Diastereoselective Synthetic Approaches to Functionalised Tetrahydropyrrolo[3,4-*a*] carbazole Derivatives

By

Matokah Mohammed Abualnaja

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

March 2016

Acknowledgments

First of all, I would like to express my grateful thanks to Dr. Michael Hall who has supervised this thesis since 2011 and never hesitated to give me wise advices, invaluable guidance and strong motivations.

I would also like to thank the members of MJH research group for their collaboration and support throughout my study.

I would also like to express my extreme gratitude to Umm Al-Qura University, the Ministry of Higher Education in the Kingdom of Saudi Arabia, and the Saudi Cultural Bureau in London for their financial support.

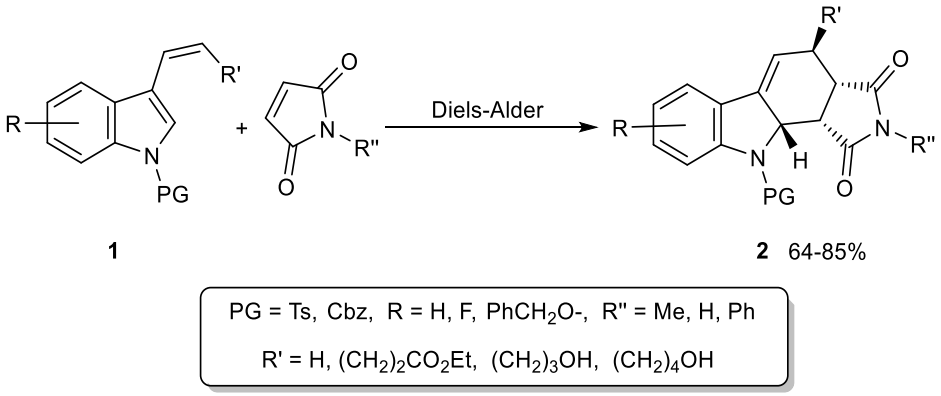
I would also like to thank my parents, who have been continuously supporting and encouraging me throughout my study as well as my life. Without their incredibly wise guidance, such a level would never be reached and such a work would never be achieved.

I would also like to express my special and sincere thanks to my husband (Mohammed Baz) for his love, constant support, and patience throughout my study.

Finally, I would like to thank my sisters (Khadijah, Kholod, Khwlah, Khamael, Abeer, Alaa and Fatimah), my brother (Abbas) and friends (especial thanks to Aseel khafaji, Einas Abbod and Nuha Halawani) for their encouragement and support throughout my study.

Abstract

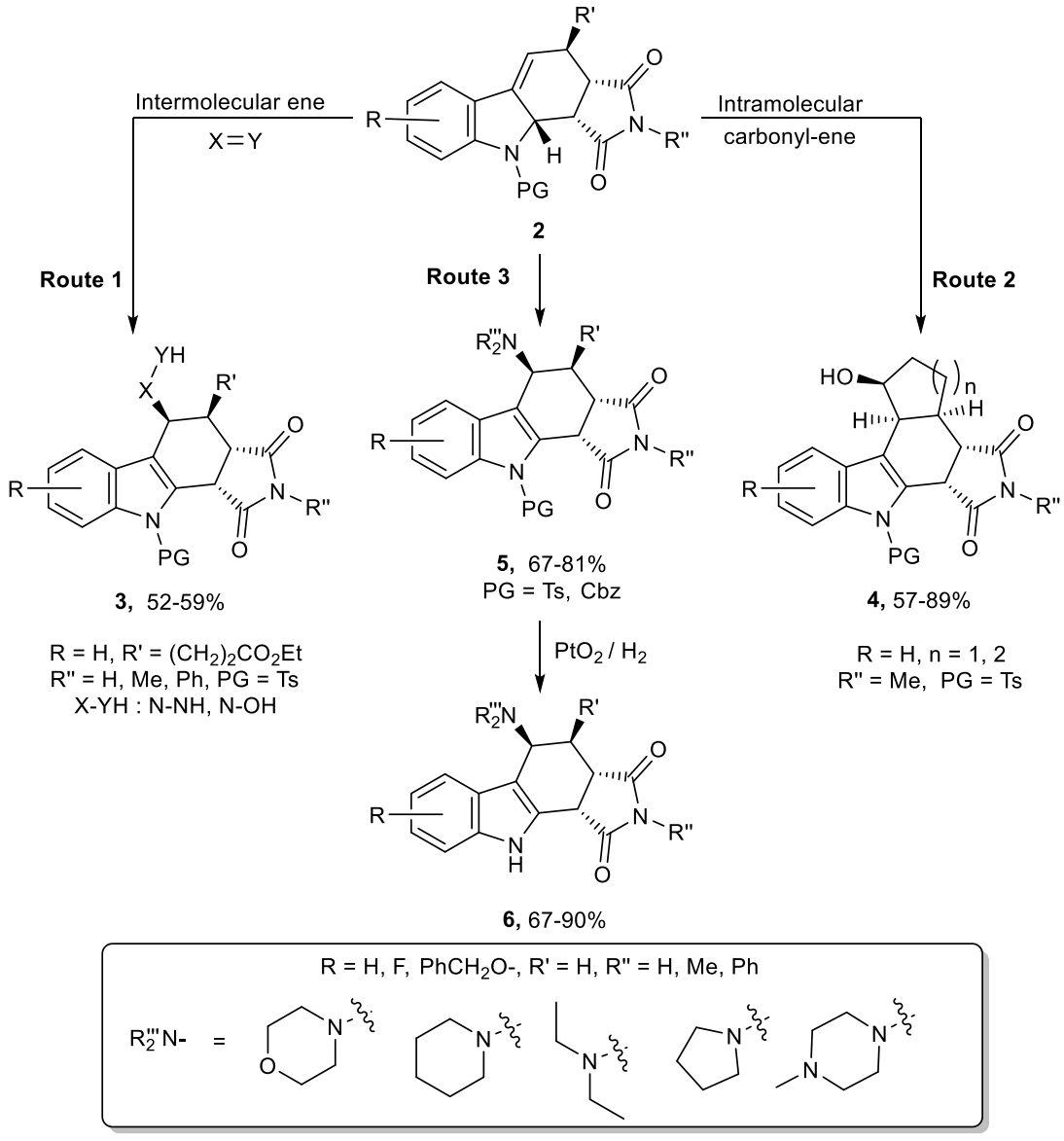
The heterocyclic carbazoles are privileged scaffolds present in many biologically active naturally occurring and synthetic compounds. Herein, we disclose our investigations into new approaches towards the diastereoselective synthesis of highly functionalised tetrahydropyrrolo[3,4-*a*] carbazole derivatives, and the subsequent evaluation of their biological activities. Our synthetic methodology is based on an initial intermolecular Diels-Alder (D-A) reaction between a substituted 3-vinyl-1*H*-indole **1,** containing an electron withdrawing *N*-protecting group, and a range of dienophiles. This key step allows access to a variety of the D-A cycloadducts **2** in good yields (64-85%) and as single diastereomers, arising from an *endo* selective D-A cycloaddition (Scheme 1).



Scheme 1. D-A reaction of *N*-protected, substituted 3-vinyl-1*H*-indole 1

The new alkene bond generated in the D-A reaction is highly reactive towards electrophiles and has a propensity towards migration, to rearomatise the indole ring. Thus we decided to exploit this reactivity to generate our target pyrrolo[3,4-*a*]carbazoles using a number of different approaches (Scheme 2). **Route 1:** D-A cycloadducts **2** was further functionalised using an intermolecular ene reaction to afford the tetrahydropyrrolo[3,4-*a*]carbazoles **3**. **Route 2:** Alternatively intramolecular carbonyl-ene reactions of D-A cycloadducts **2** were investigated as a route to polycyclic tetrahydropyrrolo[3,4-*a*]carbazoles **4**.

Route 3: Finally bromination of the reactive alkene followed by *in situ* trapping with a nucleophilic amines gave access to amine functionalised tetrahydropyrrolo[3,4-*a*]carbazoles **5.** These could in turn be deprotected *via* a PtO_2 catalysed hydrogenation to give a focussed library of biologically active molecules **6**.



Scheme 2. Synthetic approaches towards functionalised pyrrolo[3,4-*a*]carbazole

List of Abbreviations

Ar	Aromatic
Aq	Aqueous
$AlCL_3$	Aluminum chloride
br	Broad
Bn	Benzyl
$C_2O_2Cl_2$	Oxalyl chloride
COSY	Correlation spectroscopy
Cbz	Carboxybenzyl
Cs_2CO_3	Cesium carbonate
calcd.	Calculated
D-A	Diels-Alder
DCM	Dichloromethane
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAD	Dimethyl acetylenedicarboxylate
EtOH	Ethanol
Eq.	Equivalent
Et	Ethyl
Et_2NH	Diethylamine
Et_3N	Triethylamine
EWG	Electron withdrawing group
g	Gram
h	Hour
H_2O	Water
HRMS	High-resolution mass spectrometry
Hz	Hertz
IR	Infrared
K_2CO_3	Potassium carbonate
$LiAlH_4$	Lithium aluminum hydride

Me	Methyl
M	Molar
Min	Minute
Mp.	Melting point
mL	Millilitre
mg	Milligram
Me_2AlCl	Dimethylaluminum chloride
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
NMM	*N*-Methylmaleimide
NPM	*N*-Phenylmaleimide
NBS	*N*-bromosuccinimide
NaHMDS	Sodium bis(trimethylsilyl)amide
PTAD	4-Phenyl-1,2,4-triazoline-3,5-dione
Ph	Phenyl
ppm	Parts per million
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
R_f	Retention factor
r.t.	Room temperature
$SnCL_4$	Tin(IV) chloride
THF	Tetrahydrofuran
TFAA	Trifluoroacetic anhydride
Ts	Tosyl
TLC	Thin-layer chromatography
UV	Ultra-violet

Table of Contents

Chapter 1.

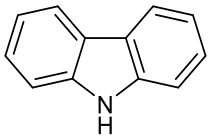
Introduction

The aim of this project is to discover and investigate efficient synthetic methodologies towards a diverse range of functionalised carbazole alkaloids. Therefore we will review the carbazole structure, related bioactive compounds and previously reported synthetic approaches towards carbazole alkaloids.

1.1. Introduction to the carbazole alkaloids

1.1.1. The discovery of the carbazole alkaloids

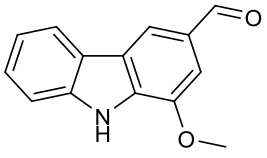
A carbazole is an aromatic heterocyclic organic compound with a tricyclic strcuture, consisting of two six-membered benzene rings fused on either side with a five membered nitrogen-containing pyrrole ring.[1] Graebe and Glazer were the first to describe 9*H*-carbazole **1** (Figure 1.1), which was extracted from coal tar in 1872.[2]



1

Figure 1.1. Structure of 9*H*-carbazole

The first carbazole alkaloid isolated from a plant source was murrayanine **2** (Figure 1.2).[3] In 1965, Chakraborty and co-workers reported the isolation and antibiotic properties of murrayanine, from the stem bark of *Murraya Koenigii* Spreng (Family-Rutaceae).[3,4] Since then, a large number of biologically active carbazole alkaloids have been isolated from natural sources over the last four decades.[5]



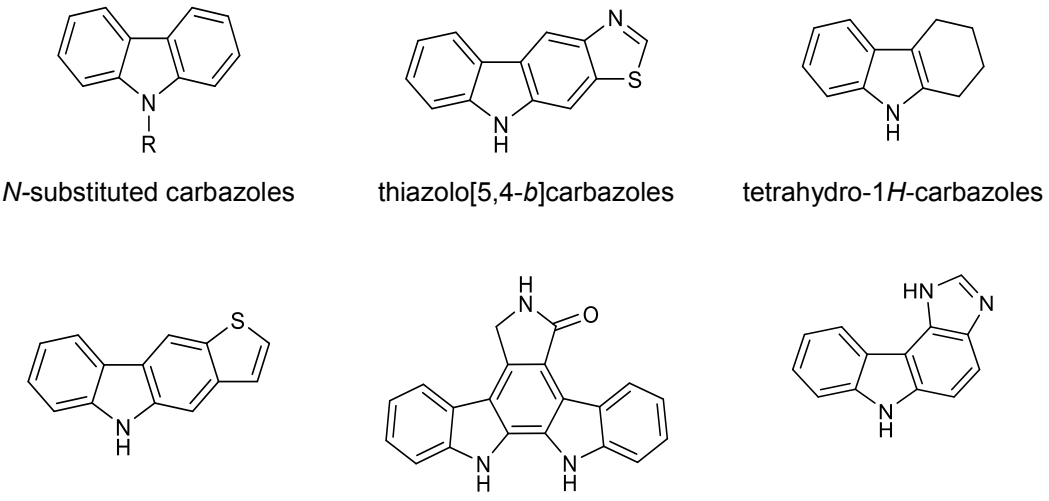
2

Figure 1.2. Structure of murrayanine

1.1.2. Classification of the carbazole alkaloids

Carbazole alkaloids are typically divided into two major classes depending upon their natural sources. The first class, which constitute a major class of carbazole alkaloids, originates from taxonomically related higher plants of the genus *Murraya*, *Clausena* and *Glycosmis*, all belonging to the family of *Rutaceae*. The second class of carbazole alkaloids are those that are isolated from microbial species, including bacteria (e.g. *Streptomyces*), blue-green *algae (*e.g. *Hyella caespitosa*), fungi (e.g. *Aspergillus)* and marine organisms (e.g. *Iotrochota* and *Didemnum granulatum*).[6,7]

Due to the diverse and interesting biological properties of the carbazole alkaloids, synthetic chemists have developed many synthetic strategies towards these structures. A number of bioactive carbazole derivatives have been synthesised, based on *N*-substituted carbazoles, thiazolo[5,4-*b*]carbazoles, tetrahydro-1*H*-carbazoles, thieno[3,2-*b*]carbazoles, indolopyrrolo[3,4-*c*]carbazoles and imidazo[4,5-*c*]carbazoles (Figure 1.3).[1,8]



N-substituted carbazoles | thiazolo[5,4-*b*]carbazoles | tetrahydro-1*H*-carbazoles

thieno[3,2-*b*]carbazoles | indolopyrrolo[3,4-*c*]carbazoles | imidazo[4,5-*c*]carbazoles

Figure 1.3. Selected Structures of various carbazole classes

1.1.3. The medicinal importance of the carbazole alkaloids

The tricyclic carbazole skeleton is an essential structural scaffold found in many natural alkaloids and biologically active synthetic compounds. Among the carbazole derivatives, heterocycle-fused carbazoles are of considerable

interest due to their anticancer properties. For example, indole-fused carbazole rebeccamycin is a topoisomerase I inhibitor,[9] whilst staurosporine, isolated from *Streptomyces*, was identified as a protein kinase C (PKC) inhibitor.[10] Granulatimide and isogranulatimide, compounds isolated from the ascidian *Didemnum granulatum* that possess the pyrrolocarbazole framework, [11,12] as well as synthetic indolocarbazole compounds such as SB-218078, were also found to be efficient checkpoint 1 kinase (ChK1) inhibitors.[7,] The structures of selected bioactive carbazole alkaloids with potential anticancer properties are given in Figure 1.4**.**

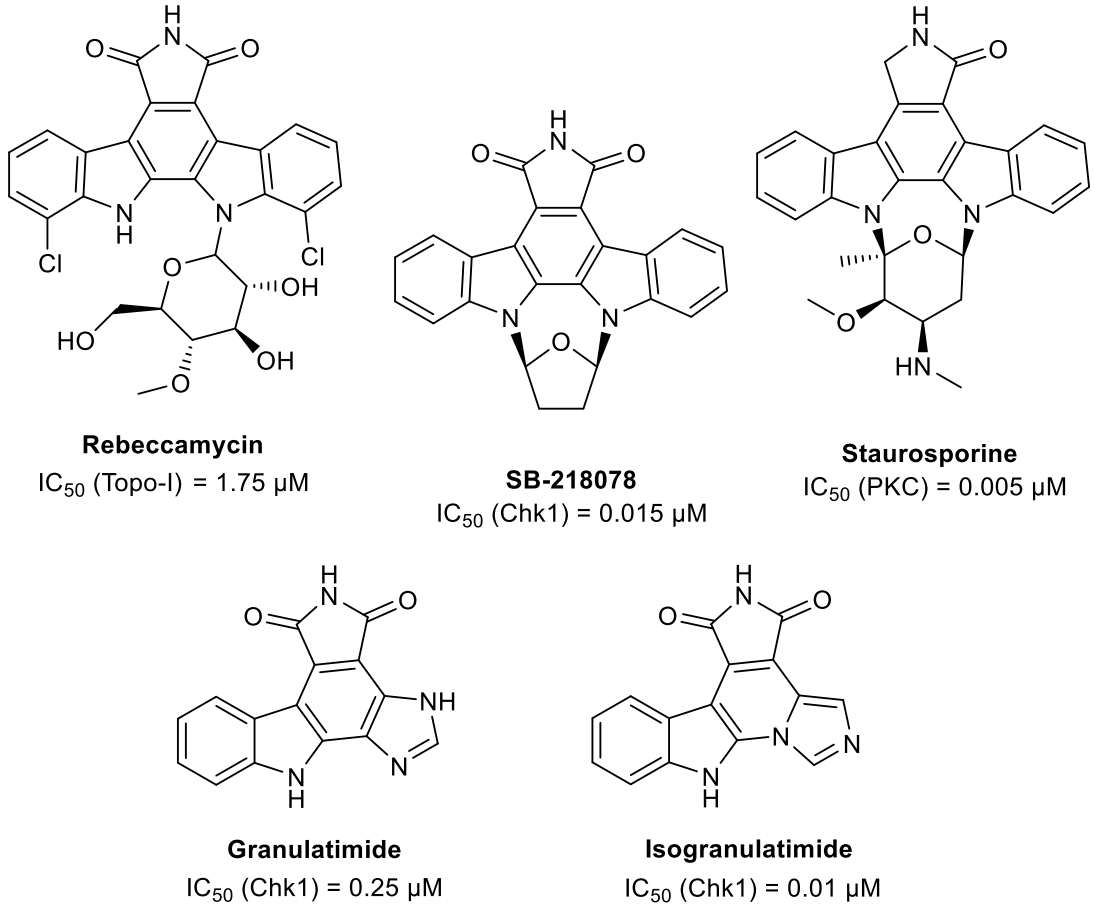


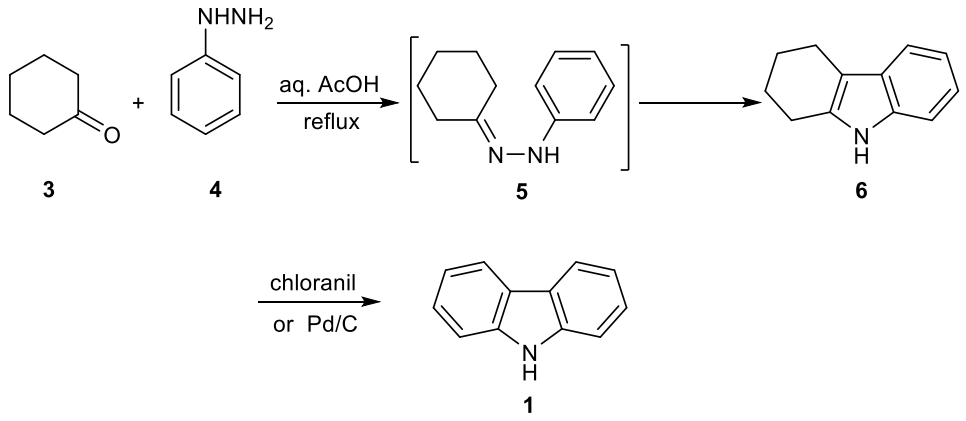
Figure 1.4. Selected structures of anticancer carbazole alkaloids

1.2. Selected synthetic approaches to the carbazole alkaloids

1.2.1. Classical routes to the carbazoles

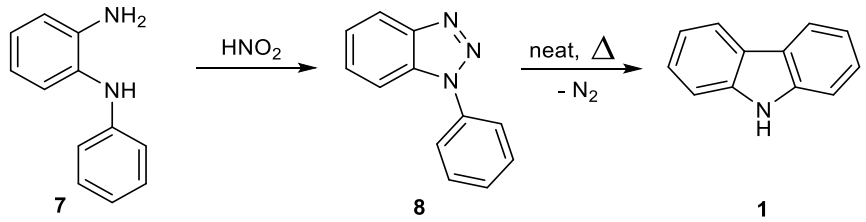
Various strategies for the synthesis of the carbazoles have been developed. The earliest synthesis of a carbazole was reported in 1883 by Fischer and

Borsche,[13] who described the synthesis of a carbazole **1** through a Fischer-indole synthesis. This method involves the condensation of cyclohexanone **3** and phenylhydrazine **4** under acidic conditions, followed by cyclisation of the formed phenylhydrazone **5** to generate tetrahydrocarbazole **6.** Finally, dehydrogenation of tetrahydrocarbazole **6** using chloranil or palladium on activated carbon generates the fully aromatised carbazole **1** (Scheme 1.1).[14,15]



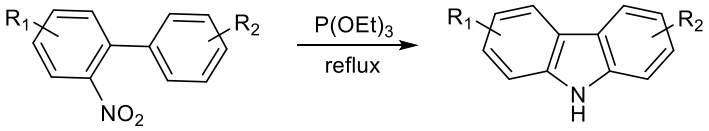
Scheme 1.1. Fischer-Borsche carbazole synthesis

Subsequently in 1896, Graebe and Ullmann reported the formation of carbazole **1** by the reaction of aminodiphenylamine **7** with nitrous acid, followed by thermolysis of the resulting benzotriazole **8** (Scheme 1.2).[13]



Scheme 1.2. Graebe-Ullmann carbazole synthesis

An alternative route to the carbazole framework **10** was developed by Cadogan, which involves deoxygenative cyclisation of *o*-nitrobiphenyls **9** in the presence of triethyl phosphite (Scheme 1.3).[16]



9 10

Scheme 1.3. Cadogan carbazole synthesis

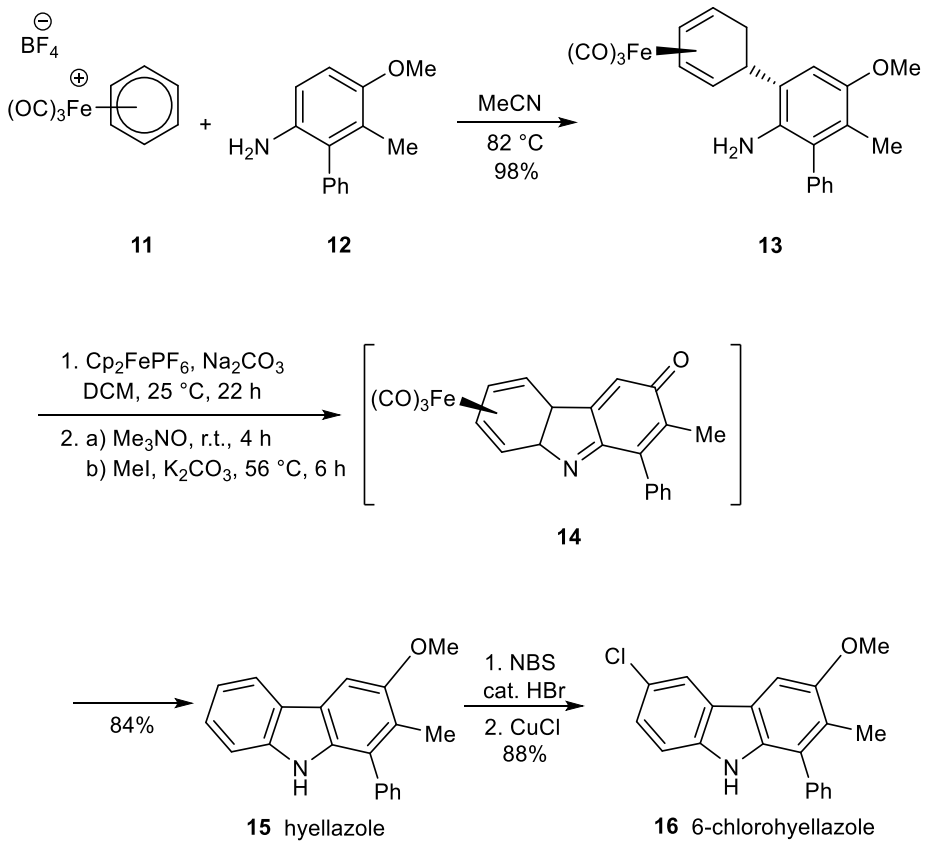
1.2.2. Transition metal–mediated routes to the carbazoles

Beyond the traditional methods discussed previously, the use of transition metals including Cu,[17] Pt,[18] Au,[19] Rh,[20] Fe[21] and Pd[22] in the synthesis of carbazoles has been well documented. The most versatile approaches for the construction of highly functionalised carbazole frameworks, are based on the use of iron and palladium catalysed C-C bond forming events.

1.2.2.1. Iron-mediated routes to carbazole alkaloids

In 1989, Knölker and Bauer described an iron-catalysed oxidative cyclisation of arylamines or quinone amines for the construction of the carbazole skeleton. The key steps of this iron-mediated route are the sequential formation of both a C–C and a C–N bond.[23] This method was subseqeuntly applied to the total synthesis of the naturally occuring alkaloids hyellazole **15** and 6-chlorohyellazole **16** by Knölker (Scheme 1.4).

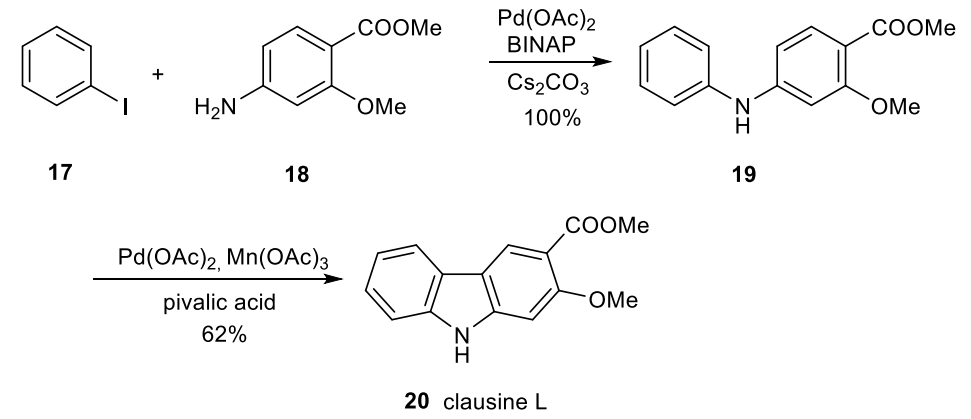
Hyellazole **15** and 6-chlorohyellazole **16** represent the first carbazoles isolated from the blue-green *algae Hyella caespitosa* by Moore and co-workers in 1979.[24] The total synthesis of hyellazole **15** begins with electrophilic aromatic substitution of arylamine **12** by the complex salt **11,** followed by rearrangement to give the desired complex **13.** Oxidative cyclisation of **13** by ferrocenium hexafluorophosphate in the presence of sodium carbonate affords hyellazole **15** in 84% yield. Hyellazole **15** can then be easily converted into 6-chlorohyellazole **16** via an NBS bromination and halogen exchange using copper (I) chloride. [24,25]



Scheme 1.4. Synthesis of hyellazole 15 and 6-chlorohyellazole 16

1.2.2.2. Palladium-catalysed synthetic routes to carbazole alkaloids

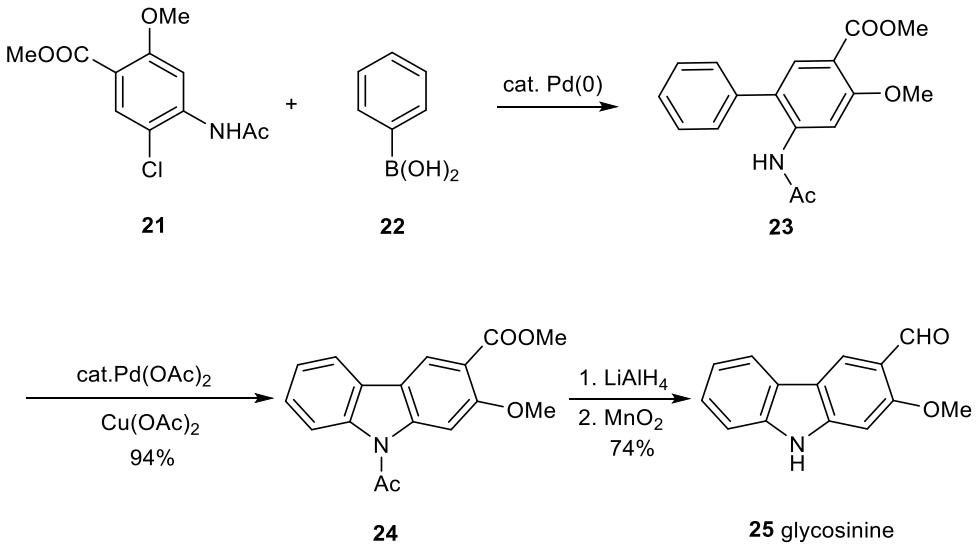
Palladium-catalysed sequential C-N/C-C coupling was used for the synthesis of the naturally occurring compound, clausine L. The synthesis of clausine L **20**, which was isolated from the Chinese medicinal plant *Clausena excavata*,[26] is based on a Buchwald–Hartwig coupling reaction of iodobenzene **17** with arylamines **18** in the presence of Pd(0) to generate diarylamine **19**.[27,28] The following oxidative cyclisation of diarylamine **19,** by the double C-H bond activation in the presence of of Pd (II) and manganese (III) acetate, provides clausine L **20** in 62% yield (Scheme 1.5).[28] -



17 **18** **19** **20** clausine L

Scheme 1.5. Synthesis of clausine L 20

A similar palladium-catalysed approach was used in the total synthesis of glycosinine **25**, involving a Suzuki-Miyaura coupling of 2-chloroarylamine **21** with phenyl boronic acid **22**, followed by an oxidative cyclisation of the formed *N*-acetylated 2-aminobiphenyl **23**. The final conversion of the ester moitey of **24** to an aldehyde by a reduction/oxidation approach gave glycosinine **25** in 74% yield (Scheme 1.6).[29]

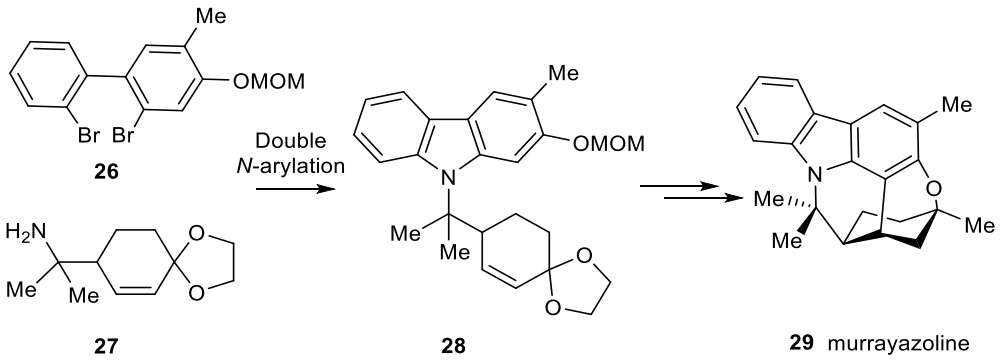


21 **22** **23** **24** **25** glycosinine

Scheme 1.6. Synthesis of glycosinine 25

Recently, Ackermann *et al*. described the domino N–H/C–H bond activation reaction of anilines with 1,2-dihaloarenes.[30,31] An analogous approach was applied to the total synthesis of murrayazoline **29**, which was isolated from the genus *Murraya*.[32,] The key steps in the synthesis of murrayazoline involved

the preparation of *N*-substituted carbazole component **28,** using the palladium catalysed Buchwald-Hartwig coupling reaction of the primary amine **27** with dibromobiphenyl **26** (Scheme 1.7).[33]



Scheme 1.7. Synthesis of murrayazoline 29

1.3. The Diels-Alder reaction

In addition to the synthetic approaches described above, the use of Diels-Alder (D-A) reactions in the synthesis of carbazole derivatives have been well documented.[34,35,36] The D-A reaction has been extensively studied since its discovery in 1928 by Otto Diels and Kurt Alder.[37] The cycloaddition reaction leads to the formation of two new C-C or C-X bonds and four new stereocentres simultaneously, with high levels of regio- and stereo selectivity, in a single step through a concerted mechanism (Scheme 1.8).

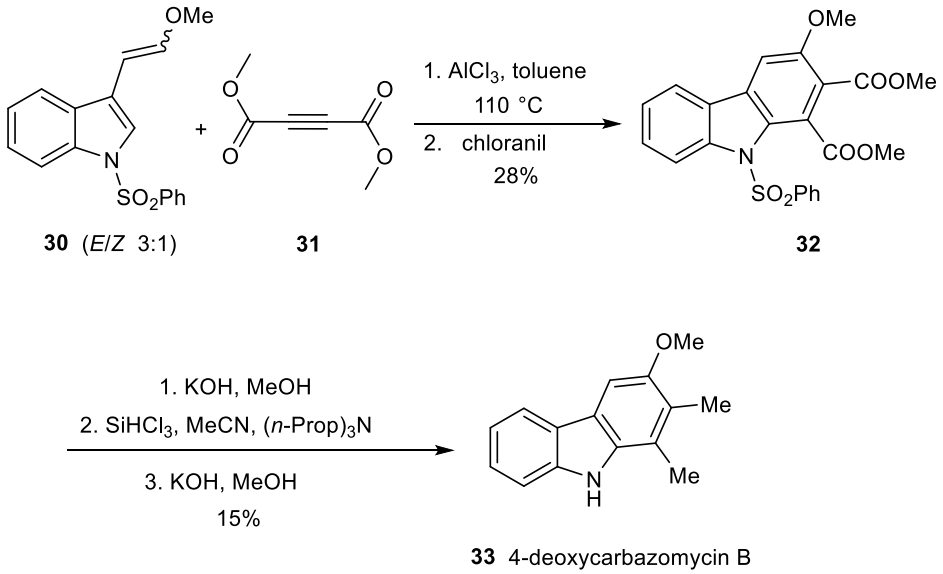
Scheme 1.8. General Diels-Alder (D-A) reaction

1.3.1. Diels-Alder reactions in the synthesis of bioactive carbazoles

Due to the selectivity of the D-A reaction, it has been widely used by organic chemists for the synthesis of complex biologically active molecules, including those based on a carbazole scaffold, from simple starting materials. In this context, Pindur *et al*., have studied the D-A cycloaddition reaction of

substituted 3-vinyl-1*H*-indole **30,** as a key step in the preparation of the antibiotic 4-deoxycarbazomycin B **33** (Scheme 1.9).

Pindur and co-workers' strategy involves a D-A reaction between substituted 3-vinyl-1*H*-indole **30** and dimethyl acetylenedicarboxylate DMAD **31**, followed by dehydrogenation with chloranil to give the trisubstituted carbazole **32**. Reduction of the ester groups to methyl groups and removal of the protecting group provides 4-deoxycarbazomycin B **33** in 15% overall yield (Scheme 1.9).[38]

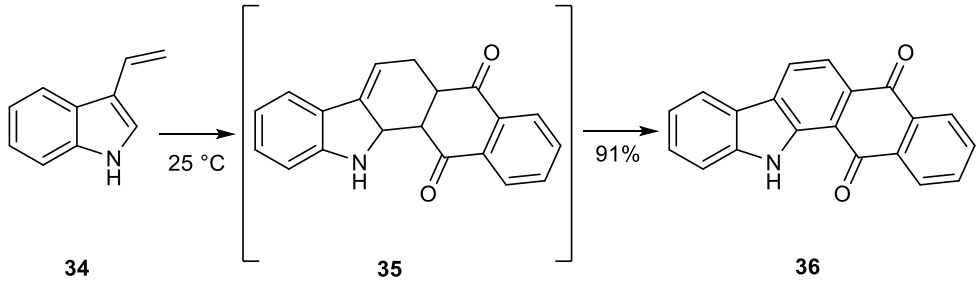


30 (*E*/*Z* 3:1) **31** **32**

33 4-deoxycarbazomycin B

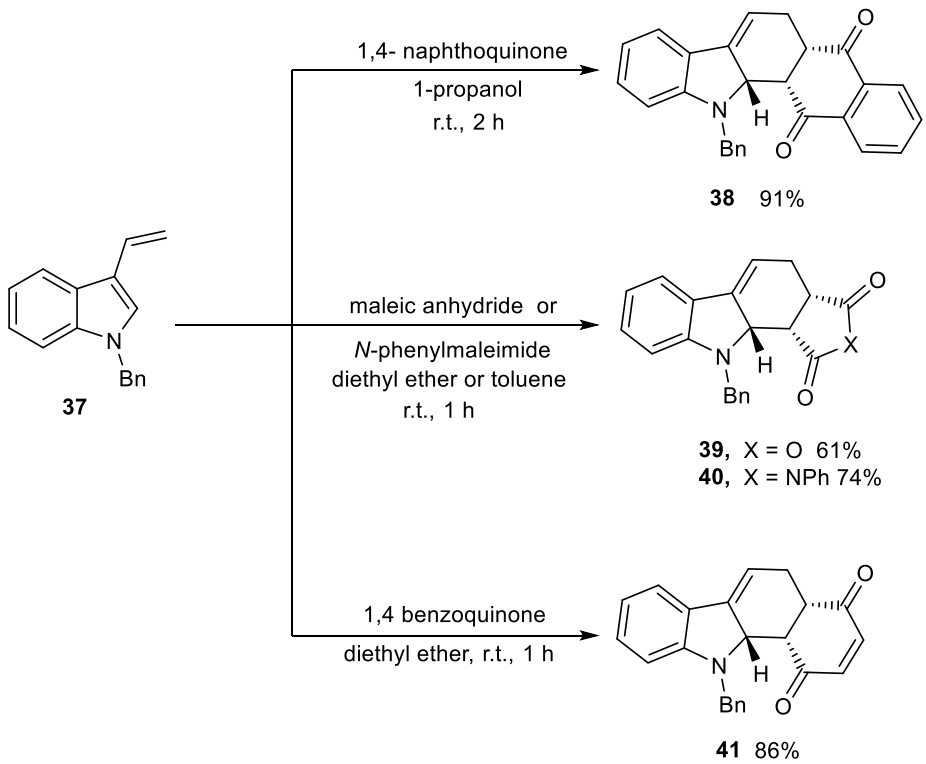
Scheme 1.9. Synthesis of 4-deoxycarbazomycin B 33 by D-A reaction

The intermolecular D-A reaction of 2- and 3-vinyl-1*H*-indoles is also a powerful synthetic strategy towards the construction of heterocycle-fused carbazole frameworks. In 1959, Noland and co-workers examined the D-A reactions of substituted 3-vinylindoles, as a route to the carbazole scaffold.[39] Subsequent work by the same author in 1963 also described the synthesis of carbazole **36** by an intermolecular D-A reaction of 3-vinyl-1*H*-indole **34** with 1,4-naphthoquinone, to give tetrahydrocarbazole intermediate **35.** The subsequent dehydrogenation of tetrahydrocarbazoles **35** provided the more stable, fully aromatised carbazole **36** in 91% yield (Scheme 1.10).[40]



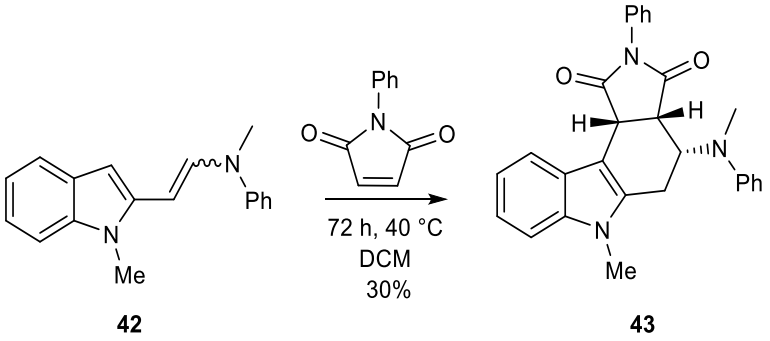
Scheme 1.10. D-A reaction to the synthesis of carbazole 36

Lambert and Porter subsequently developed a method to synthesise a range of stable tetrahydrocarbazoles (**38 - 41**) in good yields, from the D-A reaction of 1-benzyl-3-vinyl-1*H*-indole **37** with a range of dienophiles including 1,4 naphthoquinone, maleic anhydride, *N*-phenylmaleimide (NPM), and 1,4 benzoquinone (Scheme 1.11).[41]



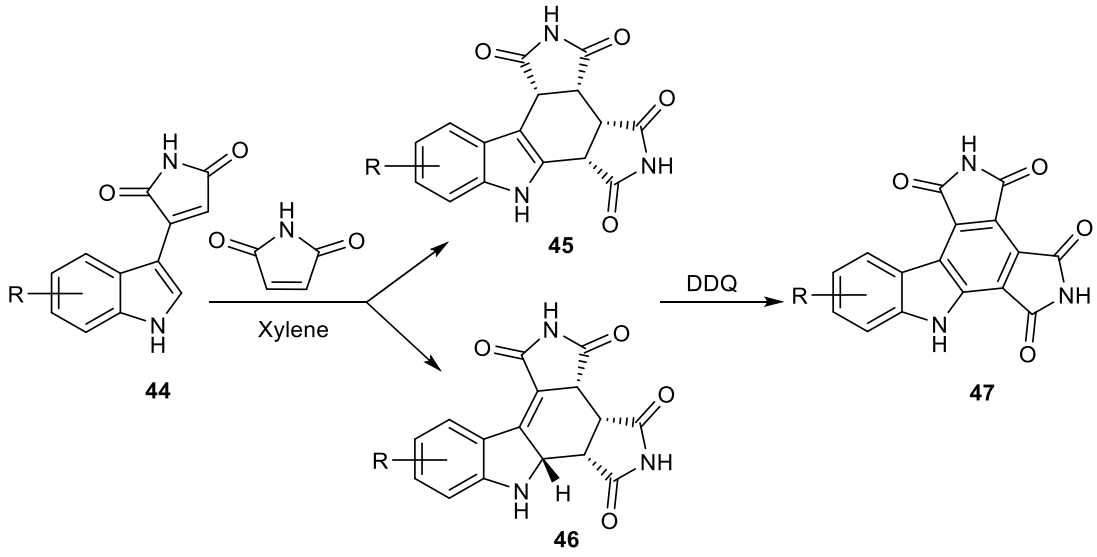
Scheme 1.11. D-A reaction towards tetrahydrocarbazoles (38 - 41)

In 1992, Pindur and Otto also developed a new synthetic strategy towards tetrahydrocarbazole **43**, which was shown to have antitumor activity, [42] using a D-A reaction between 2-vinyl-1*H*-indole **42** and NPM (Scheme 1.12).[43]



Scheme 1.12. D-A reaction towards bioactive tetrahydrocarbazole 43

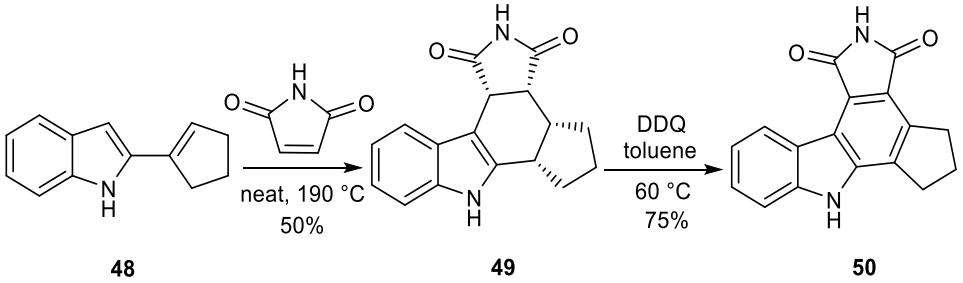
Carbazoles **47** which are structurally related to granulatimide and isogranulatimide have recently been synthesised by Prudhomme *et al.,* through the D-A reaction of 3-indolylmaleimide **44** with maleimide.[44] The formed tetrahydrocarbazole intermediates **45** and **46** can be aromatised to afford granulatimide and isogranulatimide analogues **47,** by oxidation using DDQ (Scheme 1.13).[12,45,46] These compounds proved to be potent ChK1 inhibitors.[47]



Scheme 1.13. D-A reaction to granulatimide and isogranulatimide analogues 47

In contrast, Tao *et al*., have shown a new approach for the synthesis of compounds with a pyrrolocarbazole framework, from the D-A reaction of 2-substituted-vinylindole **48** with maleimide, followed by DDQ oxidation

(Scheme 1.14). The resulting pyrrolocarbazole **50** was identified as a potential poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor with IC_{50} value of 36 μM.[48]

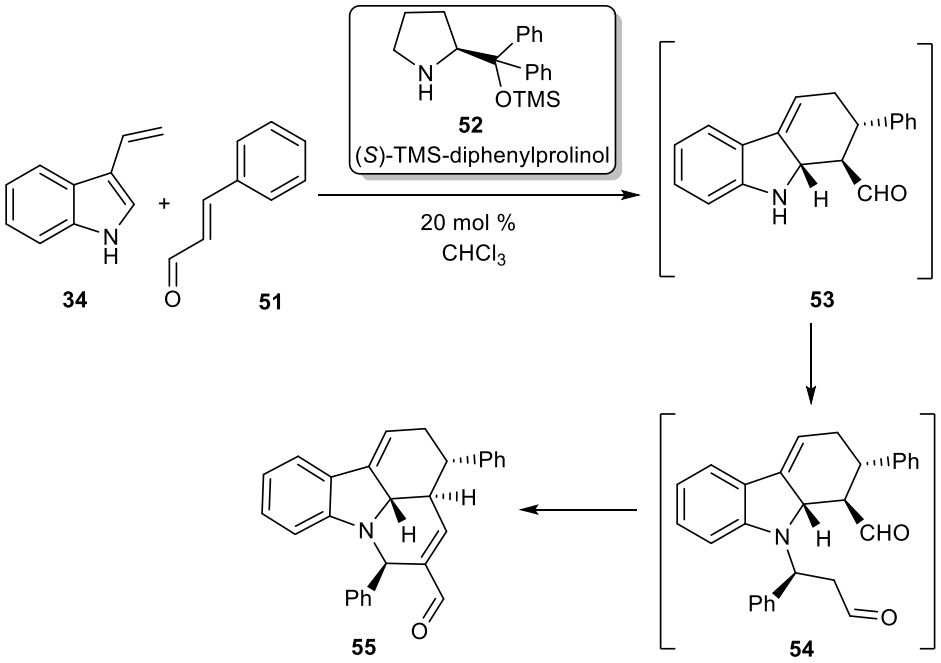


Scheme 1.14. D-A reaction in the synthesis of (PARP-1) inhibitor 50

1.4. Asymmetric Diels-Alder reactions to enantiopure carbazoles

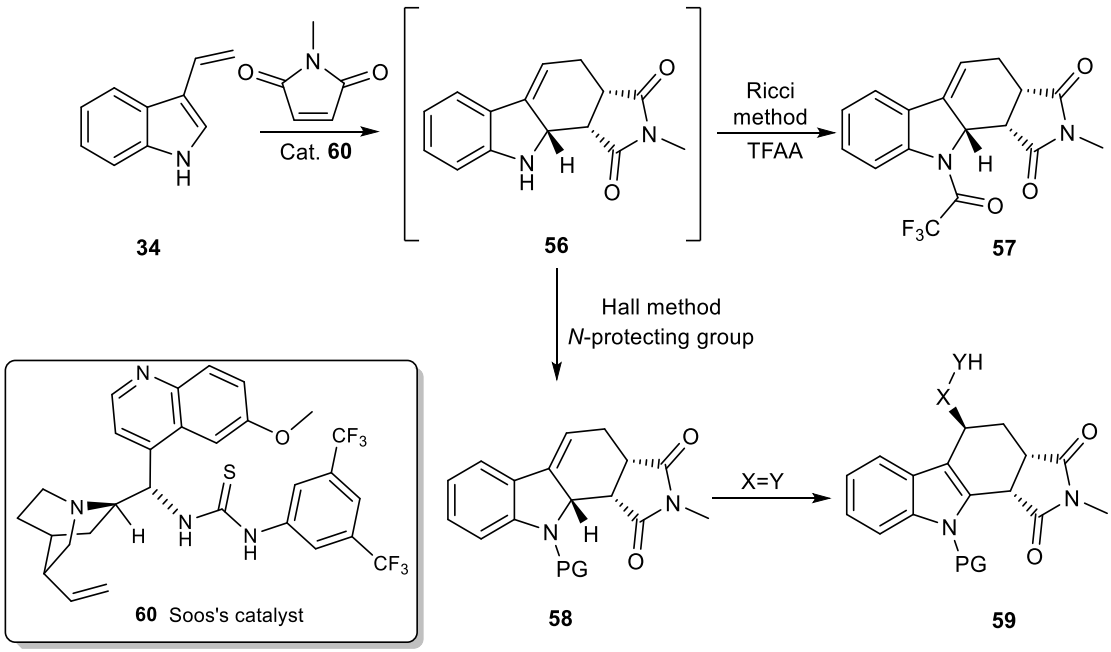
Recently, a number of organo-catalysed D-A reactions of 3-vinylindoles has been explored as an approach to the synthesis of enantioenriched tetrahydrocarbazoles. The organo-catalysed D–A reaction is dominated by activation of the LUMO of electron-poor dienophiles with chiral organic molecules. For example, Enders *et al*., used a proline **52** derived organocatalyst in a triple cascade reaction, to target tetracyclic pyridocarbazole derivatives **55** in a high enantiomeric excess.[49]

The first step of this triple cascade reaction involves the preparation of tetrahydrocarbazole intermediate **53,** through a D-A cycloaddition between 3-vinyl-1*H*-indole **34** with cinnamaldehyde **51** under iminium activation. In the next step, the indolic nitrogen of **53** reacts with another molecule of cinnamaldehyde **51** in an aza-Michael addition to give the intermediate **54**. The intramolecular aldol condensation of **54**, under enamine activation, gives the fused tetracyclic pyridocarbazole **55** (Scheme 1.15).



Scheme 1.15. Proline-catalysed asymmetric D-A reaction

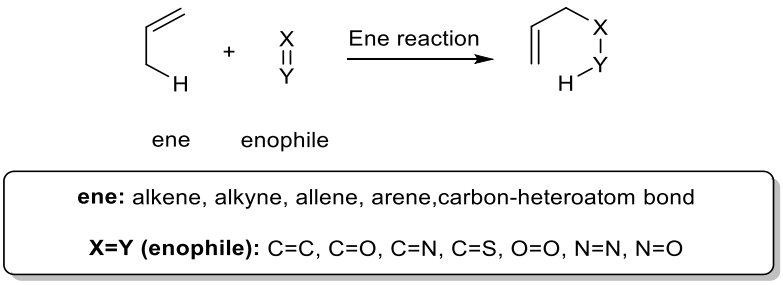
Ricci *et al.,* have also reported an interesting organo-catalysed approach to the synthesis of optically active tetrahydrocarbazole derivative **57,** through the asymmetric Diels–Alder reaction of 3-vinyl-1*H*-indole **34** with a suitable dienophile, such as *N*-Methylmaleimide (NMM) using a hydrogen-bonding thiourea catalyst **60**.[50] Subsequently, Hall and co-workers have exploited this approach to access enantiomerically pure, highly functionalised tetrahydrocarbazole derivatives **59,** through a D-A/ene reaction sequence of 3-vinyl-1*H*-indole **34** (Scheme 1.16).[51]



Scheme 1.16. Thiourea-catalysed asymmetric D-A reaction of 3-vinyl-1*H*-indole 34

1.5. Ene reaction

The ene reaction, which was discovered in 1943 by Alder, is a pericyclic process involving the reaction between an olefin containing an allylic hydrogen (ene component) and an electron deficient multiple bond (enophile), to form a new acyclic product with transposition of the π-bond and simultaneous 1,5 hydrogen shift (Scheme 1.17).[52] Several variations of the electron-deficient enophile components have been used in ene reactions, including singlet oxygen ($^1O_2$),[53] nitroso compounds,[54] aza compounds [55] and carbonyl enophiles.[56]

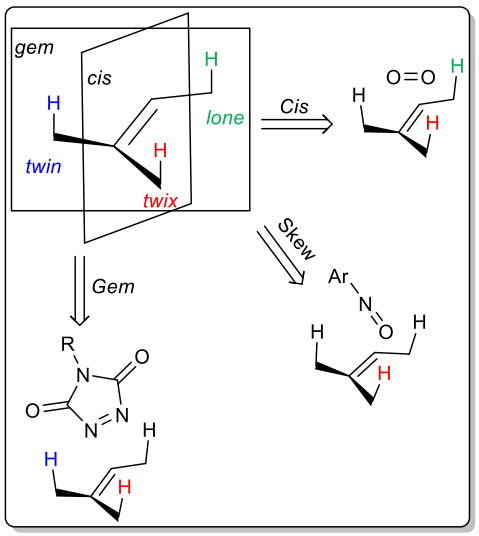


Scheme 1.17. General scheme of the ene-reaction

1.5.1. Regioselectivity of the ene reaction

The regioselectivity of ene reactions of di-, tri- and tetra-substituted alkenes with enophiles is of special interest due to the availability of several allylic hydrogen atoms that could be abstracted.

According to Krebs and co-workers,[54] the regioselectivity of the ene reactions could be rationalised in terms of conformational accessibility to the allylic hydrogen atoms and the minimisation of the steric repulsion during the reaction. For example, singlet oxygen ($^1O_2$) has a preference to abstract the allylic hydrogen from the *lone* and *twix* positions of the more substituted side of the double bond, due to the coordination with the allylic hydrogen atoms (*cis* effect). Triazolinedione (TAD) prefer to abstract the *twin or twix* allylic hydrogen from the more crowded end of the double bond, due to formation of the more stable intermediate (*gem* effect). On the other hand, nitroso compounds (ArNO) abstract the allylic hydrogen form only the *twix* position of the alkene (*skew* effect), (Scheme 1.18).[54, 57]

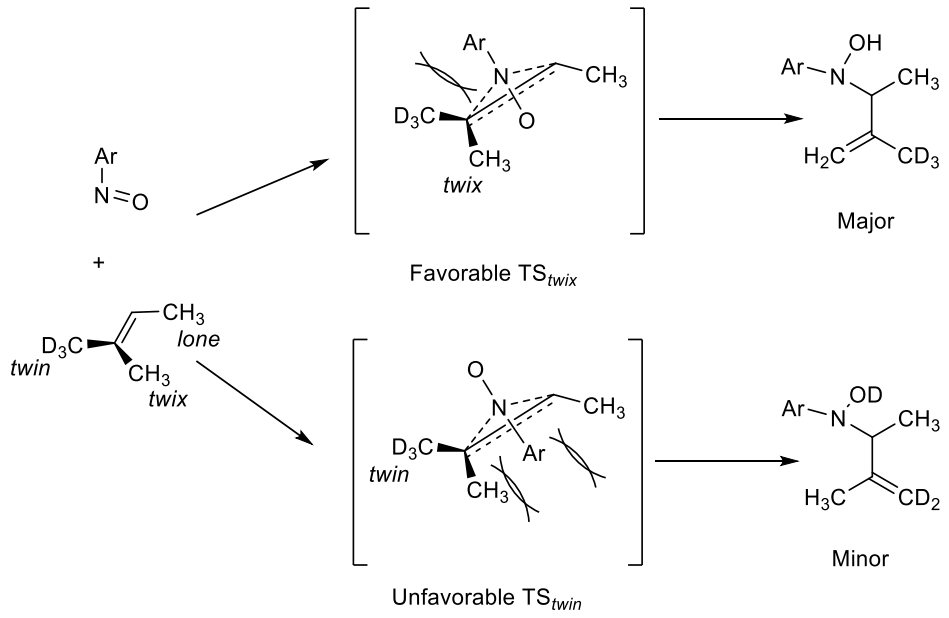


Scheme 1.18. Regioselectivity in the ene reaction of $^1O_2$, TAD and ArNO

The high *twix* regioselectivity in the ene reaction of the aryl-nitroso enophile (ArNO) can be rationalised in terms of the steric interactions between the substituents of the ene component with the aryl group of the nitroso enophile,

as well as to the conformational accessibility of the allylic hydrogen in the two possible transition states: TS_{twix} and TS_{twin}.

In TS_{twix}, the aryl group of the enophile points to the less substituted side of the alkene, with no conformational constraint on the hydrogen abstraction. Whereas when the ArNO approaches from the opposite direction in the TS_{twin}, the aryl group of the enophile is located at more sterically hindered side of the alkene, between the *lone* and *twix* substituents of the ene component. Therefore, hydrogen abstraction from the *twix* position of the alkene has a tendency to predominate (Scheme 1.19).[54, 58]



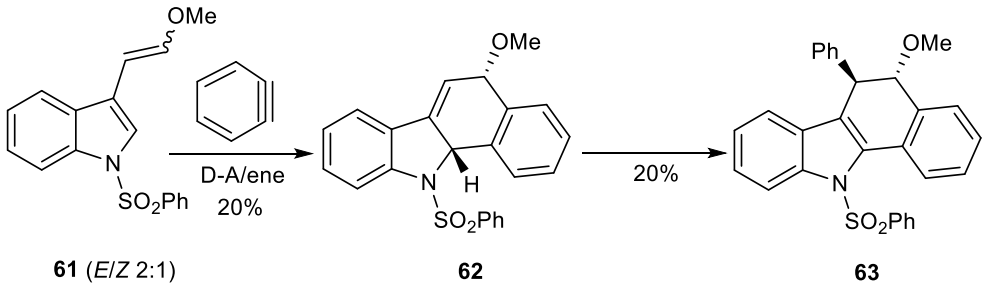
Scheme 1.19. The *twix* regioselectivity in the ene reaction of the nitroso enophile

1.6. One-pot multicomponent reactions in the synthesis of carbazoles

A multicomponent reaction is a process in which three or more starting materials react in one reaction vessel to generate the target molecule. The synthesis time, costs of solvent use and waste production are minimalised, as intermediates are not isolated.[59,60] Although the one-pot multicomponent reactions are fashionable these days, they have been investigated for over 150 years including the Strecker amino acid synthesis,[61] the Hantzsch dihydropyridine synthesis,[62] the Mannich reaction [63] and the Ugi four-component synthesis.[64]

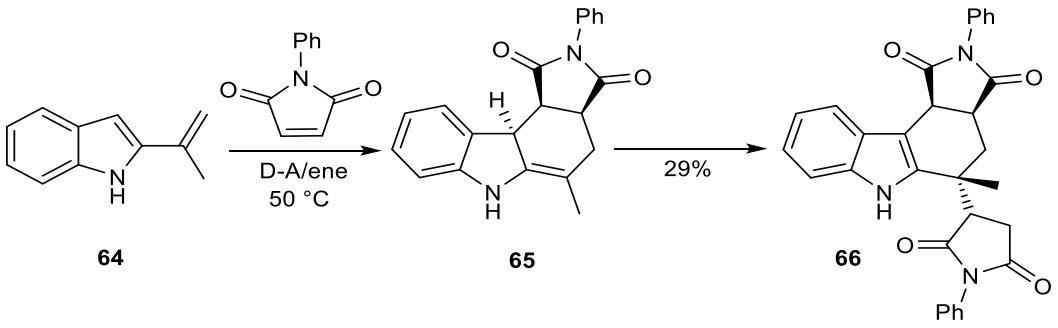
1.6.1. One-pot Diels-Alder/ene reactions in the synthesis of carbazoles

The utilisation of a one-pot D-A/ene reaction in the synthesis of functionalised carbazoles was first reported by Gonzalez and co-workers.[65] In 1996, Gonzalez *et al*., observed the formation of both D-A cycloadduct **62,** along with functionalised carbazole **63** in their study of D-A reaction between substituted-3-vinyl-1*H*-indole **61** and benzyne (Scheme 1.20). They suggested that functionalised carbazole **63** was formed *in situ* through an ene reaction of D-A cycloadduct **62** with a second molecule of benzyne.



Scheme 1.20. One pot D-A/ene reaction of substituted-3-vinyl-1*H*-indole 61

An analogous result has also been reported in the case of D-A/ene reaction sequence of 2-vinyl-indole **64** with NPM when the reaction was performed in methanol at 50 ^{o}C (Scheme 1.21). [66]

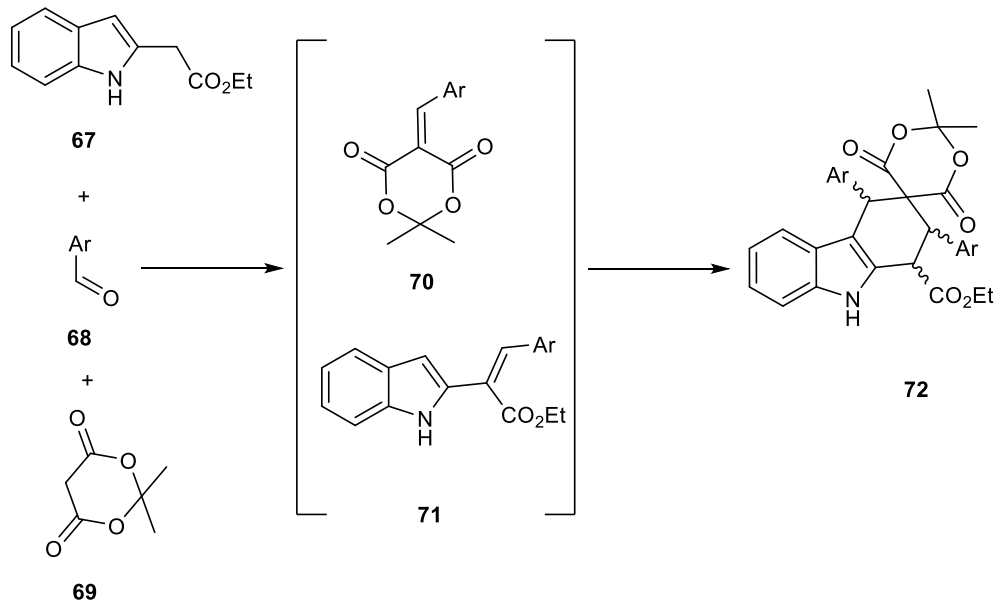


Scheme 1.21. Sequential D-A/ene reaction of 2-vinylindole 64

1.6.2. Multicomponent reactions in the synthesise of carbazoles

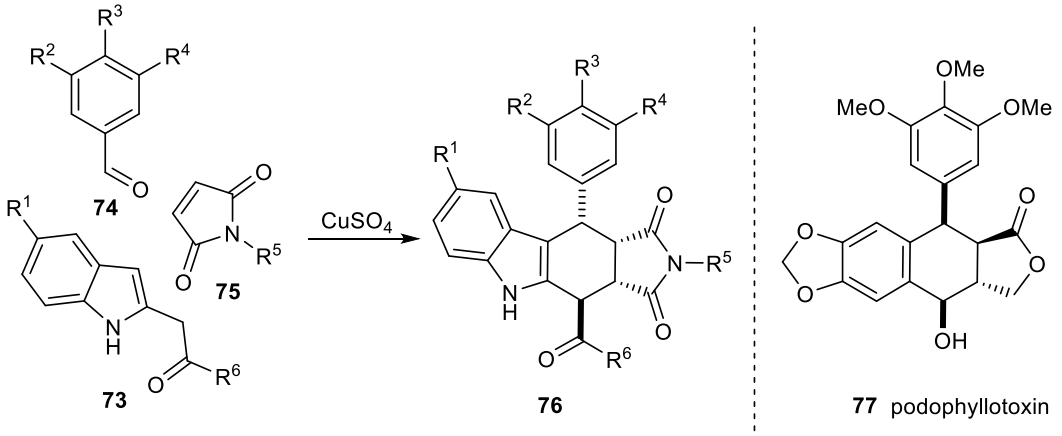
The multicomponent reactions of indoles have been extensively studied to generate large libraries of biologically active carbazoles.[67] Sapi and co-

workers reported a four component reaction to synthesise a 1,3-diaryl substituted tetrahydrocarbazole **72**, by the condensation of 2-substituted indole **67**, two equivalents of an aromatic aldehyde **68** and Meldrum's acid **69** (Scheme 1.22).[68] The product is proposed to arise from the condensation of aldehyde **68** with indole **67** to generate a 2-vinyl indole intermediate **71,** whilst condensation of Meldrum's acid **69** and a further equivalent of **68** gave intermediate **70**. Finally, D-A cycloaddition between 2-vinylindole intermediate **71** and adduct **70** afforded the desired tetrahydrocarbazole **72**.[69]



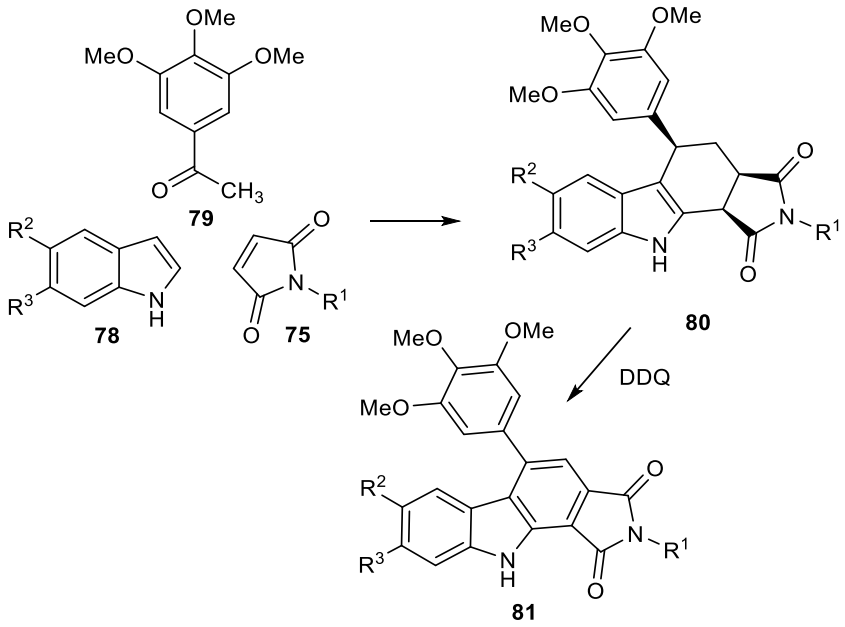
Scheme 1.22. Multicomponent reactions towards carbazole 72

Royer *et al.,* utilised D-A cycloaddition of substituted 2-indole **73**, aromatic aldehyde **74** and maleimide compounds **75** in the presence of Lewis acid catalyst ($CuSO_4$), to target molecules such as **76** which are structurally related to podophyllotoxin **77**, a naturally occurring tubulin polymerization inhibitor (Scheme 1.23).[70]



Scheme 1.23. Synthesis of podophyllotoxin analogues 76

Similarly, Ty *et al*., have reported a three component reaction of indole **78**, 3,4,5-trimethoxyacetophenone **79** and maleimides **75** to yield tetrahydrocarbazoles **80**, which could be oxidised by DDQ to give the corresponding carbazoles **81** (Scheme 1.24).[71] The biological activity of both tetrahydrocarbazoles **80** and carbazoles **81** have been investigated against murine B16 melanoma cells, and the inhibition of tubulin polymerization.[67,71]



Scheme 1.24. Multicomponent reactions to bioactive carbazoles 80 and 81

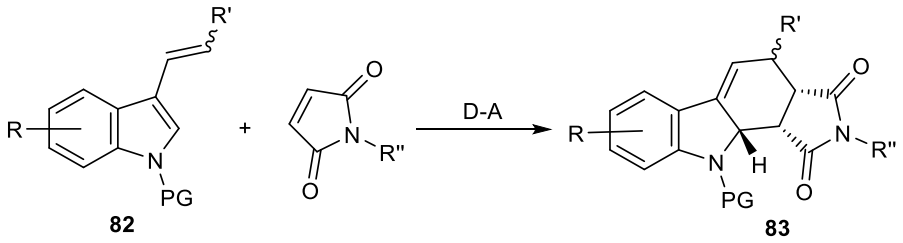
1.7. Conclusion

Although a number of well-developed synthetic strategies are available for the synthesis of bioactive functionalised carbazoles, the majority result in the synthesis of unsaturated systems. We thus wished to examine new synthetic approaches to partially saturated and polycyclic carbazole scaffolds, as new routes to biologically active molecules.

1.8. Project plan

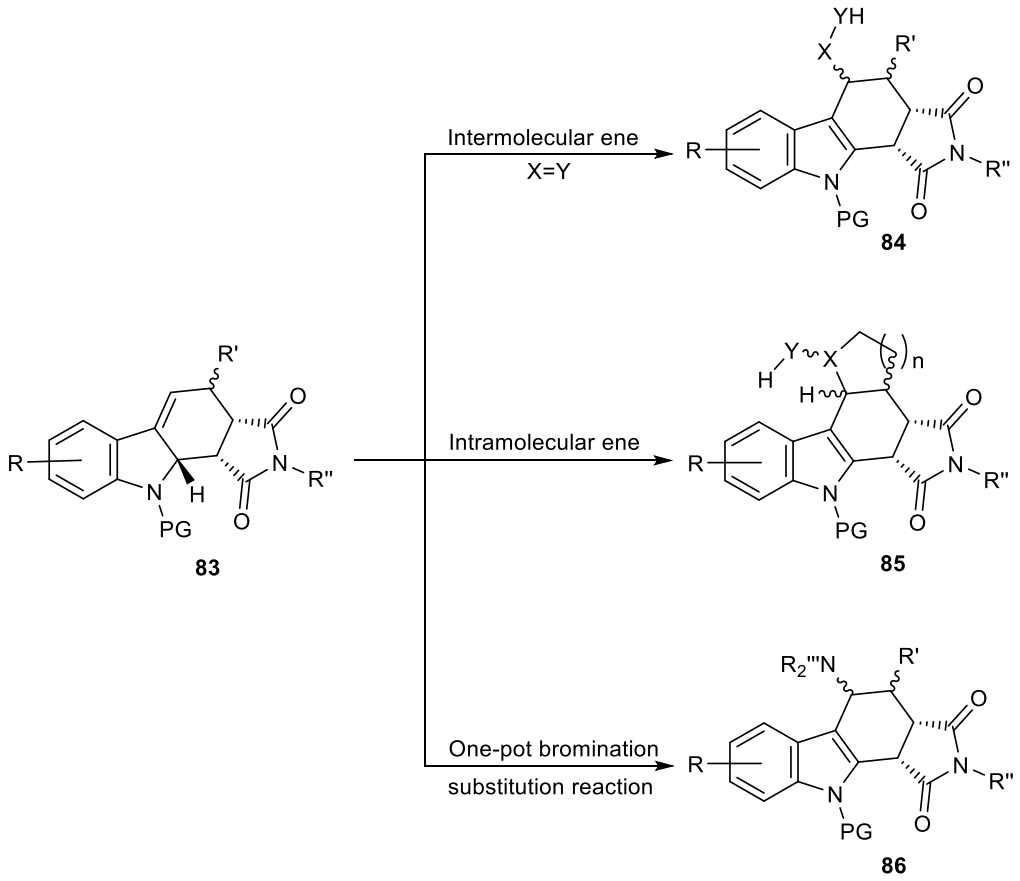
In this project we aim to explore diastereoselective approaches to synthesise novel carbazole analogues and the application of this methodology towards the synthesis of potentially biologically active compounds.

Following previous work within our research group, we decided to focus our attention on the D-A chemistry of substituted-3-vinyl-1*H*-indoles **82**, containing an electron withdrawing *N*-protecting group, to target the synthesis of D-A cycloadducts **83** (Scheme 1.25), which contain an electron rich cyclohexenyl ring suitable for further functionalisation.



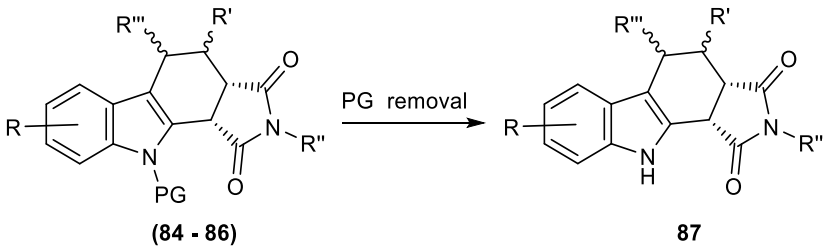
Scheme 1.25. D-A reaction plan of *N*-protected, substituted-3-vinyl-1*H*-indoles 82

We then aim to study the behaviour of the cyclohexenyl double bond of these cycloadducts **83** towards inter- and intramolecular ene reactions as well as towards the reaction with added electrophiles. This will allow access to novel, highly functionalised, partially saturated and polycyclic carbazole derivatives **84**, **85**, and **86** (Scheme 1.26).



Scheme 1.26. General plan to examine the chemistry of D-A cycloadducts 83

Due to the structural relations between our target carbazole derivatives (**84 – 86)** and the known biologically active compounds discussed in the introductory part of this thesis, we plan to remove the electron withdrawing *N*-protecting group to evaluate the biological activity of the synthesised carbazole derivatives **87** (Scheme 1.27).



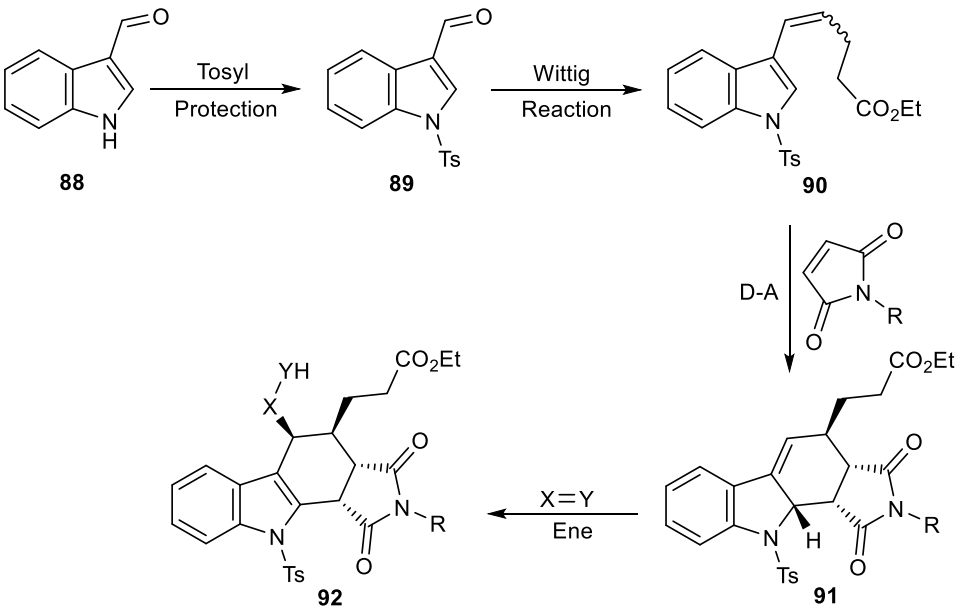
Scheme 1.27. General plan to pyrrolo[3,4-*a*]carbazole-1,3 dione derivatives 87 for biological assay

Chapter 2.

Diels-Alder/Ene Chemistry of Substituted 3-Vinyl-1*H*-Indole

In this chapter, we will discuss our work towards the synthesis of functionalised molecules containing a tetrahydropyrrolopyrrolo[3,4-*a*]carbazole-1,3-dione framework, through the use of stepwise D-A/ene chemistry of ethyl(*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate **90**.

The initial aim of this research was therefore to find a suitable method for the synthesis of the key intermediate ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate **90** in order to use it in our planned D-A/ene chemistry. We envisioned that indole **90** could be synthesised by a sequential tosyl protection, Wittig reaction starting from the commercially available indole-3-carbaldehyde **88**. Once indole **90** is obtained, the next stage of our synthetic plan is to investigate the intermolecular D-A reaction of indole **(*Z*)-90** as a diene with a range of dienophiles under different reaction conditions. We then aim to functionalise the resultant D-A cycloadducts **91** through an intermolecular ene reaction with various reactive enophiles X=Y, to generate our desired pyrrolo[3,4-*a*]carbazole-1,3-diones **92** (Scheme 2.1).



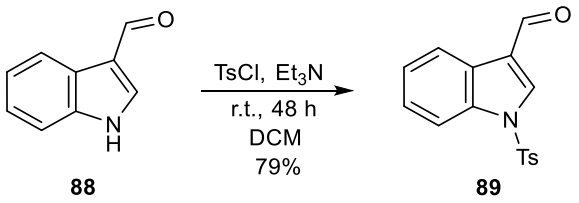
Scheme 2.1. Planned synthetic approach towards functionalised carbazoles 92

2.1. Diels-Alder reaction of ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate (90)

2.1.1. Synthesis of indole (*Z*)-90

Before our proposed D-A/ene reactions could be investigated, ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate **90** had to be synthesised. Our synthetic efforts towards compound **90** commenced with the protection of indole-3-carbaldehyde **88** with an electron withdrawing protecting group. Earlier research showed that when 3-vinyl-1*H*-indoles, incorporating free indolic nitrogen or an electron donating group, were subjected to D-A reactions, the resulting D-A cycloadducts underwent rapid rearomatisation under the reaction conditions.[39,41,40] We therefore anticipated that the addition of a moderately electron withdrawing protecting group would be required, to stabilise the desired D-A cycloadducts sufficiently to allow further chemistry to be carried out.

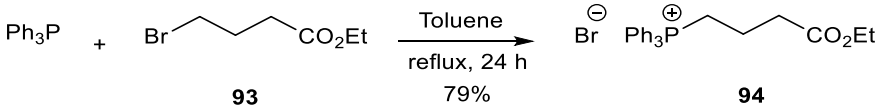
Following a literature procedure, the indolic nitrogen of indole-3-carbaldehyde **88** was protected with *p*-toluenesulfonyl chloride (TsCl) in the presence of triethylamine (Et_3N) in DCM.[72] The expected 1-tosyl-1*H*-indole-3-carbaldehyde **89** was obtained in a very good yield of 79% after recrystallisation from ethyl acetate (Scheme 2.2).



88 **89**

Scheme 2.2. Tosyl protection of indole-3-carbaldehyde 88

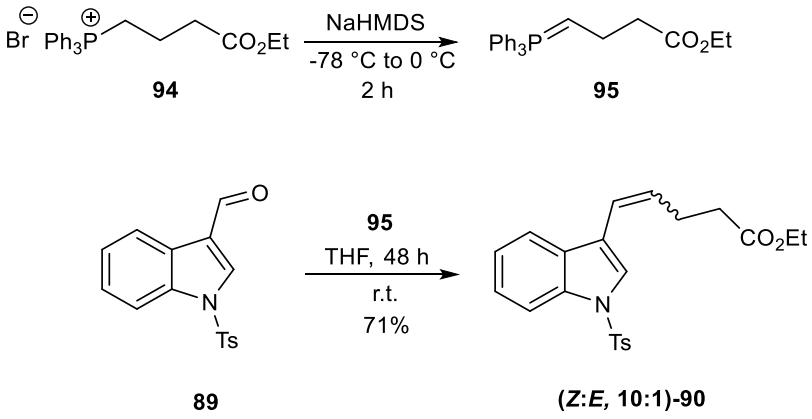
The next step involved a Wittig reaction to synthesise indole **90**. Wittig salt **94** was synthesised according to a literature procedure by an S_N2 reaction of triphenylphosphine with ethyl 4-bromobutanoate **93** (Scheme 2.3).[73] The formed phosphonium salt **94** was isolated in 79% yield by direct filtration from the reaction. ^1H NMR showed that the product was clean enough to be used with no further purification being necessary.



93 94

Scheme 2.3. Synthesis of Wittig salt 94

Ylide **95** was then generated *in situ* by deprotonation of Wittig salt **94** with sodium bis(trimethylsilyl)amide (NaHMDS). The Wittig reaction was performed between the reactive phosphonium ylide **95** and the previously synthesised 1-tosyl-1*H*-indole-3- carbaldehyde **89** at r.t. for 48 hours (Scheme 2.4), adapted from the reported procedure by Daniels and co-workers.[74] The ^{1}H NMR spectrum of the crude material showed two sets of signal corresponding to a mixture of *Z*- and *E*- alkenes of indole **90**. Purification of the crude reaction mixture by column chromatography afforded the desired indole **90** as a mixture of *Z*- and *E*- isomers in a 10:1 ratio respectively as determined by ^{1}H NMR spectrum, in 71% yield.



94 95

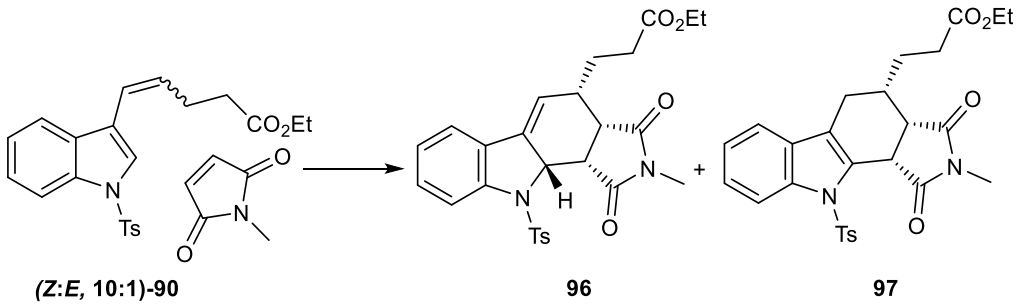
89 (*Z*:*E*, 10:1)-90

Scheme 2.4: Wittig reaction of indole 89

With indole **(*Z*:*E*, 10:1)-90** in hand, the next stage was to investigate the D-A cycloaddition of indole **(*Z*:*E*, 10:1)-90** as a diene with NMM as a dienophile under thermal conditions. The results are summarised in Table 2.1.

Our initial investigations were carried out by dissolving indole **(*Z*:*E*, 10:1)-90** and NMM in DCM. After 24 hours at 40 ^{o}C, ^{1}H NMR of the crude reaction

mixture indicated the presence of a single diastereomer, corresponding to D-A cycloadduct **96**, along with unreacted starting material. Purification by column chromatography gave the corresponding D-A cycloadduct **96** in 5% yield (entry 1). Increasing the reaction time from 24 hours to 48 hours slightly improved the yield of D-A cycloadduct **96** to 7% (entry 2). In order to optimise the yield of D-A cycloadduct **96** further, we decided to repeat the D-A reaction between indole **(*Z*:*E*, 10:1)-90** and NMM at higher temperature. Therefore, indole **(*Z*:*E*, 10:1)-90** and NMM were dissolved in toluene and the solution was refluxed for 48 hours. Under these reaction conditions, D-A cycloadduct **96** was obtained in 9% isolated yield. However, the reaction was accompanied by the unwanted rearomatisation product **97** in 3% yield (entry 3).



(Z:E, **10:1)-90** **96** **97**

Entry	Reaction condition	Isolated yield %	
		96	**97**
1	DCM, 24 h, 40 °C	5	-
2	DCM, 48 h, 40 °C	7	-
3	Toluene, 48 h, 110 °C	9	3

Table 2.1. Results of thermal D-A cycloaddition of indole (*Z*:*E*, 10:1)-90 with NMM

2.1.2. Relative stereochemistry assignment of Diels-Alder cycloadduct (96)

In a D-A reaction, two diastereomers can be formed from a diene/dienophile pair depending on the arrangement of the dienophile and the diene in the transition state.[75] Thus, the reaction of the **(*Z*)-90** with NMM can proceed via an *endo* or *exo* transition state to give either the *endo* D-A cycloadduct **98** or

the *exo* D-A cycloadduct **99** respectively, whilst the D-A reaction of the **(*E*)-90** and NMM can also give an *endo* or *exo* cycloadduct **96** and **100** (Figure 2.1).

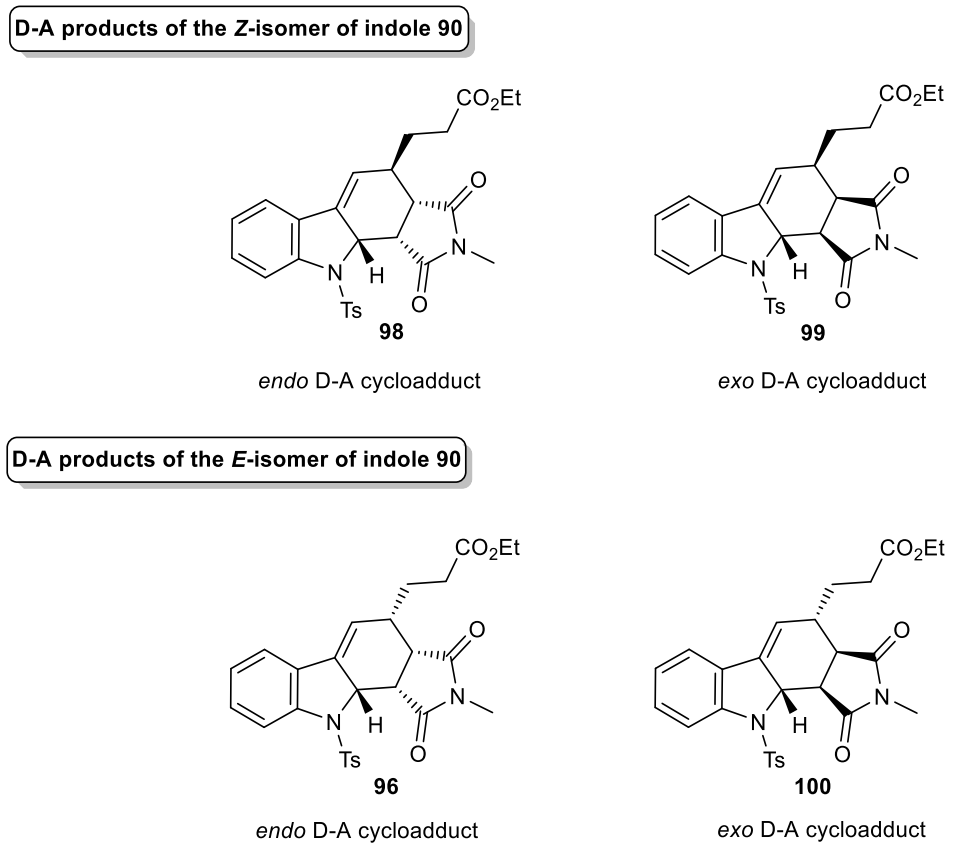


Figure 2.1. The four possible diastereomers of the D-A product

However in our D-A reaction of compound **(*Z*:*E*, 10:1)-90** with NMM, only one diastereomer was observed by the ^{1}H NMR of the crude reaction mixture. To verify the relative stereochemistry of D-A cycloadduct **96**, crystals were grown by slow evaporation of a solution of D-A cycloadduct **96** in ethyl acetate/petrol. X-Ray analysis indicated that the product **96** was formed from the **(*E*)-90** through an *endo*-selective D-A reaction with NMM (Figure 2.2). The *endo* approach of the dienophile in the transition state is usually favoured by kinetic control due to secondary orbital interactions.[75] The formation of *endo* D-A cycloadduct **96** was further supported by coupling constant analysis. The ^{3}J value of between H_{23} and H_{22} is 7.6 Hz, which indicates to their *cis* relationship with a dihedral angle of about 60^{o} as detected by the X-ray crystal structure.

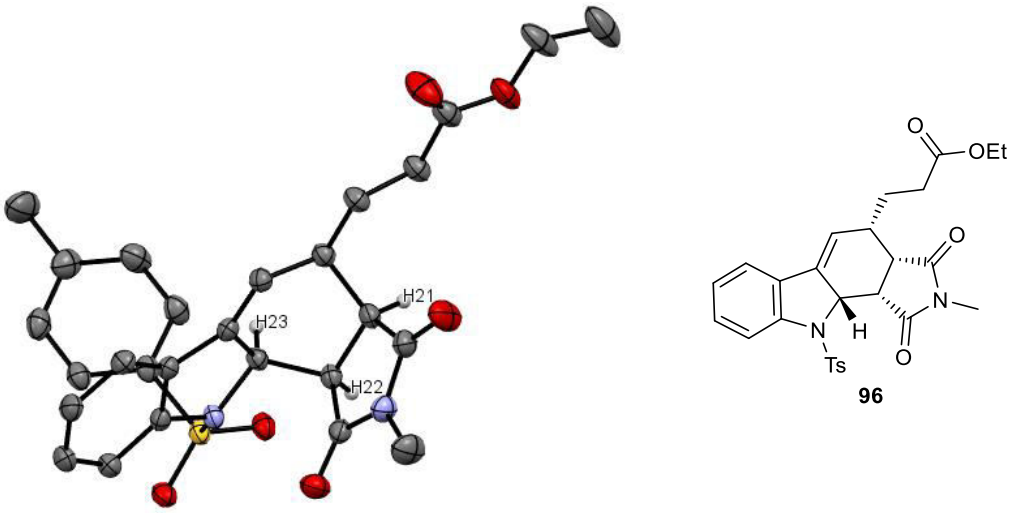
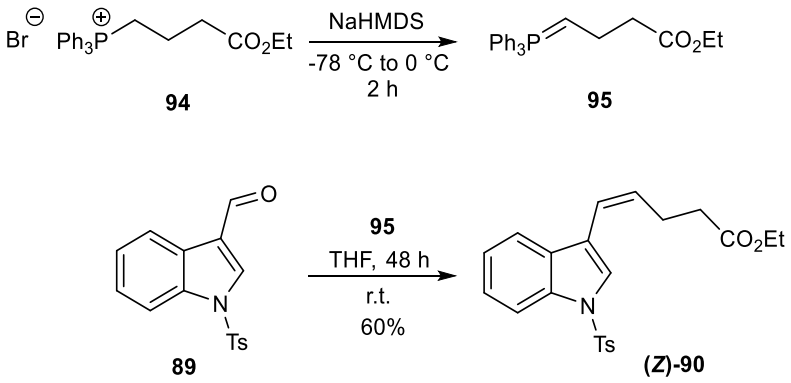


Figure 2.2. X-ray crystal structure of D-A cycloadduct 96

Based on this result we can conclude that the **(*Z*)-90** isomer was unreactive under the tested thermal D-A reaction conditions and the only observable product arising from the **(*E*)-90** isomer. We therefore postulated that the rate of the D-A reaction of the **(*E*)-90** with NMM is faster than the reaction rate of the corresponding **(*Z*)-90**. To support our hypothesis, we decided to re-examine the D-A reaction of the pure *Z*-isomer of indole **90**. For this reason, the Wittig reaction of 1-tosyl-1*H*-indole-3- carbaldehyde **89** with phosphonium ylide **95** was repeated and the desired *Z*-isomer of indole **90** was successfully separated from the reaction mixture by careful column chromatography in 60% isolated yield (Scheme 2.5)



Scheme 2.5. Wittig reaction to synthesise a pure *(Z)*-90

With the **(*Z*)-90** in hand, the D-A reaction of the **(*Z*)-90** with NMM could be investigated. However, first we decided to check the stability of *Z*-isomer to ensure that any subsequent D-A products had not been formed by a thermal isomerisation of the **(*Z*)-90** isomer to give the more stable **(*E*)-90** isomer under the reaction conditions. Thus, a mixture of **(*Z*:*E*, 10:1)-90** in DCM was refluxed for 48 hours. No change in the isomeric ratios of this mixture was observed by ^{1}H NMR, which suggested that the *Z*-isomer of indole **90** was stable under the tested reaction conditions.

The next step was to use the pure **(*Z*)-90** as a diene in a D-A cycloaddition with NMM. This reaction was examined by heating a mixture of the **(*Z*)-90** and NMM in DCM, *iso*-propanol or toluene for 5 days, with monitoring by TLC. However, in each case the starting material remained unchanged. This result clearly showed that the **(*Z*)-90** was unreactive under the thermal D-A reaction conditions. Thus, we could conclude that the previously obtained D-A cycloadduct **96** arose from the *E*-isomer of indole **90**.

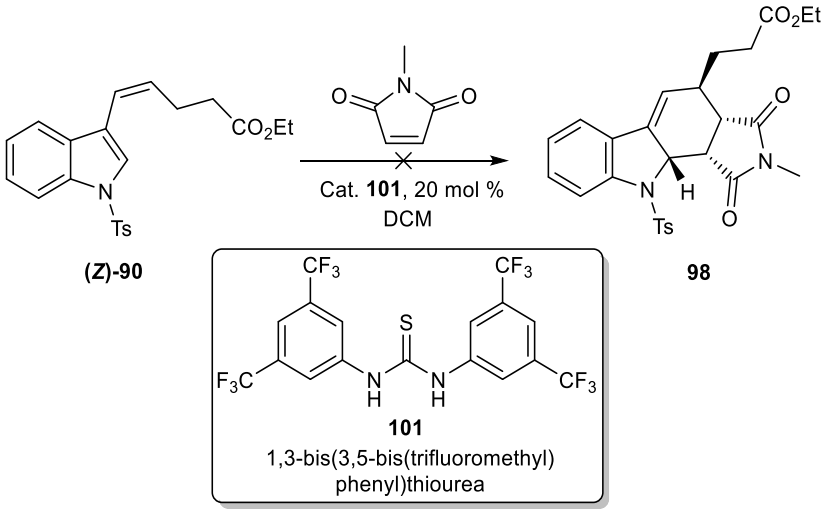
2.2. Improved conditions for the Diels-Alder reaction of the (*Z*)-90 with NMM

Our earlier study of the D-A reaction of the **(*Z*)-90** with NMM showed that the **(*Z*)-90** was unreactive under the tested thermal reaction conditions. Thus, there was a need to develop a new method to accelerate the rate of our desired D-A reaction of the **(*Z*)-90** with NMM, in order to examine our planned D-A/ene reaction sequence. One approach for accelerating our desired D-A reactions would be to examine the use of thiourea-based catalysts. Thiourea catalysts accelerate the rate of D-A reactions through hydrogen bonding to the carbonyl oxygen of the dienophile, lowering their LUMO.[76,77]

2.2.1. Diels-Alder reaction of the (*Z*)-90 with thiourea catalyst (101)

Tan *et al*., have shown the efficiency of a thiourea catalyst in promoting the D-A reaction of 1-benzyl-2-vinyl-1*H*-indole with 3-nitrocoumarin.[78] We therefore decided to investigate the effect of thiourea catalysis on our planned D-A, by

dissolving the **(*Z*)-90** and NMM in DCM in the presence of 20 mol% of bis(trifluoromethyl)phenyl)thiourea **101** (Scheme 2.6).



Scheme 2.6. D-A reaction of the (*Z*)-90 catalysed by thiourea 101

The investigation of D-A reaction between the *Z*-isomer of indole **90** and NMM in the presence of thiourea catalyst **101** was initially tested at r.t. for 24 hours. However, analysis of the ^{1}H NMR of the crude reaction mixture revealed unreacted starting material. Re-examination of the reaction at longer reaction times and higher temperatures failed to give the corresponding D-A cycloadduct **98**. From these results, we concluded that the introduction of thiourea catalyst **101** showed no improvement in the rate of our proposed D-A reaction of the **(*Z*)-90** with NMM. Therefore, we turned our attention to examine the influence of Lewis acids on the desired D-A reaction of the pure **(*Z*)-90** with NMM.

2.2.2. Diels-Alder reaction of the (*Z*)-90 with NMM catalysed by Lewis acids

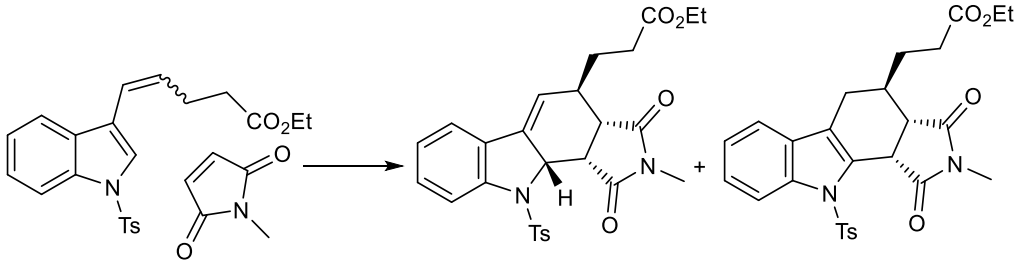
Lewis acid catalysts are well known in the literature for their ability to promote the D-A cycloaddition reactions by lowering the LUMO energy of the dienophiles, through the coordination to the carbonyl oxygen thus reducing the electron density of the double bond.[79,80] We therefore decided to investigate

the D-A reaction of the **(*Z*)-90** and NMM with various Lewis acids. The results are summarised in Table 2.2.

We first examined D-A reaction of the **(*Z*)-90** with NMM in the presence of 1.0 equivalent of aluminium chloride ($AlCl_3$) for 6 hours at both -78 °C and r.t. (entry 1-2). In both cases only starting material was observed by ^1H NMR of the crude reaction mixture. Increasing the reaction time to 48 hours at r.t. slightly improved the D-A reaction outcome (entry 3), and D-A cycloadduct **98** being isolated in 10% yield along with recovered starting material.

When the Lewis acid catalyst was changed to titanium tetrachloride ($TiCl_4$, 1.0 eq.), the D-A reaction of the **(*Z*)-90** with NMM was carried out at -78 °C for 10 min. Under these conditions, an efficient D-A reaction was achieved with no starting material observed; however the desired D-A product **98** was accompanied by the unwanted rearomatisation product **102** (entry 4). All attempts to isolate the desired D-A cycloadduct **98** by column chromatography failed due to the close similarity in the R_f values to that of the by-product **102**.

The use of dimethylaluminum chloride (Me_2AlCl) in promoting the D-A reaction between the **(*Z*)-90** with NMM was also examined. The addition of 1.0 equivalent of Me_2AlCl in DCM for 6 hours at both -78 °C and 0 °C provided only starting material (entry 5-6). Re-examining the reaction at higher temperatures, both r.t. and reflux with 1.0 or 2.0 equivalents of Me_2AlCl, gave low yields of the desired D-A cycloadduct **98** along with unreacted starting material (entry 7-9). Further optimisation resulted in the addition of 2.0 equivalents of Me_2AlCl at -78 °C to a solution of NMM in DCM, followed by the addition of a solution of the **(*Z*)-90** in DCM. Warming the reaction mixture to reflux for 48 hours led to a smooth diastereoselective D-A reaction, affording the corresponding D-A cycloadduct **98** in an excellent yield of 85% after purification by column chromatography (entry 10).



(Z/E **10:1)-90** **98** **102**

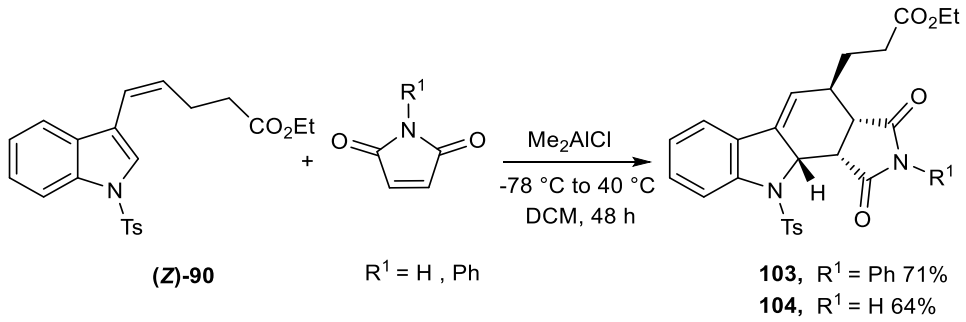
Entry	Reaction conditions	Ratio of products [a]			Yield [b] %
		90	**98**	**102**	
1	1 eq. $AlCl_3$, -78 °C, 6 h	100	0	0	-
2	1 eq. $AlCl_3$, r.t., 6 h	100	0	0	-
3	1 eq. $AlCl_3$, r.t., 48 h	81	19	0	10
4	1 eq.$TiCl_4$, -78 °C, 10 min	0	39	61	Product inseparable
5	1 eq. Me_2AlCl, -78 °C, 6 h	100	0	0	-
6	1 eq. Me_2AlCl, 0 °C, 6 h	100	0	0	-
7	1 eq. Me_2AlCl, r.t., 48 h	76	24	0	15
8	1 eq. Me_2AlCl, 40 °C, 24 h	60	40	0	38
9	2 eq. Me_2AlCl, 40 °C, 24 h	39	61	0	52
10	2 eq. Me_2AlCl, 40 °C, 48 h	0	100	0	85

[a] ratio of the products was determined by ^1H NMR of the crude reaction mixture. [b] Isolated yield of D-A cycloadduct 98

Table 2.2. Results of the D-A reaction of the (*Z*)-90 catalysed by Lewis acids

With the D-A reaction conditions optimised, we then decided to examine the D-A reaction of the pure **(*Z*)-90** with other dienophiles such as *N*-phenylmaleimide (NPM) and maleimide.

D-A reaction of the **(*Z*)-90** with NPM catalysed by Me_2AlCl led to the isolation of the D-A cycloadduct **103** as a single diastereomer in 71% yield. Maleimide was found to be less soluble in DCM, giving a cloudy reaction mixture, but still afforded a single diastereomer of the corresponding D-A cycloadduct **104** in an acceptable yield of 64% (Scheme 2.7).



Scheme 2.7. Results of the D-A reactions of the (*Z*)-90 with NPM and maleimide

2.3. Relative stereochemistry of Diels-Alder cycloadducts (98), (103) and (104)

The relative stereochemistry of the D-A cycloadduct **98**, was assigned based on the X-ray crystal structure (Figure 2.3). Crystals were grown by slow evaporation of a solution of D-A cycloadduct **98** in ethyl acetate/petrol. X-ray analysis of D-A cycloadduct **98** indicates that H_{10}, H_{13} and H_{14} are all *cis* to each other, which confirms the formation of *endo* D-A cycloadduct **98** arising from the **(*Z*)-90**.

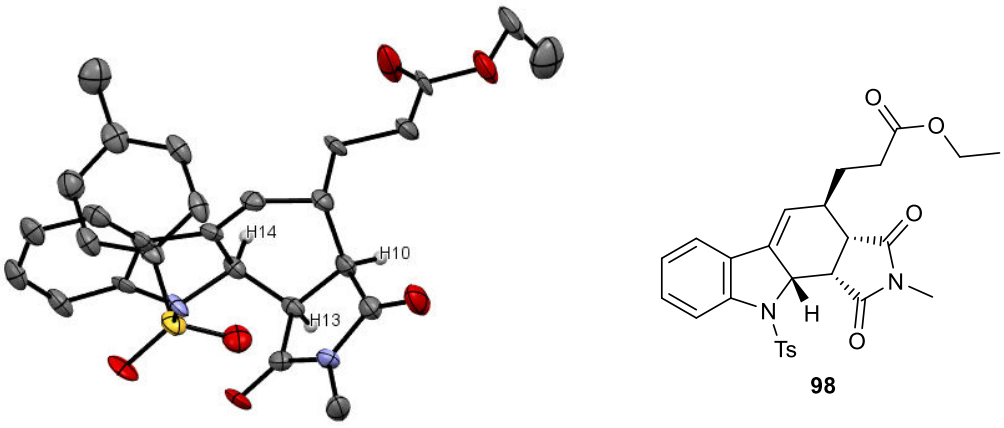


Figure 2.3. X-ray crystal structure of D-A cycloadduct 98

The formation of *endo* D-A cycloadducts **103** and **104** was also confirmed by X-ray analysis (Figure 2.4 and 2.5).

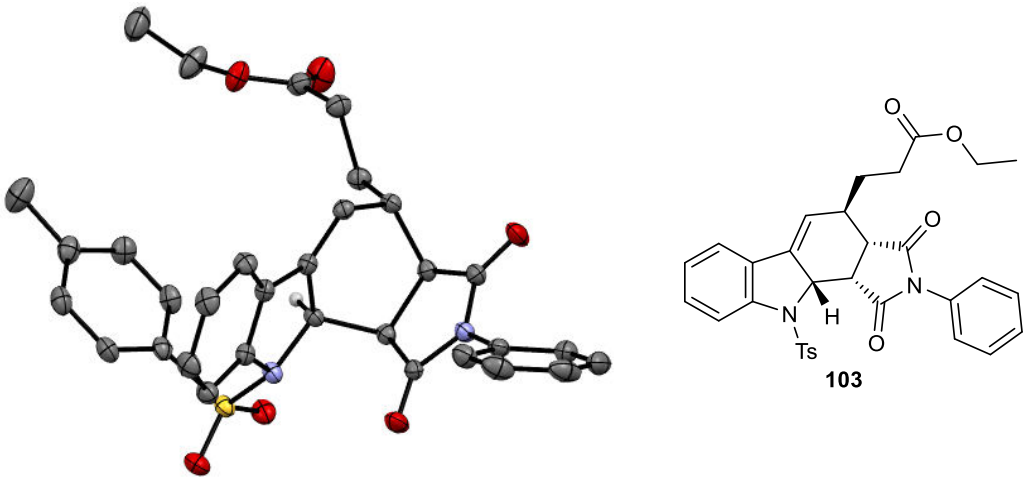


Figure 2.4. X-ray crystal structure of D-A cycloadduct 103

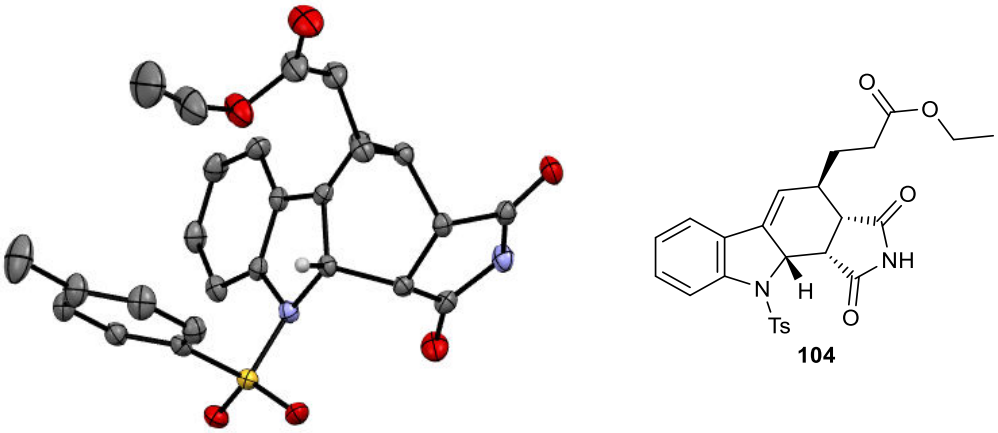
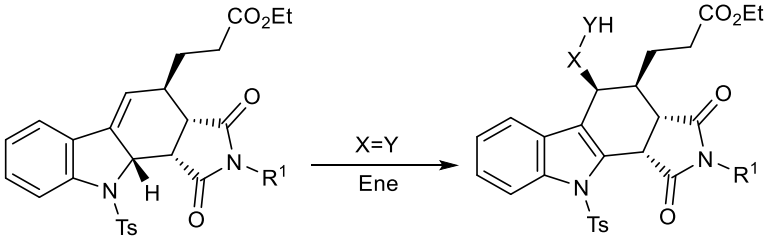


Figure 2.5. X-ray crystal structure of D-A cycloadduct 104

2.4. Intermolecular ene reactions of Diels-Alder cycloadducts (98), (103) and (104)

With successful demonstration of the diastereoselective intermolecular D-A reactions of the **(*Z*)-90** with various electron-deficient dienophiles, the next step towards the desired functionalised carbazoles, was to subject the D-A cycloadducts **89**, **103**, and **104** to intermolecular ene reactions with a range of reactive enophiles X=Y to generate pyrrolo[3,4-*a*]carbazole-1,3-dione derivatives **92** (Scheme 2.8).



98, R^1 = Me
103, R^1 = Ph
104, R^1 = H

92

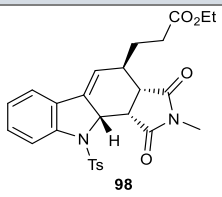
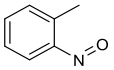
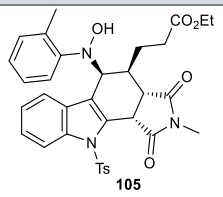
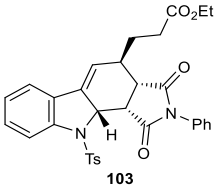
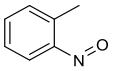
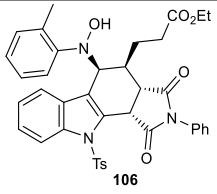
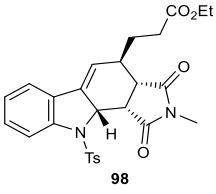
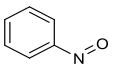
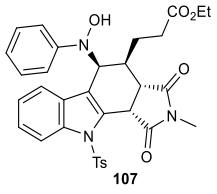
Scheme 2.8. Proposed intermolecular ene reactions of D-A cycloadduct 98,103, and 104

2.4.1. Nitroso ene reactions of Diels-Alder cycloadducts (98) and (103)

Following previous work by Hall and co-workers on the D-A/ene reactions of vinyl-imidazoles,[81] we started our investigation of the proposed intermolecular ene reactions by examining the ene chemistry of *endo* D-A cycloadducts **98** and **103** with nitroso compounds. The presence of electronegative heteroatoms in the nitroso compounds lowering their LUMO energy and thus making them powerful enophiles in the ene chemistry.[54] The nitroso compounds chosen in our investigation were 2-nitrosotoluene and nitrosobenzene (Table 2.3).

We initially examined the nitroso-ene reaction between D-A cycloadduct **98** and 2-nitrosotoluene. After 24 hours at r.t., ^{1}H NMR of the crude reaction mixture indicated the presence of a new compound and unreacted starting material in a 7:3 ratio respectively. Increasing the reaction time to 48 hours did not improve the reaction outcome. Purification by column chromatography led to the isolation of desired D-A/ene adduct **105** in 59% yield, as a single diastereomer (Table 2.3, entry 1). Analogous result was observed in the reaction of D-A cycloadduct **103** with 2-nitrosotoluene. The corresponding D-A/ene adduct **106** was isolated in 58% yield (Table 2.3, entry 2). Also the ene reaction of D-A cycloadduct **98** with nitrosobenzene at r.t. for 24 hours led to the isolation of the corresponding D-A/ene adduct **107** in 52% yield (Table 2.3, entry 3).

It is noteworthy that the ^{1}H NMR spectra of D-A/ene adduct **107** when $CDCl_3$ or CD_2Cl_2 was used showed broad peaks. However, the broad peaks were resolved into sharp, well-defined peaks when the ^{1}H NMR was performed in DMSO-d_6. This is possibly due to aggregation of the product in chlorinated solvents.

Entry	SM	Enophile	Reaction conditions	D-A/ene adducts	Yield [a] %
1	 **98**		r.t., 24 h, DCM	 **105**	59
2	 **103**		r.t., 24 h, DCM	 **106**	58
3	 **98**		r.t., 24 h, DCM	 **107**	52

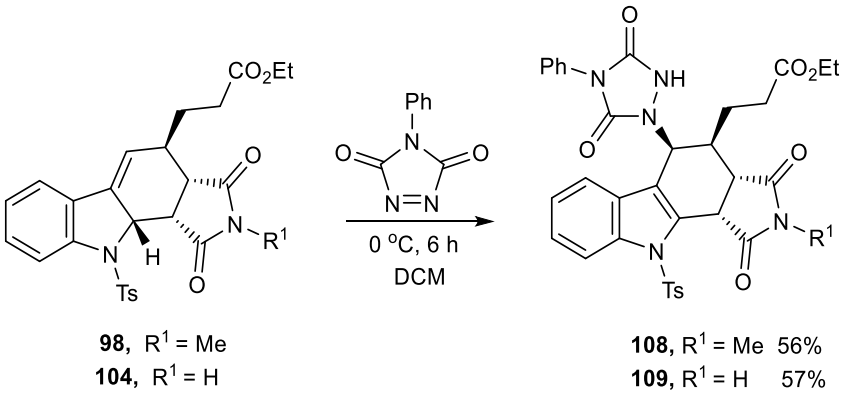
[a] Isolated yield of the desired D-A/ene adduct

Table 2.3. Nitroso-ene reactions of D-A cycloadducts 98 and 103

2.4.2. Aza ene reactions of Diels-Alder cycloadducts (98) and (104)

With a working method for the nitroso-ene reactions (Table 2.3, entry 1-3) in hand, we then moved on to look at the aza-ene reactions of D-A cycloadducts **98** and **104** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). Previous research has shown that PTAD is a highly reactive enophile,[82, 83] thus, the ene reaction between the D-A cycloadduct **98** and PTAD was performed at 0 ºC for 6 hours. The desired D-A/ene adduct **108** was isolated in 56% yield after purification through column chromatography. Under similar reaction conditions, the ene reaction of D-A cycloadduct **104** and PTAD gave the corresponding D-A/ene adduct as observed by TLC and ^{1}H NMR of the crude reaction mixture. However, when we attempted to purify the desired D-A/ene

adduct **109** through column chromatography, the crude product was poorly soluble in DCM. We therefore attempted to purify the D-A/ene adduct **109** by trituration from DCM, which led to the isolation of **109** in a 57% yield (Scheme 2.9).



98, R^1 = Me
104, R^1 = H

108, R^1 = Me 56%
109, R^1 = H 57%

Scheme 2.9. Aza-ene reactions of D-A cycloadducts 98 and 104

2.5. Assignment of the relative stereochemistry of Diels-Alder/ene adduct (109)

The relative stereochemistry of D-A/ene adduct **109** was initially determined based on the crystal structure of D-A cycloadduct **104** obtained previously, which was consistent with an *endo* D-A reaction between the *Z*-isomer of indole **90** and NMM. We envisioned that the ene reaction between D-A cycloadduct **104** as the ene component and 2-nitrosotoluene as the enophile, had one possible stereochemical outcome as a consequence of the directing effect of the allylic hydrogen (H) in the *twix* position of the ene component (Figure 2.6).[54] Thus, 2-nitrosotoluene abstracts H_{twix}, and the carbon-nitrogen bond is fully formed during hydrogen transfer, leading to the formation of D-A/ene adduct **109** with *anti* stereochemistry between the PTAD and the succinimide group. This process is consistent with a concerted ene mechanism (Figure 2.6).

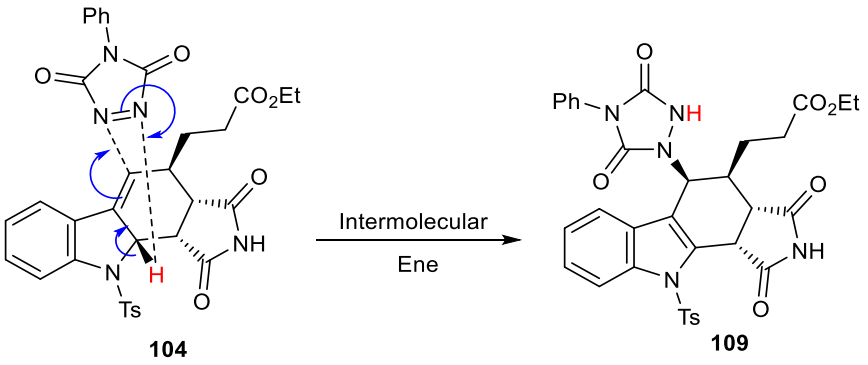


Figure 2.6. Concerted intermolecular ene mechanism

We then sought to gain X-ray crystallographic information about the D-A/ene adduct **109** to confirm our proposed relative stereochemistry. Therefore, crystals of D-A/ene adduct **109** were grown by slow evaporation from DCM. The X-ray crystallographic analysis of D-A/ene adduct **109** proved the *anti* arrangement between the PTAD and the succinimide groups (Figure 2.7.).

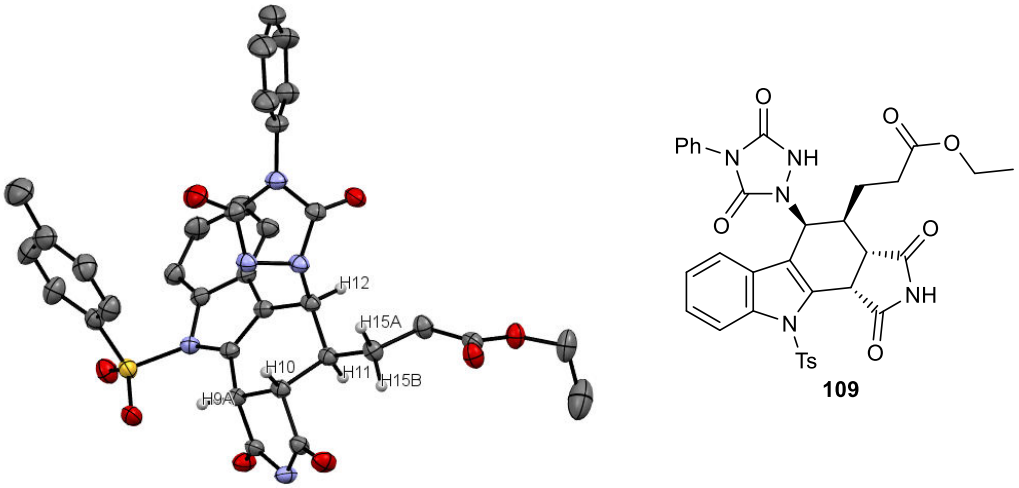


Figure 2.7. X-ray crystal structure of D-A/ene adduct 109

The structure assignment of D-A/ene adduct **109** was further supported by a ROESY experiment. Analysis of the 2D ROESY spectrum of D-A/ene adduct **109** showed a correlation between protons H_{12} and H_{11}, which suggests that H_{12} and H_{11} are close to each other in the space. Also, correlations between H_{12} and H_{15} were clearly visible. The lack of a correlation between H_{12}, H_{9A} and H_{10}, suggests a *trans*- disposition of H_{12} with respect to protons H_9 and H_{10} (Figure 2.7). Therefore the relative stereochemistry of D-A/ene adduct **109** is

consistent with our proposed structure, resulting from a concerted ene mechanism. The relative stereochemistry of D-A/ene adducts **105 - 108** was confirmed though comparisons of the ^{1}H NMR spectral data with that of D-A/ene adduct **109**.

2.6. Conclusion

Building on previous work within our research group, we have developed a diastereoselective method for the synthesis of complex tetrahydropyrrolo[3,4-*a*]carbazole derivatives, with up to four new stereogenic centres with complete control of relative stereochemistry for each of the 4 stereocentres, through a stepwise D-A/ene reaction sequence of ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate **90**.

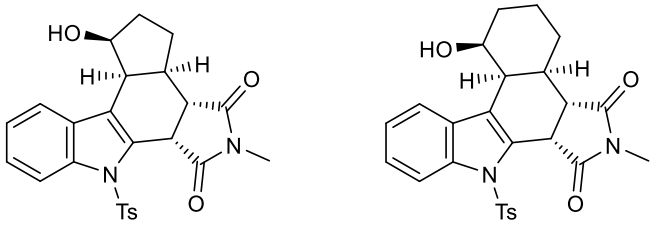
The D-A reactivity of both the **(*E*)-** and **(*Z*)** isomers of indole **90** showed significant differences under thermal conditions. The use of Me_2AlCl required to ensure high yields of D-A products arising from the **(*Z*)-90** with various dienophiles.

In addition the synthesised D-A cycloadducts **98**, **103** and **104** have been shown to undergo high stereospecific ene reactions. The stereochemistry arising from a proposed concerted ene reaction directed by the *twix* proton of the ene component.

Chapter 3.

Diels-Alder/Ene Chemistry of Substituted-3-Vinyl-1*H*-Indole

As an extension of our ongoing research, which directed toward the development of new diastereoselective synthetic methodologies for the synthesis of tetrahydropyrrolo[3,4-*a*]carbazole-1,3-dione derivatives, we aim in this chapter to report our efforts in the synthesis of pyrrolo[3,4-*a*]carbazoles incorporating a fused five- or six- membered ring, **113** and **122** respectively (Figure 3.1).

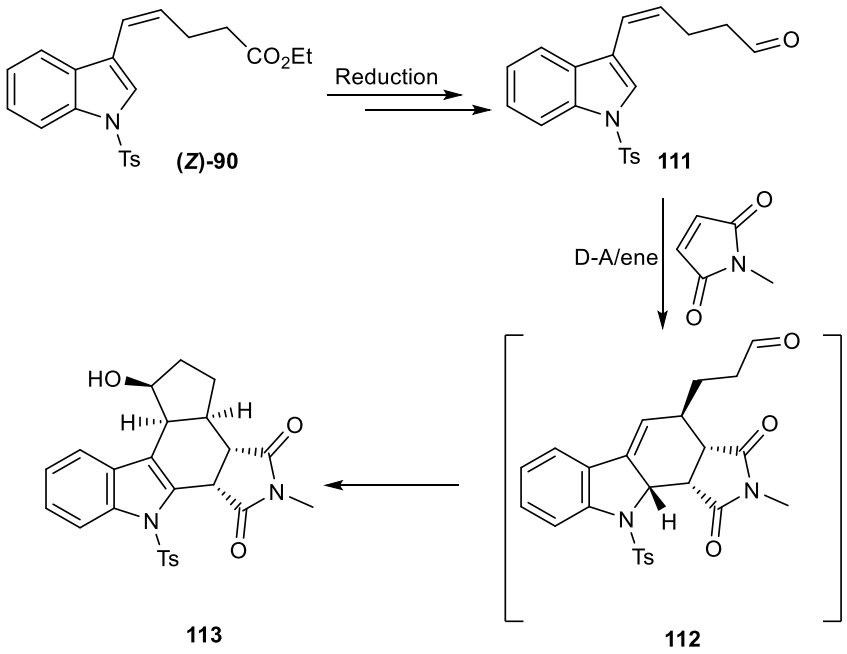


113 **122**

Figure 3.1. Chemical structures of our target compounds 113 and 122

3.1. Proposed synthetic approach for the synthesis of polycyclic pyrrolo[3,4-*a*]carbazole (113)

We postulated that our desired polycyclic pyrrolo[3,4-*a*]carbazole **113** could be synthesised in a single step, through a one-pot intermolecular D-A/intramolecular carbonyl-ene reaction sequence from indole **111**. The preparation of indole **111** could be achieved through a reduction of the previously synthesised compound ***(Z)*-90**. In this route, we hoped that once the intermediate **112** is formed from D-A reaction of indole **111** with NMM, the reactive terminal aldehyde of **112** can be serve as an enophile in an intramolecular carbonyl-ene reaction to give the desired carbazole **113** (Scheme 3.1).

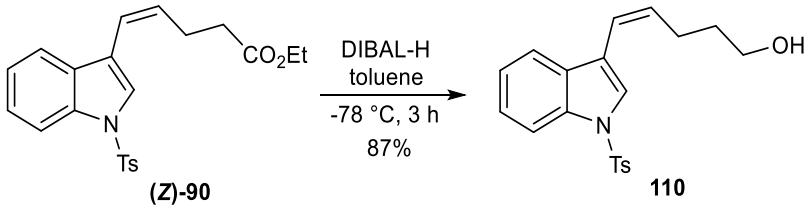


Scheme 3.1. Proposed one-pot D-A/ene reaction to synthesise carbazole 113

3.2. One-pot D-A/ene reaction to synthesise polycyclic carbazole (113)

3.2.1. Synthesis of (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol (110)

We started our synthesis by a selective reduction of the previously synthesised indole **(*Z*)-90** using DIBAL-H as a reducing agent. The reaction was performed at -78 °C in toluene for 3 hours, adapted from the written procedure.[84] The ^{1}H NMR of the crude reaction mixture indicated the disappearance of the ethyl group of the starting material. Purification of the crude reaction mixture by column chromatography afforded the corresponding (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol **110** in a good yield of 87% (Scheme 3.2).

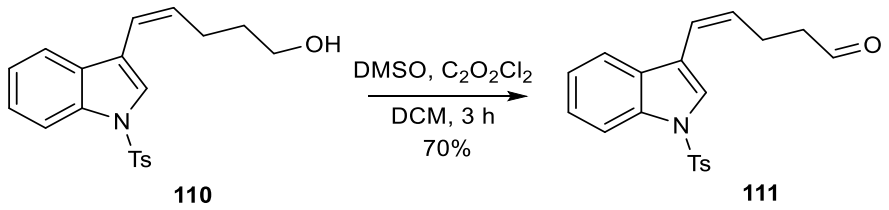


Scheme 3.2. Synthesis of indole 110

3.2.2. Oxidation of indole (*Z*)-110

In the next step, primary alcohol of indole **110** was oxidised to the corresponding aldehyde **111** under Swern conditions.[85] The oxidation reaction

was carried out in DCM for 3 hours. Following purification by column chromatography, the desire indole **111,** with terminal aldehyde, was isolated in 70% yield (Scheme 3.3).

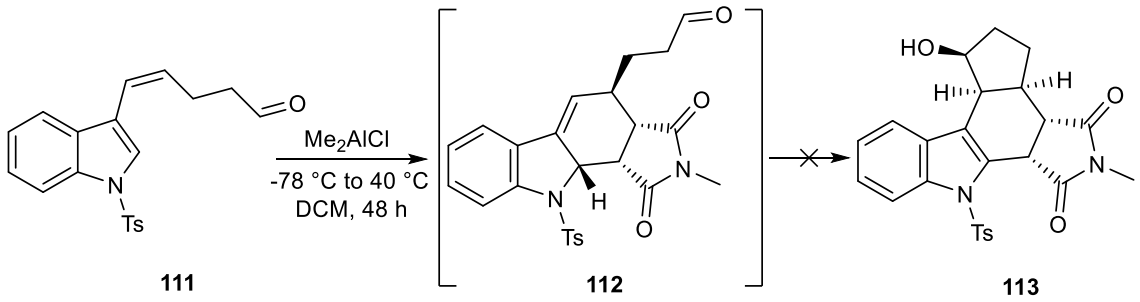


110 **111**

Scheme 3.3. Swern oxidation of 110 to form indole 111

With indole **111** in hand, we were ready to examine our proposed intermolecular D-A/intramolecular carbonyl-ene reaction of indole **111** in one-pot to synthesise polycyclic carbazole **113**.

The intermolecular D-A reaction was performed between indole **111** as a diene and NMM as a dienophile in the presence of 2.0 equivalents of Me_2AlCl in DCM (Scheme 3.4). After 24 hours at 40 °C, a single new spot was evident by TLC. However, none of the desired carbazole **113** or the expected intermediate **112** was observed by ^1H NMR of the crude reaction mixture.

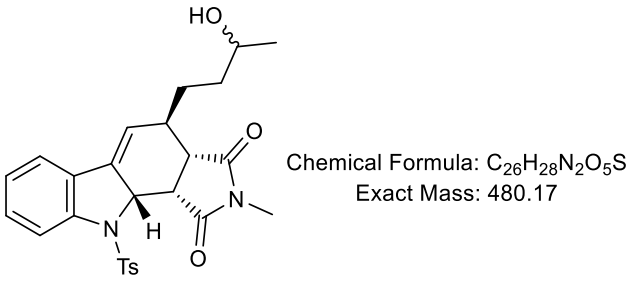


111 **112** **113**

Scheme 3.4. The outcome of the one-pot D-A/carbonyl-ene reaction of indole 111

Further analysis of the resulting crude reaction mixture by ^1H NMR spectroscopy indicated the formation of a new product. We then attempted to isolate the new product in a pure form through column chromatography to allow further analysis to elucidate its structure. A new carbazole was isolated

in 52% yield. Examination of ^{1}H NMR of the purified carbazole indicated the presence of a new 3H doublet at 1.22 ppm, corresponding to a methyl group. High-resolution mass spectroscopy (HRMS) of the purified carbazole showed a parent ion of m/z 481.1787, consistent with a chemical formula of $C_{26}H_{29}N_2O_5S$. Therefore, based on our analysis, the structure of the isolated carbazole was assigned as shown in Figure 3.2.



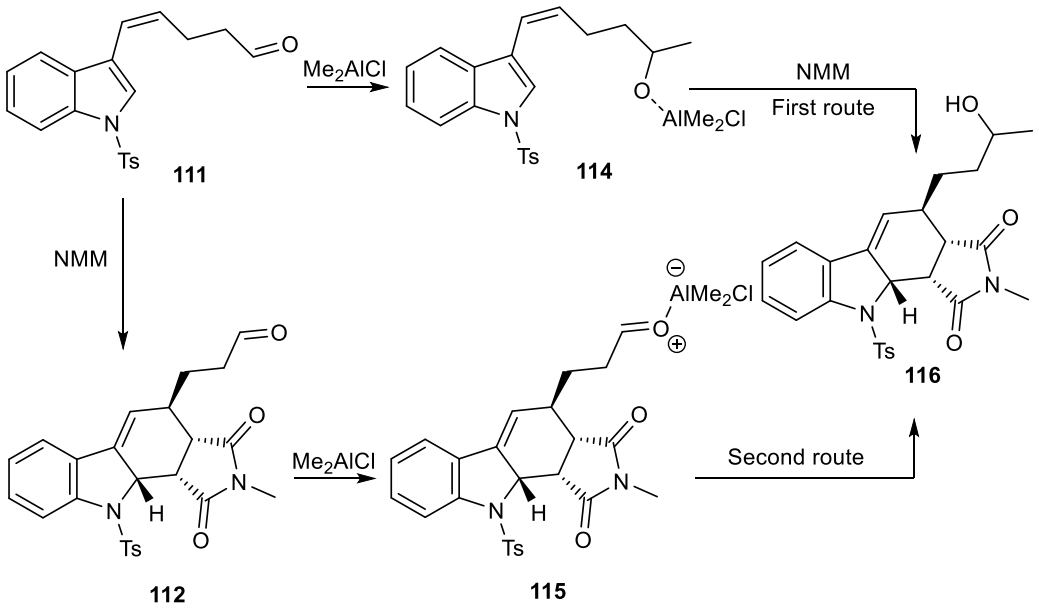
116

Figure 3.2. Chemical structure of the resulting carbazole 116 from the one-pot D-A/ene reaction of indole 111

3.2.3. Proposed mechanism to give by-product (116)

Snider *et al*., found that treatment of a terminal aldehyde with 2.0 equivalents of Me_2AlCl results in the formation of the corresponding secondary alcohol.[86] We therefore proposed that the formation of unexpected carbazole **116,** is due to the Me_2AlCl acting as a source of nucleophilic methyl in the reaction.

Our first proposed route to carbazole **116** involves the addition of a methyl group of Me_2AlCl to the aldehyde of indole **111** followed by D-A reaction of the intermediate **114** with NMM. In the second alternative route, the D-A reaction of indole **111** with NMM occurs first and then Me_2AlCl reacts with the aldehyde of D-A cycloadduct **112** to give the by-product **116** (Scheme 3.5).

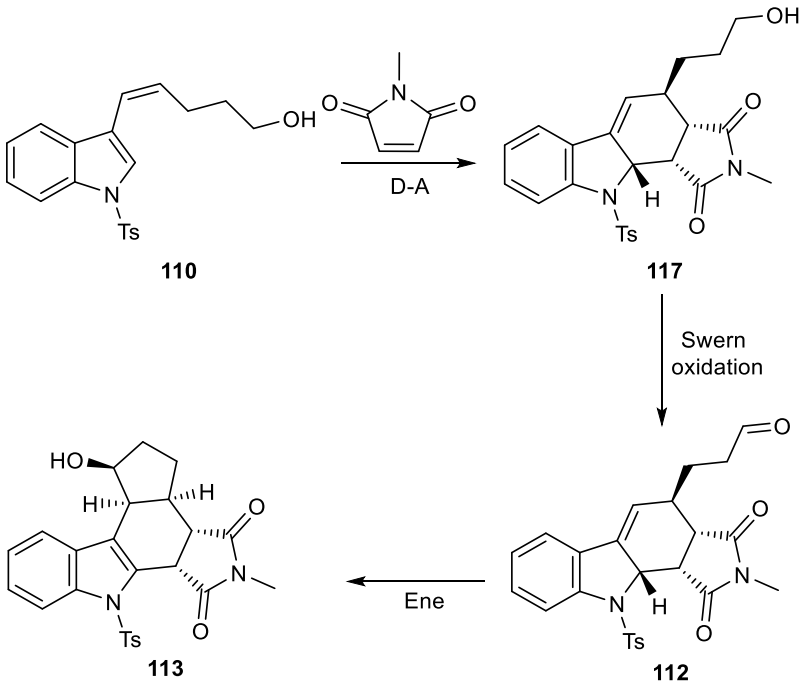


Scheme 3.5. Proposed synthetic routes to the unwanted carbazole 116

Since the one-pot intermolecular D-A/intramolecular carbonyl-ene reaction of indole **111** led to the formation of the unwanted carbazole **116**. We therefore suggested an alternative route for the synthesis of our desired polycyclic pyrrolo[3,4-*a*]carbazole **113**.

3.3. New approach to polycyclic pyrrolo[3,4-*a*]carbazole (113)

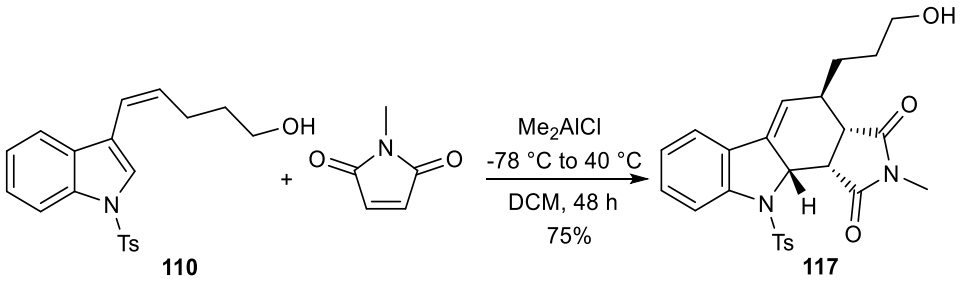
In the following route, we intend to use the previously synthesised indolic alcohol **110** as a diene in D-A reaction with NMM. Once the D-A cycloadduct **117** is obtained, ene cyclisation precursor **112** can be generated directly using a Swern oxidation. Following this, the intramolecular carbonyl-ene reaction of adduct **112** will be examined towards the desired polycyclic carbazole **113** (Scheme 3.6).



Scheme 3.6. New stepwise route to polycyclic carbazole 113

3.3.1. Synthesis of Diels-Alder cycloadduct (117)

Following our synthetic plan, the previously prepared indole **110** was utilised in a D-A reaction with NMM in the presence of 2.0 equivalents of Me_2AlCl. Following purification by column chromatography, the expected D-A cycloadduct **117** was isolated in a good yield of 75% (Scheme 3.7).



Scheme 3.7. Synthesis of D-A cycloadduct 117

The relative stereochemistry of D-A cycloadduct **117** was confirmed by X-ray diffraction analysis. Crystals of D-A cycloadduct **117** were grown from slow diffusion of petrol/ethyl acetate. The crystal structure showed that the relative

stereochemistry of D-A cycloadduct **117**, was consistent with an *endo* selective D-A reaction between indole **110** and NMM (Figure 3.3).

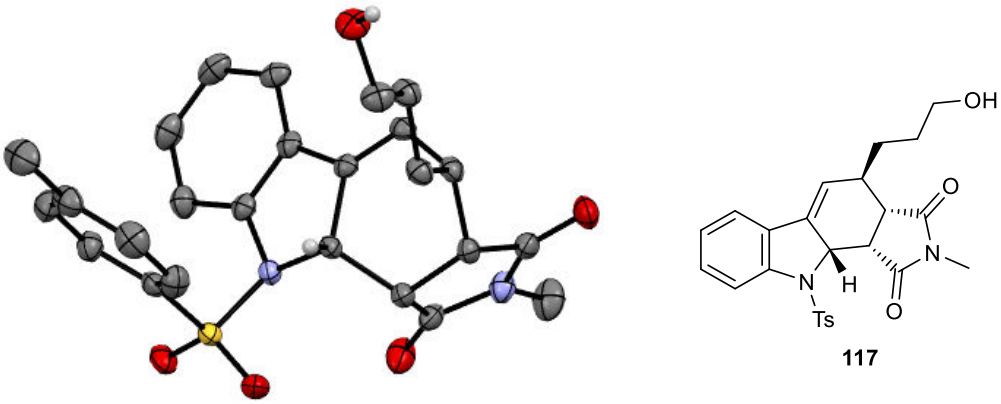
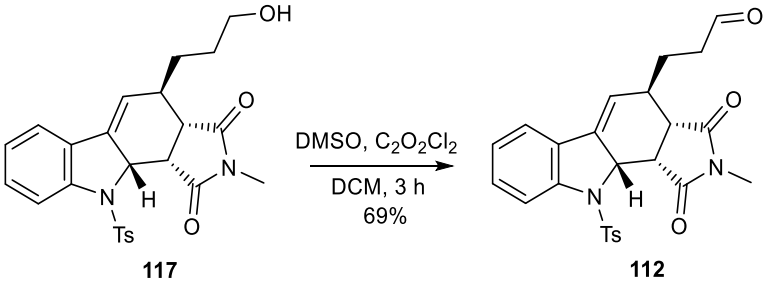


Figure 3.3. X-ray crystal structure of D-A cycloadduct 117

3.3.2. Synthesis of ene precursor (112)

Subsequently, D-A cycloadduct **117** was subjected to a Swern oxidation to provide the desired ene cyclisation precursor **112** in 69% yield (Scheme 3.8).

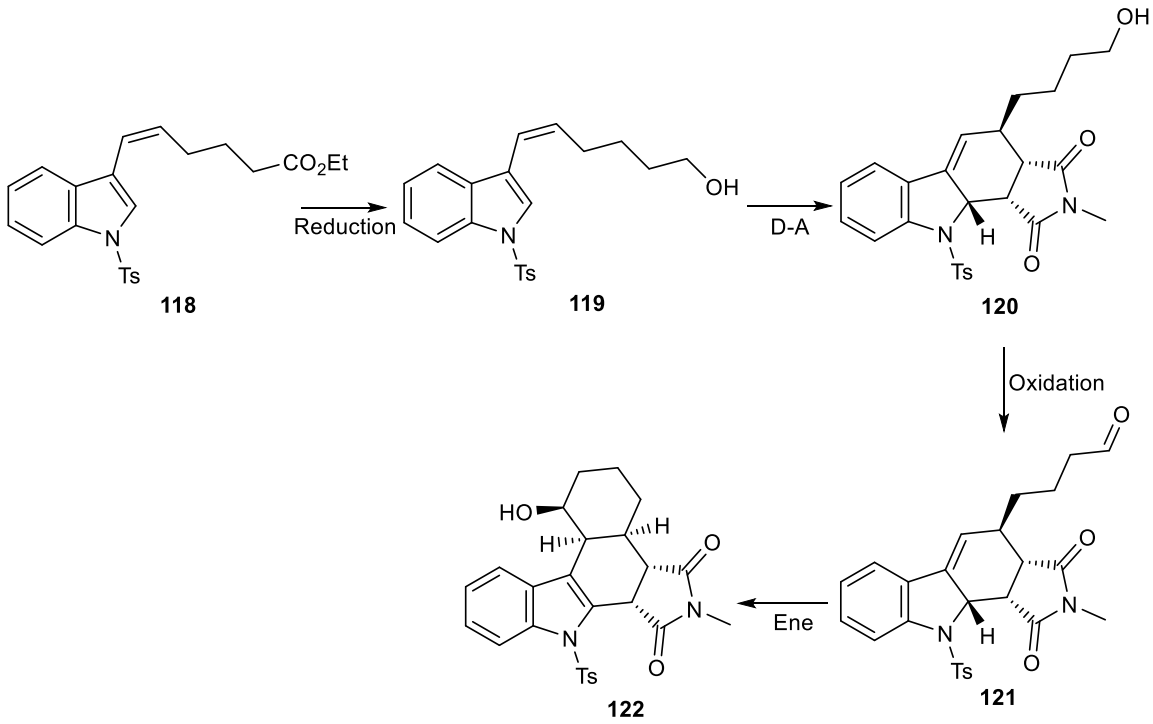


Scheme 3.8. Synthesis of ene precursor 112

3.4. Planned extensions of intramolecular ene chemistry, increase ring size

With an efficient method for the synthesis and purification of ene precursor **112**, the next step was to examine the intramolecular carbonyl-ene reaction of **112** to synthesise the desired polycyclic carbazole **113**. However, before we investigated the intramolecular carbonyl-ene reaction of compound **112**, we planned to apply our synthetic approach to the formation of other C-5 substituted indoles, such as **121**, in order to test the formation of larger rings using our planned intramolecular carbonyl-ene chemistry. Thus we decided to synthesise ene precursor **121** (Scheme 3.9), which could then be transformed

into a pyrrolo[3,4-*a*]carbazole incorporating a fused six- membered ring **122**. This approach would allow a direct comparison to be made between the rates and the yields of intramolecular carbonyl-ene reactions of the two different ene precursors **112** and **121**.

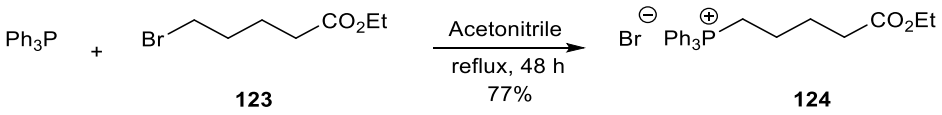


Scheme 3.9. Synthetic plan to pyrrolo[3,4-*a*]carbazole 122

3.5. Synthesis of ene precursor (121)

3.5.1. Synthesis of diene (119)

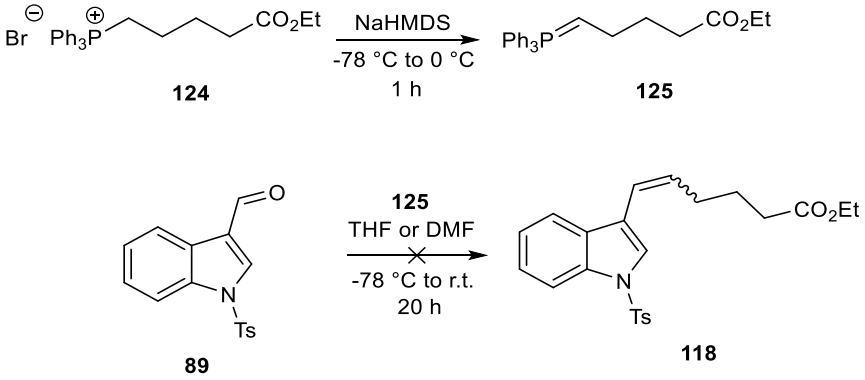
In order to synthesise ene precursor **121,** diene **119** with *Z*-stereochemistry around the double bond had to be synthesised first. We envisioned that diene **119** could be generated by a selective reduction of the ester moiety of indole **118**, which in turn could be synthesised by a Wittig reaction. Thus, the Wittig salt **124** was synthesised by a reaction of triphenylphosphine with ethyl 5-bromopentanoate **123**. The resultant white precipitate was purified by column chromatography to give the desired pure salt in 77% isolated yield as a white foam (Scheme 3.10).



123 124

Scheme 3.10. Synthesis of Wittig salt 124

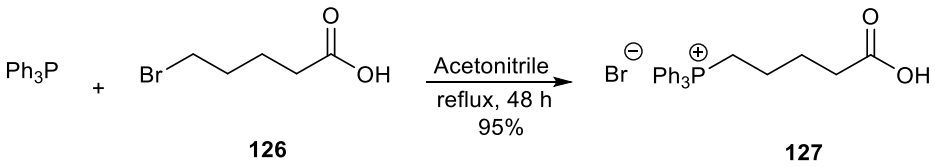
Wittig salt **124** was then converted *in situ* to the corresponding reactive ylide **125** using NaHMDS, and reacted with 1-tosyl-1*H*-indole-3-carbaldehyde **89** in THF for 20 hours (Scheme 3.11). However, no indication of the formation of the desired product **118** was detected. Analysis of the crude reaction mixture by ^{1}H NMR indicated extensive degradation of starting materials under the reaction conditions. Since the Wittig salt **124** was only partially soluble in THF, modification of the Wittig reaction outcome was attempted in a different solvent. Therefore, the Wittig reaction of indole **89** with salt **124** was re-examined in DMF (Scheme 3.11). However, only the starting material was observed by the ^{1}H NMR of the crude reaction mixture. Examination of the literature showed a few examples of the use of salt **124**, thus we decided to change the ylide to one more commonly used.



124 125 89 118

Scheme 3.11. Results from the Wittig reaction of 89 to indole 118

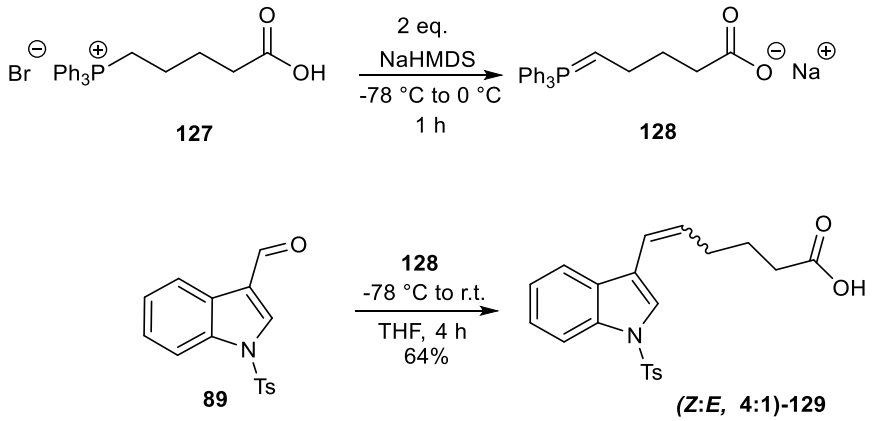
Thus alternative Wittig salt **127** was generated by a reaction of triphenylphosphine with 5-bromopentanoic acid **126** following a literature procedure.[87] The resultant phosphonium salt **127** was then isolated cleanly by direct filtration from the reaction in 95% yield (Scheme 3.12).



126 127

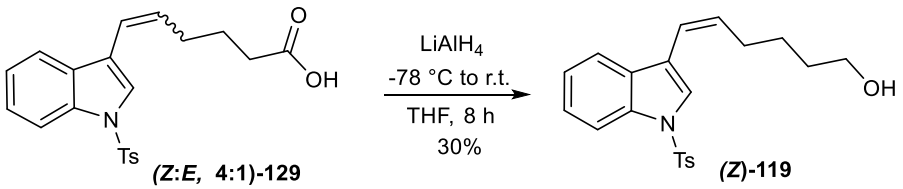
Scheme 3.12. Synthesis of Wittig salt 127

Wittig salt **127** was then deprotonated *in situ* by 2.0 equivalents of NaHMDS to generate ylide **128**, which was in turn reacted with 1-tosyl-1*H*-indole-3-carbaldehyde **89**. After 4 hours at r.t., the reaction was acidified with 1.0 M HCl to quench the added base and to protonate the carboxylic acid (Scheme 3.13).[88] Analysis of the resulting crude reaction mixture by ^{1}H NMR spectrum indicated a mixture corresponding to both the *Z*- and *E*- isomers of the desired compound **129**. However, the *Z*- and *E*- isomers could not be separated by flash column chromatography and the desired compound was obtained in 64% yield as a mixture of *Z*:*E* in a 4:1 ratio.



Scheme 3.13 Wittig reaction of 89 to form indole 129

In the next step, the inseparable mixture of **(Z:*E*, 4,1)-129** was reduced with lithium aluminium hydride ($LiAlH_4$), following a literature procedure.[89] After 8 hours at r.t.,^{1}H NMR of the crude material indicated a mixture of *Z*- and *E*-isomers of the desired diene **119** in a 2:1 isomeric ratio along with the unreacted starting material. When purification was attempted using flash column chromatography, the desired *Z*-isomer of indole **119** was isolated in 30% yield (Scheme 3.14).



Scheme 3.14. Reduction of indole 129 by $LiAlH_4$

3.5.1.1. Esterification reaction of a (*Z:E,* 4:1)-129

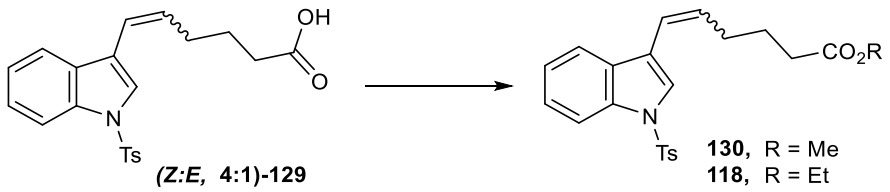
Although the diene **119** was isolated as the required *Z*-stereochemistry around the double bond, the isolated yield was very low (30%). Thus, to improve the yield of compound **119**, we decided to examine the esterification reaction of **129** followed by the DIBAL-H reduction as an alternative route to generate diene **119**.

Two different routes to generate the ester from the carboxylic acid of compound **129** have been examined. The results are summarised in Table 3.1.

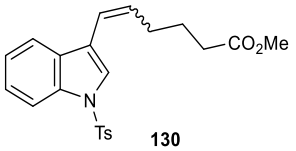
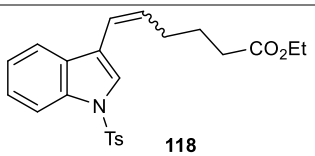
We first attempted the esterification reaction of **129** using a slight excess of methyl iodide (MeI, 1.1 eq.), under mildly basic conditions of K_2CO_3 in DMF at room temperature.[90] The reaction was stopped after 2 hours when the starting material was no longer visible by TLC. Purification of the crude reaction mixture by column chromatography was attempted. The *Z*- and *E*- isomers were inseparable due to close similarity in their R_f value, therefore the product **130** was obtained in 93% yield as a mixture of *Z*- and *E*- isomers in a 4:1 ratio (Table 3.1, entry 1).

In the second method, the carboxylic acid of compound **129** was treated with a large excess of EtOH in the presence of a catalytic amount of concentrated H_2SO_4.[91] TLC showed the esterification reaction of **129** was completed after 1.5 hours. Analysis of the ^1H NMR spectrum of the crude reaction mixture indicated the formation of the ethyl ester through the appearance of new quartet CH_2 and triplet CH_3 signals at 4.10 and 1.21 ppm respectively. An attempt to separate the *Z*-isomer through column chromatography was

successfully and compound **118** was obtained in a pure *Z*-isomer in 56% isolated yield (Table 3.1, entry 2).



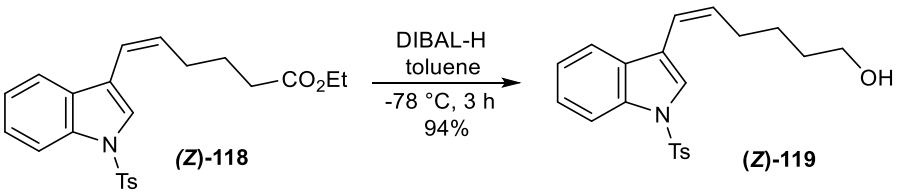
***(Z:E,* 4:1)-129**

Entry	Reaction conditions	Product	*Z*:*E* ratio [a]	Yield %
1	MeI, K_2CO_3, DMF, r.t., 2 h	 **130**	4:1	93 [b]
2	H_2SO_4(cat), EtOH, 78 °C, 1.5 h	 **118**	4:1	56 [c]

[a] *Z*:*E* ratio of the crude reaction mixture by ^{1}H NMR. [b] The isolated yield of a mixture of isomers (*Z*:*E*, 4:1) of 130. [C] The isolated yield of the pure *Z*- isomer of indole 118

Table 3.1. Results of the esterification reactions of indole (*Z*/*E* 4:1)-129

Then the ester moiety of compound **118** was reduced with DIBAL-H at -78 °C for 3 hours. The desired diene with terminal alcohol **119** was obtained in 94% yield, with no further purification being necessary as shown by ^{1}H NMR (Scheme 3.15).

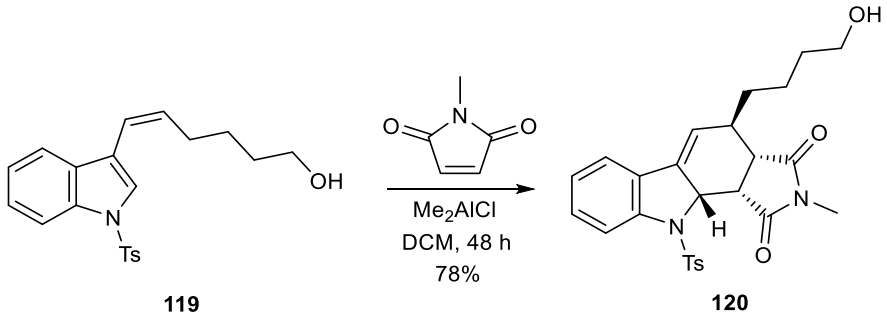


***(Z)*-118** **(*Z*)-119**

Scheme 3.15. DIBAL-H reduction of 118 to form 119

3.5.2. Diels-Alder reaction of diene (119) with NMM

In the subsequent step, diene **119** was subjected to a D-A reaction with NMM catalysed by Me_2AlCl. The corresponding D-A cycloadduct **120** was isolated in 78% yield as a single diastereomer, after purification by column chromatography (Scheme 3.16).



119 **120**

Scheme 3.16. Synthesis of D-A cycloadduct 120

The formation of *endo* D-A cycloadduct **120** was confirmed through comparison of the ^{1}H NMR spectral data of D-A cycloadduct **120** with those of D-A cycloadduct **117** (Figure 3.4)

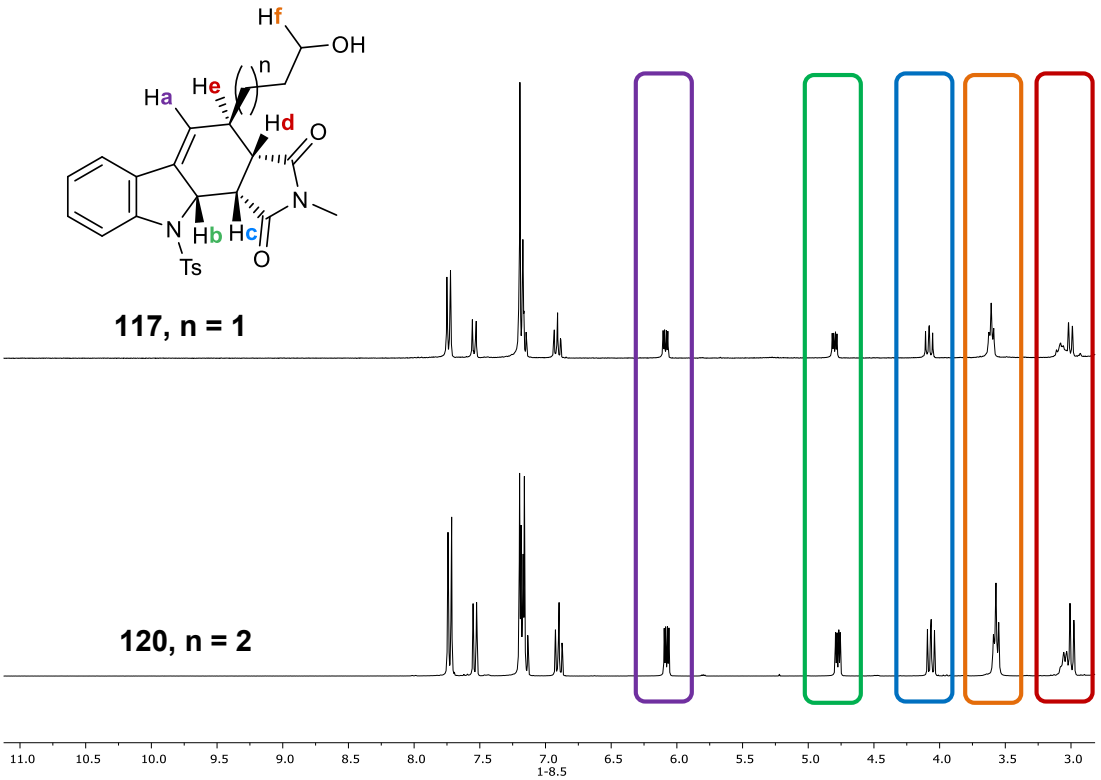
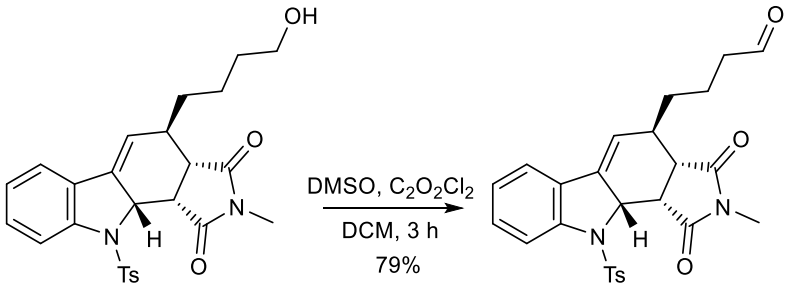


Figure 3.4.^{1}H NMR of D-A cycloadducts 117 and 120

In the next step, D-A cycloadduct **120** was transformed into the ene precursor **121**, using Swern oxidation, in 79% isolated yield (Scheme 3.17).

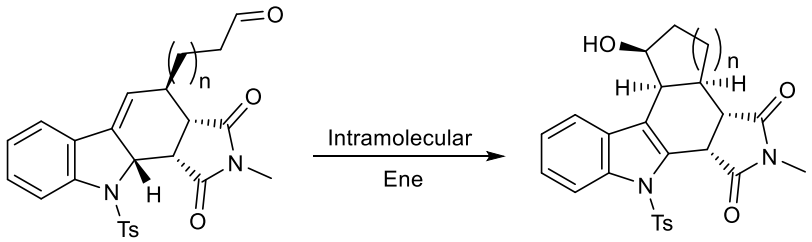


120 **121**

Scheme 3.17. Synthesis of ene precursor 121

3.6. Investigation of the intramolecular ene reaction of (112) and (121)

With ene precursors **112** and **121** in hand, we then decided to examine the ring closure of **112** and **121** to give our target pyrrolocarbazole fused compounds **113** and **122**, through an intramLocular carbonyl-ene reaction (Scheme 3.18).



112, n = 1
121, n = 2

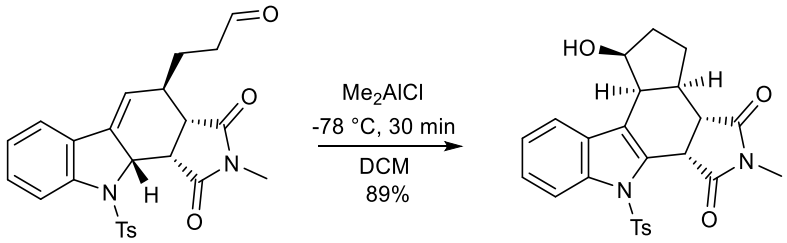
113, n = 1
122, n = 2

Scheme 3.18. Planned synthetic route to synthesise 113 and 122

A survey of the literature revealed that high temperatures or Lewis acid activation are often required in the case of carbonyl ene reactions.[92,93,94] Coordination of Lewis acids to the oxygen of the carbonyl activates the carbon centre towards the nucleophilic addition. However, a problem in the use of Lewis acid to catalyse our intramolecular carbonyl-ene reaction is the possibility of generating catalytic quantities of protic acid, thus initiating unwanted side reactions such as the rearomatisation of the D-A

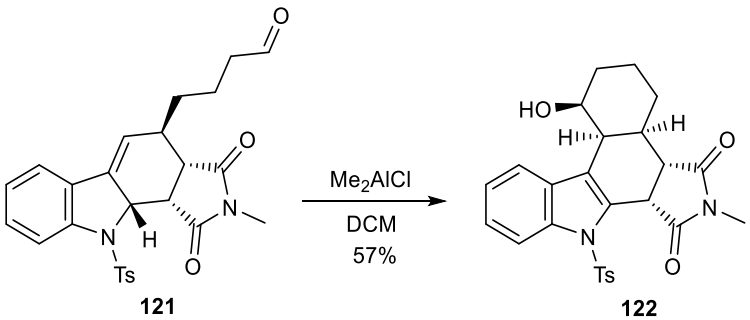
cycloadducts.[95] We therefore decided to use Me_2AlCl as the Lewis acid catalyst, due to its ability to act also as a proton scavenger.

Our investigation of the intramolecular carbonyl-ene reaction was carried out by dissolving ene precursor **112** in DCM, followed by the addition of 1.0 equivalent of Me_2AlCl at -78 ^oC. After 30 min, TLC indicated the reaction was completed when compound **112** had disappeared. Purification of the crude reaction mixture by column chromatography afforded the target polycyclic carbazole **113** in an excellent yield of 89% as a single diastereomer (Scheme 3.19).



Scheme 3.19. Intramolecular carbonyl-ene reaction of precursor 112

The investigation of the intramolecular carbonyl-ene reaction of ene precursor **121** (Scheme 3.20), was also undertaken and the results are reported in Table 3.2.



Scheme 3.20. Intramolecular carbonyl-ene reaction of 121

We initially examined the intramolecular carbonyl-ene reaction of ene precursor **121** under the previously discussed conditions for 8 hours. However,

^{1}H NMR of the crude reaction mixture showed no reaction had occurred and only the starting material was observed (Table 3.2, entry 1). Re-examined the reaction at a higher temperature (0 ^{o}C), also failed to give the desired product **122** (Table 3.2, entry 2). Optimisation of the reaction conditions involved refluxing the reaction mixture containing ene precursor **121** and 1.0 equivalent of Me_2AlCl in DCM for 3 hours. Under these reaction conditions, the corresponding polycyclic pyrrolo[3,4-*a*]carbazole **122** was obtained in 57% yield after purification by column chromatography (Table 3.2, entry 3).

Entry	Temperature/ ^{o}C	Reaction time/ h	SM: product ratio [a]	Yield [b] %
1	-78	8	100:0	-
2	0	10	100:0	-
3	25	3	40:60	57

[a] Ratio was determined by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield of the desired product 122

Table 3.2. Results of varying the temperature on the intramolecular carbonyl ene reaction of ene precursor 121

In our investigations of the intramolecular carbonyl-ene reaction of **112**, we noticed that the reaction went to completion in a very short time of 30 min at -78 ^{o}C to give the corresponding carbazole **113**. However, in the synthesis of carbazole **122**, the reaction required higher temperatures and longer reaction times. We thus proposed that varying on the length of the tether led to a major effect on the rate of the intramolecular carbonyl-ene reaction, due to the steric influence of tether length on the formation of the ene transition state.

3.7. Relative stereochemistry assignment of polycyclic carbazoles (113) and (122)

The X-ray crystallographic analysis of the synthesised polycyclic carbazoles **113** and **122** was performed to elucidate their relative stereochemistry. Crystals of carbazoles **113** and **122** were grown by slow evaporation from the DCM at room temperature. Both crystal structures showed that the aldehyde

of both ene precursors **112** and **121** is abstracted the allylic hydrogen from the *twix* position, to give the corresponding products **113** and **122** with *anti*-arrangement between the newly formed ring and succinimide groups (Figure 3.5). In addition, the formation of a *cis* fused ring of the resultant carbazole **122** was confirmed further by coupling constant analysis. The ^{3}J value between the ring junction protons (H_{14} and H_{19}) was 5.2 Hz, which is indicative of a *cis* fused ring.

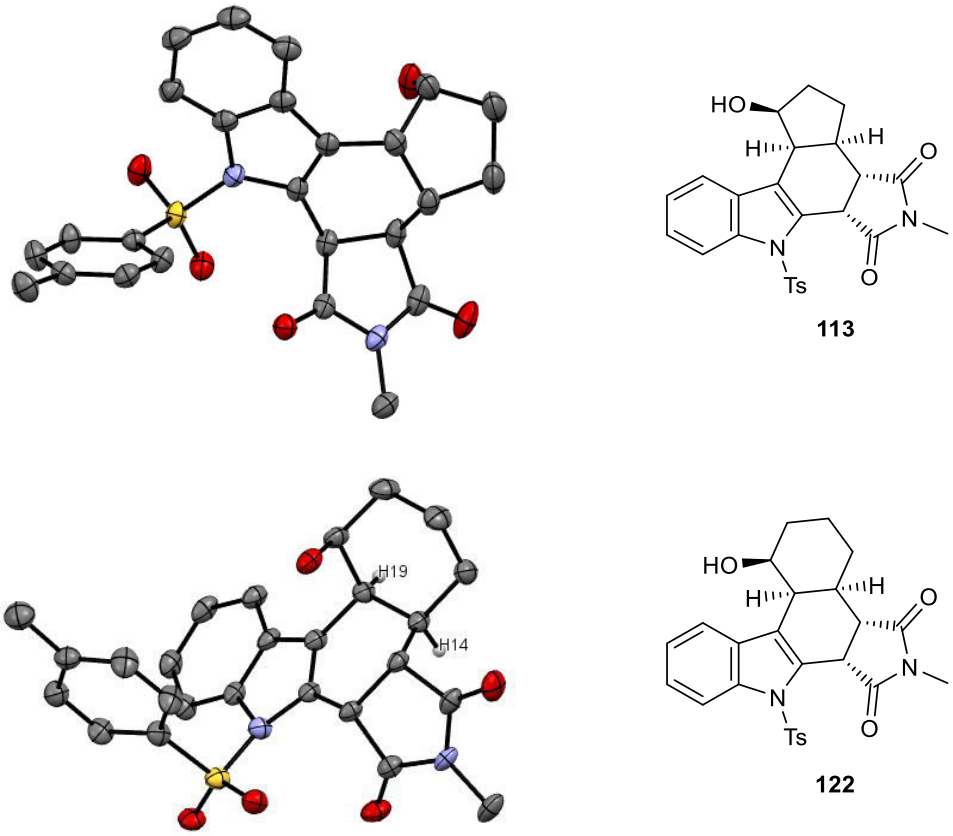


Figure 3.5. X-ray crystal structure of 113 and 122

To rationalise the relative stereochemistry of the previously synthesised carbazoles **113** and **122**, we proposed the following concerted ene mechanism with a cyclic transition state (Figure 3.6) occurs to form both the five and six membered rings.

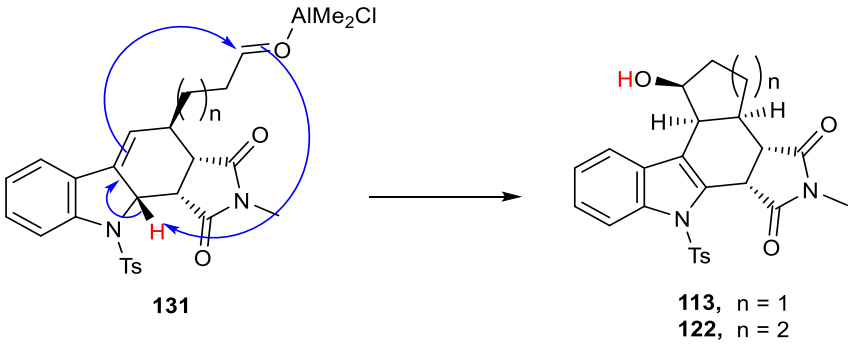


Figure 3.6. Proposed concerted intramolecular carbonyl-ene mechanism

Although the intramolecular carbonyl-ene reaction often procceds by a concerted mechanism, it can also take a place through a stepwise pathway involving the foramation of the carbocation intermediate **132** (Figure 3.7).[93]

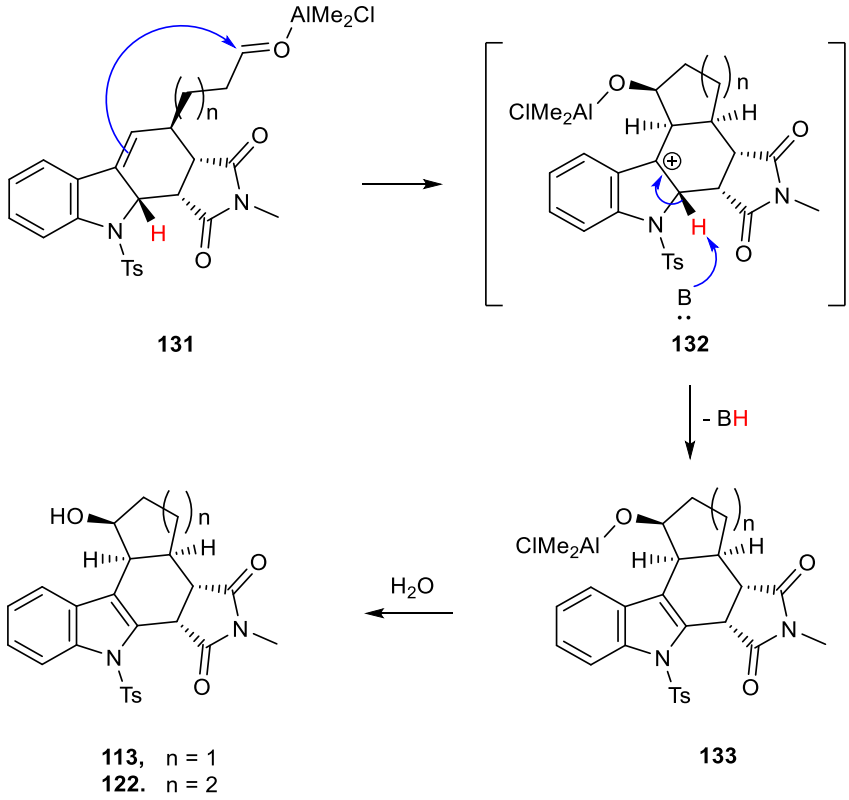
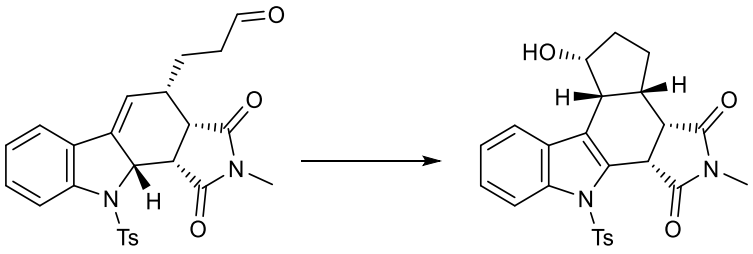


Figure 3.7. Proposed stepwise intramolecular carbonyl-ene mechanism

3.8. Investigation of the intramolecular carbonyl-ene mechanism

To confirm whether the ene mechanism occurs through a stepwise or concerted mechanism, we sought to study the intramolecular carbonyl-ene

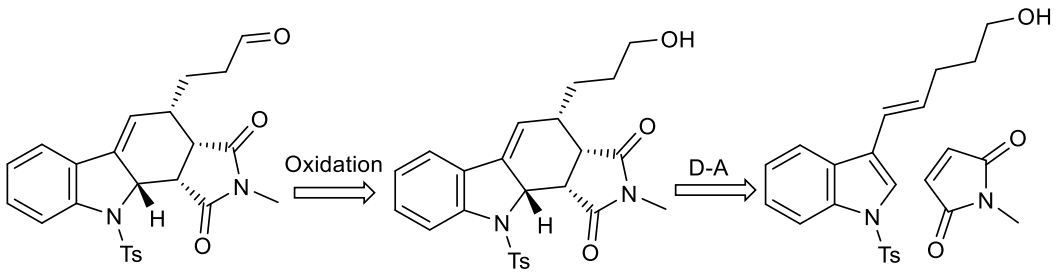
reaction of ene precursor **136** under previously discussed conditions. From a mechanistic standpoint, if the ene reaction proceeds *via* a stepwise mechanism, then in the case of ene precursor **136**, the reaction would be able to proceed with the cyclopentanol ring being formed *cis* to the succinimide group, giving product **137** (Scheme 3.21). However, if a concerted mechanism prevailed, no cyclisation process would be expected as the aldehyde would be unable to reach the *twix* hydrogen (Figure 3.6, page 56).



136 **137**

Scheme 3.21. Planned synthetic approach to investigate the intramolecular carbonyl-ene mechanism

We envisaged that the desired ene precursor **136** could be synthesised by a Swern oxidation of D-A cycloadduct **135**. In turn, the D-A cycloadduct **135** with the required alternate stereochemistry could be accessed from a D-A cycloaddition between the indole **(*E*)-134** and NMM (Scheme 3.22).



136 **135** ***(E)*-134**

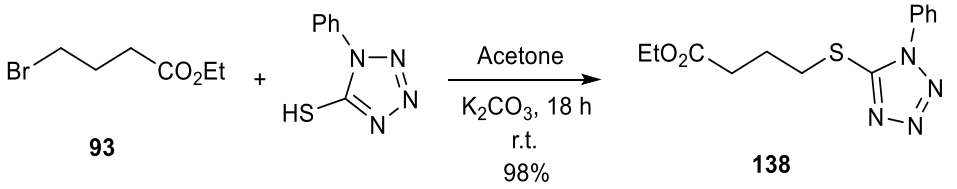
Scheme 3.22. Retrosynthetic analysis to synthesise ene precursor 136

3.9. Synthesis of (*E*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol (134)

3.9.1. Synthesis of tetrazole 139

We began our synthesis with olefination reaction of 1-tosyl-1*H*-indole-3-carbaldehyde **89** utilising *E*-selective Julia-Kocienski reaction with tetrazole

139. In order to synthesise the tetrazole **139**, compound **138** was synthesised according to the literature procedure by an S_N2 reaction of 1-phenyl-1*H*-tetrazol-5-thiol and ethyl-4-bromobutyrate **93** in the presence of K_2CO_3 (Scheme 3.23).[96] The reaction went to completion after 18 hours at room temperature as observed by the TLC. The crude reaction mixture was purified by column chromatography and the expected ethyl 4-((2-phenyl-2*H*-tetrazol-5-yl)thio)butanoate **138** was obtained in 98% isolated yield.



Scheme 3.23. Synthesis of compound 138

Selective oxidation of sulfide **138** to sulfone **139** was investigated using two different possible routes. The results are summarised in Table 3.3

In the first route, oxidation of sulfide **138** to sulfone **139** was attempted using *m*-chloroperoxybenzoic (*m*-CPBA) in DCM for 24 hours (Table 3.3, entry 1), following a literature procedure.[97] Analysis of the ^{1}H NMR of the crude reaction mixture indicated a 1:1 mixture of a new product along with unreacted starting material. Increasing the equivalents of the oxidising agent did not change the observed ratio. Purification of the crude reaction mixture by column chromatography afforded the sulfone **139** in a moderate yield of 46%.

Alternatively, oxidation of sulfide **138** was tested using 35% hydrogen peroxide (H_2O_2) solution and a molybdenum catalyst $(NH_4)_6 Mo_7O_{24} . 4H_2O$ following a literature procedure.[96, 98] Purification of the crude reaction mixture by column chromatography afforded the desired tetrazole **139** in 78% yield (Table, 3.3, entry 2).

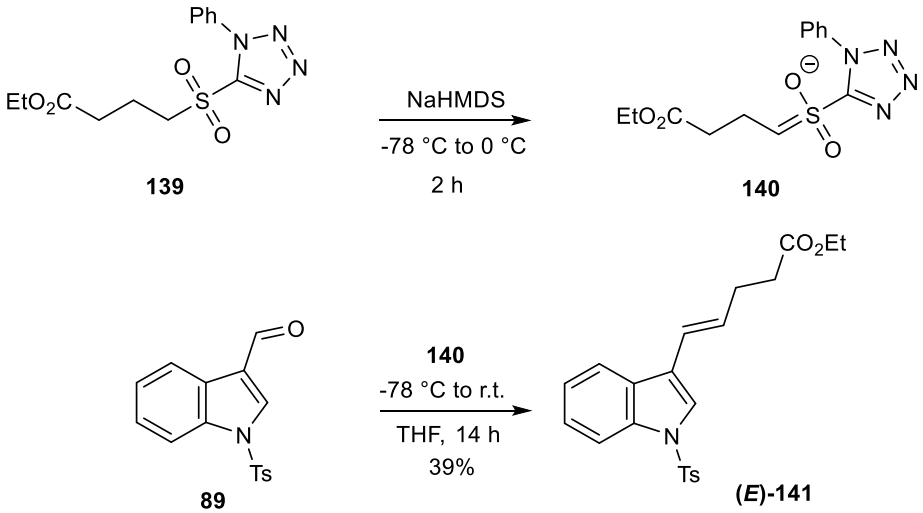
138 **139**

Entry	Reaction conditions	Isolated yield %
1	*m*-CPBA, DCM , 24 h, 0 °C to r.t.	46
2	$(NH_4)_6Mo_7O_{24}$. $4H_2O$, 35% H_2O_2, MeOH, r.t., 18 h	78

Table 3.3. Synthesis of the desired tetrazole 139

3.9.1.1. Julia-Kocienski reaction of indole (89)

With tetrazole **139** in hand, the next step was to use it in the *E*-selective Julia-Kocienski reaction in order to synthesise indole **141**. Therefore, tetrazole **139** was deprotonated *in situ* with NaHMDS to generate ylide **140**,[98] which was then reacted with 1-tosyl-1*H*-indole-3-carbaldehyde **89** (Scheme 3.24). The crude reaction mixture was purified through column chromatography to give the desired *E*-isomer of indole **141** in 39% isolated yield. The stereochemistry of **141** was confirmed using coupling constant analysis. The large coupling constant between the olefinic protons was 16.3 Hz, which indicated that compound **141** has an *E*-configuration around the double bond.

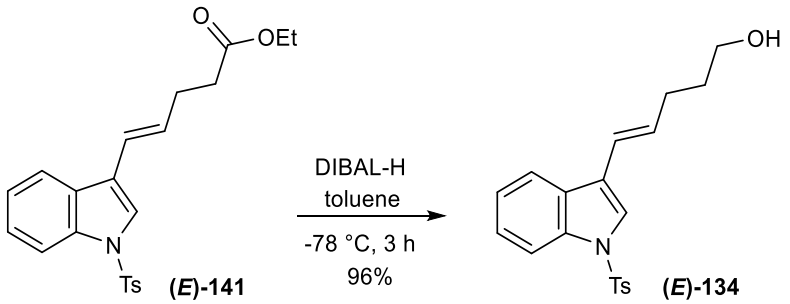


139 **140** **89** (***E***)**-141**

Scheme 3.24. Synthesis of indole (*E*)-141 using Julia-Kocienski olefination

3.9.1.2. DIBAL-H reduction of indole (*E*)-141

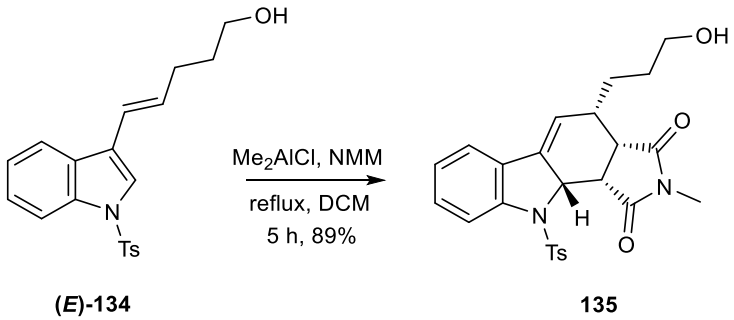
The ester group of indole **(*E*)-141** was subsequently reduced with DIBAL-H in toluene at -78 ºC to give the desired diene **(*E*)-134** in 96% isolated yield after purification by column chromatography (Scheme 3.25).



Scheme 3.25. Synthesise of diene (*E*)-134

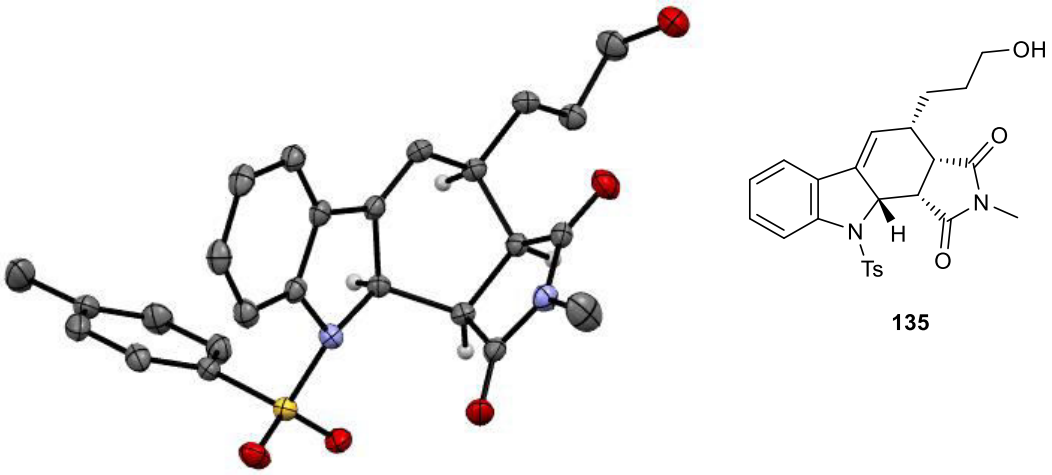
3.10. Synthesis of ene precursor (136)

The resulting **(*E*)-134** was then used as a diene in a D-A reaction with NMM in the presence of Me_2AlCl. The corresponding D-A cycloadduct **135** was obtained in 89% isolated yield (Scheme 2.26).



Scheme 2.26. Synthesis of D-A cycloadduct 135

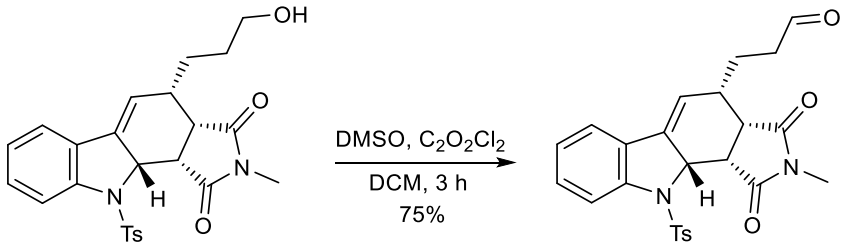
The relative stereochemistry of the D-A cycloadduct **135** was assigned based on the X-ray crystal structure (Figure 3.8). Crystals of D-A cycloadduct **135** were grown by slow evaporation of a solution of **135** in ethyl acetate/petrol. The crystal structure confirmed that compound **135** was formed through an *endo* selective cycloaddition between the **(*E*)-134** and NMM. Our desired *syn* arrangement between the alkyl side chain and the succinimide group of D-A cycloadduct **135** was also confirmed by X-ray analysis.



135

Figure 3.8. X-ray crystal structure of D-A cycloadduct 135

In the next step, the D-A cycloadduct **135** was subjected to a Swern oxidation to give the desired ene cyclisation precursor **136** in 75% isolated yield, after purification by column chromatography (Scheme 2.27).

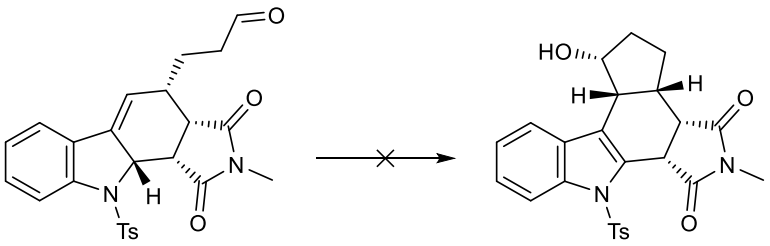


135 136

Scheme 2.27. Synthesis of ene precursor 136

3.11. Intramolecular carbonyl-ene reaction of precursor (136)

At this point, we were ready to investigate the intramolecular carbonyl-ene mechanism as the terminal aldehyde of the ene precursor **136** could serve as a reactive enophile to close the ring. All of the attempts to close the ring by intramolecular carbonyl-ene reaction of **136** in the presence of 1.0 equivalent of Me_2AlCl, failed to give the cyclised five membered ring-containing product **137** and only the starting material was recovered despite the testing of different reaction conditions (Table 3.3).



136 **137**

Entry	Temperature/ °C	Reaction time/ h	^{1}H NMR of the crude reaction mixture
1	-78	8	Only SM was observed
2	0	8	
3	25	24	
4	40	72	

Table 3.3. Investigation of the intramolecular carbonyl-ene reaction of aldehyde 136 under various reaction conditions

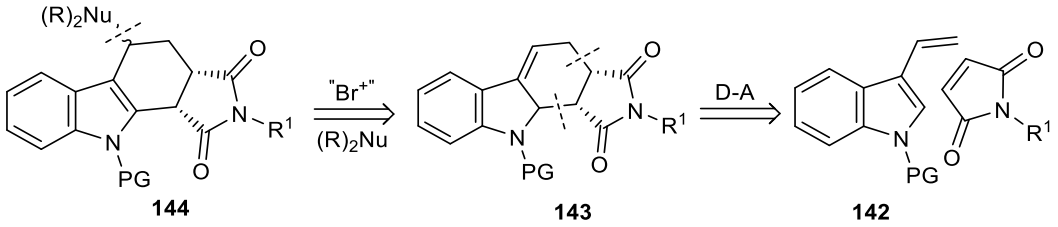
This result provides clear evidence that the intramolecular carbonyl-ene reaction of precursors **112** and **121** occurs *via* a concerted mechanism, as the reaction only proceeds when the reacting aldehyde is on the same face as the *twix* proton.

3.12. Conclusion

In this chapter, we discovered a new synthetic route to *cis*-fused polycyclic tetrahydropyrrolo[3,4-*a*]carbazole frameworks through the use of a three-step sequence; an intermolecular D-A, Swern oxidation and intramolecular carbonyl-ene reaction of *Z*-precursor indoles **110** and **119**. We also found that the synthesised polycyclic carbazoles **113** and **122** were most likely formed by a concerted ene mechanism governed by the stereochemistry of the allylic hydrogen. Therefore, only cyclisation precursor **112** and **121**, which derived from the *Z*-isomers, underwent an intramolecular carbonyl-ene reaction to give the corresponding polycyclic carbazoles **113** and **122**.

Chapter 4.
Bromination/Substitution Chemistry of 3-Vinyl-1*H*-Indole

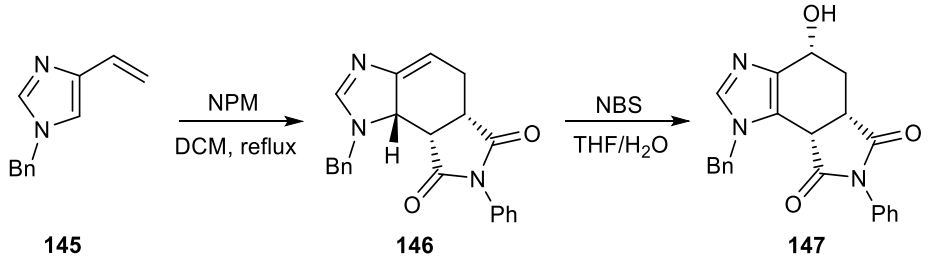
The forgoing chapters have described two successful approaches for the synthesis of functionalised tetrahydropyrrolo[3,4-*a*]carbazole-1,3-dione derivatives, through the use of an intermolecular D-A reaction in conjunction with an inter- or an intramolecular ene reaction. Our work in this chapter will focus on an alternative approach to the synthesis of tetrahydropyrrolo[3,4-*a*]carbazoles **144**, through the use of a D-A cycloaddition of the protected 3-vinyl-1*H*-indole **142** with a range of dienophiles, followed by a one-pot bromination/substitution reaction of the formed D-A cycloadducts **143** (Scheme 4.1).



Scheme 4.1. D-A/one-pot bromination/substitution reaction approach to the pyrrolo[3,4-*a*]carbazole ring system 144

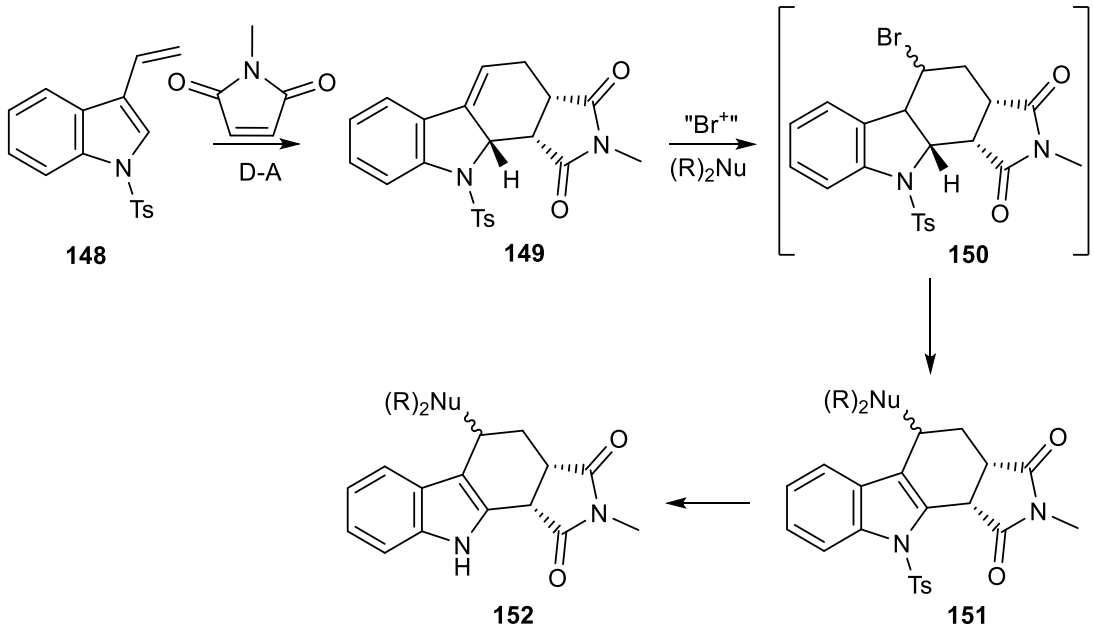
4.1. Synthetic plan to substituted carbazole (151)

Although there were no reported reactions for the functionalisation of D-A cycloadducts such as **143** through a bromination/substitution reaction sequence, our proposed synthetic plan was guided by work published by Lovely's research group.[99] Lovely *et al*., have shown that enamine **146**, the product of a D-A reaction of vinyl imidazole **145** and NPM, can be converted to an alcohol **147** in the presence of *N*-bromosuccinimide (NBS) and water via a proposed halogenation of the alkene followed by substitution by water sequence (Scheme 4.2).



Scheme 4.2. Lovely's enamine to alcohol conversion

We have therefore decided to start our investigation using tosyl protected 3-vinyl-1*H*-indole **148** in the D-A reaction with NMM, to give D-A cycloadduct **149**. Then we will test the reactivity of the formed D-A cycloadduct **149** towards electrophilic brominating reagents in the presence of alcohols or amines to investigate the potential for one-pot bromination/substitution reactions. Once the target compounds **151** are obtained, removal of the *N*-protecting group will be examined and subsequently the biological activities of the produced compounds **152** will evaluated (Scheme 4.3).

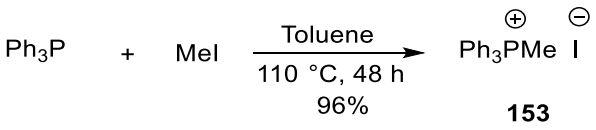


Scheme 4.3. Synthetic plan to substituted carbazoles 151 and *N*-deprotection to 152

4.2. Diels-Alder chemistry of 1-tosyl-3-vinyl-1*H*-indole (148)

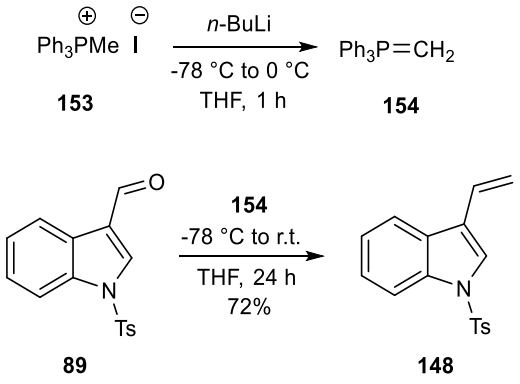
4.2.1. Synthesis of 1-tosyl-3-vinyl-1*H*-indole (148)

The first step in the investigation of our proposed bromination/substitution reactions of D-A cycloadduct **149,** was to synthesise1-tosyl-3-vinyl-1*H*-indole **148**. We envisioned that indole **148** could be synthesised by a Wittig reaction between the previously synthesised 1-tosyl-1*H*-indole-3-carbaldehyde **89** and methyltriphenylphosphonium iodide **153**. Compound **153** was synthesised by a nucleophilic substitution reaction of methyl iodide with triphenylphosphine following a literature procedure (Scheme 4.4).[100] The resulting crude phosphonium salt **153** was isolated in an almost quantitative yield of 96% by filtration, and used in the subsequent Wittig reaction without the need for further purification.



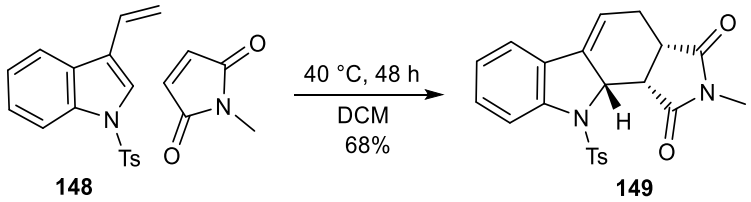
Scheme 4.4. Synthesis of Wittig salt 153

The next step was to utilise salt **153** in a Wittig reaction with 1-tosyl-1*H*-indole-3-carbaldehyde **89**. Therefore, Wittig Salt **153** was converted *in situ* to the reactive ylide **154** using *n*-butyllithium following a literature procedure (Scheme 4.5).[101] The Wittig reaction between ylide **154** and 1-tosyl-1*H*-indole-3-carbaldehyde **89** afforded the expected 1-tosyl-3-vinyl-1*H*-indole **148** in a good yield of 72% after purification by column chromatography.



Scheme 4.5. Wittig reaction of 89 to form 148

The desired D-A cycloadduct **149** was then synthesised through a thermal cycloaddition reaction between 1-tosyl-3-vinyl-1*H*-indole **148** as a diene and NMM as a dienophile. The reaction was carried out in refluxing DCM for 48 h monitored by TLC. ^{1}H NMR spectrum of the crude reaction mixture indicated the loss of the signals corresponding to the vinylic CH_2 protons at 6.75, 5.79 and 5.33 ppm, and showed significant conversion to a single major product. Purification of the crude reaction mixture by column chromatography gave the D-A cycloadduct **149** in 68% yield as a single diastereomer (Scheme 4.6).



Scheme 4.6. Synthesis of D-A cycloadduct 149

4.3. Relative stereochemistry of D-A cycloadduct (149)

To determine the relative stereochemistry of the resultant D-A cycloadduct **149,** crystals were grown from a solution of D-A cycloadduct **149** in ethyl acetate/petrol by slow evaporation. X-ray analysis indicated that the D-A cycloadduct **149** had been formed through the expected *endo*-selective D-A reaction (Figure 4.1).

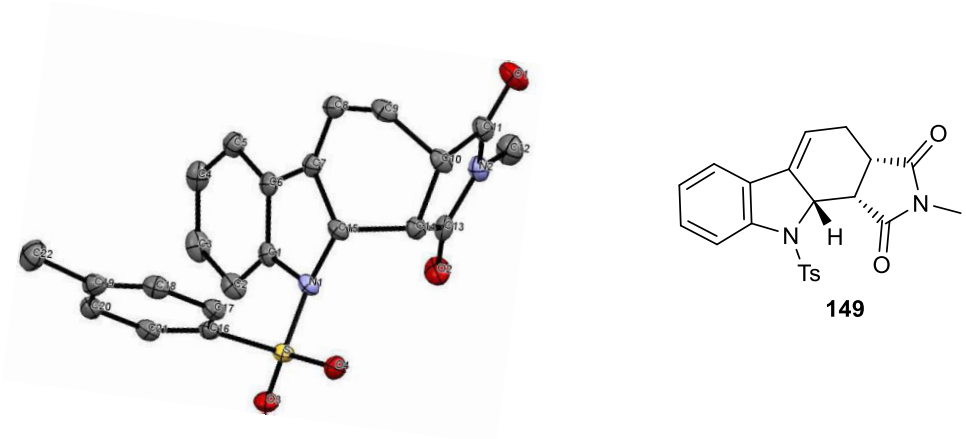


Figure 4.1. X-ray crystal structure of 149 *

* X-ray crystal structure of D-A cycloadduct **149** was done by Joseph Cowell.

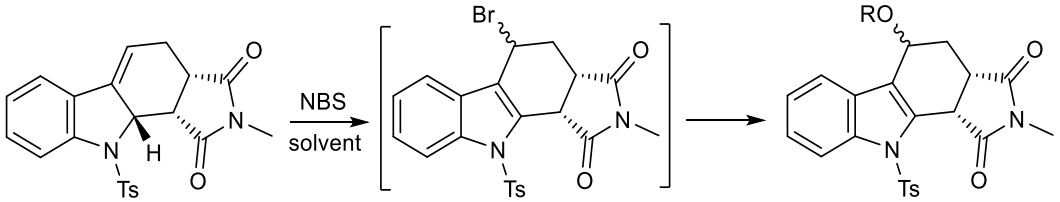
4.4. Investigation of the one-pot bromination/substitution reactions of D-A cycloadduct (149)

4.4.1. Bromination/substitution reactions using a range of alcohols

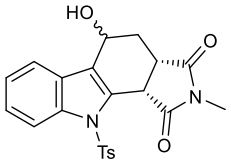
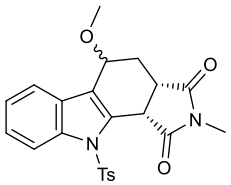
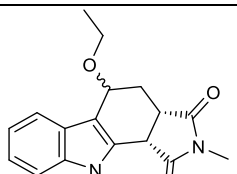
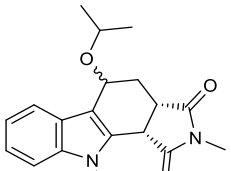
We started our investigation into a potential one-pot bromination/substitution reaction using NBS as an electrophilic source of halogen to brominate the cyclohexenyl double bond of D-A cycloadduct **149**. Water or an alcohol was used as both a co-solvent and as a nucleophile to react with the brominated intermediate *in situ* through a nucleophilic substitution reaction. The results are summarised in Table 4.1.

In the first attempt, NBS was added to a solution of D-A cycloadduct **149** in a 1:1 mixture of THF/water at 0 °C. After 2 hours at r.t., two diastereomers in a 4:1 ratio were observed in the ^{1}H NMR spectrum of the crude reaction mixture. Purification by column chromatography afforded the major diastereomer of carbazole **156** in 52% yield (Table 4.1, entry 1). Following this successful reaction to give carbazole **156**, we then decided to examine the one-pot bromination/substitution reactions of D-A cycloadduct **149** under the previously discussed conditions using a range of alcohol solvents.

Treatment of D-A cycloadduct **149** with NBS in a 1:1 mixture of THF and MeOH, EtOH or 2-propanol at 0 ^{o}C for 1 hour led to the formation of the corresponding substituted carbazole as a mixture of two diastereomers as shown by the ^{1}H NMR spectrum of the crude reaction mixture. Purification of the diastereomers was attempted by flash column chromatography and the major diastereomers **157, 158** and **159** were successfully isolated in yields ranging from 64-75% (Table 4.1, entry 2-4).



149 150 155

Entry	Solvent 1:1	Diastereomeric ratio [a]	Product	Yield [b] %
1	THF/H_2O	4:1	 **156**	52
2	THF/MeOH	14:1	 **157**	75
3	THF/EtOH	14:1	 **158**	67
4	THF/ Isopropanol	19:1	 **159**	64

[a] Diastereomeric ratio was determined by ^{1}H NMR of the crude reaction mixture
[b] Isolated yield of the major diastereomer

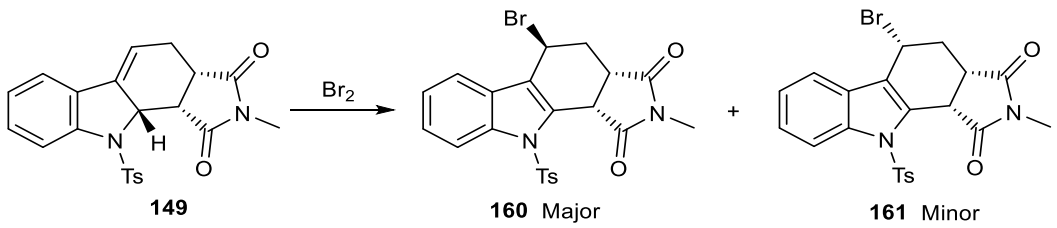
Table 4.1. Results of bromination/substitution reactions of D–A cycloadduct 149

The most notable feature of the previously reported bromination/substitution reactions is that the diastereomeric ratio of the product is strongly dependent on the nature of the external nucleophile. The use of a small nucleophile such

as water gave two diastereomers of the desired substituted product **156** in a 4:1 ratio whereas the use of isopropyl alcohol, which is a sterically more bulky nucleophile, led to the formation of the corresponding substituted carbazole **159** in a 19:1 diastereomeric ratio.

4.4.2. Proposed mechanism for the bromination/substitution reactions

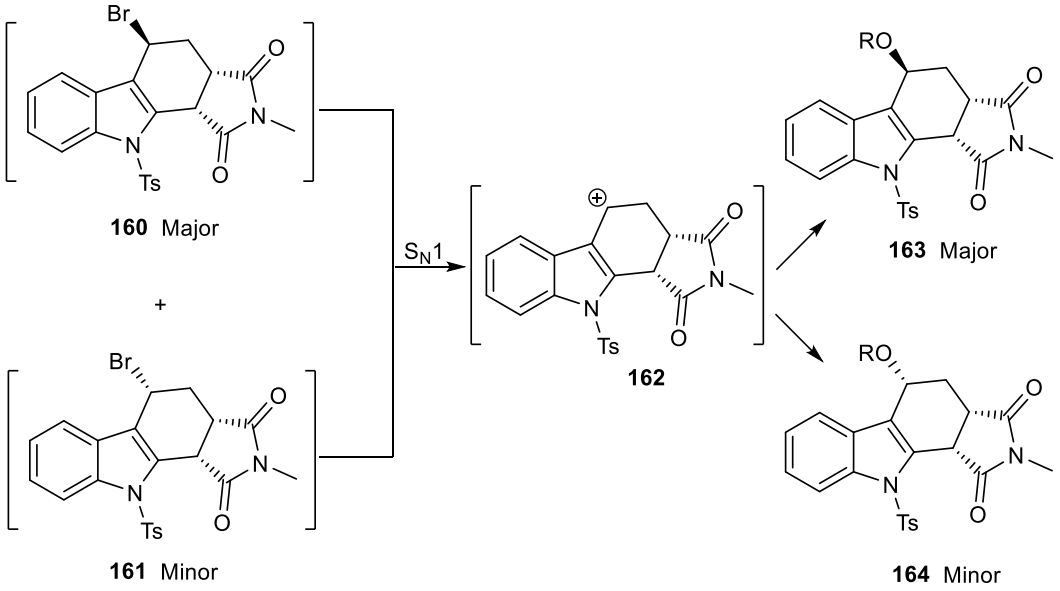
We postulated that the one-pot bromination/substitution reaction occurs *via* two successive elementary steps. The initial step may involve formation of two diastereomers of the brominated intermediates **160** and **161**. We can suppose that the bromination might occur under steric control, directed by the succinimide group. Thus, we propose that the major diastereomer **160** of the brominated intermediate would result from addition of bromine to the *si*-face of the alkene, opposite the succinimide group, whereas the minor diastereomer **161** might arise from addition to the *re*-face of the alkene, the same face as the succinimide group (Scheme 4.7).



149 **160** Major **161** Minor

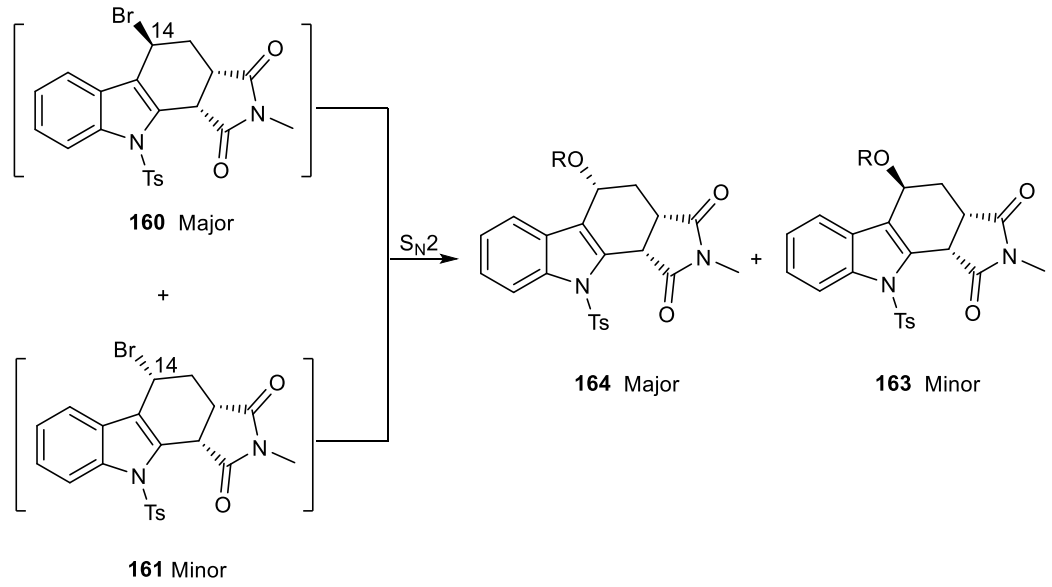
Scheme 4.7. Proposed brominated intermediates 160 and 161

The second step in the bromination/substitution reaction would be a nucleophilic substitution reaction, which could take place by either an S_N1 or an S_N2 mechanism. In the S_N1 mechanism, after loss of bromide the nucleophile can attack form either face of the planar secondary carbocation **162**, to afford the major diastereomer **163** of the corresponding carbazole with *anti*-stereochemistry and the minor diastereomer **164** with *syn*-stereochemistry, again under steric control from the succinimide group (Scheme 4.8).



Scheme 4.8. Proposed S_N1 pathway

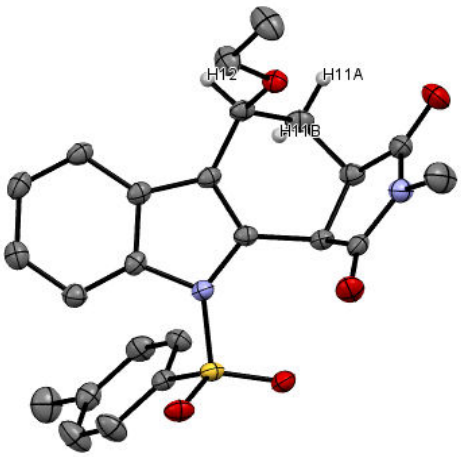
Whilst in the proposed S_N2 mechanism, the substitution reaction of bromine by the nucleophile would proceed with inversion of the configuration at position (14), to give the corresponding major diastereomer **164** and minor diastereomer **163** of the desired carbazole with *syn*- and *anti*-arrangement between the incoming nucleophile and the succinimide groups respectively (Scheme 4.9).

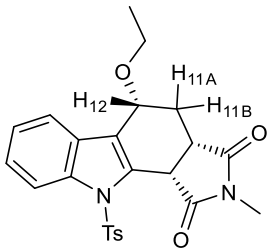


Scheme 4.9. Proposed S_N2 pathway for the substitution of Br with *O*-nucleophiles

4.4.3. Assignment of the relative stereochemistry of carbazole (158)

In order to determine whether the substitution step had occurred via an S_N1 or S_N2 mechanism, we needed to confirm the relative stereochemistry of the synthesised carbazoles **(156–159)**. Therefore, crystals of the major diastereomer of carbazole **158** were grown from a DCM solution by slow evaporation, and examined by X-ray crystallography. The X-ray analysis revealed that the ethoxy and succinimide groups were *syn* to each other (Figure 4.2), which is consistent with an S_N2 mechanism according to our mechanistic proposal (Scheme 4.9).





158

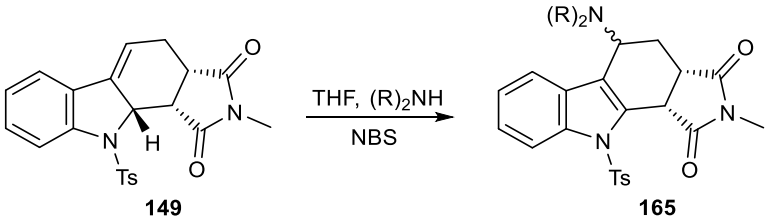
Figure 4.2. X-ray crystal structure of compound 158

The relative stereochemistry of carbazoles **156**, **157** and **159** was then determined through comparison of the ^{1}H NMR spectrum of the major diastereomers. The coupling constants between H_{12} and the two diastereotopic protons (H_{11A} and H_{11B}) were measured to be 3.2 and 2.3 Hz respectively. Similar coupling constants could be observed for carbazoles **156, 157** and 1**59**, suggesting that the major diastereomers formed by bromination and nucleophilic substitution were in a *syn*-orientation.

4.5. <u>Bromination/amination reaction of D-A cycloadduct (149)</u>

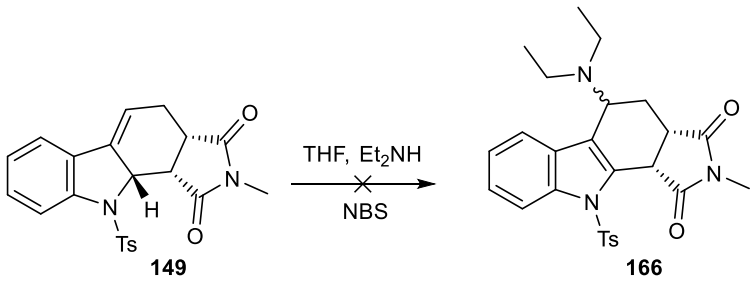
With an efficient method for the synthesis of ether substituted carbazoles in hand, we decided to examine the use of secondary amine reagents as an alternative nucleophile for the development of a novel one-pot

bromination/substitution reaction sequence, to form amino-substituted carbazole derivatives **165** (Scheme 4.10).



Scheme 4.10. Planned synthesis of amino-substituted carbazoles 165

Initially we thought that amino-substituted carbazole derivatives **165** could be synthesised using the previously discussed bromination/substitution method by simple replacement of the alcohol with a nucleophilic amine. Therefore, 2.0 equivalents of NBS were added to a solution of D-A cycloadduct **149** in a 1:1 mixture of THF/Et_2NH. However after 4 hours at 0 °C, only the starting material was observed by ^1H NMR of the crude reaction mixture (Table 4.2, entry 1). When we re-examined the bromination/amination reaction of D-A cycloadduct **149** at a higher temperature (r.t.), still with 2.0 equivalents of NBS in a 1:1 mixture of THF/Et_2NH, the ^1H NMR spectrum of the crude reaction mixture still showed no change in the starting material (Table 4.2 entry 2).



Entry	Solvent 1:1	Reaction conditions	Temperature/ °C	Result [a]
1	THF/Et_2NH	NBS, 4 h	0	Only SM observed
2	THF/Et_2NH	NBS, 4 h	r.t.	Only SM observed

[a] Result determined by ^1H NMR of the crude reaction mixture

Table 4.2. Initial examination of the one-pot bromination/amination reaction conditions of D-A cycloadduct 149

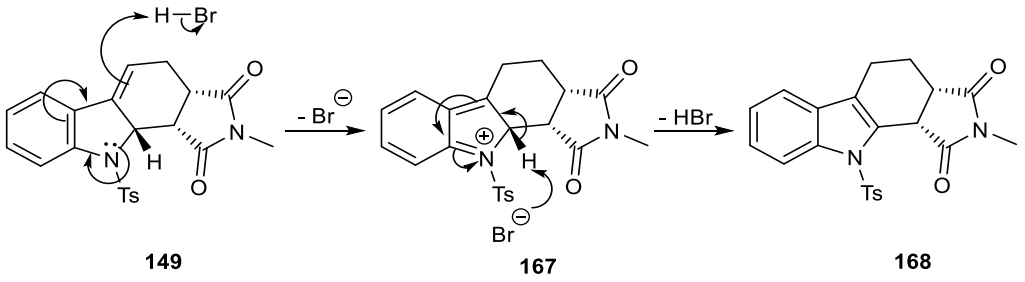
Since NBS can act as a source of Br_2 and thus a source of "Br^+", but only when catalysed by hydrogen bromide (HBr), we postulated that the presence of a base, such as diethylamine, may inhibit the desired bromination step and thus prevent the bromination/substitution reaction from occurring.

Therefore we repeated the reaction by adding 2.0 equivalents of NBS to D-A cycloadduct **149** in THF at 0 °C, without the presence of the amine. After 1 hour, diethylamine was added and the reaction mixture was stirred for a further 3 hours at 0 °C. ^{1}H NMR of the crude reaction mixture indicated a mixture of a new product and unreacted starting material in a 1:3 ratio respectively. Purification of the crude material by column chromatography afforded the corresponding substituted carbazole **166**, as a single diastereomer in 21% yield (Table 4.3, entry 1).

The formation of the desired carbazole **166** in a low yield, alongside the recovery of a significant quantity of starting material, suggested that the desired brominated intermediate was formed but the bromination had not gone to completion prior to the addition of diethylamine.

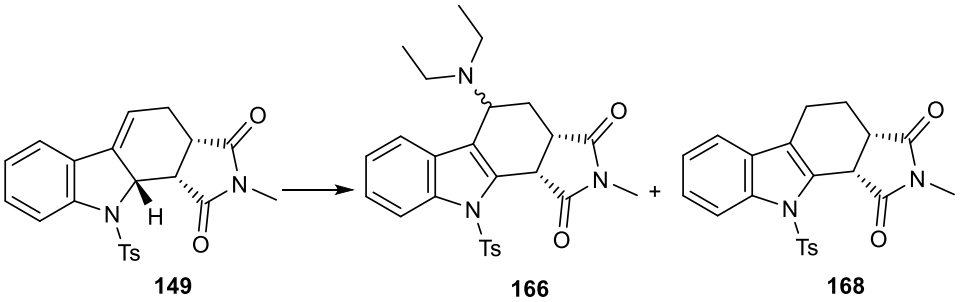
We therefore repeated the reaction, increasing the time for the bromination step from 1 hour to 3 hours. Unfortunately when the reaction was examined by ^{1}H NMR, it showed that D-A cycloadduct **149** had undergone a [1,3]-H shift under these reaction conditions to form the rearomatised product **168.** Purification by column chromatography led to the isolation of this unwanted rearomatised carbazole **168** in 72% yield (Table 4.3, entry 2).

We speculated that unwanted rearomatised product **168** could be generated in the reaction through an acid catalysed alkene rearrangement catalysed by the HBr formed in the bromination step (Scheme 4.11).



Scheme 4.11. Possible mechanism for the rearomatisation of D-A cycloadduct 149 to give 168 in the presence of HBr

Based on the above results, we decided to increase the number of equivalents of NBS whilst maintaining the reaction time for 1 hour in the bromination step, in an attempt to speed up the desired bromination in comparison to unwanted rearomatisation. A 32% yield of the desired product **166** was isolated after purification by column chromatography, giving only a marginal improvement.



Entry	Reaction conditions	NBS eq.	Isolated yield %	
			166	168
1	i. NBS, 1 h, 0 °C ii.Et_2NH, 3 h, 0 °C	2	21	0
2	i. NBS, 3 h, 0 °C ii.Et_2NH, 3 h, 0 °C	2	0	72
3	i. NBS, 1 h, 0 °C ii.Et_2NH, 3 h, 0 °C	3.5	32	0

Table 4.3. Results of initial condition screening for the bromination/amino-substitution reactions of D-A cycloadduct 149

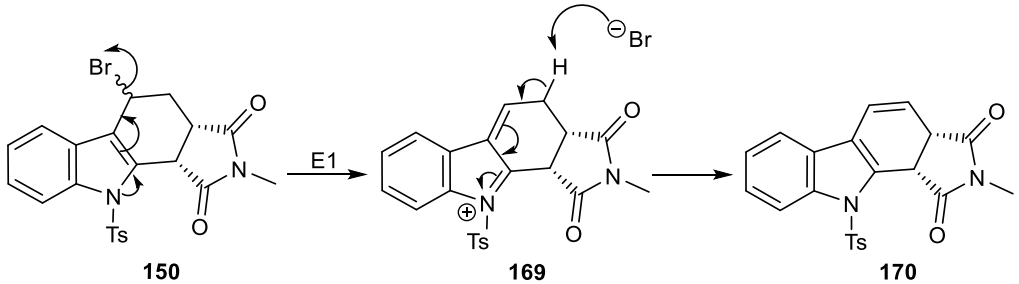
4.5.1. Optimisation of the bromination/amination reaction conditions

The limited conversion of D-A cycloadduct **149** to the desired amino-substituted carbazole **166** under the previously described conditions (Table 4.3), can be attributed to the low concentration of bromine in the reaction

(generated from NBS) and / or solubility of the starting material, as it was noticed that D-A cycloadduct **149** was only partially soluble in THF. Therefore we decided to look at the use of different solvents and brominating reagents in order to develop a convenient, practical and high yielding method for the bromination/amination reaction of D-A cycloadduct **149**, whilst avoiding the formation of unwanted rearomatised product **168**.

Optimisation of the bromination/substitution reaction of **149** to give diethylamine-substituted carbazole **166** was therefore examined using bromine (Br_2) as an electrophilic brominating agent instead of NBS, and DCM as the solvent in place of THF. The results are summarised in Table 4.4.

In our first attempt, the reaction mixture containing D-A cycloadduct **149** in DCM was stirred for 30 min, after the addition of 1.2 equivalents of Br_2. Diethylamine was then added at 0 °C and the mixture was stirred for a further 3 hours (Table 4.4, entry 1). Under these reaction conditions, three major products were isolated from the crude reaction mixture following column chromatography: the desired amino-substituted product **166** which was obtained in 15% yield, the rearomatised compound **168** in 20% yield and carbazole **170** in 12% yield. We postulated that carbazole **170** may have been generated from an elimination reaction (E1) of the brominated intermediate **150** (Scheme 4.12).



150 **169** **170**

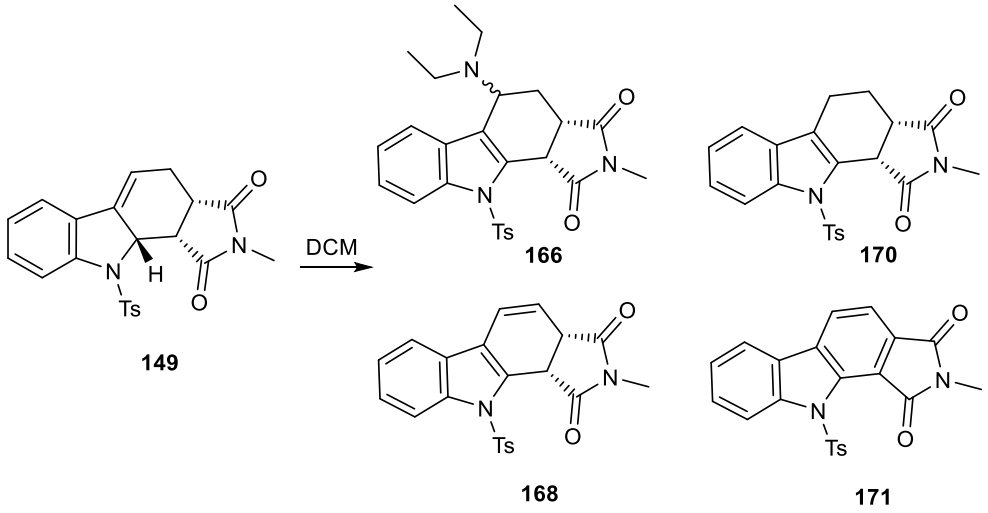
Scheme 4.12. Proposed reaction mechanism to form compound 170

We reasoned that reducing the reaction time for the bromination step might reduce the formation of these unwanted side-products. Therefore the next bromination of D-A cycloadduct **149** by 1.2 equivalents of Br_2 was performed

over 5 minutes. Diethylamine was then added and the mixture was stirred for a further 3 hours (Table 4.4, entry 2). Purification of the crude material by column chromatography gave the desired amino-substituted product **166** in 35% yield, the rearomatised compound **168** in 25% yield, and the starting material was recovered in 20% yield.

Since the rearomatised carbazole **168** is likely formed due to HBr being present during the reaction, we decided to add diethylamine at the beginning of the reaction to trap the HBr from the mixture as it is formed. Hence, diethylamine was added to the reaction first, followed by the addition of 1.2 equivalents of Br_2. After 5 min at 0 °C, the reaction was stirred for a further 3 hours. Under these reaction conditions, no rearomatised product was observed by ^{1}H NMR of the crude reaction mixture however the spectrum indicated a 1:1 mixture of unreacted D-A cycloadduct **149** and the desired amino-substituted carbazole **166**, which was subsequently isolated in 42% yield (Table 4.4, entry 3).

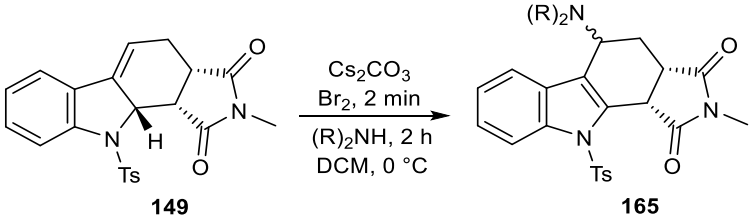
Further optimisation of the reaction conditions to form our desired diethylamine-substituted carbazole **166**, involved the use of a non-nucleophilic base to remove the HBr generated in the bromination step. When the reaction was carried out in the presence of 2.0 equivalents of potassium carbonate (K_2CO_3), in DCM and with 1.2 equivalents of bromine, followed after 2 minutes by the addition of diethylamine, an efficient bromination/amination reaction was achieved. No starting material was observed, however only 52% of desired amino-substituted product **166** was obtained along with an 11% yield of compound **170** and 8% yield of compound **171** (Table 4.4, entry 4). In contrast, an 80% yield of the desired amino-substituted carbazole **166** was obtained when the reaction was performed under the same conditions but in the presence of a more organic soluble non-nucleophilic base, cesium carbonate (Cs_2CO_3) (Table 4.4, entry 5).

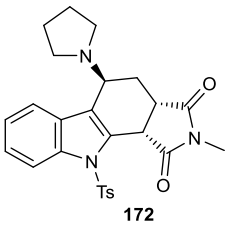
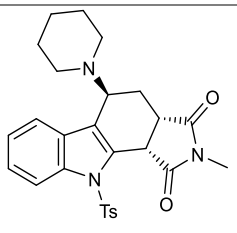
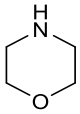
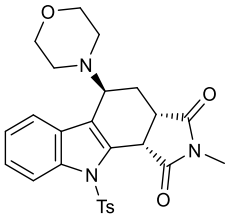


Entry	Reaction conditions	Isolated yield %				
		149	**166**	**168**	**170**	**171**
1	i. Br_2, 30 min, 0°C ii. Et_2NH, 3 h, 0°C	-	15	20	12	-
2	i. Br_2, 5 min, 0°C ii. Et_2NH, 3 h, 0°C	20	35	25	-	-
3	i. Et_2NH, 5 min, 0°C ii. Br_2, 3h, 0°C	35	42	-	-	-
4	i. K_2CO_3, Br_2, 2 min, 0°C ii. Et_2NH, 2 h, 0°C	-	52	-	11	8
5	i. Cs_2CO_3, Br_2, 2 min, 0°C ii. Et_2NH, 2h, 0°C	-	80	-	-	-

Table 4.4. Optimisation of the bromination/amination reactions of the D-A cycloadduct 149

To test the scope and limitations of our optimised reaction conditions, a variety of secondary amine derivatives including pyrrolidine, piperidine and morpholine were then examined as nucleophiles. Pleasingly, using our optimised bromination/amino-substitution conditions we were able to access a number of amino-substituted carbazoles **172**, **173** and **174** in good yields ranging from 77-92% (Table 4.5, entry 1-3).



Entry	$(R)_2NH$	Product	Yield [a] %
1		 **172**	92
2		 **173**	77
3		 **174**	83

[a] Isolated yield of the product

Table 4.5. Synthesis of amino-substituted carbazole derivatives (172-174)

4.5.2. Relative stereochemistry of carbazoles (166) and (172)

To deduce the relative stereochemistry of amino-substituted carbazoles **166** and **172**, crystals of both were grown from DCM, by slow evaporation at room temperature and examined using single crystal X-ray crystallography. The X-ray analysis revealed that the secondary amines had added to the opposite face of the molecule relative to the succinimide ring (Figure 4.3).

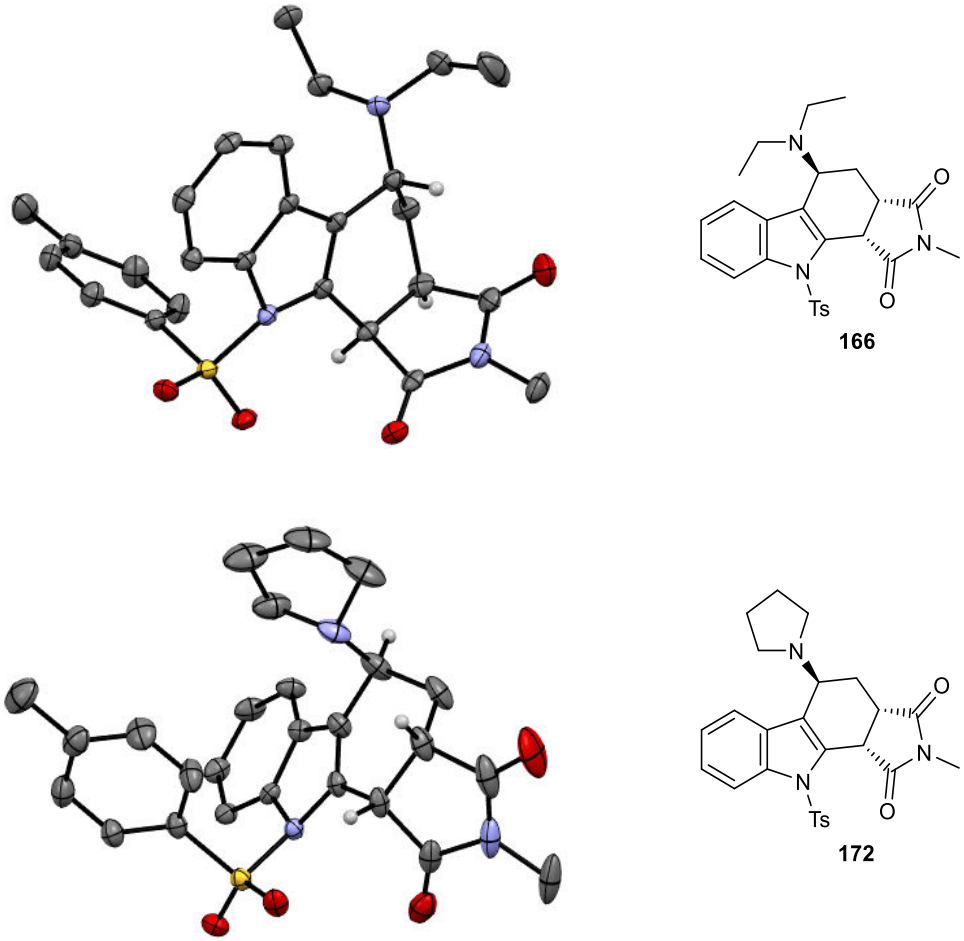
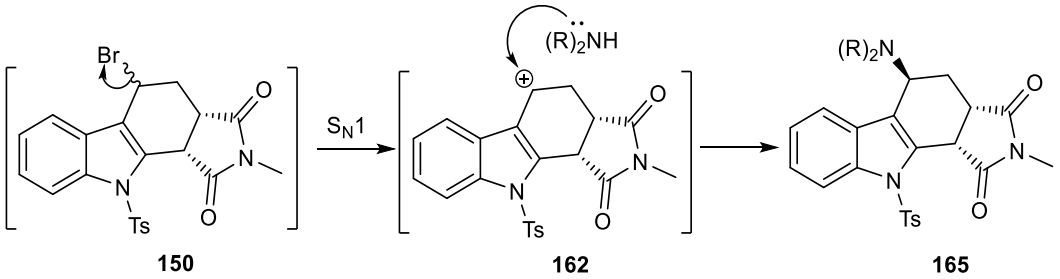


Figure 4.3. X- ray crystal structures of compounds 166 and 172

4.5.3. Proposed mechanism of bromination/amination reactions of D-A cycloadduct (149)

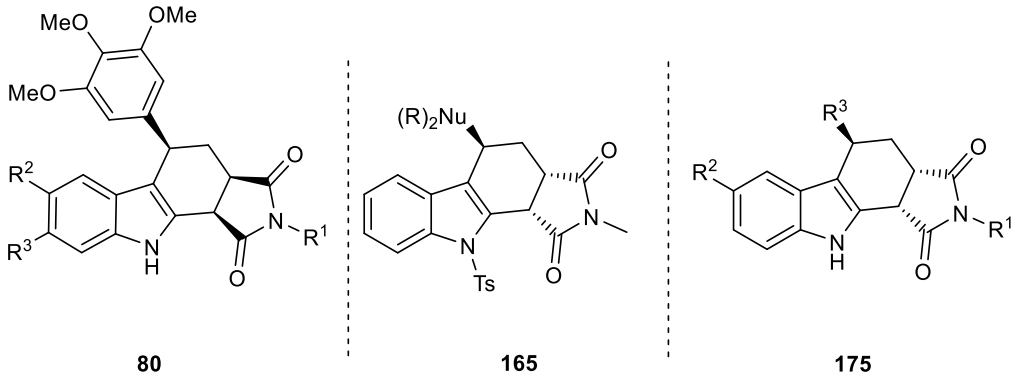
Considering the previously discussed mechanism for the bromination/substitution reactions involving alcohol nucleophiles (Scheme 4.8, page 70), we inferred that substitution of bromine by nitrogen might proceed through an S_N1 reaction mechanism. Although an S_N1 reaction might be expected to give a mixture of diastereomers as the nitrogen could attack from either face of the planar secondary carbocation intermediate **162**, in this case the addition of the secondary amine can occur selectively on the least hindered face of the carbocation, due to the steric influence of the succinimide group, leading to the observed single diastereomer of the corresponding substituted compounds **165** (Scheme 4.13).



150 162 165

Scheme 4.13. Postulated S_N1 mechanism in the synthesis of amino-substituted carbazole 165

With the successful development of a new diastereoselective approach for the construction of amino-substituted carbazoles, we then focused our attention on removal of the *N*-protecting group. Deprotection of this group is important if we wish to apply our bromination/substitution approach to the synthesis of bioactive carbazoles, such as **80** and **175** (Figure 4.4), as these systems typically have a free indolic nitrogen to engage in H-bonding to their targets.

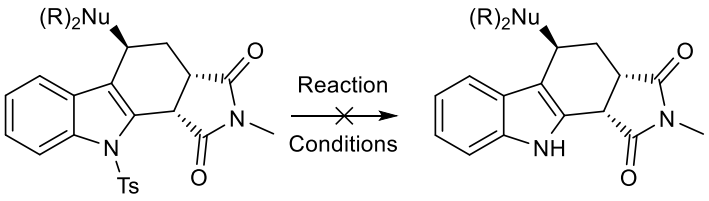


80 165 175

Figure 4.4. A comparison of the structure of the bioactive pyrrolocarbazole (80,175), and our synthesised compounds 165

4.6. Removal of the *N*-protecting group

Earlier work within our group had demonstrated the difficulties in removing the tosyl protecting group from an indolic nitrogen under basic conditions, including using sodium hydroxide, potassium hydroxide or potassium ethoxide. Single electron transfer reagents including sodium or magnesium mercury amalgam have also been investigated to no avail (Scheme 4.14).



152 **176**

Scheme 4.14. Removal of the tosyl protecting group (Reaction Conditions, see page (80)

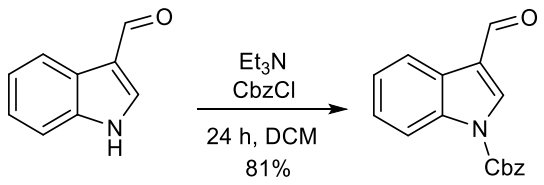
Therefore, we decided to use an alternative electron withdrawing *N*-protecting group that would be tolerated in both the D-A reactions and one-pot bromination/substitution reaction conditions and yet would readily undergo deprotection at the end of the synthesis.

4.7. Alternative electron withdrawing protecting group

4.7.1. Synthesis of benzyl 3-vinyl-1*H*-indole-1-carboxylate (179)

The previous chapters highlighted the importance of an electron withdrawing protecting group to control the rate of the D-A reaction. We therefore needed to use an electron withdrawing protecting group which would allow the formation of the precursor D-A cycloadduct under mild conditions and yet be easily cleaved in the final step of the synthesis. The carboxybenzyl group (Cbz) was chosen as an alternative protecting group to tosyl, as recent studies in our group have found that Adam's catalyst (PtO_2) can be used as a hydrogenation catalyst, to deprotect Cbz protected indolic nitrogen.[102]

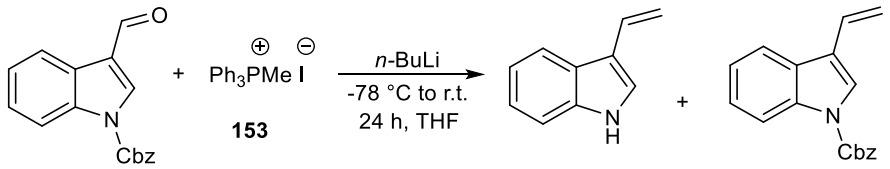
Our study began with the protection of indole-3- carbaldehyde **88** with benzyl chloroformate (CbzCl) in the presence of Et_3N following a literature procedure (Scheme 4.15).[103] The protection reaction was carried out at r.t. for 24 hours, to provide the expected benzyl 3-formyl-1*H*-indole-1-carboxylate **177** in a good yield of 81%.



88 **177**

Scheme 4.15. Cbz protection of 1*H*-indole-3-carbaldehyde 88

The subsequent step involved a Wittig reaction between the previously synthesised phosphonium salt **153**, deprotonated with *n*-butyllithium, and benzyl 3-formyl-1*H*-indole-1-carboxylate **177**, to give benzyl 3-vinyl-1*H*-indole-1-carboxylate **179** in 46% yield along with 32% yield of 3-vinyl-1*H*-indole **178** after purification by column chromatography (Scheme 4.16).



177 **178** 32% **179** 46%

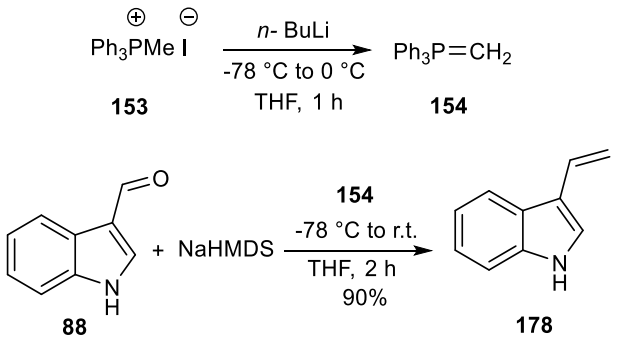
Scheme 4.16. Wittig reaction of benzyl 3-formyl-1*H*-indole-1-carboxylate 177

From these results, we speculated that compound **177** is decomposed under the Wittig reaction conditions to give deprotected 3-vinyl-1*H*-indole **178**. Due to the low yield in this step, we then turned our attention to examine an alternative route to the desired benzyl 3-vinyl-1*H*-indole-1-carboxylate **179**. We envisioned that by reversing the step order, benzyl 3-vinyl-1*H*-indole-1-carboxylate **179** could be synthesised from the Wittig reaction of indole-3-carbaldehyde **88** followed by a Cbz protection.

4.7.1.1. Alternative route to benzyl 3-vinyl-1*H*-indole-1-carboxylate (179)

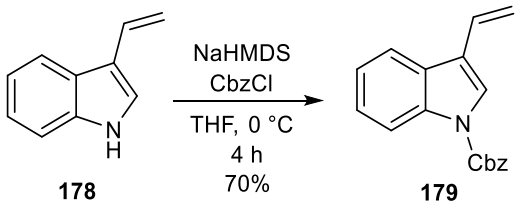
The research group of Ricci have previously investigated the Wittig reaction of indole-3- carbaldehyde **88** with phosphorus ylide **154** to form 3-vinyl-1*H*-indole **178**.[50] In this procedure, a strong non-nucleophilic base such as lithium bis(trimethylsilyl)amide (LiHMDS) was used to deprotonate the NH of indole-

3-carbaldehyde **88** before it was added to the reaction mixture, to prevent the deprotonation of the indolic NH by phosphorus ylide **154** from competing with the desired Wittig reaction. Therefore, indole-3-carbaldehyde **88** was deprotonated by NaHMDS, before addition to phosphorus ylide **154.** The corresponding 3-vinyl-1*H*-indole **178** was isolated in an excellent yield of 90% after purification by column chromatography (Scheme 4.17).



Scheme 4.17. Deprotonation/Wittig reaction of 3-formyl-1*H*-indole 88

The next step was to protect the indolic nitrogen of 3-vinyl-1*H*-indole **178** with a Cbz group. Deprotonation of the NH with NaHMDS in THF followed by addition of CbzCl gave the desired benzyl 3-vinyl-1*H*-indole-1-carboxylate **179** in 70% yield (Scheme 4.18).



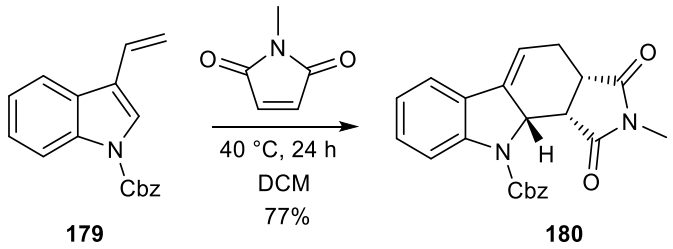
Scheme 4.18. Protection of 3-vinyl-1*H*-indole 178 with CbzCl

It is worth mentioning that a strong base, such as NaHMDS was needed to deprotonate the NH of 3-vinyl-1*H*-indole **178**, whilst only a weak base such as Et_3N was needed to deprotonate the NH in indole-3-carbaldehyde **88**. This is due to the conjugated nature of indole-3-carbaldehyde **88**, with electron withdrawing aldehyde group stabilising the formation of the anion and thus making the NH more acidic. In the absence of aldehyde, such as in compound

178, the resulting anion is not stabilised, therefore the NH is comparatively less acidic which results in the need for a strong base.

4.8. Synthesis of Cbz protected Diels-Alder cycloadduct (180)

With a reliable pathway for the synthesis and purification of benzyl 3-vinyl-1*H*-indole-1-carboxylate **179** in hand, the next step was to test the planned D-A reaction between benzyl 3-vinyl-1*H*-indole-1-carboxylate **179** as the diene, and NMM, as the dienophile. The D-A reaction of indole **179** with NMM was performed in refluxing DCM for 24 h. Gratifyingly, the corresponding D-A cycloadduct **180** was isolated in 77% yield as a single diastereomer (Scheme 4.19).



Scheme 4.19. Synthesis of Cbz protected D-A cycloadduct 180

The Cbz group showed moderate rate-enhancement of the D-A cycloaddition in comparison to the tosyl group. Whilst the D-A reaction of 1-tosyl-3-vinyl-1*H*-indole **148** with NMM took 48 h to form the corresponding D-A cycloadduct **149**, reaction of the more electron rich diene benzyl 3-vinyl-1*H*-indole-1-carboxylate **179** with NMM took only 20 h. Both reactions were performed in refluxing DCM.

The ^{1}H and ^{13}C NMR analysis of D-A cycloadduct **180,** recorded at ambient temperature, showed two sets of peaks, which revealed the presence of two rotamers, resulting from a high rotational energy barrier around the amide bond (Figure 4.5). To confirm this hypothesis, D-A cycloadduct **180** was examined by variable temperature ^{1}H NMR using DMSO-d_6 as a solvent. At 100 °C, the two sets of signals coalesced to a single set of signals (Figure 4.6).

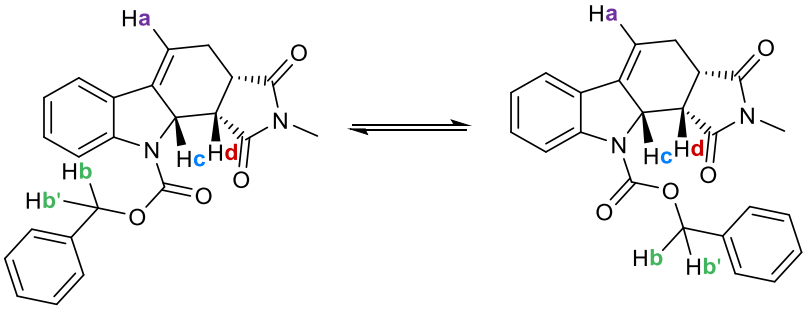


Figure 4.5. The two possible rotamers of the D-A cycloadduct 180

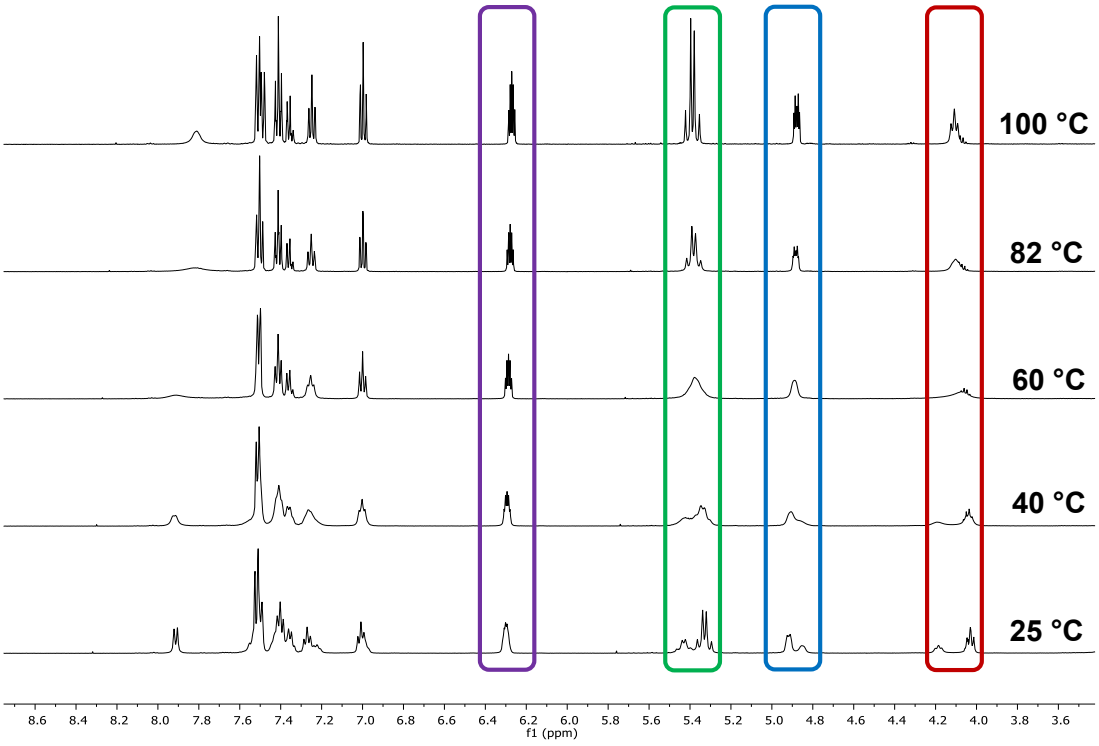
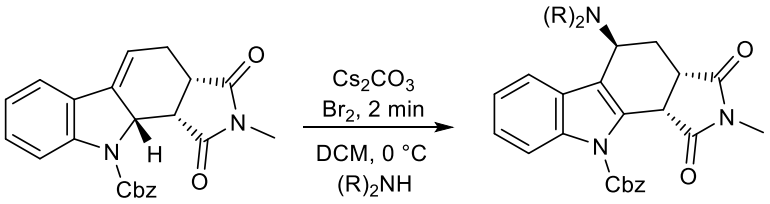


Figure 4.6. (VT) ^{1}H NMR experiment of D-A cycloadduct 180

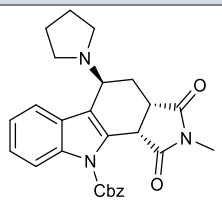
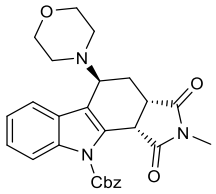
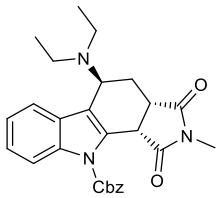
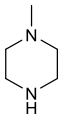
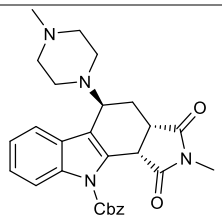
4.9. Bromination/amino-substitution reaction of D-A cycloadduct (180)

In the next step, D-A cycloadduct **180** was subjected to our previously modified bromination/amination reaction conditions with a variety of secondary amines. This allowed us to assess the influence of the Cbz protected D-A cycloadduct **180** on our bromination/substitution reactions for the synthesis of amino-substituted-carbazoles. The bromination/substitution reactions of D-A cycloadduct **180** with pyrrolidine, morpholine, diethylamine and 1-methylpiperazine, proceeded smoothly at 0 °C in DCM following our previously

optimised conditions (Br_2, Cs_2CO_3 then amine), to give the corresponding amino-substituted carbazoles (**182-185)** in yields ranging from 68-75% (Table 4.6, entry 1-4).



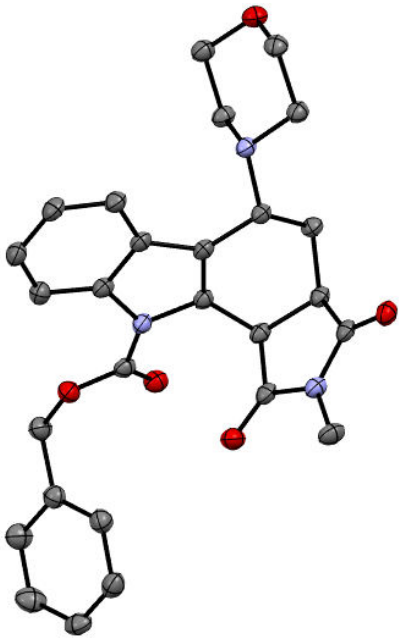
180 **181**

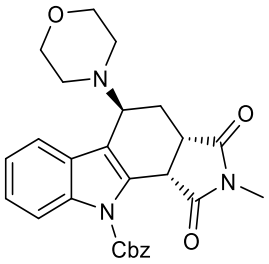
Entry	$(R)_2NH$	Time/ h	Product	Yield [a] %
1		1	 **182**	71
2		2	 **183**	69
3		2	 **184**	68
4		2.5	 **185**	75

[a] Isolated yield of the product

Table 4.6. Results of the bromination/amination reactions of D-A cycloadduct 180

The relative stereochemistry of carbazole **183** was confirmed by X-ray diffraction analysis. Crystals of **183** were grown from a DCM by slow evaporation. The crystal structure showed that the morpholine had added to the carbazole ring on the opposite face to that of the succinimide group (Figure 4.7). The relative stereochemistry of **182, 184** and **185** was confirmed though comparison of the ^{1}H NMR spectral data for each compound with those observed for carbazole **183.**





183

Figure 4.7. X-ray crystal structure of carbazole 183

4.10. The functional groups important for bioactivity

The good results obtained from the preparation of Cbz protected amino-substituted carbazoles (Table 4.6, entry 1-4) encouraged us to extend this methodology to generate a library of potentially bioactive compounds, since our target compounds shared a number of common structural features with several known biologically active molecules such as **80** and **175** (Figure 4.4).

Ty and co-workers have been reported the structure activity relationship (SAR) of the tetrahydrocarbazole series **80**, [71] based on their cytotoxicity against B16 melanoma cells and the inhibition of tubulin polymerization (ITP), (Figure 4.8).

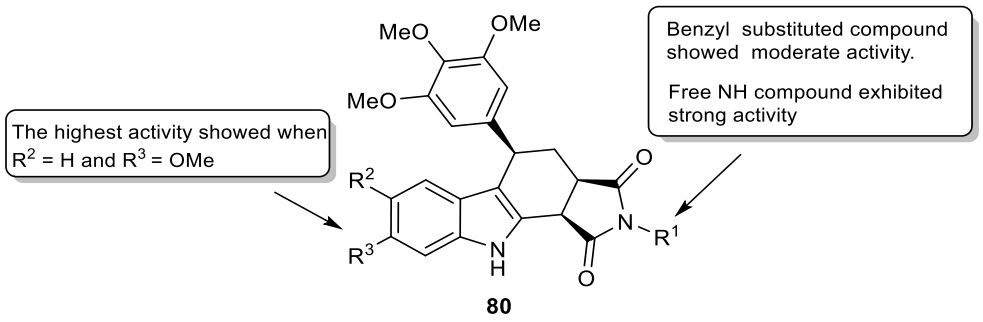


Figure 4.8. SAR of tetrahydrocarbazole series 80 against B16 melanoma cells

The biological activity of tetrahydrocarbazole derivatives **175** has recently been studied within our research group (Figure 4.9). The influence of a variety of functional groups at the R^1, R^2 and R^3 positions of the library of test compounds were determined against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*), Figure 4.9.

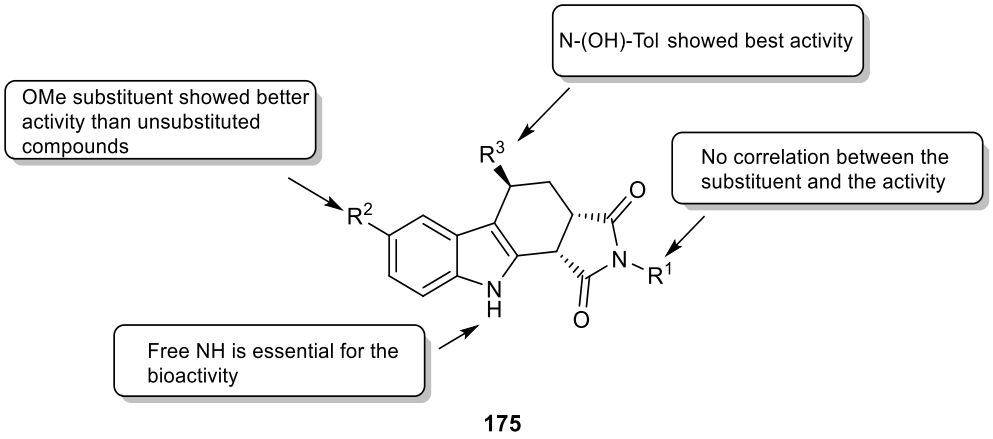
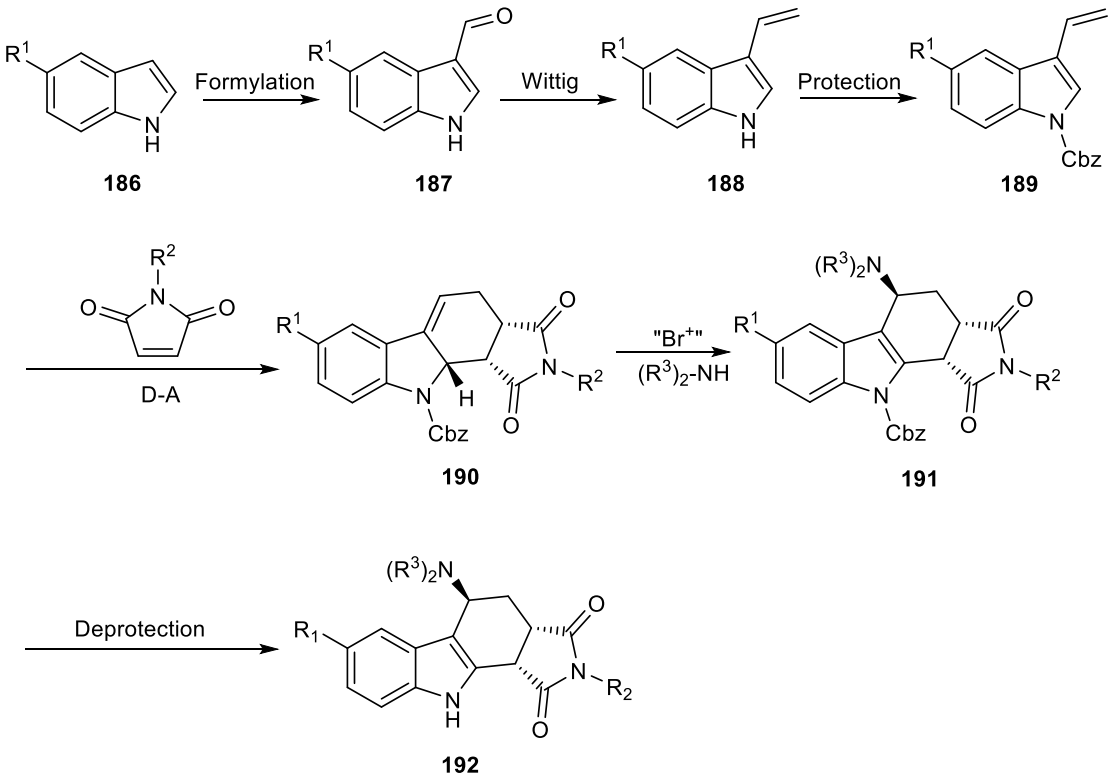


Figure 4.9. SAR of tetrahydrocarbazole series 175

4.11. Synthetic plan to pyrrolo[3,4-*a*]carbazoles for biological assay

Based on the biological activity of known tetrahydrocarbazoles **80** and **175**, we decided to synthesise a series of substituted carbazoles bearing electron withdrawing (EWG) or donating (EDG) groups at the R^1 position of the indole ring. We would then be able to generate a library of substituted carbazoles and evaluate their biological activities, after Cbz deprotection.

Following our successful bromination/substitution method, we planned to synthesise amino-substituted carbazoles **192** by a formylation reaction of the commercially available 5-substituted-1*H*-indoles **186**, followed by a Wittig/protection reaction sequence to provide dienes **188**. The D-A cycloaddition of **188** with a range of dienophiles would give cycloadducts **190,** which could then be functionalised further with different secondary amines. The Final step towards **192** involves removing the Cbz protecting group of compounds **191** (Scheme 4.20).

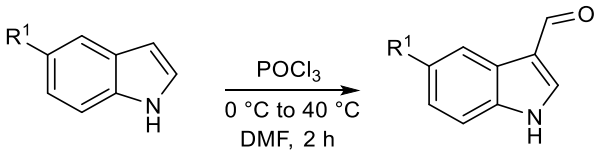


Scheme 4.20. Synthesis of amino-substituted carbazoles192 for biological assay

4.11.1. Formylation reaction of 5-substituted-1*H*-indoles (193) and (194)

We started our investigation with a formylation reaction of commercially available 5-fluoro-1*H*-indole **193** and 5-(benzyloxy)-1*H*-indole **194**, using Vilsmeier-Haack formylation conditions following a literature procedure.[104,105] In the presence of dimethylformamide (DMF) and phosphorus oxychloride ($POCl_3$), compounds **193** and **194** were regioselectively formylated at the 3-

position to give the corresponding indoles **195** and **196** in excellent yields of 97% and 83% respectively (Table 4.7, entry 1-2). Due to the high purity of the products, assessed by ^{1}H NMR of the crude reaction mixtures, both compounds were used in the next step without any further purification being necessary.



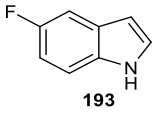
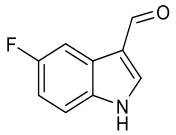
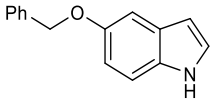
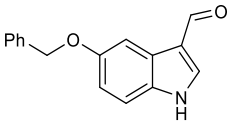
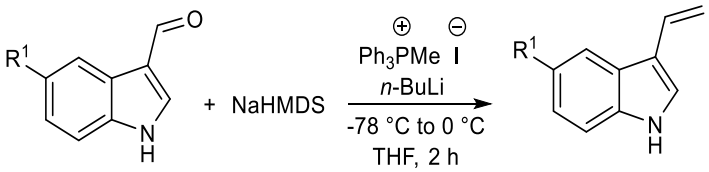
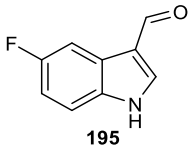
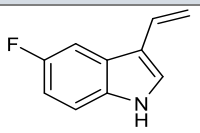
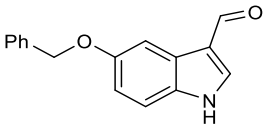
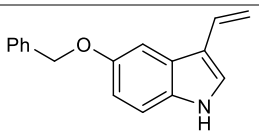
Entry	SM	Product	Yield %
1	 **193**	 **195**	97
2	 **194**	 **196**	83

Table 4.7. Results of Vilsmeier-Haack reaction to form 195 and 196

Once we had synthesised gram quantities of indoles **195** and **196**, the subsequent step was to synthesise the corresponding 3-vinyl-1*H*-indole compounds **197** and **198** through a Wittig reaction.

Following our previously optimised conditions, the NH of indoles **195** and **196** were first deprotonated with NaHMDS followed by reaction with the phosphonium ylide, formed from Wittig salt **153** and *n*-butyllithium. The expected 5-fluoro-3-vinyl-1*H*-indole **197** and 5-phenethoxy-3-vinyl-1*H*-indole **198** were obtained in very good isolated yields of 87% and 78%, respectively (Table 4.8, entry 1-2).



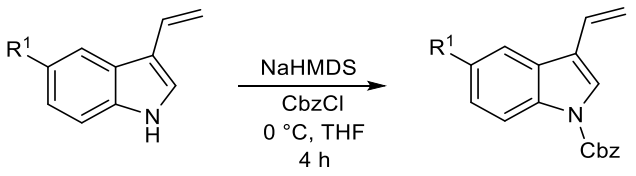
Entry	SM	product	Yield [a] %
1	 195	 197	87
2	 196	 198	78

[a] Isolated yield of the product

Table 4.8. Wittig reaction of indoles 197 and 198

4.11.2. Synthesis of dienes (199) and (200)

The indolic nitrogens of **197** and **198** were then protected with a Cbz group using CbzCl at 0 °C, in the presence of NaHMDS. After 4 hours, the corresponding Cbz protected compounds **199** and **200** were obtained in good isolated yields after purification by column chromatography (Scheme 4.20).



197, R^1= F
198, R^1= $PhCH_2O$-

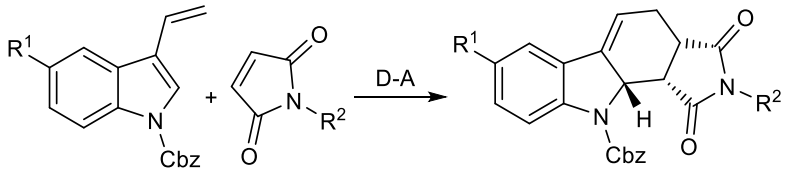
199, R^1= F 91%
200, R^1= $PhCH_2O$- 80%

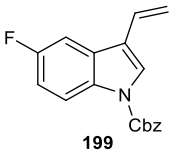
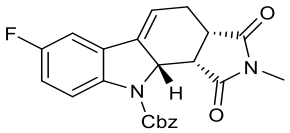
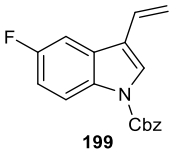
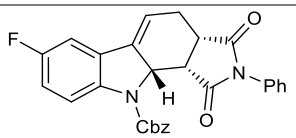
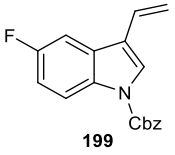
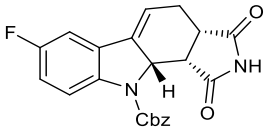
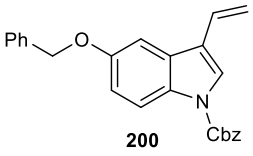
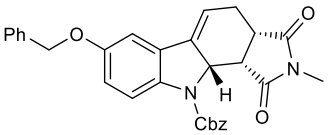
Scheme 4.20. Cbz protection reaction of 197 and 198

4.11.3. Diels-Alder reaction of dienes (199) and (200)

With dienes **199** and **200** in hand, the D-A reaction was then attempted with a range of maleimide compounds. The D-A reaction of 5-fluoro-3-vinyl-1*H*-indole **199** with NMM, NPM or maleimide, was performed in DCM at 40 °C for 24 hours. The corresponding D-A cycloadducts (**201-203)** were isolated as single

diastereomers in good yields (Table 4.7, entry 1-3). The more electron rich diene 5-phenethoxy-3-vinyl-1*H*-indole **200**, reacted more rapidly with NMM in the D-A reaction, requiring only 18 hours in refluxing DCM to give a single diastereomer of the corresponding D-A cycloadduct **204**, in 76% isolated yield (Table 4.7, entry 4).



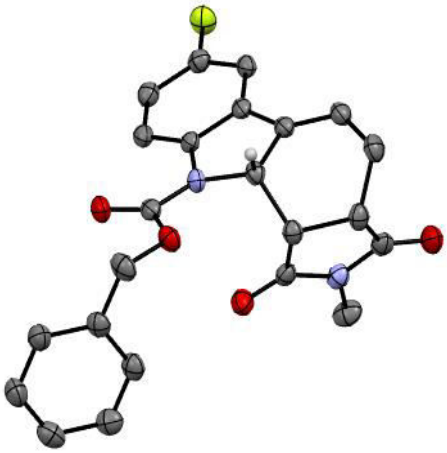
Entry	SM	Reaction conditions	D-A cycloadduct [a]	Yield[b] %
1	 **199**	NMM, 40 °C, 24 h, DCM	 **201**	69
2	 **199**	NHM, 40 °C, 24 h, DCM	 **202**	70
3	 **199**	NPM, 40 °C, 24 h, DCM	 **203**	72
4	 **200**	NMM, 40 °C, 18 h, DCM	 **204**	76

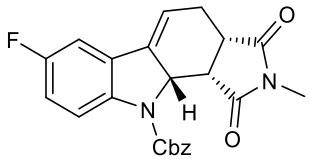
[a] Two rotamers of D-A cycloadduct were obtained. [b] Isolated yield of D-A cycloadduct

Table 4.7. Results of the D-A reaction of 199 and 200 with NMM, NPM or NHM

The relative stereochemistry of the D-A cycloadduct **201** was confirmed by X-ray diffraction analysis. Crystals of D-A cycloadduct **201** were grown from petrol/ethyl acetate by slow evaporation. The crystal structure showed that the

relative stereochemistry of D-A cycloadduct **201** was consistent with an *endo* selective D-A reaction between diene **199** and NMM (Figure 4.9).





201

Figure 4.9. X-ray crystal structure of D-A cycloadduct 201

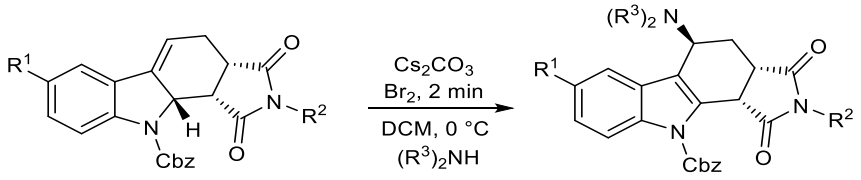
4.11.4. Bromination/ substitution reactions of D-A cycloadducts (201 - 204)

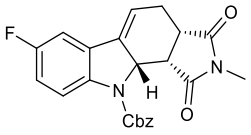
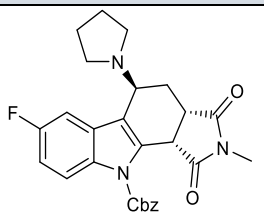
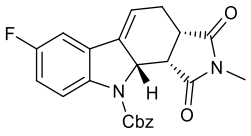
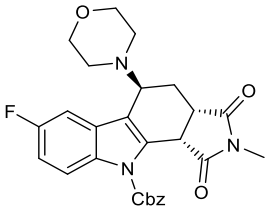
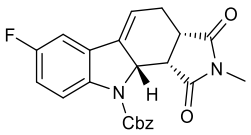
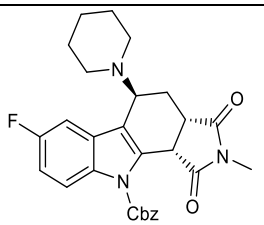
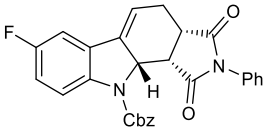
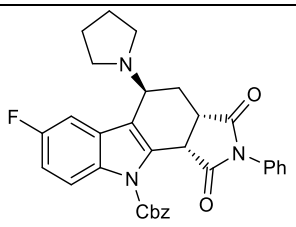
In the next step our previously synthesised substituted D-A cycloadducts **(201-204)**, were functionalised with a range of secondary amines in DCM. The outcome of these reactions are summarised in Table 4.8.

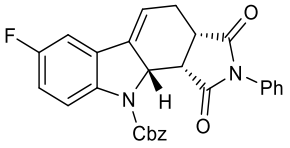
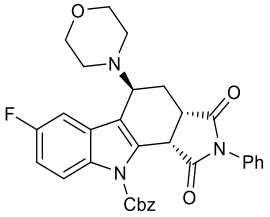
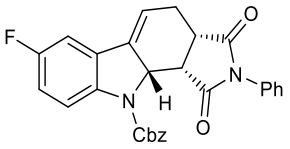
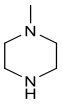
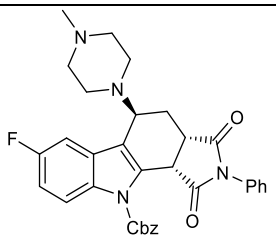
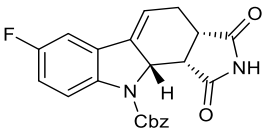
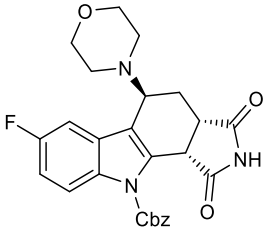
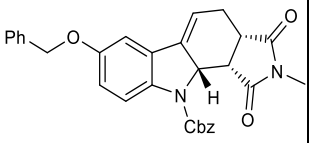
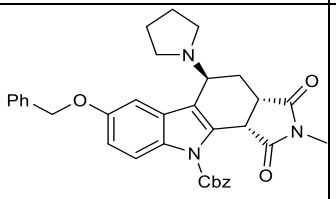
The one-pot bromination/substitution reactions of D-A cycloadducts **201** and **202** with pyrrolidine, morpholine, piperidine and 1-methylpiperazine were examined. The corresponding amino-substituted carbazoles (**205 - 210)** were isolated in good yields ranging from 67-81% (Table 4.8, entry 1-6).

A reaction between D-A cycloadduct **203** and morpholine was also investigated. This reaction was performed at 0 °C for 5 hours in DCM. Analysis of the resulting ^{1}H NMR of the crude reaction mixture indicated a 3:1 mixture of the desired substituted product **211** and unreacted starting materials (Table 4.8, entry 7). All of the attempts to purify the desired compound by column chromatography failed due to the close similarity in the R_f values to that of the starting material.

In addition, the one pot bromination/amination reaction of D-A cycloadduct **204** with pyrrolidine led to the isolation of the corresponding substituted-carbazole **212** in a 70% isolated yield (Table 4.8, entry 8).



Entry	SM	$(R^3)_2NH$	Time h	Product	Yield %[a]
1	 **201**		1	 **205**	76
2	 **201**		2	 **206**	81
3	 **201**		2	 **207**	67
4	 **202**		1	 **208**	75

5	 **202**		2	 **209**	76
6	 **202**		2	 **210**	81
7	 **203**		5	 **211**	N/A[b]
8	 **204**		1 .5	 **212**	70

[a] Isolated yield of the product. [b] A 3:1 mixture of the desired compound and the SM was observed but separation was not possible by chromatography

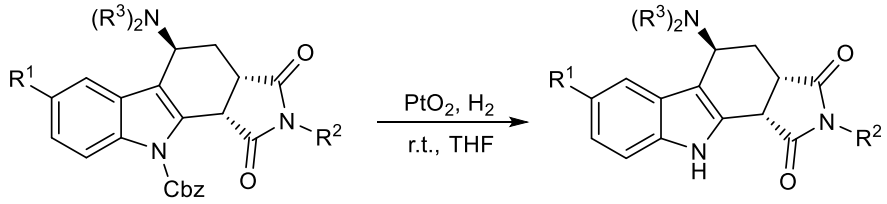
Table 4.8. Synthesis of amino-substituted carbazole derivatives (205-212)

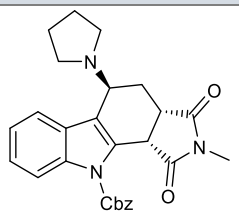
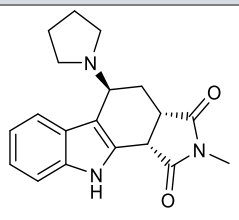
4.11.5. Removal of the Cbz protecting group

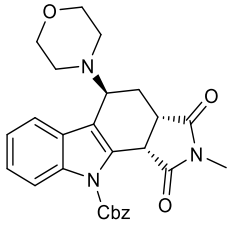
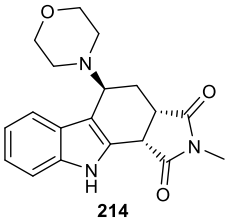
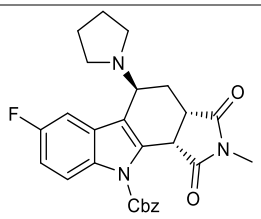
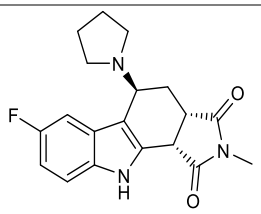
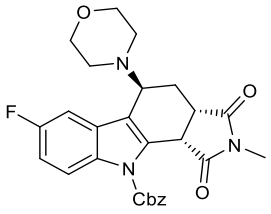
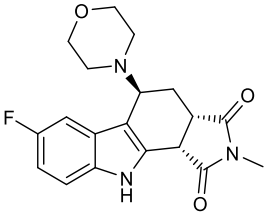
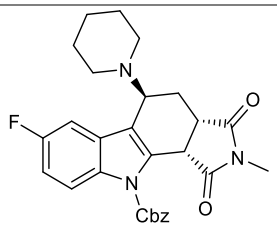
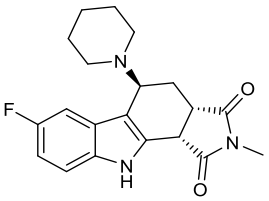
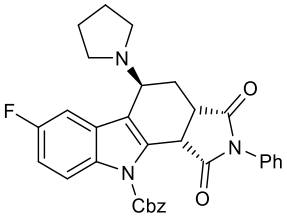
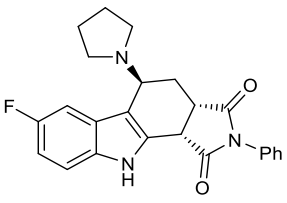
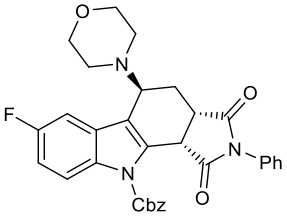
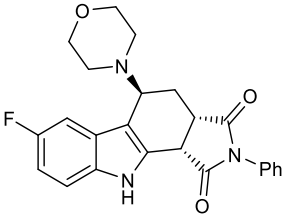
With a range the Cbz substituted carbazoles in hand, the next step in our synthetic plan was to remove the Cbz protecting group in order to explore the biological activity of the generated molecules.

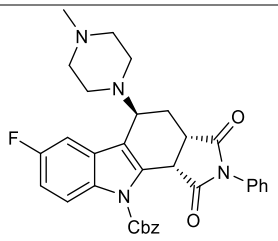
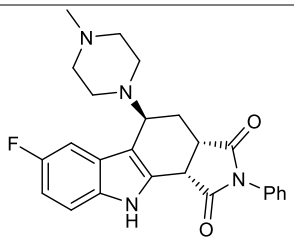
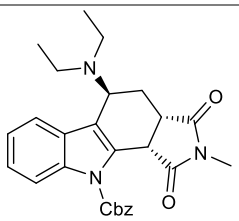
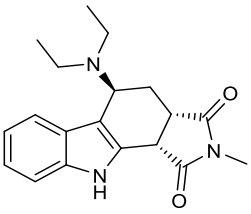
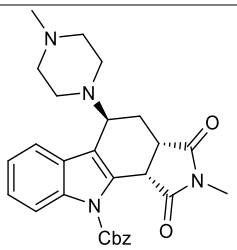
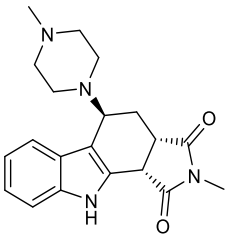
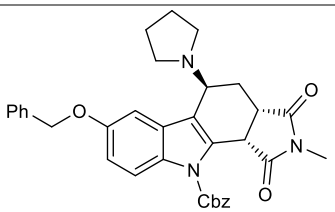
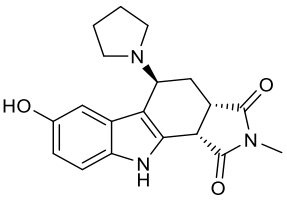
Deprotection of the Cbz group was examined using Adam's catalyst (platinum dioxide, PtO_2) in THF at r.t. under an atmosphere of hydrogen. The reaction mixture was filtered through the celite to remove the catalyst and purified by

column chromatography to give the desired compounds **(213– 220)** as single diastereomers in high yields ranging from 67-90% (Table 4.9, entry 1-8). The Cbz deprotection reaction of **184** was also examined. ^{1}H NMR of the crude reaction mixture showed a peak at 8.80 ppm corresponds to the NH of the desired product **221**. However, all attempts to isolate the desired product **221** by column chromatography were unsuccessful might due to decomposition of **184** on the acidic silica gel during chromatography. Similarly, when the Cbz removal from carbazole **185** was attempted, the ^{1}H NMR spectrum of the crude reaction mixture revealed the formation of the desired compound **222** along with unreacted starting material in a (3:1) ratio. However, all attempts to isolate the desired carbazole **222** by column chromatography failed, due to the close similarity in the R_f values to that of the starting material. Finally, the double deprotection of the Cbz and benzyl groups of carbazole **212** was investigated. ^{1}H NMR spectrum of the crude reaction mixture indicated a mixture of unidentified compounds. We expected that the desired compound **223** might be formed in the reaction, but the electron donating properties of the hydroxyl group resulted in an unstable carbazole which decomposed during purification attempts.



Entry	SM	Time/ h	Product	Yield [a] %
1	 **182**	6	 **213**	75

2	 **183**	7	 **214**	80
3	 **205**	6	 **215**	90
4	 **206**	8	 **216**	81
5	 **207**	5	 **217**	67
6	 **208**	7	 **218**	78
7	 **209**	6	 **219**	75

8	 **210**	5	 **220**	80
9	 **184**	6	 **221**	N/A[b]
10	 **185**	5	 **222**	N/A[b]
11	 **212**	7	 **223**	N/A[b]

[a] Isolated yield of the product. [b] The product was unobtainable

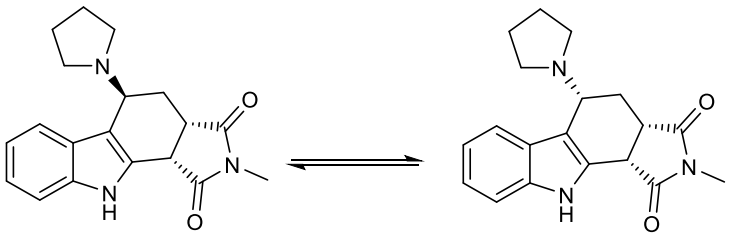
Table 4.9. Removal of the Cbz protecting group

The *anti*- arrangement between the amine and succinimide groups of the synthesised deprotected substituted carbazoles (Table 4.9, entry 1-8) was determined using coupling constant analysis in a comparison with those of Cbz-protected amino-substituted carbazole **183**, which have in turn been corroborated previously by single crystal X-ray crystallography (Figure 4.7).

4.12. Epimerisation of diastereomer (213) to (225)

Although the catalytic hydrogenation reaction of our synthesised substituted carbazoles over PtO_2 produced single diastereomers of the corresponding

deprotected compounds (Table 4.9, entry 1-8), the ^{1}H NMR spectrum of the purified product **213** showed two similar sets of signals after 24 hours in solution. Further analysis by ^{13}C, COSY, and HMQC spectroscopy indicated that this mixture appeared to be two diastereomers of carbazole **213** in a 5:1 ratio. We thus proposed that the initial isolated diastereomer **213** is not stable in solution and can epimerise to give the more thermodynamically stable diastereomer **225** (Scheme 4.21).



Scheme 4.21. Epimerisation reaction of 213 to give 225

4.12.1. Investigation of the epimerisation reaction of (213) to (225)

In order to understand the mechanism of the previously proposed epimerisation process, a solution of 5.0 milligrams of the isolated diastereomer **213** in 3.0 mL of deuterated DCM was transferred into an the NMR tube. The change in the ratio between epimers **213** and **225** was recorded over time using ^{1}H NMR spectroscopy while the solvent, sample concentration and temperature (r.t.) kept constant in each experiment. The signal intensities of selected peaks, including the broad NH, and H_a of each individual diastereomers were employed to determine the epimeric ratio of **213** to **225** in the solution (Figure 4.10). After 672 hours, the ratio of **213** to **225** was 1:3 and this ratio did not change, suggesting that equilibrium had been reached.

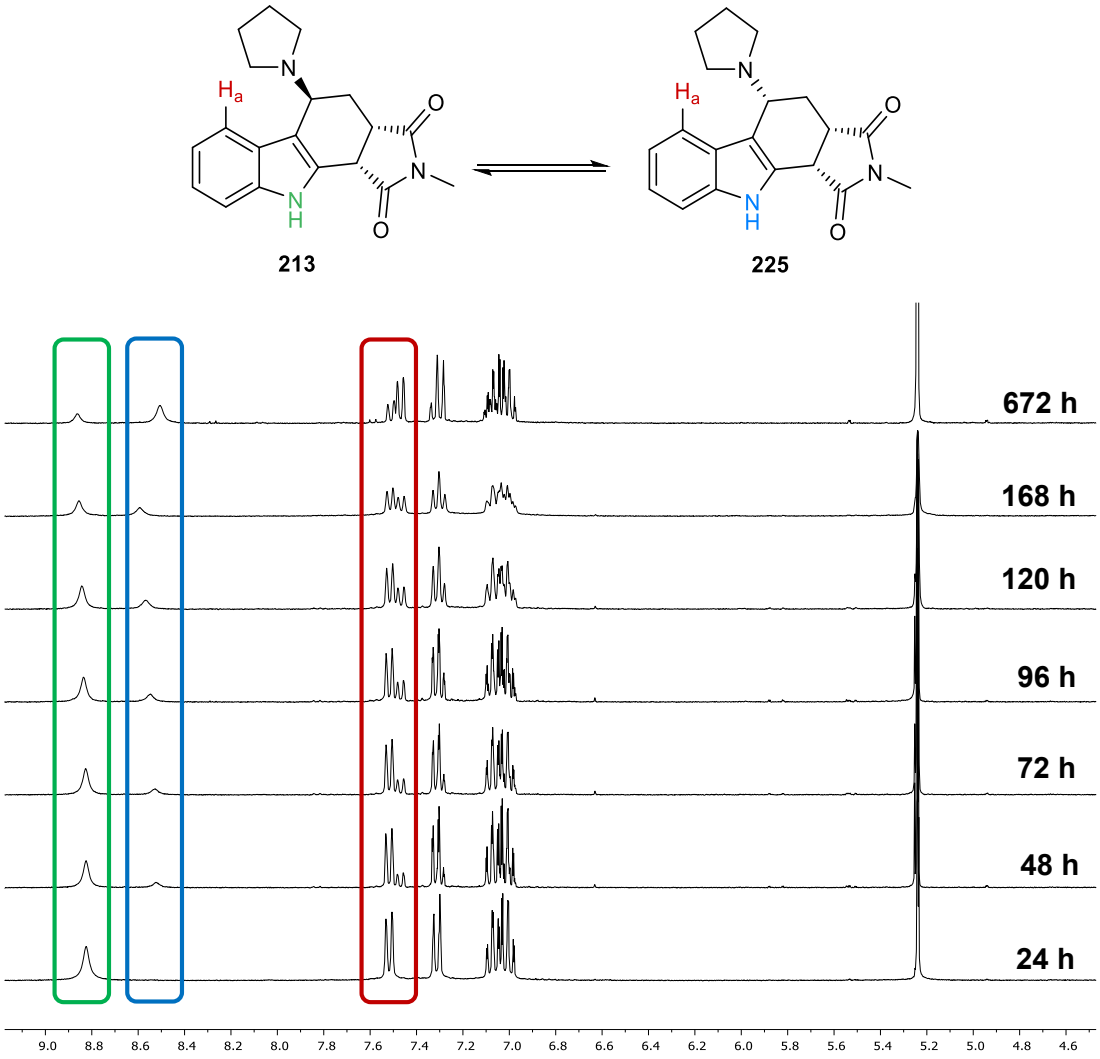


Figure 4.10. Epimerisation of isolated diastereomer 213 to 225 in DCM

This result showed that epimerisation of **213** was slow under the used conditions; therefore we decided to examine the influence of the acid on the rate of the epimerisation process. The proposed interconversion of **213** to **225** by change of the pyrrolidine configuration could proceed by either an S_N1 or S_N2 mechanism. We hypothesised that addition of catalytic amount of acid would speed up the rate of epimerisation, by protonation of the pyrrolidine and thus accelerating the rate of the formation of the carbocation intermediate in the case of an S_N1 pathway. To examine this hypothesis, 0.05 mol% of trifluoroacetic acid (TFA) was added to a solution of **213** in 3.0 mL of deuterated DCM. However, ^{1}H NMR spectrum did not show the expected epimerisation process, indicating TFA may not be the optimal catalyst in this reaction and may favour the production of other products.

Next, we decided to monitor the epimeric ratio of **213** to **225** at higher temperature as an attempt to promote the rate of the epimerisation. Therefore the ratio of **213** to **225** was recorded over time by ^{1}H NMR over 3 days in deuterated DMSO at 60 °C. Selected spectra are given in Figure 4.11.

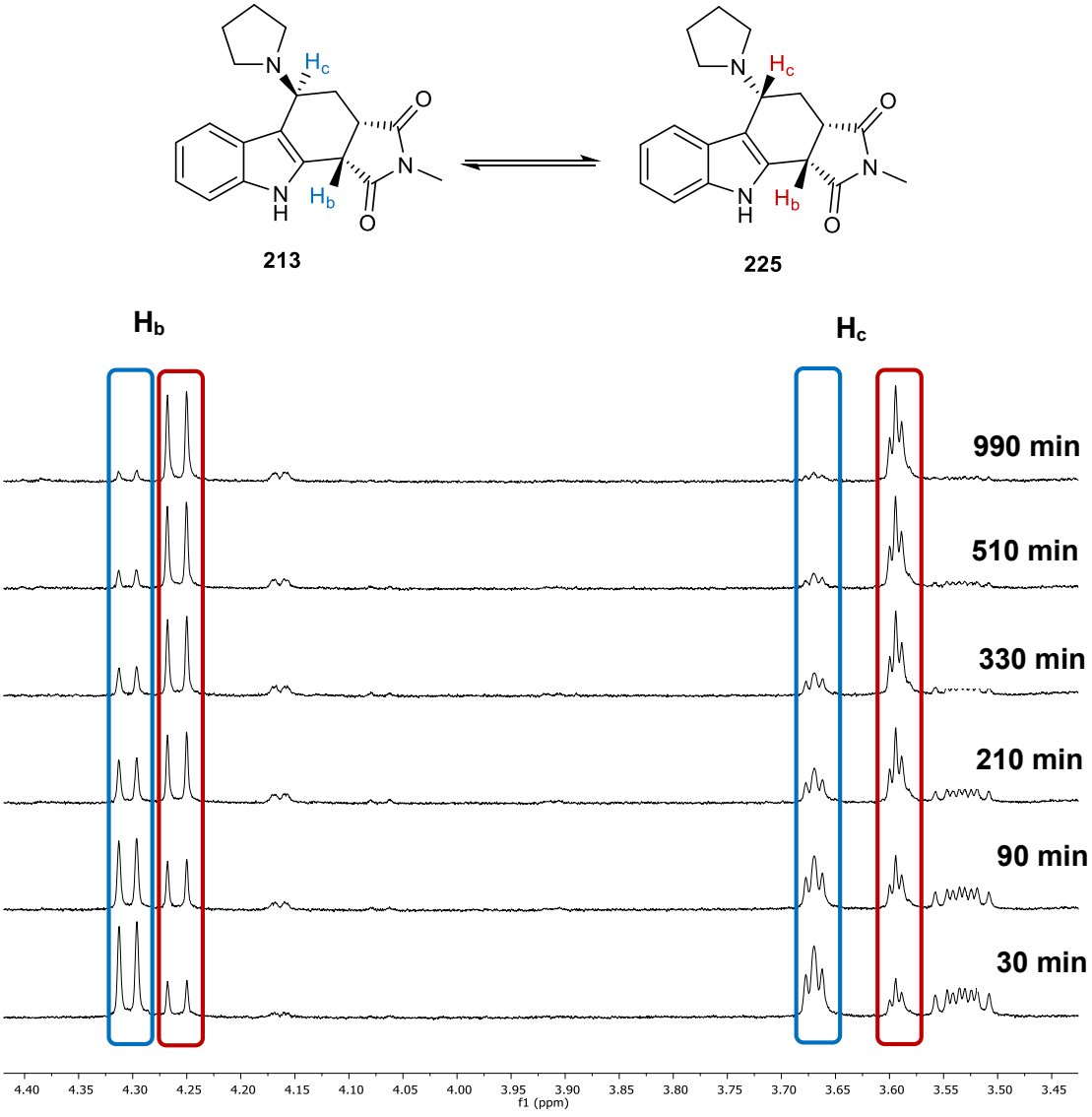


Figure 4.11. Epimerisation of isolated diastereomer 213 to 225 in DMSO

The recorded ratios of the epimers **213** and **225** were then plotted against the time (Figure 4.12), data from this study showed that diastereomer **213** undergoes epimerisation rapidly to give **225** in a solution of DMSO at 60 °C, and the system reached equilibrium after approximately 990 min, based on the integration of the ^{1}H NMR spectrum.

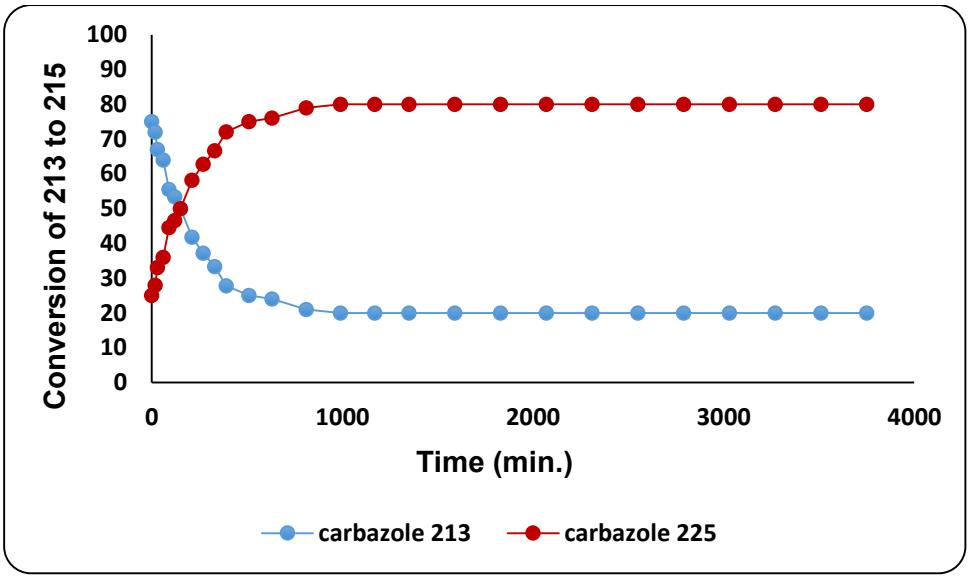
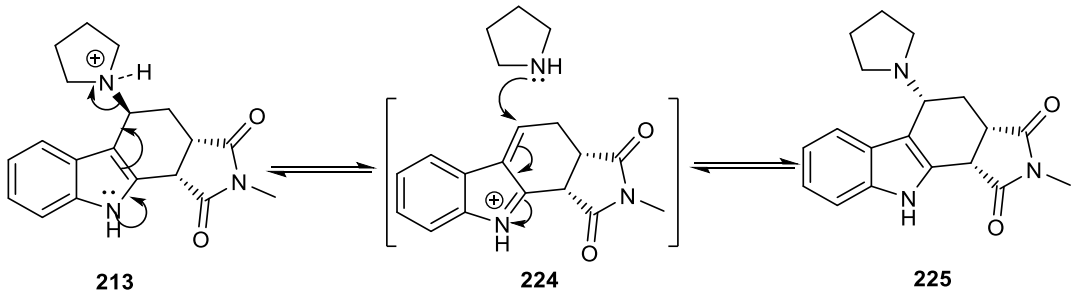


Figure 4.12. Ratio of 213 to 225 in DMSO over time

4.12.2. Proposed mechanism for the epimerisation of diastereomer (213) to (225)

We therefore propose that the observed epimerisation of **213** to **225** starts with elimination of the pyrrolidine followed by re-addition of the eliminated pyrrolidine to the sp^2 hybridised cation of **224** to give diastereomer **225** with a *syn*-arrangement between the pyrrolidine and the succinimide groups (Scheme 4.22).



Scheme 4.22. Postulated epimerisation mechanism of 213 to 225

The HRMS data of the isolated diastereomer **213** also provides supporting data for the postulated mechanism for this epimerisation. The mass spectrometric data showed an m/z of $[M-(N\text{-}CH_2)_4]^+$ as the major peak suggesting that the pyrrolidine group is labile under these conditions,

supporting the hypothesis that intermediate **224** could be generated in solution after elimination of the pyrrolidine group from compound **213**.

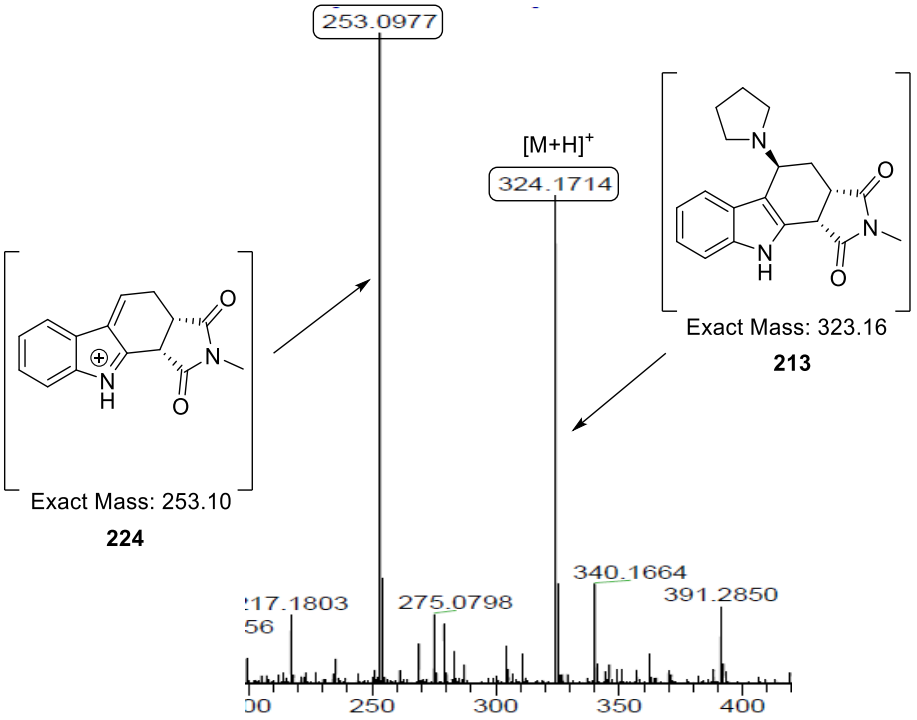


Figure 4.13. HRMS of carbazole 213

4.13. Biological evaluation

Due to the structural relationship between our synthesised amino-substituted pyrrolo[3,4-*a*]carbazole-1,3-dione derivatives with a range of biologically active compounds, discussed previously, the next stage was to evaluate the biological activity of the produced compounds **(213 - 220)** and to assess how distinct bioactivity may be correlated with structural variation. Therefore we decided to screen the biological activity of compounds **(213 - 220)** against the key ESKAPE pathogens *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Acinetobacter baumannii* (*A. baumannii*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Staphylococcus aureus* (*S. aureus*), as well as the fungi *Cryptococcus neoformans* (*C. neoformans*) and *Candida albicans* (*C. albicans*).

The antimicrobial assays of Cbz deprotected compounds **(213 - 220)** were carried by J. Zuegg at the Community for Open Antimicrobial Discovery at the

University of Queensland. The Sample preparation and procedures for the bioassay are given in appendix 2.

The obtained results from this study showed that only amino-substituted carbazole **220** showed a moderate activity against *C. albicans* at a concentration of 32 µg/mL. Further investigations need to be carried out in order to propose the mode of action of the bioactive compound **220**.

4.14. Conclusion

In this chapter, we have developed a one-pot bromination/substitution approach for the synthesis of pyrrolo[3,4-*a*]carbazole-1,3-dione frameworks. We demonstrated that a bromination/substitution reaction sequence of the tosyl protected D-A cycloadduct **149** with a range of alcohols or secondary amines could procced by either an S_N1 or an S_N2 mechanism, to give the corresponding substituted carbazole **(156 - 159)** and **(172 - 174)** in *syn*- or *anti*- stereochemistry respectively, as observed by the X-ray analysis.

Due to the difficulty in removing the tosyl protecting grouop, Cbz was used to protect the indolic nitrogen of the 5-substituted-3-vinyl-1*H*-indoles **197** and **198**. The Cbz protecting group of the amino-substituted carbazole derivatives **(182 - 185)**, and **(205 - 212)** was then easily removed using a hydrogenation reaction. The deprotected compounds **(213 - 220)** have been tested for antimicrobial activity against key ESKAPE pathogens, *E. coli*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *S. aureus* (MRSA), as well as the fungi *C. neoformans* and *C. albicans*. Only compound **220** showed some activity against *C. albicans.*

Chapter 5.
Conclusion and future work

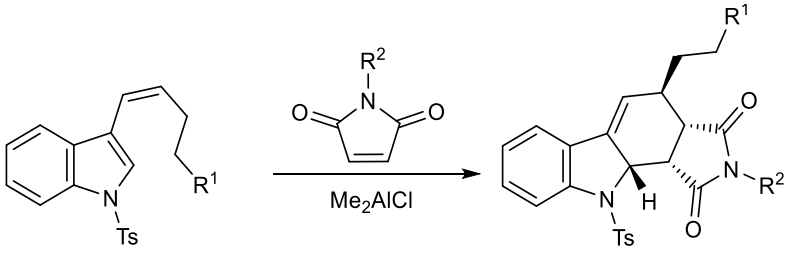
5.1. Conclusion

The overall aim of this research project was to explore new synthetic routes to the tetrahydropyrrolo[3,4-*a*]carbazole ring system, which is found in many synthetic and naturally occurring biologically active compounds. We have investigated two new synthetic approaches for the construction of molecules in this class, first via a D-A/ene approach and secondly via a D-A/ bromination/substitution approach.

5.1.1. Diels-Alder/ene approaches to the pyrrolo[3,4-*a*]carbazoles

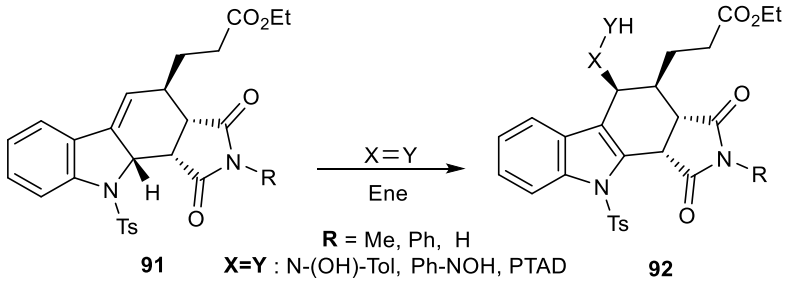
Firstly, we have developed a new diastereoselective approach for the synthesis of a functionalised pyrrolo[3,4-*a*]carbazole ring system through the use of an intermolecular D-A reaction in conjunction with an inter- or an intramolecular ene reaction.

A range of D-A cycloadducts **227** have been synthesised through a D-A reaction of *N*- protected-substituted 3-vinyl-1*H*-indoles **226** with maleimides in the presence of a Lewis acid catalyst (Scheme 5.1). We demonstrated that the Me_2AlCl catalyst was highly efficient in accelerating the rate of D-A cycloaddition of *N*- protected-substituted-3-vinyl-1*H*-indoles **226**, which was unreactive diene under either thermal or thiourea catalysed conditions.



Scheme 5.1. Route to the D-A cycloadducts 227

The intermolecular ene reactions of D-A cycloadducts **91** with nitroso and aza enophiles afforded a single diastereomer of the corresponding tetrahydropyrrolo[3,4-*a*]carbazole **92** (Scheme 5.2).

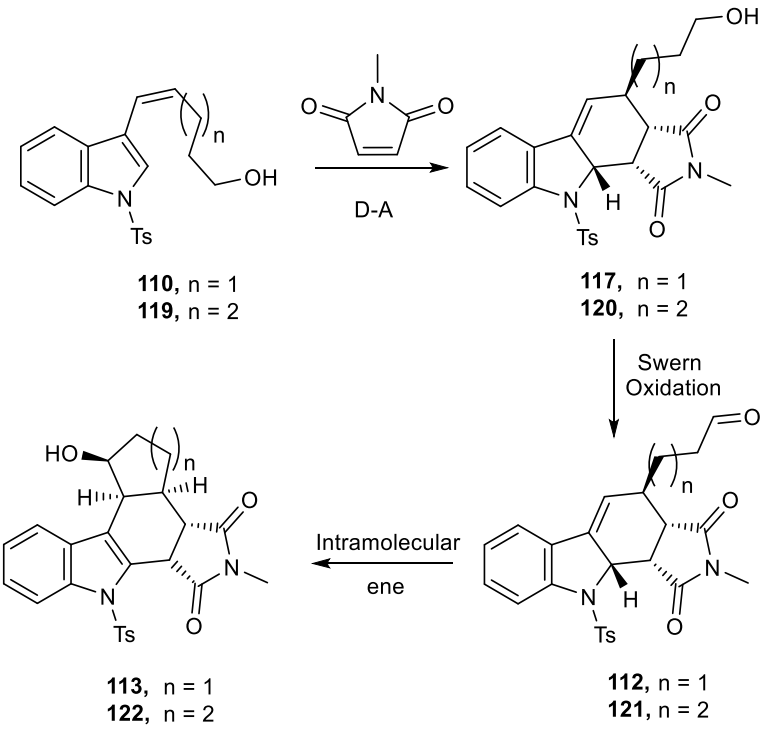


Scheme 5.2. Intermolecular ene reaction of D-A cycloadducts 91

The relative stereochemistry of the isolated D-A/ene adducts **92** was deduced using X-ray crystallography, which revealed that the enophiles was added to the opposite face of the succinimide group.

Polycyclic pyrrolo[3,4-*a*]carbazoles **113** and **122** was also synthesised in a good yield using a three-step sequence involving an intermolecular D-A, Swern oxidation and intramolecular carbonyl-ene reaction of indole **(Z)-110** and **(Z)-119** (Scheme 5.3). The X-ray crystal structures revealed that the reactive aldehyde of **112** and **121** abstracted the hydrogen from the same face, and therefore the formed ring was on the opposite face of the molecule relative to the succinimide group.

Examination of the intramolecular carbonyl-ene mechanism indicates that the intramolecular ene reaction of both precursors **112** and **121** were most likely formed by a concerted ene mechanism



110, n = 1
119, n = 2

117, n = 1
120, n = 2

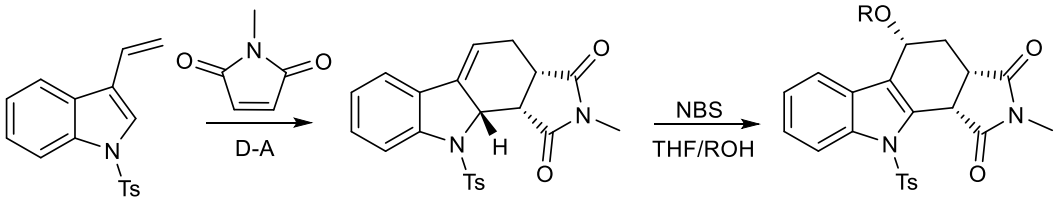
113, n = 1
122, n = 2

112, n = 1
121, n = 2

Scheme 5.3. Synthetic approach to polycyclic pyrrolo[3,4-*a*]carbazoles 113 and 122

5.1.2. Diels-Alder/one-pot bromination/substitution reaction approaches to the pyrrolo[3,4-*a*]carbazole ring system

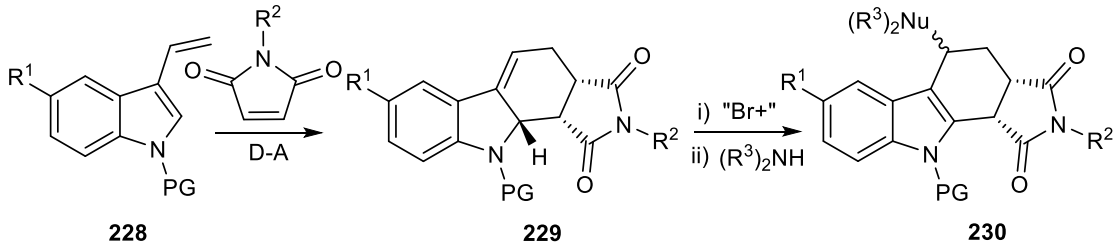
Secondly we have successfully demonstrated a sequential D-A/one-pot bromination/substitution reaction to give substituted tetrahydropyrrolo[3,4-*a*] carbazole derivatives with relative stereocontrol of up to three stereocentres (Scheme 5.4 and 5.5).



148 **149** **159**

ROH = H_2O, CH_3OH, CH_3CH_2OH,$(CH_3)_2CHOH$

Scheme 5.4. Synthesis of a range of substituted carbazoles 159



$(R^3)_2NH$ = pyrrolidine, piperidine, morpholine, diethylamine and methylpiperazine
R^1 = H, F, $PhCH_2O$- R^2 = H, Me, Ph
PG = Ts or Cbz

Scheme 5.5. Synthesis of amino-substituted carbazoles 232

Interestingly oxygen nucleophiles showed a propensity to add to the same face as the succinimide ring, whilst amine based nucleophiles added to the opposite face (Figure 5.1).This suggests that a different mechanism maybe operating in the case of the two different nucleophiles, either due to a change in the experimental conditions (reaction solvent, addition order etc.) or due to the nature of the nucleophile. Further experiments are planned to probe the mechanism and the stereoselectivity of this process.

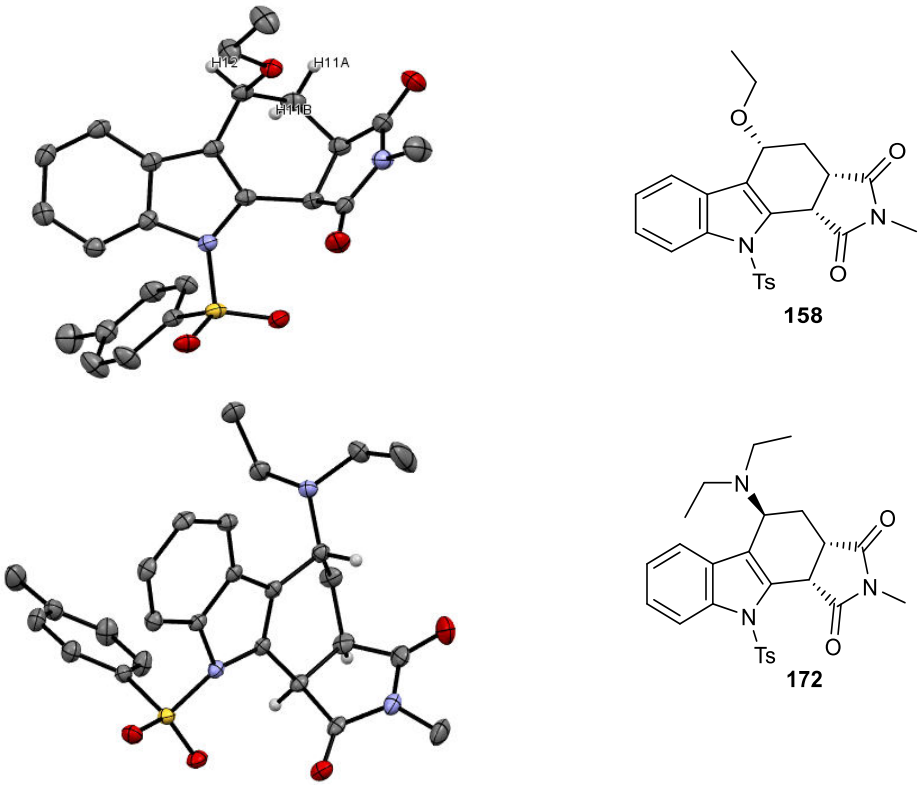
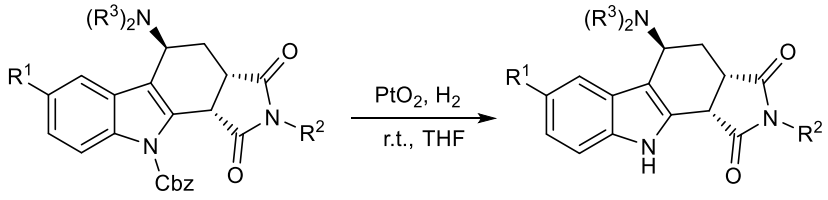


Figure 5.1. X-ray structure of substituted carbazoles 158 and 166

5.1.3. Preparation of pyrrolo[3,4-*a*]carbazole-1,3-diones for biological assay

Since our synthesised substituted compounds possess a pyrrolo[3,4-*a*] carbazole-1,3-dione framework found in many biologically active compounds,[48] we needed to remove the *N*-protecting groups (tosyl or Cbz) to free up the NH of indole as it is an important H-bonding site required for biological activity. After showing that removal of the tosyl group was difficult, we focused on the use of a Cbz protecting group that could be easily removed by hydrogenation (Scheme 5.6). The deprotected compounds **232** are currently awaiting biological evaluation for their antibiotic properties against a range of ESKAPE pathogens.



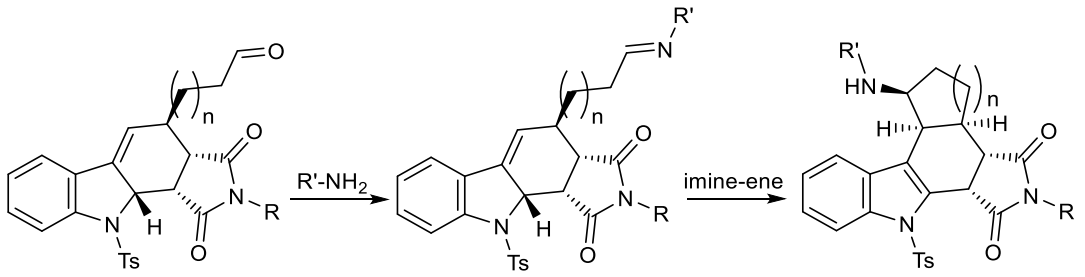
231 **232**

$(R^3)_2NH$ = pyrrolidine, piperidine, morpholine, diethylamine and methylpiperazine
R^1 = H, F, $PhCH_2O$- **R^2** = H, Me, Ph

Scheme 5.6. Deprotection of synthesised carbazoles 231 for biological assay

5.2. Future Work

Further work on the construction of fused pyrrolo[3,4-*a*]carbazole molecules would primarily focus on the investigation of the intramolecular imine-ene reactions of ene precursors **233** and **234**. The imine-ene reaction has been extensively reported,[106,107] thus an *in situ* condensation of different primary amines to the aldehyde of the previously synthesised compounds **112,** and **121**, would allow the rapid formation of a library of imines. We predict that the formed imines would undergo an imine-ene reaction to generate a range of a fused pyrrolo[3,4-*a*]carbazole compounds, which could be of potential interest as building blocks for drug design.



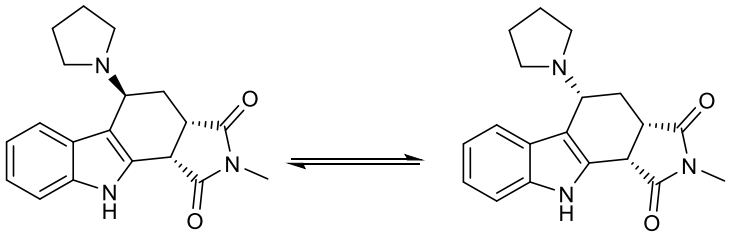
112, n = 1
121, n = 2

233, n = 1
234, n = 2

235, n = 1
236, n = 2

Scheme 5.7. Synthetic plan to investigate the intramolecular imine-ene reaction

In addition we wish to further investigate the mechanism behind the bromination/substitution chemistry developed in this thesis, to better understand the reaction and the stereocontrol observed. This would also include a study of the epimerisation reaction of **213** to give **225** (Scheme 5.8), by examining the influence of different concentrations of the substrate, the influence of different solvents and how the reaction varies with temperature.



213 **225**

Scheme 5.8. The epimerisation of 215 to 227

Finally, studying the results of bioactivity assays (currently underway) of the compound series **(213–220)** will allow us to determine whether these compounds show any promise as antibiotics or as biological probes.

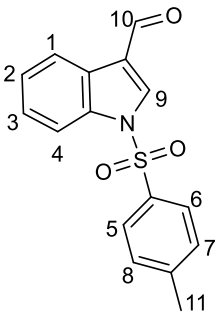
Chapter 6.
Experimental

6.1. General experimental procedures

All reactions were performed in dried glassware under a nitrogen atmosphere. The reagents and chemicals were purchased from commercial suppliers (Sigma Aldrich, Alfa Aesar and TCI.The solvents were distilled prior to use; toluene, DMF and DCM were distilled from calcium hydride; THF and diethyl ether were distilled from sodium wire in the presence of benzophenone. Thin layer chromatography (TLC) was visualized with UV light (λ = 235 nm). Purification was carried out by column chromatography (flash, Kieselgel 60 silica gel). Infrared spectra (IR) analysis was performed using Varian 800 FT-IR Scimitar Series spectrometer scanning from 4000-600 cm^{-1}. Melting points were carried out on a Stuart SMP3 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Jeol Lambda 500 spectrometer, Jeol ECS-400 spectrometer or a Brüker AMX300 spectrometer. HRMS data were provided by National Mass Spectrometry Service (University of Swansea). X-ray diffraction data was obtained on an Oxford Diffraction Gemini.

6.2. Synthetic procedures

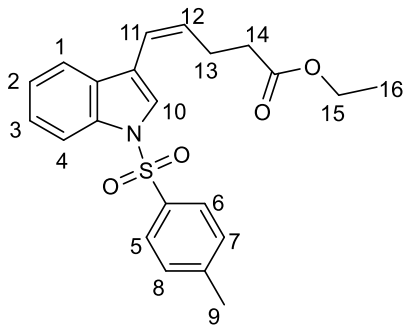
1-Tosyl-1*H*-indole-3- carbaldehyde (89)



A solution of indole-3-carbaldehyde **88** (5.00 g, 43.45 mmol) in DCM (120 mL) was cooled down to 0 °C. Triethylamine (12 mL, 86.15 mmol) was added dropwise over 10 min to the solution. The reaction mixture was stirred for 10 min and 4-toluenesulfonyl chloride (7.225 g, 37.90 mmol) was added. The mixture was stirred for 2 h at 0 °C before it warmed to room temperature. After 48 h, the reaction mixture was quenched with water (50 mL). The organic layer was extracted with DCM (2 x 150 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude red product was purified by recrystallisation from ethyl acetate to give 1-tosyl-1*H*-indole-3-carbaldehyde in (8.11 g, 27.09 mmol, 79%) as bright yellow crystals.

Mp. 145 – 147 °C (lit. 148 – 150 °C).[72] **R_f** : 0.42 (petrol / ethyl acetate 7:3). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 10.08 (s, 1H, H_{10}), 8.24 (d, *J* = 7.0 Hz, 1H, $H_{(1 \text{ or } 4)}$), 8.22 (s, 1H, H_9), 7.94 (d, *J* = 7.4 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.84 (d, *J* = 8.5 Hz, 2H, $H_{(5\text{-}6) \text{ or } (7\text{-}8)}$), 7.40 (t, *J* = 7.4 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.35 (t, *J* = 7.0 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.29 (d, *J* = 8.0 Hz, 2H, $H_{(5\text{-}6) \text{ or } (7\text{-}8)}$), 2.35 (s, 3H, H_{11}). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 185.5 (C_{10}), 146.2, 136.4, 135.2, 134.4, 130.4, 127.3, 126.4, 126.3, 125.0, 122.6, 122.4, 113.2, 22.1 (C_{11}). **IR (neat): ν_{max}/cm^{-1}:** 1663 (CHO), 1539 (C=C).

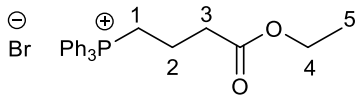
Ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate (90)



In a Schlenk flask, (4-ethoxy-4-oxobutyl) triphenylphosphonium bromide (3.32 g, 7.26 mmol) was dissolved in THF (20 mL). The solution was cooled to -78 ºC. Sodium bis (trimethylsilyl) amide (1.0 M in THF, 8.58 mL, 8.58 mmol) was added dropwise over 10 min. The mixture was warmed to 0 ºC and left to stir for 2 h. In a separate round bottomed flask, 1-(toluene-4-sulfonyl)–1*H*-indol-3-carbaldehyde **89** (2.00 g, 6.60 mmol) was dissolved in THF (10 mL) and transferred via cannula into the reaction solution. The reaction mixture was stirred at room temperature and for 48 h, quenched with saturated $NH_4Cl_{(aq)}$ (30 mL), the organic layer was extracted with EtOAc (2 x 200 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give an orange crude product as a mixture of *E* and *Z* isomers of ethyl-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate. The product was purified by column chromatography (petrol / ethyl acetate 10:1) to give the desired ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate (1.568 g, 3.94 mmol, 60%) as a colourless oil.

R_f: 0.7 (petrol / ethyl acetate 7:3).**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.97 (d, *J* = 7.9 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.77 (d, *J* = 7.8 Hz, 2H, $H_{(5, 6) \text{ or } (7,8)}$), 7.57 (s, 1H, H_{10}), 7.49 (d, *J* = 7.9 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.32 (t, *J* = 7.9 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.25 (t, *J* = 7.9 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.20 (d, *J* = 7.8 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 6.44 (d, *J* = 11.2 Hz, 1H, H_{11}), 5.78 (dt, *J* = 11.2, 7.5 Hz, 1H, H_{12}), 4.14 (q, *J* = 6.5 Hz, 2H, H_{15}), 2.67 - 2.62 (m, 2H, H_{13}), 2.48 (t, *J* = 6.9 Hz, 2H, H_{14}), 2.30 (s, 3H, H_9), 1.24 (t, *J* = 6.5 Hz, 3H, H_{16}). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 172.8 (CO_2Et), 145.1, 135.1, 134.6, 132.1, 130.8, 129.9, 126.8, 124.9, 123.6, 123.4, 119.5, 118.96, 113.6, 60.5 (C_{15}), 34.1 ($C_{13 \text{ or } 14}$), 25.2 ($C_{13 \text{ or } 14}$), 21.6 (C_9), 14.3 (C_{16}). **IR (neat): ν_{max}/cm^{-1}:** 1727 (CO), 1597 (C=C). **MS (pNSI):** 415.2 (100%, $[M+NH_4]^+$), 398.1 (20%, $[M+H]^+$), 420.1 (10%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{22}H_{24}NO_4S$ $[M+H]^+$: 398.1412; observed: 398.1412.

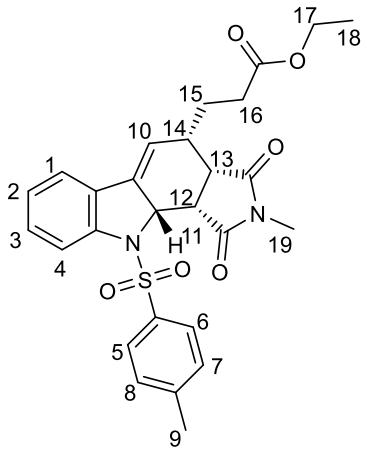
(4-Ethoxy-4-oxobutyl)triphenylphosphonium bromide (94)



A solution of triphenylphosphine (4.600 g, 17.6 mmol) and ethyl-4-bromobutyrate **93** (1.8 mL, 12.60 mmol) in toluene (20 mL) was refluxed for 24 h. The resultant white precipitate was filtered off with suction and washed with toluene to give (4-ethoxy-4-oxobutyl) triphenylphosphonium bromide in (4.531 g, 9.90 mmol, 79%) as a white solid.

Mp. 175 – 177 °C (lit. 173 - 174 °C).[73] **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.90 - 7.83 (m, 6H), 7.79 - 7.74 (m, 3H), 7.70 - 7.65 (m, 6H), 4.07 (q, *J* = 7.1 Hz, 2H, H_4), 4.07 - 3.99 (m, 2H, H_1), 2.87 (td, *J* = 6.6, 1.5 Hz, 1H), 1.95 - 1.85 (m, 2H, H_2), 1.21 (t, *J* = 7.1 Hz, 3H, H_5).**^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 173.1 (CO_2Et), 135.1 (J_{cp} = 2.8 Hz), 133.7 (J_{cp} = 10.2 Hz), 130.5 (J_{cp} = 12.2 Hz), 118.1 (J_{cp} = 87.0 Hz), 60.5(C_4), 33.2 (J_{cp} = 23.2 Hz), 21.7 (J_{cp} = 52.4 Hz), 18.0, 14.2(C_5). **IR (neat): ν_{max}/cm^{-1}:** 2890 (CH), 1720 (CO_2Et), 1598 (C=C, Ar). **HRMS (pNSI):** calcd $C_{24}H_{26}O_2P$ $[M\text{-}Br]^+$: 377.1665; observed: 377.1660.

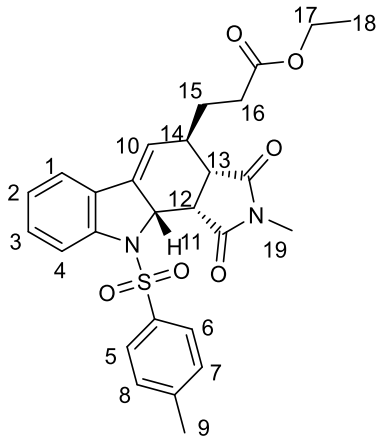
Ethyl 3-((3a*S*,4*S*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (96)



A mixture of *N*-methylmaleimide (0.421 g, 0.38 mmol) and ethyl-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate (*Z*:*E,* 10:1)-**90** (0.154 g, 0.38 mmol) in toluene (15 mL) was refluxed for 72 h. The solvent was removed under reduced pressure to give the crude product which was purified by column chromatography (petrol / ethyl acetate 2:1) to yield ethyl 3-((3a*S*,*4*S,10a*S*,10b*S*)-2- methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a, 10b-octahydropyrrolo[3,4-*a*] carbazol-4-yl) propanoate in (0.017 g, 0.03 mmol, 9%) as a white solid.

Mp. 175 – 177 °C. **R_f** : 0.3 (petrol / ethyl acetate 2:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.77 (d, *J* = 7.5 Hz, 2H, $H_{(5,6)\ or\ (7,8)}$), 7.67 (d, *J* = 7.0 Hz, 1H, $H_{(1\ or\ 4)}$), 7.26 - 7.22 (m, 4H, $H_{(5,6)\ or\ (7,8)}$, $H_{(2\ or\ 3)}$, $H_{(1\ or\ 4)}$), 6.98 (t, *J* = 7.0 Hz, 1H, $H_{(2\ or\ 3)}$), 5.84 (t, *J* = 3.7 Hz, 1H, H_{10}), 4.54 - 4.51 (m, 1H, H_{11}), 4.15 (q, *J* = 7.5 Hz, 2H, H_{17}), 4.01 (t, *J* = 7.8 Hz, 1H, H_{12}), 3.19 - 3.15 (m, 1H, H_{13}), 2.77 (s, 3H, H_{19}), 2.58 (t, *J* = 7.4 Hz, 2H, H_{16}), 2.38 - 2.22 (m, 3H, $H_{(14,\ 15)}$), 2.34 (s, 3H, H_9), 1.26 (t, *J* =7.5 Hz, 3H, H_{18}). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 176.2 (CO), 173.7 (CO), 173.0 (CO), 144.6, 139.8, 137.6, 134.1, 130.6, 129.9, 127.4, 126.0, 123.7, 121.1, 117.4, 115.2, 61.8 (C_{17}), 60.6 (C_{11}), 43.9 (C_{12}), 40.1 (C_{13}), 37.1 (C_{14}), 32.4 (C_{16}), 26.5 (C_{15}), 24.3 (C_{19}), 21.7 (C_9), 14.3 (C_{18}). **IR (neat):ν_{max}/cm^{-1}:** 1733 (CO_2Et), 1698 (N-CO), 2973 (CH). **HRMS (pNSI):** calcd $C_{27}H_{29}N_2O_6S$ $[M+H]^+$: 509.1741; observed: 509.1730.

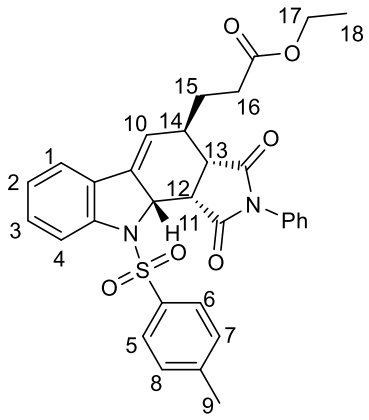
Ethyl 3-((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl 1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (98)



Dimethylaluminum chloride (1.0 M in hexane, 9.38 mL, 9.38 mmol) was added dropwise to a solution of *N*-methylmaleimide (0.521 g, 4.69 mmol) in DCM (15 mL) at -78 ºC. The mixture left to stir for 30 min. Then, a solution of ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate **90** (4.69 mmol, 1.863 g) in DCM (15 mL) was added dropwise at -78 ºC. The reaction mixture was refluxed for 48 h, quenched with saturated $NaHCO_{3\,(aq)}$. The organic layer was extracted with DCM (2 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude yellow solid. The product was purified by column chromatography (petrol / ethyl acetate 2:1) to yield ethyl 3-((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl 1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate in (2.038 g, 4.01 mmol, 85%) a bright yellow solid.

Mp. 187 – 188 ºC. **R_f :** 0.3 (petrol / ethyl acetate 2:1)**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.79 (d, *J* = 7.3 Hz, 2H, $H_{(5,6)\text{ or }(7,8)}$), 7.62 (d, *J* = 7.0 Hz, 1H, $H_{(1\text{ or }4)}$), 7.25 - 7.21 (m, 4H, $H_{(5,6)\text{ or }(7,8),}$ $H_{(2\text{ or }3),}$ $H_{(1\text{ or }4)}$), 6.95 (t, *J* = 7.0 Hz, 1H, $H_{(2\text{ or }3)}$), 6.09 (dd, *J* = 3.7, 6.7 Hz, 1H, H_{10}), 4.85 (dd, *J* = 3.7, 6.9 Hz, 1H, H_{11}), 4.15 (t, *J* = 6.9 Hz, 1H, H_{12}), 4.07 (m, 2H, H_{17}), 3.15 - 3.12 (m, 1H, H_{14}), 3.05 - 3.02 (m, 1H, H_{13}), 2.83 (s, 3H, H_{19}), 2.43 - 2.36 (m, 2H, H_{16}), 2.35 (s, 3H, H_9), 1.91 - 1.75 (m, 2H, H_{15}), 1.19 (t, *J* = 7.3 Hz, 3H, H_{18}). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 178.6 (CO), 174.0 (CO), 172.79 (CO), 144.6, 144.0, 136.6, 134.0, 130.5, 130.0, 127.5, 126.6, 123.9, 121.0, 116.3, 115.4, 60.6 (C_{17}), 59.9 (C_{11}), 44.22(C_{12}), 42.98 (C_{13}), 37.2 (C_{14}), 33.1 (C_{16}), 28.3 (C_{15}), 25.3 (C_{19}), 21.70 (C_9), 14.3(C_{18}). **IR (neat): ν_{max}/cm^{-1}:** 1776 (CO_2Et), 1698 (N-CO). **HRMS (pNSI):** calcd $C_{27}H_{29}N_2O_6S$ $[M+H]^+$: 509.1741; observed: 509.1731.

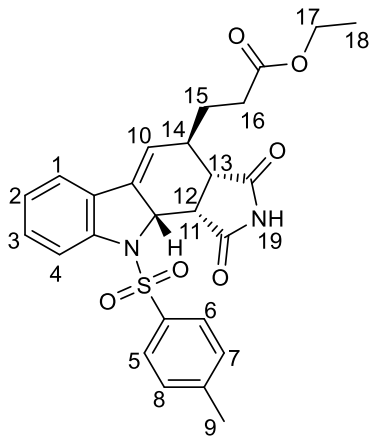
Ethyl 3-((3a*S*,4*R*,10a*S*,10b*S*)-1,3-dioxo-2-phenyl-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (103)



Dimethylaluminum chloride (1.0 M in THF, 2.39 mL, 2.39 mmol) was added dropwise to a solution of *N*-phenylmaleimide (0.207 g, 1.19 mmol) in DCM (5 mL) at -78 ºC. The mixture left to stir for 30 min. Then, a solution of ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate **90** (0.475 g, 1.19 mmol) in DCM (10 mL) was added. The reaction mixture was heated to reflux for 48 h, quenched with saturated $NaHCO_{3\,(aq)}$ (10 mL). The organic layer was extracted with DCM (1 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude yellow solid product which was purified by column chromatography (petrol / ethyl acetate 2:1) to yield ethyl3-((3a*S*,4*R*,10a*S*,10b*S*)-1,3-dioxo-2-phenyl-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate in (0.5095 g, 0.84 mmol, 71%) as a white solid.

Mp. 201 – 203 ºC. **R_f** : 0.2 (petrol / ethyl acetate 2:1)**. ^{1}H NMR (400 MHz, CDCl3):** δ_H 7. 81 (d, *J* = 7.3 Hz, 2H, $H_{(5,\,6)\ or\ (7,8)}$), 7. 60 (d, *J* = 7.3 Hz, 1H, $H_{(1\ or\ 4)}$), 7.34 – 7.21 (m, 7H, Ar), 7.06 (d, *J* = 7.3 Hz, 2H, $H_{(5,\,6)\ or\ (7,8)}$), 6.97 (t, *J* = 7.3 Hz, 1H, $H_{(2\ or\ 3)}$), 6.20 (dd, *J* = 3.4, 7,1 Hz, 1H, H_{10}), 4.59 (dd, *J* = 3.4, 7.1 Hz, 1H, H_{11}), 4.18 (t, *J* = 7.3 Hz, 1H, H_{12}), 4.13 – 4.05 (m, 2H, H_{17}), 3.26 - 3.20 (m, 2H, $H_{(13,\,14)}$), 2.45 – 2.40 (m, 2H, H_{16}), 2.35 (s, 3H, H_9), 1.89 - 1.85 (m, 2H, H_{15}), 1.20 (t, *J* = 6.9 Hz, 3H, H_{18}). **^{13}C NMR (100 MHz, $CDCL_3$)**: δ_C 177.5 (CO), 172.9 (CO), 172.7 (CO).144.6, 144.3, 137.0, 134.1, 131.7, 130.7, 130.0, 129.0, 128.5, 127.6, 126.7, 126.3, 124.0, 120.9, 116.2, 115.5, 60.8 (C_{17}), 60.0 (C_{11}), 44.3 (C_{12}), 43.1 (C_{13}), 37.7 (C_{14}), 33.2 (C_{16}), 28.3 (C_{15}), 21.6 (C_9), 14.2 (C_{18}). **IR (neat): ν_{max}/cm^{-1}:** 1776 (CO_2Et), 1703 (N-CO). **MS (pNSI):** 588.21 (100%, $[M+NH_4]^+$), 1158.39 (33%, $[2M+NH_4]^+$); **HRMS (pNSI):** calcd $C_{32}H_{31}N_2O_6S$ $[M+H]^+$: 571.18; observed: 571.1891.

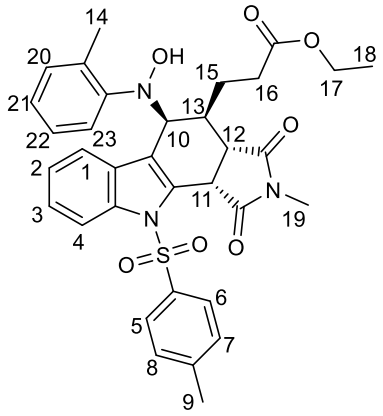
Ethyl3-((3a*S*,4*R*,10a*S*,10b*S*)-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (104)



Dimethylaluminum chloride (1.0 M in in hexane, 2.86 mL, 2.86 mmol) was added dropwise to a solution of maleimide (0.14 g, 1.43 mmol) in DCM (5 mL) at -78 ^{o}C. The mixture left to stir for 30 min. Then, a solution of ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate **90** (0.57 g, 1.43 mmol) in DCM (10 mL) was added. The reaction mixture was slowly heated to reflux for 48 h, quenched with saturated $NaHCO_{3\,(aq)}$ (5 mL). The organic layer was extracted with DCM (1 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude yellow solid product which was purified by column chromatography (petrol / ethyl acetate 2:1 gradient to 1:1 petrol / ethyl acetate) to yield ethyl 3-((3a*S*,4*R*,10a*S*,10b*S*)-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate in (0.452 g, 0.91 mmol, 64%) as a white solid.

Mp. 218 – 220 ^{o}C. **R_f** : 0.14 (petrol / ethyl acetate 1:1)**. ^{1}H NMR (400 MHz, CDCl3):** δ_H 7.78 (d, *J* = 6.9 Hz, 2H, $H_{(5,\,6)\ or\ (7,\,8)}$), 7. 64 (d, *J* = 6.8 Hz, 1H, $H_{(1\ or\ 4)}$), 7.27 – 7.22 (m, 4H, $H_{(5,6)\ or\ (7,8)}$, $H_{(1\ or\ 4)}$, $H_{(2\ or\ 3)}$), 6.98 (t, *J* = 7.8 Hz, 1H, $H_{(2\ or\ 3)}$), 6.16 (dd, *J* = 3.6, 7,1 Hz, 1H, H_{10}), 4.84 (dd, *J* = 3.6, 7.3 Hz, 1H, H_{11}), 4.18 (t, *J* = 7.3 Hz, 1H, H_{12}), 4,12 – 4.05 (m, 2H, H_{17}), 3.16 - 1.12 (m, 1H, H_{14}), 3.10 (t, *J* = 7.3 Hz, 1H, H_{13}), 2.40 (t, *J* = 7.3 Hz, 2H, H_{16}), 2.35 (s, 3H, H_9), 1.89 - 1.76 (m, 2H, H_{15}), 1.20 (t, *J* = 7.5 Hz, 3H, H_{18}). **^{13}C NMR (100 MHz, $CDCL_3$)**: δ_C 178.3 (CO), 173.6 (CO), 172.7 (CO), 144.5, 144.1, 136.6, 133.8, 130.5, 129.8, 127.5, 126.6, 123.8, 120.0, 116.4, 115.5, 60.8 (C_{17}), 59.6 (C_{11}), 45.2 (C_{12}), 44.0 (C_{13}), 36.9 (C_{14}), 33.0 (C_{16}), 27.8 (C_{15}), 21.5 (C_9), 14.1(C_{18}).**IR (neat): ν_{max}/cm^{-1}:** 3657 (br, NH), 2981 (CH), 1776 (CO_2Et), 1703 (N-CO). **MS (pNSI):** 512.18 (100 %, $[M+NH_4]^+$), 495.15 (55 %, $[M+H]^+$), 340.14 (31%, $[M-Ts]^+$); **HRMS (pNSI):** calcd $C_{26}H_{27}N_2O_6S$ $[M+H]^+$: 495.1584; observed: 495.1585.

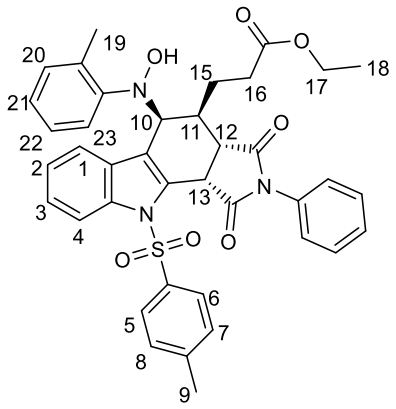
Ethyl 3-((3a*S*,4*S*,5*S*,10b*S*)-5-(hydroxy(o-tolyl)amino)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl) propanoate (105)



A solution of 2-nitrosotoluene (0.035 g, 0.29 mmol) and ethyl 3-((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate **98** (0.150 g, 0.29 mmol) in DCM (10 mL) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure to give the crude green solid product which was purified by column chromatography (petrol / ethyl acetate 2:1) to give ethyl 3-((3a*S*,4*S*,5*S*,10b*S*)-5-(hydroxy(o-tolyl)amino)-2-methyl-1,3-dioxo-10-tosyl1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoatein (0.109 g, 0.17 mmol, 59%) as a bright yellow solid.

Mp. 190 – 192 ^{o}C**.** $\mathbf{R_f}$: 0.26 (petrol / ethyl acetate 2:1)**.** ^{1}**H NMR (400 MHz, $CDCl_3$):** δ_H 7.95 (d, *J* = 7.2 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.61 (d, *J* = 7.2 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.18 (d, *J* = 7.2 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.10 (d, *J* = 7.2 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.05 (t, *J* = 7.2 Hz, 1H, $H_{(2 \text{ or } 3)}$), 6.81 (t, *J* = 7.2 Hz, 1H, $H_{(2 \text{ or } 3)}$), 6.65 (t, *J* = 7.5 Hz, 1H, $H_{(21 \text{ or } 22)}$), 6.19 (t, *J* = 7.5 Hz, 1H, $H_{(21 \text{ or } 22)}$), 5.88 (d, *J* = 7.2 Hz, 1H, $H_{(20 \text{ or } 23)}$), 5.46 (d, *J* = 7.2 Hz, 1H, $H_{(20 \text{ or } 23)}$), 4.99 (br, OH), 4.95 (d, *J* = 7.2 Hz, 1H, H_{10}), 4.30 (d, *J* = 4.6 Hz, 1H, H_{11}), 4.11 (q, *J* = 7.0 Hz, 2H, H_{17}), 3.80 - 3.75 (m, 1H, H_{12}), 3.01 (s, 3H, H_{14}), 2.70 - 2.54 (m, 4H, $H_{(15, 16)}$), 2.41 (s, 3H, H_{19}), 2.33 (s, 3H, H_9), 1.92 - 1.85 (m, 1H, H_{13}), 1.24 (t, *J* = 7.0 Hz, 3H, H_{18}). ^{13}**C NMR (100 MHz, $CDCl_3$):** δ_C 178.2 (CO), 173.3 (CO), 149.9, 144.6, 139.9, 137.1, 134.1, 131.9, 130.6, 130.3, 129.4, 128.7, 127.0, 125.7, 124.8, 124.4, 123.6, 122.1, 118.9, 118.0, 115.7, 60.6 (C_{17}), 57.8, 45.1, 42.4, 40.0, 32.5, 25.2, 23.3 (C_{19}), 21.6 (C_9), 18.5 (C_{14}), 14.3(C_{18}). **IR (neat):** $\boldsymbol{\nu_{max}}$**/cm^{-1}:** 3655 (OH), 2980 (CH), 1702 (CO).**MS (pNSI):** 507.15 (100 %, $[M-(Tol\text{-}N\text{-}OH)]^+$), 652.20 (55 %, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{34}H_{35}N_3O_7S$ $[M+Na]^+$: 652.2088; observed: 652.2082.

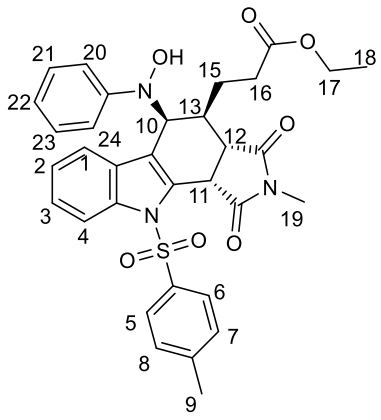
Ethyl 3-((3a*S*,4*S*,5*S*,10b*S*)-5-(hydroxy(o-tolyl)amino)-1,3-dioxo-2-phenyl-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl) propanoate (106)



A solution of 2-nitrosotoluene (0.016 g, 0.13 mmol) and ethyl 3-((3a*S*,4*R*,10a*S*,10b*S*)-1,3-dioxo-2-phenyl-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo [3,4-*a*] carbazol-4-yl) propanoate **103** (0.08 g, 0.13 mmol) in dry DCM (10 mL) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure to give the crude yellow product which was purified by column chromatography (petrol / ethyl acetate 2:1) to give ethyl 3-((3a*S*,4*S*,5*S*,10b*S*)-5-(hydroxy(o-tolyl)amino)-1,3-dioxo-2-phenyl-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-yl)propanoate in (0.415 g, 0.059 mmol, 58%) as a bright yellow solid.

Mp. 182 – 184 °C. **R_f** : 0.34 (petrol / ethyl acetate 2:1)**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.94 (d, *J* = 6.7 Hz, 1H, Ar), 7.64 (d, *J* = 6.7 Hz, 2H, Ar), 7.45 – 7.37 (m, 5H, Ar), 7.20 - 7.00 (m, 4H Ar), 6.84 (t, *J* = 6.9 Hz, 1H, Ar), 6.66 (t, *J* = 6.9 Hz, 1H, Ar), 6.24 (t, *J* = 6.2 Hz, 1H, Ar), 5.95 (d, *J* = 6.9 Hz, 1H, Ar), 5.66 (d, *J* = 6.4 Hz, 1H, Ar), 5.20 (d, *J* = 7.4 Hz, 1H, H_{10}), 4.99 (br, OH), 4.39 (d, *J* = 4.0 Hz, 1H, H_{13}), 4.08 (q, *J* = 7.2 Hz, 2H, H_{17}), 4.03 – 3.98 (m, 1H, H_{12}), 2.72 – 2.61 (m, 4H, $H_{(15,16)}$), 2.42 (s, 3H, H_{19}), 2.33 (s, 3H, H_9), 2.14 – 2.08 (m, 1H, H_{13}). 1.20 (t, *J* = 7.2 Hz, 3H, H_{18}). **^{13}C NMR (100 MHz, $CDCL_3$)**: δ_C 177.0 (CO), 173.3 (CO), 172.2 (CO), 150.1, 144.6, 137.1, 134.2, 131.0, 131.8, 130.5, 130.3, 129.4, 129.0, 128.6, 128.5, 127.0, 126.5, 125.8, 124.8, 124.5,123.5, 122.2, 119.1, 118.1, 115.6, 60.0 (C_{17}), 57.7, 45.3, 42.6, 40.0, 32.4, 23.1 (C_{19}), 21.6 (C_9), 18.5, 14.5 (C_{18}). **R (neat): ν_{max}/cm^{-1}:** 3858 (NH), 3826 (OH), 1709 (CO_2Et), 1595 (N-CO).**MS (pNSI):** 569.17 (100%, [M-tol-NOH]$^+$), 692.24 (30%, [M+H]$^+$); **HRMS (pNSI):** calcd $C_{39}H_{36}N_3O_7S$ [M-H]$^+$: 690.2268; observed: 690.2266.

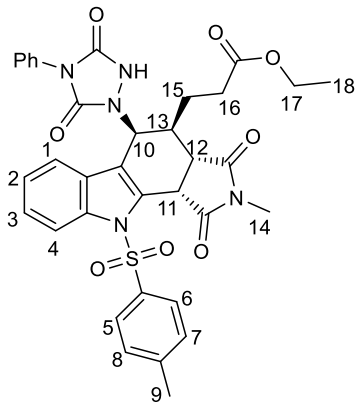
Ethyl 3-((3a*S*,4*S*,5*S*,10b*S*)-5-(hydroxy(phenyl)amino)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl) propanoate (107)



A solution of nitrosobenzene (0.026 g, 0.23 mmol) and ethyl 3-((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate **98** (0.12 g, 0.23 mmol) in DCM (5 mL) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure to give the crude green solid product which was purified by column chromatography (petrol / ethyl acetate 2:1) to give ethyl 3-((3a*S*,4*S*,5*S*,10b*S*)-5-(hydroxy(phenyl)amino)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate in (0.75 g, 0.12 mmol, 52%) as a bright yellow solid.

Mp. 175 – 177 °C. **R_f** : 0.26 (petrol / ethyl acetate 2:1)**.^{1}H NMR (700 MHz, DMSO-d_6):** δ_H 8.45 (s, 1H, OH), 7.72 (d, *J* = 8.3 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.58 (d, *J* = 8.0 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.28 (d, *J* = 8.0 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.09 (t, *J* = 7.7 Hz, 2H, Ar), 7.04 (t, *J* = 7.8 Hz, 1H, Ar), 6.87 (d, *J* = 7.9 Hz, 2H, Ar), 6.81 (t, *J* = 7.3 Hz, 1H, Ar), 6.72 (t, *J* = 7.6 Hz, 1H, Ar), 6.28 (d, *J* = 7.9 Hz, 1H, Ar), 5.18 (d, *J* = 7.5 Hz, 1H, H_{10}), 4.92 (d, *J* = 4.7 Hz, 1H, H_{11}), 4.08 (q, *J* = 7.1 Hz, 2H, H_{17}), 3.68 (dd, *J* = 12.4, 7.6 Hz, 1H, H_{12}), 2.89 (s, 3H, H_{19}), 2.73 – 2.68 (m, 1H, H_{13}), 2.48 – 2.41 (m, 2H, H_{16}), 2.32 (s, 3H, H_9), 2.31 – 2.24 (m, 1H, H_{15}), 1.96 – 1.92 (m, 1H, H_{15}), 1.19 (t, *J* = 7.1 Hz, 3H, H_{18}). **^{13}C NMR (176 MHz, DMSO-d_6):** δ_C 178.4 (CO), 174.3 (CO), 173.5 (CO), 154.0, 145.08, 136.8, 134.9, 133.1, 130.0, 129.6, 128.8, 126.7, 124.4, 123.5, 121.4, 120.5, 118.2, 117.0, 114.8, 60.2 (C_{10}), 58.7, 45.3, 42.1, 39.1, 31.8, 25.1, 24.0, 21.4 (C_{19}), 14.6 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 3659 (br, OH), 2981 (CH), 1770 (CO_2Et), 1703 (N-CO). **MS (pNSI):** 1253.39 (100%, $[2M+Na]^+$), 507.15 (22%, [[M-(Ph-N-OH)$^+$]); **HRMS (pNSI):** calcd C_3 $H_{33}N_3O_7SNa$ $[M+Na]^+$: 638.1931; observed: 638.1924.

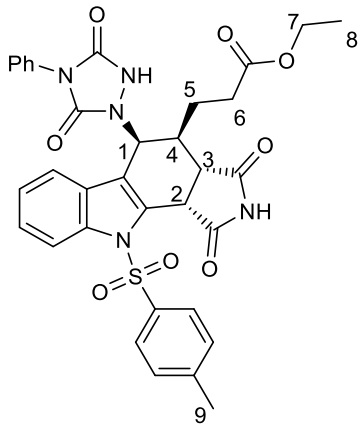
Ethyl3-((3a*S*,4*S*,5*S*,10b*S*)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (108)



A solution of 4-phenyl-1,2,4-triazoline-3,5-dione (0.052 g, 0.29 mmol) and ethyl 3 ((3aS,4R,10aS,10bS)- 2-methyl-1,3-dioxo-10-tosyl1,2,3,3a,4,10,10a,10boctahydropyrrolo[3,4-a]carbazol-4-yl) propanoate **98** (0.150 g, 0.29 mmol) in DCM (10 mL) was stirred at 0 ºC for 6 h. The solvent was removed under reduced pressure to give the crude product which was purified by column chromatography (petrol / ethyl acetate 1:1) to give ethyl 3-((3aS,4S,5S,10bS)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-a]carbazol-4-yl)propanoate in (0.110 g, 0.161 mmol, 56%) as a white solid.

Mp. 264 – 265 ºC. **R_f** : 0.3 (petrol / ethyl acetate 1:1)**.^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 8.86 (br, s, NH), 7.78 (d, *J* = 7.0 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.71 (d, *J* = 7.9 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.47 (d, *J* = 7.9 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.44 - 7.40 (m, 1H, Ar), 7.36 – 7.30 (m, 3H, Ar), 7.23 - 7.17 (m, 2H, Ar), 7.02 (d, *J* = 7.0 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 5.66 (d, *J* = 6.2 Hz, 1H, H_{10}), 5.04 (d, *J* = 6.5 Hz, 1H, H_{11}), 4.08 (q, *J* = 6.2 Hz, 2H, H_{17}), 3.44 (dd, *J* = 6.5, 11.9 Hz, 1H, H_{12}), 3.02 (s, 3H, H_{14}), 2.68 - 2.51 (m, 3H, $H_{(15 \text{ , } 16)}$), 2.15 (s, 3H, H_9), 2.14 - 2.09 (m, 1H, H_{13}), 1.90 - 1.82 (m, 1H, H_{15}), 1.20 (t, *J* = 6.2 Hz, 3H, H_{18}). **^{13}C NMR (100 MHz, $CDCL_3$)**: δ_C 176.6 (CO), 173.4 (CO), 173.2 (CO), 153.6 (CO), 152.6 (CO), 145.2, 136.8, 135.5, 132.1, 130.7, 129.7, 129.3, 128.6, 127.2, 126.8, 125.6, 124.2, 119.0, 114.8, 114.4, 60.8 (C_{17}), 44.3 (C_{10}), 42.0 (C_{11}), 39.3 (C_{12}), 30.9 (C_{13}), 25.4 ($C_{15,16}$), 23.0 (C_{14}), 21.5 (C_9), 14.2 (C_{18}). **IR (neat): ν_{max}/cm^{-1}:** 3659 (NH), 1775 (CO_2Et), 1691 (N-CO). **MS (pNSI):** 701.23 (100%, $[M+NH_4]^+$), 1384.44 (17%, $[2M+NH_4]^+$); **HRMS (pNSI):** calcd $C_{35}H_{34}N_5O_8S$ $[M+H]^+$: 684.2123 ; observed: 684.2115.

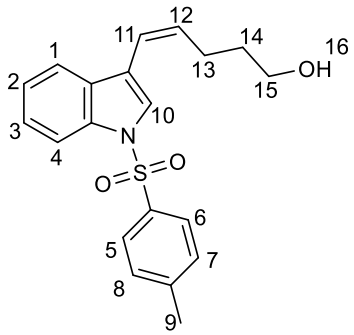
Ethyl 3-((3a*S*,4*S*,5*S*,10b*S*)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (109)



A solution of 4-phenyl-1,2,4-triazoline-3,5-dione (0.037 g, 0.21 mmol) and ethyl 3-((3a*S*,4*R*,10a*S*, 10b*S*)-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*] carbazol-4-yl)propanoate **104** (0.105 g, 0.21 mmol) in DCM (10 mL) was stirred at 0 °C for 6 h. The solvent was removed to give the crude white solid product which was purified by trituration from DCM to yield ethyl 3-((3a*S*,4*S*,5*S*,10b*S*)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b octahydropyrrolo [3,4-*a*]carbazol-4-yl) propanoate in (0.08 g, 0.119 mmol, 57%) as a white solid.

Mp. 269 – 271 °C. **^{1}H NMR (300 MHz, DMSO-d$_6$):** δ_H 11.44 (br, s, NH), 10.68 (br, s, NH), 7.87 – 7.76 (m, 3H, Ar), 7.51 – 7.39 (m, 4H, Ar), 7.29 – 7.25 (m, 6H, Ar), 5.69 (d, *J* = 6.1 Hz, 1H, H_1), 5.28 (d, *J* = 6.8 Hz, 1H, H_2), 4.05 (q, *J* = 6.8 Hz, 2H, H_7), 3.45 (dd, *J* = 6.8 , 11.3 Hz, 1H, H_3), 3.58 – 3.52 (m, 1H, H_4), 2.67 – 2.65 (m, 1H, H_5), 2.25 (s, 3H, H_9),2.49 – 2.44 (m, 2H, H_6), 1.80 – 1.70 (m, 1H, H_5), 1.18 (t, *J* = 6.8 Hz, 3H, H_8).**^{13}C NMR (75 MHz, DMSO-d$_6$)**: δ_C 178.6 (CO), 175.0 (CO), 172.9 9 (CO), 154.4 (CO), 153.1 (CO), 145.5, 136.6, 134.9, 133.1, 131.7, 130.4, 129.4, 128.6, 127.6, 127.1, 126.3, 125.6, 124.5, 119.3, 115.9, 114.9, 60.3 (C_7), 45.2, 43.0, 38.0, 30.7, 23.6, 21.4 (C_9), 14.5 (C_8).**IR (neat): ν_{max}/cm^{-1}:** 3659 (NH), 1775 (CO_2Et), 1692 (N-CO). **MS (pNSI):** 687.22 (100%, $[M+NH_4]^+$), 1356.41 (27%, $[2M+NH_4]^+$), 692.17 (12%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{34}H_{35}N_6O_8S$ $[M+H]^+$: 687.2232; observed: 687.2229.

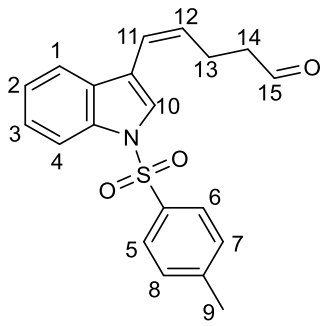
(*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol (110)



DIBAL-H (1.0 M in toluene, 11.45 mL, 11.45 mmol) was added to a solution of ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate **90** (1.300 g, 3.27 mmol) in toluene (20 mL) at -78 ^{o}C under nitrogen. The reaction mixture was stirred at room temperature for 3 h, slowly hydrolysed with 1.0 M of hydrochloric acid (20 mL). The organic layer was extracted with EtOAc (2 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude colourless oil product which was purified by column chromatography (petrol / ethyl acetate 2:1) to yield (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol in (1.009 g, 2.83 mmol, 87%) as a colourless oil.

R_f: 0.26 (petrol / ethyl acetate 2:1).**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.98 (d, *J* = 8.3 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.77 (d, *J* = 8.5 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.61 (s, 1H, H_{10}), 7.50 (d, *J* = 6.4 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.32 (t, *J* = 7.3 Hz , 1H, $H_{(2 \text{ or } 3)}$), 7.23 (t, *J* = 7.3 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.18 (d, *J* = 8.5 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 6.42 (d, *J* = 11.7 Hz, 1H, H_{11}), 5.85 (dt, *J* = 11.7, 7.3 Hz, 1H, H_{12}), 3.69 (t, *J* = 6.4 Hz, 2H, H_{15}), 2.42 (m, 2H, H_{14}), 2.29 (s, 3H, H_9), 1.76 (dt, *J* =13.2, 10.6 Hz, 1H, H_{13}).**^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 145.1, 135.1, 134.5, 133.7, 130.7, 129.8, 126.8, 124.9, 123.7, 123.3, 119.5, 119.1, 118.1, 113.6, 62.4 (C_{15}), 32.4 ($C_{13 \text{ or } 14}$), 26.13 ($C_{13 \text{ or } 14}$), 21.6 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 3335 (OH), 2972 (CH).**MS (p NSI):** 373.15 (100 %, $[M+NH_4]^+$), 356.13 (63%, $[M+H]^+$), 201.11 (21%, $[M\text{-}Ts]^+$); **HRMS (p NSI):** calcd $C_{20}H_{22}NO_3S$ $[M+H]^+$: 356.1315; observed: 356.1317.

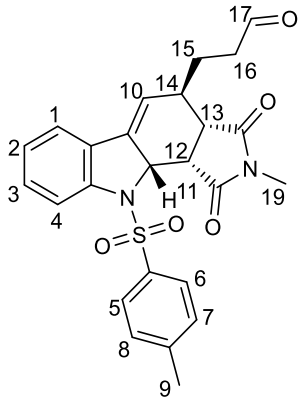
(Z)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enal (111)



DMSO (6.68 mmol, 0.47 mL) was added dropwise at -78 °C to a stirred solution oxalyl chloride (3.20 mL, 0.27 mmol) in DCM (5 mL). After 30 min, a solution of (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol **110** (0.950 g, 2.67 mmol) in DCM (10 mL) was added. The reaction mixture left to stir for 30 min at -78 °C followed by the addition of triethylamine (1.48 mL, 10.68 mmol). The reaction mixture was warmed to r.t. and stirred for 2 h, quenched with saturated $NaHCO_{3\,(aq)}$ (10 mL). The organic layer was extracted with DCM (3 x 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude yellow product which was purified by column chromatography (petrol/ ethyl acetate 2:1) to yield (Z)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enal in (0.659 g, 1.86 mmol, 70%) as a colourless oil.

R_f: 0.8 (petrol / ethyl acetate 2:1).**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 9.78 (s, 1H, H_{15}), 7.99 (d, 1H, *J* = 7.4 Hz, $H_{(1or\,4)}$), 7.77 (d, 2H, *J* = 7.4 Hz, $H_{(5,6)\,or\,(7,8)}$), 7.55 (s, 1H, H_{10}), 7.48 (d, 1H, *J* = 7.4 Hz, $H_{(1or\,4)}$), 7.32 (t, 1H, 7.4Hz ,$H_{(2\,or\,3)}$), 7.24 (t, 1H, 7.4Hz, $H_{(2\,or\,3)}$), 7.19 (d, 2H, *J*=7.4Hz, $H_{(5,6)\,or\,(7,8)}$), 6.45 (d, 1H, *J* = 11.7 Hz, H_{11}), 5.85 (dt, 1H, *J* = 11.7, 7.3 Hz, H_{12}), 2.65 - 2.95 (m, 4H, $H_{(13\,and\,14)}$), 2.29 (s, 3H, H_9).**^{13}C NMR (100 MHz, $CDCl_3$):** δ_H 201.8 (CHO), 145.1, 135.0, 134.6, 131.9, 130.7, 129.9, 126.8, 125.1, 123.6, 123.4, 119.6, 119.1, 118.7, 113.7, 43.5, 22.3, 21.6 (C_9), **IR (neat): ν_{max}/cm^{-1}:** 2890 (CHO), 1719 (CO). **HRMS (pNSI):** calcd $C_{20}H_{20}NO_3S$ $[M+H]^+$: 354.1158; observed: 354.1162.

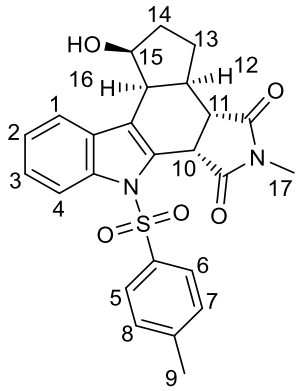
3-((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanal (112)



DMSO (0.04 mL, 0.69 mmol) was added dropwise at -78 °C to a stirred solution of oxalyl chloride (0.02 mL, 0.33 mmol) in DCM (2 mL). After 30 min, a solution of (3a*S*,4*R*,10a*S*,10b*S*)-4-(3-hydroxypropyl)- 2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo [3,4-*a*] carbazole-1,3 (2*H*,3a*H*)-dione **117** (0.130 g, 0.27 mmol) in DCM (8 mL) was added. The reaction mixture left to stir for 30 min at -78 °C followed by the addition of triethylamine (0.15 mL, 1.11 mmol). The reaction mixture was warmed to r.t. and stirred for 2 h, quenched with saturated $NaHCO_{3\,(aq)}$ (10 mL). The organic layer was extracted with DCM (1 x 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude yellow solid product which was purified by column chromatography (petrol / ethyl acetate 1:1) to yield 3-((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanal in (0.086 g, 0.185 mmol, 69%) as a white solid.

Mp. 135 – 137 °C. **R_f** : 0.30 (petrol / ethyl acetate 1:1)**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 9.74 (s, 1H, H_{17}), 7.79 (d, *J* = 7.1 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.62 (d, *J* = 7.1 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.25 - 7.21 (m, 4H, Ar), 6.95 (t, *J* = 7.1 Hz, 1H, $H_{(2 \text{ or } 3)}$), 6.08 (dd, *J* = 3.3, 6.8 Hz, 1H, H_{10}), 4.85 (dd, *J* = 3.3, 7.2 Hz, 1H, H_{11}), 4.16 (t, *J* = 7.9 Hz, 1H, H_{12}), 3.12 - 3.03 (m, 2H, $H_{(14, 13)}$), 2.81 (s, 3H, H_{19}), 2.63 - 2.49 (m, 2H, H_{16}), 2.33 (s, 3H, H_9), 1.90 – 1.74 (m, 2H, H_{15}). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 200.9 (C_{17}), 178.7 (CO), 173.8 (CO), 144.7, 144.2, 136.8, 133.9, 130.7, 130.0, 127.6, 126.6, 123.9, 121.0, 116.2, 115.4, 59.9 (C_{16}), 44.1 (C_{11}), 43.0 (C_{12}), 42.7 (C_{13}), 37.1 (C_{14}), 25.3 ($C_{15,}$), 25.2 (C_{19}), 21.6 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 1697 (CHO), 2925 (C=C). **MS (pNSI):** 482.14 (12%, $[M+NH_4]^+$), 487.17(9%, $[M+Na]^+$) ; **HRMS (pNSI):** calcd $C_{25}H_{25}N_2O_5S$ $[M+H]^+$: 465.1479 ; observed: 465.1486.

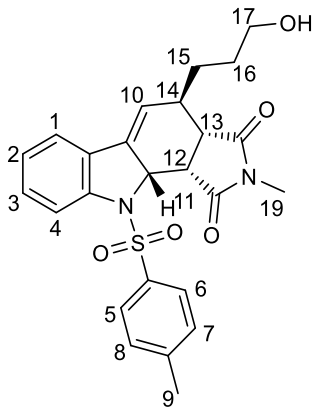
(3a*R*,3b*S*,6*R*,6a*S*,11b*R*)-6-hydroxy-2-methyl-11-tosyl 3a,3b,4,5,6,6a,11,11b-octahydro-1*H*-cyclopenta[*c*]pyrrolo[3,4 *a*] carbazole-1,3(2*H*)-dione (113)



Dimethylaluminum chloride (1.0 M in hexane, 0.09 mL, 0.09 mmol) was added dropwise at -78 °C to a solution of 3-((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl-1,2,3, 3a ,4,10, 10a,10b-octahydropyrrolo[3,4-a] carbazol-4-yl)propanal **112** (0.045 g, 0.09 mmol) in DCM (5 mL). The reaction mixture left to stir for 30 min, quenched with saturated $NaHCO_{3\ (aq)}$ (5mL). The organic layer was extracted with DCM (1 x 20 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude white solid product which was purified by column chromatography (petrol / ethyl acetate 1:1) to yield (3a*R*,3b*S*,6*R*,6a*S*,11b*R*)-6-hydroxy-2-methyl-11-tosyl-3a,3b,4,5,6,6a,11,11b-octahydro-1*H*-cyclopenta[*c*]pyrrolo[3,4-*a*]carbazole-1,3(2*H*)-dione in (0.038 g, 0.08 mmol, 89%) as a white solid.

Mp. 240 – 242 °C. **R_f** : 0.6 (petrol / ethyl acetate 1:1)**.^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.91 (d, *J* =7.3 Hz, 1H, $H_{(1\ or\ 4)}$), 7.85 (d, *J* = 7.3 Hz, 2H, $H_{(5,6)\ or\ (7,8)}$), 7.42 (d, *J* = 7.3 Hz, 1H, $H_{(1\ or\ 4)}$), 7.29 (t, *J* =7.3 Hz, 1H, $H_{(2\ or\ 3)}$), 7.24 - 7.20 (m, 3H, $H_{(5,6)\ or\ (7,8)}$, $H_{(2\ or\ 3)}$), 4.93 (d, *J* = 7.3 Hz, 1H, H_{10}), 4.50 (t, *J* = 6.1 Hz, 1H, H_{16}), 3.30 (dd, *J* = 7,3, 6.8 Hz, 1H, H_{11}), 3.19 - 3.16 (m, 1H, H_{15}), 3.02 (s, 3H, H_{17}), 2.38 - 2.33 (m, 4H, $H_{(14,\ 9)}$), 2.25 - 2.02 (m, 4H, $H_{(12,13,14)}$). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ_C 178.4 (CO), 174.1 (CO), 145.1, 137.3, 135.5, 130.6, 129.3, 128.3, 127.1, 125.8, 123.8, 118.8, 117.3, 115.5, 73.5 (C_{16}), 46.4 (C_{11}), 44.2 (C_{15}), 41.8 (C_{10}), 38.9 (C_{12}), 33.2 (C_{13}), 27.6 (C_{14}), 25.0 (C_{17}), 21.9 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 3655 (br, OH), 2980 (CH).**MS (pNSI):** 465.14 (100 %, $[M+H]^+$), 482.17 (75 %, $[M+NH_4]^+$) ; **HRMS (pNSI):** calcd $C_{25}H_{25}N_2O_5S$ $[M+H]^+$: 465.1479 ; observed: 465.1484.

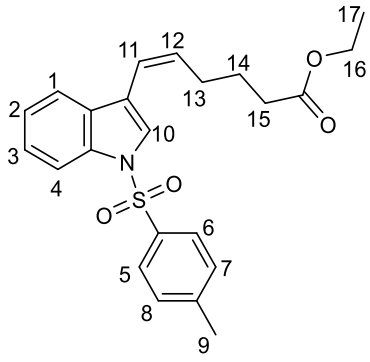
(3a*S*,4*R*,10a*S*,10b*S*)-4-(3-hydroxypropyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (117)



Dimethylaluminum chloride (1.0 M in hexane, 1.8 mL, 1.8 mmol) was added dropwise at -78 °C to a solution of *N*-methylmaleimide (0.100 g, 0.90 mmol) in DCM (10 mL). The mixture left to stir for 10 min followed by the addition of (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-en-1-ol **110** (0.32 g, 0.90 mmol) in DCM (10 mL). The reaction mixture was refluxed for 48 h, quenched with saturated $NaHCO_{3\,(aq)}$ (25 mL). The organic layer was extracted with DCM (1 x 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude white solid product which purified by column chromatography (petrol / ethyl acetate 1:1 gradient to 100 ethyl acetate) to yield (3a*S*,4*R*,10a*S*,10b*S*)-4-(3-hydroxypropyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.313 g, 0.67 mmol, 75%) as a white solid.

Mp. 112 – 114 °C. **R_f** : 0.3 (petrol / ethyl acetate 2:1).**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.79 (d, *J* = 7.4 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.59 (d, *J* = 7.2 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.24 - 7.20 (m, 4H, Ar), 6.96 (t, *J* = 7.2 Hz, 1H, $H_{(2 \text{ or } 3)}$), 6.14 (dd, *J* = 3.6, 7.3 Hz, 1H, H_{10}), 4.58 (dd, *J* = 3.6, 7.1 Hz, 1H, H_{11}), 4.14 (t, *J* = 7.9 Hz, 1H, H_{12}), 3.65 (t, *J* = 6.5 Hz, 2H, H_{17}), 3.15 - 3.05 (m, 2H, $H_{(13, 14)}$), 2.82 (s, 3H, H_{19}), 2.35 (s, 3H, H_9), 1.70 - 1.54 (m, 4H, $H_{(15, 16)}$).**^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 178.8 (CO), 174.1 (CO), 144.7, 144.2, 135.8, 134.2, 130.3, 129.9, 127.6, 126.9, 123.9, 120.9, 117.5, 115.4, 62.4 (C_{17}), 59.9 (C_{11}), 44.2 (C_{12}), 43.2 (C_{13}), 37.6 (C_{14}), 31.5 ($C_{15 \text{ or } 16}$), 29.7 ($C_{15 \text{ or } 16}$), 25.1 (C_{19}), 21.6 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 3657 (br, OH), 1639 (N-CO).**MS (pNSI):** 467.16 (100%, $[M+H]^+$), 484.18 (50%, $[M+Na]^+$), 312.14 (42%, $[M\text{-}Ts]^+$); **HRMS (pNSI):** calcd $C_{25}H_{27}N_2O_5S$ $[M+H]^+$: 467.1635 ; observed: 467.1628.

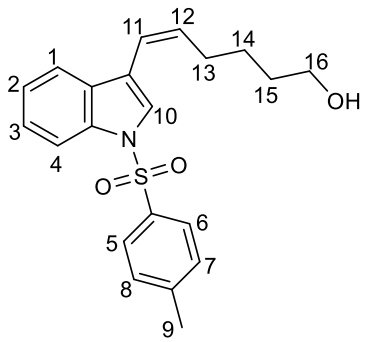
Ethyl (*Z*)-6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoate (118)



6-(1-Tosyl-1*H*-indol-3-yl)hex-5-enoic acid **129** (0.516 g, 1.34 mmol) was dissolved in anhydrous EtOH (35 mL) and treated with concentrated sulfuric acid (0.2 mL). After the solution was refluxed for 1.5 h, the reaction mixture was added to saturated $NaHCO_{3\ (aq)}$ (15 mL) and extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude as an orange solid which was purified by column chromatography in (petrol: ethyl acetate 10:1) to yield a (*Z*)-6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoate in (0.308 g, 0.75 mmol, 56%) as a colourless oil.

R_f: 0.7 (petrol / ethyl acetate 7:3).**^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.97 (d, *J* = 7.9 Hz, 1H, $H_{(1\ or\ 4)}$), 7.76 (d, *J* = 8.2 Hz, 2H, $H_{(5,\ 6)\ or\ (7,8)}$), 7.51 (s, 1H, H_{10}), 7.49 (d, *J* = 7.9 Hz, 1H, $H_{(1\ or\ 4)}$), 7.32 (t, *J* = 7.9 Hz, 1H, $H_{(2\ or\ 3)}$), 7.25 (t, *J* = 7.9 Hz, 1H, $H_{(2\ or\ 3)}$), 7.20 (d, *J* = 8.2 Hz, 2H, $H_{(5,6)\ or\ (7,8)}$), 6.42 (d, *J* = 11.5 Hz, 1H, H_{11}), 5.77 (dt, *J* = 11.5, 7.5 Hz, 1H, H_{12}), 4.10 (q, *J* = 6.8 Hz, 2H, H_{16}), 2.39 - 2.31 (m, 4H, $H_{(14,15)}$), 2.30 (s, 3H, H_9), 1.85 – 1.77 (m, 2H, H_{13}), 1.21 (t, *J* = 6.8 Hz, 3H, H_{17}). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 173.5 (CO_2Et), 145.0, 135.1, 133.4, 131.3, 130.8, 129.9, 126.9, 124.9 123.5, 123.3, 119.6, 119.0, 118.5, 113.6, 60.3 (C_{16}), 33.7, 29.1, 24.7, 21.5 (C_9), 14.3 (C_{17}). **IR (neat): ν_{max}/cm^{-1}:** 1727 (CO), 1597 (C=C). **MS (pNSI):** 429.18 (100%, $[M+NH_4]^+$), 412.15 (63%, $[M+H]^+$), 840.33 (15%, $[2M+NH_4]^+$); **HRMS (pNSI):** calcd $C_{23}H_{26}NO_4S$ $[M+H]^+$: 412.1577; 412.1575.

(*Z*)-6-(1-Tosyl-1*H*-indol-3-yl)hex-5-en-1-ol (119)



Method A

Lithium aluminum hydride (1.0 M in THF, 1.01 mL, 1.01 mmol) was added to a solution of 6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoic acid **129** (0.156 g, 0.4 mmol) in THF (10 mL) at -78 ^{o}C under nitrogen. The reaction mixture was stirred at room temperature for 24 h. The organic layer was extracted with EtOAc (2 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product as a colourless oil. Purification of the crude reaction mixture gave the desired (*Z*)-6-(1-tosyl-1*H*-indol-3-yl)hex-5-en-1-ol in (0.043 g, 0.12 mmol, 30%) as a colourless oil.

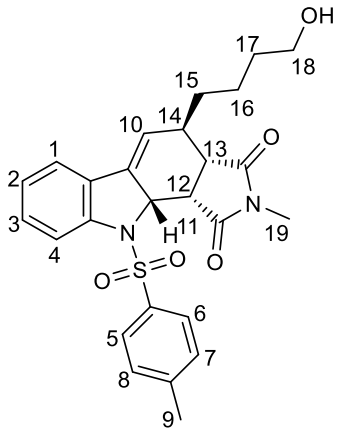
Method A

DIBAL-H (1.0 M in toluene, 1.55 mL, 3.40 mmol) was added to a solution of ethyl 6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoate **118** (0.183 g, 0.44 mmol) in toluene (10 mL) at -78 ^{o}C under nitrogen. The reaction mixture was stirred at room temperature for 3 h, slowly hydrolysed with 1.0 M of hydrochloric acid (5 mL). The organic layer was extracted with EtOAc (2 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to yield (*Z*)-6-(1-tosyl-1*H*-indol-3-yl)hex-5-en-1-ol in (0.153 g, 0.41 mmol, 94%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.90 (d, *J* = 7.5 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.67 (d, *J* = 7.5 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.45 (s, 1H, H_{10}), 7.41 (d, *J* = 7.5 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.23 (t, *J* = 7.5 Hz , 1H, $H_{(2 \text{ or } 3)}$), 7.14 (t, *J* = 7.5 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.10 (d, *J* = 7.5 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 6.32 (d, *J* = 10.1 Hz, 1H, H_{11}), 5.73 (dt, *J* = 10.1, 7.5 Hz, 1H, H_{12}), 3.57 (t, *J* = 7.5 Hz, 2H, H_{16}), 2.26 (dt, *J* = 7.5, 6.4 Hz, 2H, H_{13}), 2.21 (s, 3H, H_9), 1.61 – 1.44 (m, 4H, $H_{(14,15)}$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 144.9, 135.1, 134.6, 134.3, 130.8, 129.8, 126.8, 124.9, 123.3, 119.5119.1, 117.8, 113.6, 62.5, 32.2, 29.3, 25.6, 21.5. **IR (neat) ν_{max}/cm^{-1}:** 3435 (OH), 2972 (CH).

MS (pNSI): 387.1738 (100%, $[M+NH_4]^+$), 756.3138 (45%, $[2M+NH_4]^+$); **HRMS (pNSI):** calcd $C_{21}H_{27}N_2O_3S$ $[M+NH_4]^+$: 387.1737; observed: 387.1738.

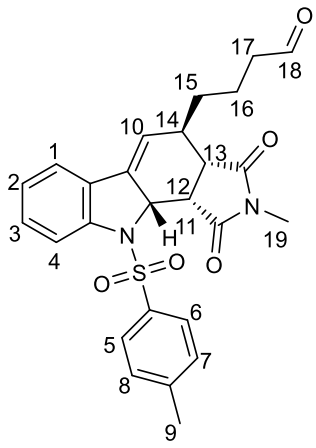
(3a*S*,4*R*,10a*S*,10b*S*)-4-(4-hydroxybutyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (120)



Dimethylaluminum chloride (1.0 M in hexane, 0.58 mL, 0. 58 mmol) was added dropwise at -78 °C to a solution of *N*-methylmaleimide (0.0325 g, 0.29 mmol) in DCM (5 mL). The mixture left to stir for 10 min followed by the addition of (*Z*)-6-(1-tosyl-1*H*-indol-3-yl)hex-5-en-1-ol **119** (0.108 g, 0.29 mmol,) in DCM (5 mL). The reaction mixture allowed to worm slowly to reflux for 48 h, quenched with saturated $NaHCO_{3\,(aq)}$ (10 mL). The organic layer was extracted with DCM (2 x 25 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the white crude solid product which was purified by column chromatography (petrol / ethyl acetate 1:1 gradient to 100 EtOAc) to yield (3a*S*,4*R*,10a*S*,10b*S*)-4-(4-hydroxybutyl)-2-methyl-10-tosyl-4,10,10a,10b tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.1093 g, 0.23 mmol, 78%) as a white solid.

Mp. 189 – 201 °C. **R_f**: 0.26 (petrol / ethyl acetate 1:1). (**^{1}H NMR 300 MHz, $CDCl_3$):** δ_H 7.73 (d, *J* = 7.7 Hz, 2H, $H_{(5,6)\text{ or }(7,8)}$), 7.53 (d, *J* = 7.9 Hz, 1H, $H_{(1\text{ or }4)}$), 7.20 - 7.15 (m, 4H, Ar), 6.96 (t, *J* = 7.9 Hz, 1H, $H_{(2\text{ or }3)}$), 6.08 (dd, *J* = 3.0, 6.9 Hz, 1H, H_{10}), 4.77 (dd, *J* = 3.0, 7.5 Hz, 1H, H_{11}), 4.06 (t, *J* = 7.5 Hz, 1H, H_{12}), 3.57 (t, *J* = 6.3 Hz, 2H, H_{18}), 3.15 - 3.05 (m, 2H, $H_{(13,\,14)}$), 2.76 (s, 3H, H_{19}), 2.30 (s, 3H, H_9), 1.56 - 1.39 (m, 6H, $H_{(15,16,17)}$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 178.8 (CO), 173.9 (CO), 144.6, 144.0, 135.6, 134.0, 130.3, 129.8, 127.4, 126.9, 123.8, 120.9, 117.6, 115.4, 62.4 (C_{18}), 59.9 (C_{11}), 44.2 (C_{12}), 43.2 (C_{13}), 37.6 (C_{14}), 33.3 ($C_{15\text{ or }16\text{ or }17}$), 31.5 ($C_{15\text{ or }16\text{ or }17}$), 25.1 ($C_{19}$), 24.8 ($C_{15\text{ or }16\text{ or }17}$), 21.6 ($C_9$). **IR (neat): ν_{max}/cm^{-1}:** 3636 (OH), 2981 (Ar, CH), 1727 (CO). **MS (pNSI):** 983.3311 (100%, $[2M+Na]^+$), 503.1598 (28%, $[M+Na]^+$), 498.2047 (15%, $[M+NH_4]^+$); **HRMS (pNSI):** calcd $C_{26}H_{29}N_2O_5S$ $[M+H]^+$: 481.1792; observed: 481.1786.

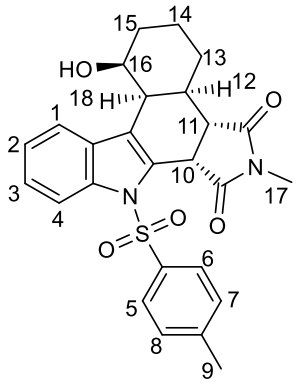
4-((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)butanal (121)



DMSO (0.07 mL, 1.04 mmol) was added dropwise at -78 °C to a stirred solution of oxalyl chloride (0.1 mL 0.49 mmol) in DCM (2 mL). After 30 min a solution of (3a*S*,4*R*,10a*S*,10b*S*) -4-(4-hydroxybutyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo [3,4-*a*] carbazole-1,3(2*H*,3a*H*)-dione **121** (0.200 g, 0.42 mmol) in DCM (8 mL) was added . The reaction mixture left to stir for 30 min at -78 °C followed by the addition of triethylamine (0.23 mL, 1.68 mmol). The reaction mixture was warmed to r.t. and stirred for 2 h, quenched with saturated $NaHCO_{3\,(aq)}$ (10 mL). The organic layer was extracted with DCM (2 x 25 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude yellow solid product which was purified by column chromatography (petrol / ethyl acetate 1:1) to yield 4-((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)butanal in (0.1588 g, 0.33 mmol, 79%) as a white solid.

Mp. 171 – 173 °C. **R_f** : 0.3 (petrol / ethyl acetate 1:1)**. ^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 9.74 (t, *J* = 1.5 Hz, 1H, H_{18}), 7.73 (d, *J* = 8.0 Hz, 2H, $H_{(5,6)\text{ or }(7,8)}$), 7.54 (d, *J* = 8.0 Hz, 1H, $H_{(1\text{ or }4)}$), 7.21 - 7.16 (m, 4H, Ar), 6.90 (t, *J* = 8.0 Hz, 1H, $H_{(2\text{ or }3)}$), 6.07 (dd, *J* = 3.4, 7.2 Hz, 1H, H_{10}), 4.77 (dd, *J* = 3.4, 7.7 Hz, 1H, H_{11}), 4.06 (t, *J* = 7.7 Hz, 1H, H_{12}), 3.10 - 2.96 (m, 2H, $H_{(14,\ 13)}$), 2.77 (s, 3H, H_{19}), 2.63 - 2.49 (m, 2H, H_{16}), 2.30 (s, 3H, H_9), 1.70 – 1.43 (m, 4H, $H_{(15,16)}$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 201.4 (C_{18}), 178.6 (CO), 173.8 (CO), 144.5, 144.2, 136.9, 134.0, 130.4, 129.9, 127.5, 126.7, 123.7, 120.9, 116.8, 115.4, 59.9 (C_{17}), 44.1 (C_{11}), 43.0 (C_{12}), 42.9 (C_{13}), 37.1 (C_{14}), 32.7 (C_{15}), 25.1 ($C_{16,}$), 21.5 (C_{19}), 20.9 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 1699 (CHO), 1773 (CO), 2944 (CH, Ar). **HRMS (pNSI):** calcd $C_{26}H_{27}N_2O_5S$ $[M+H]^+$: 479.1826; observed: 479.1628.

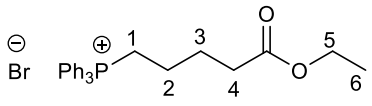
(3a*S*,3b*R*,7*S*,7a*S*,12b*S*)-7-hydroxy-2-methyl-12-tosyl-3b,4,5,6,7,7a,12,12b-octahydrobenzo[*c*]pyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (122)



Dimethylaluminum chloride (1.0 M in hexane, 0.06 mL, 0.06 mmol) was added dropwise at -78 °C to a solution of -((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo [3,4-a]carbazol-4-yl)butanal **120** (0.03 g, 0.06 mmol) in DCM (5 mL). The reaction mixture left to stir for three hours at 25 °C, quenched with saturated $NaHCO_{3\,(aq)}$ (5mL). The organic layer was extracted with DCM (1 x 20 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude white solid product which was purified by column chromatography (petrol / ethyl acetate 1:1) to yield (3a*S*,3b*R*,7*S*,7a*S*,12b*S*)-7-hydroxy-2-methyl-12-tosyl-3b,4,5,6,7,7a,12,12b-octahydrobenzo[*c*]pyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0165 g, 0.034 mmol, 57%) as a white solid.

Mp. 265 – 267 °C. **R_f** : 0.6 (petrol / ethyl acetate 1:1).**^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.96 – 7.87 (m, 1H, $H_{(1\text{ or }4)}$), 7.65 (dd, *J* = 8.2, 1.3 Hz, 2H, $H_{(5,6)\text{ or }(7,8)}$), 7.31 – 7.09 (m, 6H, Ar), 4.89 (d, *J* = 7.2 Hz, 1H, H_{10}), 3.99 (s, 1H, OH), 3.73 (dd, *J* = 12.4, 7.2 Hz, 1H, H_{11}), 3.00 (dd, *J* = 5.2, 2.7 Hz, 1H, H_{18}), 2.94 (s, 3H, H_{17}), 2.40 - 2.25 (m, 4H, $H_{(16,\ 9)}$), 2.00 – 1.42 (m, 7H, $H_{(12,\ 13,14,15)}$). **^{13}C NMR (126 MHz, $CDCl_3$):** δ_C 177.7 (CO), 174.1 (CO), 145.0, 137.8, 135.2, 130.1, 129.6, 128.1, 126.6, 125.3, 123.9, 121.4, 118.7, 115.8, 67.6, 43.3, 42.1, 38.6, 34.2, 32.0, 26.8, 24.9, 21.5 (C_{17}), 14.5 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 3655 (OH), 2980 (CH). **MS (pNSI):** 479.16 (100%, $[M+H]^+$), 501.14 (85%, $[M+Na]^+$). 496.18 $[M+NH_4]^+$); **HRMS (pNSI):** calcd $C_{26}H_{27}N_2O_5S$ $[M+H]^+$: 479.1635; observed: 479.1629.

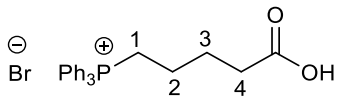
(5-Ethoxy-5-oxopentyl) triphenylphosphonium bromide (124)



Triphenylphosphine (2.000 g, 7.60 mmol) was dissolved in acetonitrile (10 mL). Ethyl 5-bromovalerate **123** (1.20 mL, 7.6 mmol) was added. The mixture was refluxed for 48 h. The resultant white precipitate was purified by column chromatography (petrol / ethanol 3:2) to give the desired compound in (5.83 mmol, 2.750 g, 77%) as white foam.

Mp. 162 – 164 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.84 – 7.74 (m, 9H, Ar), 7.69 - 7.64 (m, 6H, Ar), 3.99 (q, *J* = 6.9 Hz, 2H, H_5), 3.88 - 3.81 (m, 2H, H_1), 2.35 (t, *J* = 6.3 Hz, 2H, H_4), 2.01 – 1.94 (m, 2H, $H_{(2\ or\ 3)}$), 1.74 - 1.63 (m, 2H, $H_{(2\ or\ 3)}$), 1.14 (t, *J* = 6.9 Hz, 2H, H_6). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 173.2 (CO_2Et), 135.1 (J_{cp} = 2.8 Hz), 133.8 (J_{cp} = 10.3 Hz), 130.5 (J_{cp} = 12.9 Hz), 118.1 (J_{cp} = 85.7 Hz), 60.4 (C_4), 33.4, 25.5 (J_{cp} = 19.2 Hz), 22.6 (J_{cp} = 52.5 Hz), 21.9 (J_{cp} = 4.9 Hz), 14.2 (C_5). **IR (neat): ν_{max}/cm^{-1}:** 2890 (CH), 1778 (CO_2Et), 1598 (C=C, Ar).

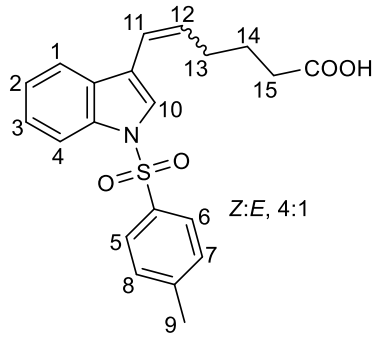
(4-Carboxybutyl) triphenylphosphonium bromide (127)



A solution of triphenylphosphine (3.18 g, 12.10 mmol) and 5-bromovaleric acid **126** (2.00 g, 11.04 mmol) in acetonitrile (20 mL) was refluxed for 48 h. The resultant white precipitate was filtered off with suction and washed with ether (2 X 50 mL) to give the desired compound in (4.6321 g, 10.44 mmol, 95%) as white crystals.

Mp. 204 – 206 ^{o}C (lit. 209 – 210 ^{o}C).[87] **^{1}H NMR (400 MHz, CDCl$_3$):** δ_H 7.79 - 7.63 (m, 15H, Ar), 5.75 (br, OH), 3.63 - 3.56 (m, 2H, H$_1$), 2.65 (t, *J* = 6.5 Hz, 2H, H$_4$), 1.95 – 1.92 (m, 2H, H$_{(2 \text{ or } 3)}$), 1.76 – 1.67 (m, 2H, H$_{(2 \text{ or } 3)}$). **^{13}C NMR (100 MHz, CDCl$_3$):** δ_C 175.0 (CO_2H), 135.2 (J_{cp} = 4.0 Hz), 133.7 (J_{cp} = 10.2 Hz), 130.7 (J_{cp} = 12.1 Hz), 118.1 (J_{cp} = 85.7 Hz), 33.7, 25.5 (J_{cp} = 19.4 Hz), 22.6 (J_{cp} = 45.9 Hz), 21.5 (J_{cp} = 4.8 Hz). **IR (neat): ν_{max}/cm^{-1}:** 3659 (OH), 2980 (CH), 1767 (CO). **HRMS (pNSI):** calcd $C_{23}H_{24}O_2P$ $[M\text{-}Br]^+$: 363.1508; observed: 363.1506.

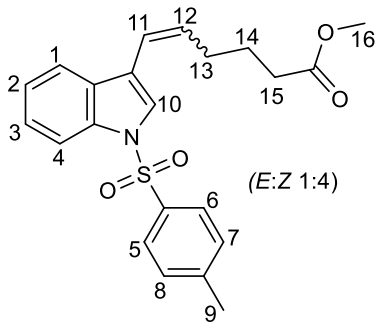
6-(1-Tosyl-1*H*-indol-3-yl)hex-5-enoic acid (129)



In a Schlenk flask, (4-carboxybutyl) triphenylphosphonium bromide **127** (3.60 g, 8.12 mmol) was dissolved in THF (20 mL) and cooled to -78 ºC. Sodium bis (trimethylsilyl) amide (1.0 M in THF, 16.24 mL, 16.24 mmol) was added dropwise over 10 min. The mixture was warmed to 0 ºC and left to stir for 1 h. In a separate round bottomed flask, 1-(toluene-4-sulfonyl)–1*H*-Indol-3-carbaldehyde **89** (1.69 g, 7.38 mmol) was dissolved in THF (10 mL) and transferred via cannula to the solution. The reaction mixture was stirred at room temperature for 4 h, quenched with water (20 mL). The aqueous layer was acidified with 2.0 M of HCl (20 mL) to pH = 1. The organic layer was extracted with EtOAc (3 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude oil product was purified by column chromatography (petrol / ethyl acetate 7:3) to give a 4:1 mixture of *(Z)* and *(E)*-6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoic acid in (1.8122 g, 4.72 mmol, 64%) as a colourless oil.

R_f *:* 0.25 (petrol / ethyl acetate 1:1).**^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.91 (d, *J* = 7.4 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.69 (d, *J* = 7.6 Hz, 2H, $H_{(5, 6) \text{ or } (7,8)}$), 7.45 (s, 1H, H_{10}), 7.45 – 7.42 (d, *J* = 7.4 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.25 (t, *J* = 7.4 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.20 – 7.12 (m, 3H, $H_{(5, 6) \text{ or } (7, 8) \text{ and } (2 \text{ or } 3)}$), 6.37 (d, *J* = 10.9 Hz, 1H, H_{11}), 5.71 (dt, *J* = 10.9, 6.5 Hz, 1H, H_{12}), 2. 36 - 2.31 (m, 4H, $H_{(14, 15)}$), 2.26 (s, 3H, H_9), 1.77 (dt, *J* = 6.5, 7.9 Hz, 1H, H_{13}).**^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 179.6 (CO), 179.2 (CO), 145.0, 135.5, 135.2, 134.7, 133.0, 131.0, 130.8, 129.9, 129.2, 126.9, 124.9, 123.4, 123.1, 121.4, 120.7, 120.4, 119.5, 119.0, 118.7, 113.7, 33.4, 32.8, 28.9, 24.3, 21.6 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 3659 (OH), 2979 (CH), 1707 (CO). **MS (pNSI):** 401.15 (100%, $[M+NH_4]^+$), 784.27 (52%, $[2M+NH_4]^+$), (15%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{21}H_{25}N_2O_4S$ $[M+NH_4]^+$: 401.1530; observed: 401.1528.

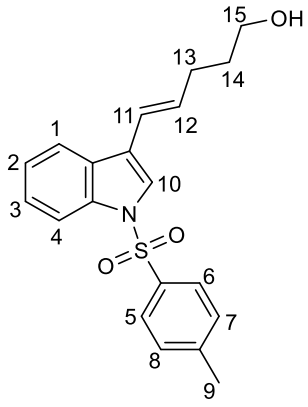
Methyl 6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoate (130)



6-(1-Tosyl-1*H*-indol-3-yl)hex-5-enoic acid **129** (0.10 g, 0.26 mmol) and MeI (17mL, 0.28 mmol) were added successively to a suspension of K_2CO_3 (0.055 g, 0.40 mmol) in DMF (5 mL). The reaction mixture left to stir for 2 h at room temperature. The mixture was poured into water and extracted with EtOAc (2 x 25 mL) washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude reaction mixture was purified by column chromatography (petrol / ethyl acetate 7:3) to give methyl 6-(1-tosyl-1*H*-indol-3-yl)hex-5-enoate as a mixture of (*E*:*Z*, 1:4) in (0.965 g, 0.24 mmol, 93%) as a colourless oil.

R_f : 0. 8 (petrol / ethyl acetate 7:3). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.91 (d, *J* = 7.5 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.70 (d, *J* = 7.7 Hz, 2H, $H_{(5, 6) \text{ or } (7,8)}$), 7.44 (s, 1H, H_{10}), 7.45 – 7.42 (m, 1H, $H_{(1 \text{ or } 4)}$), 7.19 – 7.11 (m, 3H, $H_{(2 \text{ or } 3)}$, $H_{(5, 6) \text{ or } (7, 8)}$), 6.36 (d, *J* = 11.2 Hz, 1H, H_{11}), 5.70 (dt, *J* = 11.2, 7.5 Hz, 1H, H_{12}), 3.58 (s, 3H, H_{16}), 2.33 – 2.24 (m, 7H, $H_{(9, 14, 15)}$), 1.75 (dt, *J* = 6.7, 6.3 Hz, 3H, H_{16}).**^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 173.9 (CO), 144.9, 135.1, 134.6, 133.3, 130.8, 129.8, 126.8, 125.0,124.8, 123.4, 119.6, 119.0, 118.5, 113.6, 51.6 (C_{16}), 33.5, 29.0, 24.7, 21.6 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 1727 (CO), 1597 (C=C).

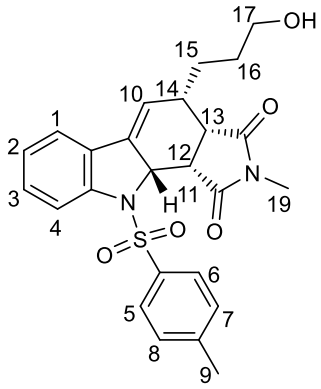
(*E*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol (134)



DIBAL-H (1.0 M in toluene, 1.5 mL, 1.5 mmol) was added to a solution of ethyl (*E*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate **141** (0.170 g, 0.43 mmol) in dry toluene (10 mL) at -78 ^{o}C under nitrogen. The reaction mixture was stirred at room temperature for 3 h, slowly hydrolysed with 1.0 M of hydrochloric acid (20 mL). The organic layer was extracted with EtOAc (2 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude cooler less oil product which was purified by column chromatography (petrol / ethyl acetate 1:1) to yield (*E*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol in (0.1461 g, 0.41 mmol, 96%) as a colourless oil.

R_f: 0.3 (petrol / ethyl acetate 1:1).**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.91 (d, *J* = 7.3 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.67 (d, *J* = 7.4 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.61 (d, *J* = 7.3 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.44 (s, 1H, H_{10}), 7.26 – 7.14 (m, 2H, $H_{(2,3)}$) 7.11 (d, *J* = 7.4 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 6.39 (d, *J* = 16.5 Hz, 1H, H_{11}), 6.20 (dt, *J* = 16.5, 6.5 Hz, 1H, H_{12}), 3.64 (t, *J* = 6.3 Hz, 2H, H_{15}), 2.29 – 2.22 (m, 5H, $H_{(14, 9)}$), 1.69 (dt, *J* = 6.5, 13.9 Hz, 1H, H_{13}).**^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 144.8, 135.4, 135.2, 131.7, 129.8, 129.2, 126.7, 124.8, 123.4, 122.8, 120.8, 120.7, 120.3, 113.7, 62.3 (C_{15}), 32.2 (C_{13}), 29.8 (C_{14}), 21.6 (C_9) **IR (neat): ν_{max}/cm^{-1}:** 3335 (OH), 2972 (CH).

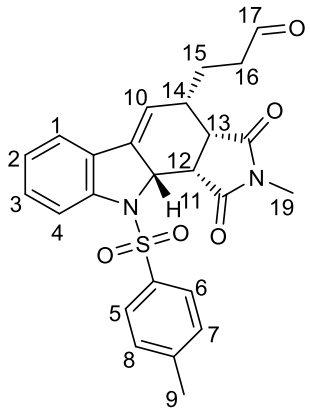
(3a*S*,4*S*,10a*S*,10b*S*)-4-(3-hydroxypropyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (135)



Dimethylaluminum chloride (1.0 M in hexane, 0.82 mL, 0.82 mmol) was added dropwise to a solution of *N*-methylmaleimide (0.046 g, 0.41 mmol) in DCM (5 mL) at -78 °C. The mixture left to stir for 30 min followed by the addition of (*E*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-en-1-ol **134** (0.146 g, 0.41 mmol) in DCM (7 mL). The reaction mixture was refluxed for 5 h, quenched with saturated $NaHCO_{3\,(aq)}$ (25 mL). The organic layer was extracted with DCM (2 x 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by column chromatography (petrol / ethyl acetate 1:1 gradient to 100 ethyl acetate) to yield (3a*S*,4*S*,10a*S*,10b*S*)-4-(3-hydroxypropyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.1699 g, 0.36 mmol, 89%) as a white solid.

Mp. 207 – 209 °C**.** **R_f**: 0.33 (petrol / ethyl acetate 1:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.74 – 7.69 (m, 2H, $H_{(5,6 \text{ or } 7,8)}$), 7.65 – 7.59 (m, 1H, $H_{(1 \text{ or } 4)}$), 7.21 – 7.16 (m, 4H, Ar), 6.92 (td, *J* = 7.5, 1.0 Hz, 1H, $H_{(2 \text{ or } 3)}$), 5.81 (t, *J* = 3.7 Hz, 1H, H_{10}), 4.49 (ddd, *J* = 7.2, 3.3, 1.8 Hz, 1H, H_{13}), 3.96 (dd, *J* = 8.6, 7.2 Hz, 1H, H_{11}), 3.69 (t, *J* = 6.2 Hz, 2H, H_{17}), 3.13 (dd, *J* = 8.6, 6.3 Hz, 1H, H_{12}), 2.71 (s, 3H, H_{19}), 2.30 (s, 3H, H_9), 2.22 – 2.16 (m, 1H, H_{14}), 2.08 –1.83 (m, 2H, $H_{(15 \text{ or } 16)}$), 1.79 – 1.69 (m, 2H, $H_{(15 \text{ or } 16)}$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 176.3 (CO), 173.7 (CO), 144.5, 136.8, 134.2, 133.8, 130.4, 129.8, 127.2, 125.9, 123.8, 120.9, 118.0, 115.2, 62.4 (C_{17}), 61.8 (C_{11}), 43.9 (C_{12}), 40.3 (C_{13}), 38.0 (C_{14}), 31.2 ($C_{15 \text{ or } 16}$), 27.4 ($C_{15 \text{ or } 16}$), 24.8 (C_{19}), 21.4 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 3553 (br, OH), 1659 (N-CO).**MS (pNSI):** 484.18 (100%, $[M+NH_4]^+$), 467.16 (90%, $[M+H]^+$); **HRMS (pNSI):** calcd $C_{25}H_{26}N_2O_5SNa$ $[M+Na]^+$: 489.1455; observed: 489.1446.

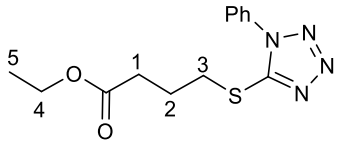
3-((3a*S*,4*S*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanal (136)



DMSO (0.02 mL, 0.33 mmol) was added dropwise at -78 °C to a stirred solution of oxalyl chloride (0.01 mL, 0.15 mmol) in DCM (2 mL). After 30 min, a solution of (3a*S*,4*S*,10a*S*,10b*S*)-4-(3hydroxypropyl)-2-methyl-10-tosyl-4,10,10a,10b tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione **135** (0.062 g, 0.13 mmol) in DCM (5 mL) was added. The reaction mixture left to stir for 30 min at -78 °C followed by the addition of triethylamine (0.10 mL, 0.53 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h, quenched with saturated $NaHCO_{3\,(aq)}$ (10 mL). The organic layer was extracted with DCM (1 x 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude yellow solid product which was purified by column chromatography (petrol / ethyl acetate 1:1) to yield 3-((3a*S*,4*S*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanal in (0.045 g, 0.097 mmol, 75%) as a white solid.

Mp. 139 – 141 °C. **R_f**: 0.2 (petrol / ethyl acetate 1:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 9.79 (t, *J* = 1.4 Hz, 1H, H_{17}), 7.73 – 7.68 (m, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.67 – 7.60 (m, 1H, $H_{(1 \text{ or } 4)}$), 7.24 – 7.15 (m, 4H, Ar), 6.93 (t, *J* = 7.5 Hz, 1H, $H_{(2 \text{ or } 3)}$), 5.77 (t, *J* = 3.4 Hz, 1H, H_{10}), 4.45 (dd, *J* = 7.3, 3.3, Hz, 1H, H_{11}), 3.96 (dd, *J* = 8.6, 7.3 Hz, 1H, H_{13}), 3.10 (dd, *J* = 8.7, 5.4 Hz, 1H, H_{12}), 2.75 – 2.63 (m, 5H, $H_{(19,16)}$), 2.34 – 2.16 (m, 6H, $H_{(9,14,15)}$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 201.7 (C_{17}), 178.7 (CO), 173.8 (CO), 144.7, 144.2, 136.8, 133.9, 130.7, 130.0, 127.6, 126.6, 123.9, 121.0, 116.2, 115.4, 59.9 (C_{16}), 44.1 (C_{11}), 43.0 (C_{12}), 42.7 (C_{13}), 37.1 (C_{14}), 25.3 ($C_{15,}$), 25.2 (C_{19}), 21.6 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 1697 (CHO), 2925 (C=C). **HRMS (pNSI):** calcd $C_{25}H_{25}N_2O_5S$ $[M+H]^+$: 465.1479; observed: 465.1485.

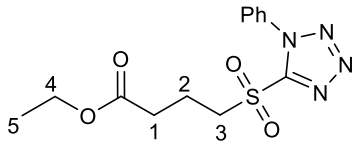
Ethyl 4-((2-phenyl-2*H*-tetrazol-5-yl)thio)butanoate (138)



Potassium carbonate (3.80 g, 27.7 mmol) was added to a stirred solution of 1-phenyl-1*H*-tetrazol-5-thiol (2.48 g, 13.9 mmol) and ethyl-4-bromobutyrate **93** (1.8 mL, 12.6 mmol) in acetone (30 mL) at room temperature and stirred vigorously for 18 h. The precipitate was filtered off and washed with acetone (2 x 15 mL), and the filtrate was evaporated under reduced pressure. The resultant residue was diluted with DCM (2 x 40 mL) and water (50 mL). The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude materials was purified by column chromatography (petrol / ethyl acetate 4:1) to give the desired compound in (3.6196 g, 12.3 mmol, 98%) as a colourless thick oil.

R_f: 0.4 (petrol / ethyl acetate 4:1)**.^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.45 – 7.36 (m, 5H, Ar), 3.96 (q, *J* = 7.5 Hz, 2H, H_4), 3.30 (t, *J* = 7.5 Hz, 2H, H_3), 2.42 – 2.38 (m, 2H, H_1), 2.09 (dt, *J* = 6.9, 13.4 Hz, 2H, H_2), 1.16 (t, *J* = 7.5 Hz, 3H, H_5). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 172.0 (CO_2Et), 153.6, 133.3, 130.1, 129.7, 123.7, 60.4 (C_4), 37.7, 32.3, 24.4, 14.2 (C_5). **IR (neat): ν_{max}/cm^{-1}:** 2982 (Ph, CH), 1727 (CO_2Et). **MS (pNSI):** 293.10 (100%, $[M+H]^+$), 247.06 (22%, $[M-OCH_2CH_3]^+$); **HRMS (pNSI):** calcd $C_{13}H_{17}N_4O_2S$ $[M+H_4]^+$: 293.1067; observed: 293.1068.

Ethyl 4-((2-phenyl-2*H*-tetrazol-5-yl)sulfonyl)butanoate (139)



Method A

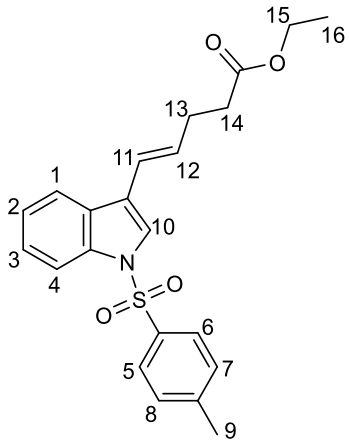
Ammonium molybdate tetrahydrate (0.0741 g, 0.06 mmol) was dissolved in 35% hydrogen peroxide (0.27 g, 8.16 mmol) to give a bright yellow solution. A solution of ethyl 4-((2-phenyl-2*H*-tetrazol-5-yl)thio)butanoate **138** (0.200 g, 0.68 mmol) in MeOH (5 mL) was added. The reaction mixture left to stir at room temperature for 18 h, diluted with water (10 mL). The organic layer was extracted with EtOAc (2 x 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the desired compound as a pale yellow oil The crude materials was purified by column chromatography (petrol / ethyl acetate 1:1) to give the desired compound in (0.174 g, 0.53 mmol, 78%) as a white solid.

Method B

A solution of *m*-chloroperoxybenzoic acid (0.587g, 3.4mmol) in DCM (10 mL) was added to a solution of ethyl 4-((2-phenyl-2*H*-tetrazol-5-yl)thio)butanoate **138** (0.2 g, 0.68 mmol) in DCM (5 mL) at 0 ^oC. The mixture was stirred at room temperature for 24 h, filtered through celite. The organic layer was extracted with DCM (2 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the desired compound as pale yellow oil. The crude materials was purified by column chromatography (petrol / ethyl acetate 1:1) to give the desired compound in (0.1 g, 0.30 mmol, 46%) as a white solid.

Mp. 87 – 89 ^oC. **R_f**: 0.8 (petrol / ethyl acetate 1:1).**^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.65 (dd, *J* = Hz, 2H, Ar), 7.61 - 7.56 (m, 3H, Ar), 4.11 (q, *J* = 7.3 Hz, 2H, H_4), 3.82 (t, *J* = 6.7 Hz, 2H, H_3), 2.52 (t, *J* = 7.5 Hz, 2H, H_1), 2.24 (dt, *J* = 6.7, 13.0 Hz, 2H, H_2), 1.23 (t, *J* = 7.3 Hz, 2H, H_5). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 171.5 (CO), 153.3, 132.9, 131.4, 129.6, 125.1, 60.9 (C_4), 55.0, 31.8, 17.8, 14.2 (C_5). **IR (neat): ν_{max}/cm^{-1}:** 1712 (CO_2Et). **HRMS (pNSI):** calcd $C_{13}H_{17}N_4O_4S$ $[M+H]^+$:325.0965; observed: 325.0960.

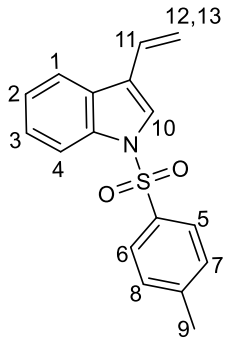
Ethyl (*E*)-5-(1-tosyl-1*H*-inol-3-yl) pent-4-enoate (141)



NaHMDS (1.0 M in THF, 1.48 mL, 1.48 mmol) was added to a solution of ethyl 4-((2-phenyl-2H-tetrazol-5-yl) sulfonyl)butanoate **139** (0.49 g, 0.34 mmol) in THF (10 mL) at -78 ^{o}C. The mixture was stirred at -78 ^{o}C for 30 min. In a separate round bottomed flask, 1-(toluene-4-sulfonyl)–1*H*-indol-3-carbaldehyde **89** (0.3 g, 1.30 mmol) was dissolved in THF (5 mL) and transferred via cannula into the reaction solution. The mixture was warmed slowly to room temperature over 4 h and left to stir for 14 h. The solution poured into a saturated NH_4Cl (5 mL), the organic layer was extracted with EtOAc (2 x 80 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography (petrol / ethyl acetate 10:1) to give ethyl (*E*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate in (0.198 g, 0.50 mmol, 39%) as a colourless oil.

R_f: 0.65 (petrol / ethyl acetate 7:3).**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.90 (d, *J* = 8.8 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.67 (d, *J* = 8.0 Hz, 2H, $H_{(5,\ 6) \text{ or } (7,8)}$), 7.60 (d, *J* = 8.0 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.44 (s, 1H, H_{10}), 7.23 (t, *J* = 8.0 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.18 (t, *J* = 8.0 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.12 (d, *J* = 8.0 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 6.40 (d, *J* = 16.3 Hz, 1H, H_{11}), 6.19 (dt, *J* = 16.3, 6.4 Hz, 1H, H_{12}), 4.07 (q, *J* = 6.9 Hz, 2H, H_{16}), 2.50 - 2.39 (m, 6H, $H_{(13,14,15)}$), 1.17 (t, *J* = 6.9 Hz, 3H, H_{16}). **^{13}C NMR (100 MHz, CDCl3):** δ_C 173.0 (CO_2Et), 145.1, 135.5, 135.2, 130.2, 129.9, 129.2, 126.9, 124.9, 123.4, 123.1, 121.5, 120.6, 120.3, 113.8, 60.5 (C_{15}), 34.1, 28.8, 21.6 (C_9), 14.3 (C_{16}). **IR (neat): ν_{max}/cm^{-1}:** 1727 (CO), 1597 (C=C). **MS (pNSI):** 415.2 (100%, $[M+NH_4]^+$), 812.30 (100%, $[2M+NH_4]^+$); **HRMS (pNSI):** calcd $C_{22}H_{24}NO_4S$ $[M+H]^+$: 398.1421; observed: 398.1417.

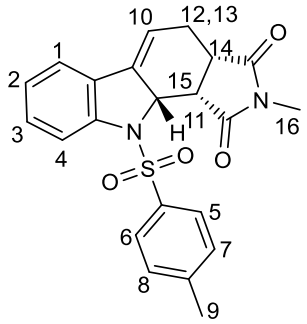
1-Tosyl-3-vinyl-1*H*-indole (148)



Methyltriphenylphosphonium iodide **153** (1.29 g, 3.2 mmol) was dissolved in THF under a nitrogen atmosphere. The reaction mixture was cooled down to -78 °C. *n*-Butyllithium (2.5 M in hexane, 1.18 mL, 2.97 mmol) was added dropwise over 10 min. The mixture was warmed to 0 °C and left to stir for 2 h. In a separate round, a solution of 1-(toluene-4-sulfonyl)–1*H*-Indol-3-carbaldehyde **89** (0.800 g, 2.7 mmol) was dissolved in THF (10 mL) and transferred via cannula to the flask which containing the solution of methyltriphenylphosphonium iodide. The reaction mixture was warmed up to room temperature and stirred for 24h. The reaction mixture was quenched with water (30 mL). The organic layer was extracted with ethyl acetate (3 x 100 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow oil product was purified by column chromatography (petrol / ethyl acetate 10:1) to give 1-tosyl-3-vinyl-1*H*-indole in (0.580 g, 1.93 mmol, 72%) as a yellow solid.

Mp. 93 – 95 °C (lit. 93 - 94 °C).[101] **R_f** : 0.31 (petrol / ethyl acetate 10:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.98 (d, *J* = 8.1 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.76 (d, *J* = 7.7 Hz, 2H, $H_{(5\text{-}6) \text{ or } (7\text{-}8)}$), 7.73 (d, *J* = 8.1 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.59 (s, 1H, H_{10}), 7.32 (t, *J* = 7.7 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.26 (t, *J* = 7.7 Hz, 1H, $H_{(2 \text{ or } 3)}$), 7.21 (d, *J* = 7.7 Hz, 2H, $H_{(5\text{-}6) \text{ or } (7\text{-}8)}$), 6.75 (dd, *J* = 16.8, 11.3 Hz, 1H, H_{11}), 5.79 (d, *J* = 16.8 Hz, 1H, H_{12}), 5.33 (d, *J* = 11.3 Hz,1H, H_{13}), 2.33 (s, 3H, H_9). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 145.0, 135.5, 135.1, 130.0, 129.0, 127.6, 126.8, 125.0, 124.1, 123.5, 120.9, 120.4, 115.3, 113.8, 21.6 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 3119 (CH).

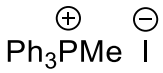
(3a*S*,10a*S*,10b*S*)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (149)



N-methylmaleimide (1, 0.373 g, 3.36 mmol) and 1-tosyl-3-vinyl-1*H*-indole **148** (1.00 g, 3.36 mmol) were dissolved in DCM (15 mL). The mixture was refluxed for 48 h and the solvent was removed under reduced pressure. The crude white product was purified by column chromatography (petrol / ethyl acetate 2:1) to give (3a*S*,10a*S*,10b*S*)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.931 g, 2.28 mmol, 68%) as a white solid.

Mp. 223 – 225 ºC. **R_f** : 0.25 (petrol / ethyl acetate 2:1).**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.78 (d, *J* = 7.5 Hz, 2H, $H_{(5\text{-}6) \text{ or } (7\text{-}8)}$), 7.66 (d, *J* = 7.5 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.23 (d, *J* = 8.0 Hz, 2H, $H_{(5\text{-}6) \text{ or } (7\text{-}8)}$), 7.26 - 7.22 (m, 4H, Ar), 6.98 (t, *J* = 7.3 Hz, 1H, $H_{(2 \text{ or } 3)}$), 6.04 (dt, *J* = 4.0, 7.0 Hz, 1H, H_{10}), 4.54 - 4.51 (m, 1H, H_{11}), 4.05 (t, *J* = 7.6 Hz, 1H, H_{15}), 3.19 (t, *J* = 7.6 Hz, 1H, $H_{(12 \text{ or } 13)}$), 3.04 - 2.98 (m, 1H, H_{14}), 2.82 (s, 3H, H_{16}), 2.35 (s, 3H, H_9), 2.20 - 2.13 (m, 1H, $H_{(12 \text{ or } 13)}$). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 178.9 (CO), 174.1 (CO), 144.6, 137.4, 134.3, 130.4, 129.9, 127.4, 127.1, 126.3, 123.9, 121.0, 115.4, 112.9, 61.5 43.2, 37.2, 25.3, 25.1 (C_{16}), 21.6 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 2972 (CH), 1693 (CO).

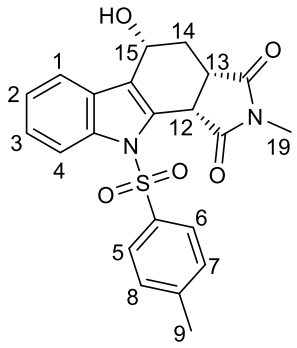
Methyltriphenylphosphonium iodide (153)



Methyl iodide (2.47 g, 17.4 mmol) was added to a solution of triphenylphosphine (5.00 g, 19.1 mmol) in toluene (40 mL). The solution was stirred at room temperature for 24 h. The resultant precipitate was filtered off with suction and washed with toluene to give methyltriphenylphosphonium iodide in (6.750 g, 16.69 mmol, 96%) as white crystals.

Mp. 186 – 188 °C (lit. 183 - 184 °C).[100] **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.81 - 7.65 (m, 15H, Ar), 3.18 (d, 3H, *J* = 13.5 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 135.3 (J_{cp} = 3.2 Hz), 133.4 (J_{cp} = 10.6 Hz), 130.6 (J_{cp} = 12.9 Hz), 11.50 (J_{cp} = 55.4 Hz, Me). **IR (neat): ν_{max}/cm^{-1}:** 2984 (CH),1441 (P-Ph).

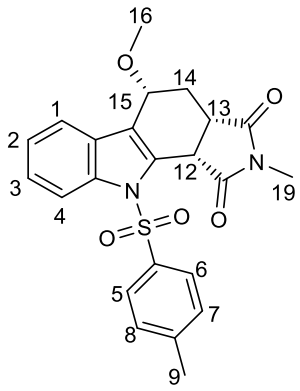
(3a*S*,5*S*,10b*S*)-5-hydroxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (156)



NBS (0.045 g, 0.24 mmol) was dissolved in (THF / H_2O, 2:2 mL) and the solution was cooled down to 0 °C. Then, (3a*S*,10a*S*,10b*S*) -2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3 (2*H*,3a*H*)-dione **149** (0.05 g, 0.12 mmol) was added to the solution in one portion. The solution was stirred at room temperature for 2 h, quenched with 5 mL of $NaHCO_{3\,(aq)}$. The organic layer was extracted with DCM (2 x 15 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to afford the crude orange solid as a mixture of two diastereomers in a 4:1 ratio. Purification of the crude material in (petrol / ethyl acetate 1:1) gave the major diastereomer of (3a*S*,5*S*,10b*S*)-5-hydroxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0263 g, 0.062 mmol, 52%) as a white solid.

M.p. 211 – 213 °C. **R_f**: 0.3 (petrol / ethyl acetate 1:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 8.01 – 7.90 (m, 2H, $H_{(5,6)\text{ or }(7,8)}$), 7.81 – 7.67 (m, 1H, $H_{(1\text{ or }4)}$), 7.51 – 7.41 (m, 1H, $H_{(1\text{ or }4)}$), 7.30 – 7.12 (m, 4H, Ar), 5.29 (d, *J* = 9.2 Hz,1H, H_{12}), 5.23 (t, *J* = 2.7 Hz,1H, H_{15}), 3.42 – 3.29 (m, 1H, H_{13}), 2.94 (s, 3H, H_{19}), 2.75 (ddd, *J* = 14.2, 3.5, 2.0 Hz, 1H, H_{14}), 2.31 (s, 3H, H_9), 1.90 (ddd, *J* = 14.2, 7.9, 2.7 Hz, 1H, H_{14}). **^{13}C NMR (176 MHz, $CDCl_3$):** δ_C 179.6 (CO), 174.7(CO), 144.8, 136.4, 135.8, 131.2, 129.7, 127.6, 127.0, 124.9, 123.6, 121.4, 118.2, 114.7, 61.3 (C_{15}), 38.9, 37.6, 32.3, 25.6 (C_{19}), 21.7 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 1692 (CO), 3659 (OH). **MS (pNSI):** 447.0 (68%, $[M+H]^+$), 871.2 (17%, $[2M+Na]^+$), 442.1 (47%, $[M+NH_4]^+$); **HRMS (pNSI):** calcd $C_{22}H_{21}N_2O_5S$ $[M+H]^+$: 425.1166; observed: 425.1166.

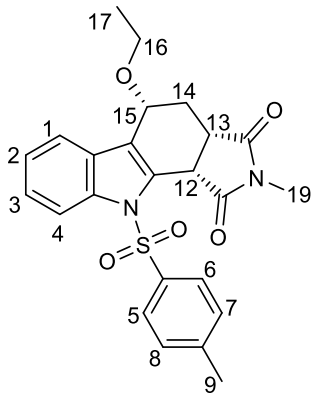
(3a*S*,5*S*,10b*S*)-5-methoxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-a]carbazole-1,3(2*H*,3a*H*)-dione (157)



NBS (0.045 g, 0.24 mmol) was dissolved in (THF / MeOH, 2:2 mL) and the solution was cooled down to 0 °C. Then, (3a*S*,10a*S*,10b*S*)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3 (2*H*,3a*H*)-dione **149** (0.05 g, 0.12 mmol) was added to the solution in one portion. The solution was stirred at 0 °C for 1 h, quenched with (5 mL) of $NaHCO_{3(aq)}$. The organic layer was extracted with DCM (2 x 15 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to afford the crude orange solid as a mixture of two diastereomers in a 14:1 ratio. Purification of the crude material in (petrol / ethyl acetate 2:1) gave the major diastereomer of (3a*S*,5*S*,10b*S*)-5-methoxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0391 g, 0.09 mmol, 75%) as a yellow solid.

Mp. 192 – 194 °C. **R_f** : 0.30 (petrol / ethyl acetate 2:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 8.06 – 7.95 (m, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.82 – 7.65 (m, 1H, $H_{(1 \text{ or } 4)}$), 7.51 – 7.36 (m, 1H, $H_{(1 \text{ or } 4)}$), 7.29 – 7.08 (m, 4H, Ar), 5.32 (d, *J* = 9.3 Hz, 1H, H_{12}), 4.66 (dd, *J* = 3.2, 2.3 Hz, 1H, H_{15}), 3.38 – 3.25 (m, 1H, H_{13}), 3.09 (s, 3H, H_{16}), 2.92 (s, 3H, H_{19}), 2.88 (ddd, *J* = 14.2, 3.2, 1.4 Hz, 1H, H_{14}), 2.30 (s, 3H, H_9), 1.74 (ddd, *J* = 14.3, 8.3, 2.4 Hz, 1H, H_{14}).**^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 179.4 (CO), 175.3 (CO), 145.0, 136.2, 135.7, 131.8, 129.8, 128.0, 127.6, 124.7, 123.7, 120.0, 118.1, 114.5, 69.4, 56.6, 38.8, 37.6, 29.7, 25.5 (C_{19}), 21.5 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 1707 (CO), 2970 (CH). **MS (pNSI):** 439.1321 (100%, $[M+H]^+$), 894.2 (47%, $[2M+NH_4]^+$), 456.1 (42%, $[M+NH_4]^+$); **HRMS (pNSI):** calcd $C_{23}H_{23}N_2O_5S$ $[M+H]^+$: 439.1322; observed: 439.1321.

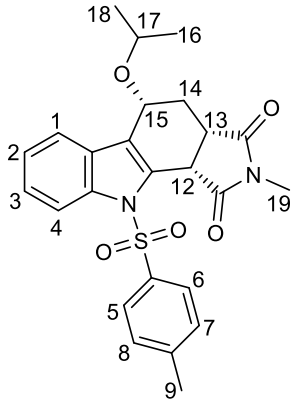
(3a*S*,5*S*,10b*S*)-5-ethoxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-a]carbazole-1,3(2*H*,3a*H*)-dione (158)



NBS (0.045 g, 0.24 mmol) was dissolved in (THF / EtOH, 2:2 mL) and the solution was cooled down to 0 °C. Then, (3a*S*,10a*S*,10b*S*)-2-methyl-10- tosyl-4,10,10a, 10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3 (2*H*,3a*H*)-dione **149** (0.05 g, 0.12 mmol) was added to the solution in one portion. The solution was stirred at 0 °C for 1 h, quenched with 5 mL of $NaHCO_{3\,(aq)}$. The organic layer was extracted with DCM (2 x 15 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to afford the crude orange solid as a mixture of two diastereomers in a 14:1 ratio. Purification of the crude material in (petrol / ethyl acetate 2:1) gave the major diastereomer of (3a*S*,5*S*,10b*S*)-5-ethoxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0362 g, 0.08 mmol, 67%) as a brown solid.

Mp. 195 – 197 °C. **R_f** : 0.38 (petrol / ethyl acetate 2:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.98 (d, *J* = 8.1 Hz, 2H, $H_{(5,6)\text{ or }(7,8)}$), 7.78 – 7.70 (m, 1H, $H_{(1\text{ or }4)}$), 7.46 – 7.38 (m, 1H, $H_{(1\text{ or }4)}$), 7.26 – 7.13 (m, 4H, Ar), 5.33 (d, *J* = 9.3 Hz, 1H, H_{11}), 4.75 (dd, *J* = 3.2, 2.3 Hz, 1H, H_{15}), 3.43 – 3.27 (m, 2H, $H_{(13,16)}$), 3.14 (dq, *J* = 8.6, 7.0 Hz, 1H, H_{16}), 2.93 (s, 3H, H_{19}), 2.87 (ddd, *J* = 14.1, 3.2, 1.4 Hz, 1H, H_{14}), 2.31 (s, 3H, H_9), 1.73 (ddd, *J* = 14.1, 8.4, 2.3 Hz, 1H, H_{14}), 0.90 (t, *J* = 7.0 Hz, 3H, H_{17}).**^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 179.5 (CO), 175.5 (CO), 145.1, 136.1, 135.7, 131.8, 129.8, 128.0,127.8, 124.7, 123.5, 120.5, 118.1, 114.6, 67.6, 64.1, 38.9, 37.7, 30.2, 25.3, 21.7 (C_9),15.2. **IR (neat): ν_{max}/cm^{-1}:** 1707 (CO), 2970 (CH). **MS (pNSI):** 470.1 (42%, $[M+NH_4]^+$), 475.1293 (25%, $[2M+Na]^+$); **HRMS (pNSI):** calcd $C_{24}H_{25}N_2O_5S$ $[M+H]^+$: 453.1479; observed: 453.1477.

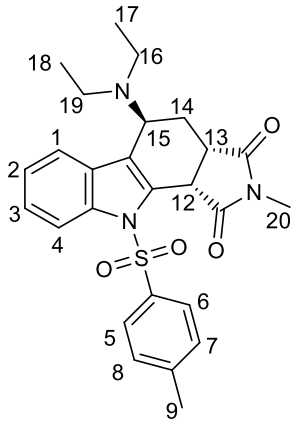
(3a*S*,5*R*,10b*S*)-5-isopropoxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (159)



NBS (0.045 g, 0.24 mmol) was dissolved in THF / 2-propanol, 2:2 mL) and the solution was cooled down to 0 °C. Then, (3a*S*,10a*S*,10b*S*)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*] carbazole-1,3 (2*H*,3a*H*)-dione (0.05 g, 0.12 mmol) was added to the solution in one portion. The solution was stirred at 0 °C for 1 h, quenched with 5 mL of $NaHCO_{3\ (aq)}$. The organic layer was extracted with DCM (2 x 15 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to afford the crude white solid as a mixture of two diastereomers in a 19:1 ratio. Purification of the crude material in (petrol / ethyl acetate 2:1) gave the major diastereomer of (3a*S*,5*R*,10b*S*)-5-isopropoxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydro pyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0341 g, 0.076 mmol, 64%) as a yellow solid.

Mp. 196 – 198 °C. **R_f** : 0.6 (petrol / ethyl acetate 2:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 8.14 – 7.94 (m, 2H, Ar), 7.83 – 7.62 (m, 1H, Ar), 7.47 – 7.33 (m, 1H, Ar), 7.27 – 7.15 (m, 4H, Ar), 5.33 (d, *J* = 9.4 Hz, 1H, H_{12}), 4.88 (dd, *J* = 3.2, 2.4 Hz, 1H, H_{15}), 3.48 – 3.38 (m, 1H, H_{17}), 3.35 – 3.22 (t, *J* = 8.5 Hz, 1H, H_{13}), 2.93 (s, 3H, H_{19}), 2.80 (ddd, *J* = 14.1, 3.2, 1.4 Hz, 1H, H_{14}), 2.31 (s, 3H, H_9), 1.72 (ddd, *J* = 14.1, 8.5, 2.4 Hz, 1H, H_{14}), 1.04 (d, *J* = 6.0 Hz, 3H, $H_{(16\ or\ 18)}$), 0.86 (d, *J* = 6.0 Hz, 3H, $H_{(16\ or\ 18)}$).**^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 179.6 (CO), 175.4 (CO), 145.1, 136.1, 135.8, 131.8, 129.8, 127.9, 127.8, 124.7, 123.5, 120.7, 118.1, 114.6, 68.5, 64.2, 38.8, 37.7, 30.6, 25.3, 22.4, 21.6, 21.4 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 170.5 (CO), 2923 (CH). **MS (pNSI):** 467.16 (100%, $[M+H]^+$), 489.14 (32%, $[M+Na]^+$), 955.30 (90%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{25}H_{27}N_2O_5S$ $[M+H]^+$: 467.1626; observed: 467.1635.

(3a*S*,5*S*,10b*S*)-5-(diethylamino)-2-methyl-10-tosyl-4,5,10,10b tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (166)

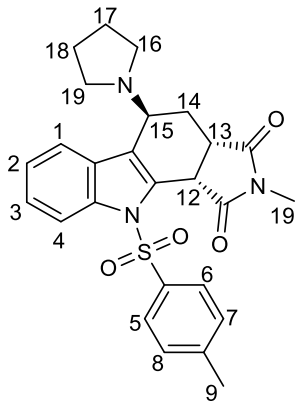


(3a*S*,10a*S*,10b*S*)- 2-methyl-10- tosyl-4,10,10a,10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione **149** (0.05 g, 0.12 mmol) and Cs_2CO_3 (0.80 g, 0.24 mmol) was dissolved in DCM (5 mL). The solution was cooled down to 0 °C and bromine (7.5 µL, 0.14 mmol) was added dropwise to the mixture. After 2 min diethylamine (0.12 mL, 1.22 mmol) was added. The reaction mixture was stirred at 0 °C for 2 h, quenched with water (5 mL). The organic layer was extracted with DCM (2 x 15 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to afford the crude yellow compound. Purification using column chromatography (petrol / ether / DCM 2:1:1) gave (3a*S*,5*S*,10b*S*)-5-(diethylamino)-2-methyl-10-tosyl-4,5,10,10b-tetrahydro pyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0469 g, 0.096 mmol, 80%) as a yellow solid.

Mp. 202 – 204 °C. **R_f** : 0.25 (petrol / ether / DCM 2:1:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 8.02 (d, *J* = 8.1 Hz, 2H, Ar), 7.95 (d, *J* = 8.1 Hz, 2H, Ar), 7.28 – 7.12 (m, 4H, Ar), 5.03 (dd, *J* = 8.3, 1.8 Hz, 1H, H_{12}), 4.00 (ddd, *J* = 9.4, 4.6, 1.8 Hz, 1H, H_{15}), 3.67 – 3.36 (m, 1H, H_{13}), 2.97 (s, 3H, H_9), 2.49 – 2.33 (m, 5H,$H_{(16,19,14)}$), 1.87 (ddd, *J* = 13.3, 9.4, 5.7 Hz, 1H, H_{14}), 0.97 (t, *J* = 7.1 Hz, 6H, $H_{(17,18)}$).**^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 178.3 (CO), 173.7 (CO), 144.6, 138.4, 134.5, 130.0, 129.8, 129.3, 126.9, 126.8, 125.2, 123.8, 122.2, 116.0, 51.4 ($C_{16, 19}$), 43.4, 40.3, 39.3, 25.3, 21.5 (C_{20}), 21.1 (C_9), 14.0 ($C_{18, 17}$). **IR (neat): ν_{max}/cm^{-1}**: 1702 (CO), 2981 (CH). **MS (pAPCI):** 407.1 (100%, [M-NEt_2^+]), 959.4 (21%, [2M+H^+]); **HRMS (pAPCI):** calcd $C_{26}H_{30}N_3O_4S$ [M+H]$^+$: 480.1592; observed: 480.1946.*

* HRMS was collected by Joseph Cowell.

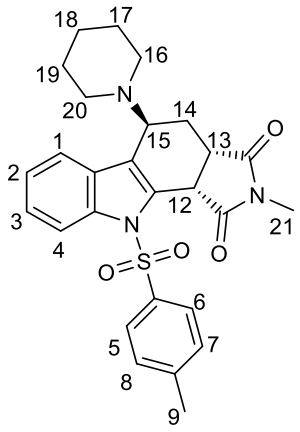
(3a*S*,5*S*,10b*S*)-2-methyl-5-(pyrrolidin-1-yl)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-a]carbazole-1,3(2*H*,3a*H*)-dione (172)



(3a*S*,10a*S*,10b*S*)-2- methyl-10-tosyl-4,10,10a,10b tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (0.05 g, 0.12 mmol) and Cs_2CO_3 (0.80 g, 0.24 mmol) was dissolved in DCM (5 mL). The solution was cooled down to 0 °C and bromine (7.5 µL, 0.14mmol) was added dropwise to the mixture. After 2 min pyrrolidine (0.1 mL, 1.22 mmol) was added to the mixture. The solution was stirred at 0 °C for 2 h, quenched with water (5 mL). The organic layer was extracted with DCM (2 x 15 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow solid product was purified using column chromatography (petrol / ethyl acetate 1:1 gradient to 100% ethyl acetate) to give (3a*S*,5*S*,10b*S*)-2-methyl-5-(pyrrolidinee-1-yl)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0528 g, 0.11 mmol, 92%) as a yellow solid.

Mp. 197 – 199 °C. **R_f** : 0.1 (petrol / ethyl acetate 1:1).**^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.88 – 7.78 (m, 1H, Ar), 7.57 – 7.49 (m, 2H, Ar), 7.49 – 7.42 (m, 1H), 7.19 – 7.08 (m, 2H, Ar), 7.09 – 7.03 (m, 2H, Ar), 4.86 (d, *J* = 7.7 Hz, 1H, H_{12}), 3.72 – 3.62 (m, 1H, H_{13}), 3.58 (t, *J* = 3.8 Hz, 1H, H_{15}), 2.95 (s, 3H, H_{19}), 2.64 – 2.51 (m, 2H, $H_{(16,19)}$), 2.40 (dt, *J* = 13.5, 4.7 Hz, 1H, H_{14}), 2.23 (s, 3H, H_9), 2.14 (m, 2H, $H_{(16 \text{ or } 19)}$), 1.70 – 1.54 (m, 5H, $H_{(17,18,14)}$).**^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 179.0 (CO), 173.3 (CO), 144.6, 137.5, 134.8, 130.0, 129.6, 129.4, 126.7, 124.8, 124.7, 123.8, 119.6, 115.8, 53.5, 51.5, 41.6, 38.8, 28.8, 25.2 (C_{19}), 23.6, 21.5 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 1710 (CO), 1593 (C=C). **MS (pNSI):** 478.17 (100%, $[M+H]^+$), 500.16 (15%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{26}H_{28}N_3O_4S$ $[M+H]^+$: 478.1795; observed: 478.1787.

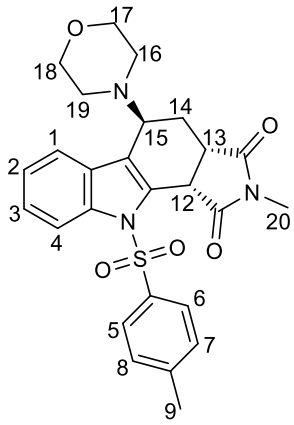
(3a*S*,5*S*,10b*S*)-2-methyl-5-(piperidin-1-yl)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2H,3a*H*)-dione (173)



(3a*S*,10a*S*,10b*S*)-2- methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione **149** (0.05 g, 0.12 mmol) and Cs_2CO_3 (0.80 g, 0.24 mmol) was dissolved in DCM (5 mL). The solution was cooled down to 0 °C and bromine (7.5 µL, 0.14 mmol) was added dropwise to the mixture. After 2 min piperidine (0.12 mL, 1.22 mmol) was added to the mixture. The solution was stirred at 0 °C for 1 h, quenched with water (5 mL). The organic layer was extracted with DCM (2 x 15 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol / ethyl acetate 1:1) to give (3a*S*,5*S*,10b*S*)-2-methyl-5- (piperidin-1-yl)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0451 g, 0.092 mmol, 77%) as a white solid.

Mp. 163 – 165 °C. **R_f** : 0.26 (petrol / ethyl acetate 2:1).**^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.91 (t, *J* = 8.3 Hz, 2H, $H_{(2, 3)}$), 7.56 (d, *J* = 8.3 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 7.21 – 7.02 (m, 4H, Ar), 4.95 (dd, *J* = 8.3, 1.4 Hz, 1H, H_{12}), 3.65 (ddd, *J* = 8.4, 4.2, 1.4 Hz, 1H, H_{15}), 3.49 (dt, *J* = 8.4, 5.8 Hz, 1H, H_{13}), 2.90 (s, 3H, H_{21}), 2.29 – 2.22 (m, 4H, $H_{(16,20)}$), 2.22 (s, 3H, H_9), 2.21 – 2.17 (m, 1H, H_{14}) 2.05 – 1.94 (m, 1H, H_{14}), 1.39 (m, 6H, $H_{(17,18,19)}$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 178.5 (CO), 173.6 (CO), 144.6, 137.9, 134.6, 129.8, 129.6, 129.4, 126.7, 125.1, 125.0, 123.9, 121.5, 115.6, 56.3, 50.1, 40.3, 39.1, 26.3, 25.2 9, 24.6, 22.5 (C_{21}), 21.5 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 1703 (CO), 2981 (Ar, CH). **HRMS (pNSI):** calcd $C_{27}H_{30}N_3O_4S$ $[M+H]^+$: 492.1952; observed: 492.1939.

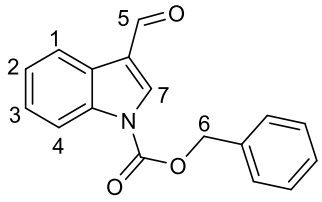
(3a*S*,5*S*,10b*S*)-2-methyl-5-morpholino-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (174)



(3a*S*,10a*S*,10b*S*)- 2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (0.05 g, 0.12 mmol) and Cs_2CO_3 (0.80 g, 0.24 mmol) was dissolved in DCM (5 mL). The solution was cooled down to 0 °C and bromine (7.5 µL, 0.14 mmol) was added dropwise to the mixture. After 2 min morpholine (0.1 mL, 1.22 mmol) was added to the mixture. The solution was stirred at 0 °C for 1 h, quenched with water (5 mL). The organic layer was extracted with DCM (2 x 15 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow solid product was purified using column chromatography (petrol / ethyl acetate 1:1) gave (3a*S*,5*S*,10b*S*)-2-methyl-5-morpholino-10-tosyl-4,5,10,10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0489 g, 0.09 mmol, 83%).

Mp. 170 – 172 °C. **R_f** : 0.24 (petrol / ethyl acetate 1:1)**^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 7.89 (d, *J* = 7.9 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.80 (d, *J* = 7.6 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.60 (d, *J* = 8.6 Hz, 2H, $H_{(5,6 \text{ or } 7,8)}$), 7.23 – 7.12 (m, 2H, $H_{(2, 3)}$), 7.08 (d, *J* = 7.6 Hz, 2H, $H_{(5,6) \text{ or } (7,8)}$), 4.95 (dd, *J* = 8.3, 1.2 Hz, 1H, H_{12}), 3.66 (t, *J* = 5.8 Hz, 1H, H_{13}), 3.55 (t, *J* = 4.6 Hz, 5H, $H_{(15, 17,18)}$), 2.92 (s, 3H, H_{20}), 2.44 – 2.37 (m, 2H, $H_{(16 \text{ or } 19)}$), 2.33 – 2.26 (m, 2H, H_{14}), 2.25 (s, 3H, H_9), 2.15 – 2.05 (m, 2H, $H_{(16 \text{ or } 19)}$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 178.3 (CO), 173.4 (CO), 144.6, 137.7, 134.7, 130.1, 129.5, 129.4, 126.7 , 125.1 , 124.3, 124.0, 120.8, 115.8, 67.2, 55.6, 49.5, 40.5, 38.8, 25.2, 23.3 (C_{19}), 21.5 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 1706 (CO), 2981 (CH). **HRMS (pNSI):** calcd $C_{26}H_{28}N_3O_5S$ $[M+H]^+$: 494.1744; observed: 494.1737.

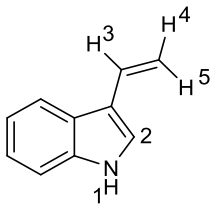
Benzyl 3-formyl-1*H*-indole-1-carboxylate (177)



A solution of 3-indole carbaldehyde **88** (5.00 g, 34.4 mmol) in DCM (100 mL) was cooled down to 0 °C. Triethylamine (12 mL, 86.15 mmol) was added to the solution. After 10 min, benzyl chloroformate (5.39 mL, 37.80 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture quenched with water (100 mL), the organic layer was extracted with DCM (2 x 150 mL), washed brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The orange crude solid was purified by column chromatography in (petrol / ethyl acetate 7:3) to give benzyl 3-formyl-1*H*-indole-1-carboxylate in (7.8 g, 27.9 mmol, 81%) as white crystals.

Mp. 89 – 91 °C. **R_f** : 0.68 (petrol / ethyl acetate 1:1).**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 10.07 (s. 1H, H_5), 8.27 (d, *J* = 7.9 Hz, 1H, $H_{(1 \text{ or } 4)}$), 8.25 (s, 1H, H_7), 8.17 (d, *J* = 7.9 Hz, 1H, $H_{(1 \text{ or } 4)}$), 7.51 (m, 7H, Ar), 5.50 (s, 2H, H_6). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 185.8 (CHO), 156.7 (CO), 150.1, 136.8, 134.2, 130.6, 129.1, 128.9, 128.5, 128.0, 127.6, 126.9, 122.0, 116.1, 70.1 (C_6). **IR (neat): ν_{max}/cm^{-1}:** 1743 (CHO), 1671 (N-CO).

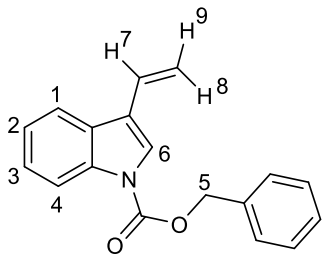
3-Vinyl-1*H*-indole (178)



n-Butyllithium (2.5 M in hexane, 3.9 mL, 9.66 mmol) was added dropwise to a solution of methyltriphenylphosphonium iodide **153** (4.5 g, 11.12 mmol) in THF (25 mL) at -78 °C. The reaction mixture was warmed up to 0 °C and left to stir for 1 h. In a separate round, NaHMDS (1.0 M in THF, 9.66 mL, 9.66 mmol) was added to a solution of 1*H*-indole-3-carbaldehyde **88** (1.402 g, 9.66 mmol) in THF (5 mL). This solution was transferred via cannula into the reaction mixture at -78 °C. The reaction mixture was stirred at room temperature for 2 h. The organic layer was extracted with ethyl acetate (2 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow oil product was purified by column chromatography (petrol / ethyl acetate 4:1) to give 3-vinyl-1*H*-indole (1.23 g, 8.6 mmol, 90%) as a yellow solid.

Mp. 90 – 92 °C (lit. 80 - 81 °C).[50] **R_f** : 0.65 (petrol / ethyl acetate 5:1).**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 7.88 – 7.70 (m, 2H, $H_{(1, Ar)}$), 7.21 – 7.01 (m, 4H, H_2, H_{Ar}), 6.77 (ddd, *J* = 17.8, 11.3, 0.6 Hz, 1H, H_3), 5.59 (dd, *J* = 17.8, 1.5 Hz, 1H, H_5), 5.07 (dd, *J* = 11.3, 1.5 Hz, 1H, H_4). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 136.7, 129.4, 125.6, 123.6, 122.5, 120.3, 120.1, 115.7, 111.3, 110.7. **IR (neat): ν_{max}/cm^{-1}:** 3390 (NH), 2980 (CH).

Benzyl 3-vinyl-1*H*-indole-1-carboxylate (179)



Method A

Methyltriphenylphosphonium iodide **153** (4.32 g, 10.7 mmol) was dissolved in THF (10mL) and the solution was cooled to -78 ^{o}C. *n*-Butyllithium (2.5 M in hexane, 3.80 mL, 9.30 mmol) was added to the solution dropwise over 10 min. The reaction mixture was warmed to 0 ^{o}C and left to stir for 2 h. In a separate round, a solution of benzyl 3-formyl-1*H*-indole-1-carboxylate **177** (2.600 g, 9.30 mmol) was dissolved in THF (10 mL) and transferred via cannula to the flask which containing the solution of methyltriphenylphosphonium iodide. The reaction mixture was warmed up to room temperature and stirred for 24 h. The reaction mixture was quenched with water (50 mL). The organic layer was extracted with ethyl acetate (3 x 100 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude orange solid product was purified by column chromatography (petrol / ethyl acetate 5:1) to give benzyl 3-vinyl-1*H*-indole-1-carboxylate in (1.176 g, 4.24 mmol, 46%) as a white solid.

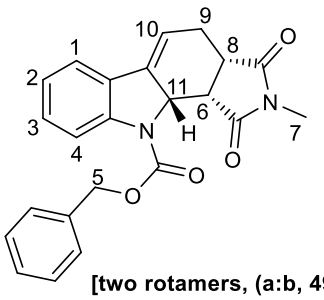
Method B

A solution of 3-vinyl-1*H*-indole **178** (0.2 g, 1.39 mmol) in THF (5 mL) was cooled down to 0 ^{o}C. NaHMDS (1.0 M in THF, 2.09 mL, 2.09 mmol) was added to the solution. After 30 min, benzyl chloroformate (0.21 mL, 1.52 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. The solution was diluted with DCM (3 x 30 mL), washed with water (2 x 20 mL), brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The orange crude solid was purified by column chromatography in (petrol / ethyl acetate 5:1) to give benzyl 3-vinyl-1*H*-indole-1-carboxylate in as a white solid in (0.262 g, 0.96 mmol, 70%).

Mp. 56 – 58 ^{o}C. **R_f** : 0.65 (petrol: ethyl acetate 5:1).**^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 8.46 – 8.20 (m, 1H, Ar), 7.89 (d, *J* = 7.6 Hz, 1H, Ar), 7.74 (s, 1H, H_6), 7.59

– 7.38 (m, 7H, Ar), 6.88 (dd, *J* = 17.9, 11.5 Hz, 1H, H_7), 5.92 (dd, *J* = 17.9, 1.8 Hz, 1H, H_8), 5.52 (s, 2H, H_5), 5.44 (dd, *J* = 11.4, 1.8 Hz, 1H, H_9). **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 155.1 (CO), 150.7, 136.1, 135.1, 128.8, 128.6, 128.4, 128.0, 128.59, 128.43, 128.06, 125.0, 123.6, 123.4, 120.19, 120.1, 115.4, 114.9, 69.7. **IR (neat): ν_{max}/cm^{-1}:** 1743 (N-CO), 2979 (CH). **HRMS (pNSI):** calcd $C_{18}H_{16}NO_2$ $[M+H]^+$: 278.1176; observed: 278.1173.

Benzyl (3a*S*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (180)

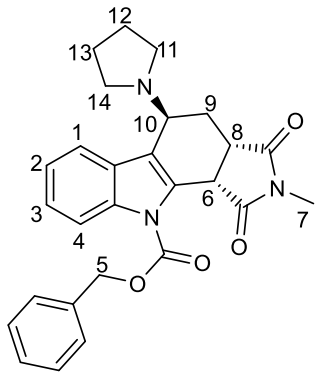


[two rotamers, (a:b, 49:51)]

Benzyl 3-vinyl-1*H*-indole-1-carboxylate **179** (0.50 g, 1.80 mmol) and *N*-methylmaleimide (0.200 g 1.80 mmol) were dissolved in DCM (10 mL). The mixture was refluxed for 20 h. The solvent was removed under reduced pressure. The crude yellow solid was purified by column chromatography (petrol / ethyl acetate 2:1) to yield benzyl (3a*S*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate in (0.5388 g, 1.38 mmol, 77%) as a white solid.

Mp. 175 – 177 °C. **R_f** : 0.4 (petrol / ethyl acetate 2:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 8.04 (d, *J* = 8.2 Hz, 1H, Ar, a), 7.55 (d, *J* = 7.6 Hz, 1H, Ar, b), 7.46 – 7.10 (m, 15H, Ar, a,b), 6.91 (dt, *J* = 11.4, 7.4 Hz, 2H, Ar, a,b), 6.08 (dt, *J* = 7.4, 3.7 Hz, 2H, H_{10}, a,b), 5.51 – 5.17 (m, 4H, H_5, a,b), 4.81 – 4.53 (m, 2H,H_{11}, a,b), 4.26 (t, *J* = 8.1 Hz, 1H, H_8, b), 3.89 (t, *J* = 8.3 Hz, 1H, H_8, a), 3.12 (t, *J* = 8.1 Hz, 1H, H_6, b), 3.04 - 2.94 (m, 3H, $H_{(6a)}$, $H_{(9b)}$), 2.70 (s, 6H, H_7, a , b), 2.25 – 2.00 (m, 2H, H_9, a). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 179.2 (CO), 178.9(CO), 175.0 (CO), 174.6 (CO), 153.1, 152.1, 145.0, 143.8, 137.4 , 137.2 , 135.95 , 130.2, 130.18 , 128.72 , 128.41 , 128.16 , 126.0, 125.6, 123.0 , 122.8, 120.6, 120.2, 115.8, 112.5, 112.4, 68.2 (C_5), 67.7 (C_5), 59.7 (C_{11}), 59.2 (C_{11}), 41.2 ($C_{6 \text{ or } 8}$), 40.3 ($C_{6 \text{ or } 8}$), 37.79 ($C_{6 \text{ or } 8}$), 37.6 ($C_{6 \text{ or } 8}$), 30.9 (C_9), 25.0 (C_9), 24.9 (C_7), 24.7 (C_7). **IR (neat): ν_{max} /cm^{-1}:** 1773 (CO), 1699 (CO), 2981 (Ar, CH). **MS (pNSI):** 406.17 (60%, $[M+NH_4]^+$), 411.13 (26%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{23}H_{21}N_2O_4$ $[M+H]^+$: 389.1496; observed: 389.1499.

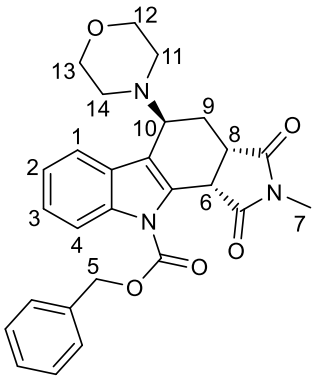
Benzyl (3a*S*,5*S*,10b*S*)-2-methyl-1,3-dioxo-5-(pyrrolidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (182)



Benzyl (3a*S*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate **180** (0.20 g, 0.51 mmol) and Cs_2CO_3 (0.332 g, 1.02 mmol) was dissolved in DCM (10 mL). The solution was cooled down to 0 °C. Bromine (31.6 µL, 0.61 mmol) was added dropwise to the mixture followed by the addition of pyrrolidine (0.42 mL, 5.10 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched with water (10 mL). The organic layer was extracted with DCM (2 x 50 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol / ethyl acetate 1:1 gradient to 100% ethyl acetate) to give benzyl (3a*S*,5*S*,10b*S*)-2-methyl-1,3-dioxo-5-(pyrrolidinee-1-yl)-2,3,3a,4,5,10bhexahydropyrrolo[3,4-*a*] carbazole-10(1*H*)-carboxylate in (0.148 g, 0.36 mmol, 71%) as yellow solid.

Mp. 156 – 158 °C. **R_f** : 0.1 (petrol / ethyl acetate 1:1).**^{1}H NMR (300 MHz, CD_2Cl_2)**: δ_H 8.16 (d, *J* = 8.1 Hz, 1H, Ar), 7.84 – 7.58 (m, 1H, Ar), 7.53 – 7.12 (m, 7H, Ar), 5.56 (d, *J* = 11.8 Hz, 1H, H_5), 5.40 (d, *J* = 11.8 Hz, 1H, H_5), 4.76 (d, *J* = 7.8 Hz, 1H, H_6), 3.71 (t, *J* = 3.7 Hz, 1H, H_{10}), 3.64 (ddd, *J* = 12.1, 7.9, 5.0 Hz, 1H, H_8), 2.96 (s, 3H, H_7), 2.83 – 2.73 (m, 2H, $H_{(11,14)}$), 2.55 – 2.38 (m, 3H, $H_{(11,14,\ 9)}$), 1.83 – 1.66 (m, 5H, $H_{(12,13,\ 9)}$). **^{13}C NMR (75 MHz, CD_2Cl_2)**: δ_C 178.8 (CO), 174.4 (CO), 173.9, 156.2, 151.5, 136.9, 136.6, 128.8, 128.7, 128.6, 124.4, 123.0, 122.7, 119.2, 114.7, 69.2, 65.6, 51.9, 41.1, 38.3, 29.0, 24.7, 23.5. **IR (neat): ν_{max} / cm^{-1}:** 1703 (CO), 2981 (CH, Ar). **MS (pNSI):** 915.40 (100%, $[2M+H]^+$), 937.38 (35%, $[2M+Na]^+$); **HRMS (pNSI):** calcd $C_{27}H_{28}N_3O_4$ $[M+H]^+$: 458.2074; observed: 458.2073.

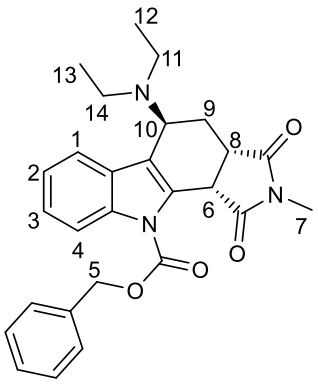
Benzyl (3a*S*,5*S*,10b*S*)-2-methyl-5-morpholino-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (183)



Benzyl (3a*S*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate **180** (0.20 g, 0.51 mmol) and Cs_2CO_3 (0.332 g, 1.02 mmol) was dissolved in DCM (10 mL). The solution was cooled down to 0 °C. Bromine (31.6 µL, 0.61 mmol) was added dropwise to the mixture followed by the addition of morpholine (0.44 mL, 5.10 mmol). The reaction mixture was stirred at 0 °C for 2 h and quenched with water (10 mL). The organic layer was extracted with DCM (2 x 50 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude green product was purified using column chromatography (petrol / ethyl acetate 1:1 gradient to 100% ethyl acetate) to give benzyl(3a*S*,5*S*,10b*S*)-2-methyl-5-morpholino-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo [3,4-*a*] carbazole-10(1*H*)-carboxylate in (0.1651 g, 0.35 mmol, 69%) as a white solid.

Mp. 175 – 177 °C. **R_f** : 0.4 (petrol / ethyl acetate 1:1).**^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.01 (dt, *J* = 8.4, 0.9 Hz, 1H, Ar), 7.96 – 7.84 (m, 1H, Ar), 7.44 – 7.10 (m, 7H, Ar), 5.48 (d, *J* = 11.9 Hz, 1H, H_5), 5.33 (d, *J* = 11.9 Hz, 1H, H_5), 4.76 (d, *J* = 8.1 Hz, 1H, H_6), 3.70 (t, *J* = 5.4, Hz, 1H, H_{10}), 3.57 (t, *J* = 4.6 Hz, 4H, $H_{(12,13)}$), 3.48 – 3.39 (m, 1H, H_8), 2.61 – 2.51 (m, 2H, $H_{(11,14)}$), 2.48 – 2.37 (m, 2H, $H_{(11,14)}$), 2.10 – 2.02 (m, 2H, H_9).**^{13}C NMR (75 MHz, CD_2Cl_2):** δ_C 178.6 (CO), 174.5 (CO), 151.2, 136.8, 134.9, 128.9, 128.8, 128.7,128.6, 128.2, 124.7, 122.8, 120.6, 119.8, 114.7, 69.2 (C_5), 67.2, 55.6, 49.7, 40.2, 38.5, 24.8, 22.8. **IR (neat): ν_{max}/cm^{-1}:** 1708 (CO), 2981 (CH, Ar). **MS (pNSI):** 947.39 (100%, $[2M+H]^+$), 969.3795 (58%, $[2M+Na]^+$); **HRMS (pNSI):** calcd $C_{27}H_{28}N_3O_5$ $[M+H]^+$: 474.2023; observed: 474.2018.

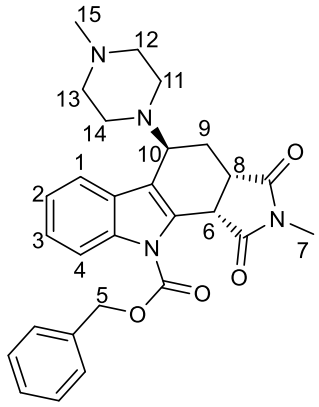
Benzyl (3a*S*,5*S*,10b*S*)-5-(diethylamino)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (184)



Benzyl (3a*S*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate **180** (0.112 g, 0.28 mmol) and Cs_2CO_3 (0.183 g, 0.57 mmol) was dissolved in DCM (5 mL). The solution was cooled down to 0 °C. Bromine (17.0 µL, 0.33 mmol) was added dropwise to the mixture followed by the addition of diethylamine (0.43mL, 2.8 mmol). The reaction mixture was stirred at 0 °C for 2 h and quenched with water (5 mL). The organic layer was extracted with DCM (2 x 30 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol / ether / DCM 2:1:1) to give benzyl (3a*S*,5*S*,10b*S*)-5-(diethylamino)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10 (1*H*) -carboxylate in (0.0861 g, 0.19 mmol, 68%) as a yellow solid.

Mp. 185 – 187 °C. **R_f** : 0.3 (petrol / ether / DCM 2:1:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.09 – 7.98 (m, 2H, Ar), 7.54 – 7.27 (m, 5H, Ar), 7.22 – 7.02 (m, 2H, Ar), 5.49 (d, *J* = 11.9 Hz, 1H, H_5), 5.35 (d, *J* = 11.9 Hz, 1H, H_5), 4.81 (d, *J* = 8.3 Hz, 1H, H_6), 3.95 (ddd, *J* = 9.7, 4.5, 1.8 Hz, 1H, H_{10}), 3.34 (dt, *J* = 8.5, 5.0 Hz, 1H, H_8), 2.78 (s, 3H, H_7), 2.63 – 2.29 (m, 5H, $H_{(9,11,14)}$), 1.82 (ddd, *J* = 13.3, 9.7, 5.6 Hz, 1H, H_9), 0.98 (t, *J* = 7.1 Hz, 6H, $H_{(12,13)}$).**^{13}C NMR (75 MHz, CD_2Cl_2):** δ_C 178.2 (CO), 174.5 (CO), 151.5, 137.0, 134.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 124.6, 122.4, 122.3, 121.9, 69.2 (C_5), 51.4 ($C_{11,14}$), 43.3 ($C_{12, 13}$), 39.8, 39.0, 24.8, 20.2, 13.7 (C_7). **IR (neat): ν_{max}/cm^{-1}:** 1703 (CO), 2981 (CH). **MS (pNSI):** 919.43 (100%, $[2M+H]^+$), 460.22 (70%, $[M+H]^+$), 941.4206 (20%, $[2M+Na]^+$); **HRMS (pNSI):** calcd $C_{27}H_{30}N_3O_4$ $[M+H]^+$: 460.2231; observed: 460.2220.

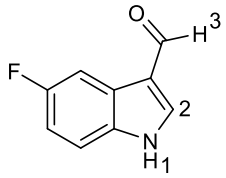
Benzyl(3a*S*,5*S*,10b*S*)-2-methyl-5-(4-methylpiperazin-1-yl)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (185)



Benzyl (3a*S*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate **180** (0.038 g, 0.09 mmol) and Cs_2CO_3 (0.064 g, 0.19 mmol) was dissolved in DCM (3 mL). The solution was cooled down to 0 °C. Bromine (6.0 µL, 0.11 mmol) was added dropwise to the mixture followed by the addition of 1-methylpiperazine (0.10 mL, 0.97 mmol). The reaction mixture was stirred at 0 °C for 2.5 h and quenched with water (5 mL). The organic layer was extracted with DCM (2 x 30 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol / ethyl acetate 2:1 gradient to 100% MeOH) to give benzyl(3a*S*,5*S*,10b*S*)-2-methyl-5-(4-methylpiperazin-1-yl)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate in (0.0326 g, 0.067 mmol, 75%) as a white solid.

Mp. 195 – 197 °C. **R_f**: 0.2 (petrol / methanol 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2)**: δ_H 8.12 (d, *J* = 8.1 Hz, 1H, Ar), 8.07 - 8.03 (m, 1H, Ar), 7.56 - 7.52 (m, 2H, Ar), 7.49 – 7.40 (m, 3H, Ar), 7.35 - 7.23 (m, 2H, Ar), 5.60 (d, *J* = 11.9 Hz, 1H, H_5), 5.46 (d, *J* = 11.9 Hz, 1H, H_5), 4.88 (d, *J* = 8.2 Hz, 1H, H_6), 3.84 (t, *J* = 5.8Hz, 1H, H_{10}), 3.54 (dt, *J* = 8.3, 6.0 Hz, 1H, H_8), 2.92 (s, 3H, H_7), 2.75 – 2.67 (m, 2H, $H_{(11,14)}$), 2.61 - 2.53 (m, 2H, $H_{(11,14)}$), 2.26 - 2.38 (m, 4H, $H_{(12,13)}$), 2.26 – 2.14 (m, 3H, H_{15}), 2.23 – 2.14 (m, 2H, H_9).**^{13}C NMR (75 MHz, CD_2Cl_2):** δ_C 178.4 (CO), 174.6 (CO), 151.5, 150.0, 136.8, 135.1, 128.8, 128.7, 128.5, 128.3, 124.6, 122.7, 120.9, 120.5, 114.6, 69.2 (C_5), 55.5, 55.4, 45.8, 40.1, 38.8, 24.7, 24.9, 22.5 (C_{15}). **IR (neat): ν_{max}/cm^{-1}:** 1703 (CO), 2980 (CH). **MS (pNSI):** 973.46 (100%, $[2M+H]^+$), 995.44 (30%, $[2M+Na]^+$), 509.21 (25%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{28}H_{31}N_4O_4$ $[M+H]^+$: 487.2340; observed: 487.2327.

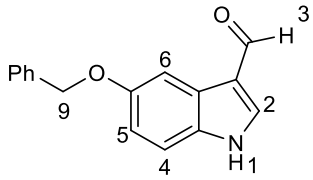
5-Fluoro-1*H*-indole-3-carbaldehyde (195)



Phosphorus oxychloride (0.82 mL, 8.87 mmol) was added dropwise to the stiring mixture of 5-fluoro-1*H*-indole **193** (1.00 g, 7.39 mmol) in DMF (2.86 mL, 36.99 mmol) at 0 °C. The reaction mixture was stirred at 40 °C for 2h and then was cooled to room temperature. Cold water (10 mL) was added followed by addition of 2.0 M solution of NaOH in water (20 mL), until pH about 10. The organic layer was extracetd with EtOAc, washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give 5-fluoro-1*H*-indole-3-carbaldehyde in (1.17 g, 7.18 mmol, 97%) as an orange solid.

Mp. 177 – 179 °C (lit. 182 – 187 °C).[104] **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ_H 12.25 (br, s, NH), 9.88 (s, 1H, H_3), 8.36 (s, 1H, H_2), 7.76 (dd, *J* = 2.8, 8.5 Hz, 1H, Ar), 7.53 (dd, *J* = 4.4, 8.4, Hz, 1H, Ar), 7.12 (t, *J* = 8.2 Hz, 1H, Ar).**^{13}C NMR (100 MHz,DMSO-*d*$_6$):** δ_C 185.5 (CO), 158.8 (d, J_{C-F} = 234.0 Hz, C_6), 140.3, 134.0, 125.2 (d, J_{C-F} = 11.2 Hz), 118.7, 114.3 (d, J_{C-F} = 9.4 Hz), 112.1 (d, J_{C-F} = 25.9 Hz), 106.3 (d, J_{C-F} = 24.4 Hz). **IR (neat): ν_{max}/cm^{-1}:** 3210 (NH), 2840 (CO), 1060 (C-F). **MS (pNSI):** 186.0 [100% $(M+Na)^+$], 164.0 $(M+H)^+$], 349.0 [95% $(2M+Na)^+$]; **HRMS (pNSI):** calcd C_9H_7FNO $[M+H]^+$: 164.0506; observed:164.0504.

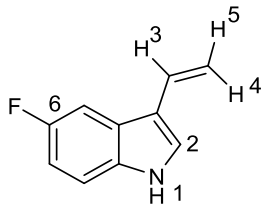
5-(Benzyloxy)-1*H*-indole-3-carbaldehyde (196)



Phosphorus oxychloride (1.00 mL, 10.74 mmol) was added dropwise to a solution of 5-(benzyloxy) -1*H*-indole **194** (2.00 g, 8.95 mmol) in DMF (3.27 mL, 44.48 mmol) at 0 ^{o}C. to the reaction mixture. The reaction mixture was stirred at 40 ^{o}C for 2h and then cooled to room temperature . Cold water (10 mL) was added followed by addition of 2.0 M solution of NaOH in water (20 mL), until pH about 10. The organic layer was extracetd with EtOAc (4 x 50 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed by reduced pressure to give 5-(benzyloxy)-1*H*-indole-3-carbaldehyde in (1.86 g, 7.41 mmol, 83%) as bright brown solid.

Mp. 231 – 233 ^{o}C (lit. 237 – 238 ^{o}C).[108] **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ_H 11.99 (br, s, NH), 9.86 (s,1H, H_3), 8.19 (s,1H, H_2), 7.66 (d, *J* = 1.9 Hz, 1H, Ar), 7.45 (d, *J* = 7.4 Hz, 1H, Ar), 7.39 – 7.33 (m, 3H, Ar), 7.30- 7.26 (m, 1H, Ar), 5.16 (s, 2H, H_9).**^{13}C NMR (100 MHz, DMSO-*d*$_6$):** δ_C 185.3 (CHO), 155.2, 139.2, 138.1, 132.3, 128.8, 128.2,128.0, 125.2, 118.3, 114.4,113.6, 104.5, 70.1 (C_5). **IR (neat): ν_{max}/cm^{-1}:**3660 (NH), 1734 (CO), 2981 (C-H). **MS (pNSI):** 274.08 (100%, $[M+Na]^+$), 525.17 (30%, $[2M+Na]^+$); **HRMS (pNSI):** calcd $C_{16}H_{13}NO_2Na$ $[M+Na]^+$: 274.0838; observed: 274.0841.

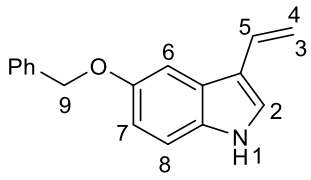
5-Fluoro-3-vinyl-1*H*-indole (197)



n-Butyllithium (2.5 M in hexane, 2.4 mL, 6.12 mmol) was added dropwise to a solution of methyltriphenylphosphonium iodide **153** (2.84 g, 7.38 mmol) in THF (10 mL) at -78 °C. The reaction mixture was warmed up to 0 °C and left to stir for 1 h. In a separate round, a solution of 5-fluoro-1*H*-indole-3-carbaldehyde **195** (1.00 g, 6.12 mmol) in THF (10 mL) was transferred via cannula into the solution at -78 °C. The reaction mixture was stirred at room temperature for 1 h. The organic layer was extracted with ethyl acetate (2 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow oil product was purified by column chromatography (petrol / ethyl acetate 4:1) to give 5-fluoro-3-vinyl-1*H*-indole in (0.8525 g, 5.29 mmol, 87%) as a yellow solid.

Mp. 79 – 81 °C. **R_f**: 0.3 (petrol / ethyl acetate 4:1).**^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ_H 11.3 (br, s, NH), 7.55 (d, *J* = 2.9 Hz, 1H, H_2), 7.51 (dd, *J* = 2.6, 9.9 Hz, 1H, Ar), 7.35 (dd, *J* = 4.7, 8.4 Hz, 1H, Ar), 6.93 (t, *J* = 6.7 Hz, 1H, Ar), 6.79 (dd, *J* = 11.3, 17.3 Hz, 1H, H_3), 5.55 (dd, *J* = 15.8, 1.8 Hz, 1H, H_4), 5.01 (dd, *J* = 11.3, 1.8 Hz, 1H, H_5).**^{13}C NMR (400 MHz, DMSO-*d*$_6$):** δ_C 159.3, 156.7, 134.0, 130.2 (d, J_{C-F} = 241.0 Hz, C_6)**,** 125.7 (d, J_{C-F} = 10.9 Hz), 114.5 (d, J_{C-F} = 4.7 Hz), 113.2 (d, J_{C-F} = 9.6 Hz), 110.0 (d, J_{C-F} = 5.8 Hz), 109.8, 104.8 (d, J_{C-F} = 23.3 Hz). **IR (neat): ν_{max}/cm^{-1}:** 3408 (NH), 1060 (C-F)**.**

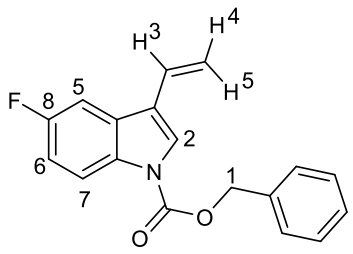
5-Phenethoxy-3-vinyl-1*H*-indole (198)



n-Butyllithium (2.5 M in hexane, 3.01 mL, 7.89 mmol) was added dropwise to a solution of methyltriphenylphosphonium iodide **153** (3.50 g, 9.07 mmol) in THF (10 mL) at -78 ^{o}C. The reaction mixture was warmed up to 0 ^{o}C and left to stir for 1 h. In a separate round, a solution of 5-(benzyloxy)-1*H*-indole-3-carbaldehyde **196** (2.00 g, 7.89 mmol) in THF (10 mL) was transferred via cannula into the solution at -78 ^{o}C. The reaction mixture stirred at room temperature for 1 h. The organic layer was extracted with ethyl acetate (4 x 150 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude orange solid product was purified by column chromatography (petrol / ethyl acetate 4:1) to give 5-phenethoxy-3-vinyl-1*H*-indole in (1.530 g, 6.14 mmol, 78%) as a yellow solid.

Mp. 148 – 150 ^{o}C. **R_f** : 0.3 (petrol / ethyl acetate 4:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 8.14 (br, s, NH), 7.59 - 7.38 (m, 6H, Ar), 7.23 (d, *J* = 7.3 Hz,1H, Ar), 7.17 (s,1H, H_2), 7.04 (d, *J* = 7.3 Hz ,1H, Ar), 6.94 (dd, *J* = 11.3, 17.2 Hz, 1H, H_3), 5.71 (d, *J* = 17.2 Hz, 1H, H_5), 5.25 (d, *J* =11.3 Hz, 1H, H_4), 5.20 (s, 2H, H_9).**^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 153.9, 137.6, 132.0, 129.5, 128.6, 127.9, 127.7, 126.0, 124.3, 115.6, 113.2, 112.0, 110.3, 103.9, 71.1. **IR (neat): ν_{max}/cm^{1}:** 3429 (NH), 1183 (C-N).

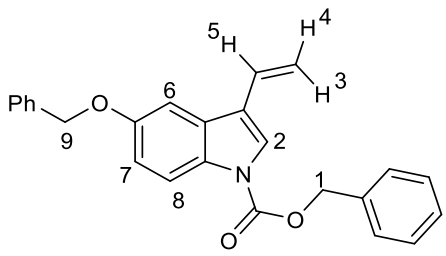
Benzyl 5-fluoro-3-vinyl-1*H*-indole-1-carboxylate (199)



A solution of 5-fluoro-3-vinyl-1*H*-indole **197** (0.833 g, 5.16 mmol) in THF (10 mL) was cooled down to 0 °C. NaHMDS (1.0 M in THF, 10.32 mL, 10.32 mmol) was added to the solution. After 30 min, benzyl chloroformate (0.81 mL, 5.67 mmol,) was added. The reaction mixture was stirred at 0 °C for 4 h. The solution was diluted with DCM (3 X 50 mL), washed with water (2 x 100 mL), brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The orange crude solid was purified by column chromatography in (petrol / ethyl acetate 4:1) to give benzyl 5-fluoro-3-vinyl-1*H*-indole-1-carboxylate (1.39 g, 4.70 mmol, 91%) as a white solid.

Mp. 189 – 200 °C. **R_f**: 0.30 (petrol / ethyl acetate 4:1).**^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ_H 8.1 (s, 1H, Ar), 7.70 (s, 1H, H_2), 7.52 – 7.36 (m, 6H, Ar), 7.09 (t, *J* = 7.0 Hz, 1H, Ar), 6.75 (dd, *J* = 11.7, 16.9 Hz, 1H, H_3), 5.77 (d, *J* = 16.9 Hz, 1H, H_5), 5.64 (s, 2H, H_1), 5.36 (d, *J* = 11.7 Hz, 1H, H_4). **^{13}C NMR (100 MHz, DMSO-*d*$_6$):** δ_C160.9 (d, J_{C-F} = 241.0 Hz, C_8), 155.2, 150.5, 135.3, 135.0, 132.3, 128.9, 128.7, 128.4, 127.6, 124.9, 119.8 (d, J_{C-F} = 4.3 Hz), 116.4 (d, J_{C-F} = 9.5 Hz), 112.6 (d, J_{C-F} = 26.5 Hz), 106.0 (d, J_{C-F} = 24.7 Hz), 69.6 (C_1). **IR (neat): ν_{max}/cm^{-1}:** 1737 (N-CO), 1066 (C-F)**. HRMS (pNSI):** calcd $C_{18}H_{15}FNO_2$ $[M+H]^+$: 296.1081; observed: 296.1084.

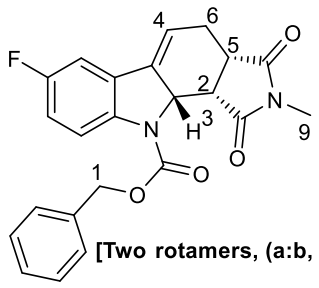
Benzyl 5-(benzyloxy)-3-vinyl-1*H*-indole-1-carboxylate (200)



A solution of 5-phenethoxy-3-vinyl-1*H*-indole **198** (0.455g, 1.72 mmol) in THF (10 mL) was cooled dawn to 0 °C. NaHMDS (1.0 M in THF, 2.07 mL, 2.07 mmol) was added dropwise over 5 min. The mixture left to stir for 30 min, and then benzyl chloroformate (0.26 mL, 1.89 mmol) was added. The reaction mixture was stirred at 0 °C for 4 h and quenched with water (15 mL). The organic layer was extracted with ethyl acetate (3 x 50 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude orange solid product was purified by column chromatography (petrol / ethyl acetate 6:1) to give benzyl 5-(benzyloxy)-3-vinyl-1*H*-indole-1-carboxylate in (0.520 g 1.36 mmol, 80%) as a white solid.

Mp. 182 – 184°C. **R_f** : 0.30 (petrol / ethyl acetate 4:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 8.11 (m, 1H, Ar), 7.64 (s, 1H, H_2), 7.50 - 7.32 (m, 11H, Ar), 7.04 (d, *J* = 8.6 Hz, 1H, Ar), 6.75 (dd, *J* = 11.6, 16.6 Hz, 1H, H_5), 5.75 (d, *J* = 16.6 Hz, 1H, H_3), 5.43 (s, 2H, H_1), 5.33 (d, *J* = 11.6 Hz, 1H, H_4), 5.12 (s, 2H, H_9).**^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 155.6, 150.7, 137.2, 135.1, 130.9, 129.6, 128.8, 128.7, 128.6, 128.4, 128.0, 127.9, 127.6, 124.3, 119.8, 116.3, 114.7, 113.8, 104.7, 70.7, 68.7. **IR (neat): ν_{max}/cm^{-1}:** 1729 (CO), 1183 (C-N). **MS (pNSI):** 384.15 (100%, $[M+H]^+$), 784.33 (57%, $[2M+NH4]^+$), 406.14 (10%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{25}H_{22}NO_3$ $[M+H]^+$: 384.1594; observed: 384.1596.

Benzyl(3a*S*,10a*S*,10b*S*)-7-fluoro-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (201)

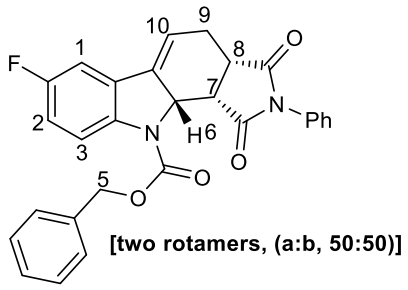


[Two rotamers, (a:b, 44:56)]

Benzyl 5-fluoro-3-vinyl-1*H*-indole-1-carboxylate **199** (0.323 g, 1.09 mmol) and *N*-methylmaleimide (0.122 g 1.09 mmol) were dissolved in DCM (10 mL). The mixture was refluxed for 24 h. The solvent was removed under reduced pressure. The crude white solid was purified by column chromatography (petrol / ethyl acetate 2:1) to yield benzyl(3a*S*,10a*S*,10b*S*)-7-fluoro-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)- carboxylate in (0.3055 g, 0.75 mmol, 69%) as a white solid.

Mp. 130 – 132 °C. **R_f** : 0.48 (petrol / ethyl acetate 2:1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 8.90 (dd, *J* = 6.4, 8.5 Hz, 1H, Ar, a), 7.53 (dd, *J* = 6.4, 8.5 Hz, 1H, Ar, b), 7.50 - 6.84 (m, 14H, Ar, a, b), 6.14 (dt, *J* = 3.7,7.4 Hz, 2H, H_4, a,b), 5.46 (d, *J* = 12.2 Hz, 1H, H_1, b), 5.41 (d, *J* = 12.2 Hz, 1H, H_1, b), 5.38 (d, *J* = 12.2 Hz, 1H, H_1, a), 5.33 (d, *J* = 12.2, 1H, H_1, a), 4.81 - 4.78 (m, 1H, H_5, b), 4.74 – 4.70 (m, 1H, H_5, a), 4.32 (t, *J* = 8.8 Hz, 1H, H_3, b), 3.93 (t, *J* = 8.8 Hz, 1H, H_3, a), 3.18 (t, *J* = 8.4 Hz, 1H, H_2, a), 3.11 - 3,03 (m, 3H, $H_{(6a)}$, $H_{(2b)}$), 2.79 (s, 6H, H_9, a,b), 2.24 - 2.11 (m, 2H, H_6, b).**^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 179.0 (CO), 178.7 (CO), 174.9 (CO), 174.5 (CO), 160.7 (d, J_{C-F} = 235.8 Hz), 160.5 (d, J_{C-F} = 232.0 Hz), 152.9, 152.0, 151.3, 141.2, 139.9, 136.7 (d, J_{C-F} = 11.9 Hz), 135.8 (d, J_{C-F} = 10.1 Hz), 134.5, 128.9, 128.3, 128.1, 127.5, 127.4, 127.0 (d, J_{C-F} = 11.9 Hz), 126.8, 117.0, 116.9, 116.8, 116.6, 114.1 (d, J_{C-F} = 5.9 Hz), 113.9, 109.9, 107.7 (d, J_{C-F} = 5.9 Hz), 106.8, 68.4, 67.7, 60.2, 59.6, 41.2, 40.3, 37.6, 37.4, 25.2, 25.0, 24.9, 24.7. **IR (neat): ν_{max}/cm^{-1}:** 1775 (CO), 1690 (N-CO), 1600 (C=C). **MS (pNSI):** 424.1 [100% $(M+NH4)^+$], 407.1 [45% $(M+H)^+$], 271.0 [10% $(M\text{-}Cbz)^+$]; **HRMS (pNSI):** calcd $C_{23}H_{20}FN_2O_4$ $[M+H]^+$: 407.1402; observed: 407.1404.

Benzyl (3a*S*,10a*S*,10b*S*)-7-fluoro-1,3-dioxo-2-phenyl-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (202)

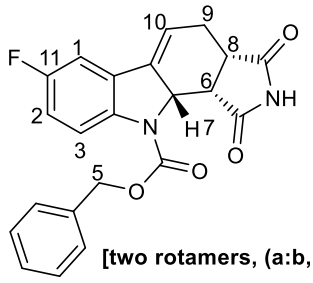


[two rotamers, (a:b, 50:50)]

Benzyl 5-fluoro-3-vinyl-1*H*-indole-1-carboxylate **199** (1.633 g, 5.50 mmol) and *N*-phenylmaleimide (0.952 g, 5.50 mmol) were dissolved in DCM (20 mL). The reaction mixture was refluxed for 24 h. The solvent was removed under reduced pressure. The crude green solid was purified by column chromatography (petrol / ethyl acetate 2:1) to yield benzyl (3a*S*,10b*S*)-7-fluoro-1,3-dioxo-2-phenyl-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate in (1.8 g, 3.84 mmol, 70%) as a white solid.

Mp. 165 – 167 ºC. **R_f** = 0.28 (petrol / ethyl acetate 2:1). **^{1}H NMR (300 MHz, $CDCl_3$):** δ_H 8.11 – 8.06 (m, 1H, Ar, 1H, a), 7.57 – 7.51 (m, 1H, Ar, b), 7.51 – 7.30 (m, 16H, Ar, a, b), 7.14 – 6.86 (m, 8H, Ar, a, b), 6.28 (dt, *J* = 7.3, 3.8 Hz, 2H, H_{10}, a, b), 5.52 – 5.31 (m, 4H, H_5, a,b), 4.93 – 4.78 (m, 2H, H_6, a, b), 4.52 (t, *J* = 7.1 Hz, 1H, H_7, a), 4.15 - 4.09 (t, *J* = 7.3 Hz, 1H, H_7, b), 3.44 – 3.11 (m, 4H, H_9, a,b), 2.39 – 2.24 (m, 2H, H_8, a,b). **^{13}C NMR (176 MHz, $CDCl_3$):** δ_C 177.9 (CO), 177.7 (CO), 173.8 (CO), 173.5 (CO), 160.7, 160.5, 158.4, 158.2, 152.9, 151.9, 141.2, 140.0, 136.9, 135.8, 135.6, 131.5 (d, J_{C-F} = 7.8 Hz), 129.2, 129.1, 128.8, 128.7, 128.5, 128.4, 128.2, 127.4 (d, J_{C-F} = 8.9 Hz), 127.3 (d, J_{C-F} = 8.9 Hz), 126.9, 126.8, 126.2, 126.1, 117.1, 117.0, 116.8, 114.1 (d, J_{C-F} = 16.5 Hz), 113.9, 107.2, 107.0 (d, J_{C-F} = 9.2 Hz), 106.8, 106.7, 68.3 (C_5, a or b), 67.8 (C_5, a or b), 60.3, 59.7, 41.2, 40.3, 37.8, 37.6, 25.6, 25.2.. **IR (neat): ν_{max}/cm^{-1}:** 2981 (CH). 1698 (N-CO). **MS (pNSI):** 486.18 (100%, $[M+NH_4]^+$), 954.33 (87%, $[2M+NH_4]^+$), 469.15 (25%, $[M+H]^+$); **HRMS (pNSI):** calcd $C_{28}H_{22}FN_2O_4$ $[M+H]^+$: 469.1558; observed: 469.1556.

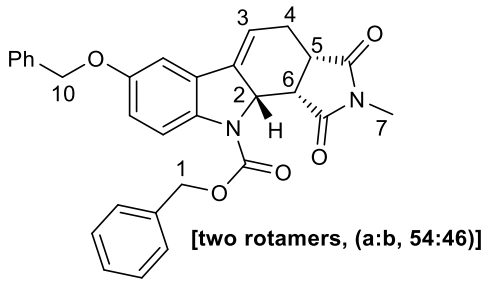
Benzyl (3a*S*,10a*S*,10b*S*)-7-fluoro-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (203)



Benzyl 5-fluoro-3-vinyl-1*H*-indole-1-carboxylate **199** (1.027g, 3.47mmol) and maleimide (0.337g, 3.47 mmol) were dissolved in DCM (10 mL). The mixture was refluxed for 24 h. The solvent was removed under reduced pressure. The crude white solid was purified by column chromatography (petrol / ethyl acetate 2:1 gradient to 100% ethyl acetate) to yield benzyl (3a*S*,10a*S*,10b*S*)-7-fluoro-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylatein (0.969 g, 2.47 mmol, 72%) as a white solid.

Mp. 213 – 215 ºC. **R_f** : 0.2 (petrol / ethyl acetate 2:1). **^{1}H NMR (300 MHz, DMSO-d_6):** δ_H 11.09 (s, 1H, NH), 7.88 (dd, *J* = 9.0, 4.7 Hz, 1H, Ar), 7.57 – 7.30 (m, 6H, Ar), 7.10 (t, *J* = 7.8 Hz, 1H, Ar), 6.45 (dt, *J* = 7.5, 3.7 Hz, 1H, H_{10}), 5.47 – 5.20 (m, 2H, H_5), 4.93 – 4.89 (m, 1H, H_7, a), 4.87 – 4.81 (m, 1H, H_7, b), 4.10 (t, *J* = 7.9 Hz, 1H, H_6, b), 3.95 (t, *J* = 8.3 Hz, 1H, H_6), 3.27 – 3.17 (m, 2H, H_8, a,b), 2.75 (dd, *J* = 15.5, 7.3 Hz, 2H, H_9, a,b), 2.21 (m, 2H, H_9, a,b). **^{13}C NMR (75 MHz, DMSO-d_6):** δ_C 180.9 (CO), 177.1 (CO), 160.3 (d, J_{C-F} = 254.1`Hz, C_{11}), 152.3, 141.5, 136.7, 136.4, 128.9, 128.6, 128.4, 128.2, 128.0, 116.5, 116.2, 108.1 (d, J_{C-F} = 24.8 Hz), 67.2 (C_5), 59.6 (C_7), 42.6 ($C_{6 \text{ or } 8}$), 38.9 ($C_{6 \text{ or } 8}$), 24.8 (C_9). **IR (neat): ν_{max}/cm^{-1}:** 3654 (NH), 1705 (CO), 2981 (CH). **MS (pNSI):** 410.15 (100%, $[M+NH_4]^+$), 802.26 (57%, [2M+NH4] $^+$), 393.12 (15%, $[M+H]^+$); **HRMS (pNSI):** calcd $C_{22}H_{18}FN_2O_4$ $[M+H]^+$: 393.1245; observed: 393.1249.

Benzyl(3a*S*,10a*S*,10b*S*)-7-(benzyloxy)-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (204)

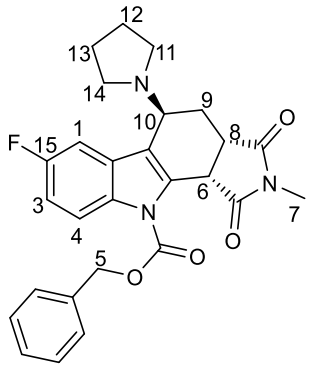


[two rotamers, (a:b, 54:46)]

Benzyl 5-(benzyloxy)-3-vinyl-1*H*-indole-1-carboxylate **200** (0.160 g, 0.41 mmol) and *N*-methylmaleimide (0.055mg, 0.41mmol) were dissolved in DCM (5 mL). The mixture was refluxed for 18 h. The solvent was removed under reduced pressure. The crude yellow solid product was purified by column chromatography (petrol / ethyl acetate 2:1) to yield benzyl (3a*S*,10a*S*,10b*S*)-7-(benzyloxy)-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*] carbazole-10(1*H*)-carboxylate in (0.155 g, 0.31 mmol, 76%) as a white solid.

Mp. 138 – 140 °C. **R_f** : 0.3 (petrol / ethyl acetate 2:1)**. ^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 8.00 (d, *J* = 9.3 Hz, 1H, Ar, a), 7.94, 7.46 - 6.81 (m, 25H, Ar, a,b). 6.09 (dt, *J* = 3.8, 6.9 Hz, 2H, H_3, a,b), 5.42 (dd, *J* = 11.5 Hz, 4H, H_1, a, b), 5.00 (s, 4H, H_{10}, a,b), 4.76 (m, 1H, H_5, b), 4. 69 (m, 1H, H_5, a), 4.30 (t, *J* = 8.3 Hz, 1H, H_2, b), 3.93 (t, *J* = 8.3 Hz, 1H, H_2, a), 3.16 (t, *J* = 7.3 Hz, 1H, H_6, b), 3.09 - 2.94 (m, 4H, $H_{6,}$), 2.96 (t, *J* = 7.3 Hz, 1H, H_4, b), 3.17 (t, *J* = 7.3 Hz, 1H, H_6, b), 3.00 (m, 3H, $H_{(6,4),}$ a), 2.78 (s, 6H, H_7, a,b), 2.15 (m, 2H, H_4, b).**^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 179.3 (CO), 179.0 (CO), 175.1 (CO), 174.9 (CO), 155.5, 154.9, 153.1, 152.1, 139.3, 138.1, 137.5, 137.3, 136.9, 136.1, 128.8, 128.7, 128.5, 128.2, 128.1, 127.6, 127.1,126.7, 117.2, 116.6, 112.9, 106.6, 106.4, 70.6, 67.7, 60.1, 59.4, 41.2, 40.4, 25.1, 24.8, 23.9, 14.7, 14.1. **IR (neat): ν_{max}/cm^{-1}:** 1770 (CO), 1694 (N-CO), 3657 (N-Me). **MS (pNSI):** 512.21 (100%, $[M+NH_4]^+$), 495.19 (15%, $[2M+H]^+$); **HRMS (pNSI):** calcd $C_{30}H_{30}N_3O_5$ $[M+NH_4]^+$: 512.2180; observed: 512.2175.

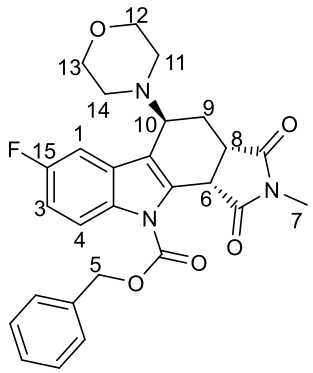
Benzyl(3a*S*,5*S*,10b*S*)-7-fluoro-2-methyl-1,3-dioxo-5-(pyrrolidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (205)



Benzyl (3a*S*,10a*S*,10b*S*)- 7-fluoro-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)- carboxylate **201** (0.100 g, 0.24 mmol) and Cs_2CO_3 (0.1596 g, 0.49 mmol) was dissolved in DCM (5 mL). The solution was cooled down to 0 °C. Bromine (14.7 µL, 0.28 mmol) was added dropwise to the mixture followed by the addition of pyrrolidine (0.20 mL, 2.4 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched with water (5 mL). The organic layer was extracted with DCM (2 x 30 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol / ethyl acetate 1:1 gradient to 100% ethyl acetate) to give benzyl 7-fluoro-2-methyl-1,3-dioxo-5-(pyrrolidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (0.837g, 0.183 mmol, 76%) as a yellow solid.

Mp. 176 – 178 °C. **R_f** : 0.3 (petrol / ethyl acetate 1:1). **^{1}H NMR (400 MHz, CD_2Cl_2):** δ_H 8.12 (dd, *J* = 9.1, 4.7 Hz, 1H, Ar), 7.63 – 7.19 (m, 6H, Ar), 7.06 (t, *J* = 9.2, 2.7 Hz, 1H, Ar), 5.56 (d, *J* = 11.8 Hz, 1H, H_5), 5.40 (d, *J* = 11.8 Hz, 1H, H_5), 4.76 (d, *J* = 7.9 Hz, 1H, H_6), 3.76 – 3.48 (m, 2H, $H_{(10, 8)}$), 2.96 (s, 3H, H_7), 2.80 – 2.71 (m, 2H, $H_{(11,14)}$), 2.59 – 2.32 (m, 3H, $H_{(11, 14, 9)}$), 1.80 – 1.70 (m, 5H, $H_{(12, 13, 9)}$). **^{13}C NMR (75 MHz, CD_2Cl_2)**: δ_C 178.6 (CO), 174.2 (CO), 160.7 (d, J_{C-F} = 237.7 Hz, C_{15}), 151.4, 134.7, 132.9, 130.1, 129.8, 129.3, 129.2, 128.9, 120.7 (d, J_{C-F} = 4.4 Hz), 115.8 (d, J_{C-F} = 10.0 Hz), 112.0 (d, J_{C-F} = 24.1 Hz), 105.0 (d, J_{C-F} = 24.1 Hz), 69.4 (C_5), 51.4, 41.0, 38.3, 28.1, 24.8, 23.5, 22.3. **IR (neat):ν_{max}/cm^{-1}:** 1729 (CO), 1597 (C=C). **MS (pNSI):** 951.38 (100%, $[2M+H]^+$), 973.37 (18%, $[2M+Na]^+$); **HRMS (pNSI):** calcd $C_{27}H_{26}FN_3O_4Na$ $[M+Na]^+$: 498.1800; observed: 498.1790.

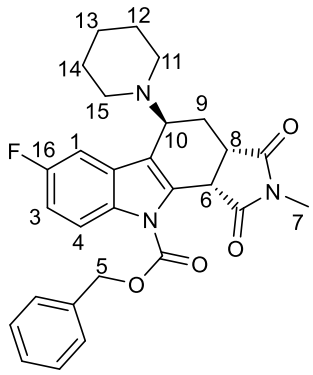
Benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-2-methyl-5-morpholino-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (206)



Benzyl(3a*S*,10a*S*,10b*S*)-7-fluoro-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo [3,4-*a*]carbazole-10(1*H*)- carboxylate **201** (0.150 g, 0.36 mmol) and Cs_2CO_3 (0.2378 g, 0.73 mmol) was dissolved in DCM (10 mL). The solution was cooled down to 0 °C. Bromine (22.0 µL, 0.43 mmol) was added dropwise to the mixture followed by the addition of the morpholine (0.31 mL, 3.6 mmol). The reaction mixture was stirred at 0 °C for 2 h and quenched with water (10 mL). The organic layer was extracted with DCM (3 x 30 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol / ethyl acetate 1:1) to give benzyl(3a*S*,5*S*,10b*S*)-7-fluoro-2-methyl-5-morpholino-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate in (0.1421g, 0.29 mmol, 81%) as a white solid.

Mp. 149 – 151 °C. **R_f**: 0.5 (petrol / ethyl acetate 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 7.97 (dd, *J* = 9.1, 4.6 Hz, 1H, Ar), 7.63 (dd, *J* = 9.4, 2.7 Hz, 1H, Ar), 7.43 – 7.26 (m, 5H, Ar), 6.94 (td, *J* = 9.1, 2.7 Hz, 1H, Ar), 5.48 (d, *J* = 11.8 Hz, 1H, H_5), 5.33 (d, *J* = 11.8 Hz, 1H, H_5), 4.77 (d, *J* = 8.2 Hz, 1H, H_6) 3.72 – 3.64 (m, 1H, H_8), 3.59 (t, *J* = 4.6 Hz, 4H, $H_{(12,13)}$), 3.45 – 3.37 (m, 1H, H_{10}), 2.81 (s, 3H, H_7), 2.58 – 2.51 (m, 2H, $H_{(11,14)}$), 2.46 – 2.39 (m, 2H, $H_{(11,14)}$), 2.18 – 2.06 (m, 2H, H_9). **^{13}C NMR (75 MHz, CD_2Cl_2):** δ_C 178.2 (CO), 174.3 (CO), 160.8 (d, J_{C-F} = 239.3 Hz, C_{15}), 151.2 (CO), 148.0, 134.9, 133.4, 130.6, 128.9, 128.8, 128.7, 119.8 (d, J_{C-F} = 5.0 Hz), 115.8 (d, J_{C-F} = 8.9 Hz), 112.0 (d, J_{C-F} = 23.9 Hz), 106.5 (d, J_{C-F} = 24.8 Hz), 69.5 (C_5), 67.1, 55.7, 49.6, 40.1, 38.6, 24.9, 22.0. **IR (neat): ν_{max}/cm^{-1}:** 1727 (CO), 2980 (CH, Ar), 1072 (C-F). **MS (pNSI):** 983.37 (100%, $[2M+H]^+$), 492.19 (85%, $[M+H]^+$), 405.12 (75%, $[M-O(CH_2)_4N]^+$; **HRMS (pNSI):** calcd C_{27} $H_{27}FN_3O_5$ $[M+H]^+$: 492.1929; observed: 492.1922.

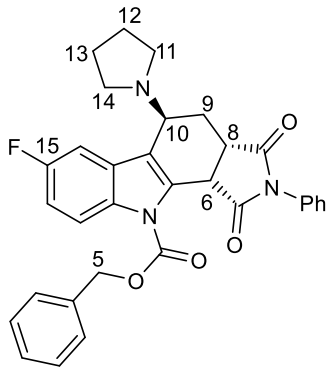
Benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-2-methyl-1,3-dioxo-5-(piperidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (207)



Benzyl (3a*S*,10a*S*,10b*S*)-7-fluoro-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo [3,4-*a*] carbazole-10 (1*H*)- carboxylate **201** (0.100 g, 0.24 mmol) and Cs_2CO_3 (0.156 g, 0.48 mmol) was dissolved in DCM (5 mL). The solution was cooled down to 0 °C. Bromine (15.1 µL, 0.29 mmol) was added dropwise to the mixture followed by the addition of piperidine (0.23 mL, 2.4 mmol). The reaction mixture was stirred at 0 °C for 2 h, and quenched with water (5 mL). The organic layer was extracted with DCM (2 x 30 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol / ethyl acetate 2:1) to give benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-2-methyl-1,3-dioxo-5-(piperidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo [3,4-*a*]carbazole-10(1*H*)-carboxylate in (0.078 g, 0.16 mmol, 67%) as a white solid.

Mp. 180 – 182 °C. **R_f**: 0.5 (petrol / ethyl acetate 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 7.95 (dd, *J* = 9.1, 4.6 Hz, 1H, Ar), 7.74 (ddd, *J* = 9.6, 2.7, 1.0 Hz, 1H, Ar), 7.45 – 7.36 (m, 2H, Ar), 7.39 – 7.26 (m, 3H, Ar), 6.92 (t, *J* = 9.1,Hz, 1H, Ar), 5.49 (d, *J* = 11.9 Hz, 1H, H_5), 5.33 (d, *J* = 11.8 Hz, 1H, H_5), 4.79 (d, *J* = 8.4 Hz, 1H, H_6), 3.66 (ddd, *J* = 9.3, 4.5, 2.5 Hz, 1H, H_{10}), 3.37 (dt, *J* = 8.4, 5.3 Hz, 1H, H_8), 2.80 (s, 3H, H_7), 2.53 – 2.35 (m, 4H, $H_{(11,15)}$), 2.29 – 2.21 (m, 1H, H_9), 1.99 – 1.90 (m, 1H, H_9), 1.56 – 1.32 (m, 6H, $H_{(12,13,14)}$).**^{13}C NMR (75 MHz, CD_2Cl_2)**: δ_C 178.3 (CO), 174.6 (CO), 160.68 (d, J_{C-F} = 236.3 Hz, C_{16}), 151.6 (CO), 134.6, 133.3, 130.3, 129.2, 128.2, 128.7, 128.8, 121.0 (d, J_{C-F} = 5.5 Hz), 115.6 (d, J_{C-F} = 9.2 Hz), 112.1 (d, J_{C-F} = 25.1 Hz), 106.8 (d, J_{C-F} = 25.1 Hz), 69.4 (C_5), 56.4, 49.9, 39.9, 38.8, 26.3, 24.9, 24.7, 20.9. **IR (neat): ν_{max}/cm^{-1}:** 1780 (CO), 1706 (CO), 1087 (C-F), 2981 (Ar, CH).**MS (pNSI):** 490.21 (100%, [M+H]+), 512.19 (35%, $[M+Na]^+$), 979.42 (15%, $[2M+H]^+$); **HRMS (pNSI):** calcd $C_{28}H_{29}FN_3O_4$ $[M+H]^+$: 490.2137; observed: 490.2131.

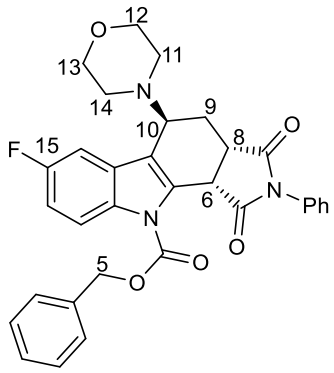
Benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-1,3-dioxo-2-phenyl-5-(pyrrolidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (208)



Benzyl(3a*S*,10a*S*,10b*S*)-7-fluoro- 1,3-dioxo-2-phenyl-2,3,3a,4,10a,10b-hexahydropyrrolo [3,4-*a*] carbazole-10(1*H*)-carboxylate **202** (0.100 g, 0.25 mmol) and Cs_2CO_3 (0.167 g, 0.51 mmol) was dissolved in DCM (5 mL). The solution was cooled down to 0 °C. Bromine (15.1 µL, 0.30 mmol) was added dropwise to the mixture followed by the addition of pyrrolidine (0.20 mL, 2.5 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched with water (5 mL). The organic layer was extracted with DCM (2 x 30 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol / ethyl acetate 2:1) to give benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-1,3-dioxo-2-phenyl-5-(pyrrolidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate in (0.101 g, 0.19 mmol, 76%) as a white solid.

Mp. 165 – 167 °C. **R_f**: 0.42 (petrol / ethyl acetate 2:1) **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.16 (dd, *J* = 9.1, 4.6 Hz, 1H, Ar), 7.59 – 7.35 (m, 9H, Ar), 7.28 – 7.15 (m, 2H, Ar), 7.08 (t, *J* = 9.2 Hz, 1H, Ar), 5.51 (d, *J* = 11.7 Hz, 1H, H_5), 5.39 (d, *J* = 11.8 Hz, 1H, H_5), 4.95 (d, *J* = 7.9 Hz, 1H, H_6), 3.85 – 3.77 (m, 1H, H_8), 3.73 (t, *J* = 4.9 Hz, 1H, H_{10}), 2.84 2.78 (m, 2H, $H_{(11,14)}$), 2.60 (dt, *J* = 13.5, 4.5 Hz, 1H, H_9), 2.52 – 2.44 (m, 2H, $H_{(11,14)}$), 1.92 – 1.86 (m, 1H, H_9), 1.83 – 1.74 (m, 4H, $H_{(12,13)}$). **^{13}C NMR (75 MHz, CD_2Cl_2):** δ_C 177.6 (CO), 173.1 (CO), 160.7 (d, J_{C-F} = 246.5 Hz, C_{15}), 151.5 (CO), 134.8, 132.7, 131.7, 129.6, 129.4, 129.3, 129.0, 128.8, 128.7, 126.6, 120.6 (d, J_{C-F} = 8.3 Hz), 116.0 (d, J_{C-F} = 10.3 Hz), 112.1 (d, J_{C-F} = 24.2 Hz), 104.8 (d, J_{C-F} = 25.1 Hz), 69.5 (C_5), 52.0, 53.6, 41.5, 38.5, 29.3, 23.4. **IR (neat): ν_{max}/cm^{-1}:** 1775 (CO), 1077 (Ar, CH). **MS (pNSI):** 538.21 (100%, $[M+H]^+$), 1075.42 (45%, $[2M+H]^+$), 560.19 (17%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{32}H_{29}FN_3O_4$ $[M+H]^+$: 538.2137; observed: 538.2129.

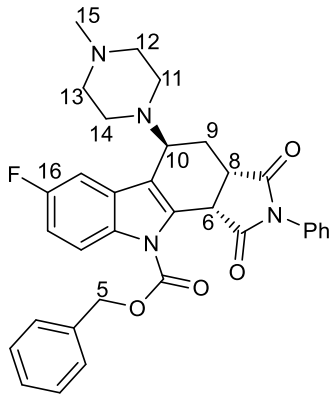
Benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-5-morpholino-1,3-dioxo-2-phenyl-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (209)



Benzyl (3a*S*,10a*S*,10b*S*)-7-fluoro-1,3-dioxo-2-phenyl-2,3,3a,4,10a,10b-hexahydropyrrolo [3,4-*a*] carbazole-10(1*H*)-carboxylate **202** (0.150 g, 0.32 mmol) and Cs_2CO_3 (0.2086g, 0.64 mmol) were dissolved in DCM (5 mL). The solution was cooled down to 0 °C. Bromine (19.6 µL, 0.38 mmol) was added dropwise to the mixture followed by the addition of morpholine (0.27 mL, 3.2 mmol). The reaction mixture was stirred at 0 °C for 2 h, and quenched with water (5 mL). The organic layer was extracted with DCM (2 x 40 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol: ethyl acetate 2:1) to give Synthesis of benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-5-morpholino-1,3-dioxo-2-phenyl-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (0.1342 g, 0.24 mmol, 76%) as a white solid.

Mp. 159 – 161 °C. **R_f**: 0.21 (petrol / ethyl acetate 2:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.12 (dd, *J* = 9.1, 4.6 Hz, 1H, Ar), 7.70 (dd, *J* = 9.3, 2.6 Hz, 1H, Ar), 7.54 – 7.41 (m, 8H, Ar), 7.26 – 7.17 (m, 2H, Ar), 7.08 (td, *J* = 9.1, 2.7 Hz, 1H, Ar), 5.57 (d, *J* = 11.8 Hz, 1H, H_5), 5.43 (d, *J* = 11.8 Hz, 1H, H_5), 4.94 (d, *J* = 8.2 Hz, 1H, H_6), 3.81 – 3.72 (m, 1H, H_8), 3.60 (dt, *J* = 9.2, 5.0 Hz, 5H, $H_{(10,12,13)}$), 2.59 (dt, *J* = 11.4, 4.6 Hz, 2H, $H_{(11,14)}$), 2.44 (dt, *J* = 11.1, 4.6 Hz, 2H, $H_{(11,14)}$), 2.32 – 2.06 (m, 2H, H_9).**^{13} C NMR (75 MHz, CD_2Cl_2):** δ_C 177.5 (CO), 173.1 (CO), 160.5 (d, J_{C-F} = 234.3 Hz, C_{15}), 151.2, 134.6, 133.2, 131.8, 130.1, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 126.5, 119.6 (d, J_{C-F} = 4.2 Hz), 115.9 (d, J_{C-F} = 8.6 Hz), 112.4 (d, J_{C-F} = 24.9 Hz), 106.0 (d, J_{C-F} = 24.9 Hz), 69.7 (C_5), 66.9, 55.8, 49.7, 40.4, 38.6, 32.2. **IR (neat): ν_{max}/cm^{-1}: MS (pNSI):** 554.20 (100%, $[M+H]^+$), 576.18 (16%, $[M+Na]^+$), 1107.41 (20%, $[2M+H]^+$); **HRMS (pNSI):** calcd $C_{32}H_{29}FNO_5$ $[M+H]^+$: 554.2086; observed: 554.2080.

Benzyl(3a*S*,5*S*,10b*S*)-7-fluoro-5-(4-methylpiperazin-1-yl)-1,3-dioxo-2-phenyl-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (210)

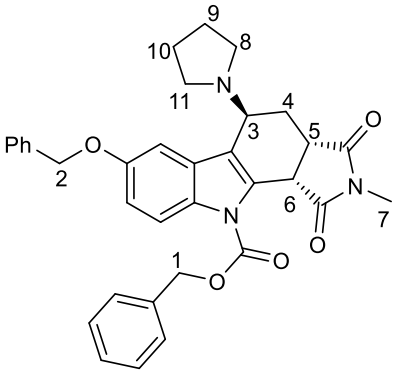


Benzyl (3a*S*,10a*S*,10b*S*)-7-fluoro-1,3-dioxo-2-phenyl-2,3,3a,4,10a,10b-hexahydropyrrolo [3,4-*a*] carbazole-10(1*H*)-carboxylate **202** (0.170 g, 0.36 mmol) and Cs_2CO_3 (0.2364 g, 0.72 mmol) were dissolved in DCM (10 mL). The solution was cooled down to 0 °C. Bromine (22.0 µL, 0.43 mmol) was added dropwise to the mixture followed by the addition of 1-methylpiperazine (0.39 mL, 3.6 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched with water (5 mL). The organic layer was extracted with DCM (2 x 50 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol / ethyl acetate 2:1 gradient to 100% methanol) to give benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-5-(4-methylpiperazin-1-yl)-1,3-dioxo-2-phenyl-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (0.164 g, 0.29 mmol, 81%) as a white solid.

Mp. 172 – 174 °C. **R_f**: 0.1 (petrol / methanol 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2)**: δ_H 8.11 (dd, *J* = 9.1, 4.6 Hz, 1H, Ar), 7.74 (dd, *J* = 9.4, 2.7 Hz, 1H, Ar), 7.56 – 7.38 (m, 8H, Ar), 7.24 – 7.12 (m, 2H, Ar), 7.07 (t, *J* = 9.2 Hz, 1H, Ar), 5.57 (d, *J* = 11.8 Hz, 1H, H_5), 5.44 (d, *J* = 11.8 Hz, 1H, H_5), 5.06 (d, *J* = 8.4 Hz, 1H, H_6), 3.92 (t, *J* = 5.8 Hz, 1H, H_{10}), 3.72 (ddd, *J* = 8.4, 6.6, 5.7 Hz, 1H, H_8), 2.77 - 2.69 (m, 2H, $H_{(11, 14)}$), 2.63 – 2.39 (m, 5H, $H_{(9,12,13)}$), 2.31 (t, *J* = 6.4 Hz, 2H, $H_{(11, 14)}$), 2.27 (s, 3H, H_{15}), 1.74 – 1.69 (m, 1H, H_9). **^{13}C NMR (75 MHz, CD_2Cl_2):** δ_C 177.3 (CO), 173.2 (CO), 160.6 (d, J_{C-F} = 241.5 Hz, C_{16}), 151.2 (CO), 135.1, 134.8, 133.2, 131.8, 129.9, 129.3, 129.1, 128.9, 128.7, 126.5, 120.3 (d, J_{C-F} = 6.3 Hz), 115.9 (d, J_{C-F} = 7.7 Hz), 112.5 (d, J_{C-F} = 24.2 Hz), 106.2 (d, J_{C-F} = 24.2 Hz), 69.5 (C_5), 55.4, 55.2, 49.1, 45.7, 40.5, 38.8, 23.0. **IR (neat): ν_{max}/cm^{-1}:** 1707 (CO), 2973 (CH). **MS (pNSI):** 1133.47 (100%, $[2M+H]^+$), 1165.46 (35%,

$[2M+Na]^+$), 979.42 (15%, $[2M+H]^+$); **HRMS (pNSI):** calcd $C_{33}H_{32}FN_4O_4$ $[M+H]^+$: 567.2402; observed: 567.2396.

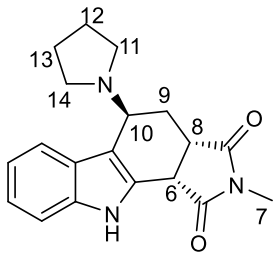
Benzyl (3a*S*,5*S*,10b*S*)-7-(benzyloxy)-2-methyl-1,3-dioxo-5-(pyrrolidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (212)



Benzyl (3a*S*,10a*S*,10b*S*)-7-(benzyloxy)-2-methyl-1,3-dioxo-2, 3, 3a,4,10a, 10b-hexahydropyrrolo [3,4-*a*] carbazole-10 (1*H*)-carboxylate **204** (0.07 g, 0.14 mmol) and Cs_2CO_3 (0.912 g, 0.28 mmol) were dissolved in DCM (5 mL). The solution was cooled down to 0 °C. Bromine (8.7 µL, 0.16 mmol) was added dropwise to the mixture followed by the addition of pyrrolidine (0.11 mL, 1.4 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched with water (5 mL). The organic layer was extracted with DCM (2 x 30 mL), washed with brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude yellow product was purified using column chromatography (petrol / ethyl acetate 2:1) to give benzyl (3a*S*,5*S*,10b*S*)-7- (benzyloxy)- 2-methyl-1,3-dioxo-5-(pyrrolidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (0.055 g, 0.098 mmol, 70%) as a bright yellow solid.

Mp. 153 – 155 °C. **R_f** : 0.16 (petrol / ethyl acetate 2:1). **^{1}H NMR (300 MHz, CD_2Cl_2)**: δ_H 8.03 (d, *J* = 9.0 Hz, 1H, Ar), 7.46 – 7.15 (m, 11H, Ar), 6.93 (d, *J* = 9.1 Hz, 1H, Ar), 5.39 (d, *J* = 11.8 Hz, 1H, H_1), 5.26 (d, *J* = 11.8 Hz, 1H,H_1), 5.07 (s, 2H, H_2), 4.75 (t, *J* = 2.9 Hz, 1H, H_3), 4.57 (d, *J* = 7.8 Hz, 1H, H_6), 3.57 (ddd, *J* = 12.9, 7.9, 5.1 Hz, 1H, H_5), 2.97 - 2.82 (m, 2H, $H_{(8,11)}$), 2.85 (s, 3H, H_7), 2.47 (ddd, *J* = 12.9, 5.1, 3.2 Hz, 1H, H_4), 2.35 -2.27 (m, 2H, $H_{(8,11)}$),1.64 – 1.54 (m, 4H, $H_{(9,10)}$), 1.43 – 1.31 (m, 1H, H_4). **^{13}C NMR (75 MHz, CD_2Cl_2):** δ_C 179.3 (CO), 174.2 (CO), 151.5, 151.3, 136.8, 134.7, 132.6, 130.7, 129.0, 128.8, 128.7, 128.4, 127.9, 127.5, 127.4, 120.6, 114.2, 111.5, 103.7, 72.0 (C_2), 69.6 (C_5), 51.4, 50.9, 41.3, 37.6, 31.1, 24.8, 23.8 (C_7). **IR (neat): ν_{max}/cm^{-1}:** 1710 (CO), 2973 (CH).

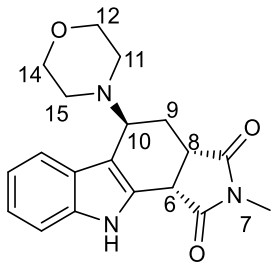
(3a*S*,5*S*,10b*S*)-2-methyl-5-(pyrrolidin-1-yl)-4,5,10,10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (213)



Benzyl (3a*S*,5*S*,10b*S*)-2-methyl-1,3- dioxo-5- (pyrrolidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo [3,4-*a*]carbazole-10(1*H*)-carboxylate **182** (0.889 g, 0.19 mmol) and platinum (IV) oxide (0.441g, 0.19 mmol) were dissolved in THF (5 mL). The reaction mixture was placed under hydrogen atmosphere for 6 h. The resulting suspension was filtered through celite and the solvent was removed under reduced pressure. The crude brown solid was purified by column chromatography (petrol / ethyl acetate 1:1 to 100% methanol) to give (3a*S*,5*S*,10b*S*)-2-methyl-5-(pyrrolidine-1-yl)-4,5,10,10b-tetrahydropyrrolo [3,4-*a*]carbazole 1,3(2*H*,3a*H*)-dione in (0.461 g, 0.14 mmol, 75%) as a yellow solid.

Mp. 123 – 125 ^{o}C. **R_f** : 0.12 (petrol / methanol 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.82 (s, 1H, NH), 7.57 – 7.40 (m, 1H, Ar), 7.35 – 7.19 (m, 1H, Ar), 7.17 – 6.91 (m, 2H, Ar), 4.10 (d, *J* = 8.6 Hz, 1H, H_6), 3.81 – 3.42 (m, 2H, $H_{(8,10)}$), 2.90 (s, 3H, H_7), 2.74 (dt, *J* = 7.9, 6.3 Hz, 2H, $H_{(11,14)}$), 2.58 (ddd, *J* = 13.6, 5.9, 3.5 Hz, 1H, H_9), 2.38 (m, 2H, $H_{(11,14)}$), 1.83 – 1.48 (m, 5H, $H_{(9,12,13)}$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ_C 179.7 (CO), 176.4 (CO), 135.9, 128.3, 126.6, 122.0, 119.7, 118.4, 113.9, 111.1, 55.1 (C_{10}), 52.9 ($C_{11, 14}$), 38.8 ($C_{6 \text{ or } 8}$), 37.2 ($C_{6 \text{ or } 8}$), 30.7 (C_9), 24.8 (C_7), 23.4 ($C_{12,13}$). **IR (neat): ν_{max}/cm^{-1}:** 3660 (NH), 2980 (CH), 1689 (CO). **MS (pNSI):** 253.09 (100%, [M-N$(CH_2)_4$H]$^+$), 324.17 (57%, [M+H]$^+$); **HRMS (pNSI):** calcd $C_{19}H_{22}N_3O_2$ [M+H]$^+$: 324.1707; observed: 324.1714.

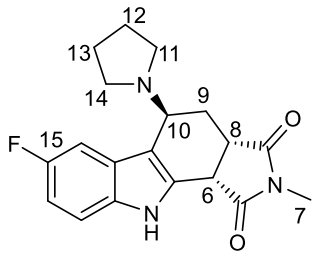
(3a*S*,5*S*,10b*S*)-5-morpholino-2-phenyl-4,5,10,10b-tetrahydropyrrolo [3,4-*a*] carbazole-1,3(2*H*,3a*H*)-dione (214)



Benzyl (3a*S*,10b*S*)-2-methyl-5-morpholino-1,3-dioxo-2,3,3a,4,10a,10b- hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate **183** (0.093 g, 0.19 mmol) and platinum (IV) oxide (0.0446 g, 0.19 mmol) were dissolved in THF (5 mL). The reaction mixture was placed under hydrogen atmosphere for 7 h. The resulting suspension was filtered through celite and the solvent was removed under reduced pressure. The crude green solid was purified by column chromatography (petrol / ethyl acetate 1:1 to 100% methanol) to give 2-methyl-5-(pyrrolidinee-1-yl)-4,5,10,10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3 (2*H*,3aH)- dione in (0.052 g, 0.15 mmol, 80%) as an orange solid.

Mp. 203 – 205 °C. **R_f** : 0.1 (petrol / ethyl acetate 1:1).**^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.80 (s, 1H, NH), 7.66 (d, *J* = 7.6, 1.5, 0.8 Hz, 1H, Ar), 7.29 (ddd, *J* = 8.1, 1.3, 0.8 Hz, 1H, Ar), 7.14 – 6.91 (m, 2H, Ar), 4.07 (d, *J* = 8.3 Hz, 1H, H_6), 3.72 – 3.64 (m, 1H, H_{10}), 3.65 – 3.46 (m, 5H, $H_{(12,14,8)}$), 2.85 (s, 3H, H_7), 2.62 (dt, *J* = 11.6, 4.6 Hz, 2H, $H_{(11,15)}$), 2.39 (m, 3H, $H_{(11,15,9)}$), 1.82 (ddd, *J* = 13.3, 9.6, 3.5 Hz, 1H, H_9).**^{13}C NMR (176 MHz, CD_2Cl_2):** δ_C 179.2 (CO), 176.1 (CO), 136.1, 128.3, 127.1, 122.0, 119.8, 119.3, 112.2, 111.0, 67.2, 55.7, 50.7, 39.0, 37.8, 25.6, 24.7. **IR (neat): ν_{max}/cm^{-1}:** 3656 (NH), 2981 (CH, Ar), 1697 (CO). **MS (pNSI):** 340.16 (100%, $[M+H]^+$), 701.30 (10%, $[2M+Na]^+$); **HRMS (pNSI):** calcd $C_{19}H_{22}N_3O_3$ $[M+H]^+$: 340.1656; observed: 340.1656.

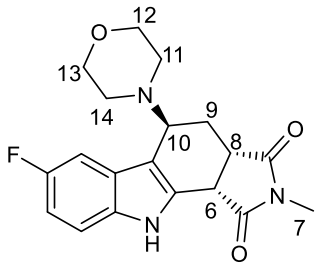
(3a*S*,5*S*,10b*S*)-7-fluoro-2-methyl-5-(pyrrolidin-1-yl)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (215)



Benzyl 7-fluoro-2-methyl-,3-dioxo- 5-(pyrrolidin-1-yl) -2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate **205** (0.75 g, 0.16 mmol) and platinum (IV) oxide (0.363 g, 0.16 mmol) were dissolved in THF (5 mL). The reaction mixture was placed under hydrogen atmosphere for 6 h. The resulting suspension was filtered through celite and the solvent was removed under reduced pressure. The crude brown solid was purified by column chromatography (petrol / ethyl acetate 1:1 to 100% methanol) to give 7-fluoro-2-methyl-5-(pyrrolidin-1-yl)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*] carbazole-1,3 (2*H*,3a*H*)-dione in (0.049 g, 0.14 mmol, 90%) as a brown solid.

Mp. 118 – 120 °C. **R_f** : 0.12 (petrol / methanol 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.97 (s, 1H, NH), 7.23 (dd, *J* = 8.8, 4.5 Hz, 1H, Ar), 7.17 (dd, *J* = 9.8, 2.6 Hz, 1H, Ar), 6.82 (td, *J* = 9.1, 2.5 Hz, 1H, Ar), 4.09 (d, *J* = 8.6 Hz, 1H, H_6), 3.62 (ddd, *J* = 12.3, 8.7, 5.8 Hz, 1H, H_8), 3.54 (t, *J* = 3.5 Hz, 1H, H_{10}), 2.89 (s, 3H, H_7), 2.80 – 2.67 (m, 2H, $H_{(11,14)}$), 2.57 (ddd, *J* = 13.6, 5.9, 3.5 Hz, 1H, H_9), 2.39 (dt, *J* = 8.6, 6.1 Hz, 2H, $H_{(11,14)}$), 1.75 – 1.50 (m, 5H, $H_{(12,13,9)}$). **^{13}C NMR (75 MHz, CD_2Cl_2):** δ_C 179.4 (CO), 176.0 (CO), 159.5 (d, J_{C-F} = 231.8 Hz, C_{15}), 132.6, 130.1, 127.1, 114.0 (d, J_{C-F} = 7.4 Hz), 111.9 (d, J_{C-F} = 11.1 Hz), 109.6 (d, J_{C-F} = 24.5 Hz), 103.4 (d, J_{C-F} = 24.5 Hz), 55.0 (C_{10}), 52.7 ($C_{11,14}$), 38.8 ($C_{6\text{ or }8}$), 37.2 ($C_{6\text{ or }8}$), 30.5 ($C_{12,13}$), 24.8 (C_9), 23.5 (C_7). **IR (neat): ν_{max}/cm^{-1}:** 3660 (NH), 1695 (CO). **HRMS (pNSI):** calcd $C_{19}H_{21}FN_3O_2$ $[M+H]^+$: 342.1612; observed: 342.1617.

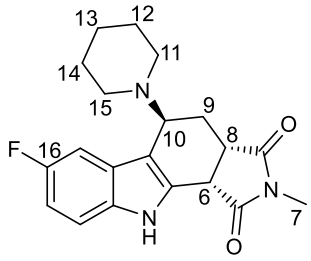
(3a*S*,5*S*,10b*S*)-7-fluoro-2-methyl-5-morpholino-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (216)



Benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-2-methyl-5-morpholino-1,3- dioxo-2,3,3a,4,5,10b-hexahydro pyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate **206** (0.05 g, 0.10 mmol) and platinum (IV) oxide (0.023 g, 0.10 mmol) were dissolved in THF (5 mL). The reaction mixture was placed under hydrogen atmosphere for 8 h. The resulting suspension was filtered through celite and the solvent was removed under reduced pressure. The crude green solid was purified by column chromatography (petrol / ethyl acetate 1:1 to 100% methanol) to give ((3aS,5S,10bS)-7-fluoro-2-methyl-5-morpholino- 4,5,10,10b-tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.029 g, 0.08 mmol, 81%) as a brown solid.

Mp. 185 – 187 °C. **R_f** : 0.11 (petrol / methanol 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.73 (s, 1H, NH), 7.35 (dd, *J* = 9.9, 2.6 Hz, 1H, Ar), 7.23 (dd, *J* = 8.8, 4.4 Hz, 1H, Ar), 6.87 – 6.80 (m, 1H, Ar), 4.07 (d, *J* = 8.4 Hz, 1H, H_6), 3.65 (dd, *J* = 6.2, 3.6 Hz, 1H, H_{10}), 3.57 (t, *J* = 4.6 Hz, 4H, $H_{(12,13)}$), 3.55 -3.50 (d, 1H, H_8), 2.86 (s, 3H, H_7), 2.60 (dt, *J* = 9.9, 4.6 Hz, 2H, $H_{(11,14)}$), 2.37 (dd, *J* = 13.4, 6.6 Hz, 3H, $H_{(11,14,\ 9)}$), 1.87 (ddd, *J* = 13.7, 9.1, 3.6 Hz, 1H, H_9). **^{13}C NMR (176 MHz, CD_2Cl_2):** δ_C 179.0 (CO), 175.7 (CO), 157.5 (d, J_{C-F} = 230.8 Hz), 132.7, 130.3, 127.6 (d, J_{C-F} = 9.7 Hz), 112.7 (d, J_{C-F} = 4.6 Hz), 111.9 (d, J_{C-F} = 9.3 Hz), 110.1 (d, J_{C-F} = 24.6 Hz), 104.3 (d, J_{C-F} = 24.6 Hz), 67.3, 55.7, 50.6, 39.2, 37.9, 25.0, 24.8. **IR (neat): ν_{max}/cm^{-1}:** 3451 (NH). **MS (pNSI):** 358.15 (100%, $[M+H]^+$); **HRMS (pNSI):** calcd $C_{19}H_{21}FN_3O_3$ $[M+H]^+$: 358.1561; observed: 358.1562.

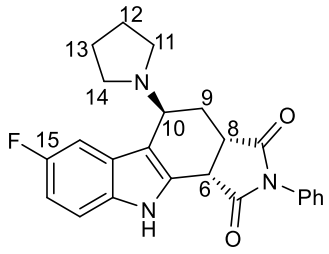
(3a*S*,5*S*,10b*S*)-7-fluoro-2-methyl-5-(piperidin-1-yl)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (217)



Benzyl(3a*S*,5*S*,10b*S*)-7-fluoro-2-methyl-1,3-dioxo-5-(piperidin-1-yl)-2,3,3a,4,5,10b-hexahydropyrrolo [3,4-*a*]carbazole-10(1*H*)-carboxylate **207** (0.077 g, 0.15 mmol) and platinum (IV) oxide (0.0357 g, 0.15 mmol) were dissolved in THF (7 mL). The reaction mixture was placed under hydrogen atmosphere for 5 h. The resulting suspension was filtered through celite and the solvent was removed under reduced pressure. The crude green solid was purified by column chromatography (petrol / ethyl acetate 1:1 to 100% methanol) to give (3aS,5S,10bS)-7-fluoro-2-methyl-5-(piperidin-1-yl)-4,5,10,10b-tetrahydro pyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0355 g, 0.1 mmol, 67%) as a green solid.

Mp. 147 – 149 ^{o}C. **R_f**: 0.1 (petrol: methanol 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.61 (s, 1H, NH), 7.44 (dd, *J* = 10.1, 2.6 Hz, 1H, Ar), 7.21 (dd, *J* = 8.8, 4.4 Hz, 1H, Ar), 6.82 (m, 1H, Ar), 4.06 (d, *J* = 8.3 Hz, 1H, H_6), 3.67 (dd, *J* = 7.3, 4.0 Hz, 1H, H_{10}), 3.58 – 3.42 (m, 1H, H_8), 2.84 (s, 3H, H_7), 2.62 – 2.47 (m, 2H, $H_{(11,15)}$), 2.40 – 12.32 (m, 2H, $H_{(11,15)}$), 2.22 (m, 1H, H_9), 2.01 (ddd, *J* = 13.4, 7.5, 4.0 Hz, 1H, H_9), 1.53 – 1.37 (m, 6H, $H_{(12,13,14)}$). **^{13}C NMR (176 MHz, CD_2Cl_2)**: δ_C 178.9 (CO), 176.0 (CO), 158.4 (d, J_{C-F} = 221.1 Hz, C_{16}), 132.9, 130.0, 127.6, 125.3, 111.5 (d, J_{C-F} = 9.1 Hz), 110.0 (d, J_{C-F} = 24.2 Hz), 105.0 (d, J_{C-F} = 24.2 Hz), 56.2 (C_{10}), 50.9, 39.3 ($C_{(12,14) \text{ or } (11,15)}$), 38.4, 26.6, 24.7 ($C_{(12,14) \text{ or } (11,15)}$), 23.6 ($C_{17}$). **IR (neat): ν_{max}/cm^{-1}:** 3655 (NH), 1694 (CO). **MS (pNSI):** 356.17 (65%, $[M+H]^+$), 378.15 (10%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{20}H_{23}FN_3O_2$ $[M+H]^+$: 356.1769; observed: 356.1768.

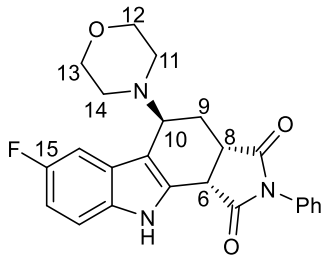
(3a*S*,5*S*,10b*S*)-7-fluoro-2-phenyl-5-(pyrrolidin-1-yl)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (218)



Benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-1,3-dioxo-2-phenyl-5-(pyrrolidin-1-yl)-2,3,3a,4,5, 10b-hexahydropyrrolo [3,4-*a*]carbazole-10(1*H*)-carboxylate **208** (0.101 g, 0.18 mmol) and platinum (IV) oxide (0.0427 g, 0.18 mmol) were dissolved in THF (5 mL). The reaction mixture was placed under hydrogen atmosphere for 7 h. The resulting suspension was filtered through celite and the solvent was removed under reduced pressure. The crude brown solid was purified by column chromatography (petrol / ethyl acetate 1:1 to 100% methanol) to give(3a*S*,5*S*,10b*S*)-7-fluoro-2-phenyl-5-(pyrrolidin-1-yl)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.056 g, 0.14 mmol, 78%) as a white solid.

Mp. 143 – 145 °C. **R_f** : 0.12 (petrol / methanol 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.99 (s, 1H, NH), 7.44 – 7.14 (m, 7H, Ar), 6.85 (t, *J* = 9.1, Hz, 1H, Ar), 4.40 (d, *J* = 8.9 Hz, 1H, H_6), 3.96 – 3.84 (m, 1H, H_{10}), 3.74 – 3.69 (m, 1H, H_8), 2.90 - 2.81 (m, 2H, $H_{(11, 14)}$), 2.70 (ddd, *J* = 13.8, 5.9, 3.3 Hz, 1H, H_9), 2.58 – 2. 50 (m, 2H, $H_{(11, 14)}$), 1.87-1.66 (m, 5H, $H_{(12, 13, 9)}$). **^{13}C NMR (176 MHz, CD_2Cl_2):** δ_C 178.1(CO), 174.9 (CO), 158.7 (d, J_{C-F} = 230.1 Hz, C_{15}), 132.6, 131.8, 129.1, 128.8, 126.8, 126.6, 124.0, 119.6, 112.2 (d, J_{C-F} = 9.1 Hz), 110.2 (d, J_{C-F} = 24.3 Hz), 103.4 (d, J_{C-F} = 24.3 Hz), 55.4 (C_{10}), 53.0 ($C_{11, 14}$), 39.0 ($C_{6 \text{ or } 8}$), 37.2 ($C_{6 \text{ or } 8}$), 30.4 ($C_{12, 13}$), 23.4 (C_9)**. IR (neat): ν_{max}/cm^{-1}:** 3660 (NH), 1694 (CO). **HRMS (pNSI):** calcd $C_{24}H_{23}FN_3O_2$ $[M+H]^+$: 404.1769; observed: 404.1765.

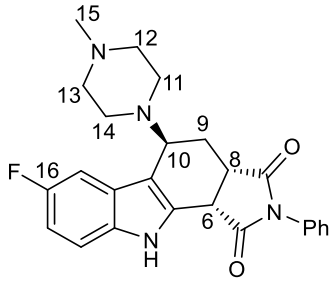
(3a*S*,5S,10b*S*)-7-fluoro-5-morpholino-2-phenyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (219)



Benzyl (3a*S*,5*S*,10b*S*)-7- fluoro-5-morpholino-1,3-dioxo-2- phenyl - 2,3,3a,4,5,10b–hexahydropyrrolo [3,4-*a*] carbazole-10(1*H*)- carboxylate **209** (0.10 g, 0.18 mmol) and platinum (IV) oxide (0.041 g, 0.18 mmol) were dissolved in THF (5 mL). The reaction mixture was placed under hydrogen atmosphere for 6 h. The resulting suspension was filtered through celite and the solvent was removed under reduced pressure. The crude brown solid was purified by column chromatography (petrol / ethyl acetate 1:1) to give (3a*S*,5S,10b*S*)-7-fluoro-5-morpholino-2-phenyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.0661 g, 0.134 mmol, 75%) as a yellow solid.

Mp. 192 – 193 ºC. **R_f** : 0.2 (petrol / ethyl acetate 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.77 (s, 1H, NH), 7.45 – 7.32 (m, 4H, Ar), 7.25 (dd, *J* = 8.8, 4.4 Hz, 1H, Ar), 7.20 – 7.09 (m, 2H, Ar), 6.89 – 6.82 (m, 1H, Ar), 4.27 (d, *J* = 8.7 Hz, 1H, H_6), 3.82 – 3.69 (m, 2H, $H_{(10, 8)}$), 3.59 (dd, *J* = 5.2, 4.0 Hz, 4H, $H_{(12,13)}$), 2.63 (dt, *J* = 9.7, 4.6 Hz, 2H, $H_{(11,14)}$), 2.53 – 2.35 (m, 3H, $H_{(11,14, 9)}$), 2.00 (ddd, *J* = 13.3, 9.3, 3.6 Hz, 1H, H_9).**^{13}C NMR (176 MHz, CD_2Cl_2):** δ_C 178.0 (CO), 174.7 (CO), 158.4 (d, J_{C-F} = 247.5 Hz, C_{15}), 132.9, 131.7, 129.9, 129.1, 128.7, 127.4 (d, J_{C-F} = 9.1 Hz), 126.5, 112.7 (d, J_{C-F} = 4.2 Hz), 111.9 (d, J_{C-F} = 9.1 Hz), 110.1 (d, J_{C-F} = 25.2 Hz), 104.4 (d, J_{C-F} = 25.2 Hz), 67.1, 55.6, 50.7, 39.3, 38.0, 25.4. **IR (neat): ν_{max}/cm^{-1}:** 3665 (NH), 2981 (CH), 1698 (CO). **MS (pNSI):** 861.31 (30%, $[2M+Na]^+$), 420.17 (20%, $[M+H]^+$); **HRMS (pNSI):** calcd $C_{24}H_{23}FN_3O_3$ $[M+H]^+$: 420.1718; observed: 420.1713.

(3a*S*,5*S*,10b*S*)-7-fluoro-5-(4-methylpiperazin-1-yl)-2-phenyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (220)



Benzyl (3a*S*,5*S*,10b*S*)-7-fluoro-5-(4-methylpiperazin-1-yl)- 1,3-dioxo-2-phenyl-2,3,3a,4,5,10b-hexahydropyrrolo [3,4-*a*]carbazole-10(1*H*)-carboxylate **210** (0.125 g, 0.22 mmol) and platinum (IV) oxide (0.05 g, 0.22 mmol) were dissolved in THF (5 mL). The reaction mixture was placed under hydrogen atmosphere for 5 h. The resulting suspension was filtered through celite and the solvent was removed under reduced pressure. The crude brown solid was purified by column chromatography (petrol / ethyl acetate 1:1) to give (3a*S*,5*S*,10b*S*)-7-fluoro-5-(4-methylpiperazin-1-yl)-2-phenyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione in (0.076 g, 0.175 mmol, 80%) as a yellow solid.

Mp. 185 – 187 °C. **R_f**: 0.2 (petrol / methanol 1:1). **^{1}H NMR (300 MHz, CD_2Cl_2):** δ_H 8.82 (s, 1H, NH), 7.43 – 7.32 (m, 3H, Ar), 7.27 – 7.10 (m, 3H, Ar), 6.82 (td, *J* = 9.1, 2.6 Hz, 1H, Ar), 4.24 (d, *J* = 7.7 Hz, 1H, H_6), 3.81 – 3.61 (m, 2H, $H_{(8,10)}$), 2.69 – 2.60 (m, 2H, $H_{(11,14)}$), 2.39 (m, 6H, $H_{(11,12,13,14)}$), 2.15 (s, 3H, H_{15}), 2.12 – 1,97 (m, 2H, H_9). **^{13}C NMR (176 MHz, CD_2Cl_2):** δ_C 178.0 (CO), 175.0 (CO), 159.1 (d, J_{C-F} = 234.3 Hz, C_{16}), 132.9, 131.7, 129.7, 129.0, 128.8, 128.7, 127.4 (d, J_{C-F} = 8.5 Hz), 126.5, 111.8 (d, J_{C-F} = 8.5 Hz), 110.1(d, J_{C-F} = 27.0 Hz), 104.8 (d, J_{C-F} = 24.3 Hz), 55.5, 55.4, 49.9, 45.7, 39.4, 38.2, 25.0 (C_{15}). **IR (neat): ν_{max}/cm^{-1}:** 3714 (NH), 1694 (CO). **MS (pNSI):** 433.20 (54%, $[M+H]^+$), 455.18 (15%, $[M+Na]^+$); **HRMS (pNSI):** calcd $C_{25}H_{26}FN_4O_2$ $[M+H]^+$: 433.2034; observed: 433.2035.

References

1. Bashir, M.; Bano, A.; Ijaz, A. S.; Chaudhary, B. A., *Molecules* **2015,** *20* (8), 13496.
2. Graebe, C.; Glaser, C., *Ber. Dtsch. Chem. Ges.* **1872,** *5*, 12.
3. Das, K. C.; Chakraborty, D. P.; Bose, P. K., *Experientia* **1965,** *21* (6), 340.
4. Chakraborty, D. P.; Barman, B. K.; Bose, P. K., *Tetrahedron* **1965,** *21* (2), 681.
5. Knolker, H. J.; Reddy, K. R., *Chem. Rev.* **2002,** *102* (11), 4303.
6. Bergman, J.; Pelcman, B., *Pure Appl. Chem.* **1990,** *62* (10), 1967.
7. Bauer, I.; Knoelker, H.-J., Synthesis of Pyrrole and Carbazole Alkaloids. In *Alkaloid Synthesis*, Knolker, H. J., Ed. 2012; Vol. 309, pp 203.
8. Heckrodt, T. J.; Mulzer, J., Marine natural products from Pseudopterogorgia elisabethae: Structures, biosynthesis, pharmacology, and total synthesis. In *Natural Products Synthesis Ii Targets, Methods, Concepts*, Mulzer, J., Ed. 2005; Vol. 244, pp 1.
9. Onaka, H.; Taniguchi, S.; Igarashi, Y.; Furumai, T., *Biosci., Biotechnol., Bioc hem.* **2003,** *67* (1), 127.
10. Jackson, J. R.; Gilmartin, A.; Imburgia, C.; Winkler, J. D.; Marshall, L. A.; Roshak, A., *Cancer Res.* **2000,** *60* (3), 566.
11. Deslandes, S.; Chassaing, S.; Delfourne, E., *Mar. Drugs* **2009,** *7* (4), 754.
12. Conchon, E.; Anizon, F.; Golsteyn, R. M.; Leonce, S.; Pfeiffer, B.; Prudhomme, M., *Tetrahedron* **2006,** *62* (48), 11136.
13. Schmidt, A. W.; Reddy, K. R.; Knoelker, H.-J., *Chem. Rev.* **2012,** *112* (6), 3193.
14. Fusko, R.; Sannikolo, F., *Khim. Geterotsikl. Soedin.* **1978,** (2), 200.
15. Xiao, F.; Liao, Y.; Wu, M.; Deng, G.-J., *Green Chem.* **2012,** *14* (12), 3277.
16. Cadogan, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G., *J. Chem. Soc.* **1965,** (0), 4831.
17. Prakash, K. S.; Nagarajan, R., *Tetrahedron Lett.* **2015,** *56* (1), 69.
18. Han, X. Q.; Widenhoefer, R. A., *Org. Lett.* **2006,** *8* (17), 3801.
19. Kong, W.; Fu, C.; Ma, S., *Chem. Eur. J.* **2011,** *17* (47), 13134.
20. Fan, W. Z.; Jiang, S.; Feng, B. N., *Tetrahedron* **2015,** *71* (23), 4035.
21. Knolker, H. J., *Chem. Soc. Rev.* **1999,** *28* (3), 151.
22. Cacchi, S.; Fabrizi, G., *Chem. Rev.* **2005,** *105* (7), 2873.
23. Knolker, H. J., *Synlett* **1992,** (5), 371.
24. Knolker, H. J.; Baum, E.; Hopfmann, T., *Tetrahedron* **1999,** *55* (34), 10391.

25. Knoelker, H.-J., *Chem. Lett.* **2009,** *38* (1), 8.

26. Tian-Shung, W.; Shiow-Chyn, H.; Jeng-Shiow, L.; Che-Ming, T.; Feng-Nien, K.; Chang-Sheng, K., *Phytochemistry* **1993,** *32* (2), 449.

27. Hartwig, J. F., *Angew. Chem. Int. Ed.* **1998,** *37* (15), 2046.

28. Forke, R.; Jaeger, A.; Knoelker, H.-J., *Org. Biomol. Chem.* **2008,** *6* (14), 2481.

29. Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L., *J. Org. Chem.* **2008,** *73* (19), 7603.

30. Ackermann, L.; Althammer, A., *Angew. Chem. Int. Ed.* **2007,** *46* (10), 1627.

31. Goo, D. Y.; Woo, S. K., *Org. Biomol. Chem.* **2015**.

32. Kureel, S. P.; Kapil, R. S.; Popli, S. P., *Tetrahedron Lett.* **1969,** *10* (44), 3857.

33. Ueno, A.; Kitawaki, T.; Chida, N., *Org. Lett.* **2008,** *10* (10), 1999.

34. Brieger, G.; Bennett, J. N., *Chem. Rev.* **1980,** *80* (1), 63.

35. Takao, K.; Munakata, R.; Tadano, K., *Chem. Rev.* **2005,** *105* (12), 4779.

36. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G., *Angew. Chem. Int. Ed.* **2002,** *41* (10), 1668.

37. Diels, O.; Alder, K., *Justus Liebigs Ann. Chem.* **1928,** *460* (1), 98.

38. Pindur, U.; Pfeuffer, L., *Heterocycles* **1987,** *26* (2), 325.

39. Noland, W. E.; Kuryla, W. C.; Lange, R. F., *J. Am. Chem. Soc.* **1959,** *81* (22), 6010.

40. Noland, W. E.; Sundberg, R. J., *J. Org. Chem.* **1963,** *28* (3), 884.

41. Lambert, J. D.; Porter, Q. N., *Aust. J. Chem.* **1981,** *34* (7), 1483.

42. Sainsbury, M., Ellipticines. In *The Chemistry of Antitumour Agents*, Wilman, D. V., Ed. Springer Netherlands: 1990; pp 410.

43. Pindur, U.; Otto, O., *Tetrahedron* **1992,** *48* (17), 3515.

44. Bergman, J.; Janosik, T.; Koch, E.; Pelcman, B., *J. Chem. Soc., Perkin Trans. 1* **2000,** (16), 2615.

45. Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M., *Tetrahedron Lett.* **2003,** *44* (20), 3935.

46. Henon, H.; Messaoudi, S.; Hugon, B.; Anizon, F.; Pfeiffer, B.; Prudhomme, M., *Tetrahedron* **2005,** *61* (23), 5599.

47. Conchon, E.; Anizon, F.; Aboab, B.; Golsteyn, R. M.; Leonce, S.; Pfeiffer, B.; Prudhomme, M., *Bioorg. Med. Chem.* **2008,** *16* (8), 4419.

48. Tao, M.; Park, C. H.; Bihovsky, R.; Wells, G. J.; Husten, J.; Ator, M. A.; Hudkins, R. L., *Bioorg. Med. Chem. Lett.* **2006,** *16* (4), 938.

49. Enders, D.; Joie, C.; Deckers, K., *Chem. Eur. J.* **2013,** *19* (33), 10818.

50. Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A., *Angew. Chem. Int. Ed.* **2008,** *47* (48), 9236.

51. Cowell, J.; Harrington, R. W.; Probert, M. R.; Hall, M. J., *Tetrahedron: Asymmetry* **2015,** *26* (20), 1189.

52. Mikami, K.; Shimizu, M., *Chem. Rev.* **1992,** *92* (5), 1021.

53. Stratakis, M.; Orfanopoulos, M., *Tetrahedron* **2000,** *56* (12), 1595.

54. Adam, W.; Krebs, O., *Chem. Rev.* **2003,** *103* (10), 4131.

55. Zhang, J. H.; Wang, M. X.; Huang, Z. T., *J. Chem. Res.* **1998,** (8), 486.

56. Grachan, M. L.; Tudge, M. T.; Jacobsen, E. N., *Angew. Chem. Int. Ed.* **2008,** *47* (8), 1469.

57. Adam, W.; Bottke, N.; Krebs, O., *Org. Lett.* **2000,** *2* (21), 3293.

58. Adam, W.; Bottke, N.; Krebs, O.; Lykakis, I.; Orfanopoulos, M.; Stratakis, M., *J. Am. Chem. Soc.* **2002,** *124* (48), 14403.

59. Ganem, B., *Acc. Chem. Res.* **2009,** *42* (3), 463.

60. DomLing, A.; Ugi, I., *Angew. Chem. Int. Ed.* **2000,** *39* (18), 3168.

61. Strecker, A., *Justus Liebigs Ann. Chem.* **1850,** *75* (1), 27.

62. Hantzsch, A., *Justus Liebigs Ann. Chem.* **1882,** *215* (1), 1.

63. Mannich, C.; Krösche, W., *Arch. Pharm.* **1912,** *250* (1), 647.

64. Ugi, I.; Meyr, R., *Angew. Chem.* **1958,** *70* (22-23), 702.

65. Gonzalez, E.; Pindur, U.; Schollmeyer, D., *J. Chem. Soc., Perkin Trans. 1* **1996,** (14), 1767.

66. Eitel, M.; Pindur, U., *J. Org. Chem.* **1990,** *55* (19), 5368.

67. Shiri, M., *Chem. Rev.* **2012,** *112* (6), 3508.

68. Sapi, J.; Laronze, J. Y., *ARKIVOC* **2004**, 208.

69. Cochard, F.; Laronze, M.; Sigaut, P.; Sapi, J.; Laronze, J.-Y., *Tetrahedron Lett.* **2004,** *45* (8), 1703.

70. Royer, D.; Wong, Y.-S.; Plé, S.; Chiaroni, A.; Diker, K.; Lévy, J., *Tetrahedron* **2008,** *64* (40), 9607.

71. Ty, N.; Dupeyre, G.; Chabot, G. G.; Seguin, J.; Quentin, L.; Chiaroni, A.; Tillequin, F.; Scherman, D.; Michel, S.; Cachet, X., *Eur. J. Med. Chem.* **2010,** *45* (9), 3726.

72. Yang, L.; Deng, G.; Wang, D.-X.; Huang, Z.-T.; Zhu, J.-P.; Wang, M.-X., *Org. Lett.* **2007,** *9* (7), 1387.

73. Izzo, I.; Maulucci, N.; Bifulco, G.; De Riccardis, F., *Angew. Chem. Int. Ed.* **2006,** *45* (45), 7557.

74. Daniels, R. N.; Fadeyi, O. O.; Lindsley, C. W., *Org. Lett.* **2008,** *10* (18), 4097.

75. Martin, J. G.; Hill, R. K., *Chem. Rev.* **1961,** *61* (6), 537.

76. Tan, B.; Hernández-Torres, G.; Barbas, C. F., *J. Am. Chem. Soc.* **2011,** *133* (32), 12354.

77. Connon, S. J., *Chem. Commun.* **2008,** (22), 2499.

78. Tan, F.; Li, F.; Zhang, X.-X.; Wang, X.-F.; Cheng, H.-G.; Chen, J.-R.; Xiao, W.-J., *Tetrahedron* **2011,** *67* (2), 446.

79. Dias, L. C., *J. Braz. Chem. Soc.* **1997,** *8*, 289.

80. Smith, C. D.; Gavrilyuk, J. I.; Lough, A. J.; Batey, R. A., *J. Org. Chem.* **2010,** *75* (3), 702.

81. Watson, L. J.; Harrington, R. W.; Clegg, W.; Hall, M. J., *Org. Biomol. Chem.* **2012,** *10* (33), 6649.

82. Pirkle, W. H.; Stickler, J. C., *Chem. Commun.* **1967,** (15), 760.

83. Medio-Simon, M.; de Laviada, M. J. A.; Sequlveda-Arques, J., *J. Chem. Soc., Perkin Trans. 1* **1990,** (10), 2749.

84. Hajbi, Y.; Neagoie, C.; Biannic, B.; Chilloux, A.; Vedrenne, E.; Baldeyrou, B.; Bailly, C.; Merour, J.-Y.; Rosca, S.; Routier, S.; Lansiaux, A., *Eur. J. Med. Chem.* **2010,** *45* (11), 5428.

85. Kinsman, A. C.; Kerr, M. A., *J. Am. Chem. Soc.* **2003,** *125* (46), 14120.

86. Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R., *J. Am. Chem. Soc.* **1982,** *104* (2), 555.

87. de los Angeles Rey, M.; Martínez-Pérez, J. A.; Fernández-Gacio, A.; Halkes, K.; Fall, Y.; Granja, J.; Mouriño, A., *J. Org. Chem.* **1999,** *64* (9), 3196.

88. Goess, B. C.; Hannoush, R. N.; Chan, L. K.; Kirchhausen, T.; Shair, M. D., *J. Am. Chem. Soc.* **2006,** *128* (16), 5391.

89. Lopez-Alvarado, P.; Steinhoff, J.; Miranda, S.; Avendano, C.; Menendez, J. C., *Tetrahedron* **2009,** *65* (8), 1660.

90. Christov, P. P.; Palamareva, M. D., *Z. Naturforsch., B: J. Chem. Sci.* **2007,** *62* (10), 1305.

91. Loy, N. S. Y.; Singh, A.; Xu, X.; Park, C.-M., *Angew. Chem. Int. Ed.* **2013,** *52* (8), 2212.

92. Snider, B. B., *Acc. Chem. Res.* **1980,** *13* (11), 426.

93. Clarke, M. L.; France, M. B., *Tetrahedron* **2008,** *64* (38), 9003.

94. Kocovsky, P.; Ahmed, G.; Srogl, J.; Malkov, A. V.; Steele, J., *J. Org. Chem.* **1999,** *64* (8), 2765.

95. Jackson, A. C.; Goldman, B. E.; Snider, B. B., *J. Org. Chem.* **1984,** *49* (21), 3988.

96. Al Dulayymi, J. a. R.; Baird, M. S.; Roberts, E.; Minnikin, D. E., *Tetrahedron* **2006,** *62* (51), 11867.

97. Cao, J.; Perlmutter, P., *Org. Lett.* **2013,** *15* (17), 4327.

98. Lievens, S. C.; Molinski, T. F., *J. Am. Chem. Soc.* **2006,** *128* (36), 11764.

99. Lovely, C. J.; Du, H. W.; He, Y.; Dias, H. V. R., *Org. Lett.* **2004,** *6* (5), 735.

100. Beaulieu, P. L.; Duceppe, J. S.; Johnson, C., *J. Org. Chem.* **1991,** *56* (13), 4196.

101. Yang, C. G.; Wang, J.; Tang, X. X.; Jiang, B., *Tetrahedron: Asymmetry* **2002,** *13* (4), 383.

102. Cowell, J.; Abualnaja, M.; Morton, S.; Linder, R.; Buckingham, F.; Waddell, P. G.; Probert, M. R.; Hall, M. J., *RSC Adv.* **2015,** *5* (21), 16125.

103. Shingarova, I. D.; Sizova, O. S.; Preobrazhenskaya, M. N., *Chem. Heterocycl. Compd.* **1983,** *19* (11), 1188.

104. Konas, D. W.; Seci, D.; Tamimi, S., *Synth. Commun.* **2012,** *42* (1), 144.

105. Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J., *Angew. Chem. Int. Ed.* **2013,** *52* (11), 3250.

106. Yang, Q.; Liu, Y.; Zhang, W., *Org. Biomol. Chem.* **2011,** *9* (18), 6343.

107. Makabe, M.; Sato, Y.; Mori, M., *J. Org. Chem.* **2004,** *69* (19), 6238.

108. Young, E. H. P., *J. Chem. Soc.* **1958,** (0), 3493.

Ethyl 3-((3a*S*,4*S*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (96)

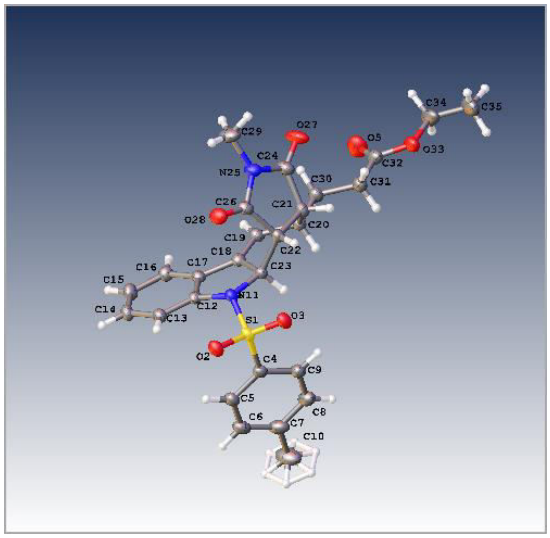


Table 1. Crystal data and structure refinement for MJH130012

Identification code	MJH130012
Empirical formula	$C_{27}H_{28}N_2O_6S$
Formula weight	508.57
Temperature/K	150.01(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	13.2104(2)
b/Å	16.9699(2)
c/Å	12.3460(2)
α/°	90.00
β/°	112.420(2)
γ/°	90.00
Volume/Å^3	2558.51(7)

Z	4
ρ_{calc}mg/mm^3	1.320
m/mm^{-1}	1.499
F(000)	1072.0
Crystal size/mm^3	0.2466 × 0.2132 × 0.1543
2Θ range for data collection	7.24 to 132.44°
Index ranges	-14 ≤ h ≤ 15, -20 ≤ k ≤ 20, -14 ≤ l ≤ 13
Reflections collected	32427
Independent reflections	4483[R(int) = 0.0372]
Data/restraints/parameters	4483/0/426
Goodness-of-fit on F^2	1.053
Final R indexes [I>=2σ (I)]	R_1 = 0.0349, wR_2 = 0.0937
Final R indexes [all data]	R_1 = 0.0396, wR_2 = 0.0987
Largest diff. peak/hole / e Å^{-3}	0.36/-0.34

Ethyl 3-((3a*S*,4*R*,10a*S*,10b*S*)-2-methyl-1,3-dioxo-10-tosyl 1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (98)

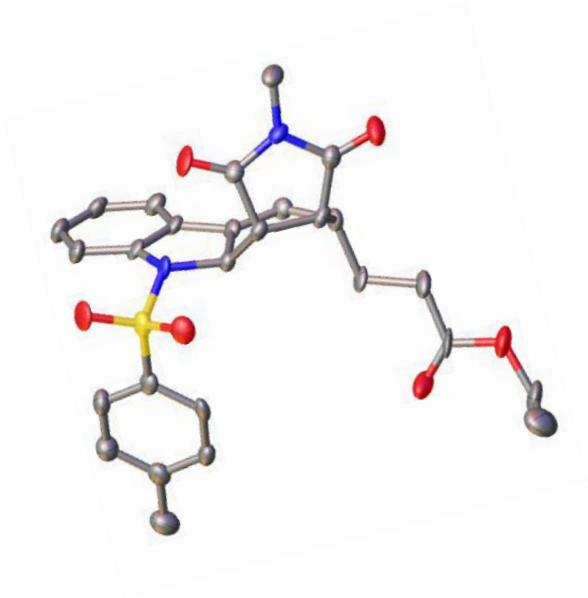


Table 1. Crystal data and structure refinement for mjh130019

Identification code	mjh130019
Empirical formula	$C_{27}H_{28}N_2O_6S$
Formula weight	508.57
Temperature/K	150.01(10)
Crystal system	monoclinic
Space group	Ia
a/Å	12.8199(2)
b/Å	35.1366(6)
c/Å	33.1373(7)
α/°	90
β/°	99.333(2)
γ/°	90
Volume/Å^3	14729.0(5)
Z	24
ρ_{calc}mg/mm^3	1.376

m/mm^{-1}	0.178
F(000)	6432.0
Crystal size/mm^3	0.366 × 0.335 × 0.192
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	5.496 to 52.892°
Index ranges	-16 ≤ h ≤ 16, -43 ≤ k ≤ 43, -41 ≤ l ≤ 41
Reflections collected	26170
Independent reflections	26170 [R_{int} = ?, R_{sigma} = 0.0719]
Data/restraints/parameters	26170/2426/1964
Goodness-of-fit on F^2	0.870
Final R indexes [I>=2σ (I)]	R_1 = 0.0497, wR_2 = 0.1082
Final R indexes [all data]	R_1 = 0.0939, wR_2 = 0.1192
Largest diff. peak/hole / e Å^{-3}	0.57/-0.87
Flack parameter	0.46(4)

Ethyl 3-((3a*S*,4*R*,10a*S*,10b*S*)-1,3-dioxo-2-phenyl-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (103)

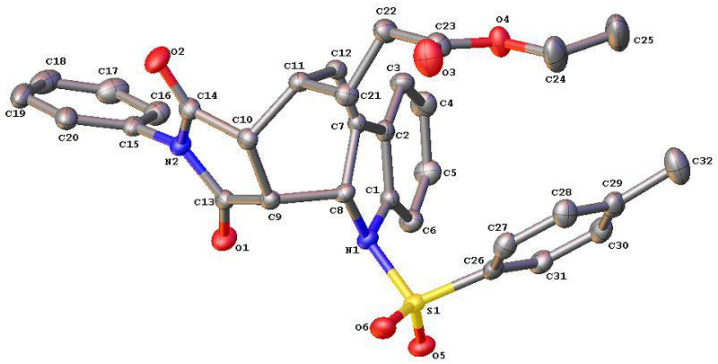


Table 1. Crystal data and structure refinement for mjh150002_fa

Identification code	mjh150002_fa
Empirical formula	$C_{32}H_{31.4}N_2O_{6.7}S$
Formula weight	583.25
Temperature/K	150.0(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.76442(14)
b/Å	16.9915(2)
c/Å	15.4288(2)
α/°	90
β/°	95.9049(13)
γ/°	90
Volume/Å^3	2807.02(6)
Z	4
ρ_{calc}g/cm^3	1.380
μ/mm^{-1}	0.168
F(000)	1228.0
Crystal size/mm^3	0.23 × 0.12 × 0.09

Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.516 to 56.196
Index ranges	-13 ≤ h ≤ 13, -22 ≤ k ≤ 22, -20 ≤ l ≤ 19
Reflections collected	43583
Independent reflections	6313 [R_{int} = 0.0461, R_{sigma} = 0.0316]
Data/restraints/parameters	6313/6/394
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0408, wR_2 = 0.0910
Final R indexes [all data]	R_1 = 0.0547, wR_2 = 0.0969
Largest diff. peak/hole / e $Å^{-3}$	0.32/-0.43

Ethyl3-((3a*S*,4*R*,10a*S*,10b*S*)-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (104)

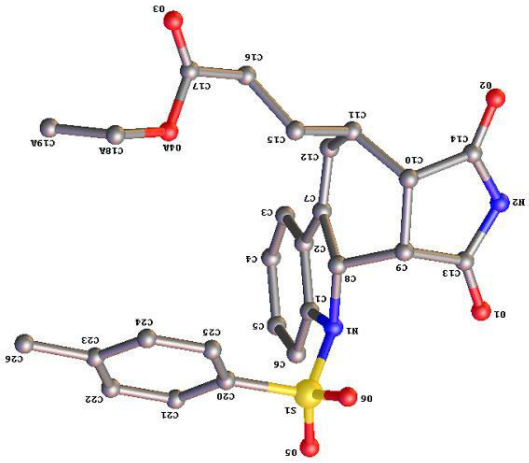


Table 1. Crystal data and structure refinement for mjh140029_fa

Identification code	mjh140029_fa
Empirical formula	$C_{26}H_{26}N_2O_6S$
Formula weight	494.55
Temperature/K	150.00(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	16.0840(2)
b/Å	8.84160(10)
c/Å	18.0999(2)
α/°	90
β/°	106.2050(14)
γ/°	90
Volume/Å^3	2471.69(6)
Z	4
ρ_{calc}g/cm^3	1.329
μ/mm^{-1}	1.537
F(000)	1040.0
Crystal size/mm^3	0.29 × 0.28 × 0.14

Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.51 to 133.56
Index ranges	-19 ≤ h ≤ 19, -10 ≤ k ≤ 10, -21 ≤ l ≤ 21
Reflections collected	65129
Independent reflections	4373 [R_{int} = 0.0518, R_{sigma} = 0.0153]
Data/restraints/parameters	4373/345/344
Goodness-of-fit on F^2	1.033
Final R indexes [I>=2σ (I)]	R_1 = 0.0350, wR_2 = 0.0889
Final R indexes [all data]	R_1 = 0.0391, wR_2 = 0.0921
Largest diff. peak/hole / e $Å^{-3}$	0.33/-0.48

Ethyl 3-((3a*S*,4*S*,5*S*,10b*S*)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (109)

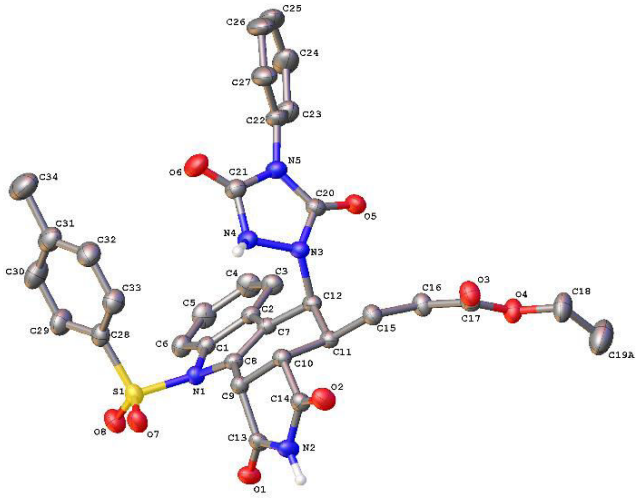


Table 1. Crystal data and structure refinement for mjh150028

Identification code	mjh150028
Empirical formula	$C_{34}H_{31}N_5O_8S$
Formula weight	669.70
Temperature/K	150.0(2)
Crystal system	triclinic
Space group	P-1
a/Å	12.6562(3)
b/Å	16.5471(3)
c/Å	17.5025(4)
α/°	80.1139(18)
β/°	72.2231(19)
γ/°	89.0852(17)
Volume/Å^3	3435.97(13)
Z	4
ρ_{calc}g/cm^3	1.295
μ/mm^{-1}	1.321
F(000)	1400.0

Crystal size/mm^3	0.19 × 0.14 × 0.05
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.386 to 133.962
Index ranges	-13 ≤ h ≤ 15, -19 ≤ k ≤ 19, -20 ≤ l ≤ 20
Reflections collected	49344
Independent reflections	12132 [R_{int} = 0.0336, R_{sigma} = 0.0250]
Data/restraints/parameters	12132/922/923
Goodness-of-fit on F^2	1.055
Final R indexes [I>=2σ (I)]	R_1 = 0.0414, wR_2 = 0.1117
Final R indexes [all data]	R_1 = 0.0489, wR_2 = 0.1166
Largest diff. peak/hole / e Å^{-3}	0.66/-0.52

(3a*R*,3b*S*,6*R*,6a*S*,11b*R*)-6-hydroxy-2-methyl-11-tosyl 3a,3b,4,5,6,6a,11,11b-octahydro-1*H*-cyclopenta[*c*]pyrrolo[3,4 *a*]carbazole-1,3(2*H*)-dione (113)

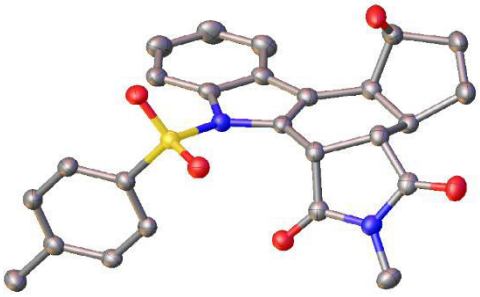


Table 1. Crystal data and structure refinement for mjh140006

Identification code	mjh140006
Empirical formula	$C_{26}H_{26}N_2O_5SCl_2$
Formula weight	549.45
Temperature/K	150.01(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	12.9390(2)
b/Å	16.4953(3)
c/Å	24.2101(5)
α/°	90
β/°	96.0290(17)
γ/°	90
Volume/Å^3	5138.64(16)
Z	8
ρ_{calc}mg/mm^3	1.420
m/mm^{-1}	3.374
F(000)	2288.0
Crystal size/mm^3	0.37 × 0.25 × 0.05
Radiation	CuKα (λ = 1.54184)

2Θ range for data collection	6.496 to 132.868°
Index ranges	-13 ≤ h ≤ 15, -18 ≤ k ≤ 19, -27 ≤ l ≤ 28
Reflections collected	42625
Independent reflections	8988 [R_{int} = 0.0491, R_{sigma} = 0.0346]
Data/restraints/parameters	8988/3/658
Goodness-of-fit on F^2	1.020
Final R indexes [I>=2σ (I)]	R_1 = 0.0443, wR_2 = 0.1103
Final R indexes [all data]	R_1 = 0.0561, wR_2 = 0.1198
Largest diff. peak/hole / e $Å^{-3}$	0.74/-0.74

(3a*S*,4*R*,10a*S*,10b*S*)-4-(3-hydroxypropyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (117)

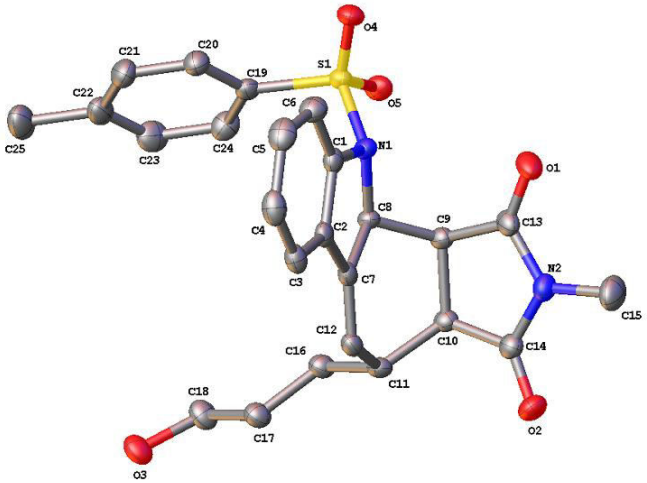


Table 1. Crystal data and structure refinement for mjh140033_fa

Identification code	mjh140033_fa
Empirical formula	$C_{25.95}H_{26.95}Cl_{2.85}N_2O_5S$
Formula weight	579.94
Temperature/K	150.01(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.33568(16)
b/Å	31.6318(5)
c/Å	8.57183(13)
α/°	90
β/°	106.4841(16)
γ/°	90
Volume/Å^3	2687.25(7)
Z	4
ρ_{calc}g/cm^3	1.433
μ/mm^{-1}	4.015

F(000)	1204.0
Crystal size/mm^3	0.37 × 0.27 × 0.2
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.588 to 133.572
Index ranges	-12 ≤ h ≤ 12, -35 ≤ k ≤ 37, -9 ≤ l ≤ 10
Reflections collected	37079
Independent reflections	4756 [R_{int} = 0.0365, R_{sigma} = 0.0164]
Data/restraints/parameters	4756/45/349
Goodness-of-fit on F^2	1.033
Final R indexes [I>=2σ (I)]	R_1 = 0.0412, wR_2 = 0.1029
Final R indexes [all data]	R_1 = 0.0444, wR_2 = 0.1054
Largest diff. peak/hole / e $Å^{-3}$	0.83/-0.43

(3a*S*,3b*R*,7*S*,7a*S*,12b)-7-hydroxy-2-methyl-12-tosyl-3b,4,5,6,7,7a,12,12b-octahydrobenzo[c]pyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (122)

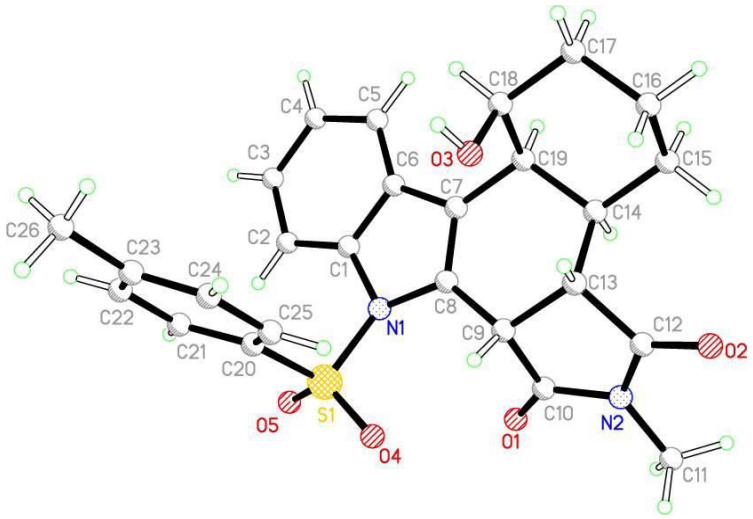


Table 1. Crystal data and structure refinement for mjh150010

Identification code	mjh150010
Chemical formula (moiety)	$C_{26}H_{26}N_2O_5S \cdot 0.5CH_2Cl_2$
Chemical formula (total)	$C_{26.5}H_{27}ClN_2O_5S$
Formula weight	521.01
Temperature	100(2) K
Radiation, wavelength	synchrotron, 0.6889 Å
Crystal system, space group	monoclinic, $P2_1/c$
Unit cell parameters	a = 13.119(3) Å α = 90°
	b = 16.319(3) Å β = 100.030(2)°
	c = 22.882(5) Å γ = 90°
Cell volume	4823.9(18) $Å^3$
Z	8
Calculated density	1.435 g/cm^3
Absorption coefficient m	0.231 mm^{-1}
F(000)	2184
Crystal colour and size	colourless, 0.070 ×0.010 × 0.010 mm^3
Reflections for cell refinement	6929 (q range 2.2 to 25.5°)
Data collection method	Rigaku Saturn 724+on kappa

diffractometer	
	wide-frame w scans
θ range for data collection	1.5 to 25.8°
Index ranges	h −16 to 16, k −20 to 17, l −28 to 28
Completeness to θ = 24.4°	99.9 %
Reflections collected	42956
Independent reflections	10111 (R_{int} = 0.0955)
Reflections with $F^2>2\sigma$	6291
Absorption correction	none
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.1315, 7.9105
Data / restraints / parameters	10111 / 67 / 664
Final R indices [$F^2>2\sigma$]	R1 = 0.0838, wR2 = 0.2270
R indices (all data)	R1 = 0.1379, wR2 = 0.2582
Goodness-of-fit on F^2	1.073
Extinction coefficient	0.0093(11)
Largest and mean shift/su	0.003 and 0.000
Largest diff. peak and hole	0.81 and −1.12 e $Å^{-3}$

(3a*S*,4*S*,10a*S*,10b*S*)-4-(3-hydroxypropyl)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (135)

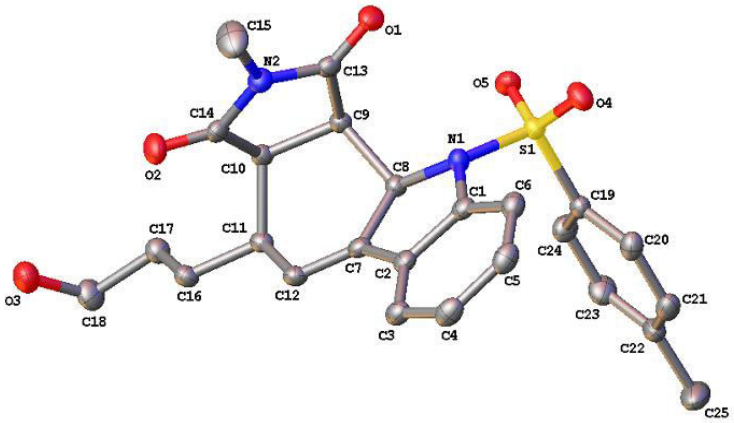


Table 1. Crystal data and structure refinement for mjh140032_fa

Identification code	mjh140032_fa
Empirical formula	$C_{25}H_{26}N_2O_5S$
Formula weight	466.54
Temperature/K	150.01(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	11.80720(10)
b/Å	11.35230(10)
c/Å	16.4724(2)
α/°	90
β/°	94.7820(10)
γ/°	90
Volume/Å^3	2200.26(4)
Z	4
ρ_{calc}g/cm^3	1.408
μ/mm^{-1}	1.654

F(000)	984.0
Crystal size/mm^3	0.38 × 0.11 × 0.06
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.874 to 133.532
Index ranges	-14 ≤ h ≤ 14, -13 ≤ k ≤ 13, -19 ≤ l ≤ 19
Reflections collected	59078
Independent reflections	3905 [R_{int} = 0.0517, R_{sigma} = 0.0161]
Data/restraints/parameters	3905/0/304
Goodness-of-fit on F^2	1.038
Final R indexes [I>=2σ (I)]	R_1 = 0.0344, wR_2 = 0.0884
Final R indexes [all data]	R_1 = 0.0403, wR_2 = 0.0933
Largest diff. peak/hole / e Å^{-3}	0.26/-0.42

(3a*S*,5*S*,10b*S*)-5-ethoxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo [3,4-a]carbazole-1,3(2*H*,3a*H*)-dione (158)

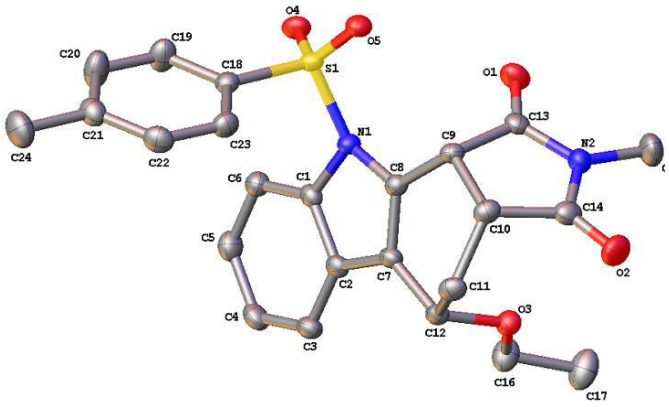


Table 1. Crystal data and structure refinement for mjh150001_fa

Identification code	mjh150001_fa
Empirical formula	$C_{24}H_{24}N_2O_5S$
Formula weight	452.51
Temperature/K	150.00(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	12.8593(4)
b/Å	12.5659(3)
c/Å	14.2001(4)
α/°	90
β/°	110.028(3)
γ/°	90
Volume/Å^3	2155.80(11)
Z	4
ρ_{calc}g/cm^3	1.394
μ/mm^{-1}	0.190
F(000)	952.0
Crystal size/mm^3	0.3 × 0.11 × 0.06

Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.484 to 56.366
Index ranges	-17 ≤ h ≤ 15, -16 ≤ k ≤ 16, -18 ≤ l ≤ 18
Reflections collected	17697
Independent reflections	4675 [R_{int} = 0.0451, R_{sigma} = 0.0461]
Data/restraints/parameters	4675/0/292
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0466, wR_2 = 0.1007
Final R indexes [all data]	R_1 = 0.0680, wR_2 = 0.1106
Largest diff. peak/hole / e $Å^{-3}$	0.36/-0.39

(3a*S*,5*S*,10b*S*)-5-(diethylamino)-2-methyl-10-tosyl-4,5,10,10b tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (166)

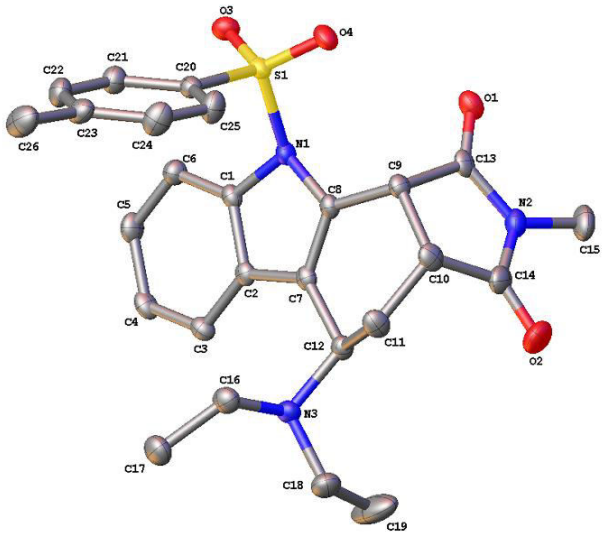


Table 1. Crystal data and structure refinement for mjh140035_fa

Identification code	mjh140035_fa
Empirical formula	$C_{26}H_{29}N_3O_4S$
Formula weight	479.58
Temperature/K	150.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.9595(3)
b/Å	10.9010(3)
c/Å	12.2897(4)
α/°	111.435(3)
β/°	108.410(3)
γ/°	91.082(2)
Volume/Å^3	1164.71(7)
Z	2
ρ_{calc}g/cm^3	1.367
μ/mm^{-1}	0.178

F(000)	508.0
Crystal size/mm^3	0.27 × 0.14 × 0.07
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.558 to 56.33
Index ranges	-12 ≤ h ≤ 13, -14 ≤ k ≤ 14, -15 ≤ l ≤ 16
Reflections collected	36925
Independent reflections	5252 [R_{int} = 0.0474, R_{sigma} = 0.0317]
Data/restraints/parameters	5252/0/311
Goodness-of-fit on F^2	1.019
Final R indexes [I>=2σ (I)]	R_1 = 0.0423, wR_2 = 0.0943
Final R indexes [all data]	R_1 = 0.0540, wR_2 = 0.1002
Largest diff. peak/hole / e Å^{-3}	1.00/-0.41

(3a*S*,5*S*,10b*S*)-2-methyl-5-(pyrrolidin-1-yl)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-a]carbazole-1,3(2*H*,3a*H*)-dione (172)

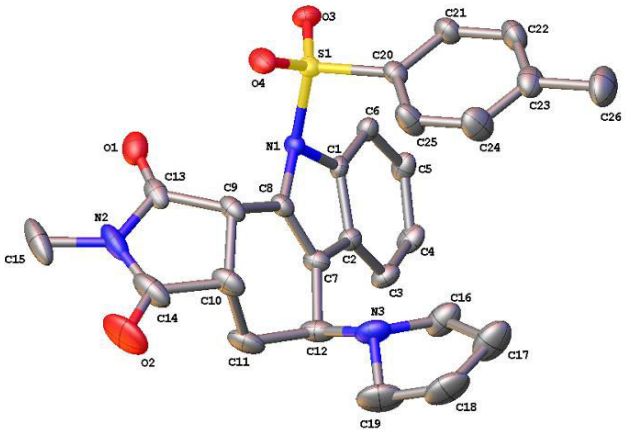


Table 1. Crystal data and structure refinement for mjh140036_fa

Identification code	mjh140036_fa
Empirical formula	$C_{26}H_{27}N_3O_4S$
Formula weight	477.56
Temperature/K	150.00(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.49030(17)
b/Å	18.7328(2)
c/Å	10.86055(13)
α/°	90
β/°	98.5172(13)
γ/°	90
Volume/Å^3	2311.90(5)
Z	4
ρ_{calc}g/cm^3	1.372
μ/mm^{-1}	0.179
F(000)	1008.0

Crystal size/mm^3	0.28 × 0.15 × 0.12
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.492 to 56.534
Index ranges	-15 ≤ h ≤ 15, -24 ≤ k ≤ 24, -14 ≤ l ≤ 14
Reflections collected	72831
Independent reflections	5399 [R_{int} = 0.0497, R_{sigma} = 0.0270]
Data/restraints/parameters	5399/300/309
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0415, wR_2 = 0.0921
Final R indexes [all data]	R_1 = 0.0573, wR_2 = 0.0985
Largest diff. peak/hole / e Å^{-3}	0.32/-0.37

Benzyl (3a*S*,5*S*,10b*S*)-2-methyl-5-morpholino-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (183)

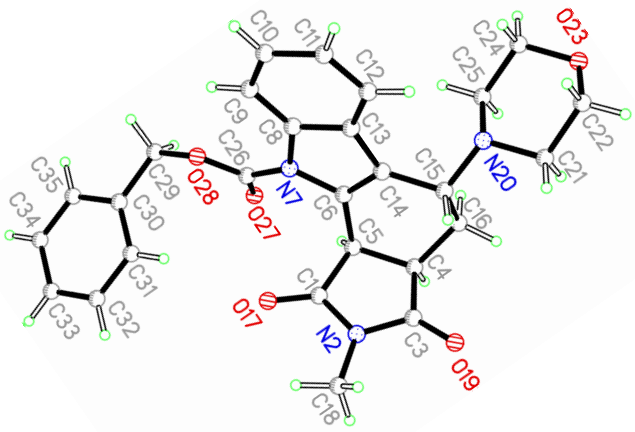


Table 1. Crystal data and structure refinement for mjh150003

Identification code	mjh150003	
Chemical formula (moiety)	$C_{27}H_{27}N_3O_5$	
Chemical formula (total)	$C_{27}H_{27}N_3O_5$	
Formula weight	473.51	
Temperature	100(2) K	
Radiation, wavelength	synchrotron, 0.6889 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 5.8848(15) Å	α = 90°
	b = 18.422(5) Å	β=91.887(3)°
	c = 20.968(5) Å	γ= 90°
Cell volume	2271.9(10) Å^3	
Z	4	
Calculated density	1.384 g/cm^3	
Absorption coefficient μ	0.091 mm^{-1}	
F(000)	1000	
Crystal colour and size	colourless,0.200 × 0.200 × 0.030 mm^3	

Reflections for cell refinement	9121 (q range 2.2 to 27.4°)
Data collection method	Rigaku Saturn 724+on kappa
diffractometer	wide- frame w scans
θ range for data collection	1.4 to 27.4°
Index ranges	h –7 to 7, k –24 to 22, l–27 to 27
Completeness to θ = 24.4°	98.6 %
Reflections collected	20359
Independent reflections	5531 (R_{int} = 0.0538)
Reflections with $F^2>2\sigma$	4375
Absorption correction	none
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0501, 2.0683
Data / restraints / parameters	5531 / 0 / 317
Final R indices [$F^2>2\sigma$]	R1 = 0.0579, wR2 = 0.1392
R indices (all data)	R1 = 0.0734, wR2 = 0.1464
Goodness-of-fit on F^2	1.060
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.38 and –0.27 e $Å^{-3}$

Benzyl(3a*S*,10a*S*,10b*S*)-7-fluoro-2-methyl-1,3-dioxo-2,3,3a,4,10a,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (201)

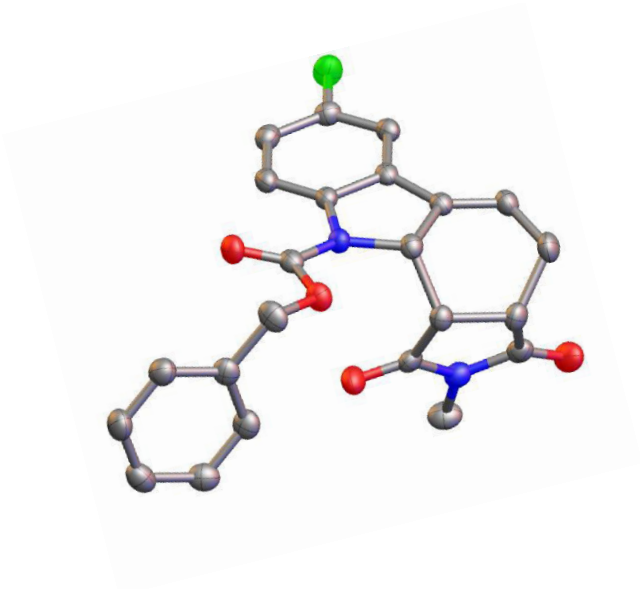


Table 1. Crystal data and structure refinement for mjh140005

Identification code	mjh140005
Empirical formula	$C_{23}H_{19}N_2O_4F$
Formula weight	406.40
Temperature/K	150.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	7.4462(5)
b/Å	9.1888(6)
c/Å	14.7869(10)
α/°	97.920(5)
β/°	102.985(6)
γ/°	104.265(6)
Volume/Å^3	935.28(11)
Z	2
ρ_{calc}mg/mm^3	1.443
m/mm^{-1}	0.885

F(000)	424.0
Crystal size/mm^3	0.42 × 0.18 × 0.11
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection	6.266 to 132.538°
Index ranges	-8 ≤ h ≤ 8, -10 ≤ k ≤ 10, -17 ≤ l ≤ 17
Reflections collected	11384
Independent reflections	3245 [R_{int} = 0.0330, R_{sigma} = 0.0286]
Data/restraints/parameters	3245/0/272
Goodness-of-fit on F^2	1.048
Final R indexes [I>=2σ (I)]	R_1 = 0.0374, wR_2 = 0.0892
Final R indexes [all data]	R_1 = 0.0479, wR_2 = 0.0959
Largest diff. peak/hole / e $Å^{-3}$	0.21/-0.20

Biological Data

Community for Open
Antimicrobial Drug Discovery

Primary Antimicrobial Screening

Bacterial and Fungal

Study Number: **P000121**

Date: **23-Feb-2016**

Report Number: **SC_0121_01**

Collaborator:

Dr Michael Hall

School of Chemistry

Newcastle University

United Kingdom

Document

Version	Author(s)	Reviewer(s)
1	Johannes Zuegg	Alysha Elliott

Content

1.0 Summary

1.1 Study

Primary antimicrobial screening study by whole cell growth inhibition assays, using the provided samples at a single concentration, in duplicate (n=2). The inhibition of growth is measured against 5 bacteria: *Escherichia coli*, *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Staphylococcus aureus*, and 2 fungi: *Candida albicans* and *Cryptococcus neoformans*.

1.2 Collaborator

Primary Investigator:	Dr Michael Hall (michael.hall@newcastle.ac.uk)
Contact Person:	Dr Michael Hall (michael.hall@newcastle.ac.uk)
Organisation:	School of Chemistry Newcastle University United Kingdom

1.3 Assay Parameters

Test concentration	32 µg/mL
QC	Duplicate (n=2) Control MIC: Pass
Plates	Non-Binding Surface, 384 well plate
Media ***Bacteria*** ***Fungi***	Cation-adjusted Mueller Hinton broth Yeast Nitrogen Base
Read Out ***Bacteria*** ***C. albicans*** ***C. neoformans***	OD_{600} OD_{530} Resazurin $OD_{600-570}$

1.4 Outcomes

Number of samples tested	**8**
Number of Actives *selected for Hit Confirmation*	**1**
E. coli	**0**
K. pneumoniae - MDR	**0**
A. baumannii	**0**
P. aeruginosa	**0**
S. aureus – MRSA	**0**
C. albicans	**1**
C. neoformans	**0**

*Actives are defined as showing ≥80% inhibition of growth at the concentration tested

A full set of results can be found in Section 3.3.

1.5 Comments

To confirm the inhibitory activity, the hit compounds will be re-tested against the strains in a dose response assay to determine the minimum inhibitory concentration (MIC) of the compounds. Furthermore, to further evaluate the antimicrobial potential of the compounds they will be assayed against a mammalian cell line to determine general cell toxicity.

1.5.1 Summary antimicrobial active compounds

Single Concentration – 32 µg/mL, n=2, where one or both replicates were deemed active the compound is deemed active.

Inactive	**I**	Inhibition < 80% OR Z-Score < 2.5
Active	**A**	Inhibition ≥ 80% AND Z-Score ≥ 2.5

Sample Name	*CO-ADD Sample ID*	*GP_020*	*GN_001*	*GN_003*	*GN_034*	*GN_042*	*FG_001*	*FG_002*
		S. aureus	*E. coli*	*K. pneumoniae*	*A. baumannii*	*P. aeruginosa*	*C. albicans*	*C. neoformans*
		ATCC 43300	*ATCC 25922*	*ATCC 700603*	*ATCC 19606*	*ATCC 27853*	*ATCC 90028*	*ATCC 208821*
		MRSA	*FDA control strain*	*MDR*	*Type strain*	*Type strain*	*FDA control strain*	*H99 Type strain*
		Antimicrobial activity at 32 µg/mL						
Mma-448-f2	C0142329	I	I	I	I	I	A	I

2.0 Methods

2.1 Sample preparation

Samples were provided by the collaborator as dry material, and were made to 10mg/mL in DMSO solution and stored frozen at -20 °C.

An aliquot of each sample was diluted to 320 µg/mL in water, and plated in 384-well polypropylene plates (**PP**). 5 µL was plated in duplicate (**n=2**) into a 384-well non-binding surface plate (**NBS**) for each strain or cell type assayed against. Once cells were added this gave a final compound concentration range of 32 µg/mL.

Final Sample Concentration:	32 µg/mL
Final DMSO Concentration	1%
Compound preparation	in Water/DMSO

2.2 Antimicrobial Assay

2.2.1 Procedure

All bacteria were cultured in Cation-adjusted Mueller Hinton broth (CAMHB) at 37 °C overnight. A sample of each culture was then diluted 40-fold in fresh broth and incubated at 37 °C for 1.5-3 h. The resultant mid-log phase cultures were diluted (CFU/mL measured by OD_{600}), then 45 µL was added to each well of the compound containing plates, giving a cell density of 5×10^5 CFU/mL and the nominated final compound concentration. All the plates were covered and incubated at 37 °C for 18 h without shaking.

2.2.2 Analysis

Inhibition of bacterial growth was determined measuring absorbance at 600 nm (OD_{600}), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references. The significance of the inhibition values was determined by Z-scores, calculated using the average and standard deviation of the sample wells (no controls) on the same plate. Samples with inhibition value above 80% and Z-Score above 2.5 for either replicate (n=2 on different plates) were classed as actives.

2.3 Antifungal Assay

2.3.1 Procedure

Fungi strains were cultured for 3 days on Yeast Extract-Peptone Dextrose (YPD) agar at 30 °C. A yeast suspension of 1 x 10^6 to 5 x 10^6 cells/mL (as determined by OD_{530}) was prepared from five colonies. These stock suspensions were diluted with Yeast Nitrogen Base (YNB) broth to a final concentration of 2.5×10^3 CFU/mL. Then, 45 µL of the fungi suspension was added to each well of the compound-containing plates. Plates were covered and incubated at 35 °C for 24 h without shaking.

2.3.2 Analysis

Growth inhibition of *C. albicans* was determined measuring absorbance at 530 nm (OD_{530}), while the growth inhibition of *C. neoformans* was determined measuring the difference in absorbance between 600 and 570 nm ($OD_{600-570}$), after the addition of resazurin (0.001% final concentration) and incubation at 35 °C for additional 2 h. The absorbance was measured using a Biotek Synergy HTX plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate. The significance of the inhibition values was determined by Z-scores, calculated using the average and standard deviation of the sample wells (no controls) on the same plate. Samples with inhibition value above 80% and Z-Score above 2.5 for either replicate (n=2 on different plates) were classed as actives.

2.4 Antibiotic standards preparation and Quality control

Colistin and Vancomycin were used as positive bacterial inhibitor standards for Gram-negative and Gram-positive bacteria, respectively. Fluconazole was used as a positive fungal inhibitor standard for *C. albicans and C. neoformans.*

The antibiotics were provided in 4 concentrations, with 2 above and 2 below its MIC value, and plated into the first 8 wells of column 23 of the 384-well NBS plates.

The quality control (QC) of the assays was determined by the antimicrobial controls and the Z'-factor (using positive and negative controls). Each plate was deemed to fulfil the quality criteria (pass QC), if the Z'-factor was above 0.4, and the antimicrobial standards showed full range of activity, with full growth inhibition at their highest concentration, and no growth inhibition at their lowest concentration.

2.5 Materials

Material	*Code*	*Brand*	*Cat No.*
Compound preparation plate	PP	Corning	3364
Assay Plates	NBS 384w	Corning	3640
Growth media - bacteria	CAMHB	Bacto Laboratories	212322
Culture agar - fungi	YPD	Becton Dickinson	242720
Growth media - fungi	YNB	Becton Dickinson	233520
Resazurin		Sigma-Aldrich	R7017

2.6 Tested Samples

Compound Barcode	Sample Name	CO-ADD Sample ID	Full MW	Amount Supplied				Stock Conc. (mg/mL)	Solvent
				Solid (mg)	Solution				
					Volume (µL)	Conc.	Unit		
FR09958692	Mma-431-f2	C0142324	323.4	1.0				10.0	DMSO
FR09958693	Mma-456-f2	C0142325	339.4	1.0				10.0	DMSO
FR09958694	Mma-428-f2	C0142326	341.39	1.0				10.0	DMSO
FR09958695	Mma-452-f2	C0142327	355.41	1.0				10.0	DMSO
FR09958784	Mma-454-f2	C0142328	357.39	1.1				10.0	DMSO
FR09958785	Mma-448-f2	C0142329	419.46	1.1				10.0	DMSO
FR09958786	Mma-449-f2	C0142330	432.5	0.7				10.0	DMSO
FR09958787	Mma-453-f2	C0142331	403.46	1.0				10.0	DMSO

2.7 Antibiotic Controls

Sample Name	Sample ID	Full MW	Stock Conc (mg/mL)	Solvent	Source
Colistin - Sulfate	MCC_000094:02	1400.63	10	DMSO	Sigma; C4461
Vancomycin - HCL	MCC_000095:02	1485.71	10	DMSO	Sigma; 861987
Fluconazole	MCC_008383:01	306.27	2.56	DMSO	Sigma; F8929

2.8 Microbial Strains

ID	Batch	Organism	Strain	Description
GN_001	02	*Escherichia coli*	ATCC 25922	FDA control strain
GN_003	02	*Klebsiella pneumoniae*	ATCC 700603	MDR
GN_034	02	*Acinetobacter baumannii*	ATCC 19606	Type strain
GN_042	02	*Pseudomonas aeruginosa*	ATCC 27853	Quality control strain
GP_020	02	*Staphylococcus aureus*	ATCC 43300	MRSA
FG_001	01	*Candida albicans*	ATCC 90028	CLSI reference
FG_002	01	*Cryptococcus neoformans*	ATCC 208821	H99 - Type strain

3.0 Results

3.1 Test Information

Raw data	PSR0082
Location	IMB/UQ, SCMB/UQ

3.2 Controls

All antibiotic controls displayed inhibitory values within the expected range.

Strain ID	*Species*	*Antibiotic*	*Pass/Fail*
GN_001:02	*E. coli*	Colistin	Pass
GN_003:02	*K. pneumoniae* (MDR)	Colistin	Pass
GN_034:02	*A. baumannii*	Colistin	Pass
GN_042:02	*P. aeruginosa*	Colistin	Pass
GP_020:02	*S. aureus* (MRSA)	Vancomycin	Pass
FG_001:01	*C. albicans*	Fluconazole	Pass
FG_002:01	*C. neoformans* (H99)	Fluconazole	Pass

3.3 Antimicrobial Activity

3.3.1 Primary Screening

Single Concentration – 32 µg/mL, n=2, where one or both replicates were deemed active the compound is deemed active.

Inactive	**I**	Inhibition < 80% OR Z-Score < 2.5
Active	**A**	Inhibition ≥ 80% AND Z-Score ≥ 2.5

Sample Name	*CO-ADD Sample ID*	*GP_020*	*GN_001*	*GN_003*	*GN_034*	*GN_042*	*FG_001*	*FG_002*
		S. aureus	*E. coli*	*K. pneumoniae*	*A. baumannii*	*P. aeruginosa*	*C. albicans*	*C. neoformans*
		ATCC 43300	*ATCC 25922*	*ATCC 700603*	*ATCC 19606*	*ATCC 27853*	*ATCC 90028*	*ATCC 208821*
		MRSA	*FDA control strain*	*MDR*	*Type strain*	*Type strain*	*FDA control strain*	*H99 Type strain*
		Antimicrobial activity at 32 µg/mL						
Mma-431-f2	C0142324	I	I	I	I	I	I	I
Mma-456-f2	C0142325	I	I	I	I	I	I	I
Mma-428-f2	C0142326	I	I	I	I	I	I	I
Mma-452-f2	C0142327	I	I	I	I	I	I	I
Mma-454-f2	C0142328	I	I	I	I	I	I	I
Mma-448-f2	C0142329	I	I	I	I	I	A	I
Mma-449-f2	C0142330	I	I	I	I	I	I	I
Mma-453-f2	C0142331	I	I	I	I	I	I	I

Publications from this work

1. Diastereoselective synthesis of functionalised carbazoles via a sequential Diels-Alder/ene reaction strategy; Cowell, J.; Abualnaja, M.; Morton, S.; Linder, R.; Buckingham, F.; Waddell, P. G.; Probert, M. R.; Hall, M. J.;. *RSC Advances* 2015, 5(21), 16125-16152

RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2015, **5**, 16125

Diastereoselective synthesis of functionalised carbazoles *via* a sequential Diels–Alder/ene reaction strategy†

Joseph Cowell, Matokah Abualnaja, Stephanie Morton,‡ Ruth Linder, Faye Buckingham, Paul G. Waddell, Michael R. Probert and Michael J. Hall*

Received 9th January 2015
Accepted 19th January 2015

DOI: 10.1039/c5ra00499c

www.rsc.org/advances

An operationally simple one-pot, three-component, diastereoselective synthesis of saturated carbazoles and related pyridazino[3,4-*b*]indoles, based on two sequential intermolecular pericyclic reactions, is described. The reaction sequence involves an intermolecular Diels–Alder (D–A) reaction of a 3-vinyl-1*H*-indole, containing an electron withdrawing N-protecting group, with a suitable dienophile. Due to the electron withdrawing nature of the N-protecting group the resultant D–A cycloadducts are sufficiently stabilised to allow for a subsequent *in situ* diastereospecific intermolecular ene reaction to take place with an added enophile, generating functionalised carbazoles with relative stereocontrol of up to four stereocentres.

Introduction

Carbazole scaffolds are common in many bioactive compounds (*e.g.* staurosporine)[1,2] with the indolocarbazole scaffold in particular being found in a number of molecules with potential therapeutic application, several of which have entered clinical trials for the treatment of cancer (midostaurin (PKC412), lestaurtinib (CEP-701), CEP-751, CEP-1347, edotecarin and becatecarin).[3,4] Therefore there is a growing interest in the development of new synthetic routes to functionalised carbozoles.[5–9] Herein we describe our progress in the development of a diastereoselective one-pot, three-component approach for the synthesis of functionalised, partially saturated carbazoles and pyridazino[3,4-*b*]indoles.

Results and discussion

The vinyl-indole synthesis of carbazoles, originally developed by Nolan, Pindur, Porter and others, involves the D–A cycloaddition of a 2- or 3-vinyl-1*H*-indole (typically either unprotected or containing an electron donating N-protecting group) with a dienophile.[10–22] The resulting D–A cycloadducts are often unstable and are therefore typically oxidised or undergo an *in situ* 1,3-H shift to rearomatise the indole. We postulated that if the intermediate D–A cycloadduct could instead be intercepted *via* an alternative intermolecular reaction this would provide a new multi-component route to functionalised carbazoles. Following on from our recent work on the D–A reactions of vinyl-imidazoles,[23,24] we decided to investigate if the D–A cycloadducts of 3-vinyl-1*H*-indoles could be reacted *in situ* with enophiles to give a new stereoselective three-component, intermolecular D–A/intermolecular ene approach to the carbazole or pyridazino[3,4-*b*]indole scaffold (Fig. 1).[25–29]

We decided to focus our investigation on the D–A reactions of 3-vinyl-1*H*-indoles containing an electron withdrawing

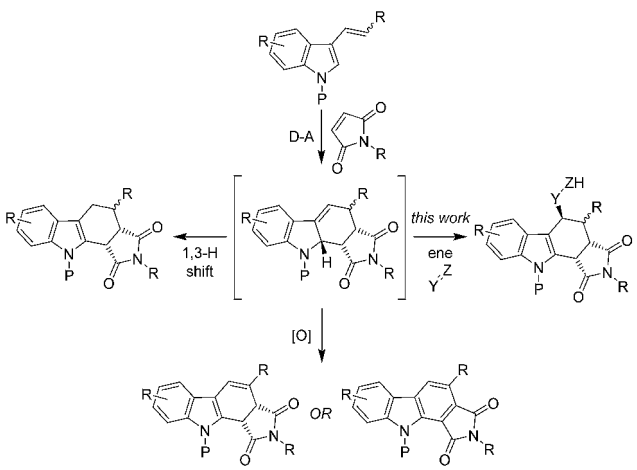
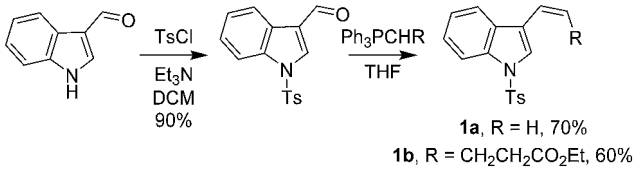


Fig. 1 Typical products of the D–A reaction between 3-vinyl-1*H*-indoles and maleimides verses our proposed trapping of the D–A cycloadduct *via* an intermolecular ene reaction.

School of Chemistry, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK. E-mail: michael.hall@newcastle.ac.uk

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C spectra for all new compounds, crystal data and structure refinement tables for compounds **2a**, **2b**, **2d**, **3l**, **3r**, **3u** and **3v**. The crystallographic coordinates of **2a**, **2b**, **2d**, **3l**, **3r**, **3u** and **3v** have been deposited with the Cambridge Crystallographic Data Centre, deposition nos. CCDC 952356, 1040305, 1040306, 952229, 1040307, 1040308 and 952357. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra00499c

‡ Authors contributed equally.



Scheme 1 Synthesis of *N*-tosyl-3-alkenyl-1*H*-indoles **1(a and b)**.

N-protecting group as we postulated that this would stabilise the desired D–A cycloadducts sufficiently to allow either isolation or further *in situ* chemistry.[19,20] Despite the extensive body of work that has been published on the vinyl-indole synthesis of carbazoles,[11–18] the incorporation of electron withdrawing N-protecting groups has been less well studied with the phenylsulfonyl group being the most common.[25,30–33] We therefore decide to focus our initial investigation on tosyl protected systems and embarked on the synthesis of two *N*-tosyl protected 3-alkenyl-indoles through reaction of 1*H*-indole-3-carbaldehyde with tosyl chloride, followed by a Wittig reaction with methylenetriphenyl-λ^5-phosphane or ethyl 4-(triphenyl-λ^5-phosphanylidene)butanoate to give **1a** and **1b** respectively (Scheme 1).

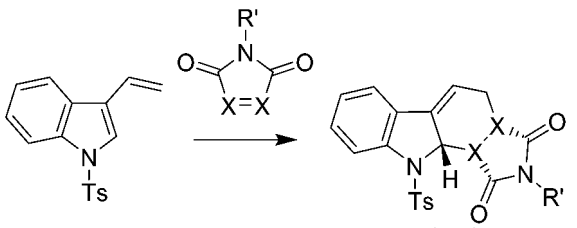
When we reacted 1-tosyl-3-vinyl-1*H*-indole **1a** with 1-methyl-1*H*-pyrrole-2,5-dione in DCM at reflux for 48 hours, we were pleased to isolate, in a 74% yield, the *N*-tosyl protected *endo*-cycloadduct **2a**, which showed little propensity towards spontaneous rearomatisation or oxidation. Whilst 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) reacted rapidly with **1a** at −78 °C in DCM to give the stable D–A cycloadduct **2b** in 88% yield (Table 1).

Attempts to react the more sterically demanding ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate **1b** with 1*H*-pyrrole-2,5-diones under thermal conditions proved unsuccessful with no D–A reaction being observed after prolonged heating in toluene, DCM or iso-propanol. The addition of 20 mol% of 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea[34] also showed no improvement in the D–A reaction, whilst the addition of one equivalent of $TiCl_4$ at −78 °C for 10 minutes resulted in an efficient D–A reaction but was accompanied by the unwanted rearomatisation of the indole. Addition of one equivalent of $AlCl_3$ or Me_2AlCl in DCM at r.t., followed by heating to reflux gave low yields of the desired product **2c** along with recovered starting material. Further optimisation resulted in a final protocol whereby 2 equivalents of Me_2AlCl were added to a DCM solution of **1b** and the requisite 1*H*-pyrrole-2,5-dione at −78 °C, followed by warming to reflux in DCM for 48 hours to give *N*-tosyl protected D–A cycloadducts **2(c–e)** in good yields (Table 2). The structures of **2(a)**, **2(b)** and **2(d)** were confirmed by single crystal X-ray analysis and are consistent with an *endo*-selective D–A reaction (see ESI†).

Next we examined the reactivity of *N*-tosyl protected *endo*-cycloadducts **2(a–e)** towards enophiles. Reaction of **2a** with nitrosobenzene proceeded well at r.t. in 18 hours to give the ene adduct **3a** in 68% isolated yield. We therefore reacted D–A adducts **2(a–e)** with nitrosobenzene and 1-methyl-2-nitrosobenzene at r.t. in DCM, giving high yields of the corresponding ene adducts **3(a, b and e–h)**. The ene reactions of **2(a–c)** also proceeded smoothly with PTAD at 0 °C to give **3(c, i and j)**. The reaction of **2a** with 2,3,4,5,6-pentafluorobenzaldehyde under thermal conditions was unsuccessful. However addition of one equivalent of Me_2AlCl at −78 °C to a mixture of **2a** and 2,3,4,5,6-pentafluorobenzaldehyde resulted in formation of the ene cycloadduct **3d** as a 6 : 1 mixture of diastereomers, epimeric at the *exo*-cyclic hydroxyl position[35] (Table 3).

Since both the D–A and ene reactions are performed in DCM we then decided to examine the potential for reaction telescoping by attempting a D–A/ene reaction sequence under "domino" conditions.[36] 1-Tosyl-3-vinyl-1*H*-indole **1a**, 1-methyl-

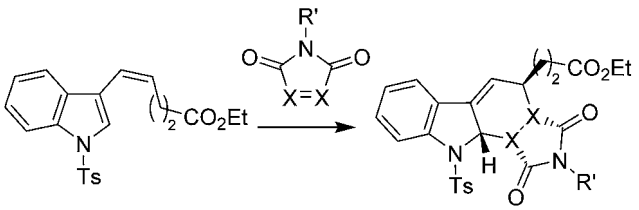
Table 1 D–A reactions of *N*-tosyl protected 1-tosyl-3-vinyl-1*H*-indole **1a**



	Starting material	Dienophile	Reaction Conditions	R′	X	Yield[a]	Product
1	**1a**		40 °C, 48 h	Me	CH	76%	**2a**[b]
2	**1a**		−78 °C, 3.5 h	Ph	N	88%	**2b**[b]

[a] Isolated yields. [b] Structure confirmed by single crystal X-ray analysis.

Table 2 D–A reactions of ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate **1b**



1b **2(c-e)**

	Starting material	Dienophile	Reaction conditions	R′	X	Yield[a]	Product
1	**1b**		2 eq. Me_2AlCl, −78 °C 30 min, then 40 °C 48 h	Me	CH	85%	**2c**
2	**1b**		2 eq. Me_2AlCl, −78 °C 30 min, then 40 °C 48 h	H	CH	64%	**2d**[b]
3	**1b**		2 eq. Me_2AlCl, −78 °C 30 min, then 40 °C 48 h	Ph	CH	71%	**2e**

[a] Isolated yields. [b] Structure confirmed by single crystal X-ray analysis.

1*H*-pyrrole-2,5-dione and nitrosobenzene were stirred together for 5 days at r.t. in DCM, until **1a** had been consumed by TLC. Examination of the crude reaction mixture showed the formation of a number of by-products (including a rearomatised isomer of D–A cycloadduct **2a**) but the desired domino D–A/ene product **3a** could be isolated as a single diastereomer in a 40% yield.

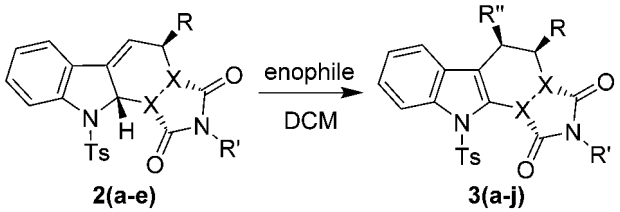
To improve both the yield and reaction flexibility whilst maintaining operational simplicity we next examined a one-pot, sequential addition approach. 1-Tosyl-3-vinyl-1*H*-indole **1a** and 5-methoxy-1-tosyl-3-vinyl-1*H*-indole **1c** (synthesised as previously *via* tosyl protection of 5-methoxy-1*H*-indole-3-carbaldehyde followed by a Wittig reaction with methylenetriphenyl-λ^5-phosphane) were reacted with 1-methyl-1*H*-pyrrole-2,5-dione or 1*H*-pyrrole-2,5-dione in refluxing DCM for 48 hours to give the corresponding D–A cycloadducts. Nitrosobenzene, 1-methyl-2-nitrosobenzene, 2,3,4,5,6-pentafluorobenzaldehyde with one equivalent of Me_2AlCl, or PTAD, were then added directly to the reaction vessels containing the D–A cycloadducts and the ene reactions conducted were under the previously optimised conditions, depending on the enophile. This one-pot three-component approach gave the corresponding D–A/ene products **3(a–d and k–q)** in excellent (70–89%) yields with no purification or work-up of the intermediate D–A cycloadducts required (Table 4).

We therefore continued with this approach, reacting **1a** and **1c** with PTAD as the dienophile followed by *in situ* addition of enophiles (nitrosobenzene, 1-methyl-2-nitrosobenzene, or PTAD) again giving the D–A/ene products **3(e, f, r and s)** cleanly and in good yields (Table 4).

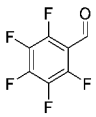
We then decided to examine the range of electron withdrawing N-protecting groups tolerated in our one-pot D–A/ene reaction sequence with a view towards flexibility in the deprotection of the products. Boc protection of 1*H*-indole-3-carbaldehyde proceeded in high yield (triethylamine, Boc anhydride, DCM, 18 h, r.t.), however attempts to synthesise *tert*-butyl 3-vinyl-1*H*-indole-1-carboxylate, by reaction of *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate with methylenetriphenyl-λ^5-phosphane, gave only a 13% yield of the desired product with the major products arising from loss of the Boc group. We therefore focused our efforts on use of the DMAS (dimethylaminosulfonyl) and Cbz protecting groups, and synthesised *N*,*N*-dimethyl-3-vinyl-1*H*-indole-1-sulfonamide **1d** (DMAS), benzyl-3-vinyl-1*H*-indole-1-carboxylate **1e** and benzyl-5-methoxy-3-vinyl-1H-indole-1-carboxylate **1f** (Cbz) *via* appropriate protection of 1*H*-indole-3-carbaldehyde followed by reaction with methylenetriphenyl-λ^5-phosphane as previously.

N,*N*-Dimethyl-3-vinyl-1*H*-indole-1-sulfonamide **1d** was reacted in DCM with 1*H*-pyrrole-2,5-dione, 1-methyl-1*H*-pyrrole-2,5-dione, 1-phenyl-1*H*-pyrrole-2,5-dione and PTAD. After 48 hours at 40 °C for the maleimides, or 1 hour at −78 °C for PTAD, the D–A reactions were complete and *in situ* ene reactions with nitrosobenzene, 1-methyl-2-nitrosobenzene, 1,3-dibromo-2-nitrosobenzene[23] or 2,3,4,5,6-pentafluorobenzaldehyde (catalysed by one equivalent of Me_2AlCl) were carried out to give 69–77% isolated yields of the desired three-component D–A/ene products **3(t–x)** (Table 4). Cbz protected 3-vinyl-1*H*-indoles **1(e and f)** also underwent D–A reactions with 1*H*-pyrrole-2,5-dione, 1-methyl-1*H*-pyrrole-2,5-dione or PTAD followed by *in situ* ene reactions with nitrosobenzene, 1-methyl-2-nitrosobenzene or PTAD to give 54–82% yields of **3(y–ll)** (Table 4). The Cbz protected products **3(y–ll)** were isolable by silica gel chromatography but proved less stable than their DMAS or Tos protected counterparts. NMR investigations of these compounds showed evidence of decomposition in solution at r.t., however they could be stored as solids under an

Table 3 Ene reactions of *N*-tosyl protected cycloadducts **2(a–e)**



2(a-e) **3(a-j)**

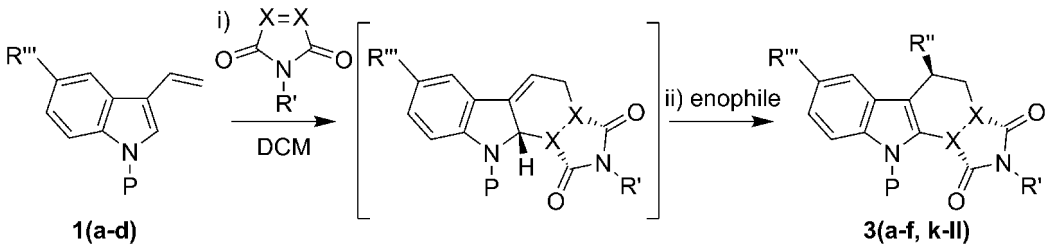
	Starting material	R	R′	X	Enophile	Reaction conditions	R″	Yield[a]	Product
1	**2a**	H	Me	CH		r.t., 18 h	N(Ph)OH	68%	**3a**
2	**2a**	H	Me	CH		r.t., 18 h	N(*o*-Tol)OH	72%	**3b**
3	**2a**	H	Me	CH		0 °C, 2.5 h		73%	**3c**
4	**2a**	H	Me	CH		1 eq. Me_2AlCl, −78 °C, 15 min r.t., 18 h	$CH(C_6F_5)OH$	82%	**3d**[b]
5	**2b**	H	Ph	N		r.t., 18 h	N(Ph)OH	74%	**3e**
6	**2b**	H	Ph	N		r.t., 18 h	N(*o*-Tol)OH	72%	**3f**
7	**2c**	$(CH_2)_2CO_2Et$	Me	CH		r.t., 24 h	N(*o*-Tol)OH	59%	**3g**
8	**2e**	$(CH_2)_2CO_2Et$	Ph	CH		r.t., 24 h	N(*o*-Tol)OH	58%	**3h**
9	**2c**	$(CH_2)_2CO_2Et$	Me	CH		0 °C, 6 h		56%	**3i**
10	**2d**	$(CH_2)_2CO_2Et$	H	CH		0 °C, 6 h		56%	**3j**

[a] Isolated yields. [b] Isolated as a 6 : 1 mixture of diastereomers.

atmosphere of nitrogen at −20 °C for months at a time. Interestingly the ene reactions of 2,3,4,5,6-pentafluorobenzaldehyde with D–A cycloadducts **3(d, m, p and v)** gave a mixture of diastereomers at the *exo*-cyclic hydroxyl group, with ratios from 5 : 1 to >25 : 1. The relative stereochemistry of **3v** was confirmed through the solution of a single crystal X-ray structure (see ESI†) and is consistent with an *endo*-selective ene reaction, providing some support for an ene mechanism in this reaction rather than a nucleophilic attack of the D–A cycloadducts to the carbonyl carbon of the aldehyde in the manner of an vinylogous enamine.[37]

Finally we investigated the deprotection of our D–A/ene reaction products. Tosyl and DMAS protected compounds **3(a–x)** proved intransient to a range of basic (NaOH, KOH or KOEt in EtOH, MeOH or H_2O with Bu_4NBr) and reducing (Mg, Mg/Hg or Na/Hg) deprotection conditions. We therefore focused on the deprotection of Cbz protected compounds **3(y–ll)**. Initial attempts at Cbz removal with H_2 and Pd/C proved unsuccessful. Atmospheric pressure hydrogenation with Adam's catalyst in either MeOH and EtOH resulted in the removal of the Cbz group from **3z**, however unexpected

Table 4 One-pot D–A/ene reactions of N-protected 3-vinyl-1*H*-indoles



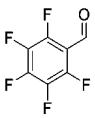
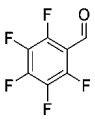
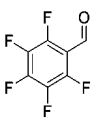
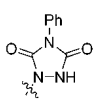
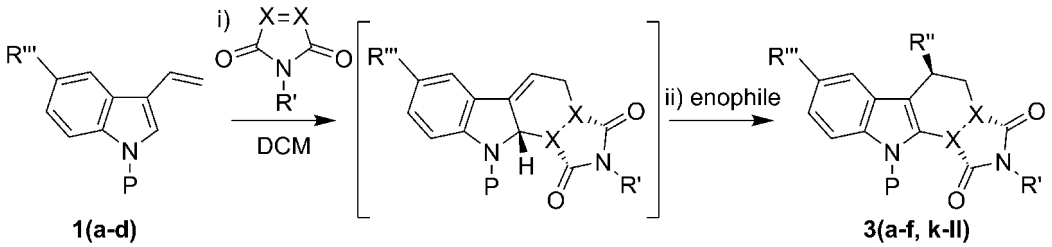
	Starting Material	P	R‴	R′	X	Enophile	R″	Reaction conditions	Product	Yield[a]
1	**1a**	Tos	H	Me	CH		–N(Ph)OH	(i) 40 °C, 48 h, (ii) r.t., 18 h	**3a**	71%
2	**1a**	Tos	H	Me	CH		–N(*o*-Tol)OH	(i) 40 °C, 48 h, (ii) r.t., 18 h	**3b**	71%
3	**1a**	Tos	H	Me	CH			(i) 40 °C, 48 h, (ii) 0 °C, 4 h	**3c**	76%
4	**1a**	Tos	H	Me	CH		–CH(C_6F_5)OH	(i) 40 °C, 48 h, (ii) Me_2AlCl, −78 °C to r.t., 18 h	**3d**	72%[b]
5	**1a**	Tos	H	Ph	N		–N(Ph)OH	(i) −78 °C, 4 h, (ii) r.t., 24 h	**3e**	66%
6	**1a**	Tos	H	Ph	N		–N(*o*-Tol)OH	(i) −78 °C, 4 h, (ii) r.t., 24 h	**3f**	66%
7	**1a**	Tos	H	H	CH		–N(Ph)OH	(i) 40 °C, 48 h, (ii) r.t., 4 h	**3k**	89%
8	**1a**	Tos	H	H	CH		–N(*o*-Tol)OH	(i) 40 °C, 48 h, (ii) r.t., 4 h	**3l**	82%[c]
9	**1a**	Tos	H	H	CH		–CH(C_6F_5)OH	(i) 40 °C, 48 h, (ii) Me_2AlCl, 0 °C to r.t., 18 h	**3m**	71%[d]
10	**1a**	Tos	H	H	CH			(i) 40 °C, 48 h, (ii) 0 °C, 4 h	**3n**	75%
11	**1c**	Tos	OMe	H	CH		–N(*o*-Tol)OH	(i) 40 °C, 48 h, (ii) r.t., 24 h	**3o**	76%
12	**1c**	Tos	OMe	Me	CH		–CH(C_6F_5)OH	(i) 40 °C, 48 h, (ii) Me_2AlCl, −78 °C, 15 min then r.t., 18 h	**3p**	70%[e]
13	**1c**	Tos	OMe	H	CH			(i) 40 °C, 48 h, (ii) 0 °C, 4 h	**3q**	72%

Table 4 (*Contd.*)



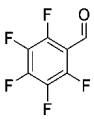
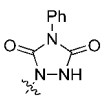
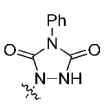
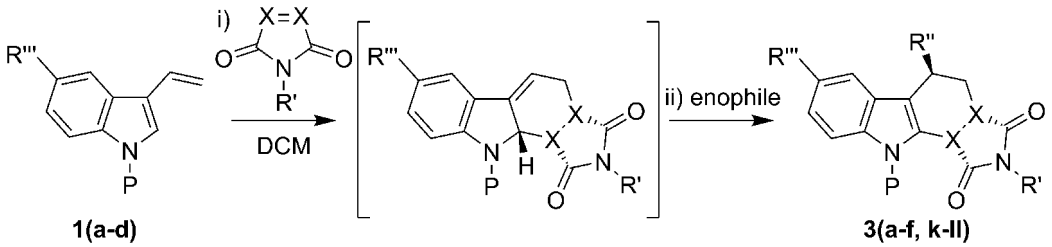
	Starting Material	P	R‴	R′	X	Enophile	R″	Reaction conditions	Product	Yield[a]
14	**1a**	Tos	H	Ph	N			(i) −78 °C, 4 h, (ii) 0 °C, 4 h	**3r**	65%[c]
15	**1c**	Tos	OMe	Ph	N		–N(*o*-Tol)OH	(i) −78 °C then r.t. 23 h, (ii) r.t., 23 h	**3s**	72%
16	**1d**	DMAS	H	Me	CH		–N(*o*-Tol)OH	(i) 40 °C, 48 h, (ii) r.t., 3 h	**3t**	74%
17	**1d**	DMAS	H	Ph	CH		–N(2,4-$(Br)_2C_6H_4$)-OH	(i) 40 °C, 48 h, (ii) r.t., 18 h	**3u**	69%[c]
18	**1d**	DMAS	H	Me	CH		–CH(C_6F_5)OH	(i) 40 °C, 48 h, (ii) Me_2AlCl, −78 °C, 1 h	**3v**	77%[c,f]
19	**1d**	DMAS	H	Ph	N		–N(*o*-Tol)OH	(i) −78 °C, 1 h, (ii) r.t., 4 h	**3w**	76%
20	**1d**	DMAS	H	H	CH		–N(*o*-Tol)OH	(i) 40 °C, 48 h, (ii) r.t., 3 h	**3x**	77%
21	**1e**	Cbz	H	Me	CH		–N(Ph)OH	(i) 40 °C, 24 h, (ii) r.t., 18 h	**3y**	74%
22	**1e**	Cbz	H	Me	CH		–N(*o*-Tol)OH	(i) 40 °C, 24 h, (ii) r.t., 18 h	**3z**	78%
23	**1e**	Cbz	H	Me	CH			(i) 40 °C, 24 h, (ii) 0 °C, 1 h then r.t., 18 h	**3aa**	54%
24	**1e**	Cbz	H	H	CH		–N(Ph)OH	(i) 40 °C, 24 h, (ii) r.t., 18 h	**3bb**	70%
25	**1e**	Cbz	H	H	CH		–N(*o*-Tol)OH	(i) 40 °C, 24 h, (ii) r.t., 4 h	**3cc**	83%
26	**1e**	Cbz	H	H	CH			(i) 40 °C, 24 h, (ii) 0 °C, 1 h	**3dd**	58%

Table 4 (*Contd.*)



	Starting Material	P	R‴	R′	X	Enophile	R″	Reaction conditions	Product	Yield[a]
27	**1e**	Cbz	H	Ph	N		–N(Ph)OH	(i) −78 °C, 5 h, (ii) r.t., 3 h	**3ee**	72%
28	**1e**	Cbz	H	Ph	N		–N(*o*-Tol)OH	(i) −78 °C, 5 h, (ii) r.t., 18 h	**3ff**	68%
29	**1f**	Cbz	OMe	Me	CH		–N(Ph)OH	(i) 40 °C, 18 h, (ii) r.t., 1.5 h	**3gg**	73%
30	**1f**	Cbz	OMe	Me	CH		–N(*o*-Tol)OH	(i) 40 °C, 18 h, (ii) r.t., 3 h	**3hh**	74%
31	**1f**	Cbz	OMe	H	CH		–N(Ph)OH	(i) 40 °C, 18 h, (ii) r.t., 2.5 h	**3ii**	79%
32	**1f**	Cbz	OMe	H	CH		–N(*o*-Tol)OH	(i) 40 °C, 18 h, (ii) r.t., 3.5 h	**3jj**	76%
33	**1f**	Cbz	OMe	Ph	N		–N(Ph)OH	(i) −78 °C, 1.5 h, (ii) r.t., 20 h	**3kk**	78%
34	**1f**	Cbz	OMe	Ph	N		–N(*o*-Tol)OH	(i) −78 °C, 1.5 h, (ii) r.t., 24 h	**3ll**	82%

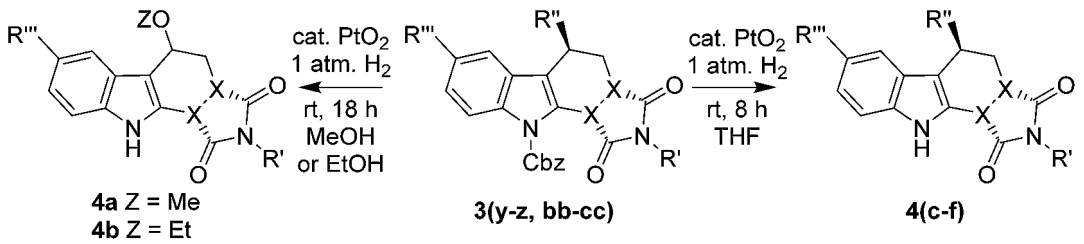
[a] Isolated yields. [b] 5 : 1 *endo* : *exo*. [c] Structure confirmed by single crystal X-ray analysis. [d] 25 : 1 *endo* : *exo*. [e] 10 : 1 *endo* : *exo*. [f] Only one diastereomer observed.

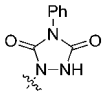
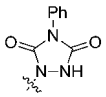
nucleophilic substitutions of the hydroxy(aryl)amino group by MeOH or EtOH also occurred to give **4a** and **4b** respectively. This gave the first indication that the removal of the electronically stabilising N-protecting group perhaps unsurprisingly lowers the activation energy barrier towards substitution chemistry at the indolylic position.[38–40] Replacement of the alcoholic solvent with THF resulted in a cleaner deprotection of Cbz protected indoles **3(y–ll)** to give **4(c–p)** in 38–91% yields. However the products **4(c–p)** showed some evidence of decomposition in $CDCl_3$ after a few hours at r.t., with the appearance of new peaks in the ^{1}H NMR spectra. Therefore NMR analysis of **4(c–p)** was carried out in either d_2-DCM or d_6-DMSO (depending on solubility) in which decomposition was slowed, although the appearance of minor peaks in the ^{1}H NMR could still be observed over time. The deprotection of indoles **3(y–ll)** with H_2 and Adam's catalyst in THF has allowed us to successfully demonstrate a one-pot, three-component approach to our target library of deprotected partially saturated carbazoles and pyridazino[3,4-*b*]indoles, which will be the focus of future investigations (Table 5).

Conclusions

In conclusion, we have developed a practically simple three-component approach to Tos, DMAS and Cbz protected partially saturated carbazoles and pyridazino[3,4-*b*]-indoles, based on a one-pot D–A/ene reaction, including the examination of a deprotection strategy of the Cbz

Table 5 Deprotection of 3(y, z, bb and cc)



	Starting material	R′	X	R″	R″	Solvent	Product	Yield[a]
1	**3z**	Me	CH	–N(*o*-Tol)OH	H	MeOH	**4a**	60%
2	**3z**	Me	CH	–N(*o*-Tol)OH	H	EtOH	**4b**	24%
3	**3y**	Me	CH	–N(Ph)OH	H	THF	**4c**	75%
4	**3z**	Me	CH	–N(*o*-Tol)OH	H	THF	**4d**	87%
5	**3aa**	Me	CH		H	THF	**4e**	91%
6	**3bb**	H	CH	–N(Ph)OH	H	THF	**4f**	41%
7	**3cc**	H	CH	–N(*o*-Tol)OH	H	THF	**4g**	70%
8	**3dd**	H	CH		H	THF	**4h**	64%
9	**3ee**	Ph	N	–N(Ph)OH	H	THF	**4i**	65%
10	**3ff**	Ph	N	–N(*o*-Tol)OH	H	THF	**4j**	44%
11	**3gg**	Me	CH	–N(Ph)OH	OMe	THF	**4k**	70%
12	**3hh**	Me	CH	–N(*o*-Tol)OH	OMe	THF	**4l**	70%
13	**3ii**	H	CH	–N(Ph)OH	OMe	THF	**4m**	60%
14	**3jj**	H	CH	–N(*o*-Tol)OH	OMe	THF	**4n**	85%
15	**3kk**	Ph	N	–N(Ph)OH	OMe	THF	**4o**	38%
16	**3ll**	Ph	N	–N(*o*-Tol)OH	OMe	THF	**4p**	61%

[a] Isolated yields.

group. Current work is looking into controlling the reactivity and biological activity of the final products as well as investigating enantioselective D–A/ene approaches for molecules of this type.

Experimental

3-Vinyl-1*H*-indole

In a Schlenk flask, methyltriphenylphosphonium iodide (2.14 g, 5.3 mmol) was dissolved in dry THF (13 mL). The solution was cooled to −78 °C and ^{n}butyllithium (2.9 mL, 4.6 mmol) was added over 10 minutes. The yellow solution was warmed to 0 °C and was left to stir for 1 hour before being cooled to −78 °C. In a separate Schlenk flask, 1*H*-indole-3-carboxylate (0.67 g, 4.6 mmol) was dissolved in THF (7 mL) and to the solution sodium bis(trimethylsilyl)amide (2.3 mL, 4.6 mmol) was added. This solution was transferred into the first Schlenk flask and the red solution was allowed to stir at room temperature for 1 hour. The reaction was poured into water (30 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under pressure to leave the crude product as yellow oil. The product was purified using column chromatography (petrol (40/60)–diethyl ether 7 : 3, column diameter = 4 cm, silica = 20 cm) to give 3-vinyl-1*H*-indole (0.636 g, 4.4 mmol, 95%) as a yellow powder.

Mp: 78.4–80.7 °C; R_f: 0.76 (Pet(40/60)–EA, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.02 (1H, br s), 7.85–7.80 (1H, m), 7.32–7.28 (1H, m), 7.18 (1H, s), 7.18–7.09 (2H, m), 6.83 (1H, ddd, J = 17.7, 11.2, 0.5 Hz), 5.65 (1H, dd, J = 17.7, 1.5 Hz), 5.11 (1H, dd, J = 11.2, 1.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.8, 129.5, 125.7, 123.6, 122.6, 120.4, 120.2, 115.9, 111.4, 110.9; IR (neat): ν_{max}/cm^{-1} 3660, 2981.

1a – 1-tosyl-3-vinyl-1*H*-indole

Into a Schlenk flask, was placed 1*H*-indole-3-carbaldehyde (5.0 g, 34.5 mmol) and DCM (100 mL). The resulting stirred solution was cooled to 0 °C before triethylamine (12 mL, 86.2 mmol) was added dropwise *via* syringe. To the stirred solution, *p*-toluenesulfonyl chloride (7.23 g, 37.9 mmol) in DCM was added dropwise over a period of 20 minutes. The solution was stirred at 0 °C for a further one hour before warming to room temperature over 18 hours. The solution was washed into a separating funnel with DCM (20 mL) and washed with water (2 × 100 mL) and brine (100 mL). The organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude product as a pale orange oil.

The product was purified by recrystallisation from hot ethyl acetate (150 mL) to give 1-tosyl-1*H*-indole-3-carbaldehyde (8.38 g, 28 mmol, 82%) as orange crystals.

Mp: 145.3–148.8 °C; R_f: 0.83 (Pet(40/60)–EA 1 : 4); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 10.11 (1H, s), 8.29–8.26 (1H, m), 8.19–8.16 (1H, m), 8.16 (1H, s), 7.89–7.85 (1H, m), 7.78 (2H, d, J = 8.4 Hz), 7.36–7.25 (2H, m), 7.22 (2H, d, J = 8.4 Hz), 2.29 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.3, 146.1, 136.2, 135.4, 134.1, 130.3, 130.2, 127.2, 127.1, 126.2, 124.9, 122.5, 122.2, 113.1, 21.5; IR (neat): ν_{max}/cm^{-1} 3140, 1663; anal. calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68. Found: C, 63.97; H, 4.52; N, 4.72.

A Schlenk flask was charged with methyltriphenylphosphonium iodide (1.29 g, 3.2 mmol) dissolved in dry THF (25 mL) under a nitrogen atmosphere. The solution was cooled to −78 °C and ^{n}butyllithium (1.81 mL, 2.97 mmol) was added dropwise *via* syringe over 10 minutes. The solution was warmed to 0 °C and left to stir for 2 hours. In a separate Schlenk flask, 1-tosylindoline-3-carbaldehyde (0.8 g, 2.7 mmol) was dissolved in THF (5 mL). The indole solution was transferred *via* cannula to the Schlenk flask containing the solution of methyltriphenylphosphonium iodide and the solution was stirred for 18 hours. The reaction poured into water (50 mL) and extracted with ether (3 × 40 mL). The organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to leave the crude product as an orange oil. The crude product was purified by column chromatography (petrol (40/60)–ethyl acetate; 10 : 1, 2 cm diameter column) to give 1-tosyl-3-vinyl-1*H*-indole (0.56 g, 3.9 mmol, 70%) as a pale yellow powder.

Mp: 90.3–94.6 °C; R_f: 0.86 (Pet(40/60)–EA, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.93–7.90 (1H, m), 7.69 (2H, d, J = 8.4 Hz), 7.70–7.65 (1H, m), 7.53 (1H, s), 7.29–7.19 (2H, m), 7.29–7.17 (2H, m), 7.15 (2H, d, J = 8.4 Hz), 6.70 (1H, app ddd, J = 17.9, 11.3, 0.7 Hz), 5.72 (dd, 1H, J = 17.9, 1.2 Hz), 5.28 (1H, dd, J = 11.3, 1.2 Hz), 2.26 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 145.1, 135.6, 135.2, 130.0, 129.1, 127.6, 126.9, 125.0, 124.2, 123.6, 121.0, 120.5, 115.4, 113.8, 21.7; IR (neat): ν_{max}/cm^{-1} 3119, 3072; anal. calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.70; H, 5.21; N, 4.61.

1b – ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate

In a Schlenk flask, (4-ethoxy-4-oxobutyl) triphenylphosphonium bromide (3.32 g, 7.26 mmol) was dissolved in dry THF (20 mL). The solution was cooled to −78 °C and sodium bis (trimethylsilyl) amide (1.00 M in THF, 8.58 mL, 8.58 mmol) was added dropwise over 10 min. The mixture was warmed to 0 °C and left to stir. After 2 hours, 1-(toluene-4-sulfonyl)-1*H*-indol-3-carboxaldehyde (2.00 g, 6.60 mmol) was dissolved in dry THF (10 mL) in a separate round bottomed flask, and transferred *via* cannula into the reaction solution. The reaction mixture was stirred at room temperature and for 48 hours, quenched with saturated $NH_4Cl_{(aq.)}$ (30 mL), extracted with EtOAc (2 × 200 mL), and the combined organic layers washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give a crude product as orange oil. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 10 : 1) to give two fractions the first containing ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate (1.568 g, 3.94 mmol, 60%) as a colourless oil, and a second fraction containing a 20 : 1 mixture of (*Z*) and (*E*) ethyl-5-(1-tosyl-1*H*-indol-3-yl)pent-4-enoate (0.294 g, 0.739 mmol, 11%) also as a colourless oil.

R_f: 0.70 (Pet(40/60)–EA 7 : 3); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.97 (1H, d, J = 7.9 Hz, 1H), 7.77 (2H, d, J = 7.8 Hz), 7.57 (1H, s), 7.49 (1H, d, J = 7.9 Hz), 7.32 (1H, t, J = 7.9 Hz), 7.25 (1H, t, J = 7.9 Hz), 7.20 (2H, d, J = 7.8 Hz), 6.44 (1H, d, J = 11.2 Hz), 5.78 (1H, dt, J = 11.2, 7.5 Hz), 4.14 (2H, q, J = 6.5 Hz), 2.67–2.62 (2H, m), 2.48 (2H, t, J = 6.9 Hz), 2.30 (3H, s), 1.24 (3H, t, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.8, 145.1, 135.1, 134.6, 132.1, 130.8, 129.9, 126.8, 124.9, 123.6, 123.4, 119.5, 118.96, 113.6, 60.5, 34.1, 25.2, 21.6, 14.3; IR (neat): ν_{max}/cm^{-1}: 1727, 1597. MS (pNSI): 415.2 (100%, $[M + NH_4]^+$), 398.1 (20%, $[M + H]^+$), 420.1 (10%, $[M + Na]^+$); HRMS (pNSI): calcd $C_{22}H_{24}NO_4S$ $[M + H]^+$: 398.14120; observed: 398.14120.

1c – 5-methoxy-1-tosyl-3-vinyl-1*H*-indole

To a stirred round bottomed flask was added 5-methoxy-1*H*-indole-3-carbaldehyde (0.70 g, 4.00 mmol) and DCM (20 mL) and the solution was cooled to 0 °C. To the stirred solution was added triethylamine (1.40 mL, 10.0 mmol) and the resulting solution was stirred at 0 °C for 1 hour. To the stirred solution was added *p*-toluenesulfonyl chloride (0.84 g, 4.40 mmol) in DCM (10 mL) and the solution was stirred at room temperature for 18 hours. The reaction was poured into water (50 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to leave the crude product as a pale orange solid. The product was purified using column chromatography (petrol (40/60)–ether–DCM 2 : 1 : 1, column diameter = 2 cm, silica = 15 cm) to give 5-methoxy-1-tosyl-1*H*-indole-3-carbaldehyde (1.14 g, 3.48 mmol, 87%) as a pale brown powder.

Mp: 126.1–128.4 °C; R_f: 0.71 (Pet(40/60)–Et_2O–DCM 2 : 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 10.07 (1H, s), 8.19 (1H, s), 7.86–7.83 (1H, m), 7.84 (2H, d, J = 8.5 Hz), 7.72 (1H, d, J = 2.6 Hz), 7.29 (2H, d, J = 8.5 Hz), 7.02 (1H, dd, J = 9.1, 2.6 Hz), 3.86 (3H, s), 2.38 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 185.6, 157.8, 146.2, 136.8, 134.4, 130.4, 129.8, 127.4, 127.2, 122.3, 116.2, 114.2, 104.1, 55.8, 21.8; IR (neat): ν_{max}/cm^{-1} 3128, 2832, 1671; anal. calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25. Found: C, 61.77; H, 4.70; N, 4.29.

In a Schlenk flask, methyltriphenylphosphonium iodide (1.35 g, 3.34 mmol) was dissolved in dry THF (30 mL). The solution was cooled to −78 °C and ^{n}BuLi (1.2 mL, 3.03 mmol) was added over 5 minutes. The yellow solution was warmed to 0 °C and was allowed to stir for 1 hour before being cooled to −78 °C. To the stirred solution, 5-methoxy-1-tosyl-1*H*-indole-3-carbaldehyde (1.00 g, 3.03 mmol) in DCM (10 mL) was added and the solution was stirred at room temperature for 3 hours. The reaction was poured into water (40 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under pressure to leave the crude product an orange oil. The product was purified using column chromatography (petrol (40/60)–

ethyl acetate 2 : 1, column diameter = 2 cm, silica = 16 cm) to give 5-methoxy-1-tosyl-3-vinyl-1*H*-indole (0.79 g, 2.42 mmol, 80%) as a brown powder.

Mp: 101.4–103.9 °C; R_f: 0.66 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.87 (1H, d, J = 9.0 Hz), 7.73 (2H, d, J = 8.4 Hz), 7.55 (1H, s), 7.19 (2H, d, J = 8.3 Hz), 7.14 (1H, d, J = 2.5 Hz), 6.93 (1H, dd, J = 9.0, 2.5 Hz), 6.72 (1H, dd, J = 17.9, 11.3 Hz), 5.73 (1H, dd, J = 17.9, 1.1 Hz), 5.32 (1H, dd, J = 11.3, 1.1 Hz), 3.82 (3H, s), 2.31 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 156.7, 145.0, 135.1, 130.3, 130.1, 130.0, 127.6, 126.9, 124.9, 121.1, 115.2, 114.7, 113.7, 103.2, 55.8, 21.7; IR (neat): ν_{max}/cm^{-1} 3128, 2832, 1671; MS (pNSI): 328.1 (100%, $(M + H)^+$), 350.1 (15%, $(M + Na)^+$), 672.2 $(2M + NH_4)^+$; HRMS (pNSI): calcd for $C_{18}H_{18}NO_3S$ $[M + H]^+$: 328.1002; observed: 328.1007.

1d – *N*,*N*-dimethyl-3-vinyl-1*H*-indole-1-sulfonamide

To a stirred round bottomed flask was added 1*H*-indole-3-carbaldehyde (3.0 g, 20.7 mmol) and THF (70 mL) and the solution was cooled to 0 °C. To the stirred solution was added sodium hydride (1.7 g, 41.4 mmol) in THF (30 mL) and the resulting solution was stirred at 0 °C for 1 hour. To the stirred solution was added dimethylsulfamoyl chloride (2.4 mL, 20.7 mmol) and the solution was stirred at room temperature for 18 hours. The reaction was poured into water (100 mL) and extracted with DCM (3 × 60 mL). The combined organic extracts were dried over MgSO4, filtered and the solvent was removed under reduced pressure to leave the crude product as a pale red pink solid. The product was purified by recrystallization from ethyl acetate to give 3-formyl-*N*,*N*-dimethyl-1*H*-indole-1-sulfonamide (97%, 5.07 g, 20.1 mmol) as a pink powder.

Mp: 149.0–150.9 °C; R_f: 0.63 (Pet(40/60)–EA, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 10.08 (1H, s), 8.31 (1H, app dd, J = 7.2, 1.4 Hz), 8.09 (1H, s), 7.94–7.88 (1H, m), 7.40 (2H, app ddd, J = 5.9, 3.3, 1.6 Hz), 2.91 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 185.5, 137.3, 136.0, 126.1, 125.9, 124.9, 122.6, 120.8, 113.6, 38.6; IR (neat): ν_{max}/cm^{-1} 3124, 2945, 1662; anal. calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10. Found: C, 52.23; H, 4.91; N, 10.92.

In a Schlenk flask, methyltriphenylphosphonium iodide (7.00 g, 17.4 mmol) was dissolved in dry THF (75 mL). The solution was cooled to −78 °C and ^{n}BuLi (6.4 mL, 15.9 mmol) was added over 10 minutes. The yellow solution was warmed to 0 °C and was left to stir for 1 hour before being cooled to −78 °C. To the stirred solution, 3-formyl-*N*,*N*-dimethyl-1*H*-indole-1-sulfonamide (4.00 g, 15.9 mmol) was added and the solution was stirred at room temperature for 3 hours. The reaction was poured into water (70 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under pressure to leave the crude product as yellow oil. The product was purified using column chromatography (petrol (40/60)–diethyl ether 4 : 1, column diameter = 3 cm, silica = 14 cm) to give *N*,*N*-dimethyl-3-vinyl-1*H*-indole-1-sulfonamide (3.11 g, 12.4 mmol, 78%) as a pale orange powder.

Mp: 68.7–67.8 °C; R_f: 0.63 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.98 (1H, dd, J = 8.0, 1.4 Hz), 7.85 (1H, dd, J = 7.7, 1.5 Hz), 7.35 (2H, app ddd, J = 7.0, 5.3, 1.6 Hz), 6.83 (1H, dd, J = 17.8, 11.2 Hz), 5.84 (1H, dd, J = 17.8, 1.2 Hz), 5.38 (1H, dd, J = 11.3, 1.2 Hz), 2.86 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 136.1, 128.2, 127.8, 125.2, 124.7, 123.1, 120.4, 118.8, 114.9, 114.0, 38.6; IR (neat): ν_{max}/cm^{-1} 3123, 2945; anal. calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.68; H, 5.75; N, 11.05.

1e – benzyl-3-vinyl-1*H*-indole-1-carboxylate

To a solution of 1*H*-indole-3-carbaldehyde (1.0 g, 6.9 mmol) in DCM (20 mL) at 0 °C was added triethylamine (1.8 mL, 17.3 mmol) dropwise. The solution was stirred at room temperature for 1 hour before benzyl chloroformate (1.4 mL, 8.3 mmol) was added. The solution was stirred for 18 hours after which it was poured into water and extracted with DCM (3 × 20 mL). The organic fractions were combined, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the crude product as an orange powder. The crude product was purified by column chromatography (column diameter = 2.5 cm, eluent = petrol (40/60)–ethyl acetate 2 : 1) to give benzyl-3-formyl-1*H*-indole-1-carboxylate (1.74 g, 6.35 mmol, 92%) as a pale orange powder.

Mp: 91–92 °C; R_f: 0.68 (Pet–EA, 2 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 10.06 (1H, s), 8.30–8.25 (1H, m), 8.23 (1H, s), 8.17 (1H, d, J = 8.0 Hz), 7.50 (2H, app dd, J = 7.7, 1.8 Hz), 7.42 (3H, app ddd, J = 6.6, 5.1, 1.5 Hz), 7.38 (1H, app t, J = 1.6 Hz), 7.37–7.34 (1H, m), 5.49 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 185.8, 150.2, 136.1, 136.1, 134.3, 129.3, 129.0, 128.9, 126.5, 126.1, 125.0, 122.3, 122.3, 115.2, 69.9; IR (neat): ν_{max}/cm^{-1} 3127, 3008, 1733; MS (pNSI): 280.1 (100%, $(M + H)^+$), 302.1 (96%, $(M + Na)^+$), 581.2 (25%, $(2M + Na)^+$); HRMS (pNSI): calcd for $C_{17}H_{14}NO_3$ $[M + H]^+$: 280.0968; observed: 280.0970.

To a stirred Schlenk flask, methylenetriphenylphosphorane (2.38 g, 5.90 mmol) was dissolved in dry THF (30 mL). The solution was cooled to −78 °C and ^{n}BuLi (2.15 mL, 5.35 mmol) was added over 10 minutes. The yellow solution was warmed to 0 °C and was left to stir for 1 hour before being cooled to −78 °C. To the stirred solution, benzyl 3-formyl-1*H*-indole-1-carboxylate (1.50 g, 5.35 mmol) was added and the solution was stirred at room temperature for 3 hours. The reaction was poured into water (50 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried with $MgSO_4$, filtered and the solvent removed under pressure to leave the crude product as yellow oil. The product was purified using column chromatography (petrol (40/60)–ethyl acetate 2 : 1, column diameter = 2 cm, silica = 15 cm) to give benzyl-3-vinyl-1*H*-indole-1-carboxylate (1.14 g, 4.07 mmol, 76%) as a yellow powder.

Mp: 43–45 °C; R_f: 0.73 (Pet(40/60)–EA, 2 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.33 (1H, d, J = 7.1 Hz), 7.91–7.86 (1H, m), 7.74 (1H, s), 7.58–7.55 (2H, m), 7.52–7.44 (4H, m), 7.43–7.36 (1H, m), 6.87 (1H, dd, J = 17.8, 11.3 Hz), 5.96–5.87 (1H, d, J = 17.8 Hz), 5.51 (2H, s), 5.44 (1H, d, J = 11.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 150.8, 135.1, 128.9, 128.9, 128.8, 128.6, 128.4, 128.0, 125.1, 123.6, 123.4, 120.2, 120.2, 115.5, 115.0, 68.9; IR (neat): ν_{max}/cm^{-1} 3153, 2962, 1729; MS (pAPCI): 181.1 (50%), 260.1 (100%), 278.1 (25%, $(M + H)^+$);

HRMS (pAPCI): calcd for $C_{18}H_{16}NO_2$ $[M + H]^+$: 278.1176; observed: 278.1173.

1f – benzyl-5-methoxy-3-vinyl-1*H*-indole-1-carboxylate

To a stirred Schlenk flask, methylenetriphenylphosphorane (3.54 g, 8.70 mmol) was dissolved in dry THF (34 mL). The solution was cooled to −78 °C and ^{n}BuLi (3.1 mL, 7.87 mmol) was added over 10 minutes. The yellow solution was warmed to 0 °C and was left to stir for 1 hour before being cooled to −78 °C. In a separate Schlenk flask, 5-methoxy-1*H*-indole-3-carbaldehyde (1.38 g, 7.87 mmol) was dissolved in THF (10 mL) and to the solution sodium bis(trimethylsilyl)amide (7.87 mL, 7.87 mmol) was added. This solution was transferred into the first Schlenk flask and the red solution was allowed to stir at room temperature for 1 hour. The reaction was poured into water (50 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried with $MgSO_4$, filtered and the solvent removed under pressure to leave the crude product as yellow oil. The product was purified using column chromatography (petrol (40/60)–diethyl ether 2 : 1, column diameter = 2.5 cm, silica = 16 cm) to give 5-methoxy-3-vinyl-1*H*-indole (1.38 g, 7.6 mmol, 97%) as a yellow powder.

Mp: 190–193 °C; R_f: 0.49 (Pet–Et_2O, 2 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.28 (1H, s), 7.66 (1H, d, J = 2.4 Hz), 7.29 (1H, d, J = 8.8 Hz), 7.24 (1H, d, J = 2.7 Hz), 7.20–7.10 (2H, m), 7.18 (1H, d, J = 2.5 Hz), 7.15 (2H, dd, J = 4.5, 2.1 Hz), 7.10 (1H, s), 5.95 (1H, dd, J = 17.8, 1.5 Hz), 5.46 (1H, dd, J = 11.2, 1.5 Hz), 4.07 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 154.4, 132.5, 130.8, 126.4, 126.1, 114.2, 113.0, 112.0, 109.1, 102.0, 55.9; IR (neat): ν_{max}/cm^{-1} 3410, 2925, 2836; MS (pNSI): 174.1 (100%, $(M + H)^+$), 520.3 (100%, $(3M + H)^+$); HRMS (pNSI): calcd for $C_{11}H_{12}NO$ $[M + H]^+$: 174.0913; observed: 174.0912.

To a stirred Schlenk flask, 5-methoxy-3-vinyl-1*H*-indole (1.15 g, 6.61 mmol) was dissolved in THF (30 mL) and the solution was cooled to 0 °C. To the stirred solution, sodium bis(trimethylsilyl)amide (7.27 mL, 7.27 mmol) was added and the solution was stirred for 30 minutes before benzyl chloroformate (0.90 mL, 6.61 mmol) was added. The solution was stirred for 30 minutes at room temperature before being added to water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic washings were dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the crude product as an orange oil. The product was purified using column chromatography (petrol (40/60)–ethyl acetate 5 : 1, column diameter = 2.0 cm, silica = 15 cm) to give benzyl-5-methoxy-3-vinyl-1*H*-indole-1-carboxylate (1.78 g, 4.7 mmol, 71%) as a pale yellow oil.

R_f: 0.82 (Pet(40/60)–EA, 5 : 1); ^{1}H NMR (400 MHz), δ_H 8.09 (1H, s), 7.66 (1H, s), 7.50 (2H, d, J = 7.2 Hz), 7.45–4.37 (1H, m), 7.25 (1H, d, J = 2.5 Hz), 6.96 (1H, dd, J = 9.0, 2.2 Hz), 6.79 (1H, dd, J = 17.8, 11.4 Hz), 5.80 (1H, d, J = 17.8 Hz), 5.42 (2H, s), 5.34 (1H, d, J = 11.4 Hz), 3.85 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 156.4, 135.2, 129.7, 128.9, 128.9, 128.7, 128.6, 128.0, 124.1, 124.1, 120.0, 116.1, 114.8, 113.3, 103.3, 68.8, 55.8; IR (neat): ν_{max}/cm^{-1} 2955, 2834, 1726; MS (pAPCI): 181.1 (32%), 260.1 (100%), 308.1 (28%, $(M + H)^+$); HRMS (pAPCI): calcd for $C_{19}H_{18}NO_3$ $[M + H]^+$: 308.1281; observed: 308.1277.

2a – (3a*S**,10b*S**)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

Into a round bottomed flask, 1-tosyl-3-vinyl-1*H*-indole (2.0 g, 6.7 mmol) and DCM (10 mL) was added. To the stirred solution, *N*-methylmalemide (0.75 g, 6.7 mmol) was added and the solution was stirred at 40 °C for 48 hours. The solvent was removed under reduced pressure to leave the crude product as orange oil. The product was purified by column chromatography (petrol (40/60)–ethyl acetate, 4 : 1, column diameter = 4 cm, silica = 15 cm) to give (3a*S**,10b*S**)-2-methyl-10-tosyl-4,10,10a,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (2.01 g, 5.0 mmol, 76%) as a white powder.

Mp: 204.2–208.0 °C; R_f: 0.09 (Pet(40/60)–EA, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.72 (2H, d, J = 8.0 Hz), 7.61 (1H, d, J = 8.5 Hz), 7.21–7.19 (2H, d, J = 8.0), 7.21–7.16 (1H, m), 6.92 (1H, app t, J = 7.5 Hz), 6.01–5.96 (1H, m), 4.47 (1H, dd, J = 7.0, 3.3 Hz), 3.99 (1H, app t, J = 8.1 Hz), 3.12 (1H, app t, J = 8.1 Hz), 2.99–2.92 (1H, m), 2.76 (3H, s), 2.30 (3H, s), 2.11 (1H, ddd, J = 18.0, 6.4, 2.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 178.9, 174.2, 144.7, 144.6, 137.4, 134.3, 130.4, 129.9, 127.5, 126.4, 123.9, 121.0, 115.4, 112.9, 61.6, 43.3, 37.2, 25.3, 25.1, 21.7; IR (neat): ν_{max}/cm^{-1} 2981, 2889, 1694; MS (pNSI): 409.2 (61%, $(M + H)^+$), 426.1 (100%, $(M + (NH_4))^+$), 834.3 (52%, $(2M + (NH_4))^+$); HRMS (pNSI): calcd $C_{22}H_{21}N_2O_4S$ $[M + H]^+$: 409.1217; observed: 409.1218.

2b – 2-phenyl-11-tosyl-11,11a-dihydro-1*H*,5*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol) and DCM (7 mL) and the solution was cooled to −78 °C. To the stirred solution was added 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (60 mg, 0.34 mmol) and the resulting solution was stirred at −78 °C for 3.5 hours before the solvent was removed under reduced pressure to leave the crude product as a pale red solid. The product was purified by column chromatography (petrol (40/60)–ether–DCM 2 : 1 : 1, column diameter = 1 cm, silica = 20 cm) to give 2-phenyl-11-tosyl-11,11a-dihydro-1*H*,5*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino-[3,4-*b*]indole-1,3(2*H*)-dione (88%, 140 mg, 0.30 mmol) as a pale red powder.

Mp: 160.1–162.8 °C; R_f: 0.14 (Pet(40/60)–Et_2O–DCM 2 : 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.86 (2H, d, J = 8.4 Hz), 7.63–7.55 (2H, m), 7.51–7.46 (2H, m), 7.46–7.42 (1H, m), 7.42–7.39 (1H, m), 7.38–7.34 (2H, m), 7.26–7.22 (2H, m), 7.09 (1H, app td, J = 7.5, 1.0 Hz), 6.26 (1H, td, J = 2.6, 1.8 Hz), 6.18 (1H, app dt, J = 5.3, 2.7 Hz), 4.56–4.46 (1H, app td, J = 17.6, 2.8 Hz), 4.39 (1H, ddd, J = 17.6, 5.2, 1.9 Hz), 2.37 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 152.7, 150.8, 144.7, 143.7, 135.6, 134.8, 131.5, 130.4, 129.6, 128.9, 128.5, 128.1, 126.8, 125.7, 125.2, 120.9, 117.4, 113.8, 74.8, 44.6, 21.4; IR (neat): ν_{max}/cm^{-1} 3070, 2926, 1719; MS (pNSI): 473.1 (100%, $(M + H)^+$),

522.2 (30%); HRMS (pNSI): calcd for $C_{25}H_{21}N_4O_4S$ $[M + H]^+$: 473.1278; observed: 473.1277.

2c – ethyl-3-((3a*S**,4*R**,10b*S**)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl) propanoate

Dimethylaluminum chloride (1.0 M in hexane, 9.38 ml, 9.38 mmol) was added dropwise to a solution of *N*-methyl-maleimide (0.521 g, 4.69 mmol) in dry DCM (15 mL) at −78 °C. The mixture left to stir for 30 min. A solution of ethyl-(*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate (4.69 mmol, 1.863 g) in dry DCM (15 mL) was added dropwise at −78 °C. The reaction mixture was then warmed to reflux for 48 hours and quenched with saturated $NaHCO_{3(aq.)}$ (20 mL) and extracted with DCM (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude yellow solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1) to yield ethyl 3-((3a*S**,4*R**,10b*S**)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]-carbazol-4-yl)propanoate in (2.038 g, 4.01 mmol, 85%) a bright yellow solid.

Mp: 187–188 °C; R_f: 0.3 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.79 (2H, d, J = 7.3 Hz), 7.62 (1H, d, J = 7.0 Hz), 7.25–7.21 (4H, m), 6.95 (1H, t, J = 7.0 Hz), 6.09 (1H, dd, J = 3.7, 6.7 Hz), 4.85 (1H, dd, J = 3.7, 6.9 Hz), 4.15 (1H, t, J = 6.9 Hz), 4.07 (2H, m), 3.15–3.12 (1H, m), 3.05–3.02 (1H, m), 2.83 (3H, s), 2.43–2.36 (2H, m), 2.35 (3H, s), 1.91–1.75 (2H, m), 1.19 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 178.6, 174.0, 172.79, 144.6, 144.0, 136.6, 134.0, 130.5, 130.0, 127.5, 126.6, 123.9, 121.0, 116.3, 115.4, 60.6, 59.9, 44.22, 42.98, 37.2, 33.1, 28.3, 25.3, 21.70, 14.3; IR (neat): ν_{max}/cm^{-1}: 1776, 1698; HRMS (pNSI): calcd $C_{27}H_{29}N_2O_6S$ $[M + H]^+$: 509.1741; observed: 509.1731.

2d – ethyl-3-((3a*S**,4*R**,10b*S**)-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl) propanoate

Dimethyl aluminum chloride (1.0 M in hexane, 2.86 mL, 2.86 mmol) was added dropwise to a solution of *N*-maleimide (0.14 g, 1.43 mmol) in dry DCM (5 mL) at −78 °C. The mixture left to stir for 30 min. A solution of ethyl-(*Z*)-5-(1-tosyl-1*H*-indol-3-yl)-pent-4-enoate (0.57 g, 1.43 mmol) in dry DCM (10 mL) was added. The reaction mixture was slowly heated to reflux for 48 h, quenched with saturated $NaHCO_{3(aq.)}$ (5 mL). The organic layer was extracted with DCM (1 × 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude yellow solid product which was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1 gradient to 1 : 1 petrol–ethyl acetate) to yield ethyl 3-((3a*S**,4*R**,10b*S**)-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octa-hydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate in (0.452 g, 0.91 mmol, 64%) as a white solid.

Mp: 218–220 °C; R_f: 0.14 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78 (2H, d, J = 6.9 Hz), 7.64 (1H, d, J = 6.8 Hz), 7.27–7.22 (4H, m), 6.98 (1H, t, J = 7.8 Hz), 6.16 (1H, dd, J = 3.6, 7.1 Hz), 4.84 (1H, dd, J = 3.6, 7.3 Hz), 4.18 (1H, t, J = 7.3 Hz), 4.12–4.05 (2H, m), 3.16–1.12 (1H, m), 3.10 (1H, t, J = 7.3 Hz), 2.40 (2H, t, J = 7.3 Hz), 2.35 (3H, s), 1.89–1.76 (2H, m), 1.20 (3H, t, J = 7.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 178.3, 173.6, 172.7, 144.5, 144.1, 136.6, 133.8, 130.5, 129.8, 127.5, 126.6, 123.8, 120.0, 116.4, 115.5, 60.8, 59.6, 45.2, 44.0, 36.9, 33.0, 27.8, 21.5, 14.1; IR (neat): ν_{max}/cm^{-1}: 3657, 2981, 1776, 1703; MS (pNSI): 512.18 (100%, $[M + NH_4]^+$), 495.15 (55%, $[M + H]^+$), 340.14 (31%, [M − Ts]); HRMS (pNSI): calcd $C_{26}H_{27}N_2O_6S$ $[M + H]^+$: 495.1584; observed: 495.1585.

2e – ethyl 3-((3a*S**,4*R**,10b*S**)-1,3-dioxo-2-phenyl-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl) propanoate

Dimethyl aluminum chloride (1.0 M in THF, 2.39 mL, 2.39 mmol) was added dropwise to a solution of *N*-phenylmaleimide (0.207 g, 1.19 mmol) in dry DCM (5 mL) at −78 °C. The mixture left to stir for 30 min. A solution of ethyl (*Z*)-5-(1-tosyl-1*H*-indol-3-yl) pent-4-enoate (0.475 g, 1.19 mmol) in dry DCM (10 mL) was added. The reaction mixture was heated to reflux for 48 h, quenched with saturated $NaHCO_{3(aq.)}$ (10 mL) and extracted with DCM (100 mL). The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude yellow solid product which was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1) to yield ethyl 3-((3a*S**,4*R**,10b*S**)-1,3-dioxo-2-phenyl-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate in (0.5095 g, 0.84 mmol, 71%) as a white solid.

Mp: 201–203 °C; R_f: 0.2 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.81 (2H, d, J = 7.3 Hz), 7.60 (1H, d, J = 7.3 Hz), 7.34–7.21 (7H, m), 7.06 (2H, d, J = 7.3 Hz), 6.97 (1H, t, J = 7.3 Hz), 6.20 (1H, dd, J = 3.4, 7.1 Hz), 4.59 (1H, dd, J = 3.4, 7.1 Hz), 4.18 (1H, t, J = 7.3 Hz), 4.13–4.05 (2H, m), 3.26–3.20 (2H, m), 2.45–2.40 (2H, m), 2.35 (3H, s), 1.89–1.85 (2H, m), 1.20 (3H, t, J = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.5, 172.9, 172.7, 144.6, 144.3, 137.0, 134.1, 131.7, 130.7, 130.0, 129.0, 128.5, 127.6, 126.7, 126.3, 124.0, 120.9, 116.2, 115.5, 60.8, 60.0, 44.3, 43.1, 37.7, 33.2, 28.3, 21.6, 14.2; IR (neat): ν_{max}/cm^{-1}: 1776, 1703; MS (pNSI): 588.21 (100%, $[M + NH_4]^+$), 1158.39 (33%, $[2M + NH_4]^+$); HRMS (pNSI): calcd $C_{32}H_{31}N_2O_6S$ $[M + H]^+$: 571.18; observed: 571.1891.

3a – (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol), DCM (5 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (38 mg, 0.34 mmol). The resulting solution was heated at reflux for 48 hours. The reaction was allowed to cool to room temperature, nitrosobenzene (40 mg, 0.34 mmol) was added, and the solution was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow solid which was purified by column chromatography (petrol (40/60)–ethyl acetate 4 : 1, column diameter = 1 cm, silica = 16 cm) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-2-methyl-10-tosyl-

4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione as a yellow powder (71%, 128 mg, 0.24 mmol).

Mp: 196.8–199.5 °C; R_f: 0.64 (Pet(40/60)–EA, 1 : 1); ^{1}H NMR (500 MHz, CD_2Cl_2): δ_H 7.94 (1H, d, J = 8.4 Hz), 7.69 (2H, d, J = 8.2 Hz), 7.60 (1H, d, J = 7.9 Hz), 7.32–7.25 (3H, m), 7.23 (2H, d, J = 8.2 Hz), 7.18–7.13 (3H, m), 7.02 (1H, t, J = 7.3 Hz), 5.06 (1H, d, J = 8.0 Hz), 4.75 (1H, app. t, J = 5.9 Hz), 4.72 (1H, s), 3.64 (1H, app q, J = 7.2 Hz), 2.95 (3H, s), 2.43 (1H, app dt, J = 13.6, 6.4 Hz), 2.35 (3H, s), 2.06 (1H, ddd, J = 13.6, 7.2, 4.9); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 178.1, 173.6, 150.7, 145.3, 137.5, 134.9, 131.4, 129.7, 128.9, 128.9, 126.8, 125.2, 124.2, 122.6, 121.7, 120.2, 117.2, 115.4, 58.0, 40.5, 39.5, 25.0, 23.3, 21.4; IR (neat): ν_{max}/cm^{-1} 3661, 2990, 2886, 1690; MS (pNSI): 407.1 (66%, $(M - (C_6H_5NOH))^+$), 516.2 (49%, $(M + H)^+$), 533.2 (100%, $(M + NH_4)^+$), 1031.3 (57%, $(2M + H)^+$), 1053.3 (13%, $(2M + Na)^+$); HRMS (pNSI): calcd for $C_{28}H_{26}N_3O_5S$ $[M + H]^+$: 516.1588; observed: 516.1584.

Note: ^{1}H NMR run at 35 °C, broad signals observed at room temperature.

3b – (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol), DCM (5 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (38 mg, 0.34 mmol). The resulting solution was heated at reflux for 48 hours. The reaction was allowed to cool to room temperature, 1-methyl-2-nitrosobenzene (42 mg, 0.17 mmol) was added and the solution was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 4 : 1, column diameter = 1 cm, silica = 14 cm) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]-carbazole-1,3(2*H*,3a*H*)-dione (71%, 128 mg, 0.24 mmol) as a yellow powder.

Mp: 193.0–196.7 °C; R_f: 0.59 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 7.89 (1H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.4 Hz), 7.40 (1H, d, J = 7.9 Hz), 7.28 (1H, d, J = 7.7 Hz), 7.21–7.18 (3H, m), 7.13–6.99 (4H, m), 5.04 (1H, d, J = 8.1 Hz), 4.87 (1H, s), 4.27 (1H, app t, J = 5.4 Hz), 3.73 (1H, app td, J = 8.0, 6.1 Hz), 2.91 (3H, s), 2.58 (1H, app dt, J = 12.9, 6.2 Hz), 2.32 (3H, s), 2.25 (3H, s), 1.95 (1H, ddd, J = 12.9, 7.8, 4.5 Hz); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 178.2, 173.6, 149.3, 145.3, 137.3, 134.9, 131.6, 130.9, 129.7, 129.7, 129.2, 126.8, 126.2, 125.0, 124.9, 124.1, 121.4, 120.5, 115.3, 57.3, 40.6, 39.4, 25.0, 24.6, 21.4, 18.3; IR (neat): ν_{max}/cm^{-1} 3662, 2990, 2886, 1701; MS (pNSI): 407.1 (98%, $(M - ((o\text{-}CH_3) - C_6H_4NOH))^+$), 530.2 (52%, $(M + H)^+$), 547.2 (65%, $(M + NH_4)^+$), 1059.3 (100%, $(2M + H)^+$); HRMS (pNSI): calcd for $C_{29}H_{28}N_3O_5S$ $[M + H]^+$: 530.1744; observed: 530.1743.

3c – (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol), DCM (5 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (38 mg, 0.34 mmol) and the resulting solution was heated at reflux for 48 hours. The reaction was cooled to 0 °C before PTAD (60 mg, 0.34 mmol) was added. The reaction was stirred at 0 °C for 4 hours. The solvent was removed under reduced pressure to leave the crude product as a pale red powder. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 4 : 1, column diameter = 1 cm, silica = 14 cm) to give (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (76%, 150 mg, 0.26 mmol) as a white powder.

Mp: 183.4–187.7 °C; R_f: 0.05 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (2H, d, J = 8.4 Hz), 7.67 (1H, d, J = 8.2 Hz), 7.52 (1H, d, J = 7.6 Hz), 7.46–7.31 (5H, m), 7.29–7.19 (2H, m), 7.17 (2H, d, J = 8.3 Hz), 5.55 (1H, app t, J = 4.7 Hz), 5.08 (1H, d, J = 7.7 Hz), 3.66 (1H, ddd, J = 10.5, 7.7, 5.8 Hz), 2.96 (3H, s), 2.49 (1H, app dt, J = 14.8, 5.3 Hz), 2.28 (3H, s), 2.14 (1H, ddd, J = 14.8, 10.5, 5.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.4, 173.4, 153.6, 152.8, 145.5, 137.0, 135.3, 132.3, 130.8, 130.0, 129.3, 128.5, 127.5, 126.9, 125.7, 125.6, 124.3, 119.4, 115.4, 114.9, 47.8, 40.3, 39.0, 28.4, 25.4, 21.7; IR (neat): ν_{max}/cm^{-1} 3665, 2984, 2884, 1699; MS (pNSI): 601.2 (100%, $(M + NH_4)^+$), 1184.3 (13%, $(2M + NH_4)^+$); HRMS (pNSI): calcd for $C_{30}H_{29}N_6O_6S$ $[M + NH_4]^+$: 601.1864; observed: 601.1861.

3d – (3a*S**,5*S**,10b*S**)-5-((*S**)-hydroxy(perfluorophenyl)methyl)-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol) DCM (5 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (38 mg, 0.34 mmol) and the resulting solution was heated at reflux for 48 hours. The reaction was cooled to −78 °C and 2,3,4,5,6-pentafluorobenzaldehyde (0.04 mL, 0.34 mmol) was added followed by DMAC (1 M in hexane, 0.34 mL, 0.34 mmol). The reaction was stirred at −78 °C for 15 minutes before being allowed to warm to room temperature. The reaction was stirred at room temperature for 18 hours. The reaction was poured into saturated sodium bicarbonate solution (10 mL) and extracted with DCM (2 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the crude product as a pale brown solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 3 : 1, column diameter = 2 cm, silica = 15 cm) to give a separable 5 : 1 mixture of (3a*S**,5*S**,10b*S**)-5-((*S**)-hydroxy(perfluorophenyl)methyl)-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]-carbazole-1,3(2*H*,3a*H*)-dione and (3a*S**,5*S**,10b*S**)-5-((*R**)-hydroxy(perfluorophenyl)methyl)-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (72%, 149 mg, 0.25 mmol).

Major diastereomer: Mp: 120.4–121.7 °C; R_f: 0.24 (Pet(40/60)–EA 3 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H δ 7.85 (3H, app d, J = 8.4 Hz), 7.31–7.22 (4H, m), 7.22–7.14 (1H, m), 5.13 (1H, d, J = 8.1 Hz), 4.99 (1H, d, J = 7.5 Hz), 3.71–3.52 (2H, m), 3.01 (3H, s), 2.38 (3H, s), 2.20–2.10 (1H, m), 1.67 (1H, app td, J = 13.8, 5.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.7, 173.3, 145.3, 137.4, 135.4, 129.8,

129.7, 129.6, 127.2, 125.3, 123.9, 120.1, 119.9, 115.2, 70.2, 41.5, 39.1, 36.9, 28.7, 25.2, 21.7; IR (neat): ν_{max}/cm^{-1} 3371, 2981, 2889, 1690; MS (pNSI): 605.1 (40%, $(M + H)^+$), 622.1 (88%, $(M + NH_4)^+$), 627.1 (100%, $(M + Na)^+$), 643.1 (17%), 709.1 (15%); HRMS (pNSI): calcd for $C_{29}H_{21}F_5N_2NaO_5S$ $[M + Na]^+$: 627.0984; observed: 627.0968. *Note: ^{13}C NMR missing peaks due to C–F coupling.*

3e – 6-(hydroxy(phenyl)amino)-2-phenyl-11-tosyl-5,6-dihydro-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*,11*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol) and DCM (5 mL) and the solution was cooled to −78 °C. To this solution PTAD (70 mg, 0.34 mmol) was added and the reaction was stirred at −78 °C for 3.5 hours. The reaction was warmed to room temperature, nitrosobenzene (44 mg, 0.34 mmol) was added and the reaction was stirred for 18 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow oil. The product was purified by column chromatography (column diameter = 1 cm, silica = 16 cm, eluent = petrol (40/60)–ether–DCM 2 : 1 : 1) to give 6-(hydroxy(phenyl)amino)-2-phenyl-11-tosyl-5,6-dihydro-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*,11*H*)-dione (72%, 54 mg, 0.09 mmol) as a white powder.

Mp: 176.1–180.0 °C; R_f: 0.48 (Pet(40/60)–Et_2O 2 : 1); ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.03 (1H, d, J = 8.3 Hz), 7.62 (2H, d, J = 8.1 Hz), 7.56 (2H, d, J = 7.6 Hz), 7.46 (2H, app t, J = 7.7 Hz), 7.42–7.36 (1H, m), 7.23–7.07 (7H, m), 7.05–6.99 (2H, m), 6.59 (1H, d, J = 7.4 Hz), 5.81 (1H, br s), 5.18 (1H, d, J = 13.5 Hz), 4.59 (1H, s), 3.23 (1H, d, J = 13.5 Hz), 2.30 (3H, s); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 152.7, 152.2, 150.5, 146.0, 134.9, 132.9, 132.5, 131.8, 130.4, 129.8, 129.3, 129.2, 128.5, 127.3, 127.3, 125.5, 125.4, 122.5, 119.8, 117.6, 116.6, 108.6, 55.9, 44.6, 21.6; IR (neat): ν_{max}/cm^{-1} 2981, 2884, 1714; MS (pAPCI): 138.1 (100%), 157.0 (95%), 213.1 (50%), 248.1 (86%), 279.1 (62%), 317.1 (33%), 333.1 (29%), 471.1 (31%), 564.2 (11%), 580.2 (10%, $(M + H)^+$); HRMS (pAPCI): calcd for $C_{31}H_{26}N_5O_5S$ $[M + H]^+$: 580.1649; observed: 580.1640.

3f – 6-(hydroxy(*o*-tolyl)amino)-2-phenyl-11-tosyl-5,6-dihydro-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*,11*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol) and DCM (5 mL) and the solution cooled to −78 °C. To this solution PTAD (70 mg, 0.34 mmol) was added and the reaction was stirred at −78 °C for 3.5 hours. The reaction was warmed to room temperature and 1-methyl-2-nitrosobenzene (42 mg, 0.34 mmol) was added and the reaction was stirred for 18 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow oil. The product was purified by column chromatography (column diameter = 1 cm, silica = 14 cm, eluent = petrol (40/60)–ether–DCM 2 : 1 : 1) to give 6-(hydroxy(*o*-tolyl)amino)-2-phenyl-11-tosyl-5,6-dihydro-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*,11*H*)-dione as a white powder (78%, 60 mg, 0.10 mmol).

Mp: 149.7–153.1 °C; R_f: 0.32 (Pet(40/60)–Et_2O–DCM 2 : 1 : 1); ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.99 (1H, d, J = 8.3 Hz), 7.61–7.58 (5H, m), 7.43–7.40 (1H, m), 7.47 (2H, app t, J = 7.7 Hz), 7.40–7.37 (1H, m), 7.18 (2H, app t, J = 7.8 Hz), 7.11 (2H, d, J = 8.2 Hz), 6.97 (2H, app q, J = 7.2 Hz), 6.85 (1H, d, J = 7.5 Hz), 6.50 (1H, d, J = 7.8 Hz), 5.93 (1H, s), 5.24 (1H, d, J = 13.5 Hz), 4.44 (1H, s), 3.11 (1H, d, J = 13.5 Hz), 2.29 (3H, s), 1.91 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 153.3, 150.3, 148.7, 145.4, 135.1, 133.7, 132.0, 131.7, 131.3, 130.6, 129.6, 129.3, 128.7, 127.9, 127.2, 127.0, 126.8, 125.9, 124.9, 124.8, 122.6, 118.0, 116.8, 107.0, 59.1, 44.5, 21.7, 17.8; IR (neat): ν_{max}/cm^{-1} 3068, 2981, 1713; MS (pAPCI): 138.1 (100%), 157.0 (82%), 262.1 (55%), 279.1 (76%), 317.1 (50%), 391.3 (37%), 471.1 (21%), 594.2 (10%, $(M + H)^+$); HRMS (pAPCI): calcd for $C_{32}H_{28}N_5O_5S$ $[M + H]^+$: 594.1806; observed: 594.1801.

3g – ethyl 3-((3a*S**,4*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate

A solution of 2-nitrosotoluene (0.035 g, 0.29 mmol) and ethyl 3-((3a*S**,4*R**,10b*S**)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (0.150 g, 0.29 mmol) in dry DCM (10 mL) was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure to give the crude green solid product which was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1) to give ethyl 3-((3a*S**,4*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (0.109 g, 0.17 mmol, 59%) as a bright yellow solid.

Mp: 190–192 °C; R_f: 0.26 (Pet(40/60)–EA 2 : 1); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.95 (1H, d, J = 7.2 Hz), 7.61 (2H, d, J = 7.2 Hz), 7.18 (2H, d, J = 7.2 Hz), 7.10 (1H, d, J = 7.2 Hz), 7.05 (1H, t, J = 7.2 Hz), 6.81 (1H, t, J = 7.2 Hz), 6.65 (1H, t, J = 7.5 Hz), 6.19 (1H, t, J = 7.5 Hz), 5.88 (1H, d, J = 7.2 Hz), 5.46 (1H, d, J = 7.2 Hz), 4.99 (1H, br s), 4.95 (1H, d, J = 7.2 Hz), 4.30 (1H, d, J = 4.6 Hz), 4.11 (2H, q, J = 7.0 Hz), 3.80–3.75 (1H, m), 3.01 (3H, s), 2.70–2.54 (4H, m), 2.41 (3H, s), 2.33 (3H, s), 1.92–1.85 (1H, m), 1.24 (3H, t, J = 7.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 178.2, 173.3, 149.9, 144.6, 139.9, 137.1, 134.1, 131.9, 130.6, 130.3, 129.4, 128.7, 127.0, 125.7, 124.8, 124.4, 123.6, 122.1, 118.9, 118.0, 115.7, 60.6, 57.8, 45.1, 42.4, 40.0, 32.5, 25.2, 23.3, 21.6, 18.5, 14.3; IR (neat): ν_{max}/cm^{-1}: 3655, 2980, 1702; MS (pNSI): 507.15 (100%, [M − (Tol-N-OH)]), 652.20 (55%, $[M + Na]^+$); HRMS (pNSI): calcd $C_{34}H_{35}N_3O_7S$ $[M + Na]^+$: 652.2088; observed: 652.2082.

3h – ethyl 3-((3a*S**,4*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-1,3-dioxo-2-phenyl-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate

A solution of 2-nitrosotoluene (0.016 g, 0.13 mmol) and ethyl 3-((3a*S**,4*R**,10b*S**)-1,3-dioxo-2-phenyl-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (0.08 g, 0.13 mmol) in dry DCM (10 mL) was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure to give the crude yellow product which was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1) to give ethyl 3-((3a*S**,4*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-1,3-dioxo-2-

phenyl-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]-carbazol-4-yl)propanoate in (0.415 g, 0.059 mmol, 58%) as a bright yellow solid.

Mp: 182–184 °C; R_f: 0.34 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.94 (1H, d, J = 6.7 Hz), 7.64 (2H, d, J = 6.7 Hz), 7.45–7.37 (5H, m), 7.20–7.00 (4H, m), 6.84 (1H, t, J = 6.9 Hz), 6.66 (1H, t, J = 6.9 Hz), 6.24 (1H, t, J = 6.2 Hz), 5.95 (1H, d, J = 6.9 Hz), 5.66 (1H, d, J = 6.4 Hz), 5.20 (1H, d, J = 7.4 Hz), 4.99 (1H, br s), 4.39 (1H, d, J = 4.0 Hz), 4.08 (2H, q, J = 7.2 Hz), 4.03–3.98 (1H, m), 2.72–2.61 (4H, m), 2.42 (3H, s), 2.33 (3H, s), 2.14–2.08 (1H, m). 1.20 (3H, t, J = 7.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.0, 173.3, 172.2, 150.1, 144.6, 137.1, 134.2, 131.0, 131.8, 130.5, 130.3, 129.4, 129.0, 128.6, 128.5, 127.0, 126.5, 125.8, 124.8, 124.5123.5, 122.2, 119.1, 118.1, 115.6, 60.0, 57.7, 45.3, 42.6, 40.0, 32.4, 23.1, 21.6, 18.5, 14.5; IR (neat): ν_{max}/cm^{-1}: 3858, 3826, 1709, 1595; MS (pNSI): 569.17 (100%, [M − N(OH)(*o*-Tol)]), 692.24 (30%, $[M + H]^+$); HRMS (pNSI): calcd $C_{39}H_{36}N_3O_7S$ $[M - H]^+$: 690.2268; observed: 690.2266.

3i – ethyl 3-((3a*S**,4*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl) propanoate

A solution of 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (0.052 g, 0.29 mmol) and ethyl 3-((3a*S**,4*R**,10b*S**)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate (0.150 g, 0.29 mmol) in dry DCM (10 mL) was stirred at 0 °C for 6 hours. The solvent was removed under reduced pressure to give the crude product which was purified by column chromatography (petrol (40/60)–ethyl acetate 1 : 1) to give ethyl 3-((3a*S**,4*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate in (56%, 0.110 g, 0.161 mmol) as a white solid.

Mp: 264–265 °C; R_f: 0.30 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.86 (1H, br s), 7.78 (2H, d, J = 7.0 Hz), 7.71 (1H, d, J = 7.9 Hz), 7.47 (1H, d, J = 7.9 Hz), 7.44–7.40 (1H, m), 7.36–7.30 (3H, m), 7.23–7.17 (2H, m), 7.02 (2H, d, J = 7.0 Hz), 5.66 (1H, d, J = 6.2 Hz), 5.04 (1H, d, J = 6.5 Hz), 4.08 (2H, q, J = 6.2 Hz), 3.44 (1H, dd, J = 6.5, 11.9 Hz), 3.02 (3H, s), 2.68–2.51 (3H, m), 2.15 (3H, s), 2.14–2.09 (1H, m), 1.90–1.82 (1H, m), 1.20 (3H, t, J = 6.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 176.6, 173.4, 173.2, 153.6, 152.6, 145.2, 136.8, 135.5, 132.1, 130.7, 129.7, 129.3, 128.6, 127.2, 126.8, 125.6, 124.2, 119.0, 114.8, 114.4, 60.8, 44.3, 42.0, 39.3, 30.9, 25.4, 23.0, 21.5, 14.2; IR (neat): ν_{max}/cm^{-1}: 3659, 1775, 1691; MS (pNSI): 701.23 (100%, $[M + NH_4]^+$), 1384.44 (17%, $[2M + NH_4]^+$); HRMS (pNSI): calcd $C_{35}H_{34}N_5O_8S$ $[M + H]^+$: 684.2123; observed: 684.2115.

3j – ethyl 3-((3a*S**,4*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate

A solution of 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (0.037 g, 0.21 mmol) and ethyl 3-((3a*S**,4*R**,10b*S**)-1,3-dioxo-10-tosyl-1,2,3,3a,4,10,10a,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)-propanoate (0.105 g, 0.21 mmol) in dry DCM (10 mL) was stirred at 0 °C for 6 h. The solvent was removed to give the crude white solid product which was purified by trituration from DCM to yield ethyl 3-((3a*S**,4*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-1,3-dioxo-10-tosyl-1,2,3,3a,4,5,10,10b-octahydropyrrolo[3,4-*a*]carbazol-4-yl)propanoate in (57%, 0.08 g, 0.119 mmol) as a white solid.

Mp: 269–271 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ_H 11.44 (1H, br s), 10.68 (1H, br s), 7.87–7.76 (3H, m), 7.51–7.39 (4H, m), 7.29–7.25 (6H, m), 5.69 (1H, d, J = 6.1 Hz), 5.28 (1H, d, J = 6.8 Hz), 4.05 (2H, q, J = 6.8 Hz), 3.45 (1H, dd, J = 6.8, 11.3 Hz), 3.58–3.52 (1H, m), 2.67–2.65 (1H, m), 2.25 (3H, s), 2.49–2.44 (2H, m), 1.80–1.70 (1H, m), 1.18 (3H, t, J = 6.8 Hz); ^{13}C NMR (101 MHz, d_6-DMSO): 178.6, 175.0, 172.99, 154.4, 153.1, 145.5, 136.6, 134.9, 133.1, 131.7, 130.4, 129.4, 128.6, 127.6, 127.1, 126.3, 125.6, 124.5, 119.3, 115.9, 114.9, 60.3, 45.2, 43.0, 38.0, 30.7, 23.6, 21.4, 14.5; IR (neat): ν_{max}/cm^{-1}: 3659, 1775, 1692; MS (pNSI): 687.22 (100%, $[M + NH_4]^+$), 1356.41 (27%, $[2M + NH_4]^+$), 692.17 (12%, $[M + Na]^+$); HRMS (pNSI): calcd $C_{34}H_{35}N_6O_8S$ $[M + H]^+$: 687.2232; observed: 687.2229.

3k – (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol), DCM (5 mL) and 1*H*-pyrrole-2,5-dione (33 mg, 0.34 mmol) and the resulting solution was heated at reflux for 48 hours. The reaction was cooled to room temperature and nitrosobenzene (36 mg, 0.34 mmol) was added. The reaction was stirred at room temperature for 4 hours before the solvent was removed under reduced pressure to leave the crude product as a white solid. The product was purified by trituration from DCM to give (3a*S**,5*S**,10b*S**)-5-(hydroxy-(phenyl)amino)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]-carbazole-1,3(2*H*,3a*H*)-dione (89%, 151 mg, 0.30 mmol) as a white powder.

Mp: 203.7–206.9 °C; R_f: 0.15 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.26 (1H, s), 8.45 (1H, s), 7.88 (1H, d, J = 8.3 Hz). 7.76 (2H, d, J = 8.2 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.33 (2H, d, J = 8.2 Hz), 7.29–7.04 (5H, m), 6.89 (1H, t, J = 7.2 Hz), 5.17 (1H, d, J = 7.8 Hz), 4.88 (1H, app t, J = 4.4 Hz), 3.65 (1H, app td, J = 8.8, 5.9 Hz), 2.32 (3H, s), 2.36–2.27 (1H, m), 1.81 (1H, ddd, J = 14.0, 9.4, 5.0 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 179.4, 174.7, 152.0, 144.7, 136.4, 135.0, 131.5, 129.8, 128.9, 128.4, 126.6, 124.4, 123.4, 121.2, 120.7, 120.6, 117.0, 114.4, 56.8, 41.5, 40.6, 25.2, 20.9; IR (neat): ν_{max}/cm^{-1} 3452, 2981, 1715; MS (pNSI): 393.1, (100%, $(M - (C_6H_5NOH)^+)$), 502.1 (14%, $(M + H)^+$), 519.2 (96%, $(M + NH_4)^+$), 524.1 (17%, $(M + Na)^+$), 1003.3 (40%, $(2M + H)^+$), 1025.3 (15%, $(2M + Na)^+$); HRMS (pNSI): calcd for $C_{27}H_{24}N_3O_5S$ $[M + H]^+$: 502.1431; observed: 502.1428.

3l – (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol), DCM (5 mL) and 1*H*-pyrrole-2,5-dione (33 mg, 0.34 mmol) was added and the resulting

solution was heated at reflux for 48 hours. The reaction was cooled to room temperature and 1-methyl-2-nitrosobenzene (41 mg, 0.34 mmol) was added. The reaction was stirred at room temperature for 4 hours before the solvent was removed under reduced pressure to leave the crude product as a pale yellow solid. The product was purified by column chromatography (petrol (40/60)–ether–DCM 2 : 1 : 1, column diameter = 2 cm, silica = 14 cm) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl) amino)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (82%, 143 mg, 0.28 mmol) as a yellow powder.

Mp: 171.1–174.0 °C; R_f: 0.13 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (1H, d, J = 8.4 Hz), 7.73 (2H, d, J = 8.2 Hz), 7.77 (1H, s), 7.35 (2H, dd, J = 15.7, 7.9 Hz), 7.20 (3H, app d, J = 8.2 Hz), 7.09 (2H, d, J = 7.5 Hz), 7.07–7.00 (2H, m), 5.17 (1H, d, J = 8.1 Hz), 4.75 (1H, s), 4.39 (1H, app t, J = 5.1 Hz), 3.80 (1H, app q, J = 8.3, 5.7 Hz), 2.64 (1H, app dt, J = 13.1, 5.5 Hz), 2.34 (3H, s), 2.26 (3H, s), 1.96 (1H, ddd, J = 15.9, 7.9, 3.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 178.3, 173.4, 149.3, 144.7, 137.4, 135.8, 131.3, 130.9, 129.8, 129.6, 129.5, 129.0, 127.0, 126.3, 125.1, 124.7, 123.7, 121.5, 120.1, 115.3, 57.3, 42.0, 40.8, 26.0, 21.4, 18.3; IR (neat): ν_{max}/cm^{-1} 3294, 2981, 1713; MS (pAPCI): 293.1 (16%), 332.1 (13%), 342.1 (16%), 393.1 (100%, (M − (*o*-Tol) N(OH))$^+$), 489.1 (54%, (M − H_2O)$^+$), 516.2 (26%, (M + H)$^+$); HRMS (pAPCI): calcd for $C_{28}H_{26}N_3O_5S$ [M + H]$^+$: 516.1588; observed: 516.1576.

3m – (3a*S**,5*S**,10b*S**)-5-((*S**)-hydroxy(perfluorophenyl) methyl)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol), DCM (5 mL) and 1*H*-pyrrole-2,5-dione (33 mg, 0.34 mmol). The resulting solution was heated at reflux for 48 hours. The reaction was cooled to 0 °C and pentafluorobenzaldehyde (67 mg, 0.34 mmol) and DMAC (1 M in hexane, 0.34 mL, 0.34 mmol) were added. The solution was stirred at 0 °C for 1 hour and then warmed to room temperature for 18 hours. The reaction was poured into sodium bicarbonate (15 mL) and extracted with DCM. The combined organic layers were dried with MgSO4, filtered and the solvent was removed under reduced pressure to give the crude product as an off white solid. The product was purified by column chromatography (diameter = 1.5 cm, silica = 15 cm, eluent = petrol (40/60)–EA 2 : 1) to give (3a*S**,5*S**,10b*S**)-5-((*S**)-hydroxy(perfluorophenyl) methyl)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (71%, 0.1427 g, 0.24 mmol) as an off white solid.

Mp: 181.3–185.1 °C; R_f: 0.22 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.03 (1H, br s), 7.81 (3H, app d, J = 7.9 Hz), 7.28 (1H, d, J = 8.0 Hz), 7.25–7.22 (3H, m), 7.16 (1H, app t, J = 7.6 Hz), 5.08 (1H, d, J = 8.3 Hz), 5.05 (1H, d, J = 7.4 Hz), 3.61–3.66 (1H, m), 3.49–3.57 (1H, m), 2.34 (3H, s), 2.09 (1H, dd, J = 14.0, 4.5 Hz), 1.74 (1H, app td, J = 13.9, 5.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.4, 173.0, 145.3, 137.4, 135.5, 129.8, 129.7, 129.1, 127.1, 125.5, 123.9, 120.2, 120.0, 115.3, 70.2, 42.5, 40.3, 36.8, 28.5, 21.7; IR (neat): ν_{max}/cm^{-1} 3240, 2981, 1717; MS (pAPCI): 157.0 (79%), 221.1 (61%), 393.1 (15%, (M − (C_6F_5COH)$^+$)), 443.1 (51%), 573.1 (8%, (M − H_2O)$^+$), 591.1 (100%, (M + H)$^+$); HRMS (pAPCI): calcd for $C_{28}H_{20}F_5N_2O_5S$ [M + H]$^+$: 591.1008; observed: 591.1001. *Note*: *^{13}C NMR missing peaks due to C–F coupling.*

3n – (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol), DCM (5 mL) and 1*H*-pyrrole-2,5-dione (33 mg, 0.34 mmol). The resulting solution was heated at reflux for 48 hours. The reaction was cooled to 0 °C and PTAD was added. The solution was stirred at 0 °C for 4 hours and the solvent was removed under reduced pressure to give the crude product as pale red. The product was purified by column chromatography (diameter = 1.5 cm, silica = 17 cm, eluent = petrol (40/60)–EA 1 : 1) to give (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-10-tosyl-4,5,10,10b-tetrahydropyrrolo-[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (23%, 0.044 g, 0.08 mmol) as an off white solid.

Mp: 206.4–209.7 °C; R_f: 0.10 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, DMSO-d_6): δ_C 11.37 (1H, s), 10.77 (1H, s), 7.82 (2H, d, J = 8.3 Hz), 7.72 (1H, d, J = 7.9 Hz), 7.48–7.43 (2H, m), 7.42–7.35 (4H, m), 7.28 (2H, d, J = 8.5 Hz), 7.25–7.18 (2H, m), 5.46 (1H, app t, J = 4.9 Hz), 5.19 (1H, d, J = 7.7 Hz), 3.77–3.65 (1H, m), 2.41 (1H, app dt, J = 9.8, 5.1 Hz), 2.26 (3H, s), 2.24–2.16 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ_H 178.8, 173.6, 153.6, 152.4, 145.4, 136.9, 135.3, 132.2, 130.9, 129.9, 129.2, 128.4, 127.5, 126.9, 125.7, 125.6, 124.2, 119.3, 115.1, 114.8, 47.3, 41.5, 40.2, 28.8, 21.7; IR (neat): ν_{max}/cm^{-1} 3194, 2981, 2980, 1699; MS (pNSI): 587.2 (100% (M + NH_4)$^+$), 592.1 (30% (M + Na)$^+$); HRMS (pNSI): calcd for $C_{29}H_{27}N_6O_6S$ [M + NH_4]$^+$: 587.1707; observed: 587.1706.

3o – (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-7-methoxy-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 6-methoxy-1-tosyl-3-vinyl-1H-indole (111 mg, 0.34 mmol), DCM (5 mL) and 1*H*-pyrrole-2,5-dione (33 mg, 0.34 mmol). The resulting solution was heated at reflux for 48 hours. The reaction was cooled to room temperature and 1-methyl-2-nitrosobenzene (41 mg, 0.34 mmol) was added. The reaction was stirred at room temperature for 24 hours before the solvent was removed under reduced pressure to leave the crude product as a pale yellow solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-7-methoxy-10-tosyl-4,5,10,10b-tetrahydro pyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (76%, 141 mg, 0.26 mmol) as a light brown solid.

Mp: 185 °C decomposed; R_f: 0.26 (Pet(40/60)–EA 4 : 3); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.19 (1H, s), 8.34 (1H, s), 7.69 (1H, d, J = 9.1 Hz), 7.61 (2H, d, J = 8.2 Hz), 7.27 (2H, d, J = 8.2 Hz), 7.08–6.97 (2H, m), 6.95–6.85 (2H, m), 6.72 (1H, dd, J = 9.1, 2.4 Hz), 6.40 (1H, s), 5.07 (1H, d, J = 7.9 Hz), 4.20 (1H, app t, J = 4.4 Hz), 3.76 (1H, app q, J = 8.4 Hz), 3.47 (3H, s), 2.53–2.47 (1H,

m), 2.28 (s, 3H), 2.08 (s, 3H), 1.75 (1H, ddd, $J = 13.6, 9.8, 4.4$ Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 180.5, 175.4, 156.3, 151.7, 145.3, 134.7, 133.1, 131.1, 131.0, 130.8, 130.3, 129.7, 127.1, 126.4, 124.6, 122.1, 121.2, 115.9, 113.8, 103.3, 57.1, 55.3, 42.2, 26.9, 21.5, 21.3, 18.5; IR (neat): $\nu_{(max)}$/cm^{-1} 3388, 3071, 2552, 1727; MS (pNSI): 355.1 (50%), 371.1 (100%), 423.1 (57%), 445.1 (30%), 546.2 (5%, $(M + H)^+$), 568.2 (16%, $(M + Na)^+$), 584.1 (21%); HRMS (pNSI): calcd for $C_{29}H_{28}N_3O_6S_1$ $[M + H]^+$: 546.1693; observed: 546.1690.

3p – (3a*S**,5*S**,10b*S**)-5-((*S**)-hydroxy(perfluorophenyl) methyl)-7-methoxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 5-methoxy-1-tosyl-3-vinyl-1*H*-indole (112 mg, 0.34 mmol), DCM (5 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (38 mg, 0.34 mmol). The reaction was heated at reflux for 48 hours. The reaction was cooled to −78 °C and pentafluorobenzaldehyde (0.04 mL, 0.34 mmol) and DMAC (1 M in hexane, 0.34 mL, 0.34 mmol) were added. The solution was stirred at −78 °C for 15 minutes and then at room temperature for 18 hours. The solvent was removed under reduced pressure to give the crude product as an off white solid. The product was purified by column chromatography (column diameter = 2 cm, silica = 15 cm, eluent = petrol (40/60)–EA 3 : 1) to give a 8 : 1 mixture of (3a*S**,5*S**,10b*S**)-5-((*S**)-hydroxy-(perfluorophenyl)methyl)-7-methoxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione and (3a*S**,5*S**,10b*S**)-5-((*R**)-hydroxy(perfluorophenyl)methyl)-7-methoxy-2-methyl-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]-carbazole-1,3(2*H*,3a*H*)-dione (70%, 0.151 mg, 0.24 mmol) as a white powder.

Major diastereomer: Mp: 136.7–139.0 °C; R_f: 0.40 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76 (2H, d, $J = 8.3$ Hz), 7.69 (1H, d, $J = 9.1$ Hz), 7.22 (2H, d, $J = 8.3$ Hz), 6.83 (1H, dd, $J = 9.1, 2.5$ Hz), 6.72 (1H, d, $J = 2.5$ Hz), 5.08 (1H, d, $J = 8.3$ Hz), 4.87 (1H, d, $J = 7.4$ Hz), 3.71 (3H, s), 3.58–3.47 (2H, m), 2.94 (3H, s), 2.34 (3H, s), 2.11–2.04 (1H, m), 1.60 (1H, td, $J = 13.9, 5.3$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.7, 173.2, 156.8, 145.2, 135.2, 132.0, 130.9, 130.3, 129.8, 127.0, 120.6, 116.2, 114.0, 102.6, 70.2, 55.6, 41.5, 39.0, 36.9, 28.6, 25.3, 21.7; IR (neat): ν_{max}/cm^{-1} 2981, 2884, 1709; MS (pAPCI): 157.0 (80%), 221.1 (92%), 281.1 (49%) 475.1 (94%), 635.1 (100%, $(M + H)^+$); HRMS (pAPCI): calcd for $C_{30}H_{24}F_5N_2O_6S$ $[M + H]^+$: 635.1270; observed: 635.1266. *Note*: *^{13}C NMR missing peaks due to C–F coupling.*

3q – (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-7-methoxy-10-tosyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*] carbazole-1,3(2*H*,3a*H*)-dione

To a stirred round bottomed flask was added 5-methoxy-1-tosyl-3-vinyl-1*H*-indole (112 mg, 0.34 mmol), DCM (5 mL) and 1*H*-pyrrole-2,5-dione (33 mg, 0.34 mmol). The reaction was heated at reflux for 48 hours. The reaction was cooled to 0 °C and PTAD (60 mg, 0.34 mmol) was added. The reaction was stirred at 0 °C for 4 hours before the solvent was removed under reduced pressure to give the crude product as a pale red solid. The product was purified by column chromatography (column diameter = 2 cm, silica = 16 cm, eluent = petrol (40/60)–EA 1 : 1) to give (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-7-methoxy-10-tosyl-4,5,10,10b-tetrahydropyrrolo-[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (75%, 0.152 mg, 0.25 mmol) as a pale yellow powder.

Mp: 189.9–193.3 °C; R_f: 0.07 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.31 (1H, br), 7.67 (2H, d, $J = 7.5$ Hz), 7.55 (1H, d, $J = 8.8$ Hz), 7.38–7.23 (5H, m), 7.00 (2H, d, $J = 7.8$ Hz), 6.90 (1H, s), 6.80 (1H, d, $J = 8.9$ Hz), 5.53 (1H, br s), 5.18 (1H, d, $J = 6.7$ Hz), 3.74–3.69 (1H, m), 3.64 (3H, s), 2.48–2.55 (1H, m), 2.17 (3H, s), 2.12–2.02 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 179.0, 173.9, 156.9, 153.7, 152.7, 145.2, 135.1, 132.7, 131.5, 131.0, 129.8, 129.2, 128.4, 128.0, 127.2, 125.6, 115.9, 115.5, 114.3, 101.9, 55.7, 47.6, 41.6, 40.1, 28.8, 21.6; IR (neat): ν_{max}/cm^{-1} 2972, 2885, 1781, 1709; MS (pNSI): 617.2 (69%, $(M + NH_4)^+$), 622.1 (100%, $(M + Na)^+$), 644.1 (48%); HRMS (pNSI): calcd for $C_{30}H_{29}N_6O_7S$ $[M + NH_4]^+$: 617.1813; observed: 617.1817.

3r – 6-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-phenyl-11-tosyl-5,6-dihydro-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*] indole-1,3(2*H*,11*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol) and DCM (5 mL). The resulting solution was cooled to −78 °C and then PTAD (70 mg, 0.34 mmol) was added. The reaction was stirred at −78 °C for 3.5 hours. The reaction was warmed to 0 °C and a further equivalent of PTAD (60 mg, 0.34 mmol) was added. The reaction was stirred 0 °C for 4 hours, resulting in the formation of a white precipitate. The reaction mixture was filtered and 6-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-phenyl-11-tosyl-5,6-dihydro-[1,2,4]triazolo[1′,2′:1,2] pyridazino[3,4-*b*]indole-1,3(2*H*,11*H*)-dione (65%, 134 mg, 0.207 mmol) was recovered as a white powder.

Mp: 227.8–230.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.76 (1H, s, NH), 7.91 (1H, d, $J = 7.8$ Hz), 7.61 (2H, d, $J = 8.3$ Hz), 7.48–7.24 (15H, m), 5.52 (1H, s), 4.76 (1H, d, $J = 13.8$ Hz), 3.86 (1H, d, $J = 13.8$ Hz), 2.24 (3H, s); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 154.3, 153.5, 150.6, 149.5, 146.0, 135.1, 133.3, 133.0, 131.7, 131.5, 130.4, 129.6, 129.5, 129.4, 128.8, 128.1, 127.6, 127.5, 126.9, 125.9, 125.4, 119.3, 116.8, 104.1, 48.8, 43.3, 21.6; IR (neat): ν_{max}/cm^{-1} 2971, 2883, 1714; MS (pNSI): 263.0 (36%), 345.0 (51%), 371.1 (42%), 665.2 (89%, $(M + NH_4)^+$), 670.1 (100%, $(M + Na)^+$); HRMS (pNSI): calcd for $C_{33}H_{25}N_7NaO_6S$ $[M + Na]^+$: 670.1479; observed: 670.1475.

3s – 6-(hydroxy(phenyl)amino)-2-phenyl-11-tosyl-5,6-dihydro-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*,11*H*)-dione

To a stirred round bottomed flask was added 1-tosyl-3-vinyl-1*H*-indole (100 mg, 0.34 mmol) and DCM (5 mL) and the solution was cooled to −78 °C. To this solution PTAD (70 mg, 0.34 mmol) was added and the reaction was stirred at −78 °C for 3.5 hours. The reaction was warmed to room temperature nitrosobenzene (44 mg, 0.34 mmol) was added and the reaction was stirred for 18 hours. The solvent was removed under reduced pressure to leave the crude product as a pale

yellow oil. The product was purified by column chromatography (column diameter = 1 cm, silica = 16 cm, eluent = petrol (40/60)–ether–DCM 2 : 1 : 1) to give 6-(hydroxy(phenyl) amino)-2-phenyl-11-tosyl-5,6-dihydro-[1,2,4]triazolo[1′,2′:1,2] pyridazino[3,4-*b*]indole-1,3(2*H*,11*H*)-dione (72%, 141 mg, 0.24 mmol) as a white powder.

Mp: 176.1–180.0 °C; R_f: 0.48 (Pet(40/60)–Et_2O 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.03 (1H, d, J = 8.3 Hz), 7.62 (2H, d, J = 8.1 Hz), 7.56 (2H, d, J = 7.6 Hz), 7.46 (2H, app t, J = 7.7 Hz), 7.42–7.36 (1H, m), 7.23–7.07 (7H, m), 7.05–6.99 (2H, m), 6.59 (1H, d, J = 7.4 Hz), 5.81 (1H, br s), 5.18 (1H, d, J = 13.5 Hz), 4.59 (1H, s), 3.23 (1H, d, J = 13.5 Hz), 2.30 (3H, s); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 152.7, 152.2, 150.5, 146.0, 134.9, 132.9, 132.5, 131.8, 130.4, 129.8, 129.3, 129.2, 128.5, 127.3, 127.3, 125.5, 125.4, 122.5, 119.8, 117.6, 116.6, 108.6, 55.9, 44.6, 21.6; IR (neat): ν_{max}/cm^{-1} 2981, 2884, 1714; MS (pAPCI): 138.1 (100%), 157.0 (95%), 213.1 (50%), 248.1 (86%), 279.1 (62%), 317.1 (33%), 333.1 (29%), 471.1 (31%), 564.2 (11%), 580.2 (10%, $(M + H)^+$); HRMS (pAPCI): calcd for $C_{31}H_{26}N_5O_5S$ $[M + H]^+$: 580.1649; observed: 580.1640.

3t – (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-*N*,*N*,2-trimethyl-1,3-dioxo-1,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(2*H*)-sulfonamide

To a stirred bottomed flask was added *N*,*N*-dimethyl-3-vinyl-1*H*-indole-1-sulfonamide (85 mg, 0.34 mmol), DCM (5 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (38 mg, 0.34 mmol). The solution was heated at reflux for 48 hours. The reaction was cooled to room temperature and 1-methyl-2-nitrosobenzene (41 mg, 0.34 mmol) was added. The reaction was stirred for 3 hours at room temperature before the solvent was removed under reduced pressure to give the crude product. The crude product was purified by column chromatography (column diameter = 2 cm, silica = 16 cm, eluent = petrol (40/60)–ethyl acetate 2 : 1) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-*N*,*N*,2-trimethyl-1,3-dioxo-1,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(2*H*)-sulfonamide (74%, 0.122 g, 0.25 mmol) as an off white solid.

Mp: 169.3–171.9 °C; R_f: 0.32 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (1H, d, J = 8.4 Hz), 7.60 (1H, d, J = 7.9 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.28 (1H, app t, J = 7.8 Hz), 7.21–7.16 (2H, m), 7.13 (1H, d, J = 8.1 Hz), 7.07–7.03 (1H, m), 4.98–4.96 (2H, m), 4.35–4.31 (1H, m), 3.69 (1H, app t, J = 7.7 Hz), 2.93 (9H, s), 2.60 (1H, app dt, J = 13.1, 6.2 Hz), 2.33 (3H, s), 1.97 (1H, ddd, J = 13.1, 7.7, 4.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 178.4, 173.8, 149.2, 137.4, 131.9, 131.1, 129.6, 128.4, 126.6, 125.3, 124.7, 123.7, 121.5, 120.4, 118.8, 115.0, 57.5, 40.5, 39.4, 38.4, 25.2, 24.7, 18.7; IR (neat): ν_{max}/cm^{-1} 3426, 2981, 1712; MS (pAPCI): 221.1 (9%), 251.1 (13%), 360.1 (100%, $(M - (o\text{-Tol})N(OH))^+$), 465.2 (15%, $(M - H_2O)^+$), 483.2 (15%, $(M + H)^+$); HRMS (pAPCI): calcd for $C_{24}H_{27}N_4O_5S_1$ $[M + H]^+$: 483.1697; observed: 483.1685.

3u – (3a*S**,5*S**,10b*S**)-5-((2,6-dibromophenyl) (hydroxy) amino)-*N*,*N*-dimethyl-1,3-dioxo-2-phenyl-1,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(2*H*)-sulfonamide

To a stirred round bottomed flask was added *N*,*N*-dimethyl-3-vinyl-1*H*-indole-1-sulfonamide (85 mg, 0.34 mmol), DCM (5 mL) and 1-phenyl-1*H*-pyrrole-2,5-dione (59 mg, 0.34 mmol) and the resulting solution was heated at reflux for 48 hours. The reaction was cooled to room temperature and 2,6-dibromonitrosobenzene (90 mg, 0.34 mmol) was added. The reaction was stirred at room temperature for 18 hours and the solvent was removed under reduced pressure to give the crude product as a pale yellow solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 3 : 1, column diameter = 2 cm, silica = 17 cm) to give (3a*S**,5*S**,10b*S**)-5-((2,6-dibromophenyl) (hydroxy)amino)-*N*,*N*-dimethyl-1,3-dioxo-2-phenyl-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-sulfonamide (69%, 162 mg, 0.23 mmol) as a pale orange powder.

Mp: 241–242 °C; R_f: 0.43 (Pet(40/60)–Et_2O 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (2H, d, J = 7.8 Hz), 7.46–7.30 (7H, m), 7.15 (1H, app t, J = 7.4 Hz), 7.02 (1H, app t, J = 7.5 Hz), 6.71 (1H, app td, J = 8.0, 2.1 Hz), 6.05 (1H, s), 5.49–5.47 (1H, m), 5.17–5.12 (1H, m), 4.35–4.27 (1H, m), 3.18–3.11 (1H, m), 2.92 (6H, s), 1.80 (1H, app t, J = 13.1 Hz); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 177.9, 172.5, 144.6, 136.1, 134.3, 132.7, 132.1, 132.0, 129.5, 129.1, 128.6, 128.2, 126.6, 124.0, 122.8, 119.2, 115.1, 113.6, 77.6, 54.7, 42.7, 39.0, 38.0, 30.0; IR (neat): ν_{max}/cm^{-1} 3431, 2927, 1780, 1715; MS (pNSI): 422.1 (25%, $(M - N(OH)C_6H_3Br_2)^+$), 689.0 (76% $(M + H)^+$), 711.0 (54%, $(M + Na)^+$), HRMS (pNSI): calcd $C_{28}H_{25}Br_2N_4O_5S$ $[M + H]^+$: 688.9888; observed: 688.9886.

3v – (3a*S**,5*S**,10b*S**)-5-((*S**)-hydroxy(perfluorophenyl) methyl)-*N*,*N*-dimethyl-1,3-dioxo-1,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(2*H*)-sulfonamide

To a stirred round bottomed flask was added *N*,*N*-dimethyl-3-vinyl-1*H*-indole-1-sulfonamide (85 mg, 0.34 mmol), DCM (5 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (38 mg, 0.34 mmol). The reaction was heated at reflux for 48 hours. The reaction was cooled to −78 °C and pentafluorobenzaldehyde (66 mg, 0.34 mmol) and DMAC (1 M in hexane, 0.34 mL, 0.34 mmol) were added and the reaction was stirred for 1 hour. The reaction was poured into a solution of sodium bicarbonate (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure to leave the crude product as a pale pink solid. The product was purified by column chromatography (diameter = 2 cm, silica = 17 cm, eluent = petrol (40/60)–EA 2 : 1) to give (3a*S**,5*S**,10b*S**)-5-((*S**)-hydroxy(perfluorophenyl)methyl)-*N*,*N*-dimethyl-1,3-dioxo-1,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(2*H*)-sulfonamide (77%, 0.145 g, 0.26 mmol) as a pale pink solid.

Mp: 255.8–257.2 °C; R_f: 0.30 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.77 (1H, d, J = 8.3 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.33–7.28 (1H, m), 7.21 (1H, app t, J = 7.8 Hz), 5.14 (1H, d, J = 8.0 Hz), 4.80 (1H, d, J = 7.3 Hz), 3.67–3.62 (1H, m), 3.48 (1H, ddd, J = 12.8, 7.2, 5.0 Hz), 2.98 (6H, s), 2.93 (3H, s), 2.49 (1H, br s), 2.06 (1H, app dd, J = 14.9, 4.1 Hz), 1.59 (1H, app dt, J = 13.8, 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.8, 173.4, 137.2, 130.0, 129.3, 125.0, 123.5, 120.0, 118.2, 114.6, 70.3, 41.5, 39.2, 38.2, 36.7, 28.6, 25.2; IR (neat): ν_{max}/cm^{-1} 3415, 2972, 2884, 1713; MS (pNSI): 371.1 (22%), 558.1 (81% $(M + H)^+$), 580.1 (100%, $(M + Na)^+$), HRMS (pNSI): calcd $C_{24}H_{20}F_5N_3O_5S$ $[M + H]^+$: 558.1117; observed: 558.1118.

Note: ^{13}C NMR missing peaks due to C–F coupling.

3w – 6-(hydroxy(*o*-tolyl)amino)-*N*,*N*-dimethyl-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11(1*H*)-sulfonamide

To a stirred round bottomed flask was added *N*,*N*-dimethyl-3-vinyl-1*H*-indole-1-sulfonamide (85 mg, 0.34 mmol), DCM (5 mL) and cooled to −78 °C. To this solution PTAD (60 mg, 0.34 mmol) was added and the reaction stirred at −78 °C for 1 hour. 1-Methyl-2-nitrosobenzene (41 mg, 0.34 mmol) was added and the reaction was stirred 4 hours before the solvent was removed under reduced pressure to give the crude product. The crude product was purified by column chromatography (column diameter = 2 cm, silica = 16 cm, eluent = petrol (40/60)–ethyl acetate 2 : 1) to give 6-(hydroxy(*o*-tolyl)amino)-*N*,*N*-dimethyl-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11(1*H*)-sulfonamide (76%, 0.141 g) as an off white solid.

Mp: 168.5–172.8 °C; R_f: 0.25 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.87 (1H, d, J = 8.3 Hz), 7.73 (1H, d, J = 8.1 Hz), 7.60 (2H, d, J = 7.4 Hz), 7.51 (2H, t, J = 7.6 Hz), 7.46–7.38 (1H, m), 7.30–7.18 (2H, m), 7.04 (2H, t, J = 7.5 Hz), 6.90 (1H, d, J = 7.6 Hz), 6.71 (1H, d, J = 7.8 Hz), 5.76 (1H, s), 5.37 (1H, d, J = 14.1 Hz), 4.66 (1H, s), 3.46 (1H, d, J = 14.1 Hz), 2.90 (6H, s), 1.94 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 153.5, 150.5, 148.7, 135.1, 132.1, 131.9, 131.2, 130.6, 129.4, 128.7, 127.1, 126.9, 126.8, 125.9, 124.4, 124.2, 122.7, 118.1, 115.9, 104.7, 59.4, 44.7, 38.7, 17.9; IR (neat): ν_{max}/cm^{-1} 3322, 2971, 1707; MS (pNSI): 339.1 (33%), 424.1 (94%, $(M - MeC_6H_4NOH)^+$), 547.2 (72%, $(M + H)^+$), 569.2 (100%, $(M + Na)^+$); HRMS (pNSI): calcd $C_{27}H_{27}N_6O_5S$ $[M + H]^+$: 547.1758; observed: 547.1761.

3x – (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-*N*,*N*-dimethyl-1,3-dioxo-1,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(2*H*)-sulfonamide

To a round bottomed flask was added *N*,*N*-dimethyl-3-vinyl-1*H*-indole-1-sulfonamide (85 mg, 0.34 mmol), DCM (5 mL) and 1*H*-pyrrole-2,5-dione (33 mg, 0.34 mmol). The reaction was heated at reflux for 48 hours and then cooled to room temperature. 1-Methyl-2-nitrosobenzene (41 mg, 0.34 mmol) was added and the reaction is stirred for 4.5 hours. The solvent was removed to give the crude product as pale yellow solid. The crude product was purified by trituration from DCM to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-*N*,*N*-dimethyl-1,3-dioxo-1,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(2*H*)-sulfonamide (77%, 123 mg, 0.26 mmol) as a white solid.

Mp: 199.9–201.0 °C; R_f: 0.64 (Pet(40/60)–EA 3 : 1); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.15 (1H, s), 8.38 (1H, s), 7.88 (1H, d, J = 8.4 Hz), 7.36 (1H, d, J = 7.9 Hz), 7.31–7.20 (2H, m), 7.13 (3H, app dt, J = 14.3, 7.3 Hz), 7.01 (1H, d, J = 7.3 Hz), 4.98 (1H, d, J = 7.8 Hz), 4.38 (1H, app t, J = 4.8 Hz), 3.73 (1H, app q, J = 7.8 Hz), 2.70 (6H, s), 2.45–2.37 (1H, m), 2.36 (3H, s), 1.77–1.65, 1.77 (1H, m); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 180.4, 175.5, 151.6, 137.2, 133.2, 131.1, 129.3, 129.1, 126.6, 124.4, 124.3, 123.4, 121.8, 121.1, 118.6, 115.3, 56.5, 42.2, 41.1, 38.7, 26.6, 18.9; IR (neat): ν_{max}/cm^{-1} 3426, 2981, 1712; MS (pAPCI): 237.1 (60%), 346.1 (100%, $(M - MeC_6H_4NOH)^+$), 451.1 (25%, $(M - H_2O)^+$), 469.2 (22%, $(M + H)^+$); HRMS (pAPCI): calcd $C_{23}H_{25}N_4O_5S$ $[M + H]^+$: 469.1540; observed: 469.1537.

3y – benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate

To a stirred Schlenk flask was added benzyl 3-vinyl-1*H*-indole-1-carboxylate (94 mg, 0.34 mmol), DCM (5 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (33 mg, 0.34 mmol). The resulting solution was heated at reflux for 24 hours. The reaction was allowed to cool to room temperature and to the stirred solution nitrosobenzene (36 mg, 0.34 mmol) was added and the solution was stirred for 18 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 3 : 1, column diameter = 2 cm, silica = 14 cm) to give benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (74%, 124 mg, 0.25 mmol) as a yellow powder.

Mp: 105.7–109.2 °C; R_f: 0.34 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 8.10 (1H, br d, J = 8.1 Hz), 7.70 (1H, br d, J = 7.3 Hz), 7.49 (2H, br d, J = 6.6 Hz), 7.39 (3H, br app q, J = 6.9, 6.4 Hz), 7.35–7.25 (3H, br m), 7.22–7.13 (3H, br m), 7.01 (1H, br app t, J = 6.7 Hz), 5.55 (1H, d, J = 11.8 Hz), 5.41 (1H, d, J = 11.8 Hz), 4.88 (1H, br d, J = 6.8 Hz), 4.87 (1H, br s), 4.80–4.77 (1H, br m), 3.54–3.41 (1H, br m), 2.85 (3H, s), 2.40–2.25 (1H, br m), 2.08–1.93 (1H, br m); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 178.4, 174.6, 151.6, 151.0, 137.0, 135.0, 130.0, 129.0, 128.9, 128.8, 128.8, 127.6, 125.0, 123.3, 122.3, 120.0, 118.3, 117.1, 115.1, 69.5, 57.7, 40.2, 39.2, 24.9, 22.6; IR (neat): ν_{max}/cm^{-1} 3433, 2953, 1699; MS (pNSI): 387.1 (97%, $(M - N(OH)Ph)^+$), 494.2 (100%, $(M - H)^+$), 518.2 (30%, $(M + Na)^+$), 991.4 (15%, $(2M + H)^+$), 1013.3 (10%, $(2M + Na)^+$); HRMS (pNSI): calcd $C_{29}H_{25}N_3O_5Na$ $[M + Na]^+$: 518.1686; observed: 518.1676.

3z – benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate

To a stirred Schlenk flask was added benzyl 3-vinyl-1*H*-indole-1-carboxylate (94 mg, 0.34 mmol), DCM (5 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (33 mg, 0.34 mmol). The resulting solution was heated at reflux for 24 hours. The reaction was allowed to cool to room temperature and to the stirred solution 1-methyl-2-nitrosobenzene (41 mg, 0.34 mmol) was added and the solution was stirred for 18 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 3 : 1, column diameter = 2 cm, silica = 16 cm) to give benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylateas (78%, 135 mg, 0.26 mmol) as a yellow powder.

Mp: 128.4–131.5 °C; R_f: 0.45 (Pet(40/60)–EA 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.11 (1H, d, J = 8.3 Hz), 7.59 (1H, d, J = 7.8 Hz), 7.55 (1H, d, J = 8.1 Hz), 7.50–7.48 (2H, m), 7.45–7.38

(3H, m), 7.29–7.23 (1H, m), 7.20 (1H, app t, $J = 7.6$ Hz), 7.14 (1H, d, $J = 7.6$ Hz), 7.10 (1H, d, $J = 7.8$ Hz), 7.05 (1H, d, $J = 7.3$ Hz), 5.56 (1H, d, $J = 11.8$ Hz), 5.46 (1H, d, $J = 11.8$ Hz), 5.02 (1H, s), 4.93 (1H, d, $J = 7.6$ Hz), 4.38 (1H, t, $J = 5.2$ Hz), 3.63 (1H, app q, $J = 6.9$ Hz), 2.91 (3H, s), 2.59 (1H, app dt, $J = 12.3$, 6.0 Hz), 2.29 (3H, s), 1.92 (1H, ddd, $J = 12.5$, 7.5, 4.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 178.5, 174.6, 151.7, 149.2, 136.8, 134.8, 131.1, 129.9, 129.0, 129.0, 128.9, 128.9, 127.7, 126.6, 125.3, 125.0, 123.3, 121.5, 120.1, 118.1, 115.3, 69.6, 57.4, 40.4, 39.1, 25.2, 24.1, 18.6; IR (neat): ν_{max}/cm^{-1} 3450, 2954, 1699; MS (pNSI): 343.1 (40%), 387.1 (82%, (M − (N(OH)(*o*-Tol)))$^+$), 508.2 (100%, (M − (H_2) + H)$^+$), 532.2 (59%, (M + Na)$^+$); HRMS (pNSI): calcd $C_{30}H_{27}N_3O_5Na$ [M + Na]$^+$: 532.1843; observed: 532.1834.

3aa – (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate

To a stirred Schlenk flask was added benzyl 3-vinyl-1*H*-indole-1-carboxylate (189 mg, 0.68 mmol), 1-methyl-1*H*-pyrrole-2,5-dione (76 mg, 0.68 mmol) and DCM (10 mL). The reaction mixture was heated at reflux for 24 hours. The reaction was cooled to 0 °C and then 4-phenyl-1,2,4-triazolidine-3,5-dione (120 mg, 0.68 mmol) was added. The reaction was stirred at 0 °C for 1 hour then at room temperature for 18 hours. The solvent was removed under reduced pressure to leave the crude product as an orange powder. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 1 : 1, column diameter = 2 cm, silica = 20 cm) to give (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]-carbazole-10(1*H*)-carboxylate (54%, 207 mg, 0.37 mmol) as an off-white powder and (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (27%, 76 mg, 0.19 mmol) as a white powder.

Mp: 202.3–203.9 °C; R_f: 0.15 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (1H, s), 8.07 (1H, d, $J = 8.4$ Hz), 7.51 (1H, app dt, $J = 7.6$, 0.9 Hz), 7.49–7.37 (4H, m), 7.39–7.33 (6H, m), 7.30 (1H, ddd, $J = 8.6$, 7.3, 1.3 Hz), 7.21 (1H, app td, $J = 7.5$, 1.0 Hz), 5.53 (1H, app t, $J = 5.2$ Hz), 5.44 (1H, d, $J = 11.8$ Hz), 5.38 (1H, d, $J = 11.8$ Hz), 4.89 (1H, d, $J = 8.0$ Hz), 3.50 (1H, ddd, $J = 9.6$, 8.0, 5.5 Hz), 2.87 (3H, s), 2.41 (1H, app dt, $J = 14.2$, 5.5 Hz), 2.14 (1H, ddd, $J = 14.2$, 9.5, 5.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 177.4, 173.6, 153.6, 152.2, 151.3, 136.9, 134.5, 130.9, 130.8, 129.3, 129.1, 128.9, 128.9, 128.4, 126.1, 125.8, 125.3, 123.8, 118.8, 115.7, 113.8, 69.8, 47.5, 40.0, 38.4, 27.5, 25.2; IR (neat): ν_{max} cm^{-1} 3462, 2969, 1699; MS (pNSI): 199.2 (16%), 387.1 (19%, (M − PTAD)$^+$), 564.2 (59%, (M + H)$^+$), 581.2 (100%, (M + NH_4)$^+$), 643.2 (15%), 1144.4 (39%, (2M + NH_4)$^+$); HRMS (pNSI): calcd $C_{31}H_{26}N_5O_6$ [M + H]$^+$: 564.1878; observed: 564.1873.

3bb – benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate

To a stirred Schlenk flask was added benzyl 3-vinyl-1*H*-indole-1-carboxylate (189 mg, 0.68 mmol), 1*H*-pyrrole-2,5-dione (66 mg, 0.68 mmol) and DCM (10 mL). The resulting solution was heated at reflux for 24 hours. The reaction was allowed to cool to room temperature and to the stirred solution nitrosobenzene (73 mg, 0.68 mmol) was added and the solution was stirred for 18 hours. The solvent was removed under reduced pressure to leave the crude product as a yellow powder. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1, column diameter = 2 cm, silica = 20 cm) to give benzyl(3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (70%, 230 mg, 0.48 mmol) as a yellow powder.

Mp: 177.1–177.8 °C; R_f: 0.38 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (500 MHz, CD_2Cl_2): δ_H 8.20 (1H, s), 8.11 (1H, d, $J = 8.3$ Hz), 7.66 (1H, d, $J = 7.8$ Hz), 7.50 (2H, dd, $J = 7.9$, 1.6 Hz), 7.43–7.36 (3H, m), 7.33 (2H, app t, $J = 7.8$ Hz), 7.28 (1H, app t, $J = 7.8$ Hz), 7.22 (2H, d, $J = 8.0$ Hz), 7.16 (1H, app t, $J = 7.5$ Hz), 7.02 (1H, app t, $J = 7.3$ Hz), 5.55 (1H, d, $J = 11.9$ Hz), 5.40 (1H, d, $J = 11.9$ Hz), 5.19 (1H, s), 4.96 (1H, br d, $J = 8.1$ Hz), 4.82 (1H, app t, $J = 5.7$ Hz), 3.56 (1H, br app q, $J = 7.4$ Hz), 2.35 (1H, br app dd, $J = 13.4$, 6.7 Hz), 2.00–1.92 (1H, br m); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 178.5, 174.5, 151.6, 150.7, 136.9, 134.9, 129.7, 129.0, 128.9, 128.9, 128.8, 127.6, 125.1, 123.3, 122.6, 119.8, 118.0, 117.3, 115.2, 69.5, 57.7, 41.4, 40.6, 23.0; IR (neat): ν_{max}/cm^{-1} = 3418, 3329, 2970, 1705; MS (pNSI): 199.2 (87%), 373.1 (68%, (M − (N(OH)Ph))$^+$), 480.2 (100%, (M − (H_2) + H)$^+$); HRMS (pNSI): calcd $C_{28}H_{23}N_3O_5Na$ [M + Na]$^+$: 504.1530; observed: 504.1522.

3cc – benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate

To a stirred Schlenk flask was added benzyl 3-vinyl-1*H*-indole-1-carboxylate (94 mg, 0.34 mmol), DCM (5 mL) and 1*H*-pyrrole-2,5-dione (33 mg, 0.34 mmol). The resulting solution was heated at reflux for 24 hours. The reaction was allowed to cool to room temperature and to the stirred solution 1-methyl-2-nitrosobenzene (41 mg, 0.34 mmol) was added and the solution was stirred for 4 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 3 : 2, column diameter = 2 cm, silica = 16 cm) to give benzyl-(3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]-carbazole-10(1*H*)-carboxylate (83%, 140 mg, 0.28 mmol) as a yellow powder.

Mp: 181.4–183.9 °C; R_f: 0.48 (Pet(40/60)–EA 3 : 2); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.26 (1H, s), 8.41 (1H, s), 7.93 (1H, d, $J = 8.3$ Hz), 7.51 (2H, d, $J = 7.0$ Hz), 7.45–7.33 (4H, m), 7.18–7.08 (3H, m), 7.03–6.91 (3H, m), 5.56 (1H, d, $J = 12.1$ Hz), 5.32 (1H, d, $J = 12.1$ Hz), 4.96 (1H, d, $J = 8.0$ Hz), 4.34 (1H, app t, $J = 3.7$ Hz), 3.73 (1H, app q, $J = 8.7$ Hz), 2.50–2.44 (1H, m), 2.17 (3H, s), 1.74–1.64 (1H, m); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 180.6, 176.5, 151.6, 136.2, 135.7, 131.1, 130.8, 130.0, 129.2, 129.1, 129.1, 128.2, 126.6, 124.7, 124.5, 122.9, 122.2, 120.6, 117.5, 114.4, 69.2, 57.1, 41.8, 40.2, 26.7, 18.6; IR (neat): ν_{max}/cm^{-1} 3495, 3325, 2953, 1711; MS (pNSI): 373.1 (51%, (M − (N(OH)(*o*-Tol)))$^+$), 494.2

(16%, (M − (H_2) + H)$^+$), 518.2 (21%, (M + Na)$^+$); HRMS (pNSI): calcd $C_{29}H_{25}N_3O_5Na$ [M + Na]$^+$: 518.1686; observed: 518.1681.

3dd – benzyl (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate

To a stirred Schlenk flask was added benzyl 3-vinyl-1*H*-indole-1-carboxylate (189 mg, 0.68 mmol), DCM (10 mL) and 1*H*-pyrrole-2,5-dione (66 mg, 0.68 mmol). The resulting solution was heated at reflux for 24 hours. The reaction was cooled to 0 °C and 4-phenyl-1,2,4-triazolidine-3,5-dione (120 mg, 0.68 mmol) was added. The solution was stirred at 0 °C for 1 hour. The solvent was removed under reduced pressure to leave the crude product as an off white solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 1 : 1, column diameter = 2 cm, silica = 13 cm) to give benzyl (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (58%, 216 mg, 0.39 mmol) as a pale pink powder.

Mp: 174.6–177.1 °C; R_f: 0.06 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 8.78 (1H, s), 8.05 (1H, d, J = 8.3 Hz), 7.54 (1H, d, J = 7.7 Hz), 7.44–7.38 (6H, m), 7.38–7.30 (4H, m), 7.30–7.24 (1H, m), 7.20 (1H, app t, J = 7.5 Hz), 5.51 (1H, app t, J = 5.3 Hz), 5.45 (1H, d, J = 11.9 Hz), 5.31 (1H, d, J = 11.9 Hz), 4.98 (1H, d, J = 7.9 Hz), 3.46 (1H, app q, J = 8.1 Hz), 2.36–2.30 (1H, m), 2.18 (1H, ddd, J = 13.9, 8.6, 5.3 Hz); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 178.1, 173.8, 153.7, 152.4, 151.4, 136.8, 134.7, 131.1, 130.6, 129.1, 128.9, 128.8, 128.8, 128.4, 126.2, 125.7, 125.6, 123.7, 119.0, 115.5, 114.2, 69.7, 47.7, 41.0, 39.5, 26.8; IR (neat): ν_{max}/cm^{-1} = 3169, 2975, 1699; MS (pNSI): 279.1 (38%), 373.1 (13%, (M − PTAD)$^+$), 550.2 (21%, (M + H)$^+$), 567.2 (100% (M + NH_4)$^+$), 1116.4 (39%, (2M + NH_4)$^+$), 1666.5 (6%, (3M + NH_4)$^+$); HRMS (pNSI): calcd $C_{30}H_{24}N_5O_6$ [M + H]$^+$: 550.1721; observed: 550.1719.

3ee – benzyl (*R**)-6-(hydroxy(phenyl)amino)-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11-carboxylate

To a stirred Schlenk flask was added benzyl 3-vinyl-1*H*-indole-1-carboxylate (189 mg, 0.68 mmol) and DCM (10 mL). The solution was cooled to −78 °C and 4-phenyl-1,2,4-triazolidine-3,5-dione (120 mg, 0.68 mmol) was added. The reaction was stirred at −78 °C for 5 hours. The reaction was warmed to room temperature, nitrosobenzene (73 mg, 0.68 mmol) was added and the reaction was stirred for 3 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow oil. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1, column diameter = 1 cm, silica = 16 cm) to give benzyl (*R**)-6-(hydroxy(phenyl)amino)-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11-carboxylate (72%, 274 mg, 0.49 mmol) as a white powder.

Mp: 101.2–103.1 °C; R_f: 0.53 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 8.09 (1H, d, J = 8.2 Hz), 7.51–7.38 (8H, m), 7.38–7.24 (5H, m), 7.23–7.07 (4H, m), 6.87 (1H, d, J = 7.9 Hz), 6.36 (1H, s), 5.52 (1H, d, J = 12.1 Hz), 5.39 (1H, d, J = 12.1 Hz), 5.22 (1H, dd, J = 14.0, 1.7 Hz), 4.97–4.89 (1H, m), 3.66 (1H, dd, J = 14.0, 3.4 Hz); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 147.2, 147.0, 146.6, 145.6, 131.0, 130.1, 127.3, 126.2, 125.4, 125.2, 124.9, 124.9, 124.9, 124.8, 124.8, 122.4, 122.3, 120.7, 120.5119.7, 115.8, 114.5, 110.5, 97.2, 66.2, 55.1, 39.6; IR (neat): ν_{max}/cm^{-1} = 3337, 3063, 1716; MS (pAPCI): 395.1 (100%), 451.1 (59%, (M − (N(OH)Ph))$^+$), 542.2 (5%, (M − (H_2O) + H)$^+$), 558.2 (1%, (M − H)$^+$), 560.2 (1%, (M + H)$^+$); HRMS (pAPCI): calcd $C_{32}H_{26}N_5O_5$ [M + H]$^+$: 560.1928; observed: 560.1913.

3ff – benzyl (*R**)-6-(hydroxy(*o*-tolyl)amino)-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11-carboxylate

To a stirred Schlenk flask was added benzyl 3-vinyl-1*H*-indole-1-carboxylate (94 mg, 0.34 mmol) and DCM (10 ml). The reaction mixture was cooled to −78 °C and 4-phenyl-1,2,4-triazolidine-3,5-dione (60 mg, 0.34 mmol) was added. The reaction mixture was stirred at −78 °C for 5 hours, 1-methyl-2-nitrosobenzene was added (41 mg, 0.34 mmol) and the reaction stirred at room temperature for 18 hours. The solvent was removed under reduced pressure to leave the crude product as a yellow powder. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 3 : 1, column diameter = 2 cm, silica = 20 cm) to give benzyl (*R**)-6-(hydroxy(*o*-tolyl)amino)-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11-carboxylate (68%, 132 mg, 0.23 mmol) as an off white powder.

Mp: 163.8–165.1 °C; R_f: 0.49 (Pet(40/60)–EA 3 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 8.01 (1H, d, J = 8.3 Hz), 7.65 (1H, dd, J = 8.1, 1.3 Hz), 7.54–7.38 (7H, m), 7.35 (3H, dd, J = 5.0, 2.1 Hz), 7.19 (2H, app dtd, J = 8.5, 7.2, 6.7, 1.4 Hz), 6.99 (2H, app tdd, J = 7.5, 3.4, 1.2 Hz), 6.90 (1H, dd, J = 7.7, 1.4 Hz), 6.75 (1H, d, J = 7.8 Hz), 5.87 (1H, s, OH), 5.48 (1H, d, J = 11.9 Hz), 5.34 (1H, d, J = 11.9 Hz), 5.19 (1H, dd, J = 14.1, 2.3 Hz), 4.63 (1H, app t, J = 2.3 Hz), 3.52 (1H, dd, J = 14.1, 2.3 Hz), 1.94 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 151.9, 150.3, 150.0, 148.8, 134.6, 133.6, 131.6, 131.1, 130.6, 130.0, 129.4, 128.9, 128.9, 128.8, 128.8, 127.0, 126.6, 126.0, 125.7, 124.4, 123.6, 122.7, 117.9, 114.6, 101.7, 70.1, 58.6, 43.5, 17.7; IR (neat): ν_{max}/cm^{-1} = 3291, 2981, 1782, 1737, 1699; MS (pNSI): 199.2 (100%), 407.2 (79%), 451.1 (81%, (M − (N(OH)(*o*-Tol)))$^+$), 572.2 (25%, (M − H)$^+$), 596.2 (65%, (M + Na)$^+$); HRMS (pNSI): calcd $C_{33}H_{27}N_5O_5Na$ [M + Na]$^+$: 596.1904; observed: 596.1898.

3gg – benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-7-methoxy-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate

To a stirred Schlenk flask was added benzyl 5-methoxy-3-vinyl-1*H*-indole-1-carboxylate (209 mg, 0.68 mmol), DCM (10 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (76 mg, 0.68 mmol). The resulting solution was heated at reflux for 18 hours. The reaction was cooled to room temperature and nitrosobenzene (72 mg, 0.68 mmol) was added and the reaction was stirred for 1.5 hours. The solvent was removed under reduced pressure to leave the crude product as a pale orange oil. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1,

column diameter = 1 cm, silica = 16 cm) to give benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-7-methoxy-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (73%, 218 mg, 0.44 mmol) as an orange powder.

Mp: 106.8–110.2 °C; R_f: 0.65 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 7.97 (1H, br d, J = 8.3 Hz), 7.49–7.47 (2H, m), 7.41–7.37 (3H, m), 7.33–7.30 (2H, m), 7.21–7.19 (2H, m), 7.05–7.00 (2H, m), 6.85 (1H, br d, J = 8.4 Hz), 5.53 (1H, d, J = 11.9 Hz), 5.39 (1H, d, J = 11.9 Hz), 5.02 (1H, br s), 4.91–4.87 (1H, m), 4.75 (1H, br s), 3.68 (3H, s), 3.50 (1H, br s), 2.86 (3H, s), 2.36 (1H, br s), 2.01 (1H, br s); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 178.3, 174.5, 156.3, 151.5, 151.1, 135.0, 131.5, 130.7, 129.0, 128.9, 128.8, 128.8, 128.4, 122.4, 117.7, 117.2, 115.9, 113.4, 102.4, 69.4, 57.9, 55.6, 40.3, 39.2, 24.9, 23.4; IR (neat): ν_{max}/cm^{-1} = 3408, 2969, 2890, 1699; MS (pNSI): 417.1 (100%, (M − (N(OH)Ph))$^+$), 524.2 (68%, (M − (H_2) + H)$^+$), 548.2 (16%, (M + Na)$^+$), 1073.4 (4%, (2M + Na)$^+$); HRMS (pNSI): calcd $C_{30}H_{27}N_3O_6Na$ [M + Na]$^+$: 548.1792; observed: 548.1785.

3hh – benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-7-methoxy-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate

To a stirred Schlenk flask was added benzyl 5-methoxy-3-vinyl-1*H*-indole-1-carboxylate (209 mg, 0.68 mmol), DCM (10 mL) and 1-methyl-1*H*-pyrrole-2,5-dione (76 mg, 0.68 mmol). The resulting solution was heated at reflux for 18 hours. The reaction was cooled to room temperature and 1-methyl-2-nitrosobenzene (82 mg, 0.68 mmol) was added. The solution was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1, column diameter = 2 cm, silica = 15 cm) to give benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-7-methoxy-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (74%, 279 mg, 0.50 mmol) as a pale yellow powder.

Mp: 107.6–110.1 °C; R_f: 0.29 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 7.93 (1H, d, J = 9.1 Hz), 7.54 (1H, dd, J = 8.1, 1.3 Hz), 7.49–7.45 (2H, m), 7.43–7.35 (3H, m), 7.19 (1H, ddd, J = 7.6, 6.9, 1.9 Hz), 7.10–7.01 (2H, m), 6.88 (1H, d, J = 2.6 Hz), 6.80 (1H, dd, J = 9.1, 2.6 Hz), 5.52 (1H, d, J = 11.9 Hz), 5.37 (1H, d, J = 11.9 Hz), 5.18 (1H, s), 4.87 (1H, d, J = 8.1 Hz), 4.33–4.29 (1H, m), 3.65 (3H, s), 3.67–3.61 (1H, m), 2.86 (3H, s), 2.61 (1H, app dt, J = 13.4, 5.9 Hz), 2.22 (3H, s), 1.86 (1H, ddd, J = 13.4, 8.5, 4.3 Hz); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 178.4, 174.4, 156.1, 151.6, 149.8, 135.0, 134.9, 131.2, 130.8, 130.6, 130.4, 128.8, 128.8, 128.5, 126.4, 125.3, 121.7, 117.5, 115.7, 113.6, 102.0, 69.3, 57.8, 55.4, 40.5, 38.9, 25.0, 24.9, 18.2; IR (neat): ν_{max}/cm^{-1} = 3370, 2965, 2887, 1699; MS (pNSI): 207.1 (39%), 417.1 (34%, (M − (N(OH)(*o*-Tol)))$^+$), 438.2 (100%, (M − (H_2) + H)$^+$), 1075.4 (15%, (2(M − (H_2) + H)$^+$)); HRMS (pNSI): calcd $C_{31}H_{28}N_3O_6$ [M − (H_2) + H]$^+$: 538.1976; observed: 538.1973.

3ii – benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-7-methoxy-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate

To a stirred Schlenk flask was added benzyl 5-methoxy-3-vinyl-1*H*-indole-1-carboxylate (209 mg, 0.68 mmol), DCM (10 mL) and 1*H*-pyrrole-2,5-dione (66 mg, 0.68 mmol). The resulting solution was heated at reflux for 18 hours. The reaction was cooled to room temperature and nitrosobenzene (72 mg, 0.68 mmol) was added and the reaction was stirred for 2.5 hours. The solvent was removed under reduced pressure to leave the crude product as a pale orange oil. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1, column diameter = 1 cm, silica = 16 cm) to give benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-7-methoxy-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (79%, 317 mg, 0.54 mmol) as a pale orange powder.

Mp: 134.2–136.9 °C; R_f: 0.34 (Pet(40/60)–EA 3 : 2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 8.42 (1H, br s), 7.94 (1H, d, J = 9.0 Hz), 7.47–7.44 (2H, m), 7.40–7.34 (3H, m), 7.30–7.27 (2H, m), 7.19–7.17 (2H, m), 7.01–6.98 (1H, m), 6.93 (1H, br s), 6.81 (1H, d, J = 9.0 Hz), 5.49 (1H, d, J = 11.9 Hz), 5.39 (1H, br s), 5.34 (1H, d, J = 11.9 Hz), 4.92 (1H, br d, J = 6.2 Hz), 4.74 (1H, br s), 3.64 (3H, s), 3.57–3.51 (1H, br m), 2.39–2.35 (1H, br m), 1.91–1.89 (1H, br m); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 178.6, 174.4, 156.2, 151.5, 151.0, 135.0, 131.4, 130.3, 129.0, 128.9, 128.8, 128.8, 128.4, 122.6, 117.5, 117.4, 116.0, 113.5, 102.3, 69.4, 57.9, 55.6, 41.5, 40.5, 24.0; IR (neat): ν_{max}/cm^{-1} = 3233, 2952, 1708; MS (pNSI): 403.1 (37%, (M − (N(OH)Ph))$^+$), 510.2 (100%, (M − (H_2) + H)$^+$), 532.1 (26%, (M − (H_2) + Na)$^+$); HRMS (pNSI): calcd $C_{29}H_{24}N_3O_6$ [M − (H_2) + H]$^+$: 510.1654; observed: 510.1660.

3jj – benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-7-methoxy-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate

To a stirred Schlenk flask was added benzyl 5-methoxy-3-vinyl-1*H*-indole-1-carboxylate (209 mg, 0.68 mmol), DCM (10 mL) and 1*H*-pyrrole-2,5-dione (66 mg, 0.68 mmol). The resulting solution was heated at reflux for 18 hours. The reaction was cooled to room temperature and 1-methyl-2-nitrosobenzene (82 mg, 0.68 mmol) was added. The solution was stirred at room temperature for 3.5 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow solid. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1, column diameter = 2 cm, silica = 14 cm) to give benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-7-methoxy-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (76%, 255 mg, 0.52 mmol) as a pale yellow powder.

Mp: 193.0–195.6 °C; R_f: 0.20 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 7.92 (1H, d, J = 9.7 Hz), 7.81 (1H, s), 7.53 (1H, d, J = 7.8 Hz), 7.46 (2H, dd, J = 7.8, 1.6 Hz), 7.42–7.33 (3H, m), 7.21–7.15 (1H, m), 7.09–7.00 (2H, m), 6.84–6.75 (2H, m), 5.50 (1H, d, J = 11.9 Hz), 5.35 (1H, d, J = 11.9 Hz), 5.16 (1H, s), 4.96 (1H, d, J = 7.6 Hz), 4.37 (1H, app t, J = 4.9 Hz), 3.71 (1H, app td, J = 8.7, 5.6 Hz), 3.64 (3H, s), 2.64 (1H, app dt, J = 13.6, 5.6 Hz), 2.21 (3H, s), 1.88 (1H, ddd, J = 13.6, 9.3, 4.3 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 180.6, 176.4, 155.6, 151.8, 151.7, 135.8, 131.6, 130.8, 130.7, 130.2, 129.1, 129.1, 129.0, 126.7, 124.8, 122.3, 117.2, 115.2, 113.5, 102.7, 69.1, 57.3, 55.5, 41.9, 40.3, 27.2, 18.5; IR (neat): ν_{max}/cm^{-1} = 3457, 3367, 2981, 2886, 1712; MS (pNSI): 403.1 (100%, (M − (N(OH)(*o*-Tol)))$^+$), 524.1 (75%, (M − (H_2) + H)$^+$), 548.2 (16%, (M + Na)$^+$),

1073.4 (5%, $(2M + Na)^+$); HRMS (pNSI): calcd $C_{30}H_{27}N_3O_6Na$ [M + Na]$^+$: 548.1792; observed: 548.1785.

3kk – benzyl (*R**)-6-(hydroxy(phenyl)amino)-8-methoxy-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11-carboxylate

To a stirred Schlenk flask was added benzyl 5-methoxy-3-vinyl-1*H*-indole-1-carboxylate (209 mg, 0.68 mmol) and DCM (10 mL). The solution was cooled to −78 °C and 4-phenyl-1,2,4-triazolidine-3,5-dione (120 mg, 0.68 mmol) was added. The reaction was stirred at −78 °C for 1.5 hours. The reaction was warmed to room temperature, nitrosobenzene (73 mg, 0.68 mmol) was added and the reaction was stirred for 20 hours. The solvent was removed under reduced pressure to leave the crude product as a pale yellow oil. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1, column diameter = 1 cm, silica = 16 cm) to give benzyl (*R**)-6-(hydroxy(phenyl)amino)-8-methoxy-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]-indole-11-carboxylate (78%, 312 mg, 0.53 mmol) as a white powder.

Mp: 110.4–113.2 °C; R_f: 0.20 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 7.88 (1H, d, J = 9.1 Hz), 7.42–7.38 (5H, m), 7.36–7.32 (3H, m), 7.29–7.26 (2H, m), 7.24–7.20 (2H, m), 7.13 (2H, d, J = 8.1 Hz), 7.05 (1H, app t, J = 7.3 Hz). 6.76 (1H, dd, J = 9.1, 2.6 Hz), 6.24 (1H, s), 6.10 (1H, d, J = 2.5 Hz), 5.43 (1H, d, J = 12.0 Hz), 5.32–5.29 (1H, m), 5.25–5.18 (1H, m), 4.84–4.80 (1H, m), 3.64 (1H, dd, J = 14.0, 3.3 Hz), 3.55 (3H, s); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 156.5, 151.1, 150.3, 149.4, 134.8, 131.2, 130.3, 129.2, 129.0, 129.0, 128.70, 128.7, 128.7, 128.6, 128.2, 126.9, 126.2, 124.6, 119.7, 115.3, 113.2, 101.0, 100.5, 69.9, 59.1, 55.5, 44.0; IR (neat): ν_{max}/cm^{-1} = 3336, 2935, 1716; MS (pNSI): 481.1 (17%, $(M - (N(OH)Ph))^+$), 588.2 (100%, $(M - (H_2) + H)^+$), 612.2 (15%, $(M + Na)^+$); HRMS (pNSI): calcd $C_{33}H_{27}N_5O_6Na$ [M + Na]$^+$: 612.1854; observed: 612.1838.

3ll – benzyl (*R**)-6-(hydroxy(*o*-tolyl)amino)-8-methoxy-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11-carboxylate

To a stirred Schlenk flask was added benzyl 5-methoxy-3-vinyl-1*H*-indole-1-carboxylate (209 mg, 0.68 mmol) and DCM (10 mL). The solution was cooled to −78 °C and 4-phenyl-1,2,4-triazolidine-3,5-dione (120 mg, 0.68 mmol) was added. The reaction was stirred at −78 °C for 1.5 hours. The reaction was warmed to room temperature, 1-methyl-2-nitrosobenzene (73 mg, 0.68 mmol) was added and the reaction was stirred for 24 hours. The solvent was removed under reduced pressure to leave the crude product as a pale orange oil. The product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1, column diameter = 2 cm, silica = 17 cm) to give benzyl (*R**)-6-(hydroxy(*o*-tolyl)amino)-8-methoxy-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11-carboxylate (82%, 338 mg, 0.56 mmol) as an off white powder.

Mp: 181.1–183.0 °C; R_f: 0.55 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.70 (1H, s), 7.84 (1H, d, J = 9.0 Hz), 7.55–7.48 (2H, m), 7.46–7.41 (3H, m), 7.41–7.33 (4H, m), 7.33–7.29 (2H, m), 7.13–7.03 (2H, m), 6.97 (1H, app td, J = 7.4, 1.3 Hz), 6.83 (1H, dd, J = 9.1, 2.6 Hz). 6.38 (1H, s), 5.43 (1H, d, J = 12.1 Hz), 5.33 (1H, d, J = 12.1 Hz), 4.80 (1H, dd, J = 13.7, 1.8 Hz), 4.71 (1H, dd, J = 3.3, 1.8 Hz), 3.68–3.61 (1H, dd, J = 13.7, 3.3 Hz), 3.58 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 156.3, 151.6, 150.8, 150.3, 149.8, 135.3, 131.6, 130.9, 130.3, 130.0, 129.7, 129.2, 129.1, 129.1, 128.9, 128.0, 127.4, 127.1, 126.8, 125.2, 121.8, 115.3, 113.2, 103.1, 101.9, 69.9, 55.9, 55.6, 43.9, 18.2; IR (neat): ν_{max}/cm^{-1} = 3212, 2939, 1720; MS (pNSI): 481.2 (100%, $(M - N(OH)(o\text{-Tol}))^+$), 602.2 (34%, $(M - (H_2) + H)^+$), 626.2 (100%, $(M + Na)^+$); HRMS (pNSI): calcd $C_{34}H_{29}N_5O_6Na$ [M + Na]$^+$: 626.2010; observed: 626.2006.

4a – (3a*S**,5*S**,10b*S**)-5-methoxy-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (120 mg, 0.24 mmol), platinum(IV) oxide (53 mg, 0.24 mmol) and methanol (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 18 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as an orange solid, The crude product was purified by column chromatography (petrol (40/60)–ethyl acetate 1 : 1, column diameter = 2 cm, silica = 13 cm) to give (3a*S**,5*S**,10b*S**)-5-methoxy-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (60%, 41 mg, 0.14 mmol) as a pale yellow powder.

Mp: 139.4–142.7 °C; R_f: 0.25 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 8.91 (1H, s), 7.56 (1H, d, J = 7.8 Hz), 7.34 (1H, d, J = 7.7 Hz), 7.14 (1H, app t, J = 7.5 Hz), 7.09 (1H, app t, J = 7.4 Hz), 4.73 (1H, app t, J = 2.7 Hz), 4.14 (1H, d, J = 8.8 Hz), 3.31–3.25 (1H, m), 3.22 (3H, s), 2.94 (1H, app t, J = 2.4 Hz), 2.90 (3H, s), 1.88 (1H, ddd, J = 14.2, 6.9, 2.2 Hz); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 178.9, 176.1, 136.4, 128.8, 126.6, 122.3, 120.1, 118.2, 111.9, 111.3, 69.4, 56.1, 39.5, 37.3, 27.4, 25.1; IR (neat): ν_{max}/cm^{-1} 3398, 2931, 2870, 1689; MS (pNSI): 285.0 (29%), 355.1 (100%), 371.1 (57%), 560.0 (21%); HRMS (pNSI): calcd $C_{15}H_{13}N_2O_2$ $[M - OMe]^+$: 253.0972; observed: 253.0974.

4b – (3a*S**,5*S**,10b*S**)-5-ethoxy-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (100 mg, 0.20 mmol), platinum(IV) oxide (45 mg, 0.20 mmol) and ethanol (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 18 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as an yellow solid, The crude product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 1, column diameter = 2 cm, silica = 15 cm) to give (3a*S**,5*S**,10b*S**)-5-

ethoxy-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (24%, 20 mg, 0.04 mmol) as a brown powder.

Mp: 100.6–102.8 °C; R_f: 0.16 (Pet(40/60)–EA 2 : 1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 8.78 (1H, s), 7.54 (1H, d, J = 7.7 Hz), 7.35 (1H, d, J = 7.7 Hz), 7.17–7.12 (1H, m), 7.09 (1H, app t, J = 7.0 Hz), 4.83 (1H, app t, J = 2.8 Hz), 4.16 (1H, d, J = 8.8 Hz), 3.55 (1H, app td, J = 6.9, 1.8 Hz), 3.32–3.26 (2H, m), 2.93–2.91 (1H, m), 2.90 (3H, s), 1.88 (1H, ddd, J = 14.3, 7.1, 2.7 Hz), 0.97 (1H, t, J = 7.0 Hz); ^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 178.9, 176.0, 136.3, 128.8, 126.5, 122.3, 120.1, 118.1, 112.5, 111.3, 67.4, 63.5, 39.5, 37.3, 27.9, 25.0, 15.2; IR (neat): ν_{max}/cm^{-1} 3300, 2969, 1690; MS (pAPCI): 108.1 (24%), 298.1 (6%, $(M)^+$), 299.1 (5%, $(M + H)^+$); HRMS (pAPCI): calcd $C_{17}H_{19}N_2O_3$ $[M + H]^+$: 299.1390; observed: 299.1387.

4c – (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (120 mg, 0.25 mmol), platinum(IV) oxide (57 mg, 0.25 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 5 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a yellow solid, The crude product was purified by trituration from DCM to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (75%, 68 mg, 0.19 mmol) as a pale yellow powder.

Mp: 157.2–161.9 °C; R_f: 0.17 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.06 (1H, s), 8.20 (1H, s), 7.35 (1H, d, J = 8.0 Hz), 7.26 (1H, d, J = 8.0 Hz), 7.24–7.19 (2H, m), 7.17–7.08 (2H, m), 6.98 (1H, app ddd, J = 8.2, 7.0, 1.2 Hz), 6.91–6.81 (1H, m), 6.81 (1H, app ddd, J = 8.0, 6.9, 1.0 Hz), 4.88 (1H app t, J = 4.9 Hz), 4.27 (1H, d, J = 8.8 Hz), 3.64 (1H, app td, J = 8.8, 6.1 Hz), 2.81 (3H, s), 2.33 (1H, app dt, J = 13.7, 6.1 Hz), 1.84 (1H, ddd, J = 13.7, 8.8, 4.9 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 179.8, 176.3, 153.3, 137.0, 130.0, 129.0, 126.3, 121.5, 121.2, 119.9, 119.0, 117.2, 111.7, 110.0, 57.4, 39.6, 39.3, 25.8, 25.1; IR (neat): ν_{max}/cm^{-1} 3374, 3306, 2919, 1683; MS (pAPCI): 108.0 (28%), 251.1 (100%), 253.1 (68%, $(M - (N(OH)Ph) + H)^+$), 344.1 (13%, $(M - (OH) + H)^+$), 361.1 (3%, $(M + H)^+$); HRMS (pAPCI): calcd $C_{21}H_{20}N_3O_3$ $[M + H]^+$: 362.1499; observed: 362.1501.

Note: H^1 NMR ran at 40 °C.

4d – (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (100 mg, 0.20 mmol), platinum(IV) oxide (45 mg, 0.20 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 7 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a yellow solid. The crude product was purified by column chromatography (petrol (40/60)–ethyl acetate 1 : 1, column diameter = 2 cm, silica = 16 cm) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (87%, 65 mg, 0.17 mmol) as a pale orange powder.

Mp: 179.3–181.0 °C; R_f: 0.60 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.08 (1H, s), 8.28 (1H, s), 7.50 (1H, d, J = 8.0 Hz), 7.29 (1H, d, J = 8.1 Hz), 7.14–7.10 (1H, m), 6.91–6.87 (4H, m), 6.67 (1H, app t, J = 7.4 Hz), 4.29 (1H, d, J = 8.2 Hz), 4.27 (1H, app t, J = 3.9 Hz), 3.83–3.74 (1H, m), 2.81 (3H, s), 2.65–2.56 (1H, m), 1.98 (3H, s), 1.67 (1H, ddd, J = 13.6, 10.5, 3.9 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 180.0, 176.3, 152.2, 136.7, 130.7, 130.5, 130.3, 126.5, 126.5, 124.5, 122.4, 121.2, 119.3, 118.9, 111.7, 109.7, 58.3, 40.0, 38.6, 27.3, 25.1, 18.3; IR (neat): ν_{max}/cm^{-1} 3379, 2955, 2873, 1691; MS (pAPCI): 108.1 (98%), 251.1 (100%), 253.1 (61%, $(M - (N(OH)(o\text{-Tol})) + H)^+$), 271.1 (6%, $(M - (N(OH)(o\text{-Tol})) + OH_2)^+$), 358.2 (13%, $(M - OH)^+$); HRMS (pAPCI): calcd $C_{22}H_{22}N_3O_3$ $[M + H]^+$: 376.1656; observed: 376.1658.

4e – (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (110 mg, 0.20 mmol), platinum(IV) oxide (46 mg, 0.20 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 5 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a yellow solid. The product was purified by trituration from DCM to give (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-2-methyl-4,5,10,10b-tetrahydropyrrolo-[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (91%, 79 mg, 0.18 mmol) as an off-white solid.

Mp: 262.4–264.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.43 (1H, s), 10.67 (1H, br s), 7.52–7.42 (4H, m), 7.39–7.37 (2H, m), 7.21 (1H, d, J = 7.9 Hz), 7.06 (1H, app t, J = 7.6 Hz), 6.94 (1H, app t, J = 7.5 Hz), 5.39 (1H, app t, J = 6.1 Hz), 4.33 (1H, d, J = 8.0 Hz), 3.72 (1H, app q, J = 6.8 Hz), 2.81 (3H, s), 2.35–2.31 (2H, m); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 178.9, 175.8, 152.7, 152.7, 137.2, 132.3, 130.7, 129.5, 128.5, 126.7, 125.3, 122.2, 119.9, 118.4, 112.3, 107.3, 48.1, 39.5, 38.3, 27.7, 25.3; IR (neat): ν_{max}/cm^{-1} 3229, 1693; MS (pAPCI): 178.1 (35%), 253.1 (100%, $(M - (PTAD) + H)^+$); HRMS (ASAP) calcd $C_{15}H_{13}N_2O_2$ $[M - PTAD + H]^+$: 253.0972; observed: 253.0969.

4f – (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (90 mg, 0.18 mmol), platinum(IV) oxide (41 mg, 0.18 mmol) and THF (5 mL). The

resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 10 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as an yellow solid, The crude product was purified by column chromatography (petrol (40/60)–ethyl acetate 1 : 1, column diameter = 2 cm, silica = 14 cm) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl) amino)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (41%, 26 mg, 0.07 mmol) as a yellow powder.

Mp: 150.0–153.1 °C; R_f: 0.33 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.22 (1H, s), 11.09 (1H, s), 8.24 (1H, s), 7.33 (1H, d, J = 8.1 Hz), 7.27–7.23 (1H, m), 7.20 (2H, app d, J = 7.3 Hz), 7.12 (2H, d, J = 7.7 Hz), 7.00–6.95 (1H, m), 6.85 (1H, app t, J = 7.2 Hz), 6.80 (1H app t, J = 7.3 Hz), 4.89 (1H, app t, J = 4.9 Hz), 4.25 (1H, d, J = 8.1 Hz), 3.63–3.52 (1H, m), 2.27 (1H, app dt, J = 13.6, 5.6 Hz), 1.80 (1H, ddd, J = 13.6, 9.2, 4.8 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 181.2, 177.6, 153.3, 137.0, 130.3, 129.0, 126.3, 121.4, 121.1, 119.9, 118.9, 117.2, 111.7, 109.9, 57.4, 40.9, 40.6, 25.7; IR (neat): ν_{max}/cm^{-1} 3302, 2924, 1706; MS (pAPCI): 108.1 (18%), 237.1 (100), 239.1 (46%, (M − (N(OH)Ph) + H)$^+$); HRMS (pAPCI): calcd $C_{14}H_{11}N_2O_2$ [M − (N(OH)Ph) + H]$^+$: 239.0815; observed: 239.0810.

4g – (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (120 mg, 0.24 mmol), platinum(IV) oxide (54 mg, 0.24 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 6 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a yellow solid, The crude product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 3, column diameter = 2 cm, silica = 17 cm) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl) amino)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione- (70%, 61 mg, 0.17 mmol) as an off white solid.

Mp: 149.9–153.2 °C; R_f: 0.52 (Pet(40/60)–EA 2 : 3); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 8.81 (1H, s), 8.21 (1H, s), 7.56 (1H, d, J = 8.0 Hz), 7.30 (1H, d, J = 7.9 Hz), 7.18 (2H, d, J = 6.9 Hz), 7.06 (1H, app t, J = 7.6 Hz), 7.03–6.99 (2H, m), 6.91–6.85 (1H, m), 5.36 (1H, s), 4.51 (1H, app t, J = 4.5 Hz), 4.19 (1H, d, J = 8.6 Hz), 3.80 (1H, app td, J = 9.3, 6.4 Hz), 2.74 (1H, app dt, J = 13.6, 5.5 Hz), 2.15 (3H, s), 1.83 (1H, ddd, J = 13.6, 10.1, 4.1 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 181.5, 177.6, 152.2, 136.7, 130.6, 130.5, 130.5, 126.5, 126.5, 124.5, 122.4, 121.1, 119.3, 118.9, 111.6, 109.5, 58.3, 55.5, 40.9, 27.3, 18.3; IR (neat): ν_{max}/cm^{-1} 3372, 3298, 1683; MS (nNSI) = 186.0 (100%), 237.1 (97%, (M − (N(OH)(*o*-Tol)) − H)$^-$), 358.1 (35%, (M − H_2)$^-$), 394.1 (23%); HRMS (nNSI): calcd $C_{21}H_{18}N_3O_3$ [M − H]$^-$: 360.1354; observed: 360.1348.

4h – (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (110 mg, 0.20 mmol), platinum(IV) oxide (46 mg, 0.20 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 5 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a white solid. The crude product was purified by trituration from DCM to give (3a*S**,5*S**,10b*S**)-5-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (64%, 53 mg, 0.13 mmol) as a white powder.

Mp: 212.6–213.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.39 (1H, s), 11.36 (1H, s), 10.66 (1H, s), 7.51–7.44 (4H, m), 7.41–7.37 (2H, m), 7.23 (1H, d, J = 7.8 Hz), 7.07 (1H, app t, J = 7.5 Hz), 6.96 (1H, app t, J = 7.5 Hz), 5.42 (1H, app t, J = 6.0 Hz), 4.29 (1H, d, J = 8.0 Hz), 3.69 (1H, app q, J = 6.8 Hz), 2.37–2.21 (2H, m); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 180.3, 177.1, 152.7, 152.6, 137.2, 132.3, 131.0, 129.5, 128.5, 126.7, 125.3, 122.2, 119.9, 118.4, 112.3, 107.1, 55.5, 48.1, 40.9, 27.5; IR (neat): ν_{max}/cm^{-1} = 3310, 3155, 3077, 1719, 1674; MS (pAPCI): 239.1 (100%, (M − (PTAD) + H)$^+$), 414.1 (2%, (M − H)$^+$); HRMS (pAPCI): calcd $C_{22}H_{16}N_5O_4$ [M − H]$^+$: 414.1197; observed: 414.1185.

4i – (*R**)-6-(hydroxy(phenyl)amino)-2-phenyl-6,11-dihydro-1*H*,5*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*)-dione

To a stirred Schlenk flask was added benzyl (*R**)-6-(hydroxy-(phenyl)amino)-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11-carboxylate (110 mg, 0.20 mmol), platinum(IV) oxide (46 mg, 0.20 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 5 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a yellow solid. The product was purified by trituration from DCM to give (*R**)-6-(hydroxy(phenyl)amino)-2-phenyl-6,11-dihydro-1*H*,5*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*)-dione (65%, 55 mg, 0.13 mmol) as an off-white solid.

Mp: 174.3–175.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.63 (1H, s), 8.61 (1H, s), 7.54–7.38 (6H, m), 7.18 (2H, app t, J = 7.8 Hz), 7.10 (2H, app d, J = 7.8 Hz), 7.00–6.96 (2H, m), 6.91–6.83 (2H, m), 5.18–5.15 (1H, m), 4.48 (1H, dd, J = 13.0, 2.0 Hz), 3.77 (1H, dd, J = 13.0, 4.2 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 152.6, 149.6, 146.6, 134.2, 131.7, 129.8, 129.6, 128.9, 128.9, 127.0, 125.8, 122.3, 121.1, 120.2, 118.5, 118.3, 112.3, 92.4, 57.4, 43.4; IR (neat): ν_{max}/cm^{-1} 3431, 3054, 1698; MS (pAPCI): 317.1 (100%, (M − (N(OH) Ph) + H)$^+$), 407.1 (5%, (M − H_2O)$^+$); HRMS (pAPCI) calcd $C_{24}H_{19}N_5O_3$ [M − H]$^+$: 424.1404; observed: 424.1398.

4j – (*R**)-6-(hydroxy(*o*-tolyl)amino)-2-phenyl-6,11-dihydro-1*H*,5*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*)-dione

To a stirred Schlenk flask was added benzyl (*R**)-6-(hydroxy(*o*-tolyl)amino)-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]-triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11-carboxylate (140 mg, 0.24 mmol), platinum(IV) oxide (55 mg, 0.24 mmol) and THF (5 mL). The resulting suspension was placed under an

atmosphere of H_2 and stirred at room temperature for 5 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a white solid. The crude product was purified by trituration from DCM to give (*R**)-6-(hydroxy(*o*-tolyl)amino)-2-phenyl-6,11-dihydro-1*H*,5*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*)-dione (44%, 46 mg, 0.11 mmol) as a white powder.

Mp: 188.1–189.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.65 (1H, s), 8.58 (1H, s), 7.59–7.51 (5H, m), 7.47–7.42 (1H, m), 7.36 (1H, d, J = 8.0 Hz), 7.17–7.13 (1H, m), 6.96–6.91 (3H, m), 6.79–6.69 (2H, m), 4.69 (1H, d, J = 12.8 Hz), 4.58 (1H, br s), 3.62 (1H, dd, J = 12.8, 3.3 Hz), 2.06 (3H, s); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 151.4, 150.4, 146.8, 134.0, 131.8, 131.2, 130.6, 129.8, 129.7, 128.9, 127.0, 126.7, 126.0, 125.1, 122.6, 121.0, 120.1, 118.1, 112.2, 92.3, 57.8, 43.5, 18.2; IR (neat): ν_{max}/cm^{-1} = 3426, 3380, 2950, 1712; MS (pAPCI): 108.1 (100%), 317.1 (37%, (M − (N(OH)(*o*-Tol)) + H)$^+$), 422.2 (4%, (M − (H_2O) + H)$^+$), 438.2 (6%, (M − H)$^+$); HRMS (pAPCI): calcd $C_{25}H_{20}N_5O_3$ [M − H]$^+$: 438.1561; observed: 438.1553.

4k – (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-7-methoxy-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-7-methoxy-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (130 mg, 0.25 mmol), platinum(IV) oxide (57 mg, 0.25 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 5 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as an orange solid. The crude product was purified by column chromatography (petrol (40/60)–ethyl acetate 3 : 2, column diameter = 2 cm, silica = 14 cm) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-7-methoxy-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (70%, 69 mg, 0.18 mmol) as a pale yellow powder.

Mp: 149.1–151.2 °C; R_f: 0.19 (Pet(40/60)–EA 3 : 2); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.95 (1H, s), 8.29 (1H, s), 7.23–7.19 (2H, m), 7.18 (1H, d, J = 2.8 Hz), 7.14–7.10 (2H, m), 6.87–6.83 (1H, m), 6.57 (1H, dd, J = 8.7, 2.5 Hz), 6.51 (1H, d, J = 2.5 Hz), 4.83 (1H, app t, J = 4.8 Hz), 4.24 (1H, d, J = 8.2 Hz), 3.64 (1H, app td, J = 9.1, 6.1 Hz), 3.48 (3H, s), 2.80 (3H, s), 2.35 (1H, ddd, J = 13.7, 6.1, 4.8 Hz), 1.83 (1H, ddd, J = 13.7, 9.1, 4.8 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 179.9, 176.3, 153.6C[1], 153.4, 132.0, 130.6, 129.0, 126.6, 121.2, 117.4, 112.3, 111.5, 109.5, 101.7, 57.7, 55.5, 39.5, 39.1, 27.1, 25.1; IR (neat): ν_{max}/cm^{-1} = 3394, 2937, 2833, 1690; MS (pAPCI): 283.1 (100%, (M − (N(OH)Ph) + H)$^+$), 374.1 (18%, (M − (H_2O) + H)$^+$), 390.1 (2%, (M − H)$^+$), 392.2 (1%, (M + H)$^+$); HRMS (pAPCI): calcd $C_{22}H_{22}N_3O_4$ [M + H]$^+$: 392.1605; observed: 392.1597.

4l – (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-7-methoxy-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-7-methoxy-2-methyl-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (108 mg, 0.20 mmol), platinum(IV) oxide (46 mg, 0.20 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 5 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a white solid. The crude product was purified by column chromatography (petrol (40/60)–ethyl acetate 1 : 1, column diameter = 2 cm, silica = 15 cm) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-7-methoxy-2-methyl-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (70%, 57 mg, 0.14 mmol) as an off white powder.

Mp: 139.7–142.5 °C; R_f: 0.36 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.89 (1H, s), 8.36 (1H, s), 7.52 (1H, d, J = 8.0 Hz), 7.15–7.11 (2H, d, J = 8.7 Hz), 6.93–6.85 (2H, m), 6.49 (1H, dd, J = 8.7, 2.4 Hz), 6.23–6.17 (1H, m), 4.28 (1H, d, J = 8.2 Hz), 4.22 (1H, app t, J = 3.8 Hz), 3.78 (1H, ddd, J = 10.8, 8.2, 6.1 Hz), 3.45 (3H, s), 2.81 (3H, s), 2.70–2.63 (1H, m), 1.89 (3H, s), 1.66 (1H, ddd, J = 14.1, 10.8, 3.8 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 180.1, 176.3, 153.2, 152.5, 131.6, 131.1, 130.7, 130.4, 126.8, 126.5, 124.7, 122.7, 112.2, 111.4, 109.2, 100.6, 58.8, 55.3, 39.6, 38.4, 28.3, 25.1, 18.1; IR (neat): ν_{max}/cm^{-1} = 3384, 2954, 2866, 1693; MS (pAPCI): 283.1 (100%, (M − (N(OH)(*o*-Tol)) + H)$^+$), 388.2 (34%, (M − (H_2O) + H)$^+$), 404.2 (13%, (M − H)$^+$), 406.2 (11%, (M + H)$^+$); HRMS (pAPCI): calcd $C_{23}H_{24}N_3O_4$ [M + H]$^+$: 406.1761; observed: 406.1750.

4m – (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (90 mg, 0.18 mmol), platinum(IV) oxide (41 mg, 0.18 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 10 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as an yellow solid, The crude product was purified by column chromatography (petrol (40/60)–ethyl acetate 1 : 1, column diameter = 2 cm, silica = 14 cm) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(phenyl)amino)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione (41%, 26 mg, 0.07 mmol) as a yellow powder.

Mp: 150.0–153.1 °C; R_f: 0.33 (Pet(40/60)–EA 1 : 1); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.22 (1H, s), 11.09 (1H, s), 8.24 (1H, s), 7.33 (1H, d, J = 8.1 Hz), 7.27–7.23 (1H, m), 7.20 (2H, app d, J = 7.3 Hz), 7.12 (2H, d, J = 7.7 Hz), 7.00–6.95 (1H, m), 6.85 (1H, app t, J = 7.2 Hz), 6.80 (1H app t, J = 7.3 Hz), 4.89 (1H, app t, J = 4.9 Hz), 4.25 (1H, d, J = 8.1 Hz), 3.63–3.52 (1H, m), 2.27 (1H, app dt, J = 13.6, 5.6 Hz), 1.80 (1H, ddd, J = 13.6, 9.2, 4.8 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 181.2, 177.6, 153.3, 137.0, 130.3, 129.0, 126.3, 121.4, 121.1, 119.9, 118.9, 117.2, 111.7, 109.9, 57.4, 40.9, 40.6, 25.7; IR (neat): ν_{max}/cm^{-1} 3302, 2924, 1706; MS (pAPCI): 108.1 (18%), 237.1 (100), 239.1 (46%, (M − (N(OH)Ph) + H)$^+$); HRMS (pAPCI): calcd $C_{14}H_{11}N_2O_2$ [M − (N(OH)Ph) + H]$^+$: 239.0815; observed: 239.0810.

4n – (3a*S,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3a*H*)-dione**

To a stirred Schlenk flask was added benzyl (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl)amino)-1,3-dioxo-2,3,3a,4,5,10b-hexahydropyrrolo[3,4-*a*]carbazole-10(1*H*)-carboxylate (120 mg, 0.24 mmol), platinum(IV) oxide (54 mg, 0.24 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 6 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a yellow solid, The crude product was purified by column chromatography (petrol (40/60)–ethyl acetate 2 : 3, column diameter = 2 cm, silica = 17 cm) to give (3a*S**,5*S**,10b*S**)-5-(hydroxy(*o*-tolyl) amino)-4,5,10,10b-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*, 3a*H*)-dione (70%, 61 mg, 0.17 mmol) as an off white solid.

Mp: 149.9–153.2 °C; R_f: 0.52 (Pet(40/60)–EA 2 : 3); ^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 8.81 (1H, s), 8.21 (1H, s), 7.56 (1H, d, J = 8.0 Hz), 7.30 (1H, d, J = 7.9 Hz), 7.18 (2H, d, J = 6.9 Hz), 7.06 (1H, app t, J = 7.6 Hz), 7.03–6.99 (2H, m), 6.91–6.85 (1H, m), 5.36 (1H, s), 4.51 (1H, app t, J = 4.5 Hz), 4.19 (1H, d, J = 8.6 Hz), 3.80 (1H, app td, J = 9.3, 6.4 Hz), 2.74 (1H, app dt, J = 13.6, 5.5 Hz), 2.15 (3H, s), 1.83 (1H, ddd, J = 13.6, 10.1, 4.1 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 181.5, 177.6, 152.2, 136.7, 130.6, 130.5, 130.5, 126.5, 126.5, 124.5, 122.4, 121.1, 119.3, 118.9, 111.6, 109.5, 58.3, 55.5, 40.9, 27.3, 18.3; IR (neat): ν_{max}/cm^{-1} 3372, 3298, 1683; MS (nNSI) = 186.0 (100%), 237.1 (97%, (M − (N(OH)(*o*-Tol)) − H)$^-$), 358.1 (35%, (M − H_2)$^-$), 394.1 (23%); HRMS (nNSI): calcd $C_{21}H_{18}N_3O_3$ [M − H]$^-$: 360.1354; observed: 360.1348.

4o – (*R)-6-(hydroxy(phenyl)amino)-8-methoxy-2-phenyl-6,11-dihydro-1*H*,5*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*] indole-1,3(2*H*)-dione**

To a stirred Schlenk flask was added benzyl (*R**)-6-(hydroxy (phenyl)amino)-8-methoxy-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*]indole-11-carboxylate (118 mg, 0.20 mmol), platinum(IV) oxide (46 mg, 0.20 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 5 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a yellow solid. The product was purified by trituration from DCM to give (*R**)-6-(hydroxy(phenyl) amino)-8-methoxy-2-phenyl-6,11-dihydro-1*H*,5*H*-[1,2,4]triazolo [1′,2′:1,2]pyridazino[3,4-*b*]indole-1,3(2*H*)-dione (38%, 35 mg, 0.08 mmol) as an off-white solid.

Mp: 173.7–176.4 °C; R_f: 0.18 (Pet–EA 3 : 1); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.44 (1H, s) 8.62 (1H, s), 7.54–7.47 (4H, m), 7.44–7.41 (1H, m) 7.25–7.18 (3H, m), 7.12 (2H, d, J = 7.7 Hz), 6.90 (1H, app t, J = 6.8 Hz), 6.56 (1H, d, J = 8.7 Hz), 6.26 (1H, s), 5.12 (1H, br s), 4.51 (1H, d, J = 13.0 Hz), 3.81 (1H, dd, J = 13.0, 3.3 Hz), 3.49 (3H, s); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 154.3, 152.9, 149.7, 146.4, 131.8, 130.1, 129.6, 129.6, 128.9, 128.9, 127.0, 126.3, 122.3, 118.4, 112.9, 110.7, 100.8, 92.3, 57.7, 55.5, 44.3; IR (neat): ν_{max}/cm^{-1} 3362, 3000, 1758, 1700; MS (pAPCI): 213.1 (70%), 347.1 (100%, (M − (N(OH)Ph) + H)$^+$); HRMS (pAPCI): calcd $C_{25}H_{20}N_5O_4$ [M − H]$^+$: 454.1510; observed: 454.1502.

4p – (*R)-6-(hydroxy(*o*-tolyl)amino)-8-methoxy-2-phenyl-6,11-dihydro-1*H*,5*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4-*b*] indole-1,3(2*H*)-dione**

To a stirred Schlenk flask was added benzyl (*R**)-6-(hydroxy(*o*-tolyl)amino)-8-methoxy-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydro-1*H*,11*H*-[1,2,4]triazolo[1′,2′:1,2]pyridazino[3,4 *b*]indole-11-carboxylate (120 mg, 0.20 mmol), platinum(IV) oxide (46 mg, 0.20 mmol) and THF (5 mL). The resulting suspension was placed under an atmosphere of H_2 and stirred at room temperature for 5 hours. The suspension was filtered through celite and the solvent was removed under reduced pressure to leave the crude product as a white solid. The crude product was purified by trituration from DCM to (*R**)-6-(hydroxy(*o*-tolyl)amino)-8-methoxy-2-phenyl-6,11-dihydro-1*H*,5*H*-[1,2,4]triazolo[1′,2′:1,2]-pyridazino[3,4 *b*]indole-1,3(2*H*)-dione (64%, 53 mg, 0.13 mmol) as a white powder.

Mp: 171.9–173.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 11.44 (1H, s), 8.64 (1H, s), 7.59 (1H, d, J = 8.1 Hz), 7.54–7.50 (4H, m), 7.46–7.43 (1H, m), 7.19 (1H, d, J = 8.5 Hz), 7.15 (1H, d, J = 7.5 Hz), 6.97–6.91 (2H, m), 6.50 (1H, dd, J = 8.7, 2.2 Hz), 6.01 (1H, s), 4.73 (1H, d, J = 12.8 Hz), 4.52 (1H, s), 3.67–3.61 (1H, m), 3.47 (3H, s), 1.96 (3H, s); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 154.1, 151.8, 150.5, 146.4, 131.8, 131.6, 130.6, 130.0, 129.7, 128.9, 128.7, 127.0, 126.7, 126.5, 125.3, 122.8, 112.7, 110.7, 100.0, 91.8, 58.3, 55.4, 44.3, 18.0; IR (neat): ν_{max}/cm^{-1} = 3442, 3394, 2939, 1699; MS (pAPCI): 347.1 (68%, (M − (N(OH)(*o*-Tol) + H)$^+$)), 391.1 (100%), 452.2 (4%, (M − (H_2O) + H)$^+$), 468.2 (2%, (M − H)$^+$); HRMS (pAPCI): calcd $C_{26}H_{22}N_5O_4$ [M − H]$^+$: 468.1666; observed: 468.1658.

Acknowledgements

The authors thank Newcastle University and EPSRC (EP/I033959/1) for funding, MA thanks the Ministry of Higher Education of Saudi Arabia for a PhD scholarship, EPSRC for X-ray crystallography facilities at Newcastle (EP/F03637X/1), Prof. W. McFarlane and Dr C. Wills (Newcastle) for NMR support, L. Watson and S. Thompson (Newcastle) for preliminary studies. Mass spectrometry data was acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

References

1 S. Omura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya, H. Tsuchiya, Y. Takahashi and R. Asuma, *J. Antibiot.*, 1977, **30**, 275–282.
2 N. Funato, H. Takayanagi, Y. Konda, Y. Toda, Y. Harigaya, Y. Iwai and S. Ōmura, *Tetrahedron Lett.*, 1994, **35**, 1251–1254.
3 O. A. B. S. M. Gani and R. A. Engh, *Nat. Prod. Rep.*, 2010, **27**, 489–498.
4 M. S. Lopez, J. W. Choy, U. Peters, M. L. Sos, D. O. Morgan and K. M. Shokat, *J. Am. Chem. Soc.*, 2013, **135**, 18153–18159.
5 E. Conchon, F. Anizon, R. M. Golsteyn, S. Léonce, B. Pfeiffer and M. Prudhomme, *Tetrahedron*, 2006, **62**, 11136–11144.

6 A. Voldoire, M. Sancelme, M. Prudhomme, P. Colson, C. Houssier, C. Bailly, S. Léonce and S. Lambel, *Bioorg. Med. Chem.*, 2001, **9**, 357–365.
7 N. Ty, G. Dupeyre, G. G. Chabot, J. Seguin, L. Quentin, A. Chiaroni, F. Tillequin, D. Scherman, S. Michel and X. Cachet, *Eur. J. Med. Chem.*, 2010, **45**, 3726–3739.
8 E. Conchon, F. Anizon, B. Aboab, R. M. Golsteyn, S. Léonce, B. Pfeiffer and M. Prudhomme, *Eur. J. Med. Chem.*, 2008, **43**, 282–292.
9 E. Pereira, A. Youssef, M. El-Ghozzi, D. Avignant, J. Bain, M. Prudhomme, F. Anizon and P. Moreau, *Tetrahedron Lett.*, 2014, **55**, 834–837.
10 M. Eitel and U. Pindur, *J. Org. Chem.*, 1990, **55**, 5368–5374.
11 W. E. Noland, W. C. Kuryla and R. F. Lange, *J. Am. Chem. Soc.*, 1959, **81**, 6010–6017.
12 W. E. Noland and S. R. Wann, *J. Org. Chem.*, 1979, **44**, 4402–4410.
13 M. Bleile, T. Wagner and H.-H. Otto, *Helv. Chim. Acta*, 2005, **88**, 2879–2891.
14 U. Pindur and M.-H. Kim, *Tetrahedron Lett.*, 1988, **29**, 3927–3928.
15 M. Medion-Simon and U. Pindur, *Helv. Chim. Acta*, 1991, **74**, 430–437.
16 U. Pindur and C. Otto, *Tetrahedron*, 1992, **48**, 3515–3526.
17 R. Bergamasco, Q. N. Porter and C. Yap, *Aust. J. Chem.*, 1977, **30**, 1531–1544.
18 J. D. Lambert and Q. N. Porter, *Aust. J. Chem.*, 1981, **34**, 1483–1490.
19 C. Gioia, A. Hauville, L. Bernardi, F. Fini and A. Ricci, *Angew. Chem., Int. Ed.*, 2008, **47**, 9236–9239.
20 C. Gioia, L. Bernardi and A. Ricci, *Synthesis*, 2010, **2010**, 161–170.
21 B. Tan, G. Hernández-Torres and C. F. Barbas, *J. Am. Chem. Soc.*, 2011, **133**, 12354–12357.
22 U. Pindur, M. H. Kim, M. Rogge, W. Massa and M. Molinier, *J. Org. Chem.*, 1992, **57**, 910–915.
23 L. J. Watson, R. W. Harrington, W. Clegg and M. J. Hall, *Org. Biomol. Chem.*, 2012, **10**, 6649–6655.
24 L. J. Cotterill, R. W. Harrington, W. Clegg and M. J. Hall, *J. Org. Chem.*, 2010, **75**, 4604–4607.
25 L. Pfeuffer and U. Pindur, *Helv. Chim. Acta*, 1988, **71**, 467–471.
26 K. Suzuki, K. Inomata and Y. Endo, *Org. Lett.*, 2004, **6**, 409–411.
27 G. A. Kraus and J. Kim, *Org. Lett.*, 2004, **6**, 3115–3117.
28 R. B. Ruggeri, M. M. Hansen and C. H. Heathcock, *J. Am. Chem. Soc.*, 1988, **110**, 8734–8736.
29 D. Li, Y. Cao, A. Shi and Z. Xi, *Chem.–Asian J.*, 2011, **6**, 392–395.
30 D. G. Hingane, S. K. Goswami, V. Puranik and R. S. Kusurkar, *Synth. Commun.*, 2011, **42**, 1786–1795.
31 B. t. Joseph, M. Facompré, H. Da Costa, S. Routier, J.-Y. Mérour, P. Colson, C. Houssier and C. Bailly, *Bioorg. Med. Chem.*, 2001, **9**, 1533–1541.
32 B. Saroja and P. C. Srinivasan, *Synthesis*, 1986, **1986**, 748–749.
33 X. Zhang, S. I. Khan and C. S. Foote, *J. Org. Chem.*, 1993, **58**, 7839–7847.
34 P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289–296.
35 J. Robertson, M. J. Hall, P. M. Stafford and S. P. Green, *Org. Biomol. Chem.*, 2003, **1**, 3758–3767.
36 L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136.
37 C. J. Lovely, H. Du, Y. He and H. V. Rasika Dias, *Org. Lett.*, 2004, **6**, 735–738.
38 N. Uludag and S. Patir, *J. Heterocycl. Chem.*, 2007, **44**, 1317–1322.
39 P. Magnus, N. L. Sear, C. S. Kim and N. Vicker, *J. Org. Chem.*, 1992, **57**, 70–78.
40 R. Yang and F. G. Qiu, *Angew. Chem., Int. Ed.*, 2013, **52**, 6015–6018.

