University of Southampton

Faculty of Engineering and Physical Sciences

School of Chemistry

The Total Synthesis of Indolocarbazole Natural Products and towards the Synthesis of (+)-Sparteine

by

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Thesis for the degree of Doctor of Philosophy

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Abstract

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The indolocarbazole alkaloids are a diverse family of natural products including staurosporine, K252a, K252d, rebeccamycin and the staurosporine aglycone. Whilst these alkaloids have been of medicinal interest in the past, most notably as protein kinase C inhibitors, recent studies have detailed inhibition of cancer stem cell formation. This is best exemplified with the FDA approval of Midostaurin©, a derivative of staurosporine, for treatment of acute myeloid leukaemia in 2017.

This thesis describes the synthetic advances towards indolocarbazole natural products, culminating in the syntheses of the staurosporine aglycone, arcyriaflavin A and the first total synthesis of K252d and its previously unknown β-anomer.

The development of the synthetic strategy is described, first exploring a photochemical cyclisation in flow applied to the synthesis of arcyriaflavin A and the staurosporine aglycone. Application of the Tsuji-Trost reaction for the glycosylation of indoles, and ensuing McMurry cyclisation and Barton-Zard pyrrole synthesis approaches were explored before the first total synthesis of K252d is described in 4% over 6 steps, utilising a Mannich-type cyclisation and indoline glycosylation. The previously unknown β-anomer was also accessed in a 1:1 ratio, and the approach presents a regioselective method to functionalise the staurosporine aglycone circumventing the need for protecting group chemistry. The approach is applied to the staurosporine aglycone in 16% yield over 5 steps.

The synthesis towards (+)-sparteine, a lupin alkaloid isolated from the papilionaceous plant species, is enclosed. The approach utilises an imino-aldol reaction with an *N*-sulfinylimine before a subsequent *anti*-selective alkylation to give *anti*-products with good diastereoselectivity (*dr* = 10:1). Progress towards (+)-sparteine utilising a cross-metathesis to install the allyl silane moiety and Mitsonobu reaction to install the glutarimide moiety is also disclosed.

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Research Thesis: Declaration of Authorship

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I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

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Definitions and Abbreviations

$[\alpha]_D$	Alpha D
°C	Degrees Celsius
Ac	Acetyl
AcOH	Acetic Acid
ADDP	1,1'-(Azodicarbonyl)dipiperidine
ADP	Adenosine diphosphate
Aq	Aqueous
atm	Atmosphere
ATP	Adenosine triphosphate
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BOM	Benzyloxymethyl
br	Broad
Bu	Butyl
ca.	Circa
Cbz	Benzyloxycarbonyl
CM	Cross Metathesis
Conc.	Concentrated
CSA	Camphor sulfonic acid
d	Doublet
d.r.	Diastereomeric ratio
DAG	1,2-Diacylglycerol
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate

DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)-pyridine
DMB	Dimethoxybenzene
DMF	*N,N'*-dimethylformamide
DMSO	Dimethylsulfoxide
e.e.	Enantiomeric excess
EI	Electron ionisation
Equiv.	Molar Equivalents
ESI	Electrospray Ionisation
Et	Ethyl
FLT3	FMS-like tyrosine kinase 3
FMS	Feline McDonough Sarcoma
FT	Fourier Transform
g	Gram
GC	Gas Chromatography
h	Hour(s)
HRMS	High-resolution Mass Spectrometry
IP_3	Inositol triphosphate
IR	Infrared
J	Coupling Constant
K	Kelvin
L	Litre
LDA	Lithium diisopropylamide
LRMS	Low-resolution Mass Spectrometry
m	Multiplet
***m*CPBA**	*meta*-Chloroperoxybenzoic acid

Me	Methyl
min	Minute(s)
mmol	Millimole(s)
MS	Mass Spectrometry
Ms	Mesyl
MW	Molecular Weight
NBS	N-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
p	Para
Ph	Phenyl
PIP_2	Phosphatidylinositol-4,5-biphosphate
PKC	Protein Kinase C
ppm	Parts per million
Pr	Propyl
PTSA	*para*-Toluenesulfonic acid
Py	Pyridine
q	Quartet
RCM	Ring Closing Metathesis
rt	Room Temperature
s	Singlet
sat.	Saturated
SEM	2-(Trimethylsilyl)ethoxymethyl
t	Triplet
t	Tertiary
T	Temperature
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide

Teoc	2-(Trimethylsilyl)ethoxycarbonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl
UCN-01	7-Hydroxystaurosporine
Δ	Heating to reflux

Chapter 1 Indolocarbazole Natural Products

1.1 Introduction

1.1.1 Indolocarbazoles

The indolocarbazoles are a family of heterocyclic natural products consisting of a carbazole core fused to an indole through its pyrrole ring. There are several indolocarbazole isomers, of which the five most commonly isolated are the 11,12-dihydroindolo-[2,3-*a*]-carbazole (**1.01**), 5,7-dihydroindolo-[2,3-*b*]carbazole (**1.02**), 5,8-dihydroindolo-[2,3-*c*]-carbazole (**1.03**), 5,12-dihydroindolo-[3,2-*a*]-carbazole (**1.04**) and the 5,11-dihydroindolo-[3,2-*b*]-carbazole (**1.05**, figure 1).[1–5]

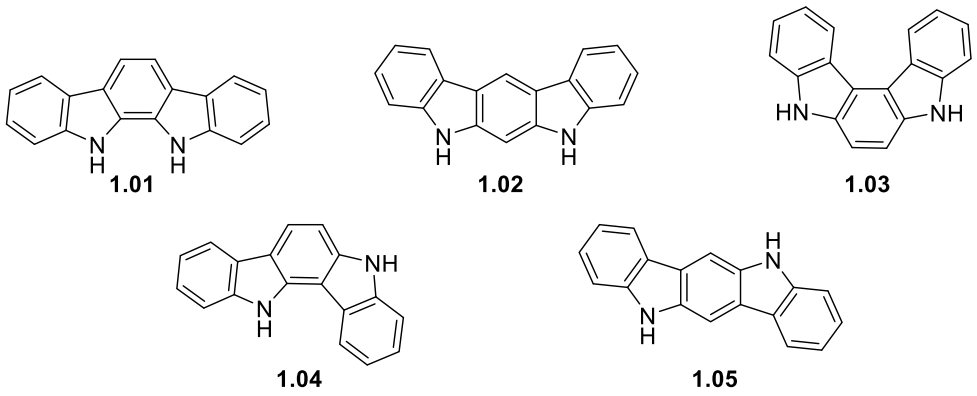


Figure 1 The indolocarbazole isomers.

The most widely investigated of these isomers is the 11,12-dihydroindolo-[2,3-*a*]-carbazole (**1.01**), and in particular a sub-family known as the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole (**1.06**) derivatives (figure 2). This broad family of natural products includes compounds both with and without indolic functionalisation, and ascended to prominence in the early 1990's after discovery of interesting biological activities associated with these compounds, most notably their nanomolar inhibition of protein kinase C (PKC).[4–6]

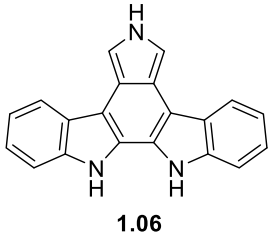


Figure 2 An isomer of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole.

1.1.2 The indolocarbazole alkaloids and their discovery

In 1977, Omura and co-workers' isolated a novel alkaloid, then named AM-2282, from the bacterium *Streptomyces staurosporeus*.[7] Preliminary testing of the alkaloid revealed strong hypotensive activity as well as antimicrobial activity against fungi and yeast. Considerable structural elucidation studies ensued, with confirmation of the structure by X-ray crystallography as an indolocarbazole core bearing two glycosyl linkages at the indolic nitrogens. AM-2282 was subsequently renamed staurosporine (**1.07**, figure 3).[8,9]

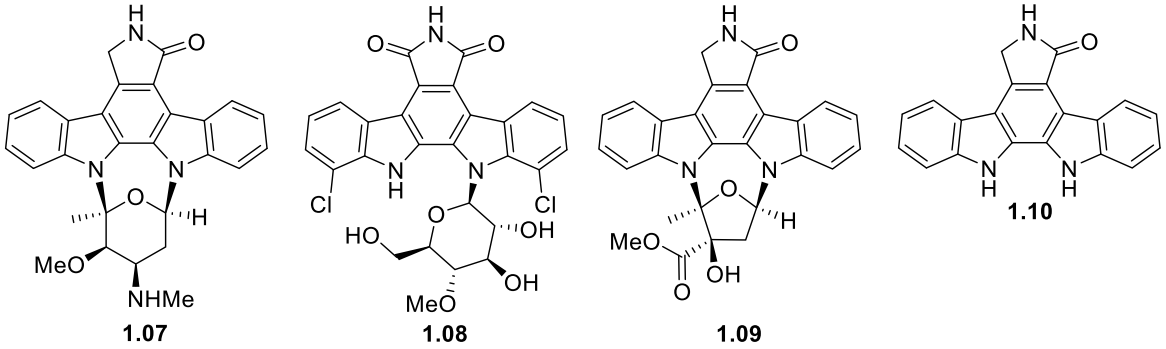


Figure 3 Structure of staurosporine (**1.07**), rebeccamycin (**1.08**), K252a (**1.09**) and staurosporine aglycone (**1.10**).

In 1985, Clardy and co-workers' isolated the first halogenated indolocarbazole, rebeccamycin (**1.08**, figure 3), and later that year, Sezaki and co-workers' reported another indolocarbazole alkaloid.[8,9] This subsequently became known as (+)-K252a (**1.09**) when Kase and co-workers' isolated several more compounds bearing the indolocarbazole core, including the staurosporine aglycone (**1.10**), thus beginning the preliminary interest in this exciting class of natural products.[10–12]

Various indolocarbazole natural products were subsequently isolated from marine sources, soil organisms and slime moulds,[13] and the isolation and discovery of these natural products has been the subject of several extensive reviews.[13–16] However the pivotal development in the indolocarbazole story was the realisation of the potential of these natural products as therapeutic agents, in particular their high potency as inhibitors of protein kinase C (PKC).[4–6,17,18]

1.1.3 Interest in indolocarbazoles as PKC inhibitors

1.1.3.1 The role of PKC and how it functions

Protein kinase C is a family of serine and threonine specific kinases and their role in signal cell transduction via the phosphorylation of specific proteins has been extensively studied.[19] An agonist, usually a hormone, begins the process by binding to an extracellular surface

receptor. This binding event then activates phospholipase C, either by direct phosphorylation if the receptor is a tyrosine-specific kinase, or alternatively via a G-protein. Phospholipase C then cleaves a molecule of phosphatidylinositol-4-5-biphosphate (PIP_2) bound to the membrane to give a molecule of inositol triphosphate (IP_3) and leaves behind a molecule of 1,2-diacylglycerol (DAG) in the membrane. The cleaved IP_3 triggers release of Ca^{2+} stored in the endoplasmic reticulum, which in conjunction with the DAG molecule activates PKC, leads to phosphorylation of specific threonine or serine residues in the target protein and ultimately regulates various cellular responses including gene expression, cell proliferation and inflammatory response (figure 4).

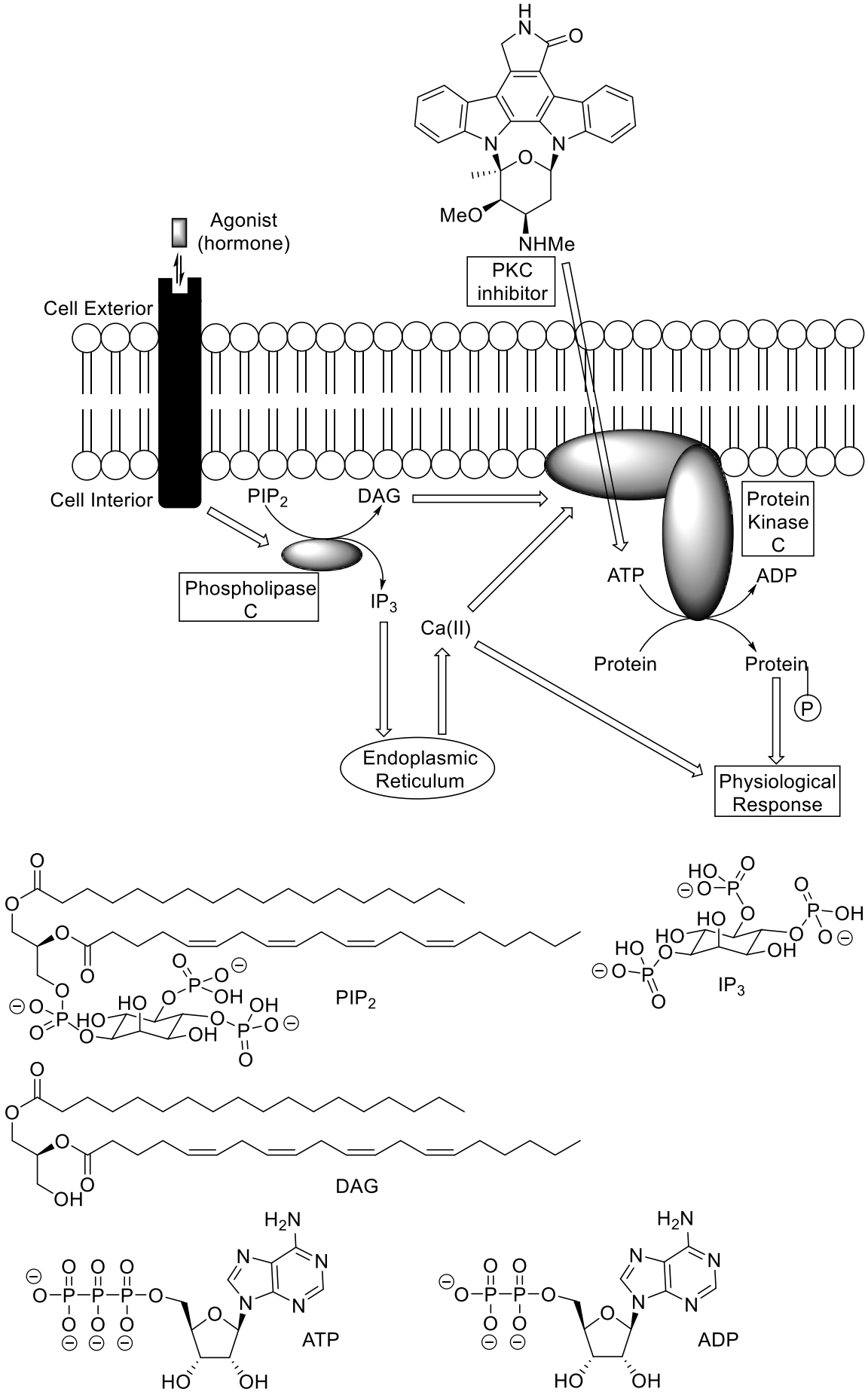


Figure 4 Protein kinase C-mediated signal transduction pathway.

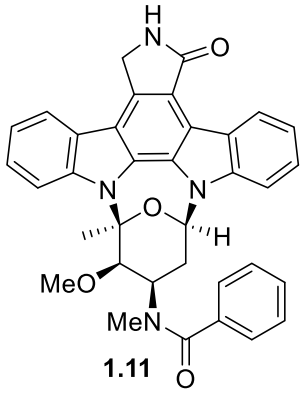
1.1.3.2 The role of indolocarbazoles

The indolocarbazoles are some of the most potent inhibitors of PKC to date. K252a (**1.09**) was reported to exhibit nanomolar inhibition of PKC (IC_{50} = 32 nM), whilst staurosporine (**1.07**) was reported to have the greatest inhibitory power (IC_{50} = 2.7 nM). They presumably act by blocking the ATP binding site in the kinase, with staurosporine (**1.07**) shown to have several binding sites overlap with ATP.[5] This inhibitory activity coupled with the pivotal role of protein phosphorylation in a cell lifecycle, led to a flurry of research into indolocarbazoles over the following 20-30 years.

1.2 Staurosporine applied to cancer therapeutics

1.2.1 Midostaurin and approved indolocarbazole treatments

The interest culminated in the FDA approval of Midostaurin© (**1.11**), a derivative of staurosporine (**7**), for the treatment of acute myeloid leukaemia (AML) in 2017. AML is the most common acute leukaemia in adults, with an annual death rate in the US of over 10000.[20] However, when we consider Midostaurin© (**1.11**) was approved not due to its inhibitory activity against PKC, but instead due to its inhibitory activity on FLT3 kinase, this highlights the indolocarbazoles as attractive potential therapeutics beyond PKC related pathways.



1.11

Figure 5 Structure of AML treatment Midostaurin© (**1.11**).

1.2.2 Proposed mechanism and ongoing work in the field

Current strategies for cancer treatment dictate identification of a biological pathway and inhibition of a target enzyme. As mentioned Midostaurin© (**1.11**) was approved due to its inhibitory activity on FMS-like tyrosine kinase 3 (FLT3), a protein kinase that acts as a cell-surface receptor and regulates cell differentiation, proliferation and decreases apoptosis.[21–

[26] Midostaurin© (**1.11**) was approved for use as a biomarker and to help prognosticate AML, however studies detailed efficacy in both FLT3 wild-type and mutated subgroups, indicating a clinical utility beyond its role as a biomarker.[27,28] Similar observations were also made with 7-hydroxystaurosporine (UCN-01) during early phase clinical trials, furthering the therapeutic interest in indolocarbazoles.[29]

In recent years, the interest in cancer stem cell therapies has led to targeted therapies for cancer metathesis. PKC inhibitors have been identified as specific inhibitors of cancer stem cell formation, both *in vitro* and *in vivo*.[30,31] Future therapies may involve indolocarbazoles, both natural and non-natural, and efficient approaches will be paramount to advances.

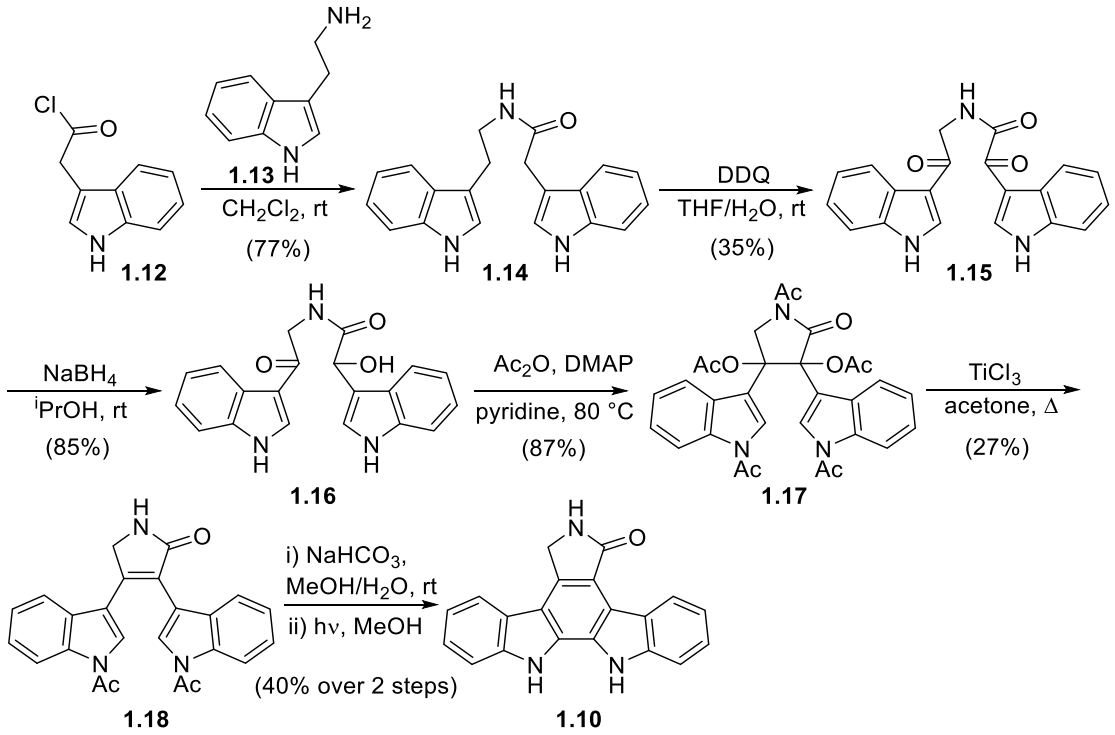
1.3 Syntheses of indolocarbazole natural products

1.3.1 Indolocarbazole natural products bearing no indolic functionalisation

1.3.1.1 Staurosporine aglycone (1.10)

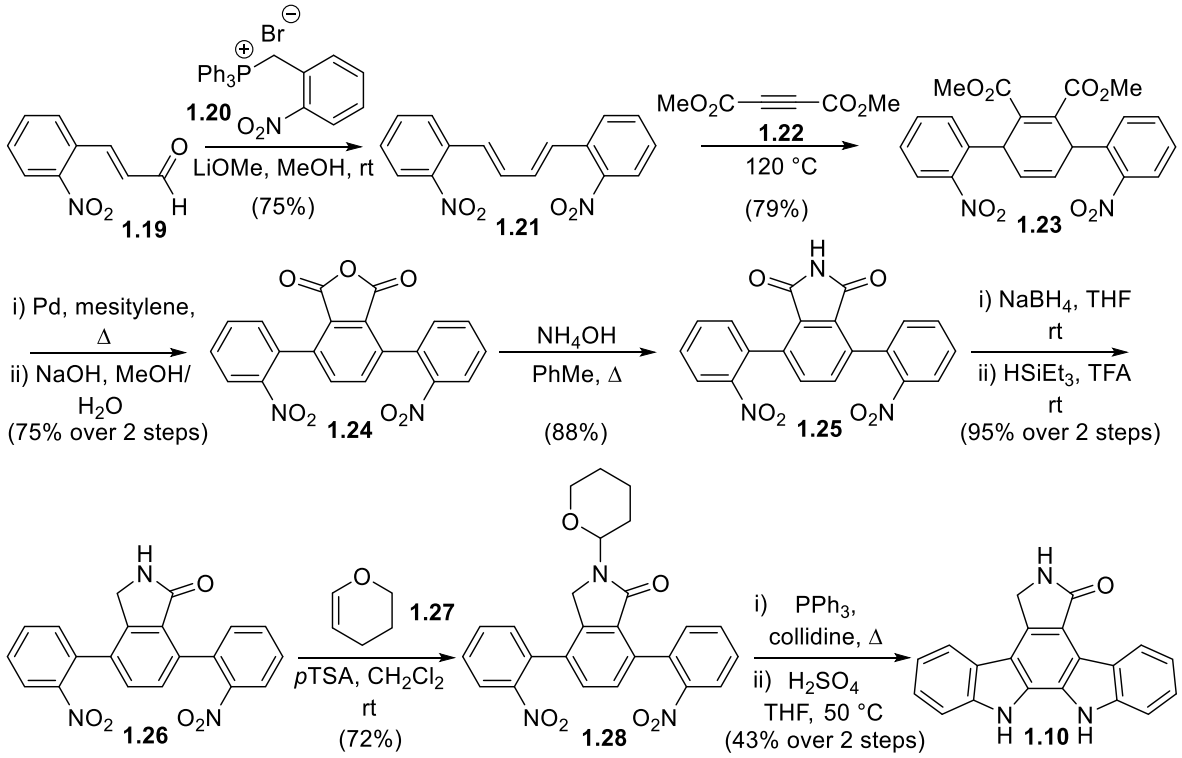
The tale of synthetic indolocarbazoles begins with the most popular natural product in the family, the staurosporine aglycone (**1.10**), also commonly referred to as K252c and staurosporinone. Devoid of functionalisation on the indolic nitrogens, this presents a less complex challenge than many of its glycosylated relatives, however serves as an excellent handle for further functionalisation in the construction of derivatives. This chapter will focus on a few specific syntheses of the aglycone (**1.10**), with extensive coverage of this natural product covered in our recently published review.[32]

The first synthesis of the staurosporine aglycone (**1.10**) was carried out by Winterfeldt and co-workers' in 1983 (scheme 1).[33] The synthesis began with acylation of tryptamine (**1.13**) to give amide (**1.14**). Benzylic oxidation with DDQ preceded a regioselective reduction of the most electron deficient ketone to give hydroxyketone **1.16**. Acylation was accompanied with cyclisation to pentaacetate **1.17**, which only underwent cyclisation to lactam **1.18** in appreciable yields when treated with $TiCl_3$.[34] Deacylation was followed by photochemical cyclisation to yield the aglycone (**1.10**) in moderate yield. Winterfeldt's approach, in particular the photochemical cyclisation, was significant and paved the way for many future approaches to the indolocarbazoles.



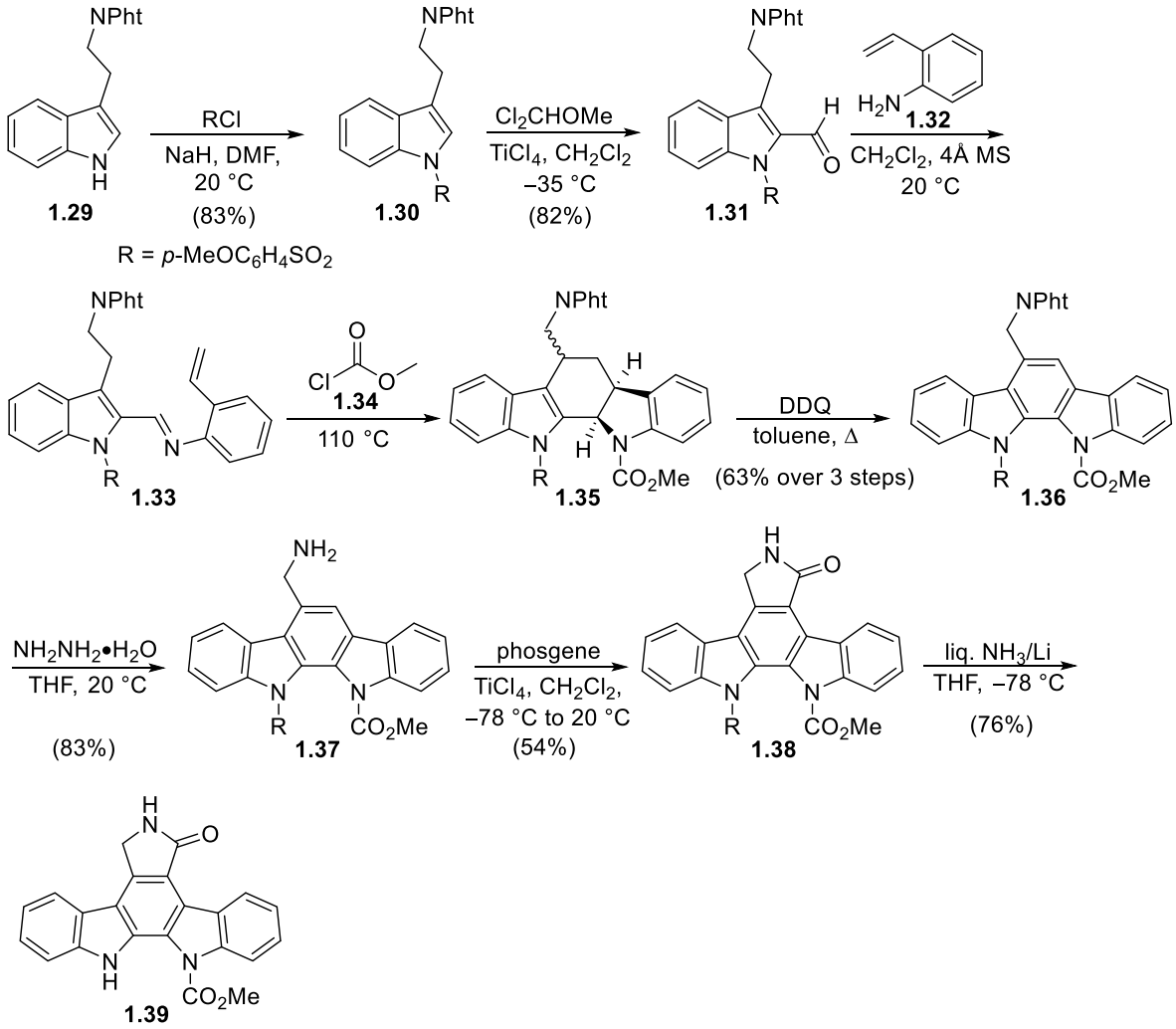
Scheme 1 Winterfeldt and co-workers' synthesis of the staurosporine aglycone (**1.10**).

After much of the biological activity of these natural products was discovered, there was a dramatic increase in interest and synthetic approaches. In 1983, Raphael and co-workers' developed a Diels-Alder/C-H insertion approach to the aglycone (**1.10**, scheme 2).[35] The initial approach led to the *N*-benzyl protected aglycone, however they could not remove the benzyl group at the end of the synthesis.[36] The full approach to the unprotected aglycone (**1.10**) was published later in 1990 and began with a Wittig reaction between 2-nitrocinnamaldehyde (**1.19**) and phosphonium salt **1.20** to give butadiene **1.21**. The ensuing Diels-Alder with dimethylacetylenedicarboxylate (**1.22**) gave the skipped diene which was subjected to aromatisation and hydrolysis/annulation to give anhydride **1.24**. Conversion of anhydride **1.24** to maleimide **1.25** was achieved with aqueous ammonia before the non-trivial sequential reduction gave lactam **1.26**.[37–39] The lactam *N*-H was then protected with dihydropyran (**1.27**) before a double nitrene insertion using methodology developed by Cadogan, and a final deprotection gave the aglycone (**1.10**). In particular, this final double nitrene insertion proved a popular method to install the carbazole moiety in many subsequent syntheses, and this *N*-H protection is interesting as it presents an early example of forming a glycosylated indolocarbazole.



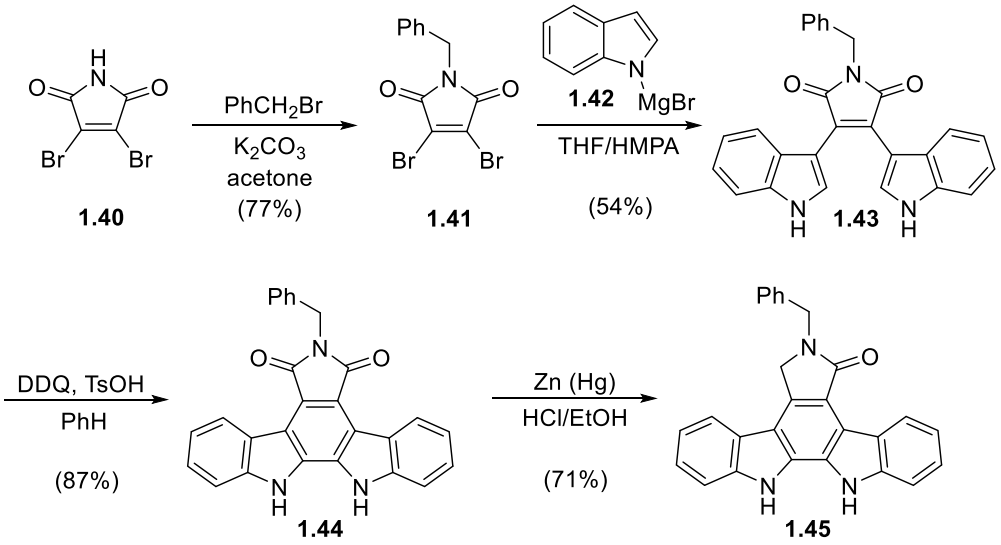
Scheme 2 Raphael and co-workers' synthesis of the staurosporine aglycone (**1.10**).

The following year Magnus and co-workers' also reported the synthesis of the aglycone (**1.10**), utilising an intramolecular Diels-Alder to install the key pentacyclic framework.[40] The synthesis began with the standard conversion of tryptamine to phthalimido derivative **1.29**.[41] Protection of the indole preceded formylation to 2-formyl indole **1.31**. Condensation with 2-aminostyrene (**1.32**) was followed by the key intramolecular Diels-Alder before dehydrogenation with DDQ gave indolocarbazole **1.36**. The phthalimido group was removed with hydrazine hydrate before acylation with phosgene gave protected indolocarbazole **1.38**. Finally, reductive cleavage of the *p*-methoxypenylsulfonyl group under Birch conditions delivered mono-protected staurosporine aglycone **1.39**, and for the first time allowed for differentiation of the indolic nitrogens.



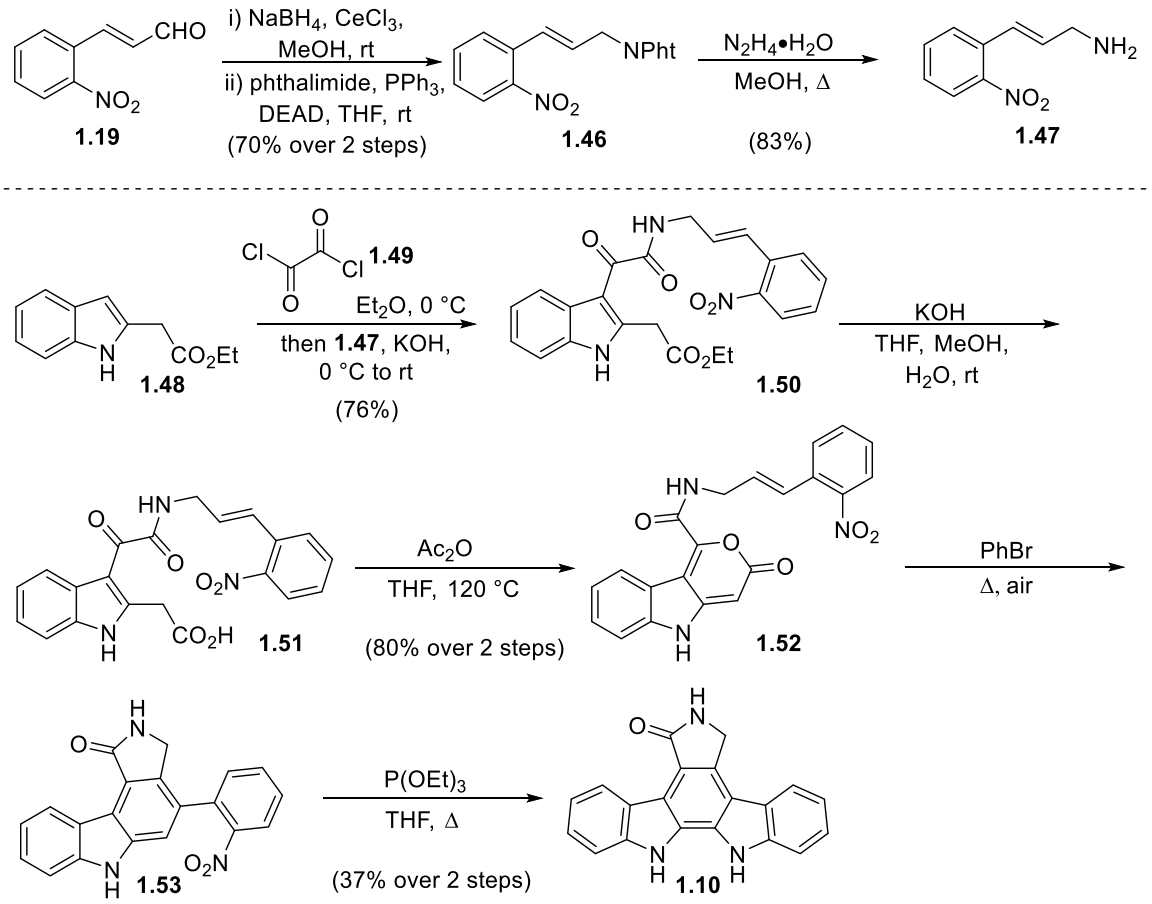
Scheme 3 Magnus and co-workers' synthesis of the protected staurosporine aglycone **1.39**.

In 1987, during their studies into both the aglycone and monosaccharide moieties of staurosporine (**1.07**), Weinreb and co-workers' utilised a modification of methodology described by Steglich and co-workers' to isolate *N*-benzyl protected staurosporine aglycone **1.45** (scheme 4).[42–44] Dibromomaleimide (**1.40**) was *N*-benzylated before treatment with excess magnesiated indole (**1.42**) gave the *N*-benzyl bisindolylmaleimide **1.43**. An alternative oxidative cyclisation with TsOH/DDQ installed the indolocarbazole core, before a Clemmensen reduction afforded the target aglycone derivative **1.45**.[35,44] The approach is notable for its brevity, and the use of magnesiated indoles and maleimides became a popular strategy to access the bisindolylmaleimide framework.



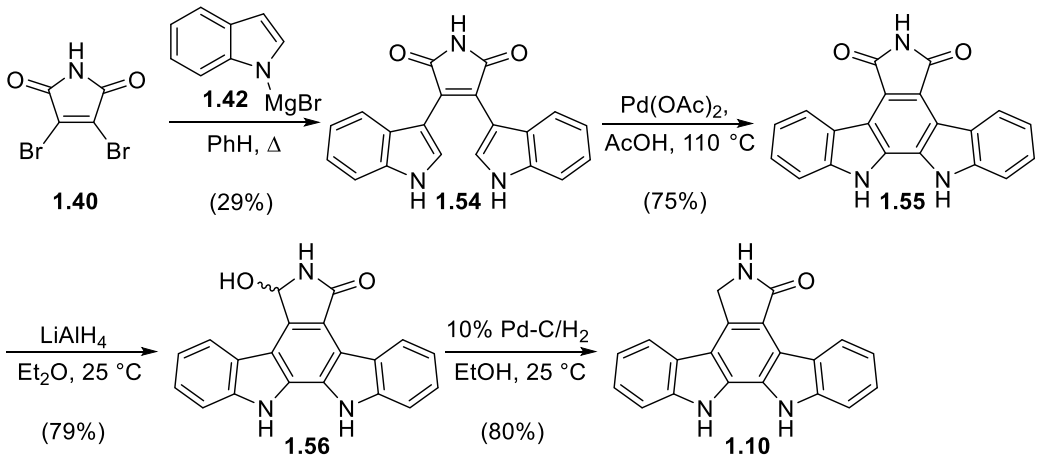
Scheme 4 Weinreb and co-workers' synthesis of *N*-benzyl protected aglycone **1.45**.

The first protecting group free synthesis was completed by Moody and co-workers' in 1990 (scheme 5).[45,46] The approach centred on an intramolecular Diels-Alder decarboxylation sequence from pyranone **1.52**. Allylic amine fragment **1.47** was prepared in 3 steps from the enal **1.19** by Luche reduction followed by coupling with phthalimide under Mitsonobu conditions and hydrazinolysis. Friedel Crafts acylation of indole **1.48** with oxalyl chloride (**1.49**) and trapping with allylic amine **1.47** gave the *α*-ketoamide **1.50**.[47,48] Ester hydrolysis and cyclisation with acetic anhydride provided pyranone **1.52**, which upon refluxing open to air, gave the desire carbazole core **1.53**. Application of Raphael's deoxygenative nitrene insertion with triethyl phosphite completed the synthesis in moderate overall yield (8% over 9 steps from enal **1.46**).[49] The approach highlights carbazole **1.53** as a useful intermediate for differentiation of the indolic nitrogens, however limitations in the synthesis arise due to the forcing thermal conditions required for the nitrene insertion.



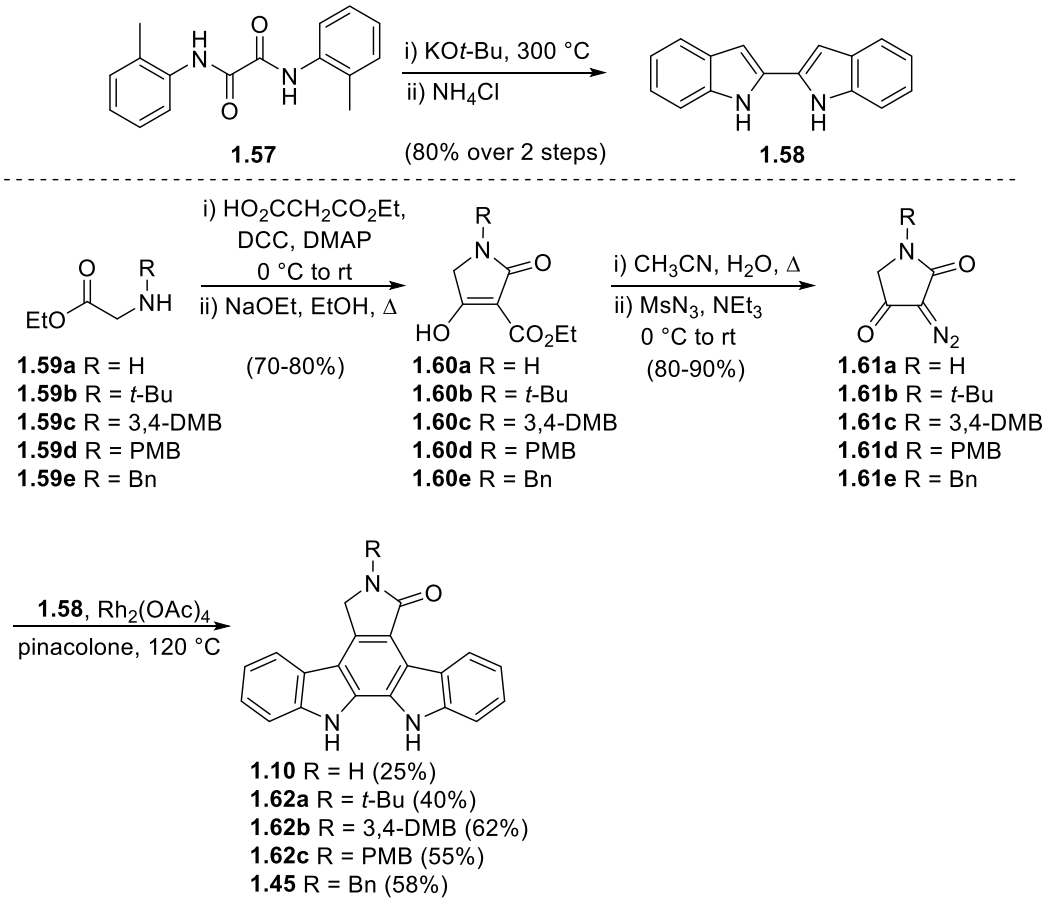
Scheme 5 Moody and co-workers' synthesis of the staurosporine aglycone (**1.10**).

Hill and co-workers' built upon the methodology developed by Steglich and later Weinreb, coupling dibromomaleimide (**1.40**) with magnesiated indole (**1.42**) to access bisindolylmaleimide (**1.55**, scheme 6).[42,44] DDQ/TsOH mediated cyclisation proved difficult, but the novel palladium acetate mediated oxidative cyclisation gave arcyriaflavin A (**1.55**), before a two-step reduction/hydrogenolysis gave the natural aglycone (**1.10**) in only 4 synthetic operations, the shortest synthesis at that time.[44,50]



Scheme 6 Hill and co-workers' synthesis of the staurosporine aglycone (**1.10**).

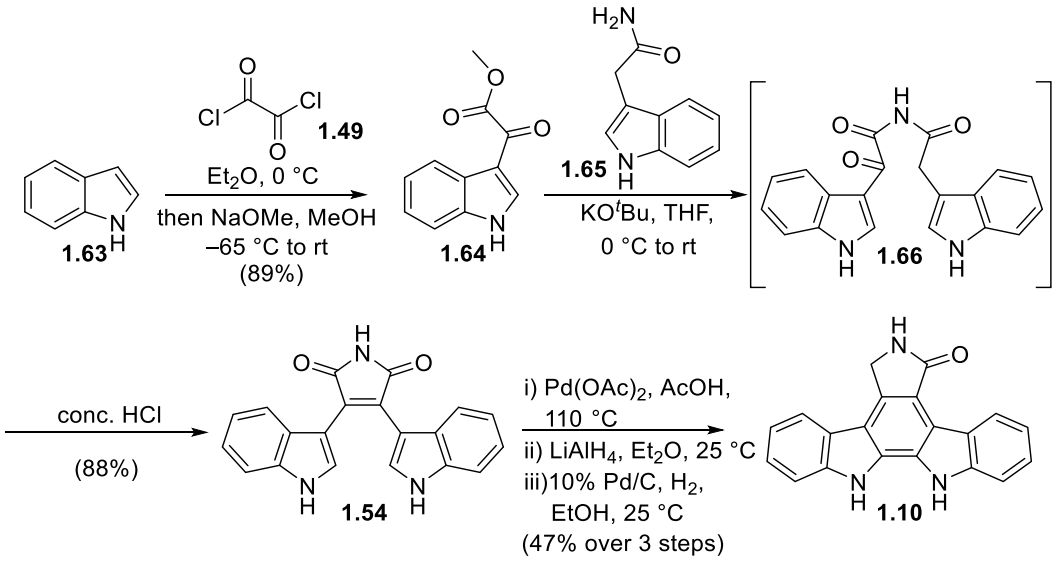
In 1995, during their pioneering studies into the indolocarbazole natural product family, Wood and co-workers' developed a novel approach to both the staurosporine aglycone (**1.10**) and a selection of protected derivatives (**1.62a**-**1.62c**, **1.45**).[51,52] The approach centred upon the addition of diazo-lactams **1.61a-e** to 2,2'-biindole (**1.58**), prepared by double-Madelung cyclisation of diamide **1.57**.[53] The diazotetramic acids were prepared using a 4 step protocol from the *N*-substituted glycine esters **1.59a-e**.[54,55] Amide coupling of the esters with ethyl hydrogen malonate followed by Dieckmann cyclisation gave lactams **1.60a-e**. The lactams were subjected to a single pot decarboethoxylation/diazo-transfer reaction to give diazotetramic acids **1.61a-e**. Finally, a novel diazo-addition in degassed pinacolone gave access to the aglycone (**1.10**) and non-natural derivatives **1.62a-e** and **1.45**.



Scheme 7 Wood and co-workers' synthesis of the staurosporine aglycone (**1.10**) and protected derivatives.

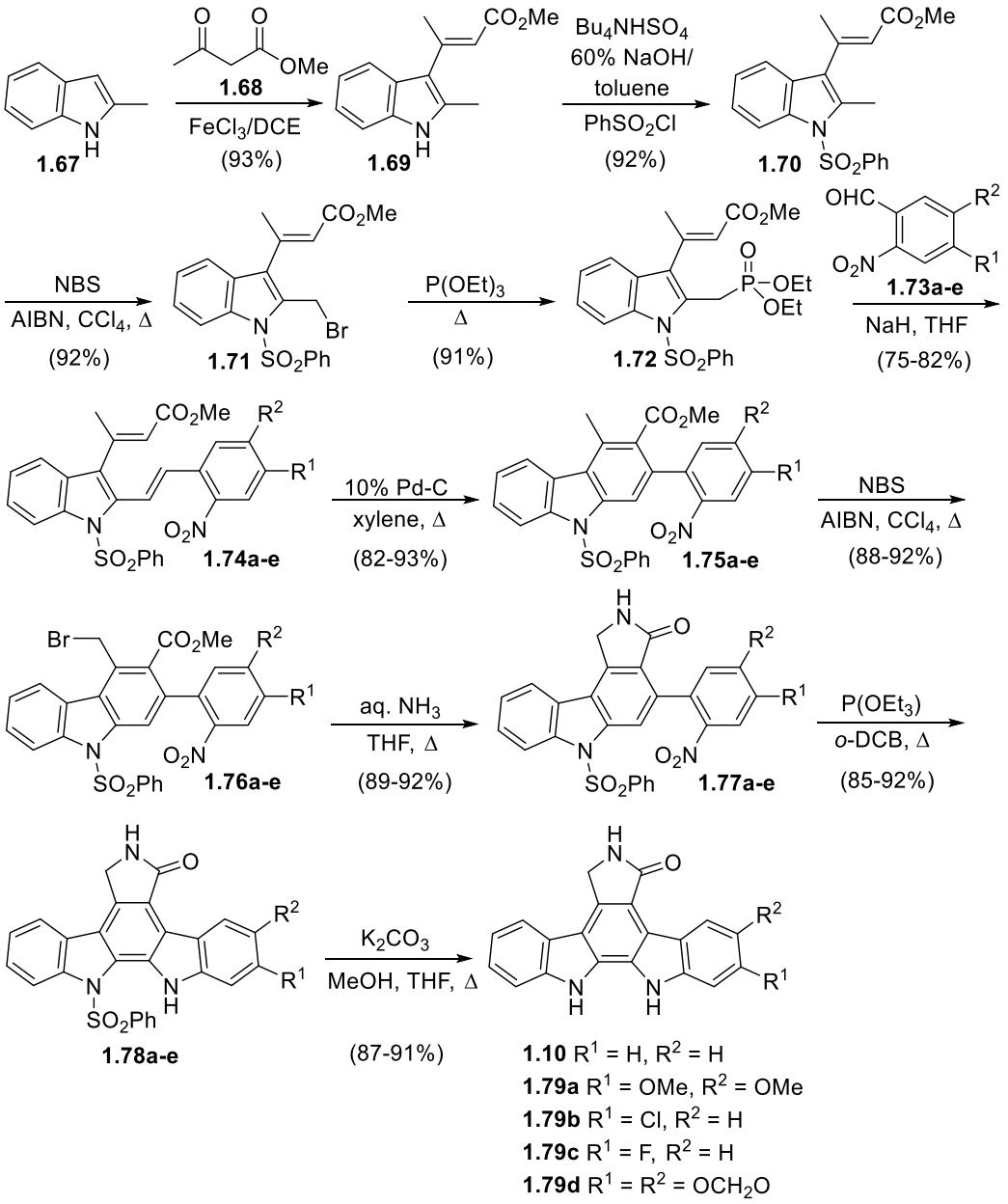
With a view to access multi-gram quantities of bisindolylmaleimide (**1.54**) for PKC-*β* inhibitor studies, Faul and co-workers' developed a novel approach that was centred on the Perkin-type condensation of amide **1.65** to access bisindolylmaleimide (**1.54**, scheme 8).[56–58] This was then subjected to the oxidative cyclisation/reduction/hydrogenation protocol described by Hill and co-workers' to access the aglycone (**1.10**). This approach represents the highest

yielding (36% over 5 steps) synthesis of the aglycone (**1.10**) to date, and was extended to a variety of bisindolylmaleimide and arcyriaflavin A analogues.



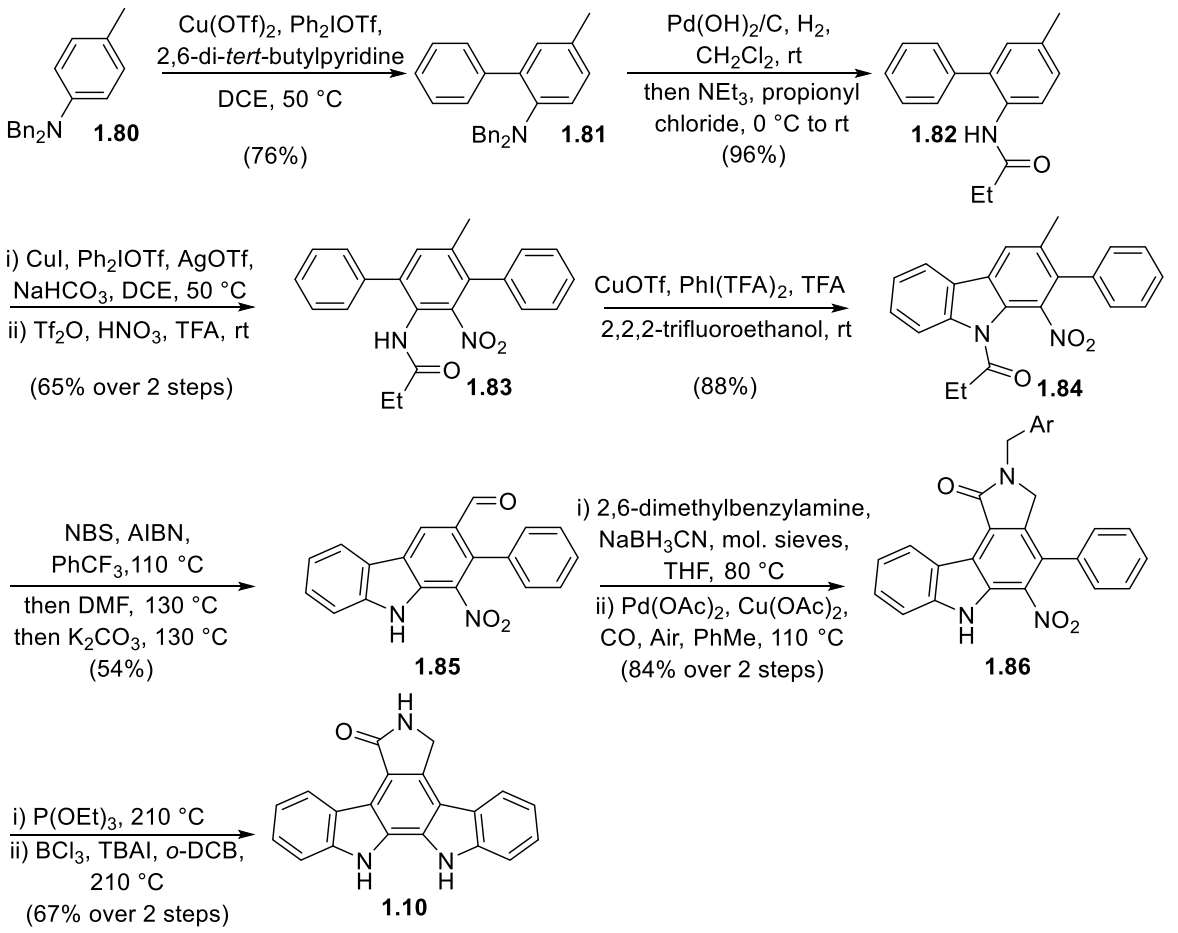
Scheme 8 Faul and co-workers' approach to the staurosporine aglycone (**1.10**).

Fast forward to 2011, and Mohanakirshnan and co-workers' published a route to various aglycone derivatives starting from 2-methylindole (**1.67**, scheme 9).[59] Reaction with ethyl acetoacetate (**1.68**) gave vinylindole **1.69** before subsequent protection with the phenylsulfonyl group gave indole **1.70**.[60] Allylic bromination preceded the Michaelis-Arbuzov reaction with triethyl phosphite to give phosphonate ester **1.72** upon work-up. This was subjected to a Wittig-Horner reaction with a variety of divinylindoles **1.73a**-**e**, which underwent electrocyclisation/aromatisation with Pd/C to afford carbazoles **1.75a**-**e**.[61] Benzylic bromination and subsequent reaction with aqueous ammonia gave amides **1.77a**-**e**. Cadogan's triethyl phosphite mediated nitrene insertion was employed to install the indolocarbazole core before a final deprotection gave access to the aglycone (**1.10**) and various derivatives **1.79a**-**d**. Later, in 2015, the same group used the approach to synthesise a variety of analogues of the staurosporine aglycone (**1.10**).[59,62]



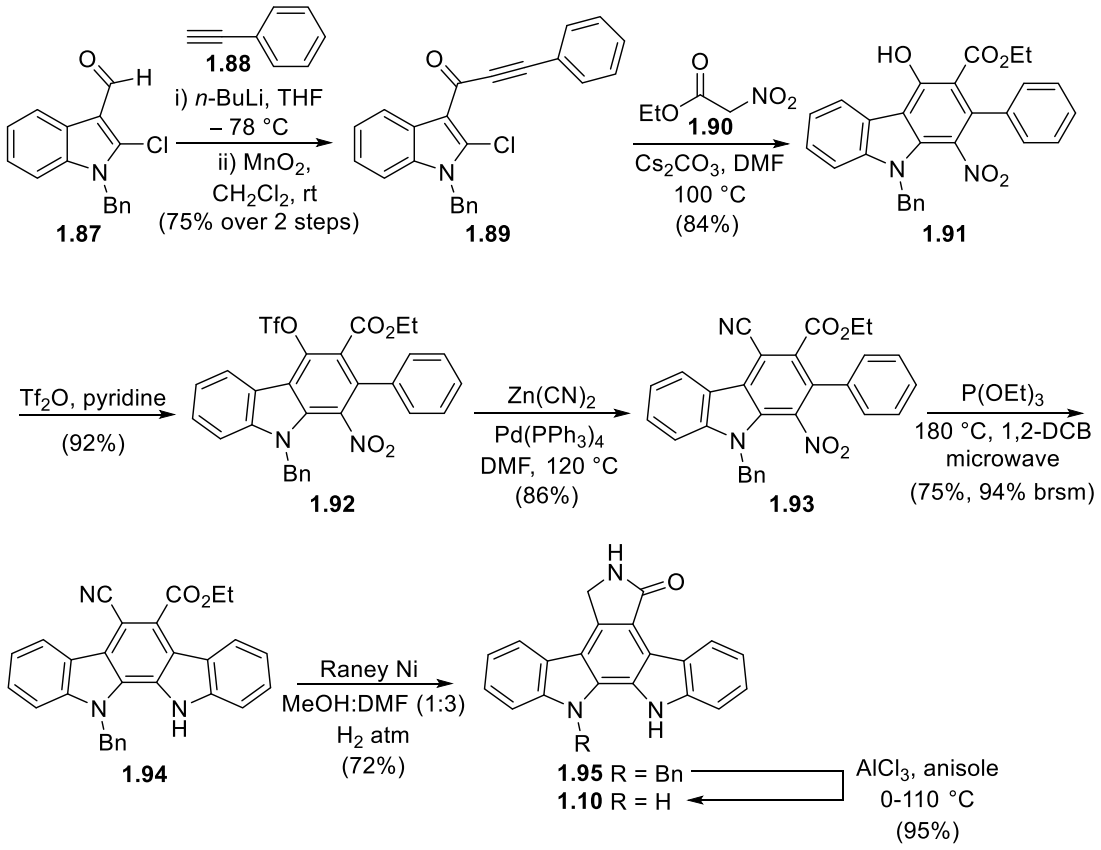
Scheme 9 Mohanakrishnan and co-workers' synthesis of staurosporine aglycone derivatives.

Gaunt and co-workers', in 2016, developed an approach centred on sequential C-H functionalisations, utilising the amine moiety in the central ring as the key directing group in four out of the seven key transformations (scheme 10).[63] *Ortho*-arylation of aniline **1.80** was followed by hydrogenolysis and carbamoylation to switch the directing nature of the group and give anilide **1.82**.[64,65] A subsequent *meta*-arylation followed by nitration gave nitro-arene **1.83**, which underwent copper mediated oxidative cyclisation to carbazole **1.84**.[66] A one pot radical bis-bromination, formylation and concomitant cleavage of the carbazole *N*-protecting group installed aldehyde **1.85**.[67] A reductive amination, C-H carbonylation gave γ-lactam **1.86**, before utilisation of Cadogan's nitrene insertion chemistry and a final *N*-debenzylation gave the staurosporine aglycone (**1.10**). [36,49,68–70]



Scheme 10 Gaunt and co-workers' synthesis of the staurosporine aglycone (**1.10**).

To date, the most recent synthesis of the staurosporine aglycone (**1.10**) was completed by Pabbaraja and co-workers' in 2019 (scheme 11).[71] The synthesis began with addition of phenyl acetylene (**1.88**) to aldehyde **1.87** before oxidation to ynone **1.89**. This was then subjected to the key cascade sequence upon treatment with ethyl nitroacetate (**1.90**), yielding carbazole **1.91**.[72] The sequence was proposed to proceed *via* an initial Michael-addition before subsequent intramolecular aldol-type addition to access a strained cyclobutane intermediate. A retro-nitroaldol followed by generation of an indolic iminium ion led to the final C-C bond formation step and concomitant aromatisation to give the carbazole core **1.91**. Formation of the triflate **1.92** was followed by Negishi-coupling to give cyanated nitrocarbazole **1.93**.[73,74] Cadogan's reductive cyclisation was again employed before reduction and debenzylation gave the staurosporine aglycone (**1.10**).



Scheme 11 Pabbaraja and co-workers' synthesis of the staurosporine aglycone (**1.10**).

1.3.1.2 The arcyriaflavins

Structurally similar to the staurosporine aglycone (**1.10**), the arcyriaflavins feature the distinctive maleimide moiety fused to the indolocarbazole core. Steglich and co-workers' first isolated arcyriaflavins A-C (**1.55**, **1.96** and **1.97**) in 1980 from the *Arcyria nutans* and *Arcyria denudata* slime moulds.[42,75–77] Arcyriaflavin D (**1.98**) was isolated from a separate slime mould *Dictydiaethalium plumbeum*, whilst arcyriaflavin E (**1.99**) was isolated years later from the bacterium *Streptomyces cinnamoneus* NBRC 13823 by Abe and co-workers' in 2015 (figure 6).[78]

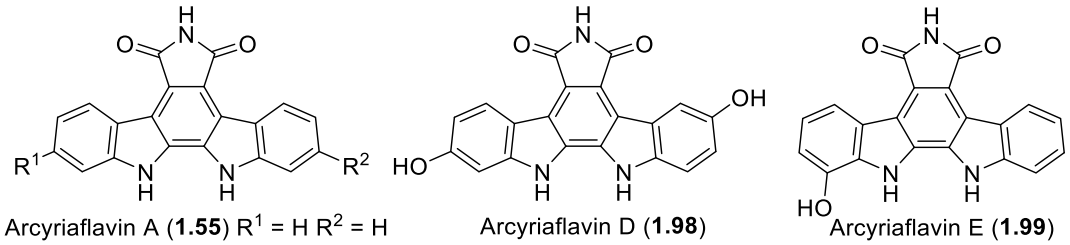
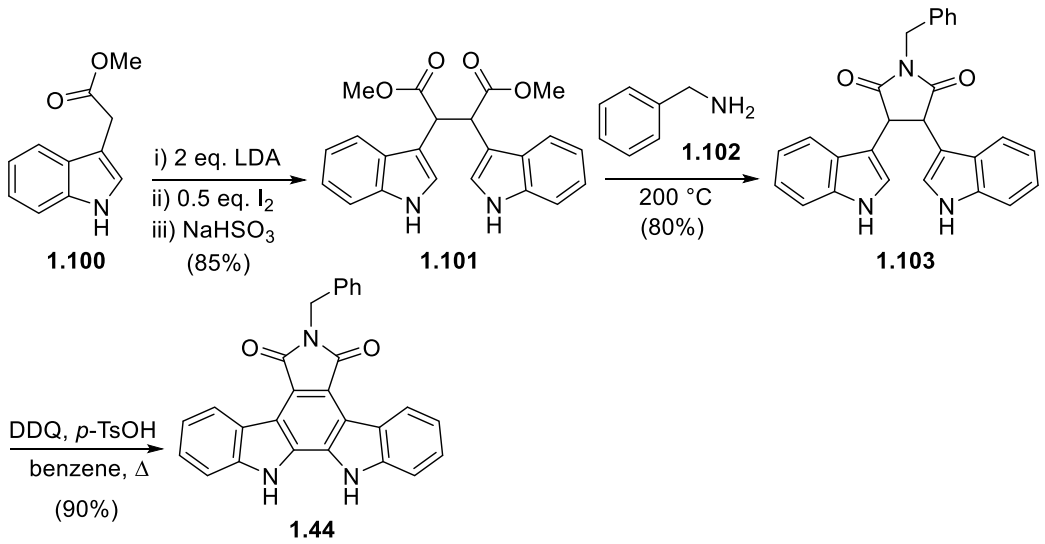


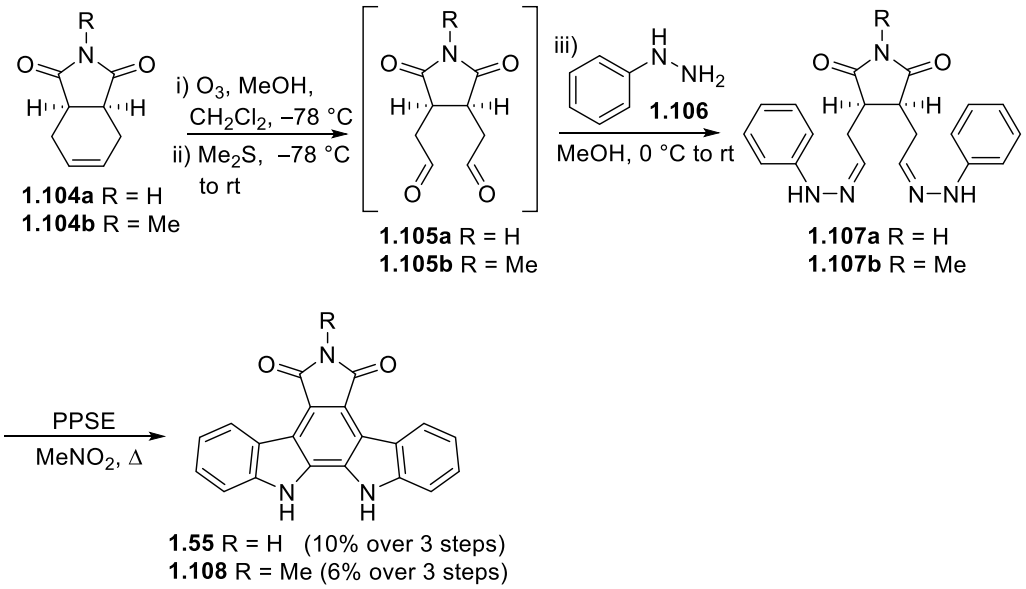
Figure 6: The structure of arcyriaflavins A-E (**1.55**, **1.96-1.99**).

The arcyriaflavins are popular synthetic targets. In particular, arcyriaflavin A has often been utilised as a key intermediate in the synthesis of more complex indolocarbazole natural products. Bergman and co-workers' completed the first synthesis of the *N*-benzyl derivative in 1987 (scheme 12).[79] The key step was the oxidative coupling methyl indol-3-ylacetate dianion to give diester **1.101** as a mixture of *di* and *meso* forms, which were easily separated by crystallisation and chromatography.[80–82] Their initial approach utilised the indol-3-ylacetate trianion, however it proved more fortuitous to proceed *via* the dianion. Diester **1.101** was then subjected to a double amidation with benzylamine (**1.102**) before an oxidative cyclisation gave the *N*-benzyl protected arcyriaflavin A (**1.44**).



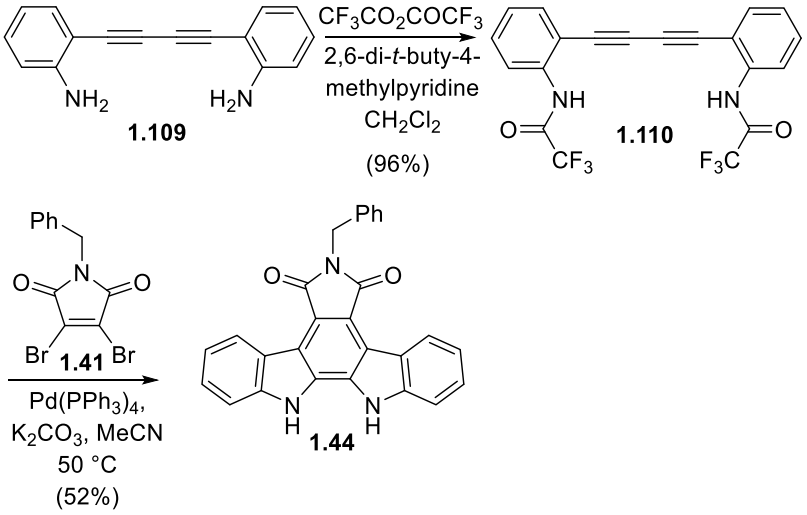
Scheme 12 Bergman and co-workers' synthesis of *N*-benzyl arcyriaflavin A (**1.44**).

Fisher indole based approaches were also commonly utilised to access arcyriaflavin A (**1.55**) and related derivative (**1.108**). Bergman, and later Gribble, both utilised a similar *bis*-hydrazone intermediate such as **1.107a** and **1.107b** in Gribble and co-workers' approach (scheme 13).[83–85] In their second generation approach, ozonolysis of cyclohexenes **1.104a** and **1.104b** gave the corresponding dialdehydes **1.105a** and **1.105b**, which were immediately condensed *in situ* with phenylhydrazine (**1.106**) to afford hydrazones **1.107a** and **1.107b**. Due to instability and decomposition on purification, these were treated immediately with polyphosphoric acid trimethylsilyl ester (PPSE) to access arcyriaflavin A (**1.55**) and *N*-methylarcyriaflavin A **1.108**. Despite the low overall yield, this represents a 3-step approach that requires no purification of the intermediates.



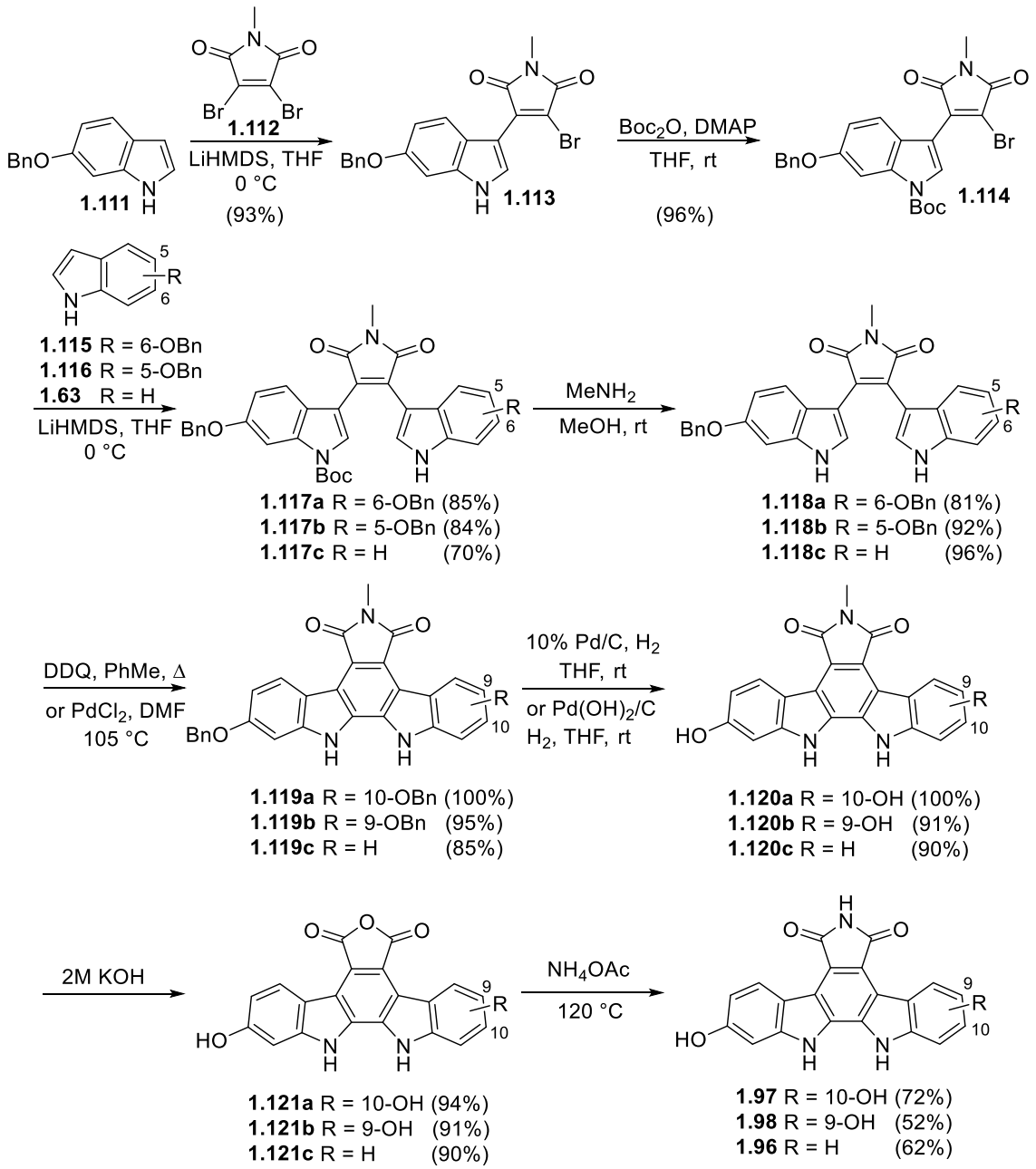
Scheme 13 Gribble and co-workers' synthesis of arcyriaflavin A (**1.55**).

Another excellent and efficient approach to *N*-benzylarcyriaflavin A (**1.44**) was described by Saulnier and co-workers' in 1995 (scheme 14).[86–88] The readily available diacetylene **1.109** was trifluoroacylated to give diamide **1.110**, which underwent a remarkable Pd(0) catalysed polyannulation with maleimide **1.41** to access the desired indolocarbazole in good yield.



Scheme 14 Saulnier and co-workers' synthesis of *N*-benzylarcyriaflavin A (**1.44**).

In 1996, during extensive studies into indolocarbazoles, Okhubo and co-workers' developed a synthetic approach to arcyriaflavins B (**1.96**), C (**1.97**), and D (**1.98**, scheme 15).[89] The approach utilised sequential addition of lithiated indole derivatives to construct the asymmetric bisindolylmaleimides **1.117a-c**.[42,90] Removal of the Boc protecting group preceded oxidative cyclisation to access the indolocarbazole core before debenzylation and demethylation *via* a two-step hydrolysis/imidation strategy furnished the natural products **1.96**-**1.98**. [91]



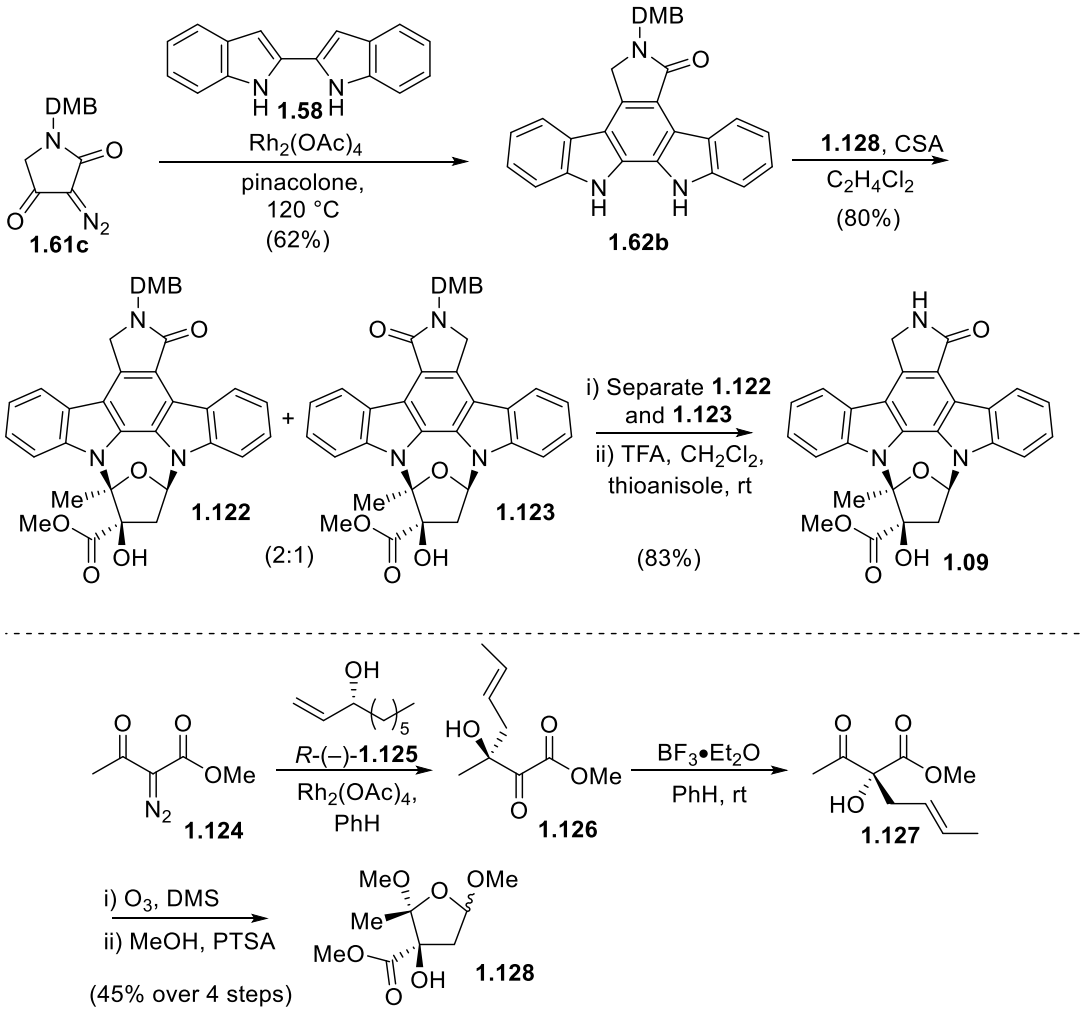
Scheme 15 Okhubo and co-workers' synthesis of arcyriaflavin B (**1.96**), C (**1.97**), and D (**1.98**).

1.4 Furanosylated indolocarbazoles

1.4.1 K252a

Indolocarbazoles with functionality on the indolic nitrogens have tended to show increased biological activity relative to the aglycone and arcyriaflavins, particularly against PKC. However a synthetic approach brings a whole new set of issues, primarily controlling regioselectivity during formation of the key glycosidic linkages. K252a (**1.9**) is no exception, and in 1995, Wood and co-workers' coupled *N*-DMB protected staurosporine aglycone

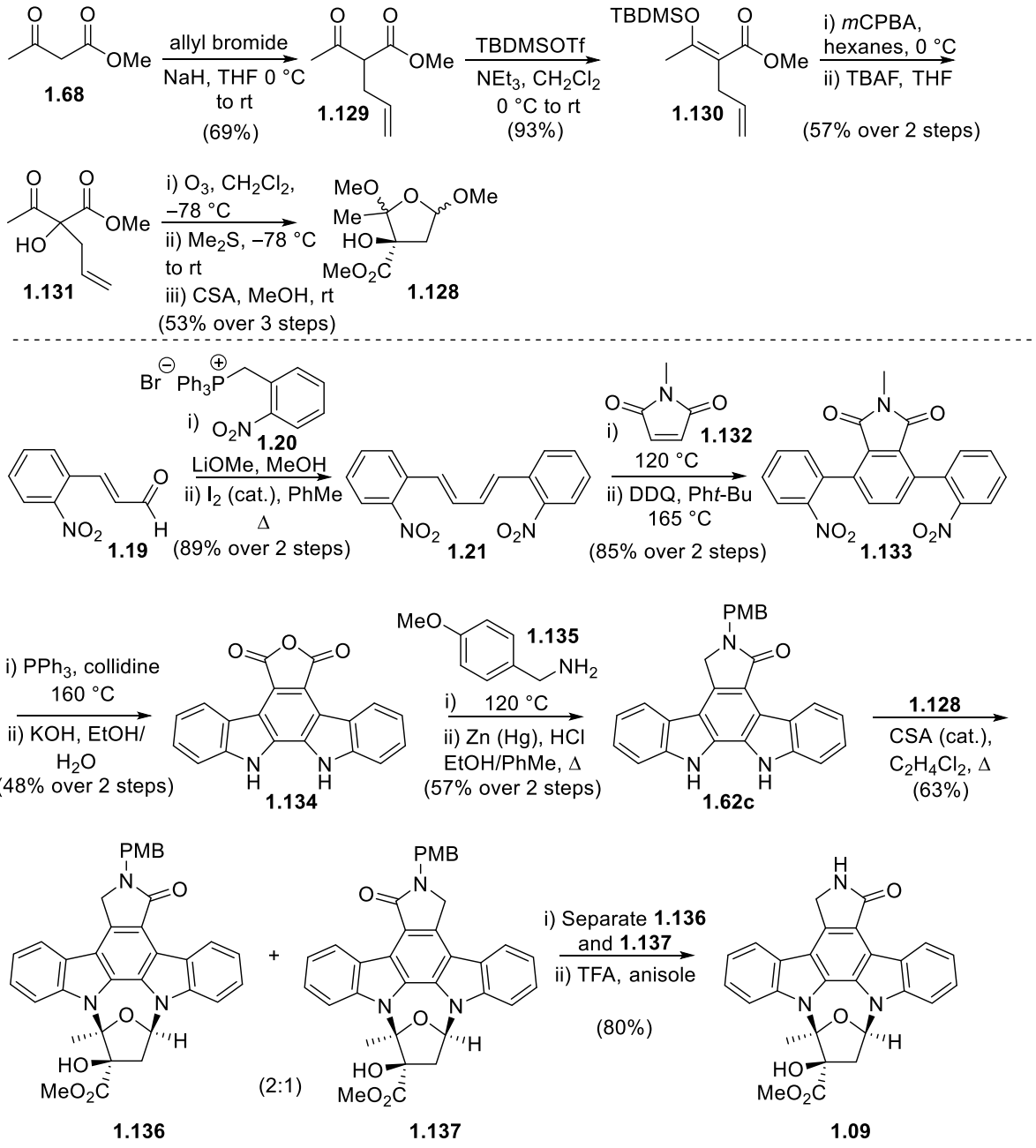
1.62b with furanose **1.128** to form both glycosidic bonds in one step.[51] The furanose fragment **1.128** was prepared from diazoester **1.124**. Reaction of diazoester **1.124** and *R*-(–)-**1.125** in the prescence of rhodium tetraacetate gave *β*-ketoester **1.126**, which upon exposure to BF_3●Et_2O gave alcohol **1.127**. Finally, ozonolysis and acid-mediated cyclisation gave furanose **1.128**. The ensuing cycloglycosidation step gave indolocarbazoles **1.122** and **1.123** as a 2:1 mixture, indicating a minor bias in the system potentially arising from transannular participation of the C(3) hydroxyl group. Separation of the mixture and a final deprotection provided K252a (**1.09**, scheme 16).



Scheme 16 Wood and co-workers' synthesis of K252a (**1.09**).

Later the same year, Lowinger and co-workers' developed a racemic synthesis of (±)-K252a (**1.09**, scheme 17).[92] The carbohydrate moiety was constructed from methyl acetoacetate (**1.68**). Allylation gave *β*-ketoester **1.129** before silyl-enol ether formation and chemoselective epoxidation/desilylation gave olefin **1.131**. Ozonolysis followed by reductive work-up gave the intermediate aldehyde which was cyclised with camphor sulfonic acid (CSA). The PMB-protected aglycone, prepared *via* a modified approach previously described by Raphael (scheme 2), was glycosylated under similar conditions to Wood and

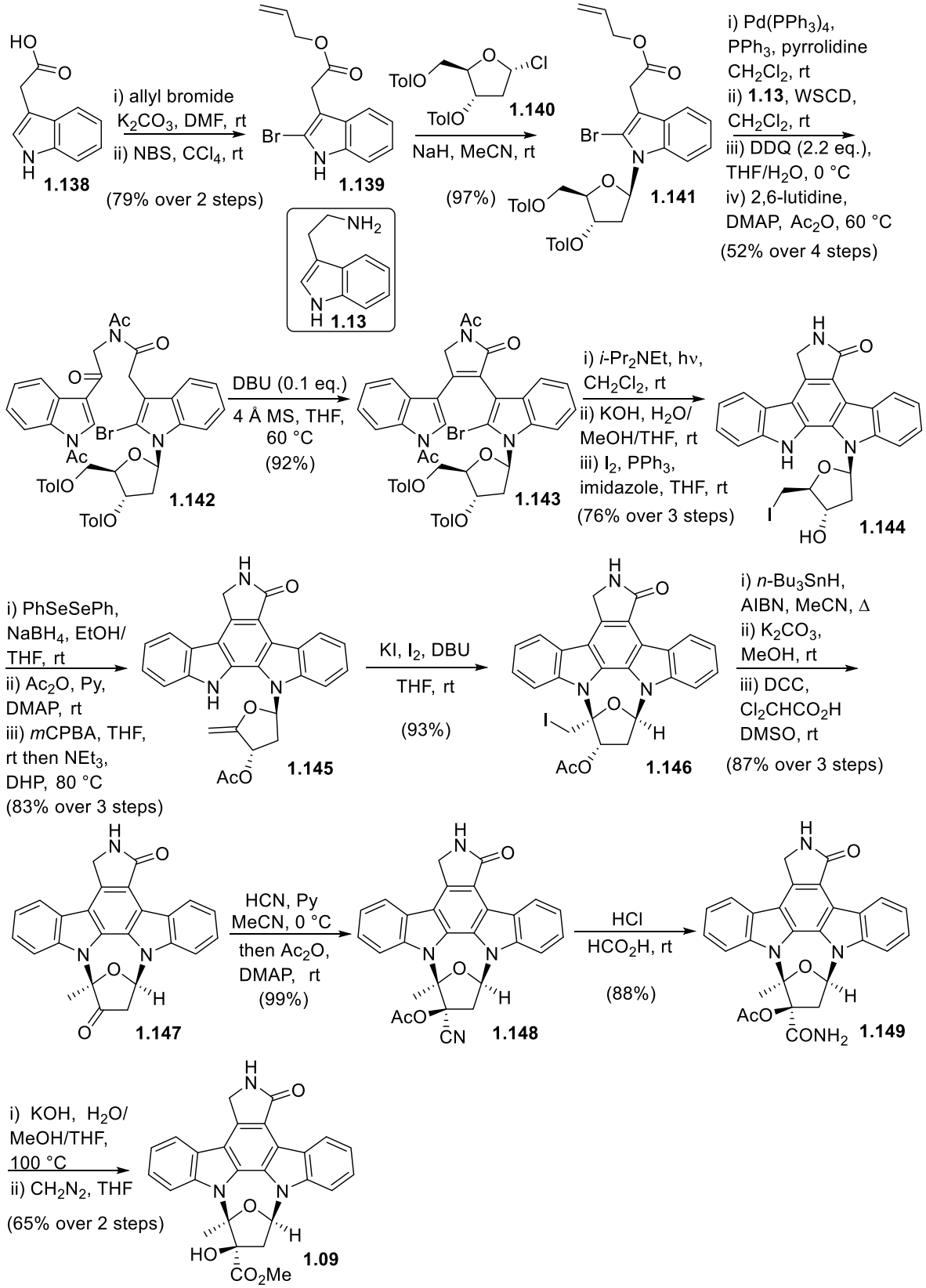
co-workers', before separation of the regioisomers and removal of the PMB protecting group gave (±)-K252a (**1.09**).[35]



Scheme 17 Lowinger and co-workers' synthesis of (±)-K252a (**1.09**).

In 1999, Fukuyama and co-workers' completed the most recent synthesis of K252a (**1.09**), with a focus on solving regiochemical issues associated with the previous syntheses of indolocarbazoles (scheme 18). Starting with commercially available indole acetic acid (**1.138**), protection as the allyl ester and regioselective bromination gave indole **1.139**. *N*-glycosidation was carried out with NaH and the readily available furanose **1.140** to give indole **1.141**.[93] Deprotection of the allyl ester and amide coupling with tryptamine (**1.13**) was followed by benzylic oxidation with DDQ and acetylation of the indole and amide nitrogens to give bisindole **1.142**. Treatment with DBU and molecular sieves gave lactam **1.143** as a

1:1 mixture of atropisomers before photocyclisation of the bromoindole formed the aromatic core, then hydrolysis of the acyl and toluoyl groups and selective iodination of the primary alcohol gave iodide **1.144**. A four step sequence was needed to advance iodide **1.144** to olefin **1.145**. Conversion to the selenide was followed by protection of the secondary alcohol, oxidation to the selenoxide and elimination to provide the desired olefin **1.145**. Iodoglycosidation was achieved with iodine and potassium iodide under basic conditions to provide cycloglycoside **1.146**, which underwent radical deiodination, methanolysis of the acetate group and oxidation of the secondary alcohol to ketone **1.147** in excellent overall yield.[94] Treatment of ketone **1.147** with hydrogen cyanide and pyridine gave the kinetically favoured cyanohydrin, which was subsequently acetylated to cyanohydrin acetate **1.148**. Treatment with gaseous HCl gave amide **1.149**, which was converted to K252a (**1.09**) via hydrolysis and esterification with diazomethane. The overall sequence provided K252a (**1.09**) in 10% overall yield and in 23 synthetic operations.[95]

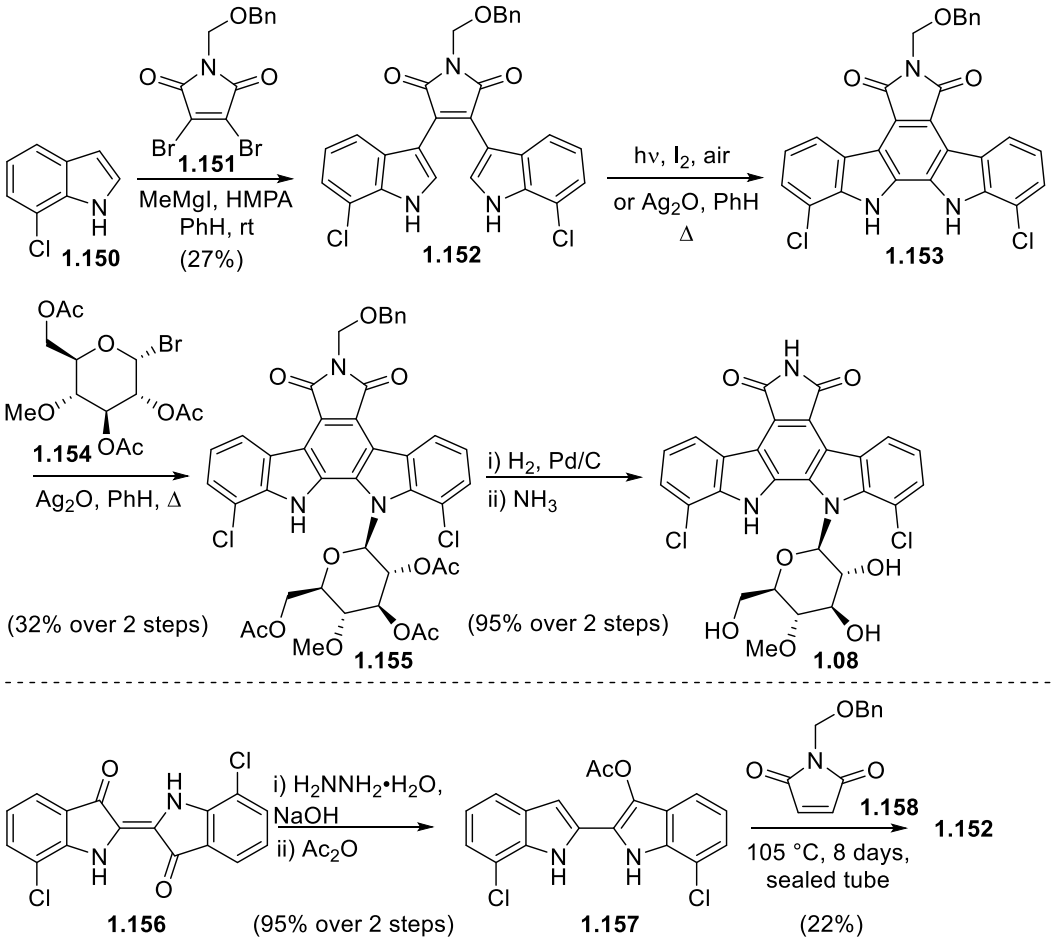


Scheme 18 Fukuyama and co-workers' synthesis of K252a (**1.09**).

1.5 Pyranosylated indolocarbazoles

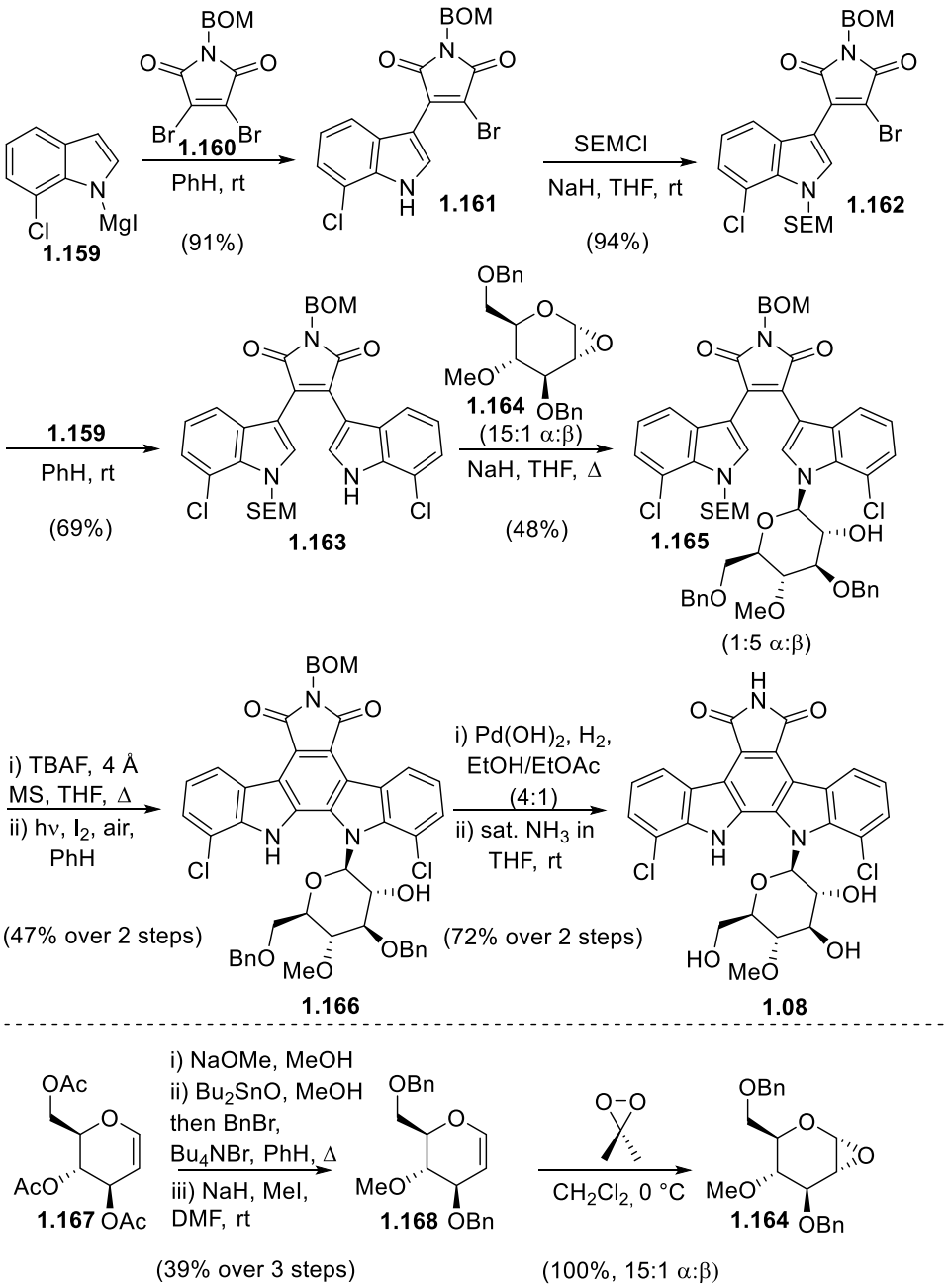
1.5.1 Rebeccamycin

As the most potent indolocarbazole antitumor agent, rebeccamycin (**1.08**) has found interest both in efforts towards its total synthesis, and routes to synthetic analogues.[96–98] First isolated by Clardy and co-workers' in 1985 from the actinomycete strain *Nocardia aerocoligenes.*, the structure of rebeccamycin (**1.08**) was elucidated during synthetic approaches carried out by the same group (scheme 19).[99,100] The approach utilised Steglich's magnesiated indole chemistry to assemble the aglycone unit, before a silver-promoted Koenigs-Knorr glycosylation gave the skeleton of the natural product **1.155**.[42] Removal of the BOM protecting group and hydrolysis of the acetate gave rebeccamycin (**1.08**), and confirmed the structure of the previously isolated natural product. The same group also demonstrated an alternative method for isolation of the key aglycone **1.152**. Reduction of 7,7'-dichloroindigo (**1.156**) via Wolff-Kishner conditions before acetylation gave 2,2'-biindole **1.157**.[101,102] Finally, a Diels-Alder cycloaddition with *N*-benzyloxymethyl maleimide (**1.158**) gave *N*-benzyloxymethyl rebeccamycin aglycone **1.152.**



Scheme 19 Clardy and co-workers' synthesis of rebeccamycin (**1.08**).

In 1993, Danishefsky and co-workers' also completed a synthesis of rebeccamycin (**1.08**, scheme 20), utilising their pioneering 1,2-anhydrosugar chemistry.[103] The synthesis began similar to their synthesis of staurosporine (**1.07**) using sequential additions of indole magnesium Grignard **1.159** to give the asymmetric bisindolylmaleimide **1.163**. The required sugar **1.164** was prepared from the commercially available tri-*O*-acetyl-D-glucal (**1.167**). Removal of the acetate protecting groups was followed by selective dibenzylation at the 3 and 6 positions using stannylene chemistry. Protection of the 4-position *via* methylation gave glucal **1.168**, before the DMDO epoxidation gave the required 1,2-anhydrosugar as a 15:1 mixture of anomers.[104] The mixture was then subjected to the pivotal glycosidation with bisindolylmaleimide **1.163** to give the major *β*-maleimide **1.165** in 48% and the *α*-anomer in 8% yield. The 5:1 ratio of **1.165** versus the 15:1 ratio in **1.164** is attributed to the greater reactivity of the minor β epoxide. Finally, deprotection of the SEM group, followed by photocyclisation gave indolocarbazole **1.166**, which underwent hydrogenation to remove the benzyl protecting groups and finally ammonolysis to give rebeccamycin (**1.08**).

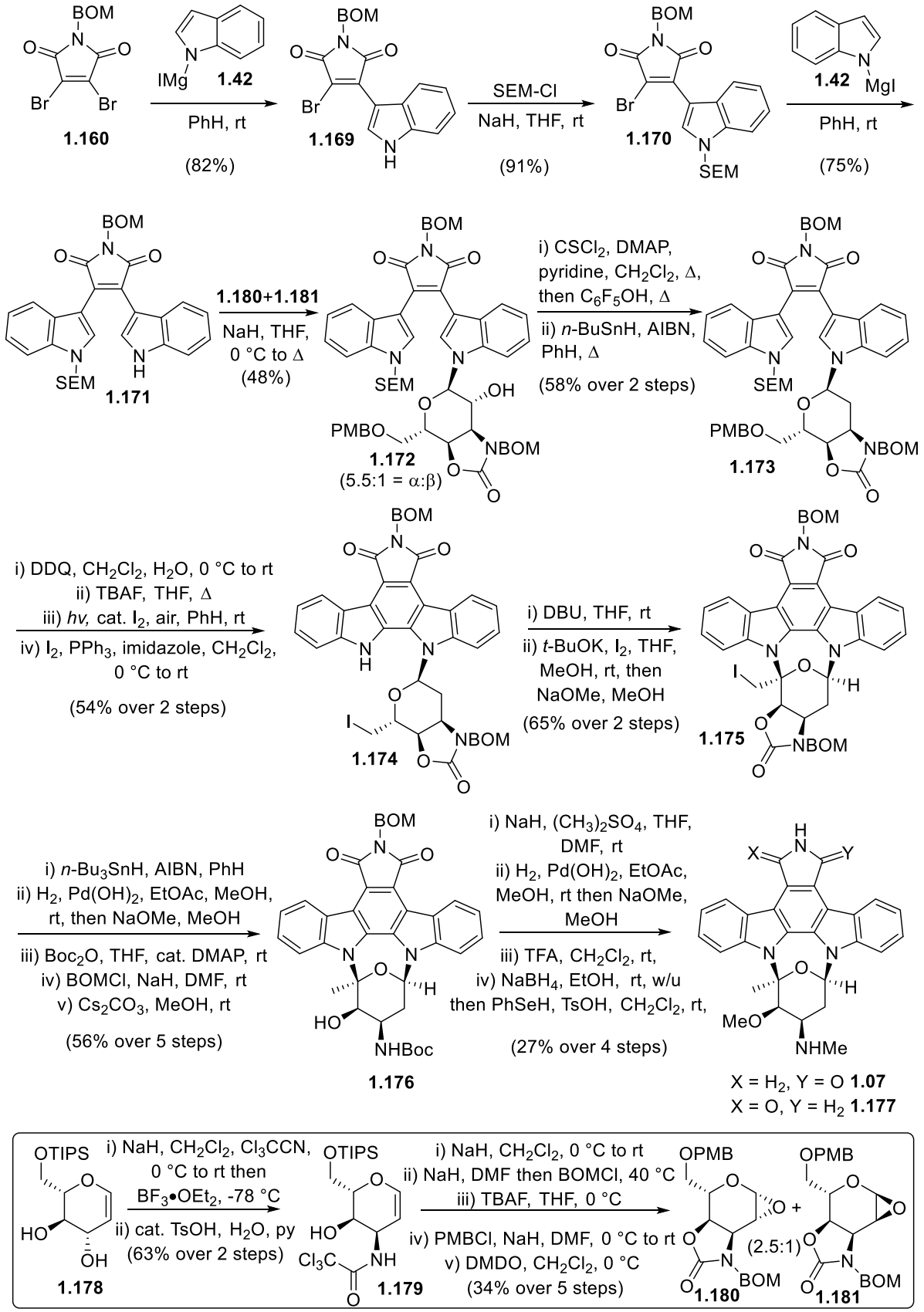


Scheme 20 Danishefsky and co-workers' synthesis of rebeccamycin (**1.08**).

1.5.2 Staurosporine

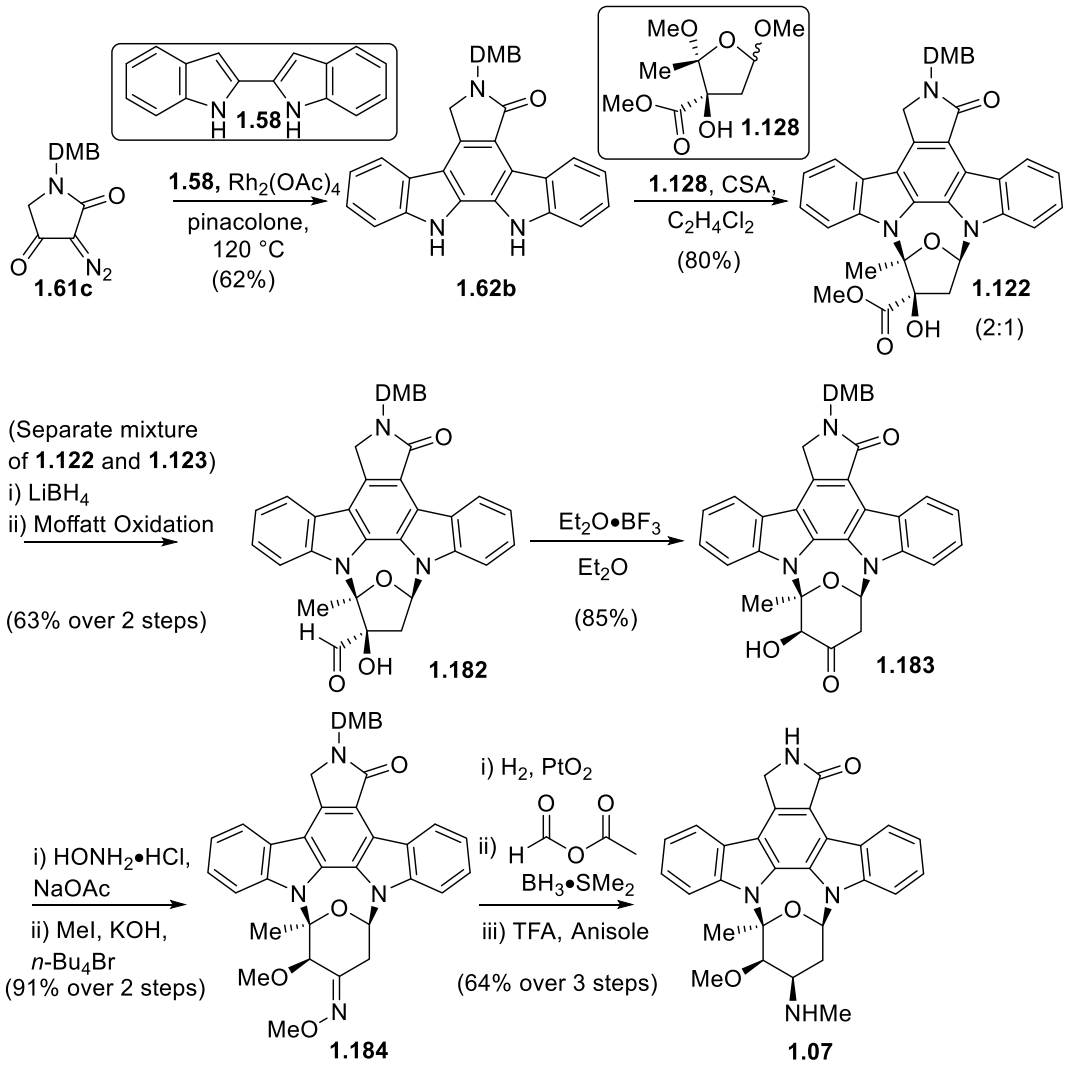
To date, there have been only two total syntheses of staurosporine (**1.07**). Danishefsky and co-workers' applied their 1,2-anhydrosugar chemistry to the first total synthesis of staurosporine (**1.07**) in 1995 (scheme 21).[94,103,105–107] Sequential addition of magnesiated indole allowed for the synthesis of protected bisindolylmaleimide **1.171**. The requisite carbohydrate was prepared from the protected L-glucal derivative **1.178**. Conversion to the corresponding bis-(trichloroacetimidate) followed by Schmidt glycosylation and hydrolysis of the obtained oxazoline gave amide **1.179**. Intramolecular annulation and protecting group manipulations, before a final glycal oxidation with 2,2-dimethyldioxirane gave a mixture of

epoxides **1.180** and **1.181**, and the stage was set for the indole glycosylation. The mixture of epoxides was treated with the sodium salt of **1.171** to provide alcohol **1.172**. Barton deoxygenation gave the subsequent bisindolylmaleimide **1.173**. Removal of the PMB and SEM groups preceded oxidative photocyclisation and iodination with molecular iodine to access arcyriaflavin A derivative **1.174**. Elimination of the iodine gave the corresponding exocyclic olefin before a novel iodine promoted glycosylation formed the second glycosidic link and gave the structural framework of staurosporine **1.175**. Dehalogenation was achieved with Bu_3SnH before removal of the BOM-groups, selective protection of the oxazolidinone ring, reprotection of the maleimide with BOMCl and finally treatment with Cs_2CO_3 in MeOH provided alcohol **1.176**. Methylation of the amine and hydroxyl residues was followed by removal of the BOM group and a final 2 step maleimide reduction to give a 1:1 mixture of staurosporine (**1.07**) and *iso*-staurosporine (**1.177**).



Scheme 21 Danishefsky and co-workers' synthesis of staurosporine (**1.07**).

The most recent synthesis of staurosporine (**1.07**), was completed in 1996 by Wood and co-workers' (scheme 22).[51,52,108] The overarching strategy was to enable access to several indolocarbazole natural products, and as such the initial focus was to couple a furanose fragment to access K252a (see scheme 16). This then underwent the key double-glycosidation step before separation of the two regioisomers, reduction of the ester and oxidation of the resulting alcohol gave aldehyde **1.182**, which upon treatment with BF_3•Et_2O, underwent ring-expansion to the ketone **1.183**. This elegant expansion allows access to both the pyranosylated and furanosylated natural products from the same intermediate. In addition, a copper mediated ring-contraction of ketone **1.183** to ester **1.122** was also detailed by the group, potentially demonstrating a biomimetic link.[52,108] To complete the synthesis, treatment of ketone **1.183** with hydroxylamine hydrochloride followed by *bis*-methylation gave methyloxime **1.184**, before finally a stereoselective reduction, mono-methylation and DMB-deprotection sequence furnished staurosporine (**1.07**).



Scheme 22: Wood and co-workers' synthesis of staurosporine (**1.07**).

1.6 Conclusions and future perspectives

The recently discovered activity of PKC inhibitors for inhibition of metastatic cancer and stem cell cancer has sparked interest in indolocarbazoles, particularly staurosporine (**1.07**).[28–31] The mode of action is currently unknown, however an efficient route to both staurosporine (**1.07**) and synthetic derivatives may prove vital in developing an improved understanding.

Current synthetic approaches to staurosporine (**1.07**) and other indolocarbazoles bearing glycosidic linkages still present an unsolved synthetic challenge, namely achieving regiocontrol in coupling the aglycone and sugar fragments. Solving this has proved non-trivial, with the distal nature of the sugar fragment from the source of asymmetry in the aglycone leading to diminished selectivity. Wood and co-workers' diazo-insertion approach and Danishefsky and co-workers' 1,2-anhydrosugar glycosylation approach have enabled the only two syntheses of staurosporine (**1.07**) to date, however regioselectivity was not fully resolved. Fukuyama and co-workers' have worked to resolve regioselectivity, yet to date a regioselective approach to staurosporine that would enable access to reasonable quantities of both the natural compound and interesting derivatives remains elusive. Given the high cost of the natural product, total synthesis presents an attractive opportunity.

In addition, a scalable approach to the aglycone (**1.10**) presents an intriguing challenge, as the isolation of large amounts would allow for functionalisation for useful derivatives, and potential as a useful intermediate in the synthesis of indolocarbazole alkaloids. In particular, the photochemical cyclisation of bisindolylmaleimide (**1.54**) to arcyriaflavin A (**1.55**) presents an intriguing prospect for application in flow and would be amendable to the synthesis of a library of interesting analogues. In addition, photochemistry necessitates the need for toxic reagents and when applied in flow, may present a solution for sustainable access to grams of indolocarbazoles per day.

Chapter 2 Flow photochemistry applied to the synthesis of the staurosporine aglycone

2.1 Background

2.1.1 6π Electrocyclisations

Electrocyclic transformations were defined by Woodward and Hoffman as either the formation or breaking of a single bond between the termini of a linear system containing k π-electrons.[109] These reactions are inherently reversible and therefore under thermodynamic control. However, they follow well defined rules outlined by Woodward and Hoffman that are centered on conservation of orbital symmetry and allow for prediction of the stereochemical outcome as either disrotary or conrotary. These terms represent the rotation about the terminal double bonds, with disrotary reflecting rotation of the two termini in opposite directions, and conrotary representing both in the same direction.

One such example of these reactions is in systems containing 6π-electrons. Thermally promoted 6π-electron cyclisation's proceed with disrotary stereochemistry as evidenced in the cyclisation of triene **2.01**. Whilst photochemical promoted cyclisation's proceed with conrotary stereochemistry, as detailed by the cyclisation of *cis*-stilbene (**2.03**), a structurally similar system to bisindolylmaleimides.

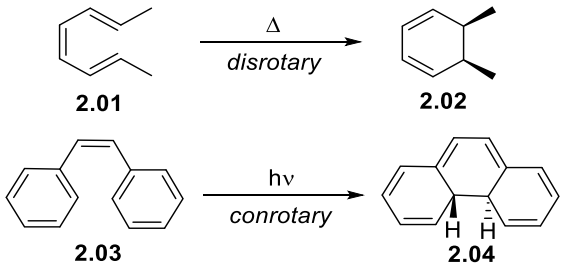


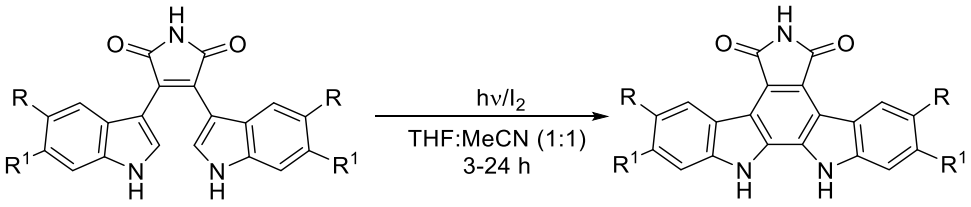
Figure 7 Examples of thermal and photochemical 6-π cyclisations.

2.1.2 Previous applications to bisindolylmaleimides

Bisindolylmaleimides have been the subject of numerous synthetic studies owing to their molecular simplicity and availability compared to the staurosporine aglycone (**1.10**). Additionally, they are useful intermediates in the construction of the indolocarbazole core, and as such the oxidative cyclisation to form the final C-C bond in the central ring has been extensively investigated. Subsequent oxidative aromatisation has been performed with palladium ($PdCl_2$, $Pd(OAc)_2$, $Pd(O_2CCF_3)_2$), DDQ (with and without TsOH) and hypervalent

iodine species (PIFA/BF_3•OEt_2), however all methods have their advantages and disadvantages.[44,50,89,110] DDQ is atom-inefficient and often removal of by-products from the cyclised indolocarbazole is difficult. Pd catalysts can be expensive, and also difficult to remove from the indolocarbazole core due to the poor solubility of the alkaloids in organic solvents. Finally, the use of hypervalent iodine has led to inconsistent yields, and therefore oxidative photocyclisation remains an attractive approach.

Winterfeldt utilised photochemistry to achieve the first synthesis of the staurosporine aglycone (**1.10**) in 1983 (scheme 1), before Danishefsky and co-workers' utilised a similar electrocyclic ring closure to access arcyriaflavin A derivatives in their total syntheses of staurosporine (**1.07**) and rebeccamycin (**1.08**, scheme 20 and 21 respectively). In 2003, Reddy and co-workers' built upon previous work and reported an optimised general procedure (scheme 23).[111] The procedure reported use of catalytic I_2 in THF-MeCN (1:1) and furnished arcyriaflavin A (**1.55**) after 12 h irradiation with two 400 W high pressure mercury lamps. The reaction was carried out in batch on 0.150 g and was limited to a concentration of 0.015 M, as more concentrated solutions led to precipitation of the product, blocking out the light and suppressing the reaction. The group reported scale to 5 g, although 96 h irradiation was required for complete conversion. It is clear whilst there is a practical and large scale approach to bisindolylmaleimide (**1.54**, scheme 8) there is no efficient process amendable to large scale production of the staurosporine aglycone (**1.10**).



1.54 R = H, R^1 = H
2.05a R = F, R^1 = H
2.05b R = Br, R^1 = H
2.05c R = OMe, R^1 = H
2.05d R = H, R^1 = Cl

1.55 R = H, R^1 = H (85%)
2.06a R = F, R^1 = H (90%)
2.06b R = Br, R^1 = H (90%)
2.06c R = OMe, R^1 = H (84%)
2.06d R = H, R^1 = Cl (87%)

Scheme 23 Reddy and co-workers' photochemical cyclisation to arcyriaflavin A (**1.55**) and derivatives.

2.1.3 Limitations and aims for photo-cyclisation in flow

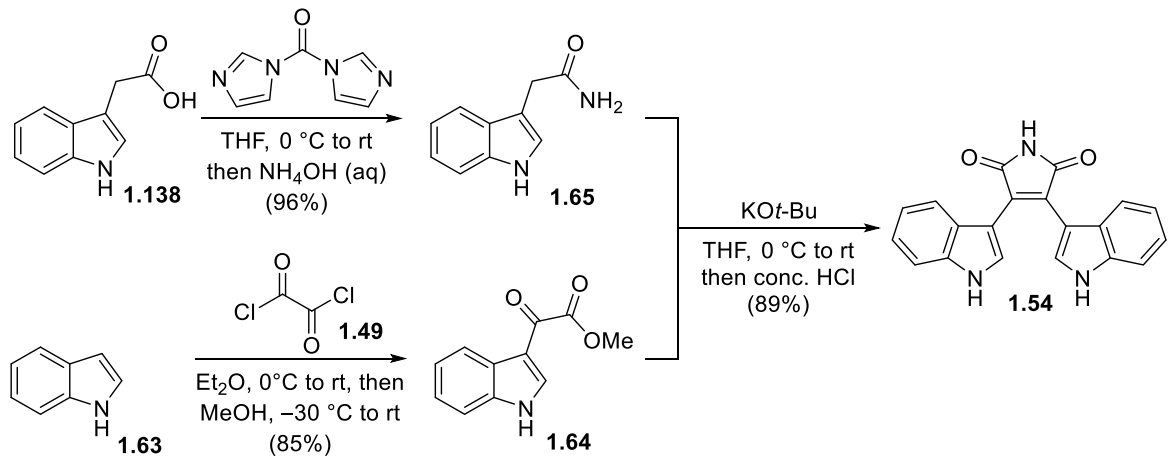
Reddy and co-workers' cyclisation conditions present a considerable advance towards a large scale synthesis of the staurosporine aglycone (**1.10**). However, the methodology is hampered by issues with solubility of the indolocarbazole product and prolonged reaction times for scale up.

As such, the aim was to utilise Reddy and co-workers' procedure as a foundation for the application of the cyclisation in flow. It was proposed that running the cyclisation in more dilute concentrations would circumvent precipitation of the indolocarbazole product, and the inherent nature of flow chemistry would enable scale up of the process and production of 10's of grams of arcyriaflavin A (**1.55**) per day, compared to the 96 h required for 5 g of material in Reddy and co-workers' work.

2.2 Synthesis of arcyriaflavin A and the staurosporine aglycone

2.2.1 Synthesis of arcyriaflavin A (1.54)

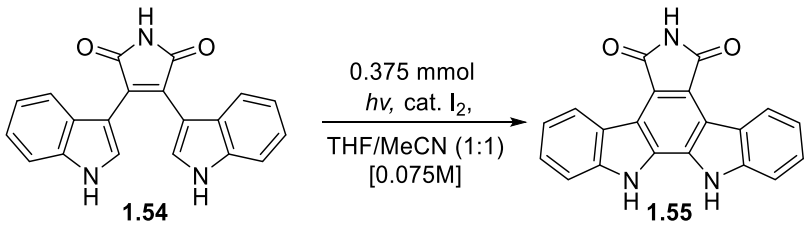
To test the feasibility of this approach, the synthesis began with isolation of bisindolylmaleimide (**1.54**) utilising the method described by Faul and co-workers' (scheme 8).[58] Activation of indole acetic acid (**1.138**) with CDI before quenching with aqueous ammonium hydroxide gave the acetamide **1.65**, whilst Friedel-Crafts acylation of indole (**1.63**) with oxalyl chloride (**1.49**) and subsequent treatment with methanol gave ester **1.64**. Condensation of these two fragments was carried out with KO^{t}Bu to give bisindolylmaleimide (**1.54**) after acidic work up. The overall process proceeded in excellent yield (76%), and was carried out on multi-gram scale without recourse to flash chromatography.



Scheme 24 Synthesis of bisindolylmaleimide (**1.54**)

With ample quantities of bisindolylmaleimide (**1.54**) in hand, studies into the oxidative cyclisation to arcyriaflavin A (**1.55**) commenced. Initial attempts saw the reaction mixture held in a 1 mm diameter tubing and irradiated with a Prolite© 25 W, 1520 lumens, 240 V white light bulb (table 1, entry 1). After 4 h, the light source was switched to Mirrorstone© 36 W, 510 lumens, 12 V blue LEDs as the temperature of the reactor had risen above 80

°C (external temperature) and the reactor was leaking. As such, the isolated yield from this attempt was poor, and an alternate setup with more efficient cooling was explored.



1.54 1.55

Table 1 Conditions employed for the oxidative photocyclisation of **1.54**.

Entry	I_2/ Mol %	Light source	Temp/ °C	Time to consumption of 1.54/ h	Isolated yield/ %
1	10	White bulb then blue LEDs	>80	10	44
2	10	Blue LEDs	~35	14	65
3	20	Blue LEDs	~35	14	59

Previous work in the group by Alex Leeder had explored the absorption profiles for both **1.54** and **1.55**. The two UV-vis spectra for bisindolylmaleimide (**1.54**) and arcyriaflavin A (**1.55**) (Figure 8 and Figure 9 respectively) indicate that bisindolylmaleimide **1.54** absorbs strongly at around 450 nm, compared to arcyriaflavin A (**1.55**), which absorbs poorly in the same range. As such, photolysis with blue LEDs (Mirrorstone©, 36 W, 510 lumens, 12 V) was chosen to minimise potential decomposition of arcyriaflavin A (**1.54**).

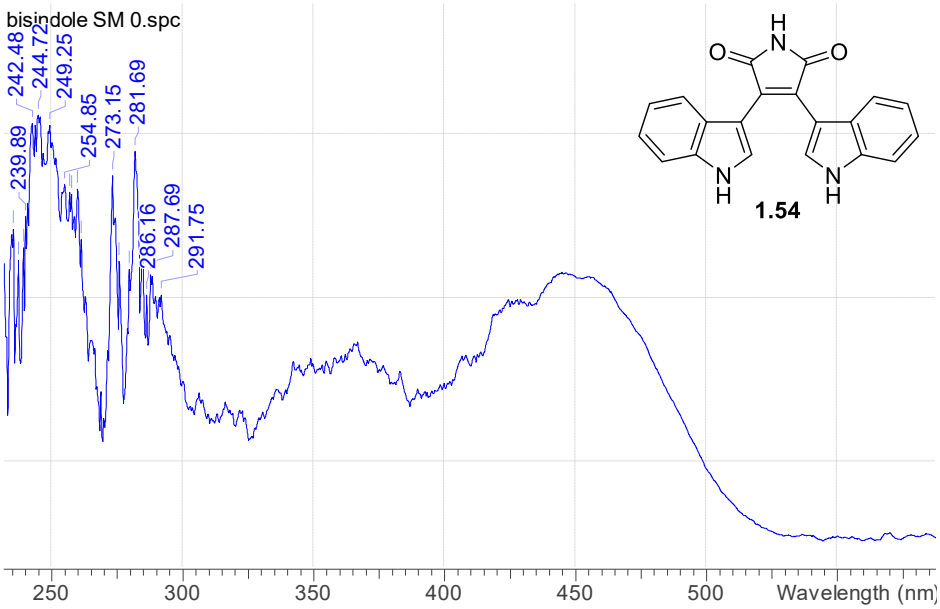


Figure 8 UV-vis spectrum for bisindolylmaleimide (**1.54**).

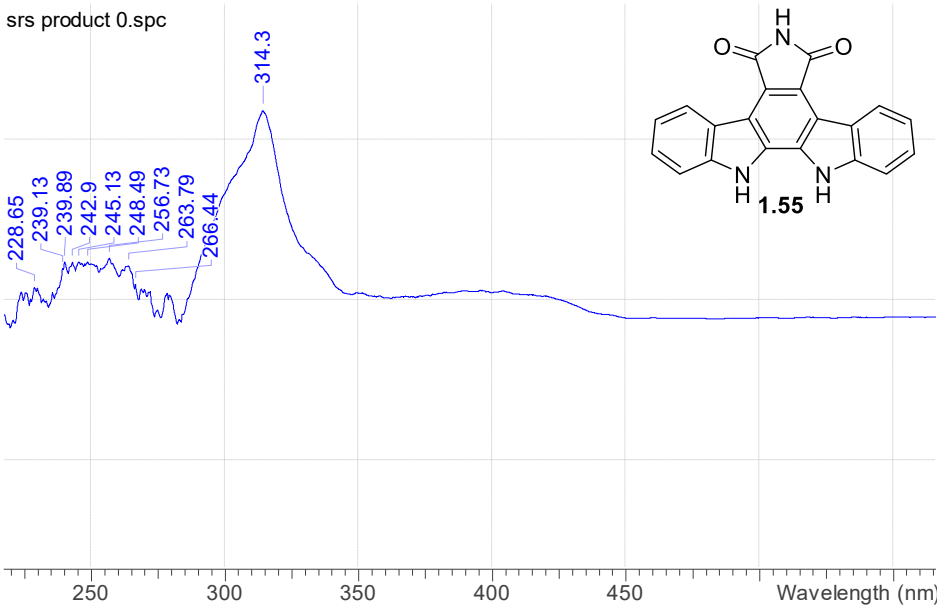
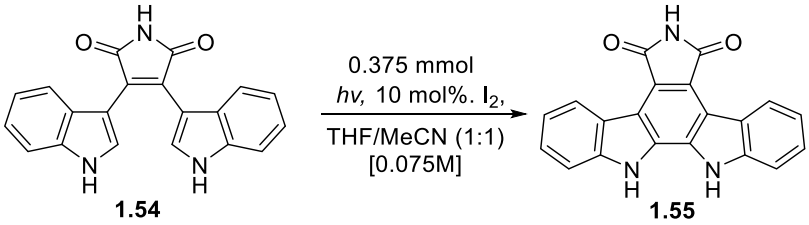


Figure 9 UV-vis spectrum for bisindolylmaleimide (**1.55**).

The blue LEDs were shown to circumvent issues relating to product decomposition, but at the expense of reaction rate, now taking 14 h for complete consumption of bisindolylmaleimide (**1.54**), and providing arcyriaflavin A (**1.55**) in good yield (table 1, entry 2). Unfortunately, the reaction times were far too long for application into flow, and it was initially believed that the oxidation step was rate limiting. As such, the reaction was run again with double the quantity of iodine (entry 3). However, this gave similar reaction times and therefore was proposed the cyclisation is the rate limiting.

Knowing full conversion of the starting bisindolylmaleimide (**1.54**) could be achieved with prolonged photolysis, attention switched to increasing the rate of consumption of bisindolylmaleimide (**1.54**) (termed productivity). The mixture was now administered under flow conditions to aid mixing, and in addition, given the absorbance of the starting material was greatest in the UVC region (200-280 nm), the cyclisation under a UVC light source was also investigated.



1.54 **1.55**

Table 2 Conditions employed for oxidative photocyclisation of bisindolylmaleimide (**1.54**).

Entry	Light Source	Temp/ °C	Flow rate/ mL min^{-1}	SM **1.54**:P **1.55** after 1 h	Time to consumption of **1.54**/ h	Productivity/ g h^{-1}
1	Blue LEDs	~35	-	1:0.07	14	0.009
2	9W UVC	45	0.171	1:0.12	7.5	0.016
3	9W UVA	45	0.171	1:0.12	-[c]	0.016
4	36W UVC	25[a]	1.83	1:0.15	-[c]	0.016
5	36W UVC	50[a]	1.83	1:0.15	-[c]	0.016
6	36W UVC	50[a,b]	1.83	1:0.15	-[c]	0.016

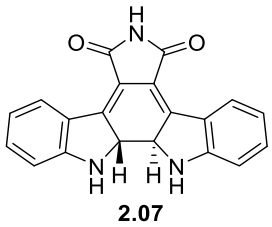
[a] Temperature within reactor

[b] Bubbles of air were introduced into the reactor with the mixture to promote the oxidation step.

[c] Reaction not driven to completion.

Using a UVC light source in a flow reactor setup led to almost half the reaction time for complete consumption of bisindolylmaleimide (**1.54**) to arcryaflavin A (**1.55**). Use of a

stronger UVC light source was then explored in an attempt to increase the productivity. However, utilising a very well cooled reactor with a stronger 36 W UVC light, the reaction showed little improvement in rate of conversion (entry 4). The lamp in the setup was switched to 36 W UVC with reactors that were not water cooled (entry 5). This led to a 3rd component present in the reaction mixture alongside the starting material and product. This was believed to be the dihydro-intermediate **2.07**, due to reports in literature of similar intermediates being isolated.[107] Unfortunately, however it was not possible to isolate the intermediate due to difficulty separating the by-product away from the desired product.

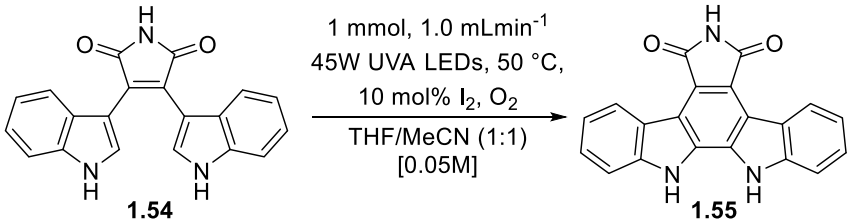


2.07

Figure 10 Proposed structure of observed intermediate in the oxidative photocyclisation.

If the species observed is indeed the proposed dihydro-intermediate **2.07,** this indicates that under the conditions, the cyclisation was no longer the rate determining step, and that the oxidation step is now limiting the reaction. In an attempt to further increase the productivity, a new reactor with a higher power UVA LED light source, developed by Dr Wei Sun in the Harrowven group, was applied to the reaction. In addition, oxygen gas was bubbled in as part of the mixture to promote the oxidation step and aim to increase the overall productivity.

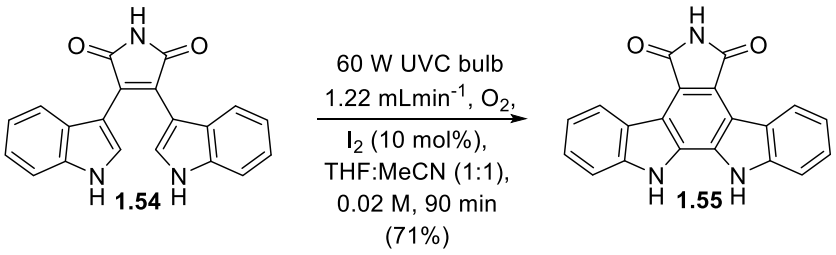
Due to the presence of the oxygen in the reactor, it is difficult to determine the exact flow rate. The pump was calibrated to 0.5 mL min^{-1}, but due the two inlets, the oxygen and the reaction solution, joining at a T-piece it can be reasonably assumed the flow rate for the overall system is double this and therefore 1.0 mL min^{-1}. In one pass through the reactor (50 mL), 35 % conversion was achieved. This marks an increase of productivity to roughly 0.14 g h^{-1}.



Scheme 25 Optimised conditions for the photolysis of **1.54**.

Unfortunately, attempts to replicate the reaction under the optimised conditions were unsuccessful due to reliability issues with the reactor. The primary issue arose due to the overheating of the circuit board during the reaction, and led to the reactor breaking, which

required a complete redesign. Instead, an alternative setup was explored with a 60 W UVC bulb, which given the slightly lower efficiency of a bulb due to emission as a broad spectrum of wavelengths, likely equates to roughly 45 W of UVC. The iodine concentration was kept consistent and again oxygen was introduced into the system via a T-piece. The concentration of the reactant solution was slightly lower due to fear of precipitation in a much larger reactor volume (120 mL), and longer residence time, and the flow rate (1.22 $mLmin^{-1}$) was chosen to provide a residence time of 90 min in the hope of achieving full conversion. Pleasingly, one pass through the reactor led to full conversion of the bisindolylmaleimide (**1.54**) and arcyriaflavin A (**1.55**) was isolated in excellent yield after removal of the iodine with activated charcoal and trituration of the crude solid with diethyl ether.

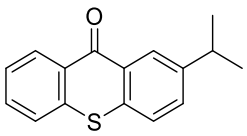


Scheme 26 Optimised photocyclisation conditions.

This result marked an increase in productivity to 0.26 g h^{-1}. Of particular interest however, was the design of these reactors to run in series (figure 11). For example, with three reactors in series utilising 3 times the flow rate (to maintain a residence time of 90 min) would treble the productivity to 0.78 g h^{-1} and allow for the production of multiple grams of arcyriaflavin A (**1.55**) per day.

Figure 11 Photochemical reactor employed (picture taken by William Raimbach).

With this result in hand, we concluded that the more powerful the light source was, the faster the rate of cyclisation observed and alternate avenues to lower the activation barrier were explored. Photosensitisers have been well-documented to improve the rate of photochemical reactions, usually by prolonging the excited state or by providing a lower energy pathway for the reaction. Booker-Milburn and co-workers' carried out extensive research on thioxanthone sensitisers and applicability to facilitate reactions using different light sources, in particular UVA.[112,113] Of interest were the sensitisers that absorbed in the UVA region, and in particular the commercially available 2-isopropylthioxanthone (ITX). Unfortunately, attempts to increase the productivity with this sensitiser were unsuccessful, resulting in no change compared to reactions without ITX.

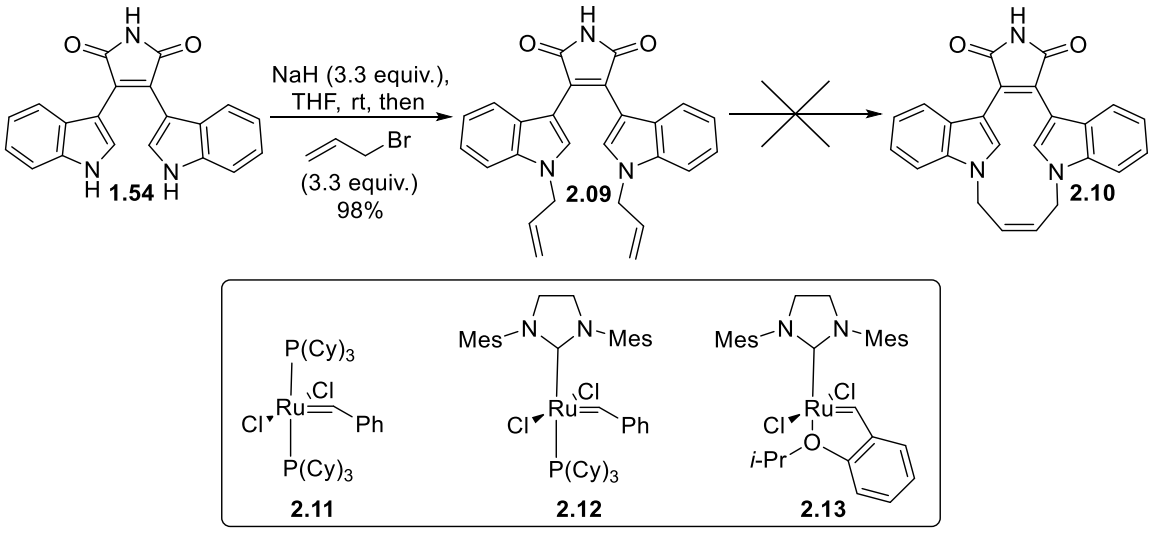


ITX (**2.08**)

Figure 12 Structure of photosensitiser 2-isopropylthioxanthone (ITX, **2.08**).

Finally, tethering the indolic nitrogens was proposed as a means to increase the rate of oxidative photocyclisation, perhaps, encouraging the system to adopt a more favourable conformation for cyclisation. This would therefore accelerate the cyclisation and enable a large scale flow-photochemical process to be developed where the tether could be removed afterwards.

Ring closure metathesis (RCM) was selected as a means to access the 12-membered macrocycle **2.10** (scheme 27). It was proposed that allylation of bisindolylmaleimide **1.54** would lead to exhaustive *N*-functionalisation, with the possibility for hydrolysis of *N*-substitued maleimide to the anhydride and then conversion back to *N*-H maleimide as previously documented.[114,115] In the event, allylation of **1.54** in the presence of more than 3 equiv. of allyl bromide led exclusively to the desired di-allyl bis-indole **2.09** with no *N*-alkylation of the maleimide (scheme 27). It was proposed that the observed chemoselectivity in this instance is due to the increased reactivity of indolic anions compared to the more stable conjugate base of maleimide. Hence, following allylation of the two indoles, stabilisation of the maleimide anion through the *π*-system leads to the decreased reactivity observed.



Scheme 27 Attempted synthesis of macrocyclic bisindolylmaleimide **2.10**.

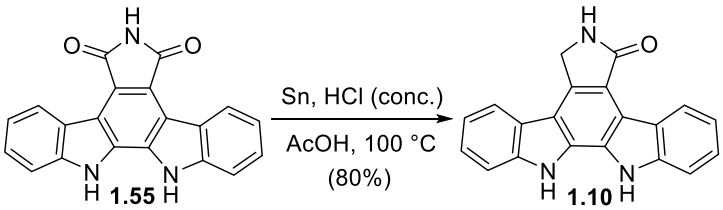
Various conditions were employed to induce macrocyclisation of maleimide **2.09** (scheme 27). Grubbs I generation catalyst (**2.11**), Grubbs II generation catalyst (**2.12**) and Hoveyda-

Grubbs II catalyst (**2.13**) were all used to no effect, with each leading to recovery of maleimide **2.09**. It is probable the starting material is more stable than the desired macrocyclic product and due to the reversible nature of metathesis, leads only to recovery of starting material. In addition, dibromobutane was also employed in an attempt to tether the indolic nitrogens. However, this was also unsuccessful, instead yielding a dark red insoluble gum attributed to polymeric by-products.

At this pointin the project, with difficulty tethering the bisindole system and having already realised an improved set of photo-cyclisation conditions, studies were placed on hold to focus other aspects of the project. Namely, achieving the synthesis of the staurosporine aglycone (**1.10**), and its further application to a regioselective approach to glycosylated indolocarbazoles.

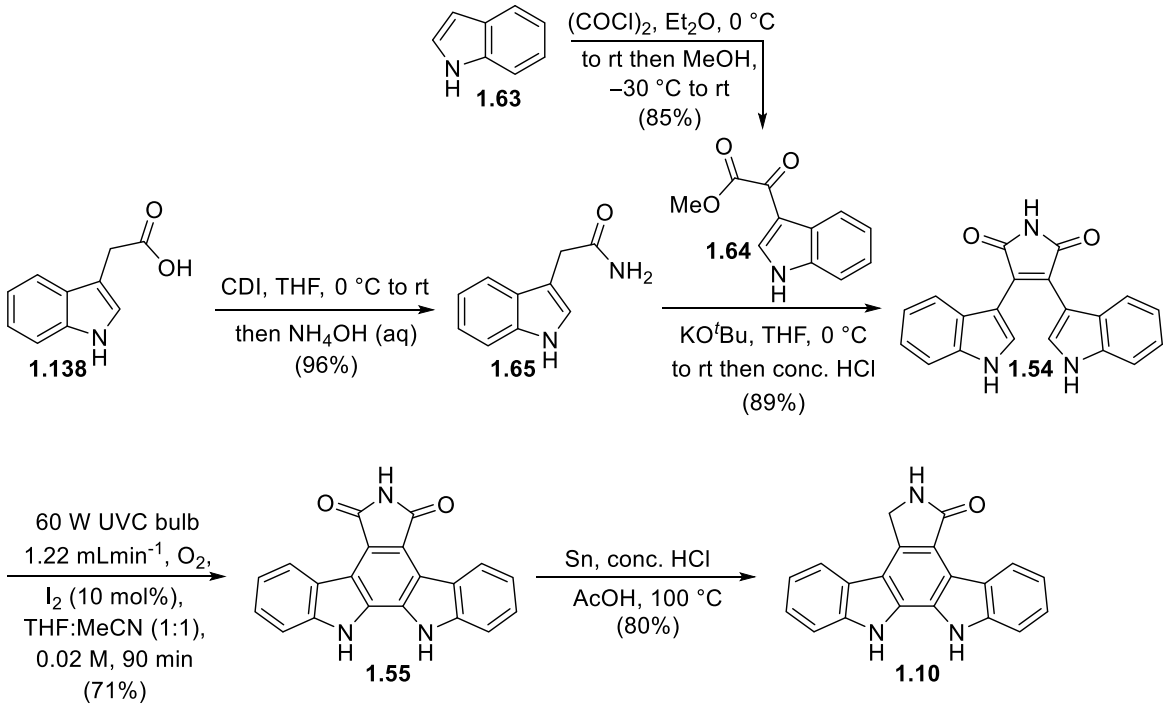
2.2.2 Synthesis of the staurosporine aglycone (1.10) from arcyriaflavin A (1.55):

With ample quantities of arcyriaflavin A (**1.55**) in hand, reduction of the maleimide to the desired lactam was carried out (scheme 28). Utilising the Clemmensen conditions described by Yang and co-workers', the staurosporine aglycone (**1.10**) was isolated in good yield and concluded the studies into arcyriaflavin A (**1.55**) and the staurosporine aglycone (**1.10**) using the photochemical approach.[116]



Scheme 28 Synthesis of the staurosporine aglycone (**1.10**).

2.3 Conclusions and future work



Scheme 29 Synthesis of arcyriaflavin A (**1.55**) and the staurosporine aglycone (**1.10**).

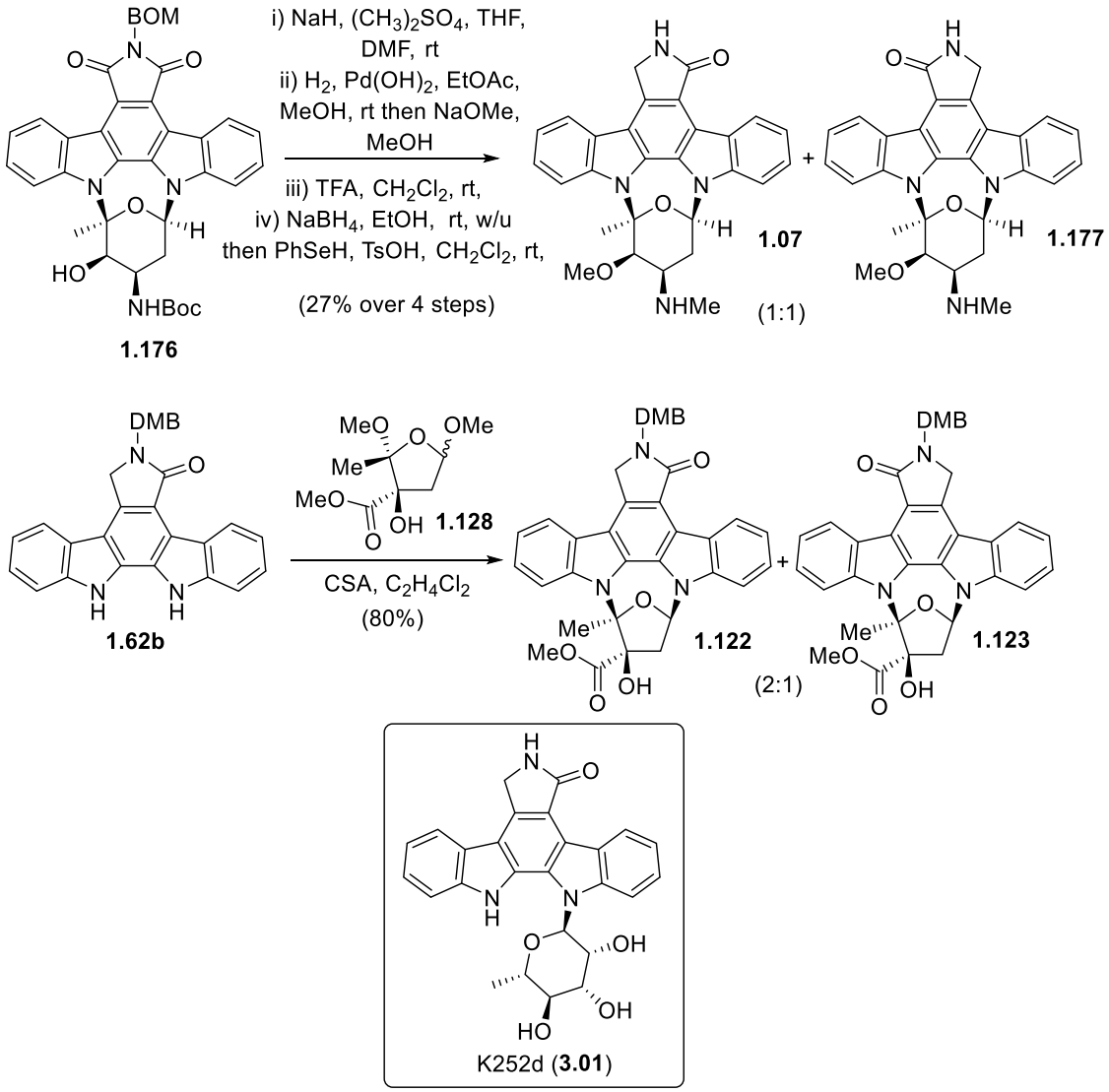
Utilising the methodology developed by Faul and co-workers', bisindolylmaleimide (**1.54**) was successfully isolated on multi-gram scale and subjected to the oxidative photocyclisation. After much optimisation, the use of 60W UVC bulb, catalytic iodine and bubbles of oxygen gave the greatest productivity of 0.26 g h^{-1} under flow conditions. In general, increasing the power of the light source, regardless of the wavelength, led to an increased productivity. Unfortunately, the use of commercially available 2-isopropylthioxanthone (ITX) as a photosensitizer gave no advantage in terms of productivity, and attempts to isolate macrocyclic bisindolylmaleimides and subject them to the cyclisation were also unsuccessful. Isolation of the staurosporine aglycone (**1.10**) after Clemmensen reduction of arcyriaflavin A (**1.55**) concluded the approach in 49% over 4 steps (LLS), representing the highest yielding synthesis of the aglycone (**1.10**) to date.

Chapter 3 Synthetic studies towards staurosporine and K252d

3.1 Project aims and route design

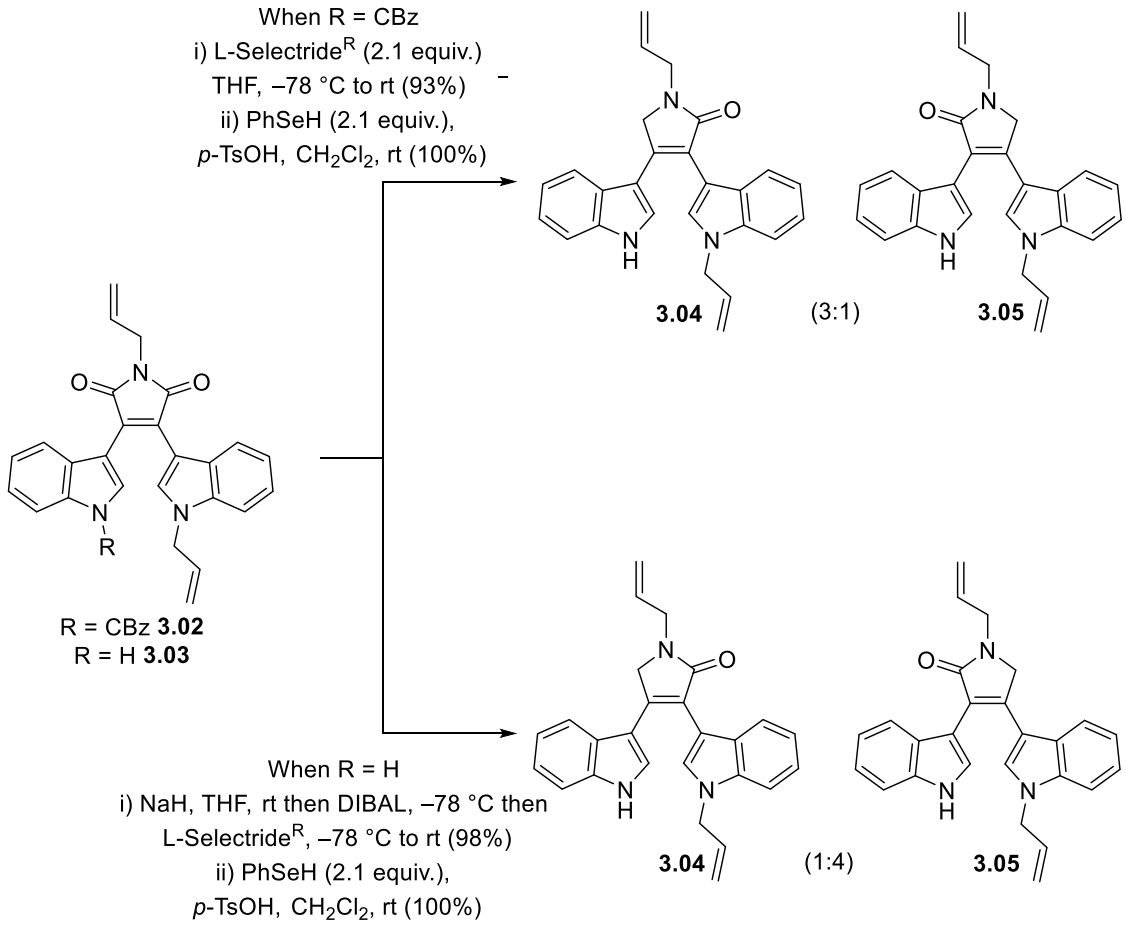
3.1.1 Issues with previous syntheses of staurosporine

Having investigated the cyclisation of bisindolylmaleimide (**1.54**) to arcyriaflavin A (**1.55**) and the staurosporine aglycone (**1.10**), focus now switched to target staurosporine (**1.07**). Of particular importance was controlling the regioselectivity associated with the coupling of the aglycone and the sugar fragments. During their studies into indolocarbazoles, Danishefsky and co-workers' isolated staurosporine (**1.07**) and iso-staurosporine (**1.177**) in a 1:1 mixture after a final stage reduction that proved non-trivial (scheme 30). Wood and co-workers' improved on this, achieving a 2:1 selectivity in favour of the desired regioisomer (**1.122**) during their cycloglycosidation strategy (scheme 30). However, if this coupling could be carried out with exclusive regiocontrol, the approach would be amendable to a variety of other indolocarbazole natural products, most notably K252d (**3.01**), an indolocarbazole that to date has not been the subject of any synthetic endeavours.



Scheme 30 Regioselectivity defining steps in Danishefsky and Wood's synthesis of staurosporine (**1.07**).

The selective reduction of bisindolylmaleimide derivatives has been explored by Danishefsky and co-workers' with the aim to impart inductive control over the site of reduction. The Cbz-group was employed in **3.02** as an electron-withdrawing group that was also cleaved upon warming to rt, whilst the free *N*-H was utilised in **3.03** as the electron-donating system after formation of its sodium salt (scheme 31) and it was concluded that the observed selectivity in the systems was governed by complexation of the reducing agent to the most electron rich carbonyl.

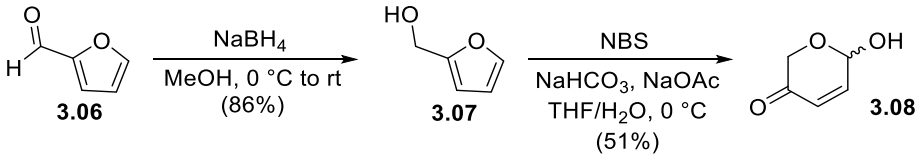


Scheme 31 Danishefsky and co-workers' studies into the regioselective reduction of bisindolylmaleimides

Despite the promising selectivity obtained in this study, Danishefsky and co-workers' were unable to apply this chemistry to staurosporine (**1.07**) and it was decided that complete control over regioselectivity would be unlikely using a late stage reduction. Instead a more fruitful approach would likely involve careful construction of the bisindole core with sufficient electronic bias to impart a regioselective glycosylation. One such method of interest was the Tsuji-Trost reaction of pyranones, which has been successfully employed for the *N*-glycosylation of benzimidazoles, purines and indolocarbazoles.[117,118] If successful, this approach would prove useful due to the ability to carry out an Noyori asymmetric hydrogenation of an acetyl furan derivative, and after the ensuing Achmatowicz rearrangement carry out a resolution to obtain the desired pyranone diastereoisomer for the stereorententive Tsuji-Trost reaction.[119,120]

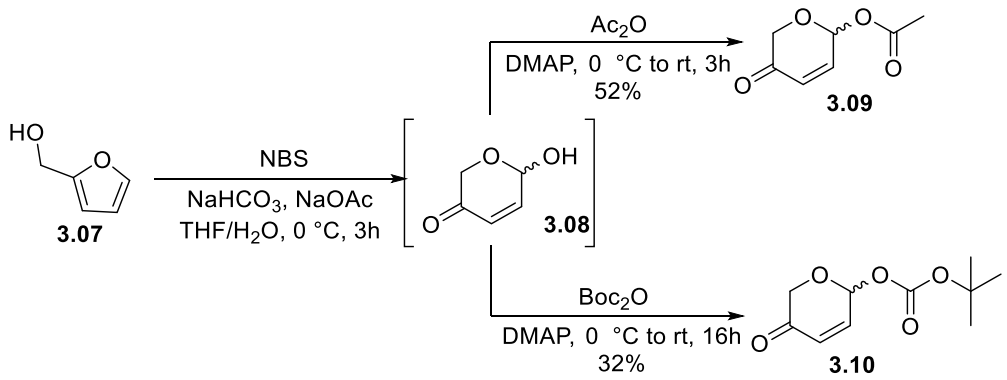
3.1.2 Tsuji-Trost as a method for *N*-glycosylation

The primary focus was to explore the viability of the Tsuji-Trost reaction as a means of glycosylating indoles. As such, the racemic synthesis of a simple pyranone fragment began with a preliminary reduction of furfural (**3.06**) to alcohol **3.07** before an NBS promoted Achmatowicz rearrangement gave pyranone **3.08** in moderate yield.[121]



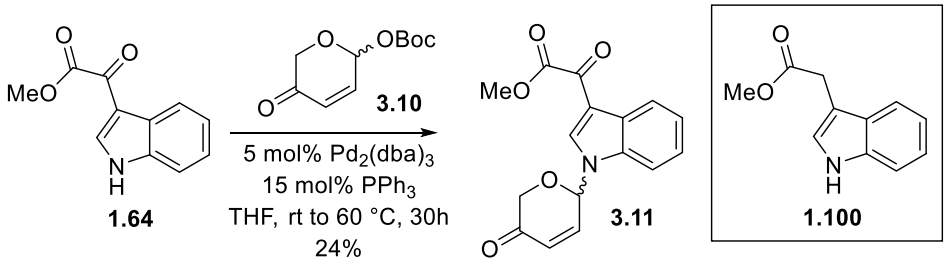
Scheme 32 Synthesis of pyranone **3.08**.

Initial attempts to advance pyranone **3.08** were thwarted with its rapid decomposition at room temperature, producing a highly insoluble dark brown/black oil. Unfortunately, attempts to characterise this product were unsuccessful. Despite this, the stability issues were solved with an *in situ* protection of the free hydroxyl, either by acetylation or Boc-protection (scheme 33).[122]



Scheme 33 Synthesis of protected pyranones **3.09** and **3.10**.

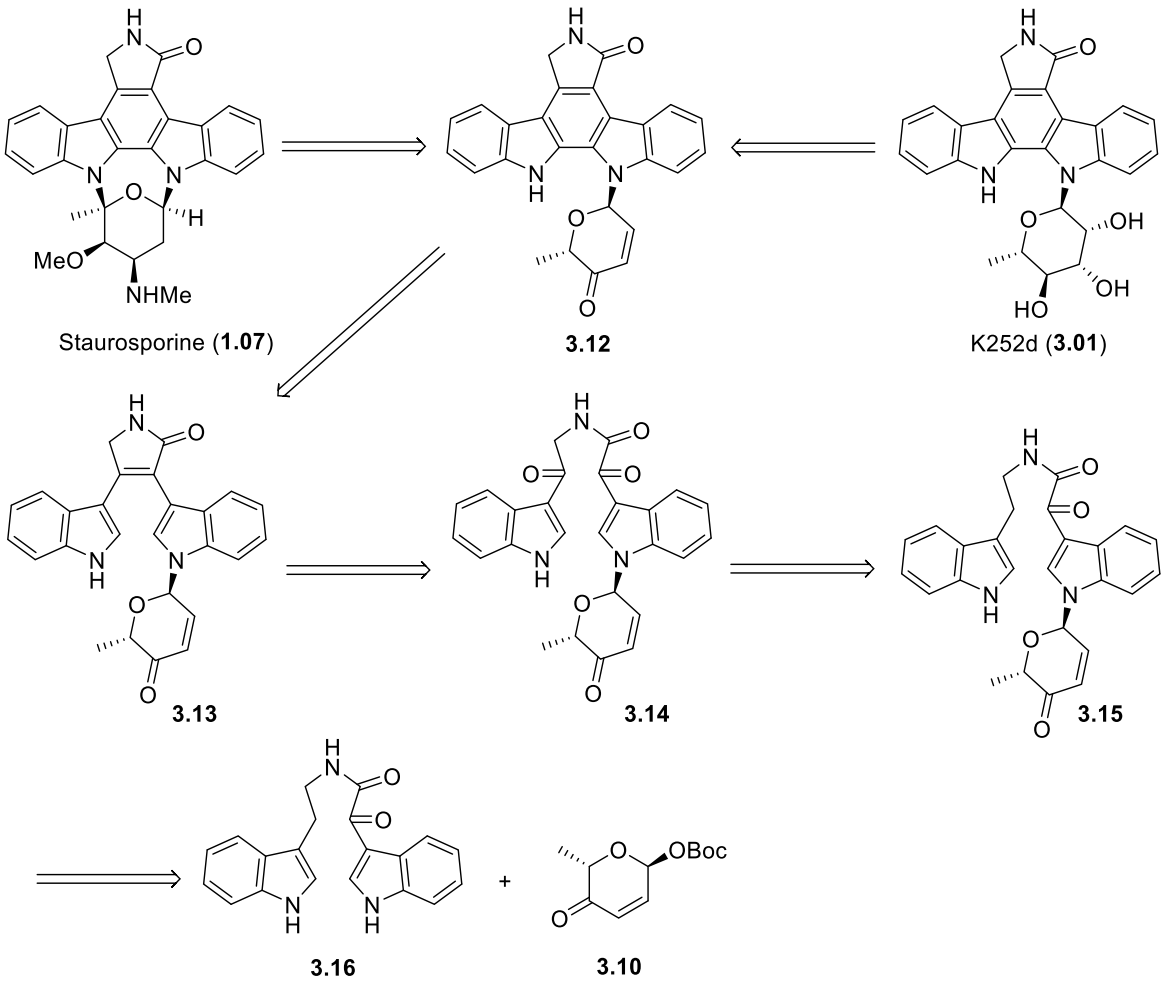
Having isolated pyranones **3.09** and **3.10**, investigations into the coupling of indole fragments could begin. Initial studies explored the potential coupling of ester **1.100** and the acetyl pyranone **3.09**. Using tetrakis(triphenylphosphine)palladium(0) and $Pd_2(dba)_3$ as the catalytic species saw no reactivity at all. Even switching to Boc-protected pyranone **3.10** still led to none of the desired product. It was proposed at this stage that the indolic *N*-H was insufficiently acidic to be deprotonated and react with the π-allyl complex. As such, the more active indole **1.64** was subjected to similar conditions (scheme 34) and, albeit in poor yield, conversion to the desired *N*-glycoside **3.11** was realised. Unfortunately, full conversion of the indole **1.64** was not possible even at extended reaction times, however this result was promising and presents the Tsuji-Trost as a method to selectively functionalise activated indoles.



Scheme 34 Tsuji-Trost *N*-glycosylation of indole **1.64**.

3.1.3 Design of approach

With the viability of the Tsuji-Trost established, in particular the selective nature of the glycosylation favouring electron poor indoles, a revised approach to staurosporine (**1.07**) and K252d (**3.01**) was devised (scheme 35). The approach centred on accessing glycosylated indolocarbazole **3.12**, a versatile intermediate that would enable access to both staurosporine (**1.07**) and K252d (**3.01**). Indolocarbazole **3.12** could be accessed via a photochemical cyclisation of bisindole **3.13**, which in turn would be accessed by a McMurry reaction from diketone **3.14**. Ketone **3.14** would be installed via benzylic oxidation to provide bisindole **3.16** as the coupling partner. The presence of the ketone was predicted to provide sufficient electronic bias to achieve a regioselective glycosylation with the key bisindole **3.16** previously demonstrated to show selectivity by Trost and co-workers'.[123]

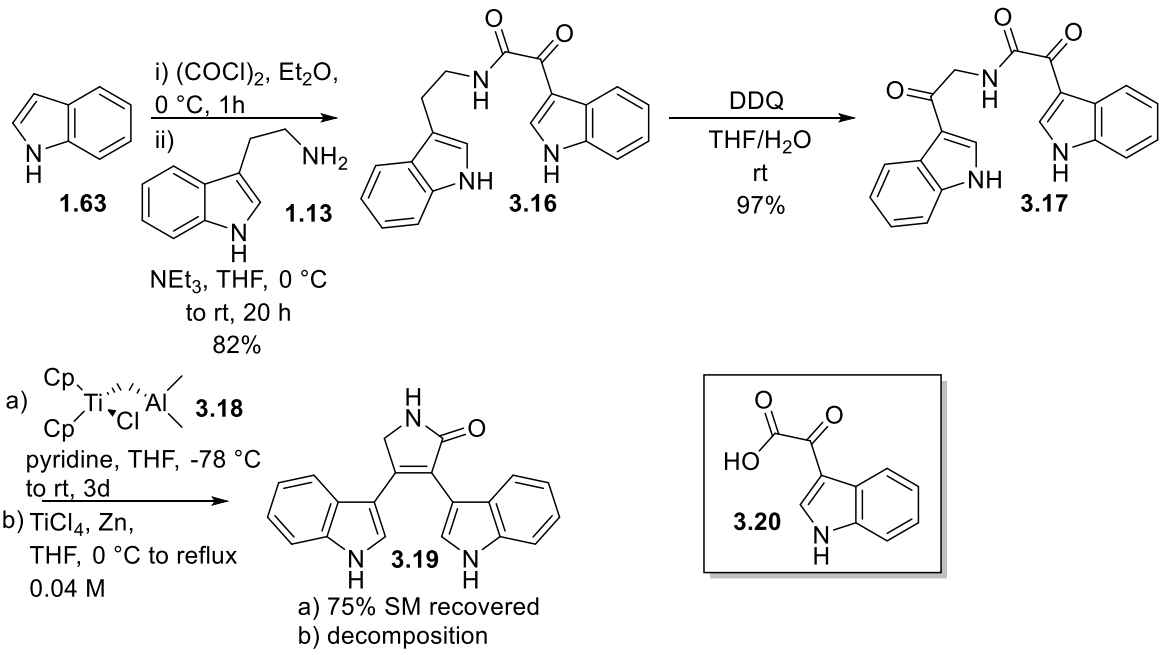


Scheme 35 Retrosynthetic analysis of staurosporine (**1.07**) and K252d (**3.01**).

3.2 Towards the staurosporine aglycone

3.2.1 McMurry cyclisation approach

Due to the precedence of bisindole **3.16** as a glycosyl acceptor, the more urgent matter of whether bisindole **3.16** could be cyclised to lactam **3.19** was attended to first (scheme 36). In an adapted procedure described by Chakrabarty and co-workers', acylation of indole (**1.63**) with oxalyl chloride followed by quenching of the mixture with tryptamine (**1.13**) in the prescence of NEt_3 gave the desired bisindole system **3.16** in excellent yield.[124] NEt_3 was found to greatly increase the yield here. In the absence of base, acid **3.20** was commonly isolated in moderate yields, indicating the base was vital in quenching the HCl produced and preventing it from protonating the amine and diminishing the reactivity. Subsequent benzylic oxidation gave bisindole **3.17** and studies into imparting the cyclisation to lactam **3.19** began.



Scheme 36 Attempted synthesis of lactam **3.19**.

The two methods investigated were a direct cyclisation utilising the McMurry reaction or alternatively, methylenation of the two ketones via a Wittig or Tebbe olefination, and then subsequent Grubbs metathesis to the desired lactam **3.19**. Due to the indolic protons in the system, it was decided that the Wittig salt would likely be quenched under the reaction conditions, and so Tebbe reaction was chosen (scheme 36). However, the attempted olefination led to almost quantitative recovery of the starting material. In contrast, McMurry conditions led to no reaction at room temperature and complete decomposition of the starting material with no sign of the desired product at elevated temperatures.

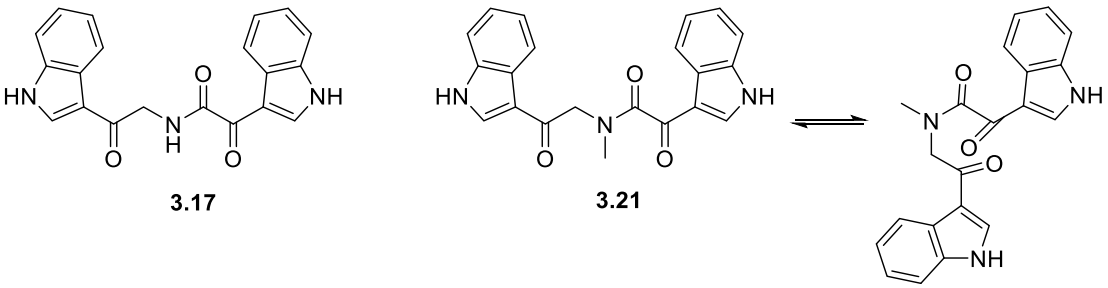
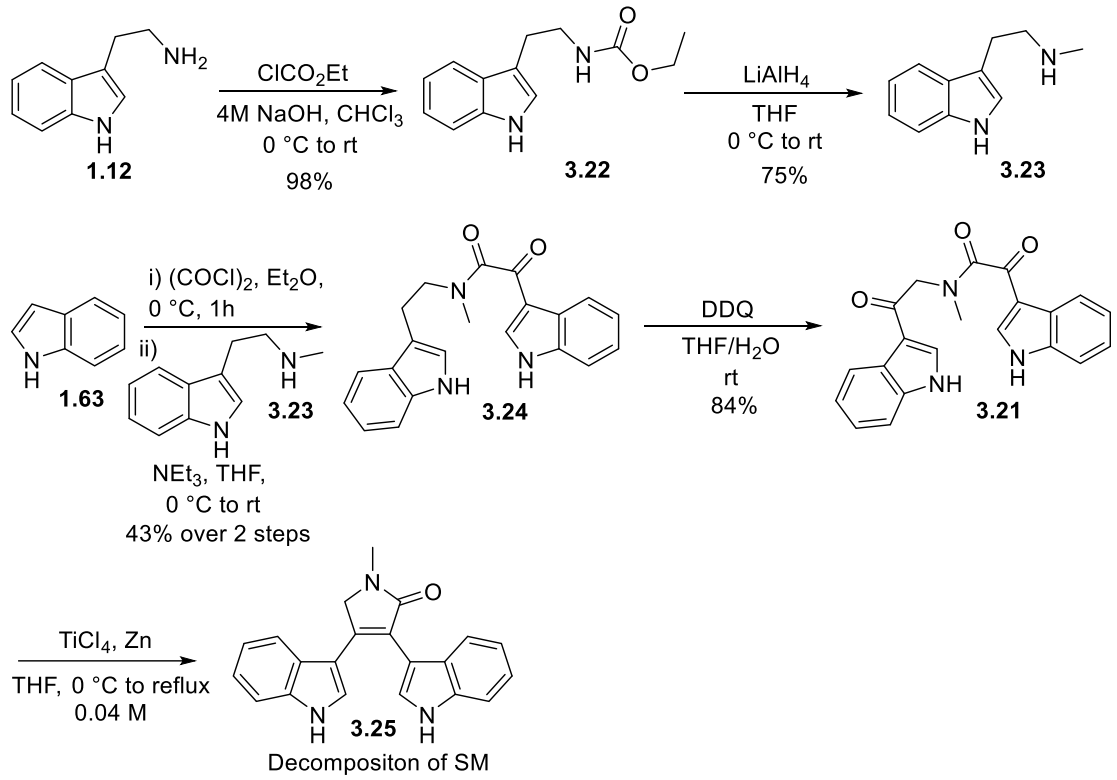


Figure 13 Proposed conformation of bisindole **3.17**.

Unable to decipher the degradation product structure, it was proposed that the reluctance to cyclisation would likely be due to the amide favouring the s-*cis* linear conformation shown (figure 12). As such, substitution at the amide nitrogen may disfavour the unwanted linear conformation sufficiently for cyclisation to the desired lactam **3.19**. To test this theory, the simple *N*-methyl amide **3.21** would be isolated and subjected to the same reaction conditions. The synthesis started according to the procedure described by Chaudhuri and

co-workers' with isolation of carbamate **3.22** before reduction to methyl tryptamine (**3.23**, scheme 37).[125] Subjection of methyl tryptamine (**3.23**) to the same acylation/amidation protocol gave the desired bisindole **3.24** in moderate yield which was subsequently oxidised with DDQ to the desired bisindole **3.21**. Unfortunately, attempts to cyclise bisindole **3.21** to the desired *N*-methyl lactam **3.25** using the McMurry conditions were again unsuccessful.



Scheme 37 Attempted synthesis of *N*-methyl lactam **3.25**.

After consideration of the variable temperature NMR of bisindole **3.21** (figure 13), it was evident the rotational energy barrier was exceedingly high for this type of amide, with very little coalescing of peaks even at elevated temperatures of 393 K. The variable temperature analysis acquired for bisindole **3.24** appeared to further enforce this and therefore reinforced the difficulty imparting the McMurry cyclisation on bisindole **3.21**. Therefore with the lack of success cyclising both the *N*-H and *N*-methyl lactams, this approach to staurosporine (**1.07**) was reviewed.

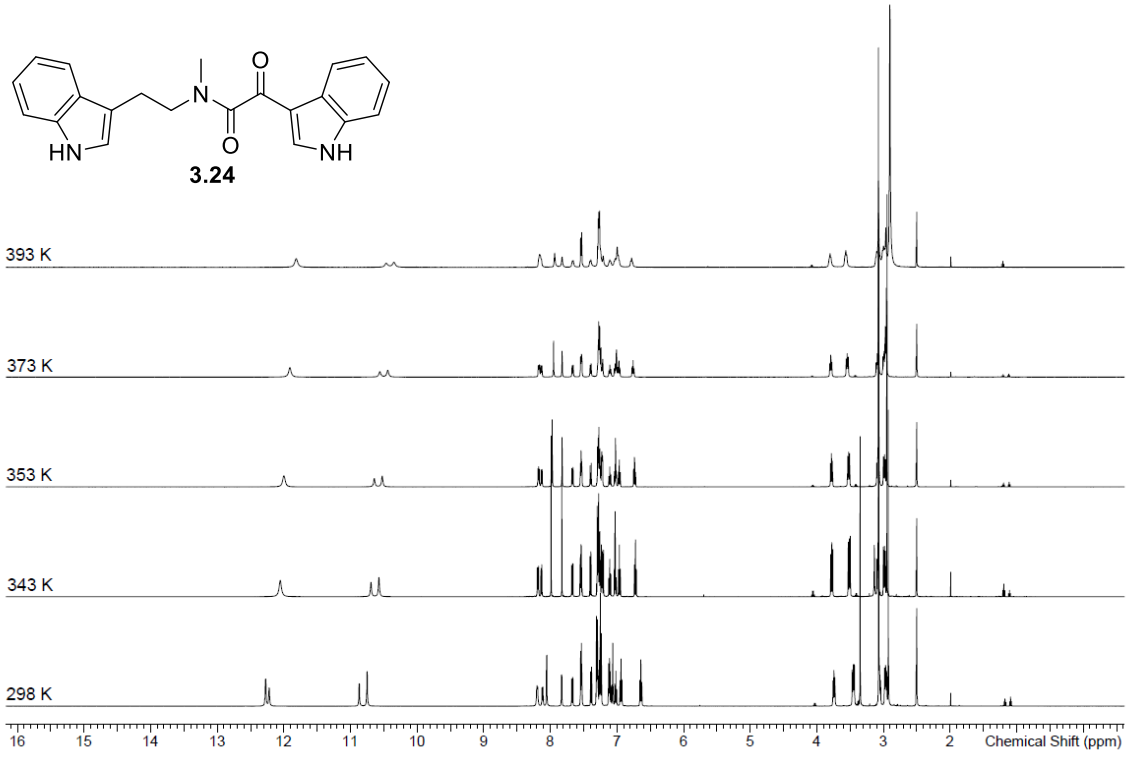


Figure 14 Variable temperature NMR for bisindole **3.24**.

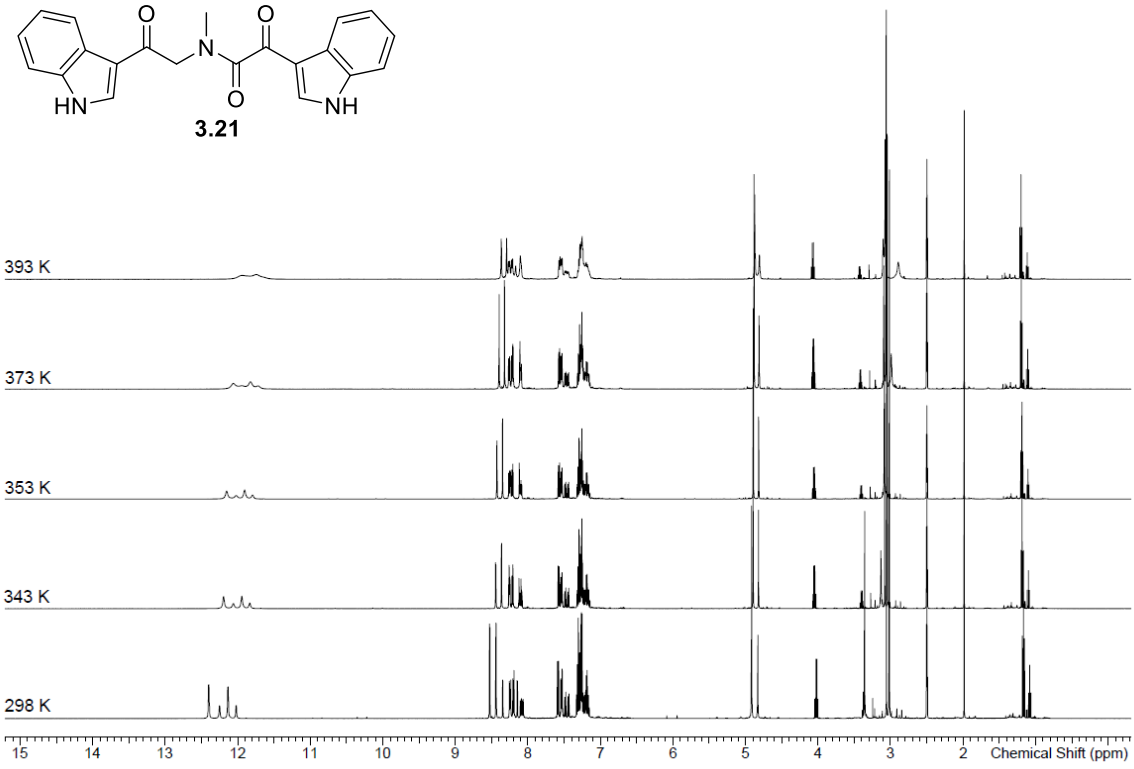
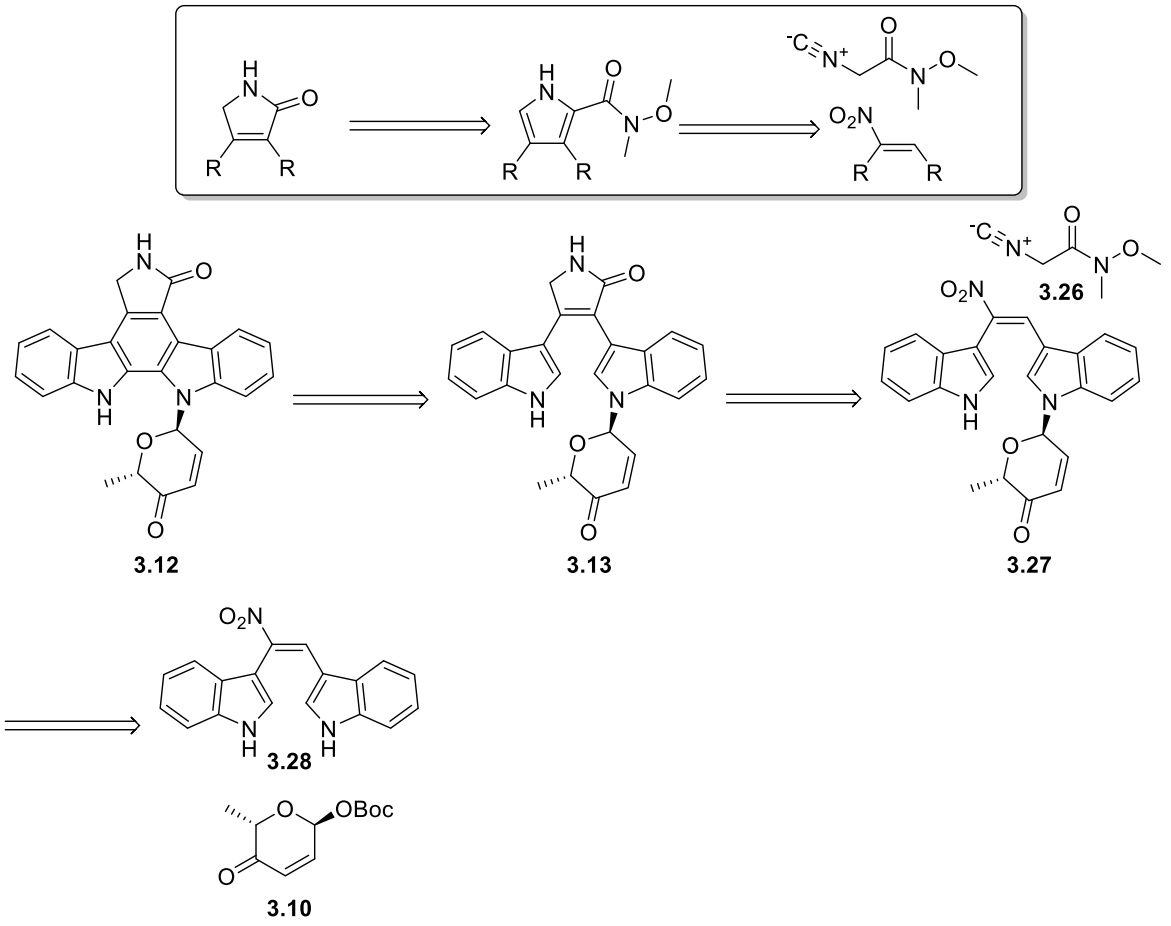


Figure 15 Variable temperatue NMR for bisindole **3.21**.

3.2.2 Barton-Zard pyrrole synthesis approach

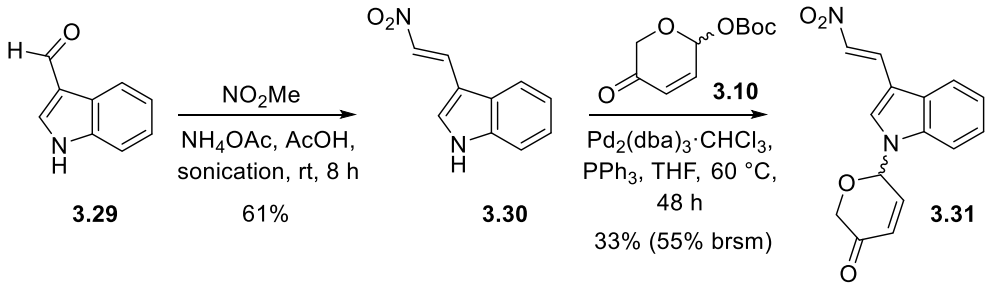
When reviewing the initial approach to staurosporine (**1.07**), glycoside **3.12** remained the key target due to its potential to access both staurosporine (**1.07**) and K252d (**3.01**). With this in mind, and alternate strategy to construct the bisindole lactam fragment was explored. One attractive method was via pyrrole Weinreb amides.[126,127] Of particular interest was the fact these pyrrole Weinreb amides can be isolated from nitro olefins via Michael-addition of isocyanates.[126,127] It was proposed the bisindole **3.26** would be a suitable acceptor for isocyanate **3.27**. Additionally, this would likely enable the desired regiochemistry in the Tsuji-Trost glycosylation reaction with pyranone **3.10**, due to the electron withdrawing nature of the nitro group activating the distal indolic nitrogen.



Scheme 38 Retrosynthetic analysis of glycoside **3.12**.

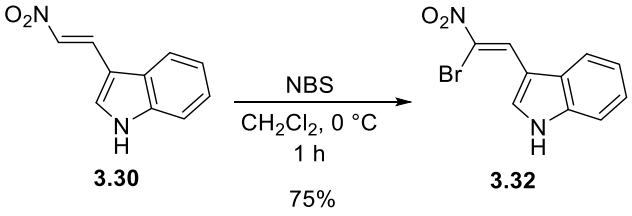
To investigate the feasibility of the approach, the reactivity of nitro-olefin indole derivatives under Tsuji-Trost conditions would first need to be confirmed. Isolation of nitro-olefin **3.30** was achieved via Henry reaction with indole carbaldehyde (**3.29**, scheme 39). The use of ammonium acetate in refluxing nitromethane provided nitro-olefin **3.30** in excellent yield on mg scale. However, issues were encountered with the scale-up of this procedure, leading to large quantities of a dark black highly insoluble syrup. This was attributed to a polymeric

by-product likely formed at elevated temperatures.[128] An excellent procedure described by McNulty and co-workers' utilised sonication to promote the reaction and circumvent the polymeric issues. Sonication of indole carbaldehyde (**3.29**) in a mixture of nitromethane, acetic acid and ammonium acetate gave clean conversion to the desired nitro-olefin **3.30** in good yield on multi-gram scale. Attempts to drive the reaction to completion were unsuccessful even at extended reaction times, however use of a stronger ultrasound bath may provide the solution. Subjection of the obtained nitro-olefin **3.30** to Tsuji-Trost conditions with pyranone **3.10** and $Pd_2(dba)_3$•$CHCl_3$ as the palladium source gave glycoside **3.31** in moderate yield, reaffirming the viability of the approach.



Scheme 39 Tsuji-Trost glycosylation of nitro-olefin **3.31**.

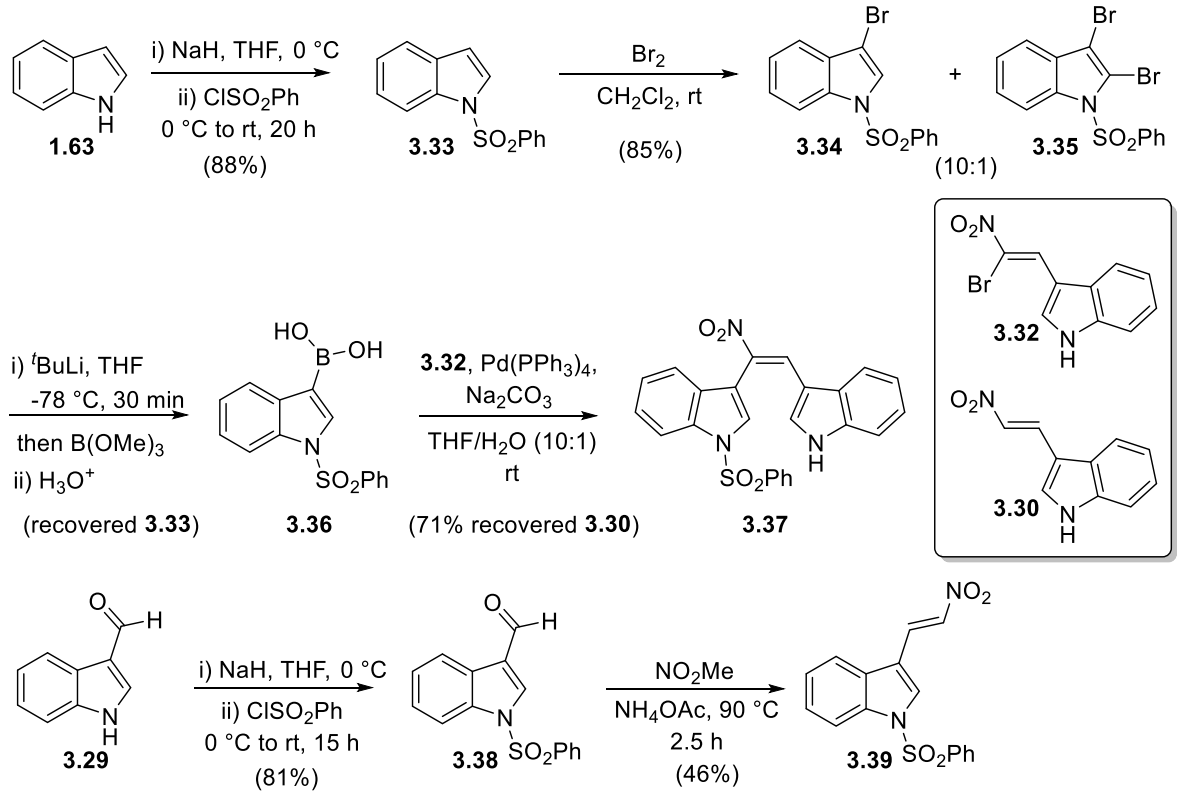
With this result in hand, studies into the synthesis of bisindole **3.28** commenced. The approach centred upon utilising a Suzuki cross-coupling between indole boronic acid **3.36** and bromo nitro-olefin **3.32** (scheme 40). It was proposed this could be accessed via a chemoselective bromination of nitro-olefin **3.30** with *N*-bromosuccinimide (NBS). Pleasingly, halogenation proceeded rapidly at reduced temperature, providing the bromo nitro-olefin **3.32** in excellent yield and allowing studies into the cross coupling to commence.



Scheme 40 Chemoselective bromination of nitro-olefin **3.32**.

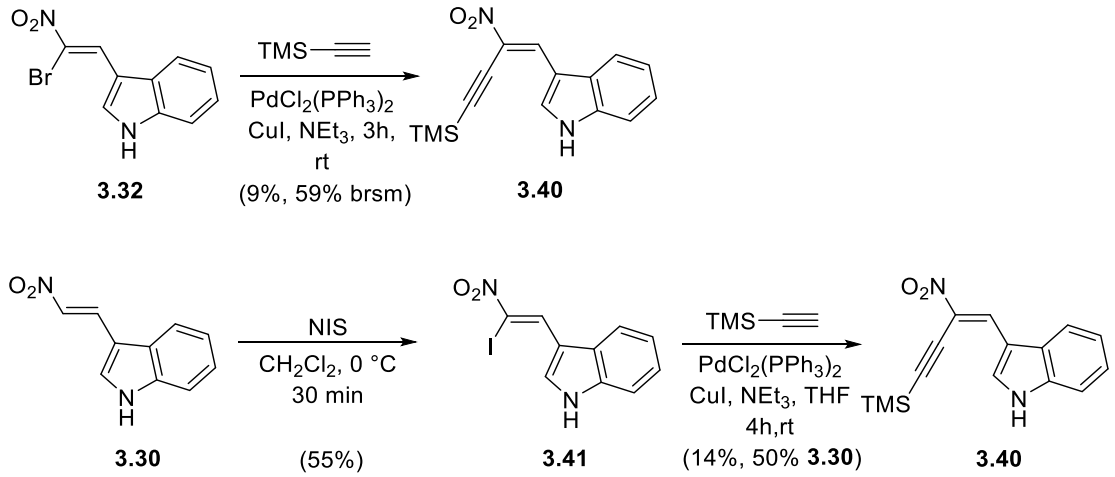
Indole boronic acid **3.36** is a commercially available compound, however due to the cost, it was decided to isolate it from the much cheaper indole (**1.63**). Protection of indole (**1.63**) with phenylsulfonyl chloride was followed by bromination with molecular bromine as described by Booker-Milburn and co-workers' (scheme 41).[129] Unfortunately, regardless of the temperature and equivalents of bromine used, an inseperable mixture of the desired mono-brominated indole **3.34** and a by-product that has been tentatively assigned as di-brominated indole **3.35**, was obtained. After multiple attempts to separate the two

compounds, the commercial mono-brominated indole **3.34** was purchased, however also as a 10:1 mixture of the same by-product by ^{1}H NMR. Despite the by-product, the synthesis proceeded with attempted halogen-lithium exchange with ^{t}BuLi followed by quenching with trimethyl borate to deliver the desired boronic acid **3.36**.[130] Unfortunately, this was unsuccessful yielding primarily indole **3.33**. The implications were that trapping of the lithiiated indole species with trimethyl borate was therefore slow, however attempts to quench with triisopropyl borate and even D_2O all led to isolation of the same indole **3.33**.



Scheme 41 Attempted synthesis of nitroolefin **3.37**.

With difficulties isolating the boronic acid **3.36**, it was instead purchased and studies into the Suzuki cross-coupling could begin. Initial attempts with tetrakis(triphenylphosphine) palladium and sodium carbonate at rt led to no conversion of the starting bromo-nitro olefin **3.32**. Heating of the reaction mixture to 50 °C, as well as to 100 °C under sealed microwave conditions both led to the nitro indole **3.30**. It was proposed that the indole *N*-H was causing issues, however attempts to isolate the protected bromo-olefin were unsuccessful, with the reduced electron density on nitroolefin **3.39** leading to no bromine incorporation even using molecular bromine and at elevated temperatures. At this stage this approach was placed on hold, with focus switched to a Sonogashira/Larrock indole synthesis approach to install the second indole ring (scheme 42).

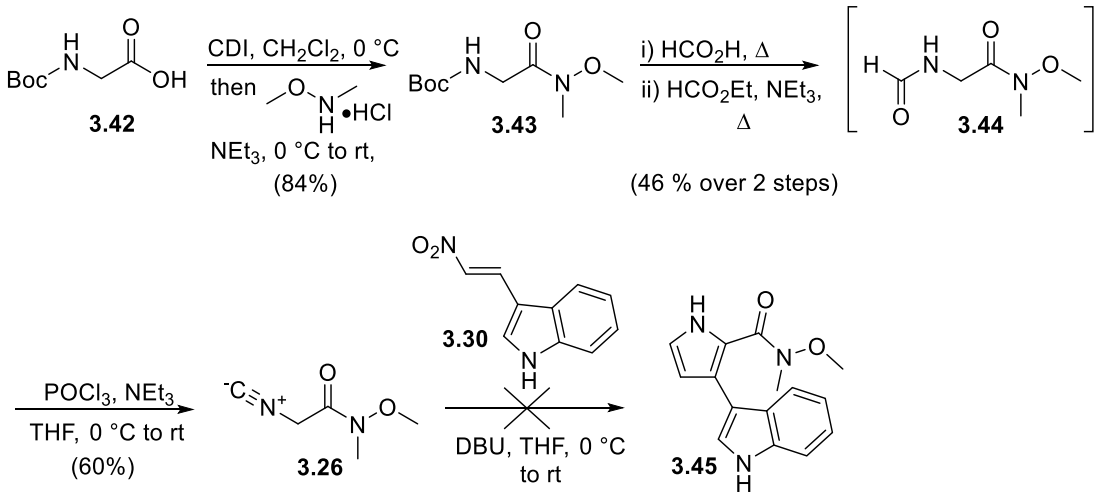


Scheme 42 Synthesis of alkyne **3.40**.

Sonogashira coupling of bromo-nitro olefin **3.32** with TMS acetylene using tetrakis(triphenylphosphine) palladium, *N*-methyl morpholine in toluene at 60 °C was attempted.[131] Unfortunately, this led to none of the desired alkyne **3.40**. Changing of the base and the palladium source however led to some success, with $PdCl_2(PPh_3)_2$ in neat NEt_3 delivering the best results. Attempts to improve the yield at elevated temperatures (60 °C, sealed in microwave) and in different solvents (THF and DMF) led to no improvement over the disappointing 9% achieved at low conversion of starting material.

It was proposed the iodo-nitro olefin **3.41** may be a better coupling partner, and this was readily prepared from the nitro olefin **3.30** using *N*-iodosuccinimide in moderate overall yield. Subjection to the same conditions, just in THF due to solubility issues associated with the iodo-nitro olefin **3.41**, led to similar yields of the desired product (14%), and around 50% recovered nitro indole **3.30**. Again, elevated temperatures and use of DMF as solvent led to clean dehalogentation giving nitro olefin **3.30**. At this stage, the best yield obtained of the desired alkyne **3.40** was only around 10%. However, before investing further time into optimisation of the Sonogashira reaction, the feasibility of the Barton-Zard pyrrole synthesis was investigated.

Following the procedure described by Ballatore and co-workers', Boc-Gly-OH (**3.42**) was converted to the correspronding Weinreb amide **3.43** (scheme 43).[132] Then utilising the protocol described by Pelkey and co-workers', deprotection of the Boc-group in formic acid and subsequent *N*-formylation gave formamide **3.44** in moderate yield, which was immediately converted to the isocyanide **3.45** via a $POCl_3$ promoted deoxygenation.[126]

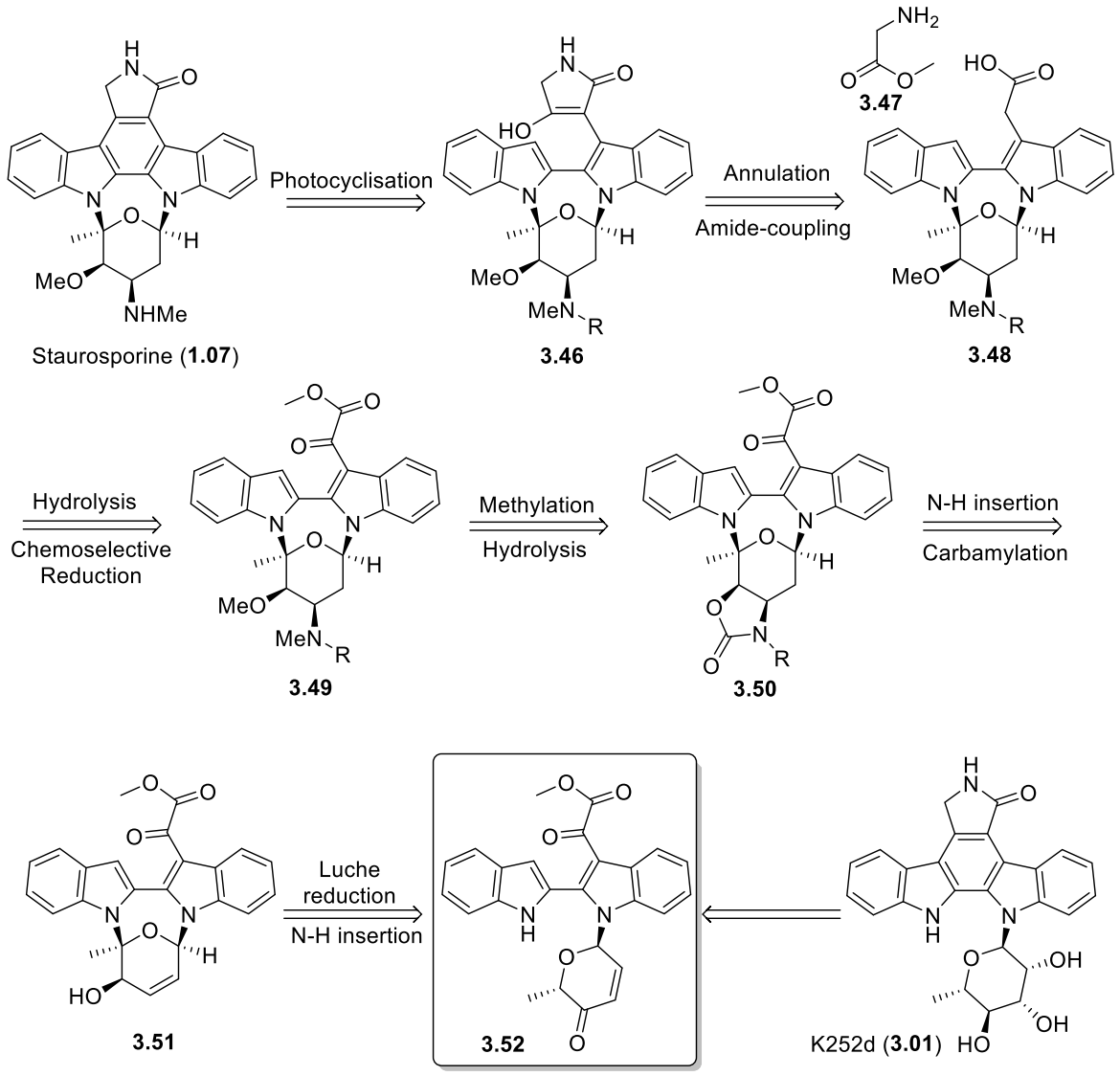


Scheme 43 Attempted synthesis of Weinreb-pyrrole **3.45**.

Disappointingly, attempts to advance the nitro-olefin **3.30** to the desired Weinreb-pyrrole **3.45** were unsuccessful. No reaction was observed at lower temperatures, and at elevated temperatures no starting material was recovered and the degradation by products were unable to be identified. Given the poor yield obtained in the Sonogashira reaction and the inability to advance nitro-olefin **3.30**, it was thought that revisiting the approach and protecting the indole *N*-H may prove effective. However, given the desire to develop an efficient and regioselective approach to these natural products, it was proposed the design of the entire approach be revisited.

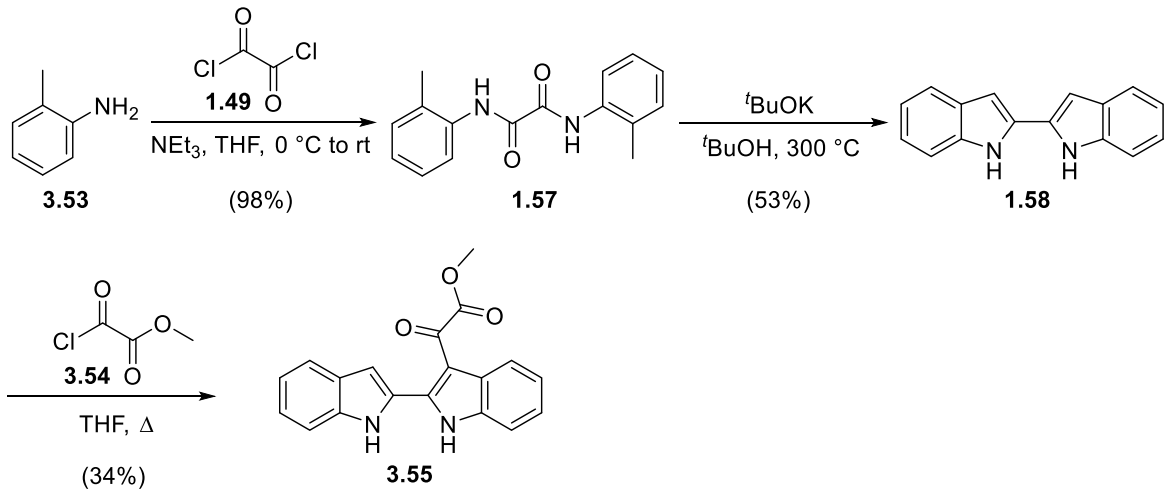
3.2.3 Double-Madelung cyclisation approach:

In all previous retrosynthesis, the key disconnection to introduce the asymmetry in the indolocarbazole core was between 2,2-positions of the two indole rings. However, a similar disconnection between the 3-position of one of the indole rings and the lactam ring can also be made, and further analysis of this intermediate eventually led back to the glycosylated oxo-ester **3.52** (scheme 44). Given previous studies into the Tsuji-Trost reaction of pyranones with activated indoles, the predicted regioselectivity here would be governed by the more acidic *N*-H conjugated to the ketone of the oxo-ester. However, before embarking on this route, a few key questions would need to be answered. Firstly, the regioselectivity of Tsuji-Trost reaction would need to be confirmed. Secondly, establishing the *N*-H insertion reaction via epoxidation of the silyl enol ether of pyranone **3.52** would need to be validated.[133] Additionally, could carbamate **3.50** be hydrolysed selectively in the precence of the methyl ester and finally, could the reduction/annulation/photocyclisation protocol successfully build the top lactam ring of the staurosporine (**1.07**).



Scheme 44 Reviewed retrosynthetic analysis of staurosporine (**1.07**) and K252d (**3.01**).

The approach began with ensuring the regiocontrol in the Tsuji-Trost reaction with isolation of the desired 2,2-biindole derivative **3.55** (scheme 45). The synthesis utilised the excellent procedure described by Bergman and co-workers' to isolate 2,2'-biindole (**1.58**).[53] *Ortho*-toluidine (**3.53**) was condensed with oxalyl chloride (**1.49**) to access diamide **1.57** before the potassium *tert*-butoxide promoted double Madelung cyclisation at elevated temperatures provided 2,2'-biindole (**1.58**) in good yield. With this in hand, studies into the acylation began. Initial attempts utilising oxalyl chloride (**1.49**) and quenching the acid chloride *in situ* with MeOH delivered none of the desired product and saw lots of degradation. Switching the acylating agent to methyl chlorooxoacetate (**3.54**) saw no productivity, even under activation of $AlCl_3$ as a Lewis acid. The addition of NEt_3 to the reaction mixture again led to no observed productivity, however some success was found by changing the temperature at which methyl chlorooxoacetate (**3.54**) was added.



Scheme 45 Synthesis of 2,2'-biindole derivative **3.55**.

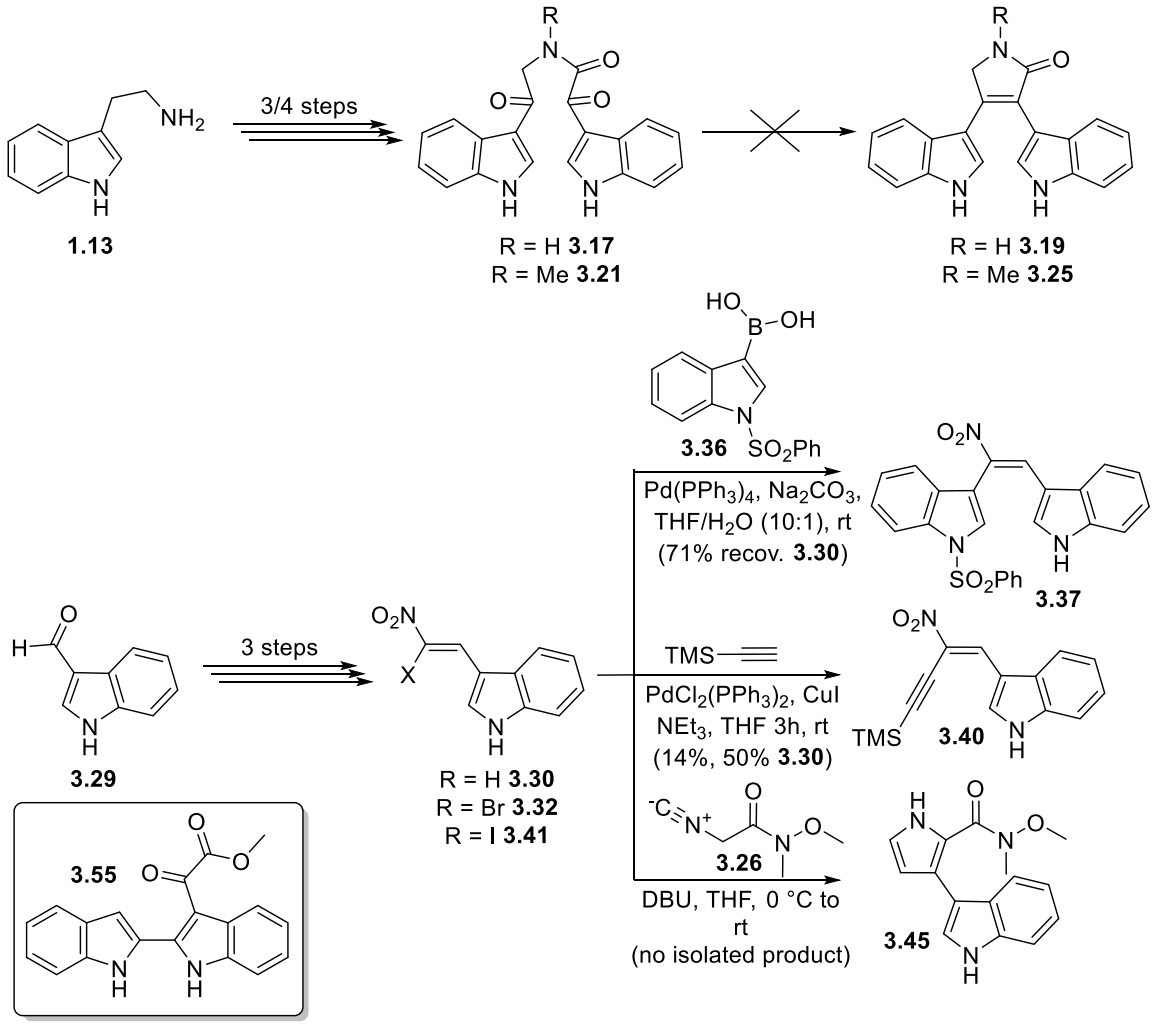
Addition of chlorooxoacetate (**3.54**) to 2,2'biindole (**1.58**) in THF at rt before warming to Δ showed trace product but predominantly several decomposition by-products, the structures of which were not elucidated. However, dropwise addition of chlorooxoacetate (**3.54**) to 2,2'-biindole (**1.58**) in THF under reflux provided the desired acylated 2,2'biindole **3.55** albeit in poor yield. Frustratingly, this material also proved particularly unstable and rapidly degraded even when stored under N_2 at ─5 °C. Elevated temperatures appeared a requisite for successful acylation, however, also led to rapid degradation and therefore a modification to the approach was required.

Interestingly, attempts to acylate 2,2'-biindole (**1.58**) with ethyl chloroformate under identical conditions led to complete recovery of the starting material, indicating the more electrophillc acid chloride was required for reactivity. Literature precedence for similar biindole systems detailed that protection of one of the indolic nitrogens can solve these stability issues, however this again moves away from the aims of the project to achieve regioselectivity in the glycosylation step by a differential in reactivity of the two indolic nitrogens, rather than a simple protection, and consequently, this approach was not advanced further.

3.2.4 Conclusions and Future Work

The Tsuji-Trost reaction was established as a viable means to glycosylate the indole core, with success using indole units bearing a carbonyl or nitro-olefin moiety at the 3-position. However, attempts to advance any of these intermediates to the staurosporine aglycone (**1.10**), staurosporine (**1.07**) or K252d (**3.01**) were unsuccessful. The initial McMurry cyclisation idea was hampered by an inability to close the top pyrrolone ring in amides **3.19** and **3.25**, presumed due to the high temperature required to overcome the rotational energy barrier (scheme 46). During the Barton-Zard pyrrole synthesis approach, the Suzuki cross-coupling between indole boronic acid **3.36** and the bromo-nitroolefin **3.32** was unfortunately

unsuccessful. However, a solution was found in the Sonogashira cross-coupling which provided access to alkyne **3.40**. Despite the poor yield, the reaction was unoptimised and given recovery of the dehalogenated material presented an option perhaps worthy of further study. Investigating the pivotal Barton-Zard pyrrole construction, reaction of isocyanide **3.26** and nitroolefin **3.30** were ineffective in providing access to the desired pyrrole and led again to a revised approach. Finally, the 2,2'-biindole approach was severely hampered by the stability of the isolated oxoester intermediate **3.55**. Attempts to advance the material to the glycosylation step were thwarted and preliminary experiments to circumvent the issues with alternative moieties to activate one of the indoles were unsuccessful, leading to a complete review of the approach including the methodology utilised to achieve glycosylation.



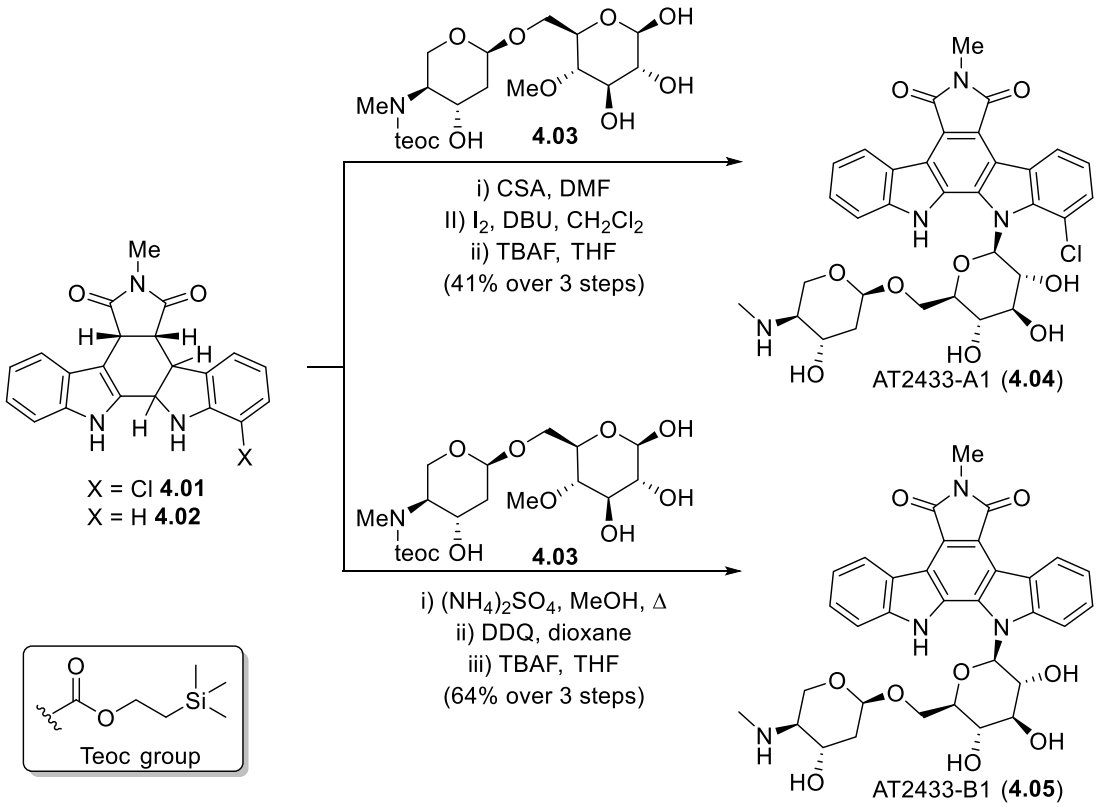
Scheme 46 Attempted synthetic approaches towards the staurosporine aglycone **3.10**.

Chapter 4 Indoline glycosylations applied to the first total synthesis of K252d

4.1 Investigations into indoline glycosylations

4.1.1 Chlorinated aglycone approach

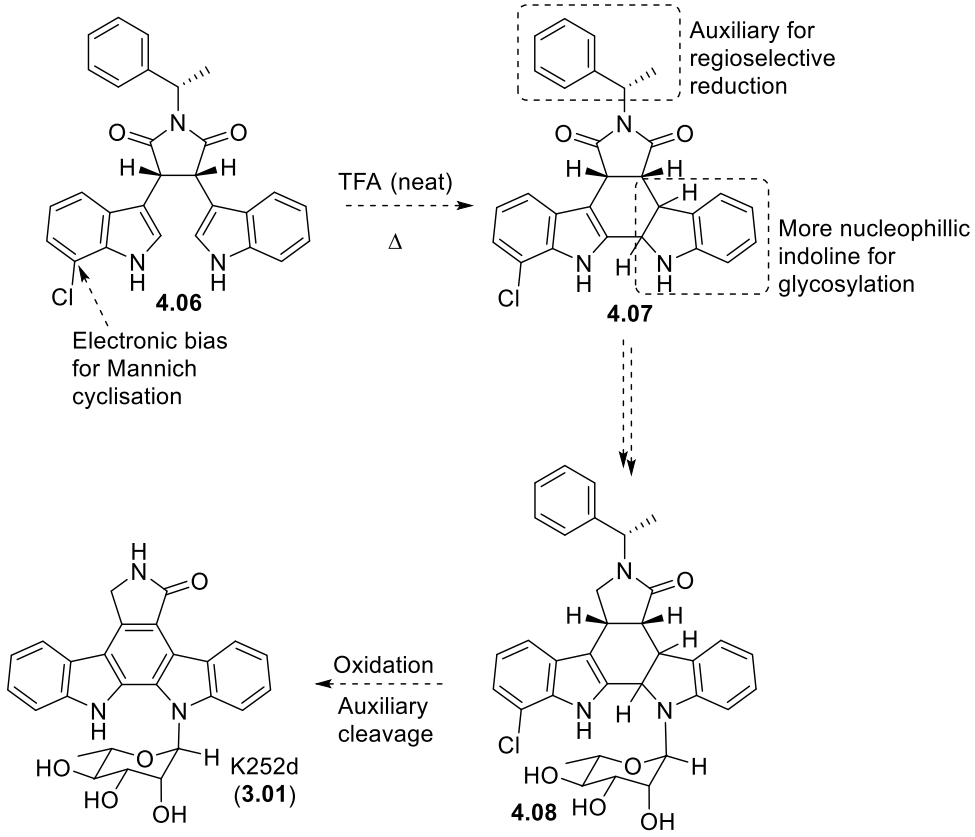
The limited success with previous approaches led to a reconsideration of the synthetic route design. Difficulty advancing an intermediate that would enable a regioselective Tsuji-Trost glycosylation of the aglycone fragment led to a reassessment of the glycosylation chemistry. One attractive alternative was to react an indoline derivative directly with a free reducing sugar, based upon work described by Van Vranken and co-workers' in their total synthesis of AT2433-A1 (**4.04**) and AT2433-B1 (**4.05**, scheme 47).[134,135]



Scheme 47 Key glycosylation in Van Vranken and co-workers' syntheses of AT2433-A1 (**4.04**) and AT2433-B1 (**4.05**).

On first inspection of Van Vranken and co-workers' approach, and inspired by Breuning and co-workers' inside-out total synthesis of sparteine, it was envisaged that a chiral auxiliary on the maleimide nitrogen may present an intriguing method to place the two maleimide carbonyls in diastereotopic environments and allow for a selective reduction (scheme 48).[136]

This auxiliary accompanied by distal asymmetry from the halogen in the indolocarbazole core, might allow for both a regioselective reduction and glycosylation.

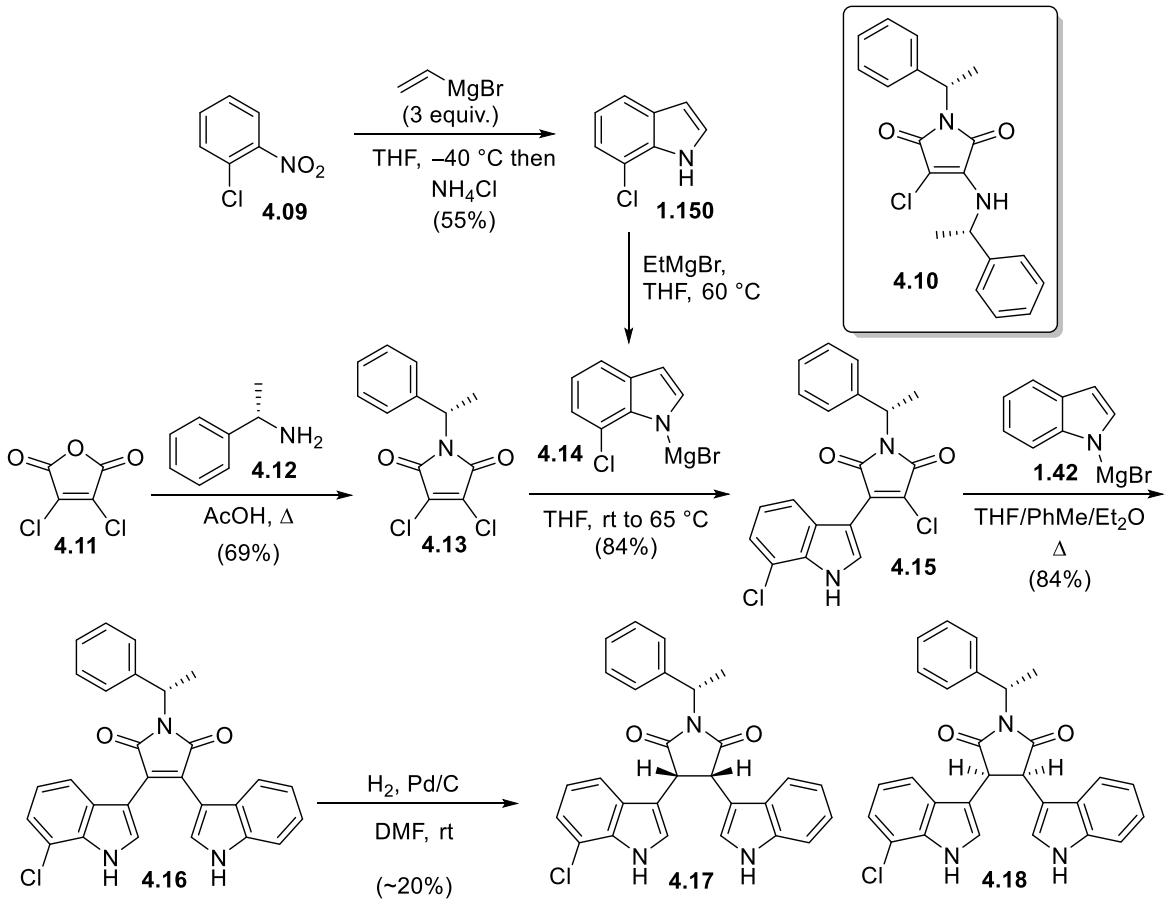


Scheme 48 Proposed strategy to achieve regiocontrol in the synthesis of K252d (**3.01**).

Whilst ambitious, the approach would prove versatile, providing one of the carbonyls could be reduced selectivity. Van Vranken and co-workers' during their endeavours to AT2433-A1 (**4.04**) described the dramatic reversal of regioselectivity in the Mannich cyclisation when an alternative acid source was used.[134] Rationalised using the classical Curtin-Hammett conditions, when trifluoroacetic acid (TFA) was employed protonation of the more electron rich indole and subsequent cyclisation via the more stable indolenium ion would provide indoline **4.07**. However, the group observed a reversal in selectivity when methane sulfonic acid (MSA) was used. As such, depending on the selectivity observed in the reduction, the system could be manipulated to ensure the indoline accessed is proximal to the carbonyl in the pyrrolidone and would enable the desired regioselectivity for the natural product K252d (**3.01**).

The primary concern associated with the design detailed above was whether an auxiliary would in fact be able to impart a regioselective reduction of the succinimide moiety in compounds such as **4.07**. To investigate the feasibility, the synthesis began by attempting to isolate indole-indoline **4.07** shown in scheme 48. Anhydride **4.11** was condensed with (*S*)-phenylethanamine (**4.12**) to give the desired maleimide **4.13** in excellent yield with a

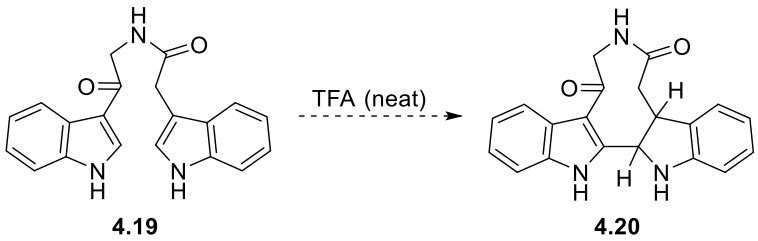
trace amount (5%) of the Michael addition product (**4.10**, scheme 49). 7-Chloroindole (**1.150**) was prepared from 2-chloronitrobenzene (**4.09**) via a Bartoli indole synthesis, before treatment with ethyl magnesium bromide gave the magnesiated indole species **4.14**.[137] This was reacted directly with maleimide **4.13** to give indole **4.15**. Treatment with magnesiated indole **1.42** constructed the bisindolylmaleimide **4.16** in excellent yield however the subsequent hydrogenation did not proceed smoothly. Unfortunately, the desired product was obtained in roughly 20% yield as a ~1:1 mixture of **4.17** and **4.18**, however difficulties isolating clean material were encountered due to the preference for the substrate to undergo palladium mediated dechlorination. As such, a complex diastereomeric mixture of both halogenated and dehalogenated material was acquired.



Scheme 49 Synthesis of bisindolemaleimide **4.16**.

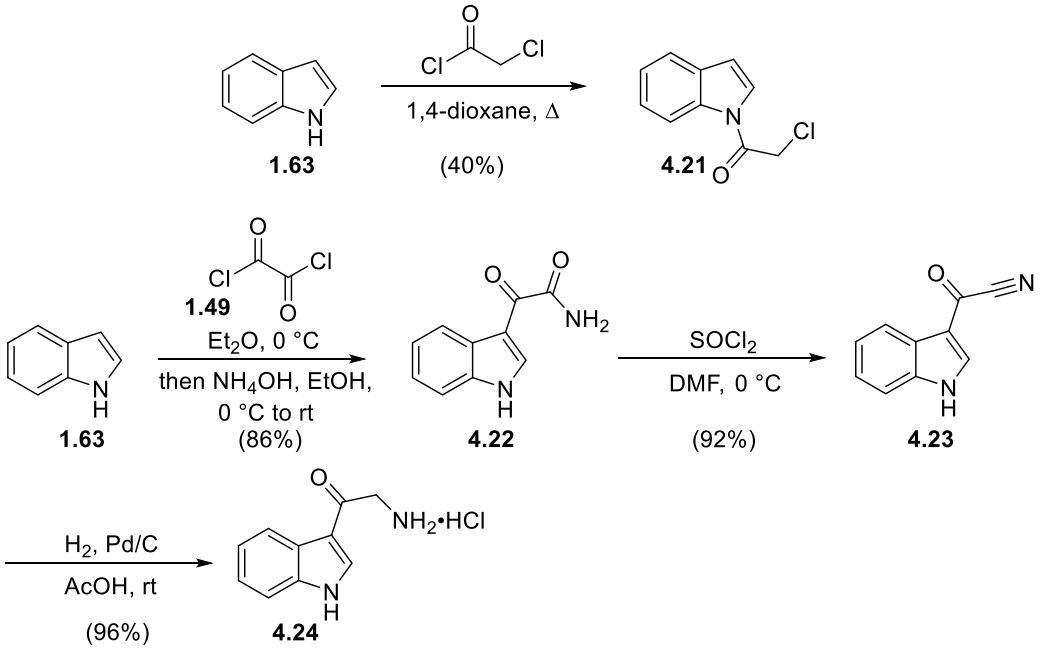
4.1.2 Macrocyclic indoline approach

Difficulty preventing the dechlorination led to a revision of the previous idea. In particular, a much simpler system, bisindole **4.19**, was selected with the hope of exploiting a similar level of regioselectivity to that observed by Van Vranken and co-workers'. The goal was to impart a macrocyclic intramolecular Mannich reaction to indole-indoline **4.20** (scheme 50).



Scheme 50 Potential intramolecular Mannich reaction of bisindole **4.19**.

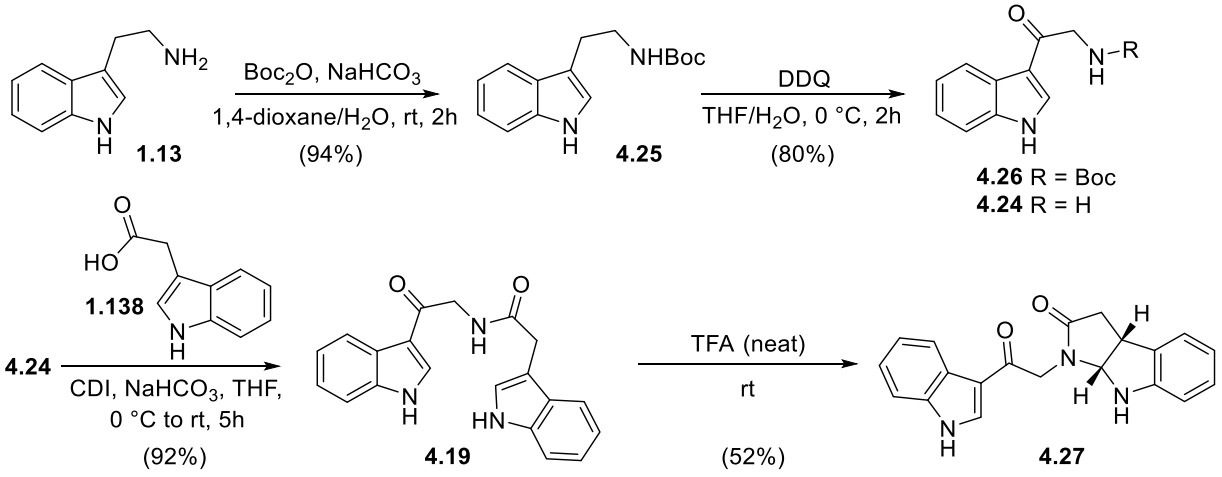
The approach began with the attempted isolation *β*-oxo-tryptamine (**4.24**) *via* Friedel-Crafts acylation of indole (**1.63**) with chloroacetyl chloride as described by Elnagdi and co-workers' (scheme 51).[138,139] This did not however give the desired C3-acylation as described, but instead the *N*-acyl indole **4.21**. An alternative approach was therefore employed that proceeded through C3 Friedel-crafts acylation with oxalyl chloride before quenching with ammonium hydroxide solution to access *β*-ketoamide **4.22**.[140] Thionyl chloride promoted elimination before hydrogenation of the nitrile gave *β*-oxo-tryptamine (**4.24**) as the HCl salt.[139,141] This route proved excellent on initial testing, however attempts to obtain reasonable quantities of the tryptamine derivative were thwarted with degradation in the elimination step.



Scheme 51 Synthesis of *β*-oxotryptamine (**4.24**).

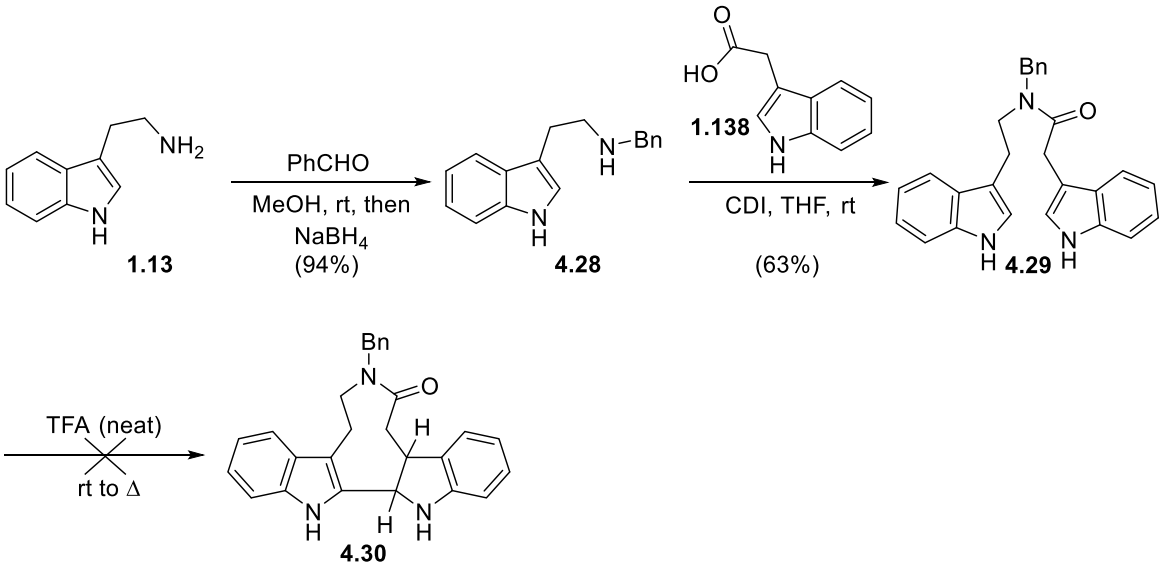
A secondary approach, described by Nicolaou and co-workers', was successfully employed and Boc-protected *β*-oxo-tryptamine (**4.26**) isolated in excellent yield from tryptamine (**1.13**, scheme 52).[142] Additionally, the substrate bearing the Boc-group could be stored and deprotected to give the free base **4.24** as required. A CDI promoted amide coupling with indole acetic acid in the presence of $NaHCO_3$ gave the desired bisindole **4.19** in excellent

yield, before subjection to neat TFA for the desired intramolecular Mannich reaction. The substrate did not undergo the desired macrocyclic annulation, but instead the much faster 5-*exo*-trig cyclisation of the amide nitrogen to give pyrrolidinone **4.27** as a single diastereoisomer. This was unsurprising, but pleasingly, proceeded with exclusive regioselectivity for the thermodynamically more stable product derived from protonation of the more electron rich indole.



Scheme 52 Synthesis of pyrrolidinone **4.27**.

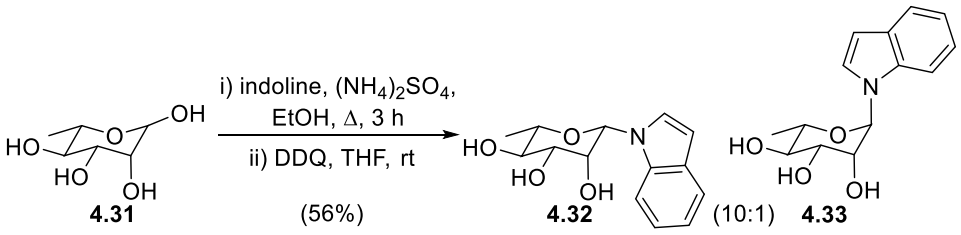
Attempts to suppress this 5-exo-trig utilising a benzyl group on the amide *N*-H, perhaps unsurprisingly resulted in none of the desired macrocyclic annulation and began to present degradation products at elevated temperatures (scheme 53).



Scheme 53 Attempted macrocyclic annulation of bisindole **4.29**.

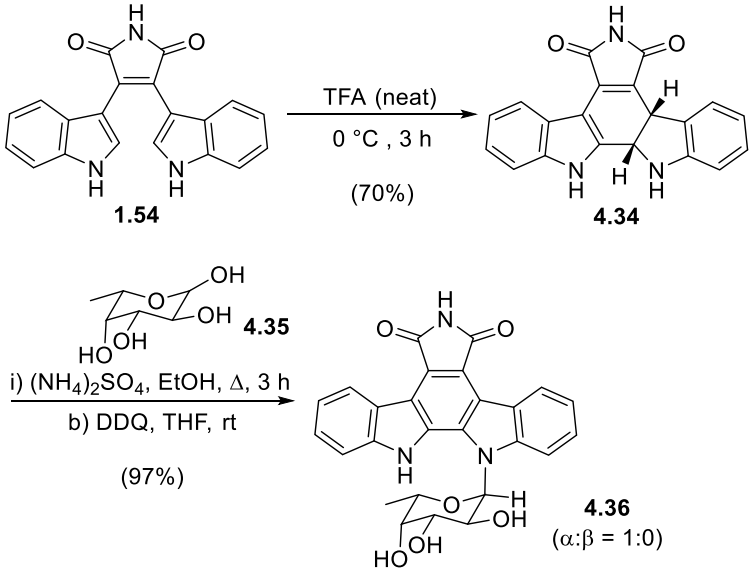
4.1.3 Indoline glycosylations

Taking a step back, the conditions required for the glycosylation of simpler indolines was explored. Treatment of indoline with L-rhamnose (**4.31**) in the prescence of $(NH_4)_2SO_4$ prior to oxidation of the crude reaction mixture gave *N*-glycosides **4.32** and **4.33** as a 1:10 (*α*:*β*) mixture of anomers by ^{1}H NMR (scheme 54).



Scheme 54 Glycosylation of indoline.

The reactivity of other indoline systems was further confirmed by repetition of Faul and co-workers' maleimide substrate **4.34** (scheme 55). Subjection of bisindolylmaleimide **1.54** to ammonium sulphate promoted glycosylation conditions with L-fucose (**4.35**) before oxidation with DDQ gave the glycosylated indolocarbazole **4.36** in excellent yield and most interestingly as a single regio- and diastereoisomer.

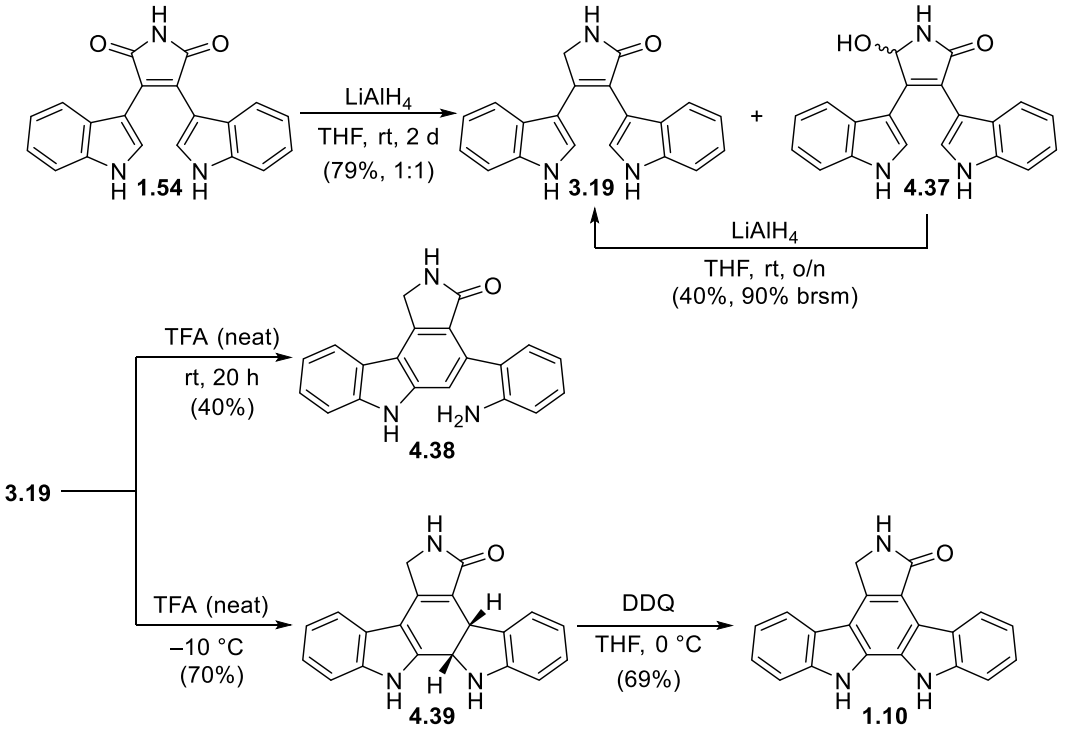


Scheme 55 Synthesis of glycosylated indolocarbazole **4.36**.

4.2 Modification of approach and total synthesis of staurosporine aglycone (1.10) and K252d (3.01)

4.2.1 Total synthesis of the staurosporine aglycone (1.10)

Given the success of Faul and co-workers' approach, attention was drawn to another system, bisindole **3.19** (scheme 56). It was proposed protonation of the more electron rich ring in this system would yield the desired indole-indoline system **4.39**, with the indoline proximal to the pyrrolone carbonyl. The desired pyrrolone **3.19** was readily accessed from bisindolylmaleimide (**1.54**) via a $LiAlH_4$ mediated reduction, isolating the pyrrolone **3.19** and hydroxyl-lactam **4.37** as a 1:1 mixture in good yield. However, attempts to drive the mixture to the pyrrolone **3.19** by warming led to degradation. Nevertheless, the hydroxyl-lactam **4.37** could be subjected to the same reaction conditions to improve the overall yield of the transformation to the lactam **3.19**. Indeed, upon subjection of pyrrolone **3.19** to the intramolecular Mannich cyclisation conditions at rt provided the expected aniline **4.38** in moderate yield, again observing decomposition at prolonged reaction times (scheme 56). However, trace amounts of the desired indole-indoline **4.39** were observed in the reaction mixture leading to further exploration of the reaction.



Scheme 56 Synthesis of the staurosporine aglycone (**1.10**).

Gratifyingly, cooling of the system to ─10 °C and maintaining the reaction at this temperature for the entire duration gave exclusively the desired indole-indoline **4.39** as it's TFA salt. This could be converted to the free base with $NaHCO_3$ prior to use, although it

was found as more convenient to keep as the more stable salt until required. Of even further importance however, was the fact that indoline **4.39** was obtained both as a single regioisomer and diastereoisomer as confirmed by 2D NMR, with the desired indoline proximal to the carbonyl in the pyrrolone ring. Pleasingly, oxidation of indoline **4.39** with DDQ provided the staurosporine aglycone (**1.10**) in good yield. The acid-cyclisation of lactam intermediate **3.19** was principally attractive due to the lack of protecting group manipulations required on the aglycone moiety, and the stage was set for investigations into the glycosylation of indoline **4.39.**

4.2.2 Glycosylation of indole-indoline 4.39 and synthesis of K252d (3.01)

Given the commercial availability of L-rhamnose (**4.31**) relative to synthetic effort required to prepare the relatively complex saccharide unit of staurosporine (**1.07**), it was decided that glycosylation studies would be carried out using L-rhamnose (**4.31**) with a preliminary focus on completing the first total synthesis of K252d (**3.01**).

Initial conditions explored were based upon the work of Faul and co-workers' who successfully employed Fisher glycosylation conditions to functionalise similar maleimide derived intermediates. Subjection of indole-indoline **4.39** to L-rhamnose (**4.31**) and $(NH_4)_2SO_4$ in EtOH saw no products at rt, and elevated temperatures resulted in partial degradation of the starting material to aniline **4.38** (table 3). After oxidation, the major product isolated was the aglycone **1.10**, with trace aniline **4.38**. Extended reaction times gave an increase in staurosporine aglycone **1.10**, but no indication of glycosylation. Additionally, removal of the acid from the reaction mixture led to clean recovery of the aglycone. However, heating the reaction in a sealed tube at 120 °C in EtOH followed by DDQ mediated oxidation again gave a complex reaction mixture, with the aglycone as the major product according to the ESI MS data of the crude mixture. Of particular interest, however, was the presence of a small peak of *m/z* = 460 in the mass spectrum after glycosylation, that did not change after treatment with DDQ. Unfortunately, attempts to isolate this intermediate were unsuccessful, but it was proposed, due to the stability of the intermediate towards oxidation by DDQ, that the aniline **4.38** had glycosylated to provide glycoside **4.40**. This result provided a great incentive to further explore this reaction, however application of basic glycosylation conditions (entry 5) saw no sign of glycosylation before the oxidation step.

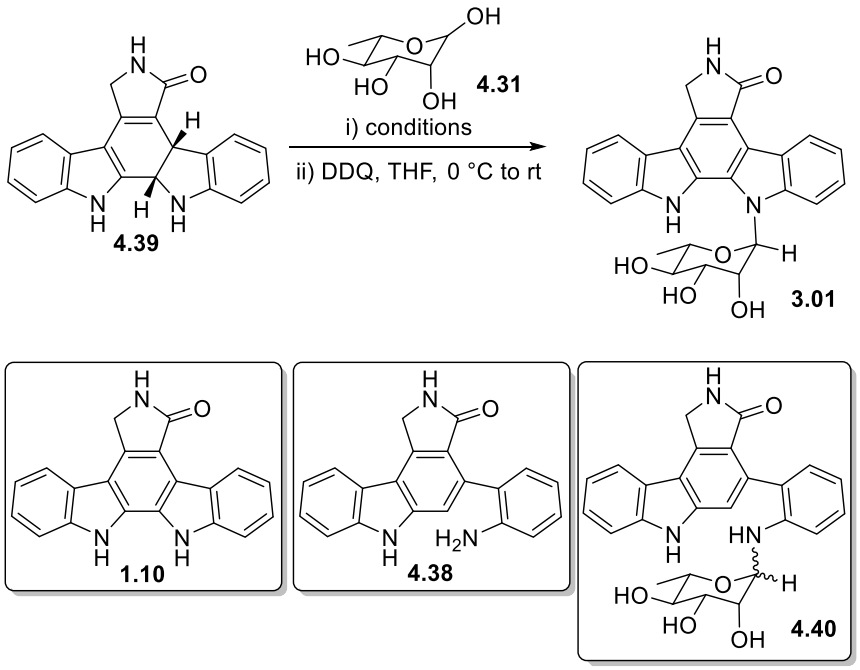
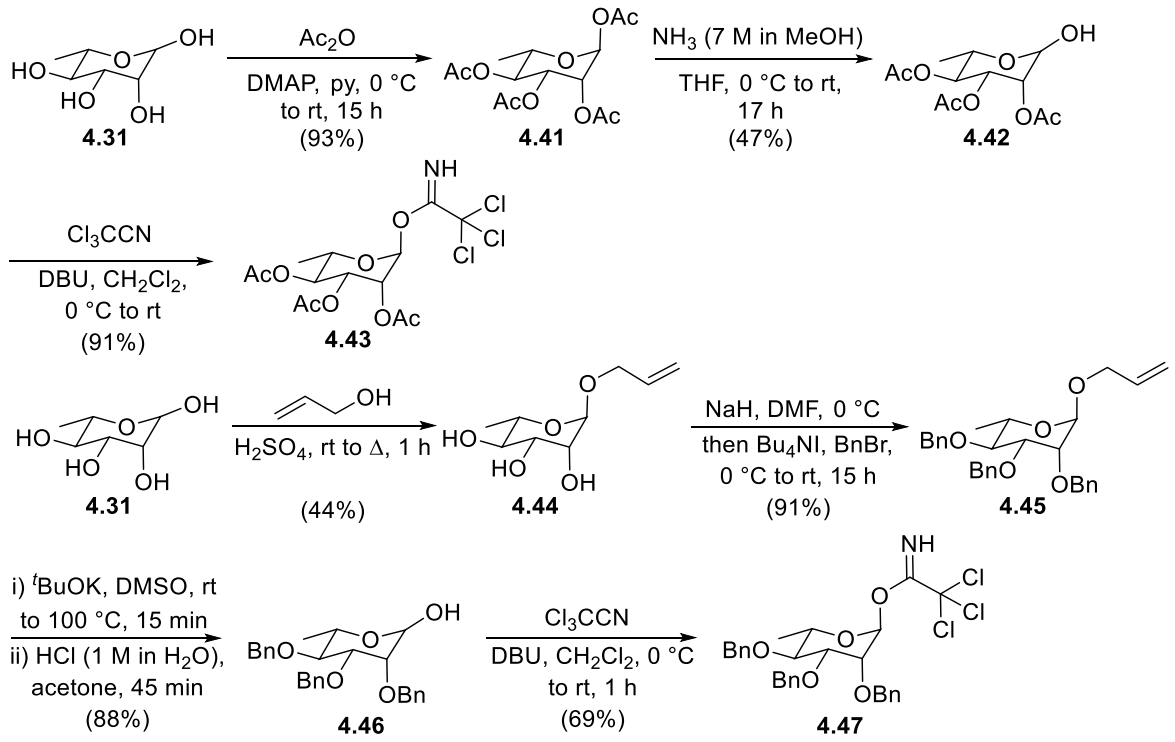


Table 3 Attempted Fisher glycosylation of indole-indoline **4.39**.

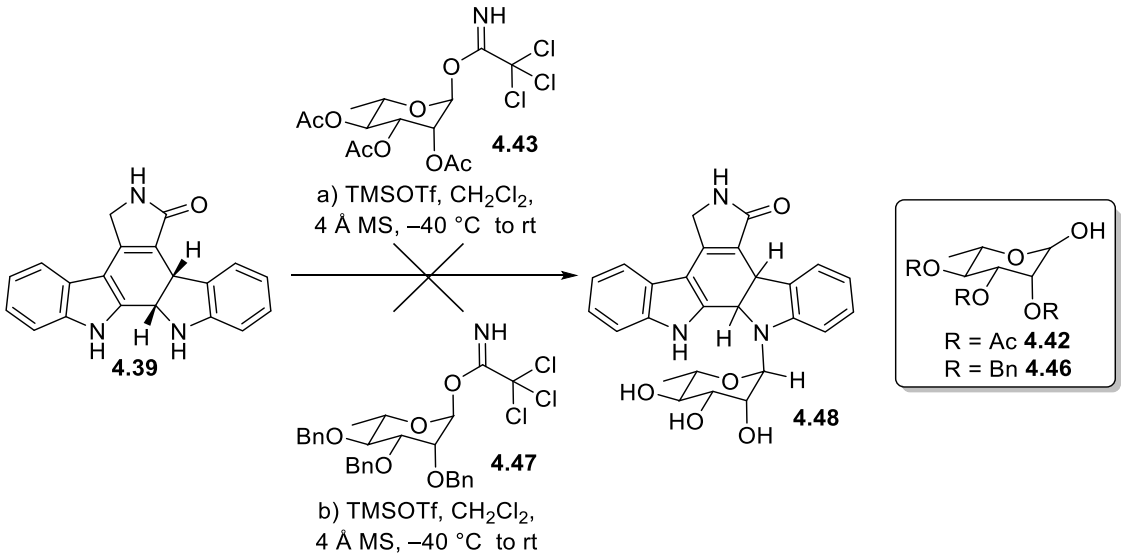
Entry	Conditions	Products (yield)
1	$(NH_4)_2SO_4$, EtOH, Δ, 14 h	aglycone **1.10** (65%)
2	$(NH_4)_2SO_4$, EtOH, Δ, 30 h	aglycone **1.10** (70%)
3	EtOH, Δ, 30 h	aglycone **1.10** (93%)
4	$(NH_4)_2SO_4$, EtOH, 120 °C (sealed tube), 8 h	aglycone **1.10**, aniline **4.38**, indoline **4.39** and trace **4.40**
5	NEt_3, MeOH, Δ, 48 h	aglycone **1.10** (64%)

It was proposed increasing the reactivity of the sugar may encourage glycosylation. As such, trichloroacetimidates **4.43** and **4.47** were isolated. Following literature precedent, L-rhamnose (**4.31**) was per-acylated to access saccharide **4.41**, before a selective anomeric deacylation with ammonia gave reducing sugar **4.42** (scheme 57). Treatment with trichloroacetonitrile and DBU furnished trichloroacetimidate **4.43** as the *α*-anomer exclusively in accordance with the literature.[143] For the benzylated sugar, again following literature precedent, L-rhamnose (**4.31**) underwent Fisher glycosylation in the prescence of allyl alcohol and acid to access saccharide **4.44**.[144,145] A Finkelstein promoted per-benzylation with BnBr accessed the fully protected rhamnose **4.45**, before a base promoted olefin isomerisation and acid hydrolysis of the resulting enol ether provided reducing sugar **4.46**. Finally, treatment with trichloroacetonitrile and DBU provided trichloroacetimidate **4.47** in good yield, enabling studies of the glycosylation of indole-indoline **4.39** to commence.



Scheme 57 Synthesis of trichloroacetimidates **4.43** and **4.47**.

Indole-indoline **4.39** and trichloroacetimidates **4.43** and **4.47** were subjected to Schmidt glycosylation conditions with TMSOTf as the Lewis acid. However, in both instances recovery of the starting material and the respective hydrolysed sugars **4.42** and **4.46** was observed (scheme 58).



Scheme 58 Attempted Schmidt glycosylation of indole-indoline **4.39**.

Koenigs-Knorr glycosylation conditions were also explored with glycosyl bromide **4.49**, which was readily isolated in one step from L-rhamnose (**4.31**) in excellent yield with HBr (33% in AcOH) in Ac_2O. Utilising the halophillic Lewis acid Ag_2CO_3 to activate the glycosyl

bromide only led to isolation of the starting material and the hydrolysed saccharide **4.42**. The more reactive silver salt AgOTf again led to isolation of the starting material and the recovered donor. Finally, inspired by the work of Payne and co-workers', the glycosyl bromide **4.49** was also subjected to TBAI and Hünigs base promoted Finkelstein to access the more reactive *β*-glycosyl iodide *in situ*.[146] Following consumption of the glycosyl bromide *via* TLC, addition of indole-indoline **4.39** again only led to hydrolysis of the saccharide unit with none of the desired product. Application of similar conditions but instead utilising a glycosyl chloride **4.50** were also unsuccessful and led to a reconsideration of the glycosylation approach.

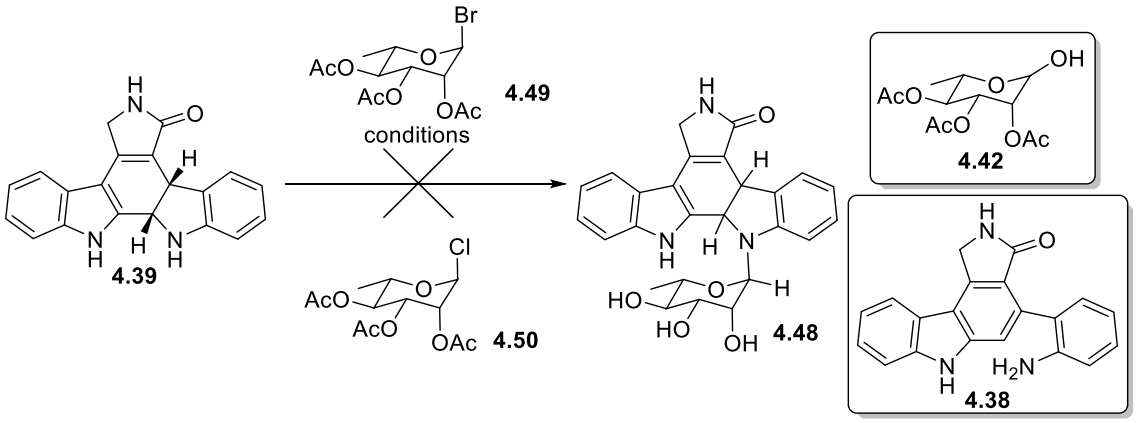


Table 4 Attempted glycosylation of indole-indoline **4.39**.

Entry	Conditions	Crude results
1	**4.49** (Br), Ag_2CO_3, CH_2Cl_2, rt	Recovered indoline **4.39** and sugar **4.42**
2	**4.49** (Br), AgOTf, 2,4,6-collidine, CH_2Cl_2, –40 °C to rt	Recovered indoline **4.39** and aniline **4.38**
3	**4.49** (Br), TBAI, NEt(^{i}Pr)$_2$, 4 Å MS, PhH, rt then Δ, 16 h	Recovered indoline **4.39** and sugar **4.42**
4	**4.50** (Cl), TBAI, 4 Å MS, MeCN, rt then Δ, 7 h	Recovered indoline **4.39** and sugar **4.42**

On review of the conditions tried thus far, the greatest promise had been found in the glycosylation of indole-indoline **4.39**. The use of more reactive glycosyl donors such as trichloroacetimidates and glycosyl bromides however had not led to any identifiable glycosylated product. It was proposed thioglycosides could be explored, however given the successful glycosylation of both indoline **4.39** and most importantly maleimide **4.34** (scheme 55), revisiting the initial Fisher glycosylation conditions seemed more pressing.

One possible contributor to the lack of N-glycosylation was possible interference from the reaction solvent EtOH, which could be tempering the reactivity of the saccharide.

Additionally, the moderate solubility of the aglycone unit in EtOH may also have been leading to the poor reactivity, and alternate solvent systems were investigated. Commonly employed conditions with water in the absence of acid, whether at reflux (table 5, entry 2) or at elevated temperatures (120 °C) under pressure (table 5, entry 3) both resulted in recovery of indoline **4.39**. Solvents of particular interest were trifluoroethanol (table 5, entry 4) and hexafluoroisopropanol (HFIP, table 5, entry 5), due to the slightly improved solubility of indoline **4.39**. Interestingly, both of these solvent systems primarily yielded the aglycone (1.10), however in HFIP, ESI of the crude reaction mixture indicated formation of a minor glycosylated intermediate.

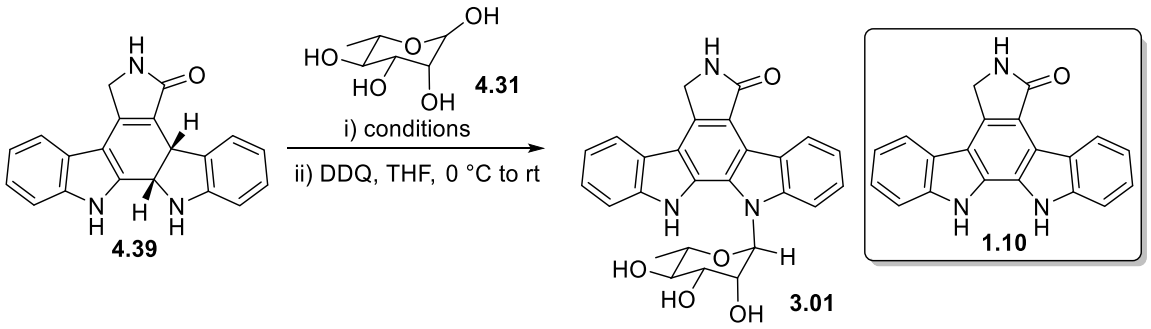


Table 5 Glycosylation of indole-indoline **4.39**.

Entry	Conditions	Results
1	$(NH_4)_2SO_4$, EtOH, Δ, 48 h	aglycone **1.10** isolated
2	EtOH/H_2O, Δ, 5 days	Clean indoline **4.39**[1]
3	EtOH/H_2O, 120 °C (sealed tube), 2 days	Clean indoline **4.39**[1]
4	$(NH_4)_2SO_4$, CF_3CH_2OH, rt	recovered indoline **4.39**[1]
5	$(NH_4)_2SO_4$, HFIP, rt	aglycone **1.10** and several glycosylated products[2]
6	AcOH, EtOH, 80 °C, 48 h	No observable glycosylated products[3]
7	$(NH_4)_2SO_4$, DMF, Δ 21 h	aglycone **1.10** isolated

[1]Mixture not subjected to oxidation step.

[2]Glycosylated material unable to be isolated. Material did not react in presence of DDQ.

[3]Lots of degradation

Attempts to isolate the proposed glycosylated compound from the reaction in HFIP led to a complex mixture, containing more than one glycoside. Unfortunately, prolonged reaction

times and elevated temperatures did not lead to an increase in production of these intermediates, but rather an increase in yield of aniline **4.38** (figure 15). This, again coupled with the inability to oxidise the intermediate led to a belief that the intermediate produced was again glycoside **4.40**, where the indoline has potentially undergone elimination to the aniline **4.38** prior to glycosylation.

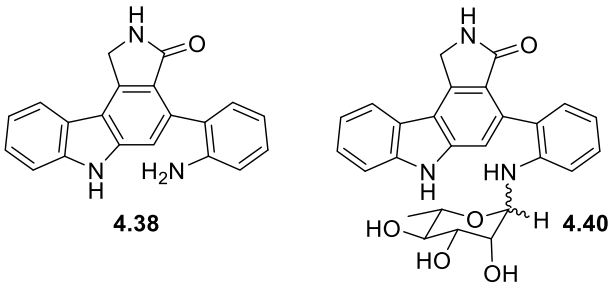


Figure 16 Carbazole **4.38** and potential glycosylated product **4.40**.

The mixture obtained indeed appeared to contain the proposed glycoside **4.40** (figure 16 and 17). All three products were glycosides with a free *N*-H signal around 11.0 ppm and the diagnostic singlet around 8.0 ppm corresponding to the C-H in carbazole (figure 17). This mixture could represent a mixture of anomers with a proposed third compound which may represent glycosylation on a different nitrogen. However, lack of material and difficulty separating the mixture left us unable to confirm structures of the components with confidence.

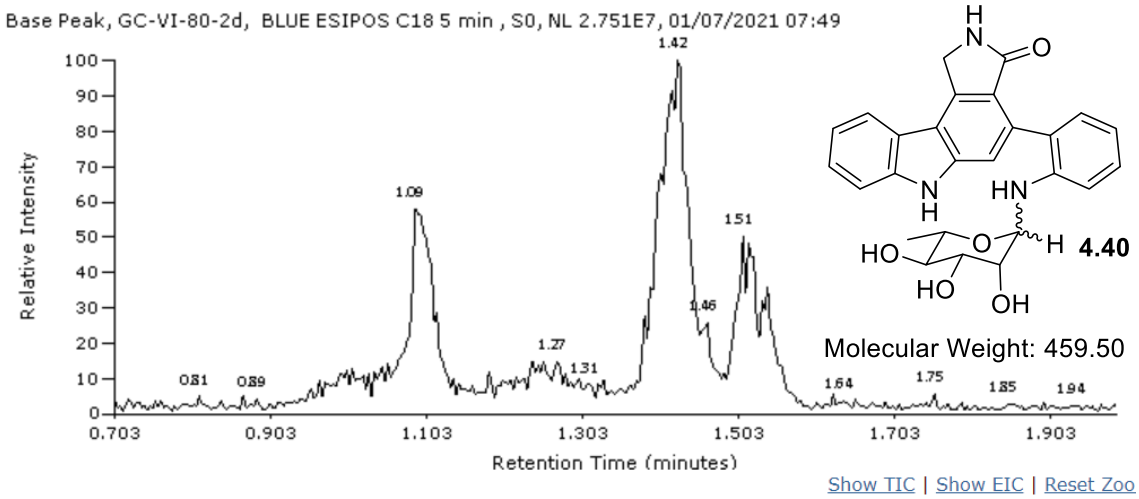


Figure 17 ESI of potential glycosylated intermediate **4.40**.

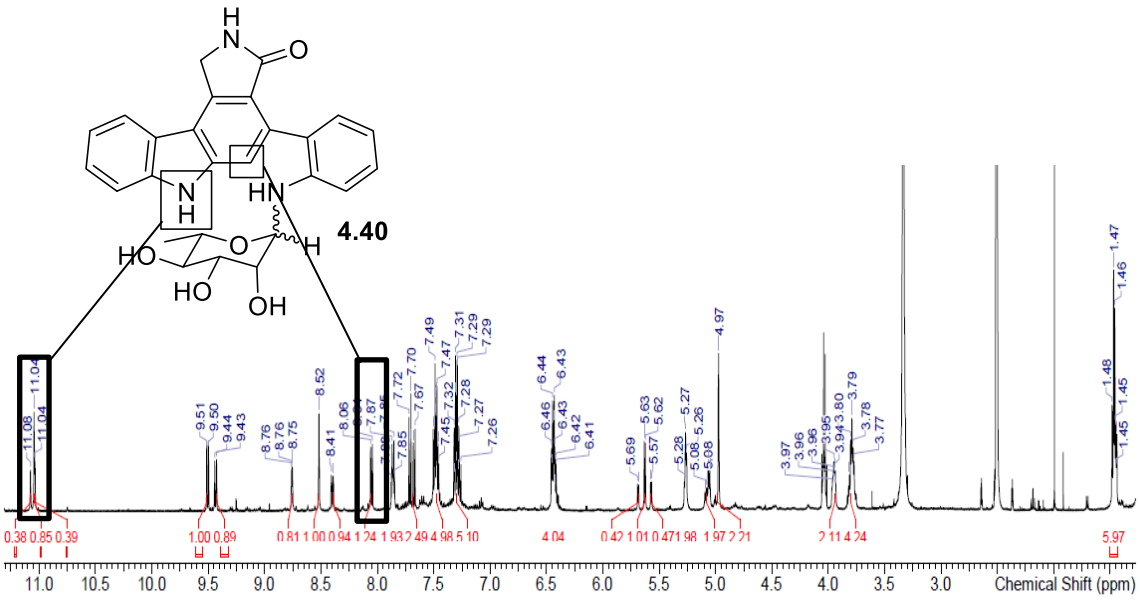
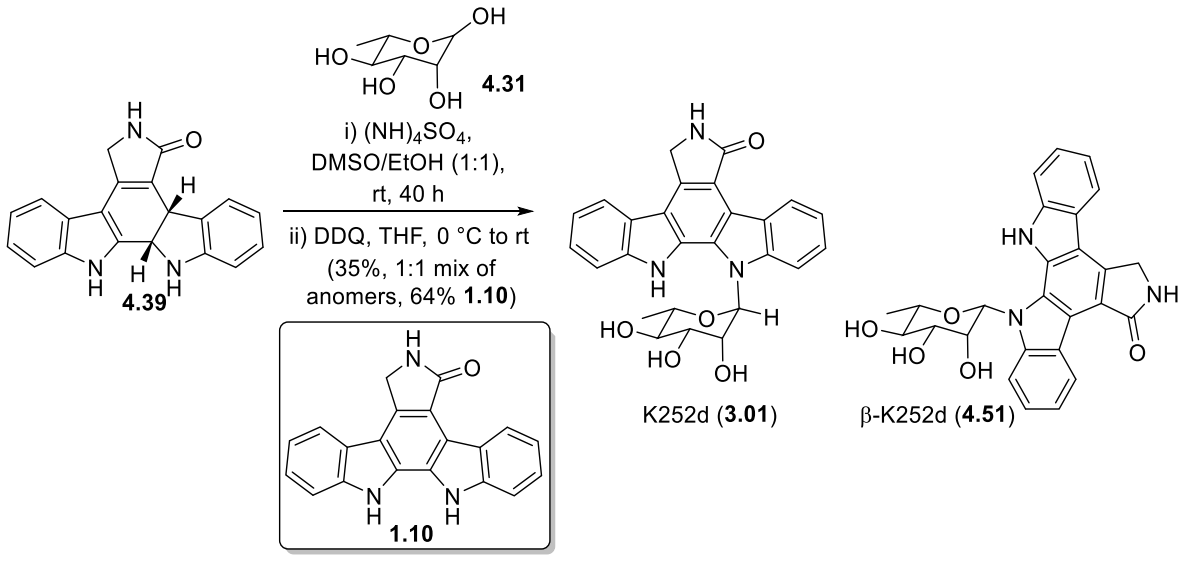


Figure 18 NMR of glycosylated products.

The only change between the unsuccessful glycosylation conditions (table 5, entry 1) and the set of conditions resulting in formation of an N-glycoside (table 5, entry 5), was the change of the reaction solvent from EtOH to HFIP. These results raised a key question; was the reactivity observed using HFIP due to the increased acidity of the system? Or was the reactivity due to slightly improved solubility of the indole-indoline **4.39** and L-rhamnose (**4.31**) in HFIP.

To explore this question, indole-indoline **4.39** was first subjected to the original reaction conditions in EtOH at elevated temperatures, but replacing $(NH_4)_2SO_4$ with AcOH as an alternative acid source (table 5 entry 6). The modified conditions led to a great deal of degradation, with many products, none of which were identified as the desired glycosylated material or the staurosporine aglycone (**1.10**). The indoline substrate **4.39** was found to be moderately soluble in DMF (table 5, entry 7), however reaction in this solvent returned only the staurosporine aglycone (**1.10**) after oxidation with DDQ. This led us to question whether a polar protic solvent was needed to help stabilise an intermediate oxonium ion.

Given the excellent solubility of indoline **4.39** in DMSO, the glycosylation was attempted in a mixture of DMSO/EtOH (1:1, v/v). Gratifyingly, the desired glycosylated indolocarbazole **3.01** was obtained as a 1:1 mixture of anomers in 35% yield. The mixture of anomers could be separated by flash chromatography, however the desired anomer **3.01** appeared to partially degrade during purification.

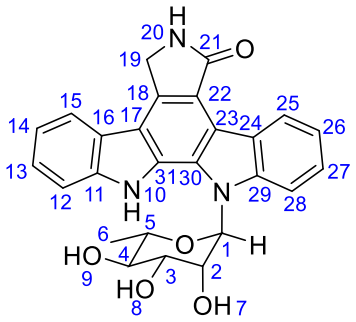


Scheme 59 Synthesis of K252d (**3.01**).

The ^{1}H NMR and ^{13}C NMR data for synthetic K252d (**3.01**) were in agreement with the previously reported literature values (table 6), deviating by 0.01 ppm or less in the ^{1}H NMR and 0.1 ppm or less in the ^{13}C NMR.[147] In addition, NOE correlations between H-15 and H-

19 and H-12 and H-10 reinforced the regioselectivity observed in the reaction, and concluded the first synthesis of K252d (**3.01**) to date.

Table 6 ^{1}H and ^{13}C NMR comparison for K252d (**3.01**). [a] 400 MHz in DMSO-d_6, [b] 100 MHz in DMSO-d_6.[147]



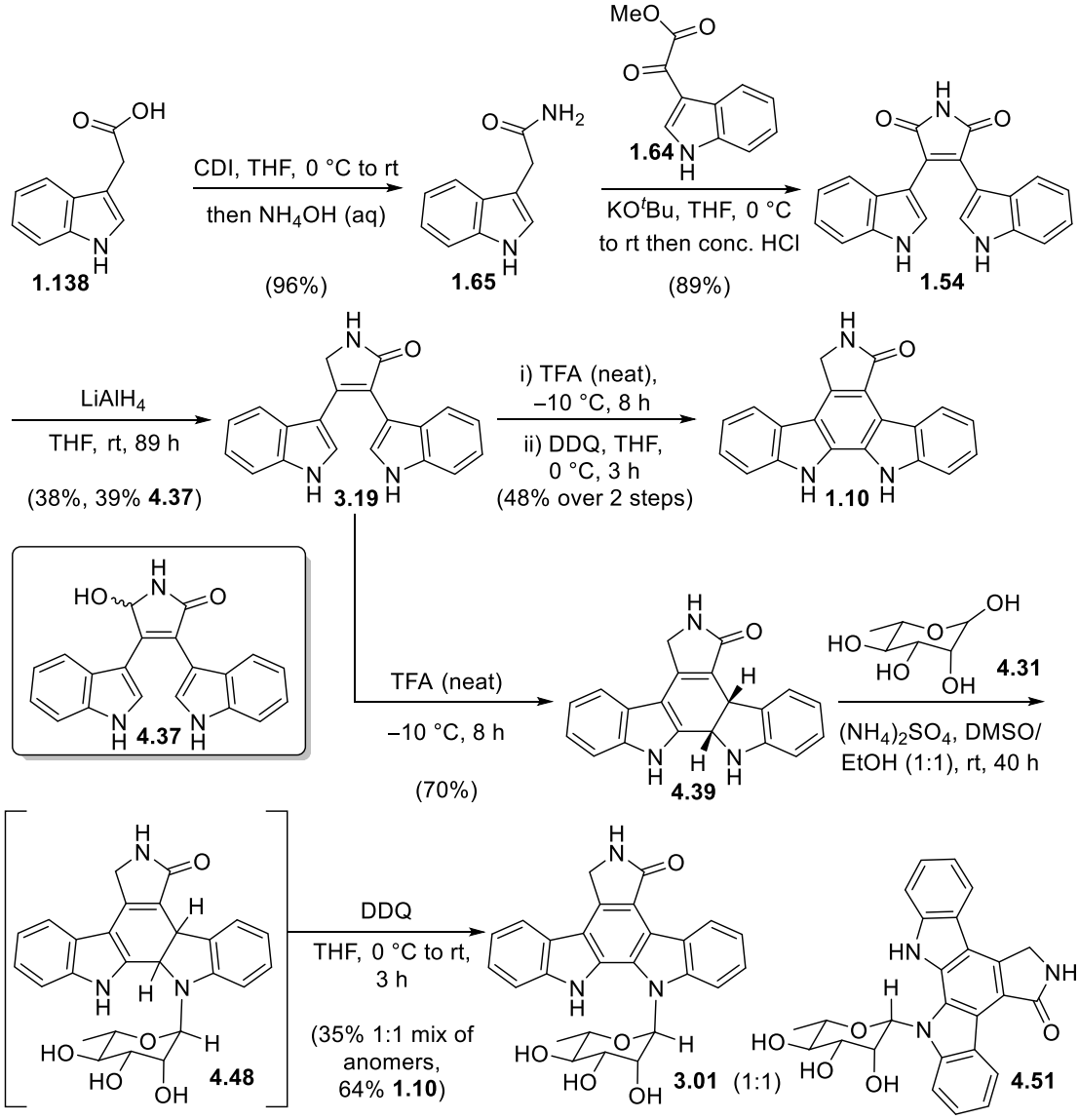
K252d (**3.01**)

^{1}H NMR			
Assigned proton	Literature δ ppm[a]	Recorded δ ppm[b]	Δδ
H-1	6.40	6.39	0.01
H-2	*ca*. 4.5	4.52-4.43	0.00
H-3	4.18	4.18	0.00
H-4	4.05	4.05	0.00
H-5	4.48	4.52-4.43	0.00
H-6	1.70	1.70	0.00
H-7	5.00	5.00	0.00
H-8	5.40	5.39	0.01
H-9	6.69	6.69	0.00
H-10	11.68	11.68	0.00
H-12	7.60	7.60	0.00
H-13	7.50	7.53-7.46	0.00
H-14	7.31	7.32	0.01
H-15	8.07	8.07	0.00
H-19	5.01	5.00	0.01
H-20	8.54	8.55	0.01
H-25	9.47	9.47	0.00
H-26	7.27	7.27	0.00
H-27	7.49	7.53-7.46	0.00
H-28	7.69	7.69	0.00

^{13}C NMR			
Assigned carbon	Literature δ ppm[a]	Recorded δ ppm[b]	Δδ
C-1	77.1	77.1	0.0
C-2	66.9	66.8	0.1
C-3	71.6	71.6	0.0
C-4	71.4	71.4	0.0
C-5	76.5	76.4	0.1
C-6	15.3	15.3	0.0
C-11	139.0	138.9	0.1
C-12	111.2	111.1	0.1
C-13	125.1	125.0	0.1
C-14	119.8	119.7	0.1
C-15	121.2	121.1	0.1
C-16	121.8	121.8	0.0
C-17	114.9	114.8	0.1
C-18	133.9	133.8	0.1
C-19	45.1	45.1	0.0
C-21	172.2	172.2	0.0
C-22	118.6	118.5	0.1
C-23	117.5	117.4	0.1
C-24	122.2	122.2	0.0
C-25	125.6	125.5	0.1
C-26	119.3	119.2	0.1
C-27	125.2	125.1	0.1
C-28	109.8	109.7	0.1
C-29	140.2	140.1	0.1
C-30	124.5	124.4	0.1
C-31	127.5	127.5	0.0

Perhaps the most exciting aspect of the reaction was the observation that the glycosylated product was isolated with exclusive regioselectivity for the indoline nitrogen. This presents the first method to regioselectively glycosylate the pyrroloindolocarbazole system, and based on the amount of the staurosporine aglycone (**1.10**) recovered, presents the potential for a greatly improved yield. The DMSO/EtOH solvent system was the best system at solvating both the indole-indoline **4.39** and saccharide unit, indicating that solvation was the likely contributor to the lack of reactivity in earlier experiments, and offers promise for further improvements. Interestingly, the product was isolated as a 1:1 mixture of anomers, compared to the exclusive selectivity observed for glycosylation of the corresponding maleimide system **4.34** (scheme 58). Whilst using a different saccharide unit, it presents the potential for achieving high regio- and stereocontrol in the glycosylation step. Unfortunately, due to time constraints it was not possible to explore this exciting result further, concluding studies into the indolocarbazoles and the first total synthesis of K252d (**3.01**) and its hitherto unknown epimer **4.51**. Excitingly, both K252d (**3.01**) and its previously unknown epimer will be the subject of bioactivity studies with our collaborator Emre Sayan at the University of Southampton Cancer Sciences department.

4.3 Conclusions and Future Work



Scheme 60 Total synthesis of staurosporine aglycone (**1.10**) and K252d (**3.01**).

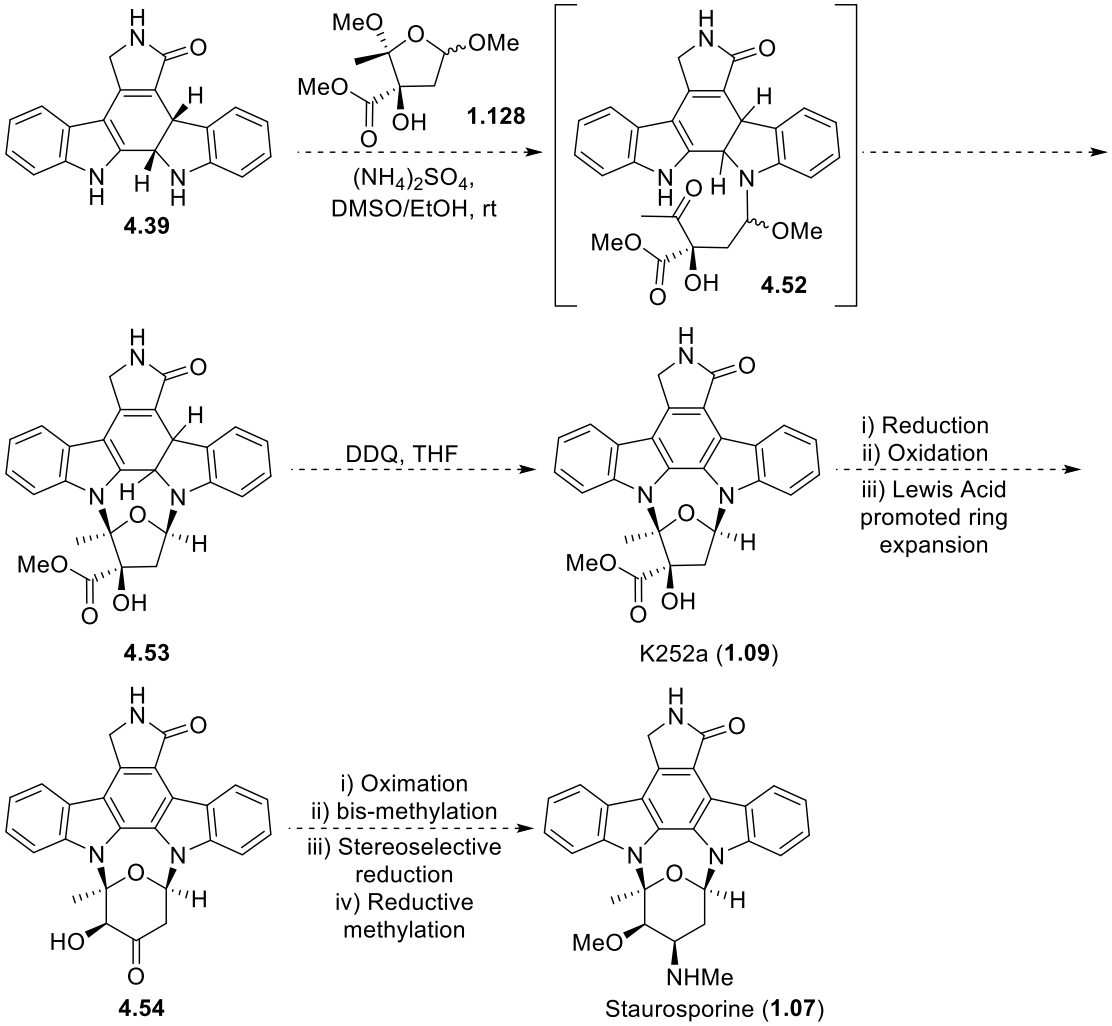
Extensive studies of Mannich-type cyclisation and glycosylation of bisindole systems has culminated in a novel approach to the staurosporine aglycone (**1.10**) and the first total synthesis of K252d (**3.01**, scheme 60). Following the preparation of bisindolylmaleimide **1.54** according to the procedure of Faul and co-workers', reductive desymmetrisation provided pyrrolone **3.19** and hemi-aminal **4.37**, with the latter re-subjected to the same reduction conditions to improve the overall yield of the step. The key intramolecular Mannich cyclisation followed by oxidation of the indole-indoline intermediate **4.39** accessed the staurosporine aglycone (**1.10**) in 16% yield over 5 steps. Significantly, indole-indoline **4.39** underwent glycosylation on the amine nitrogen with L-rhamnose (**4.31**) in the presence of $(NH_4)_2SO_4$, before DDQ promoted oxidation gave K252d (**3.01**) and *β*-K252d (**4.51**) as a separable 1:1 mixture of anomers. This presents the first total synthesis of K252d (**3.01**),

realised in 4% yield over 6 steps and constitutes the first regioselective and protecting group free approach to glycosylated indolocarbazoles.

Due to time constraints, the final regioselective glycosylation step was not optimised further and it was not possible to investigate other glycosyl donors. Of particular interest would be modulating the current solvent system (DMSO/EtOH), and also exploring alternative acid sources in an attempt to improve conversion, and potentially stereoselectivity. This would also lead to a better understanding of the importance of solubility and contribution of protic solvents towards reactivity in the glycosylation. It also remains unconfirmed whether the observed anomeric ratio for **3.01** and **4.51** is thermodynamic, and this could also be explored.

The initial aim when this journey began was to complete a regioselective total synthesis of staurosporine (**1.07**). As such, the final stage of this project would be the application of this methodology to staurosporine (**1.07**). When considering Wood and co-workers' approach, in particular their excellent and concise synthesis of the furanose **1.128** (scheme 61), the coupling reaction of furanose **1.128** and indole-indoline **4.39** would be of great interest. It is envisaged the coupling could deliver high regioselectivity for the reaction of the aldehyde oxidation level carbon and the indoline nitrogen. If the reaction pathway described by Wood and co-workers' is preserved for indoline **4.39**, ring open glycosylated intermediate **4.52** could then undergo cycloglycosidation to the desired bisglycoside **4.53**, before oxidation of the central ring would enable direct access to K252a (**1.09**). Alternatively, oxidative aromatisation could be investigated prior to cycloglycosidation. An exciting aspect of these reactions is the potential to avoid exhaustive protecting group chemistry, while enacting a regioselective assembly of a complex pharmacologically relevant target.

Finally, following the ring-expansion protocol for furanoside **1.09** described by Wood and co-workers'; where conversion of the ester moiety to the corresponding aldehyde and Lewis acid promoted expansion would enable access to the pyranose **4.54**. This key intermediate enabled Wood and co-workers' access to several indolocarbazole natural products, including staurosporine (**1.07**). As such, adaptation of Wood and co-workers' excellent cycloglycosidation/ring-expansion protocol would potentially open up access to different indolocarbazole natural products as well as derivatives of therapeutic interest.



Scheme 61 Proposed synthesis of K252a (**1.09**) and staurosporine (**1.07**).

Chapter 5 Towards the synthesis of (+)-Sparteine (5.01)

5.1 Background

5.1.1 Isolation and structural determination

The lupin (quinolizidine) alkaloids are a family of over 200 compounds, isolated from several papilionaceous plant species all bearing the key quinolizidine core.[148,149] They can be broadly sub-divided into 4 classes; bicyclic such as (—)-lupinine (**5.02**), tricyclic such as (—)-cytisine (**5.03**) and two tetracyclic classes such as (+)-sparteine (**5.01**) and (+)-matrine (**5.04**, figure 16).

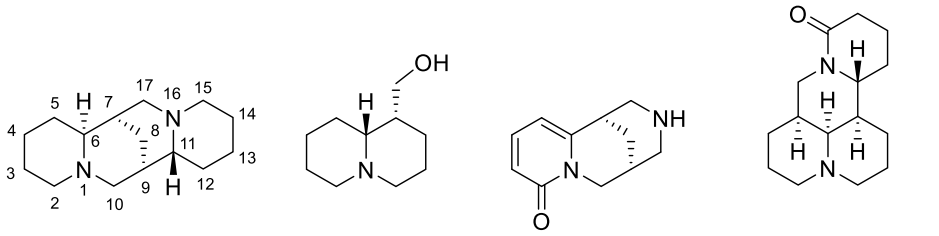


Figure 19 Structures of lupin alkaloids.

The lupin alkaloids, notably the sparteine sub-family, have been the have subject of several reviews surrounding their isolation.[148–151] The first lupin alkaloids were isolated in 1851 when Stenhouse and co-workers' reported several compounds from the plant *Cytius scoparisus*, one of which was named Spartëin.[152] Stenhouse tentatively assigned the chemical formula as $C_{15}H_{26}N_2$, and much work was subsequently undertaken into structural elucidation of these alkaloids. Despite this, it wasn't until 82 years later when Clemo and Raper characterised the key 3,11-diazatetracyclo[7.7 .1.0.0]heptadecane core of the sparteine alkaloids.[153] The group also proposed the first stereochemical assignment for these alkaloids, however it wasn't until Marion and Leonard finally clarified the relative stereochemical detail in 1951 as the *exo*-*endo* arrangement at C6 and C11.[154,155] Thirteen years later in 1965, the stereochemical studies into the alkaloids culminated with Tsuda and co-workers', who assigned the absolute stereochemistry of (—)-sparteine (**5.01**). [156]

5.1.2 Therapeutic and synthetic interest in sparteine

Lupin seeds have had medicinal applications dating back 3000 years, and as such lupin alkaloids have found various medical applications today.[157–161] Most notably (—)-cytisine

(**5.03**), marketed as Tabex®, has found application as a smoking cessation medication. (—)-Sparteine (**5.01**) has also found use as a cardiovascular agent, specifically as an anti-arrhythmia agent.[162–167] It displays a tendency to lower blood pressure and heart rates, however toxicity concerns led to withdrawal by the FDA.[168] Despite this interest, the sparteine family is popular amongst synthetic chemists due to its application in asymmetric synthesis.[169]

Both (+)-sparteine and (—)-sparteine (**5.01**) enantiomers can act as bidentate ligands for a variety of metal ions, placing the metal in a chiral environment and enabling enantioselective transformations (figure 19). Initial work by Butte and Noyori utilised lithium-sparteine chelates for asymmetric synthesis, albeit with moderate enantioselectivity.[170,171] However, Hoppe and Beak later developed upon the initial work, significantly expanding the scope and selectivity and increasing popularity in this methodology.[172,173]

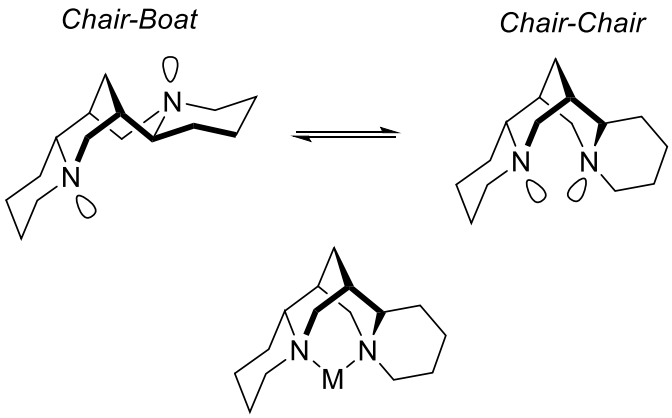


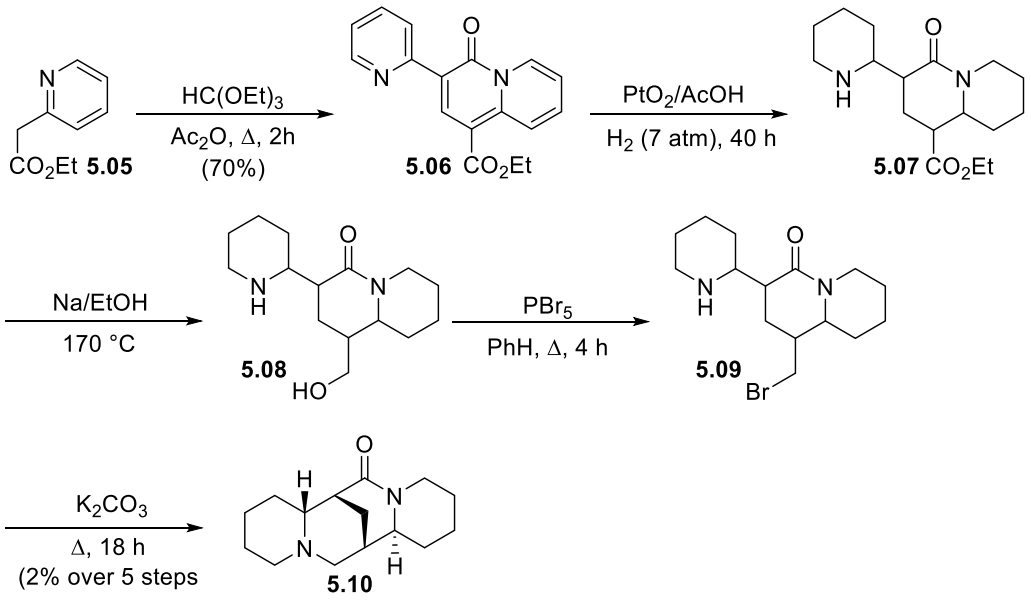
Figure 20 (—)-Sparteine chelates for asymmetric synthesis.

Asymmetric synthesis promoted by sparteine complexes has been rigorously explored and reviewed,[169,174–179] and the myriad of applications have contributed towards interest in (+)-sparteine and (—)-sparteine (**5.01**) as targets for synthetic endeavours. In addition, noted difficulty isolating (+)-sparteine (**5.01**) from natural sources, and the commercial shortage of (—)-sparteine (**5.01**) dating back to around 2010 compounded this interest further.[180] Thankfully, the shortage of both antipodes appears to have been resolved, with both now readily available from many commercial suppliers. None the less, synthetic interest in this family of structurally complex natural products remains.

5.1.3 Previous Total Syntheses of Sparteine:

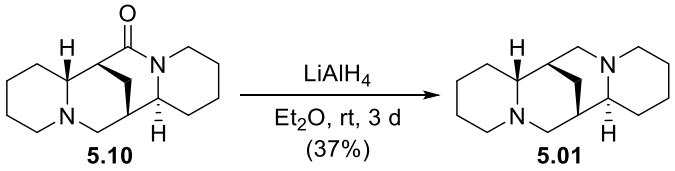
For the first synthetic approaches to either sparteine antipode, one has to look back to the work of Clemo and co-workers' in 1936.[181] The group developed an approach that began with condensation of ethyl 2-pyridylacetate (**5.05**) with triethyl orthoformate under reflux to afford the key quinolizidone core **5.06**. A subsequent reduction to octahydroquinolizidone

5.07 was followed by a reduction of the ester moiety to give alcohol **5.08**. Appel reaction with PBr_5 provided the corresponding alkyl bromide **5.09**, before a K_2CO_3 promoted cyclisation under heating in a sealed tube afforded (±)-17-oxosparteine (**5.10**) in 2% overall yield.



Scheme 62 Clemo and co-workers' synthesis of (±)-oxosparteine (**5.10**).

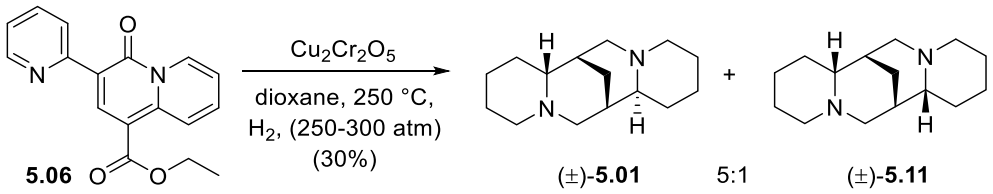
Unfortunately, attempts to advance this intermediate to the (±)-sparteine were not successful, primarily due to the limited reagents available at the time. In fact, it wasn't until 1948, 13 years after the original publication, the same group published a reduction to an optically pure sample of lactam **5.10** (scheme 63). Utilising $LiAlH_4$ at rt for an extended reaction time, (−)-oxosparteine (**5.10**) was successfully reduced to (−)-sparteine (**5.01**) in moderate yield.[182,183]



Scheme 63 Clemo and co-workers' synthesis of (−)-sparteine (**5.01**).

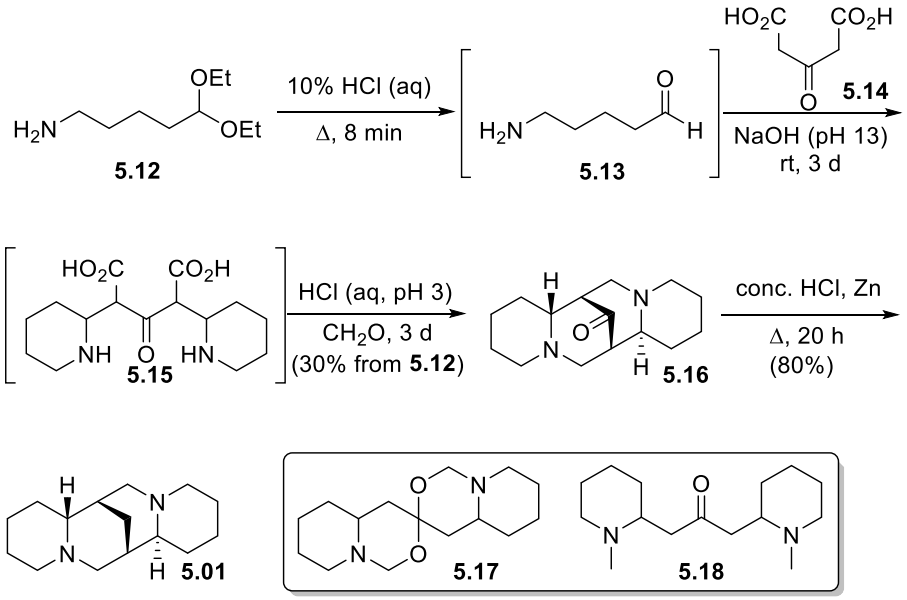
The reduction of this quinolizidone core **5.06**, subsequently became a popular method to access oxosparteine and sparteine derivatives. Leonard and Beyler built upon the methodology to achieve the first total synthesis of racemic sparteine earlier in 1948 (scheme 64).[184,185] The quinolizidone core was constructed via the simple method employed by Clemo and co-workers', before a copper chromite catalyst promoted reduction and concomitant cyclisation, giving a racemic mixture of sparteine (**5.01**) and *α*-isosparteine

(**5.11**). However, despite the moderate yield, the diastereoisomers could be separated via column chromatography.



Scheme 64 Leonard and Beyler synthesis of (±)-sparteine (**5.01**).

Significant research into approaches to sparteine derivatives via octahydroquinolizidone core **5.06** ensued over the next few years. However in 1950, Anet, Hughes and Ritchie published an alternative approach inspired by a mechanistic proposal described by Robinson years earlier (scheme 65).[186–188] Amino pentanal **5.13** was prepared *in situ* from acetal **5.12**, before condensation with acetone derivative **5.14** provided diacid **5.15**. This diacid **5.15** intermediate was the same one proposed by Robinson, and upon acidification of the medium and addition of formaldehyde provided a product that was proposed by Anet and co-workers' to be oxosparteine **5.16**. A final Clemmensen reduction then afforded what was claimed to be (±)-sparteine (**5.01**).

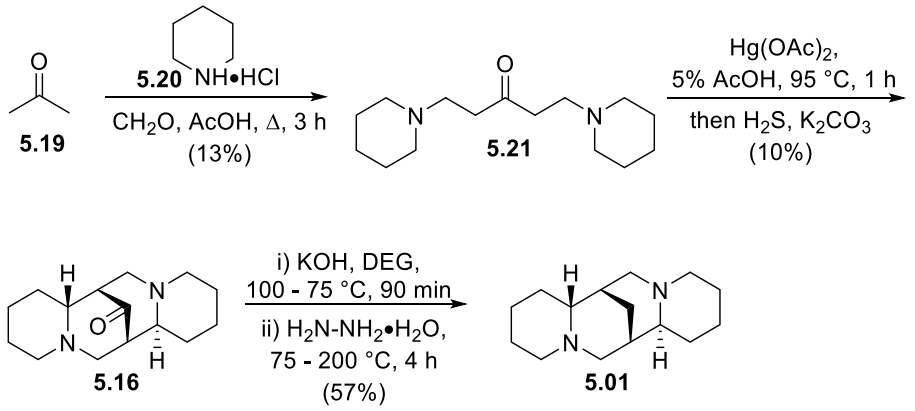


Scheme 65 Anet's proposed biomimetic synthesis of (±)-**5.01** and the structural irregularities proposed by Rokohl and Schopf.

Subsequently, however, other groups questioned the results detailed by Anet and co-workers'. Notably, the group of Rokohl stated a similar synthetic approach had been attempted in their lab, and the condensation of diacid **5.14** with Δ^1-piperidine at a pH of 11.5 had formed spiroacetal **5.17** (scheme 65). In 1953, the group of Schopf and co-workers' detailed an inability to isolate oxosparteine **5.16**, and in fact Clemmensen reduction of

spiroacetal **5.17** afforded dipiperidine **5.18**.[189,190] Interestingly, analytical data of these two intermediates **5.17** and **5.18**, aligned very closely with the products proposed by Anet and co-workers'. As such, it is widely regarded that Anet's biomimetic approach did not provide the desired result.

In 1960, the group of Van Tamelen and co-workers' built upon this work to complete a successful synthesis of (±)-sparteine (**5.01**), and later published a full account including experimental details in 1969 (scheme 66).[191,192] The route began with a double Mannich reaction of acetone (**5.19**) with 2 equivalents of piperidine (**5.20**) and formaldehyde to give bispiperidine **5.21**. A subsequent double Mannich reaction, facilitated by mercury acetate led to oxosparteine **5.16** in poor yield, before a Wolff-Kishner reduction provided the natural product **5.01**.



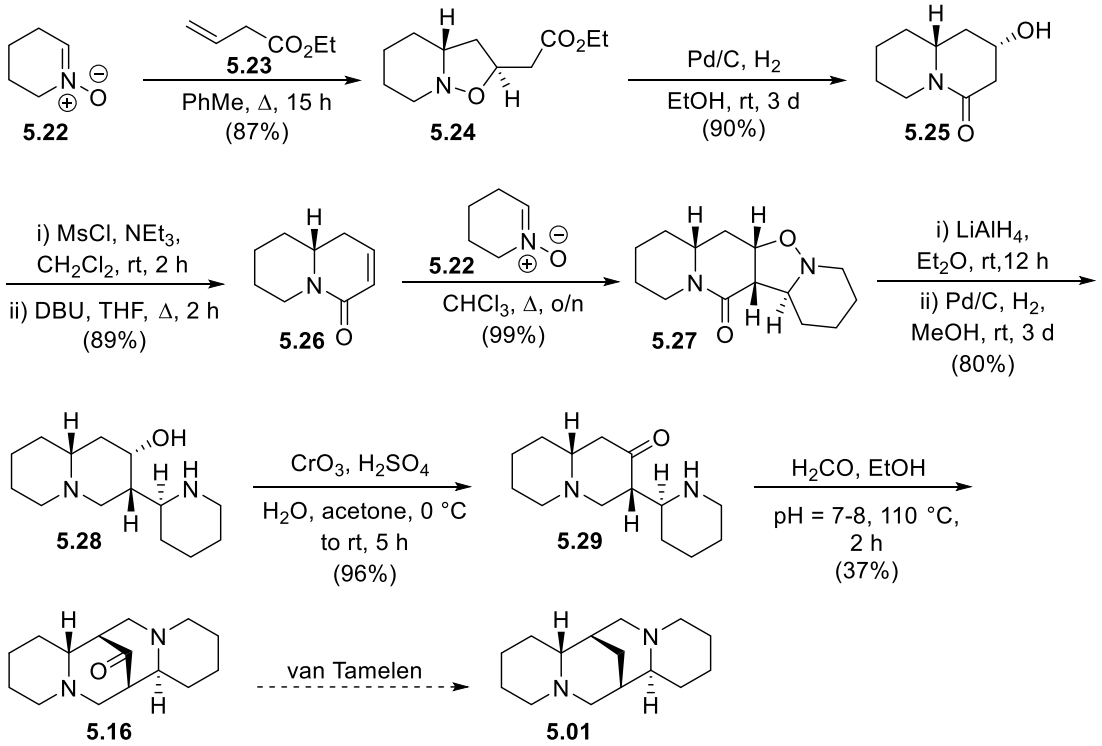
Scheme 66 Van Tamelen and co-workers' synthesis of (±)-sparteine (**5.01**).

Subsequently, mercury acetate promoted Mannich cyclisations became a popular tool in the synthesis of sparteine antipodes. The group of Bohlmann and co-workers' in 1963 and later 1973, adopted similar mercury promoted cyclisations in the successful synthesis of (±)-sparteine.[193,194]

Moving forward to 1983, and new synthetic methods were applied to this exciting family of alkaloids. With much of the previous synthetic work centred around Mannich cyclisations, and prior to that reduction of quinolizidone systems, Kakisawa described a distinctive route to (±)-*α*-isosparteine (**5.11**) utilising nitrone cycloadditions.[195]

In 1987, Otomasu and co-workers' built upon this methodology to publish a formal synthesis of (±)-sparteine (**5.01**, scheme 67).[196] The synthesis commenced with a [3+2]-cycloaddition of nitrone **5.22** and homoallyl ester **5.23** to give aminol ether **5.24**. Reductive ring opening and concurrent cyclisation gave alcohol **5.25**, which underwent mesylation and elimination to *α,β*-unsaturated amide **5.26**. This amide was subjected to another [3+2]-cycloaddition

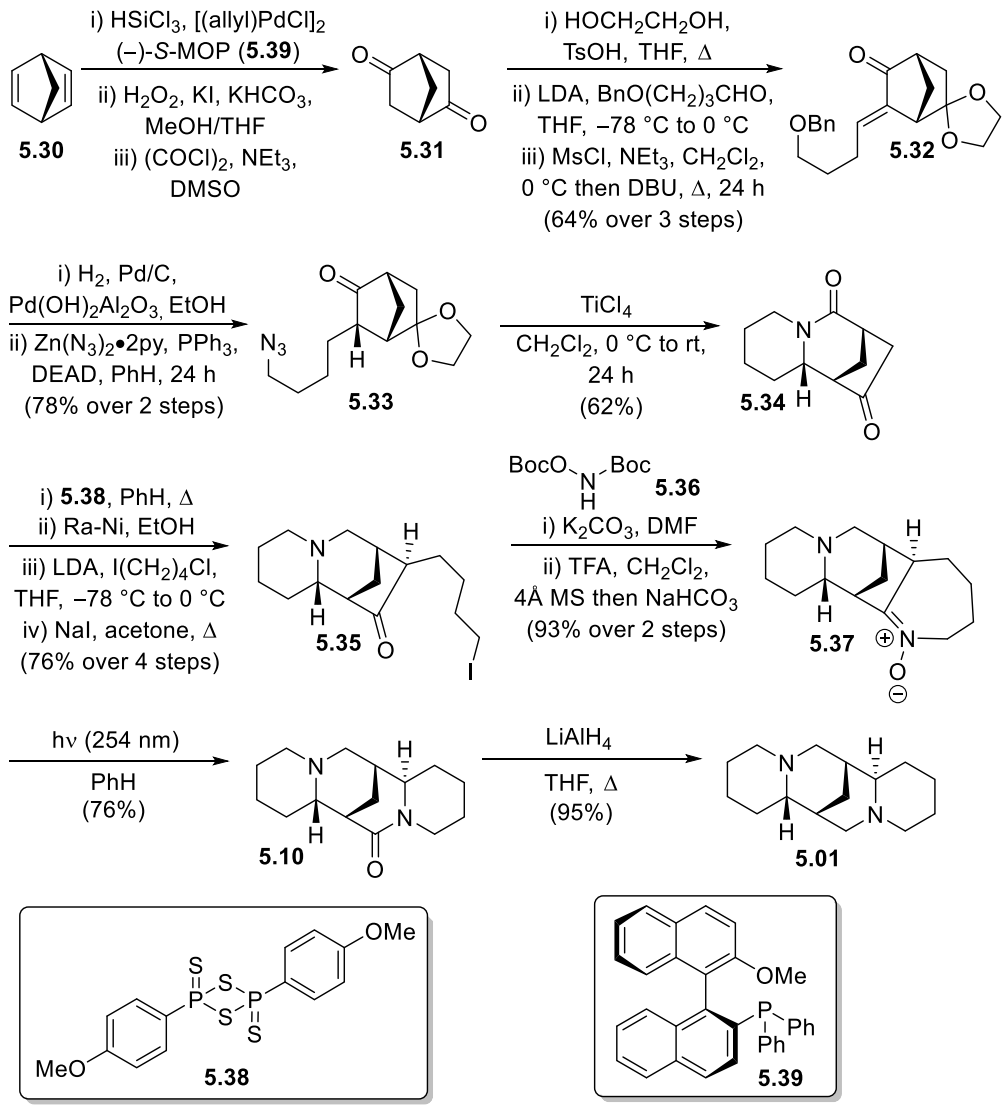
before reductive ring opening and hydrogenation gave alcohol **5.28**. Oxidation to the corresponding ketone **5.29**, and Mannich cyclisation with formaldehyde provided oxosparteine **5.16** which could be further reduced by Wolff-Kishner conditions as described by Van Tamelen and co-workers'.



Scheme 67 Otomatsu's formal synthesis of (±)-sparteine (**5.01**).

Other groups adopted similar cycloaddition chemistry, however none of them were able to obtain either sparteine antipode in an optically pure form. That remained the case until 2002, when Aubé and co-workers' published the first total synthesis of (+)-sparteine (**5.01**), utilising intramolecular Schmidt reactions to form the external piperidine rings (scheme 68).[197] The synthesis began according to previous lit. with chiral (bis)hydrosilation then treatment with peroxide to provide the corresponding diol in high enantio- and regioselectivity.[198] A subsequent Swern oxidation gave diketone **5.31**.[199] Mono-acetal protection and aldol condensation gave the corresponding exocyclic alcohol, before mesylation and elimination provided exocyclic olefin **5.32**. Deprotection of the benzyl ether and concurrent hydrogenation of the olefin preceeded Mitsunobu azidation to access azide **5.33** before a $TiCl_4$ promoted Schmidt reaction secured quinolizidone **5.34**. Treatment with Lawesson's reagent provided the thio-lactam before reduction with Raney Nickel gave the desired piperidine. Installation of the alkyl chloride side chain proceeded with exclusive selectivity for *exo* diastereoisomer, which was subsequently converted to iodide **5.35** via a NaI promoted Finkelstein. Finally, with an inability to impart a second Schmidt reaction, formation of the hydroxyimine and acid promoted formation of cyclic nitrone **5.37** preceeded

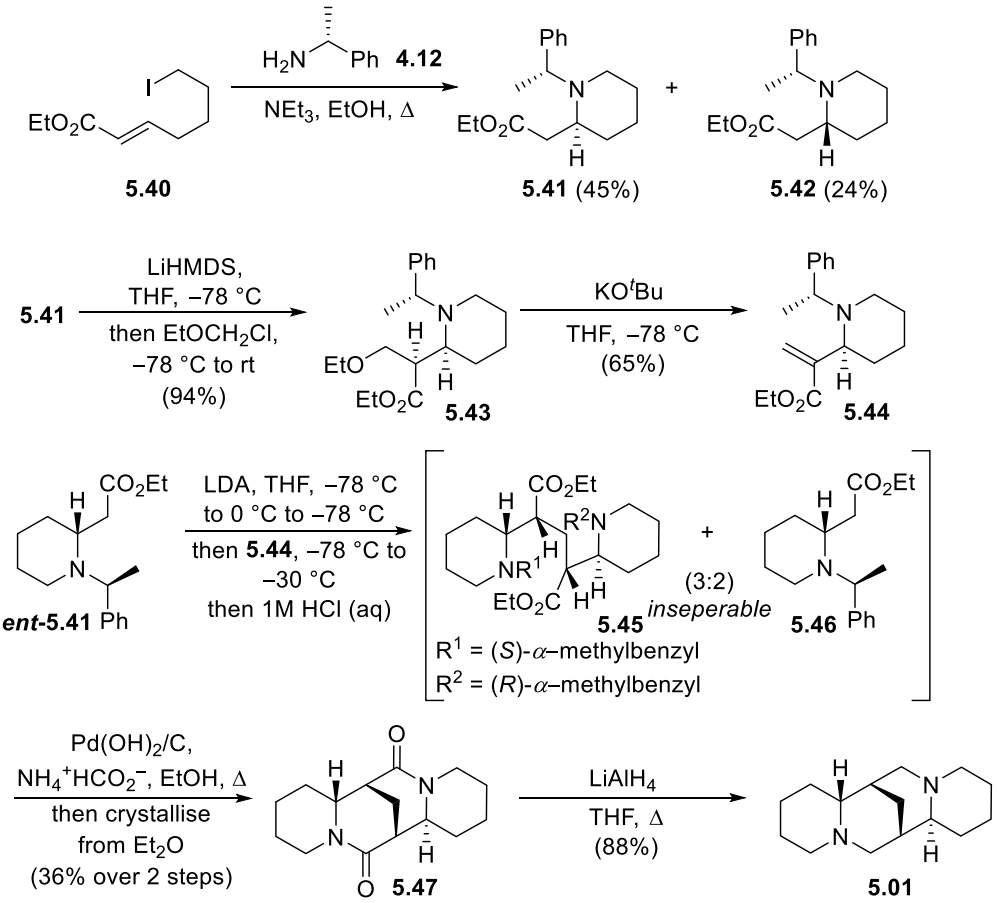
a photo-Beckmann rearrangement to provide oxosparteine **5.10**, which was treated with $LiAlH_4$ to deliver (+)-sparteine (**5.01**) in excellent yield.



Scheme 68 Aube and co-workers' synthesis of (+)-sparteine (**5.01**).

In 2004, O'Brien and co-workers' published the first total synthesis of optically pure (—)-sparteine (**5.01**, scheme 69).[200] By development of a procedure described by Bunce and co-workers', alkylation and concomitant Michael addition of (*R*)-*α*-methylbenzylamine (**4.12**) with iodoalkane **5.40** gave a roughly 2:1 mixture of cyclic *β*-amino esters **5.41** and **5.42**.[201] Separation of the diastereoisomers and alkylation of the major ester **5.41** provided adduct **5.43** as a single diastereoisomer. Base promoted elimination of ethoxide provided Michael acceptor **5.44**, which was subjected to the key Michael addition reaction with *ent*-**5.41**. *Ent*-**5.41** was isolated in accordance with the method described above with (*S*)-*α*-methylbenzylamine with iodoalkane **5.40**, before subjection to the key Michael addition reaction to provide a 3:2 mixture of diester **5.45** and recovered *ent*-**5.46**. Unable to separate the mixture, removal of the methylbenzyl groups via hydrogenation and cyclisation gave

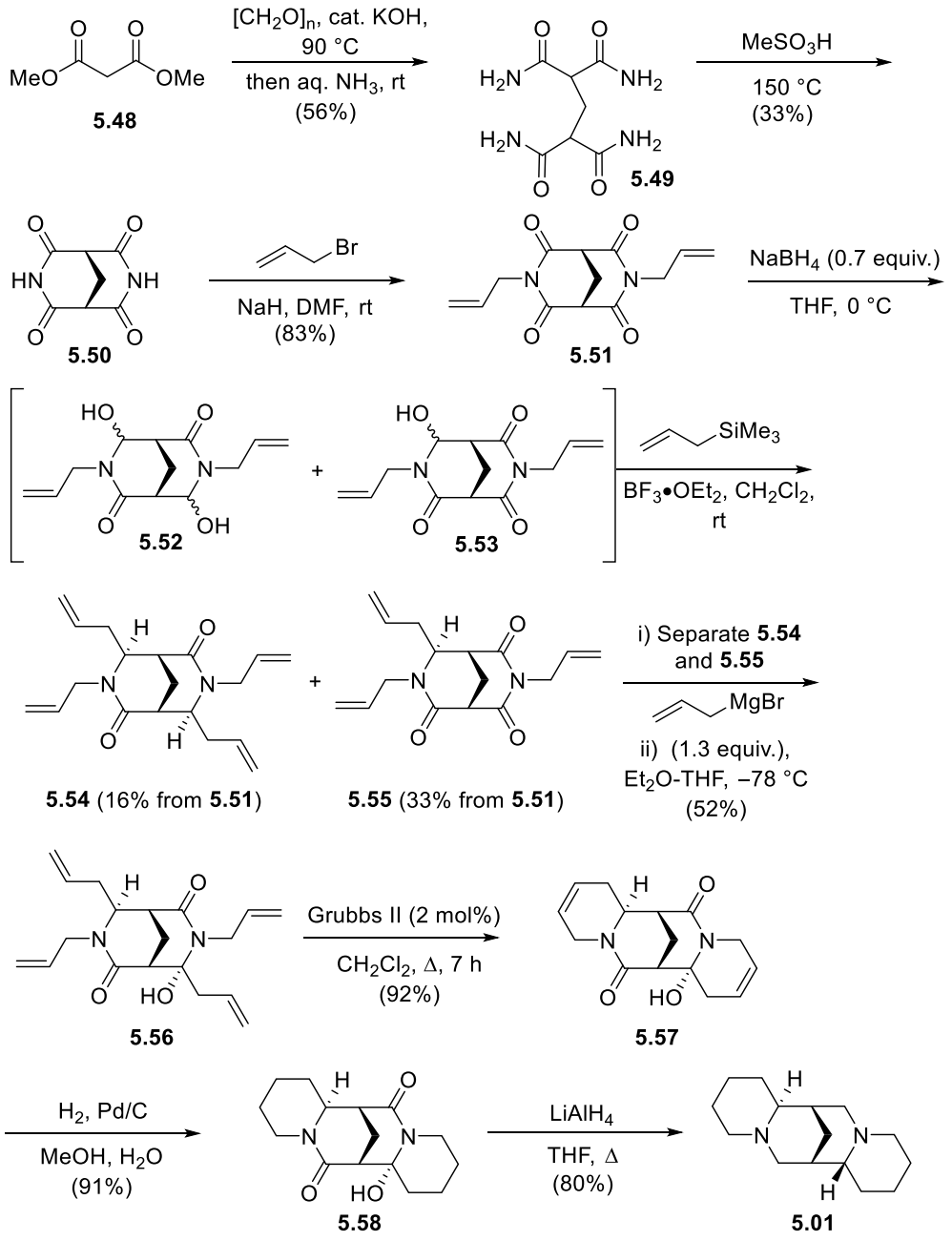
bislactam **5.47**, which could be isolated by crystallisation of the mixture from Et_2O. Finally, the total synthesis was completed with $LiAlH_4$ mediated reduction to give optically pure (—)-sparteine (**5.01**) in only 6 steps (LLS) from iodolkane **5.40**. Despite the lower 2:1 selectivity in the initial alkylation/Michael addition step, the synthesis presents both a short (6 steps) and flexible route that could be applied to either antipode.



Scheme 69 O'Brien and co-workers' synthesis of (—)-sparteine (**5.01**).

Shortly after the work from O'Brien was published, Blakemore and co-workers' published the first of a series of papers describing the synthesis of several quinolizidine alkaloids, including (±)-sparteine (**5.01**, scheme 70).[151,202,203] The synthesis began with treatment of dimethyl malonate (**5.48**) with paraformaldehyde to form the Knoevenagel adduct before addition of another molecule of dimethyl malonate (**5.48**) and treatment with aqueous ammonia gave tetramide **5.49**. Condensation with methanesulfonic acid provided tetraoxobispidine **5.50**. Treatment with sodium hydride, then allylation provided diimide **5.51**, which was subjected to sodium borohydride reduction to afford a mixture of diol **5.52** and alcohol **5.53**. Sakurai allylation of the obtained material resulted in a mixture of triene **5.55** and tetraene **5.54**. These two compounds could be separated, and the major triene **5.55** subjected to a further allylation with allyl magnesium bromide to yield alcohol **5.56**. This compound, now with all the desired stereocentres installed, was subjected to a double

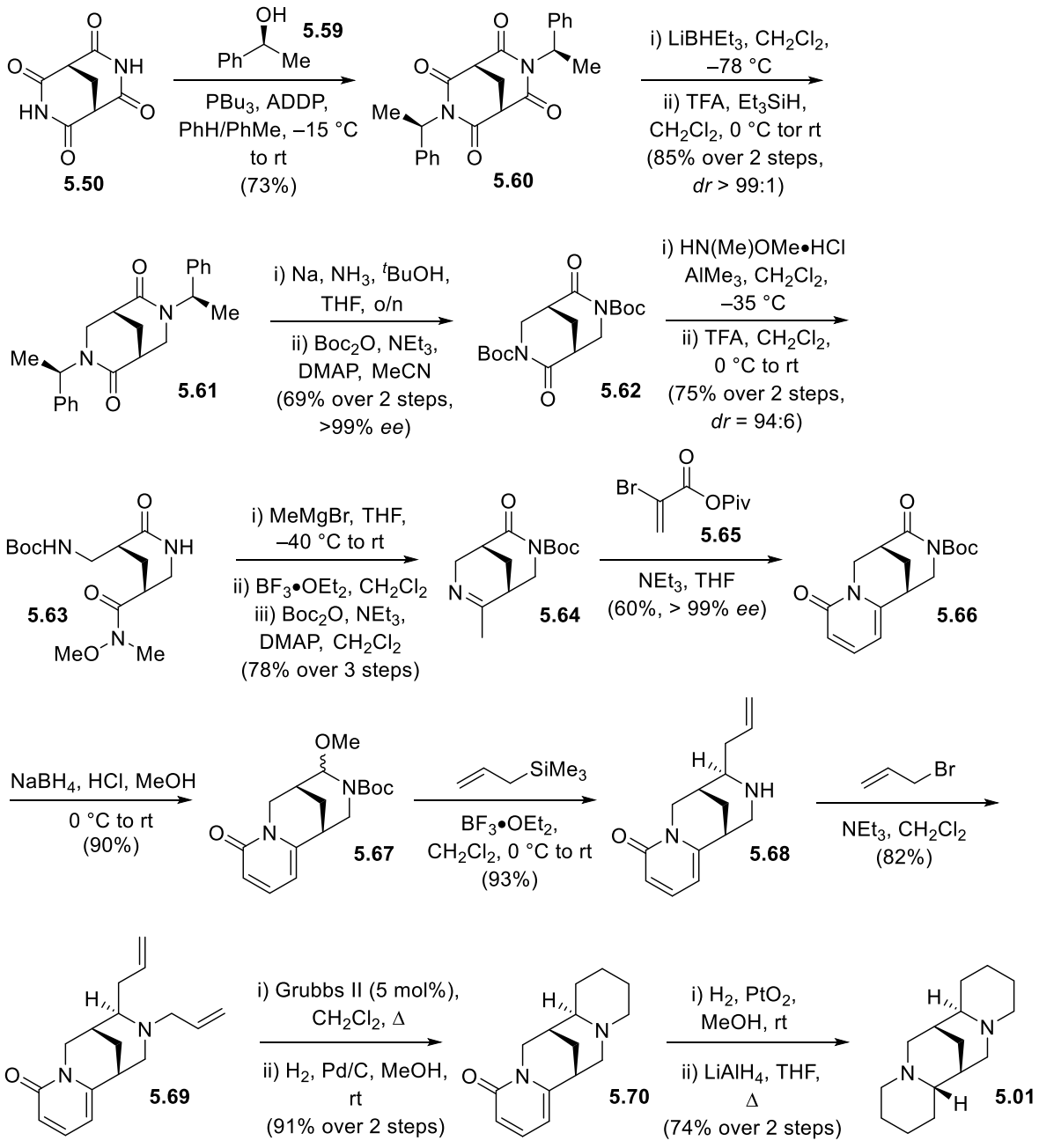
ring-closing metathesis with Grubbs II catalyst, before hydrogenation of the resulting olefins and a $LiAlH_4$ reduction secured access to the natural product **5.01**.



Scheme 70 Blakemore and co-workers' synthesis of (±)-sparteine (**5.01**).

In 2018, building upon the bispidine work described by Blakemore, Breuning and co-workers' described their "inside-out" approach to (−)-sparteine (**5.01**, scheme 71).[136] This came as part of an excellent collection of work that encompassed the synthesis of 21 bisquinolizidine alkaloids. The synthesis began from the bispidine system **5.50**. Mitsonobu reaction with (*S*)-phenylethanol (**5.59**) allowed for a regio- and stereoselective reduction to access diamide **5.61**. Birch reduction cleaved the auxiliaries before Boc protection gave diamide **5.62** in excellent yield and *ee*. Selective Lewis acid promoted ring opening and removal of the Boc group on the amide moiety provided free amide **5.63**. The authors noted

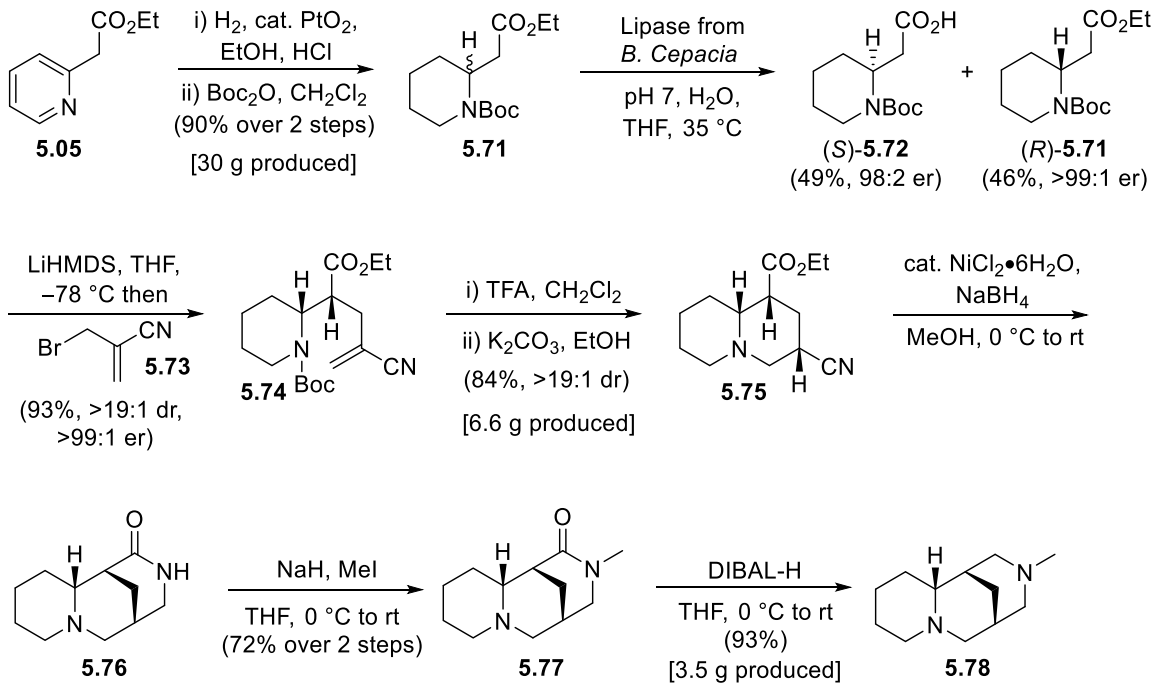
a slight depreciation in the diastereoselectivity in this step, likely due to epimerisation. Nucleophillic addition of methyl magnesium bromide to the Weinreb amide before subsequent cyclisation of the carbamate *N*-H and Boc protection of the amide provided imine **5.64**. Michael addition of the enamine tautomer of imine **5.64** with ester **5.65** and concurrent cyclisation provided the key intermediate **5.66** that enabled access to the family of quinolizidine alkaloids. For (—)-sparteine (**5.01**), the key intermediate **5.66** was reduced before treatment with MeOH provided hemiaminal ether **5.67**. Subjection of this to an *exo*-selective Sakurai alkylation and concurrent Boc-deprotection provided the free base **5.68**. Allylation with allyl bromide preceded ring closing metathesis and hydrogenation of the resulting olefin to yield the (—)-anagyrine (**5.70**). This was subjected to a final two stage reduction protocol to yield the natural product **5.01** in excellent yield.



Scheme 71 Breuning and co-workers' total synthesis of (−)-sparteine (**5.01**).

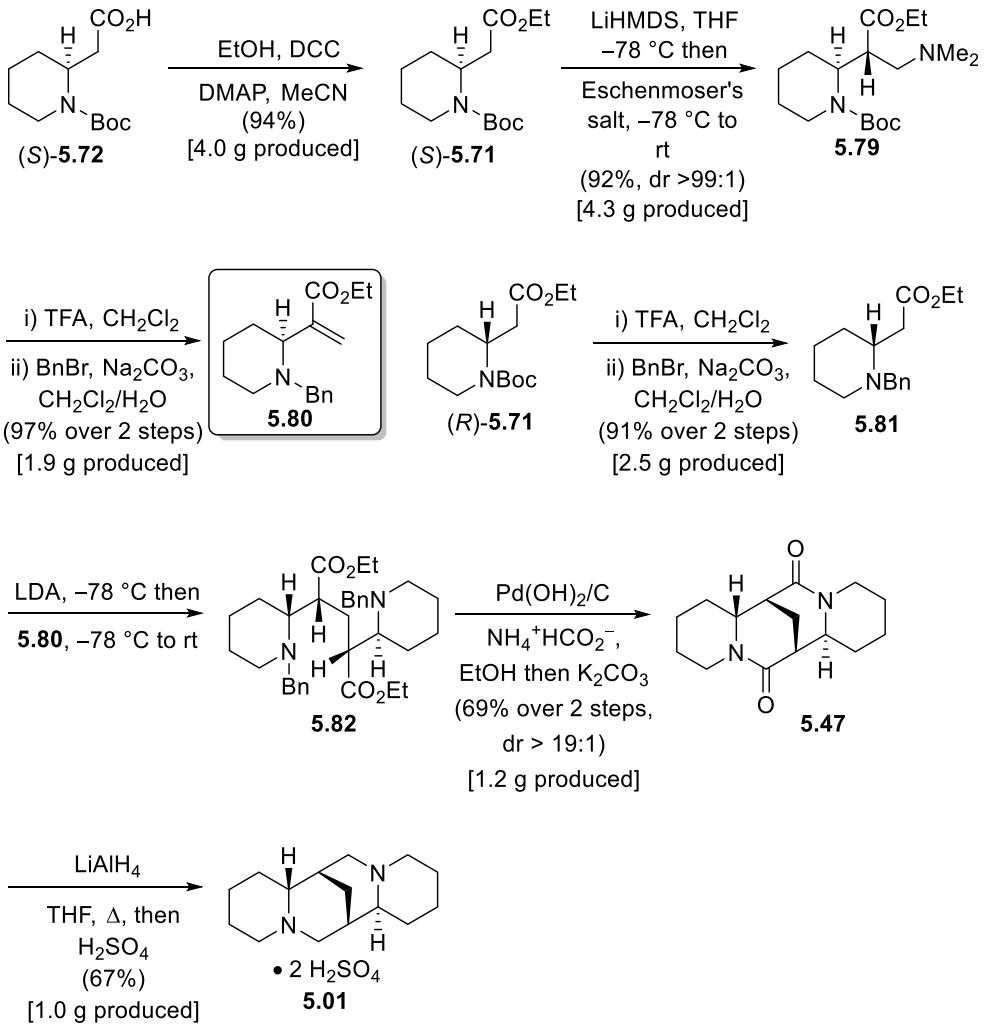
To date, the most recently published work into either sparteine antipode was carried out by O'Brien and co-workers' (scheme 72 and 73).[204] The study concluded not only with a concise synthesis asymmetric synthesis of (−)-sparteine (**5.01**), but also the synthesis of a surrogate **5.78** (scheme 73). Due to the varied availability of the sparteine isomers over the last 20 years, the group sought to develop a simpler surrogate that would be amendable to a large scale synthesis and still provide the same degree of asymmetric induction as the parent compounds. The synthesis of the surrogate began with pyridine hydrogenation and Boc protection according to a well-known procedure.[205,206] Treatment of racemic ester **5.71** with *Burkholderia cepacia* resolved the racemic mixture to acid **5.72** and the desired ester (*R*)-**5.73**. Alkylation with cyanoolefin **5.73** provided ester **5.74**, before deprotection of the

Boc group and Michael addition gave quinolizidine **5.75**, which was confirmed with X-ray crystallography. Reduction of the nitrile with *in situ* generated nickel boride and concomitant cyclisation provided amide **5.76**. Methylation of the free N-H was achieved with NaH and MeI before reduction of the amide gave the surrogate **5.78** on multi-gram scale.



Scheme 72 O'Brien and co-workers' synthesis of the (−)-sparteine surrogate (**5.78**).

As mentioned however, the groups work didn't end there. Starting from acid (*S*)-**5.72** from the enzymatic resolution described above, esterification with DCC and treatment with EtOH gave the (*S*)-enantiomer of ester **5.71**. Treatment with Eschenmoser's salt gave the desired amine **5.79** in excellent yield, before elimination and a protecting group switch gave *N*-benzylated piperidine **5.80**. This protecting group switch was required due to issues accomplishing the subsequent key Michael addition with the corresponding Boc-protected compounds. Likewise, the (*R*)-enantiomer of ester **5.71** underwent protecting group switch to the corresponding *N*-benzylated material **5.81**, before the key Michael addition reaction provided the desired 1,5-diester **5.82** with all the required stereochemical information for the natural product. Debenzylation and cyclisation provided the desired tetracycle **5.47**, before a final reduction and treatment with H_2SO_4 provided (−)-sparteine (**5.01**) as the bis sulfate.



Scheme 73 O'Brien and co-workers' improved synthesis of (−)-sparteine (**5.01**).

5.1.4 Previous work in the Brown group towards quinolizidine alkaloids

Over the last 10 years, there has been a succession of syntheses into quinolizidine alkaloids by previous members of the Brown group. The work employed *N*-sulfinyl imine chemistry, and in particular an imino aldol reaction for the successful total synthesis of (−)-epilupinine (**5.85**) and (−)-tashiromine (**5.84**).[207] The key imino-aldol reaction installed the required *syn* stereochemistry in moderate (>10:1) diastereocontrol, with the proposed Zimmerman-Traxler transition state in figure 20 accounting for the observed selectivity. The unexpected pseudo axial orientation of the larger CH_2R^2 can be rationalised due to the preferential nature of imines to adopt *trans* configurations especially when derived from aldehydes.

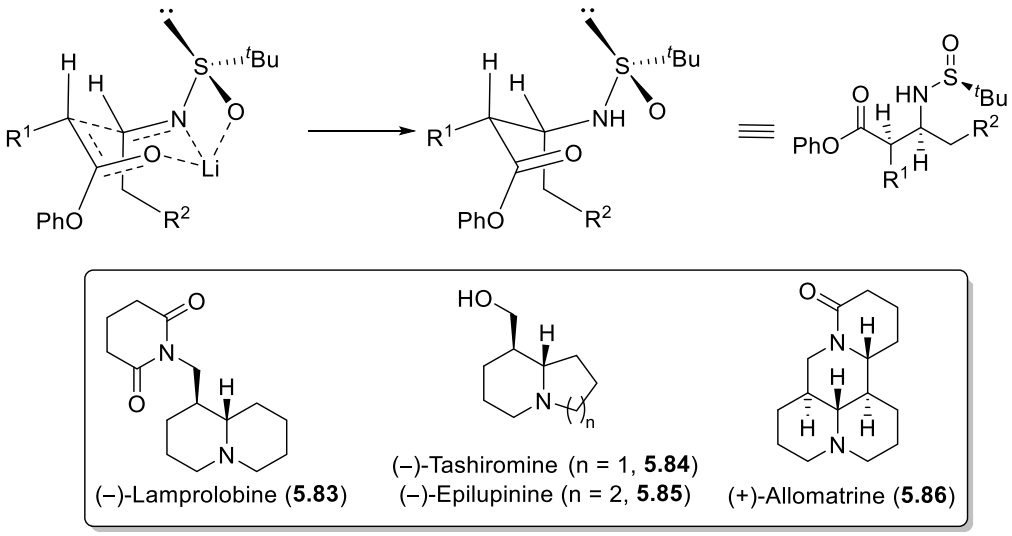
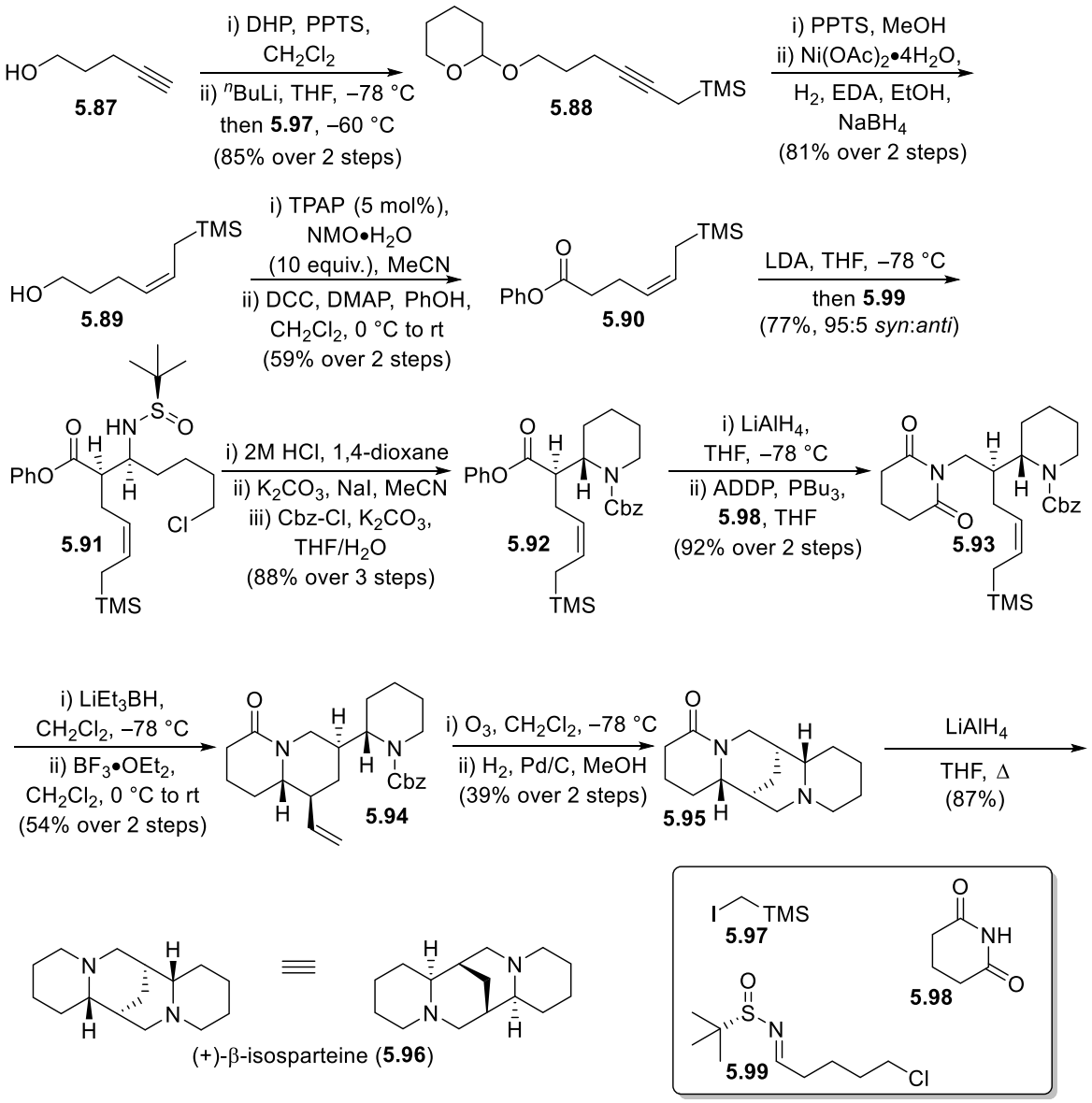


Figure 21 Proposed transition state for imino-aldol reactions and structures of and structures of (—)-lamprolobine (**5.83**), (—)-tashiromine (**5.84**), (—)-epilupinine (**5.85**) and (+)-allomatrine (**5.86**).

Further development and the work was expanded for the total synthesis of (+)-allomatrine (**5.86**) and (—)-lamprolobine (**5.83**), and the most recently published route described the total synthesis of (+)-*β*-isosparteine (**5.96**).[208,209] One synthetic endeavour not yet published from the group, carried out by David Wheatley, also describes a synthesis of (+)-*β*-isosparteine (**5.96**, scheme 74).[210] This synthesis highlights the imino-aldol chemistry in particular, with the *syn* aminoester **5.91** formed in excellent *dr*. The overall route began with alcohol **5.87**, which was protected and alkylated to give alkyne **5.88**. Removal of the THP protecting group and partial hydrogenation via a Nickel-boride catalyst produced *in situ* provided alcohol **5.89**, which underwent oxidation and esterification to ester **5.90**. The key imino-aldol ensued to provide *β*-amino ester **5.91** before removal of the auxiliary, Finkelstein promoted cyclisation and Cbz protection provided piperidine **5.92**. Chemoselective reduction of the ester provided the corresponding alcohol, which underwent a Mitsonobu reaction with glutarimide (**5.98**) to provided imide **5.93**. An *N*-acyliminium cyclisation provided the key tricycle **5.94** with all stereogenic centres in place for the natural product. Ozonolysis of the pendant olefin and hydrogenation of the intermediate trioxalane provided amide **5.95**, which was reduced to access (+)-β-isosparteine (**5.96**).



Scheme 74 Total synthesis of (+)-β-isosparteine (**5.96**).

This methodology was further advanced with introduction of an *anti*-selective alkylation. Where the ester moiety in the imino-aldol is an acetate derived ester, only one stereogenic centre is installed in the imino-aldol reaction, and a subsequent alkylation would enable access to the *anti*-products. The moderate selectivity (usually around 5:1 to 10:1) for the *anti* product can be rationalised utilising the model reported by Wang and co-workers', where the two equilibrating conformers **5.100** and **5.101** are considered (figure 21).[211] Lithium enolates were required for selectivity due to the strong chelation control compared to sodium, and after formation of the dianion, the initial conformer drawn due to the clash between the auxiliary and R^2 is disfavoured. The electrophile then approaches the *Si*-face of the favoured conformer **5.101**, with the large R^2 presumably hindering the *Re* face, resulting in the *anti* product **5.102**.

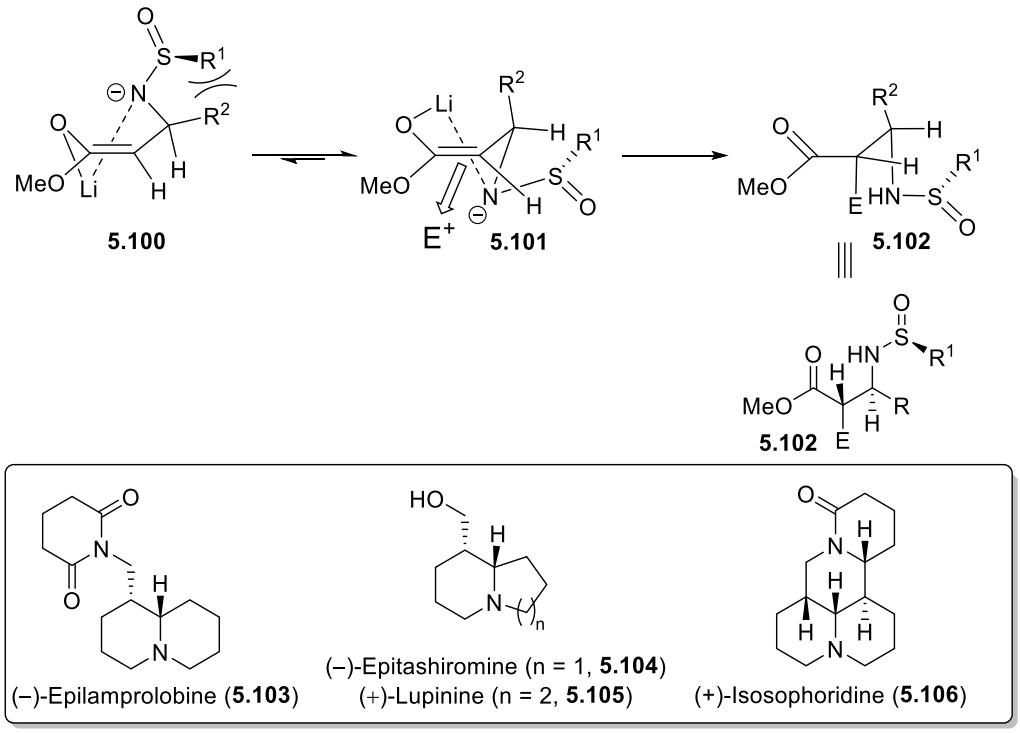
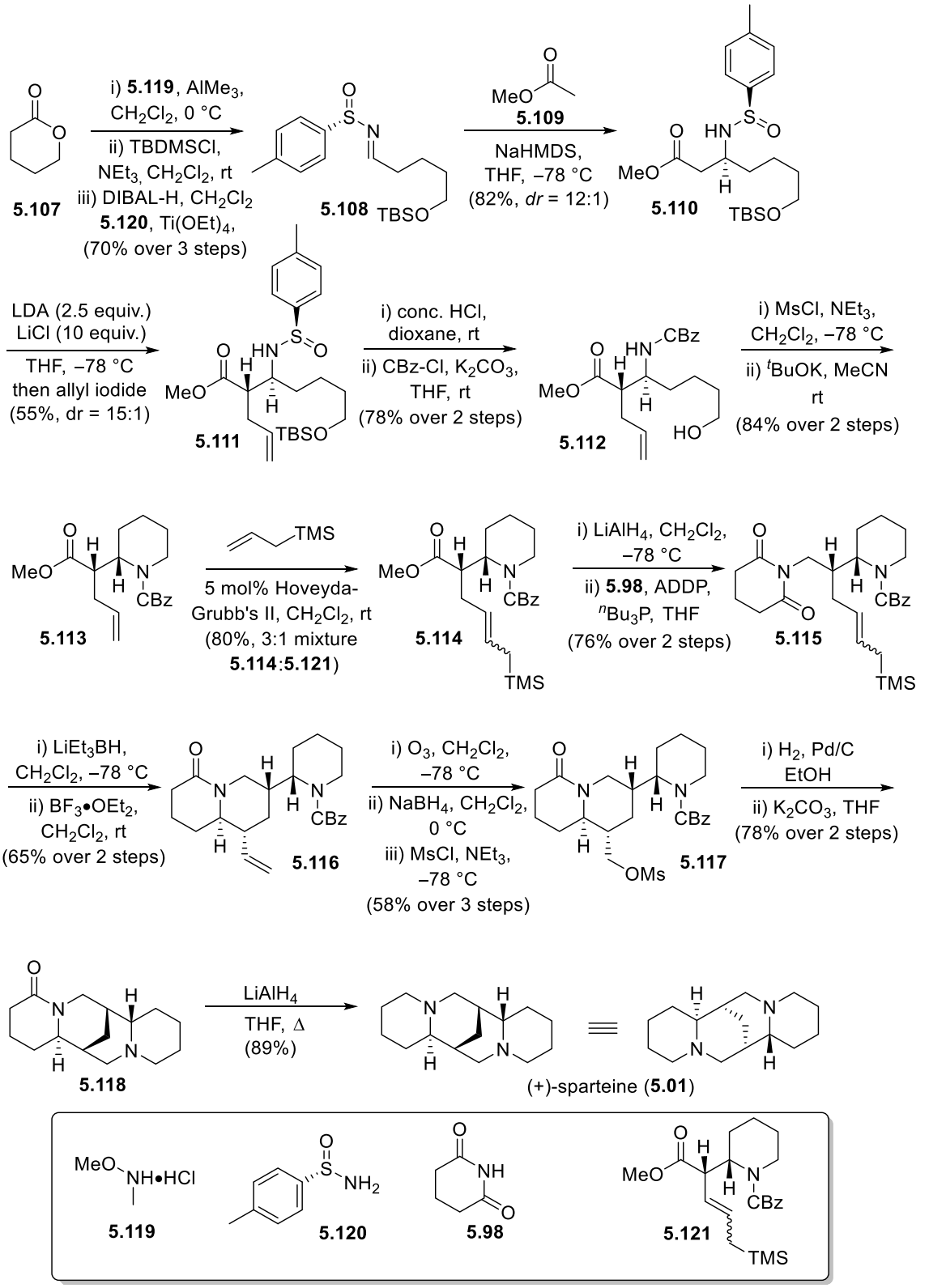


Figure 22 Proposed transition state accounting for anti-selective alkylation.

This strategy was successfully applied to the total synthesis of (+)-lupinine (**5.105**), (—)-epitashiromine (**5.104**), (—)-epilamprolobine (**5.103**) and (+)-isosophoridine (**5.106**). However, more recently in the group, the work was applied to the total synthesis of (+)-sparteine (**5.01**) by Xiang Lyu.[212] Utilising the Davis auxiliary **5.120**, sulfinimine **5.108** was isolated in 3 steps from δ-valerolactone (**5.107**). A subsequent imino-aldol reaction with methyl acetate (**5.109**) gave ester **5.110**, before the *anti*-selective alkylation with allyl iodide provided ester **5.111** in moderate yield and good diastereoselectivity. Removal of the auxiliary and TBS group with acid and Cbz-protection of the resulting amine provided carbamate **5.112**, before mesylation and cyclisation under basic conditions provided the key piperidine **5.113**. The subsequent cross-metathesis however, proved tricky. Treatment of piperidine **5.113** with allyl TMS and Hoveyda-Grubb's II provided a 3:1 mixture of the desired product and an inseparable by-product. This proved to be the by-product **5.121** with the loss of a carbon due to ruthenium hydride isomerisation of the allyl moiety. The mixture was advanced to the subsequent reduction and Mitsonobu with glutarimide (**5.98**), before an *N*-acyl iminium cyclisation provided tricycle **5.116**, at which stage the by-product **5.121**, which had not undergone the desired cyclisation, could be separated. Ozonolysis of the pendant olefin **5.116**, reductive work-up and mesylation of the resulting alcohol gave mesylate **5.117**, which after hydrogenation of the CBz group and base promoted cyclisation provided tetracycle **5.118**. The final reduction proceeded smoothly to provide (+)-sparteine (**5.01**) in good yield.



Scheme 75 Total synthesis of (+)-sparteine (**5.01**).

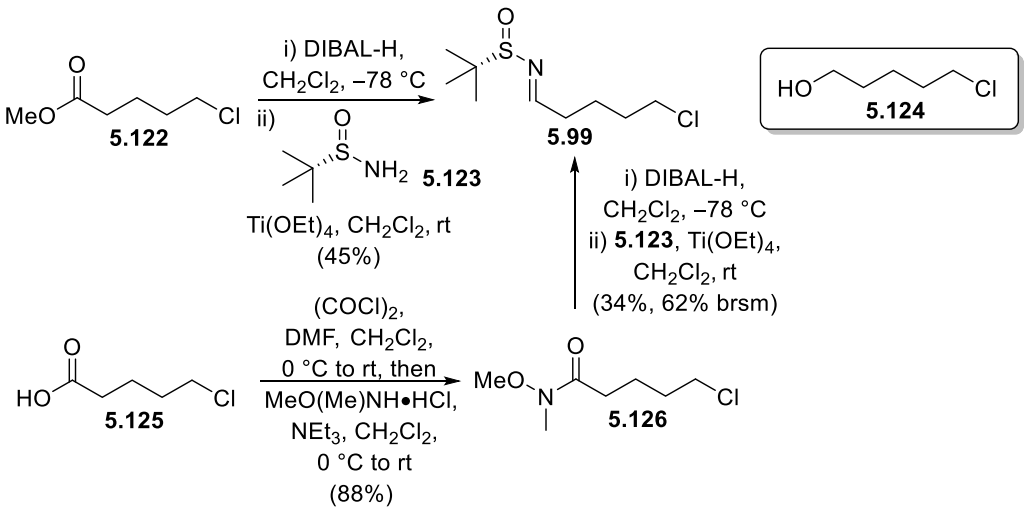
This route provided the natural product in 2% yield over 16 steps, and encompassed the Davis sulfinylamide **5.120** for the key imino-aldol and *anti*-selective alkylation reactions. This work was built upon early applications of the *anti*-selective alkylation approach, and as such early steps were not optimised. In addition, the menthol precursor to **5.120** was not isolated in enantiopure form, which had detrimental effects as the synthesis developed.

To improve the early steps of the synthesis, the Ellman auxiliary would be utilised, which can be purchased in enantiopure form and displays improved selectivity for the imino-aldol reaction compared to the Davis auxiliary **5.120**, particulary when titanium Lewis acids are employed. A subsequent switch to a Cbz group, which has detailed good selectivity for the *anti*-selective alkylation, before cyclisation would access piperidine **5.113** in less steps than previously required. As such it was decided the synthesis could be optimised and improved, particularly when considering the synthesis of (+)-*β*-isosparteine (**5.96**) described in scheme 74.

5.2 Synthesis towards (+)-Sparteine (5.01):

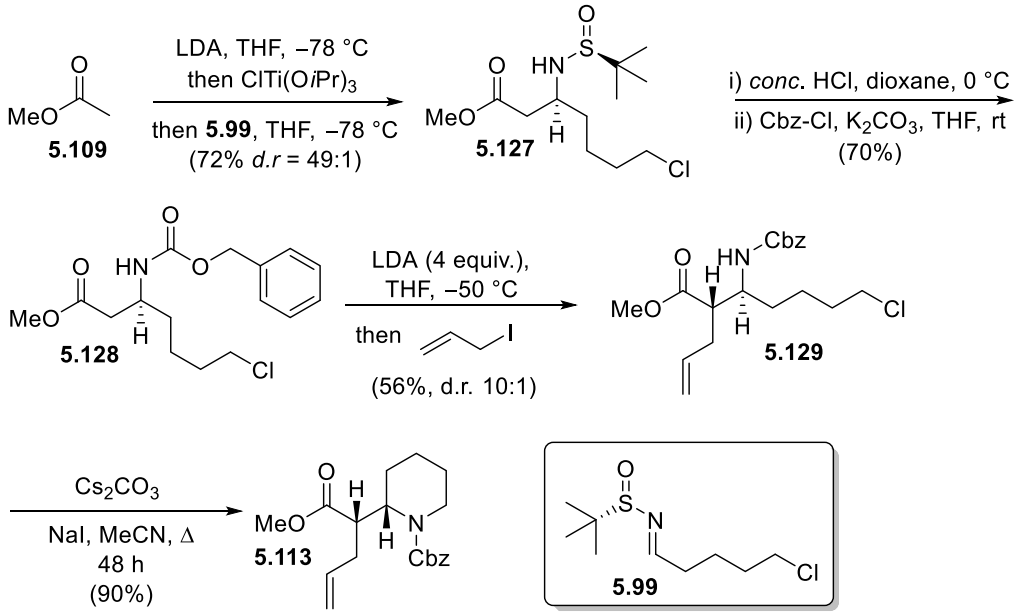
As mentioned, the synthesis plan was analogous to that developed during the (+)-*β*-isosparteine (**5.96**) synthesis (scheme 74), but incorporate an *anti*-selective alkylation to set the desired stereochemistry for (+)-sparteine (**5.01**). The end game was then envisaged to utilise the same *N*-acyliminium chemistry and ozonolysis described in both approaches.

The synthesis began with isolation of the key sulfinimine **5.99**, derived from condensation of Ellman's auxiliary **5.123** and an *in situ* prepared aldehyde.[213] 5-Chloropentanal (not shown) has been described in the literature and by previous members of the groups as being volatile, however even without concentration of the crude mixture derived from the DIBAL-H reduction of ester **5.122**, the overall yield of isolated sulfinimine **5.99** was moderate, and much lower than reported by other researchers.[207] Attempts to go via the Weinreb amide **5.126** were also successful albeit the yields were again moderate. This is likely due to over reduction, as alcohol **5.124** was often observed. However despite this inconvenience, sulfinimine **5.99** was isolated on >15 g scale.



Scheme 76 Synthesis of sulfinimine **5.99**.

With sulfinimine **5.99** in hand, the ensueing imino-aldol was investigated. Using previously described conditions, *β*-amino ester **5.127** was isolated in excellent yield and diastereoselectivity. Removal of the auxiliary with conc. HCl and protection of the free base after treatment with Cbz-Cl and base gave the desired carbamate **5.128** in good yield. As previously mentioned, this Cbz-protected chiral amine was sufficient to induce good selectivity in the *anti*-alkylation step. Treatment of carbamate **5.128** with two equivalents of LDA and then allyl iodide provided the *anti* adduct **5.129** in moderate yield and good diastereoselectivity. Cyclisation of this intermediate was achieved via a Finkelstein promoted pathway with Cs_2CO_3 and the key piperidine **5.113** was isolated in good yield and on multi-gram scale.



Scheme 77 Synthesis of piperidine **5.113**.

This now set the stage for investigation into the key cross-metathesis (CM) step. The CM step had previously been hampered by the formation of by-product **5.121** with one carbon removed due to alkene isomerisation. The by-product was proposed to arise *via* a RuH assisted mechanism, where degradation of the catalyst in the reaction mixture would lead to a RuH. Grubbs and co-workers' have reported that the use of 1,4-benzoquinone is effective at preventing formation of isomerised species, and our work began exploring this option.[214,215]

The initial conditions followed those used previously in the group with 1,4-benzoquinone (entry *a*). The CM product was isolated in moderate yield, but the by-product **5.121** was also observed. The LC-ESI trace indicated that the chain shortened product was produced in a considerably reduced amount, however the exact ratio was not determined. In an attempt to further improve the efficiency of the process, an alternate catalytic system was employed. Designed to have a slightly reduced steric bulk on the top NHC ligand leading to

improved reactivity, the new system (entry *b*) was employed to a slightly improved yield and again with only trace of the undesired by-product **5.121** according to the ESI.[216] The catalyst was added in portions throughout these experiments, and it was noted a slight increase in product was observed in bursts shortly after each addition. As such, in an attempt to further boost the yield, the batchwise addition of catalyst was continued the allyl TMS also added slowly via syringe pump. However, this led to a depreciation in yield and again formation of the unwanted by-product **5.121**, perhaps due to the dilution in the reaction resulting from the required solvent. As such, with no method to completely eliminate formation of by-product **5.121**, and the Stewart-Grubbs catalytic system offering the best yield, the reaction was rerun with an increased catalyst and 1,4-benzoquinone loading. Pleasingly, this led to an improved yield of 70% (82% brsm) with again only trace of the chain shortened by-product **5.121**.

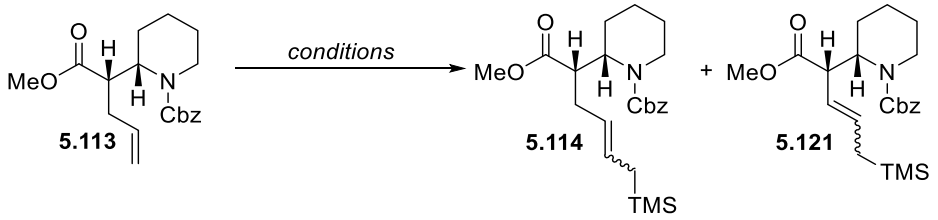
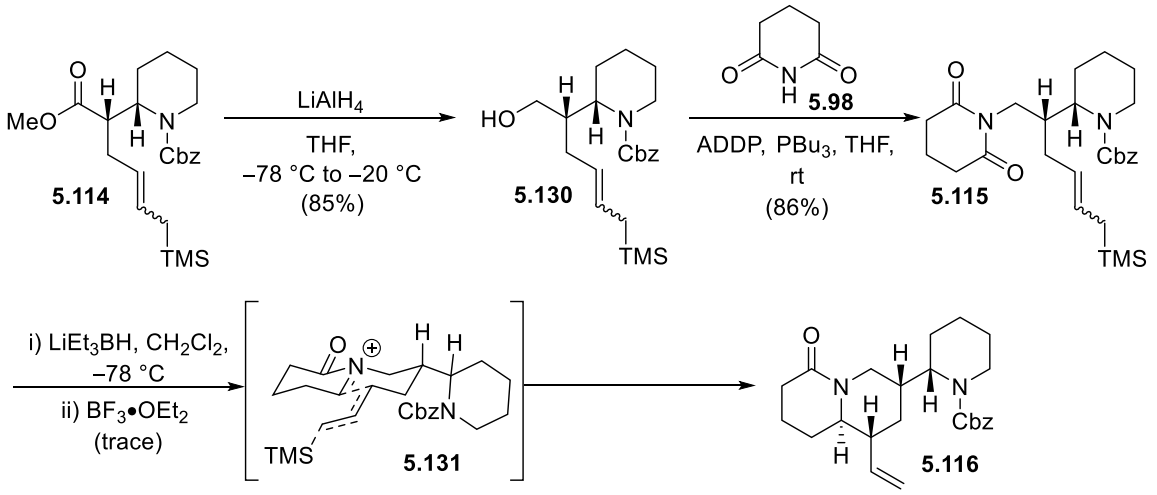


Table 7 Cross-metathesis of olefin **5.113**.

Entry	Conditions	Yield **5.114**/ %	**5.121** formed
a	Hoveyda-Grubb's II (7.5 mol%), 1,4-benzoquinone (10 mol%), allyl TMS (5 equiv.)	48	Yes
b	Stewart-Grubbs (7.5 mol%), 1,4-benzoquinone (10 mol%), allyl TMS (5 equiv.)	55	Yes
c	Stewart-Grubbs (7.5 mol%), 1,4-benzoquinone (10 mol%), DCE, allyl TMS (5 equiv. syringe pump addition)	43	Yes
d	Stewart-Grubbs (12.5 mol%), 1,4-benzoquinone (20 mol%), allyl TMS (5 equiv.)	70 (82 brsm)	Yes

The cross-metathesis derived olefin **5.114** was subjected to the subsequent reduction with $LiAlH_4$. If the reaction was carried out at 0 °C, or even worse at rt, considerable amounts the *N*-Me amine was observed, both with and without reduction of the ester. For the desired chemoselectivity, this reaction had to be carried out at lower temperatures for the addition, before allowing it to warm no higher than −20 °C resulting in alcohol **5.130** in excellent yield. A subsequent Mitsunobu reaction with glutarimide (**5.98**) secured imide **5.115** in good yield before subjection to the key *N*-acyl iminium reaction.



Scheme 78 Synthesis of imide **5.115**.

The allylsilane cyclisation, unfortunately, only provided the desired tricyclic product **5.116** in trace amounts. Previous work in the group supported a sole diastereomeric product formed in this cyclisation, rationalised by the favoured transition state **5.131**, however after purification, we were unable to obtain suitable amounts of tricycle **5.116.** Upon reviewing the conditions used for the iminium cyclisation, 5 equiv of the Lewis acid was employed, which may be excessive and led to the observed degradation. Two particular by-products were expected to be imide **5.132** and enaminde **5.133**, however ^{1}H NMR analysis of the mixture proved ineffective due to signal broadening caused by amide rotamers. Peaks in the ESI trace of the crude reaction mixture corresponding to *m/z* = 397.4 and 413.4 were observed, however these were unable to be isolated.

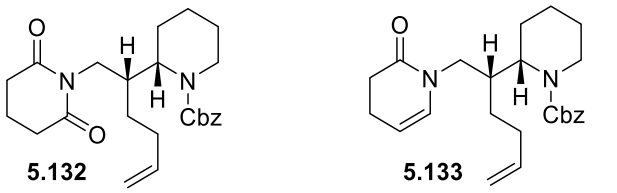


Figure 23 Potential *N*-acyl iminium by-products **5.132** and **5.133**.

Due to time constraints, we were unable advance olefin **5.115** to the desired tetracyclic core required for (+)-sparteine (**5.01**). The synthesis of olefin **5.115** was successfully completed in 9 steps from sulfinimine **5.99** in around 13% overall yield. The use of the imino-aldol and *anti*-alkylation chemistries were successfully utilised to install the desired anti-linkage within the target alkaloid. The following cross-metathesis step was optimised to reduce formation of the unwanted chain-shortened by-product, and the use of Stewart-Grubbs catalyst achieved a moderate improvement in yield compared to the Hoveyda-Grubbs II catalyst. Installation of the second piperidine ring began via the Mitsonobu of glutarimide, however the following *N*-acyl iminium chemistry proved to be very low yielding. It is proposed the large excess of Lewis acid utilised led to the poor results, and future synthesis should focus on optimising this step. Subjection of olefin **5.116** to final ozonolysis, cyclisation and reduction sequence should provide (+)-sparteine (**5.01**) and conclude studies into the quinolizidine alkaloids.

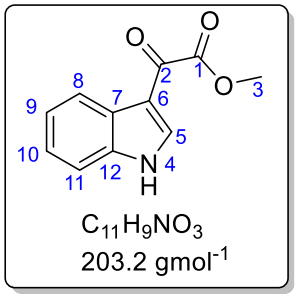
Chapter 6 Experimental

6.1 General Procedures

Chemicals were purchased from Sigma–Aldrich, Fisher Scientific or Alfa Aesar. NaH was used as a 60% dispersion in oil. All air/moisture sensitive reactions were carried out under an inert atmosphere, in oven–dried or flame–dried glassware. CH_2Cl_2 (from CaH_2) was distilled before use, and where appropriate, other reagents and solvents were purified by standard techniques. TLC was performed on aluminium–precoated plates coated with silica gel 60 with an F_{254} indicator; visualised under UV light (254 nm) and/or by staining with potassium permanganate. Flash column chromatography was performed using high purity silica gel, pore size 60 Å, 230–400 mesh particle size, purchased from Merck. ^{1}H NMR and NMR spectra were recorded in $CDCl_3$ (purchased from Cambridge Isotope Laboratories) at 298 K using Bruker DPX400 (400 and 101 MHz respectively) spectrometers. Chemical shifts are reported on the δ scale in ppm and were referenced to residual solvent ($CDCl_3$: 7.27 ppm for ^{1}H NMR spectra and 77.0 ppm for ^{13}C NMR spectra. DMSO-d_6: 2.50 ppm for ^{1}H NMR spectra and 39.52 ppm for ^{13}C NMR spectra). All spectra were reprocessed using ACD/Labs software version 2015 or ACD/Spectrus. Coupling constants (*J*) were recorded in Hz. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), br (broad), and m (multiplet). Electrospray (ES) low resolution mass spectra were recorded on a Waters TQD quadrupole spectrometer coupled to a waters UPLC. Electronimpact (EI) low resolution mass spectra were recorded on a Trace 2000 Series GC–MS coupled to a HP5890 GC. High resolution mass spectra were recorded on a Bruker APEX III FT–ICR mass spectrometer. Fourier–transform infrared (FT–IR) spectra are reported in wavenumbers (cm^{-1}) and were collected as solids or neat liquids on a Nicolet 380 using OMNIC software package. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the spectra. Melting points were obtained using a Gallenkamp Electrothermal apparatus. Microwave synthesis was performed in a sealed tube using a CEM discover microwave synthesizer.

6.2 Procedures and Characterisation Data

Methyl 2-(1*H*-indol-3-yl)-2-oxoacetate (1.64):



$C_{11}H_9NO_3$
203.2 $gmol^{-1}$

Methyl 2-(1*H*-indol-3-yl)-2-oxoacetate (**1.64**) was prepared by adaptation of a procedure described by Faul and co-workers'.[58]

To a solution of indole (5.01 g, 42.8 mmol) in Et_2O (50 mL) at 0 °C under N_2 was added oxalyl chloride (4.40 mL, 52.0 mmol) dropwise over 5 min. The resulting orange slurry was stirred at 0 °C for 2 h before cooling to –30 °C and adding MeOH (5 mL) dropwise over 5 min. The resulting red slurry was warmed to rt and stirred for a further 30 min. The red precipitate was filtered and washed with H_2O (40 mL) and Et_2O (60 mL). The red solid was taken up in MeOH (90 mL) and refluxed at 80 °C for 30 min before cooling to rt overnight. The slurry was filtered and the orange precipitate washed with ice-cold MeOH (30 mL) and ice-cold Et_2O (30 mL). The solid was dried under high vacuum to yield the title compound as an orange solid (7.35 g, 36.2 mmol, 85%). The physical and spectroscopic data were consistent with those reported.[58]

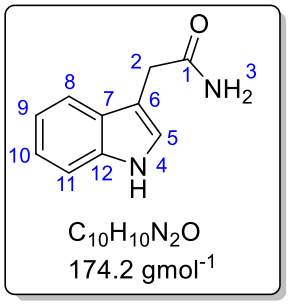
M.P. 218-220 °C (lit. 218-220 °C).[17]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.42 (br s, 1H, **4**), 8.45 (d, *J* = 3.3 Hz, 1H, **5**), 8.22-8.14 (m, 1H, **8**), 7.59-7.53 (m, 1H, **11**), 7.33-7.24 (m, 2H, **9**, **10**), 3.90 (s, 3H, **3**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 178.7 (**2**), 164.0 (**1**), 138.4 (**5**), 136.7 (**12**), 125.5 (**7**), 123.8 (**10**), 122.8 (**9**), 121.1 (**8**), 112.7 (**11**), 112.4 (**6**), 52.5 (**3**) ppm.

LRMS (ES$^+$) *m/z* = 204 $[M+H]^+$.

2-(1*H*-Indol-3-yl)acetamide (1.65):



$C_{10}H_{10}N_2O$
174.2 $gmol^{-1}$

2-(1*H*-Indol-3-yl)acetamide (**1.65**) was prepared according to a procedure described by Li and co-workers'.[217]

To a solution of 3-indole acetic acid (0.505 g, 2.88 mmol) in THF (10 mL) at 0 °C under N_2 was added CDI (0.489, 3.01 mmol). After 30 min the solution was warmed to rt and stirred for a further 2h. The reaction was quenched with NH_4OH (35%, 1.4 mL) dropwise and stirred for a further 30 min before being concentrated under reduced pressure to yield an off-white solid. The solid was taken in EtOAc (20 mL) and H_2O (20 mL) and the phases were separated. The organic phase was washed with H_2O (20 mL) and brine (20 mL) and concentrated under vacuum to yield white crystals. The crystals were dried under high vacuum to yield the title compound as colourless crystals (0.474 g, 2.75 mmol, 96%). The physical and spectroscopic data were consistent with those reported.[217]

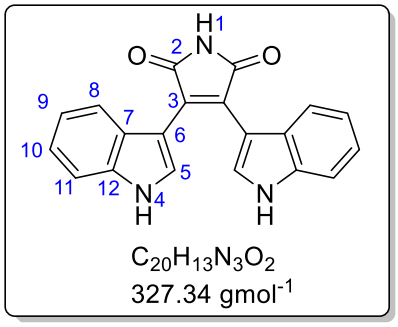
M.P. 152-154 °C (lit. 150-151 °C).[218]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.88 (br, s, 1H, **4**), 7.57 (d, *J* = 7.5 Hz, 1H, **8**), 7.36 (dt, *J* = 8.1, 0.9 Hz, 1H, **11**), 7.32 (s, 1H, **3a**), 7.21 (d, *J* = 2.3 Hz, 1H, **5**), 7.08 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, **10**), 6.99 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H, **9**), 6.86 (s, 1H, **3b**), 3.49 (s, 2H, **2**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 173.0 (**1**), 136.1 (**12**), 127.3 (**7**), 123.8 (**5**), 120.9 (**10**), 118.7 (**8**), 118.3 (**9**), 111.3 (**11**), 109.0 (**6**), 32.5 (**2**) ppm.

LRMS (ES^+) *m/z* = 175 $[M+H]^+$.

3,4-Di(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione/ bisindoylmaleimide (1.54):



$C_{20}H_{13}N_3O_2$
327.34 $gmol^{-1}$

3,4-Di(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (**1.54**) was prepared according to a procedure described by Faul and co-workers'.[58]

To a solution of 2-(1*H*-indol-3-yl)acetamide (**1.65**, 2.51 g, 14.4 mmol) and methyl 2-(1*H*-indol-3-yl)-2-oxoacetate (**1.64**, 3.54 g, 17.4 mmol) in THF (42 mL) at 0 °C under N_2, was added KO^{t}Bu (4.86 g, 43.3 mmol) portionwise over 15 min. The resulting purple slurry was warmed to rt and stirred for a further 16 h before cooling to 0 °C and conc. HCl (6.6 mL) added dropwise over 10 min. The resulting red slurry was warmed to rt and stirred for a further 6 h before diluting with H_2O (30 mL) and EtOAc (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to a red solid. The solid was recrystallized in EtOH to yield an EtOH mono-adduct of the title compound as a red solid (4.21 g, 12.9 mmol, 90%). The physical and spectroscopic data were consistent with those reported.[58]

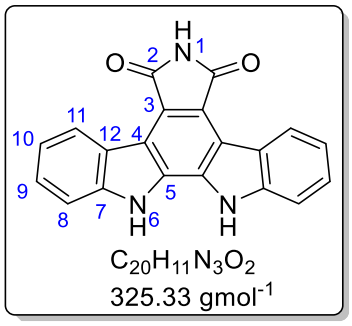
M.P. 162-164 °C (lit. 158-160 °C).[219]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.65 (d, *J* = 2.1 Hz, 2H, **4**), 10.89 (s, 1H, **1**), 7.74 (d, *J* = 2.8 Hz, 2H, **5**), 7.37 (d, *J* = 8.1 Hz, 2H, **11**), 6.97 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 2H, **10**), 6.81 (d, *J* = 8.1 Hz, 2H, **8**), 6.63 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 2H, **9**), 4.36 (br s, 1H, $CH_3CH_2O\mathbf{H}$), 3.45 (q, *J* = 6.4 Hz, 2H, $CH_3C\mathbf{H_2}OH$), 1.06 (t, *J* = 7.0 Hz, 3H, $C\mathbf{H_3}CH_2OH$) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 173.0 (**2**), 136.0 (**12**), 129.1 (**5**), 127.7 (**3**), 125.4 (**7**), 121.6 (**10**), 120.9 (**8**), 119.3 (**9**), 111.7 (**11**), 105.6 (**6**), 56.0 ($CH_3C\mathbf{H_2}OH$), 18.6 ($C\mathbf{H_3}CH_2OH$) ppm

LRMS (ES$^+$) *m/z* = 328 $[M+H]^+$.

12,13-Dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione /arcyriaflavin a (1.55):



12,13-Dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (**1.55**) was prepared by adaptation of a procedure described by Reddy and co-workers'.[111]

A 0.075 M solution of bisindolylmaleimide **1.54** (0.123 g, 0.375 mmol) and iodine (9.2 mg, 0.036 mmol) in THF/MeCN (5 mL, 1:1) was irradiated with blue LEDs (Mirrorstone©, 36 W, 510 lumens, 12 V) for 14 h. The reaction mixture was concentrated under reduced pressure to a brown solid which was taken in THF and stirred with activated charcoal for a 15 min. The mixture was filtered through a pad of celite, washed with THF, and concentrated under reduced pressure to give a brown solid. The solid was triturated in ice-cold Et_2O to give the title compound as a dark red solid (79.2 mg, 0.243 mmol, 65%). The physical and spectroscopic data were consistent with those reported.[111]

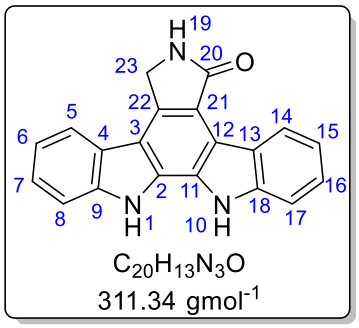
M.P. 162 °C decomposed.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.72 (s, 2H, **6**), 10.98 (s, 1H, **1**), 9.00 (d, *J* = 7.9 Hz, 2H, **11**), 7.81 (d, *J* = 8.1 Hz, 2H, **8**), 7.55 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 2H, **9**), 7.35 (t, *J* = 7.5 Hz, 2H, **10**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 171.3 (**2**), 140.3 (**7**), 129.0 (**5**), 126.8 (**9**), 124.3 (**11**), 121.6 (**12**), 120.2 (**10**), 119.9 (**3**), 115.5 (**4**), 112.0 (**8**) ppm.

LRMS (ES$^+$) *m/z* = 326 [M+H]$^+$.

Staurosporine aglycone/K252c (1.10):



A solution of arcyriaflavin A (**1.55**, 1.00, 3.07 mmol) and tin (9.01 g, 76.5 mmol) in AcOH (50 mL) was wamed to 100 °C. Conc. HCl (22.5 mL) was added dropwise and the mixture stirred for 2 h. The reaction was cooled to rt, THF (50 mL) was added and the mixture filtered through a pad of celite. The pad was washed with THF (100 mL) and acetone (100 mL) before the combined washings were poured over ice. The precipitate was filtered, washed with Et_2O and dried to yield the title compound as a light yellow solid (770 mg, 2.47 mmol, 80%). The physical and spectroscopic data were consistent with those reported.[59,63]

M.P. >300 °C (lit. 310 °C).[59]

IR IR (neat) ν 3434, 3307, 1645, 1575, 1454, 1390, 1330, 1262 cm^{-1}.

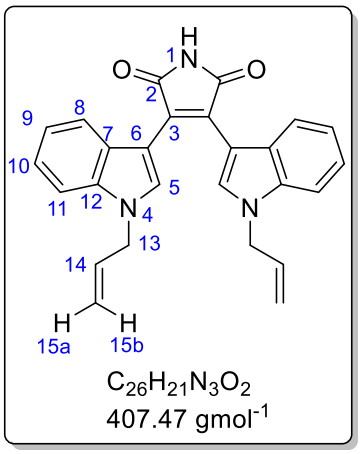
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.49 (s, 1H, **1**), 11.32 (s, 1H, **10**), 9.27-9.18 (m, 1H, **14**), 8.48 (s, 1H, **19**), 8.04 (d, *J* = 7.9 Hz, 1H, **5**), 7.79 (dt, *J* = 8.1, 0.8 Hz, 1H, **8**), 7.72 (dt, *J* = 8.1, 0.9 Hz, 1H, **17**), 7.48 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, **7**), 7.43 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, **16**), 7.31 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H, **6**), 7.23 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, **15**), 4.96 (s, 2H, **23**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 172.4 (**20**), 139.2 (**9**), 139.1 (**18**), 132.9 (**22**), 127.8 (**2/11**), 125.4 (**2/11**), 125.2 (**14**), 125.0 (**7**), 125.0 (**16**), 122.8 (**13**), 122.6 (**4**), 121.1 (**5**), 119.9 (**6**), 118.9 (**15**), 118.9 (**21**), 115.6 (**3/12**), 114.1 (**3/12**), 111.9 (**8**), 111.3 (**17**), 45.3 (**23**) ppm.

LRMS (ES^+) *m/z* = 312 $[M+H]^+$.

HRMS (ES^+) *m/z* for $C_{20}H_{14}N_3O$ calculated 312.1131, measured 312.1134; for $C_{20}H_{13}N_3NaO$ calculated 334.0951, measured 334.0951.

3,4-Bis(1-allyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (2.09):



To a solution of bisindolylmaleimide **1.54** (101 mg, 0.307 mmol) in THF (3 mL) at rt under N_2 was added NaH (52 mg mg, 60% mineral oil, 1.3 mmol). After 1h, allyl bromide (0.1 mL, 1.16 mmol) was added dropwise over 20 min and the mixture stirred. After a further 4 h, the mixture was concentrated to a dark red solid. The solid was taken in EtOAc (20 mL) and H_2O (15 mL) and the phases separated. The aqueous phase was extracted with EtOAc (3 x 25 mL) and the combined organics dried (MgSO4) and concentrated to yield the title compound as a dark red solid (121 mg, 0.297 mmol, 97%).

M.P. Decomposed 195 °C.

IR IR (neat) ν 2922, 2611, 2363, 2260, 2014 cm^{-1}.

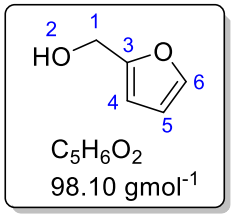
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.95 (br s, 1H, **1**), 7.80 (s, 2H, **5**), 7.39 (br d, *J* = 8.1 Hz, 2H, **11**), 7.00 (br t, *J* = 7.5 Hz, 2H, **10**), 6.80 (br d, *J* = 7.9 Hz, 2H, **8**), 6.63 (t, *J* = 7.3 Hz, 2H, **9**), 6.08-5.89 (m, 2H, **14**), 5.17 (br d, *J* = 10.1 Hz, 2H, **15b**), 5.01 (br d, *J* = 17.2 Hz, 2H, **15a**), 4.90 (br d, *J* = 3.9 Hz, 4H, **13**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 172.8 (**2**), 135.7 (**12**), 133.8 (**14**), 131.9 (**5**), 127.3 (**3**), 126.0 (**11**), 121.7 (**7**), 121.1 (**8**), 119.5 (**9**), 116.7 (**15**), 110.4 (**10**), 105.1 (**6**), 48.2 (**13**) ppm

LRMS (ES$^+$) *m/z* = 408 [M+H]$^+$.

HRMS (ES$^+$) *m/z* for $C_{26}H_{22}N_3O_2$ calculated 408.1707, found 408.1708.

Furan-2-ylmethanol (3.07):



Furan-2-ylmethanol (**3.07**) was prepared according to a procedure described by Huang and co-workers'.[220]

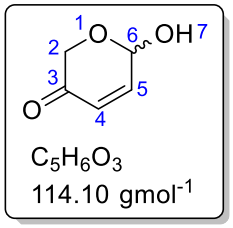
To a solution of furfural (0.43 mL, 5.20 mmol) in MeOH (2.6 mL) at 0 °C under N_2 was added $NaBH_4$ (99.0 mg, 2.62 mmol) portionwise over 5 min. After 15 min, the mixture was warmed to rt and stirred for a further 2 h. The reaction mixture was concentrated under reduced pressure and the crude brown oil was taken in Et_2O (30 mL) and H_2O (15 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound as a light yellow oil (440 mg, 4.49 mmol, 86%). The spectroscopic data were consistent with those reported.[220,221]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.48-7.34 (m, 1H, **6**), 6.38-6.34 (m, 1H, **5**), 6.32-6.29 (m, 1H, **4**), 4.61 (s, 2H, **1**), 2.35-2.00 (m, 1H, **2**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ =153.9 (**3**), 142.5 (**6**), 110.3 (**5**), 107.7 (**4**), 57.3 (**1**) ppm.

LRMS (EI) *m/z* = 98.1 $[M]^{+\bullet}$.

6-Hydroxy-2H-pyran-3(6H)-one (3.08):



6-Hydroxy-2H-pyran-3(6H)-one (**3.08**) was prepared according to a procedure described by Waldmann and co-workers'.[121]

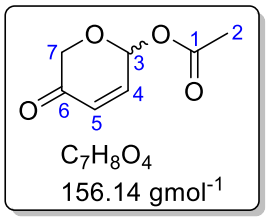
To a solution of furan-2-ylmethanol (**3.07**, 0.200 g, 2.04 mmol), $NaHCO_3$ (0.347 g, 4.13 mmol), NaOAc (0.169 g, 2.06 mmol) in THF:H_2O (4:1, 3.4 mL) at 0 °C under N_2 was added *N*-bromosuccinimide (0.365 g, 2.05 mmol) and stirred. After 15 min, the mixture was diluted with EtOAc (20 mL) and H_2O (10 mL) and the phases were separated. The organic phase was washed with H_2O (10 mL) and the combined aqueous layers were extracted with EtOAc (3 x 30 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude compound as a colourless oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 1:9 to 1:0) gave the title compound as a colourless syrup that crystallised upon scratching (0.119 g, 1.04 mmol, 51%). The spectroscopic data were consistent with those reported.[222]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.97 (dd, *J* = 10.4, 3.2 Hz, 1H, **5**), 6.18 (d, *J* = 10.5 Hz, 1H, **4**), 5.65 (ddd, *J* = 5.5, 3.1, 0.7 Hz, 1H, **6**), 4.58 (d, *J* = 16.9 Hz, **2**), 4.15 (d, *J* = 17.0 Hz, 1H, **2'**), 3.46 (d, *J* = 5.6 Hz, 1H, **7**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 194.5 (**3**), 145.7 (**5**), 127.9 (**4**), 88.2 (**6**), 66.6 (**2**) ppm.

LRMS (EI) *m/z* = 114.2 $[M]^{+\bullet}$.

5-Oxo-5,6-dihydro-2*H*-pyran-2-yl acetate (3.09):



$C_7H_8O_4$
156.14 $gmol^{-1}$

5-Oxo-5,6-dihydro-2*H*-pyran-2-yl acetate (**3.09**) was prepared by adaptation of a procedure described by Dutta and co-workers'.[122]

To a solution of furan-2-ylmethanol (**3.07**, 1.00 g, 10.2 mmol), $NaHCO_3$ (1.72 g, 20.4 mmol), NaOAc (0.843 g, 10.3 mmol) in THF:H_2O (9:1, 15 mL) at 0 °C under N_2 was added NBS (1.82 g, 10.2 mmol) portionwise over 10 min and the mixture stirred. After 2 h, a further portion of NBS (0.183 g, 1.02 mmol) was added and the mixture stirred. After a further 1 h, DMAP (0.254 g, 2.04 mmol) and Ac_2O (1.95 mL, 20.6 mmol) were added sequentially and the mixture warmed to rt. After a further 3 h, the mixture was quenched with 2M NaOH until pH = 6. The resulting mixture was extracted with EtOAc (3 x 40 mL) and the combined organics washed with saturated aq. $NaHCO_3$ solution (50 mL) and concentrated to an orange oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 5:95) gave the title product as an amorphous white solid (0.833 g, 5.33 mmol, 52%). The physical and spectroscopic data were consistent with those reported.[121]

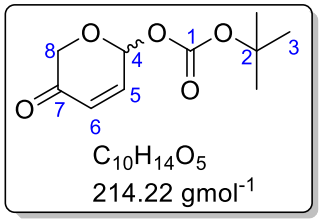
M.P. 40-41 °C (lit. 40-41 °C).[223]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.92 (dd, *J* = 10.3, 3.6 Hz, 1H, **4**), 6.49 (dd, *J* = 3.5, 0.6 Hz, 1H, **3**), 6.27 (d, *J* = 10.4, 1H, **5**), 4.51 (d, *J* = 17.0 Hz, 1H, **7a**), 4.22 (d, *J* = 17.0 Hz, 1H, **7b**), 2.14 (s, 3H, **2**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 193.3 (**6**), 169.4 (**1**), 142.2 (**4**), 128.7 (**5**), 86.6 (**3**), 67.3 (**7**), 20.8 (**2**) ppm.

LRMS (EI) *m/z* = 156 $[M]^{+\bullet}$, 96 $[M\text{-}OAc^{\bullet}]^{+}$,

tert-Butyl (5-oxo-5,6-dihydro-2*H*-pyran-2-yl) carbonate (3.10):



$C_{10}H_{14}O_5$
214.22 gmol^{-1}

tert-Butyl (5-oxo-5,6-dihydro-2*H*-pyran-2-yl) carbonate (**3.10**) was prepared by adaptation of a procedure described by Dutta and co-workers'.[122]

To a solution of furan-2-ylmethanol (**3.07**, 1.00 g, 10.2 mmol), $NaHCO_3$ (1.72 g, 20.4 mmol) and NaOAc (0.839 g, 10.9 mmol) in THF:H_2O (9:1, 15 mL) at 0 °C under N_2 was added NBS (1.82 g, 10.2 mmol) portionwise over 10 min and the mixture stirred. After 1 h, a further portion of NBS (0.189 g, 1.06 mmol) was added and the mixture stirred. After a further 1 h, DMAP (0.254 g, 2.04 mmol) and Boc_2O (2.66 g, 12.2 mmol) were added sequentially and the mixture warmed to rt. The mixture was stirred for 16 h before being quenched with saturated aq. $NaHCO_3$ solution (30 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL), dried ($MgSO_4$) and concentrated to a brown oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 1:9) gave the title compound as a white crystalline solid (0.706 g, 3.30 mmol, 32%). The physical and spectroscopic data were consistent with those reported.[224]

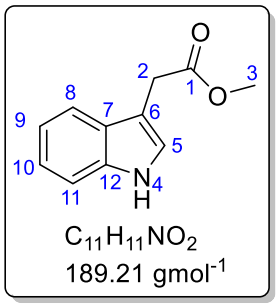
M.P. 85-87 °C (lit. 83-85 °C).[67]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.15 (dd, *J* = 10.4, 3.5 Hz, 1H, **5**), 6.33 (dd, *J* = 3.5, 0.7 Hz, 1H, **4**), 6.30 (d, *J* = 10.4 Hz, 1H, **6**), 4.43 (d, *J* = 17.1 Hz, 1H, **8a**), 4.22 (d, *J* = 17.0 Hz, 1H, **8b**), 1.45 (s, 9H, **3**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 193.5 (**7**), 151.3 (**1**), 143.2 (**5**), 128.2 (**6**), 88.6 (**4**), 82.9 (**2**), 66.7 (**8**), 27.2 (**3**) ppm.

LRMS (EI) *m/z* = 214 $[M]^{+\bullet}$, 97 $[M\text{-}OBoc^{\bullet}]^{+}$.

Methyl 2-(1H-indol-3-yl)acetate (1.100):



$C_{11}H_{11}NO_2$
189.21 $gmol^{-1}$

Methyl 2-(1H-indol-3-yl)aceteate (**1.100**) was prepared according to a procedure described by Webb-Smith and co-workers'.[225]

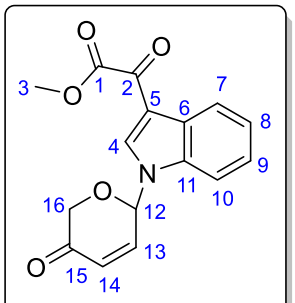
To a solution of indole acetic acid (508 mg, 2.90 mmol) in MeOH (20 mL) at rt was added H_2SO_4 (1 mL) dropwise and stirred. After 1 h the reaction was quenched with a saturated aq. $NaHCO_3$ solution (10 mL) and stirred for 30 min. The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL), dried ($MgSO_4$) and concentrated to give the title compounds a dark brown oil (0.539 g, 2.84 mmol, 98%). The crude oil was used without any further purification. Spectroscopic data were consistent with those reported.[226]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.95 (br s, 1H, **4**), 7.49 (d, *J* = 7.5 Hz, 1H, **8**), 7.36 (dt, *J* = 8.1, 0.8 Hz, 1H, **11**), 7.25 (d, *J* = 2.4 Hz, 1H, **5**), 7.09 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, **10**), 6.99 (ddd, *J* = 7.9, 7.2, 1.1 Hz, 1H, **9**), 3.75 (d, *J* = 0.6 Hz, **2**), 3.61 (s, 3H, **3**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 172.0 (**1**), 136.1 (**12**), 127.1 (**7**), 124.1 (**5**), 121.1 (**10**), 118.5 (**9**), 118.4 (**8**) 111.4 (**11**), 106.9 (**6**), 51.5 (**3**), 30.6 (**2**) ppm

LRMS (ES$^+$) *m/z* = 190 $[M+H]^+$.

Methyl 2-oxo-2-(1-(5-oxo-5,6-dihydro-2*H*-pyran-2-yl)-1*H*-indol-3-yl)acetate (3.11):



$C_{16}H_{13}NO_5$
299.28 gmol^{-1}

To a solution of *ter*t-butyl (5-oxo-5,6-dihydro-2*H*-pyran-2-yl) carbonate (**3.10**, 138 mg, 0.644 mmol), methyl 2-(1*H*-indol-3-yl)-2-oxoacetate (**1.64**, 102 mg, 0.502 mmol) in degassed THF (1.5 mL) at rt under N_2 was added a pre-mixed solution of $Pd_2(dba)_3$ (23.1 mg, 0.025 mmol), PPh_3 (18.7 mg, 0.071 mmol) in degassed THF (1 mL) and the mixture warmed to 50 °C. After 5 h, the mixture was warmed to 60 °C and stirred. After a further 10 h, the mixture was concentrated to a black solid. Purification of the crude solid via flash chromatography (Et_2O:toluene = 3:7) gave the title compound as a colourless oil (35.3 mg, 0.118 mmol. 24%).

IR IR (neat) ν 2953, 1728, 1703, 1647, 1140, 1071 cm^{-1}.

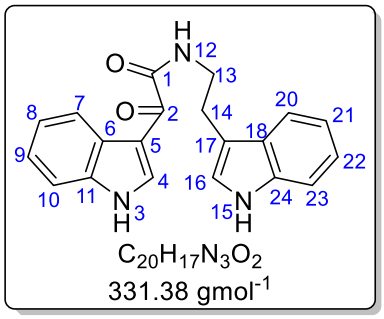
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.49-8.42 (m, 2H, **4+7**), 7.62-7.56 (m, 1H, **10**), 7.44-7.38 (m, 2H, **8+9**), 7.23 (dd, *J* = 10.4, 3.2 Hz, 1H, **13**), 6.59 (dd, *J* = 10.4, 1.8 Hz, 1H, **14**), 6.57-6.55 (m, 1H, **12**), 4.29 (d, *J* = 16.9 Hz, 1H, **16a**), 4.21 (d, *J* = 16.9 Hz, 1H, **16b**), 3.94 (s, 3H, **3**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 192.3 (**15**), 177.4 (**2**), 162.7 (**1**), 142.0 (**13**), 137.0 (**4**), 136.3 (**11**), 131.1 (**14**), 127.3 (**6**), 125.0 (**8/9**), 124.4 (**8/9**), 123.0 (**7**), 114.2 (**5**), 111.0 (**10**), 78.0 (**12**), 68.3 (**16**), 52.9 (**3**) ppm.

LRMS (ES^+) *m/z* = 300 $[M+H]^+$.

HRMS (ES^+) *m/z* for $C_{16}H_{13}NNaO_5$ calculated 322.0686, found 322.0689.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-2-(1*H*-indol-3-yl)-2-oxoacetamide (3.16):**



$C_{20}H_{17}N_3O_2$

331.38 gmol^{-1}

N-(2-(1*H*-Indol-3-yl)ethyl)-2-(1*H*-indol-3-yl)-2-oxoacetamide (**3.16**) was prepared according to a procedure described by Chakrabarty and co-workers'.[124]

To a solution of indole (1.17 g, 9.99 mmol) in Et_2O (25 mL) at 0 °C under N_2 was added oxalyl chloride (0.93 mL, 10.8 mmol). After 1.5 h, the mixture was concentrated to a yellow solid, taken in THF (15 mL), and added dropwise to a stirred solution of tryptamine (1.78 g, 11.1 mmol), NEt_3 (4.40 mL) in THF (15 mL) at 0 °C under N_2. The mixture was stirred for 15 min before allowing to warm to rt. After 17 h, the mixture was taken in H_2O (50 mL) and EtOAc (50 mL) and the phases separated. The aqueous phase was washed with EtOAc (3 x 70 mL) and the combined organics dried ($MgSO_4$) and concentrated to a yellow solid. The crude solid was triturated in Et_2O and dried under high vacuum to yield the title product as an amorphous white solid (2.70 g, 8.15 mmol, 82%). The physical and spectroscopic data were consistent with those reported.[124]

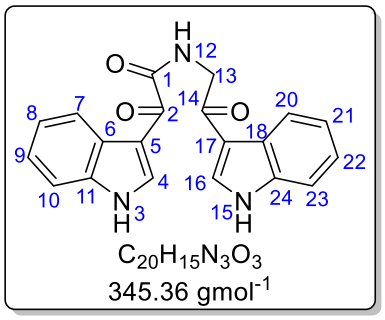
M.P. 193-195 °C (lit. 199-201 °C).[124]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.23 (br d, *J* = 1.7 Hz, 1H, **3**), 10.83 (br s, 1H, **15**) 8.82 (br t, *J* = 5.9 Hz, **12**), 8.78 (d, *J* = 3.2 Hz, 1H, **4**), 8.29-8.21 (m, 1H, **7**), 7.61 (d, *J* = 7.8 Hz, 1H, **20**), 7.58-7.50 (m, 1H, **10**), 7.35 (d, *J* = 8.1 Hz, 1H, **23**), 7.30-7.23 (m, 2H, **8+9**), 7.21 (d, *J* = 2.1 Hz, 1H, **16**), 7.11-7.05 (m, 1H, **22**), 7.02-6.96 (m, 1H, **21**), 3.59-3.48 (m, 2H, **13**), 2.97 (t, *J* =7.5 Hz, 2H, **14**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 182.2 (**2**), 163.4 (**1**), 138.5 (**4**), 136.3 (**11+24**), 127.2 (**18**), 126.2 (**6**), 123.4 (**8/9**), 122.7 (**16**), 122.5 (**8/9**), 121.3 (**7**), 121.0 (**22**), 118.3 (**20**), 118.3 (**21**), 112.5 (**10**), 112.2 (**5**), 111.6 (**17**), 111.4 (**23**), 39.4 (**14**), 24.9 (**13**) ppm.

LRMS (ES$^+$) *m/z* =332 $[M+H]^+$, 354 $[M+Na]^+$.

_N_-(2-(1_H_-Indol-3-yl)-2-oxoethyl)-2-(1_H_-indol-3-yl)-2-oxoacetamide (3.17):



$C_{20}H_{15}N_3O_3$
345.36 gmol^{-1}

_N_-(2-(1_H_-Indol-3-yl)-2-oxoethyl)-2-(1_H_-indol-3-yl)-2-oxoacetamide (**3.17**) was prepared according to a modified procedure described by Nicolaou and co-workers'.[142]

To a solution of _N_-(2-(1_H_-Indol-3-yl)ethyl)-2-(1_H_-indol-3-yl)-2-oxoacetamide (**3.16**, 500 mg, 1.51 mmol) in THF (19 mL) and H_2O (2mL) at 0 °C under N_2 was added DDQ (753 mg, 3.32 mmol) and stirred for 2 h. The reaction mixture was taken in EtOAc (50 mL) and extracted with sat. aqueous $NaHCO_3$ solution (8x50 mL) until all coloured by-products were removed. The organic phase was dried ($MgSO_4$) and concentrated to a light brown solid. The crude solid was triturated in Et_2O and dried under high vacuum to yield the title compound as an amorphous white solid (508 mg, 1.47 mmol, 96%). The physical and spectroscopic data were consistent with those reported.[227,228]

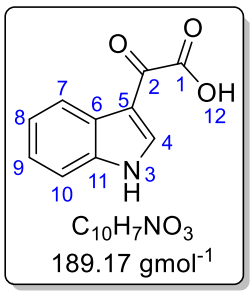
M.P. 258-261 °C (lit. 264-265 °C).[228]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.27 (br d, J =2.1 Hz, 1H, **3**), 12.08 (br s, 1H, **15**), 8.94 (t, J = 5.8 Hz, 1H, **12**), 8.86 (d, J = 3.2 Hz, 1H, **4**), 8.53 (d, J = 3.1 Hz, 1H, **16**), 8.34-8.26 (m, 1H, **7**), 8.24-8.16 (m, 1H, **20**), 7.60-7.47 (m, 2H, **10+23**), 7.33-7.19 (m, 4H, **8+9+21+22**), 4.67 (d, J = 5.9 Hz, 2H, **13**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 189.2 (**14**), 181.9 (**2**), 163.8 (**1**), 138.7 (**4**), 136.5 (**11**), 136.3 (**24**), 133.8 (**16**), 126.2 (**6**), 125.4 (**18**), 123.5 (**8/9**), 123.0 (**21/22**), 122.6 (**8/9**), 121.9 (**21/22**), 121.4 (**7**), 121.2 (**20**), 114.0 (**17**), 112.6 (**10**), 112.3 (**6**), 112.2 (**23**), 45.7 (**13**) ppm.

LRMS (ES$^+$) m/z =346 [M+H]$^+$, 368 [M+Na]$^+$.

2-(1*H*-Indol-3-yl)-2-oxoacetic acid (3.20):



2-(1*H*-Indol-3-yl)-2-oxoacetic acid (**3.20**) was prepared according to a procedure described by Benedetti and co-workers'.[229]

A solution of methyl 2-(1*H*-indol-3-yl)-2-oxoacetate (**1.64**, 1.50 g, 7.38 mmol) in a 1M solution of Na_2CO_3 in H_2O (8.2 mL) under N_2, was heated to 80 °C and stirred. After 90 min the reaction was cooled to rt and quenched via dropwise addition of 1M HCl solution (9 mL). The mixture was extracted with EtOAc (3 x 40 mL), dried (Na_2SO_4) and concentrated to a yellow solid. The solid was triturated in Et_2O and dried under vacuum to yield the title compound as a yellow solid (1.23 g, 6.50 mmol, 66%). The physical and spectroscopic data were consistent with those reported.[230]

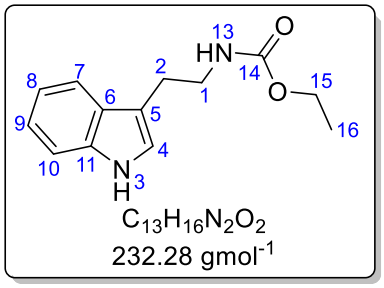
M.P. Decomposed 215 °C (lit. Decomposed 218 °C).[231]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 14.16-13.52 (m, 1H, **12**), 12.38 (br s, 1H, **3**), 8.44 (d, *J* = 3.2 Hz, 1H, **4**), 8.24-8.14 (m, 1H, **7**), 7.60-7.52 (m, 1H, **10**), 7.34-7.23 (m, 2H, **8**+**9**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 180.9 (**2**), 165.3 (**1**), 138.0 (**4**), 136.7 (**5**), 125.6 (**6**), 123.7 (**8/9**), 122.7 (**8/9**), 121.1 (**7**), 112.7 (**10**), 112.3 (**11**) ppm.

LRMS (ES$^+$) *m/z* = 190 [M+H]$^+$.

Ethyl (2-(1*H*-indol-3-yl)ethyl)carbamate (3.22):



Ethyl (2-(1*H*-indol-3-yl)ethyl)carbamate (**3.22**) was prepared according to a procedure described by Chaudhuri and co-workers'.[125,232]

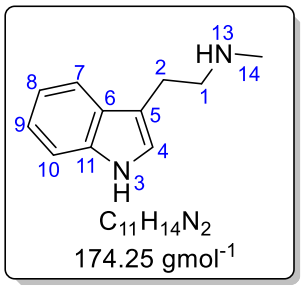
To a solution of tryptamine (2.00 g, 12.5 mmol) in $CHCl_3$ (32 mL) at 0 °C under N_2 was added ethyl chloroformate (1.2 mL) and 4M aqueous NaOH (3.2 mL) sequentially. The mixture was then warmed to rt and stirred for 2h before diluting with water (50 mL) and stirring for a further 15 min. The phases were separated and the aqueous phase washed with CH_2Cl_2 (3 x 50 mL). The combined organics were dried ($MgSO_4$) and concentrated to yield the title compound as a colourless syrup, which was used without any further purification (2.77 g, 11.9 mmol, 95%). The spectroscopic data were consistent with those reported.[232]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.48 (br s, 1H, **3**), 7.65 (br d, *J* = 7.6 Hz, 1H, **7**), 7.38 (dd, *J* = 8.0, 0.7 Hz, 1H, **10**), 7.28-7.20 (m, 1H, **9**), 7.20-7.12 (m, 1H, **8**), 6.99 (br s, 1H, **4**), 4.91 (br s, 1H, **13**), 4.18 (m, 2H, **15**), 3.55 (br d, *J* = 5.9 Hz, 2H, **2**), 3.00 (br t, *J* = 6.5 Hz, 2H, **1**), 1.28 (br s, 3H, **16**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 156.8 (**14**), 136.4 (**11**), 127.2 (**6**), 122.1 (**4**), 121.9 (**9**), 119.2 (**7**), 118.6 (**8**), 112.6 (**5**), 111.2 (**10**), 60.7 (**15**), 41.1 (**1**), 25.7 (**2**), 14.6 (**16**) ppm.

LRMS (ES^+) *m/z* = 233 $[M+H]^+$.

2-(1*H*-Indol-3-yl)-*N*-methylethan-1-amine (3.23):



2-(1*H*-Indol-3-yl)-*N*-methylethan-1-amine (**3.23**) was prepared according to a procedure described by Chaudhuri and co-workers'.[232]

To a solution of ethyl (2-(1*H*-indol-3-yl)ethyl)carbamate (**3.22**, 1.41g, 6.07 mmol) in THF (16 mL) at 0 °C under N_2 was added $LiAlH_4$ (1M in THF, 18.2 mL) dropwise over 30 min. The mixture was stirred at 0 °C for 15 min, before warming to reflux. After 45 min, the mixture was cooled to 0 °C and H_2O (1 mL) was added dropwise over 10 min. NaOH (15% in H_2O, 1mL) followed by H_2O (3 x 1 mL) was added and the mixture warmed to rt and stirred for 15 min. $MgSO_4$ was added and the mixture stirred for a further 15 min, before the mixture was filtered, and the filtrate concentrated to an off white solid. Recrystallisation of the solid (hexane, CH_2Cl_2) gave the title compound as a white solid (791 mg, 4.54 mmol, 75%). The physical and spectroscopic data were consistent with those reported.[232,233]

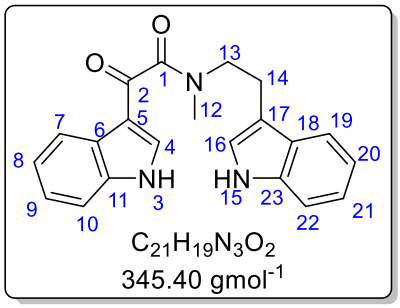
M.P. 82-84 °C (lit. 82 °C).[233]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.81 (br s, 1H, **3**), 7.52 (d, *J* = 7.8 Hz, 1H, **7**), 7.34 (d, *J* = 8.1 Hz, 1H, **10**), 7.13 (d, *J* = 2.1 Hz, 1H, **4**), 7.09-7.03 (m, 1H, **9**), 7.00-6.92 (m, 1H, **8**), 2.87-2.80 (m, 2H, **2**), 2.79-2.73 (m, 2H, **1**), 2.33 (s, 3H, **14**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 136.2 (**11**), 127.3 (**6**), 122.5 (**4**), 120.8 (**9**), 118.3 (**7**), 118.1 (**8**), 112.5 (**5**), 111.3 (**10**), 52.2 (**1**), 35.9 (**14**), 25.1 (**2**) ppm.

LRMS (ES$^+$) *m/z* = 175 [M+H]$^+$.

_N_-(2-(1_H_-Indol-3-yl)ethyl)2-(1_H_-indol-3-yl)-_N_-methyl-2-oxoacetamide (3.24):



To a solution of indole (1.93 g, 16.5 mmol) in Et_2O (30 mL) at 0 °C under N_2 was added $(COCl)_2$ (1.60 mL, 18.9 mmol) and stirred for 1 h. The mixture was concentrated to a yellow solid, taken in THF(40 mL) and added dropwise over 30 min, to a stirred solution of 2-(1*H*-Indol-3-yl)-*N*-methylethan-1-amine (**3.23**, 1.93 g, 11.0 mmol), NEt_3 (4.6 mL, 33.0 mmol) in THF (25 mL) at 0 °C under N_2. After 30 min, the mixture was warmed to rt and stirred for 18 h. The mixture was concentrated and taken in EtOAc (100 mL) and H_2O (100 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 100 mL). The combined organics were dried ($MgSO_4$) and concentrated to a yellow foam. Purification of the crude foam via flash chromatography (EtOAc) gave a 1:0.65 mixture of rotamers of the title compound as a yellow solid (769 mg, 2.22 mmol, 43%).

MP 171-173 °C.

IR IR (neat) ν 3353, 2928,, 1615, 1596, 1492 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.28 (br s, 1H, **3a**), 12.23 (br s, 1H, **3b**), 10.87 (br s, 1H, **15b**), 10.75 (br s, 1H, **15a**), 8.20 (br dd, *J* = 6.2, 2.6 Hz, 1H, **7a**), 8.12 (d, *J* = 7.1 Hz, 1H, **7b**), 8.06 (s, 1H, **4a**), 7.83 (s, 1H, **4b**), 7.67 (d, *J* = 7.8 Hz, 1H, **19b**), 7.57-7.51 (m, 2H, **8a+8b**), 7.39 (d, *J* = 8.1 Hz, 1H, **22b**), 7.33-7.22 (m, 5H, **9a+9b+10a+10b+16b+22a**), 7.15-7.08 (m, 2H, **19a+21b**), 7.06 (d, *J* = 2.2 Hz, 1H, **16a**), 7.04-6.99 (m, 1H, **20b**), 6.98-6.90 (m, 1H, **21a**), 6.67-6.61 (m, 1H, **20a**), 3.75 (t, *J* = 7.6 Hz, 1H, **13b**), 3.49-3.42 (m, 2H, **13a**), 3.07 (m, 4H, **12a+14b**), 3.00-2.94 (m, 2H, **14a**), 2.93 (s, 2H, **12b**) ppm.

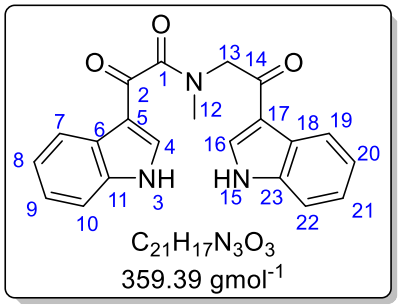
^{13}C NMR (DMSO-d_6, 101 MHz): δ = 186.8 (2**a**), 186.7 (**2b**), 167.6 (**1a**), 167.2 (**1b**), 136.9 (**4a**), 136.9 (**11a+11b**), 136.8 (**4b**), 136.3 (**23a**), 136.1 (**23b**), 127.2 (**18b**), 126.8 (**18a**), 124.9 (**6a**), 124.9 (**6b**), 123.5+123.0+122.9+122.5 (**9a+9b+10a+10b+16a+16b**), 121.0 (**7a**), 120.9 (**7b**), 120.9 (**21a+21b**), 118.4 (**19b**), 118.3 (**20b**), 118.1 (**20a**), 117.9 (**19a**), 113.1 (**5a**), 112.9 (**5b**), 112.6 (**8a+8b**), 111.5 (**22b**), 111.3 (**22a**), 111.1 (**17b**), 110.3 (**17a**), 50.3

(**13a**), 46.4 (**13b**), 34.9 (**12b**), 31.5 (**12a**), 24.4 (**14a**), 22.4 (**14b**) ppm.

LRMS (ES$^+$) *m/z* = 346 $[M+H]^+$, 368 $[M+Na]^+$.

HRMS (ES$^+$) *m/z* for $C_{21}H_{19}N_3NaO_2$ calculated 368.1369, found 368.1372.

_N_-(2-(1_H_-Indol-3-yl)-2-oxoethyl)-2-(_1H_-indol-3-yl)-_N_-methyl-2-oxoacetamide (3.21):



To a solution of N-(2-(1H-Indol-3-yl)ethyl)2-(1H-indol-3-yl)-N-methyl-2-oxoacetamide (**3.24**, 501 mg, 1.45 mmol) in a mixture of THF/H_2O (9:1, 27.5 mL) at 0 °C under N_2 was added DDQ (723 mg, 3.18 mmol) portionwise over 10 min. After 5 h, the mixture was taken in EtOAc (100 mL) and washed with sat. aqueous $NaHCO_3$ solution (6 x 100 mL). The organic phase was dried ($MgSO_4$) and concentrated to an off-white solid that was triturated in Et_2O to give a 1:0.4 mixture of rotamers of the title compound as an off white solid (437 mg, 1.22 mmol, 84%).

MP 202-206 °C.

IR IR (neat) ν 3221, 1609, 1582, 1413 cm^{-1}.

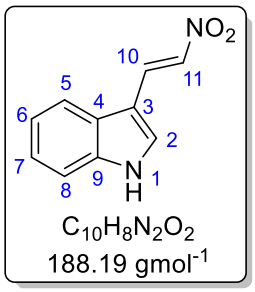
^{1}H NMR ($DMSO-d_6$, 400 MHz): δ = 12.39 (br d, *J* = 1.8 Hz, 1H, **3a**), 12.25 (br s, 1H, **3b**), 12.13 (br s, 1H, **15a**), 12.02 (br d, *J* = 1.6 Hz, 1H, **15b**), 8.52 (d, *J* = 3.2 Hz, 1H, **16a**), 8.43 (d, *J* = 3.2 Hz, 1H, **4a**), 8.34 (d, *J* = 3.1 Hz, 1H, **16b**), 8.26-8.21 (m, 1H, **19a**), 8.21-8.17 (m, 1H, **7a**), 8.14 (d, *J* = 3.2 Hz, 1H, **4b**), 8.11-8.04 (m, 1H, **19b+7b**), 7.60-7.56 (m, 1H, **10a**), 7.55-7.51 (m, 1H, **22a**), 7.48 (dt, *J* = 7.9, 0.9 Hz, 1H, **10b**), 7.46-7.42 (m, 1H, **22b**), 7.34-7.14 (m, 6H, **8a+9a+20a+21a+8b+9b+20b+21b**), 4.91 (s, 2H, **13a**), 4.82 (s, 1H, **13b**), 3.05 (s, 1H, **12b**), 3.01 (s, 3H, **12a**) ppm

^{13}C NMR ($DMSO-d_6$, 101 MHz): δ = 188.8 (**14a**), 188.6 (**14b**), 186.6 (**2a**), 185.9 (**2b**), 168.3 (**1b**), 168.2 (**1a**), 137.7 (**4b**), 137.5 (**4a**), 137.0 (**11a**), 136.6 (**11b**), 136.5 (**23a**), 136.3 (**23b**), 134.2 (**16a**), 134.0 (**16b**), 125.3 (**18a**), 125.1 (**18b**), 125.1 (**6b**), 124.8 (**6a**), 123.7, 123.4, 123.0, 123.0, 122.6, 122.4, 122.0, 121.9 (**8a+8b+9a+9b+20a+20b+21a+21b**), 121.1 (**19a**), 121.1 (**7b+19b**), 121.0 (**7a**), 114.0 (**17a**), 113.5 (**17b**), 113.2 (**5a**), 112.9 (**5b**), 112.7 (**10a**), 112.6 (**10b**), 112.3 (**22a**), 112.2 (**22b**), 55.3 (**13b**), 52.7 (**13a**), 36.6 (**12a**), 33.5 (**12b**) ppm.

LRMS (ES$^+$) *m/z* = 360 $[M+H]^+$, 382 $[M+Na]^+$.

HRMS (ES$^+$) *m/z* for $C_{21}H_{17}N_3NaO_3$ calculated 382.1162, found 382.1163.

(*E*)-3-(2-Nitrovinyl)-1*H*-indole (3.30):



(*E*)-3-(2-Nitrovinyl)-1*H*-indole (**3.30**) was prepared according to a procedure described by McNulty and co-workers'.[128]

A solution of indole-3-carbaldehyde (9.80 g, 67.5 mmol), NH_4OAc (11.2 g, 145 mmol) and AcOH (11.4 mL, 199 mmol) in NO_2Me (45 mL) was sonicated at rt using an Allendale Ultrasonic cleaning bath for 9 h. The resulting yellow precipitate was filtered, washed with cyclohexane and dried under high vacuum to yield the title compound as a bright yellow solid (9.11 g, 48.2 mmol, 71%) which was used without any further purification. Analytical samples were obtained by recrystallisation (EtOH/ H_2O). Spectroscopic data were consistent with those reported.[234]

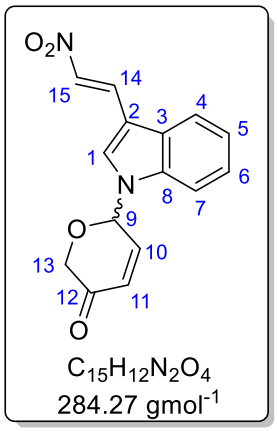
M.P. 164-166 °C (lit. 167-168 °C).[235]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.24 (br s, 1H, **1**), 8.41 (d, *J* = 13.3 Hz, 1H, **10**), 8.25 (s, 1H, **2**), 8.01 (d, *J* = 13.3 Hz, 1H, **11**), 7.96 (d, *J* = 7.3 Hz, 1H, **5**), 7.52 (d, *J* = 7.6 Hz, 1H, **8**), 7.28 (td, *J* = 7.3, 1.1 Hz, 1H, **7**), 7.23 (td, *J* = 7.3, 1.1 Hz, 1H, **6**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 137.7 (**9**), 136.4 (**2**), 134.7 (**10**), 131.1 (**11**), 124.6 (**4**), 123.4 (**7**), 121.9 (**6**), 120.5 (**5**), 112.8 (**8**), 108.2 (**3**) ppm.

LRMS (ES^+) *m/z* = 189 $[M+H]^+$.

(*E*)-6-(3-(2-Nitrovinyl)-1*H*-indol-1-yl)-2*H*-pyran-3(6*H*)-one (3.31):



A solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (28.2 mg, 0.027 mmol) and PPh_3 (20.3 mg, 0.077 mmol) in degassed THF (1 mL) at rt under N_2 was stirred for 30 min. The mixture was added to stirred solution of (*E*)-3-(2-Nitrovinyl)-1*H*-indole (**3.30**, 100 mg, 0.531 mmol) and *tert*-butyl (5-oxo-5,6-dihydro-2*H*-pyran-2-yl) carbonate (**3.10,** 149 mg,) in degassed THF (1.5 mL) at rt under N_2 and warmed to 60 °C. After 16 h, a further portion of *tert*-butyl (5-oxo-5,6-dihydro-2*H*-pyran-2-yl) carbonate (74) (30.0 mg,) was added and stirred. After a further 22 h, the mixture was cooled to rt and filtered through a pad of celite. The pad was washed with EtOAc (3 x 5 mL) and the filtrate concentrated to a dark brown oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 3:7) gave the title compound as a light yellow oil (49.6 mg, 33%). Eluting with EtOAc gave the starting (*E*)-3-(2-Nitrovinyl)-1*H*-indole (**3.31**, 21.7 mg, 21%) as a yellow solid.

IR IR (neat) ν 2360, 2342, 1623, 1317, 668 cm^{-1}.

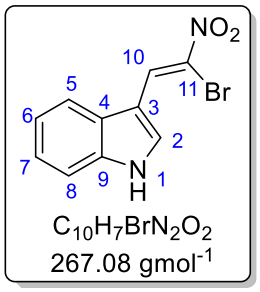
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.22 (d, *J* = 13.6 Hz, 1H, **14**) 7.85-7.77 (m, 2H, **4+15**), 7.66-7.62 (m, 2H, **1+7**), 7.43 (quin d, *J* = 7.3, 1.3 Hz, 2H, **5+6**), 7.20 (dd, *J* = 10.3, 3.2 Hz, 1H, **10**), 6.60 (dd, *J* = 10.3 1.7 Hz, 1H, **11**), 6.57 (dd, *J* = 3.2, 1.6 Hz, 1H, **9**), 4.31 (d, *J* = 17.1 Hz, 1H, **13**), 4.21 (d, *J* = 17.0 Hz, 1H, **13'**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 192.3 (**12**), 142.1 (**10**), 137.6 (**8**), 134.1 (**15**), 132.5 (**1**), 132.3 (**14**), 131.2 (**11**), 126.1 (**3**), 124.8 (**6**), 123.5 (**5**), 120.9 (**4**), 111.5 (**7**), 110.0 (**2**), 77.6 (**9**), 68.4 (**13**) ppm.

LRMS (ES^+) *m/z* = 285 $[M+H]^+$.

HRMS (ES^+) *m/z* for $C_{15}H_{12}N_2NaO_4$ calculated 307.0689, found 307.0684.

(*Z*)-3-(2-Bromo-2-nitrovinyl)-1*H*-indole (3.32):



$C_{10}H_7BrN_2O_2$
267.08 $gmol^{-1}$

To a solution of (*E*)-3-(2-nitrovinyl)-1*H*-indole (**3.30**, (96.0 mg, 0.51 mmol) in CH_2Cl_2 (5 mL) at 0 °C under N_2 was added *N*-bromosuccinimide (89.4 mg, 0.50 mmol) and stirred. After 1h, the reaction was quenched with sat. aqueous $NaHCO_3$ solution (5 mL) and warmed to rt. The phases were separated and the organic phase washed with sat. aqueous $Na_2S_2O_3$ solution (3 x 5 mL), dried (Na_2SO_4) and concentrated to a dark orange solid. The crude solid was purified via flash chromatography (EtOAc:hexane = 1:3) to yield the title compound as a yellow solid (102 mg, 0.38 mmol, 75%).

MP Decomposed 97 °C.

IR IR (neat) ν 2362, 2342, 1213, 669, 419 cm^{-1}.

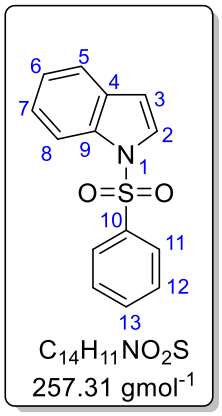
^{1}H NMR ($DMSO-d_6$, 400 MHz): δ = 12.53 (br s, 1H, **1**), 9.13 (s, 1H, **10**), 8.63 (d, *J* = 2.3 Hz, 1H, **2**), 7.96 (d, *J* = 7.6 Hz, 1H, **5**), 7.56 (d, *J* = 7.7 Hz, 1H, **8**), 7.36-7.20 (m, 2H, **6+7**) ppm.

^{13}C NMR ($DMSO-d_6$, 101 MHz): δ = 136.2 (**9**), 131.7 (**2**), 130.5 (**10**), 127.7 (**4**), 123.6 (**7**), 121.8 (**6**), 121.2 (**11**), 118.4 (**5**), 112.8 (**8**), 107.4 (**3**) ppm.

LRMS (ES^+) *m/z* = 267 $[MBr^{79}+H]^+$ 269 $[MBr^{81}+H]^+$.

HRMS (ES^+) *m/z* for $C_{10}H_7BrN_2NaO_2$ calculated 288.9583, found 288.9585.

1-(Phenylsulfonyl)-1*H*-indole (3.33):



$C_{14}H_{11}NO_2S$
257.31 $gmol^{-1}$

1-(Phenylsulfonyl)-1*H*-indole (**3.33**) was prepared according to a procedure described by Kondo and co-workers'.[236]

To a solution of indole (2.00 g, 17.1 mmol) in THF (30 mL) at 0 °C under N_2 was added NaH (60% dispersion in oil, 892 mg, 22.2 mmol) and stirred. After 1 h, benzene sulfonyl chloride (2.2 mL, 17.2 mmol) was added dropwise and the reaction warmed to rt. After 19.5 h, the reaction was quenched with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated to an orange oil. The crude oil was crystallised in MeOH to give the title compound as a white crystalline solid (3.25 g, 12.6 mmol, 74%). Spectroscopic data were consistent with those reported.[129]

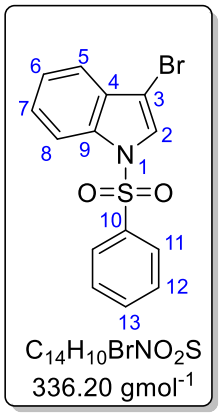
M.P. 76-78 °C (lit. 76-78 °C).[129]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.04 (dd, *J* = 8.3 Hz, 0.9 Hz, 1H, **5**), 7.95-7.86 (m, 2H, **11**), 7.60 (d, *J* = 3.7 Hz, 1H, **2**), 7.57-7.49 (m, 2H, **8+13**), 7.47-7.40 (m, 2H, **12**), 7.34 (td, *J* = 7.8, 1.2 Hz, 1H, **6**), 7.28-7.22 (m, 1H, **7**), 6.69 (dd, *J* = 3.7, 0.7 Hz, 1H, **3**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 138.2 (**10**), 134.8 (**9**), 133.7 (**13**), 130.7 (**4**), 129.2 (**12**), 126.7 (**11**), 126.3 (**2**), 124.6 (**6**), 123.3 (**7**), 121.5 (**8**), 113.5 (**5**), 109.2 (**3**) ppm.

LRMS (ES^+) *m/z* = 258 $[M+H]^+$.

3-Bromo-1-(phenylsulfonyl)-1*H*-indole (3.34):



3-Bromo-1-(phenylsulfonyl)-1*H*-indole (**3.34**) was prepared according to a procedure described by Booker-Milburn and co-workers'.[129]

To a solution of 1-(phenylsulfonyl)-1H-indole (**3.33**, 2.00 g, 7.77 mmol) in CH_2Cl_2 (25 mL) at rt under N_2 was added bromine (0.39 mL, 7.61 mmol) dropwise over 30 min. After a further 90 min, the mixture was quenched with sat. aqueous $NaHCO_3$ solution (30 mL) and the phases separated. The organic phase was washed with a sat. aqueous $Na_2S_2O_3$ solution (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated to an off-white solid. Purification of the crude solid via flash chromatography (EtOAc:hexane = 1:19) gave a 5:1 mixture of the title compound and the di-brominated by-product tentatively assigned as dibromoindole **3.35** (2.30 g, 6.60 mmol, 85%). Spectroscopic data were consistent with those reported.[129]

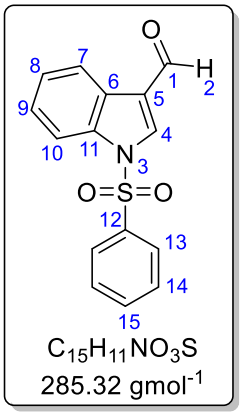
M.P. 115-117 °C

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.02 (dt, *J* = 8.2, 0.7 Hz, 1H, **8**), 7.93-7.88 (m, 2H, **11**), 7.64 (s, 1H, **2**), 7.60-7.54 (m, 1H, **13**), 7.53-7.49 (m, 1H, **5**), 7.49-7.44 (m, 2H, **12**), 7.40 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H, **7**), 7.35-7.30 (m, 1H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 137.8 (**10**), 134.3 (**9**), 134.1 (**13**), 129.8 (**4**), 129.4 (**12**), 126.8 (**11**), 125.8 (**7**), 124.7 (**2**), 124.0 (**6**), 120.1 (**5**), 113.6 (**8**), 99.8 (3) ppm.

LRMS (ES^+) *m/z* = 336 $[MBr^{79}+H]^+$, 338 $[MBr^{81}+H]^+$.

1-(Phenylsulfonyl)indole-3-carbaldehyde (3.38):



1-(Phenylsulfonyl)indole-3-carboxaldehyde (**3.38**) was prepared according to a procedure described by Yang and co-workers'.[237]

To a solution of indole-3-carbaldehyde (2.90 g, 20.0 mmol) in THF (50 mL) at 0 °C under N_2 was added NaH (60% dispersion in mineral oil, 0.970 g, 24.2 mmol) portionwise over 15 min before warming to rt. After 30 min, benzenesulfonyl chloride (3.1 mL, 24.3 mmol) was added dropwise and stirred for a further 15 h. The reaction mixture was concentrated cooled to 0 °C and taken in H_2O (200 mL). The resulting yellow precipitate was filtered and washed with Et_2O to yield the title compound as a burgundy solid (4.62 g, 16.2 mmol, 81%) which was used without any further purification. Spectroscopic data were consistent with those reported.[237,238]

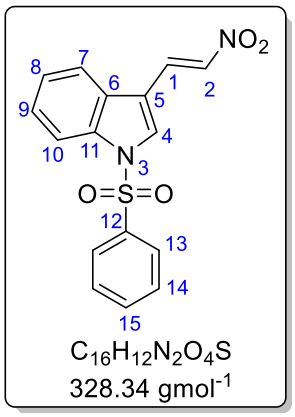
M.P. 157-159 °C (lit. 156-158 °C).[238]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.11 (s, 1H, **2**), 8.31-8.21 (m, 2H, **4+7**), 8.00-7.94 (m, 3H, **10+13**), 7.64-7.59 (m, 1H, **15**), 7.54-7.48 (m, 2H, **14**), 7.42 (ddd, *J* = 8.6, 7.3, 1.3 Hz, 1H, **9**), 7.37 (td, *J* = 7.7, 1.2 Hz, 1H, **8**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 185.3 (**1**), 137.3 (**12**), 136.1 (**4**), 135.2 (**11**), 134.7 (**15**), 129.7 (**14**), 127.1 (**13**), 126.3 (**9**), 126.2 (**6**), 125.1 (**8**), 122.6 (**5**), 122.4 (**7**), 113.2 (**10**) ppm.

LRMS (ES^+) *m/z* = 286 $[M+H]^+$.

(*E*)-3-(2-Nitrovinyl)-1-(phenylsulfonyl)-1H-indole (3.39):



$C_{16}H_{12}N_2O_4S$
328.34 gmol^{-1}

(*E*)-3-(2-Nitrovinyl)-1-(phenylsulfonyl)-1*H*-indole (**3.39**) was prepared according to a procedure described by Rollin and co-workers'.[239]

To a solution of 1-(phenylsulfonyl)indole-3-carboxaldehyde (**3.38**, 980 mg, 3.43 mmol) in NO_2Me (20 mL) at rt under N_2 was added NH_4OAc (841 mg, 10.9 mmol) and warmed to 90 °C. The mixture was stirred for 2.5 h before being concentrated under reduced pressure. The resulting syrup was taken in CH_2Cl_2 (50 mL) and H_2O (50 mL) and the phases separated. The aqueous phase was washed with CH_2Cl_2 (50 mL) and the combined organics washed with brine (50 mL), dried (Na_2SO_4), and concentrated a light yellow solid. The crude solid was purified via flash chromatography (EtOAc:hexane = 1:3) to give the title compound as a bright yellow solid (520 mg, 1.58 mmol, 46%). Spectroscopic data were consistent with those reported.[239]

MP 204-206 °C (lit. 207-209 °C).[239]

IR IR (neat) ν 3129, 1326, 1243, 1215, 1179 cm^{-1}.

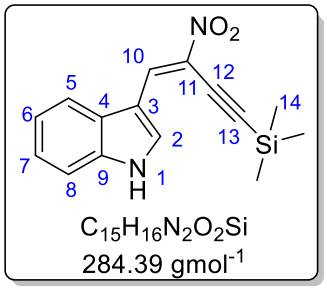
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.16 (dd, *J* = 13.7, 0.4 Hz, 1H, **1**), 8.07-8.02 (m, 2H, **4+10**), 7.99-7.94 (m, 2H, **13**), 7.75 (d, *J* = 13.7 Hz, 1H, **2**), 7.71 (dt, *J* = 8.0, 0.9 Hz, 1H, **7**), 7.65-7.60 (m, 1H, **15**), 7.55-7.49 (m, 2H, **14**), 7.46 (ddd, *J* = 8.4, 7.5, 1.2, 1H, **9**), 7.40 (td, *J* = 7.9, 1.1 Hz, 1H, **8**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 137.4 (**12**), 136.4 (**2**), 135.6 (**11**), 134.7 (**15**), 131.5 (**4**), 130.7 (**1**), 129.7 (**14**), 127.0 (**6+13**), 126.2 (**9**), 124.8 (**8**), 120.6 (**7**), 114.0 (**10**), 113.8 (**5**) ppm.

LRMS (ES$^+$) *m/z* = 329 [M+H]$^+$.

HRMS (ES$^+$) *m/z* for $C_{16}H_{12}N_2NaO_4S$ calculated 351.0410, found 351.0413.

(*E*)-3-(2-Nitro-4-(trimethylsilyl)but-1-en-3-yn-1-yl)-1*H*-indole (3.40):



A solution of (*Z*)-3-(2-Iodo-2-nitrovinyl)-1*H*-indole (**3.40**, 196 mg, 0.624 mmol) in THF (5 mL) and NEt_3 (5 mL) at rt under N_2 was degassed for 10 min before adding trimethylsilylacetylene (1.2 mL, 8.43 mmol), followed by $PdCl_2(PPh_3)_2$ (23 mg, 0.033 mmol) and CuI (9 mg, 0.047 mmol). The mixture was stirred for 4 h before filtering through a pad of celite and washing with EtOAc (3 x 5 mL). The filtrate was concentrated to a brown oil and the crude oil was purified via flash chromatography (Biotage© Selekt, EtOAc:hexane = 1:9 to 1:0) to yield the title compound as an orange solid (23.1 mg, 0.088 mmol, 14%) and (*E*)-3-(2-Nitrovinyl)-1*H*-indole (**93**) (60 mg, 0.32 mmol, 51%) as a yellow solid.

MP Decomposed >204 °C.

IR IR (neat) ν 3276, 1596, 1200, 729 cm^{-1}.

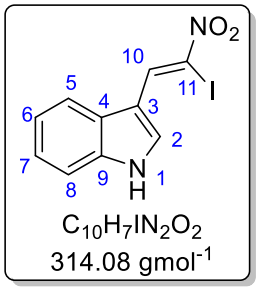
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.19 (br s, 1H, **1**), 8.80 (s, 1H, **10**), 8.56 (d, *J* = 2.8 Hz, 1H, **2**), 7.91-7.84 (m, 1H, **5**), 7.52-7.47 (m, 1H, **8**), 7.38-7.31 (m, 2H, **6+7**), 0.37 (s, 9H, **14**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 135.8 (**9**), 132.8 (**10**), 130.1 (**2**), 127.9 (**12**), 127.6 (**4**), 124.2 (**7**), 122.4 (**6**), 118.6 (**5**), 112.1 (**8**), 111.3 (**13**), 109.6 (**3**), 95.8 (**11**), −0.3 (**14**) ppm.

LRMS (ES^+) *m/z* = 285 $[M+H]^+$

HRMS (ES^+) *m/z* for $C_{15}H_{16}N_2NaO_2Si$ calculated 307.0873, found 307.0874.

(*Z*)-3-(2-Iodo-2-nitrovinyl)-1*H*-indole (3.41):



$C_{10}H_7IN_2O_2$
314.08 gmol^{-1}

To a solution of (*E*)-3-(2-nitrovinyl)-1*H*-indole (**3.30**, 501 mg, 2.66 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0 °C under N_2 was added *N*-iodosuccinimide (570 mg, 2.53 mmol) and stirred for 30 min. The reaction was quenched with sat. aqueous $NaHCO_3$ solution (30 mL) and the phases separated. The organic phase was washed with sat. aqueous $Na_2S_2O_3$ solution (30 mL), dried $NaSO_4$ and concentrated to a bright red solid. The crude solid was triturated with CH_2Cl_2 to give the title product as an orange solid (460 mg, 1.46 mmol, 55%). Analytically pure samples were obtained by recrystallization in EtOH/H_2O.

MP Decomposed 135 °C.

IR IR (neat) ν 3294, 1709, 1571, 751 cm^{-1}.

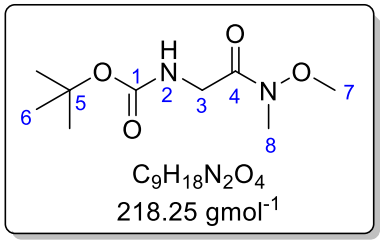
^{1}H NMR ($DMSO-d_6$, 400 MHz): δ = 12.41 (br s, 1H, **1**), 9.27 (s, 1H, **10**), 8.83 (d, *J* = 3.2 Hz, 1H, **2**), 7.88 (d, *J* = 7.9 Hz, 1H, **5**), 7.56 (dt, *J* = 7.9, 1.0 Hz, 1H, **8**), 7.29 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H, **7**), 7.24 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, **6**) ppm.

^{13}C NMR ($DMSO-d_6$, 101 MHz): δ = 137.1 (**10**), 136.1 (**9**), 129.8 (**2**), 128.0 (**4**), 123.5 (**7**), 121.6 (**6**), 118.1 (**5**), 112.8 (**8**), 108.1 (**3**), 97.8 (**11**) ppm.

LRMS (ES$^+$) *m/z* = 315 [M+H]$^+$

HRMS (ES$^+$) *m/z* for $C_{10}H_7IN_2NaO_2$ calculated 336.9444, found 336.9444.

tert-Butyl (2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (3.43):



$C_9H_{18}N_2O_4$
218.25 gmol^{-1}

tert-Butyl (2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (**3.43**) was prepared according to a procedure described by Pelkey and co-workers'.[126]

To a solution of Boc-Gly-OH (**3.42**, 3.01 g, 17.1 mmol) in CH_2Cl_2 (50 mL) at 0 °C under N_2 was added CDI (4.01 g, 24.7 mmol) and stirred. After 30 min, NEt_3 (24.4 mmol) and *N,O*-dimethylhydroxylamine hydrochloride salt (2.36 g, 24.2 mmol) were added sequentially and the mixture stirred for 30 min before warming to rt. After 20 h, the mixture was taken in Et_2O (100 mL) and quenched with 1M HCl solution (50 mL). The phases were separated and the organic washed with 1M HCl solution (2 x 50 mL), sat. aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated to a white solid. The crude solid was recrystallized with EtOAc to give the title compound as colourless needles (2.09 g, 9.60 mmol, 84%). Spectroscopic data were consistent with those reported.[126]

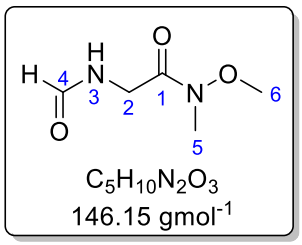
M.P. 100-103 °C (lit. 102-103 °C).[126]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.27 (br s, 1H, **2**), 4.08 (br d, *J* = 4.2 Hz, 2H, **3**), 3.71 (s, 3H, **7**), 3.20 (s, 3H, **8**), 1.45 (s, 9H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 170.2 (**1**), 155.9 (**4**), 79.6 (**5**) 61.4 (**7**), 41.7 (**3**), 32.4 (**8**), 28.3 (**6**) ppm.

LRMS (ES$^+$) *m/z* = 241 [M+Na]$^+$.

2-Formamido-*N*-methoxy-*N*-methylacetamide (3.44):

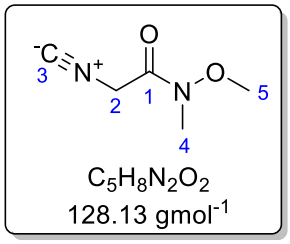


2-Formamido-*N*-methoxy-*N*-methylacetamide (**3.44**) was prepared according to a procedure described by Pelkey and co-workers'.[126]

A solution of *tert*-Butyl (2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (**3.43**, 1.96 g, 8.98 mmol) in formic acid (10 mL) was warmed to reflux and stirred for 90 min. The mixture was cooled to rt and concentrated to a dark brown oil. The crude oil was taken in NEt_3 (2.6 mL, 18.7 mmol) and ethyl formate (15 mL) and warmed to reflux. The mixture was stirred for 16.5 h before being concentrated to an amber oil. The crude oil was taken in H_2O (90 mL) and CH_2Cl_2 (100 mL) and the phases separated. The aqueous phase was washed with CH_2Cl_2 (3 x 100 mL) and the combined organics dried (Na_2SO_4) and concentrated to a light yellow oil (610 mg, 4.17 mmol, 46%). The crude aldehyde was used without any further purification. Spectroscopic data were consistent with those reported.[126]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.28 (d, *J* = 0.9 Hz, 1H, **3**), 4.25 (br d, *J* = 4.4 Hz, 2H, **2**), 3.74 (s, 3H, **6**), 3.24 (s, 3H, **5**) ppm.

2-Isocyano-*N*-methoxy-*N*-methylacetamide (3.26):



$C_5H_8N_2O_2$
128.13 gmol^{-1}

2-Isocyano-*N*-methoxy-*N*-methylacetamide (**3.26**) was prepared according to a procedure described by Pelkey and co-workers'.[126]

To a solution of the crude *2*-formamido-*N*-methoxy-*N*-methylacetamide (**3.44**, 610 mg, 4.17 mmol) in THF (13 mL) at 0 °C under N_2 was added NEt_3 (2.4 mL, 17.2 mmol) followed by $POCl_3$ (0.43 mL, 4.66 mmol) dropwise over 10 min and stirred for 2 h. The mixture was then warmed to rt and stirred for a further 3.5 h. The mixture was diluted with CH_2Cl_2 (15 mL) and sat. aqueous $NaHCO_3$ solution (15 mL) was added and the phases separated. The aquous was washed with CH_2Cl_2 (6 x 30 mL) and the combined organics concentrated to a yellow solid. Purification of the crude solid via flash chromatography (EtOAc:hexane = 1:1) gave the title compound as an off white solid (317 mg, 2.51 mmol, 60%). Spectroscopic data were consistent with those reported.[126]

M.P. 82-85 °C (lit. 85-86 °C).[126]

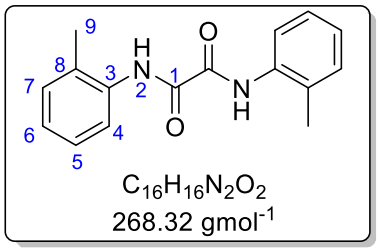
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.41 (s, 2H, **2**), 3.72 (s, 3H, **5**), 3.23 (s, 3H, **4**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 163.8 (**1**), 160.8 (**3**), 61.6 (**5**), 43.6 (**2**), 32.6 (**4**) ppm.

LRMS (ES^+) *m/z* = 129 $[M+H]^+$.

HRMS (ES^+) *m/z* for $C_5H_8N_2NaO_2$ calculated 151.0478, found 151.0477.

_N,N'_-Bis(_o_-tolyl)oxamide (1.57):



N,N'-Bis(*o*-tolyl)oxamide (**1.57**) was prepared according to a procedure described by Schrodi and co-workers'.[240]

To a solution of *o*-toluidine (10.7 mL, 100 mmol) in THF (200 mL) and NEt_3 (13.9 mL, 100 mmol) at 0 °C under N_2 was added $(COCl)_2$ (4.23 mL, 50.0 mmol) dropwise over 15 min. The mixture was stirred for 15 min before warming to rt. After 1.5 h, the mixture was concentrated under reduced pressure and the off-white solid taken in H_2O (100 mL) and filtered. The precipitate was washed with 1M HCl (100 mL), H_2O (2 x 100 mL) and dried in a vacuum oven to give the title compound as a white solid (13.2 g, 49.2 mmol, 98%). Physical and spectroscopic data were consistent with those reported.[241]

M.P. 215-217 °C (lit. 215 °C).

IR IR (neat) ν 3284, 1662, 1454, 705 cm^{-1}.

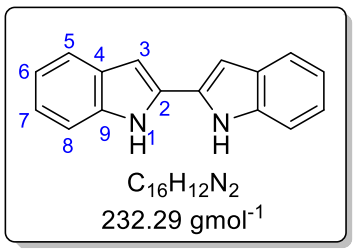
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.31 (s, 2H, **2**), 7.50 (dd, *J* = 7.8, 1.1 Hz, 2H, **4**), 7.28 (dd, *J* = 7.1, 0.9 Hz, 2H, **7**), 7.24 (td, *J* = 7.6, 1.8 Hz, 2H, **5**), 7.18 (td, *J* = 7.5, 1.5 Hz, 2H, **6**), 2.25 (s, 6H, **9**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 158.5 (**1**), 135.1 (**3**), 132.4 (**8**), 130.4 (**7**), 126.2 (**5/6**), 126.2 (**6/5**), 124.9 (**4**), 17.6 (**9**) ppm.

LRMS (ES$^+$) *m/z* = 269 [M+H]$^+$.

HRMS (ES$^+$) *m/z* for $C_{16}H_{17}N_2O_2$ calculated 269.1285, found 269.1282 and for $C_{16}H_{16}N_2NaO_2$ calculated 291.1104, found 294.1100.

2,2'-Biindole (1.58):



$C_{16}H_{12}N_2$
232.29 $gmol^{-1}$

2,2'-Biindole (**1.58**) was prepared according to a procedure described by Bergman and co-workers'.[53]

A 3-neck RBF equipped with a thermometer, distillation head, stirrer bar and stopper was charged with *N,N'*-Bis(*o*-tolyl)oxamide (**1.57**, 1.99 g, 7.42 mmol), ^{t}BuOH (22 mL) followed by KO^{t}Bu (8.2 g, 73.0 mmol) and warmed to 225 °C. Once all of the ^{t}BuOH had distilled off, the internal T was slowly warmed to 275 °C with vigorous gas evolution. After 1h, the internal T was slowly raised to 300 °C and maintained until the gas evolution ceased. The reaction mixture was then cooled slowly to rt overnight under a flow of N_2. The reaction mixture was taken in H_2O (20 mL) and the solid crushed and filtered. The crude yellow solid was taken in EtOH (20 mL) and heated to reflux for 1 h before being cooled to rt and filtered. The precipitate was washed with ice-cold EtOH (5mL) and dried under vacuum to yield the title compound as an off-white solid (810 mg, 3.90 mmol, 53%).[53,242]

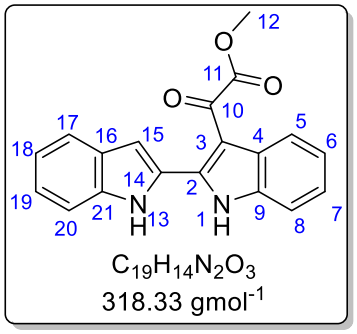
M.P. 303-305 °C

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.58 (br s, 2H, **1**), 7.56 (dt, *J* = 7.7, 1.0 Hz, 2H, **5**), 7.40 (dd, *J* = 8.1, 0.9 Hz, 2H, **8**), 7.11 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 2H, **7**), 7.00 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 2H, **6**), 6.92 (d, *J* = 0.6 Hz, 2H, **3**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 136.9 (**9**), 131.4 (**2**), 128.4 (**4**), 121.7 (**7**), 120.0 (**5**), 119.4 (**6**), 111.0 (**8**), 98.4 (**3**) ppm.

LRMS (ES^{+}) *m/z* =233 $[M+H]^{+}$.

Methyl 2-(1H,1H'-[2,2'-biindol]-3-yl)-2-oxoacetate (3.55):



A solution of 2,2'-biindole (**3.05**, 101 mg, 0.435 mmol) in THF (3 mL) was warmed to reflux. Methyl 2-chloro-2-oxoacetate (0.05 mL, 0.543 mmol) was added dropwise and the mixture stirred for 45 min. The mixture was then cooled to rt, quenched with H_2O (20 mL). The solution was extracted with EtOAc (3 x 20 mL) and the combined organics were dried ($MgSO_4$), and concentrated to a brown oil. Purification of the crude oil via flash chromatography (EtOAc:hexane 1:4) gave the title compound as a yellow oil (47.0 mg, 0.148 mmol, 34%). Note the compound darkened upon leaving out and instantly when added to MeCN with an orange precipitate produced.

MP Darkened at 60 °C and turned dark red at 180 °C. No further melting/degradation up to 300 °C.

IR IR (neat) ν 3359, 1717, 1628, 1244, 739 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 12.29 (br s, 1H, **1**), 9.44 (br s, 1H, **13**), 7.65 (dd, *J* = 8.1, 0.9 Hz, 1H, **17**), 7.51-7.45 (m, 2H, **20+5**), 7.41 (d, *J* = 8.1 Hz, 1H, **8**), 7.32-7.26 (m, 2H, **19+7**), 7.21 (ddd, *J* = 8.3, 7.2,1.1 Hz, 1H, **6**), 7.16 (ddd, *J* = 7.9, 7.2, 0.9 Hz, 1H, **18**), 7.08 (d, *J* = 1.2 Hz, 1H, **15**), 4.08 (s, 3H, **12**) ppm.

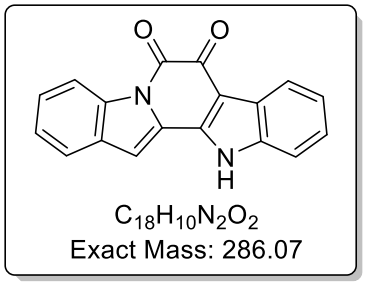
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 181.9 (**10**), 166.8 (**11**), 140.1 (**2**), 136.6 (**21**), 135.5 (**9**), 127.8 (**16**), 127.4 (**14**), 126.5 (**4**), 124.5 (**19**), 124.5 (**7**), 123.3 (**6**), 121.0 (**18**), 120.9 (**17**), 119.1 (**5**), 112.5 (**20**), 111.5 (**8**), 108.0 (**3**), 103.0 (**15**), 53.0 (**12**) ppm.

LRMS (ES^+) *m/z* = 319 $[M+H]^+$

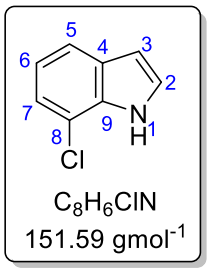
HRMS Cyclised prior to acquisition:

(ES^+) *m/z* for $C_{18}H_{11}N_2O_2$ calculated 287.0815, found 287.0813 and for

$C_{18}H_{10}N_2NaO_2$ calculated 309.0634, found 309.0634.



7-Chloro-1*H*-indole (1.150):



C_8H_6ClN
151.59 $gmol^{-1}$

7-Chloro-1H-indole (**1.150**) was prepared according to a procedure described by Smith III and co-workers'.[137]

To a solution of 1-chloro-2-nitrobenzene (2.00 g, 12.7 mmol) in THF (60 mL) at –40 °C under N_2 was added vinyl magnesium bromide (38.1 mL, 1M in THF, 38.1 mmol) via dropping funnel over 45 min. The reaction was stirred at this temperature for a further 1 h before addition of sat. aqueous NH_4Cl (100 mL) and stirred at 0 °C for 30 min. The phases were separated and the aqueous layer extracted with EtOAc (100 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and concentrated to a viscous brown syrup. Purification of the crude syrup via flash chromatography (Biotage© Selekt, EtOAc:hexane 1:1 to EtOAc:hexane = 1:0) gave the title compound as an off-white solid (921 mg, 6.08 mmol, 48%). Physical and spectroscopic data were consistent with those reported.[243–245]

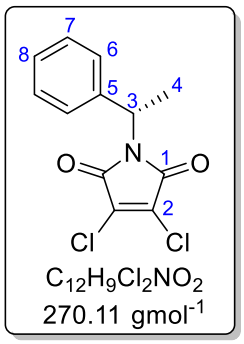
M.P. 56-58 °C (lit. 58 °C).[244]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.37 (br s, 1H, **1**), 7.58 (dt, *J* = 7.9, 0.8 Hz, 1H, **5**), 7.27 (t, *J* = 2.8 Hz, 1H, **2**), 7.23 (dd, *J* = 7.8, 0.7 Hz, 1H, **7**), 7.08 (t, *J* = 7.8 Hz, 1H, **6**), 6.63 (dd, *J* = 3.2, 2.2 Hz, 1H, **3**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 133.1 (**9**), 129.3 (**8**), 124.7 (**2**), 121.3 (**7**), 120.6 (**6**), 119.3 (**5**), 116.6 (**4**), 103.7 (**3**) ppm.

LRMS (ES^+) *m/z* = 152 $[M+H]^+$.

(*S*)-3,4-Dichloro-1-(1-phenylethyl)-1*H*-pyrrole-2,5-dione (4.13):



$C_{12}H_9Cl_2NO_2$
270.11 $gmol^{-1}$

(*S*)-3,4-Dichloro-1-(1-phenylethyl)-1*H*-pyrrole-2,5-dione (**4.13**) was prepared according to a procedure described by Börner and co-workers'.[246]

To a solution of 3,4-dichlorofuran-2,5-dione (1.00 g, 5.99 mmol) in acetic acid (25 mL) at rt under N_2 was added (*S*)-1-phenylethan-1-amine (0.85 mL, 6.59 mmol) dropwise before warming to Δ. After 19 h, the mixture was cooled to rt and poured into H_2O (50 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organics dried ($MgSO_4$) and concentrated to an orange oil. Purification of the crude oil via flash chromatography (CH_2Cl_2:hexane = 3:7 to 1:1) gave the title compound as a colourless solid (1.11 g, 4.11 mmol, 69%). Physical and spectroscopic data were consistent with this reported.

$[\alpha]_D$ —65.9 ° (*c* = 0.54, acetone). (lit. —64.0 °, c = 1.00, $CHCl_3$).[246]

MP 55-57 °C (lit. 52-53 °C).[246]

IR IR (neat) ν 2359, 1711, 1341, 731 cm^{-1}.

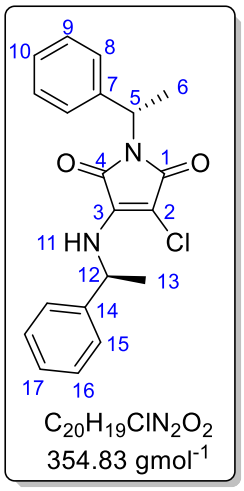
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.48-7.41 (m, 2H, **6**), 7.38-7.28 (m, 3H, **7+8**), 5.43 (q, *J* = 7.3 Hz, 1H, **3**), 1.87 (d, *J* = 7.5 Hz, 3H, **4**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 162.7 (**1**), 139.1 (**5**), 133.1 (**2**), 128.7 (**7**), 128.2 (**8**), 127.4 (**6**), 51.5 (**3**), 17.6 (**4**) ppm.

LRMS (EI) *m/z* = 269 $[MCl^{35}]^{+\bullet}$, 271 $[MCl^{37}]^{+\bullet}$.

HRMS (EI) *m/z* for $C_{12}H_9Cl_2NO_2$ calculated 269.0005, found 269.0005.

3-Chloro-1-((*S*)-1-phenylethyl)-4-(((*S*)-1-phenylethyl)amino)-1*H*-pyrrole-2,5-dione (4.10):



Eluting with CH_2Cl_2:hexane = 1:1 gave 3-chloro-1-((*S*)-1-phenylethyl)-4-(((*S*)-1-phenylethyl)amino)-1*H*-pyrrole-2,5-dione (**4.10**) as a bright yellow oil (112 mg, 0.316 mmol, 5%).

$[\alpha]_D$ −90.7 ° (*c* = 0.34, acetone)

IR IR (neat) ν 3321, 1708, 1654, 741, 656 cm^{-1}.

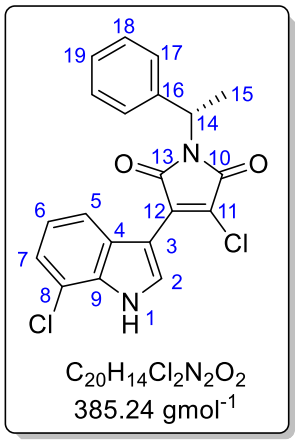
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.45-7.24 (m, 10H, **8+9+10+15+16+17**), 5.46 (br d, *J* = 8.7 Hz, 1H, **11**), 5.38-5.23 (m, 2H, **5+12**), 1.81 (d, *J* = 7.3 Hz, 3H, **6**), 1.60 (d, *J* = 6.8 Hz, 3H, **13**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 167.4 (**1/4**), 165.3 (**4/1**), 142.5 (**14**), 140.1 (**7**), 138.8 (**2+3**), 129.0, 128.5, 127.9, 127.7, 127.3, 125.8 (**8/9/10/15/16/17**), 52.3 (**12**), 50.1 (**5**), 23.6 (**13**), 17.7 (**6**) ppm.

LRMS (ES^+) *m/z* = 355 $[M+H]^+$

HRMS (ES^+) *m/z* for $C_{20}H_{20}ClN_2O_2$ calculated 355.1208, found 355.1206; *m/z* for $C_{20}H_{19}ClN_2NaO_2$ calculated 377.1027, found 377.1029.

(*S*)-3-Chloro-4-(7-chloro-1*H*-indol-3-yl)-1-(1-phenylethyl)-1*H*-pyrrole-2,5-dione (4.15):



$C_{20}H_{14}Cl_2N_2O_2$
385.24 $gmol^{-1}$

To a solution of 7-chloroindole (563 mg, 3.71 mmol) in THF (4 mL) at rt under N_2 was added EtMgBr (3.70 mL, 1M in THF, 3.70 mmol) dropwise over 10 min. The mixture was warmed to 60 °C and stirred for 1 h. The mixture was cooled to rt and a solution of (*S*)-3,4-Dichloro-1-(1-phenylethyl)-1*H*-pyrrole-2,5-dione (**4.13**, 503 mg, 1.86 mmol) in THF (2 mL) was added dropwise. The resulting solution was warmed to 65 °C and stirred at this temperature for 2 h. After cooling to rt, the mixture was diluted with EtOAc (20 mL), washed with sat. aqueous NH_4Cl (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated to a dark orange oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 1:4) gave the title compound as an orange solid (600 mg, 1.56 mmol, 84%).

$[\alpha]_D$ —140.0 ° (*c* = 0.04, acetone)

M.P. 106-108 °C

IR IR (neat) ν 2359, 1699, 1354, 742 cm^{-1}.

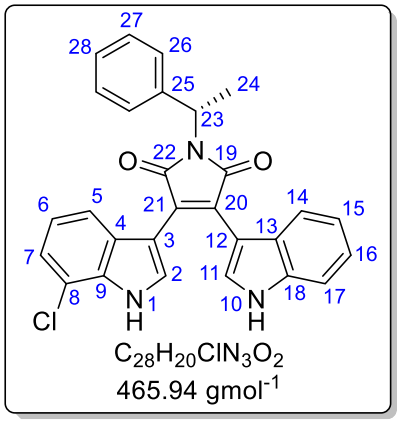
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.52 (br s, 1H, **1**), 8.04 (d, *J* = 3.1 Hz, 1H, **2**), 7.86 (d, *J* = 8.1 Hz, 1H, **5**), 7.43-7.39 (m, 2H, **17**), 7.38-7.31 (m, 3H, **7+18**), 7.28 (tt, *J* = 7.3, 2.2 Hz, 1H, **19**), 7.18 (t, *J* = 7.9 Hz, 1H, **6**), 5.40 (q, *J* = 7.1 Hz, 1H, **14**), 1.81 (d, *J* = 7.2 Hz, 3H, **15**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 168.0 (**10/13**), 165.4 (**10/13**), 140.5 (**16**), 133.3 (**9**), 132.5 (**11/12**), 131.9 (**2**), 128.5 (**18**), 127.4 (**19**), 126.6 (**17**), 126.5 (**4**), 123.7 (**11/12**), 122.2 (**7**), 121.5 (**6**), 121.0 (**5**), 116.6 (**8**), 104.1 (**3**), 49.6 (**14**), 17.7 (**15**) ppm.

LRMS (ES$^+$) *m/z* = 385 $[MCl^{35}+H]^+$ and 387 $[MCl^{37}+H]^+$.

HRMS (ES^+) *m/z* for $C_{20}H_{15}Cl_2N_2O_2$ calculated 385.0505, found 385.0502; *m/z* for $C_{20}H_{14}Cl_2N_2NaO_2$ calculated 407.0322, found 407.0324.

(*S*)-3-(7-chloro-1*H*-indol-3-yl)-4-(1*H*-indol-3-yl)-1-(1-phenylethyl)-1*H*-pyrrole-2,5-dione (4.16):



To a solution of indole (360 mg, 3.07 mmol) in PhMe (6 mL) at rt under N_2 was added EtMgBr (3.05 mL, 1M in THF, 3.05 mmol) and warmed to 50 °C. After 30 min, the solution was cooled to rt and cannulated into a stirred solution of (*S*)-3-chloro-4-(7-chloro-1*H*-indol-3-yl)-1-(1-phenylethyl)-1*H*-pyrrole-2,5-dione (**4.15**, 309 mg, 0.802 mmol) in THF/PhMe/Et_2O (3 mL, 5:5:1) and warmed to 95 °C.

After 24 h, another portion of magnesiated indole was prepared. Indole (303 mg, 2.59 mmol) was dissolved in PhMe (5 mL) at rt under N_2 and EtMgBr (2.6 mL, 1M in THF, 2.6 mmol) was added and the mixture warmed to 50 °C for 30 min. The solution was cooled to rt and added via cannula to the reaction mixture. The mixture was again heated to 95 °C and stirred for 21 h. The mixture was then quenched with sat. aqueous NH_4Cl (20 mL) and stirred. The mixture was then poured into brine (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were dried ($MgSO_4$) and concentrated to a dark red oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 1:4 to 3:7) gave the title compound as a bright red solid (588 mg, 0.676 mmol, 84%)

$[\alpha]_D$ —15.0 ° (*c* = 0.08, acetone)

M.P. 162-165 °C

IR IR (neat) ν 2359, 1696, 1684 cm^{-1}.

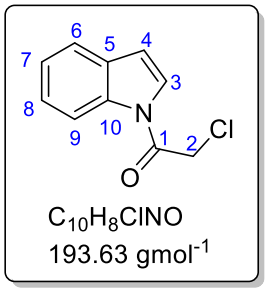
^{1}H NMR (acetone-d_6, 400 MHz): δ = 11.09 (br s, 1H, **1**), 10.88 (br s, 1H, **10**), 7.94 (d, *J* = 2.9 Hz, 1H, **11**), 7.91 (d, *J* = 2.8 Hz, 1H, **2**), 7.56-7.50 (m, 2H, **26**), 7.41 (dt, *J* = 8.2, 0.9 Hz, 1H, **14**), 7.38-7.32 (m, 2H, **27**), 7.25 (tt, *J* = 7.3, 2.0 Hz, 1H, **28**), 7.05 (dd, *J* = 7.6, 0.7 Hz, 1H, **5**), 6.99 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H, **15**), 6.90 (dt, *J* = 8.1, 0.7 Hz, 1H, **7**), 6.86 (dd, *J* = 8.1, 0.9 Hz, 1H, **17**), 6.66-6.61 (m, 2H, **6+16**), 5.56 (q, *J* = 7.3 Hz, 1H, **23**), 1.94 (d, *J* = 7.3 Hz, 3H, **24**) ppm.

^{13}C NMR (acetone-d_6, 101 MHz): δ = 172.3 (**19+22**), 142.5 (**26**), 137.3 (**18**), 134.1 (**9**), 130.5 (**2**), 130.4 (**11**), 129.4 (**20/21**), 129.2 (**27**), 128.7 (**21/20**), 128.1 (**28**), 127.9 (**26**), 127.0 (**25**), 126.6 (**13**), 122.9 (**15**), 122.3 (**5**), 122.1 (**17**), 121.3 (**7**), 121.2 (**6/16**), 120.6 (**16/6**), 117.1 (**4**), 112.5 (**14**), 108.7 (**3**), 107.2 (**12**), 50.4 (**23**), 18.3 (**24**) ppm.

LRMS (ES^+) *m/z* = 466 $[MCl^{35}+H]^+$ and 468 $[MCl^{37}+H]^+$.

HRMS (ES^+) *m/z* for $C_{28}H_{21}ClN_3O_2$ calculated 466.1317, found 466.1316; *m/z* for $C_{28}H_{20}ClN_3NaO_2$ calculated 488.1136, found 488.1139.

2-Chloro-1-(1*H*-indol-1-yl)ethan-1-one (4.21):



$C_{10}H_8ClNO$
193.63 $gmol^{-1}$

2-Chloro-1-(1*H*-indol-1-yl)ethan-1-one (**4.21**) was prepared according to a procedure described by Elnagdi and co-workers'.[138]

To a solution of indole (1.20 g, 10.2 mmol) in 1,4-dioxane (20 mL) at rt under N_2 was added 2-chloroacetyl chloride (0.81 mL, 10.2 mmol) and the mixture warmed to reflux. After 4 h, the mixture was cooled to rt and a further potion of 2-chloroacetyl chloride (0.24 mL, 3.02 mmol) added before warming to reflux. After a further 15 h, the mixture was poured onto ice-cold H_2O. The resulting red precipitate was collected by filtration and attempted recrystallization MeOH were unsuccessful. Purification of the crude solid via flash chromatography (EtOAc:hexane = 2:8) gave the title compound as an amorphous white solid (0.785 g, 4.05 mmol, 40%). The spectroscopic data were consistent with those reported.[247]

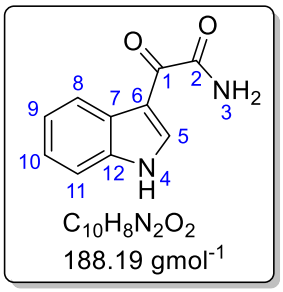
M.P. 116-118 °C (lit. 115-117 °C).[247]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.34 (dd, *J* = 8.1, 1.2 Hz, 1H, **6**), 7.87 (d, *J* = 3.8 Hz, 1H, **3**), 7.67-7.61 (m, 1H, **9**), 7.36 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H, **7**), 7.30 (td, *J* = 7.5, 1.6 Hz, 1H, 1H, **8**), 6.81 (dd, *J* = 3.8, 0.6 Hz, 1H, **4**), 5.12 (s, 2H, **2**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 165.4 (**1**), 135.0 (**10**), 130.1 (**5**), 126.3 (**3**), 124.9 (**7**), 123.9 (**8**), 121.0 (**9**), 115.8 (**6**), 109.2 (**4**), 43.5 (**2**) ppm.

LRMS (ES$^+$) *m/z* = 194 [M^{35}Cl+H]$^+$, 196 [M^{37}+H]$^+$.

2-(1*H*-Indol-3-yl)-2-oxoacetamide (4.22)



2-(1*H*-indol-3-yl)-2-oxoacetamide (**4.22**) was prepared by adaptation of a procedure described by V. H. Rawal and co-workers'.[248]

To a solution of indole (2.00 g, 17.1 mmol) in Et_2O (20 mL) at 0 °C under N_2 was added oxalyl chloride (1.72 mL, 20.1 mmol) dropwise over 30 min. After 1 h the yellow precipitate was filtered and washed with Et_2O (3 x 20 mL). The solid was dried under vacuum and added portion wise to a vigorously stirred solution of NH_4OH (12.8 mL, 35% in H_2O) and EtOH (28 mL) at rt under N_2. After 1h the precipitate was filtered, washed with H_2O (3 x 20 mL), ice-cold Et_2O (3 x 20 mL) to give the title compound as a white solid (2.76 g, 14.7 mmol, 86%). Spectroscopic data were consistent with those reported.[249]

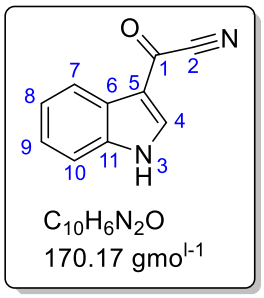
M.P. 250-252 °C (lit. 249-251 °C).[249]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.64-11.71 (m, 1H, **4**), 8.69 (s, 1H, **5**), 8.26-8.19 (m, 1H, **8**), 8.06 (br s, 1H, **3**), 7.70 (br s, 1H, **3'**), 7.58-7.49 (m, 1H, **11**), 7.31-7.20 (m, 2H, **9+10**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 183.0 (**1**), 166.0 (**2**,) 138.2 (**5**), 136.3 (**12**), 126.1 (**7**), 123.3 (**9/10**), 122.4 (**9/10**), 121.2 (**8**), 112.5 (**11**), 112.1 (**6**) ppm.

LRMS (ES$^+$) *m/z* = 189 $[M+H]^+$

1*H*-indol-3-yl(oxo)acetonitrile (4.23)



$C_{10}H_6N_2O$
170.17 gmo^{l-1}

1*H*-Indol-3-yl(oxo)acetonitrile (**4.23**) was prepared according to a procedure described by C. G. L. Veale.[139]

To a solution of 2-(1*H*-indol-3-yl)-2-oxoacetamide (102 mg, 0.54 mmol) in DMF (1 mL) at 0 °C under N_2 was added $SOCl_2$ (0.08 mL, 1.10 mmol) dropwise. After 1.5 h the mixture was quenched via slow addition of H_2O (5 mL) and warmd to rt. The organic was extracted with EtOAc (20 mL) and the organic phase washed with H_2O (3 x 10 mL), dried (MgSO4) and concentrated to give the title compound as a light yellow solid (84.3 mg, 0.495 mmol, 92%). The title compound was carried through without any further purification. Spectroscopic data were consistent with those reported.[250]

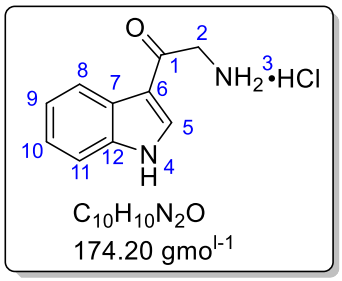
M.P. 222-224 °C (lit. 224-226 °C).[250]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.90 (br s, 1H, **3**), 8.63 (s, 1H, **4**), 8.07-8.01 (m, 1H, **7**), 7.62-7.54 (m, 1H, **10**), 7.35 (two overlapping ddd, *J* = 7.2, 1.5 Hz, 2H, **8+9**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 158.5 (**1**), 141.4 (**4**), 137.5 (**11**), 124.9 (**8/9**), 124.2 (**5**), 123.8 (**8/9**), 121.0 (**7**), 116.2 (**6**), 114.3 (**2**), 113.3 (**10**) ppm

LRMS (ES$^+$) *m/z* = 171 $[M+H]^+$.

2-Amino-1-(1*H*-indol-3-yl)ethan-1-one (4.24):



2-Amino-1-(1*H*-indol-3-yl)ethan-1-one (**4.24**) was prepared according to a procedure described by D. Horne and co-workers'.[141]

A mixture of 1*H*-Indol-3-yl(oxo)acetonitrile (47.1 mg, 0.277 mmol), Pd/C (10% by wt, 13.8 mg, 0.0130 mmol) in AcOH (1.5 mL) at rt was stirred under a balloon of H_2. After 20 h, the mixture was filtered through a pad of celite and washed with MeOH (5 mL). The filtrate was concentrated under reduced pressure to yield a dark brown solid. The crude solid was taken in solution of conc. HCl (5% by vol.) in EtOH (10 mL) and concentrated to give the HCl salt of the title compound as a light pink solid. (46.3 mg, 0.266 mmol, 96%). Spectroscopic data were consistent with those reported.[251, 62]

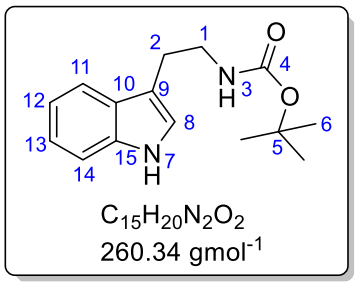
M.P. 258-260 °C (lit. >260 °C).[251]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.53 (br s, 1H, **4**), 8.52 (br d, *J* = 2.8 Hz, **5**), 8.43 (br s, 3H, **3**), 8.16 (br dd, *J* = 5.5, 2.4 Hz, 1H, **8**), 7.53 (br dd, *J* = 5.9, 2.2 Hz, 1H, **11**), 7.31-7.16 (m, 2H, **9+10**), 4.35 (br s, 2H, **2**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 186.7 (**1**), 136.6 (**12**), 135.1 (**5**), 125.1 (**7**), 123.2 (**9/10**), 122.3 (**9/10**), 120.9 (**8**), 113.1 (**11**), 112.5 (**6**), 43.9 (**2**) ppm

LRMS (ES^+) *m/z* = 175 $[M+H]^+$.

tert-Butyl (2-(1*H*-indol-3-yl)ethyl)carbamate (4.25):



$C_{15}H_{20}N_2O_2$
260.34 gmol^{-1}

tert-Butyl (2-(1*H*-indol-3-yl)ethyl)carbamate (**4.25**) was prepared by adaptation of a procedure described by K. C. Nicolaou and co-workers'.[142]

To a solution of tryptamine (1.51 g, 9.43 mmol) in 1,4-dioxane (35 mL), at rt under N_2 was added saturated aq. $NaHCO_3$ solution (17 mL) and Boc_2O (3.12 g, 14.3 mmol) sequentially. After 2 h, the reaction was quenched with H_2O (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organics were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated to a light brown oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 1:1) followed by trituration of the obtained oil gave the title compound as a white solid (2.29 g, 8.80 mmol, 94%). Spectroscopic data were consistent with those reported.[63]

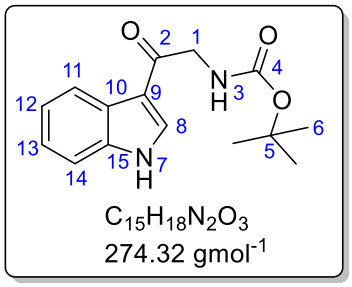
M.P. 90-92 °C (lit. 90-92 °C).[63]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.79 (br s, 1H, **7**), 7.52 (d, *J* = 7.8 Hz, 1H, **11**), 7.33 (d, *J* = 8.1 Hz, 1H, **14**), 7.13 (d, *J* = 2.0 Hz, 1H, **8**), 7.06 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, **13**), 6.97 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H, **12**), 6.88 (br t, *J* = 5.6 Hz, 1H, **3**), 3.20 (q, *J* = 7.1 Hz, 2H, **2**), 2.80 (t, *J* = 7.5 Hz, 2H, **1**), 1.39 (s, 9H, **6**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 155.6 (**4**), 136.2 (**15**), 127.3 (**10**), 122.5 (**8**), 120.9 (**13**), 118.2 (**11**), 118.2 (**12**), 111.8 (**9**), 111.3 (**14**), 77.4 (**5**), 40.8 (**2**), 28.3 (**6**), 25.5 (**1**) ppm

LRMS (ES$^+$) *m/z* = 283 [M+Na]$^+$, .

tert-Butyl (2-(1_H_-indol-3-yl)-2-oxoethyl)carbamate (4.26):



tert-Butyl (2-(1_H_-indol-3-yl)-2-oxoethyl)carbamate (**4.26**) was prepared by adaptation of a procedure described by K. C. Nicolaou and co-workers'.[142]

To a solution of _tert_-butyl (2-(1_H_-indol-3-yl)ethyl)carbamate (105.5 mg, 0.405 mmol) in THF:H_2O (9:1, 5.5 mL) at 0 °C under N_2 was added DDQ (176.2 mg, 0.776 mmol) and stirred. After 2 h, the mixture was poured into EtOAc (20 mL) and washed with $NaHCO_3$ (5 x 40 mL) to remove any coloured DDQ by products. The organic phase was dried ($MgSO_4$) and concentrated to a colourless oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 3:7) gave the title compound as an amorphous white solid (77.8 mg, 0.308 mmol, 80%). Spectroscopic data were consistent with those reported.[142]

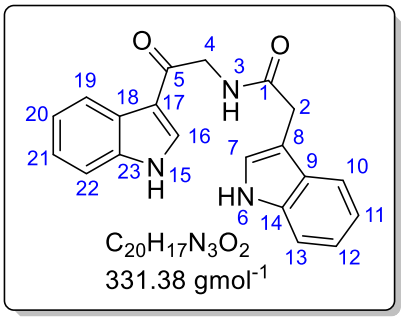
M.P. 215-216 °C (lit. 215-220 °C).[251]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.97 (br s, 1H, **7**), 8.40 (s, 1H, **8**), 8.21-8.11 (m, 1H, **11**), 7.51-7.44 (m, 1H, **14**), 7.25-7.16 (m, 2H, **12+13**), 6.98 (br t, _J_ = 5.9 Hz, 1H, **3**), 4.30 (d, _J_ = 6.0 Hz, 2H, **1**), 1.41 (s, 9H, **6**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 190.8 (**2**), 156.9 (**4**), 136.4 (**15**), 133.3 (**8**), 125.4 (**10**), 122.8 (**12/13**), 121.7 (**12/13**), 121.2 (**11**), 113.9 (**9**), 112.1 (**14**), 77.8 (**5**), 46.8 (**1**), 28.2 (**6**) ppm

LRMS (ES$^+$) _m/z_ = 297 [M+Na]$^+$.

***N*-(2-(1*H*-Indol-3-yl)-2-oxoethyl)-2-(1*H*-indol-3-yl)acetamide (4.19):**



To a solution of indole acetic acid (0.504 g, 2.88 mmol) in THF (10 mL) at 0°C under N_2 was added CDI (0.559 g, 3.44 mmol) and warmed to rt. After 30 min, the mixture was added dropwise to a stirred solution of 2-amino-1-(1*H*-indol-3-yl)ethan-1-one•HCl (**4.24**, 0.731 g, 3.47 mmol) and $NaHCO_3$ (0.381 g, 4.54 mmol) in THF (10 mL) at rt under N_2. After 6 h, the mixture was taken in EtOAc (100 mL) and H_2O (50 mL) and the phases separated. The organic was washed with H_2O (2x50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated to white solid. Purification of the crude solid via trituration (acetone) gave the title compound as an amorphous white solid (0.877 g, 2.65 mmol. 92%).

M.P. Decomposed 227 °C

IR IR (neat) ν 3356, 3292, 1637, 748 cm^{-1}.

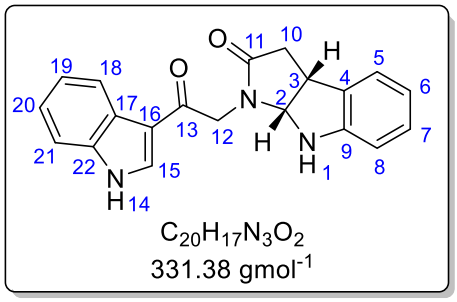
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.00 (br s, 1H, **15**), 10.91 (br s, 1H, **6**), 8.42 (d, *J* = 2.8 Hz, 1H, **16**), 8.17 (d, *J* = 7.2 Hz, 1H, **19**), 8.13 (t, *J* = 5.1 Hz, 1H, **3**), 7.61 (d, *J* = 7.8 Hz, 1H, **10**), 7.49 (br d, *J* = 7.1 Hz, 1H, **22**), 7.37 (d, *J* = 8.1 Hz, 1H, **13**), 7.30 (d, *J* = 1.2 Hz, 1H, **7**), 7.26-7.17 (m, 2H, **20+21**), 7.09 (t, *J* = 7.4 Hz, 1H, **12**), 6.99 (t, *J* = 7.3 Hz, 1H, **11**), 4.50 (d, *J* = 5.5 Hz, 2H, **4**), 3.66 (s, 2H, **2**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 190.2 (**5**), 171.0 (**1**), 136.4 (**23**), 136.1 (**14**), 133.6 (**16**), 127.3 (**9**), 125.4 (**18**), 123.9 (**7**), 122.8 (**20/21**), 121.8 (**20/21**), 121.1 (**19**), 120.9 (**12**), 118.7 (**10**), 118.3 (**11**), 114.0 (**17**), 112.1 (**22**), 111.3 (**13**), 108.8 (**8**), 45.8 (**4**), 32.5 (**2**) ppm.

LRMS (ES$^+$) *m/z* = 332 [M+H]$^+$.

HRMS (ES$^+$) *m/z* for $C_{20}H_{17}N_3NaO_2$ calculated 354.1213, found 354.1212.

(±)-1-(2-(1*H*-Indol-3-yl)-2-oxoethyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (4.27):



$C_{20}H_{17}N_3O_2$
331.38 $gmol^{-1}$

To *N*-(2-(1*H*-Indol-3-yl)-2-oxoethyl)-2-(1*H*-indol-3-yl)acetamide (**4.19**, 100 mg, 0.302 mmol) at rt under N_2 was added TFA (3 mL) and stirred for 30 min. The mixture was concentrated, taken in EtOAc (20 mL) and added sat. aqueous $NaHCO_3$ (30 mL). The phases were separated and the aqueous extracted with EtOAc (3 x 20 mL). The combined organics were dried ($MgSO_4$) and concentrated to a colourless solid. The crude solid was triturated with CH_2Cl_2 to yield the title compound as a colourless solid (52 mg, 0.157 mmol, 52%).

M.P. 215-217 °C

IR IR (neat) ν 3406, 3327, 1669, 1648 cm^{-1}.

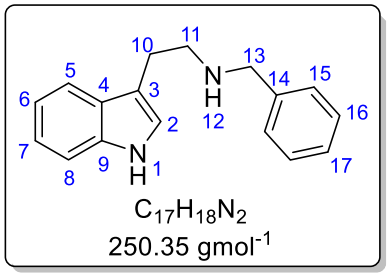
^{1}H NMR ($DMSO-d_6$, 400 MHz): δ = 12.07 (br s, 1H, **14**), 8.49 (d, *J* = 1.2 Hz, 1H, **15**), 8.20-8.13 (m, 1H, **18**), 7.54-7.47 (m, 1H, **21**), 7.24 (td, *J* = 7.1, 1.6 Hz, 1H, **20**), 7.21 (td, *J* = 7.0, 1.3 Hz, 1H, **19**), 7.13 (d, *J* = 7.3 Hz, 1H, **5**), 7.01 (td, *J* = 7.6, 1.0 Hz, 1H, **7**), 6.72 (d, *J* =1.8 Hz, 1H, **1**), 6.66 (td, *J* = 7.4, 0.9 Hz, 1H, **6**), 6.55 (d, *J* = 7.7 Hz, 1H, **8**), 5.46 (dd, *J* = 7.2, 2.1 Hz, 1H, **2**), 4.83 (d, *J* =17.5 Hz, 1H, **12a**), 4.46 (d, *J* = 17.4 Hz, 1H, **12b**), 4.01 (br t, *J* = 8.1 Hz, 1H, **3**), 2.96 (dd, *J* = 17.2, 9.5 Hz, 1H, **10a**), 2.51 (dd, *J* = 17.0, 1.3 Hz, 1H, **10b**) ppm.

^{13}C NMR ($DMSO-d_6$, 101 MHz): δ = 189.0 (**13**), 172.5 (**11**), 149.1 (**9**), 136.4 (**22**), 134.0 (**15**), 131.3 (**4**), 128.1 (**7**), 125.3 (**17**), 124.3 (**5**), 122.9 (**20**), 121.9 (**19**), 121.1 (**18**), 118.2 (**6**), 114.0 (**16**), 112.2 (**21**), 109.2 (**8**), 76.4 (**2**), 45.5 (**12**), 39.2 (**3**), 36.2 (**10**) ppm.

LRMS (ES^+) *m/z* = 332 $[M+H]^+$.

HRMS (ES$^+$) *m/z* for $C_{20}H_{18}N_3O_2$ calculated 332.1394, found 332.1397; *m/z* for $C_{20}H_{17}N_3NaO_2$ calculated 354.1213, found 354.1217.

_N_-Benzyl-2-(1_H_-indol-3-yl)ethan-1-amine (4.28):



$C_{17}H_{18}N_2$
250.35 $gmol^{-1}$

_N_-Benzyl-2-(1_H_-indol-3-yl)ethan-1-amine (**4.28**) was prepared according to a procedure described by Abe and co-workers'.[252]

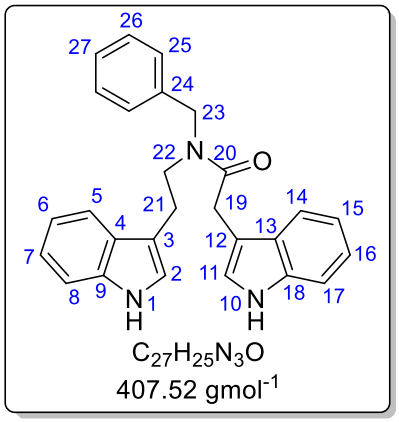
A solution of tryptamine (5.00 g, 31.2 mmol) and benzaldehyde (3.50 mL, 34.3 mmol) in MeOH (150 mL) at rt under N_2 was stirred for 15 h before a further portion of benzaldehyde (1.80 mL, 17.6 mmol). After a further 3 h, $NaBH_4$ (1.78 g, 47.1 mmol) was added portionwise over 15 min and stirred. After 1.5 h the mixture was concentrated, taken in H_2O (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and concentrated to a brown oil. Purification via flash chromatography ($CHCl_3$:MeOH:35% aqueous NH_3 = 45:4.5:0.5) gave the title compound as a pale brown oil (7.32 g, 29.2 mmol, 94%). The spectroscopic data were consistent with those reported.[252]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.39 (br s, 1H, **1**), 7.70-7.65 (m, 1H, **5**), 7.44-7.22 (m, 7H, **7+8+15+16+17**), 7.18 (ddd, _J_ = 7.9, 7.1, 1.2 Hz, 1H, **6**), 6.98 (d, _J_ = 2.2 Hz, 1H, **2**), 3.88 (s, 2H, **13**), 3.07 (s, 4H, **10+11**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 140.2 (**14**), 136.3 (**9**), 128.3 (**15/16**), 128.1 (**15/16**), 127.4 (**4**), 126.8 (**17**), 122.0 (**2**), 121.8 (**7**), 119.1 (**6**), 118.8 (**5**), 113.7 (**3**), 111.1 (**8**), 53.8 (**13**), 49.3 (**10/11**), 25.7 (**10/11**) ppm.

LRMS (ES^+) _m/z_ = 251 $[M+H]^+$.

***N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-benzyl-2-(1*H*-indol-3-yl)acetamide (4.29):**



$C_{27}H_{25}N_3O$

407.52 $gmol^{-1}$

To a solution of indole-3-acetic acid (0.998 g, 5.71 mmol) in THF (20 mL) at 0 °C under N_2 was added CDI (1.11 g, 6.85 mmol) and warmed to rt. After 30 min, a solution of *N*-Benzyl-2-(1*H*-indol-3-yl)ethan-1-amine (**4.28**, 1.71 g, 6.85 mmol) in THF (20 mL) was added and stirred. After 2 h, the mixture was taken in EtOAc (100 mL) and washed with H_2O (3 x 50 mL), brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated to an orange/brown oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 4:6 to 1:1) gave a mixture of rotamers of the title compound as a colourless solid (1.41 g, 3.46 mmol, 63%).

M.P. 70-71 °C

IR IR (neat) ν 3405, 3274, 1615, 1455, 1420, 739 cm^{-1}.

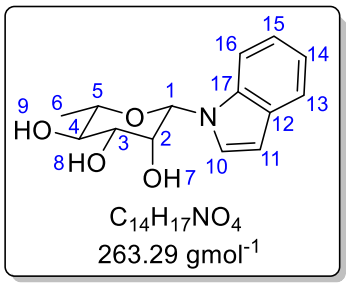
^{1}H NMR (298 K) (DMSO-d_6, 400 MHz): δ =10.93-10.72 (m, 2H, **1+10**), 7.59-6.87 (m, 15H, 15 x **ArH**), 4.66-4.61 (m, 2H, **19**), 3.80 (s, 1H, **23**), 3.67 (s, 1H, **23'**), 3.55-3.43 (m, 2H, **22**), 2.85 (q, *J* = 7.3 Hz, 2H, **21**) ppm.

^{13}C NMR (298 K) (DMSO-d_6, 101 MHz): δ = 171.3 (**20a**), 171.2 (**20b**), 138.9 (**ArC**), 138.4 (**ArC**), 136.7 (**ArC**), 136.5 (**ArC**), 129.1 (**ArC**), 128.8 (**ArC**), 128.1 (**ArC**), 127.7 (**ArC**), 127.7 (**ArC**), 127.6 (**ArC**), 127.6 (**ArC**), 127.4 (**ArC**), 127.4 (**ArC**), 127.3 (**ArC**), 124.1 (**ArC**), 123.7 (**ArC**), 123.7 (**ArC**), 123.1 (**ArC**), 121.5 (**ArC**), 121.4 (**ArC**), 119.2 (**ArC**), 118.8 (**ArC**), 118.8 (**ArC**), 118.7 (**ArC**), 118.7 (**ArC**), 118.5 (**ArC**), 112.0 (**ArC**), 111.9 (**ArC**), 111.8 (**ArC**), 111.8 (**ArC**), 111.3 (**ArC**), 108.8 (**ArC**), 108.7 (**ArC**), 51.7 (**23a**), 48.4 (**23b**), 47.8 (**22a**), 47.2 (**22b**), 31.5 (**19a**), 30.9 (**19b**), 24.4 (**21a**), 23.6 (**21b**) ppm.

LRMS (ES$^+$) *m/z* = 408 $[M+H]^+$.

HRMS (ES$^+$) *m/z* for $C_{27}H_{26}N_3O$ calculated 408.2070, found 408.2078; for $C_{27}H_{25}N_3NaO$ calculated 430.1890, found 430.1895.

(1*H*-Indol-1-yl) β-L-rhamnopyranoside (4.32):



$C_{14}H_{17}NO_4$
263.29 $gmol^{-1}$

To a solution of indoline (0.094 mL, 0.839 mmol) in EtOH (5 mL) was added L-rhamnose (0.689 g, 4.20 mmol) followed by $(NH_4)_2SO_4$ (0.333 g, 2.52 mmol) and warmed to reflux. After 3 h the mixture was concentrated and taken in EtOAc (20 mL). The organic was washed with H_2O (15 mL), brine (15 mL), dried ($MgSO_4$) and concentrated to a viscous orange syrup. Flash chromatography of the crude syrup gave a mixture of anomers which was used without further purification.

The mixture was dissolved in THF (3 mL) and cooled to 0 °C. DDQ (0.111 g, 0.490 mmol) was added and the mixture stirred. After 3 h, the mixture was taken in EtOAc (20 mL) and washed with sat. aqueous $NaHCO_3$ (4 x 20 mL), dried ($MgSO_4$) and concentrated to a green solid. Purification of the crude solid via flash chromatography (MeOH:EtOAc = 0:1 to 2:98) gave the desired product in a 9:1 (β:α, **4.32**:**4.33**) mixture of anomers as an off white solid (0.124 g, 0.471 mmol, 56%).

$[\alpha]_D$ —13.0 ° (*c* = 0.35, MeOH).

M.P. Darkened 150 °C, melted 207-209 °C.

IR IR (neat) ν 3419, 3299, 1460, 1312, 1055, 742 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.70 (d, *J* = 3.3 Hz, 1H, **10**), 7.55 (dd, *J* = 8.3, 0.8 Hz, 1H, **13**), 7.53 (dq, *J* = 7.8, 0.7 Hz, 1H, **16**), 7.12 (ddd, *J* = 8.2, 7.1, 12 Hz, 1H, **14**), 7.03 (ddd, *J* = 7.9, 7.1, 1.1 Hz, 1H, **15**), 6.41 (dd, *J* = 3.4, 0.7 Hz, 1H, **11**), 5.75 (s, 1H, **1**), 5.07 (dd, *J* = 5.4, 0.5 Hz, 1H, **7**), 4.95 (d, *J* = 5.4 Hz, 1H, **9**), 4.89 (d, *J* = 5.6 Hz, 1H, **8**), 3.90 (ddd, *J* = 5.4, 3.1, 1.0 Hz, 1H, **2**), 3.60 (ddd, J = 9.2, 5.8, 3.1 Hz, 1H, **3**), 3.49 (dd, *J* = 9.2, 6.2 Hz, 1H, **4**), ~3.33 (m, under DMSO, 1H, **5**) 1.21 (d, *J* = 6.2 Hz, 3H, **6**) ppm.

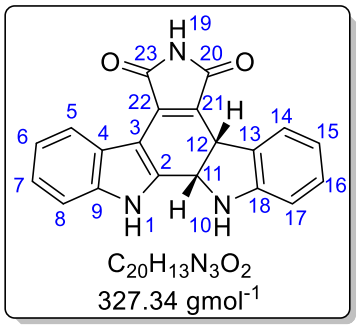
^{13}C NMR (DMSO-d_6, 101 MHz): δ = 135.7 (**17**), 127.8 (**10**), 127.5 (**12**), 121.0 (**15**), 120.1 (**13**), 119.5 (**14**), 110.3 (**16**), 100.9 (**11**), 82.0 (**1**), 74.6 (**4**), 73.6 (**3**),

71.7 (**5**), 71.2 (**2**), 18.0 (**6**) ppm.

LRMS (ES$^+$) *m/z* = 264 [M+H]$^+$.

HRMS (ES$^+$) *m/z* for $C_{14}H_{17}NNaO_4$ calculated 286.1050, found 286.1049.

4b,12,12b,13-Tetrahydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (4.34):



$C_{20}H_{13}N_3O_2$
327.34 $gmol^{-1}$

4b,12,12b,13-Tetrahydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (**4.34**) was prepared according to a procedure described by Faul and co-workers'.

To a solution of TFA (24 mL) at 0 °C under N_2 was added bisindolylmaleimide (**1.54**, 990 mg, 3.02 mmol) and the mixture stirred. After 4 h, hexane (20 mL) was added dropwise and the resulting red precipitate was filtered. The precipitate was washed with hexane and taken in EtOAc (100 mL). The organic phase was washed with sat. aqueous $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated to yield the title compound as an orange/red solid (706 mg, 2.16 mmol, 72%),

M.P. Turned yellow at 255 °C, no further melting/degradation up to 300 °C.

IR IR (neat) ν 3290, 3201, 1690, 1541, 1338, 756 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.89 (s, 1H, **1**), 10.69 (s, 1H, **19**), 8.30-8.24 (m, 1H, **5**), 7.49-7.43 (m, 1H, **8**), 7.20 (dt, *J* = 7.5, 1.1 Hz, 1H, **14**), 7.19-7.11 (m, 2H, **6+7**), 6.99-6.94 (m, 1H, **16**), 6.63 (dt, *J* = 7.7, 0.7 Hz, 1H, **17**), 6.61 (td, *J* = 7.5, 1.0 Hz, 1H, **15**), 6.15 (d, *J* = 1.8 Hz, 1H, **10**), 5.51 (dd, *J* = 11.7, 2.0 Hz, 1H, **11**), 4.70 (d, *J* = 11.7 Hz, 1H, **12**), 4.03 (q, *J* = 7.1 Hz, 1H, $H_3CCOOC\mathbf{H_2}CH_3$), 1.99 (s, 1H, $\mathbf{H_3}CCOOCH_2CH_3$), 1.17 (t, *J* = 7.1 Hz, 1H, $H_3CCOOCH_2C\mathbf{H_3}$) ppm.

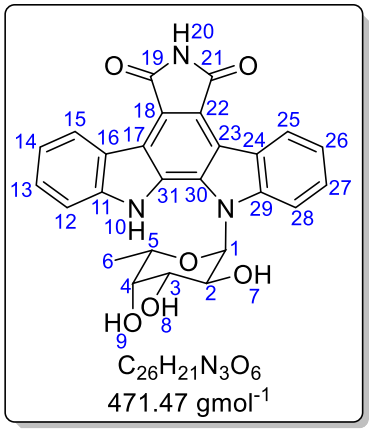
^{13}C NMR (DMSO-d_6, 101 MHz): δ = 172.5 (**20/23**), 170.9 (**20/23**), 150.0 (**18**), 142.4 (**2**), 136.8 (**9**), 136.3 (**22**), 128.2 (**13**), 127.9 (**16**), 126.4 (**21**), 125.0 (**14**), 122.7 (**4**), 122.4 (**7**), 121.6 (**5**), 121.3 (**6**), 118.2 (**15**), 112.1 (**8**), 109.1 (**17**), 102.0 (**3**), 55.7 (**11**), 39.1 (**12**) ppm.

LRMS (ES^+) *m/z* = 328 $[M+H]^+$

HRMS (ES$^+$) *m/z* for $C_{20}H_{14}N_3O_2$ calculated 328.1081, found 328.1084; for $C_{20}H_{13}N_3NaO_2$ calculated 350.0900, found 350.0902.

12-((2R,3S,4R,5S,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (4.36):

12-((2R,3S,4R,5S,6S)-3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (**4.36**) was prepared according to a procedure described by Faul and co-workers'.[253]



To solution of 4b,12,12b,13-tetrahydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (**4.34**, 0.100 g, 0.315 mmol) in EtOH (3 mL) at rt under N_2 was added L-fucose (0.252 g, 1.53 mmol) followed by $(NH_4)_2SO_4$ (0.122 g, 0.923 mmol) and warmed to Δ. After 4 h, the mixture was concentrated and the crude solid taken in THF (3 mL) and DDQ (0.076 g, 0.335 mmol) added. After 16 h, the mixture was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organics were dried ($MgSO_4$) and concentrated to an orange solid. Purification of the crude solid trituration with Et_2O gave the title compound as an orange solid (0.139 g, 0.295 mmol, 94%). Spectroscopic data were consistent with those reported.[253]

$[\alpha]_D$ −77.6 ° (*c* = 0.47, MeOH).

M.P. 275-277 °C

IR IR (neat) ν 3319, 1691, 1458, 1320, 1069, 743 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.20 (s, 1H, **10**), 11.09 (s, 1H, **20**), 9.20 (dd, *J* = 8.0, 0.7 Hz, 1H, **15**), 9.11 (d, *J* = 7.9 Hz, 1H, **25**), 7.93 (d, *J* = 8.8 Hz, 1H, **12**), 7.73 (dt, *J* = 8.1, 0.7 Hz, 1H, **28**), 7.61 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H, **13**), 7.58 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H, **27**), 7.39 (ddd, *J* = 7.9, 7.2, 0.7 Hz, 1H, **14**), 7.36 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H, **26**), 6.88 (d, *J* = 3.5 Hz, 1H, **1**), 6.16 (d, *J* = 9.2 Hz, 1H, **9**), 5.32 (br s, 1H, **8**), 5.18 (br d, *J* = 5.0 Hz, 1H, **7**), 4.30 (q, *J* = 6.3 Hz, 1H, **5**), 4.20 (td, *J* = 8.8, 4.0 Hz, 1H,

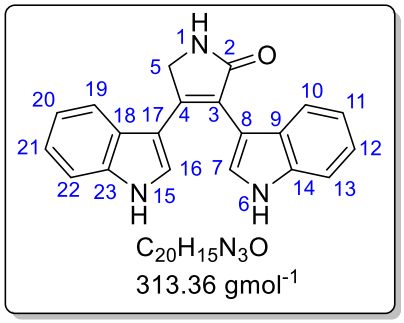
4), 3.96 (t, *J* = 3.0 Hz, 1H, **2**), 3.85 (br d, *J* = 9.0 Hz, 1H, **3**), 1.34 (d, *J* = 6.4 Hz, 3H, **6**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 171.2 (**19/21**), 171.1 (**19/21**), 141.5 (**11**), 140.4 (**29**), 128.8 (**18/22**), 127.8 (**18/22**), 126.9 (**13/27**), 126.7 (**13/27**), 124.5 (**15+25**), 120.9 (**30**), 120.8 (**31**), 120.7 (**23**), 120.6 (**17**), 120.1 (**14/26**), 119.2 (**14/26**), 117.4 (**16/24**), 116.4 (**16/24**), 111.6 (**28**), 111.0 (**12**), 84.7 (**1**), 74.0 (**3**), 73.7 (**5**), 71.9 (**2**), 70.9 (**4**), 17.0 (**6**) ppm.

LRMS (ES^+) *m/z* = 472 $[M+H]^+$.

HRMS (ES^+) *m/z* for $C_{26}H_{22}N_3O_6$ calculated 472.1503, found 472.1505.

3,4-Di(1*H*-indol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-one (3.19)



$C_{20}H_{15}N_3O$

313.36 $gmol^{-1}$

3,4-Di(1*H*-indol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-one (**3.19**) and 5-hydroxy-3,4-di(1*H*-indol-3-yl)-1,5-dihydro-*2H*-pyrrol-2-one (**4.37**) were prepared according to a procedure described by P. D. Davis and co-workers'.[254]

To a solution of bisindolylmaleimide (2.50 g, 7.64 mmol mmol) in THF (70 mL) at 0 °C under N_2 was added $LiAlH_4$ (23.0 mL, 1M in THF, 23.0 mmol) dropwise over 20 min. The reaction mixture was warmed to rt and stirred for 88 h. The mixture was then cooled to 0 °C and quenched via addition of H_2O (50 mL). The mixture was acidified to pH = 2 with 2M aq. HCl and the resulting solution extracted with EtOAc (3 x 100 mL). The combined organics were washed with sat. aq. $NaHCO_3$ sol. (50 mL), dried (Na_2SO_4) and concentrated to a dark brown solid. Purification of the crude solid via flash chromatography (MeOH :CH_2Cl_2 = 2:98) gave the title compound as an off white solid (910 mg, 2.90 mmol, 38%). The spectroscopic data were consistent with those reported.[254]

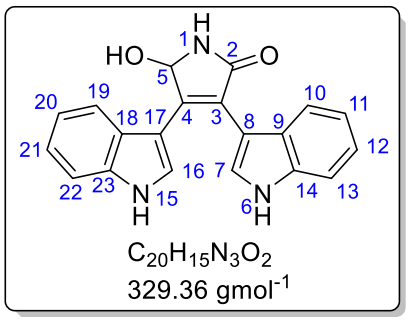
M.P. 291-293 °C (lit. 290-293 °C).[254]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.38 (br d, *J* = 2.1 Hz, 1H, **15**), 11.26 (d, *J* = 2.1 Hz, 1H, **6**), 8.22 (s, 1H, **1**), 7.50 (d, *J* = 2.6 Hz, 1H, **7**), 7.41 (dt, *J* = 8.1, 1.0 Hz, 1H, **13**), 7.37 (dt, *J* = 8.1, 0.9 Hz, 1H, **22**), 7.33-7.29 (m, 2H, **16+19**), 7.02 (2 overlapping ddd, *J* = 8.1, 7.1, 1.0 Hz, 2H, **12+21**), 6.97 (d, *J* = 7.9 Hz, 1H, **10**), 6.87 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H, **20**), 6.76 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, **11**), 4.56 (s, 2H, **5**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 174.5 (**2**), 144.7 (**4**), 136.5 (**23**), 136.5 (**14**), 127.0 (**16**), 126.5 (**7**), 125.8 (**9**), 125.5 (**18**), 122.0 (**21**), 121.9 (**3**), 121.3 (**12**), 121.0 (**10**), 120.8 (**19**), 120.1 (**20**), 118.9 (**11**), 112.3 (**22**), 112.0 (**13**), 110.3 (**17**), 108.0 (**8**), 48.6 (**5**) ppm.

LRMS (ES$^+$) *m/z* = 314 $[M+H]^+$.

5-Hydroxy-3,4-di(1*H*-indol-3-yl)-1,5-dihydro-*2H*-pyrrol-2-one (4.37)



$C_{20}H_{15}N_3O_2$
329.36 gmol^{-1}

Eluting with MeOH in CH_2Cl_2 1:9 gave the title compound as a light brown solid (970 mg g, 2.95 mmol, 39%). The spectroscopic data were consistent with those reported.[254]

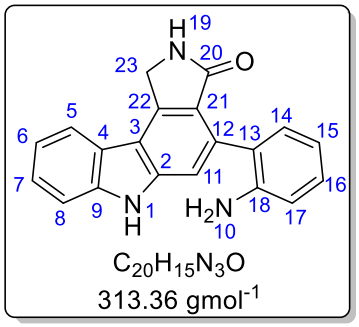
M.P. Decomposed 254 °C (lit. >250 °C).[254]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.38 (d, *J* = 2.3 Hz, 1H, **15**), 11.25 (d, *J* = 2.2 Hz, 1H, **6**), 8.47 (d, *J* = 1.0 Hz, 1H, **1**), 7.49 (d, *J* = 2.6 Hz, 1H, **7**), 7.45 (d, *J* = 2.8 Hz, 1H, **16**), 7.37 (d, *J* = 8.1 Hz, 1H, **13**), 7.34 (d, *J* = 8.1 Hz, 1H, **22**), 7.16 (d, *J* = 8.1 Hz, 1H, **19**), 7.03-6.94 (m, 3H, **10+12+21**), 6.73 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H, **20**), 6.70 (ddd, *J* = 8.0, 7.2, 1.0, 1H, **11**) 6.07-5.97 (m, 2H, **5+OH**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 172.2 (**2**), 145.9 (**4**), 136.0 (**23**), 135.9 (**14**), 127.4 (**16**), 126.4 (**7**), 125.6 (**18**), 125.5 (**9**), 121.3 (**3**), 121.2 (**19**), 121.2 (**10**) 120.8 (**12/21**), 120.8 (**12/21**), 119.1 (**20**), 118.4 (**11**), 111.5 (**13/22**), 111.4 (**13/22**), 109.4 (**17**), 107.1 (**8**), 79.4 (**5**) ppm.

LRMS (ES$^+$) *m/z* = 330 [M+H]$^+$.

4-(2-Aminophenyl)-1,6-dihydropyrrolo[3,4-*c*]carbazol-3(2*H*)-one (4.38):



To a solution of TFA (3 mL) at rt under N_2 was added 3,4-di(1*H*-indol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-one (**3.19**, 0.201 g, 0.641 mmol) and stirred. After 20 h, H_2O (20 mL) was added and the precipitate filtered. The solid was taken in EtOAc (30 mL), washed with sat. aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated to a light yellow solid. Purification of the crude via flash chromatography (MeOH:CH_2Cl_2 = 2:98 to 1:9) gave the title compound as a grey solid (0.081 g, 0.258 mmol, 40%).

M.P. 252-255 °C

IR IR (neat) ν 3301, 1671, 1439, 1245, 744 cm^{-1}.

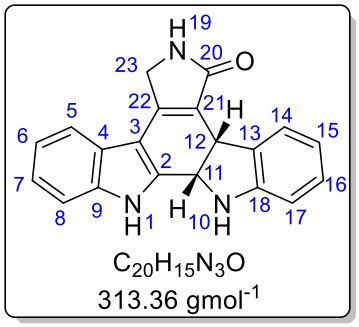
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.68 (s, 1H, **1**), 8.29 (s, 1H, **19**), 8.02 (d, *J* = 7.9 Hz, 1H, **5**), 7.59 (d, *J* = 8.1 Hz, 1H, **8**), 7.47 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H, **7**), 7.30 (s, 1H, **11**), 7.27 (ddd, *J* = 7.9, 7.2, 1.0 Hz, 1H, **6**), 7.05 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H, **16**), 6.98 (dd, *J* = 7.5, 1.5 Hz, 1H, **14**), 6.73 (dd, *J* = 8.1, 1.0 Hz, 1H, **17**), 6.61 (td, *J* = 7.3, 1.2 Hz, 1H, **15**), 4.82 (s, 2H, **23**), 4.49 (s, 2H, **10**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 170.5 (**20**), 145.8 (**18**), 141.6 (**2**), 140.3 (**9**), 140.2 (**22**), 134.6 (**12**), 130.7 (**14**), 127.7 (**16**), 125.9 (**7**), 124.7 (**13**), 121.7 (**5**), 121.3 (**4**), 120.6 (**21**), 119.5 (**6**), 116.2 (**3**), 115.9 (**17**), 114.7 (**15**), 112.5 (**11**), 111.3 (**8**), 43.8 (**23**) ppm.

LRMS (ES$^+$) *m/z* = 314 $[M+H]^+$.

HRMS (ES$^+$) *m/z* for $C_{20}H_{16}N_3O$ calculated 314.1288, found 314.1292; for $C_{20}H_{15}N_3NaO$ calculated 336.1107, found 336.1108.

4b,6,7,12,12b,13-Hexahydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5-one (4.39):



$C_{20}H_{15}N_3O$
313.36 $gmol^{-1}$

To a solution of TFA (3 mL) at −10 °C under N_2 was added 3,4-di(1*H*-indol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-one (**3.19**, 0.101 g, 0.322 mmol) and stirred. After 4 h, H_2O (10 mL) was added dropwise and the resulting precipitate filtered. The crude solid was triturated with Et_2O to yield the TFA salt of the title compound as an off white solid (0.071 g, 0.227 mmol, 70%). The free base was accessed immediately prior to use. The solid was taken in sat. aqueous $NaHCO_3$ and sonicated for 5 min. The precipitate was filtered, washed with Et_2O and dried.

M.P. Darkened 230 °C, degraded 275 °C.

IR IR (neat) ν 3206, 1638, 1436, 1359, 1230, 1207, 1125 cm^{-1}.

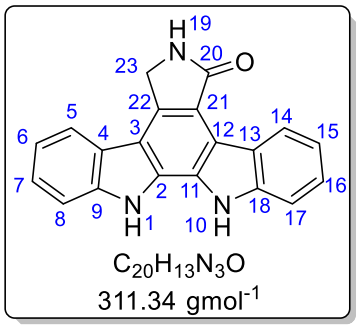
^{1}H NMR (DMSO-d_6, 400 MHz): δ =11.58 (s, 1H, **1**), 8.11-7.83 (m, 1H, **19**), 7.50 (d, *J* = 7.7 Hz, 1H, **5**), 7.44 (d, *J* = 7.9 Hz, 1H, **8**), 7.33 (d, *J* = 7.5 Hz, 1H, **14**), 7.13 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H, **7**), 7.07 (ddd, *J* = 7.8, 7.1, 1.1 Hz, 1H, **6**), 6.93 (tt, *J* = 7.5, 1.1 Hz, 1H, **16**), 6.62 (d, *J* = 7.7 Hz, 1H, **17**), 6.59 (td, *J* = 7.5, 0.9 Hz, 1H, **15**), 5.49 (d, *J* = 11.4 Hz, 1H, **11**), 4.58-4.46 (m, 2H, **12+23a**), 4.40 (dd, *J* = 19.4, 2.0 Hz, 1H, **23b**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 173.8 (**20**), 149.8 (**18**), 146.4 (**22**), 139.6 (**2**), 136.4 (**9**), 130.4 (**13**), 127.5 (**16**), 124.9 (**14**), 123.0 (**4+21**), 121.8 (**7**), 120.5 (**6**), 118.9 (**5**), 117.9 (**15**), 112.1 (**8**), 108.7 (**17**), 105.2 (**3**), 56.0 (**11**), 45.4 (**23**), 39.6 (**12**) ppm.

LRMS (ES^+) *m/z* = 314 $[M+H]^+$.

HRMS (ES^+) *m/z* for $C_{20}H_{16}N_3O$ calculated 314.1288, measured 314.1292.

Staurosporine aglycone/K252c (1.10):



To a solution of 4b,6,7,12,12b,13-hexahydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5-one (**4.39**, 0.048 g, 0.153 mmol) in THF (3 mL) at 0 °C under N_2 was added DDQ (0.035 g, 0.154 mmol) and stirred. After 30 min, the mixture was diluted with EtOAc (10 mL) and washed with sat. aqueous $NaHCO_3$ (6 x 10 mL) to remove coloured DDQ by products. The organic phase was dried ($MgSO_4$) and concentrated to a brown solid. Trituration of the crude solid with Et_2O gave the title compound as a light yellow solid (33 mg, 0.106 mmol, 69%). Physical and spectroscopic data were consistent with those reported.[59,63]

M.P. >300 °C (lit. 310 °C).[59]

IR IR (neat) ν 3434, 3307, 1645, 1575, 1454, 1390, 1330, 1262 cm^{-1}.

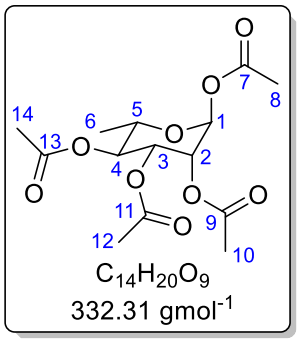
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.49 (s, 1H, **1**), 11.32 (s, 1H, **10**), 9.27-9.18 (m, 1H, **14**), 8.48 (s, 1H, **19**), 8.04 (d, *J* = 7.9 Hz, 1H, **5**), 7.79 (dt, *J* = 8.1, 0.8 Hz, 1H, **8**), 7.72 (dt, *J* = 8.1, 0.9 Hz, 1H, **17**), 7.48 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, **7**), 7.43 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, **16**), 7.31 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H, **6**), 7.23 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, **15**), 4.96 (s, 2H, **23**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 172.4 (**20**), 139.2 (**9**), 139.1 (**18**), 132.9 (**22**), 127.8 (**2/11**), 125.4 (**2/11**), 125.2 (**14**), 125.0 (**7**), 125.0 (**16**), 122.8 (**13**), 122.6 (**4**), 121.1 (**5**), 119.9 (**6**), 118.9 (**15**), 118.9 (**21**), 115.6 (**3/12**), 114.1 (**3/12**), 111.9 (**8**), 111.3 (**17**), 45.3 (**23**) ppm.

LRMS (ES^+) *m/z* = 312 $[M+H]^+$.

HRMS (ES^+) *m/z* for $C_{20}H_{14}N_3O$ calculated 312.1131, measured 312.1134; for $C_{20}H_{13}N_3NaO$ calculated 334.0951, measured 334.0951.

1,2,3,4-Tetra-*O*-acetyl-L-rhamnopyranose (4.41):



1,2,3,4-Tetra-*O*-acetyl-L-rhamnopyranose (**4.41**) was prepared according to a procedure described by Johnston and co-workers'.[255]

To a solution of L-rhamnose (2.00 g, 12.2 mmol) in pyridine (15 mL) at 0 °C under N_2 was added DMAP (15.0 mg, 0.123 mmol) followed by Ac_2O (13.8 mL, 147 mmol) dropwise over 10 min. The mixture was stirred for 10 min before warming to rt. After 15 h, the mixture was diluted with toluene (10 mL) and washed with 1M HCl (3 x 25 mL) and brine (2 x 25 mL). The organic phase was dried ($MgSO_4$) and concentrated to a light yellow oil. The crude oil was taken in toluene (10 mL) and concentrated. This process was repeated three times before the oil was dried under high vacuum to yield the title compound as a light yellow syrup (3.76 g, 11.3 mmol, 93%). Physical and spectroscopic data were consistent with those reported.[255]

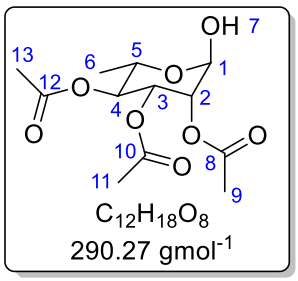
$[\alpha]_D$ −48.1 ° (*c* = 0.47, $CHCl_3$). (lit. −65 c =1.00, $CHCl_3$).[256]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.01 (d, *J* = 2.0 Hz, 1H, **1**), 5.30 (dd, *J* = 10.0, 3.5 Hz, 1H, **3**), 5.25 (dd, *J* = 3.7, 2.0 Hz, 1H, **2**), 5.12 (t, *J* = 10.0 Hz, 1H, **4**), 3.94 (dqd, *J* = 9.9, 6.4, 0.6 Hz, 1H, **5**), 2.17 (s, 3H, COC**H$_3$**), 2.16 (s, 3H, COC**H$_3$**), 2.06 (s, 3H, COC**H$_3$**), 2.00 (s, 3H, COC**H$_3$**), 1.23 (d, *J* = 6.2 Hz, 3H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 170.0 (**C**OCH$_3$), 169.8 (**C**OCH$_3$), 169.8 (**C**OCH$_3$), 168.3 (**C**OCH$_3$), 90.6 (**1**), 70.4 (**4**), 68.7 (**3**), 68.7 (**5**), 68.6 (**2**), 20.9 (COC**H$_3$**), 20.7 (COC**H$_3$**), 20.7 (COC**H$_3$**), 20.6 (COC**H$_3$**), 17.4 (**6**) ppm.

LRMS (ES$^+$) *m/z* = 355 [M+Na]$^+$.

2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranose (4.42):



2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranose (**4.42**) was prepared according to a procedure described by Lee and co-workers'.[143]

To a solution of 1,2,3,4-tetra-*O*-acetyl-L-rhamnopyranose (**4.41**, 3.35 g, 10.1 mmol) in THF (10 mL) at 0 °C under N_2 was added NH_3 (7 M in MeOH, 2.2 mL, 15.1 mmol) dropwise before warming to rt. After 3 h, a further portion of NH_3 (7 M in MeOH, 1.1 mL, 7.55 mmol) was added and the mixture stirred for 17 h before being concentrated under reduced pressure to a light yellow syrup. Trituration of the crude syrup with Et_2O gave a 10:1 (*α:β*) mixture of anomers of the title compound as an amorphous white solid (0.469 g, 1.62 mmol, 16%). Purification of the filtrate (Biotage Selekt, MeOH:CH_2Cl_2 = 2:98) gave a further portion of a 10:1 (*α:β*) mixture of anomers of the title compound (1.39 g, 4.79 mmol, 47%) as an amorphous white solid. Physical and spectroscopic data were consistent with those reported.[143]

$[\alpha]_D$ —22.8 ° (*c* = 0.5, $CHCl_3$, anomers equilibrated for 24 h).

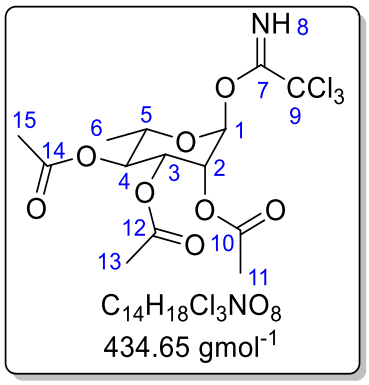
MP 94-96 °C (lit. 87-90 °C).[255]

^{1}H NMR (major) ($CDCl_3$, 400 MHz): δ = 5.32 (dd, *J* = 10.1, 3.4 Hz, 1H, **3**), 5.21 (dd, *J* = 3.4, 1.8 Hz, 1H, **2**), 5.11 (s, 1H, **1**), 5.03 (t, *J* = 10.0 Hz, 1H, **4**), 4.14 (d, *J* = 3.9 Hz, 1H, **7**), 4.10 (dq, *J* = 9.8, 6.4 Hz, 1H, **5**), 2.12 (s, 3H, COC**H$_3$**), 2.02 (s, 3H, COC**H$_3$**), 1.96 (s, 3H, COC**H$_3$**), 1.18 (d, *J* = 6.4 Hz, 3H, **6**) ppm.

^{13}C NMR (major) ($CDCl_3$, 101 MHz): δ = 170.6 (**C**OCH_3), 170.4 (**C**OCH_3), 170.4 (**C**OCH_3), 92.4 (**1**), 71.4 (**4**), 70.6 (**2**), 69.1 (**3**), 66.7 (**5**), 21.2 (CO**C**H_3), 21.1 (CO**C**H_3), 21.0 (CO**C**H_3), 17.8 (**6**) ppm.

LRMS (ES$^+$) *m/z* = 313 $[M+Na]^+$.

2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl 1-trichloroacetimidate (4.43):



2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (**4.43**) was prepared according to a procedure described by Lee and co-workers'.[143]

To a solution of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranose (**4.42**, 0.469 g, 1.62 mmol) in CH_2Cl_2 (16.5 mL) at 0 °C under N_2 was added Cl_3CCN (2.42 mL, 24.1 mmol) followed by DBU (0.05 mL, 0.335 mmol) and stirred. After 15 min, the mixture was warmed to rt and stirred for a further 30 min before being concentrated to a light yellow oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 1:4 to 1:1) gave the title compound as a colourless oil (0.638 g, 1.47 mmol, 91%). Spectroscopic data were consistent with those reported.[143]

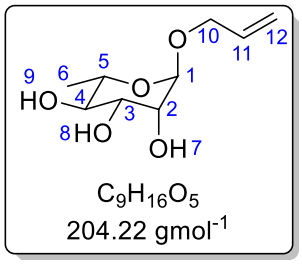
$[\alpha]_D$ −47.0 ° (*c* = 0.41, $CHCl_3$), (lit. −52.0, *c* = 1.00, $CHCl_3$).[143]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.74 (s, 1H, **8**), 6.21 (d, *J* = 2.0 Hz, 1H, **1**), 5.47 (dd, *J* = 3.5, 2.0 Hz, 1H, **2**), 5.38 (dd, *J* = 10.2, 3.5 Hz, 1H, **3**), 5.18 (t, *J* = 10.0 Hz, 1H, **4**), 4.10 (dqd, *J* = 9.5, 6.3, 0.6 Hz, 1H, **5**), 2.20 (s, 3H, COC**H$_3$**), 2.08 (s, 3H, COC**H$_3$**), 2.01 (s, 3H, COC**H$_3$**), 1.28 (d, *J* = 6.2 Hz, 3H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 169.9 (**C**OCH_3), 169.9 (**C**OCH_3), 169.8 (**C**OCH_3), 160.0 (**C**$NHCCl_3$), 94.7 (**1**), 90.6 ($CNHCCl_3$), 70.3 (**4**), 69.3 (**5**), 68.8 (**3**), 68.1 (**2**), 20.8 ($COCH_3$), 20.8 ($COCH_3$), 20.6 ($COCH_3$), 17.5 (**6**) ppm.

LRMS (ES^+) *m/z* = 457 $[M+Na]^+$

Allyl α-L-rhamnopyranoside (4.44):



$C_9H_{16}O_5$
204.22 gmol^{-1}

Allyl α-L-rhamnopyranoside (**4.44**) was prepared according to a procedure described by Fürstner and co-workers'.[257]

To a solution of L-rhamnose (2.00 g, 12.2 mmol) in allyl alcohol (15 mL, 22.1 mmol) at rt under N_2 was added H_2SO_4 (0.2 mL) and warmed to reflux. After 1 h, the mixture was cooled to rt and K_2CO_3 (0.032 g) was added and the mixture concentrated to a viscous brown syrup. Purification of the crude syrup via flash chromatography (EtOAc to MeOH:EtOAc = 2:98) gave the title compound as a colourless oil (1.10 g, 5.39 mmol, 44%). Physical and spectroscopic data were consistent with those reported.[257]

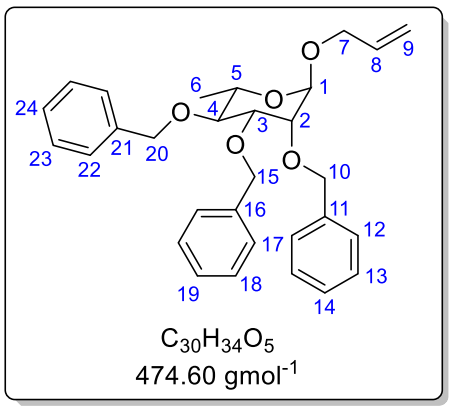
$[\alpha]_D$ −73.9 ° (*c* = 0.44, $CHCl_3$), (lit. −83.0, *c* = 1.29, CH_2Cl_2).[257]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.90 (dddd, *J* = 17.1, 10.4, 6.1, 5.1 Hz, 1H, **11**), 5.30 (dq, *J* = 17.2, 1.6 Hz, 1H, **12a**), 5.21 (dq, *J* = 10.4, 1.3 Hz, 1H, **12b**), 4.82 (d, *J* = 1.3 Hz, 1H, **1**), 4.18 (ddt, *J* = 13.1, 5.0, 1.6 Hz, 1H, **10a**), 4.03-3.93 (m, 2H, **10b+2**), 3.88-3.62 (m, 3H, **3+5+OH**), 3.48 (br t, *J* = 9.4 Hz, 3H, **4+OH+OH**), 1.32 (d, *J* = 6.2 Hz, 3H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 133.6 (**11**), 117.6 (**12**), 98.8 (**1**), 73.1 (**4**), 71.8 (**3**), 71.0 (**2**), 68.1 (**5**), 68.0 (**10**), 17.5 (**6**) ppm.

LRMS (EI) *m/z* (%) = 131 (3), 100 (20), 87 (12), 85 (10), 83 (4), 74 (), 73 (), 71 (100), 60 (94), 58 (48), 57 (27), 41 (41).

Allyl 2,3,4-tri-*O*-benzyl- α-L-rhamnopyranoside (4.45):



$C_{30}H_{34}O_5$
474.60 gmol^{-1}

Allyl 2,3,4-tri-*O*-benzyl- α-L-rhamnopyranoside (**4.45**) was prepared according to a procedure described by Heathcock and co-workers'.[145]

To a solution of allyl α-L-rhamnopyranoside (**4.44**, 0.500 g, 2.45 mmol) in DMF (10 mL) at 0 °C under N_2 was added NaH (60% dispersion in mineral oil, 0.589 g, 14.7 mmol), followed by Bu_4NI (0.277 g, 0.750 mmol) and BnBr (1.75 mL, 14.7 mmol) and warmed to rt. After 16 h, MeOH (2 mL) was added and stirred for 1 h. The resulting mixture was taken in Et_2O (20 mL) and washed with H_2O (20 mL), $Na_2S_2O_3$ (10% solution in H_2O, 20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated to a colourless oil. Purification of the crude oil via flash chromatography (Biotage Selekt, EtOAc:hexane = 2:98 to 1:4) gave the title compound as a colourless oil (1.06 g, 2.23 mmol, 91%). Physical and spectroscopic data were consistent with those reported.[145]

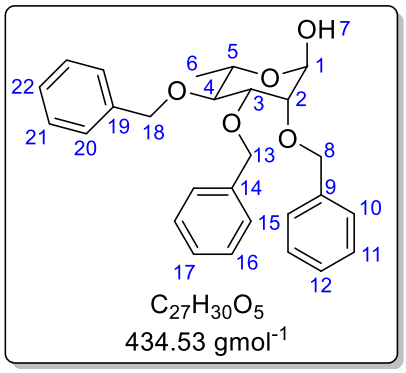
$[\alpha]_D$ −40.7 ° (*c* = 0.58, $CHCl_3$), (lit. −15.0, *c* = 2.01, CH_2Cl_2).[145]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.41-7.27 (m, 15H, 3 x $OCH_2C_6\mathbf{H_5}$), 5.84 (dddd, *J* = 17.0, 10.5, 6.1, 5.3 Hz, 1H, **8**), 5.22 (dq, *J* = 17.2, 1.6 Hz, 1H, **9a**), 5.16 (dq, *J* = 10.4, 1.5 Hz, 1H, **9b**), 4.96 (d, *J* = 10.8 Hz, 1H, $OC\mathbf{H_2}C_6H_5$), 4.82 (d, *J* = 1.6 Hz, 1H, **1**), 4.78 (d, *J* = 12.5 Hz, 1H, $OC\mathbf{H_2}C_6H_5$), 4.73 (d, *J* = 12.5 Hz, 1H, $OC\mathbf{H_2}C_6H_5$), 4.68-4.63 (m, 3H, $OC\mathbf{H_2}C_6H_5$), 4.13 (ddt, *J* = 13.0, 5.0, 1.4 Hz, 1H, **7a**), 3.96-3.88 (m, 2H, **3+7b**), 3.82 (dd, *J* = 2.9, 2.0 Hz, 1H, **2**), 3.73 (dq, *J* = 9.5, 6.2 Hz, 1H, **5**), 3.64 (t, *J* = 9.3 Hz, 1H, **4**), 1.35 (d, *J* = 6.1 Hz, 3H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 138.6 (2 x $OCH_2\mathbf{C}_6H_5$), 138.3 ($OCH_2\mathbf{C}_6H_5$), 133.8 (**8**), 128.3 ($OCH_2\mathbf{C}_6H_5$), 128.3 ($OCH_2\mathbf{C}_6H_5$), 128.0 ($OCH_2\mathbf{C}_6H_5$), 127.9 ($OCH_2\mathbf{C}_6H_5$), 127.6 ($OCH_2\mathbf{C}_6H_5$), 127.6 ($OCH_2\mathbf{C}_6H_5$), 127.5 ($OCH_2\mathbf{C}_6H_5$), 117.1 (**9**), 97.1 (**1**), 80.5 (**4**), 80.2 (**3**), 75.4 ($O\mathbf{C}H_2C_6H_5$), 74.8 (**2**), 72.8 ($O\mathbf{C}H_2C_6H_5$), 72.2 ($O\mathbf{C}H_2C_6H_5$), 68.1 (**5**), 67.7 (**7**), 18.0 (**6**) ppm.

LRMS (ES$^+$) *m/z* = 497 [M+Na]$^+$.

2,3,4-Tri-O-benzyl- α-L-rhamnopyranose (4.46):



$C_{27}H_{30}O_5$
434.53 gmol^{-1}

2,3,4-Tri-O-benzyl- α-L-rhamnopyranose (**4.46**) was prepared according to a procedure described by Heathcock and co-workers'.[145]

To a solution of allyl 2,3,4-tri-*O*-benzyl- α-L-rhamnopyranoside (**4.45**, 0.500 g, 1.05 mmol) in DMSO (3 mL) at rt under N_2 was added ^{t}BuOK (0.118 g, 1.05 mmol) and warmed to 100 °C. After 15 min, the mixture was diluted with Et_2O (30 mL) and washed with H_2O (30 mL). The organic phase was concentrated and the resulting yellow oil taken in acetone (5 mL) and HCl (1 M in H_2O, 1 mL) added. The mixture was warmed to reflux and stirred for 45 min before cooling to rt and quenching with sat. aqueous $NaHCO_3$ (10 mL). The mixture was concentrated to approximately 2 mL before diluting with H_2O (25 mL) and CH_2Cl_2 (30 mL) and the phases separated. The aqueous phase was washed with CH_2Cl_2 (2 x 30 mL) and the combined organics dried (Na_2SO_4) and concentrated to an off white solid. Purification of the crude solid via flash chromatography (Biotage, EtOAc:hexane = 7:93 to 6:4) gave the title compound as a 5:1 (*α*:*β*) mixture of anomers as a colorless solid (0.400 g, 0.921 mmol, 88%). Physical and spectroscopic data were consistent with those reported.[145,258]

$[\alpha]_D$ −16.0 ° (*c* = 0.5, $CHCl_3$, anomers allowed to equilibrate for 24 h)

MP 92-94 °C (lit. 88-89 °C).[145]

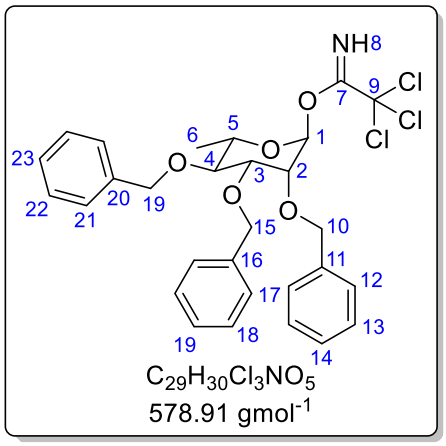
^{1}H NMR (major) ($CDCl_3$, 400 MHz): δ = 7.41-7.28 (m, 18H, 3 x $OCH_2C_6\mathbf{H_5}$+minor anomer), 5.19 (dd, J = 3.2, 2.0 Hz, 1H, **1**), 4.96 (d, J = 10.9 Hz, 1H, $OC\mathbf{H_2}C_6H_5$), 4.80 (d, J = 12.5 Hz, 1H, $OC\mathbf{H_2}C_6H_5$), 4.73 (d, J = 12.5 Hz, 1H, $OC\mathbf{H_2}C_6H_5$), 4.68-4.64 (m, 3H, $OC\mathbf{H_2}C_6H_5$), 3.98-3.89 (m, 2H, **3+5**), 3.83 (dd, J = 3.1, 2.0 Hz, 1H, **2**), 3.65 (t, J = 9.3 Hz, 1H, **4**), 2.35 (br s, 1H, **7**) 1.34 (d, J = 6.2 Hz, 3H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ =138.6 ($OCH_2\mathbf{C}_6H_5$), 138.5 ($OCH_2\mathbf{C}_6H_5$), 138.3

(major) ($OCH_2\mathbf{C}_6H_5$), 128.6 ($OCH_2\mathbf{C}_6H_5$), 128.5 ($OCH_2\mathbf{C}_6H_5$), 128.4 ($OCH_2\mathbf{C}_6H_5$), 128.4 ($OCH_2\mathbf{C}_6H_5$), 128.2 ($OCH_2\mathbf{C}_6H_5$), 128.1 ($OCH_2\mathbf{C}_6H_5$), 128.0 ($OCH_2\mathbf{C}_6H_5$), 128.0 ($OCH_2\mathbf{C}_6H_5$), 127.9 ($OCH_2\mathbf{C}_6H_5$), 127.8 ($OCH_2\mathbf{C}_6H_5$), 127.8 ($OCH_2\mathbf{C}_6H_5$), 127.7 ($OCH_2\mathbf{C}_6H_5$), 127.7 ($OCH_2\mathbf{C}_6H_5$), 127.6 ($OCH_2\mathbf{C}_6H_5$), 127.5 ($OCH_2\mathbf{C}_6H_5$), 93.0 (**1**), 80.5 (**4**), 79.6 (**3**), 75.3 ($O\mathbf{C}H_2C_6H_5$), 74.9 (**2**), 72.9 ($O\mathbf{C}H_2C_6H_5$), 72.3 ($O\mathbf{C}H_2C_6H_5$), 68.2 (**5**), 18.1 (**6**) ppm.

LRMS (ES^+) *m/z* = 457 $[M+Na]^+$.

2,3,4-Tri-O-benzyl α-L-rhamnopyranose 1-trichloroacetimidate (4.47):



2,3,4-Tri-O-benzyl α-L-rhamnopyranose 1-trichloroacetimidate (**4.47**) was prepared according to a procedure described by Kumar and co-workers'.[259]

To a solution of 2,3,4-Tri-O-benzyl- α-L-rhamnopyranose (**4.46**, 0.296 g, 0.681 mmol) in CH_2Cl_2 (7 mL) at 0 °C under N_2 was added CCl_3CN (0.69 mL, 6.90 mmol) followed by DBU (0.01 mL, 0.069 mmol) and stirred. After 10 min, the mixture was warmed to rt and stirred for a further 1 h before being concentrated to a yellow oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 1:9 to 1:4) gave the title compound as a colourless oil (0.271 g, 0.468 mmol, 69%). Physical and spectroscopic data were consistent with those reported.[259]

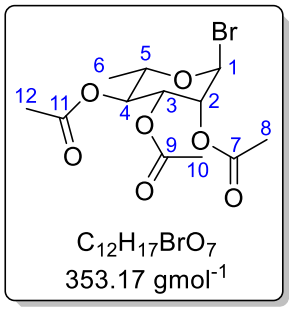
$[\alpha]_D$ −41.1 ° (*c* = 0.40, $CHCl_3$). (lit. −34.0, no concentration given, $CHCl_3$).[260]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.52 (s, 1H, **8**), 7.46-7.27 (m, 15 H, 3 x $OCH_2C_6\mathbf{H_5}$), 6.26 (d, J = 1.8 Hz, 1H, **1**), 4.98 (d, J = 10.8 Hz, 1H, $OC\mathbf{H}_2C_6H_5$), 4.78 (s, 2H, $OC\mathbf{H}_2C_6H_5$), 4.67 (d, J = 10.8 Hz, 1H, $OC\mathbf{H}_2C_6H_5$), 4.65 (d, J = 11.9 Hz, 1H, $OC\mathbf{H}_2C_6H_5$), 4.60 (d, J = 11.9 Hz, 1H, $OC\mathbf{H}_2C_6H_5$), 3.98-3.83 (m, 3H, **2**+**3**+**5**), 3.72 (t, J = 9.4 Hz, 1H, **4**), 1.37 (d, J = 6.2 Hz, 3H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 160.5 (**7**), 138.3 ($OCH_2\mathbf{C}_6H_5$), 138.1 ($OCH_2\mathbf{C}_6H_5$), 137.9 ($OCH_2\mathbf{C}_6H_5$), 128.4 ($OCH_2\mathbf{C}_6H_5$), 128.4 ($OCH_2\mathbf{C}_6H_5$), 128.4 ($OCH_2\mathbf{C}_6H_5$), 128.2 ($OCH_2\mathbf{C}_6H_5$), 127.9 ($OCH_2\mathbf{C}_6H_5$), 127.8 ($OCH_2\mathbf{C}_6H_5$), 127.8 ($OCH_2\mathbf{C}_6H_5$), 127.7 ($OCH_2\mathbf{C}_6H_5$), 96.0 (**1**), 91.0 (**9**), 79.8 (**4**), 78.9 (**3**), 75.6 ($O\mathbf{C}H_2C_6H_5$), 73.8 (**2**), 72.8 ($O\mathbf{C}H_2C_6H_5$), 72.3 ($O\mathbf{C}H_2C_6H_5$), 71.1 (**5**), 18.0 (**6**) ppm.

LRMS (ES^+) *m/z* = unable to collect due to instability.

2,3,4-Tri-*O*-acetyl--α-L-rhamnopyranosyl bromide (4.49):



$C_{12}H_{17}BrO_7$
353.17 gmol^{-1}

2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl bromide (**4.49**) was prepared according to a procedure described by Pietruszka and co-workers'.[261]

To a solution of -L-rhamnose (1.00 g, 6.09 mmol) in Ac_2O (5 mL) at rt under N_2 was added HBr (33% in AcOH, 1.5 mL) and stirred. After complete dissolution of the solid (around 5 min), a further portion of HBr (33% in AcOH, 7.5 mL) was added and the mixture stirred. After 2 h the mixture was concentrated under reduced pressure and the crude oil taken in PhMe (20 mL) and concentrated. The process was repeated 3 times to give the title compound as a light yellow solid which was used without further purification (2.14 g, 6.06 mmol, quant). Physical and spectroscopic data was consistent with those reported.[261,262]

$[\alpha]_D$ —138.3 ° (*c* = 0.63, $CHCl_3$). (lit. —181.0 °, no concentration given, $CHCl_3$).[263]

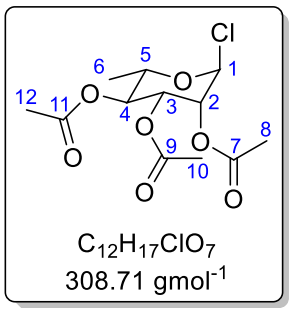
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.26 (dd, *J* = 1.6, 0.6 Hz, 1H, **1**), 5.68 (dd, *J* = 10.2, 3.5 Hz, 1H, **3**), 5.45 (dd, *J* = 3.5, 1.9 Hz, 1H, **2**), 5.16 (t, *J* = 10.0 Hz, 1H, **4**), 4.11 (dqd, *J* = 9.9, 6.2, 0.7 Hz, 1H, **5**), 2.17 (s, 3H, COC**H$_3$**), 2.09 (s, 3H, COC**H$_3$**), 2.01 (s, 3H, COC**H$_3$**), 1.29 (d, *J* = 6.2 Hz, 3H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 169.8 (**C**OCH_3), 169.7 (**C**OCH_3), 169.6 (**C**OCH_3), 83.7 (**1**), 72.4 (**2**), 71.1 (**5**), 70.3 (**4**), 67.9 (**3**), 20.8 (CO**C**H_3), 20.7 (CO**C**H_3), 20.6 (CO**C**H_3), 16.9 (**6**) ppm.

LRMS (ES^+) *m/z* = unable to collect due to instability.

2,3,4-Tri-*O*-acetyl--α-L-rhamnopyranosyl chloride (4.50):

2,3,4-Tri-*O*-acetyl--α-L-rhamnopyranosyl chloride (**4.50**) was prepared according to a procedure described by Lassak and co-workers'.[264]



To L-rhamnose monohydrate (1.00 g, 5.49 mmol) at rt under N_2 was added AcCl (2.2 mL) and stirred. After 2 h, mixture diluted with CH_2Cl_2 (15 mL) and washed with sat. aq. $NaHCO_3$ (20 mL), dried (Na_2SO_4) and concentrated to a yellow oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 1:4) gave the title compound as a colourless crystalline solid (0.774 g, 2.51 mmol, 46%). NMR data were consistent with those reported.[146,264]

$[\alpha]_D$ −124.7 ° (*c* = 0.43, $CHCl_3$).

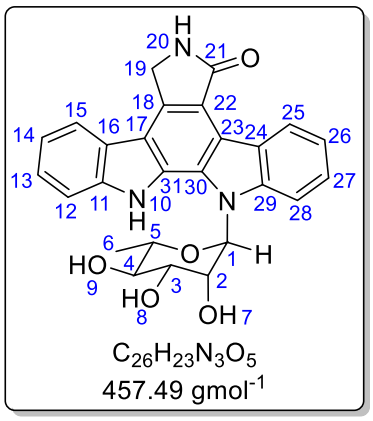
MP 71-73 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.94 (d, *J* = 1.3 Hz, 1H, **1**), 5.57 (dd, *J* = 10.3, 3.4 Hz, 1H, **3**), 5.39 (dd, *J* = 3.4, 1.7 Hz, 1H, **2**), 5.15 (t, *J* = 10.1 Hz, 1H, **4**), 4.17 (dqd, *J* = 9.9, 6.3, 0.7 Hz, 1H, **5**), 2.18 (s, 3H, OCOC**H$_3$**), 2.08 (s, 3H, OCOC**H$_3$**), 2.01 (s, 3H, OCOC**H$_3$**), 1.28 (d, J = 6.2 Hz, 3H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 169.8 (O**C**OCH$_3$), 169.8 (O**C**OCH$_3$), 169.7 (O**C**OCH$_3$), 89.0 (**1**), 71.9 (**2**), 70.4 (**4**), 69.4 (**5**), 67.7 (**3**), 20.8 (OCO**C**H$_3$), 20.7 (OCO**C**H$_3$), 20.6 (OCO**C**H$_3$), 17.1 (**6**) ppm.

LRMS (ES^+) *m/z* = unable to collect due to instability.

K252d (3.01):



$C_{26}H_{23}N_3O_5$

457.49 gmol^{-1}

To a solution of 4b,6,7,12,12b,13-Hexahydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5-one (**4.39**, 35.0 mg, 0.111 mmol) in DMSO:EtOH (1:1, 1.5 mL) at rt under N_2 was added rhamnose monohydrate (36.6 mg, 0.200 mmol) and $(NH_4)SO_4$ (7.3 mg, 0.056 mmol). The mixture was stirred for 44 h and partially concentrated under reduced pressure before THF (0.75 mL) and DDQ (38.0 mg, 0.166 mmol) were added. The mixture was stirred for a further 3 h before EtOAc (10 mL) was added. The mixture was washed with sat. aqueous $NaHCO_3$ (7 x 10 mL) until the coloured DDQ by-products were removed. The combined organics were dried ($MgSO_4$) and concentrated to a dark orange solid. Purification of the crude solid via flash chromatography (MeOH:EtOAc = 1:99, column neutralised with NEt_3) gave staurosporine aglycone (**1.10**, 22.0 mg, 0.071 mmol, 64%) and K252d as a ~1:1 mixture of anomers (18.0 mg, 0.039 mmol, 35%). The anomers could be separated via flash chromatography (acetone:hexane = 1:1) to give K252d as a pale yellow solid and β-K252d as an off-white/light yellow solid.

$[\alpha]_D$ +30.0 ° (*c* = 0.18, MeOH), (lit. +35.0 °, *c* = 0.4, MeOH).[147]

M.P. 235-240 °C (decomp.), (lit. 240~245 °C decomp.)[147]

IR IR (neat) ν 3353, 1666, 1588, 1459, 1329, 1246, 1047, 744 cm^{-1}.

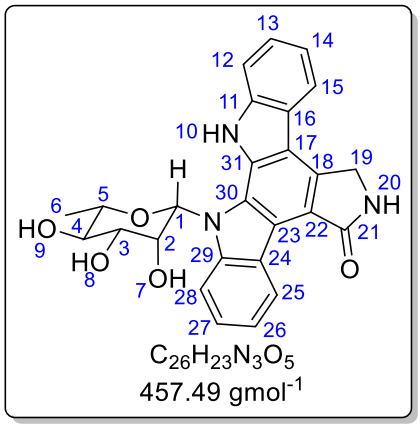
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.68 (s, 1H, **10**), 9.47 (d, *J* = 7.7 Hz, 1H, **25**), 8.55 (br s, 1H, **20**), 8.07 (d, *J* = 7.9 Hz, 1H, **15**), 7.69 (d, *J* = 8.6 Hz, 1H, **28**), 7.60 (br d, *J* = 8.1 Hz, 1H, **12**), 7.53-7.46 (m, 2H, **13+27**), 7.32 (t, *J* = 7.4 Hz, 1H, **14**), 7.27 (t, *J* = 7.6 Hz, 1H, **26**), 6.69 (br d, *J* = 2.3 Hz, 1H, **9**), 6.39 (d, *J* = 9.4 Hz, 1H, **1**), 5.39 (d, *J* = 3.5 Hz, 1H, **8**), 5.00 (m, 3H, **19+7**), 4.52-4.43 (m, 2H, **2+5**), 4.18 (br d, *J* = 2.7 Hz, 1H, **3**), 4.05 (br s, 1H, **4**), 1.70 (d, *J* = 7.2 Hz, 3H, **6**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 172.2 (**21**), 140.2 (**29**), 139.0 (**11**), 133.9 (**18**), 127.5 (**31**), 125.6 (**25**), 125.2 (**27**), 125.1 (**13**), 124.5 (**30**), 122.2 (**24**), 121.8 (**16**), 121.2 (**15**), 119.8 (**14**), 119.3 (**26**), 118.6 (**22**), 117.5 (**23**), 114.9 (**17**), 111.2 (**12**), 109.8 (**28**), 77.1 (**1**), 76.5 (**5**), 71.6 (**3**), 71.4 (**4**), 66.9 (**2**), 45.1 (**19**), 15.3 (**6**) ppm.

LRMS (ES^+) *m/z* = 458 $[M+H]^+$.

HRMS (ES^+) *m/z* for $C_{26}H_{24}N_3O_5$ calculated 458.1710, found 458.1716.

β-K252d (4.51):



[α]$_D$ +14.4 ° (*c* = 0.08, MeOH).

M.P. 235-240 °C decomp.

IR IR (neat) ν 3397, 1664, 1588, 1460, 1330, 1247, 1067, 743 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.04 (s, 1H, **10**), 9.50 (dd, *J* = 7.9, 0.7 Hz, 1H, **25**), 8.51 (s, 1H, **20**), 8.05 (d, *J* = 7.9 Hz, 1H, **15**), 7.86 (d, *J* = 8.6 Hz, 1H, **28**), 7.70 (dt, *J* = 8.1, 0.7 Hz, 1H, **12**), 7.48 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H, **13**), 7.47 (ddd, *J* = 8.3, 7.0, 1.5 Hz, 1H, **27**), 7.30 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H, **14**), 7.29 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H, **26**), 6.44 (s, 1H, **1**), 5.62 (d, *J* = 4.8 Hz, 1H, **7**), 5.25 (d, *J* = 4.6 Hz, 1H, **9**), 5.05 (d, *J* = 5.9 Hz, 1H, **8**), 4.97 (s, 2H, **19**), 4.04 (t, *J* = 3.4 Hz, 1H, **2**), 3.98-3.92 (m, 1H, **3**), 3.84-3.73 (m, 2H, **4**+**5**), 1.46 (d, *J* = 5.5 Hz, 3H, **6**) ppm.

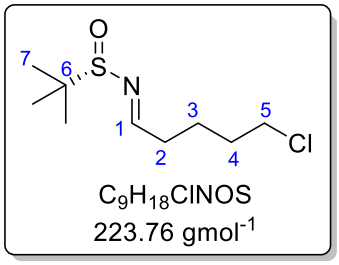
^{13}C NMR (DMSO-d_6, 101 MHz): δ = 172.3 (**21**), 138.8 (**29**), 138.1 (**11**), 133.8 (**18**), 128.2 (**31**), 126.2 (**30**), 125.6 (**25**), 125.2 (**13+27**), 122.7 (**24**), 121.8 (**16**), 121.1 (**15**), 119.6 (**26**), 119.6 (**14**), 118.3 (**22**), 117.1 (**23**), 114.7 (**17**), 111.0 (**12**), 110.4 (**28**), 84.9 (**1**), 76.0 (**4**), 72.8 (**3**), 72.0 (**5**), 71.4 (**2**), 45.1 (**19**), 18.5 (**6**) ppm.

LRMS (ES$^+$) *m/z* = 458 $[M+H]^+$.

HRMS (ES$^+$) *m/z* for $C_{26}H_{24}N_3O_5$ calculated 458.1710, found 458.1708.

(+)-(*S*)-*N*-[(1*E*)-5-Chloropentylidene]-2-methylpropane-2-sulfinamide (5.99):

Prepared according to a procedure described by D. E. Wheatley.[210]



To a solution of methyl 5-chloropentanoate (8.00 g, 53.1 mmol) in CH_2Cl_2 (80 mL) at –78 °C under N_2 was added DIBAL-H (58.4 mL, 1M in CH_2Cl_2, 58.4 mmol) via dropping funnel over 45 min, and the reaction stirred at this temperature for a further 2 h. The reaction was quenched with 2M HCl (100 mL), warmed to rt and stirred vigorously for 2 h until both phases were colourless. The phases were separated and the aqueous washed with CH_2Cl_2 (100 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and added via cannula over 1 h to a stirred solution of (*S*)-(–)-2-methyl-2-propanesulfinamide (7.09 g, 58.5 mmol), $Ti(OEt)_4$ (25 mL, 119 mmol) in CH_2Cl_2 (50 mL) at 0 °C under N_2. The mixture was warmed to rt and stirred for 20 h. The mixture was quenched with H_2O (100 mL) and brine (100 mL) and stirred for 1.5 h. The mixture was filtered through a pad of celite, washed with CH_2Cl_2 (100 mL) and the phases separated. The aqueous was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organics washed with brine (200 mL), dried ($MgSO_4$) and concentrated to a light yellow oil. Purification of the crude oil via flash chromatography gave the title compound as a light yellow oil (5.33 g, 23.8 mmol, 45%). Physical and spectroscopic data were consistent with those reported.[207]

$[\alpha]_D$ +216.7 ° (*c* = 1.20, $CHCl_3$), (lit. +222, *c* = 1.2, $CHCl_3$).[207]

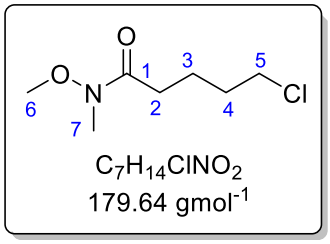
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.06 (t, *J* = 4.4 Hz, 1H, **1**), 3.55 (t, *J* = 6.2 Hz, 2H, **5**), 2.55 (td, *J* = 7.0, 4.4 Hz, 2H, **2**), 1.89-1.79 (m, 4H, **3**+**4**), 1.18 (s, 9H, **7**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 168.7 (**1**), 56.5 (**6**), 44.7 (**5**), 35.1 (**2**), 31.8 (**4**), 22.6 (**3**), 22.3 (**7**) ppm.

LRMS (ES^+) *m/z* = 224 $[M+H]^+$.

5-Chloro-*N*-methoxy-*N*-methylpentamide (5.126):

Prepared according to a procedure described by D. E. Wheatley.[210]



$C_7H_{14}ClNO_2$
179.64 $gmol^{-1}$

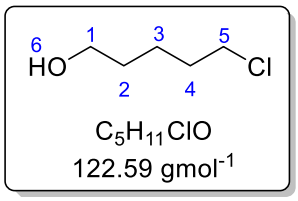
To a solution of 5-chlorovaleric acid (10 mL, 85.7 mmol) in CH_2Cl_2 (100 mL) at 0 °C under N_2 was added $(COCl)_2$ (7.97 mL, 94.2 mmol) followed by DMF (10 drops). The reaction was stirred at 0 °C for 30 min, warmed to rt and stirred for a further 2.5 h until gas evolution had ceased. A solution of *N*,*O*-dimethylhydroxylamine (10.4 g, 107 mmol) in CH_2Cl_2 (300 mL) was cooled to 0 °C and NEt_3 (30 mL, 215 mmol) was added. The suspension was stirred for 30 min and the freshly prepared acid chloride was added dropwise via cannula over 1 h at 0 °C. The mixture was warmed to rt and stirred for 21 h. The reaction was quenched with sat. aqueous NH_4Cl (200 mL). The phases were separated and the aqueous extracted with CH_2Cl_2 (3 x 200 mL). The combined organics were washed with brine (300 mL), dried ($MgSO_4$) and concentrated to a yellow oil. Purification of the crude oil via flash chromatography (EtOAC:hexane = 1:3) gave the title compound as a colourless oil (13.6 g, 64.5 mmol, 75%). Spectroscopic data were consistent with those reported.[265]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.67 (s, 2H, **6**), 3.55 (t, *J* = 6.4 Hz, 2H, **5**), 3.17 (s, 3H, **7**), 2.45 (br t, *J* = 6.8 Hz, 2H, **2**), 1.88-1.71 (m, 4H, **3**+**4**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 173.6 (**1**), 61.0 (**7**), 44.4 (**5**), 31.9 (**6**+**4**), 30.6 (**2**), 21.6 (**3**) ppm.

LRMS (ES^+) *m/z* = 180 $[M+H]^+$

5-Chloropentan-1-ol (5.124):



5-Chloropentan-1-ol was isolated as colourless oil.[266]

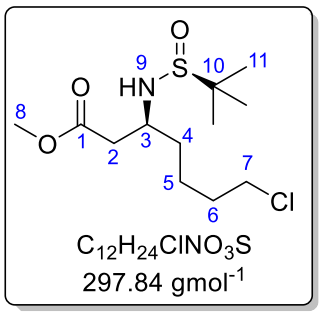
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.67 (br t, *J* = 6.2 Hz, 2H, **5**), 3.56 (t, *J* = 6.7 Hz, 2H, **1**), 1.87-1.77 (m, 2H, **2**), 1.66-1.48 (m, 4H, **3**+**4**), 1.32 (br s, 1H, **6**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 62.4 (**5**), 44.9 (**1**), 32.2 (**2**), 31.8 (**4**), 23.1 (**3**) ppm.

LRMS (EI) *m/z* = 121 $[MCl^{35}]^{+\bullet}$, 123 $[MCl^{37}]^{+\bullet}$, 91 $[MCl^{35}\text{-}CH_2OH]^{+\bullet}$, 93 $[MCl^{37}\text{-}CH_2OH]^{+\bullet}$.

(+)-Methyl (*S*)-3-(((*S*)-tert-butylsulfinyl)amino)-7-chloroheptanoate (5.127):

Prepared according to a procedure described by D. E. Wheatley.[210]



$C_{12}H_{24}ClNO_3S$
297.84 gmol^{-1}

A solution of LDA (4.6 mL, 1M in THF/hexanes, 4.6 mmol) in anhydrous THF (10 mL) was to −78 °C. Methyl acetate (0.36 mL, 4.47 mmol) was added dropwise and the mixture stirred at this temperature for 40 min. $ClTi(OiPr)_3$ (9.2 mL, 1M in hexanes, 9.2 mL, was added dropwise and the mixture stirred for 1 h in which time it turned a deep orange colour. A solution of (+)-(*S*)-N-[(1*E*)-5-chloropentylidene]-2-methylpropane-2-sulfinamide (**5.99**, 500.3 mg, 2.24 mmol) in THF (2 mL) added dropwise over 5 min. The mixture was stirred at this temperature for 2.5 h before quenching with sat. aqueous NH_4Cl (10 mL) and warming to rt. The solution was poured into brine (40 mL), diluted with EtOAc (40 mL) and stirred for 30 min. The organic was decanted and EtOAc (50 mL) added and stirred for a further 30 min. The organic layer was again decanted and the aqueous extracted EtOAc (3 x 50 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and concentrated to a yellow oil. Purification of the crude oil via flash chromatography (Et_2O:$CHCl_3$ = 4:6) gave the title compound as a yellow oil (477 mg, 1.60 mmol, 72%). Integration of the NH peaks in the ^{1}H NMR of the crude reaction mixture gave a *d.r.* of 49:1.

$[\alpha]_D$ +58.8 ° (*c* = 0.97, $CHCl_3$)

IR IR (neat) ν 3215, 2952, 1731, 1436, 1197, 1050 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.11 (d, *J* = 8.7 Hz, 1H, **9**), 3.67 (s, 3H, **8**), 3.58-3.47 (m, 3H, **3+7**), 2.77 (dd, *J* = 16.1, 5.3 Hz, 1H, **2**), 2.60 (dd, *J* = 16.0, 5.5 Hz, 1H, **2'**), 1.83-1.69 (m, 2H, **6**), 1.66-1.42 (m, 4H, **4+5**), 1.20 (s, 9H, **11**) ppm.

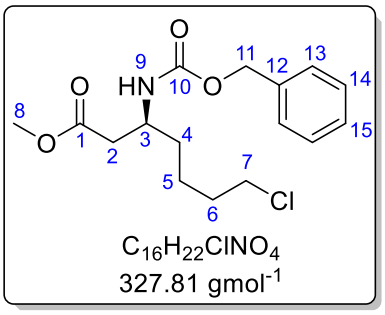
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 172.3 (**1**), 55.9 (**10**), 53.6 (**3**), 51.6 (**8**), 44.7 (**7**), 40.2 (**2**), 34.6 (**4**), 31.9 (**6**), 23.2 (**5**), 22.6 (**11**) ppm.

LRMS (ES$^+$) *m/z* = 298 $[M+H]^+$

HRMS (ES$^+$) *m/z* for $C_{12}H_{25}ClNO_3S$ calculated 298.1238, measured 298.1237; for $C_{12}H_{24}ClNNaO_3S$ calculated 320.1058, measured 320.1056.

Methyl (*S*)-3-(((benzyloxy)carbonyl)amino)-7-chloroheptanoate (5.128):

Prepared according to a procedure described by D. E. Wheatley.[210]



To a solution of (+)-methyl (*S*)-3-(((*S*)-tert-butylsulfinyl)amino)-7-chloroheptanoate (**5.127**, 1.00 g, 3.36 mmol) in 1,4-dioxane (5 m) at 0 °C under N_2 was added conc. HCl (0.87 mL) dropwise and stirred at this temperature for 1 h. The mixture was concentrated under reduced pressure, the residue dissolved in CH_2Cl_2 (3 mL) and again concentrated. This process was repeated a further 3 times before the residue was dissolved in THF (5 mL) and K_2CO_3 (692 mg, 5.01 mmol) and Cbz-Cl (0.72mL, 5.04 mmol) were added. The mixture was stirred at rt for 1 h before being quenched with H_2O (10mL). EtOAc (10 mL) was added and the phases separated. The aqueous phase was washed with EtOAc (3 x 10 mL) and the combined organics dried ($MgSO_4$) and conc to a light yellow oil. Purification of the crude oil via flash chromatography (Et_2O:hexane = 3:7) gave the title compound as a light yellow oil (771 mg, 2.35 mmol, 70%).

$[\alpha]_D$ —50.2 ° (*c* = 0.43, $CHCl_3$)

IR IR (neat) ν 3336, 2951, 1697, 1522, 1437, 1233, 1062 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ =7.41-7.30 (m, 5H, **13+14+15**), 5.22 (br d, *J* = 8.8 Hz, 1H, **9**), 5.10 (s, 2H, **11**), 4.05-3.94 (m, 1H, **3**), 3.68 (s, 3H, **8**), 3.57-3.47 (m, 2H, **7**), 2.66-2.49 (m, 2H, **2**), 1.89-1.69 (m, 2H, **6**), 1.66-1.42 (m, 4H, **4+5**) ppm.

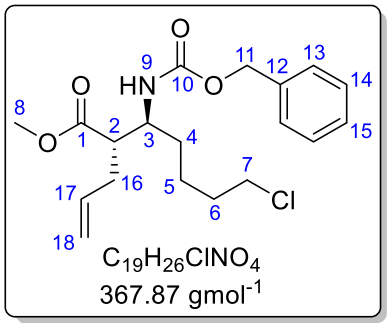
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.9 (**1**), 155.8 (**10**), 136.5 (**12**), 128.5 (**14**), 128.1 (**15**), 128.0 (**13**), 66.7 (**11**), 51.7 (**8**), 47.9 (**3**), 44.7 (**7**), 38.7 (**2**), 33.6 (**4**), 32.1 (**6**), 23.4 (**5**) ppm.

LRMS (ES^+) *m/z* = 328 $[M^{35}Cl+H]^+$, 330 $[M^{37}Cl+H]^+$.

HRMS (ES^+) *m/z* for $C_{16}H_{22}ClNNaO_4$ calculated 350.1130, measured 350.1133.

Methyl (2*S*,3*S*)-2-allyl-3-(((benzyloxy)carbonyl)amino)-7-chloroheptanoate (5.129):

Prepared according to a procedure described by D. E. Wheatley.[210]



To a solution of LDA (3.05 mL, 2 M in THF, 6.10 mmol) at −50 °C under N_2 was added methyl (*S*)-3-(((benzyloxy)carbonyl)amino)-7-chloroheptanoate (**5.128**, 502 mg, 1.53 mmol) in THF (10 mL) dropwise and stirred. After 45 min, allyl iodide (0.35 mL, 3.83 mmol) was added dropwise and the mixture stirred for a further 3.5 h before the mixture was quenched with sat. aqueous NH_4Cl (10 mL). The mixture was warmed to rt and the phases separated. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to a dark yellow oil. Purification of the crude oil via flash column chromatography (EtOAc:hexane = 1:19 to 1:5) gave the title compound as a light yellow oil (318 mg, 0.866 mmol, 56%). Integration of the NH peak in the ^{1}H NMR of the crude reaction mixture gives *d.r.* 10:1 *anti:syn*.

$[\alpha]_D$ −39.4 ° (*c* = 0.39, $CHCl_3$)

IR IR (neat) ν 3339, 2951, 1716, 1507, 1438, 1223, 1053, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.41-7.29 (m, 5H, **13+14+15**), 5.75 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H, **17**), 5.55 (br d, *J* = 9.9 Hz, 1H, **9**), 5.17-5.02 (m, 4H, **11+18**), 3.94-3.84 (m, 1H, **3**), 3.68 (s, 3H, **8**), 3.56-3.45 (m, 2H, **7**), 2.65 (ddd, *J* = 8.2, 6.9, 3.8 Hz, 1H, **2**), 2.48-2.37 (m, 1H, **16a**), 2.36-2.27 (m, 1H, **16b**), 1.86-1.68 (m, 2H, **6**), 1.56-1.41 (m, 4H, **4+5**) ppm.

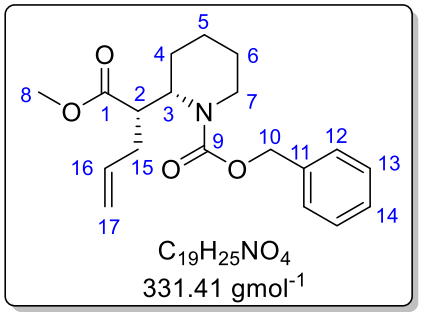
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 174.8 (**1**), 156.4 (**10**), 136.6 (**12**), 134.5 (**17**), 128.5 (**14**), 128.1 (**15**), 128.0 (**13**), 117.6 (**18**), 66.7 (**11**), 51.7 (**8**), 51.3 (**3**), 48.5 (**2**), 44.7 (**7**), 34.2 (**16**), 33.9 (**4**), 32.2 (**6**), 23.4 (**5**) ppm.

LRMS (ES$^+$) *m/z* = 368 [M^{35}Cl+H]$^+$, 370 [M^{37}Cl+H]$^+$, 390 [M^{35}Cl+Na]$^+$, 392 [M^{37}Cl+Na]$^+$.

HRMS (ES^+) *m/z* for $C_{19}H_{27}ClNO_4$ calculated 368.1623, measured 368.1628; for $C_{20}H_{26}ClNNaO_4$ calculated 390.1443, measured 390.1453.

Benzyl (*S*)-2-((*S*)-1-methoxy-1-oxopent-4-en-2-yl)piperidine-1-carboxylate (5.113):

Prepared according to a procedure described by D. E. Wheatley.[210]



To a solution of methyl (2*S*,3*S*)-2-allyl-3-(((benzyloxy)carbonyl)amino)-7-chloroheptanoate (**5.129**, 1.44 g, 3.91 mmol) in MeCN (10 mL) at rt under N_2, was added Cs_2CO_3 (5.13 g, 15.7 mmol) followed by NaI (591 mg, 3.94 mmol) and the mixture warmed to 105 °C. After 48 h, the mixture was cooled to rt and filtered. The solid was washed with MeCN (3 x 20 mL) and the combined filtrates were dried ($MgSO_4$) and concentrated to an orange oil. Purification of the crude oil via flash column chromatography (EtOAc;petroleum ether = 1:9 to 1:4) gave the title compound as a yellow oil (1.17 g, 3.52 mmol, 90%).

$[\alpha]_D$ —34.8 ° (*c* = 0.27, $CHCl_3$)

IR IR (neat) ν 2947, 1734, 1692, 1421, 1250, 1168, 697 cm^{-1}.

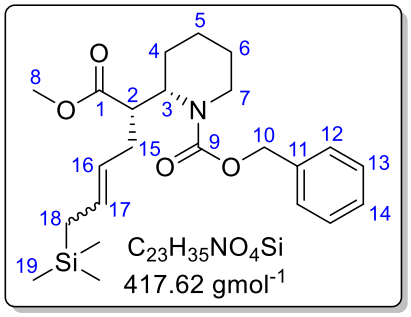
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.43-7.19 (m, 5H, **12+13+14**), 5.74 (dddd, *J* = 16.7, 10.3, 7.6, 6.2 Hz, 1H, **16**), 5.11-4.96 (m, 4H, **10+17**), 4.32 (br dd, *J* = 11.1, 3.4 Hz, 1H, **3**), 3.90 (br dd, *J* = 13.6, 3.4 Hz, 1H, **7$_{eq}$**), 3.41 (s, 3H, **8**), 3.06 (td, *J* = 10.3, 4.4 Hz, 1H, **2**), 2.95 (br t, *J* = 12.2 Hz, 1H, **7$_{ax}$**), 2.30-2.13 (m, 2H, **15**), 1.78 (br d, *J* = 13.7 Hz, 1H, **4$_{eq}$**), 1.63-1.21 (m, 5H, **4$_{ax}$, 5, 6**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 173.0 (**1**), 154.2 (**9**), 137.0 (**11**), 135.2 (**16**), 128.3 (**13**), 127.7 (**14**), 127.3 (**12**), 116.9 (**17**), 66.1 (**10**), 52.6 (**3**), 51.1 (**8**), 44.1 (**2**), 39.1 (**7**), 33.2 (**15**), 25.4 (**4**), 24.8 (**6**), 18.2 (**5**) ppm.

LRMS (ES$^+$) *m/z* = 332 [M+H]$^+$.

HRMS (ES$^+$) *m/z* for $C_{19}H_{25}NNaO_4$ calculated 354.1676, measured 354.1682.

Benzyl (S)-2-((S)-1-methoxy-1-oxo-6-(trimethylsilyl)hex-4-en-2-yl)piperidine-1-carboxylate (5.114):



To a solution of benzyl (*S*)-2-((*S*)-1-methoxy-1-oxopent-4-en-2-yl)piperidine-1-carboxylate (**5.113**, 415 mg, 1.25 mmol) in allyl TMS (1 mL) at rt under N_2 was added, 1,4-benzoquinone (13.5 mg, 0.125 mmol) followed by Stewart-Grubbs catalyst© (35.0 mg, 0.053 mmol) and warmed to reflux. After 1 h, a further portion of Stewart-Grubbs catalyst© (18.3 mg, 0.032 mmol) followed by allyl TMS (0.3 mL). After a further 1 h, 1,4-benzoquinone (0.007 g, 0.065 mmol) Stewart-Grubbs catalyst© (17.0 mg, 0.030 mmol) were added followed by allyl TMS (0.3 mL) and the mixture heated at reflux for a further 16 h. A further portion of 1,4-benzoquinone (0.007 g, 0.065 mmol, total = 27.5 mg, 0.254 mmol) Stewart-Grubbs catalyst© (18.0 mg, 0.032 mmol, total = 88.3 mg, 0.155 mmol) and allyl TMS (0.3 mL) were added and the mixture heated at reflux for a further 6 h before quenching with EtOAc:H_2O (1:1, 30 mL). The phases were separated and the aqueous extracted with EtOAc (3 x 30 mL). Then combined organics were washed with brine (50 mL) and dried ($MgSO_4$) before concentrating to a black slurry. Purification of the crude slurry via flash column chromatography (EtOAc;hexane = 1:9 to 3:17) gave the title compound as a colourless oil (364 mg, 0.873 mmol, 70%) and recovered benzyl (*S*)-2-((*S*)-1-methoxy-1-oxopent-4-en-2-yl)piperidine-1-carboxylate (**5.113**, 51.1 mg, 0.154 mmol, 12%).

$[\alpha]_D$ −26.7 ° (*c* = 0.26, $CHCl_3$)

IR IR (neat) ν 2949, 1736, 1696, 1421, 1268, 1246, 1167, 838, 696 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.46-7.27 (m, 5H, **12**+**13**+**14**), 5.54-5.39 (m, 1H, **17**), 5.25-5.01 (m, 3H, **16**+**10**), 4.46 (br d, *J* = 9.3 Hz, 1H, **3**), 4.17-3.96 (m, 1H, $\mathbf{7_{eq}}$), 3.51-3.45 (m, 3H, **8**), 3.10-2.90 (m, 3H, **2**+$\mathbf{7_{ax}}$), 2.41-2.23 (m, 1H, **15**), 2.22-2.07 (m, 1H, **15'**), 1.85-1.74 (m, 1H, $\mathbf{4_{eq}}$), 1.70-1.35 (m, 7H, $\mathbf{4_{ax}}$**, 5, 6, 18**), 0.01 (s, 3H, Si**Me**$_3$ (*Z*)), −0.03 (s, 6H, Si**Me**$_3$ (*E*)) ppm.

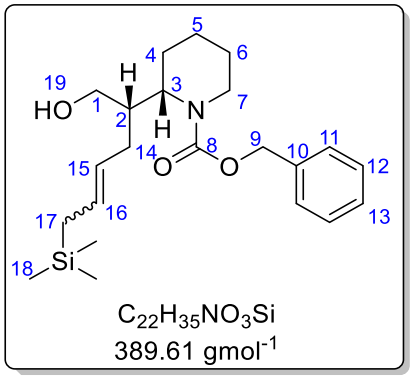
^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.7 (**1**), 155.0 (**9**), 136.9 (**11**), 129.3 (**13**), 128.3 (**17**), 128.1 (**14**), 127.8 (**12**), 124.2 (**16**), 67.0 (**10**), 52.9 (**3**), 51.3 (**8**), 45.7 (**2**), 39.6 (**7**), 32.9 (**15**), 25.8 (**4**), 25.2 (**6**), 22.7 (**18**), 18.8 (**5**), −1.8 (**19**

(*Z*)), –2.1 (**19** (*E*)) ppm.

LRMS (ES$^+$) *m/z* =418 [M+H]$^+$.

HRMS (ES$^+$) *m/z* for $C_{23}H_{36}NO_4Si$ calculated 418.2408, measured 418.2415, for $C_{23}H_{35}NNaO_4Si$ calculated 440.2228, measured 440.2238.

Benzyl (S)-2-((S)-1-hydroxy-6-(trimethylsilyl)hex-4-en-2-yl)piperidine-1-carboxylate (5.130):



To a solution of benzyl (S)-2-((S)-1-methoxy-1-oxo-6-(trimethylsilyl)hex-4-en-2-yl)piperidine-1-carboxylate (**5.114**, 0.500 g, 1.20 mmol) in THF (8.5 mL) at −78 °C under N_2 was added $LiAlH_4$ (1M in THF, 1.32 mL, 1.32 mmol) dropwise over 10 min. The mixture was allowed to slowly warm to −20 °C over 3 h before stirring at this temperature for a further 2 h. The reaction was quenched via addition of H_2O (5 mL) dropwise, 20% aq. NaOH (5 mL), and H_2O (10 mL) before warming to rt. The phases were separated and the aqueous extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$) and concentrated to a colourless oil. Purification of the crude oil via flash chromatography (EtOAc:hexane = 1:9) provided the title compound as a colourless oil (0.398 g, 1.02 mmol, 85%) with the inseparable one carbon missing isomer.

$[\alpha]_D$ −16.6 ° (*c* = 0.97, $CHCl_3$).

IR IR (neat) ν 3463, 2950, 2360, 1696, 1669, 1430, 1263, 852 cm^{-1}.

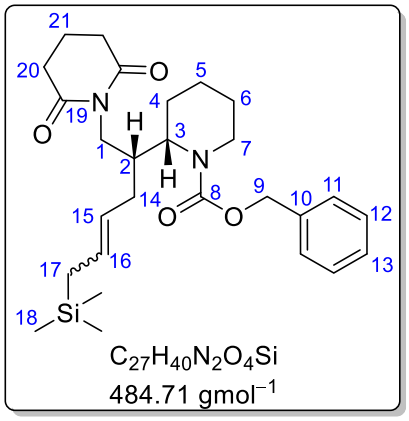
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42-7.29 (m, 5H, **11**, **12**, **13**), 5.49 (dt, *J* = 15.3, 7.9 Hz, 1H, **16**), 5.40-5.25 (m, 1H, **15**), 5.23-5.09 (m, 2H, **9**), 4.17 (br d, *J* = 9.3 Hz, 1H, **3**), 4.08 (br d, *J* = 12.6 Hz, 1H, $\mathbf{7_{eq}}$), 3.63-3.52 (m, 1H, **1**), 3.40 (d, *J* = 10.8 Hz, 1H, **1'**), 3.18 (br d, *J* = 9.2 Hz, 1H, **19**), 2.75 (br t, *J* = 12.5 Hz, 1H, $\mathbf{7_{ax}}$), 2.30-2.12 (m, 1H, **14**), 2.07 (br s, 1H, **14'**), 1.99-1.76 (m, 2H, $\mathbf{2+4_{eq}}$), 1.67-1.41 (m, 7H, $\mathbf{4_{ax}+5+6+17}$), 0.02 (s, 1H, **18**), 0.00 (s, 8H, **18**) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 156.8 (**8**), 136.6 (**10**), 128.5 (**16+12**), 128.1 (**11**), 127.8 (**13**), 126.4 (**15**), 67.5 (**9**), 60.1 (**1**), 51.3 (**3**), 39.8 (**7**), 38.5 (**2**), 31.3 (**14**), 25.6 (**4**), 25.4 (**5/6**), 22.8 (**17**), 18.9 (**5/6**), −1.7 (**18** (*Z*)), −1.9 (**18** (*E*)) ppm.

LRMS (ES^+) *m/z* = 390 $[M+H]^+$.

HRMS (ES$^+$) *m/z* for $C_{22}H_{35}NNaO_3Si$ calculated 412.2278, measured 412.2285.

Benzyl (*S*)-2-((*R*)-1-(2,6-dioxopiperidin-1-yl)-6-(trimethylsilyl)hex-4-en-2-yl)piperidine-1-carboxylate (5.115):



$C_{27}H_{40}N_2O_4Si$
484.71 $gmol^{-1}$

To a solution of benzyl (*S*)-2-((*S*)-1-hydroxy-6-(trimethylsilyl)hex-4-en-2-yl)piperidine-1-carboxylate (**5.130**, 0.371 g, 0.952 mmol) in THF (5 mL) at rt under N_2 was added glutarimide (**5.98**, 0.216 g, 1.90 mmol), ADDP (0.479 g, 1.90 mmol) and PBu_3 (0.47 mL, 1.90 mmol). The mixture was stirred for 48 h before a further portion of glutarimide (0.107 g, 0.946 mmol), ADDP (0.239 g, 0.947 mmol) and PBu_3 (0.23 mL, 0.921 mmol). After a further 24 h, the mixture was quenched H_2O (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (3 x 20 mL), dried ($MgSO_4$) and concentrated to a white solid. Trituration of the crude solid in hexane (30 mL) and concentration of the filtrate gave a crude oil that was purified via flash chromatography (EtOAc:hexane = 2:8 to 4:6) to yield the title compound as a colourless oil (0.396 g, 0.817 mmol, 86%) with the inseparable one carbon missing isomer.

$[\alpha]_D$ +72.1 ° (*c* = 1.00, $CHCl_3$).

IR IR (neat) ν 2954, 1673, 1426, 1353, 1248, 855 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.49-7.11 (m, 5H, **11+12+13**), 5.45-5.34 (m, 1H, **16**), 5.33-5.21 (m, 1H, **15**), 5.07-5.02 (m, 2H, **9**), 4.08-3.93 (m, 2H, **3+7$_{eq}$**), 3.91-3.77 (m, 1H, **1**), 3.30-3.19 (m, 1H, **1'**), 3.16-2.99 (m, 1H, **7$_{ax}$**), 2.62-2.54 (m, 4H, **20**), 2.47-2.28 (m, 1H, **2**), 1.92-1.69 (m, 5H, **4$_{eq}$+14+21**), 1.64-1.20 (m, 7H, **4$_{ax}$+5+6+17**), 0.12-—0.17 (m, 9H, **18**) ppm.

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 173.0 (**19**), 154.5 (**8**), 137.0 (**10**), 128.3 (**2xArC**), 127.7 (**16**), 127.3 (**ArC**), 124.1 (**15**), 66.1 (**9**), 51.5 (**3**), 39.4 (**7**), 38.3 (**1**), 32.3 (**2**), 30.0 (**20**), 25.5 (**4/6**), 25.2 (**14**), 25.0 (**4/6**), 18.5 (**17** (*Z*)), 18.1 (**5**), 16.5 (**21**), —1.7 (**18** (*Z*)), —2.0 (**18** (*E*)) ppm.

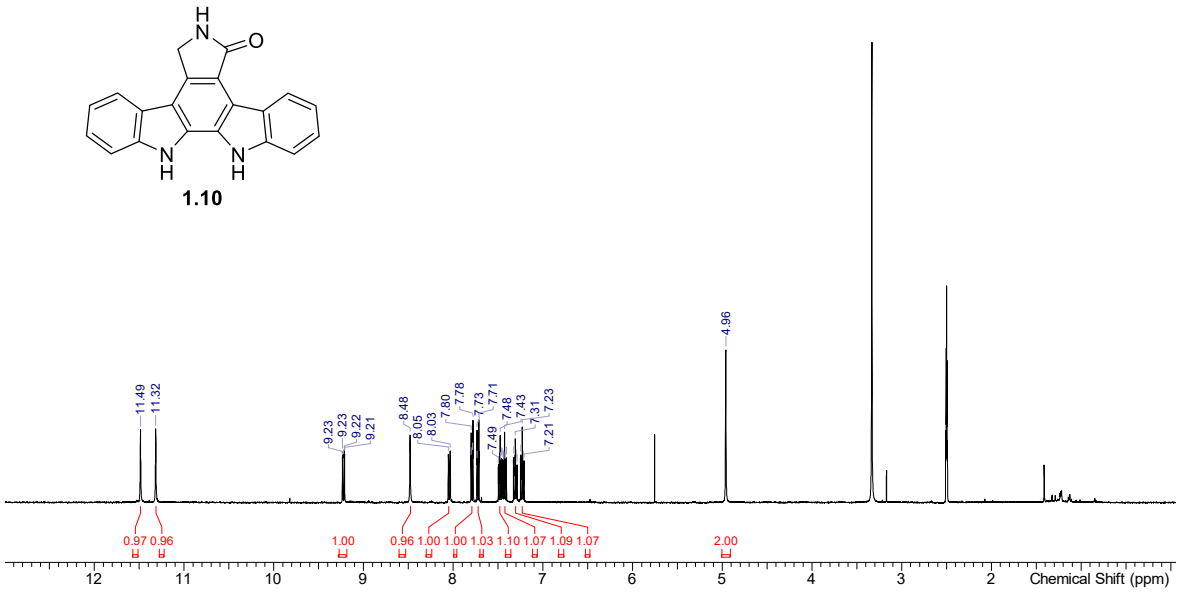
LRMS (ES$^+$) *m/z* = 485 [M+H]$^+$.

HRMS (ES$^+$) *m/z* for $C_{27}H_{41}N_2O_4Si$ calculated 485.2830, measured 485.2834, for $C_{27}H_{40}N_2NaO_4Si$ calculated 507.2650, measured 507.2657.

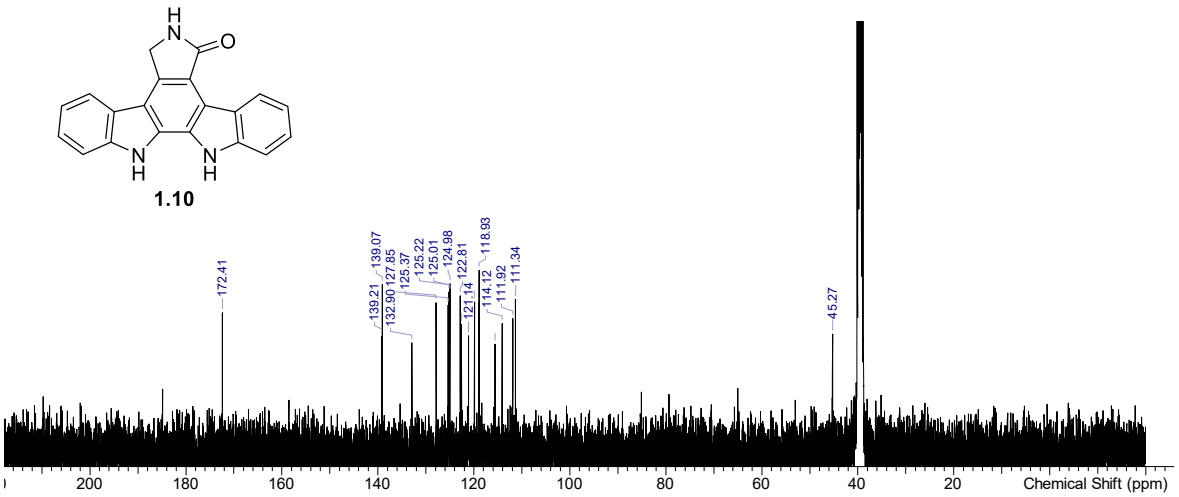
Appendix A Supplementary Data

A.1 NMR of 1.10:

A.1.1 ^{1}H NMR

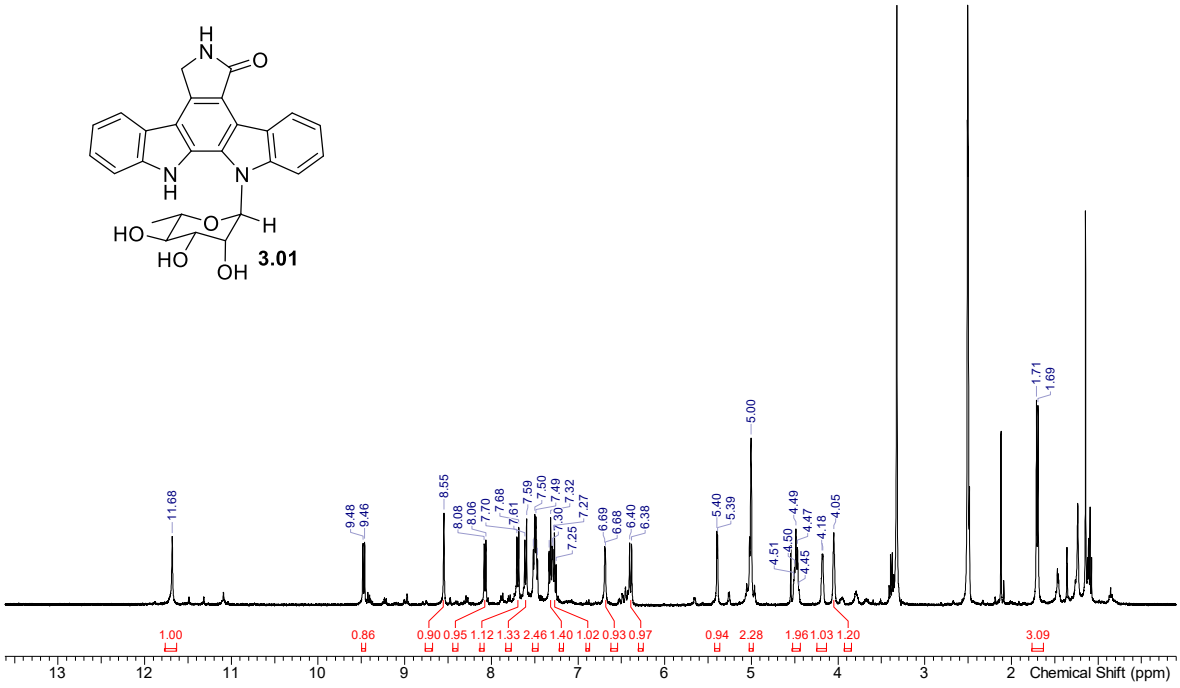


A.1.2 ^{13}C NMR

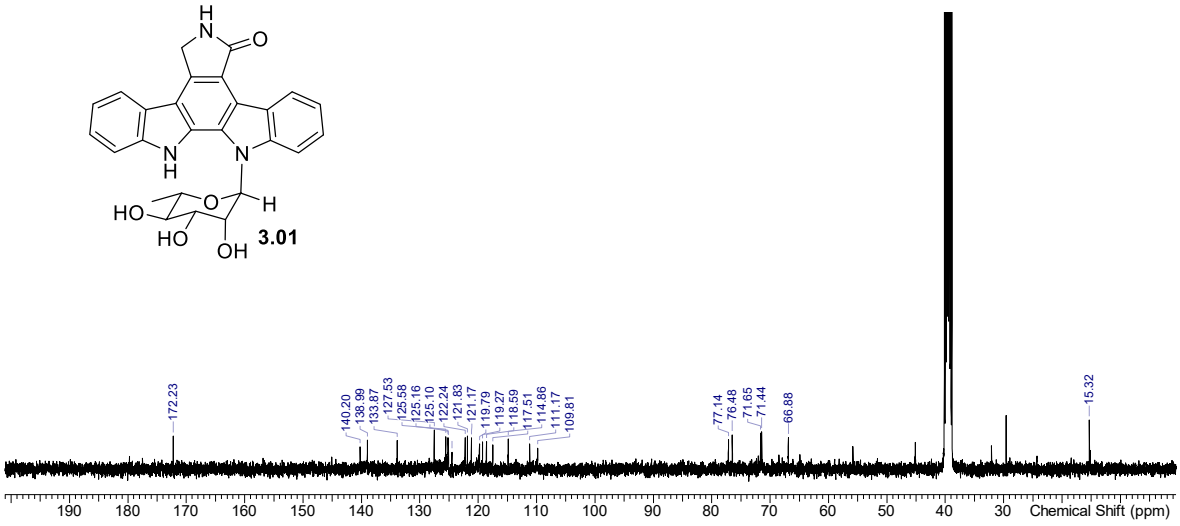


A.2 NMR of 3.01

A.2.1 ^{1}H NMR



A.2.2 ^{13}C NMR



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