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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

By

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Doctor of Philosophy

Department of Chemistry

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By

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B.S., North Carolina State University, 2002

Advisor: Dr. Albert Padwa

An Abstract of
A dissertation submitted to the Faculty of the Graduate School of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Department of Chemistry
Graduate School of Arts and Sciences

2008

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 pentacylic 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.

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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I am also greatly indebted to my church family and friends over the years, whether it be at Triangle RPCNA, Geneva OPC, or North Atlanta RPCNA. All of you have supported and prayed for me and kept me growing in faith though trying times. Your prayers are a large part of the reason I am writing this today and I am thankful to have been a part of your lives. Larry and Jackie Bray and family, thanks for adopting me and giving me "Atlanta Family" even while I am so far away from home.

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FCGS to this campus. You wil never realize how much of an impact you are making in the lives of those like me here at Emory!

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Table of Schemes

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List of Abbreviations

μ	micro
[a]	specific rotation
Ac	acetyl
anal	analysis
Aq	aqueous
Ar	argon
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
^{o}C	degree Celsius
calcd	calculated
δ	chemical shift(s)
d	doublet
DIBAL-H	Diisobutylaluminum hydride
DMAP	demethylamino pyridine
Decomp	decomposition
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
E	entgegen
ee	enantiomeric excess
ESI	electrospray ionization
EDG	electron donating group(s)
EWG	electron withdrawing group(s)
Et	ethyl
FT	Fourier transform
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IBCF	Isobutylchloroformate
i-Pr	isopropyl
IR	Infrared Spectroscopy
J	coupling constant
LA	Lewis acid
LHMDS	lithium bis(trimethylsilyl)amide
mol	mole
m	multiplet
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl

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

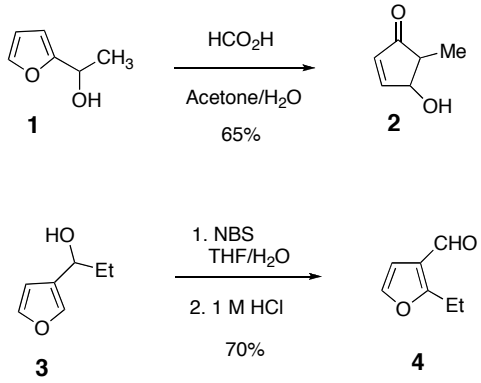
Introduction

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),[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.[3,4]

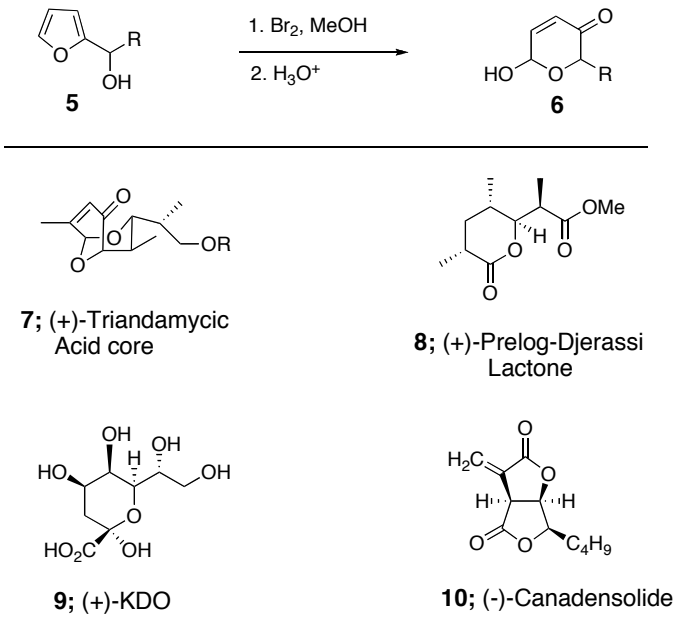
The literature dealing with furans indicates that these systems can readily rearrange to a variety of products, depending on both the nature of furan substitution as well as the reaction conditions. For example, Piancatelli has demonstrated that treatment of 2-furyl carbinol **1** with acid under mild conditions results in the formation of 5-hydroxy-3-oxocyclopentene **2** (Scheme 1-1).[5] Many years later, an interesting and related discovery by Walsh and coworkers[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.[7] 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**,[8] (+)-KDO **9**,[9] (-)-canadensolide **10**,[10] and the (+)-Prelog-Djerassi lactone **8**.[11]

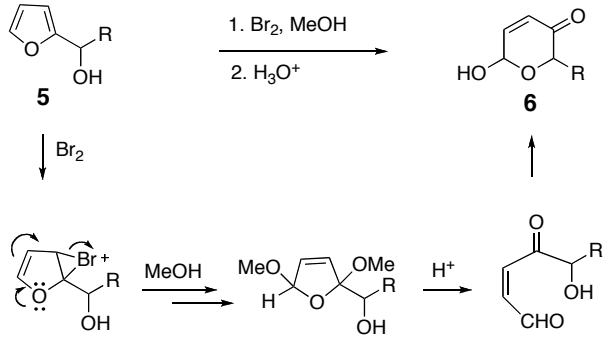
Scheme 1-2: The Achmatowicz Reaction and Application in Synthesis



This widely applied oxidative rearrangement reaction often proceeds under a variety of conditions,[12] including the use of *m*-CPBA, NBS, and PCC, although the original oxidative conditions reported by Achmatowicz employed Br_2 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**.

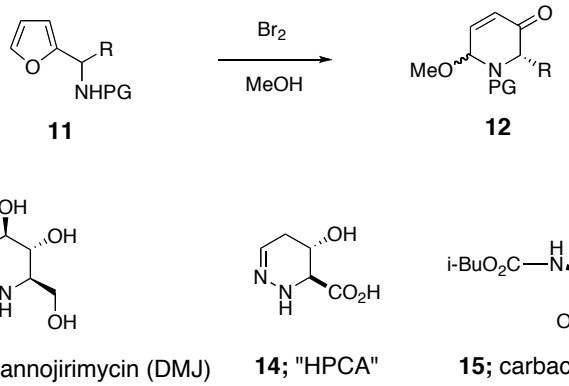
Scheme 1-3: Proposed Mechanism of the Achmatowicz Reaction



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.[13] The aza-Achmatowicz reaction has proven useful for accessing the azasaccharide deoxymannojirimycin (**13**),[14] as well as izidine and aminoacid building blocks,[15] and a variety of medicinally important substances such as "HPCA" (**14**)[15] and the carbacephem antibiotics (**15**)[16] (Scheme 1-4).

In connection with ongoing studies in natural product synthesis in the Padwa lab based on amidofuran chemistry,[17] the group also became interested in employing the aza-

Scheme 1-4: The Aza-Achmatowicz Reaction for Formation of Nitrogen Heterocycles

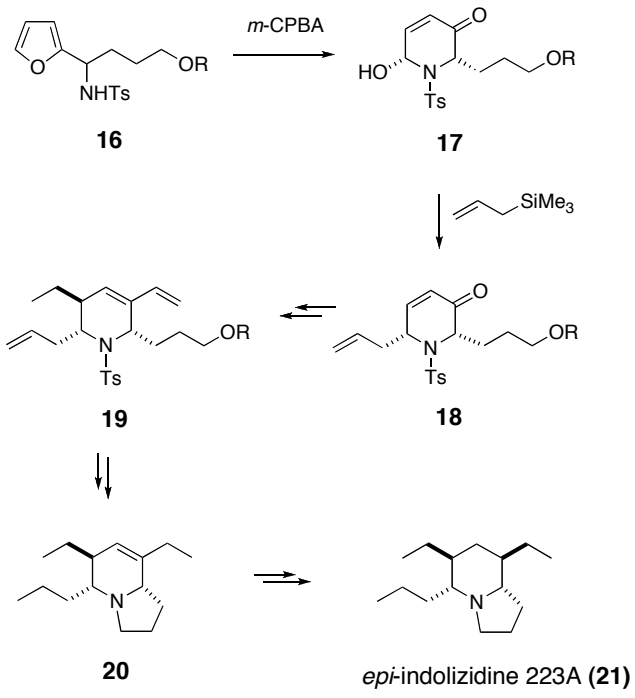


Achmatowicz reaction of *N*-tosylaminofurans for the synthesis of various piperidine and related alkaloids. In an earlier study from the Padwa laboratory,[3] it was shown that the aza-Achmatowicz oxidation of a furyl-substituted benzenesulfonamide could be used for the synthesis of the putative indolizidine alkaloid 223A (**21)**, which had been isolated from the skin secretion of a neotropical frog.[18] 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.[20] 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.[21] As a

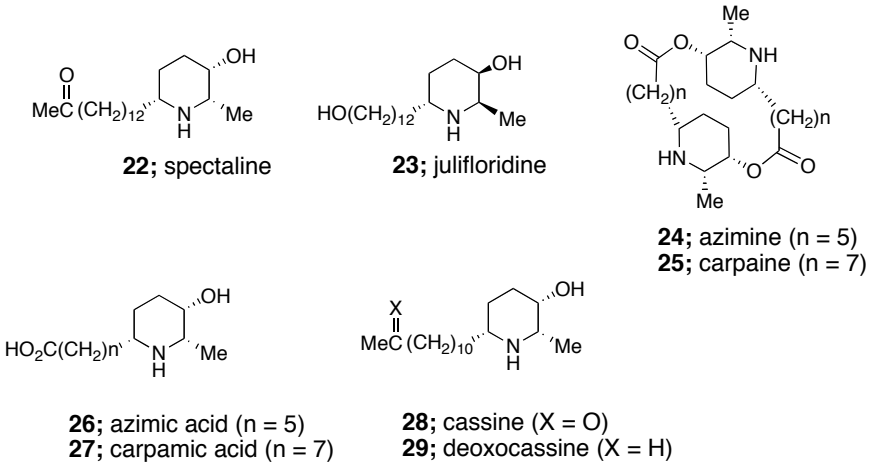
Scheme 1-5: Padwa's aza-Achmatowicz Approach to *epi*-Indolizidine 223A



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

Figure 1-1: Some Representative 2,6-Disubstituted Piperidin-3-ol Alkaloids



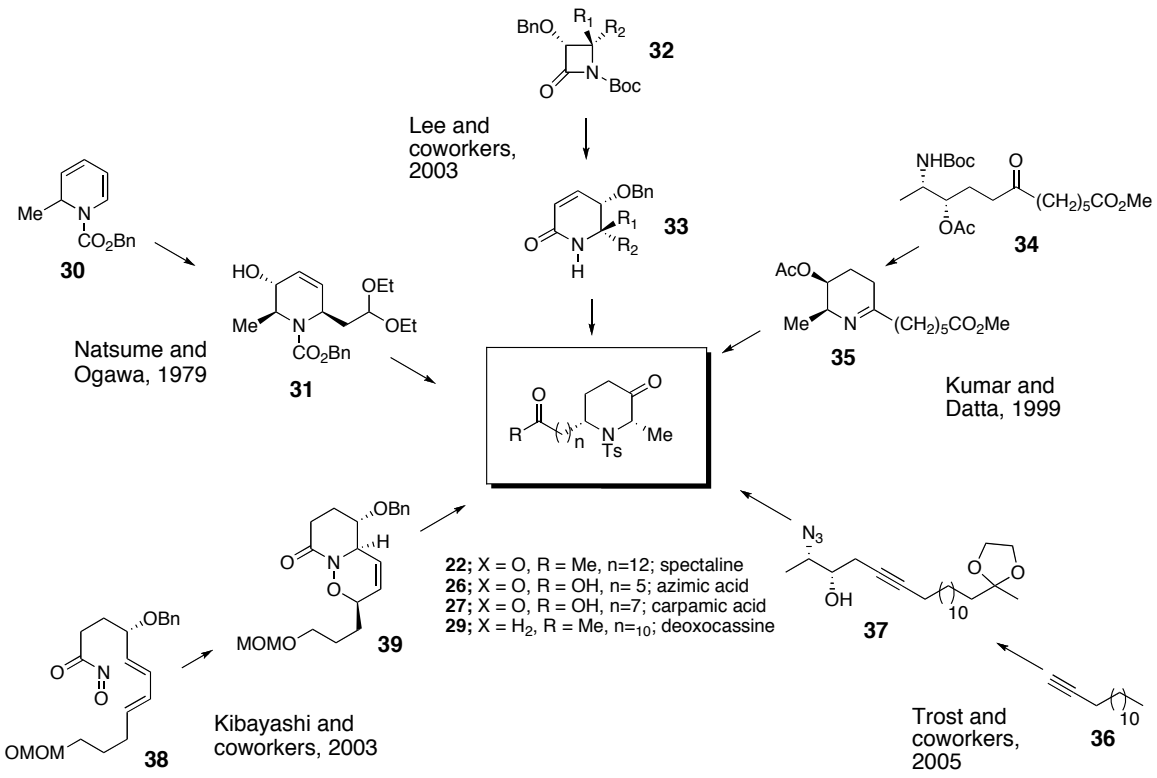
natural products is the *cis*-2-methyl-6-substituted piperidin-3-ol skeleton. Structural variation is due to a long aliphatic side chain at C_6 which provides for a number of different stereochemical and oxygenation patterns (Figure 1-1). Typical representatives of this family include spectaline (**22**), 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 C_6 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.[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 *Cassia* and *Prosopis* alkaloids are of special synthetic significance, and many have been prepared using a wide variety of methods.[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.[37] More recently, Lee and co-workers demonstrated the usefulness of a two-carbon homologation of b-lactams to access the piperidine core.[38] Kumar and Datta reported a stereoselective total synthesis of (+)-azimic acid (**26**) starting with L-alanine from the chiral pool.[39] Kibayashi demonstrated an elegant route to azimic acid (**26**) employing a hetero Diels-Alder cycloaddition.[40] Finally, Trost and coworkers reported a route to (+)-spectaline (**22**) using a hydrosilylation-oxidation strategy (Scheme 1-6).[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 *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**).

Scheme 1-6: Known Routes to *Cassia* and *Prosopis* Alkaloids

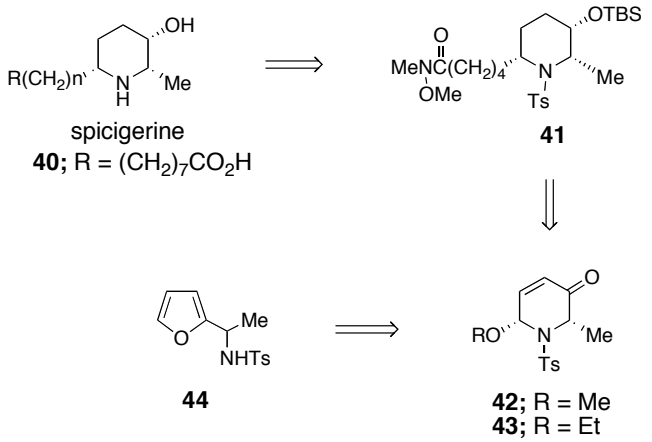


Results and Discussion

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.[42] Independent work by Zhou[43] and Altenbach,[44] 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.[44] 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-2*H*-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



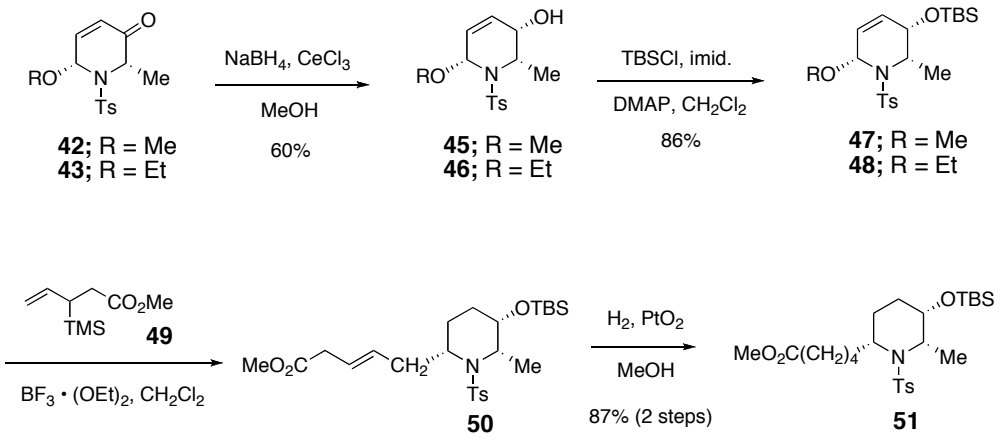
(±)-Azimic Acid Synthesis

Our studies began by subjecting the readily available furyl sulfonamide **44**[45] to an oxidative ring expansion with *m*-CPBA according to the conditions reported by Ciufolini.[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 $CeCl_3$•$7H_2O$ (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

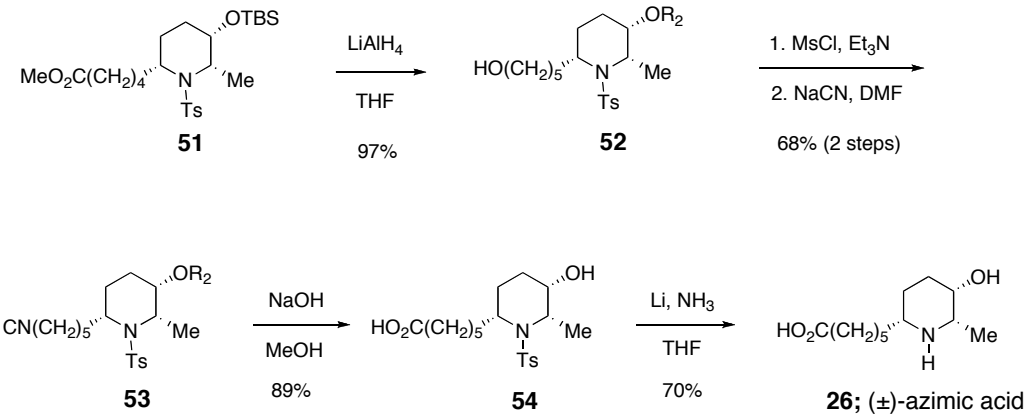


which was immediately hydrogenated (H_2, PtO_2, MeOH) to give the key intermediate **51** in 57% yield. The choice of the hydrogenation catalyst proved to be crucial for the success of the reduction. Our first attempts used palladium on carbon (Pd/C) as the catalyst in ethanol. The desired product was isolated in low yield with a nearly equal amount of the isomerized *N*-tosylenamine. On the other hand, using PtO_2 (Adams catalyst) afforded the desired saturated piperidine **51** as the exclusive product, with no evidence of epimerization at C_6. 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 C_2-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/NH_3 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

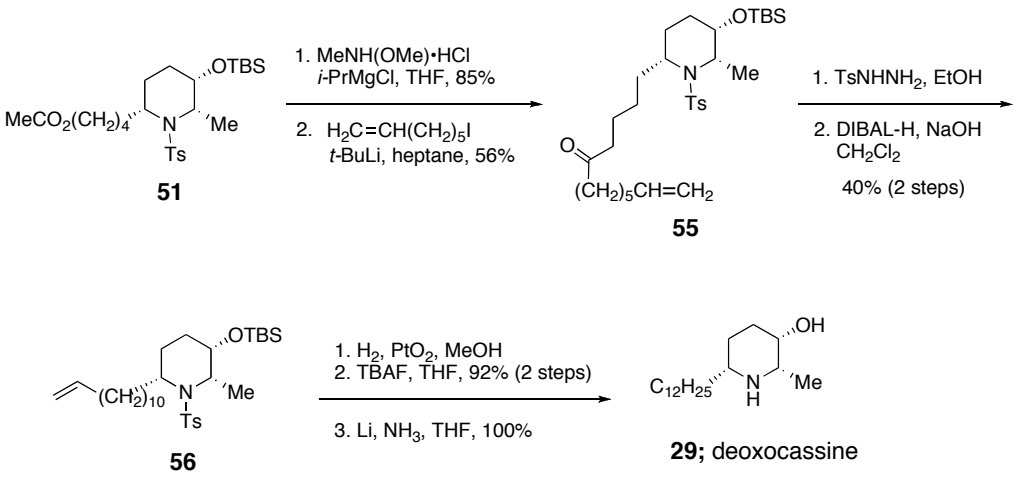


(±)-Deoxocassine Synthesis

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*-methylamides are generally prepared from the ester using an aluminum-based reagent,[50] we found that the use of *i*-PrMgCl[51] 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[52] which afforded **56** in reasonable yield. After hydrogenation of the double bond with PtO_2, the TBS protecting group was removed with TBAF and the tosyl group was cleaved using Li/NH_3 to furnish deoxocassine (**29**) in 92% yield for the three-step sequence.

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



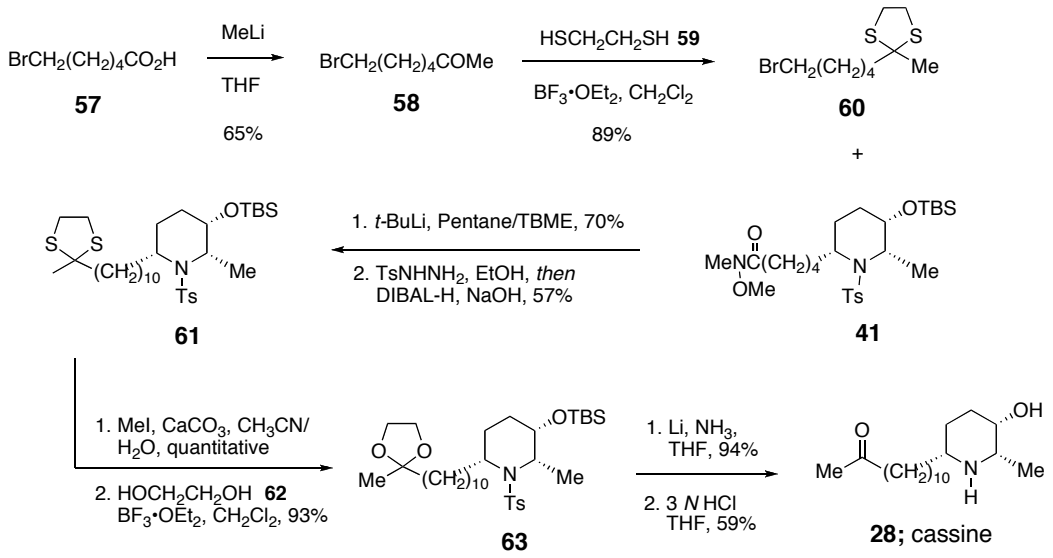
(±)-Cassine Synthesis

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 oxidation[53] 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 ºC in THF afforded a 65% yield of the requisite bromopentyl methyl ketone.[54] The ketone was then allowed to react with 1,2-ethanedithiol in CH_2Cl_2 with BF_3•OEt_2 to give bromo-dithiolane **60** in 89% yield. Treating **60** with *t*-BuLi at -78 ºC followed by reaction of the resulting lithiate with Weinreb's amide **41** afforded the expected coupled ketone which was subsequently reduced with $TsNHNH_2$-DiBAL-H/NaOH[52] 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/NH_3 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**).[55] 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

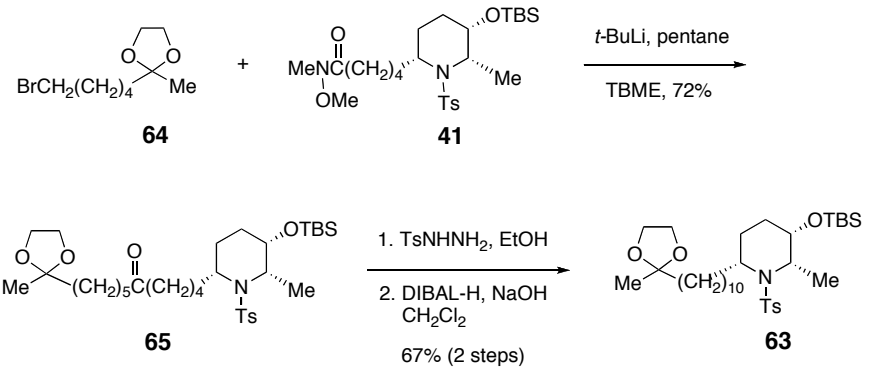


proceeded in good yield to give ketone **65**. Conversion of the keto group to the corresponding tosylhydrazone was followed by reduction with DIBAL-H/NaOH to give the same piperidinyl dioxolane **63** as had previously been prepared. This latter route represents a considerable improvement over the earlier 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

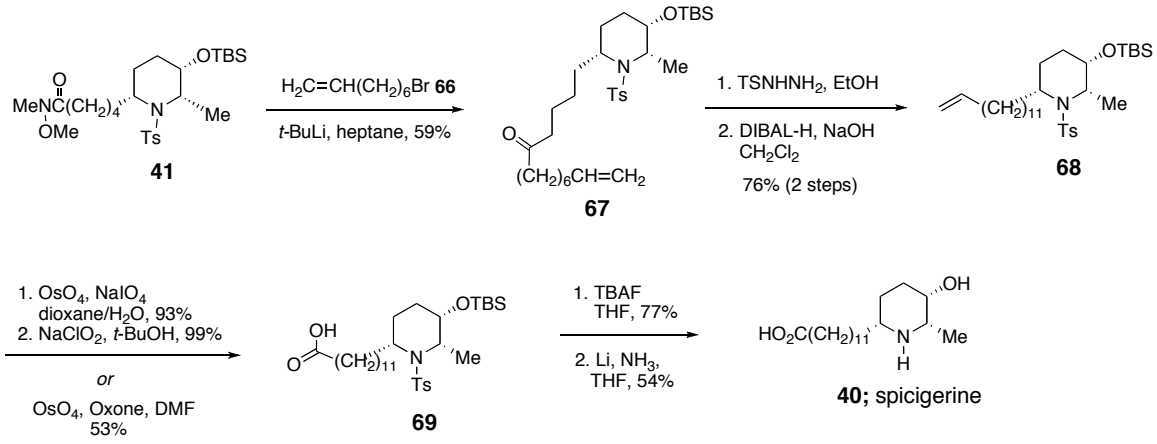
Scheme 1-12: Second Generation Synthesis of (±)-Cassine



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 OsO_4 and Oxone.[58] 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[59] followed by a subsequent oxidation to **69** with sodium chlorite.[60] In line with our expectations, exposure of **69** to the TBAF and Li/NH_3 conditions effects

deprotection of the TBS and tosyl groups producing (±)-spicigerine (**40**) in 64% isolated yield.

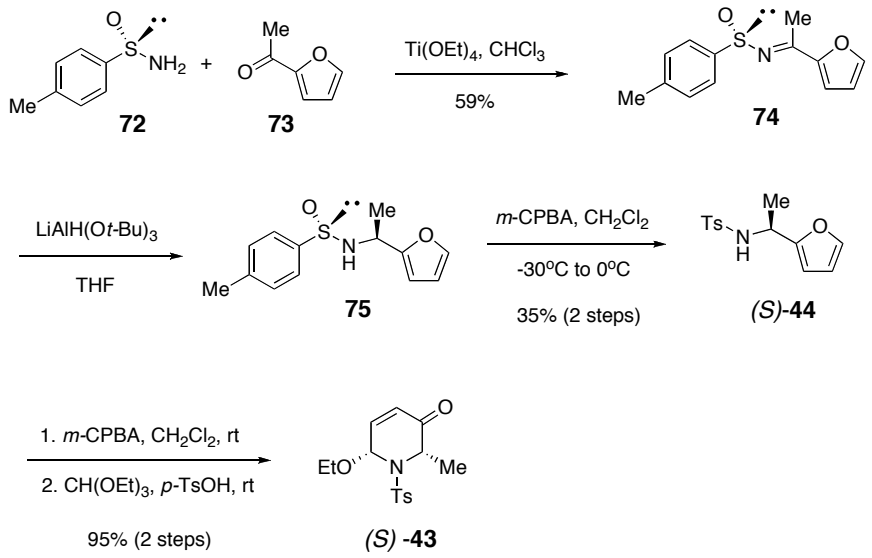
Scheme 1-13: Total Synthesis of (±)-Spicigerine



Asymmetric Approach

The construction of versatile chiral building blocks for the efficient synthesis of biologically active natural products is a topic of current interest.[61] A large number of methods leading to the synthesis of chiral piperidine, decahydroquinoline, indolizidine and quinolizidine systems have already been developed.[62] Several methods for the stereoselective construction of 2,6-disubstituted piperidinols have also been reported.[63] In earlier work the Ciufolini group demonstrated that a chemoenzymatic hydrolysis of *N*-protected furanylglycine methyl esters could be used to prepare chiral furan derivatives.[64] 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.[65] However, no example of an asymmetric synthesis of a *cis*-2,6-disubstituted

Scheme 1-14: Synthetic Route to the Chiral *(S)*-*N*-Tosylaminofuran



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.[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).[67] Stereoselective reduction of the resulting sulfilimine was carried out at low temperatures (-78 to -55 ºC) with LiAlH(O-*t*Bu)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** ($[\alpha]_D$ -63.5) with that reported by Zhou and coworkers[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**).

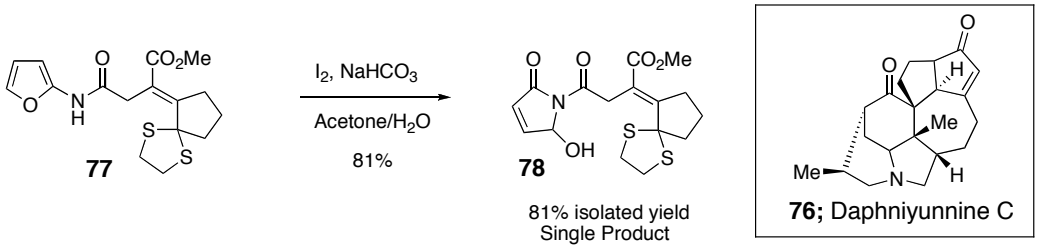
Part B: Iodine-Promoted Rearrangement of 2-Amidofurans to Acyloxypyrrolinones as a Route Toward the Formation of Functionalized Pyrroles

Introduction

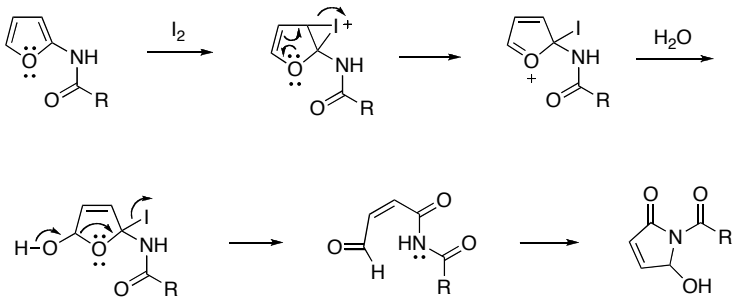
As part of an ongoing project in the Padwa laboratories using amidofurans for total synthesis, synthetic work was directed towards the synthesis of the novel alkaloid daphniyunnine C **(76)**. During the course of these studies an unexpected furan rearrangement reaction was encountered (Scheme 1-15). 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



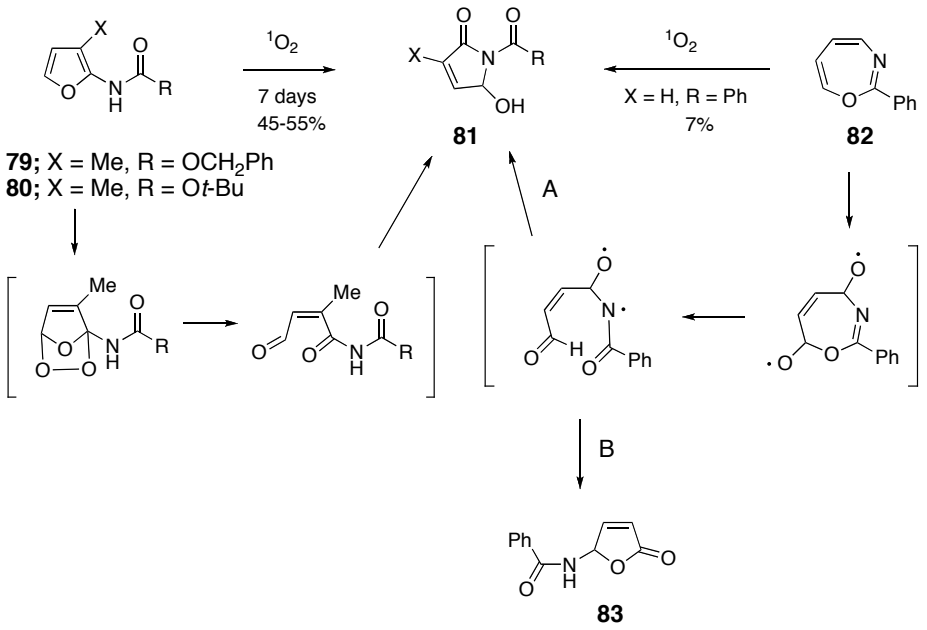
Proposed Mechanism



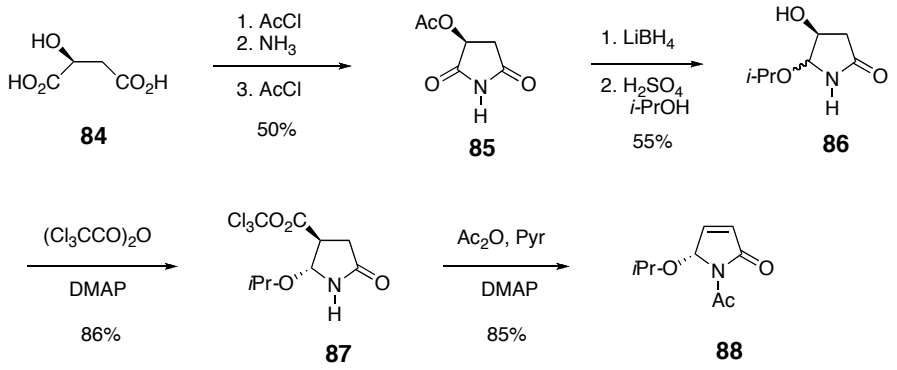
furans.[70] However, the reaction time required (7 days) and low yield (45-55%) of the desired product **81** was not particularly useful (Scheme 1-16). More recently, the same group described a similar route to these intermediates starting from diazepines (**82** to **81**, Figure 2).[71] Unfortunately, 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.[72] 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



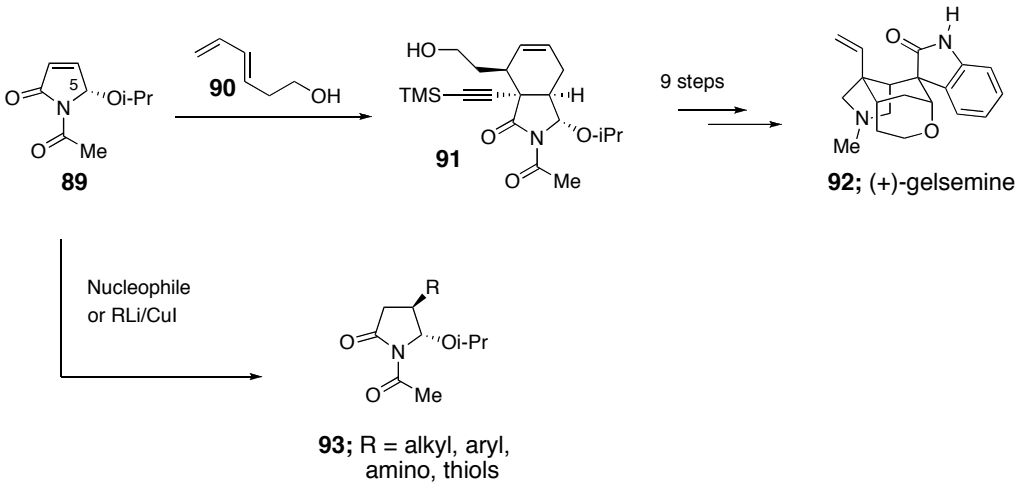
Scheme 1-17: Speckamp's Route to the Versatile Chiral Acyloxypyrrolinone Intermediate



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]

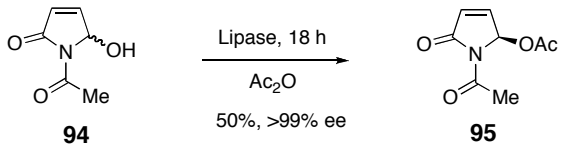
Scheme 1-18: Speckamp's Acyloxypyrrolinone-based Methodology and Routes to Natural Products



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 Ac_2O 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.

Scheme 1-19: Van Der Deen's Route for Accessing Chiral Acyloxypyrrolinones



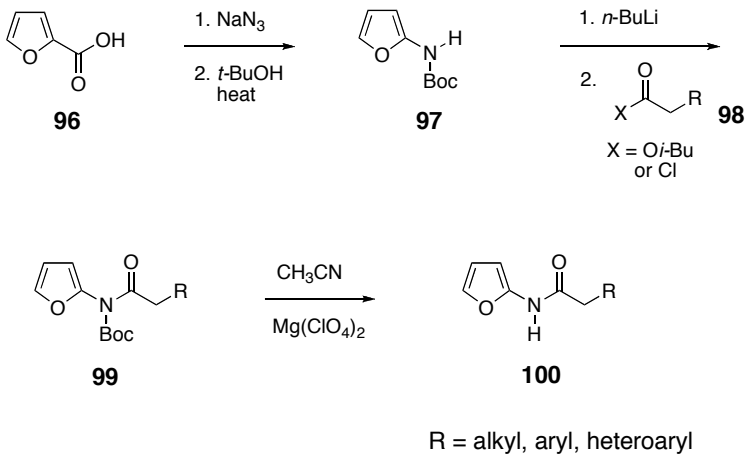
94 **95**

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.[75] 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).[76] 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[77] 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 $Mg(ClO_4)_2$ in CH_3CN[78] 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.

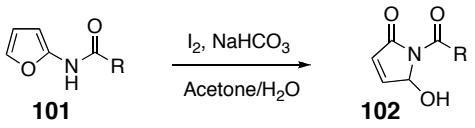
Scheme 1-20: General Route for Formation of the Furan Carbamate and 2-Amidofuran Substrates



We discovered that treatment of a variety of amidofurans with 3.0 eq. of iodine and 6.0 eq. of $NaHCO_3$ in aqueous acetone at either 0^oC or 25^oC allowed for an efficient route to prepare various acyloxypyrrolinones. The compounds synthesized included products which contain alkyl (**94;** R = Me), aryl (**105;** R = phenyl, **107;** R = dimethoxyphenyl, **111;** R = indolyl) or heteroaryl (**109;** R = 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



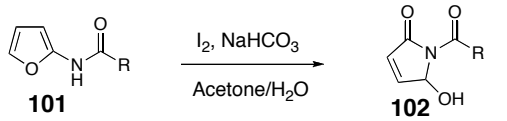
101 **102**

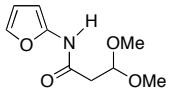
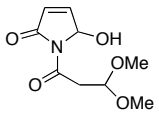
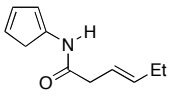
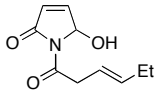
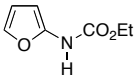
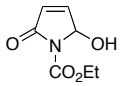
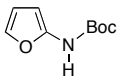
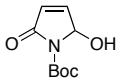
Entry	Substrate	Conditions	Product	Isolated yield
1)	**103**	3 eq, I_2, rt, 0.5 h	**94**	**57%**
2)	**104**	3 eq. I_2, rt, 0.5 h	**105**	**67%**
3)	**106**	3 eq. I_2, rt, 3 h	**107**	**77%**
4)	**108**	3 eq. I_2, rt, 3 h	**109**	**70%**
5)	**110**	3 eq. I_2, rt, 3 h	**111**	**69%**
6)		1 eq. I_2, rt, 3 h		**63%**

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

Table 1-2: Furan Rearrangement with Alkenyl, Acetal, and Furanyl Carbamate Substrates

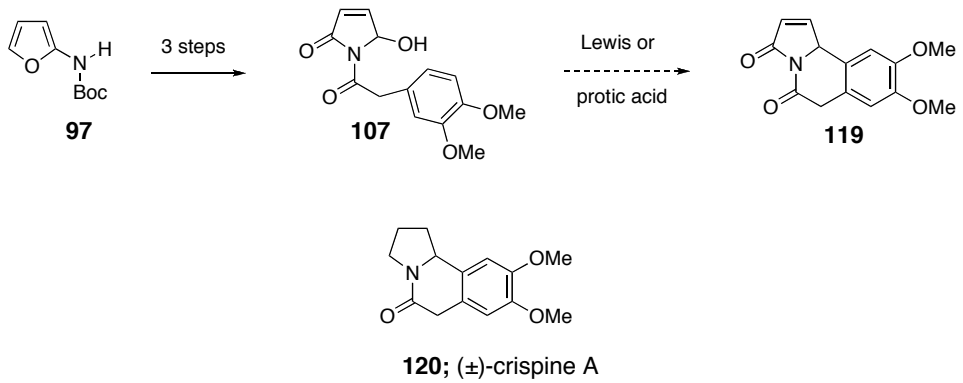


Entry	Substrate		Conditions	Product		Isolated yield
1)		**112**	3 eq. I_2, 0°C, 3 h		**113**	**78%**
2)		**114**	3 eq. I_2, 0°C, 3 h		**115**	**65%**
3)		**116**	3 eq. I_2, 0°C, 3 h		**117**	**63%**
4)		**97**	3 eq. I_2, 0°C, 3 h		**118**	**87%**

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)**.[80] 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,[81] 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 $SnCl_4$, $TiCl_4$, or BF_3•OEt_2 as Lewis acids. Disappointingly, all the conditions tried failed to promote the cyclization of **107**, instead resulting in only the recovery of the acyloxypyrrolinone

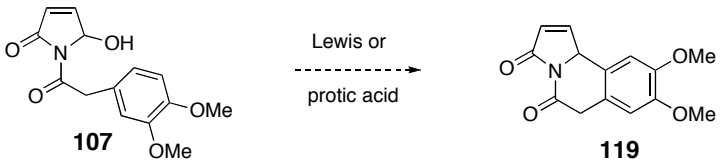
Scheme 1-21: Furan Rearrangement/Iminium Ion Approach to Synthetically Important Intermediates



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).[73,82,83] Thus, while the cyclization of iminium ions derived from simple *N*-acylamines has been well explored in many laboratories,[81] 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

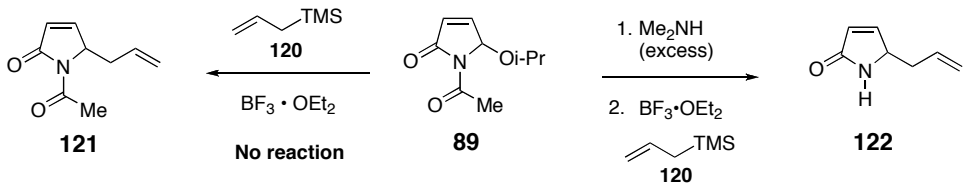
Table 1-3: Conditions Tested for Intramolecular Iminium Ion Cyclization



Entry	Conditions	Result
1)	1.0 eq. $SnCl_4$, CH_2Cl_2, -78°C to rt overnight	No reaction
2)	1.0 eq. $TiCl_4$, CH_2Cl_2, -78°C to rt overnight	No reaction
3)	1.0 eq. BF_3•OEt_2, CH_2Cl_2, -78°C to rt overnight	No reaction
4)	1.0 eq. TsOH•H_2O, benzene, 0°C to reflux overnight	No reaction
5)	1.0 eq. $Sc(OTf)_3$, CH_2Cl_2, -78°C to reflux overnight	No reaction
6)	1.0 eq. HCl, Et_2O, EtOH, reflux 1h	nucleophilic addn of EtOH
7)	TFA (excess), CH_2Cl_2, rt, 24 h, the reflux 24 h	No reaction
8)	TFA/TFAA (12:1), CH_2Cl_2, reflux 48 h	decomposition
9)	HCO_2H (excess), THF, rt, 24 h, then reflux 24 h	No reaction
10)	TfOH (2.0 eq), CH_2Cl_2, rt, 24h, then reflux 24h	decomposition
11)	PPA (excess), 90°C, 18 h	No reaction
12)	10% H_2SO_4, 90 -95°C, 20 h	decomposition

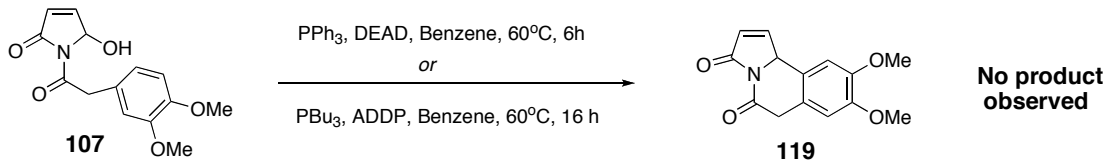
product **122** (Scheme 1-22).[82] This result is somewhat related to the observations that we have made and clearly shows that iminium ions are not readily formed from imides.

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



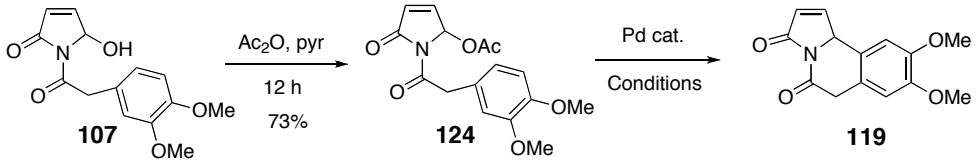
We also tested whether a metal-catalyzed cyclization might be induced to occur. Earlier work by Speckamp showed that a successful intermolecular nucleophilic substitution reaction of acyloxypyrrolinones could take place *via* olefin complexation with tetracarbonyliron complexes.[85] Other examples in 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).

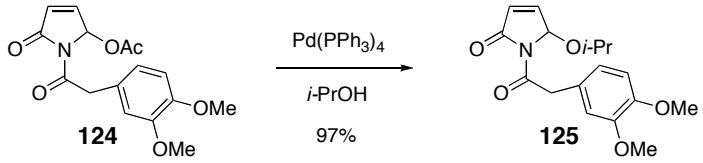
With this test substrate in hand, we tried to induce the cyclization of **124** to give **119** using several palladium-catalyzed conditions, such as the use of $Pd(PPh_3)_4$, $Pd(OAc)_2$, and $Pd(dba)_2$ catalysts with a variety of ligands. However, only decomposition products were observed in all cases (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 $Pd(PPh_3)_4$ and *i*-PrOH as the solvent and nucleophile (Scheme 1-24).[87] 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



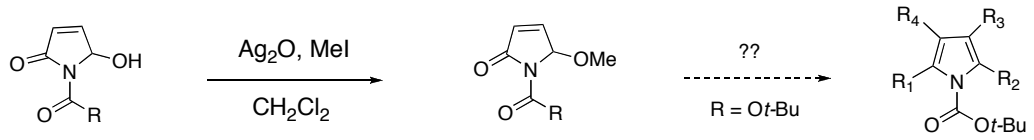
Entry	Conditions (124 to 119)	Result
1)	20 mol% $Pd(PPh_3)_4$, toluene, 100°C, 24 h	Decomposition
2)	10 mol% $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, toluene, 100°C, 18 h	Decomposition
3)	$Pd(dba)_2$, THF, 100°C, 18 h	Decomposition



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 Ag_2O/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

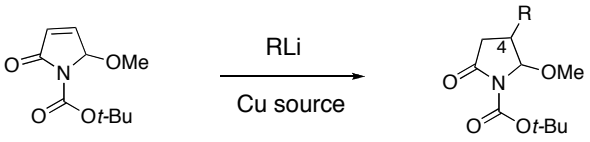


118; R = O*t*-Bu
117; R = OEt
107; R = CH_2-(3,4)-dimethoxyphenyl

126; R = O*t*-Bu, 99%
127; R = OEt, 98%
128; R = CH_2-(3,4)-dimethoxyphenyl, 91%

of the case where R = Ph, which utilized CuBr•Me_2S 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

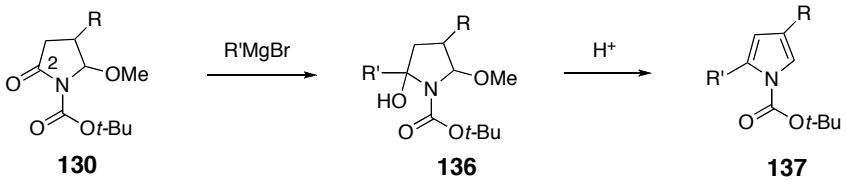


126 **130**

Entry	Conditions	Product	Yield
1)	*t*-BuLi, CuI, -78°C to rt 2 h	**131;** R = *t*-Bu	80%
2)	PhLi, CuBr•Me_2S, -78°C to rt 3 h	**132;** R = Ph	78%
3)	*n*-BuLi, CuI, -78°C to rt 1h	**133;** R = *n*-Bu	92%
4)	MeLi, CuI, -78°C 45 min.	**134;** R = Me	80%
5)	Hexyllithium, CuI, -78°C to rt 2h	**135;** R = hexyl	58%

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[88] 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.[81] 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

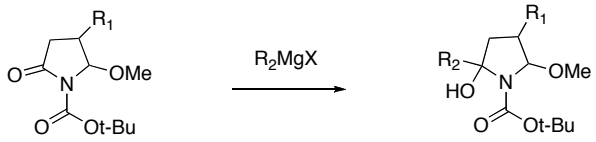


130 **136** **137**

Indeed, we were pleased to discover that the addition of various Grignard reagents at -78^{o}C or 0^{o}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



138 **139**

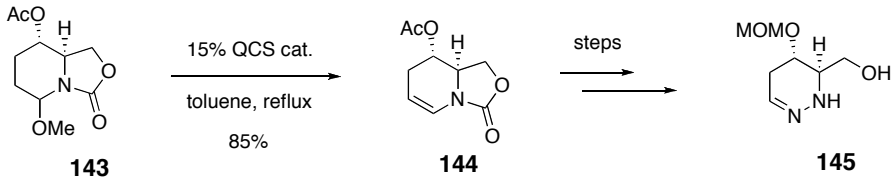
Entry	Substrate	Conditions	Product
1)	**131;** R_1 = *t*-Bu	AllylMgBr, -78°C 0.5 h, 0°C 1.5 h	**140;** R_1 = *t*-Bu, R_2 = allyl
2)	**132;** R_1 = Ph	VinylMgBr, -78°C 0.5 h, 0°C 1.5 h	**141;** R_1 = Ph, R_2 = vinyl
3)	**133;** R_1 = *n*-Bu	VinylMgBr, -78°C 1 h	**142;** R_1 = Bu, R_2 = vinyl

Thus, having the hemiaminal products 1**40-142** 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[90] and Ciufolini[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.

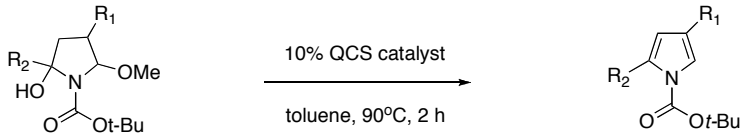
Scheme 1-28: QCS-Promoted Method for Enamide Formation



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

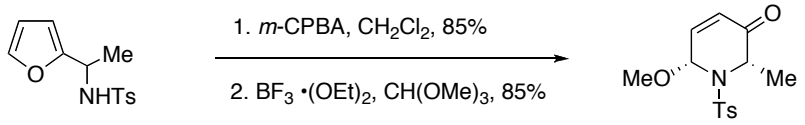


142; R_1 = Bu, R_2 = vinyl
140; R_1 = *t*-Bu, R_2= allyl
141; R_1 = Ph, R_2 = vinyl

146; R_1 = Bu, R_2 = vinyl (17% from **133**)
147; R_1 = *t*-Bu, R_2= *trans*-$CHCHCH_3$ (54% from **131)**
148; R_1 = Ph, R_2 = vinyl (19% from **132**)

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

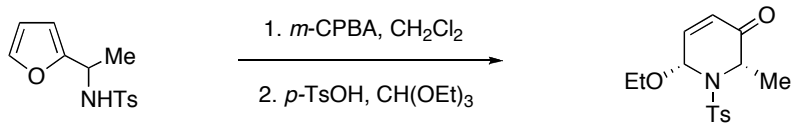


44 **42**

6-Methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (42). A 0.39 g (1.1 mmol) sample of furyl sulfonamide **44**,[45] 4 mL of CH_2Cl_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, $CDCl_3$) δ 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, $CDCl_3$) δ 21.5, 22.1, 57.0, 73.3, 126.2, 126.7, 130.0, 136.5, 143.5, 144.3, and 195.3.

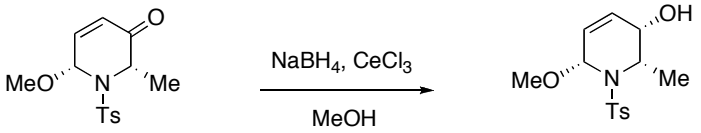
A 1.0 g (3.5 mmol) sample of the above 6-hydroxy-2*H*-pyridin-3-one was dissolved in 20 mL of CH_2Cl_2 and trimethyl orthoformate (777 μL, 7.1 mmol) and BF_3•OEt_2 (45 μL, 0.36 mmol) were added to the solution. The solution was stirred for 3 h at 0 ^{o}C and was quenched with a saturated aqueous $NaHCO_3$ 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 ^{o}C; IR (thin film) 1692, 1597, 1453, 1340, 1168, 1080, and 1014 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.81; N, 4.75. Found: C, 56.81; H, 5.69; N, 4.70.



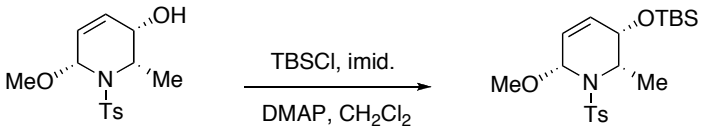
44 **43**

6-Ethoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.17; H, 6.17; N, 4.44.



42 **45**

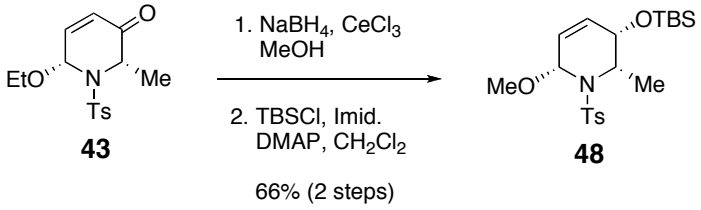
6-Methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridin-3-ol (45). To a solution of 4.7 g (12.5 mmol) of cerium trichloride heptahydrate in 100 mL of MeOH was added 3.7 g (12.5 mmol) of *N*-tosyl aminal **42**. The solution was chilled to -40 °C, and 0.5 g (14 mmol) of $NaBH_4$ was added. The solution was stirred for 10 min at -40 °C, and was then quenched with a saturated $NaHCO_3$ solution. The solution was extracted with CH_2Cl_2 and the combined extracts were dried over $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{19}NSO_4$: 297.1035. Found: 297.1033.



45 **47**

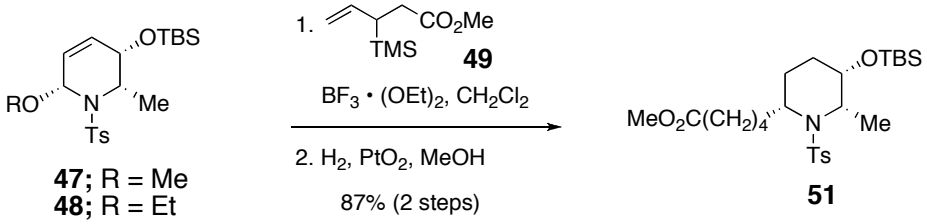
3-(*tert*-Butyl-dimethyl-silanyloxy)-6-methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine (47). To a solution of 0.7 g (2.3 mmol) of **45** in 25 mL of

CH_2Cl_2 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 $MgSO_4$. 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{33}NSiSO_4$: 411.1899. Found: 411.1903.



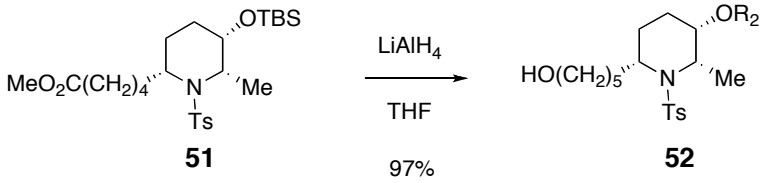
3-(*tert*-Butyl-dimethyl-silanyloxy)-6-ethoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine (48). To a solution of 6-ethoxy-2*H*-pyridin-3-one **43** (0.78 g, 2.5 mmol) at –50 °C in MeOH (30 mL) was added $CeCl_3 \cdot 7H_2O$ (0.95 g, 2.5 mmol) followed by the portionwise addition of $NaBH_4$ (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 H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$, 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 CH_2Cl_2 (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 H_2O and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 [($C_{21}H_{35}NO_4SSi$) + H^+]: 426.2056. Found: 426.2129.



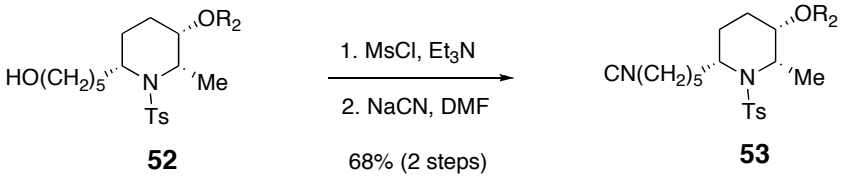
5-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-pentanoic Acid Methyl Ester (51). To a solution of 0.7 g of TBS ether **47** or **48** (1.7 mmol) in 20 mL of CH_2Cl_2 at -78 °C was added 0.6 g (2.9 mmol) of methyl-3-(trimethylsilyl)-4-pentenonate (24) followed by 4 drops of BF_3•OEt_2. 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 CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{25}H_{43}NO_5SSi$: C, 60.32; H, 8.71; N, 2.81. Found: C, 60.21; H, 8.58; N, 2.81.



5-[5-(*tert*-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

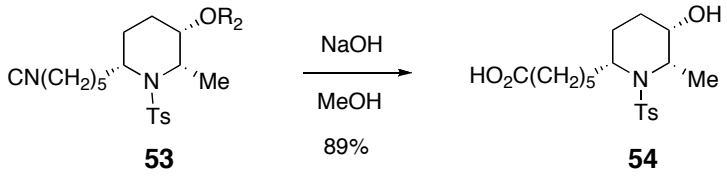
$Na_2SO_4 \cdot 10H_2O$. After stirring for 30 min at rt, $MgSO_4$ was added and the solution was filtered. The solution was concentrated under reduced pressure and the crude product was subjected to flash silica gel chromatography to give 0.12 g (97%) of the titled compound **52** as a clear oil; IR (thin film) 3418, 2855, 1462, and 1095 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ -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, $CDCl_3$) δ -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.



52 **53**

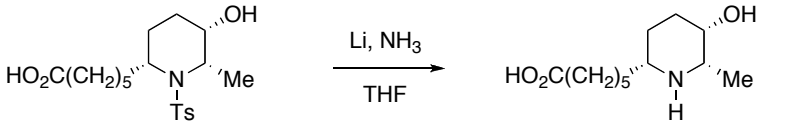
6-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-hexanenitrile (53). To a solution of 0.26 g (0.6 mmol) of alcohol **52** in 5.5 mL of CH_2Cl_2 was added methanesulfonyl chloride (0.09 g, 0.8 mmol). The solution was cooled to 0˚C and 0.09 g of triethylamine was added dropwise. After warming to rt over 30 min, the reaction was quenched by the addition of water. The solution was extracted with CH_2Cl_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 $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{25}H_{42}N_2SiSO_3$: 478.2685. Found: 478.2677.



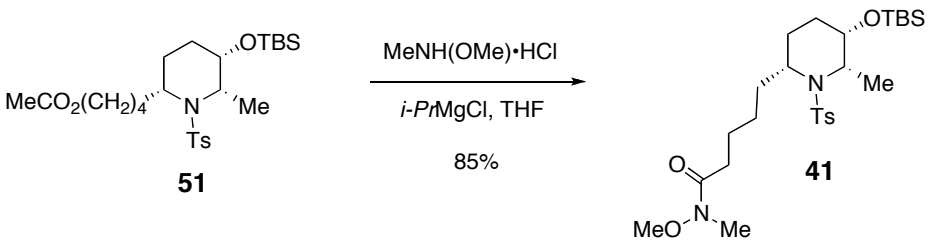
6-[5-Hydroxy-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-hexanoic Acid (54). To a solution of 0.09 g (0.19 mmol) of nitrile **53** in 2 mL of methanol was added 2 mL of a 50% NaOH solution. The mixture was heated at reflux for 3 h and cooled to rt. The solution was extracted once with ether and then the aqueous portion was acidified to pH 2 using a 6 *N* HCl solution. The acidified solution was extracted with $CHCl_3$ and the combined extracts were dried over $MgSO_4$ 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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), and 7.70 (d, 2H, J = 8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{29}NSO_5$: 383.1766. Found: 383.1772.

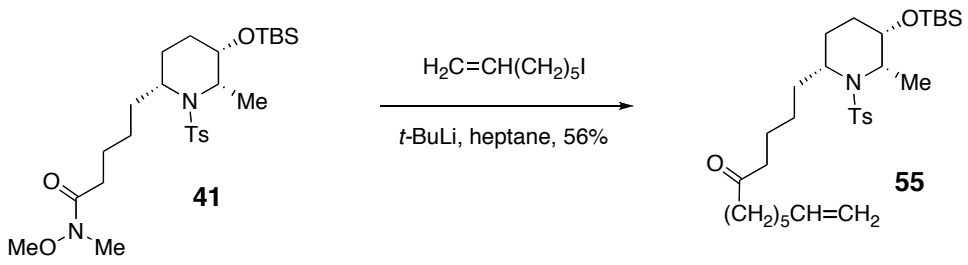


54 **26;** (±)-azimic acid

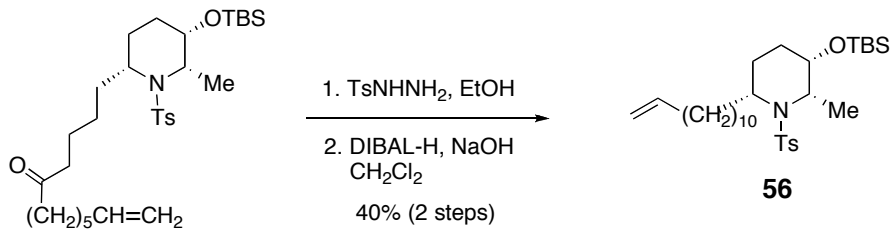
6-(5-Hydroxy-6-methyl-piperidin-2-yl)-hexanoic Acid (26). To a solution of 0.002 g (0.044 mmol) of carboxylic acid **54** in 0.6 mL of THF at -78˚C was condensed 3 mL of NH_3 using a dry ice condenser. To this solution was added lithium chips which resulted in the formation of a deep blue color. The 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[15d] 214-215 ˚C); IR (thin film) 3344, 1633, and 1551 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) 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); ^{13}C-NMR (150 MHz, $CDCl_3$) 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 [($C_{12}H_{23}NO_3$)+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 CH_2Cl_2, dried over $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{26}H_{46}N_2SiSO_5$: 526.2897. Found: 526.2889.

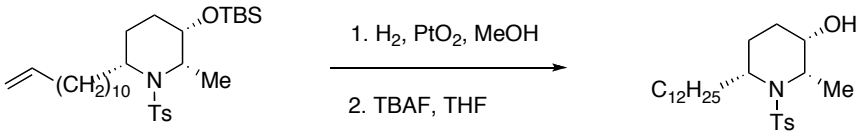


1-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-dodec-11-en-5-one (55). To a solution of 0.1 g (0.6 mmol) of 1-iodo-6-heptene in 0.5 mL of heptane at -78˚C was added 1.6 mL of a 1.4 M solution of *tert*-butyllithium in pentane. The mixture was stirred for 5 min 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 NH_4Cl solution. The mixture 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 0.1 g (56%) of the titled compound **55** as a colorless oil; IR (thin film) 2932, 2857, 1712, 1337, and 1162 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $C_{31}H_{53}NSiSO_4$: 563.3464. Found: 563.3472.



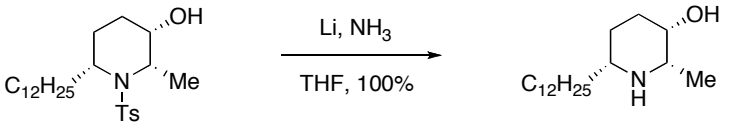
55 **56**

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 *p*-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 CH_2Cl_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, $CDCl_3$) δ -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, $CDCl_3$) δ -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.



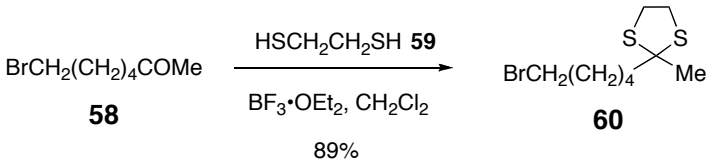
56

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 mixtured 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 uL of a 1M solution in THF) was added at 0 ^{o}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 $MgSO_4$, 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}; ^{1}H-NMR (600 MHz, $CDCl_3$) 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); ^{13}C-NMR (150 MHz, $CDCl_3$) 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 $C_{25}H_{43}NSO_4$: 453.2913. Found: 453.2924.



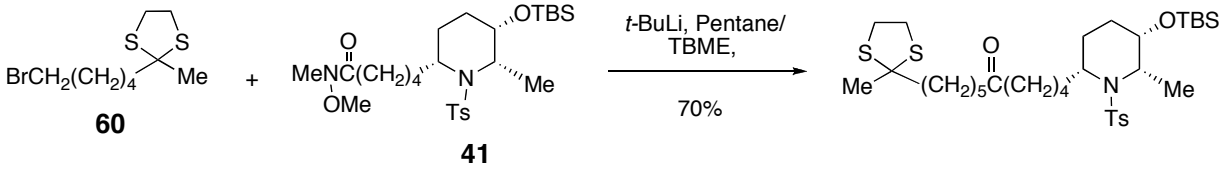
29; deoxocassine

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 NH_3 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 $CHCl_3$. After extracting the aqueous layer with additional $CHCl_3$, the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give 0.03 g (100%) of deoxocassine **(29)**; IR (thin film) 3394, 2916, 2848, and 1455 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (150 MHz, $CDCl_3$) 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 [($C_{18}H_{37}NO$)+H^+]: 284.2953. Found: 284.2941.



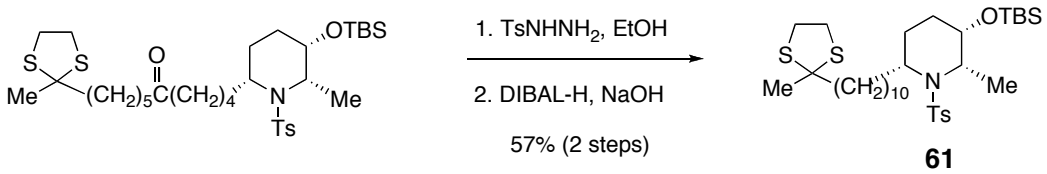
2-(5-Bromo-pentyl)-2-methyl-[1,3]dithiolane (60). A mixture of BF_3•OEt_2 (0.04 mL) and 1,2-ethanedithiol (0.3 mL, 4.0 mmol) was added to a solution of 7-bromo-2-heptanone **(58)** (0.5 g, 2.7 mmol) in CH_2Cl_2 and the reaction mixture was stirred for 18 h at rt. The resulting solution was then quenched with an aqueous 1 M NaOH solution and

the organic layer was washed with H_2O, dried over $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.6, 28.3, 32.5, 32.7, 33.9, 40.0, 45.6, and 66.8; HRMS Calcd for [$(C_9H_{17}BrS_2)+H^+$]: 268.9955. Found: 269.0028.



1-[5-(*tert*-Butyl-dimethyl-silanyloxy)-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 ºC 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 NH_4Cl solution. The aqueous layer was extracted with ether and the organic layer was dried over $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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),

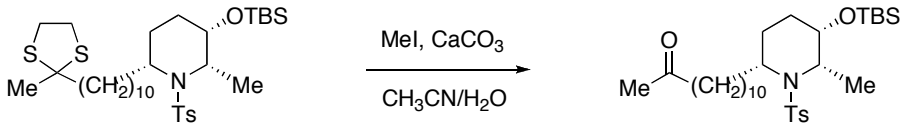
1.74 (s, 3H), 1.92 (m, 2H), 2.41 (m, 7H), 3.17 (m, 1H), 3.32 (m, 4H), 3.95 (m, 2H), 7.28 (d, 2H, J = 8.6 Hz), and 7.68 (d, 2H, J = 8.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.8, -4.6, 15.0, 18.2, 21.7, 23.6, 23.8, 23.9, 25.9, 27.0, 27.3, 27.5, 29.5, 32.5, 35.1, 40.0, 42.9, 45.8, 51.9, 53.2, 67.0, 69.4, 126.9, 129.8, 139.1, 143.1, and 211.5; HRMS Calcd for [($C_{33}H_{57}NO_4S_3Si$)+H^+]: 656.3219. Found: 656.3298.



61

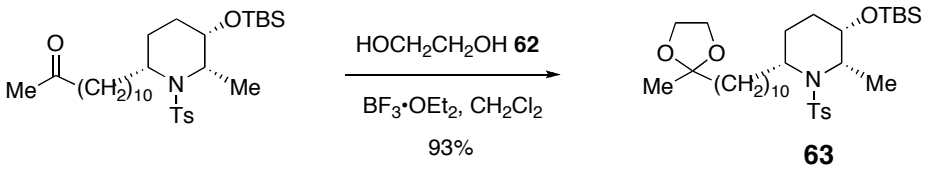
3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-6-[10-(2-methyl-[1,3]dithiolan-2-yl)-decyl]-1-(toluene-4-sulfonyl)piperidine (33). To a solution of the above ketone (0.07 g, 0.1 mmol) in absolute EtOH (1.2 mL) was added *p*-toluenesul-fonylhydrazide (0.02 g, 0.11 mmol) and the reaction mixture was stirred at rt for 17 h. The solvent was removed under reduced pressure and the residue was taken up in CH_2Cl_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, $CDCl_3$) δ -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 [($C_{33}H_{59}NO_3S_3Si$)+H^+]: 642.3426. Found: 642.3490.



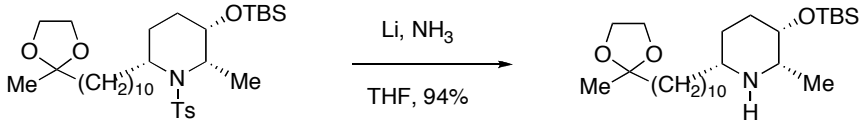
61

12-[5-(*tert*-Butyl-dimethyl-silanyloxy)-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_3CN/H_2O 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_2O 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 [($C_{31}H_{55}NO_4SSi$)+H^+]: 566.3621. Found: 566.3700.



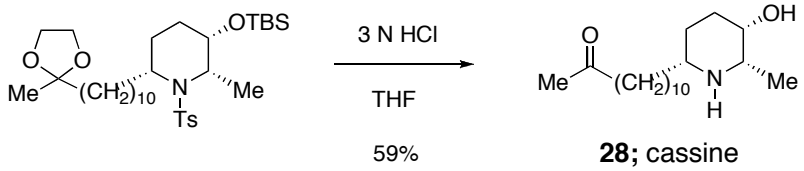
63

3-(*tert*-Butyl-dimethyl-silanyloxy)-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 CH_2Cl_2 (0.5 mL) was added ethylene glycol (0.5 mL) and BF_3•OEt_2 (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 CH_2Cl_2. The organic layer 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 (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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 [($C_{33}H_{59}NO_5SSi$)+H^+]: 610.3883. Found: 610.3962.



63

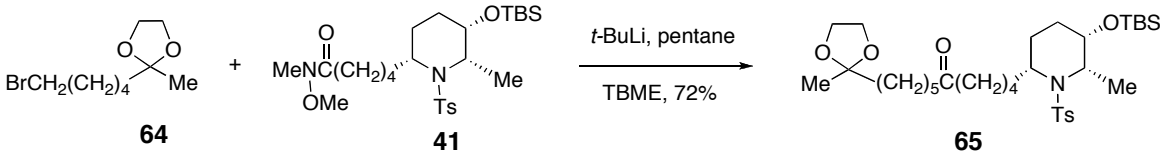
3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-6-[10-(2-methyl-[1,3]dioxolan-2-yl)decyl]piperidine. To a solution of **63** (0.03 g, 0.04 mmol) in THF (3 mL) at –78 °C was added 5 mg of lithium wire. The flask was fitted with an acetone/dry ice condenser and 3 mL NH_3 was added which resulted in a dark 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 NH_4Cl and extracted with EtOAc. The organic layer 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 (94%) of the titled compound as a clear oil; IR (thin film) 2927, 2854, 1463, 1373, 1252, 1070, 1032, and 837 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 [($C_{26}H_{53}NO_3Si$)+H^+]: 456.3795. Found: 456.3863.



28; cassine

(±)-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 $MgSO_4$,

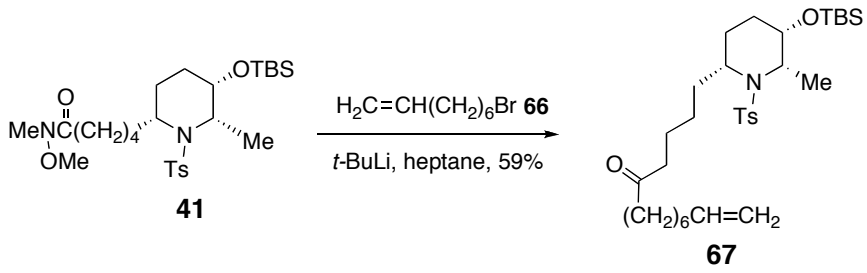
filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over basic alumina to afford 0.007g (59%) of the titled compound as a white solid; mp 64-65 °C (lit[59] mp 57-58 °C); IR (thin film) 3405, 2926, 2852, 1716, 1464, 1363, 1166, and 967 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 [($C_{18}H_{35}NO_2$)+H^+]: 298.2668. Found: 298.2740.



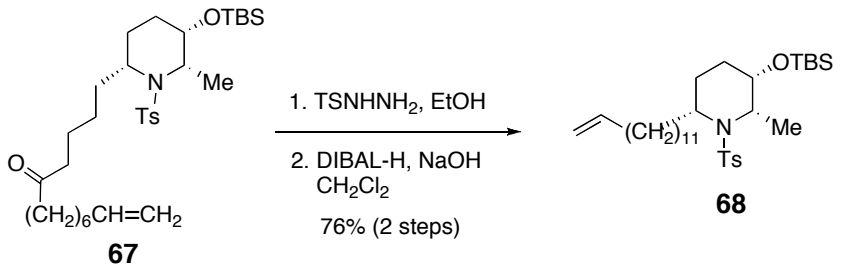
1-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)piperidin-2-yl]-10-(2-methyl-[1,3]dioxolan-2-yl)-decan-5-one (65). To a solution of 2-(5-bromopentyl)-2-methyl-1,3-dioxolane (**64**)[45] (0.06 g, 0.27 mmol) in *t*-butyl methyl ether (1.25 mL) at –78 °C was added *t*-BuLi (0.22 mL, 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 NH_4Cl solution and allowed to warm to rt. The aqueous layer was extracted with ether, dried over $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ -0.10 (d, 6H, *J* = 3.6 Hz), 0.80 (s, 9H), 1.21 (d, 3H, *J* = 6.8 Hz), 1.30 (s, 3H), 1.50 (m, 16H), 2.40 (m, 7H), 3.17 (ddd, 1H, *J* = 10.8, 6.0, and 4.0 Hz), 3.84 (m, 6H), 7.27 (d, 2H, *J* = 8.4 Hz), and 7.68 (d, 2H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -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 [($C_{33}H_{57}NO_6SSi$)+H^+]: 624.3676. Found: 624.3763.

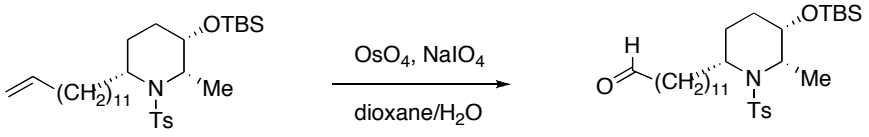
To a solution of the above ketone (0.06 g, 0.09 mmol) in absolute EtOH (1.0 mL) was added *p*-toluenesulfonylhydrazide (0.02 g, 0.01 mmol) and the reaction mixture was stirred at rt for 18 h. The solvent was removed under reduced pressure and the residue was taken up in CH_2Cl_2 (1.0 mL). The solution 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 *t*-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 NH_4Cl solution and the mixture was warmed to rt. The aqueous layer was extracted with ether, dried over $MgSO_4$, 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, 934, 838, and 776 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.10d, 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).; ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $[(C_{32}H_{55}NO_4SSi)+H^+]$: 578.3621 Found: 578.3697.

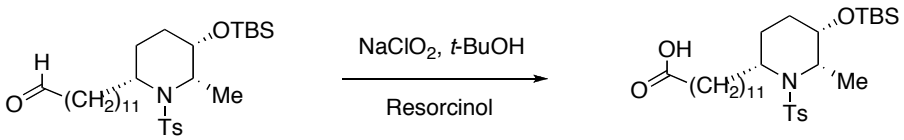


3-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-6-tridec-12-enyl-piperidine (68). To a solution of ketone **67** (0.06 g, 0.095 mmol) in absolute EtOH (1.0 mL) was added *p*-toluenesulfonhydrazide (0.02 g, 0.1 mmol) and the reaction mixture was stirred at rt for 18.5 h. The solvent was removed under reduced pressure and the residue was taken up in CH_2Cl_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_2Cl_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 chromato-graphy 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 [($C_{32}H_{57}NO_3SSi$)+H^+]: 564.3828. Found: 564.3903.



68

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/H_2O mixture (5.5 mL) was added 2,6-lutidine (0.05 mL, 0.43 mmol), OsO_4 (7 drops, 2.5% in *t*-BuOH), and $NaIO_4$ (0.16 g, 0.75 mmol). After stirring for 3.5 h at rt, an aqueous mixture of Na_2SO_3 was added and the aqueous layer was then extracted with CH_2Cl_2. The organic layer was washed with 1 N HCl, dried over $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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 9.76 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 $[(C_{31}H_{55}NO_4SSi)+H^+]$: 566.3621. Found: 566.3698.

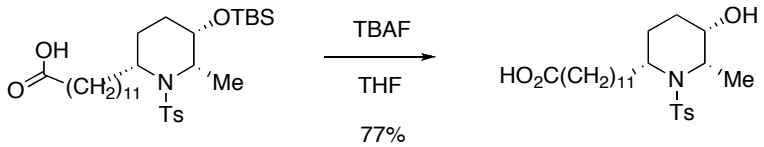


69

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_2O (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, $CDCl_3$) δ -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); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -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 $[(C_{31}H_{55}NO_5SSi)+H^+]$: 582.3570. Found: 582.3643.

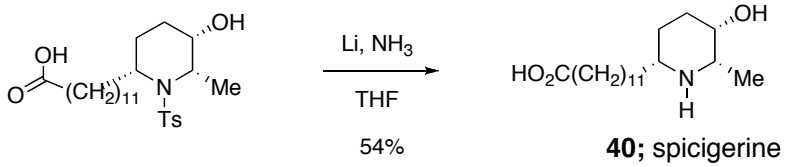
The same carboxylic acid **69** was prepared by the direct oxidation of piperidinyl alkene **68**. To a solution of alkene **68** (0.03 g, 0.05 mmol) in DMF (1.2 mL) was added OsO_4 (3 drops, 2.5% in *t*-BuOH) and the reaction mixture was stirred at rt for 5 min. Oxone was added in one portion, and the 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**.



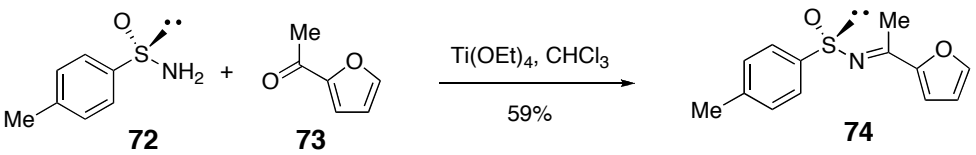
69

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 H_2O and brine and extracted with EtOAc. The organic layer was dried over $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 [($C_{25}H_{41}NO_5S$)+H^+]: 468.2705. Found: 468.2779.



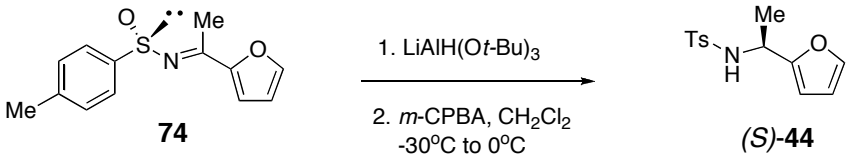
40; spicigerine

(±)-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 NH_4Cl 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 $CHCl_3$/*i*-PrOH. The resulting organic layer was dried over Na_2SO_4, 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 (lit[46] 196 °C); IR (thin film) 3416, 2914, 2848, 1726, 1460, 1408, 1173, 1102, and 1010 cm-1; ^{1}H-NMR (400 MHz, CD_3OD) 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); ^{13}C-NMR (100 MHz, CD_3OD) 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 [($C_{18}H_{35}NO_3$)+H^+]: 314.2617. Found: 314.2685.



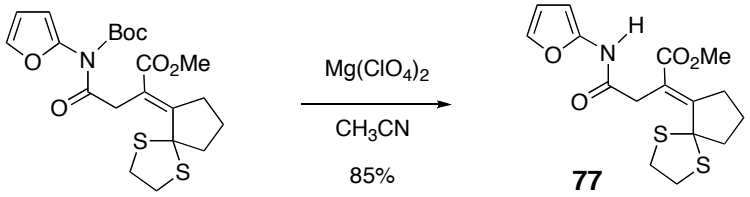
72 **73** **74**

(*S,E*)-*N*-(1-Furan-2-yl-ethyl)toluene *p*-Sulfinamide (74). A mixture of (*S*)-(+)-*p*-toluenesulfinamide[57] (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 $CHCl_3$ (4 mL) was heated at reflux for 41 h. The reaction mixture was then cooled to 0 °C, H_2O was added, and the resulting suspension was filtered over celite. The filtrate was extracted with CH_2Cl_2, dried over $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.6, 112. 7, 115.9, 125.3, 130.0, 142.0, 143.4, 146.4, 152.5, and 164.2.

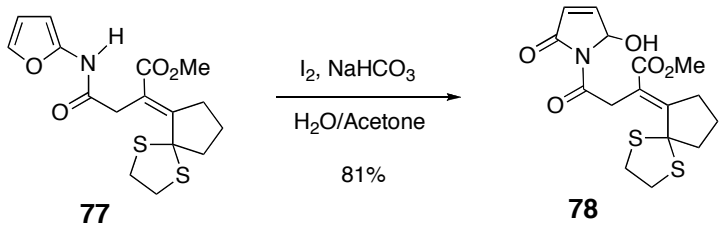


(*S*)-*N*-(1-(furan-2-yl)ethyl)-4-methylbenzenesulfonamide (*S*-44). To a -78 °C solution of the above sulfinimine **74** (0.08 g, 0.33 mmol) in 4.7 mL of THF was added LiAlH(O*t*-Bu)$_3$ (0.11 g, 0.43 mmol) in 2.5 mL of THF over a 15 min. period. The mixture was stirred at -78 °C for 2 h and then warmed and stirred between -50 and -55 °C for 20 h. The solution was quenched with a saturated aqueous NH_4Cl solution, warmed to room temperature, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, 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_2Cl_2 was added to a solution of *m*-CPBA in 5 mL CH_2Cl_2 at -30 ^oC. The mixture was stirred and allowed to warm to 0 ^oC over 1.5 h. A saturated aqueous $NaHCO_3$ solution was added, and the aqueous layer was extracted with CH_2Cl_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: $[a]_D$ -63.5 (*c* 1.0, EtOH) 0.58

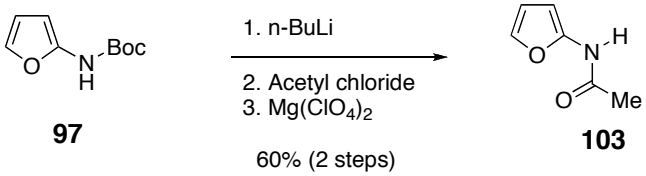


2-(1,4-Dithia-spiro[4.4]non-6-ylidene)-*N*-furan-2-yl-succinamic Acid Methyl Ester (77). To a solution of the above Boc amidofuran (0.22 g, 0.49 mmol) in CH_3CN (5 mL) was added $Mg(ClO_4)_2$ (0.14 g, 0.6 mmol) in one portion. The solution was heated at 45 ^oC for 1.5 h then cooled to room temperature 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}; ^1H 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.



77 **78**

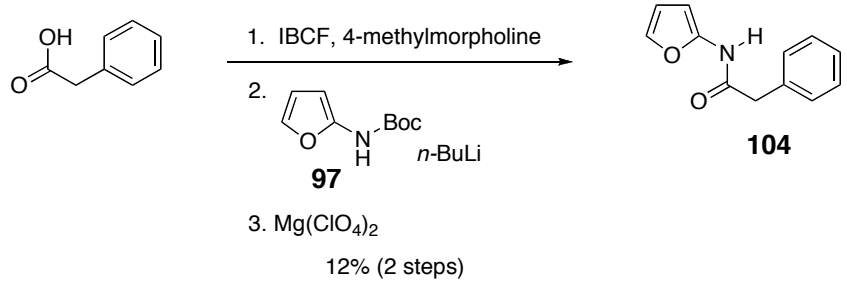
2-(1,4-Dithia-spiro[4.4]non-6-ylidene)-4-(2-hydroxy-5-oxo-2,5-dihydro-pyrrol-1-yl)-4-oxo-butyric Acid Methyl Ester (78). To a 0 ^{o}C stirred solution of compound **77** (0.025 g, 0.07 mmol) in acetone/H_2O (4.8 mL/0.26 mL) was added $NaHCO_3$ (0.036 g, 0. 43 mmol) and I_2 (0.054 mg, 0.21 mmol). The mixture was stirred for 3 h at 0 ^{o}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 $MgSO_4$, 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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.



97 **103**

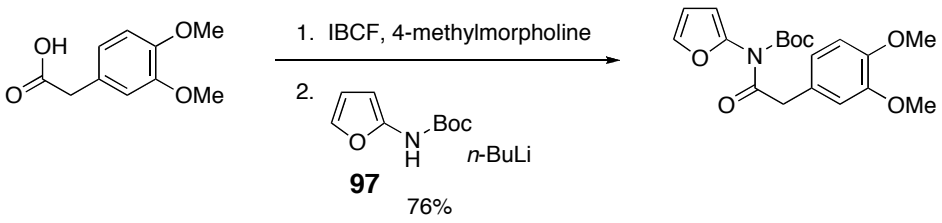
***N*-(Furan-2-yl)acetamide (103).** To a stirred solution of furan **97** (0.2 g, 1.09 mmol) in THF (12 mL) at 0 ^{o}C was added *n*-BuLi (0.46 mL, 1.14 mmol, 2.5 M in hexanes)

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 H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_3CN (12 mL) and $Mg(ClO_4)_2$ (304 mg, 1.36 mmol) was added. The mixture was heated at 40 °C for 25 min, cooled to 0 °C, diluted with H_2O, and extracted with Et_2O. The organic layer was dried over $MgSO_4$, 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;[92] mp 96-98 °C; ^{1}H-NMR ($CDCl_3$, 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).



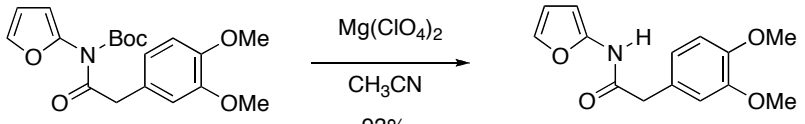
***N*-(Furan-2-yl)-2-phenylacetamide (104).** To a stirred solution of furan **97** (200 mg, 1.09 mmol) in THF (8 mL) at 0 °C was added *n*-BuLi (0.52 mL, 1.31 mmol, 2.5 M in hexanes) dropwise and the mixture was stirred at 0 °C for 30 min. In a separate flask, phenylacetic acid (148 mg, 1.09 mmol) was 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

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 H_2O and extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered over a pad of silica gel, and concentrated under reduced pressure. The residue was dissolved in CH_3CN (10 mL) and was added to a stirred solution of $Mg(ClO_4)_2$ (226 mg, 1.01 mmol) in CH_3CN (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 H_2O and extracted with Et_2O. The organic layer was dried over $MgSO_4$, 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}; ^{1}H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 44.0, 95.6, 111.7, 128.0, 129.5, 129.7, 134.1, 135.6, 145.2, and 167.6.



***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

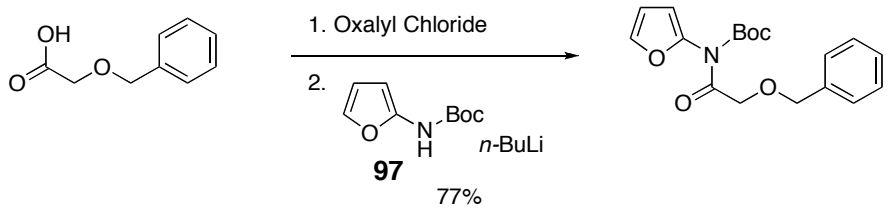
mmol) and isobutyl chloroformate (1.83 mL, 14.0 mmol) was added dropwise and the solution was stirred for 5 min. The mixture was filtered over celite with THF (4 mL). The filtrate was cooled to 0 ^{o}C and the preformed furanyl lithiate was added dropwise by cannula. The resulting reaction mixture was stirred for 30 min and quenched with H_2O 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 (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}; ^{1}H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 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.



106

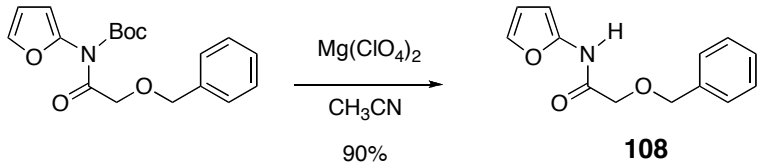
2-(3,4-Dimethoxyphenyl)-*N*-(furan-2-yl)acetamide (106). To a stirred solution of $Mg(ClO_4)_2$ (237 mg, 1.06 mmol) in CH_3CN (9 mL) at 45 ^{o}C was added a solution of the above Boc amidofuran (304 mg, 0.841 mmol) in CH_3CN (2 mL). The mixture was stirred at 45 ^{o}C for 15 min and was then diluted with H_2O 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 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}; ^{1}H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 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.

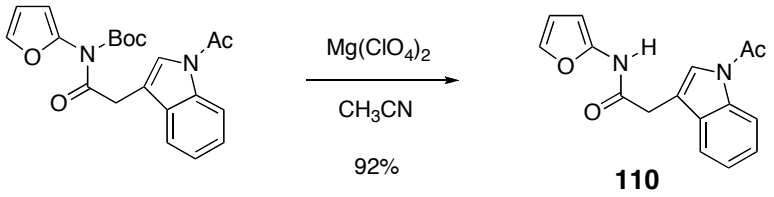


***tert*-Butyl-2-(Benzyloxy)acetyl(furan-2-yl)carbamate.** To a stirred solution of the above acid (1.0 g, 6.02 mmol) in CH_2Cl_2 (15 mL) was added oxalyl chloride (1.58 mL, 18.07 mmol) followed by 2 drops of DMF. The reaction mixture was stirred at rt for 1 h and was then concentrated under reduced pressure, dissolved in THF (15 mL), and cooled to -78 ^{o}C. In a separate flask, furan **97** (1.32 g, 7.22 mmol) was dissolved in THF (10 mL) and cooled to 0 ^{o}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 ^{o}C for 0.5 h. The resulting solution was transferred dropwise by cannula into a solution of the above acid chloride at -78^{o}C. The solution was stirred for 1 h while slowly warming from -78 ^{o}C to 0 ^{o}C. The mixture was then quenched with H_2O, extracted with EtOAc, dried over $MgSO_4$, 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^{o}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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 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.

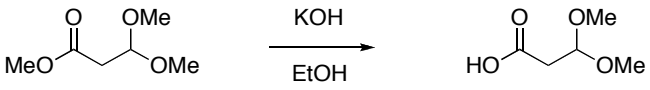


2-(Benzyloxy)-*N*-(furan-2-yl)acetamide (108). The above Boc amidofuran (1.09 g, 3.02 mmol) was dissolved in CH_3CN (5 mL) and was added to a stirred solution of $Mg(ClO_4)_2$ (0.84 g, 3.78 mmol) in CH_3CN (53 mL) at 40 ^oC. The reaction mixture was heated at 40 ^oC for 10 min, cooled to rt, and diluted with H_2O. 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, $CDCl_3$) δ 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, $CDCl_3$) δ 69.3, 74.0, 95.6, 111.8, 128.3, 128.7, 129.0, 135.8, 136.5, 144.7 and 166.1.

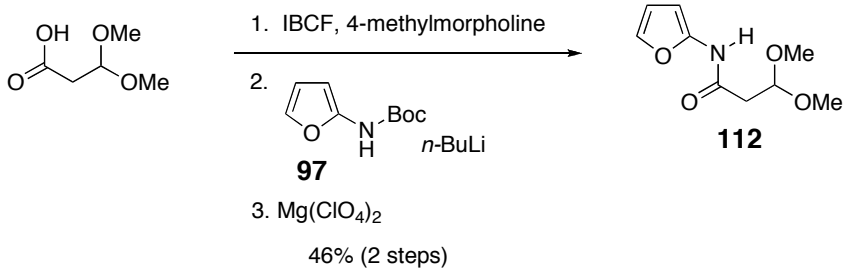


2-(1-Acetyl-1*H*-indol-3-yl)-*N*-(furan-2-yl)acetamide (20). To a stirred solution of $Mg(ClO_4)_2$ (730 mg, 3.27 mmol) in CH_3CN (25 mL) at 45 ^oC was added a solution of the above Boc amidofuran (1.0 g, 2.62 mmol) in CH_3CN (5 mL). The mixture was stirred at

45 ^{o}C for 15 min, diluted with H_2O 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 (50% EtOAc/hexanes) to provide 683 mg (92%) of **20** as a white solid, mp 116-118^{o}C; IR (thin film) 3263, 3056, 2931, 1700, 1672, 1608, 1554, 1451, 1386, 1331, 1224, 1145, 1011, 749, and 647 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) d 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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.

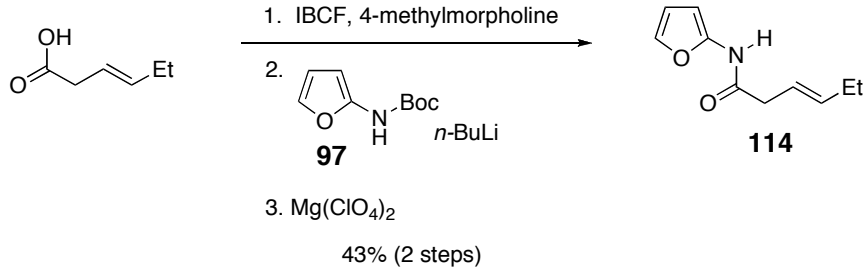


3,3-Dimethoxypropanoic acid. To a stirred solution of methyl 3,3-dimethoxy propanoate (1.58 g, 10.7 mmol) in EtOH (140 mL) was added KOH (2.99 g, 53.3 mmol) and the reaction mixture was stirred at rt for 17 h. The ethanol was removed under reduced pressure and H_2O was added. The aqueous layer was extracted with Et_2O and then acidified to pH = 3 and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated to provide 222 mg (16%) of the title compound as a yellow oil;[3] ^{1}H-NMR (400 MHz, $CDCl_3$) 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).



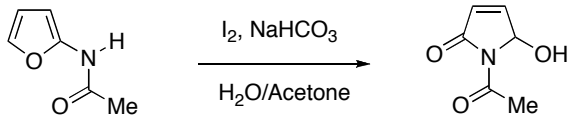
***N*-(Furan-2-yl)-3,3-dimethoxypropanamide (112).** To a stirred solution of furan **97** (1.37 g, 7.46 mmol) in THF (27 mL) at 0 ^{o}C was added *n*-BuLi (3.22 mL, 8.05 mmol, 2.5 M in hexanes) dropwise and the mixture was stirred for 20 min at 0 ^{o}C. In a separate flask, 3,3-dimethoxypropanoic acid (1.0 g, 7.46 mmol) was dissolved in THF (35 mL) and the solution was cooled to 0 ^{o}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 ^{o}C and the preformed lithiate from above was added dropwise by cannula. The resulting mixture was stirred for 25 min and then quenched with H_2O 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 filtered over a plug of silica gel and concentrated to a yellow oil. The oil was dissolved in CH_3CN (5 mL) and added to a stirred solution of $Mg(ClO_4)_2$ (1.08 g, 4.84 mmol) in CH_3CN (15 mL) at 40 ^{o}C and the solution was heated at 40 ^{o}C for 10 min, diluted with H_2O, 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}; ^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 40.8, 54.2, 95.0, 101.7, 111.4, 135.0, 145.2 and 165.4.



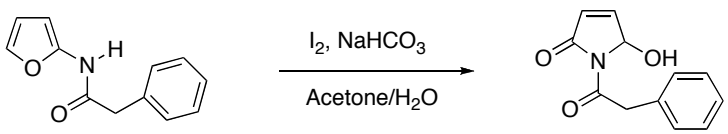
(*E*)-*N*-(Furan-2-yl)hex-3-enamide (114). To a stirred solution of furan **97** (1.9 g, 10.38 mmol) in THF (30 mL) at 0 ^{o}C was added *n*-BuLi dropwise (4.48 mL, 11.21 mmol, 2.5 M in hexane) and the mixture was stirred at 0^{o}C for 20 min. In a separate flask, (*E*)-hex-3-enoic acid (3.2 g, 28 mmol) was dissolved in THF (40 mL) and the solution was cooled to 0 ^{o}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 ^{o}C and the preformed lithiate from above was added dropwise by cannula. The resulting mixture was stirred for 20 min, quenched with H_2O, 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_3CN (5 mL) and was added to a stirred solution of $Mg(ClO_4)_2$ (2.89 g, 13.0 mmol) in CH_3CN (53 mL) at 40 ^{o}C and the mixture was heated at 40 ^{o}C for 10 min. The solution was diluted with H_2O, 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 ^{o}C; IR (thin film) 3202, 3159, 3057, 2971, 2901, 2885, 1659,

1606, 1563, 1517, 1406, 1381, 1241, 1205 and 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 13.2, 25.4, 40.2, 95.2, 111.3, 120.7, 135.2, 138.2, 145.2 and 168.5.



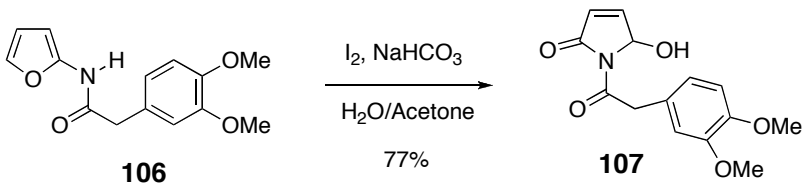
103 **94**

1-Acetyl-5-hydroxy-1*H*-pyrrol-2(5*H*)-one (94). To a stirred solution of compound **103** (81 mg, 0.65 mmol) in acetone/H_2O (20/1, 48.3 mL) at 0 °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 °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 °C;[74] ^1H-NMR ($CDCl_3$, 400 MHz) δ 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).



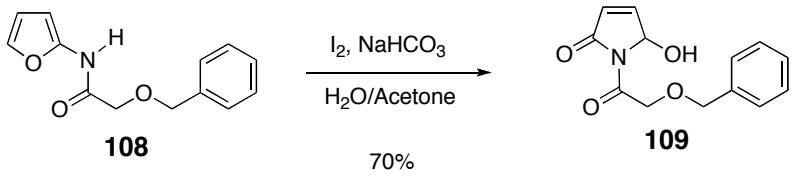
104 **105**

5-Hydroxy-1-(2-phenylacetyl)-1*H*-pyrrol-2(5*H*)-one (105). To a stirred solution of **104** (24 mg, 0.119 mmol) in acetone/H_2O (18/1, 9.5 mL) at 0°C was added $NaHCO_3$ (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 $MgSO_4$, 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 ($CDCl_3$, 400 MHz) d 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, $CDCl_3$) δ 42.7, 82.4, 127.5, 128.8, 130.0, 133.5, 147.7, 167.8, and 172.6.

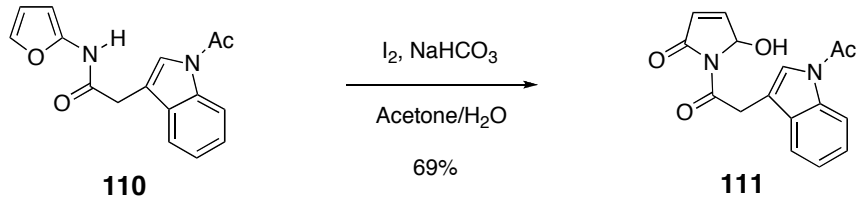


1-(2-(3,4-Dimethoxyphenyl)acetyl)-5-hydroxy-1*H*-pyrrol-2(5*H*)-one (107). To a stirred solution of compound **106** (1.66 g, 6.35 mmol) in acetone/H_2O (20/1, 50 mL) at 0°C was added $NaHCO_3$ (3.2 g, 38.1 mmol) and the mixture was stirred at 0°C for 5 min. A sample of iodine (4.84 g, 19.06 mmol) was 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 $MgSO_4$, 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 ^{o}C; IR (thin film) 3454, 3101, 3002, 2938, 2837, 1736, 1686, 1517, 1349, 1264, 1228, and 1141 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

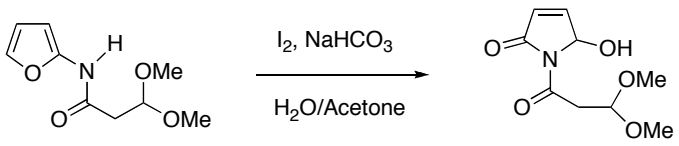


1-(2-(Benzyloxy)acetyl)-5-hydroxy-1*H*-pyrrol-2-(5*H*)-one (109). To a stirred solution of compound **108** (350 mg, 1.52 mmol) in acetone/H_2O (18.8/1, 50.6 mL) at 0 ^{o}C was added $NaHCO_3$ (767 mg, 9.13 mmol) and the mixture was stirred for 10 min. A sample of iodine (1.17g, 4.61 mmol) was added in 3 portions. The reaction mixture was stirred at 0 ^{o}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 ^{o}C; IR (thin film) 3403, 3056, 2925, 2855, 1742, 1707, 1265, 1132, 1092 and 738 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 69.9, 73.1, 81.1, 127.2, 127.7, 127.8, 128.2, 136.9, 148.6, 168.0 and 170.8.



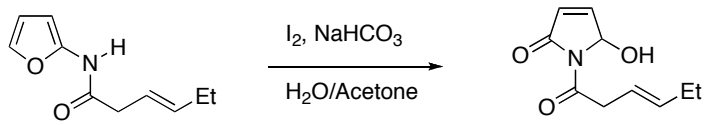
110 **111**

1-(2-(1-Acetyl-1*H*-indol-3-yl)acetyl)-5-hydroxy-1*H*-pyrrol-2-(5*H*)-one (111). To a stirred solution of **110** (150 mg, 0.532 mmol) in acetone/H_2O (20/1, 25.2 mL) at 0 ^oC 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 ^oC 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 ^oC; IR (thin film) 3441, 2925, 1737, 1698, 1451, 1373, 1254, 1219, 1130, and 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.



112 **113**

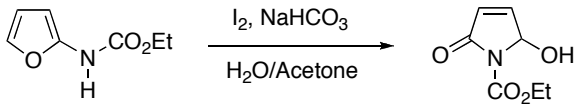
1-(3,3-Dimethoxypropanoyl)-5-hydroxy-1*H*-pyrrol-2(5*H*)-one (113). To a stirred solution of compound **112** (400 mg, 2.0 mmol) in acetone/H_2O (18/1, 34 mL) at 0^oC was added $NaHCO_3$ (1.01 g, 12.0 mmol) and the reaction mixture was stirred for 10 min. A sample of iodine (1.52 g, 6.0 mmol) was added in 3 portions and the mixture was stirred at 0 ^oC 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, $CDCl_3$) δ 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, $CDCl_3$) δ 40.1, 53.1, 53.4, 81.5, 100.3, 127.7, 147.8, 167.7 and 169.8.



114 **115**

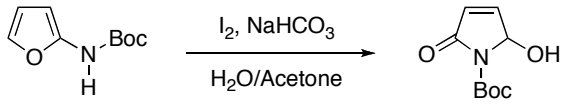
(*E*)-1-Hex-3-enoyl-5-hydroxy-1*H*-pyrrol-2(5*H*)-one (115). To a stirred solution of compound **114** (200 mg, 1.12 mmol) in acetone/H_2O (18/1, 19 mL) at 0^oC was added $NaHCO_3$ (564 mg, 6.72 mmol) and the reaction mixture was stirred for 5 min. A sample of iodine (851 mg, 3.35 mmol) was added in 3 portions and the mixture was stirred at 0 ^oC 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, $CDCl_3$) δ 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, $CDCl_3$) δ 13.7, 25.8, 40.2, 82.2, 119.7, 128.7, 137.4, 147.6, 167.8, and 173.3.



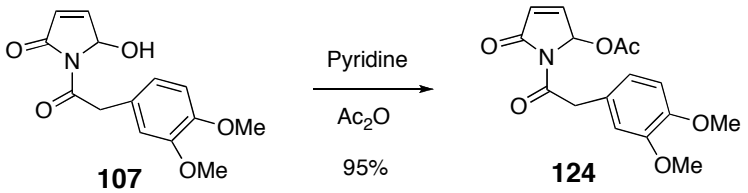
116 **117**

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_2O (18/1, 667 mL) at 0 ^oC 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 ^oC 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, $CDCl_3$) δ 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, $CDCl_3$) δ 14.6, 63.5, 82.4, 128.9, 146.7, 151.9, and 166.3.



97 **118**

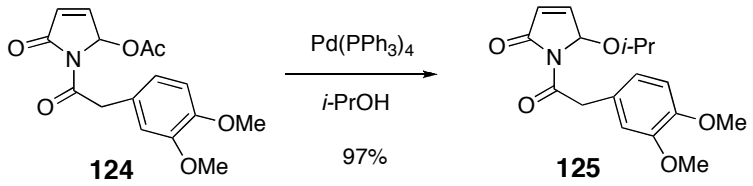
***tert*-Butyl 2-Hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (118).** To a stirred solution of **97** (366 mg, 2.0 mmol) in acetone/H_2O (18/1, 34 mL) at 0^oC was added $NaHCO_3$ (1.0 g, 12.0 mmol) and the reaction mixture was stirred for 10 min. A sample of iodine (1.52 g, 6.0 mmol) was added in 3 portions and the mixture was stirred at 0 ^oC 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 ^oC; 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.



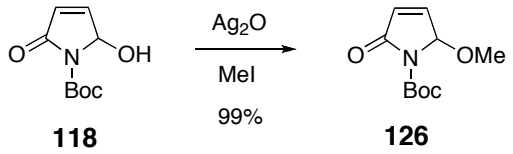
107 **124**

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_2O and extracted with EtOAc. The organic layer was washed with 1 *N* HCl and H_2O 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.

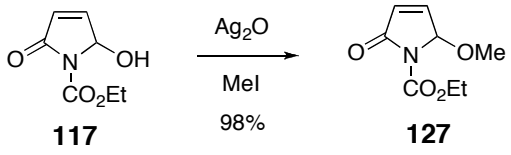


1-[2-(3,4-Dimethoxy-phenyl)-acetyl]-5-isopropoxy-1,5-dihydro-pyrrol-2-one (125). To a stirred solution of compound **124** (417 mg, 1.45 mmol) in *i*-PrOH (20 mL) was added $Pd(PPh_3)_4$ (84 mg, 0.073 mmol) and the reaction mixture was stirred at rt for 5 h. The mixture was then concentrated under reduced 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.



118 **126**

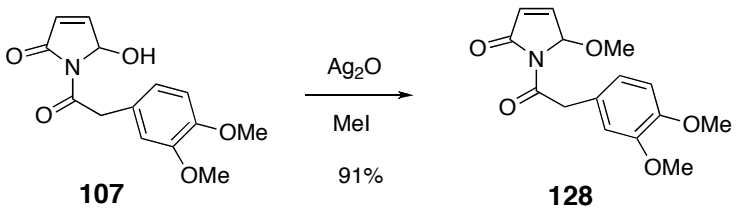
2-Methoxy-5-oxo-2,5-dihydro-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (126). To a stirred solution of compound **118** (240 mg, 1.21 mmol) in CH_2Cl_2 (10 mL) was added silver (I) oxide (1.4 g, 6.03 mmol) and iodomethane (3 mL, 48.2 mmol). The reaction mixture was stirred for 14 h at rt then filtered 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.7, 53.1, 82.9, 87.8, 128.4, 145.3, 148.7, 167.1.



117 **127**

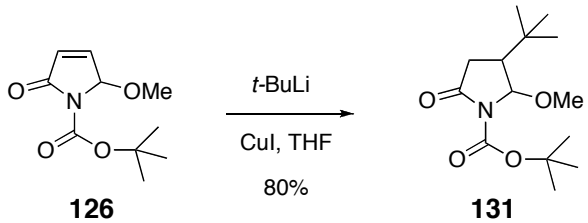
2-Methoxy-5-oxo-2,5-dihydro-pyrrole-1-carboxylic Acid Ethyl Ester (127). To a stirred solution of compound **117** (4.24 g, 24.8 mmol) in CH_2Cl_2 (206 mL) was added silver (I) oxide (28.7 g, 124 mmol) and iodomethane (61.9 mL, 992 mmol). The reaction mixture was stirred for 14 h at rt then filtered 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}; ^{1}H-NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 14.3, 53.6, 62.9, 88.1, 128.6, 145.9, 150.6 and 166.9.



107 **128**

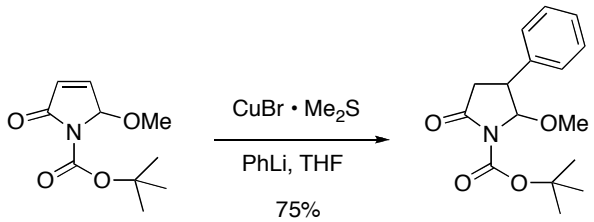
1-(2-(3,4-Dimethoxyphenyl)acetyl)-5-methoxy-1*H*-pyrrol-2(5*H*)-one (128). To a stirred solution of compound **107** (22 mg, 0.089 mmol) in CH_2Cl_2 (2 mL) was added silver (I) oxide (103 mg, 0.445 mmol) and iodomethane (0.22 mL, 3.56 mmol). The reaction mixture was stirred for 6 h at rt then filtered 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.



126 **131**

***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 ^{o}C was added *t*-BuLi (1.38

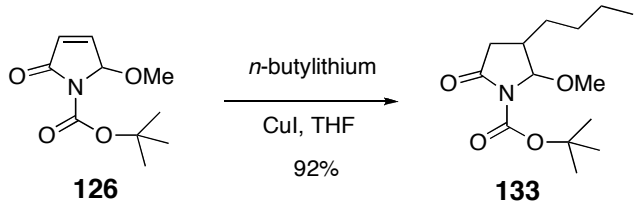
mL, 2.2 mmol, 1.6 M in pentane) dropwise. The reaction mixture was stirred at 0 °C for 1.5 h, then cooled to -78 °C and TMSCl (5.78 mL) was added. The reaction mixture was stirred for 5 min and a solution of compound **126** (60 mg, 0.282 mmol) in THF (1 mL) was slowly added. The mixture was stirred 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 NH_4Cl solution and extracted with Et_2O. The organic layer was washed with a saturated 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 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}; ^{1}H-NMR ($CDCl_3$, 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, 1 H, J = 18.4 and 9.2 Hz), 3.39 (s, 3H), and 5.20 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.0, 28.2, 31.9, 33.4, 47.6, 56.1, 83.5, 91.3, 150.1, and 174.2.



126 **132**

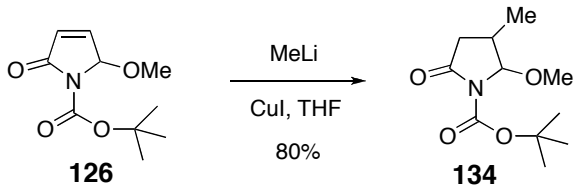
***tert*-Butyl 2-Methoxy-5-oxo-3-phenylpyrrolidine-1-carboxylate (132).** To a 0 °C stirred suspension of CuBr • Me_2S (1.01 g, 4.94 mmol) in THF (10 mL) was added phenyllithium (6.2 mL, 11.0 mmol, 1.8 M in cyclohexane) dropwise. The reaction mixture was stirred at 0 °C for 1.5 h, then cooled to -78 °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 ^{o}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 NH_4Cl solution and then extracted with Et_2O. The organic layer was washed with a saturated 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 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}; ^{1}H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 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 ^{o}C was added *n*-BuLi (14.7 mL, 36.75 mmol, 2.5 M in hexanes) dropwise. The reaction mixture was stirred at 0 ^{o}C for 1.5 h, then cooled to -78 ^{o}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 ^{o}C for 10 min, then warmed to rt and stirred for an additional 1

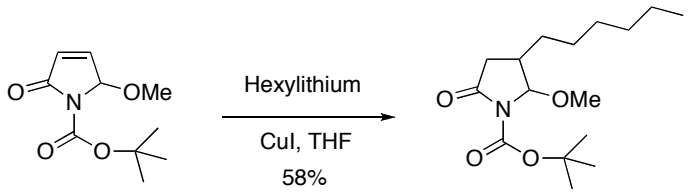
h. The mixture was quenched by the slow addition of saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and dried over $MgSO_4$, then filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (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}; ^{1}H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 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.



126 134

***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 Et_2O) 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 NH_4Cl and then extracted with Et_2O. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (20%

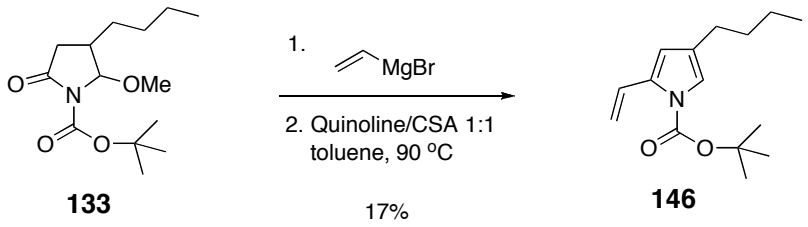
EtOAc/hexanes) to yield 61 mg (80%) of **134** as a colorless oil; IR (thin film) 2976, 2935, 1790, 1760, 1721, 1368, 1310, 1156, 1093 and 1023 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.07 (d, 3H, *J* = 7.2 Hz), 1.55 (s, 9H), 2.03 (d, 1H, *J* = 17.2 Hz), 2.30 (p, 1H, *J* = 14.8 and 7.6 Hz), 2.90 (dd, 1H, *J* = 25.2 and 8.0 Hz), 3.42 (s, 3H), and 4.98 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 18.6, 28.2, 32.4, 38.8, 56.7, 83.5, 95.3, 150.5, and 173.9.



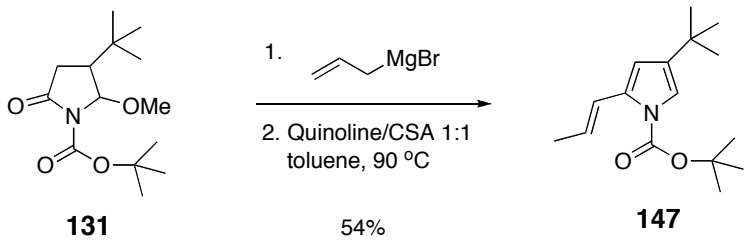
126 **135**

***tert*-Butyl 3-Hexyl-2-methoxy-5-oxopyrrolidine-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_4Cl solution and extracted with Et_2O. 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) δ 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

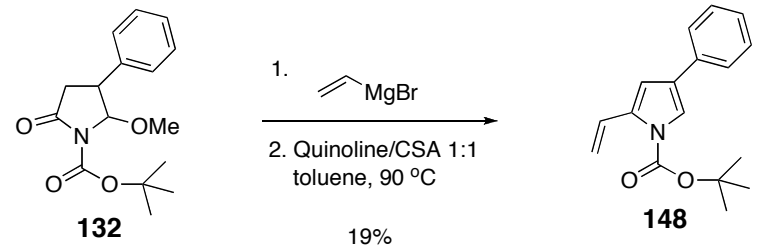
and 7.6 Hz), 3.40 (s, 3H), and 5.04 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.3, 22.8, 27.0, 28.2, 29.3, 31.8, 32.7, 37.1, 37.7, 56.5, 83.5, 94.1, 150.5, and 174.0.



***tert*-Butyl 4-Butyl-2-vinyl-1*H*-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_2O. 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) δ 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) δ 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)-1*H*-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 Et_2O) 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 $NaHCO_3$ solution and the aqueous layer was extracted with Et_2O. The organic layer was dried over $MgSO_4$, 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}; ^{1}H-NMR ($CDCl_3$, 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-1*H*-pyrrole-1-carboxylate (148).** To a -78 ^{o}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 ^{o}C for 0.5 h and at 0 ^{o}C for 2 h. The reaction mixture was quenched with a saturated $NaHCO_3$ solution and the aqueous layer was extracted with Et_2O. The organic layer was dried over $MgSO_4$, 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 ^{o}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}; ^{1}H-NMR ($CDCl_3$, 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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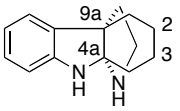
Chapter 2:

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

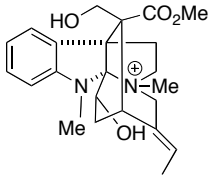
Introduction

Nitrogenous natural products containing the highly congested pentacyclic 1,2,3,4-tetrahydro-9*a*,4*a*-(iminoethano)9*H*-carbazole ring system **(149)** have been isolated from a variety of sources (Figure 2-1).[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 *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.[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.

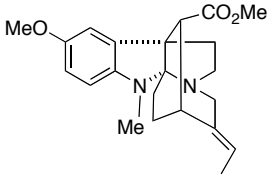
Figure 2-1: Alkaloids Containing the 1,2,3,4-tetrahydro-9*a*,4*a*-(iminoethano)9*H*-carbazole Ring System



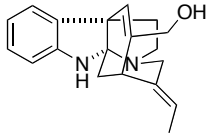
149



150; echitamine



151; vincorine

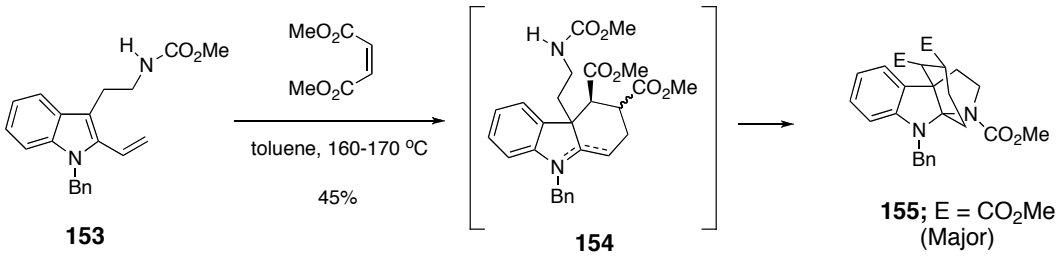


152; minfiensine

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

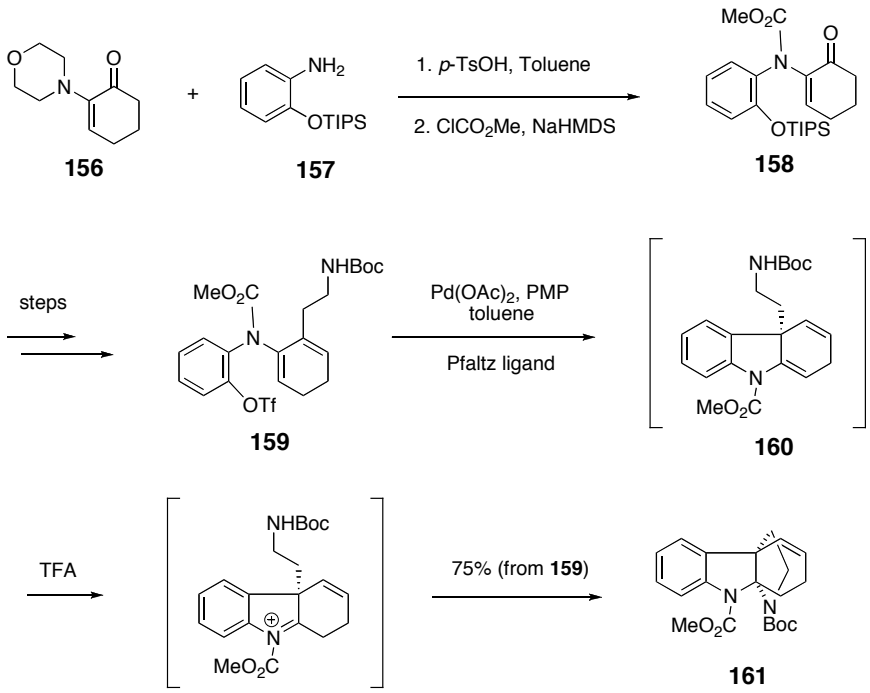
To date, the only known approach to the akuammiline alkaloids was reported by Levy and coworkers (Scheme 2-1).[4] Starting from 2-vinylindole **153**, its Diels-Alder cycloaddition with dimethyl maleate led to the iminium/enamine intermediate **154**, which upon further heating resulted in the formation 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.[5] 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.[6] 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-9*a*,4*a*-(iminoethano)9*H*-carbazole ring system (Scheme 2-2).[7] Starting from enamine **156** and

Scheme 2-2: Overman's Route to the Minfiensine Core



Pfaltz ligand = *(S)*-4-*tert*-butyl-2-[2-(diphenylphosphinyl)phenyl]-4,5-dihydrooxazole

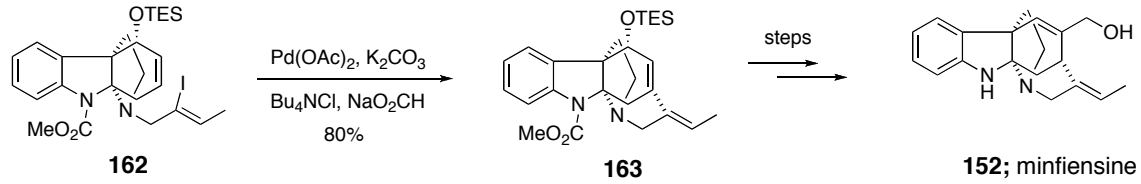
aniline **157**, formation of the key Heck cyclization precursor **158** was made possible through an acid-catalyzed transamination sequence. Treatment of this substrate with

$Pd(OAc)_2$ 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).[8] 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.

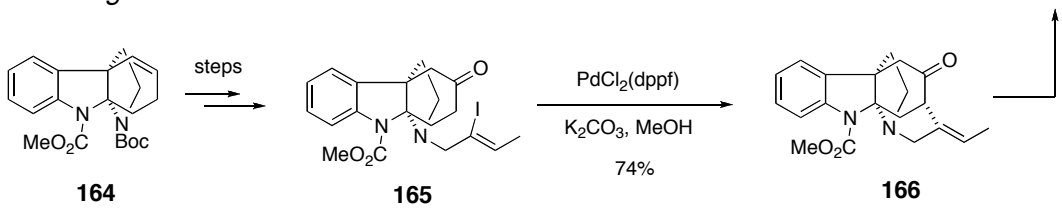
Scheme 2-3: Overman's End-Game strategies Toward Minfiensine

First generation route to minfiensine



162 **163** **152;** minfiensine

Second generation route to minfiensine

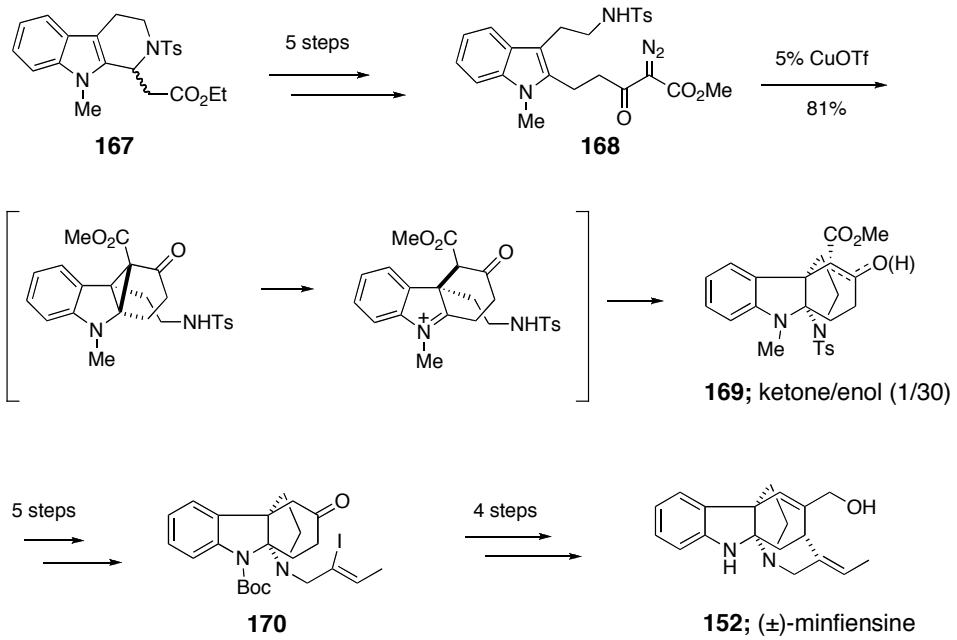


164 **165** **166**

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.[9] 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.

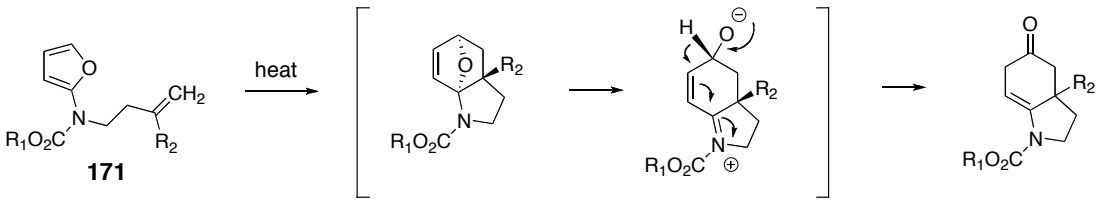
The IMDAF Cycloaddition/Rearrangement Cascade of 2-Amidofurans

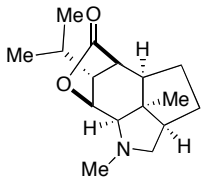
A significant portion of the furan-based research in the Padwa laboratories has involved the utilization of the Intramolecular Diels-Alder reaction of Furans (IMDAF). The IMDAF cycloaddition/rearrangement sequence (Scheme 2-5) represents a useful strategy for generating tetrahydroindolinones present in a number of natural products.[10,11,12] Specifically, this sequence provides for a ready route to functionalized tetrahydroindolinones containing a variety of R_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[10] **(174)** and lycorane **(175)**.[13]

The IMDAF reaction has also been utilized by the Padwa group with a variety of aryl substituents for the R_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**)**.[11] One of the primary challenges of generating these alkaloids involves the formation of the sterically-congested quaternary carbon stereocenter C_{3a}. Indeed, the IMDAF cycloaddition/rearrangement cascade sequence allowed for facile formation of

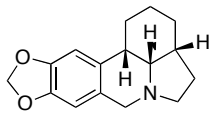
this stereocenter, giving rise to the desired tetrahydroindolinone skeleton which was then converted in several additional steps to (±)-mesembrane **(178)** and (±)-crinane **(181)**,

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





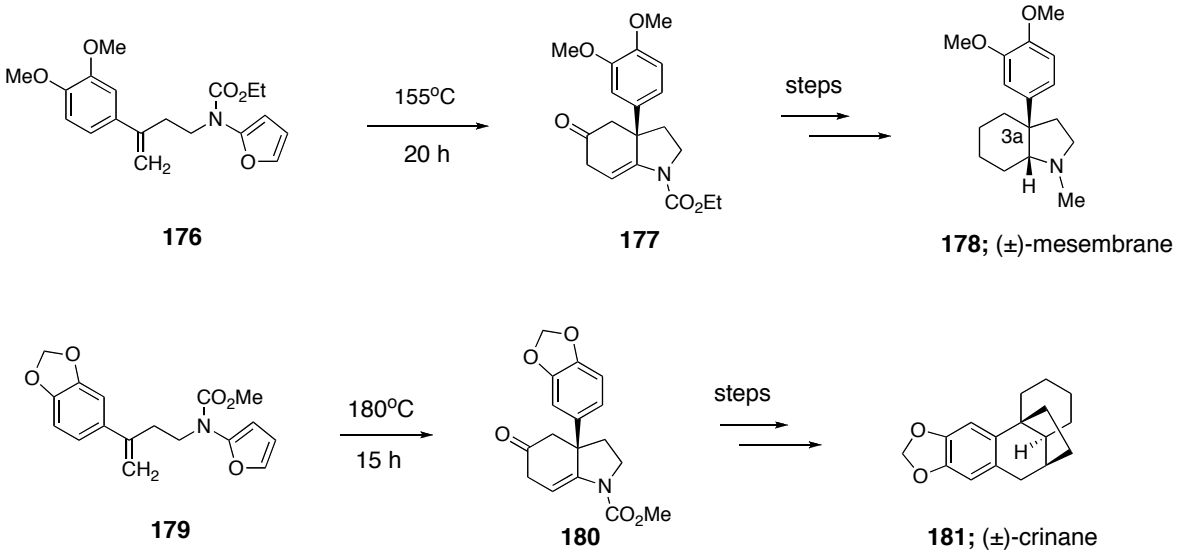
174; dendrobine



175; lycorane

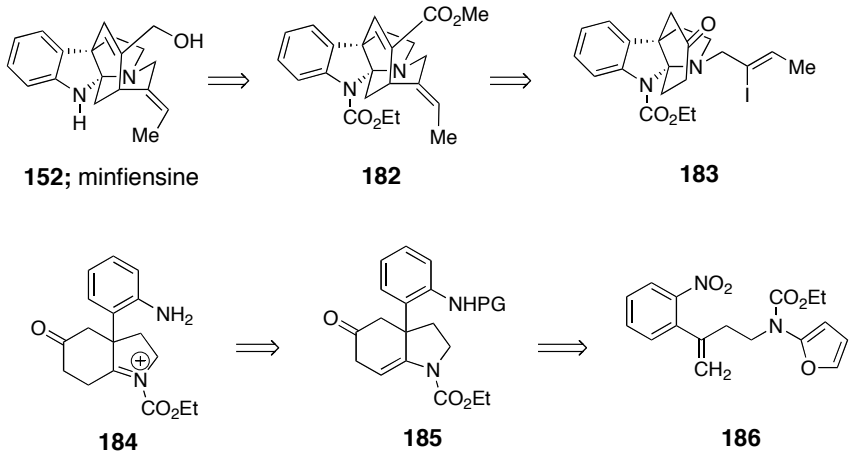
respectively. As a consequence of the efficient IMDAF method for preparing the sterically-congested stereocenter of the hexahydroindoline core structure, as well as the general shortage of methods for accessing the 1,2,3,4-tetrahydro-9*a*,4*a*-(iminoethano)9*H*-carbazole core structure found in (±)-minfiensine **(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



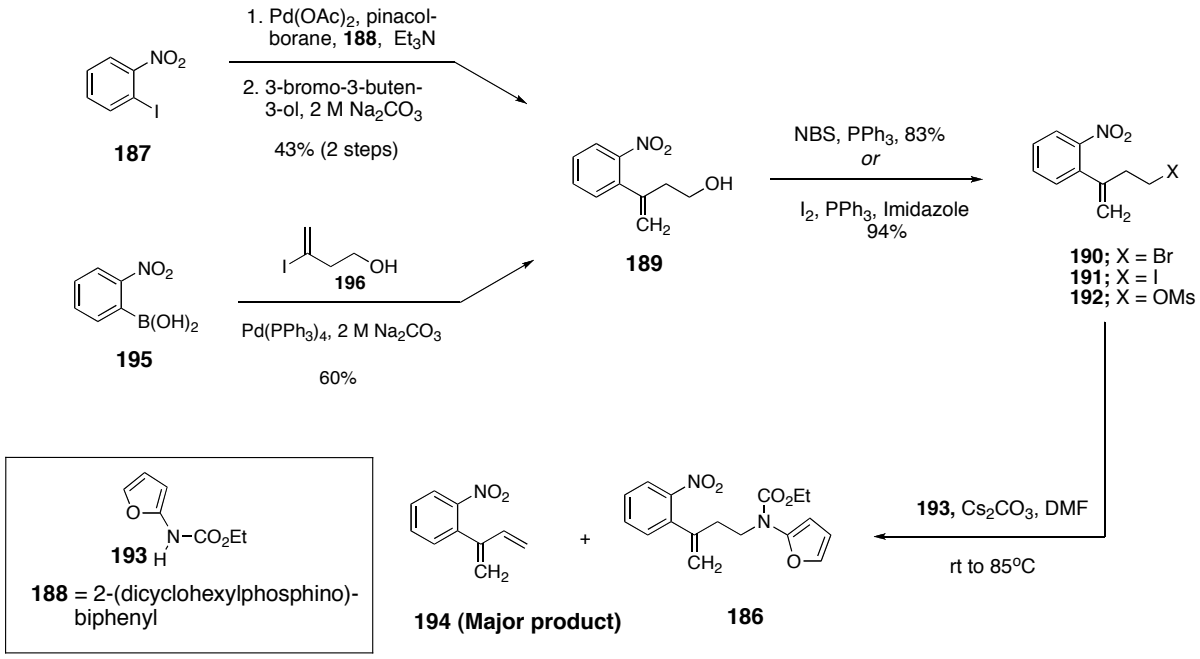
(**186,** Scheme 2-7). Additionally, upon treatment with acid, the resulting enamine/aniline intermediate **185** was expected to undergo an intramolecular iminium ion cyclization to generate the desired core structure **183**. This approach would not only provide rapid access to **183** but this intermediate 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.[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[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 asociated 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.[16] Thus, iodide **196** was coupled with the commercially available 2-nitrophenylboronic acid **(195)** to give **189** in 60% yield.[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 PPh_3 and NBS. While this transformation occurred in good yield, treatment of the resulting bromide **190** with furanyl carbamate **193** in the presence of Cs_2CO_3 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 (I_2, PPh_3, and imidazole), also led to significant amounts of the elimination byproduct **194**.

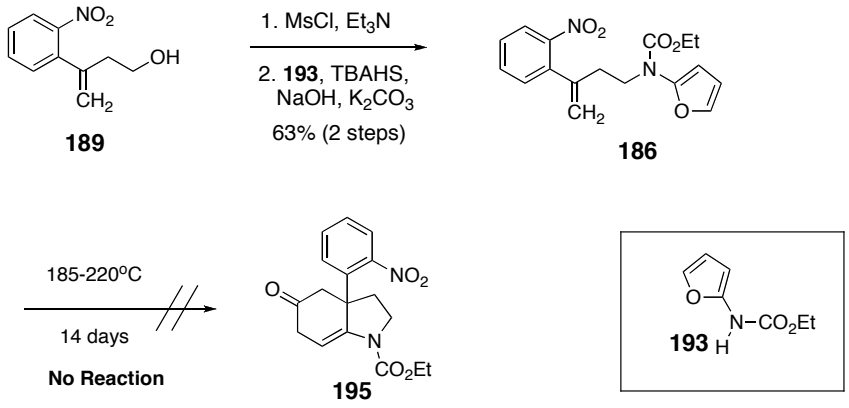
Scheme 2-8: Routes for Accessing the Amidofuran Precursor



In an attempt to avoid the formation of the undesired elimination byproduct, alcohol **189** was converted under standard conditions (MsCl, Et_3N) 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 ^{o}C.

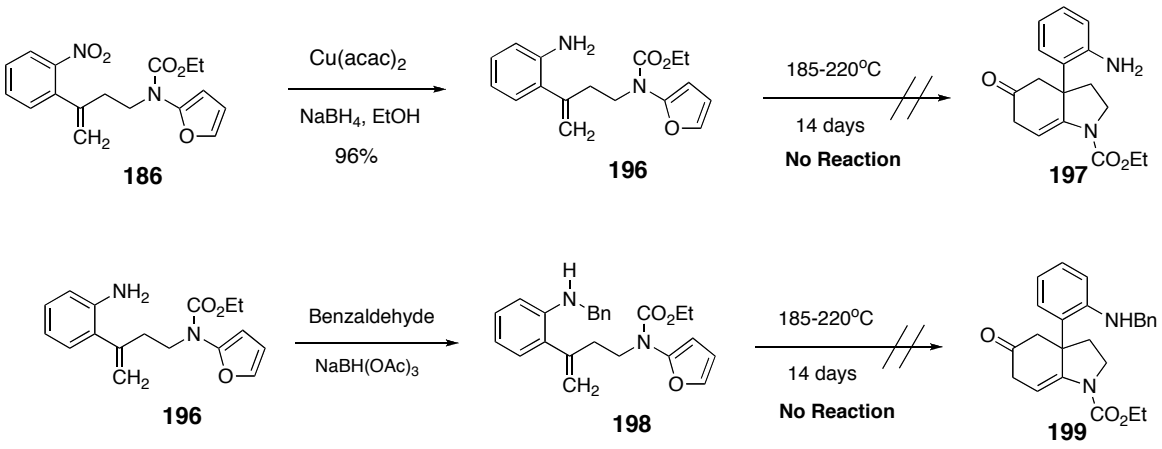
Scheme 2-9: Amidofuran Formation and Preliminary IMDAF Cycloaddition Results



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[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[18] ($Cu(acac)_2$ and $NaBH_4$ in EtOH) and this cleanly provided the desired aniline intermediate **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 **186.** Having aniline **196** on hand, we next decided to alter the electronics of the anilino group by the installation of a benzyl *N*-protecting group. Once again, cycloaddition was still not observed upon heating the furanyl carbamate precursor **198** at 220 °C.

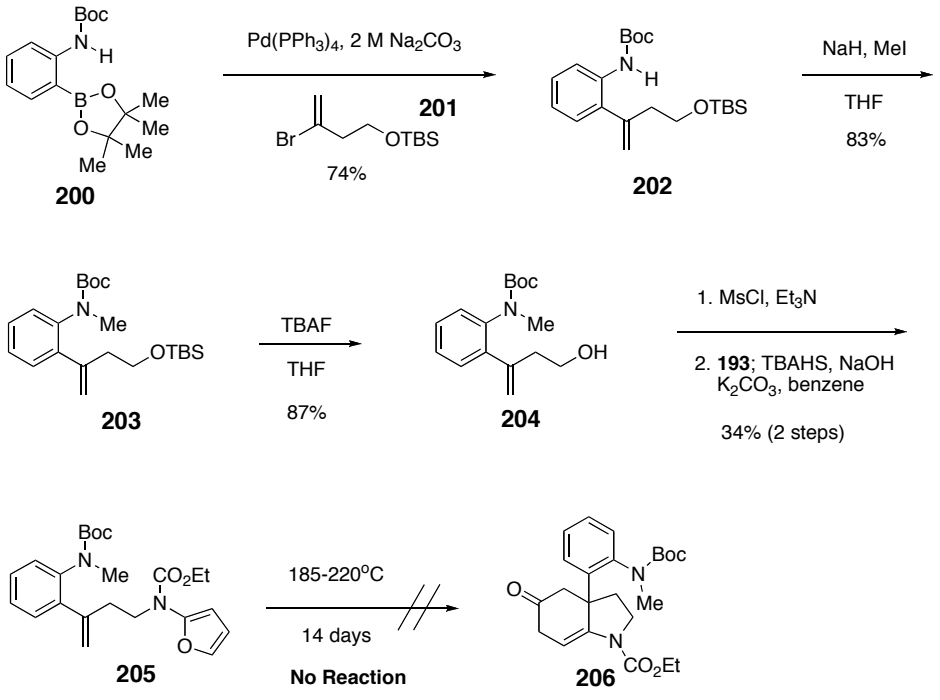
Scheme 2-10: Synthesis of Aniline and Benzylamine Substrates and Attempted IMDAF Cycloaddition



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 **205** was synthesized in five steps starting from the commercially available 2-(*N*-Boc-amino)phenylboronic acid pinacol ester (**200**)

(Scheme 2-11). First, Suzuki cross coupling of **200** with the known silyl ether **201**[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_3N) 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 ^oC for 14 days.

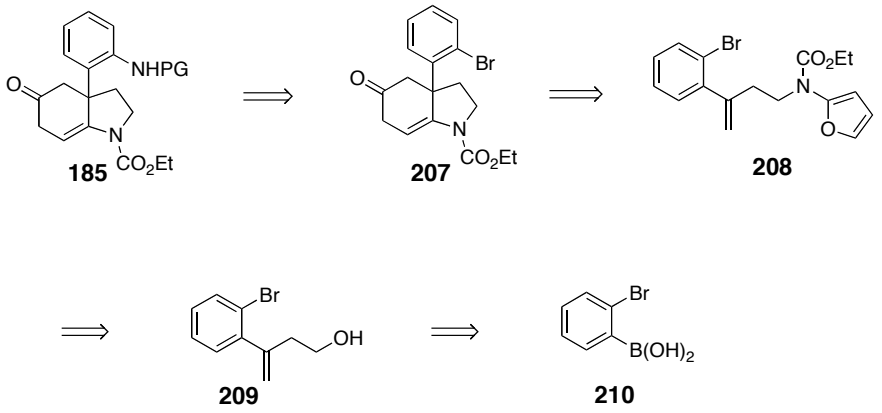
Scheme 2-11: Synthesis of the Disubsituted Amine IMDAF Cycloaddition Precursors



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[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[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

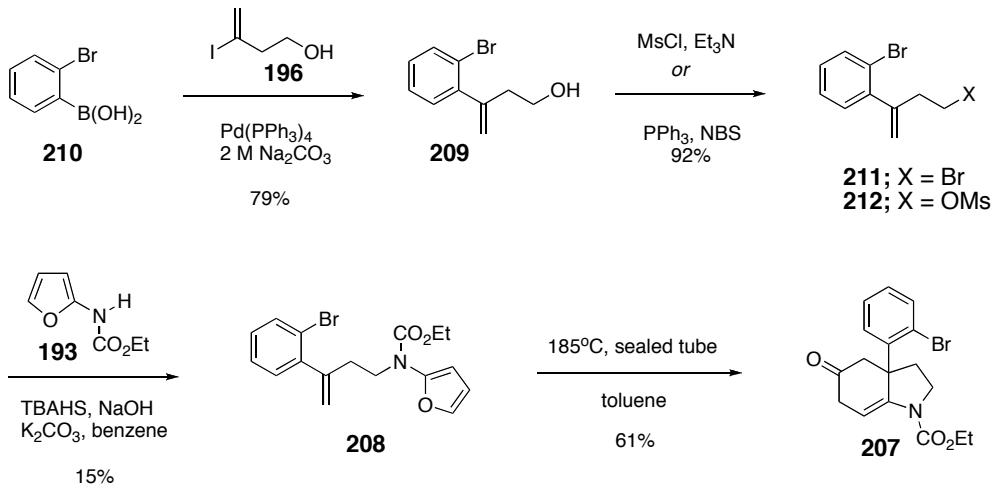
Scheme 2-12: Revised Retrosynthetic Strategy Utilizing IMDAF Cycloaddition of Aryl Bromide



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 ^{o}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 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[23] and this approach was found to be useful for the generation of a wide

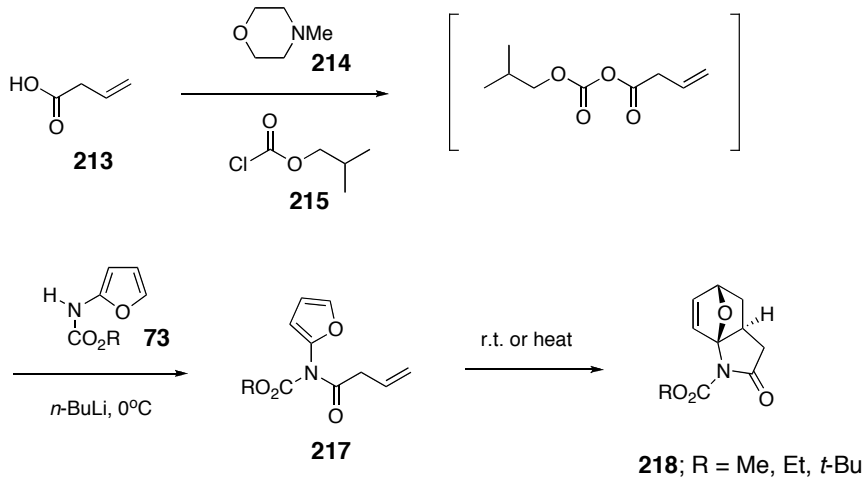
Scheme 2-13: Synthesis of the Amidofuran and IMDAF Formation of the Tetrahydroindolinone Core



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.

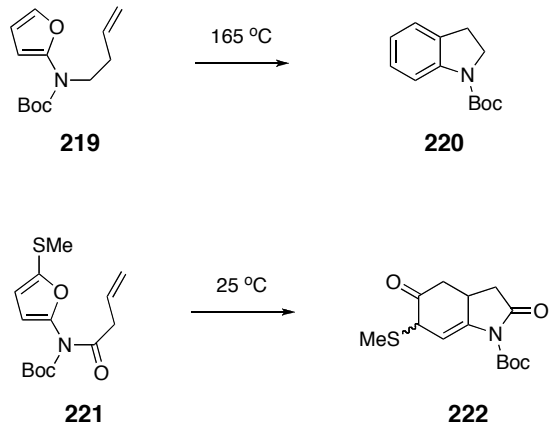
In addition to addressing the issue of poor alkylation yields in our synthetic plan, we also needed to increase the overall rate of the cycloaddition. Our group had previously found that a significant rate enhancement of the IMDAF cycloaddition reaction occurs when imidofurans are used instead of amidofurans for the reaction. Thus, it was previously found that amidofuran **219** underwent the cycloaddition/rearrangement reaction to give **220** upon heating at 165 ^{o}C, whereas the imidofuran system **221** underwent the IMDAF reaction to afford the related compound **222** at 25 ^{o}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



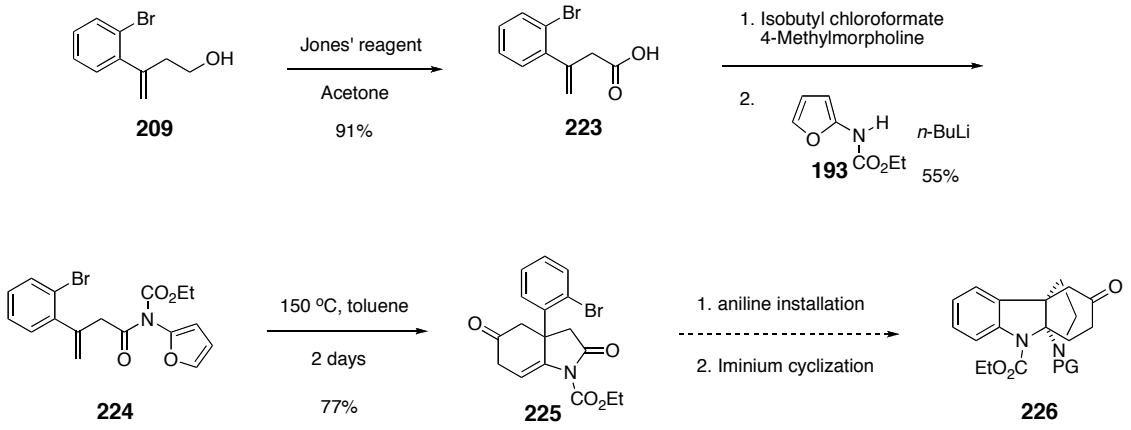
spatially places the olefinic π-bond in closer proximity to the furan ring, thereby decreasing the activation energy of the reaction and resulting in a significant rate enhancement.

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 **224** (Scheme 2-16). Oxidation of alcohol **209** with Jones' reagent led to the corresponding acid **223** in 91% yield. Treatment of this acid with isobutyl chloroformate and 4-methylmorpholine at 0 ^{o}C followed by the addition of the anion of furanyl carbamate **193** led to formation of the desired imidofuran cyclization precursor **224**. Following the trend previously seen in the Padwa labs, we discovered that heating a sample of imidofuran **224** for only 2 days at 150 ^{o}C cleanly provided the desired tetrahydroindolinone intermediate in 77% isolated yield.

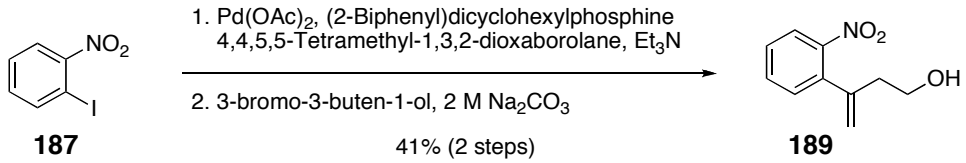
Scheme 2-16: Synthesis and Successful Diels-Alder Cycloaddition of Imidofuran



Thus, having discovered a more efficient route for generating the tetrahydroindolinone intermediate **225** by the IMDAF cycloaddition/rearrangement sequence, studies are currently underway to convert aryl bromide **225** into the desired aniline intermediate by making use of a metal-catalyzed coupling of the aryl bromide

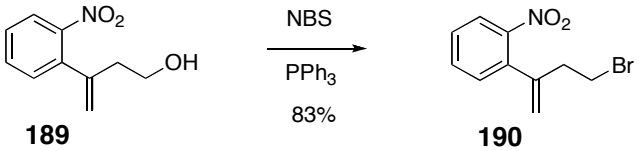
with various nitrogen sources. Based on the earlier results reported by the Overman and Qin groups, iminium ion cyclization of an aniline intermediate derived from **225** is expected to provide **226**, the core skeleton of minfiensine **(152).** This approach would not only provide a feasible route for completing the total synthesis, but would also allow for the generation of the 1,2,3,4-tetrahydro-9*a*,4*a*-(iminoethano)9*H*-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



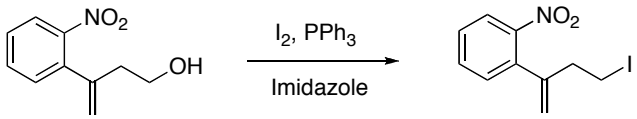
187 **189**

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 Et_3N (4.5 mL), (2-biphenyl)dicyclohexylphosphine (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 ^oC for 2 h, cooled to rt and 2 M Na_2CO_3 (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^oC for 19 h, then filtered over celite. To the filtrate was added brine and the aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, 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, 048, 911, 787, 762, and 721 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 40.5, 60.6, 117.6, 124.5, 128.4, 130.8, 132.8, 137.4, 143.2, and 149.1.



189 **190**

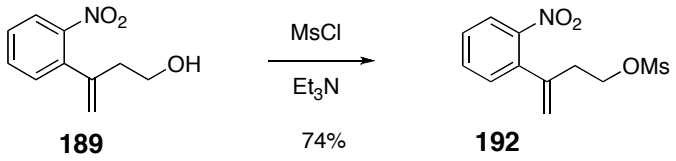
1-(4-Bromobut-1-en-2-yl)-2-nitrobenzene (190). To a stirred solution of alcohol **189** (68 mg, 0.352 mmol) in CH_2Cl_2 (45 mL) was added PPh_3 (111 mg, 0.422 mmol). The reaction mixture was cooled to 0°C and NBS (75 mg, 0.422 mmol) was added in one portion. The mixture was stirred at 0°C for 0.5 h and 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) δ 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) δ 30.7, 40.1, 117.4, 124.6, 128.7, 131.6, 133.2, 137.1, 144.0, and 148.3.



189 **191**

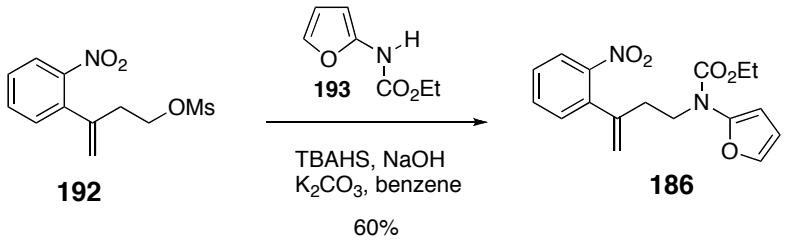
1-(4-Iodobut-1-en-2-yl)-2-nitrobenzene (191). To a stirred solution of alcohol **189** (40 mg, 0.207 mmol) in Et_2O/CH_3CN (4/1, 2.5 mL) was added PPh_3 (109 mg, 0.414 mmol) and imidazole (28 mg, 0.414 mmol). The reaction mixture was stirred for 10 min at rt, cooled to 0°C, and I_2 (105 mg, 0.414 mmol) 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_2O 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) δ 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) δ 3.0, 41.0, 116.9, 124.6, 128.7, 131.7, 133.2, 136.9, 145.4, and 148.3.

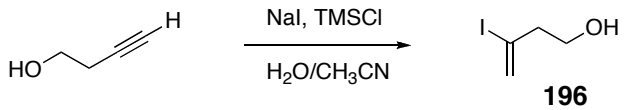


189 74% **192**

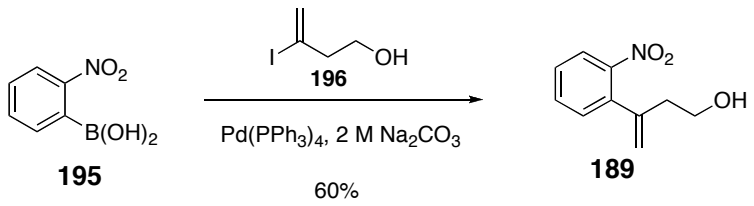
3-(2-Nitrophenyl)but-3-enyl Methanesulfonate (192). To a stirred solution of alcohol **189** (160 mg, 0.828 mmol) and methanesulfonyl chloride (0.07 mL, 0.911 mmol) in CH_2Cl_2 (20 mL) at 0^{o}C was added triethylamine (0.14 mL, 0.994 mmol) and the resulting reaction mixture was stirred for 1 h at 0^{o}C. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_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) δ 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) δ 36.5, 37.6, 67.7, 117.9, 124.6, 128.8, 131.4, 133.3, 137.0, 142.0, and 148.3.



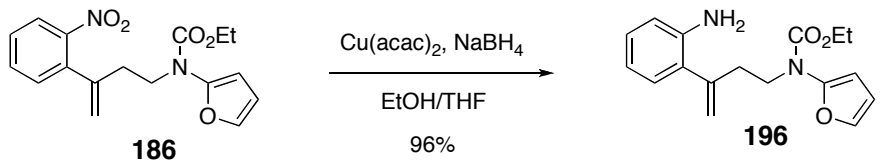
Ethyl Furan-2-yl(3-(2-nitrophenyl)but-3-enyl)carbamate (186). A solution of furan **193** (37 mg, 0.243 mmol), K_2CO_3 (80 mg, 0.480 mmol), tetrabutylammonium hydrogensulfate (15 mg, 0.044 mmol), and freshly powdered NaOH (33 mg, 0.823 mmol) in benzene (10 mL) was heated at reflux for 30 min. The mixture 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 Et_2O, and quenched with H_2O. The aqueous layer was extracted with Et_2O and the organic layer 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 (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}; ^{1}H-NMR ($CDCl_3$, 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). ^{13}C-NMR ($CDCl_3$, 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.



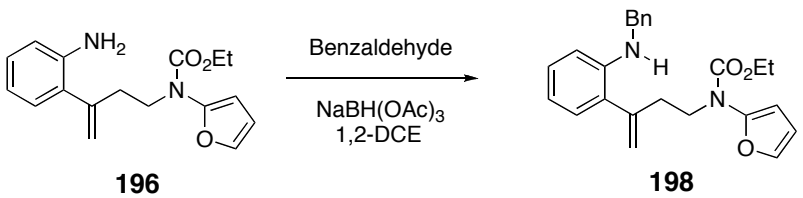
3-iodobut-3-en-1-ol (196). Prepared according to a known literature procedure.[16] ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.64 (t, 2H, *J* = 5.6 Hz), 3.77 (t, 2H, *J* = 6.0 Hz), 5.87 (s, 1H), and 6.19 (d, 1H, *J* = 1.2 Hz).



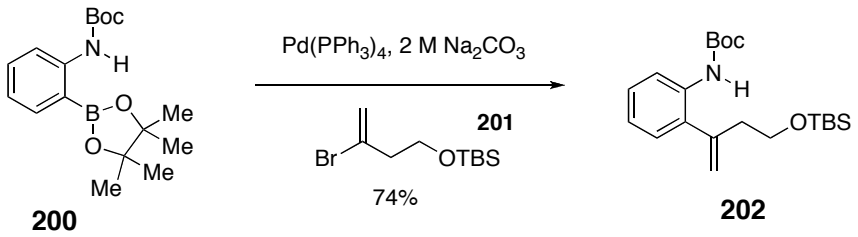
3-(2-Nitrophenyl)but-3-en-1-ol (189). To a stirred solution containing nitrophenylboronic acid **195** (598 mg, 3.58 mmol), iodide **196 (**592 mg, 2.98 mmol), benzene (30 mL), EtOH (15 mL), and 2 M aqueous Na_2CO_3 (15.2 mL) was added $Pd(PPh_3)_4$ (138 mg, 0.06 mmol) and the reaction mixture was heated to 65 ˚C for 12 h. After cooling to room temperature, the mixture was diluted with ether and washed with brine, dried over $MgSO_4$, 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, 048, 911, 787, 762, and 721 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 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), and 7.84-7.86 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 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) δ 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) δ 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.

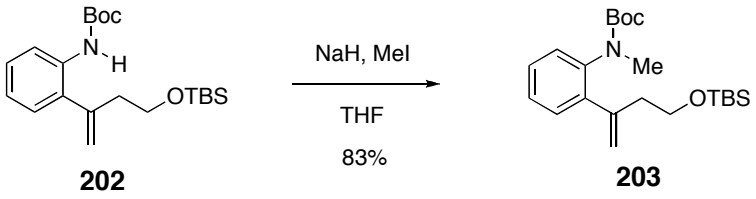


Ethyl 3-(2-(benzylamino)phenyl)but-3-enyl(furan-2-yl)carbamate (198). To a stirred solution of amine **196** (35 mg, 0.117 mmol) and benzaldehyde (0.012 mL, 12.4 mg, 0.117 mmol) in 1,2-dichloroethane (2 mL) was added $NaBH(OAc)_3$ (35 mg, 0.164 mmol) in one portion. The reaction mixture was stirred at 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) δ 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).



***tert*-Butyl 2-(4-(*tert*-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_2CO_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

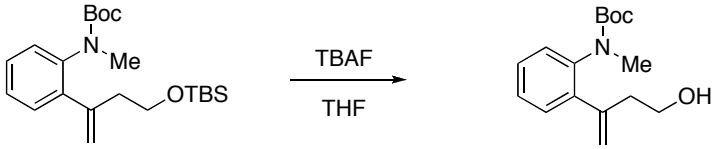
to 80 ˚C for 18 h then cooled to rt. A sample of Na_2SO_4 was added and the suspension was allowed to stand for 30 min. The mixture was filtered and concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography to provide 1.31 g (74%) of **202** as a colorless 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 $[C_{21}H_{36}NO_3Si]^+$: 378.24. Found: 378.24.



202 **203**

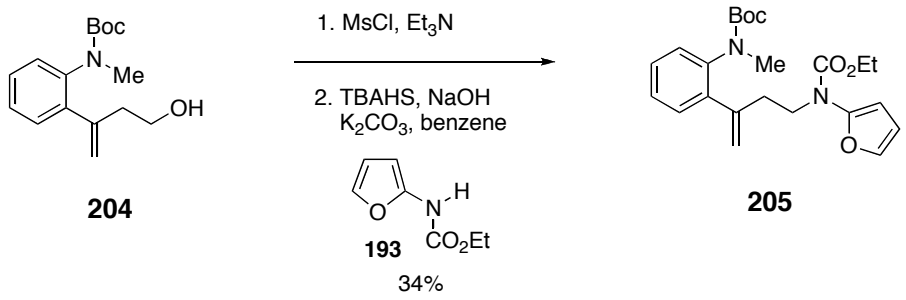
***tert*-Butyl 2-(4-(*tert*-Butyldimethylsilyloxy)but-1-en-2-yl)phenyl(methyl)carbamate (203)**. To a stirred solution of NaH (0.064 g, 1.6 mmol, 60% in mineral oil) in THF (10 mL) at 0 ˚C was added silyl ether **202** (0.4 g, 1.1 mmol) dropwise. After stirring for 0.5 h, MeI (0.1 mL, 1.6 mmol) was added dropwise. The reaction mixture was allowed to stir for 12 h and was then quenched with H_2O and extracted with CH_2Cl_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) δ -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 $[C_{22}H_{38}NO_3Si]^+$: 392.25. Found: 392.26.



203 **204**

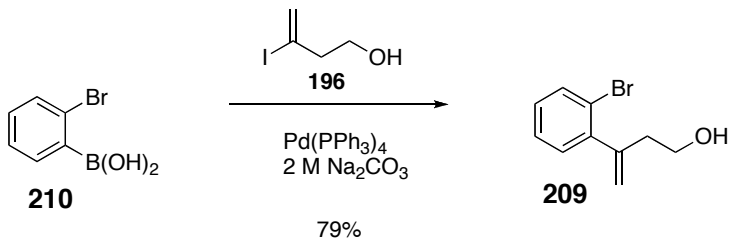
***tert*-Butyl 2-(4-Hydroxybut-1-en-2-yl)phenyl(methyl)carbamate (204)**. To a stirred solution of **203** (0.279 g, 0.71 mmol) in THF (5 mL) at 0 ˚C was added dropwise TBAF (2.14 mL, 2.14 mmol, 1.0 M in THF). The reaction mixture was allowed to stir at room temperature for 18 h and was then diluted with H_2O and extracted with CH_2Cl_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) δ 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) δ 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.



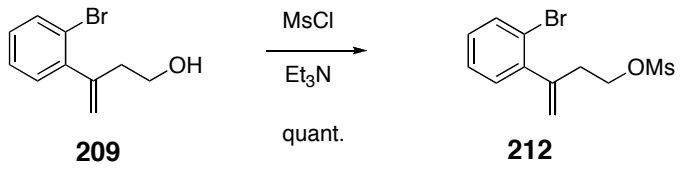
Ethyl 3-(2-(tert-Butoxycarbonyl)methylamino)phenyl) but-3-enyl(furan-2-yl)carbamate (205). To a stirred solution of alcohol **204** (0.136 g, 0.49 mmol) and Et_3N (0.09 mL, 0.64 mmol) in CH_2Cl_2 (5 mL) at 0 ˚C was added methanesulfonyl chloride (0.05 mL, 0.59 mmol). The mixture was stirred at room temperature for 12 h, diluted with H_2O, and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, 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_2CO_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^{o}C for 1 h. The mixture was cooled to room temperature and quenched with H_2O. The aqueous phase was extracted with CH_2Cl_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) δ 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

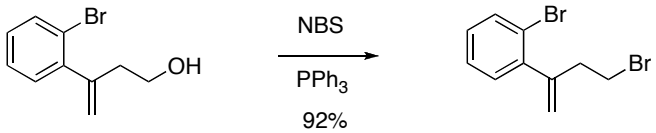
(brs, 1H), 6.33 (s, 1H), 7.06 (d, 1H, J = 6.8 Hz), and 7.11-7.32 (m, 4H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.6, 28.3, 34.9, 37.3, 38.1, 48.1, 62.3, 80.0, 111.1, 111.5, 116.9, 127.1, 128.2, 128.4, 128.7, 129.7, 130.1, 138.8, 140.0, 141.0, 145.4, and 155.1.



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_2CO_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^{o}C for 14 h, cooled to rt, diluted with Et_2O, 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, 1024, 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.



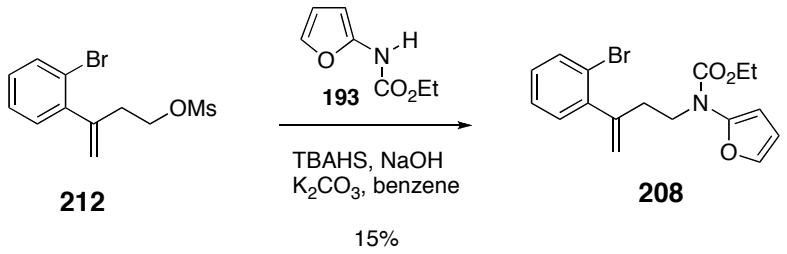
3-(2-Bromophenyl)but-3-enyl methanesulfonate (212). To a stirred solution of alcohol **209** (186 mg, 0.82 mmol) and methanesulfonyl chloride (0.07 mL, 0.9 mmol) in CH_2Cl_2 (20 mL) at 0°C was added Et_3N (0.14 mL, 0.98 mmol) and the resulting mixture was stirred for 0.5 h. The mixture was diluted with H_2O and extracted with CH_2Cl_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) δ 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) δ 36.3, 37.7, 67.7, 119.1, 122.1, 127.7, 129.3, 130.8, 133.1, 142.3, and 144.6.



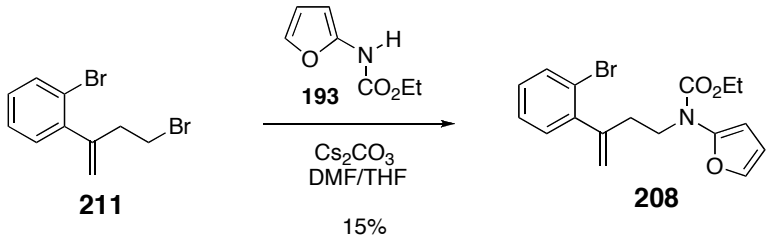
209 **211**

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_2Cl_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) δ 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 =

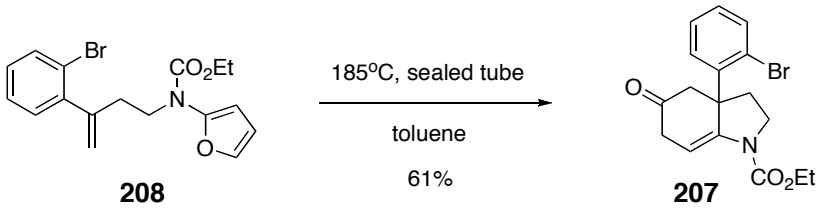
7.6 and 2.0 Hz), 7.27-7.31 (m, 1H), 7.56 (dd, 1H, J = 8.0 and 0.8 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 30.9, 40.0, 118.4, 122.1, 127.5, 129.2, 131.0, 133.0, 142.3, and 146.7.



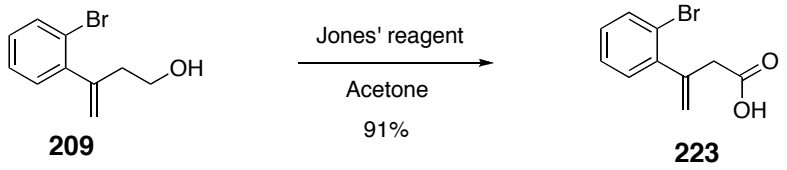
Ethyl 3-(2-Bromophenyl)but-3-enyl(furan-2-yl)carbamate (208). A solution of furan **193** (37 mg, 0.243 mmol), K_2CO_3 (88 mg, 0.533 mmol), tetrabutylammonium hydrogen sulfate (16 mg, 0.047 mmol), and freshly powdered NaOH (33 mg, 0.825 mmol) in benzene (10 mL) was heated at reflux for 30 min. The mixture 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^{o}C for 1 h. The mixture was cooled to room temperature, diluted with Et_2O, and quenched with H_2O. The aqueous layer was extracted with Et_2O, 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_2CO_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 ^oC for 30 min, cooled to rt, quenched with H_2O, and extracted with Et_2O. 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) 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 155.07.



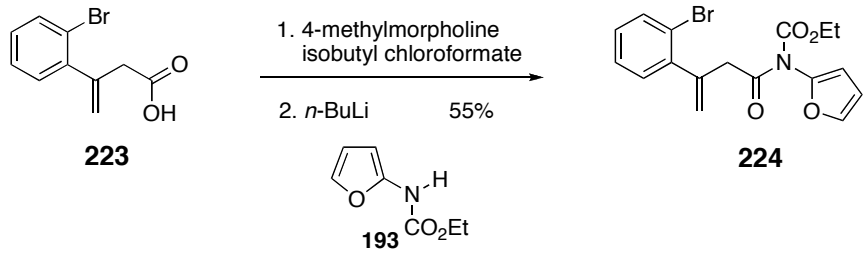
Ethyl 3a-(2-Bromophenyl)-5-oxo-2,3,3a,4,5,6-hexahydro-1*H*-indole-1-carboxylate (207). A sample of furanyl carbamate **208** (12 mg, 0.033 mmol) in toluene (1.5 mL) was heated in a sealed tube at 185°C for 6 days. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. 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 $^{-1}$; ^{1}H-NMR ($CDCl_3$, 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), ^{13}C-NMR ($CDCl_3$, 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 [($C_{17}H_{18}BrNO_3$) + H^+]: 364.0470. Found: 364.0546.



209 **223**

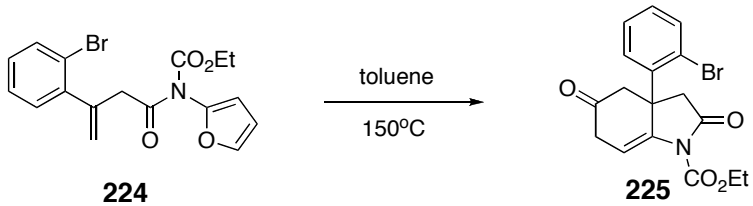
3-(2-Bromophenyl)but-3-enoic acid (223). To a stirred solution of alcohol **209** (150 mg, 0.661 mmol) in acetone (27 mL) at 0°C was added freshly prepared Jones' reagent (1.32 mL, 1.32 mmol, 1.0 M). The resulting solution was stirred at 0°C for 1 h, then warmed to rt and stirred for an additional 1 h. The mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, 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) δ 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) δ 42.1, 121.1, 122.2, 127.8, 129.6, 131.7, 133.2, 142.2, 142.6, and 177.0.



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_2O 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) δ 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) δ 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.



224 **225**

Ethyl 3a-(2-bromophenyl)-2,5-dioxo-2,3,3a,4,5,6-hexahydro-1*H*-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°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) δ 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) δ 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.

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Chapter 3

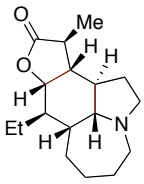
Studies Towards the Generation of

Morphine via IMDAF Reactions of Benzofuran Dienophiles

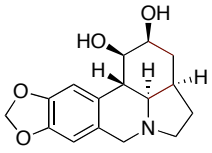
Introduction

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*,[1] *stemona*,[2] and *amaryllidaceae*[3] 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.

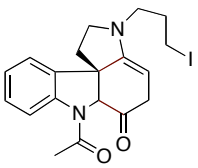
Figure 3-1: Natural Products Accessible *via* the IMDAF Reaction of 2-amidofurans



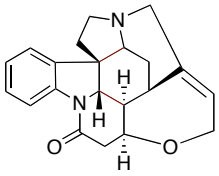
227; (±)-Stenine
Stemona alkaloids



228; (±)-*epi*-Zephyranthine
Amaryllidaceae alkaloids



229; Aspidosperma/Strychnos Core

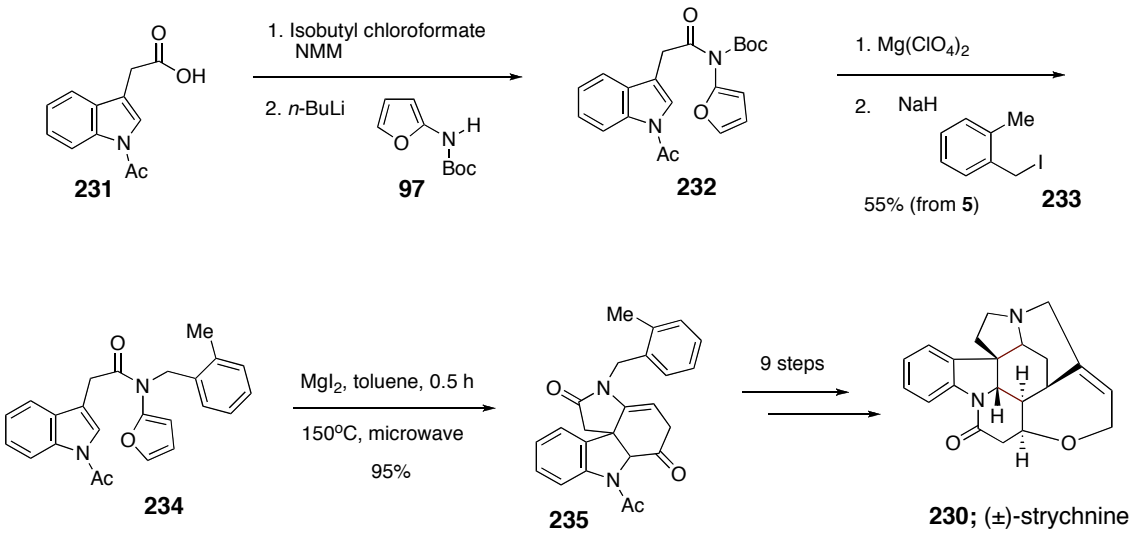


230; (±)-Strychnine

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).[4] The key

cycloaddition precursor **234** was generated by the acylation of furanyl carbamate **97** with the mixed anhydride of 2-(1-acetyl-1*H*-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.

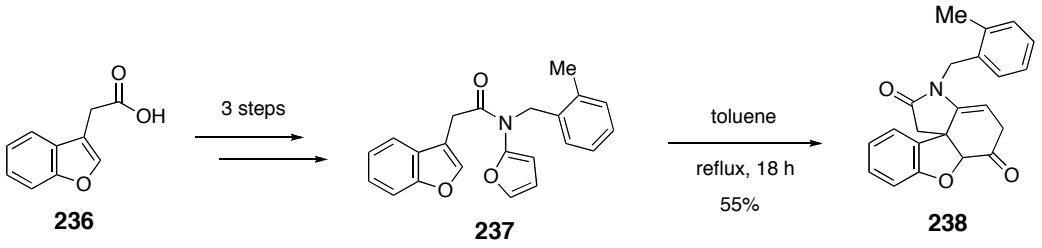
Scheme 3-1: Indole IMDAF Cycloaddition Route to (±)-Strychnine



Having displayed the ability to rapidly generate numerous natural products[1] *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).[5] 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.

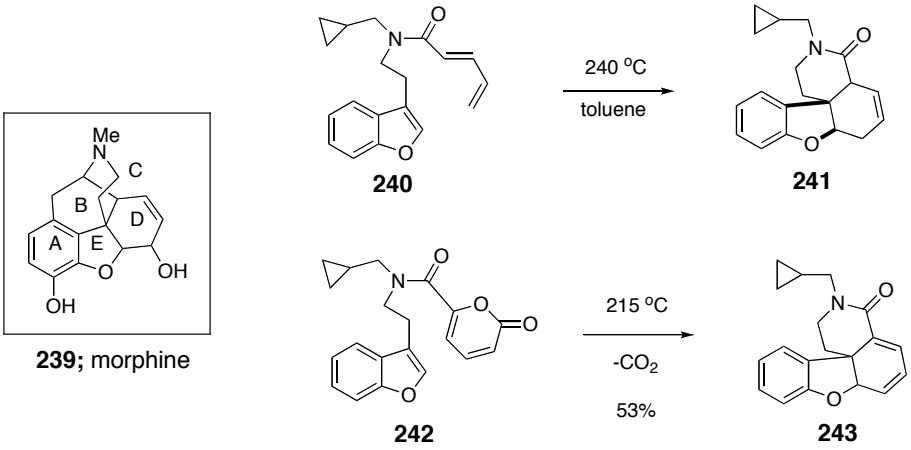
Scheme 3-2: IMDAF Cyloaddition/Rearrangement Reaction of 2-amidofurans with Benzofuran Dienophiles



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).[6] 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).[7] Specifically, Ciganek reported on the Diels-Alder cycloaddition of benzofuran **240**, which occurred at 240 ºC 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-

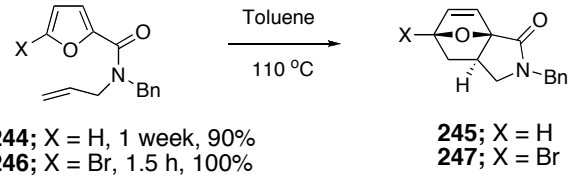
Scheme 3-3: Reported Benzofuran Diels-Alder Reactions Towards Morphine



unsubstituted analogs (**244,** Scheme 3-4).[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.[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).[8] Unfortunately, none of the desired

Scheme 3-4: IMDAF Cycloaddition Reactions of Halogen-Substituted Amidofurans

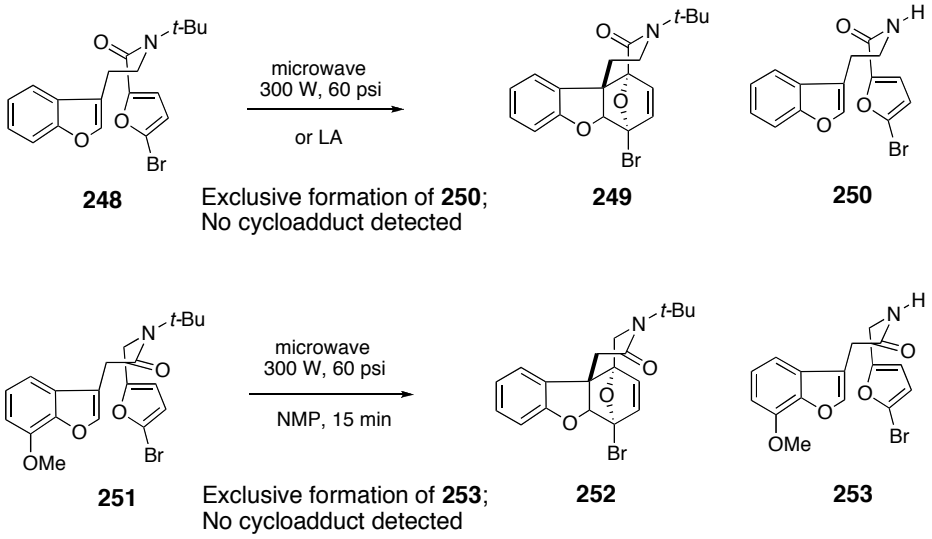


244; X = H, 1 week, 90%
246; X = Br, 1.5 h, 100%

245; X = H
247; X = Br

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



248 Exclusive formation of **250**; No cycloadduct detected **249** **250**

251 Exclusive formation of **253**; No cycloadduct detected **252** **253**

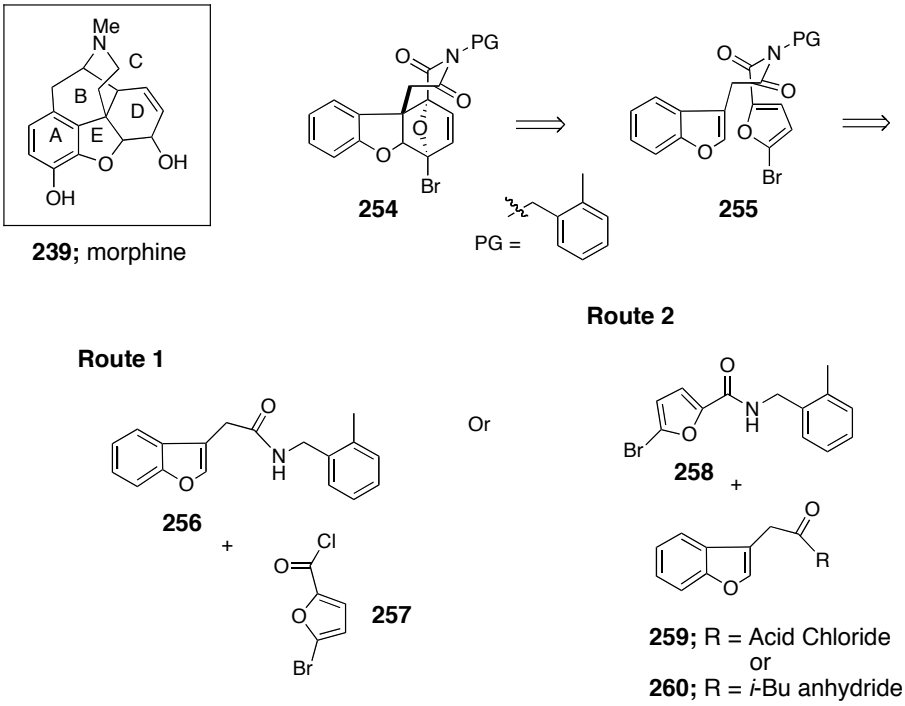
Results and Discussion

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

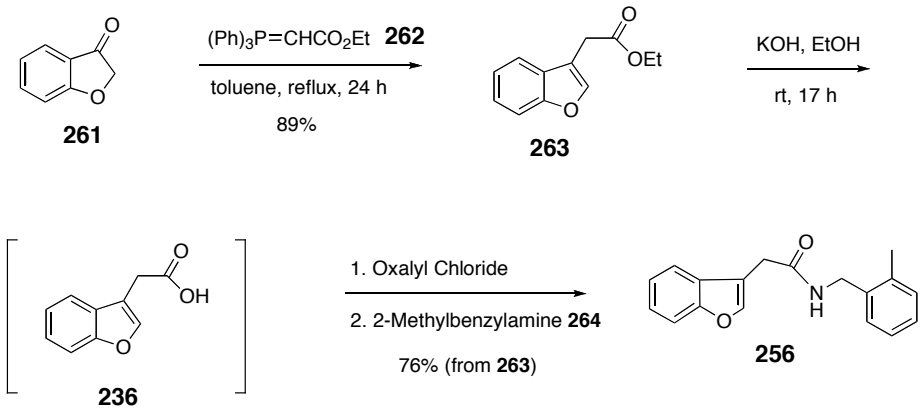
carbonyl group in the tether was affecting the cycloaddition efficiency, we decided to carry out the IMDAF reaction using imide **255**, with the intention of preparing the morphine core **254** (Scheme 3-6). We also decided to replace the thermally labile Boc protecting group with a more stable aryl 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.[4] 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



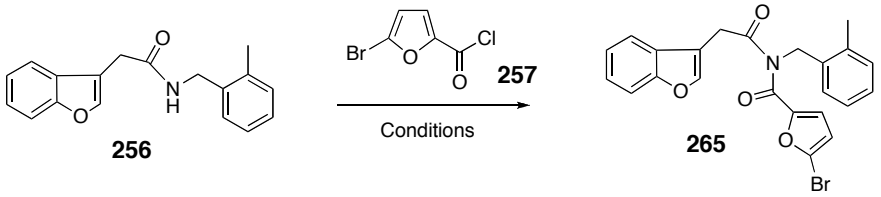
Our initial attempts to generate the desired cycloaddition precursor began with commercially available benzofuran-3(2*H*)-one (**261,** Scheme 3-7). Wittig olefination of **261** with carbethoxymethylene triphenylphosphorane (**262)** in toluene at 120ºC provided the desired ester intermediate **263** in 89% yield.[11] 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, K_2CO_3, and Cs_2CO_3 with temperatures ranging from 0 ºC to 120 ºC 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**.

Table 3-1: Conditions Tested for Amide Acylation

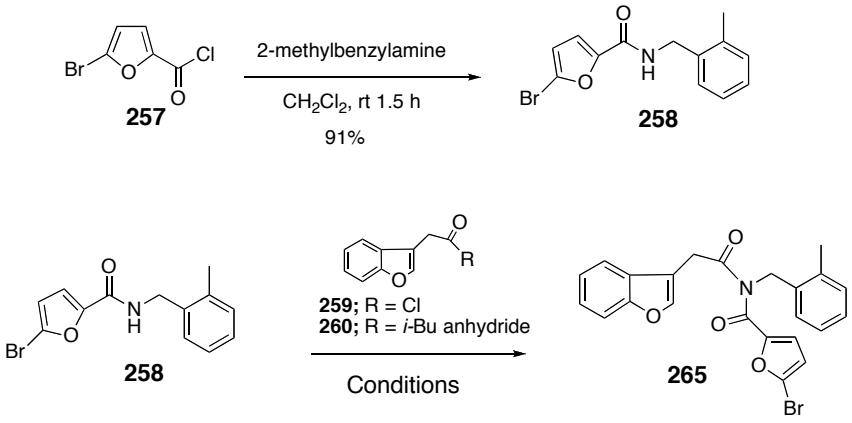


Entry	Base	Conditions	Result
1	NaH	THF, 0°C 1 h, then rt 2h	SM only
2	NaH	THF, rt 48 h, then reflux 20 h	SM only
3	none	Toluene, 24 h, reflux	SM only
4	none	THF, microwave, 70°C, 15 min	SM only
5	*n*-BuLi	THF, 0°C to rt, 8 h	messy
6	Et_3N	CH_2Cl_2, cat. DMAP, rt 8 h, then reflux 18 h	SM only
7	KHMDS	CH_2Cl_2, rt 24 h	SM only
8	K_2CO_3	DMF, rt 18 h, then reflux 24 h	SM, byproducts
9	Cs_2CO_3	CH_3CN, 85°C, 24 h	SM only

We therefore turned our attention to the alternate approach (Route 2) to prepare the desired cyloaddition 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, Et_3N, and LHMDS) and

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 Et_3N in a sealed tube overnight.

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

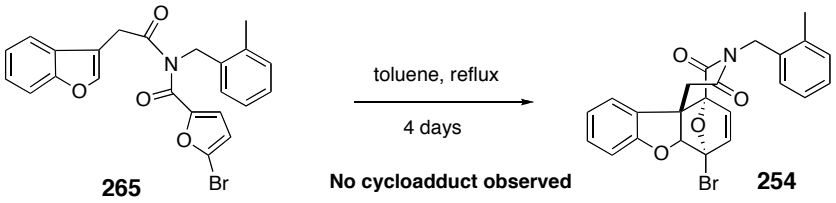


Entry	Base	Conditions	Result
1	NaH	Anhydride **260**; THF, rt 24 h, then reflux 18 h	SM only
2	Et_3N	Acid chloride **259**; CH_2Cl_2, Cat. DMAP, rt 18 h	SM only
3	LHMDS	Acid chloride **259**; THF, sealed tube, reflux 24 h	SM only
4	Et_3N	Acid Chloride **259**; benzene, reflux, 18 h	20% yield **265**

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.

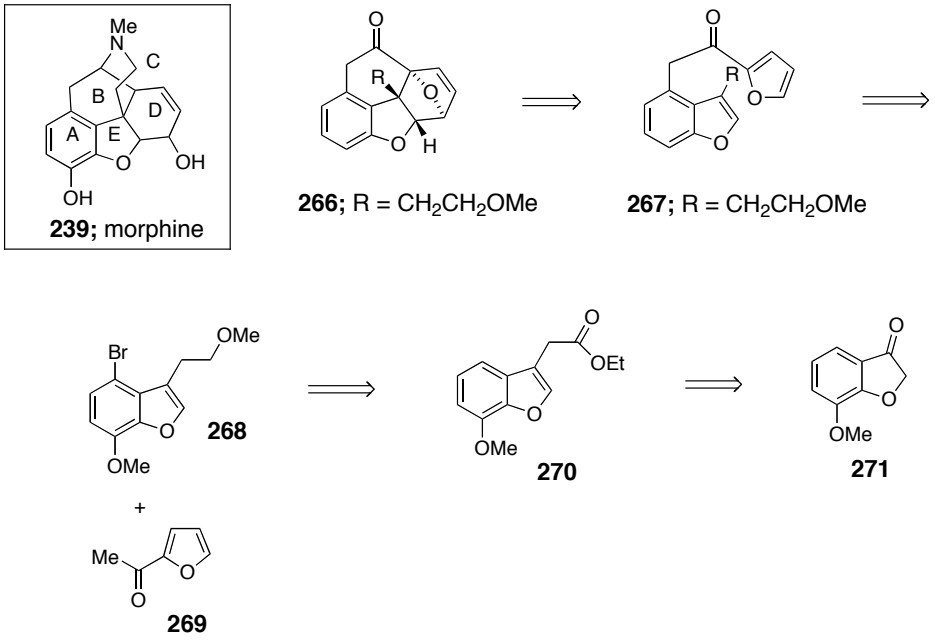
Scheme 3-8: Attempted IMDAF Cycloaddition Reaction



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 **267**, would occur to give cycloadduct **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 **268** and the anion derived from 2-acetylfuran. The functionalized benzofuran substrate **268** could be synthesized from the methoxy-directed bromination of the known benzofuran ester **270**.

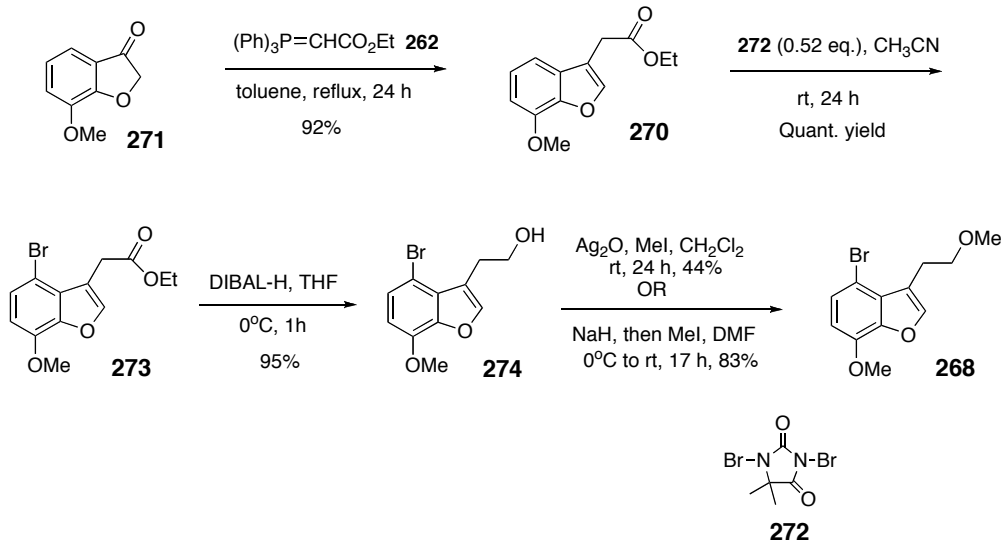
Scheme 3-9: Second Generation IMDAF Approach to Morphine



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(2*H*)-benzofuranone **(271)** with carbethoxymethylene triphenylphosphorane (**262**) in toluene at 120 ºC provided the desired ester intermediate **270**.[11] 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)**.[12] We were pleased to find that a modification of the Auerbach bromination conditions (0.52 eq. 1,3-DBMH, CH_3CN, 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 Ag_2O/MeI or NaH/MeI, which afforded methyl ester **268** in 44% and 83% yield, respectively.

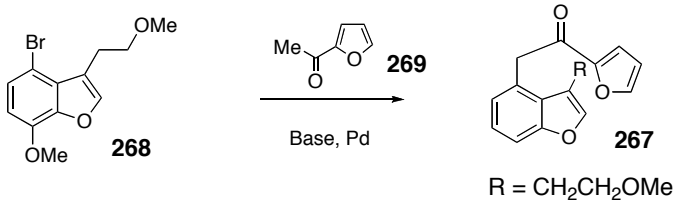
Scheme 3-10: Preparation of the Functionalized Benzofuran



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] Hartwig[14,15] and others[16] 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 $Pd(PPh_3)_4$. 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 ºC in a sealed tube using Cs_2CO_3 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 150ºC 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

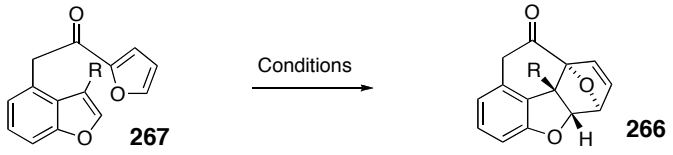


Entry	Base	Conditions	Result
1	KHMDS	$Pd(dba)_2$ (8 mol%), dppf (9 mol%), DMF, sealed tube, 150°C, 4 h	Trace amt. Product
3	Cs_2CO_3	$Pd(OAc)_2$ (4 mol%), PPh_3 (16 mol%), DMF, sealed tube, 150°C, 4 h	19% yield
4	Cs_2CO_3	$Pd(OAc)_2$ (6 mol%), PPh_3 (24 mol%), DMF, sealed tube, 150°C, 16 h	40% yield
5	Cs_2CO_3	$Pd(PPh_3)_4$ (6 mol%), DMF, sealed tube, 150°C, 16 h	24% yield

After developing the conditions necessary for formation of the cycloaddition precursor **267**, we tested the key cycloaddition step by heating **267** in toluene at 150ºC 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.[4] 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 MgI_2 and $EtAlCl_2$ 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



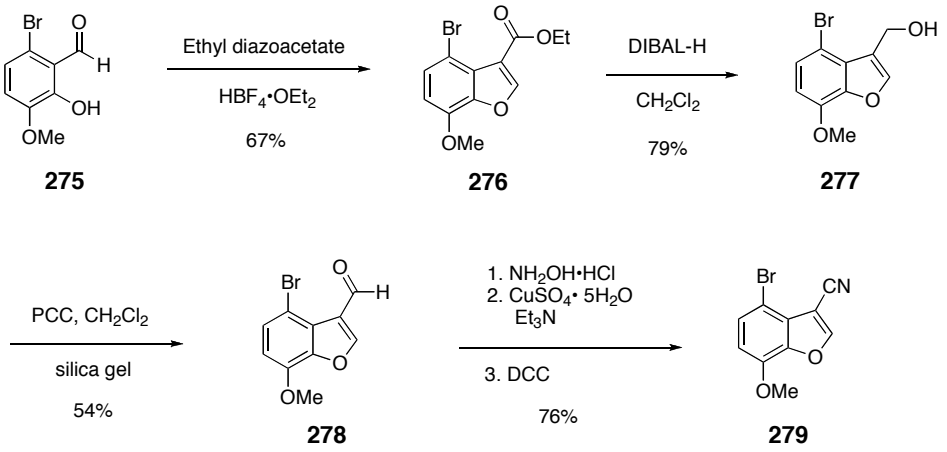
R = CH_2CH_2OMe R = CH_2CH_2OMe

Entry	Conditions	Result
1	150°C, 48 h, toluene	SM only
2	150°C, 6 days, toluene	SM only
3	200°C, 12 h, 300 W, 90 psi, toluene	SM only
4	0.2 eq. $EtAlCl_2$, 200°C, 4 h, 300 W, 90 psi, toluene	SM only
5	Cat. MgI_2, 150°C, 8 h, 300 W, 90 psi, toluene	SM, decomposition
6	200°C, 8 h, 300 W, 90 psi, DMF	SM only

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,[17] 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]

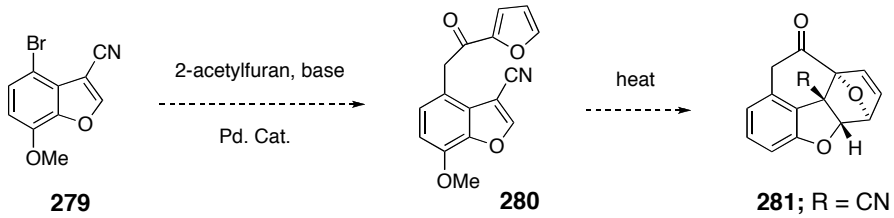
Scheme 3-11: Route to the C-3 Cyano-Substituted Benzofuran



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**

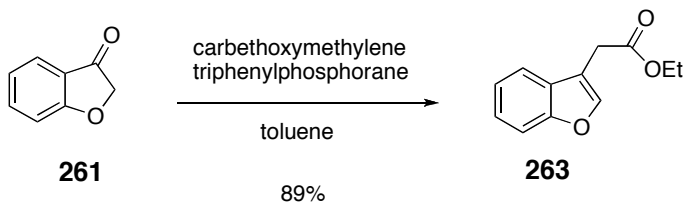
and to determine whether cyano group activation would allow the cycloaddition to proceed, thereby providing a route to access the morphine core.

Scheme 3-12: Cross-Coupling and IMDAF Reaction of the C-3 Cyanobenzofuran

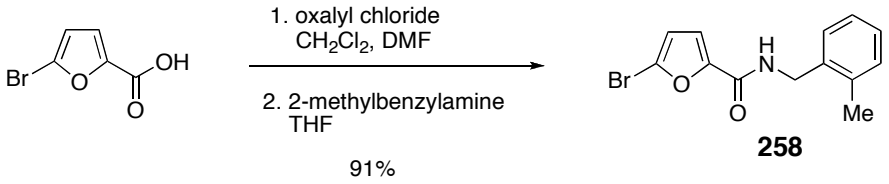


279 **280** **281;** R = CN

Experimental Section

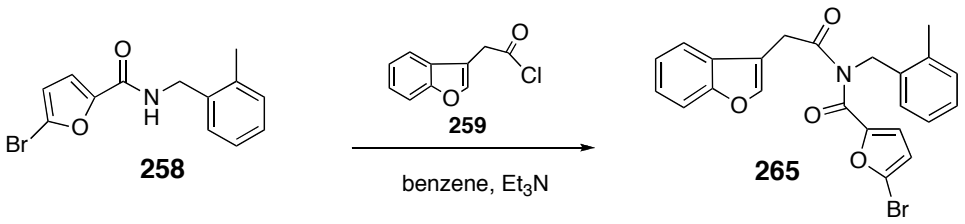


Ethyl 2-(benzofuran-3-yl)acetate (263). To a stirred solution of ketone **261** (3.0 g, 22.4 mmol) in toluene (44 mL) was added carbethoxymethylene triphenylphosphorane **262** (13.6 g, 39.1 mmol). The reaction mixture was heated at reflux for 21 h, then concentrated under reduced pressure and the residue 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}; ^{1}H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 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.



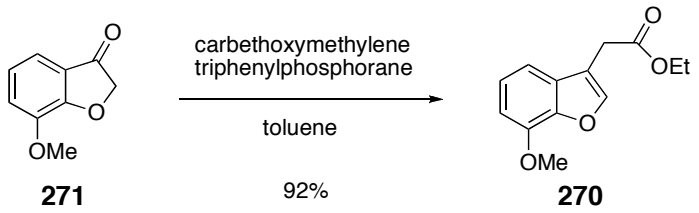
5-Bromo-*N*-(2-methylbenzyl)furan-2-carboxamide (258). To a stirred suspension of 5-bromo-2-furoic acid (286 mg, 1. 5 mmol) and 4 Å MS in CH_2Cl_2 (7 mL) was added oxalyl chloride (0.26 mL, 3.0 mmol) and 2 drops of DMF. The reaction mixture was stirred at rt for 1.5 h, filtered over celite, and concentrated 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 H_2O, and extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated to provide 400 mg (91%) of **258** as a yellow solid, mp 86-88 ^oC; IR (thin film) 3287, 3125, 3064, 2925, 1646, 1597, 1530, 1471, 1306, 1125, 1012, 927, 798, and 740 cm^{-1}; ^1H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 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).**

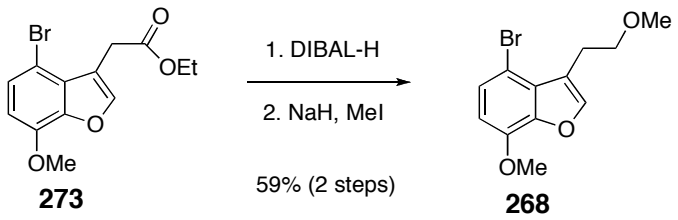
To a stirred solution of amide **258** (0.5 g, 1.70 mmol) and Et_3N (0.33 mL, 2.33 mmol) in THF (15 mL) was added compound **259** (0.453 g, 2.33 mmol) dropwise. The mixture was heated at reflux for 18 h, cooled to rt, concentrated under reduced pressure, and purified by silica gel chromatography to afford 7.0 mg of **265**; ^1H-NMR ($CDCl_3$, 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) δ 1.26 (t, 3H, *J* = 7.2 Hz), 3.68 (s, 2H), 4.00 (s, 3H), 4.18 (q, 2H, *J* = 14.4 and 7.2 Hz), 6.81 (dd, 1H, *J* = 6.8 and 2.0 Hz), 7.16-7.18 (m, 2H), and 7.64 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.3, 30.0, 56.2, 61.2, 106.7, 112.1, 113.7, 123.5, 129.5, 143.0, 144.6, 145.6, and 170.8.

Ethyl 2-(4-Bromo-7-methoxybenzofuran-3-yl)acetate (273). To a stirred solution of ester **270** in CH_3CN (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

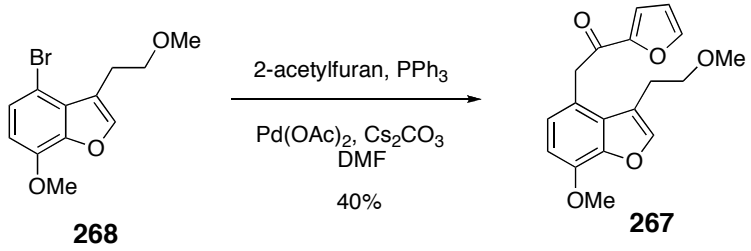
diluted with H_2O. The aqueous layer was extracted with EtOAc and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (30% EtOAc/hexanes) to provide 330 mg (quant. yield) of **273** as a white solid, mp 58-60 ^oC; IR (thin film) 2981, 1735, 1581, 1489, 1344, 1393, 1251, 1179, 1285, 1121, 1028, and 897 cm^{-1}; ^1H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 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.



273 **268**

4-Bromo-7-Methoxy-3-(2-methoxyethyl)benzofuran (268). To a -78^oC 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^oC and was stirred for 1 h. To the mixture was added H_2O and the aqueous layer was extracted with EtOAc, dried over $MgSO_4$, 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^oC 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 $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (30% EtOAc/hexanes) to give 381 mg (59%) of **268** as a clear

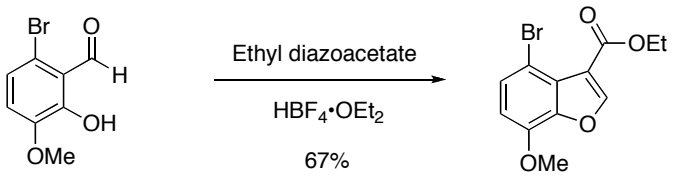
oil; IR (thin film) 2933, 2874, 1578, 1487, 1392, 1285, 1117, and 897 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.16-3.20 (m, 2H), 3.40 (s, 3H), 3.72 (t, 2H), 3.97 (s, 3H), 6.65 (d, 1H, *J* = 8.4 Hz), 7.27 (d, 1H, *J* = 8.4 Hz), 7.52 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.7, 56.4, 58.9, 72.4, 104.7, 107.6, 118.4, 127.0, 128.1, 143.6, 145.4, and 145.5.



268 **267**

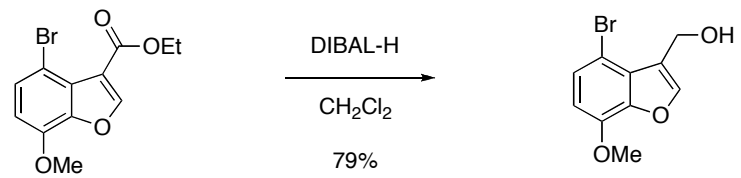
1-(Furan-2-yl)-2-(7-methoxy-3-(2-methoxyethyl)benzofuran-4-yl)ethanone (267).

To a stirred solution of bromide **268** (30 mg, 0.105 mmol), 2-acetylfuran (12 mg, 0.105 mmol) and Cs_2CO_3 (86 mg, 0.263 mmol) in degassed DMF (4 mL) was added PPh_3 (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 Et_2O. 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 (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}; ^{1}H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 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.



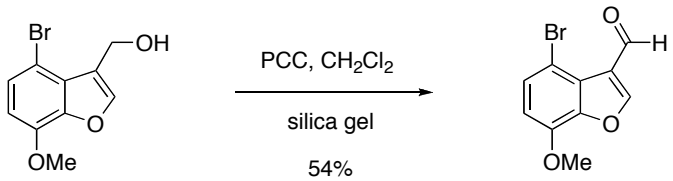
275 **276**

Ethyl 4-Bromo-7-methoxybenzofuran-3-carboxylate (276). To a stirred solution of aldehyde **275** (0.1 g, 0.433 mmol) in CH_2Cl_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_2Cl_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_2SO_4 (0.05 mL) and stirred vigorously for 5 min. Afterwards, CH_2Cl_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_2Cl_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 ^{o}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.



276 **277**

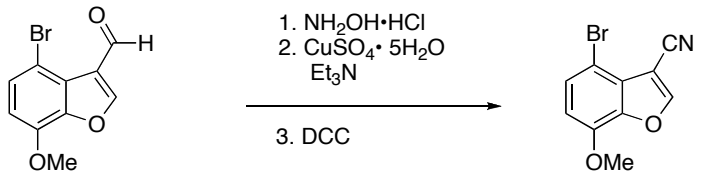
(4-Bromo-7-methoxybenzofuran-3-yl)methanol (277). To a 0 ^{o}C solution of ester **276** (609 mg, 2.03 mmol) in CH_2Cl_2 (64 mL) was added DIBAL-H (6.1 mL, 6.1 mmol, 1.0 M in hexanes) dropwise over 5 min. The reaction mixture was stirred while slowly warming to rt over 4 h, then cooled to 0^{o}C and 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 CH_2Cl_2, dried over $MgSO_4$, 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 ^{o}C; IR (thin film) 3318, 2936, 1621, 1488, 1397, 1302, 1248, 1171, 1120, and 1014 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 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); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.5, 56.5, 103.9, 108.1, 121.6, 127.0, 127.8, 144.3, 145.5, and 145.8.



277 **278**

4-Bromo-7-methoxybenzofuran-3-carbaldehyde (278). To a stirred solution of alcohol **277** (42 mg, 0.16 mmol) in CH_2Cl_2 (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) δ 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); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 56.6, 103.8, 108.8, 123.6, 125.9, 129.0, 145.6, 146.0, 151.2, and 185.9.



278 76% **279**

4-Bromo-7-methoxybenzofuran-3-carbonitrile (279). To a stirred solution of aldehyde **278** (81 mg, 0.34 mmol) in H_2O (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_2O (17 mg, 0.07 mmol) was added, followed by a solution of Et_3N (0.093 mL, 0.67 mmol) in CH_2Cl_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_2Cl_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_2Cl_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 ^oC; 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) δ 4.01 (s, 3H), 6.81 (d, 1H, *J* =

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.

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