Studies Directed Toward the Synthesis of Aristopyridinone A

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Studies Directed Toward the Synthesis of Aristopyridinone A

A thesis submitted in partial fulfillment of the requirement for the degree of Bachelor of Science in Chemistry from the College of William and Mary

by

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Accepted for Honors in Chemistry

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Abstract

This thesis outlines progress towards the synthesis of aristopyridinone A. Aristopyridinone A is a compound isolated from the traditional Chinese medicine plant *Aristolochia manshuriensis*. While the plant has been used in a variety of medicinal capacities, the biological activity of aristopyridinone A is unknown. The synthetic pathways presented in this thesis expand on previous work using a merged Diels Alder \([4+2]\) cycloaddition and cycloreversion strategy to form the 2-pyridone core of the aristopyridinone A molecule. These studies also explore the chemistry of the inter-molecular Diels-Alder reaction using a diketopiperazine-derived azadiene.
Dedication

This work is dedicated to my parents, Ian Leibowitz and Donna Oishi, who have been a constant source of support and encouragement throughout all my academic endeavors.
Acknowledgements

First and foremost, I must thank Dr. Scheerer for all his support and encouragement throughout my undergraduate research experience. Under his guidance, I have grown as a chemist, a problem solver, and a team member. It is a truly unique experience to work under someone so talented and dedicated to his work. Although I am leaving the realm of bench chemistry research for the field of medicine, his mentorship these past years has helped shape my future, and for that I am ever grateful. Additionally, I would like to thank Dr. Dalgleish, Dr. Harbron, and Dr. Hinkle for serving on my Honor’s committee. This thesis would not have been possible without their involvement.

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Last, but certainly not least, I would like to thank my family. Although they may not have understood a word I said when I talked about my project, they smiled and nodded along, and somehow still knew the right thing to say. I would not be where I am today without the support of all of them.
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Chapter One

Introduction:

The use of alternative medicine, like traditional Chinese medicine, is becoming increasingly popular in our society. While not based on scientific evidence, many alternative medicinal remedies do show some healing or restorative effects. The plant *Aristolochia manshuriensis* has historically been used as an anti-inflammatory, an antibacterial, and as a cure for snakebites. However, its toxicity and carcinogenic properties have led to the end of its use in traditional Chinese medicine, and prompted isolation studies of active compounds. Renewed isolation efforts have yielded a variety of compounds, including aristopyridinone A (Figure 1.1). While its bioactivity is unknown, the 2-pyridone core of aristopyridinone A is found in many biologically active compounds, and thus makes the compound an attractive target for chemical synthesis.

**Figure 1.1** Aristopyridinone A with 2-pyridone core highlighted in red
Traditional Chinese Medicine and *Aristolochia manshuriensis*:

The use of plants as medicine dates back to the beginning of humankind. The earliest records of medical therapeutics come from an Egyptian scroll dating back to 1500 B.C.E. and detail herbal remedies for a variety of ailments. The first synthetic drug was not discovered until 1869. Today, the majority of clinically viable drugs are either directly or indirectly derived from natural sources. Aspirin, one of the most widely distributed drugs in the world, is a modified version of salicylic acid, the major active component in the centuries-old, herbal remedy for fevers: willow bark tea. Despite the rise of the pharmaceutical industry, our continued confidence in plant remedies is seen clearly in the current prevalence of alternative medicine. The use of traditional Chinese medicine, a practice steeped in history and tradition, continues to be the leading source of alternative remedies in our society. In China alone, more than 3000 hospitals provide traditional Chinese remedies to 234 million people every year.

Traditional Chinese medicine dates back to 475 BCE, and continues to function on the importance of balance between different theories of the body. These theories began as a compilation of six meridians that governed one’s well being, and have since been summarized into the theories of yin, yang, and chi. Chi is the life force of the human body and travels through the body via the blood stream. The balance of chi in the five major organs, the heart, liver, spleen, lungs, and kidneys, is crucial for health of the whole body. Similar to the humors theory of medicine from medieval Western Europe, yin and yang represent wet, cold and female and hot, dry and male, respectively. It is the balance of these two forces that maintains health. Practitioners of traditional Chinese medicine believe that disease is caused by either too much yin or too much yang, and will prescribe herbal treatments aimed at restoring levels of yin and yang. This is also known as the warm disease theory of medicine. There are extensive records
describing the classification of diseases as hot or cold, and which plants or plant mixtures are necessary to regain balance of yin and yang.\textsuperscript{21} Currently, the compilation of plants used in traditional Chinese medicine is published as the Chinese \textit{Materia Medica}, and has been used by scientists as a resource for modern drug discovery.\textsuperscript{1} It is also used to track toxicities of plants and efficacy of traditional treatments, as in the case of \textit{Aristolochia manshuriensis}.

\textit{Aristolochia manshuriensis} (Mu Tong or Guanmutong) is a leafy, shrub-like plant belonging to the Aristolochiaceae family found in northeastern China and Korea.\textsuperscript{3} The climbing vine thrives in warmer, moist climates where they can be exposed completely to the sun. Horticulturalists now use the plant in landscaping, and it can now be found in parks and backyards around the world.\textsuperscript{9} It is believed that the use of the stem of \textit{A. manshuriensis} in Chinese folk medicine can be traced to the 3\textsuperscript{rd} century BCE. It was originally classified as a damp-draining herb, meaning that it helps with diseases associated with too much yin, and was administered as a tea brewed from the stems of the plant. Despite current knowledge of its nephrotoxicity, early Chinese documents fail to mention the high toxicity of Mu Tong, leading historians to conclude that the plant source of the herbal mix prescribed as Mu Tong has possibly changed throughout centuries. The inclusion of \textit{A. manshuriensis} in lieu of a related species would change the alkaloid composition of the herbal medicine enough to affect toxicity. This is the most probable reason that toxicity and compound isolation studies of Mu Tong only began at the end of the 20\textsuperscript{th} century.\textsuperscript{22}

Widely distributed as an anti-inflammatory and diuretic, approximately twenty tons of \textit{A. manshuriensis} were exported from China every year from 1984-2004.\textsuperscript{9} The first reported cases of nephropathy related to the ingestion of \textit{A. manshuriensis} came from Belgium in 1993, followed by reports of renal failure associated with the herb in Japan. Reports of \textit{A.}
*manshuriensis*-associated renal and urothelial cancers subsequently followed. Follow-up studies attribute this nephrotoxicity to the high concentrations of aristolochic acids found in the plant. One toxicity experiment found that the dose of an alcoholic extract of *A. manshuriensis* lethal to 50% of animals is 15.5 ± 0.6 g/kg in mice. A second experiment found an LD$_{50}$ of 29.1 ± 3.71 g/kg. This study also found differing lethality of *A. manshuriensis* depending on the region it is grown, pointing to the environmental effects of toxin concentrations in the plant and potentially explaining the two different LD$_{50}$ results. In 2003, the use of *Aristolochia manshuriensis* was banned in the mainland of China. By 2007, most countries had banned the use of *Aristolochia manshuriensis* and other aristolochic acid containing plants.
Aristolochic acids and derivatives:

Aristolochic acids were isolated from *A. manshuriensis* in 1994, but were not categorized as the toxic agents until 2002. While concentrations depend on the region in which the plant is grown, aristolochic acids are the dominant metabolites in *A. manshuriensis*, making up 0.45% to 1.06% of the plant by weight. They are currently ranked among the top 2% of most potent carcinogens. Comparisons of the chemical components of plants from the Aristolochiaceae family, all known to be toxic, and plants from the Akebia family, a benign herb with anti-inflammatory properties found aristolochic acids and their ester and amide derivatives (Figure 1.2) to be the major component difference and thus the basis of Aristolochiaceae nephrotoxicity. Toxicity studies using Wistar rats and NMRI (Naval Medical Research Institute) mice found an LD$_{50}$ of 56 to 203 mg/kg orally and 38 to 83 mg/kg intravenously. The large ranges are accounted for by species and sex of animal. Renal function was severely impaired at daily dosages as low as 10 mg aristolochic acid per kg of body weight.

**Figure 1.2** Structures of aristolochic acids (1), aristolochic esters (2), aristolamides (3), aristolactams (4)

Histological analysis of organ tissue post-treatment with *Aristolochia manshuriensis* or aristolochic acids shows extensive damage to the kidneys in the form of renal tubular necrosis. Induced apoptosis of the tubular cells is the most probable mechanism for the resulting necrosis.
Longer exposure to aristolochic acids also results in tubular atrophy and interstitial fibrosis. Mitochondrial damage and deactivation of antioxidative enzymes due to tubular atrophy impair tubular cell regeneration and lead to the formation of the fibroblasts. Although it is unknown why these compounds preferentially affect the kidneys, it is hypothesized that genetic expression of aristolochic acid transporters is up regulated in the kidneys.\textsuperscript{13} Also of concern are the relatively higher concentrations of aristolochic acid found in the lungs of rats.\textsuperscript{9} While there are no known reports of lung disease associated with aristolochic acid, it remains a potential side effect of using aristolochic acid containing substances, like \textit{Aristolochia manshuriensis}.

Aristolochic acids affect gene expression, and therefore cell behavior. Aristolochic acids, in the form of aristolactams, are able to form covalent linkages to DNA (see Figure 1.3). Human enzymes p450 1A1 and 1A2 activate the aristolactam, forming a cyclic nitrenium ion that then reacts with the amino groups of adenine and guanine. These DNA adducts assist in DNA fragmentation, forcing the cell to lyse, and cause chromosomal damage, interfering with correct chromosomal exchange during the cell cycle. The nitro group of aristolochic acids is important in the compounds’ mutagenetic effect. Reduction of the nitro group in vivo to form the aristolactam functionality activates the metabolite for DNA addition.\textsuperscript{18} The mutation frequency of mitotic genes in cells treated with aristolochic acid increases by 10 to 33-fold. Correlation studies between mutagenicity and carcinogenicity reveal that aristolochic acids induce tumor formation through this increased mutation frequency.\textsuperscript{2} Activation of the H-ras oncogene and inactivation of the p53 tumor suppressor gene by A:T \(\rightarrow\) T:A mutations have been implicated in aristolochic acid-initiated tumors.\textsuperscript{14}
However, the increased mutation frequency does not fully explain the tissue-specific carcinogenicity of aristolochic acids. A comparison of gene expression in liver and kidney cells found significant mutations in kidney genes associated with defense response, apoptosis, and immune response, but these mutations were absent in the liver cells. It is suggested that
conjugation of aristolochic acids in the liver and other tissues are exported into the bloodstream, where they are then taken up by renal and urothelial cells, attributing to the specificity of cancer these compounds cause.\textsuperscript{2} Transcription of genes encoding sulfotransferases, SULTs, is also increased in renal and urothelial cells in the presence of aristolochic acids. This corresponds with data supporting evidence that phase II metabolites of aristolochic acids have higher mutagenic and cytotoxic potential.\textsuperscript{18}

The dangers of aristolochic acids encouraged scientists to focus on the isolation of other biologically active molecules in the \textit{Aristolochia manshuriensis} stem. A study in 2010 isolated two potential antitumor compounds, both phenanthrene derivatives (Figure 1.4, 1a,b). Compounds 1a and 1b were isolated 0.00892\% and 0.00446\% by weight from the \textit{Aristolochia manshuriensis} stems. Both compounds showed significant CDK-2 inhibition. CDK-2, cyclin dependent kinase 2, is a cell cycle regulatory enzyme and thus an attractive potential target for anticancer research.\textsuperscript{8} Further extraction efforts led to the isolation of ferulic acid (Figure 1.4, 2a), 0.00100\% by weight, and \textit{p}-hydroxycinnamic acid (Figure 1.4, 2b), 0.00150\% by weight. Ferulic acid is a well-known antibacterial, and may account for some of \textit{Aristolochia manshuriensis}’s antibacterial properties. Hydroxycinnamic acids are antioxidants derived from cinnamic acid. They are found in a wide variety of plants and foods.\textsuperscript{12} A study in 2011 isolated two compounds (Figure 1.4, 3a,b) from \textit{Aristolochia manshuriensis} that showed significant anti-inflammatory activity by inhibiting neutrophil elastase release and superoxide anion generation. The chemists were surprised to discover that they were aristolochic acid derivatives because this was the first time that aristolochic acid derivatives had shown any anti-inflammatory response. Aristolamide 3a was isolated 0.00198\% by weight from the \textit{Aristolochia manshuriensis} stems. Aristolactam 3b was isolated 0.00197\% by weight from the stems.\textsuperscript{3}
Figure 1.4 Biologically active molecules isolated from *Aristolochia manshuriensis*
Aristopyridinone A:

The 2011 study by Chung, et al. that isolated two anti-inflammatory compounds from Aristolochia manshuriensis also isolated another novel molecule, which was named aristopyridinone A (see Figure 1.1). Unfortunately, insufficient amounts of the compound prevented evaluation of bioactivity.\textsuperscript{3} The structure of aristopyridinone A is significantly different from the other molecules isolated from Aristolochia manshuriensis, which makes it difficult to predict its potential bioactivity although the 2-pyridone scaffold is found in many biologically active compounds.\textsuperscript{10} With the aim of exploring its biological activity, we designed a synthetic route towards aristopyridinone A, which is the focus of this thesis.
Synthetic strategies for making the 2-Pyridone scaffold:

Pyridone alkaloids provide a rich diversity of compounds of varying biological activity. The first isolated pyridone was the poison ricinine, isolated in the 19th century from the castor bean, although scientists didn’t verify the structure until 1904 (Figure 1.5).\textsuperscript{10} Camptothecin, a potent anti-cancer drug, is a natural product isolated from the tree \textit{Camptheca acuminata}. Topotecan, a semisynthetic derivative of camptothecin, continues to be used in the treatment of certain colon and ovarian cancers.\textsuperscript{6} Huperzine A is a current lead compound for the treatment of Alzheimer’s disease and age-related memory loss. Leporin A shows anti-insect properties against the corn earworm \textit{Helicoverpa 200}. The anti-fungal compound ilicicolin H is isolated from the fungus \textit{Cylindrocladium ilicicola}.\textsuperscript{20} The potent biological activity of 2-pyridones is partly attributed to the amide functionality that can structurally mimic a peptide backbone.\textsuperscript{6} The broad array of applications of this medicinally privileged scaffold makes this chemical functionality an important and well-studied target for medicinal chemists.

\textbf{Figure 1.5} 2-pyridone examples

![Ricinine](image1)

![Camptothecin](image2)

![Topotecan](image3)

![Huperzine A](image4)

![Leporin A](image5)

![Ilicicolin H](image6)
Several synthetic approaches exist to construct the 2-pyridone scaffold, but all strategies can be separated into two main categories: generation of the 2-pyridone ring system from other cyclic systems or generation of the 2-pyridone ring system by condensation of acyclic systems. The categories can be further classified depending on starting material or bond formed during cyclization.

Pyridines and 2-pyranones comprise the main heterocycle starting materials for the synthesis of 2-pyridones, although 5-member heterocycles are also used. Oxidation of pyridines (Scheme 1.1a) and hydrolysis of 2-halopyridines (Scheme 1.1b) are common methods of 2-pyridone preparation.

**Scheme 1.1** Synthesis of 2-pyridones from pyridine starting materials

(a) \[ \text{1. Me}_2\text{SO}_4, 110 \degree \text{C} \rightarrow \text{2. NaOH, K}_3\text{Fe(CN)}_6 \]

(b) \[ \text{Ar} \begin{array}{c} \text{Ar} \\ \text{O} \\ \text{F} \end{array} \rightarrow \text{Ar} \begin{array}{c} \text{Ar} \\ \text{N} \\ \text{O} \end{array} \text{1,4 Dioxane/H}_2\text{O} \]

The reaction of 2-pyranone derivatives with urea affords a 1:1 mixture of the corresponding 2-pyridone and 2-aminopyridine (Scheme 1.2). This occurs through a nucleophile-induced ring rearrangement. Replacement of the nitrile group with a methoxycarbonyl yields the 2-pyridone product exclusively.

**Scheme 1.2** Synthesis of 2-pyridones from 2-pyranones
Multiple strategies for synthesizing 2-pyridones from 5-member heterocycles utilize cycloaddition reactions. One example is the synthesis developed by Padwa and colleagues, transforming imidosulfoxides through a Pummerer cyclization-deprotonation-cycloaddition cascade reaction (Scheme 1.3a). This reaction works via an isomünchnone intermediate that can be trapped with a variety of dipolarophiles. Acidic cleavage of the cycloadduct yields the corresponding 2-pyridone. An alternative pathway using 5-member heterocycle starting materials utilizes 5-silylmethylisoxazole as a β-enaminoketone source after catalytic hydrogenation, which affords 2-pyridones upon treatment with nucleophiles like malononitrile (Scheme 1.3b).

**Scheme 1.3** Synthesis of 2-pyridones from 5-member heterocycles

There are a wide variety of syntheses that generate the 2-pyridone ring system via condensation strategies. One of the first syntheses to utilize condensation chemistry to construct the 2-pyridone scaffold was the racemic total synthesis of tenellin by David Williams and colleagues, which created the saturated heterocycle by Dieckmann condensation (Scheme 1.4). Further oxidation establishes the aromatic 2-pyridone core. Synthetic strategies involving an aldolic condensation to form the 2-pyridone continue to be widely used.
Isocyanates have also shown to be starting materials for 2-pyridones through multiple pathways. They will undergo a transition metal-catalyzed cyclotrimerization with two alkyne moieties to deliver substituted 2-pyridones (Scheme 1.5a). Vinyl isocyanates will react with enamines or enolates to afford an enamide intermediate that will cyclize to the 2-pyridone heterocycle, as demonstrated in the synthesis of pyridovericin by Zhang and colleagues (Scheme 1.5b).

Palladium chemistry has been utilized in the construction of 2-pyridones. 4,6-disubstituted-2-pyridones can be synthesized from (Z)-3-substituted-3-iodoprop-2-enamides and tributylstannylallenes. A proposed mechanism for the reaction is shown in Scheme 1.6. Palladium is also the catalyst for the decarboxylative carbonylation of 5-vinylloxazolidin-2-ones to afford tri-substituted 2-pyridones.

**Scheme 1.4** 2-pyridone formation in Williams’ 1982 synthesis of tenellin

**Scheme 1.5** Synthesis of 2-pyridones from isocyanate starting materials
Other advancements in the synthesis of 2-pyridones include strategies involving a β-lactam precursor, Michael addition with acetonitrile derivatives, and a Diels-Alder cycloaddition. The hetero-Diels-Alder reaction between azadienes and a variety of dieneophiles has delivered a range of pyridone products (Scheme 1.7a). A vinylthioamide starting material will undergo a [4+2] cycloaddition with a ketene dieneophile upon activation with methyl iodide to afford the corresponding 2-pyridone (Scheme 1.7b).
A novel synthetic strategy reported by Margrey, Hazzard, and Scheerer accesses the 2-pyridone structure through the cycloreversion of [2.2.2]-diazabicyclic alkene diketopiperazines (Scheme 1.8). Original work by Sammes and colleagues showed the conversion of 2-pyrazinones to 2-pyridones via a cycloaddition with alkyne substrates and subsequent extrusion of isocyanate to form the planar aromatic heterocycle. Margrey and colleagues used two different diketopiperazines as starting materials and were able to perform selective cycloreversion of [2.2.2] cycloadducts for 2-pyridone products through activation of one aza bridging function. This method was shown to be viable with a variety of intramolecular Diels-Alder cycloadducts. An intermolecular Diels-Alder approach using the symmetrical, electron-deficient dieneophile dimethyl acetylenecarboxylate (DMAD) afforded the corresponding 2-pyridone, but further investigation of the intermolecular Diels-Alder reaction using diketopiperazine-derived azadienes has yet to be explored.¹⁵

**Scheme 1.8** Synthesis of 2-pyridones via cycloreversion of [2.2.2]-bicycloalkene diketopiperazines
Conclusion:

The potent biological activity of 2-pyridone compounds makes accessing the chemical scaffold of interest to synthetic chemists. While several methods exist for making 2-pyridones, new synthetic strategies for their preparation are relevant and broaden the array of compounds that are synthetically accessible. The synthesis of aristopyridinone A expands on work done by Margrey, Hazzard, and Scheerer on the synthesis of 2-pyridones via a merged Diels-Alder [4+2] cycloaddition and cycloreversion. Of note is the intermolecular Diels-Alder reaction to form the [2.2.2]-diazabicyclic cycloadduct. Aristopyridinone A is a compound of particular interest due to its unexplored biological activity and its isolation from the traditional Chinese medicinal herb *A. manshuriensis*. 
References:

Chapter Two

Introduction:

Inspired by the 2014 study by Margrey, Hazzard, and Scheerer, we began developing a synthesis towards aristopyridinone A. Our general strategy (see Scheme 2.1) accesses the 2-pyridone moiety through a cycloreversion of a [2.2.2]-diazabicyclic alkene. While previous work focused on an intramolecular Diels-Alder [4+2] cycloaddition to form the desired cycloadduct, our route probes the chemistry of the intermolecular Diels-Alder reaction. In particular, our route explores the regioselectivity of the Diels-Alder [4+2] cycloaddition from a diketopiperazine-derived azadiene. Our studies have led to a nine-step proposed synthesis of aristopyridinone A from a dimethoxybenzyl (DMB) protected diketopiperazine starting material.

Scheme 2.1 General strategy toward the synthesis of aristopyridinone A
**Diels-Alder cycloaddition:**

The identification of products arising from the reaction of cyclopentadiene and quinone in 1928 by Otto Diels and Kurt Alder (Scheme 2.2) was the first description of the [4+2] cycloaddition that was eventually named the Diels-Alder reaction. The 4 and 2 identify the number of π electrons involved in the electronic rearrangement, as well as the number of atoms originating the unsaturated six-member ring. The pericyclic reaction occurs between a conjugated diene (4 π electrons) and a dieneophile (2 π electrons). The classic Diels-Alder reacts butadiene with ethylene to afford cyclohexene (Scheme 2.3a). There is a huge diversity of dienes and dieneophiles that will undergo a Diels-Alder reaction, but electron-donating substituents on the diene and electron-withdrawing substituents on the dieneophile provide faster cycloaddition. Substituted dienes and dieneophiles can also provide regioselectivity for intermolecular cycloadditions (Scheme 2.3b,c). Recent advancements have studied the hetero-Diels-Alder reaction, which utilizes nitrogen and oxygen-containing diene and dieneophiles.

**Scheme 2.2 Discovery of the Diels-Alder [4+2] cycloaddition**

![Scheme 2.2 Discovery of the Diels-Alder [4+2] cycloaddition](image-url)
Diels-Alder reactions are described by a concerted, pericyclic mechanism (Scheme 2.4). Two different pathways have been proposed to explain the concerted transition state: simultaneous formation of new bonds or the formation of one σ bond induces electronic rearrangement. The nature of the reagents and reaction conditions will determine the reaction pathway.³ The concerted cycloaddition mechanism also means that the Diels-Alder reaction is stereospecific, and is capable of installing up to four new stereogenic centers. Stereoselectivity of the Diels-Alder reaction is often rationalized from the endo transition state, which is stabilized by favorable interactions the π electron system of the dieneophile substituent and the π electron system of the diene (Scheme 2.5).²
Electronically, the Diels-Alder reaction proceeds through the interaction of the 4 π electron system of the diene and the 2 π electron system of the dieneophile. The energy difference between the diene’s highest occupied molecular orbital (HOMO) and the dieneophile’s lowest unoccupied molecular orbital (LUMO) helps establish the rate of cycloaddition. These HOMO-LUMO interactions can be categorized into three different types: the “normal” HOMO\textsubscript{diene}-controlled cycloaddition, the neutral cycloaddition, and the “inverse electron demand” LUMO\textsubscript{diene}-controlled cycloaddition (Figure 2.1).\textsuperscript{2} Electronic and structural features of the diene and dieneophile determines type of cycloaddition.
In the original 1928 communication, Diels and Alder understood the implications of their [4+2] cycloaddition for natural product synthesis, noting, “Thus it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps even alkaloids, has been moved to the near prospect.”\(^1\) However, it was not until 1952, when Woodward and colleagues described a novel synthesis of steroid cortisol and cortisone involving a Diels-Alder reaction, that the [4+2] cycloaddition entered the mainstream set of reactions for total synthesis.\(^5\) The Diels-Alder reaction is now a widely used, versatile method for constructing six-membered rings as a part of simple and complex molecules.
Methods and Results:

In order to help determine optimal Diels-Alder reaction conditions and to gain a baseline for the regioselectivity of the cycloaddition, we created a model system using benzaldehyde in our aldol condensation step and propargyl alcohol as our dieneophile (Scheme 2.6).

Scheme 2.6 Synthetic route for model system

Our starting material is the dimethoxybenzyl (DMB) protected diketopiperazine 1, prepared in 4 steps (55% overall yield) from glycine methyl ester. Enolization of the DKP substrate was accomplished using the amide base LiHMDS, followed by aldol addition into
benzaldehyde. Acylation of the $\beta$-hydroxy intermediate preceded elimination to the exocyclic azadiene 2 upon exposure to DBU. The aldol condensation, acetylation, and elimination were accomplished in a “one-pot” reaction. Azadiene 2 was isomerized to the endocyclic diene under basic conditions, and underwent a Diels-Alder $[4+2]$ cycloaddition with propargyl alcohol as the dieneophile at 110 °C to deliver cycloadducts 3 and 4 as an inseparable 1:3 mixture. Following precedent from Margrey, Hazzard, and Scheerer, the lactim $O$-methyl ether of 3 and 4 was converted the lactam in 5 and 6. In the lactam form, the two regioisomers were separable. Upon activation of the aza bridging function (Ac$_2$O, pyr, 110 °C), we were able to deliver the retro Diels-Alder products, DMB protected pyridones 7 and 8, diverging from precedent, which required more vigorous thermolysis conditions.

Cycloadduct 3 and the derived 3,4-disubstituted pyridone 7 possess the structural relationship apparent in aristopyridinone A. On our real system, we chose ethyl propiolate as the dieneophile (Scheme 2.7) with the hope that the reversed electronics would provide reversed regioselectivity of the Diels-Alder reaction.

An aldol condensation was performed with DMB-protected DKP 1 and aldehyde 9, which can be prepared by ozonolysis of 4-allylanisole (63% yield). Acetylation of the $\beta$-hydroxy intermediate immediately followed, delivering product 10. The instability of endocyclic azadiene 11 to purification required us to stop the previously “one pot” reaction at the acetylated intermediate. Elimination and isomerization of 10 yielded azadiene 11 upon exposure to DBU. The exocyclic azadiene was not observed. Product 11 was immediately submitted to an intermolecular Diels-Alder cycloaddition, using ethyl propiolate as the dieneophile, delivering cycloadducts 12 and 13 as an inseparable mixture (ratio 1:2). The desired regioisomer was again the minor product of $[4+2]$ cycloaddition. The lactim $O$-methyl ether in 12 and 13 was
converted to the lactam in 14 and 15. The regioisomers 14 and 15 were still inseparable.

**Scheme 2.7** First proposed synthesis of aristopyridinone A and synthesis of its C-isomer

i) LiHMDS, THF, -78 °C

\[
\text{ii) } \text{Ac}_2\text{O, pyridine, toluene, 110 °C, 69% yield}
\]

\[
\text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO}
\]

\[
\text{NDMB} \quad \text{NDMB} \quad \text{NDMB} \quad \text{NDMB}
\]

\[
\text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe}
\]

\[
\text{1} \quad \text{9} \quad \text{10} \quad \text{11}
\]

\[
\text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO}
\]

\[
\text{NDMB} \quad \text{NDMB} \quad \text{NDMB} \quad \text{NDMB}
\]

\[
\text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe}
\]

\[
\text{14} \quad \text{15} \quad \text{12} \quad \text{13}
\]

\[
\text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et}
\]

\[
\text{regioisomeric ratio 1:2}
\]

\[
\text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO}
\]

\[
\text{NDMB} \quad \text{NDMB} \quad \text{NDMB} \quad \text{NDMB}
\]

\[
\text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe}
\]

\[
\text{16} \quad \text{17} \quad \text{18} \quad \text{19}
\]

\[
\text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et}
\]

\[
\text{99% yield, TFA/CH}_2\text{Cl}_2 (1:2), \text{Et}_3\text{SiH, µw, 130 °C}
\]

\[
\text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO}
\]

\[
\text{NDMB} \quad \text{NDMB} \quad \text{NDMB} \quad \text{NDMB}
\]

\[
\text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe}
\]

\[
\text{20} \quad \text{21} \quad \text{18} \quad \text{19}
\]

\[
\text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et}
\]

\[
\text{22% yield, LiAlH}_4, \text{THF, 0 °C to rt}
\]
Thermolysis of the mixture of regioisomers 14 and 15 (Ac₂O, 140°C, 2d) afforded two separable products 16 and 17. Analysis of ¹H NMR spectra led us to conclude that one product was due to the desired cycloreversion reaction, and the other product was due to a rearrangement. HMBC/HSQC analysis of the retro Diels-Alder product proved to be 3,5-disubstituted pyridone 16. Proposed mechanisms for the rearrangement (Equation a) and successful cycloreversion (Equation b) are shown in Scheme 2.8.

Scheme 2.8 Rearrangement and cycloreversion mechanisms

The divergent reactivity with allylic acetate versus the unsaturated ester possibly implies a highly asynchronous transition state for the retro Diels-Alder reaction. For the unsaturated ester substrate, as the carbon-nitrogen bond of the imide breaks, elimination of the bridgehead hydrogen, yielding rearrangement, appears faster than the carbon-carbon bond cleavage, yielding cycloreversion. The indicated bridgehead hydrogen in cycloadduct 14 (Scheme 2.8a) is more acidic than the bridgehead hydrogen in cycloadduct 5 (Scheme 2.8b) because it is doubly activated located both α- to the imide and γ- to the unsaturated ester.

Although cycloreversion conditions yielded the 3,5-disubstituted pyridone, we continued
functional group manipulation to afford C-isomer aristopyridinone A. Deprotection of the pyridone 16 was accomplished on exposure to TFA in CH₂Cl₂ and Et₃SiH (microwave heating) to afford pyridone 18. The ethyl ester functionality in 18 was then reduced using LiAlH₄, affording 4-hydroxymethyl pyridone 19. Cleavage of the methyl ether in 19 was attempted under basic and neutral conditions to avoid ionization of the alcohol. However, attempts at demethylation using LiI in lutidine and TMSCl-NaI in acetonitrile provided multiple products and poor yields, so an alternative route was used. Demethylation of pyridone 18 was accomplished using BBr₃ in dichloromethane starting at -78 ºC and warming to room temperature to afford pyridone 20. Reduction of the ethyl ester using LiAlH₄ delivered C-isomer aristopyridinone A (product 21) in 2.2% overall yield.

The lack of regioselectivity of the intermolecular Diels-Alder led us to investigate another dieneophile of differing electronic properties (Scheme 2.9). Azadiene 11 was submitted to a Diels-Alder reaction using methyl nitroacrylate as the dieneophile starting at 0 ºC and warming to room temperature overnight to provide the separable cycloadducts 22 and 23 in a 1:1 regioisomeric ratio. Elimination of the nitro group was accomplished on both regioisomers using DBU to deliver products 24 and 25. In the hopes of avoiding rearrangement of the desired cycloadduct regioisomer, lactim 25 was demethylated to lactam 26 and reduction of the methyl ester was attempted using DIBAI-H. Unfortunately, efficient reduction could not be easily realized.
Scheme 2.9 Synthetic strategy towards aristopyridinone A using methyl nitroacrylate dieneophile

A summary of our efforts towards cycloreversion is shown in Scheme 2.10. The presence of an unsaturated ester in the 4-C position of the cycloadduct inhibits cycloreversion, instead favoring a ring-opening rearrangement. Our model system showed that saturation at the allylic position, in this case the allylic acetate group, in the cycloadduct favors the retro Diels-Alder reaction over rearrangement under similar conditions. However, reduction of the ester functionality to the corresponding saturated allylic position proved difficult, and was not a promising direction for our synthesis.
With these results in mind, we decided that the most direct route to aristopyridinone A was performing the Diels-Alder with propargyl alcohol and carrying through the cycloreversion and functional group manipulation on the minor isomer (Scheme 2.11).
The acetylated diketopiperazine derivative 10 was reacted with DBU and propargyl alcohol at 110 °C, creating the endocyclic azadiene in situ and undergoing the Diels-Alder [4+2] cycloaddition to afford products 27 and 28 as an inseparable 1:4 mixture. Conversion of the lactim ether to the lactam in 29 and 30 failed to improve separation of the cycloadducts.
Thermolysis of the mixture of regioisomers 29 and 30 (Ac₂O, pyr, 110 °C, 48h) delivered the two DMB protected pyridones 31 and 32. The mixture of regioisomers remained difficult to separate; however, cleavage of the acetate group improved separation and products 33 and 34 were separated using flash column chromatography.

Following precedent from the C-isomer aristopyridinone A synthesis (Scheme 2.7), and once again using the major regioisomer to validate our deprotection strategy, acidic deprotection of the pyridone 32 and 34 was attempted. However, loss of the acetate or hydroxy group was observed in each case. Therefore, we moved to an oxidative cleavage of the DMB protecting group (Scheme 2.12). Oxidation of pyridone 34 with CAN yielded multiple products with very little detection of desired product by ¹H NMR spectroscopy. A second attempt at oxidative cleavage of the DMB group with CAN of 34 afforded primary oxidation product 35 and a secondary oxidation product 36. Further oxidation of 36 failed to afford the de-protected pyridone. Oxidation of 34 with DDQ afforded product 35, but did not cleave the DMB group upon further oxidation.
Given these difficulties with oxidative cleavage, we returned to an acidic cleavage of the DMB group (Scheme 2.11). The benzylic alcohol of pyridone 34 was oxidized to the aldehyde with MnO₂ to deliver product 35 in 87% yield. Deprotection of 35 was accomplished with microwave heating (130 °C, 30 min) in TFA and CH₂Cl₂. Successful deprotection of 35 gave us the confidence to follow the same sequence with our desired regioisomer 33. Product 33 was oxidized with MnO₂ to yield pyridone 37, which was submitted to microwave heating in TFA and CH₂Cl₂ to afford de-protected pyridone 38. Demethylation of the phenolic ether was carried out with BBr₃ to provide 39. Reduction of the aldehyde of 39 to the alcohol was accomplished using NaBH₄ to afford aristopyridinone A (40).
Discussion:

The synthesis discussed details our studies directed toward the first synthesis of aristopyridinone A and its C-isomer. Synthesis of C-isomer aristopyridinone was accomplished in eight steps, while the final synthetic route affords aristopyridinone A in nine steps. The 2-pyridone scaffold was successfully achieved through a merged Diels-Alder cycloaddition-cycloreversion. Although the syntheses are relatively short, we ran into several complications with regards to regioselectivity and desired reactivity. We were unsuccessful in achieving desired regioselectivity in the Diels-Alder cycloaddition despite trying a variety of dieneophiles, and faced issues with performing the retro Diels-Alder reaction and with deprotection of the pyridone functionality.

The results from the model system led us to try dieneophiles with reverse electronics from propargyl alcohol in the hope that it would reverse the regioselectivity of the Diel-Alder reaction. Ethyl propiolate has opposite electronics than propargyl alcohol, and methyl nitroacrylate has differing electronics from both. Surprisingly, our attempts show that the regioselectivity of our intermolecular [4+2] cycloaddition is largely insensitive to electronics of the dieneophile (Table 2.1). Also of note is the differing reaction conditions under which the Diels-Alder reaction occurs. The energy threshold is significantly lower for the cycloaddition of the azadiene and nitroacrylate than either of the alkyne-derived dieneophiles.
An unexpected obstacle was the rearrangement of our desired cycloadduct instead of the cycloreversion upon activation with Ac₂O. We hypothesize that an asynchronous transition state of the retro Diels-Alder reaction allows for elimination of the bridgehead hydrogen in our desired regioisomer, which is doubly activated located both α- to the imide and γ- to the unsaturated ester. The rate of this elimination appears faster than the [4+2] cycloreversion. Substituting the ester for a saturated group at the allylic position in the desired cycloadduct afforded the cycloreversion product upon activation.
A second complication was problems with the de-protection of the 2-pyridone functionality through cleavage of the DMB protecting group. Reduction at the benzylic position of \textbf{32}, resulting in the loss of the acetate group, was a concern upon our initial attempt at acidic deprotection. Protonation of the acetate group creates a good leaving group and the presence of Et$_3$SiH provides a hydride source to capture the cation produced. However, the major oxidation product was not what we expected, nor was the ensuing difficulty with oxidative removal of the DMB group. Although we reverted back to an acidic cleavage strategy, future investigation of oxidation products may be worthwhile.
Conclusion:

Outlined in this paper are syntheses of aristopyridinone A and its C-isomer that explore the chemistry of the intermolecular Diels-Alder using a diketopiperazine-derived azadiene. The C-isomer of aristopyridinone A was achieved in eight steps and 2.2% total yield. Aristopyridinone A will be completed in nine steps from DMB-protected diketopiperazine starting material. Our studies showed that the intermolecular Diels-Alder using a DKP-derived azadiene does not respond to electronic properties of the dieneophile alone. Since both syntheses were only performed once, optimization of reaction conditions for both routes should be feasible. Optimization, along with running the reactions on a larger scale, should improve yields. Future endeavors may also investigate the possibilities of creating other isomers of aristopyridinone A via selective extrusion of the other aza bridging function in any of the cycloadducts. Synthesis of sufficient quantities of aristopyridinone A and its isomers can be used for biological testing.
References:

Experimental Procedures:

**General Information.** All reactions were carried out under an atmosphere of nitrogen in flame or oven-dried glassware with magnetic stirring unless otherwise indicated. Dichloromethane was distilled from CaH₂ prior to use. All reagents were used as received unless otherwise noted. Flash column chromatography was performed using SiliCycle siliaflash P60 silica gel (230-400 mesh). Microwave reactions were performed in a CEM Discover System Model 908005. Melting points were taken using Mel-Temp II device. Analytical thin layer chromatography was performed on SiliCycle 60Å glass plates. Visualization was accomplished with UV light and ceric ammonium molybdate followed by heating. Film infrared spectra were obtained using a Digilab FTS 7000 FTIR spectrophotometer. ¹H and ¹³C NMR spectra were obtained on a Agilent 400/54 ASP spectrometer (400 MHz and 100 MHz, respectively) and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm or CD₃OD at 3.34 ppm) or tetramethylsilane (0.00 ppm). Mass spectra data analysis was obtained through positive electrospray ionization (w/ NaCl) on a Bruker 12 Tesla APEX-Qe FTICR-MS with an Apollo II ion source.

(Z)-3-benzylidene-1-(3,4-dimethoxybenzyl)-5-methoxy-3,6-dihydropyrazin-2(1H)-one (2):
To a solution of DMB protected diketopiperazine 1 (375 mg, 1.35 mmol) dissolved in toluene (10 mL) and cooled to -78 °C was added LiHMDS solution (1.5 mL, 1M in THF) dropwise over 5 minutes. After allowing 15 minutes for enolization, benzaldehyde (150 μL, 1.48 mmol) was added slowly. The aldol condensation was shown to be complete by TLC after 30 minutes. The reaction was quenched with saturated NH₄Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined and washed with saturated NaCl solution (15 mL), dried with Na₂SO₄, and concentrated in vacuo. The resulting residue was dissolved in
dichloromethane (4 mL). To the solution was added AC\textsubscript{2}O (255 \mu\text{L}, 2.7 mmol), NEt\textsubscript{3} (375 \mu\text{L}, 2.7 mmol), and DMAP (10 mg, 0.082 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with saturated NH\textsubscript{4}Cl solution (5 mL) and extracted with ether (3 x 5 mL). The organic layers were combined and washed with saturated NaHCO\textsubscript{3} solution (5 mL), dried with Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. The resulting residue was dissolved in DMF (2.5 mL) and toluene (4 mL). To the solution was added DBU (300 \mu\text{L}, 2.0 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH\textsubscript{4}Cl solution (8 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined and washed with saturated NaCl solution (10 mL), dried with Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. The resulting residue was purified by flash column chromatography on silica gel (0% to 5% methanol in CHCl\textsubscript{3}) to afford exocyclic diene 2 (217 mg, 58% yield) as a yellow orange oil. TLC (60% EtOAc in hexanes) \textit{Rf} = 0.53 (CAM/UV); IR (film) cm\textsuperscript{-1} 3055, 2998, 2946, 2836, 2360, 2339, 1665, 1614, 1559, 1504, 1477, 1442, 1423, 1369, 1288, 1252, 1207, 1157, 1122, 1033, 1005, 927, 835, 763, 693; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 8.03-8.01 (2H, d, J = 7.8 Hz), 7.37-7.26 (5H, m), 6.48-6.47 (1H, d, J = 2.4 Hz), 6.46-6.45 (1H, d, J = 2.0 Hz), 4.67 (2H, s), 4.09 (2H, s), 3.91 (3H, s), 3.82 (3H, s), 3.79 (3H, s); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 160.9, 159.3, 135.8, 131.9, 131.5, 131.4, 128.4, 128.3, 126.2, 116.6, 104.7, 98.6, 55.7, 54.2, 46.8, 44.3; Exact mass calculated for C\textsubscript{21}H\textsubscript{22}N\textsubscript{2}O\textsubscript{4}Na [M+Na] 389.1472. Found 389.1467.

(1S,4S)-4-benzyl-2-(3,4-dimethoxybenzyl)-8-(hydroxymethyl)-6-methoxy-2,5-diazabicyclo[2.2.2]octa-5,7-dien-3-one (3): To a solution of exocyclic azadiene 2 (71.1 mg, 0.194 mmol) in toluene (2 mL) was added DBU (29 \mu\text{L}, 0.194 mmol) and excess propargyl alcohol (1.0 mL). The reaction mixture was heated to 110 \degree C and was found to be complete after 48 hours by TLC. The reaction was concentrated \textit{in vacuo} and the resulting residue was redissolved in CHCl\textsubscript{3} (5 mL). The solution was washed with saturated NH\textsubscript{4}Cl solution (3 mL), washed with saturated NaHCO\textsubscript{3} solution (3 mL), washed with saturated NaCl solution (5 mL), dried with Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. The resulting residue was purified by flash column chromatography on silica gel (40% to 100% EtOAc in hexanes) to afford an inseparable mixture of Diels-Alder cycloadducts, desired product 3 and regioisomer 4 (50.2 mg, 61% yield) in a ratio of 1:3. TLC (60% EtOAc in hexanes) \textit{Rf} = 0.30 (CAM/UV); IR (film) cm\textsuperscript{-1} 3396, 3061, 2969, 2838, 2362, 2060, 1954, 1876, 1706, 1576, 1582, 1513, 1430, 1306, 1208, 1145, 1031, 984, 930, 899, 858, 833, 730, 697; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 7.63-7.62 (1H, d, J = 7.5 Hz), 7.52-7.50 (1H, d, J = 8.6 Hz), 7.31-7.20 (10H, m), 7.05-7.03 (1H, d, J = 7.8 Hz), 6.43-6.40 (4H, m), 6.33 (1H, d, J = 1.9 Hz), 4.64 (1H, s), 4.63-4.60 (1H, d, J = 7.8 Hz), 4.50-4.27 (6H, m), 4.21-4.01 (2H, m), 3.87 (1H, s), 3.82 (1H, s), 3.78-3.69 (18H, m), 3.52-3.45 (4H, m); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 174.7, 174.2, 172.6, 172.3, 160.8, 160.7, 158.2, 155.0, 146.2, 138.3, 137.9,
134.0, 131.3, 131.2, 130.8, 127.8, 127.7, 127.1, 126.3, 126.1, 116.7, 116.4, 104.2, 104.0, 98.4, 98.3, 77.3, 73.6, 72.0, 60.9, 60.6, 58.3, 56.3, 55.3, 55.1, 43.9, 43.2, 37.6, 35.1; Exact mass calculated for C\textsubscript{24}H\textsubscript{26}N\textsubscript{2}O\textsubscript{5}Na [M+Na] 445.1734. Found 445.1734.

(1S,4S)-1-benzyl-5-(3,4-dimethoxybenzyl)-7-(hydroxymethyl)-2,5-diazabicyclo[2.2.2]oct-7-ene-3,6-dione (5): To a solution of cycloaducts 3 and 4 (77.2 mg, 0.198 mmol) in acetic acid (3.0 mL) was added potassium iodide (98.53 mg, 0.594 mmol). The reaction mixture was heated to 110 °C and was found to be complete after 2 hours by TLC. It was diluted and neutralized with saturated NaHCO\textsubscript{3} solution (10 mL) and extracted with EtOAc (3 x 6 mL). The organic layers were combined and washed with saturated NaHCO\textsubscript{3} solution (6 mL), washed with saturated NaCl solution (6 mL), dried with Na\textsubscript{2}SO\textsubscript{4}, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (40% to 100% EtOAc in hexanes with 10% CHCl\textsubscript{3}) to afford desired product 5 and regioisomer 6 (13.4 mg and 31.7 mg, respectively, 61% total yield) as yellow oils. 

Product 5: TLC (60% EtOAc in hexanes) R\textsubscript{f} = 0.14 (CAM/UV); IR (film) cm\textsuperscript{-1} 3394, 3249, 3068, 3011, 2933, 2842, 1746, 1705, 1613, 1588, 1509, 1454, 1294, 1211, 1158, 1037, 967, 921, 839, 754; Exact mass calculated for C\textsubscript{23}H\textsubscript{24}N\textsubscript{2}O\textsubscript{5}Na [M+Na] 431.1577. Found 431.1581.

Product (6): TLC (60% EtOAc in hexanes) R\textsubscript{f} = 0.22 (CAM/UV); IR (film) cm\textsuperscript{-1} 3327, 3071, 1008, 2935, 2838, 2362, 2075, 1966, 1704, 1673, 1610, 1586, 1454, 1412, 1333, 1294, 1212, 1140, 1038, 968, 923, 835, 751, 701; \textsuperscript{1}H NMR \textsuperscript{δ} 7.36-7.27 (4H, m), 7.10-7.08 (1H, d, J = 7.8 Hz), 6.42 (1H, s), 6.40-6.39 (1H, d, J = 2.3 Hz), 6.37-6.36 (1H, d, J = 2.0 Hz), 6.30 (1H, s), 4.66-4.62 (1H, d, J = 14.5 Hz), 4.40 (1H, s), 4.43-4.35 (1H, d, J = 2.7 Hz), 3.97-3.93 (1H, dd, J = 11.8 Hz and 3.1 Hz), 3.86-3.81 (2H, dd, J = 9.8 Hz and 4.7 Hz), 3.77 (3H, s), 3.76 (3H, s), 3.46-3.42 (1H, d, J = 14.9 Hz), 3.39-3.35 (1H, d, J = 14.8 Hz); \textsuperscript{13}C (100 MHz, CDCl\textsubscript{3}) δ 172.2, 170.8, 161.3, 158.9, 150.2, 134.9, 131.8, 131.5, 130.4, 129.2, 127.7, 116.4, 104.6, 98.7, 77.6, 63.7, 62.9, 61.1, 55.6, 55.5, 44.0, 35.4; Exact mass calculated for C\textsubscript{23}H\textsubscript{24}N\textsubscript{2}O\textsubscript{5}Na [M+Na] 431.1577. Found 431.1581.
(3-benzyl-1-(3,4-dimethoxybenzyl)-2-oxo-1,2-dihydropyridin-4-yl)methyl acetate (7): To a solution of cycloadduct 5 (13.5 mg, 0.036 mmol) in Ac₂O (1.0 mL) was added pyridine (1.0 mL). The reaction mixture was heated to 110 ºC and allowed to react for 3.5 days. The reaction was concentrated in vacuo, washed three times with CHCl₃, and again concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (20% to 100% EtOAc in hexanes) to afford DMB-protected pyridone 7 (8.0 mg, 67% yield). TLC (60% EtOAc in hexanes) Rₐ = 0.72 (CAM/UV); IR (film) cm⁻¹ 3084, 3064, 3026, 3001, 2960, 2926, 2857, 1739, 1700, 1695, 1653, 1613, 1589, 1558, 1507, 1495, 1464, 1457, 1436, 1419, 1375, 1363, 1288, 1264, 1225, 1210, 1158, 1138, 1122, 1031, 964, 939, 919, 831, 786, 757, 733, 701, 667; Exact mass calculated for C₂₄H₂₅NO₅Na [M+Na] 430.1625. Found 430.1625.

(5-benzyl-1-(3,4-dimethoxybenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl acetate (8): To a solution of cycloadduct 6 (30.0 mg, 0.0798 mmol) in Ac₂O (2.0 mL) was added pyridine (2.0 mL). The reaction mixture was heated to 110 ºC and allowed to react for 2.5 days. The reaction was concentrated in vacuo, washed three times with CHCl₃, and again concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (20% to 100% EtOAc in hexanes) to afford DMB-protected pyridone 8 (25.8 mg, 97% yield). TLC (60% EtOAc in hexanes) Rₐ = 0.78 (CAM/UV); IR (film) cm⁻¹ 3082, 3060, 3026, 3002, 2955, 2934, 2836, 2739, 1734, 1717, 1700, 1695, 1684, 1671, 1661, 1635, 1616, 1613, 1589, 1576, 1569, 1558, 1507, 1495, 1464, 1436, 1419, 1378, 1362, 1289, 1265, 1226, 1210, 1158, 1138, 1121, 1075, 1030, 948, 941, 919, 872, 831, 787, 757, 734, 701, 667; ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.40 (1H, d, J = 2.7 Hz), 7.38 (1H, m), 7.33-7.20 (5H, m), 6.95 (1H, m), 6.48-6.47 (1H, d, J = 2.4 Hz), 6.45 (1H, s), 5.05 (2H, s), 4.72 (2H, s), 3.86 (2H, s), 3.82 (3H, s), 3.80 (3H, s), 2.02 (3H, d); ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 162.4, 161.2, 159.0, 139.6, 137.5, 136.7, 133.3, 132.8, 129.6, 128.7, 116.7, 113.0, 104.5, 98.7, 63.9, 55.6, 55.5, 48.0, 36.8, 21.2; Exact mass calculated for C₂₄H₂₅NO₅Na [M+Na] 430.1625. Found 430.1628.
1-(4-(2,4-dimethoxybenzyl)-6-methoxy-3-oxo-2,3,4,5-tetrahydropyrazin-2-yl)-2-(4-methoxyphenylethyl)acetate (10): To a solution of DMB-diketopiperazine 1 (338 mg, 1.21 mmol) dissolved in THF (5 mL) was added LiHMDS solution (1.28 mL, 1M in THF) at -78°C dropwise over 5 minutes. After allowing 15 minutes for enolization, a solution of aldehyde 9 (158.5 mg, 1.33 mmol in 2 mL THF) was added slowly. The reaction proceeded for 30 minutes at -78°C. To the solution, pyridine (152 µL, 1.57 mmol) and acetic anhydride (126 µL, 1.57 mmol) were added. The reaction was allowed to come to room temperature overnight. The solution was concentrated in vacuo and redissolved in dichloromethane (10 mL). This was washed with 0.1M HCl (10 mL) and the aqueous layer was extracted with dichloromethane (3x10 mL). The combined organic layers were washed with saturated NaHCO₃ solution (40 mL), saturated NaCl solution (40 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuo. The product was purified by flash chromatography on silica gel (10% to 60% EtOAc in hexanes with added constant 5% chloroform) to afford the DMB-Diketopiperazine Acetate 3 (390 mg, 69% yield) as an inseparable mixture of diastereomers. TLC (60% EtOAc in hexanes) Rf = 0.76 (CAM/UV); IR (film) cm⁻¹ 3054, 2998, 2948, 2837, 2358, 2336, 2060, 1741, 1701, 1652, 1615, 1587, 1558, 1515, 1489, 1465, 1457, 1373, 1320, 1296, 1248, 1211, 1179, 1158, 1131, 1034, 938, 859, 788, 735; ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.19 (6H, m), 6.94-6.81 (4H, m), 6.47-6.41 (4H, m), 5.54-5.50 (1H, m), 5.37-5.33 (1H, m), 4.82-4.75 (4H, d, J = 14.9 Hz), 4.44-4.40 (2H, d, J = 14.4 Hz), 4.28-4.25 (2H, d, J = 14.5 Hz), 4.09-4.08 (1H, d, J = 2.0 Hz), 3.89-3.88 (1H, d, J = 2.0 Hz), 3.87-3.65 (24H, m), 3.17-3.11 (1H, m), 3.04-2.91 (3H, m), 1.87 (3H, s), 1.70 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 170.1, 169.7, 167.0, 165.9, 160.8, 160.7, 160.0, 159.1, 158.9, 158.8, 158.6, 158.5, 151.9, 131.2, 131.1, 131.0, 129.4, 129.2, 116.8, 116.3, 114.1, 114.0, 104.8, 104.7, 98.5, 78.0, 77.7, 77.1, 60.6, 59.8, 55.6, 55.5, 55.4, 53.3, 46.1, 46.0, 43.5, 43.2, 36.5, 35.8, 21.2, 21.1; Exact mass calculated for C₂₅H₃₀N₂O₇Na [M+Na] 493.1945. Found 493.1941.

1-(2,4-dimethoxybenzyl)-5-methoxy-3-(4-methoxyphenylethyl)pyrazin-2(1H)-one (11): To a solution of DMB-DKP 10 (390 mg, 0.83 mmol) in toluene (5 mL) was added DBU (0.136 mL, 0.911 mmol). The reaction mixture was heated to 110 °C and stirred with a magnetic stirrer. The
reaction was tracked by TLC and appeared to be complete after 16 hours. The reaction was quenched with saturated aqueous NH₄Cl solution, and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with saturated NaHCO₃ solution, dried with Na₂SO₄, and concentrated in vacuo. This afforded azadiene 11 as a brown oil (354 mg) with a small amount of another highly UV active product, presumably the exocyclic azadiene. Azadiene 11 is not stable to silica gel and was used in subsequent reactions without purification.

TLC (60% EtOAc in hexanes) Rf = 0.60 (CAM / UV).

IR (film) cm⁻¹ 3083, 3001, 2940, 2842, 2597, 2546, 2484, 2425, 2328, 2146, 2058, 1876, 1698, 1672, 1580, 1509, 1442, 1360, 1241, 1206, 1170, 1121, 1076, 1034, 931, 834, 749;

¹H NMR (400 MHz, CDCl₃) δ 7.34-7.32 (1H, d, J = 9.0 Hz), 7.19-7.17 (2H, d, J = 8.6 Hz), 6.81-6.78 (2H, d, J = 8.6 Hz), 6.75 (1H, s), 6.45 (2H, m), 4.99 (2H, s), 3.79 (3H, s), 3.76 (3H, s), 3.74 (3H, s), 3.14-3.10 (2H, t, J = 7.6 Hz), 3.02-2.98 (2H, t, J = 7.6 Hz);

¹³C NMR (100 MHz, CDCl₃)


(1S,4S)-ethyl-5-(2,4-dimethoxybenzyl)-3-methoxy-1-(4-methoxyphenethyl)-6-oxo-2,5-
diazabicyclo[2.2.2]octa-2,7-diene-7-carboxylate (12): To a solution of azadiene 11 (320 mg, 0.78 mmol) in toluene (2.5 mL) was added excess ethyl propiolate (2.5 mL). The reaction was heated to 110°C for 18 hours, when the reaction was complete as judged by TLC. The reaction was concentrated in vacuo and purified by flash column chromatography on silica gel (20% to 80% EtOAc in hexanes) to afford a largely inseparable mixture of Diels-Alder cycloadducts, desired product 12 and regioisomer 13 (250 mg, 63% combined yield) in a ratio of 1:2.

TLC (60% EtOAc in hexanes) Rf = 0.72 (UV, CAM); IR (film) cm⁻¹ 2994, 2944, 2909, 1836, 2360, 1717, 1686, 1646, 1612, 1587, 1512, 1456, 1438, 1419, 1368, 1328, 1291, 1246, 1210, 1175, 1158, 1124, 1034, 936, 833, 733;

¹H NMR (400 MHz, CDCl₃) δ 7.30-7.29 (1H, d, J = 2.0 Hz), 7.24 (1H, s), 7.19 (1H, s), 7.15-7.14 (1H, d, J = 5.5 Hz), 7.01-6.96 (2H, m), 6.82-6.78 (4H, m), 6.38 (2H, s), 6.37-6.34 (4H, m), 5.09-5.08 (1H, d, J = 2.0 Hz), 4.64-4.62 (1H, d, J = 5.8 Hz), 4.47-4.39 (2H, m), 4.32-4.31 (1H, d, J = 4.7 Hz), 4.29-4.28 (1H, d, J = 4.6 Hz), 4.16-4.10 (2H, q, J = 7.1 Hz), 4.09-4.00 (2H, m), 3.76-3.67 (24H, m), 3.00-2.40 (8H, m), 1.25-1.17 (6H, m);

¹³C NMR (100 MHz, CDCl₃) δ 175.0, 173.8, 171.2, 163.8, 162.1, 160.91, 160.89, 158.6, 158.5, 157.7, 157.5, 150.2, 145.7, 140.8, 138.0, 135.5, 134.6, 131.5, 129.5, 129.4, 116.2, 116.0, 113.7, 113.6, 104.1, 104.0, 98.4, 98.3, 77.3, 73.4, 73.0, 61.1, 61.0, 56.9, 56.3, 55.6, 55.4, 55.3, 55.2,
55.1, 44.0, 43.9, 34.1, 32.4, 30.4, 29.5, 14.1, 14.0; Exact mass calculated for C_{28}H_{32}N_{2}O_{7}Na [M+Na] 531.2102. Found 531.2100.

(1S,4S)-ethyl-5-(2,4-dimethoxybenzyl)-1-(4-methoxyphenethyl)-3,6-dioxo-2,5-diazabicyclo[2.2.2]oct-7-ene-7-carboxylate (14): To a solution of cycloadducts 12 and 13 (509 mg, 0.90 mmol) in AcOH (5 mL) was added potassium iodide (445 mg, 2.68 mmol). The reaction proceeded at 100°C for approximately 2.5 hours. It was diluted and neutralized with 30 mL saturated sodium bicarbonate solution. This was extracted with EtOAc (3x20 mL). The organic layers were combined and washed with saturated NaHCO₃ solution (20 mL) and 10% NaS₂O₃ solution (10 mL). It was then washed with saturated NaCl solution and dried with Na₂SO₄. The product was then concentrated in vacuo. The product was then purified by flash column chromatography on silica gel (20% to 100% EtOAc in hexanes with added constant 5% CHCl₃) resulting in a largely inseparable mixture of demethylated products 14 and 15 (254 mg, 57% yield). TLC (60% EtOAc in hexanes) Rₚ = 0.57 (CAM/UV); IR (film) cm⁻¹ 3197, 2997, 2958, 2935, 2837, 2063, 1717, 1701, 1686, 1612, 1587, 1512, 1465, 1438, 1404, 1368, 1293, 1266, 1246, 1209, 1158, 1140, 1116, 1096, 1036, 935, 835; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.36 (1H, d, J = 5.9 Hz), 7.29-7.28 (1H, d, J = 1.9 Hz), 7.24-7.19 (2H, m), 7.10-7.06 (2H, m), 6.96-6.94 (2H, d, J = 7.4 Hz), 6.88-6.85 (4H, m), 6.43-6.37 (4H, m), 4.88-4.87 (1H, d, J = 2.0 Hz), 4.68-4.64 (1H, d, J = 14.1 Hz), 4.61-4.57 (1H, d, J = 14.6 Hz), 4.49-4.47 (2H, m), 4.42-4.35 (2H, m), 4.23-4.17 (2H, q, J = 6.0 Hz), 4.15-4.06 (3H, m), 3.81-3.75 (18H, m), 2.89-2.81 (4H, m), 2.78-2.59 (2H, m), 2.45-2.33 (2H, m), 1.28-1.25 (3H, t, J = 7.0 Hz), 1.23-1.20 (3H, t, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 171.6, 169.4, 169.3, 162.8, 161.8, 161.3, 158.8, 158.3, 158.1, 146.2, 140.9, 133.8, 133.0, 131.8, 129.7, 129.6, 115.8, 115.7, 114.2, 114.0, 104.4, 104.3, 98.7, 98.6, 98.5, 77.6, 66.0, 64.5, 61.6, 61.5, 61.2, 61.0, 55.5, 55.4, 55.3, 55.2, 44.8, 44.6, 31.6, 30.0, 29.9, 29.0, 14.3, 14.2, 14.1; Exact mass calculated for C_{27}H_{30}N_{2}O_{7}Na [M+Na] 517.1945. Found 517.1945.
ethyl-1-(2,4-dimethoxybenzyl)-3-(4-methoxyphenethyl)-2-oxo-1,2-dihydropyridine-4-carboxylate (16): To a solution of mixed regioisomers 14 and 15 (134 mg, 0.27 mmol) in Ac₂O (2.5 mL) was added pyridine (0.066 mL, 0.81 mmol). The reaction mixture was heated to 140 ºC and allowed to react for 48 hours. The reaction was concentrated in vacuo after adding toluene and then CHCl₃. The resulting residue was purified by flash column chromatography on silica gel (10% to 60% EtOAc in hexanes with added constant 10% CHCl₃) to afford product 16 and another product 17 (78 mg and 18 mg, respectively). Product 16: TLC (60% EtOAc in hexanes) Rƒ = 0.74 (CAM/UV); IR (film) cm⁻¹ 2958, 2934, 2836, 1889, 1868, 1844, 1783, 1717, 1652, 1615, 1588, 1559, 1512, 1456, 1437, 1368, 1298, 1245, 1210, 1178, 1158, 1131, 1033, 940, 822, 764; ¹H NMR (400 MHz, CDCl₃) δ 8.31 (1H, s), 7.61 (1H, s), 7.39-7.38 (1H, d, J = 7.8 Hz), 7.14-7.12 (2H, d, J = 8.6 Hz), 6.82-6.80 (2H, d, J = 8.2 Hz), 6.49-6.48 (1H, d, J = 2.3 Hz), 6.46 (1H, s), 5.09 (2H, s), 4.31-4.26 (2H, q, J = 7.2 Hz), 3.84 (3H, s), 3.80 (3H, s), 3.78 (3H, s), 2.85-2.78 (4H, m), 1.36-1.32 (3H, t, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 164.8, 162.7, 161.1, 158.7, 157.7, 141.4, 134.8, 133.7, 132.4, 131.5, 129.3, 116.0, 113.6, 108.6, 104.2, 98.5, 60.6, 55.2, 48.4, 33.4, 33.1, 14.3; Exact mass calculated for C₂₆H₂₉NO₆Na [M+Na] 474.1887. Found 474.1887.

Product 17: TLC (60% EtOAc in hexanes) Rƒ = 0.55 (CAM/UV); IR (film) cm⁻¹ 2957, 2925, 2854, 1942, 1919, 1888, 1868, 1843, 1825, 1791, 1771, 1733, 1717, 1700, 1695, 1684, 1675, 1653, 1616, 1576, 1558, 1457, 1436, 1373, 1245, 1209, 1176, 1158, 1032, 826; ¹H NMR (400 MHz, CDCl₃) δ 8.01 (1H, s), 7.17-7.15 (3H, m), 6.83-6.81 (2H, d, J = 8.6 Hz), 6.61 (1H, s), 6.42-6.40 (1H, d, J = 8.2 Hz), 6.38 (1H, s), 5.42 (2H, s), 4.33-4.28 (2H, q, J = 7.2 Hz), 3.79 (3H, s), 3.77 (3H, s), 3.70 (3H, s), 3.19-3.15 (2H, t, J = 8.0 Hz), 2.81-2.78 (2H, t, J = 7.8 Hz), 2.50 (3H, s), 2.30 (3H, s), 1.37-1.34 (3H, t, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 172.1, 165.3, 162.7, 161.4, 160.9, 158.5, 157.8, 139.2, 138.9, 135.6, 133.7, 132.1, 129.5, 116.5, 113.7, 106.5, 104.0, 98.5, 62.0, 55.4, 55.2, 44.0, 33.8, 31.1, 25.4, 24.9, 14.2; Exact mass calculated for C₂₉H₃₃N₂O₆Na [M+Na] 559.2056. Found 559.2049.
ethyl 3-(4-methoxyphenethyl)-2-oxo-1,2-dihydropyridine-4-carboxylate (18): To a solution of product 16 (25 mg, 0.055 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added trifluoracetic acid (0.25 mL) and triethylsilane (0.25 mL). The reaction mixture was heated in the microwave (temperature mode = 130 ºC, 30 min). The reaction mixture was concentrated in vacuo and purified by flash column chromatography on silica gel (1% to 10% methanol in CHCl$_3$) to afford pyridone 18 (16.5 mg, 99% yield) as a yellow solid. mp 86-88 ºC; TLC (5% methanol in CHCl$_3$) R$_f$ = 0.48 (UV, CAM); IR (film) cm$^{-1}$ 2927, 2855, 2835, 1868, 1771, 1733, 1700, 1695, 1652, 1616, 1576, 1539, 1539, 1465, 1436, 1368, 1300, 1244, 1209, 1177, 1130, 1108, 1094, 1036, 822; ¹H NMR (400 MHz, CDCl$_3$) δ 12.96 (1H, s), 8.15-8.14 (1H, d, J = 2.3 Hz), 7.79-7.78 (1H, d, J = 2.3 Hz), 7.16-7.14 (2H, d, J = 8.6 Hz), 6.85-6.82 (2H, d, J = 8.6 Hz), 4.34-4.31 (2H, q, J = 7.0 Hz), 3.79 (3H, s), 2.90-2.83 (4H, m), 1.37-1.34 (3H, t, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl$_3$) δ 165.3, 164.5, 157.9, 137.5, 137.2, 133.4, 121.9, 129.4, 113.8, 111.0, 61.0, 55.2, 33.3, 32.3, 14.3; Exact mass calculated for C$_{17}$H$_{19}$NO$_4$Na [M+Na] 324.1206. Found 324.1206.

4-(hydroxymethyl)-3-(4-methoxyphenethyl)pyridin-2(1H)-one (19): To a solution of LiAlH$_4$ (8.5 mg, 0.21 mmol) in THF (0.250 mL) at 0 ºC was added a solution of pyridone 18 (21 mg, 0.07 mmol) in THF (0.750 mL). The reaction was stirred and allowed to slowly come to room temperature. The reaction was tracked by TLC and found to be complete after 4 hours. The reaction was quenched with 1.0 M HCl (5 mL) and extracted with EtOAc (3 x 8 mL). The organic layers were combined and washed with saturated NaCl solution, dried with Na$_2$SO$_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (25% to 100% EtOAc in hexanes) to afford pyridone 19 (7.6 mg, 42% yield) as a pale yellow solid. mp 143-144 ºC; TLC (100% EtOAc) R$_f$ = 0.27 (CAM/UV). IR (film) cm$^{-1}$ 3198, 3007, 2929, 2835, 2360, 2337, 1695, 1653, 1622, 1511, 1456, 1296, 1244, 1207, 1180, 1106, 1032, 1000, 818, 735, 540; ¹H NMR (400 MHz, CD$_3$OD ) δ 7.34-7.33 (1H, d, J = 2.4 Hz), 7.24-7.23 (1H, d, J = 2.4 Hz), 7.11-7.09 (2H, d, J = 8.6 Hz), 6.81-6.79 (2H, d, J = 8.6 Hz), 4.32 (2H, s), 3.75 (3H, s), 2.82-2.75 (4H, m); ¹³C NMR (100 MHz, CD$_3$OD) δ 165.0, 159.6, 141.2, 135.1,
133.6, 131.2, 130.6, 122.2, 114.9, 61.9, 55.8, 34.9, 34.0; Exact mass calculated for C\textsubscript{15}H\textsubscript{17}NO\textsubscript{3}Na [M+Na] 282.1101. Found 282.1101.

**ethyl 3-(4-hydroxyphenethyl)-2-oxo-1,2-dihydropyridine-4-carboxylate (20):** To a solution of pyridone 18 (17.0 mg, 0.056 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (0.5 mL) cooled to -78 ºC was added BBr\textsubscript{3} (0.226 mL, 0.226 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 2.5 hours. The reaction was diluted and quenched with saturated sodium bicarbonate solution (5 mL). It was then extracted with EtOAc (3 x 5mL). The organic layers were combined and washed with saturated NaCl solution, dried with Na\textsubscript{2}SO\textsubscript{4}, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (15% to 100% EtOAc in hexanes) to afford pyridone 20 (15.0 mg, 93% yield) as a pale yellow solid. mp 166-168 ºC; TLC (60% EtOAc in hexanes) R\textsubscript{f} = 0.26 (UV, CAM); IR (film) cm\textsuperscript{-1} 3357, 2923, 2853, 1716, 1696, 1653, 1636, 1515, 1457, 1430, 1367, 1294, 1242, 1169, 1135, 1022, 1094, 825, 788, 722, 695, 639, 540; \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}OD) \delta 8.01-8.00 (1H, d, J = 2.7 Hz), 7.68-7.67 (1H, d, J = 2.2 Hz), 7.01-6.99 (2H, d, J = 8.6 Hz), 6.68-6.66 (2H, d, J = 8.6 Hz), 4.31-4.25 (2H, q, J = 7.0 Hz), 2.78-2.75 (4H, m), 1.35-1.31 (3H, t, J = 7.0 Hz); \textsuperscript{13}C NMR (100 MHz, CD\textsubscript{3}OD) \delta 166.1, 165.5, 156.7, 138.7, 138.6, 133.6, 133.3, 120.6, 116.2, 111.9, 62.2, 34.6, 33.9, 14.7.

**5-(hydroxymethyl)-3-(4-hydroxyphenethyl)pyridin-2(1H)-one (21):** To a solution of LiAlH\textsubscript{4} (6.6 mg, 0.17 mmol) in THF (0.250 mL) at 0 ºC was added a solution of pyridone 20 (12.4 mg, 0.043 mmol) in THF (0.750 mL). The reaction was stirred and allowed to slowly come to room temperature. The reaction was tracked by TLC and found to be complete after 2.5 hours. The reaction was quenched with 1.0 M HCl (5 mL) and extracted with EtOAc (4 x 8 mL). The organic layers were combined and washed with saturated NaCl solution, dried with Na\textsubscript{2}SO\textsubscript{4}, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (0% to 5% methanol in EtOAc) to afford iso-aristopyridinone 21 (1.6 mg, 15% yield).
as an off-white solid. mp >260°C; TLC (100% EtOAc) Rf = 0.10 (CAM/UV). IR (film) cm\(^{-1}\) 2954, 2923, 2854, 2360, 2340, 1716, 1700, 1683, 1635, 1653, 1558, 1539, 1506, 1457, 1260, 1099, 1020, 802, 680, 649, 668; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.34-7.33 (1H, d, J = 2.3 Hz), 7.24-7.23 (1H, d, J = 2.4 Hz), 7.02-7.00 (2H, d, J = 8.6 Hz), 6.68-6.66 (2H, d, J = 8.6 Hz), 4.32 (2H, s), 2.78-2.75 (4H, m); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD) \(\delta\) 165.0, 156.7, 141.2, 133.9, 133.7, 131.2, 122.2, 116.2, 62.0, 34.9, 34.1.

methyl-5-(3,4-dimethoxybenzyl)-3-methoxy-1-(4-methoxyphenethyl)-8-nitro-6-oxo-2,5-diazabicyclo[2.2.2]oct-2-one-7-carboxylate (22): To a solution of azadiene 11 (452 mg, 1.10 mmol) in toluene (5 mL) cooled to 0°C was added a solution of nitroacrylate (131 mg, 1.0 mmol) in toluene (3 mL). The reaction was stirred and allowed to come to room temperature overnight. The reaction mixture was concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (10% to 100% EtOAc in hexanes) to afford desired cycloadduct 22 and regioisomer 23 (335.8 mg total, 56% total yield) as yellow oils. Product 22: TLC (40% EtOAc in hexanes) Rf = 0.33 (CAM/UV); IR (film) cm\(^{-1}\) 3004, 2951, 2836, 2359, 2342, 1741, 1694, 1648, 1612, 1588, 1512, 1456, 1439, 1419, 1371, 1333, 1299, 1267, 1246, 1209, 1175, 1159, 1125, 1034, 980, 960, 932, 915, 832, 755, 667; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.28-7.27 (1H, d, J = 9.0 Hz), 7.21-7.19 (2H, d, J = 8.6 Hz), 6.84-6.82 (2H, d, J = 8.6 Hz), 6.48-6.46 (2H, m), 5.04-5.02 (1H, dd, J = 3.2 Hz and 4.7 Hz), 4.82-4.81 (1H, d, J = 3.1 Hz), 4.60-4.57 (1H, d, J = 14.0 Hz), 4.47-4.44 (1H, d, J = 14.0 Hz), 3.87 (3H, s), 3.80-3.77 (9H, m), 3.64 (3H, s), 3.29-3.28 (1H, d, J = 5.1 Hz), 2.93-2.87 (2H, m), 2.27-2.24 (1H, m), 2.02-1.97 (1H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 169.6, 169.4, 169.0, 161.1, 158.5, 157.7, 134.6, 132.5, 129.4, 115.8, 113.7, 104.5, 98.4, 84.5, 67.1, 55.5, 55.4, 55.3, 55.2, 54.8, 52.9, 51.1, 43.9, 34.6, 29.1.

Product 23: TLC (40% EtOAc in hexanes) Rf = 0.22 (CAM/UV); IR (film) cm\(^{-1}\) 3005, 2952, 2914, 2837, 2359, 2334, 1743, 1694, 1643, 1612, 1588, 1557, 1512, 1456, 1439, 1419, 1371, 1333, 1298, 1267, 1246, 1209, 1175, 1159, 1125, 1034, 980, 960, 932, 915, 832, 755, 667; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.30-7.28 (1H, d, J = 7.8 Hz), 7.20-7.18 (2H, d, J = 8.6 Hz), 6.83-6.81 (2H, d, J = 8.6 Hz), 6.48-6.46 (2H, m), 4.98-4.97 (1H, d, J = 4.7 Hz), 4.68-4.65 (1H, d, J = 14.5 Hz), 4.61-4.60 (1H, d, J = 2.7 Hz), 4.52-4.49 (1H, d, J = 14.1 Hz), 3.84 (3H, s), 3.80-3.77 (9H, m), 3.73 (3H, s), 3.41-3.39 (1H, dd, J = 1.9 Hz and 2.8 Hz), 2.95-2.87 (2H, m), 2.35-2.27 (1H, m), 2.04-1.97 (1H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.1, 168.4, 168.3, 161.1, 158.5, 157.7, 157.6, 154.7, 153.7, 134.2, 132.5, 129.5, 115.9, 113.7, 104.3, 98.4, 87.0, 67.3, 55.4, 55.3, 55.2, 54.9, 54.8, 53.2, 49.5, 43.8, 33.2, 28.8.
methyl-(1S,4S)-5-(3,4-dimethoxybenzyl)-3-methoxy-1-(4-methoxyphenethyl)-6-oxo-2,5-
diazabicyclo[2.2.2]octa-7-diene-7-carboxylate (24): To a solution of cycloadduct 22 (115 mg, 0.213 mmol) in toluene (3 mL) was added DBU (0.054 mL, 0.361 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was quenched with 0.1 M HCl (5 mL) and extracted with EtOAc (3 x 8 mL). The organic layers were combined and washed with saturated NaHCO₃ solution (5 mL), washed with saturated NaCl solution (5 mL), dried with Na₂SO₄, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (10% to 60% EtOAc in hexanes) to afford product 24 (47 mg, 45% yield) as a yellow oil. TLC (40% EtOAc in hexanes) Rƒ = 0.30 (CAM/UV); IR (film) cm⁻¹ 2999, 2947, 2835, 2058, 1725, 1688, 1650, 1612, 1588, 1512, 1456, 1438, 1417, 1331, 1292, 1266, 1245, 1210, 1171, 1159, 1112, 1090, 1036, 965, 936, 833, 791, 734, 702, 588, 521; ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.27 (2H, d, J = 8.6 Hz), 7.21-7.20 (1H, d, J = 5.8 Hz), 7.06-7.03 (1H, d, J = 8.6 Hz), 6.86-6.83 (2H, d, J = 8.7 Hz), 6.48-6.41 (2H, m), 5.00 (1H, s), 4.69-4.68 (1H, d, J = 5.5 Hz), 4.47-4.43 (1H, d, J = 14.5 Hz), 4.36-4.32 (1H, d, J = 14.5 Hz), 3.83-3.71 (15H, m), 3.12-2.97 (2H, m), 2.85-2.66 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 173.8, 171.8, 164.2, 160.9, 158.5, 145.4, 141.2, 135.5, 131.5, 129.5, 116.2, 113.7, 113.6, 104.2, 98.4, 73.3, 56.3, 55.5, 55.4, 55.3, 55.2, 55.1, 44.0, 32.6, 30.1.

methyl-(1S,4S)-2-(3,4-dimethoxybenzyl)-6-methoxy-4-(4-methoxyphenethyl)-3-oxo-2,5-
diazabicyclo[2.2.2]octa-5,7-diene-7-carboxylate (25): To a solution of cycloadduct 23 (50 mg, 0.092 mmol) in toluene (1.5 mL) was added DBU (0.023 mL, 0.157 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was quenched with 0.1 M HCl (3 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were combined and washed with saturated NaHCO₃ solution (5 mL), washed with saturated NaCl solution (5 mL), dried with Na₂SO₄, and concentrated in vacuo to afford product 25 (44.7 mg, 99% yield) as a yellow oil. TLC (40% EtOAc in hexanes) Rƒ = 0.28 (CAM/UV); IR (film) cm⁻¹ 3000, 2949, 2836, 2359,
methyl-(1S,4S)-2-(3,4-dimethoxybenzyl)-4-(4-methoxyphenethyl)-3,6-dioxo-2,5-diazabicyclo[2.2.2]oct-7-ene-7-carboxylate: To a solution of cycloadduct 18 (35 mg, 0.071 mmol) in acetic acid (1.0 mL) was added potassium iodide (35 mg, 0.212 mmol). The reaction mixture was heated to 100 °C and stirred for one hour. The reaction mixture was washed with toluene (2.0 mL) and concentrated in vacuo. The resulting residue was then quenched with saturated NaHCO$_3$ solution (3.0 mL) and extracted with EtOAc (3 x 6 mL). The organic layers were combined and washed with saturated NaHCO$_3$ solution (5.0 mL), washed with 10% NaS$_2$O$_3$ solution (5.0 mL), washed with saturated NaCl solution (5.0 mL), dried with Na$_2$SO$_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (15% to 100% EtOAc in hexanes with constant 5% CHCl$_3$) to afford product 19 (13.9 mg, 41% yield) as a yellow oil. TLC (60% EtOAc in hexanes) R$_f$ = 0.55 (CAM/UV; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30-7.29 (1H, d, J = 2.3 Hz), 7.20-7.18 (2H, d, J = 8.6 Hz), 7.08-7.06 (1H, d, J = 7.8 Hz), 6.87-6.85 (2H, d, J = 8.6 Hz), 6.40-6.37 (2H, m), 4.87-4.86 (1H, m), 4.66-4.63 (1H, d, J = 14.5 Hz), 4.38-4.35 (1H, d, J = 14.1 Hz), 3.80 (3H, s), 3.76 (3H, s), 3.75 (3H, s), 3.64 (3H, s), 2.87-2.8 (2H, m), 2.42-2.34 (2H, m); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 171.3, 169.1, 162.1, 161.2, 158.7, 158.3, 146.2, 140.6, 132.6, 131.8, 129.3, 115.5, 114.2, 104.2, 98.3, 64.3, 61.1, 55.32, 55.29, 55.1, 52.3, 44.5, 31.3, 28.9.
(1S,4S)-2-(3,4-dimethoxybenzyl)-8-(hydroxymethyl)-6-methoxy-4-(4-methoxyphenethyl)-2,5-diazabicyclo[2.2.2]octa-5,7-dien-3-one (27): To a solution of DMB-DKP 10 (1052 mg, 2.23 mmol) in toluene (6 mL) was added DBU (0.666 mL, 4.47 mmol) and excess propargyl alcohol (6 mL). The reaction mixture was raised to 110 ºC and shown to be complete by TLC after 26 hours. The reaction was quenched with saturated NH₄Cl solution (15 mL), and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with saturated NaHCO₃ solution (30 mL), washed with saturated NaCl solution (30 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (10 to 100% EtOAc in hexanes with added constant 5% chloroform) to afford a largely inseparable mixture of Diels-Alder cycloadducts 27 and 28 (811 mg, 78% yield) as a yellow oil in a ratio of 1:4. TLC (60% EtOAc in hexanes) Rƒ = 0.60 (UV, CAM); IR (film) cm⁻¹ = 13428, 3005, 2946, 2836, 1674, 1635, 1612, 1588, 1512, 1456, 1439, 1418, 1351, 1332, 1293, 1245, 1209, 1179, 1158, 1121, 1035, 935, 878, 834, 757, 667, 638; ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.28 (1H, d, J = 8.6 Hz), 7.26-7.24 (2H, d, J = 9.4 Hz), 7.18-7.16 (2H, d, J = 8.2 Hz), 7.05-7.03 (1H, d, J = 8.3 Hz), 7.04-7.02 (1H, d, J = 8.3 Hz), 6.86-6.83 (2H, d, J = 8.6 Hz), 6.84-6.82 (2H, d, J = 8.6 Hz), 6.45-6.39 (4H, m), 6.36-6.35 (1H, d, J = 2.0 Hz), 4.68 (1H, m), 4.63-4.62 (2H, d, J = 1.9 Hz), 4.61 (2H, s), 4.49-4.45 (1H, d, J = 14.1 Hz), 4.45-4.44 (1H, d, J = 7.5 Hz), 4.42-4.40 (1H, d, J = 7.4 Hz), 4.35-4.31 (1H, d, J = 14.4 Hz), 4.27 (1H, s), 3.97 (1H, s), 3.80 (3H, s), 3.79 (3H, s), 3.78 (3H, s), 3.77 (3H, s), 3.73 (3H, s), 3.72 (3H, s), 3.71 (3H, s), 3.70 (3H, s), 3.06-2.80 (4H, m), 2.57-2.49 (2H, m), 2.41-2.33 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 175.0, 172.6, 160.8, 158.8, 158.6, 158.5, 157.5, 157.2, 155.2, 135.0, 131.3, 131.15, 131.11, 130.7, 130.3, 129.6, 129.4, 116.8, 115.9, 113.8, 113.7, 113.6, 104.4, 104.2, 98.5, 98.4, 98.3, 71.8, 61.9, 61.0, 60.2, 58.2, 55.4, 55.34, 55.32, 55.3, 55.2, 52.9, 43.0, 34.3, 29.4, 27.4.

(1S,4S)-5-(3,4-dimethoxybenzyl)-7-(hydroxymethyl)-1-(4-methoxyphenethyl)-2,5-diazabicyclo[2.2.2]octa-7-ene-3,6-dione (29): To a solution of cycloadducts 27 and 28 (223 mg, 0.479 mmol) in acetic acid (4 mL) was added potassium iodide (238 mg, 1.436 mmol).

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reaction proceeded at 100 ºC for 1.25 hours. The reaction mixture was diluted with toluene (5 mL), concentrated in vacuo, redissolved in toluene (5 mL), and quenched with saturated NaHCO$_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with saturated NaHCO$_3$ solution (20 mL), 10% Na$_2$SO$_3$ solution (10 mL), saturated NaCl solution (30 mL), dried with Na$_2$SO$_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography (40% to 100% EtOAc in hexanes with added constant 10% chloroform) to afford the largely inseparable mixture of demethylated products 29 and 30 (150 mg, 69% yield) as a yellow oil. TLC (60% EtOAc in hexanes) R$_f$ = 0.13 (UV, CAM); IR (film) cm$^{-1}$ 3405, 3232, 3007, 2937, 2837, 2248, 1699, 1619, 1587, 1456, 1408, 1349, 1294, 1246, 1210, 1180, 1158, 1120, 1035, 911, 836, 755, 667; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28-7.21 (2H, d, J = 8.6 Hz), 7.20 (1H, s), 7.19-7.16 (2H, d, J = 8.6 Hz), 7.08-7.06 (2H, d, J = 7 Hz), 7.06-7.04 (1H, d, J = 8.2 Hz), 6.85-6.83 (2H, d, J = 8.6 Hz), 6.53-6.51 (1H, d, J = 5.9 Hz), 6.41-6.37 (4H, m), 6.29-6.28 (1H, d, J = 1.9 Hz), 4.62-5.58 (1H, d, J = 14.4 Hz), 4.45 (1H, s), 3.37-3.33 (3H, m), 4.23-4.15 (2H, m), 4.03-3.85 (2H, m), 3.78-3.75 (18H, m), 2.86-2.83 (2H, t, J = 7.8 Hz, 8.6 Hz), 2.33-2.21 (2H, t, J = 5.9 Hz, 6.3 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) 172.9, 172.8, 170.6, 170.2, 161.0, 160.8, 158.6, 158.03, 158.0, 150.1, 133.6, 133.1, 131.4, 131.3, 131.2, 129.6, 129.5, 129.3, 116.2, 116.0, 114.0, 113.9, 104.3, 104.2, 98.5, 98.4, 77.2, 65.5, 63.6, 62.6, 61.2, 60.9, 59.5, 55.31, 55.27, 55.24, 55.22, 44.3, 43.5, 31.6, 29.0, 28.8.

(1-(3,4-dimethoxybenzyl)-3-(4-methoxyphenethyl)-2-oxo-1,2-dihydropyridin-4-yl)methyl acetate (31): To a solution of mixed regioisomers 29 and 30 (404 mg, 0.894 mmol) in acetic anhydride (6 mL) was added pyridine (6 mL). The reaction mixture was heated to 110 ºC and allowed to react for 48 hours. The reaction mixture was concentrated in vacuo after adding toluene and chloroform. The resulting residue was purified by flash column chromatography on silica gel (10% to 85% EtOAc in hexanes) to afford a largely inseparable mixture of DMB-protected pyridones 31 and 32 (371 mg, 88% yield) as a orange-yellow oil. TLC (60% EtOAc in hexanes) R$_f$ = 0.57 (UV, CAM); IR (film) cm$^{-1}$ 3005, 2956, 2939, 2837, 1702, 1739, 1661, 1613, 1590, 1562, 1512, 1464, 1440, 1378, 1363, 1245, 1210, 1180, 1158, 1123, 1034, 942, 830, 755; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.38 (1H, d, J = 2.4 Hz), 7.37-7.35 (1H, d, J = 9.0 Hz), 7.36-7.34 (1H, d, J = 7.1 Hz), 7.30-7.28 (1H, d, J = 7.1 Hz), 7.12-7.10 (2H, d, J = 8.7 Hz), 7.12-7.10 (2H, d, J = 7.1 Hz), 7.06-7.05 (1H, d, J = 2.7 Hz), 6.81-6.79 (2H, d, J = 8.6 Hz), 6.80-6.79 (2H, d, J = 6.7 Hz), 6.48-6.46 (4H, m), 6.08-6.06 (1H, d, J = 7.0 Hz), 5.08 (2H, s), 5.06 (2H, s), 4.74 (2H, s), 4.72 (2H, s), 3.83-3.78 (18H, m), 2.86-2.77 (8H, m), 2.30 (3H, s), 2.08 (3H, s), 2.04 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) 170.8, 170.5, 162.3, 160.9, 158.6, 157.7, 143.1, 137.1, 136.3, 134.9, 134.0, 133.9, 132.7, 132.3, 132.2, 130.1, 129.6, 129.5, 129.4, 116.7, 116.6, 113.7,
113.7, 112.7, 105.0, 104.3, 98.5, 98.4, 77.2, 63.7, 62.4, 55.4, 55.3, 55.2, 55.1, 47.5, 47.4, 33.5, 33.4, 33.3, 29.8, 24.9, 21.0, 20.8.

1-(3,4-dimethoxybenzyl)-4-(hydroxymethyl)-3-(4-methoxyphenethyl)pyridin-2(1H)-one (33): To a solution of pyridones 31 and 32 (40.8 mg, 0.09 mmol) in methanol (2 mL) was added K$_2$CO$_3$ (13.8 mg, 0.271 mmol). The reaction was stirred at room temperature and found to be done after 1 hour by TLC. The reaction mixture was diluted with saturated NH$_4$Cl solution (6 mL) and the aqueous layers were extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with saturated NaCl solution (20 mL), dried with Na$_2$SO$_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (15% to 100% EtOAc in hexanes with added constant 10% chloroform) to afford de-acetylated products 33 and 34 (8.4 mg and 21.4 mg, 81% total yield) as a pale yellow solid (34) and pale yellow oil (33). Product 33: TLC (60% EtOAc in hexanes with 10% chloroform) R$_f$ = 0.25 (UV, CAM); IR (film) cm$^{-1}$ 3354, 2999, 2959, 2836, 2052, 1643, 1616, 1587, 1511, 1456, 1428, 1289, 1245, 1209, 1179, 1158, 1123, 1085, 1033, 928, 823, 753, 668; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35-7.33 (1H, d, J = 9.0 Hz), 7.31-7.30 (1H, d, J = 7.1 Hz), 7.06-7.04 (2H, d, J = 8.6 Hz), 7.80-7.78 (2H, d, J = 8.6 Hz), 6.48-6.46 (2H, m), 6.24-6.23 (1H, d, J = 7.0 Hz), 5.08 (2H, s), 4.24-4.23 (2H, d, J = 5.5 Hz), 3.81 (3H, s), 3.79 (3H, s), 3.77 (3H, s), 2.84-2.79 (4H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 162.4, 160.9, 158.6, 157.8, 148.0, 135.0, 134.2, 132.1, 129.7, 129.5, 128.1, 116.9, 113.6, 104.6, 104.3, 98.5, 77.2, 61.3, 55.4, 55.3, 55.2, 47.4, 33.4, 29.3.

1-(3,4-dimethoxybenzyl)-5-(hydroxymethyl)-3-(4-methoxyphenethyl)pyridin-2(1H)-one (34): mp 100-101$^\circ$C; TLC (60% EtOAc in hexanes with 10% chloroform) R$_f$ = 0.16 (UV, CAM); IR (film) cm$^{-1}$ 3365, 3006, 2938, 2835, 1658, 1616, 1588, 1558, 1511, 1456, 1439, 1419, 1289, 1265, 1244, 1209, 1179, 1158, 1122, 1034, 985, 824, 754, 638; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31-7.28 (1H, d, J = 9.0 Hz), 7.27 (1H, s), 7.13-7.11 (2H, d, J = 8.6 Hz), 7.11 (1H, s), 6.81-6.79 (2H, d, J = 8.6 Hz), 6.47-6.44 (2H, m), 5.05 (2H, s), 4.33-4.31 (2H, d, J = 5.5 Hz), 3.81 (3H, s), 3.79 (3H, s), 3.77 (3H, s), 2.84-2.79 (4H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 162.4, 160.8, 158.5, 157.7, 136.5, 134.0, 133.8, 132.7, 132.0, 129.4, 117.7, 116.9, 113.6, 104.3, 98.5, 62.5, 55.4, 55.2, 47.1, 33.5, 33.4.
1-(3,4-dimethoxybenzyl)-5-(4-methoxyphenethyl)-6-oxo-1,6-dihydropyridine-3-carbaldehyde (35): To a solution of pyridone 34 (35 mg, 0.086 mmol) in dichloromethane (1.5 mL) was added MnO₂ (15 mg, 0.17 mmol). The reaction was stirred at room temperature and followed by TLC. After reacting for 1.5 hours, 15 mg (0.17 mmol) of MnO₂ were added. After 23 hours of reacting, starting material remained by TLC and 15 mg (0.17 mmol) MnO₂ were added. The reaction was found to be complete by TLC after 42 hours. The reaction mixture was filtered with celite, washed with dichloromethane (4 x 5 mL), and was concentrated in vacuo to afford aldehyde 35 (31 mg, 89% yield) as a yellow oil. TLC (80% EtOAc in hexanes) R₆ = 0.70 (UV, CAM); IR (film) cm⁻¹ 2958, 2920, 2847, 2837, 1684, 1652, 1612, 1511, 1452, 1436, 1390, 1288, 1245, 1209, 1177, 1158, 1134, 1033, 815; ¹H NMR (400 MHz, CDCl₃) δ 9.49 (1H, s), 7.92-7.91 (1H, d, J = 2.4 Hz), 7.57-7.56 (1H, d, J = 2.4 Hz), 7.40-7.38 (1H, d, J = 8.2 Hz), 7.13-7.11 (2H, d, J = 8.6 Hz), 6.81-6.79 (2H, d, J = 8.6 Hz), 6.51-6.48 (2H, m), 5.11 (2H, s), 3.84 (3H, s), 3.81 (3H, s), 3.78 (3H, s), 2.86-2.82 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ 186.7, 163.1, 161.4, 158.8, 157.8, 145.3, 133.4, 133.0, 132.8, 131.5, 129.3, 117.3, 115.2, 113.7, 104.5, 98.7, 55.4, 48.5, 33.2, 33.0.

1-(3,4-dimethoxybenzyl)-3-(4-methoxyphenethyl)-2-oxo-1,2-dihydropyridine-4-carbaldehyde (37): To a solution of pyridone 33 (15 mg, 0.037 mmol) in dichloromethane (2 mL) was added MnO₂ (10 mg, 0.110 mmol). The reaction was stirred at room temperature and followed by TLC. After 5 hours, starting material remained by TLC and 6.5 mg (0.074 mmol) MnO₂ were added. The reaction was found to be complete by TLC after 17.5 hours. The reaction mixture was filtered with celite, washed with dichloromethane (3 x 5 mL), and concentrated in vacuo to afford aldehyde 36 (12.5 mg, 83% yield). TLC (60% EtOAc in hexanes) R₆ = 0.64 (UV, CAM); IR (film) cm⁻¹ 3004, 2958, 2925, 2853, 2360, 2340, 1716, 1695, 1684, 1653, 1616, 1600, 1539, 1558, 1506, 1457, 1419, 1289, 1246, 1245, 1209, 1177, 1158, 1033, 822, 789, 668, 649; ¹H NMR (400 MHz, CDCl₃) δ 9.84 (1H, s), 7.38-7.36 (1H, d, J = 7.4 Hz), 7.37-7.35 (1H, d, J = 8.2 Hz), 7.03-7.01 (2H, d, J = 8.6 Hz), 6.79-6.77 (2H, d, J = 8.6 Hz), 6.49-6.47 (2H, m), 6.42-6.40 (1H, d, J = 7.1 Hz), 5.09 (2H, s), 3.82 (3H, s), 3.80 (3H, s), 3.77 (3H, s), 3.25-3.21 (2H, t, J = 7.4 Hz), 2.87-2.84 (2H, t, J = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 190.2, 163.2, 158.7, 158.1, 139.8, 137.3, 135.6, 132.7, 132.4, 129.8, 116.1, 113.8, 104.3, 100.7, 98.6, 76.7, 55.4, 55.2, 48.2, 34.6, 29.7, 27.4.
3-(4-methoxyphenethyl)-2-oxo-1,2-dihydropyridine-4-carbaldehyde (38): To a solution of product 37 (22.4mg, 0.055 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added trifluoracetic acid (0.25 mL). The reaction mixture was heated in the microwave (temperature mode = 130 ºC, 30 min). The reaction mixture was concentrated in vacuo and purified by flash column chromatography on silica gel (0% to 10% methanol in CHCl$_3$) to afford pyridone 38 (11.6 mg, 83% yield) as a yellow solid. mp 134-136 ºC; TLC (3% methanol in CHCl$_3$) R$_f$ = 0.25 (UV, CAM); IR (film) cm$^{-1}$ 3271, 3145, 3001, 2957, 2916, 1849, 2252, 1696, 1653, 1617, 1558, 1512, 1457, 1301, 1248, 1206, 1177, 1108, 1037, 910, 812, 732, 649; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.80 (1H, s), 7.34-7.33 (1H, d, J = 6.6 Hz), 7.02-7.00 (2H, d, J = 8.6 Hz), 6.81-6.78 (2H, d, J = 8.6 Hz), 6.58-6.57 (1H, d, J = 6.7 Hz), 3.77 (3H, s), 3.26-3.22 (2H, t, J = 7.0, 7.4 Hz); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 189.7, 158.3, 141.9, 132.3, 131.9, 129.8, 113.9, 102.6, 77.2, 55.3, 38.1, 34.5, 31.2, 29.7, 26.7.

3-(4-hydroxyphenethyl)-2-oxo-1,2-dihydropyridine-4-carbaldehyde (39): To a solution of pyridone 38 (11.0 mg, 0.043mmol) in CH$_2$Cl$_2$ (1 mL) cooled to -78 ºC was added BBr$_3$ (0.128 mL, 0.128 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 4 hours. The reaction was diluted and quenched with saturated sodium bicarbonate solution (5 mL). It was then extracted with EtOAc (5 x 5mL). The organic layers were combined and washed with saturated NaCl solution (10 mL), dried with Na$_2$SO$_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (0% to 7% methanol in EtOAc) to afford pyridone 9 (3.9 mg, 38% yield) as a pale yellow solid. TLC (100% EtOAc) R$_f$ = 0.11 (UV, CAM).
ii) LiHMDS, toluene, -78°C

iii) Ac₂O, NEt₃, DMAP, CH₂Cl₂

iv) DBU, DMF/toluene

1

2

NDMB

OMe
KI, AcOH 110 "C
HN
DMB
O
NDMB
AcO
8
10
The End!