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___________________________
Carolyn A. Leverett
Use of Furans as Vehicles for Heterocyclic Synthesis:
An aza-Achmatowicz Approach to Piperidine Alkaloids, a Novel
Oxidative Route to Acyloxypyrrolinones, and IMDAF Studies
Toward a Synthesis of Minfiensine and Morphine

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An Abstract of
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Abstract

Several cis-2-methyl-6-substituted piperidin-3-ol alkaloids exhibit numerous biological activities and thus have become important synthetic targets. In order to develop more efficient approaches to alkaloids from furanyl substituted systems, we have employed the aza-Achmatowicz oxidative rearrangement of N-tosylaminofurans to access the cis-2,6-disubstituted piperidine core. This key oxidation reaction was used to prepare a versatile intermediate which was then utilized to access several related piperidine alkaloids. The methodology was demonstrated by the total synthesis of azimic acid, deoxocassine, cassine, and spicigerine. Additionally, we report a new method for obtaining optically active N-tosylaminofurans, thereby providing a route to a number of optically-active piperidine natural products.

Work in the area of furan rearrangement chemistry has also resulted in the discovery of a novel iodine-promoted rearrangement reaction of 2-amidofurans to acyloxypyrrolinones. The mechanism of this transformation resembles the aza-Achmatowicz mechanism and was found to be general for preparing a variety of substituted acyloxypyrrolinones in good yields. Elaboration of these substrates provides a novel route to synthesize 2,4-disubstituted pyrroles which are present in many natural products.

Our interest in using furans to generate alkaloids also led us to test the IMDAF reaction as a method for accessing the pentacyclic alkaloid known as minfiensine. Since its discovery, minfiensine has shown a wide variety of medicinal activity. Its synthesis continues to be a significant challenge for organic chemists. The preparation and cycloaddition of both 2-amidofuran and 2-imidofuran substrates were studied as an
approach to minfiensine. It was possible to prepare the desired tetrahydroindoline using the intramolecular cycloaddition methodology. Conversion to the core skeleton of minfiensine is expected to be possible through a Buchwald/Hartwig amination/iminium cyclization protocol and is currently being pursued.

Extensive work in the Padwa laboratories has also been performed using IMDAF reactions of indolo substituted systems, thereby providing routes to a variety of natural products. As an extension of this methodology, we tested the possibility of using the IMDAF reaction of the related benzofuran system as a potential route for generating morphine. A variety of 2-substituted benzofurans were generated and submitted to the cycloaddition conditions. The results obtained from these reactions indicate that a significant amount of research is still necessary to determine both the electronic and conformational requirements for such the IMDAF reaction, before the methodology can be applied toward a synthesis of morphine.
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FCGS to this campus. You will never realize how much of an impact you are making in the lives of those like me here at Emory!

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<tr>
<td>µ</td>
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<tr>
<td>[a]</td>
<td>specific rotation</td>
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<td>analysis</td>
</tr>
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<td>aqueous</td>
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<td>argon</td>
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<td>Boc</td>
<td>tert-butoxycarbonyl</td>
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<td>butyl</td>
</tr>
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<td>calculated</td>
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<td>δ</td>
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<td>doublet</td>
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<td>DIBAL-H</td>
<td>Diisobutylaluminum hydride</td>
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<td>demethylamino pyridine</td>
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<td>Decomp</td>
<td>decomposition</td>
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<td>dimethyl formamide</td>
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<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<tr>
<td>E</td>
<td>entgegen</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>EDG</td>
<td>electron donating group(s)</td>
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<td>EWG</td>
<td>electron withdrawing group(s)</td>
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<td>Et</td>
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<td>FT</td>
<td>Fourier transform</td>
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<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
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<td>high resolution mass spectroscopy</td>
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<td>LHMDS</td>
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<tr>
<td>m-CPBA</td>
<td>meta-chloroperbenzoic acid</td>
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</table>
mg  milligram(s)
MHz  megahertz
min  minute(s)
mL  milliliter(s)
mL  microliter(s)
mmol  millimole(s)
mp  melting point
Ms  Methanesulfonyl
NMM  4-methylmorpholine
NMR  Nuclear Magnetic Resonance
q  quartet
rt  room temperature
s  singlet
SM  starting material
t  triplet
TBAF  Tetrabutylammonium fluoride
TBAHS  Tetrabutylammonium hydrogen sulfate
TBS  tert-butyldimethylsilyl
TFA  trifluoroacetic acid
TFAA  trifluoroacetic anhydride
$p$-TsOH  para-toluenesulfonic acid
Chapter 1

Part A: Application of the Aza-Achmatowicz Oxidative Rearrangement for the Stereoselective Synthesis of the *Cassia* and *Prosopis* Alkaloid Family
Introduction

Furan Rearrangement Reactions in Synthesis

Over the past several years, the Padwa group has developed a continuing interest in the use of furans as vehicles for generating core structures found in many natural products. While a significant portion of this work has included studies dealing with the intramolecular Diels-Alder reactions of amidofurans (IMDAF),\textsuperscript{1,2} the group has also been interested in demonstrating the synthetic versatility of 2-furans in rearrangement reactions which provide routes for alkaloid formation.\textsuperscript{3,4}

The literature dealing with furans indicates that these systems can readily rearrange to a variety of products, depending on both the nature of furan substitution as well as the reaction conditions. For example, Piancatelli has demonstrated that treatment of 2-furyl carbinol 1 with acid under mild conditions results in the formation of 5-hydroxy-3-oxocyclopentene 2 (Scheme 1-1).\textsuperscript{5} Many years later, an interesting and related discovery by Walsh and coworkers\textsuperscript{6} showed that 3-furfural 3 is easily converted to the 2,3-disubstituted furan 4 by sequential treatment with NBS and aqueous acid.

Scheme 1-1: Known Furan Rearrangement Reactions
However, the most extensive use of furan rearrangement chemistry generally employs a reaction originally discovered by Achmatowicz and coworkers in 1971. This oxidative rearrangement, now referred to as the Achmatowicz reaction, has become an important method for the conversion of furylcarbinols 5 into hydropyranones 6 (Scheme 1-2). Since its discovery, this oxidation reaction has been employed for the generation of numerous synthetic intermediates and natural products, including such molecules as the triandamycic acid core 7, (+)-KDO 9, (-)-canadensolide 10, and the (+)-Prelog-Djerassi lactone 8.

Scheme 1-2: The Achmatowicz Reaction and Application in Synthesis

This widely applied oxidative rearrangement reaction often proceeds under a variety of conditions, including the use of m-CPBA, NBS, and PCC, although the original oxidative conditions reported by Achmatowicz employed Br₂ in MeOH. The
mechanism of this rearrangement is thought to proceed through formation of a bromonium intermediate, followed by a bromonium ring-opening reaction (Scheme 1-3). Eventually, the furan ring undergoes hydrolysis to give a 1,4-dicarbonyl species, which upon nucleophilic addition of the alcohol provides the corresponding hydropyranone 6.

Scheme 1-3: Proposed Mechanism of the Achmatowicz Reaction

As an extension of the Achmatowicz reaction, the Ciufolini group has pioneered much work in the area of furan rearrangement chemistry using aminofurans of type 11 as a means to achieve access to a variety of nitrogen heterocycles.\textsuperscript{13} The aza-Achmatowicz reaction has proven useful for accessing the azasaccharide deoxymannojirimycin (13),\textsuperscript{14} as well as izidine and aminoacid building blocks,\textsuperscript{15} and a variety of medicinally important substances such as “HPCA” (14)\textsuperscript{15} and the carbacephem antibiotics (15)\textsuperscript{16} (Scheme 1-4).

In connection with ongoing studies in natural product synthesis in the Padwa lab based on amidofuran chemistry,\textsuperscript{17} the group also became interested in employing the aza-
Achmatowicz reaction of N-tosylaminofurans for the synthesis of various piperidine and related alkaloids. In an earlier study from the Padwa laboratory, it was shown that the aza-Achmatowicz oxidation of a furyl-substituted benzenesulfonamide could be used for the synthesis of the putative indolizidine alkaloid 223A (21), which had been isolated from the skin secretion of a neotropical frog. The approach that was employed is shown in Figure 5 and involves a flexible combination of an aza-Achmatowicz oxidative rearrangement followed by a stereoselective allylsilane addition to a N-sulfonyliminium ion followed by subsequent 1,4-conjugate addition (Scheme 1-5).

**Piperidine-Containing Natural Products**

The piperidine ring system is a frequently encountered heterocyclic unit found in many naturally occurring and biologically-important compounds. In particular, 2,6-disubstituted piperidines have attracted much attention because they are found in various ring forms and exhibit a broad range of biological activities. As a
Scheme 1-5: Padwa’s aza-Achmatowicz Approach to epi-Indolizidine 223A

consequence, numerous synthetic methods have been developed for the stereoselective synthesis of 2,6-disubstituted piperidines.\(^{22}\) Most of the earlier procedures have been directed toward the synthesis of simple cis-\(^{23}\) or trans-2,6-dialkylpiperidines.\(^{24}\) The stereoselective synthesis of more complex polysubstituted piperidines still remains a substantial challenge in organic chemistry.\(^{25}\) Among this class of products, 2,6-disubstituted-3-piperidinol alkaloids are frequently encountered in biologically active natural products (Figure 1-1).\(^{26}\)

A small yet important subgroup of piperidin-3-ol alkaloids which are still of continuing interest to synthetic chemists are those of the Cassia and Prosopis species, found in leaves and twigs throughout the world.\(^{27}\) The characteristic framework of these
natural products is the cis-2-methyl-6-substituted piperidin-3-ol skeleton. Structural variation is due to a long aliphatic side chain at C6 which provides for a number of different stereochemical and oxygenation patterns (Figure 1-1). Typical representatives of this family include spectaline (22), julifloridine (23), azimine (24) and carpaine (25).28,29 The latter two structures correspond to macrocyclic dilactones containing two molecules of the 2-methyl-3-piperidinol skeleton together with a carboxyl group as a terminal substituent at the C6 position.30,31 These compounds can be readily hydrolyzed to azimic (26) and carpamic acid (27), which are presumably their biological precursors. Since their discovery in the 1960s, much effort has been directed to the synthesis of these and other related alkaloids such as cassine (28) and deoxocassine (29).32 Besides the interesting structural features, these alkaloids are also of pharmaceutical interest as they
exhibit a wide range of biological activities.\textsuperscript{33} The physiological effects stem from their ability to mimic carbohydrate substrates in a variety of enzymatic processes.

Due to their medicinal potential and characteristic all $cis$-relative stereochemistry, the \textit{Cassia} and \textit{Prosopis} alkaloids are of special synthetic significance, and many have been prepared using a wide variety of methods.\textsuperscript{34,35,36} One of the earliest routes to (±)-carpamic acid (27) relied on singlet oxygen addition to a functionalized pyridine as the key step.\textsuperscript{37} More recently, Lee and co-workers demonstrated the usefulness of a two-carbon homologation of b-lactams to access the piperidine core.\textsuperscript{38} Kumar and Datta reported a stereoselective total synthesis of (+)-azimic acid (26) starting with L-alanine from the chiral pool.\textsuperscript{39} Kibayashi demonstrated an elegant route to azimic acid (26) employing a hetero Diels-Alder cycloaddition.\textsuperscript{40} Finally, Trost and coworkers reported a route to (+)-spectaline (22) using a hydrosilylation-oxidation strategy (Scheme 1-6).\textsuperscript{41}

While there are a number of methods currently known for generating these alkaloids, their vast occurrence in nature and significant biological activity led us to pursue an alternative method for their generation. Specifically, we were inspired by the potential of using the aza-Achmatowicz reaction for generating a variety of nitrogen-containing substances. This interest was based on earlier work in our labs which generated the $cis$-2,6 disubstituted-piperidone 17 and its use for the synthesis of \textit{epi}-indolizidine 223A (21). Therefore, one of the early goals of this thesis was to demonstrate the applicability of furans in total synthesis using an aza-Achmatowicz rearrangement route to produce (±)-azimic acid (26), (±)-deoxocassine (29), (±)-cassine (28), and (±)-spicigerine (40).
Results and Discussion

Aza-Achmatowicz products incorporate functionality that is easily modified and can be utilized to construct complex nitrogen heterocycles. In his early studies of the aza-Achmatowicz reaction, Ciufolini reported that carbamate protected furfurylamines are somewhat unstable and readily hydrolyze to 3-hydroxypiperidines under typical oxidation conditions. Independent work by Zhou and Altenbach, however, showed that a sulfonamide protecting group was nicely compatible with the aza-Achmatowicz oxidation reaction. Consequently, we chose to work with an N-tosyl protecting group because of its robust nature and the ease of purification of the resulting products. Our retrosynthetic strategy for the synthesis of a 3-piperidinol alkaloid system such as
spicigerine (40) envisages initial construction of the functionalized piperidino Weinreb amide 41 from a 6-alkoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2H-pyridin-3-one intermediate (i.e., 42 or 43). The required dihydropyridone 42 (or 43) is easily procured by the aza-Achmatowicz oxidation of furyl sulfonamide 44 (Scheme 1-7). The availability of the Weinreb amide intermediate 41 would also allow for the ready synthesis of cassine (28), deoxocassine (29) and spicigerine (40) by its reaction with an appropriate lithiate derived from either commercially available or easily synthesized alkyl halides.

Scheme 1-7: Key Disconnections for the Synthesis of the 3-piperidinol Alkaloid System

\[
\begin{align*}
\text{spicigerine} & \quad \text{40; } R = (\text{CH}_2)_7\text{CO}_2\text{H} \\
\text{41} & \quad \text{42; } R = \text{Me} \\
\text{44} & \quad \text{43; } R = \text{Et}
\end{align*}
\]

(±)-Azimic Acid Synthesis

Our studies began by subjecting the readily available furyl sulfonamide 44\textsuperscript{45} to an oxidative ring expansion with \textit{m}-CPBA according to the conditions reported by Ciufolini.\textsuperscript{46} The initially formed hemiaminal was immediately treated with trimethyl
orthoformate and catalytic BF$_3$•OEt$_2$ which furnished aminal 42 (R = Me) in 85% yield. Whereas the hemiaminal was difficult to purify, the resulting N-tosyl-O-methylaminal 42 is a stable crystalline solid that could be stored for extended periods of time. A similar procedure was also utilized to transform 44 into the corresponding O-ethylaminal 43 by making use of triethyl orthoformate. Even though both procedures worked well, the synthesis of 44 from 43 proceeded in a somewhat higher yield (95% vs. 85%). Also, the synthetic steps following the aza-Achmatowicz oxidation were higher yielding with the ethoxy substituent, leading us to routinely adopt this more efficient protocol over the previously reported conditions. The exclusive cis-orientation of the substituent group in 42/43 can be rationalized by assuming that A$_{1,3}$-strain of the tosyl group forces the alkoxy and methyl groups to adopt a pseudoaxial orientation. Reduction of 42 with NaBH$_4$ in the presence of CeCl$_3$•7H$_2$O (Luche conditions)$^{47}$ stereoselectively produced alcohol 45 (Scheme 1-8), whose configuration was elucidated by NMR studies. The reduction proved to be remarkably stereospecific, providing the desired cis-alcohol 45 in high diastereomeric form and in 60% isolated yield. This result may be attributed to steric hindrance between the pseudoaxially oriented 2,6-bulky substituents and an equatorially approaching hydride reagent which nicely explains the exclusive formation of the cis-alcohol by axial approach of the hydride.$^{48}$ Alcohol 45 was converted into the corresponding TBS ether 47 using TBSCl and imidazole in 86% yield. A similar set of experiments was also carried out with 43 and this compound was easily converted into the TBS ether 48 in 66% yield (vs. 49% overall yield for formation of 47).

The reaction of the TBS ether 47 or 48 with methyl 3-(trimethylsilyl)-4-pentenoate (49) in the presence of BF$_3$•OEt$_2$ led to the somewhat labile allylic ester 50,
Scheme 1-8: Synthesis of the cis-Trisubstituted Core

which was immediately hydrogenated (H₂, PtO₂, MeOH) to give the key intermediate 51 in 57% yield. The choice of the hydrogenation catalyst proved to be crucial for the success of the reduction. Our first attempts used palladium on carbon (Pd/C) as the catalyst in ethanol. The desired product was isolated in low yield with a nearly equal amount of the isomerized N-tosylenamine. On the other hand, using PtO₂ (Adams catalyst) afforded the desired saturated piperidine 51 as the exclusive product, with no evidence of epimerization at C₆. As suggested by others,⁴⁹ the preference for the cis-substitution pattern in 50 can be rationalized by assuming that the steric bulk associated with the tosyl group directs the attack of the allylsilane on the iminium ion to the side of the C₂-methyl group, thereby leading to the formation of the all cis-stereochemistry.

Having achieved a reliable preparation of the key piperidine intermediate 51, we proceeded to use this compound for the synthesis of azimic acid (26). Our approach to 26 began with the LAH reduction of ester 51 which afforded the corresponding alcohol 52 in 97% yield (Scheme 1-9). Conversion of 52 to the mesylate in the normal fashion
followed by cyanide displacement (NaCN, DMF) provided nitrile 53 which was hydrolyzed to carboxylic acid 54 in 89% yield. Deprotection of the TBS group occurred during the basic hydrolysis conditions used to convert 53 into 54 (NaOH, MeOH). Removal of the tosyl group with Li/NH₃ gave (±)-azimic acid (26) in 70% yield. The spectral data were in good agreement with those reported in the literature.³⁴

Scheme 1-9: Total Synthesis of (±)-Azimic Acid

(±)-Deoxocassine Synthesis

Having successfully obtained azimic acid (26) from piperidine 51, we extended the above strategy to the synthesis of deoxocassine (29). Accordingly, the ester functionality present in piperidine 51 was converted (85% yield) into the corresponding Weinreb amide 41 with methoxymethyl amine hydrochloride and isopropylmagnesium chloride. Although N-methoxy-N-methyl amides are generally prepared from the ester using an aluminum-based reagent,⁵⁰ we found that the use of i-PrMgCl⁵¹ gave higher yields and resulted in a cleaner overall reaction. Treatment of 41 with 6-heptenyllithium in heptane at -78 ºC provided the expected ketone 30 in 56% unoptimized yield (Scheme
1-10). The terminal π-bond present in 56 can be utilized for a synthesis of either deoxocassine (29) or cassine (28) depending on the experimental conditions. Reduction of the carbonyl group in 55 proved more difficult than we originally anticipated. A Wolff-Kishner reduction of 55 provided a complex, intractable mixture of products. Instead, ketone 55 was converted to the corresponding tosylhydrazone and then treated with DiBAL-H/NaOH which afforded 56 in reasonable yield. After hydrogenation of the double bond with PtO₂, the TBS protecting group was removed with TBAF and the tosyl group was cleaved using Li/NH₃ to furnish deoxocassine (29) in 92% yield for the three-step sequence.

Scheme 1-10: Total Synthesis of (±)-Deoxocassine

(±)-Cassine Synthesis

With these encouraging results in hand, the total synthesis of (±)-cassine (28) was next undertaken. We realized that it should be possible to obtain 28 by a Wacker oxidation⁵³ of the piperidinyl substituted alkene 56, but thought it would be more
convergent to employ a side chain that already contained a protected keto group. With this in mind, we prepared 2-(5-bromopentyl)-2-methyl-[1,3]dithiolane (60) in two steps from commercially available 6-bromohexanoic acid. Thus, slow addition of 2.2 equiv of methyllithium to the above acid at -78 °C in THF afforded a 65% yield of the requisite bromopentyl methyl ketone. The ketone was then allowed to react with 1,2-ethanediethiol in CH2Cl2 with BF3•OEt2 to give bromo-dithiolane 60 in 89% yield. Treating 60 with t-BuLi at -78 °C followed by reaction of the resulting lithiate with Weinreb's amide 41 afforded the expected coupled ketone which was subsequently reduced with TsNHNH2-DiBAL-H/NaOH to furnish [1,3]-dithiolane 61 in 45% overall yield. Hydrolysis of 61 afforded the expected methyl ketone in near quantitative yield which was subsequently protected as the dioxolane 63 by reaction with ethylene glycol. Conversion of 63 to (±)-cassine (28) was then accomplished by a series of reactions involving Li/NH3 reduction of the tosyl group and deprotection of the TBS ether in 55% overall yield (Scheme 1-11).

Although the above synthesis served to define the viability of the critical Weinreb amide coupling step, difficulties at the ketone reduction stage and a modest yield in formation of the lithiate derived from dithiolane 60 resulted in a sequence that was less efficient than what we had envisioned. In considering a more direct approach to piperidinyl-ketal 63, we became intrigued by the prospect of generating a lithium reagent directly from 2-(5-bromopentyl)-2-methyl-1,3-dioxolane (64). This led us to reinvestigate the key coupling step using ketal 64 and the Weinreb amide 41 (Scheme 1-12). Although the critical coupling step required some optimization, it ultimately
Scheme 1-11: First Generation Synthesis of (±)-Cassine

(proceeded in good yield to give ketone 65. Conversion of the keto group to the corresponding tosylhydrazone was followed by reduction with DIBAL-H/NaOH to give the same piperidinyldioxolane 63 as had previously been prepared. This latter route represents a considerable improvement over the earlier approach. Thus, a complete synthesis of (±)-cassine (28) is now possible in four short steps starting from the Weinreb amide intermediate 41.

(±)-Spicigerine Synthesis

(±)-Spicigerine (40) represents still another member of the piperidinol alkaloid family and was isolated in minute amounts from Prosopis Spicigera and possesses noteworthy antibiotic and anesthetic properties.\(^{56}\) Surprisingly, only two syntheses of (±)-spicigerine have been reported to date,\(^ {57}\) perhaps as a consequence of the presence of the terminal carboxylic acid functionality. The considerable potential of using Weinreb's
amide 41 for the synthesis of various *Prosopis* alkaloids motivated us to undertake the synthesis of spicigerine (Scheme 1-13). We reasoned that an efficient approach toward this particular alkaloid would involve an oxidative cleavage of the piperidinyl alkene 67, which in turn should be easily available from Weinreb's amide 41. Thus, we extended our earlier two-step strategy and treated Weinreb's amide 41 with 8-octenyl-lithium and this was followed by a subsequent reduction of the resulting ketone 68 using the tosylhydrazone method to give 68. Several different conditions were examined for the oxidation of the terminal π-bond of 68 into the carboxylic acid functionality of 69. The most successful method was a one-pot dihydroxylation/oxidation step using OsO₄ and Oxone. While this method allowed for a one-step synthesis of 69 from 68, the yields were generally poor with the highest being only 53%. Instead, a much higher yield of 69 was obtained (92%) using a two-step sequence where 68 was first oxidized to the aldehyde intermediate followed by a subsequent oxidation to 69 with sodium chlorite. In line with our expectations, exposure of 69 to the TBAF and Li/NH₃ conditions effects
deprotection of the TBS and tosyl groups producing (±)-spicigerine (40) in 64% isolated yield.

Scheme 1-13: Total Synthesis of (±)-Spicigerine

Asymmetric Approach

The construction of versatile chiral building blocks for the efficient synthesis of biologically active natural products is a topic of current interest. A large number of methods leading to the synthesis of chiral piperidine, decahydroquinoline, indolizidine and quinolizidine systems have already been developed. Several methods for the stereoselective construction of 2,6-disubstituted piperidinols have also been reported. In earlier work the Ciufolini group demonstrated that a chemoenzymatic hydrolysis of N-protected furanyl glycine methyl esters could be used to prepare chiral furan derivatives. The resolved furylglycines were shown to be excellent substrates for the synthesis of trans-2,6-disubstituted piperidines by subjecting them to an aza-Achmatowicz oxidation reaction. However, no example of an asymmetric synthesis of a cis-2,6-disubstituted
piperidin-3-ol has appeared to date. As a consequence of our earlier synthetic work in this area, we wondered whether the aza-Achmatowicz oxidation could also be used for the enantiocontrolled synthesis of various members of the *Cassia* and *Prosopis* family of alkaloids. To this end, we examined a new strategy for the asymmetric construction of tosylaminofuran 44 by making use of the elegant sulfilimine chemistry developed independently by the Davis and Ellman groups.\(^\text{66}\) Our synthesis of (S)-44 began by condensing (S)-(+) -p-toluenesulfinimide 72 with 2-acetyl furan 73 in the presence of Ti(OEt)\(_4\) using a modification of conditions reported by Davis (Scheme 1-14).\(^\text{67}\) Stereoselective reduction of the resulting sulfilimine was carried out at low temperatures (−78 to −55 °C) with LiAlH(O-tBu)\(_3\) and this was followed by an immediate oxidation with m-CPBA to give the desired N-tosylaminofuran 44 in ≥73% ee as determined by chiral HPLC. Comparison of the optical rotation of (S)-44 ([α]_D \(-63.5\)) with that reported by Zhou and coworkers\(^\text{68}\) clearly indicates that hydride delivery occurred on the
S$_i$-face of the imine as expected for a sulfoxide directed addition.$^{66}$ Having a sample of (S)-44 on hand, it was then submitted to the aza-Achmatowicz protocol, thereby providing a formal chiral synthesis of azimic acid (26), deoxocassine (29), cassine (28) and spicigerine (40).
Part B: Iodine-Promoted Rearrangement of
2-Amidofurans to Acyloxypyrrrolinones as a Route
Toward the Formation of Functionalized Pyrroles
Introduction

As part of an ongoing project in the Padwa laboratories using amidofurans for total synthesis, synthetic work was directed towards the synthesis of the novel alkaloid daphniyunnine C (76). During the course of these studies an unexpected furan rearrangement reaction was encountered (Scheme 1-15). Specifically, in an attempt to remove the thioketal protecting group\(^{69}\) of furanyl carbamate 77 with iodine and NaHCO\(_3\) in aqueous acetone, none of the expected ketone was formed. Instead, the rearranged product acyloxypyrrolinone 78 was obtained as the exclusive compound. More than likely, the reaction of 77 with iodine proceeds first by formation of an iodonium intermediate and this is followed by an oxygen-assisted ring opening and conversion to a 1,4-dicarbonyl intermediate. Attack of the nitrogen lone pair on the adjacent aldehyde nicely accounts for the rearranged acyloxypyrrolinone product 78. The suggested mechanism is actually an interesting variant of the aza-Achmatowicz oxidative rearrangement reaction that was employed in our earlier synthesis of the Cassia and Prosopis alkaloids. We thought that this reaction could be a potentially useful method for the generation of acyloxypyrrolinones from 2-amidofurans and consequently we decided to investigate the reaction in greater detail.

It is interesting to note that there are only a limited number of routes currently reported for the synthesis of acyloxypyrrolinones. The known routes to these versatile intermediates generally suffer from either low yields or long reaction times and thus represent inefficient methods for generating such species. The Yakushijin group had previously reported on a singlet oxygen-promoted route to acyloxypyrrolinones from
Scheme 1-15: A Novel I$_2$-Promoted Formation of Acyloxypyrrolinones

![Scheme 1-15](image)

**Proposed Mechanism**

However, the reaction time required (7 days) and low yield (45-55%) of the desired product 81 was not particularly useful (Scheme 1-16). More recently, the same group described a similar route to these intermediates starting from diazepines (82 to 81, Figure 2). Unfortunately, the yields were also quite low, providing only 7% yield of the corresponding acyloxypyrrolinone system.

In spite of the fact that there are only a few methods for preparing acyloxypyrrolinones, these compounds have proven to be extremely important substrates for generating a number of biologically-interesting natural products. Most notably, the chiral acyloxypyrrolinone isopropoxy derivative 88 has become an important building block in the Speckamp laboratories. Unfortunately, the synthesis of this compound required a lengthy 7-step synthesis from (R)- or (S)-malic acid (Scheme 1-17).
Scheme 1-16: Other Known Methods for Generating Acyloxypyrrolinones

Scheme 1-17: Speckamp’s Route to the Versatile Chiral Acyloxypyrrolinone Intermediate

Even though the synthesis of 88 is quite long, Speckamp has made use of this versatile intermediate for a wide variety of stereoselective transformations, including Diels-Alder chemistry as well as conjugate addition reactions.72 Both modes of reaction
are stereoselective as a consequence of the directing effect of the isopropoxy substituent at C-5 (Scheme 1-18). The Speckamp group has further used some subsequent transformations of 89 as a means to synthesize several biologically-important natural products, one example being the enantioselective synthesis of (+)-gelsemine (92). 73

Scheme 1-18: Speckamp’s Acyloxypyrrolinone-based Methodology and Routes to Natural Products

Since the development of Speckamp’s original route to the chiral acyloxypyrrolinone 88 from (S)-malic acid, Van Der Deen and coworkers have also demonstrated that acyloxypyrrolinone intermediates such as 94 can be kinetically resolved with Ac₂O and lipase, thereby providing the corresponding enantiopure acylated intermediate 95 (Scheme 1-19). 74 As a consequence of these earlier studies, we became interested in determining whether a set of general conditions could be developed for the rearrangement of 2-amidofurans to acyloxypyrrolinones. A 3-step racemic or possibly a 4-step enantioselective synthesis of these synthetically important intermediates starting
from 2-amidofurans would be most useful. Such a sequence would provide for a much improved and versatile method for their synthesis which would hold much potential for use in natural product chemistry.

**Results and Discussion**

In order to determine whether the iodine-promoted furan rearrangement reaction represents a general method for the synthesis of other acyloxypyrrolinones, we sought to determine the generality of this oxidation reaction with a number of related 2-amidofuran substrates. Our research group has employed 2-amidofurans such as 100 as well as the furanyl carbamate precursor 99 as key intermediates for accessing a variety of natural products. The earlier work allowed us to develop an efficient, scalable method for the synthesis of furanyl carbamate 99 in two steps from commercially available 2-furoic acid (96) by an acyl azide formation/Curtius rearrangement sequence (Scheme 1-20). Treatment of the resulting carbamate 99 with NaH or n-BuLi provides the corresponding anion which is capable of reacting with a number of acid chlorides or mixed anhydrides such as 98, providing various acylated intermediates of type 99. The Boc protecting group of the acylated imidofuran intermediates can be readily removed by treatment with Mg(ClO₄)₂ in CH₃CN to provide the corresponding amidofuran intermediates 100. Since we had found this method to be a reliable route for preparing a variety of 2-
amidofuran derivatives, we decided to employ this general route for preparing the substrates necessary for further testing of the iodine-promoted rearrangement reaction.

Scheme 1-20: General Route for Formation of the Furan Carbamate and 2-Amidofuran Substrates

\[
\begin{align*}
&\text{96} & \begin{array}{c}
1. \text{NaN}_3 \\
2. \text{t-BuOH}
\end{array} \\
&\text{97} & \begin{array}{c}
1. n-\text{BuLi}
\end{array} \\
&\text{99} & \begin{array}{c}
\text{CH}_3\text{CN}
\end{array} \\
&\text{100} & \begin{array}{c}
\text{Mg(ClO}_4\text{)_2}
\end{array}
\end{align*}
\]

\[R = \text{alkyl, aryl, heteroaryl}\]

We discovered that treatment of a variety of amidofurans with 3.0 eq. of iodine and 6.0 eq. of NaHCO\textsubscript{3} in aqueous acetone at either 0°C or 25°C allowed for an efficient route to prepare various acyloxypyrrolinones. The compounds synthesized included products which contain alkyl (94; \(R = \text{Me}\)), aryl (105; \(R = \text{phenyl}\), 107; \(R = \text{dimethoxyphenyl}\), 111; \(R = \text{indolyl}\)) or heteroaryl (109; \(R = \text{OBn}\)) substituents and all the iodine promoted oxidations of these systems occurred in good yield (Table 1-1).

In addition to finding that the oxidation reaction is quite general, we further discovered that compounds containing dimethoxy acetal and alkenyl substituents could
Table 1-1: Furan Rearrangement Reaction with Alkyl, Aryl, and Heteroaryl Substrates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>![Substrate 1]</td>
<td>3 eq. I₂, rt, 0.5 h</td>
<td>![Product 1]</td>
<td>57%</td>
</tr>
<tr>
<td>2)</td>
<td>![Substrate 2]</td>
<td>3 eq. I₂, rt, 0.5 h</td>
<td>![Product 2]</td>
<td>67%</td>
</tr>
<tr>
<td>3)</td>
<td>![Substrate 3]</td>
<td>3 eq. I₂, rt, 3 h</td>
<td>![Product 3]</td>
<td>77%</td>
</tr>
<tr>
<td>4)</td>
<td>![Substrate 4]</td>
<td>3 eq. I₂, rt, 3 h</td>
<td>![Product 4]</td>
<td>70%</td>
</tr>
<tr>
<td>5)</td>
<td>![Substrate 5]</td>
<td>3 eq. I₂, rt, 3 h</td>
<td>![Product 5]</td>
<td>69%</td>
</tr>
<tr>
<td>6)</td>
<td>![Substrate 6]</td>
<td>1 eq. I₂, rt, 3 h</td>
<td>![Product 6]</td>
<td>63%</td>
</tr>
</tbody>
</table>

also be obtained (113 and 115, Table 1-2). At this point we became curious as to whether the oxidation reaction of simple carbamyl furans such as 116 or 97 was also possible using the same general reaction conditions. Indeed, the Boc and ethyl carbamate furans were found to react in the same manner, providing the expected products in good to excellent yield (Table 1-2).

Having ascertained the reaction conditions for acyloxypyrrolinone formation, we then became interested in exploring the use of these intermediates for synthesis. Because of our group’s history in using iminium ion chemistry for total synthesis,79 we decided to
explore the possibility of using such a cyclization reaction to generate the core structure 119 whose skeleton is found in a number of natural products, including (±)-crispine A (120). This potential synthetic route would allow us to readily convert furanyl carbamate 97 into an intermediate of type 119 in only four steps (Scheme 1-21).

Because of the known ability of the dimethoxy substituted aryl group to undergo iminium ion cyclization, we decided to use compound 107 as a model system for exploring the desired cyclization reaction (Table 1-3). Our first attempts to induce cyclization of 107 included the use of a variety of conditions, such as using SnCl₄, TiCl₄, or BF₃•OEt₂ as Lewis acids. Disappointingly, all the conditions tried failed to promote the cyclization of 107, instead resulting in only the recovery of the acyloxypyrrolinone
starting material. We next tried a variety of acids at higher temperatures to induce the cyclization, including the use of \( p \)-TsOH, HCl, TFA, TFAA/TFA, TfOH, and PPA. However, even these attempts to induce the cyclization of 107 to 119 either led to recovered starting material or the complete decomposition of 107.

While these results were somewhat disappointing, a search of the chemical literature revealed only a few isolated cases of iminium ion cyclization employing similar substrates such as 89 (Scheme 1-22).\(^7\)\(^3\),\(^8\)\(^2\),\(^8\)\(^3\) Thus, while the cyclization of iminium ions derived from simple \( N \)-acylamines has been well explored in many laboratories,\(^8\)\(^1\) iminium ion cyclization of \( N \)-diacylamine substrates is dramatically different. More than likely, the failure of these systems to cyclize is due to lack of participation of the nitrogen lone pair which is adjacent to both carbonyl groups in the diacylated species. While Speckamp had previously noted that iminium ion formation from the diacylated nitrogen substrate 89 was not possible, removal of the acyl substituent group on the nitrogen atom followed by treatment with TiCl\(_4\) and allyltrimethylsilane did lead to the desired addition
product 122 (Scheme 1-22). This result is somewhat related to the observations that we have made and clearly shows that iminium ions are not readily formed from imides.

### Table 1-3: Conditions Tested for Intramolecular Iminium Ion Cyclization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>1.0 eq. SnCl₄, CH₂Cl₂, -78°C to rt overnight</td>
<td>No reaction</td>
</tr>
<tr>
<td>2)</td>
<td>1.0 eq. TiCl₄, CH₂Cl₂, -78°C to rt overnight</td>
<td>No reaction</td>
</tr>
<tr>
<td>3)</td>
<td>1.0 eq. BF₃•OEt₂, CH₂Cl₂, -78°C to rt overnight</td>
<td>No reaction</td>
</tr>
<tr>
<td>4)</td>
<td>1.0 eq. TsOH•H₂O, benzene, 0°C to reflux overnight</td>
<td>No reaction</td>
</tr>
<tr>
<td>5)</td>
<td>1.0 eq. Sc(OTf)₃, CH₂Cl₂, -78°C to reflux overnight</td>
<td>No reaction</td>
</tr>
<tr>
<td>6)</td>
<td>1.0 eq. HCl, Et₂O, EtOH, reflux 1h</td>
<td>nucleophilic addn of EtOH</td>
</tr>
<tr>
<td>7)</td>
<td>TFA (excess), CH₂Cl₂, rt, 24 h, the reflux 24 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>8)</td>
<td>TFA/TFAA (12:1), CH₂Cl₂, reflux 48 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>9)</td>
<td>HCO₂H (excess), THF, rt, 24 h, then reflux 24 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>10)</td>
<td>TiOH (2.0 eq), CH₂Cl₂, rt, 24h, then reflux 24h</td>
<td>decomposition</td>
</tr>
<tr>
<td>11)</td>
<td>PPA (excess), 90°C, 18 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>12)</td>
<td>10% H₂SO₄, 90 -95°C, 20 h</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

### Scheme 1-22: Speckamp’s Iminium Studies of Acyloxypyrrolinones
Realizing that simple iminium ion generation and cyclization is unlikely to produce the desired cyclization product 119, we were interested in determining whether any other type of cyclization reaction was possible using the acyloxypyrrolinone structure. We first tested standard Mitsunobu conditions (Scheme 1-23) similar to those employed by Boger to facilitate an aryl-nucleophile-promoted cyclization reaction in his total synthesis of (+)-duocarmycin A.84 We soon discovered that the desired cyclization reaction still did not occur, and only unreacted starting material was recovered from the reaction.

Scheme 1-23: Attempted Mitsunobu Cyclization Reactions

![Scheme 1-23: Attempted Mitsunobu Cyclization Reactions](image)

We also tested whether a metal-catalyzed cyclization might be induced to occur. Earlier work by Speckamp showed that a successful intermolecular nucleophilic substitution reaction of acyloxypyrrolinones could take place via olefin complexation with tetracarbonyliron complexes.85 Other examples in the chemical literature also showed that a significant number of reactions can occur via a π-allyl-mediated nucleophilic addition of allylic acetates.86 Consequently, we thought it might be possible to induce an intramolecular nucleophilic addition of 124 to give 119 by making use of a metal-catalyzed promoted process. In order to prepare the necessary allylic acetate
intermediate, acyloxypyrrolinone 107 was treated with acetic acid and pyridine, and this reaction cleanly provided the desired acetate 124 in 73% yield (Scheme 1-24).

With this test substrate in hand, we tried to induce the cyclization of 124 to give 119 using several palladium-catalyzed conditions, such as the use of Pd(PPh₃)₄, Pd(OAc)₂, and Pd(dba)₂ catalysts with a variety of ligands. However, only decomposition products were observed in all cases (Scheme 1-24). It was not obvious whether the outcome of these attempted cyclizations was due to the harshness of the conditions or the lack of nucleophilicity of the methoxy-substituted aromatic ring. Therefore, we chose to examine the palladium-mediated intermolecular π-allyl substitution reaction of 124 using Pd(PPh₃)₄ and i-PrOH as the solvent and nucleophile (Scheme 1-24). Indeed, under these conditions, a substitution reaction was possible and this resulted in the formation of the corresponding isopropoxy intermediate 125 in excellent yield. The intermolecular reaction making use of i-PrOH as the solvent certainly involved a much higher concentration of the nucleophile than the previously attempted intramolecular conversion of 124 to 119. This observation led us to conclude that a large excess of nucleophile must be present before addition to the pyrrolinone core can occur.

Even though our attempted cyclization studies did not take place using these acyloxypyrrolinones, we did see some other potential for the synthetic utility of these substituted acyloxypyrrolinones. Because of the importance of functionalized pyrroles as synthetic intermediates in heterocyclic chemistry as well as their presence in natural products, we became interested in developing a method for the formation of functionalized pyrroles starting from acyloxypyrrolinone intermediates. Specifically, we were interested in developing conditions that would allow us to prepare highly
Scheme 1-24: Palladium-Catalyzed π-allyl Reactions of Acyloxypyrrolinones

![Scheme 1-24](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions (124 to 119)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>20 mol% Pd(PPh₃)₄, toluene, 100°C, 24 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2)</td>
<td>10 mol% Pd(OAc)₂, P(o-Tol)₃, Et₃N, toluene, 100°C, 18 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3)</td>
<td>Pd(db)₂, THF, 100°C, 18 h</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

functionalized 2,4-disubstituted pyrroles. At first we thought it necessary to protect the hydroxyl group present on the pyrrolinone ring. Thus, we found that the Ag₂O/MeI treatment of the hydroxy group present in the acyloxypyrrolinone provided an almost quantitative yield of several methoxy derivatives (Scheme 1-25). Our ability to easily prepare compound 126 in only two steps from furanyl carbamate 97 led us to probe whether this intermediate could be used for a new synthesis of various substituted pyrroles.

We clearly recognized the potential of using Speckamp’s conjugate addition method for C-4 functionalization.⁸² Thus, a variety of lithiate/cuprate addition reactions were examined using substrate 126 and this resulted in the preparation of tert-butyl, methyl, phenyl, butyl, and hexyl substituted products (Scheme 1-26). With the exception
Scheme 1-25: Methylation and Synthesis of the Pyrrole-Formation Test

**Substrate**

```
\[
\begin{array}{c}
\text{N} & \text{O} & \text{O} \\
\text{O} & \text{N} & \text{O} \\
\text{Me} & \text{Ag_2O, MeI} & \text{CH_2Cl_2} \\
\end{array}
\] \\
118; R = O-t-Bu \\
117; R = OEt \\
107; R = CH_2-(3,4)-dimethoxyphenyl
```

of the case where R = Ph, which utilized CuBr•MeS as the source of copper, all of the other reaction conditions made use of the corresponding alkyl lithiate reagent together with CuI. This reaction afforded the expected conjugate addition product in good to excellent yield.

Scheme 1-26: C-4 Functionalization by Conjugate Addition Reactions

```
\[
\begin{array}{c}
\text{N} & \text{O} & \text{OMe} \\
\text{O} & \text{O} & \text{t-Bu} \\
\text{RLi} & \text{Cu source} & \text{R} \\
\end{array}
\] \\
126; R = t-Bu, 99% \\
127; R = OEt, 98% \\
128; R = CH_2-(3,4)-dimethoxyphenyl, 91%
```

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>t-BuLi, Cul, -78°C to rt 2 h</td>
<td>131; R = t-Bu</td>
<td>80%</td>
</tr>
<tr>
<td>2)</td>
<td>PhLi, CuBr•MeS, -78°C to rt 3 h</td>
<td>132; R = Ph</td>
<td>78%</td>
</tr>
<tr>
<td>3)</td>
<td>n-BuLi, Cul, -78°C to rt 1h</td>
<td>133; R = n-Bu</td>
<td>92%</td>
</tr>
<tr>
<td>4)</td>
<td>MeLi, Cul, -78°C 45 min.</td>
<td>134; R = Me</td>
<td>80%</td>
</tr>
<tr>
<td>5)</td>
<td>Hexyllithium, Cul, -78°C to rt 2h</td>
<td>135; R = hexyl</td>
<td>58%</td>
</tr>
</tbody>
</table>
Having ready access to the corresponding C-4 alkylated/arylated products, we were ready to next examine the Grignard addition to the C-2 carbonyl group. The resulting product would then be subjected to acid-catalyzed dehydration conditions to provide the corresponding pyrrole substrate (Scheme 1-27). Based on earlier results by Moeller and coworkers\(^8\) who showed that it was possible to selectively reduce the C-2 carbonyl of acyloxypyrrolidinones, we thought it might be possible to selectively add a Grignard reagent to the C-2 carbonyl group. Also, Grignard addition generally favors addition to the less hindered carbonyl in imide systems of this type.\(^8\) In addition, the Grignard addition was expected to take place more readily with the less hindered C-2 carbonyl group over the sterically more hindered Boc carbonyl group.

Scheme 1-27: The Proposed Two-Step Grignard Functionalization/Elimination Route to Pyrroles

\[
\begin{align*}
\text{R}_{\text{MgBr}} & \quad \xrightarrow{\text{H}^+} \\
\text{130} & \quad \text{136} & \quad \text{137}
\end{align*}
\]

Indeed, we were pleased to discover that the addition of various Grignard reagents at -78°C or 0°C to compound 130 occurred and led to formation of the corresponding hemiaminal intermediates 136 (Table 1-4). While this reaction gave the desired product, the yields were found to be somewhat low in a majority of the studied cases. A number of optimization studies are currently underway in our laboratories to increase the yield of the desired hemiaminal product. We also found that intermediates such as 136 are
extremely unstable and readily decomposed, especially during purification on silica gel chromatography. While some of the corresponding Grignard addition products could be purified using alumina chromatography, we found that it was advantageous to simply take the crude hemiaminal intermediate and convert it to the corresponding pyrrole.

Table 1-4: Formation of Hemiaminal Products by Grignard Addition to Acyloxypyrrolidinones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>131; R$_1$ = t-Bu</td>
<td>AllylMgBr, -78°C 0.5 h, 0°C 1.5 h</td>
<td>140; R$_1$ = t-Bu, R$_2$ = allyl</td>
</tr>
<tr>
<td>2)</td>
<td>132; R$_1$ = Ph</td>
<td>VinylMgBr, -78°C 0.5 h, 0°C 1.5 h</td>
<td>141; R$_1$ = Ph, R$_2$ = vinyl</td>
</tr>
<tr>
<td>3)</td>
<td>133; R$_1$ = n-Bu</td>
<td>VinylMgBr, -78°C 1 h</td>
<td>142; R$_1$ = Bu, R$_2$ = vinyl</td>
</tr>
</tbody>
</table>

Thus, having the hemiaminal products 140-142 in hand, we next examined a number of conditions for their conversion to the pyrrole ring. We expected that subjectation of these compounds to acid dehydration conditions would generate the pyrrole by a mechanism similar to that involved in the Paal-Knorr pyrrole synthesis.$^{89}$ Even though this widely-used protocol for pyrrole formation typically utilizes acidic conditions, we found that treatment of hemiaminal 140 with aqueous HCl only resulted in decomposition.

Probably a consequence of the instability of hemiaminals such as 139 under strongly acidic conditions, we decided to use another set of conditions which had
previously been used by Fukuyama\textsuperscript{90} and Ciufolini\textsuperscript{91} (Scheme 1-28). These newer dehydration conditions employ a QCS salt catalyst, formed by mixing a 1:1 molar ratio of quinoline and camphorsulfonic acid. This reagent had been widely used as a method for forming enamides from their corresponding hemiaminal precursors. Even though these conditions had not been specifically applied toward formation of pyrroles, we recognized this simple catalyst might be used to induce a “double elimination” in order to generate the pyrrole ring from the hemiaminal substrates.

**Scheme 1-28: QCS-Promoted Method for Enamide Formation**

![Scheme 1-28: QCS-Promoted Method for Enamide Formation](image)

Indeed, we found that heating a sample of 142 in toluene with 10 mol % of the QCS catalyst for 2 h at reflux provided the desired pyrrole 146 in 19% overall yield (Scheme 1-29). These same conditions were applied to several other analogs, which also allowed for the formation of other functionalized pyrroles in a slightly higher yield (147-148, Scheme 1-29). Unfortunately, at this time the yield for this two-step sequence is still rather low. Knowing that the initial Grignard addition reaction to the C-2 carbonyl group is unreliable, we suspect that the initial step could be the cause of the low-yielding sequence. Further work is necessary to develop a more optimized set of reaction conditions for hemiaminal formation. Our expectation is that the overall yield for pyrrole
formation will increase dramatically and this will allow for the ready synthesis of a wide range of 2,4-disubstituted pyrroles.

Scheme 1-29: QCS-Mediated “Double Elimination” Route to Functionalized Pyrroles

In summary, the above studies led us to develop the use of the QCS catalyst as a reagent for preparing several functionalized pyrroles from various hemiaminal intermediates. Grignard addition to the C-2 position of several substituted pyrrolidinones demonstrates the versatility of this method for generating the required hemiaminal intermediates. The reaction to generate pyrroles is currently being further optimized in our laboratories. The overall reaction sequence does allow for some synthetic versatility and also demonstrates that the iodine-promoted reaction of amidofurans can be used for the eventual synthesis of 2,4-disubstituted pyrroles thereby providing a route for the preparation of this important 5-membered ring heterocycle.
Experimental Section
6-Methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2H-pyridin-3-one (42). A 0.39 g (1.1 mmol) sample of furyl sulfonamide 44, 4 mL of CH$_2$Cl$_2$, and m-CPBA (0.39 g, 2.3 mmol) were placed in a round bottom flask and the mixture was stirred for 2 h at rt. The reaction mixture was quenched with a saturated aqueous NaHCO$_3$ solution (15 mL) and 15 mL of ether was added. The solution was extracted with ether, the layers were separated, and the organic layer was dried (MgSO$_4$). Concentration under reduced pressure and purification by silica gel chromatography gave 0.27 g (0.96 mmol, 85%) of the labile hemiaminal as a clear oil; IR (thin film) 1686, 1597, 1449, 1332, 1165, 1110, and 1006 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.59 (d, $J$ = 7.2 Hz, 3H), 2.38 (s, 3H), 3.82 (brs, 1H), 4.36 (q, 1H, $J$ = 7.2 Hz), 5.90 (dd, 1H, $J$ = 4.8 and 1.2 Hz), 5.96 (dd, 1H, $J$ = 10.0 and 1.2 Hz), 6.86 (dd, 1H, $J$ = 10.4 and 4.8 Hz), 7.25 (d, 2H, $J$ = 8.4 Hz), and 7.62 (d, 2H, $J$ = 8.4 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 21.5, 22.1, 57.0, 73.3, 126.2, 126.7, 130.0, 136.5, 143.5, 144.3, and 195.3.

A 1.0 g (3.5 mmol) sample of the above 6-hydroxy-2H-pyridin-3-one was dissolved in 20 mL of CH$_2$Cl$_2$ and trimethyl orthoformate (777 $\mu$L, 7.1 mmol) and BF$_3$•OEt$_2$ (45 $\mu$L, 0.36 mmol) were added to the solution. The solution was stirred for 3 h at 0 °C and was quenched with a saturated aqueous NaHCO$_3$ solution (25 mL) and 40 mL of ether was added. The solution was extracted with ether, the layers were separated, and the organic layer was dried (MgSO$_4$). Concentration under reduced pressure and
purification by silica gel chromatography gave 0.89 g (3.0 mmol, 85%) of 42 as a white solid; mp 113-115 °C; IR (thin film) 1692, 1597, 1453, 1340, 1168, 1080, and 1014 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.56 (d, 3H, \(J = 7.6\) Hz), 2.38 (s, 3H), 3.57 (s, 3H), 4.30 (q, 1H, \(J = 7.6\) Hz), 5.58 (dd, 1H, \(J = 4.8\) and 0.8 Hz), 5.82 (dd, 1H, \(J = 10.4\) and 0.8 Hz), 6.82 (dd, 1H, \(J = 10.4\) and 4.8 Hz), 7.24 (dd, 2H, \(J = 8.0\) and 1.2 Hz), and 7.56 (dd, 2H, \(J = 8.0\) and 1.2 Hz); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 20.8, 21.5, 56.0, 57.2, 80.7, 126.6, 126.8, 130.0, 136.1, 142.5, 144.1, and 195.5; Anal. Calcd for C\(_{14}\)H\(_{17}\)NO\(_4\)S: C, 56.93; H, 5.81; N, 4.75. Found: C, 56.81; H, 5.69; N, 4.70.

\[ \begin{array}{c}
\begin{array}{c}
\text{Me} \\
\text{NHTs}
\end{array}
\end{array} \rightarrow \begin{array}{c}
\begin{array}{c}
\begin{array}{c}
\text{Me} \\
\text{NHTs}
\end{array}
\end{array}
\end{array} \] \begin{array}{c}
1. m-CPBA, CH\(_2\)Cl\(_2\) \\
2. p-TsOH, CH(OEt)\(_3\)
\end{array} \rightarrow \begin{array}{c}
\begin{array}{c}
\begin{array}{c}
\text{EtO}^\bullet \\
\text{Ts}
\end{array}
\end{array} \\
\text{Me}
\end{array}
\] \(95\%\) (2 steps)

6-Ethoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2H-pyridin-3-one (43). A procedure similar to that described above was used to prepare 43 (95%); mp 94-96 °C; IR (thin film) 2981, 1690, 1357, 1335, 1169, 1072, 1012, 815, and 677 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.26 (t, 3H, \(J = 7.2\) Hz), 1.58 (d, 2H, \(J = 7.6\) Hz), 2.38 (s, 3H), 3.71 (dq, 1H, \(J = 14.0\) and 7.2 Hz), 4.02 (dq, 1H, \(J = 14.0\) and 7.2 Hz), 4.30 (q, 1H, \(J = 7.2\) Hz), 5.68 (d, 1H, \(J = 4.8\) Hz), 5.82 (d, 1H, \(J = 10.4\) Hz), 6.82 (dd, 1H, \(J = 4.8\) and 4.8 Hz), 7.24 (d, 2H, \(J = 8.4\) Hz), and 7.56 (d, 2H, \(J = 8.4\) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 15.1, 21.1, 21.7, 57.4, 64.2, 79.4, 126.7, 127.0, 130.2, 136.4, 143.1, 144.3, and 195.8; Anal. Calcd for C\(_{15}\)H\(_{19}\)NO\(_4\)S: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.17; H, 6.17; N, 4.44.
6-Methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridin-3-ol (45). To a solution of 4.7 g (12.5 mmol) of cerium trichloride heptahydrate in 100 mL of MeOH was added 3.7 g (12.5 mmol) of N-tosyl aminal 42. The solution was chilled to -40 °C, and 0.5 g (14 mmol) of NaBH₄ was added. The solution was stirred for 10 min at -40 °C, and was then quenched with a saturated NaHCO₃ solution. The solution was extracted with CH₂Cl₂ and the combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to give 2.2 g (60% yield) of the titled compound 45 as a colorless oil; IR (thin film) 2939, 1332, and 1167 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.20 (d, 3H, J = 6.8 Hz), 1.68 (d, 1H, J = 7.6 Hz), 2.42 (s, 3H), 3.49 (s, 3H), 3.87 (m, 1H), 4.03 (dq, 1H, J = 7.2 and 7.2 Hz), 5.37 (m, 1H), 5.62 (ddd, 1H, J = 10.8, 3.2 and 1.6 Hz), 5.81 (ddd, 1H, J = 10.4, 3.6 and 2.4 Hz), 7.28 (d, 2H, J = 8.0 Hz), and 7.69 (d, 2H, J = 8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 13.2, 21.7, 49.8, 56.3, 65.5, 80.9, 125.3, 127.2, 129.9, 130.7, 138.1, and 143.9; HRMS Calcd. for C₁₄H₁₉NSO₄: 297.1035. Found: 297.1033.

3-(tert-Butyl-dimethyl-silanyloxy)-6-methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine (47). To a solution of 0.7 g (2.3 mmol) of 45 in 25 mL of
CH₂Cl₂ was added 0.3 g (4.6 mmol) of imidazole and a catalytic amount of 4-(dimethylamino)pyridine followed by 0.4 g (2.8 mmol) of tert-butyldimethylchlorosilane. The resulting solution was stirred at rt for 30 min, water was added, and the solution was extracted with ether and dried over MgSO₄. After removal of the solvent under reduced pressure, the crude product was purified by silica gel chromatography to give 0.82 g (86% yield) of the titled compound 47 as a colorless oil; IR (thin film) 2935, 1469, 1382, 1159 and 1073 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.12 (d, 6H, J = 5.6 Hz), 0.80 (s, 9H), 1.17 (d, 3H, J = 7.2 Hz), 2.42 (s, 3H), 3.49 (s, 3H), 3.69 (m, 1H), 3.84 (dq, 1H, J = 6.8 and 6.8 Hz), 5.36 (m, 1H), 5.50 (dd, 1H, J = 10.8 and 1.6 Hz), 5.72 (ddd, 1H, J = 10.0, 7.2 and 7.2 Hz), 7.29 (d, 2H, J = 8.4 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -5.01, -4.85, 13.2, 18.2, 21.7, 25.8, 50.3, 56.1, 65.6, 80.9, 124.2, 127.3, 129.9, 132.0, 138.5, and 143.8; HRMS Calcd. for C₂₀H₃₃NSiSO₄: 411.1899. Found: 411.1903.

3-(tert-Butyl-dimethyl-silanyloxy)-6-ethoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine (48). To a solution of 6-ethoxy-2H-pyridin-3-one 43 (0.78 g, 2.5 mmol) at −50 °C in MeOH (30 mL) was added CeCl₃•7H₂O (0.95 g, 2.5 mmol) followed by the portionwise addition of NaBH₄ (0.1 g, 2.5 mmol) over a 20 min period. The reaction mixture was stirred at −40 to −50 °C for an additional 30 min, and was then
diluted with H₂O and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Silica gel chromatography gave 0.64 g of 21 as a clear oil which was immediately used in the next step. The oil was taken up in CH₂Cl₂ (20 mL), cooled to 0 °C, and then TBSCl (0.37 g, 2.4 mmol) was added, followed by imidazole (0.28 g, 4.0 mmol) and a catalytic amount of DMAP. The solution was stirred from 0 °C to 25 °C over 16 h, diluted with H₂O and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄, filtered, and concentrated to an oil which was purified by silica gel chromatography to provide 0.7 g (66%) of 48 as a clear oil; IR (thin film) 2929, 2853, 1470, 1393, 1343, 1171, 1114, 1076, 987, 885, and 835 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.15 (d, 6H, J = 6.0), 0.78 (s, 9H), 1.19 (m, 6H), 2.40 (s, 3H), 3.64 (m, 2H), 3.85 (m, 2H), 5.47 (m, 2H), 5.71 (m, 1H), 7.27 (d, 2H, J = 8.0 Hz), and 7.68 (d, 2H, J = 8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -5.0, -4.9, 13.3, 15.3, 18.2, 21.6, 25.8, 50.3, 63.8, 65.5, 79.5, 124.7, 127.3, 129.9, 131.8, 138.5, and 143.7; HRMS Calcd for [(C₂₁H₄₅NO₄SSi) + H⁺]: 426.2056. Found: 426.2129.

5-[5-(tert-Butyl-dimethyl-silyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-pentanoic Acid Methyl Ester (51). To a solution of 0.7 g of TBS ether 47 or 48 (1.7 mmol) in 20 mL of CH₂Cl₂ at -78 °C was added 0.6 g (2.9 mmol) of methyl-3-(trimethylsilyl)-4-pentenonate (24) followed by 4 drops of BF₃•OEt₂. The reaction was
stirred at -78 °C for 7 h and was then quenched with a saturated sodium bicarbonate solution. After warming to room temperature, the layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. The crude unsaturated ester 25 was dissolved in 20 mL of methanol and a catalytic amount of platinum (IV) oxide was added. The flask was purged with hydrogen gas three times before being allowed to stir under a hydrogen balloon for 17 h. The solution was filtered through a pad of Celite, concentrated under reduced pressure and subjected to flash silica gel chromatography to give 0.72 g (87%) of 51 as a white solid; mp 75-76 °C; IR (thin film) 2950, 1739, 1463, 1339, and 1109 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.08 (d, 6H, J = 3.6 Hz), 0.80 (s, 9H), 1.22 (d, 3H, J = 7.2 Hz), 1.50 (m, 10H), 2.32 (t, 2H, J = 7.2 Hz), 2.41 (s, 3H), 3.19 (m, 1H), 3.67 (s, 3H), 3.96 (m, 3H), 7.28 (d, 2H, J = 7.4 Hz), and 7.69 (d, 2H, J = 7.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -4.8, -4.6, 14.9, 18.1, 21.6, 23.6, 24.9, 25.9, 26.9, 27.5, 34.1, 34.9, 51.7, 51.9, 53.1, 69.4, 126.9, 129.8, 139.1, 143.1, and 174.3; Anal. Calcd for C₂₅H₄₃NO₅SSi: C, 60.32; H, 8.71; N, 2.81. Found: C, 60.21; H, 8.58; N, 2.81.

5-[5-<i>tert</i>-Butyl-dimethyl-silanyloxy]-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-pentan-1-ol (52). To a solution of 0.13 g (0.26 mmol) of piperidino ester 51 at 0°C was slowly added 0.3 mL of a solution of lithium aluminum hydride (1M in THF). After the addition was complete, the reaction was quenched by the careful addition of
Na$_2$SO$_4$·10H$_2$O. After stirring for 30 min at rt, MgSO$_4$ was added and the solution was filtered. The solution was concentrated under reduced pressure and the crude product was subjected to flash silica gel chromatography to give 0.12 g (97%) of the titled compound 52 as a clear oil; IR (thin film) 3418, 2855, 1462, and 1095 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ -0.08 (d, 6H, $J = 3.6$ Hz), 0.82 (s, 9H), 1.23 (d, 3H, $J = 7.2$ Hz), 1.30-1.80 (m, 13H), 3.43 (s, 3H), 3.19 (m, 1H), 3.66 (dt, 2H, $J = 2.8$ and 6.8 Hz), 3.98 (m, 2H), 7.28 (d, 2H, $J = 8.0$ Hz), and 7.70 (d, 2H, $J = 8.4$ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ -4.8, -4.6, 14.9, 18.2, 21.7, 23.6, 25.6, 25.9, 27.0, 27.5, 32.8, 35.2, 51.9, 53.1, 63.0, 69.4, 126.9, 129.8, 139.1, and 143.0; HRMS Calcd. for C$_{24}$H$_{43}$NSiSO$_4$: 469.2682. Found: 469.2675.

![](image)

6-[(tert-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-hexanenitrile (53). To a solution of 0.26 g (0.6 mmol) of alcohol 52 in 5.5 mL of CH$_2$Cl$_2$ was added methanesulfonyl chloride (0.09 g, 0.8 mmol). The solution was cooled to 0°C and 0.09 g of triethylamine was added dropwise. After warming to rt over 30 min, the reaction was quenched by the addition of water. The solution was extracted with CH$_2$Cl$_2$, dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was dissolved in 2 mL of DMF, and 0.05 g of sodium cyanide was added. The reaction mixture was heated at 50 °C for 15 h. After cooling to rt, water was added, and the mixture was extracted with ether. The ether extracts were washed three time with
brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.18 g (68%) of the titled compound 53 as a clear oil; IR (thin film) 2943, 2242, 1592, 1150 and 1104 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.08 (d, 6H, J = 3.6 Hz), 0.82 (s, 9H), 1.24 (d, 3H, J = 7.2 Hz), 1.30-1.74 (m, 12H), 2.36 (t, 2H, J = 7.2 Hz), 2.43 (s, 3H), 3.17 (m, 1H), 3.96 (m, 1H), 7.29 (d, 2H, J = 8.4 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -4.8, -4.6, 14.9, 17.3, 18.1, 21.7, 23.6, 25.5, 25.9, 26.4, 27.6, 28.6, 35.0, 51.8, 53.2, 69.3, 120.0, 126.9, 129.8, 139.0, and 143.1; HRMS Calcd. for C₂₅H₄₂N₂SiSO₃: 478.2685. Found: 478.2677.

6-[5-Hydroxy-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-hexanoic Acid (54).

To a solution of 0.09 g (0.19 mmol) of nitrile 53 in 2 mL of methanol was added 2 mL of a 50% NaOH solution. The mixture was heated at reflux for 3 h and cooled to rt. The solution was extracted once with ether and then the aqueous portion was acidified to pH 2 using a 6 N HCl solution. The acidified solution was extracted with CHCl₃ and the combined extracts were dried over MgSO₄ and concentrated under reduced pressure. The crude product contained 0.06 g (89%) of the titled compound 54 as a clear oil; IR (thin film) 3453, 2934, 2871, 1705, 1328 and 1155 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.25 (d, 4H, J = 7.2 Hz), 1.35-1.64 (m, 13H), 2.36 (t, 2H, J = 7.6Hz), 2.42 (s, 3H), 3.37 (m, 1H), 3.94 (q, 1H, J = 6.8Hz), 4.17 (dq, 1H, J = 6.8 and 6.8 Hz), 7.28 (d, 2H, J = 8.4 Hz).
Hz), and 7.70 (d, 2H, J = 8.4 Hz); 13C-NMR (100 MHz, CDCl₃) δ 14.7, 21.7, 23.0, 24.7, 27.1, 27.3, 29.0, 34.1, 35.0, 51.9, 52.4, 69.1, 126.9, 129.9, 138.9, 143.2, and 179.2; HRMS Calcd. for C₁₉H₂₉NSO₅: 383.1766. Found: 383.1772.

6-(5-Hydroxy-6-methyl-piperidin-2-yl)-hexanoic Acid (26). To a solution of 0.002 g (0.044 mmol) of carboxylic acid 54 in 0.6 mL of THF at -78°C was condensed 3 mL of NH₃ using a dry ice condenser. To this solution was added lithium chips which resulted in the formation of a deep blue color. The mixture was allowed to stir at -78°C for 30 min, and then 0.5 mL of isoprene was added to quench the reaction. The solution was warmed to rt and water was added to the resulting residue. The solution was brought to pH 7 by the addition of 6 N HCl, and the solvent was subsequently removed under reduced pressure. Methanol was added to precipitate any inorganic salts, and the resulting solution was filtered and concentrated under reduced pressure to give 0.007 g (70%) of (±)-azimic acid (26) as a white solid, mp 217-218 °C (lit 214-215 °C); IR (thin film) 3344, 1633, and 1551 cm⁻¹; 1H-NMR (400 MHz, CD₃OD) δ 1.33 (d, 2H, J = 6.8 Hz), 1.22-1.81 (m, 11H), 1.96 (m, 1H), 2.17 (t, 2H, J = 7.4 Hz), 3.03 (bs, 1H), 3.21 (q, 1H, J = 6.4 Hz), and 3.83 (brs, 1H); 13C-NMR (150 MHz, CDCl₃) δ 16.4, 24.0, 26.1, 27.3, 30.4, 31.4, 35.0, 39.0, 57.6, 58.7, 66.3, and 182.9; FAB HRMS Calcd. for [(C₁₂H₂₃NO₃)+H⁺]: 230.1756. Found: 230.1759.
5-[5-(tert-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-pentanoic Acid Methoxymethylamide. To a solution of 0.3 g (0.6 mmol) of piperidino ester 51 in THF (1.2 mL) was added methoxymethylamine hydrochloride. The resulting slurry was chilled to approximately -20 °C, and iso-propylmagnesium chloride (0.9 mL of a 2M solution in THF (1.8 mmol)) was added. The solution was stirred at this temperature for 20 min and was then quenched by addition of a saturated ammonium chloride solution. The reaction mixture was extracted with CH₂Cl₂, dried over MgSO₄, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.27 g (85% yield) of 41 as a white solid, mp 77-78 °C; IR (thin film) 2947, 2848, 1663, 1461, 1161, and 999 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.10 (d, 6H, J = 3.6 Hz), 0.79 (s, 9H), 1.21 (d, 3H, J = 7.2 Hz), 1.29-1.73 (m, 10H), 2.40 (s, 3H), 2.43 (m, 2H), 3.16 (m, 4H), 3.67 (s, 3H), 3.95 (m, 2H), 7.26 (d, 2H, J = 8.0 Hz), and 7.67 (d, 2H, 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -4.9, -4.7, 14.8, 18.0, 21.6, 23.5, 24.6, 25.8, 27.2, 27.4, 31.9, 32.2, 35.0, 51.9, 53.1, 61.4, 69.3, 126.8, 129.7, 139.0, 143.0, and 174.7; HRMS Calcd. for C₂₆H₄₆N₂SiO₅: 526.2897. Found: 526.2889.
1-[5-(tert-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-dodec-11-en-5-one (55). To a solution of 0.1 g (0.6 mmol) of 1-iodo-6-heptene in 0.5 mL of heptane at -78˚C was added 1.6 mL of a 1.4 M solution of tert-butyllithium in pentane. The mixture was stirred for 5 min and then a solution of 0.17 g (0.3 mmol) of 41 was added slowly. After warming to 0˚C over 30 min, the reaction was quenched by the addition of a saturated NH₄Cl solution. The mixture was extracted with ether, dried over MgSO₄, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.1 g (56%) of the titled compound 55 as a colorless oil; IR (thin film) 2932, 2857, 1712, 1337, and 1162 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ: -0.12 (d, 6H, J = 4.0 Hz), 0.77 (s, 9H), 1.18 (d, 3H, J = 7.2 Hz), 1.23-1.72, (m, 16H), 2.00 (q, 2H, J = 6.8 Hz), 2.36 (t, 2H, J = 7.6 Hz), 2.38 (m, 5H), 3.14 (m, 1H), 3.92 (m, 2H), 4.92 (m, 2H), 5.75 (m, 1H), 7.24 (d, 2H, J = 8.0 Hz), and 7.65 (d, 2H, J = 7.6 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ: -4.8, -4.6, 14.2, 14.9, 18.1, 21.6, 23.6, 23.7, 23.9, 25.9, 27.0, 27.5, 28.8, 28.9, 33.8, 35.1, 42.8, 42.9, 51.9, 53.1, 69.4, 114.5, 126.9, 129.8, 139.1, 143.0, and 211.6; HRMS Calcd. for C₃₁H₅₃NSiSO₄: 563.3464. Found: 563.3472.
3-(tert-Butyl-dimethyl-silanyloxy)-6-dodec-11-enyl-2-methyl-1-(toluene-4-sulfonyl)-piperidine (56). To a solution of 0.1 g (0.18 mmol) of ketone 55 in 1.5 mL of absolute ethanol was added 0.037 g (0.19 mmol) of \( \text{p}-\text{toluenesulfonyl-hydrazide} \). The solution was stirred for 15 h at room temperature and was then was concentrated under reduced pressure. To the residue was added 1.5 mL of \( \text{CH}_2\text{Cl}_2 \) and the resulting solution was cooled to 0°C. To this solution was added 0.35 mL (0.34 mmol) of diisobutylaluminum hydride solution (1 M in hexane). The solution was warmed to rt over 30 min and was quenched with a 3.0 M solution of NaOH. The solution was extracted with ether, dried over MgSO\(_4\), and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.04 g (40% yield) of the titled compound 56 as a colorless oil; IR (thin film) 2852, 1640, 1598, and 1163 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \) -0.07 (d, 6H, \( J = 4.0 \) Hz), 0.82 (s, 9H), 1.22 (d, 3H, \( J = 7.6 \) Hz), 1.27-1.72, (m, 22H), 2.04 (q, 2H, \( J = 7.6 \) Hz), 2.42 (s, 3H), 3.23 (m, 1H), 3.98 (m, 2H), 4.96 (m, 2H), 5.82 (m, 1H), 7.28 (d, 2H, \( J = 8.0 \) Hz), and 7.70 (d, 2H, \( J = 7.6 \) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \( \delta \) -4.8, -4.6, 14.2, 14.9, 18.1, 21.6, 23.6, 23.7, 23.9, 25.9, 26.5, 27.0, 27.5, 28.8, 28.9, 33.8, 35.1, 52.0, 53.1, 69.4, 114.3, 126.9, 129.8, 139.2, 139.5, and 142.9; HRMS Calcd. for C\(_{31}\)H\(_{55}\)NSiSO\(_3\): 549.3672. Found: 549.3661.
6-Dodecyl-2-methyl-1-(toluene-4-sulfonyl)-piperidin-3-ol. To a solution of 0.03 g (0.06 mmol) of alkene 56 in 0.1 mL of methanol was added a catalytic amount of platinum (IV) oxide. After purging the reaction vessel 3 times with hydrogen gas, the mixture was stirred for 1 h under a hydrogen balloon. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude reaction mixture was taken up in 0.6 mL of THF and a solution of tetrabutylammonium fluoride (66 µL of a 1M solution in THF) was added at 0 °C. After warming to rt over 30 min, water was added and the reaction mixture was extracted with ether. The ether extracts were dried over MgSO₄, and concentrated under reduced pressure. The crude product was subjected to preparative thin-layer chromatography to give 0.024 g (92%) of the titled compound as a clear oil; IR (thin film) 3444, 2923, 2852, and 1460 cm⁻¹; ¹H-NMR (600 MHz, CDCl₃) δ 0.89 (t, 3H, J = 7.2 Hz), 1.25-1.66, (m, 30H), 2.42 (s, 3H), 3.40 (m, 1H), 3.95 (q, 1H, J = 6.6 Hz), 4.18 (dq, 1H, J = 6.6 and 6.6 Hz), 7.28 (d, 2H, J = 9.0 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ¹³C-NMR (150 MHz, CDCl₃) δ 14.3, 14.7, 21.7, 22.9, 23.2, 27.3, 27.7, 29.6, 29.7, 29.8, 29.9, 32.1, 35.3, 52.1, 52.4, 69.2, 126.9, 129.9, 139.1, and 143.1; HRMS Calcd. for C₂₅H₄₃NO₅S: 453.2913. Found: 453.2924.
6-Dodecyl-2-methyl-piperidin-3-ol (29). To a solution of 0.05 g of the above alcohol in 0.5 mL of THF at -78°C was condensed 2 mL of NH₃ using a dry ice condenser. To this mixture was added lithium chips (approximately 2 mg) and the solution immediately turned a deep blue color. The reaction mixture was allowed to stir at -78°C for 30 min and then 0.5 mL of isoprene was added to quench the reaction. The mixture was warmed to rt and water was added followed by a drop of 50% NaOH solution and CHCl₃. After extracting the aqueous layer with additional CHCl₃, the combined organic layer was dried over MgSO₄ and concentrated under reduced pressure to give 0.03 g (100%) of deoxocassine (29); IR (thin film) 3394, 2916, 2848, and 1455 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.89 (t, 3H, J = 7.2 Hz), 1.15, (d, 3H, J = 6.8 Hz), 1.22-1.36 (m, 22H), 1.46 (m, 2H), 1.90 (m, 2H), 2.50 (m, 2H), 2.72 (qd, 1H, J = 6.8 and 1.2 Hz), and 3.52 (d, 1H, J = 4.8 Hz); ¹³C-NMR (150 MHz, CDCl₃) δ 14.3, 18.9, 22.9, 26.0, 26.4, 29.6, 29.8, 29.9, 30.0, 32.1, 32.3, 37.2, 56.0, 57.5, and 68.3; FAB HRMS Calcd. for [(C₁₈H₃₇NO)+H⁺]: 284.2953. Found: 284.2941.

2-(5-Bromo-pentyl)-2-methyl-[1,3]dithiolane (60). A mixture of BF₃•OEt₂ (0.04 mL) and 1,2-ethanedithiol (0.3 mL, 4.0 mmol) was added to a solution of 7-bromo-2-heptanone (58) (0.5 g, 2.7 mmol) in CH₂Cl₂ and the reaction mixture was stirred for 18 h at rt. The resulting solution was then quenched with an aqueous 1 M NaOH solution and
the organic layer was washed with H2O, dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.65 g (89%) of the titled compound 60 as a pale yellow oil; IR (thin film) 2935, 2856, 1445, and 1374 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.51 (m, 4H), 1.75 (s, 3H), 1.90 (m, 4H), 3.33 (m, 4H), and 3.42 (t, 2H, J = 6.8 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 26.6, 28.3, 32.5, 32.7, 33.9, 40.0, 45.6, and 66.8; HRMS Calcd for [(C₉H₁₇BrS₂)+H⁺]: 268.9955. Found: 269.0028.

1-[5-(tert-Butyl-dimethyl-silyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-10-(2-methyl-[1,3]dithiolan-2-yl)-decan-5-one. To a solution of the above bromide 60 (0.7 g, 0.27 mmol) in pentane (2.5 mL) and t-butyl methyl ether (1.25 mL) at -78 °C was added t-BuLi (0.22 mL, 0.38 mmol, 1.7 M in pentane) over 15 min, and the resulting solution was stirred for an additional 25 min at -78 °C. A 0.1 g (0.19 mmol) sample of Weinreb’s amide 41 in ether (1.8 mL) was added over a 15 min period and the reaction mixture was stirred at -78 °C for 2.2 h before being quenched with an aqueous NH₄Cl solution. The aqueous layer was extracted with ether and the organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography to give 0.09 g (70%) of the titled compound as a clear oil; IR (thin film) 2935, 2857, 1713, 1463, 1338, and 1253 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.10 (d, 6H, J = 4.0 Hz), 0.81 (s, 9H), 1.22 (d, 3H, J = 7.2 Hz), 1.49 (m, 16H),
1.74 (s, 3H), 1.92 (m, 2H), 2.41 (m, 7H), 3.17 (m, 1H), 3.32 (m, 4H), 3.95 (m, 2H), 7.28 (d, 2H, $J = 8.6$ Hz), and 7.68 (d, 2H, $J = 8.6$ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ -4.8, -4.6, 15.0, 18.2, 21.7, 23.6, 23.8, 23.9, 25.9, 27.0, 27.3, 27.5, 29.5, 32.5, 35.1, 40.0, 42.9, 45.8, 51.9, 53.2, 67.0, 69.4, 126.9, 129.8, 139.1, 143.1, and 211.5; HRMS Calcd for [(C$_{33}$H$_{57}$NO$_4$S$_3$Si)$^+$]: 656.3219. Found: 656.3298.

3-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-6-[10-(2-methyl-[1,3]dithiolan-2-yl)-decyl]-1-(toluene-4-sulfonyl)piperidine (33). To a solution of the above ketone (0.07 g, 0.1 mmol) in absolute EtOH (1.2 mL) was added p-toluenesulfonylhydrazide (0.02 g, 0.11 mmol) and the reaction mixture was stirred at rt for 17 h. The solvent was removed under reduced pressure and the residue was taken up in CH$_2$Cl$_2$ (1.2 mL). The solution was cooled to 0 °C and DIBAL-H (0.5 mL, 0.5 mmol, 1.0 M in hexane) was slowly added over a 15 min period. The reaction mixture was stirred at 0 °C and then gradually warmed to rt over 1 h. The solution was quenched by the dropwise addition of an aqueous 3 M NaOH solution. The mixture was extracted with ether and the organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography to give 0.04 g (57%) of the titled compound 33 as a clear oil; IR (thin film) 2924, 2848, 1470, 1163, 1107, 999, 881, and 835 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ -0.08 (d, 6H, $J = 4.0$ Hz), 0.81 (s, 9H), 1.20 (d, 3H, $J = 6.8$ Hz), 1.94 (m, 2H), 2.41 (s, 3H), 3.22 (ddd, 1H, $J = 11.2$, 6.0, and 4.0 Hz),
3.32 (m, 4H), 3.97 (m, 2H), 7.27 (d, 2H, J = 8.4 Hz), and 7.70 (d, 2H, J = 8.4 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ -4.8, -4.6, 14.9, 18.1, 21.7, 23.6, 25.9, 27.4, 27.56, 27.64, 29.7, 29.8, 29.9, 30.0, 32.5, 35.3, 39.9, 46.1, 52.2, 53.1, 67.2, 69.6, 126.9, 129.8, 139.2, and 142.9; HRMS Calcd for [(C$_{33}$H$_{59}$NO$_3$S$_3$Si)+H$^+$]: 642.3426. Found: 642.3490.

$^{12}$-[5-(tert-Butyl-dimethyl-silyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-dodecan-2-one. To a solution of dithiolane 61 (0.03 g, 0.04 mmol) in a 2:1 CH$_3$CN/H$_2$O mixture (2.1 mL) was added CaCO$_3$ (0.05 g, 0.45 mmol) and MeI (0.5 mL). The solution was heated at 60 °C for 12 h, cooled to rt and diluted with H$_2$O and brine. The aqueous layer was extracted with ether and the organic phase was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.02 g (100%) of the titled compound as a clear oil; IR (thin film) 2937, 2855, 1717, 1463, 1339, 1253, 1163, 838, and 776 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) δ -0.09 (d, 6H, J = 3.6 Hz), 0.81 (s, 9H), 1.22 (d, 3H, J = 7.2 Hz), 1.44 (m, 22H), 2.13 (s, 3H), 2.39 (m, 5H), 3.20 (ddd, 1H, J = 11.2, 6.0, and 4.2 Hz), 3.96 (m, 2H), 7.27 (d, 2H, J = 8.4 Hz), and 7.69 (d, 2H, J = 8.4 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ -4.8, -4.6, 14.9, 18.2, 21.7, 23.6, 24.1, 25.9, 27.4, 27.5, 29.4, 29.6, 29.64, 29.68, 29.7, 30.1, 35.3, 44.0, 52.2, 53.1, 69.6, 127.0, 129.8, 139.2, 143.0, and 209.7; HRMS Calcd for [(C$_{31}$H$_{55}$NO$_4$SSi)+H$^+$]: 566.3621. Found: 566.3700.
3-(tert-Butyl-dimethyl-silyloxy)-2-methyl-6-[10-(2-methyl-[1,3]dioxolan-2-yl)-decyl]-1-(toluene-4-sulfonyl)piperidine (63). To a solution of the above ketone (0.02 g, 0.03 mmol) in CH₂Cl₂ (0.5 mL) was added ethylene glycol (0.5 mL) and BF₃•OEt₂ (8 drops) and the resulting solution was stirred at rt for 27 h. The reaction mixture was then diluted with 1 M NaOH and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.02 g (93%) of the titled compound 63 as a clear oil; IR (thin film) 2929, 2855, 1463, 1339, 1254, 1163, 1107, 1055, 879, 839, and 776 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.09 (d, 6H,  J = 4.0 Hz), 0.81 (s, 9H), 1.22 (d, 3H,  J = 7.2 Hz), 1.31 (s, 3H), 1.48 (m, 24H), 2.41 (s, 3H), 3.22 (ddd, 1H,  J = 10.0, 6.0, and 4.0 Hz), 3.94 (m, 6H), 7.27 (d, 2H,  J = 8.4 Hz), and 7.69 (d, 2H,  J = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -4.8, -4.6, 14.9, 18.2, 21.7, 23.6, 23.9, 24.3, 25.9, 27.4, 27.6, 29.6, 29.7, 29.8, 30.1, 35.3, 39.4, 52.2, 53.1, 64.8, 69.6, 110.4, 127.0, 129.8, 139.2, and 142.9; HRMS Calcd for [(C₃₃H₅₉N⁵O₅S₅Si)+H⁺]: 610.3883. Found: 610.3962.
3-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-6-[10-(2-methyl-[1,3]dioxolan-2-yl)decyl]piperidine. To a solution of 63 (0.03 g, 0.04 mmol) in THF (3 mL) at −78 °C was added 5 mg of lithium wire. The flask was fitted with an acetone/dry ice condenser and 3 mL NH₃ was added which resulted in a dark blue solution. The reaction mixture was stirred at −78 °C for 30 min, warmed to rt and quenched by the careful dropwise addition of methanol. The solution was diluted with aqueous NH₄Cl and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.02 g (94%) of the titled compound as a clear oil; IR (thin film) 2927, 2854, 1463, 1373, 1252, 1070, 1032, and 837 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.04 (d, 6H, J = 6.0 Hz), 0.91 (s, 9H), 1.01 (d, 3H, J = 6.8 Hz), 1.30 (s, 3H), 1.44 (m, 22H), 1.81 (m, 2H), 2.49 (brs, 1H), 2.68 (m, 1H), 3.55 (brs, 1H), and 3.93 (m, 4H); ¹³C-NMR (100 MHz, CDCl₃) δ -4.7, -4.3, 18.4, 19.5, 23.9, 24.3, 26.0, 26.1, 26.2, 29.8, 29.9, 30.1, 32.7, 37.6, 39.4, 55.6, 56.5, 64.8, 68.4, 77.5, and 110.4; HRMS Calcd for [(C₂₆H₅₃NO₃Si)+H⁺]: 456.3795. Found: 456.3863.

(±)-Cassine (28). To a solution of the above acetal (0.02 g, 0.04 mmol) in THF (3.3 mL) was added a 3 N HCl solution (0.33 mL, 1.0 mmol) and the solution was stirred at rt for 27 h. The reaction mixture was then quenched with 1 M NaOH (5.0 mL, 5.0 mmol) and the aqueous layer was extracted with EtOAc. The organic layer was dried over MgSO₄,
filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over basic alumina to afford 0.007g (59%) of the titled compound as a white solid; mp 64-65 °C (lit mp 57-58 °C); IR (thin film) 3405, 2926, 2852, 1716, 1464, 1363, 1166, and 967 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.11 (d, 3H, J = 6.8 Hz), 1.39 (m, 20H), 1.90 (m, 2H), 2.13 (s, 3H), 2.41 (t, 2H, J = 7.6 Hz), 2.54 (m, 1H), 2.76 (m, 1H), and 3.55 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 18.7, 24.0, 26.0, 26.1, 29.4, 29.60, 29.63, 29.7, 29.8, 30.0, 30.1, 32.2, 37.0, 44.0, 56.0, 57.4, 68.1, and 209.7; HRMS Calcd for [(C₁₈H₃₅NO₂)+H⁺]: 298.2668. Found: 298.2740.

1-[5-(tert-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)piperidin-2-yl]-10-(2-methyl-[1,3]dioxolan-2-yl)-decan-5-one (65). To a solution of 2-(5-bromopentyl)-2-methyl-1,3-dioxolane (64)⁴₅ (0.06 g, 0.27 mmol) in t-butyl methyl ether (1.25 mL) at −78 °C was added t-BuLi (0.22 mL, 0.38 mmol, 1.7 M in pentane) over a 15 min period. The reaction mixture was then stirred at −78 °C for 25 min and a solution of Weinreb’s amide 41 (0.1 g, 0.19 mmol) in t-butyl methyl ether (1.8 mL) was added over 15 min. The resulting solution was stirred at −78 °C for 2.5 h and was subsequently quenched with an aqueous NH₄Cl solution and allowed to warm to rt. The aqueous layer was extracted with ether, dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography to give 0.07 g (72%) of the titled compound 65 as a clear oil; IR (thin film) 2941, 1713, 1464, 1338,
1254, 1107, and 839 cm\(^{-1}\); \(\text{\(^1\)}\text{H-NMR (400 MHz, CDCl}_3\) \(\delta\) -0.10 (d, 6H, \(J = 3.6 \text{ Hz}\)), 0.80 (s, 9H), 1.21 (d, 3H, \(J = 6.8 \text{ Hz}\)), 1.30 (s, 3H), 1.50 (m, 16H), 2.40 (m, 7H), 3.17 (ddd, 1H, \(J = 10.8, 6.0, \text{ and } 4.0 \text{ Hz}\)), 3.84 (m, 6H), 7.27 (d, 2H, \(J = 8.4 \text{ Hz}\)), and 7.68 (d, 2H, \(J = 8.4 \text{ Hz}\)); \(\text{\(^{13}\)}\text{C-NMR (100 MHz, CDCl}_3\) \(\delta\) -4.8, -4.6, 14.9, 18.1, 21.6, 23.6, 23.7, 23.9, 24.0, 24.1, 25.9, 27.0, 27.5, 29.6, 35.1, 39.2, 42.8, 42.9, 51.9, 53.1, 64.8, 69.4, 110.3, 126.9, 129.8, 139.1, 143.0, and 211.5; HRMS Calcd for \([\text{C}\text{\(_{33}\)}\text{H}\text{\(_{57}\)}\text{NO}\text{\(_6\)}\text{SSi}]+\text{H}^+\]: 624.3676. Found: 624.3763.

To a solution of the above ketone (0.06 g, 0.09 mmol) in absolute EtOH (1.0 mL) was added \(p\)-toluenesulfonylhydrazide (0.02 g, 0.01 mmol) and the reaction mixture was stirred at rt for 18 h. The solvent was removed under reduced pressure and the residue was taken up in \(\text{CH}_2\text{Cl}_2\) (1.0 mL). The solution was cooled to 0 °C and DIBAL-H (0.35 mL, 0.35 mmol, 1.0 M in hexane) was added slowly over 10 min. The solution was stirred at 0 °C and then gradually warmed to rt over 1 h. The mixture was quenched by the dropwise addition of an aqueous 3 M NaOH solution and was extracted with ether. The organic layer was dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography to give 0.02 g (41%) of compound 63 which was subsequently converted to cassine (7) as described above.
1-[5-(tert-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)piperidin-2-yl]-tridec-12-en-5-one (67). To a solution of 8-bromo-1-octene (0.25 mL, 0.29 g, 1.5 mmol) in tert-butyl methyl ether (4.2 mL) at −78 °C was added t-BuLi (1.1 mL, 1.9 mmol, 1.7 M in pentane) over 15 min. The reaction mixture was stirred at −78 °C for 25 min, and then a solution of Weinreb’s amide 41 (0.5 g, 0.95 mmol) in ether (8.8 mL) was added over 15 min. The resulting solution was stirred at −78°C for 3 h, and was then quenched with an aqueous NH₄Cl solution and the mixture was warmed to rt. The aqueous layer was extracted with ether, dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography to afford 0.33 g (59%) of the titled compound 67 as a clear oil; IR (thin film) 2936, 2856, 1713, 1463, 1339, 1163, 1107, 936, 838, and 776 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ: 0.10 (d, 6H, J = 3.6), 0.81 (s, 9H), 1.22 (d, 3H, J = 6.8 Hz), 1.50 (m, 18H), 2.03 (m, 2H), 2.39 (m, 7H), 3.17 (ddd, 1H, J = 10.0, 6.0, and 4.0 Hz), 3.95 (m, 2H), 4.89 (bd, 1H, J = 10.0 Hz), 4.98 (dq, 1H, J = 17.2 and 1.6 Hz), 5.79 (ddt, 1H, J = 17.2, 10.0, and 6.8 Hz), 7.27 (d, 2H, J = 8.4 Hz) and 7.68 (d, 2H, J = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ: -4.8, -4.6, 15.0, 18.1, 21.7, 23.6, 23.8, 24.0, 25.9, 27.0, 27.5, 28.9, 29.1, 29.3, 33.9, 35.1, 42.8, 43.0, 51.9, 53.1, 69.4, 114.4, 126.9, 129.8, 139.1, 139.3, 143.0, and 211.6; HRMS Calcd for [(C₃₂H₅₅NO₄SSi)+H⁺]: 578.3621 Found: 578.3697.
3-(*tert-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-6-tridec-12-enyl-piperidine (68). To a solution of ketone 67 (0.06 g, 0.095 mmol) in absolute EtOH (1.0 mL) was added *p*-toluenesulfonylhydrazide (0.02 g, 0.1 mmol) and the reaction mixture was stirred at rt for 18.5 h. The solvent was removed under reduced pressure and the residue was taken up in CH$_2$Cl$_2$ (0.9 mL). The solution was cooled to 0 °C and DIBAL-H (0.3 mL, 0.34 mmol, 1.0 M in hexane) was slowly added over 15 min. The solution was stirred at 0 °C and was gradually warmed to rt over 1 h. The mixture was diluted with CH$_2$Cl$_2$, quenched by the dropwise addition of an aqueous 3.0 M NaOH solution, and extracted with ether. The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography to give 0.04 g (76%) of the titled compound 68 as a clear oil; IR (thin film) 2928, 2855, 1463, 1340, 1254, 1164, 1105, 880, 838, 776, and 611 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) δ -0.08 (d, 6H, $J = 4.0$ Hz), 0.82 (s, 9H), 1.22 (d, 3H, $J = 7.6$ Hz), 1.49 (m, 24H), 2.04 (m, 2H), 2.41 (s, 3H), 3.22 (ddd, 1H, $J = 11.2$, 6.0, and 4.0 Hz), 3.98 (m, 2H), 4.92 (dt, 1H, $J = 10.0$ and 1.2 Hz), 4.99 (dt, 1H, $J = 16.8$ and 1.6 Hz), 5.80 (ddt, 1H, $J = 17.2$, 10.4, and 6.8 Hz), 7.27 (d, 2H, $J = 8.4$ Hz), and 7.70 (d, 2H, $J = 8.4$ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ -4.8, -4.6, 14.9, 18.2, 21.1, 21.7, 23.6, 25.9, 26.2, 27.4, 27.6, 29.2, 29.4, 29.7, 29.8, 29.9, 34.0, 35.3, 52.2, 53.1, 69.6, 114.3, 127.0, 129.8, 139.2, 139.5, and 142.9; HRMS Calcd for [(C$_{32}$H$_{57}$NO$_3$SSi)+H$^+$]: 564.3828. Found: 564.3903.
12-[5-(tert-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-dodecanal. To a solution of 68 (0.1 g, 0.17 mmol) in a 2:1-dioxane/H₂O mixture (5.5 mL) was added 2,6-lutidine (0.05 mL, 0.43 mmol), OsO₄ (7 drops, 2.5% in t-BuOH), and NaIO₄ (0.16 g, 0.75 mmol). After stirring for 3.5 h at rt, an aqueous mixture of Na₂SO₃ was added and the aqueous layer was then extracted with CH₂Cl₂. The organic layer was washed with 1 N HCl, dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel to give 0.09 g (93%) of the titled compound as a yellow oil; IR (thin film) 2933, 2854, 1725, 1463, 1338, 1254, 1164, 1107, 879, 838, 776, and 660 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ ~0.10 (d, 6H, J = 3.6 Hz), 0.81 (s, 9H), 1.22 (d, 3H, J = 7.2 Hz), 1.48 (m, 24H), 2.42 (m, 5H), 3.21 (ddd, 1H, J = 10.4, 5.6, and 4.0 Hz), 4.00 (m, 2H), 7.27 (d, 2H, J = 8.4 Hz), 7.70 (d, 2H, J = 8.4 Hz), and 9.76m (1H); ¹³C-NMR (100 MHz, CDCl₃) δ -4.8, -4.7, 14.9, 18.1, 21.6, 22.3, 23.6, 25.9, 27.4, 27.5, 29.3, 29.5, 29.6, 29.7, 29.9, 35.3, 44.1, 52.2, 53.1, 69.5, 127.0, 129.8, 139.2, 142.9, and 203.2; HRMS Calcd for [(C₃₁H₅₅NO₄SSi)+H⁺]: 566.3621. Found: 566.3698.
12-[5-(tert-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-dodecanoic acid (69). To a solution of the above aldehyde (0.36 g, 0.64 mmol) in t-BuOH (4.5 mL) was added resorcinol (0.09 g, 0.83 mmol) followed by an acetate buffer (pH = 3.6, 1.3 mL). To the resulting mixture was added a solution of NaClO\(_2\) (0.07 g, 0.8 mmol) in H\(_2\)O (5 mL) and the mixture was stirred at rt for 6 h. The organic layer was diluted with brine and extracted with ether, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.37 g (99%) of the titled compound 69 as a yellow oil; IR (thin film) 2936, 2854, 1709, 1463, 1338, 1254, 1164, 1105, 838, and 777 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) -0.09 (d, 6 H, \(J = 3.6\) Hz), 0.81 (s, 9H), 1.25 (m, 24H), 1.22 (d, 3H, \(J = 6.8\) Hz), 2.34 (t, 2H, \(J = 7.6\) Hz), 2.41 (s, 3H), 3.22 (ddd, 1H, \(J = 11.2, 5.6\) and 4.0 Hz), 3.97 (m, 2H), 7.27 (d, 2H, \(J = 8.4\) Hz), and 7.69 (d, 2H, \(J = 8.4\) Hz); \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) -4.8, -4.6, 14.9, 18.2, 21.7, 23.6, 24.9, 25.9, 27.4, 27.6, 29.3, 29.4, 29.6, 29.7, 34.2, 35.3, 52.2, 53.1, 69.6, 127.0, 129.8, 139.2, 143.0, and 180.0; HRMS Calcd for [(C\(_{31}\)H\(_{55}\)NO\(_{5}\)SSi)+H\(^+\)]: 582.3570. Found: 582.3643.

The same carboxylic acid 69 was prepared by the direct oxidation of piperidinyl alkene 68. To a solution of alkene 68 (0.03 g, 0.05 mmol) in DMF (1.2 mL) was added OsO\(_4\) (3 drops, 2.5% in t-BuOH) and the reaction mixture was stirred at rt for 5 min. Oxone was added in one portion, and the mixture was stirred at rt for an additional 35 min and was then diluted with EtOAc. The aqueous layer was acidified with 10% HCl and extracted with EtOAc. The organic layer was dried over MgSO\(_4\), filtered, and
concentrated to give a clear oil which was purified by silica gel chromatography to give 0.02 g (53%) of 69.

12-[5-Hydroxy-6-methyl-1-(toluene-4-sulfonyl)piperidin-2-yl] Dodecanoic Acid. To a solution of carboxylic acid 69 (0.37 g, 0.6 mmol) in THF (8 mL) at 0 °C was added TBAF (0.8 mL, 0.76 mmol, 1.0 M in THF) and the mixture was gradually warmed to rt over 40 min. The solution was stirred at rt for an additional 3 h, over which time an additional 2.0 equiv (1.3 mL) of TBAF was added in portions. The mixture was then diluted with H₂O and brine and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.23 g (77%) of the titled compound as a yellow oil; IR (thin film) 3448, 2927, 2853, 1709, 1458, 1404, 1330, 1166, 1098, 985, 911, 814, 732, and 664 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.47 (m, 27H), 2.34 (t, 2H, J = 7.2 Hz), 2.40 (s, 3H), 3.38 (ddd, 1H, J = 10.4, 6.0, and 4.4 Hz), 3.93 (q, 1H, J = 6.8 Hz), 4.17 (p, 1H, J = 6.8 Hz), 7.26 (d, 2H, J = 8.4 Hz), and 7.69 (d, 2H, J = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 14.7, 21.7, 23.1, 24.9, 27.3, 27.6, 29.2, 29.4, 29.56, 29.65, 29.70, 29.90, 34.2, 35.2, 52.1, 52.4, 69.2, 126.9, 129.9, 139.0, 143.1, and 179.5; HRMS Calcd for [(C₂₅H₄₁NO₅S)+H⁺]: 468.2705. Found: 468.2779.
(±)-Spicigerine (40). To a solution containing 0.04 g (0.08 mmol) of the above compound in THF (3 mL) at −78 °C was added 5 mg of lithium wire. The flask was fitted with an acetone/dry ice condenser and 3 mL of ammonia was added which gave rise to a dark blue solution. The mixture was stirred at −78 °C for 0.5 h, allowed to warm to rt and was quenched by the careful dropwise addition of methanol. The solution was diluted with an aqueous NH₄Cl solution and extracted with EtOAc. The aqueous layer was acidified to pH = 2 with 6 N HCl and extracted with EtOAc. The aqueous layer was further extracted with a 3:1-mixture of CHCl₃/i-PrOH. The resulting organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to provide 0.02 g (64%) of spicigerine (40) as a white solid requiring no further purification; mp 168-169 °C (lit¹⁶ 196 °C); IR (thin film) 3416, 2914, 2848, 1726, 1460, 1408, 1173, 1102, and 1010 cm⁻¹; ¹H-NMR (400 MHz, CD₃OD) δ 1.61 (m, 27H), 2.26 (t, 2H, J = 8.0 Hz), 3.05 (brs, 1H), 3.22 (m, 1H), and 3.82 (m, 1H); ¹³C-NMR (100 MHz, CD₃OD) δ 16.1, 23.7, 26.2, 26.5, 30.4, 30.5, 30.6, 30.7, 30.8, 30.9, 31.1, 34.9, 35.1, 57.6, 58.8, 66.0, and 177.9; HRMS Calcd for [(C₁₈H₃₅NO₃)+H⁺]: 314.2617. Found: 314.2685.
(S,E)-N-(1-Furan-2-yl-ethyl)toluene p-Sulfinamide (74). A mixture of (S)-(+-p-toluenesulfinamide57 (0.03 g, 0.19 mmol), 2-acetylfuran (0.02 g, 0.19 mmol), and Ti(OEt)₄ (0.3 mL, 1.5 mmol) in CHCl₃ (4 mL) was heated at reflux for 41 h. The reaction mixture was then cooled to 0 °C, H₂O was added, and the resulting suspension was filtered over celite. The filtrate was extracted with CH₂Cl₂, dried over MgSO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to give 0.03 g (69%) of the titled compound 74 as a yellow solid; mp 65-67 °C; IR (thin film) 3129, 2925, 2243, 1581, 1479, 1397, 1307, 1168, 1099, 1066, 1029, 907, 813, and 727 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 2.38 (s, 3H), 2.66 (s, 3H), 6.48 (s, 1H), 7.09 (d, 1H, J = 3.6 Hz), 7.29 (d, 2H, J = 8.0 Hz), 7.53 (s, 1H) and 7.69 (d, 2H, J = 8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 19.2, 21.6, 112.7, 115.9, 125.3, 130.0, 142.0, 143.4, 146.4, 152.5, and 164.2.

(S)-N-(1-(furan-2-yl)ethyl)-4-methylbenzenesulfonamide (S-44). To a -78 °C solution of the above sulfinimine 74 (0.08 g, 0.33 mmol) in 4.7 mL of THF was added LiAlH(Ot-Bu)₃ (0.11 g, 0.43 mmol) in 2.5 mL of THF over a 15 min. period. The mixture was stirred at -78 °C for 2 h and then warmed and stirred between -50 and -55 °C for 20 h. The solution was quenched with a saturated aqueous NH₄Cl solution, warmed to room temperature, and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure to provide a 1:1 inseperable mixture of
74 and 75, which was used immediately in the next step. A solution of the crude mixture in 5 mL of CH$_2$Cl$_2$ was added to a solution of $m$-CPBA in 5 mL CH$_2$Cl$_2$ at -30 °C. The mixture was stirred and allowed to warm to 0 °C over 1.5 h. A saturated aqueous NaHCO$_3$ solution was added, and the aqueous layer was extracted with CH$_2$Cl$_2$. The resulting organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting clear oil was purified by silica gel chromatography to give 0.03 g (35%) of the title compound: $[\alpha]_D$ -63.5 (c 1.0, EtOH) 0.58

![](image)

2-(1,4-Dithia-spiro[4.4]non-6-ylidene)-N-furan-2-yl-succinamic Acid Methyl Ester (77). To a solution of the above Boc amidofuran (0.22 g, 0.49 mmol) in CH$_3$CN (5 mL) was added Mg(ClO$_4$)$_2$ (0.14 g, 0.6 mmol) in one portion. The solution was heated at 45 °C for 1.5 h then cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to give 140 mg (85%) of 77 as a colorless oil; IR (thin film) 3282, 2957, 2925, 1694, 1608, 1548, 1435, 1279, 1238, and 1198 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.74-1.83 (m, 2H), 2.26 (t, 2H, $J = 6.4$ Hz), 2.86 (t, 2H, $J = 6.4$ Hz), 3.32-3.37 (m, 2H), 3.46-3.51 (m, 2H), 3.73 (s, 3H), 3.91 (s, 2H), 6.25 (d, 1H, $J = 3.2$ Hz), 6.33 (m, 1H), 6.99 (s, 1H), and 8.16 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 24.9, 35.7, 37.8, 40.8, 50.7, 52.3, 71.4, 95.1, 111.7, 124.2, 135.2, 145.8, 159.9, 167.1 and 168.4.
2-(1,4-Dithia-spiro[4.4]non-6-ylidene)-4-(2-hydroxy-5-oxo-2,5-dihydro-pyrrol-1-yl)-4-oxo-butryic Acid Methyl Ester (78). To a 0 °C stirred solution of compound 77 (0.025 g, 0.07 mmol) in acetone/H₂O (4.8 mL/0.26 mL) was added NaHCO₃ (0.036 g, 0.43 mmol) and I₂ (0.054 mg, 0.21 mmol). The mixture was stirred for 3 h at 0 °C then quenched by the addition of a saturated aqueous sodium thiosulfate solution (15 mL). The mixture was extracted with EtOAc and washed with brine. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (50% EtOAc/hexanes) to yield 21 mg (81%) of 78 as a pale yellow oil; IR (thin film) 3441, 2926, 1731, 1434, 1361, 1232, and 1201 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.75-1.79 (m, 2H), 2.24 (t, 2H, J = 6.8 Hz), 2.92 (t, 2H, J = 6.8 Hz), 3.27-3.32 (m, 2H), 3.40-3.46 (m, 2H), 3.73 (s, 3H), 4.30 (d, 1H, J = 3.2 Hz), 4.39 (d, 1H, J = 18.8 Hz), 4.60 (d, 1H, J = 19.2 Hz), 6.15 (brs, 1H), 6.20-6.22 (m, 1H), and 7.16 (dd, 1H, J = 4.0 and 2.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 24.7, 35.2, 37.2, 40.3, 50.4, 51.7, 71.5, 82.1, 123.2, 128.4, 147.5, 158.7, 167.8, 168.1 and 172.4.

N-(Furan-2-yl)acetamide (103). To a stirred solution of furan 97 (0.2 g, 1.09 mmol) in THF (12 mL) at 0 °C was added n-BuLi (0.46 mL, 1.14 mmol, 2.5 M in hexanes)
dropwise and the reaction mixture was stirred at 0 °C for 40 min. The mixture was added dropwise by cannula to a -78 °C solution of acetyl chloride (0.1 mL, 1.42 mmol) in THF (6.5 mL) and was stirred for 0.5 h at 0 °C. The solution was warmed to rt and quenched with H₂O and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was dissolved in CH₃CN (12 mL) and Mg(ClO₄)₂ (304 mg, 1.36 mmol) was added. The mixture was heated at 40 °C for 25 min, cooled to 0 °C, diluted with H₂O, and extracted with Et₂O. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% to 30% EtOAc/hexanes) to yield 81 mg (60%) of 103 as an off-white solid;° mp 96-98 °C; ¹H-NMR (CDCl₃, 400 MHz) d 2.16 (s, 3H), 6.28-6.29 (m, 1H), 6.35-6.37 (m, 1H), 7.03-7.04 (m, 1H), and 7.61 (brs, 1H).

![Chemical Structure](image)

N-(Furan-2-yl)-2-phenylacetamide (104). To a stirred solution of furan 97 (200 mg, 1.09 mmol) in THF (8 mL) at 0 °C was added n-BuLi (0.52 mL, 1.31 mmol, 2.5 M in hexanes) dropwise and the mixture was stirred at 0 °C for 30 min. In a separate flask, phenylacetic acid (148 mg, 1.09 mmol) was dissolved in THF (8 mL) and the mixture was cooled to 0 °C. 4-Methylmorpholine (0.12 mL, 1.09 mmol) and isobutyl chloroformate (0.14 mL, 1.09 mmol) was added dropwise and the solution was stirred for 5 min. The mixture was filtered over celite with THF (4 mL) and the filtrate was cooled.

![Chemical Structure](image)
to 0°C. The preformed furanyl lithiate from above was added dropwise by cannula. The resulting reaction mixture was stirred for 2 h at 0 °C and then quenched with H₂O and extracted with EtOAc. The organic layer was washed with a saturated aqueous NaHCO₃ solution, dried over MgSO₄, filtered over a pad of silica gel, and concentrated under reduced pressure. The residue was dissolved in CH₃CN (10 mL) and was added to a stirred solution of Mg(ClO₄)₂ (226 mg, 1.01 mmol) in CH₃CN (5 mL) at 40 °C and the mixture was heated at 40 °C for 25 min. The solution was cooled to 0 °C and quenched with H₂O and extracted with Et₂O. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% to 30% EtOAc/hexanes) to yield 27 mg (12%) of 104 as thick oil; IR (thin film) 3242, 3064, 2918, 1666, 1562, 1379, 1248, 1196, 1147, 791, and 703 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 3.73 (s, 2H), 6.31-6.35 (m, 2H), 7.00 (dd, 1H, J = 2.0 and 0.8 Hz), 7.30-7.41 (m, 5H), and 7.65 (brs, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 44.0, 95.6, 111.7, 128.0, 129.5, 129.7, 134.1, 135.6, 145.2, and 167.6.

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**tert-Butyl 2-(3,4-dimethoxyphenyl)acetyl(furan-2-yl)carbamate.** To a stirred solution of furan 97 (2.14 g, 11.7 mmol) in THF (20 mL) at 0 °C was added n-BuLi (4.91 mL, 12.3 mmol, 2.5 M in hexane) dropwise and the reaction mixture was stirred at 0 °C for 30 min. In a separate flask 3,4-dimethoxybenzoic acid (2.75 g, 14.0 mmol) was dissolved in THF (20 mL) and the mixture was cooled to 0 °C. 4-Methylmorpholine (1.54 mL, 14.0
mmol) and isobutyl chloroformate (1.83 mL, 14.0 mmol) was added dropwise and the solution was stirred for 5 min. The mixture was filtered over celite with THF (4 mL). The filtrate was cooled to 0 °C and the preformed furanyl lithiate was added dropwise by cannula. The resulting reaction mixture was stirred for 30 min and quenched with H₂O and extracted with EtOAc. The organic layer was washed with a saturated aqueous NaHCO₃ solution, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% to 35% EtOAc/hexanes) to yield 3.11 g (76%) of the title compound as a yellow oil; IR (thin film) 2980, 2936, 2836, 1783, 1746, 1609, 1516, 1265, 1154, 1093, and 1029 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.40 (s, 9H), 3.85 (s, 6H), 4.04 (s, 2H), 6.11-6.12 (m, 1H), 6.39-6.41 (m, 1H), 6.77-6.81 (m, 3H), and 7.32 (dd, 1H, J = 2.0 and 0.8 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ 27.9, 43.3, 56.00, 56.03, 84.1, 106.2, 111.2, 111.4, 112.9, 121.9, 126.5, 140.7, 144.0, 148.2, 148.9, 151.5, and 173.3.

2-(3,4-Dimethoxyphenyl)-N-(furan-2-yl)acetamide (106). To a stirred solution of Mg(ClO₄)₂ (237 mg, 1.06 mmol) in CH₃CN (9 mL) at 45 °C was added a solution of the above Boc amidofuran (304 mg, 0.841 mmol) in CH₃CN (2 mL). The mixture was stirred at 45 °C for 15 min and was then diluted with H₂O and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 205 mg (93%) of 106 as a yellow oil; IR (thin film) 3268, 3151, 3061, 2943, 2836, 1666, 1608, 1552, 1515,
1464, 1263, 1235, 1143, and 1027 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 3.67 (s, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 6.33-6.35 (m, 1H), 6.31-6.32 (m, 1H), 6.80-6.89 (m, 3H), 6.99 (dd, 1H, J = 2.0 and 0.8 Hz), and 7.59 (brs, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 43.6, 56.1, 95.5, 111.7, 111.9, 112.6, 122.0, 126.4, 135.6, 145.2, 148.9, 150.7, and 167.8.

**tert-Butyl-2-(Benzyloxy)acetyl(furan-2-yl)carbamate.** To a stirred solution of the above acid (1.0 g, 6.02 mmol) in CH₂Cl₂ (15 mL) was added oxalyl chloride (1.58 mL, 18.07 mmol) followed by 2 drops of DMF. The reaction mixture was stirred at rt for 1 h and was then concentrated under reduced pressure, dissolved in THF (15 mL), and cooled to -78 °C. In a separate flask, furan 97 (1.32 g, 7.22 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. To this mixture was added n-BuLi (2.64 mL, 6.60 mmol, 2.5 M in hexane) dropwise and the mixture was stirred at 0 °C for 0.5 h. The resulting solution was transferred dropwise by cannula into a solution of the above acid chloride at -78°C. The solution was stirred for 1 h while slowly warming from -78 °C to 0 °C. The mixture was then quenched with H₂O, extracted with EtOAc, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% EtOAc/hexanes) to yield 1.54 g (77%) of the title compound as a white solid, mp 64-66°C; IR (thin film) 3127, 2981, 2934, 1790, 1745, 1611, 1500, 1371, 1306, 1271, 1153, 1092, 1013, 955, 847, 772, 738, and 698 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.41 (s, 9H), 4.65 (s, 2H), 4.66 (s, 2H), 6.17-6.18 (m, 1H), 6.43 (dd, 1H, J = 3.6
and 2.0 Hz), and 7.27-7.41 (m, 6H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 27.9, 71.2, 73.5, 84.6, 106.4, 111.5, 128.1, 128.3, 128.6, 137.7, 140.9, 142.8, 151.6, and 172.8.

2-(Benzyloxy)-N-(furan-2-yl)acetamide (108). The above Boc amidofuran (1.09 g, 3.02 mmol) was dissolved in CH$_3$CN (5 mL) and was added to a stirred solution of Mg(ClO$_4$)$_2$ (0.84 g, 3.78 mmol) in CH$_3$CN (53 mL) at 40 °C. The reaction mixture was heated at 40 °C for 10 min, cooled to rt, and diluted with H$_2$O. The aqueous layer was extracted with EtOAc, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% to 30% EtOAc/hexanes) to afford 625 mg (90%) of 108 as a pale yellow oil; IR (neat) 3375, 3281, 3155, 3064, 2914, 2867, 1694, 1608, 1531, 1455, 1376, 1344, 1239, 1208, 1108, and 1011 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.11 (s, 2H), 4.64 (s, 2H), 6.35-6.39 (m, 2H), 7.07 (dd, 1H, $J = 2.0$ and 0.8 Hz), 7.32-7.42 (m, 5H), and 8.65 (brs, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 69.3, 74.0, 95.6, 111.8, 128.3, 128.7, 129.0, 135.8, 136.5, 144.7 and 166.1.

2-(1-Acetyl-1H-indol-3-yl)-N-(furan-2-yl)acetamide (20). To a stirred solution of Mg(ClO$_4$)$_2$ (730 mg, 3.27 mmol) in CH$_3$CN (25 mL) at 45 °C was added a solution of the above Boc amidofuran (1.0 g, 2.62 mmol) in CH$_3$CN (5 mL). The mixture was stirred at
45 °C for 15 min, diluted with H₂O and extracted with EtOAc. The organic layer was
dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was
purified by silica gel chromatography (50% EtOAc/hexanes) to provide 683 mg (92%) of
20 as a white solid, mp 116-118°C; IR (thin film) 3263, 3056, 2931, 1700, 1672, 1608,
1554, 1451, 1386, 1331, 1224, 1145, 1011, 749, and 647 cm⁻¹; ¹H-NMR (CDCl₃, 400
MHz) δ 2.65 (s, 3H), 3.84 (d, 2H, J = 1.2 Hz), 6.33-6.36 (m, 2H), 6.99-7.0 (m, 1H), 7.31-
7.35 (m, 1H), 7.42 (dt, 1H, J = 7.2 and 1.2 Hz), 7.49 (s, 1H), 7.54 (d, 1H, J = 8.0 Hz),
7.71 (brs, 1H), and 8.46 (d, 1H, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 24.2, 33.5,
96.0, 111.7, 114.9, 117.1, 118.9, 124.4, 124.7, 126.3, 129.7, 135.8, 136.1, 144.9, 166.4,
and 168.6.

3,3-Dimethoxypropanoic acid. To a stirred solution of methyl 3,3-dimethoxy
propanoate (1.58 g, 10.7 mmol) in EtOH (140 mL) was added KOH (2.99 g, 53.3 mmol)
and the reaction mixture was stirred at rt for 17 h. The ethanol was removed under
reduced pressure and H₂O was added. The aqueous layer was extracted with Et₂O and
then acidified to pH = 3 and extracted with Et₂O. The organic layer was dried over
MgSO₄, filtered, and concentrated to provide 222 mg (16%) of the title compound as a
yellow oil; ¹H-NMR (400 MHz, CDCl₃) δ 2.71 (d, 2H, J = 7.6 Hz), 3.39 (s, 6H) and 4.83
(dd, 1H, J = 8.0 and 7.2 Hz).
**N-(Furan-2-y1)-3,3-dimethoxypropanamide (112).** To a stirred solution of furan 97 (1.37 g, 7.46 mmol) in THF (27 mL) at 0 °C was added n-BuLi (3.22 mL, 8.05 mmol, 2.5 M in hexanes) dropwise and the mixture was stirred for 20 min at 0 °C. In a separate flask, 3,3-dimethoxypropanoic acid (1.0 g, 7.46 mmol) was dissolved in THF (35 mL) and the solution was cooled to 0 °C. 4-Methylmorpholine (0.82 mL, 7.46 mmol) and isobutyl chloroformate (0.98 mL, 7.46 mmol) was added and the resulting mixture was stirred for 5 min and filtered over celite with THF (4 mL). The filtrate was cooled to 0 °C and the preformed lithiate from above was added dropwise by cannula. The resulting mixture was stirred for 25 min and then quenched with H₂O and extracted with EtOAc. The organic layer was washed with a saturated aqueous NaHCO₃ solution, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was filtered over a plug of silica gel and concentrated to a yellow oil. The oil was dissolved in CH₃CN (5 mL) and added to a stirred solution of Mg(ClO₄)₂ (1.08 g, 4.84 mmol) in CH₃CN (15 mL) at 40 °C and the solution was heated at 40 °C for 10 min, diluted with H₂O, extracted with EtOAc, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to yield 678 mg (46%) of 112 as a colorless oil; IR (thin film) 3273, 2982, 2935, 1745, 1609, 1383, 1268, 1154, and 1096 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.74 (d, 2H, J = 4.4 Hz), 3.36 (s, 6H), 4.69 (t, 1H, J = 4.4 Hz), 6.22-6.23 (m, 1H), 6.27-
6.28 (m, 1H), 7.00 (dd, 1H, \( J = 0.8 \) Hz), and 9.21 (brs, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 40.8, 54.2, 95.0, 101.7, 111.4, 135.0, 145.2 and 165.4.

\((E)-N-(\text{Furan-2-yl})\text{hex-3-enoic acid (114).} \) To a stirred solution of furan 97 (1.9 g, 10.38 mmol) in THF (30 mL) at 0 \( ^\circ \)C was added \( n \)-BuLi dropwise (4.48 mL, 11.21 mmol, 2.5 M in hexane) and the mixture was stirred at 0 \( ^\circ \)C for 20 min. In a separate flask, \((E)\)-hex-3-enoic acid (3.2 g, 28 mmol) was dissolved in THF (40 mL) and the solution was cooled to 0 \( ^\circ \)C. 4-Methylmorpholine (3.07 mL, 28 mmol) and isobutyl chloroformate (3.66 mL, 28 mmol) was added and the reaction mixture was stirred for 5 min and filtered over celite with THF (4 mL). The filtrate was cooled to 0 \( ^\circ \)C and the preformed lithiate from above was added dropwise by cannula. The resulting mixture was stirred for 20 min, quenched with H\(_2\)O, and extracted with EtOAc. The organic layer was washed with a saturated aqueous NaHCO\(_3\) solution, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The resulting residue was dissolved in CH\(_3\)CN (5 mL) and was added to a stirred solution of Mg(ClO\(_4\))\(_2\) (2.89 g, 13.0 mmol) in CH\(_3\)CN (53 mL) at 40 \( ^\circ \)C and the mixture was heated at 40 \( ^\circ \)C for 10 min. The solution was diluted with H\(_2\)O, extracted with EtOAc, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% to 30% EtOAc/hexanes) to yield 0.8 g (43%) of 114 as a colorless solid, mp 48-49 \( ^\circ \)C; IR (thin film) 3202, 3159, 3057, 2971, 2901, 2885, 1659,
1606, 1563, 1517, 1406, 1381, 1241, 1205 and 1011 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.96 (t, 3H, $J=7.2$ Hz), 2.00-2.05 (m, 2H), 3.07 (dd, 1H, $J=7.2$ and 0.8 Hz), 5.49-5.57 (m, 1H), 5.64-5.71 (m, 1H), 6.25-6.27 (m, 1H), 6.29-6.31 (m, 1H), 6.99 (s, 1H), and 8.58 (brs, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 13.2, 25.4, 40.2, 95.2, 111.3, 120.7, 135.2, 138.2, 145.2 and 168.5.

1-Acetyl-5-hydroxy-1H-pyrrol-2(5H)-one (94). To a stirred solution of compound 103 (81 mg, 0.65 mmol) in acetone/H$_2$O (20/1, 48.3 mL) at 0 $^\circ$C was added NaHCO$_3$ (326 mg, 3.88 mmol) and the reaction mixture was stirred for 10 min. A sample of iodine (492 mg, 1.94 mmol) was added in 3 portions and the mixture was stirred at 0 $^\circ$C for 3 h, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (50 to 65% EtOAc/hexanes) to provide 52 mg (57%) of 94 as a white solid, mp 86-87 $^\circ$C; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 2.54 (s, 3H), 4.38 (d, 1H, $J=4.0$ Hz), 6.140-6.148 (m, 1H), 6.21 (dd, 1H, $J=6.0$ and 1.2 Hz), and 7.16 (dd, 1H, $J=6.0$ and 1.6 Hz).
5-Hydroxy-1-(2-phenylacetyl)-1H-pyrrol-2(5H)-one (105). To a stirred solution of 104 (24 mg, 0.119 mmol) in acetone/H2O (18/1, 9.5 mL) at 0°C was added NaHCO3 (60 mg, 0.71 mmol) and the solution was stirred at 0°C for 10 min. A sample of iodine (91 mg, 0.358 mmol) was added in 3 portions and the mixture was stirred at 0°C for 40 min, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% EtOAc/hexanes) to provide 16 mg (67%) of 105 as a white solid, mp 109-110 °C; IR (thin film) 3450, 3102, 2924, 1738, 1686, 1348, 1242, 1197, and 1089 cm\(^{-1}\); \(^1\)H-NMR (CDCl3, 400 MHz) δ 4.28 (s, 1H), 4.29 (s, 2H), 6.15-6.16 (m, 1H), 6.22 (d, 1H, \(J = 6.0\) Hz), 7.17 (dd, 1H, \(J = 6.0\) and 1.6 Hz) and 7.28-7.36 (m, 5H); \(^{13}\)C NMR (100 MHz, CDCl3) δ 42.7, 82.4, 127.5, 128.8, 130.0, 133.5, 147.7, 167.8, and 172.6.

1-(2-(3,4-Dimethoxyphenyl)acetyl)-5-hydroxy-1H-pyrrol-2(5H)-one (107). To a stirred solution of compound 106 (1.66 g, 6.35 mmol) in acetone/H2O (20/1, 50 mL) at 0°C was added NaHCO3 (3.2 g, 38.1 mmol) and the mixture was stirred at 0°C for 5 min. A sample of iodine (4.84 g, 19.06 mmol) was added in 3 portions and the reaction was stirred at 0 °C for 3 h, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel
chromatography (40% to 50% EtOAc/hexanes) to provide 1.76 g (77%) of 107 as a white solid, mp 109-110 °C; IR (thin film) 3454, 3101, 3002, 2938, 2837, 1736, 1686, 1517, 1349, 1264, 1228, and 1141 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 3.86 (s, 3H), 3.87 (s, 3H), 4.23 (s, 2H), 4.30 (d, 1H, $J = 3.6$ Hz), 6.15-6.16 (m, 1H), 6.22 (dd, 1H, $J = 6.0$ and 0.4 Hz), 6.82-6.88 (m, 3H), and 7.17 (dd, 1H, $J = 6.4$ and 2.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 42.1, 56.0, 56.1, 82.4, 111.3, 113.0, 122.1, 125.8, 128.7, 147.7, 148.4, 149.0, 167.8, and 172.8.

\[ \text{1-(2-(Benzyloxy)acetyl)-5-hydroxy-1H-pyrrol-2-(5H)-one (109).} \]

To a stirred solution of compound 108 (350 mg, 1.52 mmol) in acetone/H$_2$O (18.8/1, 50.6 mL) at 0 °C was added NaHCO$_3$ (767 mg, 9.13 mmol) and the mixture was stirred for 10 min. A sample of iodine (1.17g, 4.61 mmol) was added in 3 portions. The reaction mixture was stirred at 0 °C for 40 min, and then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (50% EtOAc/hexanes) to provide 263 mg (70%) of 109 as a white solid, mp 105-106 °C; IR (thin film) 3403, 3056, 2925, 2855, 1742, 1707, 1265, 1132, 1092 and 738 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 4.61 (s, 2H), 4.64 (s, 2H), 4.99 (s, 1H), 6.04 (d, 1H, $J = 6.4$ Hz), 6.09 (s, 1H), 7.01 (dd, 1H, $J = 6.4$ and 2.0 Hz), and 7.25-7.36 (s, 5H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 69.9, 73.1, 81.1, 127.2, 127.7, 127.8, 128.2, 136.9, 148.6, 168.0 and 170.8.
1-(2-(1-Acetyl-1H-indol-3-yl)acetyl)-5-hydroxy-1H-pyrrol-2-(5H)-one (111). To a stirred solution of 110 (150 mg, 0.532 mmol) in acetone/H$_2$O (20/1, 25.2 mL) at 0 °C was added NaHCO$_3$ (268 mg, 3.19 mmol) and the reaction mixture was stirred for 10 min. A sample of iodine (405 mg, 1.60 mmol) was added in 3 portions and the mixture was stirred at 0 °C for 3 h, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (50% EtOAc/hexanes) to provide 103 mg (69%) of 111 as a pale yellow solid, mp 134-136 °C; IR (thin film) 3441, 2925, 1737, 1698, 1451, 1373, 1254, 1219, 1130, and 1088 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.56 (s, 3H), 4.32 (s, 2H), 4.58 (brs, 1H), 6.07 (s, 1H), 6.17 (dd, 1H, $J$ = 6.4 and 2.0 Hz), 7.09 (dd, 1H, $J$ = 6.4 and 2.0 Hz), 7.23-7.27 (m, 1H), 7.30-7.34 (m, 1H), 7.44 (s, 1H), 7.54 (d, 1H, $J$ = 7.6 Hz), and 8.36 (d, 1H, $J$ = 7.6 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 23.9, 32.5, 90.0, 114.2, 116.5, 119.1, 123.6, 124.5, 125.3, 128.1, 130.2, 135.5, 147.9, 167.8, 168.5 and 170.8.
1-(3,3-Dimethoxypropanoyl)-5-hydroxy-1H-pyrrol-2(5H)-one (113). To a stirred solution of compound 112 (400 mg, 2.0 mmol) in acetone/H$_2$O (18/1, 34 mL) at 0°C was added NaHCO$_3$ (1.01 g, 12.0 mmol) and the reaction mixture was stirred for 10 min. A sample of iodine (1.52 g, 6.0 mmol) was added in 3 portions and the mixture was stirred at 0°C for 3 h, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (50-65% EtOAc/hexanes) to provide 338 mg (78%) of 113 as a yellow oil; IR (thin film) 3445, 2918, 2852, 1737, 1392, 1349, and 1121 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 3.21 (t, 2H, $J = 4.8$ Hz), 3.28 (s, 6H), 4.82 (d, 1H, $J = 3.6$ Hz), 4.85 (t, 1H, $J = 5.6$ Hz), 6.08-6.10 (m, 2H), 7.08 (dd, 1H, $J = 6.0$ and 2.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 40.1, 53.1, 53.4, 81.5, 100.3, 127.7, 147.8, 167.7 and 169.8.

\[\text{O} \quad \text{N} \quad \text{H} \quad \text{O} \quad \text{Et} \quad \text{I}_2 \quad \text{NaHCO}_3 \quad \text{H}_2\text{O}/\text{Acetone} \quad 65\% \quad \text{O} \quad \text{N} \quad \text{OH} \quad \text{Et}\]

(E)-1-Hex-3-enoyl-5-hydroxy-1H-pyrrol-2(5H)-one (115). To a stirred solution of compound 114 (200 mg, 1.12 mmol) in acetone/H$_2$O (18/1, 19 mL) at 0°C was added NaHCO$_3$ (564 mg, 6.72 mmol) and the reaction mixture was stirred for 5 min. A sample of iodine (851 mg, 3.35 mmol) was added in 3 portions and the mixture was stirred at 0°C for 3 h, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to provide 142 mg (65%) of 115 as a yellow oil; IR (thin film) 3450,
2964, 2933, 1741, 1686, 1426, 1348, 1230, 1194, 1137, 1088, 970, and 700 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.00 (t, 3H), 2.04-2.11 (m, 2H), 3.61-3.71 (m, 2H), 4.29 (d, 1H, \(J = 18.4\) and 4.0 Hz), 5.54-5.61 (m, 1H), 5.65-5.72 (m, 1H), 6.14-6.15 (m, 1H), 6.21 (dd, 1H, \(J = 6.4\) and 0.8 Hz), and 7.16 (dd, 1H, \(J = 6.4\) and 2.0 Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 13.7, 25.8, 40.2, 82.2, 119.7, 128.7, 137.4, 147.6, 167.8, and 173.3.

![Chemical reaction diagram](image)

**Ethyl 2-Hydroxy-5-oxo-2,5-dihydro-1\(H\)-pyrrole-1-carboxylate (117).** To a stirred solution of 116 (6.1 g, 39.3 mmol) in acetone/H\(_2\)O (18/1, 667 mL) at 0 °C was added NaHCO\(_3\) (19.8 g, 235.8 mmol) and the reaction mixture was stirred for 5 min. A sample of iodine (30.0 g, 118.1 mmol) was added in 3 portions and the mixture was stirred at 0 °C for 3 h, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to provide 4.24g (63%) of 117 as a yellow oil; IR (thin film) 3424, 3103, 2985, 1775, 1726, 1532, 1427, 1374, 1305, 1207, 1172, 1098, and 1052 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.40 (t, 3H, \(J = 7.2\) Hz), 4.11 (brs, 1H), 4.40 (q, 2H, \(J = 14.0\) and 7.2 Hz), 6.05 (s, 1H), 6.19-6.21 (m, 1H), and 7.10 (dd, 1H, \(J = 6.0\) and 2.0 Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 14.6, 63.5, 82.4, 128.9, 146.7, 151.9, and 166.3.
**tert-Butyl 2-Hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (118).** To a stirred solution of 97 (366 mg, 2.0 mmol) in acetone/H$_2$O (18/1, 34 mL) at 0°C was added NaHCO$_3$ (1.0 g, 12.0 mmol) and the reaction mixture was stirred for 10 min. A sample of iodine (1.52 g, 6.0 mmol) was added in 3 portions and the mixture was stirred at 0°C for 3 h, then quenched with a saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to provide 346 mg (87%) of 118 as a pale yellow solid, mp 80-81°C; IR (thin film) 3428, 3102, 2981, 2935, 1766, 1368, 1314, 1258, 1160, 1106, and 1047 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) δ 1.51 (s, 9H), 4.267-4.274 (m, 1H), 5.93 (d, 1H, $J = 2.4$ Hz), 6.09 (d, 1H, $J = 4.4$ Hz), and 7.00 (dd, 1H, $J = 4.4$ and 1.2 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 28.0, 82.1, 83.9, 128.4, 146.3, 149.9 and 166.4.

**Acetic Acid 1-[2-(3,4-dimethoxy-phenyl)-acetyl]-5-oxo-2,5-dihydro-1H-pyrrol-2-yl Ester (124).** To a stirred solution of 107 (0.5 g, 2.02 mmol) in pyridine (10 mL) was added acetic anhydride (0.23 mL, 2.43 mmol). The reaction mixture was stirred at rt for 16 h then quenched with H$_2$O and extracted with EtOAc. The organic layer was washed with 1 N HCl and H$_2$O then dried over MgSO$_4$, filtered, and concentrated under reduced
pressure. The residue was purified by silica gel chromatography (50% EtOAc/hexanes) to provide 0.6 g (95%) of 124 as a colorless oil; IR (thin film) 3098, 2938, 2837, 1742, 1704, 1516, 1351, 1265, 1237, and 1027 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) δ 2.07 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.17 (d, 1H, $J$ = 16.0 Hz), 4.23 (d, 1H, $J$ = 16.0 Hz), 6.23 (d, 1H, $J$ = 6.0 Hz), 6.79-6.86 (m, 3H), and 7.12-7.16 (m, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 20.6, 42.1, 55.8, 80.4, 111.0, 112.7, 121.9, 125.5, 128.7, 145.1, 148.1, 148.7, 167.9, 169.3 and 169.9.

![Chemical Structure](image)

1-[2-(3,4-Dimethoxy-phenyl)-acetyl]-5-isopropoxy-1,5-dihydro-pyrrol-2-one (125).

To a stirred solution of compound 124 (417 mg, 1.45 mmol) in i-PrOH (20 mL) was added Pd(PPh$_3$)$_4$ (84 mg, 0.073 mmol) and the reaction mixture was stirred at rt for 5 h. The mixture was then concentrated under reduced pressure and purified by silica gel chromatography (20% to 50% EtOAc/hexanes) to yield 407 mg (97%) of 125 as a colorless oil; IR (thin film) 2971, 2934, 2836, 1737, 1699, 1516, 1465, 1342, 1263, 1222, and 1028 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) δ 1.15 (d, 3H, $J$ = 6.4 Hz), 1.19 (d, 3H, $J$ = 6.0 Hz), 3.86 (s, 3H), 3.87 (s, 3H), 4.22 (s, 2H), 4.27 (p, 1H, $J$ = 12.4, 6.4, and 6.0 Hz), 5.98 (d, 1H, $J$ = 2.0 Hz), 6.10 (d, 1H, $J$ = 6.0 Hz), 6.81-6.87 (m, 3H), and 7.01 (dd, 1H, $J$ = 6.0 and 2.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 23.3, 42.7, 55.99, 56.0, 73.6, 87.0, 111.3, 112.9, 122.1, 126.5, 127.1, 148.1, 148.2, 149.0, 168.7, and 171.4.
2-Methoxy-5-oxo-2,5-dihydro-pyrrole-1-carboxylic Acid tert-Butyl Ester (126). To a stirred solution of compound 118 (240 mg, 1.21 mmol) in CH₂Cl₂ (10 mL) was added silver (I) oxide (1.4 g, 6.03 mmol) and iodomethane (3 mL, 48.2 mmol). The reaction mixture was stirred for 14 h at rt then filtered over celite. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography to yield 254 mg (99%) of 126 as a colorless oil; IR (thin film) 3095, 2981, 2937, 2835, 1783, 1723, 1612, 1458, 1356, 1285, 1275, 1163, and 1046 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.56 (s, 9H), 3.33 (s, 3H), 5.86-5.87 (m, 1H), 6.18-6.20 (m, 1H), and 6.96 (dd, 1H, J = 6.4 and 0.8 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 27.7, 53.1, 82.9, 87.8, 128.4, 145.3, 148.7, 167.1.

2-Methoxy-5-oxo-2,5-dihydro-pyrrole-1-carboxylic Acid Ethyl Ester (127). To a stirred solution of compound 117 (4.24 g, 24.8 mmol) in CH₂Cl₂ (206 mL) was added silver (I) oxide (28.7 g, 124 mmol) and iodomethane (61.9 mL, 992 mmol). The reaction mixture was stirred for 14 h at rt then filtered over celite. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (EtOAc/hexanes) to yield 4.48 g (98%) of 127 as a colorless oil; IR (thin film) 3096, 2985, 1788, 1753, 1466, 1373, 1350, 1299, 1272, and 1100 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.35 (d, 3H, J = 7.2 Hz), 3.34 (s, 3H), 4.34 (q, 2H, J = 7.2 Hz), 5.90 (dd, 1H, J = 2.0 and 0.8 Hz), 6.18
(dd, 1H, $J = 6.4$ and 0.8 Hz), and 7.00 (d, 1H, $J = 6.4$ and 2.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 14.3, 53.6, 62.9, 88.1, 128.6, 145.9, 150.6 and 166.9.

To a stirred solution of compound 107 (22 mg, 0.089 mmol) in CH$_2$Cl$_2$ (2 mL) was added silver (I) oxide (103 mg, 0.445 mmol) and iodomethane (0.22 mL, 3.56 mmol). The reaction mixture was stirred for 6 h at rt then filtered over celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (EtOAc/hexanes) to yield 21 mg (91%) of 128 as a colorless oil; IR (thin film) 3090, 2999, 2937, 2836, 1739, 1703, 1516, 1343, 1264, 1225, 1190 and 1142, and 1027 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 3.33 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.15 (d, 1H, $J = 15.6$ Hz), 4.27 (d, 1H, $J = 15.6$ Hz), 5.98 (dd, 1H, $J = 2.0$ and 0.8 Hz), 6.15 (dd, 1H, $J = 6.4$ and 0.8 Hz), 6.78-6.87 (m, 3H), and 7.06 (dd, 1H, $J = 6.0$ and 2.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 42.4, 55.3, 55.8, 87.8, 111.0, 112.7, 121.8, 126.1, 127.9, 146.8, 148.0, 148.7, 168.3, 171.0.

**1-(2-(3,4-Dimethoxyphenyl)acetyl)-5-methoxy-1H-pyrrol-2(5H)-one (128).** To a stirred solution of compound 107 (22 mg, 0.089 mmol) in CH$_2$Cl$_2$ (2 mL) was added silver (I) oxide (103 mg, 0.445 mmol) and iodomethane (0.22 mL, 3.56 mmol). The reaction mixture was stirred for 6 h at rt then filtered over celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (EtOAc/hexanes) to yield 21 mg (91%) of 128 as a colorless oil; IR (thin film) 3090, 2999, 2937, 2836, 1739, 1703, 1516, 1343, 1264, 1225, 1190 and 1142, and 1027 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 3.33 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.15 (d, 1H, $J = 15.6$ Hz), 4.27 (d, 1H, $J = 15.6$ Hz), 5.98 (dd, 1H, $J = 2.0$ and 0.8 Hz), 6.15 (dd, 1H, $J = 6.4$ and 0.8 Hz), 6.78-6.87 (m, 3H), and 7.06 (dd, 1H, $J = 6.0$ and 2.0 Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 42.4, 55.3, 55.8, 87.8, 111.0, 112.7, 121.8, 126.1, 127.9, 146.8, 148.0, 148.7, 168.3, 171.0.

**tert-Butyl 3-tert-Butyl-2-methoxy-5-oxopyrrolidine-1-carboxylate (131).** To a stirred suspension of CuI (295 mg, 1.56 mmol) in THF (5 mL) at 0 °C was added t-BuLi (1.38
mL, 2.2 mmol, 1.6 M in pentane) dropwise. The reaction mixture was stirred at 0 °C for 1.5 h, then cooled to -78 °C and TMSCl (5.78 mL) was added. The reaction mixture was stirred for 5 min and a solution of compound 126 (60 mg, 0.282 mmol) in THF (1 mL) was slowly added. The mixture was stirred at -78 °C for 5 min then warmed to rt and stirred for an additional 2 h. The mixture was quenched by the slow addition of a saturated aqueous NH₄Cl solution and extracted with Et₂O. The organic layer was washed with a saturated aqueous NaHCO₃ solution and dried over MgSO₄, then filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (20% EtOAc/hexanes) to yield 61 mg (80%) of compound 131 as a colorless oil; IR (thin film) 2963, 1792, 1760, 1723, 1476, 1370, 1304, 1202, 1158, and 1088 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 0.90 (s, 9H), 1.54 (s, 9H), 1.92 (dd, 1H, J = 9.2 and 1.2 Hz), 2.33 (d, 1H, J = 18.4 and 1.6 Hz), 2.76 (dd, 1H, J = 18.4 and 9.2 Hz), 3.39 (s, 3H), and 5.20 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 27.0, 28.2, 31.9, 33.4, 47.6, 56.1, 83.5, 91.3, 150.1, and 174.2.

![Chemical Structure](image.png)

tert-Butyl 2-Methoxy-5-oxo-3-phenylpyrrolidine-1-carboxylate (132). To a 0 °C stirred suspension of CuBr • Me₂S (1.01 g, 4.94 mmol) in THF (10 mL) was added phenyllithium (6.2 mL, 11.0 mmol, 1.8 M in cyclohexane) dropwise. The reaction mixture was stirred at 0 °C for 1.5 h, then cooled to -78 °C and TMSCl (3.63 mL) was
added. The mixture was stirred for an additional 10 min and a solution of compound 126 (300 mg, 1.41 mmol) in THF (3 mL) was slowly added. The mixture was stirred at -78 °C for 5 min, then warmed to rt and stirred for an additional 3 h. The reaction mixture was quenched by the slow addition of a saturated aqueous NH₄Cl solution and then extracted with Et₂O. The organic layer was washed with a saturated aqueous NaHCO₃ solution and dried over MgSO₄, then filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (20% EtOAc/hexanes) to yield 410 mg (75%) of 132 as a colorless oil; IR (thin film) 2980, 2935, 1792, 1723, 1758, 1455, 1369, 1338, 1303, 1154, 1085, 1022, and 943 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.51 (s, 9H), 2.54 (dd, 1H, J = 17.6 and 0.8 Hz), 3.17 (dd, 1H, J = 17.6 and 8.8 Hz), 3.38 (d, 1H, J = 8.8 Hz), 3.47 (s, 3H), 5.17 (s, 1H), 7.14-7.16 (m, 2H), and 7.24-7.36 (m, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ 27.9, 37.7, 42.9, 56.6, 83.5, 95.2, 126.6, 127.5, 129.1, 140.6, 149.7, and 173.5.

**tert-Butyl 3-Butyl-2-methoxy-5-oxopyrrolidine-1-carboxylate (133).** To a stirred suspension of CuI (4.9 g, 25.82 mmol) in THF (83 mL) 0 °C was added n-BuLi (14.7 mL, 36.75 mmol, 2.5 M in hexanes) dropwise. The reaction mixture was stirred at 0 °C for 1.5 h, then cooled to -78 °C and TMSCl (12.07 mL) was added. The mixture was stirred for 5 min and compound 126 (1.0 g, 4.69 mmol) in THF (3 mL) was added slowly. The mixture was stirred at -78 °C for 10 min, then warmed to rt and stirred for an additional 1
h. The mixture was quenched by the slow addition of saturated aqueous NH₄Cl solution and extracted with Et₂O. The organic layer was washed with a saturated aqueous NaHCO₃ solution and dried over MgSO₄, then filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (10 to 25% EtOAc/hexanes) to yield 1.17 g (92%) of 133 as a colorless oil; IR (thin film) 2958, 2933, 2860, 1793, 1760, 1721, 1458, 1368, 1305, 1158, 1092, 1022, and 843 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 0.87 (t, 3H, J = 7.2 Hz), 1.21-1.43 (m, 6H), 1.52 (s, 9H), 2.08-2.12 (m, 2H), 2.82 (dd, 1H, J = 17.6 and 7.6 Hz), 3.37 (s, 3H), and 5.01 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 13.9, 22.5, 27.9, 29.0, 32.2, 36.9, 37.4, 56.2, 83.2, 93.8, 150.2, and 173.7.

**tert-Butyl 2-Methoxy-3-methyl-5-oxopyrrolidine-1-carboxylate (134).** To a 0 °C stirred suspension of CuI (0.98 g, 5.14 mmol) in THF (20 mL) was added MeLi (4.58 mL, 7.2 mmol, 1.6 M in Et₂O) dropwise. The reaction mixture was stirred at 0 °C for 1.5 h, then cooled to -78 °C and TMSCl (2.42 mL) was added. The mixture was stirred for 5 min and a solution of compound 126 (200 mg, 0.94 mmol) in THF (3 mL) was slowly added. The mixture was stirred at -78 °C for 5 min, then warmed to rt and stirred for an additional 45 min. The mixture was quenched by the slow addition of aqueous NH₄Cl and then extracted with Et₂O. The organic layer was washed with a saturated aqueous NaHCO₃ solution and dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (20%
EtOAc/hexanes) to yield 61 mg (80%) of 134 as a colorless oil; IR (thin film) 2976, 2935, 1790, 1760, 1721, 1368, 1310, 1156, 1093 and 1023 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.07 (d, 3H, \(J = 7.2\) Hz), 1.55 (s, 9H), 2.03 (d, 1H, \(J = 17.2\) Hz), 2.30 (p, 1H, \(J = 14.8\) and 7.6 Hz), 2.90 (dd, 1H, \(J = 25.2\) and 8.0 Hz), 3.42 (s, 3H), and 4.98 (s, 1H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) 18.6, 28.2, 32.4, 38.8, 56.7, 83.5, 95.3, 150.5, and 173.9.

**tert-Butyl 3-Hexyl-2-methoxy-5-oxypyrrolidine-1-carboxylate (135).** To a stirred suspension of CuI (0.98g, 5.14 mmol) in THF (20 mL) at 0 °C was added hexyllithium (3.2 mL, 7.2 mmol, 2.3 M in hexane) dropwise. The mixture was stirred at 0 °C for 1.5 h, then cooled to -78 °C and TMSCl (2.42 mL) was added. The solution was stirred for 5 min and compound 126 (200 mg, 0.94 mmol) in THF (3 mL) was added slowly. The mixture was stirred at -78 °C for 5 min, then warmed to rt and stirred for an additional 2 h. The reaction mixture was quenched by the slow addition of a saturated aqueous NH\(_4\)Cl solution and extracted with Et\(_2\)O. The organic layer was washed with aqueous NaHCO\(_3\) solution and dried over MgSO\(_4\), then filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (20% EtOAc/hexanes) to afford 158 mg (58%) of 135 as a colorless oil; IR (thin film) 2930, 2857, 1794, 1760, 1721, 1459, 1368, 1304, 1157, and 1093 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.88 (t, 3H, \(J = 6.8\) Hz), 1.25-1.55 (m, 10H), 1.55 (s, 9H), 2.10-2.15 (m, 2H), 2.85 (dd, 1H, \(J = 17.6\) Hz), 3.42 (s, 3H), 4.98 (s, 1H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) 18.6, 28.2, 32.4, 38.8, 56.7, 83.5, 95.3, 150.5, and 173.9.
and 7.6 Hz), 3.40 (s, 3H), and 5.04 (s, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 14.3, 22.8, 27.0, 28.2, 29.3, 31.8, 32.7, 37.1, 37.7, 56.5, 83.5, 94.1, 150.5, and 174.0.

**133**

1. $\text{MgBr}$

2. Quinoline/CSA 1:1

toluene, 90°C

17%

**146**

*tert*-Butyl 4-Butyl-2-vinyl-1H-pyrrole-1-carboxylate (146). To a -78 °C stirred solution of 133 (100 mg, 0.276 mmol) in THF (5 mL) was added vinyl magnesium bromide (0.55 mL, 0.55 mmol, 1.0 M in THF) dropwise and the resulting reaction mixture was stirred at -78 °C for 1 h. The mixture was quenched with a saturated aqueous NaHCO$_3$ solution and the aqueous layer was extracted with Et$_2$O. The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting oil was taken up in toluene (4 mL) and the CSA/quinoline catalyst (1:1, 5 mg, 0.014 mmol) was added. The reaction mixture was heated at 90 °C for 2 h then cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/hexanes) to give 16 mg (17%) of 146 as a pale yellow oil. IR (thin film) 2930, 2858, 2360, 2337, 1741, 1423, 1347, 1369, 1252, 1163, 1091, and 851 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 0.92 (t, 3H, $J = 8.0$ Hz), 1.24-1.57 (m, 4H), 1.58 (s, 9H), 2.37 (t, 2H, $J = 8.0$ Hz), 5.07 (dd, 1H, $J = 11.2$ and 1.6 Hz), 5.49 (dd, 1H, $J = 17.6$ and 2.0 Hz), 6.31 (d, 1H, $J = 2.0$ Hz), 6.96 (s, 1H), and 7.20 (m, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 14.2, 22.6, 26.6, 28.3, 32.6, 83.6, 112.1, 113.1, 118.7, 126.9, 128.3, 134.5, and 149.7.
(E)-tert-Butyl 4-tert-Butyl-2-(prop-1-enyl)-1H-pyrrole-1-carboxylate (147). To a -78 °C stirred solution of 131 (137 mg, 0.505 mmol) in THF (8 mL) was added allyl magnesium bromide (0.76 mL, 0.76 mmol, 1.0 M in Et₂O) dropwise and the resulting reaction mixture was stirred at -78 °C for 0.5 h and then at 0 °C for 1.5 h. The reaction mixture was quenched with a saturated aqueous NaHCO₃ solution and the aqueous layer was extracted with Et₂O. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting oil was dissolved in toluene (5 mL) and the CSA/quinoline catalyst (1:1, 9 mg, 0.025 mmol) was added. The mixture was heated at 90 °C for 2 h, then cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexanes) to give 133 mg (54%) of 147 as a pale yellow oil; IR (thin film) 2961, 2869, 1743, 1475, 1393, 1369, 1346, 1256, 1163, 1118, 1082, 961, and 854 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.19 (s, 9H), 1.57 (s, 9H), 1.82 (dd, 3H, J = 6.8 and 1.6 Hz), 5.93-6.02 (m, 1H), 6.24 (d, 1H, J = 1.6 Hz), and 6.83-6.93 (m, 2H).
**tert-Butyl 4-Phenyl-2-vinyl-1H-pyrrole-1-carboxylate (148).** To a -78 °C stirred solution of 132 (75 mg, 0.258 mmol) in THF (8 mL) was added vinyl magnesium bromide (0.39 mL, 0.39 mmol, 1.0 M in THF) dropwise and the resulting reaction mixture was stirred at -78 °C for 0.5 h and at 0 °C for 2 h. The reaction mixture was quenched with a saturated NaHCO₃ solution and the aqueous layer was extracted with Et₂O. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting oil was dissolved in toluene (4 mL) and the CSA/quinoline catalyst (1:1, 4 mg, 0.013 mmol) was added. The reaction mixture was heated at 90 °C for 2 h then cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to give 13 mg (19%) of 148 as a pale yellow oil; IR (thin film) 2979, 2931, 1743, 1353, 1273, 1160, 1102, and 751 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.61 (s, 9H), 5.143-5.171 (m, 1H), 5.567-5.614 (m, 1H), 6.726-6.731 (m, 1H), 7.191-262 (m, 1H), 7.311-7.368 (m, 3H), and 7.472-7.531 (m, 3H).
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Chapter 2:

An IMDAF-Based Approach to the Core Structure of (±)-Minfiensine
Introduction

Nitrogenous natural products containing the highly congested pentacyclic 1,2,3,4-tetrahydro-9a,4a-(iminoethano)9\textit{H}-carbazole ring system (149) have been isolated from a variety of sources (Figure 2-1).\textsuperscript{1} These alkaloids include members of the akuammiline class represented by echitamine (150), and vincorine (151). This core structure is also found in some members of the \textit{Strychnos} family of alkaloids, including minfiensine (152). Both classes of natural products which contain this core skeleton have been found to exhibit a wide variety of biological activities, including significant anticancer properties.\textsuperscript{2,3} Even though these alkaloids show impressive biological activity, the challenging pentacyclic core structure has only been prepared by a few successful routes and this skeleton continues to be an important challenge for synthetic chemists.

Figure 2-1: Alkaloids Containing the 1,2,3,4-tetrahydro-9a,4a-(iminoethano)9\textit{H}-carbazole Ring System

![Structure 149](image1)

149

![Structure 150](image2)

150; echitamine

![Structure 151](image3)

151; vincorine

![Structure 152](image4)

152; minfiensine
Known Synthetic Approaches to the 1,2,3,4-Tetrahydro-9a,4a-(iminoethano)9H-carbazole Core

To date, the only known approach to the akuammiline alkaloids was reported by Levy and coworkers (Scheme 2-1). Starting from 2-vinylindole 153, its Diels-Alder cycloaddition with dimethyl maleate led to the iminium/enamine intermediate 154, which upon further heating resulted in the formation of the complex core structure 155 via a novel iminium ion cyclization. The Diels-Alder cycloaddition of related diene-activated 2-vinylindoles has also been extensively explored by Kuehne in his biomimetic approaches to various natural products. Related work by Pindur was reported to result in successful cycloaddition of some unactivated 2-vinyl indoles and was used as an approach toward several natural products. However, the route developed by Levy and coworkers toward echitamine 150 is significant, not only because it represents a less common example of the ability to perform Diels-Alder reactions on unactivated 2-vinylindoles, but it also corresponds to the first known example of a Diels-Alder reaction making use of a 2-vinyl tryptamine derivative.

Scheme 2-1: Levy’s 2-Vinyltryptamine Diels-Alder Approach to the Akuammiline Alkaloid Core
Although there is only a single reported example directed to the akuammiline alkaloid framework, there has recently been an increased amount of interest in the synthesis of the related *Strychnos* indole alkaloid minfiensine (152). A great deal of the work in this area has been carried out by Overman and coworkers, who recently completed an enantioselective total synthesis of (+)-minfiensine using a novel sequential asymmetric Heck-iminium ion cyclization to form the 1,2,3,4-tetrahydro-9a,4a-(iminoethano)9H-carbazole ring system (Scheme 2-2).7 Starting from enamine 156 and aniline 157, formation of the key Heck cyclization precursor 158 was made possible through an acid-catalyzed transamination sequence. Treatment of this substrate with
Pd(OAc)$_2$ using a variety of chiral ligands under microwave conditions allowed for the enantioselective formation of the key quaternary center present in 160. The second key cyclization step was made possible by the treatment of 160 with TFA to form an iminium ion intermediate which then underwent a subsequent cyclization to generate the core structure of minfiensine.

Following the development of the sequential Heck-iminium ion cyclization route to the core skeleton, Overman then completed two independent end-game strategies for the natural product structure, both relying on a palladium-mediated coupling step to close the final ring of the natural product (Scheme 2-3). In the first generation synthesis, epoxidation of 161 was followed by ring opening, elimination, and a subsequent transformation to the vinyl iodide to provide the key coupling precursor 162. While this approach was somewhat lengthy, requiring eight steps to complete the synthesis from the core structure, compound 162 was found to undergo ready Heck cyclization to generate the critical intermediate 163 which was then transformed into (+)-minfiensine.

Scheme 2-3: Overman’s End-Game strategies Toward Minfiensine

First generation route to minfiensine

Second generation route to minfiensine
More recently, the overall synthesis was improved by application of a palladium-catalyzed enolate coupling reaction in order to synthesize the pentacyclic framework (Scheme 2-3). Thus, sequential conversion of olefin 164 to the corresponding ketone followed by a palladium-mediated enolate coupling provided the known intermediate 166, which was then readily converted into minfiensine in only four additional steps.

Following Overman’s pioneering total synthesis of (+)-minfiensine, this natural product has also been pursued by Qin and coworkers, who utilized a three-step one-pot cascade reaction to generate the core structure of (±)-minfiensine. The cascade sequence, starting from intermediate 168, involved a copper-catalyzed cyclopropanation of diazo keto ester 168, a nitrogen-assisted ring-opening, and an intramolecular amine addition sequence to install the final ring of the core structure 169 (Scheme 2-4). Completion of

Scheme 2-4: Qin’s Cascade Cyclopropane-Mediated Approach to (±)-Minfiensine
the total synthesis was made possible by use of a protocol similar to that employed in the Overman synthesis of (+)-minfiensine, namely a palladium-catalyzed enolate coupling reaction to close the final ring. The total synthesis was completed in four additional steps, which included formation of an enol triflate and a successive hydroxymethylation reaction under Still cross-coupling conditions.

**The IMDAF Cycloaddition/Rearrangement Cascade of 2-Amidofurans**

A significant portion of the furan-based research in the Padwa laboratories has involved the utilization of the Intramolecular Diels-Alder reaction of Furans (IMDAF). The IMDAF cycloaddition/rearrangement sequence (Scheme 2-5) represents a useful strategy for generating tetrahydroindolinones present in a number of natural products.\textsuperscript{10,11,12} Specifically, this sequence provides for a ready route to functionalized tetrahydroindolinones containing a variety of R\textsubscript{2} substituents, including methoxycarbonyl, alkyl, and aryl derivatives. Furthermore, this method has been shown to be useful for the total synthesis of several natural products, including dendrobine\textsuperscript{10} (174) and lycorane (175).\textsuperscript{13}

The IMDAF reaction has also been utilized by the Padwa group with a variety of aryl substituents for the R\textsubscript{2} group, and the method has been directly applied toward the total synthesis of mesembrane (178) and the Amaryllidaceae alkaloid crinane (181, Scheme 2-6).\textsuperscript{11} One of the primary challenges of generating these alkaloids involves the formation of the sterically-congested quaternary carbon stereocenter C\textsubscript{3a}. Indeed, the IMDAF cycloaddition/rearrangement cascade sequence allowed for facile formation of
this stereocenter, giving rise to the desired tetrahydroindolinone skeleton which was then converted in several additional steps to (±)-mesembrane (178) and (±)-crinane (181).

Scheme 2-5: The IMDAF Cyloaddition/Rearrangement Cascade Sequence of Amidofurans

\[
\text{171} \xrightarrow{\text{heat}} \begin{array}{c}
\text{172; } R_1 = \text{Et, } R_2 = \text{CO}_2\text{Me (80\%)} \\
\text{173; } R_1 = \text{t-Bu, } R_2 = \text{Me (71\%)}
\end{array}
\]

\[
\begin{array}{c}
174; \text{dendrobine} \\
175; \text{lycorane}
\end{array}
\]

respectively. As a consequence of the efficient IMDAF method for preparing the sterically-congested stereocenter of the hexahydroindoline core structure, as well as the general shortage of methods for accessing the 1,2,3,4-tetrahydro-9a,4a-(iminoethano)9H-carbazole core structure found in (±)-minfiensine (152), we set out to determine if it was possible to use this methodology to achieve a total synthesis of this biologically interesting natural product.
Scheme 2-6: Padwa’s IMDAF Cycloaddition/Rearrangement Approach to Mesembrane and Crinane

Based on the methodology previously established in the Padwa group, we anticipated that a synthesis of the quaternary stereocenter of the minfiensine core structure could occur via a IMDAF cycloaddition/rearrangement reaction of amidofuran.

Scheme 2-7: Retrosynthetic Analysis for the Synthesis of Minfiensine
Additionally, upon treatment with acid, the resulting enamine/aniline intermediate 185 was expected to undergo an intramolecular iminium ion cyclization to generate the desired core structure 183. This approach would not only provide rapid access to 183 but this intermediate could also be easily converted to minfiensine using known conditions developed by Overman and Qin as well as related chemistry obtained in the Padwa group’s synthesis of (±)-strychnine.\textsuperscript{14}

**Results and Discussion**

To avoid the need for amine protecting groups, we began our synthesis using the commercially available 1-iodo-2-nitrobenzene (187). We found that application of the conditions developed by Baudoin and coworkers\textsuperscript{15} allowed for a two-step, one-pot synthesis of the desired olefin 189 using a sequential borylation-Suzuki coupling procedure (Scheme 2-8). Even though this procedure was useful for obtaining the necessary starting material, the overall yield was low and the cost associated with the 3-bromo-3-buten-3-ol coupling component was a significant factor. Therefore there was still a need to develop a more efficient method for the generation of olefin 189. We soon discovered that the more reactive vinyl iodide coupling component 196 could readily be synthesized on a large scale by applying a known procedure developed by Sugiyama.\textsuperscript{16} Thus, iodide 196 was coupled with the commercially available 2-nitrophenylboronic acid (195) to give 189 in 60% yield.\textsuperscript{17} There are a number of conditions which had previously been developed in our group for the alkylation of furanyl carbamates such as 47. The alkylation typically involves a displacement reaction of either the corresponding
mesylate, bromide, or iodide intermediates (190; X = Br; 191; X = I; 192; X = OMs) with the anion derived from the carbamate. We first submitted alcohol 189 to bromination conditions using PPh₃ and NBS. While this transformation occurred in good yield, treatment of the resulting bromide 190 with furanyl carbamate 193 in the presence of Cs₂CO₃ in DMF at 80°C led to large quantities of the undesired elimination product 194. Likewise, an attempted alkylation of the iodo intermediate 191, formed from standard iodination conditions (I₂, PPh₃, and imidazole), also led to significant amounts of the elimination byproduct 194.

Scheme 2-8: Routes for Accessing the Amidofuran Precursor

In an attempt to avoid the formation of the undesired elimination byproduct, alcohol 189 was converted under standard conditions (MsCl, Et₃N) to the corresponding mesylate 192 which was immediately treated with furanyl carbamate 193 under phase
transfer conditions (Scheme 2-9). These conditions provided the desired amidofuran intermediate in 63% yield over two steps. Having the key cycloaddition precursor in hand, amidofuran 186 was heated in toluene in a sealed tube to induce the desired IMDAF reaction. Unfortunately, no cycloaddition product was obtained, even after heating for extended periods of time (14 days) at temperatures up to 220 °C.

Scheme 2-9: Amidofuran Formation and Preliminary IMDAF Cycloaddition Results

Considering the precedence for the IMDAF cyclization reaction when similar substrates were used, we were curious as to the reason for the absence of cycloaddition with furan 186 and thus were led to consider whether this result was due to either an electronic or a steric effect of the ortho nitro substituent. Because the aryl cyclization precursors used in the synthesis of both mesembrine and crinane\textsuperscript{11} contained meta or para substitution on the phenyl ring, we considered the possibility of an unexpected electronic factor as the major source for the unreactivity of our ortho-substituted analog. We therefore sought to determine the effect of other substituent groups in the ortho
position on the IMDAF cycloaddition. Reduction of the nitro functionality was carried out using conditions employed by Heathcock\textsuperscript{18} (Cu(acac)\textsubscript{2} and NaBH\textsubscript{4} in EtOH) and this cleanly provided the desired aniline intermediate \textbf{196} (Scheme 2-10). However, heating this compound to 220°C in a sealed tube only led to recovered starting material as was encountered in our earlier attempted reaction using the nitro precursor \textbf{186}. Having aniline \textbf{196} on hand, we next decided to alter the electronics of the anilino group by the installation of a benzyl \textit{N}-protecting group. Once again, cycloaddition was still not observed upon heating the furanyl carbamate precursor \textbf{198} at 220°C.

Scheme 2-10: Synthesis of Aniline and Benzyamine Substrates and Attempted IMDAF Cycloaddition

We next set out to test whether disubstitution at the amino group or perhaps the presence of an electron-withdrawing group on the nitrogen atom would facilitate the IMDAF reaction. Consequently, intermediate \textbf{205} was synthesized in five steps starting from the commercially available 2-(\textit{N}-Boc-amino)phenylboronic acid pinacol ester (\textbf{200})
(Scheme 2-11). First, Suzuki cross coupling of 200 with the known silyl ether 201\textsuperscript{19} using the previously-applied cross-coupling conditions led to the desired TBS-protected alcohol 202. Methylation at the nitrogen atom with MeI and NaH in THF followed by TBAF deprotection of the resulting silane provided alcohol 204. This compound was then converted to the corresponding mesylate (MsCl, Et\textsubscript{3}N) and then alkylated under phase transfer conditions as was done earlier to provide amidofuran 205. Following the same trends as was previously found, no cycloaddition product was observed upon heating 205 at 220 °C for 14 days.

Scheme 2-11: Synthesis of the Disubstituted Amine IMDAF Cycloaddition Precursors
Having probed the electronic effects of a variety of Diels-Alder substrates, we suspected that lack of cycloaddition was due to an unfavorable steric interaction between the amidofuran ring and the ortho substituent present on the aromatic core. As an alternative approach, we set out to determine if cycloaddition was possible using a less bulky substituent on the ortho position which might then be used to install the required amino functionality. Recognizing that a large number of conditions exist in the literature for converting aryl bromides into the corresponding anilines or protected aniline counterparts\textsuperscript{20,21} we revised the strategy of our synthesis and focused our attention on determining whether cycloaddition of an ortho-substituted bromo analog such as 208 would be possible. As outlined in Scheme 2-12, we anticipated that synthesis of the protected aniline 185 would then be possible from a metal-mediated coupling of aryl bromide 207 and an appropriate nitrogen source. Compound 207 could possibly be generated by the IMDAF cycloaddition/rearrangement sequence of amidofuran 208. Amidofuran 208 would be available from the corresponding boronic acid via a Suzuki cross-coupling reaction as employed previously in our earlier syntheses.

In order to test whether the IMDAF cycloaddition reaction would occur with aryl bromide 208, we began our synthesis by preparing the necessary precursor making use of 2-bromophenylboronic acid (210). Suzuki cross coupling of this commercially available bromide with iodide 196 using a modification of the conditions developed by Kitawaki\textsuperscript{22} provided the desired alcohol 209 in good yield (Scheme 2-13). Although furanyl carbamate alkylation of the corresponding bromide and mesylate substrate is possible, the reaction of 209 only resulted in low yields of the required furanyl carbamate 208, even after examining a large number of experimental conditions. However, the 2-step
Scheme 2-12: Revised Retrosynthetic Strategy Utilizing IMDAF Cycloaddition of Aryl Bromide

The mesylation-alkylation sequence did provide a small quantity of the necessary amidofuran 208. Much to our delight, heating a sample of amidofuran 208 in toluene in a sealed tube for 6 days at 185 °C provided a 61% yield of the desired IMDAF cycloaddition/rearrangement product. This result demonstrates the significant importance of ortho vs para or meta substitution in the IMDAF cycloaddition reaction of these systems.

Having developed a route to the desired cycloadduct 202, a major issue became the need to generate more material in order to install the required ortho amino group. Even though we tested a large number of conditions for increasing the yield of the alkylation step, it was still not possible to obtain significant amounts of material for an eventual synthesis. As a result, we considered the possibility of removing the alkylation step from our synthetic plan, and thought instead about using the corresponding imidofuran system 217 (Scheme 2-14). Similar chemistry had already been developed in our laboratories and this approach was found to be useful for the generation of a wide
variety of natural products. While the cycloaddition reaction would produce an additional carbonyl substituent in the product, this functionality could simply be removed by reduction at a later stage of the synthesis, and overall this would represent an improved route to the desired Diels-Alder cycloadduct.

In addition to addressing the issue of poor alkylation yields in our synthetic plan, we also needed to increase the overall rate of the cycloaddition. Our group had previously found that a significant rate enhancement of the IMDAF cycloaddition reaction occurs when imidofurans are used instead of amidofurans for the reaction. Thus, it was previously found that amidofuran 219 underwent the cycloaddition/rearrangement reaction to give 220 upon heating at 165 °C, whereas the imidofuran system 221 underwent the IMDAF reaction to afford the related compound 222 at 25 °C (Scheme 2-15).²⁴,²⁵ Computational studies had previously been carried out on a number of related systems in order to explain this phenomenon. Incorporating a carbonyl group in the tether...
Scheme 2-14: Synthesis and IMDAF Cycloaddition of 2-Imidofurans

Spatially places the olefinic π-bond in closer proximity to the furan ring, thereby decreasing the activation energy of the reaction and resulting in a significant rate enhancement.

Scheme 2-15: Rates of Cycloaddition Reactions of Imidofurans Versus Amidofurans
In order to determine whether a related rate enhancement would occur with our system, we set out to examine the thermal behavior of the modified imidofuran substrate \( \text{224} \) (Scheme 2-16). Oxidation of alcohol \( \text{209} \) with Jones’ reagent led to the corresponding acid \( \text{223} \) in 91% yield. Treatment of this acid with isobutyl chloroformate and 4-methylmorpholine at 0 °C followed by the addition of the anion of furanyl carbamate \( \text{193} \) led to formation of the desired imidofuran cyclization precursor \( \text{224} \).

Following the trend previously seen in the Padwa labs, we discovered that heating a sample of imidofuran \( \text{224} \) for only 2 days at 150 °C cleanly provided the desired tetrahydroindolinone intermediate in 77% isolated yield.

Scheme 2-16: Synthesis and Successful Diels-Alder Cycloaddition of Imidofuran

Thus, having discovered a more efficient route for generating the tetrahydroindolinone intermediate \( \text{225} \) by the IMDAF cycloaddition/rearrangement sequence, studies are currently underway to convert aryl bromide \( \text{225} \) into the desired aniline intermediate by making use of a metal-catalyzed coupling of the aryl bromide...
with various nitrogen sources. Based on the earlier results reported by the Overman and Qin groups, iminium ion cyclization of an aniline intermediate derived from 225 is expected to provide 226, the core skeleton of minfiensine (152). This approach would not only provide a feasible route for completing the total synthesis, but would also allow for the generation of the 1,2,3,4-tetrahydro-9a,4a-(iminoethano)9H-carbazole system found in a large number of related natural products. Further work along these lines is currently being pursued in our laboratories.
Experimental Section
**3-(2-Nitrophenyl)but-3-en-1-ol (189).** To a stirring solution of 1-iodo-2-nitrobenzene (187) (2.0 g, 8.0 mmol) in degassed 1,4-dioxane (18 mL) was added Et₃N (4.5 mL), (2-biphenyl)dicyclohexylphosphone (562 mg, 1.6 mmol), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.6 mL, 12.6 mmol, 1.0 M in THF), and Pd(OAc)₂ (90 mg, 0.402 mmol). The reaction mixture was heated at 80 °C for 2 h, cooled to rt and 2 M Na₂CO₃ (6 mL) was added, followed by a solution of 3-bromo-3-buten-1-ol (604 mg, 4.0 mmol) in dioxane (2 mL). The mixture was heated at 80°C for 19 h, then filtered over celite. To the filtrate was added brine and the aqueous layer was extracted with CH₂Cl₂, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (10% to 30% EtOAc/hexanes) and the resulting product was washed with 1 N HCl and concentrated under reduced pressure to provide 315 mg (41%) of 189 as a brown oil; IR (thin film) 3376, 2950, 2882, 1608, 1571, 1526, 1349, 848, 911, 787, 762, and 721 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 2.68-2.71 (m, 2H), 3.71 (t, 2H, J = 6.0 Hz), 5.07 (s, 1H), 5.29 (d, 1H, J = 0.8 Hz), 7.35 (dd, 1H, J = 7.6 Hz and 1.2 Hz), 7.41-7.45 (m, 1H), 7.56 (dt, 1H, J = 7.6 and 1.2 Hz), 7.84-7.86 (m, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 40.5, 60.6, 117.6, 124.5, 128.4, 130.8, 132.8, 137.4, 143.2, and 149.1.
1-(4-Bromobut-1-en-2-yl)-2-nitrobenzene (190). To a stirred solution of alcohol 189 (68 mg, 0.352 mmol) in CH$_2$Cl$_2$ (45 mL) was added PPh$_3$ (111 mg, 0.422 mmol). The reaction mixture was cooled to 0°C and NBS (75 mg, 0.422 mmol) was added in one portion. The mixture was stirred at 0°C for 0.5 h and then at rt for an additional 2 h. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (10% EtOAc/hexanes) to provide 75 mg (83%) of 190 as a pale yellow oil; IR (thin film) 2962, 1608, 1570, 1525, 1345, 1212, 915, 856, and 786 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 2.97 (t, 2H, $J = 6.8$ Hz), 3.43 (t, 2H, $J = 7.2$ Hz), 5.11 (s, 1H), 5.29 (d, 1H, $J = 0.8$ Hz), 7.36-7.39 (m, 1H), 7.40 (dt, 1H, $J = 7.6$ and 1.6 Hz). 7.60 (dt, 1H, $J = 7.6$ and 1.2 Hz) and 7.93 (dd, 1H, $J = 8.4$ and 1.2 Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 30.7, 40.1, 117.4, 124.6, 128.7, 131.6, 133.2, 137.1, 144.0, and 148.3.

\[
\begin{array}{c}
\text{NO}_2 \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \\
189 \\
\text{I}_2, \text{PPh}_3, \text{Imidazole} \\
\rightarrow \\
\text{NO}_2 \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{I} \\
191 \\
94\%
\end{array}
\]

1-(4-Iodobut-1-en-2-yl)-2-nitrobenzene (191). To a stirred solution of alcohol 189 (40 mg, 0.207 mmol) in Et$_2$O/CH$_3$CN (4/1, 2.5 mL) was added PPh$_3$ (109 mg, 0.414 mmol) and imidazole (28 mg, 0.414 mmol). The reaction mixture was stirred for 10 min at rt, cooled to 0°C, and I$_2$ (105 mg, 0.414 mmol) was added in one portion. The reaction mixture was warmed to rt and was stirred for an additional 8 h. The mixture was then diluted with Et$_2$O and filtered over celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (20% to 30% EtOAc/hexanes) to provide 59 mg (94%) of 191 as a clear oil; IR (thin film) 3083, 2860, 1607, 1524, 1345, 1173, 913, and 856 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 2.96 (t, 2H, $J$
= 7.6 Hz), 3.20 (t, 2H, $J = 7.6$ Hz), 5.11 (d, 1H, $J = 0.8$ Hz), 5.26 (d, 1H, $J = 0.8$ Hz), 7.37 (dd, 1H, $J = 7.2$ and 1.6 Hz), 7.44-7.48 (m, 1H), 7.57-7.61 (m, 1H), and 7.93-7.95 (m, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 3.0, 41.0, 116.9, 124.6, 128.7, 131.7, 133.2, 136.9, 145.4, and 148.3.

![Chemical structure](image)

3-(2-Nitrophenyl)but-3-enyl Methanesulfonate (192). To a stirred solution of alcohol 189 (160 mg, 0.828 mmol) and methanesulfonyl chloride (0.07 mL, 0.911 mmol) in CH$_2$Cl$_2$ (20 mL) at 0°C was added triethylamine (0.14 mL, 0.994 mmol) and the resulting reaction mixture was stirred for 1 h at 0°C. The reaction mixture was diluted with H$_2$O and extracted with CH$_2$Cl$_2$ and the organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed over a short pad of silica gel and concentrated to provide 167 mg (74%) of 192 as a pale yellow oil; IR (thin film) 3031, 2941, 1638, 1608, 1571, 1526, 1352, 1175, 960, 913, and 790 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 2.86 (dt, 2H, $J = 6.8$ and 0.8 Hz), 2.97 (s, 3H), 4.31 (t, 2H, $J = 6.8$ Hz), 5.11 (s, 1H), 5.31 (d, 1H, $J = 0.8$ Hz), 7.34 (dd, 1H, $J = 7.6$ and 1.6 Hz), 7.44-7.48 (m, 1H), 7.59 (dt, 1H, $J = 7.6$ and 1.2 Hz), and 7.92 (dd, 1H, $J = 8.0$ and 1.2 Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 36.5, 37.6, 67.7, 117.9, 124.6, 128.8, 131.4, 133.3, 137.0, 142.0, and 148.3.
Ethyl Furan-2-yl(3-(2-nitrophenyl)but-3-enyl)carbamate (186). A solution of furan 193 (37 mg, 0.243 mmol), K₂CO₃ (80 mg, 0.480 mmol), tetrabutylammonium hydrogensulfate (15 mg, 0.044 mmol), and freshly powdered NaOH (33 mg, 0.823 mmol) in benzene (10 mL) was heated at reflux for 30 min. The mixture was cooled to room temperature and a solution containing the above mesylate 192 (78 mg, 0.288 mmol) in benzene (3 mL) was added. The mixture was heated at 80°C for 1 h and was then cooled to rt, diluted with Et₂O, and quenched with H₂O. The aqueous layer was extracted with Et₂O and the organic layer washed with a saturated aqueous NaHCO₃ solution, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography (10% EtOAc/hexanes) to provide 47 mg (60%) of 186 as a pale yellow oil; IR (thin film) 3085, 2983, 2935, 1717, 1610, 1527, 1350, 1297, 1378, 1195, 1145, 911, and 765 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.21 (t, 3H, J = 6.8 Hz), 2.66 (t, 2H, J = 7.6 Hz), 3.70-3.74 (m, 2H), 4.15 (q, 2H, J = 14.0 and 6.8 Hz), 5.04 (s, 1H), 5.23 (d, 1H), 6.01 (brs, 1H), 6.34-6.36 (m, 1H), 7.19 (s, 1H), 7.30-7.32 (m, 1H), 7.40-7.44 (m, 1H), 7.53-7.57 (m, 1H), and 7.88-7.90 (m, 1H). ¹³C-NMR (CDCl₃, 100 MHz) δ 14.6, 35.8, 48.0, 62.4, 102.0, 111.2, 116.5, 124.4, 128.4, 131.3, 132.8, 138.0, 138.7, 144.2, 148.1, 148.8, and 155.0.
3-iodobut-3-en-1-ol (196). Prepared according to a known literature procedure.\textsuperscript{16} \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) $\delta$ 2.64 (t, 2H, $J = 5.6$ Hz), 3.77 (t, 2H, $J = 6.0$ Hz), 5.87 (s, 1H), and 6.19 (d, 1H, $J = 1.2$ Hz).

\[ \begin{array}{c}
\text{B(OH)\textsubscript{2}} \quad \text{195} \\
\text{I} \quad \text{196} \\
\text{Pd(PPh\textsubscript{3})\textsubscript{4}, 2 M Na\textsubscript{2}CO\textsubscript{3}}
\end{array} \]

\[ \text{60\%} \]

3-(2-Nitrophenyl)but-3-en-1-ol (189). To a stirred solution containing nitrophenylboronic acid 195 (598 mg, 3.58 mmol), iodide 196 (592 mg, 2.98 mmol), benzene (30 mL), EtOH (15 mL), and 2 M aqueous Na\textsubscript{2}CO\textsubscript{3} (15.2 mL) was added Pd(PPh\textsubscript{3})\textsubscript{4} (138 mg, 0.06 mmol) and the reaction mixture was heated to 65 °C for 12 h. After cooling to room temperature, the mixture was diluted with ether and washed with brine, dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography to provide 370 mg (64%) of 189 as a dark brown oil; IR (thin film) 3376, 2950, 2882, 1608, 1571, 1526, 1349, 911, 787, 762, and 721 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) $\delta$ 2.68-2.71 (m, 2H), 3.71 (t, 2H, $J = 6.0$ Hz), 5.07 (s, 1H), 5.29 (d, 1H, $J = 0.8$ Hz), 7.35 (dd, 1H, $J = 7.6$ Hz and 1.2 Hz), 7.41-7.45 (m, 1H), 7.56 (dt, 1H, $J = 7.6$ and 1.2 Hz), and 7.84-7.86 (m, 1H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 100 MHz) $\delta$ 40.5, 60.6, 117.6, 124.5, 128.4, 130.8, 132.8, 137.4, 143.2, and 149.1.
**Ethyl 3-(2-Aminophenyl)but-3-enyl(furan-2-yl)carbamate (196).** To a stirred solution of Cu(acac)$_2$ (22 mg, 0.085 mmol) in absolute EtOH (5.7 mL) was added NaBH$_4$ (104 mg, 2.76 mmol). The reaction mixture changed color from purple to brown. The mixture was stirred at rt for 25 min, during which time the color turned clear and a brown precipitate formed. A solution of 186 (93 mg, 0.282 mmol) in THF (5.7 mL) was added and the resulting mixture was stirred for 1.25 h at rt. The mixture was then poured into a saturated aqueous NaHCO$_3$ solution and extracted with CHCl$_3$. The resulting organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure to provide 75 mg (93%) of 196, requiring no further purification; IR (thin film) 3447, 3369, 2980, 2931, 1713, 1615, 1495, 1409, 1379, 1298, 1194, 1155, and 1057 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.21 (t, 3H, $J = 7.2$ Hz), 2.65 (d, 1H, $J = 6.8$ Hz), 2.67 (d, 1H, $J = 8.4$ Hz), 3.68-3.72 (m, 2H), 4.15 (q, 2H, $J = 7.2$ Hz), 5.16 (d, 1H, $J = 1.6$ Hz), 5.32 (d, 1H, $J = 1.6$ Hz), 6.01 (brs, 1H), 6.35 (dd, 1H, $J = 3.6$ and 2.4 Hz), 6.68-6.74 (m, 2H), 6.97 (dd, 1H, $J = 7.2$ and 1.6 Hz), 7.06 (td, 1H, $J = 7.6$ and 1.6 Hz) and 7.19-7.20 (brs, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 14.6, 36.1, 48.0, 62.5, 111.2, 115.9, 116.7, 118.5, 127.6, 128.3, 128.7, 138.3, 138.8, 143.3, 144.4, 147.9, and 155.2.
Ethyl 3-(2-(benzylamino)phenyl)but-3-enyl(furan-2-yl)carbamate (198). To a stirred solution of amine 196 (35 mg, 0.117 mmol) and benzaldehyde (0.012 mL, 12.4 mg, 0.117 mmol) in 1,2-dichloroethane (2 mL) was added NaBH(OAc)$_3$ (35 mg, 0.164 mmol) in one portion. The reaction mixture was stirred at 0°C for 1.5 h and then warmed to rt and stirred for 16 h. The mixture was diluted with a saturated aqueous NaHCO$_3$ solution and extracted with EtOAc. The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (100% hexanes) to yield 6 mg (13%) of 198 as a yellow oil; IR (thin film) 3420, 3063, 2980, 2931, 1717, 1615, 1507, 1452, 1407, 1378, 1193, 1139, 1060, and 910 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.20 (t, 3H, $J = 6.8$ Hz), 2.66 (t, 2H, $J = 7.2$ Hz), 3.71 (t, 2H, $J = 7.2$ Hz), 4.14 (q, 2H, $J = 14.4$ and 6.8 Hz), 4.32 (s, 2H), 4.45 (brs, 1H), 5.17 (d, 1H, $J = 1.6$ Hz), 5.32 (d, 1H, $J = 1.6$ Hz), 6.00 (brs, 1H), 6.34 (dd, 1H, $J = 3.2$ and 2.0 Hz), 6.57 (d, 1H, $J = 8.0$ Hz), 6.66 (t, 1H, $J = 7.4$ Hz), 6.96 (dd, 1H, $J = 7.2$ and 1.6 Hz), 7.07-7.11 (m, 1H), 7.24 (d, 1H, $J = 1.2$ Hz), and 7.24-7.35 (m, 5H).

**tart-Butyl 2-(4-(tart-Butyldimethylsilyloxy)but-1-en-2-yl)phenylcarbamate (202).** A solution containing boronic ester 200 (1.5 g, 4.7 mmol) and silyl ether 201 (1.14 g, 4.27 mmol) in a mixture of benzene (100 mL), EtOH (25 mL), and 2 M aqueous Na$_2$CO$_3$ (10 mL) was deoxygenated by bubbling a stream of N$_2$ through the reaction mixture for 10 min. A sample of Pd(PPh$_3$)$_4$ (0.99 g, 0.85 mmol) was added and the mixture was heated
to 80 °C for 18 h then cooled to rt. A sample of Na$_2$SO$_4$ was added and the suspension was allowed to stand for 30 min. The mixture was filtered and concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography to provide 1.31 g (74%) of 202 as a colorless oil; $^1$H-NMR (CDCl$_3$, 400 MHz) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.50 (s, 9H), 2.55 (t, 2H, $J = 6.1$ Hz), 3.58 (t, 2H, $J = 6.1$ Hz), 5.08 (d, 1H, $J = 1.6$ Hz), 5.39 (d, 1H, $J = 0.8$ Hz), 6.95-7.10 (m, 3H), 7.23 (m, 1H, $J = 8.0$ and 2.0 Hz), and 8.03 (d, 1H, $J = 8.2$ Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ -5.1, 18.6, 26.2, 28.6, 41.7, 60.9, 80.3, 118.3, 120.2, 122.6, 127.9, 128.0, 131.7, 135.8, 143.7, and 153.4; IR (film) 1161, 1452, 1518, 1731, 2858, 2933, 2959, and 3409 cm$^{-1}$; HRMS m/z calcd. for [C$_{21}$H$_{36}$NO$_3$Si]$^+$: 378.24. Found: 378.24.

**tert-Butyl 2-(4-(tert-Butyldimethylsilyloxy)but-1-en-2-yl)phenyl(methyl)carbamate (203).** To a stirred solution of NaH (0.064 g, 1.6 mmol, 60% in mineral oil) in THF (10 mL) at 0 °C was added silyl ether 202 (0.4 g, 1.1 mmol) dropwise. After stirring for 0.5 h, MeI (0.1 mL, 1.6 mmol) was added dropwise. The reaction mixture was allowed to stir for 12 h and was then quenched with H$_2$O and extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$, concentrated under reduced pressure, and purified by column chromatography to provide 0.35 g (83%) of olefin 203 as a colorless oil; IR (thin film) 1100, 1156, 1255, 1366, 1704, 2930, and 2956 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) δ -0.02 (s, 6H), 0.86 (s, 9H), 1.22-1.52 (m, 9H), 2.49-2.62 (m, 2H), 3.08 (s, 3H), 3.52-3.70
(m, 2H), 5.05 (s, 1H), 5.19 (s, 1H), 7.06 (d, 1H, $J = 7.4$ Hz), and 7.16-7.29 (m, 3H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ -5.2, 18.4, 26.1, 28.4, 28.6, 29.9, 37.2, 39.6, 61.8, 80.0, 116.6, 127.0, 127.9, 128.6, 130.4, 140.3, 141.0, 146.0, and 155.2; HRMS calcd. for [C$_{22}$H$_{38}$NO$_3$Si]$^+$: 392.25. Found: 392.26.

**tert-Butyl 2-(4-Hydroxybut-1-en-2-yl)phenyl(methyl)carbamate (204).** To a stirred solution of 203 (0.279 g, 0.71 mmol) in THF (5 mL) at 0 °C was added dropwise TBAF (2.14 mL, 2.14 mmol, 1.0 M in THF). The reaction mixture was allowed to stir at room temperature for 18 h and was then diluted with H$_2$O and extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford 0.17 g (87%) of alcohol 204 as a colorless oil; IR (thin film) 1367, 1449, 1491, 1681, 1698, 2884, 2977, and 3440 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.31 and 1.45 (minor and major rotamers, 9H), 2.48-2.68 and 2.70-2.86 (major and minor rotamers, 2H), 3.06 and 3.17 (minor and major rotamers, 3H), 3.46-3.68 (m, 2H), 5.06 (d, 1H, $J = 7.4$ Hz), 5.22 (s, 2H), and 7.05-7.33 (m, 4H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 28.3, 28.6, 37.2, 38.9, 39.4, 41.0, 60.2, 60.6, 80.1, 80.9, 116.2, 117.1, 127.2, 128.1, 128.3, 128.4, 128.5, 128.6, 130.2, 138.8, 139.7, 140.8, 141.1, 143.4, 145.6, and 155.2; HRMS calcd. for [C$_{16}$H$_{24}$NO$_3$]$^+$: 278.17. Found: 278.17.
Ethyl 3-(2-(tert-Butoxycarbonyl)methylamino)phenyl) but-3-enyl(furan-2-yl)carbamate (205). To a stirred solution of alcohol 204 (0.136 g, 0.49 mmol) and Et$_3$N (0.09 mL, 0.64 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C was added methanesulfonyl chloride (0.05 mL, 0.59 mmol). The mixture was stirred at room temperature for 12 h, diluted with H$_2$O, and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with H$_2$O, dried over MgSO$_4$, and concentrated under reduced pressure to give the crude mesylate, which was used without further purification.

A solution of furan 193 (0.068 g, 0.44 mmol), K$_2$CO$_3$ (0.123 g, 0.89 mmol), tetrabutylammonium hydrogensulfate (0.03 g, 0.09 mmol), and freshly powdered NaOH (0.053 g, 1.34 mmol) in benzene (5 mL) was heated at reflux for 30 min. The mixture was cooled to room temperature and a solution containing the crude mesylate derived from alcohol 204 (~0.5 mmol) in benzene (5 mL) was added and the reaction mixture was heated at 80°C for 1 h. The mixture was cooled to room temperature and quenched with H$_2$O. The aqueous phase was extracted with CH$_2$Cl$_2$, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography to provide 0.063 g (34%) of 205 as a pale yellow oil; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.20 (t, 3H, $J = 6.8$ Hz), 1.30 and 1.46 (major and minor rotamers, 9 H), 2.56-2.70 (m, 2H), 3.04 and 3.07 (major and minor rotamers, 3H), 3.59-3.79 (m, 2H), 4.06-4.18 and 4.18-4.28 (major and minor rotamers, 2H), 5.06 (s, 1H), 5.18 (s, 1H), 6.00
(brs, 1H), 6.33 (s, 1H), 7.06 (d, 1H, J = 6.8 Hz), and 7.11-7.32 (m, 4H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ 14.6, 28.3, 34.9, 37.3, 38.1, 48.1, 62.3, 80.0, 111.1, 111.5, 116.9, 127.1, 128.2, 128.4, 128.7, 129.7, 130.1, 138.8, 140.0, 141.0, 145.4, and 155.1.

3-(2-Bromophenyl)but-3-en-1-ol (209). To a stirred solution of iodide 196 (588 mg, 2.97 mmol) in benzene (10 mL) was added Pd(PPh$_3$)$_4$ (138 mg, 0.12 mmol), 2 M Na$_2$CO$_3$ (12 mL), and a solution of 2-bromophenylboronic acid 210 (708 mg, 3.52 mmol) in EtOH (15 mL). The reaction mixture was heated to 65°C for 14 h, cooled to rt, diluted with Et$_2$O, washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (30% EtOAc/hexanes) to yield 674 mg (79%) of 209 as a red-brown oil; IR (thin film) 3339, 2944, 1638, 1468, 1427, 1042, 910, 761, and 733 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) δ 2.70-2.73 (m, 2H), 3.64 (t, 2H, J = 6.0 Hz), 5.10-5.11 (m, 1H), 5.35-5.36 (m, 1H), 7.12-7.19 (m, 2H), 7.26-7.30 (dt, 1H, J = 8.0 and 1.2 Hz), 7.57 (dd, 1H, J = 8.0 and 1.2 Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ 40.5, 60.4, 118.3, 122.2, 127.5, 128.9, 130.4, 133.0, 143.1, and 146.3.
3-(2-Bromophenyl)but-3-enyl methanesulfonate (212). To a stirred solution of alcohol 209 (186 mg, 0.82 mmol) and methanesulfonyl chloride (0.07 mL, 0.9 mmol) in CH$_2$Cl$_2$ (20 mL) at 0°C was added Et$_3$N (0.14 mL, 0.98 mmol) and the resulting mixture was stirred for 0.5 h. The mixture was diluted with H$_2$O and extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography to provide 272 mg of mesylate 212 as a dark green oil; IR (thin film) 2937, 1719, 1468, 1427, 1353, 1173, 1028, 958, and 910 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 2.91-2.95 (m, 5H), 4.22-4.25 (m, 2H), 5.14 (s, 1H), 5.36-5.37 (m, 1H), 7.14-7.18 (m, 2H), 7.27-7.31 (m, 1H), 7.57 (d, 1H, $J = 8.0$ Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 36.3, 37.7, 67.7, 119.1, 122.1, 127.7, 129.3, 130.8, 133.1, 142.3, and 144.6.

1-Bromo-2-(4-bromobut-1-en-2-yl)benzene (211). To a stirred solution of alcohol 209 (300 mg, 1.32 mmol) in CH$_2$Cl$_2$ (45 mL) was added PPh$_3$ (416 mg, 1.59 mmol). The mixture was cooled to 0°C and NBS (283 mg, 1.59 mmol) was added in one portion. The mixture was stirred at 0°C for 15 min and then at rt for an additional 19 h. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (15% EtOAc/hexanes) to provide 354 mg (92%) of 211 as a clear oil; IR (thin film) 3082, 2967, 1638, 1469, 1425, 1267, 1210, 1024, 916, 761, and 734 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 3.03 (dd, 2H, $J = 7.6$ and 6.8 Hz), 3.37 (dd, 2H, $J = 7.6$ and 6.8 Hz), 5.11 (d, 1H, $J = 0.8$ Hz), 5.32-5.33 (m, 1H), 7.14-7.18 (m, 1H), 7.20 (dd, 1H, $J =$
7.6 and 2.0 Hz), 7.27-7.31 (m, 1H), 7.56 (dd, 1H, J = 8.0 and 0.8 Hz); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) δ 30.9, 40.0, 118.4, 122.1, 127.5, 129.2, 131.0, 133.0, 142.3, and 146.7.

**Ethyl 3-(2-Bromophenyl)but-3-enyl(furan-2-yl)carbamate (208).** A solution of furan 193 (37 mg, 0.243 mmol), K\(_2\)CO\(_3\) (88 mg, 0.533 mmol), tetrabutylammonium hydrogen sulfate (16 mg, 0.047 mmol), and freshly powdered NaOH (33 mg, 0.825 mmol) in benzene (10 mL) was heated at reflux for 30 min. The mixture was cooled to room temperature and a solution containing the above mesylate 212 (89 mg, 0.292 mmol) in benzene (3 mL) was added and the reaction mixture was then heated at 80°C for 1 h. The mixture was cooled to room temperature, diluted with Et\(_2\)O, and quenched with H\(_2\)O. The aqueous layer was extracted with Et\(_2\)O, washed with a saturated aqueous NaHCO\(_3\) solution, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography (20% EtOAc/hexanes) to provide 12 mg (15%) of 208 as a pale yellow oil; IR (thin film) 2984, 2929, 1718, 1614, 1407, 1467, 1295, 1194, 1025, 911, and 734 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) δ 1.21 (t, 3H, J = 7.2 Hz), 2.72 (t, 2H, J = 7.6 Hz), 3.67-3.70 (m, 2H), 4.15 (q, 2H, J = 14.4 and 7.2 Hz), 5.04 (s, 1H), 5.27 (d, 1H, J = 1.2 Hz), 6.02 (brs, 1H), 6.35 (m, 1H), 7.10-7.27 (m, 4H), 7.53-7.55 (m, 1H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) δ 14.6, 35.5, 47.7, 62.4, 102.5, 111.2, 117.4, 122.1, 127.4, 128.9, 130.6, 133.0, 138.8, 143.4, 146.8, 147.9, and 155.1.
Ethyl 3-(2-Bromophenyl)but-3-enyl(furan-2-yl)carbamate (208). To a stirred solution of furan 193 (44 mg, 0.284 mmol) in DMF (4 mL) at rt was added Cs$_2$CO$_3$ (111 mg, 0.341 mmol). After stirring for 45 min at rt, a solution of bromide 211 (99 mg, 0.341 mmol) in THF (1 ml) was added dropwise. The reaction mixture was heated at 60 °C for 30 min, cooled to rt, quenched with H$_2$O, and extracted with Et$_2$O. The organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% EtOAc/hexanes) to provide 15 mg (15%) of 208 as a pale yellow oil; IR (thin film) 2984, 2929, 1718, 1614, 1407, 1467, 1295, 1194, 1025, 911, and 734 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.21 (t, 3H, $J$ = 7.2 Hz), 2.72 (t, 2H, $J$ = 7.6 Hz), 3.67-3.70 (m, 2H), 4.15 (q, 2H, $J$ = 14.4 and 7.2 Hz), 5.04 (s, 1H), 5.27 (d, 1H, $J$ = 1.2 Hz), 6.02 (brs, 1H), 6.35 (m, 1H), 7.10-7.27 (m, 4H), 7.53-7.55 (m, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 14.6, 35.5, 47.7, 62.4, 102.5, 111.2, 117.4, 122.1, 127.4, 128.9, 130.6, 133.0, 138.8, 143.4, 146.8, 147.9, and 155.07.
Ethyl 3a-(2-Bromophenyl)-5-oxo-2,3,3a,4,5,6-hexahydro-1H-indole-1-carboxylate (207). A sample of furanyl carbamate 208 (12 mg, 0.033 mmol) in toluene (1.5 mL) was heated in a sealed tube at 185°C for 6 days. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% to 20% EtOAc/hexanes) to yield 7.3 mg (61%) of 207 as a yellow oil; IR (thin film) 2984, 2927, 1715, 1672, 1408, 1326, 1175, 1140, 1024, and 763 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.30 (brs, 3H), 2.00-2.09 (m, 1H), 2.62 (d, 1H, J = 15.2 Hz), 2.73 (dd, 1H, J = 22.4 and 2.4 Hz), 2.97 (dd, 1H, J = 22.4 and 5.6 Hz), 3.14 (m, 2H), 3.78 (t, 1H, J = 9.2 Hz), 3.98 (d, 1H, J = 15.2 Hz), 4.14-4.32 (m, 2H), 6.50 (brs, 1H), 7.11 (td, 1H, J = 7.6 and 1.6 Hz), 7.21 (td, 1H, J = 7.6 and 1.6 Hz), 7.33 (d, 1H, J = 7.6 Hz), and 7.62 (dd, 1H, J = 8.0 and 1.2 Hz), ¹³C-NMR (CDCl₃, 100 MHz) δ 14.8, 35.9, 37.6, 46.8, 50.0, 53.2, 61.8, 102.9, 122.4, 128.1, 129.7, 130.2, 136.5, 137.0, 142.5, 153.7, and 209.0; HRMS Calcd for [(C₁₇H₁₈BrNO₃) + H⁺]: 364.0470. Found: 364.0546.

3-(2-Bromophenyl)but-3-enoic acid (223). To a stirred solution of alcohol 209 (150 mg, 0.661 mmol) in acetone (27 mL) at 0°C was added freshly prepared Jones’ reagent (1.32 mL, 1.32 mmol, 1.0 M). The resulting solution was stirred at 0°C for 1 h, then warmed to rt and stirred for an additional 1 h. The mixture was diluted with H₂O and extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, filtered, and
concentrated under reduced pressure to provide 157 mg (91%) of 223 as a brown oil requiring no further purification; IR (thin film) 3088, 2920, 1709, 1295, 1220, 1025, 1163, and 759 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) 3.55 (d, 2H, \(J = 0.8\) Hz), 5.23 (s, 1H), 5.45 (d, 1H, \(J = 1.2\) Hz), 7.13-7.15 (m, 1H), 7.25-7.29 (m, 2H), 7.54 (d, 1H, \(J = 8.4\) Hz); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) 42.1, 121.1, 122.2, 127.8, 129.6, 131.7, 133.2, 142.2, 142.6, and 177.0.

\[ \text{Br} \quad \begin{array}{c} \text{OH} \\ \text{Br} \end{array} \quad \begin{array}{c} \text{CO}_2\text{Et} \\ \text{Br} \end{array} \]

\(223\) \quad 1. 4-methylmorpholine isobutyl chloroformate

\(55\%\)

\[ \begin{array}{c} \text{N} \\ \text{H} \\ \text{Fur} \\ \text{O} \end{array} \quad \begin{array}{c} \text{CO}_2\text{Et} \\ \text{Br} \end{array} \]

\(224\)

**Ethyl 3-(2-bromophenyl)but-3-enoyl(furan-2-yl)carbamate (224).** To a stirred solution of furan 193 (215 mg, 1.39 mmol) in THF (7 mL) at -78°C was added \(n\)-BuLi (0.61 mL, 1.52 mmol, 2.5 M in hexane) dropwise and the reaction mixture was stirred at -78°C for 45 min. In a separate flask, compound 223 (391 mg, 1.62 mmol) was dissolved in THF (13 mL) and the mixture was cooled to 0°C. 4-Methylmorpholine (0.18 mL, 1.62 mmol) and isobutyl chloroformate (0.21 mL, 1.62 mmol) was added dropwise and the solution was stirred for 5 min. The mixture was filtered over celite with THF (7 mL). The filtrate was cooled to 0°C and the preformed furanyl lithiate was added dropwise by cannula. The resulting reaction mixture was stirred for 30 min and quenched with H\(_2\)O and extracted with EtOAc. The organic layer was washed with a saturated aqueous NaHCO\(_3\) solution, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc/hexanes) to yield 288
mg (55%) of 224 as a yellow oil; IR (thin film) 3128, 2984, 2936, 1790, 1750, 1610, 1500, 1426, 1288, 1255, 1165, 1091, 1017, 840, and 762 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.22 (t, 3H, $J = 6.8$ Hz), 4.10 (s, 2H), 4.21 (q, 2H, $J = 6.8$ Hz), 5.24 (d, 1H, $J = 0.4$ Hz), 5.42 (d, 1H, $J = 1.2$ Hz), 6.11 (dd, 1H, $J = 3.2$ and 1.2 Hz), 6.41 (dd, 1H, $J = 3.2$ and 2.0 Hz), 7.13 (td, 1H, $J = 7.6$ and 2.0 Hz), 7.27 (td, 1H, $J = 7.2$ and 1.2 Hz), 7.33 (dd, 1H, $J = 2.0$ and 1.2 Hz), 7.40 (dd, 1H, $J = 7.6$ and 2.0 Hz), and 7.54 (dd, 1H, $J = 8.0$ and 1.2 Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 14.1, 44.5, 63.7, 106.5, 111.4, 120.7, 121.7, 127.3, 128.9, 131.6, 132.5, 140.9, 142.3, 142.4, 142.9, 152.8, and 172.0.

![Chemical structure](image)

**Ethyl 3a-(2-bromophenyl)-2,5-dioxo-2,3,3a,4,5,6-hexahydro-1H-indole-1-carboxylate (225).** A stirred solution of 224 (77 mg, 0.204 mmol) in toluene (2.5 mL) was heated in a sealed tube at 150$^\circ$C for 48 h. The reaction was cooled to rt and concentrated under reduced pressure. The residue purified by silica gel chromatography (30% EtOAc/hexanes) to provide 60 mg (78%) of 225 as a yellow oil; IR (thin film) 2925, 2982, 1771, 1730, 1680, 1463, 1421, 1370, 1293, 1225, 1104, 1038, and 765 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 1.41 (t, 3H, $J = 7.6$ Hz), 2.75 (d, 1H, $J = 15.2$ Hz), 2.84 (dd, 1H, $J = 22.8$ and 2.8 Hz), 2.98 (d, 1H, $J = 18.0$ Hz), 3.06 (dd, 1H, $J = 22.8$ and 5.6 Hz), 3.61 (d, 1H, $J = 18.0$ Hz), 3.99 (d, 1H, $J = 15.2$ Hz), 4.37-4.49 (m, 2H), 6.57 (dd, 1H, $J = 5.6$ and 2.8 Hz), 7.15 (td, 1H, $J = 7.2$ and 1.6 Hz), 7.25 (td, 1H, $J = 7.6$ and 1.6 Hz), 7.38 (dd, 1H, $J = 7.6$ and 1.6 Hz), and 7.64 (dd, 1H, $J = 7.6$ and 1.6 Hz); $^{13}$C-NMR
(CDCl$_3$, 100 MHz) $\delta$ 14.4, 38.0, 45.7, 47.9, 49.8, 64.0, 109.0, 122.6, 128.4, 128.9, 130.3, 136.7, 136.8, 139.7, 151.1, 171.2, and 206.4. HRMS Calcd for [(C$_{17}$H$_{16}$BrNO$_4$) + H$^+$]: 378.0263. Found: 378.0334.
References


8 Dounay, A.B.; Humphreys, P.G.; Overman, L.E.; Wroblefski, A.D. *2008*, *130*, 5368.


Chapter 3

Studies Towards the Generation of

Morphine via IMDAF Reactions of Benzofuran Dienophiles
Introduction

The IMDAF methodology developed in the Padwa laboratories has provided a versatile route for accessing a number of natural products, including members of the *aspidosperma*, *stemono*, and *amaryllidaceae* alkaloid families (Figure 3-1). One of the more interesting and useful applications of this methodology is the ability to use indoles as dienophiles in the IMDAF cycloaddition/rearrangement cascade sequence. This allows for the construction of a wide variety of structurally and biologically-interesting alkaloids.

Figure 3-1: Natural Products Accessible via the IMDAF Reaction of 2-amidofurans

![Chemical structures](image)

A recent example of the utility of the IMDAF methodology using indole as the dienophile involves the total synthesis of (±)-strychnine (230). The synthesis occurs in only 13 steps starting from commercially available 231 (Scheme 3-1). The key
cycloaddition precursor 234 was generated by the acylation of furanyl carbamate 97 with the mixed anhydride of 2-(1-acetyl-1H-indol-3-yl)acetic acid 231, followed by Boc removal and alkylation using 1-(iodomethyl)-2-methylbenzene 233. The Diels-Alder cycloaddition/rearrangement sequence provided the desired intermediate 235. From this core structure, the completion of the synthesis was possible in 9 steps making use of a palladium-catalyzed enolate coupling reaction as a key step for closing the final ring.

Having displayed the ability to rapidly generate numerous natural products via the indole-based IMDAF cycloaddition methodology, we became interested in extending the methodology to analogous reactions using benzofurans as the tethered dienophile. Using a parallel route to that employed for the synthesis of the indole-based amidofuran 234, the benzofuran-substituted amidofuran 237 was generated in 3 steps from carboxylic acid 236 (Scheme 3-2). Upon heating in toluene under reflux conditions for 18 h, we
were delighted to find that cycloadduct 238 was formed in 55% yield, further demonstrating the usefulness of the IMDAF cycloaddition/rearrangement sequence.

Scheme 3-2: IMDAF Cyloaddition/Rearrangement Reaction of 2-amidofurans with Benzofuran Dienophiles

Having shown that the IMDAF cyclization occurs with benzofurans, this led us to determine whether we could use the cycloaddition method for a synthesis of (±)-morphine (239, Scheme 3-3). It is worth noting that two approaches to the morphine core have been previously attempted based on a Diels-Alder reaction involving a benzofuran dienophile (Scheme 3-3). Specifically, Ciganek reported on the Diels-Alder cycloaddition of benzofuran 240, which occurred at 240 °C in toluene, but only provided the desired Diels-Alder product 241 in 10% yield. However, an improvement was made with the Diels-Alder cycloaddition of benzofuran 242, which provided a 53% yield of cycloadduct 243.

Recognizing that some IMDAF cycloaddition reactions are possible using benzofuran dienophiles, we decided to probe the possibility of using the IMDAF methodology to generate the morphine core. Earlier studies in the Padwa laboratories showed that 5-halo substituted furans such as 246 react at a much faster rate than their 5-
unsubstituted analogs (244, Scheme 3-4).\textsuperscript{8,9} For example, while furan 244 gave the desired cyclization product 245 in 90% yield, it required 168 h of heating for the reaction to proceed to completion. On the other hand, placement of a bromo substituent at the C-5 position of the furan ring decreased the reaction time to only 1.5 h, and provided a quantitative yield of the corresponding Diels-Alder product 247. The remarkable rate enhancement of this reaction was attributed to two factors, which involved a lowered reaction enthalpy and an increased reaction exothermicity.\textsuperscript{10} Both factors provide a much improved enhanced rate for generating the Diels-Alder product.

We thought that the rate enhancement encountered using 5-halo furans might help promote the Diels-Alder cycloaddition reactions with benzofurans. With this in mind, we began our studies toward the synthesis of morphine by studying the cycloaddition of 5-bromofuran substrates 248 and 251, which differ by the location of the carbonyl substituent within the tether (Scheme 3-5).\textsuperscript{8} Unfortunately, none of the desired
Scheme 3-4: IMDAF Cycloaddition Reactions of Halogen-Substituted Amidofurans

![Scheme 3-4]

A cycloaddition product was observed, even heating under microwave conditions. Only the Boc-deprotected products 250 or 253 were formed.

Scheme 3-5: Initial IMDAF Cycloaddition Reactions Towards Morphine

![Scheme 3-5]

Results and Discussion

First Generation IMDAF Approach to the Morphine Core

Since the 5-bromo furans 248 and 251 did not react, we decided to revise our synthetic strategy toward morphine (239). Since we were unsure whether placing a
carbonyl group in the tether was affecting the cycloaddition efficiency, we decided to carry out the IMDAF reaction using imide 255, with the intention of preparing the morphine core 254 (Scheme 3-6). We also decided to replace the thermally labile Boc protecting group with a more stable aryl protecting group. As was shown in the (±)-strychnine synthesis (Scheme 3-1), the choice of protecting group on the amidofuran was important in generating the desired core structure via the IMDAF cycloaddition. The presence of a bulky protecting group helps force the amidofuran as well as the indole moiety into the required s-trans conformation which is essential for the reaction to occur. Two routes for generating the necessary precursor 255 are possible, both of which involved amide formation starting from either 256 or 258 (Scheme 3-6).

Scheme 3-6: First Generation Retrosynthetic Route to Morphine

**Route 1**

256 + 257

**Route 2**

258 + 259; R = Acid Chloride
or
260; R = i-Bu anhydride
Our initial attempts to generate the desired cycloaddition precursor began with commercially available benzofuran-3(2H)-one (261, Scheme 3-7). Wittig olefination of 261 with carbethoxymethylene triphenylphosphorane (262) in toluene at 120°C provided the desired ester intermediate 263 in 89% yield. Saponification of the ester group with KOH in EtOH cleanly provided acid 236. The carboxylic acid was immediately treated with oxalyl chloride and then 2-methylbenzylamine 264 to produce the desired amide 256.

Scheme 3-7: Synthesis of the Amide Intermediate (Route 1)

A number of conditions were employed for the acylation of amide 256 using 5-bromo-2-furoyl chloride (257, Table 3-1). Using a variety of bases, such as NaH, n-BuLi, KHMDS, K₂CO₃, and Cs₂CO₃ with temperatures ranging from 0 °C to 120 °C only led to the recovery of the starting amide. We noticed the significant stability of acid chloride 257, which could even be purified and recovered after silica gel chromatography. Consequently, we thought it worthwhile to probe the acylation reaction using an intermediate such as 259 or 260.
We therefore turned our attention to the alternate approach (Route 2) to prepare the desired cycloaddition precursor 265 and considered possible methods for obtaining amide 258 (Table 3-2). Even though acylation with acid chloride 257 had proven problematic, we recognized that the increased nucleophilicity of amines versus amides might allow us to synthesize the desired amide 258 by reaction with 2-methylbenzylamine 264. Indeed, treating 2-methylbenzylamine 264 with 5-bromo-2-furoyl chloride 257 at rt provided the desired amide 258 in 91% yield. Having this compound in hand, we tested a variety of conditions for the final acylation step in order to obtain the desired cycloaddition precursor 265. Once again, the acylation reaction proved to be challenging. We used a variety of bases (NaH, Et₃N, and LHMDS) and

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>THF, 0°C 1 h, then rt 2 h</td>
<td>SM only</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>THF, rt 48 h, then reflux 20 h</td>
<td>SM only</td>
</tr>
<tr>
<td>3</td>
<td>none</td>
<td>Toluene, 24 h, reflux</td>
<td>SM only</td>
</tr>
<tr>
<td>4</td>
<td>none</td>
<td>THF, microwave, 70°C, 15 min</td>
<td>SM only</td>
</tr>
<tr>
<td>5</td>
<td>n-BuLi</td>
<td>THF, 0°C to rt, 8 h</td>
<td>messy</td>
</tr>
<tr>
<td>6</td>
<td>Et₃N</td>
<td>CH₂Cl₂, cat. DMAP, rt 8 h, then reflux 18 h</td>
<td>SM only</td>
</tr>
<tr>
<td>7</td>
<td>KHMDS</td>
<td>CH₂Cl₂, rt 24 h</td>
<td>SM only</td>
</tr>
<tr>
<td>8</td>
<td>K₂CO₃</td>
<td>DMF, rt 18 h, then reflux 24 h</td>
<td>SM, byproducts</td>
</tr>
<tr>
<td>9</td>
<td>Cs₂CO₃</td>
<td>CH₃CN, 85°C, 24 h</td>
<td>SM only</td>
</tr>
</tbody>
</table>
employed both the mixed anhydride and acid chloride intermediates generated from the benzofuran carboxylic acid. We finally discovered that the desired cycloaddition precursor 265 could be obtained by heating amide 258 and acid chloride 259 in benzene and Et₃N in a sealed tube overnight.

Table 3-2: Synthesis of the Desired IMDAF Cycloaddition Precursor

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>Anhydride 260; THF, rt 24 h, then reflux 18 h</td>
<td>SM only</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N</td>
<td>Acid chloride 259; CH₂Cl₂, Cat. DMAP, rt 18 h</td>
<td>SM only</td>
</tr>
<tr>
<td>3</td>
<td>LHMDS</td>
<td>Acid chloride 259; THF, sealed tube, reflux 24 h</td>
<td>SM only</td>
</tr>
<tr>
<td>4</td>
<td>Et₃N</td>
<td>Acid Chloride 259; benzene, reflux, 18 h</td>
<td>20% yield 265</td>
</tr>
</tbody>
</table>

Having the key cycloaddition precursor in hand, we were now ready to test whether this amidofuran would undergo the IMDAF cycloaddition reaction to generate the morphine core 254 (Scheme 3-8). Unfortunately, heating a sample of 265 in toluene at reflux only led to the recovery of starting material and did not lead to any
cycloaddition product. There are a number of factors which might explain the absence of
cycloaddition, including both conformational and electronic issues. These issues have not
been investigated and further studies are necessary if such a route is to be employed for
generating the morphine core.

Scheme 3-8: Attempted IMDAF Cycloaddition Reaction

Second Generation Approach to the Morphine Core

While pursuing the above cycloaddition method, we also were interested in
testing whether the IMDAF cycloaddition of a benzofuran substrate such as \( \text{267} \), would
occur to give cycloadduct \( \text{266} \) (Scheme 3-9). This approach is attractive since the
presence of a functionalized ethyl group at C-3 of the benzofuran substrate would allow
for easy ring closure of the final (C) ring. We envisioned the potential for installing the
acetylfuran moiety by a palladium-catalyzed enolate coupling reaction of bromo
substituted benzofuran \( \text{268} \) and the anion derived from 2-acetylfuran. The functionalized
benzofuran substrate \( \text{268} \) could be synthesized from the methoxy-directed bromination of
the known benzofuran ester \( \text{270} \).
Preparation of the desired benzofuran substrate 268 was possible in four short steps beginning with the Wittig olefination reaction employed previously in our first generation approach to morphine (Scheme 3-10). Thus, treatment of the commercially available 7-methoxy-3(2H)-benzofuranone (271) with carboxethoxymethylene triphenylphosphorane (262) in toluene at 120 °C provided the desired ester intermediate 270. Various bromine sources were tested to induce a methoxy-directed bromination of 270, including the use of bromine and NBS. However, both reagents resulted in either a low regioselectivity of bromination or else led to a mixture of overbromination products. A search of the literature led to a report by Auerbach and coworkers who demonstrated highly-selective $p$-methoxy-directed bromination of methoxybenzoic acids using 1,3-dibromomethylhydantoin (1,3-DBMH) (272). We were pleased to find that a modification of the Auerbach bromination conditions (0.52 eq. 1,3-DBMH, CH$_3$CN, rt,
24 h) cleanly led to the formation of bromide 273 in quantitative yield. At this stage, we thought it important to remove any acidic protons present in 273 that could present problems in the contemplated palladium-mediated enolate cross-coupling step. Therefore, reduction of ester 273 with DIBAL-H provided the corresponding alcohol 274 in 95% yield. Protection of the alcohol intermediate was found to be possible using either Ag₂O/MeI or NaH/MeI, which afforded methyl ester 268 in 44% and 83% yield, respectively.

Scheme 3-10: Preparation of the Functionalized Benzofuran

We next set out to determine the experimental conditions which would lead to a palladium-catalyzed coupling of 2-acetylfuran with aryl bromide 268 (Table 3-3). A wide variety of conditions have already been studies by both Buchwald,¹³ Hartwig¹⁴,¹⁵ and others¹⁶ for palladium-catalyzed enolate couplings of ketones. We began our studies by testing known conditions using three different palladium catalysts, which included Pd(OAc)₂, Pd(dba)₂ and Pd(PPh₃)₄. Although quite a variety of coupling conditions were
examined, this key reaction proved to be very difficult to carry out. However, we eventually discovered that carrying out the reaction at 150 °C in a sealed tube using Cs₂CO₃ as a base led to formation of the desired coupled product. The highest yields of product were consistently obtained using Pd(OAc)₂ in combination with the triphenylphosphine ligand (1:4) in DMF.¹⁶ Carrying out the reaction for 4 h at 150°C led to a 19% yield of furan 267. However, increasing the reaction time to 16 h provided a 40% yield of the desired coupled substrate.

Table 3-3: Conditions Tested for Palladium-Mediated Formation of the cycloaddition precursor

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHMDS</td>
<td>Pd(dba)₂ (8 mol%), dppf (9 mol%), DMF, sealed tube, 150°C, 4 h</td>
<td>Trace amt. Product</td>
</tr>
<tr>
<td>3</td>
<td>Cs₂CO₃</td>
<td>Pd(OAc)₂ (4 mol%), PPh₃ (16 mol%), DMF, sealed tube, 150°C, 4 h</td>
<td>19% yield</td>
</tr>
<tr>
<td>4</td>
<td>Cs₂CO₃</td>
<td>Pd(OAc)₂ (6 mol%), PPh₃ (24 mol%), DMF, sealed tube, 150°C, 16 h</td>
<td>40% yield</td>
</tr>
<tr>
<td>5</td>
<td>Cs₂CO₃</td>
<td>Pd(PPh₃)₄ (6 mol%), DMF, sealed tube, 150°C, 16 h</td>
<td>24% yield</td>
</tr>
</tbody>
</table>

After developing the conditions necessary for formation of the cycloaddition precursor 267, we tested the key cycloaddition step by heating 267 in toluene at 150°C for 6 days (Table 3-4). Unfortunately, the thermal reaction resulted in recovery of only starting material with no signs of a cycloadduct. We had previously found that
microwave heating helped significantly in the (±)-strychnine synthesis. Thus, we heated furan 267 under a variety of microwave conditions at 200 °C, but no cycloaddition product was observed. Further, addition of both catalytic MgI₂ and EtAlCl₂ as Lewis acids failed to induce the cycloaddition of furan 267 and only led to either decomposition or recovery of starting material.

Table 3-4: Attempted IMDAF Reaction of Benzofuran

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150°C, 48 h, toluene</td>
<td>SM only</td>
</tr>
<tr>
<td>2</td>
<td>150°C, 6 days, toluene</td>
<td>SM only</td>
</tr>
<tr>
<td>3</td>
<td>200°C, 12 h, 300 W, 90 psi, toluene</td>
<td>SM only</td>
</tr>
<tr>
<td>4</td>
<td>0.2 eq. EtAlCl₂, 200°C, 4 h, 300 W, 90 psi, toluene</td>
<td>SM only</td>
</tr>
<tr>
<td>5</td>
<td>Cat. MgI₂, 150°C, 8 h, 300 W, 90 psi, toluene</td>
<td>SM, decomposition</td>
</tr>
<tr>
<td>6</td>
<td>200°C, 8 h, 300 W, 90 psi, DMF</td>
<td>SM only</td>
</tr>
</tbody>
</table>

Even though the IMDAF cycloaddition did not occur using the C-3 alkyl-substituted benzofuran 267, we considered the possibility of promoting the IMDAF reaction by employing an electron withdrawing group on the C-3 position of the benzofuran. With this activation in mind, we developed a 4-step procedure for the formation of the cyano-substituted benzofuran 279 (Scheme 3-11). By using a modification of conditions developed by Dudley and coworkers, the treatment of aryl...
aldehyde 275 with ethyl diazoacetate and HBF$_4$·OEt$_2$ delivered benzofuran 276 in 67% yield. The ester could be easily reduced with excess DIBAL-H to give the corresponding alcohol in 79% yield. Allylic oxidation of alcohol 277 with PCC on silica gel provided the benzofuranyl substituted aldehyde 278. While a number of conditions exist in the literature for the conversion of aldehydes to nitriles,$^{18,19}$ we found that the desired C-3 cyano-substituted benzofuran could be generated in good yield from aldehyde 278 using a one-pot oxime formation/dehydration protocol developed by Vowinkel and coworkers.$^{20}$

Scheme 3-11: Route to the C-3 Cyano-Substituted Benzofuran

A limited number of palladium-catalyzed cross-coupling reactions of bromonitrile 279 with 2-acetylfuran were tested using conditions previously used for the synthesis of 267 (Scheme 3-12). Unfortunately these conditions only led to trace amounts of the desired product and clearly additional work is necessary in order to optimize the cross-coupling reaction with this system. Thus, further work is necessary to prepare furan 280.
and to determine whether cyano group activation would allow the cycloaddition to proceed, thereby providing a route to access the morphine core.

Scheme 3-12: Cross-Coupling and IMDAF Reaction of the C-3 Cyanobenzofuran
Experimental Section
Ethyl 2-(benzofuran-3-yl)acetate (263). To a stirred solution of ketone 261 (3.0 g, 22.4 mmol) in toluene (44 mL) was added carbethoxymethylene triphenylphosphorane 262 (13.6 g, 39.1 mmol). The reaction mixture was heated at reflux for 21 h, then concentrated under reduced pressure and the residue was purified by column chromatography (10% EtOAc/hexanes) to provide 4.07 g (89%) of 263 as a yellow oil; IR (thin film) 2982, 1736, 1453, 1278, 1163, 1097, 1029, and 746 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.28 (t, 3H, J = 7.2 Hz), 3.71 (s, 2H), 4.20 (q, 2H, J = 14.4 and 6.8 Hz), 7.24-7.34 (m, 2H), 7.48-7.51 (m, 1H), 7.58-7.60 (m, 1H), and 7.65 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 14.4, 30.0, 61.3, 111.7, 113.3, 119.9, 122.8, 124.6, 127.8, 143.0, 155.4, and 170.9.

5-Bromo-N-(2-methylbenzyl)furan-2-carboxamide (258). To a stirred suspension of 5-bromo-2-furoic acid (286 mg, 1.5 mmol) and 4 Å MS in CH₂Cl₂ (7 mL) was added oxalyl chloride (0.26 mL, 3.0 mmol) and 2 drops of DMF. The reaction mixture was stirred at rt for 1.5 h, filtered over celite, and concentrated under reduced pressure. The residue was dissolved in THF (3 mL) and was added to a stirred suspension of 2-methylbenzylamine (200 mg, 1.65 mmol) and 4 Å MS in THF (7 mL). The reaction
mixture was stirred at rt for 1.5 h, filtered over celite, diluted with H₂O, and extracted with EtOAc. The organic layer was washed with a saturated aqueous NaHCO₃ solution, dried over MgSO₄, filtered, and concentrated to provide 400 mg (91%) of 258 as a yellow solid, mp 86-88 °C; IR (thin film) 3287, 3125, 3064, 2925, 1646, 1597, 1530, 1471, 1306, 1125, 1012, 927, 798, and 740 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 2.37 (s, 3H), 4.61 (d, 2H, J = 5.2 Hz), 6.39 (brs, 1H), 6.44 (dd, 1H, J = 3.6, 0.8 Hz), 7.10 (d, 1H, J = 3.6 Hz) and 7.21-7.31 (m, 4H); ¹³C-NMR (CDCl₃, 100 MHz) δ 19.3, 41.6, 114.4, 117.0, 124.6, 126.5, 128.3, 129.1, 130.9, 135.5, 136.9, 150.0, 157.1.

N-(2-(Benzofuran-3-yl)ethanoyl)-N-(2-methylbenzyl)furan-2-carboxamide (265).

To a stirred solution of amide 258 (0.5 g, 1.70 mmol) and Et₃N (0.33 mL, 2.33 mmol) in THF (15 mL) was added compound 259 (0.453 g, 2.33 mmol) dropwise. The mixture was heated at reflux for 18 h, cooled to rt, concentrated under reduced pressure, and purified by silica gel chromatography to afford 7.0 mg of 265; ¹H-NMR (CDCl₃, 400 MHz) δ 2.26 (s, 3H), 4.08 (s, 2H), 5.05 (s, 2H), 6.39 (d, 1H, J = 3.9 Hz), 6.95 (d, 1H, J = 3.6 Hz), 6.98-7.04 (m, 2H), 7.11 (d, 2H, J = 3.6 Hz), 7.21 (t, 1H, J = 7.4 Hz), 7.28 (dt, 1H, J = 7.8 Hz and 1.4 Hz), 7.44 (d, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 7.6 Hz), and 7.58 (s, 1H).
Ethyl 2-(7-Methoxybenzofuran-3-yl)acetate (270). To a stirring solution of ketone 271 (100 mg, 0.609 mmol) in toluene (3.0 mL) was added carbethoxymethylene triphenylphosphorane (374 mg, 1.07 mmol). The reaction mixture was heated at reflux for 24 h, then concentrated under reduced pressure and the residue was purified by column chromatography (30% EtOAc/hexanes) to provide 135 mg (92%) of 270 as a yellow oil; IR (thin film) 3120, 2982, 2841, 1739, 1626, 1590, 1436, 1369, 1268, 785, 733, 683, and 627 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta 1.26\ (t, 3\ H, J = 7.2 \text{ Hz}), 3.68\ (s, 2\ H), 4.00\ (s, 3\ H), 4.18\ (q, 2\ H, J = 14.4 \text{ and } 7.2 \text{ Hz}), 6.81\ (dd, 1\ H, J = 6.8 \text{ and } 2.0 \text{ Hz}), 7.16-7.18\ (m, 2\ H), \text{ and } 7.64\ (s, 1\ H); \(^1^3\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta 14.3, 30.0, 56.2, 61.2, 106.7, 112.1, 113.7, 123.5, 129.5, 143.0, 144.6, 145.6, \text{ and } 170.8.

Ethyl 2-(4-Bromo-7-methoxybenzofuran-3-yl)acetate (273). To a stirred solution of ester 270 in CH\(_3\)CN (25 mL) was added 1,3-dibromo-5,5-dimethyl hydantoin (145 mg, 0.508 mmol) and the resulting solution was stirred at rt for 24 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up in EtOAc and
diluted with H₂O. The aqueous layer was extracted with EtOAc and the organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (30% EtOAc/hexanes) to provide 330 mg (quant. yield) of 273 as a white solid, mp 58-60 °C; IR (thin film) 2981, 1735, 1581, 1489, 1344, 1393, 1251, 1179, 1285, 1121, 1028, and 897 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 1.28 (t, 3H, J = 7.0 Hz), 3.92 (s, 2H), 3.98 (s, 3H), 4.22 (q, 2H, J = 7.6 and 2.0 Hz), 6.67 (d, 1H, J = 8.4 Hz), 7.27 (d, 1H, J = 7.6 Hz), and 7.65 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 14.4, 30.2, 56.5, 61.3, 104.5, 107.9, 114.6, 127.2, 127.9, 144.6, 145.5, and 171.2.

4-Bromo-7-Methoxy-3-(2-methoxyethyl)benzofuran (268). To a -78°C stirred solution of ester 273 (647 mg, 2.1 mmol) in THF (18 mL) was added DIBAL-H (6.2 mL, 6.2 mmol) dropwise over 5 min. The reaction mixture was warmed to 0°C and was stirred for 1 h. To the mixture was added H₂O and the aqueous layer was extracted with EtOAc, dried over MgSO₄, filtered, and concentrated to leave behind a clear oil. The resulting oil was filtered through a short pad of silica gel, concentrated under reduced pressure, and dissolved in DMF (60 mL). The solution was cooled to 0°C and NaH was added in one portion. After stirring for 0.5 h, MeI (6 mL) was added and the reaction mixture was stirred for 17 h while slowly warming to rt. The solution was extracted with EtOAc, washed with brine, dried over MgSO₄ and concentrated. The residue was purified by silica gel chromatography (30% EtOAc/hexanes) to give 381 mg (59%) of 268 as a clear
oil; IR (thin film) 2933, 2874, 1578, 1487, 1392, 1285, 1117, and 897 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 3.16-3.20 (m, 2H), 3.40 (s, 3H), 3.72 (t, 2H), 3.97 (s, 3H), 6.65 (d, 1H, J = 8.4 Hz), 7.27 (d, 1H, J = 8.4 Hz), 7.52 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 24.7, 56.4, 58.9, 72.4, 104.7, 107.6, 118.4, 127.0, 128.1, 143.6, 145.4, and 145.5.

[Chemical Structure Image]

1-(Furan-2-yl)-2-(7-methoxy-3-(2-methoxyethyl)benzofuran-4-yl)ethanone (267).

To a stirred solution of bromide 268 (30 mg, 0.105 mmol), 2-acetylfuran (12 mg, 0.105 mmol) and Cs₂CO₃ (86 mg, 0.263 mmol) in degassed DMF (4 mL) was added PPh₃ (6.6 mg, 0.025 mmol) and Pd(OAc)₂ (4 mg, 0.0063 mmol) and the reaction mixture was heated in a sealed tube at 150°C for 4 h. The mixture was cooled to rt, quenched with 10% HCl, and extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (40% EtOAc/hexanes) to yield 13 mg (40%) of 267 as a clear oil; IR (thin film) 2932, 1676, 1626, 1568, 1512, 1466, 1392, 1287, 1108, 1055, and 913 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 3.01 (t, 2H, J = 6.8 Hz), 3.33 (s, 3H), 3.65 (t, 2H, J = 6.8 Hz), 3.98 (s, 3H), 4.44 (s, 2H), 6.54-6.56 (m, 1H), 6.74 (d, 1H, J = 8.0 Hz), 6.96 (d, 1H, J = 8.4 Hz), 7.22 (d, 1H, J = 3.2 Hz), 7.47 (s, 1H), and 7.610-7.614 (m, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 29.4, 42.0, 56.2, 58.8, 72.3, 106.3, 112.7, 117.8, 118.1, 119.4, 125.5, 128.5, 142.5, 145.1, 145.2, 146.7, 152.6, and 187.1.
Ethyl 4-Bromo-7-methoxybenzofuran-3-carboxylate (276). To a stirred solution of aldehyde 275 (0.1 g, 0.433 mmol) in CH$_2$Cl$_2$ (1.5 mL) was added HBF$_4$•OEt$_2$ solution (2 drops). A solution of ethyl diazoacetate (0.07 mL, 0.692 mmol) in CH$_2$Cl$_2$ (1.5 mL) was added slowly over 10 min. The reaction mixture was stirred at rt for 10 min and was then concentrated under reduced pressure. The residue was treated with H$_2$SO$_4$ (0.05 mL) and stirred vigorously for 5 min. Afterwards, CH$_2$Cl$_2$ (3 mL) was added, followed by solid NaHCO$_3$ and the suspension was stirred for 10 min at rt. The residue was filtered over a pad of celite/silica gel and eluted with CH$_2$Cl$_2$. The filtrate was concentrated under reduced pressure and purified by flash silica gel chromatography (40% EtOAc/hexanes) to yield 90 mg (69%) of 276 as a white solid, mp 47-48 °C; IR (thin film) 2981, 1724, 1618, 1488, 1384, 1331, 1263, 1177, 1125, 1037, and 895 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 400 MHz) δ 1.42 (t, 3H, $J = 7.2$ Hz), 4.00 (s, 3H), 4.41 (q, 2H, $J = 14.0$ and 7.2 Hz), 6.75 (d, 1H, $J = 8.4$ Hz), 7.46 (d, 1H, $J = 8.4$ Hz), and 8.21 (s, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ 14.5, 56.5, 61.4, 104.5, 108.5, 116.2, 125.7, 129.7, 145.3, 145.9, 151.3, and 162.3.

Ethyl diazoacetate
(4-Bromo-7-methoxybenzofuran-3-yl)methanol (277). To a 0 °C solution of ester 276 (609 mg, 2.03 mmol) in CH₂Cl₂ (64 mL) was added DIBAL-H (6.1 mL, 6.1 mmol, 1.0 M in hexanes) dropwise over 5 min. The reaction mixture was stirred while slowly warming to rt over 4 h, then cooled to 0°C and an additional 1.0 eq. DIBAL-H (2.03 mL, 2.0 mmol, 1.0 M in hexanes) was added dropwise. The reaction mixture was stirred for 3 h while warming to rt, then quenched with a saturated aqueous Rochelle’s salt solution and stirred vigorously overnight. The mixture was extracted with CH₂Cl₂, dried over MgSO₄, filtered, and concentrated to give an off-white solid. The solid was purified by silica gel chromatography (30% EtOAc/hexanes) to provide 0.41 g (79%) of 277 as a white solid, mp 66-67 °C; IR (thin film) 3318, 2936, 1621, 1488, 1397, 1302, 1248, 1171, 1120, and 1014 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 2.14 (t, 1H, J = 6.8 Hz), 3.99 (s, 3H), 4.94 (d, 2H, J = 6.8 Hz), 6.70 (d, 1H, J = 8.4 Hz), 7.31 (d, 1H, J = 8.4 Hz), and 7.67 (s, 1H); ¹³C-NMR (CDCl₃, 100 MHz) δ 55.5, 56.5, 103.9, 108.1, 121.6, 127.0, 127.8, 144.3, 145.5, and 145.8.

4-Bromo-7-methoxybenzofuran-3-carbaldehyde (278). To a stirred solution of alcohol 277 (42 mg, 0.16 mmol) in CH₂Cl₂ (10 mL) was added silica gel (0.27 g). The resulting reaction mixture was stirred at rt for 18 h, then an additional 0.5 eq. (18 mg, 0.082 mmol) of PCC was added and the reaction mixture was stirred at rt for 24 h. The suspension was concentrated under reduced pressure and purified by silica gel chromatography (30%
EtOAc/hexanes) to provide 22 mg (54%) of 278 as a clear oil; IR (thin film) 3126, 1678, 1543, 1490, 1311, 1259, and 1139 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) 4.01 (s, 3H), 6.78 (d, 1H, \(J = 8.4\) Hz), 7.45 (d, 1H, \(J = 8.4\) Hz), 8.34 (s, 1H), and 10.8 (s, 1H); \(^1\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) 56.6, 103.8, 108.8, 123.6, 125.9, 129.0, 145.6, 146.0, 151.2, and 185.9.

4-Bromo-7-methoxybenzofuran-3-carbonitrile (279). To a stirred solution of aldehyde 278 (81 mg, 0.34 mmol) in H\(_2\)O (3.0 mL) and pyridine (6.0 mL) was added hydroxylamine hydrochloride (23 mg, 0.33 mmol) in one portion. After stirring at rt for 1.75 h, CuSO\(_4\)•5 H\(_2\)O (17 mg, 0.07 mmol) was added, followed by a solution of Et\(_3\)N (0.093 mL, 0.67 mmol) in CH\(_2\)Cl\(_2\) (4.0 mL). The reaction mixture was stirred until the solution color changed from yellow to green (0.75 h), then DCC (79 mg, 0.38 mmol) in CH\(_2\)Cl\(_2\) (16 mL) was added and the reaction mixture was stirred for 2.5 h. The mixture was acidified with formic acid and stirred vigorously for 5 min, then filtered over celite eluting with CH\(_2\)Cl\(_2\). The organic layer was washed with 1.25 N HCl, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 10% EtOAc/Hexanes) to yield 61 mg (76%) of 279 as a white solid, mp 167 °C; IR (thin film) 3140, 2925, 2848, 2239, 1584, 1496, 1327, 1255, 1141, 1174, 1039, and 803 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) 4.01 (s, 3H), 6.81 (d, 1H, \(J = 8.4\) Hz), 7.45 (d, 1H, \(J = 8.4\) Hz), 8.34 (s, 1H), and 10.8 (s, 1H); \(^1\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) 56.6, 103.8, 108.8, 123.6, 125.9, 129.0, 145.6, 146.0, 151.2, and 185.9.
8.8 Hz), 7.43 (d, 1H, $J = 8.8$ Hz) and 8.20 (s, 1 H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ 56.7, 96.3, 104.3, 109.7, 112.0, 125.6, 129.1, 144.5, 145.6, and 153.5.
References


5 Boonsombat, J.; France, S.A. Unpublished results.


