 3.72-3.61 (1 H, m, H-13b), 3.46-3.37 (1 H, m, H-12a), 3.06-2.94 (2 H, m, H-12b, 8a), 2.68 (1 H, dddd, *J* 18.2, 8.8, 4.2, 1.8, H-8b); δ_C (100 MHz; $CDCl_3$) 208.0 (C), 158.2 (C), 157.7 (C, q, *J* 37.1), 148.9 (C), 144.3 (C), 141.8 (C), 136.2 (C), 133.2 (CH), 131.7 (CH), 129.8 (C), 129.7 (CH), 128.7 (CH), 128.3 (CH), 127.6 (CH), 126.2 (C), 124.7 (CH), 115.7 (C, q, *J* 287), 103.7 (CH), 76.2 (CH), 70.5 (CH_2), 40.2 (CH_2), 36.5 (CH_2), 28.7 (CH_2).

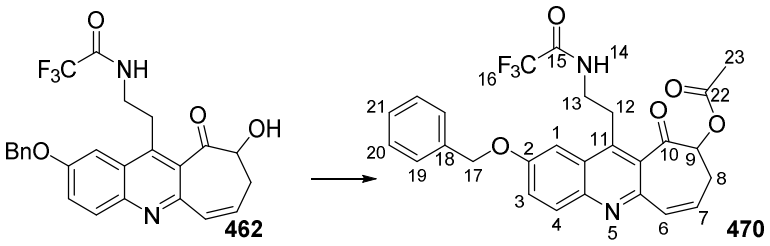
_N_-(2-(7-(Benzyloxy)-3-hydroxy-4-oxo-1a,3,4,10b-tetrahydro-2*H*-oxireno[2', 3', 6, 7]cyclohepta[1,2-*b*]quinolin-5-yl)ethyl)-2,2,2-trifluoroacetamide 467



N-(2-(2-(Benzyloxy)-9-hydroxy-10-oxo-9,10-dihydro-8*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **462** (22.0 mg, 0.05 mmol) was dissolved in dichloromethane (0.50 mL) and to the stirring solution *m*-chloroperoxybenzoic acid (77%; 13.0 mg, 0.06 mmol) was added. The reaction mixture was stirred for 9 h before being quenched with saturated sodium thiosulfate solution (1 mL), extracted with ethyl acetate (3 x

5 mL) and the combined organic layers washed with brine (10 mL). The solution was dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 1:1 then neat ethyl acetate) gave the *title compound* **467** as a colourless solid (15.0 mg, 62%); mp 166-167 °C; (Found $M+H^+$, 487.1468. $C_{25}H_{21}F_3N_2O_5 + H^+$ requires 487.1462); ν_{max} ($CHCl_3$)/cm^{-1} 3694, 3606, 2927, 2854, 1602, 1465; δ_H (400 MHz: $CDCl_3$) 8.71 (1 H, d, *J* 9.5, H-4), 7.66-7.59 (2 H, m, H-1, NH-14), 7.56-7.50 (3 H, m, H-3, 19), 7.44 (2 H, t, *J* 7.0, H-20), 7.38 (1 H, t, *J* 7.0, H-21), 7.32 (1 H, d, *J* 12.2, H-6), 6.30 (1 H, dt, *J* 12.2, 5.5, H-7), 5.35 (2 H, s, H-17), 4.79 (1 H, t, *J* 5.8, H-9), 3.80-3.70 (1 H, m, H-13a), 3.69-3.58 (1 H, m, H-13b), 3.39-3.29 (1 H, m, H-12a), 3.04-2.90 (2 H, m, H-12b, 8a), 2.75 (1 H, dt, *J* 17.9, 5.8, H-8b); δ_C (100 MHz: $CDCl_3$) 205.1 (C), 159.4 (C), 158.4 (C, q, *J* 37.7), 137.8 (C), 137.1 (C), 135.8 (C), 133.1 (CH), 132.7 (C), 129.4 (C), 129.2 (C), 128.7 (CH), 128.4 (CH), 127.6 (CH), 124.5 (CH), 123.0 (CH), 122.5 (CH), 115.7 (C, q, *J* 286), 105.4 (CH), 78.5 (CH), 70.7 (CH_2), 40.2 (CH_2), 35.7 (CH_2), 28.4 (CH_2).

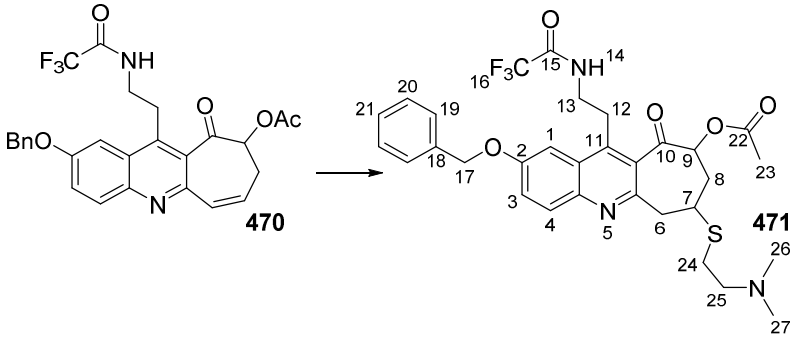
2-(Benzyloxy)-10-oxo-11-(2-(2,2,2,-trifluoroactamido)ethyl)-9,10-dihydro-8*H*-cyclohepta[*b*]quinolin-9-yl acetate 470



N-(2-(2-(Benzyloxy)-9-hydroxy-10-oxo-9,10-dihydro-8*H*-cyclohepta[b]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **462** (50.0 mg, 0.10 mmol) was dissolved in dichloromethane (1.00 mL) and to the stirring solution acetic anhydride (0.05 mL, 0.50 mmol) and pyridine (0.04 mmol, 0.05 mmol) were added. The reaction mixture was stirred at 20 °C for 48 h before being diluted with water (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with saturated copper sulfate solution (5 mL) and brine (10 mL) before being dried over $MgSO_4$ and the solvent removed *in vacuo*. Column

chromatography (ethyl acetate: light petroleum; 1:1) gave the *title compound* **470** as a colourless powder (49.0 mg, 90%); mp 155-156 °C; (Found M+H$^+$, 513.1624. $C_{27}H_{23}F_3N_2O_5$ + H$^+$ requires 513.1637); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 3040, 3020, 3011, 2928, 2856, 2400, 1750, 1721, 1502, 1237, 1221; δ_H (400 MHz: $CDCl_3$) 7.99 (1 H, d, J 9.9, H-4), 7.94 (1 H, br s, NH-14), 7.55-7.50 (4 H, m, H-1,3,19), 7.43 (2 H, t, *J* 7.2, H-20), 7.37 (1 H, t, *J* 7.2, H-21), 6.86 (1 H, dt, *J* 12.9, 1.9, H-6), 6.06 (1 H, dt, *J* 12.9, 4.5, H-7), 5.37 (1 H, dd, *J* 8.3, 5.1, H-9), 5.31 (2 H, s, H-17), 3.78-3.61 (2 H, m H-13), 3.39-.3.21 (2 H, m, H-12), 3.04-2.86 (2 H, m, H-8), 1.99 (3 H, s, H-23); δ_C (100 MHz: $CDCl_3$) 203.6 (C), 171.0 (C), 158.0 (C), 157.6 (C, q, *J* 37.3), 148.0 (C), 144.2 (C), 142.4 (C), 136.2 (C), 133.2 (CH), 131.8 (CH), 129.6 (C), 128.7 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 126.2 (C), 124.5 (CH), 115.8 (C, q, *J* 287.6), 103.8 (CH), 77.7 (CH), 70.5 (CH_2), 40.0 (CH_2), 33.3 (CH_2), 27.4 (CH_2), 20.3 (CH_3).

2-(Benzyloxy)-7-((2-(dimethylamino)ethyl)-10-oxo-11-(2,2,2-trifluoroacetam ido)ethyl)-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-9-yl acetate 471

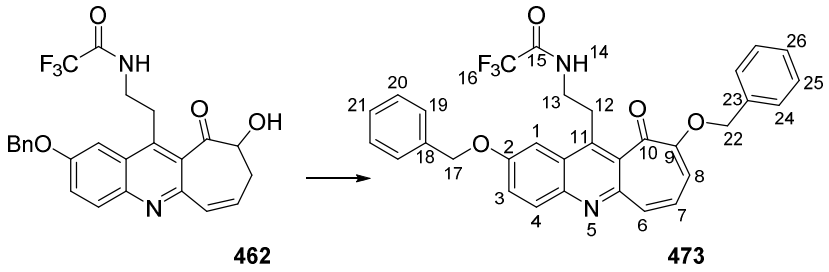


2-(Benzyloxy)-10-oxo-11-(2-(2,2,2,-trifluoroactamido)ethyl)-9,10-dihydro-8*H*-cyclohepta[*b*]quinolin-9-yl acetate **470** (38.0 mg, 0.07 mmol) was dissolved in ethanol (1.40 mL) and to the stirring solution 2-(dimethylamino)ethanethiol hydrochloride (21.0 mg, 0.15 mmol) was added and the reaction mixture was heated to 50 °C for 6.5 h. Silica was added and the solvent removed *in vacuo*. Column chromatography (dichloromethane: methanol; 4:1) gave the *title compound* **471** as a colourless oil (30.0 mg, 67%) in a mixture of

diastereoisomers (73:28); (Found $M+H^+$, 618.2250. $C_{31}H_{34}N_3O_5F_3S + H^+$ requires 618.2250); ν_{max} ($CHCl_3$)/cm^{-1} 3692, 3605, 2964, 2929, 2856, 1718, 1620, 1602, 1565, 1240, 1172, 909; Major isomer: δ_H (400 MHz: $CDCl_3$) 7.96 (1 H, d, *J* 8.9, H-4), 7.69 (1 H, br s, NH-14), 7.55-7.47 (4 H, m, H-1, 3, 19), 7.42 (2 H, t, *J* 7.2, H-20), 7.35 (1 H, t, *J* 7.2, H-21), 5.50 (1 H, dd, *J* 9.7, 5.9, H-9), 5.30 (2 H, s, H-17), 3.78-3.66 (2 H, m, H-7, 13a), 3.65-3.54 (1 H, m, H-13b), 3.52-3.39 (2 H, m, H-6), 3.27-3.13 (3 H, m, H-12, 24a/25a), 3.09-2.92 (3 H, m, H-24b/25b, 24/25), 2.56 (8 H, br s, H-26, 8), 2.17 (3 H, s, H-23); δ_C (100 MHz: $CDCl_3$) 205.2 (C), 170.8 (C), 157.8 (C), 157.7 (C, q, *J* 36.8), 149.7 (C), 143.8 (C), 141.7 (C), 136.3 (C), 132.2 (C), 131.4 (CH), 128.7 (CH), 128.2 (CH), 127.7 (CH), 126.5 (C), 124.0 (CH), 115.7 (C, q, *J* 288.0), 103.8 (CH), 76.3 (CH), 70.5 (CH_2), 57.8 (CH_2), 57.4 (CH_2), 43.9 (CH_3), 43.8 (CH_3), 40.3 (CH), 39.9 (CH_2), 38.8 (CH_2), 27.3 (CH_2), 26.4 (CH_2), 20.5 (CH_3).

Minor isomer: δ_H (400 MHz: $CDCl_3$) 7.98 (1 H, d, *J* 9.5, H-4), 7.67 (1 H, br s, NH-14), 7.56-7.49 (4 H, m, H-1, 3, 19), 7.46-7.33 (3 H, m, H-20, 21), 5.31 (2 H, s, H-17) 5.22 (1 H, dd, *J* 11.2, 5.1, H-9), 3.78-3.64 (2 H, m, H-13), 3.63-3.51 (2 H, m, H-25a, 12a), 3.38-3.12 (4 H, m, H-7, 6a, 25b, 12b), 2.90-2.80 (1 H, m, H-6b), 2.79-2.65 (3 H, m, H-8a, H-24), 2.41 (6 H, s, H-26), 2.34-2.25 (1 H, m, H-8b). 2.21 (3 H, s, H-23); δ_C (100 MHz: $CDCl_3$) 204.5 (C), 170.8 (C), 157.8 (C), 157.7 (C, q, *J* 36.4), 149.8 (C), 144.0 (C), 141.8 (C), 136.3 (C), 132.1 (C), 131.4 (CH), 128.7 (CH), 128.2 (CH), 127.7 (CH), 126.5 (C), 124.3 (CH), 115.9 (C, q, *J* 286.5), 103.7 (CH), 78.2 (CH), 70.5 (CH_2), 58.5 (CH_2), 46.2 (CH_2), 44.6 (CH_3), 41.0 (CH), 40.0 (CH_2), 27.2 (CH_2), 20.3 (CH_3).

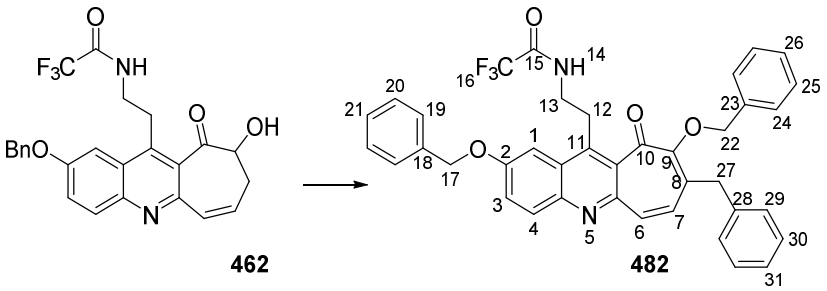
_N_-(2-(2,9-Bis(benzyloxy)-10-oxo-10_H_-cyclohepta[_b_]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 473



462 473

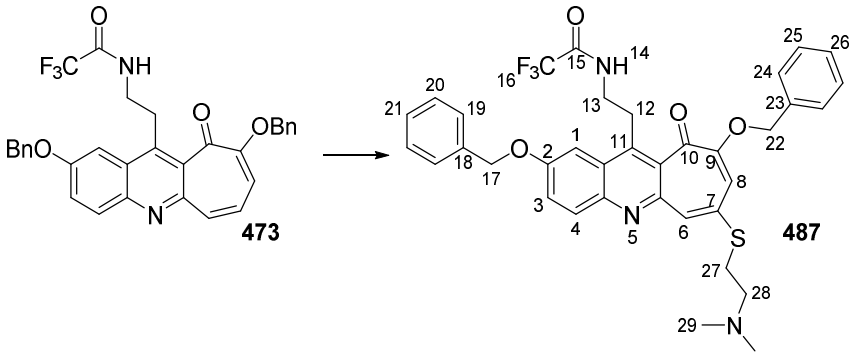
N-(2-(2-(Benzyloxy)-9-hydroxy-10-oxo-9,10-dihydro-8*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **462** (60.0 mg, 0.12 mmol) was dissolved in acetone (1.20 mL) and cooled to 0 °C. To the stirring solution benzyl bromide (0.02 mL, 0.19 mmol) and potassium hydroxide (13.0 mg, 0.24 mmol) was added to give a red solution. After 30 min the reaction mixture was warmed to room temperature and was stirred for a further 1.5 h. The reaction mixture was diluted with ethyl acetate (5 mL) and water (5 mL) before being acidified to pH 4 with hydrochloric acid (1 M) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: pentane; 1:5) gave the *title compound* **473** as a yellow powder (20 mg, 30%); mp 168-170 °C; (Found $M+H^+$, 559.1844. $C_{32}H_{25}F_3N_2O_4 + H^+$ requires 559.1839); λmax (MeOH)/nm 285 (log ε 5.55), 407 (4.69); ν_{max} ($CHCl_3$)/cm^{-1} 2931, 1721, 1620, 1574, 1540, 1376, 1171; δ_H (400 MHz; $CDCl_3$) 8.09 (1 H, d, *J* 9.2, H-4), 7.84 (1 H, br s, NH-14), 7.73 (1 H, d, *J* 2.5, H-1), 7.61 (1 H, dd, *J* 2.5, 9.2, H-3), 7.57-7.52 (2 H, m, H-19), 7.47-7.33 (9 H, m, H-6, 20, 21, 24, 25, 26), 6.71 (1 H, dd, *J* 8.5, 3.8, H-7), 6.26 (1 H, d, *J* 8.5, H-8), 5.39 (2 H, s, H-17), 5.08 (2 H, s, H-22), 3.90 (2 H, app q, *J* 6.7, 6.7, H-13), 3.36 (2 H, t, *J* 6.8, H-12); δ_C (100 MHz; $CDCl_3$) 191.7 (C), 157.9 (C), 157.7 (C, q, *J* 36.8), 157.0 (C), 149.0 (C), 145.2, (C), 143.5 (C), 136.3 (C), 135.3 (C), 131.9 (CH), 131.4 (CH), 130.6 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 127. 7 (C), 127.6 (CH), 127.5 (CH), 126.0 (CH), 124.7 (CH), 115.8 (C, q, *J* 287.7), 106.6 (CH), 103.0 (CH), 71.0 (CH_2), 70.5 (CH_2), 40.6 (CH_2), 29.4 (CH_2).

_N_-(2-(Benzyl-2,9-bis benzyloxy-10-oxo-10_H_-cyclohepta[_b_]quinoline-11-yl)ethyl)-2,2,2-trifluroacetamide 482



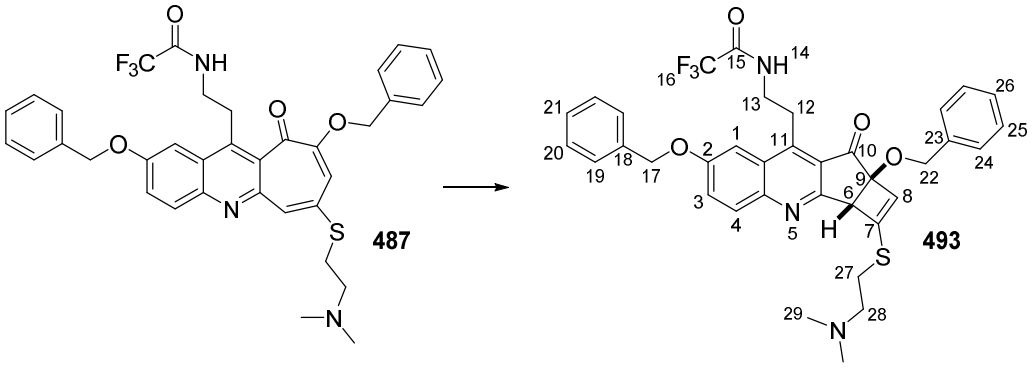
_N_-(2-(Benzyl-2,9-bis(benzyloxy)-10-oxo-10_H_-cyclohepta[_b_]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **482** was also isolated as a side-product from the reaction as a yellow solid (6 mg, 8%); (Found M+Na^+, 671.2115. $C_{39}H_{31}F_3N_2O_4$ + Na^+ requires 671.2134); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 2953, 2872, 1722, 1620, 1551, 1501, 1455, 1239, 1171, 1123; δ_H (400 MHz: $CDCl_3$) 8.12- 8.05 (2 H, m, H-4, NH-14), 7.67- 7.59 (2 H, m, H-3, H- 1), 7.56-7.50 (2 H, m, H-19), 7.47-7.29 (9 H, m, H-7, H-24 or 29, 30, 31, 25, 26), 7.26-7.17 (3 H, m, H-20, H-21), 7.13 (2 H, d, _J_ 7.0, H-24 or 29), 6.65 (1 H, d, J 13.9, H-6), 5.37 (2 H, s, H-17), 5.06 (2 H, s, H-22), 3.93 (2 H, s, H-27), 3.87 (2 H, app q, _J_ 6.9, 6.9, H-13), 3.32 (2 H, t, J 6.9, H-12); δ_C (100 MHz: $CDCl_3$) 192.2 (C), 158.0 (C), 157.2 (C, q, _J_ 36.8), 153.1 (C), 148.8 (C), 145.2 (C), 143.3 (C), 138.7 (C), 136.4 (C), 136.2 (C), 133.0 (CH), 132.0 (CH), 131.6 (C), 131.4 (C), 129.5 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.6 (CH), 127.4 (C), 126.5 (CH), 125.9 (CH), 115.8 (C, q, _J_ 285.6), 103.1 (CH), 73.8 (CH_2), 70.6 (CH_2), 40.5 (CH_2), 37.7 (CH_2), 28.6 (CH_2).

_N_-(2-(2,9-Bisbenzyloxy-7-((2-(dimethylamino)ethyl)thio)-10-oxo-10_H_-cyclohepta[_b_]quinolin-11-yl)ethyl-2,2,2-trifluoroacetamide 487



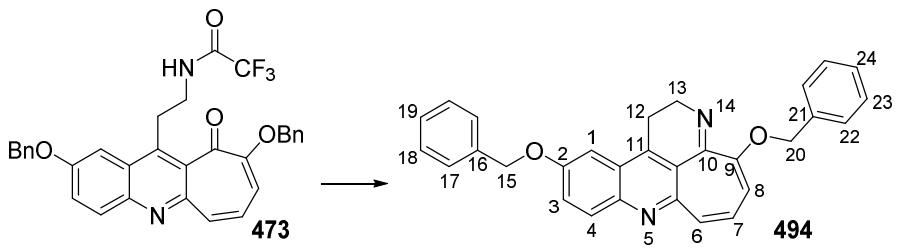
N-(2-(2,9-Bis(benzyloxy)-10-oxo-10H-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **473** (29.0 mg, 0.05 mmol) was dissolved in ethanol (1.50 mL) and to the stirring solution 2-(dimethylamino)ethanethiol hydrochloride (17.0 mg, 0.11 mmol) was added and the solution heated at 80 °C for 15 h. The reaction mixture was diluted with ethanol (2 mL) and silica was added. The solvent was removed *in vacuo* before column chromatography (methanol: ethyl acetate; 1:4) gave the *title compound* **487** as a yellow film (15.0 mg, 45%); (Found M+H$^+$, 662.2267. $C_{36}H_{34}F_3N_3O_4S$ + H$^+$ requires 662.2295); ν_{max} ($CHCl_3$)/cm^{-1} 3631, 2958, 2929, 2872, 2854, 2840, 1727, 1620, 1465, 1263, 1045, 1016; δ_H (500 MHz: CD_3OD) 7.95 (1 H, d, *J* 9.1, H-4), 7.92 (1 H, d, *J* 2.3, H-1), 7.59 (1 H, dd, *J* 9.1, 2.3, H-3), 7.52 (2 H, d, *J* 7.1, H-19/24), 7.47 (2 H, d, *J* 7.1, H-19/24), 7.41-7.39 (6 H, m, H-20, 21, 25, 26), 7.24 (1 H, s, H-6), 6.24 (1 H, s, H-8), 5.38 (2 H, s, H-17), 5.11 (2 H, s, H-22), 3.73-3.70 (2 H, m, H-13), 3.30-3.26 (2 H, m, H-12), 3.25-3.21 (2 H, m, H-27), 3.09 (2 H, t, *J* 7.2, H-28), 2.68 (2 H, s, H-29); δ_C (125 MHz: CD_3OD) 192.4 (C), 159.6 (C, q, *J* 36.8), 159.4 (C), 157.4 (C), 149.2 (C), 146.0 (C), 145.6 (C), 138.2 (C), 137.1 (C), 136.4 (C), 132.2 (C), 131.8 (CH), 129.9 (CH), 129.7 (CH), 129.7 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 129.6 (C), 127.5 (CH), 126.6 (CH), 117.6 (C, q, *J* 286.6), 107.3 (CH), 104.8 (CH), 72.4 (CH_2), 71.8 (CH_2), 58.0 (CH_2), 44.5 (CH_3), 41.9 (CH_2), 30.8 (CH_2), 29.4 (CH_2).

_N_-(2-(6,9a-Bis(benzoyloxy)-2-((2-(dimethylamino)ethyl)thio)-9-oxo-2,2a,9,9a-tetrahydro-1_H_-cyclobuta[4,5]cyclopenta[1,2-_b_]quinolin-8-yl)ethyl)-2,2,2-trifluoroacetamide 493



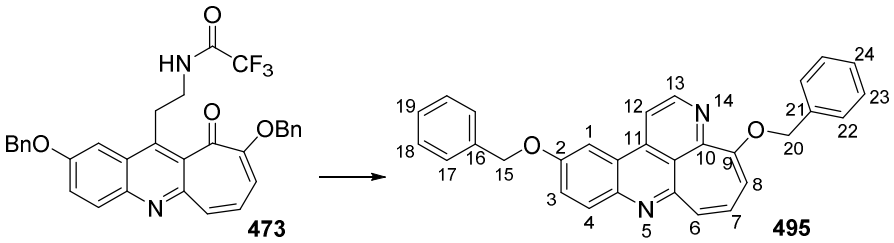
N-(2-(2,9-Bis(benzyloxy)-7-((2-(dimethylamino)ethyl)thio)-10-oxo-10*H*-cyclohepta[*b*]quinolin-11-yl)ethyl-2,2,2-trifluoroacetamide was left in deuterated chloroform at 20 °C for 48 h, resulting in the *title compound* **493** as a yellow film; (Found M+H$^+$, 662.2283. $C_{36}H_{34}F_3N_3O_4S$ + H$^+$ requires 662.2295); ν_{max} ($CHCl_3$)/cm^{-1} 3031, 3012, 2972, 1720, 1620, 1585, 1546, 1243, 1235, 1171; δ_H (400 MHz: $CDCl_3$) 8.03 (1 H, d, *J* 9.2, H-4), 7.68-7.59 (2 H, m, H-1, 3), 7.57-7.51 (4 H, m, H-19, 24), 7.48-7.30 (7 H, m, H-20, 21, 25, 26, NH-14), 6.36 (1 H, s, H-8), 5.33 (2 H, s, H-17), 4.91 (1 H, d, *J* 11.4, H-22a), 4.77 (1 H, d, *J* 11.4, H-22b), 4.40 (1 H, s, H-6), 3.96-3.63 (4 H, m, H-12, 13), 3.59-2.03 (4 H, m, H-27, 28), 2.78 (6 H, s, H-29); δ_C (100 MHz: $CDCl_3$) 200.8 (C), 177.4 (C), 162.1 (C), 157.8 (C), 157.6 (C, q, *J* 37.7), 147.6 (C), 147.0 (C), 137.8 (C), 136.1 (C), 131.4 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.1 (C), 128.1 (CH), 128.0 (CH), 127.7 (CH), 126.2, (CH), 126.2 (CH), 124.8 (C), 116.3 (C, q, *J* 286), 104.2 (CH), 86.3 (C), 70.5 (CH_2), 69.2 (CH_2), 57.7 (CH_2), 56.0 (CH), 43.1 (CH_3), 39.8 (CH_2), 29.7 (CH_2), 25.7 (CH_2).

4, 11-Bis (benzyloxy)-1,2-dihydrobenzo[c]cyclohepta[*ij*][2,7]napthyridine 494



N-(2-(2,9-Dihydroxy-10-oxo-10*H*-cyclohepta[*b*]quinolin-11-yl)ethyl-2,2,2-trifluoroacetamide **473** (16.0 mg, 0.03 mmol) was dissolved in methanol (0.60 mL), sodium hydroxide solution (40%, 0.03 ml) was added and the reaction mixture stirred for 2 h. Silica was added to the reaction mixture and the solvent was removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 1:2) gave the *title compound* **494** as a yellow film (5.00 mg, 38%); (Found M+H$^+$, 445.1915. $C_{30}H_{24}N_2O_2$ + H$^+$ requires 445.1916); λmax EtOH)/nm 209 (log ε 4.35), 265 (4.31), 403 (3.68); ν_{max} ($CHCl_3$)/cm^{-1} 2960, 1583, 1541, 1493, 1432, 1171, 1129, 900; δ_H (400 MHz: CD_3OD) 7.99 (1 H, d, *J* 9.2, H-4), 7.54-7.49 (3 H, m, H-3, 17), 7.47-7.28 (9 H, m, H-1, 18, 19, 22, 23, 24), 6.96 (1 H, d, *J* 12.0, H-6), 6.44 (1 H, dd, *J* 12.0, 8.5, H-7), 5.93 (1 H, d, *J* 8.5, H-8), 5.23 (2 H, s, H-15), 5.15 (2 H, s, H-20), 3.90-3.85 (2 H, m, H-13), 3.07-3.01 (2 H, m, H-12); δ_C (100 MHz: CD_3OD) 160.2 (C), 157.1 (C), 156.0 (C), 149.4 (C), 145.1 (C), 144.5 (C), 136.4 (C), 136.2 (C), 131.2 (CH), 130.3 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.0 (CH), 126.0 (CH), 124.8 (C), 124.5 (CH), 123.3 (C), 105.7 (CH), 102.7 (CH), 70.7 (CH_2), 70.4 (CH_2), 45.8 (CH_2), 22.4 (CH_2).

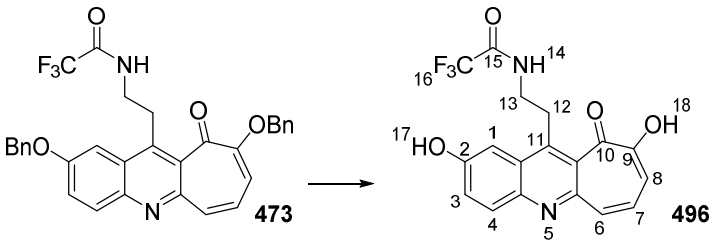
4, 11-Bis (benzyloxy)-1,2-benzo[*c*]cyclohepta[*ij*][2,7]napthyridine 485



Column chromatography (ethyl acetate: light petroleum; 1:2) gave the *title compound* **495** as a yellow film (3 mg, 23%); (Found M+H$^+$, 443.1752. $C_{30}H_{22}N_2O_2$ + H$^+$ requires 443.1760); (λ_{max} EtOH)/nm 208 (log ε 4.36), 247 (4.38), 368 (3.85); ν_{max} ($CHCl_3$)/cm^{-1} 3090, 2968, 1615, 1581, 1533, 1239; δ_H (400 MHz: CD_3OD) 8.96 (1 H, d, *J* 5.5, H-13), 8.14 (1 H, d, *J* 5.5, H-12), 7.96 (1 H, d, *J* 9.0, H-4), 7.82 (1 H, d, *J* 2.6, H-1), 7.56-7.52 (3 H, m, H-3, 17/22), 7.52-7.46 (2 H, m, H-17/22), 7.46-7.35 (5 H, m, H-18, 23, 24), 7.32 (1 H, m, H-19), 7.12 (1 H, d, *J*

12.0, H-6), 6.50 (1 H, dd, *J* 9.0, 12.0, H-7), 6.20 (1 H, d, *J* 9.0, H-8), 5.29 (2 H, s, H-15), 5.28 (2 H, s, H-20); δ_C (100 MHz: CD_3OD) 158.3 (C), 157.4 (C), 153.4 (C), 152.4 (C), 146.9 (CH), 140.4 (C), 136.5 (C), 136.4 (C), 135.6 (CH), 130.6 (CH), 128.8 (CH), 128.6 (CH), 128.5 (C), 128.3 (CH), 128.1 (C), 127.9 (CH), 127.6 (CH), 127.6 (CH), 126.9 (CH), 125.6 (C), 122.1 (CH), 115.0 (CH), 109.7 (CH), 104.2 (CH), 71.3 (CH_2), 70.6 (CH_2).

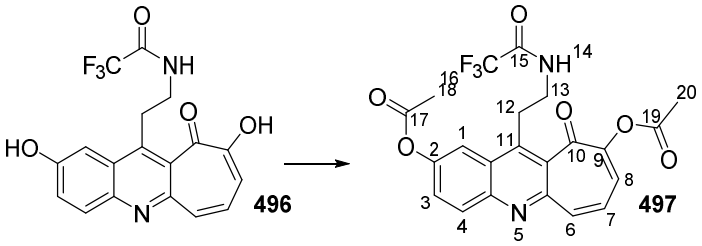
_N_-(2-(2,9-Dihydroxy-10-oxo-10_H_-cyclohepta[_b_]quinolin-11-yl)ethyl-2,2,2-trifluoroacetamide 496



N-(2-(2,9-Bis(benzyloxy)-10-oxo-10H-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide **473** (8.00 mg, 0.01 mmol) was dissolved in dichloromethane (0.30 mL) under argon and the solution cooled to 0 °C. Boron tribromide (0.05 mL, 0.05 mmol, 1 M in dichloromethane) was added and the solution stirred at 0 °C for 15 min. The reaction mixture was quenched with saturated sodium hydrogen carbonate solution (1 mL) and the mixture diluted with ethyl acetate (5 mL). The mixture was neutralised to pH 7 (1 M HCl) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to give a the *title compound* **496** as a brown powder which was used without further purification (4 mg, 73%); mp decomposes above 300°C; (Found $M+H^+$, 379.0902. $C_{18}H_{13}F_3N_2O_4 + H^+$ requires 379.0902); ν_{max} (ATR)/cm^{-1} 3321, 2980, 2924, 1701, 1619, 1600, 1437, 1209, 1156; δ_H (400 MHz: $CDCl_3$) 9.52 (1 H, br s, OH-18), 8.96 (1 H, br s, NH-14), 8.74 (1 H, br s, OH-17), 8.04 (1 H, d, *J* 9.0, H-4), 7.80 (1 H, d, *J* 2.0, H-1), 7.61 (1 H, dd, *J* 9.0, 2.0, H-3), 7.50 (1 H, d, *J* 12.0, H-6), 6.86 (1 H, dd, *J* 12.0, 9.0, H-7), 6.76 (1 H, d, *J* 9.0, H-8), 3.97-3.89 (2 H, m, H-13), 3.60 (2 H, t, *J* 7.8, H-12).; δ_C (100 MHz: $CDCl_3$) 188.5 (C), 157.6 (C), 157.5 (C), 157.5 (C, q, *J* 36.0), 150.3

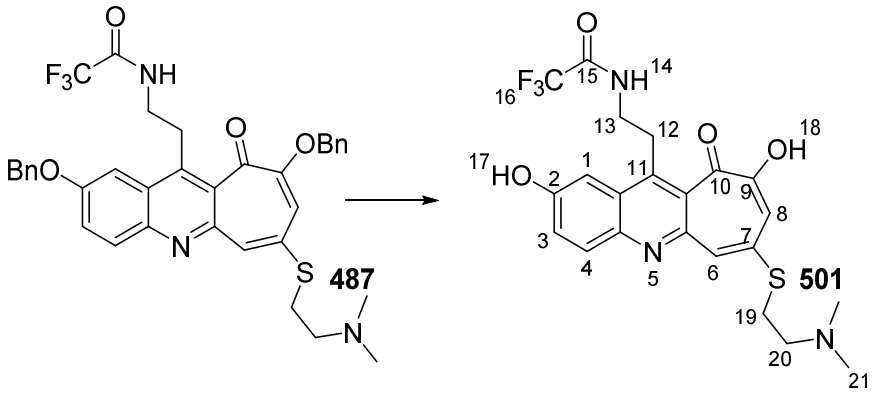
(C), 147.3 (C), 145.7 (C), 133.5 (CH), 132.7 (CH), 129.0 (C), 127.7 (C), 126.4 (CH), 126.3 (CH), 117.1 (C, q, J 287), 111.0 (CH), 106.1 (CH), 41.5 (CH_2), 29.11 (CH_2).

10-Oxo-11-(2-(2,2,2-trifluoroacetamido)ethyl)-10*H*-cyclohetpa[*b*]quinolone-2,9-diyl diacetate 497



N-(2-(2,9-Dihydroxy-10-oxo-10*H*-cyclohepta[*b*]quinolin-11-yl)ethyl-2,2,2-trifluoroacetamide **486** (10.0 mg, 0.03 mmol) was dissolved in dichloromethane (0.30 mL) and to the stirring solution acetic anhydride (0.03 mL, 0.26 mmol) and pyridine (0.02 mL, 0.26 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h before being diluted with water (5 mL). The reaction mixture was extracted with dichloromethane (3 x 5 mL) and the combined organic layers washed with saturated copper sulfate solution (5 mL) and brine (10 mL). The organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography (ethyl acetate: light petroleum; 3:7) gave the *title compound* **497** as a colourless film (3 mg, 25%); (Found $M+H^+$, 463.1113. $C_{22}H_{17}F_3N_2O_6 + H^+$ requires 463.1117); ν_{max} ($CHCl_3$)/cm^{-1} 3297, 3051, 2927, 2854, 1757, 1720, 1642, 1371, 1178; δ_H (400 MHz: $CDCl_3$) 8.22 (1 H, d, *J* 9.3, H-4), 8.16 (1 H, br s, NH-14), 8.05 (1 H, d, *J* 2.4, H-1), 7.70-7.63 (2 H, m, H-3, 6), 6.84-6.73 (2 H, m, H-7, 8), 3.93-3.84 (2 H, m, H-13), 3.53 (2 H, t, *J* 6.9, H-12), 2.43 (3 H, s, H-18/20), 2.35 (3 H, s, H-18/20); δ_C (100 MHz: $CDCl_3$) 189.1 (C), 169.2 (C), 168.6 (C), 157.5 (C, q, *J* 36.7), 150.4 (C), 150.0 (C), 149.0 (C), 147.9 (C), 146.8 (C), 137.7 (CH), 132.1 (CH), 130.7 (C), 127.8 (CH), 127.0 (C), 123.9 (CH), 121.0 (CH), 115.7 (C, q, *J* 287.5), 115.6 (CH), 40.9 (CH_2), 27.4 (CH_2), 21.2 (CH_3), 20.4 (CH_3).

***N*-(2-(7-((2-(Dimethylamino)ethyl)thio)-2,9-dihydroxy-10-oxo-10*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 501**



N-(2-(2,9-Bis(benzyloxy)-7-((2-(dimethylamino)ethyl)thio)-10-oxo-10*H*-cyclohepta[*b*]quinolin-11-yl)ethyl-2,2,2-trifluoroacetamide **487** (7.00 mg, 0.01 mmol) was dissolved in chloroform (0.30 mmol) under argon. To the stirring solution boron tribromide (0.1 mL, 0.1 mmol, 1 M in dichloromethane) was added and the reaction stirred at room temperature for 3 h. The reaction mixture was poured into water (3 mL) and silica was added to the mixture before the solvent was removed *in vacuo*. Column chromatography (ethyl acetate: methanol; 4:1 to 7:3) gave the *title compound* **501** as a red solid (5.00 mg, quant) which was unstable in deuterated methanol; mp decomposes above 300 °C; (Found $M+H^+$, 482.1355. $C_{22}H_{22}F_3N_3O_4S_1 + H^+$ requires 482.1361); δ_H (400 MHz; CD_3OD) 8.37 (1 H, d, *J* 9.2, H-4), 7.93 (1 H, d, *J* 2.4, H-1), 7.83 (1 H, dd, *J* 9.2, 2.4, H-3), 7.50 (1 H, d, *J* 1.2, H-6), 6.53 (1 H, d, *J* 1.2, H-8), 3.92-3.86, (2 H, m, H-13), 3.68-3.56 (6 H, m, H-12, 19, 20), 3.04 (6 H, s, H-21).

Appendix

Crystallographic experimental details

tert-Butyl (2-(2-benzyloxy-10-oxo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinolin-11-yl)ethyl)carbamate **406**

	Ercjma
Crystal data	
Chemical formula	$C_{28}H_{32}N_2O_4$
M_r	460.55
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	120
a, *b*, *c* (Å)	9.9370 (5), 11.4859 (7), 12.3351 (6)
α, β, γ (°)	89.148 (4), 68.229 (5), 66.716 (6)
V (Å^3)	1186.55 (13)
Z	2
Radiation type	Cu *K*α
μ (mm^{-1})	0.69
Crystal size (mm)	0.42 × 0.24 × 0.15
Data collection	
Diffractometer	SuperNova, Dual, Cu at zero, Atlas
Absorption correction	Gaussian *CrysAlis PRO*, Agilent Technologies, Version 1.171.36.32 (release 02-08-2013 CrysAlis171 .NET) (compiled Aug 2 2013,16:46:58) Numerical absorption correction based on gaussian integration over a multifaceted crystal model
T_{min}, T_{max}	0.493, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	17029, 4747, 4308
R_{int}	0.022
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.625

Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.037, 0.102, 1.04
No. of reflections	4747
No. of parameters	313
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.42, -0.25

Computer programs: *CrysAlis PRO*, Agilent Technologies, Version 1.171.36.32 (release 02-08-2013 CrysAlis171 .NET) (compiled Aug 2 2013, 16:46:58), olex2.solve (Bourhis *et al.*, 2013), *SHELXL* (Sheldrick, 2008), Olex2 (Dolomanov *et al.*, 2009).

_N_-(2-(2-Benzyloxy-9-hydroxy-10-oxo-9,10-dihydro-8_H_-cyclohepta[b]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 462

	Ercjmb
Crystal data	
Chemical formula	$C_{25}H_{21}F_3N_2O_4$
M_r	470.44
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	120
a, b, c (Å)	6.3966 (6), 31.150 (3), 11.3695 (11)
β (°)	101.538 (9)
V (Å^3)	2219.6 (4)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.96
Crystal size (mm)	0.62 × 0.52 × 0.39
Data collection	
Diffractometer	SuperNova, Titan S2
Absorption correction	Gaussian *CrysAlis PRO*, Agilent Technologies, Version 1.171.37.35 (release 13-08-2014 CrysAlis171 .NET) (compiled Aug 13 2014,18:06:01) Numerical absorption correction based on gaussian integration over a multifaceted crystal model Empirical absorption correction using spherical harmonics, implemented in

	SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.665, 0.768
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	19659, 4419, 4107
R_{int}	0.038
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.631
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.042, 0.105, 1.03
No. of reflections	4419
No. of parameters	313
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.23, -0.26

Computer programs: *CrysAlis PRO*, Agilent Technologies, Version 1.171.37.35 (release 13-08-2014 CrysAlis171 .NET) (compiled Aug 13 2014, 18:06:01), olex2.solve (Bourhis *et al.*, 2015), *SHELXL* (Sheldrick, 2015), Olex2 (Dolomanov *et al.*, 2009).

_N_-(2-(2,9-Bis(benzyloxy)-10-oxo-10_H_-cyclohepta[_b_]quinolin-11-yl)ethyl)-2,2,2-trifluoroacetamide 473

	ercjmc
Crystal data	
Chemical formula	$C_{32}H_{25}F_3N_2O_4$
M_r	558.54
Crystal system, space group	Monoclinic, *C*2/*c*
Temperature (K)	120
a, *b*, *c* (Å)	16.2025 (4), 12.5736 (3), 26.7673 (7)
β (°)	95.189 (2)
V (Å^3)	5430.8 (2)
Z	8
Radiation type	Cu $K\alpha$

μ (mm^{-1})	0.88
Crystal size (mm)	0.22 × 0.17 × 0.06
Data collection	
Diffractometer	SuperNova-Duo, Atlas
Absorption correction	Gaussian *CrysAlis PRO* 1.171.38.41n (Rigaku Oxford Diffraction, 2015) Numerical absorption correction based on gaussian integration over a multifaceted crystal model Empirical absorption correction using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.866, 0.947
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	10817, 4800, 4283
R_{int}	0.018
$(\sin\theta/\lambda)_{max}$ ($Å^{-1}$)	0.595
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.048, 0.131, 1.04
No. of reflections	4800
No. of parameters	373
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e $Å^{-3}$)	0.92, -0.46

Computer programs: *CrysAlis PRO* 1.171.38.41n (Rigaku OD, 2015), olex2.solve (Bourhis *et al.*, 2015), *SHELXL* (Sheldrick, 2015), Olex2 (Dolomanov *et al.*, 2009).

Carbon-carbon bond	Bond length (Å)	Bond lengths in tropolone (Å)
C5a—C6	1.454(2)	1.417(7)
C6—C7	1.336(3)	1.341(7)
C7—C8	1.430(3)	1.403(7)
C8—C9	1.350(3)	1.336(6)
C9—C10	1.489(2)	1.459(6)
C10—C10a	1.487(2)	1.446(6)
C10a—C5a	1.433(2)	1.336(6)

Table 14: Bond lengths (Å) in the tropolone ring of 473 (numbers in brackets denote estimated standard deviation).

Carbon atom	Distance from the mean plane(Å)
C5a	0.1759(13)
C6	-0.1465(14)
C7	-0.1288(15)
C8	0.1765(15)
C9	0.1311(14)
C10	-0.3408(13)
C10a	0.1327(12)

Table 15: Distance (Å) from the mean plane of the tropolone ring 473 (numbers in brackets denote estimated standard deviation).

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