UNIVERSITY OF CALIFORNIA SAN DIEGO

Synthetic Strategies Toward Conipyridoins

A Thesis submitted in partial satisfaction of the requirements
for the degree Master of Science

in

Chemistry

by

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2022

The Thesis of Shrinav Bhakta is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

2022

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ABSTRACT OF THE THESIS

Synthetic Strategies Toward Conipyridoins

by

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Professor Emmanuel Theodorakis, Chair

Decalin-containing natural products along with tetramic acid moieties present characteristic functionalities for antibiotic and antifungal activity. Thus, the total synthesis of a

natural product in this class was determined to be of importance in a world where antibiotic resistance is an ever-growing issue. This creates the need to consistently develop novel antibiotics that can effectively attack different targets that are essential to the microorganism's survival. Exploring the total synthesis of Conipyridoin analogs, which are decalin and tetramic acid-containing natural products, was carried out in this paper in 12 efficient steps. Major transformations in this synthesis include the creation of the decalin moiety through a Lewis acid-mediated intramolecular Diels-Alder reaction along with a Lacey-Dieckmann condensation with an amino acid to build the tetramic acid core. This biomimetic synthesis allows for similar analogs of Conipyridoin to be synthesized with ease.

Chapter 1: Introduction to *Coniochaeta* Natural Products

The first signs of fungi existing on this planet can be traced back to almost 1,500 million years ago.[1] During this time, fungi, along with bacteria, have continuously been faced with environmental stresses that have induced faster mutations and more potent secondary metabolites to be produced. Due to their rapid reproduction rate and their ability to share DNA, bacteria and fungi have been able to develop antibacterial and antifungal resistance at an alarming rate.[2] Methicillin-resistant *Staphylococcus aureus* (MRSA), for example, continue to cause fatal infections as they affect over 1.2 million patients in the U.S. each year.3,[4] This creates the need to consistently develop novel drugs that can effectively target various aspects that are essential to the microorganism's survival. One-way researchers develop these drugs is by isolating natural products from fungi themselves. Several reports indicate fungi produce secondary metabolites to compete with other colonies, thus isolating and characterizing these compounds give insight into their efficacy as potential drugs.[5] These secondary metabolites represent potent drug hits and can be further modified to combat fungal infections and diseases.

One class of fungi that has been shown to produce potent secondary metabolites is *Coniochaeta*. These specialized metabolites contain thiepinols, pyran-4-ones, and even decalin and tetramic acid moieties, as seen in Figure 1.1.[6–9] Coniosetin, from the class *Coniochaeta ellipsoidea*, contains a unique decalin-containing tetramic acid that has been shown to exhibit similar bioactivity to other members in its family.[9] This further supports the notion that both the decalin and tetramic acid elements are key pharmacophores in antifungal and antibiotic activity. The biosynthesis for Coniosetin is likely manufactured through a Polyketide Synthase modular approach in which carbons and different functional groups are added in sequence before finally undergoing a cyclization. Next an amino acid, threonine in this case, is inserted into the natural

product. The pre-cyclized product contains a polyene system with a skipped set of two dienes which suggests *Coniochaeta ellipsoidea* produces several other cyclized secondary metabolites that may exhibit bioactivity.[9]

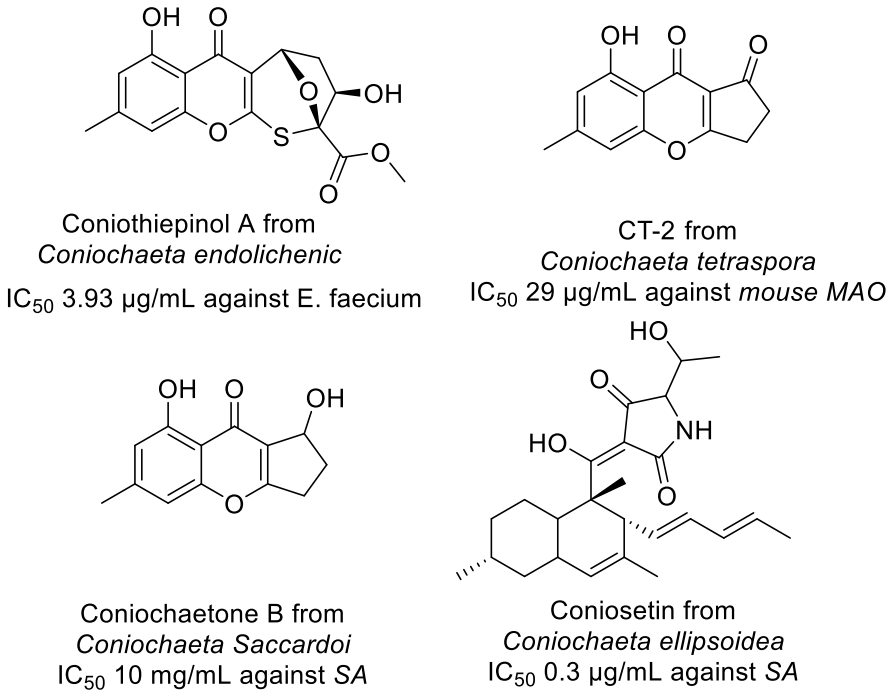


Figure 1.1 Representative secondary metabolites produced from different subgroups in *Coniochaeta*. IC_{50}: inhibitory concentration; MAO: monoamine oxidase; SA: Staphylococcus Aureus

Kamiya and Uchiyama in 1995 discovered and identified a new subfamily of *Coniochaeta* called *Coniochaeta cephalothecoides* as seen in Figure 1.2.[10] Unfortunately, further studies had not been carried out on this fungus as its scarcity in nature prevented additional analyses from being executed. This seemingly "forgotten" fungus within the genus of *Coniochaeta* needed to be explored more to determine the secondary metabolites' viability as drug candidates. Recently, Yin and Liu worked on isolating and characterizing secondary metabolites from different samples collected in a Tibetan Plateau called Medog.[11] What they uncovered was a fungus that had not been observed in over 20 years, *Coniochaeta cephalothecoides*. A number of these natural products they found were decalin-containing tetramic acids, which further indicates that these two

moieties are key pharmacophores in antifungal and antibacterial activity. Notable chemical structures within this small collection are included in Figure 1.3.

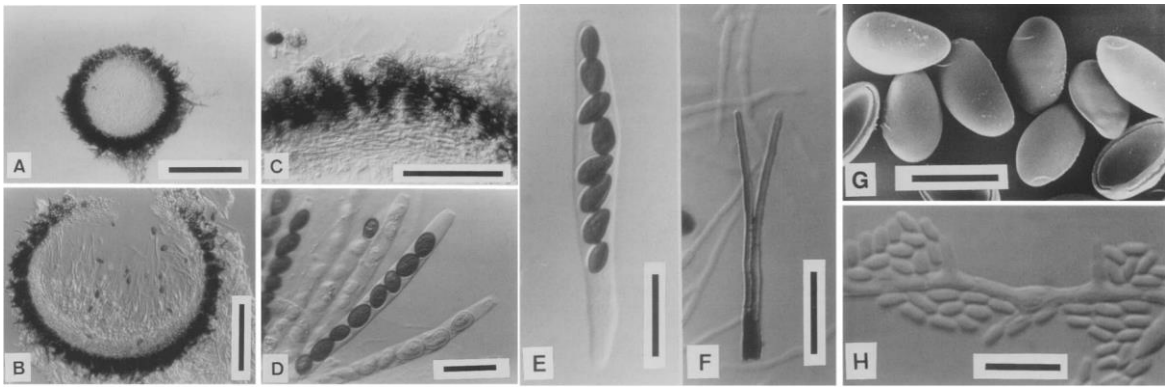


Figure 1.2 Images of *Coniochaeta cephalothecoides*. Reprinted from reference [10]: Mycoscience 36: 377-383, 1995

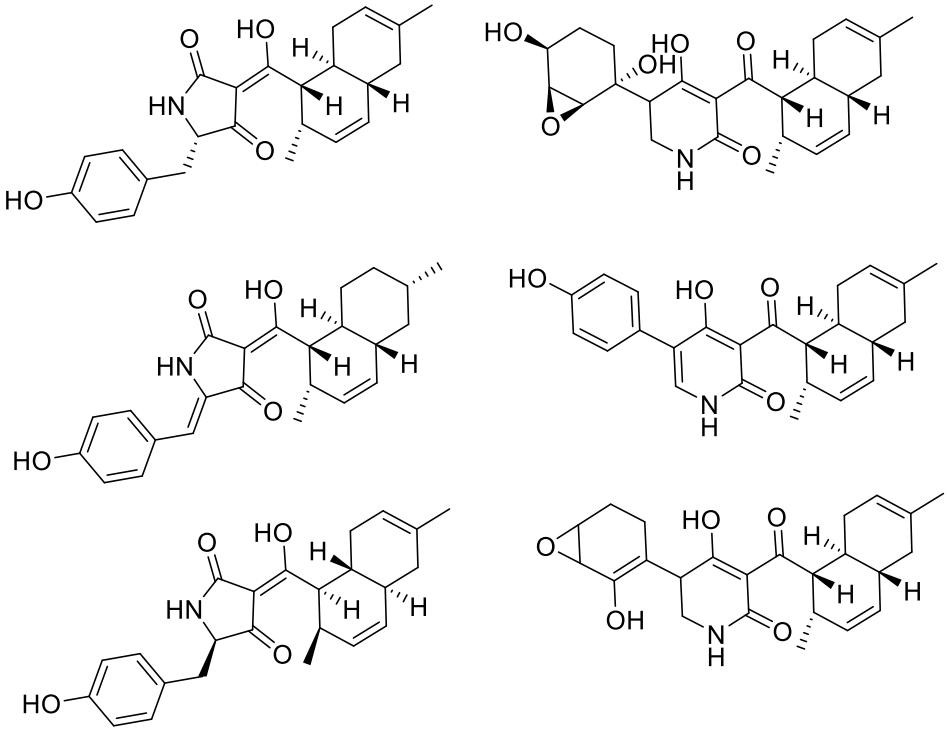


Figure 1.3 Representative natural products extracted from *Coniochaeta cephalothecoides*

Although all the extracted natural products contained the decalin pharmacophore, one analog possessed the greatest bioactivity with MIC_{50} values of 3.90μM for *Enterococcus faecalis*

and 0.97μM for *Staphylococcus aureus*, MRSA, and *Bacillus subtilis*. This Conipyridoin E analog also had a notable tetramic acid moiety with a *p*-hydroxybenzyl group at carbon-5, as seen in Figure 1.4. It was determined that an efficient total synthesis for this analog would need to be carried out to further assess the biological activity and the viability as a potential target. With low minimum inhibitory concentrations against a variety of bacteria, this analog is a promising natural product candidate for additional studies. The low MIC values can also be attributed to a variety of pharmacophores such as the decalin, the tetramic acid, and the aromatic ring.

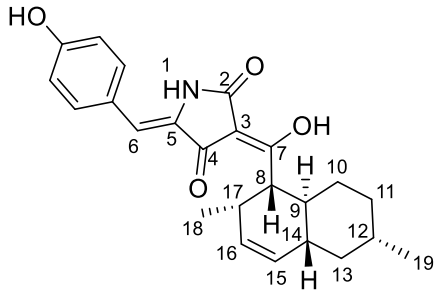


Figure 1.4 Chemical structure for Conipyridoin E

Decalin-containing monacolins and statins have been reported to be a potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase which facilitates the biosynthesis of cholesterol.[12] However, it should be noted that natural products such as Aldecalmycin and Australifungin with decalin structures also exhibit strong antibacterial and antifungal activity with MIC_{50} values <1μM against lines such as *Candida*.[13,14] A common structural feature within these antibiotics is a rigid, hydrophobic decalin unit presumably deriving from an intramolecular Diels-Alder reaction.[15] Further biological studies need to be carried out to depict the role this decalin plays in antifungal or antibiotic activity.

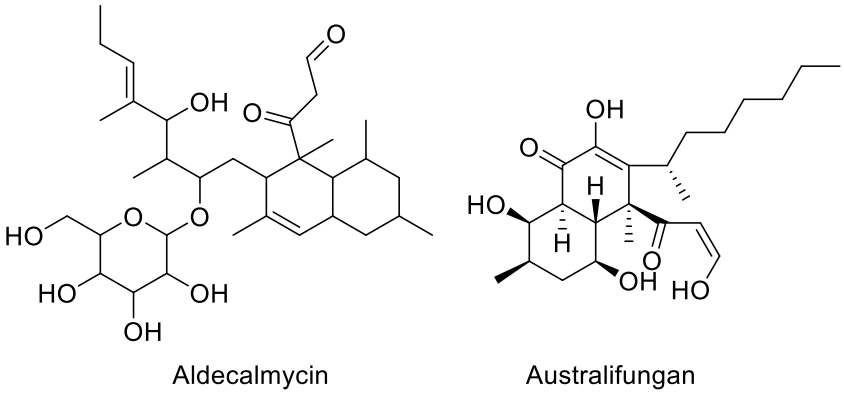


Figure 1.5 Chemical structures for Aldecalmycin & Australifungan

Tetramic acids are prevalent moieties in many antifungal and antibiotic natural products.[16] This pharmacophore, however, can have a variety of modes of action when destroying bacteria to ensure cell death cannot be avoided by a single defense mechanism. Although the bioactivity in Conipyridoin has not been thoroughly investigated to decipher pharmacophores, it is possible that the tetramic acid inhibits peptidoglycan synthesis or RNA synthesis due to mechanisms of action in similar natural products.[17] By inhibiting peptidoglycan and RNA syntheses in Gram-positive bacteria, cell walls cannot be produced making it susceptible to a variety of attacks from antibiotics and secondary metabolites from other bacteria.[18] Another characteristic this unique tetramic acid possesses is its ability to chelate metals. Metals such as copper (II), iron (III), nickel (II), and magnesium (II) ions can complex to the strongly acidic tetramic acid carbonyl systems, which could allow this drug to have a stronger binding affinity to bacterial receptors.[19] Evidence suggests that this ligand-receptor binding occurs in nature as isolation of metal-complexed tetramic-containing natural products has been reported.[20]

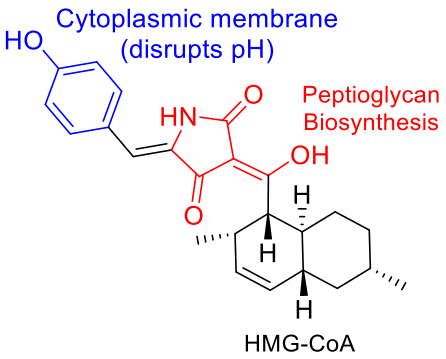
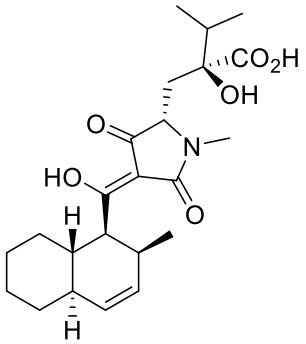


Figure 1.6 Potential targets for antifungal & antibiotic activity

Another potential pharmacophore is the aryl substituent attached to the tetramic acid. Based off virtual screenings and pharmacophore modeling studies by Sun et al for chalcone-derived natural products with antibiotic activity, it was determined that the aromatic alcohol's hydrogen bond accepting ability along with the aromatic ring were pharmacophore hits.[21] Though the mechanism of action needs more investigation, similarities can be drawn to the phenol in Conipyridoin E as a potential pharmacophore.

Conipyridoin is of particular interest due to presence of the tetramic acid moiety, which has been widely reported in antibacterial drugs, working in tandem with the unique decalin structure. A small family of these 3-decalinoyltetramic acids have been reviewed by Mo et al. and established the significant bioactivity in this class of natural products.[22] JBIR-22 is an additional antibiotic in this class that has been recently synthesized by Westwood et al.[23]



JBIR-22

Figure 1.7 Chemical structure for decalin and tetramic acid-containing JBIR-22.

The authors account for its antiretroviral drug activity as a protein-protein inhibitor (PPI) of CCR5, which is a GPCR responsible for managing T lymphocytes and macrophages.[24] By inhibiting these cells, it also allows HIV to be blocked from entering cells and thus prevents entry of viruses into human cells. While Conipyridoin has not yet been screened as a small molecule antiretroviral drug, it is interesting to note that other decalin-containing tetramic acids possess these characteristics.

A proposed biosynthesis of the Conipyridoin E decalin skeleton is initiated by a Type I polyketide synthase (PKS) mechanism. First, the initiation module starts the sequence with acetyl-CoA and is then elongated in a modular fashion with PKS by using either malonyl CoA or methyl malonyl CoA. Post-tailoring synthase modifications are crucial in manufacturing the necessary functional groups at the appropriate positions before attaining the Diels-Alder precursor. Next, a stereospecific IMDA reaction occurs after which amino acid residue L-Tyrosine is inserted and cyclized in a Dieckmann condensation manner. Finally, either a selective dehydrogenation occurs to install the final olefin, or a dehydration occurs once a hydroxy group is present at the benzylic position. These dehydrogenation reactions may occur through catalysis using enzymes from PKS

I, PKS II, or fatty acid synthase or even common oxidants with iron, copper, or hydrogen peroxide.[25,26]

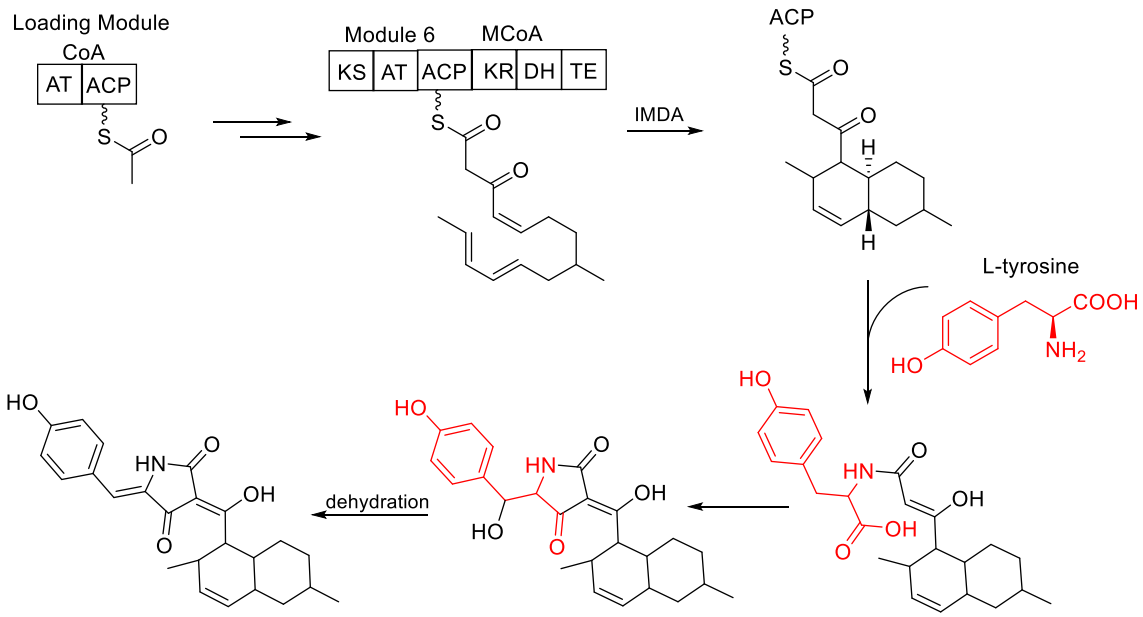


Figure 1.8 Proposed Biosynthesis of Conipyridoin E

Chapter 2: Retrosynthesis and Synthetic Plans

2.1 Development of Synthetic Strategies

Initial retrosynthetic plans led to two potential synthetic routes, each having its advantages and drawbacks. The first involved a more modular route in which Conipyridoin is disconnected into its three core moieties: the decalin, the tetramic acid, and the phenol, as seen in Figure 2.1. By splitting these components, it allows for three individual linear syntheses to be carried out before convergently integrating the products together. This allows the concern for yield to be alleviated as the longest linear synthesis would be the in the production of the decalin. The second involves a more biomimetic, albeit linear, approach in which racemic amino acid D-L tyrosine is coupled to an extended decalin system followed by intramolecular cyclization to give the tetramic acid. These retrosynthetic strategies diverge after the construction of the decalin, thus allowing concurrent investigations of both routes before fully committing to one.

The first method's integrations could be carried out using the Heck reaction with an aryl halide, as seen in Figure 2.1, and a lithiation reaction using carbon-3 as a nucleophile. The decalin can be synthesized from commercially available (S)-Citronellal, the tetramic acid is commercially available in a protected form as 4-methoxy- 1,5-dihydro-2*H*-pyrrol-2-one, and the *p*-bromophenol is easily obtainable. This has the potential to be the most efficient and effective way to synthesize Conipyridoin E, if protecting groups do not need to be implemented.

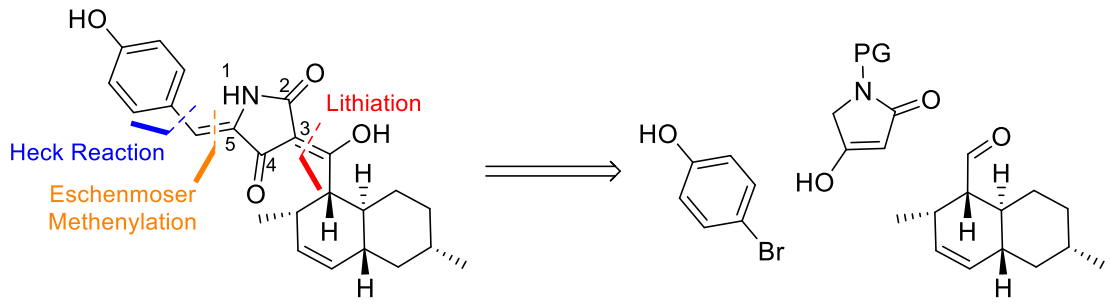


Figure 2.1 Modular Retrosynthetic Approach to Conipyridoin

Preliminary synthetic plans to produce the decalin involved first forming the precursor to the decalin using (S)-citronellal as the starting material. Through a series of Wittig reactions to elongate the carbon chain, this precursor would be formed with ease after which cyclization would occur through a Lewis acid-catalyzed intramolecular Diels-Alder reaction, which has been well established.[27] Then, using the carbonyl from the decalin as an electrophile, an alkylation reaction with a fully synthesized tetramic acid can take place. Next, the tetramic acid moiety would be subjected to Eschenmoser's salt to first undergo dimethyl aminomethylation at carbon-5 which would ultimately afford a terminal olefin after base-induced elimination. The final step in this synthesis would be to couple this product to yield a phenol. This could be accomplished via a palladium-catalyzed Heck reaction with *p*-bromophenol to finally afford Conipyridoin E.

The second route that could be explored may be most closely related to the proposed biosynthesis. After a thorough review of previously synthesized decalin and tetramic acid-containing natural products, an established precedent for synthesizing this natural product has been set for synthesizing similar decalins and tetramic acids in more biomimetic fashion.[23,28] In the proposed biosynthesis, L-tyrosine is introduced through aminolysis with coenzyme A being eliminated, once the decalin is constructed. A thioester could be a suitable replacement for coenzyme A.

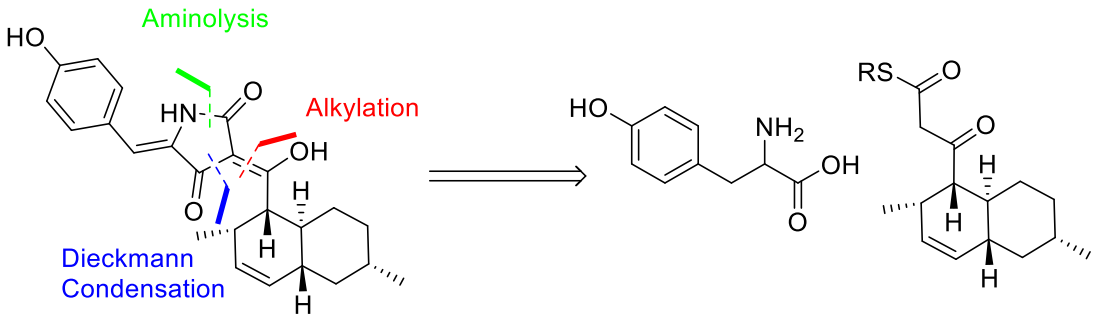


Figure 2.2 Biomimetic Retrosynthetic Approach towards Conipyridoin

Next, for the intramolecular Diels-Alder reaction to take place, a stereoselective Lewis acid would need to mediate a preferential cyclization to the endo configuration of the carbonyl. Subsequently, the appropriate starting material would need to be chosen to create this IMDA precursor in as few steps as possible.

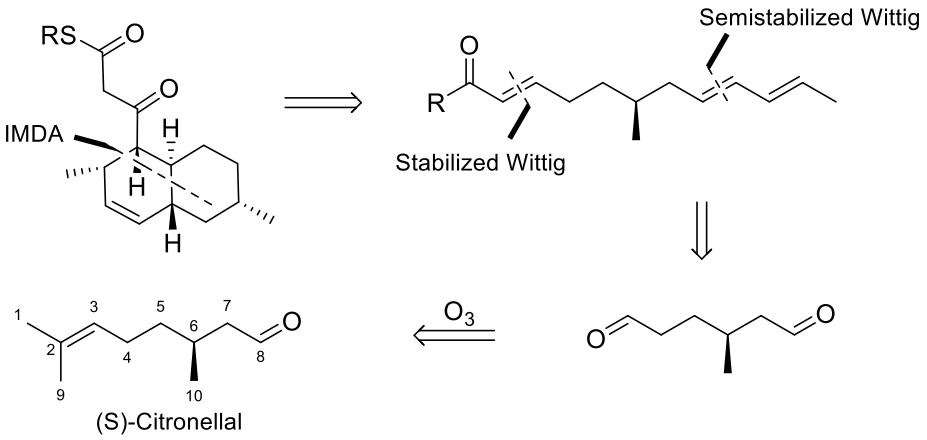


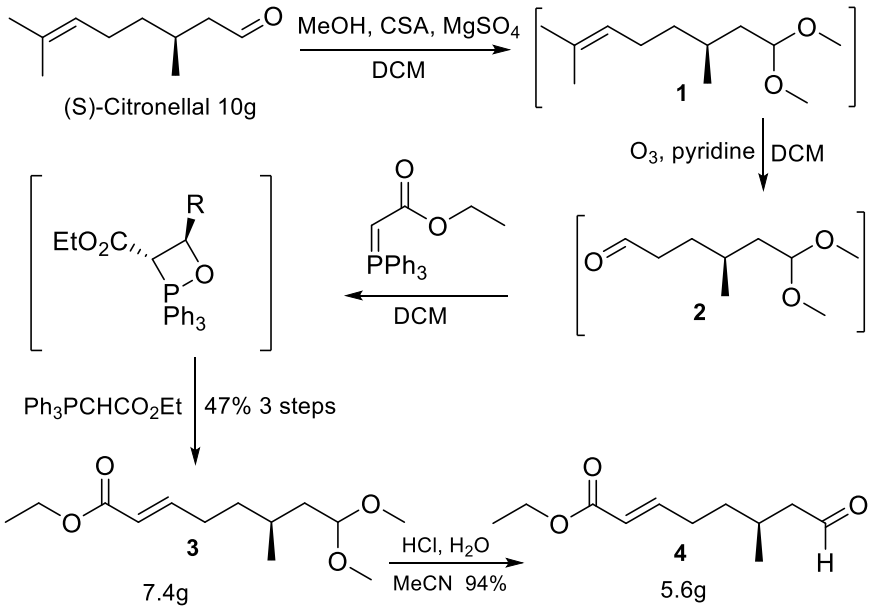
Figure 2.3 Retrosynthetic Approach to the Decalin

The structure of citronellal, a readily available aldehyde that contains one chiral methyl group, was considered as the appropriate starting material for the intramolecular Diels Alder reaction. Previous studies by the Theodorakis group and others have shown that the chiral methyl at carbon-6 can influence the preorganization of the Diels-Alder precursor in favor of one enantiomer (Figure 2.3).[29,30] Starting with the Diels-Alder precursor, there are two apparent bond

disconnections that should be made: the diene and the α-β unsaturated ester. Both disconnections can be accomplished through retro-olefination reactions. The last bond disconnection jumps from an aldehyde to a substituted alkene giving us commercially available (S)-Citronellal.

2.2 Concise Synthesis of Decalin Aldehyde

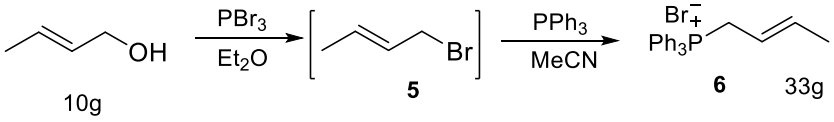
The first step in the synthesis involves a protection of the (S)-Citronellal through an acid-catalyzed reaction using methanol and $MgSO_4$ to drive the reaction forward with quantitative yield of dimethyl acetal **1**. The crude product can then be mixed with stoichiometric amounts of pyridine and subsequently bubbled with O_3 to reduce peroxide complexes in-situ to afford aldehyde **2**.[31] It should be noted that the characteristic blue color due to excess ozone that indicates the complete cleavage of the alkene has not been observed in this reaction. Dussault et al. theorized that the lack of blue color may be attributed to pyridine-derived byproducts reacting with ozone to produce a yellow-orange color.[31] To confirm that the ozonolysis had gone to completion, we ran a proton NMR of the crude material and observed no starting materials. Anticipating the byproducts of the reaction not interfering with subsequent reactions or yields led to crude product **2** being carried forward once again.



Scheme 2.1 Synthesis of α-β unsaturated ester from (S)-Citronellal as the starting material

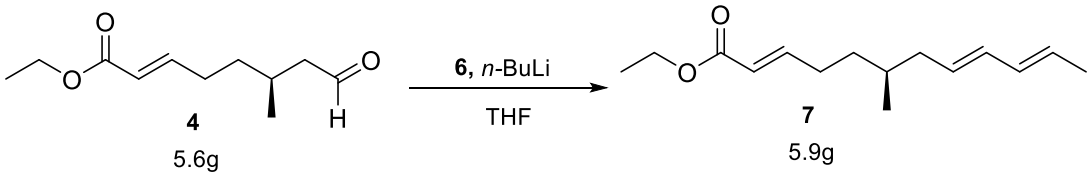
Crude aldehyde **2** can be subjected to commercially available, stabilized Wittig reagent

(Carbethoxymethylene)triphenylphosphorane at room temperature to afford α-β unsaturated ethyl ester **3** with >99:1 *E*: *Z* and a 46.7% yield over 3 steps. The significant *E* selective reaction can be attributed to the bulky triphenyl rings eclipsing the smaller aldehyde substituent, influencing an antiperiplanar attack of the carbanion from the semi-stabilized ylide to the carbonyl. In other words, the bulkier phenyl rings influence the formation of the *E* isomer once the 4-membered oxaphosphetane ring intermediate collapses, due to stable, electron withdrawing ylides predominantly forming *E* isomers, as seen in Scheme 2.1. Preparation for subsequent Wittig olefination can be accomplished after the deprotection of the dimethyl acetal is carried out under acidic conditions to afford aldehyde **4** with 94% yield.



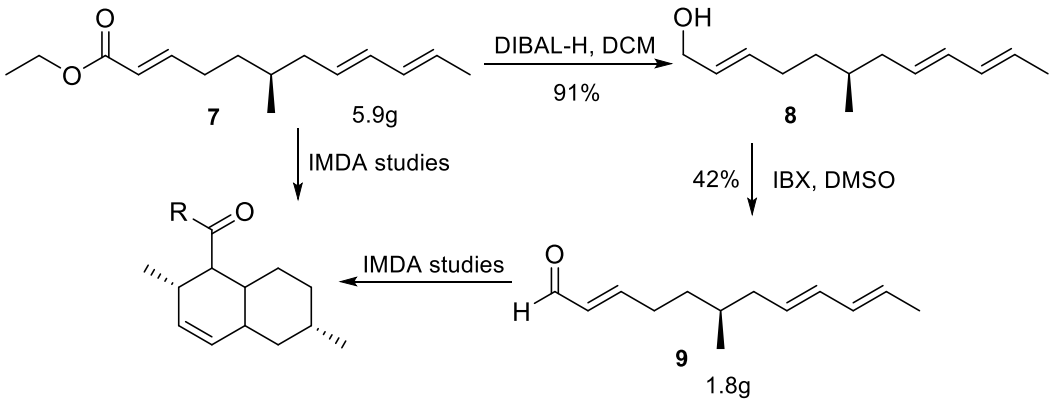
Scheme 2.2 Synthesis of Phosphonium salt **6**

Wittig salt **6** can be generated in 2 short steps by first brominating commercially available crotyl alcohol using PBr_3 to generate crotyl bromide **5**. ^{1}H-NMR from the crotyl alcohol vendor indicates ~19:1 *E:Z*, so further isomerization is not necessary. To avoid evaporation of this relatively volatile product, the diethyl ether was carefully distilled off under atmospheric pressure. The resulting liquid was then combined with triphenylphosphine in an argon-flushed sealed microwave vial and heated to an internal temperature of 82 ℃ to afford phosphonium salt **6** after triturating with ethyl acetate, as seen in Scheme 2.2.[32] This conversion resulted in a satisfactory 60% yield over two steps and was quickly carried forward to the subsequent olefination to avoid aldehyde decomposition.



Scheme 2.3 Semi-stabilized Wittig olefination to afford diene **7**

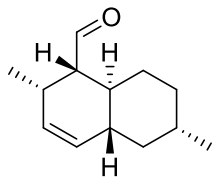
Using prepared phosphonium salt **6**, aldehyde **4** can be undergo olefination with a satisfactory isomeric ratio to afford diene **7** (3:1 *E:Z*), as determined by ^{1}H NMR. An effort to optimize the isomeric ratio to predominantly the *E* isomer was carried out by irradiating I_2 using a sunlamp as a source of visible light. However, it was observed that only a 4:1 *E:Z* ratio was seen even after about 4 hours of irradiation on a large scale. It was also noted that the sunlamp produced a considerable amount of heat and due to the fear of carrying out a non-stereoselective IMDA, irradiation was never left overnight, despite it potentially optimizing this *E:Z* ratio. Other methods of optimizing this isomerization are currently being carried out. With an α-β unsaturated ester as the dienophile and an isomerized diene, IMDA studies were carried out under various conditions, as seen in Table 2.1.



Scheme 2.4 Studies toward the IMDA precursor

Although most Lewis-acid-mediated IMDA reactions to form decalins implement an

aldehyde as their dienophile, it was thought that a more stable ester could potentially work while saving two overall steps in the synthesis.[33] However, to no avail, ester **7** was unable to be cyclized under a number of Lewis acids and conditions. The next clear step in this troubleshooting was to test out this cyclization with a more reactive dienophile such as the aldehyde. The ester was simply reduced to alcohol **8** and oxidized to aldehyde **9**, using 2 equivalents of diisobutylaluminum hydride (DIBAL-H) with a 91% yield and 2-iodoxybenzoic acid (IBX) with a surprisingly poor 42% yield, respectively. The poor yield in the oxidation step may be attributed to inadequate solubility in the required solvent of DMSO or decomposition of the IBX, resulting in poor conversion. To no surprise, an inseparable mixture of diastereomers for *trans*-decalin **10** was smoothly constructed using 2 equivalents of Lewis acid BF_3-Et_2O in DCM at -78℃ (85%, dr ~4:1).



10

Figure 2.4 Trans-decalin **10** synthesized through a Lewis acid-mediated IMDA

While Me_2AlCl was able to convert aldehyde **9** to IMDA product **10** with a higher yield and a significantly better diastereomeric ratio, as seen in Table 2.1 (91% and dr >30:1), this Lewis acid was unable to be used on the larger scale due to supply chain issues related to COVID-19. The reason Me_2AlCl has a better conversion and a more favorable diastereomeric ratio may be attributed to the aluminum species being able to chelate the carbonyl more strongly, causing an increase in electrophilicity. These changes can influence the IMDA reaction to take place more favorably than other tested Lewis acids.

Confirmation of the structure with the appropriate chiral centers for decalin **10a** can be first

be predicted based off the *endo* product and then confirmed through various 2D NMR experiments. By using 2D-COSY, correlations of protons through bonds can aid in assigning each proton to its corresponding chemical shift in ^{1}H-NMR. Next, a 2D-NOESY experiment can be carried out to examine how these protons interact with each other through space. Protons on opposite sides of the decalin face should not display cross-peaks on the spectrum, while protons on the same face should. Using these 2D NMRs in tandem, we can confirm the desired *endo* product **10a** to be the major diastereomer, as seen in Figure 2.5.

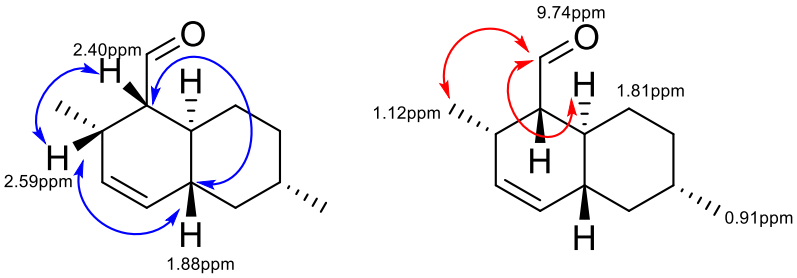


Figure 2.5 NOESY correlations to confirm the major diastereomer for decalin **10a**

Table 2.1 Intramolecular Diels-Alder reaction conditions with varying Lewis acids *All reactions slowly brought to room temperature after about 1 hour; r.t. = room temperature; n.r. = no reaction or <10% conversion; reaction outcomes evaluated by crude proton NMR

Functional Group	Lewis Acid	Equivalents	Solvent	Temperature*	Yield
ethyl ester	BF_3-Et_2O	2	DCM	25℃	decomposition
	BF_3-Et_2O	0.5	DCM	-78℃	n.r.
	BF_3-Et_2O	2	DCM	-78℃	n.r.
	BF_3-Et_2O	2	toluene	-78℃	n.r.
	Me_2AlCl	2	DCM	25℃	decomposition
	Me_2AlCl	2	DCM	-78℃	n.r.
	Me_2AlCl	2	toluene	-78℃	n.r.
	$ZnCl_2$	1	DCM	25℃	n.r.
	HFIP	excess	HFIP	-78℃	n.r.
	$AlCl_3$	0.5	DCM	-78℃	decomposition
	Et_2AlCl	2	DCM	-78℃	decomposition
aldehyde	**Me_2AlCl**	**2**	**DCM**	**-78℃**	**91%**
	Me_2AlCl	2	toluene	-78℃	27%
	BF_3-Et_2O	**2**	**DCM**	**-78℃**	**85%**
	BF_3-Et_2O	2	toluene	-78℃	11%

2.3 Studies Toward Tetramic Acid Synthesis

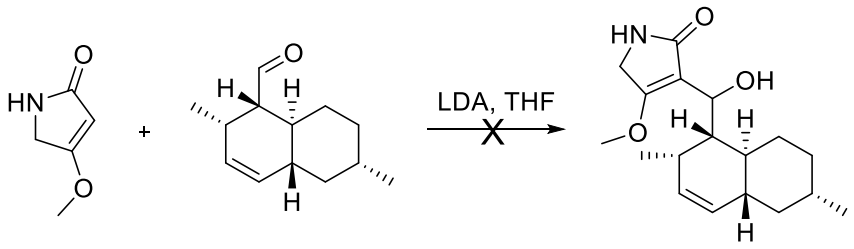
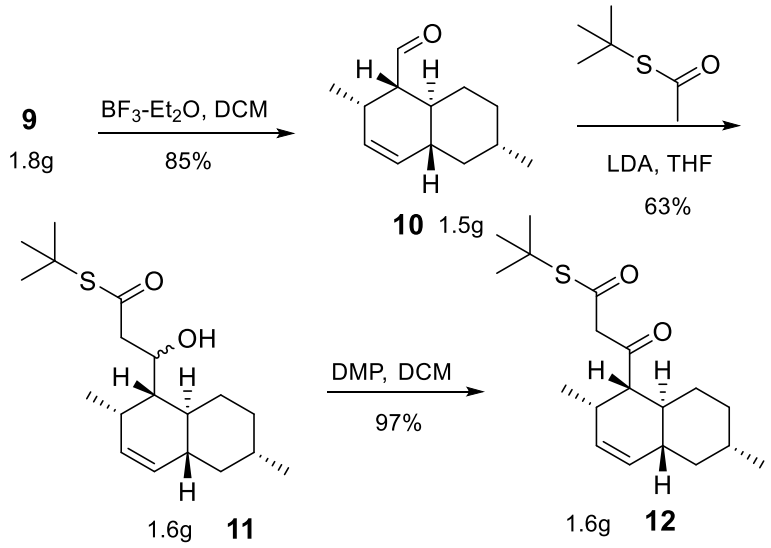


Figure 2.6 Attempted Coupling of decalin with 4-methoxy-1,5-dihydro-2H-pyrrol-2-one

Initial studies, as indicated above, aimed to target coupling 4-methoxy-1,5-dihydro-2H-pyrrol-2-one and the aldehyde from decalin **10**. Preliminary results of poor coupling yields and undesired byproducts of the decalin coupling with the commercially available pyrrol-2-one led to second thoughts on carrying out this route. It was noted that there were more drawbacks than originally anticipated compared to the first synthetic route: more protecting groups would need to be introduced to the tetramic acid leading to more steps, poor Z selectivity in the Heck reaction, and less of a biomimetic approach. It became clear that a more facile and bio-relevant synthesis would be superior. Thus, the second planned synthetic route was chosen to synthesize Conipyridoin.

The next step using the second synthetic route included elongating the mixture of diastereomers for decalin **10** through an aldol reaction using S-*tert*-butyl thioacetate with lithium diisopropylamide (LDA) to afford trivial mixture of diastereomers in β-hydroxy thioesters **11**. Evidence of a successful coupling included a foul odor coming from the crude and pure products, which is indicative of the well-known thioester smell. This of course can be characterized and confirmed by H-NMR, as seen in the Supporting Information. This mixture was then oxidized using Dess-Martin periodinane to afford β-keto thioesters **12** with a 61% yield over two steps, as seen in Scheme 2.5. Purifying diketone **12** presented some challenges as running the product

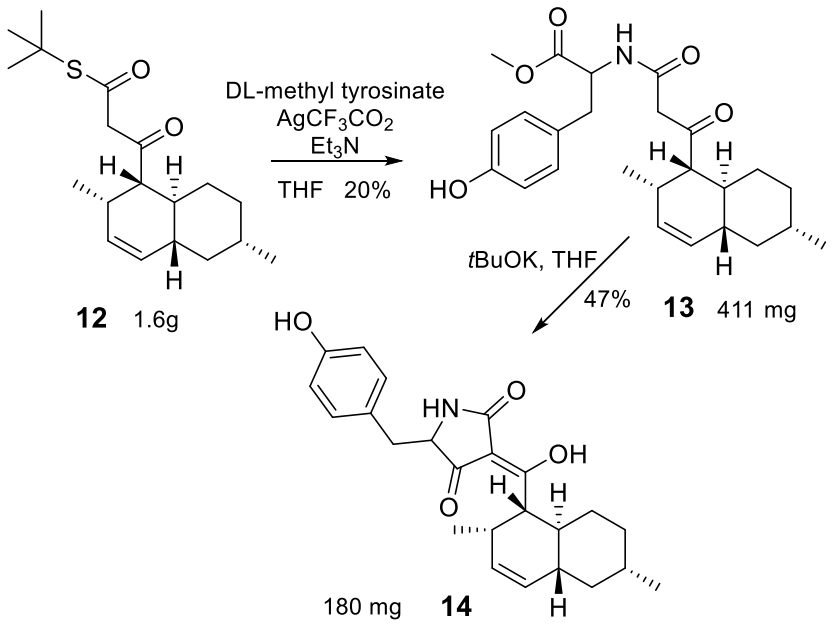
through a silica gel column at 100% hexanes two times was required to afford a pure inseparable mixture of keto/enol forms.



Scheme 2.5 Synthesis of β-keto thioester

The purpose of creating a β-keto thioester with this bulky substituent is twofold: to create a good leaving group during the amino acid coupling and to create the 1,3 diketone species in the tetramic acid with ease. It has been reported that this reaction is reproduceable with high yields by using silver trifluoroacetate as a necessary coupling agent as the sulfur and silver species chelate to form a favorable reaction to cleave the thioester bond via aminolysis[23]. It is worthy to note that Westwood et al. use a substituted amine during the coupling, meaning the reaction they are trying to achieve might be more preferential as a more nucleophilic amine is cleaving this bond. By subjecting **12** to methyl tyrosinate with silver trifluoroacetate under basic conditions, a yellow-orange-colored β-keto acid **13** was attained in 20% yield. The poor conversion obtained for this step may be attributed to an unsubstituted amine from the DL- methyl tyrosinate carrying out this aminolysis. A potential solution to increasing the yield and rate of this reaction is to protect this amine by using a large protecting group, such as an *ortho*-nitro benzyl group or a methyl

substituent. The former protecting group can aid in the penultimate cyclization step by the influencing s-*cis* isomer, bringing the nucleophile and electrophile closer in space. The latter can increase nucleophilicity by substituting the free amine with an electron donating group. Another possible reason an unacceptably low yield was attained is the poor solubility of β-keto acid **13** in solvents that cannot hydrogen bond with the product or low solubility in nonpolar solvents, such as THF which was the reaction solvent. **13** was observed to be only soluble in MeCN, acetone, DMSO, MeOH, and EtOH. This made purification by column chromatography extremely difficult even in a DCM-MeOH solvent system. Optimization of this reaction was carried out using a model system described in Figure 2.8 in which the yield of this amino acid coupling was increased to 88% with Et_3N at 65℃ without the use of the silver trifluoroacetate reagent.



Scheme 2.6 Insertion of amino acid and cyclization to afford Conipyridoin E analog

The strategy to cyclize 1,3 diketone **13** into a tetramic acid appears to be a straightforward Lacey-Dieckmann condensation, using the ester from the tyrosine derivative as the electrophile, which has been widely reported. 28,[35] **13** was subjected to potassium tert-butoxide in THF to give

Conipyridoin E analog **14** with poor yield of 47%. The presence of an insoluble amorphous solid in the reaction mixture was consistently observed indicating a less soluble, cyclized product may be forming. This amorphous solid has been reported in similar reactions involving the formation of a tetramic acid.[23,28,35] Evidence of this ring formation occurring can be confirmed by H-NMR with the disappearance of the methyl ester-protected amino acid peaks along with the disappearance of the α protons in the diketone motif. Similar purification issues that were previously discussed were dealt with in cyclized product **14** and exacerbated by TLC indicating the product consistently remained at the baseline at a range of DCM-MeOH eluent ratios. Struggles to cyclize this product have been reported.[36,37] In Kaul et al.'s efforts to cyclize their Hymenosetin product in a similar fashion, they ran into yield issues and messy side product.[36] Their solution to this problem was to fully substitute the amine through methylation before finally undergoing Dieckmann cyclization. This removes an acidic proton that may be in competition with the alpha proton from being deprotonated first.

Optimization of the cyclization step to form the tetramic acid was also carried out using model system intermediates. Due to reports indicating the poor conversion of **13** to **14**, this step also needed some further studies.[36–38] It was determined that substituting this amine would allow for free rotation about the nitrogen, compared to the previously locked *anti* rotomer which placed the alpha protons from the dicarbonyl species too far, both in space and through bonds, from the amino acid ester group to allow for cyclization. Substitution of this amine was executed in the hopes of influencing Lacey-Dieckmann condensation. Previously reported syntheses found the photolabile 2-nitrobenzyl group to be useful in this cyclization as it can be easily cleaved once cyclization has taken place.[38] Although cyclization attempts without a substituted nitrogen were successful to some extent, fully substituting the amine allowed for complete conversion of the

uncyclized product to the desired tetramic acid with potassium tert-butoxide in high yields.

The final step in this total synthesis includes a seemingly simple dehydrogenation reaction at the benzylic position to afford a *Z* alkene and a hyper-conjugated pi system. Pi bonds can be delocalized from the phenol ring and can push down into the tetramic acid amide or enol through resonance to form a stable product. However, the fear of attaining a benzoquinone through similar dehydrogenation methods was kept in mind as it also possesses this conjugated system. First, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in boiling DCM with catalytic amounts of H_2O was attempted to dehydrogenate this benzylic position but was unsuccessful[39]. Pattenden and others synthesized a large library of tetramic acid analogs and maleimides to examine chemo and regioselectivity within these moieties. These experiments were crucial in understanding how the tetramic acid structure was going to be manipulated in the initial stages of the synthesis, as they explored the reactive sites by adding several substituents and protecting groups to the pyrrol-2-(5*H*)-ones. Changing solvents to benzene, methanol, or dioxane surprisingly led to decomposition of the starting material. It was believed that incompatibility of DDQ with the requisite solvents for **14** led to minimal conversion.

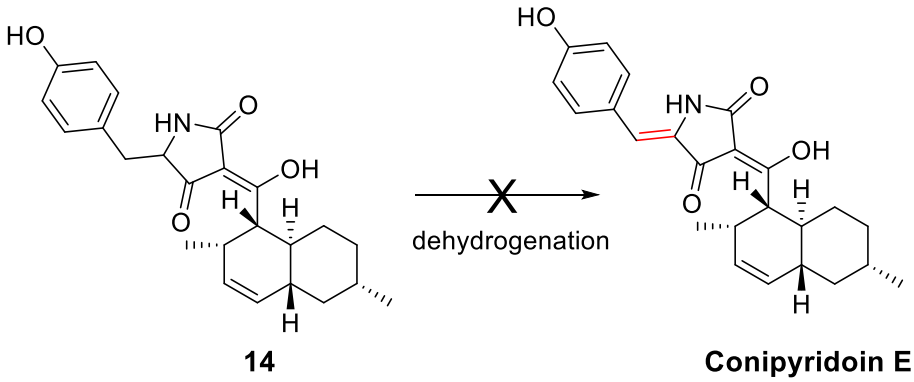


Figure 2.7 Failed Dehydrogenation attempts on **14**

Next, copper (II) acetate was used in stoichiometric amounts in MeCN as Xie et al. have

demonstrated dehydrogenation reactions at the benzylic position on a small library of amino acids.[40] Unfortunately, they were unable to dehydrogenate a similar amino acid structure with a phenol and similar results were observed when experiments were carried out.

As seen in Figure 2.8, a model system was constructed to test the applicability of different oxidants on the Conipyridoin derivative. Using cyclohexanecarboxaldehyde as the starting material, **15** was synthesized in 4 short steps in a comparable manner to Schemes 2.5 and 2.6, using S-*tert*-Butyl thioacetate to elongate the carbonyl system and subsequent insertion and cyclization of ester-protected amino acid tyrosine. It was on this model system that many of these dehydrogenation experiments were performed.

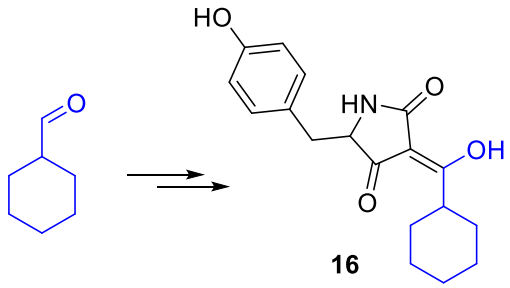


Figure 2.8 Construction of Model System from cyclohexanecarboxaldehyde as the starting material

General procedure for model system studies: To a 1-dram glass vial was added 15mgs of **15** in 0.5mL of solvent along 1 equivalent of the appropriate reagent. The vial was then sparged with Argon, sealed with Teflon tape, and stirred. Reactions were monitored by TLC.

Table 2.2 Model system studies on the dehydrogenation of **15**

Reagent	Solvent	Reaction Time	Temperature	Yield
DDQ	DCM	16 hrs	reflux	decomposition
	DCM	8 hrs	reflux	n.r.
	DCM	16 hrs	r.t.	n.r.
	MeCN	3 hrs	reflux	n.r.
	MeOH	16 hrs	reflux	decomposition
	Benzene	16 hrs	reflux	n.r.
	Dioxane	16 hrs	reflux	n.r.
Cu(OAc)2	MeCN	16 hrs	reflux	decomposition
	MeCN	4 hrs	reflux	decomposition
	MeCN	2 hrs	reflux	n.r.
	MeOH	16 hrs	reflux	decomposition
	MeOH	4 hrs	reflux	n.r.
	Acetone	2 hrs	reflux	n.r.
CAN	MeCN	8 hrs	r.t.	n.r.
Br_2, HBr	MeCN	0.5 hrs	reflux	decomposition
Et_3N, HBr	MeCN	3 hrs	r.t.	n.r.
AIBN, NBS	MeCN	4 hrs	hv	n.r.

Since metal-catalyzed dehydrogenations failed to afford Conipyridoin E, a different approach of α-halogenation followed by subsequent β-elimination at the benzylic position was explored. Alpha halogenation has been well established by using bromine as an electrophile and under acidic conditions. However, bromination was unable to be achieved under a variety of conditions as monitored by ^{1}H NMR. Thus, olefin generation through elimination was not achieved, leaving analog **14** of Conipyridoin E to be left for future studies.

Future Directions

Conipyridoin analog **14** may exhibit some antifungal and antibiotic activity as its dehydrogenated counterpart, Conipyridoin E, has been shown to be a potent inhibitor against the growth of *Staphylococcus aureus*, MRSA, *Bacillus subtilis* with MIC_{50} values reaching 0.97μM. Further biological studies need to be carried out on this analog in order for it to be deemed a viable drug to synthesize to combat different bacteria and fungi. Although Yin and Liu theorize the mode of action could be an inhibitor of chitin biosynthesis, the exact mechanism is still unknown. The discovery of the mode of action could significantly aid in optimization of structure-activity relationships as more efficacious antibiotics could be modified and synthesized. In order for these experiments to be carried out, one major issue needs to be resolved before carrying out biological studies, the final dehydrogenation at the benzylic position. This issue of the final dehydrogenation can be resolved by exploring different metal-based oxidants or optimizing alpha halogenation-elimination to avoid decomposition. Perhaps this reaction could also be executed prior to coupling with the thioester where there could be stronger regio and chemoselectivity. Another idea that has not been explored by groups is to use biological dehydrogenases to carry out this reaction enzymatically. This may allow for a much more facile and biomimetic approach to synthesizing this natural product.

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