ABSTRACT

**Young, Damian Winston.** Studies Toward the Total Synthesis of the *Lycopodium* Alkaloid Spirolucidine Using the *N*-Acyl-2,3-dihydro-4-pyridone as a Building Block. (Under the Direction of Daniel Lee Comins).

Spirolucidine is a complex alkaloid isolated from the club moss *Lycopodium lucidulum*. A three fragment convergent plan for the title compound was envisioned, with each fragment being derived from a chiral *N*-acyl-2,3-dihydro-4-pyridone. The synthesis of the bicyclic enecarbamate referred to as zone C was investigated. The first effort centered on a tandem intramolecular Diels-Alder reaction/retro Mannich ring opening reaction to set the key stereogenic centers within zone C. A second strategy aimed to ring open the tricyclic adduct which arises from the Diels-Alder reaction through an E1cB mechanism. Finally, a third attempt was made to utilize chirality transfer as a means to implement the necessary stereochemical elements of the bicyclic scaffold.

The convergent union of the key fragments of spirolucidine was modeled on a simple substrate. The directed lithiation of *N*-Boc-dihydropyridines was utilized to prepare model 2,5,6-trisubstituted dihydropyridones of a general type needed for the completion of the spirolucidine synthesis.
STUDIES TOWARD THE TOTAL SYNTHESIS OF THE
LYCOPODIUM ALKALOID SPIROLUCIDINE USING THE
N-ACYL-2,3-DIHYDRO-4-PYRIDONE AS A BUILDING
BLOCK

By

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A dissertation to the Graduate Faculty of the North Carolina State University
in partial fulfillment of the requirements of the Degree of

Doctor of Philosophy

DEPARTMENT OF CHEMISTRY

Raleigh

2004

Approved by:

________________________   _________________________
Chair of Advisory Committee
DEDICATION

I would like to dedicate this work in loving memory of my father, the late Ronald Winston Young, and my grandmother, the late Edith Sibert Macon. Although, they are no longer with me physically, they will forever remain with me in spirit. It is through their unconditional love that I was able to develop into the person that I am today. I will continually strive to live in the exemplary ways of upbringing that they taught me.
The author, Damian Winston Young, was born in Savannah, Georgia on June 29, 1975 to Attorney Ronald Young and Mrs. Sherill Young. After graduating from Glynn Academy in Brunswick, Georgia, Damian successfully completed a Bachelor of Science degree in chemistry with a minor in mathematics from Howard University in Washington, D.C. Damian gained a plethora of research experience through internships, co-ops and post-undergraduate jobs.

In January of 2000, Damian began his graduate studies under the direction of Professor Daniel L. Comins. In 2001, he was awarded the National Institutes of Health Pre-Doctoral Fellowship. In 2002, he was invited to join the PLU Chemistry Honor Society at North Carolina University. Upon completion of his Ph.D., he began a postdoctoral position at Harvard University under the direction of Professor Stuart L. Schreiber.
ACKNOWLEDGEMENTS

I truly believe that a person moves forward in life only as a result of those people who are placed in his life. The very dynamic span of time which will henceforth be known as “my graduate school years”, are brimming with memories of wonderful people to whom I am most indebted to. In this regard, I would like to thank Dr. Daniel Comins for his mentorship, advice, and support throughout these years. I would also like to thank my committee members, Dr. Bruce Novak, Dr. Suzanne Purrington, and Dr. Jonathan Lindsey for their helpful comments in the preparation of this dissertation. A special acknowledgement is given to Dr. Novak, who saw in me the potential to be a professor, and whose effort toward realization of this will never be forgotten.

Friendships have been essential to my experience in graduate school. I would like to thank all the present and past members of the Comins research group. I would like to especially acknowledge Mr. Ibrahim Bori, Mr. Brian DeCamp, Mr. Jason Dinsmore, Ms. Florence “Flo” Fevrier, Dr. Dimitar Gotchev, Mr. Lucas Marks, Mr. Stephen McCall, Dr. Michel Nuchols, and Dr. Bradley Wolfe. Much of what I learned throughout this experience is because of all of you. I thank you all for being my colleagues, but more importantly for being my friends. The confidence that you have in me inspires me to move forward. I would like to thank Dr. Angela Allen and Dr. Chiamaka Porter for being the sisters that I never had. I value our relationship more than you will ever know. Thank you for teaching me some very important lessons that transcend chemistry.

My family has been my backbone, and I am truly blessed to have such wonderful people in my corner. To my mother, Mrs. Sherill Young, I thank you for being an extraordinary mother and my lifelong best friend. I would not be where I am today without
your love and guidance throughout my entire life. To my grandfather, Mr. Ralph Macon, you are a continual inspiration to me of what a strong man should be. To Mr. William Crosby, I thank you for the unfailing support and peace of mind that you have given me during these past five years. To Mr. Jack Hester and Mrs. Maryln Hester, I thank you for accepting me as your new son and providing me with the strong encouragement necessary to make it through these years. And finally, to my loving wife Shawna, I find it exceedingly difficult to articulate words that appropriately express my thanks for what you have done for me. The sacrifices that you have made and are making now go far beyond what most would give. Thank you for loving me enough to allow me the freedom to pursue my dreams. Truly I say that you are my friend, confidant, and soul mate, and I look happily forward to spending the rest of my life with you.
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<tr>
<td>A</td>
<td>allylic strain</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2’azobisisobutyronitrile</td>
</tr>
<tr>
<td>anal.</td>
<td>analysis</td>
</tr>
<tr>
<td>APT</td>
<td>attached proton test</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>bd</td>
<td>broad doublet</td>
</tr>
<tr>
<td>bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BOC</td>
<td>t-butoxycarbonyl</td>
</tr>
<tr>
<td>brine</td>
<td>saturated aqueous sodium chloride</td>
</tr>
<tr>
<td>bs</td>
<td>broad singlet</td>
</tr>
<tr>
<td>n-Bu</td>
<td>normal butyl</td>
</tr>
<tr>
<td>s-Bu</td>
<td>secondary butyl</td>
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<tr>
<td>t-Bu</td>
<td>tertiary butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoate</td>
</tr>
<tr>
<td>calcd</td>
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</tr>
<tr>
<td>Cbz</td>
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</tr>
<tr>
<td>cm⁻¹</td>
<td>reciprocal centimeters</td>
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<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
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<tr>
<td>d</td>
<td>doublet</td>
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<tr>
<td>DBU</td>
<td>1, 8-diazabicyclo[5.4.0]undec-7-ene</td>
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<tr>
<td>dt</td>
<td>doublet of triplets</td>
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dd    doublet of doublets
ddd    doublet of doublet of doublets
ppm    parts per million chemical shift from tetramethyl silane
de    diastereomeric excess
DMAP   4-(dimethylamino)pyridine
DMF    N,N-dimethylformamide
DMSO   dimethyl sulfoxide
DMPU   N,N-dimethylpropyleneurea
dq     doublet of quartets
dt     doublet of triplets
ee     enantiomeric excess
EtOAc  ethyl acetate
GC     gas chromatography
h      hour(s)
HMPA   hexamethylphosphoramide
HMQC   heteronuclear multiple quantum coherence
HPLC   high-performance liquid chromatography
HRMS   high resolution mass spectrometry
Hz     hertz
IBX    o-iodoxybenzoic acid
IR     infrared
J      coupling constant
KHMDS  potassium bis(trimethylsilyl)amide
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<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>MPO</td>
<td>4-methoxypyridine N-oxide</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>NHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectrometry</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>PTAP</td>
<td>phenyltrimethylammonium tribromide</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million (in NMR)</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>radial PLC</td>
<td>radial preparative-layer chromatography</td>
</tr>
<tr>
<td>r</td>
<td>rotamer(s)</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
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INTRODUCTION.

Nitrogen containing heterocycles are widely expressed among natural products ranging from amino acids to the more structurally elaborate alkaloids. Moreover, nitrogen containing heterocycles are ubiquitous within the pharmaceutical arena as they serve as important scaffolds for medicinally relevant molecules. There exists a wide array of chemical methodologies aimed at the formation of aza heterocycles, which rivals the diversity seen in the structures themselves. Amongst this structural diversity is the dihydropyridone class. Figure 1 shows the structural variation within this important family.

Dihydropyridones are typified by a 6-membered ring system containing one nitrogen, an alkene, and a carbonyl function. These three constituents may be disposed in five ways as illustrated in Figure 1. While each of the members in Figure 1 are defined, the 2,3-dihydro-4-pyridone (1) is quite prominent among the group. Structure 1, unlike its relatives constitutes a cyclic vinylogous amide that allows for the controlled regiochemical
functionalization of the ring system that the others do not. The remaining portion of this section aims to illustrate the preparation and chemical utilization of this valuable heterocycle according to recent literature. Unless stated otherwise, the term dihydropyridone will refer exclusively to the 2,3-dihydro-4-pyridone throughout the body (1) of this dissertation.

I. Preparation of 2,3-Dihydro-4-pyridones.

1.1. Dihydropyridones Arising From Acyclic Precursors.

There have been some recent accounts of the formation of 2,3-dihydro-4-pyridones from acyclic molecules. For example, the condensation of β-amino esters with β-ketoesters has been recently reported by Ma (Scheme 1).²

![Scheme 1. Preparation of Dihydropyridones from Chiral β-Amino Esters](image)

This method of dihydropyridone formation is attractive because it allows for the preparation of enantiopure dihydropyridones from a readily obtained source of chiral starting material.
(the β-amino ester). The reaction shown above was utilized in the synthesis of the dendrobate alkaloid (+)-241D.

Tripathi and coworkers investigated the condensation of β-keto esters and acetylacetone with glycosylated amino esters (Scheme 2). This reaction was catalyzed by acidic resin to afford eneaminones of the type 6. The latter substrates were induced to cyclize on treatment with NaH to give 2-glycosyl-2,3-dihydro-4-pyridones as shown in Scheme 2.

**Scheme 2. Cyclization of Glycosyl Enamines to Glycosyl Dihydropyridones**

The union of acylic constituents through the Diels-Alder reaction has proven to be an invaluable strategy for the formation of carbocycles; however, the reaction is also useful for the construction of heterocycles. In 1982, Danishefsky and coworkers reported the efficient Diels-Alder reaction of imines with a siloxydiene (commonly known today as Danishefsky’s
diene) to generate dihydropyridones. This reaction continues to be used today to access the dihydropyridone ring system. Contemporary variants of this methodology employ asymmetric catalysis, and solid phase applications. For example, the use of the aza Diels-Alder approach toward dihydropyridones has very recently been applied to the liquid phase on a soluble polymer. Ding and coworkers prepared a polyethylene glycol (PEG) supported amine which reacted with aryl aldehydes and Danishefsky’s diene with zinc perchlorate catalysis to yield the PEG bound dihydropyridone 11 (Scheme 3). Upon addition of diethyl ether, compound 11 precipitated from solution and was obtained by simple filtration. The dihydropyridone was subsequently cleaved from the polymer support by basic hydrolysis and was then acidified to obtain 12 as crystalline solid in good to excellent yields and purities.

Scheme 3. Liquid Phase Synthesis of 2,3-Dihydro-4-pyridones

To expand the utility of this valuable hetero Diels-Alder reaction, other functionalities can be incorporated within the imine to provide means for further elaboration. An exemplary
facet of this methodology is shown in Scheme 4 wherein the amino allylsilane 13 readily undergoes Schiff base formation with aryl aldehydes.\textsuperscript{8} It was noted that alkyl aldehydes gave imines that were considerably less stable. Catalytic Yb(OTf)\textsubscript{3} promoted cycloaddition of imine 15 with Danishefsky’s diene to afford the N-substituted dihydropyridone 16. Addition of the anhydrous fluoride ion source TBAT incites a stereoselective intramolecular Sakurai reaction on the vinylogous amide to provide indolizidine systems. The observed selectivity of C-C bond formation in the Sakurai reaction can be rationalized by an axial trajectory of the ensuing allylsilane on the lower energy half-chair of 16a leading to structure 16c. This stereoelectronic effect governs many reactions of dihydropyridones, often providing a means for high facial selectivity.
Asymmetric catalysis has emerged, as a vital field in modern organic chemistry, particularly pertaining to the formation of heterocycles.\cite{9} Hoveyda recently disclosed the application of a practical and efficient silver catalyzed cycloaddition between arylimines and Danishefsky’s diene (Scheme 5).\cite{10}
The reported yields and enantioselectivities for formation of dihydropyridones of the type 20 were high for this system, and the reaction proceeds efficiently at catalyst loadings as low as 0.1 mol%. Remarkably, the silver catalyst based on ligand 19 is extremely versatile given that the reaction can be run in an air atmosphere with undistilled THF.

Carretero and coworkers reported the asymmetric preparation of substituted 2,3-dihydro-4-pyridones from the reaction of Danishefsky’s diene and N-sulfonyl imines using chiral copper phosphino sulfenyl ferrocenyl complexes (Scheme 6).\textsuperscript{11} In this case, formation of the dihydropyridone proceeds through a formal aza-[4+2] cycloaddition whereby the Mannich addition product 23 serves as the key asymmetric intermediate that undergoes Michael ring closure on acid treatment to furnish 24. The additive silver perchlorate is required to generate the active cationic complex of 22. The enantioselectivities reported were generally excellent over a wide range of sulfonyl imines used. Moreover, the products obtained were all crystalline and required only one recrystallization to supply dihydropyridones in greater than 99.5% ee.
Scheme 6. Enantioselective Formal Aza Diels-Alder Reactions Employing Chiral Copper Complexes

This methodology was expanded using the functionalized siloxydiene 25 to afford the 2,5-disubstituted dihydropyridone 26 in moderate yield and good enantioselectivity.

1.2. Dihydropyridones from Pyridine Precursors.

The N-acyl-2,3-dihydropyridone of the general type 27 has come to occupy an important position in the field of heterocyclic chemistry (Figure 2), owing largely to the efforts of Comins and coworkers. This building block has been successfully employed in natural product syntheses and the production of pharmacophores for over a decade.
Figure 2. General Structure and Utility of N-Acyl-2,3-dihydro-4-pyridones

One of the most pleasing attributes of 27 is the ease with which it can be prepared from readily available starting materials (Scheme 7).

Scheme 7. Preparation of Racemic N-Acylidihydropyridones

4-methoxypyridine

racemic N-acylidihydropyridone
The reaction of 4-methoxypyridine with a chloroformate at low temperature gives a pyridinium salt 29, which is activated toward nucleophilic attack at the 2- and 6- positions. Grignard reagents are excellent nucleophiles for this purpose and attack the in situ generated pyridinium salt at the activated positions to give a dihydropyridine of type 30. The enol ether of the dihydropyridine is subsequently hydrolyzed with acid to furnish the racemic dihydropyridone 27 in good to excellent yields. This very useful methodology was further expanded by Comins in the early 90’s with the ability to obtain N-acyldihydropyridones in enantiomERICLY pure form (Scheme 8).13

Scheme 8. Preparation of Enantiopure N-AcylDihydropyridones

In a very analogous manner, 4-methoxy-3-(triisopropylsilyl)pyridine (31) is acylated with the chloroformate of either antipode of the commercially available trans-2-(α-cumyl)cyclohexyl alcohol (TCC). Treatment of this resulting homochiral pyridinium salt with a Grignard
reagent gives upon acid hydrolysis dihydropyridones (32) in diastereomeric excesses ranging from 85 to 95%. The pure diastereomer is obtained by chromatography or recrystallization. In one pot, the carbamate is removed with NaOMe and the TIPS group is protodesilylated resulting in 33. The chiral auxiliary, TCC alcohol, is recovered and the pure dihydropyridone is obtained by chromatography. Finally, the NH dihydropyridone is reprotected by reaction with n-BuLi and a chloroformate to give 34 as a single enantiomer. It should be emphasized that either antipode of 34 can be obtained depending on the particular TCC enantiomer used to form the acylpyridinium salt which lends to the versatility of this method as compared to previously discussed methods. Furthermore, a range of organometallics have been found effective in this reaction; giving great flexibility to what can be installed at the 2-position. In addition to its facile preparation, the dihydropyridone can be functionalized in a myriad of ways. Figure 3 illustrates some general reactions that have been performed on this ring system. Many of these reactions will be discussed in this section and throughout the body of this dissertation.

\[
\text{Figure 3. The Versatility of } N\text{-Acyl-2,3-dihydro-4-pyridones}
\]
In addition to its role as a protecting group, it is of great importance that the carbamate function induces the group in the 2-position of the dihydropyridone to be axially positioned by virtue of $A^{(1,3)}$ strain.\textsuperscript{16} This renders the face effectively blocked, and reagents approach \textit{anti} to this axial group in such reactions that are heavily influenced by steric approach control. Reactions such as these include enolate alkylations at the 3-position and [2+2] photocycloadditions across the C5-C6 double bond to give the \textit{trans} products. However, stereoelectronic effects sometimes govern the stereochemical outcome of some reactions of \textit{N}-acyldihydropyridones. The conjugate addition of nucleophiles to the vinylogous amide is one such example. Under the appropriate conditions, the \textit{cis} piperidones can be obtained in high ratios relative to the \textit{trans}. Therefore, the reactivity profile of the \textit{N}-acyldihydropyridone can be summarized that it allows for highly regioselective and many times highly stereoselective outcomes. Along these lines, the Comins group has built a very active research program around asymmetric synthesis utilizing this highly functional building block. This has brought forth a sizable body of general methodology and natural products syntheses.\textsuperscript{17}

\section*{II. Reactions of 2,3-Dihydro-4-pyridones.}

Garbaccio studied the thermodynamic enolization of \textit{N}-acyldihydropyridones (Scheme 9).\textsuperscript{18} Conjugate reduction of the vinylogous amide at 0 °C with L-Selectride\textsuperscript{®} resulted in an equilibration of the enolate from the kinetically formed C4-C5 enolate 37 to the thermodynamically more stable C3-C4 enolate 38. This can be explained by the enolate
half-chair conformations in which the C3-C4 enolate places the R group into a pseudo-axial position 38a, mitigating the 1,3-diaxial interaction that is present with the group disposed precisely axial as in the case of the kinetic enolate 37a. Larger substituents at the 2-position provide more of a pseudo-axial perturbation and thus lend toward greater thermodynamic ratios. This explanation is supported by calculations at the AM1 level.

Scheme 9. The Equilibration of Dihydropyridone Enolates

The utilization of this thermodynamic enolate trapping was applied toward the total synthesis of (+/-)-epiuleine. The acylpyridinium salt 39 reacted with the indolyl Grignard reagent which on acidic hydrolysis and N-Boc protection gave dihydropyridone 41. Enolization of
the latter under thermodynamic conditions and trapping with Comins’ triflimide (36) resulted in 42 in good yield. The vinyl triflate underwent an intermolecular Heck reaction with butyl vinyl ether to afford 43. A conjugate addition reaction of an ethyl group was performed and this key intermediate was advanced toward the target (+/-)-20-epiuleine (Scheme 10).

**Scheme 10.** Utilization of Dihydropyridones Toward the Synthesis of (+/-)-20-Epiuleine

Another example of a stereocontrolled synthesis employing a 2,3-dihydro-4-pyridone was the total synthesis of cylindrospermopsin, reported by Snider (Scheme 11). The synthesis commenced with the reaction of the 3-methyl-4-methoxypyridine with TrocCl followed by the Grignard of TMS-acetylene to give 45 on acid workup. It is noteworthy that the regioselectivity of Grignard addition during the acylpyridinum salt reaction was virtually complete even with a methyl group. Stereoselective conjugate addition of a vinyl group
provided piperidone 46 containing three stereogenic centers. The observed stereoselectivity of the latter reaction may be explained by axial attack of the organocopper species on enone 45 which results in an intermediate copper enolate that is protonated axially upon workup. These events can both be attributed to stereoelectronic effects. The Troc group was removed with Zn and HOAc, and during this process, the C3 center epimerized to give piperidone 47. The thermodynamic driving force of the epimerization results from placing the methyl group in the more favorable equatorial position as depicted in chair 47a. Reduction of the C4 carbonyl function with L-Selectride® gave the alcohol 48 which contains 4 stereogenic centers set as the A ring of the natural product cylindrospermopsin.
Weinreb used a similar strategy in the construction of the A ring of 7-epicylindropermopsin (Scheme 12). The silyl Grignard reagent 49 was employed in an acylpyridinium salt reaction as a masked hydroxymethyl anion equivalent. Enolization of the ketone followed by reaction with methyl iodide gave the trans-dihydropyridone 51 as the only stereoisomer. Enolate alkylation rarely proceed with stereoelectronic control. Therefore, selectivity in this alkylation likely arises from a steric approach controlled
trajectory of the methyl iodide which engages the heterocycle through the less encumbered path opposite the axial C2 group. Reduction of the C4 carbonyl function with L-Selectride® and protection as the benzyl ether furnished 53. Oxidation of the allylsilane and cyclization gave 54 as ring A of the target compound.

**Scheme 12.** Weinreb's Application of the Dihydropyridone Toward 7-Epicylindrospermopsin

Ring closing metathesis (RCM) of bis-olefinic substrates is a widely utilized tactic for cyclization in modern organic synthesis. The technique has also found wide applicability in the synthesis of heterocycles, an area that has recently been reviewed. Martin and
coworkers applied the RCM reaction of a bis-olefin moiety which derived from a dihydropyridone scaffold to give bridged azabicyclic structures (Scheme 13). Addition of an olefinic Grignard reagent of the general type 55 and ZnCl2 to the acylpyridinium salt generated in situ rendered dihydropyridone 56 on aqueous acidic workup. A stereoselective conjugate vinyl addition to the latter substrate affords the cis-2,6-disubstituted piperidone 57. Due to the inherent A(1,3) strain in 57, both substituents are relegated to the axial positions (see conformer 57a). This diaxial nature of the two alkenes allows for an efficient cyclization (with ruthenium catalysts 58 or 59) as the reaction occurs cleanly to provide 60 at room temperature.

**Scheme 13. Ring Closing Metathesis Reactions of Substrates Derived from Dihydropyridones**
The vinyl conjugate addition was also accompanied by trapping of the intermediate copper enolate with methyl cyanoformate (Scheme 14) to give 62. Ring closing metathesis of the latter substrate using 58 as a catalyst gave 63 which has a marked skeletal similarity to the tropane alkaloids (e.g. cocaine). This illustrates the utility of the dihydropyridone nucleus as a building block toward the synthesis of biologically active structures.

**Scheme 14.** Tandem Conjugate Addition-Acylation of Dihydropyridones

Dihydropyridones can be functionalized to participate in cycloaddition reactions. Comins has investigated the Diels-Alder reaction of 5-vinyl substituted dihydropyridones typified by 65. Vinylation of dihydropyridone 64 was achieved in good yield over a 2-step sequence involving iodination with NIS, followed by a Stille coupling with tributyl(vinyl)tine.
The diene unit underwent smooth cycloaddition with various dienophiles, such as maleic anhydride in good yield to furnish the octahydroquinolone 66. The diastereoselectivity of the Diels-Alder reaction is explained by a steric approach control wherein the dienophile engages the diene in an endo fashion anti to the axial 2-substituent in the dihydropyridone 65 (see transition state 67).

Comins also exploited the use of benzoquinone as a dienophile in the Diels-Alder reaction with dihydropyridone 64. In this case, the product of cycloaddition (68a) was not stable, and likely oxidized in air to give intermediate 68b. A fragmentation-aromatization reaction of 68b led to the anthraquinone product 69. This example illustrates the potential use of dihydropyridones to provide disparate ring systems.
Scheme 16. The Fragmentation of Benzoquinone Diels-Alder Adducts

The intermolecular Diels-Alder reaction on the C5-C6 enone of dihydropyridones was investigated by Lhommet, who illustrated that 5-(carboethoxy)-dihydropyridones (70) underwent regioselective [4+2] cycloaddition reactions to dihydropyridones with electron rich dienes such as diene 10. The Diels-Alder reaction was not an absolute pathway with dienes as in the presence of Lewis acids, furan and 2-trimethylsilyl furan gave the conjugate addition products 72 and 73.
Scheme 17. Diels-Alder and Michael Reactions of Dihydropyridones

In addition to [4+2] cycloadditions, the C5-C6 alkene of the vinylogous amide readily participates in [2+2] photocycloadditions with alkenes to furnish cyclobutane fused piperidones. Neier and coworkers first reported the photochemical reaction of 2,3-dihydro-4-pyridones (Scheme 18). Both electron poor and rich alkenes were successful in this cycloaddition reaction to provide diastereomeric cyclobutyl adducts.
The photochemical reactivity of dihydropyridones has proven to be a very lucrative source of stereoselective carbon-carbon bond formations. An intramolecular photocycloaddition strategy was employed by Comins to implement the quaternary center within the natural product perhydrohistrionicotoxin (Scheme 19).²⁸ The dihydropyridone 77 underwent a [2+2] photocyclization on irradiation in acetone to give the cyclobutane fused piperidones 78a and 78b. Mild cyclobutane cleavage conditions employing SmI₂ gave spiropiperidone 79 which was fashioned into the target compound.
Scheme 19. Intramolecular Photocyclization of Dihydropyridones Toward Perhydrohistrionicotoxin

Other types of cyclizations have proven useful in stereoselective bond formation. For instance, vinyl groups at the C2 position of the dihydropyridone may also participate in iodocarbamylation reactions with benzyl carbamates (81 to 82). Methodology of this type was employed to stereoselectively install the hydroxyl group on the C2 side chain in the synthesis of the amino alcohol (+)-β-conhydrine (Scheme 20).
Scheme 20. Synthesis of (+)-β-Conhydrine

Many of the natural product syntheses utilizing dihydropyridones have involved the transformation to bicyclic systems of the hydroquinoline,\textsuperscript{30} quinolizidine,\textsuperscript{31} or indolizidine\textsuperscript{32} type. For example, the formation of hydroquinolines is possible through the intermolecular acid catalyzed aldol reaction of 2,3-dihydro-4-pyridones (Scheme 21).\textsuperscript{33} Ozonolysis of the pentenyl substituted dihydropyridone 84 gave the ketoaldehyde 85 which underwent an acid catalyzed condensation to provide enone 86. This quinolone was further elaborated to provide the bicyclic fragment of the alkaloid phlegmarine.
Finally, there exists the possibility of ring opening the C5-C6 olefin of the dihydropyridone to provide acyclic molecules of interest (Scheme 22). Wanner and coworkers recently employed an oxidative cleavage of N-acyldihydropyridones toward the preparation of chiral β-amino acids (91). It should be noted that this reaction constitutes the reverse of the approach illustrated by Ma (Scheme 1) wherein β-amino esters were used to construct dihydropyridones.
Taken together, the reactions highlighted in this section portray the considerable synthetic activity surrounding dihydropyridones. It is our desire to utilize this important heterocycle toward the synthesis of complex molecules.
CHAPTER 1: SPIROLUCIDINE AND ITS BIOSYNTHETIC ORIGINS

The species of club moss *Lycopodium lucidulum*, is a rich source of alkaloid natural products. Manske and Marion reported the isolation of seven alkaloids from *L. lucidulum* in 1942. The structures of many of these alkaloids were solved by William Ayer and coworkers in the decades that followed. Spirolucidine (92) was isolated from the extracts of the club moss *Lycopodium lucidulum* by Ayer in 1986. The natural product bears a stark resemblance to other alkaloids found within the same source known as the lucidines also possessing a C$_{30}$N$_{3}$ general formula.

Spirolucidine was obtained as a component of the weak bases by a countercurrent distribution technique. The molecular structure was determined by $^{1}$H NMR, $^{13}$C NMR, IR, and HRMS. Based on the $^{13}$C NMR spectrum alone, it was concluded that the skeleton of spirolucidine was aberrant from the other lucidines. Crystallization of spirolucidine could not be effected; however, the product of reduction by LAH, tetrahydrodeoxyspirolucidine
formed crystals from ether/pentane. Accordingly, the relative stereochemistry of 92 was determined from this analog by X ray crystallography, ultimately leading to the assignment given Figure 4. Spirolucidine and the lucidine family of alkaloids is given in Figure 5.  

![Chemical Structures]

**Figure 5.** The Lucidine Family: Alkaloids of the *Lycopodium Lucidulum*

It is often constructive to consider the synthesis of a natural product *in vivo* as this exercise may lend fruitful and efficient pathways for the chemical synthesis. The biosynthetic origin of spirolucidine and its relatives has to date not been fully elucidated. There are several pertinent hypotheses related to the latter topic toward which there is not adequate data to support.
Nyembo suggested that the skeletons of the complex *Lycopodium* alkaloids result from the natural product phlegmarine, another alkaloid which is common to the *Lycopodium* genus. In this way, it can be envisioned that spirolucidine, lycolucine, and lucidine B arise from the attachment of two C$_{11}$N units onto a core piperidine ring. The biosynthetic pathway of the phlegmarines is shown in Scheme 23. The synthesis initiates with the amino acid L-lysine which is converted to cadaverine through a PLP mediated decarboxylation. Oxidative deamination of cadaverine results in piperideine, which undergoes nucleophilic attack by acetoacetyl-CoA twice to provide an intermediate which cyclizes to form the perhydroquinoline ring system. Phlegmarine itself arises from the condensation of piperideine with the latter perhydroquinoline carboxylic acid moiety.
Scheme 23. Biogenesis of the Phlegmarine Skeleton

The precise sequence of events by which the phlegmarine skeleton is converted to the complex alkaloids (lucidine, lycolucine, and spirolucidine) is currently without explanation.
Furthermore, despite the similarity in the structure of these alkaloids, it is not known which one is the precursor of the others if they are linked through one common biosynthetic pathway. Several observations suggest that these alkaloids lie on different biosynthetic pathways despite their seemingly analogous structures. Stemming from Ayer’s studies on these alkaloids, it is noteworthy that Lucidine B undergoes a facile oxidation in air to oxolucidine B (Scheme 24).

\[ \text{Scheme 24. Ayer's Oxidation of Lucidine B} \]

![Diagram of Lucidine B and Oxolucidine B](image)

This would seem to provide support for the obvious hypothesis for the implementation of the spirocyclic ring with concomitant ketone formation through an iminium ion promoted rearrangement as given in Scheme 25.
Scheme 25. Ayer's Attempted Rearrangements to Support Biogenic Hypothesis

A) Attempted Rearrangement To Give Spirocenter

Various Conditions:
- a) Sulfuric Acid
- b) HCl
- c) TFA/THF
- d) p-TsOH/PhH

Oxolucidine B

Spirolucidine

Spirooxolucidine B (proposed)

B) Attempted Rearrangement From Spirocenter

Tetrahydrodeoxyspirolucidine (x-ray crystal structure obtained)

Possible structures from migration of either bond of spirocenter.
Surprisingly, the rearrangement of the oxolucidine to its spirocyclic congener could not be effected under various conditions. Additionally, the spirofused center of dihydrodesoxyspirolucidine failed to reorganize upon treatment with phosphorous oxychloride, or by a mesylation. The latter conditions led only to unidentified byproducts. These experiments would tend to suggest that lycolucine or lucidine is not a precursor to spirolucidine, which in turn is not a precursor to the former compounds. However, these empirical findings do not entirely rule out the fact that spirolucidine might arise from such a mechanism. It is noteworthy that the southern perhydroquinoline of spirolucidine is distinct from the other *Lycopodium* alkaloids. In spirolucidine, the methyl group is *anti* to the ring junction whereas in the other natural products it is *syn*. One possibility is that spirolucidine diverges from these structural relatives early in its biosynthesis (Scheme 26). Furthermore, it can be reasoned that possession of this particular perhydroquinoline of pre-spirolucidine selects it for an enzymatically assisted iminium ion rearrangement reaction to furnish the spirocenter, whereas the others do not.
Scheme 26. Divergent Biosynthetic Proposal for Spirolucidine

Lucidine B

Different Pathways

Prespirolucidine I

Oxolucidine B

Has not been isolated from Lycopodium lucidulum

Prespirolucidine II

Spirolucidine

Oxidation

Enzymatically Assisted Rearrangement
Irrespective of its biogenetic origins, spirolucidine’s structure is quite complex. Housed within this structure are 11 stereogenic carbon atoms, of which one is the coveted spirocenter, from which the name of the natural product derives. There have been no reports of synthetic studies aimed at spirolucidine outside the Comins group.
I. The Synthetic Plan for Spirolucidine.

The synthesis of complex molecules has been a central focus of organic chemistry over the past seventy-five years. Advancements in chemoselective reagents, catalysts, and the field of asymmetric synthesis have developed concurrently with this activity in total synthesis. This concerted effort has culminated in the synthesis of many complex molecules, many of which are among the alkaloid class. Figure 6 illustrates some impressive achievements in the total synthesis of alkaloid substances.
Figure 6. Fifty Years of Alkaloid Total Synthesis
Listed in this figure is an alkaloid representative from each decade since the 1950’s. A landmark achievement by Woodward and coworkers was realized in 1954 with the total synthesis of strychnine. This disclosure by many accounts marked the beginning of complex molecule synthesis. Today, this effort continues at a strong pace, as alkaloids that display novel structures and interesting biological activities continue to be found and await a total synthesis in the laboratory. Given the great wealth of methodologies and reagents available to today’s synthetic chemist, the challenge of “can it be done?” has transitioned to “how efficiently can it be done?” As a testament to this, one merely needs to pay attention to the abundance of referrals to the “number of steps” and the “overall chemical yield” in synthetic publications. In this regard, a continued effort from the synthetic community is needed to fashion alkaloids and other types of complex small molecules more reliably and effectively. In light of this discussion, spirolucidine fits well into the mold of a contemporary synthetic challenge. This molecule presents an array of chemical functionalities and stereocenters structurally arranged in such a way that might befit the description of novel. Toward this end, a synthetic endeavor of this type is sure to expand the scope and illuminate the utilities of current methodologies. However, this undertaking is also likely to fabricate new methodologies, where preexisting ones fail. These two outcomes are key justifications for conducting total syntheses of complex molecules. In this regard, it is hoped that our efforts toward a total synthesis of spirolucidine, and our findings along the way to this goal will be considered of general use to others.

Retrosynthetic analysis is the process by which a target structure is deconstructed in reverse and stepwise fashion according to allowed synthetic transformations. This is an
iterative process which continues until a readily available starting material is achieved.\textsuperscript{42}

Retrosynthetic analysis is often referred to as the disconnection approach because lines are drawn through bonds indicating that the bond will be broken. In the synthesis of larger molecules, the convergent approach is usually desirable. This entails dividing the molecule into fragments of approximately equal size and complexity such that they can be united late in the synthesis plan to complete the molecule. Retrosynthetically, convergent disconnections are typically drawn first and require a great deal of consideration of how the complex fragments can be coupled to one another. One must choose disconnections that allow for the efficient union of the complex constituent molecular fragments. Moreover, if the disconnection proceeds at a stereogenic carbon center, a high degree of control of the stereochemical outcome must be realized in the bond forming event. Finally, key to the implementation of any synthetic plan for spirolucidine in particular would be the formation of the spirocyclic center with the proper stereochemical configuration. These principles guided our deconvolution of spirolucidine as shown in Scheme 27.
Spirolucidine can be dissected into three fragment molecules or zones. The retrosynthetic scheme dictates that 92 could arise from the coupling of a *cis*-fused decahydroquinoline ring system (zone A) and a *cis*-fused bicyclic enecarbamate (zone C) to a central 3-piperidone core (zone B). It was further surmised that a 5-(carbomethoxy)dihydropyridone could serve as a latent functional heterocyclic core to the zone B 3-piperidone moiety of spirolucidine. This latter realization opens for us a potentially efficient methodology for the incorporation of the advanced bicyclic heterocycles with a high degree of regio- and stereocontrol using the established chemistry of the dihydropyridone. It also sets up a novel proposal for framing the spirocyclic center (Scheme 28) of the target compound.
Our more detailed retrosynthetic plan proposes that spirolucidine would arise from a cyclobutane fused 4-piperidone 93. In the synthetic direction, the top bond of the cyclobutane ring can be cleaved in structure 93 using dissolving metal conditions. The methyl ester in
the 5-position of 93 would then serve as a synthetic handle to facilitate the transposition of the 4-piperidone to spirolucidine’s 3-piperidone core after the cyclobutane ring cleavage (*vide infra*). It is of paramount importance that the complex pentacyclic core of 93 contains the spirocenter of 92. Along these lines we envision that the cyclobutane 93 would arise as a consequence of a photochemically promoted [2+2] cycloaddition reaction; consequently, disconnection along the two bonds of the cyclobutane ring in the manner shown gives 94. It can now be appreciated that the double bond of the enecarbamate and the C5-C6 double bond of the zone B dihydropyridone form the di-alkene unit needed to confer this key step. In this powerful strategy, the spirocyclic center would be fashioned in a stereocontrolled way. By reason of the A\(^{(1,3)}\) strain induced by the carbamate, zone A will be forced into an axial position. The presence of this large axial substituent will block the cycloaddition from this π-face of the double bond, encouraging cyclization from the α-face of the molecule. This chemistry is substantiated by model studies to be presented later. The structural complexity of 94 is mitigated when it is realized that it is simply a 2,6-disubstituted dihydropyridone. Structures of this type can be fashioned in a protocol standard to Comins’ dihydropyridone methodologies. Accordingly, the zone C-zone B union can now be disconnected as shown in Scheme 28 to provide compounds 95 and 96 through a conjugate addition-double bond regeneration sequence. Dissection of the zone C ester gives rise to dihydropyridone 97. Finally, the zone A-zone B union can arise from a homochiral 1-acylpyridinium salt reaction with (+)-TCC and the preformed organometallic of zone A (98). The latter reaction will allow for control of the absolute stereochemistry at this step.
II. The Synthesis of Zone A.

With the framework of the convergent plan laid down, we can now turn our attention to the synthesis of the target fragments. Zone A’s skeleton and relative stereochemistry was suited to methodology previously investigated in the synthesis of the alkaloid phlegmarine. Toward this end, much of the methodology was used to prepare this fragment asymmetrically and the synthesis is given in Scheme 29.
Treatment of 3-TIPS-4-methoxy pyridine with the (+)-TCC chlorofomate generates a homochiral salt which is reacted with the chiral Grignard reagent 100 and hydrolyzed to dihydropyridone 101. Removal of the TIPS and the TCC carbamate and reprotction of the
nitrogen as a phenyl carbamate generated dihydropyridone 102 in excellent yield. Reduction of the C4-C5 olefin with Zn and acetic acid provides piperidone 103. Oxidative cleavage of the terminal olefin gave the ketoaldehyde 104, which underwent an acid catalyzed aldol condensation to furnish bicycle 105. Conjugate addition of the dimethylphenylsilyl cuprate 106 and enolate trapping with Comins’ triflimide gave enol triflate 107. The stereoselectivity for the silyl addition can be explained by axial attack on 105 which proceeds through a chair transition state. Reduction of the vinyl triflate with Pd/C provided 108 possessing all the stereogenic centers of the target zone A. It is noteworthy that the diastereoselectivity of this hydrogenation arises as a consequence of the A(1,3) strain of the carbamate which forced 107 to adopt a pseudo cup type conformation. The catalytic hydrogenation occurred from the sterically more accessible convex face of the molecule leading to 108.\textsuperscript{43} Completion of the zone A fragment of spirolucidine is marked by a carbamate reduction to the N-methyl compound followed by a final iodination reaction to give zone A.

The enecarbamate, zone C, poses some new frontiers for us and progress toward its synthesis will be delineated in the following section. A brief examination of the structure of zone C reveals that it is diastereomeric to zone A with respect to C5 and C7. The stereochemistry of C5 is of little consequence, because as with zone A, it can be installed by a chiral auxiliary (\textit{vide infra}) and ushered in as a side chain. It is the configuration at C5 that forces us to use an entirely different synthesis than that depicted for zone A. This statement is made based on the empirical observation that the conjugate addition reaction renders a completely diastereoselective event to generate the \( \alpha \)-adduct (the wrong configuration at C7 for zone C).
Despite the difference in structure of the C zone, its octahydroquinoline skeleton befits synthesis from a chiral dihydropyridone building block. Toward this end, a chiral 1-acylpyridinium salt reaction will be used as the fundamental starting point for each zone of spirolucidine (Scheme 30). Hence, our global approach en route to 92 is predicated on the homochiral acylpyridinium salt as the key building block.

**Scheme 30.** Underlying Strategy for the Synthesis of Spirolucidine
III. Progress towards the Synthesis of the Zone C Fragment of Spirolucidine.


A structural comparison between the zone C portion of spirolucidine and that of the *Lycopodium Lucidulum* relative luciduline reveals that all of the stereogenic centers possessed by zone C are contained within the skeleton of luciduline (Scheme 31).\(^{45}\)

**Scheme 31.** Similarity in Structure of Zone C and Luciduline

The asymmetric total synthesis of (+)-luciduline was achieved in the Comins labs using the dihydropyridone technology described in the introductory section. As such, our first efforts toward the target fragment took aim at incorporating this methodology. As shown in Scheme 31, the key step in the luciduline synthesis was an intramolecular Diels-Alder (IMDA) reaction of \(110\) to establish the stereochemical configurations at the carbon atoms indicated.
Our efforts in this regard began with the synthesis of the chiral side chain. The synthesis is achieved using Evans’ oxazolidinone chemistry (Scheme 32).^{46}

Scheme 32. Preparation of Chiral Grignard Reagent 118

Oxazolidinone 113 was prepared by treatment of the commercially available (1R,2S)-norephedrine with diethyl carbonate. Acylation of 113 with propionyl chloride proceeded smoothly to furnish the imide 114. Deprotonation with LDA at -78 °C followed by the addition of allyl bromide provided 115. Reductive cleavage from the oxazolidinone gave the chiral alcohol 116 along with recovered chiral auxiliary 113. Chlorination of the alcohol was
achieved with PPh₃ and N-chlorosuccinimide to give the alkyl chloride 117. The Grignard reagent was prepared by refluxing the alkyl chloride over activated Mg powder to provide 118.

The synthesis toward zone C was initiated by the addition of the chiral Grignard reagent 118 to the homochiral 1-acylpyridinium salt formed from 3-TIPS-4-methoxypyridine and (+)-TCC chloroformate (Scheme 33). Upon aqueous acidic workup, dihydropyridone 119 was generated in 88% yield and 90% de (determined by HPLC). Recrystallization of the crude product from toluene provided 119 as a single diastereomer. The ease of purification allowed for the preparation of this chiral starting material on a 45 g scale. The TCC carbamate was removed by sodium methoxide in refluxing methanol, and without workup, the pot was acidified with concentrated aqueous HCl to effect a protodesilylation reaction to furnish the fully deprotected N-H dihydropyridone 120. The nitrogen was reacylated by deprotonation with n-BuLi at low temperature followed by quenching with benzyl chloroformate to give the enantiomerically pure N-acyldihydropyridone 121. Oxidative cleavage of the terminal olefin with catalytic OsO₄ and stoichiometric NaIO₄ provided the aldehyde 122 in excellent yield which was followed by a Horner-Wadsworth-Emmons reaction leading to the α,β-unsaturated ester 123. This reaction gave the trans olefin exclusively. Reduction of the C4 carbonyl with CeCl₃·7H₂O and NaBH₄ gave a 7:1 ratio of diastereomers at 0 °C.⁴⁷ Without purification, this mixture of diastereomers was treated with a premixed solution of MsCl, DMAP, and H₂O (known henceforth as Furukawa’s reagent)⁴⁸ affording the key IMDA substrate 112 in excellent yield.
Scheme 33. First Generation Route to Zone C

The completion of the synthesis is given in Scheme 34. Upon refluxing in toluene for 5 days the intramolecular Diels-Alder adduct 124 is obtained in 60% yield. It was observed that reaction times are decreased substantially in xylenes, albeit at a lower yield of final product.
This Diels-Alder reaction is entirely stereoselective and the tricyclic adduct 124 is in accord with the Alder rule predicting the product of the *endo* approach transition state. The reaction sets all of the stereogenic centers contained in zone C; however, it also incorporates an auxiliary bond that must be broken to realize the bicyclic compound. This task was accomplished by simultaneous removal of the Cbz group and olefin reduction using Pd on carbon under an atmosphere of hydrogen to furnish 125. The bond cleavage reaction was then achieved through a retro-Mannich reaction sequence which entails treatment of 125 with 10 equivalents of LDA and 10 equivalents of diisopropylamine, followed by trapping the intermediate dianion generated with chlorotrimethylsilane. Reprotection of the nitrogen as a benzyl carbamate, and acid hydrolysis affords 126. The methyl ester is then saponified with LiOH to provide the carboxylic acid 127 as the precursor to decarboxylation. Although the
yield of this overall sequence was poor (17-29%), the reaction is of considerable merit given that a stable C-C bond is being cleaved. The mechanism of the retro-Mannich reaction is given in Scheme 35.

**Scheme 35. Retro-Mannich Reaction Mechanism**

Treatment of 125 with excess LDA gives the dianion 128. There is a small equilibrium established between the 128 and the monoanion 129. The pKa of a methyl ester is
approximately 25, and diisopropylamine is 36; therefore, the equilibrium lies far to the left (dianion). However, formation of 129 through this equilibrium is followed by an irreversible retro-Mannich ring opening reaction giving rise to the ester enolate 130. The favorable free energy of formation for 130 likely results from beneficial enthalpic and entropic parameters. In the presence of the excess LDA, the generated imine is deprotonated to establish the more thermodynamically stable metalloenamine 131. Quenching of the dianion with TMSCl, produces intermediate 132, which in turn is treated with benzyl chloroformate to give 133. Hydrolysis of the silylketene acetal affords the methyl ester 126 that is saponified by LiOH to the carboxylic acid 127. At this stage, only a decarboxylation/iodination reaction separated us from arrival of the target fragment of spirolucidine. Unfortunately, treatment of 127 with the mild Suarez halodecarboxylation conditions employing iodobenzene diacetate (IDBA) resulted in complete decomposition of the starting material (Scheme 36).49

**Scheme 36. Attempted Iododecarboxylation Reaction**

We attribute the presence of the olefin to the failure of the reaction to provide product. The decarboxylation is a radical mediated process, and the intermediate radicals that are formed
in the reaction may undergo attack on the electron rich olefin by an intermolecular or intramolecular mechanism. This iododecarboxylation reaction is still under investigation, and may require protection of the olefin.

3.2. Ring Opening through an E1cB Type Elimination.

Faced with the poor yields of the retro-Mannich reaction, we decided to investigate another means of ring opening the tricyclic adduct obtained from the Diels–Alder reaction. As illustrated in Scheme 35, the retro-Mannich reaction was thwarted by reversible proton transfers which favor a dianionic intermediate that is incapable of ring opening. As a means to circumvent this equilibrium, it was envisioned that if the anion could be formed next to the bridge on an N-protected intermediate 135, ring opening could be achieved in a facile manner yielding 126 (Scheme 37).

Scheme 37. Anionic Ring Opening Reaction

This concept could in principle be synthetically borne out by instituting a halogen atom alpha to the bridge as in 135 (Scheme 38). Oxidative addition of a zero valent metal such as zinc
would render the σ-organometallic 137 that should undergo rapid ring opening through an E1cB mechanism to yield the target bicycle.

**Scheme 38. Organometallic Elimination Ring Opening Reaction**

![Scheme 38](image)

Faced with this notion, our attention now turned toward how to incorporate the bromine atom within the scaffold. The solution to the problem was rather apparent given that the 5-position of a dihydropyridone corresponds to this position in the bicycle as shown in Scheme 39. Moreover, the 5-position is susceptible to electrophilic substitutions with the appropriate reagents.

**Scheme 39. Retrosynthetic Incorporation of Bromine**

![Scheme 39](image)
A model study was launched in which a racemic dihydropyridone lacking the chiral side chain was prepared in place of the more costly enantiopure compound. Accordingly, dihydropyridone 139 was formed by treatment of the pyridinium salt of 4-methoxypyridine and benzyl chloroformate with pentenyl Grignard, followed by acid hydrolysis (Scheme 40). Bromination of the 5-position was achieved using \( N \)-bromosuccinimide (NBS) to give the 5-bromodihydropyridone 140 in excellent yield.

**Scheme 40.** Preparation of the 5-Bromodihydropyridone

\[
\begin{align*}
\text{OMe} &\quad \text{28} \\
\text{pyridine} &\quad 1) \text{BnOCl, -50 °C, THF} \\
\quad &\quad 2) \text{THF, MgBr} \\
\quad &\quad 3) \text{H}^+ \\
&\quad \quad \quad 88\% \\
&\quad \quad \quad \text{139} \\
&\quad \quad \quad \text{NBS, CH}_2\text{Cl}_2 \\
&\quad \quad \quad \quad \quad 92\% \\
&\quad \quad \quad \quad \quad \text{140}
\end{align*}
\]

From this juncture, the rest of the synthesis was initially projected to take the same course as previously outlined up to the Diels-Alder cyclization. The olefin was subsequently cleaved with catalytic OsO\(_4\) and NaIO\(_4\) with success yielding 141, but it was rapidly discovered that beyond this reaction, the bromine atom greatly alters the reactivity of the later intermediates. One manifestation of this was the failure of the Horner-Wadsworth-Emmons reaction to work which gave instead mostly decomposition (Scheme 41).
Scheme 41. Attempted Elaboration of the Side Chain

By NMR analysis it was determined that the phosphonate anion was reacting primarily with the vinylogous amide in a Michael fashion instead of the aldehyde of 141. This problem was assuaged by an initial installation of the α,β-unsaturated ester followed by a selective bromination reaction (Scheme 42).
In this manner, the bromo-dihydropyridone 142 was delivered in high isolated yield. Reduction of the C4 carbonyl gave an 8:1 (trans:cis) mixture of alcohol diastereomers (145). It was quite unexpected however, that 145 did not undergo elimination to the diene on treatment with Furukawa’s reagent. This result is in stark contrast to the non-brominated analog which dehydrated in a rapid and high yielding manner under these conditions. The obdurate nature of 145 to eliminate forced us to employ other reagents to achieve this means. Table 1 illustrates our effort in this regard.
Table 1. Attempted Elimination Reaction of 145a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Furukawa's Reagent, CH$_2$Cl$_2$, rt</td>
<td>Mesylation observed, but no elimination</td>
</tr>
<tr>
<td>2</td>
<td>Furukawa's Reagent, CHCl$_3$</td>
<td>Mesylation observed, but no elimination</td>
</tr>
<tr>
<td>3</td>
<td>Burgess Reagent, PhH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>MsCl, DMAP; then DBU -20 °C, CH$_2$Cl$_2$</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>Ac$_2$O, pyridine, DMAP, then DBU</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Sadly, the elimination did not occur under any of the conditions tried. We subsequently attempted a radical mediated elimination.$^{50}$ Bromination of the dihydropyridone 144 with PTAP, gave the di-bromodihydropyridone 147. Reduction of the ketone under Luche conditions and acylation with thiocarbonyldiimidazole gave adduct 149 which was worked up and directly treated with Bu$_3$SnH and AIBN to effect radical mediated formation of the alkene. The reaction was unproductive and provided many unidentified products, none of which was the desired dihydropyridine 146.
We then rationalized that the orientation of the hydroxyl group might be preventing the reaction from occurring. The major product of the Luche reduction is the trans alcohol of 145. Given that the C2 substituent is axial owing to $A^{1,3}$ strain, the hydroxyl function is necessarily equatorial. It was reasoned that if the hydroxyl moiety were axial, the elimination may occur due to better overlap of the molecular orbitals involved. The C4 epimer was therefore prepared by reaction of 142 with DIBAL, and 2,6-di-tert-butyl-4-methyl-phenol (150) which gave 145b as the only detectable diastereomer. $^{51}$
The relative stereochemistry of 145b was confirmed to be the cis stereoisomer by 1D-NOESY. The turnover of stereochemistry using this reagent versus the Luche reduction is illustrated in Figure 7.
There is a stereoelectronic preference for small nucleophiles to approach from the axial direction to avoid torsional interactions with flanking methylene groups (151). However, the aluminum reagent with the bulky phenolic ligand must approach from the less encumbered equatorial direction. Hydride delivery then proceeds through an oxy ene mechanism (153). Gratifyingly, on treatment with Furukawa’s reagent, 150 formed bromodihydropyridine 146 in 60% yield (Scheme 45).
**Scheme 45.** Preparation of the Bromo Diels-Alder Adduct

The following model is offered to account for the behavior of the C4 epimers toward elimination. Mesylation of compound \textbf{145a}, the product of the Luche reduction results in intermediate \textbf{156} (Scheme 46).
Scheme 46. Rationale for Reactivity of the C4 Epimers

Apparently, the orbital overlap of the equatorial mesylate is not sufficient to allow elimination. Moreover, **156** does not ring flip to place the mesylate in an axial position (**157**). Torsional strain caused by the bromine atom may provide this barrier to the ring flip. In the case of the successful pathway involving **150a**, mesylation yields compound **158** which is prone to elimination by virtue of the axially disposed mesylate. This compound need not cross over a barrier in order to achieve the necessary conformation for elimination to **146a**. It is likely that the elimination reaction is promoted by the nitrogen and is unimolecular in rate (E1). However, the axial orientation of the mesylate would also place the H at C3 in an antiperiplanar configuration with the mesylate. Accordingly, an E2 reaction mechanism cannot be entirely ruled out.
With compound 146 in hand, the IMDA reaction was executed by refluxing in xylenes to cede the tricyclic vinyl bromide 155 (Scheme 45). It was noted that the presence of the bromine atom rendered some additional stability to the diene relative to its nonbrominated counterpart. We had now arrived at a critical point in the synthesis. The only reaction that needed to be performed before the proposed ring opening was a reduction of the alkene in 155 without concomitant reduction of the carbon-bromine bond. The literature is relatively void of reactions of this type as most reductions involving transition metal catalysts would also reductively dehalogenate. However, one important reagent in this regard was diimide.\textsuperscript{52} We therefore hoped that diimide could successfully be employed to reduce the vinyl bromide to render the alkyl bromide precursor to ring opening. Table 2 illustrates the effort toward this goal.
Table 2. Attempted Reduction of Vinyl Bromide 155 by Diimide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0 eq PADA, AcOH, THF</td>
<td>only SM isolated</td>
</tr>
<tr>
<td>2</td>
<td>2.0 eq PADA, AcOH, pyridine</td>
<td>only SM isolated</td>
</tr>
<tr>
<td>3</td>
<td>10 eq. PADA, AcOH, pyridine 50 °C</td>
<td>only SM isolated</td>
</tr>
<tr>
<td>4</td>
<td>100 eq. PADA, AcOH, pyridine, 15 d</td>
<td>only SM isolated</td>
</tr>
<tr>
<td>5</td>
<td>5.0 eq H₂NNH₂, CuSO₄, H₂O₂</td>
<td>only SM isolated</td>
</tr>
<tr>
<td>6</td>
<td>5.0 eq H₂NNH₂, O₂, EtOH</td>
<td>only SM isolated</td>
</tr>
</tbody>
</table>

Sadly, diimide was not able to reduce the olefin under any set of conditions tried. Based on the precedent illustrated in Figure 8⁵³, it must be concluded that the presence of the methyl ester sterically prohibits the reduction by diimide from the exocyclic face.
favorable approach of diimide

\[
\begin{align*}
\text{N=N} & \quad \text{H} \\
\text{H} & \quad \text{N=N} \\
\text{O} & \quad \text{H} \\
\text{O} & \quad \text{Br}
\end{align*}
\]

160 \quad \text{PADA} \quad \text{HOAc}

161

precedent from reference 53

diimide blocked by carbomethoxy group

\[
\begin{align*}
\text{N=N} & \quad \text{H} \\
\text{H} & \quad \text{N=N} \\
\text{O} & \quad \text{H} \\
\text{BnO}_2\text{C} & \quad \text{N} \\
\text{Br} & \quad \text{Br}
\end{align*}
\]

155 \quad \text{H}

159

**Figure 8.** Comparison of Diimide Reductions

A final effort was made at reducing 155 by catalytic hydrogenation using rhodium on an alumina support (Scheme 47). \(^{54}\)
Scheme 47. Catalytic Hydrogenation of the Vinyl Bromide

As seen in the scheme, the reaction resulted in a mixture alkyl bromide and alkane, along with benzyl carbamate reduction down to the cyclohexylmethyl carbamate. The conditions could not be modified to change this outcome. Therefore, this route had to be abandoned for lack of a way to establish the ring opening precursor (Scheme 48).

3.3. Chirality Transfer Reactions.

Concerted reactions are powerful tools in organic synthesis, particularly when they establish a chiral center. The utility of these reactions is further enhanced when the chirality can be set at one center and transferred to another part of the molecule that would otherwise be difficult to install with stereochemical control. The following retrosynthetic scheme is based on such a concept.
It is envisioned that zone C could arise from a regioselective and diastereoselective reduction of alcohol 163. The TIPS group would serve to block the C5-C6 double bond thereby giving rise to the regioselectivity. The pseudo cup shaped structure of the molecule would lend toward a diastereoselective hydrogenation from the convex face giving rise to the cis- fused ring system. The bicyclic diene 163 would come from a [2,3]-sigmatropic (Wittig) rearrangement of 164, which would in turn be formed through a Williamson etherification of 165. The allylic alcohol would be fashioned from the diastereoselective reduction on bicyclic ketone 166. Finally, the ketone is formed by an intramolecular aldol reaction of the aldehyde-tethered dihydropyridone 167.
The retrosynthetic analysis was shown for the chiral target molecule, but efficacy of this route was probed using racemic material. Accordingly, the synthesis began with the reaction of pentenylmagnesium bromide with the acylpyridinium salt of 3-TIPS-4-methoxypyridine and benzyl chloroformate, which on aqueous acidic workup gave dihydropyridone 168 in excellent yield (Scheme 49).

Scheme 49. Generation of Ketone 171

The terminal olefin is cleaved to give aldehyde 169 which was then subsequently treated with tosic acid in benzene to give the di-α,β-unsaturated ketone 171. It should be noted here that the elimination of the intermediate β-hydroxyketone diastereomers 170 is particularly slow.
The observation that there is always some amount of starting ketoaldehyde present is likely indicative of the fact that the $\beta$-hydroxyketone intermediate undergoes a retro-aldol reaction. Also complicating this reaction is the fact that the product undergoes isomerization to the bicyclic pyridone 172 when heated to temperatures higher than 50 °C (Scheme 50).

**Scheme 50. Olefin Isomerization Induced by Heating**

To circumvent this problem, the reaction was worked up after 2 h and then purified. The $\beta$-hydroxy ketone and the ketoaldehyde were isolated by purification and resubmitted to the dehydration conditions. This protocol allowed for the build up of a sufficient quantity of 171. The ketone of 171 was subsequently reduced using Luche conditions to give compound 173 as the only observed diastereomer (Scheme 51) which is confirmed by 1D-NOESY analysis.
The stereochemistry of this outcome is explained by steric approach control wherein the NaBH₄ attacks the ketone from the convex face of the pseudo cup shaped molecule. The significance of this event is that the stereochemistry set by this reduction at C4 would be transferred in the proposed Wittig rearrangement. To test the key rearrangement, all that remained was an etherification to install a methylcarbanion precursor. The iodomethyltributyltin reagent was chosen based on the methodology of Still. The tributylstannyl group undergoes facile lithium-tin exchange with n-BuLi at low temperature to result in the α-alkoxy anion. However, on treatment of 173 with KH at 0 °C followed by iodomethyltributyltin, 174 was not observed, but rather compound 175 was obtained in nearly quantitative yield, the product of a presumed Brook rearrangement.
This unexpected silyl migration presumably results from a 4-membered ring transition state shown in Scheme 53.

**Scheme 52. Attempted Williamson Ether Reaction**

![Chemical structures and reactions](image)

**Scheme 53. Rationale for Brook Rearrangement**

![Chemical structures](image)

Attack of the potassium alkoxide on the silicon results in the intermediary pentavalent silicon ate complex 176. This weakens the silicon-carbon bond substantially and upon addition of H$_2$O at workup, an ipso protonation readily occurs to provide 175. While this reaction type is
well substantiated in the literature, the one shown here is a rather remarkable example given the rigidity of the bicyclic system. The TIPS blocking group is crucial to our plan for completion of the synthesis; consequently, this route had to be modified to account for this unexpected result.

Given the difficulty in maintaining the vinyl TIPS group, it was conceived that the olefin the TIPS was designed to protect could be reduced and subsequently reintroduced after the Wittig rearrangement (Scheme 54).

**Scheme 54. Preparation of the Second Wittig Substrate**

![Scheme 54 Diagram](attachment:image.png)
This synthesis initiated with the formation of dihydropyridone 139 thorough an acylpyridinium salt reaction. Reduction of the C5-C6 alkene was accomplished by zinc in acetic acid at room temperature to give piperidone 177 in excellent yield. Cleavage of the terminal olefin with OsO₄ and NaIO₄ was executed to render the ketoaldehyde 178. The bicycle was formed by an intramolecular acid-catalyzed ring closure to afford the α,β-unsaturated ketone 179. Reduction of the ketone under Luche conditions led to the completely stereoselective formation of alcohol diastereomer 180 which was confirmed by 1D-NOESY. The stereochemical outcome of the latter reaction may once again be explained by the attack of the reducing agent from the convex face of the pseudo cup shaped molecule. With alcohol 180 in hand, a Williamson etherification was successful to furnish 181 as the key Wittig rearrangement precursor. Hence we had reached a critical step along this synthesis. Table 3 details the attempts at promoting the key chirality transfer step.
Table 3. Attempted [2,3]-Sigmatropic Rearrangement

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 eq n-BuLi, THF, -78 °C</td>
<td>only sm 181 isolated</td>
</tr>
<tr>
<td>2</td>
<td>2.0 eq, n-BuLi, THF, -78 °C</td>
<td>isolated 183</td>
</tr>
<tr>
<td>3</td>
<td>2.0 eq, n-BuLi, THF, -78 °C, warm to -50 °C</td>
<td>isolated 184</td>
</tr>
<tr>
<td>4</td>
<td>1.0 eq n-BuLi -78 °C, THF, warm to -40 °C</td>
<td>isolated 181 and 183</td>
</tr>
</tbody>
</table>

Treatment of stannane 181 with 1.0 eq of n-BuLi at -78 °C for 1 h, resulted only in recovered stannane. The reaction was repeated (entry 2) using 2.0 eq’s of n-BuLi, which resulted in the formation of methyl ether 183. This experiment showed that lithium-stannyl exchange
was occurring but the [2,3]-sigmatropic rearrangement was not. Raising the temperature from -78 °C to -50 °C after addition of the n-BuLi resulted in the formation of butyl amide 184 (entry 3). It was concluded from these studies that the transition state energy for the desired [2,3]-sigmatropic rearrangement was relatively high and could not be accessed at these temperatures. Contributing to this high energy intermediate are a) the requirement for formation of a five membered ring and hence some incorporated ring strain and b) the bicycle is relatively rigid and does not allow a great deal of conformational freedom to access proper alignment of the molecular orbitals for the reaction to take place. Toward the former argument, we proposed a [3,3]-sigmatropic rearrangement as opposed to a [2,3]-sigmatropic rearrangement. The ring strain of a six membered ring is absent which would contribute to a lower transition state energy than that needed in the Wittig rearrangement of 181. An Ireland-Claisen reaction was envisioned to address this new hypothesis. The precursor of this reaction was generated by treatment of the bicyclic allylic alcohol 180 with acetic anhydride to arrive at acetate 185 (Scheme 55). Following known procedure, conversion of the acetate to the lithium enolate at -78 °C and quenching with chlorotrimethylsilane formed the silyl ketene acetal 186. However, once again, rearrangement was not observed to give 187, and only acetate 185 was isolated on workup.
Given the failure of the Claisen type rearrangement to occur on this system, we investigated yet another type of rearrangement. Goering reported a syn selective S_N2’ reaction on allylic urethanes and organocuprates. This reaction is formally S_N2’; however, its actual mechanism is more appropriately placed in the pericyclic category. The proposed mechanism for the transformation is given in Scheme 56.
Deprotonation of the carbamate following addition of CuI would form a copper amide complex 188. This complex can then be treated with organolithiums or Grignard reagents to result in intermediates of the type 189. A [3,3]-sigmatropic rearrangement involving copper would result in a copper(III) intermediate 190 which would on reductive elimination provide 192. The utility of this reaction in the context proposed here is that hydroxyl can be used to deliver a group in a facially specific manner that is in the form of an organocuprate, thereby illustrating the use of chirality transfer. The formation of the phenyl carbamate 188 was executed by treatment of alcohol 180 with phenyl isocyanate and catalytic DMAP. It was decided that the SN2’ reaction depicted in Scheme 56 would be probed with the use of a methyl group. Accordingly, treatment of 188 with 1 eq. of methyl lithium followed by
treatment with CuI seemed to form the copper complex 189 by visual observations pointed out in the Goering paper. However, the complex on treatment with another equivalent of MeLi did not yield the expected product 193, and only the starting carbamate was isolated.

**Scheme 57. Attempted S_N2' Reaction**

Having explored various sigmatropic reactions to no avail, we turned our attention toward the conformational freedom of the bicycle. The \( A^{(1,3)} \) strain induced by the carbamate forces the bicycle into a pseudo cup shaped conformation which is rigid in nature. It was surmised that by reducing the carbamate, we might achieve greater conformational flexibility of the system, which would ultimately result in product formation. Elimination of the \( A^{(1,3)} \) strain of the carbamate could be achieved through removal of the acyl group on the nitrogen. This transformation could easily be realized by LAH reduction of the benzyl carbamate to the N-methyl compound. Thusly, carbamate 180 was treated with lithium aluminum hydride in refluxing THF to provide the amino alcohol 194 (Scheme 58). Without chromatography, the crude amino alcohol was directly treated with phenyl isocyanate to give the N-methyl urethane 195.
**Scheme 58. Attempted S_N2' Reaction of the N-Methyl Compound**

Once again however, the conditions described for the S_N2’ reaction failed to provide 196 on this system and we withdrew from these routes altogether.

### 3.4. Other Methods of Bicycle Formation.

In our efforts to form a bicyclic ring of the type displayed by zone C of spirolucidine, several other strategies were attempted. One such route involved the ring closure through a reductive Heck reaction of a vinyl triflate tethered dihydropyridine (Scheme 59).
An acylpyridinium salt reaction provided dihydropyridone 197. A subsequent Wacker reaction on the terminal olefin gave the expected methyl ketone 198 in good yield. The ketone was protected as ketal 199 using triethyl orthoformate and molecular sieves. A Luche reduction of the ketone to the allylic alcohol 200 proceeded smoothly and this substrate on treatment with Furukawa’s reagent gave the dihydropyridine methyl ketone 201. The
deprotection of the acetal under the latter conditions is attributed to the DMAP hydrochloride contained in the reaction. A kinetic enolization of the methyl ketone was achieved using LDA, and the generated enolate was trapped with Comins’ triflimide to result in vinyl triflate dihydropyridine 202. Subjection of the reaction to Pd(PPh₃)₂(OAc)₂ and sodium formate did not generate the product of an intramolecular Heck reaction, and gave mostly decomposition of the sensitive dihydropyridine.

A radical reaction of a tethered alkyne was also attempted based on precedent of forming 6-6 bicyclic systems (Scheme 60).

Scheme 60. Attempted Radical Formation of Bicycle

The TMS alkynyl Grignard reagent was used as the nucleophile in an acylpyridinium salt reaction to give dihydropyridone 205. Enolization with LDA followed by quenching with NBS gave bromodihydropyridone 206 as the only observed diastereomer. The bromo ketone
was not stable and was submitted quickly to treatment with tributyltin hydride and AIBN by slow addition using a syringe pump. The reaction gave a complete recovery of reduced ketone 205. This result indicates that the ring closing radical reaction occurs much more slowly than reduction.
CHAPTER 3: MODEL STUDIES TOWARD THE CONVERGENCE OF ZONES IN SPIROLUCIDINE

Introduction.

The completion of spirolucidine rests on the success of a highly convergent plan in which the two advanced bicyclic zones are coupled to a core dihydropyridone. This will inevitably lead to the formation of the spirocenter and functional group modifications to render the target compound. Model studies were needed to address some of the issues laid out in the retrosynthetic Scheme 28. The key step in the synthetic plan is the [2+2] photocycloaddition of an enecarbamate of zone C across the C5-C6 alkene of the zone B dihydropyridone. This reaction installs the spirocenter at C6 of the zone B. A model study of this photochemical reaction was executed in the Comins lab prior to synthesis of the key zone A and C fragments.\textsuperscript{62}

Scheme 61. [2+2] Photocyclization of Substrate 208

Photolysis of compound 208 gave tricycle 209 in a completely diastereoselective fashion. We attribute the diastereoselectivity to the axially disposed isobutyl substituent at the 2-
position which encourages photocyclization from the opposite $\pi$-face of the olefin. This model study lent a great deal of credence to our plan for the spirocyclic center formation in the target compound. However, there were several aspects that this model did not address, the first being that the ester function at C5 was not in place. Although this ester is not located in our target, its implementation will serve as a handle for incorporation of the 3-piperidone through the planned sequence shown below (Scheme 62).
From Scheme 62 it can be seen that the photoadduct 93, will be ring opened under dissolving metal conditions to give the spiropiperidone 210. A reduction of the ketone and elimination will form the α,β-unsaturated ester 211 that can be hydrolyzed and subjected to a Curtius rearrangement to afford the 3-piperidone nucleus of the title compound. It can also be
pointed out that investigation of the photochemistry was the key aim of the model study shown in Scheme 61; consequently, substrate 208 was not assembled in a means commensurate with our convergent plan for the actual synthesis. More specifically, our goal for the incorporation of the zone C fragment was to prepare an organocuprate from the iodide of C and perform a Michael addition into the zone B vinylogous amide. This reaction would be followed by a reinstallation of the olefin to give back the dihydropyridone with a 2,5,6-trisubstituted pattern (Scheme 63).

**Scheme 63. Implementation of Zone C and Enone Regeneration**
I. Olefin Addition Olefin Regeneration Model Studies

Given the issues described above, it was thought wise to probe the chemistry on a simple dihydropyridone system. Accordingly, the following model study was performed (Scheme 64).

Scheme 64. Preparation of Intermediate 218

Formation of an acylpyridinium salt by reaction of 4-methoxypyridine and phenyl chloroformate at low temperature was followed by treatment of benzylmagnesium chloride to
furnish dihydropyridone 214 on aqueous acidic workup. This reaction is a surrogate of how zone A will be coupled to the central zone B. While this reaction was performed in a racemic fashion here, the actual synthesis will employ the (+)-TCC chloroformate chiral auxiliary to control the absolute configuration of this new stereogenic center. The phenyl carbamate of 214 was removed and the nitrogen was reacylated with Boc₂O to afford 216. With the latter dihydropyridone achieved, the next focus was installing the critical ester at C5. This was achieved with a two-step sequence involving electrophilic iodination and palladium mediated carbyonylation. Toward this end, 216 was treated with iodine monochloride at -78 °C to provide the 5-iododihydropyridone 217. Subjecting of the iodide to Pd(OAc)₂(PPh₃)₂ and CO in MeOH furnished the key carbomethoxy group at C5 (218) in 60% yield. This corresponds to the zone A-zone B intermediate of spirolucidine (structure 95), which is the critical Michael substrate for the incorporation of zone C. Installation of the zone C mimetic was probed using the sequence in Scheme 65.
A copper mediated Grignard addition to of cyclohexylmethylmagnesium bromide was performed in the presence of chlorotrimethylsilane to give the enol silane adduct 219. The relative diastereomeric ratio of this reaction could not be determined due to the unstable nature of these compounds. This hydrolytically unstable intermediate was carefully worked up with NH₄OH/ NH₄Cl buffer to give crude 219, which was then treated with catalytic Pd(OAc)₂ and CuCl in an oxygen atmosphere to give dihydropyridone 220 in a very acceptable yield over two steps. The mechanism of this reaction is given in Scheme 66.
Nucleophilic attack of enol silane 219 on electrophilic palladium (II) renders a σ-organometallic (a palladium enolate) 221 which is followed by a β-hydride elimination with a hydrogen at C6 (222). This renders the desired dihydropyridone 220 and Pd(0) which is oxidized by the cooxidants CuCl₂ to Pd(II) that reenters the catalytic cycle. The CuCl₂ generated from the latter step is reoxidized in the presence of molecular oxygen. In the examination of this mechanism, it should be noted that one strict stereochemical requirement of the β-hydride elimination is that the hydrogen and the palladium be configurationally syn, otherwise this key aspect of the reaction cannot proceed. This critical aspect of the reaction
will be underscored later. The formation of the trifunctionalized dihydropyridone 220 completed this model study by supporting our plan for the cross coupling of the advanced zones A and C, and ester incorporation at C5.

With the success of the latter study we began the synthesis of zone C as outlined in Chapter II. During the course of this effort, it was deemed relevant to investigate the photochemistry of the zone B dihydropyridone containing the methyl ester at C5 (note that the model study in Scheme 61 did not include this methyl ester). At the outset, preparation of the desired substrate was deemed a trivial task as the methodology previously described would be adhered to leading toward the construction of a suitable photosubstrate. Accordingly, we chose to add the simple acyclic hexenyl group to circumvent the problem of producing diastereomers. The sequence is given in Scheme 67.

**Scheme 67. Attempted Olefin Regeneration of 223**

![Scheme 67](image)

218 → 223

218

223

224

225

Not formed

from hydrolyzed 223

99%

85%

35%

decomposition also observed

99%
The conjugate addition of the hexenyl group to the model zone A-B ester under the previously determined conditions gave 223 as expected. However, the oxidative rearrangement of the enol silane gave only 225, the product of simple hydrolysis of the enol silane accompanied by a copious amount of decomposition. It was reasoned that this reaction was stymied by the presence of the alkene, for which a mechanistic justification is depicted in Scheme 68.

**Scheme 68.** Mechanistic Rationale for the Failed Oxidative Rearrangement of 223
In can be postulated that there are two competing sites of reactivity and hence two different rate constants for the treatment of 223 with Pd(II). The first reaction, corresponds to the attack of the enol silane on the electrophilic Pd(II) (226), which leads to the desired dihydropyridone 221. We may assign the rate constant $k_1$ to this pathway. Alternatively, it is well known that Pd(II) coordinates to unactivated olefins. In this specific case, coordination to the terminal olefin of 223 defined by rate $k_2$ would give complex 227. Based on the experimental outcome, $k_2$ is apparently much faster than $k_1$, which may be attributed to the steric crowding around the silyl enol ether. Complex 227 leads to unproductive reaction pathways and thus, no detectable amounts of product are seen. This explanation is supported by the absence of the terminal olefin in the decomposition matrix. Interestingly, the observation of large amounts of decomposition in this reaction would seem to indicate that the palladium is being turned over catalytically, albeit by an unknown mechanism. Based on the reports from Nicolaou, we also attempted the oxidation with IBX using 4-methoxypyridine-N-oxide (MPO). This reaction also proved devoid of product formation and primarily gave hydrolysis (Scheme 69).
Scheme 69. Attempted Oxidation of Silyl Enol Ether by IBX

![Chemical structure]

The lack of response of silyl enol ether 223 toward olefin regeneration prompted us to investigate the ketoester 225. In general, dialkylcuprates prepared from the Grignard reagents were found to give the best outcomes with substrate 218 (Scheme 70).

Scheme 70. The Conjugate Addition of Dialkylcuprates to Dihydropyridone 218

![Chemical structure]
The conjugate addition reaction of the dialkylcuprate 228 gave the best overall yield of products 225a/b. A 4:1 cis: trans diastereoselectivity was obtained from the reaction, and it is notable from the $^1$H NMR that the enol tautomer of structures 225a/b predominates. Although these diastereomers could be separated, the mixture was taken on to the selenation step in hopes that both diastereomers would converge back to the dihydropyridone. Reaction of the 225a/b with phenylselenyl chloride and pyridine yielded an inseparable mixture of compounds, 229 and 230 (Scheme 71).

**Scheme 71. Selenation of Compound 225**

![Scheme 71](image)

The reaction of selenium at the terminal olefin is a result commensurate with the palladium mediated olefin regeneration (Scheme 68). We were able to circumvent the problem of phenylselenide addition to the olefin in the side chain by preparing the sodium enolate of the β-keto ester in THF followed by slow addition of the phenylselenyl chloride to provide 229 (Scheme 72).
Structure 229 contains 3 stereogenic centers, and therefore the mixture can be composed of four diastereomers. The NMR of selenide 229 is exceedingly complex and therefore inconclusive as to the number or ratio of diastereomers obtained from this reaction. Moreover, this diasteromeric selenide mixture is inseparable on TLC. We therefore proceeded to the oxidation step in hopes that the problem of diastereomers generated would be inconsequential given a successful thermal elimination. Treatment of 229 with 30% aqueous peroxides in dichloromethane gave two polar spots on the TLC, which were presumed to be the selenoxides 231 (NMR seems to support the formation of selenoxide diastereomers). However, stirring the reaction over 12 hours at rt resulted in no observed dihydropyridone formation of 224. The reaction was subsequently heated to 40 °C for 3 h,
but resulted in decomposition. The failure of this elimination to occur would seem to indicate that we obtained diastereomers of 229 which place the selenium and the hexenyl group in a \textit{syn} facial configuration on the piperidone.

**II. Directed Lithiations toward the Desired Model Compound**

Given the preceding discussion, we were challenged to find yet another method to achieve the task of rendering the photochemical precursor. The sp$^3$ hybridization of C5 and C6 presents a difficult barrier to the formation of an olefin by standard methods due to relative stereochemical requirements of what is placed on C5 and C6. Furthermore, we cannot rule out that the conformational bias of structures of the type 231 have transition state energies for thermal elimination in an unattainable regime even for the configurationally \textit{syn} diastereomer. Given our rigorous, but rather dismal efforts at this juncture, we devised a conceptually different strategy that directly addressed these key problems. Our new approach took aim at installing the desired substituents on C5 and C6 on sp$^2$ carbons on a system generalized as 232 instead of the asymmetric sp$^3$ carbons (Figure 9).

![Figure 9. New Strategy for Producing the Zone A-B-C Model](image-url)
This strategy eliminates the need to reinstall the olefin where our efforts were entirely unsuccessful in previous cases. The new plan was wrought with challenges as well, as it became immediately necessary as to what to place on C5 and C6 as X and Y respectively that would favor functionalization. Our consideration gave way to the retrosynthetic analysis in Scheme 73.

Scheme 73. Retrosynthetic Analysis Based on a Directed Lithiation to Functionalize C6

Disconnection of the C-C bond at C6 of the generalized target 233 could provide the 6-chlorodihydropyridone 234 that contains the ester group at C5. It was also surmised that 234 would serve as a valuable intermediate to our target, due to the possibility of installing the critical C6 fragment to provide compounds of the type 233 in one step without the problem of intermediate diastereomers. This could likely be achieved with organocopper chemistry or
with palladium, the latter being considered of greater utility in the context of complex molecule synthesis. Compound 234 would arise from the chloro-iodo-dihydropyridone 235, and it was rationalized that a carbonylation reaction at the C5 carbon-iodide bond could be achieved preferentially over the carbon-chloride bond at C6. It was plausible to supply the iodine at C5 by an electrophilic substitution reaction on the chlorodihydropyridone. Finally, 236 would be generated from the 6-chlorodihydropyridine 237 which in turn would be supplied from lithiate 238.65

In deference to this new plan, our synthesis began with an acylpyridinium salt reaction of 4-methoxypyridine and phenyl chloroformate with butylmagnesium chloride to give dihydropyridine 239 on workup with aqueous NH₄Cl/ NH₄OH (Scheme 74).

**Scheme 74. Directed Litiation to Form a C6 Substituted Dihydropyridone**
A carbamate exchange was effected by subjecting 239 to 3 eq of KOTBu in THF to provide the N-Boc dihydropyridine 240. This carbamate exchange is necessary to prevent attack of the reactive alkyllithium at the carbamate carbonyl center. A comment concerning the stability of compounds of the type 240 is warranted. It is known that dihydropyridines are not stable compounds and are prone to decomposition by acid, oxygen, and light. As a measure of precaution, the compounds (all thick oils) were stored under an atmosphere of argon, at -50 °C, in a flask covered with foil. Under these conditions the dihydropyridines were preserved for well over a month without detection of decomposition products in the NMR. The directed lithiation of 240 was achieved with 1.3 eq of n-BuLi in THF at -42 °C and was followed by quenching with the electrophile hexachloroethane at -78 °C to provide the chlorinated dihydropyridine 242. Aqueous oxalic acid was added to hydrolyze the enol ether affording 243 in excellent yield. The next step of the plan required the installation of iodine at C5. We employed the reagent ICl to accomplish this; however, the yield using our previously developed conditions was poor (table 4; entry 1). We determined that there was an interesting solvent effect in our attempt to optimize this reaction which is detailed in Table 4.
The formation of the N-acylpyridone 245 was a byproduct and is most likely catalyzed by acid generated from the reaction. Acid scavengers were found ineffective (data not shown), but fortunately, this pathway can be suppressed in other solvents. The optimized yield resulted from ethyl acetate at low temperature (entry 3). Dihydropyridone 244 was then subjected to the carbonylation conditions (Scheme 75).

Table 4. Electrophilic Iodination Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1 eq ICl, CH₂Cl₂, 0 °C, 1 h</td>
<td>45% 244; 37% 245</td>
</tr>
<tr>
<td>2</td>
<td>1.1 eq ICl, -78 °C, THF, 1 h</td>
<td>64% 244; 21% 245</td>
</tr>
<tr>
<td>3</td>
<td>1.1 eq ICl, -78 °C, EtOAc, 3 h</td>
<td>88% 244; 5% 245</td>
</tr>
<tr>
<td>4</td>
<td>1.1 eq ICl, -50 °C, PhCH₃</td>
<td>76% 244, 12% 245</td>
</tr>
</tbody>
</table>
We were disappointed to find that the previously employed conditions for this reaction resulted in mostly diester 246, along with decomposition products. The reaction was repeated at room temperature and under atmospheric CO; however, no carbylation was observed under these mild conditions.

Failed attempts at installing the ester forced us to devise an alternate plan. This strategy can be depicted in a second retrosynthetic analysis shown in Scheme 76.
**Scheme 76. Second Generation Retrosynthetic Analysis of Target Structure 233 Based on Tandem Directed Lithiations**

It was surmised that the target compound 233 could still arise from key chloroester-dihydropyridone 234 which itself might be spawned from the hydrolysis of the dihydropyridine 248 that has these substituents attached. Moreover, this substituted dihydropyridone could be generated from lithiated intermediate 249 through treatment of methyl chloroformate as the electrophile. The organolithiate 249 might be rendered on treatment of an alkyllithium with the functionalized dihydropyridine 237. It should be recalled that dihydropyridine 237 is also the product of a directed lithiation of 238. Therefore, this new strategy can be summarized by invoking tandem lithiations at C6 followed by C5, to load the necessary components on the dihydropyridine leading to the synthetically useful dihydropyridone. The chemistry toward this new plan began with the preparation of dihydropyridine 250 (Scheme 77).
Carbamate exchange to the N-Boc dihydropyridine 251 was uneventful, as was the directed lithiation and chlorination to provide 252. To probe the second lithiation step in this sequence, 252 was treated with 1.3 eq of n-BuLi at -78 °C, and the temperature was warmed to -50 °C for 30 min, followed by D₂O addition. Workup with aqueous oxalic acid rendered the 5-deuterio-6-chloro-dihydropyridone 255 as the only product. This impressive result lent much credence to our plan for a directed lithiation to install an ester group at this position. A review of the literature has shown this lithiation, which occurs at the relatively electron rich position of the dihydropyridine to be very novel. In this regard, one cannot
underestimate the value of the chloro substituent at C6 which combined with the C4 methoxy group contributes a powerful directing and stabilizing effect to render 253. We proceeded to test this reaction with the appropriate electrophile to provide a methyl ester (Scheme 78).

Scheme 78. Formation of the Chloro Ester 256

Deprotonation under the same conditions and fast quenching with excess methyl chloroformate gave the intermediate dihydropyridine. On hydrolysis with oxalic acid, we were delighted to arrive at the key precursor, dihydropyridone 256. The latter compound possesses the desired ester at C5 and a handle for the direct coupling of the zone C surrogate at C6. The latter methodology proved to be quite general and will be discussed in the final chapter in this dissertation.

It can be appreciated that the C6 chloro-substituent provides a useful handle for us to substitute a carbon nucleophile. Moreover, we have a choice as to which mechanistic genre to employ toward accomplishing this task. Strong nucleophiles, such as organocuprates can add to 256 in a Michael fashion to produce intermediates of the type 257 and eliminate chloride through an addition-elimination mechanism (the elimination step to 258 is classified as an E1cB mechanism). Alternatively, palladium chemistry can be used to provide access to
substitutions using a variety of potential coupling partners. The latter mechanistically employs oxidative addition of palladium into the C-Cl bond (259) followed by transmetallation from a number of possible sources (such as organotin or organoboron compounds) to facilitate the C-C bond. These approaches are summarized in Scheme 79.

**Scheme 79.** Substitution of C6 by Different Mechanisms

**Addition - Elimination**

**Palladium Chemistry**

The following reaction conditions shown in Scheme 80 were found to be effective in the substitution of the desired hexenyl group at C6.
Scheme 80. Substitution at the 6-position

Treatment of the monoalkylcyano cuprate 262 with 256 at -30 °C resulted in the desired coupled substrate 263 in good yield. The reactivity of 256 toward other organocuprates is discussed in the following chapter.

We had now reached the critical stage of probing the photocycloaddition reaction. However, it was a disappointment that photolysis of 263 in acetone for 30 min gave only decomposition (Scheme 81).

Scheme 81. Attempted Photochemical Cycloaddition of 263

Shortening the reaction time to 15 minutes, or running the reaction in acetonitrile gave the same undesirable outcome. It was known that there was no precedent for photocyclization
on systems of the type shown here. We therefore rationalized that the C5 ester perturbs the photochemical reactivity to a great extent, and had to be excised.

Armed with the knowledge that dihydropyridones possessing no substitution at C5 readily photolyze to give cyclobutyl adducts in good yield, we propose to alter our plan by removing the ester. It was discussed earlier that the ester was incorporated into zone B for the purpose of providing a synthetic handle to prepare the 3-piperidone nucleus that the natural product contains. Therein, a new challenge arises for us, which can be seen in Scheme 82.

**Scheme 82. The Challenge of Regiochemically Manipulating Substrate 267**

The photochemical reaction of 265 would provide 266. In the absence of the ester at C5, there is good precedent that the cycloadduct will form.\(^\text{28}\) If we proceed to cleave the
cyclobutyl ring, spiropiperidone 267 would result. We are now faced with the task of functionalizing this substrate in a regioselective manner. Substituting α,α'-methylene ketones in a nonsymmetrical molecule such as 267 is a difficult task to accomplish, and is made further daunting by the fact that functionalization is needed adjacent to the spirocenter at C3. It can thusly be appreciated why such effort was put forth to install the ester function to chemically differentiate these two sides of the ketone. However, in light of our need for a new plan, the following route was devised (Scheme 83).

**Scheme 83.** Proposed Allylic Selenoxide Rearrangement Toward the Completion of Spirolucidine

![Scheme 83](image-url)
It was rationalized that under the proper conditions, we might be able to kinetically deprotonate at C5 due to the bulky spirocyclic center at C2. Trapping of this enolate with phenyl selenylchloride should provide 268. A second deprotonation of the ketone should provide the C3-C4 enolate, which on trapping with Comins’ triflimide provide enol triflate 269. Upon oxidation to a selenoxide, this substrate would be expected to undergo a [2,3]-sigmatropic rearrangement (270) to provide 271 on aqueous workup. The vinyl triflate can be completely reduced by catalytic hydrogenation and the secondary hydroxyl group oxidized to the ketone to complete the model study.
I. Directed Lithiations to Form 2,6-Disubstituted Dihydropyridones.

Directed ortho metalation (DoM) is an effective way of controlling regiochemistry in the substitution of various electron rich and electron deficient aromatic systems. Although this chemistry has been utilized primarily in the realm of various aromatic compounds, its utility can be extended beyond such systems. We utilized directed lithiations as a means of providing access to key intermediates during model studies aimed at the total synthesis of the alkaloid spirolucidine (chapter II). As shown in Scheme 84, we initiated the study with the iodination of the C6 position following hydrolysis to afford the 6-iododihydropyridone 275.
In this regard, the C6 position of the dihydropyridone can be efficiently substituted with various electrophiles. Several limitations of this reaction are worth mention. First, a hindered carbamate must be utilized to thwart attack on the carbonyl by $n$-BuLi in the lithiation step. Secondly, it was noted that an aryl group cannot serve as a substituent at the 2-position given the following experiment that was run as Scheme 85.
Scheme 85. Directed Lithiation of 2-Aryl Dihydropyridines

Treatment of 276 with 1.3 eq of n-BuLi, followed by I₂ quenching under the same conditions as described above yielded only decomposition. It is surmised that if an aryl substituent resides at C2, the deprotonation at C2 is favored to form 277 as an anti-aromatic but highly resonance delocalized anion. This anion itself may undergo autodecomposition. Alternatively, 277 might iodinate to render the 2-iododihydropyridine intermediate, which decomposes on workup. Further investigations to determine if 277 can be trapped by other electrophiles are warranted.

With iodide 275 in hand, several reactions were explored to evaluate its reactivity and utility. The substrate proved remarkably receptive to Stille cross coupling conditions to produce the 6-vinylidihydropyridone 280 (Scheme 86).
The reaction illustrates that oxidative addition readily and effectively occurs on this system. This should open the door to many carbon-carbon bond forming reactions which proceed through such a mechanism. Compound 280 contains a diene, and it was thought that this system might undergo a Diels-Alder reaction. In this regard, 280 was refluxed with N-phenylmaleimide for 14 hours to give the adduct of cycloaddition 281 (Scheme 87).
Only one diastereomer was observed from the reaction; however, the identification of the relative stereochemistry has been inconclusive by NMR. The confirmation of the stereochemistry is pending X-ray crystallography.

II. Tandem Directed Lithiations to Form 2,5,6-Trisubstituted Dihydropyridones.

It was presented in the previous chapter that dihydropyridine 252 is an effective substrate for a second directed lithiation reaction. This discovery allowed the development of methodology for the preparation of a zone B mimic for spirolucidine. However, we were also interested in the generality of this reaction for installing various electrophiles at C5 (Table 5).
The scope of reactivity of the reaction is quite impressive, as it can be seen that a wide range of electrophiles were found to be effective. Furthermore, this route allows us to establish functionality at C5 that we had previously been unable to install. The latter is attributed to the strong nucleophilic character of the lithio-intermediate 253.

Given our very effective method of gaining entry into dihydropyridones of the type 282, we turned our attention to substituting the C6 position for delivering 2,5,6-trisubstituted dihydropyridones. As previously discussed in Chapter 3 (Scheme 79), we may choose from two methods to achieve this task; through the use of organocuprates or through palladium chemistry. Table 6 details the optimization of the reaction of organocuprates.

Table 5. Substitution of C5 with Various Electrophiles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile (E⁺)</th>
<th>Structure(E)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClCO₂Me (4.0 eq)</td>
<td>-CO₂CH₃ 256</td>
<td>77 %</td>
</tr>
<tr>
<td>2</td>
<td>MeSSMe (1.5 eq)</td>
<td>-SMe 282a</td>
<td>87%</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CH₂I (5.0 eq)</td>
<td>-CH₂CH₃ 282b</td>
<td>56%</td>
</tr>
<tr>
<td>4</td>
<td>I₂ (1.5 eq)</td>
<td>-I 282c</td>
<td>91%</td>
</tr>
</tbody>
</table>
Table 6. Conjugate Addition to Substrate 256 Using Various Organocopper Reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cuprate Formed</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
</table>
| 1     | Cu   | i.)add 2.05 eq of i-BuMgCl to CuBr·SM2, -78°C, THF  
      |     |  ii.) complex SM and 3.0 eq BF3OEt  
      |     | and cannulate to cuprate above | only Sm 256 isolated |
| 2     | CuCN(MgCl)2 | i) 2 eq i-BuMgCl added to CuCN  
      |     | ether slurry at -78°C; warm to -30°C for 5 min then  
      |     | then cool back to -78°C  
      |     | ii) cannulate SM in ether to cuprate and stir for 1 h  
      |     | at -78°C then 6 h at -50°C | only Sm 256 isolated |
| 3     | CuCN(MgCl)2 | modification of entry 1 by using THF | 2:1 256:283 obtained |
| 4     | CuCN(MgCl)2 | modification of entry 1 using 5 eq HMPA  
      |     | added to SM prior to addition to the | 2:3 256:283 |
| 5     | CuSPh(MgCl) | i) 1 eq i-BuMgCl added to CuSPh  
      |     | THF slurry at -78°C; warm to -15°C  
      |     | ii) cannulate SM in THF to cuprate and stir for 1 h  
      |     | at -15°C then warm to rt and stir 30 min | Product formed with  
      |     |  no trace of the sm 256  
      |     | however an unidentified side  
      |     | product results |
| 6     | CuCN(MgCl) | i) 2 eq i-BuMgCl added to CuCN  
      |     | THF slurry at -78°C; warm to -30°C quickly  
      |     | and stir for 10 min  
      |     | ii) cannulate SM in THF to cuprate and stir for 1 h  
      |     | at -20°C then warm to rt and stir 30 min | 76% 283 |
While we have had a great deal of success with organocopper reagents adding to dihydropyridones, many of these familiar conditions were not effective on the 6-halo derivatives. Entry 1 shows that the addition of a preformed dialkylcuprate with BF$_3$OEt$_2$ as a Lewis acid was ineffective. In general, dialkylcuprates alone were either sluggish or totally unreactive; however, the use of the additive HMPA promoted some reactivity but the yield was still generally low (data not shown). The use of higher order cyanocuprates (entry’s 2-4) gave a substantial increase in the observed reactivity, but the reactions could not be forced to completion. It was then discovered that the use of monalkylcuprates of the type shown in entry 6 were effective in adding an alkyl group to 256 at temperatures of -30 °C. Taken together, the results listed in Table 6, are indicative that the chlorine atom at C6 is actually deactivating the vinylogous amide system. This result can also be confirmed based on the substrate which lacks the C6 Cl atom (substrate 218) and undergoes reaction with cuprates in a facile and high yielding fashion. Although the chlorine inductively withdraws electron density, it can donate mesomerically. This effect would increase electron density within the π-system, raising the LUMO energy. Therefore, more thermal energy is required for the nucleophile to attack the enone system. Cuprates with cyanide ligands are more stable at higher temperatures (-20 °C) and thusly can react at these higher temperatures without suffering from decomposition pathways that are characteristic of other cuprates. We also cannot rule out that steric hindrance of the chloride might also play a role in deactivating the system as well.
Heteroatom substitutions were also investigated and it was found that an effective substitution of a methoxyl group at C6 could be achieved with NaOMe in MeOH (Scheme 88).

We were also intrigued by the use of palladium couplings on this system. The first investigations were toward a B-alkyl Suzuki type coupling using conditions described by Marshall (Scheme 89).66

**Scheme 88.** Attempted B-Alkyl Suzuki Type Cross Coupling of Compound 256

![Chemical Structure](image)

The failure of this reaction to give product was equated with the decomposition caused by the hydrolysis of the ester moiety (which was lacking in the NMR) by the aqueous base. Scheme 90 illustrates that a Negishii reaction was also attempted, but the result was equally unimpressive.
The failure of 256 to engage in a cross coupling reaction can likely be attributed to the use of a catalyst that is not reactive enough to insert into the C-Cl bond. There have been many developments in recent years pertaining to the coupling of aryl and vinyl chlorides using more electron rich catalysts. Accordingly, the application of these catalysts toward C6 functionalization of our dihydropyridone system is highly warranted.
A detailed account of the 2,3-dihydropyridone as a useful synthetic building block in organic synthesis was given. Furthermore, a plan was delineated that would, utilize the dihydropyridone toward a total synthesis of the alkaloid spirolicidine in Chapter 2. The key steps in the proposed synthesis are the preparation of two advanced hydroquinoline ring systems and their cross coupling to a central dihydropyridone scaffold. The synthesis of the enecarbamate fragment, zone C was considered at length. The first route investigated toward its synthesis involved an intramolecular Diels-Alder route to set the key stereogenic centers. However, we were unable to execute the last step of the sequence which was an iodo-decarboxylation reaction, and continued effort to achieve this transformation must be put forth. Other routes were investigated to generate this key fragment, based on an E1cB ring opening, several chirality transfer reactions, an intramolecular Heck reaction, and a radical mediated ring closure, but none were found effective to generate the target compound.

In Chapter 3, the strategy for coupling the key fragments together was examined. Palladium (II) initially seemed to provide an acceptable method of reestablishing the double bond, after a Michael addition of a zone C surrogate at C6 of the dihydropyridone. However, this methodology failed to work in the presence of an alkene. Toward this end, directed lithiation chemistry was found to be effective to provide a means for coupling both the zone C mimetic at C6 and an ester group at C5. This methodology allowed us to investigate the photochemistry of 5-(carbomethoxy)-dihydropyridones. The latter substrate was found not to undergo photocyclization with tethered olefins. Based on this finding, our plan will have to
be modified to excise this ester, while still maintaining control of functionalization of the central zone B ring.

Finally, Chapter four detailed some key reactions pertaining to the directed lithiation chemistry of N-Boc dihydropyridines. More specifically, both the C5 and the C6 positions can in tandem fashion be functionalized from lithio-dihydropyridine precursors which hydrolyze to give the dihydropyridones functionalized at those positions. This methodology will open several new avenues regarding the utility of the dihydropyridone.
**EXPERIMENTAL**

**General Experimental and Procedures.** All reactions were performed in oven or flame dried glassware under argon atmosphere and stirred magnetically. Tetrahydrofuran (THF), toluene, and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Diisopropylamine, triethylamine, and benzene were distilled from calcium hydride and stored under argon over 4 Å molecular sieves. n-Butyllithium was titrated periodically against diphenylacetic acid according to the method of Kofron and Baclawski. Grignard reagents, lithium bis(trimethylsilyl)amide (1.0 M solution in THF), anhydrous o-xylene, hydrazine, sodium methoxide (25% solution in MeOH), potassium tert-butoxide, palladium tetrakistriphenylphosphine, tributylvinyl tin, triphenylphosphine, copper(I) chloride, copper(I) bromide dimethyl sulfide complex, 5% palladium on carbon, phenyl chloroformate, benzyl chloroformate, DBU, DMSO, trimethylphosphono acetate, cerium chloride heptahydrate, iodine monochloride (1.0 M solution in dichloromethane), 4-methoxypyrididine, iodine beads, 5-bromo-1 hexene, diisobutylaluminum hydride, 1,2-dibromoethane, p-toluenesulfonic acid monohydrate, methanesulfonyl chloride were purchased from Aldrich Chemical Company and stored over 4 Å sieves. The 4-methoxy-3-(triisopropylsilyl)pyrididine was prepared from 4-methoxypyrididine according to procedure reported by Comins et al. \(^{17}\) (+)-TCC was prepared and resolved according to the method of Comins and Salvador. \(^{68}\) \(N\)-(5-chloropyridine-2-pyridyl)triflimide was prepared based on the procedure reported by Comins et al. \(^{59}\) Other reagents and solvents from commercial sources were stored under argon and used directly. Melting points were obtained from a Thomas-Hoover capillary
melting point apparatus and were uncorrected. Radial preparative layer chromatography (radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1, 2, or 4 mm layers of Kieselgel 60 PF254 containing gypsum. High-resolution mass spectral analysis (HRMS) was performed at North Carolina State University. Elemental analyses were performed by Atlantic Microlabs Inc. NMR spectra were obtained using Varian Gemini GN-300 (300 MHz), Varian Mercury 300 (300 MHz), or Varian Mercury 400 (400 MHz) spectrometer. Chemical shifts are in δ units (ppm) with TMS (0.0 ppm) used as the internal standard for H-NMR spectra and the CDCl₃ absorption (77.2 ppm) or C₆D₆ absorption (128.4) for ¹³C NMR spectra. IR spectra were recorded on a Perkin-Elmer 1430 spectrometer. HPLC was performed using Waters and Associates (Milifrod, MA) 600 E multi solvent delivery system with a 486 tunable detector equipped with an YMC-pack sil (150 x 4.6 mm I.D.) analytical column or an YMC-pack sil (150 x 100 mm I.D.) preparative column.

5-Carboxymethyl-7-methyl-4a,5,6,7,8,8a-hexahydro-4H-quinoline-1-carboxylic acid benzyl ester (127). To a solution of methyl ester 126 (135 mg, 0.38 mmol) in MeOH:H₂O 4:1 (2 mL) was added LiOH (13.7 mg, 0.57 mmol) and the mixture was stirred
at rt for 18 h. The solution was neutralized with dropwise addition of 10% HCl as determined by pH paper. Solid MgSO$_4$ was added along with EtOAc (5 mL), and the reaction mixture was filtered through Celite. Several volumes of 1% MeOH/EtOAc were used to wash the filter cake, and the filtrate was concentrated in vacuo to provide the crude product. Purification by silica gel chromatography (1-5% MeOH/EtOAc) gave 129.2 mg (99%) of 127 as a white solid: $\left[\alpha\right]_{D}^{23} = -112$ (c 0.20, CHCl$_3$); mp 110-112 °C; IR (neat) 1781, 1675, 1561, 1384, 1337, 1272, 1117; $^1$H NMR (CDCl$_3$, 300 MHz) δ 11.2 (bs, 1 H), 7.36 (m, 5 H), 6.82 and 6.73 (pair of d, due to rotomers, $J = 8.2$ Hz, 2 H), 5.18 (m, 2 H), 4.89 and 4.78 (pair of d, due to rotomers, $J = 12.4$ Hz, 1 H), 2.67 (m, 1 H), 2.32-1.75 (m, 5 H), 1.70-1.34 (m, 3 H), 1.30-0.79 (m, 5 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 177.2, 153.3 and 152.8 (due to rotomers), 136.6, 128.3, 128.2 and 128.0 (due to rotomers), 124.0 and 123.5 (due to rotomers), 111.6, 104.3, 67.6, 38.5, 34.9 and 34.8 (due to rotomers), 31.9, 31.6, 30.5 and 29.7 (due to rotomers), 27.6, 26.3, 22.0, 18.7, 17.2; HRMS (M+H)$^+$ calcd for C$_{25}$H$_{24}$NO$_5$ 344.1862, found 344.1866.

4-Oxo-2-pent-4-enyl-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (139). Magnesium turnings (4.1 g, 170.0 mmol) and anhydrous THF (10 mL) were placed in a flask.
equipped with a reflux condenser and magnetic stir bar, and 0.2 mL of 1,2-dibromoethane was added. The mixture was refluxed for 20 min and then cooled to rt. The solution was removed from the turnings by syringe, 10 mL of fresh THF were added, and the mixture was cooled to 0 °C. Neat 5-bromo-1-pentene (3.4 mL, 34.0 mmol) was added dropwise over a period of 30 min. After the addition was complete, the cooling bath was removed and the mixture was stirred for 2 h at rt.

To a solution of 4-methoxypyridine (3.1 mL, 31.0 mmol) in 40 mL of anhydrous THF at -23 °C was added dropwise benzyl chloroformate (4.4 mL, 31.0 mmol). The reaction mixture was stirred at -23 °C for 1.5 h. The previously prepared Grignard reagent was transferred dropwise by syringe, and the mixture was stirred at -23 °C for 2 h. Aqueous 10% HCl (25 mL) was added, and the reaction was warmed to rt and stirred for 2 h. The aqueous layer was extracted with diethyl ether (3 x 20 mL), and the combined ether extracts were washed with water (30 mL) and brine (30 mL), and dried over anhydrous MgSO₄. Filtration through Celite and concentration in vacuo gave the crude product. Purification by silica gel chromatography (5-20% EtOAc/hexanes) yielded 8.16 g (88%) of dihydropyridone 139 as a clear oil: IR (neat) 2367, 1728, 1676, 1606, 1421, 1385, 1333, 1263, 1196 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.75 (s, 1 H), 7.38 (s, 5 H), 5.70 (m, 1 H), 5.31 (d, J = 8.0 Hz, 1 H), 5.26 (d, J = 4.8 Hz, 2 H) 4.94 (m, 2 H), 4.60 (bs, 1 H), 2.81 (d, J = 16.4 Hz, 1 H), 2.45 (d, J = 16.4 Hz, 1 H), 2.00 (d, J = 7.6 Hz, 2 H), 1.60 (m, 2 H), 1.43 (m, 1 H), 1.30 (m, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 193.3, 150.2 141.7, 138.1, 135.2, 129.0, 128.9, 128.7, 115.4, 107.4, 69.3, 53.6, 40.0, 33.5, 30.2, 25.1; HRMS (M+H)⁺ calcd for C₁₈H₂₁NO₃ 300.1600, found 300.1613.
5-Bromo-4-oxo-2-pent-4-enyl-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (140). To a solution of dihydropyridone 139 (500 mg, 1.6 mmol) in 7.0 mL of anhydrous dichloromethane, cooled to 0 °C, was added recrystallized N-bromosuccinimide (623 mg, 3.5 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at rt for 48 h. The reaction was filtered through Celite to remove the solids, and the filter pad was washed with hexanes. The solvent was removed in vacuo to provide the crude product. Purification by silica gel chromatography (5 % EtOAc/hexanes) provided 556 mg (92%) of 140 as a white solid: mp 112-115 °C dec.; IR (neat) 2361, 1731, 1719, 1683, 1593, 1395, 1325, 1256, 1115 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 8.15 (s, 1 H), 7.40 (s, 5 H), 5.17 (m, 1 H), 5.28 (d, J = 3.6Hz, 2 H), 4.98 (d, J = 6.6 Hz, 1 H), 4.93 (s, 1 H), 4.63 (d, J = 5.7 Hz, 1 H), 2.90 (dd, J = 6.3, 16.5 Hz, 1 H), 2.70 (d, J = 18 Hz, 1 H), 2.01 (dd, J = 6.9, 13.8, 2 H), 1.65 (m, 2 H), 1.47 (m, 1 H), 1.33 (s, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 185.8, 150.1, 142.1, 137.8, 134.8, 129.2, 129.0, 128.9, 115.5, 103.6, 69.9, 54.1, 39.9, 33.5, 30.4, 25.2.; HRMS (M+H)⁺ calcd for C₁₈H₂₀BrNO₃ 378.0705, found 378.0711.
4-Oxo-2-(4-oxo-butyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (143).

Dihydropyridone 139 (1.0 g, 3.3 mmol) in 1:1 THF: H₂O (150 mL) was degassed with argon for 30 min at 0 °C. A solution of OsO₄ (4 % in H₂O, 1.1 mL, 0.17 mmol) was added dropwise. The osmate ester was allowed to form for 30 min at 0 °C during which time, the solution became deep purple. A solution of NaIO₄ (dissolved in 15 mL of H₂O, 2.8 g, 13.0 mmol) was added over 6 h by syringe pump at rt. Diethyl ether (100 mL) was added and the phases were separated. The aqueous layer was extracted with ether (3 x 30 mL), and the combined organic layers were washed with brine (30 mL). The solvent was removed in vacuo to provide the crude product. Purification by silica gel chromatography (30-50% EtOAc/hexanes) provided 881 mg (87%) of 143 as a clear oil: IR (neat) 2360, 2342, 1669, 1655, 1602, 1455, 1331, 1271, 1196 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 9.67 (s, 1 H), 7.76 (d, J = 7.2 Hz, 1 H), 7.40 (bs, 5 H), 5.30 (d, J = 6.9 Hz, 1 H), 5.26 (d, J = 3.6 Hz, 2 H), 4.63 (bs, 1 H), 2.83 (dd, J = 6.6, 16.8 Hz, 1 H), 2.44 (d, J = 16.8 Hz, 3 H), 1.69 (m, 4 H); ¹³C NMR (CDCl₃, 100 MHz) δ 201.5, 192.9, 150.3, 141.6, 135.1, 129.1, 129.0, 128.8, 107.5,
69.4, 53.2, 43.5, 40.1, 30.3, 18.4; HRMS (M+H)^+ calcd for C_{17}H_{19}NO_{4} 302.1392, found 302.1396.

5-Bromo-4-oxo-2(4-oxo-butyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (141). A solution of dihydropyridone 140 (193 mg, 0.51 mmol) dissolved in 10 mL of 1:1 THF: H₂O was degassed with argon for 30 min at 0 °C and then OsO₄ (4 wt % in H₂O, 0.032 mL, 0.051 mmol) was added. The osmate ester was allowed to form for 30 min at 0 °C during which time the solution became deep purple. A solution of NaIO₄ (428 mg, 2.0 mmol) dissolved in water (2 mL) was added over 6 h by syringe pump at rt. Diethyl ether (100 mL) was added and the phases were separated. The aqueous layer was extracted with ether (3 x 2 mL), and the combined organic layers were washed with brine (2 mL). The solvent was removed \textit{in vacuo} to provide the crude product. The crude material was purified by silica gel chromatography using 20-30 % EtOAc/hexanes to provide 169 mg (87 %) of the bromoaldehyde 141: IR (neat) 1727, 1680, 1595, 1395, 1258, 1148 cm⁻¹; ^1H NMR (CDCl₃, 300 MHz) δ 9.68 (s, 1 H), 8.14 (s, 1 H), 7.37 (s, 5 H), 5.25 (dd, \textit{J} = 6.6, 16.8 Hz, 2 H), 4.63 (s, 1 H) 2.91 (dd, \textit{J} = 6.6, 16.8 Hz, 1 H), 2.69 (dd, \textit{J} = 1.8, 16.5 Hz, 1 H), 2.41 (s, 2 H) 1.64
(m, 4 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 205.9, 201.3, 152.0, 141.9, 134.7, 129.3, 129.0, 128.9, 103.3, 70.0, 53.6, 43.3, 39.9, 30.3, 18.3; HRMS (M+H)$^+$ calcd for C$_{17}$H$_{18}$BrNO$_4$ 380.0497, found 380.0495.

2-(5-Methoxycarbonyl-pent-4-enyl)-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (144). To a solution of trimethylphosphonoacetate (0.41 mL, 2.53 mmol) in THF (15 mL) at 0 °C was added KOtBu (1.0 M in THF, 2.3 mL, 2.3 mmol) dropwise, and the solution was stirred for 30 min at 0 °C then cooled to -78 °C. A solution of aldehyde 143 (692 mg, 2.3 mmol) in THF (5 mL) was added to the phosphonate anion by a double tipped stainless steel needle. The reaction was allowed to stir for 20 min at -78 °C and then the solution was warmed to rt and stirred an additional 6 h. The reaction was diluted with Et$_2$O (20 mL) and water (20 mL), and the layers were separated. The aqueous layer was extracted with Et$_2$O (2 x 20 mL), and the combined organic layers were washed with brine (10 mL) and then dried over anhydrous MgSO$_4$. The solvent was removed in vacuo to give the crude product. Purification by radial PLC (SiO$_2$, 30-50% EtOAc/hexanes) provided 682 mg (83%) of 144 as a clear oil: IR 1754, 1712, 1654, 1453, 1333, 1227 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300
MHz) δ 7.50 (d, J = 7.2 Hz, 1 H), 7.38 (s, 5 H), 6.86 (m, 1 H), 5.77 (d, J = 15.6 Hz, 1 H), 5.32 (d, J = 6.3 Hz, 1 H), 5.26 (s, 2 H), 4.62 (bs, 1 H), 3.71 (s, 3 H), 2.82 (dd, J = 16.8 Hz, 1 H), 2.39 (d, J = 16.5 Hz, 1 H), 2.17 (d, J = 6.6 Hz, 2 H), 1.17-1.53 (m, 2 H), 1.47 (m, 1 H), 1.37 (m, 1 H); 13C NMR (CDCl3, 100 MHz) δ 206.4, 193.1, 167.1, 148.4, 141.7, 135.1, 129.1, 128.0, 128.8, 121.8, 107.5, 69.3, 53.3, 51.7, 40.1, 32.0, 30.4, 24.4; HRMS (M+H)+ calcd for C20H23NO5 358.1654, found 358.1661.

5-Bromo-2-(5-methoxycarbonyl-pent-4-enyl)-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (142). To a solution of 144 (164 mg, 0.46 mmol) in anhydrous dichloromethane (5 mL) was added of N-bromosuccinimide (81.9 mg, 0.46 mmol), and the reaction mixture was stirred for 4 d at rt. The mixture was poured into saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 x 3 mL). The combined organic layers were washed once with brine, and the solvent was removed in vacuo to provide the crude product. Purification by silica gel chromatography (20-50% EtOAc/hexanes) gave 183 mg (91%) of 142 as a light brown solid: mp 123-126 °C; IR (neat) 2948, 1721, 1682, 1594, 1396, 1326, 1257 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 8.14 (bs, 1
H), 7.74 (s, 5 H), 6.85 (m, 1 H), 5.77 (d, \( J = 11.7 \) Hz, 1 H), 5.28 (dd, \( J = 4.2 \) Hz, 9.0 Hz, 2 H) 4.64 (bs, 1 H), 3.74 (s, 3 H), 2.91 (dd, \( J = 4.8, 12.3 \) Hz, 1 H), 2.67 (d, \( J = 12.3 \) Hz, 1 H), 2.15 (bs, 2 H), 1.70 (m, 1 H), 1.64 (m, 1 H), 1.47 (m, 1 H), 1.35 (m, 1 H); \(^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz)} \delta 185.7, 167.1, 152.0, 148.1, 141.9, 134.8, 129.3, 129.2, 129.1, 129.0, 121.9, 120.4, 69.9, 53.7, 51.7, 39.9, 30.5, 29.4; HRMS (M+H)\(^+\) calcd for C\(_{20}\)H\(_{22}\)BrNO\(_5\) 436.0759, found 436.0768.

5-Bromo-4-hydroxy-3-(5-methoxycarbonyl-4-pent-4-enyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (145). To a solution of 142 (177 mg, 0.41 mmol) in reagent grade methanol (10 mL) at 0 °C was added CeCl\(_3\)·7H\(_2\)O (168 mg, 0.45 mmol), and the reaction mixture was stirred at 0 °C for 15 min. Solid NaBH\(_4\) (46.5 mg, 1.26 mmol) was then added in small portions at 0 °C and the mixture was allowed to stir at 0 °C for 30 min. The cooling bath was removed and the reaction mixture was allowed to warm to rt and stirred for 2 h. The mixture was poured into water (2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered through Celite. The solvent was removed \textit{in vacuo} to give the crude product. Purification by radial
PLC (SiO₂, 10-30 % EtOAc/hexanes) provided 174 mg (97%) of alcohol 145 as a clear oil: IR (neat) 3449, 1714, 1707, 1647, 1438, 1399, 1326, 1297, 1269, 1115 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.36 (s, 5 H), 7.12 (bs, 1 H), 6.89 (m, 1 H), 5.79 (d, J = 15.6 Hz, 1 H), 5.12 (s, 2 H), 4.31 (m, 1 H), 3.73 (s, 3 H), 2.30 (m, 2 H), 2.18 (bs, 2 H), 1.91 (m, 1 H), 1.60 (m, 1 H), 1.48 (m, 4 H); ¹³C NMR (CDCl₃, 100 MHz) δ 167.1, 152.3, 148.6, 135.7, 128.8, 128.7, 128.5, 126.0, 121.6, 107.1, 68.4, 64.2, 51.9, 51.6, 34.1, 32.0, 31.1, 24.9; HRMS (M+H)⁺ calcd for C₂₀H₂₄BrNO₄ 438.0916, found 438.0923.

3,5-Dibromo-2-(5-methoxycarbonyl-pent-4-enyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (147). To a flask containing a solution of dihydropyridone 144 (134 mg, 0.48 mmol) in anhydrous THF (5 mL), was added solid PTAP (267 mg, 1.9 mmol). The resulting solution was stirred at rt for 2 d, poured into saturated aqueous NaHCO₃ solution (5 mL), and extracted with diethyl ether (3 x 2 mL). The combined extracts were washed with water (2 mL) followed by brine (2 mL), and then dried over anhydrous MgSO₄. The solvent was removed in vacuo to provide the crude product. Purification by radial PLC (SiO₂) with 5-10% EtOAc/hexanes gave 214 mg (86%) of 147 as a white foam: IR (neat)
1727, 1681, 1589, 1454, 1395, 1330, 1290, 1244 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.14 (s, 1 H), 7.39 (s, 5 H), 6.80 (m, 1 H), 5.77 (d, \(J = 15.6\) Hz, 1 H); 5.32 (s, 2 H), 4.35 (s, 1 H), 4.72 (bs, 1 H), 3.73 (s, 3 H), 2.15 (d, \(J = 5.2\) Hz, 2 H), 1.7 (m, 1 H), 1.57 (m, 1 H), 1.51 (m, 1 H), 1.43 (bs, 1 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 180.2, 166.8, 151.9, 147.2, 141.5, 134.6, 129.3, 129.1, 128.8, 122.3, 102.4, 70.3, 60.9, 51.6, 45.1, 31.6, 29.7, 24.7. HRMS (M+H\(^+\)) calcd for C\(_{20}\)H\(_{21}\)Br\(_2\)NO\(_5\) 513.9864, found 513.9862.

3,5-Dibromo-4-hydroxy-2-(5-methoxycarbonyl-pent-4-enyl)-3,4-dihydropyridone-2H-1-carboxylic acid benzyl ester (148). To a solution of 147 (71.4 mg, 0.16 mmol) dissolved in reagent grade methanol (5 mL) at 0 °C was added CeCl\(_3\)·7H\(_2\)O (60.0 mg, 0.16 mmol), and the reaction mixture was stirred at 0 °C for 15 min. Solid NaBH\(_4\) (12.5, 0.33 mmol) was then added in small portions at 0 °C to avoid over bubbling. Once the addition was complete, the reaction was allowed to stir at 0 °C for 30 min. The cooling bath was removed and the mixture was allowed to warm to rt and then stirred for 2 h. The mixture was poured into water (2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic extracts were dried over anhydrous sodium sulfate and filtered through Celite. The solvent was removed \textit{in}
vacuo to give the crude product. Purification by radial PLC (SiO₂, 10-30% EtOAc/hexanes) afforded 63.9 mg (91%) of alcohol 147 as a clear oil: IR (neat) 3440, 1714, 1707, 1647, 1438, 1399, 1326, 1297, 1269, 1115 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, 50 °C) δ 7.36 (s, 5 H), 7.17 (bs, 1 H), 6.85 (bm, 1 H), 5.79 (d, J = 11.4 Hz, 1 H), 5.23 (s, 2 H), 4.65 (bs, 1 H), 4.29 (s, 1 H), 4.28 (m, 1 H), 3.91 (m, 1 H), 3.74 (s, 3 H), 2.28 (d, J = 8.1 Hz, 1 H), 2.10 (bs, 1 H), 1.70 (bs, 1 H), 1.15 (s, 3 H); ¹³C NMR (CDCl₃, 100 MHz) δ 167.1, 152.3, 148.6, 135.7, 128.8, 128.7, 128.5, 126.0, 121.6, 107.1, 70.4, 62.2, 51.9, 51.6, 34.1, 32.0, 31.1, 24.9; HRMS (M+H)⁺ calcd for C₂₀H₂₃Br₂NO₅ 517.0099, found 517.0105.

5-Bromo-4-hydroxy-2-(5-methoxycarbonyl-pent-4-enyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (150). To a solution of 2,6-di-tert-butyl-4-methyl-phenol (1.06 g, 4.8 mmol) in toluene (50 mL) at 0 °C was added DIBAL (1.0 M in toluene, 2.4 mL, 2.4 mmol) dropwise over 1 h by syringe pump. After the addition was complete, the solution was stirred for an additional hour at 0 °C and subsequently cooled to -78 °C. A solution of 142 (105 mg, 0.24 mmol) in toluene (2.0 mL) was added by syringe over 5 min resulting in a deep red colored solution. The reaction mixture was stirred for 30 min at -78 °C and then
warmed to -20 °C and stirred for 2 h, during which time the solution became yellow. The mixture was poured into 10 mL of 1 N HCl and then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (3 x 10 mL) and then dried over anhydrous Na₂SO₄. Filtration through Celite and concentration of the solution in vacuo provided the crude product. Purification by silica gel chromatography (30-40% EtOAc/hexanes) gave 76.6 mg (73%) of cis alcohol 150 as a clear oil: IR (neat) 3449, 1713, 1647, 1499, 1438, 1296, 1154 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ (bs, 5 H), 7.12 (bs, 1 H), 6.91 (bs, 1 H), 5.79 (d, J = 11.7 Hz, 1 H), 5.20 (t, J = 9.6 Hz, 2 H) 4.32 (bs, 1 H), 4.22 (bs, 1 H), 3.72 (s, 3 H), 2.26 (d, J = 14.8 Hz, 1 H), 2.17 (m, 3 H), 1.99 (m, 1 H), 1.78 (m, 2 H), 1.55 (bs, 1 H) 1.39 (bs, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 167.2, 149.1, 135.9, 128.8, 128.7, 128.5, 126.2, 121.4, 120.1, 105.4, 68.4, 66.7, 51.4, 49.5, 32.9, 32.0, 31.0, 25.3; HRMS (M+H)+ calcd for C₂₀H₂₄BrNO₅ 439.0994, found 439.0990.

**5-Bromo-2-(5-methoxycarbonyl-pent-4-enyl)-2H-pyridine-1-carboxylic acid benzyl ester (146).** Preparation of Furukawa’s Reagent: To a solution of methane sulfonylchloride (2.5 g, 21.8 mmol) in anhydrous dichloromethane (30 mL) at rt was added H₂O (0.17 mL, 9.4
mmol) followed by DMAP (1.33 g, 10.9 mmol). A white solid results which was stirred at rt for 5 d or until complete dissolution of the solid. The reagent was transferred to an amber bottle and stored at 0 °C.

To a solution of compound 150 (640 mg, 1.46 mmol) in dichloromethane (5 mL) at 0 °C was added the above described solution (1.6 mL, 2.2 mmol), and the reaction mixture was allowed to warm to rt and stirred for 3 h. The mixture was poured into water and extracted with dichloromethane. The organic layer was washed with cold 1 N HCl (2 x 3 mL), saturated sodium bicarbonate (2 x 3 mL), and finally brine (3 mL). The organic layer was subsequently dried over MgSO₄, filtered through Celite, and the volatiles were removed under reduced pressure to provide the crude product. Purification by radial PLC (SiO₂, 5-10% EtOAc/hexanes) gave 368 mg (60%) of dihydropyridine 146 as a colorless oil which must be submitted quickly to the next step: IR (neat) 3449, 2360, 1713, 1445, 1296, 1154, 1067 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.30 (s, 5 H), 6.90 (m, 1 H), 5.98 (d, J = 9.3, 1 H), 5.79 (m, 1 H), 5.59 (m, 1 H), 5.22 (s, 2 H), 4.84 and 4.72 (due to rotomers, 1 H), 3.74 (s, 3 H), 2.19 (m, 2 H), 1.50 (m, 5 H); ¹³C NMR (CDCl₃, 100 MHz) δ 168.6, 149.0, 129.4, 128.9, 128.5, 128.2, 126.3, 126.2, 125.8, 124.6, 121.4, 68.5, 51.6 51.3, 33.9, 33.4, 32.2, 23.1; HRMS (M+H)^+ calcd for C₂₀H₂₂BrNO₄ 420.0081, found 420.0077.
7-Bromo-1,2,3,4,4a,5,6,8a-octahydro-1,6-epiazano-naphthalene-5,9-dicarboxylic acid 9-benzyl ester 5-methyl ester (155). A solution of 146 (172 mg, 0.41 mmol) in xylenes was degassed for 30 min and then heated to reflux for 18 h with aluminum foil surrounding the flask. The solution was cooled to rt and the solvent was removed in vacuo to give the crude product. Purification by silica gel chromatography (5-15 % EtOAc/hexanes) gave 118 mg (70%) of 155 as a clear oil which solidified on standing: mp 101-103 °C; IR (neat) 2455, 1754, 1722, 1645, 1601, 1567, 1445, 1300, 1223 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.37 (s, 5 H), 6.51 (d, J = 6.8 Hz, 1 H), 5.23 (d, J = 13.2 Hz, 2 H ), 5.09 (d, J = 12 Hz, 1 H), 3.70 (s, 3 H), 3.39 (s, 1 H), 2.85 (bs, 1 H), 2.50 (bs, 1 H), 2.31 (bs, 1 H), 2.21 (bs, 1 H), 1.69 (bs, 1 H), 1.59 (m, 2 H), 1.25 (bs, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ 172.4, 135.8, 128.9, 128.7, 128.2, 127.9, 67.3, 56.4, 52.2, 51.3, 45.4, 31.7, 31.4, 30.2, 29.9, 28.2, 16.4, 14.9; HRMS (M+H)⁺ calcd for C₂₀H₂₂BrNO₄ 420.0081, found 420.0085.
4-Oxo-2-pent-4-enyl-5-triisopropylsilanyl-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (168). Magnesium turnings (2.9 g, 117.5 mmol) and anhydrous THF (10 mL) were placed in a flask, equipped with reflux condenser and a magnetic stir bar, and 0.2 mL of 1,2-dibromoethane was added. The mixture was brought to reflux for 20 min and then cooled to rt. The solution was removed from the turnings by syringe, 10 mL of fresh THF was added, and the mixture was cooled to 0 °C by an ice bath. Neat 5-bromo-1-pentene (2.8 mL, 23.5 mmol) was added dropwise over a period of 30 min. After the addition was complete, the ice bath was removed and the mixture was stirred for 2 h at rt.

To a solution of 31 (5.6 g, 21.0 mmol) dissolved in freshly distilled THF (25 mL) was added benzyl chloroformate (3.0 mL, 21.0 mmol) dropwise at -45 °C while stirring rapidly. After the addition was complete, the reaction was stirred for an additional 1 h at -45 °C before the Grignard reagent was added dropwise by syringe pump over 30 min. The reaction was stirred at -45 °C for an additional 1 h after the addition, then 15 mL of 10% HCl was added, and the reaction was warmed to rt and stirred for 30 min. The mixture was diluted with Et₂O (30 mL) and the phases were separated. The aqueous layer was extracted with Et₂O (2 x 10 mL), and the combined organic layers were washed with brine (15 mL) and dried over anhydrous MgSO₄. Filtration through Celite and removal of the volatiles under reduced pressure provided the crude product. Purification by silica gel chromatography (10-30% EtOAc/hexanes) afforded 7.64 g (80%) of dihydropyridone 168 as a clear syrup: IR (neat) 2360, 1725, 1661, 1573, 1389, 1326, 1298, 1256, 1115 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.82 (s, 1 H); 7.39 (s, 5 H), 5.70 (m, 1 H), 4.90 (m, 2 H), 4.56 (bs, 1 H), 2.80 (dd, J = 6.6, 15.9 Hz, 1 H), 2.41 (d, J = 15.9 Hz, 1 H) 1.99 (m, 2 H), 1.58 (m, 3 H), 1.46 (m, 1 H),
1.30 (m, 5 H), 1.05 (m, 18 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 196.9, 147.0, 138.1, 135.4, 128.9, 128.5, 115.4, 100.1, 69.0, 53.2, 40.7, 33.5, 30.5, 25.0, 19.1, 19.0, 17.9, 11.3; HRMS (M+H)$^+$ calcd for C$_{27}$H$_{41}$NO$_3$Si 456.2934, found 456.2924.

[Chemical structure image]

4-Oxo-2-(4-oxo-butyl)-5-triisopropylsilanyl-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (169). Dihydropyridone 168 (1.7 g, 3.7 mmol) dissolved in 1:1 THF: H$_2$O (300 mL) was degassed with argon for 30 min at 0 °C, and OsO$_4$ (4 % in H$_2$O, 0.45 mL, 0.07 mmol) was added dropwise. The osmate ester was allowed to form for 30 min at 0 °C during which time the solution became purple. A solution of NaIO$_4$ (dissolved in 15 mL of H$_2$O, 3.2 g, 14.8 mmol) was added over 6 h by syringe pump at rt. Diethyl ether (100 mL) was added and the phases were separated. The aqueous layer was extracted with Et$_2$O (3 x 30 mL), and the combined organic layers were washed with brine (30 mL) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed in vacuo to provide the crude product. Purification by silica gel chromatography (20-30% EtOAc/hexanes) provided 1.36 g (80%) of 169 as a clear oil: IR (neat) 2942, 2864, 1722, 1658, 1572, 1390, 1322, 1256, 1119 cm$^{-1}$; $^1$H NMR (CDCl$_3$,
300 MHz) δ 9.67 (s, 1 H), 7.82 (s, 1 H), 7.39 (s, 5 H), 5.27 (dd, J = 4.8, 17.1 Hz, 2 H), 4.58 (bs, 1 H), 2.83 (dd, J = 6.6, 16.2 Hz, 1 H), 2.41 (d, J = 15.9 Hz, 3 H), 1.61 (m, 4 H), 1.30 (m, 3 H), 1.02 (m, 18 H); δ 201.7, 196.6, 151.1, 147.2, 135.2, 129.0, 121.5, 112.8, 69.2, 52.9, 43.6, 40.6, 19.1, 18.9, 18.4, 11.6, 11.3; HRMS (M+H)⁺ calcd for C_{26}H_{39}NO_{4}Si 458.6855, found 458.6861.

4-Oxo-3-triisopropylsilanyl-6,7,8,8a-tetrahydro-4H-quinoline-1-carboxylic acid benzyl ester (171). To a solution of 169 (156 mg, 0.34 mmol) in benzene was added para-toluenesulphonic acid monohydrate (97.0 mg, 0.51 mmol), and the mixture was heated to 45 °C and stirred for 3 h. The mixture was poured into saturated sodium bicarbonate (5 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO₄, and filtered through Celite. The solvent was removed in vacuo to provide the crude product. Purification by radial PLC (SiO₂, 5-10% EtOAc/hexanes) gave 43.2 mg (30 %) of 171 as a clear oil. The remaining bands which contained the β-hydroxyketone and keto-aldehyde were resubmitted to the reaction
conditions to give 44.0 mg of 171 (60% over 2 recycles) as a clear oil: IR (neat) 2942, 2863, 1733, 1653, 1578, 1383, 1266, 1220 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.81 (s, 1 H), 7.38 (s, 5 H), 6.68 (m, 1 H), 5.28 (dd, \(J = 9.0, 32.4\) Hz, 2 H), 4.64 (m, 1 H), 2.83 (m, 1 H), 2.30 (m, 2 H), 1.80 (m, 1 H), 1.72 (m, 2 H), 1.48 (m, 1 H), 1.32 (m, 3 H), 1.03 (m, 18 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 186.7, 153.2, 148.5, 135.3, 134.6, 134.3, 131.1, 128.9, 128.3, 110.0, 69.0, 55.5, 28.8, 25.1, 19.6, 19.1, 11.4; HRMS (M+H)\(^+\) calcd for C\(_{26}\)H\(_{37}\)NO\(_3\)Si 440.2621, found 440.2628.

![Diagram](image)

4-Hydroxy-3-triisopropylsilanyl-6,7,8,8a-tetrahydro-4H-quinoline-1-carboxylic acid benzyl ester (173). To a solution of 171 (245 mg, 0.58 mmol) dissolved in reagent grade methanol (10 mL) at 0 °C was added CeCl\(_3\)·7H\(_2\)O (216 mg, 0.58 mmol). The reaction was stirred at 0 °C for 15 min and then NaBH\(_4\) (109 mg, 2.9 mmol) was added in small potions at 0 °C so as to avoid over bubbling. On completion of the addition, the reaction was allowed to stir at 0 °C for 30 min. The cooling bath was then removed and the reaction was allowed to warm to rt and stirred for 3 d. The mixture was poured into water (3 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate.
and filtered through Celite. The solvent was removed in vacuo to give the crude product. Purification was achieved by radial PLC (silica gel) using 10-30 % EtOAc/hexanes to provide 227 mg (89%) of alcohol 173 as a clear oil: IR (neat) 3345, 2942, 2863, 1733, 1653, 1578, 1383, 1266, 1220 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.38 (s, 5 H), 6.61 (s, 1 H), 5.62 (s, 1 H), 5.20 (q, \(J = 12.2\) Hz, 2 H), 4.77 (bs, 1 H), 4.20 (bs, 1 H) 2.61 (bs, 1 H), 2.15 (bs, 2 H), 1.80 (m, 1 H), 1.72 (m, 3 H), 1.52 (m, 3 H) 1.03 (m, 18 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 151.2, 147.3, 141.0, 130.1, 128.9, 128.7, 128.6, 127.9, 123.4, 122.1, 71.3, 70.2, 49.2, 33.9, 29.4 15.4 12.2; HRMS (M+H)\(^+\) calcd for C\(_{26}\)H\(_{39}\)NO\(_3\)Si 442.2777, found 442.2769.

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\text{139} & \quad \rightarrow \quad \text{177}
\end{align*}
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**4-Oxo-2-pent-4-enyl-piperidine-1-carboxylic acid benzyl ester (177).** To a solution of 139 (1.3 g, 4.3 mmol) in glacial acetic acid (30 mL) was added zinc dust (4.3 g, 65.2 mmol), and the suspension was stirred rapidly for 16 h at rt and then filtered through Celite. The solvent was removed in vacuo to provide the crude product. Purification by silica gel chromatography (10-20% EtOAc/hexanes) gave 383 mg (98%) of 177 as a clear oil: IR (neat) 3584, 1695, 1425, 1343, 1310, 1263, 1178, 1120, 1056 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.36 (m, 5 H), 5.74 (m, 1 H), 5.20 (m, 2 H), 4.97 (m, 2 H), 4.67 (bs, 1 H), 3.23 (m, 1
H), 2.64 (m, 1 H), 2.48 (m, 1 H), 2.31 (m, 2 H), 2.04 (bs, 2 H), 1.48 (m, 5 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 217.3, 205.6, 123.1, 128.7, 128.4, 128.2, 115.2, 112.9, 67.8, 52.4, 45.7, 40.7, 38.8, 33.2, 31.9, 25.1; HRMS (M+H)$^+$ calcd for C$_{18}$H$_{23}$NO$_3$ 302.1756, found 302.1767.

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\text{177} \\
\text{178}
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4-Oxo-2-(4-oxo-butyl)-piperidine-1-carboxylic acid benzyl ester (178). Piperidone 177 (1.0 g, 3.3 mmol) was dissolved in 1:1 THF:H$_2$O (150 mL) and degassed with argon for 30 min at 0 °C after which time an aqueous solution of OsO$_4$ (4 % in H$_2$O, 1.1 mL, 0.17 mmol) was added dropwise. The osmate ester was allowed to form for 30 min at 0 °C during which time the solution became deep purple. A solution of NaIO$_4$ (2.8 g, 13.2 mmol) dissolved in H$_2$O (25 mL) was added over 6 h by syringe pump to the mixture at rt and then diethyl ether (100 mL) was added. The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO$_4$, and the solvent was removed in vacuo to provide the crude product. Purification by silica gel chromatography (30-50% acetone/hexanes) provided 845 mg (84%) of piperidone 178 as a clear oil: IR (neat) 1696, 1424, 1310, 1238, 1178, 1117 cm$^{-1}$; $^1$H NMR 9.64 (s, 1 H), 7.35 (s, 5 H), 5.19 (m, 2 H), 4.70 (bs, 1 H), 4.40 (bs, 1 H), 3.24 (t, $J = 12.6$ Hz, 1 H), 2.67
(dd, $J = 6.6, 14.1$ Hz, 1 H), 2.44 (s, 2 H), 2.37 (m, 3 H); 1.5 (m, 4 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 207.3, 201.5, 155.5, 136.4, 128.8, 128.7, 128.3, 68.0, 52.3, 45.8, 43.3, 39.7, 38.8, 31.9, 18.4; HRMS (M+H)$^+$ calced for C$_{17}$H$_{21}$NO$_4$ 304.1549, found 304.1538.

4-Oxo-3,4,6,7,8,8a-hexahydro-2H-1-carboxylic acid benzyl ester (179). To a solution of aldehyde 178 (590 mg, 1.9 mmol) in benzene was added para-toluenesulphonic acid monohydrate (555 mg, 2.9 mmol), and the mixture was heated to 45 °C and stirred for 3 h. The mixture was poured into saturated sodium bicarbonate (10 mL) and then extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, and filtered. The solvent was removed in vacuo to provide the crude product. Purification by radial PLC (SiO$_2$, 5-20% EtOAc/hexanes) gave 384 mg (71 %) of 179 as a clear oil: IR (neat) 1695, 1622, 1453, 1421, 1356, 1314, 1257, 1186, 1110 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.34, (s, 5 H), 6.73 (m, 1 H), 5.18 (s, 2 H), 4.62 (m, 1 H), 4.30 (d, $J = 9.2$ Hz, 1 H), 3.14 (dt, $J = 2.8, 13.2$ Hz, 1 H), 2.52 (dd, $J = 5.2, 12.8$, 1 H), 2.49 (dt, $J = 2.8, 18.4$ Hz, 1 H), 2.29 (m, 3 H), 1.89 (m, 1 H), 1.71 (m, 1 H), 1.48 (m, 1 H); $^{13}$C NMR
(CDCl$_3$, 100 MHz) $\delta$ 199.5, 139.8, 136.7, 133.7, 128.8, 128.7, 128.4, 67.5, 52.7, 40.4, 38.1, 27.8, 25.6, 20.5; HRMS (M+H)$^+$ calcd for C$_{17}$H$_{19}$NO$_3$ 286.1443, found 286.1458.

4-Hydroxy-3,4,6,7,8,8a-hexahydro-2H-quinoline-1-carboxylic acid benzyl ester (180).

To a solution of the bicyclic enone 179 (758 mg, 2.7 mmol) in MeOH at 0 °C was added CeCl$_3$·7H$_2$O (1.0 g, 2.7 mmol). The solution was stirred at 0 °C for 30 min followed by the addition of NaBH$_4$ (306 mg, 8.1 mmol) in small portions. The reaction was stirred at 0 °C for 4 h. The mixture was diluted with water (2 mL) and EtOAc (5 mL), and the phases were separated. The aqueous layer was extracted with EtOAc (3 x 3 mL), and the combined organic layers were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to afford 729 mg (94%) of alcohol 180 as a clear oil: IR (neat) 3433, 1699, 1431, 1360, 1310, 1271, 1067 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.36 (s, 5 H), 5.83 (s, 1 H), 5.14 (s, 2 H), 4.44 (s, 1 H), 4.32 (s, 1 H), 3.90 (t, 9.6 Hz, 1 H), 2.93 (m, 1 H), 2.54 (m, 1 H), 2.10 (bs, 3 H), 1.83 (m, 1 H), 1.73 (s, 1 H), 1.59 (m, 1 H), 1.40 (m, 2 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 155.6, 138.3, 137.1, 128.7, 128.2, 127.9, 120.1, 67.8, 67.1, 54.2, 37.7, 34.9, 26.7, 24.5, 21.1; HRMS (M+H)$^+$ calcd for C$_{17}$H$_{21}$NO$_3$ 288.1600, found 288.1610.
4-Tributylstannylmethoxy-3,4,6,7,8,8a-hexahydro-2H-quinoline-1-carboxylic acid benzyl ester (181). To a solution of alcohol 180 (158 mg, 0.550 mmol) in THF at 0 °C was added 18-crown-6 (145 mg, 0.550 mmol) and KH (26.4 mg, 0.66 mmol). The mixture was stirred at 0 °C for 30 min. A solution iodomethyltributylstannane (238 mg, 0.550 mmol) in THF (2 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for 20 min and then at rt for 2 d. The reaction was diluted with H2O and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 5 mL), and the combined organic layers were dried over MgSO4 and filtered through Celite. The solvent was removed under reduced pressure to provide the crude product. Purification by silica gel chromatography (3 % Et3N/hexanes) afforded 289 mg (89 %) of 181 as a clear oil: IR (neat) 2352, 2342, 1699, 1422, 1310, 1238 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.32 (s, 5 H), 5.71 (s, 1 H), 5.13 (s, 2 H), 4.40 (s, 1 H), 3.88 (dd, J = 8.1, 13.2, 1 H), 3.71 (dd, J = 6.9, 16.8, 2 H), 3.67 (m, 1 H), 2.89 (ddd, J = 5.1, 7.2, 6.6 Hz, 1 H), 2.46 (m, 1 H), 2.07 (bs, 3 H), 1.78 (m, 1 H), 1.51 (m, 8 H), 1.24 (m, 6 H), 0.91 (m, 18 H); ¹³C NMR (CDCl₃, 75 MHz) δ 137.2, 135.3, 128.6, 128.1, 127.9, 120.7, 67.1, 60.8, 54.5, 37.7, 32.9, 29.4, 27.5, 26.9, 24.6, 21.1, 14.0, 10.3, 8.9, 9.2; HRMS (M+H)⁺ calcd for C₃₀H₄₉NO₃Sn 592.2812, found 592.2811.
4-Acetoxy-3,4,6,7,8,8a-hexahydro-2H-quinoline-1-carboxylic acid benzyl ester (185).

To a solution of alcohol 180 (363 mg, 1.3 mmol) in dichloromethane was added freshly distilled acetic anhydride (0.19 mL, 2.0 mmol) followed by triethylamine (0.28 mL, 2.0 mmol) and 4-dimethylaminopyridine (16.0, 0.13 mmol). The solution was stirred for 6 h and then diluted with water (2 mL) and dichloromethane (2 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (2 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous MgSO₄, and filtered through Celite. Concentration of the solvent in vacuo provided the crude product. Purification by radial PLC (SiO₂, 10-20% EtOAc/hexanes) provided 407 mg (95%) of 185 as a clear syrup: IR (neat) 1766, 1720, 1645, 1556, 1501, 1476, 1385, 1222 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.39 (s, 5 H), 5.67 (s, 1 H), 5.30 (m, 1 H), 5.13 (s, 2 H), 4.50 (bs, 1 H), 3.94 (dd, J = 8.1, 13.8 Hz, 1 H), 2.54 (m, 1 H), 2.10 (s, 3 H), 2.07 (m, 2 H), 1.77 (m, 1 H), 1.60 (m, 1 H), 1.51 (m, 4 H); ¹³C NMR (CDCl₃, 100 MHz)  δ 170.1, 155.2, 147.8, 146.5, 129.0, 128.9, 128.7, 120.2, 69.3, 69.8, 55.2, 39.8, 36.5, 32.0, 24.4, 22.0, 21.1; HRMS (M+H)⁺ calcd for C₁₉H₂₃NO₄ 330.1705, found 330.1711.
4-Phenylcarbamoyloxy-3,4,6,7,8,8a-hexahydro-2H-quinoline-1-carboxylic acid benzyl ester (188). A solution of 180 (195 mg, 0.68 mmol) in pyridine (2 mL) and dichloromethane (2 mL) was cooled to 0 °C followed by the addition of 4-dimethylaminopyridine (8.3 mg, 0.068 mmol). Phenyl isocyanate (0.19 mL, 1.7 mmol) was added in one portion and the solution was stirred for 20 min at 0 °C, then at rt for 18 h. To the mixture was added 3 mL of 10% HCl and the phases were separated. The organic layer was washed with 10% HCl (2 x 5 mL) and brine (2 x 10 mL), dried over anhydrous MgSO₄, and filtered through Celite. The solvent was removed under reduced pressure to give the crude urethane. Purification by flash chromatography gave 221 mg (80%) of 188 as a clear oil: IR (neat) 1747, 1699, 1422, 1238, 1178, 1117 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.35 (m, 10 H), 5.67 (s, 1 H), 5.30 (m, 1 H), 5.14 (s, 2 H), 4.49 (s, 1 H), 3.94 (dd, J = 8.1, 13.8 Hz, 1 H), 2.95 (m, 1 H), 2.54 (m, 1 H), 2.09 (s, 3 H), 1.8 (m, 1 H), 1.67-1.32 (m, 4 H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.1, 155.5, 137.0, 133.6, 128.7, 128.5, 128.3 128.2, 128.1, 121.1, 69.6, 67.3, 54.0, 37.5, 32.3, 29.9, 26.8, 24.5, 21.2, 20.8; HRMS (M+H)⁺ calcd for C₂₄H₂₆N₂O₄ 407.1971, found 407.1977.
Phenylcarbamic acid 1-methyl-1,2,3,4,6,7,8,8a-octahydro-quinolin-4yl ester (195). To solution of 180 (104 mg, 0.36 mmol) in 2 mL of anhydrous THF was added lithium aluminum hydride (53.1 mg, 1.4 mmol) at rt with stirring. After 20 min, the reaction was heated to reflux for 12 h and then cooled to rt. A solution of 1 N NaOH (0.1 mL) was added along with 100 mg of Celite, and the mixture was stirred for 30 min then filtered through Celite with an EtOAc wash. The filtrate was concentrated under reduced pressure to give the crude amino alcohol which was then dissolved in pyridine (2 mL) and dichloromethane (2 mL). Solid 4-dimethylaminopyridine (4.4 mg, 0.036 mmol) was added followed by phenyl isocyanate (0.08 mL, 0.72 mmol). The mixture was stirred for 20 min at 0 °C, then at rt for 18 h. To the mixture was added 5 drops of concentrated HCl, followed by MgSO₄ to absorb the water. Filtration through Celite with an EtOAc wash, and concentration of the solvent in vacuo gave the crude product. Purification by silica gel chromatography using 50-80 % EtOAc/ hexanes gave 78.4 mg (76%) of 195 as a clear oil: IR (neat) 1730, 1711, 1601, 1505, 1444, 1315, 1225 cm⁻¹; ¹H NMR (CD₃OD, 300 MHz) δ 7.42 (d, J = 8.1 Hz, 2 H), 7.28 (t, J = 7.2 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 2 H), 5.83 (s, 1 H), 5.07 (m, 1 H), 2.94 (dt, 3.0, 11.7 Hz, 1 H), 2.59 (bs, 1 H), 2.39 (dt, J = 2.4, 12.9 1 H), 2.30 (s, 3 H), 2.05 (m, 4 H), 1.8 (m, 2 H), 1.4 (m, 3 H) ¹³C NMR (CD₃OD, 75 MHz) δ 155.3, 134.2, 128.9, 128.6, 122.9, 120.6, 118.7,
72.4, 61.5, 54.1, 41.3, 32.0, 28.6, 24.5, 20.4; HRMS (M+H)\textsuperscript{+} calcd for C\textsubscript{17}H\textsubscript{22}N\textsubscript{2}O\textsubscript{4} 287.1759, found 287.1756.

4-Oxo-2-pent-4-enyl-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (197)

Magnesium turnings (7.8 g, 320.5 mmol) and anhydrous THF (30 mL) were placed in a flask equipped reflux condenser and a magnetic stir bar, and 0.5 mL of 1,2-dibromoethane was added. The mixture was refluxed for 20 min and cooled to rt. The solution was removed from the turnings by syringe, 30 mL of fresh THF was added, and the mixture was cooled to 0 °C. Neat 5-bromo-1-pentene (5.6 mL, 64.1 mmol) was added dropwise over a period of 30 min. After the addition was complete, the ice bath was removed and the mixture was stirred for 2 h at rt.

In a separate flask containing a solution of 4-methoxypyridine (6.0 mL, 58.3 mmol) in freshly distilled THF (55 mL) was added phenyl chloroformate (7.1 mL, 58.3 mmol) dropwise at -45 °C with rapid stirring. After the addition was complete, the reaction was stirred for an additional 1 h at -45 °C before the Grignard reagent was added dropwise by syringe pump over 30 min. The reaction mixture was stirred at -45 °C for an additional 1 h.
A solution of 10% HCl (25 mL) was added, and the reaction was warmed to rt and stirred for 30 min. The reaction was then diluted with Et$_2$O (30 mL) and the phases were separated. The aqueous layer was extracted with Et$_2$O (2 x 20 mL), and the combined organic layers were washed with brine (25 mL) and dried over anhydrous MgSO$_4$. Filtration through Celite and removal of the volatiles under reduced pressure provided the crude product. Purification by silica gel chromatography (10-30% EtOAc/hexanes) afforded 13.6 g (82%) of dihydropyridone 197 as a clear syrup: IR (neat) 2367, 1728, 1676, 1606, 1421, 1385, 1333, 1263, 1196 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.84 (s, 1 H), 7.38 (s, 5 H), 5.70 (m, 1 H), 5.31 (d, $J = 8.0$ Hz, 1 H), 4.86 (m, 2 H), 4.60 (bs, 1 H), 2.78 (d, $J = 16.4$ Hz, 1 H), 2.40 (d, $J = 16.4$ Hz, 1 H), 2.00 (d, $J = 7.6$ Hz, 2 H), 1.60 (m, 2 H), 1.43 (m, 1 H), 1.30 (m, 1 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 193.3, 150.2 141.7, 138.1, 135.2, 129.0, 128.9, 128.7, 115.4, 107.4, 53.6, 40.0, 33.5, 30.2, 25.1; HRMS (M+H)$^+$ calcd for C$_{17}$H$_9$NO$_3$ 286.1443, found 286.1442.

\[
\text{CO}_2\text{Ph}
\]
4-Oxo-2-(4-oxo-pentyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (198).

To a solution of 197 (1.0 g, 3.8 mmol) in 40 mL of 4:1 DMF: H₂O was added Pd(OAc)₂ (0.426 g, 1.9 mmol) and CuCl (99.0 mg, 0.752 mmol), and the mixture was stirred under an O₂ atmosphere for 3 h during which time it became dark green. The mixture was filtered through Celite and extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with saturated NaHCO₃ (25 mL), followed by brine (25 mL), and dried over anhydrous MgSO₄. The solvent was removed in vacuo first by rotovap and second by vacuum distillation to provide the crude product. Purification by silica gel chromatography (10-20% EtOAc/hexanes) gave 836 mg (73%) of 198 as a clear oil: IR (neat) 3076, 2942, 1736, 1717, 1671, 1605, 1494, 1422, 1336, 1268, 1198 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.84 (d, J = 8.4 Hz, 1 H), 7.39 (m, 2 H), 7.24 (m, 1 H), 7.14 (d, J = 7.8 Hz, 2 H), 5.38 (d, J = 7.8 Hz, 1 H) 4.70 (bs, 1 H), 2.89 (dd, J = 6.6 Hz, 16.5 Hz, 1 H), 2.46 (m, 3 H), 2.07 (s, 3 H), 1.67 (bm, 4 H); ¹³C NMR (CDCl₃, 100 MHz) δ 208.0, 193.0, 151.4, 150.6, 141.2, 129.9, 126.6, 121.5, 108.3, 53.7, 43.0, 40.2, 30.3, 30.2, 20.0; HRMS (M+H)⁺ calcd for C₁₇H₁₉NO₄ 302.1392, found 302.1386.
2-(4,4-Diethoxypentyl)-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (199). To a solution of dihydropyridone 198 (96mg, 0.32 mmol) in absolute ethanol (2.0 mL) was added triethyl orthoformate (0.27 mL, 1.6 mmol) followed by TsOH (2.0 mg, 0.01 mmol) and 4 Å mol sieves (200 mg). The reaction was stirred at rt for 4 h and then filtered through Celite. The filtrate was poured into diethyl ether (10 mL) and washed with saturated NaHCO$_3$ (2 x 3 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$, and filtered. The solvent was removed in vacuo to provide the crude product. Purification by radial PLC (SiO$_2$, 5-20% EtOAc/hexanes) afforded 114 mg (95%) of 199 as a clear oil. IR (neat) 1737, 1674, 1605, 1494, 1333, 1270, 2288, 2057 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.88 (d, $J =$ 8.4 Hz, 1 H), 7.42 (m, 2 H), 7.26 (t, 7.2 Hz, 1 H), 7.2 (d, $J =$ 7.8 Hz, 2 H), 5.43 (d, $J =$ 8.1 Hz, 1 H) 4.75 (bs, 1 H), 3.39 (m, 4 H), 2.92 (dd, 6.3,16.5 Hz, 1 H), 2.54 (d, $J =$ 16.8 Hz, 1 H), 1.73 (m, 2 H), 1.62 (m, 2 H), 1.35 (m, 2 H), 1.26 (s, 3 H), 1.14 (t, $J =$ 6.9 Hz, 6 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 193.1, 150.7, 141.3, 129.9, 126.6, 125.5, 101.3, 55.8, 54.1, 40.0, 37.4, 31.8, 31.1, 22.9, 22.3, 21.0, 15.7, 15.6, 14.4; HRMS (M+H)$^+$ calcd for C$_{21}$H$_{29}$NO$_5$ 376.2124, found 376.2132.
2-(4,4-Diethoxypentyl)-4-hydroxy-3,4-dihydro-2H-pyridine-1carboxylic acid benzyl ester (200). To a solution of 199 (177 mg, 0.41 mmol) in 10 mL of absolute ethanol at 0 °C was added CeCl$_3$·7H$_2$O (168 mg, 0.45 mmol). The reaction mixture was stirred at 0 °C for 15 min, then NaBH$_4$ was added in small portions at 0 °C so as to avoid over bubbling. The reaction was stirred at 0 °C for 30 min and then at rt for 2 h. The reaction was poured into water (2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered through Celite. The solvent was subsequently removed in vacuo to give the crude product. Purification was achieved by radial PLC (SiO$_2$) using 10-30 % EtOAc/hexanes to provide 151 mg (98%) of 200 as a clear oil. IR (neat) 3459, 1727, 1654, 1353, 1203 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.37 (t, $J = 7.2$ Hz, 2 H), 7.25 (m, 1 H) 7.12 (d, 6.3 Hz, 2 H), 6.90 (bs, 1 H), 5.00 (bs, 1 H), 4.45 (bm, 2 H), 3.43 (m, 4 H), 2.32 (m, 1 H), 1.91-1.42 (m, 6 H), 1.28 (s, 3 H), 1.15 (t, $J = 6.9$ Hz, 8 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 151.7, 141.3, 129.9, 126.6, 123.5, 102.3, 67.5, 56.8, 39.0, 37.4, 36.6, 31.8, 30.1, 25.2, 24.9, 22.6, 21.3, 21.0, 15.7; HRMS (M+H)$^+$ calcd for C$_{21}$H$_{31}$NO$_5$ 378.2280, found 378.2284.
2-(4-Oxopentyl)-2H-pyridine-1-carboxylic acid benzyl ester (201). To a solution of 200 (22.0 mg, 0.056 mmol) in anhydrous dichloromethane at 0 °C was added Furukawa’s reagent (0.73 M in dichloromethane, 0.16 mL, 0.12 mmol), and the mixture was stirred for 30 min at 0 °C then warmed to rt and stirred for 6 h. The reaction was poured into water and extracted with dichloromethane (2 x 2 mL). The organic extract was washed with cold 1 N HCl (1 x 3 mL), saturated sodium bicarbonate (2 x 3 mL), and brine (1 x 3 mL), and then dried over MgSO₄. Filtration through Celite and removal of the volatiles by reduced pressure gave the crude product. Purification by radial PLC (SiO₂, 2-5% EtOAc/hexanes) afforded 7.2 mg (43%) of ketone 201 as clear oil: IR (neat) 2360, 2342, 1721, 1992, 1335, 1202 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.38 (m, 2 H), 7.26 (m, 1 H), 7.14 (m, 2 H), 6.82 (dd, J = 7.8, 13.5 Hz, 1 H), 5.97 (m, 1 H), 5.68 (m, 1 H), 5.37 (m, 1 H), 4.86 (m, 1 H), 2.46 (m, 2 H), 2.12 (s, 3 H), 1.68 (m, 4 H); ¹³C NMR (CDCl₃, 100 MHz) δ 209.0, 152.3 and 151.1 (due to totoners), 129.7 and 129.6 (due to rotomers), 125.9 and 124.7 (due to rotomers), 123.4, 122.9, 100.1, 52.8, 52.2, 43.5. 34.0, 33.2, 30.2, 18.9 and 18.8 (due to rotomers; HRMS (M+H)⁺ calcd for C₁₇H₁₉NO₃ 286.1443, found 286.1440.
2-(4-Trifluoromethanesulfonyloxy-pent-4-enyl)-2H-pyridine-1-carboxylic acid phenyl ester (202). To a solution of diisopropylamine (31 µL, 0.20 mmol) in THF (1.0 ml) was added n-BuLi (2.5 M in hexanes, 80 µL, 0.20 mmol) dropwise at -23 °C, and the resulting pale yellow solution was stirred for 30 min. Meanwhile, a solution of dihydropyridine 201 (22.7 mg, 0.13 mmol) in THF (1.0 mL) was prepared and cooled to -78 °C, and the LDA prepared above was transferred to the flask by a double ended stainless steel needle. The reaction was stirred at -78 °C for 30 min and then N-(5-chloro-2-pyridyl)triflimide 36 (78.3 mg, 0.26 mmol) was added quickly. The reaction was stirred for 30 min at -78 °C and then water (2 mL) was added followed by Et₂O (2 mL). The reaction was warmed to rt, the phases were separated, and the aqueous layer was extracted with ether (3 x 1 mL). The combined organic layers were washed with brine (2 mL) and then dried over anhydrous MgSO₄. Filtration through Celite and removal of the volatiles under reduced pressure provided the crude product. Purification by radial PLC (SiO₂, 2-10% EtOAc/hexanes) provided 34.7 mg (64%) of 202 as a clear oil: IR (neat) 2345, 2300, 1392, 1330, 1202, 1195 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.41 (m, 2 H), 7.22 (m, 1 H), 7.18 (m, 1 H), 6.85 and 6.80 (pair of d due to rotomers , J = 6.8, 1 H), 6.05 (m, 1 H), 6.68 (m, 1 H), 6.59 (s, 1 H), 6.40 (m, 2 H) 4.90 and 4.81 (pair of m due to rotomers, 1 H), 2.44 (m, 2 H), 1.60 (m, 5 H); ¹³C NMR (CDCl₃, 100 MHz) δ 169.7, 151.2, 149.1, 136.5, 129.9 and 129.8 (due to rotomers), 128.6 and 128.5 (due to rotomers), 128.0 and 127.9 (due to rotomers), 127.6, 127.0, 126.5, 79.8, 51.2, 57.8, 35.2; HRMS (M+H)⁺calcd for C₁₈H₁₈F₃NO₅S 418.0936, found 418.0940.
4-Oxo-2-(5-trimethylsilanyl-pent-4-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (205). Magnesium turnings (1.01 g, 41.7 mmol) and anhydrous THF were placed in a flask, equipped reflux condenser and a magnetic stir bar, and 0.2 mL of 1,2-dibromoethane was added. The mixture was refluxed to initiate and then stirred for 20 min. The solution was cooled and then removed from the turnings by syringe, fresh THF (30 mL) was added, and the mixture was cooled to 0 °C. Neat 1-trimethylsilylacetylene (3.05 g, 13.9 mmol) was added drop wise over a period of 30 min. After the addition was complete, the cooling bath was removed and the mixture was stirred for 2 h at rt.

To a solution of 4-methoxypyridine (1.4 mL, 13.3 mmol) in 40 mL of anhydrous THF at -23 °C was added dropwise phenyl chloroformate (1.6 mL, 13.3 mmol). The reaction mixture was stirred at -23 °C for 1.5 h. The previously prepared Grignard reagent was transferred dropwise by syringe, and the mixture was stirred at -23 °C for 2 h. A solution of 10 % HCl (25 mL) was added, and the mixture was warmed to rt and stirred for 2 h. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined ether extracts were washed with water (20 mL) and brine (20 mL), and dried over anhydrous MgSO₄. Filtration through Celite and concentration in vacuo gave the crude product. Purification by radial PLC (SiO₂, 5-20% EtOAc/ hexanes) yielded 4.16 g (88%) of dihydropyridone 205 as a clear oil: IR (neat) 2173, 1738, 1674, 1606, 1333, 1187 cm⁻¹;运转;
NMR (CDCl₃, 400 MHz) δ 7.87 (d, J = 8.4 Hz, 1 H), 7.39 (m, 2 H), 7.28 (m, 1 H), 7.17 (m, 2 H), 5.43 (bs, 1 H), 4.77 (bs, 1 H), 2.93 (dd, J = 6.4, 16.8 Hz, 1 H), 2.51 (d, 16.8 Hz, 1 H), 2.25 (m, 2 H), 1.9 (bs, 1 H), 1.78 (m, 1 H), 1.65 (bs, 1 H), 1.53 (bs, 1 H), 0.13 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz) δ 192.9, 150.6, 141.1, 129.9, 128.0, 127.6, 121.5, 108.2, 106.3, 85.7, 53.6, 40.4, 30.2, 25.2, 19.8, 0.32; HRMS (M+H)+ calcd for C₂₀H₂₅NO₃Si 356.1682 found, 356.1688.

3-Bromo-4-oxo-2-(5-trimethylsilyl-pent-4-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (206). To a solution of the dihydropyridone 205 (130 mg, 0.38 mmol) in freshly distilled THF (2 mL) at -78 °C was added LiHMDS (1.0 M in THF, 0.40 mL, 0.40 mmol). The mixture was stirred for 30 min at -78 °C and then NBS (81.9 mg, 0.46 mmol) in 2 mL of THF was added dropwise by syringe over 5 min. The reaction mixture was stirred for an additional hour at -78 °C. The mixture was poured into water (3 mL) and extracted with Et₂O (3 x 2 mL). The combined organic layers were dried over MgSO₄ and filtered through Celite. Concentration of the solvent in vacuo gave the crude product. Purification by radial PLC (SiO₂, 5-10% EtOAc/hexanes) gave 102 mg (62%) of 206, as a
light yellow oil: IR (neat) 3066, 2952, 1736, 1715, 1671, 1605, 1491, 1422, 1336, 1268, 1200 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.91 (d, \(J = 6.9\) Hz, 1 H), 7.42 (m, 2 H), 7.35 (m, 1 H), 7.22 (m, 2 H), 5.44 (m, 1 H), 4.95 (bs, 1 H), 4.23 (s, 1 H), 2.31 (bs, 2 H), 1.99 (m, 1 H), 1.82-1.55 (m, 3 H), 0.12 (s, 9 H); HRMS (M+H)\(^+\) calcd for C\(_{20}\)H\(_{24}\)BrNO\(_3\)Si 434.0787, found 434.0780.

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\begin{align*}
\text{OMe} & \quad \rightarrow \\
\text{N} & \quad \text{Ph} \quad \text{CO}_2\text{Ph}
\end{align*}
\]

\(28 \quad \rightarrow \quad 214\)

2-Benzyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (214). To a solution of 4-methoxypyridine (5.5 g, 48.0 mmol) in toluene (300 mL) at -23 °C was added phenyl chloroformate (6.0 mL, 48.0 mmol) dropwise over 5 min. The reaction was stirred for 1 h at -23 °C and then cooled to -45 °C. Benzylmagnesium chloride (1.0 M in diethyl ether, 57.6 mL, 57.6 mmol) was added dropwise to the pyridinium salt, and the solution was stirred for 2 h at -45 °C. The reaction was quenched with 10% HCl (20 mL) and stirred for 1 h. The reaction was extracted with diethyl ether (2 x 50 mL), and the combined organic layers were washed with brine (50 mL) and dried over MgSO\(_4\). Filtration through Celite and concentration of the solution in vacuo gave the crude product. Purification by silica gel chromatography (5-10% EtOAc/hexane) gave 10.5 g (71%) of 214 as a clear oil: IR (neat)
1621, 1573, 1455, 1408, 1343, 1305, 1277, 1239, 1198 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.94 (dd, \(J = 1.5, 8.4\) Hz, 1 H), 7.26 (m, 8 H), 7.07 (bs, 1 H), 6.86 (bs, 1 H), 5.53 (bs, 1 H) 4.90 (bs, 1 H), 3.12 (bs, 1 H), 2.91 (dd, \(J = 8.7, 13.2\) Hz, 1 H), 2.80 (bs, 1 H), 2.50 (d, \(J = 16.5\) Hz, 1 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 193.2, 151.5, 142.2, 136.9, 129.8, 129.6, 129.5, 128.8, 127.9, 127.0, 106.7, 83.6, 39.1, 36.5, 28.3; HRMS (M+H\(^+\)) calcd for C\(_{19}\)H\(_{17}\)NO\(_3\) 308.1286, found 308.1288.

2-Benzyl-2,3-dihydro-1H-pyrdin-4-one (215). To a solution of dihydropyridone 214 (9.69 g, 32.0 mmol) in methanol (130 mL) at 0 °C was added solid K\(_2\)CO\(_3\) (8.8 g, 64.0 mmol) over a period of 5 min. The reaction was stirred at 0 °C for 1 h then at rt for 8 h. The mixture was filtered through Celite and the filter cake was washed with several portions of EtOAc. The solvent was removed \textit{in vacuo} to give the crude dihydropyridone. Purification by silica gel chromatography (60-80 % EtOAc/hexanes) gave 5.8 g (94%) of 215 as a clear oil which became solid on standing: mp 153 -155 °C; IR (neat) 3242, 3029, 1621, 1573, 1455, 1408, 1343, 1305, 1277, 1239, 1198 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.28 (m, 5 H); 7.08 (t, \(J = 6.9\) Hz, 1 H), 5.04 (d, \(J = 7.2\) Hz, 1 H), 4.68 (bs, 1 H), 3.86 (m, 1 H), 2.96 (dd, \(J = 5.1, 13.5\) Hz, 1 H).
Hz, 1 H), 2.85 (dd, $J = 9.6, 10.2$ Hz, 1 H), 2.57 (dd, $J = 5.1, 21.3$ Hz, 1 H), 2.45 (dd, $J = 7.8, 16.2$ Hz, 1 H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 192.9, 151.6, 136.9, 129.4, 129.1, 127.3, 99.1, 54.5, 42.1, 40.4; HRMS (M+H)$^+$ calc for C$_{12}$H$_{13}$NO 188.1075, found 188.1079.

![Chemical structure images]

2- Benzyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid tert- butyl ester (216).

To a solution of dihydropyridone 215 (4.63 g, 24.0 mmol) in dichloromethane (50 mL) at 0 °C was added triethylamine (3.3 mL, 24.0), Boc$_2$O (7.86 g, 36.0 mmol) and 4-dimethylaminopyridine (293 mg, 2.4 mmol). The solution was stirred at 0 °C for 30 min at rt for 4 h. The mixture was poured into saturated NaHCO$_3$ solution and extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (1 x 15 mL), and dried over MgSO$_4$. Filtration of the combined organic layers through Celite and concentration of the filtrate in vacuo to gave the crude product. Purification by silica gel chromatography (10-20% EtOAc/hexanes) afforded 5.86 g (85%) of 216 as a clear oil: IR (neat) 1621, 1573, 1455, 1408, 1343, 1305, 1277, 1239, 1198 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.81 (bs, 1 H), 7.26 (m, 3 H), 7.17 (d, $J = 6.9$ Hz, 2 H), 5.37 (d, $J = 6.6$ Hz, 1 H), 4.68 (bs, 1 H), 2.96 (dd, $J = 6.3, 13.2$ Hz, 1 H), 2.83 (dd, $J = 9.0, 12.9$ Hz, 1 H),
2.70 (dd, J = 6.3, 16.5 Hz, 1 H), 2.39 (J = 1.2, 16.5, 1 H), 1.45 (s, 9 H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 196.5, 151.8, 139.8, 137.6, 129.1, 128.5, 128.2, 127.4, 113.3, 72.0, 47.1, 39.2, 27.4; HRMS (M+H)$^+$ calcd for C$_{17}$H$_{21}$NO$_3$ 288.1599, found 288.1600.

2-Benzyl-5-iodo-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (217).

To a solution of dihydropyridone 216 (6.02 g, 21.0 mmol) in 100 mL of anhydrous dichloromethane at 0 °C was rapidly added iodine monochloride (1.0 M in dichloromethane, 31.5 mL, 31.5 mmol) and stirring was continued at 0 °C for 1 hr. The mixture was poured into ice cold saturated NaHCO$_3$ solution (50 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with saturated aqueous Na$_2$S$_2$O$_3$ solution (2 x 20 mL) and brine (20 mL), dried over MgSO$_4$, and filtered through Celite. The solvent was removed in vacuo to provide the crude product. Purification by silica gel chromatography (10-20% EtOAc/hexanes) provided 7.55 g (87%) dihydropyridone 217 as a yellow solid; mp 138-141 °C; IR (neat) 2360, 2339, 1723, 1674, 1579, 1294, 1253, 1159, 1135 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.32 (bs, 1 H), 7.27 (m, 3 H), 7.1 (d, 6.6 Hz, 2 H), 4.71 (bs, 1 H), 2.95 (dd, J = 6.0, 13.2 Hz, 1 H) 2.78 (m, 3 H), 1.47 (s, 9 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$
187.2, 151.2, 147.6, 136.4, 129.8, 129.0, 127.3, 100.1, 84.6, 73.2, 38.8, 37.9, 36.3, 28.1; HRMS (M+H)⁺ calcd for C₁₇H₂₀INO₃ 414.0566, found 414.0581.

6-Benzyl-4-oxo-5-6-dihydro-4H-pyridine-1,3-dicarboxylic acid 1-tert-butyl 3-methyl ester (218). To a solution of dihydropyridone 217 (250 mg, 0.61 mmol) in DMF (5.0 mL) was added triethylamine (0.17 mL, 1.2 mmol), toluene (5.0 mL), and anhydrous methanol (2.5 mL). The solution was transferred by syringe to a Paar bomb and the Pd(OAc)₂(PPh₃)₂ was quickly added. The bomb was flushed with argon for 5 min and then sealed and pressurized to 100 psi of CO, heated to 60 °C, and stirred for 12 h. The reactor was cooled to rt and depressurized. The reaction mixture was diluted with 30 mL of H₂O and 10 mL of EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous MgSO₄. Filtration and removal of the solvent *in vacuo* gave the crude product. Purification by radial PLC (SiO₂, 30-50% EtOAc/hexanes) afforded 125 mg (60%) of 218 as a light brown solid: mp 115-119 °C; IR (neat) 1734, 1698, 1590, 1397, 1370, 1323, 1248, 1137 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 8.84 (s, 1 H), 7.28 (m, 3 H), 7.15 (d, J = 6.3 Hz, 2 H), 4.69 (dd, J = 7.2, 7.8 Hz, 1 H), 3.84 (s, 3 H) 2.94 (dd, J = 5.7, 12.9 Hz, 1 H), 2.78 (d, J
= 9.3 Hz, 1 H), 2.70 (dd, J = 9.3, 18.6 Hz, 1 H), 2.46 (dd, J = 1.8, 16.2 Hz, 1 H) 1.50 (s, 9 H); \( ^{13} \text{C NMR (CDCl}_3, 100 \text{ MHz)} \delta 188.5, 164.9, 150.3, 136.2, 129.8, 129.0, 128.3, 127.3, 118.7, 107.7, 85.5, 55.3, 52.2, 39.6, 36.9, 28.0; \) HRMS (M+H)\(^+\) calcd for C\(_{19}\)H\(_{23}\)NO\(_3\) 356.1682, found 356.1710.

\[ \begin{align*}
\text{218} & \quad \text{220}
\end{align*} \]

6-Benzyl-2-cyclohexylmethyl-4-oxo-5,6-dihydro-4H-pyridine-1,3-dicarboxylic acid 1-\textit{tert}-butyl ester 3-methyl ester (220). Magnesium turnings (141mg, 5.8mmol) were mechanically activated by stirring at rt overnight under argon, and anhydrous THF (3 mL) was added. Cyclohexylmethyl bromide (0.16 mL, 1.16 mmol) was added dropwise over 30 min to the activated turnings, and the mixture was cooled to 10 °C once the reaction initiated. After the addition was complete, the reaction mixture was allowed to warm to rt and was stirred for 6 h to form the cyclohexylmethylmagnesium bromide.

In a separate flask, copper bromide dimethyl sulfide complex (301 mg, 1.5 mmol) was mixed with freshly distilled THF (5 mL) and cooled to -78 °C. A solution of 218 (150 mg, 0.29 mmol) in THF (2 mL) was added, followed by a premixed solution of freshly distilled TMSCl (0.41 mL, 3.20 mmol) and Et\(_3\)N (0.47 mL, 3.35 mmol). Finally, a solution of
the above prepared Grignard reagent in THF was added dropwise over a period of 1 h. Once
the addition was complete, the resulting slurry was stirred at -78 °C for 2 h and then warmed
to -45 °C. After 24 h, the reaction mixture was quenched with a carefully buffered solution
of 50 mL of NH₄OH and NH₄Cl (1:1, pH 8), and the phases were separated. The aqueous
phase was extracted with ether (2 x 30 mL), and the combined organic layers were washed
with 10 % NH₃OH until no blue color was observed in the aqueous layer. After drying over
anhydrous K₂CO₃ and filtering through Celite, the solvent was removed under reduced
pressure to afford 150 mg (100%) of the crude enol silane 237 which was then dissolved in
anhydrous CH₃CN (12 mL). To this solution was added Pd(OAc)₂ (10.1 g, 0.045 mmol) and
CuCl (29.0 mg, 0.291 mmol). The reaction mixture was purged with oxygen and warmed to
60 °C under an O₂ balloon pressure atmosphere. The reaction was stirred vigorously
overnight. Upon completion, the reaction mixture was cooled to rt, filtered through Celite
with CH₂Cl₂, and the solvent was removed in vacuo to yield the crude product. Purification
by silica gel chromatography (10-25% EtOAc/hexanes) gave 69.4 mg (54 %) of 220 as a
clear oil: IR (neat) 2318, 1718, 1623, 1522, 1500, 1444, 1316, 1245 cm⁻¹; ¹H NMR (CDCl₃,
400 MHz) δ 7.26 (m, 3 H), 7.20 (m, 2 H), 4.81 (s, 1 H), 4.19 (bs, 1 H), 3.79 (s, 3 H), 3.04 (d,
J = 12.8 Hz, 1 H), 2.54 (dd, J = 6.7, 17.2 Hz, 1 H), 2.47 (dd, 10.8, 12.8 Hz, 1 H), 2.24 (d,
16.4 Hz, 1 H), 1.62 (bs, 1 H), 1.57 (s, 11 H), 1.41-1.09 (m, 9 H); ¹³C NMR (CDCl₃, 100
MHz) δ 198.2, 156.5, 151.3, 141.2, 137.6, 128.9, 128.7, 127.6, 126.6, 121.5, 99.6, 72.3, 50.1,
42.5, 41.6, 39.8, 29.3, 25.5, 20.4, 15.5; HRMS (M+H)⁺ calcd for C₂₆H₃₅NO₅ 442.2593, found
442.2591.
6-Benzyl-2-hex-5-enyl-4-hydroxy-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (225a). Magnesium turnings (0.907 g, 37.3 mmol) and THF (15 mL) were placed in a flask, equipped with reflux condenser and magnetic stir bar. To the mixture was added 0.2 mL of 1,2-dibromoethane. The mixture was refluxed for 20 min and then cooled to rt. The solution was removed from the turnings by syringe, 15 mL of fresh THF was added, and the flask cooled to 0 °C. Neat 6-bromo-1-hexene (1.0 mL, 7.5 mmol) was added dropwise over a period of 30 min. After the addition was complete, the cooling bath was removed and the mixture was stirred for 2 h at rt. In a separate flask, copper(I) bromide dimethylsulfide complex (770 mg, 3.8 mmol) was suspended in freshly distilled anhydrous THF and cooled to -78 °C. The Grignard reagent from above was added to the slurry by a double ended stainless steel needle. The mixture was stirred at -78 °C for 10 min and then allowed to warm to -50 °C for 15 min, during which time the solution turned a deep orange red and homogeneous. The reaction mixture was cooled back down to -78 °C. A solution of dihydropyridone 218 (645 mg, 1.87 mmol) in THF (10 mL) was added dropwise to the dialkylcuprate at -78 °C and the mixture was stirred for 1 h. The reaction was quenched with saturated NH₄Cl (10 mL) and extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with saturated NH₄Cl (20 mL portions) till no blue color was observed in the aqueous layer. The combined organic layers were dried over
anhydrous MgSO₄ and filtered through Celite. The solvent was removed under reduced pressure to provide the crude product. Purification by radial PLC (10-15% EtOAc/hexanes) gave 796 mg (99.6 %) of 225a/b (4.2:1) as a clear oil: **225a**: IR (neat) 2345, 1718, 1623, 1522, 1500, 1472, 1322, 1245 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.26 (m, 3 H), 7.20 (m, 2 H), 5.77 (m, 1 H), 4.94 (dd, J = 1.6, 17.2 Hz, 2 H), 4.81 (s, 1 H), 4.19 (bs, 1 H), 3.79 (s, 3 H), 3.04 (d, J = 12.8 Hz, 1 H), 2.54 (dd, J = 5.6, 16.0 Hz, 1 H), 2.47 (dd, 10.8, 12.8 Hz, 1 H), 2.24 (d, 16.4 Hz, 1 H), 1.75 (bs, 1 H), 1.57 (s, 9 H), 1.38-1.02 (m, 8 H); ¹³C NMR (CDCl₃, 75 MHz) δ 198.2, 156.5, 151.3, 141.2, 137.6, 128.9, 128.7, 127.6, 126.6, 121.5, 99.6, 72.3, 50.1, 42.5, 41.6, 39.8, 29.3, 26.3, 24.4, 22.5, 19.4; HRMS (M+H)⁺ calcd for C₂₅H₃₅NO₅ 430.2595, found 430.2590.

**225b**: IR (neat) 2342, 1725, 1623, 1522, 1362, 1245 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.30 (m, 3 H), 7.22 (m, 2 H), 5.87 (m, 1 H), 4.94 (dd, J = 1.6, 17.2 Hz, 2 H), 4.77 (s, 1 H), 4.23 (s, 1 H), 3.79 (s, 3 H), 3.04 (d, J = 12.8 Hz, 1 H), 2.54 (dd, J = 5.6, 16.0 Hz, 1 H), 2.47 (dd, 10.8, 12.8 Hz, 1 H), 2.24 (d, 16.4 Hz, 1 H), 1.75 (bs, 1 H), 1.57 (s, 9 H), 1.38-1.02 (m, 8 H); ¹³C NMR (CDCl₃, 75 MHz) δ 200.1, 156.5, 151.3, 141.2, 137.6, 128.9, 128.7, 127.0, 126.0, 121.5, 100.1, 74.4, 53.1, 47.0, 41.6, 39.4, 29.3, 26.3, 24.4, 22.5, 20.1; HRMS (M+H)⁺ calcd for C₂₅H₃₅NO₅ 430.2595, found 430.2598.
2-Butyl-4-methoxy-2H-pyridine-1-carboxylic acid phenyl ester (239). To a stirred solution of 4-methoxypyridine (0.57 mL, 5.6 mmol) in anhydrous THF (10 mL) at -23 °C under a nitrogen atmosphere was added dropwise phenyl chloroformate (0.68 mL, 5.6 mmol). A white precipitate developed during the addition and rapid stirring was maintained. The reaction was stirred at -23 °C for 1 h and butylmagnesium chloride (2.0 M in Et₂O, 3.4 mL, 7.3 mmol) was added. The reaction mixture was stirred at -23 °C for 1.5 h. Aqueous 20% NH₄Cl/NH₄OH (1:1) (10 mL) was added and the reaction mixture was warmed to rt. The aqueous layer was extracted with diethyl ether (3 x 10 mL), and the combined organic layers were washed with brine (10 mL) and then dried over K₂CO₃. Filtration through Celite and concentration in vacuo gave 1.58 g (~ 99%) of crude product. (This crude material was used directly in the next step).
2-Butyl-4-methoxy-2H-pyridine-1-carboxylic acid tert-butyl ester (240). A solution of crude dihydropyridine 239 (1.6 g, 5.6 mmol) in freshly distilled anhydrous THF (30 mL) was transferred by a double ended stainless steel needle to a solution of KOTBu (1.6 g, 14.0 mmol) in THF (30 mL) at -42 °C. The reaction temperature was maintained at -42 °C for 3 h and then the reaction mixture was poured into a mixture of saturated aqueous NaHCO₃ solution (50 mL) and diethyl ether (50 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over anhydrous K₂CO₃ and filtered through Celite. Concentration under reduced pressure gave the crude product. Purification by silica gel chromatography (5% Et₃N/hexanes) gave 1.49 g (88%) of 240 as a clear oil: IR (neat) 3087, 2957, 3870, 2722, 1714, 1599, 1469, 1424, 1337, 1156, 1001, 964 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.81 and 6.72 (pair of bs due to rotomers, 1 H), 5.09 and 5.03 (pair of bs due to rotomers, 1 H), 4.80 and 4.74 (pair of bs due to rotomers, 1 H), 4.51 (bs, 1 H), 3.57 (s, 3 H), 1.61 (m, 1 H), 1.50 (s, 9 H), 1.30 (m, 5 H), 0.91 (bs, 3 H); ¹³C NMR (CDCl₃,100 MHz) δ 152.0, 127.7, 104.0 and 103.3 (due to rotomers), 90.3 and 89.8 (due to rotomers), 81.3, 54.6, 51.2 and 50.4 (due to rotomers), 28.4, 23.8, 23.4, 22.0, 15.1. (This material should be stored under argon at -50 °C in the dark).
2-Butyl-6-iodo-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (243).

To a solution of 240 (423 mg, 1.6 mmol) in freshly distilled THF (10 mL) was added \( n \)-BuLi at -42 °C (2.2 M in hexanes, 0.90 mL, 2.0 mmol), and the mixture was stirred for 1 h at -42 °C. The resulting orange colored solution was then cooled to -78 °C. A solution of hexachloroethane (568 mg, 2.4 mmol) in THF (5.0 mL) was added by syringe, and the mixture was allowed to warm to rt with stirring for 2 h. The reaction was diluted with water, oxalic acid (432 mg, 4.8 mmol) was added, and stirring was continued at rt for an additional 2 h. The reaction was poured into 10 mL of saturated sodium bicarbonate solution and then extracted with ether (3 x 20 mL). The combined organic layers were dried over \( \text{MgSO}_4 \), filtered through Celite, and concentrated \( \text{in vacuo} \) to give the crude product. Purification by radial PLC (SiO\(_2\), 10-20% EtOAc/hexanes) gave 372 mg (81%) of 243 as an oil: IR (neat) 3435, 2290, 2111, 1788,1752, 1422, 1331 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.70 (s, 1 H), 4.78 (m, 1 H), 2.80 (dd, \( J = 5.7, 17.4, 1 \) H), 2.41 (dd, 0.9, 17.4, 1 H), 1.90 (m, 1 H), 1.6 (s, 9 H), 1.2 (m, 5 H), 0.9 (t, \( J = 6.7 \) Hz, 3 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 191.3, 151.9, 129.3, 110.1, 84.6, 57.8, 42.8, 30.0, 28.8, 28.5, 22.6, 14.3; HRMS (M+H\(^+\)) calcd for C\(\text{_{14}}\)H\(\text{_{22}}\)ClNO\(_3\) 288.1366, found 288.1368.
6-Iodo-2-isobutyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid tert butyl ester (275). To a solution of 251 (97.5 mg, 0.36 mmol) in freshly distilled THF (2.0 mL) was added n-BuLi at -42 °C (2.2 M in hexanes, 0.20 mL, 0.43 mmol), and the mixture was stirred for 1 h at -42 °C. The resulting orange colored solution was cooled to -78 °C. A solution of iodine beads (170 mg, 0.72 mmol) in THF (2.0 mL) that had been stirred over 2 g of 4 Å mol sieves for 1 h was added by syringe. Stirring was continued for 20 min at -78 °C, the cooling bath was removed, and the reaction was allowed to warm to room temperature over 30 min. The reaction mixture was diluted with water (3 mL) and oxalic acid (100 mg, 1.1 mmol) was added. The mixture was stirred for 3 h, poured into 10 mL of saturated sodium bicarbonate solution, and extracted with diethyl ether (3 x 3 mL). The combined organic extracts were dried over MgSO₄ and filtered through Celite. Concentration under reduced pressure provided the crude product. Purification by radial PLC (SiO₂, 10% EtOAc/hexanes) gave 84.2 mg (81%) of the dihydropyridone 275 as a pale yellow oil: IR ( neat) 1722, 1683, 1530, 1369, 1321, 1255, 1212 cm⁻¹; ^1H NMR (CDCl₃, 400 MHz) δ 6.34 (s, 1 H), 4.83 (m, 1 H), 2.80 (dd, J = 5.6, 17.2, 1 H), 2.32 (d, J = 17.6, 1 H), 1.75 (m, 1 H), 1.6 (m, 1 H), 1.55 (s, 9 H), 1.42 (m, 1 H), 0.94 (m, 6 H); ^13C NMR (CDCl₃, 100 MHz) δ 190.3, 120.3, 112.3, 98.4,
54.3, 42.9, 41.8, 27.1, 24.6, 22.6; HRMS (M+H)$^+$ calcd C$_{14}$H$_{22}$INO$_3$ (M+H)$^+$ 380.0722, found 380.0711.

2-Isobutyl-4-oxo-6-vinyl-3-4-dihydro-2H-pyridine-1-carboxylic acid tert butyl ester (280). To a solution of 275 (326 mg, 0.86 mmol) in toluene (20 mL) was added tributylvinylstannane (0.29 mL, 1.0 mmol) and copper(I) iodide (16.3 mg, 0.086 mmol). Palladium tetrakistriphenylphosphine (69.3 mg, 0.06) was added to the reaction, and the solution was degassed for 20 min then heated to 100 °C for 8 h. The reaction was cooled to rt and then filtered over a pad of Celite with EtOAc. The solvent was removed under reduced pressure to give the crude product. Purification of the crude material by silica gel chromatography (5-10% EtOAc/hexanes) gave 236 mg (99%) of 280 as an oil: IR (neat) 1633, 1601, 1562, 1499, 1450, 1259, 1230 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.44 (dd, $J = 10.8$ Hz, 17.0, 1 H), 5.65 (dt, $J = 1.2$, 17.2, 2 H), 5.33 (d, $J = 10.8$, 1 H), 4.77 (m, 1 H), 2.81 (dd, $J = 6.0$, 17.2 Hz, 1 H), 2.26 (dt, $J = 4.62$, 17.2, 1 H), 1.66 (m, 1 H), 1.56 (m, 1 H), 1.50 (s, 9 H), 1.45 (m, 1 H) 0.92 (m, 6 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 197.6, 156.3, 151.2, 138.6, 117.5, 105.2, 71.3, 46.5, 42.3, 39.9, 25.5, 25.3, 21.2; HRMS (M+H)$^+$ calcd for C$_{16}$H$_{25}$NO$_3$ 280.1912, found 280.1915.
6-Chloro-5-iodo-4-oxo-2-butyl-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (244). To a solution of dihydropyridone 243 (171 mg, 0.60 mmol) in freshly distilled ethyl acetate was added iodine monochloride solution (1.0 M in dichloromethane, 2.7 mL, 0.66 mmol) at -78 °C. The solution was stirred for 2 h at -78 °C and then poured onto saturated sodium bicarbonate solution (10 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with saturated Na₂S₂O₃ solution (2 x 5 mL), and brine (5 mL), and then dried over MgSO₄. Filtration through Celite followed by removal of the volatiles in vacuo gave the crude product. Purification by silica gel chromatography (10-15% EtOAc/hexanes) gave 256 mg (88%) of 244 as a clear oil: IR (neat) 1681, 1537, 1368, 1316, 1159, 1120 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.74 (m, 1 H), 3.04 (m, 1 H), 2.63 (m, 1 H), 1.76 (m, 1 H), 1.56 (s, 9 H), 1.44 (m, 5 H), 0.92 (m, 3 H); ¹³C NMR (CDCl₃, 100 MHz) δ 198.0, 153.1, 149.9, 76.1, 65.2, 43.1, 37.6, 32.6, 28.8, 28.0, 22.1, 15.3; HRMS (M+H)⁺ calcd for C₁₄H₂₁ClINO₃ 414.0333, found 414.0335.
2-Isobutyl-4-methoxy-2H-pyridine-1-carboxylic acid phenyl ester (250). To a stirred solution of 4-methoxypyridine (1.0 g, 9.17 mmol) in anhydrous THF (100 mL) at -23 °C under a nitrogen atmosphere was added dropwise phenyl chloroformate (1.27 mL, 10.1 mmol). A white precipitate developed. The mixture was stirred at -23 °C for 1 h and then iso-butylmagnesium chloride (2.0 M in Et₂O, 6.0 mL, 11.9 mmol) was added dropwise. The reaction mixture was stirred at -23 °C for 1.5 h. Aqueous 20% NH₄Cl/NH₄OH (1:1, 50 mL) was added and the reaction mixture was warmed to rt. The aqueous layer was extracted with diethyl ether (3 x 30 mL), and the combined organic layers were washed with brine (20 mL) and then dried over K₂CO₃. Filtration through Celite, and concentration in vacuo gave 2.6 g (~ 98%) of crude product 250 as a clear oil. (This crude material was used directly in the next step).
2-Isobutyl-4-methoxy-2H-pyridine-1-carboxylic acid tert-butyl ester (251). A solution of crude dihydropyridine 250 (5.4 g, 18.3 mmol) in freshly distilled anhydrous THF (50 mL) was transferred by a double ended stainless steel needle to a solution of KOtBu (4.8 g, 42.3 mmol) in THF (60 mL) at -42 °C. The reaction temperature was maintained at -42 °C for 3 h and then the mixture was poured into saturated NaHCO₃ solution (50 mL). Diethyl ether (50 mL) was added and the phases were separated. The aqueous layer was extracted with diethyl ether (3 x 30 mL), and the combined organic layers were dried over anhydrous K₂CO₃ and filtered through Celite. Concentration under reduced pressure gave the crude product. Purification by silica gel chromatography (5% Et₃N/hexanes) gave 4.62 g (87%) of 251 as a clear oil: IR (neat) 3087, 2957, 3870, 2722, 1714, 1599, 1469, 1424, 1337, 1156, 1001, 964 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.81 and 6.72 (pair of bs due to rotomers, 1 H), 5.09 and 5.03 (pair of bs due to rotomers, 1 H), 4.80 and 4.74 (pair of bs due to rotomers, 1 H), 4.51 (bs, 1 H), 3.57 (s, 3 H), 1.75 (m, 1 H), 1.60 (m, 1 H), 1.55 (s, 9 H), 1.42 (m, 1 H), 0.94 (m, 6 H); ¹³C NMR (CDCl₃,100 MHz) δ 152.0, 127.7, 104.0 and 103.3 (due to rotomers), 90.3 and 89.8 (due to rotomers), 81.3, 54.6, 51.2 and 50.4 (due to rotomers), 28.4, 23.8, 23.4, 22.0.
6-Chloro-2-isobutyl-4-methoxy-2H-pyridine-1-carboxylic acid *tert*-butyl ester (252).

To a solution of dihydropyridine 251 (97.5 mg, 0.36 mmol) in freshly distilled THF (2.0 mL) was added *n*-BuLi at -42 °C (2.2 M in hexanes, 0.20 mL, 0.43 mmol), and the mixture was stirred for 1 h at -42 °C. The resulting orange colored solution was cooled to -78 °C. A solution of hexachlorethane (170 mg, 0.72 mmol) in THF (2.0 mL) was added by syringe. Stirring was continued for 20 min at -78 °C and then the cooling bath was removed. The mixture was allowed to warm to room temperature and stirred for 30 min. The mixture was diluted with saturated sodium bicarbonate (5 mL) and ether (5 mL), and the phases were separated. The aqueous layer was extracted with Et₂O (3 x 3 mL), and the combined organic extracts were washed with brine (5 ml) and dried over K₂CO₃. The solvent was removed under reduced pressure to give the crude product. Purification by silica gel chromatography (2% Et₃N/hexanes) gave 88.0 mg (81%) of 252 as a yellow oil: IR (neat) 2950, 3860, 2722, 1714, 1471, 1424, 1337, 1156, 1001, 970 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.61 (s, 1 H), 4.81 (m, 1 H), 4.63 (d, *J* = 6.9 Hz, 1 H), 3.50 (s, 3 H), 1.60 (m, 1 H), 1.55 (s, 9 H), 1.42 (m, 1 H), 0.97 (m, 6 H); ¹³C NMR (CDCl₃, 100 MHz) δ 158.2, 150.2, 130.3, 103.6, 71.2, 51.0, 43.1, 39.6, 28.8, 22.0, 21.0; HRMS (M+H)⁺ calcd for C₁₅H₂₄ClNO₃ 302.1523, found 302.1520.
2-Chloro-6-isobutyl-4-oxo-5,6-dihydro-4H-pyridine-1,3-dicarboxylic acid 1-tert-butyl ester 3 methyl ester (256). To a solution of 252 (275 mg, 0.91 mmol) in freshly distilled THF (10 mL) at -78 °C was added n-BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol) dropwise by syringe. The resulting orange-red colored solution was stirred at -78 °C for 30 min and subsequently warmed to -50 °C. The reaction was maintained at -50 °C for an additional 30 min and then cooled back to -78 °C and methylchloroformate (0.28 mL, 3.64 mmol) was added quickly by syringe. Stirring was continued for 15 min at -78 °C, the dry ice bath was removed, and the reaction was allowed to warm to room temperature and stirred for an additional 30 min. The reaction was quenched by the addition of 5 mL of water, solid oxalic acid (250 mg, 2.73 mmol) was added, and the mixture was stirred for 6 h. The reaction was poured into a large Erlenmeyer flask and saturated sodium bicarbonate was added until the bubbling ceased. Diethyl ether (10 mL) was added and the phases were separated. The aqueous layer was extracted with diethyl ether (2 x 5 mL), and the combined organic layers were washed with brine (1 x 5 mL) and dried over anhydrous K2CO3. The volatiles were removed in vacuo and the crude oil was purified by radial PLC (SiO2, 10-20% EtOAc/hexanes) to provide 241 mg (77%) of the product 256 as a orange-yellow oil: IR
(neat) 1750, 1718, 1681, 1537, 1368, 1316, 1159, 1120 cm^{-1}; ¹H NMR (CDCl₃, 400 MHz) δ 4.84 (m, 1 H), 3.86 (s, 3 H), 2.85 (dd, J = 5.6, 17.2 Hz, 1 H), 2.42 (d, J = 17.2 Hz, 1 H), 1.80 (m, 1 H), 1.62 (m, 1 H), 1.55 (s, 9 H), 1.40 (m, 1 H), 0.90 (dd, J = 6.8, 17.2 Hz, 6 H); ¹³C NMR (CDCl₃, 100 MHz) δ 199.2, 165.3, 152.4, 147.6, 112.0, 68.8, 50.0, 44.2, 43.1, 38.1, 26.0 23.3, 23.0; HRMS (M+H)^+ calcd for C₁₆H₂₄ClNO₅ 346.1421, found 346.1429.

2-Hex-5-enyl-6-isobutyl-4-oxo-5,6-dihydro-4H-pyridine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (263). Magnesium turnings (91.0 mg, 3.8 mmol) and anhydrous THF (2.0 mL) were placed in a flask, equipped reflux condenser and magnetic stir bar and to the mixture was added 1,2-dibromoethane (50 µL). The mixture was refluxed for 20 min and then cooled to rt. The solution was removed from the turnings by syringe and then 2 mL of fresh THF was added. The mixture was cooled to 0 °C by ice bath and neat 6-bromo-1-hexene (0.10 mL, 0.75 mmol) was added dropwise over a period of 30 min. After the addition was complete, the ice bath was removed and the mixture was stirred for 2 h at rt. In a separate flask was placed CuCN (67.2 mg, 0.75 mmol) in 2.0 mL of THF and cooled to -78 °C, and the Grignard as described above was added dropwise. Once the Grignard addition
was complete, the temperature of the cooling bath was raised to -30 °C. A solution of dihydropyridone 256 (169 mg, 0.50 mmol) in THF (1 mL) was added to the organocopper reagent at -30 °C resulting in a bright orange color. The reaction was stirred at -30 °C for 2 h and then quenched with 10% NH₄OH solution (3 mL). After extraction with ether (3 x 2 mL), the combined organic layers were washed 10% NH₄OH (3 mL) and then dried over anhydrous K₂CO₃. The mixture was filtered through Celite and the solvent was removed under reduced pressure to give the crude product. Purification by radial PLC (SiO₂, 10-25% EtOAc/hexanes) gave 210 mg (71%) of 263 as a clear oil: IR (neat) 2345, 1718, 1623, 1522, 1500, 1472, 1322, 1245 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 5.77 (m, 1 H), 4.94 (dd, J = 1.6, 17.2 Hz, 2 H), 4.74 (m, 1 H), 3.76 (s, 3 H), 3.42 (dd, J = 2.3, 17.2 Hz, 1 H) 2.85 (dd, J = 5.6, 17.2 Hz, 1 H), 2.42 (d, J = 17.2 Hz, 1 H), 1.80 (m, 1 H), 1.62 (m, 1 H), 1.55 (s, 11 H), 1.40 (m, 6 H), 0.90 (dd, J = 6.8, 17.2 Hz, 6 H); ¹³C NMR (CDCl₃, 75 MHz) δ 198.2, 165.1, 156.5, 151.3, 141.2, 137.6, 121.5, 114.1, 99.6, 72.3, 50.1, 42.5, 32.8, 29.3, 26.3, 24.4, 23.5, 23.2; HRMS (M+H)⁺ calcd for C₂₂H₃₅NO₅ 394.2593, found 394.2599.
2,6-Diisobutyl-4-oxo-5,6-dihydro-4H-pyridine-1,3-dicarboxylic acid 1-tert-butyl ester 3 methyl ester (283). A mixture of CuCN (84.0 mg, 0.94 mmol) in 1.0 mL of THF was cooled to -78 °C, and isobutylmagnesium chloride (2.0 M in Et₂O) was added dropwise. Once the Grignard addition was complete, the temperature of the cooling bath was raised rapidly to -30 °C. A solution of dihydropyridone 256 (163 mg, 0.48 mmol) in 0.5 mL of THF was added to the organocopper reagent at -30 °C resulting in a bright orange color. The mixture was stirred at -30 °C for 2 h and then at 0 °C for 1 h before being quenched with 10% NH₄OH solution (2 mL). After extraction with ether (3 x 2 mL), the combined organic layers were washed with 10% NH₄OH (3 mL) and then dried over anhydrous K₂CO₃. The reaction was filtered through Celite and the solvent was removed under reduced pressure to give the crude product. Purification by radial PLC (SiO₂, 10-20% EtOAc/hexanes) gave 252 mg (76%) of 283 as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 4.74 (m, 1 H), 3.76 (s, 3 H), 3.46 (dd, J = 2.3, 17.2 Hz, 1 H) 2.83 (dd, J = 5.6, 17.2 Hz, 1 H), 2.44 (d, J = 17.2 Hz, 1 H), 1.91 (m, 1 H), 1.62 (m, 1 H), 1.51 (s, 9 H), 1.48 (m, 3 H), 0.90 (dd, J = 6.8, 17.2 Hz, 12 H); ¹³C NMR (CDCl₃, 100 MHz) δ 198.3, 163.2, 155.3, 150.1, 110.2, 71.3, 52.6, 40.2, 39.6, 29.6, 28.6, 25.9, 25.3, 25.4; HRMS (M+H)⁺ calcd for C₂₀H₃₃NO₅ 368.2437, found 368.2433.
6-Chloro-2-isobutyl-5-methylsulfanyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (282a). To a solution of 252 (134 mg, 0.44 mmol) in freshly distilled THF (5 mL) at -78 °C was added n-BuLi (2.45 M in hexanes, 0.24 mL, 0.58 mmol) resulting in a orange-red colored solution. The reaction was stirred at -78 °C for 30 min and subsequently warmed to -50 °C by the addition of warm acetone to the cooling bath. The reaction was maintained at -50 °C for an additional 30 min and then cooled to -78 °C and neat dimethyl disulfide (50 µL, 0.58 mmol) was added. The reaction temperature was gradually raised to rt over 30 min. Water (5 mL) and oxalic acid (118 mg, 1.32 mmol) were added, and the resulting solution was allowed to stir for 4 h. Diethyl ether (5 mL) was added and the phases were separated. The aqueous layer was extracted with Et₂O (2 x 5 mL), and the combined organic extracts were washed with brine, dried over MgSO₄, and concentrated in vacuo to give the crude product. Purification by radial PLC (SiO₂, 10-20 % EtOAc/hexanes) gave 127.8 mg (87%) of 282a as a light yellow oil: IR (neat) 1718, 1681, 1537, 1368, 1316, 1159, 1120 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.79 (m, 1 H), 2.91 (dd,  J = 5.6, 18.0, 1 H), 2.44 (d,  J = 18.0 Hz, 1 H), 2.30 (s, 3 H), 1.75 (m, 1 H), 1.60 (m, 1 H), 1.54 (s, 9 H), 1.22 (m, 1 H), 0.95 (dd,  J = 6.4, 15.6 Hz, 6 H); ¹³C NMR (CDCl₃, 100 MHz) δ 199.2, 152.4, 147.6,
124.3, 112.0, 44.2, 43.1, 38.1, 26.0 23.3, 23.0 14.3; HRMS (M+H)$^+$ calcd for $C_{15}H_{24}ClNO_3S$ 334.8818, found 334.8820.

6-Chloro-5-ethyl-2-isobutyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (282b). To a solution of 252 (91.3 mg, 0.30 mmol) in freshly distilled (5 mL) THF at -78 °C was added $n$-BuLi (2.45 M in hexanes, 0.16 mL, 0.39 mmol) resulting in a orange-red colored solution. The reaction was stirred at -78 °C for 30 min and subsequently warmed to -50 °C by the addition of warm acetone to the cooling bath. The reaction was maintained at -50 °C for an additional 30 min and then cooled to -78 °C. Neat iodoethane (0.12 mL, 1.50 mmol) was added and the reaction temperature was gradually raised to rt over 30 min. The mixture was stirred for 8 h, and was quenched by addition of water (3 mL) and oxalic acid (81 mg, 0.90 mmol). The mixture was stirred overnight and then poured into saturated sodium bicarbonate (5 mL). Diethyl ether (5 mL) was added, the phases were separated, and the aqueous layer was extracted with ether (2 x 5 mL). The combined organic extracts were dried over $K_2CO_3$, filtered through Celite, and concentrated \textit{in vacuo} to give the crude product. Purification by radial PLC (SiO$_2$, 5-10% EtOAc/hexanes) gave 53.0 mg (56%) of 282b as a pale yellow oil: IR (neat); 2370, 1772, 1653, 1656, 1236, 1114 cm$^{-1}$; $^1$H NMR
(CDCl₃, 300 MHz) δ 4.77 (m, 1 H), 2.92 (dd, J = 5.7, 11.7 Hz, 1 H), 2.44 (m, 2 H), 2.32 (d, J = 17.7, 1 H), 1.68 (m, 2 H) 1.54 (s, 9 H), 1.20 (m, 1 H), 0.95 (m, 9 H); ¹³C NMR (CDCl₃, 100 MHz) δ 192.5, 128.7, 83.5, 54.9, 43.4, 39.6, 28.2, 25.9, 25.6, 28.3, 22.2, 19.9, 12.6; HRMS (M+H)⁺ calcd for C₁₆H₂₆ClNO₃ 316.1687, found 316.1690.

6-Chloro-5-iodo-2-isobutyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (282c). To a solution of 252 (74.0mg, 0.22 mmol) in freshly distilled (3 mL) THF at -78 °C was added n-BuLi (2.45 M in hexanes, 0.13 mL, 0.29 mmol) resulting in a orange-red colored solution. The reaction was stirred at -78 °C for 30 min and subsequently warmed to -50 °C by the addition of warm acetone to the cooling bath. The temperature was maintained at -50 °C for an additional 30 min and then cooled to -78 °C. Iodine (78.2 mg, 0.31 mmol) in 2 mL THF was added and the mixture was stirred at -78 °C for 30 min. To the solution was added water (3 mL) and solid oxalic acid (81 mg, 0.90 mmol), and the mixture was stirred overnight. The mixture was poured into saturated sodium bicarbonate (5 mL) and ether (5 mL). The phases were separated and the aqueous layer was extracted with ether (2 x 5 mL). The combined extracts were washed with sat. Na₂S₂O₃ (2 mL), dried over K₂CO₃, filtered
through Celite, and concentrated in vacuo to give the crude product. Purification by radial PLC gave 82.4 mg (91%) of 282c as a light yellow oil: IR (neat) 1681, 1537, 1368, 1316, 1159, 1120 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.81 (m, 1 H), 3.07 (m, 1 H), 2.63 (m, 1 H), 1.72 (m, 1 H), 1.56 (s, 9 H), 1.48 (m, 5 H), 0.97 (m, 3 H); ¹³C NMR (CDCl₃, 100 MHz) δ 198.3, 153.1, 149.9, 76.8, 65.9, 44.1, 37.6, 32.6, 28.8, 28.0, 22.1; HRMS (M+H)+ calcd for C₁₄H₂₁ClINO₃ 414.0333, found 414.0335.
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