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Chapter 1. J. Nat. Prod., 2017, 80, 2178-2187. (This thesis contains no schemes or text present in this publication).

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### CO-AUTHORS

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<td>Jonathan Sperry</td>
<td>Supervision of research and review of publication.</td>
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The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
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Last updated: 28 November 2017
SYNTHETIC STUDIES TOWARDS TRICHOLOMA-DERIVED 2-METHYLINDOLES

Joshua A. Homer

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

School of Chemical Sciences
The University of Auckland

2018
PREFACE

All the work described in this thesis was carried out by the author under the supervision of A/Prof. Jonathan Sperry in the School of Chemical Sciences at the University of Auckland.

Some parts of this work have been previously published:


This thesis describes synthetic efforts towards the bisindole alkaloid (+)-sciodole (209). Isolated from the pungent fruit bodies of the mushroom species *Tricholoma sciodes*, this alkaloid contains a bond between the nitrogen of an indole and C7 of a tetrahydroindole unit bearing an alkoxyalkene.

The synthesis of the natural product 209 required a supply of the ‘lower half’, specifically 5-methoxy-2,4-dimethylindole (185), which led to a scalable route to this indole. Reduction of o-quinone methide (o-QM) 258, itself generated from Mannich base 257, enabled installation of the key C4-methyl group. Selective O-methylation gave the desired indole 185 in gram quantities. Two additional *Tricholoma*-derived 2-methylindoles (186 and 187) were also attainable via the same o-QM.
Using 5-methoxy-2,4-dimethylindole (185), various C7-H activated derivatives (273, 290, 295) were synthesised and an assortment of cross-coupling reactions were attempted; disappointingly Chan-Evans-Lam, Ullmann and Buchwald-Hartwig coupling reactions all failed to produce the key carbon-nitrogen bond. Using the indoline 317 in a Buchwald-Hartwig coupling did lead to the desired compound 322, but in very poor yields that were not synthetically viable.
Given the failure of the cross-coupling routes, we considered the biosynthesis of sciodole. We suspected that lascivol, 195, a bitter component isolated from *Tricholoma lascivum*, likely produced as a deterrent to predation, is the precursor to 209. Revealingly, lascivol (195) has been shown to degrade into indole 185, presumably via dimethoxydihydroindole 198. We posit that coupling of the N-H of indole 185 to 198 via either an SN1 or SN2 addition followed by an alkene tautomerisation could generate this sciodole (209) in vivo.

Tetrahydroindole 402, accessed in six steps from pyrrole 332, was ultimately chosen as a bioinspired coupling partner to react with indole 185. Synthesis of an electrophile (409) required to explore the SN2-based route failed to produce any of the desired product 408. Alternatively, SN1 conditions proceeding via azafulvenium 412, readily formed the C3'-linked dimer 414. Since dimer 414 had formed based on a biomimetic disconnection, we suspected that sciodole (209) could in fact be a C3'-linked regioisomer. Allylic oxidation of 414 afforded dimer 415 (the *anti* diastereomer as the major product), the spectroscopic data of which was inconsistent with that reported for sciodole (209). In an effort to eliminate C3-attack, indoline 317 was investigated as the nucleophile under both SN1 and SN2 conditions; disappointingl
no N-linked compounds were observed. Although the total synthesis of sciodole (209) was not achieved, this work has laid the foundations for the eventual synthesis of this unique alkaloid.
ACKNOWLEDGEMENTS

Most importantly, I would like to thank A/Prof. Jonathan Sperry, for seeing promise in me as an organic chemist. You approached me at a university event during my honours year and inspired me to pursue this career path, helping me find a huge passion for organic synthesis along the way. I could not put a value on what I have learnt from you over these past four years. Thank you, sincerely, for your patience and your supervision.

Emma, the lab couldn’t have been the same without you. From bouncing ideas off each other, to annoying each other (more me than you), to sneaking off for beersies at 3 pm, to yelling ‘I hope you made the wrong regioisomer’ across the lab; you have been the best side-kick I could have asked to share this PhD with. Along with Rachel and Nelson, we now have such a great (and global) network of friends all moving forward in our careers. Everyone in the Sperry group has had a role to play in making this such a memorable adventure. From the seniors that taught me the way Emily, Lachlan, Matthew and Ashley, Andrew, to the newcomers who readily found lifelong places in my life, Steph and Kirsty.

My family have always been so supportive of me and I could not do the things I do without them. To Mum and Dad, thank you for your unwavering support and words of confidence, even if you aren’t 100% certain of what I actually do. To Nan, thank you for the fortnightly wine nights and cooked meals throughout all of my studies; they have been irreplaceable.

After 10 years of friendship and support, I had no doubt you would see me through this journey. We lived together during a significant part of my studies and you truly have seen the raw highs and lows. Thank you Haley, for the endless friendship you offer me. You will always have a place in my life, and I look forward to the next 10 years of friendship. Rob, you’re lovely too.

Finally, Ryan, you came into my life when I was fresh-faced and ready for this challenge. Obviously that passed, but your unceasing confidence in my ability saw me rise above so many of the challenges that I ended up facing. Although we are heading different directions in life now, I have no doubt we will always have a role to play in each other’s future success. I could not have done this without you.
### Abbreviations

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<th>Description</th>
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<td>2D</td>
<td>two dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>three dimensional</td>
</tr>
<tr>
<td>5-HT</td>
<td>serotonin (5-hydroxytryptamine)</td>
</tr>
<tr>
<td>[O]</td>
<td>oxidation</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td>carbon 13</td>
</tr>
<tr>
<td>$^1$H</td>
<td>proton</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Aib</td>
<td>2-aminobutyric acid</td>
</tr>
<tr>
<td>app t</td>
<td>apparent triplet</td>
</tr>
<tr>
<td>approx.</td>
<td>approximately</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
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<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
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<tr>
<td>BPin</td>
<td>4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl</td>
</tr>
<tr>
<td>B$_2$Pin$_2$</td>
<td>bis(pinacolato)diboron</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2’-bispyridine</td>
</tr>
<tr>
<td>BQ</td>
<td>para-benzoquinone</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>BzOH</td>
<td>benzoic acid</td>
</tr>
<tr>
<td>CHDA</td>
<td>1,2-cyclohexanediamine</td>
</tr>
<tr>
<td>CEL</td>
<td>Chan-Evans-Lam</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
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cm\textsuperscript{-1} wave number
COD 1,5-cyclooctadiene
CSA camphorsulfonic acid
d doublet
d app t doublet of apparent triplets
dba dibenzylideneacetone
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE 1,2-dichloroethane
DCM dichloromethane
dd doublet of doublets
DEPT Distortionless Enhancement by Polarization Transfer
DMA N,N-dimethylacetamide
DMAP 4-dimethylanilinopyridine
DME 1,2-dimethoxyethane
DMEDA N,N′-dimethylethylene-1,2-diamine
DMF N,N-dimethylformamide
DMSO dimethylsulfoxide
DNA deoxyribonucleic acid
dppf bis(diphenylphosphino)ferrocene
dt doublet of triplets
dtbp 4,4′-di-tert-butyl-2,2′-bispyridine
E electrophile
E\textsubscript{1} unimolecular elimination
E\textsubscript{1}cb unimolecular elimination conjugate base
EDG electron donating group
EOM ethoxymethyl
Eq equivalent
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<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>FM</td>
<td>Fujiwara-Moritani</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
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<tr>
<td>G3P</td>
<td>glyceraldehyde 3-phosphate</td>
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<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
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<tr>
<td>GC</td>
<td>gas chromatography</td>
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<tr>
<td>h</td>
<td>hour(s)</td>
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<tr>
<td>HBPin</td>
<td>pinacolborane</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple-quantum correlation</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single-quantum correlation</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
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<tr>
<td>IAA</td>
<td>indole 3-acetic acid</td>
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<tr>
<td>IBX</td>
<td>2-iodobenzoic acid</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>NMR coupling constant (Hertz)</td>
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<tr>
<td>L</td>
<td>litre</td>
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<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>lethal dose (50%)</td>
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<tr>
<td>LD&lt;sub&gt;90&lt;/sub&gt;</td>
<td>lethal dose (90%)</td>
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<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
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<td>lit.</td>
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LSD  lysergic acid diethylamide
M  moles per litre (mol L⁻¹)
m  multiplet
m.p.  melting point
MALDI  matrix-assisted laser desorption/ionisation
Me  methyl
Me₄Phen  3,4,7,8-tetramethyl-1,10-phenanthroline
MeCN  acetonitrile
mg  milligram
MHₙ  metal hydride (where n = number of hydrogens)
MHz  megahertz
MIC  minimum inhibitory concentration
min  minute(s)
ml  millilitre
mm  millimetre
mmol  millimole
mol L⁻¹  moles per litre
mol  mole
mol%  mole percent
Ms  methanesulfonyl
MS  molecular sieves
NBS  N-bromosuccinimide
nBu  n-butyl
nBuLi  n-butyl lithium
nm  nanometre
NMP  N-methyl-2-pyrrolidone
NMR  nuclear magnetic resonance
NOE  nuclear Overhauser effect
NOESY nuclear Overhauser effect spectroscopy
NSAID non-steroidal anti-inflammatory drug
\textit{o-QM} \textit{ortho-quinone methide}
OAc acetoxy
OTf trifluoromethylsulfonyl
pH $-\log[H^+]$
Ph phenyl
Phen 1,10-phenanthroline
pKa acid dissociation constant
ppm parts per million
pTSA \textit{para-toluenesulfonic acid}
q quartet
quant. quantitative
r.t. room temperature
RNA ribonucleic acid
s singlet
sat. saturated
SEM 2-(trimethylsilyl)ethoxymethyl
S_N1 unimolecular nucleophilic substitution
S_N2 bimolecular nucleophilic substitution
\textit{t} triplet
TAA \textit{tert-}amyl alcohol
TBAB tetrabutylammonium bromide
TBS \textit{tert-}butyldimethylsilyl
\textit{tBHP} \textit{tert-}butylhydroperoxide
\textit{tBu} \textit{tert-}butyl
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<td>t-BuLi</td>
<td>tert-butyllithium</td>
</tr>
<tr>
<td>TBAC</td>
<td>tetra-butylammonium chloride</td>
</tr>
<tr>
<td>td</td>
<td>triplet of doublets</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethylsulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
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<td>THF</td>
<td>tetrahydrofuran</td>
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<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>TMEDA</td>
<td>tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
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<tr>
<td>Trpol</td>
<td>tryptophanol</td>
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<tr>
<td>Ts</td>
<td>p-toluenesulfonyl</td>
</tr>
<tr>
<td>tt</td>
<td>triplet of triplets</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>WKR</td>
<td>Wolff-Kishner reduction</td>
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<td>α</td>
<td>alpha</td>
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<tr>
<td>δ</td>
<td>delta/chemical shift</td>
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Chapter 1: INTRODUCTION
1.1 General Indole Introduction

The indole heterocycle is a $\pi$-excessive, aromatic compound comprising a fused pyrrole and benzene ring. The structure of the indole nucleus was first proposed in 1869 by Adolf von Baeyer after synthesising the compound during experimentation involving indigo dyes several years earlier; isatin (1) was reduced in the presence of zinc dust to oxindole (2) and further to generate indole (3). The configuration and accepted numbering convention of indole is presented in Figure 1.

![Indole nucleus with numbering convention.](image1)

Figure 1: Indole nucleus with numbering convention.

![von Baeyer's seminal synthesis of indole from isatin.](image2)

Scheme 1: von Baeyer’s seminal synthesis of indole from isatin.

1.1.1 Clinically-used Indole Alkaloids

The indole moiety has been identified in countless natural products isolated from a variety of sources. These alkaloids have been demonstrated to impart a range of biological activities, with notable examples being used clinically. Physostigmine (4), produced by the Calabar bean of tropical Africa, is a reversible cholinesterase inhibitor used today for the treatment of glaucoma, hypotension and Alzheimer’s disease. Mitomycin C (5), one of the aziridine-containing chemotherapeutic agents isolated from various *Streptomyces* species, is used to treat upper gastro-intestinal, anal and breast cancers. The monoterpenoid alkaloids vincamine (6)
and vincristine (7) are members of the so-called “Vinca alkaloids”. Vincamine (6) acts as a peripheral vasodilator, increasing blood flow to the brain and thus reducing the effects of aging. Vincristine (7) however is a potent inhibitor of tubulin polymerisation, halting chromosome separation during metaphase and inducing apoptosis in carcinogenic cells.

Figure 2: Examples of indole-containing natural products used as drugs. Indole heterocycle highlighted in blue.
Cabergoline (8) and methysergide (9) are both “ergot alkaloids”; while 8 acts as a potent dopamine receptor agonist (specifically the D\textsubscript{2} receptors) and has applications clinically in the treatment of Parkinson’s disease,\textsuperscript{9} prolactinomas and hyperprolactinaemia, 9 has been used to treat both episodic and chronic migraines and cluster headaches (by antagonising various serotonin receptors).\textsuperscript{10} Although rarely used today, reserpine (10) is an antipsychotic agent that has also found use in alleviating high blood pressure.\textsuperscript{11} This alkaloid had a pivotal role in the development of the “monoamine hypothesis of depression” in the 1950s.\textsuperscript{12}

\subsection*{1.1.2 Synthetic Drugs Containing the Indole Heterocycle}
Due to this presence in biologically active alkaloids, the indole heterocycle features heavily in both approved synthetic drugs and those undergoing clinical trials and is considered to be a ‘privileged scaffold’ in the drug development process.\textsuperscript{3,13–15} Ondansetron (11) and tropisetron (12) are drugs both indicated in treating chemotherapy-induced nausea and emesis.\textsuperscript{16,17} Both act as serotonin receptor antagonists (specifically 5-HT\textsubscript{3}).\textsuperscript{16,17} Oxypertine (13), containing an indole and phenylpiperazine motif, is an antipsychotic drug utilised to treat both anxiety and schizophrenia.\textsuperscript{18,19} Acting in the central nervous system, 13 decreases concentrations of the catecholamine-based neurotransmitters while leaving serotonin levels untouched.\textsuperscript{18} Delavirdine (14) is a non-nucleoside reverse transcriptase inhibitor that was approved in 1997 for the combination therapy of HIV.\textsuperscript{20,21} Currently, due to drug interactions and the risk of cross-resistance, 14 is rarely used and holds a place as a second-line therapeutic agent. Arbidol (15) is an antiviral agent bearing a heavily substituted indole-core that is readily used in both Russia and China to treat influenza.\textsuperscript{6,22} Indometacin (16) is a nonsteroidal anti-inflammatory drug (NSAID) used commonly to reduce fever, pain and swelling.\textsuperscript{6} Like all NSAIDs, this compound interacts with the cyclooxygenase enzymes, crucial regulators in the inflammation pathway. Finally, zafirlukast (17) is a leukotriene receptor antagonist indicated for maintenance treatment of asthma; this drug prevents the action of cysteinyl leukotrienes in the lungs, alleviating airway constriction and mucus build-up.\textsuperscript{23}
Figure 3: Examples of indole-containing, synthetic drugs.

1.1.3 Indole Biosynthesis via L-Tryptophan

The vast majority of the indole-containing natural products are bio-derived from the amino acid L-tryptophan (18). This amino acid, though comparatively under-represented in proteins, holds a key role in membrane anchoring. L-Tryptophan is also the precursor of several vitamins, neurotransmitters and hormones in both animals, fungi and plants. The biogenesis of L-tryptophan (18) is notably conserved across the kingdoms. Synthesis begins with anthranilate (19), an aromatic compound generated via the shikimate pathway, which is converted to 5-phosphoribosylanthranilate (20) through enzymatic-mediated condensation with phosphoribosyl pyrophosphate (PRPP). The ribose ring is then opened to afford...
intermediate 21 that subsequently undergoes reductive decarboxylation, producing indole-3-glycerol phosphate (22) by forming the key pyrrole ring of the indole motif. Indole 22 then collapses, liberating a molecule of glyceraldehyde 3-phosphate (G3P), to give the unfunctionalised indole heterocycle (3). A final, enzyme-mediated coupling between 3 and the amino acid L-serine (23) affords 18.

Scheme 2: Biosynthesis of L-tryptophan (18) from anthranilate (19).

1.2 Mushroom-Derived Natural Products
Mushrooms have played a key role in human development, serving as both a nutrient-laden food supply and a source of many traditional medicines, particularly in Asian culture. Consequently, mushrooms are a well-established source of bioactive compounds and much effort has been dedicated to the isolation and structural elucidation of mushroom-derived natural products, with the isolation of quinoid pigments from the fruiting bodies of the
mushroom species *Tapinella atrotomentosus* and *Polyporus purpurascens* in 1878 being an early example. Over the years, lectins, lanostanoids and other terpenoids, sterols, phenolic compounds and alkaloids have been identified as key compound classes responsible for the variety of medicinal properties associated with mushrooms, including antitumor, anti-inflammatory, antifungal, antimicrobial and antiviral activity.

Numerous mushroom-derived natural products have served as lead compounds for the development of new agrochemicals and pharmaceuticals. Strobilurins A-H (24-31), isolated from *Strobilurus tenacellus* and a variety of other mushroom species, are fungicidal compounds containing a conserved methyl (E)-3-methoxy-2-(5-phenylpenta-2,4-dienyl) acrylate functionality. Later experimental findings revealed that the epoxide-containing putative strobilurin D (27) had been misassigned and was in fact found to be identical to strobilurin G (30). The strobilurins interrupt electron transfer within mitochondria and thus causing fungal death, a characteristic that inspired the development of azoxystrobin (32) by Syngenta, a broad spectrum fungicide launched in 1996 with widespread use in the agricultural sector. The diterpene natural product pleuromutilin (33) was isolated from the mushrooms *Pleurotus mutilus* and *Clitopilus passeckerianus* in 1951 and the structure fully elucidated in 1962. The potent antibiotic properties of this natural product led to the development of tiamulin (34) and valnemulin (35) for veterinary use and the 2007 approval of retapamulin (36) for topical use in humans. Current developments have seen the pleuromutilin-derived antibiotic lefamulin (37) enter phase III clinical trials for community-acquired bacterial pneumonia, the first potential systemic use of a pleuromutilin in humans. The illudins are a class of antitumoral natural products isolated from a variety of mushroom species, most notably *Omphalotus olearius*. In 1963, the structures of illudins M (38) and S (39) were fully assigned as sesquiterpenes with a characteristic spirocyclopropane motif. The structurally related compounds illudin A (40) and B (41) were identified in 1991 from the species *Clitocybe illudens*. Subsequent efforts to improve the selectivity of these DNA alkylating agents led to irofulven (42), which has displayed significant activity against ovarian, prostate, hepatocellular, pancreatic and gastrointestinal cancers in numerous clinical trials. The potential of this experimental drug has been limited by haematological side effects and as such 42 has yet to be approved for clinical use.
Figure 4: Examples of mushroom-derived agrochemicals and pharmaceuticals.
1.2.1 Mushroom-Derived Indole Alkaloids

In addition to these compounds, various mushroom species have been found to produce indole-containing natural products. For the purposes of this thesis, a mushroom has been defined as a higher Basidiomycota, predominantly the class Agaricomycetes, that produces visible fruiting bodies and generally have stem, cap and gill structures. Indoles produced by filamentous fungi that do not meet these criteria have been omitted.

1.2.2 Simple Indoles

Certain mushroom species are notorious for their potent, disagreeable odours. The smell of *Hygrophorus paupertinus* is distinctly faecal in nature and this has been linked to the odoriferous indole (3), skatole (43) and 3-chloroindole (44). The isolation of 44 from *H. paupertinus* was the first time this compound had been identified in a terrestrial organism. Indoles 3 and 43 have also been identified within the pungent extracts of numerous members of the genus *Tricholoma*. Indole-3-carboxaldehyde (45), found in the volatile extract of *Tricholoma sulphureum*, has been associated with an unpleasant coal or tar-like odour.

![Chemical structures](image)

**Figure 5**: Simple indoles from numerous mushroom species.

1-Methylindole-3-carboxaldehyde (46) and 7-methoxyindole-3-carboxylic acid methyl ester (47) were isolated from *Phellinus linteus*, a mushroom species used as a treatment for inflammation and a variety of cancers in Eastern Asia. No biological testing was conducted on these natural products. Methylindole-3-carboxylate (48), was isolated from the extracts of *Antrodiella albocinnamomea*, a mushroom found throughout the subtropical regions of China. Investigation into the biological activity of 48 highlighted no significant inhibition of
protein-tryosine phosphatase activity at 50 µg mL\(^{-1}\); specifically enzymes MEG2 and PTP1B, both implicated in breast cancer development.\(^{55-57}\)

### 1.2.2.1 Auxin-related Indoles

Auxins are a class of hormones that play an important role in gravitropism; the orientation of plants with respect to gravity.\(^{58}\) Indole-3-acetic acid (49, IAA) is the most abundant auxin and, although the mechanisms of fungus orientation remain poorly understood, its production in several mushroom species has been attributed to a positive impact on organism growth.\(^{59}\) 5-Hydroxyindole-3-acetic acid (50) and indole-3-acetonitrile (51) have been also been identified in numerous mushroom extracts.\(^{60}\)

![Diagram of indoles](image)

**Figure 6:** Auxin-related indoles.

### 1.2.2.2 6-Hydroxyindoles from *Agrocybe cylindracea*

*Agrocybe cylindracea* (also known as *Cyclocybe aegerita*), an edible mushroom that has long been used in traditional Chinese medicine as a diuretic, is an important source of bioactive metabolites that impart cytotoxic and antifungal properties.\(^{61}\) Two indole derivatives possessing free radical scavenging activity, 6-hydroxyindole-3-carbaldehyde (52) and 6-hydroxyindole-3-acetamide (53), have been isolated from *A. cylindracea*.\(^{62,63}\) Both 52 and 53 were found to inhibit lipid peroxidation in rat liver microsomes with IC\(_{50}\) values of 4.1 and 3.9 µg mL\(^{-1}\) respectively.\(^{62}\)
Figure 7: 6-Hydroxyindoles produced by *A. cylindracea*.

1.2.2.3 Oxindoles

Indigo (54) is a pigment with a strong blue colour and has been found in mutant variants of the North American ‘meadow mushroom’ *Agaricus campestris*, whereby the mycelium of the mushroom presents as a dark blue colour.\(^{64,65}\) The structurally-related red indirubin (55) was also tentatively identified in this species based on a characteristic ultraviolet absorption maximum.\(^{65}\) Indirubin (55) has been identified as the active constituent of the traditional Chinese medicine Danggui Longhui Wan, a mixture of plants used to effectively treat chronic myeloid leukemia.\(^{66}\) This molecule inhibits a variety of cyclin-dependant kinases (associated IC\(_{50}\) values ranging from 2.2-12 µM), and thus induces cell cycle arrest in cancerous cells.\(^{66,67}\)

The edible mushroom *Pleurotus salmoneostramineus* has a bright pink colouration and is referred to as the pink oyster mushroom; this vibrant colouration has been attributed to 3-indolone (56).\(^{68}\)

Figure 8: Oxindole-containing natural products.
1.2.2.4 N-Glycosylated Indoles
A collection of N-glycosylated indoles (57-60) were isolated from the fruiting bodies of Cortinarius brunneus.\(^{69}\) Investigation into the activity of these molecules via root growth assays revealed no significant auxin-like activity,\(^{69}\) inferring that 57 (the N-glucoside of IAA) has an endogenous role as an inactive storage or detoxification product of the growth hormone; similar to the role of IAA-O-glucose (61) in plant tissues.\(^{69}\) Indoles 58-60 are assumed to be metabolic intermediates of 57.

![Figure 9: N-Glycosylated indoles.](image)

1.2.3 Indoleamines and Tryptophols
L-Tryptophan (18) is ubiquitous within mushroom species and, consequently, edible mushrooms are a dietary source of this essential amino acid.\(^{70,71}\) The structurally related indoles 5-hydroxy-L-tryptophan (62), tryptamine (63), serotonin (5-HT, 64), melatonin (65) and bufotenin (66) are found (at varying concentrations) in a diverse range of mushrooms.\(^{60,70}\) This collection of indoleamines display endogenous activity within the human central nervous system.\(^{70}\) The genus Astraeus contains the earthstar mushrooms that are characterised by an exoperidium that opens in a star-like fashion to expose a spore sac.\(^{72}\) The trimethylated derivative of L-tryptophan, hypaphorine (67), was found in specimens of Astraeus odoratus along with its corresponding 5-hydroxyderivative (68).\(^{72}\) Hypaphorine (67) acts as an auxin antagonist, limiting root growth and elongation.\(^{72-74}\) Biological testing of 67 and 68 showed no significant antimycobacterial activity against Mycobacterium tuberculosis or cytotoxic activity against various cancer cell lines.\(^{72}\)
*Termitomyces titanicus* is a large, edible mushroom from Western Africa that is noted for its symbiotic relationship with termites; the mushroom is cultivated by the insect as a food source. Termitomycamide B (69), a fatty acid amide isolated from this species, shows protective activity against endoplasmic reticulum stress induced by tunicamycin, with analogue studies highlighting the fatty acid side-chain as essential for this biological activity. The yellow parasol or *Leucocoprinus birnbaumii* is a tropical mushroom known for its bright yellow caps. The pigments responsible for this hue have been identified as the indole derivatives birnbaumin A (70) and B (71), structurally unprecedented natural products containing an N-hydroxyoxamidine motif and a N-hydroxyindole heterocycle. No biological testing was performed on these alkaloids.
Figure 11: Termitomycamide B and birnbaumins A and B.

The mushroom *Hericium coralloides* has interesting fruiting bodies that are reminiscent of off-white coral. This species produces the indole alkaloid corallocin C (72). Although no antiproliferative activity was identified against a variety of cancer cell lines, 72 was found to stimulate neurotrophin expression in human 1321N1 astrocytes; approximately 30% of neural PC12 cells differentiated when exposed to a medium containing 19.6 µM of 72.

Figure 12: Corallocin C.
1.2.3.1 Psilocin and Related Tryptamines

The narcotic effect of certain mushroom species has been well established for thousands of years and has been summarised in numerous reviews. Psilocin (73) is an indole alkaloid found in the genus *Psilocybe* that exhibits bioactivity similar to lysergic acid diethylamide (LSD), harmine and other psychoactive tryptamines (bufotenin, dimethyltryptamine etc.); inducing psychoactive effects such as changes in perception, alteration to mood and colourful hallucinations. Its mode of action is believed to occur through non-selective agonism of various serotonin receptors present within the central nervous system; specifically the 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors. The phosphorylated derivative psilocybin (75) is also present and acts a prodrug, readily converted to 73 in vivo. Promising results arising from the use of 75 as a treatment for depression and other psychiatric disorders have been disclosed. Baeocystin (76) and norbaeocystin (77) are also found as minor components in psychoactive mushrooms from the genus *Psilocybe*. The trimethylated derivative of 75, aeruginascin (78), has been isolated from another hallucinogenic mushroom, *Inocybe aeruginascens*. This collection of psychoactive compounds contain the 4-hydroxyl motif, rarely seen in indole-derived natural products.

![Figure 13: Psychoactive, psilocin-related indoles.](Image)
1.2.3.2 Tryptophols

The edible *Craterellus cornucopioides* is commonly referred to as the horn of plenty due to its unusual funnel-shaped fruiting body and highly sought after ‘black truffle’ flavour. This species has been shown to enzymatically couple externally-supplied tryptophol (79) with the endogenous fatty acids dehydrocrepenynic, oleic and linoleic acids to generate esters 80, 81 and 82. The physiological significance of these compounds remains unknown although similar esters are produced by a variety of bacteria and plant species, suggesting an evolutionarily conserved process.

![Figure 14: Tryptophols.](image)
1.2.4 β-Carbolines

Alkaloids containing a β-carboline motif are widely distributed throughout Nature. The general biosynthesis of these compounds involves a key Pictet-Spengler-type reaction between either L-tryptophan (18), or the enzymatically-reduced tryptamine (63), and various pyruvic acid derivatives (83) to afford tetrahydro-β-carboline 84. This intermediate undergoes subsequent oxidative decarboxylation and aromatisation to forge the β-carboline core heterocycle, though a number of saturated or partially oxidised natural products have also been isolated. As a result of this biogenic pathway, the majority of β-carboline-containing natural products carrying a C1-substituent with some retaining a C3-carboxyl group.

Scheme 3: General biosynthesis of β-carbolines.

Hygrophorus eburneus, a white, edible mushroom characterized by its extremely slimy cap, has been found to produce the norharmane (85) along with harmane (86), a tremorogenic neurotoxin that acts as both a monoamine oxidase inhibitor and a potent inhibitor of the benzodiazepine receptor. The olive-coloured fruit bodies of the inedible mushroom Cortinarius infractus have been found to produce the highly fluorescent β-carboline derivatives infractine A (87) and B (88). β-Carboline-1-propanoic acid (89) and its methylated derivative (90) have been identified in specimens of Boletus curtisii, a mushroom that forms a mycorrhizal
relationship with hardwood and conifer trees across North America. Cytotoxic assessment of highlighted no inhibitory activity against five cancer cell lines, although it has been suggested this molecule could interact with both the benzodiazepine and GABA receptors. Brunneins A-C (91-93) along with 3-(7-hydroxy-9H-β-carboline-1-yl)propanoic acid (94) are 7-hydroxylated β-carboline pigments produced by Cortinarius brunneus. Brunnein A (91) has also been found in the fruiting bodies of Hygrophorus hyacinthinus. Biological testing of showed very low acetylcholinesterase inhibition (less than 50% inhibition at a concentration of 10⁻⁴ M against both acetylcholinesterase and the related enzyme butyrylcholinesterase) with no associated cytotoxicity.

**Figure 15:** Simple β-carboline-containing alkaloids including the infractines and brunneins.
The furyl-linked β-carboline flazin (95) has been isolated from *Suillus granulatus*, the so-called weeping bolete that grows in a symbiotic relationship with pine trees, as well as the fruiting bodies of *Boletus umbriniporus*.\(^{104,105}\) Flazin (95) was found to exhibit anti-HIV activity with an EC\(_{50}\) of 2.36 µM and a therapeutic index of 12.1; consequently a series of flazin analogues have been synthesised to probe this activity further.\(^{106}\)

![Flazin](image)

**Figure 16:** Flazin.

1.2.4.1 Canthin-6-one-derived β-Carbolines

The fruit bodies of *Cortinarius infractus* also contains infractopicrin (96) and 10-hydroxyinfractopicrin (97).\(^{103,107}\) The acetylcholinesterase inhibiting activity of these compounds (IC\(_{50}\) values of 9.72 and 12.7 µM respectively) is comparable to that of galantamine, a drug used for the treatment of mild to moderate Alzheimer’s disease.\(^{103,107}\) Good selectivity for acetylcholinesterase infers these alkaloids are excellent lead compounds for further development.\(^{103,107}\) The aforementioned *B. curtisii* produces an interesting collection of sulfur-containing β-carboline derivatives.\(^{99}\) The bright yellow colouration of this species has been attributed to the optically active, sulfoxide-containing pigments curtisin (98) and 9-deoxycurtisin (99).\(^{99}\) These compounds are derived from canthin-6-one (100) which was also identified in the extracts of *B. curtisii* along with four thiomethyl β-carboline derivatives (101-104).\(^{99}\) Canthin-6-one (100) is found in a variety of higher plants and possesses antifungal and cytotoxic properties.\(^{108}\)
Metatacarbolines

The inedible mushroom *Mycena metata* has been found to contain the sixteen β-carboline natural products metatacarbolines A-G (105-111) and 6-hydroxymetatacarbolines A-I (112-120) bearing a variety of different amino acids coupled to the C3 carboxyl moiety (Table 1).\(^\text{109}\)

High-resolution matrix-assisted laser desorption-ionization mass spectrometry imaging (HR-MALDI-MS imaging) was used to identify these alkaloids.\(^\text{109}\) Compounds 105 and 107-110 have been synthesised and subjected to cytotoxicity evaluation; metatacarbolines D (108) and F (110) demonstrated limited antiproliferative activity against glioma cell lines with IC\(_{50}\) values of 150 and 250 μM respectively.\(^\text{110}\)
Table 1: Metatacarbolines.

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1.2.4.3 Pyrroloquinolines

Numerous pyrroloquinoline natural products have been isolated as pigment molecules from the genus *Mycena*.\(^{111}\) Two red alkaloids, mycenarubin A (121) and the associated dimer mycenarubin B (122) were found in the species *Mycena rosea*, or rosy bonnet.\(^{112}\) This was the first isolation of a dimeric pyrroloquinoline from a natural source.\(^{112}\) The monomer 121 showed no antimicrobial activity against a variety of bacteria and fungi, consistent with the diminished bioactivities of other \(o\)-quinones comparative to their \(p\)-quinone counterparts.\(^{112}\)

![Figure 18: Mycenarubin A and B.](image)

The blue pyrroloquinolines, sanguinones A (123) and B (124) were isolated from the mushroom *Mycena sanguinolenta*,\(^{113}\) along with the the decarboxylated species (125) and a red alkaloid sanguinolentaquinone (126).\(^{113}\) The related mushroom *Mycena haematopus*, or bleeding mycena, exudes a bright red liquid if the fruit bodies are damaged.\(^{114}\) This mushroom has been found to produce the red pyrroloquinolines mycenarubins D-F (127-129) as well as haematopodin (130) and haematopodin B (131).\(^{114,115}\) Comparative metabolic profiling also indicated the presence of the aforementioned mycenarubin A (121) and sanguinolentaquinone (126).\(^{114}\)
Figure 19: Additional mycenarubins, sanguinones and haematopodins.

The so called black-edged bonnet, *Mycena pelianthina*, is a purple mushroom widely found throughout Europe and Northern America. Two novel pyrroloquinolines were identified in the fruiting bodies of this species and structurally assigned as pelianthinarubins A (132) and B (133); both contain a trimethylated histidine, (S-hercynine) residue. Biological testing indicated no antibacterial or herbicidal activity.
Figure 20: Pelianthinarubin A and B.
1.2.5 Peptides and peptaibols

*Lentinus strigellus*, a medicinal mushroom from South America, has been found to produce the triprenylated tryptophan-based diketopiperazine echinulin (134) under a variety of culture conditions.\(^{117}\) This bioactive secondary metabolite has modest activity against *Mycobacterium tuberculosis* H37Ra (MIC value of 169.92 µM) and is cytotoxic to HeLa cells at 100 µg mL\(^{-1}\).\(^{118,119}\) Macrolepiotin (135), isolated from the poisonous mushroom *Macrolepiota neomastoidea*, comprises the dipeptide (Trp-Ile) coupled to lepiotin B (136).\(^{120}\) No significant biological activity was found when tested against A549, SK-OV-3, SK-MEL-2 or HCT-15 cancer cell lines.\(^{120}\) The relative and absolute stereochemistry of 135 was not determined.\(^{120}\)

*Inonotus obliquus* is a widespread parasitic mushroom that has been used for centuries in traditional Russian medicine for its antitumor and immunostimulating properties.\(^{121}\) Investigation into the bioactive compounds present within *I. obliquus* afforded the tripeptide 137, a molecule that exhibited platelet aggregation inhibitory activity of 83.3% in a mouse antithrombotic assay at a dose of 20 mg kg\(^{-1}\).\(^{121}\)

![Figure 21: Short-chain peptides.](image-url)
1.2.5.1 Amatoxins and Related Peptides

*Amanita phalloides*, aptly referred to as the death cap, contains a cocktail of toxic peptides and as such has been implicated in the majority of human deaths resulting from mushroom consumption.\textsuperscript{122} The cyclic peptides produced by *Amanita* mushrooms, covered in numerous review articles,\textsuperscript{123,124} are categorised into three groups; amatoxins, phallotoxins and virotoxins. The nine amatoxins (138-146) comprise the largest subgroup and have also been identified in mushrooms of the *Galerina* and *Lepiota* genera (Table 2).\textsuperscript{125,126}

**Table 2:** Amatoxins.

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</tbody>
</table>
The first amatoxin to be isolated was α-amanitin \( (138) \) by Wieland and co-workers in 1941.\(^{127}\) The amatoxins are bicyclic octapeptides, with seven members of the group (compounds \( 138-143 \) and \( 146 \)) containing a relatively rare 6-hydroxylated L-tryptophan residue, that act as selective inhibitors of RNA polymerase II, a vital enzyme in the synthesis of messenger RNA.\(^{123}\) Pivotal X-ray crystallographic data presented by Bushnell and co-workers explored the enzyme binding mechanism of α-amanitin \( (138) \) in great detail; binding of \( 138 \) prevents the conformational changes required by RNA polymerase II to conduct transcription and thus reduces DNA translocation from several thousand to a handful of nucleotides per minute.\(^{128}\) Although inhibition of protein synthesis causes widespread damage in the human body, it is irreversible lesions to the heart and liver cells that prove fatal.\(^{129}\) α-, β- and γ-Amanitins \( (138-140) \) have been identified as the most potent members of this compound family with LD\(_{50}\) values in the range of 0.2 to 0.5 mg kg\(^{-1}\).\(^{123}\)

**Table 3: Phallotoxins.**

<table>
<thead>
<tr>
<th>Name</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>( R^4 )</th>
<th>( R^5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phalloidin (147)</td>
<td>OH</td>
<td>Me</td>
<td>CH(_2)OH</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>Prophalloin (148)</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>Phalloidin (149)</td>
<td>OH</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>Phallisin (150)</td>
<td>OH</td>
<td>CH(_2)OH</td>
<td>CH(_2)OH</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>Phallacidin (151)</td>
<td>OH</td>
<td>Me</td>
<td>CH(_2)OH</td>
<td>CHMe(_2)</td>
<td>CO(_2)H</td>
</tr>
<tr>
<td>Phallacin (152)</td>
<td>OH</td>
<td>Me</td>
<td>Me</td>
<td>CHMe(_2)</td>
<td>CO(_2)H</td>
</tr>
<tr>
<td>Phallisacin (153)</td>
<td>OH</td>
<td>CH(_2)OH</td>
<td>CH(_2)OH</td>
<td>CHMe(_2)</td>
<td>CO(_2)H</td>
</tr>
</tbody>
</table>
The closely related phallotoxins (147-153) are a group of seven bicyclic heptapeptides also isolated from the genus *Amanita* (Table 3). Phallloidin (147) was the first toxic peptide to be isolated from the genus *Amanita* in 1937. The phallotoxins damage hepatocytes, interact with cellular actin and disrupt microfilament depolymerisation. This interaction with actin has led to the use of phallloidin (147) as an imaging tool in biomedical research, with fluorescent analogues being used to visualise actin filaments in living and fixed cells, as well as in vivo. Although extremely toxic when administered intravenously, the phallotoxins have been found to contribute little to the genus’ lethality due to poor gut uptake when consumed orally.

**Table 4: Virotoxins.**

<table>
<thead>
<tr>
<th>Name</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viroidin (154)</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>Me</td>
<td>CHMe&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Desoxoviroidin (155)</td>
<td>SOMe</td>
<td>Me</td>
<td>CHMe&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Alaviroidin (156)</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>Aladesoxoviroidin (157)</td>
<td>SOMe</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>Viroisin (158)</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>CHMe&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Desoxoviroisin (159)</td>
<td>SOMe</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>CHMe&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
</tbody>
</table>
The virotoxins (Table 4) are six monocyclic peptides that induce haemorrhagic hepatic necrosis in mice through a similar actin-binding mode of action displayed by the phallotoxins.\textsuperscript{131,133} As with the phallotoxins, the virotoxins (154-159) are not considered to have any significant toxic effects after oral consumption.\textsuperscript{123}
1.2.5.2 Putative Cortinarins

Another mushroom notorious for its acute toxicity is *Cortinarius speciosissimus*. Early investigation by Tebbett and Caddy into the toxic components of this species led to the isolation of cortinarins A-C \((160-162)\), cyclic peptides with a characteristic fluorescence structurally reminiscent of the aforementioned phallotoxins. It was hypothesised that these cyclic peptides are converted \textit{in vivo} to an unknown active metabolite that induces the observed toxicity.\(^{135}\)

\[\text{Figure 22: Putative cortinarins A-C.}\]
However, several research groups have been unable to replicate these studies, most notably, the research conducted by Laatsch and Matthies; no isolation was achieved of any cyclic peptides similar to the cortinarins from specimens of *C. speciosissimus*.\textsuperscript{136,137} Furthermore, it has been strongly suggested that the dimeric pyridine-N-oxide, orellanine (163), repeatedly isolated from other members of the genus *Cortinarius* and found as the corresponding diglycoside *in vivo*, is the potent compound responsible for the toxicity of these toadstools.\textsuperscript{136,138,139} Biological studies conducted on 163 revealed significant nephrotoxic activity; an average oral LD\textsubscript{50} value in mice of 39 mg kg\textsuperscript{-1} of body weight and intraperitoneal LD\textsubscript{50} in mice of 5 mg kg\textsuperscript{-1} of body weight have been reported though clinical data suggests a greater sensitivity to the toxin in humans than mice.\textsuperscript{139} Additionally, a strong fluorescence is associated with orellinine (164) and orelline (165), decomposition products of 163; most likely the same fluorescence originally attributed to the putative cortinarins.\textsuperscript{136} Further investigation into the existence of the cortinarins may be required.

![Figure 23: Orellanine and decomposition products.](image)

**1.2.5.3 Omphalotins**

Omphalotins A-I (166-174) are a family of dodecapeptides isolated from the jack-o’-lantern mushroom *Omphalotus olearius*, a poisonous, orange species noted for its bioluminescence.\textsuperscript{140} Members of this family exhibit strong, selective nematicidal activity against the economically important plant pathogen *Meloidogyne incognita* with LD\textsubscript{90} values falling between 2 and 5 µg mL\textsuperscript{-1} and low associated cytotoxicity (at concentrations below 50 µg mL\textsuperscript{-1}).\textsuperscript{140-142} This collection of peptides have been found to comprise a characteristically large number of both valine residues and methylated \(\alpha\)-nitrogens. Omphalotins B-I (167-174) contain an unusual oxidatively-modified tricyclic tryptophan residue with omphalotins F-I (171-174) also bearing an intriguing \(N\)-hydroxyl motif.\textsuperscript{140,141}
Table 5: Omphalotins.

<table>
<thead>
<tr>
<th>Name</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omphalotin B (167)</td>
<td>OCOCH₂C(Me)₂OH</td>
<td>OH</td>
<td>H</td>
</tr>
<tr>
<td>Omphalotin C (168)</td>
<td>OCOCH₂C(Me)₂OH</td>
<td>OAc</td>
<td>H</td>
</tr>
<tr>
<td>Omphalotin D (169)</td>
<td>OAc</td>
<td>OAc</td>
<td>H</td>
</tr>
<tr>
<td>Omphalotin E (170)</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>Omphalotin F (171)</td>
<td>H</td>
<td>H</td>
<td>OH</td>
</tr>
<tr>
<td>Omphalotin G (172)</td>
<td>H</td>
<td>OH</td>
<td>OH</td>
</tr>
<tr>
<td>Omphalotin H (173)</td>
<td>OAc</td>
<td>OAc</td>
<td>OH</td>
</tr>
<tr>
<td>Omphalotin I (174)</td>
<td>OCOCH₂C(Me)₂OH</td>
<td>OAc</td>
<td>OH</td>
</tr>
</tbody>
</table>
1.2.5.4 Peptaibols

Peptaibols are a class of fungal peptides characterised by a C-terminal amino alcohol in conjunction with a N-alkylated terminus and a high content of α,α-dialkylated amino acids such as α-aminoisobutyric acid (Aib). These compounds have pronounced antibiotic activity and act through the formation of transmembrane, voltage-gated ion channels that subsequently disrupt cell wall permeability and ultimately cause bacterial cell death. Two such peptaibols, tylopeptins A (175) and B (176), were isolated from the mushroom *Tylopilus neofelleus*. Biological testing via the agar diffusion test indicated activity against various Gram-positive bacteria with inhibition zones ranging from 13 to 18 mm.

![Figure 24: Tylopeptins A and B.](image)

Chrysospermins A-D (177-180) and boletusin (181) were isolated from the methanol extract of the fruiting body of the mushroom *Boletus spp* (Table 6). These peptaibols contain a labile Aib-Pro bond, an acetylated N-terminus and a C-terminal tryptophanol (trpol) residue. Investigation into the antimicrobial activity of 178, 180 and 181 by agar diffusion method showed inhibition zones ranging from 9-25 mm against numerous Gram-positive bacteria; the mode of action for these compounds being related to that of the previously mentioned peptaibols. Peptaibols 177-180 have been since patented as nematicidal and anthelmintic agents.
Table 6: Chrysospermins A-D (177-180) and boletusin (181).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Amino Acid Residue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1  2   3  4  5  6  7  8  9  10  11  12  13  14  15  16  17  18  19</td>
</tr>
<tr>
<td>177</td>
<td>AcPhe Aib Ser Aib Aib Leu Gln Gly Aib Aib Ala Ala Aib Pro Aib Aib Aib Gln Trpol</td>
</tr>
<tr>
<td>178</td>
<td>AcPhe Aib Ser Aib Aib Leu Gln Gly Aib Aib Ala Ala Aib Pro Iva Aib Aib Gln Trpol</td>
</tr>
<tr>
<td>179</td>
<td>AcPhe Aib Ser Aib Iva Leu Gln Gly Aib Aib Ala Ala Aib Pro Aib Aib Aib Gln Trpol</td>
</tr>
<tr>
<td>180</td>
<td>AcPhe Aib Ser Aib Iva Leu Gln Gly Aib Aib Ala Ala Aib Pro Iva Aib Aib Gln Trpol</td>
</tr>
<tr>
<td>181</td>
<td>AcPhe Aib Ala Aib Iva Leu Gln Gly Aib Aib Ala Ala Aib Pro Aib Aib Aib Gln Trpol</td>
</tr>
</tbody>
</table>
1.3 C2-Substituted Indole Alkaloids from the *Tricholoma* Genus

The *Tricholoma* genus of toadstools is a variety of white-spored, gilled mushrooms found worldwide, with a number of species being noted for a distinctive pungency and bitter taste.\textsuperscript{150} Investigation into the molecules responsible for this trait has proven difficult; the pungency has a delayed onset and is short-lived, suggesting the enzymatic generation of reactive compounds which promptly degrade.\textsuperscript{1} During these studies, a collection of indoles (182-185) were isolated and characterised from the fruiting bodies of *Tricholoma sciodes* and *Tricholoma virgatum*.\textsuperscript{150,151} 5-Methoxy-4-methoxymethyl-2-methylindole (186) has also been identified in the aroma bouquet of the related species *Tricholoma caligatum*.\textsuperscript{52,152} Most recently, 5,7-dimethoxy-2,4-dimethylindole (187) was isolated from specimens of *Tricholoma flavovirens*.\textsuperscript{153} While no biological activity has been identified for indoles 182-184 and 186, indoles 185 and 187 were both found to promote lettuce root growth and hinder hypocotyl growth at a concentration of 1 µmol/paper.\textsuperscript{153} Structurally, these compounds all share an unprecedented C2-methyl group and vacant C3-site, suggesting a biogenic origin other than L-tryptophan (18).

![Figure 25: 2-Methylindole derivatives from the *Tricholoma* genus.](image)

1.3.1 Dimeric Indoles from the *Tricholoma* Genus

In addition to the monomeric indoles, a number of bisindole natural products also bearing the same C2-methyl group have been isolated from various *Tricholoma* species. Indoles 188-190 are produced by *Tricholoma sciodes*.\textsuperscript{151} A collection of 2,2'-bisindoline-3,3'-diones were isolated from injured specimens of *Collybia peronata* and *Tricholoma scalpturatum*: peronatins A (191) and B (192) from *C. peronata* and the oxygenated derivatives (193 and 194) from *T. scalpturatum*.\textsuperscript{154} The bioactivities of 191-194 remain to be investigated.
1.3.2 Lascivol

While investigating the source of the bitter taste of *Tricholoma lascivum*, Eizenhöfer and co-workers isolated and structurally assigned the glutamate-derivative lascivol (195). This compound is believed to be produced as a chemical deterrent to predation and the structure was deduced using a combination of spectroscopic techniques and degradation studies. Labelling studies involving viable *T. lascivum* specimens revealed that the biosynthetic origin of 195 is via neither the shikimate or polyketide pathways; the methyl component of both methoxy groups present were found to be L-[\(^{13}\)C-methyl]methionine-derived while \(^{13}\)C-alanine and \(^{13}\)C-acetate were not incorporated.

Interestingly, it was observed that during the acid-induced degradation of 195, 5-methoxy-2,4-dimethylindole (185) was generated. The authors proposed a mechanism for this transformation (Scheme 4). Acid-mediated cleavage of the glutamic acid residue (196) affords hypothetical intermediate 197, which readily undergoes cyclisation and aromatisation with the
loss of two molecules of water and one of methanol, generating 5-methoxy-2,4-dimethyldindole (185) via intermediate 198. This was the first evidence of the alternative biosynthetic origin to L-tryptophan; the peculiar structural characteristics of the *Tricholoma*-produced indoles likely arise biosynthetically from lascivol.

**Scheme 4:** Degradation studies of lascivol (195) and proposed mechanism for the generation of indole 185 as reported by Eizenhöfer and co-workers.$^2$
1.3.2.1 Biosynthesis of *Tricholoma*-Produced C2-Substituted Indole Alkaloids

Later work published by Fons and co-workers investigating the composition of volatile extracts obtained from fresh *Clitocybe amoenolens*, *Tricholoma caligatum* and *Hebeloma radicosum* mushrooms, further explored the link between indoles 182-186 and lascivol (195). The aroma profiles of these fresh mushroom species were qualified by GC-MS techniques in combination with mass spectral databases and a noticeably high level of indole derivatives (compounds 182-186 along with numerous unidentifiable indole alkaloids comprised 84.4 % of the total isolated compounds) were detected in the extracts from *T. caligatum*. Considering the presence of these 2-methylated monomeric indole derivatives 182-186, Fons and co-workers proposed a tentative biosynthetic scheme that rationalises the experimental observations (Scheme 5).  \(^{152}\) 

Contrary to the work presented previously, \(^2\) it was suggested that the indoles found in various *Tricholoma* specimens could arise from polyketide intermediates 199 and 200. Oxidation and reduction processes could form intermediates 201-204 which, upon cyclisation and aromatisation, would form previously isolated indoles 182-186 (via presumed intermediates 205-207). Fons and co-workers also saw a link to lascivol (195) and postulated it could be formed from intermediate 204 through methylation and coupling with glutamic acid. \(^{152}\) The *Tricholoma*-produced bisindoles could also be included in this biosynthetic proposal. It was originally proposed that the peronatins (191 and 192) formed via an enzymatic hydrolysis and radical-mediated oxidative coupling of an unidentified, pungent indole precursor. \(^{154}\) Oxidation of indole 182 to reactive intermediate 208 would give access to the 2,2’-bisindolone framework. Stachel and co-workers, having carried out a biomimetic total synthesis of dimers 191, 192 and 194, verified this process. \(^{155}\) Upon isolating dimers 188-190, Pang and Sterner hypothesised that the nucleophilic addition of indole 183 or 184 to an electrophilic derivative (such as 4-methoxymethylindole 184) could be the route of formation. \(^{151}\)
Scheme 5: Proposed biosynthesis of indoles 182-186, lascivol (195)\textsuperscript{152} and related dimers.\textsuperscript{151,154} Isolated secondary metabolites highlighted in green.
1.3.3 Sciodole

Perhaps the most structurally unique of the known 2-methylindoles produced by the *Tricholoma* genus is sciodole (209). This natural product was isolated by Olov Sterner in 1993 from the pungent extract of the fruiting bodies of the mushroom *Tricholoma sciodes*. Sciodole was identified when fresh fruiting bodies of the mushroom species were damaged in a meat grinder in the presence of an extraction solvent. The unprecedented structure of sciodole was assigned based on HMQC and HMBC correlations. Two key structural features of this molecule appear relatively unique; the presence of a N-C7 bisindole linkage in the presence of a free C3-carbon on the indole, and the partially reduced carbocycle present within the dimer. It was suggested by Sterner that 209 was a dimer of 5-methoxy-2,4-dimethylindole (185) which, at the time, had not been isolated as a natural product. Sciodole is chiral with an associated $[\alpha]_{D}^{20} = +44^\circ$ ($c$ 1.5 in CDCl$_3$) however, the enantiomeric excess was not reported.

![Figure 27: Assigned structure of sciodole (209) and observed long-range HMBC correlations.](image)

NOESY experiments and $^1$H-NMR coupling constants were used to confirm the *anti*-relationship between the two substituents in sciodole (209). The proton at C7 was proposed to be in a pseudoaxial arrangement due to the coupling constants exhibited by the two C6 protons (10.3 Hz and 5.7 Hz), aligning with approximate dihedral angles of 160° and 50°, respectively. The C5-methoxy group was also assigned as pseudoaxial as it displayed a NOESY correlation to the C7-proton. The pseudoequatorial positioning of the C5-proton was confirmed by a NOESY correlation to the terminal alkene group (suggesting they are situated in a similar plane) and the comparable coupling constants of 3.6 Hz and 2.3 Hz with the two protons at C6.
1.3.3.1 Proposed Biosynthesis of Sciodole

When considering the biosynthesis of sciodole (209), the information put forth by the numerous research groups mentioned prior is enlightening. We propose a dimerization event occurring between 5-methoxy-2,4-dimethylindole (185) and one of the lascivol-degradation intermediates (Scheme 6). The absolute stereochemistry of sciodole (209) would be dictated by the stereochemistry originally present in lascivol (195), which was determined by NMR experiments and X-ray crystallography; the C8-methoxy group of lascivol (195) was found to have an (S)-configuration and be positioned in a pseudoaxial orientation, while the methoxy group at C6 was anti to this and in a pseudoequatorial arrangement.²

Lascivol (195) could undergo acid-mediated cleavage within the mushroom and subsequent cyclisation as proposed by Eizenhöfer to afford intermediate 198.² Upon cyclisation to form the pyrrole ring, the half chair conformation of 195 would flatten into the amino-1,3-cyclohexadiene ring of intermediate 198. An S_N2-type attack of indole 185 to 198 could then occur at C7, generating dimeric species 210. In this dimer, the protons at C6 and the proton and bulky indole substituent bonded to C7 would eclipse one another, generating significant torsional strain across the C6-C7 bond (highlighted in red). To reduce this strain, the internal alkene would rapidly migrate out of the ring, thus creating the tetrahydroindole moiety of sciodole (209). This type of 1,3-hydrogen migration to form exocyclic double bonds has been
observed to occur in highly strained ring systems and can be either an acid- or metal-mediated process.\textsuperscript{156,157} Positioning of the larger indole substituent in a pseudoequatorial position would force the methoxy group at C5 to adopt a pseudoaxial orientation during this bond migration. The final outcome of this is in agreement with the proposed structure for sciodole (209).\textsuperscript{1}

As with all biogenic pathways, the aforementioned transformation could be enzymatically-mediated. However, there are a limited number of enzymes that catalyse S\textsubscript{N}2 reactions due to the energetically-disfavoured bispyrimidal transition state involved in bimolecular nucleophilic substitution processes.\textsuperscript{158} In addition to this, the enzymes that do catalyse S\textsubscript{N}2 reactions are much more likely to react at primary carbons, not the secondary carbon (C7) present in postulated intermediate 198.\textsuperscript{158} These considerations suggest that if this key coupling reaction were to be an S\textsubscript{N}2 process, it could more likely be a non-enzymatic process.
Scheme 6: Our proposed $S_N2$-type biosynthesis of sciodole with accompanying 3D representations. Torsional strain highlighted in red.
An alternative $S_N1$-type dimerization event could also be considered (Scheme 7, A). In this instance, the aforementioned alkene isomerisation would occur first, driven by the torsional strain in dihydroindole 198, generating tetrahydroidole 211. Donation of the nitrogen lone pair into the pyrrole ring would then displace the C7-methoxy group and afford azafulvenium intermediate 212. Finally, nucleophilic attack of indole 185 to this electrophilic species would generate sciodole (209). The stereochemistry at C5 would direct indole addition to the opposite face, explaining the observed anti-relationship of 209.

The generation of such pyrrolic electrophiles is well represented in the biosyntheses of various porphyrins, key structural components of both chlorophyll and heme. For example, porphobilinogen (213) is a pyrrole-containing intermediate which is oligomerised to the tetrapyrrole hydroxymethylbilane (214) via the activity of porphobilinogen deaminase (PBG deaminase) (Scheme 7, B). Investigation into the likely mechanism through which this transformation occurs has indicated that an $S_N1$ process is very likely, involving an enzyme-bound azafulvenium intermediate 215.
Scheme 7: A) Our proposed $S_N1$-type biosynthesis of sciocole (209) with accompanying 3D representations; B) Biosynthesis of hydroxymethylbilane (214) via an azafulvenium intermediate. Formed bonds highlighted in green.
1.4 Research Objectives

The aims of this doctoral research project pivot around the total synthesis of a number of the unusual 2-methylindoles isolated from the *Tricholoma* genus of mushrooms, namely the bisindole sciodole (209). During these synthetic endeavours, we hope to extend the application of various methodologies with respect to both the indole and pyrrole heterocycles.

Our research aims are therefore to:

- Explore the biosynthesis associated with the of numerous 2-methylindoles produced by the *Tricholoma* genus.

- Utilise a novel *o*-quinone methide electrophile, generated from a Mannich base, as a means of accessing a variety of C4-functionalised indoles.

- Extend the use of iridium-catalysed C-H activation as a means of accessing C7-substituted indoles. Once obtained, C7-activated indoles will be utilised in various coupling reactions to form the key carbon-nitrogen bisindole linkage of sciodole (209).

- Access the novel tetrahydroindole derivatives implicated in the biosynthesis of sciodole (209) and explore the chemistry of these intermediates in a bioinspired approach.

- Confirm the assigned structure of sciodole (209) and investigate any bioactivities associated with this natural product.
Chapter 2: **FIRST GENERATION APPROACH TO SCIODOLE**
2.1 Proposed Synthesis of (±)-Sciodole

Our first generation route to (±)-sciodole (209) is presented in Scheme 8. The synthesis would start from 5-hydroxy-2,4-dimethylindole (205) that upon C-H functionalisation would afford boronate ester 216. This compound would subsequently undergo a Chan-Evans-Lam coupling with indole 185 to form the key bisindole linkage (highlighted in blue) found in the natural product. Appending an electron-withdrawing group to the phenol of 217 could help realise a ring-selective Birch reduction to afford intermediate 218. An ambitious tautomerisation process could possibly lead to dimer 219, containing the required anti-relationship between the C5- and C7-substituents; this relative stereochemistry could be driven by orientating the smaller methoxy group into a pseudoaxial position, away from the bulky indole substituent (in a similar fashion to that presented in Section 1.3.3.1). Finally, phenol deprotection and subsequent methylation would afford (±)-sciodole (209).

Scheme 8: Proposed synthesis of (±)-sciodole (209).
2.2 Synthesis of 5-Hydroxy-2,4-dimethylindole (205)

The required substitution pattern of indole 205 was envisaged to be accessible through a Nenitzescu reaction, affording 5-hydroxy-2-methylindole (220) from \( p \)-benzoquinone (221) and a 3-aminocrotonate (222) (Scheme 9). The installation of the methyl group at C4 would be achieved by a phenol-directed Mannich reaction to give aminoalkylated intermediate 223, followed by reductive deamination.

![Scheme 9: Proposed synthesis of 5-hydroxy-2,4-dimethylindole (205).]

2.2.1 Nenitzescu Indole Synthesis

The condensation of \( p \)-benzoquinone derivatives with \( \beta \)-amino-\( \alpha,\beta \)-unsaturated carbonyl compounds to afford 5-hydroxyindoles is known as the Nenitzescu reaction.\textsuperscript{161} C. D. Nenitzescu first reported this transformation in 1929 after observing the formation of 5-hydroxyindole 224 upon refluxing \( p \)-benzoquinone (221) with ethyl 3-aminocrotonate (225) in acetone (Scheme 10, A).\textsuperscript{162} However, it wasn’t until the 1960s when the scope of this reaction was really explored.\textsuperscript{161,163} A notable contribution to the development of the Nenitzescu reaction was the work conducted by Allen and co-workers whereby mitomycin-related indoloquinone 226 and a collection of associated analogues were synthesised (Scheme 10, B).\textsuperscript{164} Today, the Nenitzescu indolisation is generally considered to be the most reliable method to access 5-hydroxyindoles.\textsuperscript{165}
2.2.1.1 Mechanism of the Nenitzescu Indole Synthesis

The mechanism and regiochemical outcome of the Nenitzescu reaction has been thoroughly investigated. Although the exact mechanism remains debated, two distinct routes have been proposed (Scheme 11). The most likely first step, accepted by both mechanistic proposals, is a Michael-type addition of the enamine to the benzoquinone to afford the adduct. Following Allen’s proposed mechanism (Scheme 11, A), cyclisation then occurs through imine attack to give bicyclic hemiaminal. A final loss of water affords the aromatised indole. The alternative mechanism, originally proposed by Patrick and Saunders, hinges on an oxidation-reduction process (Scheme 11, B). After enamine addition to the benzoquinone, tautomerisation to hydroquinone occurs. This compound is oxidised, via a bimolecular face-to-face electron transfer complex, to give p-benzoquinone. Cyclisation can then occur to generate hemiaminal, which upon entering the ‘electron transfer complex’, is reduced to the desired 5-hydroxyindole.
More recently, it has been found that depending on the conditions employed, the Nenitzescu reaction proceeds via either of the pathways outlined in Scheme 4.\textsuperscript{165} If a polar solvent with a high dielectric constant (such as nitromethane) is used, the oxidation-reduction mechanism dominates (Scheme 11, B).\textsuperscript{165} However, when the reaction is conducted in non-polar solvents and in the presence of weak Lewis or Brønsted acids, the original mechanism proposed by Allen operates (Scheme 11, A).\textsuperscript{165}
2.2.1.2 Regioselectivity of the Nenitzescu Indole Synthesis

The Nenitzescu reaction is highly regioselective with substituents on the quinone fragment dictating the site of enamine attack.\textsuperscript{161} For monosubstituted quinone 233, the formation of 4-, 6- and 7-substituted indoles are possible (Scheme 12). The presence of an electron-donating group at the C2-position of quinone 233 deactivates the adjacent C3-position towards enamine attack. As a consequence, the initial nucleophilic addition is driven to either C5 or C6, affording a mixture of both C6- and C7-substituted indoles (234 and 235). The size of the quinone substituent (R) dictates the ratio of these two products, with bulkier groups preferentially forming C6-substituted indoles.\textsuperscript{168} 2-Halo-p-benzoquinones give rise to mixtures of C6- and C7-substituted indoles, indicating that in this system the resonance effect outweighs inductive withdrawal and the halogens act predominantly as an electron-donating group.\textsuperscript{168} Conversely, a C2-electron withdrawing group on p-benzoquinone 233 affords exclusively the C4-substituted indole (236).\textsuperscript{168} The inductive effect of both carbomethoxy and trifluoromethyl substituents significantly activates the adjacent C3-position towards nucleophilic addition of the enamine, counteracting the steric effects disfavouring ortho-addition.\textsuperscript{168}

Scheme 12: Effect of quinone substituent on regiochemical outcome.

The regiochemical effect exerted by the trifluoromethyl group has been exploited to access indoles bearing substitution patterns that are otherwise difficult to install (Scheme 13).\textsuperscript{168} For example, treatment of 3-chloro-2-trifluoromethyl-p-benzoquinone (237) with ethyl 3-aminocrotonate gives exclusively indole 238 which, upon acid-mediated decarboxylation,
affords 6-chloro-5-hydroxyindole (239). \(^\text{168}\) Alternatively, quinone 240 can undergo identical reaction conditions to generate the 7-chloroindole 241. \(^\text{168}\)

**Scheme 13:** Access to 6- and 7-chloroindoles using the Nenitzescu reaction as reported by Littell and Allen. \(^\text{168}\)

Moreover, the C4-trifluoromethyl group can be retained and converted to a methyl group through use of the more labile tert-butyl 3-aminocrotonate (Scheme 14). Nenitzescu indolisation and subsequent methyl protection generates indole 242 which, upon decarboxylation using \(p\)-toluenesulfonic acid (\(p\)-TSA), affords C4-trifluoromethylindole 243. \(^\text{168}\) Subsequent reduction using lithium aluminium hydride (LiAlH₄) installs a methyl group at the C4-position, outlining a synthetic route to 5-methoxy-2,4-dimethylindole (185). \(^\text{168}\)
Scheme 14: Littell and Allen’s synthesis of 5-methoxy-2,4-dimethylindole (185) using the Nenitzescu reaction.\textsuperscript{168}

2.2.1.3 Synthesis of 5-Hydroxy-2-methylindole (220)

The first generation approach to sciodole began with synthesis of 5-hydroxy-2-methylindole (220). Following the literature procedure, \( p \)-benzoquinone (221) and methyl 3-aminocrotonate (244) underwent a Nenitzescu reaction to give indole 245 (Scheme 15).\textsuperscript{169} Decarboxylation afforded the desired 5-hydroxy-2-methylindole (220) in good yield.

Scheme 15: Synthesis of 5-hydroxy-2-methylindole (220).
2.2.2 Mannich Reaction of 5-Hydroxyindoles

With indole $\text{220}$ in hand, attention turned to the subsequent Mannich reaction. The Mannich reaction of 5-hydroxyindoles has been well explored by Monti and Johnson.\textsuperscript{170} Reaction of indoles with Mannich reagents (such as iminium ions and aminomethylols) generally proceeds at the more reactive C3 position (Scheme 16). However, introduction of a hydroxyl group at C5 on the carbocycle overrides this intrinsic reactivity and allows for preferential functionalisation at C4.\textsuperscript{170} Although electronic effects can be taken into consideration (i.e., the C4-position is now more nucleophilic due to the electron-donating effect of the hydroxyl group), a strong proposal for a hydrogen bonding interaction between the phenol and incoming electrophile has been made due to the lack of ortho-functionalisation observed when 5-alkoxyindoles are used as substrates.\textsuperscript{170,171} Mechanistic studies\textsuperscript{172} show that under basic conditions, formaldehyde and dialkylamines exist in equilibrium with dialkylaminomethylol (246). Reaction of the nucleophilic indole with the species 246 via a 6-membered transition state 247 then affords the C4 aminomethylated product 248.\textsuperscript{171} The aforementioned chelate has also been implicated in the ortho-substitution of phenol in the Mannich reaction.\textsuperscript{173}

**Scheme 16**: Mannich reaction of unsubstituted indoles and 5-hydroxyindoles.\textsuperscript{170}
The regioselectivity of this reaction (between the two available ortho sites) is governed by electronics and can be explained by considering the cationic intermediates involved.\textsuperscript{170} As presented in Scheme 17, allylic delocalisation of the positive charge resulting from initial reaction at C4 affords three possible resonance contributors (249-251), two of which not requiring participation of the pyrrole ring π-system (an energetically less favourable pathway). This is not the case when substitution occurs at C6; charge delocalisation generates only two resonance contributors (252 and 253) with one disrupting the aromaticity of the pyrrole ring.\textsuperscript{170}

**Scheme 17:** Cationic intermediates responsible for Mannich reaction regioselectivity.\textsuperscript{170} Energetically disfavoured resonance contributors highlighted in red.
2.2.2.1 Reductive Deamination of ortho-Hydroxy Mannich Bases

By far the most common method for the reductive deamination of Mannich bases to corresponding methylated compounds is hydrogenolysis in the presence of palladium or platinum on carbon.\textsuperscript{174} In the presence of an ortho-hydroxy substituent, an attractive alternative to this functional group interconversion is a hydride-mediated reduction. Yamada and coworkers originally demonstrated that the quaternary ammonium salt of various ortho-(dimethylamino)methylphenols (254) readily convert to the corresponding ortho-methylated derivatives (255) upon reaction with sodium cyanoborohydride (Scheme 18, A).\textsuperscript{175} Later work by Minami and Kijima showed that a similar process could be achieved by heating Mannich base 256 with sodium borohydride in DMSO (Scheme 18, B).\textsuperscript{176}

Scheme 18: A) Conversion of quaternary ammonium Mannich bases to ortho-methylphenols by Yamada;\textsuperscript{175} B) Reduction of 256 by Minami and Kijima.\textsuperscript{176}

Despite this literature precedent, the Mannich reaction has not yet been used to facilitate the installation of a methyl group at C4 of indole. Upon treatment of indole 220 with formaldehyde and dimethylamine, the desired C4-substituted Mannich base 257 was exclusively formed (Scheme 19). To our delight, the reductive deamination of 257 using sodium borohydride in refluxing ethanol proceeded in good yield, affording the desired indole
205. This outlines the first application of this hydride-mediated deamination process on the indole carbocycle.

Scheme 19: Achieved installation of the C4-methyl group through reductive deamination.

2.2.2.2 Mechanism

The hydride-mediated deamination of Mannich base 257 is proposed to occur through the pyrolytic formation of ortho-quinone methide (o-QM) intermediate 258 via loss of dimethylamine (Scheme 20). Subsequent nucleophilic attack of hydride followed by aromatisation would result in the installation of a methyl group at C4.

Scheme 20: Proposed mechanism for hydride reduction of Mannich base 257.
2.2.2.3 Synthesis of 5-methoxy-4-methoxymethyl-2-methylindole

With \(\alpha\)-QM 258 acting as a key synthetic intermediate, we saw a unique opportunity to access an additional *Tricholoma*-derived natural product, 5-methoxy-4-methoxymethyl-2-methylindole (186). Fons and co-workers isolated this 2-methylindole from specimens of *Tricholoma caligatum* while investigating the key odorants produced by various mushroom species.\(^{152}\) We predicted that by trapping the \(\alpha\)-QM with methanol (Scheme 21), Mannich base 257 could be converted to hydroxyindole 259. Subsequent \(O\)-methylation would give access to natural product 186.

Scheme 21: Proposed synthesis of 5-methoxy-4-methoxymethyl-2-methylindole (186).

Initial attempts to install the C4-methoxymethyl group through thermal generation of \(\alpha\)-QM 258 was met with limited success (Table 7, entry 1); a trace amount of the hydroxyindole 259 was isolated. Adding one equivalent of acetic acid to generate the \(\alpha\)-QM resulted in a slightly improved yield (entry 2).\(^ {177}\) Amberlyst 15 (entry 3) and silica gel (entry 4), used as heterogeneous acids in methanol, both resulted in starting material degradation. Ammonium chloride also failed to produce a reaction (entry 5). Generating the \(\alpha\)-QM 258 thermally in the presence of sodium methoxide (entry 6) gave hydroxyindole 259 in low yield. Suspecting that the formation of hydroxyindole 259 was reversible at the high reaction temperatures needed to generate \(\alpha\)-QM 258,\(^ {178}\) we next attempted to quaternarise the dimethylamino group through methylation; converting Mannich bases to ammonium salts has been shown to allow \(\alpha\)-QM generation to proceed at room temperature.\(^ {179}\) The addition of iodomethane to the reaction (entry 7) gave the desired hydroxyindole 259 in 47% yield in combination with trace amounts of the methylated indole 186 arising from concomitant \(O\)-alkylation. Inspired by this, we increased the equivalents of iodomethane and generated 186 in an acceptable yield of 24% for two synthetic transformations (entry 8).
Table 7: Reaction of Mannich base 257 with methanol.

![Reaction of Mannich base 257 with methanol.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (eq)</th>
<th>Additive(s) (eq)</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>Outcome (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>259 (trace)</td>
</tr>
<tr>
<td>2</td>
<td>AcOH (1)</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>259 (5%)</td>
</tr>
<tr>
<td>3</td>
<td>Amberyst 15</td>
<td>-</td>
<td>40</td>
<td>6</td>
<td>Degradation</td>
</tr>
<tr>
<td>4</td>
<td>Silica gel</td>
<td>-</td>
<td>100</td>
<td>48</td>
<td>Degradation</td>
</tr>
<tr>
<td>5</td>
<td>NH₄Cl (5)</td>
<td>-</td>
<td>100</td>
<td>24</td>
<td>Degradation</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>NaOMe (2)</td>
<td>100</td>
<td>24</td>
<td>259 (trace)</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>NaOMe (3)</td>
<td>rt</td>
<td>4</td>
<td>259 (47%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MeI (3)</td>
<td></td>
<td></td>
<td>186 (trace)</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>NaOMe (3)</td>
<td>rt</td>
<td>13</td>
<td>186 (24%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MeI (8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All reactions carried out in methanol.

This details the first total synthesis of 5-methoxy-4-methoxymethyl-2-methylindole 186. In the work published by Fons and co-workers, the compounds isolated from the mushroom specimens were characterised by mass spectrometry fingerprinting.¹⁵² As a consequence, no NMR data was available for a direct comparison.
2.3 Synthesis of N-linked Dimer 217

Shifting our focus back to the CEL-based route to sciodole, we sought to access boronate ester 216 via a C7-H functionalisation reaction of synthesised hydroxyindole 205 (Scheme 22). Concurrently, the 5-methoxyindole coupling partner 185 could be synthesised through methylation of the same indole 205. The bisindole 217 would be accessed through the Chan-Evans-Lam coupling of indole 185 and 216, forming the key C-N bisindole linkage (highlighted in blue).


2.3.1 Selective Functionalisation of Indole at C7

The selective C7-functionalisation of the indole heterocycle has historically relied on directed metalations followed by reaction with an electrophile. In 1999, Iwao and co-workers originally reported the unusual C7-lithiation of various N-2,2-diethylbutanoyl-protected, C3-substituted indoles (260) (Scheme 23, A). In this case, the directing group sterically impeded lithiation of the more thermodynamically acidic C2 site (blue) and favoured kinetic C7-deprotonation (red) via a complex-induced proximity effect (transition state 261); this transformation was not completely selective with small amounts (<13%) of C2-substituted products isolated for some examples. In 2003, Snieckus and co-workers published work expanding on this, enabling the C7-H functionalisation of C3-unsubstituted indoles (262) (Scheme 23, B); the di-tert-butylphosphinoyl directing group improved on the site-
selectivity achieved by Iwao, however this methodology was disadvantaged by harsh and low yielding deprotection conditions.\textsuperscript{183}

![Scheme 23: A) Work by Iwao and co-workers;\textsuperscript{181} B) Selective C7-functionalisation as reported by Snieckus and co-workers.\textsuperscript{183}]

### 2.3.1.1 Iridium-catalysed Borylation of Indole

Smith and co-workers streamlined the access to C7-functionalised indoles (263) with their 2006 work on the iridium-catalysed borylation reaction (Scheme 24).\textsuperscript{180} This reaction provided the first general and reliable method to install a synthetic handle at the indole C7 site without the need for pre-installation of a directing group onto the nitrogen of 264.\textsuperscript{180} The generally accepted explanation for this regioselectivity is through coordination of the heteroatom to the active iridium catalyst (as demonstrated in transition state 265) and delivery of the BP\textsubscript{in} group to the adjacent C7 site (Scheme 24).
Scheme 24: N-Directed, C7-borylation of the indole heterocycle as reported by Smith and co-workers.\textsuperscript{180}

2.3.1.2 Catalytic Cycle

The catalytic cycle of the iridium-catalysed borylation has been thoroughly probed and is summarised in Scheme 25.\textsuperscript{184} Active Ir\textsuperscript{III} species 266 is formed \textit{in situ} from pre-catalysts, ligands and a boron source (such as pinacolborane, HBPin, or bis(pinacolato)diboron, B\textsubscript{2}Pin\textsubscript{2}). This species oxidatively inserts across the C-H bond in the substrate, forming the unusual Ir\textsuperscript{V} species 267. Reductive elimination generates iridium-hydride species 268 and the borylated product. Catalyst regeneration occurs through consumption of a HBPin or B\textsubscript{2}Pin\textsubscript{2} molecule (generating intermediate 269) which, upon H\textsubscript{2} or HBPin liberation respectively, gives active catalyst 266. This catalytic cycle has been supported by computational studies.\textsuperscript{184,185}
Scheme 25: Catalytic cycle of the iridium-catalysed C-H borylation.\textsuperscript{184}

### 2.3.1.3 Attempted C-H Borylation of Hydroxyindole 205

Application of this iridium-catalysed C-H functionalisation to 5-hydroxy-2,4-dimethylindole (205) began promptly to install the synthetic handle at C7. Employing the standard iridium-catalysed borylation procedure as presented in early work by Ishiyama, Takagi, Hartwig and Miyaura,\textsuperscript{186} various reaction conditions were screened (Table 8). Initial conditions utilising 3 mol\% of the (1,5-cyclooctadiene)(methoxy)iridium(I) dimer ([Ir(OMe)COD]\textsubscript{2}) and 6 mol\% of the 4,4′-di-\textit{tert}-butyl-2,2′-bipyridine ligand (dtbpy, 270) in THF at 60 °C gave no reaction after 24 hours (Table 8, entry 1). Increasing both the catalyst and ligand loading, amount of B\textsubscript{2}Pin\textsubscript{2} and temperature (entry 2) also failed to give the desired product. A solvent change to dioxane and temperature increase to 100 °C (entry 3) also proved futile. Increasing the reactivity of the catalyst by employing the more rigid and electron-rich 3,4,7,8-tetramethyl-1,10-phenanthroline ligand (Me\textsubscript{4}Phen, 271) in both THF and dioxane (entries 4 and 5 respectively) failed to produce a reaction.\textsuperscript{184} In all instances, starting material 205 was recovered.
Table 8: Attempted C7-H borylation of hydroxyindole 205.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Ligand (mol%)</th>
<th>B₂Pin₂ (eq)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>dtbpy (6)</td>
<td>1.5</td>
<td>THF</td>
<td>60</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>dtbpy (12)</td>
<td>2.5</td>
<td>THF</td>
<td>80</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>dtbpy (12)</td>
<td>2.5</td>
<td>dioxane</td>
<td>100</td>
<td>48</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>Me₄Phen (12)</td>
<td>2.5</td>
<td>THF</td>
<td>80</td>
<td>48</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Me₄Phen (12)</td>
<td>2.5</td>
<td>dioxane</td>
<td>100</td>
<td>24</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

All reactions carried out in sealed tubes in dry, degassed solvent.

The reason for the failure of the C7-H borylation, outlined in Table 8, could be due to the reactivity of hydroxyindole 205; the presence of acidic protons, such as phenols, can make substrates incompatible with the iridium-catalysed C-H borylation reaction.¹⁸⁴ Reaction of hydroxyindole 205 with the active catalyst 266 could generate iridium hydride species 268 and O-borylated indole 272, significantly hampering the desired C7-H borylation (Scheme 26). Since O-boronate esters have been demonstrated to readily cleave upon workup,¹⁸⁷ this could explain the observed lack of reaction and recovery of starting material 205.
Scheme 26: Suggested $O$-borylation of hydroxyindole 205 and reconversion to starting material.
2.3.2 Synthesis of 5-Methoxy-2,4-dimethylindole

Given that the 5-hydroxyindole 205 failed to undergo C7-H borylation, we moved forward to synthesise methoxyindole 185. The hydroxyindole 205 was subjected to standard methylating conditions using dimethylsulfate (Me₂SO₄) and potassium carbonate in acetone, affording 185 in good yield (Scheme 27). Methylation of the indole nitrogen was not observed; the pKa difference between the phenol and indole N-H allowed for selective protection through use of potassium carbonate as a base. Coincidentally, 5-methoxy-2,4-dimethylindole (185) is a natural product produced by the Tricholoma genus and as such this synthesis outlines a novel route to this compound.¹⁵¹

![Scheme 27: Synthesis of 5-methoxy-2,4-dimethylindole 185.](image)

Pang and Sterner isolated indole 185 from *Tricholoma sciodes*,¹⁵¹ stating that the NMR data they had recorded was identical to that of a synthetic sample previously prepared by Eizenhöfer and co-workers.² The ¹H NMR data for indole 185 was found to be in good agreement with that presented by Eizenhöfer (Table 9).²
**Table 9:** $^1$H NMR and $^{13}$C NMR spectroscopic data for synthetic and natural 5-methoxy-2,4-dimethylinindole (185).

![Indole structure](image)

<table>
<thead>
<tr>
<th>H</th>
<th>Synthetic 185</th>
<th>Our Synthetic 185</th>
<th>Difference in chemical shift</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\delta_H$ (CDCl$_3$, 200/400 MHz)</td>
<td>$\delta_H$ (CDCl$_3$, 400 MHz)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.71, br s</td>
<td>7.71, br s</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>6.16, m</td>
<td>6.18, m</td>
<td>+0.02</td>
</tr>
<tr>
<td>6</td>
<td>6.78, d (9)</td>
<td>6.80, d (8.7)</td>
<td>+0.02</td>
</tr>
<tr>
<td>7</td>
<td>7.05, d (9)</td>
<td>7.07, d (8.7)</td>
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</tr>
<tr>
<td>8</td>
<td>2.42, d (1)</td>
<td>2.44, d (1.0)</td>
<td>+0.02</td>
</tr>
<tr>
<td>9</td>
<td>2.38, s</td>
<td>2.39, s</td>
<td>+0.01</td>
</tr>
<tr>
<td>OMe</td>
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<td>3.84, s</td>
<td>+0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C</th>
<th>Synthetic 185</th>
<th>Our Synthetic 185</th>
<th>Difference in chemical shift</th>
</tr>
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<tr>
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<td>$\delta_C$ (CDCl$_3$, 75 MHz)</td>
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</tr>
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<td>+0.3</td>
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</tr>
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<td>5</td>
<td>151.2</td>
<td>151.4</td>
<td>+0.2</td>
</tr>
<tr>
<td>6</td>
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<td>107.7</td>
<td>+0.1</td>
</tr>
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</tr>
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<td>7a</td>
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<td>+0.2</td>
</tr>
<tr>
<td>8</td>
<td>12.1</td>
<td>12.2</td>
<td>+0.1</td>
</tr>
<tr>
<td>9</td>
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</tr>
<tr>
<td>OMe</td>
<td>57.8</td>
<td>58.0</td>
<td>+0.2</td>
</tr>
</tbody>
</table>

$^a$ NMR frequency not specified in paper. J values in brackets and reported in Hz.
2.3.2.1 C7-H Borylation of 5-Methoxy-2,4-dimethylindole

With methoxyindole 185 in hand, we revisited the iridium-catalysed C7-borylation. Indole 185 was submitted to standard borylation conditions utilising the Me₄Phen ligand in THF at 80 °C (Scheme 28). To our delight, 7-borylindole 273 was obtained in good yield, suggesting that the phenol of hydroxyindole 205 was indeed limiting the iridium-catalysed borylation reaction. With revised coupling partners 185 and 273 at hand, we moved towards investigating the Chan-Evans-Lam coupling.

**Scheme 28:** Borylation of 5-methoxy-2,4-dimethylindole (185).
2.3.3 Chan-Evans-Lam Coupling

The oxidative formation of bonds between aryl boron species and heteroatoms is known as the Chan-Evans-Lam coupling (CEL coupling).\textsuperscript{161} This transformation was reported in 1998 as three consecutive publications (Scheme 29).\textsuperscript{188} Chan and co-workers found that various amines and alcohols could be coupled to aryl boron species in the presence of cupric acetate and an amine base (Scheme 29, A).\textsuperscript{188} In an almost identical procedure, Evans and co-workers synthesised a variety of diaryl ethers from phenols and aryl boron species (Scheme 29, B).\textsuperscript{189} Finally, Lam and co-workers explored the carbon-nitrogen bond formation between aryl boron species and a myriad of nitrogen-heterocycles (Scheme 29, C).\textsuperscript{190} The CEL reaction occupies a niche area in cross-couplings; the use of copper as a catalyst allows for a cheaper, less toxic and air stable alternative to other metal-catalysed coupling reactions.\textsuperscript{191}

\begin{align*}
\textbf{A)} & \quad \begin{align*}
\text{R}^1 \text{B(OH)}_2 & + \text{XR}^2 \\
& \xrightarrow{\text{Cu(OAc)}_2, \text{NEt}_3 \text{ or pyridine, DCM, rt}} \text{R}^1 \text{X} \\
& \quad \text{X = NH, O}
\end{align*} \\

\textbf{B)} & \quad \begin{align*}
\text{R}^1 \text{B(OH)}_2 & + \text{R}^2 \text{OH} \\
& \xrightarrow{\text{Cu(OAc)}_2, \text{NEt}_3, \text{DCM, 4Å MS, rt}} \text{R}^1 \text{R}^2 \\
& \quad \text{O}
\end{align*} \\

\textbf{C)} & \quad \begin{align*}
\text{R} \text{B(OH)}_2 & + \text{HN}_X \quad X = \text{N, CH} \\
& \xrightarrow{\text{Cu(OAc)}_2, \text{NEt}_3 \text{ or pyridine, DCM, rt}} \text{R} \\
& \quad \text{N} \\
& \quad \text{X = N, CH}
\end{align*}
\end{align*}

\textbf{Scheme 29}: Seminal work published by A) Chan and co-workers;\textsuperscript{188} B) Evans and co-workers;\textsuperscript{189} and C) Lam and co-workers.\textsuperscript{190}
2.3.3.1 Catalytic Cycle of the Chan-Evans-Lam Coupling

A detailed investigation into the catalytic cycle of the CEL coupling reaction is presented in Scheme 30. Although not all aspects of the process are understood, recent work by Watson and co-workers has elucidated the key steps involved in the amination variant of this reaction.\textsuperscript{192} $[X_2Cu(OAc)_2]$ (274) is denucleated by the amine substrate to give the active Cu$^{II}$-complex 275.\textsuperscript{192} Transmetallation with the aryl boron species affords Cu$^{II}$-intermediate 276 which subsequently undergoes oxidation to Cu$^{III}$-species 277 through a disproportionation process.\textsuperscript{192} Reductive elimination forms the desired arylamine product 278 and Cu$^I$-species 279. The catalytic cycle is completed by oxidation of 279 to the active Cu$^{II}$-complex 275 in the presence of O$_2$, AcOH and the amine substrate.\textsuperscript{192}

\textbf{Scheme 30}: Catalytic cycle of the Chan-Evans-Lam amination as proposed by Watson and co-workers.\textsuperscript{192} $X = OH$, OAc, solvent, appropriate leaving group.
2.3.3.2 Synthesis of 5,7-Dimethoxy-2,4-dimethylindole

With 7-borylindole 273 in hand, yet another 2-methylindole from the *Tricholoma* genus of mushrooms caught our attention as readily accessible from the methodology we had developed (Scheme 31). 5,7-Dimethoxy-2,4-dimethylindole (187) was recently isolated from specimens of *Tricholoma flavovirens* by Kawagishi and co-workers. We envisioned that CEL etherification with methanol would install the C7-methoxy group and complete the first total synthesis of 187.

**Scheme 31:** Proposed synthesis of 5,7-dimethoxy-2,4-dimethylindole (187).

Our attempts to synthesise indole 187 via the CEL etherification reaction are presented in Table 10. Using stoichiometric Cu(OAc)$_2$·H$_2$O in a 1:1 solvent mixture of dichloromethane and methanol (Table 10, entry 1) resulted in protodeborylation to give methoxyindole 185 as the only product. Reducing the temperature from 40 °C to room temperature (entry 2) gave a small amount of the desired product 187 along with a significant amount of indole 185. Decreasing the amount of Cu(OAc)$_2$·H$_2$O to 60 mol% (oxygen being sufficient to reoxidise the copper(I) catalyst) and changing the solvent to methanol (entry 3) resulted in a slightly decreased yield of 187. Altering the base to triethylamine and pyridine (entries 4 and 5 respectively) resulted in complete protodeborylation of 7-borylindole 273. With the DMAP-assisted CEL conditions being crucial for the formation of 187, we next decreased the amount of methanol used. Employing a 3:1 solvent mixture of dichloromethane and methanol gave the desired product 187 as the only observed product, though in modest yield (entry 6). Decreasing the amount of methanol (entry 7) resulted in a significantly decreased yield of 187.
Table 10: CEL etherification of 7-borylindole 273 with methanol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu(OAc)$_2$$\cdot$H$_2$O (mol%)</th>
<th>Additive (eq)</th>
<th>Solvent (ratio)</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>Outcome (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>DMAP (2.0)</td>
<td>DCM/MeOH (1:1)</td>
<td>40</td>
<td>3</td>
<td>185 (30%)</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>DMAP (2.0)</td>
<td>DCM/MeOH (1:1)</td>
<td>rt</td>
<td>5</td>
<td>187 (21%)</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>DMAP (2.0)</td>
<td>MeOH</td>
<td>rt</td>
<td>1</td>
<td>187 (18%)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>NEt$_3$ (2.0)</td>
<td>MeOH</td>
<td>rt</td>
<td>2</td>
<td>185</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>Pyridine (2.0)</td>
<td>MeOH</td>
<td></td>
<td></td>
<td>185</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>DMAP (2.0)</td>
<td>DCM:MeOH (3:1)</td>
<td>rt</td>
<td>1</td>
<td>187 (32%)</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>DMAP (2.0)</td>
<td>DCM:MeOH (9:1)</td>
<td>rt</td>
<td>4</td>
<td>187 (5%)</td>
</tr>
</tbody>
</table>

All reactions carried out open to air and in the presence of 4Å molecular sieves. Indole 185 observed by TLC for entries 2-7.

A comparison of the spectroscopic data from our synthetic 187 and that presented in the isolation report found the two to be in good agreement (Table 11). This outlines the first total synthesis of this natural product with the modest yield of 32% for the CEL etherification suspected to be due to the electron-rich nature, and resultant instability, of 187.
**Table 11:** \(^1\)H NMR and \(^{13}\)C NMR spectroscopic data for synthetic and natural 5,7-dimethoxy-2,4-dimethylindole (187).

![Structure of 5,7-dimethoxy-2,4-dimethylindole](image)

<table>
<thead>
<tr>
<th>H</th>
<th>Natural 187(^{153})</th>
<th>Our Synthetic 187</th>
<th>Difference in chemical shift</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\delta_H) (CDCl(_3), 500 MHz)</td>
<td>(\delta_H) (CDCl(_3), 300 MHz)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.29, br s</td>
<td>7.93, br s</td>
<td>+0.64</td>
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<tr>
<td>3</td>
<td>6.14, br s</td>
<td>6.16, m</td>
<td>+0.02</td>
</tr>
<tr>
<td>6</td>
<td>6.36, s</td>
<td>6.38, s</td>
<td>+0.02</td>
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<tr>
<td>8</td>
<td>2.41, s</td>
<td>2.43, d (0.8)</td>
<td>+0.02</td>
</tr>
<tr>
<td>9</td>
<td>2.31, s</td>
<td>2.32, s</td>
<td>+0.01</td>
</tr>
<tr>
<td>5-OMe</td>
<td>3.83, s</td>
<td>3.84, s</td>
<td>+0.01</td>
</tr>
<tr>
<td>7-OMe</td>
<td>3.91, s</td>
<td>3.93, s</td>
<td>+0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C</th>
<th>Natural 187(^{153})</th>
<th>Our Synthetic 187</th>
<th>Difference in chemical shift</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\delta_C) (CDCl(_3), 125 MHz)</td>
<td>(\delta_C) (CDCl(_3), 75 MHz)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>135.0</td>
<td>135.1</td>
<td>+0.1</td>
</tr>
<tr>
<td>3</td>
<td>99.4</td>
<td>99.5</td>
<td>+0.2</td>
</tr>
<tr>
<td>3a</td>
<td>130.6</td>
<td>130.7</td>
<td>+0.1</td>
</tr>
<tr>
<td>4</td>
<td>109.2</td>
<td>109.3</td>
<td>+0.1</td>
</tr>
<tr>
<td>5</td>
<td>151.1</td>
<td>151.3</td>
<td>+0.2</td>
</tr>
<tr>
<td>6</td>
<td>92.3</td>
<td>92.4</td>
<td>+0.1</td>
</tr>
<tr>
<td>7</td>
<td>143.5</td>
<td>143.6</td>
<td>+0.1</td>
</tr>
<tr>
<td>7a</td>
<td>121.7</td>
<td>121.8</td>
<td>+0.1</td>
</tr>
<tr>
<td>8</td>
<td>13.7</td>
<td>13.9</td>
<td>+0.2</td>
</tr>
<tr>
<td>9</td>
<td>11.4</td>
<td>11.6</td>
<td>+0.2</td>
</tr>
<tr>
<td>5-OMe</td>
<td>58.6</td>
<td>58.8</td>
<td>+0.2</td>
</tr>
<tr>
<td>7-OMe</td>
<td>55.5</td>
<td>55.7</td>
<td>+0.2</td>
</tr>
</tbody>
</table>

\(J\) values in brackets and reported in Hz.
2.3.3.3 Attempted CEL Coupling of 7-Borylindole 273 and Methoxyindole 185

Having successfully used 7-borylindole 273 in the CEL etherification, methoxyindole 185 was next utilised as a coupling partner in a CEL amination reaction in an effort to assemble the skeleton of sciodole (Table 12). 4Å molecular sieves were used in all instances except when stated otherwise. Standard CEL coupling conditions using Cu(OAc)$_2$·H$_2$O (1 eq) in the presence of molecular oxygen and triethylamine (2 eq) in acetonitrile did not give the desired product 280 (Table 12, entry 1). Instead a novel compound, tentatively assigned as 3-indolone 281 by $^1$H NMR and high-resolution mass spectrometry, was isolated in trace amounts. Attempts to obtain full characterisation data for 3-indolone 281 proved unsuccessful due to rapid degradation upon reaction work-up. Removal of oxygen from the reaction and increasing the equivalents of Cu(OAc)$_2$·H$_2$O (entry 2) resulted in no reaction. When an excess of the copper salt (6 eq) was used, no improvement to the isolated yield of 281 was observed (entry 3). When the temperature was increased from rt to 40 °C (entry 4), a multitude of brightly coloured spots were identified by TLC analysis (suggesting oxidative dimerization of 281). Decreasing the amount of Cu(OAc)$_2$·H$_2$O to 10% and using potassium fluoride as a base in acetonitrile at 80 °C still afforded a trace amount of compound 281 (entry 5) but none of the desired product. Employing conditions developed by Kuninobu$^{196}$ and Jang$^{197}$ (entries 6 and 7 respectively) gave no reaction. Finally, employing the reaction conditions presented by Ghanbari and co-worker$^{198}$ using catalytic Cu(OAc)$_2$·H$_2$O in the presence of oxygen and potassium tert-butoxide in aqueous tetrabutylammonium hydroxide surprisingly led to the formation of ether 282 (entry 8).
Table 12: Attempted CEL coupling between 7-borylindole 273 and methoxyindole 185.

![Diagram of attempted CEL coupling between 7-borylindole 273 and methoxyindole 185.]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu(OAc)$_2$·H$_2$O (mol%)</th>
<th>Oxidant (eq)</th>
<th>Base/ Additive (eq)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>Outcome (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>O$_2$</td>
<td>NEt$_3$ (2)</td>
<td>MeCN</td>
<td>rt</td>
<td>8</td>
<td>281 (trace)</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>-</td>
<td>NEt$_3$ (2)</td>
<td>DCM</td>
<td>rt</td>
<td>12</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>600</td>
<td>O$_2$</td>
<td>NEt$_3$ (2)</td>
<td>DCM</td>
<td>rt</td>
<td>24</td>
<td>281 (trace)</td>
</tr>
<tr>
<td>4</td>
<td>600</td>
<td>O$_2$</td>
<td>NEt$_3$ (2)</td>
<td>DCM</td>
<td>40</td>
<td>24</td>
<td>Degradation</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>O$_2$</td>
<td>KF (1)</td>
<td>MeCN</td>
<td>80</td>
<td>24</td>
<td>281 (trace)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>(tBuO)$_2$</td>
<td>-</td>
<td>Toluene</td>
<td>50</td>
<td>48</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>O$_2$</td>
<td>K$_2$CO$_3$ (1)</td>
<td>EtOAc</td>
<td>80</td>
<td>96</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BzOH (0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8$^a$</td>
<td>20</td>
<td>O$_2$</td>
<td>tBuOK (2)</td>
<td>Bu$_3$NOH</td>
<td>rt</td>
<td>42</td>
<td>282 (78%)</td>
</tr>
</tbody>
</table>

$^a$4Å molecular sieves not used. BzOH = benzoic acid.
2.3.3.4 Mechanistic Considerations for CEL Side Product Formation

The formation of 3-indolone 281 and ether 282 will be discussed henceforth. Numerous examples of the copper-catalysed conversion of indoles to 3-indolones are presented in the literature and a plausible mechanism involving only Cu$^{II}$ and oxygen is presented in Scheme 32.\textsuperscript{199–202} The process begins with a Cu$^{II}$-mediated radical initiation (as presented by Ohkubo and co-workers),\textsuperscript{202} generating Cu$^I$ and radical cation 283.\textsuperscript{202–204} The re-oxidation of Cu$^I$ to Cu$^{II}$ is achieved through reaction with dioxygen, generating a molecule of superoxide (O$_2^-$).\textsuperscript{202} Subsequent NH-proton abstraction from radical cation 283 generates a peroxide radical (HO$_2^-$) and N-centred radical 284. Migration of the radical to the C3-position affords intermediate 285 which is readily attacked by the aforementioned peroxide radical.\textsuperscript{200,201} The indolenyl hydroperoxide 286 formed from this reaction then fractionates, liberating a molecule of water, to afford the observed 3-indolone 281.\textsuperscript{200}

![Scheme 32: Plausible mechanism for the formation of 3-indolone 281.](image)

Ether 282 was structurally assigned based on the following spectroscopic data. The $^1$H NMR spectrum indicated that a coupling reaction had occurred due to the presence of two methoxy groups and four methyl groups within the molecule. This was corroborated by mass spectrometry; a molecular ion of 365.1857 was identified which correlated to a molecular formula of $[C_{22}H_{24}N_2O_3 + H]^+$, indicating that a dimer had formed with the inclusion of one additional oxygen atom. The observed NOESY correlations (Figure 29) agreed with this structural assignment; a NOESY correlation was identified between the C4′-methyl group and the C6-H (pink correlation). The absence of a C3-proton on the bottom fragment suggested the additional oxygen atom was present as part of an ether-linkage between the two indoles.

![NOESY spectrum for ether 282.](image)

Ether 282 was only formed when aqueous base was present within the reaction. It is plausible that coordination of Cu$^{II}$ to the indole heterocycle double bond of 185 could occur in a similar fashion to that proposed for Cu(OTf)$_2$ or Pd(OAc)$_2$ (Scheme 33, A). The C3-position would consequentially be activated toward nucleophilic attack by a hydroxide ion, generating...
intermediate 287. Subsequent re-aromatisation, driven by base, could afford 3-hydroxyindole 288, which would exist as a tautomeric mixture with indoxyl 289. The 3-hydroxyindole 288 could participate in the CEL etherification with 7-borylindole 273, affording the isolated ether 282. Suggestion has been made in the literature that the rate of etherification is significantly greater than that of amination when boronate esters are employed in CEL couplings,207 perhaps explaining the observed formation of 282 over a N-linked regioisomer.41 An alternative mechanism for the formation of indole 288 (Scheme 33, B) could be considered whereby nucleophilic addition of the indole 185 (via C3) to a copper species bearing oxygen-containing leaving groups (ie hydroxide or water) occurs. This would be followed by rearomatization of the indole heterocycle and reductive elimination to install in the C3-hydroxyl group.208–211
Scheme 33: A) Tentative mechanism for the copper(II)-catalysed formation of ether 282; B) Alternative proposed mechanism to form indole 288.
2.3.3.5 Synthesis of Potassium C7-Indolyltrifluoroborate 290

Undeterred by the failure of the boronate ester 273 in the CEL amination, we considered changing the aryl boron coupling partner. It is well known that boronate esters (such as BPin) can perform poorly in cross-coupling reactions\textsuperscript{212} and that the reactivity can be increased through conversion to the corresponding boronic acid.\textsuperscript{42,43} Attempts to hydrolyse 7-borylindole 273 to the corresponding C7-boronic acid 289 proved unsuccessful under various reaction conditions (Scheme 34); boronic acids are often less stable than the boronate ester counterparts and thus we suspect that to be the case for compound 289.\textsuperscript{194} An attractive alternative to boronic acids are potassium trifluoroborate salts (also known as Molander salts or trifluoroborates) which are stable to both air and moisture.\textsuperscript{194,212} Batey and Quach originally investigated the application of potassium trifluoroborate salts as coupling partners in the CEL coupling;\textsuperscript{194} etherification of various aliphatic alcohols was achieved in greater yields than that observed for the corresponding boronic acids.\textsuperscript{194} 7-Borylindole 273 was readily converted to the corresponding potassium C7-indolyltrifluoroborate 290 in good yield using potassium hydrogen difluoride in a methanol-water mixture (Scheme 25).

![Conversion of 7-borylindole 273 to potassium C7-indolyltrifluoroborate 290](image)

**Scheme 34**: Conversion of 7-borylindole 273 to potassium C7-indolyltrifluoroborate 290.
2.3.3.6 Attempted CEL Coupling of Potassium C7-Indolyltrifluoroborate 290 and Methoxyindole 185

With potassium C7-indolyltrifluoroborate 290 in hand, we reinvestigated the CEL amination reaction (Table 13). When using 0.1 equivalents of Cu(OAc)$_2$·H$_2$O under an oxygen balloon in DCM, a small amount of 3'-hydroxy dimer 291 was isolated (Table 13, entry 1). Increasing the Cu(OAc)$_2$·H$_2$O and removing the oxygen led to no reaction (entry 2). Adding pyridine as a base also gave the same compound 291 in trace amounts (entry 3). Utilising tert-butylperoxide as an oxidant and catalytic Cu(OAc)$_2$·H$_2$O (entry 4) gave no reaction. 196 3'-Hydroxy dimer 291 was isolated in good yield when 1 equivalent of Cu(OAc)$_2$·H$_2$O was used in toluene at 50 ºC and in the presence of an oxygen balloon (entry 5).

Table 13: Attempted CEL coupling between potassium C7-indolyltrifluoroborate 290 and methoxyindole 185.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu(OAc)$_2$·H$_2$O (mol%)</th>
<th>Oxidant (eq)</th>
<th>Base/Additive (eq)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>Outcome (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>O$_2$</td>
<td>NEt$_3$ (2)</td>
<td>DCM</td>
<td>rt</td>
<td>12</td>
<td>291 (8%)</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>-</td>
<td>NEt$_3$ (2)</td>
<td>DCM</td>
<td>rt</td>
<td>20</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>-</td>
<td>Pyridine (2)</td>
<td>DCM</td>
<td>rt</td>
<td>24</td>
<td>291 (trace)</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>($^{('}$BuO)$_2$ (2eq)</td>
<td>-</td>
<td>Toluene</td>
<td>50</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>O$_2$</td>
<td>Pyridine (2)</td>
<td>Toluene</td>
<td>50</td>
<td>24</td>
<td>291 (83%)</td>
</tr>
</tbody>
</table>

*All reactions carried out in the presence of 4Å molecular sieves.*
3'-Hydroxy dimer 291 was structurally assigned based on the following spectroscopic data. Mass spectrometry reported a molecular ion of 387.1682, corresponding to the sodium adduct of C_{22}H_{24}N_{2}O_{3}. The observed NOESY correlations (Figure 30) indicated that the N-H was in the same space as the C2- and C2'-methyl groups (black and red correlations). The C2-methyl group correlated to a C3-proton (green correlation). The C2'-methyl group observed a correlation with an aromatic singlet (pink) that was adjacent to a methoxy group (blue correlation), assigned as C6-H. The additional oxygen identified in the molecular formula and lack of one C3-proton suggested a C3'-hydroxy group was present.

Figure 30: NOESY spectrum of 3'-hydroxy dimer 291.

When considering the mechanism resulting in the formation of 3'-hydroxy dimer 291, we suspect the increased reactivity of the potassium trifluoroborate salt allowed for the formation of the key carbon-nitrogen bond (Scheme 35). Potassium trifluoroborate salts have been demonstrated to be superior in numerous cross-coupling reactions. The enhanced reactivity of these compounds has been attributed to the tetracoordinate nature of...
trifluoroborate group, offering both an increased stability toward oxidative side reactions\(^1\) and a more facile transmetallation step.\(^2\) Once formed however, desired dimer \(280\) could readily undergo a copper-mediated oxidation\(^3\) to indolin-3-one \(292\) which could tautomerize to give the observed hydroxyindole \(291\). We suggest that the oxidation occurs after the \(N\)-arylation because, as previously observed, the rate of etherification is significantly faster than amination in CEL couplings; ether \(282\) would be expected to form if copper-mediated oxidation had occurred first.

Scheme 35: Synthesis of 3'-hydroxy dimer 291.
2.3.3.7 Attempted Hydrogenolysis of 3’-Hydroxy Dimer 291

With the carbon-nitrogen framework of sciodole in hand, we made numerous attempts to dehydroxylate 3'-hydroxy dimer 291 through hydrogenolysis (Scheme 36). Activation of the hydroxyl group by base-mediated conversion to the corresponding mesylate, tosylate and triflate highlighted that these compounds were unstable; attempts to purify and characterise these intermediates proved futile. To remedy this instability, we attempted to carry the activated compounds through to the hydrogenolysis step crude. Upon consumption of the starting material, the crude reaction mixture was exposed to Pd/C under a hydrogen atmosphere. Disappointingly, all attempts resulted in rapid degradation and dimer 280 was not obtained.

![Scheme 36: Attempted hydrogenolysis of 3’-hydroxy dimer 291.](image-url)
2.3.4 Copper- and Palladium-mediated N-Arylation of 7-Haloindoles

With the formation of the aforementioned dimers limiting the usefulness of the CEL coupling as a means of generating the key carbon-nitrogen bond of sciodole, we turned our attention towards alternative transition metal-catalysed N-arylation methodologies (Scheme 37). 7-Borylindole 273 could readily be utilised as a precursor to access the corresponding 7-haloindole 293, which in turn is a compatible substrate for both the Ullmann-type coupling and the Buchwald-Hartwig cross coupling reaction, providing an alternative means to access dimer 280. Although both coupling partners contain a free indole N-H, we suspected homodimerisation of 293 would be unlikely on steric grounds.

Scheme 37: Revised synthesis of dimer 280.

2.3.4.1 Halodeborylation of 7-Borylindole 273

A common method for the conversion of arylboron species to the corresponding arylhalides is through the use of copper salts (in either catalytic or stoichiometric amounts) in the presence of metal halides.²¹⁸ Application of such reaction conditions to 7-borylindole 273 is presented in Table 14. Initial attempts to convert 273 to the corresponding 7-bromoindole 294 using CuBr₂ at both 50 °C and room temperature (entries 1 and 2 respectively) led to complete degradation of the starting material.²¹⁹ Changing the copper catalyst to CuBr resulted in protodeboronation, affording methoxyindole 185 (entry 3). In an effort to access 7-iodoindole
Cu₂O was used as a catalyst in the presence of ammonia and sodium iodide (entry 4); this afforded small amounts of 7-iodoindole 295. Increasing the amount of Cu₂O gave degradation (entry 5) while increasing the amount of sodium iodide gave a complex mixture of products (entry 6). Changing the catalyst to CuI in the presence of 1,10-phenanthroline (Phen, 296) as a ligand and potassium iodide as a source of iodide (entry 7) gave 7-iodoindole 295 in improved yield. This yield was further increased by lowering the temperature to 50°C (entry 8) and by increasing the equivalents of potassium iodide (entry 9).

**Table 14: Halodeborylation of 7-borylindole 273.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Cu species</th>
<th>Ligand</th>
<th>Additive</th>
<th>Temp.</th>
<th>Time</th>
<th>Outcome</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>CuBr₂ (300)</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>4</td>
<td>Degradation</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>CuBr₂ (300)</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>20</td>
<td>Degradation</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>CuBr (120)</td>
<td>-</td>
<td>-</td>
<td>rt</td>
<td>24</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>Cu₂O (10)</td>
<td>-</td>
<td>NH₃ (2.5)</td>
<td>rt</td>
<td>5</td>
<td>295 (15%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NaI (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>Cu₂O (30)</td>
<td>-</td>
<td>NH₃ (5)</td>
<td>rt</td>
<td>2.5</td>
<td>Degradation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NaI (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>I</td>
<td>Cu₂O (10)</td>
<td>-</td>
<td>NH₃ (2.5)</td>
<td>rt</td>
<td>3</td>
<td>Complex mixture</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NaI (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>I</td>
<td>CuI (10)</td>
<td>Phen (0.2)</td>
<td>KI (1.5)</td>
<td>80</td>
<td>0.5</td>
<td>295 (26%)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>I</td>
<td>CuI (10)</td>
<td>Phen (0.2)</td>
<td>KI (1.5)</td>
<td>50</td>
<td>1.5</td>
<td>295 (40%)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>I</td>
<td>CuI (10)</td>
<td>Phen (0.2)</td>
<td>KI (2.5)</td>
<td>50</td>
<td>5</td>
<td>295 (52%)</td>
<td></td>
</tr>
</tbody>
</table>

*All reactions carried out under air and in a MeOH-H₂O (approx. 95:5) solvent mixture.*
2.3.4.2 Ullmann-type N-arylation

With reliable access to the 7-iodoindole 295, we subsequently explored the copper-mediated, Ullmann-type coupling to form the key C-N bisindole linkage. The first Ullmann-type coupling of an indole substrate with an activated arylhalide was reported by Yamamoto and co-workers in 1976; this was achieved by refluxing indole 297 and bromobenzene (298) in the presence of potassium carbonate and copper(I) bromide (Scheme 38, A). This methodology was expanded when Unangst and co-workers showed a similar N-arylation was rapidly sped up in the presence of potassium hydroxide (Scheme 38, B). The inclusion of diamine ligand 299 (Figure 31) by Buchwald and co-workers in 2001 brought about a more accessible and general Ullmann-type N-arylation methodology (Scheme 38, C), however it was later shown that ligands 300 and 301 (Figure 31) were better suited to indole substrates.
Scheme 38: A) $N$-arylation of indole 297 achieved by Yamamoto and co-workers;\textsuperscript{220} B) similar reaction presented by Unangst and co-workers;\textsuperscript{221} C) Diamine ligand assisted $N$-arylation as reported by Buchwald and co-workers.\textsuperscript{222,223}

Figure 31: Diamine ligands utilised by Buchwald and co-workers.\textsuperscript{222,223}
2.3.4.3 Mechanism for the Copper-mediated N-Arylation

Scheme 39 outlines the generally accepted catalytic cycle for the copper-catalysed $N$-arylation process.$^{224}$ Coordination of the diamine ligand to the copper salt generates active Cu$^1$-species 302. Nucleophilic addition of the indole to the catalyst then occurs to give intermediate 303. Oxidative addition of this Cu$^1$-species across the arylhalide bond then occurs to give Cu$^{III}$-intermediate 304 that undergoes reductive elimination, generating the desired product and regenerating the catalyst 302. The chelating diamine ligands assist the coupling reaction by preventing multiple ligation of the amine to the copper catalyst.$^{224-226}$

Scheme 39: Mechanism for the copper-catalysed $N$-arylation of indole.$^{227}$
2.3.4.4 Attempted Copper-mediated N-Arylations of 7-Iodoindole 295

Our attempts at the copper-mediated, Ullmann-type coupling of 7-iodoindole 295 with methoxyindole 185 are presented in Table 15. Treatment of the two coupling partners with copper(I) iodide in the presence of potassium carbonate in DMA\textsuperscript{228} gave no reaction (entry 1). Increasing the amount of copper(I) iodide to one equivalent and changing both the base and solvent (entry 2) gave the same result. Employing catalytic copper(I) iodide with various nitrogen-containing ligands (CHDA, NNDMEDA and L-proline, refer to Figure 31 for structures)\textsuperscript{223,227,229} and in the presence of potassium phosphate (entries 3-7) also gave no desired product. Changing the base to potassium carbonate (entries 8 and 9) resulted in no reaction. Using potassium tert-butoxide as a base at 80 °C gave no reaction (entry 10) while increasing the temperature to 160 °C resulted in protodehalogenation of 7-iodoindole 295 to give methoxyindole 185 (entry 11). Employing the use of various other copper catalysts and solvents (entries 12-15) disappointingly failed to generate dimer 280.
Table 15: Attempted copper-catalysed N-arylation of 7-iodoindole 295 with methoxyindole 185.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Ligand (mol%)</th>
<th>Base (eq)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Outcome (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuI (50)</td>
<td>-</td>
<td>K₂CO₃ (1.4)</td>
<td>DMA</td>
<td>150</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>CuI (100)</td>
<td>-</td>
<td>CsOAc (2.5)</td>
<td>DMF</td>
<td>90</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>CuI (10)</td>
<td>CHDA (10)</td>
<td>K₃PO₄ (2.1)</td>
<td>Dioxane</td>
<td>110</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>CuI (5)</td>
<td>CHDA (20)</td>
<td>K₃PO₄ (2.1)</td>
<td>Toluene</td>
<td>110</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>CuI (5)</td>
<td>NNDMEDA (20)</td>
<td>K₃PO₄ (2.1)</td>
<td>Toluene</td>
<td>110</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>CuI (5)</td>
<td>L-Proline (20)</td>
<td>K₃PO₄ (2.1)</td>
<td>Toluene</td>
<td>110</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>CuI (5)</td>
<td>L-Proline (20)</td>
<td>K₃PO₄ (2.1)</td>
<td>Dioxane</td>
<td>110</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>CuI (100)</td>
<td>NNDMEDA (200)</td>
<td>K₂CO₃ (2.0)</td>
<td>Dioxane</td>
<td>90</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>CuI (30)</td>
<td>CHDA (30)</td>
<td>K₂CO₃ (7.0)</td>
<td>Dioxane</td>
<td>110</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>CuI (5)</td>
<td>CHDA (10)</td>
<td>'BuOK (10)</td>
<td>Dioxane</td>
<td>80</td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>CuI (5)</td>
<td>CHDA (10)</td>
<td>'BuOK (10)</td>
<td>Dioxane</td>
<td>160</td>
<td>185</td>
</tr>
<tr>
<td>12</td>
<td>CuSO₄ (10)</td>
<td>-</td>
<td>K₂CO₃ (1.1)</td>
<td>Toluene</td>
<td>110</td>
<td>No reaction</td>
</tr>
<tr>
<td>13</td>
<td>Cu₂O (10)</td>
<td>-</td>
<td>Cs₂CO₃ (2.0)</td>
<td>DMF</td>
<td>100</td>
<td>No reaction</td>
</tr>
<tr>
<td>14</td>
<td>Cu(OAc)₂ (110)</td>
<td>-</td>
<td>-</td>
<td>DMA</td>
<td>160</td>
<td>No reaction</td>
</tr>
<tr>
<td>15</td>
<td>CuBr (25)</td>
<td>-</td>
<td>K₂CO₃ (2.5)</td>
<td>NMP</td>
<td>110</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

All reactions carried out for 24 hours.
2.3.4.5 Buchwald-Hartwig Cross Coupling Reaction

With the copper-mediated couplings proving unsuccessful in forming the desired bisindole linkage, we turned our attention towards palladium-catalysed procedures.\textsuperscript{227} Hartwig and co-workers were the first to report the palladium-catalysed \( N \)-arylation of the indole heterocycle (Scheme 40, A).\textsuperscript{230} \( \text{Pd(OAc)}_2 \) was utilised as a catalyst in the presence of 1,1′-bis(diphenylphosphino)ferrocene (dpff, \textbf{305}) as a ligand\textsuperscript{230} to achieve the coupling of indole (3) with various arylbromides (ranging from electron-poor to neutral). This transformation was extended to electron-rich arylbromides and even arylchlorides through the use of bis(dibenzylideneacetone)palladium(0) (\( \text{Pd}_2\text{dba}_3 \)) in combination with tris-\( \text{tert} \)-butylphosphine as a ligand (Scheme 40, B).\textsuperscript{231}

\begin{equation}
\text{A)} \quad \text{Pd(OAc)}_2 (1 \text{ mol\%}), \text{ dpff} (1.5 \text{ mol\%}), \text{ Cs}_2\text{CO}_3 (1.2 \text{ eq}), \text{ toluene, 100°C, 12 h} \quad \text{seven examples} \quad 72-98\%
\end{equation}

\begin{equation}
\text{B)} \quad \text{Pd}_2\text{dba}_3 (1-3 \text{ mol\%}), \text{ P(\text{Bu})}_3 (0.8-2.4 \text{ mol\%}), \text{ Cs}_2\text{CO}_3 (1.5-1.7 \text{ eq}), \text{ toluene, 100°C} \quad \text{four examples} \quad 64-88\%
\end{equation}

\textbf{Scheme 40:} A) Palladium-catalysed \( N \)-arylation of indole (3),\textsuperscript{230} B) Extended scope of the reaction.\textsuperscript{231}
The development of numerous bulky, biaryl phosphine ligands by Buchwald and co-workers (a collection of these ligands is shown in Figure 33) drastically improved the scope of the palladium-catalysed \( N \)-arylation.\textsuperscript{232,233} Combining these ligands with Pd\textsubscript{2}dba\textsubscript{3} provides a powerful catalyst for the cross-coupling of a wide variety of indoles with both arylhalides and pseudohalides.\textsuperscript{232} The preferred ligand for this transformation is dependent on the nature of the leaving group and the steric hindrance of the indole heterocycle;\textsuperscript{234} simple indoles undergo \( N \)-arylation with DavePhos (306), while sterically demanding indoles are more easily \( N \)-arylated by employing ligands 307 and 308.\textsuperscript{234} Ligands 309-312 have also been employed in numerous \( N \)-arylation reactions with great success.\textsuperscript{234,235} Numerous other ligands have since been developed by Buchwald and co-workers and this methodology remains a mainstay in the \( N \)-arylation field.\textsuperscript{234}

![Figure 33: Phosphine ligands developed by Buchwald and co-workers.](image)

### 2.3.4.6 Mechanism

A generalised mechanism for the palladium-catalysed \( N \)-arylation is presented in Scheme 41.\textsuperscript{234} Initial formation of the active Pd\textsuperscript{0}-catalyst (313) is achieved by coordination of donor ligands to a palladium pre-catalyst. Once formed, 313 oxidatively inserts across the aryl-halogen bond
to afford Pd$^\text{II}$-species 314. Binding of the indole nitrogen to the palladium centre then occurs to give intermediate 315.\textsuperscript{230} A base-mediated deprotonation of the chelated indole and halide abstraction affords complex 316. Finally, reductive elimination regenerates the active palladium(0) catalyst (313) and affords the desired N-arylated product. An alternative mechanism involving the displacement of a ligand coordinated to the palladium by a tert-alkoxide anion, that is then displaced by the nitrogen-containing coupling partner to give intermediate 315, has also been considered (not depicted in Scheme 41).\textsuperscript{236}

Scheme 41: General mechanism for the palladium-catalysed N-arylation of indoles.\textsuperscript{227,234}

2.3.4.7 Attempted Palladium-catalysed N-Arylation of 7-Iodoindole 295 and Methoxyindole 185

Table 16 presents our attempted palladium-catalysed N-arylation of indole 185 with 295. Using Pd$_2$dba$_3$ as a pre-catalyst with either rac-BINAP, dpf or XPhos as ligands gave no desired product (Table 16, entries 1, 2 and 3 respectively). Retaining XPhos as a ligand but altering the base from sodium tert-butoxide to potassium phosphate (entry 4) and cesium carbonate (entry 5) also gave no reaction. A change in pre-catalyst to Pd(OAc)$_2$ disappointingly failed to produce the desired coupling (entries 6 and 7). A final screen of ligands (SPhos, XantPhos and
DavePhos) proved unsuccessful; SPhos and XantPhos gave no reaction (entries 8 and 9) while DavePhos resulted in degradation of starting materials (entry 10).

Table 16: Attempted palladium-catalysed *N*-arylation of 7-iodoindole 295 with methoxyindole 185.

![chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
<th>Temp. (°C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$(dba)$_3$ (10)</td>
<td>rac-BINAP (20)</td>
<td>NaO(Bu) (2.0)</td>
<td>100</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Pd$_2$(dba)$_3$ (10)</td>
<td>dppf (20)</td>
<td>NaO(Bu) (2.0)</td>
<td>100</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Pd$_2$(dba)$_3$ (5)</td>
<td>XPhos (10)</td>
<td>NaO(Bu) (2.0)</td>
<td>100</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Pd$_2$(dba)$_3$ (5)</td>
<td>XPhos (10)</td>
<td>K$_3$PO$_4$ (1.2)</td>
<td>90</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>Pd$_2$(dba)$_3$ (5)</td>
<td>XPhos (10)</td>
<td>Cs$_2$CO$_3$ (1.2)</td>
<td>100</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$ (5)</td>
<td>XPhos (10)</td>
<td>K$_3$PO$_4$ (1.2)</td>
<td>100</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$ (5)</td>
<td>XPhos (10)</td>
<td>Cs$_2$CO$_3$ (1.2)</td>
<td>100</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)$_2$ (15)</td>
<td>SPhos (60)</td>
<td>K$_3$PO$_4$ (4.0)</td>
<td>120</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$ (15)</td>
<td>XantPhos (60)</td>
<td>K$_3$PO$_4$ (4.0)</td>
<td>120</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$ (15)</td>
<td>DavePhos (60)</td>
<td>K$_3$PO$_4$ (4.0)</td>
<td>120</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

Reactions conducted in a sealed tube. All reactions carried out for 24 hours. Dry and degassed toluene used as a reaction solvent.
2.3.4.8 Electronic and Steric Considerations

The disappointing lack of $N$-arylation observed under both copper- and palladium-catalysed reaction conditions warrants discussion. It is well acknowledged that electron-rich arylhalides (such as 7-iodoindole 295) can react poorly in a variety of cross-coupling reactions;\textsuperscript{230} oxidative insertion of the catalyst into the carbon-halogen bond is disfavoured (Scheme 42). Furthermore, when the N-H of the approaching nucleophile is hindered, such as in 2-methylindole 185, $N$-arylation reactions are reported to be sluggish.\textsuperscript{232,234} It could be envisaged that the combination of these two factors, coupled with the limited nucleophilicity of the indole nitrogen,\textsuperscript{230} may be a reasonable explanation for the failure of this reaction (Scheme 42).

**Scheme 42:** Considerations for the failure of the $N$-arylation reaction. EDG = electron-donating groups.
2.3.5 Revised N-Arylation
A revised strategy would be to use a more nucleophilic indoline in the N-arylation. Increasing the nucleophilicity of the nitrogen-containing coupling partner can have a positive effect on the rate of N-arylation, specifically the amine binding and reductive elimination steps.\textsuperscript{230,234}

2.3.5.1 Reduction of Methoxyindole 185
To access the corresponding methoxyindoline 317 we utilised the tris-(pentafluorophenyl)borane-catalysed hydrogenation protocol reported by Zhang and Tan (Scheme 43).\textsuperscript{237} This metal-free reduction of the indole heterocycle utilises a hydrosilane as a hydride source to allow for mild reaction conditions.\textsuperscript{237} We were delighted to observe that methoxyindole 185 was readily reduced to corresponding methoxyindoline 317 upon treatment with phenyldimethylsilane in the presence of catalytic tris-(pentafluorophenyl)borane (B(C\textsubscript{6}F\textsubscript{5})\textsubscript{3}) in dichloromethane at 50 °C.

![Scheme 43: Reduction of methoxyindole 185.](image)

2.3.5.2 Reduction Mechanism
A mechanism for the reduction of indoles via the B(C\textsubscript{6}F\textsubscript{5})\textsubscript{3}/silane catalytic system has been proposed by Paradies and co-workers and is presented in Scheme 44.\textsuperscript{238} It is known that the Lewis acid B(C\textsubscript{6}F\textsubscript{5})\textsubscript{3} readily reacts with hydrosilanes to form silylum-hydridoborate ion pairs (such as complex 318).\textsuperscript{237} The indole substrate undergoes B(C\textsubscript{6}F\textsubscript{5})\textsubscript{3}-catalysed silyl transfer to give N-silylated intermediate 319. Subsequent rearrangement via a [1,3]-hydride shift occurs to afford the more stable compound 320 (numerous experimental results observed strongly indicate against an intermolecular proton-transfer).\textsuperscript{238} The final step of the suspected catalytic cycle is a hydride transfer from the boron species to the highly reactive iminium of 320. As we
did not observe any of the $N$-silylated species 321, we suggest $N$-Si bond cleavage readily occurred upon aqueous work up to give the desired indoline 317.

Scheme44: Postulated mechanism for the reduction of methoxyindole 185 to indoline 317.
2.3.5.3 Attempted N-Arylation of 7-Iodoindole 295 and Methoxyindoline 317

With methoxyindoline 317 in hand, we revisited the N-arylation reaction and our results are presented in Table 17. Stoichiometric CuI with cesium acetate in DMF failed to facilitate N-arylation, instead leading to rapid dehydrogenation of methoxyindoline 317 to 185 (Table 17, entry 1). Changing to catalytic systems utilising various amine ligands (entries 2 and 3) gave a similar result. Two additional copper catalysts were trialled (entries 4 and 5) which also failed to facilitate the reaction and again dehydrogenated the methoxyindoline 317 to indole 185. Changing to a palladium-catalysed method using Pd$_2$dba$_3$ and XPhos (entry 6) gave a trace amount of a novel product, but significant dehydrogenation again dominated. The $^1$H NMR and mass spectrum inferred the new product was the desired N-arylated product 322, but the poor yield precluded full characterisation. Altering the base to potassium phosphate (entry 7) gave no desired product while a change in solvent to dioxane (entry 8) gave a trace amount of the suspected dimer 322. Reduction of the reaction temperature from 100 °C to 80 °C also gave a trace amount of product 322 (entry 9). Attempts to improve the product yield by changing the catalyst to Pd(OAc)$_2$ and PdCl$_2$ (entries 10 and 11 respectively) afforded only methoxyindole 185. Final attempts to change the ligand to SPhos and XantPhos (entries 12 and 13) led to no improvement. Numerous examples are presented in the literature whereby palladium and other transition metals facilitate the dehydrogenation of indoline to give the corresponding indole; it seems feasible that at the elevated temperatures required for the N-arylation, this side reaction could be leading to the observed indole 185.
Table 17: Attempted N-arylation between 7-iodoindole 295 and methoxyindoline 317.

![Diagram showing the reaction of 7-iodoindole 295 and methoxyindoline 317](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hr)</th>
<th>322 (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuI (100)</td>
<td></td>
<td>CsOAc</td>
<td>DMF</td>
<td>90</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>CuI (5)</td>
<td>CHDA (20)</td>
<td>K3PO4 (2.1)</td>
<td>Toluene</td>
<td>110</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>CuI (5)</td>
<td>L-Proline (20)</td>
<td>K2CO3 (2.0)</td>
<td>Toluene</td>
<td>110</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Cu2O (10)</td>
<td></td>
<td>Cs2CO3 (2.0)</td>
<td>DMF</td>
<td>100</td>
<td>22</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>CuBr (25)</td>
<td></td>
<td>K2CO3 (2.5)</td>
<td>NMP</td>
<td>100</td>
<td>24</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Pd2dba3 (10)</td>
<td>XPhos (20)</td>
<td>Cs2CO3 (2.0)</td>
<td>Toluene</td>
<td>100</td>
<td>24</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Pd2dba3 (10)</td>
<td>XPhos (20)</td>
<td>K3PO4 (2.0)</td>
<td>Toluene</td>
<td>100</td>
<td>24</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Pd2dba3 (10)</td>
<td>XPhos (20)</td>
<td>Cs2CO3 (2.0)</td>
<td>Dioxane</td>
<td>100</td>
<td>48</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Pd2dba3 (10)</td>
<td>XPhos (20)</td>
<td>Cs2CO3 (2.0)</td>
<td>Toluene</td>
<td>80</td>
<td>48</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)2 (10)</td>
<td>XPhos (20)</td>
<td>Cs2CO3 (2.0)</td>
<td>Toluene</td>
<td>100</td>
<td>12</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>PdCl2 (10)</td>
<td>XPhos (20)</td>
<td>Cs2CO3 (2.0)</td>
<td>Toluene</td>
<td>100</td>
<td>12</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)2 (10)</td>
<td>SPhos (20)</td>
<td>Cs2CO3 (2.0)</td>
<td>Toluene</td>
<td>100</td>
<td>12</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)2 (10)</td>
<td>XantPhos (20)</td>
<td>Cs2CO3 (2.0)</td>
<td>Toluene</td>
<td>100</td>
<td>12</td>
<td>Yes</td>
</tr>
</tbody>
</table>

All reactions carried out in a sealed tube. Reaction solvents thoroughly dried and degassed. Indole 185 observed by TLC analysis in all cases.
2.3.6 Concluding Remarks for the First Generation Approach to Sciodole

This chapter details our first generation approach towards the bisindole alkaloid sciodole (209). To achieve the synthesis of this natural product, a reliable source of 5-methoxy-2,4-dimethylindole (185) was required, inspiring us to develop a novel route to this indole (Scheme 45). Utilising o-QM 258, itself generated from Mannich base 257, a hydride reduction allowed access to the key C4-methyl group, with subsequent selective O-methylation affording indole 185 in gram quantities. Two additional Tricholoma-derived 2-methylindoles (186 and 187) were also attainable via the same o-QM.

Scheme 45: Synthesis of monomeric indoles from the Tricholoma genus of mushrooms.
With the indole 185 in hand, it was subsequently subjected to an iridium-catalysed C7-H borylation to give the 7-borylindole 273 (Scheme 46). Subsequent Chan-Evans-Lam amination conditions between 185 and 273 were plagued with various oxidative side products, most likely arising from copper-mediated aerobic reactions: the unstable 3-indolone 281 and ether 282 were the only identifiable products. Converting 273 to the corresponding potassium indolyltrifluoroborate 290 followed by CEL coupling with 185 again gave an undesired product (3'-hydroxy dimer 291). 7-Iodoindole 295, accessed from 273, was subjected to numerous palladium- and copper-mediated N-arylation conditions with indole 185 with no success (presumably due to steric and electronic reasons). Using the corresponding indoline 317 in the coupling did lead to the desired product 322, though in very poor yields that were not synthetically viable.
Scheme 46: Summary of C-H activation approach to C-N bond formation.
Chapter 3: SECOND GENERATION APPROACH TO SCIODOLE
3.1 Proposed Biomimetic Synthesis of (+)-Sciodole

Our second generation approach to sciodole (209) drew inspiration from the previously postulated biosynthesis of this natural product, summarised in Scheme 47. Formation of the key carbon-nitrogen bisindole bond would occur through either $S_N^1$ or $S_N^2$ addition of indole 185 to the dimethoxydihydroindole 198. Alkene migration out of the carbocycle to form the exocyclic olefin observed in the natural product 209 would occur either prior to or after carbon-nitrogen bond formation depending on the mode of nucleophilic addition (as per previous discussion in Section 1.3.3.1).

Scheme 47: Summary of the proposed biosynthesis of sciodole (209).

In order to pursue a biomimetic synthesis of sciodole, a suitable reaction partner for the key dimerization with our previously synthesised indole 185 was required. Although the dimethoxydihydroindole 198 is the hypothesised intermediate in the biosynthesis, we suspected that this compound would be significantly prone to aromatisation through loss of methanol, giving indole 185. To help alleviate this issue, we sought a bioinspired coupling
partner that would be more amenable to experimental handling (Scheme 48). Exchange of the C7-methoxy group for a poorer leaving group (such as a hydroxyl group) would decrease the likelihood of aromatisation. In addition to this, moving the alkene out of the carbocycle to afford a tetrahydroindole moiety (as opposed to a dihydroindole) would give rise to a more stable ring structure with less torsional strain. Once in hand, the C7-hydroxyl group of tetrahydroindole 323 could be primed for nucleophilic displacement by indole 185 (through chemical conversion to a more activated leaving group for example). The syn-diastereomer was chosen as it would give the anti-bisindole if either the $S_N 1$ or $S_N 2$ approach was pursued (Scheme 48). With these considerations in mind, tetrahydroindole 323 was chosen as the coupling partner for our biomimetic approach towards sciodole.

**Scheme 48: Proposed biomimetic coupling.**
3.2 Proposed Route to Bioinspired Coupling Partner 323

To access the bioinspired coupling partner 323, we envisaged that a directed lithiation could be used to assemble 324 from 2-methylpyrrole (325) and Weinreb amide 326 (Scheme 49). β-Alkoxyketone 324 could undergo stereoselective reduction\(^\text{241}\) to give syn-1,3-monoether diol 327 that upon intramolecular Fujiwara-Moritani reaction would form the desired tetrahydroindole 323.

![Scheme 49: Proposed synthesis of bioinspired coupling partner 323.](image-url)
3.3 Synthesis of Weinreb Amide 326

We began our biomimetic approach with the synthesis of the Weinreb amide 326, ultimately achieved using the sequence reported by Ghosh and Yuan (Scheme 50). Acetamide 328 was generated upon treatment of N,O-dimethylhydroxylamine 329 with acetyl chloride in the presence of trimethylamine, the anion of which underwent reaction with acrolein to give 330. Methylation of the allylic alcohol was achieved using iodomethane in the presence of sodium hydride in a DMF:THF (1:4) solvent mixture, affording Weinreb amide 326 in modest yield (starting material unable to be recovered).

Scheme 50: Synthesis of (±)-Weinreb amide 326.

3.4 Metalation of Pyrroles

With Weinreb amide 326 in hand, we turned our attention to the synthesis of the pyrrole nucleophile. N-H pyrroles can undergo both nitrogen and carbon alkylation, depending on the nature of the cation employed (ie Li, Na, Mg), the polarity of the reaction solvent and the use of phase-transfer catalysts (Scheme 51, A). In general, harder metals that associate more strongly with the pyrrolyl anion, such as magnesium, favour C-alkylation while the alternative holds true for softer cations, such as sodium. Protection of the pyrrole nitrogen generally leads to metalation at the most acidic ortho positions (C2 and C5) though this is subject to directing effects of substituents around the heterocycle. Protecting groups that contain oxygen atoms are capable of acting as directing groups by chelating the 2-metalopyrrole 331 (Scheme 51, B), thus further stabilising this reactive
species and overriding any substituent-directing effects. Upon reaction with electrophiles, these 2-metalopyrroles give rise exclusively to 2-substituted pyrroles. Examples of such directing groups include tert-butyloxycarbonyl (Boc), p-toluenesulfonyl (Ts), phenylsulfonyl (SO$_2$Ph) and 2-((trimethylsilyl)ethoxymethyl (SEM).

\begin{center}
\textbf{Scheme 51:} A) Metalation of unprotected pyrrole; B) ortho-Directed lithiation.
\end{center}

For our purposes, we prepared numerous pyrroles bearing N-directing groups (Scheme 52). This began with Wolff-Kishner reduction of pyrrole-2-carboxaldehyde (332) to give 2-methylpyrrole (325), from which 2-methyl-N-Boc-pyrrole (333), 2-methyl-N-tosylpyrrole (334) and 2-methyl-N-SEM-pyrrole (335) were all prepared in modest to good yields. Of these directing groups, the SEM-group was deemed most desirable for our synthetic purposes due to its significant durability; the SEM-group is stable to acidic, basic, oxidative and reductive conditions.
Scheme 52: Synthesis of various 2-methylpyrroles bearing N-directing groups.

3.4.1 Nucleophilic Coupling of Protected 2-Methylpyrroles with Weinreb Amide

With a collection of protected pyrroles (333-335) and the required Weinreb amide 326 in hand, we moved forward to explore various lithiation conditions (Table 18). Initial metalation of 2-methyl-N-SEM-pyrrole (335) with n-butyllithium (n-BuLi) (Table 18, entry 1) led to the conversion of the Weinreb amide 326 to dienone 336 through elimination of the methoxy group. Switching to lithium diisopropylamide (LDA) (entry 2) also gave a similar outcome. Changing the nucleophile to 2-methyl-N-Boc-pyrrole (333) also proved unsuccessful; n-BuLi resulted in slow cleavage of the Boc-directing group to give 2-methylpyrrole (325) (entry 3) in conjunction with dienone 336 while LDA and lithium bis(trimethylsilyl)amide (LiHMDS) (entries 4 and 5) generated only dienone 336. Finally, the tosylated pyrrole 334 was used (entries 6 and 7) to no avail.
Table 18: Attempted base-mediated coupling of pyroles 333-335 and Weinreb amide 326.

![Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Base</th>
<th>Reaction Temp.</th>
<th>Time (hours)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SEM</td>
<td>n-BuLi</td>
<td>-78°C</td>
<td>0.5</td>
<td>336</td>
</tr>
<tr>
<td>2</td>
<td>SEM</td>
<td>LDA</td>
<td>0°C</td>
<td>1</td>
<td>336</td>
</tr>
<tr>
<td>3</td>
<td>Boc</td>
<td>n-BuLi</td>
<td>0°C</td>
<td>2</td>
<td>325, 336</td>
</tr>
<tr>
<td>4</td>
<td>Boc</td>
<td>LDA</td>
<td>0°C</td>
<td>1</td>
<td>336</td>
</tr>
<tr>
<td>5</td>
<td>Boc</td>
<td>LiHMDS</td>
<td>0°C</td>
<td>1</td>
<td>336</td>
</tr>
<tr>
<td>6</td>
<td>Ts</td>
<td>n-BuLi</td>
<td>-78°C</td>
<td>0.5</td>
<td>336</td>
</tr>
<tr>
<td>7</td>
<td>Ts</td>
<td>LDA</td>
<td>0°C</td>
<td>2</td>
<td>336</td>
</tr>
</tbody>
</table>

All reactions carried out in dry THF. Pyrrole (333-325) and base combined at -78°C and allowed to stir for 15 minutes; Weinreb amide 326 was added and the reaction was stirred at temperature stated.

3.4.2 Synthesis of Various Weinreb Amide Coupling Partners

With the results presented in Table 18 suggesting that the Weinreb amide coupling partner was incompatible with the lithiation conditions due to competing elimination, we explored other protecting groups for the allylic alcohol moiety (Scheme 53). Starting from the previously synthesised (±)-Weinreb amide 330, the acetylated (337),251 tert-butyldimethylsilyl- or TBS-protected (338) and trimethylsilyl- or TMS-protected (339) derivatives were synthesised in acceptable yields.
Scheme 53: Synthesis of Weinreb amides 337-339.

3.4.3 Lithiation of SEM-pyrrole with various Weinreb amides

Choosing 2-methyl-N-SEM-pyrrole (335), we screened various lithiation conditions with the collection of Weinreb amides 337-339 (Table 19). The acetylated Weinreb amide 337 immediately proved incompatible with the reaction conditions; n-BuLi at -78°C and LiHMDS at 0°C (Table 19, entries 1 and 2) both afforded the dienone 336 resulting from elimination. The TBS-protected Weinreb amide 338 did not react with pyrrole 335 when deprotonation was attempted with n-BuLi and t-BuLi (entries 3 and 4 respectively) at 0°C. The TMS protecting group proved particularly labile when treated with n-BuLi and LiHMDS (entries 5 and 6), cleaving to give the corresponding allylic alcohol 330 in combination with dienone 336.
Table 19: Attempted base-mediated coupling of pyrrole 335 and Weinreb amides 337-339.

![Image of chemical structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Base</th>
<th>Reaction Temp.</th>
<th>Time</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac</td>
<td>n-BuLi</td>
<td>-78°C</td>
<td>1</td>
<td>336</td>
</tr>
<tr>
<td>2</td>
<td>Ac</td>
<td>LiHMDS</td>
<td>0°C</td>
<td>1</td>
<td>336</td>
</tr>
<tr>
<td>3</td>
<td>TBS</td>
<td>n-BuLi</td>
<td>0°C</td>
<td>5</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>TBS</td>
<td>t-BuLi</td>
<td>0°C</td>
<td>12</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>TMS</td>
<td>nBuLi</td>
<td>-78°C</td>
<td>0.5</td>
<td>330, 336</td>
</tr>
<tr>
<td>6</td>
<td>TMS</td>
<td>LiHMDS</td>
<td>-78°C</td>
<td>0.5</td>
<td>330, 336</td>
</tr>
</tbody>
</table>

All reactions carried out in dry THF. Pyrrole 335 and base combined at -78°C and allowed to stir for 30 minutes; Weinreb amide (325-327) was added and the reaction was stirred at temperature stated.

These results indicate that the Weinreb amide coupling partners (326, 337-339) were unsuited for reaction with 2-lithiopyrrole 335 (Scheme 54). Instead of reacting with the carbonyl (blue), the 2-lithiopyrrole predominately causes elimination of the OR group in an E₂-type process (red), driven by the formation of the conjugated dienone system of 336. An E₁cB process can also be considered. Given these failures, we revised our approach to the desired tetrahydroindole fragment of sciodole (209).
Scheme 54: Formation of dienone 336.
3.5 Revised Approach to Tetrahydroindole 343

It was envisaged that by changing the pyrrole starting material to 5-methylpyrrole-2-carboxaldehyde (340), we could carry out an asymmetric Grignard addition with 3-butenylmagnesium bromide (341) to give cyclisation substrate 342 (Scheme 55). The originally planned Fujiwara-Moritani reaction would be used to form the key tetrahydroindole ring and give 343; resulting in a slightly revised bioinspired coupling partner. Nucleophilic addition of previously synthesised indole 185 would afford N-linked species 344 which, upon allylic oxidation (directed anti by the steric bulk of the C7-indole substituent) and subsequent methylation, could be converted to sciodole (209) in an enantioselective fashion.

Scheme 55: Revised biomimetic route to sciodole (209).
3.5.1 Synthesis of Cyclisation Precursor 346
Starting from previously synthesised 2-methylpyrrole (325), standard Vilsmeier-Haack formylation conditions were used to access 5-methylpyrrole-2-carboxaldehyde (340) (Scheme 56). Protection of the pyrrole nitrogen using the ethoxymethyl or EOM group (attempts to SEM-protect pyrrole 340 proved unsuccessful) was readily achieved using EOMCl and sodium hydride in THF to give pyrrole 345. Before investigating an asymmetric Grignard addition as a means of accessing the correct enantiomer of sciodole, a racemic route was first explored. Standard Grignard addition of freshly prepared 3-butenylmagnesium bromide 341 to 345 gave cyclisation precursor 346 in good yield. With this compound in hand, we turned our attention to the intramolecular Fujiwara-Moritani reaction.

Scheme 56: Synthesis of cyclisation substrate 346.
3.5.2 Fujiwara-Moritani Reaction

The palladium(II)-mediated oxidative coupling of aromatic C-H bonds with alkenes is known as the Fujiwara-Moritana reaction (FM reaction). This well-known variant of the Heck reaction is attractive as it does not require a halogenated substrate. This reaction was first discovered in 1967 when the styrene-palladium chloride complex reacted with aromatic hydrocarbons to give stilbene derivatives when heated in acetic acid (Scheme 57, A). It was subsequently found that stoichiometric amounts of palladium acetate could effectively promote this transformation (Scheme 57, B). Catalytic variants of this transformation have since been developed that utilise co-oxidants to regenerate the Pd$^{II}$-catalyst.

![Scheme 57](image)

Scheme 57: A) Seminal work by Fujiwara and Moritani; B) Scope expansion with Pd(OAc)$_2$.

Intramolecular application of the FM reaction has featured numerous times in natural product synthesis. One of the earliest examples of this transformation was presented by Trost and co-workers in their total synthesis of (+)-ibogamine (348) (Scheme 58, A). After the palladium-catalysed cyclisation of indole 349, a subsequent reduction using sodium borohydride afforded the natural product. The FM reaction also proved an invaluable transformation during the synthesis of (+)-dragmacidin F (350) by Stoltz and co-workers (Scheme 58, B). Addition of 2-bromopyrrole 351 to Weinreb amide 352 proceeded smoothly in the presence of $n$-BuLi to give the cyclisation precursor for the FM reaction (353).
Oxidative ring closure is facilitated by stoichiometric palladium acetate gave tricyclic intermediate 354 which was converted to the natural product in 13 further steps.\textsuperscript{258}

\begin{center}
\textbf{Scheme 58:} A) Synthesis of (+)-ibogamine (348);\textsuperscript{256} B) Synthesis of (+)-dragmacidin F (350).\textsuperscript{258} Formed bonds highlighted in blue.
\end{center}

\textbf{3.5.2.1 Mechanism for the Catalytic Fujiwara-Moritani Reaction}

The most widely accepted mechanism for the FM reaction is presented in Scheme 59.\textsuperscript{259,260} The Pd\textsuperscript{II}-catalyst 355 begins the catalytic cycle by reacting with the aryl coupling partner via a Friedel-Crafts type metalation process to form cationic species 356.\textsuperscript{259,260} Loss of a molecule of AcOH converts 356 to palladium-aryl species 357. The alkene then coordinates to the
palladium, followed by a 1,2-migratory insertion to form the new C-C bond. Finally, β-hydride elimination occurs to yield the olefin product 358 and palladium hydride species 359, itself converted back to the active catalyst through deprotonation and oxidation. Various electron-poor, pyridine-derived ligands have been employed in the FM reaction; these ligands facilitate both arene palladation and alkene coupling by increasing the electrophilicity of the palladium. Dimethylsulfoxide (DMSO) has also found significant use as a ligand in oxidative palladium(II) chemistry. Not only does DMSO promote the reoxidation of palladium(0) by dioxygen, DMSO can also significantly influence reaction regioselectivity through ligation to the palladium.

Scheme 59: Generally accepted catalytic cycle for the Fujiwara-Moritani reaction.
3.5.2.2 Attempted Fujiwara-Moritani Reaction on Pyrrole 346

Our attempts to form tetrahydroindole 360 from 346 using an intramolecular FM reaction are presented in Table 20. Initial use of stoichiometric Pd(OAc)₂ in the presence of oxygen in a AcOH-THF-H₂O solvent mixture led to degradation of starting material (Table 20, entry 1). Using similar conditions with DMSO as a ligand in a solvent mixture of t-BuOH and AcOH (entry 2) also led to degradation. A catalytic variant of this reaction using oxygen as the oxidant (entry 3) gave the same result. Catalytic Pd(OAc)₂ in the presence of pyridine, 2,2'-bipyridine (361), ethyl nicotinate (362) and phenanthroline (Phen, 296) (entries 4-7 respectively) all gave either degradation or an inseparable mixture of products. Reaction conditions using silver(I) trifluoroacetate as an oxidant in DCE (entry 8) and silver(I) carbonate in a DMSO-dioxane solvent mixture (entry 9) both caused degradation of 346. The use of p-benzoquinone (221) as an oxidant proved unsuccessful at both 100°C (entry 10) and at room temperature (entry 11). Continuing to explore reaction conditions at lower temperatures, trifluoroacetic acid was used as an additive (entry 12) to no benefit. Various conditions using Cu(OAc)₂ as an oxidant in combination with various additives and solvents (entries 13-16) all gave degradation or very complex mixtures of products that were indeterminable by NMR. Finally, Pd(OAc)₂ in the presence of tetra-butylammonium bromide (TBAB) in DMSO at 60°C (entry 17) gave a similar mixture of products.

Figure 34: Ligands used in Table 20.
Table 20: Attempted intramolecular Fujiwara-Moritani reaction of pyrrole 346.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(OAc)₂ (mol%)</th>
<th>Ligand (mol%)</th>
<th>Additive(s) (eq)</th>
<th>Solvent (ratio)</th>
<th>Temp. (°C)</th>
<th>Outcome (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ᵃ</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>AcOH-THF-H₂O (1:1:1)</td>
<td>rt</td>
<td>Degradation</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>DMSO (200)</td>
<td>-</td>
<td>t-BuOH-AcOH (4:1)</td>
<td>60</td>
<td>Degradation</td>
</tr>
<tr>
<td>3ᵃ</td>
<td>20</td>
<td>DMSO (40)</td>
<td>-</td>
<td>t-BuOH-AcOH (4:1)</td>
<td>80</td>
<td>Degradation</td>
</tr>
<tr>
<td>4ᵃ</td>
<td>10</td>
<td>Pyridine (40)</td>
<td>-</td>
<td>Toluene</td>
<td>80</td>
<td>Degradation</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>361 (20)</td>
<td>Ag₂CO₃ (1.0)</td>
<td>DMF</td>
<td>100</td>
<td>Degradation</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>362 (20)</td>
<td>BQ (1.0)</td>
<td>TAA-AcOH (4:1)</td>
<td>100</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7ᵃ</td>
<td>10</td>
<td>Phen (13)</td>
<td>Ag₂CO₃ (0.5)</td>
<td>DMF</td>
<td>140</td>
<td>Degradation</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>-</td>
<td>AgOTFA (2.0)</td>
<td>DCE</td>
<td>100</td>
<td>Degradation</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>-</td>
<td>Ag₂CO₃ (0.5)</td>
<td>DMSO-dioxane (1:20)</td>
<td>110</td>
<td>Degradation</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>-</td>
<td>BQ (2.0)</td>
<td>AcOH</td>
<td>100</td>
<td>Degradation</td>
</tr>
<tr>
<td>11ᵃ</td>
<td>10</td>
<td>-</td>
<td>BQ (2.0)</td>
<td>AcOH-DMSO (1:1)</td>
<td>rt</td>
<td>Degradation</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>-</td>
<td>TFA (8.0)</td>
<td>DCM</td>
<td>rt</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>-</td>
<td>Cu(OAc)₂ (2.5)</td>
<td>DMSO</td>
<td>60</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>KHCO₃ (4.0)</td>
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</tr>
</tbody>
</table>
Reactions carried out in a sealed tube and degassed with argon unless otherwise stated. “Reaction carried out under oxygen atmosphere. TAA = tert-amyl alcohol. “Degradation” represents decomposition of starting material while “complex mixture” implies a mixture of compounds that were either intractable or unidentifiable.

### 3.5.2.3 Oxidation of Alcohol 346

With the complete degradation of pyrrole 346 upon exposure to FM reaction conditions in almost all cases, we sought to oxidise the alcohol to the corresponding ketone prior to cyclisation (Scheme 60). The introduction of the carbonyl π-bond would change the electronics of the pyrrole heterocycle, hopefully facilitating the reductive elimination step of the catalytic cycle.\(^{273}\) In combination with this, it could be envisaged that conjugation of the carbonyl with the aromaticity of the pyrrole could limit rotation of the alkyl chain and potentially facilitate the desired ring closure. Conversion of pyrrole 346 to the corresponding ketone 363 was readily achieved using a literature protocol;\(^{274}\) 3 equivalents of 2-iodoxybenzoic acid (IBX) in ethyl acetate gave the desired product.

![Scheme 60: Oxidation of pyrrole 346.](image)

![Scheme 60: Oxidation of pyrrole 346.](image)
3.5.2.4 Attempted Fujiwara-Moritani Reaction on Pyrrole 363

Our attempts to cyclise pyrrole 363 to give 364 via the FM reaction are presented in Table 21. Initial use of stoichiometric (Table 21, entry 1) and catalytic (entry 2) Pd(OAc)$_2$ in conjunction with DMSO as a ligand led to degradation of the cyclisation substrate 363. Use of $p$-benzoquinone as an oxidant produced an intractable mixture of products (entry 3) while use of 1,10-phenanthroline (Phen) (entry 4) and 2,2'-bipyridine (361) (entry 5) as ligands resulted in starting material degradation. A final attempt to facilitate the desired cyclisation through use of trifluoroacetic acid in DCM at room temperature also failed to give any identifiable product (entry 6).

Table 21: Attempted intramolecular Fujiwara-Moritani reaction of pyrrole 363.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(OAc)$_2$ (mol%)</th>
<th>Ligand (mol%)</th>
<th>Additive(s) (eq)</th>
<th>Solvent (ratio)</th>
<th>Temp. (°C)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>DMSO (200)</td>
<td>-</td>
<td>$r$-BuOH-AcOH (4:1)</td>
<td>60</td>
<td>Degradation</td>
</tr>
<tr>
<td>2$^a$</td>
<td>20</td>
<td>DMSO (40)</td>
<td>-</td>
<td>$r$-BuOH-AcOH (4:1)</td>
<td>80</td>
<td>Degradation</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>-</td>
<td>BQ (2.0)</td>
<td>AcOH</td>
<td>100</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4$^a$</td>
<td>10</td>
<td>Phen (13)</td>
<td>Ag$_2$CO$_3$ (0.5)</td>
<td>DMF</td>
<td>140</td>
<td>Degradation</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>361 (20)</td>
<td>Ag$_2$CO$_3$ (1.0)</td>
<td>KOAc (2.0)</td>
<td>100</td>
<td>Degradation</td>
</tr>
<tr>
<td>6$^a$</td>
<td>10</td>
<td>-</td>
<td>TFA (8.0)</td>
<td>DCM</td>
<td>rt</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

*Reactions carried out in a sealed tube and degassed with argon unless otherwise stated. *"Reaction carried out under oxygen atmosphere."
3.6 Revised Approach – Heck Cyclisation

With the FM reaction failing to cyclise 346 and 363 under a wide variety of reaction conditions, we moved our attention towards a more ‘classical’ Heck reaction utilising a halogenated cyclisation substrate 365 (Scheme 61). Access to this compound would be achieved through the Grignard addition of 341 to the pyrrole 366.

**Scheme 61**: Revised approach to tetrahydroindole 343.

3.6.1 Bromination of Pyrrole 345

With EOM-protected 5-methylpyrrole-2-carboxaldehyde 345 already in hand, we attempted a direct electrophilic bromination (Scheme 62); although the undesired product was suspected to dominate on electronic grounds, with the starting material already in hand it seemed pragmatic to attempt the bromination and examine the regioselectivity of the process. Using N-bromosuccinimide (NBS) in THF at room temperature, a new compound (367) was rapidly generated. However, NOESY correlations suggested the bromination had indeed occurred at the undesired C4-site (as opposed to the desired C3-position).
3.6.2 Carbonyl-Direct Borylation of Pyrrole 345

An alternative approach to installing the halogen to pyrrole 345 at the desired C3-site would involve a carbonyl-directed, iridium-catalysed borylation followed by halodeborylation to give compound 368 (Scheme 63, A). Although iridium-catalysed borylations are generally governed by steric factors, carbonyl-containing moieties can direct BPin delivery to the respective ortho sites. Ishiyama and co-workers aptly demonstrated this transformation on a variety of heterocycles (Scheme 63, B). The use of phosphine- and arsine-based ligands (highlighted in blue) allow for site-selective borylation at the 3-position in 2,5-disubstituted furans, thiophenes and pyrroles, ortho to the carbonyl group. This was contrasted to a similar catalytic system employing the dtbpy ligand (highlighted in red) in which steric factors dominated and borylation occurred at C4-H.

Scheme 63: A) Planned route to 3-bromopyrrole 368; B) Site-selectivity between dtbpy and AsPh₃ systems.
The suspected reason for the observed regioselectivity when using triphenylphosphine (PPh$_3$) or triphenylarsine (AsPh$_3$) is due to the denticity of the ligand.$^{275}$ When utilising bidentate ligands, such as dtbpy, oxidative insertion of the catalyst into the aromatic C-H bond is dictated by steric factors.$^{275}$ Conversely, with monodentate ligands, such as PPh$_3$, the additional available coordination site on the iridium allows for chelation of the carbonyl oxygen (Scheme 64).$^{275}$ This facilitates the oxidative insertion of the catalyst ortho to the more sterically demanding carbonyl, affording intermediate 369. Reductive elimination then occurs to produce the iridium-hydride complex 370 and borylated compound 371.$^{275}$ The hydride complex is regenerated through reaction with B$_2$Pin$_2$.$^{275}$

Scheme 64: Suggested catalytic cycle for the carbonyl-directed, iridium-catalysed borylation.$^{275}$
3.6.2.1 Attempted Carbonyl-Directed Borylation of EOM-Protected 345

Our attempts to direct a borylation ortho to the formyl group of pyrrole 345 are presented in Table 22. Initial reaction conditions using PPh3 in dioxane at 120 °C (Table 22, entry 1) gave degradation of starting material. Changing the solvent to octane (entry 2) gave no observed reaction. Altering the ligand to tris(pentafluorophenyl)phosphine (P(C6F5)3) (entry 3) gave a small amount of CH2-linked dimer 372. Varying the solvent to THF (entry 4) and the ligand to AsPh3 (entry 5) both gave no reaction.

Table 22: Attempted carbonyl-directed borylation of pyrrole 345.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hr)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh3</td>
<td>Dioxane</td>
<td>120</td>
<td>20</td>
<td>Degraded</td>
</tr>
<tr>
<td>2</td>
<td>PPh3</td>
<td>Octane</td>
<td>120</td>
<td>42</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>P(C6F5)3</td>
<td>Octane</td>
<td>120</td>
<td>18</td>
<td>359 (10%)</td>
</tr>
<tr>
<td>4</td>
<td>P(C6F5)3</td>
<td>THF</td>
<td>80</td>
<td>48</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>AsPh3</td>
<td>Octane</td>
<td>80</td>
<td>48</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

All reactions carried out in dry and degassed solvents. 2 equivalents of B2Pin2 used in all cases.

Mechanistic considerations into the formation of dimer 372 will be discussed forthwith. We suspect a decarbonylation initially occurs, followed by a nucleophilic coupling. The Tsuji-Wilkinson decarbonylation of aromatic aldehydes, although generally performed using rhodium complexes,161 has been shown to readily proceed using iridium catalysts in the presence of phosphine ligands.276,277 Based on mechanistic studies involving rhodium-based systems, our proposed cycle is presented in Scheme 65. Firstly, chelation of the IrI-complex 373 to the aldehyde functionality of pyrrole 345 occurs followed by oxidative insertion to afford IrIII-intermediate 374.278 A rate-determining, migratory extrusion of carbon monoxide
then occurs to give complex 375. Finally, reductive elimination generates decarbonylated pyrrole 376 and CO-ligated species 377. In the absence of high temperatures and CO-scavengers, aldehyde decarbonylations generally proceed in a stoichiometric fashion; our isolated 10% product yield suggests that liberation of the CO from the iridium to regenerate catalyst 373 is not occurring and the catalyst is consumed during the reaction. Once formed, EOM-protected, 2-methylpyrrole 376 could undergo nucleophilic addition to a molecule of formylpyrrole 345 to give intermediate 378. Subsequent deoxygenation would then occur to afford the observed dimer 372.
Scheme 65: Proposed formation of dimer 372.
3.6.3 Halogenation of Various 2-Methylpyrroles

With the direct functionalisation of our already synthesised EOM-protected pyrrole 345 proving unsuccessful, we attempted to install the required halogen earlier in the synthesis of our required cyclisation precursor 379 (Scheme 66). Starting with unprotected and protected 2-methylpyrroles (325, 333, 335, 380), various halogenation conditions were explored. Although multiple products formed during the reaction in all cases, isolation of the halogenated products proved unsuccessful; rapid degradation occurred when any workup attempts were made. Although a detailed overview is not provided, the conclusions from these studies were that N-H, N-Boc, N-SEM and N-TIPS-pyrroles (325, 333, 335, 380) were all unstable once halogenated.

Scheme 66: Attempts to halogenate various 2-methylpyrroles.

In light of the above failures, we considered a strongly electron-withdrawing protecting group to stabilise the halogenated pyrrole. Gratifyingly, NBS-mediated bromination of 2-methyl-N-tosylpyrrole (334) afforded a complex mixture of stable products (Scheme 67). $^1$H NMR of the crude mixture implied that bromination had occurred at various sites and over bromination was also present. A small amount of the major product formed during this reaction (381) was able to be isolated, however NOESY correlations suggested that the bromine had been installed ortho to the C2-methyl group (this structure was suspected over the alternative 5-bromo regioisomer due to the lack of a NOESY correlation between either of the aromatic protons and the C2-methyl group). Evidently, the C2-methyl substituent was not sterically demanding enough to drive bromination to the C4-carbon and thus the ortho-direction of the alkyl group was prevailing.
3.6.4 Bromination of Pyrrole-2-carboxaldehyde (332)

A revised strategy utilised the formyl group present in pyrrole-2-carboxaldehyde (332) to direct bromination to the correct site followed by tosylation. Following literature conditions, pyrrole-2-carboxaldehyde (332) was brominated using N-bromosuccinimide in THF to afford 4-bromopyrrole-2-carboxaldehyde (382) quantitatively (Scheme 68). Pyrrole 382 was then tosyl protected through deprotonation with sodium hydride in DMF to afford N-protected pyrrole 383 in good yield.

Scheme 68: Synthesis of 4-bromo-N-tosylpyrrole-2-carboxaldehyde (383).
3.6.5 Reduction of Brominated Pyrrole 383

With 4-bromopyrrole 383 now in hand, we moved our attention towards the reduction of the formyl group to the corresponding methyl moiety (Scheme 69). This would require the bromine to remain intact during the reduction.

Scheme 69: Reduction of brominated pyrrole 383 to give pyrrole 384.

3.6.5.1 Wolff-Kishner Reduction of Brominated Pyrrole 383

It was envisaged that the reduction of 383 to 384 could be achieved using a Wolff-Kishner reduction (WKR); treatment of pyrrole 383 with hydrazine hydrate in the presence of potassium hydroxide caused only starting material degradation (Scheme 70). In an attempt to reduce the high reaction temperature required for the WKR, the Cram modification was next explored;\(^{280}\) conversion of the aldehyde to the corresponding hydrazone 385 prior to the reduction step allows for the reaction to proceed at room temperature.\(^{280}\) Although the hydrazone 385 was unstable (precluding a complete characterisation), \(^1\)H NMR of the crude reaction mixture suggested 385 was present. Disappointingly, upon exposing hydrazone 385 to potassium tert-butoxide in DMSO, only rapid degradation was observed. Secondly, the Caglioti modification\(^{281}\) of the WKR reaction was attempted. This modification uses tosylhydrazones that are subsequently reduced with hydride sources such as aluminium hydride or sodium cyanoborohydride.\(^{281}\) Unfortunately, the formation of the required tosylhydrazone 386 from freshly prepared \(p\)-toluenesulfonyl hydrazide (TsNHNH\(_2\)) was unsuccessful.
Scheme 70: Attempted Wolff-Kishner reduction (and associated modifications) of pyrrole 383.

3.6.5.2 Hydride-mediated Reduction of Brominated Pyrrole 383

With the WKR proving inappropriate for the reduction of 383, attention was turned towards the hydride-mediated conversion to methylpyrrole 384 (Table 23). The use of lithium aluminium hydride and sodium borohydride at various temperatures (Table 23, entries 1-3) proved unsuccessful; the reaction stalled at the hydroxymethyl stage to give 387 as the only product. Employing a boron-silane catalyst system\(^{282}\) led to a mixture of silyl ether 388 and the desired 2-methylpyrrole 384. Increasing the equivalents of triethylsilane (entry 5) and decreasing the temperature from 50°C to 40°C (entry 6) led to a satisfactory 73% yield of 2-methylpyrrole 384.
Table 23: Reduction of formylpyrrole 383.

![Reduction reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reductant</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Outcome (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH₄ (3)</td>
<td>-</td>
<td>THF</td>
<td>60</td>
<td>387 (65%)</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH₄ (3)</td>
<td>-</td>
<td>Dioxane</td>
<td>100</td>
<td>387 (52%)</td>
</tr>
<tr>
<td>3</td>
<td>NaBH₄ (3)</td>
<td>-</td>
<td>THF</td>
<td>60</td>
<td>387 (23%)</td>
</tr>
<tr>
<td>4ᵃ</td>
<td>Et₃SiH (3)</td>
<td>B(C₆F₅)₃ (5)</td>
<td>DCM</td>
<td>50</td>
<td>384 (14%)</td>
</tr>
<tr>
<td>5ᵃ</td>
<td>Et₃SiH (6)</td>
<td>B(C₆F₅)₃ (5)</td>
<td>DCM</td>
<td>50</td>
<td>384 (45%)</td>
</tr>
<tr>
<td>6ᵃ</td>
<td>Et₃SiH (6)</td>
<td>B(C₆F₅)₃ (5)</td>
<td>DCM</td>
<td>40</td>
<td>384 (73%)</td>
</tr>
</tbody>
</table>

ᵃReaction carried out in a sealed tube with degassed solvent under an argon atmosphere.

3.6.5.3 Mechanism for the B(C₆F₅)₃-mediated Reduction of Pyrrole 383

The proposed mechanism for the boron-mediated reduction of pyrrole 383 is presented in Scheme 71.²⁸² Silylum-hydridoborate ion pair 389 forms in situ and subsequently coordinates to formylpyrrole 383 to give intermediate 390.²⁸² Reduction via hydride attack generates silyl ether 391. An additional ion pair 389 then interacts with pyrrole 391 to give disilylated species 392, that is again reduced by hydride to afford 2-methylpyrrole 384 and regenerate the active catalyst.²⁸²
Scheme 71: Suspected mechanism for the reduction of formylpyrrole 383 by Et₃SiH-B(C₆F₅)₃.
3.6.6 Formylation of 2-Methylpyrrole 384

Turning our attention towards the formylation of 2-methylpyrrole 384, various Vilsmeier-Haack reaction conditions were initially screened (utilising phosphorous oxychloride and DMF), but all failed to generate the desired product (Scheme 72). Further attempts utilising a lithiation followed by electrophilic quench with DMF also proved futile. Alternatively, a variation of the Rieche formylation using aluminium chloride and dichloromethyl methyl ether (Cl₂CHOMe) in dichloroethane²⁸³ proved successful, affording the desired compound 393 in excellent yield.

Scheme 72: Formylation of 2-methylpyrrole 384.

A possible mechanism for the Rieche formylation facilitated by aluminium chloride (based on a similar mechanism suspected for TiCl₄)²⁸⁴ is presented in Scheme 73. Initial attack of the pyrrole to the Lewis acid-activated substrate 394 occurs, displacing a chloride and generating intermediate 395. The lone pair of the methoxy group pushes in to displace a second chloride. The resulting cation is subsequently attacked by water to give hemiacetal 396, which then collapses to give the formylated product 393.
Scheme 73: Proposed mechanism for the Rieche formylation of pyrrole 384.

3.6.7 Grignard addition to Pyrrole 393
Having successfully synthesised the pyrrole 393, we promptly carried out the Grignard reaction; addition of 3-butenylmagnesium bromide (341) to formylpyrrole 393 proceeded in good yield to afford 397, the key substrate for the proposed intramolecular Heck cyclisation (Scheme 74).

Scheme 74: Grignard addition to pyrrole 393.
3.6.8 ‘Classical’ Heck Reaction

Since the conception of the Heck reaction in the early 1970s, this C–C bond forming reaction has been a mainstay in organic synthesis. The high functional group tolerance of this reaction has led to its wide spread application in natural product synthesis. Naturally, the development of this transformation resulted in Richard Heck being awarded the Nobel Prize in 2010 (shared with Ei-ichi Negishi and Akira Suzuki) for his significant contribution to palladium-catalysed cross coupling reactions.

3.6.8.1 Catalytic Cycle of the Heck Reaction

The catalytic cycle for the Heck reaction is presented in Scheme 75. The process begins with the oxidative addition of Pd\(^0\)-species 398 to the aryl halide bond to give Pd\(^{II}\)-intermediate 399. Insertion of 399 to the alkene then occurs to give species 400 which subsequently undergoes syn-\(\beta\)-hydride elimination to generate a palladium halide species 401 and the coupled product. Base-mediated regeneration of the active Pd\(^0\)-catalyst 398 restarts the catalytic cycle. The observed trans-alkene can be explained by considering the requirement of an internal C–C bond rotation to bring an \(sp^3\)-bonded \(\beta\)-H syn to the palladium atom prior to elimination. If there are no available \(\beta\)-hydrogens for elimination, the alkyl palladium species can persist and participate in sequential reactions (ie \(\pi\)-allyl reactions).

Scheme 75: Catalytic cycle of the Heck reaction.
3.6.8.2 Attempted Heck Cyclisation of Pyrrole 383

With our cyclisation substrate in hand, the intramolecular Heck reaction could be attempted (Table 24). Employing Pd(OAc)$_2$ as a catalyst and PPh$_3$ as a ligand in the presence of triethylamine (Table 24, entry 1), a low yielding mixture of tetrahydroindole 402 and indole 403 was isolated. In an attempt to increase the reaction yield, the temperature was lowered from 80°C to 50°C (entry 2), however this resulted in no reaction. Suspecting that the aromatisation of tetrahydroindole 402 to form indole 403 could be occurring after an alkene migration into the ring during the Heck reaction, we sought to incorporate various silver(I) salts into the reaction mixture; these salts are commonly added to Heck reactions to suppress alkene isomerisation. The addition of silver(I) nitrate (entry 3) generated a complex mixture of products. Changing to silver(I) carbonate gave a complex mixture at 40°C (entry 4) and no reaction at room temperature (entry 5). With the aforementioned silver(I) salts proving ineffective at preventing the formation of indole 403, we next investigated the use of the reductive Heck reaction conditions in an effort to suppress this aromatisation. Utilising reaction conditions that have previously excelled in our own lab, sodium formate (HCO$_2$Na), tetrabutylammonium chloride (TBAC) and silver(I) nitrate were used as additives in NMP at room temperature (entry 6); this unfortunately only caused degradation. Suspecting that cyclisation substrate 397 could be incompatible with silver(I) salts, silver(I) nitrate was removed (entry 7) and this gratifyingly produced exclusively the tetrahydroindole 402, albeit in low yield. Altering the solvent from NMP to DMF (entry 8) gave an improved yield. Using sodium formate in combination with sodium acetate gave a complex mixture of products (entry 9) while utilising potassium formate as a reductant (entry 10) gave only trace amounts of tetrahydroindole 402. Finally, the addition of sodium formate to the Pd(OAc)$_2$/PPh$_3$ system (entry 12) afforded tetrahydroindole 402 in good yield along with an acceptable amount of the aromatised indole 403 that was readily separable by column chromatography.
**Table 24:** Attempted Heck cyclisation of pyrrole 397.

![Molecular structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(OAc)$_2$ (mol%)</th>
<th>Ligand (mol%)</th>
<th>Additive(s) (eq)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>Outcome</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>PPh$_3$ (40)</td>
<td>NEt$_3$ (2.0)</td>
<td>MeCN</td>
<td>80</td>
<td>24</td>
<td></td>
<td>402 (6%) 403 (13%)</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>PPh$_3$ (40)</td>
<td>NEt$_3$ (2.0)</td>
<td>MeCN</td>
<td>50</td>
<td>48</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>PPh$_3$ (40)</td>
<td>NEt$_3$ (2.0)</td>
<td>MeCN</td>
<td>80</td>
<td>24</td>
<td>Complex mixture</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>10</td>
<td>PPh$_3$ (40)</td>
<td>Ag$_2$CO$_3$ (2.0)</td>
<td>MeCN</td>
<td>40</td>
<td>24</td>
<td>Complex mixture</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>PPh$_3$ (40)</td>
<td>Ag$_2$CO$_3$ (2.0)</td>
<td>MeCN</td>
<td>rt</td>
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<td>No reaction</td>
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<td></td>
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<td>HCO$_2$Na (2.0)</td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>-</td>
<td>TBAC (3.0)</td>
<td>NMP</td>
<td>rt</td>
<td>12</td>
<td>Degradation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AgNO$_3$ (1.0)</td>
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<tr>
<td>7</td>
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<td>NMP</td>
<td>rt</td>
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<td>402 (12%)</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td>TBAC (3.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>10</td>
<td>-</td>
<td>HCO$_2$Na (1.2)</td>
<td>DMF</td>
<td>rt</td>
<td>30</td>
<td>402 (26%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBAC (3.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>-</td>
<td>NaOAc (2.5), HCO$_2$Na (1.2)</td>
<td>DMF</td>
<td>rt</td>
<td>20</td>
<td>Complex mixture</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td>TBAC (3.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>-</td>
<td>HCO$_2$K (1.2), TBAC (3.0)</td>
<td>DMF</td>
<td>rt</td>
<td>24</td>
<td>402 (trace)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>PPh$_3$ (40)</td>
<td>NEt$_3$ (2.0), HCO$_2$Na (1.2)</td>
<td>MeCN</td>
<td>80</td>
<td>19</td>
<td>402 (70%), 403 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

All reactions carried out dry, degassed solvents under nitrogen.
The structure of tetrahydroindole 402 was assigned by the followed spectroscopic data. Mass spectrometry reported a molecular ion of 340.0989, corresponding to the sodium adduct of C\textsubscript{17}H\textsubscript{19}NO\textsubscript{3}S, indicating that a molecule of HBr had been removed from the molecular formula of the starting material. The presence of the \textit{exo}-methylene was confirmed by HSQC correlations (Figure 35); the two vinyl protons (blue box) are bound to the same carbon, indicating that no alkene isomerisation had occurred.

\textbf{Figure 35:} HSQC spectrum of tetrahydroindole 402.
The formation of ‘normal’ Heck products (retaining the alkene) under reductive Heck conditions has been presented in the literature numerous times. Furthermore, this transformation has been exploited in our own laboratory (Scheme 76). A double Mori-Ban cyclisation (in effect, an intramolecular Heck reaction) of various o-haloanilines (404) under reductive conditions gave exclusively the ‘normal’ Heck product 405 (Scheme 76, A). Additionally, cyclisation of compound 406 under similar reaction conditions to give spiroindoline also solely afforded the product 407 with the alkene retained (Scheme 76, B).


We suspect the formation of the ‘normal’ product, tetrahydroindole 402 under reductive conditions is due to rapid syn-β-hydride elimination, occurring before the relatively slow sodium formate-mediated reduction step (Scheme 77). There is evidence to suggest that sodium formate also plays a role in the initial formation of the palladium(0) active species, thus facilitating the catalytic cycle. This is in agreement with our experimental results whereby the inclusion of sodium formate was crucial for the cyclisation to proceed in high yield.
Scheme 77: Formation of tetrahydroindole 402 under reductive Heck conditions. Ligands omitted for clarity.
3.7 $S_N2$ Addition of Indole 185 to Tetrahydroindole 402

Having accessed the bioinspired coupling partner 402, formation of the key carbon-nitrogen bisindole bond via a $S_N2$ addition of indole 185 could be explored (Scheme 78). Conversion of the alcohol of 402 to various leaving groups, followed by the addition of indole 185 failed to generate the $N$-linked compound 408 under a variety of reaction conditions (temperatures ranging from -78°C to room temperature and numerous solvents were explored). This reaction was dominated by base-mediated elimination of HX from 409, giving indole 403. Attempts to use the more nucleophilic indoline 317 also failed to produce any novel products.

![Chemical reactions and structures](image)

**Scheme 78**: Attempted $S_N2$ couplings.

Given the incompatibility of this reaction with base, we investigated trichloroacetimidate 410 as an alternative electrophile (Scheme 79). These species enable $N$-alkylation reactions to be performed under acidic conditions.\(^{297}\) In addition to this, trichloroacetimidates can be conveniently prepared *in situ* under relatively mild conditions.\(^{297}\) Formation of the trichloroacetimidate 410 was readily achieved using trichloroacetonitrile (Cl$_3$CCN) in the presence of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), as confirmed by $^1$H NMR and mass spectrometry (Scheme 79). Next, indoline 317 was added followed by a catalytic amount of acid. Various acids were trialled however degradation was observed in all cases.
Scheme 79: Formation of trichloroacetimidate 410 and attempted acid-mediated N-alkylation.
3.8  \textit{S}_{\text{N}}1\textit{ Addition of Indole 185 to Tetrahydroindole 402}

With the \textit{S}_{\text{N}}2 addition of indole 185 or indoline 317 to tetrahydroindole 402 failing to produce any of the desired product, we shifted our attention towards the \textit{S}_{\text{N}}1 alternative (Scheme 80). As outlined previously, this would be expected to proceed via the azafulvenium ion 412 which could be generated via an acid-mediated elimination of 402; this type of chemistry holds a significant role in porphyrin synthesis.\textsuperscript{298} A model reaction using tetrahydroindole 402 in methanol with catalytic HCl (0.1 M, aqueous), led to the 7-methoxytetrahydroindole 413 in excellent yield, presumably via the desired azafulvenium ion 412 (Scheme 80).

![Scheme 80: Acid-mediated coupling of tetrahydroindole 402 and methanol.](image)

Encouraged by this result, we applied these conditions using indole 185 as a nucleophile in dioxane solvent (Table 25, entry 1); this gave a mixture of both indole 403 (as the major product) and the C3'-coupled product 414. Compound 414 was determined to be the C3-coupled product, not the desired N-linked product 408. This structure was assigned due to the absence of a correlation in the HSQC spectrum for a broad singlet at 9.32 ppm in deuterated acetone (identified as an indole N-H) in combination with the presence of only three aromatic C-H signals integrating to one proton each. In an effort to prevent the aromatisation event from occurring, the reaction solvent was changed to THF and the temperature was lowered to 0°C (entry 2) and -78°C (entry 3); disappointingly this failed to increase the yield of the coupled product 414. Acetic acid was subsequently trialled in both catalytic (entry 4) and in excess (entry 5) amounts, however this failed to produce any reaction at all. Using silica gel as a heterogeneous acid in THF (entry 6) gave a trace amount coupled compound 414. Finally Amberlyst 15, a strongly acidic cation exchange resin useful for heterogeneous acid catalysis,
was used (entry 7), leading to the coupled product 414 as the major product with only trace amounts of the aromatised indole 403.

Table 25: Acid-mediated coupling of indole 185 to tetrahydroindole 402.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (eq)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hr)</th>
<th>Outcome (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCl (0.1)</td>
<td>Dioxane</td>
<td>rt</td>
<td>0.5</td>
<td>403 (58%) 414 (10%)</td>
</tr>
<tr>
<td>2</td>
<td>HCl (0.1)</td>
<td>THF</td>
<td>0</td>
<td>0.5</td>
<td>403 (42%) 414 (trace)</td>
</tr>
<tr>
<td>3</td>
<td>HCl (0.1)</td>
<td>THF</td>
<td>-78</td>
<td>1</td>
<td>403 (23%)</td>
</tr>
<tr>
<td>4</td>
<td>AcOH (0.1)</td>
<td>Dioxane</td>
<td>rt</td>
<td>6</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>AcOH (10)</td>
<td>Dioxane</td>
<td>rt</td>
<td>12</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>Silica gel</td>
<td>THF</td>
<td>50</td>
<td>6</td>
<td>414 (trace)</td>
</tr>
<tr>
<td>7</td>
<td>Amberlyst 15</td>
<td>Dioxane</td>
<td>rt</td>
<td>3</td>
<td>403 (trace) 414 (53%)</td>
</tr>
</tbody>
</table>

3 equivalents of indole 185 used in all cases.
3.8.1 Allylic Oxidation in C3'-linked Compound 414

With the coupling between indole 185 and tetrahydroindole 402 indicating that dimerization had occurred through C3 under biomimetic conditions (no N-linked compounds were observed), we considered that we may have formed the correct structure and sciodole (209) could in fact be a C3'-linked dimer. Thus, we proceeded to install in the allylic alcohol so that a more accurate comparison of the spectroscopic data to sciodole could be made (Scheme 81). Gratifyingly, allylic oxidation of 414 proceeded well to give a 9:1 mixture of diastereomers (415a and 415b) under standard selenium dioxide conditions.\(^{299}\) The observed preference for *anti*-addition of the hydroxyl group relative to the C7-indolyl substituent can be explained by considering the steric bulk that would be imposed on the bottom face of the envelope-like transition state 416.\(^ {300}\) The configuration of the introduced stereogenic center reflects preferential attack of the oxidant from the less hindered face of the alkene (affording compound 415a as the major product).

Scheme 81: Allylic oxidation of C3-linked compound 414.
Mass spectrometry reported a molecular ion of 513.1821 corresponding to the sodium adduct of C_{28}H_{30}N_{2}O_{4}S, thus confirming the inclusion of one additional oxygen atom to the starting material. The NOESY spectrum of compound 415 (Figure 36) suggested that the major diastereomer was in an anti-configuration (415a). The observed NOESY correlation between the C4'-methyl group and the C7-H (green) and the correlation between the C2'-methyl and C5-H (pink) indicate that the indole portion of compound 415a is orientated perpendicular to the carbocycle. As the C2'- and C4'-methyl groups are situated in different environments, exhibiting NOESY correlations to different C-H protons, an anti-arrangement is implied; in the syn-configuration the pink correlation would not be expected (Figure 36). This proposed major anti-configuration is strengthened by the absence of a correlation between the C5-H and C7-H, which could be expected if they were syn.

Comparison of our 2D data to the NOESY correlations presented in the isolation report of sciodole\textsuperscript{1} highlight some key discrepancies (Figure 36). A correlation between C7'-H and axial C6-H is noted along with correlations between the C2'-methyl/C4'-methyl and the C3'-H, all of which are absent in C3'-linked compound 415a. The culmination of this information supports that, although our biomimetic studies showed that C3-attack predominates, the bisindole bond of sciodole (209) is indeed via the indole nitrogen and the originally proposed structure is likely correct.
Figure 36: NOESY spectrum for C3-linked species 415a and comparison to analogous data reported for sciodole (209).
3.8.2 S_N1 Addition of Indoline 317 to Tetrahydroindole 402

Hoping to facilitate the formation of the carbon-nitrogen bond via azafulvenium ion 412, we next utilised indoline 317 as the nucleophile and thus eliminate C3-attack (Scheme 82). The resulting product 411 would then undergo selective oxidation to give the desired compound 408.

![Scheme 82: Revised synthesis of N-linked compound 408 via indoline 317.]

Our attempts to effect a biomimetic coupling between indoline 317 with tetrahydroindole 402 are presented in Table 26. Use of Amberlyst 15 in dioxane resulted in slow aromatisation of 402 to give indole 403 (Table 26, entry 1). Aqueous HCl in both catalytic (entry 2) and stoichiometric amounts (entry 3) also generated indole 403 as the sole product. p-Toluenesulfonic acid (p-TSA) and trifluoroacetic acid (TFA) were screened as acid catalysts (entries 4 and 5 respectively), with no success. These results suggest that Brønsted acids could be protonating the indoline nitrogen and thus preventing nucleophilic addition; to help overcome this, various oxophilic Lewis acids were next screened. Aluminium chloride (entry 6), aluminium trifluoromethanesulfonate (entry 7) and scandium trifluoromethanesulfonate (entry 8) were trialled, but all gave no reaction. Boron trifluoride in THF at 0°C (entry 9) afforded a complex mixture of products while changing the solvent to DCM and warming to room temperature (entry 10) led to degradation of tetrahydroindole 402. Finally, zinc acetate (entry 11), indium chloride (entry 12) and titanium chloride (entry 13) were used to generate azafulvenium 412, all to no avail.
Table 26: Acid-mediated coupling of indoline 317 to tetrahydroindole 402.

![Reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (eq)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hours)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amberylst 15</td>
<td>Dioxane</td>
<td>rt</td>
<td>20</td>
<td>403</td>
</tr>
<tr>
<td>2</td>
<td>HCl (0.1)</td>
<td>Dioxane</td>
<td>0</td>
<td>1</td>
<td>403</td>
</tr>
<tr>
<td>3</td>
<td>HCl (1.0)</td>
<td>THF</td>
<td>-78</td>
<td>2</td>
<td>403</td>
</tr>
<tr>
<td>4</td>
<td>p-TSA (0.1)</td>
<td>THF</td>
<td>40</td>
<td>4</td>
<td>403</td>
</tr>
<tr>
<td>5</td>
<td>TFA (0.1)</td>
<td>THF</td>
<td>rt</td>
<td>6</td>
<td>403</td>
</tr>
<tr>
<td>6</td>
<td>AlCl₃ (0.5)</td>
<td>THF</td>
<td>rt</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>Al(OTf)₃ (1.0)</td>
<td>MeCN</td>
<td>rt</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>Sc(OTf)₃ (1.0)</td>
<td>MeCN</td>
<td>40</td>
<td>24</td>
<td>Degradation</td>
</tr>
<tr>
<td>9</td>
<td>BF₃·Et₂O (0.1)</td>
<td>THF</td>
<td>0</td>
<td>6</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>10</td>
<td>BF₃·Et₂O (0.1)</td>
<td>DCM</td>
<td>rt</td>
<td>2</td>
<td>Degradation</td>
</tr>
<tr>
<td>11</td>
<td>Zn(OAc)₂ (1.0)</td>
<td>DCM</td>
<td>60</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>12</td>
<td>InCl₃ (1.0)</td>
<td>DCM</td>
<td>rt</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>13</td>
<td>TiCl₄ (1.0)</td>
<td>THF</td>
<td>rt</td>
<td>24</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

3 equivalents of indoline 317 used in all cases.
3.9 Amination by Hydrogen Autotransfer

As the biomimetic coupling was not compatible with the indoline 317, we turned our attention towards amination by hydrogen autotransfer (hydrogen borrowing) as an alternative means of forming the key carbon-nitrogen bond (Scheme 83). The ‘borrowing hydrogen’ process would involve the metal-catalysed oxidation of alcohol 402 to the corresponding carbonyl 417 which is then converted \textit{in situ} to the corresponding iminium 418\textsuperscript{301}. Finally this would be reduced by the originally generated hydrogen via M-H\textsubscript{2} to give the alkylated indoline 411. Although technically a multistep process, the hydrogen-borrowing methodology occurs in one pot, generating water as the only by-product and offering significant atom economy, eliminating the need to pre-activate the alcohol\textsuperscript{301,302}.

\begin{center}
\includegraphics[width=\textwidth]{scheme83.png}
\end{center}

\textbf{Scheme 83}: Hydrogen-borrowing amination.

Table 27 outlines our attempts to carry out a hydrogen-borrowing coupling between indoline 317 and tetrahydroindole 402. Use of [Cp*IrCl\textsubscript{2}]\textsubscript{2} as a catalyst in the presence of sodium hydrogen carbonate in toluene (Table 27, entry 1) led to elimination of the tetrahydroindole
to give indole 403, along with oxidation of indoline 317. Changing the base to potassium carbonate (entry 2) gave a similar outcome as did changing the catalyst to [IrCl(COD)]$_2$ and adding dpff as a ligand (entry 3). Using [Ru($p$-cymene)Cl]$_2$ as a catalyst with dpff (entry 4) and DPEPhos (entry 5) as ligands in the absence of a base failed to produce a reaction. Adding triethylamine (entry 6) and potassium carbonate (entry 7) again resulted in formation of indole 403.

Table 27: Attempted hydrogen autotransfer reaction of indoline 317 and tetrahydroindole 402.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Ligand (mol%)</th>
<th>Additive (eq)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Outcome (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Cp*IrCl$_2$]$_2$ (10)</td>
<td>-</td>
<td>NaHCO$_3$ (0.5)</td>
<td>Toluene</td>
<td>110</td>
<td>185 403</td>
</tr>
<tr>
<td>2$^a$</td>
<td>[Cp*IrCl$_2$]$_2$ (10)</td>
<td>-</td>
<td>K$_2$CO$_3$ (0.5)</td>
<td>Toluene</td>
<td>110</td>
<td>185 403</td>
</tr>
<tr>
<td>3$^a$</td>
<td>[IrCl(COD)$_2$]$_2$ (5)</td>
<td>dpff (5)</td>
<td>K$_2$CO$_3$ (0.5)</td>
<td>Toluene</td>
<td>110</td>
<td>185 403</td>
</tr>
<tr>
<td>4$^a$</td>
<td>[Ru($p$-cymene)Cl$_2$]$_2$ (5)</td>
<td>dpff (10)</td>
<td>-</td>
<td>Toluene</td>
<td>80</td>
<td>No reaction</td>
</tr>
<tr>
<td>5$^a$</td>
<td>[Ru($p$-cymene)Cl$_2$]$_2$ (5)</td>
<td>DPEPhos (10)</td>
<td>-</td>
<td>Toluene</td>
<td>80</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>[Ru($p$-cymene)Cl$_2$]$_2$ (5)</td>
<td>DPEPhos (10)</td>
<td>NEt$_3$ (0.2)</td>
<td>Toluene</td>
<td>100</td>
<td>403</td>
</tr>
<tr>
<td>7</td>
<td>[Ru($p$-cymene)Cl$_2$]$_2$ (5)</td>
<td>dpff (10)</td>
<td>K$_2$CO$_3$ (0.2)</td>
<td>Toluene</td>
<td>100</td>
<td>403</td>
</tr>
</tbody>
</table>

All reactions carried out for 24 hours. $^a$4Å molecular sieves added.
3.10  \( \text{Sn2} \) Addition of Indoline 317 to Pyrrole 397

With the aromatisation of tetrahydroindole 402 dominating all attempted reactions, we considered a change in the order of events whereby the carbon-nitrogen bond would be formed prior to the Heck cyclisation (Scheme 84). In this instance, the alcohol of compound 397 would be activated and displaced via an \( \text{Sn2} \) addition of indoline 317. Disappointingly, attempts to convert the hydroxyl group of pyrrole 397 to a variety of electrophilic species (419) proved unsuccessful (Scheme 84); the reaction was dominated by elimination of HX and generation of the conjugated vinyl pyrrole 420.

Scheme 84: Attempted \( \text{Sn2} \) addition of indoline 317 to pyrrole 397.
3.11 Reductive Amination

In a final bid to form the carbon-nitrogen bond of sciodole, we explored numerous reductive amination conditions that would again be followed by the Heck cyclisation. Access to ketone \(421\), which would be reacted with indoline \(317\), was achieved by exposing pyrrole \(397\) to IBX in ethyl acetate (Scheme 85).

\[
\begin{align*}
397 & \quad \xrightarrow{\text{IBX, EtOAc, 80°C, 18 h}} \quad 421
\end{align*}
\]

**Scheme 85:** Oxidation of pyrrole \(397\).

Initial attempts to carry out the reductive amination of indoline \(317\) and ketone \(421\) with catalytic acetic acid in ethanol using sodium triacetoxyborohydride as a reducing agent failed to produce the desired product (Table 28, entry 1). Increasing the amount of acetic acid to 1 equivalent in DCE at a higher temperature (entry 2) also failed to generate a reaction while carrying the reaction out in neat acetic acid at room temperature resulted in degradation of the starting materials (entry 3). Silica gel, anhydrous HCl, benzoic acid, and citric acid all failed to produce any discernible products (entries 4-8). Zinc chloride in ethanol and bismuth nitrate in acetonitrile were also explored (entries 9 and 10 respectively) though again these failed to generate a reaction. Finally, altering the reducing agent to sodium cyanoborohydride (entry 11), sodium borohydride (entry 12) and triethylsilane (entry 13) failed to produce any of the desired product.
Table 28: Attempted reductive amination between indoline 317 and ketone 421.

![Diagram showing attempted reductive amination between indoline 317 and ketone 421.]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (eq)</th>
<th>Reductant (2.0 eq)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Outcome (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH (0.1)</td>
<td>NaBH(OAc)$_3$</td>
<td>EtOH</td>
<td>rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>AcOH (1.0)</td>
<td>NaBH(OAc)$_3$</td>
<td>DCE</td>
<td>80</td>
<td>No reaction</td>
</tr>
<tr>
<td>3$^a$</td>
<td>-</td>
<td>NaBH(OAc)$_3$</td>
<td>AcOH</td>
<td>rt</td>
<td>Degradation</td>
</tr>
<tr>
<td>4</td>
<td>Silica gel</td>
<td>NaBH(OAc)$_3$</td>
<td>THF</td>
<td>50</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>HCl (1.0)</td>
<td>NaBH(OAc)$_3$</td>
<td>EtOH</td>
<td>rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>HCl (1.0)</td>
<td>NaBH(OAc)$_3$</td>
<td>THF</td>
<td>60</td>
<td>No reaction</td>
</tr>
<tr>
<td>7$^b$</td>
<td>BzOH (0.2)</td>
<td>NaBH(OAc)$_3$</td>
<td>Toluene</td>
<td>125</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>Citric acid (1.0)</td>
<td>NaBH(OAc)$_3$</td>
<td>DCE</td>
<td>80</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>ZnCl$_2$ (0.1)</td>
<td>NaBH(OAc)$_3$</td>
<td>EtOH</td>
<td>80</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>Bi(NO$_3$)$_3$ (0.1)</td>
<td>NaBH(OAc)$_3$</td>
<td>MeCN</td>
<td>120</td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>HCl (1.0)</td>
<td>NaBH$_3$CN</td>
<td>THF</td>
<td>80</td>
<td>No reaction</td>
</tr>
<tr>
<td>12</td>
<td>HCl (1.0)</td>
<td>NaBH$_4$</td>
<td>THF</td>
<td>80</td>
<td>No reaction</td>
</tr>
<tr>
<td>13</td>
<td>HCl (1.0)</td>
<td>Et$_3$SiH</td>
<td>THF</td>
<td>80</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Indoline 317 and ketone 421 allowed to stir together for 1 hour at room temperature before the addition of reductant. Reactions carried out for 24 hours. $^a$Complete degradation after 2 hours. $^b$4Å molecular sieves added.
3.12 Summary

This thesis describes our synthetic efforts towards the bisindole alkaloid sciodole (209). To achieve the synthesis of this natural product, a reliable source of 5-methoxy-2,4-dimethylindole (185) was required, driving us to develop a novel route to this indole (Scheme 86). Indole 185 was readily synthesised from Mannich base 257; this transformation proceeded through thermal generation of \( o\)-QM 258, reaction with hydride and selective \( O\)-methylation. Inspired by this transformation, we sought out to access two additional 2-methylindoles (186 and 187) from the same \( o\)-QM electrophile. By altering the nucleophile to methanol and generating the \( o\)-QM 258 through quaternarisation, 5-methoxy-4-methoxymethyl-2-methylindole (186) was synthesised. 5,7-Dimethoxy-2,4-dimethylindole (187) was synthesised from 273 through use of an iridium-catalysed C7-H borylation and subsequent Chan-Evans-Lam (CEL) coupling with methanol.

\[ \text{Scheme 86: Synthesis of 2-methylindoles (185-187) via } o\text{-quinone methide 258.} \]
The attempted CEL amination between 7-borylindole 273 and 185 failed to facilitate the desired coupling (Scheme 87). Conversion of 273 to the corresponding potassium indolyltrifluoroborate 290 followed by CEL amination with 185 also proved unsuccessful. Next, 7-iodoindole 295 was synthesised from 273 and was subjected to numerous Ullmann and Buchwald-Hartwig cross-coupling conditions with indole 185; no desired N-linked product was observed. Utilising the corresponding indoline 317 in a Buchwald-Hartwig coupling with 7-iodoindole 295 did lead to the desired compound 322, though in very poor yields that were not synthetically viable.

Scheme 87: Summary of cross-coupling route to sciodole (209).
Given that various $N$-arylation conditions failed to efficiently install the desired carbon-nitrogen bond, we turned our attention towards a biomimetic synthesis of the natural product (Scheme 89). Based on our proposed biosynthesis of sciodole (209) (highlighted in green), drawing inspiration from the proposals presented by Eizenhöfer$^2$ and Fons,$^{152}$ we considered tetrahydroindole 323 as a viable substrate for the proposed biomimetic coupling with indole 185 (highlighted in blue).

![Scheme 89](image)

**Scheme 89:** Proposed biosynthesis of sciodole (209) (green) and our biomimetic approach using tetrahydroindole 323 (blue).
In an effort to synthesise the tetrahydroindole 323 required for the biomimetic approach, the nucleophilic addition of various pyrroles (333-335) to a collection of Weinreb amides (326, 337-339) was attempted (Scheme 90); however formation of the dienone 336 was the only observed product in most cases. Owing to the failure of this route, the synthesis to a suitable tetrahydroindole was revised. Pyrrole 340 was EOM-protected and treated with 3-butenyl magnesium bromide (341) to give cyclisation substrate 346. However, all attempts to effect an intramolecular Fujiwara-Moritani reaction to install the tetrahydroindole failed.

Scheme 90: Attempted syntheses of bioinspired coupling partners.
With the Fujiwara-Moritani reaction failing to facilitate cyclisation under a variety of conditions, we moved our attention towards a more ‘classical’ Heck reaction (Scheme 91). Compound 397, available in 5 steps from pyrrole 332, readily cyclised under reductive Heck conditions to give tetrahydroindole 402.

Scheme 91: Synthesis of bioinspired coupling partner 402.

With both coupling partners in hand, various biomimetic couplings between indole 185 and tetrahydroindole 402 were explored (Scheme 92). Synthesis of an electrophile (409) required to explore the S_N2-based route was complicated by a competing base-mediated elimination-aromatisation, converting tetrahydroindole 402 to indole 403 before any nucleophilic addition of indole 185 could occur. Alternatively, S_N1 conditions proceeding via azafulvenium 412, readily formed the C3'-linked dimer 414. Since dimer 414 had formed under biomimetic conditions, we suspected that sciodole (209) could in fact be a C3'-linked regioisomer. Allylic oxidation of 414 afforded dimer 415 as a mixture of anti (415a) and syn (415b) diastereomers (dr 9:1), the spectroscopic data of which was compared to that reported for sciodole (209). Numerous discrepancies between the NOESY spectrum of 415a and sciodole (209) inferred that the original structure reported for the natural product was correct. In an effort to eliminate C3-attack, indoline 317 was investigated as the nucleophile under both S_N1 and S_N2 conditions; disappointingly no N-linked compounds were observed.
**Scheme 92:** Summary of biomimetic couplings.
3.13 Future Work

The failings encountered during our biomimetic studies prompted us to review our hypothesised biosynthesis of sciodole (209). Although the tetrahydroindole 402 reacted as an electrophile with the desired C7-regioselectivity with methanol (Scheme 93), both 5-methoxy-2,4-dimethylindole (185) and the corresponding indoline 317 failed under analogous conditions to form the required carbon-nitrogen bisindole bond of the natural product. Contrary to our original hypothesis, these results suggest that indole 185 tentatively may not be the coupling partner in the biosynthesis of sciodole (209).

Scheme 93: Nucleophilic addition to azafulvenium 412.

In light of this, we posit that key carbon-nitrogen bond forms prior to the cyclisation that forms the aromatic indole moiety of sciodole (Scheme 94). As previously presented (Section 1.3.2), lascivol (209) forms 5-methoxy-2,4-dimethylindole (185) and glutamic acid residue 196 under acidic conditions, likely via cyclohexenone 197 and dimethoxydihydroindole 198. The coupling of these two intermediates, facilitated by the increased nucleophilicity of the amino group of 197 relative to an indole N-H, to give compound 422, followed by cyclisation and aromatisation would result in the formation of sciodole (209).
Scheme 94: Originally proposed (green) and revised (blue) biosynthesis of sciodole (209).

To explore this revised biosynthesis, two new bioinspired coupling partners would be required (Scheme 95). Although the tetrahydroindole 402 performed well as a substitute for dimethoxydihydroindole 198 in our original studies, an asymmetric Kharasch-Sosnovsky reaction to give compound 423 would allow for diastereocontrol during the nucleophilic addition (a single azafulvenium enantiomer would be generated in situ). In combination with this, benzylamine 424 would serve as an aromatised derivative of the aminocyclohexenone 197; this compound was chosen to reduce any unwanted cyclisation or dimerization reactions that would likely occur with heteroatom-rich 197. Synthesis of benzylamine 424 would start from methyl 2-methoxybenzoate (425) with a proposed route presented in Scheme 96.
Scheme 95: Revised bioinspired coupling partners.

To access benzylamine 424, methyl 2-methoxybenzoate (425) would undergo a carbonyl-directed borylation/halodeborylation sequence to install a halide ortho to the ester. Subsequent Suzuki coupling with the boron species 426 would install the 2-aminopropane chain to give compound 427. Electrophilic aromatic substitution could give selective halogenation of 427 (protection of the nucleophilic amine may be required), affording compound 428. Finally, carbonyl reduction to afford the corresponding methyl group would achieve the synthesis of benzylamine 424.

Scheme 96: Proposed synthesis of benzylamine 424.
To complete the total synthesis of sciodole (209), a biomimetic S_N1 coupling between 423 and 424 would be conducted to generate a single diastereomer of intermediate 429 with the key carbon-nitrogen bond in place (Scheme 97). An intramolecular, copper- or palladium-catalysed amination, followed by phenol methylation and careful dehydrogenation of the resultant indoline would generate indole 430. A late-stage tosyl deprotection would then afford the natural product 209.

Scheme 97: Revised biomimetic synthesis of sciodole (209).
Chapter 4: **EXPERIMENTAL PROCEDURES**
4.1 General Details

Commercially available reagents were used throughout without purification unless otherwise stated. Anhydrous solvents were used as supplied. Diethyl ether, tetrahydrofuran, dichloromethane, acetonitrile, dimethylformamide and toluene were dried using an LC Technology Solutions Inc. SP-1 solvent purification system (utilising columns packed with 4Å molecular sieves) under an atmosphere of dry nitrogen. Ether refers to diethyl ether. All reactions were routinely carried out in oven-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using silica plates and compounds were visualized at 254 and/or 360 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Infrared spectra were obtained using a Perkin Elmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm\(^{-1}\)). Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on an NMR spectrometer operating at 500, 400 and 300 MHz for \(^1\)H nuclei and 125, 100 and 75 MHz for \(^{13}\)C nuclei. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as \(\delta 0.00\) ppm in CDCl\(_3\)/TMS solvent, or the residual acetone (\(\delta 2.05\) ppm), chloroform (\(\delta 7.26\) ppm), or DMSO (\(\delta 2.50\) ppm) peaks. The \(^{13}\)C NMR values were referenced to the residual acetone (\(\delta 29.9\) ppm), chloroform (\(\delta 77.1\) ppm) or DMSO (\(\delta 39.5\) ppm) peaks. \(^{13}\)C NMR values are reported as chemical shift \(\delta\) and assignment. \(^1\)H NMR shift values are reported as chemical shift \(\delta\), relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet), coupling constant (\(J\) in Hz) and assignment. Assignments are made with the aid of DEPT 90, DEPT 135, COSY, NOESY and HSQC experiments. All experiments were conducted at 298 K. Conventional NMR tubes (5 mm diameter, Norell) using a sample volume of 500 \(\mu\)L were used. High resolution mass spectra were obtained by electrospray ionization in positive ion mode at a nominal accelerating voltage of 70 eV on a microTOF mass spectrometer.
Methyl 5-hydroxy-2-methylindole-3-carboxylate (245)

![Chemical Structure](image)

To a stirred solution of \(p\)-benzoquinone (6.210 g, 57.45 mmol) in acetic acid (400 mL) was added methyl 3-aminocrotonate (5.680 g, 49.34 mmol). The resulting mixture was allowed to stir at room temperature for 48 hours, during which time a light brown precipitate formed. The solid was filtered off and subsequently washed with small portions of cold petroleum ether to afford the title compound 245 (7.275 g, 35.45 mmol, 72%) as a pale pink solid, m.p. 229 – 232 °C (lit.\(^{306}\) 234 °C); \(\delta_H\) (400 MHz, (CD\(_3\))\(_2\)SO) 11.53 (1 H, s, NH), 8.82 (1 H, s, OH), 7.29 (1 H, d, J 2.4, ArH), 7.12 (1 H, d, J 8.6, ArH), 6.59 (1 H, dd, J 8.6, 2.4, ArH), 3.77 (3 H, s, OMe), 2.58 (3 H, s, Me). Spectroscopic data in agreement with literature values.\(^{306}\)

5-Hydroxy-2-methylindole (220)

![Chemical Structure](image)

To a stirred solution of indole 245 (7.275 g, 35.45 mmol) in ethanol (15 mL) was slowly added aqueous hydrochloric acid (20%, 150 mL). The resulting mixture was stirred under reflux for 6 hours, during which time the reaction turned black in colour. The mixture was then poured onto ice and basified to approximately pH 7 using sodium hydrogen carbonate. The resulting aqueous phase was extracted with ethyl acetate (5 × 100 mL). The organic fractions were combined, washed with brine (100 mL) and dried over sodium sulfate before being concentrated in vacuo. The resulting crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:1) to afford the title compound 220 (3.891 g, 26.44 mmol, 75%) as an off-white solid, m.p. 125 – 130 °C (lit.\(^{169}\) 158 °C); \(\delta_H\) (400 MHz, (CD\(_3\))\(_2\)SO) 10.51 (1 H, s, NH), 8.44 (1 H, s, OH), 7.02 (1 H, d, J 8.6, ArH), 6.70 (1 H, d, J 2.3, ArH), 6.47 (1 H, dd, J 8.6, 2.3, ArH), 5.90 (1 H, s, ArH), 2.31 (3 H, s, Me). Spectroscopic data in agreement with literature values.\(^{307}\)
5-Hydroxy-4-(dimethylamino)methyl-2-methylindole (257)

Prepared according to the procedure reported by Monti and Johnson, but with changes to purification. The product 257 was not completely characterised in the literature.

A solution of formaldehyde (37% aqueous, 1.53 mL, 20.55 mmol) and dimethylamine (40% aqueous, 2.84 mL, 22.42 mmol) in ethanol (30 mL) was prepared and warmed to 80 °C for 30 minutes. This solution was then cooled to room temperature before 5-hydroxy-2-methylindole (3.300 g, 22.42 mmol) in ethanol (70 mL) was added. The reaction was stirred under reflux for 1 hour, during which time a colour change from yellow to dark red was observed. The reaction mixture was concentrated in vacuo and the resulting crude material was purified by flash column chromatography on silica gel eluting with dichloromethane-methanol-ammonium hydroxide (94:5:1) to afford the title compound 257 (3.187 g, 15.60 mmol, 70%) as a light brown solid, m.p. 128 – 132 °C (lit.170 130 – 131°C); ν max (neat)/cm⁻¹ 3392, 2981, 2949, 2826, 2780, 1706, 1621, 1596, 1555, 1511, 1439, 1427, 1361, 1319, 1270, 1202, 1055, 1039, 1000, 991, 837, 794, 774, 748, 737, 674; δH (400 MHz, CDCl₃) 7.71 (1 H, s, NH), 7.07 (1 H, d, J 9.2, ArH), 6.69 (1 H, d, J 8.8, ArH), 6.08 (1 H, m, ArH), 3.83 (2 H, s, CH₂NMe₂), 2.42 (3 H, s, Me), 2.36 (6 H, s, NMe₂); δC (100 MHz, CDCl₃) 151.4 (C), 135.7 (C), 130.4 (C), 128.4 (C), 111.2 (CH), 110.02 (C), 109.97 (CH), 97.4 (CH), 59.4 (CH₂), 44.8 (NMe₂), 13.8 (Me); HRMS (ESI) found: 205.1333 [C₁₂H₁₆N₂O + H]⁺ requires 205.1335.

5-Hydroxy-2,4-dimethylindole (205)

To a stirred solution of Mannich base 257 (2.886 g, 14.07 mmol) in ethanol (150 mL) cooled to 0 °C, was slowly added sodium borohydride (2.660 g, 70.35 mmol). The resulting slurry was
stirred under reflux for 6 hours, after which time the solution was cooled back to 0 °C and an additional portion of sodium borohydride (1.064 g, 28.14 mmol) was added. The reaction mixture was stirred under reflux for one further hour before being cooled again to 0 °C and quenched by the slow addition of water (100 mL). The resulting slurry was allowed to gradually warm to room temperature. The aqueous phase was extracted with ethyl acetate (5 × 75 mL). The organic extracts were combined, washed with brine (100 mL) and dried over sodium sulfate, filtered and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (2:3) to afford the title compound 205 (1.875 g, 11.70 mmol, 83%) as an off-white solid, m.p. 65 – 67 °C; $v_{\text{max}}$ (neat)/cm$^{-1}$ 3503, 3380, 2921, 1590, 1498, 1425, 1386, 1360, 1330, 1302, 1279, 1206, 1161, 1129, 1112, 1060, 1015, 897, 790, 755, 739; $\delta_H$ (400 MHz, CDCl$_3$) 7.72 (1 H, s, NH), 7.00 (1 H, d, $J$ 8.5, ArH), 6.66 (1 H, d, $J$ 8.5, ArH), 6.16 (1 H, s, ArH), 4.31 (1 H, s, OH), 2.43 (3 H, d, $J$ 0.8, Me), 2.38 (3 H, s, Me); $\delta_C$ (100 MHz, CDCl$_3$) 146.8 (C), 135.7 (C), 131.1 (C), 130.3 (C), 112.7 (C), 110.7 (CH), 108.1 (CH), 99.0 (CH), 14.0 (Me), 11.9 (Me); HRMS (ESI) found: 184.0735 [C$_{10}$H$_{11}$NO + Na]$^+$ requires 184.0733.

5-Hydroxy-4-methoxymethyl-2-methylindole (259)

Sodium metal (17.5 mg, 0.76 mmol) was added portionwise to methanol (5 mL) at 0 °C. The resulting solution was allowed to stir for 15 minutes until the consumption of the sodium had been observed. Mannich base 257 (50 mg, 0.24 mmol) was then slowly added, followed by the dropwise addition of iodomethane (0.046 mL, 0.73 mmol). The resulting solution was allowed to warm to room temperature and a nitrogen stream was gently bubbled through the solution for 4 hours. After this time, the reaction was quenched with the slow addition of water (10 mL) and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic fractions were combined, washed with brine (20 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (2:3) to afford the title compound 259 (22 mg, 0.12 mmol,
47%) as an orange oil; $v_{\text{max}}$ (neat)/cm$^{-1}$ 3389, 2921, 1707, 1589, 1498, 1432, 1358, 1241, 1184, 1153, 1076, 1042, 940, 781, 741; $\delta_H$ (300 MHz, CDCl$_3$) 7.75 (1 H, br s, NH), 7.32 (1 H, s, OH), 7.11 (1 H, d, $J = 8.8$, ArH), 7.02 (1 H, d, $J = 8.4$, ArH), 6.07 (1 H, m, ArH), 4.92 (2 H, s, CH$_2$), 3.49 (3 H, s, OMe), 2.42 (3 H, d, $J = 1.0$, Me); $\delta_C$ (75 MHz, CDCl$_3$) 149.9 (C), 136.1 (C), 130.7 (C), 128.0 (C), 111.5 (CH), 109.6 (CH), 105.3 (C), 97.6 (CH), 71.4 (CH$_2$), 58.5 (OMe), 13.9 (Me); HRMS (ESI) found: 214.0833 [C$_{11}$H$_{13}$NO$_2$ + Na]$^+$ requires 214.0838.

5-Methoxy-4-methoxymethyl-2-methylindole (186)

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\text{MeO} \quad \text{OMe} \quad \text{Me} \quad \text{N}
\]

Sodium metal (101 mg, 4.41 mmol) was added portionwise to methanol (10 mL) at 0 °C. The resulting solution was allowed to stir for 15 minutes until the consumption of the sodium had been observed. Mannich base 257 (300 mg, 1.47 mmol) was then slowly added, followed by the dropwise addition of iodomethane (0.275 mL, 4.41 mmol). The resulting solution was allowed to warm to room temperature and a nitrogen stream was gently bubbled through the solution for 1 hour. After this time, an additional portion of iodomethane (0.460 mL, 7.35 mmol) was added and the resulting reaction was sealed and stirred at room temperature for 12 hours. The reaction was concentrated in vacuo and the crude material purified by flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (2:3) to afford the title compound 186 (73 mg, 0.36 mmol, 24%) as a light brown solid, m.p. 85 – 88 °C; $v_{\text{max}}$ (neat)/cm$^{-1}$ 3270, 2940, 1592, 1497, 1449, 1429, 1362, 1325, 1279, 1253, 1225, 1171, 1152, 1097, 1065, 1049, 894, 765, 740; $\delta_H$ (300 MHz, CDCl$_3$) 7.94 (1 H, br s, NH), 7.14 (1 H, d, $J = 8.7$, ArH), 6.81 (1 H, d, $J = 8.7$, ArH), 6.32 (1 H, m, ArH), 4.82 (2 H, d, $J = 1.5$, CH$_2$), 3.87 (3 H, s, OMe), 3.43 (3 H, s, Me), 2.38 (3 H, s, Me); $\delta_C$ (75 MHz, CDCl$_3$) 152.1 (C), 136.9 (C), 131.8 (C), 130.5 (C), 115.7 (C), 110.5 (CH), 107.6 (CH), 99.0 (CH), 66.9 (CH$_2$), 58.0 (OMe), 57.8 (OMe), 13.8 (Me); HRMS (ESI) found: 228.0997 [C$_{12}$H$_{15}$NO$_2$ + Na]$^+$ requires 228.0995. The natural product 186 was only detected by mass spectrometry in the isolation report. 152
5-Methoxy-2,4-dimethylindole (185)

To a stirred solution of hydroxyindole 205 (1.000 g, 6.20 mmol) and potassium carbonate (2.143 g, 15.51 mmol) in acetone (60 mL) was added dimethylsulfate (0.880 mL, 9.30 mmol). The reaction was stirred under reflux for 36 hours after which the reaction was quenched by the addition of aqueous sodium hydroxide (1 M, 10 mL). The resulting aqueous phase was diluted with water (20 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:4) to afford the title compound 185 (742 mg, 4.24 mmol, 68%) as a colourless solid, m.p. 56 – 59 °C (lit.2 50 – 52 °C); \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3394, 2920, 1593, 1497, 1424, 1324, 1260, 1228, 1168, 1097, 1007, 774, 736, 666; \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.71 (1 H, s, NH), 7.07 (1 H, d, \( J \) 8.7, ArH), 6.80 (1 H, d, \( J \) 8.7, ArH), 6.18 (1 H, m, ArH), 3.84 (3 H, s, OMe), 2.43 (3 H, d, \( J \) 1.0, Me), 2.39 (3 H, s, Me); \( \delta_C \) (75 MHz, CDCl\(_3\)) 151.4 (C), 136.0 (C), 131.7 (C), 130.5 (C), 116.8 (C), 108.5 (CH), 107.7 (CH), 99.2 (CH), 58.0 (OMe), 14.1 (Me), 12.2 (Me); HRMS (ESI) found: 176.1067 [C\(_{11}\)H\(_{13}\)NO + H\(^+\) requires 176.1070. Spectroscopic data in agreement with literature values.\(^{2,151}\)

5-Methoxy-2,4-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole (273)

In a sealed tube, a catalyst solution containing [Ir(OMe)COD]\(_2\) (68 mg, 0.10 mmol, 6 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (47 mg, 0.20 mmol, 12 mol%) and bis(pinacolato)-diboron (652 mg, 2.57 mmol) in tetrahydrofuran (1.5 mL) was prepared under a heavy stream
of N₂ and stirred for approximately 5 minutes at room temperature, during which time the solution became deep green in colour. A solution of methoxyindole 185 (300 mg, 1.71 mmol) in tetrahydrofuran (1.5 mL) was subsequently added. The resulting mixture was sealed under nitrogen and stirred at 80 °C for 24 hours. The reaction was then diluted with ethyl acetate (10 mL) and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:9) to afford the title compound 273 (376 mg, 1.25 mmol, 73%) as a colourless solid, m.p. 124 – 127 °C; νmax (neat)/cm⁻¹ 3445, 2976, 2928, 1607, 1561, 1503, 1445, 1388, 1370, 1292, 1211, 1167, 1137, 1108, 971, 846, 792, 757, 684; δH (300 MHz, CDCl₃) 8.69 (1 H, s, NH), 7.18 (1 H, s, ArH), 6.15 (1 H, m, ArH), 3.88 (3 H, s, OMe), 2.47 (3 H, s, Me), 1.39 (12 H, s, 4× Me, BPin); δC (75 MHz, CDCl₃) 151.1 (C), 137.2 (C), 135.8 (C), 129.6 (C), 121.2 (C), 113.8 (CH), 98.3 (CH), 83.8 (2 × C, BPin), 57.7 (OMe), 25.1 (4 × Me, BPin), 14.1 (Me), 12.6 (Me), 1 × C not observed; HRMS (ESI) found: 324.1732 [C₁₇H₂₄BNO₃ + Na]⁺ requires 324.1744.

5,7-Dimethoxy-2,4-dimethylindole (187)

To a solution of 7-borylindole 273 (10 mg, 0.033 mmol) in a mixture of dichloromethane (0.75 mL) and methanol (0.25 mL) was added Cu(OAc)₂·H₂O (3.3 mg, 0.016 mmol, 50 mol%), 4-dimethylaminopyridine (8.0 mg, 0.066 mmol) and 4Å molecular sieves (100 mg). The reaction was allowed to stir at room temperature under an atmosphere of air for 1 hour. The mixture was filtered through a plug of Celite and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:9) to afford the title compound 187 (2.2 mg, 0.011 mmol, 32% yield) as an off-white solid, m.p. 172 – 177 °C (lit.¹⁵³ 178 – 180 °C, decomps.); νmax (neat)/cm⁻¹ 3360, 2926, 2851, 1598, 1514, 1451, 1398, 1319, 1200, 1125, 1018; δH (300 MHz, CDCl₃) 7.93 (1 H, br s, NH), 6.38 (1 H, s, ArH), 6.16 (1 H, m, ArH), 3.93 (3 H, s, OMe), 3.84 (3 H, s, OMe), 2.43 (3 H, d, J 0.8, Me), 2.32 (3 H, s, Me); δC (75 MHz, CDCl₃) 151.3 (C), 143.6 (C), 135.1 (C), 130.7 (C), 121.8 (C), 109.3 (C), 99.5 (CH), 92.4 (CH), 58.8 (OMe), 55.7 (OMe), 13.9 (Me), 11.6
(Me); HRMS (ESI) found: 228.0997 [C_{12}H_{15}NO_2 + Na]^+ requires 228.0995. Spectroscopic data in agreement with literature values.\textsuperscript{153}

5-Methoxy-2,4-dimethylindol-3-one (281)

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\text{MeO} \quad \text{N}
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To a stirred solution of methoxyindole 185 (23.3 mg, 0.13 mmol) and 7-borylindole 273 (39.2 mg, 0.13 mmol) in acetonitrile (5 mL) with 4Å molecular sieves (50 mg) was added Cu(OAc)$_2$·H$_2$O (25.9 mg, 0.13 mmol) and pyridine (0.021 mL, 0.26 mmol). The resulting solution was allowed to stir at room temperature for 8 hours under an oxygen atmosphere. After this time, the reaction was passed through a short plug of Celite and concentrated \textit{in vacuo}. Full characterisation was not possible due to rapid degradation of \textit{title compound 281}; $\delta_H$ (300 MHz, CDCl$_3$) 7.02 (1 H, d, $J$ 8.0, ArH), 6.74 (1 H, d, $J$ 8.1, ArH), 3.84 (3 H, s, OMe), 2.39 (3 H, s, Me), 2.18 (3 H, s, Me); HRMS (ESI) found: 212.0682 [C$_{11}$H$_{11}$NO$_2$ + Na]$^+$ requires: 212.0687.

5-Methoxy-7-((5-methoxy-2,4-dimethyl-1H-indol-3-yl)oxy)-2,4-dimethylindole (282)

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\text{MeO} \quad \text{N}
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To a stirred solution of 7-borylindole 273 (40 mg, 0.13 mmol) and methoxyindole 185 (16 mg, 0.09 mmol) in aqueous $n$-Bu$_4$NOH (20 wt%, 2 mL) were added potassium tert-butoxide (20.2 mg, 0.18 mmol) and Cu(OAc)$_2$·H$_2$O (3.6 mg, 0.018 mmol, 20 mol%). The reaction was stirred
at room temperature under an oxygen atmosphere for 42 hours before being filtered through Celite. The reaction mixture was then diluted with water (5 mL) and extracted with ethyl acetate (4 × 5 mL). The organic phases were combined, washed with brine (20 mL), dried over sodium sulfate and concentrated *in vacuo*. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:1) to give the *title compound* 282 (26 mg, 0.071 mmol, 78%) as an off-white solid, m.p. 88 – 93 °C; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3399, 2924, 1698, 1594, 1566, 1505, 1479, 1445, 1387, 1348, 1307, 1214, 1190, 1172, 1142, 1115, 1015, 812, 799, 778, 704; \( \delta_H \) (400 MHz, CDCl\(_3\)) 9.51 (1 H, s, NH), 7.74 (1 H, s, NH), 7.01 (1 H, d, \( J = 8.0 \) Hz, ArH), 6.77 (1 H, d, \( J = 8.5 \) Hz, ArH), 5.54 (1 H, s, ArH), 5.54 (1 H, m, ArH), 3.70 (3 H, s, OMe), 3.69 (3 H, s, OMe), 2.69 (3 H, s, Me), 2.23 (3 H, s, Me), 2.00 (3 H, s, Me), 1.69 (3 H, s, Me); \( \delta_C \) (100 MHz, CDCl\(_3\)) 184.4 (C), 177.1 (C), 151.7 (C), 145.7 (C), 135.7 (C), 134.5 (C), 131.0 (C), 128.7 (C), 124.1 (C), 119.6 (C), 111.5 (C), 109.2 (CH), 107.4 (CH), 106.0 (CH), 99.7 (CH), 56.7 (OMe), 36.3 (Me), 18.1 (Me), 13.5 (Me), 12.1 (Me), 1 × C not observed; HRMS (ESI) found: 365.1857 [C\(_{22}\)H\(_{24}\)N\(_2\)O\(_3\) + H]\(^+\) requires: 365.1860.

**Potassium 7-(5-methoxy-2,4-dimethylindolyl)trifluoroborate (290)**

![Chemical Structure](image)

To a solution of 7-borylindole 273 (100 mg, 0.33 mmol) in methanol (2.8 mL) and stirred at room temperature. Potassium hydrogen fluoride (1.092 g, 13.98 mmol) suspended in water (2 mL) was added dropwise to the aforementioned solution, causing a white precipitate to immediately form. The reaction was stirred for a further 30 minutes until the complete disappearance of starting material as determined by thin-layer chromatography. The reaction was concentrated *in vacuo* and the resulting crude solid was washed with cold ether (3 × 5 mL). The crude solid was then washed with warm acetone (3 × 5 mL). The acetone washings were combined and concentrated *in vacuo* to afford the *title compound* 290 (74 mg, 0.26 mmol, 79%) as a white solid that was used without further purification, m.p. 227 – 228 °C; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3471, 3396, 2987, 2917, 1602, 1557, 1501, 1447, 1400, 1363, 1278, 1128, 1109, 1096, 1038,
To a stirred solution of potassium 7-indolyltrifluoroborate 290 (25 mg, 0.09 mmol) and methoxyindole 185 (15.7 mg, 0.09 mmol) in toluene (1 mL) was added Cu(OAc)₂·H₂O (17.7 mg, 0.09 mmol), pyridine (0.015 mL, 0.18 mmol) and 4Å molecular sieves (50 mg). The resulting solution was stirred at 50 °C for 24 hours under an oxygen atmosphere. After this time, the reaction was passed through a plug of Celite and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:4) to afford the title compound 291 (27 mg, 0.07 mmol, 83%) as a yellow oil; νmax (neat)/cm⁻¹: 3333, 2925, 1678, 1593, 1492, 1462, 1260, 1103, 1008, 966, 807; δH (400 MHz, CDCl₃) 9.65 (1 H, s, NH), 7.15 (1 H, d, J 8.9, ArH), 7.05 (1 H, s, ArH), 6.81 (1 H, d, J 8.7, ArH), 6.17 (1 H, m, ArH), 4.63 (1 H, s, OH), 3.84 (3 H, s, OMe), 3.80 (3 H, s, OMe), 2.46 (3 H, s, Me), 2.45 (3 H, s, Me), 2.35 (3 H, s, Me), 1.82 (3 H, s, Me); δC (100 MHz, CDCl₃) 205.2 (C), 154.9 (C), 152.0 (C), 151.2 (C), 136.5 (C), 131.8 (C), 129.4 (C), 128.8 (C) 123.0 (CH), 120.9 (C), 118.9 (C), 116.9 (C), 110.0 (CH), 106.6 (CH), 99.1 (CH), 69.7 (C), 58.6 (OMe), 57.7 (OMe), 25.1 (Me), 14.2 (Me), 12.0 (Me), 10.7 (Me). HRMS (ESI) found: 387.1682 [C₂₂H₂₄N₂O₃ + Na]⁺ requires: 387.1685.
7-Iodo-5-methoxy-2,4-dimethylindole (295)

A solution of 7-borylindole 273 (200 mg, 0.66 mmol), copper(I) iodide (12.6 mg, 0.07 mmol, 10 mol%), 1,10-phenanthroline (23.8 mg, 0.13 mmol, 20 mol%) and potassium iodide (204 mg, 1.23 mmol) in methanol (16 mL) was prepared. The resulting solution was stirred at room temperature for 15 minutes. After this time, water (1 mL) was added and the resulting solution was warmed to 40 °C and stirred open to air for 5 hours. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (5 × 20 mL). The organic phases were combined, washed with brine (50 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:19) to afford the title compound 295 (132 mg, 0.44 mmol, 66%) as an off-white solid, m.p. 93 – 95 °C; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3350, 2953, 2923, 1614, 1584, 1551, 1493, 1465, 1382, 1318, 1210, 1185, 1169, 1106, 1006, 916, 814, 796, 780, 737; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.71 (1 H, s, NH), 7.10 (1 H, s, ArH), 6.31 (1 H, m, ArH), 3.83 (3 H, s, OMe), 2.46 (3 H, Me), 2.34 (3 H, s, Me); $\delta_{\text{C}}$ (75 MHz, CDCl$_3$) 152.0 (C), 136.4 (C), 133.8 (C), 129.9 (C), 117.2 (C), 116.5 (CH), 100.6 (CH), 70.7 (C), 57.9 (OMe), 14.0 (Me), 12.0 (Me); HRMS (ESI) found: 323.9852 [C$_{11}$H$_{12}$INO + Na]$^+$ requires: 323.9856.

5-Methoxy-2,4-dimethylindoline (317)

To a solution of methoxyindole 185 (1.000 g, 5.71 mmol) and phenyldimethylsilane (1.75 mL, 11.42 mmol) in degassed and dry dichloromethane (15 mL) was added tris-(pentafluorophenyl)borane (146 mg, 0.29 mmol, 5 mol%), resulting in the evolution of gas which was subsequently allowed to vent under a stream of nitrogen. Once complete, the reaction was sealed under nitrogen and heated to 50 °C. After 24 hours, the reaction was...
quenched by the slow addition of triethylamine (1 mL) before being diluted with dichloromethane (20 mL). The organic phase was washed with water (3 × 20 mL) and then brine (20 mL) before being dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:4) to afford the title compound 317 (855 mg, 4.82 mmol, 84%) as a dark orange oil; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3361, 2958, 2831, 1606, 0114, 1437, 1376, 1288, 1236, 1096, 1003, 796, 732; $\delta_H$ (400 MHz, CDCl$_3$) 6.56 (1 H, d, $J$ 8.4, ArH), 6.42 (1 H, d, $J$ 8.3, ArH), 3.98 (1 H, m, CH), 3.76 (3 H, s, OMe), 3.32 (1 H, br s, NH), 3.10 (1 H, dd, $J$ 15.2, 8.4, CH$_2$), 2.56 (1 H, dd, $J$ 15.7, 8.2, CH$_2$), 2.11 (3 H, s, Me), 1.30 (3 H, d, $J$ 6.3, Me); $\delta_C$ (100 MHz, CDCl$_3$) 151.7 (C), 144.4 (C), 130.2 (C), 123.7 (C), 109.6 (CH), 106.5 (CH), 56.5 (OMe), 55.5 (CH), 37.3 (CH$_2$), 22.5 (Me), 12.6 (Me); HRMS (ESI) found: 178.1225 [C$_{11}$H$_{15}$NO + H]$^+$ requires: 178.1226.

$N$-Methoxy-$N$-methylacetamide (328)

\[
\begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{O} \\
\text{N} \\
\end{array}
\]

Prepared according to the procedure presented by Kerr and co-workers.$^{308}$

Purified via distillation under reduced pressure (60 °C at 50 mBar) to afford the title compound 328 (595 mg, 3.74 mmol, 23%) as a colourless oil; $\delta_H$ (400 MHz, CDCl$_3$) 3.69 (3 H, s, NOMe), 3.19 (3 H, s, NMe), 2.13 (3 H, s, Me). Spectroscopic data in agreement with literature values.$^{308}$
3-Hydroxy-N-methoxy-N-methylpent-4-enamide (330)

\[
\begin{array}{c}
\text{OH} \\
\text{H} \\
\text{N} \text{OMe}
\end{array}
\]  

To a stirred solution of diisopropylamine (0.316 mL, 2.26 mmol) in tetrahydrofuran (8 mL) cooled to -78 °C was slowly added n-butyllithium solution (1.6 molL\(^{-1}\) in hexanes, 1.413 mL, 2.26 mmol). The resulting solution was warmed to 0 °C and allowed to stir for 1 hour, during which time a pale-yellow solution formed. The mixture was again cooled to -78 °C before the addition of acetamide 328 (0.200 mL, 1.88 mmol). The resulting solution was warmed to 0 °C and allowed to stir for 1 hour before being cooled to -78 °C. Acrolein (0.140 mL, 1.88 mmol) was then slowly added before the solution was warmed to 0 °C. The reaction was stirred at this temperature for 4.5 hours after which time it was quenched by the addition of water (10 mL). The resulting aqueous phase was extracted with dichloromethane (3 × 10 mL). The organic fractions were combined, washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:1) affording the title compound 330 (165 mg, 1.04 mmol, 55%) as a pale yellow oil; \(\delta_H\) (400 MHz, CDCl\(_3\)) 5.91 (1 H, ddd, \(J\) 17.1, 10.3, 5.4, CH), 5.33 (1 H, d app t, \(J\) 17.6, 1.5, CH\(_2\)), 5.15 (1 H, d app t, \(J\) 10.7, 1.5, CH\(_2\)), 4.56 (1 H, m, CH), 3.85 (1 H, s, OH), 3.67 (3 H, s, OMe), 3.20 (3 H, s, Me), 2.72 (1 H, d, \(J\) 15.2, CH\(_2\)), 2.60 (1 H, dd, \(J\) 16.5, 8.9, CH\(_2\)). Spectroscopic data in agreement with literature values.\(^{309}\)

\[N,3\text{-dimethoxy-N-methylpent-4-enamide (326)}\]

\[
\begin{array}{c}
\text{OMe} \\
\text{H} \\
\text{N} \text{OMe}
\end{array}
\]  

To a stirred solution of Weinreb amide 330 (50 mg, 0.31 mmol) in tetrahydrofuran (2 mL) cooled to 0 °C, was added dimethylformamide (0.5 mL) and iodomethane (0.195 mL, 3.14 mmol). Sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol) was then added. The solution was warmed to room temperature and stirred for 1.5 hours. The reaction was
quenched with phosphate buffer (2 mL), diluted with water (5 mL) and dichloromethane (10 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The organic phases were combined, dried with sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:2) to afford the title compound 326 (20 mg, 0.12 mmol, 37%) as a colourless oil; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3486, 2940, 2823, 1658, 1421, 1386, 1179, 1095, 993, 926, 833, 781, 734, 693; $\delta_H$ (400 MHz, CDCl$_3$) 5.74 (1 H, m, CH), 5.30 (1 H, d app t, $J$ 17.3, 1.1, CH$_2$), 5.22 (1 H, d app t, $J$ 9.5, 0.9, CH$_2$), 4.13 (1 H, m, CH), 3.68 (3 H, s, OMe), 3.29 (3 H, s, OMe), 3.19 (3 H, s, Me), 2.85 (1 H, m, CH$_2$), 2.45 (1 H, dd, $J$ 15.4, 5.1, CH$_2$); $\delta_C$ (100 MHz, CDCl$_3$) 171.7 (C=O), 137.7 (CH), 117.6 (CH$_2$), 79.0 (CH), 61.4 (OMe), 56.7 (Me), 38.2 (CH$_2$), 32.2 (Me); HRMS (ESI) found: 196.0942 [C$_8$H$_{15}$NO$_3$ + Na]$^+$ requires: 196.0944.

2-Methylpyrrole (325)

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{C} \\
\text{H} \\
\end{array}
\]

Prepared according to the procedure reported by Fu and Lo.$^{250}$ Purified by flash column chromatography on silica gel eluting with ether:pentane (1:2) to afford the title compound 325 (3.987 g, 41.19 mmol, 94%) as a pale yellow oil; $\delta_H$ (400 MHz, CDCl$_3$) 7.90 (1 H, br s, NH), 6.66 (1 H, m, ArH), 6.12 (1 H, m, ArH), 5.89 (1 H, m, ArH), 2.28 (3 H, s, Me). Spectroscopic data in agreement with literature values.$^{310}$
N-(tert-butoxycarbonyl)-2-methylpyrrole (333)

To a stirred solution of 2-methylpyrrole (325) (100 mg, 1.23 mmol) and 4-dimethylaminopyridine (150 mg, 1.23 mmol) in tetrahydrofuran (3 mL) was added triethylamine (0.134 mL, 1.23 mmol). This was followed by the dropwise addition of di-tert-butyl dicarbonate (538 mg, 2.46 mmol) in tetrahydrofuran (2 mL). The resulting reaction mixture was allowed to stir at room temperature for 1 hour. After this time the solvent was removed in vacuo and the crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:9) to afford the title compound 333 (187 mg, 1.03 mmol, 84%) as a colourless oil; δ_H (400 MHz, CDCl_3) 7.17 (1 H, m, ArH), 6.05 (1 H, t, J 3.6, ArH), 5.91 (1 H, m, ArH), 2.42 (3 H, s, Me), 1.58 (9 H, s, 3 × Me, Boc). Spectroscopic data in agreement with literature values.\(^{311}\)

2-Methyl-N-tosylpyrrole (334)

To a stirred solution of 2-methylpyrrole (325) (50 mg, 0.62 mmol) in tetrahydrofuran (5 mL) cooled to 0 °C was added sodium hydride (60% dispersion in mineral oil, 61 mg, 1.54 mmol). The resulting slurry was allowed to stir at that temperature for 15 minutes before the portionwise addition of p-toluenesulfonyl chloride (295 mg, 1.54 mmol). The reaction mixture was stirred under reflux for 15 hours. The reaction was quenched by the slow addition of water (10 mL) and the resulting aqueous phase was extracted with dichloromethane (4 × 10 mL). The organic factions were then combined, washed with brine (15 mL), dried over sodium sulfate,
and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with hexane:toluene (3:1) to afford the title compound 334 (54 mg, 0.23 mmol, 37%) as a yellow oil; δH (400 MHz, CDCl3) 7.66 (2 H, d, J 8.4, ArH), 7.29 (2 H, d, J 8.0, ArH), 6.16 (1 H, t, J 3.2, ArH), 5.94 (1 H, m, ArH), 2.41 (3 H, s, Me), 2.29 (3 H, s, Me). Spectroscopic data in agreement with literature values.312

2-Methyl-N-((2-(trimethylsilyl)ethoxy)methyl)pyrrole (335)

![Structure of 2-Methyl-N-((2-(trimethylsilyl)ethoxy)methyl)pyrrole](image)

To a stirred solution of 2-methylpyrrole (325) (50 mg, 0.62 mmol) in dimethylformamide (1.5 mL) cooled to 0 °C was added sodium hydride (60% dispersion in mineral oil, 27 mg, 0.68 mmol). The resulting slurry was allowed to stir for 30 minutes before the slow addition of 2-(trimethylsilyl)ethoxymethyl chloride (0.109 mL, 0.62 mmol). The reaction mixture was stirred at room temperature for 24 hours. After this time the reaction was quenched by the slow addition of aqueous ammonium chloride solution (saturated, 2 mL) before being diluted with water (10 mL) and extracted with ether (5 × 10 mL). The organic phases were combined, washed with brine (15 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:9) to afford the title compound 335 (35 mg, 0.17 mmol, 27%) as a yellow oil; νmax (neat)/cm⁻¹ 2952, 2920, 2894, 2159, 2022, 1713, 1492, 1397, 1374, 1287, 1247, 1077, 857, 832, 753, 697, 609; δH (400 MHz, CDCl3) 6.65 (1 H, m, ArH), 6.04 (1 H, t, J 3.2, ArH), 5.91 (1 H, br s, ArH), 5.15 (2 H, s, NCH₂O), 3.46 (2 H, t, J 8.2, CH₂), 2.28 (3 H, s, Me), 0.89 (2 H, t, J 7.9, CH₂), -0.02 (9 H, s, SiMe₃); δC (75 MHz, CDCl₃) 129.2 (C), 121.2 (CH), 108.0 (CH), 107.4 (CH), 65.3 (CH₂), 17.9 (CH₂), 11.8 (Me), -1.3 (3 × Me), 1 × CH₂ not observed; HRMS (ESI) found: 234.1286 [C₁₁H₂₁NOSi +Na]⁺ requires: 234.1285.
(E)-N-Methoxy-N-methylpenta-2,4-dienamide (336)

To a stirred solution of pyrrole 333 (56 mg, 0.31 mmol) in tetrahydrofuran (1 mL) cooled to -78 °C was added n-butyllithium solution (1.6 molL⁻¹ in hexanes, 0.913 mL, 0.31 mmol). The resulting solution was warmed to 0 °C and stirred for 15 minutes, after which time the solution turned yellow in colour. The reaction was cooled back to -78 °C and Weinreb amide 326 (50 mg, 0.35 mmol) was slowly added. After 1 hour, the reaction was quenched by the slow addition of water (5 mL). The resulting aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic fractions were combined, washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:1) to give the title compound 336 (20 mg, 0.14 mmol, 45%) as a colourless oil; δH (400 MHz, CDCl₃) 7.32 (1 H, dd, J 14.9, 11.6, CH), 6.51 (2 H, m, CH + CH₂), 5.60 (1 H, d, J 16.9, CH₂), 5.46 (1 H, d, J 10.6, CH), 3.71 (3 H, s, OMe), 3.26 (3 H, s, Me). Spectroscopic data in agreement with literature values.

5-Methoxy(methyl)amino-5-oxopent-1-en-3-yl acetate (337)

Prepared according to the procedure presented by Breit and co-worker. Obtained as a colourless oil that required no purification (157 mg, 0.780 mmol, 62%); δH (400 MHz, CDCl₃) 5.90 (1 H, ddd, J 17.4, 11.2, 6.2, CH), 5.70 (1 H, m, CHOAc), 5.31 (1 H, d, J 17.5, 1.4, CH₂), 5.20 (1 H, m, CH₂), 3.71 (3 H, s, OMe), 3.17 (3 H, s, Me), 2.87 (1 H, dd, J 15.6, 8.0, CH₂), 2.69 (1 H, dd, J 15.7, 5.5, CH₂), 2.05 (3 H, s, OAc). Spectroscopic data in agreement with literature values.
3-((tert-Butyldimethylsilyl)oxy)-N-methoxy-N-methylpent-4-enamide (338)

To a stirred solution of Weinreb amide 330 (250 mg, 1.57 mmol) in dimethylformamide (10 mL) cooled to 0 °C was added imidazole (213 mg, 3.13 mmol). This was stirred for 15 minutes before the addition of tert-butyldimethylsilyl chloride (355 mg, 2.36 mmol). The reaction was stirred at room temperature for 12 hours. After this time, the solution was diluted with water (20 mL) and then extracted with ethyl acetate (5 × 10 mL). The organic phases were combined, washed with a water:brine mixture (1:1, 3 × 20 mL), washed with brine (20 mL), dried over sodium sulfate and then concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:9) to afford the title compound 338 (194 mg, 0.72 mmol, 46% yield) as a colourless oil; δH (400 MHz, CDCl3) 5.87 (1 H, m, CH), 5.23 (1 H, d, J 17.2, CH2), 5.04 (1 H, d, J 10.4, CH2), 4.67 (1 H, m, CHOSi), 3.67 (3 H, s, OMe), 3.16 (3 H, s, Me), 2.76 (1 H, m, CH2), 2.40 (1 H, dd, J 14.6, 5.2, CH2), 0.86 (9 H, s, 3 × Me), 0.03 (6 H, s, SiMe2). Spectroscopic data in agreement with literature values.314

N-Methoxy-N-methyl-3-((trimethylsilyl)oxy)pent-4-enamide (339)

To a stirred solution of Weinreb amide 330 (250 mg, 1.57 mmol) in tetrahydrofuran (10 mL) cooled to 0 °C was added imidazole (213 mg, 3.13 mmol). This was allowed to stir for 15 minutes before the addition of trimethylsilyl chloride (0.300 mL, 2.36 mmol). The reaction was slowly warmed to room temperature and stirred for 4 hours. After this time, the solution was diluted with water (20 mL) and then extracted with ethyl acetate (5 × 10 mL). The organic phases were combined, washed with brine (20 mL), dried over sodium sulfate and then
concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:1) to afford the title compound 339 (229 mg, 0.99 mmol, 63%) as a colourless oil; $v_{\text{max}}$ (neat)/cm$^{-1}$ 2959, 1659, 1418, 1385, 1250, 1179, 1133, 1079, 1029, 951, 923, 887, 839, 750, 679; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 5.86 (1 H, ddd, $J$ 17.3, 10.9, 5.5, CH), 5.21 (1 H, d app t, $J$ 17.5, 1.7, CH$_2$), 5.03 (1 H, d app t, $J$ 10.2, 1.4, CH$_2$), 4.65 (1 H, m, CHOSi), 3.65 (3 H, s, OMe), 3.14 (3 H, s, Me), 2.77 (1 H, m, CH$_2$), 2.40 (1 H, dd, $J$ 15.1, 4.9, CH$_2$), 0.07 (9 H, s, SiMe$_3$); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 171.9 (C=O), 140.7 (CH), 114.3 (CH$_2$), 70.6 (OMe), 61.5 (Me), 40.4 (CH$_2$), 32.1 (CH), 0.2 (SiMe$_3$); HRMS (ESI) found: 254.1179 [C$_{10}$H$_{21}$NO$_3$Si + Na]$^+$ requires: 254.1183.

5-Methylpyrrole-2-carbaldehyde (340)

![Structure of 5-Methylpyrrole-2-carbaldehyde](image)

To a solution of pyrrole 325 (4.260 g, 52.57 mmol) in petroleum ether (100 mL) cooled to 0 °C was added dimethylformamide (6.100 mL, 78.86 mmol), followed by the dropwise addition of phosphorous oxychloride (5 mL, 52.57 mmol). The resulting reaction mixture was slowly warmed to room temperature and allowed to stir for 2 hours, during which time a bright red oil had separated from the reaction mixture. The clear petroleum ether solvent was decanted off and the red oil was washed with cold petroleum ether (3 × 10 mL). The red oil in dichloromethane (20 mL) was then added dropwise to a stirred solution of aqueous sodium hydroxide (10 molL$^{-1}$, 50 mL). The resulting biphasic solution was stirred for a further 12 hours. Once complete, the reaction was partitioned and the aqueous phase extracted with additional dichloromethane (3 × 15 mL). The organic fractions were combined, washed with brine (20 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:4) to afford the title compound 340 (3.384 g, 31.02 mmol, 59%) as a pale yellow solid, m.p. 76 – 77 °C (lit.$^{315}$ 72 – 74 °C); $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 9.38 (1 H, s, CHO), 8.98 (1 H, br s, NH), 6.87 (1 H, m, ArH), 6.06 (1 H, m, ArH), 2.34 (1 H, s, Me). Spectroscopic data in agreement with literature values.$^{315}$
N-(Ethoxymethyl)-5-methylpyrrole-2-carbaldehyde (345)

\[
\begin{align*}
\text{OHC} & \quad \text{N} \\
& \quad \text{O}
\end{align*}
\]

To a stirred solution of 5-methylpyrrole-2-carboxaldehyde (340) (700 mg, 6.41 mmol) in tetrahydrofuran (25 mL) cooled to 0 °C was added sodium hydride (60% dispersion in mineral oil, 772 mg, 19.23 mmol). The resulting slurry was stirred for 15 minutes before the dropwise addition of chloromethyl ethyl ether (1.71 mL, 19.23 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction was then cooled to 0 °C and quenched by the addition of water (50 mL). The resulting solution was warmed slowly to room temperature and extracted with ethyl acetate (5 × 15 mL). The organic fractions were combined, washed with brine (50 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography eluting with ethyl acetate:petroleum ether (1:9) to give the title compound 345 (796 mg, 4.76 mmol, 74%) as a pale yellow oil; \(v_{\text{max}}\) (neat)/cm\(^{-1}\) 2976, 2798, 1656, 1487, 1431, 1356, 1314, 1284, 1195, 1149, 1133, 1102, 1084, 1032, 785, 754; \(\delta_H\) (400 MHz, CDCl\(_3\)) 9.44 (1 H, s, CHO), 6.87 (1 H, d, \(J\) 3.9, ArH), 6.07 (1 H, d, \(J\) 3.8, ArH), 5.80 (2 H, s, NCH\(_2\)), 3.52 (2 H, q, \(J\) 7.2, CH\(_2\)), 2.37 (3 H, s, Me), 1.14 (3 H, t, \(J\) 6.8, Me); \(\delta_C\) (100 MHz, CDCl\(_3\)) 178.9 (C=O), 142.0 (C), 132.3 (C), 126.2 (CH), 111.0 (CH), 73.5 (CH\(_2\)), 63.7 (CH\(_2\)), 15.1 (Me), 12.3 (Me); HRMS (ESI) found: 190.0840 [C\(_9\)H\(_{13}\)NO\(_2\) + Na]\(^+\) requires: 190.0838.

N-(1-(Ethoxymethyl)-5-methyl-1H-pyrrol-2-y)pent-4-en-1-ol (346)

\[
\begin{align*}
\text{O} & \quad \text{N} \\
& \quad \text{O} & \quad \text{OH}
\end{align*}
\]

To an oven-dried round bottom flask was added magnesium powder (1 g, excess). This was evacuated and backfilled with argon. 4-Bromobut-2-ene (0.840 mL, 8.27 mmol) in ether (10 mL) was then added (0.16 mL min\(^{-1}\)). Once addition was completed, the reaction was allowed
to stir for 12 hours. After this time it was added dropwise to a stirred solution of pyrrole 345 (200 mg, 1.20 mmol) in tetrahydrofuran (10 mL) cooled to 0°C. The resulting reaction mixture was allowed to warm to room temperature and allowed to stir for 10 hours. The reaction was quenched with water (30 mL) and extracted with ethyl acetate (4 × 20 mL). The organic fractions were combined, washed with brine (50 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:4) to afford the title compound 346 (135 mg, 0.60 mmol, 50%) as a yellow oil; \(v_{\text{max}}\) (neat)/cm\(^{-1}\): 3430, 2975, 2924, 1640, 1509, 1421, 1378, 1284, 1087, 1008, 909, 846, 804, 760; \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 6.06 (1 H, d, \(J = 3.5\), ArH), 5.88 (2 H, m, CH and ArH), 5.28 (2 H, q, \(J = 10.8\), CH\(_2\)), 5.07 (1 H, m, CH\(_2\)), 4.99 (1 H, m, CH\(_2\)), 4.70 (1 H, m, CHOH), 3.49 (2 H, q, \(J = 7.5\), CH\(_2\)), 2.64 (1 H, s, OH), 2.28 (3 H, s, Me), 2.25 (2 H, m, CH\(_2\)), 2.01 (2 H, m, CH\(_2\)), 1.19 (3 H, t, \(J = 7.3\), Me); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 138.4 (CH), 135.2 (C), 130.2 (C), 114.9 (CH\(_2\)), 106.7 (CH), 106.1 (CH), 72.7 (CH\(_2\)), 65.3 (CH), 63.4 (CH\(_2\)), 34.4 (CH\(_2\)), 30.6 (CH\(_2\)), 15.0 (Me), 12.4 (Me); HRMS (ESI) found: 246.1469 [C\(_{13}\)H\(_{21}\)NO\(_2\) + Na]\(^+\) requires: 246.1464.

\[N-(1-(\text{Ethoxymethyl})-5\text{-methylpyrrol-2-yl})\text{pent-4-en-1-one} \quad (363)\]

To a stirred solution of pyrrole 346 (100 mg, 0.45 mmol) in ethyl acetate (2 mL) was added 2-iodoxybenzoic acid (378 mg, 1.35 mmol). The reaction mixture was stirred at 80 °C for 18 hours. The reaction was then filtered through a short plug of silica (flushing with ethyl acetate) and concentrated in vacuo to afford the title compound 363 (80 mg, 0.36 mmol, 81%) as a pale yellow oil which was used without further purification; \(v_{\text{max}}\) (neat)/cm\(^{-1}\): 2966, 2916, 1644, 1482, 1378, 1258, 1085, 1011, 915; \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 6.95 (1 H, d, \(J = 4.6\), ArH), 5.97 (1 H, d, \(J = 3.9\), ArH), 5.87 (1 H, m, CH), 5.84 (2 H, s, NCH\(_2\)), 5.08 (1 H, m, CH\(_2\)), 4.98 (1 H, m, CH\(_2\)), 3.50 (2 H, q, \(J = 7.3\), CH\(_2\)), 2.85 (2 H, m, CH\(_2\)), 2.44 (2 H, m, CH\(_2\)), 2.34 (3 H, s, Me), 1.13 (3 H, t, \(J = 6.8\), Me); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 190.1 (C=O), 140.2 (C), 137.8 (CH), 137.5 (C), 120.6
(CH), 115.1 (CH2), 109.2 (CH), 73.6 (CH2), 63.6 (CH2), 38.5 (CH2), 29.5 (CH2), 15.2 (Me), 12.5 (Me); HRMS (ESI) found: 244.1312 [C13H19NO2 + Na]+ requires: 244.1308.

4-Bromo-N-(ethoxymethyl)-5-methylpyrrole-2-carbaldehyde (367)

To a solution of pyrrole 345 (10 mg, 0.06 mmol) in tetrahydrofuran (2 mL) was added N-bromosuccinimide (10.6 mg, 0.06 mmol). After 15 minutes, the reaction was concentrated in vacuo and the resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:19) to afford the title compound 367 (7 mg, 0.03 mmol, 48%) a red oil; νmax (neat)/cm⁻¹ 2962, 2923, 2851, 1668, 1485, 1406, 1318, 1258, 1084, 1013, 793, 662; δH (400 MHz, CDCl3) 9.41 (1 H, s, CHO), 6.91 (1 H, s, ArH), 5.80 (2 H, s, NCH2), 3.51 (2 H, q, J 6.9, CH2), 2.35 (3 H, s, Me), 1.14 (3 H, t, J 7.1, Me); δC (100 MHz, CDCl3) 178.6 (C=O), 139.6 (C), 131.5 (C), 126.6 (CH), 99.3 (C), 74.2 (CH2), 64.0 (CH2), 15.1 (Me), 10.9 (Me); HRMS (ESI) found: 267.9953 [C9H12BrNO2 + Na]+ requires: 267.9944.

bis(N-(Ethoxymethyl)-5-methyl-1H-pyrrol-2-yl)methane (372)

A catalyst solution containing [Ir(OMe)COD]2 (9.94 mg, 0.02 mmol, 5 mol%), tris-(pentafluorophenyl)phosphine (31.8 mg, 0.06 mmol, 20 mol%) and bis(pinacolato)-diboron (151.9 mg, 0.60 mmol) was prepared in n-octane (1 mL) under a heavy stream of nitrogen. Pyrrole 345 (50 mg, 0.30 mmol) in degassed n-octane (3 mL) was then added and the resulting
solution was stirred at 120 °C for 18 hours. The reaction was diluted with ethyl acetate (10 mL) and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (2:98) to afford the title compound 372 (8.7 mg, 0.03 mmol, 10%) as a yellow oil; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3355, 2975, 2929, 1710, 1660, 1442, 1378, 1282, 1257, 1169, 1093, 1015, 744; \( \delta_H \) (400 MHz, CDCl\(_3\)) 5.78 (2 H, d, \( J = 3.3 \), ArH), 5.72 (2 H, d, \( J = 3.8 \), ArH), 5.12 (4 H, s, NCH\(_2\)O), 4.00 (2 H, s, CH\(_2\)), 3.39 (4 H, q, \( J = 6.8 \), CH\(_2\)), 2.26 (6 H, s, Me), 1.16 (6 H, t, \( J = 6.8 \), Me); \( \delta_C \) (100 MHz, CDCl\(_3\)) 130.1 (C), 129.3 (C), 107.4 (CH), 106.4 (CH), 72.9 (CH\(_2\)), 63.0 (CH\(_2\)), 25.0 (CH\(_2\)), 15.1 (Me), 12.4 (Me); HRMS (ESI) found: 313.1883 [C\(_{17}\)H\(_{26}\)N\(_2\)O\(_2\) + Na]\(^+\) requires: 313.1886.

2-Methyl-N-(triisopropylsilyl)pyrrole (380)

![Structure](image)

Prepared according to the procedure presented by Oliveira and co-workers.\(^{316}\)

Purified via flash column chromatography on silica gel eluting with petroleum ether to afford the title compound 380 (449 mg, 1.89 mmol, 77%) as a colourless oil; \( \delta_H \) (400 MHz, CDCl\(_3\)) 6.74 (1 H, m, ArH), 6.15 (1 H, t, \( J = 2.3 \), ArH), 6.01 (1 H, m, ArH), 2.33 (3 H, s, Me), 1.53 (3 H, quint, \( J = 7.5 \), CH), 1.13 (18 H, d, \( J = 7.7 \), Me). Spectroscopic data in agreement with literature values.\(^{316}\)}
4-Bromopyrrole-2-carboxaldehyde (382)

Prepared according to the procedure presented by Lindsey and co-workers. Purified by recrystallization from ethanol:water (1:9) to afford the title compound 382 (18.063 g, 103.81 mmol, 99%) as a light purple solid, m.p. 114 – 115 °C (lit.279 120 °C); δH (400 MHz, CDCl₃) 9.49 (1 H, s, CHO), 9.25 (1 H, br s, NH), 7.09 (1 H, m, ArH), 6.96 (1 H, m, ArH). Spectroscopic data consistent with literature values.279

4-Bromo-N-tosylpyrrole-2-carboxaldehyde (383)

To a stirred solution of pyrrole 382 (4.300 g, 24.71 mmol) in dimethylformamide (100 mL) cooled to 0 °C was added sodium hydride (60% dispersion in mineral oil, 1.700 g, 42.50 mmol). The resulting slurry was allowed to stir for 15 minutes before the addition of p-toluenesulfonyl chloride (7.2 g, 37.77 mmol) in dimethylformamide (30 mL). The reaction was stirred at room temperature for 30 hours. The reaction was then quenched by the slow addition of water (300 mL) and subsequently extracted with dichloromethane (7 × 150 mL). The organic fractions were combined and washed with a mixture of brine:water (1:1, 3 × 150 mL), washed with brine (200 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:4) to afford the title compound 383 (4.675 g, 14.25 mmol, 58%) as an off-white solid, m.p. 76 – 80 °C (lit. 83 – 85 °C); δH (400 MHz, CDCl₃) 9.95 (1 H, s, CHO), 7.81 (2 H, d, J 8.2, ArH), 7.57 (1 H, d, J 1.8, ArH), 7.35 (2 H, d, J 8.3, ArH), 7.07 (1 H, d, J 2.2, ArH), 2.44 (3 H, s, Me). Spectroscopic data consistent with literature values.279
To a stirred solution of pyrrole 383 (20 mg, 0.06 mmol) in tetrahydrofuran (1 mL) cooled to 0 °C was added lithium aluminium hydride (6.9 mg, 0.18 mmol). The resulting solution was stirred at 60 °C for 1 hour. After this time the reaction was cooled to 0 °C and quenched by the slow addition of water (5 mL). The resulting aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic fractions were combined, washed with brine (10 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate:hexanes (1:4) to afford the title compound 387 (13 mg, 0.04 mmol, 65%) as a yellow oil; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3394, 2923, 1704, 1596, 1437, 1365, 1160, 1087, 1054, 914, 812, 665; $\delta_H$ (300 MHz, CDCl$_3$) 7.74 (2 H, dt, $J$ 8.6, 1.7, ArH), 7.33 (2 H, m, ArH), 7.26 (1 H, d, $J$ 1.9, ArH), 6.25 (1 H, d, $J$ 1.8, ArH), 4.58 (2 H, d, $J$ 4.7, CH$_2$), 2.63 (1 H, br s, OH), 2.43 (3 H, s, Me); $\delta_C$ (100 MHz, CDCl$_3$) 146.0 (C), 135.6 (C), 135.3 (C), 130.5 (CH), 127.1 (CH), 122.3 (CH), 117.6 (CH), 100.9 (C), 56.8 (CH$_2$), 21.8 (Me); HRMS (ESI) found: 351.9615 [C$_{12}$H$_{12}$BrNO$_3$S + Na]$^+$ requires: 351.9613.
4-Bromo-N-tosyl-2-(((triethylsilyl)oxy)methyl)pyrrole (388)

In a sealed tube, a solution of 4-bromo-N-tosylpyrrole-2-carboxaldehyde (383) (25 mg, 0.076 mmol) and triethylsilane (0.036 mL, 0.228 mmol) in dichloromethane (1 mL) was prepared. *tris*-(Pentafluorophenyl)borane (1.9 mg, 0.004 mmol, 5 mol%) was added under a blanket of nitrogen and hydrogen evolution was observed. Once complete, the solution was sealed and heated to 50 °C for 24 hours. The reaction was then quenched with triethylamine (0.1 mL), diluted with additional dichloromethane (5 mL) and washed with water (3 × 5 mL). The organic phase was washed with brine (15 mL), dried over sodium sulfate and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:19) to afford the *title compound* 388 (9 mg, 0.02 mmol, 26%) as a yellow oil; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2955, 2913, 2876, 1597, 1457, 2520, 1373, 1229, 1174, 1114, 1051, 1006, 914, 811, 736, 660; $\delta_H$ (400 MHz, CDCl$_3$) 7.73 (2 H, d, $J$ 8.7, ArH), 7.30 (2 H, d, $J$ 8.3, ArH), 7.23 (1 H, d, $J$ 1.8, ArH), 6.24 (1 H, s, ArH), 4.76 (2 H, s, CH$_2$), 2.41 (3 H, s, Me), 0.91 (9 H, t, $J$ 7.7, Me), 0.57 (6 H, q, $J$ 7.7, CH$_2$); $\delta_C$ (100 MHz, CDCl$_3$) 145.5 (C), 135.8 (2 × C), 130.1 (CH), 127.3 (CH), 121.4 (CH), 115.6 (CH), 100.9 (C), 57.8 (CH$_2$), 21.8 (CH$_2$), 6.8 (Me), 4.5 (Me); HRMS (ESI) found: 466.0474 [C$_{18}$H$_{26}$BrNO$_3$Si + Na]$^+$ requires: 466.0478.
4-Bromo-2-methyl-1-tosylpyrrole (384)

In a sealed tube, a solution of 4-bromo-N-tosylpyrrole-2-carboxaldehyde (383) (500 mg, 1.52 mmol) and triethylsilane (1.460 mL, 9.14 mmol) in dichloromethane (10 mL) was prepared. *tris*-Pentafluorophenyl)borane (42 mg, 0.08 mmol, 5 mol%) was added under a blanket of nitrogen and hydrogen evolution was observed. Once complete, the solution was sealed and heated to 40 °C for 24 hours. The reaction was then quenched with triethylamine (5 mL), diluted with additional dichloromethane (10 mL) and washed with water (3 × 10 mL). The organic phase was washed with brine (30 mL), dried over sodium sulfate and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:19) to afford the *title compound* 384 (348 mg, 1.108 mmol, 73%) as an off-white solid, m.p. 87 – 94 °C; ν<sub>max</sub> (neat)/cm<sup>-1</sup> 3149, 2961, 2923, 1594, 1591, 1366, 1226, 1169, 1088, 1052, 987, 909, 797, 744, 710, 658; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.69 (2 H, d, J 8.4, ArH), 7.32 (2 H, d, J 7.9, ArH), 7.27 (1 H, d, J 2.1, ArH), 5.95 (1 H, s, ArH), 2.42 (3 H, s, Me), 2.27 (3 H, s, Me); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 145.4 (C), 135.9 (C), 131.8 (C), 130.3 (CH), 127.2 (CH), 120.9 (CH), 115.8 (CH), 100.2 (C), 21.8 (Me), 13.5 (Me); HRMS (ESI) found: 335.9658 [C<sub>12</sub>H<sub>12</sub>BrNO<sub>2</sub>S + Na]<sup>+</sup> requires: 335.9664.
3-Bromo-5-methyl-N-tosylpyrrole-2-carboxaldehyde (393)

A solution of pyrrole 384 (1000 mg, 3.18 mmol) in 1,2-dichloroethane (20 mL) was cooled to -15 °C. Aluminium chloride (850 mg, 6.37 mmol) was added in one portion and the resulting slurry was allowed to stir for 10 minutes. 1,1-Dichloromethyl methyl ether (0.55 mL, 4.77 mmol) was then added dropwise. The resulting solution was allowed to slowly warm to room temperature. After 20 hours, the solution was cooled back to -15 °C and an additional portion of 1,1-dichloromethyl methyl ether (0.25 mL, 2.17 mmol) was added dropwise. The resulting solution was again slowly warmed to room temperature and allowed to stir for a further 7 hours. The reaction was then quenched by the slow addition of water (20 mL) and extracted with dichloromethane (3 × 10 mL). The organic phases were combined, washed with brine (20 mL), dried over sodium sulfate, and concentrated in vacuo. The resulting crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:9) to afford the title compound 393 (898 mg, 2.62 mmol, 82%) as a light pink solid, m.p. 113 – 115 °C; νmax (neat)/cm⁻¹ 1668, 1595, 1555, 1468, 1364, 1277, 1216, 1172, 1172, 1144, 1099, 1009, 806, 667; δH (400 MHz, CDCl₃) 10.07 (1 H, s, CHO), 7.75 (2 H, d, J 8.3, ArH), 7.33 (2 H, d, J 8.1, ArH), 6.18 (1 H, s, ArH), 2.54 (3 H, s, Me), 2.43 (3 H, s, Me); δC (100 MHz, CDCl₃) 179.4 (C=O), 146.1 (C), 140.3 (C), 135.8 (C), 130.4 (CH), 130.3 (C), 127.3 (CH), 118.4 (CH), 114.0 (C), 21.8 (Me), 15.7 (Me); HRMS (ESI) found: 363.9621 [C₁₃H₁₂BrNO₃S + Na]⁺ requires: 363.9613.
To an oven-dried round bottom flask was added magnesium powder (1 g, excess) and a few crystals of iodine. This was evacuated and backfilled with argon before being heated to cause sublimation of the iodine. Once cooled back to room temperature, a small volume of ether was added while stirring. Next, 4-bromobut-2-ene (0.600 mL, 5.91 mmol) in ether (15 mL) was added to the magnesium (0.16 mL min\(^{-1}\)). Once completed, the reaction was allowed to stir for 3 hours. After this time, the solution was added dropwise to a stirred solution of 3-bromo-5-methyl-N-tosylpyrrole-2-carboxaldehyde (393) (500 mg, 1.46 mmol, 1 eq.) in tetrahydrofuran (15 mL) cooled to 0\(^\circ\)C. The resulting reaction mixture was allowed to warm to room temperature and stir for 1 hour. The reaction was then quenched with water (30 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, washed with brine (50 mL), dried over sodium sulfate and concentrated \(\textit{in vacuo}\). The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:9) to afford the \textit{title compound} 397 (484 mg, 1.22 mmol, 83%) as a yellow oil; \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3552, 2976, 2930, 1640, 1596, 1579, 1448, 1403, 1365, 1190, 1170, 1102, 1017, 910, 811, 664; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 7.66 (2 H, d, J 8.5, ArH), 7.30 (2 H, d, J 8.1, ArH), 5.96 (1 H, s, ArH), 5.86 (1 H, m, CH), 5.16 (1 H, m, CHO\(_3\)), 5.03 (1 H, d, J 17.4, CH\(_2\)), 4.97 (1 H, d, J 11.6, CH\(_2\)), 3.53 (1 H, d, J 10.5, OH), 2.41 (3 H, s, Me), 2.24 (3 H, s, Me), 2.19 (2 H, m, CH\(_2\)), 2.02 (2 H, m, CH\(_2\)); \(\delta\)\(_C\) (100 MHz, CDCl\(_3\)) 145.5 (C), 138.0 (CH), 136.4 (C), 135.1 (C), 134.0 (C), 130.3 (CH), 126.5 (CH), 116.2 (CH), 115.0 (CH\(_2\)), 68.1 (CH), 53.6 (C), 36.4 (CH\(_2\)), 30.5 (CH\(_2\)), 21.8 (Me), 15.3 (Me); HRMS (ESI) found: 420.0233 [C\(_{17}\)H\(_{30}\)BrNO\(_3\)S + Na]\(^+\) requires: 420.0239.
2-Methyl-4-methylene-1-tosyl-4,5,6,7-tetrahydro-1H-indol-7-ol (402) and 2,4-dimethyl-1-tosyl-1H-indole (403)

A sealed tube was charged with Pd(OAc)$_2$ (10 mg, 0.45 mmol, 10 mol%), triphenylphosphine (47 mg, 0.181 mmol, 20 mol%) and sodium formate (36 mg, 0.54 mmol) and subsequently purged with argon. Triethylamine (0.125 mL, 0.90 mmol) was then added. A solution of pyrrole (180 mg, 0.45 mmol) in dry acetonitrile (3 mL) was thoroughly degassed with argon before being added to the aforementioned mixture. The resulting reaction mixture was sealed and heated to 80 °C. After 19 hours, the reaction was diluted with ethyl acetate (5 mL), passed through a short plug of Celite and concentrated in vacuo. The resulting crude oil was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:9) to afford the tetrahydroindole (100 mg, 0.32 mmol, 70%) as a yellow oil; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2920, 2852, 1674, 1597, 1435, 1362, 1173, 1090, 1016, 909, 729, 703, 660; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.65 (2 H, dt, $J$ 8.6, 1.72, ArH), 7.30 (2 H, d, $J$ 8.2, ArH), 6.11 (1 H, m, ArH), 5.12 (1 H, m, C$_2$H$_5$OH), 5.09 (1 H, m, CH$_3$), 4.89 (1 H, m, CH$_2$), 3.23 (1 H, dd, $J$ 3.5, 1.5, OH), 2.75 (1 H, m, CH$_2$), 2.41 (3 H, s, Me), 2.36 (1 H, m, CH$_2$), 2.32 (3 H, d, $J$ 1.32, Me), 2.13 (1 H, m, CH$_2$), 1.86 (1 H, m, CH$_2$); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 145.1 (C), 138.5 (C), 136.9 (C), 134.0 (C), 133.5 (C), 130.3 (CH), 126.5 (CH), 124.5 (C), 108.9 (CH), 107.3 (CH$_2$), 61.4 (CH), 32.0 (CH$_2$), 26.4 (CH$_2$), 21.8 (Me), 15.0 (Me); HRMS (ESI) found: 340.0989 [C$_{17}$H$_{19}$NO$_3$S + Na]$^+$ requires: 340.0978.

Indole (27 mg, 0.09 mmol, 20%) was isolated as an off-white solid, m.p. 90 – 92 °C; $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2959, 2918, 2849, 1597, 1446, 1363, 1257, 1187, 1173, 1163, 1149, 1093, 1073, 1010, 1000, 805, 776, 681, 542; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.98 (1 H, d, $J$ 8.6, ArH), 7.66 (2 H, dt, $J$ 8.5, 2.03, ArH), 7.20 (2 H, d, $J$ 8.1, ArH), 7.15 (1 H, t, $J$ 7.7, ArH), 7.00 (1 H, dd, $J$ 7.8, 0.9, ArH), 6.37 (1 H, m, ArH), 2.61 (3 H, s, Me), 2.41 (3 H, s, Me), 2.34 (3 H, s, Me) $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 144.7 (C), 136.9 (C), 136.6 (C), 130.0 (CH), 129.5 (C), 129.3 (C), 126.5 (CH), 124.0 (CH), 123.9 (CH), 121.2 (C), 112.2 (CH), 108.1 (CH), 21.7 (Me), 18.5 (Me), 16.0 (Me); HRMS (ESI) found: 300.1052 [C$_{17}$H$_{18}$NO$_2$S + Na]$^+$ requires: 300.1053.
2-Methyl-4-methylene-N-tosyl-4,5,6,7-tetrahydroindol-7-yl 2,2,2-trichloroacetimidate (410)

To a stirred solution of tetrahydroindole 402 (10 mg, 0.03 mmol) in ether (0.5 mL) was added trichloroacetonitrile (0.05 mL, 0.50 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.013 mL, 0.09 mmol). After 4 hours, the reaction mixture was used without further purification. Full characterisation was not possible due to rapid degradation of compound 410; δ_H (300 MHz, CDCl_3) 7.59 (2 H, d, J 8.7, ArH), 7.30 (2 H, m, ArH), 6.76 (1 H, d, J 6.3, NH), 6.18 (1 H, fd, J 1.0, ArH), 5.42 (1 H, m, CHOC=NH), 5.18 (1 H, m, CH_2), 4.94 (1 H, m, CH_2), 4.24 (3 H, d, J 0.8, Me), 2.41 (3 H, s, Me), 2.24-2.35 (2 H, m, CH_2), 0.98-1.86 (2 H, m, CH_2); HRMS (ESI) found: 483.0060 [C_{19}H_{19}Cl_3N_2O_3S + Na]^+, theory: 483.0074.

7-Methoxy-2-methyl-4-methylene-N-tosyl-4,5,6,7-tetrahydroindole (413)

To a stirred solution of tetrahydroindole 402 (5 mg, 0.016 mmol) in methanol (1 mL) was added aqueous hydrochloric acid (0.1 molL^{-1}, 0.016 mL, 10 mol%). The resulting reaction mixture was allowed to stir at room temperature for 2 hours, after which time was diluted with ethyl acetate (10 mL). This solution was washed with sodium hydrogen carbonate (5 mL), brine (10 mL) and dried over sodium sulfate. The solvent was removed in vacuo to afford the title compound 413 (5 mg, 0.015 mmol, 94%) as a white solid that required no further purification, m.p. decomposed at 200 °C; ν_{max} (neat)/cm^{-1} 3302, 2928, 2159, 2031, 1796, 1738, 1675, 1595,
To a stirred solution of tetrahydroindole 402 (50 mg, 0.16 mmol) and 5-methoxy-2,4-dimethylindole (185) (82 mg, 0.47 mmol) in dioxane (5 mL) was added Amberlyst 15 (50 mg). The resulting suspension was allowed to stir at room temperature for 3 hours. After this time, the reaction was diluted with ethyl acetate (10 mL) and passed through a plug of cotton wool. The crude solution was concentrated in vacuo and purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:4) to afford the title compound 414 (40 mg, 0.08 mmol, 53%) as a bright yellow solid, mp 112 – 118 °C; νmax (neat)/cm⁻¹ 3470, 2932, 2160, 2021, 1697, 1634, 1596, 1492, 1419, 1362, 1254, 1172, 1145, 1108, 1016, 877, 803, 707, 662; δH (400 MHz, CDCl3) 7.19 (2 H, d, J 8.5, ArH), 7.10 (1 H, br s, NH), 6.99 (1 H, d, J 8.6, ArH), 6.94 (2 H, d, J 8.1, ArH), 6.84 (1 H, d, J 8.5, ArH), 6.18 (1 H, d, J 0.8, ArH), 5.55 (1 H, m, CH), 5.08 (1 H, m, CH2), 4.79 (1 H, s, CH2), 3.86 (3 H, s, OMe), 2.71 (3 H, s, Me), 2.53 (3 H, s, Me), 2.52-2.05 (4 H, m, 2 × CH2), 2.32 (3 H, s, Me), 1.38 (3 H, s, Me); δC (75 MHz, (CD3)2CO) 152.2 (C), 145.3 (C), 140.0 (C), 137.4 (C), 135.8 (C), 133.8 (C), 133.4 (C), 132.3 (C), 130.1 (CH), 128.6 (C), 127.3 (CH), 124.8 (C) 117.8 (C), 114.0 (C), 109.3 (2 × CH), 108.8 (CH), 106.0 (CH2), 58.1 (OMe), 34.3 (Me), 31.7 (CH), 27.3 (Me), 21.5 (CH2), 15.9
(CH$_2$)$_n$, 12.2 (Me), 11.7 (Me); HRMS (ESI) found: 475.2036 [C$_{28}$H$_{30}$N$_2$O$_3$S + H]$^+$ requires: 475.2050.

5-Hydroxy-5'-methoxy-2,2',4'-trimethyl-4-methylene-N-tosyl-4,5,6,7-tetrahydro-3',7-biindole (415)

Selenium dioxide (1.7 mg, 0.015 mmol) was suspended in tetrahydrofuran (1 mL) and cooled to 0 °C. tert-Butylhydroperoxide (5.5 molL$^{-1}$ in decane, 0.036 mL, 0.15 mmol) was added. The resulting solution was allowed to stir for 15 minutes before the addition of C3-linked compound 414 (15 mg, 0.03 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 3 hours. The reaction was then quenched by the addition of saturated aqueous sodium sulphite (0.5 mL). The resulting aqueous phase was extracted with ethyl acetate (3 × 2 mL). The organic fractions were combined, washed with brine (3 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified via flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (2:3) to afford the title compound 415 (2.6 mg, 0.005 mmol, 36%) as a yellow oil containing a 9:1 mixture of anti:syn diastereomers; $\nu$$_{max}$ (neat)/cm$^{-1}$ 3405, 2920, 2851, 1702, 1596, 1493, 1419, 1363,1255, 1167, 1147, 1110, 1043, 969, 885, 808, 741, 714, 669; Major product 415a (anti) - $\delta$$_H$ (500 MHz, (CD$_3$)$_2$CO) 9.32 (1 H, s, NH), 7.21 (2 H, d, $J$ 8.3, ArH), 7.07-7.09 (3 H, m, 2 × ArH), 6.84 (1 H, d, $J$ 8.5, ArH), 6.30 (1 H, s, ArH), 5.66 (1 H, m, CH), 5.25 (1 H, app t, $J$ 2.0, CH$_2$), 5.22 (1 H, app t, $J$ 2.0, CH$_2$), 4.38-4.40 (1 H, m, CHO$_2$), 3.94 (1 H, d, $J$ 6.2, OH), 3.82 (3 H, s, OMe), 2.68 (3 H, s, Me), 2.52 (3 H, s, Me), 2.34 (3 H, s, Me), 2.20-2.23 (2 H, m, CH$_2$), 1.31 (3 H, s, Me); $\delta$$_C$ (125 MHz, (CD$_3$)$_2$CO) 152.2 (C), 145.3 (C), 144.0 (C), 137.3 (C), 134.4 (C) 134.1 (C), 133.2 (C), 132.3 (C), 130.1 (CH), 128.5 (C), 127.3 (CH), 124.6 (C), 117.7 (C), 114.3 (C), 109.5 (CH), 109.4 (CH), 108.6 (CH), 104.3 (CH$_2$), 66.2 (CH), 58.1 (OMe), 43.9 (CH$_2$),
32.2 (CH), 21.5 (Me), 16.0 (Me), 12.2 (Me), 11.7 (Me); HRMS (ESI) found: 513.1821 \([C_{28}H_{30}N_2O_4S + Na]^+\) requires: 513.1818. Minor product 415b (syn) was not characterised due to insufficient material.

(E)-3-Bromo-5-methyl-2-(penta-1,4-dien-1-yl)-N-tosylpyrrole (420)

To a stirred solution of pyrrole 397 (20 mg, 0.05 mmol) and triethylamine (0.007 mL, 0.05 mmol) in dichloromethane (1 mL) cooled to -10 °C was added phosphorous tribromide (0.005 mL, 0.05 mmol). After 30 minutes, the reaction was quenched with aqueous sodium hydrogen carbonate (saturated, 1 mL). The resulting aqueous phase was extracted with dichloromethane (3 × 2 mL) and the organic fractions were combined, washed with brine (5 mL), dried over sodium sulfate and concentrated in vacuo. The resulting crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate:petroleum ether (1:9) to afford the title compound 420 (18 mg, 0.047 mmol, 94%) as a yellow oil; \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 2929, 1637, 1597, 1574, 1448, 1433, 1369, 1170, 1139, 1104, 991, 914, 810, 666; \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.59 (2 H, d, \(J = 8.5\), ArH), 7.25 (2 H, d, \(J = 8.0\), ArH), 6.55 (1 H, d, \(J = 16.0\), CH), 6.07 (1 H, dt, \(J = 16.0, 6.8\), CH), 5.98 (1 H, s, ArH), 5.90 (1 H, m, CH), 5.14 (1 H, dq, \(J = 17.0, 2.0\), CH\(_2\)), 5.09 (1 H, dq, \(J = 10.3, 1.5\), CH\(_2\)), 2.97 (2 H, tq, \(J = 6.5, 1.53\), CH\(_2\)), 2.43 (3 H, s, Me), 2.40 (3 H, s, Me); \(\delta_C\) (100 MHz, CDCl\(_3\)) 145.1 (C), 136.6 (C), 136.0 (C), 134.8 (CH), 132.6 (C), 130.7 (C), 129.9 (CH), 126.9 (CH), 119.8 (CH), 116.7 (CH), 116.0 (CH\(_2\)), 101.3 (C), 37.3 (CH\(_2\)), 21.8 (Me), 15.8 (Me); HRMS (ESI) found: 402.0122 \([C_{17}H_{18}BrNO_2S + Na]^+\) requires: 402.0134.
1-(3-Bromo-5-methyl-1-tosyl-1H-pyrrol-2-yl)pent-4-en-1-one (421)

To a stirred solution of pyrrole 397 (180 mg, 0.45 mmol) in ethyl acetate (3 mL) was added 2-iodoxybenzoic acid (560 mg, 2.00 mmol). The resulting slurry was heated to 80 °C for 18 hours after which time it was cooled back to room temperature, diluted with ethyl acetate (10 mL) and passed through a short plug of Celite. The solvent was removed in vacuo to afford the title compound 421 (179 mg, 0.45 mmol, quantitative) as a yellow oil that was used without further purification; \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2981, 2931, 1738, 1697, 1596, 1495, 1446, 1371, 1240, 1173, 1100, 1046, 993, 915, 813, 703, 662; \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.82 (2 H, d, \( J = 8.3 \), ArH), 7.33 (2 H, d, \( J = 8.3 \), ArH), 5.95 (1 H, m, ArH), 5.89 (1 H, m, CH), 5.10 (1 H, dq, \( J = 17.1, 1.6 \), CH\(_2\)), 5.01 (1 H, dq, \( J = 10.2, 1.4 \), CH\(_2\)) 3.05 (2 H, m, CH\(_2\)), 2.50 (2 H, m, CH\(_2\)), 2.43 (3 H, s, Me), 2.33 (3 H, fd, \( J = 0.9 \), Me); \( \delta_C \) (100 MHz, CDCl\(_3\)) 196.1 (C=O), 145.8 (C), 137.2 (CH), 135.23 (C), 135.17 (C) 133.3 (C), 130.2 (CH), 127.7 (CH), 116.4 (CH), 115.4 (CH\(_2\)), 103.4 (C), 43.8 (CH\(_2\)), 28.2 (CH\(_2\)), 21.8 (Me), 14.7 (Me); HRMS (ESI) found: 418.0085 [C\(_{17}\)H\(_{18}\)BrNO\(_3\)S + Na]\(^+\) requires: 418.0083.
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