Oxidative C–C Bond Formation in Heterocyclic Chemistry

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List of Abbreviations
b = broad
BAIB = bisacetoxyiodobenzene
brsm = based on recovered starting material
BzCl = benzoyl chloride
CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine
CPC = cetylpyridinium chloride
CPME = cyclopentylmethylether
CTAP = cetyltrimethylammonium permanganate
d = doublet
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DCB = o-dichlorobenzene
DCC = dicyclohexylcarbodiimide
DCE = 1,2-dichloroethane
DCM = dichloromethane (CH₂Cl₂)
DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone
DEAD = diethylazodicarboxylate
DIPEA = diisopropylethylamine (i-Pr₂NEt)
DMAP = (4-dimethylamino)pyridine
DME = dimethoxyethane
DMF = dimethylformamide
DMP = Dess-Martin periodinane
ESI-TOF = electrospray ionization-time of flight
hv = UV irradiation
HRMS = high resolution mass spectrometry
IBX = \( o \)-iodoxybenzoic acid
IR = infrared
KHMDS = potassium hexamethyldisilazide
LCMS = liquid chromatography mass spectrometry
LDA = lithium diisopropylamide
LHMDS = lithium hexamethyldisilazide
LRMS = low resolution mass spectrometry
m = multiplet
MALDI = matrix assisted laser desorption and ionization
\( m \)CPBA = \( m \)-chloroperoxybenzoic acid
MMPP = magnesium monoperphthalate
MOM = methoxymethyl
mp = melting point
Ms = methansulfonyl
NBS = \( N \)-bromosuccinimide
NCS = \( N \)-chlorosuccinimide
NMM = \( N \)-methylmorpholine
NMR = nuclear magnetic resonance
[O] = oxidant
PhH = benzene (\( C_6H_6 \))
PIFA = bistrifluoroacetoxyiodobenzene
PivCl = pivaloyl chloride
PMA = phosphomolybdic acid
PTLC = preparative thin layer chromatography
PWA = phosphotungstic acid
Pyr. = pyridine
q = quartet
s = singlet
t = triplet
TBAH = tetrabutylammonium hydroxide (Bu₄NOH)
TCI = trichloroisocyanuric acid
TCT = 2,4,6-trichloro-1,3,5-triazine
TEA = triethylamine (Et₃N)
TFA = trifluoroacetic acid
TFAA = trifluoroacetic anhydride
TFDO = (trifluoromethyl)methyldioxirane
THF = tetrahydrofuran
TLC = thin layer chromatography
TMS = trimethylsilyl
TMSOTf = trimethylsilyl trifluoromethane sulfonate
Ts = tosyl
Abstract
Details are provided for the total synthesis of several members of the hapalindole family of natural products, including hapalindole Q, 12-epi-hapalindole D, 12-epi-fischerindole U, 12-epi-fischerindole G, 12-epi-fischerindole I, and welwitindolinone A. The original biosynthetic proposal is reviewed and a revised biosynthetic hypothesis is put forth and validated by these syntheses. These syntheses are efficient, practical, scaleable, and protecting group-free and are enabled through the use of the direct indole coupling developed herein. Details are provided for this method to couple indoles and pyrroles to carbonyl compounds. The reaction is ideally suited for structurally complex substrates and exhibits high levels of chemoselectivity (functional group tolerability), regioselectivity (coupling occurs exclusively at C-3 of indole or C-2 of pyrrole), stereoselectivity (substrate control), and practicality (amenable to scale-up). In addition, quaternary stereocenters are easily and predictably generated. In addition to the natural products listed above, this reaction has been applied to the synthesis of ketorolac, acremoauxin A, and oxazinin 3. Mechanistically, this coupling protocol appears to operate by a single electron-transfer process requiring generation of an electron-deficient radical adjacent to a carbonyl that is then intercepted by an indole or pyrrole anion.
Chapter 1:

Background and Historical Significance
1.1 The Hapalinole Alkaloids

The first members of the hapalindole-type natural products were isolated from the Stigonemataceae family of cyanobacteria in 1984 by Moore and colleagues. In the 24 years since their discovery, 62 members have been added to this family of alkaloids, which include the hapalindoles, fischerindoles, welwitindolinones, ambiguines, hapalindolinones, hapaloxindoles, and fontonamides (See Figure 1). These natural products have been isolated from soil samples in a myriad of habitats around the globe (including the Marshall Islands, the Everglades, Australia, Micronesia, Papua New Guinea, and Israel), and a broad range of biological activities arise from the different structural classes. Insecticidal activity is observed for several hapalindoles and welwitindolinones. Reports have surfaced of antialgal activity from the hapalindoles, antimycotic activity from the hapalindoles, welwitindolinones, and ambiguines, and antibacterial activity from the hapalindoles and ambiguines. Additionally, the hapalindolinones have been found to inhibit arginine vasopression binding. Finally, potent anticancer activity against multiple drug resistant ovarian cancer cell lines has been reported for the welwitindolinones, which apparently exert this effect through microtubule depletion.
Figure 1. All known hapalindole-type natural products.
Not only do the vast number of the members of this natural product family exhibit potent and exciting biological activities, but they also contain intriguing and unprecedented molecular architectures. Though distinct, they are united by several structural features, most notably an indole (or indole derived) heterocycle with a monoterpene unit appended at C-3 (See Scheme 1, Section 1.2 for numbering), comprising the core of these molecules. All but one contain an isonitrile or an isothiocyanate at C-11, with an all carbon quaternary center, composed of a methyl and vinyl group, vicinal to this moiety (C-12). The hapalindoles are the simplest members of this family, containing the core structure described above, housed within a tricyclic framework. Many contain further functionalization, either in the form of unsaturation (at C-10) or chlorination (at C-13), and several contain an additional carbocycle arising from the union of C-4 of indole with the isopropylidene unit at C-15. The fischerindoles, tetracycles formed via the union of C-2 of indole with the isopropylidene unit at C-15, are also characterized by varying degrees of functionalization and oxidation. The hapaloxindoles and fontonamides are structurally related to the tetracyclic hapalindoles, although the indole has been either oxidized to give the oxindole or oxidatively cleaved to form the formyl kynurenine. Also related to the hapalindoles, albeit much more complex, are the ambiguines, which contain additional functionalization at C-2 of indole, specifically a tert-prenyl moiety. In the most complex ambiguines, this tert-prenyl is further cyclized and oxidized. In addition to the unifying structural features of this family of natural products, the hapalindolinones contain a unique component within their molecular architecture, specifically a spirocyclopropane that joins C-11 with C-3 of the oxindole heterocycle. Finally, the welwitindolinones are found in one of two structural
classes, the first being welwitindolinone A, which contains a spirocyclobutane centered around C-3. The remaining welwitindolinones are comprised of a [4.3.1]-bicyclononanone core, which contains an assortment of oxidative functionalization.

With a family of such diverse and unique molecular architectures, it should come as no surprise that several syntheses have been reported for these natural products, specifically focusing on the simpler members of the family. Syntheses have been reported for hapalindoles G,19 H,20 J,21-23 M,21-23 Q,24-27 O,28 and U,20 in addition to approaches to various other hapalindoles.29-31 There are no reported efforts towards the hapalindolinones, hapaloxindoles, and fontonamides and only one approach towards an ambiguine.32 The first total synthesis of an ambiguine (ambiguine H) was completed in our laboratory.33 Despite the many approaches to the welwitindolinones,34-43 at the time of the initial communication33,44 of the work presented herein, no members of the welwitindolinone family had succumbed to synthesis; however, the Wood group reported a very elegant synthesis of welwitindolinone A shortly thereafter.45,46

1.2 Biosynthetic Relationships

Biomimetic syntheses are often more efficient due to the tactics that Nature employs, namely rapid assembly of skeletal complexity, a linear increase of oxidation state, use of mild and simple reagents, and the ability to control chemoselectivity (lack of protecting groups).47,48 Despite their inherent advantages, biomimetic syntheses can be exceedingly difficult, due to the inability of chemists to attain the chemo-, regio-, and stereocontrol characterizing most enzymatic processes. The careful practitioner can make use of many abiotic tools in solving these problems; however, these methods
usually demand significant departure from the ideal biomimetic route. In light of these
difficulties it is certainly possible, and perhaps prudent, to find an appropriate balance
when envisioning a retrosynthesis. An ideal synthesis would likely entail the use of
powerful synthetic methods, coupled with a flexible adherence to the general synthetic
blueprint provided by Nature.

Given these considerations, and with such a large and diverse family of complex
natural products, a biosynthetic proposal that comprehensively describes the
interrelationships between each of the members would undoubtedly be enlightening to
any synthetic undertaking. The Moore group, in conjunction with their elegant isolation
studies, put forth many plausible biosynthetic ruminations that are summarized in
Scheme 1. Moore’s biosynthesis begins with the tryptophan derivative (1) and terpene
(2), which are enzymatically joined \textit{via} chloronium-promoted polyolefin cyclization to
provide the tricyclic hapalindole core \textit{[i.e., 12-epi-hapalindole E (3), Scheme 1]. At this
point, Moore proposed that the tricycle can progress through multiple divergent
pathways; the first of which (Path A) commences with a cyclization between C-4 of
indole and the isopropylidene unit at C-15, leading to the tetracyclic hapalindoles \textit{[i.e.,
12-epi-hapalindole G (4)]}. These natural products can then undergo further oxidation at
the indole moiety, leading to the oxindole \textit{[i.e., anhydrohapaloxindole A (5)]}, which can
be oxidatively cleaved to give the formyl kynurenine \textit{[i.e., hapalonamide V (6)]}. Alternate-
ly, the tetracyclic hapalindoles can have a tert-prenyl moiety appended at C-2
\textit{[i.e., ambiguine A (7)]}, which can be engaged in an intramolecular cyclization, leading to
the pentacyclic ambiguines \textit{[i.e., ambiguine E (8)]}. These alkaloids can then be further
oxidized \textit{[i.e., ambiguine D (9)]} or rearranged \textit{[i.e., ambiguine G (10)]}. Furthermore, the
tricyclic hapalindoles can undergo cyclization between C-2 and the isopropylidene at C-15, providing the fischerindoles \([i.e., 12\text{-}epi\text{-}fischerindole G (11)]\). Finally, Moore proposed that the tricyclic hapalindoles can be oxidized to give the putative intermediate 12, which has not been isolated as a natural product. He further proposed that this intermediate undergoes an acid-catalyzed cyclization to afford welwitindolinone A (13), presumably in the pocket of an enzyme. If 13 could be further oxidized, leading to the epoxide 14, the [4.3.1]-bicyclononanone system could be formed after rearrangement \([i.e., welwitindolinone B (15)]\). Moore proposed that an oxidation of 15 could lead to \(N\)-methylwelwitindolinone C (16) and further demonstrated the conversion of 16 into 3-hydroxy-\(N\)-methylwelwitindolinone C (18) and \(N\)-methylwelwitindolinone D (20).
Scheme 1. Moore's proposed biosynthetic relationships within the hapalindole family.
1.3 Revised Biosynthetic Relationships

While the Moore biosynthetic hypothesis provides an adequate explanation of the possible relationships between many of the distinct structural classes, a few points remain uncertain, primarily relating to the formation of the welwitindolinones. First, the proposal that 13 arises from the unsaturated intermediate 12 via an acid-catalyzed cyclization seems unlikely. The fact that 62 members of this natural product family have been isolated, while 12 has not been one of them, casts doubt on whether this compound is a plausible intermediate. Given the stability that 12 should demonstrate, at least trace quantities of this compound would be expected in the isolation broths. More importantly, there seems to be little thermodynamic driving force for the conversion of 12 to 13, due to the generation of a strained spirocyclobutane in this transformation. Second, the mechanistic explanation for the conversion of welwitindolinone A (13) into welwitindolinone B (15) lacks proper literature precedent. Third, the proposal that N-methylwelwitindolinone C (16) arises from remote oxidation of 15 could conceivably be explained by an alternate hypothesis. Finally, the isolation literature lacks a biosynthetic hypothesis to account for the genesis of the hapalindolinones.

Given the concerns delineated above, an alternative biosynthetic hypothesis is proposed in Scheme 2. Rather than arising from hypothetical metabolite 12, welwitindolinone A (13) could arise from an oxidative ring contraction of 12-epi-fischerindole I (22). 12-epi-fischerindole I could be formed via benzylic oxidation of 12-epi-fischerindole G (11), which could arise from the tricyclic hapalindole 12-epi-hapalindole E (3). Furthermore, an alternate, albeit untested, mechanistic hypothesis for the conversion of 13 into welwitindolinone B (15) is put forth, which is more in line with
literature precedent. Isonitriles are relatively electron withdrawing, inductively stabilizing negative charges, and have not been invoked as electron donating entities.\textsuperscript{49} It is therefore unlikely that the isonitrile would participate in a fracture of the epoxide \textit{via} electron donation, leading to a fissure of the cyclobutane ring. Alternatively, based on evidence gleaned in this laboratory,\textsuperscript{50,51} it is more reasonable to invoke electron donation from the N-1 lone pair, through the aromatic ring, to break the cyclobutane, leading to the $\alpha$-isocyanoketone enolate (\textsuperscript{23}). This enolate could then attack the highly unstable, extremely electrophilic azaorthoquinodimethane generated in the reaction, leading to \textsuperscript{15} after tautomerization.\textsuperscript{52} Additionally, the remote oxidation of \textsuperscript{15} to N-methylwelwitindolinone C (\textsuperscript{16}), although certainly possible with enzymatic intervention, is unlikely. Rather, if \textsuperscript{22} were to undergo allylic oxidation, intermediate \textsuperscript{24} could be accessed. Upon oxidative ring contraction, similar to that proposed for \textsuperscript{13}, the direct product would contain an unstable spirocyclobutane with vicinal exocyclic olefins. The trisubstituted olefin might then isomerize to form the vinyl chloride (\textsuperscript{25}), thus alleviating this additional strain on the spirocyclobutane. Oxidative ring expansion of \textsuperscript{25} could then lead directly to \textsuperscript{16}. Finally, it is proposed that the hapalindolinones could arise from an oxidative coupling event between the C-3 and C-11 carbons of an appropriate tricyclic hapalindole \textit{i.e.}, \textit{12-epi}-hapalindole Q (\textsuperscript{26}), generating the oxindole with the unprecedented spirocyclopropane moiety \textit{i.e.}, hapalindolinone B (\textsuperscript{27}).
1.4 Oxidative Enolate Couplings

As will be discussed in Section 3.2, the total synthesis of the hapalindole alkaloids would require a specially designed direct indole coupling reaction, inspired by the known oxidative dimerization of enolates. As such, a review of the oxidative coupling literature would be helpful at this point. There is a myriad of chemical literature concerning the radical reactions of ketones, specifically the oxidation and subsequent dimerization of ketone enolates. It is instructive at this juncture to review a brief history of the development of this C–C bond forming reaction, in an effort to convey the context in which these current investigations were undertaken. The prototypical oxidative enolate
coupling was first reported over 70 years ago in 1934, when Ivanoff and Spassoff treated the magnesium chloride enolate of sodium phenylacetate with molecular bromine and observed a 22% yield of the dimer. The authors posited that the reaction occurred through a radical intermediate; however, it would be many years before any formal mechanistic insights were gained.

This observation by Ivanoff subsequently lay dormant for several decades. During these intervening years, little was truly known about the reaction or substrate scope. In fact, to this day, many questions remain unanswered concerning this intriguing reaction. In 1968, Kauffmann reported the first example of an oxidative dimerization of a ketone enolate, namely acetophenone, using copper(I) salts, albeit in modest yields. Following this publication, Rathke reported the first use of a soluble copper(II) oxidant [copper(II) valerate] in the oxidative dimerization of ester enolates in moderate to excellent yields. Saegusa subsequently demonstrated efficient, high-yielding dimerizations of ketone enolates, using a variety of copper(II) based oxidants. He also described the heterocoupling of two different ketone enolates, which required three equivalents or more of one of the coupling partners to furnish acceptable yields of the heterocoupled product. Many reports have appeared employing a wide variety of oxidants to effect the couplings, including copper salts, iron salts, iodine, \( N \)-iodosuccinimide, hypervalent iodine reagents, silver salts, titanium salts, potassium permanganate, short chain alkyl polyhalides, and bromine, or by use of direct electrochemical oxidation. A few studies involving the dimerization of enolates conjugated throughout an aromatic system have been reported, which show the versatility of this coupling reaction in the
formation of a wide variety of dimerized compounds. Several reports exist that elicit the coupling of other stabilized anions, such as phosphine oxides, sulfoxides/sulfones, and methylpyridines under similar conditions. Oxidative dimerizations of indole have been reported using hypervalent iodine in the context of a biomimetic calycanthaceous alkaloid synthesis. Asymmetric dimerizations can be performed using a variety of chiral auxiliaries, and there is even one report describing the oxidation of a chiral titanium enolate to achieve modest asymmetric induction. Several groups have shown that intramolecular couplings can proceed in impressive yields. However, the inability to extend such successes to intermolecular reactions is both disappointing and expected due to the assumed mechanistic explanation.

Given the extensive history of oxidative enolate coupling chemistry, it was clear that the homodimerization of two enolates to form a symmetrical diketone was straightforward using a wide range of oxidants. The use of intermolecular oxidative coupling to selectively form a heterocoupled product without a prohibitive excess of one of the coupling partners remained a far more daunting task. In fact, the technology was so limited in scope that it had been scarcely utilized in total synthesis, mainly in the construction of various symmetrical lignans. In order to address the selectivity problem (homocoupling vs. heterocoupling) in intermolecular couplings, a few potential solutions have been put forth. In these reports, selective homo- or heterocouplings are performed by first converting one or both coupling partners into either the enol ethers or silyl enol ethers and reacting those with either ketones or other silyl enol ethers to give coupled products in reasonable yields. A similar reaction manifold has been observed for the coupling of enamines with various nucleophilic $\pi$-
A variety of oxidants have been utilized in such couplings including Mn(OAc)_3, Ag_2O, TiCl_4, Cu(OTf)_2, CAN, (EtO)VOCl_2, and Fe(phen)_3(PF_6)_3, or by use of direct electrochemical oxidation. Using vanadium oxidants, it was discovered that selective heterocouplings could be performed by exploiting the differing rates of oxidation of sterically dissimilar enol silanes. Silicon or titanium tethers can be employed to ensure that a heterocoupling will occur between two distinct carbonyl compounds. Similarly, it was shown that two different esters could be heterocoupled by constructing the mixed diester of BINOL. The reaction of silyl enol ethers with furans has also been reported. Unfortunately, these studies stopped short of achieving a selective heterocoupling of two free carbonyl compounds without resorting to prefunctionalization of one or more of the substrates. It is likely that enolate-type couplings would find more widespread use if this were possible.
Chapter 2:

Oxidative Indole Coupling
2.1 Introduction

Chemoselectivity stands as one of the greatest challenges to overcome in the invention of useful synthetic methodologies for C–C bond formation between two different organic entities (cross-coupling). Figure 2 depicts such a cross-coupling scenario using indole as an example. Of these five different paradigms, the union of heteroaryl boronic acids with halogenated \( sp^2 \) and \( sp^3 \) hybridized carbon atoms (Suzuki coupling, \textit{e.g.}, 1) is the most widely employed.\textsuperscript{146} Indeed, strategic substrate prefuctionalization has historically served as the most reliable means by which to direct such couplings. In the second type of coupling, a functionalized, protected indole is merged with an unfunctionalized substrate. A Heck reaction is an example of this transformation.\textsuperscript{147,148} The third type of coupling is another version of the Heck reaction, involving the union of an unfunctionalized, \( N \)-protected indole with a suitably functionalized substrate.\textsuperscript{149,150} The fourth tactic involves merging unfunctionalized \( N \)-protected indole with an unfunctionalized substrate.\textsuperscript{151-153} This method has been successfully demonstrated numerous times in both inter- and intramolecular contexts based on the ability of electron-rich aromatics to undergo electrophilic palladation. The fifth and final coupling paradigm requires no prefuctionalization or protection and relies solely on the innate reactivity of the indole and substrate. A regioselective Friedel-Crafts alkylation\textsuperscript{154} would fit into this or the previous category. Several of the coupling strategies shown in Figure 2 might be aptly marketed under the banner of “C–H functionalization”.\textsuperscript{155} In this chapter, the scope, mechanism, and application of a new reaction fitting into the fifth category will be discussed. This reaction accomplishes the coupling of unfunctionalized indoles\textsuperscript{24,156} with various carbonyl compounds such as
esters, imides, lactones, lactams, ketones, and amides. The reaction exhibits high levels of chemoselectivity (functional group tolerability), regioselectivity (coupling occurs exclusively at C-3), stereoselectivity (substrate control), and practicality (amenable to scale-up). As a meaningful demonstration of its utility, the method has been applied effectively to a number of problems in total synthesis, including several members of the hapalindole family (See chapter 3), ketorolac, acremoauxin A, and oxazinin 3.

This research program initiated when the hapalindole family of natural products was targeted for synthesis (See Section 1.1, Figure 1). In principle, the most efficient means to secure the core of these molecules would be via the direct attachment of indole to a terpene such as carvone. The literature revealed only one method that directly attaches two such compounds in the desired manner, ironically also reported in the
context of an elegant total synthesis of hapalindole Q. As delineated in Scheme 3, this coupling falls into the first category (see Figure 2) and as such required prefunctionalization of both substrates in order to achieve the desired reactivity. Although his was a clever solution to the problem, a different approach was sought that could avoid any “preprogramming” of the substrates. In addition, potential regioselectivity issues could arise as a consequence of using the enol-acetate derived from carvone as a coupling partner in the Albizati approach (i.e., the coupling could occur on any one of the three olefins present). Indeed, the coupling of the enol acetate of carvone with 3-bromo-\(N\)-triisopropylsilylindole has been attempted using Albizati’s conditions, and none of the desired product was obtained.

\[
\begin{align*}
\text{Scheme 3. Albizati’s indole coupling reaction.}
\end{align*}
\]
Barton’s classic synthesis\textsuperscript{158} and structural reassignment\textsuperscript{159} of usnic acid (39) provided invaluable inspiration for the development of an alternative route to the desired indole–carvone adduct (28, Figure 2). In Barton’s synthesis, treatment of phenol 34 with potassium ferricyanide elicited oxidation to the delocalized phenoxy radical, initiating a cascade reaction. Two of the resonance contributors, 35 and 36, selectively heterodimerized to form adduct 37. Subsequent tautomerization, hemiketalization, and elimination of water directly furnished usnic acid (39) in one synthetic operation (Scheme 4).

One of the most impressive aspects of Barton’s synthesis resides in the selective formation of a coupling product that arises from the heterodimerization of ortho- and para- localized radicals (35 and 36). This precedent led to a simple hypothesis: if the heterocoupling of two radicals was truly occurring in the usnic acid synthesis, then an analogous reaction might occur between indole and a carbonyl containing entity (Scheme 5). Theoretically, if an appropriate oxidant was found that could simultaneously oxidize the carvone enolate to the radical and the indole anion to the radical, then perhaps a heterocoupling could be achieved between the two species. For the indole anion, the
HOMO coefficient is largest on C-3, which causes indole to be nucleophilic at this position. In light of this knowledge, our hopes for successfully accomplishing the desired coupling were further bolstered by the fact that the same orbital is invoked for the radical species (SOMO). It therefore seemed reasonable to assume that the indole radical should also react at C-3.\textsuperscript{160} However, there were still several potential pitfalls to this proposed transformation: (1) securing an oxidant that could simultaneously oxidize both species, (2) avoiding a statistical product distribution in the intermolecular coupling to obtain a good yield of the heterodimer without requiring prohibitive excesses of reagents or starting materials, (3) overoxidation of the indole partner, and (4) controlling the diastereoselectivity of the coupling due to the intermediacy of a radical species.

\begin{center}
\includegraphics[width=\textwidth]{Scheme5.png}
\end{center}

\textbf{Scheme 5.} Initial mechanistic rationale in developing the oxidative indole coupling reaction.

2.2 Discovery and optimization

Given the somewhat daunting precedent (See Section 1.4) and aforementioned considerations, success of an oxidative coupling to forge the key bond in the hapalindoles
seemed unlikely. However, experimental studies were therefore initiated in the hope that a greater understanding of the process could be realized and perhaps the methodology could be rendered more synthetically useful. Indeed, when a mixture of carvone enolate and indole anion were treated with FeCl$_3$ as oxidant, a minor amount (8%) of the desired coupled product ($\text{28}$) was obtained as a single diastereomer (Table 1, entry 15).

Given the initial success, a more detailed study and optimization of the direct indole coupling reaction was undertaken. It was initially reasoned that the oxidant played a major role in the efficiency of the reaction, so a variety of oxidants were screened that were known (See Section 1.4), or predicted, to promote the direct coupling reaction (Table 1). It was quickly discovered that FeCl$_3$ did not have to be used as a DMF solution (as is commonly reported in enolate oxidation)\textsuperscript{76} but could simply be added to the reaction as a solid, a finding that greatly facilitated the screening of the remaining oxidants. In addition to the technical simplicity, the reactions were much cleaner in the absence of DMF. While many common oxidants [$\text{I}_2$, $\text{K}_3\text{Fe(CN)}_6$, $\text{Mn(OAc)}_3$] failed to furnish any of the desired coupled product, success was realized when copper-based oxidants were explored. A screen of several readily available soluble copper salts led to the selection of copper(II)2-ethylhexanoate as the optimum oxidant for the desired coupling reaction, in part due to its high solubility in organic solvents. It should also be noted that these reactions were extremely “clean” as monitored by TLC; only $\text{28}$, indole, and two diastereomeric carvone dimers were observed.
Table 1. Indole–carvone coupling optimizations.
In addition to the “standard” oxidants precedent in the literature for these coupling reactions, several other oxidants should be mentioned, since they unexpectedly provided product. For example, ceric ammonium nitrate (CAN) cleanly provided the desired product in 16% yield, even though it was not soluble in THF and had never before been used in an oxidative enolate coupling (however, it has been used in enol silane couplings, see Section 1.4). Interestingly, if CAN was added as a solution in DMF, no product was observed. Surprisingly, Pb(OAc)$_4$ also gave a 17% yield of the product when used as a solution in DMF, even though it too had never been employed in an oxidative enolate coupling. It was also discovered that by changing the ligand environment (and therefore tuning the oxidation potential of the metal center), the outcome of the coupling could be modulated \([i.e., \text{Mn(acac)}_3 \text{ vs. Mn(OAc)}_3]\). Also worthy of note is that stoichiometric palladium(II) provided no detectable product.$^{152,161,162}$

Once the proper oxidant was selected, a systematic screen of the other reaction parameters was undertaken, beginning with a search for the optimum solvent. A screen of common solvents revealed that DCM and THF provided identical results, so THF was selected for its ease of use with various bases. A study of an assortment of bases showed that LHMDS was optimal, but LDA provided similar results. Changing the cation \(i.e., \text{Na}^+, \text{K}^+\) only proved detrimental to the yield. It was also found that the optimum concentration was 1.0 M in THF as shown in Table 1. There was a subtle trend toward higher yields with increasing concentration, but this was limited by the solubility of the copper oxidants. Various methods of adding the oxidant were also investigated, and the
highest yield was observed when the copper salt was added as a solid (instead of in solution) presumably due to increased reaction concentration.

Next, a temperature screen revealed that the ideal temperature for oxidant addition was –20 ºC. [The experimental procedure involved immediately transferring the flask containing the reaction mixture and the oxidant at –78 ºC into a bath of the desired temperature (i.e., –20 ºC in this entry) and allowing the reaction to stir for ten minutes before quenching.] However, adding the oxidant at –78 ºC, removing the cooling bath, and allowing the reaction to naturally warm to ambient temperature before quenching provided a slightly higher yield than that of the corresponding reaction at –20 ºC. The effect on the yield with varying equivalents of indole was also examined, and not surprisingly, as the amount of indole was increased, the yield also increased proportionately (Table 1). However, limiting the loading to two equivalents provides an appropriate balance between yield and amount of oxidant.

Perhaps the most mechanistically revealing of all the optimization studies undertaken was that of oxidant stoichiometry. As is clearly evident from the graphical depiction in Figure 3, a full molar equivalent of oxidant was not required to drive the reaction to completion. In fact, only 0.5 equivalents, relative to both coupling partners, was required to completely consume the carvone, and any excess oxidant only caused minor fluctuations in yield. The short-term lesson learned is that less oxidant was needed to obtain the same yield, thus simplifying the procedure. The mechanistic implications of this finding will be discussed in Section 2.6.
The optimizations delineated above led to the following simple procedure: To a solution of carbonyl compound (1.0 equivalent) and indole (2.0 equivalents) in THF (1.0 M) at –78 °C in a flame-dried flask under a nitrogen atmosphere was added a 1.0 M solution of LHMDS (3.3 equivalents). After stirring for 30 minutes at –78 °C, the septum was removed, solid copper(II)2-ethylhexanoate (1.5 equivalents) was rapidly added in one portion, and the septum was quickly replaced. [It was found that opening the reaction flask to the ambient atmosphere for the time required for addition was not detrimental to the reaction yield. Comparison studies were performed in which the reaction was performed under meticulous Schlenk technique (degassed, rigorously dry, and the oxidant was added as a solution in THF) and an identical yield of the product was obtained.] The flask was then removed from the cooling bath and allowed to warm to ambient temperature, and the reaction was quenched. Using this procedure, the reaction was found to be efficient and practical, even on a large scale, with no diminution in yield.
2.3 Scope

Table 2 summarizes the range of couplings that were examined during the investigation of this reaction. Most simple ketones couple efficiently, including carvone (28), chromanone (51), tetralone (52), and menthone (74). Ketones that are much smaller (coupling at a terminal methyl group) are more prone to homodimerization, which explains the lower yield with substrates such as propiophenone (62). More highly substituted carbonyl compounds such as chloroketone 60, vinyl ketone 55, steroid 50, and decalin 63 proceed as well as, if not better than, simpler ketones. Such reactions allow tremendous complexity to be built into a target molecule using simple chemistry, which would otherwise require multiple steps to accomplish.
Functional group tolerance was an important parameter to consider while developing the oxidative indole coupling reaction. Several noteworthy examples include
unprotected or reactive functional groups that could potentially undergo competing side reactions. For example, chloroketone 60 is unreactive toward the radical-generating reaction conditions. Steroid 58 proceeds without requiring protection of the secondary hydroxyl group; an extra equivalent of base was added to deprotonate this potentially troublesome functional group. Epoxide 59 is obtained in acceptable yield, even though multiple side reactions could be envisioned in the presence of this reactive moiety. Quaternary centers can be formed in moderate (benzyl carvone 56) to good (tricycle 68 and lactone 61) yields, and coupling can even occur at hindered neopentyl centers such as that of isophorone (54). The reaction is amenable to asymmetric synthesis with either the Evans (73) or Oppolzer (64 – 67) chiral auxiliaries in good to excellent diastereoselectivities and yields. The coupling of β-ionone (53) is especially noteworthy, in spite of the moderate yield, because this represents the first ketone that was selectively coupled at a methyl group using the standard conditions, even though these types of compounds are extremely prone to homodimerization. Finally the reaction can be performed on a myriad of carbonyl compounds including esters (70), lactones (61), amides (73, 64 – 67), and ketones, and a wide variety of substitution patterns are tolerated on the indole (28, 40 – 49, 64 – 67).

2.4 Application to Total Synthesis

The direct indole coupling reaction is a useful method for the synthesis of complex natural products as will be discussed further in the context of the total synthesis of various members of the hapalindole family of natural products (See Chapter 3). As a further demonstration of this point, the indole coupling reaction has been applied to the
total synthesis of two additional natural products: acremoauxin A (83) and oxazinin 3 (90).

Acremoauxin A (83) was isolated in 1989 from Acremonium roseum and exhibits potent plant-growth inhibition.\textsuperscript{163} Structurally, 83 is composed of an indole moiety attached to an arabinitol-containing propionate ester. Synthetically, the challenge arises due to the difficulty of introducing the indole moiety onto the propionate ester with stereocontrol at the alpha center. Indeed, one synthesis of 83 has been reported in the literature,\textsuperscript{164} from the isolation group, in which an enzymatic resolution was employed to produce enantio-enriched indole propionate. Only 21\% of the desired indole enantiomer was recovered though, which contributed to an overall yield for the synthesis of 2.4\% over four steps (from indole).

Our synthesis commenced with the union of indole and camphorsultam propionate to provide a 49\% yield of the coupled product (64) as a single diastereomer (Section 2.3, Table 2). Hydrolysis of the chiral auxiliary provided the indole propionate 80 in 83\% yield (Scheme 6). Coupling of 80 with the known arabinitol derivative 81 (derived in four steps and one chromatographic purification from mannitol) provided 82 in 69\% yield. Compound 82 was deprotected with acetic acid to give a 62\% yield of acremoauxin A (83), which was spectroscopically identical to the natural product. This synthesis highlights the utility of the direct indole coupling reaction in asymmetric synthesis and proceeds in only four steps from indole with an overall yield of 17\% (six steps, longest linear sequence from mannitol).
As a further demonstration of the utility of this cross-coupling reaction, a total synthesis of the natural product oxazinin 3 (90)\textsuperscript{165} was undertaken.\textsuperscript{166} The major challenge was expected to be forging the C–C bond joining the indole and the \(\alpha\)-carbon adjacent to the amide, which has proven problematic in previous coupling reactions. The uncertainty of forming the \textit{cis} relative stereochemistry across the oxazinine ring was also troubling. However, it should be noted that enolate alkylation is expected to proceed with this configuration, but it was unknown if a similar stereochemical outcome would predominate with the indole coupling reaction.

The synthesis began with known compound 84 (derived in six steps and two chromatographic purifications from tyrosine), which was protected as the pivaloyl amide (85, Scheme 7). Direct indole coupling on this substrate provided the coupled product (89) in moderate yield and good diastereoselectivity (8:1), consistent with the transition state model (see Figure 4) for enolate alkylation at that position. The observed selectivity
can be accounted for by invoking a chair-type transition state for the cis facial selectivity, whereas the trans facial selectivity would proceed through a twist-boat transition state.\textsuperscript{167} Deprotection of the pivaloyl and benzoyl groups furnished oxazinin 3 (90) as a single enantiomer in 29\% overall yield and only four steps from known compounds.

![Scheme 7. Total synthesis of oxazinin 3 (90). Reagents and conditions: (a) TEA (2.0 equiv.), THF, PivCl (1.1 equiv.), 2 h., 93\%; (b) indole (3 equiv.); LHMDS (4.4 equiv.), –78 °C, 30 min.; copper(II)2-ethylhexanoate (1.5 equiv.), –78 to 25 °C, 10 min., 40\%; (c) TBAH (2.0 equiv.), H₂O₂ (2.0 equiv.), DME, 0 °C, 2 h., 82\%; (d) Pd/C (0.1 equiv.), MeOH, H₂, 15 h., 96\%.]

In addition to its brevity and efficiency, this synthesis also highlights how problematic couplings can be coaxed to proceed by varying the electronic nature around the carbonyl partner. Specifically, it was possible to induce the coupling of an amide with indole, a union that has generally proven to be more elusive in the past. This
difficulty may be due, in part, to the electron-rich nature of an amide carbonyl as compared to a ketone, which potentially correlates to mismatched oxidation potentials for selective coupling with electron-rich heterocyclic anions. Indeed, attempted coupling of the bis-anion derived from the unprotected amide (86) did not provide any detectable product. Also of note, coupling of the bis-benzyl protected compound (87) required a specialized iron-based oxidant [iron(III)trifluoroacetylacetylnaphthylate] and proceeded in only 19% yield. As a side note, this particular reaction demonstrates how careful tuning of the oxidation potential of the oxidant can allow heterocouplings to proceed, since copper-based oxidants were completely ineffective in this reaction.\textsuperscript{168} Coupling with the Boc-protected amide (88) was also tested but did not provide any improvement over the benzyl [5 – 18% using copper(II)2-ethylhexanoate or iron(III)acetylacetonates]. Success was finally realized when the pivaloyl group was introduced, which provided an appropriate balance between electron density, base stability, and ease of removal.

2.5 Extension to Other Heterocycles

Indoles are the most ubiquitous heterocycle found in naturally occurring substances and medicinal agents.\textsuperscript{169} However, other heterocycles also feature prominently in natural products and medicinal chemistry. Investigations were therefore focused on determining if the direct indole coupling reaction developed above could be extended to the construction of other complex heterocyclic scaffolds.

Initial studies centered around those heterocycles most prevalent in either natural products or medicinal chemistry: specifically pyridine, pyrimidine, pyrazole, indazole, furan, thiophene, imidazole, and pyrrole. It was quickly discovered that pyridine,
pyrimidine, furan, and thiophene could not participate in the direct coupling reaction using the developed conditions, presumably because they lacked the requisite free N–H bond (see Section 2.6 for mechanistic reasoning). Furthermore, pyrazole and indazole did not work, likely due to the decreased electron density on the aromatic heterocycle. Similarly, imidazole was not a competent coupling partner, perhaps because of the extremely high metal chelating ability of this heterocycle.

A successful coupling was realized with pyrrole under the developed conditions to furnish products that are the result of pyrrole coupling at C-2 with the α-carbon of carbonyl compounds (Section 2.3, Table 2). Pyrrole is more reactive and less stable than indole, requiring the reaction conditions to be slightly modified to allow for a more efficient process. In fact, due to pyrrole’s propensity to polymerize via both radical and acidic mechanisms, extra care and celerity were required during purification, otherwise significant product decomposition was observed (unless the heterocycle was deactivated with either electron-deficient groups or by blocking the open positions of the ring). Pyrroles are also versatile heterocyclic intermediates because they can be converted into pyridines,170 pyrrolinone,171 and pyrrolidines.172 A broad substrate scope was observed in the direct pyrrole coupling reaction, as shown in Table 2 (Section 2.3). Ketones (72, 76 – 79), esters (57), amides (75), lactams (71), and lactones (69) all participated in couplings, tolerating a range of functional groups. As with indoles, quaternary centers could be forged in reasonable yield (72) and the reaction could also be applied to asymmetric synthesis using the Oppolzer sultam (75). A range of substitution patterns around the pyrrole nucleus are tolerated, which can provide highly complex heterocyclic scaffolds in good yield (76 – 79).
Pyrrole is also found in a wide variety of medicinal compounds, so as a further
testament to the utility of the direct pyrrole coupling reaction, the method was showcased
in a synthesis of the nonsteroidal anti-inflammatory drug ketorolac (95).\textsuperscript{173,174} It was
known that the (S)-enantiomer is significantly more active than the (R)-antipode,\textsuperscript{175} and
therefore an asymmetric synthesis was preferred. (Ketorolac is marketed as a racemate,
despite the fact that one enantiomer is known to be more active than the other.) The
pioneering syntheses by Muchowski and co-workers at Syntex (now Hoffman-LaRoche)
served as inspiration in developing a route based upon the oxidative pyrrole coupling.
Any new synthesis would be hard-pressed to improve upon Syntex’s orginal route (ca
45% yield from pyrrole, racemic) but would at least serve as a proving ground for the
versatility of the pyrrole coupling reaction in a discovery-scale setting.

The synthesis commenced by installing the appropriate Oppolzer sultam as a
chiral auxiliary on the known\textsuperscript{176} pyrrole acid 9 (Scheme 8). Unexpectedly, even after
extensive experimentation, the intramolecular coupling could not be accomplished using
a wide variety of oxidants [including both copper(II) and iron(III) salts] to forge the
bicyclic core of ketorolac. This result was quite surprising, because the oxidative
coupling literature has consistently invoked oxidation of an enolate to an \(\alpha\)-radical (\textit{vide supra}). Were this mechanism operable, this electrophilic radical should be attacked by
the electron-rich heterocyclic system, yielding the desired product. Success was finally
realized when ferrocenium hexafluorophosphate (93)\textsuperscript{79,177-181} was used as the oxidant,
providing the annulated product (94), where no other attempted oxidants were successful.
This particular oxidant has been unambiguously shown by Jahn and co-workers to
oxidize enolates to discrete radicals, which can react with a wide variety of olefinic
The unique success of this iron-based oxidant implies that copper-based reactions are not proceeding via oxidation to the discrete radical. Also of note is the fact that ferrocenium hexafluorophosphate is not a competent oxidant for the intermolecular pyrrole or indole coupling reactions.

Once annulated, the pyrrole product (94) was extremely unstable, requiring that the material be immediately benzoylated in order to remove electron density from the pyrrole and lend increased stability. This provided the full carbon skeleton of the medicinal agent. Hydrolysis of the chiral auxiliary without epimerization of the final product initially proved problematic; however, optimized conditions were found using tetrabutylammonium hydroxide and hydrogen peroxide, giving ketorolac (95) in good yield and enantiopurity. Highlights of this route include the avoidance of protecting.

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Scheme 8. Total synthesis of ketorolac (95). Reagents and conditions: (a) TEA (1.1 equiv.), MeOCOCl (1.0 equiv.), THF, 0 °C, 1 h., then 92, 100%; (b) LHMDS (1.2 equiv.), TEA (2.0 equiv.), THF, –78 °C, 30 min.; then 12 °C, 93 (0.75 equiv.), 5 min., $d_r = 4.5:1$, extremely unstable; (c) BzCl, 70 °C, 4 h., 27% brsm; (d) TBAH (2.0 equiv.), H$_2$O$_2$ (2.0 equiv.), 2-methylbut-2-ene (3.0 equiv.), DME, –10 °C, 3 h., 58%.
groups, conservation of oxidation state, and the stereochemical induction observed in the key coupling reaction.

**2.6 Mechanistic Analysis**

A Hammett analysis was performed to probe the nature of the rate-limiting step of this intriguing reaction and, perhaps, oxidative couplings in general. A series of couplings were executed between carvone and C-5 and C-6 substituted indoles, from which a set of Hammett plots was derived. As can be observed from the plot for C-6 substituted indoles (Figure 5), a linear correlation between the ratio of reaction rates \( \frac{k_{rxn}}{k_{ref}} \) and the substituent parameter \( \sigma_p^{+} \) was obtained, which provided a small, negative reaction constant \( \rho = -0.61, R^2 = 0.996 \). This relatively small \( \rho \)-value correlates to a slight dependence of the reaction on the polarizing influence of the aromatic substituents, which is indicative of a radical-based mechanism. Were the rate-determining step proceeding through an ionic pathway, a much larger \( \rho \)-value would be expected, with a larger dependence on the electronic nature of the aromatic ring. Additionally, the negative sign of \( \rho \) suggests an electron-deficient transition state for the reaction relative to the ground state. In other words, negative charge is lost during the transition state, which could be explained by a radical-based coupling in which C-3 might transform from a stabilized anion into a tetrasubstituted center bearing no charge.
Figure 5. Hammett plot for C-6 substituted indoles. $k_{\text{ref}}$ = rate constant of the reaction of indole with carvone; $k_{\text{rxn}}$ = rate constant of the reaction of substituted indoles with carvone. For the determination of $r$, the following expression was used: $\frac{k_{\text{rxn}}}{k_{\text{ref}}} = \log\left[1 - \frac{x_p}{x_r}\right]/\log\left[1 - \frac{y_p}{y_r}\right]$. $r$ = reaction constant; $x_p$ = mmol product formed from substituted indole; $x_r$ = mmol starting carvone placed in the reaction; $y_p$ = mmol product formed from unsubstituted indole; $y_r$ = mmol starting carvone placed in the reaction.

In contrast, the Hammett plot for C-5 substituted indoles does not exhibit a linear relationship (Figure 6) between the ratio of reaction rates ($\frac{k_{\text{rxn}}}{k_{\text{ref}}}$) and the substituent parameter ($\sigma_p^+\$). A gradual curve is instead observed, indicating increased charge localization at the activated center during the course of the reaction but that the transition state does not change significantly as a consequence of this charge development. This suggests that negative charge is increased at N-1 during the course of the reaction, even though this center is not participating in the rate-limiting step. This data would be consistent with nucleophilic attack of the indole anion onto an electrophilic $\alpha$-ketoradical, resulting in a radical anion at N-1, which would be less resonance stabilized, and therefore more localized, than the initial anion located at the same position (i.e., the anion can also reside at C-3, whereas the radical anion cannot).
In addition to the above Hammett analysis, several observations have been made over the course of these and other studies involving oxidative enolate couplings in this laboratory, providing further clues to the mechanism of the oxidative coupling reaction. (1) Dimerization of indole is never observed, unless a ketone is either not present or cannot be oxidized under the reaction conditions, in which case the trimer (98, Figure 7) and tetramer (99, clear cubes, mp 234 – 235 ºC, See Figure 7 for X-ray crystallographic analysis.) are obtained. This suggests that the ketone is oxidized first and then reacts with indole. This also provides evidence that selective heterocouplings can be designed by tuning the oxidation potential of the oxidant to react preferentially with one coupling partner over the other. (2) N-Protected indoles or pyrroles are unreactive; in fact, the free N–H is required for the reaction to proceed. This suggests that the reaction is not proceeding via oxidation to a discrete α-radical on the carbonyl compound (which could
react with the $N$-protected heterocycles$^{157}$ but instead supports a chelated transition state. (3) Ferrocenium hexafluorophosphate is not a competent oxidant for the intermolecular couplings, and copper(II) does not effect the annulation. This provides evidence against the intermediacy of a discrete $\alpha$-radical on the carbonyl compound. There is also limited evidence in the literature that questions the widely accepted view that this reaction proceeds via the dimerization of two carbonyl $\alpha$-radicals.$^{56,57}$ (4) Only one equivalent of oxidant, relative to the ketone, is necessary for the reaction to proceed (1.5 equivalents provides a slightly improved yield). This suggests that the reaction is proceeding by preferential oxidation of the carbonyl compound, which theoretically could react with the indole or pyrrole anion, providing a radical anion intermediate. This radical anion could then be further oxidized by the remaining copper(I). (5) Excellent diastereoselectivity is observed in the intramolecular coupling of an amide and an ester during the stephacidin B synthesis to form two adjacent stereocenters, one of which is quaternary (regardless of the oxidant used).$^{185-187}$ In an intermolecular setting, moderate to low diastereoselectivity is observed using the Evans chiral auxiliary.$^{168}$ These results can be explained by invoking a chelated transition state; however, substrate control cannot be excluded based on these findings. Thus, the extent of metal complexation in the transition state of the coupling is unclear. It should be noted that a chelated transition state in oxidative enolate couplings has been implicated in the literature based on observed diastereoselectivities.$^{55}$
Figure 7: Indole trimer (98) and tetramer (99).

The mechanistic evidence delineated above is suggestive of two plausible mechanistic interpretations (Scheme 9). Both invoke a metal-chelated transition state and involve reduction of the copper species to copper(0). In pathway A, an enolate and an indole anion initially coordinate to the copper(II) center, giving the chelated intermediate (100). This intermediate could undergo a net two-electron reductive elimination of the metal center to give 28 after tautomerization.

While this mechanism cannot be ruled out based on the above evidence, pathway B is certainly more compelling. In this pathway, the same chelate 100 can undergo single-electron transfer to form the chelated α-keto radical 101. Due to its proximity to
the indole anion, the radical can suffer attack by this nucleophilic species, resulting in radical anion 102. This high-energy intermediate can then be further oxidized by the proximal copper(I) center, expelling, after tautomerization, the coupled product (28) and copper(0). In light of the fact that copper(I) is a viable oxidant for the oxidative coupling reaction62 and that the radical anion would be prone to oxidation by the coordinated, albeit weakly oxidizing, copper(I) species, this mechanistic interpretation is certainly reasonable. It should also be clearly noted that alternative mechanisms could easily be drawn that do not invoke a chelated transition state or the eventual reduction to copper(0), but given the evidence presented herein, pathway B is certainly preferred.

2.7 Conclusions:

In this chapter, a novel C–C bond forming reaction has been developed for the direct union of indoles and pyrroles with carbonyl compounds. This reaction demonstrates a wide substrate scope through the coupling of substituted indoles and pyrroles with esters, amides, imides, lactones, lactams, and ketones. While the reaction demonstrates admirable scope and generality for a range of pyrrole and indole couplings, it has clear limitations. For instance, the reaction is not amenable to a wide range of heterocyclic scaffolds, electron-deficient indoles do not couple well, and methyl ketones are prone to homodimerization. However, despite these limitations, this method has already been shown to be an efficient and enabling technology in natural products total synthesis (83 and 90, Section 2.4), medicinal synthesis (95, Section 2.5), and asymmetric synthesis (64 – 67, 73, 75 – 79, Section 2.3) and many further applications are
anticipated. Finally, mechanistic insight has been gained and has allowed for a clearer understanding of this oxidative coupling protocol.

The studies performed in this chapter were accomplished with the assistance of several talented coworkers. Ms. M. Pilar Castroviejo was responsible for the investigations with pyridines and protected indoles. Mr. Brandon W. Whitefield performed the coupling of 41, 42, and 62, in addition to the total synthesis of 90. Mr. Thomas J. Maimone performed the coupling of 50, 51, 53, 54, 55, 63, 61, 68, and 74, as well as obtained the X-ray crystal structure of 99. Finally, Mr. David W. Lin was responsible for the optimization of the direct pyrrole coupling, the coupling of substrates 69, 71, 72, and 75 – 79, as well as the studies with furan and thiophene.
Chapter 3:

Total Synthesis of Hapalindoles, Fischerindoles, and

Welwitindolinone A
3.1 Retrosynthetic Analysis of Hapalindole Q

With a compelling biosynthetic hypothesis in hand, attention could be turned towards designing a synthesis of welwitindolinone A (13, Section 1.3, Scheme 2). However, before such a task was undertaken, it seemed prudent to first consider a synthesis of simpler members of the family, such as hapalindole Q (103) and 12-epi-fischerindole U (104, Scheme 10). Such efforts should reveal hidden clues into the fundamental reactivity of these alkaloids as well as help develop a general route by which to access the core structure. Hapalindole Q (103) had been synthesized previously by the Albizati (eight steps, 7.2% overall yield)\textsuperscript{25} and Kerr (twelve steps, 1.5% overall yield)\textsuperscript{26,27} groups, but no syntheses of 104 had been reported. Since a route to 13 was the ultimate goal, a more efficient route to the core (\textit{i.e.}, 103 and 104) of this alkaloid was required, as described in Scheme 10. Although a cyclization of 103 could certainly be investigated to form 104, this transformation was instead planned at the ketone stage (105), given the acid-sensitivity of the isothiocyanate group. As such, both natural products can be traced to their ketone analogues (105 and 106), the latter of which should be accessible from the former \textit{via} an acid-catalyzed cyclization. Ketone 105 can be further simplified to the indole/carvone adduct (28) through straightforward functional group transformations. At this stage, a strictly biomimetic synthesis would require a chloronium-promoted polyolefin cyclization to install the terpene moiety; however, a potentially more direct and powerfully simplifying transformation would involve direct formation of the key C(3)–C(10) bond.
3.2 Total Synthesis of Hapalindole Q

Several strategies were investigated for the synthesis of the requisite carvone–indole adduct (28) before a method was finally developed to successfully provide the desired material. Initially, it was reasoned that 28 could be accessed from an aldol reaction with subsequent reduction to form the requisite indole moiety (Scheme 11). Indeed, quenching of the enolate of carvone with MOM-protected isatin (107)\textsuperscript{188} provided the desired aldol product (108) in excellent yield. Unfortunately, reduction of
this intermediate proved problematic. Any methods investigated to directly reduce this compound to the indole 112 (i.e., LiAlH₄, BH₃•THF) were met with failure, so a step-wise solution was sought. Assuming that the C-3 hydroxyl was preventing reduction of the oxindole, various deoxygenation conditions [Barton,¹⁸⁹ CS(imid)_2/hv¹⁹⁰] were brought to bear for the removal of this alcohol (113) prior to indole reduction; however, all attempts were unsuccessful. (Retro-aldol reaction was the major competing pathway.) Reasoning that elimination of the hydroxyl moiety would provide an intermediate upon which further reductions could be performed, various conditions were screened to elicit dehydration (Martin sulfurane,¹⁹¹ MsCl/base, TFA/TFAA) before Burgess reagent¹⁹² successfully provided the enone (111). However, the yield of this process was irreparably dismal, precluding further chemistry. Since the alcohol could not be reduced, removed, or efficiently eliminated, methods to exchange this moiety for a chlorine atom, which could theoretically be removed with greater facility, were investigated. Employing the conditions developed by Nicolaou,¹⁹³ 108 was dissolved in thionyl chloride, which provided the cyclic ether 110 (colorless cubes, mp 166 – 168 °C, See Scheme 11 for X-ray crystallographic analysis) and the unexpectedly stable, semi-deprotected compound 109, once again leading to a dead-end.
The resistance of intermediate 108 to reduction necessitated the investigation of alternate means to forge the key bond in 28. Since removal of the tertiary alcohol had proved to be an intractable problem in the previous route, an approach that circumvented the generation of this group was sought, leading to an oxidative enolate coupling approach to form the desired bond (Scheme 12). The oxidative dimerization of carbonyl compounds has been known for more than 70 years, however it has yet to become widely utilized by the synthetic community. Even though a myriad of literature concerning oxidative enolate couplings was available (See Section 1.4), many potential pitfalls could be encountered while pursuing this route. By the inception of this work, only one example of an oxindole oxidative dimerization had been reported. Additionally, in order to achieve high yields of heterodimerized products in an oxidative enolate coupling, three or more equivalents of one coupling partner were usually required. Finally, few investigations into the factors that govern the heterodimerization event had been performed; thus it was unknown whether any of the desired heterocoupled product would be obtained. Despite such potential pitfalls, an examination of the oxidative coupling
was undertaken, which would, at the minimum, provide further insight into the elements that govern such transformations.

As a starting point for the examination of this heterocoupling reaction, treatment of carvone and MOM-protected oxindole (114) with FeCl₃ in DMF provided the desired product (115) in ca. 15% yield. Given the success of this coupling, an optimization of this particular reaction was undertaken, centering primarily on oxidant selection (Table 3). Hypervalent iodine and cupric-based oxidants were less efficient at promoting the coupling than the ferric-based systems, so the focus of further studies was thus narrowed. Success was finally realized when the acetylacetonate-type ligands were utilized on the iron center. Specifically, Fe(t-BuCOCHCOCH₃)₃ was exceptionally efficient, providing an 83% isolated yield of the desired product (as a 1:1 mixture of diastereomers at C-3), utilizing only equimolar quantities of both coupling partners!

These results have led to the hypothesis that careful tuning of the oxidant’s oxidation
potential to more closely match one of the coupling partners could lead to selective heterodimerizations. With high-yielding access to intermediate 115, efforts were turned towards the reduction of oxindole 115 to indole 116 (Scheme 12). Once again, the reduction proved recalcitrant, necessitating yet another reevaluation of the synthetic strategy.

![Chemical structure](image)

**Table 3.** Optimum oxidant selection.

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<thead>
<tr>
<th>Oxidant</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhI(OAc)$_2$</td>
<td>10%</td>
</tr>
<tr>
<td>Cu(2-ethylhexanoate)$_2$</td>
<td>15%</td>
</tr>
<tr>
<td>FeCl$_3$</td>
<td>ca 15%</td>
</tr>
<tr>
<td>Fe(PhCOCHCOCH$_3$)$_3$</td>
<td>30%</td>
</tr>
<tr>
<td>Fe(CH$_3$COCHCOCH$_3$)$_3$</td>
<td>40%</td>
</tr>
<tr>
<td>Fe(C$_{10}$H$_7$COCHCOCF$_3$)$_3$</td>
<td>40%</td>
</tr>
<tr>
<td>Fe(CH$_3$COCHCOCH$_3$)$_3$</td>
<td>45%</td>
</tr>
<tr>
<td>Fe(2-BuCOCHCOCH$_3$)$_3$</td>
<td>83%</td>
</tr>
</tbody>
</table>

As with the aldol route, an alternative to the oxindole coupling was sought that would avoid a problematic reduction step. As such, the most straightforward method by which to circumvent this difficulty would be to directly attach the indole to the carvone moiety. Unfortunately, no such method had been reported, requiring the invention of chemistry to fill this gap. Inspired by the oxidative coupling literature, in conjunction with Barton’s classic synthesis of usnic acid (See Section 2.2), the oxidative indole
coupling was conceived. In this reaction, an indole can be directly attached to a variety of carbonyl compounds in good yields. The method was found to generate the desired indole/carvone adduct (28, colorless cubes, mp 129 – 130 °C, See Scheme 13 for X-ray crystallographic analysis) in good yield in one synthetic operation from commodity starting materials.
Scheme 13. Total synthesis of hapalindole Q (103) and 12-epi-fischerindole U (104). Reagents and conditions: (a) indole (2.0 equiv.), carvone (1.0 equiv.), LHMDS (3.3 equiv.), THF, –78 °C, 30 min.; then copper(II)2-ethylhexanoate (1.5 equiv.), –78 to 23 °C, 15 min., 49-53%; (b) LHMDS (1.5 equiv.), THF, –78 º C, 20 min.; then L-Selectride (1.05 equiv.), 1 h., then CH₃CHO (6.0 equiv.), –78 to 23 º C, 2 h.; (c) Martin sulfurane (1.1 equiv.), CHCl₃, 10 min., 75% (2 steps); (d) TMSOTf (3.0 equiv.), MeOH (1.1 equiv.), DCM, 0 ºC, 1 h., 75% brsm; (e) NaCNBH₃ (10 equiv.), NH₃OAc (40 equiv.), MeOH, THF, microwave, 150 ºC, 2 min., 61%; (f) CS(imid)₂ (1.1 equiv.), DCM, 0 to 23 ºC, 3 h.; (g) NaCNBH₃ (10 equiv.), NH₃OAc (40 equiv.), MeOH, THF, 23 ºC, 7 d., 55%. 

α-NCS: hapalindole Q (103, 38%)
β-NCS: ent-12-epi-hapalindole D (117, 12%)

ent-12-epi-fischerindole U (104, 33%)
With gram quantities of 28 in hand, attention was turned to completion of the total synthesis of 103 and 104, which first required vicinal difunctionalization of the C(12)–C(13) olefin. Treatment of 28 with two equivalents of L-Selectride was expected to first deprotonate N(1)–H, then perform a conjugate reduction to generate the enolate, which could be trapped with acetaldehyde. Surprisingly, 1,4-hydride addition preceded N(1)–H deprotonation, thus generating the enolate, which then deprotonated N-1, forming 118 (See Figure 8). Rather than protecting this center, N(1)–H was first deprotonated with LHMDS, followed by addition of L-Selectride, and the resulting enolate was trapped with acetaldehyde. This intermediate alcohol was immediately dehydrated with Martin sulfurane to give vinylated compound 105, which intersected Albizati’s synthesis. Reductive amination using Albizati’s conditions (NH₄OAc, NaCNBH₃, RT, 7 days) provided the desired amine in 61% yield as a 3:1 mixture of diastereomers. Alternatively, microwave irradiation (150 °C, 2 min.) provided an identical yield of the product, with an increased diastereomeric ratio of 6:1. To the best of our knowledge, this is an unique example of an increase in diastereoselectivity as a consequence of microwave irradiation. Treatment of the amine with CS(imid)$_2$ installed the isothiocyanate, completing the total synthesis of 103 and the first total synthesis of ent-12-epi-hapalindole D (117). Tricyclic ketone 105 could also undergo a biomimetic acid-catalyzed cyclization to provide the tetracyclic ketone 106 upon exposure to triflic acid. (Prolonged exposure to triflic acid led to product decomposition; therefore, the reaction was quenched early and the starting material was recycled.) Reductive amination and formation of the isothiocyanate completed the first total synthesis of 104, which also allowed the determination of the absolute stereochemistry of the
fischerindole-type natural products (opposite that depicted in Scheme 13). The syntheses of 103, 117, and 104 proceeded enantioselectively in 15%, 4.8%, and 9.8% overall yields respectively, without resorting to protecting groups or superfluous redox manipulations.24

![Figure 8. Vicinal difunctionalization byproduct (118).](image)

### 3.3 Retrosynthetic Analysis of Welwitindolinone A

Having demonstrated that the direct indole coupling could enable rapid access to several of the simpler members of the hapalindole family of natural products, attention could be turned to the more complex members. Welwitindolinone A (13) was an attractive target for total synthesis due to its strikingly unique molecular architecture. It contains two all-carbon quaternary stereocenters and a chiral, neopentyl chlorine atom, all incorporated into a highly strained spirocyclobutane-containing oxindole. As already discussed (See Section 1.3), the revised biosynthetic hypothesis proposes that 12-epi-fischerindole I (22) is converted into 13 via oxidative ring contraction (Scheme 14).196 Such ring contractions are primarily utilized for the preparation of spirocyclic 5-membered rings from annulated 6-membered rings and often require relatively harsh reaction conditions to proceed.197-199 Only one example has been reported for the direct preparation of a spirocyclic 4-membered ring from an annulated 5-membered ring,200 however, a related conversion has been observed in this laboratory to generate a strained β-lactam (121, Figure 9).50,51 Furthermore, it is conceivable that 22 could arise from 12-
*epi*-fischindole G (11) via benzylic oxidation. Through straightforward functional group manipulations, 11 could be derived from the tetracyclic ketone 119, which in turn could arise from an acid-catalyzed cyclization of tricyclic ketone 60. Exploiting the direct coupling methodology developed for the synthesis of 103, 60 could be obtained from the coupling of indole with 120. Chloroketone 120 was a new chemical entity; however, a very similar analogue had been prepared by Fukuyama *en route* to hapalindole G.19 Fukuyama’s chloroketone (122, Figure 10) is diastereomeric at C-12 and the chemistry utilized for its preparation was not amenable for the preparation of 120.

**Scheme 14.** Retrosynthesis of welwitindolinone A (13).
3.4 Total Synthesis of Ent-12-epi-Fischerindole G

Historically, installation of chlorine atoms adjacent to quaternary centers has been met with difficulty and it was anticipated that 120 would be no exception.\textsuperscript{201,202} Forays into the preparation of this compound focused on direct means for concurrent installation of the chlorine and quaternary stereocenter (Scheme 15). As such, attempts were made to apply a modified Balis-Hillman-type reaction\textsuperscript{203} in which β-chloroketones are generated from the corresponding enones, with concomitant incorporation of an aldehyde. However, this reaction was never utilized to install a quaternary center at the α-position prior to this work. Unfortunately, none of the desired product (128) was obtained using these conditions. Given the limited prospects for direct installation of the hallmark chlorine atom, attention was instead focused on a variety of chlorine equivalents. Carboxylic acids can be readily converted into chlorines \textit{via} a Hunsdiecker reaction, so several acyl anion equivalents \textit{i.e.}, 1,3-dithiane, (MeO)\textsubscript{3}CH, (PhS)\textsubscript{3}CH\textsubscript{3} were examined in 1,4-additions to carvone, but none provided the desired product. Encouragingly,
successful 1,4-addition was observed with phenylcuprate and the incipient enolate was trapped with acetaldehyde to give 123. However, attempts to oxidatively degrade the aromatic ring\textsuperscript{204} led to significant over-oxidation. A thiophenyl group was next targeted as a chlorine equivalent, due to the propensity of such moieties to undergo α-chlorination or Pummerer rearrangements. Thiophenol participated in an efficient vicinal difunctionalization of carvone with Me\textsubscript{3}Al catalysis\textsuperscript{205} to provide, after dehydration with Martin sulfurane, thioether 125. Attempts to directly chlorinate 125 were unsuccessful using a variety of reagents (NCS, Raney Ni/CCl\textsubscript{4}, SO\textsubscript{2}Cl\textsubscript{2}, CCl\textsubscript{4}/hv, Cl\textsubscript{3}CCOCCl\textsubscript{3}). Chlorination with concomitant removal of the thiol under numerous conditions (PIFA/LiCl, LiNaphthalenide/TsCl, TiCl\textsubscript{4}/CCl\textsubscript{4}, MeI/NaCl\textsuperscript{206}) were also investigated, to no avail. Routes in which the ketone was first converted into the chlorine, followed by sulfide oxidation, were also considered. Attempted direct reductive chlorination of the ketone,\textsuperscript{207} instead of providing the desired product, led to the unexpected bicycle 126. Attempts to generate the vinyl chloride (POCl\textsubscript{3}), which could be carefully hydrogenated to the alkyl chloride, were also fruitless. Unable to perform a direct reductive chlorination of the carbonyl, 125 was first reduced to the neopentyl alcohol (127), then unsuccessfully subjected to a variety of chlorination conditions (SOCl\textsubscript{2}/base, PPh\textsubscript{3}/CCl\textsubscript{4},\textsuperscript{208} TCT/DMF\textsuperscript{209}). These chlorinations presumably failed due to the extremely hindered nature of this particular alcohol. Before further effort was expended on this chlorination, the Pummerer rearrangement of thioether 125 was investigated to determine its feasibility in this system, which revealed that the reaction was not possible under a variety of conditions (IBX,\textsuperscript{210} mCPBA,\textsuperscript{211} H\textsubscript{2}O\textsubscript{2},\textsuperscript{212} t-BuOOH, BAIβ).
Repeated failure to convert carvone into the desired chloroketone via any sort of vicinal difunctionalization necessitated yet another strategic reevaluation. Therefore, carvone oxide (129) was examined as a starting material for the production of 120. It was reasoned that 1,2-addition of vinyl magnesium bromide into the α,β-epoxy ketone, followed by a semi-pinacol rearrangement, could allow installation of the quaternary stereocenter, contingent upon β-face attack of the organometallic reagent. Unfortunately, such conformationally constrained systems are known to favor axial (i.e., α-face) attack of nucleophiles, thus sterically precluding a successful semi-pinacol rearrangement. However, if the ring was less conformationally constrained, a nucleophile might favor
equatorial approach, especially if the $\alpha$-carbon could synergistically shield the $\alpha$-face. As such, chlorohydrin 131 met these criteria and was prepared from carvone oxide in good yield. Unfortunately, 131 was unstable, even upon storage in an inert atmosphere, and failed to provide any desired product when treated with a variety of nucleophiles. Attempts were also made to trap the alcohol with an appropriate leaving group (Ms, Ts) before addition of the nucleophile, to no avail.

Investigations subsequently turned towards sequences that would install the quaternary stereocenter and perform the chlorination in separate operations. Initial attempts to install the vinyl group via dissolving metal-promoted reductive alkylation of the epoxide217 to give 130 proved fruitless, as any electrophile that could be subsequently converted into the vinyl group (i.e., TBSOCH$_2$CH$_2$I, oxirane) failed to participate in the reaction. Alternatively, reduction to the known carveol oxide allowed investigations into the direct chlorination of this alcohol, which would be followed by installation of the quaternary stereocenter and regeneration of the ketone. Unfortunately, such chlorinations were unsuccessful due to the instability of the epoxy-alcohol. The enol acetate 132 was prepared from carvone oxide, in order to test an intramolecular enolate addition into the epoxide, which proved fruitless. Condensation with hydroxylamine provided the oxime 133, which was poised to undergo an $\alpha$-substitution reaction reported by Corey and coworkers.218 Reaction of the oxime with two equivalents of a cuprate reagent would first deprotonate the oxime, which could open the epoxide and lead to the vinylnitroso compound 134 (Figure 11). The second equivalent of cuprate could then participate in a 1,4-addition into the vinylnitroso, thereby installing the quaternary center. Unfortunately, divinylcuprate was unsuccessful at accomplishing this transformation.
After several other failed attempts to generate 120, a successful route to the desired chloroketone (120) was finally developed, inspired by a reaction developed in the Wender laboratory. In Wender’s study, α,β-epoxy ketones were first treated with strong base to form the enolate. Nucleophilic addition of an organometallic reagent (usually Grignard) to the α-carbon of the epoxide (as opposed to the usual β-attack), followed by elimination of the hydroxyl group, furnished the substituted enones. However, no examples were given in which a quaternary carbon was installed during the course of this reaction. Despite this potential limitation, the reaction was attempted on carvone oxide to provide 136 in about 30% yield (Scheme 16). Extensive optimization efforts (solvent, nucleophile, base, additives, temperature, addition rates) did not result in significant improvement in the overall efficiency of the reaction. The low yield is likely due to the sterically hindered nature of the α-position of the epoxide, which causes SN2’ attack (135, dashed arrow) to be favored over the desired SN2 attack (135, solid arrow). This alternate reaction pathway was also noted in Wender’s studies. Nevertheless, with alcohol 136 readily available, the chlorination was accomplished (NCS/PPh₃) in acceptable yield to provide the key chloroketone (120). Alternate chlorination conditions were attempted (SOCl₂/base, PPh₃/CCl₄, PPh₃/ZnCl₂/DEAD, MsCl/Pyr., PPh₃/Cl₂, DMAP/CS(imid)₂, (COCl)₂, TCT, TMSCl/BiCl₃) but were unsuccessful at providing the desired product. However, retro-aldol product was observed on at least one occasion.
Despite the modest overall yield of this two-step sequence, it can be used to rapidly prepare multi-gram quantities of 120 and was therefore deemed an acceptable solution to this problem, especially given the difficulties is preparing 120 via other routes (*vide supra*). It is noteworthy that 120 was the only neopentyl alcohol that could be successfully chlorinated during the course of these studies. It is also interesting that varying amounts of the diastereomer (at C-13) are generated, although these chlorination conditions usually proceed with complete inversion of stereochemistry. Perhaps this alcohol is more accessible to electrophiles due to a slight bond lengthening effect (*i.e.*, retro-aldol ability), thus mitigating the neopentyl hindrance and allowing limited epimerization.
With 120 in hand, the stage was finally set to invoke the direct indole coupling reaction, which proceeded smoothly to provide the coupled product (60) in 62% yield as a single diastereomer (clear cubes, mp 169 – 170 °C, See Scheme 16 for X-ray crystallographic analysis). Several aspects of this particular coupling are noteworthy. First, it is remarkable that no chloride elimination is observed with 120 during the course of this coupling. Second, it was discovered that as the reaction concentration was
increased, the yield improved. Third, if there was any of the C-13 diastereomer of 120 present, it did not participate in the coupling reaction, but rather suffered elimination, presumably due to the axial disposition of the chlorine atom. Finally, this effective method for direct C–C bond formation enables all the necessary carbon atoms of these complex natural products to be secured in only three steps and was routinely carried out on multi-gram scale. Functional group manipulations are all that remained to complete the synthesis of 13.

Conditions (TfOH) previously applied to the conversion of 105 to 106, unfortunately provided significant quantities of several byproducts in the attempted conversion of 60 to 119, including 143, 144, and 145 (Scheme 17). (In fact, the reactivity of 60 and downstream intermediates differed significantly from that observed with the 12-epi-fischerindole U series.) In this particular cyclization reaction, two modes of activation are feasible at the gem-disubstituted olefin. This olefin can be protonated to give the tertiary carbocation, which is intercepted by the indole ring to give intermediate 139, leading to the desired product (119). Alternatively, protonation to give the primary carbocation, which is also intercepted by the indole ring, leads to intermediate 140. A [1,5]-sigmatropic shift generates 141, which can rearrange to carbocation 142. The three possible modes of elimination to quench this carbocation provide the three observed products (143, 144, and 145, clear cubes, mp 128 – 129 °C, See Scheme 17 for X-ray crystallographic analysis). In order to circumvent the formation of such undesired byproducts, a variety of Lewis and Brønsted acids were screened [TFA, HCl, MeOSO₂H, H₂SO₄, heat, TsOH, BF₃•Et₂O, AcOH, Tf₂NH, Dy(OTf)₃, PPTS, AlCl₃, FeCl₃, silicotungstic acid, PtCl₂, Zeolite NaY, RuCl₃/AgOTf, Cu(OTf)₂, Pd(OAc)₂,
Co(acac)$_2$/PhSiH$_3$, many of which did not catalyze the cyclization and none of which provided either any improvement in the yield or reduction in the quantity of byproducts. Attempted cyclizations of the amine or alcohol derivatives of 60 were equally unsuccessful. However, it was found that Montmorillonite K-10 acidic clay, with microwave irradiation, provided the desired product (119) without formation of the undesired products, although recycling of unreacted starting material was required. It was assumed, based on the reactivity observed for 106, that reductive amination of the ketone 119 would provide amine 138 directly. However, reductive amination under the previously employed conditions (See Scheme 13) provided amine 148 (Scheme 19) as a single diastereomer, which was epimeric at C-11 (as required for 138). Attempts to utilize microwave irradiation to promote this reaction led to dechlorination of the compound and was therefore not amenable for this series of natural products. This unexpected complete inversion in diastereoselectivity seems to be due solely to the presence of the C-13 chlorine atom. A more circuitous route was therefore required to access the desired amine (138), necessitating reduction to the alcohol, mesylation, azidation, and reduction (Scheme 16), similar to the sequence developed by Fukuyama for hapalindole G. Formylation$^{220}$ of the amine (138) followed by dehydration with Burgess reagent$^{221}$ provided ent-12-epi-fischerindole G (11) in good yield,$^{44}$ which was spectroscopically identical to the natural material with the exception of optical rotation. Thus, in principle, the naturally occurring enantiomer of 11 could be prepared from (S)-carvone oxide (vide infra). Until this point, for initial studies into the synthesis of these natural products, (R)-carvone oxide was used because of its significantly lower cost.
3.5 Total Synthesis of 12-epi-fischerindole I

With reasonable quantities of 11 available, the oxidation to form 12-epi-fischerindole I (22) could be investigated. Treatment of 11 with a variety of oxidants (i.e., DDQ, MnO2, p-chloranil, t-BuOCl) failed to produce any 22 (Scheme 18). Reasoning that the isonitrile could preferentially react with these oxidants, the formamide derivative (146) was subjected to an assortment of oxidants (same as for 11, in addition to
DMDO and DMP), but this also failed to form any of the desired product. Putative formation of stable 3-chloro- or 3-hydroxyindolenines was the only reactivity observed with either 11 or 146, which could not be utilized to install the desired olefin. Additionally, Leuckart reaction on cyclized ketone 119 failed to provide any of the vinyl formamide, which could have allowed access to 22. (From this point on, (S)-carvone oxide was utilized to prepare the correct enantiomer of the natural product.)

Turning to the amine diastereomer 148 (Scheme 19), which was ineffective for the preparation of 11, it was hoped that this intermediate would allow the desired oxidation to proceed through subtle stereoelectronic effects. The amine 148 was formylated in quantitative yield to give 149, which was then subjected to various oxidation conditions. It was assumed that the isonitrile might react disastrously with various oxidants, therefore the formamide was utilized in these trials. Remarkably, 22 was produced in 46% overall yield when formamide 149 was treated first with t-BuOCl and triethylamine and then with Burgess reagent. Although the intermediates in this reaction are unstable and difficult to purify, it is reasonable to assume that the reaction proceeds via the intermediates delineated in Scheme 19. Initial chlorination of the indole leads to the chloroindolenine 150, which undergoes elimination to generate methylene indolenine 157. This intermediate can tautomerize to 12-epi-fischerindole I formamide (147), which is extremely unstable and immediately dehydrates upon exposure to Burgess reagent to provide 22. Methylene indolenine 151 can alternatively be hydrated (presumably on silica gel) at the imine carbon. Reprotonation of the olefin from the β-face and attack by water at C-3, via the intermediacy of an azaorthoquinodimethane intermediate, would provide the major side product isolated (152, colorless cubes, mp 132 – 133 °C, See
Scheme 19 for X-ray crystallographic analysis). The presence of the epimerized C-10 center provides evidence for the existence of 152 en route to 22.

![Scheme 19: Original and improved total synthesis of 12-epi-fischerindole I (22). Reagents and conditions: (a) NH₄OAc (40 equiv.), NaCNBH₃ (7.5 equiv.), 3 Å molecular sieves, MeOH, THF, sonication, 18 h., 42%; (b) HCO₂H (2.0 equiv.), CDMT (2.2 equiv.), DMAP (0.1 equiv.), NMM (2.2 equiv.), DCM, 23 º C, 30 min., 100 %; (c) THF, TEA (1.0 equiv.), t-BuOCl (1.5 equiv.), 0 º C, 10 min.; then SiO₂/TEA (PTLC); then CDCl₃; then PhH, Burgess reagent (2.0 equiv.), 23 º C, 30 min., 46% overall; (d) TEA (17.5 equiv.), DCM, COCl₂ (2.0 equiv.), 0 º C, 10 min., 95%; (e) DDQ (2.5 equiv.), H₂O, THF, 0 º C, 30 min., 92%.]

Although this sequence provided the first synthetic sample of 22, it was plagued with numerous problems, specifically: low overall yields, difficult and unscalable synthetic procedures, the formation of byproducts, and the intermediacy of several unstable species. It was reasoned that the low overall efficiency of this route likely stemmed from two mitigating factors. First, t-BuOCl is not commonly employed as an oxidant for benzylic oxidations. Perhaps an oxidant more chemoselective for such
transformations would provide a higher yield of the desired product. Secondly, the penultimate intermediate (147, Figure 12) in this sequence is an extremely unstable compound due to a severe steric interaction between the formamide N–H and the C(4)–H of the indole ring, which leads to an approximate 25 kcal/mol calculated destabilization compared to its isomer 154 (as determined by AM1 calculations). Therefore, an alternate sequence was sought to accomplish this transformation that would bypass these difficulties. It was subsequently discovered that initial dehydration of the formamide 149 (Scheme 19) provided compound 153, which is epimeric at C-11 to 12-epi-fischerindole G (11), in 95% yield. Treatment of this compound with DDQ,223 in contrast to the identical reaction with 11, provided 12-epi-fischerindole I (22) in 92% yield, allowing access to large quantities of this natural product in short order.33 Based on this divergence in reactivity, it is proposed that 153 (not yet isolated as a natural product), rather than 11, is the actual biosynthetic precursor to 22.

![Figure 12. Calculated stability of the 12-epi-fischerindole I penultimate intermediate (147).](image)

3.6 Total Synthesis of Welwitindolinone A

With 12-epi-fischerindole I (22) in hand, it was finally possible to investigate the conversion of this natural product into welwitindolinone A (13). Although the proposed conversion of 22 to 13 might appear intuitive, practical difficulties were expected due to
the sensitivity of both alkaloids to acidic media and the sheer ring strain of the resulting product. Such concerns were intensified by the knowledge that oxidative ring contractions to generate five- and six-membered rings typically require elevated temperatures, and hence, forming a strained four-membered ring should be even more difficult. Before using valuable material to probe this transformation, a model system was sought on which to test this ring-contraction. To our delight, treatment of cyclized ketone 119 with t-BuOCl then dilute AcOH (1.7%) furnished two major products, the oxidized compound 155 and ring-contracted compound 156 in approximately 20% unoptimized yield each. Given the aforementioned considerations, it is remarkable that this reaction occurs at low temperature and within minutes. Although ketone 156 represents a potentially viable intermediate to complete the synthesis of 13, attention was returned to 22, in the hope that it could be directly converted into 13, thus lending credence to the proposed biosynthetic hypothesis (See section 1.3).
Extensive experimentation led to conditions by which 22 could be converted directly into 13. 12-epi-Fischerindole I (22) was exposed to t-BuOCl and triethylamine in THF at –30 ºC for one minute and the solvent was rapidly removed (Scheme 21). The crude residue was then dissolved in a THF:H₂O:TFA mixture (95:4:1) and warmed to 0 ºC. Strict adherence to this protocol resulted in the first total synthesis of 13 in 25% yield, along with minor amounts of its C-3 epimer (161, See Figure 13). This transformation most likely proceeds through initial chlorination of the indole to provide 157, followed by attack of water to give 158. Elimination of the chloride, to generate the azaorthoquinodimethane 159, followed by [1,5]-sigmatropic rearrangement, would then install the spirocyclobutane of 13. Although 13 was accessible via this procedure, there were several problems with this route, most notably the low yield and the exclusive formation of 161 upon scale-up. Seeking to circumvent these obstacles, it was determined that the chief difficulty arose from the isonitrile moiety, which has been shown to be unstable to electrophilic chlorinating reagents in this laboratory.33 It was reasoned that a hitherto-unknown fluorohydroxylation of indole rather than chlorohydroxylation should suppress isonitrile-derived byproduct formation, owing to the increased hardness of fluorine over chlorine. Therefore, a milder method to accomplish this transformation was developed in which 22 was treated with a solution of XeF₂ in wet acetonitrile to provide 13 in 44% yield, via the intermediacy of 160.33 This reaction was routinely performed on more than 50 mg of 22, and more than 580 mg of 13 have been prepared to date. A screen of various halogenating reagents confirmed that XeF₂ was the most efficient at promoting this reaction (Table 4). The chemoselectivity of this reagent
is also noteworthy, given the presence of an olefin, which is known to react with XeF$_2$, and the reactive isonitrile moiety.

**Scheme 21.** Original and improved total synthesis of welwitindolinone A (13). Reagents and conditions: (a) THF, TEA (1.0 equiv.), t-BuOCl (1.5 equiv.), −30 °C, 1 min.; then 95:4:1 THF:H$_2$O:TFA, −30 to 0 °C, 5 min., 25%; (b) XeF$_2$, H$_2$O, MeCN, 23 °C, 5 min., 44%.
3.7 Conclusions

In this chapter, the total syntheses of hapalindole Q (103), ent-12-epi-hapalindole D (117), ent-12-epi-fischerindole U (104), ent-12-epi-fischerindole G (11), 12-epi-fischerindole I (22), and welwitindolinone A (13) are detailed, utilizing the direct indole coupling reaction (Chapter 2) as a key step. The total synthesis of 13 was the first one reported and proceeds in only nine steps and is characterized by a convergent and rapid assembly of the core, a hitherto unknown fluorohydroxylative ring contraction to install
the spirocyclobutane, and the absence of protecting groups. Furthermore, evidence is garnered that supports the alternate biosynthetic hypothesis put forth in Section 1.3.

The studies performed in this chapter were accomplished with the assistance of several talented coworkers. Dr. Tomás Llamas was responsible for optimizing the oxindole/carvone coupling reaction (Table 3). Mr. Brandon W. Whitefield was responsible for screening the cyclization of 60 to 119 using PtCl$_2$, RuCl$_3$/AgOTf, and Cu(OTf)$_2$ in addition to general scale-up assistance. Mr. Antti Phjakallio was responsible for the investigations towards 120 via 131, 132, and 133. Finally, Mr. Yoshihiro Ishihara was responsible for the purification and characterization of 143, 144, and 145 as well as general manuscript preparation assistance.
Chapter 4:

Progress Towards the Total Synthesis of Welwitindolinone B
In the previous chapter, the original and improved total synthesis of welwitindolinone A (13) was described, which provided access to large quantities of the natural product. As proposed in the isolation literature, it was still reasonable that welwitindolinone A (13) should directly provide welwitindolinone B (15) upon oxidative ring expansion (Section 1.3, Scheme 2). Therefore, the stage was finally set to probe the proposed transformation of 13 into 15. However, with initially limited quantities of 13 (before the revised synthesis detailed in Section 3.6) and facing an unprecedented transformation, a model system was sought on which to test the proposed oxidation. As such, the known compound 163 (Scheme 22), containing a trisubstituted vinyl isonitrile and a chromophore, was an acceptable system on which to test various oxidation conditions. However, it was still uncertain whether this substrate would closely model the natural product, as it lacked a tetrasubstituted olefin and the strain-inducing spirocyclobutane. Nevertheless, 163 was utilized in a search for conditions that could effectively promote the desired oxidation.

Ideally, conditions were preferred which could directly oxidize 163, without requiring hydrolysis to the vinyl formamide (or other such means to activate the olefin). Furthermore, it was unknown whether electrophilic or nucleophilic oxidants would be more applicable to the substrate in question. Mechanistically, either reaction pathway could be envisioned, either through the intermediacy of a carbocation at the β-position for
electrophilic oxidants, or an inductively stabilized carbanion at the $\alpha$-position for nucleophilic oxidants. As such, 163 was treated with a variety of electrophilic and nucleophilic oxidants (DMDO, $m$CPBA, in situ TFDO, Urea $\cdot$ H$_2$O$_2$/DBU, t-BuOOH/DBU, t-BuOOH/V$_2$O$_5$, t-BuOOH/SiO$_2$, MMPP, Urea $\cdot$ H$_2$O$_2$/TFAA, CH$_3$CO$_3$H/NaOAc, t-BuOOH/KF $\cdot$ Alumina, KMnO$_4$/CuSO$_4$, NBS, I$_2$/Ag$_2$O, NaBO$_3$/Ac$_2$O, NCS, Chloramine T/H$_2$SO$_4$, TCI, t-BuOOH/TiCl$_4$, Oxone, PMA/CPC/H$_2$O$_2$, PWA/CPC/H$_2$O$_2$, NaOCl, O$_2$/sensitizer/hv, Pb(OAc)$_4$, HClO, H$_2$O$_2$/NaHCO$_3$, DMP, CTAP, Peroxycarbonic acid, PyrBr$_2$HBr, RuCl$_3$/NaIO$_4$/CeCl$_3$, and Amberlyst A-26 Br$_3$). Unfortunately, none of the conditions listed above provided any detectable oxidation product, other than putative isonitrile oxidation. To investigate the reactivity of activated olefins, compound 162 was evaluated in response to several oxidizing conditions (PhNO/TsOH, KOtBu/Davis Oxaziridine, PhNO/ZrCl$_4$, t-BuOOH/VO(acac)$_2$, N$_2$O$_4$/NaOAc, CuNO$_2$/TEA). Through these experiments, it was discovered that the formamide derivative was unstable, not providing any of the desired oxidation product. Given the unreactive nature of 163 and instability of 162, it was reasoned, or at least hoped, that this model system was not an accurate representative of 13 and that several of these conditions might actually be amenable to the direct oxidation of welwitindolinone A (13). However, before efforts were directed towards such investigations, 163 was utilized to probe the conversion of an isonitrile into the corresponding isothiocyanate [welwitindolinone B (15, Section 1.3, Scheme 2) contains an isothiocyanate]. Several conditions are known for such conversions, and it was found that treatment of 163 with elemental sulfur and selenium led to the isothiocyanate 164 in short order.
Since the model compound 163 was of little utility for investigating the conversion of 13 into 15, attention was turned to 13 in the hopes that the natural system might be more susceptible to direct oxidation (Scheme 23). Treatment of 13 (or the diastereomer 161) with a variety of oxidizing or rearranging conditions (H₂O₂/Na₂WO₄,²⁵⁹,²⁶⁰ Urea•H₂O₂/TFAA,²³² (BzO)₂, KOtBu/O₂, O₂/sensitizer/hv, copper(II)/DIPEA/O₂,²⁶¹ time, H₂O₂/LiOH,²⁶² PdCl₂/HCl,²⁶³ Na₂PdCl₄/AcOH,²⁶⁴ XeF₂, RuCl₃/CeCl₃/NaIO₄,²⁵² OsO₄, DMDO, Ni(PPh₃)₂Cl₂, Rh(PPh₃)₃Cl, AgOTf, AuCl₃, Fe(TPP)Cl, Pd(OAc)₂, Cu(acac)₂, Cu(OAc)₂/H₂O₂, Urea•H₂O₂/DBU,²²⁷ O₂/heat, t-BuOCℓ/TEA, Oxone/NaHCO₃/Na₂SO₃,²⁶⁵ AIBN/(BzO)₂, AgNO₃/(NH₄)₂S₂O₃,²⁶⁶ TMSI,²⁶⁷ [Rh(Nor)Cl]₂,²⁶⁸ and Fe(TPP)Cl/PhIO²⁶⁹) failed to provide any of the desired oxidized or ring-expanded product. However, some reactions are noteworthy, not for their ability to procure 15, but for the formation of unexpected byproducts. When 13 was treated with TFDO,²⁷⁰ the isonitrile was quantitatively oxidized to the isocyanate 165, which was unstable upon storage at ambient temperature and atmosphere, slowly decomposing to the urea dimer 168. Mechanistically, this transformation likely proceeds via attack of the isocyanate by water, forming the carbamic acid, which further decomposes to the enamine. Before this enamine can be hydrolyzed to the ketone, it attacks another equivalent of isocyanate, leading to 168. Partial hydrolysis of the isonitrile with formic acid resulted in the surprisingly stable vinyl formamide 169 (tentative assignment). Treatment of this compound with a variety of electrophilic oxidants (DMDO, O₂/sensitizers/hv, base/O⁺, t-BuOCl/TEA, t-BuOOH/VO(acac)₂, XeF₂) failed to provide any oxidized compounds. Heating of either 13 or 165 in the microwave at 250 ºC furnished the rearranged products 166 and 167 respectively (tentative
assignments). Mechanistically, fragmentation of the cyclobutane ring to regenerate the isopropylidene, followed by nucleophilic attack of the oxindole enolate onto the isonitrile or isocyanate would account for the observed products.

![Scheme 23. Attempted oxidation of welwitindolinone A (13) to welwitindolinone B (15).](image)

Scheme 23. Attempted oxidation of welwitindolinone A (13) to welwitindolinone B (15).

Concurrent with these studies, preparation of the isothiocyanate analogues of 12-epi-fischerindole I (22, Section 3.5) and welwitindolinone A (13, Section 3.6) was investigated (Scheme 25), since 15 contains this moiety and late stage sulfuration attempts on 13 were met with failure. Treatment of amine 148 with CS(imid)₂ provides isothiocyanate 170, which can be oxidized to the 12-epi-fischerindole I analogue 171 (colorless cubes, mp 202 °C decomposition, See Scheme 25 for X-ray crystallographic...
analysis) in 76% yield. Treatment of 171 with XeF2 provides the isothiocyanate analogue of welwitindolinone A (172) in an unoptimized 27% yield.

Reagents and conditions: (a) DCM, CS(imid)$_2$ (3.3 equiv.), 23 ºC, 24 h., 60%; (b) THF, H$_2$O, DDQ (2.5 equiv.), 0 ºC, 30 min., 68%; (c) DCM, XeF$_2$ (1.0 equiv.), 23 ºC, 15 min., 27%.

The inability to directly oxidize 13, or derivatives thereof, prompted a reevaluation of the strategy to access welwitindolinone B (15). Specifically, it was reasoned that if appropriate functional handles were installed earlier in the sequence, the desired oxidation might be more easily accomplished (Scheme 26). As a replacement for the isonitrile, installation of an ester (or ester equivalent) should allow for facile basic epoxidation of the C(10)–C(11) olefin at an appropriate stage of the synthesis. After successful ring-expansion, a Curtius rearrangement should provide the requisite amine to complete the synthesis of 15. Pursuant this strategy, an efficient method to install an ester at C-11 would be through a palladium-catalyzed carbonylation of an appropriate vinyl triflate (i.e., 177, 178, or 186); however, attempts to directly install either one or
two triflates on 119 were fruitless (Scheme 26). Reasoning that blocking the nitrogen from reaction would allow access to the desired triflate, methylations at N-1 (119) were investigated [the natural product N-methylwelwitindolinone B (189, Figure 14) contains an N-methyl moiety]. Surprisingly, this transformation proved problematic and only provided the dimethylated compound (190, Figure 15), in poor yields and with no detectable monomethylation. Therefore, 119 was protected as the Boc carbamate (179), which also proved recalcitrant to triflation. In order to probe the use of a Shapiro reaction to install the α,β-unsaturated ester, access to the hydrazone (175, 176, 180, or 181) was sought, which similarly met with failure. Formation of the cyanohydrin 173 proceeded in acceptable yield; however, the alcohol thus formed was unstable and could not be eliminated. Similar attempts to form the cyanohydrin or azidohydrin on Boc-compound 179 were unsuccessful. Addition of a trichloromethyl anion, which could then be hydrolyzed to the acid, to 179 failed to provide any desired product (182). Furthermore, nucleophilic additions and Wittig-type couplings using a variety of acyl anion equivalents or phosphines (respectively) failed to provide any of the addition or homologation products.
Scheme 26. Failed attempts to access potential welwitindolinone B precursors. Reagents and conditions: (a) NaCN (4.6 equiv.), AcOH (2.6 equiv.), MeOH, H₂O, 23 ºC, 3.5 h., ca 70% (ca 1.5:1); (b) (Boc)₂O (1.0 equiv.), DMAP (0.1 equiv.), DCM, MeCN, 23 ºC, 20 min., 83%; (c) THF, TEA (1.0 equiv.), t-BuOCl (1.7 equiv.), 0 ºC, 10 min.; then 40:20:1 MeOH:H₂O:AcOH, 5 min.
Since the installation of an isonitrile replacement was not feasible under the conditions evaluated, presumably due to the sterically demanding environment surrounding the C-11 ketone, it was reasoned that perhaps installation of an oxygen atom directly at C-10 (i.e., 183) could provide an intermediate from which 15 could be accessed. Should the alcohol successfully traverse the cyclobutane forming ring-contraction unscathed, ring expansion should provide the welwitindolinone B skeleton with an alcohol in place of the isonitrile (191, Figure 16). Such bridgehead alcohols have been successfully converted directly to the isonitrile\textsuperscript{271} or the amine\textsuperscript{272} providing encouraging precedent for the total synthesis of 15 utilizing this route. Unfortunately, all such attempts either returned unreacted starting material or the corresponding enone (Scheme 26). Therefore, strategies were investigated that utilized the ring-contracted product 156 (See Scheme 20, Section 3.6). The vinyl cyanide (188) was not accessible
and other homologation attempts were unsuccessful. Furthermore, attempts to directly oxidize this intermediate to form 187 were similarly met with failure.

![Figure 16. Welwitindolinone B skeleton (191).](image)

Despite the many studies detailed in this chapter, all options for the preparation of welwitindolinone B (15) via the proposed biosynthetic hypothesis have not yet been exhausted. Efforts towards this end are still ongoing in the laboratory by Mr. Yoshihiro Ishihara and Dr. Takeshi Masuda. Current investigations are focused on activating the olefin for oxidation, either by modification of the isonitrile directly or through metal-chelated activation.
Chapter 5:

Conclusions
Due to their stunning molecular architectures and potent bioactivities, the hapalindoles, fischerindoles, and welwitindolinones were targeted for synthesis, with the goals of inventing useful chemistry, discovering basic reactivity, understanding their biosynthesis, and allowing access to large quantities of these rare marine natural products. It is instructive to evaluate these syntheses from the vantage points of chemoselectivity, stereocontrol, and “redox economy”.

Numerous steps throughout these syntheses exhibit high levels of chemoselectivity, despite the presence of other reactive functionality. For example, the conversion of 120 to 60 (Section 3.4, Scheme 16) proceeds in good yield, in the presence of a chlorine atom that could potentially be eliminated under the reaction conditions. The vast majority of conditions screened for the cyclization of 60 to 119 (Section 3.4, Scheme 16) formed numerous byproducts (including 143, 144, and 145, Section 3.4, Scheme 17); however the use of Montmorillonite K-10 acidic clay completely avoided such chemical entities. The conversion of 153 into 22 (Section 3.5, Scheme 19) proceeds in excellent yield, despite the ease with which isonitriles can be oxidized and the conversion of 22 to 13 (Section 3.6, Scheme 21) proceeds in good yield, even though isonitriles have been observed to react with halogenating reagents. Functional group manipulations were minimized and the percentage of C–C bond-forming reactions was maximized. It is difficult to imagine how any steps could be “removed” from these syntheses, since all are necessary for the installation of requisite C–C bonds, functional groups, or key stereocenters. Furthermore, no protecting groups are utilized throughout the course of these syntheses, despite numerous opportunities in which they could potentially have been employed to circumvent undesirable reactivity. In fact, rather than resorting to
protecting group chemistry, the innate reactivities of the functional groups were employed, which led to the invention of new chemistry (direct indole coupling, extremely mild fluorohydroxylative ring-contraction using XeF₂, installation of the key quaternary stereocenter and neopentyl chlorine atom) or discovery of intriguing reactivity [125 to 126 (Section 3.4, Scheme 15), 60 to 143, 144, and 145 (Section 3.4, Scheme 17), 149 to 22 and 152 (Section 3.5, Scheme 19), 153 to 22 (Section 3.5, Scheme 19), 119 to 156 (Section 3.6, Scheme 20), and 22 to 13 (Section 3.6, Scheme 21)].

High levels of stereochemical induction are observed throughout the synthesis. For example, the direct indole coupling reaction (28 and 60, Section 2.3, Table 2) provides a single diastereomer of coupled product and the vicinal difunctionalization of 28 to provide 105 (Section 3.2, Scheme 13) only gives a single diastereomer. The reductive aminations proceed in moderate (105 to 103, Section 3.2, Scheme 13, which could be increased with the use of microwave irradiation) to complete diastereoselectivities (106 to 104, Section 3.2, Scheme 13, and 119 to 148, Section 3.5, Scheme 19). Furthermore, by utilizing XeF₂, complete diastereomeric induction is observed in the conversion of 22 to 13 (Section 3.6, Scheme 21), even though facial bias for this transformation is minimal.

Furthermore, the syntheses are characterized by an adherence to the concept of “redox economy”. Analogous to “atom economy”²⁷³ or “step economy”,²⁷⁴ “redox economy” minimizes the superfluous redox manipulations within a synthesis; rather, the oxidation state of intermediates linearly and steadily increases throughout the course of the synthesis. Only one reduction step (reductive amination) is utilized during these syntheses, which is strategically placed to install a key stereocenter. In fact, the flexible
adherence of these syntheses to the proposed biogenesis of these alkaloids reinforces the minimization of redox reactions, as is commonly observed in Nature’s biosynthesis of terpenes and alkaloids. Such considerations allowed the efficient, practical, and concise syntheses of numerous members of this natural product family, including hapalindole Q (103), ent-12-epi-hapalindole D (117), ent-12-epi-fischerindole U (104), ent-12-epi-fischerindole G (11), 12-epi-fischerindole I (22), and welwitindolinone A (13). Overall, this total synthesis program is characterized by inventive retrosynthetic disconnections, which rapidly assemble the skeletal structure and allow for rapid increase in complexity.

Finally, these studies are yet another example of how natural products can lead to new discoveries in chemical reactivity. This research program was initiated with the structures of the hapalindole family in mind and with a conscious effort to eliminate prefunctionalization steps that are often found in cross-coupling chemistry (Figure 2). Inspired by Barton’s landmark total synthesis of usnic acid (Scheme 4), a method was devised for the direct oxidative coupling of indoles and pyrroles to a range of carbonyl compounds. Viewed within the proper historical context, this method represents an important advance in the field of oxidative enolate coupling. Specifically, it has been shown that the heterocoupling of two different anionic species is a synthetically pragmatic process. Indeed, work from this laboratory has shown that this reaction paradigm is not limited to cross coupling between heteroaromatic systems and carbonyl compounds, as two different carbonyl compounds can also be coupled in an intramolecular setting. Exploiting the innate reactivity of the coupling partners has led, in part, to such selectivity (substrate control), and practicality (easily scaleable). Methods that rapidly generate meaningful complexity with exquisite chemoselectivity will not
only benefit the science of synthesis as a whole but also find further applications in biology and medicine.
Experimental
General Procedures. All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry THF, TEA, DCM, MeOH, DMF, Et₂O, DME, and PhH were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Copper(II)2-ethylhexanoate was dried and stored under high vacuum prior to use. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and p-anisaldehyde in ethanol/aqueous H₂SO₄/CH₃CO₂H and heat or Seebach’s stain and heat as developing agents. NMR spectra were recorded on a Bruker DRX 600, DRX 500, AMX 400, or AV 400 spectrometer and were calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on a Perkin-Elmer Spetrum BX spectrometer. HRMS were recorded on an Agilent Mass spectrometer using ESI-TOF. LRMS were recorded on an Agilent LCMS. Photochemical reactions were conducted using a 450-watt Hanovia lamp with a quartz filter. Melting points are uncorrected and were recorded on a Fisher-Johns 12-144 melting point apparatus. Optical rotations were obtained on a Perkin-Elmer 431 Polarimeter. Azeotroping refers to dissolving the compound to be dried in benzene and removing the solvent by rotary evaporation.
**General Procedure for the Direct Indole Coupling:**

To a solution of carbonyl compound (1.0 equiv.) and indole (2.0 equiv.) in THF (1.0 M) at –78 °C in a flame-dried flask under a nitrogen atmosphere was added a 1.0 M solution of LHMDS (3.3 equiv.). After stirring for 30 minutes at –78 °C, the septum was removed, solid copper(II)2-ethylhexanoate (1.5 equiv.) was rapidly added in one portion, and the septum quickly replaced. It was found that opening the reaction flask to the ambient atmosphere for the time required for addition was not detrimental to the reaction yield. The flask was then removed from the cooling bath and allowed to warm to ambient temperature. Once the flask reached ambient temperature, the reaction was partitioned between 1 N HCl and EtOAc. The organic layer was further washed with 1 N NaOH, water, then brine and dried (MgSO₄). The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (silica gel). Using this procedure, it was found that the reaction was efficient and practical, even on large scale (multi-gram quantities), with no diminution in yield.

**General Procedure for the Direct Pyrrole Coupling:**

Carbonyl compound (1.0 equiv.) was dissolved in benzene (1.0 mL) and the solvent removed *in vacuo*. Pyrrole (3.0 equiv.) was then added and the starting materials were dissolved in THF (0.125 M). The solution was cooled to –78 °C and a solution of LHMDS (0.50 M, 4.0 equiv.) was added. The reaction was allowed to stir for 30 minutes, after which time the septum was removed and copper(II)2-ethylhexanoate (1.5 equiv.) was rapidly added as a solid and then the septum was replaced. The reaction was allowed to warm to –60 °C and stirred for 3 hours. The reaction was subsequently
warmed slowly to ambient temperature and partitioned between 5% NH₄OH and EtOAc. The organic layer was separated and washed successively with water then brine, dried (MgSO₄), filtered, and the solvent removed in vacuo. Flash chromatography (silica gel) of the crude reaction afforded pure coupled product. In general, the pyrroles began to darken in color immediately after concentration, but NMR analysis showed no loss in purity.

**General Procedure for the Preparation of Iron(III)acetylacetonate-Type Oxidants.**

Iron(III)chloride hexahydrate (1 equiv.) was dissolved in water at room temperature. To this solution was added a solution of the acetylacetonate ligand (3.1 equiv.) in MeOH (0.4 M) drop-wise via an addition funnel over the course of 15 minutes. After the addition was complete, a solution of sodium acetate (5.1 equiv.) in water (4.0 M) was added drop-wise via the addition funnel over the course of 5 minutes. After completing the addition, the reaction was immediately heated to 80 ºC for 15 minutes, then cooled slowly to 0 ºC and allowed to stand overnight (to ensure complete precipitation of the oxidant). The oxidant was then collected by suction filtration, rinsing with water. Azeotropic removal of water and evaporation in vacuo provided dry oxidant for use in the oxidative coupling reactions.

**Preparation of Ferrocenium Hexafluorophosphate:**

Ferrocene (5.58 g, 30.0 mmol, 1.0 equiv.) was dissolved in sulfuric acid (10 mL, 3.0 M) and stirred for 45 minutes at room temperature. The reaction was then poured into a mixture of tert-butanol (6.4 mL, 4.7 M) and water (170 mL, 0.18 M) and stirred for 15
minutes at room temperature. The reaction was then filtered and the filtrate was cooled to 0 ºC. Once at this temperature, a 0 ºC solution of potassium hexafluorophosphate (11.0 g, 59.8 mmol, 2.0 equiv.) in water (235 mL, 0.26 M with respect to KPF₆) was slowly added. Stirring was continued for 1 hour, after which the reaction was filtered to collect the solid precipitate. The solid was further washed with cold water (40 mL), ethanol (50 mL), then Et₂O (until solvent rinses through clear). Azeotropic removal of water and evaporation in vacuo provided dry oxidant for use in the oxidative coupling reactions.

**General Procedure for the Oxindole Coupling:**

Oxindole (0.1 mmol, 1.0 equiv.) and carbonyl compound (0.1 mmol, 1.0 equiv.) were azeotroped twice with benzene. The starting materials were then dissolved in THF (340 mL, 0.3 M), and the solution cooled to –78 ºC. A solution of LDA (0.5 M in THF, 428 mL, 2.1 equiv.) was added drop-wise by syringe over the course of 30 seconds. The reaction was allowed to stir for 30 minutes at –78 ºC, and was then warmed to ambient temperature. After 5 minutes, a solution of oxidant (0.5 M in THF, 2.0 equiv.) was added in one portion. The reaction was stirred at ambient temperature for 20 minutes then quenched by the addition of 1 N HCl (1.0 mL). The aqueous layer was extracted with EtOAc (3 x 2.0 mL). The combined organic layers were washed with brine (5.0 mL), dried (MgSO₄), and the solvent removed in vacuo. Flash column chromatography (silica gel) of the crude reaction afforded pure coupled product.
**Compound 28:**

![Chemical Structure](image)

**Yield:** 0.02 – 10 g, 49-53%

**Physical State:** colorless cubes  
**mp:** 129 – 130 °C  
(4:1:0.1 cyclohexane:Et₂O:benzene)

**Rf:** 0.25 (silica gel, 3:1 hexane:EtOAc)

**|α|D:** + 55 (DCM, c 3.6)

**IR (film) νₘₐₓ:** 3338, 2919, 1655, 1458, 1365, 1248, 1098, 907 cm⁻¹

**¹H NMR (500 MHz, CDCl₃):**  
δ 8.15 (s, 1 H, D₂O exchangeable), 7.44 (d, J = 7.5 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 7.07 (t, J = 7.5 Hz, 1 H), 6.82 (s, 1 H), 6.71 (d, J = 2.0 Hz, 1 H), 4.67 (s, 1 H), 4.63 (s, 1 H), 3.91 (d, J =10.5 Hz, 1 H), 3.25-3.30 (m, 1 H), 2.44 – 2.60 (m, 2 H), 1.90 (s, 3 H), 1.62 (s, 3 H)

**¹³C NMR (125 MHz, CDCl₃):**  
δ 199.7, 146.1, 143.9, 136.5, 135.6, 127.2, 123.0, 121.8, 119.4, 119.3, 113.0, 112.7, 111.6, 49.3, 48.5, 31.1, 19.6, 16.5

**HRMS (MALDI):**  
calcd. for C₁₈H₂₀NO [M + H⁺] 266.1545, found 266.1532

See pages 229 – 230 for spectra.

Structure verified by X-ray crystallography.
Compound 40:

**Yield:** 23.8 mg, 49%

**Physical State:** yellow oil

**Rf:** 0.28 (silica gel, 2:1 hexane:EtOAc)

**[α]_D:** −48.8 (DCM, c 1.84)

**IR (film) ν<sub>max</sub>:** 3342, 2918, 1662, 1628, 1457, 1160, 1026 cm<sup>−1</sup>

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ 7.98 (bs, 1 H, D<sub>2</sub>O Exchangeable), 7.28 (d, J = 8.4 Hz, 1 H), 6.79 (s, 1 H), 6.69 – 6.73 (m, 3 H), 4.65 (s, 1 H), 4.63 (s, 1 H), 3.84 (d, J = 10.7 Hz, 1 H), 3.79 (s, 3 H), 3.21 – 3.25 (m, 1 H), 2.52 – 2.57 (m, 1 H), 2.43 – 2.46 (m, 1 H), 1.86 (s, 3 H), 1.61 (s, 3 H)

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 200.4, 157.1, 146.8, 144.5, 137.9, 136.3, 122.4, 122.3, 120.6, 113.6, 113.5, 110.2, 95.7, 56.4, 50.1, 49.2, 31.8, 20.2, 17.2

**HRMS (ESI):** calcld. for C<sub>19</sub>H<sub>22</sub>NO<sub>2</sub> [M + H<sup>+</sup>] 296.1645, found 296.1635

See pages 231 – 232 for spectra.
Compound 41:

Yield: 26 mg, 57%

Physical State: yellow oil

Rf: 0.24 (silica gel, 3:1 hexane:EtOAc)

[\alpha]D: –49.3 (DCM, c 1.88)

IR (film) \( \nu_{\text{max}} \): 3342, 2917, 1663, 1457, 1371, 1097 cm\(^{-1}\)

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.94 (bs, 1 H, D\(_2\)O Exchangeable), 7.31 (d, \( J = 8.1 \) Hz, 1 H), 7.06 (s, 1 H), 6.89 (d, \( J = 8.1 \) Hz, 1 H), 6.78 (s, 1 H), 6.74 (d, \( J = 2.2 \) Hz, 1 H), 4.66 (s, 1 H), 4.64 (s, 1 H), 3.87 (d, \( J = 10.6 \) Hz, 1 H), 3.24 (td, \( J = 9.4, 5.0 \) Hz, 1 H), 2.52 – 2.57 (m, 1 H), 2.42 – 2.47 (m, 1 H), 2.42 (s, 3 H), 1.87 (s, 3 H), 1.62 (s, 3 H)

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 200.3, 146.9, 144.4, 137.6, 136.3, 132.3, 125.8, 122.8, 121.9, 119.7, 113.6, 113.5, 112.2, 50.0, 49.2, 31.7, 22.5, 20.3, 17.2

HRMS (ESI): calcd. for C\(_{19}\)H\(_{22}\)NO [M + H\(^+\)] 280.1696, found 280.1691

See pages 233 – 234 for spectra.
Compound 42:

Yield: 15 mg, 32%

Physical State: white solid  mp: 151 – 152 °C (DCM)

Rf: 0.22 (silica gel, 3:1 hexane:EtOAc)

[α]D: −44.1 (DCM, c 0.870)

IR (film) νmax: 3327, 2920, 1661, 1457, 1344, 1242, 1138, 1093, 954 cm⁻¹

H NMR (600 MHz, CDCl3): δ 8.08 (bs, 1 H, D2O Exchangeable), 7.31 (dd, J = 8.7, 5.3 Hz, 1 H), 6.94 (dd, J = 9.7, 2.2 Hz, 1 H), 6.80 – 6.83 (m, 3 H), 4.64 (s, 1 H), 4.61 (s, 1 H), 3.84 (d, J = 11.5 Hz, 1 H), 3.23 (td, J = 10.0, 4.9 Hz, 1 H), 2.55 – 2.60 (m, 1 H), 2.43 – 2.47 (m, 1 H), 1.86 (s, 3 H), 1.59 (s, 3 H)

C NMR (150 MHz, CDCl3): δ 200.1, 161.5, 159.9, 146.6, 144.6, 137.1 (J = 49.7 Hz), 136.3, 124.5, 123.9 (J = 13.6 Hz), 120.8 (J = 40.6 Hz), 113.8 (J = 48.1 Hz), 109.0 (J = 97.7 Hz), 98.5 (103.2 Hz), 50.0, 49.4, 32.0, 20.0, 17.1

HRMS (ESI): calcd. for C18H19FNO [M + H⁺] 284.1445, found 284.1443

See pages 235 – 236 for spectra.
Compound 43:

Yield: 26.4 mg, 23%

Physical State: pink solid  mp: 182 – 183 °C (DCM)

Rf: 0.21 (silica gel, 3:1 hexane:EtOAc)

$[\alpha]_D$: −56.8 (DCM, c 1.62)

IR (film) $\nu_{\text{max}}$: 3327, 1653, 1457, 1368, 1049 cm$^{-1}$

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.27 (bs, 1 H, D$_2$O Exchangeable), 7.33 (s, 1 H), 7.27 (d, $J = 7.7$ Hz, 1 H), 7.13 (d, $J = 8.5$ Hz, 1 H), 6.84 (s, 1 H), 6.61 (s, 1 H), 4.61 (s, 1 H), 4.58 (s, 1 H), 3.81 (d, $J = 11.8$ Hz, 1 H), 3.22 (td, $J = 11.0$, 4.6 Hz, 1 H), 2.56 – 2.61 (m, 1 H), 2.43 – 2.46 (m, 1 H), 1.87 (s, 3 H), 1.59 (s, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 200.5, 146.5, 145.0, 138.0, 136.2, 126.8, 124.6, 123.3, 121.2, 116.0, 115.2, 114.0, 113.4, 50.0, 49.5, 32.3, 19.8, 17.2

HRMS (ESI): calcd. for C$_{18}$H$_{19}$BrNO [M + H$^+$] 344.0644, found 344.0638

See pages 237 – 238 for spectra.
Compound 44:

\[
\begin{array}{c}
\text{Me} \\
\text{H} \\
\text{Cl} \\
\text{H} \\
\text{H} \\
\text{Me} \\
\text{Me} \\
\end{array}
\]

Yield: 24.5 mg, 25%

Physical State: white solid  
mp: 167 – 168 ºC (DCM)

Rf: 0.24 (silica gel, 3:1 hexane:EtOAc)

\[\alpha\]D: −63.0 (DCM, c 3.71)

IR (film) \(\nu_{\text{max}}\): 3327, 1660, 1452, 1368, 1060, 906 cm\(^{-1}\)

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 8.37 (bs, 1 H, D\(_2\)O Exchangeable), 7.28 (d, \(J = 8.5\) Hz, 1 H), 7.11 (d, \(J = 1.0\) Hz, 1 H), 6.99 (d, \(J = 8.5\) Hz, 1 H), 6.85 (s, 1 H), 6.49 (d, \(J = 2.2\) Hz, 1 H), 4.61 (s, 1 H), 4.57 (s, 1 H), 3.81 (d, \(J = 11.9\) Hz, 1 H), 3.22 (td, \(J = 10.7, 4.6\) Hz, 1 H), 2.56 – 2.61 (m, 1 H), 2.42 – 2.47 (m, 1 H), 1.89 (s, 3 H), 1.55 (s, 3 H)

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 200.8, 146.5, 145.3, 137.6, 136.2, 128.2, 126.4, 124.9, 120.7, 120.6, 114.0, 113.0, 112.3, 50.1, 49.5, 32.3, 19.7, 17.2

HRMS (ESI): calcd. for C\(_{18}\)H\(_{19}\)ClNO [M + H\(^+\)] 300.1150, found 300.1156

See pages 239 – 240 for spectra.
Compound 45:

Yield: 28.3 mg, 46%

Physical State: yellow solid  mp: 128 – 129 °C (DCM)

Rf: 0.28 (silica gel, 2:1 hexane:EtOAc)

[α]D: −45.9 (DCM, c 1.93)

IR (film) νmax: 3338, 2917, 1663, 1482, 1452, 1375, 1189, 1025, 907 cm⁻¹

¹H NMR (600 MHz, CDCl₃): δ 7.99 (bs, 1 H, D₂O Exchangeable), 7.45 (d, J = 7.4 Hz, 2 H), 7.37 (t, J = 7.4 Hz, 2 H), 7.30 (t, J = 7.4 Hz, 1 H), 7.16 (d, J = 8.8 Hz, 1 H), 6.95 (d, J = 2.2 Hz, 1 H), 6.88 (dd, J = 8.8, 2.3 Hz, 1 H), 6.79 (d, J = 2.3 Hz, 1 H), 2.07 (s, 2 H), 4.62 (s, 1 H), 3.83 (d, J = 10.7 Hz, 1 H), 3.18 (td, J = 9.5, 1.6 Hz, 1 H), 2.52 – 2.57 (m, 1 H), 2.43 – 2.46 (m, 1 H), 1.87 (s, 3 H), 1.59 (s, 3 H)

¹³C NMR (150 MHz, CDCl₃): δ 200.2, 153.8, 146.8, 144.5, 138.7, 136.3, 132.6, 129.3 (2 C), 128.6 (2 C), 128.5, 128.3, 124.4, 113.7, 113.4, 113.3, 112.8, 104.1, 71.9, 50.0, 49.1, 31.8, 20.2, 17.2

HRMS (ESI): calcd. for C₂₅H₂₆NO₂ [M + H⁺] 372.1958, found 372.1951

See pages 241 – 242 for spectra.
Compound 46:

![Chemical Structure Image]

**Yield:** 48.2 mg, 52%

**Physical State:** yellow solid  
**mp:** 138 – 140 °C (DCM)

**Rf:** 0.29 (silica gel, 3:1 hexane:EtOAc)

**[α]D:** −63.7 (DCM, c 3.64)

**IR (film) ν_{max}:** 3347, 2918, 1663, 1430, 1364, 1097, 909 cm⁻¹

**¹H NMR (600 MHz, CDCl₃):** δ 8.05 (bs, 1 H, D₂O Exchangeable), 7.21 (s, 1 H), 7.13 (d, J = 8.2 Hz, 1 H), 6.96 (d, J = 8.2 Hz, 1 H), 6.80 (s, 1 H), 6.66 (d, J = 2.1 Hz, 1 H), 4.67 (s, 1 H), 4.64 (s, 1 H), 3.88 (d, J = 10.6 Hz, 1 H), 3.25 (td, J = 9.7, 5.0 Hz, 1 H), 2.53 – 2.58 (m, 1 H), 2.42 – 2.48 (m, 1 H), 2.42 (s, 3 H), 1.89 (s, 3 H), 1.62 (s, 3 H)

**¹³C NMR (150 MHz, CDCl₃):** δ 200.6, 146.9, 144.6, 136.3, 135.5, 129.1, 128.2, 124.2, 123.7, 119.6, 113.6, 112.8, 111.9, 49.9, 49.1, 31.7, 22.5, 20.3, 17.2

**HRMS (ESI):** calcd. for C₁₉H₂₂NO [M + H⁺] 280.1696, found 280.1693

See pages 243 – 244 for spectra.
Compound 47:

![Molecule Diagram]

**Yield:** 19.6 mg, 42%

**Physical State:** white foam

**Rf:** 0.16 (silica gel, 3:1 hexane:EtOAc)

**\([\alpha]_D\):** $-44.7$ (DCM, c 1.10)

**IR (film) \(\nu_{max}\):** 3327, 1663, 1653, 1487, 1457, 934 cm$^{-1}$

**\(^1\)H NMR (600 MHz, CDCl\(_3\)):** 
\[\delta 8.12 \text{ (bs, 1 H, D}_2\text{O Exchangeable)}, 7.16 \text{ (dd, } J = 8.8, 4.4 \text{ Hz, 1 H}), 7.04 \text{ (dd, } J = 9.7, 2.3 \text{ Hz, 1 H}), 6.82 - 6.88 \text{ (m, 3 H)}, 4.64 \text{ (s, 1 H)}, 4.61 \text{ (s, 1 H)}, 3.80 \text{ (d, } J = 11.6 \text{ Hz, 1 H}), 3.22 \text{ (td, } J = 10.1, 4.8 \text{ Hz, 1 H}), 2.55 - 2.61 \text{ (m, 1 H)}, 2.43 - 2.47 \text{ (m, 1 H)}, 1.86 \text{ (s, 3 H)}, 1.58 \text{ (s, 3 H)}\]

**\(^{13}\)C NMR (150 MHz, CDCl\(_3\)):** 
\[\delta 200.1, 159.3, 157.7, 146.6, 144.7, 136.3, 133.6, 128.3 \text{ (} J = 38.8 \text{ Hz}), 125.5, 113.9 \text{ (} J = 85.9 \text{ Hz}), 112.8 \text{ (} J = 38.9 \text{ Hz}), 111.1 \text{ (} J = 104.6 \text{ Hz}), 105.1 \text{ (} J = 93.6 \text{ Hz}), 50.0, 49.3, 32.1, 19.9, 17.1\]

**HRMS (ESI):** calcd. for C\(_{18}\)H\(_{19}\)FNO \([\text{M} + \text{H}^+]\) 284.1445, found 284.1442

See pages 245 – 246 for spectra.
Compound 48:

Yield: 26.4 mg, 33%

Physical State: white foam

Rf: 0.17 (silica gel, 3:1 hexane:EtOAc)

[α]D: −68.3 (DCM, c 2.36)

IR (film) υmax: 3327, 2918, 1663, 1457, 1368, 1244, 1103, 904 cm⁻¹

1H NMR (600 MHz, CDCl₃): δ 8.33 (bs, 1 H, D₂O Exchangeable), 7.50 (s, 1 H), 7.15 (dd, J = 8.5, 1.4 Hz, 1 H), 7.08 (d, J = 8.6 Hz, 1 H), 6.84 (s, 1 H), 6.62 (d, J = 2.3 Hz, 1 H), 4.63 (s, 1 H), 4.59 (s, 1 H), 3.79 (d, J = 11.9 Hz, 1 H), 3.22 (td, J = 10.4, 4.7 Hz, 1 H), 2.55 – 2.61 (m, 1 H), 2.42 – 2.47 (m, 1 H), 1.88 (s, 3 H), 1.56 (s, 3 H)

13C NMR (150 MHz, CDCl₃): δ 200.5, 146.4, 145.1, 136.2, 135.8, 129.6, 125.3, 125.3, 122.4, 114.1, 113.7, 113.4, 112.7, 49.9, 49.4, 32.3, 19.8, 17.2

HRMS (ESI): calcd. for C₁₈H₁₉BrNO [M + H⁺] 344.0644, found 344.0641

See pages 247 – 248 for spectra.
Compound 49:

Yield: 17.0 mg, 34%

Physical State: white solid  
mp: 156 – 157 °C (DCM)

Rf: 0.20 (silica gel, 3:1 hexane:EtOAc)

[α]D: −49.5 (DCM, c 1.30)

IR (film) \( \nu_{\text{max}} \): 3325, 1667, 1456, 893 cm\(^{-1}\)

\(^1\)H NMR (600 MHz, CDCl\(_3\)):  \( \delta \) 8.17 (bs, 1 H, D\(_2\)O Exchangeable), 7.36 (s, 1 H), 7.14 (d, \( J = 8.6 \) Hz, 1 H), 7.06 (d, \( J = 7.1 \) Hz, 1 H), 6.82 (s, 1 H), 6.80 (d, \( J = 2.2 \) Hz, 1 H), 4.64 (s, 1 H), 3.80 (s, 1 H), 3.23 (td, \( J = 10.6, 4.7 \) Hz, 1 H), 2.56 – 2.61 (m, 1 H), 2.42 – 2.47 (m, 1 H), 1.87 (s, 3 H), 1.57 (s, 3 H)

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)):  \( \delta \) 200.1, 146.5, 144.8, 136.3, 135.5, 129.0, 125.9, 125.2, 122.9, 119.5, 114.0, 113.3, 113.2, 49.9, 49.4, 32.2, 19.8, 17.2

HRMS (ESI): calcd. for C\(_{18}\)H\(_{19}\)ClNO [M + H\(^+\)] 300.1150, found 300.1156

See pages 249 – 250 for spectra.
Compound 52:

Yield: 45 mg, 43%

Physical State: clear oil

Rf: 0.20 (silica gel, 3:1 hexane:EtOAc)

IR (film) ν_{max}: 3405, 1686, 1604, 1477, 1458, 1326, 1214 cm⁻¹

¹H NMR (500 MHz, CDCl₃): δ 8.15 (bs, 1 H, D₂O exchangeable), 7.96 (d, J = 8 Hz, 1 H), 7.68 (d, J = 8 Hz, 1 H), 7.50 (t, J = 8.5 Hz, 1 H), 7.37 (d, J = 8 Hz, 1 H), 7.27 (d, J = 2 Hz, 1 H), 7.21 (t, J = 7.5 Hz, 1 H), 7.15 (t, J = 8 Hz, 1 H), 7.02 – 7.06 (m, 2 H), 4.72 – 4.79 (m, 2 H), 4.30 (dd, J = 5, 7.5 Hz, 1 H)

¹³C NMR (100 MHz, CDCl₃): δ 192.7, 162.3, 136.9, 136.7, 128.8, 127.5, 123.5, 123.4, 122.4, 121.5, 120.9, 119.9, 118.6, 112.2, 110.1, 72.2, 45.2

HRMS (MALDI): calcd. for C₁₇H₁₄NO₂ [M + H⁺] 264.1024, found 264.1021

See pages 251 – 252 for spectra.
Compound 56:

Yield: 11.8 mg, 30% brsm

Physical State: clear oil

Rf: 0.48 (silica gel, 3:1 hexane:EtOAc)

$[\alpha]_D$: –112 (DCM, $c$ 1.2)

IR (film) $\nu_{\text{max}}$: 3348, 2969, 1736, 1654, 1493, 1458, 1376, 1216 cm$^{-1}$

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.03 (bs, 1 H, D$_2$O exchangeable), 7.55 (bs, 1 H), 7.33 (d, $J = 8.4$ Hz, 1 H), 7.17 (t, $J = 7.8$ Hz, 1 H), 7.03 (t, $J = 7.2$ Hz, 2 H), 6.96 (t, $J = 7.2$ Hz, 2 H), 6.70 (s, 1 H), 6.54 (bd, $J = 4.2$ Hz, 2 H), 6.25 (s, 1 H), 5.05 (s, 1 H), 4.85 (s, 1 H), 3.57 (d, $J = 13.8$ Hz, 1 H), 3.30 (d, $J = 13.8$ Hz, 1 H), 3.11 (bs, 1 H), 2.81 (bd, $J = 12.0$ Hz, 1 H), 2.21 (bd, $J = 22.2$ Hz, 1 H), 1.81 (s, 3 H), 1.77 (s, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 202.8, 145.9, 140.7, 138.9, 136.8, 135.9, 131.3 (2 C), 127.3 (2 C), 126.6, 126.0, 123.2, 122.3, 121.0, 120.2, 115.1, 111.6, 53.4, 47.4, 38.9, 30.2, 24.1, 17.2, 14.6

HRMS (MALDI): calcd. for C$_{25}$H$_{26}$NO $[M + H]^+$ 356.2019, found 356.1999

See pages 253 – 254 for spectra.
Compound 57:

![Structure of Compound 57](image)

**Yield:** 1.9 mg, 41% brsm

**Physical State:** light brown oil

**Rf:** 0.67 (silica gel, DCM)

**IR (film)** $\nu_{\text{max}}$: 3378, 2960, 2927, 1719, 1603, 1456, 1392, 1368, 1316, 1220, 1148, 1122 cm$^{-1}$

**$^1H$ NMR (400 MHz, CDCl$_3$):** $\delta$ 8.12 (bs, 1 H, D$_2$O exchangeable), 3.47 (s, 2 H), 2.37 (dd, $J = 7.5$, 15 Hz, 2 H), 2.16 (s, 3 H), 1.94 (s, 3 H), 1.47 (s, 9 H), 1.06 (t, $J = 7.5$ Hz, 3 H)

**$^{13}C$ NMR (125 MHz, CDCl$_3$):** $\delta$ 171.2, 122.0, 120.5, 117.3, 114.5, 81.2, 32.4, 28.3 (3 C), 17.8, 15.9, 11.1, 9.1

**HRMS (ESI):** calcd. for C$_{10}$H$_{17}$NO$_2$ [M + H$^+$] 182.1181, found 182.1179 (mass reported for the acid – tert-butyl ester lost during ionization)

See pages 255 – 256 for spectra.

Compound 58:
Yield: 12.8 mg, 33% brsm

Physical State: white foam

Rf: 0.29 (silica gel, 1:1 hexane:EtOAc)

[α]D: +2.5 (DCM, c 0.16)

IR (film) νmax: 3378, 2925, 2855, 1729, 1454, 1338, 1290, 1127, 1037 cm⁻¹

¹H NMR (400 MHz, CDCl₃): δ 8.03 (bs, 1 H, D₂O exchangeable), 7.56 (d, J = 8.0 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 7.20 (t, J = 8.0 Hz, 1 H), 7.12 (t, J = 8.0 Hz, 1 H), 6.92 (d, J = 1.6 Hz, 1 H), 4.07 (d, J = 8.8 Hz, 1 H), 3.56 (sep, J = 4.8 Hz, 1 H), 2.23 – 2.05 (m, 2 H), 1.92 – 1.66 (m, 5 H), 1.64 – 1.54 (m, 3 H), 1.44 – 1.25 (m, 7 H), 1.15 – 1.05 (m, 1 H), 1.06 (s, 3 H), 0.99 – 0.85 (m, 2 H), 0.85 (s, 3 H), 0.75 – 0.70 (m, 1 H)

¹³C NMR (150 MHz, CDCl₃): δ 221.2, 136.7, 127.3, 122.5, 121.5, 119.8, 119.4, 115.4, 111.5, 71.5, 54.8, 49.9, 48.8, 45.1, 42.9, 38.4, 37.2, 36.0, 35.3, 32.3, 31.7, 31.1, 31.0, 28.7, 20.8, 15.1, 12.7

HRMS (ESI): calcd. for C₂₇H₃₆NO₂ [M + H⁺] 406.2740, found 406.2739

See pages 257 – 258 for spectra.

Compound 59:

Yield: 32.2 mg, 35%
**Physical State:** yellow solid  \( \text{mp: } 143 – 144 \, ^\circ \text{C (DCM)} \)

**Rf:** 0.17 (silica gel, 3:1 hexane:EtOAc)

\([\alpha]_D:\) $-15.3 \, (\text{DCM, c } 1.00)$

**IR (film) \( \nu_{\text{max}} \):** 3396, 1705, 1457, 1339, 1102 cm$^{-1}$

**$^1H$ NMR (600 MHz, CDCl$_3$):**
\[ \delta \]
- 8.10 (bs, 1 H, D$_2$O Exchangeable),
- 7.55 (d, \( J = 8.0 \) Hz, 1 H),
- 7.19 (s, 1 H),
- 7.17 (t, \( J = 7.9 \) Hz, 1 H),
- 7.10 (t, \( J = 7.3 \) Hz, 1 H),
- 4.68 (s, 1 H),
- 4.48 (d, \( J = 4.4 \) Hz, 1 H),
- 4.46 (s, 1 H),
- 3.60 (s, 1 H),
- 3.03 – 3.06 (m, 1 H),
- 2.49 (dd, \( J = 15.4, 4.5 \) Hz, 1 H),
- 2.31 (dd, \( J = 15.4, 7.9, \) 2.7, 1 H),
- 1.54 (s, 3 H),
- 1.50 (s, 3 H)

**$^{13}C$ NMR (150 MHz, CDCl$_3$):**
\[ \delta \]
- 205.2, 145.8, 136.3, 128.3, 123.5, 123.1, 120.6, 119.6, 113.4, 111.9, 111.0, 63.9, 60.1, 46.2, 43.9, 27.9, 23.1, 16.7

**HRMS (ESI):** calcd. for C$_{18}$H$_{20}$NO$_2$ [M + H$^+$] 282.1488, found 282.1495

See pages 259 – 260 for spectra.

**Compound 60:**

\[ \text{Yield: } 0.02 – 7.5 \, \text{g, 62%} \]

**Physical State:** clear cubes  \( \text{mp: } 169 – 170 \, ^\circ \text{C} \)

(4:1:0.1 cyclohexane:Et$_2$O:benzene)
R<sub>r</sub>: 0.35 (silica gel, 3:1 hexane:EtOAc)

[α]<sub>D</sub>: +28.8 (DCM, c 1.11)

**IR (film) ν<sub>max</sub>:** 3414, 1712, 1584, 1548, 1453 cm<sup>-1</sup>

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):**

δ 8.08 (bs, 1 H, D<sub>2</sub>O exchangeable), 7.28 (t, <i>J</i> = 7.5 Hz, 2 H), 7.15 (t, <i>J</i> = 7.0 Hz, 1 H), 7.07 (t, <i>J</i> = 7.0 Hz, 1 H), 6.77 (d, <i>J</i> = 2.5 Hz, 1 H), 6.61 (dd, <i>J</i> = 18.0 Hz, 11.0 Hz, 1 H), 5.50 (d, <i>J</i> = 10.5 Hz, 1 H), 5.24 (d, <i>J</i> = 17.5 Hz, 1 H), 4.68 (s, 1 H), 4.63 (s, 1 H), 4.32 (d, <i>J</i> = 12.5 Hz, 1 H), 4.15 (dd, <i>J</i> = 12.5, 4.5 Hz, 1 H), 2.86 (td, <i>J</i> = 12.5, 3.5 Hz, 1 H), 2.55 (q, <i>J</i> = 26.0 Hz, 12.5 Hz, 1 H), 2.36 (dt, <i>J</i> = 13.5, 4.0 Hz, 1 H), 1.56 (s, 3 H), 1.46 (s, 3 H)

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):**

δ 207.1, 145.2, 138.0, 136.4, 127.7, 123.8, 122.2, 120.0, 119.1, 119.0, 113.8, 111.8, 110.9, 66.9, 58.9, 48.9, 48.4, 39.6, 22.7, 18.6

**HRMS (ESI):** calcd. for C<sub>20</sub>H<sub>23</sub>ClNO [M + H<sup>+</sup>] 328.1463, found 328.1456

See pages 261 – 262 for spectra.

**Compound 62:**

![Compound 62 diagram]

**Yield:** 23.8 mg, 30%

**Physical State:** light yellow oil

R<sub>r</sub>: 0.31 (silica gel, 3:1 hexane:EtOAc)

**IR (film) ν<sub>max</sub>:** 3402, 1675, 1457, 1232, 1208, 1097 cm<sup>-1</sup>
\textbf{1H NMR (600 MHz, CDCl\textsubscript{3})}: \\delta 8.04 \text{ (bs, 1 H, D}_2\text{O Exchangeable)}, 7.99 \text{ (d, } J = 7.8 \text{ Hz, 2 H)}, 7.72 \text{ (d, } J = 7.8 \text{ Hz, 1 H)}, 7.45 \text{ (t, } J = 7.4 \text{ Hz, 1 H)}, 7.33 - 7.36 \text{ (m, 3 H)}, 7.20 \text{ (t, } J = 7.3 \text{ Hz, 1 H)}, 7.16 \text{ (t, } J = 7.6 \text{ Hz, 1 H)}, 6.98 \text{ (s, 1 H)}, 4.99 \text{ (dd, } J = 13.6, 6.8 \text{ Hz, 1 H}), 1.61 \text{ (d, } J = 6.8 \text{ Hz, 3 H})

\textbf{13C NMR (150 MHz, CDCl\textsubscript{3})}: \\delta 201.7, 137.4, 137.2, 133.5, 129.5 (2 C), 129.3 (2 C), 127.0, 123.2, 122.9, 120.6, 119.5, 117.3, 112.2, 39.6, 19.4

\textbf{HRMS (ESI)}: calcd. for C\textsubscript{17}H\textsubscript{16}NO \([M + H]^+ \) 250.1226, found 250.1221

See pages 263 – 264 for spectra.

**Compound 64:**

\begin{center}
\includegraphics[width=0.5\textwidth]{compound64.png}
\end{center}

\textbf{Yield}: 61.4 mg, 48%

\textbf{Physical State}: light pink foam

\textbf{R} \textbf{f}: 0.53 (silica gel, 1:1 hexane:EtOAc)

\[\alpha\] \textbf{D}: $-$ 33 (DCM, $c$ 3.5)

\textbf{IR (film)} $\nu_{\text{max}}$: 3406, 2960, 1686, 1458, 1412, 1376, 1328, 1266, 1236, 1210, 1165, 1133, 1059, 1031, 1011, 963, 910 cm$^{-1}$

\textbf{1H NMR (500 MHz, CDCl\textsubscript{3})}: \\delta 8.18 \text{ (s, 1 H, D}_2\text{O exchangeable)}, 7.84 \text{ (d, } J = 8 \text{ Hz, 1 H)}, 7.32 \text{ (d, } J = 8 \text{ Hz, 1 H)}, 7.15 - 7.17 \text{ (m, 2 H)}, 7.09 \text{ (t, } J = 7.5 \text{ Hz, 1 H)}, 6.08
(s, 1 H), 4.67 (d, J = 6.5 Hz, 1 H), 3.91 (s, 1 H), 3.50 (d, J = 13.5 Hz, 1 H), 3.45 (d, J = 13.5 Hz, 1 H), 1.79 – 1.96 (m, 4 H), 1.71 (t, J = 3.5 Hz, 1 H), 1.63 (d, J = 7 Hz, 3 H), 1.38 (t, J = 9 Hz, 1 H), 0.91 (s, 3 H), 0.90 (s, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 174.4, 136.2, 126.2, 122.7, 122.0, 119.6, 119.5, 114.9, 111.1, 65.2, 53.2, 48.4, 47.7, 44.5, 38.3, 37.9, 32.8, 26.5, 20.6, 19.9, 17.7

HRMS (MALDI): calcd. for C$_{21}$H$_{27}$N$_2$O$_3$S [M + H$^+$] 387.1737, found 387.1733

See pages 265 – 266 for spectra.

**Compound 65:**

![Chemical Structure](image)

**Yield:** 15.0 mg, 30% (90% brsm)

**Physical State:** light pink foam

**R$_f$:** 0.52 (silica gel, 1:1 hexane:EtOAc)

**$[\alpha]_D$:** −51 (DCM, c 1.1)

**IR (film) $\nu_{max}$:** 3382, 2961, 1686, 1486, 1328, 1266, 1236, 1210, 1165, 1133, 1058 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.09 (bs, 1 H, D$_2$O exchangeable), 7.52 (dd, J = 10.0, 2.0 Hz, 1 H), 7.24 (d, J = 5.2 Hz, 1 H), 7.22 (d, J = 5.2 Hz, 1 H), 6.91 (td, J = 8.8, 2.4 Hz, 1 H), 4.61 (bq, J = 6.8 Hz, 1H), 3.91 (dd, J = 7.6, 4.8 Hz, 1 H), 3.52
(d, J = 14.0 Hz, 1 H), 3.46 (d, J = 14.0 Hz, 1 H), 1.98 – 1.70 (m, 4 H), 1.61 (d, J = 6.8 Hz, 3 H), 1.41 – 1.21 (m, 3 H), 0.93 (s, 3 H), 0.91 (s, 3 H)

^{13}\text{C NMR (100 MHz, CDCl}_3\text{: } \delta 174.4, 158.0 (d, J = 232.9 Hz), 132.9, 126.8 (d, J = 9.9 Hz), 124.7, 115.6, 111.8, (d, J = 9.4 Hz), 110.8 (d, J = 26.1 Hz), 104.9 (d, J = 24.2 Hz), 65.5, 53.5, 48.7, 48.0, 44.8, 38.6, 38.1, 33.1, 26.8, 20.8, 20.1, 17.7

HRMS (MALDI): calcd. for C_{21}H_{26}FN_2O_3S [M + H]^+ 405.1650, found 405.1650.

See pages 267 – 268 for spectra.

Compound 66:

![Chemical Structure Image]

**Yield:** 18.0 mg, 36% (96% brsm)

**Physical State:** light yellow foam

**R_f:** 0.59 (silica gel, 1:1 hexane:EtOAc)

**[a]_D:** – 44 (DCM, c 1.8)

**IR (film) \( \nu_{\text{max}} \):** 3400, 2960, 1686, 1458, 1329, 1266, 1235, 1211, 1133, 1058 cm\(^{-1}\)

^{1}\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.94 (bs, 1 H, D\_2O exchangeable), 7.71 (d, J = 8.0 Hz, 1 H), 7.11 (s, 1 H), 6.92 (d, J = 8.0 Hz, 1 H), 4.63 (bq, J = 7.2 Hz, 1H), 3.91 (dd, J = 7.6, 4.8 Hz, 1 H), 3.50 (d, J = 14.0 Hz, 1 H), 3.40 (d, J = 14.0 Hz, 1 H), 2.44 (s, 3 H), 1.98 – 1.70 (m, 4 H), 1.61 (d, J = 7.2 Hz, 3 H), 1.41 – 1.21 (m, 4 H),
1H NMR (500 MHz, CDCl3): \( \delta \) 7.97 (bs, 1 H, D\( _2 \)O exchangeable), 7.70 (d, \( J = 9.0 \) Hz, 1 H), 7.06 (d, \( J = 2.0 \) Hz, 1 H), 6.80 (d, \( J = 2.0 \) Hz, 1 H), 6.75 (dd, \( J = 8.5 \), 2.0 Hz, 1 H), 4.61 (bd, \( J = 6.5 \) Hz, 1 H), 3.91 (bs, 1 H), 3.82 (s, 3 H), 3.75 (bs, 1 H), 3.47 (dd, \( J = 22.5 \), 13.5 Hz, 2 H), 1.94 – 1.72 (m, 6 H), 1.60 (d, \( J = 7.0 \) Hz, 1 H), 0.92 (s, 3 H), 0.90 (s, 3 H)

\[ ^{13} \text{C NMR (100 MHz, CDCl}_3\] : \( \delta \) 174.6, 136.9, 132.1, 124.3, 122.2, 121.6, 119.6, 115.2, 111.3, 65.5, 53.5, 50.6, 48.7, 47.9, 44.8, 38.6, 38.3, 33.1, 26.8, 22.0, 20.9, 20.2

HRMS (MALDI): calcd. for C\(_{22}\)H\(_{29}\)N\(_2\)O\(_3\)SNa [M + Na\(^+\)] 423.1713, found 423.1718

See pages 269 – 270 for spectra.

**Compound 67:**

![Compound 67](image)

**Yield:** 19.3mg, 37% (49% brsm)

**Physical State:** light yellow foam

**\( R_f \):** 0.53 (silica gel, 1:1 hexane:EtOAc)

**[\( \alpha \]D):** \(-36\) (DCM, \( c 0.9\))

**IR (film) \( \nu \)max:** 3402, 2959, 1690, 1629, 1457, 1329, 1265, 1236, 1209, 1163, 1132, 1032 cm\(^{-1}\)

**1H NMR (500 MHz, CDCl3):** \( \delta \) 7.97 (bs, 1 H, D\( _2 \)O exchangeable), 7.70 (d, \( J = 9.0 \) Hz, 1 H), 7.06 (d, \( J = 2.0 \) Hz, 1 H), 6.80 (d, \( J = 2.0 \) Hz, 1 H), 6.75 (dd, \( J = 8.5 \), 2.0 Hz, 1 H), 4.61 (bd, \( J = 6.5 \) Hz, 1 H), 3.91 (bs, 1 H), 3.82 (s, 3 H), 3.75 (bs, 1 H), 3.47 (dd, \( J = 22.5 \), 13.5 Hz, 2 H), 1.94 – 1.72 (m, 6 H), 1.60 (d, \( J = 7.0 \) Hz, 1 H),
1.40 – 1.28 (m, 2 H), 0.91 (s, 3 H), 0.90 (s, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$):  δ 174.5, 156.6, 137.1, 121.6, 120.8, 120.5, 115.2, 109.7, 94.7, 65.4, 55.8, 53.4, 48.6, 47.9, 44.7, 38.5, 38.2, 33.0, 26.7, 20.8, 20.1, 17.9

HRMS (MALDI): calcd. for C$_{22}$H$_{29}$N$_2$O$_4$S [M + H$^+$] 417.1842, found 417.1840

See pages 271 – 272 for spectra.

Compound 70:

Identical to commercially available 3-indole acetic acid after hydrolysis.

Compound 73:

Yield: 51 mg, 54%

Physical State: clear oil

R$_f$: 0.21 (silica gel, 3:1 hexane:EtOAc)

[α]$_D$: –73 (DCM, c 1.7)

IR (film) $\nu_{\text{max}}$: 3380, 2978, 1774, 1690, 1383, 1355, 1209, 1109 cm$^{-1}$
$^1$H NMR (500 MHz, CDCl$_3$, data for major diastereomer given): δ 8.18 (bs, 1 H, D$_2$O exchangeable), 7.40 – 7.10 (m, 10 H), 4.68 – 4.62 (m, 1 H), 4.23 – 4.61 (m, 3 H), 3.13 (dd, $J = 13.5$, 3.0 Hz, 1 H), 2.82 (dd, $J = 13.5$, 9.0 Hz, 1 H), 1.30 (d, $J = 6.0$ Hz, 3 H)

$^{13}$C NMR (125 MHz, CDCl$_3$, data for major diastereomer given): δ 177.3, 153.0, 135.6, 129.7 (2 C), 129.6, 129.1 (2 C), 129.0, 127.5, 127.3, 123.6, 122.3, 119.9, 114.7, 111.4, 66.0, 55.6, 41.6, 38.0, 15.4

HRMS (MALDI): calcd. for C$_{21}$H$_{20}$N$_2$O$_3$Na [M + Na$^+$] 371.1366, found 371.1358

See pages 273 – 274 for spectra.

Scheme 27. Preparation of compound 81.
**Compound 192:**

Mannitol (50 g, 275 mmol, 1.0 equiv.) was suspended in acetone (624 mL, 0.44 M) at room temperature (did not fully solubilize, but remained a slurry). Sulfuric acid (5.0 mL, 93.8 mmol, 0.34 equiv.) was added at ambient temperature and the suspension was allowed to stir for 40 hours. During this time, the reaction became a clear solution instead of a cloudy suspension, as the equilibrium moved to the protected product. After the reaction was finished, it was quenched by the sequential addition of NH₄OH (30 wt. % solution, 17.6 mL, 151 mmol, 0.55 equiv.) and powdered Na₂CO₃ (31.2 g, 294 mmol, 1.07 equiv.). The resulting slurry was evaporated *in vacuo*, then reslurried with EtOH (3 x 150 mL) and filtered to remove the salts. The combined organic layers were evaporated *in vacuo* then recrystallized from acetone to provide mannitol triacetonide, **compound 192** (62.3 g, 75%), which was spectroscopically identical with the known compound.²⁷⁵

**Compound 193:**
**Compound 192** (5.0 g, 16.5 mmol, 1.0 equiv.) was dissolved in EtOH (79.6 mL, 0.21 M) and H₂O (34.1 mL, 0.48 M) at room temperature. To this solution was added concentrated HCl (351 µL, 3.56 mmol, 0.22 equiv.) and the reaction was heated to 45 °C for one hour. After one hour, K₂CO₃ was added to the reaction mixture until the HCl was quenched and two layers had formed in the flask. The layers were separated and the aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were evaporated in vacuo and dissolved in H₂O (100 mL). The insoluble materials were filtered off and discarded. The aqueous layer was then extracted with EtOAc (3 x 100 mL) and the combined organic layers were evaporated in vacuo, to provide **compound 193** (1.19 g, 28%), of sufficient purity for use in the next step and spectroscopically identical with the known compound.²⁷⁶

**Compound 194:**

**Compound 192** (6.12 g, 23.4 mmol, 1.0 equiv.) was dissolved in Et₂O (93.4 mL, 0.25 M) and cooled to 0 °C. Periodic acid (6.92 g, 30.4 mmol, 1.3 equiv.) was added portionwise (5 x 1.38 g) over the course of 20 minutes and the reaction was allowed to stir for another three hours. After completion, the reaction was filtered through celite and the solvent removed in vacuo. Flash column Chromatography (silica gel, gradient from 5:1 to 3:1
hexane:EtOAc) provided **compound 194** (2.59 g, 48%), which was spectroscopically identical with the known compound.277

**Compound 81:**

![Compound 81](image)

**Compound 194** (2.59 g, 11.3 mmol, 1.0 equiv.) was dissolved in MeOH (11.3 mL, 1.0 M) and cooled to 0 °C. Sodium borohydride (494 mg, 13.1 mmol, 1.16 equiv.) was added and the reaction was allowed to stir at the same temperature. After one hour, the reaction was quenched by the addition of saturated NH₄Cl (10 mL). The resulting mixture was evaporated *in vacuo*, leaving behind the aqueous layer (without MeOH). The aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO₄) and evaporated *in vacuo* to provide **compound 81** (2.62 g, 100%) that was sufficiently pure for the next reaction and spectroscopically identical to the known compound.277

**Compound 80:**

![Compound 80](image)
**Compound 64** (86.0 mg, 0.223 mmol, 1.0 equiv.) was dissolved in DME (890 µL, 0.25 M) and cooled to –15 ºC (MeOH/ice bath). In another flask, TBAH (1.0 M in MeOH, 445 µL, 0.445 mmol, 2.0 equiv.) and hydrogen peroxide (43.3 µL, 0.445 mmol, 2.0 equiv.) were mixed and cooled to –15 ºC. This pre-mixed, pre-cooled solution was then added drop-wise to the pre-cooled solution of starting material over the course of 5 minutes. The reaction was allowed to stir for 50 minutes, then was quenched by the addition of a solution of Na₂SO₃ (1.5 M, 1.0 mL). The quenched reaction was then warmed to room temperature and diluted with 1 N HCl (10 mL), which was extracted with EtOAc (4 x 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), and evaporated *in vacuo*. Flash column chromatography (silica gel, gradient from 3:1 to 1:1 hexane:EtOAc) gave **compound 80** (35.0 mg, 83%) which was unstable and rapidly decomposed so it was immediately utilized in the next step.

**Physical State:** dark yellow oil

**Rf:** 0.32 (silica gel, 1:1 hexane:EtOAc)

**[α]D:** +41.5 (DCM, c = 0.13)

**IR (film)** ν\text{max}: 3407, 2921, 1700, 1459, 1214 cm⁻¹

**¹H NMR (600 MHz, CDCl₃):**  δ 8.03 (bs, 1 H, D₂O Exchangeable), 7.69 (d, J = 7.9 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.20 (t, J = 7.3 Hz, 1 H), 7.13 (t, J = 7.5 Hz, 1 H), 7.10 (d, J = 1.6 Hz, 1 H), 4.04 (q, J = 14.2, 7.1 Hz, 1 H), 1.62 (d, J = 7.2 Hz, 3 H), Acid proton not observed.

**¹³C NMR (150 MHz, CDCl₃):**  δ 181.9, 137.1, 127.2, 123.2, 122.6, 120.6, 120.1, 115.7, 112.1, 37.8, 18.4

**HRMS (ESI):** calcd. for C₁₁H₁₂NO₂ [M + H⁺] 190.0863, found 190.0868
See pages 275 – 276 for spectra.

**Compound 82:**

To a solution of dicyclohexyl carbodiimide (DCC, 47.4 mg, 0.23 mmol, 1.1 equiv.) in Et<sub>2</sub>O (558 µL, 0.46 M) was added DMAP (3.3 mg, 0.0271 mmol, 0.13 equiv.). In another flask, compound 81 (50.9 mg, 0.219 mmol, 1.05 equiv.) and compound 80 (39.5 mg, 0.209 mmol, 1.0 equiv.) were dissolved in Et<sub>2</sub>O (563 µL, 0.76 M). This solution of starting materials was then transferred via syringe into the DCC/DMAP solution. The starting material flask was then rinsed successively with Et<sub>2</sub>O (200 µL and 100 µL) and transferred to the DCC/DMAP solution. The combined reaction mixture was allowed to stir for one hour, then quenched by the addition of brine (7.0 mL). The reaction mixture was then extracted with EtOAc (4 x 10 mL). The combined organic extracts were dried (Na<sub>2</sub>SO₄) and evaporated in vacuo. Flash column chromatography (silica gel, 19:1 DCM:EtOAc) gave compound 82 (57.8 mg, 69%).

**Physical State:** clear oil

**R<sub>f</sub>**: 0.30 (silica gel, 9:1 DCM:EtOAc)

**[α]<sub>D</sub>**: + 40.1 (DCM, c 1.67)

**IR (film) ν<sub>max</sub>:** 3379, 2983, 1734, 1459, 1371, 1213, 1168, 1062 cm<sup>-1</sup>
\[^1H\text{NMR (600 MHz, CDCl}_3\text{):} \] d 8.09 (bs, 1 H, D\textsubscript{2}O Exchangeable), 7.69 (d, J = 7.9 Hz, 1 H), 7.33 (d, J = 8.1 Hz, 1 H), 7.18 (t, J = 7.2 Hz, 1 H), 7.11 (t, J = 7.9 Hz, 1 H), 7.11 (s, 1 H), 4.46 (d, J = 11.3 Hz, 1 H), 4.07 – 4.15 (m, 3 H), 4.03 (t, J = 7.5 Hz, 1 H), 3.95 – 3.98 (m, 1 H), 3.77 – 3.79 (m, 1 H), 3.62 (t, J = 8.0 Hz, 1 H), 1.62 (d, J = 7.1 Hz, 3 H), 1.36 (s, 3 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.19 (s, 3 H)

\[^{13}C\text{NMR (150 MHz, CDCl}_3\text{):} \] d 175.7, 137.1, 127.2, 123.1, 122.5, 120.5, 120.2, 116.3, 112.0, 110.6, 110.5, 79.2, 78.0, 77.9, 68.5, 64.8, 37.8, 27.9, 27.7, 27.2, 26.1, 18.7

HRMS (ESI): calcd. for C\textsubscript{22}H\textsubscript{30}NO\textsubscript{6} [M + H\textsuperscript{+}] 404.2068, found 404.2076

See pages 277 – 278 for spectra.

Acremoauxin A (83):

\[ \text{Compound 82 (9.2 mg, 0.0228 mmol, 1.0 equiv.) was dissolved in a solution of AcOH (60\% aqueous, 230 \mu L, 0.1 M) at ambient temperature. The reaction was then heated to 50 °C and held at this temperature for 19 hours at which point it was cooled back to ambient temperature. The solvent was removed in vacuo. PTLC (silica gel, 9:1 DCM:MeOH) provided acremoauxin A (83, 4.6 mg, 62\%).} \]

Physical State: yellow solid \[ \text{mp: 130 – 131 °C (MeOH)} \]

\[ R_f: 0.18 \text{ (silica gel, 9:1 DCM:MeOH)} \]
\[ \alpha_d \] : +53.6 (1:1 DCM:MeOH, c 0.405)

**IR (film) \( \nu_{\text{max}} \):** 3367, 1715, 1649, 1457, 1178, 1030 cm\(^{-1} \)

**\( ^1H \) NMR (600 MHz, CDCl\(_3\)):** \( \delta \) 7.58 (d, \( J = 8.0 \) Hz, 1 H), 7.32 (d, \( J = 8.1 \) Hz, 1 H), 7.14 (s, 1 H), 7.08 (t, \( J = 7.3 \) Hz, 1 H), 6.99 (t, \( J = 7.4 \) Hz, 1 H), 4.11 – 4.17 (m, 2 H), 4.02 – 4.06 (m, 2 H), 3.72 (dd, \( J = 11.2 \), 3.4 Hz, 1 H), 3.62 – 3.65 (m, 1 H), 3.52 – 3.55 (m, 1 H), 3.39 (d, \( J = 8.3 \) Hz, 1 H), 1.57 (d, \( J = 7.1 \) Hz, 3 H), Exchangeable protons not observed.

**\( ^{13}C \) NMR (150 MHz, CDCl\(_3\)):** \( \delta \) 176.6, 137.6, 127.1, 122.6, 122.0, 119.3, 119.2, 114.9, 111.8, 72.1, 71.5, 68.6, 66.4, 64.4, 37.8, 17.7

**HRMS (ESI):** calcd. for C\(_{16}\)H\(_{22}\)NO\(_6\) [M + H\(^+\)] 324.1442, found 324.1454

See pages 279 – 280 for spectra.
**Compound 195:**

Acetyl chloride (28 mL, 392 mmol, 7.0 equiv.) was added to MeOH (220 mL, 0.25 M), followed by tyrosine (10.0 g, 55.2 mmol, 1.0 equiv.). The resulting solution was heated to reflux for 15 hours. After this time, the reaction was cooled to ambient temperature and the solvent removed *in vacuo*, providing **compound 195** (10.8 g, 100%) that was sufficiently pure for the next step and spectroscopically identical to the known compound.

**Compound 196:**

**Compound 195** (5.0 g, 25.6 mmol, 1.0 equiv.) was dissolved in EtOH (102 mL, 0.25 M) while vigorously stirring at ambient temperature. Sodium bicarbonate (21.5 g, 256 mmol, 10 equiv.) followed by di-tert-butyl dicarbonate (5.6 g, 25.6 mmol, 1.0 equiv.) were added sequentially. The resulting suspension was allowed to stir 15 hours at ambient temperature, after which time it was filtered through a fritted funnel. The solvent was removed *in vacuo* to provide **compound 196** (7.56 g, 100%) that was sufficiently pure for the next step and spectroscopically identical to the known compound.
Compound 197:  

**Compound 196** (6.86 g, 23.2 mmol, 1.0 equiv.) was dissolved in acetone (23 mL, 1.0 M) at room temperature. Powdered potassium carbonate (3.53 g, 25.5 mmol, 1.1 equiv.) followed by benzyl bromide (3.17 mL, 26.5 mmol, 1.14 equiv.) were added sequentially and the resulting suspension was heated to reflux. After 15 hours, the reaction was cooled to ambient temperature and the solvent removed *in vacuo*. The solid obtained after evaporation was diluted with H₂O (125 mL) and extracted with DCM (5 x 75 mL). The combined organic layers were dried (MgSO₄) and the solvent removed *in vacuo*. Flash column chromatography (silica gel, gradient 12:1 to 6:1 hexane:EtOAc) provided **compound 197** (7.10 g, 80%) that was spectroscopically identical with the known compound.²⁷⁸

**Compound 198:**  

**Compound 197** (5.08 g, 13.2 mmol, 1.0 equiv.) was dissolved in THF (53 mL, 0.25 M) at room temperature. Lithium iodide (1.94 g, 14.5 mmol, 1.1 equiv.) followed by sodium borohydride (549 mg, 14.5 mmol, 1.1 equiv.) were added sequentially and the resulting suspension heated to reflux. After two hours, the reaction was cooled to ambient temperature and quenched by the careful addition of saturated NH₄Cl (50 mL). The
reaction was then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (MgSO₄) and the solvent removed *in vacuo*, to provide **compound 198** (4.34 g, 94%) that was sufficiently pure for the next step and spectroscopically identical to the known compound.²⁷⁹

**Compound 199:**

![Compound 199](image)

**Compound 198** (3.49 g, 9.74 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid (6.20 g, 19.5 mmol, 2.0 equiv.) were dissolved in DCM (48.7 mL, 0.2 M) and THF (48.7 mL, 0.2 M) at ambient temperature. The reaction was refluxed for six hours, after which it was cooled to ambient temperature and diluted with 1 N NaOH (100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried (MgSO₄) and the solvent removed *in vacuo*. The **compound 199** (2.48 g, 100%) thus obtained was sufficiently pure for the next step and spectroscopically identical to the known compound.²⁷⁹

**Compound 84:**

![Compound 84](image)

*O*-Benzyltyrosinol (**Compound 199**, 1.40 g, 5.48 mmol, 1.0 equiv.) was dissolved in THF (82 mL, 0.067 M) at room temperature in a flame dried, nitrogen purged flask.
Sodium hydride (220 mg, 5.48 mmol, 1.0 equiv.) was then added with stirring. The reaction was stirred for 30 minutes at room temperature, after which chloroethyl acetate (584 µL, 5.48 mmol, 1.0 equiv.) was added dropwise over the course of five minutes. The reaction was then refluxed for three hours, after which it was cooled to ambient temperature, quenched with 1 N HCl (25 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with H2O (50 mL) then brine (50 mL), dried (Na2SO4) and the solvent removed in vacuo. Flash column chromatography (silica gel, 6:1 hexane:EtOAc) provided compound 84 (1.09 g, 66%), which was identical with the known material.²⁸⁰

**Compound 85:**

![Chemical Structure](image)

Compound 84 (190.2 mg, 0.640 mmol, 1.0 equiv.) was dissolved in THF (6.4 mL, 0.1 M) at ambient temperature in a flame-dried flask under a nitrogen atmosphere. Triethylamine (178 µL, 1.28 mmol, 2.0 equiv.) was then added to the reaction solution and allowed to stir for ten minutes. Pivaloyl chloride (86.6 µL, 0.704 mmol, 1.1 equiv.) was then added at the same temperature. The reaction was allowed to stir for two hours, at which point it was quenched with 1 N NaOH (10 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried (Na2SO4) and the solvent removed in vacuo. Flash column chromatography (silica gel, 12:1 hexane:EtOAc) provided compound 85 (190.2 mg, 93%).

**Physical State:** yellow oil
$R_f$: 0.88 (silica gel, EtOAc)

$|\alpha|_D$: $-23.8$ (DCM, $c = 2.28$)

**IR (film) $\nu_{\text{max}}$:** 2962, 1686, 1510, 1392, 1160, 1138, 1073, 1024 cm$^{-1}$

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.43 (d, $J = 7.2$ Hz, 2 H), 7.38 (t, $J = 7.2$ Hz, 2 H),
7.33 (d, $J = 7.2$ Hz, 1 H), 7.16 (d, $J = 8.5$ Hz, 2 H), 6.93 (d, $J = 8.6$ Hz, 1 H), 5.05
(s, 2 H), 4.37 (d, $J = 17.0$ Hz, 1 H), 4.25 (d, $J = 11.0$ Hz, 1 H), 4.13 (d, $J = 17.0$
Hz, 1 H), 3.83 (d, $J = 12.2$ Hz, 1 H), 3.50 (dd, $J = 12.2$, 1.4 Hz, 1 H), 2.92 (t, $J =$
13.2 Hz, 1 H), 2.81 (dd, $J = 13.1$, 3.4 Hz, 1 H), 1.35 (s, 9 H)

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 187.3, 169.5, 158.2, 137.4, 130.9 (2 C), 129.8,
129.0 (2 C), 128.4, 127.9 (2 C), 115.5 (2 C), 70.5, 69.1, 65.5, 57.1, 44.3, 37.9,
27.8 (3 C)

**HRMS (ESI):** calcd. for C$_{23}$H$_{28}$NO$_4$ [M + H$^+$] 382.2013, found 382.2018

See pages 281 – 282 for spectra.

**Compound 89:**

**Compound 85** (37.3 mg, 0.0978 mmol, 1.0 equiv.) and indole (34.4 mg, 0.293 mmol, 3.0
equiv.) were dissolved in THF (400 $\mu$L, 1.0 M) in a flame-dried flask under a nitrogen
atmosphere. The solution was cooled to $-78$ °C and LHMDS (1.0 M, 430 $\mu$L, 0.430
mmol, 4.4 equiv.) was added. The mixture was allowed to stir for 30 minutes, at which
point the septum was removed, solid copper(II)2-ethylhexanoate (68.4 mg, 0.196 mmol,
2.0 equiv.) was rapidly added, and the septum replaced. After addition of the oxidant, the reaction flask was removed from the cooling bath and allowed to naturally warm to ambient temperature. The reaction was then quenched with 1 N HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 1 N NaOH (10 mL), water (10 mL), brine (10 mL), dried (MgSO₄), and the solvent removed in vacuo. Flash column chromatography (silica gel, gradient from 8:1:1 to 3:1:1 hexane:Et₂O:DCM) provided pure compound 89 (19.4 mg, 40%).

**Physical State:** white solid  
**mp:** 68 – 70 ºC (DCM)

Rf: 0.45 (silica gel, 2:1:1 hexane:Et₂O:DCM)

[a]D: +59.2 (DCM, c = 0.13)

**IR (film) nmax:** 3386, 2927, 1684, 1510, 1455, 1395, 1241, 1153, 1095, 1025 cm⁻¹

**¹H NMR (600 MHz, CDCl₃):**  
d 8.17 (bs, 1 H, D₂O Exchangeable), 7.76 (d, J = 7.9 Hz, 1 H), 7.42 (d, J = 7.4 Hz, 1 H), 7.36 – 7.39 (m, 5 H), 7.32 (d, J = 7.2 Hz, 1 H), 7.18 – 7.25 (m, 3 H), 7.15 (t, J = 7.6 Hz, 1 H), 6.92 (d, J = 8.5 Hz, 2 H), 5.84 (s, 1 H), 5.04 (s, 2 H), 4.30 (dd, J = 10.9, 1.9 Hz, 1 H), 3.75 (dd, J = 12.5, 2.9 Hz, 1 H), 3.62 (d, J = 12.5 Hz, 1 H), 3.04 (dt, J = 12.8, 1.5 Hz, 1 H), 2.84 (dd, J = 13.1, 3.1 Hz, 1 H), 1.40 (s, 9 H)

**¹³C NMR (150 MHz, CDCl₃):**  
d 189.3, 171.2, 158.6, 137.8, 137.2, 131.4 (2 C), 130.2, 129.4 (2 C), 128.8, 128.3 (2 C), 127.3, 124.8, 123.5, 121.1, 115.9, 115.4, 112.4 (2 C), 112.1, 74.7, 70.9, 61.6, 58.2, 45.0, 38.7, 28.5 (3 C)

**HRMS (ESI):** calcd. for C₃₁H₃₃N₂O₄ [M + H⁺] 497.2440, found 497.2420

See pages 283 – 284 for spectra.
Piv Deprotection Product:

**Compound 89** (28.5 mg, 0.0574 mmol, 1 equiv.) was dissolved in DME (230 mL, 0.25 M) at 0 ºC. In a separate flask tetra-N-butylammonium hyroxide (40 wt. % in H2O, 75 mL, 0.115 mmol, 2 equiv.) and H2O2 (9.8 mL, 0.115 mmol, 2 equiv.) were premixed at 0 ºC. This solution of tetr-N-butylammonium hydroperoxide was added dropwise to the starting material solution. The reaction was allowed to stir for 2 hours, at which point it was quenched with 1.5 M Na2SO3 (5 mL) and allowed to warm to room temperature. The reaction was diluted with 6 M HCl (5 mL) and extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na2SO4), and the solvent removed *in vacuo*. Flash column chromatography (silica gel, gradient from 3:1 to 1:1 to 1:3 hexane:EtOAc) provided the **Piv Deprotection product** (19.5 mg, 82%)

**Physical State:** clear oil

**Rf:** 0.58 (silica gel, EtOAc)

**[α]D:** –11.9 (DCM, c = 0.62)

**IR (film) ν<sub>max</sub>:** 3245, 2924, 1663, 1510, 1453, 1340, 1239, 1089, 1054, 1011 cm<sup>-1</sup>

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.24 (bs, 1 H, D2O Exchangeable), 7.67 (d, J = 7.9 Hz, 1 H), 7.32 – 7.44 (m, 6 H), 7.12 – 7.25 (m, 5 H), 6.97 (d, J = 8.7 Hz, 2 H), 6.08 (bs, 1 H, D2O Exchangeable), 5.50 (s, 1 H), 5.07 (s, 2 H), 4.10 (dd, J = 11.7, 3.6 Hz 1 H), 3.88 – 3.91 (m, 1 H), 3.64 (dd, J = 11.8, 7.0 Hz, 1 H), 2.92 (dd, J = 18.9, 5.3 Hz, 1 H), 2.71 (dd, J = 13.6, 9.2 Hz, 1 H)
\[ ^{13}C \text{ NMR (150 MHz, CDCl}_3) : \delta 170.7, 158.9, 137.7, 137.3, 131.1 (2 \text{ C}), 129.5 (2 \text{ C}), 128.9, 128.3 (2 \text{ C}), 126.9, 125.5, 123.3, 121.0, 120.4, 116.3 (2 \text{ C}), 112.4, 112.2, 74.9, 71.0, 66.8, 54.5, 39.5 \]

**HRMS (ESI):** calcd. for C\text{\textsubscript{2}6}H\text{\textsubscript{2}4}N\text{\textsubscript{2}}O\text{\textsubscript{3}} [M + H\textsuperscript{+}] 413.1860, found 413.1865

See pages 285 – 286 for spectra.

**Oxazinin 3 (90):**

![Chemical Structure]

**Piv Deprotected product** (17.2 mg, 0.0417 mmol, 1.0 equiv.) was dissolved in MeOH (1.0 mL) and Pd/C (10%, 4.4 mg, 0.1 equiv.) was added in a flask with a septum covering the opening. A hydrogen balloon was placed on the flask, with the needle tip below the level of solution and a vent needle on top of the flask. The solution was stirred vigorously for three hours while bubbling hydrogen gas. The balloon was lifted above the level of the solution, the vent needle removed, and the reaction allowed to stir under and atmosphere of hydrogen for 12 hours. After completion of the reaction, the Pd/C was removed by filtration through a pad of celite with EtOAc as the eluent. The solvent was then removed *in vacuo*, providing **oxazinin 3 (90)**, 12.9 mg, 96%) as a single diastereomer.

**Physical State:** white solid  
**mp:** 97 – 99 °C (MeOH)

**R\text{\textsubscript{R}}:** 0.46 (silica gel, EtOAc)

**[\alpha]_D:** +47.3 (MeOH, c = 0.11)
\textbf{IR (film)} ν_{\text{max}}: 3331, 1658, 1514, 1341, 1093 cm\textsuperscript{−1}

\textbf{\textsuperscript{1}H NMR (600 MHz, CD\textsubscript{3}CN):} \delta 9.26 (bs, 1 H, D\textsubscript{2}O Exchangeable), 7.58 (d, J = 7.8 Hz, 1 H), 7.40 (d, J = 8.4 Hz, 1 H), 7.24 (d, J = 2.4 Hz, 1 H), 7.03 – 7.15 (m, 4 H), 6.90 (bs, 1 H, D\textsubscript{2}O Exchangeable), 6.77 (d, J = 8.4 Hz, 2 H), 6.44 (bs, 1 H, D\textsubscript{2}O Exchangeable), 5.30 (s, 1 H), 3.86 – 3.90 (m, 2 H), 3.53 (dd, J = 11.4, 7.2 Hz, 1 H), 2.79 (d, J = 7.2 Hz, 2 H)

\textbf{\textsuperscript{13}C NMR (150 MHz, CD\textsubscript{3}CN):} \delta 170.0, 156.6, 137.3, 131.3 (2 Carbons), 128.9, 127.1, 126.0, 122.7, 120.2, 120.2, 116.2 (2 Carbons), 113.0, 112.3, 74.4, 66.1, 54.3, 38.9

\textbf{HRMS (ESI):} calcd. for C\textsubscript{19}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3} [M + H\textsuperscript{+}] 323.1390, found 323.1388

See pages 287 – 288 for spectra.

\textbf{Scheme 29.} Total synthesis of ketorolac (95).
Compound 200:

![Diagram of Compound 200]

**Compound 91** (460 mg, 3.00 mmol, 1.0 equiv.) was dissolved in benzene (3.0 mL) and the solvent removed *in vacuo*. The compound was then dissolved in anhydrous THF (15 mL, 0.2 M) and cooled to 0 °C. Triethylamine (433 µL, 3.25 mmol, 1.08 mL) was then added, followed by methyl chloroformate (232 µL, 3.00 mmol, 1.0 equiv.), and stirring was continued for one hour. In a separate flask, (S)-2,10-camphorsultam (538 mg, 2.50 mmol, 0.83 equiv.) was dried *in vacuo* for 30 minutes, was dissolved in THF (12.5 mL, 0.2 M) and cooled to –78 °C. A solution of butyl lithium (2.50 M, 1.05 mL, 2.63 mmol, 0.88 equiv.) was then added and the solution stirred for 20 minutes. The anhydride solution was then filtered through a medium porosity glass frit under a blanket of nitrogen to remove the triethylamine hydrochloride salt. The filtrate was then cannulated into a solution of the lithiate (92) at –78 °C. The reaction was allowed to immediately warm to ambient temperature then was quenched with 20% potassium carbonate solution (20 mL) and partitioned with EtOAc (30 mL). The organic layer was washed with water (20 mL) then brine (20 mL) and dried (MgSO₄). Removal of the solvent *in vacuo* gave pure pyrrole sultam 200 (876 mg, 100%).

**Physical State:** light brown oil

**Rᶠ:** 0.32 (silica gel, 3:1 hexane:EtOAc)

**[α]ᵦ:** – 49 (DCM, c = 10.6)

**IR (film) ** νₓₐₓ:** 2958, 1813, 1734, 1693, 1500, 1456, 1412, 1390, 1327, 1279, 1237, 1215, 1167, 1118, 1089, 1052, 1035, 987, 948 cm⁻¹
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.65 (t, $J = 2$ Hz, 2 H), 6.13 (t, $J = 2.4$ Hz, 2 H), 3.90 – 3.99 (m, 2 H), 3.84 – 3.87 (m, 2 H), 2.68 – 2.74 (m, 2 H), 2.04 – 2.15 (m, 4 H), 1.87 – 1.92 (m, 2 H), 1.35 – 1.45 (m, 2 H), 1.14 (s, 3 H), 0.97 (s, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.8, 120.5 (2 C), 108.1 (2 C), 65.1, 52.8, 48.4 (2 C), 47.7, 44.6, 38.4, 32.8, 32.3, 26.4, 26.3, 20.8, 19.8


See pages 382 – 383 for spectra.

**Compound 201:**

![Compound 201](image)

**Compound 200** (39.5 mg, 0.113 mmol, 1.0 equiv.) was dried in vacuo for 30 minutes, dissolved in anhydrous THF (8.0 mL), and cooled to −78 °C. Triethylamine (30 µL, 0.225 mmol, 2.0 equiv.) was added to the reaction mixture, followed by LHMDS solution (1.0 M, 135 µL, 1.2 equiv.). Stirring was continued for 20 minutes, after which time the reaction was warmed to 12 °C. After 15 minutes the septum was removed and solid ferrocenium hexafluorophosphate (28.0 mg, 0.0845 mmol, 0.75 equiv.) was added rapidly, after which the septum was replaced. The reaction was vigorously stirred for approximately 5 minutes, until the reaction was yellow and all the ferrocenium salt was consumed. After this time, the reaction was diluted with 3:1 hexane:EtOAc (15 mL) and filtered through a short plug of silica gel. The solvent was removed in vacuo to give 54.8 mg of the crude reaction mixture ($dr = 4.5:1$). (See attached $^1$H NMR spectra of purified
This compounds was quite unstable and was reacted immediately after preparation. Thus, the crude mixture was dissolved in benzoyl chloride (200 mL) and stirred at 70 °C for 4 hours. The reaction was then cooled to ambient temperature, diluted with dichloromethane (10 mL) and washed with 2 N NaOH (3 x 10 mL), water (10 mL), then brine (10 mL). The organic layer was dried (MgSO₄) and the solvent removed in vacuo.

The crude reaction mixture was then subjected to preparative TLC purification (silica gel, dichloromethane), which gave pure annulation product 201 (5.6 mg, 27% yield brsm) and recovered 200 (23.7 mg). At this point, the two diastereomers were also successfully separated (3.9 mg major, 1.7 mg minor). Pyrrole 201 was a stable compound unlike its precursor.

**Ketorolac (95):**

The major diastereomer of 201 (3.9 mg, 0.00860 mmol, 1.0 equiv.) was dissolved in DME (35 µL) and cooled to –10 °C. Isobutylene (2.7 µL, 0.0258 mmol, 3.0 equiv.) was then added to the reaction mixture, followed by a 30% hydrogen peroxide solution (1.9 µL, 0.0172 mmol, 2.0 equiv.) then a 40% TBAH solution (11.2 µL, 0.0172 mmol, 2.0 equiv.). Stirring was continued at –10 °C for three hours then quenched with four drops of 1.5 M Na₂SO₃, followed by stirring for one hour. The reaction was then acidified with 1 N HCl (5 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried (MgSO₄), and the solvent removed in vacuo. **Ketorolac (95)** was isolated by preparative TLC (silica gel, EtOAc) to give material (1.2 mg, 58%) that was
spectroscopically identical with an authentic sample. The ee (90%) was determined by HPLC analysis (chiralpak AD, hexane:isopropanol:trifluoroacetic acid = 90:10:0.1 v/v%, 310 nm, 0.8 mL/min); retention times of enantiomers: 12.6 min (R-isomer) and 13.9 min (S-isomer).

**Physical State:** off-white solid  
**mp:** >250 °C

**Rr:** 0.17 (EtOAc)

**IR (film)** ν<sub>max</sub>: 2917, 2848, 1735, 1713, 1596, 1467, 1431, 1403, 1270, 1205 cm<sup>-1</sup>

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.79 (d, J = 7.2 Hz, 2 H), 7.51 (t, J = 7.2 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 6.81 (d, J = 4 Hz, 1 H), 6.13 (d, J = 4 Hz, 1 H), 4.53-4.58 (m, 1 H), 4.43-4.48 (m, 1 H), 4.08-4.12 (m, 1 H), 2.79-2.92 (m, 2 H), Acid proton not observed.

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ 186.0, 176.6, 142.4, 140.0, 132.3, 129.8 (2 Carbons), 129.0 (2 Carbons), 128.2, 125.9, 104.2, 48.4, 43.1, 31.9

**HRMS (ESI):** calc’d for C<sub>15</sub>H<sub>14</sub>NO<sub>3</sub> [M + H<sup>+</sup>]: 256.0968, found 256.0975.

See pages 290 – 291 for spectra.

**Compounds 98 and 99:**

To a flame dried flask under nitrogen was added indole (500 mg, 4.27 mmol, 1.0 equiv.) and THF (4.2 mL, 1.0 M). The solution was cooled to –78 °C and LHMDS (1.0 M solution, 6.5 mL, 6.5 mmol, 1.5 equiv.) was added drop-wise. The reaction was stirred at –78 °C for 30 minutes. After 30 minutes, the flask was quickly opened and solid copper(II)2-ethylhexanoate (1.12 g, 3.2 mmol, 0.75 equiv.) was rapidly added in one
portion and the flask resealed (rapid stirring is essential). The reaction mixture was stirred for five minutes at –78 °C then warmed to ambient temperature, at which point it was immediately poured into 1 N HCl (100 mL) and extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with 1 N HCl (75 mL), 1 N NaOH (75 mL), brine (75 mL) and dried Na2SO4. LCMS analysis of the crude reaction mixture indicated the presence of only three compounds: indole, compound 98, and compound 99. Flash column chromatography (silica gel, gradient from 2:1 hexanes:ether to 2:1 ether:hexanes) provided recovered indole (250 mg) as a white solid, followed by compound 98 (ca 100 mg), and finally compound 99 (ca 100 mg). PTLC of compound 98 (silica gel, DCM) provided an analytically pure sample that rapidly darkens. PTLC of compound 99 (Et2O) provided an analytically pure sample that darkens upon standing. Recrystallization from chloroform provided crystals suitable for X-ray analysis.

**Compound 98:**

![Chemical Structure of Compound 98](image)

**Physical State:** yellow oil

**Rf:** 0.31 (silica gel, 2:1:1 hexane:Et2O:DCM)

**IR (film) νmax:** 3400, 1455, 1407, 1336, 1246, 1092, 1011 cm⁻¹

**¹H NMR (600 MHz, CDCl₃):** δ 8.44 (bs, 1 H, D₂O Exchangeable), 8.14 (bs, 1 H, D₂O Exchangeable), 8.05 (bs, 1 H, D₂O Exchangeable), 7.76 (d, J = 7.8 Hz, 1 H),
7.60 (d, J = 7.2 Hz, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.42 (d, J = 7.8 Hz, 1 H), 7.37 – 7.38 (m, 2 H), 7.09 – 7.23 (m, 7 H), 6.96 – 6.99 (m, 1 H)

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 137.2, 136.7, 131.3, 128.2, 126.7, 125.1, 124.2, 123.4, 122.7, 122.0, 121.4, 120.6, 120.3, 112.3, 111.8, 111.6, 111.4, 110.1, 97.0 (5 C’s not observed, quaternary carbons).

HRMS (ESI): calcd. for C$_{24}$H$_{18}$N$_3$ [M + H$^+$] 348.1495, found 348.1487

See pages 292 – 293 for spectra.

**Compound 99:**

![Compound 99](image)

**Physical State:** clear cubes  
**mp:** 234 – 235 °C (CDCl$_3$)

**R$_f$:** 0.10 (silica gel, 2:1:1 hexane:Et$_2$O:DCM)

**IR (film) $\nu_{\text{max}}$:** 3406, 1545, 1455, 1420, 1336, 1247, 1097, 1011 cm$^{-1}$

$^1$H NMR (600 MHz, acetone-$d_6$): $\delta$ 10.56 (bs, 1 H, D$_2$O Exchangeable), 10.25 (bs, 2 H, D$_2$O Exchangeable), 9.03 (d, J = 7.8 Hz, 1 H), 7.82 – 7.84 (m, 2 H), 7.73 (d, J = 7.8 Hz, 1 H), 7.40 – 7.48 (m, 4 H), 7.27 – 7.35 (m, 6 H), 7.06 – 7.11 (m, 3 H), 6.90 – 6.93 (m, 2 H)

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 179.0, 156.3, 148.0, 138.1 (2 carbons), 137.1, 131.9 (2 carbons), 128.2, 127.7, 127.1, 126.0 (2 carbons), 125.0, 124.4, 123.9, 123.3,
122.1 (2 carbons), 121.8 (3 carbons), 120.6, 119.4 (2 carbons), 116.5, 112.4 (2 carbons), 112.2 (2 carbons), 111.8, 62.5

**HRMS (ESI):** calcd. for C_{32}H_{23}N_{4}O [M + H^+] 463.1917, found 463.1915

Structure verified by X-ray crystallographic analysis

See pages 294 – 295 for spectra.

**Compound 108:**

Carvone (944 mg, 6.28 mmol, 1.2 equiv.) was azeotroped. The flask was cooled to –78 °C, LDA (62.8 mL, 6.28 mmol, 1.2 equiv., 0.1 M in THF) was added, and the reaction was stirred for 30 minutes. MOM-protected isatin (107, 1.00 g, 5.24 mmol, 1.0 equiv.) was added to the carvone enolate as a solution in a minimal amount of THF. The reaction was allowed to stir at –78 °C for 15 minutes, then warmed to ambient temperature for 15 minutes. The reaction was quenched with glacial acetic acid (5.0 mL) then water (50 mL). The aqueous layer was extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with saturated NaHCO₃ (100 mL) and brine (100 mL), dried (MgSO₄), and the solvent removed in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel, gradient from 6:1 to 2:1 hexane:EtOAc) to give **compound 108** (1.65 g, 92%) as an inseparable mixture of 4 diastereomers.
Physical State: yellow oil

Rf: 0.12 (silica gel, 4:1 hexane:EtOAc)

[α]D: + 8.2 (DCM, c 0.72)

IR (film) νmax: 3354, 2920, 1736, 1641, 1613, 1469, 1365, 1186, 1090 cm⁻¹

¹H NMR (600 MHz, CDCl₃): δ 7.30 (dt, J = 7.8, 1.2 Hz, 1 H), 7.13 (d, J = 7.2 Hz, 1 H), 7.02 (t, J = 8.4 Hz, 1 H), 6.98 (d, J = 7.8 Hz, 1 H), 6.76 (bs, 1 H), 6.36 (s, 1 H), 5.08 (d, J = 10.8 Hz, 1 H), 4.86 (d, J = 10.8 Hz, 1 H), 4.53 (s, 1 H), 4.20 (s, 1 H), 3.34 – 3.38 (m, 2 H), 3.36 (s, 3 H), 2.40 – 2.49 (m, 2 H), 1.86 (s, 3 H), 1.64 (s, 3 H)

¹³C NMR (150 MHz, CDCl₃): δ 204.0, 175.9, 147.3, 145.4, 143.8, 136.7, 130.9, 129.6, 125.1, 124.1, 115.6, 110.9, 79.2, 72.8, 57.4, 52.9, 46.4, 31.5, 19.8, 16.8

HRMS (ESI): calcd. for C₂₀H₂₄NO₄ [M + H⁺] 342.1700, found 342.1693

See pages 303 – 304 for spectra.

Compounds 109 and 110:

Compound 108 (117 mg, 0.342 mmol, 1.0 equiv.) was dissolved in thionyl chloride (1.37 mL, 0.25 M) at ambient temperature and stirred for 100 minutes. The thionyl chloride was removed in vacuo and the crude reaction mixture purified by flash column chromatography (silica gel, gradient from 4:1 to 2:1 hexane:EtOAc) to give compounds 109 (49.5 mg, 44%) and 110 (42.7 mg, 37%).
Compound 109:

\[
\begin{align*}
\text{Physical State: clear cubes} & \quad \text{mp: } 178 – 179 \degree C \\
R_f: & \quad 0.13 \text{ (silica gel, 4:1 hexane:EtOAc)} \\
[\alpha]_D: & \quad +120 \text{ (DCM, } c \ 0.29) \\
\text{IR (film) } \nu_{\max}: & \quad 3428, 2966, 1726, 1677, 1618, 1468, 1353, 1189, 1148, 1045, 1002 \ \text{cm}^{-1} \\
\text{H NMR (600 MHz, CDCl}_3\text{:} & \quad \delta 7.31 \ (t, J = 7.8 \text{ Hz, } 1 \text{ H}), 7.22 \ (d, J = 7.8 \text{ Hz, } 1 \text{ H}), 7.05 – 7.08 \ (m, 2 \text{ H}), 6.72 \ (d, J = 5.4 \text{ Hz, } 1 \text{ H}), 5.39 \ (dd, J = 10.8, 6.0 \text{ Hz, } 1 \text{ H}), 5.13 \ (t, J = 9.0 \text{ Hz, } 1 \text{ H}), 3.29 – 3.34 \ (m, 2 \text{ H}), 2.80 \ (dd, J = 9.0, 6.6 \text{ Hz, } 1 \text{ H}), 2.50 – 2.53 \ (m, 1 \text{ H}), 2.30 – 2.34 \ (m, 1 \text{ H}), 1.70 \ (s, 3 \text{ H}), 1.50 \ (s, 3 \text{ H}), 1.40 \ (s, 3 \text{ H}) \\
\text{C NMR (150 MHz, CDCl}_3\text{:} & \quad \delta 198.0, 177.2, 145.0, 143.1, 137.2, 130.9, 129.3, 124.3, 124.1, 110.7, 84.2, 82.4, 64.9, 62.5, 50.9, 28.9, 28.8, 25.7, 16.1 \\
\text{HRMS (ESI):} & \quad \text{calcd. for C}_{19}\text{H}_{21}\text{NNaO}_4 \ [\text{M + Na}^+] \ 350.1363, \text{ found } 350.1363 \\
\text{See pages 305 – 306 for spectra.}
\end{align*}
\]
Compound 110:

Physical State: clear cubes  mp: 166 – 168 °C

Rf: 0.34 (silica gel, 4:1 hexanes:EtOAc)

[α]D: +38 (DCM, c 0.26)

IR (film) νmax: 2960, 1734, 1686, 1468, 1351, 1186, 1095, 1034 cm⁻¹

¹H NMR (600 MHz, CDCl₃): δ 7.30 (dt, J = 7.8, 1.2 Hz, 1 H), 7.22 (d, J = 7.2 Hz, 1 H), 7.04 – 7.08 (m, 2 H), 6.73 (dd, J = 5.4, 1.2 Hz, 1 H), 5.16 (d, J = 11.4 Hz, 1 H), 5.05 (d, J = 10.8 Hz, 1 H), 3.44 (s, 3 H), 3.38 (dd, J = 11.4, 4.2 Hz, 1 H), 2.53 (dtd, J = 16.8, 4.8, 1.2 Hz, 1 H), 2.31 – 2.36 (m, 2 H), 1.71 (d, J = 0.6 Hz, 3 H), 1.50 (s, 3 H), 1.40 (s, 3 H)

¹³C NMR (150 MHz, CDCl₃): δ 196.5, 176.9, 144.0, 143.0, 136.5, 130.3, 128.4, 123.5, 123.4, 110.2, 83.4, 81.5, 71.9, 61.0, 56.6, 50.1, 28.2, 28.1, 25.0, 15.4

HRMS (ESI): calcd. for C₂₀H₂₄NO₄ [M + H⁺] 342.1700, found 342.1695

See pages 307 – 308 for spectra.

Structure verified by X-ray crystallography.
Compound 111:

**Compound 108** (125.0 mg, 0.366 mmol, 1.0 equiv.) was dissolved in benzene (3.66 mL, 0.1 M). Burgess reagent (174.5 mg, 0.732 mmol, 2.0 equiv.) was added at ambient temperature. The reaction was then heated to 50 °C for three hours, after which time the reaction was cooled back to ambient temperature and the solvent removed in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel, gradient from 6:1 to 4:1 hexane:EtOAc) to give compound 111 (14.4 mg, 12%).

**Physical State:** yellow oil

**Rf:** 0.34 (silica gel, 4:1 hexane:EtOAc)

**[α]D:** + 10.4 (DCM, c 0.52)

**IR (film) νmax:** 3370, 2941, 1702, 1612, 1485, 1468, 1348, 1239, 1190, 1090 cm⁻¹

**¹H NMR (600 MHz, CDCl₃):** δ 7.70 (d, J = 8.4 Hz, 1 H), 7.28 (t, J = 7.8 Hz, 1 H), 6.97 – 6.99 (m, 2 H), 6.74 (s, 1 H), 5.92 (s, 1 H), 5.18 (d, J = 10.8 Hz, 1 H), 5.14 (d, J = 10.8 Hz, 1 H), 4.92 (s, 1 H), 4.76 (s, 1 H), 3.34 (s, 3 H), 2.76 (m, 2 H), 1.92 (s, 3 H), 1.77 (s, 3 H)

**¹³C NMR (150 MHz, CDCl₃):** δ 193.3, 169.9, 152.3, 144.4, 143.7, 142.5, 138.6, 131.4, 126.9, 126.0, 123.6, 121.4, 113.9, 110.1, 72.0, 57.2, 44.4, 32.3, 22.6, 16.8

**HRMS (ESI):** calcd. for C₂₀H₂₂NO₃ [M + H⁺] 324.1594, found 324.1586
See pages 309 – 310 for spectra.

**Compound 115a (upper diastereomer, unassigned):**

![Chemical Structure](image)

**Physical State:** colorless oil

**Rf:** 0.36 (silica gel, 1:1 hexane:Et₂O)

**[α]D:** + 120 (DCM, c 0.31)

**IR (film) νmax:** 1721, 1607, 1480, 1466, 1350, 1088 cm⁻¹

**¹H NMR (600 MHz, CDCl₃):** δ 7.24 (t, J = 7.8 Hz, 1 H), 6.98 – 7.02 (m, 3 H), 6.75 (d, J = 5.8 Hz, 1 H), 5.12 (d, J = 10.9 Hz, 1 H), 5.01 (d, J = 10.9 Hz, 1 H), 4.62 (bs, 1 H), 4.42 (bs, 1 H), 4.24 (bs, 1 H), 3.39 (s, 3 H), 3.33 (dd, J = 13.5, 1.6 Hz, 1 H), 3.11 (bs, 1 H), 2.49 – 2.55 (m, 1 H), 2.28 (dt, J = 18.6, 4.6 Hz, 1 H), 1.79 (s, 3 H), 1.67 (s, 3 H)

**¹³C NMR (150 MHz, CDCl₃):** δ 198.3, 178.2, 144.4, 144.0, 143.2, 134.9, 127.7 (2 carbons), 123.2, 122.2, 114.8, 109.3, 71.7, 56.4, 51.0, 46.4, 44.1, 31.5, 18.5, 16.1

**HRMS (ESI):** calcd. for C₂₀H₂₃NO₃Na [M + Na⁺] 348.1570, found 348.1565

See pages 311 – 312 for spectra.
Compound 115b (lower diastereomer, unassigned):

Physical State: colorless needles  mp: 115 – 118 °C

Rf: 0.30 (silica gel, 1:1 hexane:Et₂O)

[α]D: –237 (DCM, c 0.31)

IR (film) ν\text{max}: 1717, 1670, 1540, 1488, 1351, 1090 cm\(^{-1}\)

\(^1\)H NMR (600 MHz, CDCl\(_3\)): δ 7.25 (t, \(J = 7.7\) Hz, 1 H), 7.19 (d, \(J = 7.4\) Hz, 1 H), 7.13 (d, \(J = 7.8\) Hz, 1 H), 6.98 (t, \(J = 7.5\) Hz, 1 H), 6.71 (d, \(J = 5.9\) Hz, 1 H), 5.21 (s, 2 H), 5.11 (s, 1 H), 4.98 (s, 1 H), 3.53 (s, 1 H), 5.50 (dd, \(J = 13.9, 2.7\) Hz, 1 H), 3.44 (s, 3 H), 3.29 (ddd, \(J = 13.9, 11.3, 4.5\) Hz, 1 H), 2.56 – 2.63 (m, 1 H), 2.42 (dt, \(J = 18.4, 5.0\) Hz, 1 H), 1.86 (s, 3 H), 1.62 (s, 3 H)

\(^13\)C NMR (150 MHz, CDCl\(_3\)): δ 196.9, 178.3, 144.9, 143.7, 143.6, 135.3, 127.8, 127.1, 123.3, 122.3, 115.0, 109.5, 71.7, 56.4, 52.5, 47.5, 44.1, 31.7, 18.2, 15.7

HRMS (ESI): calcd. for C\(_{20}\)H\(_{23}\)NO\(_3\)Na [M + Na\(^+\)] 348.1570, found 348.1566

See pages 313 – 314 for spectra.
Compound 105:

Compound 28 (100 mg, 0.377 mmol, 1.0 equiv.) was azeotroped and cooled to –78 °C. A solution of LHMDS (5.65 mL, 0.565 mmol, 1.5 equiv., 0.1 M in THF) was then added to the flask over the course of one minute at –78 °C. After 20 minutes, a solution of L-Selectride (396 µL, 0.396 mmol, 1.05 equiv., 1.0 M) was added and stirring continued for an additional hour. Acetaldehyde (140 µL, 2.26 mmol, 6.0 equiv.) was then added and stirred for 15 minutes at that temperature. After this time, a solution of H₂O₂ (1.3 mL, 35 wt.%) and 2 N NaOH (1.8 mL) was added drop-wise to the reaction which was then allowed to warm to ambient temperature and stir vigorously for 12 hours. The reaction was extracted with EtOAc (3 x 3.0 mL). The combined organic extracts were washed with water (2 x 4.0 mL), 5 % NaHSO₄ (4.0 mL), brine (4.0 mL), and dried (MgSO₄). The solvent was then removed in vacuo and the crude residue was azeotroped. The residue was then dissolved in CHCl₃ (3.8 mL, 0.1 M) and Martin’s Sulfurane (280 mg, 0.415 mmol, 1.1 equiv.) was added. After ten minutes, the solvent was removed in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel, gradient from 5:1 to 2:1 hexane:EtOAc) to give compound 105 (83 mg, 75% over 2 steps).

Physical State: clear cubes     mp: 178 – 179 °C (DCM)

Rₜ: 0.36 (silica gel, DCM)
$[\alpha]_D: + 119$ (DCM, c 1.3)

**IR (film) $\nu_{max}$:** 3369, 2928, 1702, 1458, 1371, 1099 cm$^{-1}$

**$^1$H NMR (500 MHz, CDCl$_3$):** δ 8.05 (bs, 1 H, D$_2$O exchangeable), 7.33 (d, $J = 8.0$ Hz, 1 H), 7.29 (d, $J = 8.0$ Hz, 1 H), 7.13 (t, $J = 8.0$ Hz, 1 H), 7.05 (t, $J = 8.0$ Hz, 1 H), 6.89 (d, $J = 2.5$ Hz, 1 H), 6.16 (dd, $J = 17.5, 11.0$ Hz, 1 H), 5.34 (d, $J = 11.0$ Hz, 1 H), 5.18 (d, $J = 17.5$ Hz, 1 H), 4.62 (s, 1 H), 4.54 (s, 1 H), 4.29 (d, $J = 12.5$ Hz, 1 H), 2.92 (td, $J = 12.0, 3.5$ Hz, 1 H), 2.19 (td, $J = 14.5, 2.5$ Hz, 2 H), 1.86 – 1.77 (m, 2 H), 1.54 (s, 3 H), 1.21 (s, 3 H)

**$^{13}$C NMR (125 MHz, CDCl$_3$):** δ 211.0, 147.0, 143.2, 136.2, 127.8, 123.4, 121.8, 119.4, 119.1, 116.3, 112.2, 111.9, 111.4, 53.6, 52.5, 48.9, 39.4, 28.8, 25.2, 18.6

**HRMS (ESI):** calcd. for C$_{20}$H$_{24}$NO [M + H$^+$] 294.1852, found 294.1850

See pages 299 – 300 for spectra.

**Compound 118:**

![Compound 118](image)

**Physical State:** clear oil

$R_f$: 0.25 (silica gel, 3:1 hexanes:EtOAc)

$[\alpha]_D$: + 20 (DCM, c 0.05)

**IR (film) $\nu_{max}$:** 3405, 2927, 1707, 1654, 1458, 1101 cm$^{-1}$

**$^1$H NMR (600 MHz, CDCl$_3$):** δ 8.01 (bs, 1 H, D$_2$O exchangeable), 7.39 (d, $J = 8.4$ Hz, 1 H), 7.32 (d, $J = 7.8$ Hz, 1 H), 7.14 (t, $J = 7.8$ Hz, 1 H), 7.05 (t, $J = 7.8$ Hz, 1
H), 6.95 (d, J = 2.4 Hz, 1 H), 4.60 (s, 1 H), 4.53 (s, 1 H), 3.93 (d, J = 12.6 Hz, 1 H), 2.90 (dt, J = 12.6, 3.6 Hz, 1 H), 2.64 – 2.71 (m, 1 H), 2.21 – 2.25 (m, 1 H), 2.05 (dq, J = 13.2, 3.6 Hz, 1 H), 1.93 – 197 (m, 1 H), 1.56 – 1.64 (m, 1 H), 1.56 (s, 3 H), 1.05 (d, J = 6.0 Hz, 3 H)

13C NMR (150 MHz, CDCl3): δ 210.8, 146.7, 136.2, 127.6, 123.2, 121.8, 119.4, 119.3, 112.2, 111.9, 111.3, 54.1, 52.5, 45.5, 35.8, 32.4, 18.7, 15.0

HRMS (ESI): calcd. for C18H22NO [M + H+] 268.1696, found 268.1694

See pages 317 – 318 for spectra.

Hapalindole Q (103) and ent-12-epi-hapalindole D (117):

Ammonium acetate (606 mg, 7.87 mmol, 40 equiv.) and NaCNBH3 (124 mg, 1.97 mmol, 10 equiv.) were dissolved in MeOH (1.97 mL, 0.01 M). Compound 105 (57.7 mg, 0.20 mmol, 1.0 equiv.) was dissolved in THF (390 µL, 0.5 M), added to the methanol solution, stirred for seven days at room temperature, then quenched with 5% NaHCO3 (3.0 mL) and extracted with Et2O (3 x 5.0 mL). The organic extracts were washed with 1 N HCl (5.0 mL) and the aqueous layer was brought to above pH 8.0 with 2 N NaOH (10 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), which were subsequently washed with brine (20 mL), dried (MgSO4), and the solvent removed in vacuo to give the crude amine (35.2 mg, 61%, dr = 3:1) and recovered compound 105 (5.0 mg). The amine (9.0 mg, 0.031 mmol, 1.0 equiv.) was then dissolved in DCM (0.5 mL) and thioacyonimidazole (6.0 mg, 0.034 mmol, 1.1 equiv.) was added. The solution was allowed to stir at ambient temperature for 4 hours to afford, after flash column chromatography (silica gel, 3:2 hexane:DCM), hapalindole Q (103, 6.5 mg, 63%) and
11-epi-hapalindole Q (117, 2.0 mg, 19%). Performing the same scale reductive amination in a Biotage/Personal Chemistry microwave at 150 ºC for two minutes provided a similar yield but with a $dr = 6:1$.

**Hapalindole Q (103):**

![Hapalindole Q (103) structure]

**Physical State:** clear oil

$R_f$: 0.29 (silica gel, 3:2 hexane:DCM)

$[\alpha]_D$: +28 (DCM, c 1.2)

**IR (film)** $\nu_{\text{max}}$: 3423, 2931, 2095, 1458, 1334, 1096 cm$^{-1}$

**$^1$H NMR (500 MHz, CDCl$_3$):** $\delta$ 8.00 (bs, 1 H, D$_2$O exchangeable), 7.65 (d, $J = 8.0$ Hz, 1 H), 7.35 (d, $J = 8.0$ Hz, 1 H), 7.18 (t, $J = 8.0$ Hz, 1 H), 7.11 (t, $J = 8.0$ Hz, 1 H), 7.00 (d, $J = 2.0$ Hz, 1 H), 6.23 (dd, $J = 17.5$, 11.0 Hz, 1 H), 5.38 (d, $J = 11.0$ Hz, 1 H), 5.28 (d, $J = 17.5$ Hz, 1 H), 4.52 (bs, 1 H), 4.46 (s, 1 H), 3.88 (vbs, 1 H), 3.14 (bs, 1 H), 2.76 (vbs, 1 H), 2.00 (dt, $J = 14.0$, 2.0 Hz, 1 H), 1.82 (qd, $J = 13.0$, 2.0 Hz, 1 H), 1.63 – 1.47 (m, 2 H), 1.47 (s, 3 H), 1.24 (s, 3 H)

**$^{13}$C NMR (125 MHz, CDCl$_3$):** $\delta$ 147.3, 139.3, 131.5, 130.1, 127.1, 122.4, 122.3, 119.9, 119.7, 116.8, 112.3, 112.1, 111.9, 50.3, 42.6, 36.8, 30.2, 27.8, 25.7, 19.4, 14.6

**HRMS (ESI):** calcd. for $C_{21}H_{25}N_2S$ [M + H$^+$] 337.1733, found 337.1732

See pages 296 – 297 for spectra.
Ent-12-epi-hapalindole D (117):

Physical State: clear oil

Rf: 0.37 (silica gel, 3:2 hexane:DCM)

[α]D: – 111 (DCM, c 0.2)

IR (film) \( \nu_{\text{max}} \): 3415, 2928, 2097, 1456, 1338, 1097 cm\(^{-1} \)

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 8.10 (bs, 1 H, D\(_2\)O exchangeable), 7.44 (d, \( J = 8.0 \) Hz, 1 H), 7.38 (d, \( J = 8.0 \) Hz, 1 H), 7.19 (t, \( J = 8.0 \) Hz, 1 H), 7.12 (t, \( J = 8.0 \) Hz, 1 H), 7.10 (d, \( J = 2.0 \) Hz, 1 H), 6.01 (dd, \( J = 18.0 \), 11.0 Hz, 1 H), 5.38 (d, \( J = 11.0 \) Hz, 1 H), 5.29 (dd, \( J = 18.0 \) Hz, 1 H), 4.80 (s, 1 H), 4.64 (s, 1 H), 3.95 (d, \( J = 2.0 \) Hz, 1 H), 3.51 (dd, \( J = 12.0 \), 2.0 Hz, 1 H), 2.84 – 2.80 (m, 1 H), 1.83 – 1.79 (m, 3 H), 1.71 – 1.67 (m, 1 H), 1.47 (s, 3 H), 1.16 (s, 3 H)

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 147.8, 143.0, 136.0, 126.9, 124.0, 122.2, 119.7, 117.8, 115.2, 114.7, 112.5, 111.6, 66.9, 43.9, 42.0, 37.9, 31.6, 28.9, 28.7, 18.9 (in accord with the literature spectrum, the isothiocyanate carbon is not visible)

HRMS (ESI): calcd. for C\(_{21}\)H\(_{25}\)N\(_2\)S [M + H\(^+\)] 337.1733, found 337.1725

See pages 315 – 316 for spectra.
Compound 106:

[Chemical Structure Image]

**Compound 105** (14.4 mg, 0.049 mmol, 1.0 equiv.) was dissolved in DCM (490 µL, 0.1 M) and cooled to 0 ºC. Trimethylsilyltrifluoromethanesulfonate (26.6 µL, 0.147 mmol, 3.0 equiv.) and MeOH (2.2 µL, 0.054 mmol, 1.15 equiv.) were added and the solution stirred at 0 ºC for one hour. The reaction was then quenched by the addition of 5% NaHCO₃ (2.0 mL) and diluted with EtOAc (4.0 mL). The organic layer was washed with water (2.0 mL) then brine (2.0 mL), dried (MgSO₄), and the solvent removed *in vacuo*. The crude reaction mixture was purified by flash column chromatography (silica gel, gradient from 3:1 hexane:DCM to DCM) to give **compound 106** (4.4 mg, 31%) and recovered **compound 105** (8.5 mg, 59%).

**Physical State:** white foam

**R_f:** 0.53 (silica gel, DCM)

**[α]D:** – 41 (DCM, c 1.4)

**IR (film) ν_max:** 3393, 2927, 2360, 1705, 1629, 1448, 1296 cm⁻¹

**¹H NMR (500 MHz, CDCl₃):** δ 7.88 (bs, 1 H, D₂O exchangeable), 7.71 (d, J = 8.0 Hz, 1 H), 7.13 – 7.05 (m, 2 H), 6.08 (dd, J = 17.4, 10.2 Hz, 1 H), 5.23 (d, J = 17.4 Hz, 1 H), 5.21 (d, J = 10.2 Hz, 1 H), 4.04 (d, J = 12.0 Hz, 1 H), 2.37 (td, J = 12.0, 2.4 Hz, 1 H), 2.30 (d, J = 13.8 Hz, 1 H), 1.97 (qd, J = 150
13.2, 4.2 Hz, 1 H), 1.78 (d, J = 12.6 Hz, 1 H), 1.70 (td, J = 13.2, 4.2 Hz, 1 H),
1.37 (s, 3 H), 1.26 (s, 3 H), 1.13 (s, 3 H)

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 211.2, 151.7, 143.5, 140.2, 124.9, 121.5, 120.7 (2
carbons), 115.7, 113.8, 111.9, 65.1, 53.2, 52.9, 41.7, 40.9, 25.7, 24.7, 22.7, 20.9

HRMS (ESI): calcd. for C$_{20}$H$_{24}$NO [M + H$^+$] 294.1852, found 294.1847

See pages 301 – 302 for spectra.

*Ent-12-epi-fischerindole U (104):*

Ammonium acetate (126 mg, 1.64 mmol, 40 equiv.), NaCNBH$_3$ (25.7 mg, 0.41 mmol, 10
equiv.), and compound 106 (12 mg, 0.041 mmol, 1.0 equiv.) were dissolved in MeOH
(1.64 mL, 0.025 M) and THF (330 μL, 0.1 M) and allowed to stir at ambient temperature
for 48 hours. After this time, the reaction was quenched with 5% NaHCO$_3$ (3.0 mL) and
extracted with Et$_2$O (3 x 5.0 mL). The combined organic extracts were dried (MgSO$_4$),
concentrated *in vacuo*, and purified by flash column chromatography (silica gel, DCM
then 1:1 DCM:acetone then 9:1 DCM:MeOH) to give pure amine (7.0 mg, 55%) and
recovered compound 106 (1.2 mg, 10%). The amine (7.0 mg, 0.024 mmol, 1.0 equiv.)
was then dissolved in DCM (0.24 mL, 0.1 M) and thiocarbonyldiimidazole (4.7 mg,
0.026 mmol, 1.1 equiv.) was added. The solution was allowed to stir at ambient
temperature for 4 hours to afford, after flash column chromatography (silica gel, 1:1 hexane:DCM), 12-epi-fischerindole U isothiocyanate (104, 4.8 mg, 60%).

Physical State: white foam

Rf: 0.32 (silica gel, 1:1 hexane:DCM)

[α]D: – 200 (DCM, c 0.02)

IR (film) υmax: 3401, 2958, 2100, 1638, 1448, 1363, 1248 cm⁻¹

¹H NMR (500 MHz, CD₂Cl₂): δ 8.02 (bs, 1 H, D₂O exchangeable), 7.43 (dd, J = 6.0, 1.5 Hz, 1 H), 7.34 (dd, J = 6.0, 1.5 Hz, 1 H), 7.11 – 7.05 (m, 2 H), 5.91 (dd, J = 17.5, 11.0 Hz, 1 H), 5.22 (d, J = 17.5 Hz, 1 H), 5.19 (d, J = 11.0 Hz, 1 H), 4.50 (d, J = 2.0 Hz, 1 H), 3.21 (dd, J = 10.5, 3.0 Hz, 1 H), 2.25 (td, J = 12.0, 3.0 Hz, 1 H), 1.95 – 1.93 (m, 1 H), 1.70 – 1.60 (m, 3 H), 1.40 (s, 3 H), 1.13 (s, 3 H), 1.04 (s, 3 H)

HRMS (ESI): calcd. for C₂₁H₂₅N₂S [M + H⁺] 337.1733, found 337.1732

See page 298 for spectrum.

Compound 123:

Copper(I) iodide (615 mg, 3.23 mmol, 1.0 equiv.) was suspended in dry THF (32.3 mL, 0.1 M) and cooled to –78 ºC. Phenylmagnesium bromide (1.18 mL, 3.55 mmol, 1.1 equiv., 3.0 M) was added to the cuprous iodide suspension and stirred for 30 minutes. After this time, the reaction was warmed to 0 ºC for 30 minutes, during which time a
color change was observed. The reaction was again cooled to −78 °C and carvone (500 µL, 3.23 mmol, 1.0 equiv.) was added drop-wise. The reaction was stirred for 30 minutes, then acetaldehyde (364 µL, 6.46 mmol, 2.0 equiv.) was added. The reaction was stirred for an additional 30 minutes, then warmed to ambient temperature and quenched with saturated NH₄Cl (50 mL). The mixture was extracted with EtOAc (2 x 75 mL). The combined organic extracts were washed with water (75 mL) and brine (75 mL), dried (MgSO₄), and the solvent removed in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel, gradient from 15:1 to 4:1 hexane:EtOAc) to give compound 123 (535 mg, 61%) as an inseparable mixture of diastereomers.

**Physical State:** clear oil

R₉: 0.20 (silica gel, 4:1 hexane:EtOAc)

[α]D: −19.3 (DCM, c 0.44)

IR (film) νmax: 3406, 2936, 1698, 1646, 1498, 1451, 1377, 1218, 1090 cm⁻¹

¹H NMR (600 MHz, CDCl₃): δ 7.27 (t, J = 7.2 Hz, 2 H), 7.22 (t, J = 7.2 Hz, 1 H), 7.13 (d, J = 7.2 Hz, 2 H), 4.90 (s, 1 H), 4.71 (s, 1 H), 3.63 – 3.66 (m, 1 H), 3.35 (dd, J = 9.6, 4.2 Hz, 1 H), 2.69 – 2.77 (m, 3 H), 2.54 (dd, J = 15.6, 6.6 Hz, 1 H), 2.22 – 2.26 (m, 1 H), 2.10 – 2.14 (m, 1 H), 1.70 (s, 3 H), 1.26 (d, J = 6.6 Hz, 3 H), 1.15 (s, 3 H)

¹³C NMR (150 MHz, CDCl₃): δ 218.7, 147.7, 141.7, 130.0 (2 carbons), 129.0 (2 carbons), 127.6, 112.8, 71.9, 56.7, 45.2, 44.4, 40.7, 31.8, 22.4, 19.7, 17.3

HRMS (ESI): calcd. for C₁₈H₂₅O₂ [M + H⁺] 273.1849, found 273.1849

See pages 323 – 324 for spectra.
Compound 124:

Trimethylaluminum (3.87 mL, 7.75 mmol, 1.2 equiv., 2.0 M solution) was dissolved in DCM (6.46 mL, 1.0 M) and cooled to 0 °C. Thiophenol (792 µL, 7.75 mmol, 1.2 equiv.) was added drop-wise and the mixture stirred for 20 minutes. The reaction was then cooled to −78 °C and more DCM (6.46 mL, 1.0 M) was added. Carvone (1.0 mL, 6.46 mmol, 1.0 equiv.) was then added drop-wise and stirred for 15 minutes. After this time, THF (32.3 mL, 0.2 M) was added and stirring continued for five minutes, after which time, acetaldehyde (438 µL, 7.75 mmol, 1.2 equiv.) was added slowly. Stirring was continued for an additional 20 minutes then the reaction was poured into water (50 mL) and diluted with DCM (50 mL). The organic layer was separated and washed with 1 N HCl (50 mL). Meanwhile, the aqueous layer from the reaction was extracted with EtOAc (2 x 50 mL). The organic layers were all recombined then washed with water (100 mL) and brine (100 mL), dried (MgSO₄), and the solvent removed in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel, gradient from 5:1 to 3:1 hexane:EtOAc) to give compound 124 (1.23 g, 62%).

Physical State: white solid  mp: 85 – 86 °C

Rₚ: 0.16 (silica gel, 4:1 hexane:EtOAc)

[α]ᵦ: + 7.2 (DCM, c 0.32)

IR (film) νₘₐₓ: 3422, 2938, 1707, 1646, 1583, 1438, 1378, 1215, 1068 cm⁻¹

¹H NMR (400 MHz, CDCl₃): δ 7.44 (td, J = 6.8, 1.6 Hz, 2 H), 7.27 – 7.34 (m, 3 H),
4.80 (d, \( J = 1.2 \) Hz, 1 H), 4.68 (s, 1 H), 4.43 (bt, \( J = 6.0 \) Hz, 1 H), 3.74 (dd, \( J = 7.6, 4.0 \) Hz, 1 H), 2.87 (bq, \( J = 6.0 \) Hz, 1 H), 2.64 (dd, \( J = 14.8, 8.4 \) Hz, 1 H), 2.59 (dd, \( J = 14.8, 6.0 \) Hz, 1 H), 2.11 (ddd, \( J = 14.4, 8.0, 3.6 \) Hz, 1 H), 1.97 – 2.05 (m, 2 H), 1.58 (s, 3 H), 1.32 (d, \( J = 6.4 \) Hz, 3 H), 1.24 (s, 3 H)

\[^{13}\text{C} \text{ NMR (100 MHz, CDCl}_3\):} \quad \delta 212.6, 146.2, 134.5, 132.6 (2 carbons), 129.2 (2 carbons), 127.6, 111.3, 70.6, 56.8, 52.2, 42.5, 40.0, 30.8, 21.1, 18.7, 15.1

\textbf{HRMS (ESI):} \quad \text{calcld. for } \text{C}_{18}\text{H}_{25}\text{O}_{2}\text{S }[\text{M} + \text{H}^+] \text{ 305.1570, found 305.1562}

See pages 325 – 326 for spectra.

\textbf{Compound 125:}

\[
\text{O} \quad \text{Me} \\
\text{PhS} \quad \text{Me}
\]

\textbf{Compound 124} (196 mg, 0.644 mmol, 1.0 equiv.) was dissolved in CCl\(_4\) (6.44 mL, 0.1 M) at ambient temperature. Martin sulfurane was then added until TLC showed that the reaction was complete. After complete consumption of the starting material, the reaction was diluted with DCM (25 mL), washed with 1 N NaOH (25 mL), water (25 mL), and brine (25 mL), dried (Na\(_2\)SO\(_4\)), and the solvent removed \textit{in vacuo}. The crude reaction mixture was purified by flash column chromatography (silica gel, 40:1 hexane:EtOAc) to give \textbf{compound 125} (168 mg, 91%).

\textbf{Physical State:} \text{yellow oil}

\textbf{R}_f: \text{0.63 (silica gel, 4:1 hexane:EtOAc)}

\(|\alpha|_D: +31.2 \text{ (DCM, } c 0.59)\)
IR (film) $\nu_{\text{max}}$: 2918, 1709, 1647, 1583, 1438, 1375, 1206, 1025 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.43 (dt, $J = 8.4$, 1.2 Hz, 2 H), 7.25 – 7.32 (m, 3 H), 6.01 (dd, $J = 17.6$, 10.8 Hz, 1 H), 5.21 (d, $J = 10.8$ Hz, 1 H), 5.03 (d, $J = 17.6$ Hz, 1 H), 4.75 (s, 1 H), 4.68 (s, 1 H), 3.76 (t, $J = 3.2$ Hz, 1 H), 3.01 (tt, $J = 11.6$, 4.0 Hz, 1 H), 2.65 (dd, $J = 14.4$, 12.0 Hz, 1 H), 2.45 (ddd, $J = 14.0$, 4.8, 1.6 Hz, 1 H), 2.11 (ddd, $J = 14.4$, 11.2, 3.2 Hz, 1 H), 1.89 (ddt, $J = 14.4$, 4.0, 2.0 Hz, 1 H), 1.61 (s, 3 H), 1.36 (s, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 210.5, 146.9, 142.5, 134.6, 132.7 (2 carbons), 129.1 (2 carbons), 127.5, 116.2, 110.3, 56.8, 55.9, 42.8, 40.1, 31.2, 21.9, 20.8

HRMS (ESI): calcd. for C$_{18}$H$_{23}$OS [M + H$^+$] 287.1464, found 287.1460

See pages 327 – 328 for spectra.

**Compound 126:**

**Compound 125** (41.1 mg, 0.144 mmol, 1.0 equiv.) and indium(III) hydroxide (1.2 mg, 0.0072 mmol, 0.05 equiv.) were dissolved in CHCl$_3$ (287 $\mu$L, 0.5 M). Chlorodimethylsilane (18.7 $\mu$L, 0.172 mmol, 1.2 equiv.) was added and the reaction stirred at ambient temperature for five hours. Upon completion of the reaction, it was poured into EtOAc (10 mL), washed with saturated NaHCO$_3$ (5.0 mL), dried (MgSO$_4$), and the solvent removed *in vacuo*. The crude reaction mixture was purified by flash column chromatography (silica gel, 1:1 hexane:DCM) to give **compound 126** (3.7 mg, 9%).
Physical State: amorphous solid

Rf: 0.59 (silica gel, 3:1 hexane:EtOAc)

$[\alpha]_D$: + 57.4 (DCM, c 0.35)

IR (film) $\nu_{\text{max}}$: 2971, 2927, 1638, 1583, 1479, 1438, 1382, 1210, 1118, 1068, 1025 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 – 7.44 (m, 2 H), 7.19 – 7.30 (m, 3 H), 6.11 (dd, $J = 17.6$, 10.8 Hz, 1 H), 5.15 (dd, $J = 12.4$, 1.2 Hz, 1 H), 5.11 (dd, $J = 5.6$, 1.2 Hz, 1 H), 3.93 (d, $J = 6.4$ Hz, 1 H), 3.67 (dd, $J = 12.0$, 6.4 Hz, 1 H), 2.16 – 2.22 (m, 1 H), 2.07 – 2.14 (m, 1 H), 1.95 (d, $J = 12.4$ Hz, 1 H), 1.87 – 1.89 (m, 1 H), 1.76 (ddd, $J = 14.4$, 12.0, 2.8 Hz, 1 H), 1.31 (s, 3 H), 1.18 (s, 3 H), 1.08 (s, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 145.6, 136.1, 132.0 (2 carbons), 129.0 (2 carbons), 126.9, 113.0, 84.8, 81.9, 51.0, 45.2, 42.5, 34.3, 32.4, 30.2, 23.1, 18.1

HRMS (ESI): calcd. for C$_{18}$H$_{25}$OS [M + H$^+$] 289.1621, found 289.1626

See pages 329 – 330 for spectra.

Compound 127:

Compound 125 (114.8 mg, 0.401 mmol, 1.0 equiv.) was dissolved in THF (4.0 mL, 0.1 M) and cooled to –78 ºC. L-Selectride (481 µL, 0.481 mmol, 1.2 equiv.) was added and the reaction stirred for 4.5 hours, after which time it was quenched with saturated NH$_4$Cl (1.0 mL), 1 N NaOH (1.0 mL), and H$_2$O$_2$ (35% w/v, 10 drops). Stirring was continued
for 18 hours, then the reaction was diluted with H₂O (5.0 mL) and extracted with EtOAc (3 x 7.0 mL). The combined organic extracts were washed with H₂O (10 mL) and brine (10 mL), dried (MgSO₄), and the solvent removed in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel, 9:1 hexane:EtOAc) to give compound 127 (84.3 mg, 73%).

**Physical State:** colorless oil

Rᵣ: 0.44 (silica gel, 3:1 hexane:EtOAc)

[α]D: –32.8 (DCM, c 1.67)

**IR (film)** νₘₐₓ: 3455, 3080, 2936, 1639, 1579, 1449, 1438, 1235, 1056 cm⁻¹

**¹H NMR (400 MHz, CDCl₃):** δ 7.43 – 7.46 (m, 2 H), 7.23 – 7.32 (m, 3 H), 5.84 (dd, J = 17.6, 10.8 Hz, 1 H), 5.26 (d, J = 10.8 Hz, 1 H), 5.21 (d, J = 17.6 Hz, 1 H), 4.81 (d, J = 1.2 Hz, 1 H), 4.65 (s, 1 H), 3.62 – 3.64 (bm, 1 H), 3.24 – 3.25 (bm, 1 H), 2.55 (bs, 1 H), 2.00 – 2.03 (bm, 3 H), 1.82 – 1.89 (m, 1 H), 1.73 – 1.79 (m, 1 H), 1.63 (s, 3 H), 1.22 (s, 3 H)

**¹³C NMR (150 MHz, CDCl₃):** δ 146.7, 145.6, 135.8, 132.7, 129.0 (2 carbons), 127.8 (2 carbons), 115.4, 110.5, 71.7 (2 carbons), 53.1, 47.0, 37.0, 31.1 (2 carbons), 22.2

**HRMS (ESI):** calcd. for C₁₈H₂₅OS [M + H⁺] 289.1621, found 289.1622

See pages 331 – 332 for spectra.
**Compound 129:**

![Compound 129](image)

A 12 L reaction vessel was placed in a 0 ºC ice bath open to the atmosphere and a mechanical stirrer was placed inside the flask. A 1 L addition funnel was clamped with its tip inside the opening of the flask. The flask was charged with carvone (1 kg, 6.66 mol, 1.0 equiv.), MeOH (6.0 L, 1.1 M), and H$_2$O$_2$ (1.92 L, 19.8 mol, 3.0 equiv.). The resulting solution was allowed to cool to below 10 ºC. Meanwhile, the addition funnel was charged with 6 N NaOH (550 mL, 3.3 mol, 0.5 equiv.). The NaOH solution was added drop-wise to the peroxide solution, while carefully monitoring the internal reaction temperature. The flow rate was adjusted so that the internal temperature did not rise above 10 ºC [Should care not be exercised in monitoring the temperature, an explosively exothermic reaction may be witnessed.] Total addition time was approximately 2.5 hours. The reaction was then diluted with water (8.0 L). The resulting mixture was then submitted to extractive work-up in portions (approximately 1-2 L per portion). Each batch was extracted with EtOAc (3 x 200% volume). The combined organic layers were washed with saturated Na$_2$S$_2$O$_3$ (until starch paper showed complete destruction of H$_2$O$_2$ in the organic layer) and brine (100% volume), dried (MgSO$_4$), and the solvent removed in vacuo to give compound **129** (961 g, 87%), which was identical to the commercially available material.
Titanium tetrachloride (540 µL, 4.95 mmol, 1.1 equiv.) was added to THF (15 mL, 0.3 M) at –78 ºC. This yellow, heterogeneous mixture was warmed to –20 ºC and a solution of LiCl (10 mL, 4.95 mmol, 1.1 equiv., 0.5 M in THF) was added slowly over the course of six minutes. After addition, the mixture was cooled back to –78 ºC and a solution of carvone oxide (129, 748 mg, 4.5 mmol, 1.0 equiv.) in THF (6 mL, 0.75 M) was added. The reaction was then warmed to –20 ºC and stirring continued. After six hours, the reaction was quenched by pouring into saturated NaHCO₃ (50 mL). The reaction was extracted with Et₂O (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄), and the solvent removed in vacuo to give compound 131 (811 mg, 89%), which was characterized as the crude material due to extreme instability, even upon storage in an inert atmosphere (turns from colorless to black).

**Physical State:** clear liquid

**Rf:** 0.27 (silica gel, 3:1 hexane:EtOAc)

**IR (film)** ν max: 3482, 2938, 1715, 1646, 1442, 1357, 1116, 1025 cm⁻¹

**¹H NMR (400 MHz, CDCl₃):** δ 4.82 (t, J = 1.6 Hz, 1 H), 4.80 (s, 1 H), 4.26 (t, J = 3.0 Hz, 1 H), 3.04 (t, J = 12.8 Hz, 1 H), 2.83 (tt, J = 12.7, 3.8 Hz, 1 H), 2.37 – 2.48 (m, 2 H), 2.03 (br, 1 H), 1.91 (dtd, J = 14.0, 3.6, 2.4 Hz, 1 H), 1.76 (s, 3 H), 1.67 (s, 3 H)

**¹³C NMR (100 MHz, CDCl₃):** δ 204.6, 145.5, 110.6, 70.3, 68.0, 41.1, 39.0, 32.9,
Carvone oxide (129, 166 mg, 1.0 mmol, 1.0 equiv.) was dissolved in DME (4 mL, 0.25 M) and cooled to −78 ºC. KHMDS (2.0 mL, 1.0 mmol, 1.0 equiv., 0.5 M in toluene) was then added and the reaction allowed to stir for 25 minutes. Meanwhile, acetic anhydride (280 µL, 3.0 mmol, 3.0 equiv.) was dissolved in DME (2.0 mL, 1.5 M) and cooled to −20 ºC. The enolate solution was then cannulated into the anhydride solution and allowed to continue stirring. After 30 minutes, the reaction was quenched by pouring into water (15 mL) and extracted with Et₂O (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), and the solvent removed in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel, gradient from 1:1 to 4:1 DCM:hexane) to give compound 132 (113 mg, 54%).

Physical State: colorless oil

Rᵣ: 0.51 (silica gel, 3:1 hexane:EtOAc)

[α]₀: −11.9 (DCM, c 0.72)

IR (film) ν_max: 3447, 2932, 1741, 1686, 1438, 1370, 1210, 1057 cm⁻¹

¹H NMR (400 MHz, CDCl₃): δ 5.34 (d, J = 2.0 Hz, 1 H), 4.73 (dd, J = 2.8, 1.2 Hz, 1
H), 4.70 (d, J = 0.8 Hz, 1 H), 3.31 (dd, J = 2.4, 1.2 Hz, 1 H), 2.90 (dd, J = 11.2, 7.2, 2.0 Hz, 1 H), 2.27 (ddd, J = 15.2, 7.2, 2.8 Hz, 1 H), 2.14 (s, 3 H), 1.66 (s, 3 H), 1.63 (ddd, J = 14.4, 11.2, 0.8 Hz, 1 H), 1.32 (s, 3 H)

$^{13}$C NMR (100 MHz, CDCl₃): δ 169.3, 146.4, 146.0, 119.8, 111.4, 61.2, 53.6, 38.0, 27.6, 20.5, 20.3, 17.1

HRMS (ESI): calcd. for C₁₂H₁₆NaO₃ [M + Na⁺] 231.0992, found 231.0990

See pages 335 – 336 for spectra.

Compound 133:

Carvone oxide (129, 1.24 g, 7.46 mmol, 1.0 equiv.) was dissolved in MeOH (5.74 mL, 1.3 M) and cooled to 0 ºC. Sodium acetate (1.35 g, 16.4 mmol, 2.2 equiv.) was then added, followed by hydroxylamine hydrochloride (570 mg, 8.21 mmol, 1.1 equiv.). The reaction was stirred for 100 minutes then diluted with EtOAc (50 mL). The organic layers were washed with water (25 mL) then brine (25 mL), dried (Na₂SO₄), and the solvent removed in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel, gradient from 10:1 to 5:1 hexane:EtOAc) to give compound 133 (920 mg, 68%).

Physical State: white solid  
mp: 64 – 65 ºC

Rf: 0.30 (silica gel, 4:1 hexane:EtOAc)

$[\alpha]_D$: – 2.1 (DCM, c 0.81)
**IR (film)** ν<sub>max</sub>: 3300, 2974, 2920, 1647, 1438, 1377, 1280, 1183, 1134, 1059 cm<sup>−1</sup>

**1H NMR (600 MHz, CDCl<sub>3</sub>):** δ 9.13 (bs, 1 H), 4.77 (s, 1 H), 4.74 (s, 1 H) 3.32 (d, J = 3.0 Hz, 1 H), 2.89 (dd, J = 18.6, 4.8 Hz, 1 H), 2.46 – 2.50 (m, 1 H), 2.24 (bd, J = 14.4 Hz, 1 H), 1.90 (dd, J = 18.0, 12.0 Hz, 1 H), 1.70 – 1.77 (m, 1 H), 1.72 (s, 3 H), 1.49 (s, 3 H)

**13C NMR (150 MHz, CDCl<sub>3</sub>):** δ 157.7, 148.1, 111.0, 61.8, 57.3, 34.2, 29.7, 27.9, 21.6, 19.4

**HRMS (ESI):** calcd. for C<sub>10</sub>H<sub>16</sub>NO<sub>2</sub> [M + H<sup>+</sup>] 182.1175, found 182.1173

See pages 337 – 338 for spectra.

**Compound 136:**

![Compound 136](image)

Magnesium turnings (14.6 g, 602 mmol, 10 equiv.) were flame dried in a round bottom flask equipped with a stir bar and addition funnel and allowed to cool under HIVAC. The magnesium turnings were then suspended in dry THF (120 mL) and the temperature of the flask controlled by an ambient-temperature water bath. Vinyl bromide solution (1.0 M, 120 mL, 2.0 equiv.) was added dropwise over the course of two hours. Meanwhile, a flame-dried flask was charged with THF (100 mL) and cooled to – 78 ºC. Hexamethyldisilazane (16.0 mL, 75.2 mmol, 1.25 equiv.) was added, followed by n-butyllithium solution (2.50 M, 28.9 mL, 1.2 equiv.). The resulting solution of LHMDS was then warmed to 0 ºC for 30 minutes and cooled back to – 78 ºC, at which point a solution
of carvone oxide (129, 10.0 g, 60.2 mmol, 1.0 equiv.) in THF (60.2 mL) was cannulated into the pre-cooled LHMDS solution. After stirring for 30 minutes, the enolate was warmed to – 15 ºC and the vinyl grignard solution was cannulated into the enolate solution. The reaction was stirred for an additional 15 minutes then quenched with saturated NH₄Cl (300 mL), which was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with saturated NaHCO₃ (200 mL), water (200 mL), then brine (200 mL), dried (MgSO₄), and the solvent removed in vacuo. The crude reaction was purified by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) to give compound 136 (3.51 g, 30%).

Physical State: yellow oil

Rₛ: 0.25 (silica gel, 3:1 hexane:EtOAc)

[α]D: nat: – 45.8 (DCM, c 3.32); ent: + 69.8 (DCM, c 0.56)

IR (film) νmax: 3453, 2936, 1702, 1640, 1373, 1107, 1054 cm⁻¹

¹H NMR (400 MHz, CDCl₃): δ 5.90 (dd, J = 17.6, 10.8 Hz, 1 H), 5.15 (d, J = 10.8 Hz, 1 H), 4.97 (d, J = 17.6 Hz, 1 H), 4.75 (s, 1 H), 4.71 (s, 1 H), 4.04 (dd, J = 5.6, 3.2 Hz, 1 H), 2.83 – 2.89 (m, 1 H), 2.57 (t, J = 14.0 Hz, 1 H), 2.32 – 2.37 (m, 1 H), 2.27 (d, J = 3.2 Hz, 1 H), 2.00 – 2.07 (m, 1 H), 1.91 – 1.96 (m, 1 H), 1.71 (s, 3 H), 1.21 (s, 3 H)

¹³C NMR (100 MHz, CDCl₃): δ 212.0, 147.2, 140.4, 116.5, 110.0, 76.5, 56.9, 43.2, 39.3, 33.5, 20.6, 19.4

HRMS (MALDI): calcd. For C₁₂H₁₇O₂ [M – H⁺] 193.1234, found 193.1232

See pages 339 – 340 for spectra.
Compound 120:

![Chemical Structure of Compound 120](attachment:compound_120_structure.png)

**Compound 136** (2.47 g, 12.7 mmol, 1.0 equiv.) was azeotroped. Meanwhile, in a flame-dried flask, triphenyl phosphine (3.33 g, 12.7 mmol, 1.0 equiv.) was dissolved in dry THF (50 mL). After dissolution, *N*-chlorosuccinimide (1.70 g, 12.7 mmol, 1.0 equiv.) was added and the solution and stirred for 30 minutes. Meanwhile, **compound 136** was dissolved in dry THF (50 mL) and added to the previously prepared mixture of triphenyl phosphine and NCS. The reaction was allowed to stir 18 hours at ambient temperature. The solvent was then removed *in vacuo* and the residue dissolved in DCM (200 mL), washed with water (3 × 150 mL), brine (150 mL), and dried (MgSO4). The solvent was removed *in vacuo* and the crude material purified by flash column chromatography (silica gel, 5:1 hexane:DCM) to give pure **compound 120** (1.49 g, 55%).

**Physical State:** yellow oil

**Rf:** 0.62 (silica gel, 1:1 hexane:DCM)

**[α]D:** nat. = + 45.6 (DCM, c 0.55), ent. = – 39.9 (DCM, c 0.67)

**IR (film) νmax:** 2977, 1716, 1647, 1450, 1374, 1294, 1226, 1113 cm⁻¹

**1H NMR (400 MHz, CDCl3):** δ 6.28 (dd, *J* = 17.6, 10.8 Hz, 1 H), 5.27 (d, *J* = 10.8 Hz, 1 H), 5.03 (d, *J* = 17.6 Hz, 1 H), 4.78 (s, 1 H), 4.72 (s, 1 H), 3.91 (dd, *J* = 12.4, 4.0 Hz, 1 H), 2.59 (t, *J* = 13.6 Hz, 1 H), 2.24 – 2.34 (m, 3 H), 2.10 – 2.16 (m, 1 H), 1.70 (s, 3 H), 1.32 (s, 3 H)

**13C NMR (100 MHz, CDCl3):** δ 207.3, 145.5, 136.6, 118.4, 110.8, 66.5, 57.9, 43.0,
LRMS (GC-MS): calcd. for C_{12}H_{18}ClO [M + H^+] 213, found 213

See pages 321 – 322 for spectra.

**Compound 119:**

Compound 60 (39.3 mg, 0.12 mmol) was dissolved in DCE (7.0 mL) and added to Montmorillonite K–10 (1.57 g, 40 wt. equiv.) in a microwave reactor vessel. The slurry was irradiated at 120 °C for six minutes then cooled to ambient temperature. The slurry was diluted with EtOAc and the clay filtered off. The clay was further washed with EtOAc. This filtration should be done as rapidly as possible after cooling the vessel as the compounds will adsorb onto the clay upon prolonged exposure. The combined organic washings were evaporated in vacuo and the crude reaction was purified by flash column chromatography (silica gel, gradient from 3:1 to 1:1 hexane:DCM) to give compound 119 (10.1 mg, 26%) plus recovered compound 60 (21.5 mg, 55%). The recovered compound 60 was then resubmitted to the same procedure. After recycling, the overall isolated yield of compound 119 was 40% plus recovered compound 60 (30%).

**Physical State:** light yellow foam
$R_f$: 0.56 (silica gel, DCM)

$[\alpha]_D$: nat. = $+179.2$ (DCM, c 0.13), ent. = $-109.4$ (DCM, c 0.31)

**IR (film)** $\nu_{\text{max}}$: 3395, 2959, 1718, 1655, 1448, 1297, 1052 cm$^{-1}$

**$^1H$ NMR (400 MHz, CDCl$_3$)**: $\delta$ 7.96 (bs, 1 H, D$_2$O exchangeable), 7.68 – 7.70 (m, 1 H), 7.26 – 7.28 (m, 1 H), 7.11 – 7.15 (m, 2 H), 6.47 (dd, $J = 17.6$, 10.8 Hz, 1 H), 5.38 (d, $J = 10.8$ Hz, 1 H), 5.30 (d, $J = 17.6$ Hz, 1 H), 4.10 (d, $J = 12.0$ Hz, 1 H), 4.05 (dd, $J = 11.2$, 5.2 Hz, 1 H), 2.24 – 2.41 (m, 3 H), 1.51 (s, 3 H), 1.40 (s, 3 H), 1.15 (s, 3 H)

**$^{13}C$ NMR (100 MHz, CDCl$_3$)**: $\delta$ 205.6, 150.8, 139.7, 137.5, 124.1, 121.3, 120.3, 120.1, 118.2, 112.5, 111.6, 68.0, 58.8, 53.5, 52.2, 41.2, 33.4, 25.0, 21.0, 20.3

**HRMS (ESI)**: calcd. For C$_{20}$H$_{23}$ClNO [M + H$^+$] 328.1463, found 328.1470

See pages 319 – 320 for spectra.

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**Compound 143:**

![Chemical Structure](image)

**Physical State:** beige foam

$R_f$: 0.21 (silica gel, 3:1 hexane:EtOAc)

$[\alpha]_D$: $+81.8$ (DCM, c 0.11)

**IR (film)** $\nu_{\text{max}}$: 2918, 1708, 1608, 1459, 1262 cm$^{-1}$
\textbf{\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3})}: \delta 7.03 (t, J = 7.5 Hz, 1 H), 6.83 (d, J = 7.2 Hz, 1 H), 6.68 (t, J = 7.5 Hz, 1 H), 6.65 (d, J = 7.8 Hz, 1 H), 6.33 (dd, J = 10.8, 17.4 Hz, 1 H), 5.31 (d, J = 10.8 Hz, 1 H), 5.11 (d, J = 17.4 Hz, 1 H), 4.85 (s, 1 H), 4.77 (s, 1 H), 4.09 (dd, J = 3.6, 11.4 Hz, 1 H), 3.97 (dd, J = 3.6, 7.8 Hz, 1 H), 3.83 (td, J = 5.4, 7.8 Hz, 1 H), 3.80 (vbs, 1 H), 2.80 (dd, J = 3.6, 12.0 Hz, 1 H), 2.42 (dd, J = 5.4, 13.8 Hz, 1 H), 2.34 (m, 3 H), 2.05 (dd, J = 8.1, 13.8 Hz, 1 H), 1.50 (s, 3 H)

\textbf{\textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3})}: \delta 207.0, 151.4, 146.1, 136.8, 128.0, 127.7, 126.4, 119.2, 118.5, 110.7, 109.0, 65.9, 60.2, 58.1, 50.7, 41.8, 39.0, 37.9, 35.6, 22.2

\textbf{HRMS (ESI)}: calcd. for C\textsubscript{20}H\textsubscript{23}NOCl [M + H\textsuperscript{+}] 328.1463, found 328.1467

See pages 343 – 344 for spectra.

\begin{center}
\textbf{Compound 144:}
\end{center}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

\textbf{Physical State}: beige foam

R\textsubscript{f}: 0.26 (silica gel, 3:1 hexane:EtOAc)

[\textbf{[a]}\textsubscript{D}]: – 91.7 (DCM, c 0.01)

\textbf{IR (film) }\nu_{\text{max}}: 2926, 1712, 1672, 1608, 1458, 1260, 1042 cm\textsuperscript{-1}

\textbf{\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3})}: \delta 7.02 (t, J = 7.2 Hz, 2 H), 6.72 (t, J = 7.2 Hz, 1 H), 6.67 (d, J = 7.8 Hz, 1 H), 6.36 (dd, J = 10.8, 17.4 Hz, 1 H), 5.26 (d, J = 10.8 Hz, 1 H)
H), 4.99 (d, J = 17.4 Hz, 1 H), 4.01 (m, 1 H), 3.94 (dd, J = 5.4, 7.2 Hz, 1 H), 3.85 (vbs, 1 H), 3.79 (dd, J = 4.2, 12.6 Hz, 1 H), 3.43 (m, 1 H), 3.20 (dd, J = 4.5, 14.1 Hz, 1 H), 2.65 (t, J = 13.8 Hz, 1 H), 2.29 (dd, J = 5.1, 17.7 Hz, 1 H), 2.12 (d, J = 16.8 Hz, 1 H), 1.72 (s, 3 H), 1.39 (s, 3 H)

$^{13}\text{C NMR (150 MHz, CDCl}_3\text{: } \delta 205.1, 149.7, 136.9, 134.6, 127.7, 127.6, 123.6, 122.7, 119.8, 118.7, 110.6, 65.5, 58.0, 57.1, 52.0, 36.7, 36.6, 34.3, 22.2, 20.0$

HRMS (ESI): calcd. for C$_{20}$H$_{23}$NOCl [M + H$^+$] 328.1463, found 328.1464

See pages 345 – 346 for spectra.

**Compound 145:**

![Chemical Structure](image)

**Physical State:** clear cubes  
**mp:** 128 – 129 °C

**R$_f$:** 0.20 (silica gel, 3:1 hexane:EtOAc)

**$[\alpha]_D$:** +52.0 (DCM, $c$ 0.25)

**IR (film) $\nu_{\text{max}}$:** 2921, 2854, 1712, 1604, 1460, 1228, 1029 cm$^{-1}$

$^1\text{H NMR (600 MHz, CDCl}_3\text{: } \delta 7.00 (t, J = 7.2 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 6.67 (t, J = 7.8 Hz, 1 H), 6.63 (d, J = 7.8 Hz, 1 H), 6.34 (dd, J = 18.0, 10.8 Hz, 1 H), 5.32 (d, J = 10.8 Hz, 1 H), 5.18 (bs, 1 H), 5.15 (d, J = 18.0 Hz, 1 H), 4.20 (bd, J = 7.2 Hz, 1 H), 4.00 – 4.03 (m, 2 H), 3.65 (bs, 1 H), 2.99 (dd, J = 12.0, 1.8 Hz, 1 H)
H, 2.52 – 2.54 (bm, 1 H), 2.34 (bt, \(J = 12.0\) Hz, 1 H), 2.02 (dd, \(J = 25.8, 13.2\) Hz, 1 H), 1.64 (s, 3 H), 1.50 (s, 3 H)

\(^{13}\text{C NMR (150 MHz, CDCl}_3\):} \(\delta\) 207.1, 151.4, 137.8, 136.9, 127.8, 127.7, 126.3, 126.1, 119.2, 118.6, 110.9, 66.6, 59.0, 58.0, 49.7, 39.8, 36.4, 36.0, 21.8, 20.7

HRMS (ESI): calcd. for C_{20}H_{23}NOCl [M + H\(^+\)] 328.1463, found 328.1467

See pages 347 – 348 for spectra.
Structure verified by X-ray crystallographic analysis.
Compound 119 (78.9 mg, 0.24 mmol, 1.0 equiv.) was dissolved in MeOH (2.41 mL, 0.1 M) and cooled to 0 °C. To this solution was added sodium borohydride (8.9 mg, 0.24 mmol, 1.0 equiv.) and stirring was continued for five minutes, after which time the reaction was quenched with saturated NH₄Cl (5.0 mL). The reaction was diluted with EtOAc (20 mL) and washed with water (10 mL) then brine (10 mL), dried (MgSO₄), and the solvent removed in vacuo. The crude 202 was sufficiently pure for further reaction (79.0 mg, 100%).

Physical State: white solid

Rf: 0.49 (silica gel, DCM)

[α]D: −21.2 (DCM, c 0.40)

IR (film) νmax: 3397, 2984, 2868, 1455, 1428, 1300, 1191, 1104 cm⁻¹

¹H NMR (400 MHz, CDCl₃): δ 7.84 (s, 1 H, D₂O Exchangeable), 7.78 (d, J = 6.4 Hz, 1 H), 7.31 (dd, J = 6.4, 1.6 Hz, 1 H), 7.06 – 7.14 (m, 2 H), 6.20 (dd, J = 17.2, 10.8 Hz, 1 H), 5.55 (d, J = 11.2 Hz, 1 H), 5.38 (dd, J = 17.2, 1.2 Hz, 1 H), 3.97 (dd, J = 11.2, 7.6 Hz, 1 H), 3.44 (t, J = 10.8 Hz, 1 H), 2.82 (t, J = 10.4 Hz, 1 H), 1.94 – 2.20 (m, 4 H), 1.50 (s, 3 H), 1.39 (s, 3 H), 1.10 (s, 3 H)

¹³C NMR (100 MHz, CDCl₃): δ 151.1, 139.4, 136.1, 124.1, 120.8, 120.4, 119.8, 111.3, 79.3, 67.8, 64.3, 57.7, 50.3, 46.5, 40.7, 32.0, 29.6, 25.1, 22.0, 20.3

HRMS (ESI): calcd. for C₂₀H₂₃ClNO [M – H⁺] 328.1474, found 328.1484

See pages 384 – 385 for spectra.
Compound 137:

**Compound 202** (17.1 mg, 0.052 mmol, 1.0 equiv.) was dissolved in pyridine (515 µL, 0.1 M) and freshly recrystallized methanesulfonic anhydride (18.0 mg, 0.103 mmol, 2.0 equiv.) was added. The reaction was heated to 65 ºC for 30 minutes then cooled to ambient temperature. The reaction was diluted with Et₂O (10 mL) and washed with 1 N HCl (2 x 10 mL), water (5.0 mL), and brine (5 mL), then dried (MgSO₄), and the solvent removed *in vacuo*. The crude reaction was purified by flash column chromatography (silica gel, gradient from 1:1 to 1:2 hexane:DCM), to give the **compound 137** (15.2 mg, 69%).

**Physical State:** yellow powder

**R_f:** 0.35 (silica gel, DCM)

**[α]_D:** – 32.9 (DCM, c 0.085)

**IR (film)** ν_max: 3394, 2919, 1654, 1560, 1458, 1342, 1242, 1175, 1067 cm⁻¹

**¹H NMR (600 MHz, CDCl₃):** δ 7.88 (bs, 1 H, D₂O exchangeable), 7.68 (d, J = 7.2 Hz, 1 H), 7.31 (dd, J = 8.4, 1.2 Hz, 1 H), 7.09 – 7.13 (m, 2 H), 6.12 (dd, J = 17.4, 11.4 Hz, 1 H), 5.48 (d, J = 17.4 Hz, 1 H), 5.46 (d, J = 11.4 Hz, 1 H), 4.51 (d, J = 11.4 Hz, 1 H), 3.97 (dd, J = 12.0, 4.8 Hz, 1 H), 3.42 (t, J = 10.2 Hz, 1 H), 3.10 (s, 3 H), 2.05 – 2.21 (m, 3 H), 1.57 (s, 3 H), 1.45 (s, 3 H), 0.99 (s, 3 H)
\(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta 152.3, 140.6, 135.1, 124.6, 121.7, 120.7, 120.0, 120.0, 115.2, 111.8, 90.3, 67.4, 57.7, 49.7, 45.2, 40.8, 39.2, 33.0, 25.6, 24.3, 21.6\)

HRMS (MALDI): calcd. for C\(_{21}\)H\(_{27}\)NO\(_3\)SCl \([M + H^+]\) 408.1395, found 408.1401

See pages 341 – 342 for spectra.

**Compound 203:**

![Chemical Structure of Compound 203]

**Compound 137** (134 mg, 0.328 mmol, 1.0 equiv.) was dissolved in DMF (10 mL, 0.03 M) and lithium azide solution (20% in water, 500 \(\mu\)L) was added. The reaction was warmed to 100 °C and heating continued for two days. After cooling to ambient temperature, the reaction was diluted with Et\(_2\)O (50 mL) and washed with water (3 x 25 mL) then brine (25 mL). The organic layer was dried (MgSO\(_4\)) and the solvent removed \textit{in vacuo}. The crude reaction mixture was purified by flash column chromatography (silica gel, gradient from 1:1 hexane:DCM to DCM), to give **compound 203** (64.7 mg, 58%).

**Physical State:** white powder

\(R_f\): 0.54 (silica gel, 3:1 hexane:EtOAc)

\([\alpha]_D\): + 14.4 (DCM, \(c\ 1.07\))

**IR (film) \(\nu_{max}\):** 2363, 2250, 1704, 1613, 1472, 1380, 1094 cm\(^{-1}\)
$^1$H NMR (600 MHz, CDCl$_3$): δ 7.85 (bs, 1 H, D$_2$O exchangeable), 7.44 (d, $J = 6.6$ Hz, 1 H), 7.31 (d, $J = 8.4$ Hz, 1 H), 7.08 – 7.12 (m, 2 H), 6.42 (dd, $J = 17.4$, 10.8 Hz, 1 H), 5.36 – 5.40 (m, 2 H), 4.96 (s, 1 H), 4.26 (dd, $J = 11.4$, 4.8 Hz, 1 H), 3.56 (dd, $J = 10.8$, 2.4 Hz, 1 H), 2.68 (dt, $J = 13.2$, 3.0 Hz, 1 H), 2.10 – 2.17 (m, 2 H), 1.51 (s, 3 H), 1.41 (s, 3 H), 1.11 (s, 3 H)

$^{13}$C APT NMR (150 MHz, CDCl$_3$): δ 151.5, 140.3, 139.7, 123.9, 121.2, 120.3, 118.5, 116.9, 115.9, 112.1, 71.2, 65.1, 54.3, 47.6, 44.0 (2 carbons), 40.7, 33.0, 26.2, 25.3

LRMS (GC-MS): calcd. for C$_{20}$H$_{24}$N$_4$Cl [M + H$^+$] 355, found 355

See pages 386 – 387 for spectra.

**Compound 138:**

![Compound 138](image)

**Compound 203** (47.4 mg, 0.133 mmol, 1.0 equiv.) was dissolved in EtOH (1.33 mL, 0.1 M) and sodium-mercury amalgam (266 mg, 1.33 mmol, 10 equiv.) was added. The reaction was heated to reflux for two hours then cooled to ambient temperature. The reaction was diluted with EtOAc (25 mL) and washed with water (3 x 15 mL) then brine (15 mL). The organic layer was dried (MgSO$_4$) and the solvent removed in vacuo. The
crude reaction was purified by flash column chromatography (silica gel, gradient from 5:1 to 3:1 hexane:EtOAc), to give **compound 138** (29.2 mg, 66%).

**Compound 146:**

![Diagram of compound 146]

The following compounds were added sequentially to a flask, maintained at ambient temperature, in the following order: **compound 138** (29.2 mg, 0.088 mmol, 1.0 equiv.), formic acid (3.6 μL, 0.097 mmol, 1.1 equiv.), 2-chloro-4,6-dimethoxy-1,3,5-triazine (18.6 mg, 0.106 mmol, 1.2 equiv.), DMAP (0.3 mg, 0.003 mmol, 0.03 equiv.), N-methylmorpholine (11.6 μL, 0.106 mmol, 1.2 equiv.), and DCM (232 μL, 0.38 M). The reaction was stirred for two hours at ambient temperature, after which time the reaction was diluted with DCM (25 mL) and washed with 1 N HCl (2 x 15 mL), saturated NaHCO₃ (15 mL), water (15 mL), and brine (15 mL). The organic layer was dried (MgSO₄) and evaporated *in vacuo*. The crude reaction was purified by flash column chromatography (silica gel, gradient from 3:1 to 1:1 hexane:EtOAc) to give **compound 146** (27.4 mg, 87%).
**ent-12-epi-Fischerindole G (11):**

[Chemical structure image]

**Compound 146** (1.8 mg, 0.0053 mmol, 1.0 equiv.) was dissolved in benzene (500 µL, 0.01 M) and Burgess reagent (5.0 mg, 0.021 mmol, 4.0 equiv.) was added at ambient temperature. Upon completion of the reaction, as determined by TLC, the solvent was removed *in vacuo* and the crude reaction purified by preparative thin layer chromatography (3:1 hexane:EtOAc), to give **ent-12-epi-fischerindole G (11)**, 1.4 mg, 82%.

**Physical State:** white powder

**Rf:** 0.48 (silica gel, 3:1 hexane:EtOAc)

**[α]D:** – 50.0 (DCM, c 0.02)

**IR (film) νmax:** 3302, 2954, 2123, 1716, 1668, 1456, 1364, 1127, 1065 cm⁻¹

**¹H NMR (500 MHz, CD₂Cl₂):** δ 8.05 (bs, 1 H, D₂O exchangeable), 7.41 (d, J = 7.5 Hz, 1 H), 7.05 – 7.12 (m, 2 H), 6.30 (dd, J = 18.0, 11.0 Hz, 1 H), 5.33 – 5.40 (m, 2 H), 4.53 (d, J = 3.0 Hz, 1 H), 4.18 (dd, J = 11.5, 4.5 Hz, 1 H), 3.31 – 3.35 (m, 1 H), 2.45 (ddd, J = 13.5, 11.0, 3.0 Hz, 1 H), 2.16 – 2.20 (m, 1 H), 2.00 – 2.11 (m, 1 H), 1.52 (s, 3 H), 1.44 (s, 3 H), 1.11 (s, 3 H)

**HRMS (EI):** calcd. for C₂₁H₂₄N₂Cl [M + H⁺] 338.1544, found 338.1561

See page 224 for spectrum.
Compound 148:

NH₄OAc (4.53 g, 60.0 mmol, 40 equiv.) and NaCNBH₃ (707 mg, 11.25 mmol, 7.5 equiv.) were dissolved in MeOH (60 mL, 0.025 M) at ambient temperature in a sealed tube. Molecular Sieves (3Å, 6.0 g) were then added to the solution. Finally, cyclized ketone 119 (492 mg, 1.50 mmol, 1.0 equiv.) was dissolved in THF (12.0 mL, 0.125 M) and added to the MeOH solution. The reaction mixture was degassed by bubbling with argon for 30 minutes then sealed in the reaction vessel. The sealed tube was placed in a sonicator and exposed to ultrasonic radiation for 18 hours. The reaction was filtered through a pad of celite and concentrated in vacuo. The crude reaction was then diluted with 2 N NaOH (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄), and the solvent removed in vacuo. The crude reaction was purified by flash column chromatography (silica gel, gradient from 3:1 to 1:1 hexane:EtOAc) to give compound 148 (206 mg, 42%).

Physical State: yellow foam

Rₛ: 0.14 (silica gel, 1:1 hexane:EtOAc)

[α]₀: + 1.9 (DCM, c 0.31)

IR (film) νₘₐₓ: 3400, 2956, 1655, 1584, 1448, 1364, 1334, 1304, 1269, 1241 cm⁻¹
**1H NMR (600 MHz, CDCl3):** \( \delta \) 7.87 (bs, 1 H, D2O exchangeable), 7.52 (d, \( J = 7.2 \) Hz, 1 H), 7.30 (d, \( J = 7.8 \) Hz, 1 H), 7.06 – 7.11 (m, 2 H), 5.78 (dd, \( J = 17.4 \), 11.4 Hz, 1 H), 5.13 (d, \( J = 17.4 \) Hz, 1 H), 5.04 (d, \( J = 10.8 \) Hz, 1 H), 3.95 (dd, \( J = 7.2 \), 3.6 Hz, 1 H), 3.64 (t, \( J = 4.8 \) Hz, 1 H), 2.98 (d, \( J = 5.4 \) Hz, 1 H), 2.44 – 2.48 (m, 1 H), 2.13 (dd, \( J = 25.8 \), 12.6 Hz, 1 H), 2.01 – 2.04 (m, 1 H), 1.78 (bs, 2 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.20 (s, 3 H)

**13C NMR (150 MHz, CDCl3):** \( \delta \) 150.0, 140.5, 136.0, 124.6, 120.9, 120.7, 120.0, 118.6, 117.1, 111.6, 68.9, 59.6, 54.3, 48.9, 45.4, 41.9, 32.7, 25.8, 22.4, 21.1

**HRMS (MALDI):** calcd. for C20H26N2Cl [M + H+] 329.1779, found 329.1782

See pages 349 – 350 for spectra.

**Compound 149:**

To **compound 148** (1.83 g, 5.59 mmol, 1.0 equiv.) was added sequentially formic acid (422 \( \mu \)L, 11.2 mmol, 2.0 equiv.), 2-chloro-4,6-dimethoxy-1,3,5-triazine (2.16 g, 12.3 mmol, 2.2 equiv.), DMAP (68.3 mg, 0.56 mmol, 0.1 equiv.), \( N \)-methylmorpholine (1.35 mL, 12.3 mmol, 2.2 equiv.), and DCM (14.7 mL, 0.38 M). The resulting suspension was stirred rapidly at ambient temperature for 30 minutes. The reaction was then diluted with DCM (100 mL) and washed sequentially with 1N HCl (2 x 75 mL),
saturated NaHCO₃ (75 mL), brine (75 mL), dried (MgSO₄), and the solvent removed in vacuo. It was found that the intermediate formamide (149), once fully dried, crystallized into a polymorph that was completely insoluble in most organic solvents. It was therefore necessary to leave ca 5.0 mL of DCM in the flask after removing from the rotary evaporator and use the material crude in the next step. As such, it was also impossible to obtain full characterization of this compound.

**Compound 153:**

![Compound 153 structure](image)

**Compound 149** was immediately dissolved in DCM (280 mL, 0.02 M) and cooled to 0 °C. Triethylamine (13.4 mL, 97.9 mmol, 17.5 equiv.) was added, followed by phosgene solution (20 wt% in toluene, 5.53 mL, 11.2 mmol, 2.0 equiv.). This mixture was allowed to stir at 0 °C until TLC showed that the starting material was fully consumed (usually ca. ten minutes), adding more phosgene solution as needed to push to completion, as judged by TLC. The reaction mixture was then poured into saturated NaHCO₃ (200 mL) and diluted with EtOAc (300 mL). The organic layer was separated and washed with brine (200 mL), dried (MgSO₄), and the solvent removed in vacuo to give crude compound 153 (1.89 g, 95% from amine), which was sufficiently pure for further reaction.

**Physical State:** white powder  **mp:** 218 – 220 °C (decomposition)
Rf: 0.40 (silica gel, 3:1 hexane:EtOAc)

$[\alpha]_D$: +119.3 (DCM, c 0.27)

**IR (film)** $\nu_{\text{max}}$: 3380, 2963, 2139, 1448, 1303 cm$^{-1}$

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.01 (bs, 1 H, D$_2$O exchangeable), 7.88 (d, $J$ = 7.6 Hz, 1 H), 7.32 (d, $J$ = 7.3 Hz, 1 H), 7.06 – 7.11 (m, 2 H), 5.77 (dd, $J$ = 11.0, 17.3 Hz, 1 H), 5.30 (d, $J$ = 17.3 Hz, 1 H), 5.04 (d, $J$ = 11.0 Hz, 1 H), 3.95 (t, $J$ = 5.1 Hz, 1 H), 3.90 (d, $J$ = 4.9 Hz, 1 H), 3.85 (dd, $J$ = 4.2, 12.7 Hz, 1 H), 2.45 – 2.49 (m, 1 H), 2.02 – 2.14 (m, 2 H), 1.46 (s, 3 H), 1.35 (s, 3 H), 1.24 (s, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 159.4, 150.7, 141.2, 134.3, 125.1, 122.9, 121.7, 120.8, 120.1, 115.4, 112.1, 67.2, 55.0, 47.2, 44.3, 42.6, 33.0, 30.5, 25.9, 23.5, 21.4

**HRMS (ESI):** calcd. for C$_{21}$H$_{24}$ClN$_2$ [M + H$^+$] 339.1622, found 339.1619

See pages 353 – 354 for spectra.

**12-epi-Fischerindole I (22):**

![Diagram of 12-epi-Fischerindole I (22)]

**Original Procedure:** Freshly prepared compound 149 (8.2 mg, 0.023 mmol, 1.0 equiv.) was dissolved in THF (600 µL, 0.04 M) and cooled to 0 °C. An aluminum foil covering was placed around the flask to prevent light from entering the reaction. Triethylamine (3.1 µL, 0.023 mmol, 1.0 equiv.) was added, followed by freshly prepared tert-butyl
hypochlorite (4.0 µL, 0.034 mmol, 1.5 equiv.). After stirring for ten minutes, the solvent was removed *in vacuo*. The crude reaction was then loaded onto a PTLC plate, which was then treated with TEA vapor and eluted (1:1 hexane:EtOAc). The compound was then dissolved in CDCl₃, which proved to be crucial for successful completion of the reaction, to give **compound 147** (7.3 mg, 89%). **Compound 147** was an unstable compound in solution and could not be fully characterized, therefore it was immediately reacted further. **Compound 147** (4.6 mg, 0.013 mmol) was dissolved in benzene (1.0 mL, 0.1 M) and Burgess reagent (6.2 mg, 0.026 mmol, 2.0 equiv.) was added at ambient temperature. Upon completion of the reaction, as determined by TLC, the solvent was removed *in vacuo* and the crude material purified by PTLC (3:1 hexane:EtOAc), to give 12-*epi*-fischerindole I (22, 2.3 mg, 53%).

**Revised Procedure:** **Compound 153** (169 mg, 0.50 mmol, 1.0 equiv.) was dissolved in THF (5.0 mL, 0.1 M) and H₂O (1.0 mL, 0.5 M) and cooled to 0 °C. To this cold solution was added freshly recrystallized (from benzene) DDQ (283 mg, 1.24 mmol, 2.5 equiv.) The reaction was allowed to stir for 30 minutes then poured into saturated NaHCO₃ (30 mL) and diluted with EtOAc (30 mL). The organic layer was washed further with water (30 mL) and brine (30 mL), dried (Na₂SO₄), and the solvent removed *in vacuo*. The crude product was then filtered through a short silica gel plug, eluted with 3:1 hexanes:EtOAc, to give pure 12-*epi*-fischerindole I (22, 155 mg, 92%). [Note: 12-*epi*-fischerindole I is not stable to acid so precautions should be taken while handling and should be stored frozen in a benzene matrix.]

**Physical State:** pale yellow foam

**Rf:** 0.34 (silica gel, 3:1 hexane:EtOAc)
[\alpha]D: – 39.1 (DCM, c 0.33)

IR (film) \(\nu_{\text{max}}\): 3276, 2958, 2136, 1718, 1570, 1473, 1450, 1363, 1254, 1207 cm\(^{-1}\)

\(^1\)H NMR (500 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 8.47 (bs, 1 H, D\(_2\)O exchangeable), 8.39 (d, \(J = 8.0\) Hz, 1 H), 7.48 (d, \(J = 7.5\) Hz, 1 H), 7.25 – 7.31 (m, 2 H), 5.99 (dd, \(J = 10.5, 17.5\) Hz, 1 H), 5.43 (d, \(J = 13.0\) Hz, 1 H), 5.24 (d, \(J = 17.5\) Hz, 1 H), 4.24 (dd, \(J = 6.0, 8.5\) Hz, 1 H), 3.21 (dd, \(J = 8.5, 11.0\) Hz, 1 H), 2.18 – 2.22 (m, 2 H), 1.68 (s, 3 H), 1.54 (s 3 H), 1.27 (s, 3 H)

\(^{13}\)C NMR (125 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 164.7, 159.3, 141.1 (2 carbons), 140.9, 138.7, 123.0, 122.5, 122.4, 121.6, 117.6, 114.3, 112.3, 66.2, 57.0, 46.9, 41.4, 29.9, 25.2, 25.1, 22.9

HRMS (ESI): calcd. for C\(_{21}\)H\(_{20}\)Cl\(_2\N 2\) [M – H\(^+\)] 335.1320, found 335.1312

See pages 227 – 228 for spectra.

Compound 152:

Physical State: Colorless cubes  \(\text{mp:}\ 132 – 133^\circ\text{C}\)

\(R_f:\ 0.32\) (silica gel, EtOAc)

[\alpha]D: + 134 (DCM, c 0.25)

IR (film) \(\nu_{\text{max}}\): 3406, 2919, 1676, 1610, 1500, 1467, 1364, 1074 cm\(^{-1}\)
$^1$H NMR (600 MHz, CDCl$_3$): \( \delta \) 8.33 (s, 1 H), 7.14 – 7.18 (m, 2 H), 6.76 (t, \( J = 7.2 \) Hz, 1 H), 6.64 (d, \( J = 7.8 \) Hz, 1 H), 5.97 (d, \( J = 9.0 \) Hz, 1 H), 4.72 – 4.75 (m, 2 H), 4.58 (dd, \( J = 5.4, 7.2 \) Hz, 1 H), 4.20 (t, \( J = 9.0 \) Hz, 1 H), 4.19 (s, 1 H), 3.66 (dd, \( J = 3.6, 13.2 \) Hz, 1 H), 3.41 (t, \( J = 8.1 \) Hz, 1 H), 3.21 (bs, 1 H), 2.99 (bs, 1 H), 2.49 (q, \( J = 13.2 \) Hz, 1 H), 1.96 (m, 1 H), 1.89 (dt, \( J = 4.5, 13.8 \) Hz, 1 H), 1.17 (s, 3 H), 1.16 (s, 3 H), 1.10 (s, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$): \( \delta \) 161.0, 149.7, 134.5, 130.4, 130.3, 126.5, 120.0, 117.4, 110.8, 104.1, 88.4, 67.6, 53.4, 50.8, 47.2, 45.6, 44.5, 31.8, 25.2, 23.4, 20.0

HRMS (ESI): calcd. for C$_{21}$H$_{28}$N$_2$O$_3$Cl [M + H$^+$] 391.1783, found 391.1786.

See pages 351 – 352 for spectra.

Structure verified by X-ray crystallographic analysis.

Compounds 155 and 156:

**Compound 119** (13.1 mg, 0.040 mmol, 1.0 equiv.) was dissolved in THF (400 \( \mu \)L, 0.1 M) and cooled to 0 °C. Triethylamine (5.5 \( \mu \)L, 0.040 mmol, 1.0 equiv.) and then \( t \)-BuOCl (8.0 \( \mu \)L, 0.068 mmol, 1.7 equiv.) were added. The reaction was stirred for 10 minutes, then the solvent was removed \textit{in vacuo}. The crude residue was then dissolved in a 40:20:1 mixture of MeOH:H$_2$O:AcOH (500 \( \mu \)L, 0.08 M) with gentle heating (to dissolve), and stirred for ten minutes. The reaction was quenched with saturated NaHCO$_3$ (5.0 mL) and extracted with EtOAc (10 mL). The organic layer was further washed with water (5.0 mL) then brine (5.0 mL), dried (MgSO$_4$), and evaporated \textit{in vacuo}. The crude reaction mixture was purified by flash column chromatography (silica
gel, gradient from 8:1 to 3:1 hexanes:EtOAc) to give **compound 155** (2.7 mg, 20%) and **compound 156** (2.7 mg, 21%).

**Compound 155:**

![Chemical Structure: Compound 155](image)

**Physical State:** yellow oil

**Rf:** 0.31 (silica gel, 3:1 hexane:EtOAc)

**[α]D:** –10.3 (DCM, c 0.29)

**IR (film) νmax:** 3391, 2927, 1661, 1480, 1446, 1418, 1264 cm⁻¹

**¹H NMR (500 MHz, CDCl₃):** δ 8.25 (bs, 1 H, D₂O exchangeable), 8.20 (d, J = 7.5 Hz, 1 H), 7.35 (d, J = 7.0 Hz, 1 H), 7.14 – 7.20 (m, 2 H), 6.16 (dd, J = 17.5, 11.0 Hz, 1 H), 5.25 (d, J = 10.5 Hz, 1 H), 5.17 (d, J = 17.5 Hz, 1 H), 4.39 (dd, J = 9.5, 5.0 Hz, 1 H), 2.90 – 3.01 (m, 2 H), 1.55 (s, 3 H), 1.40 (s, 3 H), 1.36 (s, 3 H)

**¹³C NMR (150 MHz, CDCl₃):** δ 195.0, 163.1, 153.5, 140.7, 135.9, 134.4, 122.7, 122.5, 121.5, 118.9, 118.7, 116.6, 112.4, 65.3, 61.3, 47.1, 32.1, 23.4, 23.3, 21.2

**HRMS (ESI):** calcd. for C₂₀H₂₁ClNO [M + H⁺] 326.1306, found 326.1303

See pages 355 – 356 for spectra.
Compound 156:

Physical State: clear needles

Rf: 0.18 (silica gel, 3:1 hexane:EtOAc)

[α]D: + 84.7 (DCM, c 0.64)

IR (film) νmax: 3371, 2962, 2927, 2869, 1704, 1621, 1471, 1372, 1330, 1266, 1195, 1115 cm⁻¹

¹H NMR (600 MHz, CDCl₃): δ 7.79 (bs, 1 H, D₂O exchangeable), 7.17 – 7.21 (m, 2 H), 6.98 (t, J = 7.2 Hz, 1 H), 6.84 (d, J = 7.8 Hz, 1 H), 6.36 (dd, J = 17.4, 10.8 Hz, 1 H), 5.26 (d, J = 10.8 Hz, 1 H), 5.02 (d, J = 17.4 Hz, 1 H), 4.15 (dd, J = 11.4, 4.8 Hz, 1 H), 3.43 (d, J = 13.8 Hz, 1 H), 3.12 (t, J = 12 Hz, 1 H), 2.31 – 2.34 (m, 1 H), 2.10 – 2.17 (m, 1 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.15 (s, 3 H)

¹³C NMR (150 MHz, CDCl₃): δ 199.8, 177.8, 141.4, 137.9, 128.8, 127.0, 124.6, 122.0, 118.2, 109.9, 68.4, 59.4, 50.9 (2 carbons), 49.1, 44.6, 36.2, 23.5, 21.2, 20.1

HRMS (ESI): calcd. for C₂₀H₂₃ClNO₂ [M + H⁺] 344.1412, found 344.1409

See pages 357 – 358 for spectra.

Structure verified by X-ray crystallographic analysis.
Welwitindolinone A (13):

Original Procedure:

12-epi-fischerindole I (22, 1.7 mg, 0.00479 mmol, 1.0 equiv.) was dissolved in THF (40 µL, 0.1 M) and cooled to –30 ºC in a flask wrapped in aluminum foil. Triethylamine (0.66 µL, 0.00479 mmol, 1.0 equiv.) was added, followed by freshly prepared t-BuOCl (0.79 µL, 0.00719 mmol, 1.5 equiv.) and stirring was continued for one minute. The reaction mixture was then evaporated under reduced pressure (HIVAC) while at –30 ºC. When all the volatile material was removed from the flask, the crude material was then dissolved in a mixture of 95:4:1 THF:H2O:TFA (100 µL) at –30 ºC. The reaction was stirred for five minutes after which it was diluted with EtOAc (2.0 mL) and quenched with 5% NaHCO3 (1.0 mL). The organic layer was further washed with brine (1.0 mL), dried (Na2SO4), and the solvent removed in vacuo. The crude material was purified by preparative thin layer chromatography (silica gel, 10:1 DCM:isooctane) to give welwitindolinone A (13, 0.4 mg, 25%) and 3-epi-12 (161, 0.05 mg, 3%), ratio as determined by 1H NMR.

Revised Procedure:

A solution of xenon difluoride was prepared by dissolving XeF2 (ca 93 mg) in a 0 ºC solution of acetonitrile (5.0 mL) and water (500 mL) and stirred at that temperature for
three hours. The resulting solution was titrated for oxidation capacity with triphenylphosphine. **12-epi-fischerindole I** (22, 7.3 mg, 0.022 mmol, 1.0 equiv.) was suspended in acetonitrile (217 µL, 0.1 M). To this solution was added XeF₂ (0.1 M, 0.022 mmol, 1.0 equiv.) at ambient temperature. The reaction progress was monitored by TLC, with more oxidant added as necessary to push to completion (reaction normally finished in under five minutes). After all the starting material was consumed, the reaction was diluted with EtOAc (2.0 mL) and washed with saturated NaHCO₃ (2.0 mL) then brine (2.0 mL), dried (Na₂SO₄), and the solvent removed *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, DCM) to give **welwitindolinone A** (13, 3.4 mg, 44%).

**Physical State:** pale yellow foam

**Rₚ:** 0.09 (silica gel, 10:1 DCM:iso-octane)

**[α]D:** +102 (DCM, c 0.25)

**IR (film) νₘᵢₐₓ:** 2918, 2359, 1700, 1617, 1470, 1116 cm⁻¹

**¹H NMR (600 MHz, CD₂Cl₂):** δ 8.36 (bs, 1 H, D₂O exchangeable), 7.29 (td, J = 1.1, 7.7 Hz, 1 H), 7.25 (d, J = 7.5 Hz, 1 H), 7.06 (td, J = 0.8, 7.6 Hz, 1 H), 6.94 (d, J = 7.7 Hz, 1 H), 5.95 (dd, J = 10.7, 17.4 Hz, 1 H), 5.47 (d, J = 10.7 Hz, 1 H), 5.33 (d, J = 16.6 Hz, 1 H), 4.05 (dd, J = 3.2, 12.4 Hz, 1 H), 3.62 (dd, J = 6.8, 10.5 Hz, 1 H), 2.02 – 2.06 (m, 1 H), 1.91 – 1.96 (m, 1 H), 1.44 (s, 3 H), 1.27 (s, 3 H), 1.21 (s, 3 H)

**¹³C NMR (150 MHz, CD₂Cl₂):** δ 176.1, 167.3, 141.7, 137.84, 137.82, 129.2, 127.0, 122.8, 121.5, 120.7, 117.8, 110.1, 65.1, 64.0, 55.3, 47.8, 47.4, 47.0, 28.8, 23.2, 21.1
MS (DIOS): natural: m/z 352/354 (3:1 M+ ion cluster), 317 (M+ – Cl–), synthetic:
m/z 353/355 (3:1 M + H+), 317 (M+ – Cl–)

HRMS (EI): calcd. for C<sub>21</sub>H<sub>22</sub>ON<sub>2</sub>Cl [M + H+] 352.1337, found 352.1333

See pages 225 – 226 for spectra.

3-epi-X (161):

![Chemical structure of 3-epi-X (161)]

Physical State: light yellow oil

R<sub>f</sub>: 0.17 (silica gel, 10:1 DCM:isooctane)

[α]<sub>D</sub>: + 17.5 (DCM, c 0.08)

IR (film) ν<sub>max</sub>: 3427, 2070, 1700, 1620, 1468, 1110 cm<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.37 (bs, 1 H, D<sub>2</sub>O exchangeable), 7.21 (t, J = 8.0 Hz, 1 H), 7.00 (t, J = 7.5 Hz, 1 H), 6.92 (d, J = 7.5 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 6.07 (dd, J = 17.5, 11.0 Hz, 1 H), 5.40 (d, J = 11.0 Hz, 1 H), 5.26 (d, buried under residual solvent, 1 H), 4.11 (dd, J = 11.0, 5.0 Hz, 1 H), 3.62 (t, J = 8.0 Hz, 1 H), 1.96 – 1.99 (m, 2 H), 1.22 (s, 3 H), 1.18 (s, 3 H), 1.15 (s, 3 H)

HRMS (ESI): calcd. for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>OCl [M + H+] 352.1337, found 352.1334

See page 359 for spectrum.
**Compound 162:**

![Compound 162](image)

4-Phenylcyclohexanone (5.0 g, 28.7 mmol, 1.0 equiv.) was dissolved in toluene (14.3 mL, 2.0 M). Formamide (1.25 mL, 31.6 mmol, 1.1 equiv.) and H$_2$SO$_4$ (14.3 µL, 2000 M) were added and the reaction heated to reflux under Dean-Stark conditions for 18 hours. The reaction was cooled back to ambient temperature then diluted with EtOAc (100 mL), washed with water (50 mL) then brine (50 mL), dried (MgSO$_4$), and the solvent removed *in vacuo*. The crude reaction mixture was purified by flash column chromatography (silica gel, gradient from 3:1 to 1:1 hexanes:EtOAc) to provide **compound 162** (1.54 g, 27%), which was spectroscopically identical to the known material.$^{225}$

**Compound 163:**

![Compound 163](image)

**Compound 162** (1.0 g, 4.97 mmol, 1.0 equiv.) was dissolved in benzene (49.7 mL, 0.1 M). Burgess reagent (1.78 g, 7.45 mmol, 1.5 equiv.) was added and the reaction was stirred at ambient temperature for 30 minutes. After this time, the solvent was removed *in vacuo* and the crude material purified by flash column chromatography (silica gel, gradient from 24:1 to 16:1 hexanes:EtOAc) to provide **compound 163** (717 mg, 79%), which was spectroscopically identical to the known material.$^{225}$
Compound 164:

**Compound 163** (74.1 mg, 0.404 mmol, 1.0 equiv.) was dissolved in THF (809 µL, 0.5 M) along with TEA (132.7 µL, 0.970 mmol, 2.4 equiv.), selenium (1.6 mg, 0.0202 mmol, 0.05 equiv.), and sulfur (15.6 mg, 0.485 mmol, 1.2 equiv.) at ambient temperature. The reaction was heated to 60 ºC for one hour, then cooled back to ambient temperature. The solvent was removed *in vacuo* and the crude reaction purified by flash column chromatography (silica gel, 20:1 hexanes:EtOAc) to give **compound 164** *(ca 43 mg, ca 50%).*

**Physical State:** off-white powder

**Rf:** 0.64 (silica gel, 9:1 hexane:EtOAc)

**1H NMR (600 MHz, CDCl3):**  δ 7.32 (t, J = 7.4 Hz, 2 H), 7.20 – 7.24 (m, 3 H), 5.83 (t, J = 2.7 Hz, 1 H), 2.76 – 2.82 (m, 1 H), 2.45 – 2.51 (m, 1 H), 2.31 – 2.45 (m, 2 H), 2.23 – 2.29 (m, 1 H), 2.01 – 2.05 (m, 1 H), 1.86 – 1.90 (m, 1 H)

**LRMS (ESI):** calcd. for C_{13}H_{13}NaNS [M + Na^+] 238, found 238

See page 360 for spectrum.
Compound 166:

Welwitindolinone A (13, 6.3 mg, 0.0179 mmol, 1.0 equiv.) was dissolved in DCB (1.79 mL, 0.01 M) and heated to 250 ºC for five minutes in the microwave. The crude reaction was filtered through a silica gel plug to remove the DCB (hexanes, then EtOAc). PTLC (silica gel, 1:1 hexanes:EtOAc) of the filtered product provided compound 166 (ca 4 mg, ca 60%, dr = ca 1:1). Only one diastereomer characterized, both spectra given. Tentative structure proposed, in part, by analogy to comparison with compound 167.

**Physical State:** clear oil

**Rf:** 0.11 (silica gel, 4:1 DCM:EtOAc)

**IR (film) ν_{max}:** 2964, 1650, 1646, 1489, 1436, 1420, 1333, 1268 cm^{-1}

**{H NMR (600 MHz, CD2Cl2):** δ 10.37 (bs, 1 H), 10.12 (bs, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.32 – 7.35 (m, 2 H), 7.18 – 7.21 (m, 1 H), 6.19 (dd, J = 17.2, 10.4 Hz, 1 H), 5.17 (d, J = 10.7 Hz, 1 H), 4.90 (s, 1 H), 4.88 (s, 1 H), 4.73 (d, J = 17.3 Hz, 1 H), 4.23 (dd, J = 13.0, 3.1 Hz, 1 H), 3.99 (dd, J = 10.3, 7.3 Hz, 1 H), 2.49 – 2.54 (m, 1 H), 2.13 – 2.19 (m, 1 H), 1.73 (s, 3 H), 1.66 (s, 3 H)

**LRMS (ESI):** calcd. for C_{21}H_{21}ClN_{2}O [M + H^+] 353.1, found 353.1

See pages 363 – 364 for spectra.
Compound 169:

Welwitindolinone A (13, 1.1 mg, 0.00312 mmol, 1.0 equiv.) was dissolved in THF (200 µL, 0.0156 M) and H2O (10 µL, 0.312 M) and cooled to 0 °C. To this solution, HCO2H (100 µL, 0.0312 M) was added and the reaction stirred for 12 hours. The reaction was then concentrated in vacuo and the residue dissolved in EtOAc (2.0 mL), washed with saturated NaHCO3 (1.0 mL) and brine (1.0 mL), dried (Na2SO4), and the solvent removed in vacuo to give the tentatively assigned compound 169 (1.1 mg, 95%), which was sufficiently pure for further reaction. The compound was characterized as a mixture of rotamers, which could not be completely suppressed.

Rf: 0.26 (silica gel, 19:1 DCM:MeOH)

^1H NMR (600 MHz, CD3OD): δ 7.29 (s, 1 H), 7.05 (dt, J = 7.2, 1.2 Hz, 1 H), 6.94 (d, J = 7.2 Hz, 1 H), 6.79 (dt, J = 7.2, 0.6 Hz, 1 H), 6.71 (d, J = 7.8 Hz, 1 H), 5.91 (dd, J = 17.4, 10.2 Hz, 1 H), 5.38 (d, J = 9.6 Hz, 1 H), 5.24 (dd, J = 17.4, 1.2 Hz, 1 H), 4.08 (dd, J = 10.8, 4.8 Hz, 1 H), 3.40 – 3.43 (m, 1 H), 1.82 – 1.88 (m, 2 H), 1.19 (s, 3 H), 1.12 (s, 3 H), 1.01 (s, 3 H), (N–H’s are not visible in CD3OD)

See page 371 for spectrum.
Compound 165:

Welwitindolinone A (13, 19.4 mg, 0.055 mmol, 1.0 equiv.) was dissolved in DCM (550 mL, 0.1 M) and cooled to –78 ºC. To this solution was added TFDO (393 µL, 0.055 mmol, 1.0 equiv.) and the reaction stirred for five minutes. The reaction was then quenched with 1 drop of DMS and warmed to room temperature. The volatile materials were removed in vacuo and the crude reaction purified by flash column chromatography (silica gel, gradient from 19:1 to 9:1 DCM:EtOAc) to give compound 165 (20.3 mg, 100%). When compound 165 was left open to the ambient atmosphere for three days, it was quantitatively converted into compound 168.

**Physical State:** clear oil

**Rf:** 0.59 (silica gel, 9:1 DCM:EtOAc)

**[α]D:** + 209.9 (DCM, c 0.92)

**IR (film) νmax:** 3244, 2924, 2258, 1706, 1619, 1469, 1326, 1224, 1114 cm\(^{-1}\)

**\(^1\)H NMR (600 MHz, CD$_2$Cl$_2$):** δ 8.04 (bs, 1 H, D$_2$O exchangeable), 7.27 (dt, J = 7.7, 1.1 Hz, 1 H), 7.20 (d, J = 7.5 Hz, 1 H), 7.04 (dt, J = 7.6, 0.8 Hz, 1 H), 6.91 (d, J = 7.7 Hz, 1 H), 5.99 (dd, J = 17.4, 10.7 Hz, 1 H), 5.47 (d, J = 10.7 Hz, 1 H), 5.32 (d, J = 17.3 Hz, 1 H), 4.11 (dd, J = 12.3, 3.5 Hz, 1 H), 3.51 (dd, J = 10.5, 6.7 Hz, 1 H), 1.95 – 2.02 (m, 2 H), 1.41 (s, 3 H), 1.25 (s, 3 H), 1.19 (s, 3 H)
$^{13}$C NMR (150 MHz, CD$_2$Cl$_2$): $\delta$ 178.0, 142.4, 139.7, 129.6, 128.7, 127.3, 125.1, 124.2, 122.5, 118.6, 110.7, 65.7, 65.3, 49.9, 48.5, 47.6, 30.5, 30.1, 24.0, 22.0 (in accord with other isocyanate containing compounds, this carbon is not visible)

HRMS (ESI): calcd. for C$_{21}$H$_{22}$N$_2$O$_2$Cl [M + H$^+$] 369.1364, found 369.1363

See pages 361 – 362 for spectra.

**Compound 167:**

![Chemical Structure of Compound 167]

**Compound 165** (9.2 mg, 0.0249 mmol, 1.0 equiv.) was dissolved in DCB (1.25 mL, 0.02 M) and heated to 250 °C in the microwave for six minutes. The crude reaction was purified by flash column chromatography (silica gel, gradient from 9:1 to 3:2 DCM:EtOAc) to give **compound 167** (6.3 mg, 68%, $dr = ca 2:1$). The major diastereomer’s characterization data is given below (tentative structure assignment), but spectra for both are given.

**Physical State:** clear oil

$R_f$: 0.079 (silica gel, 9:1 DCM:EtOAc)

**IR (film) $\nu_{max}$:** 3210, 2923, 2852, 1720, 1619, 1472, 1284, 1216, 1175, 1105 cm$^{-1}$

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.19 (bs, 1 H), 7.75 (bs, 1 H), 7.28 (td, $J = 7.7$, 1.1 Hz, 1 H), 7.06 (t, $J = 7.5$ Hz, 1 H), 7.00 (d, $J = 7.4$ Hz, 1 H), 6.87 (d, $J = 7.8$ Hz, 1 H), 6.00 (dd, $J = 17.3$, 10.4 Hz, 1 H), 5.55 (d, $J = 17.3$ Hz, 1 H), 5.46 (d, $J = 10.4$ Hz, 1 H).
Hz, 1 H), 4.48 (s, 1 H), 4.11 (dd, \( J = 12.7, 3.1 \) Hz, 1 H), 4.05 (s, 1 H), 2.98 (dd, \( J = 11.0, 5.8 \) Hz, 1 H), 2.16 – 2.22 (m, 1 H), 1.95 – 2.00 (m, 1 H), 1.56 (s, 3 H), 1.48 (s, 3 H)

\( ^{13}C \) NMR (150 MHz, CDCl\(_3\)): \( \delta \) 176.9, 173.9, 144.3, 143.8, 143.1, 138.2, 130.3, 126.8, 124.3, 123.5, 119.7, 117.0, 115.5, 111.1, 66.4, 44.7, 43.6, 35.0, 30.5, 23.3, 19.2

LRMS (ESI): calcd. for C\(_{21}\)H\(_{22}\)ClN\(_2\)O\(_2\) [M + H\(^+\)] 369.1, found 369.1

See pages 365 – 366 for spectra.

**Compound 168:**

![Compound 168](image)

**Physical State:** yellow powder

**R\(_f\):** 0.32 (silica gel, EtOAc)

**[\( \alpha \)]\(_D\):** + 160 (DCM, c 0.04)

**IR (film) \( \nu_{max} \):** 3358, 2930, 1694, 1650, 1514, 1471, 1411, 1264, 1107, 1038 cm\(^{-1}\)

\( ^1H \) NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.91 (bs, 2 H, D\(_2\)O exchangeable), 7.04 (td, \( J = 1.0, 7.5 \) Hz, 2 H), 6.84 (d, \( J = 7.5 \) Hz, 2 H), 6.74 (d, \( J = 7.8 \) Hz, 2 H), 6.72 (td, \( J = 1.0, 7.5 \) Hz, 2 H), 5.82 (dd, \( J = 10.5, 17.5 \) Hz, 2 H), 5.30 (d, \( J = 1.0, 10.5 \) Hz, 2 H), 5.11 (d, \( J = 1.0 \) Hz, 17.5 Hz, 2 H), 4.53 (s, 2 H, D\(_2\)O exchangeable), 3.91 (dd, \( J = \ldots \)
3.5, 12.5 Hz, 2 H), 3.29 (dd, $J = 6.3, 10.8$ Hz, 2 H), 1.87 (ddd, $J = 3.3, 6.2, 12.0$ Hz, 2 H), 1.77 (dt, $J = 11.0, 12.3$ Hz, 2 H), 1.17 (s, 6 H), 1.02 (s, 6 H), 0.72 (s, 6 H)

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 180.5 (2 carbons), 150.5, 144.0 (2 carbons), 140.9 (2 carbons), 128.4 (2 carbons), 127.2 (2 carbons), 125.6 (2 carbons), 124.3 (2 carbons), 123.0 (2 carbons), 120.6 (2 carbons), 117.2 (2 carbons), 110.1 (2 carbons), 66.9 (2 carbons), 66.2 (2 carbons), 47.3 (4 carbons), 45.8 (2 carbons), 30.2 (2 carbons), 24.0 (2 carbons), 22.1 (4 carbons).

HRMS (ESI): calcd. for C$_{41}$H$_{45}$N$_4$O$_3$Cl$_2$ [M + H$^+$] 711.2863, found 711.2868

See pages 369 – 370 for spectra.

Compound 170:

Compound 148 (63.9 mg, 0.195 mmol, 1.0 equiv.) was dissolved in DCM (3.25 mL, 0.06 M) and thiocarbonyl diimidazole (38.2 mg, 1.1 equiv.) was added at ambient temperature. Stirring was continued for 2.5 hours, after which time more thiocarbonyl diimidazole (38.2 mg, 1.1 equiv.) was added. Stirring was continued for five hours, after which time more thiocarbonyl diimidazole (38.2 mg, 1.1 equiv.) was added. Stirring was continued for 15 hours and the solvent removed in vacuo. The crude reaction mixture
was purified by flash column chromatography (silica gel, 8:1 hexanes:EtOAc) to give compound 170 (43.2 mg, 60%).

**Physical State:** Colorless cubes  
**mp:** 220 – 221 ºC

**Rf:** 0.40 (silica gel, 3:1 hexane:EtOAc)

**[α]D:** + 161 (DCM, c 0.37)

**IR (film) υ**\(_\text{max}\): 3390, 2964, 2087, 1654, 1474, 1458, 1448, 1303, 1272, 1241 cm\(^{-1}\)

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):**  
δ 7.88 (bs, 1 H, D\(_2\)O exchangeable), 7.65 – 7.67 (m, 1 H), 7.31 – 7.33 (m, 1 H), 7.14 – 7.19 (m, 2 H), 5.81 (dd, \(J = 17.2, 10.8\) Hz, 1 H), 5.28 (dd, \(J = 17.6, 1.2\) Hz, 1 H), 5.08 (dd, \(J = 10.8, 0.8\) Hz, 1 H), 4.09 (d, \(J = 5.6\) Hz, 1 H), 3.80 – 3.86 (m, 2 H), 2.45 (dt, \(J = 10.8, 5.6\) Hz, 1 H), 2.01 – 2.16 (m, 2 H), 1.48 (s, 3 H), 1.36 (s, 3 H), 1.24 (s, 3 H)

**\(^13\)C NMR (100 MHz, CDCl\(_3\)):**  
δ 149.4, 140.2, 133.8, 124.3, 121.1, 121.1, 120.4, 119.7, 115.2, 111.4, 66.1, 65.7, 53.8, 47.8, 42.8, 42.0, 32.1, 25.6, 23.2, 21.0 (in accord with other isothiocyanate containing natural products, this carbon is not visible)

**HRMS (ESI):** calcd. for C\(_{21}\)H\(_{24}\)N\(_2\)SCl [M + H\(^+\)] 371.1343, found 371.1343

See pages 372 – 373 for spectra.
Compound 171:

**Physical State:** colorless cubes  
**mp:** 202 °C (Decomposition)

**R_f:** 0.26 (silica gel, 3:1 hexane:EtOAc)

**[α]_D:** –206 (DCM, c 0.12)

**IR (film) ν max:** 3399, 2964, 2098, 1655, 1648, 1530, 1474, 1450, 1364, 1308, 1254 cm⁻¹

**¹H NMR (400 MHz, CD₂Cl₂):**  δ  8.36 (bs, 1 H, D₂O exchangeable), 7.87 – 7.91 (m, 1 H), 7.39 – 7.43 (m, 1 H), 7.21 – 7.25 (m, 2 H), 5.97 (dd, J = 17.2, 10.4 Hz, 1 H), 5.38 (d, J = 10.8 Hz, 1 H), 5.18 (dd, J = 17.2, 0.8 Hz, 1 H), 4.20 – 4.24 (m, 1 H), 3.11 – 3.16 (m, 1 H), 2.06 – 2.16 (m, 2 H), 1.63 (s, 3 H), 1.48 (s, 3 H), 1.18 (s, 3 H), 1.13 (s, 3 H)
$^1$H NMR (100 MHz, CD$_2$Cl$_2$): \( \delta \) 158.0, 140.6, 138.7, 135.8, 122.4, 122.1, 121.4, 121.1, 117.3, 114.9, 114.3, 111.9, 100.0, 66.1, 56.0, 48.6, 41.3, 29.7, 24.9, 24.5, 22.3

**HRMS (ESI):** calcd. for C$_{21}$H$_{22}$N$_2$SCl \([\text{M} + \text{H}^+]\) 369.1187, found 369.1191

See pages 374 – 375 for spectra.

Structure verified by X-ray crystallographic analysis.

### Compound 172:

![Compound 172 structure](image)

**Compound 171** (26.4 mg, 0.718 mmol, 1.0 equiv.) was dissolved in DCM (718 mL, 0.1 M). A solution of XeF$_2$ (0.1 M in 9:1 MeCN:H$_2$O, 720 \( \mu \)L, 1.0 equiv.) was then added at ambient temperature. Stirring was continued for 15 minutes then the reaction was partitioned between saturated NaHCO$_3$ (5.0 mL) and EtOAc (10 mL). The organic layer was washed with brine (5.0 mL), dried (Na$_2$SO$_4$), and the solvent removed \textit{in vacuo}. The crude reaction mixture was purified by flash column chromatography (silica gel, 24:1 DCM:EtOAc) to give \textbf{compound 172} (7.5 mg, 27%)

**Physical State:** yellow oil

**R$_f$:** 0.28 (silica gel, 3:1 hexane:EtOAc)
[α]D: +266 (DCM, c 0.19)

IR (film) ν_{max}: 3260, 2927, 2960, 1702, 1619, 1468, 1112 cm⁻¹

^1^H NMR (500 MHz, CD₂Cl₂): δ 7.65 (bs, 1 H), 7.27 (dt, J = 8.0, 1.5 Hz, 1 H), 7.19 (d, J = 7.5 Hz, 1 H), 7.06 (dt, J = 7.5, 1.0 Hz, 1 H), 6.91 (d, J = 7.5 Hz, 1 H), 5.99 (dd, J = 17.5, 11.0 Hz, 1 H), 5.47 (d, J = 10.5 Hz, 1 H), 5.32 (d, J = 17.5 Hz, 1 H), 4.07 (dd, J = 12.0, 3.0 Hz, 1 H), 3.56 (dd, J = 10.5, 7.0 Hz, 1 H), 2.02 (ddd, J = 12.5, 7.0, 3.5 Hz, 1 H), 1.90 – 1.97 (m, 1 H), 1.43 (s, 3 H), 1.25 (s, 3 H), 1.18 (s, 3 H)

^1^3^C NMR (150 MHz, CD₂Cl₂): δ 176.7, 142.0, 138.9, 134.0, 129.5, 126.9, 124.2, 123.0, 122.6, 118.4, 110.5, 65.4, 64.9, 49.4, 48.4, 47.7, 29.6, 23.7, 21.7 (2 carbons) (in accord with other isothiocyanate containing compounds, the isothiocyanate carbon is not visible)

HRMS (ESI): calcd. for C₂₁H₂₀N₂O₅Cl [M – H⁺] 383.0990, found 383.0984

See pages 376 – 377 for spectra.

Compound 173:

Compound 119 (8.8 mg, 0.0268 mmol, 1.0 equiv.) was dissolved in H₂O (54 µL, 0.5 M) and MeOH (500 µL, 0.05 M). Sodium cyanide (6.05 mg, 0.123 mmol, 4.6 equiv.) was
added, followed by AcOH (4.0 µL, 0.0698 mmol, 2.6 equiv.) at ambient temperature.
Stirring was continued for an additional 3.5 hours, after which time the reaction was
diluted with DCM (6.0 mL). This mixture was filtered through silica gel and eluted with
EtOAc. The solvent was removed in vacuo and the crude material purified by PTLC
(silica gel, DCM) to provide compound 173 (ca 6.7 mg, ca 70%, dr = ca 1:1). The
characterization data is given for the top diastereomer (tentative assignment), but spectra
are given for both.

Physical State: clear oil

Rf: 0.38 (silica gel, DCM)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.91 (bs, 1 H), 7.72 (dd, $J = 6.8$, 2.0 Hz, 1 H), 7.32
(dd, $J = 6.4$, 1.2 Hz, 1 H), 7.08 – 7.15 (m, 2 H), 6.18 (dd, $J = 17.6$, 11.2 Hz, 1 H),
5.67 (d, $J = 10.8$ Hz, 1 H), 5.55 (d, $J = 17.2$ Hz, 1 H), 4.19 (dd, $J = 11.2$, 5.2 Hz, 1
H), 3.11 (d, $J = 11.2$ Hz, 1 H), 2.78 (s, 1 H), 2.39 – 2.50 (m, 1 H), 2.14 – 2.22 (m,
2 H), 1.67 (s, 3 H), 1.46 (s, 3 H), 1.11 (s, 3 H)
See pages 378 – 379 for spectra.

Compound 189:
**Compound 119** (19.6 mg, 0.0598 mmol, 1.0 equiv.) was dissolved in THF (598 µL, 0.1 M) and cooled to −78 ºC. KHMDS (132 µL, 0.0658 mmol, 1.1 equiv., 0.5 M solution) was added and the reaction slowly turned deep orange. Methyl iodide (4.5 µL, 0.0717 mmol, 1.2 equiv.) was added after 30 minutes and the reaction allowed to slowly warm to ambient temperature. After 2 hours, the reaction was quenched with saturated NH₄Cl (5.0 mL) and extracted with Et₂O (10 mL). The organic layer was washed with H₂O (5.0 mL) and brine (5.0 mL), dried (Na₂SO₄), and the solvent removed *in vacuo*. The crude reaction mixture was purified by PTLC (silica gel, 1:1 hexanes:DCM) to give **compound 189** (*ca* 7 mg, *ca* 30%, *dr* = 1.7:1), which was characterized as a mixture of diastereomers (tentative assignment).

**Physical State:** clear oil

**Rf:** 0.35 (silica gel, 1:1 hexane:DCM)

**¹H NMR (600 MHz, CDCl₃):** δ 7.84 (d, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 8.2 Hz, 1 H), 7.15 (t, *J* = 7.0 Hz, 1 H), 7.09 (t, *J* = 7.9 Hz, 1 H), 5.90 (dd, *J* = 17.4, 10.9 Hz, 1 H), 5.04 (d, *J* = 10.9 Hz, 1 H), 4.89 (d, *J* = 17.4 Hz, 1 H), 4.37 – 4.39 (m, 1 H), 3.70 (s, 3 H), 2.65 (t, *J* = 9.7 Hz, 1 H), 2.30 – 2.34 (m, 2 H), 1.60 (s, 3 H), 1.51 (s, 3 H), 1.48 (s, 3 H)

**LRMS (ESI):** caled. for C₂₂H₂₇ClNO [M + H⁺] 356.2, found 356.1

See page 381 for spectrum.
Compound 179:

Compound 119 (153.8 mg, 0.469 mmol, 1.0 equiv.) was dissolved in DCM (782 µL, 0.6 M) and MeCN (782 µL, 0.6 M). DMAP (5.7 mg, 0.0469 mmol, 0.1 equiv.) and Boc₂O (102.4 mg, 0.469 mmol, 1.0 equiv.) were added and stirring continued at ambient temperature for 20 minutes. The reaction was then diluted with EtOAc (20 mL) and washed with 1 N HCl (10 mL), H₂O (10 mL), then brine (10 mL), dried (MgSO₄), and the solvent removed in vacuo. The crude reaction was then purified by flash column chromatography (silica gel, gradient from 3:1 to 1:1 hexanes:DCM) to provide compound 179 (166.8 mg, 83%).

Physical State: pale yellow solid

Rₚ: 0.24 (silica gel, DCM)

¹H NMR (400 MHz, CDCl₃): δ 8.00 – 8.02 (m, 1 H), 7.64 – 7.67 (m, 1 H), 7.20 – 7.24 (m, 2 H), 6.45 (dd, J = 17.6, 10.8 Hz, 1 H), 5.37 (d, J = 10.8 Hz, 1 H), 5.27 (d, J = 17.6 Hz, 1 H), 3.98 – 4.06 (m, 2 H), 2.33 – 2.38 (m, 2 H), 2.18 – 2.23 (m, 1 H), 1.70 (s, 9 H), 1.51 (s, 3 H), 1.48 (s, 3 H), 1.28 (s, 3 H)

LRMS (ESI): calcd. for C₂₅H₃₁ClNO₃ [M + H⁺] 428, found 428

See page 380 for spectrum.
References


Appendix 1: Spectra
Weiwiandolino A (13)
Compound 44
Compound 45
Pin Deprotection Product
Compound 115a
Compound 127
Compound 168
Compound 170
Appendix 2: List of Publications
“Enantioselective Total Synthesis of the Hapalindoles, Fischerindoles, and
Welwitindolinones via Oxidative C–C Bond Formation.” Manuscript Prepared.

Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran,
P. S. “Scope and Mechanism of Direct Indole and Pyrrole Couplings Adjacent to
Carbonyl Compounds: Total Synthesis of Acremoauxin A and Oxazinin 3.” J.

Baran, P. S.; Maimone, T. J.; Richter, J. M. “Total Synthesis of Marine Natural Products

Richter, J. M. “Oxidative C–C Bond Formation in Heterocyclic Chemistry.”
Arkivoc. 2006, 310 – 325.

Baran, P. S.; Richter, J. M. “Enantioselective Total Synthesis of Welwitindolinone A and

Baran, P. S.; Richter, J. M.; Lin, D. W. “Direct Coupling of Pyrroles with Carbonyl
Compounds: Short, Enantioselective Synthesis of (S)-Ketorolac.” Angew. Chem.