Part I: Synthesis of Pyrrolo[1,2-A]Indoles Part II: Studies Towards Arboflorine

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Graduate Program in Chemistry
A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy
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PART I: SYNTHESIS OF PYRROLO[1,2-α]INDOLES
PART II: STUDIES TOWARDS ARBOFLORINE

(Spine title: Synthetic Approaches to Indole Natural Products)

(Thesis format: Monograph)

by

Michael B. Johansen

Graduate Program in Chemistry

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

School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

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The thesis by

Michael B. Johansen

entitled:

Part I: Synthesis of Pyrrolo[1,2-α]Indoles
Part II: Studies Towards Arboflorine

is accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

November 18th, 2010

Chair of the Thesis Examination Board
Abstract and Key Words

Abstract – Part one of this thesis focuses on the synthesis of pyrrolo[1,2-\(a\)]indoles from nitrones and 1,1-cyclopropanediesters, by way of tetrahydro-1,2-oxazines. A five step synthetic sequence through tetrahydro-1,2-oxazine synthesis, intramolecular Heck reaction, Krapcho dealkoxycarbonylation, reductive N-O bond cleavage, and acid catalyzed transannular alcohol displacement, is developed to access the desired pyrrolo[1,2-\(a\)]indoles.

Part two of this thesis details the functionalization of indoles by installation of a malonate moiety, by means of copper catalyzed carbenoid reactivity. A wide range of malonyl indoles with varying substitution patterns is shown to be accessible through the developed method. The final chapter focuses on the application of this reaction in a biomimetic approach towards the total synthesis of the indole alkaloid arboflorine. This reaction provided access to an advanced intermediate which allowed for the study of a key Mannich ring closure step that was proposed in the postulated biogenesis of the natural product. The current synthetic sequence includes the copper catalyzed malonyl carbenoid insertion, reduction of a pyridinium salt, reductive ammination, and a Polonovski-Potier reaction to install and mask an iminium motif. As of yet, the proposed Mannich reaction has been unsuccessful in securing the required azepane ring.

Key Words: Pyrrolo[1,2-\(a\)]indole, Cyclopropane, Carbene, Copper Catalysis, Indole Functionalization, Natural Product Synthesis, Arboflorine, Biomimetic, Indole.
For my friends and family.

These are the results of your love and support.
Acknowledgements

I can still remember my first day in the lab just over four years ago. Bright eyed and bushy-tailed I couldn’t wait to jump into the learning experience that was before me. Prof. Michael Kerr had assembled a large research group full of brilliant young chemists and had provided me with an opportunity to join them and learn from both him and his students. Above all I owe Prof. Kerr many thanks for allowing me to join this group and for all his inspiration, guidance and support these past few years. His unabashed enthusiasm for chemistry is truly inspirational.

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conversation. Andrew (Duke) was always eager to supply his opinion (often with a healthy dose of pessimism) but was also eager to help and teach, and I owe him many thanks for our collaboration on the balasubramide project. He taught me a lot over the past few years, and especially in my early research career.

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List of Abbreviations

A  acceptor substituent/electron-withdrawing group
Ac  acetyl
Ac₂O  acetic anhydride
AcCl  acetyl chloride
ap.  apparent
aq.  aqueous
Ar  aryl
Bn  benzyl
Boc  tert-butylloxycarbonyl
Boc₂O  di-tert-butyl-dicarbonate
br  broad
Bz  benzoyl
C  Celsius
CAN  ceric ammonium nitrate
D  donor/electron-donating group
d  doublet
dba  dibenzyleacetone
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DCC  N,N'-dicyclohexylcarbodiimide
DCE  1,2-dichloroethane
DCM  dichloromethane
DDQ  2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD  diisopropyl azodicarboxylate
DIBAL  diisobutylaluminum hydride
DMAP  N,N-dimethylamino-4-pyridine
DME  1,2-dimethoxyethane
DMF  N,N-dimethylformamide
DMP  Dess-Martin periodinane
DMSO  dimethyl sulfoxide
DNA  deoxyribonucleic acid
DPPA  diphenylphosphorylazide
dr  diastereomeric ratio
E  electrophile
ee  enantiomeric excess
Et  ethyl
EtOAc  ethyl acetate
EWG  electron-withdrawing group
FT  Fourier transform
g  grams or gradient selected
HMDS  hexamethyldisilazane
HMPA  hexamethylphosphoramide
HPLC  high performance liquid chromatography
HRMS  high-resolution mass spectrometry
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>hv</td>
<td>light</td>
</tr>
<tr>
<td>i-</td>
<td>iso</td>
</tr>
<tr>
<td>IBX</td>
<td>iodoxybenzoic acid</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>NMR coupling constant</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>L.A.</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LHMDS</td>
<td>lithium hexamethyldisilazide</td>
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<tr>
<td>M</td>
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<td>m</td>
<td>meta substitution</td>
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<td>multiplet</td>
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<tr>
<td>m-CPBA</td>
<td>meta-chloroperbenzoic acid</td>
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<td>acetonitrile</td>
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<td>methanesulfonyl chloride</td>
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<td>microwave irradiation</td>
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<td>normal</td>
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<td>NIS</td>
<td>N-iodosuccinimide</td>
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<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
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<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<td>Nu</td>
<td>generic nucleophile</td>
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<td>ortho substitution</td>
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<tr>
<td>p</td>
<td>pentet (or may refer to p atomic orbital)</td>
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<tr>
<td>p</td>
<td>para substitution</td>
</tr>
<tr>
<td>p-ABSA</td>
<td>para-acetamidobenzenesulfonylazide</td>
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<tr>
<td>Pg</td>
<td>unspecified protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
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<tr>
<td>Phth</td>
<td>phthalimide</td>
</tr>
<tr>
<td>Piv</td>
<td>trimethylacetyl</td>
</tr>
<tr>
<td>Piv-Cl</td>
<td>trimethylacetyl chloride</td>
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<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
</tbody>
</table>
q  quartet
R  generic substituent
R_f  retention factor
rt  room temperature
s  singlet (or may refer to s atomic orbital)
SM  starting material
S_N2  second order nucleophilic substitution
t  triplet
TBAF  tetrabutylammonium fluoride
TBDPS  tert-butyldiphenylsilyl
TBDPSCI  tert-butyldiphenylsilyl chloride
TBS  tert-butyldimethylsilyl
'^Bu  tert-butyl
TEA  triethylamine
TFA  trifluoroacetic acid
TFAA  trifluoroacetic anhydride
THF  tetrahydrofuran
TLC  thin layer chromatography
TMS  trimethylsilyl
Ts  para-toluenesulfonyl
TsCl  para-toluenesulfonyl chloride
TsOH  para-toluenesulfonic acid
X,Y,Z  generic atoms (usually heteroatoms)
Chapter 1: The Synthesis of Pyrrolo[1,2-\textit{a}]indoles from Nitrones and Cyclopropanes

Chapter one describes the expansion of current group methodology through the synthesis of pyrrolo[1,2-\textit{a}]indoles from vinyl substituted cyclopropanes and nitrones \textit{via} tetrahydro-1,2-oxazines. A brief overview of cyclopropane bonding and reactivity will be provided, along with a review of the applications of 1,1-cyclopropanediesters in heterocycle synthesis. A brief review of the applications of the nitrone/cyclopropane tetrahydro-1,2-oxazine synthesis is then presented. This is followed by an overview of the chemistry of pyrrolo[1,2-\textit{a}]indoles and the synthetic approaches to this heterocycle. The research presented in this chapter (Section 1.5) was carried out by me alone, and the results were published in a peer-reviewed journal.\textsuperscript{1} Reproduced in part with permission from Johansen, M. B.; Kerr, M. A. \textit{Org. Lett.} \textbf{2008}, \textit{10}, 3497-3500. Copyright 2008 American Chemical Society.

Section 1.1: Introduction

Section 1.1.1: Structure and Bonding of Cyclopropanes

The simplest graphical representations of cyclopropanes are as planar equilateral triangles. The trigonal arrangement of the three carbon atoms suggest 60° bond angles, which is a large deviation from 109.5° generally observed for tetrahedral $sp^3$ carbon atoms. This departure from the tetrahedral angle imparts a large degree of ring strain energy and moreover, the geometric constraints of the cyclopropyl ring results in the eclipsing of ring substitutents which in turn causes unfavourable Pitzer interactions. Both the ring strain and unfavourable Pitzer interactions render cyclopropanes susceptible to reactions which open the ring and alleviate said strains. These facts render conventional bonding theory inapplicable to cyclopropanes, and as such alternative models have been
presented, with the Förster-Coulson-Moffit model being the most widely accepted (Figure 1.1).²⁻⁴

**Figure 1.1** – Förster-Coulson-Moffitt Model of Cyclopropane Bonding

The Förster-Coulson-Moffit model of cyclopropane bonding postulates an inequivalent hybridization of the $s$ and $p$ atomic orbitals. The C-C bonding orbitals which constitute the ring (the *endo* orbitals) are postulated to be enriched in $p$ character and can be approximated as $sp^5$, as opposed to the typical $sp^3$ hybridization for tetrahedral carbon atoms. This increase in $p$ character of the C-C ring bonding orbitals allows for some ring strain relief, as the $sp^5$ bonding geometry permits a divergence from the standard $sp^3$ bonding angle, and is closer to $101°$.⁵ Consequently, the orbitals which lie on the periphery (the *exo* orbitals) have a higher percentage of $s$ character and are approximated as $sp^{2.28}$. This has been corroborated by NMR spectroscopy, with a 160 Hz $^{13}$C-$^1$H coupling constant observed for cyclopropane, which is in closer agreement to the $sp^2$ $^{13}$C-$^1$H coupling constant observed for benzene (159 Hz) than the $sp^3$ coupling constant for methane (125 Hz).⁶

Considering the geometrical constraints imposed on the cyclpropane, it has been suggested that the electron density of the cyclopropyl bonds lie off-center and just outside the ring in a bent or banana type bond.⁷ This bending or banana type bonding imparts reactivity which often resembles that of alkenes and, as with alkenes, the reactivity of cyclopropanes can be increased by incorporating an activating group which induces bond polarization.⁸ In general there are three different classes of activated cyclopropanes;
electron-accepting (or withdrawing) substituted cyclopropanes 1.1, electron-donating group substituted cyclopropanes 1.3, and those which contain both an electron accepting and a donating group vicinally disposed 1.5 (Scheme 1.1). Electron-accepting groups (e.g. carbonyls and sulfones) can stabilize a negative charge when cyclopropanes are opened by nucleophiles (equation 1). Electron-donating groups (e.g. ethers, amines) donate electron density to cyclopropanes effecting reactions with electrophiles and stabilizing resultant positive charges (equation 2). The most effective way to activate a cyclopropane is by vicinal incorporation of both electron donating and withdrawing groups which can work in concert to polarize and weaken the bond between them. This reactivity can be further enhanced through the addition of a Lewis acid which can coordinate to the electron withdrawing group and increase bond polarization (equation 3).

\[ \text{Nu} \quad 1.1 \xrightarrow{A} \quad \text{Nu} \quad 1.2 \]  
\[ \text{D} \quad 1.3 \xrightarrow{E} \quad \text{D} \quad 1.4 \]  
\[ \text{D} \quad 1.5 \xrightarrow{\text{Lewis acid}} \quad \text{D} \quad 1.6 \]

**Scheme 1.1 – Conceptual Reactivity of Acceptor, Donor and Donor-Acceptor Substituted Cyclopropanes**

Donor-acceptor substituted cyclopropanes display a wide range of reactivity and the chemistry of these compounds has been extensively studied and reviewed.\(^9\text{--}^{14}\) With the appropriate substitution, and often under relatively mild reaction conditions, donor-acceptor cyclopropanes can behave as 1,3-dipole equivalents, and react with other dipolar reagents or dipole equivalents to generate useful annulated products. The ring opening
and annulations of 1,1-cyclopropanediesters to form heterocyclic products is the focus of the next section.

Section 1.2: Synthesis of Heterocycles from 1,1-Cyclopropanediesters

The ring expansion reactions of donor-acceptor cyclopropanes have found numerous applications in synthesis, and have proven to be versatile intermediates in total synthesis.\(^{14}\) This section will provide a brief review of the methods reported for heterocycle synthesis from 1,1-cyclopropanediesters. Reactions which incorporate one of the ester functionalities in the ring forming event (e.g. by lactonization) will be omitted. Ring expansions to five membered rings through encorporation of a vicinal functional group (e.g. imine or carbonyl) also will be excluded. This section has been organized first by ring size and reactive partners and closes with an overview of the synthesis of fused and bridged bicyclic systems.

Section 1.2.1: Five Membered Heterocycles

One of the earliest examples of heterocycle synthesis from cyclopropanes was presented by the Tsuji group in 1987. They presented that vinyl-substituted cyclopropanes \(^{1.7}\) could be activated under palladium catalysis to react with aryl isocyanates \(^{1.9}\) in the formation of pyrrolidin-2-ones \(^{1.10}\) (Scheme 1.2).\(^ {15}\) The reaction was believed to proceed via the \(\pi\)-allylpalladium zwitterion \(^{1.8}\). Optimal results were observed when tributyl phosphine ligands were employed in polar aprotic solvents such as hexamethylphosphoramide (HMPA), facilitating oxidative addition and zwitterion formation. Both electron rich and electron poor aryl isocyanates were well tolerated, as well as methyl substitution at \(R^1\) and \(R^2\) of the 2-vinyl cyclopropanes \(^{1.7}\). Unfortunately the reaction was restricted to aryl isocyanates as alkyl derivatives did not afford the
desired pyrrolidin-2-ones. It should be noted that this mode of activation of the cyclopropane is complimentary to the use of Lewis acids, which are generally understood to activate the 1,1-cyclopropanediesters through ester coordination, increasing the electron withdrawing properties of the esters.

\[ \text{Scheme 1.2} \] – Synthesis of 2-Pyrrolidinones from 2-Vinyl Cyclopropanes

Carbonyls have also been demonstrated as suitable dipoles in ring expansion reactions of 1,1-cyclopropanediesters to form substituted tetrahydrofurans (Scheme 1.3). The Christie group has employed Nicholas activated 1,1-cyclopropanediesters 1.12 in reactions with aldehydes 1.11 to form 1,2,5-substituted tetrahydrofurans 1.13.\(^{16}\) The dicobalthexacarbonyl complex attached to the 2-position of the cyclopropane stabilizes the developing positive charge at the 2-position of the cyclopropane upon Lewis acid activation of the diester moiety. This facilitates cyclopropane bond polarization and ring expansion by incorporating the aldehyde 1.11 to form the tetrahydrofuran products 1.13. Both electron poor and aliphatic aldehydes partake in the reaction, but electron rich aldehydes were incompatible. Diastereoselectivity is typically 1:1 and a three fold excess of the Lewis acid is required to avoid a lactonization by-product. The Johnson group has recently developed an active research program in the synthesis of tetrahydrofurans 1.16 from carbonyls 1.14 and 1,1-cyclopropanediesters 1.15. Initial studies from the Johnson group focused on tin(II) triflate Lewis acid catalysis with aryl and vinyl substituted
cyclopropane diesters 1.15. A variety of aldehydes 1.14 (R$_1$=H) were shown to partake in the reaction, and excellent yields and cis-diastereoselectivities were observed.$^{17,18}$

Scheme 1.3 – Tetrahydrofuran Synthesis by Carbonyl Addition to Cyclopropanes

Aliphatic aldehydes required tin tetrachloride as the Lewis acid and the diastereoselectivities of the reaction suffered. A ketone could also be used to generate a quaternary centre at the 2 position of the product 1.16, but so far this has been solely limited to acetone. A palladium catalysed variant of the tetrahydrofuran synthesis was also developed by the Johnson group, using 2-vinyl cyclopropanes much in the same manner as Tsuji (Scheme 1.2). Unfortunatley the diastereoselectivity for this reaction was typically lower than that observed for the tin catalysed reactions.$^{19}$ During the course of a mechanistic study, the Johnson group observed cyclopropane racemization under the
reaction conditions. This could be attenuated by switching to a halfnium(IV) triflate Lewis acid but, more importantly, the racemization observation led to the development of a dynamic kinetic asymmetric variant of their tetrahydrofuran synthesis. By using a magnesium(II) iodide catalyst with a chiral pybox ligand, enantioenriched tetrahydrofurans could be obtained from racemic 1,1-cyclopropanediesters and aldehydes.

In 2006 the Yadav group published the reaction of alkyl silane substituted cyclopropanes with aldehydes (R=H) and ketones. Scandium(III) triflate was identified as the optimum Lewis acid for aldehydes and cyclic ketones, where tin tetrachloride achieved the best results for acyclic ketones. Yields ranged from moderate to excellent and diastereoselectivities favoured the formation of the cis products. The use of the tetrahydrofuran synthesis from aldehydes and cyclopropanes has been demonstrated in the successful total syntheses of the natural products (+)-virgatusin, (+)-polyanthellin A and (+)-isatisine A (Figure 1.2).

![Figure 1.2](image_url)  
**Figure 1.2 – THF Natural Products Prepared from Carbonyls and Cyclopropanes**

In an analogous fashion to carbonyls, imines have also been used in ring opening annulations of cyclopropanes (Scheme 1.4). In 2005 the Kerr group reported the diastereoselective synthesis of 2,5-cis-pyrrolidines from aldimes.
1,1-cyclopropanediesters 1.15. The aldimines could be generated in situ by stirring the parent amine 1.22 and aldehyde 1.23 over molecular sieves before addition of the

cyclopropane 1.15 and ytterbium catalyst, followed by heating the reaction. While a wide variety of amines and cyclopropanes could be utilized, the reaction was restricted to aromatic substitution at R². The Tang group reported similar findings in their scandium(III) triflate catalysed system, though the milder reaction conditions and stronger Lewis acid provided a modest to good increase in diastereoselectivities.

Following their initial report on the synthesis of tetrahydrofurans from Nicholas activated cyclopropanes 1.12 and aldehydes 1.11 (Scheme 1.3), the Christie group disclosed the parallel reaction with aldimines 1.24 to form pyrrolidines 1.26 in 2006.
Only five examples were provided, but the study covered a small range of reaction temperatures for each pyrrolidine example, demonstrating modest increases in yields at lower temperatures and surprisingly no observed changes in diastereoselectivities across the temperature ranges. Again, the reaction was limited to aromatic substitution at R².

The synthesis of substituted pyrazolidines 1.29 and 1.30 from diazenes 1.27 and 1,1-cyclopropane diesters 1.28 has been demonstrated by the de Meijere group (Scheme 1.5).²⁸ Gallium trichloride proved to be the Lewis acid of choice to promote the cyclopropane ring expansion reaction. The regiochemistry is dictated by the geometry of the starting diazene, with trans diazenes providing pyrazolidines 1.29 and cis diazenes leading to pyrazolidines 1.30.

![Scheme 1.5 – de Meijer’s Synthesis of Pyrazolidines](image)

**Section 1.2.2: Six Membered Heterocycles**

1,1-Cyclopropane diesters have also been utilized in the synthesis of six membered heterocycles. In 2003 the Kerr group disclosed a seminal publication introducing the reaction of nitrones 1.31 with 1,1-cyclopropane diesters 1.15 to form tetrahydro-1,2-oxazines 1.32 in high yields and with high 3,6-cis selectivity (R² and R³) (Scheme 1.6).²⁹ Ytterbium(III) triflate was identified as an ideal Lewis acid catalyst, and though efforts were made to switch the diastereoselectivity towards the 3,6-trans product, the cis product remained dominant.³⁰ Though originally believed to proceed through a
concerted reaction pathway, mechanistic studies have revealed a step-wise reaction that proceeds through nucleophilic cyclopropane ring opening follow by a Mannich-type ring closure.\textsuperscript{31} A one pot 3 component coupling procedure was also developed where the nitrone 1.31 could be generated \textit{in situ} from the requisite aldehyde and hydroxylamine through condensation prior to cyclopropane addition.\textsuperscript{32} Both the Sibi and Tang groups have developed enantioselective variants of this reaction.\textsuperscript{33,34} The Sibi group observed high yields and moderate to good enantioselectivities for unsubstituted cyclopropanes 1.15 (R\textsubscript{3}=H) in their reaction system, but poor diasteroselectivities for substituted cyclopropanes 1.15 (R\textsubscript{3}\neq H). The reaction developed by the Tang group showed higher diastereoselectivities for C2 substituted cyclopropanes 1.15, (up to 12:1 dr and 97% ee)
and was cleverly applied in the kinetic resolution of cyclopropanes allowing access to either enantiomer of the tetrahydro-1,2-oxazine 1.32.

2009 Kerr Group:

\[
\begin{align*}
\text{1.35} & \quad \text{1.28} \\
\text{Zn(NTf₂)₂} & \quad \text{C₆H₆, reflux} \\
\text{1.36} & \quad \text{15 examples, 59-99\% dr 1:1}
\end{align*}
\]

Scheme 1.7 – Tandem Ring-Opening/Conia-ene Heterocycle Syntheses

Recently the Kerr group has developed a tandem cyclopropane ring opening/Conia-ene reaction for the synthesis of piperidines 1.36 and tetrahydropyrans 1.38 (Scheme 1.7). It was found that benzyl protected propargyl amines 1.35 could open 1,1-cyclopropanediesters 1.28 and that the resulting malonate moiety could undergo a Conia-ene cyclization onto the tethered alkyne to furnish the desired piperidines 1.36. Zinc(II) triflimide was identified as a suitable catalyst to promote both ring-opening and cyclization in a tandem process. The analogous reaction with propargyl alcohols 1.37 has also been developed. A single metal catalyst system was identified in indium(III) triflate with the addition of N,N-dimethylaniline as catalytic base. Unfortunately the single metal system was restricted to electron neutral and electron deficient aromatic cyclopropanes 1.28. This problem was circumvented by first inducing ring-opening ether formation with catalytic indium(III) triflate, followed by addition of base and a three fold excess of
zinc(II) bromide to promote Conia-ene cyclization. The use of this two step procedure greatly increased the reaction scope to include aliphatic, electron rich aryl and heteroaromatic substituted cyclopropanes, providing the desired products in good yields.

Section 1.2.3: Fused Heterocyclic Systems

The Kerr group’s interest in 1,1-cyclopropanediester chemistry began with the ring opening of cyclopropanes \(1.40\) with indoles \(1.39\)\(^{37,38}\). Early investigations showed that if the indole \(1.39\) lacked substitution at the 3 position (\(R^1=H\)), ring opening of the cyclopropane took place to provide the 3-alklyated indole. In instances where the 3 position did bear substitution, either an alkyl migration to the 2 position or an annulation event occurred upon reaction with the cyclopropane.

As annulated indole products \(1.41\) piqued interest for synthetic applications towards kopsane alkaloids, the ring opening annulation reaction was further developed (Scheme 1.8)\(^{39}\). The study revealed that unsubstituted cyclopropanes \(1.40\) (\(R^4=H\)) would undergo the annulation reaction to \(1.41\) in low to moderate yields, but alkyl and aryl substituted cyclopropanes \(1.40\) provided the products \(1.41\) in significantly higher yields.

\[
\begin{array}{c}
\text{Scheme 1.8 – Cyclopentannulation of Indoles} \\
\text{In 2000 and 2001 the Sugita group demonstrated the ring expansion reactions of methanochromanone} \ 1.42 \ \text{with carbonyls} \ 1.14 \ \text{to form tetrahydrofuro[2,3-b]benzopyranones} \ 1.43 \ (\text{Scheme 1.9}). \ \text{The preliminary publication}
\end{array}
\]
demonstrated the reaction of symmetrical ketones $1.14$ ($R^1=R^2$) with $1.42$ to provide the product $1.43$ in high yields with almost complete trans selectivity. The subsequent report examined the reaction with aldehydes and unsymmetrical ketones. Again yields were typically high and a trans geometry at the ring fusion was the norm. Aldehydes and ketones with large substitutions favoured a 2,5-trans geometry at the tetrahydrofuran positions, but the diastereoselectivity dropped significantly with unsymmetrical ketones $1.14$ where $R^1$ and $R^2$ were comparable in size.

Scheme 1.9 – Synthesis of Tetrahydrofuran Fused Benzopyranones

In an impressive display of diastereocntrol, the Kerr group has reported the selective synthesis of cis $1.46$ or trans $1.45$ pyrrolo-isoxazolines from alkoxy amine tethered cyclopropane $1.44$ (Scheme 1.10). During optimization studies it was observed that the $E$ or $Z$ geometry of the oxime (formed through condensation of the alkoxy amine $1.44$ and an aldehyde $1.11$) dictated the trans or cis geometry of the resulting products respectively. As the $E$ oxime geometry typically dominated to provide the trans products $1.45$, a method was devised wherein the cyclopropane ring was opened by the tethered alkoxyamine opening prior to aldehyde addition, so that the intermediate product could then condense with the aldehyde $1.11$ and steric would favour the $Z$ oxime equivalent. A Mannich-type ring closure would then ensue to generate the cis product $1.46$. It was
found that by simply altering the order of addition of the ytterbium catalyst and the aldehyde 1.11 the relative stereochemical outcome of the reaction could be controlled.

Scheme 1.10 – Intramolecular Cyclizations of Oxime ether and Hydrazone Tethered Cyclopropanes

Shortly after the initial study, the alkyl hydrazine equivalent system was developed and again the stereochemistry of the bicyclopyprazolidines 1.48 and 1.49 could be controlled by the order of addition of the reagents.42 Both the pyrrolo-isoxazolines 1.45 and 1.46 and bicyclopyprazolidine ring systems 1.48 and 1.49 could undergo reductive cleavage of the N-O and N-N bonds respectively to provide highly functionalized pyrrolidines.

A research group at the Central Pharmaceutical Research Institute of Japan Tobacco Inc. developed a novel method for the synthesis of heteroaromatic fused pyrrolidines 1.52 (Scheme 1.11).43 The reaction involves nitrogen containing aromatic heterocycles 1.50, which contain a leaving group vicinal to the nitrogen, and 1,1-cyclopropanediester 1.51. Imidazoles, indoles and benzimidazoles were found to open cyclopropane 1.51 under basic conditions, and a subsequent addition of the resulting malonate anion into the position adjacent to the nitrogen followed by elimination of the
leaving group ensued to provide the fused heterocycles 1.52. The utility of this transformation was demonstrated in the synthesis of the pyrrolo[1,2-α]indole JTT-010 1.53, a protein kinase C-β inhibitor.

Scheme 1.11 – Synthesis of Pyrrolidine Fused Heteroaromatics

The synthesis of tricyclic dihydroquinoline derivatives 1.56 was reported by the Charette group in 2008 (Scheme 1.12). Under nickel(II) perchlorate catalysis, azomethine imine 1.54 was observed to induce ring expansion reactions of 1,1-cyclopropanediesters 1.55 and generate the fused tricyclic products 1.56. The mechanism is believed to proceed in a stepwise fashion via nucleophilic ring opening of the cyclopropane followed by a Mannich-type ring closure. Electron rich aromatic substituted cyclopropanes 1.55 where found to be the optimal cyclopropanes in the reaction, as electron poor aromatics, vinyl, and unsubstituted cyclopropanes gave
significantly decreased yields. Diastereoselectivities were modest in most cases, with the highest observed being 6.6:1 favouring the cis product.

Recently the Wu group has reported the synthesis of dihydroisoquinoline fused tetrahydro-1,2-oxazines 1.58 (Scheme 1.13). A two metal co-catalyst system of ytterbium(III) and silver(I) triflates was found to promote the tandem ring forming events. The reaction is suspected to proceed through N-alkylation of the 2-alkynylbenzaldoxime 1.57 with the pendant alkyne to generate a nitrene, which can then react with the cyclopropane 1.15 to form the fused tetrahydro-1,2-oxazine 1.58 in the manner described by the Kerr group. Both phenyl and unsubstituted cyclopropanes 1.15 were proficient reacting partners, but alkyne substitution at R<sup>2</sup> was restricted to phenyl.

**Scheme 1.13 – Dihydroisoquinoline Fused Tetrahydro-1,2-oxazines**

**Section 1.2.4: Bridged Bicyclic Heterocycles from Cyclopropanes**

A formal [4+3] cycloaddition of isobenzofuran 1.59 with cyclopropanes 1.60 has been developed by the Ivanova group (Scheme 1.14). The reaction has been proposed to proceed through a concerted cycloaddition analogous to the Diels-Alder reaction. Arguable support is garnered by the formation of the less stable exo isomer as the major product, whereas a step-wise mechanism would likely favour the endo isomer, despite the moderate exo:endo selectivity observed. Ytterbium (III) triflate was identified as the
optimal catalyst and the combined yields for the exo:endo mixtures were high in all cases.

The Kerr group has demonstrated that by tethering an aldehyde to a cyclopropane as in 1.62, the nitron/cyclopropane reaction to generate tetrahydo-1,2-oxazines 1.64 can be accomplished in an intramolecular fashion (Scheme 1.15). The aldehyde tether is responsible for forming a second ring, generating the bridged bicyclic products 1.64. A variety of alkyl, alkenyl, aromatic and heteroaromatic tethered aldehyde cyclopropanes 1.62 were demonstrated to partake in this reaction, but a two carbon chain length between the aldehyde and cyclopropane was an evident limitation. Reductive cleavage of the N-O bond allow access to cis disposed 1,4-aminocyclohexanols.

Scheme 1.15 – Intramolecular Nitrone-Cyclopropane Formal Cycloaddition

The Kerr group was also successful in developing the first intramolecular imine-cyclopropane ring expansion cyclization, which was showcased in the total synthesis of FR901483 1.67 (Scheme 1.16). When cyclohexylcyclopropane 1.65 was heated in the presence of paraformaldehyde and ytterbium(III) triflate, the intramolecular imine-cyclopropane ring expansion took place to generate the tricyclic core 1.66 of
FR901483. Incorporation of the methyl amine and phosphate moieties followed by protecting group removal secured the complex natural product 1.67 in a total of eighteen synthetic steps.

Scheme 1.16 – The First Intramolecular Imine-Cyclopropane Cyclization

Finally, the Wang group has demonstrated intramolecular reactions of both tethered carbonyls and imines with cyclopropanes 1.68 (Scheme 1.17).49 Both ketones and aldehydes proved efficient in the synthesis of substituted tetrahydrofurans 1.69 (Y=O) with a variety of 3 atom tethers to generate [3.2.1] bridged bicyclic products under scandium(III) triflate catalysis. The imines were generated in situ through condensation of an amine with the parent tethered aldehyde, and generally out-performed the analogous aldehyde in the synthesis of [3.2.1] bridged bicyclic pyrrolidines 1.69 (Y=N). One example of a [4.2.1] bridged bicyclic pyrrolidine was also demonstrated, though the stronger Lewis acid catalyst tin tetrachloride was required. The utility of this transformation was also exemplified in the formal synthesis of the natural antibiotic platensimycin 1.70.
Section 1.3: Applications of the Nitrone/Cyclopropane Tetrahydro-1,2-oxazine Synthesis

Section 1.3.1: Synthesis of Phyllantidine

The tetrahydro-1,2-oxazine heterocycle is a motif rarely observed in natural products. It is present, however, in two of the Securinega alkaloids, specifically phyllantidine \textbf{1.71} and the methoxy analogue secu’amamine D \textbf{1.72} (Scheme 1.18).\textsuperscript{50-53} Both phyllantidine \textbf{1.71} and secu’amamine D \textbf{1.72} are proposed to come from the Securinega alkaloids securinine \textbf{1.73} and securitinine \textbf{1.74} respectively, through \textit{N}-oxidation followed by a Meisenheimer rearrangement, which generates the tetrahydro-1,2-oxazine heterocyclic core (Scheme 1.18).\textsuperscript{54}

\begin{scheme}
  \textbf{Scheme 1.18} – Selected \textit{Securinega} Alkaloids and Proposed Meisenheimer Rearrangement
\end{scheme}
Having successfully developed a new synthesis of tetrahydro-1,2-oxazines (Scheme 1.6) the Kerr group selected the natural product phyllantidine 1.71 as a target for total synthesis to showcase the utility of the methodology. Application of the three component coupling protocol began the synthesis of phyllantidine, with vinyl cyclopropane 1.76, aldehyde 1.77 and hydroxylamine 1.78 combining under ytterbium catalysis to generate the tetrahydro-1,2-oxazine 1.79 (Scheme 1.19).

Scheme 1.19 – The Total Synthesis of Phyllantidine

Tetrahydro-1,2-oxazine 1.79 was then fully elaborated to the natural product through Krapcho dealkoxycarbonylation, enolate oxidation with a Davis oxaziridine, ring closing metathesis and an intramolecular Horner-Wadsworth-Emmons reaction to secure the butenolide. The final piperidine ring was closed via a Mitsunobu reaction to provide (+)-phyllantidine 1.71 in 6% overall yield and in a short thirteen step sequence.55

Section 1.3.2: Skeletal Congeners of FR900482

Two other naturally occurring tetrahydro-1,2-oxazines that have attracted the attention of the synthetic community are FR900482 1.80 and the dihydro congener FR66979 1.81, both of which were isolated from the fermentation broth of *Streptomyces sandaensis* by the Fujisawa Pharmaceutical company in 1987 (Figure 1.3).56,57 Since its isolation and identification as a potential antitumor agent, FR900482 has been the subject
of a number of synthetic studies and total syntheses. These studies also led to the identification of the synthetic derivatives FK317 1.83 and FK973 1.84 as possible antitumor agents.\textsuperscript{58,59} The FR900482 family of alkaloids bear striking resemblances to mitomycin C 1.82 (an antitumor and antibiotic agent), and are believed to follow a similar mode of action \textit{in vivo} (Scheme 1.20). Clinical studies have also revealed a three fold increase in potency of the FR900482 type molecules over mitomycin C 1.82, along with a significant decrease in toxicity in comparison to mitomycin C.\textsuperscript{60,61}

**Scheme 1.20** – DNA Crosslinking Activity of the FR900482 Class of Alkaloids
The Danishefsky group developed a racemic synthesis of FR900482 1.80 in 1995, which relied on a hetero-Diels-Alder reaction of the functionalized nitroso aromatic 1.89 with diene 1.90 to secure the dihydro-1,2-oxazine 1.91 (Scheme 1.21). Following installation of the aziridine, the primary alcohol was converted to the vinyl group present in intermediate 1.92. An intramolecular Heck reaction merged the aromatic and vinyl groups, forming the bridged bicycle 1.93 in the process, which could be further elaborated to FR900482 1.80.

![Scheme 1.21 – Danishefsky’s Synthesis of (±)-FR900482](image)

Intrigued by the tetrahydro-1,2-oxazine core of these molecules, and inspired by the work developed by the Danishefsky group in their total synthesis of FR900482 1.80, the Kerr group again demonstrated the utility of their tetrahydro-1,2-oxazine methodology in the synthesis of skeletal congeners of FR900482 1.80 (Scheme 1.22). Through judicious choice of an ortho-iodo aryl hydroxylamine 1.94 and vinyl cyclopropane 1.76, and by varying the aldehyde 1.10, the 3 component protocol (vide supra) was exploited to produce a variety of tetrahydro-1,2-oxazines 1.95. The vinyl and iodo substitution pattern
of these tetrahydro-1,2-oxazines matched that reported by Danishefsky, and underwent a similar Heck reaction to produce the skeletal congeners of FR900482 1.96. Yields for the two step procedure were good, and a variety of aromatic aldehydes 1.11 could be incorporated at the R position of 1.96. Unfortunately the substrate scope was limited to aromatic aldehydes due to the instability of hydroxylamine 1.94, thus precluding synthetic efforts towards FR900482 1.80 and related molecules which would require a formaldehyde equivalent.63

Section 1.3.3: Conversion of Tetrahydro-1,2-oxazines to Pyrrolidines and the Total Synthesis of Nakadomarin A

With the high yields and complete cis selectivity observed for the tetrahydro-1,2-oxazine synthesis from cyclopropanes and nitrones (or hydroxylamines and aldehydes, vide supra) efforts were undertaken to convert these rare heterocycles to the more prevalent pyrrolidine heterocycles (Scheme 1.23).64
Scheme 1.23 – Five Step Synthesis of trans-Pyrrolidines

Conceptually, reductive cleavage of the N-O bond in the tetrahydro-1,2-oxazines and subsequent displacement of the alcohol by the amine would generate 2,5-trans pyrrolidines. During identification of suitable reductants to cleave the N-O bond, it was observed that a retro-Mannich decomposition pathway existed, due to the β-disposition of the amine with respect to the malonate moiety. To circumvent this mode of decomposition, the diesters of the tetrahydro-1,2-oxazines 1.32 were reduced to diols and protected as the acetonide 1.98 (Scheme 1.23). N-O bond cleavage could then be achieved with samarium diiodide, forming amino-alcohol 1.99. Alcohol mesylation, with ensuing SN2 displacement by the amine, constructed the desired trans-pyrrolidine 1.100.

Figure 1.4 – (+)-Nakadomarin A
The successful application of this pyrrolidine forming methodology from tetrahydro-1,2-oxazines culminated in the total synthesis of the complex alkaloid (+)-nakadomarin A \( \text{1.101} \) (Figure 1.4).\(^6\) Benzyl ether cyclopropane \( \text{1.102} \), 3-bromo furfural \( \text{1.103} \) and \( p \)-methoxylbenzyl hydroxylamine \( \text{1.78} \) were combined via the three component protocol to generate the highly functionalized tetrahydro-1,2-oxazine \( \text{1.105} \) (Scheme 1.24).

Scheme 1.24 – Three Component Synthesis of Tetrahydro-1,2-oxazine \( \text{1.105} \)

A five step sequence, including a highly selective DIBAL reduction of one of the esters to the aldehyde, Horner-Wadsworth-Emmons extension of the aldehyde to the enoate, and an intramolecular Heck reaction was used to close the cyclopentane ring. \( p \)-Metoxylbenzyl deprotection and subsequent amide formation provided the N-O bond reduction precursor \( \text{1.106} \) (Scheme 1.25). Treatment of \( \text{1.106} \) with samarium diiodide reductively cleaved the N-O bond to reveal the alcohol \( \text{1.107} \), which was then mesylated and displaced by the adjacent amide to form the pyrrolidine ring in \( \text{1.108} \).

Scheme 1.25 – Pyrrolidine Core Formation in the Synthesis of Nakadomarin A
The tricyclic pyrrolidine 1.108 beared appropriate functional handles for completion of the total synthesis in a further 14 steps. The successful total synthesis of this large and complex alkaloid underscores the merit of the tetrahydro-1,2-oxazine synthesis and successive transformation to highly substituted and stereodefined pyrrolidines.

Section 1.4: Pyrrolo[1,2-\(a\)]indoles

The chemistry of the pyrrolo[1,2-\(a\)]indole heterocycle 1.109 (Figure 1.5) has progressed significantly since the isolation and structural identification of the antitumor and antibiotic mitomycin C 1.82 and related compounds (Figure 1.6).\textsuperscript{66-68} The pyrrolo[1,2-\(a\)]indole heterocycle 1.109 derives the [1,2-\(a\)] designation through the conceptual fusion of the 1 and 2 positions of a pyrrolidine ring 1.111 with the \(a\) face of an indole 1.110. This ring fusion, along with the pyrrolo[1,2-\(a\)]indole positional numbering and ring lettering system are depicted in figure 1.5.

![Figure 1.5](image)

**Figure 1.5** – Pyrrolo[1,2-\(a\)]indole Labelling System and Derivation from an Indole and a Pyrrolidine Ring

The structural identification of mitomycin C 1.82, and later clinical use as a potent chemotherapeutic agent against a variety of solid tumors, has spurred synthetic studies on pyrrolo[1,2-\(a\)]indoles. These studies have been largely driven towards mitosane 1.113 and mitosene 1.114 frameworks with aims of preparing compounds which retain the activity of mitomycin C 1.82, but with greatly reduced toxicity (Figure 1.6).
Figure 1.6 – Mitomycin C and the Mitosane and Mitosene Pyrrolo[1,2-α]indole Based Structures

The synthetic approaches to pyrrolo[1,2-α]indoles have been extensively studied and reviewed, and can be subdivided into five main classes A-E (Scheme 1.26). \(^{69,70}\) Paths A, B, and C represent syntheses which rely on the formation of the A, B, or C rings respectively. Path D involves the synthesis of the B and C rings via a transannular ring closure between N4 and C9a. The final broader classification, via path E, involves the synthesis of the B and C rings using other methods. The following section will provide a brief overview of some representative approaches to pyrrolo[1,2-α]indoles with an example given for each synthetic pathway as presented in scheme 1.26.

Scheme 1.26 – Conceptual Synthetic Pathways to Pyrrolo[1,2-α]indoles
Section 1.4.1: Pyrrolo[1,2-α]indoles by Synthesis of the A Ring

The synthesis of pyrrolo[1,2-α]indoles by formation of the A ring remains an uncommon route to these class of molecules. Carelli, Cardellini and Morlacchi presented the synthesis of quinone 1.117 in 1967, which falls into the path A classification (Scheme 1.27). When dihydro-pyrrolizine 1.116 was heated with phthalic anhydride 1.115 in the presence of aluminum trichloride, two sequential Friedel-Crafts reactions proceeded to generate the pyrrolo[1,2-α]indole 1.117. Further studies revealed that the reaction progressed through the carboxylic acid 1.118, which would then cyclize in the second Friedel-Crafts step to generate the quinone A ring. It was observed that the one-pot, higher temperature procedure proved more efficient overall.

![Scheme 1.27 – Friedel-Crafts Reaction to Generate the A Ring]

Section 1.4.2: Pyrrolo[1,2-α]indoles by Synthesis of the B Ring

In their synthetic studies towards the mitomycins, the Coleman group developed a novel pyrrolo[1,2-α]indole synthesis which falls into the path B classification (Scheme 1.28). An elegant cinnamylstannane addition to an iminium ion allowed for the
synthesis of the advanced intermediates 1.119 and 1.121. Oxidation of the electron rich aromatic system in 1.119 with ceric ammonium nitrate allowed for quinone formation by pyrrolidine Michael addition and re-oxidation to provide mitosane 1.120. Ultimately aziridine incorporation into 1.120 was hindered by unwanted oxidation to the mitosene state, and an alternate route was devised which relied on aziridine incorporation prior to B ring formation. Removal of the benzyl carbamates in the advanced intermediate 1.121 was accomplished by hydrogenolysis, which also reduced the quinone moiety to the dihydroquinone. Exposure to an oxygen atmosphere re-oxidized the dihydroquinone to the quinone, allowing for the B ring cyclization, by Michael addition, to provide mitosane 1.122.

Scheme 1.28 – Intramolecular Michael Addition B Ring Synthesis

Section 1.4.3: Pyrrolo[1,2-α]indoles by Synthesis of the C Ring

Recently, two very similar asymmetric organocatalytic pyrrolo[1,2-α]indole syntheses have been developed independently by the Enders and Wang groups (Scheme 1.29). Both methodologies employed indole-2-carboxaldehydes 1.123 and 1.127 with α,β-unsaturated aldehydes 1.124 through organocatalysis with 1.125. The reactions are
suggested to proceed by catalytic iminium ion formation through condensation of the catalyst 1.125 and the unsaturated aldehydes, followed by a cascade aza-Michael addition and aldol dehydration to form the C ring of the pyrrolo[1,2-\(a\)]indole products. Both methods found modest to good yields with respectable enantioselectivities. The reactions were both optimal at room temperature and usually complete within two to three days. The Wang group was also able to screen a small selection of 5-substituted indoles 1.127, with both electron rich and poor groups at R\(^2\) having little influence on the reaction outcome. Aldehydes 1.124 were restricted to aromatic substitutions at R in both systems.

\[
\begin{align*}
\text{Wang group:} & \\
\text{1.123} + \text{1.124} & \xrightarrow{\text{MTBE or CH}_2\text{Cl}_2, \text{rt}} \text{1.126} & \text{8 examples, 30-71\% ee 85- >99\%} \\
\text{2010 Wang Group:} & \\
\text{1.127} + \text{1.124} & \xrightarrow{4 \AA \text{ MS, toluene, rt}} \text{1.128} & \text{13 examples, trace-84\% ee 71-96\%} \\
\end{align*}
\]

\textbf{Scheme 1.29} – Organocatalytic C Ring Synthesis

\textbf{Section 1.4.4: Pyrrolo[1,2-\(a\)]indoles by Transannular Ring Closure}

The first total syntheses of the mitomycins were accomplished by the Kishi lab in 1977. The route which they developed relied on a late stage transannular ring closure between the dimethyl ketal and secondary amine in 1.129 (Scheme 1.30).\textsuperscript{75-77}
Initial studies focused on substrates with dimethyl hemithioketals with the hopes that acidic conditions could be avoided for sensitive late stage intermediates, but transketallization was hampered by lack of reactivity or elimination side reactions to provide mitosene by-products. Fortunately tetrafluoroboric acid was identified as a suitable reagent to promote methanol elimination and subsequent ring closure to secure the pyrrolo[1,2-\(\alpha\)]indole core 1.130, which was further elaborated to the natural product 1.131. This sequence was first applied to the total synthesis of porfiromycin 1.131 and then to the successful syntheses of mitomycins A, B and C.

**Section 1.4.5: Pyrrolo[1,2-\(\alpha\)]indoles by Path E**

The final classification of pyrrolo[1,2-\(\alpha\)]indole synthesis involves the formation of the B and C rings, and one exemplary method was developed by the Danishefsky group (Scheme 1.31). The donor-acceptor substituted cyclopropane 1.132 underwent a ring opening reaction and B ring formation, when the amine functionality was unveiled by phthalimide deprotection. Heating the diester 1.134 in the presence of CSA induced lactamization and C ring synthesis, completing the pyrrolo[1,2-\(\alpha\)]indole core of 1.135.
Section 1.5: Synthesis of Pyrrolo[1,2-α]indoles from Nitrones and Cyclopropanes

To further explore the utility of the nitrone/cyclopropane tetrahydro-1,2-oxazine synthesis, we sought after a synthetic route to pyrrolo[1,2-α]indoles. Our initial approach is shown in scheme 1.32, where it was proposed that the FR900482 skeletal congeners 1.96, previously synthesized in a two step procedure developed by our group (Section 1.32), could be converted to pyrrolo[1,2-α]indoles 1.137 through N-O bond cleavage and transannular ring closure, making this a path D approach (Scheme 1.26). This intended synthetic route would also mimic the bioactivation pathway which has been proposed for the FR900482 family of compounds, vide supra (Scheme 1.20).
Section 1.5.1: Results and Discussion

Section 1.5.1.1: Preliminary Studies in N-O Bond Cleavage

To assess the viability of the proposed pyrrolo[1,2-a]indole synthesis (Scheme 1.32), we chose to begin our investigations with the phenyl substituted FR900482 skeletal congener 1.140, as it was easily prepared from nitrone 1.138 and vinyl cyclopropane 1.76 (Scheme 1.33). The nitrone/cyclopropane reaction was chosen over the three component protocol due to the instability of the requisite hydroxyl amine 1.94. Both the tetrahydro-1,2-oxazine synthesis and Heck reactions proceeded without difficulty, providing the bridged bicyclic tetrahydro-1,2-oxazine 1.140 as a model system for screening N-O bond cleavage conditions. Aware of the possibility for retro-Mannich fragmentation, it was hoped that the relatively strained bicyclic system of 1.140 might allow for facile N-O bond cleavage in comparison to the pyrrolidine synthesis (Section 1.3.3).
The first investigations into N-O bond cleavage were based on a zinc mediated reduction. Following literature precedent for the cleavage of strained bicyclic oxazines, tetrahydro-1,2-oxazine 1.140 was submitted to the conditions reported for the reductive cleavage of 1.141 (Scheme 1.34).  

After 6 days and two cycles of 15 equivalents of zinc metal under acidic conditions, the reaction was quenched, and amino alcohol 1.143 was isolated in 45% yield with 24% recovered starting material 1.140. Many efforts at optimizing this reaction were attempted, but unfortunately none of the zinc reduction reactions were found to be superior to the initial result, which suffered from lengthy reaction times, failure to proceed to completion and poor reproducibility. Since the zinc mediated reduction proved impractical, we turned to other methods for N-O bond cleavage. A brief survey of the
literature provided a number of reductive protocols applied to N-O bond cleavage, but none were found to be effective in our system, and most resulted in either no reaction or decomposition (Scheme 1.35).

![Scheme 1.35 – Attempts at Reductive N-O Bond Cleavage](image)

During the transformation of tetrahydro-1,2-oxazines to pyrrolidines it was observed that hydrogenolysis of the N-O bond could be effected in some cases. If hydrogenolysis was to be employed in our system, we understood this would also likely reduce the exo-methylene moiety, but we reasoned that an oxidation of the resultant alcohol in 1.143, followed by an intramolecular condensation, would provide the desired pyrrolo[1,2-a]indole 1.144 (Scheme 1.36).

![Scheme 1.36 – Conceptual Route through Hydrogenolysis of the N-O Bond](image)

Palladium on carbon, Raney nickel and Adam’s catalysts with a hydrogen atmosphere were all screened, and each was successful at reducing the exo-methylene of 1.140 providing 1.147, but these systems were unsuccessful at cleaving the N-O bond. When an attempt was made to cleave the N-O bond under Raney nickel conditions at
increased temperature, N-O bond cleavage was observed; however the intermediate amino alcohol 1.145 lactonized onto one of the ester moieties providing lactone 1.146 as a mixture of diastereomers along with considerable amounts of 1.147 (Scheme 1.37).

Scheme 1.37 – Partial Reduction and Competitive Lactonization

Section 1.5.1.2: Circumventing the Retro-Mannich Problem

Since N-O bond cleavage was impeded by lack of reactivity, decomposition, and/or unwanted side reactions of our desired amino alcohol, we decided it would be prudent to contend with the diester moiety in 1.140, in an attempt to attenuate these unwanted reaction pathways. The pyrrolidine synthesis (Section 1.3.3, Scheme 1.23) called for reduction of the diesters and protection of the resultant diol as the acetonide to prevent retro-Mannich upon N-O bond cleavage. In terms of simplicity, accessibility,
and step economy, a Krapcho dealkoxycarbonylation seemed most advantageous for our system, in that by removing one of the esters the propensity for a retro-Mannich fragmentation should be greatly reduced. After moderate optimization, it was found that Krapcho dealkoxycarbonylation could be achieved at 160 °C in damp dimethylsulfoxide with lithium chloride to afford the monoester 1.148 as a mixture of diastereomers (Scheme 1.38).

With monoester 1.148 in hand we revisited the samarium diiodide reductive cleavage of the N-O bond which had proven successful in the pyrrolidine syntheses. Using the optimal conditions identified in that work, we did observe amino alcohol 1.149, but only in 35% yield (entry 1, table 1). We found that a slight increase in temperature to 40 °C, along with the addition of hexamethylphosphoramide (HMPA), which is known to increase the reduction potential of samarium diiodide, provided amino alcohol 1.149 in 65% yield. (entry 4, table 1). \textsuperscript{84,85}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature</th>
<th>Additive</th>
<th>Yield 1.149</th>
<th>Recovered 1.148</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66 °C</td>
<td>none</td>
<td>35%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>22 °C</td>
<td>none</td>
<td>0%</td>
<td>88%</td>
</tr>
<tr>
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<td>22 °C</td>
<td>HMPA (3 equiv.)</td>
<td>47%</td>
<td>40%</td>
</tr>
<tr>
<td>4</td>
<td>40 °C</td>
<td>HMPA (3 equiv.)</td>
<td>65%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Section 1.5.1.3: Final Ring Closure

With amino alcohol 1.149 in hand the final ring closure could be attempted (Scheme 1.39). Using a method similar to that used in the pyrrolidine synthesis, mesylation of the alcohol and \textit{in situ} displacement by the aniline nitrogen produced the pyrrolo[1,2-\textit{a}]indole 1.150 with the exomethylene moiety, which ultimately proved to be unstable. Moderate heating, chromatography on silica and standing for prolonged periods both in and out of solution resulted in migration of the double bond to generate pyrrolo[1,2-\textit{a}]indole 1.151 accompanied by moderate decomposition. This double bond migration would not have been of concern since 1.151 was ultimately desired, but the overall yield for this transformation was low. We then envisioned an acid catalysed process which would displace the allylic alcohol and allow for double bond migration in a single procedure. This was realized through subjecting amino alcohol 1.149 to microwave irradiation in benzene at 80 °C with catalytic \( p \)-toluenesulfonic acid, providing near quantitative amounts of pyrrolo[1,2-\textit{a}]indole 1.151.

\begin{center}
\textbf{Scheme 1.39} – Mesylation and Acid Catalysed Transannular Ring Closure
\end{center}
With the synthetic route optimized for the synthesis of pyrrolo[1,2-\(a\)]indole 1.151, five additional pyrrolo[1,2-\(a\)]indoles were generated through the five-step sequence of tetrahydro-1,2-oxazine synthesis, Heck cyclization, Krapcho dealkoxycarbonylation, N-O bond reductive cleavage, and acid catalysed indole formation, and the results are summarized in scheme 1.40. Substitution at \(R^1\) by incorporation into the nitrone 1.136 was possible, with a small variety of phenyl and heteroaromatic groups integrated. The position at \(R^2\) was also substituted with a phenyl group in the synthesis of pyrrolo[1,2-\(a\)]indole 1.160, though the Heck reaction required microwave irradiation conditions to bring the reaction to completion. This reaction generated a mixture of inseparable products, but upon subjecting the mixture to the Krapcho decarboxylation conditions we were able to isolate the monoester in 73% over the two steps, which was carried forward through N-O bond cleavage and ring closure to 1.160.
Section 1.6: Summary and Future Work

In summary we have developed a five step synthesis of 3-aryl pyrrolo[1,2-a]indoles 1.157 from o-iodo nitrones 1.136 and 2-vinyl-1,1-cyclopropanediesters 1.152. The methodology proceeds through the tetrahydro-1,2-oxazines 1.153 and FR900482 skeletal congeners 1.154 and requires a Krapcho dealkoxycarbonylation prior to samarium iodide reductive cleavage of the N-O.
The final ring closure is best achieved by heating under microwave conditions in the presence of catalytic toluenesulfonic acid to afford the pyrrolo[1,2-\textit{a}]indoles \textit{1.157}. Six different pyrrolo[1,2-\textit{a}]indoles were synthesized by this method with the overall yields for the five step procedure ranging from 14-41%.

In future studies, this methodology may find application in the total synthesis of the pyrrolo[1,2-\textit{a}]indole yuremamine \textit{1.163} (figure 1.7). Isolated in 2005 from the stem bark of \textit{Mimosa hostilis}, yuremamine \textit{1.163} poses as an interesting target for total synthesis. Along with a novel structure, there is also a folklore surrounding the supposed biological activity of this natural product.\textsuperscript{86} The root bark of \textit{Mimosa hostilis}, a perennial evergreen shrub native to northern Brazil and southern Mexico, is still used by the indigenous people of north-eastern Brazil in the preparation of \textit{yurema}, a medico-religious tea (also known as \textit{jurema preta} or \textit{vinho da jurema}). The root bark of this shrub (and other similar plants native to this part of the world) are reported to contain some of the highest concentrations of tryptamines, including \textit{N,N}-dimethyltryptamine (DMT) \textit{1.164} which is a psychoactive compound known to cause hallucinations. Since DMT \textit{1.164} is not orally active due to its rapid metabolism, it was suggested by the isolation chemists that yuremamine \textit{1.163} may act as a monoamine oxidase inhibitor,
allowing DMT 1.164 to be active for longer periods, and be responsible for the hallucinations observed when yurema is consumed. Currently no biological testing has been conducted on yuremamine 1.163 to fully clarify its biological properties. Possessing a methodology which can be employed for the rapid assembly of the core of this natural product, and having prepared a pyrrolo[1,2-\textit{a}]indole 1.158 with a pendant aryl ring pertaining to the correct oxidation pattern observed in the natural product, it is our plan to employ this methodology in the total synthesis of this natural product.

Section 1.7: Experimental

General

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments and samples were obtained in CDCl$_3$ (referenced to 7.26 ppm for $^1$H and 77.0 for $^{13}$C). Coupling constants ($J$) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 spectrometer at 70 eV. Microwave reactions were performed in a 400 W Biotage Initiator 2.0 microwave reactor. Acetonitrile, tetrahydrofuran (THF) and dichloromethane (DCM) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Aldrich, Strem, Caledon or VWR. Reaction progress was monitored by TLC (EM Science, silica gel 60 F$_{254}$), visualizing with UV light, and the plates were developed using $p$-anisaldehyde, or basic potassium permanganate stains. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh).
General Procedure for the Preparation of Nitrones 1.136a-e & 1.138

Nitrones were prepared using the procedure of Gautheron-Chapoulaud, V.; Pandya, S. U.; Cividino, P.; Masson, G.; Py, S.; Vallee, Y. Synlett, 2001, 1281. The procedures have not been optimized.

General Procedure for the preparation of tetrahydro-1,2-oxazines 1.153a-e & 1.139:


Yb(OTf)$_3$ (20 mol%) was added to a solution of vinyl cyclopropane 1.76 (1 equiv.) and nitrone 1.136 (1.2 equiv.) in dichloromethane at room temperature. Reaction progress was monitored by TLC. Upon completion the reaction mixture was pre-adsorbed onto silica gel and the tetrahydro-1,2-oxazine 1.153 was obtained after flash column chromatography on silica gel (ethyl acetate in hexanes as eluent).

General procedure for Heck reactions 1.154a-e & 1.140:

A solution of tetrahydro-1,2-oxazine (1 equiv.) and tetrakis(triphenylphosphine)palladium(0) Pd(Ph$_3$)$_4$ (0.1 equiv.) with triethylamine (3 equiv.) in dry acetonitrile was refluxed for 18 hours under an argon atmosphere. The reaction mixture was then concentrated and pre-adsorbed onto silica gel and the Heck product was obtained after flash column chromatography on silica gel (ethyl acetate in hexanes as eluent).

General procedure for Krapcho decarboxylation 1.155a-e & 1.141:

The Heck product was heated in damp dimethylsulfoxide with lithium chloride (10 equiv.) at 160 °C until the starting material was consumed as monitored by TLC. The reaction mixture was then washed with distilled water and extracted with diethyl ether. The combined organic layers were washed with brine and then dried over magnesium
sulphate. When required the products could be further purified by flash column chromatography (ethyl acetate in hexanes as eluent).

Procedure for the preparation of a 0.1M solution of SmI$_2$

A flame dried 50 mL round bottom flask was charged with 20 mL THF and then iodine (0.506 g, 2 mmol, 1 equiv.). Samarium metal (40 mesh, 0.330 g, 2.19 mmol, 1.1 equiv.) was added and the reaction flask was fitted with a reflux condenser, evacuated and refilled with argon four times and set to reflux. A deep navy blue colour should appear after about 20 minutes. Reflux was maintained for 3 hours, at which point the reaction was cooled to room temperature and the 0.1M SmI$_2$ was dispensed as needed by cannula or syringe.

General procedure for N-O bond cleavage for 1.156a-e & 1.142:

To a solution of Krapcho product in dry THF under an argon atmosphere was added a freshly prepared solution of SmI$_2$ (3 equiv. of a 1 M solution) at room temperature. To this solution was added hexamethylphosphoramide (HMPA) (3 equiv. freshly distilled and stored over sieves). The reaction mixture was then heated to 40 °C and monitored by TLC. Upon consumption of the starting material, the reaction mixture was quenched by passing air over the open reaction flask until a bright yellow colour was sustained at which point methanol (10 equiv.) was added. The solution was concentrated under reduced pressure and pre-adsorbed onto silica gel and the amino-alcohol product was obtained after flash column chromatography on silica gel (ethyl acetate in hexanes as eluent).

General procedure for formation of pyrrolo[1,2-a]indoles 1.151 & 1.158-1.162:

Amino-alcohol (1 equiv.) and toluene sulfonic acid (0.1 equiv.) was taken up in benzene and heated to 80 °C under microwave conditions for the time indicated. The reaction mixture was then concentrated under reduced pressure and pre-adsorbed onto silica gel.
The pyrrolo[1,2-\(\alpha\)]indole product was obtained after flash column chromatography on silica gel (ethyl acetate in hexanes as eluent).

**Compound Characterization Data**

Note: Compounds that do not appear in the main text have been given secondary letter designators for clarity

Reagents employed: 2-Iodonitrobenzene (4.00 g, 16.1 mmol, 2 equiv.), benzaldehyde (0.812 mL, 8.03 mmol, 1 equiv.) zinc dust (1.58 g, 65.4 mmol, 3 equiv.), acetic acid (3.00 mL, 50.0 mmol, 6 equiv.) in 100 mL 95% ethanol. Yielded nitrone 1.138 (2.27 g, 7.02 mmol, 88%) as a flakey orange solid: \(R_f = 0.22\) (30% ethyl acetate in hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.36\) (d, \(J = 2.4\) Hz, 1H) 8.35 (d, \(J = 3.5\) Hz, 1H), 7.89 (dd, \(J = 8.0, 1.2\) Hz, 1H), 7.52 (s, 1H), 7.50-7.46 (m, 4H), 7.43 (ddd, \(J = 7.8, 7.8, 1.2\) Hz, 1H), 7.13 (ddd, \(J = 7.8, 7.6, 1.2\) Hz, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 151.6, 140.1, 138.4, 131.2, 130.6, 129.9, 129.3, 129.0, 128.6, 124.8, 90.5\); IR (thin film, cm\(^{-1}\)): 3853, 3744, 3584, 1736, 1579, 1464, 1436, 1403, 1233, 1194, 1118, 1093, 1075, 1021, 935, 886, 818, 756; HRMS calc’d for C\(_{13}\)H\(_{10}\)INO = 322.9807, found 322.9784.

Reagents employed: Nitrone 1.138 (758 mg, 2.35 mmol, 1.2 equiv.), vinyl cyclopropane 1.76 (360 mg, 1.96 mmol, 1 equiv.) Yb(OTf\(_3\))\(_2\)H\(_2\)O (242 mg, 0.391 mmol, 20 mol%) in 20 mL dichloromethane. Yielded tetrahydro-1,2-oxazine 1.139 (0.873 g, 1.72 mmol, 88%) as a clear yellow oil: \(R_f = 0.54\) (30% ethyl acetate in hexanes);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): See spectra on page 167

\(^13\)C NMR (100 MHz, CDCl\(_3\)): See spectra on page 167

IR (thin film, cm\(^{-1}\)): 3058, 3023, 2949, 2901, 1736, 1579, 1464, 1436, 1255, 1147, 1084, 1021, 989, 933, 766, 720; HRMS calc’d for C\(_{22}\)H\(_{22}\)O\(_5\)NI = 507.0543, found 507.0542.
Reagents employed: tetrahydro-1,2-oxazine \textbf{1.139} (0.616 g, 1.22 mmol, 1 equiv.), Pd(PPh$_3$)$_4$ (84.0 mg, 0.0727 mmol, 6%) triethylamine (1.5 mL, 10.7 mmol, 9 equiv.) in 10 mL acetonitrile. Yielded Compound \textbf{1.140} (0.365 g, 0.972 mmol, 80%) as a yellow amorphous solid: $R_f = 0.43$ (30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.72$-$7.70$ (m, 2H), 7.65 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.40-$7.32$ (m, 3H), 7.29-$7.24$ (m, 1H), 7.10 (dd, $J = 8.2$, 8.2 Hz, 1H), 7.01 (dd, $J = 8.0$, 1.0 Hz, 1H), 5.74 (s, 1H), 5.33 (s, 1H), 5.06 (s, 1H), 5.05-5.03 (m, 1H), 3.34 (s, 3H), 3.29 (dd, $J = 14.5$, 6.6 Hz, 1H), 3.27 (s, 3H), 2.54 (dd, $J = 14.5$, 2.3 Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 169.9$, 168.9, 146.6, 139.0, 138.3, 129.1, 128.7, 128.2, 128.0, 124.8, 123.1, 122.8, 121.7, 107.5, 71.6, 68.3, 52.9, 52.5, 52.1, 30.9; IR (thin film, cm$^{-1}$): 3060, 3027, 2948, 2927, 2922, 1737, 1627, 1601, 1482, 1436, 1251, 1202, 1073, 1024, 953, 910, 759; HRMS calc’d for C$_{22}$H$_{21}$O$_5$N = 379.1420, found 379.1421

Reagents employed: Heck product \textbf{1.140} (0.300 g, 0.790 mmol, 1 equiv.), lithium chloride (0.335 g, 7.91 mmol, 10 equiv.) in 25 mL damp dimethylsulfoxide. Yielded compound \textbf{1.148} (0.222 g, 0.688 mmol, 87%) as a clear colourless oil: $R_f = 0.47$ (30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$) major isomer representative peaks: $\delta = 7.65$ (dd, $J = 8.0$, 1.6 Hz, 1H), 7.60-$7.58$ (m, 2H), 7.42-$7.38$ (m, 2H) 7.34-7.30 (m, 1H), 7.23 (ddd, $J = 8.2$, 7.6, 1.6 Hz, 1H) 7.06 (ddd, $J = 8.2$, 7.5, 1.6 Hz, 1H), 6.88 (dd, $J = 8.2$, 0.8 Hz, 1H), 5.66 (s, 1H), 5.02 (s, 1H), 4.81 (d, $J = 7.0$ Hz, 1H), 4.71 (dd, $J = 8.2$, 5.9 Hz, 1H), 3.47 (s, 3H) 2.98 (ddd $J = 11.7$, 7.0, 4.7 Hz, 1H), 2.50 (ddd, $J = 13.3$, 8.2, 5.1, 1H), 2.02 (ddd, $J = 15.6$, 9.8, 2.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) major isomer representative peaks: $\delta = 173.6$, 147.6, 142.2, 139.2, 129.0, 128.5, 127.4, 126.6, 123.9, 123.7, 120.9, 120.1, 106.5, 72.3, 69.1, 52.0, 41.2, 27.9; IR (thin film, cm$^{-1}$): 3063, 3030, 3002, 2951, 2927, 2873, 2852, 1733, 1643, 1602, 1571, 1497, 1454, 1435, 1361, 1300, 1258, 1242, 1204, 1169, 1078, 1059, 977, 902, 701; HRMS calc’d for C$_{20}$H$_{19}$O$_3$N = 321.1365, found 321.1357.
Reagents employed: Krapcho product 1.148 (0.057 g, 0.177 mmol, 1 equiv.), 0.1M SmI$_2$ in THF (5.5 mL, 0.530 mmol, 3 equiv.) HMPA (0.10 mL, 0.530 mmol, 3 equiv.) in 2 mL THF. Yielded amino alcohol 1.149 (0.038 g, 0.12 mmol, 65%) as a white foam, decomposes at 58 °C: R$_f$ = 0.17 (30% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): δ = 7.35-7.33 (m, 2H), 7.30-7.27 (m, 3H), 7.08-7.05 (m, 2H), 6.72 (t, $J$ = 7.6 Hz, 1H), 6.45 (d, $J$ = 8.2 Hz, 1H), 5.52 (d, $J$ = 1.8 Hz, 1H), 5.45 (d, $J$ = 11.1 Hz, 1H), 5.34 (d, $J$ = 1.8 Hz, 1H), 4.66 (dd, $J$ = 11.1, 4.7 Hz, 1H), 3.87-3.63 (br. s, 1H) 3.52 (s, 3H), 3.22 (dt, $J$ = 11.1, 4.7 Hz, 1H), 2.44 (ddd, $J$ = 14.0, 11.7, 4.7 Hz, 1H), 2.33, (dt, $J$ = 14.0, 4.7 Hz, 1H), 2.16-1.95 (br. s, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ = 173.0, 152.9, 145.3, 142.4, 134.2, 129.0, 128.8, 127.9, 126.9, 121.8, 119.3, 118.1, 116.5, 75.7, 56.8, 51.5, 50.6, 34.2; IR (thin film, cm$^{-1}$): 3546, 3402, 3060, 3031, 2952, 2929, 1734, 1600, 1480, 1456, 1436, 1373, 1320, 1302, 1273, 1238, 1197, 1169, 1103, 1090, 1049, 1031, 914, 862, 747, 702; HRMS calc’d for C$_{20}$H$_{21}$O$_3$N = 323.1521, found 323.1523.

Reagents employed: Amino alcohol 1.149 (20 mg, 0.062 mmol, 1 equiv.), toluene sulfonic acid monohydrate (~1 mg, 6 µmol, 10 mol %) in 1 mL benzene. Yielded pyrrolo[1,2-a]indole 1.151 (0.018 g, 0.059 mmol, 95%) as a clear colourless oil: R$_f$ = 0.54 (30% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): δ = 7.51 (d, $J$ = 8.2 Hz, 1H), 7.36-7.32 (m, 3H), 7.21 (m, 2H), 7.04 (t, $J$ = 7.0 Hz, 1H), 6.93, (t, $J$ = 8.2 Hz, 1H), 6.64 (d, $J$ = 8.2 Hz, 1H), 5.67 (d, $J$ = 6.4 Hz, 1H), 5.30 (d, $J$ = 15.8, 7.0 Hz, 1H), 2.31 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ = 172.8, 139.8, 138.8, 133.5, 132.3, 129.0, 128.2, 126.6, 120.3, 118.8, 118.5, 110.1, 101.6, 63.2, 56.6, 52.4, 26.6, 8.9; IR (thin film, cm$^{-1}$): 3049, 3032, 2951, 2919, 2857, 1738, 1621, 1457, 1436, 1383, 1371, 1342, 1265, 1249, 1229, 1195, 1173, 1028, 841, 740, 701; HRMS calc’d for C$_{20}$H$_{19}$O$_2$N = 305.1416, found 305.1412.
Reagents employed: 2-Iodonitrobenzene (1.21 g, 4.84 mmol, 2 equiv.), 3,4,5-trimethoxybenzaldehyde (0.475 g, 2.42 mmol, 1 equiv.) zinc dust (0.475 g, 7.26 mmol, 3 equiv.), acetic acid (1.00 mL, 16.7 mmol, 6 equiv.) in 100 mL 95% ethanol. Yielded nitrone 1.136a (0.893 g, 2.16 mmol, 88%) as white flakes; decomposes at 143 °C; \( R_f = 0.29 \) (50% ethyl acetate in hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta =7.92 \) (dd, \( J = 8.0, 1.4 \) Hz, 1H), 7.71 (s, 2H), 7.54 (dd, 7.8, 1.6 Hz, 1H), 7.46 (m, 2H), 7.16, (ddd, 9.6, 8.0, 1.6 Hz, 1H), 3.94 (s, 6H), 3.93 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 152.7, 151.4, 140.3, 139.8, 138.0, 130.5, 129.1, 125.3, 124.7, 106.2, 90.3, 60.7, 55.9; \) IR (thin film, cm\(^{-1}\)): 3106, 3056, 2993, 2965, 2940, 2839, 1581, 1502, 1462, 1437, 1416, 1339, 1245, 1158, 1126, 1089, 1044, 1022, 1002, 987, 881, 864, 770, 719; HRMS calc’d for C\(_{16}\)H\(_{16}\)O\(_4\)NI = 413.0124, found 413.0134.

Reagents employed: Nitrone 1.136a (240 mg, 0.581 mmol, 1 equiv.), vinyl cyclopropane 1.76 (140 mg, 0.760 mmol, 1.3 equiv.) Yb(OTf)\(_3\)\( \times \)H\(_2\)O (72.0 mg, 0.116 mmol, 20%) in 10 mL dichloromethane. Yielded tetrahydro-1,2-oxazine 1.153a (0.279 g, 0.466 mmol, 80%) as a 1:1 mixture of atropisomers, low melting beige foam; \( R_f = 0.27 \) (30% ethyl acetate in hexanes);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): See spectra on page 173.

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)): See spectra on page 173.

IR (thin film, cm\(^{-1}\)): 3001, 2952, 2839, 1741, 1589, 1508, 1466, 1433, 1424, 1328, 1246, 1129, 1062, 1019, 932, 860; HRMS calc’d for C\(_{25}\)H\(_{28}\)O\(_8\)NI = 597.0860, found 597.0847.

Reagents employed: tetrahydro-1,2-oxazine 1.153a (0.494 g, 0.827 mmol, 1 equiv.), Pd(PPh\(_3\))\(_4\) (191 mg, 0.165 mmol, 20%) triethylamine (0.346 mL, 2.48 mmol, 3 equiv.) in 20 mL acetonitrile. Yielded Compound 1.154a (0.368 g, 0.784 mmol, 95%) as large white flakes from dichloromethane/hexanes, M.p.
55-57 °C; Rf = 0.23 (30% ethyl acetate in hexanes); 1H NMR (400 MHz, CDCl3): δ = 7.64 (d, J = 8.2 Hz, 1H), 7.27 (dd, J = 7.4, 7.0 Hz, 1H), 7.10 (dd, J = 7.8, 7.0 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.95 (s, 2H), 5.74 (s, 1H), 5.23 (s, 1H), 5.06 (s, 1H), 5.05 (dd, J = 6.6, 2.7 Hz, 1H), 3.89 (s, 6H), 3.85 (s, 3H), 3.38 (s, 3H), 3.34 (s, 3H), 3.25 (dd, J = 14.4, 6.6, Hz, 1H), 2.49 (dd, J = 14.4, 3.1 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ = 169.9, 168.8, 152.7, 146.5, 138.1, 137.7, 134.7, 129.1, 124.8, 122.9, 122.8, 121.5, 107.6, 105.9, 71.5, 68.3, 60.8, 56.1, 52.9, 52.6, 52.3, 31.0; IR (thin film, cm\(^{-1}\)): 3003, 2952, 2840, 1738, 1590, 1479, 1455, 1423, 1353, 1331, 1246, 1203, 1181, 1128, 1075, 1008, 908; HRMS calc’d for C\(_{25}\)H\(_{27}\)O\(_8\)N = 469.1737, found 469.1727.

Reagents employed: Heck product 1.154a (0.200 g, 0.426 mmol, 1 equiv.), lithium chloride (0.180 g, 4.26 mmol, 10 equiv.) in 25 mL damp dimethylsulfoxide. Yielded compound 1.155a (0.169 g, 0.375 mmol, 78%) 4:1 mixture of diastereomers; recrystallization from dichloromethane/hexanes gave clear white crystals, M.p. 56-58 °C; Rf = 0.26 (30% ethyl acetate in hexanes); 1H NMR (400 MHz, CDCl3): major isomer representative peaks δ = 7.64 (d, J = 8.2, 1.6 Hz, 1H), 7.24 (m, 1H), 7.05 (ddd, J = 1.2, 7.4, 9.4 Hz, 1H), 6.87 (dd, J = 8.2, 1.2 Hz, 1H), 6.80 (s, 2H), 5.65 (s, 1H), 5.02 (s, 1H), 4.73 (dd, J = 6.2, 6.2 Hz, 1H), 4.71 (d J = 7.4 Hz, 1H) 3.88 (s, 6H), 3.86 (s, 3H), 3.52 (s, 3H), 2.96 (ddd, J = 12.1, 7.4, 4.7 Hz, 1H), 2.48 (ddd, J = 13.4, 8.2, 4.7 Hz, 1H) 1.95 (m, 1H); 13C NMR (150 MHz, CDCl3): major isomer representative peaks δ = 172.9, 153.2, 147.7, 139.2, 138.2, 137.1, 133.5, 129.1, 124.1, 123.6, 119.8, 106.5, 103.5, 72.4, 69.5, 60.8, 56.1, 52.0, 41.8, 28.1; IR (thin film, cm\(^{-1}\)): 3000, 2951, 2940, 2839, 1732, 1591, 1455, 1422, 1356, 1332, 1258, 1239, 1128, 1007, 900; HRMS calc’d for C\(_{25}\)H\(_{27}\)O\(_6\)N = 411.1682, found 411.1663.

Reagents employed: Krapcho product 1.155a (0.096 g, 0.23 mmol, 1 equiv.), 0.1M SmI\(_2\) in THF (7.0 mL, 0.70 mmol, 3 equiv.) and HMPA (0.12 mL, 0.70 mmol, 3 equiv.) in 3 mL THF. Yielded amino alcohol 1.156a (0.070 g, 0.17 mmol, 73%)
as a white foam, decomposes at 63 °C; Rf = 0.22 (50% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.07$ (m, 2H), 6.75 (m, 1H), 6.50 (m, 1H) 6.48 (s, 2H), 5.52 (s, 1H), 5.34 (m, 2H), 4.64 (dd, $J = 11.1$, 4.7 Hz, 1H), 3.84 (s, 6H), 3.83 (s, 3H), 3.80-3.65 (br. s, 1H), 3.58 (s, 3H), 3.20 (ddd, $J = 11.1$, 4.7, 4.7 Hz, 1H), 2.43 (ddd, $J = 11.1$, 11.1, 4.3 Hz, 1H), 2.32 (ddd, $J = 13.3$, 4.5, 4.5 Hz, 1H), 2.23-1.94 (br. s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 173.0$, 153.4, 152.8, 145.2, 138.0, 137.4, 134.2, 128.7, 121.9, 119.4, 118.1, 116.6, 103.9, 75.6, 60.7, 57.1, 56.1, 51.6, 50.2, 34.1; IR (thin film, cm$^{-1}$): 3486, 3386, 3004, 2940, 2840, 1732, 1593, 1509, 1480, 1464, 1433, 1422, 1322, 1302, 1240, 1196, 1163, 1127, 1032, 1006, 916, 846, 751; HRMS calc’d for C$_{23}$H$_{27}$O$_6$N = 413.1838, found 413.1852.

Reagents employed: Amino alcohol **1.156a** (20 mg, 0.048 mmol, 1 equiv.), toluene sulfonic acid monohydrate (~1 mg, 5 µmol, 10 mol %) in 1 mL benzene. Yielded pyrrolo[1,2-a]indole **1.158** (0.018 g, 0.045 mmol, 94%) as a white film; Rf = 0.31 (30% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.50$ (d, $J = 7.6$ Hz, 1H), 7.05 (ddd, $J = 8.2$, 8.2, 1.2 Hz, 1H), 6.96 (ddd, $J = 8.2$, 8.2, 1.2 Hz, 1H), 6.72 (d, $J = 8.2$ Hz, 1H), 6.45 (s, 2H), 5.55 (d, $J = 6.4$ Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.75 (s, 6H), 3.65 (m, 1H), 3.44 (dd, $J = 15.8$, 9.4 Hz, 1H), 3.25 (dd, $J = 16.8$, 8.2 Hz, 1H), 2.30 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 172.8$, 153.6, 138.6, 137.8, 135.3, 133.6, 132.6, 120.4, 119.0, 118.4, 110.3, 103.5, 101.8, 63.5, 60.9, 56.4, 56.2, 52.4, 26.8, 8.9; IR (thin film, cm$^{-1}$): 3048, 2998, 2952, 2924, 2853, 1737, 1594, 1507, 1459, 1424, 1344, 1328, 1234, 1195, 1173, 1128, 1027, 1008, 983, 926, 844, 823, 775, 741, 711; HRMS calc’d for C$_{23}$H$_{25}$O$_5$N = 397.1733, found 395.1734.

Reagents employed: 2-Iodonitrobenzene (1.40 g, 5.62 mmol, 1.3 equiv.), piperonal (0.650 g, 4.32 mmol, 1 equiv.), zinc dust (0.847 g, 13.0 mmol, 3 equiv.), acetic acid (1.60 mL, 25.9 mmol, 6 equiv.) in 20 mL 95% ethanol. Yielded nitronone **1.136b** (1.29 g, 3.51 mmol,
81%) as large opaque flakes; decomposes at 116 °C; \( R_f = 0.24 \) (30% ethyl acetate in hexanes); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta = 8.22 \) (s, 1H), 7.87 (d, \( J = 8.2 \) Hz, 1H), 7.63, (dd, \( J = 8.2 \), 1.8 Hz, 1H), 7.49 (dd, \( J = 8.2 \), 1.2 Hz, 1H), 7.40 (m, 2H), 7.11 (ddd, \( J = 7.6 \), 7.6, 1.8 Hz, 1H), 6.88 (d, \( J = 8.2 \) Hz, 1H), 6.02 (s, 2H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta = 151.4, 150.0, 147.6, 140.0, 138.0, 130.5, 129.2, 125.2, 124.9, 124.4, 108.6, 108.4, 101.6, 90.63; \) IR (thin film, cm\(^{-1}\)): 3062, 2985, 2901, 2785, 1620, 1600, 1576, 1502, 1485, 1449, 1404, 1361, 1267, 1207, 1138, 1106, 1078, 1034, 927, 879, 823, 793, 713; HRMS calc’d for C\(_{14}\)H\(_{10}\)O\(_3\)NI = 312.9600, found 312.9590.

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Reagents employed: Nitrone 1.136b (0.485 g, 1.32 mmol, 1.3 equiv.), vinyl cyclopropane 1.76 (187 mg, 1.02 mmol, 1 equiv.), Yb(OTf)\(_3\)xH\(_2\)O (127 mg, 0.204 mmol, 20 mol%) in 25 mL dichloromethane. Yielded tetrahydro-1,2-oxazine 1.153b (0.473 g, 0.857 mmol, 84%) as a yellow foam: \( R_f = 0.31 \) (30% ethyl acetate in hexanes);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): See spectra on page 179.

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): See spectra on page 179.

IR (thin film, cm\(^{-1}\)): 3127, 2953, 2897, 1741, 1661, 1641, 1550, 1530, 1488, 1466, 1442, 1250, 1039, 932, 800, 761; HRMS calc’d for C\(_{23}\)H\(_{22}\)O\(_7\)NI = 551.0440, found: 551.0439.

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Reagents employed: tetrahydro-1,2-oxazine 1.153b (0.31 g, 0.57 mmol, 1 equiv.), Pd(PPh\(_3\))\(_4\) (66 mg, 0.057 mmol, 10%), triethylamine (0.25 mL, 1.7 mmol, 3 equiv.) in 8 mL acetonitrile. Yielded Compound 1.154b (0.18 g, 0.43 mmol, 80%) as a yellow amorphous solid: \( R_f = 0.32 \) (30% ethyl acetate in hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.63 \) (dd, \( J = 8.0 \), 1.2 Hz, 1H), 7.37 (d, \( J = 1.6 \) Hz, 1H), 7.29-7.25 (m, 1H), 7.10 (dt, \( J = 1.2 \), 8.0 Hz, 1H), 7.04 (dd, \( J = 8.0 \), 1.6 Hz, 1H), 7.00 (dd, \( J = 8.0 \), 1.2 Hz, 1H), 6.78 (d, \( J = 8.4 \) Hz, 1H), 5.97 (d, \( J = 1.4 \) Hz, 1H), 5.96 (d, \( J = 1.4 \) Hz, 1H), 5.74 (s, 1H), 5.22 (s, 1H), 5.05 (s, 1H), 5.02-4.99 (m, 1H),
3.37 (s, 3H), 3.32 (s, 3H), 3.27 (dd, J = 14.6, 6.0 Hz, 1H), 2.53 (dd, J = 14.6, 2.4 Hz, 1H); 
$^{13}$C NMR (100 MHz, CDCl$_3$): δ = 169.8, 168.8, 147.6, 147.1, 146.5, 138.2, 132.7, 129.1, 124.9, 123.2, 122.8, 122.4, 121.8, 109.4, 107.7, 107.6, 101.0, 71.6, 67.7, 52.9, 52.6, 52.0, 30.8); IR (thin film, cm$^{-1}$): 2952, 1737, 1651, 1490, 1442, 1252, 1039, 912, 760, 734; HRMS calc’d for C$_{23}$H$_{21}$O$_7$N = 423.1317, found 423.1320.

Reagents employed: Heck product 1.154b (0.087 g, 0.205 mmol, 1 equiv.), lithium chloride (0.087 g, 2.05 mmol, 10 equiv.) in 6 mL damp dimethylsulfoxide. Yielded compound 1.155b (0.060 g, 0.164 mmol, 80%) 5:2 mixture of diastereomers as a viscous yellow film; R$_f$ = 0.41 (30% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): For the diastereomeric mixture δ = (dd, J = 8.2, 1.2 Hz, 1H), 7.23 (ddd, J = 8.2, 8.2, 1.2 Hz, 1H), 7.17, (d, J = 1.8 Hz, 1H), 7.05 (ddd, J = 8.2, 8.2, 1.2 Hz, 1H), 6.96 (dd, J = 8.2, 1.2 Hz, 1H), 6.87, (d, J = 8.2 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.97 (s, 2H), 5.64 (s, 1H), 5.01 (s, 1H), 4.72 (dd, J = 8.2, 6.1 Hz, 1H), 4.67 (d, J = 7.6 Hz, 1H), 3.49 (s, 3H), 2.95 (m, 1H), 2.49 (ddd, J = 13.5, 8.2, 4.7 Hz, 1H), 1.95 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 173.6, 172.8, 148.0, 147.8, 147.7, 147.0, 146.9, 145.8, 139.3, 138.6, 136.5, 131.8, 129.1, 129.0 125.6, 125.2, 124.1, 123.6, 122.8, 122.1, 121.9, 120.6, 119.9, 119.7, 109.5, 108.0, 107.8, 107.8, 107.4, 106.4, 101.0, 73.5, 72.4, 69.5, 66.6, 52.0, 51.6, 41.7, 33.8, 28.4, 28.0, (missing one carbon resonance due to overlap); IR (thin film, cm$^{-1}$): 3072, 3019, 2951, 2899, 2780, 1734, 1636, 1603, 1503, 1490, 1443, 1363, 1324, 1302, 1248, 1172, 1128, 1102, 1039, 976, 936, 900, 868, 819, 791; HRMS calc’d for C$_{21}$H$_{19}$O$_5$N = 365.1263, found 365.1264.

Reagents employed: Krapcho product 1.155b (0.055 g, 0.15 mmol, 1 equiv.), 0.1M SmI$_2$ in THF (4.5 mL, 0.45 mmol, 3 equiv.) HMPA (0.080 mL, 0.45 mmol, 3 equiv.) in 3 mL THF. Yielded amino alcohol 1.156b (0.039 g, 0.11 mmol, 71%) 3:1 mixture of diastereomers as an opaque viscous film; R$_f$ = 0.10
(30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): major isomer representative peaks $\delta = 7.10$-$7.02$ (m, 2H), 6.82, (ddd, $J = 7.8$, 7.4, 1.8 Hz, 1H), 6.78 (dd, $J = 1.2$, 1.2 Hz, 1H), 6.75 (s, 1H), 6.72 (ddd, $J = 7.4$, 7.4, 1.2 Hz, 1H), 6.45 (dd, $J = 8.2$, 1.2 Hz, 1H), 5.95 (s, 2H), 5.50 (d, $J = 1.6$ Hz, 1H), 5.39-5.36 (m, 1H), 5.32 (d, $J = 1.6$ Hz, 1H), 4.66-4.59 (m, 1H), 3.67 (br. s, 1H), 3.56 (s, 3H), 3.14 (ddd, $J = 11.3$, 4.7, 4.7 Hz, 1H), 2.39, (dd, $J = 10.9$, 4.3 Hz, 1H), 2.32 (dd, $J = 4.7$, 4.7 Hz, 1H), 1.95 (d, $J = 6.3$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): For the diastereomeric mixture $\delta = 173.1$, 173.0, 152.9, 147.9, 147.8, 147.1, 146.7, 145.2, 144.3, 136.3, 134.5, 134.2, 133.1, 129.1, 128.8, 121.8, 120.2, 119.7, 119.3, 119.1, 118.1, 117.5, 116.5, 108.5, 108.1, 107.3, 107.0, 101.1, 101.0, 76.5, 75.6, 56.5, 56.0, 51.6, 50.7, 48.0, 34.5, 34.2, (missing 4 carbon signal resonances due to overlap); IR (thin film, cm$^{-1}$): 3521, 3407, 3009, 2952, 2926, 1728, 1601, 1503, 1481, 1443, 1371, 1315, 1243, 1200, 1167, 1101, 1088, 1038, 932, 810; HRMS calc’d for C$_{21}$H$_{21}$O$_5$N = 367.1420, found 367.1406.

Reagents employed: Amino alcohol $^{1.156b}$ (25 mg, 0.068 mmol, 1 equiv.), toluene sulfonic acid monohydrate (~1.3 mg, 6.8 µmol, 10 mol %) in 1 mL benzene. Yielded pyrrolo[1,2-$a$]indole $^{1.159}$ (0.016 g, 0.046 mmol, 67%) as a clear viscous film; $R_f = 0.49$ (30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.50$ (d, $J = 7.8$ Hz, 1H), 7.05 (ddd, $J = 8.0$, 8.0, 1.0 Hz, 1H), 6.95 (ddd, $J = 8.0$, 8.0, 1.0 Hz, 1H), 6.80 (d, $J = 7.8$ Hz, 1H), 6.75 (dd, $J = 8.2$, 1.6 Hz, 1H), 6.70 (d, $J = 8.2$ Hz, 1H), 6.65 (d, $J = 1.6$ Hz, 1H), 5.96 (AB d $J = 1.4$ Hz, 1H) 5.95 (AB d $J = 1.4$ Hz, 1H), 5.57 (d, $J = 6.4$ Hz, 1H), 3.76 (s, 3H), 3.65-3.58 (m, 1H), 3.41 (dd, $J = 16.1$, 9.0 Hz 1H) 3.27 (dd, 16.1, 7.5 Hz, 1H), 2.29 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): 172.8, 148.2, 147.6, 138.6, 133.7, 133.6, 132.2, 120.4, 120.2, 118.9, 118.5, 110.1, 108.4, 106.8, 101.6, 101.2, 63.1, 56.6, 52.4, 26.6, 8.9; IR (thin film, cm$^{-1}$): 3049, 2952, 2918, 2860, 2779, 1734, 1621, 1612, 1503, 1490, 1460, 1446, 1344, 1319, 1251, 1197, 1173, 1126, 1101, 1039, 933, 862, 810, 773, 740; HRMS calc’d for C$_{21}$H$_{19}$O$_4$N = 349.1314, found 349.1307.
Reagents employed: Nitrone 1.138 (1.09 g, 3.36 mmol, 1.2 equiv.), styrenyl cyclopropane 1.76a (0.730 g, 2.80 mmol, 1 equiv.) Yb(OTf)$_3$·2H$_2$O (350 mg, 0.561 mmol, 20 mol%) in 70 mL dichloromethane. Yielded tetrahydro-1,2-oxazine 1.153c (1.60 g, 2.74 mmol, 98%) as large white flakes; decomposes at 107 °C; $R_f$ = 0.39 (30% ethyl acetate in hexanes);

$^1$H NMR (400 MHz, CDCl$_3$): See spectra on page 184.

$^{13}$C NMR (100 MHz, CDCl$_3$): See spectra on page 184.

IR (thin film, cm$^{-1}$): 3083, 3061, 3028, 2952, 2842, 1734, 1600, 1578, 1495, 1467, 1454, 1435, 1256, 1215, 1180, 1086, 1073, 1056, 1030, 1020, 966, 920, 720, 703, 695; HRMS calc’d for C$_{28}$H$_{26}$O$_5$NI = 583.0856, found 583.0870.

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Procedure for the synthesis of Krapcho product 1.155c:

Triethylamine (0.072 mL, 0.514 mmol, 3 equiv.) was added to a solution of tetrahydro-1,2-oxazine 1.153c (0.100 g, 0.171 mmol, 1 equiv.) and Pd(PPh$_3$)$_4$ (0.010 g, 0.0086 mmol, 5%) in 1.5 mL acetonitrile in a 2 mL microwave vial. The solution was purged with argon and then heated to 120 °C under microwave conditions for 3 h at which point TLC analysis indicated the consumption of the starting material. The resulting solution was concentrated and passed through a plug of silica to give the desired Heck product 1.154c which was inseparable from at least one other compound. The mixture was then submitted to the Krapcho decarboxylation. The reaction mixture was dissolved in 5 mL damp dimethylsulfoxide and lithium chloride (0.072 g, 1.71 mmol, 10 equiv.) was added. The reaction was heated to 160 °C for 90 minutes, at which point TLC analysis showed consumption of the starting material. The reaction mixture was diluted with 50 mL ethyl acetate and washed three times with distilled water. The aqueous fractions were combined and washed with 50 mL ethyl acetate. The organic fractions were combined, washed once more with 30 mL distilled water and then with 50
mL brine. The organic layer was dried over MgSO$_4$ (s), filtered and concentrated. The Krapcho product **1.155c** (0.50 g, 0.125 mmol, 73% over 2 steps) was then isolated by flash column chromatography (ethyl acetate in hexanes as eluent). Recrystallization from dichloromethane/hexanes gave **1.155c** as white opaque flakes; M.p. = 166-167 °C; R$_f$ = 0.51 (30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.69 (dd, $J$ = 8.2, 1.2 Hz, 1H), 7.56 (d, $J$ = 7.4 Hz, 2H), 7.40 (t, $J$ = 7.0 Hz, 2H), 7.38 (t, $J$ = 7.4 Hz, 2H); 7.34-7.29 (m, 2H), 7.25-7.21 (m, 4H), 7.09 (ddd, $J$ = 8.2, 8.2, 1.2 Hz, 1H), 6.87 (dd, $J$ = 8.2, 1.2 Hz, 1H), 5.14 (dd, $J$ = 8.6, 7.6 Hz, 1H), 4.76 (d, $J$ = 8.2 Hz, 1H), 3.58 (s, 3H), 3.06 (ddd, $J$ = 12.3, 8.2, 4.3 Hz, 1H), 2.62 (ddd, $J$ = 13.6, 8.6, 4.3 Hz, 1H), 2.11 (ddd, $J$ = 13.6, 12.3, 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): 173.8, 148.2, 142.7, 136.0, 132.2, 128.8, 128.7, 128.6, 128.5, 127.5, 126.5, 124.4, 123.4, 121.9, 121.0, 119.5, 70.7, 66.8, 52.1, 42.7, 28.4, (missing one carbon resonance due to overlap); IR (thin film, cm$^{-1}$): 3062, 3028, 2952, 2927, 2854, 1735, 1600, 1496, 1478, 1455, 1437, 1363, 1305, 1264, 1226, 1194, 1170, 1051, 1029, 968, 904, 872, 700; HRMS calc’d for C$_{26}$H$_{23}$O$_3$N = 397.1678, found 397.1678. Olefin geometry confirmed by detailed nOe correlations.

Reagents employed: Krapcho product **1.155c** (0.078 g, 0.20 mmol, 1 equiv.), 0.1M SmI$_2$ in THF (5.9 mL, 0.59 mmol, 3 equiv.) HMPA (0.10 mL, 0.59 mmol, 3 equiv.) in 3 mL THF.

Yielded amino alcohol **1.156c** (0.048 g, 0.12 mmol, 62%) as small clear cubes from chloroform/hexanes, decomposes at 147 °C; R$_f$ = 0.28 (30% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.51 (d, $J$ = 7.6 Hz, 2H), 7.41 (t, $J$ = 7.6 Hz, 2H), 7.34 (t, $J$ = 7.6 Hz, 2H), 7.31-7.27 (m, 4H), 7.12-7.09 (m, 2H), 6.79 (s, 1H), 6.73 (dd, $J$ = 7.6, 7.2 Hz, 1H), 6.50 (dd, $J$ = 8.8, 1.2 Hz, 1H), 5.62 (d, $J$ = 11.5 Hz, 1H), 5.06 (dd, $J$ = 11.7, 4.1 Hz, 1H), 4.05-3.70 (br. s , 1H), 3.12 (dd, $J$ = 11.5, 4.1, 4.1 Hz, 1H), 3.02 (s, 3H), 2.46 (ddd, $J$ = 13.8, 11.7, 4.1 Hz, 1H), 2.29 (ddd, $J$ = 13.8, 4.1, 4.1 Hz, 1H), 1.95-1.68 (br. s , 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): 172.5, 146.0, 145.4, 142.3, 137.0, 135.0, 133.8, 129.0, 128.9, 128.8, 128.3, 128.0, 127.1, 127.0, 121.9, 117.5, 116.0, 68.3, 56.0, 51.4, 51.0, 34.3; IR (thin film, cm$^{-1}$): 3520, 3055, 3022, 2949, 2363, 1728, 1599, 1575, 1478, 1454, 1436, 1320, 1267, 700; HRMS calc’d for C$_{26}$H$_{23}$O$_3$N = 397.1678, found 397.1678. Olefin geometry confirmed by detailed nOe correlations.
Reagents employed: Amino alcohol 1.156c (40 mg, 0.10 mmol, 1 equiv.), toluene sulfonic acid monohydrate (2.0 mg, 10 µmol, 10 mol %) in 1.3 mL benzene. Yielded pyrrolo[1,2-α]indole 1.160 (0.033 g, 0.087 mmol, 87%) as a bright yellow viscous film; Rf = 0.59 (30% ethyl acetate in hexanes); 1H NMR (600 MHz, CDCl3): δ = 7.51 (d, J = 7.6 Hz, 1H), 7.39-7.34 (m, 3H), 7.34-7.29 (m, 4H), 7.24-7.21 (m, 3H), 7.04 (t, J = 7.6 Hz, 1H), 6.95, (t, J = 7.3 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 5.68, (d, J = 5.9 Hz, 1H), 4.14 (s, 2H), 3.75 (s, 3H), 3.62 (ddd, J = 15.2, 7.02, 7.02 Hz, 1H), 3.19 (dd, J = 16.4, 8.8 Hz, 1H), 3.09 (dd, J = 16.4, 7.0 Hz, 1H); 13C NMR (150 MHz, CDCl3): 172.8, 141.2, 139.7, 139.5, 132.8, 132.3, 128.9, 128.7, 128.4, 128.3, 126.6, 125.7, 120.5, 119.1, 118.8, 110.2, 105.6, 63.2, 56.6, 52.3, 30.9, 26.9; IR (thin film, cm⁻¹): 3060, 3029, 2952, 2923, 2851, 1738, 1603, 1494, 1478, 1455, 1436, 1408, 1348, 1264, 1251, 1230, 1197, 1075, 1028, 1002, 931, 743, 701; HRMS calc’d for C26H25O3N = 399.1834, found 399.1845.

Reagents employed: 2-Iodonitrobenzene (0.701 g, 2.82 mmol, 1.5 equiv.), N-tosyl indole-3-carboxaldehyde (0.562 g, 2.17 mmol, 1 equiv.), zinc dust (0.370 g, 5.64 mmol, 3 equiv.), acetic acid (0.70 mL, 11.3 mmol, 6 equiv.) in 40 mL 95% ethanol. Yielded nitrone 1.136d (0.863 g, 1.93 mmol, 89%) as shiny beige flakes, decomposes at 181 °C; Rf = 0.32 (50% ethyl acetate in hexanes); 1H NMR (400 MHz, CDCl3): δ = 9.52 (s, 1H), 8.08, (d, J = 8.2 Hz, 1H), 7.95-7.90 (m, 3H), 7.87 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.55 (dd, J = 7.8, 1.6 Hz, 1H), 7.47 (td, J = 7.8, 1.2 Hz, 1H), 7.40 (t, J = 7.4 Hz, 1H), 7.30 (dd, J = 8.2, 7.8 Hz, 1H), 7.28-7.24 (m, 2H), 7.18 (ddd, 8.2, 7.8, 1.6 Hz, 1H), 2.36 (s, 3H); 13C NMR (100 MHz, CDCl3): 151.1, 145.4, 140.3, 134.9, 134.2, 131.0, 130.0, 129.9, 129.6, 129.3, 128.3, 127.3, 125.5, 125.3, 123.7, 118.4, 114.0, 112.0, 90.7, 21.6; IR (thin film, cm⁻¹): 3165, 3064, 2982, 1595, 1526, 1462,
Reagents employed: Nitrone **1.136d** (0.423 g, 0.819 mmol, 1.3 equiv.), vinyl cyclopropane **1.76** (0.113 g, 0.611 mmol, 1 equiv.), Yb(OTf)$_3$$\times$H$_2$O (76.0 mg, 0.122 mmol, 20%) in 20 mL dichloromethane. Yielded tetrahydro-1,2-oxazine **1.153d** (0.320 g, 0.458 mmol, 75%) approx. 3:1 mixture of atropisomers, as clear shiny flakes M.p. = 62-64 °C; $R_f = 0.37$ (30% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): major isomer representative peaks δ = 7.91 (s, 1H), 7.73 (dd, $J = 7.6$, 1.8 Hz, 1H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.35 (d, $J = 7.6$ Hz, 1H), 7.23 (dd, $J = 8.2$, 8.2 Hz, 1H), 7.17 (d, $J = 8.2$ Hz, 2H), 7.13 (dd, $J = 7.1$, 1.8 Hz, 1H), 6.58 (ddd, $J = 7.6$, 7.6, 1.8 Hz, 1H), 6.53 (dd, $J = 7.6$, 7.6 Hz, 1H), 6.45 (d, $J = 7.6$ Hz, 1H), 6.07 (ddd, $J = 17.0$, 11.1, 5.3 Hz, 1H), 5.79 (s, 1H), 5.54 (d, $J = 17.6$ Hz, 1H), 5.39 (d, $J = 11.1$ Hz, 1H), 5.07 (bd, $J = 7.6$ Hz, 1H), 3.92, (s, 3H), 3.77-3.71 (m, 1H), 3.06 (s, 3H), 2.71 (dd, $J = 14.6$, 1.8 Hz, 1H), 2.39-2.34 (m, 1H), 2.33 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): major isomer representative peaks δ = 169.1, 168.0, 148.4, 144.8, 139.9, 135.8, 135.1, 133.8, 131.2, 129.8, 127.8, 126.9, 126.7, 124.8, 123.3, 122.6, 119.2, 117.5, 116.3, 113.5, 77.3, 58.4, 57.6, 53.4, 52.3, 30.3, 21.5; IR (thin film, cm$^{-1}$): 3157, 3027, 2953, 2926, 2855, 1741, 1598, 1465, 1448, 1436, 1371, 1261, 1214, 1189, 1176, 1134, 1121, 1096, 1084, 1019, 969, 931, 907, 813, 720, 705; HRMS calc’d for C$_{31}$H$_{29}$O$_7$N$_2$IS = 700.0740, found 700.0760.

Reagents employed: tetrahydro-1,2-oxazine **1.153d** (0.11 g, 0.15 mmol, 1 equiv.), Pd(PPh$_3$)$_4$ (17 mg, 0.015 mmol, 10%), triethylamine (0.063 mL, 0.45 mmol, 3 equiv.) in 8 mL acetonitrile. Yielded compound **1.154d** (0.078 g, 0.14 mmol, 91%) as light yellow cubes, M.p. = 91-92 °C; $R_f = 0.28$ (30% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): δ = 8.08 (s, 1H), 7.96 (d, $J = 7.6$ Hz, 1H), 7.76 (d, $J = 8.2$ Hz, 2H), 7.68 (dd, $J = 8.2$, 8.2 Hz, 2H),
7.31 (dd, $J = 7.6, 6.4$ Hz, 1H), 7.28 (dd, $J = 7.6, 1.2$ Hz, 2H), 7.23 (d, $J = 8.2$ Hz, 2H), 7.12 (ddd, $J = 8.2, 1.2$ Hz, 1H), 7.05 (d, $J = 8.2$ Hz, 1H), 5.78 (s, 1H), 5.70 (s, 1H), 5.10 (s, 1H), 5.05 (d, $J = 5.9$ Hz, 1H), 3.31 (dd, $J = 14.6, 5.6$ Hz, 1H), 3.27 (s, 3H), 2.82 (s, 3H), 2.75 (d, $J = 14.6$ Hz, 1H), 2.32 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 169.04, 168.37, 145.40, 144.79, 137.93, 135.17, 134.04, 130.03, 129.83, 129.09, 126.89, 126.15, 125.19, 124.71, 123.82, 123.11, 122.64, 122.35, 119.59, 119.24, 113.52, 107.88, 71.80, 59.28, 52.89, 52.28, 50.75, 30.54, 21.51; IR (thin film, cm$^{-1}$): 3157, 3031, 2953, 2927, 2855, 1738, 1631, 1598, 1560, 1480, 1449, 1370, 1292, 1257, 1218, 1205, 1176, 1122, 1096, 1082, 1022, 979, 944, 916, 887, 814, 792, 712, 704, 680; HRMS calc’d for C$_{31}$H$_{28}$O$_7$N$_2$S = 572.1617, found 572.1596.

Reagents employed: Heck product 1.154d (0.140 g, 0.244 mmol, 1 equiv.), lithium chloride (0.104 g, 2.45 mmol, 10 equiv.) in 16 mL damp dimethylsulfoxide. Yielded compound 1.155d (0.070 g, 0.136 mmol, 56%) 5:2 mixture of diastereomers, as small white flakes; M.p. = 88-89 °C; $R_f = 0.30$ (30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): Major isomer representative peaks $\delta = 8.02$ (s, 1H), 7.93 (m, 1H), 7.82 (d, $J = 8.2$ Hz, 2H), 7.67 (dd, $J = 7.4, 7.4$ Hz, 2H), 7.36-7.30 (m, 2H), 7.27-7.23 (m, 3H), 7.10 (ddd, $J = 8.2, 8.2, 1.2$ Hz, 1H), 6.98 (dd, $J = 7.8, 1.2$ Hz, 1H), 5.73 (s, 1H), 5.23 (d, $J = 3.1$ Hz, 1H), 5.05 (s, 1H), 4.74 (dd, $J = 7.0, 3.1$ Hz, 1H), 3.30 (s, 3H), 2.84 (dd, $J = 8.2, 4.7$ Hz, 1H), 2.55 (m, 1H), 2.35 (s, 3H), 2.32-2.28 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): For the diastereomeric mixture $\delta = 172.54, 172.29, 145.93, 145.08, 144.90, 138.72, 138.73, 135.32, 135.07, 130.14, 129.87, 129.11, 128.89, 126.93, 126.85, 125.71, 125.26, 124.78, 124.71, 124.61, 124.01, 123.30, 123.27, 123.04, 122.89, 122.36, 121.94, 121.41, 119.87, 119.82, 118.42, 113.78, 113.51, 108.04, 107.20, 73.30, 71.86, 61.15, 59.69, 51.88, 51.59, 37.11, 33.10, 29.68, 28.79, 26.37, 21.55 (missing 7 carbon signal resonances due to overlap); IR (thin film, cm$^{-1}$): 3028, 2951, 2926, 2854, 1734, 1598, 1479, 1449, 1370, 1278, 1258, 1214, 1188, 1175, 1123, 1094, 1058, 1021, 984, 894, 813, 708, 680; HRMS calc’d for C$_{29}$H$_{26}$O$_5$N$_2$S = 514.1562, found 514.1560.
Reagents employed: Krapcho product 1.155d (0.050 g, 0.097 mmol, 1 equiv.), 0.1M SmI$_2$ in THF (3.0 mL, 0.30 mmol, 3 equiv.) HMPA (0.050 mL, 0.30 mmol, 3 equiv.) in 3 mL THF. Yielded amino alcohol 1.156d (0.033 g, 0.064 mmol, 66%) as light yellow flakes, decomposes at 94 °C; R$_f$ = 0.21 (50% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.98 (d, $J$ = 8.2 Hz, 1H), 7.72 (d, $J$ = 8.2 Hz, 2H), 7.48 (s, 1H), 7.45 (d, $J$ = 7.6 Hz, 1H), 7.32 (dd, $J$ = 8.2, 8.2, 1.2 Hz, 1H), 7.22 (d, $J$ = 8.2 Hz, 2H), 7.20 (dd, $J$ = 8.2, 8.2, 1.2 Hz, 1H), 7.08-7.05 (m, 2H), 6.73 (ddd, $J$ = 8.2, 7.6, 1.2 Hz, 1H), 6.40 (d, $J$ = 7.6 Hz, 1H), 5.84 (d, $J$ = 11.7 Hz, 1H), 5.53 (d, $J$ = 1.8 Hz, 1H), 5.35 (d, $J$ = 1.8 Hz, 1H), 4.64 (dd, $J$ = 11.1, 4.7 Hz, 1H), 3.87-3.73 (br. s, 1H), 3.57, (s, 3H), 3.27 (ddd, $J$ = 11.1, 4.7, 4.7 Hz, 1H), 2.46-2.41 (m, 1H), 2.35 (ddd, $J$ = 14.1, 4.1, 4.1 Hz 1H), 2.34 (s, 3H) 1.77 (br. s, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): 172.97, 152.84, 145.08, 135.33, 135.09, 134.33, 130.00, 129.89, 129.13, 128.91, 126.78, 125.23, 123.47, 123.41, 122.84, 121.36, 120.06, 119.88, 118.00, 116.17, 113.80, 75.68, 51.65, 48.84, 48.55, 33.47, 21.54; IR (thin film, cm$^{-1}$): 3746, 3547, 3411, 2953, 2926, 2855, 1734, 1600, 1482, 1457, 1448, 1436, 1369, 1307, 1282, 1214, 1189, 1175, 1135 ,1123, 1091, 1032, 1019, 982, 913, 813, 748, 704, 688; HRMS calc’d for C$_{29}$H$_{28}$O$_5$N$_2$S = 516.1719, found 516.1725.

Reagents employed: Amino alcohol 1.156d (30 mg, 0.050 mmol, 1 equiv.), toluene sulfonic acid monohydrate (~1 mg, 5 µmol, 10 mol %) in 1.2 mL benzene. Yielded pyrrolo[1,2-a]indole 1.161 (15 mg, 0.030 mmol, 56%) as small white cubes, decomposes at 184 °C; R$_f$ = 0.30 (30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.02 (d, $J$ = 8.2 Hz, 1H), 7.68 (d, $J$ = 8.2 Hz, 2H), 7.50 (d, $J$ = 7.8 Hz, 1H), 7.32 (dd, $J$ = 7.8, 7.8 Hz, 1H), 7.31 (s, 1H), 7.25-7.23 (m, 3H), 7.15, (dd, $J$ = 8.2, 8.2 Hz, 1H), 7.03 (dd, $J$ = 7.0, 7.0 Hz, 1H), 6.82 (ddd, $J$ = 7.8, 7.8, 1.2 Hz, 1H), 6.54 (d, $J$ = 8.2 Hz, 1H), 5.91 (d, $J$ = 5.9 Hz, 1H), 3.83-3.79 (m, 1H), 3.76 (s, 3H), 3.46-3.32 (m, 2H), 2.39 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$):
Reagents employed: 2-Iodonitrobenzene (2.07 g, 8.30 mmol, 1.3 equiv.), furfural (0.614 g, 6.39 mmol, 1 equiv.), zinc dust (1.25 g, 19.2 mmol, 3 equiv.), acetic acid (2.30 mL, 368.3 mmol, 6 equiv.) in 100 mL 95% ethanol. Yielded nitrone 1.136e (1.26 g, 4.02 mmol, 63%) as transparent yellow prisms; decomposes at 94 °C; R_f = 0.45 (50% ethyl acetate in hexanes); \(^1\)H NMR (600 MHz, CDCl₃): δ = 7.95 (d, \(J = 2.9\) Hz, 1H), 7.84 (d, \(J = 7.6\) Hz, 1H), 7.67 (s, 1H), 7.53 (s, 1H), 7.44 (d, \(J = 7.6\) Hz, 1H), 7.38 (dd, \(J = 7.6, 7.6\), 1H), 7.09 (dd, \(J = 7.6, 7.6, 1H\), 6.59 (s, 1H); \(^{13}\)C NMR (150 MHz, CDCl₃): δ = 150.5, 146.3, 144.5, 140.0, 130.7, 129.0, 128.4, 124.9, 116.4, 112.4, 90.3; IR (thin film, cm\(^{-1}\)): 3145, 3113, 3067, 1582, 1479, 1461, 1439, 1390, 1368, 1269, 1244, 1147, 1117, 1088, 1037, 1021, 1010, 888, 875, 777, 750, 712, 653; HRMS calc’d for C₁₁H₆O₂NI = 312.9600, found 312.9590.

Reagents employed: Nitrone 1.136e (0.850 g, 2.72 mmol, 1.3 equiv.), vinyl cyclopropane 1.76 (385 mg, 2.09 mmol, 1 equiv.), Yb(OTf)₃:xH₂O (130 mg, 0.209 mmol, 10 mol%) in 20 mL dichloromethane. Yielded tetrahydro-1,2-oxazine 1.153e (0.997 g, 2.00 mmol, 96%) as a deep yellow foam; R_f = 0.48 (30% ethyl acetate in hexanes);

\(^1\)H NMR (400 MHz, CDCl₃): δ = See spectra on page 195.

\(^{13}\)C NMR (100 MHz, CDCl₃): δ = See spectra on page 195.
IR (thin film, cm⁻¹): 2998, 2953, 1745, 1645, 1580, 1465, 1435, 1266, 1151, 1085, 1017, 991, 932, 905, 867, 807, 748; HRMS calc’d for C₂₀H₂₀O₆NI = 497.0332, found 497.0325.

Reagents employed: tetrahydro-1,2-oxazine 1.153e (0.997 g, 2.01 mmol, 1 equiv.), Pd(PPh₃)₄ (232 mg, 0.201 mmol, 10%), triethylamine (0.84 mL, 6.01 mmol, 3 equiv.) in 15 mL acetonitrile. Yielded compound 1.154e (0.542 g, 1.47 mmol, 73%) as a light orange foam; Rf = 0.38 (30% ethyl acetate in hexanes); ¹H NMR (400 MHz, CDCl₃): δ = 7.66 (dt, J = 8.0, 0.8 Hz, 1H), 7.39 (m, 1H), 7.28 (t, J = 8.0 Hz,1H), 7.13-7.18 (m, 2H), 6.59 (dd, J = 3.4, 0.8 Hz, 1H), 6.40-6.39 (m, 1H), 5.75 (s, 1H), 5.49 (s, 1H), 5.05 (s, 1H), 4.91 (d, J = 6.4 Hz, 1H), 3.48 (s, 3H), 3.25 (dd, J = 14.6, 6.2 Hz, 1H), 3.22 (s, 3H), 2.71 (dt, J = 14.6, 1.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 168.8, 168.6, 151.6, 145.1, 141.7, 137.9, 129.0, 125.2, 124.0, 122.6, 122.4, 110.6, 109.2, 107.8, 72.1, 61.8, 53.0, 52.9, 50.2, 30.8; IR (thin film, cm⁻¹): 3151, 3124, 3084, 2998, 2953, 1826, 1738, 1651, 1636, 1456, 1434, 1255, 1203, 1182, 1078, 1023, 976, 920, 913, 882, 802, 758; HRMS calc’d for C₂₀H₁₉O₆N = 369.1212, found 379.1209.

Reagents employed: Heck product 1.154e (0.160 g, 0.433 mmol, 1 equiv.), lithium chloride (0.092 g, 2.17 mmol, 5 equiv.) in 8 mL damp dimethylsulfoxide. Yielded compound 1.155e (0.078 g, 0.245 mmol, 58%) 5:2 mixture of diastereomers as a viscous yellow film; Rf = 0.38 (30% ethyl acetate in hexanes); ¹H NMR (600 MHz, CDCl₃): major isomer representative peaks δ = 7.76 (dd, J = 8.2, 1.2 Hz, 1H), 7.39 (m, 1H), 7.29 (dd, J = 8.2, 1.8 Hz, 1H), 7.17 (dd, J = 7.6, 1.2 Hz, 1H), 7.10 (dd, J = 8.2, 1.2 Hz, 1H), 6.59 (d, J = 3.5 Hz, 1H), 6.50 (dd, J = 3.5, 1.8 Hz, 1H), 5.80 (s, 1H), 5.01 (s, 1H), 4.87 (d, J = 5.3 Hz, 1H), 4.76 (d, J = 5.3 Hz, 1H), 3.59 (s, 3H), 3.12 (ddd, J = 14.0, 8.8, 4.1 Hz, 1H), 2.77 (ddd, J = 13.5, 5.3, 5.3 Hz, 1H), 1.97 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): For the diastereomeric mixture δ = 172.7, 172.5, 154.0, 153.7, 151.2
(2 signals coincide), 146.2, 144.8, 141.9, 141.7, 138.8, 138.4, 129.0, 128.9, 125.7, 125.3, 124.4, 123.5, 122.8, 122.4, 122.0, 110.5, 109.0, 107.9, 107.2, 107.0, 73.7, 72.1, 62.5, 62.0, 52.0, 51.8, 36.04, 32.4, 29.3, 27.1; IR (thin film, cm$^{-1}$): 3119, 3071, 2951, 2852, 1738, 1617, 1601, 1547, 1456, 1437, 1363, 1342, 1321, 1305, 1255, 1242, 1206, 1175, 1147, 1130, 1104, 1078, 1055, 1007, 973, 948, 918, 902, 885, 808, 775; HRMS calc’d for C$_{18}$H$_{17}$O$_4$N = 311.1158, found 311.1169.

Reagents employed: Krapcho product 1.155e (0.075 g, 0.24 mmol, 1 equiv.), 0.1M SmI$_2$ in THF (7.2 mL, 0.72 mmol, 3 equiv.), HMPA (0.13 mL, 0.72 mmol, 3 equiv.) in 3 mL THF. Yielded amino alcohol 1.156e (0.045 g, 0.14 mmol, 59%) as a clear viscous film; R$_f$ = 0.16 (30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.36 (d, $J$ = 2.0 Hz, 1H), 7.09 (ddd, $J$ = 8.2, 8.2, 1.6 Hz, 1H), 7.03 (dd, $J$ = 7.4, 1.6 Hz, 1H), 6.72 (ddd, $J$ = 7.4, 7.4, 1.2 Hz, 1H). 6.52 (d, $J$ = 8.2, 1.2 Hz, 1H), 6.30 (dd, $J$ = 3.1, 1.6 Hz, 1H), 6.16 (d, $J$ = 3.1 Hz, 1H), 5.62 (d, $J$ = 11.7, 1H), 5.50 (d, $J$ = 2.0 Hz, 1H), 5.31 (d, $J$ = 2.0 Hz, 1H), 4.60 (m, 1H), 3.98 (br. s, 1H), 3.64 (s, 3H), 3.17 (ddd, $J$ = 11.3, 4.7, 4.7 Hz, 1H), 2.32 (m, 2H), 1.83 (d, $J$ = 5.5 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 172.9, 154.0, 152.5, 144.7, 142.1, 134.1, 128.9, 121.6, 119.8, 118.1, 116.4, 110.3, 106.5, 75.6, 51.7, 50.6, 48.7, 33.6; IR (thin film, cm$^{-1}$): 3533, 3405, 3015, 2928, 2855, 1732, 1631, 1602, 1574, 1484, 1435, 1415, 1367, 1316, 1295, 1240, 1199, 1169, 1132, 1106, 1091, 1078, 1032, 922, 849, 808, 747; HRMS calc’d for C$_{18}$H$_{19}$O$_4$N = 313.1314, found 313.1314.

Reagents employed: Amino alcohol 1.156e (30 mg, 0.096 mmol, 1 equiv.), toluene sulfonic acid monohydrate (~2 mg, 10 µmol, 10 mol %) in 1 mL benzene. Yielded pyrrolo[1,2-$a$]indole 1.162 (0.022 g, 0.076 mmol, 79%) as a clear viscous film; R$_f$ = 0.48 (30% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.48 (d, $J$ = 7.6 Hz, 1H), 7.39 (m, 1H), 7.05 (ddd, $J$ = 8.2, 8.2, 1.2 Hz, 1H), 7.02 (ddd, $J$ = 8.2, 8.2, 1.2 Hz, 1H), 6.94, (d, $J$ = 8.2 Hz, 1H), 6.36 (m, 2H), 5.78 (d, $J$ = 5.9 Hz, 1H),
3.96 (m, 1H), 3.77 (s, 3H), 3.45 (dd, \( J = 15.8, 7.9 \) Hz, 1H) \( 3.31 (dd, J = 15.8, 7.9 \) Hz, 1H) \( 2.27 \) (s, 3H); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta = 172.6, 151.4, 143.0, 137.9, 133.4, 132.3, 120.6, 118.9, 118.5, 110.4, 108.5, 101.8, 56.4, 52.6, 52.5, 26.5, 8.8 \); IR (thin film, cm\(^{-1}\)): 3052, 2953, 2922, 2859, 1739, 1622, 1479, 1459, 1440, 1344, 1327, 1265, 1230, 1214, 1196, 1174, 1073, 1011, 937, 814, 739; HRMS calc’d for C\(_{18}\)H\(_{17}\)O\(_3\)N = 295.1208, found 295.1199

Section 1.8: References

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Chapter 2: Copper Catalyzed Malonyl Carbenoid Insertions into Indoles

Chapter two describes the development of group methodology in the synthesis of malonyl indoles through the reaction of dimethyl diazomalonate with indoles of varying substitution. A short overview of diverse indole functionalization methods will be presented, focusing on relatively new developments in this field of research. The general structure and reactivity of carbenes follows, with examples of their reactivity with indoles. The research presented in this chapter (Section 2.4) was carried out by myself alone, with the results published in a peer-reviewed journal. Reproduced in part with permission from Johansen, M. B.; Kerr, M. A. Org. Lett. 2010, 12, 4956-4959. Copyright 2010 American Chemical Society.

Section 2.1: Introduction to Methods for Indole Functionalization
Section 2.1.1: The Importance of Indole Derivatives

The bicyclic aromatic nitrogen heterocycle indole 2.1 is arguably the most ubiquitous nitrogen heterocycle (Figure 2.1). Virtually all proteins contain indole through incorporation of the essential amino acid tryptophan 2.2 (Figure 2.2). Other biological systems rely on indole based compounds such as serotonin 2.3, which is an important neurotransmitter, and indole-3-acetic acid 2.4, which acts as a growth hormone in plants. Indole derivatives have also found broad applications in pharmacy (Figure 2.3). In the 1950’s the alkaloid reserpine 2.6 was introduced as one of the first drugs for the treatment
of anxiety and mental disorders, and the 1960’s saw the introduction of the antitumor compound vincristine 2.5. More recently the synthetic indole derivatives sumatriptan 2.8 and Cialis 2.7 have been used for the treatments of migraine headaches and erectile dysfunction, respectively. Notorious indole compounds include the hallucinogenic indole psilocybin 2.10 (the active ingredient in “magic mushrooms”) and the illegal drug lysergic acid diethylamide (LSD) 2.9. One of the most historically interesting indole derived natural products is the highly poisonous alkaloid strychnine 2.11, which has been implicated in the deaths of Alexander the Great and famous blues guitarist Robert
Johnson, and served as the *modus operandi* of 19th century serial killer Thomas Neil Cream (Figure 2.4).\(^{3-5}\)

\[ \text{LSD 2.9} \quad \text{psilocybin 2.10} \quad \text{strychnine 2.11} \]

**Figure 2.4** – Selected Notorious Indoles

Given the broad spectrum of applications of diverse indole compounds, significant efforts have been directed toward the development of efficient synthetic protocols for their preparation and functionalization. In general, there are two different approaches to accomplish this; the first being through the direct synthesis of the indole heterocycle with functionalization pre-installed in the starting materials, and the second is through the elaboration of the indole nucleus by chemical transformation. The latter method will be the focus of the next section.

**Section 2.1.2: Direct Functionalization of Indoles**

Indole is typically described as a \(\pi\)-excessive aromatic heterocyclic (Scheme 2.1).\(^6\) This is a consequence of the nitrogen atom donating an electron pair to the \(\pi\)-system of the compound, making indole an electron rich aromatic and rendering it susceptible to electrophilic substitution reactions and oxidations. Indole is most reactive towards electrophiles at the 3-position, and the proton on the nitrogen atom is the most
acidic. Though indole is electron rich, direct substitution of the benzenoid portion of the molecule remains difficult, without prior activation (e.g. such as a halide or triflate enabling cross-coupling reactions). In rare cases where the 1-, 2-, and 3-positions all bear substitution, direct functionalization of the benzenoid portion can be made possible. The chemistry of indole is so extensive that a full discussion of all modes of indole functionalization is beyond the scope of this thesis. As such, only a short selection of relatively new methods for indole derivatization will be presented, with a focus on transition metal mediated processes which do not require preactivation of the indole nucleus.

Section 2.1.3: N-tert-Prenylation of Indoles

During synthetic studies toward stephacidin A 2.12 the Baran group had occasion to attempt the installation of a prenyl group at the C2 position of a N-Boc protected tryptophan methyl ester 2.13 (Scheme 2.2). Though the reaction did not proceed as planned, small quantities of the N1-prenylated indole 2.16 was observed. Recognizing the potential of such a transformation, and since no methods for the direct N-prenylation of indoles existed, the Baran group chose to optimize this reaction and subsequently developed a methodology (Scheme 2.3). The optimal conditions were found to be under palladium catalysis (either Pd(OAc)$_2$ or [Pd$_2$(dba)$_3$]-CHCl$_3$) with silver(I) and copper(II) acetate cooxidants and 30 equivalents of 2-methyl-2-butene 2.14. Intermediates which
Scheme 2.2 – Baran Group’s Studies Toward Stephacidin A

contained the $N$-prenyl moiety, and had been used in total synthesis projects by other groups, were chosen to demonstrate the utility of this transformation. This methodology allowed access to these targets in comparable or better yields using this single step, whereas the previous routes required four or more steps. The mild reaction conditions afforded broad functional group tolerance and gram scale preparations were also demonstrated. The only apparent limitations were that indoles required substitution at the 3-position, and where 2-substitution was present the reactions required higher oxidant equivalents.

Scheme 2.3 – Direct $N$-tert-Prenylation of Indoles
Section 2.1.4: Palladium Catalyzed Indole Arylation

In an impressive display of chemoselectivity and C-H bond activation, the Fagnou group developed a palladium catalyzed cross-coupling of \( N \)-acyl indoles 2.19 (\( R^3 = \text{Ac} \)) with unactivated arenes 2.20 (Scheme 2.4).\(^8\) It was found that \( N \)-acylation of the indoles was necessary to avoid homo-coupling of the indole reacting partner, and a large excess of the arene 2.20 (~30 equiv.) was required for high conversions. The addition of both 3-nitropyridine and cesium pivolate were suspected to stabilize the catalyst and increase turnover. Up to 13.8:1:0.3 regioselectivity was observed for 2.21:2.22:2.23 respectively, with no homo-coupling products detected. Both electron donating and withdrawing group substitutions at C5 and C6 of the indole 2.19 were well tolerated in the reaction, but substitution on the arene 2.20 (\( R^2 \)) incurred moderate decreases in yields.

![Scheme 2.4 – Palladium Catalyzed Arylation of Indoles](image)

In a subsequent publication, the Fagnou group demonstrated that by changing both the \( N \)-acyl group to \( N \)-pivalyl (\( R^3 \)) and the oxidant from copper(II) acetate to silver(I) acetate, a complete inversion of selectivity from C3 to C2 cross coupling could be achieved.\(^9\) Indole substrates 2.19 were again well tolerated and arene substitution (\( R^2 \))
saw only moderate decreases in yields. Overall the yields for C2 arylation were higher than those observed in the first study in C3 arylation. The role of the silver salts and N-pivalyl group in determining the regiochemical outcome remains unclear, but the utility of two complementary methods for the introduction of an arene unit with high selectivity at C2 or C3 is of high merit.

Section 2.1.5: Installation of a 3-Cyano Group

Recently the Wang group disclosed a method for the direct 3-cyanation of indoles (Scheme 2.5). Potassium ferrocyanide (K₄[Fe(CN)₆]) was chosen as the cyanide source since it is safe and non-toxic in comparison to other cyanide salts. During optimization studies, the addition of potassium acetate was observed to reduce the occurrence of homo-coupling of the indole substrate, but was unnecessary when the indole 2.24 was C2 substituted. The reaction was shown to be highly sensitive to the electronic nature of the indole 2.24. Electron donating substituents at R¹, R² and R³ were generally well tolerated, whereas withdrawing groups at R¹ gave moderate yields of 2.25, and withdrawing groups at R² and R³ gave only trace amounts of the desired product. The authors also postulated a mechanism for this transformation (Scheme 2.6). It was suggested that the cyanide anion undergoes transmetallation from K₄[Fe(CN)₆] to the palladium catalyst. The catalyst could then insert in the 3-position of the indole substrate 2.24 via electrophilic

![Scheme 2.5 – 3-Cyanation of Indoles with K₄[Fe(CN)₆]](image-url)
palladation and generate the product $2.25$ through subsequent reductive elimination. Regeneration of the catalyst occurs through a redox process with the copper oxidant and/or oxygen. It was also suggested that the success of this cyanation process is due to the slow liberation of cyanide from $K_4[Fe(CN)_6]$, as other cyanide sources formed stable and inactive palladium cyanide complexes.

**Scheme 2.6** – Proposed Catalytic Cycle for Indole Cyanation

**Section 2.1.6: A Palladium Catalyzed Tandem Alkylation/Arylation of Indoles**

The Lautens group has recently disclosed a synthetic method to access highly functionalized 2,3-annulated indoles $2.30$ (Scheme 2.7). This reaction involved a palladium catalyzed, norbornene mediated, tandem alkylation and biaryl coupling. Close examination of the products revealed that the alkyl bromide $2.27$ and aryl iodide $2.28$ form connectivity *ortho* to the iodine position, and that the biaryl coupling occurred between the indole C2 position and the halogen position of the aryl iodide $2.28$. Though both substrates require preactivation by incorporation of a halide, two C-C bonds are formed from two C-H bonds in a one-pot tandem process. Both $n=1$ and $n=2$ bromoalkanes $2.27$ were used to generate 6 and 7 membered rings, and a variety of both
electron rich and poor substituents on the benzenoid portion of the indole 2.27 were well tolerated. Aryl iodides 2.28 all bore substitution \textit{ortho} to the iodide (R$^2$ = methyl or N-tosyl), and \textit{meta} substitution greatly reduced yields. The authors suggested that the

catalytic cycle proceeds by an analogous process to that previously described by Catellani.$^{12}$ Scheme 2.8 shows the cycle provided by the Lautens group, with oxidation
states and ligands on the catalyst removed for clarity. Oxidative insertion of the palladium catalyst into aryl iodide 2.32 leads to 2.33 which can undergo migratory insertion into norbornene 2.34. C-H bond insertion at the aryl ortho position follows to generate palladacycle 2.36. Then oxidative insertion into the alkyl bromide tethered indole 2.37 and subsequent migratory insertion forges the aryl-alkyl bond in 2.39. Reductive elimination of norbornene 2.34 and final indole C2 C-H insertion with concomitant reductive elimination provides the annulated product 2.41.

Section 2.2: Introduction to Carbenes
Section 2.2.1: Structure and Reactivity of Carbenes

Highly reactive, often transient, carbon based synthetic intermediates with abnormal valences at carbon are among the most versatile synthons in organic chemistry. Carbocations, carbanions and carbon centred radicals are all examples of abnormal carbon valences which have seen a plethora of applications in synthesis.\textsuperscript{13} Carbenes are uncharged divalent carbon derivatives with two non-bonding electrons, and are another class of abnormal valences at carbon which have seen growing interest and applications in synthetic chemistry.\textsuperscript{14-17} There are many factors that contribute to the stability and reactivity of carbenes: the electronic nature of the substituents attached to carbon, the electronic spin state of the carbene and whether the carbene is bound to a transition metal. The orbital hybridization and electronic configurations of carbenes are also influenced by the carbene geometry (Figure 2.5).
A linear carbene is believed to possess \( sp \) hybridized orbitals on carbon, with two degenerate non-bonding \( p \) orbitals (\( p_x \) and \( p_y \)). When the carbene adopts a bent geometry, the two non-bonding orbitals are no longer degenerate and \( sp^2 \) hybridization is invoked. One \( p \) orbital remains largely unaltered (\( p_x \)) and the other is stabilized by obtaining some \( s \) character (\( \sigma \)). Though there are examples of linear \( sp \) hybridized carbenes, most carbenes have a bent geometry and are considered to be \( sp^2 \) hybridized with frontier orbitals \( \sigma \) and \( p_x \).

With \( sp^2 \) hybridization, four different electronic configurations of the non-bonding electrons can occur (Figure 2.6). A triplet state occurs when both orbitals contain a single electron and their spins are parallel. Triplet state carbenes occur when there is a small energy gap between the \( \sigma \) and \( p_x \) orbitals and typically behave as diradicals. Three different singlet state electronic configurations are also possible. There

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**Figure 2.6** – Carbene Electronic Configurations
are two ground state spin paired configurations, with spin paired occupancy of the \( \sigma \) orbital being more stable, and the final configuration is an excited singlet state.

Carbenes can be further stabilized when bound to transition metals. This stabilization can result in decreased reactivity and consequently increased reaction selectivity, making carbene reactions more predictable and synthetically useful. There are two main classifications used to describe carbene-metal complexes (Figure 2.7). Fischer type carbenes are best described as donor-acceptor complexes with singlet carbene to metal \( \sigma \) donation, and metal to carbene \( \pi \) back bonding. Fischer type complexes are generally observed with low valent metals and carbenes with \( \sigma \) donor groups attached to the central carbon. A covalent bonding mode is used to describe the bonding of Schrock type carbene-metal complex. Covalent bonding arises through the interaction of a triplet carbene and a triplet metal fragment, and is usually observed with higher oxidation state metals and alkyl substituted carbenes. Though these two classifications can be useful in describing carbene-metal complexes, there are many species which do not necessarily fall into either category.\(^{18}\)

Many methods for the generation of carbenes have been explored and developed, such as the base induced formation of dihalocarbenes from haloforms, elimination of
tosylhydrazones as in the Bamford-Stevens reaction, and through relatively new methods such as iodonium ylide decomposition, but diazo compounds remain the most prevalent carbene progenitors in organic synthesis. Organic diazo compounds are transformed into reactive carbene intermediates by the expulsion of nitrogen gas, which has been observed to occur through thermal and photochemical conditions (Scheme 2.9).

Scheme 2.9 – Carbene Generation through Diazo Decomposition

Early investigations revealed that copper metal and copper salts also induced diazo decomposition. This led to the development of a variety of catalytic systems capable of inducing carbene transformations, which are generally superior to the uncatalyzed methods which require harsher reaction conditions. A typical metal mediated catalytic cycle is shown in scheme 2.10.

Scheme 2.10 – Tranisition Metal Catalyzed Diazo Decomposition
Electrophilic addition of the metal catalyst 2.45 to the diazo compound 2.43 forms zwitterionic complex 2.46. Nitrogen gas explosion forms the metal stabilized carbene 2.47. Introduction of an electron rich substrate 2.48 allows for transfer of the electrophillic carbene, providing product 2.49 and regeneration of the catalyst 2.45. Important factors in transition metal catalyzed carbene formation include: a) the electrophilicity of the metal catalyst, b) stability of the diazo carbene precursor, c) free coordination sites on the metal, and d) ability of the metal to stabilize the bound carbene. Typically late transition metals such as copper, cobalt, iron, palladium, ruthenium and rhodium have seen widespread applications in carbene forming reactions from diazo compounds.

Typically late transition metals such as copper, cobalt, iron, palladium, ruthenium and rhodium have seen widespread applications in carbene forming reactions from diazo compounds.

A general reactivity trend for diazo compounds towards decomposition and carbene formation is shown in figure 2.8. Alkyl diazo compounds 2.50 are highly reactive and often difficult to prepare and isolate, and some are even known to be explosive, and therefore they are often prepared in situ. Conjugation with an aryl or carbonyl group (2.51 and 2.52) further imparts stability to diazo compounds, as does branching at the carbene carbon 2.53. Additional conjugation and electron withdrawing groups have been shown to stabilize diazo compounds even further.

The reactivity of metal bound carbenes are generally electrophilic in nature and best rationalized by the two resonance structures of 2.47; as a formal metal carbene and 2.56, a metal stabilized carbocation (Scheme 2.11). Chemical processes with selectivities...
that better resemble those of free carbenes 2.44, as generated under thermal or photochemical processes, are often rationalized by dissociation of the metal-carbene complex 2.56, but this is not commonly observed in transition metal catalyzed reactions.\textsuperscript{20} Ligands on the metal centre and the substitution pattern on the carbene carbon can also greatly affect the electrophilic nature of the carbene.

\[
\begin{aligned}
&\text{L}_n\text{M} \rightleftharpoons \text{L}_n\text{M} \\
&\text{2.47} \quad \text{R}^1 \quad \text{R}^2
\end{aligned}
\]

\[
\begin{aligned}
&\text{L}_n\text{M} \rightleftharpoons \text{L}_n\text{M} \\
&\text{2.56} \quad \text{R}^1 \quad \text{R}^2
\end{aligned}
\]

\[
\begin{aligned}
&\text{M} \quad \text{L}_n\text{M} \rightleftharpoons \text{L}_n\text{M} \\
&\text{2.45} \quad \text{R}^1 \quad \text{R}^2
\end{aligned}
\]

\[
\begin{aligned}
&\text{R}^1 \quad \text{R}^2
\end{aligned}
\]

\textbf{Scheme 2.11 – Metal Stabilized Carbenes}

Carbenes typically react with electron rich substrates and have found applications in a variety of synthetic processes. Conventional carbene reactions include cyclopropanation, dimerization, C-H and X-H insertions (X = heteroatom) and ylide formation (Scheme 2.12). The reactive nature of carbenes with electron rich substrates, and the versatile synthetic approaches to their varied diazo precursors, has established the use of carbenes as effective methods for the derivatization of heterocycles.\textsuperscript{24,25} The next section will provide an overview of the reactions of carbenes generated from diazo compounds and their use in the functionalization of indoles.
Scheme 2.12 – Examples of Typical Carbene Reactions
Section 2.3: Functionalization of Indoles with Diazo Compounds
Section 2.3.1: Classic Reactions of Indoles with Diazo Compounds

The early studies on the metal catalyzed reactions of diazo-decomposition generated carbenes with indoles, were generally focused on exploring the reactive nature of the transient carbenes and determining the identity of the products. In 1935, Jackson and Manske published an account on the reactions of ethyl diazoacetate 2.58 with indole

![Scheme 2.13](image)

**Scheme 2.13** – Early Investigations in Reactions of Diazo Esters with Indoles

They found that by heating indole 2.1 and ethyl diazoacetate 2.58 in the presence of trace copper powder, indole-3-acetic acid ethyl ester 2.70 was formed as the major product. When the amount of ethyl diazoacetate 2.58 was increased to far exceed the equivalence of indole 2.1, 1,3-indole diethyl acetate 2.71 was identified as a new reaction product. Jackson and Manske also demonstrated the addition of a diethyl succinate moiety to indole from the diazo precursor 2.72, providing an early insight in the applicability of diazo compounds in the derivatization of indoles.
A more systematic study of the reactions of ethyl diazoacetate \textit{2.58} and \(N\)-aryloylated indoles \textit{2.74} was undertaken by Welstead and co-workers in 1974 (Scheme 2.14).\textsuperscript{27} These reactions were found to proceed under copper(I) cyanide catalysis to afford the 2,3-cyclopropanated products \textit{2.75}. The deactivating nature of the aroyl group was suggested to prevent the cyclopropane ring-opening rearrangement that had been previously proposed. Only methyl substitution at \(R^2\) was screened, and \(R^1\) was shown to tolerate 4- and 5-methoxy and 5-chloro groups. Substitution at \(R^3\) was well tolerated across a variety of \textit{2.74} substrates. Yields of \textit{2.75} were low on average and typically around 30\%.

![Scheme 2.14 – Reactions of Ethyl Diazoacetate with \(N\)-Aroyl Indoles](image)

The Wenkert group published a subsequent study that examined the reaction products for different substitution at nitrogen on indoles (Scheme 2.15).\textsuperscript{28} \(N\)-Methyl (\textit{2.76} and \textit{2.77}), \(N\)-acetyl (\textit{2.78}) and \(N\)-carbomethoxy (\textit{2.79} and \textit{2.80}) indole substrates were screened in the copper bronze catalyzed reaction with ethyl diazoacetate \textit{2.58}. The reactions with methyl substitution on the nitrogen of the indole proceeded smoothly at room temperature to provide the ethyl acetate derivatives \textit{2.81} and \textit{2.82}. When \(N\)-methyl skatole \textit{2.77} was subjected to the reaction, the acetate was incorporated at the 2-position of the indole to provide \textit{2.82}, albeit in poor yield. Deactivation of the indole by incorporation of an electron withdrawing group on nitrogen (\textit{2.78-2.80}), required higher reaction temperatures. The carbenoid insertion products of these reactions were the
2,3-cyclopropanated indoles 2.83-2.85, which was suggestive of similar cyclopropane intermediates in the preceding reactions, but in these cases the electron withdrawing nature of the N-substitution in 2.78-2.80 prohibited cyclopropane ring opening and re-aromatization of the products.

Scheme 2.15 – Effects of N-Substitution in Reactions of Ethyl Diazooacetate with Indoles

Section 2.3.2: Recent Advances in Derivatization of Indoles with Diazoc Compounds

Diazo derived carbene insertions into indoles have advanced significantly since the seminal investigations in ethyl diazoacetate 2.58 reactivity. The invention of mild and simple diazo transfer reagents allow access to increasingly more complex diazo
compounds, and new catalyst systems are being used in the functionalization of indole derivatives, generating intricate indole products often under very mild conditions.\textsuperscript{20,29}

In 2004, the Cuevas-Yañez group from Mexico City disclosed the intramolecular annulation reactions of a series of diazo-tethered indoles (Scheme 2.16).\textsuperscript{30} α-Diazo-β-ketoesters and α-diazoketones tethered to the 3-position of indole underwent rhodium catalyzed carbene formation and subsequent insertion into the 2-position of the indole heterocyclic forging a new ring in the same process. Synthesis of both 5- and 6-membered rings was demonstrated, with the α-diazoketone precursors (2.90 and 2.92) outperforming the α-diazo-β-ketoesters (2.86 and 2.88) in the annulation reactions.

\textbf{Scheme 2.16} – Intramolecular Annulations of Diazo Substituted Indoles
A related study in intramolecular carbene-indole annulations was presented by the Hansen group in 2009 (Scheme 2.17). In their system they investigated the intramolecular carbene insertions of an α-diazo-β-ketoester tethered to the C4 position of indole 2.94. This work demonstrated a remarkable change in regioselectivity for carbene insertion from C3 to C5 when the catalyst was switched from palladium(II) acetate to dirhodium(II) tetraacetate generating annulated indoles 2.95 and 2.97 respectively. The rationale given for the regiochemical switch was based on the increased kinetics generally observed for Rh$_2$(OAc)$_4$ catalyzed systems, thus favouring the formation of 5-membered rings, whereas the palladium catalyzed system likely favoured addition at the more electron rich position at C3 forming 2.95.

Scheme 2.17 – Inversion of Regioselectivity by Changing the Catalyst

The intermolecular reactions of diazo derived carbenes and indoles have also come to the forefront of synthetic methodology in recent years. The Yadav group published a comparative study on indole alkylation with α-diazo carbonyl compounds catalyzed by indium tribromide or copper(II) triflate (Scheme 2.18). Only the 3-alkylated product 2.100 was observed with a variety of terminal diazo ketones and
esters 2.99, and product yields ranged from good to excellent. The indium tribromide
catalyst proved slightly superior to the copper system by an average of about 5%. Only
electron rich indole substrates 2.98 were presented, with a single indole substrate 2.98
example with a C2 methyl substitution.

Scheme 2.18 – Indium Tribromide Catalyzed Indole Functionalization

The Davies group has had a long standing interest in the investigations of diazo
decomposition generated metal stabilized carbenes and their applications in synthesis.24
Recent developments from their group include the applications of vinyl substituted diazo
compounds in synthesis, which can display interesting vinylogous carbene reactivities. In
the first study, a [3+2] annulation of indoles 2.101 with aryl substituted trans-vinyl
diazoacetates 2.102 was discussed (Scheme 2.19).33 The dirhodium catalyst with the
proline derived S-DOSP ligands 2.104 promoted the annulation reactions in good yields
and with high enantioselectivities to provide the 2,3-cyclopentannulated indoles 2.103.
The regiochemical outcome of the reaction was highly dependent on the substitution
patterns at C2 and C3 of the indole substrates 2.101. When R³ = methyl and R⁴ = H the
product with the aryl group vicinal to R³ (2.103) is formed. Interestingly, the inverse
substitution pattern (R³ = H and R⁴ = methyl) switches the regiochemistry such that the
aryl group becomes vicinal to R⁴ and sits in a trans disposition to R⁴ (not shown). The
reaction is proposed to proceed through the zwitterionic intermediate 2.105, which
collapses to release the rhodium catalyst and furnish the cyclopentannulated product

**Scheme 2.19** – [3+2] Annulations with Vinyl Diazo Compounds and Indoles

In a second study, the reactions of methyl substituted *cis*-vinyl diazoacetates **2.108** with 2-substituted indoles **2.107** was examined (Scheme 2.20). The sterically encumbered dirhodium esp **2.110** catalyst induced C3 alkylation of the vinyl diazoacetates **2.108** at the vinylogous position to give the products **2.109** in modest to good yields. When *trans*-vinyl diazoacetates **2.111** were screened in the reaction only alkylation at the carbon bearing the diazo functionality was observed. This was rationalized by the facile *s-cis* **2.111** to *s-trans* **2.112** equilibrium, whereas the *cis*-vinyl diazoacetates favour an *s-trans* **2.114** carbenoid geometry, which in turn promotes vinylogous reactivity. NH, *N*-methyl, *N*-benzyl and *N*-TIPS substitution of **2.107** (R²) was examined, as was electron rich substitution at C4 and C5. Substitution at C2 was typically methyl, with R³ = H and R³ = CH₂OTBS providing markedly decreased yields.
Overall, both vinyl carbene methodologies provide interesting techniques to introduce large degrees of functionality to indole substrates in single transformations and under very mild conditions.

A study on the indole insertion products of donor-acceptor substituted α-diazoesters 2.115 has just recently been presented by the Yu group (Scheme 2.21).\textsuperscript{35} They found that under ruthenium catalysis, 2-alkylated indoles 2.116 could be generated from indoles 2.17 and α-diazoesters 2.115. This methodology stands apart from the typical C3 or NH insertion products generally observed in carbenoid reactivity with indoles (\textit{vide supra}). The reaction proceeded smoothly at room temperature in dichloromethane for a wide range of indole substrates 2.17 and aryl diazoesters 2.115. Incorporation of heteroaromatic rings on the diazoester 2.115 was also demonstrated (i.e. 3-indolyl and 3-thiophenyl) but were less successful than phenyl substitutents. Likewise
3-substituted indoles 2.17 were also examined, but led to decreased product yields. Interestingly, when an N-methyl indole substrate was used in the reaction, the C3 insertion product was observed in 52% yield. To probe the mechanism for this C2 selective reaction, kinetic isotope effects were examined, but the small values observed were not compatible with direct C-H insertion, and the authors suggest cyclopropyl indolines 2.117 as intermediates followed by selective cyclopropyl ring opening at C3 and indole re-aromatization. The factors that effect C3-selective ring opening still remain unclear, but the usefulness of this method is largely apparent as direct incorporation of functionality at C2 remains synthetically challenging, especially with N1 and C3 unsubstituted substrates.

Scheme 2.21 – C2 Selective Ruthenium Catalyzed Carbene Insertions

The Qin group has developed a cascade carbene alkylation and aza-annulation strategy for the synthesis of pyrroloindolines 2.119 and 2.122 (Scheme 2.22). When tryptamine 2.118 or tryptophan 2.120 derivatives are treated with ethyl diazoacetate 2.58 under copper(I) triflate catalysis the pyrroloindoline products 2.119 and 2.122 resulted respectively. The reaction is proposed to proceed through indole cyclopropanation followed by cyclopropyl ring opening and subsequent annulation of the tethered amine to
provide the products. For the tryptamine derivatives 2.119, the electronic nature of R\textsuperscript{1} and R\textsuperscript{2} heavily determined the reaction course. It was found that both electron rich R\textsuperscript{1} groups (e.g. Me and Bn) and electron withdrawing groups at R\textsuperscript{2} (Ac, Tf and Ns) were necessary for the reaction to proceed. The tryptophan derived cyclic carbamates 2.120 were found to be superior substrates for the cascade alkylation annulation reaction with various diazoacetates 2.121. Again electron rich R\textsuperscript{1} groups (Me or Bn) were a requisite for the cascade to proceed, and both ethyl and t-butyl diazo esters were screened, with t-butyl diazo esters providing superior diastereoselectivity. Though optical purity was maintained in the products, the methodology was limited to tryptophan derivatives 2.120 with substitution only varied at R\textsuperscript{1} and R\textsuperscript{2}. The utility of this cascade was demonstrated in the total syntheses of the complex indole alkaloids (±)-vincorine 2.123, (±)-minfiensine 2.124 and (−)-ardeemin 2.125 (Figure 2.9).\textsuperscript{37-39}
Section 2.3.3: Diazomalonate Carbenoid Insertions into Indoles

During synthetic studies on the annulation reactions of indoles and cyclopropane diesters (see Section 1.2.3, Scheme 1.8), Romelo Gibe of the Kerr group had occasion to attempt the preparation of the indole tethered 1,1-cyclopropanediester 2.128 (Scheme 2.23). A rhodium catalyzed dimethyl malonyl carbenoid insertion on the olefin of 2.126 was attempted, in an effort to generate the cyclopropyl moiety of 2.128. Upon consumption of diazomalonate 2.127 no cyclopropane product 2.128 was observed, but instead the C2 malonyl substituted indole 2.129 was generated as the major product, albeit in low yield. Immediately recognizing the potential for such a transformation, and
following moderate reaction optimization, the reaction was developed into a methodology and the scope was evaluated with a number of readily accessible indole substrates. Figure 2.10 shows the products derived from indole substrates which did not bear substitution on C2 or C3 of the indoles. In all cases the malonyl moiety is incorporated at the C3 position. Both electron withdrawing and donating groups were well tolerated in the 5-position of the substrates (2.134 and 2.135 respectively), to allow access to the malonyl indole products in high yields. N-Tosyl substitution (2.132) resulted in a low yield, which is in accord with the reduced reactivities generally observed for electron poor substrates in reactions with electrophilic carbenes (vide supra).

![Products from 2,3-Unsubstituted Indole Substrates](image)

**Figure 2.10** – Products from 2,3-Unsubstituted Indole Substrates

Next, a series of 3-substituted indoles were screened in the malonyl carbenoid insertion reaction (Figure 2.11). A terminal pentene and methyl substitution at C3 of the indole substrates were subjected to the reaction, with the sterically less demanding methyl group providing better results. When skatole was used as the indole reacting partner, a
mixture of C2 2.138 and NH 2.137 insertion products was obtained, stressing the need for N1 substitution. All C2 insertion products were typically lower yielding than both 2,3-unsubstituted (Figure 2.10) and 2-substituted indole substrates (Figure 2.12).

For C2 substitution, again carbenoid insertion at the 3-position prevailed, with methyl, phenyl and methoxy ether C2 substitution patterns screened. Interestingly when 2-methyl indole was employed in the reaction, NH insertion was not a competitive process and C3 insertion predominated (2.142).
To ascertain whether the carbenoid insertion would take place with 1,2,3-trisubstituted indole substrates, \(N\)-methyl tetrahydrocarbazole 2.143 was subjected to the reaction conditions (Scheme 2.24). Interestingly, carbenoid insertion did occur and the malonate moiety was incorporated at the C6 position of the benzenoid ring to provide 2.144. Currently no regiochemical explanation for this reaction has been provided.

![Scheme 2.24 – Malonyl Carbene Insertion with \(N\)-Methyl Tetrahydrocarbazole](image)

Section 2.4: Copper Catalyzed Malonly Carbenoid Insertions into Indoles

During synthetic studies toward arboflorine (see Chapter 3), we had reason to revisit the malonyl carbenoid insertions into indole, as that chemical transformation would provide access to a key synthetic intermediate. The synthetic strategy to be applied to arboflorine called for a terminally substituted 3-ethyl sidechain with a 2-malonyl indole core. As the 3-substituted indole substrates in the dirhodium(II) tetraacetate catalyzed process proved to be inferior nucleophiles in the reaction with dimethyl diazomalonate 2.127, a new reaction system required development. The results of these efforts are the focus of the next section.¹

Section 2.4.1: Results and Discussion

Section 2.4.1.1: Development of the Copper Catalyzed Malonly Carbenoid Insertions into Indoles

As was discussed in the previous section, the dirhodium(II) tetraacetate catalyzed diazomalonate decomposition and carbenoid insertion into indoles worked superbly for 2,3-unsubstituted substrates, but was not well suited for 2- or 3-substituted indole starting
materials and generally resulted in vastly decreased yields (Section 2.3.3). Since the
direct functionalization of indoles by carbenoid insertion remains an attractive method of
installing substitution on indoles, and as the direct installation of a malonate moiety into
the 2-position of a 3-substituted indole was required en route to arboflorine, we set out to
develop a new method for malonyl carbenoid insertion into indoles that would exceed the
results found in the dirhodium(II) tetraacetate catalyzed reaction developed by Romelo
Gibe.

Section 2.4.1.2: Reaction Optimization

Since the synthetic proposal for arboflorine called for a 3-substituted 2-malonyl
indole, we decided to screen conditions for the metal catalyzed dimethyl diazomalonate
\(^{2.127}\) insertion into the 2-position of \(N\)-methyl skatole \(^{2.77}\). A brief selection of these
results and reaction optimizations are presented in table 2.1. Entry 1 shows the conditions
previously developed by former Kerr group member Romelo Gibe, with a similar low
yielding result observed, though a lower ratio of dimethyl diazomalonate \(^{2.127}\) was
employed. Copper catalysts, known to promote diazo decomposition and carbene
formation, were next screened (entries 2 and 3) with no observable reaction at room
temperature.\(^{20}\) When the solvent was switched and the temperature was increased, both
copper(II) triflate and copper(II) acetylacetonate exhibited diazo decomposition
reactivity, but only copper(II) acetylacetonate showed appreciable amounts of productive
carbene insertion, and was thus chosen for further optimization. A slight decrease in
reaction temperature by changing the solvent from toluene at reflux to benzene afforded a
modest increase in 2-malonyl-\(N\)-methylskatole \(^{2.136}\). Much to our surprise, by lowering
the catalyst loading to 1% another increase in product yield was observed, at the expense
of slightly increased reaction times. Next, the ratio of dimethyl diazomalonate 2.127 to \( N \)-methylskatole 2.77 was examined. Though 2:1 indole to dimethyl diazomalonate provided the highest yield observed, a ratio of 1.5:1 was favoured for the reaction, since comparable results were obtained without the need for an extra half equivalent of indole substrate. Entry 10 represents the optimized reaction conditions for the copper catalyzed dimethyl malonyl carbenoid insertion into indoles.
**Section 2.4.1.3: Examining the Reaction Scope**

Having identified optimal conditions for malonyl carbenoid insertion into the 2-position of *N*-methylskatole 2.77, we next screened a variety of indole substrates in carbenoid insertion. Table 2.2 shows the substrates and products of 3- and 2-substituted indole starting materials. Substitution at the 3-position with methyl, TBS-protected ethanol and methyl acetate were tolerant to the reaction with good to high yields observed for carbenoid insertion (entries 1-4). It is interesting to note that both *N*-methyl and *N*-benzyl substrates 2.77 and 2.145 gave comparable results. Entry 3b was done to show that the reaction could be conducted on appreciable scale.\(^4\) Substitution at the 2 position was also well tolerated under the reaction conditions (entries 5-7). Both 2-methyl 2.151 and the more sterically demanding 2-phenyl 2.152 substrates proceeded to incorporate a 3-malonate moiety in high yield. The 2-methyl ester substrate 2.154 did not undergo the reaction in as high yield as the other substrates, which is likely due to the electron withdrawing nature of the ester.
Table 2.3 demonstrates a variety of benzenoid substituted indole substrates. Both electron withdrawing and electron donating functional groups were well tolerated in the reaction, with encorporation of the malonate in the 3-position for all products. Entry 11 represents the only outlier in the series, with a lower yield of 55%. Currently the reasons why the 5-acetoxy substrate 2.160 did not provide higher yields of 2.161 remain unclear.
The effects of N1 substitution were examined in the carbenoid insertion reaction in the following set of indole substrates (Table 2.4). As would be expected the electron withdrawing \(N\text{-}t\text{-}butyl\) carbamate 2.163 and \(N\text{-}tosyl\) 2.165 substrates gave much reduced yields in comparison to the electron rich \(N\text{-}benzyl\) substituted indole 2.166. Much to our surprise when NH indoles were subjected to the reaction conditions, appreciable yields of C3 and C2 insertion products were observed (entries 16-18) without competitive NH insertion, as was observed in the dirhodium tetraacetate catalyzed system (\textit{vide supra}).\textsuperscript{42}
Finally a 1,2,3-trimethylindole 2.170 was subjected to the carbenoid reaction conditions to ascertain whether, or with what regioselectivity, carbenoid insertion would occur when the most reactive positions of the indole were occupied (Scheme 2.25). Surprisingly we observed malonate incorporation on the C2 methyl group. It is unclear whether this reaction proceeds through cyclopropanation of the indole followed by ring-opening and rearrangement or direct CH insertion on the methyl group takes place, and accordingly, this reaction certainly warrants further study.

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We also investigated microwave irradiation conditions which also proved sufficient to promote the malonyl carbenoid insertion into indoles (Scheme 2.26). It was found that by a slight increase in temperature to 100 °C, the carbenoid insertion could be achieved with considerably reduced reaction times. A selection of indoles were subjected to the microwave irradiation conditions and the observed yields were typically in good comparison to the previously described method, with only moderate decreases observed in a few cases. Both catalyst loading and ratio of indole 2.172 to dimethyl diazomalonate 2.127 was kept consistent with the previous method.
Scheme 2.26 – Microwave Promoted Malonyl Carbene Insertions

Section 2.5: Summary and Future Work

In summary we have developed a copper catalyzed dimethyl malonyl carbenoid reaction with indoles.1 The reaction proceeded regioselectively to give the 3-malonyl indole products for 2,3-unsubstituted and 2-substituted indole starting materials and 2-malonyl indoles for 3-substituted indoles. Yields for this process compare exceptionally with the previously disclosed dirhodium tetraacetate catalyzed reaction, and yields for 2- and 3-substituted indole substrates generally exceed the rhodium system.40 With 1,2,3-trimethylindole 2.170 the carbenoid reaction proceeded in moderate yield to give the formal carbene insertion product on the 2-methyl group providing 2.171, displaying new and interesting reactivity which may be further developed. Malonyl substituted indoles have proven versatile synthetic intermediates in total synthesis (Scheme 2.27)43,44 and to fully demonstrate the utility of our new method, we plan to apply this reaction in
the synthesis of the indole alkaloid arboflorine 2.177 from 2-malonyl indole 2.148. Endeavours to this end are the focus of the following chapter.

Scheme 2.27 – Alkaloids from 2-Malonyl Indoles

Section 2.6: Experimental

**General**

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments and samples were obtained in CDCl₃ (referenced to 7.26 ppm for ¹H and 77.0 for ¹³C). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, b = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 spectrometer at 70 eV. Microwave reactions were performed in a 400 W Biotage Initiator 2.0 microwave reactor. Tetrahydrofuran (THF), benzene, dimethylformamide (DMF), toluene and dichloromethane (DCM) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Aldrich, Strem, Caledon or VWR. Reaction
progress was monitored by TLC (EM Science, silica gel 60 F\textsubscript{254}) visualizing with UV light, and the plates were developed using \( p \)-anisaldehyde or basic potassium permanganate stains. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh).

**Experimental Procedures and Compound Characterization:**

Indole starting materials were used as purchased from commercial sources. Where not available, these substrates were obtained by \( N \)-alkylation of the parent indole and confirmed by comparison to the reported data for these known compounds: \( 2.77, 2.145, 2.149, 2.151, 2.152, 2.153, 2.155, 2.156, 2.158, 2.162, 2.163, 2.165, 2.166 \).

**General Indole alkylation procedure:**

Indole substrates were synthesized using the following indole alkylation conditions: To a cooled (0 °C) solution of indole (1 equiv.) in DMF was added NaH (1.1 equivalent as 60% dispersion in paraffin oil) and kept at 0 °C for 30 minutes. 1 equivalent of iodomethane (indoles \( 2.77, 2.149, 2.151, 2.152, 2.153, 2.155, 2.156, 2.158, 2.162 \)) or benzyl bromide (indoles \( 2.145, 2.166 \)) was then added dropwise and the solution maintained at 0 °C for a further 30 minutes. The reaction was then warmed to room temperature, quenched with distilled water, transferred to a separatory funnel and diluted with diethyl ether. The aqueous layer was washed twice with diethyl ether, the organic fractions where combined and washed twice with distilled water and once with brine. The organic fraction was dried over \( \text{MgSO}_4 \) then filtered and concentrated. The crude product was purified by flash column chromatography.

\[ \text{3-(2-(\text{tert-Butyldimethylsilyloxy})ethyl)-1H-indole}^{56} \] (8.31 g, 30.2 mmol) was dissolved in 150 mL dimethyl formamide at 0 °C in a 500 mL round bottomed flask. Sodium hydride 60% dispersion in paraffin oil (1.57 g, 39.2 mmol) was then added and the solution was stirred at 0 °C for 20 minutes at which point gas evolution had ceased. Benzyl bromide (4.00 mL, 33.2 mmol) was then added dropwise via syringe and the solution was kept at 0 °C.
for a further 15 minutes before it was warmed to room temperature for 30 minutes, at
which point TLC analysis indicated the reaction was complete. The reaction was
quenched with 100 mL water, transferred to a separatory funnel and diluted with 100 mL
ethyl acetate. The aqueous layer was washed two times with 100 mL ethyl acetate. The
combined organic fractions where then washed twice with distilled water (100 mL) and
once with brine (70 mL). The organic fraction was dried over MgSO₄ then filtered and
concentrated. The crude product was then pre-absorbed on silica and purified by flash
column chromatography (10% ethyl acetate/hexanes) yielding benzylated indole 2.147
(10.7 g, 29.3 mmol, 97%) as a clear and colourless viscous oil. Rf = 0.64 (30% ethyl
acetate in hexanes); ¹H NMR (400 MHz, CDCl₃): δ = 7.61 (d, J = 7.6 Hz, 1H), 7.29-7.24
(m, 5H), 7.16, (dd, J = 8.0, 7.0, 1.2 Hz, 1H) 7.12-7.10 (m, 2H), 6.97, (s, 1H), 5.27 (s,
2H), 3.87 (dd, J = 7.4, 7.4 Hz, 2H), 2.99 (dd, J = 7.4, 7.4 Hz, 2H), 0.89 (s, 9H), 0.02 (2,
6H); ¹³C NMR (100 MHz, CDCl₃): δ = 137.7, 136.5, 128.7, 128.4, 127.5, 126.8 126.3,
121.6, 119.1, 118.9, 112.3, 109.6, 63.9, 49.9, 29.0, 26.0, 18.4, -5.3; IR (thin film, cm⁻¹):
3058, 3031, 2954, 2928, 2897, 2856, 1615, 1559, 1496, 1467, 1454, 1388, 1369, 1333,
1255, 1215, 1174, 1093, 1051, 1029, 1013, 920, 836, 812, 776, 737, 698; HRMS calc’d
for C23H31ONSi = 365.2175, found 365.2180.

5-acetoxyindole (0.342 g, 1.95 mmol) was dissolved in 5 mL dimethyl
formamide at 0 °C in a 25 mL round bottom flask. Sodium hydride
60% dispersion in paraffin oil (0.86 g, 2.15 mmol) was then added and
the solution was stirred at 0 °C for 30 minutes at which point gas evolution had ceased.
Methyl iodide (0.121 mL, 1.95 mmol) was then added dropwise via syringe and the
solution was kept at 0 °C for a further 30 minutes before it was warmed to room
temperature for 5 minutes, at which point TLC analysis indicated the reaction was
complete. The reaction was quenched with 5 mL water, transferred to a separatory funnel
and diluted with 50 mL diethyl ether. The aqueous layer was washed two times with 25
mL diethyl ether. The combined organic fractions where then washed twice with distilled
water (50 mL) and once with brine (50 mL). The organic fraction was dried over MgSO₄
then filtered and concentrated. The crude product was then recrystallized from
dichloromethane and hexanes yielding 1-methyl-5-acetoxyindole 2.160 (0.255 g, 1.35
mmol, 69%) as shiny flat beige crystals; M.p. 82-83 °C; R$_f$ = 0.64 (30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.33$ (br. s, 1H), 7.39 (br. s, 1H), 7.03 (d, $J = 2.4$ Hz, 1H), 6.96 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.57 (d, $J = 3.5$ Hz, 1H), 3.86 (s, 3H), 2.61 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 168.2$, 156.4, 131.3, 130.3, 125.8, 117.3, 113.4, 109.0, 103.5, 55.6, 23.7; IR (thin film, cm$^{-1}$): 3058, 3031, 2954, 2928, 2897, 2856, 1615, 1559, 1496, 1467, 1454, 1388, 1369, 1333, 1255, 1215, 1174, 1093, 1051, 1029, 1013, 920, 836, 812, 776, 737, 698; HRMS calc’d for C$_{23}$H$_{31}$ONSi = 365.2175, found 365.2180.

**General procedure for malonyl copper carbenoid insertion (A):**

Copper(II) acetylacetonate (0.58 µmol, 1%) was added to a solution of indole (0.88 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.58 mmol, 1 equiv.) dissolved in 3 mL benzene in a 5 mL round bottom flask. The flask was fitted with a reflux condenser, purged with Ar (g) and set to reflux. Once the reaction was determined to be complete by TLC it was cooled to room temperature and concentrated. The reaction mixture was then pre-adsorbed on silica and purified by flash column chromatography.

**General microwave conditions for malonyl copper carbenoid insertion (B):**

A 5 mL microwave vial was charged with copper(II) acetylacetonate (0.58 µmol, 1%), indole (0.88 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.58 mmol, 1 equiv.) dissolved in 3 mL benzene. The vial was purged with Ar (g) and then fitted with a septa and vial seal. The reaction was then heated to 100 °C under microwave conditions for 2 hours. The reaction mixture was then concentrated and purified by flash column chromatography.

Indole 2.136: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.4 mg, 5.4 µmol, 1%), indole 2.77 (0.117 g, 0.806 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.085 g, 0.538 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.136 (0.131 g, 0.476 mmol, 88%).

![Indole 2.136](image_url)
Using general microwave malonyl carbene insertion procedure B. Reagents employed: copper(II) acetylacetonate (1.4 mg, 5.4 µmol, 1%), indole 2.77 (0.117 g, 0.806 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.085 g, 0.538 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.136 (0.131 g, 0.476 mmol, 88%).

Recrystallization from diethyl ether/hexanes gave indole 2.136 as small off-white flakes. M.p. 77-78 °C.; R<sub>f</sub> = 0.36 (30% ethyl acetate in hexanes);<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.56 (d, <i>J</i> = 8.2 Hz, 1H), 7.30 (d, <i>J</i> = 8.2 Hz, 1H), 7.25 (ddd, <i>J</i> = 8.2, 8.2, 1.2 Hz, 1H), 7.12 (ddd, <i>J</i> = 8.2, 8.2, 1.2 Hz, 1H), 5.11 (s, 1H), 3.79 (s, 6H), 3.73 (s, 3H), 2.32 (s, 3H);<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 167.8, 137.3, 127.6, 126.7, 122.3, 119.0, 119.0, 111.0, 109.1, 53.0, 49.00, 30.8, 8.9; IR (thin film, cm<sup>-1</sup>): 3038, 2953, 2844, 1738, 1613, 1471, 1435, 1386, 1366, 1313, 1250, 1216, 1194, 1149, 1030, 801, 741; HRMS calc’d for C<sub>15</sub>H<sub>17</sub>NO<sub>4</sub> = 275.1158, found 275.1157.

Indole 2.146: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.6 mg, 6.0 µmol, 1%), indole 2.145 (0.200 g, 0.904 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.095 g, 0.602 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.146 (0.196 g, 0.556 mmol, 92%).

Using general microwave malonyl carbene insertion procedure B. Reagents employed: copper(II) acetylacetonate (1.7 mg, 6.6 µmol, 1%), indole 2.145 (0.218 g, 0.987 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.104 g, 0.658 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.146 (0.201 g, 0.572 mmol, 87%).

Indole 2.146 was obtained as a clear yellow oil; R<sub>f</sub> = 0.36 (30% ethyl acetate in hexanes);<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.61 (ddd, <i>J</i> = 7.0, 1.6, 1.6 Hz, 1H), 7.26-7.15 (m, 5H), 7.13 (ddd, <i>J</i> = 5.1, 5.1, 2.0 Hz, 1H), 6.92 (dd, <i>J</i> = 8.2, 1.2 Hz, 2H), 5.46 (s, 2H), 5.02 (s, 1H), 3.53 (2, 6H), 2.35 (s, 3H);<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 167.5, 137.5, 137.0, 128.5, 128.1, 127.1, 126.8, 125.9, 122.6, 119.4, 119.0, 111.7, 109.9, 52.7, 49.1, 47.3, 9.1; IR (thin film, cm<sup>-1</sup>): 3030, 2952, 2922, 1739, 1496, 1465, 1453, 1435, 1357, 1336, 1309, 1283, 1262, 1224, 1195, 1148, 1029, 740; HRMS calc’d for C<sub>21</sub>H<sub>21</sub>NO<sub>4</sub> = 351.1471, found 351.1467.
Indole *2.148*: Using general malonyl carbene insertion procedure
A. Reagents employed: copper(II) acetylacetonate (1.7 mg, 6.5 µmol, 1%), indole *2.147* (0.358 g, 0.977 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.103 g, 0.651 mmol, 1 equiv.) in 3 mL benzene. Yielded indole *2.148* (0.252 g, 0.508 mmol, 78%).

Using general microwave malonyl carbene insertion procedure B. Reagents employed: copper(II) acetylacetonate (1.9 mg, 7.5 µmol, 1%), indole *2.147* (0.409 g, 1.12 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.118 g, 0.746 mmol, 1 equiv.) in 3 mL benzene. Yielded indole *2.148* (0.255 g, 0.514 mmol, 69%).

**Large scale preparation of 2.148:**

Copper(II) acetylacetonate (23 mg, 0.087 mmol, 1 equiv.) was added to a solution of indole *2.147* (4.7 g, 13 mmol) dissolved in 25 mL benzene in a 50 mL round bottom flask. The flask was fitted with a reflux condenser, purged with Ar (g) and set to reflux. Once the solution had begun to reflux a solution of dimethyl 2-diazomalonate (1.4 g, 8.7 mmol) in 4 mL benzene was added dropwise *via* syringe over 40 minutes. The syringe was then rinsed with 3 mL benzene and this was added to the reaction mixture. After 18 hours at reflux TLC analysis showed the dimethyl diazomalonate was consumed. The reaction mixture was then pre-adsorbed on silica and purified by flash column chromatography. Elution gradient began at 5% ethyl acetate in hexanes until the remaining starting material indole *2.147* eluted (1.8 g, 4.9 mmol), and then adjusted to 10% ethyl acetate in hexanes to obtain the desired malonyl indole *2.148* (3.5 g, 7.1 mmol, 81%).

Indole *7c* was obtained as a pale yellow oil: R<br><br>_f_ = 0.51 (30% ethyl acetate in hexanes); *1^H* NMR (400 MHz, CDCl₃): δ = 7.62 (dd, _J_ = 5.9, 2.2 Hz, 1H), 7.20-7.04 (m, 6H), 6.84 (m, 2H), 5.48 (s, 2H), 5.13 (s, 1H), 3.80 (dd, _J_ = 7.7, 7.4 Hz, 2H), 3.42, (s, 6H), 3.03 (dd, _J_ = 7.7, 7.4 Hz, 2H), 0.87 (s, 9H), 0.02 (s, 6H); *13^C* NMR (100 MHz, CDCl₃): δ = 167.4, 137.4, 137.2, 128.3, 127.6, 127.5, 126.9, 125.8, 122.5, 119.5, 119.2, 112.7, 110.2, 63.6, 52.6, 48.9, 47.7, 28.6, 18.4, -5.4; IR (thin film, cm⁻¹): 3059, 3032, 3004, 2953, 2929, 2884, 2856, 1741, 1606, 1560, 1497, 1467, 1453, 1436, 1418, 1387, 1361, 1345, 1313,
Indole \textbf{2.150}: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.8 mg, 6.7 µmol, 1%), indole \textbf{2.149} (0.204 g, 0.101 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.106 g, 0.670 mmol, 1 equiv.) in 3 mL benzene. Yielded indole \textbf{2.150} (0.184 g, 0.552 mmol, 83%).

Using general microwave malonyl carbene insertion procedure B. Reagents employed: copper(II) acetylacetonate (1.6 mg, 6.1 µmol, 1%), indole \textbf{2.149} (0.185 g, 0.911 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.960 g, 0.607 mmol, 1 equiv.) in 3 mL benzene. Yielded indole \textbf{2.150} (0.143 g, 0.429 mmol, 70%).

Recrystallization from dichloromethane/hexanes gave indole \textbf{2.150} as shiny white prisms. M.p. 94-95 °C; R$_f$ = 0.16 (50% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.63 (d, $J = 7.8$ Hz, 1H), 7.33 (d, $J = 8.2$ Hz, 1H) 7.28 (ddd, $J = 8.2$, 8.2, 1.2 Hz, 1H), 7.17 (ddd, $J = 8.2$, 7.8, 1.2 Hz, 1H), 5.25 (s, 1H), 3.82 (s, 2H), 3.81 (s, 6H), 3.77(s, 3H), 3.65 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 171.6, 167.4, 137.3, 128.3, 126.8, 122.5, 119.7, 118.8, 109.4, 107.9, 53.0, 51.9, 49.1, 30.9, 30.3; IR (thin film, cm$^{-1}$): 3027, 3004, 2953, 2845, 1737, 1615, 1559, 1472, 1435, 1370, 1316, 1251, 1195, 1150, 1036, 970, 929, 885, 846, 822, 743; HRMS calc’d for C$_{17}$H$_{19}$NO$_6$ = 333.1212, found 333.1205.

Indole \textbf{2.139}: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.6 mg, 6.3 µmol, 1%), indole \textbf{2.151} (0.138 g, 0.949 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.100 g, 0.633 mmol, 1 equiv.) in 3 mL benzene. Yielded indole \textbf{2.139} (0.172 g, 0.626 mmol, 99%).

Using general microwave malonyl carbene insertion procedure B. Reagents employed: copper(II) acetylacetonate (1.7 mg, 6.6 µmol, 1%), indole \textbf{2.151} (0.145 g, 0.996 mmol,
1.5 equiv.) and dimethyl 2-diazomalonate (0.105 g, 0.996 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.139 (0.126 g, 0.458 mmol, 69%).

Recrystallization from dichloromethane/hexanes gave indole 2.139 as small beige flakes. M.p. 189-190 °C; R_f = 0.24 (30% ethyl acetate in hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.60\) (d, \(J = 8.2\) Hz, 1H), 7.26 (d, \(J = 8.2\) Hz, 1H), 7.19 (\(J = 8.2, 8.2, 1.2\) Hz, 1H), 7.12 (ddd, \(J = 8.2, 8.2, 1.2\) Hz, 1H), 4.96 (s, 1H), 3.76 (s, 6H), 3.67 (s, 3H), 2.43 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 169.2, 136.5, 135.4, 126.5, 121.0, 119.6, 118.7, 108.8, 102.7, 52.6, 29.6, 10.7\); IR (thin film, cm\(^{-1}\)): 2951, 2928, 1742, 1729, 1473, 1431, 1408, 1369, 1319, 1290, 1255, 1221, 1189, 1156, 1063, 1028, 1016, 1006, 976, 934, 891, 806, 774, 749; HRMS calc’d for C\(_{15}\)H\(_{17}\)NO\(_4\) = 275.1158, found 275.1166.

Indole 2.144: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.6 mg, 6.4 µmol, 1%), indole 2.152 (0.199 g, 0.958 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.101 g, 0.639 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.144 (0.201 g, 0.596 mmol, 93%).

Using general microwave malonyl carbene insertion procedure B. Reagents employed: copper(II) acetylacetonate (1.4 mg, 5.4 µmol, 1%), indole 2.152 (0.169 g, 0.816 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.086 g, 0.544 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.144 (0.144 g, 0.427 mmol, 79%).

Recrystallization from dichloromethane/hexanes gave indole 2.144 as small pink-white cubes; M.p. 149-151 °C; R_f = 0.22 (30% ethyl acetate in hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.82\) (d, \(J = 8.2\) Hz, 1H), 7.57-7.47 (m, 5H), 7.39 (d, \(J = 8.2\) Hz, 1H), 7.31 (ddd, \(J = 8.2, 8.2, 0.8\) Hz, 1H), 7.22 (ddd, \(J = 8.2, 8.2, 0.8\) Hz, 1H), 4.84 (s, 1H), 3.73 (s, 6H), 3.63 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 169.2, 140.1, 137.1, 130.8, 130.5, 128.7, 128.6, 126.2, 122.1, 120.7, 120.1, 109.5, 104.6, 52.5, 49.7, 30.9\); IR (thin film, cm\(^{-1}\)): 3054, 3033, 2953, 2914, 2836, 1741, 1603, 1552, 1468, 1433, 1402, 1365, 1309, 1237, 1152, 1065, 1041, 1017, 980, 931, 905, 848, 818, 793, 749, 707; HRMS calc’d for C\(_{20}\)H\(_{19}\)NO\(_4\) = 337.1314, found 337.1320.
Indole 2.154: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.8 mg, 7.0 µmol, 1%), indole 2.153 (0.199 g, 1.05 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.111 g, 0.702 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.154 (0.134 g, 0.420 mmol, 60%).

Using general microwave malonyl carbene insertion procedure B. Reagents employed: copper(II) acetylacetonate (1.5 mg, 5.6 µmol, 1%), indole 2.153 (0.158 g, 0.835 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.088 g, 0.557 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.154 (0.086 g, 0.269 mmol, 48%).

Recrystallization from chloroform/hexanes gave indole 2.154 as shiny white flat flakes. M.p. 139-141 °C; Rf = 0.26 (30% ethyl acetate in hexanes); ¹H NMR (400 MHz, CDCl₃): δ = 7.70 (ddd, J = 8.2, 1.2, 1.2 Hz, 1H), 7.40-7.35 (m, 2H), 7.17 (ddd, J = 5.9, 5.9, 2.3 Hz, 1H) 5.82 (s, 1H), 4.02 (s, 3H), 3.95 (s, 3H), 3.75 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 168.9, 162.4, 138.6, 126.1, 125.6, 125.4, 121.7, 121.0, 114.2, 110.4, 52.7, 51.8, 49.4, 32.3; IR (thin film, cm⁻¹): 3009, 2955, 2849, 1751, 1738, 1717, 1614, 1532, 1438, 1400, 1368, 1319, 1253, 1155, 1130, 1108, 1050, 1022, 978, 906, 869, 819, 748; HRMS calc’d for C₁₆H₁₇NO₆ = 319.1056, found 319.1067.

Indole 2.135: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (2.0 mg, 7.6 µmol, 1%), indole 2.155 (0.244 g, 1.15 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.121 g, 0.765 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.135 (0.250 g, 0.735 mmol, 96%).

Using general microwave malonyl carbene insertion procedure B. Reagents employed: copper(II) acetylacetonate (1.5 mg, 5.6 µmol, 1%), indole 2.155 (0.178 g, 0.845 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.0891 g, 0.563 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.135 (0.174 g, 0.512 mmol, 91%).

Recrystallization from chloroform/hexanes gave indole 2.135 as small flat white flakes. M.p. 167-168 °C; Rf = 0.21 (30% ethyl acetate in hexanes); ¹H NMR (400 MHz, CDCl₃): δ = 7.75 (d, J = 2.0 Hz, 1H), 7.31 (dd, J = 8.6, 2.0 Hz, 1H), 7.28 (s, 1H), 7.17 (d, J = 8.6
Hz, 1H), 4.89 (s, 1H), 3.77 (s, 6H), 3.76 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): \( \delta = 168.8, 135.4, 129.8, 128.5, 124.9, 121.6, 113.2, 111.0, 105.2, 52.9, 49.0, 33.1; \) IR (thin film, cm$^{-1}$): 2954, 2938, 2851, 1739, 1731, 1481, 1430, 1384, 1320, 1274, 1223, 1191, 1155, 1034, 1016, 974, 868, 793, 753, 729; HRMS calc’d for C$_{14}$H$_{14}$BrNO$_4$ = 339.0106, found 339.0110.

Indole 2.157: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.5 mg, 5.6 \( \mu \)mol, 1%), indole 2.156 (0.149 g, 0.844 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.089 g, 0.563 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.157 (0.137 g, 0.448 mmol, 79%).

Recrystallization from dichloromethane/hexanes gave indole 2.157 as long yellow filaments; M.p. 151-152 °C; \( R_f = 0.32 \) (30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): \( \delta = 8.60 \) (d, \( J = 2.3 \) Hz, 1H), 8.12 (dd, \( J = 9.0, 2.3 \) Hz, 1H), 7.45 (s, 1H), 7.34 (d, \( J = 9.0 \) Hz, 1H), 4.97 (s, 1H), 3.83 (s, 3H), 3.79 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): \( \delta = 168.4, 141.8, 139.4, 131.9, 126.2, 117.6, 116.6, 109.5, 108.6, 53.1, 48.8, 33.3; \) IR (thin film, cm$^{-1}$): 3120, 3008, 2955, 2844, 1736, 1619, 1578, 1551, 1516, 1486, 1454, 1435, 1396, 1335, 1222, 1202, 1148, 1100, 1048, 1013, 982, 928, 901, 782, 743; HRMS calc’d for C$_{14}$H$_{14}$N$_2$O$_6$ = 306.0852, found 306.0848.

Indole 2.159: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (2.3 mg, 8.9 \( \mu \)mol, 1%), indole 2.158 (0.235 g, 1.33 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.141 g, 0.892 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.159 (0.220 g, 0.718 mmol, 80%).

Recrystallization from dichloromethane/hexanes gave indole 2.159 as long yellow crystals. M.p. 127-128 °C; \( R_f = 0.17 \) (30% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): \( \delta = 7.89 \) (dd, \( J = 7.6, 1.2 \) Hz, 1H), 7.82 (d, \( J = 8.2 \) Hz, 1H), 7.37 (s, 1H), 7.17 (ddd, \( J = 8.2, 7.6, 1.2 \) Hz, 1H) 4.95 (s, 1H), 3.84 (s, 3H), 3.78 (s, 6H); $^{13}$C NMR (150
MHz, CDCl₃): δ = 168.4, 136.7, 133.4, 131.7, 127.6, 125.2, 120.1, 118.9, 107.1, 53.0, 48.8, 37.5; IR (thin film, cm⁻¹): 3090, 3009, 2958, 2844, 1737, 1693, 1620, 1552, 1520, 1487, 1434, 1369, 1345, 1289, 1225, 1195, 1151, 1120, 1070, 1023, 983, 917, 805, 790, 729; HRMS calc’d for C₁₄H₁₄N₂O₆ = 306.0852, found 306.0851.

Indole 2.161: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.8 mg, 6.8 µmol, 1%), indole 2.160 (0.192 g, 1.02 mmol, 1.5 equiv.) and dimethyl 2-diazo malonate (0.107 g, 0.677 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.161 (0.106 g, 0.332 mmol, 49%).

Recrystallization from chloroform/hexanes gave indole 2.161 as fluffy opaque white flakes. M.p. 158-159 °C; Rᵉ = 0.24 (50% ethyl acetate in hexanes); ¹H NMR (600 MHz, CDCl₃): δ = 8.34 (d, J = 8.5 Hz, 1H), 7.67 (s, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 8.5, 2.4 Hz, 1H), 4.87 (s, 1H), 3.86 (s, 3H), 3.79 (s, 6H), 2.62 (s, 3H); ¹³C NMR (150 MHz, CDCl₃): δ = 168.2, 167.9, 156.6, 130.3, 130.1, 125.5, 117.6, 113.8, 113.3, 101.8, 55.7, 53.1, 48.8, 23.7; IR (thin film, cm⁻¹): 2999, 2956, 2836, 1739, 1713, 1612, 1593, 1479, 1435, 1387, 13 ×-×× 28, 1283, 1251, 1198, 1156, 1118, 1078, 1033, 943, 908, 843, 817, 799, 757, 732; HRMS calc’d for C₁₆H₁₇NO₄ = 319.1056, found 319.1051.

Indole 2.135: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (2.1 mg, 8.2 µmol, 1%), indole 2.162 (0.198 g, 1.23 mmol, 1.5 equiv.) and dimethyl 2-diazo malonate (0.130 g, 0.822 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.135 (0.227 g, 0.779 mmol, 95%).

Using general microwave malonyl carbene insertion procedure B. Reagents employed: copper(II) acetylacetonate (1.7 mg, 6.3 µmol, 1%), indole 2.162 (0.153 g, 0.949 mmol, 1.5 equiv.) and dimethyl 2-diazo malonate (0.100 g, 0.633 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.135 (0.172 g, 0.590 mmol, 93%).
Recrystallization from chloroform/hexanes gave indole 2.135 as dull white flakes. M.p. 109-110 °C; R_f = 0.13 (30% ethyl acetate in hexanes); ^1H NMR (400 MHz, CDCl_3): δ = 7.24 (s, 1H), 7.20 (d, J = 9.0 Hz, 1H), 7.06 (d, J = 2.3 Hz, 1H), 6.90 (dd, J = 9.0, 2.3 Hz, 1H), 4.92 (s, 1H), 3.86 (s, 3H), 3.77 (s, 6H), 3.75 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ = 169.1, 154.3, 132.1, 129.1, 127.3, 112.3, 110.2, 105.0, 100.8, 55.9, 52.7, 49.2, 33.0; IR (thin film, cm\(^{-1}\)): 3117, 2999, 2952, 2835, 1756, 1735, 1623, 1577, 1544, 1493, 1456, 1434, 1387, 1305, 1278, 1225, 1197, 1149, 1064, 1027, 984, 908, 840, 796, 775, 754, 735; HRMS calc’d for C_{15}H_{17}NO_5 = 291.1107, found 291.1113.

Indole 2.164: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.7 mg, 6.5 µmol, 1%), indole 2.163 (0.210 g, 0.968 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.102 g, 0.645 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.164 (0.153 g, 0.441 mmol, 68%). Recrystallization from chloroform/hexanes gave indole 2.164 as dull opaque white flakes. M.p. 118-119 °C; R_f = 0.18 (30% ethyl acetate in hexanes); ^1H NMR (400 MHz, CDCl_3): δ = 8.16 (d, J = 7.8 Hz, 1H), 7.77 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H) 7.33 (ddd, J = 7.8, 7.6, 1.2 Hz, 1H) 7.26 (ddd, J = 8.2, 7.6, 1.2 Hz, 1H) 4.90 (s, 1H), 3.78 (s, 6H), 1.66 (s, 9H); ^13C NMR (100 MHz, CDCl_3): δ = 168.2, 149.4, 135.3, 129.1, 125.5, 124.7, 122.8, 119.2, 115.3, 111.9, 84.0, 53.0, 49.2, 28.2; IR (thin film, cm\(^{-1}\)): 3459, 3175, 3119, 2979, 2954, 2847, 1736, 161, 1569, 1477, 1454, 1435, 1370, 1337, 1309, 1258, 1198, 1156, 1088, 1043, 1020, 984, 929, 853, 767, 748; HRMS calc’d for C_{18}H_{21}NO_6 = 347.1369, found 347.1357.

Indole 2.132: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (2.0 mg, 7.5 µmol, 1%), indole 2.165 (0.306 g, 0.113 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.119 g, 0.753 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.132 (0.137 g, 0.341 mmol, 45%).
Indole 2.132 was obtained as a viscous clear oil: $R_f = 0.23$ (30% ethyl acetate in hexanes); $^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.97$ (d, $J = 8.2$ Hz, 1H), 7.82 (s, 1H), 7.79 (d, $J = 8.2$ Hz, 2H), 7.55 (d, $J = 8.2$ Hz, 1H) 7.32 (ddd, $J = 8.2$, 7.0, 1.2 Hz, 1H), 7.25 (ddd, $J = 8.2$, 7.0, 1.2 Hz, 1H), 7.21 (d, $J = 8.2$ Hz, 2H), 4.88 (s, 1H), 3.76 (2, 6H), 2.32 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 167.7, 145.0, 135.0, 134.7, 129.9, 129.4, 126.9, 125.8, 124.9, 123.3, 119.8, 113.5, 113.5, 53.0, 49.0, 21.5$; IR (thin film, cm$^{-1}$): 3159, 3108, 3029, 2954, 2925, 2851, 1754, 1739, 1597, 1494, 1448, 1436, 1371, 1307, 1280, 1189, 1174, 1131, 1123, 1096, 1022, 967, 814, 748, 710; HRMS calc’d for C$_{20}$H$_{19}$NO$_6$S = 401.0933, found 401.0921.

Using general microwave malonyl carbene insertion procedure B. Reagents employed: copper(II) acetylacetonate (2.3 mg, 8.9 µmol, 1%), indole 2.166 (0.1927 g, 0.929 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.098 g, 0.620 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.130 (0.281 g, 0.833 mmol, 93%).

Indole 2.130 was obtained as a clear colourless viscous oil; $R_f = 0.28$ (30% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.66$ (dd, $J = 7.4$, 1.2 Hz, 1H), 7.37, (s, 1H), 7.33-7.24 (m, 4H), 7.19 (ddd, $J = 7.0$, 1.2, 1.2 Hz, 1H), 7.17-7.12 (m 3H), 5.31 (s, 2H) 4.99 (s, 1H), 3.77 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 169.0, 137.0, 136.3, 128.8, 128.1, 127.7, 127.2, 126.9, 122.1, 119.9, 119.12 110.0, 106.3, 52.8, 50.3, 49.3$; IR (thin film, cm$^{-1}$): 3030, 2952, 1736, 1614, 1550, 1496, 1482, 1468, 1454, 1435, 1396, 1356, 1310, 1195, 1151, 1079, 1017, 984, 928, 743, 699. HRMS calc’d for C$_{20}$H$_{19}$NO$_4$ = 337.1314, found 337.1310.
Indole 2.142: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.6 mg, 6.1 µmol, 1%), indole 2.167 (0.121 g, 0.920 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.097 g, 0.614 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.142 (0.131 g, 0.510 mmol, 81%). Recrystallization from diethyl ether/hexanes gave indole 2.142 as thin shiny light pink crystals. M.p. 140-141 °C; R_f = 0.19 (30% ethyl acetate in hexanes); ¹H NMR (600 MHz, CDCl₃): δ = 8.01 (br. s, 1H) 7.58 (dd, J = 7.6, 1.2 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H) 7.14-7.09 (m, 2H), 4.91 (s, 1H), 3.75 (s, 6H), 2.37 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 169.2, 135.0, 133.8, 127.4, 121.4, 119.8, 118.8, 110.4, 103.4, 52.6, 48.8, 11.9; IR (thin film, cm⁻¹): 3395, 3029, 2953, 2845, 1736, 1622, 1585, 1566, 1461, 1434, 1307, 1248, 1197, 1150, 1028, 926, 768, 748; HRMS calc’d for C₁₄H₁₅NO₄ = 260.1001, found 216.0991

Indole 2.168: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.7 mg, 6.3 µmol, 1%), indole 2.1 (0.111 g, 0.948 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.100 g, 0.633 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.168 (0.126 g, 0.510 mmol, 80%). Recrystallization from diethyl ether/hexanes gave indole 2.168 as thin shiny white crystals. M.p. 129-130 °C; R_f = 0.17 (30% ethyl acetate in hexanes); ¹H NMR (600 MHz, CDCl₃): δ = 8.31 (br. s, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.32 (s, 1H), 7.21 (dd, J = 8.2, 7.0 Hz, 1H), 7.16 (dd, J = 8.2, 7.0 Hz, 1H), 4.99 (s, 1H), 3.77 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 169.1, 135.9, 126.4, 124.1, 122.3, 120.0, 118.9, 11.4, 107.1, 52.8, 49.3; IR (thin film, cm⁻¹): 3383, 3064, 3036, 3002, 2952, 2847, 1745, 1720, 1623, 1551, 1494, 1458, 1435, 1336, 1314, 1285, 1253, 1200, 1161, 1081, 1026, 981, 935, 906, 767, 748; HRMS calc’d for C₁₃H₁₃NO₄ = 247.0845, found 247.0843
Indole 2.138: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.6 mg, 6.3 µmol, 1%), skatole 2.169 (0.123 g, 0.939 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.099 g, 0.626 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.138 (0.142 g, 0.543 mmol, 87%).

Recrystallization from hexanes gave indole 2.138 as shiny white flakes. M.p. 114-115 °C; R_f = 0.34 (30% ethyl acetate in hexanes); ^1H NMR (600 MHz, CDCl_3): δ = 8.83 (br. s, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.20 (dd, J = 8.2, 7.0 Hz, 1H), 7.11 (dd, J = 8.2, 7.0 Hz, 1H) 5.01 (s, 1H), 3.79 (s, 6H), 2.31 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ = 167.7, 135.8, 128.2, 124.2, 122.5, 119.3, 118.8, 111.1, 110.7, 53.1, 48.9, 8.5; IR (thin film, cm\(^{-1}\)): 3409, 3086, 3058, 3034, 3021, 2999, 2952, 2919, 2860, 1742, 1730, 1692, 1620, 1589, 1568, 1488, 1460, 1437, 1387, 1335, 1308, 1287, 1246, 1208, 1160, 1025, 986, 933, 907, 804, 752, 741; HRMS calc’d for C_{14}H_{15}NO_4 = 261.1001, found 261.0997.

Indole 2.171: Using general malonyl carbene insertion procedure A. Reagents employed: copper(II) acetylacetonate (1.6 mg, 6.2 µmol, 1%), indole 2.170 (0.148 g, 0.930 mmol, 1.5 equiv.) and dimethyl 2-diazomalonate (0.098 g, 0.620 mmol, 1 equiv.) in 3 mL benzene. Yielded indole 2.171 (0.093 g, 0.321 mmol, 52%).

Recrystallization from hexanes gave indole 2.171 as long thin shiny white crystals. M.p. 94-96 °C.; R_f = 0.31 (30% ethyl acetate in hexanes); ^1H NMR (400 MHz, CDCl_3): δ = 7.51 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.20 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.09 (ddd, J = 7.5, 7.0, 1.2 Hz, 1H), 3.71 (s, 6H), 3.70 (s, 3H), 3.68 (t, J = 7.6 Hz, 1H), 3.44 (d, J = 7.4 Hz, 2H), 2.27 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ = 168.9, 136.9, 131.8, 128.2, 121.3, 118.8, 118.4, 108.8, 108.6, 52.7, 51.6, 29.7, 23.9, 8.7; IR (thin film, cm\(^{-1}\)): 3450, 3086, 3058, 3028, 3008, 1736, 1617, 1569, 1473, 1434, 1409, 1386, 1362, 1330, 1256, 1228, 1193, 1153, 1077, 1056, 1013, 952, 919, 857, 809, 791, 739; HRMS calc’d for C_{16}H_{19}NO_4 = 289.1314, found 289.1322.
Section 2.7: References

(41) See experimental section for 2.148 on page 109.
(42) Less than 10% as determined by 1H-NMR.
(54) Wagger, J.; Svete, J.; Stanovnik, B. *Synthesis* **2008**, *1436*.
Chapter 3: A Biomimetic Approach Towards Arboflorine

Chapter three discusses the progress towards the total synthesis of the indole alkaloid arboflorine. The current route relies on the application of the copper catalyzed carbenoid insertion into indoles developed in chapter two. An introduction to arboflorine is provided, followed by a selection of synthetic work from the literature which pertains to the syntheses of similar ring systems. Relevant work from the Kerr group regarding indole and malonate reactivity is then discussed, with possible applications for the synthesis of arboflorine. Synthetic progress to arboflorine then closes out the chapter.

Section 3.1: Introduction to Arboflorine

Section 3.1.1: Isolation and Related Natural Products

Plants of the genus *Kopsia* have proven to be exceptional sources of indole alkaloids. In total there have been 24 distinct plant species in the *Kopsia* genus, many of which occur in South Eastern Asia, and are particularly diverse in Malaysia with 18 distinct species identified thus far. Some species of the genus *Kopsia* have also found use in traditional medicines. The roots of *K. larutensis*, *K. profunda*, *K. pauciflora*, and *K. singapurensis* are used for poulticing in patients with syphilis. In China *K. arborea* has been used for the treatment of rheumatoid arthritis, edema, and tonsillitis, and *K. flavida* has been used as a contraceptive.

![Arboflorine](image)

**Figure 3.1** – The Indole Alkaloid Arboflorine
The indole alkaloid arboflorine 3.1 was isolated from the basic extracts of the stem bark of *Kopsia arborea* (Figure 3.1). During these isolation studies, *Kopsia arborea* proved to be a rich source of indole alkaloids, with 62 distinct indole alkaloids identified, and 25 of which were previously unknown. Figure 3.2 provides a selection of ten indole natural products isolated from *Kopsia arborea*.

![Figure 3.2 – A Selection of Kopsia Natural Products](image)

The structure of arboflorine 3.1 was established by spectroscopic analyses. It was identified to contain a pentacyclic carbon skeleton, with three stereocentres and three distinct nitrogen functional groups with the indole, the amide and the tertiary amine. As of yet the absolute configuration of arboflorine 3.1 remains to be determined, there has been no reported biological activity of the alkaloid, and no synthetic efforts towards the synthesis of arboflorine 3.1 have been reported.
Section 3.1.2: Kam’s Biosynthetic Postulation

In addition to isolating and identifying the structure of arboflorine 3.1, the Kam group presented a plausible biosynthetic route to arboflorine which is shown in Scheme 3.1. They proposed that arboflorine may arise from a diester derivative of preakuammicine 3.12. A Grob type fragmentation of 3.12 could open the pyrrolidine ring, generating the iminium ion 3.13. Isomerization to form the conjugated iminium species 3.14 and conjugate addition of an ammonia equivalent would provide the third nitrogen atom in 3.15. A vinylogous retro-Mannich reaction may then generate the 2-malonyl indole 3.16, which can undergo a subsequent Mannich reaction to create the azepane ring in 3.17. Mono-decarboxylation, followed by a final lactamization of the remaining ester, would afford arboflorine 3.1.

Scheme 3.1 – Proposed Biosynthesis of Arboflorine
The key malonyl indole intermediate 3.16 piqued our interest in this natural product, and provided us with the inspiration to begin investigations to probe this proposed biogenesis. We hoped to achieve a synthesis of this natural product much in the manner described in the proposed biosynthesis via an intermediate such as 3.16, and assess the plausibility of the Mannich reaction to generate 3.17, en route to arboflorine 3.1.

**Section 3.2: Synthesis of Similar Ring Systems**

The indole 2,3-annulated azepane ring system containing a nitrogen atom in a tryptamine-type disposition, as is observed in arboflorine 3.1, is an uncommon natural structural motif. Despite this disparity, syntheses of these ring systems have been reported. A selection of synthetic routes to this rare tricyclic ring system follows.

Reyes-Gutiérrez and co-workers have recently described a radical mediated functionalization of N-Boc typtamine 3.19, which was further elaborated into the synthesis of azepino[4,5-b]indolones (Scheme 3.2). This method relied on the substitution of the tryptamine core 3.19 by an oxidative radical addition of a xanthate 3.20. The radical addition also incorporated an ester functionality which, after Boc deprotection, allowed for lactam formation which generated the azepane ring in 3.22. Primary (R^1=R^2=H), secondary (R^2=H) and tertiary xanthates were all capable of C2 alkylation of 3.19 under the radical conditions, though the secondary xanthates proved to be moderately superior. The two step deprotection-lactamization process was then developed and applied to the synthesis of 11 azepane annulated indoles 3.22. The synthetic potential of this methodology was further demonstrated in the synthesis of 3.23, which constitutes the tetracyclic core of the natural product tronocarpine 3.24.
During synthetic studies on a variety of indole alkaloids, the Kuehne group recognized the importance for a facile synthesis of 2,3-annulated azepane indoles, and developed a two step procedure for their synthesis (Scheme 3.3).\textsuperscript{4} By heating tryptamine 3.25 in the presence of methyl chloropyruvate 3.26, a Pictet-Spengler reaction ensued to provide the tetrahydro-β-carboline 3.27. When 3.27 was heated in pyridine, a ring expansion to the seven-membered ring 3.29 took place presumably via the aziridine intermediate 3.28. Application of this procedure was recently found in the synthesis of
structural analogues of the anti-narcotic ibogaine 3.30, as well as in a protecting group free synthesis of (±)-subincanadine F 3.31. The authors of the latter study found that the yield of the key ring expansion could be increased to 85% by employing the bromo derivative of 3.26.

While pursuing syntheses of strychnos alkaloids, the Bosch group encountered the opportunity to investigate the chemical transformations of α-cyano-tetrahydropyridine derivative 3.32 (Scheme 3.4). They postulated that by unfurling the α-cyano amine to the iminium state 3.33 through loss of cyanide, three different reaction scenarios could potentially occur. The first sequence could proceed through 1,4-addition of the enolizable carbon into the conjugated iminium moiety, followed by a second addition of the indole 3-position into the iminium carbon (after isomerisation of the resultant enamine 3.35 from the first process). This would generate the pentacyclic framework 3.34, which constitutes a significant portion of the carbon framework found in the Strychnos alkaloids. The second process which could result would be only the first
addition of the α-ester carbon into the conjugated iminium, providing enamine 3.35. Finally, the alternative addition of the α-ester position into the iminium moiety in a 1,2-fashion would provide the 2,3-annulated azepane derivative 3.36. After screening a variety of conditions, the Bosch group found that, by generating the O-silyl ketene acetal of the ester and then treating the crude mixture with titanium tetrachloride, 1,2-addition occurred to give the ngouniensine-type structure 3.36 (Scheme 3.5). Unfortunately the reaction suffered from poor diastereoselectivity and provided the incorrect regiochemistry of the ethyl side-chain precluding a synthesis of ngouniensine 3.37.

Scheme 3.5 – Synthesis of the Tetracyclic Core of Ngouniensine

Section 3.3: 2-Malonyl Indole Methodologies Developed by the Kerr Group

As was noted above, the Mannich precursor 3.16 (Section 3.1.2, Scheme 3.1) was the proposed intermediate which brought arborflorine 3.1 to our attention. This was attributable to two previously developed methodologies from the Kerr group which focused on the installation of a malonate moiety onto indoles.7,8 As such, a 2-malonyl indole such as 3.16 appeared to be a plausible target for either of these methods of indole derivatization, and would allow us to study the biogenetic hypothesis proposed by Kam for arboflorine 3.1.2
Section 3.3.1: Oxidative Radical Cyclizations

The oxidative radical cyclizations of malonates, β-ketoesters and 1,3-diones into aromatic systems has seen considerable development, particularly by the Snider and Chuang groups. The Kerr group has also delved into this particular mode of reactivity, examining the manganese(III) acetate promoted cyclizations of malonyl tethered pyrroles 3.38, indoles 3.40 and indolines 3.42 (Scheme 3.6). In all three systems, both alkyl and amide derived tethers were successfully employed with little differences observed for either tether on the nitrogen atom despite the electron withdrawing capabilities of the amide. Only 3 pyrrole substrates 3.38 were examined,

Scheme 3.6 – Radical Cyclizations of Malonyl Tethered Heterocycles

with a single example containing a phenyl substituent at R, providing a 2:1 mixture of regioisomeric products 3.39. The indole series was slightly higher yielding on average, with both electron donating and withdrawing functionalities equally tolerated at R. Alkyl substitution at R was also suitable under the reaction conditions, but substrates with
electron withdrawing R² groups did not partake in the reaction. Interestingly, when indoline substrates 3.42 were submitted to the reaction conditions, both oxidation to the indole and radical cyclization took place to furnish the annulated products, but yields were generally modest for this domino oxidation-cyclization process. It should be noted that all indole and indoline radical reactions proceeded to provide the 2-malonyl indole products 3.41 and 3.43. The successful application of this methodology culminated in the total synthesis of the *Kopsia* alkaloid mersicarpine 3.11 (Scheme 3.7).

![Scheme 3.7 – Malonyl Radical Cyclization in the Total Synthesis of Mersicarpine](image)

**Section 3.3.2: Diazomalonate Decomposition and Carbene Insertions**

As was discussed in chapter 2 (Section 2.3.3), the Kerr group developed a dirhodium tetraacetate catalyzed carbenoid insertion into indoles (Scheme 3.8). When indole 3.47 was treated with dimethyl diazomalonate 3.48 under rhodium catalysis, the expected olefin cyclopropanation to generate indole 3.49 did not occur, and instead C2 insertion took place to provide the 2-malonyl indole 3.50. This serendipitous outcome stimulated a full methodology development, which demonstrated that if 3-substituted
indoles were subjected to the carbenoid insertion protocol, 2-malonyl indole products could be attained. A full discussion of this methodology is presented in Chapter 2.

Scheme 3.8 – Rhodium Catalyzed Carbenoid Insertion into Indoles

Section 3.4: Retrosynthetic Proposal for Arboflorine

We began our synthetic postulations towards arboflorine 3.1 with the above two methodologies in mind. It was thought that the application of either the manganese(III) acetate promoted radical cyclization or carbenoid insertion chemistry would allow access to a 2-malonyl indole. Such a 2-malonyl indole would be suitable to investigate the Mannich reaction in the proposed biosynthesis put forth by Kam (Scheme 3.1).\textsuperscript{13} Our initial retrosynthetic strategies are shown in Scheme 3.9. In the first route, the azepane ring of arboflorine 3.1 would be formed through alkylation of the tetrahydropyridine fragment. Intermediate 3.53 was disconnected into two fragments of similar size: indole 3.54 and pyridinyl amide 3.55, with plans for their union through either the carbenoid insertion or radical cyclizations described previously. The second proposal follows the postulated biogenesis in a more pragmatic fashion. A late stage intramolecular aminolysis would form the lactam ring of arboflorine 3.1, and the Mannich reaction proposed by
Kam would generate the azepane ring. Introduction of the tetrahydropyridine unit through quaternization and subsequent reduction of a pyridinium moiety 3.56 would secure the correct olefin regiochemistry. The malonate moiety in 3.57 would be installed through a carbenoid insertion reaction with diazomalonate 3.48.

**Scheme 3.9 – 1st Generation Retrosyntheses for Arboflorine**

### Section 3.5: Results and Discussion

#### Section 3.5.1: Early Attempts and Model Systems

Studies towards arboflorine began with the synthesis of the diester pyridine 3.62 (Scheme 3.10). A sodium borohydride reduction of 3-acetylpyridine 3.59 provided secondary alcohol 3.60 which was then coupled to the potassium salt of methyl malonic acid 3.61 using dicyclohexylcarbodiimide (DCC).\(^{14}\) With 3.62 in hand, we tested the manganese(III) acetate oxidative radical additions to N-methyl skatole 3.63 (Scheme 3.11).
Unfortunately neither of the conditions identified in the oxidative radical cyclizations of malonyl tethered indoles was successful in promoting the radical addition of diester 3.62 to $N$-methyl skatole 3.63. In methanol at reflux only transesterification was observed, providing dimethyl malonate 3.64 and alcohol 3.60. It should also be noted that no oxidative radical addition of dimethyl malonate 3.64 into $N$-methyl skatole 3.63 was observed during the course of the reaction. When acetic acid was employed as the reaction solvent, extensive decomposition occurred and no starting material was recovered.

Scheme 3.11 – Attempted Oxidative Radical Insertions

We next set out to investigate the carbenoid insertion reactions of the diazo compounds 3.65 and 3.67 into $N$-methyl skatole 3.63. Both diazo compounds were
prepared under the standard diazo transfer conditions with diazo transfer reagent
\( p \)-acetamidobenzensulfonyl azide (\( p \)-ABSA) (Scheme 3.12). \(^{15,16} \) Though the yield for
diazo compound 3.65 was low, it provided sufficient material to attempt the carbenoid
insertion reaction.

![Scheme 3.12 – Synthesis of Diazo Compounds 3.65 and 3.67](image)

The diazo compounds 3.65 and 3.67 were subjected to the carbenoid insertion
protocol, which had been previously developed in our laboratory, with \( N \)-methyl skatole
3.63. \(^8 \) We were surprised to find that, upon complete consumption of the diazo
compounds as indicated by TLC, we observed near complete recovery of the indole
starting material 3.63 after separation by chromatography. It appeared as if the diazo
compounds had been consumed and converted to indistinguishable materials, as indicated
by \(^1\text{H} \) NMR of the crude reaction mixture.
The difficulties encountered in the attempts at intermolecular radical addition and carbenoid insertions (Schemes 3.11 and 3.13) prompted us to develop a route which would allow for an intramolecular addition of the malonate moiety to the indole. To this end, indole-3-acetic acid \(3.70\) was reduced and bis-tosylated to provide indole \(3.71\) (Scheme 3.14). Reaction with pyridine \(3.60\) at reflux in diethyl ether generated the pyridinium salt \(3.72\).

Scheme 3.14 – Synthesis of Indole Tethered Pyridinium Salt \(3.72\)
Reduction of the pyridinium salt 3.72 with sodium borohydride secured the tetrahydropyridine indole 3.73 with the correct olefin regiochemistry required for arboflorine 3.1 (Scheme 3.15). The secondary alcohol of 3.73 was then esterified with 3.61 with the aid of DCC, provided diester indole 3.74.

Diester 3.74 was then subjected to the oxidative radical cyclization conditions previously described, but as before no radical addition product 3.75 was observed (Scheme 3.16). When the reaction was conducted in methanol at reflux transesterification predominated. The use of acetic acid at reflux resulted in decomposition, and all reactions conducted at temperatures below reflux showed no change in the starting materials.

Section 3.5.2: Revised Retrosynthetic Proposal

With the successful installation of the tetrahydropyridine fragment in 3.73 (Scheme 3.15) and the lack of success incorporating a 2-malonyl moiety, either through
radical or carbenoid insertion chemistry, prompted us to revise our retrosynthesis of arboflorine 3.1 (Scheme 3.17). Arboflorine 3.1 would be completed through a late stage lactamization of one of the ester groups of 3.76 and the pendant secondary amine. The azepane ring would be formed in a biomimetic fashion from a 2-malonyl indole with the tethered tetrahydropyridine 3.77. Oxidation of the tetrahydropyridine to the iminium state and masking as the α-cyano amine would be accomplished via a Polonovski-Potier reaction.\textsuperscript{18} Reductive amination would merge the tetrahydropyridine 3.78 and indole fragments 3.79. Finally, the 2-malonyl indole would be generated by carbenoid insertion of diazomalonate into a 3-substituted indole, appropriately suited for the incorporation of the tetrahydropyridine fragment.

Scheme 3.17 – Revised Retrosynthesis for Arboflorine

Section 3.5.3: Synthetic Progress to Arboflorine

We began our revised route to arboflorine with the synthesis of the indole fragment 3.79 (Scheme 3.18). Lithium aluminum hydride reduction of indole-3-acetic acid 3.70, TBS protection of the resultant alcohol and N-benzylation provided the doubly
protected indole 3.80 in high yield over three steps. At this point installation of the malonate into the 2-position of the indole was required. Direct application of the rhodium catalyzed method was unsuccessful, and we sought new conditions to accomplish this transformation.\(^8\) We developed a copper(II) acetylacetonate catalyzed procedure which far surpassed the rhodium catalyzed methods (see chapter 2, section 2.4).\(^{19}\) This new carbenoid insertion protocol was then used to install the 2-malonyl moiety in indole 3.81. A dissolving metal reduction cleaved the benzyl group from the indole, and hydrochloric acid in methanol removed the silyl ether, providing the diester indole-3-ethanol 3.82. Treatment of alcohol 3.82 with 2-iodoxybenzoic acid (IBX) in refluxing ethyl acetate secured the requisite indole fragment 3.79.

![Scheme 3.18 – Synthesis of Indole 3.79](image)

The synthesis of the tetrahydropyridine fragment 3.87 was then accomplished as depicted in Scheme 3.19. Secondary alcohol 3.60 was obtained through reduction of 3-acetyl pyridine 3.59 with sodium borohydride.\(^{14}\) Installation of the secondary amine, protected as the phthalimide, was accomplished via a Mitsunobu reaction in good yield.
Quaternization of 3.83 with benzyl bromide formed the pyridinium bromide 3.84. Reduction of the pyridinium salt 3.84 was accomplished with sodium borohydride at −78 °C to limit competing reduction of the carbonyls in the phthalimide moiety. Interestingly, attempts at reduction with either sodium cyanoborohydride or sodium triacetoxyborohydride were unsuccessful at providing the requisite tetrahydropyridine 3.85. Finally, the benzyl group was removed by treatment of tetrahydropyridine 3.85 with 1-chloroethyl chloroformate 3.86 providing the tetrahydropyridine 3.87 as the ammonium salt, which was used directly without further purification.²⁰

![Scheme 3.19 – Synthesis of Tetrahydropyridine 3.87](image)

Indole 3.79 and tetrahydropyridine 3.87 were joined through reductive amination to provide the advanced intermediate 3.88, which contained the total atomic balance required for arboflorine 3.1 (Scheme 3.20).²¹ Oxidation of 3.88 with m-chloroperbenzoic acid (m-CPBA) provided the N-oxide precursor for the Polonovski-Potier sequence, which was accomplished with trifluoroacetic anhydride (TFAA) and trimethylsilyl
cyanide (TMSCN) to provide the α-cyano amine 3.90 as a 1:1 mixture of diastereomers.\textsuperscript{18} Unfortunately 3.90 was highly unstable to chromatographic purification under all conditions attempted, and was carried forward without purification. With α-cyano amine 3.90 in hand, we were able to probe the Mannich ring closure which was proposed in the biosynthesis of arboflorine 3.1 (Section 3.1.2, Scheme 3.1).\textsuperscript{2}

\begin{equation}
\text{Scheme 3.20} – \text{Synthesis of } \alpha\text{-Cyano Amine 3.90}
\end{equation}

**Section 3.5.4: Attempts at Mannich Ring Closure**

Initial attempts at performing the Mannich azepane ring formation were conducted through liberation of the masked iminium in α-cyano amine 3.90 (Scheme 3.21). Table 3.1 lists representative conditions tested towards the Mannich ring closure. Treatment of 3.90 with silver(I) salts effected iminium 3.91 formation, but the planned Mannich reaction did not proceed, and instead decomposition was observed (entries 1-5).

Next the addition of base was examined, with the idea that enolization or deprotonation
of the malonate moiety would facilitate the Mannich reaction (entries 6-8). Unfortunately, as before only decomposition was observed. The $^1$H-NMR of the crude reaction mixture revealed signals which corresponded to both pyridinium and tetrahydopyridine ring protons, suggesting disproportionation of the iminium intermediate \(3.91^{17,22}\).

Oxophilic Lewis acids ytterbium(III) and scandium(III) triflates were used in the next series of reactions, as they have proven proficient in promoting Mannich-type ring closures in our cyclopropane-1,1-diester ring expansion reactions (see chapter 1).\(^23\) Direct exposure of \(3.90\) to ytterbium(III) triflate had no effect, and the starting material was recovered unaltered (entry 9). When ytterbium(III) or scandium(III) triflate was used in concert with silver(I) tetrafluoroborate or silver(I) triflate, iminium ion \(3.91\) formation and subsequent decomposition of the material was observed (entries 10 and 11). Titanium tetrachloride was next screened as a Lewis acid which also has the propensity to form iminium compounds from $\alpha$-cyano amines through removal of the cyanide functionality (entry 12).\(^6\) With no reaction observed at $\sim$78 °C, the solution was slowly warmed to 0 °C, at which point slow decomposition proceeded, consuming \(3.90\) without formation of azepane \(3.92\).
### Table 3.1 – Attempted Mannich Ring Closure Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Reagent(s)</th>
<th>Base</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>0 °C to rt</td>
<td>Ag₂CO₃</td>
<td>-</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>0 °C</td>
<td>Ag₂SO₄</td>
<td>-</td>
<td>Slow decomposition</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>0 °C</td>
<td>AgOTf</td>
<td>-</td>
<td>Slow decomposition</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>0 °C to rt</td>
<td>AgOTf</td>
<td>-</td>
<td>3.91 observed then decomposition on warming</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>0 °C to rt</td>
<td>AgBF₄</td>
<td>-</td>
<td>3.91 observed then decomposition on warming</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>0 °C</td>
<td>i) AgBF₄</td>
<td>ii) NaH</td>
<td>Fast decomposition upon addition of base</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>0 °C to rt</td>
<td>ii) AgBF₄</td>
<td>i) NaH</td>
<td>Decomposition on warming to rt</td>
</tr>
<tr>
<td>8</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>AgBF₄</td>
<td>Et₃N</td>
<td>Slow decomposition</td>
</tr>
<tr>
<td>9</td>
<td>CH₂Cl₂</td>
<td>0 °C to rt</td>
<td>Yb(OTf)₃</td>
<td>-</td>
<td>No observed reaction</td>
</tr>
<tr>
<td>10</td>
<td>CH₂Cl₂</td>
<td>0 °C to rt</td>
<td>i) AgOTf</td>
<td>ii) Sc(OTf)₃</td>
<td>3.91 observed then decomposition on warming</td>
</tr>
<tr>
<td>11</td>
<td>DCE</td>
<td>0 °C to rt</td>
<td>i) AgBF₄</td>
<td>ii) Yb(OTf)₃</td>
<td>Slow decomposition on warming</td>
</tr>
<tr>
<td>12</td>
<td>CH₂Cl₂</td>
<td>-78 °C to 0 °C</td>
<td>TiCl₄</td>
<td>-</td>
<td>Slow decomposition on warming</td>
</tr>
</tbody>
</table>

### Section 3.5.5: 2nd Generation Mannich Attempts

Finding great difficulty in effecting the azepane forming Mannich reaction, we postulated that if the reaction did proceed to form 3.92, the diester may allow for a Mannich/retro-Mannich equilibrium and subsequent decomposition (Scheme 3.22). To reduce the susceptibility for retro-Mannich, 3.88 was converted to the monoester 3.94 by Krapcho dealkoxycarbonylation (Scheme 3.22). With removal of one of the esters we
anticipated the need to use stronger bases to enucleate enolization and accomplish the Mannich ring closure. To avoid complications with indole deprotonation under basic conditions, indole 3.94 was N-Boc protected to negate the moderately acidic NH proton, providing indole 3.95. N-Oxidation and Polonovski-Potier sequence proceeded as before providing α-cyano amine 3.97. As was the case with α-cyano amine 3.90, 3.97 was also unstable to chromatography, and was used directly without further purification.

Scheme 3.22 – Retro-Mannich Decomposition Pathway

Scheme 3.23 – Synthesis of Monoester α-Cyano Amine 3.97
Having secured the synthetic route to 3.97, we next explored conditions for the annulated azepane ring formation via a Mannich reaction (Table 3.2). Initial attempts at unveiling the iminium ion 3.98 by cyanide removal were unsuccessful at bringing about the Mannich reaction (entries 1-4 and Scheme 3.24). Silver salts, with the addition of mild bases such as triethylamine or pyridine, resulted in disproportionation and decomposition as before.

**Table 3.2 – 2nd Generation Attempted Mannich Ring Closure Studies**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Reagent(s)</th>
<th>Base</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>AgBF₄</td>
<td>Et₃N</td>
<td>Slow decomposition</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>AgOTf</td>
<td>Pyridine</td>
<td>Slow decomposition</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>0 °C</td>
<td>Ag₂O</td>
<td>-</td>
<td>No Reaction</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>0 °C</td>
<td>AgOAc</td>
<td>-</td>
<td>Iminium observed then slow decomposition</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>–78 °C to 0 °C</td>
<td>ii) AgBF₄</td>
<td>i) LDA</td>
<td>Decomposition on warming to 0 °C</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>–78 °C to 0 °C</td>
<td>ii) TMSOTf</td>
<td>i) LDA</td>
<td>Slow decomposition at 0 °C</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>–78 °C to 0 °C</td>
<td>ii) TMSOTf</td>
<td>i) LDA</td>
<td>Decomposition upon addition of base</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>–78 °C to 0 °C</td>
<td>ii) TMSOTf</td>
<td>i) KHMDS</td>
<td>Decomposition on warming to 0 °C</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>–78 °C to 0 °C</td>
<td>ii) TMSOTf</td>
<td>i) LiHMDS</td>
<td>Decomposition on warming to 0 °C</td>
</tr>
<tr>
<td>10</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>i) TMSOTf</td>
<td>ii) AgOTf</td>
<td>Et₃N</td>
</tr>
<tr>
<td>11</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>TiCl₄</td>
<td>-</td>
<td>Decomposition</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>–78 °C to 0 °C</td>
<td>Ti(O/Pr)₄</td>
<td>-</td>
<td>Slow decomposition on warming</td>
</tr>
</tbody>
</table>
Scheme 3.24 – Iminium Ion Formation and Attempted Mannich

Where silver(I) oxide had no effect on 3.97, the addition of silver(I) acetate formed the iminium ion as observed by $^1$H-NMR, which then slowly decomposed in solution. We then attempted to generate the enolate of 3.97, followed by addition of silver(I) tetrafluoroborate to induce iminium formation and Mannich ring closure (entry 5). Unfortunately only decomposition was observed upon addition of the silver salt. Lacking success in finding conditions to accomplish the Mannich ring closure, we next examined the strategy of enolate generation and trapping as the silyl ketene acetal, followed by iminium generation and Mannich ring closure, as was employed in Bosch’s study on ngouniensine 3.37 (Section 3.1.3, Scheme 3.5).\(^6\) Disappointingly, application of Bosch’s conditions were unsuccessful at completing the azepane ring synthesis (entry 6 and Scheme 3.25). Bases, TMS sources and silver salts were next varied and screened in the subsequent tests, but no successful conditions were identified (entries 7-10). Finally, we tested titanium tetrachloride and titanium(IV) isopropoxide directly with 3.97, and again only decomposition was observed.

Scheme 3.25 – Silyl Ketene Acetal Formation and Mannich Reaction
Section 3.6: Summary and Future Work

In summary, we have employed our recently developed copper catalyzed malonyl carbenoid insertion reaction in the synthesis of 2-malonyl indole 3.81 as part of 12 step synthesis of N-oxide 3.96 in an overall yield of 33% (Scheme 3.26). Conversion of N-oxide 3.97 to the trapped iminium 3.97 was accomplished by a Polonovski-Potier reaction. Attempts at Mannich ring closure for both the diester 3.90 and N-Boc protected 3.96 led to the arboflorine 3.1.
monoester 3.97 have thus far been unsuccessful at azepane ring formation. Mannich ring closure, deprotection of both the Boc and phthalimide groups, and lactamization remain as the final 4 conceptual synthetic steps towards arboflorine 3.1. Efforts towards the synthesis of arboflorine 3.1 and further development and applications of the copper catalyzed malonyl carbenoid insertion reaction will continue in the Kerr group, with the results to be presented in due course.

**Section 3.7: Experimental**

**General**

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments and samples were obtained in CDCl$_3$ (referenced to 7.26 ppm for $^1$H and 77.0 for $^{13}$C). Coupling constants ($J$) are in Hz. The multiplicities of the signals are described using the following abbreviations: $s =$ singlet, $d =$ doublet, $t =$ triplet, $q =$ quartet, dd $=$ doublet of doublets, $m =$ multiplet, br $=$ broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 spectrometer at 70 eV. Microwave reactions were performed in a 400 W Biotage Initiator 2.0 microwave reactor. Tetrahydrofuran (THF), benzene, dimethylformamide (DMF) and dichloromethane (DCM) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Aldrich, Strem, Caledon or VWR. Reaction progress was monitored by TLC (EM Science, silica gel 60 F$_{254}$) visualizing with UV light, and the plates were developed using $p$-anisaldehyde, phosphomolybdic acid, or basic potassium permanganate stains. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh).
Experimental Procedures and Compound Characterization:

To a solution of 1-(pyridin-3-yl)ethanol 3.60 (0.337 g, 2.74 mmol, 1 equiv.), potassium monomethyl malonate (0.940 g, 5.48 mmol, 2 equiv.), dicyclohexylcarbodiimide (DCC) (1.13 g, 5.48 mmol, 2 equiv.) and N,N-dimethyl aminopyridine (DMAP) (0.033 g, 0.248 mmol, 0.1 equiv.), in 60 mL THF was added toluene sulfonic acid (1.04 g, 5.48 mmol, 2 equiv.). Immediate formation of a white precipitate was observed. When alcohol 3.60 was consumed as indicated by TLC, the reaction was filtered through Celite® and concentrated in vacuo. The reaction mixture was then pre-adsorbed onto silica and purified by flash column chromatography to afford malonate 3.62 (0.478 g, 2.14 mmol, 78%). Compound 3.62 was obtained as a viscous clear oil: \( R_f = 0.28 \) (70% ethyl acetate in hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 8.61 \) (s, 1H), 8.55, 7.68, 7.30 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 3.71 (s, 3H), 3.40 (s, 2H), 1.59 (d, J = 6.6 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 166.7, 165.5, 149.2, 147.6, 134.0, 123.5, 110.8, 71.4, 52.5, 41.4, 21.7 \); IR (thin film, cm\(^{-1}\)): 3033, 2986, 2954, 2849, 1740, 1735, 1589, 1481, 1437, 1412, 1344, 1324, 1275, 1203, 1152, 1068, 1042, 1024, 961, 850, 811; HRMS calc’d for C\(_{11}\)H\(_{13}\)O\(_4\)N = 223.0845, found 223.0847.

A 10 mL solution of acetonitrile, malonate 3.62 (0.133 g, 0.596 mmol, 1 equiv.), \( p \)-acetamido benzensulfonyl azide (0.157 g, 0.655 mmol, 1.1 equiv.) was cooled to 0 °C. Triethyl amine (0.25 mL, 1.78 mmol, 3 equiv.) was then added and the solution was gradually warmed to room temperature. After 48 h the reaction no longer showed signs of progress and was then concentrated and pre-adsorbed onto silica. Purification by flash column chromatography provided diazomalonate 3.65 (0.058 g, 0.232 mmol, 40%). Compound 3.65 was obtained as a clear colourless oil: \( R_f = 0.26 \) (70% ethyl acetate in hexanes); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta = 8.64 \) (s, 1H), 8.57 (d, J = 4.6 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.31 (dd, J = 7.6, 4.6 Hz, 1H), 6.06 (q, J = 7.0 Hz, 1H), 5.68 (t, J = 7.6 Hz, 1H), 4.89 (s, 1H), 4.73 (s, 1H), 4.56 (s, 1H), 3.76 (s, 3H), 2.01 (s, 3H), 1.56 (d, J = 6.6 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 166.7, 165.5, 149.2, 147.6, 134.0, 123.5, 110.5, 76.4, 52.5, 41.4, 21.7 \); IR (thin film, cm\(^{-1}\)): 3033, 2986, 2954, 2849, 1740, 1735, 1594, 1579, 1481, 1437, 1412, 1344, 1324, 1275, 1203, 1152, 1068, 1042, 1024, 961, 850, 811; HRMS calc’d for C\(_{21}\)H\(_{17}\)N\(_4\)O\(_{2}\)S = 395.1160, found 395.1164.
Hz, 1H), 3.84 (s, 3H), 1.64 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 161.2, 160.3, 149.6, 147.9, 136.4, 133.8, 123.5, 71.6, 52.5, 22.1 (Missing one carbon resonance); IR (thin film, cm$^{-1}$): 2985, 2956, 2140, 1761, 1734, 1695, 1480, 1437, 1344, 1318, 1272, 1181, 1083, 1041, 957, 811; HRMS calc’d for C$_{13}$H$_{11}$O$_4$N$_3$ = 249.0750, found 249.0747.

To a solution of 2-(indol-3-yl)ethanol$^{25}$ (0.100 g, 0.620 mmol, 1 equiv.) in 10 mL THF at 0 °C was added sodium hydride (60% dispersion in paraffin oil, 0.055 g, 0.136 mmol, 2.2 equiv.) and the reaction was maintained at 0 °C for 1 h. A 5 mL solution of toluene sulfonic chloride (0.248 g, 1.30 mmol, 2.2 equiv.) in THF was then added to the reaction mixture via cannula. The reaction was then allowed to slowly warm to room temperature overnight. The reaction was then quenched with 5% v/v HCl solution, transferred to a separatory funnel, diluted with 100 mL distilled water and extracted with ethyl acetate (2 x 50 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated. The crude reaction mixture was purified by flash column chromatography to yield compound 3.71, which was obtained as a bright white foam (0.186 g, 0.397 mmol, 64%): $R_f$ = 0.63 (70% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.94 (dd, J = 8.2, 2.0 Hz, 1H) 7.74, (dd, J = 8.6, 2.0 Hz, 2H), 7.57 (dd, J = 8.6, 2.0 Hz, 2H), 7.32-7.27 (m, 3H), 7.21 (d, J = 8.2 Hz, 2H), 7.18-7.16 (m, 1H), 7.15 (d, J = 8.6 Hz, 2H), 4.25 (t, J = 6.6 Hz, 2H), 3.01 (t, J = 6.6 Hz, 2H), 2.38 (s, 3H), 2.31 (s 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 144.9, 144.7, 135.1, 135.0, 132.4, 130.1, 129.9, 129.6, 127.6, 126.7, 124.7, 124.0, 123.1, 119.0, 117.1, 113.6, 68.7, 24.8, 21.6, 21.5; IR (thin film, cm$^{-1}$): 3112, 3052, 2958, 2923, 1597, 1448, 1362, 1307, 1293, 1281, 1212, 1188, 1175, 1134, 1121, 1097, 1086, 1020, 995, 976, 904, 748; HRMS calc’d for C$_{23}$H$_{24}$O$_5$NS$_2$ = 469.1018, found 469.1012.

A 5 mL microwave reaction vial was charged with 1-(pyridin-3-yl)ethanol 3.60$^{14}$ (0.087 g, 0.706 mmol, 1.01 equiv.), bistosylated indole 3.71 (0.328 g, 0.694 mmol, 1 equiv.) and 4 mL diethyl ether. The reaction vial was purged
with argon, sealed and heated under microwave irradiation conditions at 130 °C for 50 min. The reaction was then allowed to cool to room temperature, the supernatant was transferred to a 50 mL round bottom flask and the oily viscous residue was dissolved in CHCl$_3$ and combined with the supernatant in the round bottom flask. Concentration in vacuo provided pyridinium salt 3.72 as a bright white foam. Attempts at recrystallization were unsuccessful, and 3.72 was carried forward without further purification. $^1$H NMR (400 MHz, CDCl$_3$): δ = 8.77 (s, 1H), 8.61 (d, $J$ = 3.5 Hz, 1H), 8.06 (d, $J$ = 7.8 Hz, 1H), 7.83 (d, $J$ = 8.6 Hz, 1H), 7.67 (d, $J$ = 8.2 Hz, 2H), 7.64 (d, $J$ = 7.4 Hz, 2H), 7.53 (dd, $J$ = 5.9, 5.9 Hz, 1H), 7.45 (s, 1H), 7.23 (d, $J$ = 7.8 Hz, 1H), 7.18 (dd, $J$ = 7.8, 7.8 Hz, 1H), 7.09 (d, $J$ = 8.2 Hz, 2H), 7.02-7.00 (m, 1H), 7.00 (d, $J$ = 8.2 Hz, 2H), 4.87 (m, 2H), 4.82 (q, $J$ = 6.2 Hz, 1H), 3.25 (m, 2H), 2.20 (s, 3H), 2.19 (s, 3H), 1.13 (d, $J$ = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 148.2, 145.1, 142.9, 142.7, 142.3, 142.1, 139.7, 134.6, 134.5, 129.9, 129.8, 128.7, 127.3, 126.8, 125.7, 124.9, 124.8, 123.4, 119.0, 116.6, 113.2, 65.8, 61.1, 26.6, 24.0, 21.4, 21.1; IR (thin film, cm$^{-1}$): 3322, 3085, 3061, 2976, 2925, 2869, 2239, 1597, 1496, 1449, 1367, 1283, 1215, 1174, 1122, 1034, 1011, 926, 816, 748; HRMS for C$_{31}$H$_{32}$O$_6$N$_2$S$_2$ could not be obtained on multiple attempts.

Crude pyridinium salt 3.72 (0.279 g, 0.471 mmol, 1 equiv.) was dissolved in 5 mL methanol at 0 °C. Sodium borohydride (0.053 g, 1.41 mmol, 3 equiv.) was then added in small portions over 3 min. and the reaction was allowed to slowly warm to room temperature. At 3 h TLC analysis indicated consumption of starting material 3.72 and the reaction was quenched with 5 mL distilled water, diluted with 10 mL ethyl acetate and transferred to a separatory funnel. The organic layer was washed 2 x with 50 mL saturated NaHCO$_3$ solution and then 50 mL water. The aqueous layer was extracted with 30 mL ethyl acetate, the organic layers were then combined, washed once with 50 mL brine solution and then dried over MgSO$_4$. The salts were then removed by filtration and the organic filtrates concentrated. Purification by flash column chromatography afforded compound 3.73 as a light beige foam (0.113 g, 0.268 mmol, 57% over 2 steps): $R_f$ = 0.21 (10% methanol in ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.97 (d, $J$ = 8.2 Hz, 1H), 7.74 (d, $J$ = 8.6 Hz, 2H), 7.50 d, $J$ = 7.4 Hz, 1H),
7.37 (s, 1H), 7.30 (dd, J = 8.2, 7.0 Hz, 1H), 7.24 (dd, J = 7.8, 7.0 Hz, 1H), 7.19 (d, J = 8.6 Hz, 2H), 5.72 (bs, 1H), 4.24 (q, J = 6.3 Hz, 1H), 3.21 (d, J = 15.3 Hz, 1H), 3.00 (dd, J = 15.2, 2.0 Hz, 1H), 2.95-2.91 (m, 2H), 2.87-2.72 (m, 3H), 2.71 (dd, J = 11.3, 5.6 Hz, 1H), 2.53 (dd, J = 12.1, 7.0, 5.0 Hz, 1H), 2.32 (s, 3H), 2.28-2.14 (m, 2H), 1.28 (d, J = 6.3 Hz, 3H); 

13C NMR (100 MHz, CDCl3): δ = 144.7, 140.0, 135.2, 130.9, 129.8, 126.7, 124.6, 123.0, 122.9, 120.9, 119.5, 119.4, 113.7, 70.2, 57.8, 51.4, 50.2, 25.5, 22.8, 21.7, 21.5; IR (thin film, cm⁻¹): 2967, 2920, 2837, 1448, 1368, 1305, 1206, 1172, 1120, 1096, 1021, 973, 809, 669; HRMS calc’d for C24H28O3N2S = 424.1821, found 424.1805.

To a solution of 3.73 (0.120 g, 0.283 mmol, 1 equiv.), potassium monomethyl malonate24 (0.096 g, 0.565 mmol, 2 equiv.), dicyclohexylcarbodiimide (DCC) (0.116 g, 0.565 mmol, 2 equiv.) and N,N-dimethyl amino pyridine (DMAP) (0.005 g, 0.028 mmol, 0.1 equiv.), in 60 mL THF was added toluene sulfonic acid (0.108 g, 0.565 mmol, 2 equiv.). Immediate formation of a white precipitate was observed. When alcohol 3.73 was consumed as indicated by TLC, the reaction was filtered through Celite® and concentrated in vacuo. The reaction mixture was then pre-adsorbed onto silica and purified by flash column chromatography to afford diester 3.74 (0.109 g, 0.209 mmol, 74%). Compound 3.74 was obtained as a viscous yellow oil: Rf = 0.72 (10% methanol in ethyl acetate); 1H NMR (600 MHz, CDCl3): δ = 7.97, (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 7.30 (dd, J = 8.2 Hz, 7.0 Hz, 1H), 7.23 (dd, J = 8.2 Hz, 7.0 Hz, 1H), 7.20 (d, J = 8.8 Hz, 2H), 5.83 (s, 1H), 5.38 (q, J = 6.4 Hz, 1H), 3.72 (s, 3H), 3.37 (s, 2H), 3.05 (d, J = 2.3 Hz, 2H), 2.92 (dd, J = 8.8, 7.0 Hz, 2H), 2.76 (dd, J = 8.2, 7.6 Hz, 2H), 2.66 (ddd, J = 11.2, 11.2, 5.3 Hz, 1H), 2.56 (ddd, J = 11.7, 6.4, 5.3 Hz, 1H), 2.33 (s, 3H), 2.29-2.16 (m 2H), 1.37 (d, J = 6.4 Hz, 3H); 13C NMR (150 MHz, CDCl3): δ = 167.0, 165.8, 144.7, 135.2, 135.0, 131.0, 129.8, 126.7, 124.6, 123.0, 122.9, 122.8, 121.0, 119.4, 113.7, 110.0, 73.6, 57.6, 52.4, 51.8, 49.7, 41.6, 25.6, 22.9, 21.5, 18.6; IR (thin film, cm⁻¹): 2927, 2853, 2804, 1755, 1733, 1653, 1597, 1447, 1368, 1274, 1173, 1122, 1097, 1020, 975, 814, 703; HRMS calc’d for C28H32O6N2S = 524.1981, found 524.1988.
2-Iodoxybenzoic acid (IBX) (1.93 g, 6.90 mmol, 2.1 equiv.) was suspended in a solution of alcohol 3.82 (0.967, 3.32 mmol, 1 equiv.) in 50 mL ambient ethyl acetate and then set to reflux for 2 hours. The reaction mixture was then cooled to room temperature and filtered through Celite®. Aldehyde 3.79 could then be obtained by recrystallization from hexanes and ethyl acetate to give fine transparent pink cubes (0.892 g, 3.08 mmol, 93%) M.p. = 90-91 °C; R_f = 0.58 (70% ethyl acetate in hexanes); ^1H NMR (400 MHz, CDCl_3): δ = 9.66 (dd, _J_ = 2.5, 2.5 Hz, 1H), 9.22 (br. s, 1H), 7.52 (dddd _J_ = 8.0, 1.0, 0.8, 0.8 Hz, 1H), 7.41 (ddd, _J_ = 8.0, 1.0, 1.0 Hz, 1H), 7.25 (ddd, _J_ = 7.0, 7.0, 1.2 Hz, 1H), 7.15 (ddd, _J_ = 7.0, 7.0, 1.2 Hz, 1H), 4.97 (s, 1H), 3.80 (d, _J_ = 2.5 Hz, 2H), 3.79 (s, 6H); ^13C NMR (100 MHz, CDCl_3): δ = 198.6, 167.3, 135.8, 127.5, 126.6, 123.1, 120.2, 118.4, 111.5, 105.1, 53.4, 48.8, 39.2; IR (thin film, cm^{-1}): 3398, 3021, 2957, 2846, 2726, 1728, 1623, 1459, 1436, 1385, 1340, 1274, 1244, 1211, 1153, 1020, 930, 908, 745; HRMS calc’d for C_{15}H_{15}O_{5}N = 289.0950, found 289.0957.

3-[2-(tert-Butyldimethylsilyloxy)ethyl]indole\textsuperscript{26} (8.31 g, 30.2 mmol, 1 equiv.) was dissolved in 150 mL DMF at 0 °C in a 500 mL round bottom flask. Sodium hydride 60% dispersion in paraffin oil (1.57 g, 39.2 mmol, 1.3 equiv.) was then added and the solution was stirred at 0 °C for 20 minutes at which point gas evolution had ceased. Benzyl bromide (4.00 mL, 33.2 mmol, 1.1 equiv.) was then added dropwise via syringe and the solution was kept at 0 °C for a further 15 minutes before it was warmed to room temperature for 30 minutes, at which point TLC analysis indicated the reaction was complete. The reaction was quenched with 100 mL water, transferred to a separatory funnel and diluted with 100 mL ethyl acetate. The aqueous layer was washed two times with 100 mL ethyl acetate. The combined organic fractions where then washed twice with distilled water (100 mL) and once with brine (70 mL). The organic fraction was dried over MgSO_4 then filtered and concentrated. The crude product was then pre-
absorbed on silica and purified by flash column chromatography (10% ethyl acetate in hexanes) yielding benzylated indole 3.80 (10.7 g, 29.3 mmol, 97%) as a clear and colourless viscous oil. \( R_f = 0.64 \) (30% ethyl acetate in hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.61 \) (d, \( J = 7.6 \) Hz, 1H), 7.29-7.24 (m, 5H), 7.16, (dd, \( J = 8.0, 7.0, 1.2 \) Hz, 1H) 7.12-7.10 (m, 2H), 6.97, (s, 1H), 5.27 (s, 2H), 3.87 (dd, \( J = 7.4, 7.4 \) Hz, 2H), 2.99 (dd, \( J = 7.4, 7.4 \) Hz, 2H), 0.89 (s, 9H), 0.02 (2, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 137.7, 136.5, 128.7, 128.4, 127.5, 126.8, 126.3, 121.6, 119.1, 118.9, 112.3, 109.6, 63.9, 49.9, 29.0, 26.0, 18.4, -5.3; IR (thin film, cm\(^{-1}\)): 3058, 3031, 2954, 2928, 2897, 2856, 1615, 1559, 1496, 1467, 1454, 1388, 1369, 1333, 1255, 1215, 1174, 1093, 1051, 1029, 1013, 920, 836, 812, 776, 737, 698; HRMS calc’d for C\(_{23}\)H\(_{31}\)ONSi = 365.2175, found 365.2180.

Copper(II) acetylacetonate (5 mg, 0.0204 mmol, 1%) was added to a solution of benzyl indole 3.80 (1.12 g, 3.06 mmol, 1.5 equiv.) dissolved in 8 mL benzene in a 25 mL round bottom flask. The flask was fitted with a reflux condenser, purged with Ar (g) and set to reflux. Once the solution had begun to reflux a solution of dimethyl 2-diazomalonate 3.48 (0.323 g, 2.04 mmol, 1 equiv.) in 4 mL benzene was added dropwise via syringe over 40 minutes. The syringe was then rinsed with 3 mL benzene and this was added to the reaction mixture. After 22 hours at reflux TLC analysis showed the dimethyl 2-diazomalonate was consumed. The reaction mixture was then pre-adsorbed on silica and purified by flash column chromatography. Elution gradient began at 5% ethyl acetate in hexanes until remaining benzylated indole 3.80 eluted, and then adjusted to 10% ethyl acetate in hexanes to obtain the desired malonyl indole 3.81 (0.805 g, 1.62 mmol, 80%) as a pale yellow oil. \( R_f = 0.51 \) (30% ethyl acetate in hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.62 \) (dd, \( J = 5.9, 2.2 \) Hz, 1H), 7.20-7.04 (m, 6H), 6.84 (m, 2H), 5.48 (s, 2H), 5.13 (s, 1H), 3.80 (dd, \( J = 7.7, 7.4 \) Hz, 2H), 3.42, (s, 6H), 3.03 (dd, \( J = 7.7, 7.4 \) Hz, 2H), 0.87 (s, 9H), 0.02 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 167.4, 137.4, 137.2, 128.3, 127.6, 127.5, 126.9, 125.8, 122.5, 119.5, 119.2, 112.7, 110.2, 63.6, 52.6, 49.0, 47.7, 28.6, 18.4, -5.4; IR (thin film, cm\(^{-1}\)): 3059, 3032, 3004, 2954, 2928, 2897, 2856, 1615, 1559, 1496, 1467, 1454, 1388, 1369, 1333, 1255, 1215, 1174, 1093, 1051, 1029, 1013, 920, 836, 812, 776, 737, 698; HRMS calc’d for C\(_{23}\)H\(_{31}\)ONSi = 365.2175, found 365.2180.
Malonyl indole 3.81 (2.54 g, 5.12 mmol, 1 equiv.) was dissolved in 50 mL THF in a 250 mL round bottom flask and then cooled to -78 °C. Ammonia (approx. 50 mL) was then condensed into the flask by slowly bubbling ammonia gas into the cooled solution for 1 hour. Lithium metal (0.178 g, 25.6 mmol, 5 equiv.) was then added in small portions over 5 minutes. The reaction was kept at -78 °C for 1 hour, at which point TLC analysis indicated that the reaction was complete. The reaction was opened to atmosphere and carefully quenched with 25 mL saturated ammonium chloride. The reaction was then slowly warmed to room temperature with stirring overnight to dissipate the ammonia gas. The residue was then transferred to a separatory funnel with 100 mL distilled water and 100 mL ethyl acetate. The aqueous layer was washed two times with 50 mL ethyl acetate. The combined organic fractions where then washed twice with distilled water (100 mL) and once with brine (100 mL). The organic fraction was dried over MgSO₄ then filtered and concentrated to give indole 3.82a (2.02 g, 4.98 mmol, 97%) as flat shiny white flakes (recrystallized from hexanes), M.p. = 60-61 °C; R_f = 0.49 (30% ethyl acetate in hexanes); ¹H NMR (400 MHz, CDCl₃): δ = 8.94 (br. s, 1H), 7.58 (dd, J = 8.0, 0.7 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.21 (dd, J = 7.0, 7.0, 1.2 Hz, 1H), 7.12 (dd, J = 7.0, 7.0, 1.2 Hz, 1H), 5.14 (s, 1H), 3.82 (dd, J = 7.4, 7.4 Hz, 2H), 3.79 (s, 6H), 3.02 (dd, J = 7.4, 7.4 Hz, 2H), 0.89 (s, 9H), 0.03 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 167.7, 135.9, 127.6, 125.2, 122.4, 119.4, 118.8, 112.0, 111.2, 63.5, 53.2, 48.9, 27.9, 25.9, 18.4, -5.4; IR (thin film, cm⁻¹): 3408, 3060, 3035, 2955, 2929, 2885, 2858, 2740, 1740, 1676, 1621, 1472, 1459, 1436, 1410, 1324, 1256, 1213, 1150, 1093, 1010, 939, 836, 742, 663; HRMS calc’d for C₂₁H₃₁O₅NSi = 405.1971, found 405.1986.

To a solution of debenzylated indole 3.82a (0.592, 1.46 mmol, 1 equiv.) in 12 mL dry MeOH at 0 °C was added acetyl chloride (0.11 mL, 1.61 mmol, 1.1 equiv.) dropwise via syringe to
generate dry HCl by acylation of methanol. The reaction was kept at 0 °C for 10 minutes
and then quenched with 6 mL saturated sodium bicarbonate solution. The reaction
mixture was transferred to a separatory funnel and diluted with 70 mL ethyl acetate. The
aqueous layer was washed with 70 mL ethyl acetate. The combined organic fractions
were washed with 30 mL saturated sodium bicarbonate solution, then 50 mL distilled
water and finally with brine. The organic fraction was dried over MgSO$_4$ then filtered and
concentrated. The reaction mixture was then purified by flash column chromatography.
Elution gradient began at 30% ethyl acetate in hexanes and was gradually increased to
70% ethyl acetate in hexanes to give alcohol 3.82 (0.394, 1.35 mmol, 93%) which was
recrystallized from diethyl ether and hexanes to give shiny transparent beige cubes M.p. = 86-87 °C; R$_f$ = 0.19 (50% ethyl acetate in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ = 8.93 (br. s, 1H), 7.58 (dd, $J$ = 8.0, 1.0 Hz, 1H), 7.37 (ddd, $J$ = 8.0, 1.0, 1.0 Hz, 1H), 7.23 (ddd, $J$ = 7.0, 7.0, 1.2 Hz, 1H), 7.13 (ddd, $J$ = 7.0, 7.0, 1.0 Hz, 1H), 5.12 (s, 1H), 3.85 (dd, $J$ = 6.1, 6.1 Hz, 2H), 3.79 (s, 6H), 3.03 (dd, $J$ = 6.1, 6.1 Hz, 2H), 1.92 (br. s, 1H); $^{13}$C
NMR (150 MHz, CDCl$_3$): δ = 168.0, 136.1, 127.3, 126.0, 122.8, 119.6, 118.8, 111.8,
111.3, 62.5, 53.3, 48.9, 27.6; IR (thin film, cm$^{-1}$): 3548, 3404, 3116, 3059, 3010, 2955,
2882, 1734, 1676, 1621, 1559, 1491, 1459, 1436, 1312, 1278, 1243, 1209, 1156, 1104,
1043, 1010, 932, 909, 851, 746, 668; HRMS calc’d for C$_{15}$H$_{17}$O$_5$N = 219.1107, found
219.1112.

A solution of 1-(pyridin-3-yl)ethanol 3.60$_{14}$ (0.713 g, 5.78 mmol, 1
equiv.), thalimide (0.936 g, 6.36 mmol, 1.1 equiv.) and triphenyl phosphine (1.67 g, 6.36 mmol, 1.1 equiv.) in 50 mL THF was cooled to
0 °C. Diisopropyl azodicarboxylate (DIAD) (1.25 mL, 6.36 mmol, 1.1
equiv.) was then added dropwise by syringe. After 20 minutes at 0 °C
the reaction was concentrated and pre-adsorbed onto silica and purified by flash column
chromatography. Elution gradient began at 10% dichloromethane in hexanes until the
triphenyl phosphine oxide by-product eluted and then adjusted to 10% ethyl acetate in
hexanes and gradually increased to 50% ethyl acetate in hexanes until the product
pyridine 3.83 (1.14 g, 4.52 mmol, 78%) eluted. Recrystallization from diethyl ether and
hexanes gave large white flakes M.p. = 83-84 °C. R$_f$ = 0.45 (100% ethyl acetate); $^1$H
NMR (400 MHz, CDCl₃): δ = 8.69 (d, J = 1.4 Hz, 1H), 8.48 (dd, J = 4.8, 1.4 Hz, 1H), 7.86 (ddd, J = 8.0, 1.6, 1.6 Hz, 1H), 7.81-7.75 (m, 2H), 7.70-7.65 (m, 2H), 7.24 (ddd, J = 8.0, 4.8, 0.8 Hz, 1H), 5.57 (q, J = 7.2 Hz, 1H), 1.91 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 167.8, 149.2, 149.0, 135.6, 135.0, 134.0, 131.7, 128.3, 123.2, 47.3, 17.2; IR (thin film, cm⁻¹): 3036, 2983, 2940, 1774, 1757, 1711, 1468, 1427, 1387, 1357, 1333, 1173, 1146, 1128, 1061, 1025, 879, 723, 711, 618; HRMS calc’d for C₁₅H₁₂O₂N₂ = 252.0899, found 252.0900.

Benzyl bromide (1.36 mL, 11.4 mmol, 1 equiv.) was added to a solution of pyridine 3.83 (2.87 g, 11.4 mmol, 1 equiv.) in 25 mL ambient acetonitrile in a 100 mL round bottom flask. The flask was then fitted with a reflux condenser, purged with Ar (g) and set to reflux for 30 minutes at which point the pyridinium salt 3.84 was observed to precipitate from the reaction mixture. The reaction was then cooled to room temperature, the acetonitrile was removed in vacuo and the resultant residue was recrystallized from chloroform and diethyl ether to give pyridinium salt 3.84 (4.53 g, 10.7 mmol, 94%) as bright white small opaque flakes, M.p. = 199-201 °C; ¹H NMR (400 MHz, CDCl₃): δ = 9.62 (d, J = 6.1 Hz, 1H), 9.64 (s, 1H), 8.36 (d, J = 8.2 Hz, 1H), 8.01 (dd, J = 8.0, 6.1 Hz, 1H), 7.80-7.75 (m, 2H), 7.73-7.66 (m, 4H), 7.35-7.30 (m, 3H), 5.70 (q, J = 7.2 Hz, 1H), 1.98 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 167.3, 144.3, 143.9, 141.1, 134.5, 132.8, 131.3, 129.8, 129.6 (2 overlapping resonances), 129.5, 128.0, 123.6, 64.1, 46.5, 17.5; IR (thin film, cm⁻¹): 3463, 3024, 2941, 2189, 1776, 1711, 1634, 1611, 1508, 1498, 1468, 1457, 1385, 1335, 1238, 1205, 1138, 1064, 1030, 1014, 1003, 923, 881, 804, 772, 723, 685, 641; HRMS for C₂₂H₁₉O₂N₂Br could not be obtained on multiple attempts.

Pyridinium salt 3.84 (0.908 g, 2.15 mmol, 1 equiv.) was dissolved in 25 mL of 2:1 MeOH:THF and then cooled to -78 °C. Solid sodium borohydride (0.528 g, 13.9 mmol, 6.5 equiv.) was then added in 6 x 0.088 g portions at twenty minute intervals. The
reaction was then kept at –78 °C for 3.5 hours after the final NaBH₄ addition. The reaction was then quenched with 10 mL acetone and allowed to warm to room temperature. The reaction mixture was transferred to a separatory funnel and diluted with 100 mL ethyl acetate. The organic layer was washed twice with 50 mL 1M NaOH then 100 mL brine. The organic layer was dried over MgSO₄ then filtered and concentrated. The reaction mixture was then purified by flash column chromatography to give tetrahydropyridine 3.85 as a viscous yellow oil (0.541 g, 1.56 mmol, 73%). When this reaction was carried out on larger scales (>1 g) yields generally dropped to 40-50%. Rₓ = 0.56 (100% ethyl acetate); ¹H NMR (400 MHz, CDCl₃): δ = 7.84-7.79 (m, 2H), 7.74-7.68 (m, 2H), 7.31-7.18 (m, 5H), 5.85 (ap. dq J = 1.8, 1.6, 1H), 4.83, (dq, J = 7.2, 1.0 Hz, 1H), 3.58 (A of AB d, J = 13.1 Hz, 1H), 3.50 (B of AB d, J = 13.1 Hz, 1H), 3.04 (ap. dd, J = 15.6, 1.4 Hz, 1H), 2.90 (ap. dd, J = 15.4, 1.8 Hz, 1H), 2.52 (ap. q, J = 5.7 Hz, 1H), 2.41 (ap. q, J = 5.7 Hz, 1H), 2.17 (br. s, 2H), 1.62 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 168.2, 138.2, 134.2, 133.8, 131.9, 129.1, 128.1, 126.9, 122.1, 122.1, 62.3, 53.9, 49.3, 48.7, 25.6, 16.0; IR (thin film, cm⁻¹): 3086, 3063, 3029, 2979, 2913, 2805, 1775, 1718, 1612, 1495, 1468, 1454, 1387, 1331, 1214, 1173, 1156, 1134, 1047, 1031, 1004, 960, 880, 848, 794, 752, 724, 700, 668, 610; HRMS calc’d for C₂₂H₂₂O₂N₂ = 346.1681, found 346.1681.

Tetrahydropyridine 3.85 was de-benzylated by the reported procedure.²⁰ Tetrahydropyridine 3.85 (0.428 g, 1.24 mmol, 1 equiv.) was dissolved in 10 mL dichloromethane and cooled to 0 °C. 1-Chloroethyl chloroformate 3.86 (0.170 mL, 1.61 mmol, 1.3 equiv.) was then added dropwise via syringe and the solution was kept at 0 °C for 30 minutes. The reaction mixture was then concentrated and then re-dissolved in 15 mL dry methanol. The round bottom flask was fitted with a reflux condenser and set to reflux for 40 minutes. The crude reaction mixture was then concentrated and dried in vacuo. ¹H-NMR analysis confirmed the crude ammonium chloride salt 3.87 along with small amounts benzyl chloride. Attempts at purification at this stage were unsuccessful so the ammonium salt 3.87 was
carried forward without further purification. The crude ammonium chloride salt 3.87 was dissolved in THF and cooled to °C. After 30 minutes at 0 °C the solution amine was transferred by cannula (with 5 mL THF rinse) to a 50 mL round bottom flask containing aldehyde 3.79 (0.382 g, 1.32 mmol, 1.05 equiv.) dissolved in 5 mL THF at 0 °C. This solution was stirred at 0 °C for 1 hour, then NaBH(OAc)$_3$ (s) (0.524 g, 2.47 mmol, 2 equiv.) was added. The reaction mixture was kept at 0 °C for 4 hours then allowed to warm to room temperature for a further 16 hours. The reaction was then quenched with 10 mL saturated NaHCO$_3$, transferred to a separatory funnel and diluted with 100 mL ethyl acetate. The organic fraction was washed twice with 100 mL saturated NaHCO$_3$ then with 100 mL water and finally with 50 mL brine. The organic fraction was dried over Na$_2$SO$_4$, filtered and then purified by flash column chromatography, elution gradient from 30% to 100% ethyl acetate in hexanes. Reductive ammination product 3.88 (0.653 g, 1.23 mmol, 83%) was obtained as a bright white foam, M.p. = 62-63 °C; $R_f = 0.28$ (100% ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.88$ (br s, 1H), 7.81 (m, 2H), 7.70 (m, 2H), 7.54 (d, $J = 8.2$ Hz, 1H), 7.33 (d, $J = 8.2$ Hz, 1H), 7.17 (dd, $J = 8.2$, 8.2 Hz, 1H), 7.06 (dd, $J = 7.0$, 7.0 Hz, 1H), 5.90 (br s, 1H), 5.08 (s, 1H), 4.89 (q, $J = 7.0$ Hz, 1H), 3.75 (s, 6H), 3.13 (br d, $J = 15.8$ Hz, 1H), 3.00-2.94 (m, 3H), 2.69 (ap. q, $J = 5.9$ Hz, 1H), 2.62 (dd, $J = 8.2$, 8.2 Hz, 1H), 2.56 (ap. q, $J = 5.9$ Hz, 1H), 2.27 (br. s, 2H), 1.67 (d, $J = 7.0$ Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 168.2$, 167.7, 135.9, 134.3, 133.8, 131.9, 127.4, 124.7, 123.1, 122.4, 122.2, 119.3, 118.8, 113.3, 111.2, 58.7, 53.8, 53.1, 49.5, 49.3, 48.8, 25.7, 22.1, 16.0; IR (thin film, cm$^{-1}$): 3404, 3026, 2954, 2810, 1735, 1711, 1459, 1437, 1387, 1352, 1331, 1287, 1242, 1215, 1149, 1067, 880, 748, 724, 668; HRMS calc’d for C$_{30}$H$_{31}$O$_6$N$_3$ = 529.2213, found 529.2225.

Indole 3.88 (0.184 g, 0.347 mmol, 1 equiv.) was dissolved in 3 mL dichloromethane and cooled to 0 °C. A solution of meta-chloroperbenzoic acid (mCPBA) (0.085 g, 0.381 mmol, 1.1 equiv.) in 4 mL dichloromethane was then added dropwise over 30 minutes. Five minutes after the addition of mCPBA was completed K$_2$CO$_3$ (0.047 g,
0.340 mmol, 1 equiv.) was added and the reaction was stirred at 0 °C for a further 30 minutes, at which point the reaction was filtered through Celite®, concentrated and then purified by flash column chromatography. Elution gradient of 0-30% MeOH in ethyl acetate gave N-oxide 3.89 as an approximately 1:1 mixture of inseparable diastereomers (0.150 g, 0.275 mmol, 79%) as small opaque white flakes, decomposition at 116 °C; R_f = 0.28 (30% MeOH in ethyl acetate);

^1^H NMR (400 MHz, CDCl_3): See spectra on page 309.

^13^C NMR (150 MHz, CDCl_3): See spectra on page 309.

IR (thin film, cm^-1): 3385, 3011, 2954, 2926, 2856, 2742, 1773, 1752, 1735, 1712, 1617, 1611, 1596, 1560, 1507, 1458, 1437, 1385, 1350, 1331, 1245, 1218, 1201, 1145, 1075, 1019, 880, 750, 723; HRMS calc'd for C_{30}H_{31}O_7N_3 = 545.2162, found 545.2147.

The modified Polonovski-Potier reaction was carried out as follows. N-oxide 3.89 (0.157 g, 0.288 mmol, 1 equiv.) was dissolved in 3 mL dichloromethane. Trimethylsilylcyanide (46 µL, 0.346 mmol, 1.2 equiv.) was added and the reaction mixture was cooled to 0 °C. Trifluoroacetic anhydride 47 µL, 0.346 mmol, 1.2 equiv.) was then added dropwise over 5 minutes and the solution gradually changed colour from pale yellow to bright yellow. After 20 minutes at 0 °C the reaction was warmed to room temperature for 5 minutes, then quenched with 2 mL saturated NaHCO_3 solution then transferred to a separatory funnel and diluted with 50 mL ethyl acetate. The organic fraction was washed with 50 mL saturated NaHCO_3, then with 50 mL distilled water followed by 50 mL brine. The organic fraction was dried over Na_2SO_4, filtered and then concentrated to give the crude mixture of approximately 1:1 diastereomers of the α-cyano amine 3.90 (0.149 g, 0.269 mmol, 93% crude) as a bright orange foam, decomposes at 89 °C.

^1^H NMR (400 MHz, CDCl_3): See spectra on page 310.

^13^C NMR (150 MHz, CDCl_3): See spectra on page 310.
IR (thin film, cm$^{-1}$): 3397, 3023, 2955, 2843, 2222, 2189, 1774, 1735, 1710, 1617, 1595, 1459, 1437, 1385, 1351, 1330, 1289, 1216, 1181, 1148, 1025, 881, 852, 751, 725, 668;
HRMS for C$_{31}$H$_{30}$O$_6$N$_4$ could not be obtained on multiple attempts.

Indole 3.88 (0.160 g, 0.302 mmol, 1 equiv.), lithium chloride (0.260 g, 0.604 mmol, 2 equiv.) and triethylammonium chloride (0.029 g, 0.302 mmol, 1 equiv.) were placed in a 5 mL microwave vial and then covered in 2 mL DMF. The reaction vial was purged with Ar (g), capped and then heated in the microwave to 120 °C for 1.5 hours. The reaction is then poured into 30 mL distilled water and 30 mL ethyl acetate in a separatory funnel. The organic layer is washed with 20 mL saturated NaHCO$_3$, then with 20 mL distilled water followed by 30 mL brine. The organic fraction is dried over MgSO$_4$ then filtered and concentrated. The reaction mixture was then purified by flash column chromatography to give monoester indole 3.94 (0.112 g, 0.237 mmol, 79%) as a light beige foam, M.p. = 62-64 °C. R$_f$ = 0.56 (30% MeOH in ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$): δ = 8.58 (br. s, 1H), 7.81 (ap. dd, $J = 5.3, 3.2$ Hz, 2H), 7.69 (ap. dd, $J = 5.3, 3.2$ Hz, 2H), 7.50 (br. d, $J = 7.6$ Hz, 1H), 7.28 (d, $J = 8.2$ Hz, 1H), 7.12 (dd, $J = 8.2$ Hz, 1H, 7.0 Hz, 1H), 7.05 (dd, $J = 8.2$ Hz, 7.0 Hz, 1H), 5.90 (m, 1H), 4.89 (q, $J = 7.0$ Hz, 1H), 3.76 (s, 2H), 3.70 (s, 3H), 3.13 (d, $J = 15.2$ Hz, 1H), 2.98 (d, $J = 15.2$ Hz, 1H), 2.95-2.88 (m, 2H), 2.70 (ap. q, $J = 5.3$ Hz, 1H), 2.61 (ap. dd, $J = 8.8, 7.6$ Hz, 2H), 2.57 (ap. q, $J = 5.9$ Hz, 1H), 2.27 (br. s, 2H), 1.67 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ = 170.9, 168.2, 135.6, 134.2, 133.8, 131.9, 127.9, 126.6, 119.2, 118.4, 111.4, 110.7, 58.8, 53.8, 52.2, 49.4, 49.3, 31.5, 25.7, 22.1, 16.0; IR (thin film, cm$^{-1}$): 3397, 3058, 3027, 2949, 2925, 2856, 2837, 2810, 2768, 1775, 1738, 1711, 1682, 1612, 1455, 1439, 1386, 1352, 1331, 1265, 1240, 1217, 1171, 1147, 1120, 1044, 1025, 1011, 880, 749, 724; HRMS calc’d for C$_{28}$H$_{29}$O$_4$N$_3$ = 471.2158, found 471.2170.
Monoester indole 3.94 (0.194 g, 0.411 mmol, 1 equiv.) and N,N-dimethyl 4-aminopyridine (DMAP) (0.005 g, 0.0411 mmol, 10%) was dissolved in 5 mL dichloromethane at room temperature. A solution of di-tert-butyl dicarbonate (0.269 g, 1.23 mmol, 3 equiv.) in 3 mL dichloromethane was added dropwise over 5 minutes. After 1 hour at room temperature the reaction mixture was poured into 30 mL distilled water in a separatory funnel and then diluted with 50 mL dichloromethane. The organic fraction was washed with 30 mL saturated NaHCO₃, and then with 20 mL distilled water followed by 30 mL brine. The organic fraction was then dried over Na₂SO₄ then filtered and concentrated. The crude residue was then purified by flash column chromatography to give Boc protected indole 3.95 (0.195 g, 0.342 mmol, 83%) as a white foam. Rₚ = 0.29 (100% ethyl acetate); ¹H NMR (400 MHz, CDCl₃): δ = 8.05 (d, J = 8.2 Hz, 1H), 7.79 (dd, J = 5.3, 2.9 Hz, 2H), 7.67 (dd, J = 5.3, 2.9 Hz, 2H), 7.46 (d, J = 8.2 Hz, 1H), 7.24 (dd, J = 8.2, 7.0 Hz, 1H), 7.18 (dd, J = 8.2, 7.0 Hz, 1H), 5.89 (br. s, 1H), 4.87 (q, J = 7.0 Hz, 1H), 4.00 (s, 2H), 3.66 (s, 3H), 3.10 (d, J = 15.8 Hz, 1H), 2.95 (d, J = 15.8 Hz, 1H), 2.89-2.84 (m, 2H), 2.66 (ap. q, J = 5.3 Hz, 1H), 2.56 (dd, J = 8.8, 7.6 Hz, 2H), 2.53 (ap. q, J = 5.3 Hz, 1H), 2.25 (br. s, 2H), 1.65 (d, J = 7.0 Hz, 3H), 1.62 (s, 9H); ¹³C NMR (150 MHz, CDCl₃): δ = 170.6, 168.1, 150.3, 135.7, 134.1, 133.8, 131.8, 129.2, 129.1, 124.00, 123.0, 122.3, 122.2, 118.8, 118.2, 115.6, 83.8, 58.00, 53.7, 51.8, 49.4, 49.2, 32.8, 28.0, 25.6, 22.1, 15.9; IR (thin film, cm⁻¹): 3050, 3006, 2980, 2950, 2836, 2809, 2770, 1774, 1728, 1712, 1612, 1459, 1436, 1387, 1371, 1362, 1331, 1276, 1251, 1230, 1196, 1171, 1134, 1117, 1044, 1026, 955, 880, 754, 723, 668; HRMS calc’d for C₃₅H₃₇O₆N₃ = 571.2682, found 571.2681.

N-Oxide 3.96 was prepared in an analogous manner to that used for N-oxide 3.89, to give an opaque, off-white foam as an approximate 1:1 mixture of diastereomers (0.165 g, 0.280 mmol, 82%), M.p. = 82-84 °C; Rₚ = 0.56 (30% MeOH in ethyl acetate);
$^1$H NMR (400 MHz, CDCl$_3$): See spectra on page 313.

$^{13}$C NMR (150 MHz, CDCl$_3$): See spectra on page 313.

IR (thin film, cm$^{-1}$): 3463, 2982, 2951, 2498, 1775, 1717, 1612, 1578, 1560, 1458, 1436, 1362, 1331, 1276, 1259, 1232, 1197, 1173, 1135, 1090, 1042, 1015, 954, 920, 880, 851, 795, 751, 724, 667, 656, 616; HRMS calc’ed for C$_{33}$H$_{37}$O$_7$N$_3$ = 587.2632, found 587.2613.

$\alpha$-Cyano amine 3.97 was prepared in an analogous manner to $\alpha$-cyano amine 3.90 to give a light orange foam as an approximate 1:1 mixture of diastereomers (0.190 g, 0.383 mmol, 86% crude) as a bright orange foam.

$^1$H NMR (400 MHz, CDCl$_3$): See spectra on page 314.

$^{13}$C NMR (150 MHz, CDCl$_3$): See spectra on page 314.

IR (thin film, cm$^{-1}$): 2980, 2929, 2851, 2217, 2188, 1775, 1713, 1654, 1612, 1458, 1437, 1363, 1330, 1276, 1253, 1232, 1198, 1171, 1134, 1118, 1071, 1042, 1025, 960, 890, 881, 850, 753, 724, 689, 667; HRMS for C$_{34}$H$_{36}$O$_6$N$_4$ could not be obtained on multiple attempts.

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**Section 3.8: References**

(22) Lavilla, R. Current Organic Chemistry 2004, 8, 715.
Appendix 1: American Chemical Society’s Policy on Theses and Dissertations

American Chemical Society’s Policy on Theses and Dissertations

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Appendix 2:

NMR Spectra for Synthesis of Pyrrolo[1,2-a]indoles from Nitrones and Cyclopropanes
**MJ-13-033-I**

**STANDARD PROTON PARAMETERS**

Sample Name: Mito
Data Collected on: mmftp400.chem.uwo.ca-1024400
Archive Directory: /home/kerr/Krr/Mits
Sample directory: MJ-13-033-I_20-04-10_01
PifFile: PROTON

Dule Sequence: PROTON (s2pol)
Solvent: dd313
Data collected on: Jun 28 2010

Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.860 sec
Width 6452.6 Hz
16 repetitions
GDEQVN Hz, 199.7897469 MHz
DATA PROCESSING
PT nits 65536
Total time 1 min 6 sec

ppm

![Proton Spectrum](image)

**MJ-13-033-1C**

**STANDARD CARBON PARAMETERS**

Sample Name: Mito
Data Collected on: mmftp400.chem.uwo.ca-1024400
Archive Directory: /home/kerr/Krr/Mits
Sample directory: MJ-13-033-I_20-04-10_01
PifFile: CARBON

Dule Sequence: CARBON (s2pol)
Solvent: dd313
Data collected on: Jun 28 2010

Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.302 sec
Width 25171.1 Hz
128 repetitions
GDEQVN C13, 100.5194007 MHz
DECOUPLE Hz, 399.7477612 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Lm broadasting 1.0 Hz
PT nits 65536
Total time 41 min

ppm

![Carbon Spectrum](image)
MJ-13-033-2
STANDARD PHOTON PARAMETERS

Sample Name: Mix
Data Collected on: 2011-08-03
Archive directory: /home/data/Kerr/Mixs
Sample directory: MJ-13-033-2
Pulse: PHOTON

Dulse Sequence: PHOTON (s2pul)
Solvent: c9d0dli
Data collected on: Jun 28 2010

Temp. 25.0 °C / 290.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 4452.6 Hz
8 repetitions

CHEVRON 31P, 199.7997463 MHz
DATA PROCESSING
PT nits 32768
Total time 0 min 33 sec

MJ-13-033-2C

Sample Name: Mix
Data Collected on: 2011-08-03
Archive directory: /home/data/Kerr/Mixs
Sample directory: MJ-13-033-2C
Pulse: CHEVRON

Dulse Sequence: CHEVRON (s2pul)
Solvent: c9d0dli
Data collected on: Jun 28 2010

Temp. 25.0 °C / 290.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 41.0 degrees
Acq. time 3.04 sec

CHEVRON 31P, 199.7997463 MHz
DATA PROCESSING
PT nits 65536
Total time 40 min
KJ-13-033-3
STANDARD PROTON PARAMETERS

Sample Name: Mixx
Data Collected on:
mr450.chem.uci.edu-isoa400
Archive directory:
/home/data/Kerry/Mixx
Sample directory:
KJ-13-033-3_20-04-10_01
PipPhi:
PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: dodecane
Data collected on: Jun 28 2010

Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.659 sec
Width 4402.6 Hz
16 repetitions

G8EGVR B1, 199.7897446 MHz
DATA PROCESSING
PT site 37768
Total time 1 min 6 sec

KJ-13-033-3C

Sample Name: Mixx
Data Collected on:
mr450.chem.uci.edu-isoa400
Archive directory:
/home/data/Kerry/Mixx
Sample directory:
KJ-13-033-3C_20-04-10_01
PipPhi: CABBIN

Pulse Sequence: CABBIN (s2pul)
Solvent: dodecane
Data collected on: Jun 28 2010

Temp. 25.0 C / 298.1 K
Sample #5, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.304 sec
Width 25125.6 Hz
1500 repetitions

G8EGVR B1, 101.6002266 MHz
DECOUP B1, 100.0002444 MHz

Power 40 dB
continuously on
MULTX-16 modulation
DATA PROCESSING
Line broadening 0.5 Hz
PT site 65536
Total time 40 min
** Recovered SN **

Sample Name: Mike
Data Collected on: 2007-07-07
Archive directory: /home/kerr/varian/data/Mike
Sample directory: MJ-1-31-C_05-07-07_01
PipFile: PROTON

** Pulse Sequence: PROTON (z2pul) **
Solvent: odo13
Data collected on: Jul 13 2007

- Temp.: 21.0 C / 298.1 K
- Operator: kerr
- Relax. delay 1.000 sec
- Pulse 45.0 degrees
- Acq. time 3.542 sec
- Width 6395.9 Hz
- 16 repetitions
- OBSERV2: 299.7397470 MHz
- DATA PROCESSING
- FT size 22768
- Total time 1 min 0 sec

---

** MJ-1-31-C **

Sample Name: Mike
Data Collected on: 2007-07-07
Archive directory: /home/kerr/varian/data/Mike
Sample directory: MJ-1-31-C_05-07-07_01
PipFile: CARBON

** Pulse Sequence: CARBON (z2pul) **
Solvent: odo13
Data collected on: Jul 5 2007

- Operator: kerr
- Relax. delay 1.000 sec
- Pulse 45.0 degrees
- Acq. time 0.870 sec
- Width 37682.2 Hz
- 256 repetitions
- OBSERV2: 133.5931048 MHz
- OBSERV2: 299.4279956 MHz
- Power 42 dB
- continuously on
- Pulse 16 modulated
- DATA PROCESSING
- Line broadening 0.5 Hz
- FT size 65536
- Total time 8 min 23 sec
NJ-3-97-3

STANDARD PROTON PARAMETERS

Sample Name: Mlsa
Data Collected on: 2007-06-01
Archive Directory: /home/kerr/vnmrsys/data/Mlsa
Sample Directory: NJ-3-97-3.25-07-0751
PipFlines: PROTON

Pulse Sequence: PROTON (s2pol)
Solvent: cdcl3
Data collected on: Jul 25 2007

Temp. 25.0 C / 298.1 K
Operator: kerr

Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.700 sec
Width 5931.2 Hz
16 repetitions

CHESS360 51.599.41.4008 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 46 sec

NJ-3-97-3

STANDARD CARBON PARAMETERS

Sample Name: Mlsa
Data Collected on: 2007-06-01
Archive Directory: /home/kerr/vnmrsys/data/Mlsa
Sample Directory: NJ-3-97-3.25-07-0752
PipFlines: CARBON

Pulse Sequence: CARBON (s2pol)
Solvent: cdcl3
Data collected on: Jul 25 2007

Temp. 25.0 C / 298.1 K
Operator: kerr

Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.870 sec
Width 37602.1 Hz
512 repetitions

CHESS360 51.599.41.4008 MHz
DATA PROCESSING
FT size 65536
Total time 16 min
**MJ-2-33-1 STANDARD PROTON PARAMETERS**

Sample Name: Mix

Data Collected on: unaffixed

Archive Directory:

Sample directory:

Pulse Sequence: PROTON

Solvent: dcd13

Data collected on: Aug 15 2007

Operator: kerr

Relax. delay 1.000 sec

Pulse 45.0 Degrees

Avg. times 1.708 sec

Width 5512.4 Hz

16 repetitions

OBSERVE B1 599.649000 MHz

DATA PROCESSING

PT size 32768

Total time 0 min 46 sec

---

**MJ-2-33-1C STANDARD CARBON PARAMETERS**

Sample Name: Mix

Data Collected on: unaffixed

Archive Directory:

Sample directory:

Pulse Sequence: CARBON

Solvent: dcd13

Data collected on: Aug 15 2007

Operator: kerr

Relax. delay 1.000 sec

Pulse 45.0 Degrees

Avg. times 0.970 sec

Width 37682.9 Hz

512 repetitions

OBSERVE B1 139.723952 MHz

DECOUPLE B1 599.647056 MHz

Power 42 dB continuously on

MACTE-16 modulated

DATA PROCESSING

Line broadening 2.4 Hz

PT size 65535

Total time 16 min
**Sample Name:**

**Archive directory:** /export/home/kerr/vnmrsys/data
**Sample directory:** mre_22#24#2507
**PidFile:** 24

**Pulse Sequence:** 2pulg
**Solvant:** cdcl3
**Data collected on:** Jan 22 2007

**Sample Name:**

**Memory:** 400000

**Relax. delay:** 1.000 sec
**Pulse:** 45.0 degrees
**Acq. time:** 4000 sec
**Width:** 4402.0 Hz
**10 repetitions**

**OBSERVE 65.1405547 MHz**
**DATA PROCESSING**
**PT size:** 65536
**Total time:** 0 min 44 sec

---

**Sample Name:**

**MiKa**

**Data Collected on:** mnr4560.chem.wo sideline
**Archive directory:** /homes/kerr/vnmrsys/data/Mika
**Sample directory:** mre_22#24#2507_09_07_01
**PidFile:** MiKa

**Pulse Sequence:** CARBON (s2pulg)
**Solvant:** cdcl3
**Data collected on:** Sep 10 2007

**Temp.:** 26.0 C / 299.1 K
**Operator:** kerr

**Relax. delay:** 1.000 sec
**Pulse:** 45.0 degrees
**Acq. time:** 1.004 sec
**Width:** 2533.5 Hz
**128 repetitions**

**OBSERVE C13: 100.5164927 MHz**
**DECOUPLE B1: 39.974167612 MHz**
**Decay:** 99.5 dB
**Continuous on**
**MULT1-16 modulated**
**DATA PROCESSING**
**PT size:** 65536
**Total time:** 10 min
KJ-3-95-3
STANDARD PROTON PARAMETERS

Sample Name: Mko
Data Collected on: mar58400.com.chem.uwo.ca-inov400
Archive directory: /home/turr/vnmrsys/data/Mko
Sample directory: KJ-3-95-3-29-27-47.0
PipFile: PROTON

 Pulse sequence: PROTON (s2pol)
 Solvent: cdcl3
 Date collected on: Jul 30 2007

Temp. 26.0 C / 299.1 K
Operator: krnr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.562 sec
Width 6356.9 Hz
22 repetitions

CHEVY l, 119.769745 MHz
DATA PROCESSING
PT time 37788
Total time 1 min 57 sec

---------

9 8 7 6 5 4 3 2 1 ppm

---------

KJ-3-95-3
STANDARD CARBON PARAMETERS

Sample Name: Mko
Data Collected on: mar58400.com.chem.uwo.ca-inov400
Archive directory: /home/turr/vnmrsys/data/Mko
Sample directory: KJ-3-95-3-29-27-47.0
PipFile: CARBON

Pulse sequence: CARBON (s2pol)
Solvent: cdcl3
Date collected on: Jul 30 2007
Temp. 26.0 C / 299.1 K
Operator: krnr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.548 sec
Width 25133.5 Hz
512 repetitions

CHEVY l, 100.518942 MHz
DCOUPPLE l, 399.7647612 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
PT time 65536
Total time 20 min

---------

220 200 180 160 140 120 100 80 60 40 20 ppm

---------
**KJ-13-019-1**

**STANDARD PROTON PARAMETERS**

Sample Name: KJ
Data Collected on: mnr4f400.chem.uwo.ca-inoVa400
Archive Directory: /home/str/Sky/KJ/Kit
Sample directory: KJ-13-019-1_02-07-10_01
PipFile: PROTON

- Pulse Sequence: PROTON (s2pol)
- Solvent: ocd13
- Data collected on: Jul 2 2010

- Temp. 25.0 °C / 298.1 K
- Operator: Kerr
- Relax, delay 1.000 sec
- Pulse 45.0 degrees
- Acq. time 2.659 sec
- Width 6452.6 Hz
- 127 repetitions
- GDESV: BI, 199.7997486 MHz
- DATA PROCESSING
- FT size 32768
- Total time 1 min 0 sec

![Proton NMR spectrum](image)

**KJ-13-019-1C**

**STANDARD CARBON PARAMETERS**

Sample Name: KJ
Data Collected on: mnr4f400.chem.uwo.ca-inoVa400
Archive Directory: /home/str/Sky/KJ/Kit
Sample directory: KJ-13-019-1C_02-07-10_01
PipFile: CARBON

- Pulse Sequence: CARBON (s2pol)
- Solvent: ocd13
- Data collected on: Jul 2 2010

- Temp. 25.0 °C / 298.1 K
- Operator: Kerr
- Relax, delay 1.000 sec
- Pulse 45.0 degrees
- Acq. time 2.652 sec
- Width 25731.1 Hz
- 128 repetitions
- GDESV: C13, 100.5196745 MHz
- DECOUPLE BI, 399.749612 MHz
- Dowe 39 dB continuously on
- WALTZ-16 modulated
- DATA PROCESSING
- Linewidth broadening 3.8 Hz
- FT size 65536
- Total time 41 min

![Carbon NMR spectrum](image)
**MJ-3-183-4C**

**STANDARD NMR OBSERVATIONS**

Sample Name: MIK

Archive directory: /data/kyoto/mickers/1997/08/MIK

Data collected on: Oct 1 2007

Dipole Sequence: s2pul

Solvent: d6DMSO

Data collected on: Oct 1 2007

Temp. 26.0°C / 298.1 K

Operator: hert

Relax delay 1.000 sec

Pulse 45° degrees

Acq. time 2.962 sec

Width 63.6 Hz

22 repetitions

OBSERVE (H) 1.155b

DATA PROCESSING

FT lines 33749

Total time 1 min 57 sec

---

**MJ-3-183-6C**

**STANDARD NMR OBSERVATIONS**

Sample Name: MIK

Archive directory: /data/kyoto/mickers/1997/08/MIK

Data collected on: Oct 1 2007

Dipole Sequence: s2pul

Solvent: d6DMSO

Data collected on: Oct 1 2007

Temp. 26.0°C / 298.1 K

Operator: hert

Relax delay 1.000 sec

Pulse 45° degrees

Acq. time 2.962 sec

Width 63.6 Hz

22 repetitions

OBSERVE (H) 1.155b

DATA PROCESSING

FT lines 33749

Total time 1 min 57 sec
**MJ-4.19-2**

**STANDARD PROTON PARAMETERS**

Sample Name: M132
Data Collected on: neurx/400.chem.uwo.ca-inovia400
Archive directory: /home/kerr/nmr400/data/M132
Sample directory: MJ-4.19-2.24-10-07_01
PipFits: PROTON

Pulse Sequence: PROTON (s2pol)
Solvent: ocd13
Data collected on: Oct 24 2007

Temp. 25.0 °C / 299.1 K
Operator: kerr

Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.662 sec
Width 635.0 Hz
16 repetitions

![Proton NMR spectrum](image)

**MJ-4.19-2C**

**STANDARD CARBON PARAMETERS**

Sample Name: M132
Data Collected on: neurx/400.chem.uwo.ca-inovia400
Archive directory: /home/kerr/nmr400/data/M132
Sample directory: MJ-4.19-2.24-10-07_01
PipFits: CARBON

Pulse Sequence: CARBON (s2pol)
Solvent: ocd13
Data collected on: Oct 24 2007

Temp. 25.0 °C / 299.1 K
Operator: kerr

Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.662 sec
Width 2513.5 Hz
320 repetitions

![Carbon NMR spectrum](image)
**KJ-4.105-1**

**STANDARD PROTON PARAMETERS**

Sample Name: M105
Data Collected on: 05/16/10, Chem.W.U.O.C.A.-INOVAT600
Archive Directory: /home/kerr/VMRsys/data/M105
Sample Directory: KJ-4.105-1.07-01-0001
Pipefile: proton

**Dulse Sequence:** proton (s2pol)
Solvent: cdcl3
Data collected on: Jan 7 2005

Temp. 25.0 °C / 298.1 K
Operator: Krr

Relax delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.000 sec
Width 50.0 Hz
16 repetitions

CH3CH2MnH 3.00, 4.85, 6.20, 7.91, 8.01, 10.71, 12.51, 13.21

**DATA PROCESSING**

RT time 0 min 46 sec

**KJ-4.105-1C**

**STANDARD CARBON PARAMETERS**

Sample Name: M105
Data Collected on: 05/16/10, Chem.W.U.O.C.A.-INOVAT600
Archive Directory: /home/kerr/VMRsys/data/M105
Sample Directory: KJ-4.105-1.07-01-0001
Pipefile: carbon

**Dulse Sequence:** carbon (s2pol)
Solvent: cdcl3
Data collected on: Jan 7 2005

Temp. 25.0 °C / 298.1 K
Operator: Krr

Relax delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.800 sec
Width 50.0 Hz
16 repetitions

CH3CH2MnC 20.0 C1, 24.3 C2, 24.7 C3, 31.0 C4, 37.0 C5, 125.0 C6, 127.8 C7, 129.8 C8, 130.0 C9, 142.6 C10, 144.7 C11, 145.9 C12, 150.9 C13, 151.5 C14, 152.0 C15, 153.9 C16, 155.1 C17

**DATA PROCESSING**

RT time 16 min
**MJ-4.109-2**

**STANDARD PROTON PARAMETERS**

Sample Name: Mi6

Data Collected on:

/nmr/shared/CHRM.chem.uwo.ca-inova600

Archive Directory:

/home/kerr/nmr600/data/Mi6

Sample directory:

MJ-4.109-2_00-01-0001

ProcFile: PROTON

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jan 8 2009

Temp. 25.0 C / 298.1 K

Operator: kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.760 sec

Width 5030.0 Hz

16 repetitions

CHEMICAL SHIFT 310.4, 999.4017550 MHz

DATA PROCESSING

PT size 32768

Total time 0 min 46 sec

---

**MJ-4.109-2C**

**STANDARD CARBON PARAMETERS**

Sample Name: Mi6

Data Collected on:

/nmr/shared/CHRM.chem.uwo.ca-inova600

Archive Directory:

/home/kerr/nmr600/data/Mi6

Sample directory:

MJ-4.109-2C_00-01-0001

ProcFile: CARBON

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jan 8 2009

Temp. 25.0 C / 298.1 K

Operator: kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 0.870 sec

Width 77602.5 Hz

320 repetitions

CHEMICAL SHIFT 310.4, 150.71905 MHz

DECOUPLED 310.4, 999.4017550 MHz

Power 42 dB

continuously on

MALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

PT size 65536

Total time 32 min
KJ-4-65-5
STANDARD PROTON PARAMETERS

Sample Name: Mix
Data Collected on: mnr650.chem.wo.ca-Inova600
Archive Directory: 
Sample directory: KJ-4-65-5 29-31-0001
Pipefile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 29 2000

Temp. 26.0 C / 299.1 K
Operator: kerr

Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.700 sec
Width 5030.0 Hz
512 repetitions
GDESVN H1, 599.4021000 MHz
DATA PROCESSING
PT size 32768
Total time 0 min 46 sec

ppm
1.57 3.51 0.94 0.86 1.65 2.13 2.01

KJ-4-65-5
STANDARD CARBON PARAMETERS

Sample Name: Mix
Data Collected on: mnr650.chem.wo.ca-Inova600
Archive Directory: 
Sample directory: KJ-4-65-5 29-31-0002
Pipefile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jan 29 2000

Temp. 26.0 C / 299.1 K
Operator: kerr

Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.870 sec
Width 37622.5 Hz
512 repetitions
GDESVN C13, 150.719851 MHz
DECOUPLE H1, 599.400532 MHz
Power 42 dB continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
PT size 65536
Total time 16 min

ppm
MJ-4.103-1
STANDARD PROTON PARAMETERS

Sample Name: Mix
Data Collected on: marrf6x0.chem.umu.ca-inaova600
Archive Directory: /home/arrf/marrf6x0/data/Mix
Sample directory: MJ-4-103-1_07-01-0001
Profil: PROTON

Dulse Sequence: PROTON (s2pol)
Solvent: cdcl3
Data collected on: Jan 7 2006

Temp. 25.0 C / 298.1 K
Operator: kerr

Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.700 sec
Width 5090.0 Hz
16 repetitions
CD3COCH3 31, 599.4621036 MHz
DATA PROCESSING
PT size 32768
Total time 0 min 46 sec

9 8 7 6 5 4 3 2 1 0 ppm
0.95 1.03 1.01 0.96 1.17 0.78 1.04 0.70 1.03
1.87 1.01 1.01 0.10 1.02 1.03 0.70 1.04 1.03

MJ-4.103-1C
STANDARD CARBON PARAMETERS

Sample Name: Mix
Data Collected on: marrf6x0.chem.umu.ca-inaova600
Archive Directory: /home/arrf/marrf6x0/data/Mix
Sample directory: MJ-4-103-1C_07-01-0001
Profil: CARBON

Dulse Sequence: CARBON (s2pol)
Solvent: cdcl3
Data collected on: Jan 7 2006

Temp. 25.0 C / 298.1 K
Operator: kerr

Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.670 sec
Width 37620.5 Hz
32 repetitions
CD3COCH3 31, 150.7198261 MHz
DECOUPLE 31, 599.463539 MHz
Power 42 dB
continuously on
MALTZ-16 modulated
DATA PROCESSING
Limit broadening 3.0 Hz
PT size 65536
Total time 16 min

220 200 180 160 140 120 100 80 60 40 20 0 ppm

**KJ-13-043-2**

**STANDARD PHOTON PARAMETERS**

Sample Name: M1x8

Data Collected on: /home/fabart/cps/ps0008b

Archive Directory: /home/fabart/cps

Sample directory: KJ-13-043-2 05-07-10 01

**PFG**

**PFG**

Dilution: PROTON (82pul)

Solvent: CDO313

Data collected on: Jul 5 2010

**Temp. 22.0 C / 295.1 K**

Operator: Kerr

Relax delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.700 sec

Width 5932.5 Hz

16 repetitions

**CHEV **

B1: 1.0994.2271 MHz

**DATA PROCESSING**

FT size 32768

Total time 0 min 46 sec

---

**KJ-13-043-2C**

**STANDARD CARBON PARAMETERS**

Sample Name: M1x8

Data Collected on: /home/fabart/cps/ps0008b

Archive Directory: /home/fabart/cps

Sample directory: KJ-13-043-2 05-07-10 01

**PFG**

**PFG**

Dilution: CARBON (82pul)

Solvent: CDO313

Data collected on: Jul 5 2010

**Temp. 22.0 C / 295.1 K**

Operator: Kerr

Relax delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.700 sec

Width 77728.1 Hz

16 repetitions

**CHEV**

B1: 150.765197 MHz

**DCOUPLE**

B1: 599.597294 MHz

Dower 42 dB

continuously on

**WALTZ-16 modulated**

**DATA PROCESSING**

Line broadening 3.8 Hz

FT size 65536

Total time 33 min
MJ-J-185-3
STANDARD PHOTON PARAMETERS

Sample Name: Hiko
Data Collected on: NMR/400.chem.unc.ca-1nvrk600
Archive directory: /home/terra/nmrsys/data/Hiko
Sample directory: MJ-J-185-3 02-10-0700
Pulse: PROTON
Pulse sequence: PROTON (s2pul)
Solvent: d6DMSO
Data collected on: Oct 2 2007

Operator: kerr
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.700 sec
Width 0.590.6 Hz
16 repetitions
OBSERVES HIK 0.999.60090.20 MHz
DATA PROCESSING
PT size 32768
Total time 0 min 46 sec

MJ-J-185-3C
STANDARD 1H OBSERVES

Sample Name: Hiko
Archive directory: /export/home/mmr/nmrsys/data/Hiko
Sample directory: auto_02Oct2007
PulsPile: C13
Pulse sequence: s2pul
Solvent: d6DMSO
Data collected on: Oct 2 2007

Sample #1. Operator: kerr
Mercury-400DG "nrm/400.chem.unc.ca"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 0.5125.6 Hz
512 repetitions
OBSERVES HIK 0.999.60090.20 MHz
DECOUPLER H1 60.462763 MHz
Power 40 dB
continuously on
MARKER-if modulated
DATA PROCESSING
Line broadening 2.8 Hz
PT size 65536
Total time 19 min
**MJ-4.7-1**

**STANDARD PROTON PARAMETERS**

Sample Name: NMR
Data Collected on: SunMar06.chem.ubc.ca
Archive directory: /home/kerr/vnmrsys/data/NMR
Sample directory: MJ-4.7.1 19-10-0701
Problems: PROTON

**Dipole Sequence:** PROTON (s2pul)

**Solvent:** d6DMSO

Data collected on: Oct 19 2007

**Temp.** 25.0 °C / 298.1 K

**Operator:** Kerr

**Relax. delay 1.000 sec**

**Pulse 45.0 degrees**

**Acq. time 1.700 sec**

**Width 6590.0 Hz**

**16 repetitions**

**OBSCOVN HI, 599.4001022 MHz**

**DATA PROCESSING**

FT size 32768

Total time 0 min 46 sec

---

**MJ-4.7-2C**

**STANDARD 1H OBSERVE**

Sample Name: NMR

Data Collected on: SunMar06.chem.ubc.ca

Archive directory: /home/kerr/vnmrsys/data/NMR

Sample directory: MJ-4.7.1 19-10-0701

Problems: C12

**Dipole Sequence:** s2pul

**Solvent:** d6DMSO

Data collected on: Oct 19 2007

**Sample No.** Operator: Kerr

**Mercury-400SE "nmsa80.chem.ubc.ca"**

**Relax. delay 1.000 sec**

**Pulse 45.0 degrees**

**Acq. time 1.199 sec**

**Width 6512.6 Hz**

**16 repetitions**

**OBSERVE C13, 599.6157565 MHz**

**OBSERVE HI, 599.4001022 MHz**

**Power 40 dB**

**Continuously on**

**NALT, if modulated**

**DATA PROCESSING**

**Line broadening 1.4 Hz**

FT size 65536

Total time 19 min
Appendix 3:

NMR Spectra for Copper Catalyzed Malonyl Carbenoid Insertion into Indoles
NM-12-043-D
STANDARD PROTON PARAMETERS

Sample Name: Mika
Data Collected on: mrm600.chem.uwo.ca-inova600
Archive directory:/home/data/Kerr/Mika
Sample directory: NM-12-043-D 03-05-10_01
File/Type: PROTON_01
Pulse Sequence: PROTON (x2pul)
Solvent: odol3
Data collected on: May 3 2010

Temp. 22.0 C / 295.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.788 sec
Width 5555.5 Hz
16 repetitions

Observe 31.99998200 MHz
DATA PROCESSING
PT size 512
Plotname: NM-12-043-D-good

NM-12-043-D-C
STANDARD CARBON PARAMETERS

Sample Name: Mika
Data Collected on: mrm600.chem.uwo.ca-inova600
Archive directory:/home/data/Kerr/Mika
Sample directory: NM-12-043-D-C 03-05-10_01
File/Type: CARBON_01
Pulse Sequence: CARBON (x2pul)
Solvent: odol3
Data collected on: May 3 2010

Temp. 22.0 C / 295.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.869 sec
Width 37755.3 Hz
596 repetitions

Observe 125.76000000 MHz
DECODER Hz 125.76000000 MHz
Power 12 GD
continuously on
MULTI-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
PT size 65536
Total time 31 min
MJ-12-021

Sample Name: Mika2D
Data Collected on: mmrmi00.chem.uwm.edu-mercury400
Archive directory: /home/data/karr/Mika2D
Sample directory: MJ-12-021_24-05-10_01
PfPile: gHQC_01

Pulse Sequence: gHQC
Solvent: cdcl3
Data collected on: May 25 2010

Temp. 25.0 °C / 298.1 K
Sample #: Operator: Kerr
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6400.0 Hz
2D Width 1701.3 Hz
4 repetitions
2 x 128 increments

Gauss apodization 0.009 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2400 x 2400
Total time 23 min

Plotname: MJ-12-021_gHQC-1

MJ-12-021

Sample Name: Mika2D
Data Collected on: mmrmi00.chem.uwm.edu-mercury400
Archive directory: /home/data/karr/Mika2D
Sample directory: MJ-12-021_24-05-10_01
PfPile: gHQC_01

Pulse Sequence: gHQC
Solvent: cdcl3
Data collected on: May 25 2010

Temp. 25.0 °C / 298.1 K
Sample #: Operator: Kerr
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6400.0 Hz
2D Width 1701.3 Hz
4 repetitions
2 x 128 increments

Gauss apodization 0.009 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 2400 x 2400
Total time 23 min

Plotname: MJ-12-021_gHQC-2
NM-12-015-SC
Sample Name: Mike
Data Collected on: mm400.chem.uwo.ca-mercury400
Archive directory: /home/data/Kerry/Mike
Sample directory: MJ-12-015-SC_21-03-10_01
Pipe file: C6IR6H.CS
Pulse Sequence: CARSHN (x2pul)
Solvent: d2o13
Data collected on: Mar 31 2010
Temp. 25.0 C / 298.1 K
Sample N°1, Operator: Kerr
Delay, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.334 sec
Width 25.256 Hz
512 repetitions
OBSERVED C1, 100.6802648 MHz
SPECTRUM B, 400.6822444 MHz
Power 40 dB
continuously on
MALTIE-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
PT size 65536
Total time 20 min

Plotname: MJ-12-015-C

NM-12-015
Sample Name: Mike2D
Data Collected on: mm400.chem.uwo.ca-mercury400
Archive directory: /home/data/Kerry/Mike2D
Sample directory: MJ-12-015-24-05-10_01
Pipe file: p200Y_01
Pulse Sequence: g2OXY
Solvent: d2o13
Data collected on: May 24 2010
Temp. 25.0 C / 298.1 K
Sample #3, Operator: Kerr
Delay, delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
OBSERVED A1, 400.0802606 MHz
DATA PROCESSING
Eq. size 0.001 Hz
Pt DATA PROCESSING
Eq. size 0.024 Hz
PT size 2048 x 2048
Total time 4 min 12 sec

Plotname: MJ-12-015-p200Y-1
Sample Name: Mite2D
Data Collected on: mmox/chem, mcm.ca, mercury400
Archive directory: /nca/data/kerr/mite2D
Sample directory: MI-12-015_24-08-10_01
Pipfile: g2DQC_01

Pulse Sequence: g2DQC
Solvent: cdcl3
Data collected on: May 24, 2010

Temp. 26.0 C / 298.1 K
Sample #3, Operator: Kerr
Relax. delay 1.000 sec
Acq. Time 0.150 sec
Width 6442.0 Hz
2D Width 6442.0 Hz
Single scan
128 increments

Observe E1: 400.0002 MHz
DECOUPLE C13: 100.6000 MHz
Power 43.00 on during acquisition
off during delay
G2DQC-1 modulated

Data processing
Gauss apodisation 0.069 sec
F1 DATA PROCESSING
Gauss apodisation 0.014 sec
FT size 2048 x 2048
Total time 23 min

Plotname: MI-12-015-g2DQC-01
**MJ-12-019**

Sample Name: Mike2D
Data Collected on: mmrm400_chem.ucm.ca.mercury600
Archive directory: /home/data/Kerr/Mike2D
Sample directory: MJ-12-019_20-05-10_01
PfDrive: PROTON_01

Pulse Sequence: PROTON (x2pul)
Solvent: CDCl3
Data Collected on: May 20 2010

Temp. 298.1 K
Sample #44: Operator: Kerr

Relax. delay 1.000 sec
Pulse 49.0 degrees
Acq. time 2.259 sec
Width 4462.6 Hz
16 repetitions

OBSERVE 1H. 400.0022662 MHz

DATA PROCESSING
PT size 32768
Total time 1 min 0 sec

---

Plotname: MJ-12-019-K-Good

**MJ-12-019-D**

Sample Name: Mike
Data Collected on: mmrm400_chem.ucm.ca.mercury600
Archive directory: /home/data/Kerr/Mike
Sample directory: MJ-12-019-D_10-04-10_01
PfDrive: CARBON

Pulse Sequence: CARBON (x2pul)
Solvent: cdcl3
Data collected on: Apr 10 2010

Temp. 298.1 K
Sample #42: Operator: Kerr

Relax. delay 1.000 sec
Pulse 49.0 degrees
Acq. time 1.304 sec
Width 3712.8 Hz
1000 repetitions

OBSERVE 13C. 100.0002709 MHz
DECOUPL 1H. 400.0022444 MHz
Power 40 dB
Continuously on

MULTI-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
PT size 65536
Total time 40 min

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Plotname: MJ-12-019-C-Good
NM-12-041-D
Sample Name: Mike
Data Collected on: mmri00.chem.uwo.ca-mercury400
Archive directory: /home/data/Kerr/Mike
Sample directory:
NM-12-041-D_12-04-10_01
PfdPile: PROTON

Pulse Sequence: PROTON (a2pul)
Solvent: CDCl3
Data collected on: Apr 12 2010
Temp. 25.0 C / 298.1 K
Sample #10, Operator: Kerr
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.659 sec
Width 6622.0 Hz
10 repetitions
OBSERVE C13, 600.0802678 MHz
DATA PROCESSING
PT size 32768
Total time 1 min 0 sec

NM-12-041-D
Sample Name: Mike
Data Collected on: mmri00.chem.uwo.ca-mercury400
Archive directory: /home/data/Kerr/Mike
Sample directory:
NM-12-041-D_12-04-10_01
PfdPile: CARBON_02

Pulse Sequence: CARBON (a2pul)
Solvent: cdcl3
Data collected on: Apr 12 2010
Temp. 25.0 C / 298.1 K
Sample #10, Operator: Kerr
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.304 sec
Width 25125.8 Hz
1000 repetitions
OBSERVE C13, 100.6002955 MHz
DECOUPLER Ll, 600.0022444 MHz
Power 40 dB continuously on
MULTI 16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
PT size 65536
Total time 40 min

Plotname: MJ-12-041-1H

Plotname: MJ-12-041-C
MJ-12-079-2-C
STANDARD CARBON PARAMETERS

Sample Name: Mike
Data Collected on: mercury@chem.uow.ca-inovia600
Archive directory: /home/data/Kerr/Mike
Sample directory: MJ-12-079-2-C_01-05-10_01
Filename: CANNON01
Pulse Sequence: CARBON (x2pul)
Solvent: cdcl3
Data collected on: May 1 2010

Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. Line 1.263 sec
Width 25167.3 Hz
335 repetitions

OBSERVED 523, 1032, 1387, 1374, 1694
DISCHARGE B1, 359.7, 78166 MHz
Power 39 dB
continuously on

MATLAB-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 6144
Total time 3 min 41 sec

Plotname: MJ-12-079-c

MJ-12-079

Sample Name: Mike
Data Collected on: mercury@chem.uow.ca-mercury600
Archive directory: /home/data/Kerr/Mike
Sample directory: MJ-12-079-26-05-10_01
Filename: gCOSY01
Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: May 20 2010

Temp. 25.0 C / 298.1 K
Sample #15, Operator: Kerr

Relax. delay 1.000 sec
Acq. Line 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single 5000
100 increments

OBSERVED Ex. 800.0002666 MHz
DATA PROCESSING
Eq. size 309 0.275 sec
F1 DATA PROCESSING
Eq. size 309 0.524 sec
FT size 2048 x 2048
Total time 4 min 12 sec

Plotname: MJ-12-079-gCOSY-1
Sample Name: Mike
Data Collected on: mmr100_chem.mcm.ca-mercury400
Archive directory:/home/data/Kerr/Mike
Sample directory: MJ-12-079_20-05-10_01
Pf3File: gCOSY_01

Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: May 20 2010

Temp. 26.0 C / 298.1 K
Sample #15, Operator: Kerr
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
Observe 400.000000 MHz
Data processing
Eq. nine balls 0.075 sec
FI DATA PROCESSING
Eq. nine balls 0.020 sec
FT size 2048 x 2048
Total time 4 min 14 sec

Plotname: MJ-12-079-gCOSY-2

Sample Name: Mike
Data Collected on: mmr100_chem.mcm.ca-mercury400
Archive directory:/home/data/Kerr/Mike
Sample directory: MJ-12-079_20-05-10_01
Pf3File: gHSQC_01

Pulse Sequence: gHSQC
Solvent: cdcl3
Data collected on: May 20 2010

Temp. 26.0 C / 298.1 K
Sample #15, Operator: Kerr
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 17011.3 Hz
4 repetitions
2 x 128 increments
Observe 400.000000 MHz
DECOUPL C13: 100.607056 MHz
Power 43 W
on during acquisition
off during delay
GNS-1 modulated
Data processing
Chase apodisation 0.069 sec
FI DATA PROCESSING
Chase apodisation 0.014 sec
FT size 2048 x 2048
Total time 23 min

Plotname: MJ-12-079-gHSQC-1
Sample Name: Mike
Data Collected on: nmr400.chen.mcm.cs-mercury400
Archive directory: /home/data/Kerr/Mike
Sample directory: MJ-12-039-D_10-04-10_01
PipFile: PROTON
Pulse Sequence: PROTON (x2pul)
Solvent: CDCl3
Data Collected on: Apr 10 2010
Temp. 25.0 C / 298.1 K
Sample #11, Operator: Kerr
Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.659 sec
Width 6462.0 Hz
14 repetitions
OBSERVE: 600.0802682 MHz
DATA PROCESSING
PT size 32768
Total time 1 min 0 sec

Plotname: MJ-12-039-H

Sample Name: Mike
Data Collected on: nmr400.chen.mcm.cs-mercury400
Archive directory: /home/data/Kerr/Mike
Sample directory: MJ-12-039-D_10-04-10_01
PipFile: CASHD_81
Pulse Sequence: CASHD (x2pul)
Solvent: chloroform-d
Data collected on: Apr 10 2010
Temp. 25.0 C / 298.1 K
Sample #11, Operator: Kerr
Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 2525.6 Hz
1000 repetitions
OBSERVE: 13.180, 600.0802686 MHz
DECoupled: 60.0802444 MHz
Power 40 dB
continuously on
MULTI-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
PT size 65536
Total time 40 min

Plotname: MJ-12-039-C
MJ-12-069-DC
STANDARD CARBON PARAMETERS

Sample Name: Mike
Data Collected on: mercury00.chem.uwo.ca-inova600
Archive directory:/home/data/Kerr/Mike
Sample directory:
MJ-12-069-DC-05-25-95_01
File name: CARBON_01
Pulse Sequence: CARBON (x2pul)
Solvent: od03
Data collected on: May 6, 2010

Temp. 25.0 C / 298.1 K
Operator: Kerr

Delay, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.849 sec
Width 3770.5 Hz
340 repetitions

OBSERVES 213, 150, 7688631 MHz
DISCOV4 Ir, 599, 6002983 MHz
Power 43 dB
continuously on

WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.6 Hz
PT size 65536
Total time 35 min

Plotname: MJ-12-067-C

MJ-12-087-2D
Sample Name: Mike-2D
Data Collected on: mercury00.chem.uwo.ca-mercury400
Archive directory:/home/data/Kerr/Mike-2D
Sample directory:
MJ-12-087-2D-05-10-01
File name: gCOSY_2D
Pulse Sequence: gCOSY
Solvent: od03
Data collected on: May 10, 2010

Temp. 25.0 C / 298.1 K
Sample #4, Operator: Kerr

Delay, delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
340 increments

OBSERVES 400, 0002656 MHz
DATA PROCESSING
Ss, size 1024 x 1024 sec
F2 DATA PROCESSING
Ss, size 2048 x 2048 sec
Total time 4 min 12 sec

Plotname: MJ-12-089-gCOSY-1
NMR-12-055-D2
STANDARD PROTON PARAMETERS

Sample Name: Mike
Data Collected on: mass600.chm.uwo.ca-inova600
Archive directory:
/home/data/Kerr/Mike
Sample directory:
NMR-12-055-02-27-04-18_02
Filetype: PROTON

Pulse Sequence: PROTON (2pul)
Solvent: adol3
Data collected on: Apr 27 2010

Temp. 22.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.798 sec
Width 5573.5 Hz
16 repetitions

RESOLVE Hz, 598.597290 MHz

DATA PROCESSING
PT size 33768
Total time 0 min 43 sec

Plotname: NMR-12-055-1H

NMR-12-055-D2
STANDARD CARBON PARAMETERS

Sample Name: Mike
Data Collected on: mass600.chm.uwo.ca-inova600
Archive directory:
/home/data/Kerr/Mike
Sample directory:
NMR-12-055-02-27-04-18_02
Filetype: CARBON

Pulse Sequence: CARBON (2pul)
Solvent: adol3
Data collected on: Apr 28 2010

Temp. 22.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.869 sec
Width 37760.3 Hz
800 repetitions

RESOLVE Hz, 599.600526 MHz
DECOUPLE Hz, 599.600526 MHz
Power 42 DD
continuously on
MULTI-16 modulated

DATA PROCESSING
Line broadening 3.0 Hz
PT size 65536
Total time 33 min

Plotname: NMR-12-055-C
Sample Name: AcO
Data Collected on: 2004-09-08
Archive directory: /home/data/Kerry/Varian3
Sample directory: MJ-12-055_20-08-20_01
PID fille: gCOSY_01

Pulse Sequence: gCOSY
Solvent: CDCl3
Data collected on: May 23, 2010

Temp. 25.0 C / 298.1 K
Sample #: 0, Operator: Kerr

Relax. delay 1.000 sec
Acq. Time 0.150 sec
Width 6402.0 Hz
2D Width 4402.0 Hz

Single scan
128 increments

DATA PROCESSING
Eq. size b bell 0.075 sec
F1 DATA PROCESSING
Eq. size b bell 0.025 sec
F2 size 2048 x 2048
Total time 4 min 12 sec

Plotname: MJ-12-055-gCOSY-1
Sample Name: MJ-12-055
Data Collected on: 2011-06-10_02
Archive directory: /home/data/Kerry/Varian/2D
Sample directory: MJ-12-055_23-06-10_01
PIDfile: gHMBE_01

**Dimensions:**
- **P1 (ppm):**
  - 0.0  0.2  0.4  0.6  0.8  1.0  1.2  1.4  1.6
  - 0  10  20  30  40  50  60  70  80  90

- **P2 (ppm):**
  - 0  10  20  30  40  50  60  70  80

**Plotname:** MJ-12-055-Varian_01
MJ-12-077-C

Sample Name: Mike
Data Collected on: mercury00.chen.ueo.ca-mercury00
Archive directory: /home/data/kere/mike
Sample directory: MJ-12-077-C-01-08-23_01
Filetype: CARBON

Pulse Sequence: CARBON (x2pul)
Solvent: cdcl3
Data collected on: May 1 2010

Temp. 25.0 C / 296.1 K
Operator: Kerr

Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. Time 1.203 sec
Width 25157.3 Hz
116 repetitions

OBSERVES: 213, 103.5185742 NHz
DISCPEAK: 213, 103.5185742 MHz
Power 55 dB
continuously on

MULT1-16 modulated
DATA PROCESSING
Line broadening: 2.0 Hz
PT size 65536
Total time: 43 min

Plotname: MJ-12-077-C

MJ-12-077

Sample Name: Mike
Data Collected on: mercury00.chen.ueo.ca-mercury00
Archive directory: /home/data/kere/mike
Sample directory: MJ-12-077-C-24-05-19_01
Filetype: gCOSY

Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: May 24 2010

Temp. 25.0 C / 296.1 K
Sample #1, Operator: Kerr

Relax. delay 1.500 sec
Ampl. Time 0.152 sec
Width 6402.9 Hz
2D Width 6402.9 Hz
Single scan
128 increments

OBSERVES: 650.0002656 MHz
DATA PROCESSING
Eq. size: 30 0.755 sec
P1 DATA PROCESSING
Eq. size: 30 0.755 sec
PT size: 2048 x 2048
Total time: 4 min 12 sec

Plotname: MJ-12-077-gCOSY-1
M12-077
Sample Name: 
M12077
Data Collected on: 
nrmr00019.nnw.nm.nm.mercury400
Archive directory: 
/home/data/Kerry/M12077
Sample directory: 
M12-077_24-08-10_01
PIDfile: qHNOC_01

Pulse Sequence: gHNOC
Solvent: d6DMSO
Data collected on: May 24 2010

Temp. 25.0 C / 298.1 K
Sample #1, Operator: Kerry
Relax, delay 1.000 sec
Acq. time 0.050 sec
Width 6402.0 Hz
2D Width 24147.3 Hz
4 repetitions
2 x 200 increments

Observe F1, 400.0002068 MHz
DATA PROCESSING
Eq. size 6400 0.073 sec
F1 DATA PROCESSING
Gauss apodization 0.013 sec
FT slice 2545 x 4096
Total time 37 min

Plotname: M12-077-gHNOC.0

M12-061-3C
Sample Name: 
M12061
Data Collected on: 
nrmr00019.nnw.nm.nm.mercury400
Archive directory: 
/home/data/Kerry/M12061
Sample directory: 
M12-061-3C_04-10-10_01
PIDfile: PROTON

Pulse Sequence: gHNOC (2pul)
Solvent: d6DMSO
Data collected on: Apr 15 2010

Temp. 25.0 C / 298.1 K
Sample #1, Operator: Kerry
Relax, delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.0 Hz
16 repetitions

Observe F1, 400.0002068 MHz
DATA PROCESSING
FT slice 25769
Total time 1 min 0 sec

Plotname: M12-061-3C
**Sample Name:**
Mika

**Data Collected on:**
nmrm065.chem.wo.ao.mercury400

**Archive directory:**
/home/data/Kerry/Mike

**Sample directory:**
MJ-12-061-HE

**Plotname:** MJ-12-061-HE

---

**Sample Name:**
Mika

**Data Collected on:**
nmrm065.chem.wo.ao.mercury400

**Archive directory:**
/home/data/Kerry/Mike

**Sample directory:**
MJ-12-061-HE

**Plotname:** MJ-12-061-HE

---

**Sample Name:**
Mika

**Data Collected on:**
nmrm065.chem.wo.ao.mercury400

**Archive directory:**
/home/data/Kerry/Mike

**Sample directory:**
MJ-12-061-HE

**Plotname:** MJ-12-061-HE
Sample Name: Me0000
Data Collected on: mnm000, chem.moe.ca.mercury400
Archive directory:
/home/data/Kerr/Me0000
Sample directory:
Me-06-05-29-29-10_01
PIDFile: qCOSY_01

Pulse Sequence: gCOSY
Solvent: dcd3
Data collected on: May 25 2010

Temp. 26.0 C / 298.1 K
Sample #: Operator: Kerr

Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
Q4 EXCERN 81, 600.000000 MHz
DATA PROCESSING
Eq. size bell 0.075 sec
Ft. DATA PROCESSING
Eq. size bell 0.250 sec
Ft. size 2048 x 2048
Total time 4 min 12 sec

Plotname: Me-06-05-29-29-10_01-qCOSY_01

Sample Name: Me0000
Data Collected on: mnm000, chem.moe.ca.mercury400
Archive directory:
/home/data/Kerr/Me0000
Sample directory:
Me-06-05-29-29-10_01
PIDFile: qCOSY_02

Pulse Sequence: gCOSY
Solvent: dcd3
Data collected on: May 25 2010

Temp. 26.0 C / 298.1 K
Sample #: Operator: Kerr

Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
Single scan
128 increments
Q4 EXCERN 81, 600.000000 MHz
DATA PROCESSING
Eq. size bell 0.075 sec
Ft. DATA PROCESSING
Eq. size bell 0.250 sec
Ft. size 2048 x 2048
Total time 4 min 12 sec

Plotname: Me-06-05-29-29-10_01-qCOSY_02
MeO₂C

CO₂Me

N

Ts

2.132

P1 (ppm)

170

160

150

140

130

120

Temp. 25.0 C / 298.1 K
Sample #: Operator: Kerr
Relax. delay 1.000 sec
Acq. time 0.160 sec
Width 6402.0 Hz
2D Width 24147.3 Hz
4 repetitions
2 x 200 increments

DATA PROCESSING
Eq. shift -0.630 0.075 sec
F1 DATA PROCESSING

Total time 37 min

Plotname: MJ-12-059-9NNBC_3

MeO₂C

CO₂Me

N

Bn

2.130

P2 (ppm)

4.88

4.92

4.96

5.00

5.04

5.08

5.12

5.16

5.20

5.24

5.28

5.32

Plotname: MJ-12-017-9-good
NJ-12.111-D
STANDARD PROTON PARAMETERS

Sample Name: Mike
Data Collected on: nmrdb60.chem.uwo.ca-inovaS80
Archive directory: /home/data/Kerr/Mike
Sample directory:
NJ-12.111-D_24-15-10_01
PfdFile: PROTON

Pulse Sequence: PROTON (x2pul)
Solvent: ccd13
Data collected on: May 26 2010

Temp. 22.0 C / 295.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.758 sec
Width 9922.3 Hz
16 repetitions

OBSERVES R1, 599.5972897 MHz
DATA PROCESSING
PT size 32768
Total time 9 min 43 sec

Plotname: MJ-12.111-12

---

NJ-12.111-D

Sample Name: Mko2D
Data Collected on: nmrdb60.chem.uwo.ca-mercury400
Archive directory: /home/data/Kerr/Mko2D
Sample directory:
NJ-12.111-D_24-05-10_01
PfdFile: CARBON_01

Pulse Sequence: CARBON (x2pul)
Solvent: ccd13
Data collected on: May 28 2010

Temp. 25.0 C / 298.1 K
Sample 816, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.504 sec
Width 25125.0 Hz
1000 repetitions

OBSERVES CS1, 100.6002646 MHz
DECouple Res 400.2024444 MHz
Power 40 dB
continuously on
MALDI-16 modulated
DATA PROCESSING
Line broadening 5.5 Hz
PT size 65536
Total time 40 min

Plotname: MJ-12.111-C
null
NJ-12-095-D-0
Sample Name: Mike
Data Collected on: nmrn01.chem.uos.es-mercury400
Archive directory: /home/data/Kerry/Mike
Sample directory: MJ-12-095-D-0_11-05-10_01
Plotname: gMNHC_01

Pulse Sequence: gMNHC
Solvent: odol3

Temp. 26.0 C / 290.1 K
Sample #41, Operator: Kerr

Delay, delay 1.000 sec
Acq. Time 0.150 sec
Width 6420.0 Hz
2D Width 24147.3 Hz
4 repetitions
2 x 200 increments

1H, 600.000000-MHz
DATA PROCESSING
Eq. size 0.013 sec
F1 DATA PROCESSING
Gauss apodization 0.013 sec
F1 size 2048 x 4096
Total time 37 min

Plotname: MJ-12-095-gMNHC-1

NJ-12-095-D-2
Sample Name: Mike
Data Collected on: nmrn01.chem.uos.es-mercury400
Archive directory: /home/data/Kerry/Mike
Sample directory: MJ-12-095-D-0_11-05-10_02
Plotname: gMNHC_02

Pulse Sequence: gMNHC
Solvent: odol3

Temp. 26.0 C / 290.1 K
Sample #41, Operator: Kerr

Delay, delay 1.000 sec
Acq. Time 0.150 sec
Width 6420.0 Hz
2D Width 24147.3 Hz
4 repetitions
2 x 200 increments

1H, 600.000000-MHz
DATA PROCESSING
Eq. size 0.013 sec
F1 DATA PROCESSING
Gauss apodization 0.013 sec
F1 size 2048 x 4096
Total time 37 min

Plotname: MJ-12-095-gMNHC-2
Appendix 4:

NMR Spectra for A Biomimetic Approach Towards Arboflorine
**MJ-13-061-H**

**STANDARD PROTON PARAMETERS**

- **Sample Name:** Mike
- **Data Collected on:** Mar 2011 - 09-09-09
- **Archive Directory:** /home/data/Kerry/Mike
- **Sample Directory:** MJ-13-061-H
- **Pulse Sequence:** PROTON (x2pul)
- **Solvent:** d6-ds
- **Data collected on:** Sep 13 2010

- **Temp.:** 298.1 K
- **Operator:** Kerry
- **Relax. delay:** 1.000 sec
- **Pulse:** 45.0 degrees
- **Acq. time:** 2.559 sec
- **Width:** 6452.6 Hz
- **18 repetitions**
- **OBSERVE:** H1, 399.709760 MHz

**DATA PROCESSING**

- **FT size:** 32768
- **Total time:** 1 min 0 sec

---

**MJ-13-061-C**

**STANDARD CARBON PARAMETERS**

- **Sample Name:** Mike
- **Data Collected on:** Mar 2011 - 09-09-09
- **Archive Directory:** /home/data/Kerry/Mike
- **Sample Directory:** MJ-13-061-C
- **Pulse Sequence:** CARBON (x2pul)
- **Solvent:** d6-ds
- **Data collected on:** Sep 13 2010

- **Temp.:** 298.1 K
- **Operator:** Kerry
- **Relax. delay:** 1.000 sec
- **Pulse:** 45.0 degrees
- **Acq. time:** 1.902 sec
- **Width:** 25173.1 Hz
- **83 repetitions**
- **OBSERVE:** C13, 100.519671 MHz

**DECOUPLE:** H1, 399.709760 MHz

**Power:** 39 dB continuously on

**DATA PROCESSING**

- **Line broadening:** 0.5 Hz
- **FT size:** 65536
- **Total time:** 42 min
**MJ-13-059-E**

**STANDARD PROTON PARAMETERS**

**Sample Name:**
Milk

Data Collected on:
/mrhr400.chen.chem.uwo.ca-inova4000

Archive directory:
/home/data/Kerr/Milk

Sample directory:
/MJ-13-059-E_13-09-09_01

Pulse/Spin: PROTON

Pulse Sequence: PROTON (s2pul)

Solvent: cdol3

Data collected on: Sep 13 2010

Temp. 25.0 °C / 298.1 K

Operator: Kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 2.559 sec

Width 6402.6 Hz

if repetitions

OBSERVE E1, 599.7997464 MHz

DATA PROCESSING

FT size 32768

Total time 4 min 0 sec

---

**MJ-13-059-C**

**STANDARD CARBON PARAMETERS**

**Sample Name:**
Milk

Data Collected on:
/mrhr400.chen.chem.uwo.ca-inova4000

Archive directory:
/home/data/Kerr/Milk

Sample directory:
/MJ-13-059-E_13-09-10_01

Pulse/Spin: CARBON (s2pul)

Solvent: cdol3

Data collected on: Sep 13 2010

Temp. 25.0 °C / 298.1 K

Operator: Kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.902 sec

Width 25173.1 Hz

if repetitions

OBSERVE C13, 100.5183753 MHz

DISCOUPLE H1, 599.7657612 MHz

Power 39 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.1 Hz

FT size 65536

Total time 43 min
MJ-13-075-34
STANDARD PROTON PARAMETERS

Sample Name: Mike
Data Collected on: March 2007 Chem. 000.1 Co Inova 600
Archive directory: /home/data/Erick/Mike
Sample directory: MJ-13-075_A03-09-10_01
Pulse/field: PROTON

Pulse Sequence: PROTON (x2pul)
Solvent: cd013
Data collected on: Sep 23 2010

Temp. 25.0 °C / 298.1 K
Operator: Karr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.768 sec
Width 550 Hz
16 repetitions
Observe H1 599.645282 MHz
Data Processing
FT size 32768
Total time 0 min 50 sec

10 9 8 7 6 5 4 3 2 1

ppm

MeO2C

O

3.74

VARIAN

MJ-13-073-4C
STANDARD CARBON PARAMETERS

Sample Name: Mike
Data Collected on: March 2007 Chem. 000.1 Co Inova 600
Archive directory: /home/data/Erick/Mike
Sample directory: MJ-13-073_A03-09-10_01
Pulse/field: CARBON

Pulse Sequence: CARBON (x2pul)
Solvent: cd013
Data collected on: Sep 23 2010

Temp. 25.0 °C / 298.1 K
Operator: Karr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.669 sec
Width 37718 Hz
157 repetitions
Observe C13 150.765185 MHz
Decoupler H1 599.5478626 MHz
Power 42 dB continuously on
WALTZ-16 modulated
Data Processing
Line broadening 1.5 Hz
PT size 65536
Total time 32 min

220 200 180 160 140 120 100 80 60 40 20

ppm

MeO2C

O

3.74

VARIAN
Sample Name:
Archive directory: /export/home/cmrs1/vnmrsys/data
Sample directory: auto_10Feb2009-194929
PfdFile: H1

Pulse Sequence: zg
Solvent: dcl3
Data collected on: Feb 10 2009

Sample #6. Operator: kerr
Mercury-400SH "mercury400.chen.woo.ca"

Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 4.000 sec
Width 6422.0 Hz
16 repetitions
OBSESS H1, 400.0002773 MHz
DATA PROCESSING
PT size 65536
Total time 1 min 24 sec

0.99 0.99 1.99 2.24 1.99
1.99 2.24 1.99 2.24

Sample Name:
Archive directory: /export/home/cmrs1/vnmrsys/data
Sample directory: auto_10Feb2009-194929
PfdFile: C13

Pulse Sequence: zg
Solvent: dcl3
Data collected on: Feb 10 2009

Sample #6. Operator: kerr
Mercury-400SH "mercury400.chen.woo.ca"

Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
64 repetitions
OBSESS C13, 100.0002691 MHz
DECOUPLE H1, 403.0002447 MHz
Power 40 dB
Data recorded
MULTI-16 modulated
DATA PROCESSING
Line broadening 1.4 Hz
PT size 65536
Total time 19 min

200 180 160 140 120 100 80 60 40 20

ppm

ppm
Sample Name: 3.83

Archive directory: /export/home/nnm1/vnmrsyv/data
Sample directory: /auto_12Dec2000
PdFile: Ni

Pulses Sequence: 2pul
Solvent: CDCl3
Data collected on Dec 12 2000

Sample #4. Operator: kerr
Mercury-4008B "nnm4008c.chem.uwo.ca"
Sample Name:

Archive directory: /export/home/vmsrv1/vmsrv3/data
Sample directory: auto_12Dec2008
PIDFile: B

Pulse Sequence: z2psl
Solvent: CDCl3
Data collected on: Dec 12 2000

Sample #1: Operator: kerr
Mercury-4000B "mcm4000.chem.uwo.ca"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 4.000 sec
Width 6402.0 Hz
16 repetitions

OBSERVE B2, 400.0002674 Hz
DATA PROCESSING
FT size 65536
Total time 1 min 24 sec

---

Sample Name:

Archive directory: /export/home/vmsrv1/vmsrv3/data
Sample directory: auto_12Dec2008
PIDFile: C13

Pulse Sequence: z2psl
Solvent: CDCl3
Data collected on: Dec 11 2000

Sample #1: Operator: kerr
Mercury-4000B "mcm4000.chem.uwo.ca"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 6512.6 Hz
512 repetitions

OBSERVE C13, 100.0002699 MHz
DECOPLE B2, 400.0002674 Hz
Power 40 dB
continuously on

DATA PROCESSING
Line broadening 1.4 Hz
FT size 65536
Total time 19 min

---

200 180 160 140 120 100 80 60 40 20

10 9 8 7 6 5 4 3 2 1

2.03 1.92 3.15 0.99 5.87 2.00 1.00 3.03

---

200 180 160 140 120 100 80 60 40 20

MJ-09-043.4
STANDARD PROTON PARAMETERS

Sample Name: Mika
Data Collected on: march600.chm.uwo.ca-inova600
Archive directory: /homes/tert/vmxsys/data/Mika
Sample directory: MJ-09-043.4_27-04-0901
Pulse file: PROTON

Pulse Sequence: PROTON (x2pul)
Solvent: ddo13
Data collected on: Apr 27 2009

Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.798 sec
Width 6594.6 Hz
16 repetitions

OBSERVE H1, 599.628605 MHz
DATA PROCESSING
FT along 317868
Total time 5 min 46 sec

9 8 7 6 5 4 3 2 1 ppm
0.96 2.110.95 1.02 1.05 0.94 6.00 1.06 4.11 3.52

MJ-09-043.4C
STANDARD CARBON PARAMETERS

Sample Name: Mika
Data Collected on: march600.chm.uwo.ca-inova600
Archive directory: /homes/tert/vmxsys/data/Mika
Sample directory: MJ-09-043.4C_27-04-0901
Pulse file: CARBON

Pulse Sequence: CARBON (x2pul)
Solvent: ddo13
Data collected on: Apr 27 2009

Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.209 sec
Width 37710.3 Hz
256 repetitions

OBSERVE C13, 150.782791 MHz
DECOUPLER H1, 599.6558706 MHz
Power 42 dm continuously on
MULTI-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT along 65536
Total time 32 min

220 200 180 160 140 120 100 80 60 40 20 ppm
MJ-03-067-2
STANDARD PROTON PARAMETERS

Sample Name: Mike
Data Collected on: marc6000.chem.ncy.ca-inovox0v
Archive directory: /home/terz/vnmrsys/data/Mike
Sample directory: MJ-03-067-2 29-04-1000
File: PROFON
Pulse Sequence: PROTON (x2pol)
Solvent: D2O
Data collected on: Apr 29 2009

Temp. 25.0 C / 298.1 K
Operator: terz

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.766 sec
Width 558.4 Hz
16 repetitions

OBSERVED H1 598.6126605 MHz
DATA PROCESSING
FT size 3176
Total time 0 min 46 sec

MJ-03-067-2C
STANDARD CARBON PARAMETERS

Sample Name: Mike
Data Collected on: marc6000.chem.ncy.ca-inovox0v
Archive directory: /home/terz/vnmrsys/data/Mike
Sample directory: MJ-03-067-2C 29-04-1000
File: CARBON
Pulse Sequence: CARBON (x2pol)
Solvent: D2O
Data collected on: Apr 29 2009

Temp. 25.0 C / 298.1 K
Operator: terz

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.406 sec
Width 37700.3 Hz
129 repetitions

OBSERVED C13 598.6126605 MHz
DECOPRIME H1 598.6126605 MHz
Power 42 dB continuously on
MULTI-16 modulated DATA PROCESSING

Line broadening 0.5 Hz
FT size 65536
Total time 32 min
Curriculum Vitae for Michael B. Johansen

A) Education

The University of Western Ontario (Sept. 2006 – Nov. 2010). Graduate studies in chemistry.
Research Advisor: Professor Michael Kerr

The University of Western Ontario (Sept. 2002 – April 2006). Honors B.Sc. (Honors Specialization Chemistry with an Advanced Minor in Chemistry)
Thesis Title: Anion Receptors Based on the 1,4-Thiazine-1,1-Dioxide Moiety
Undergraduate Honors Supervisor: Assistant Professor James A. Wisner

B) Research and Relevant Work Experience

The University of Western Ontario, Department of Chemistry (2006 – 2010)
Teaching Assistant, Chemistry 2213a, 2273a.

The University of Western Ontario, (2006 – 2010) Research Assistant
Research Supervisor: Professor Michael A. Kerr

The University of Western Ontario, (May 2006 – August 2006), NSERC USRA Research Assistant
Research Supervisor: Assistant Professor James A. Wisner

The University of Western Ontario, (Sept. 2008 – June 2010), Student Representative for Chemistry Health and Safety Committee.


C) Publications


D) Presentations


8) Johansen, M. B; Wisner, J. A.; *Synthesis Towards Thiazine-1,1-Dioxide Based Anion Receptors;* The 34th Southern Ontario Undergraduate Student Chemistry Conference, York University, Toronto, Ontario, 2006. Oral Presentation

E) Awards

<table>
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<tr>
<th>Name of Award</th>
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<tr>
<td>NSERC Canadian Graduate Scholarship Doctoral</td>
<td>$35,000/yr</td>
<td>U. Western Ontario</td>
<td>Sept. 2008 – Aug. 2010</td>
</tr>
<tr>
<td>NSERC Postgraduate Scholarship Masters</td>
<td>$17,300</td>
<td>U. Western Ontario</td>
<td>Sept. 2006 – Sept. 2007</td>
</tr>
<tr>
<td>Graduate Tuition Scholarship</td>
<td>~$6,100/yr</td>
<td>U. Western Ontario</td>
<td>Sept. 2006 – Aug. 2010</td>
</tr>
<tr>
<td>Ontario Graduate Scholarship (Declined for NSERC PGS-M)</td>
<td>$15,000</td>
<td>U. Western Ontario</td>
<td>N/A</td>
</tr>
<tr>
<td>NSERC Undergraduate Student Research Award</td>
<td>$4500</td>
<td>U. Western Ontario</td>
<td>May 2006 – Aug. 2006</td>
</tr>
<tr>
<td>Alfred Bader Scholarship</td>
<td>$1000</td>
<td>U. Western Ontario</td>
<td>Aug. 2006</td>
</tr>
<tr>
<td>Alumni Association Gold Medal</td>
<td>N/A</td>
<td>U. Western Ontario</td>
<td>June 2006</td>
</tr>
<tr>
<td>Society of Chemical Industry Student Merit Award</td>
<td>N/A</td>
<td>U. Western Ontario</td>
<td>June 2006</td>
</tr>
<tr>
<td>Hypercube Scholar Award</td>
<td>N/A</td>
<td>U. Western Ontario</td>
<td>June 2006</td>
</tr>
<tr>
<td>Varian Canada Prize for Analytical Chemistry</td>
<td>$250</td>
<td>U. Western Ontario</td>
<td>Feb. 2006</td>
</tr>
<tr>
<td>UWO Debt Reduction Bursary</td>
<td>$1000</td>
<td>U. Western Ontario</td>
<td>Feb. 2006</td>
</tr>
<tr>
<td>Western Entrance Scholarship</td>
<td>$2000</td>
<td>U. Western Ontario</td>
<td>Sept. 2002</td>
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