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Sustainable chemistry, synthesis and structure-activity relationship studies of biologically important small molecules

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Sustainable chemistry, synthesis and structure-activity relationship studies of biologically important small molecules

by

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ABSTRACT

With growing concerns for the environment, dwindling amounts of fossil fuels available for worldwide consumption and more resistant strains of diseases and infections becoming a reality, organic chemistry plays a vital role in the improvement and sustainability of modern society. Industrial chemicals from renewable sources has become an important area of research in recent years, while the synthesis and study of biologically active small molecules and their analogues leads to advancements which can help improve overall human health.

In this dissertation, we explore methods to create important industrial molecules from biorenewable sources, extend a novel cyclization to make heterocyclic compounds, and develop a new route towards a natural product that is active against tumor cells which resist current cancer treatments. Chapter 1 discusses the synthesis of an important industrial compound, terephthalic acid, from malic acid, which can be obtained from biorenewable feedstocks. This work was performed in collaboration with chemical engineers at the Center for Biorenewable Chemicals. Chapter 2 describes the extension of the Kraus indole synthesis to biologically important natural products such as isocryptolepine and the indolo[2,1-*a*]isoquinoline series. Chapter 3 discusses advances made towards the total synthesis of a marine alkaloid, oroidin, including a novel cyclization to install the important 2-aminoimidazole portion of the molecule.

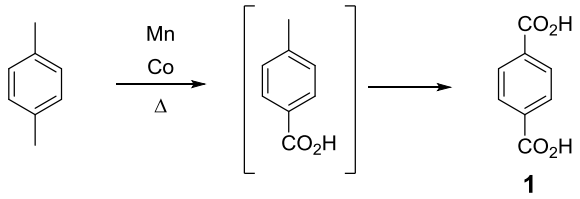
CHAPTER 1

EVALUATION OF A BIORENEWABLE ROUTE TO AROMATICS FROM PYRONES

Introduction

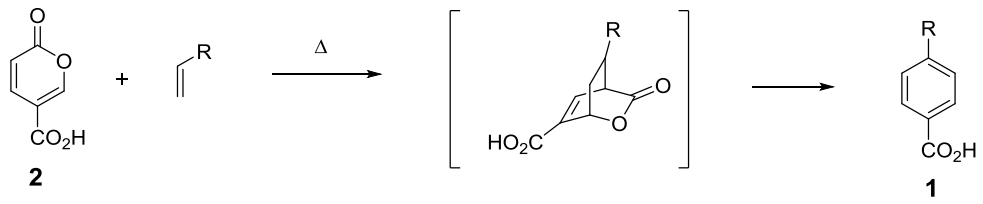
As the availability of fossil fuels decreases, growing worldwide energy demands necessitate the development of a sustainable economy. New, cost-effective methods to create commodity chemicals from renewable feedstocks are gaining importance. Some biobased routes to industrially significant compounds, such as 1,3-propanediol, have been reported.[1] Unfortunately, there are few reported preparations of aromatic chemicals such as terephthalic acid.[2]

Terephthalic acid is an important commodity chemical produced from petroleum feedstocks.[3] Terephthalic acid (**1**) and its dimethyl ester, dimethyl terephthalate are used in the preparation of polyethylene terephthalate (PET), a thermoplastic polymer used in beverage and food containers and in fabrics and in polytrimethylene terephthalate, a material found in carpets and upholstery. Traditionally, it is synthesized by the stepwise oxidation of *para*-xylene with molecular oxygen in acetic acid using a catalyst consisting of cobalt, manganese and bromine (Scheme 1). The reaction is conducted at elevated temperatures in the range of 175 – 225 °C and pressures reaching 3000 kPa.[4] This oxidation process occurs in near quantitative yields, necessitating an alternative route to give a high conversion as well.



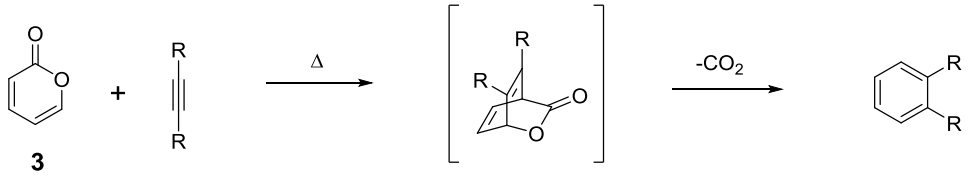
Scheme 1. Oxidation of *p*-xylene to **1**

In 2009, global terephthalic acid production was greater than 50 million tons.[5] Therefore, an efficient, green route to terephthalic acid could have a large impact. Green chemistry is broadly defined as the development of chemical processes that control the generation of hazardous materials.[6] In 1998, the *12 Principles of Green Chemistry* was published by Paul Anastas and John Warner.[7] These principles helped define how to improve chemical processes, especially at the industrial scale, to be better for the environment. As part of a collaborative effort to produce biorenewable chemicals using enzyme catalysis followed by chemical catalysis,[8] we were interested in developing a synthesis of terephthalic acid following green principles. Of the most importance to us were the use of renewable feedstocks and the use of catalysts instead of stoichiometric reagents. Our goal was to use a Diels-Alder reaction of a known 2-pyrone, coumalic acid (**2**), with a suitable dienophile to give terephthalic acid (R = CO_2H, **1**) without the need for oxidation (Scheme 2). This would eliminate the need for transition metal catalysts in the oxidation step of the current industrial preparation of **1**. In order for this route to be effective, a renewable route to coumalic acid would need to be developed, this will be discussed later.



Scheme 2. Proposed synthesis of **1**

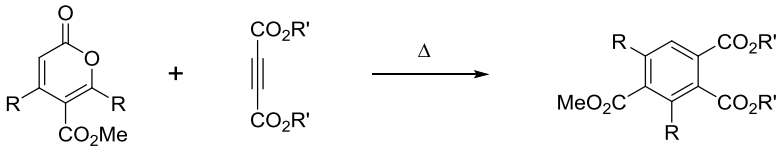
The Diels-Alder reaction of 2-pyrone (**3**) with symmetrical and unsymmetrical alkenes and alkynes is well known in the literature.[9] Not surprisingly, Diels and Alder published the first [4+2] cycloaddition of a 2-pyrone and appropriate dienophile in 1931.[10] An important result was discovered in 1937, when Alder and Ricket showed that by using an acetylenic dienophile, the intermediate oxabicyclo[2.2.2]ocetene would spontaneously lose CO_2 to give aromatic products (Scheme 3).[11] Along the pathway to terephthalic acid, we sought to employ coumalic acid or possibly coumalate esters. The Diels-Alder sequence to aromatic products also has good literature precedent when coumalates are used as the diene.[9]



Scheme 3. Aromatic compounds from **3** and acetylenes

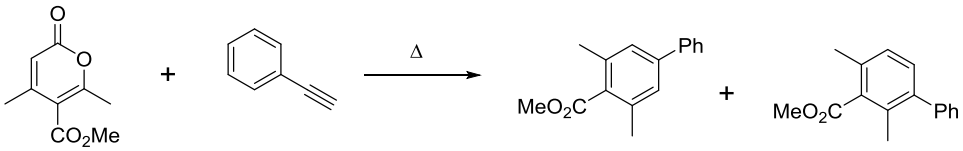
When an acetylenic dienophile is employed, the bicyclic intermediate is too unstable to be isolated and rapidly loses CO_2 to give aromatic products. If the alkyne is symmetrical, only one possible product is possible. Ziegler and coworkers reacted many symmetrical alkynes with 2-pyrones.[12] The electronics of the diene and dienophile play

an important role in the yield of this reaction sequence. When an electron-poor dienophile is matched with an electron-rich diene, better yields are generally achieved. When methyl coumalate (**4a**) was heated with acetylene **5a**, the triester **6a** was formed in 48% yield. When a more electron-rich pyrone, **4b**, was used with electron-poor acetylene **5b**, the product **6b** was achieved in 96% yield (Scheme 4).



Scheme 4. Aromatic compounds from coumalates and symmetrical acetylenes

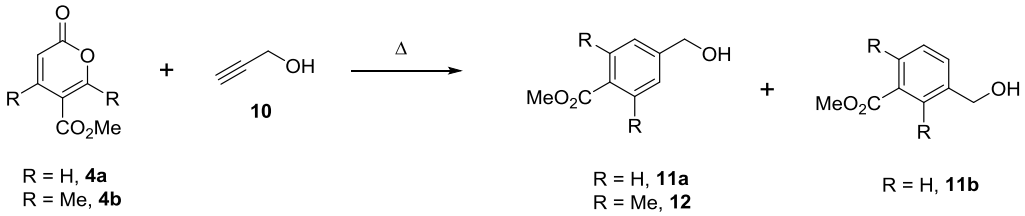
Unsymmetrical acetylenes have also been successful for the Diels-Alder reaction with 2-pyrones, although they can give two different regioisomers as products. When **4b** is reacted with phenylacetylene (**7**) only modest regioselectivity is observed.[13] The product where the ethyl ester is *para* to the phenyl substituent (**8**) is favored 4 to 1 over the *meta* isomer (**9**, Scheme 5).



Scheme 5. Aromatic products from coumalates and unsymmetrical acetylenes

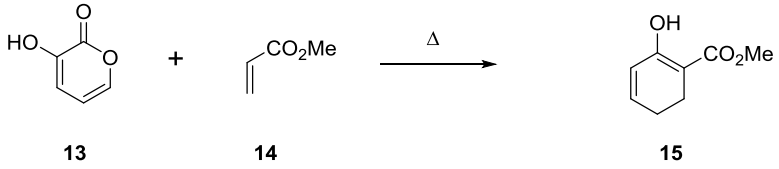
Leonard and coworkers have shown that the cycloaddition with coumalates and alkynes can also follow an inverse-electron-demand Diels-Alder pathway.[14] When electron-rich propargyl alcohol (**10**) is reacted with methyl coumalate (**4a**), a 2.3 : 1

mixture of the *para* (**11a**) and *meta* (**11b**) disubstituted products are obtained in 71% overall yield. If a more electron-rich pyrone, methyl isodehydroacetate (**4b**) is employed with **10**, longer reaction times are needed and a lower yield is observed, although only **12** is isolated (Scheme 6).



Scheme 6. Reaction of coumalates with **10**

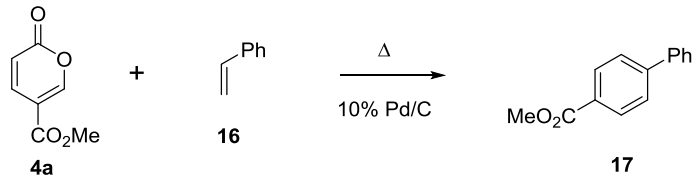
The natural progression of this chemistry is to expand to using alkenes as the dienophile. In this case, after decarboxylation, the formed cyclohexane ring is one oxidation short of aromaticity. In 1975, Corey proved that this dihydrobenzene can be isolated as the major product.[15] When 3-hydroxy-2-pyrone (**13**) was reacted with methyl acrylate (**14**), the dihydro compound **15** was obtained in 56% yield (Scheme 7). It was reasoned that the strongly electron-donating hydroxyl group helps direct the Diels-Alder reaction to give the *ortho* disubstituted product.



Scheme 7. Isolation of dihydro product (**15**) from methyl acrylate (**14**)

In an attempt to produce aromatic products in one step from coumalates and alkenes, Matsushita and coworkers used palladium on activated carbon (Pd/C) to

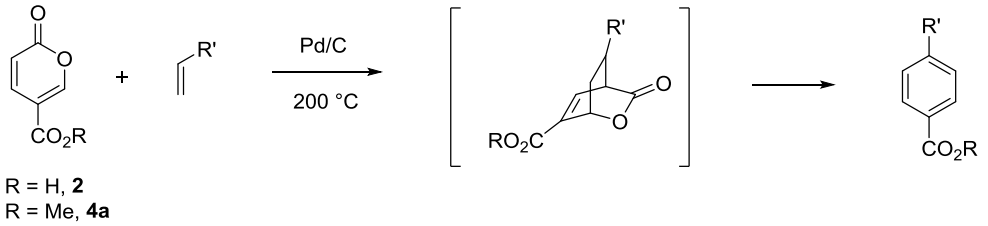
dehydrogenate the dihydro intermediate *in situ*.[16] When methyl coumalate is used as the diene with alkene dienophiles, the intermediate cyclohexadiene is prone to participating in subsequent cycloadditions to give bicyclo[2.2.2]oct-2-ene derivatives. The use of Pd/C alleviates that problem and allows aromatics to be synthesized directly from 2-pyrones and alkenes. Aromatic alkenes have also been shown to be successful dienophiles. The reaction of methyl coumalate (**4a**) with styrene (**16**) in refluxing *m*-xylene with 2.5 weight percent of 10% Pd/C gave the *para*-disubstituted product (**17**) in 81% yield (Scheme 8). When methyl groups were added to the 4 and 6 positions of the pyrone, comparable yields were achieved although higher temperatures were required (200 °C).



Scheme 8. Direct formation of aromatics from styrene and **4a**

Recently, Kraus and Riley developed a method to prepare disubstituted aromatic compounds from methyl coumalate or coumalic acid and unactivated terminal alkenes, otherwise known as alpha-olefins.[17] A similar route was followed, dehydrogenation of the bicyclic intermediate with Pd/C to give the aromatic products after loss of CO_2. As is the case with other unsymmetrical dienophiles, both the *meta* and *para* disubstituted products can form. Surprisingly, when 1-decene (R' = $CH_2(CH_2)_6CH_3$) was reacted with **4a**, only the *para* product was formed (Scheme 9). Although the reason for the observed regioselectivity is not known, it has been hypothesized that steric interactions could play

a role, as well as selective oxidation by Pd/C of only the intermediate leading to the desired product. Other long-chain alpha-olefins as well as allyl benzene and allyl ethers gave good yields (51-85%) with methyl coumalate and coumalic acid, which both showed greater than 99% selectivity. The 4-alkyl benzoate products are known to be able to be able to be oxidized to terephthalic acid or its mono ester.[18]



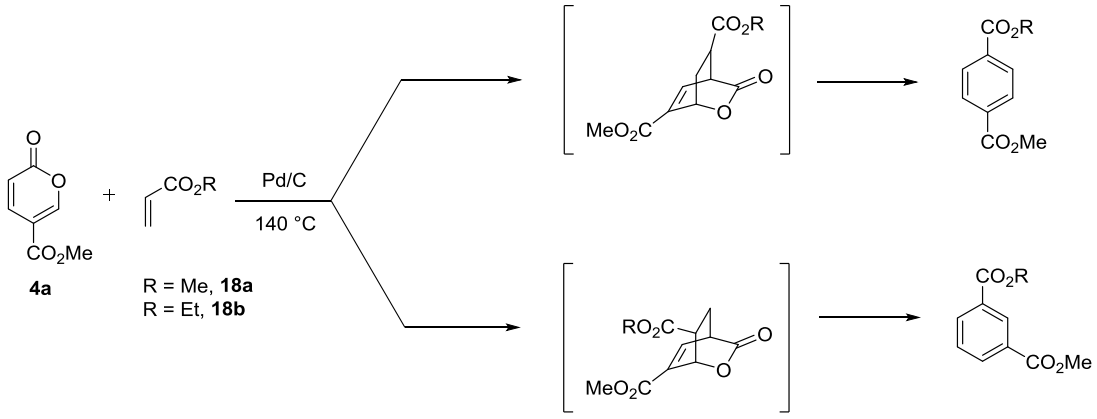
Scheme 9. Reaction of alpha-olefins with **2** and **4a**

Results and Discussion

Literature reports have shown that cycloaddition reactions with coumalates and a wide variety of alkenes or alkynes are possible *via* either a traditional or inverse-electron-demand process. To reach our goal of terephthalic acid or dimethyl terephthalate production from either methyl coumalate or coumalic acid, we envisaged a reaction with activated alkenes or alkynes bearing an ester group to give the terepthalate derivative.[19] If an acrylate or acrylate equivalent could be used, the oxidation of the alkyl group to the final product could be avoided. For the initial scope of this study, methyl coumalate is generally used due to its increased solubility in toluene and its lowered solubility in water compared to coumalic acid.

The reaction of activated alkenes with methyl coumalate gave bicyclic lactones that are oxidized *in situ* by a catalytic amount of Pd/C to the aromatic products. An

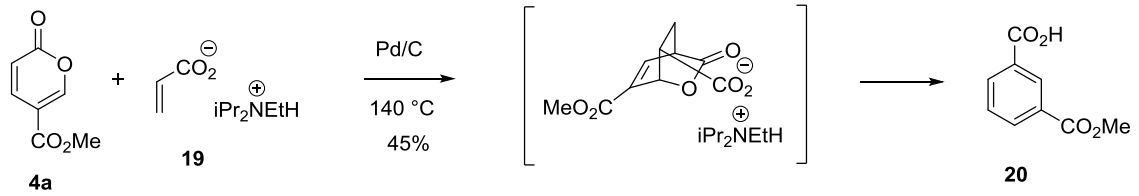
advantage to using activated alkenes is the ability to conduct the reactions at lower temperatures in the range of 140 to 160 °C instead of 200 °C when alpha-olefins were employed. Initially, methyl (**18a**) and ethyl acrylate (**18b**) were reacted with methyl coumalate (**4a**) under our standard conditions (Scheme 10). Unfortunately, these reactions displayed little regioselectivity. The ratio of 1,4- to 1,3-disubstituted products was about 3:1 in both cases, while the yields were 25% and 38% for methyl and ethyl acrylate, respectively. The low yields could be due to poor matching of the electronics of the diene and dienophile. A more electron-rich 2-pyrone would be expected to give better yields when reacted with acrylates.[9] There have been reports where the potassium salts of isophthalic acid and phthalic acid were converted into terephthalic acid, although the reaction was run using cadmium salts and temperatures over 400 °C.[20, 21]



Scheme 10. Diels-Alder reaction with activated alkenes

Analysis of the proposed intermediates in Scheme 10 show that the two esters are spatially closer in the intermediate leading to the 1,3-disubstituted product than the 1,4-product. By increasing the steric size of the ester, it could be possible to improve on the regioselectivity of the *para* product. Our attempt to realize this goal was to use the much

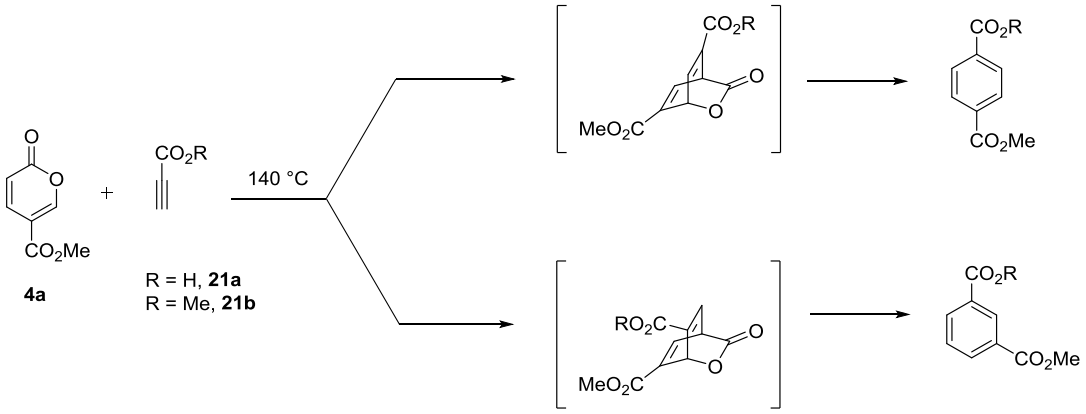
larger N,N-diisopropylethylamine salt of acrylic acid (**19**). When reacted with **4a**, this salt gave the mono ester of isophthalic acid (**20**) as the only isolated aromatic product in 45% yield. This is still an interesting result even though the opposite regiochemistry of what was expected was observed. Although we do not know enough about the mechanism of this transformation to give a definitive explanation for the selectivity, it could be hypothesized that the reaction proceeds through the exo transition state shown in Scheme 11 to minimize non-bonded interactions. Using the salts of coumalic acid and acrylic acid could be envisioned to improve selectivity. Unfortunately, these compounds showed limited solubility in organic solvents such as toluene or ethyl acetate. Attempts to use water as the solvent gave complex mixtures containing no aromatic compounds.



Scheme 11. Diels-Alder reaction with an amine salt of acrylic acid

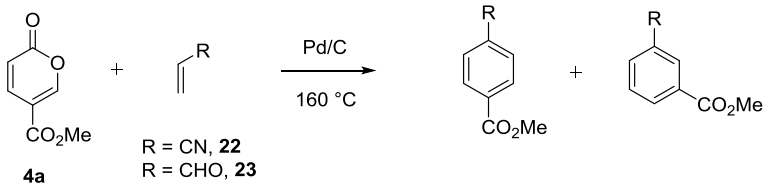
As discussed previously, when acetylenic dienophiles are used, the final oxidation step, and therefore Pd/C, was not necessary. We also employed propiolic acid (**21a**) and methyl propiolate (**21b**) for our Diels-Alder processes. It was believed that the additional double bond in the bicyclic intermediate would enforce the proximity of the two esters leading to the 1,3-product (Scheme 12). The steric interactions would disfavor the formation of this intermediate. Surprisingly, a 1:1 mixture of regioisomers was the outcome with either propiolate. Propiolic acid gave a 64% overall yield of the mixture of products, while the yield for methyl propiolate was 58%. Attempts to use the

tert-butyl ester to increase steric demand led to a mixture of products involving loss of the *tert*-butyl group. Since salts of propiolic acid have been reported to decompose under thermal conditions,[22] these reactions were not attempted.



Scheme 12. Diels-Alder reactions of propiolates

In an attempt to understand the lack of selectivity for these Diels-Alder reactions with activated dienophiles, we looked to other commercially available compounds such as acrylonitrile and acrolein. As shown in Scheme 13, the reaction of **4a** with acrylonitrile (**22**) showed better regiochemical control than the propiolates. A mixture of the isomers was obtained in 60% yield with a 1.7:1 ratio favoring the 1,4-product. Our best result came with the reaction of acrolein (**23**), which gave a 4.3:1 ratio in 47% overall yield of the purified isomers. This result is important because the conversion of 4-formyl benzoates into terephthalates has been reported by Borhan.[23]



Scheme 13. Diels-Alder reactions with acrylonitrile and acrolein

In attempting to understand the regiochemical outcome of the Diels-Alder reaction of activated dienophiles with methyl coumalate we explored the influence of steric effects on the distribution of *meta* and *para* products. It quickly became apparent that electronic effects also must play a significant role in determining the outcome. In order to better understand this role and possibly help predict future experiments, we sought the expertise of Dr. Arthur Winter's group at Iowa State University to calculate transition state energies by performing density functional theory (DFT) calculations.

All DFT calculations were performed using the Gaussian09 software suite[24] employing the B3LYP functional, which consists of the Becke hybrid 3-parameter exchange functional with the correlation functional of Lee, Yang, and Parr.[25] The 3-21G basis set was employed to identify the lowest energy product rotamers, and the 6-31+G(d,p) basis set was used to calculate the geometries and energies of the starting materials, products, and transition states. In all cases for starting materials and products, optimized geometries were found to have zero imaginary frequencies, indicating that the structures represent local minima on the potential energy surfaces. Energy corrections for the zero-point vibrational energy were added unscaled. Transition states for forming these products were located using the Quasi-Newton Synchronous Transit method (QST3). Of note, transition state barriers for related Diels-Alder reactions with this level of theory have been shown to give good agreement with experiment.[26] Computed transition state structures were all found to have one imaginary frequency that connected the starting materials and the product.

The calculations were performed for the reactions with methyl acrylate, acrylonitrile, acrolein, and methyl propiolate as dienophiles. The basis for the calculation was to find the lowest energy transition states which lead to the *meta* and *para* isomers, respectively. Comparison of these energies should correspond to the experimentally observed results. There are different rotamers possible for each transition state, some of which are shown in Figure 1 for methyl acrylate.

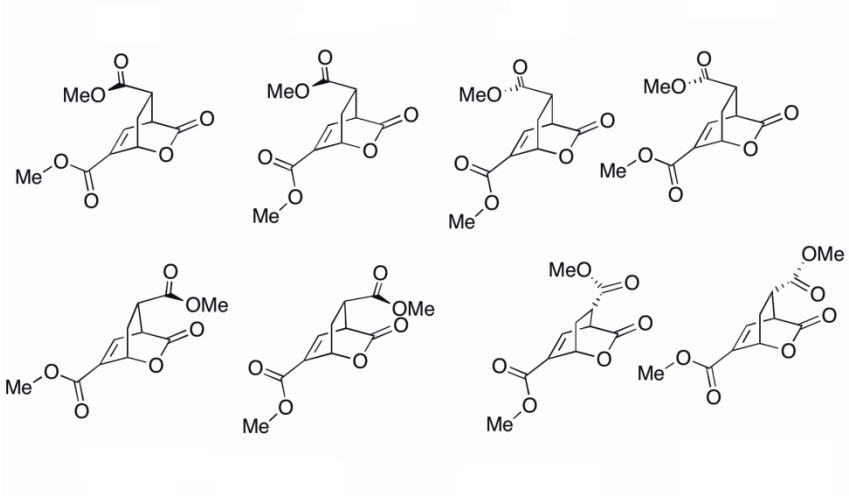


Figure 1. Representation of the different stereoisomers and rotamers

The lowest-energy rotamer for each isomer for the Diels-Alder products was determined by optimizing each structure at the B3LYP/3-21G level of theory. The lowest energy rotamer for each stereoisomer computed at this level of theory was used as the product for transition state searches. The geometries and energies of the starting materials, product and transition states for each isomer were then computed at the B3LYP/6-31+G(d,p) level of theory. The transition states are shown in Figure 2.

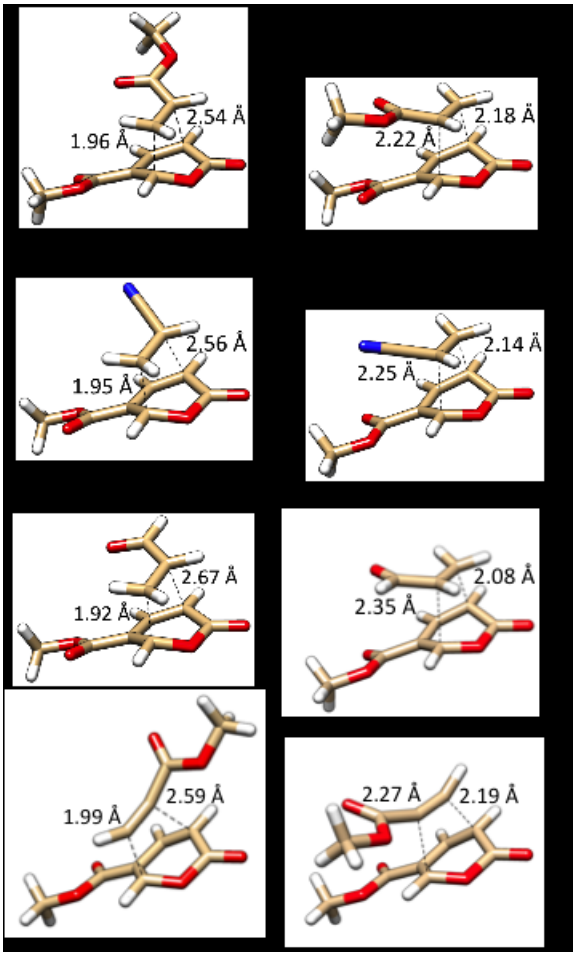
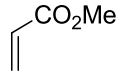
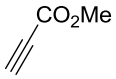


Figure 2. Computed lowest-energy transition states

The computations suggest nearly degenerate transition states leading to the *meta* and *para* bicyclic adducts for methyl acrylate and methyl propiolate, which would be expected to lead to nearly equal product mixtures (Table 1). This is found experimentally with methyl propiolate, although methyl acrylate leads to a larger experimental ratio of *para* over *meta* (3:1). The transition state leading to the *para* isomer is computed to be lower for the acrylonitrile and acrolein dienophiles by 1.52 and 2.20 kcal/mol, respectively, which would be expected to yield product ratios of ~6:1 and 13:1 of the *para* product over *meta* product. The trend in the computed ratios is in

reasonable agreement with the experimentally observed ratios of 1.7:1 and 4.3:1 favoring the *para* isomer, respectively.

Table 1. Computed energies and differences between *meta* and *para* transition states

Dienophile	**$\Delta\Delta H^{\ddagger}$ (kcal/mol)[a]**	**Computed para/meta ratio[b]**	**$\Delta H^{\ddagger}$ *para* (kcal/mol)**	**$\Delta H^{\ddagger}$ *meta* (kcal/mol)**
	-0.07	0.9	28.10	28.03
	1.52	5.8	29.09	30.60
	2.20	12.9	25.50	27.70
	0.21	1.3	29.53	29.74

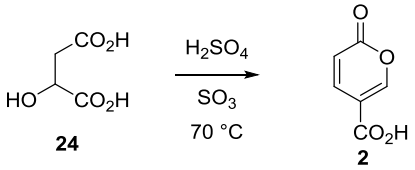
a. $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{meta} - \Delta H^{\ddagger}_{para}$

b. para/meta ratio = e^(($\Delta H^{\ddagger}_{meta} - \Delta H^{\ddagger}_{para}$)/RT)

An important result is that it appears there is no evidence of steric effects being important to the regiochemical outcome. A search of the literature shows the regiochemistry of Diels-Alder reactions can normally be predicted using frontier molecular orbital theory.[27] This approach, however, predicts the *meta* isomer should be

favored. This leads us to believe that a secondary orbital interaction may be the reason why the opposite, *para* isomer is experimentally and computationally favored.[28] We attribute this unexpected regioselectivity to a secondary orbital interaction between the pyrone oxygen contribution to the HOMO and LUMO on the dienophile that favors the transition state leading to the *para* product. This interaction may be strong enough to invert the natural electronic preference for these reactions.

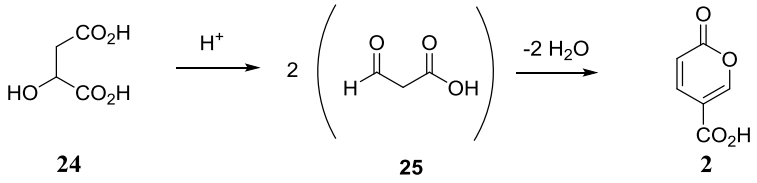
Although many advances have been made towards producing terephthalic acid derivatives from methyl coumalate, the coumalates are still compounds derived from petroleum sources. In order for this chemistry to become relevant and a possible replacement for current technologies, coumalic acid, or its esters must be able to be derived from a renewable source. After reviewing the literature, the solution to this problem became evident. In 1891, von Pechmann reported the transformation of malic acid (**24**) into coumalic acid (**2**) by the action of fuming sulfuric acid at steam bath temperatures (Scheme 14).[29] Surprisingly, this seems to be the only reported preparation of coumalic acid, although the von Pechmann conditions were described in an *Organic Synthesis* article on a 100 gram scale.[30] Kaminski and Kirsh have also recently described a synthesis using a more concentrated solution of sulfuric acid.[31]



Scheme 14. von Pechmann coumalic acid (**2**) synthesis from malic acid (**24**)

Malic acid is a naturally occurring compound found in fruits such as apples and grapes. More importantly, it is primarily derived from fermentation processes. It has been shown that malic acid can be biomass-derived *via* enzymatic processes from glucose. In one case, a genetically altered *Saccharomyces cerevisiae* enzyme is able to produce 0.42 moles of malate per mole of glucose.[32] Although the conversion would preferably be 100%, this result still shows that malic acid can be derived from a renewable source.

The intermediate in this transformation is formyl acetic acid (**25**). Two molecules of this aldehyde acid react to produce one molecule of coumalic acid after loss of two molecules of water (Scheme 15). Although this reaction is suitable for a multigram laboratory scale, scaling these corrosive reaction conditions to a pilot plant scale would not be feasible. Therefore, alternative reaction conditions are needed. The mechanism by which malic acid is transformed into the aldehyde acid was recently studied.[33] There is vigorous gas evolution at the beginning of the reaction. The gas is carbon monoxide, suggesting a direct protonation of the carboxylic acid as an early step. Interestingly, less than five percent of fumaric acid is produced under these strongly acidic conditions.

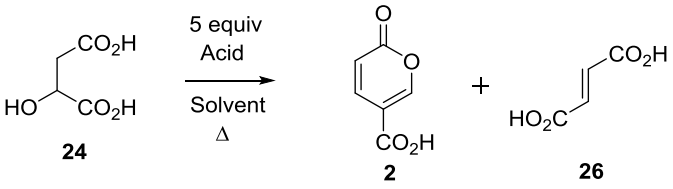


24 **25** **2**

Scheme 15. Conversion of malic acid (**24**) into coumalic acid (**2**)

Since a strong acid and heat are needed to protonate the carboxylic acid, we examined several strong anhydrous acids. The results are collated in Table 2. Concentrated sulfuric acid in dichloroethane (DCE) afforded coumalic acid in very good yield. Adding a weaker co-acid such as acetic acid (AcOH) or trifluoroacetic acid (TFA) lowered the reaction yields. The respective anhydrides, acetic anhydride (Ac_2O) and trifluoroacetic anhydride (TFAA), were also employed to remove water, but there was no significant difference observed. Using acetic or trifluoroacetic acid without sulfuric acid present gave small amounts of o-acylated products and returned starting material. The more strongly acidic sulfonic acids, triflic acid and nonafluorobutanesulfonic acid, gave coumalic acid in good yields, while methanesulfonic acid gave mixtures of **2** and **26**. Unexpectedly, *para*-toluenesulfonic acid gave a 71% yield of fumaric acid. This is probably not industrially significant since the thermal conversion of malic acid into fumaric acid is known.[5] With the best conditions discovered to date, we scaled up the reaction with triflic acid as well as sulfuric acid and obtained an 86% and 80% yield of coumalic acid, respectively, on a five-gram scale.

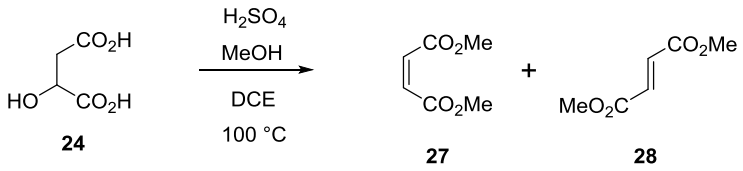
Table 2. Conditions for the conversion of **24** into **2**



Acid	Temperature	Solvent	Additive	Yield **2**	Yield **26**
H_2SO_4	100	DCE	None	80	5
H_2SO_4	120	AcOH	None	4	3
H_2SO_4	120	AcOH	Ac_2O	6	9
H_2SO_4	80	TFA	None	51	1
H_2SO_4	80	TFA	TFAA	44	0
$MeSO_3H$	100	DCE	None	14	25
CF_3SO_3H	100	DCE	None	86	4
$C_4F_9SO_3H$	100	DCE	None	65	2
PTSA	120	None	None	0	71

Considering much of our current studies have been with methyl coumalate instead of coumalic acid, it is reasonable to attempt to extend the coumalic acid synthesis from malic acid to be able to make methyl coumalate as well. With excess amounts of a

strong acid already in the reaction pot to undergo the formation of coumalic acid from malic acid, we believed we could just add methanol to convert the forming carboxylic acid into the methyl ester. When an excess of methanol was added before heating the reaction, mixtures of dimethyl maleate (**27**) and dimethyl fumarate (**28**) were formed (Scheme 16). These products must have formed due to esterification of the carboxylic acids followed by acid-catalyzed dehydration.



Scheme 16. Attempt at methyl coumalate from malic acid (**24**)

Gratifyingly, when the reaction mixture was cooled, and then methanol was added to the crude coumalic acid solution and heated again, methyl coumalate was afforded in 70% overall yield. Concentrated sulfuric acid was used in this case due to its ease of handling compared to the stronger triflic acid. This one-pot reaction sequence was scaled up to 5 grams and gave similar results.

Conclusion

In the near future, there is a pressing need for alternative sources of industrially significant chemicals. The current path to terephthalic acid is through the oxidation of *p*-xylene, acquired from petroleum sources. We have sought to create a greener route from sustainable sources. We have studied an interesting Diels-Alder reaction between coumalates and activated dieneophiles, bearing an electron-withdrawing group towards

the goal of biobased terephthalic acid production. After decarboxylation, these adducts give disubstituted aromatic products either directly if an alkyne is employed, or after concomitant dehydrogenation by a Pd/C catalyst in the case of alkene dienophiles. Both pathways have the potential to form either the *para* or *meta* disubstituted aromatic products based on which transition state predominates. Through experimental and computational studies, we have extended our knowledge of the possible steric and electronic factors that control the regiochemical outcome. Although the regioselectivity has been modest for this system, we have gained valuable knowledge for formulating future reactions and conditions.

Along the way, we explored coumalic acid and methyl coumalate as platform chemicals. We have shown that these compounds can be transformed into a variety of disubstituted aromatic compounds and in a few cases, monosubstituted benzenes. These examples are shown in Figure 3. Unexpectedly, when the diisopropylethylamine salts of coumalic acid and acrylic acid are reacted under our conditions, a decarboxylation occurs, giving benzoic acid as the major product. When butyl vinyl ether is used as the dienophile, butanol is lost in the aromatization step and benzoates are formed. Studies are ongoing in the Kraus lab currently to explore the effects of different leaving groups on the aromatization.

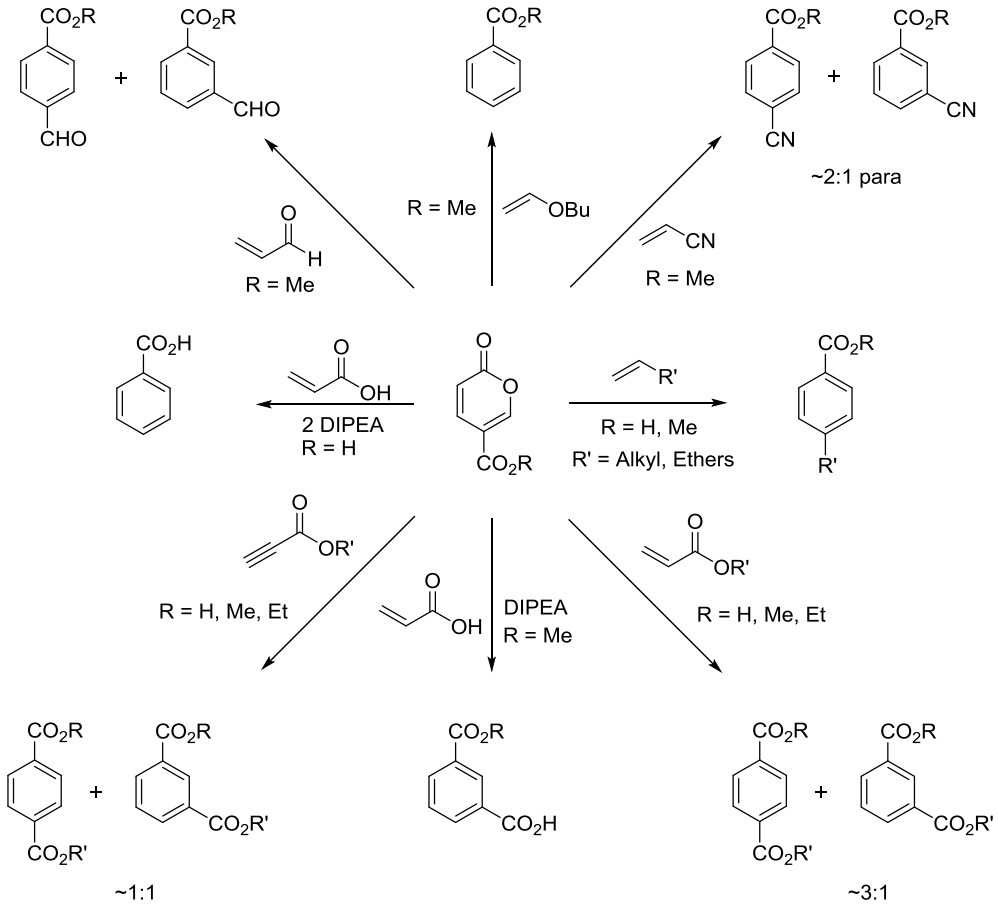


Figure 3. Coumalates as platform chemicals

In order to make our route to terephthalates from coumalates renewable, we needed a sustainable source of coumalic acid and its esters. We developed a synthesis that improved upon previous work using malic acid which can be available from glucose through fermentation processes. Our route avoids the use of corrosive, dehydrating fuming sulfuric acid, and demonstrates the utility of other strong acids, such as sulfonic acids. Using dichloroethane as the solvent allowed for much lower quantities of acid used. When concentrated sulfuric acid is employed an 80% yield of coumalic acid is obtained, while triflic acid gives 86% yield. By converting the pre-formed carboxylic

acid of coumalic acid to its methyl ester with methanol, methyl coumalate has also been synthesized in one-pot in 70% yield using concentrated sulfuric acid as the reagent. We have demonstrated the scalability of our syntheses of coumalic acid and methyl coumalate by successfully repeating the reactions on a 5 gram scale. Considerable advances have been made towards the biorenewable synthesis of terephthalic acid and other aromatic compounds through coumalates produced from malic acid as a renewable source and electron-deficient, activated dienophiles.

Experimental

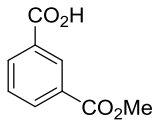
All NMR spectra were obtained on a Varian VXR spectrometer, operating at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR instrument. Thin-layer chromatography was performed using commercially available 250 micron silica gel plates (Analtech). Preparative thin-layer chromatography was performed using commercially available 1000 micron silica get plates (Analtech). Visualization of TLC plates was effected with short wavelength ultraviolet light (254 nm). All reagents were used as obtained commercially unless otherwise noted. All products were either commercially available or known in the literature. Product ratios were determined by ^{1}H NMR integration (300 MHz) of purified mixtures of the isomers for the Diels-Alder procedure, or similar integration of crude mixtures of the reaction products for the conversion of malic acid to coumalic acid. Products were determined by comparison of ^{1}H NMR to known spectra.

Methyl coumalate Diels-Alder general procedure (alkenyl dienophiles):

To a solution of methyl coumalate (0.078g, 0.5 mmol) and 10% Pd/C (0.020g, 25 wt%) dissolved in toluene in a sealable tube was added alkenyl dienophile (1.5 mmol, 3 equiv.) at rt. The mixture was sealed and stirred for 16 h at the temperature described. The reaction was cooled to rt, opened, filtered through Celite, washing with ethyl acetate, and concentrated *in vacuo* to give the crude product which was purified *via* flash column chromatography (hexanes:ethyl acetate) to give the desired compounds as inseparable mixtures of *meta* and *para* isomers. ^{1}H NMR data was consistent with literature reported values for methyl 3-cyanobenzoate,[34] methyl 4-cyanobenzoate,[35] ethyl methyl isophthalate,[14] ethyl methyl terephthalate,[14] methyl 3-formylbenzoate[36] and methyl 4-formyl benzoate.[37]

Methyl coumalate Diels-Alder general procedure (alkynyl dienophiles):

To a solution of methyl coumalate (0.078 g, 0.5 mmol) dissolved in toluene in a sealable tube was added alkynyl dienophile (1.5 mmol, 3 equiv.) at rt. The mixture was sealed and stirred for 16 h at the temperature described. The reaction was cooled to rt, opened, filtered through Celite, washing with ethyl acetate, and concentrated *in vacuo* to give the crude product which was purified *via* flash column chromatography (hexanes:ethyl acetate) to give the desired compounds as inseparable mixtures of *meta* and *para* isomers. ^{1}H NMR data was consistent with literature reported values for mono-methyl isophthalate,[38] mono-methyl terephthalate,[39] dimethyl isophthalate[40] and dimethyl terephthalate.[41]



mono-Methyl isophthalate (20):

To a solution of acrylic acid (0.206 mL, 3 mmol), distilled to remove polymerized material, in toluene (5 mL, 0.2 M) was added N,N-diisopropylethylamine (0.174 mL, 1 mmol) dropwise at rt. The mixture was stirred for 30 min after which methyl coumalate (0.152 g, 1 mmol) was added, followed by 10% Pd/C (0.038 g, 25% / mass). The reaction was heated to 140 °C for 16 h, then cooled and quenched with sat. aq. NH_4Cl solution (10 mL). The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product which was purified *via* flash column chromatography (5:1–3:1 hexanes:EtOAc) to give mono-methyl isophthalate in 45% yield as a light yellow solid. The ^1H NMR spectrum was identical to published reports for mono-methyl isophthalate.[38]

General procedures for coumalic acid (2) from malic acid (24):

Procedure for sulfuric acid:

To a solution of DL-malic acid (5g, 37.29 mmol) in dichloroethane (75 mL) was added concentrated sulfuric acid (9.94 mL, 186.45 mmol) and heated to 100 °C for 16 h. After cooling to rt, the red solution was poured onto ice and stirred for 30 min. The mixture was extracted with ethyl acetate (3x) and the combined organic extracts were washed

with ice-cold water (3x), dried over $MgSO_4$, and concentrated in vacuo to give a 16:1 mixture of coumalic acid and fumaric acid (**26**).

Procedure for acetic acid and trifluoroacetic acid:

To a solution of DL-malic acid (0.268 g, 2 mmol) in concentrated sulfuric acid (10 mL) was added solvent (10 mL) and additive (10 vol %) if needed as described in Table 1. The solution was heated to the specified temperature for 16 h, cooled to rt and poured onto ice. The mixture was extracted with ethyl acetate (3x) and the combined organic layers were washed with ice-cold water (3x), dried over $MgSO_4$, filtered and concentrated to give the crude products.

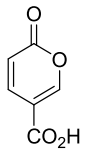
General procedure for sulfonic acids:

To a solution of DL-malic acid (0.268 g, 2 mmol) in dichloroethane (10 mL) was added sulfonic acid (5 equiv) and the solution was heated to 100 °C for 16 h. After cooling to rt, the solution was poured onto ice (50 g) and stirred 30 min. The mixture was extracted with EtOAc (25 mL x 3) and the combined organic extracts were washed with ice-cold water (25 mL x 3), dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products.

Procedure for *para*-toluenesulfonic acid:

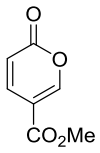
A mixture of L-malic acid and *para*-toluenesulfonic acid was heated to 120 °C with stirring, which resulted in melting of both solids into a red, viscous solution. After 16 h,

the mixture was cooled to rt and quenched with H_2O, extracted with ethyl acetate and washed with brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give fumaric acid (**26)** as a tan solid in 71% yield.



Coumalic Acid (2):

Prepared using the previously described general procedures from malic acid, most successfully by using sulfuric acid (80%) and trifluoroacetic acid (86%). Light yellow solid. ^{1}H NMR (300 MHz, CD_3OD): δ = 8.42 (dd, J = 0.9, 2.4 Hz, 1H), 7.86 (dd, J = 2.7, 9.9 Hz, 1H), 6.36 (dd, J = 1.2, 9.6 Hz, 1H).



Methyl Coumalate (4a):

To a solution of DL-malic acid (1g, 7.46 mmol) in dichloroethane (10 mL, ~1 M) was added H_2SO_4 (1.99 mL, 37.29 mmol) slowly at 0 °C. The mixture was warmed to rt then heated to 100 °C for 16 h. After cooling to rt, methanol (1.51 mL, 37.29 mmol) was added and the solution was heated to 80 °C for 8 h. After cooling, the reaction was carefully quenched with water and a saturated solution of sodium bicarbonate at 0 °C. The solution was extracted with EtOAc, washed with brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product which was purified *via* flash column chromatography (5:1-1:1 hexanes:EtOAc) to give methyl coumalate as a

yellow solid in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$): d = 8.31 (dd, J = 1.2, 2.7 Hz, 1H), 7.79 (dd, J = 2.4, 9.6 Hz, 1H), 6.35 (dd, J = 0.9, 9.9 Hz, 1H), 3.91 (s, 3H).

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CHAPTER 2

EXTENSION OF A NOVEL INDOLE SYNTHESIS TO NATURAL PRODUCTS

Introduction

The indole substructure is present in a wide variety of biologically significant natural products.[1] Not surprisingly, numerous successful methods have been developed for the synthesis of indoles from a variety of different starting materials. These synthetic approaches have been reviewed by Sundberg,[2] and more recently, Taber and Tirunahari,[3] who categorized the syntheses based on how the final bond of the indole subunit was formed (Figure 1).

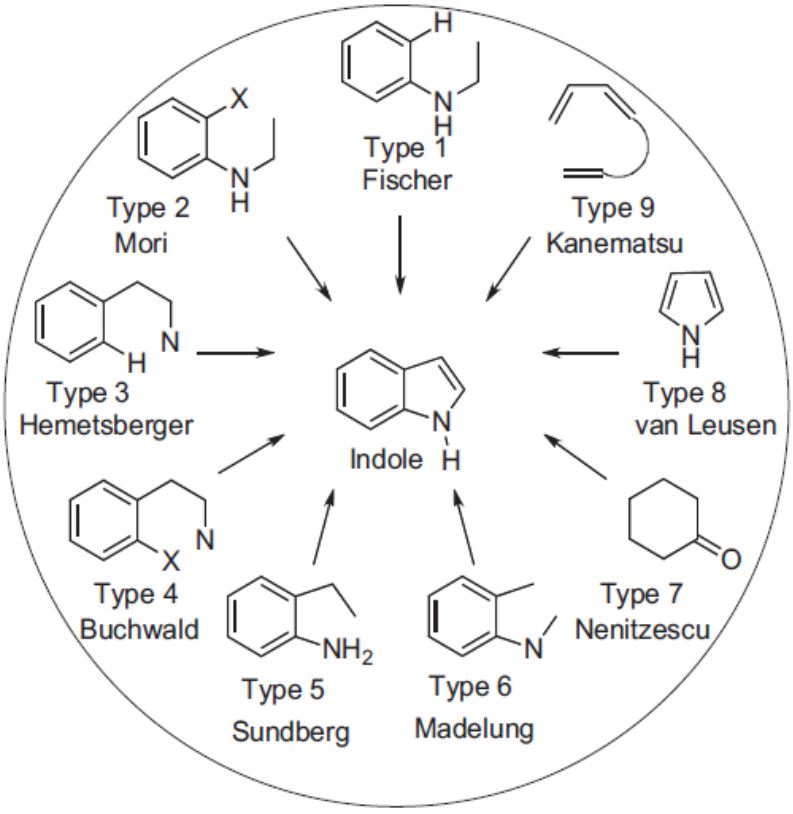
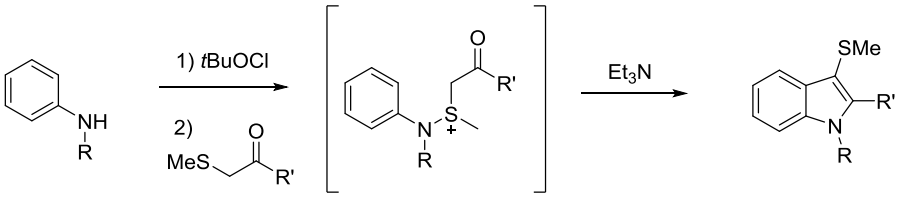


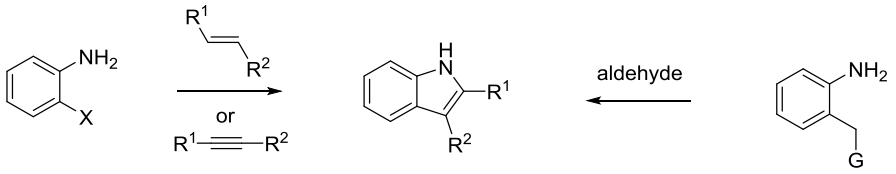
Figure 1. Taber and Tirunahari classification of indole syntheses[3]

The nine types of indole syntheses categorized were identified by named reactions associated with the strategy or pioneering research groups. A type 1 indole synthesis, such as the Fischer indole synthesis,[4] involves a final bond forming step between an aryl C-H and the second sp^3 hybridized carbon atom (C2) away from the indole nitrogen. Another method of forming this carbon-carbon bond to close the indole ring is the Bartoli indole synthesis. Reaction of ortho-substituted nitrobenzenes with vinyl Grignard reagents gives indoles with substitution possible on either the 5 or 6-membered ring.[5] Since the same final bond is formed, this is also a type 1 indole synthesis. The Gassman approach[6] to 2-substituted indoles from anilines also belongs to this class of indole formation reactions (Scheme 1).



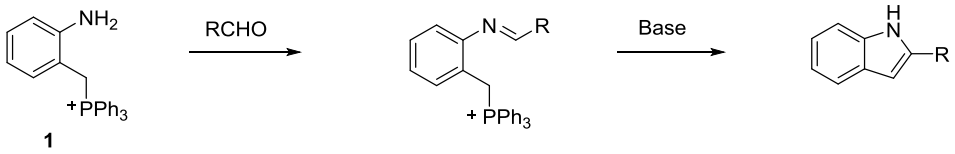
Scheme 1. Gassman indole synthesis

Anilines and hydrazones are some of the most common precursors to indoles. Hydrazones are intermediates in the Fischer and Japp-Klingemann[7] syntheses of indoles. Larock developed a method which reacts an alkyne with an *ortho*-iodoaniline in the presence of palladium(0) and base to give indoles.[8] Since the intermediate palladium species cyclizes onto the arylamine, this is classified as a type 5 reaction. *Ortho*-haloanilines also react with substituted alkenes and a palladium catalyst to give indole products (Scheme 2).[9] The use of palladium in indole cyclization reactions has been well documented.[10]



Scheme 2. Indoles from *ortho*-substituted anilines

ortho-Alkylindoles have been less frequently used. The Madelung synthesis is an example, employing cyclization of the dianion of an anilide at elevated temperatures.[11] Another example is the Bischler indole synthesis, a convenient route to 2-arylindoles *via* microwave-assisted coupling of anilines and bromoacetophenones.[12] In 2008, Kraus published a novel indole synthesis.[13] This flexible strategy involves electrocyclic closure of the anion of an imine which arose from the reaction of an aromatic aldehyde with commercially-available phosphonium salt **1** (Scheme 3). This sequence proceeds in one pot under mild reaction conditions.



Scheme 3. Kraus indole synthesis

2-substituted indoles are readily available through this route by modifying the aldehyde component. By adjusting the substitution at the benzylic position of **1**, 2,3-disubstituted indoles are also accessible.[14] When using a phosphonium salt as the activating group, this method allows the synthesis of a wide range of substitution patterns; both electron-withdrawing and electron-donating groups are compatible. These compounds are shown in Figure 2 and are achieved in high yields (72 – 100%) from **1**

and the requisite aldehyde.[13] The best conditions developed for our indole synthesis consisted of imine formation with a catalytic amount of acetic acid in methanol using microwave irradiation. Conventional heating gave formation of the imine in lower yields and required longer reaction times. Potassium *tert*-butoxide was employed as the base in tetrahydrofuran to afford cyclization to the indoles.

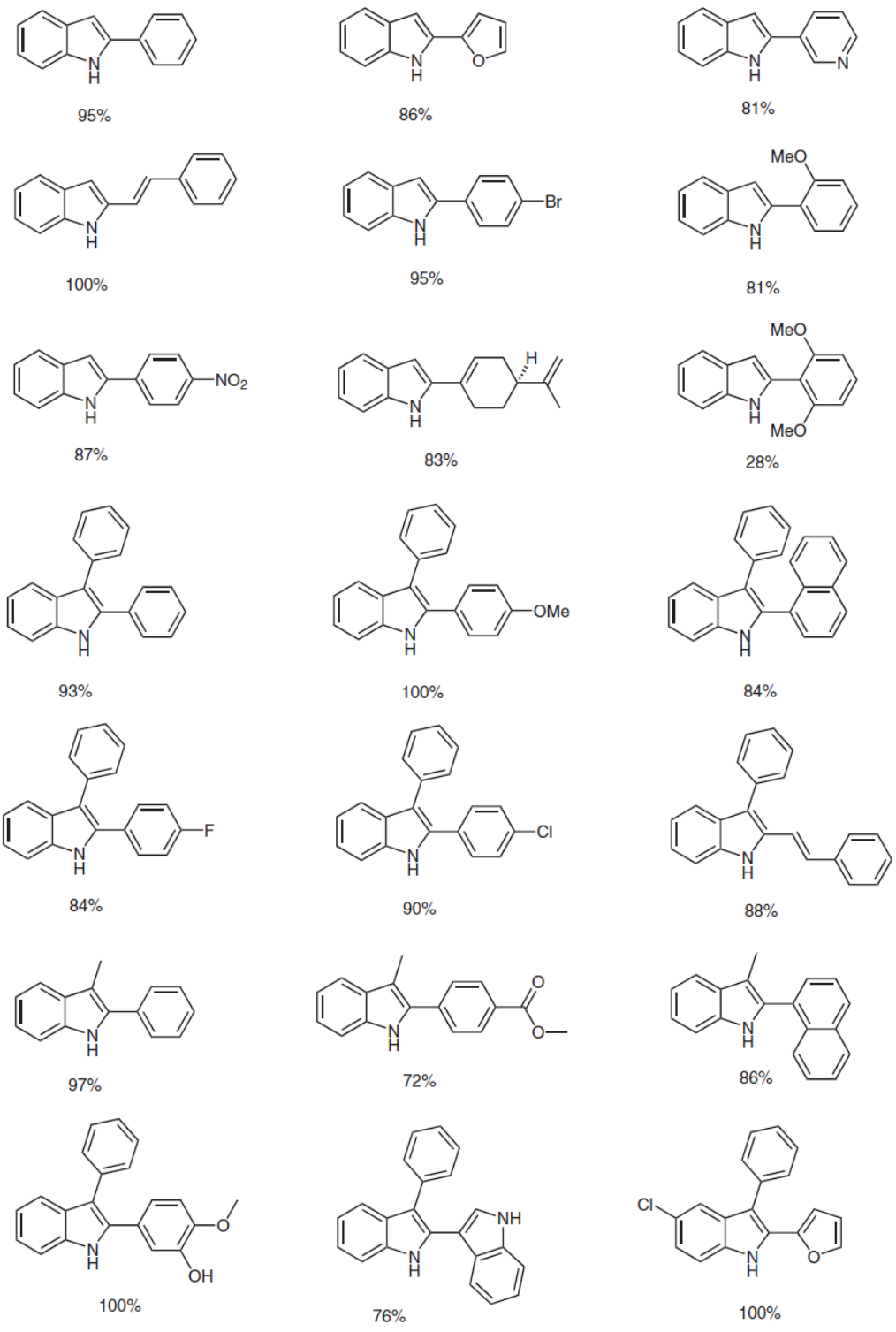


Figure 2. Scope of indoles prepared by Kraus and Guo[13]

The Kraus group also sought to understand which types of activating groups (G, Scheme 1) would allow cyclization to occur to form the indole.[15] Sulfones, nitriles, phosphonates and sulfides were also employed as activating groups. In an effort to extend the scope of this process, the synthesis of indole-containing natural products such as isocryptolepine (**2,** Figure 3), an indolo[2,3-b]quinoline alkaloid isolated from the roots of *Cryptolepis sanguinolenta* were attempted. Compound **2** displays potent antimalarial activity, inhibiting *Plasmodium falciparum* with an IC_{50} of 0.8 μm.[16] Isocryptolepine has been synthesized many times,[17] most commonly by organopalladium-mediated coupling of substituted quinolines (Scheme 4).[18]

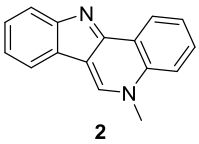
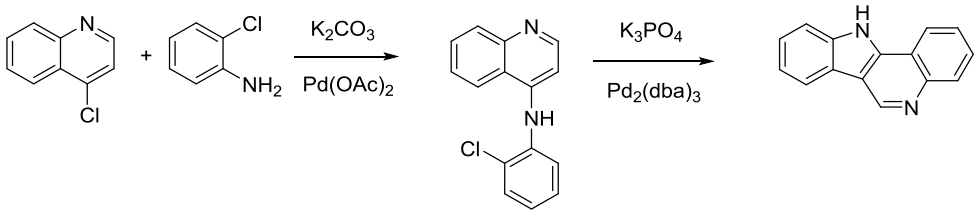


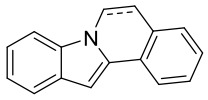
Figure 3. Structure of isocryptolepine (**2**)



Scheme 4. Palladium-catalyzed "amination-arylation" approach to **2**

Also of interest was the skeleton of indolo[2,1-*a*]isoquinolines (**3**, Figure 4), a diverse class of natural compounds which, along with its dihydro equivalents, exhibit a wide range of biological activities such as tubulin-binding,[19] estrogen receptor modulation,[20] and acting as semiconductors.[21] This class of compounds is also well known in the literature. The most common strategy involves organopalladium coupling

of 2-aryl indoles followed by cyclization.[22] By choosing an appropriate aniline derivative and aldehyde, we were able to extend the Kraus indole synthesis to these natural product systems.

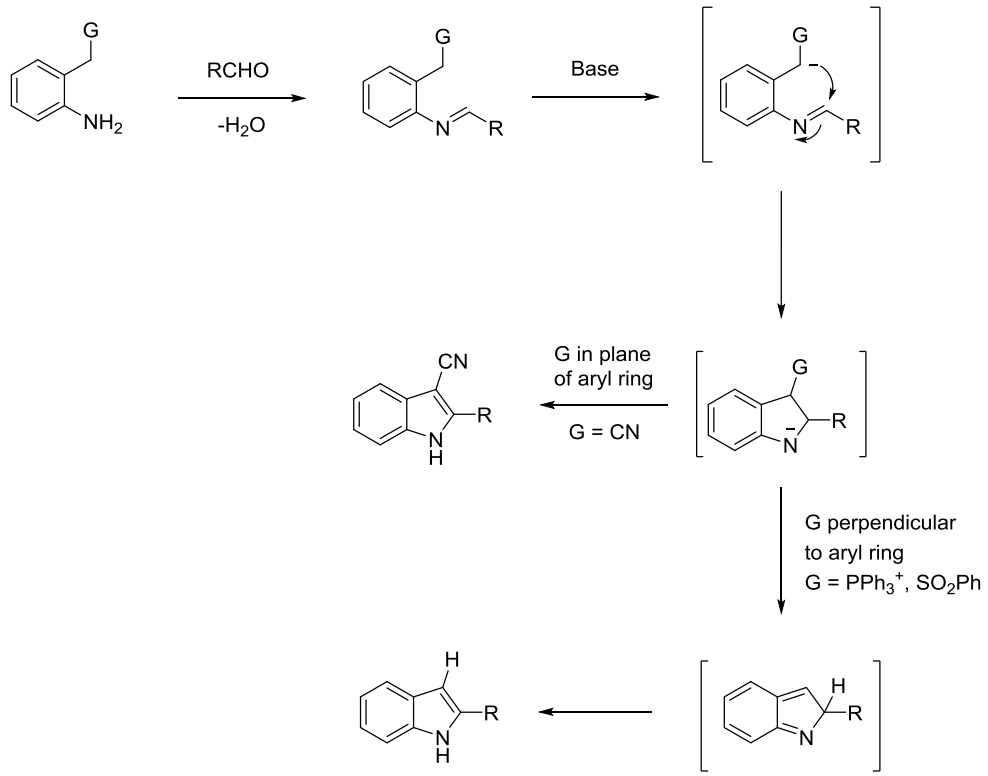


3

Figure 4. Indolo[2,1-*a*]isoquinoline skeleton (**3**)

Results and Discussion

Through attempts to modify the activating group towards the Kraus indole synthesis, our group has discovered that triphenylphosphine and arylsulfone groups are eliminated during the cyclization, while cyano groups remained in the structure of the final indole product.[15] Based on these studies, a mechanism for indole formation was proposed (Scheme 4). Formation of the imine from the aniline and aldehyde, followed by a base-mediated electrocyclic ring closure and a 1,5-hydrogen atom shift gave indole products.

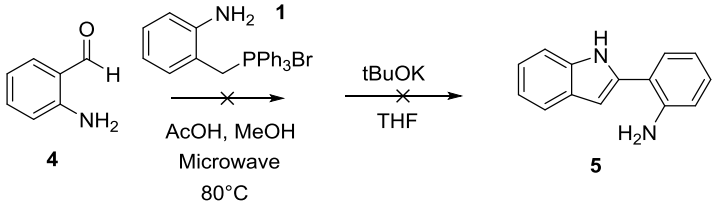


Scheme 4. Proposed mechanism of Kraus indole synthesis

Two types of products can be formed depending on the nature of the activating group, G. If G is sterically large, it is more likely to be oriented perpendicular to the aromatic ring in order to minimize nonbonded interactions. Therefore, G would be in a successful position for elimination to give an intermediate that could form the indole after a 1,5-hydrogen shift. On the other hand, if G is smaller, such as a nitrile, a wider range of conformations is possible. If G is in the plane of the benzene ring, the benzylic hydrogen alpha to the nitrile would be very acidic. Deprotonation, instead of elimination, could occur, followed by oxidation to give the 3-cyanoindole.

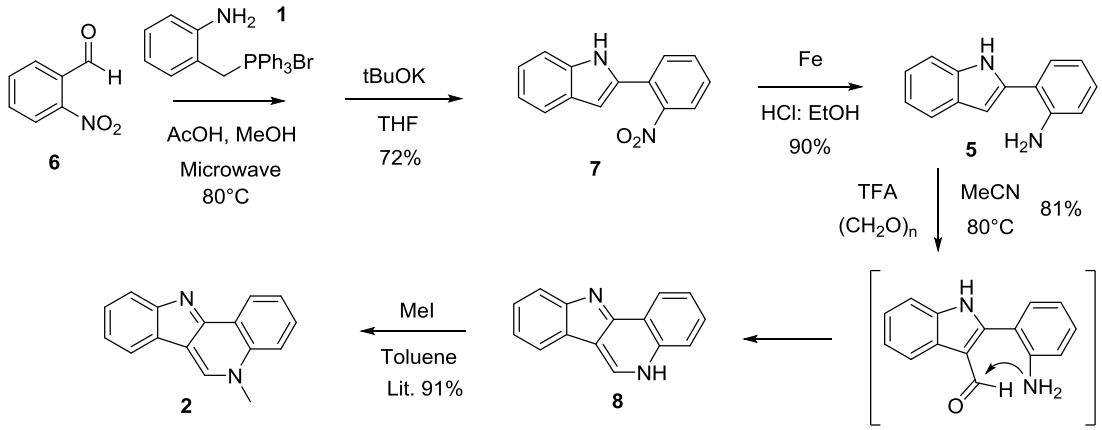
In an attempt to extend this chemistry to natural product synthesis, we set out to prepare indole-containing isocryptolepine and the skeleton of indolo[2,1-*a*]isoquinolines.

In order to incorporate the Kraus indole synthesis towards isocryptolepine, we set out to choose an appropriate aniline and benzaldehyde. The intermediate we desired was aminophenylindole **5**, which could come from the reaction of aminobenzaldehyde **4**, and our traditional phosphonium salt **1** (Scheme 5). Unfortunately, **4** was too unstable due to the molecule reacting with itself.



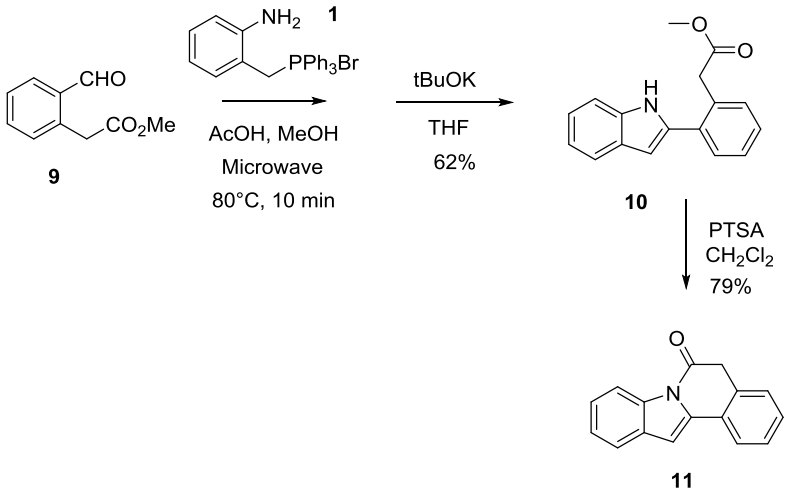
Scheme 5. First approach to key intermediate **5**

We then turned to nitrobenzaldehyde **6** to react with **1** to give nitrophenylindole **7** in good yield under standard conditions (Scheme 6). **7** can be reduced readily by iron and hydrochloric acid in ethanol to give the desired aminophenylindole **5**. Paraformaldehyde and trifluoroacetic acid furnished the aldehyde on the 3-position of the indole which cyclized *in situ* to give the tetracyclic system of isocryptolepine (**8**) The N-methylation of **8** has been accomplished previously using methyl iodide.[17] Therefore, our efforts constitute a formal synthesis of isocryptolepine (**2**) using the Kraus indole synthesis as the key transformation.



Scheme 6. Formal synthesis of **2**

We next turned our attention to the skeleton of indolo[2,1-*a*]isoquinolines. We were interested to see if we could use our indole technology to quickly gain access to the tetracyclic core. Since this class of natural products is very diverse and displays a wide variety of biological activities,[19, 20, 21] it is important to develop new, direct ways to put together the tetracyclic framework. Our contribution to this system comes from the concise synthesis of 5H-indolo[2,1-*a*]isoquinoline (**11**). Our synthesis (Scheme 7) commences with Kraus indole formation using **1** and benzaldehyde **9**, which is known to come from the ozonolysis of indene.[23] The obtained indole **10** contains a tethered ester which allows for acid-catalyzed cyclization with the indole nitrogen using *para*-toluenesulfonic acid to give **11** in 49% yield over 2 steps.[24]



Scheme 7. Synthesis of a 5H-indolo[2,1-*a*]isoquinoline (**11**)

Conclusion

The Kraus indole synthesis is a novel approach to 2-substituted and 2,3-disubstituted indoles. Normally, an aminobenzyl phosphonium salt is employed with an appropriate aldehyde to give indoles in one pot in high yields. A wide range of substitution patterns are achievable from simple benzaldehydes or α,β-unsaturated aldehydes. Studies have shown that aminobenzyl sulfones and nitriles are also compatable with the cyclization, although the nitrile is retained in the 3-position of the final product. The Kraus indole synthesis is very direct, forming indoles in one step from commercially available or easily synthesized materials. There is also flexibility inherent to this strategy due to the ability to modify substitution on the aldehyde component.

A wide variety of biologically important natural products containing the indole subunit are known and are continually being discovered, enhancing the utility of indole

syntheses. The Kraus indole synthesis has been successfully applied to the synthesis of two natural product systems containing tetracyclic cores, isocryptolepine and a 5H-indolo[2,1-*a*]isoquinoline. This strategy was direct, creating three of the four rings in one step while leaving a functional group available to allow for formation of the final ring. An advanced intermediate in the synthesis of isocryptolepine was accomplished in 3 steps in 53% overall yield, while an entry into the indolo[2,1-*a*]isoquinoline series was achieved in 2 steps in 49% overall yield.

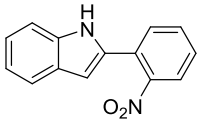
Experimental

All NMR spectra were obtained on a Varian VXR spectrometer, operating at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR instrument. Thin-layer chromatography was performed using commercially available 250 micron silica gel plates (Analtech). Preparative thin-layer chromatography was performed using commercially available 1000 micron silica get plates (Analtech). Visualization of TLC plates was effected with short wavelength ultraviolet light (254 nm). All reagents were used as obtained commercially unless otherwise noted. High resolution mass spectra were recorded on an Agilent 6540 QTOF using EI, ESI, or ACPI. All reagents were used directly as obtained from commercial suppliers unless otherwise noted.

General procedure for 2-substituted indoles from aniline 1:

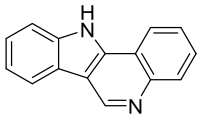
In a 10 mL microwave reaction vessel (CEM Discover System) equipped with a magnetic stir bar, the 2-aminobenzyl phosphonium salt **1** (0.5 mmol), respective

aldehyde (0.5 mmol), and glacial acetic acid (11.4 μL, 0.2 mmol) were added to distilled MeOH (3 mL). The vial was capped properly and placed in the microwave. Microwave irradiation was carried out at 80 °C for 10 min (fixed temperature). After cooling the vial to rt, MeOH was removed under vacuum. All MeOH must be removed before the next step. Tetrahydrofuran (4 mL) was added to the mixture, followed by dropwise addition of a 1M *t*BuOK solution in THF (0.8 mL). The resulting mixture was stirred at 25 °C under argon for 1 h. A saturated aqueous solution of NH_4Cl (10 mL) was added to quench the reaction and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined and washed with brine (2 x 10 mL), dried with $MgSO_4$, and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel flash column chromatography (hexanes:EtOAc) to give the pure indole products.



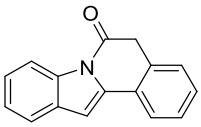
2-(2-Nitrophenyl)indole (7):

Prepared using the described general indole synthesis procedure. ^{1}H NMR (400 MHz, acetone-d_6): δ = 10.65 (br s, 1H), 7.90 (d, J = 8 Hz, 1H), 7.81 (d, J = 6.8 Hz, 1H), 7.71 (t, J = 15.2 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 7.57 (t, J = 14 Hz, 1H), 7.48 (d, J = 8 Hz, 1H), 7.20 (t, J = 14.4 Hz, 1H), 7.10 (t, J = 15.6 Hz, 1H), 6.68 (s, 1H). ^{13}C NMR (acetone-d_6): δ = 205.8, 149.4, 137.8, 132.9, 132.5, 131.5, 129.1, 129.0, 127.1, 122.8, 120.9, 120.1, 111.6, 102.7. HRMS: *m/z* calcd for $C_{14}H_{10}N_2O_2$ [M^+]: 238.07422; found: 238.07453.



Indolo[2,3-*b*]quinoline (8):[17]

To a solution of **5** and paraformaldehyde (1.2 equiv) in MeCN in a sealable tube was added TFA (1 equiv) and heated to 80 °C for 2 h. After cooling and concentrating *in vacuo*, the residue was dissolved in EtOAc and washed with sat. aq. $NaHCO_3$, water, and brine. The combined organic extracts were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography to give 8 as a white solid in 81% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.68 (br s, 1H), 9.58 (s, 1H), 8.51 (dd, J = 1.0, 7.5 Hz, 1H), 8.30 (d, J = 7.7 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.75-7.64 (m, 3H), 7.47 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 7.1 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ = 145.8, 145.1, 140.0, 139.3, 130.0, 128.6, 126.5, 125.9, 122.3, 122.1, 121.0, 120.6, 117.4, 114.9, 112.0. HRMS: *m/z* calcd for $C_{15}H_{10}N_2$ [M^+]: 218.0844; found: 218.0854.



Indolo[2,1-*a*]isoquinolin-6(5*H*)-one (11):[24]

The crude mixture obtained from the indole synthesis reaction of **1** and **9** was dissolved in CH_2Cl_2 and PTSA (1 equiv) was added. After stirring for 6 h at RT, the reaction was quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a residue which was purified by flash chromatography to give **11** in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54

(d, J = 7.6 Hz, 1H), 7.84 (d, J = 6.4 Hz, 1H), 7.59 (d, J = 6.8 Hz, 1H), 7.31-7.36 (m, 5H), 7.03 (s, 1H), 4.10 (s, 2H). ^{13}C NMR ($CDCl_3$): δ = 167.0, 135.3, 134.2, 130.6, 130.2, 129.8, 128.7, 128.1, 127.8, 125.5, 124.8, 124.1, 120.7, 116.8, 103.5, 37.8. HRMS: *m/z* calcd for $C_{16}H_{11}NO$ [M^+]: 233.08406; found: 233.08431.

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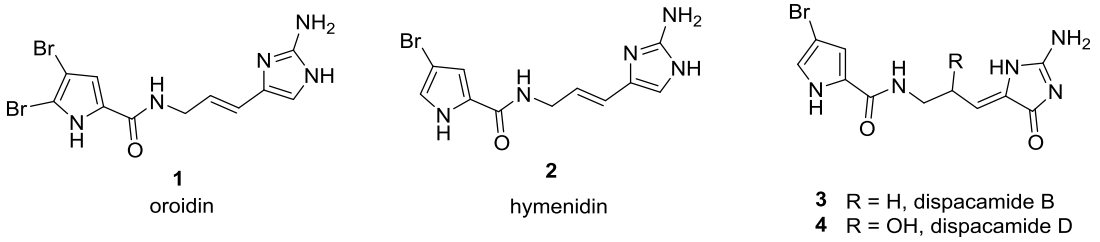
CHAPTER 3

SYNTHETIC STUDIES TOWARDS OROIDIN

Introduction

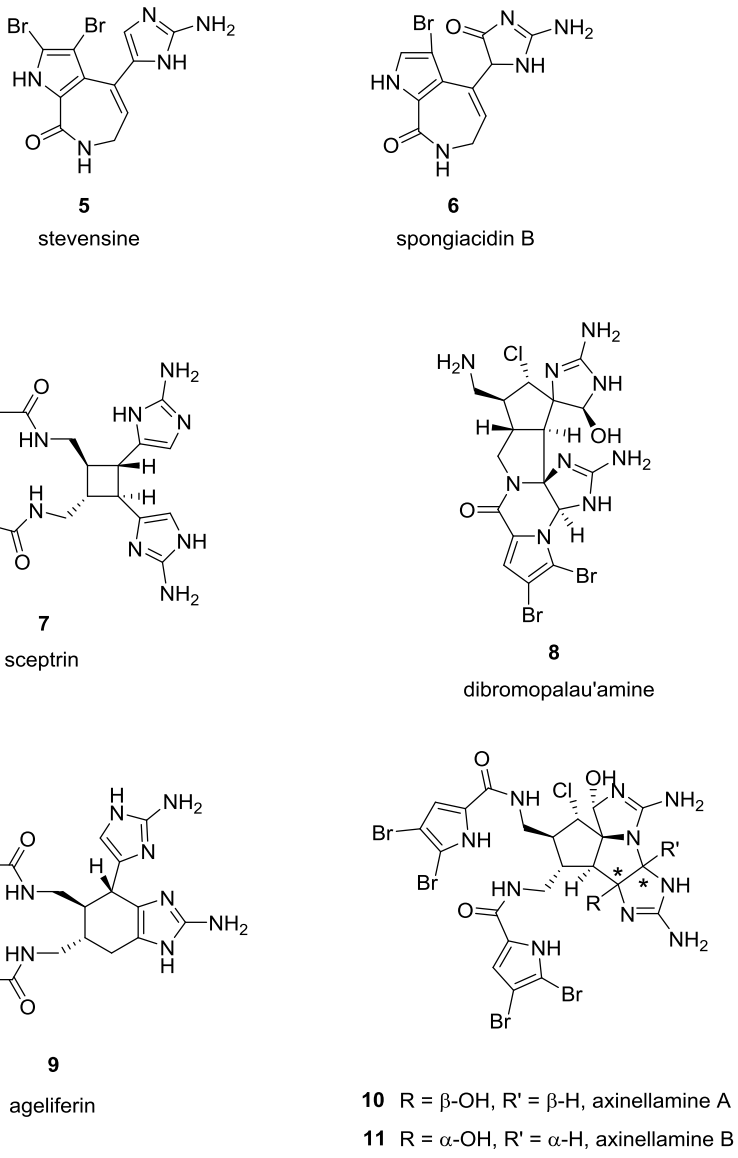
Natural products have traditionally possessed a wide variety of biological activities. Alkaloids are one of the largest classes of natural compounds, with marine organisms being abundant sources.[1] An important set of natural products are the bromopyrrole-imidazole alkaloids. Although the structures of these alkaloids are very diverse, it appears that they all are derived biosynthetically from a common secondary metabolite, oroidin (**1**) and related compounds.[2] These congeners are characterized by a bromopyrrole carboxamide linked by a propenyl chain to a 2-aminoimidazole (Scheme 1). Some of these congeners are represented by hymenidin **(2)**, dispacamide B (**3**) and D (**4**).



Scheme 1. Selected type 1 non-cyclized oroidin monomers

The bromopyrrole-imidazole alkaloids are generally classified into three separate types. The first type is non-cyclized monomers which are represented by hymenidin (**2**) and dispacamide B and D (**3, 4**), as well as oroidin (**1**). Intramolecular cyclized monomers such as stevensine (**5**) and spongiacidin B (**6**) are examples of a second type

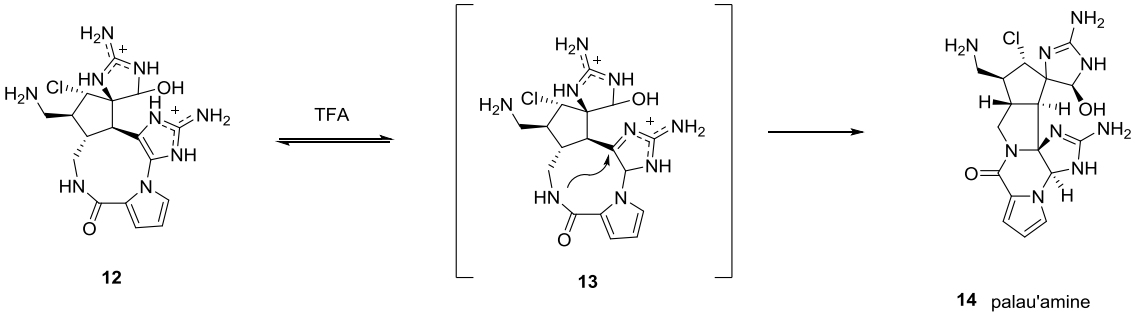
of oroidin-based alkaloids (Scheme 2). The third type of compounds is classified as monomeric intermolecular dimers. A few examples are sceptrin (**7**), dibromopalau'amine (**8**), ageliferin (**9**), and axinellamine A and B (**10, 11**). The second and third type of compounds are speculated to come from the group of non-cyclized monomers.[3] Specifically, compounds **5**, **7**, **8**, **9**, **10** and **11** are believed to derive from oroidin through dimerization and consecutive functionalizations, while **6** comes from dispacamide.[4] Interestingly, since these molecules are often found together in nature, the evidence points towards a divergent natural product library from **1** itself.[5]



Scheme 2. Selected type 2 and 3 oroidin bromopyrrole-imidazole alkaloids

Due to the fascinating biosyntheses and biological activities, a great deal has been published towards the synthesis of oroidin-derived small molecules.[6] All of the compounds listed in Scheme 2 have been accomplished to date,[7] with palau'amine (**14**) proving the most difficult and attracting the most attention. The synthesis of **14** was accomplished in 2010 by Baran and coworkers (Scheme 3).[8] The key proved to be in the

macrocyclic compound **12**, which was formed through a transannular cyclization from a previously synthesized compound. This set up the key ring closure through its amidine tautomer (**13**) to give **14** in 0.015% overall yield in 25 steps from commercially available materials.



Scheme 3. Key end-game of Baran synthesis of palau'amine (**14**)

This diverse class of alkaloids contains compounds which have antiviral, antibacterial and antihistaminic activities to name a few.[2] Perhaps the most publicized compound in the group, **14** has historically shown immunosuppressive and cytotoxic properties.[9] It has recently been determined that this activity is due to **14** being able to modulate proteolytic activity of the human proteasome and immunoproteasome, thereby slowing the degradation of proteins.[10] The similar dibromopalau'amine (**8**) has been shown to have promising activity as a trypanocidal (IC_{50} = 0.46 μg/mL) and antileishmanial agent (IC_{50} = 1.09 μg/mL).[11] This study also proved that spongiacidin B (**6**) and dispacamide B (**3**) are promising antimalarial compounds with IC_{50} values of 1.09 and 1.34 μg/mL, respectively against *P. falciparum*.

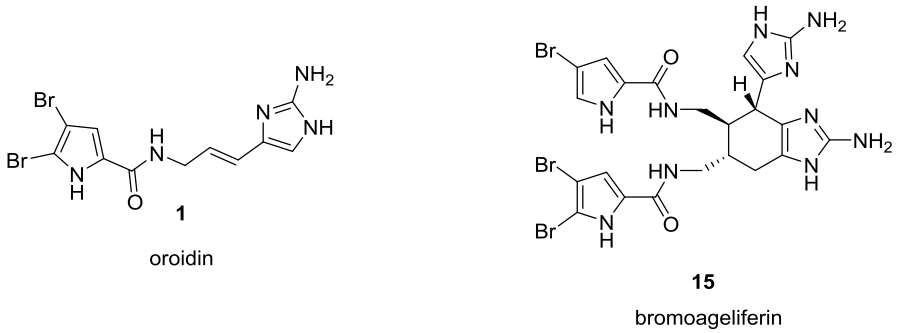
While there are numerous compounds with more complex structures in the bromopyrrole-imidazole class of marine alkaloids, the main building block, oroidin (**1**)

possesses important biological activity as well. Although the compound at the high end of molecular complexity in the oroidin alkaloid series, palau-amine (**14**) was ultimately synthesized, it still takes 25 steps to accomplish. While the various modes of cyclization and dimerization of the non-cyclized monomers are intriguing and have received much attention in recent years, the relative simplicity of oroidin (**1**) would allow for a much more direct synthesis, greater ability for scale-up and the synthesis of analogues for structure-activity relationship studies. It would also be interesting to see if analogues of oroidin would develop new modes of dimerization, cyclization and functionalization to create even more compounds related to this system which could show interesting activities.

Oroidin (**1**) was isolated from the *Agelas sventres* marine sponge in 1971 which is typically found in tropical water environments.[12] Oroidin has been shown to possess fish-deterrent,[13] antimalarial,[14] and membrane depolarization interference[15] activities. Recently, it has been discovered that oroidin also acts as an antibiofilm agent[16] and inhibits the activity of multidrug resistant yeast enzymes.[17]

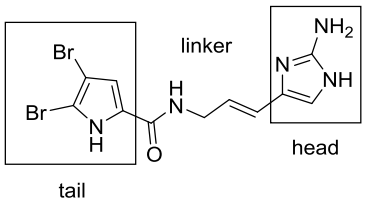
Bacterial biofilms have become a global threat causing billions of dollars of damage to engineering, medical and agricultural operations.[18] A bacterial biofilm is defined as a community of microorganisms attached to a surface which are encased in an extracellular layer of biomolecules. This encasing affords enhanced protection from conventional antibiotic treatments, sometimes greater than 1000 times more resistant than regular bacteria.[19] Biofilms are becoming increasingly more prevalent in bacteria found in hospitals and medical facilities.[20] The NIH estimates that 65-80% of human

infections are currently caused by bacterial biofilms.[21] Initially, oroidin (**1**) and bromoageliferin (**15**) showed activity inhibiting *Rhodospirillum salexigens*, a gram-negative marine bacterium which forms biofilms (Scheme 4).[22] Compound **15** showed greater activity than parent compound **1**, with IC_{50} values of 2.43 and 169 μM, respectively. In a separate study, oroidin (**1**) prevented *V. vulnificus* bacteria from producing biofilm colonies, showing it too could be an effective agent.[23]



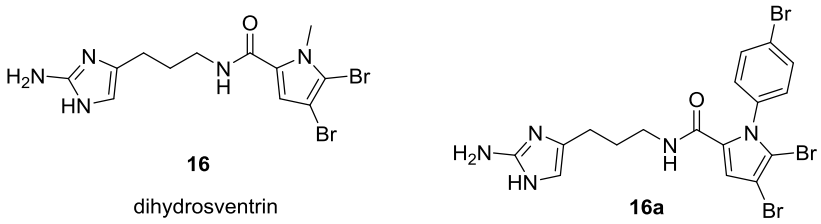
Scheme 4. First oroidin compounds to show antibiofilm activity

Based on this exciting activity, structure activity relationship (SAR) studies have been performed on the oroidin class of compounds as well as oroidin itself. Based on the hypothesis from previous results that the 2-aminoimidazole subunit of oroidin has antibiofilm properties, analogues of oroidin were prepared to evaluate the role of the head, tail and linker of the molecule (Scheme 5).[24]



Scheme 5. SAR studies of oroidin skeleton

It was discovered that the 2-aminoimidazole head of oroidin was absolutely necessary to the antibiofilm activity of the molecule. The unsaturation of the linker was found to not be necessary, while incorporation of the two bromine atoms on the pyrrole ring was important.[24] Also, adjusting the linker chain length to two or four carbons lowered the activity of the compound. N-methylation of the pyrrole ring gave a derivative, dihydrosventrin (**16**) which showed the best activity of the group of compounds tested with an IC_{50} of 115 μm against *A. baumannii* (Scheme 6). Additional compounds were prepared to increase the lipophilicity and steric bulk of the group attached to the pyrrole nitrogen.[25] A 4-bromophenyl substituent (**16a**) proved to be the most active with an IC_{50} of 27 μm. These studies discovered some interesting trends in the biological activity of simple oroidin alkaloids. It also showed that oroidin itself can be considered a valid starting point for making compounds that inhibit biofilms.

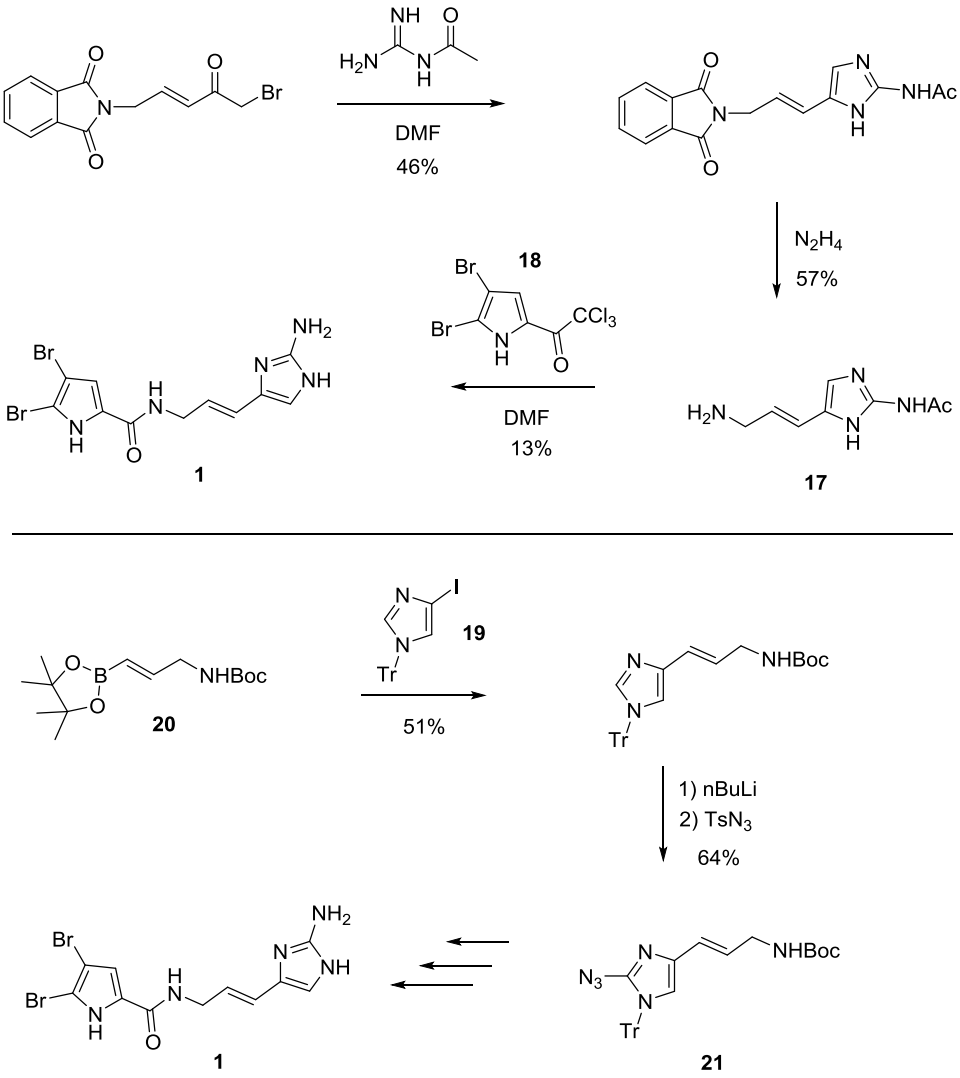


Scheme 6. Select effective antibiofilm compounds

Oroidin has also been shown to inhibit the yeast enzyme Pdr5p, which is responsible for multidrug resistance in *Saccharomyces cerevisiae*.[17] Multidrug resistance (MDR) refers to the ability of cells to resist many structurally diverse antitumor agents. It is a critical problem in trying to develop treatments for cancer.[26] A cell which has expressed the MDR phenotype creates excess amounts of membrane

proteins which act as efflux pumps, thus ejecting the anticancer agent before it can affect the tumor.[27] When MDR is present, the cancer treatment is significantly less effective, regardless of the agent employed. Oroidin showed an IC_{50} of 20 μm against the Pdr5p yeast enzyme and initial studies have shown that it is a possible lead drug for health problems stemming from MDR.

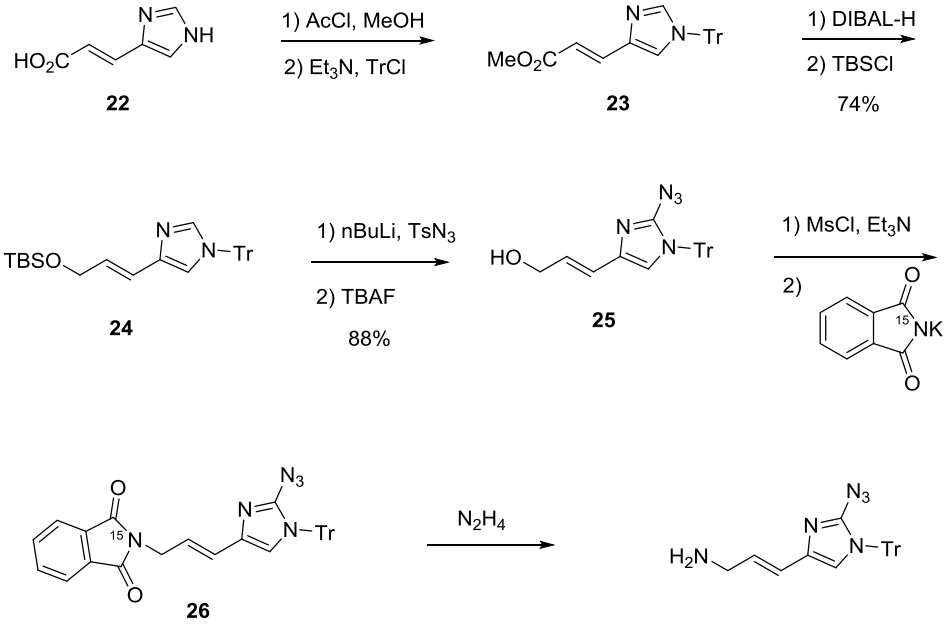
Based on these studies that show oroidin, or analogues thereof, possess interesting biological activities, we were interested in developing a strategically distinct synthesis of oroidin. In line with the amount of interest and synthetic effort towards the oroidin class of compounds, there have been many reported syntheses of oroidin. One example (Scheme 7) is the cyclization of α-halo ketones and N-acetylguanidine to give allylic amine (**17**) after deprotection which can react with pyrrole (**18**) to form the requisite amide bond.[28] Another route utilizes Suzuki coupling[29] between imidazole iodide (**19**) and vinyl boronate (**20**) followed by electrophilic addition of tosyl azide to give an intermediate (**21**) which can be elaborated similarly to oroidin (**1**). The condensation of cyanamide and an α-halo ketone, is also well known.[30]



Scheme 7. Selected oroidin syntheses

Romo and coworkers expanded on the synthesis of key intermediate **21** towards ^{15}N-labeled oroidin (Scheme 8), starting with commercially available urocanic acid (**22**).[31] After esterification, the imidazole nitrogen was protected by a trityl group to give compound **23**. Reduction of the ester to the alcohol and concomitant *tert*-butyldimethylsilyl (TBS) protection gave **24** which was converted into the azide **25** in 88% yield after deprotection with tetra-n-butylammonium fluoride (TBAF). The allylic

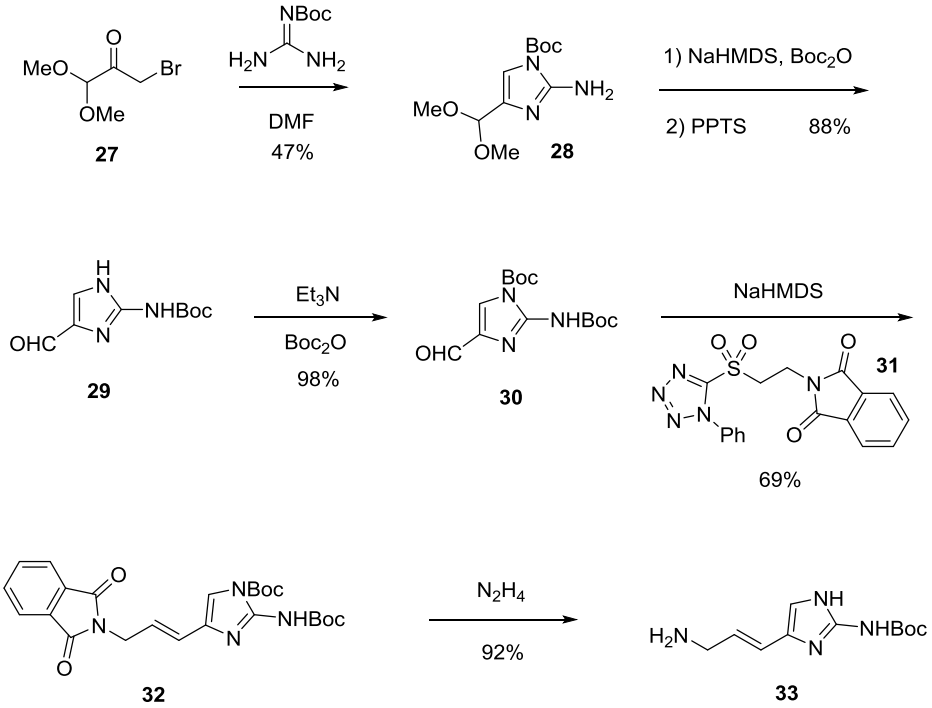
alcohol was then transformed into the allylic chloride through a mesylate intermediate. A Gabriel synthesis was performed on the chloride with ^{15}N potassium phthalimide to give the protected allylic amine **26**, which intersects previous syntheses after deprotection. This nitrogen-labeled oroidin will help study the biosynthetic pathway of this class of compounds.



Scheme 8. Romo synthesis of ^{15}N oroidin

In 2010, Ando published a route to oroidin using the condensation of an α-halo ketone with a protected guanidine (Scheme 9).[32] Ketone **27**, containing a masked aldehyde moiety, reacted with Boc-guanidine to give the functionalized 2-aminoimidazole (**28**) in 47% yield as the only isolated product. Attempts to Boc-protect the exocyclic amine, followed by acid catalyzed deprotection of the acetal gave the aldehyde **29** with the Boc group now on the other amine. This was easily mitigated by using protection conditions again to obtain the bis-Boc-protected imidazole (**30**), which

underwent a Julia-Kocienski olefination[33] with known sulfone **31** to give the key protected intermediate **32** in 69% yield. After deprotection, the allylic amine was produced, which has been used many times previously to form the key oroidin amide bond with the appropriate trichloromethylpyrrole derivative (**18**).

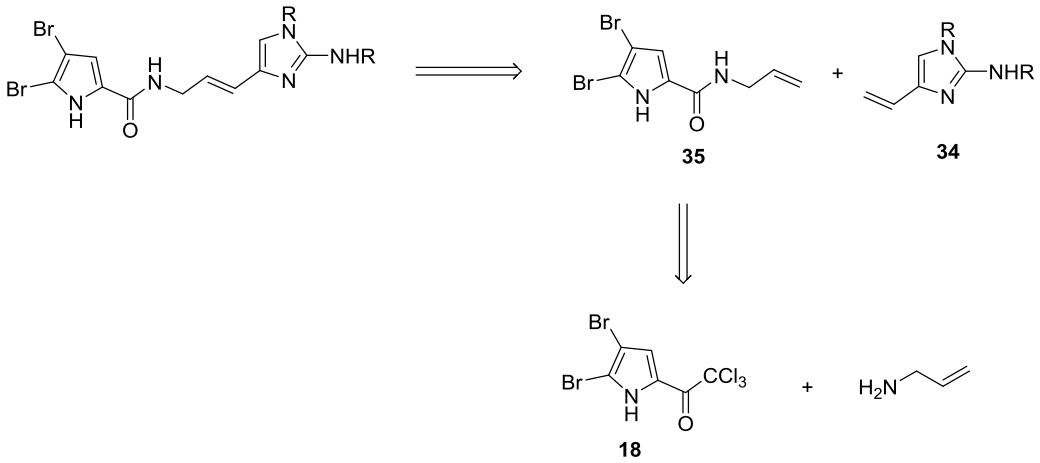


Scheme 9. Ando synthesis of oroidin

Results and Discussion

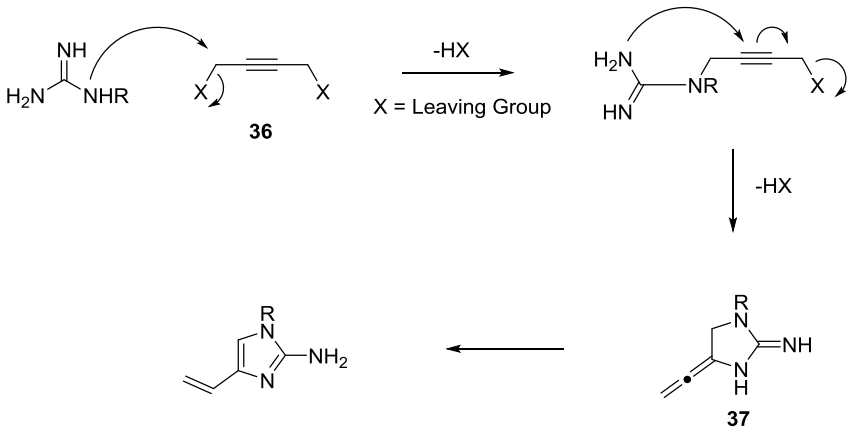
The more recent discoveries of multidrug resistance and biofilm inhibition sparked our interest in oroidin. With numerous syntheses already published, we sought a strategically distinct method to create the core structure of oroidin, namely how to link the two important heterocycles together. Our novel route was determined to be through a cross metathesis reaction (Scheme 10) of a 2-amino-4-vinylimidazole (**34**) and a

pyrrole allylic amide (**35**). Compound **35** can come from often-used pyrrole (**18**) and allyl amine while we aim to develop a new route to imidazole **34**.



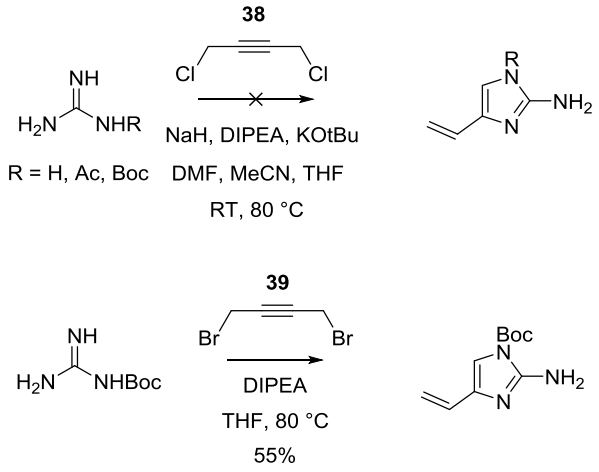
Scheme 10. Retrosynthesis of oroidin

Previous work has shown that the 2-aminoimidazole piece can be constructed from an α-halo ketone and a guanidine derivative.[28, 32] Essentially, the partner to the guanidine compound needs to possess two electrophilic sites in a position to cyclize to the 5-membered ring and possess the necessary oxidation state of the imidazole. Functionality attached to the 4-position of the ring would also be necessary to extend to oroidin. Our approach to this problem centered on using an alkyne with two propargylic leaving groups (**36**) to cyclize with a protected guanidine (Scheme 11). The mechanism is believed to happen by an S_N2 displacement followed by an intramolecular S_N2' reaction to give a cyclized intermediate (**37**) containing an allene which can aromatize to give the protected 2-amino-4-vinylimidazole.



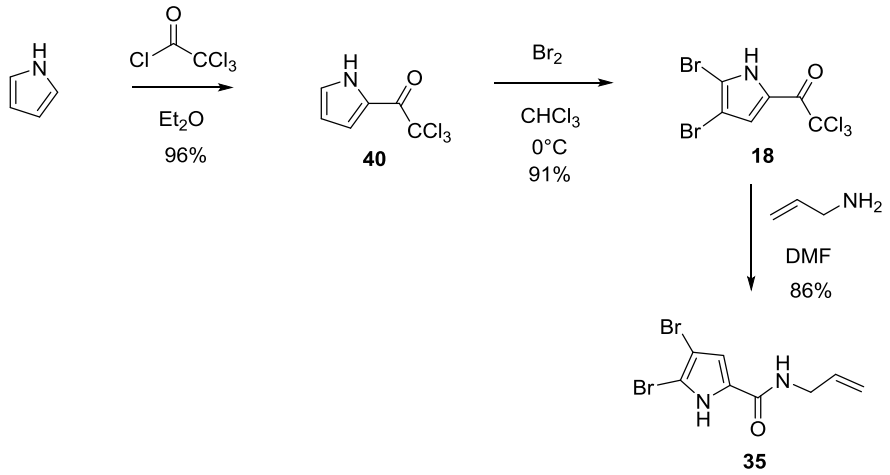
Scheme 11. Approach towards 4-vinyl-2-aminoimidazoles

We started with commercially available 1,4-dichloro-2-butyne (**38**). Attempts were made to cyclize with guanidine as well as acetyl- and Boc-protected guanidine (Scheme 12). Differing polar solvents as well as bases ultimately proved unsuccessful. Considering the chlorides seemed to not be good enough leaving groups, we turned to the dibromobutyne (**39**), which was prepared from the corresponding diol.[34] Employing Boc-guanidine[35] due to its increased solubility in organic solvents and greater nucleophilicity, we obtained the cyclized product in 55% yield in refluxing tetrahydrofuran. Not surprisingly, the 1,4-ditosyl-2-butyne[36] also gave the desired product in 52% yield.



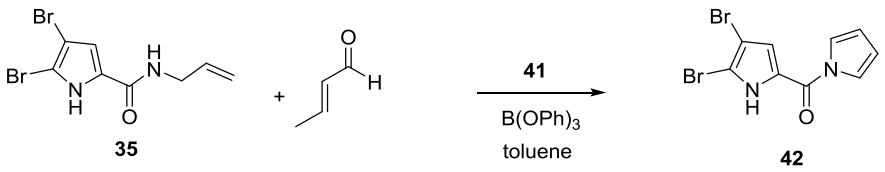
Scheme 12. Studies towards 4-vinyl-2-aminoimidazoles

With a new route to vinylaminoimidazoles in hand, we focused our attention on the metathesis partner, pyrrole **35**. Starting from pyrrole, acylation at the 2-position with trichloroacetyl chloride gave compound **40**,[37] which was dibrominated to give **18**[38] in high yields (Scheme 13). Amide formation using allylamine in dimethylformamide gave the metathesis precursor **35** in 86% yield.[39]



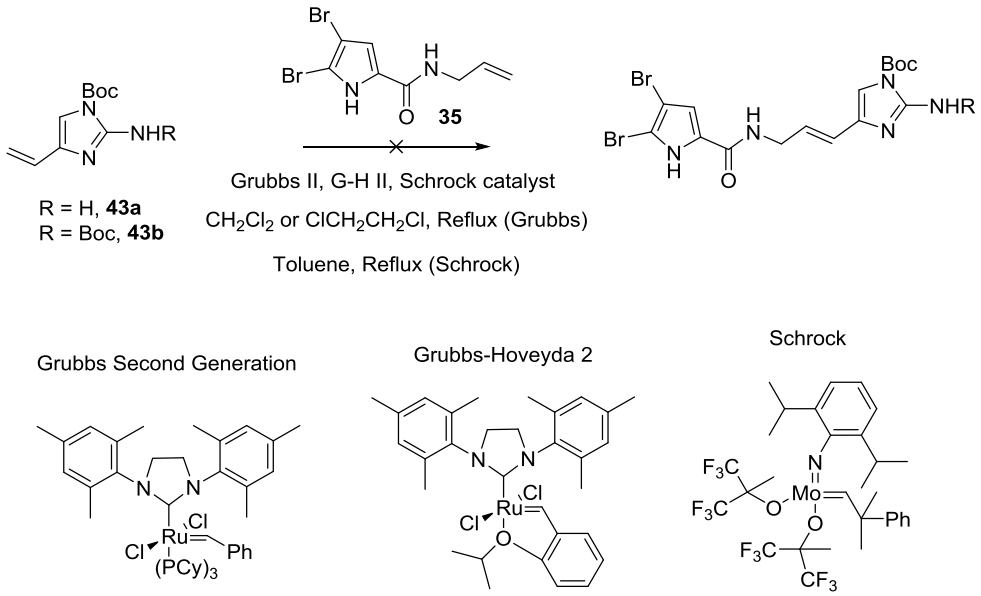
Scheme 13. Synthesis of metathesis precursor **35**

With the necessary compounds in hand, we moved forward to the key cross metathesis. Grubbs has reported the cross metathesis of styrenes with allylic substituted olefins,[40] while other vinyl aromatic heterocycles such as furans and thiophenes, as well as styrenes have successfully reacted with 1-octene[41] using a Schrock molybdenum catalyst. Allylic amide **35** has also been employed for cross metathesis with crotonaldehyde (Scheme 14) using Grubbs-Hoveyda second generation catalyst (**41**) and triphenyl borate in refluxing toluene.[42] Compound **42** was ultimately obtained in 60% yield after concomitant cyclization.



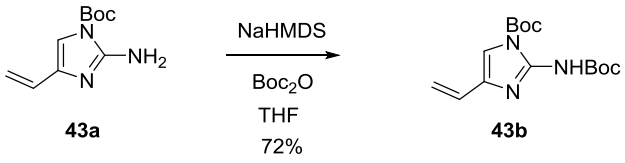
Scheme 14. Cross metathesis of **35** with crotonaldehyde

Based on this precedent, we then studied the metathesis reaction. The reaction of allylic amide **35** and 2-amino-4-vinylimidazole (**43a**) was attempted using Grubbs' second generation, Grubbs-Hoveyda second generation and Schrock catalysts. Standard conditions were employed for each catalyst, refluxing dichloromethane or dichloroethane for Grubbs' II, and refluxing toluene for Grubbs-Hoveyda II and the Schrock catalyst (Scheme 15). Unfortunately, none of these conditions gave the desired cross metathesis product with mainly only returned starting materials observed in all of these cases.



Scheme 15. Cross metathesis attempts

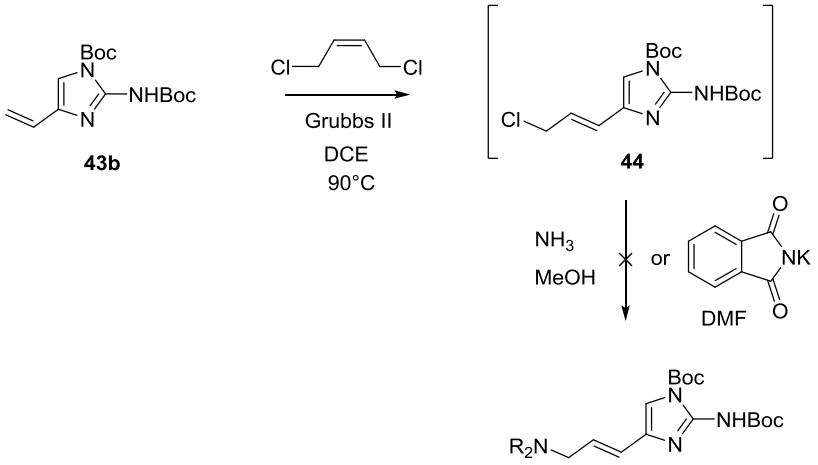
Since amines are known to coordinate with the transition metal centers of metathesis catalysts,[43] we protected the exocyclic amine of **43a** with a Boc group using sodium bis(trimethylsilyl)amide and Boc anhydride to give compound **43b** in 72% yield (Scheme 16). Surprisingly, we still did not see any promise in the cross metathesis reaction series of **43b** with **35**.



Scheme 16. Synthesis of di-Boc-protected imidazole (**43b**)

Based on research by Grubbs and coworkers which shows a high-yielding metathesis between styrene and cis-1,4-dichloro-2-butene with Grubbs II catalyst,[40] we employed this allylic chloride as the metathesis partner for **43b**. The product (**44**) could

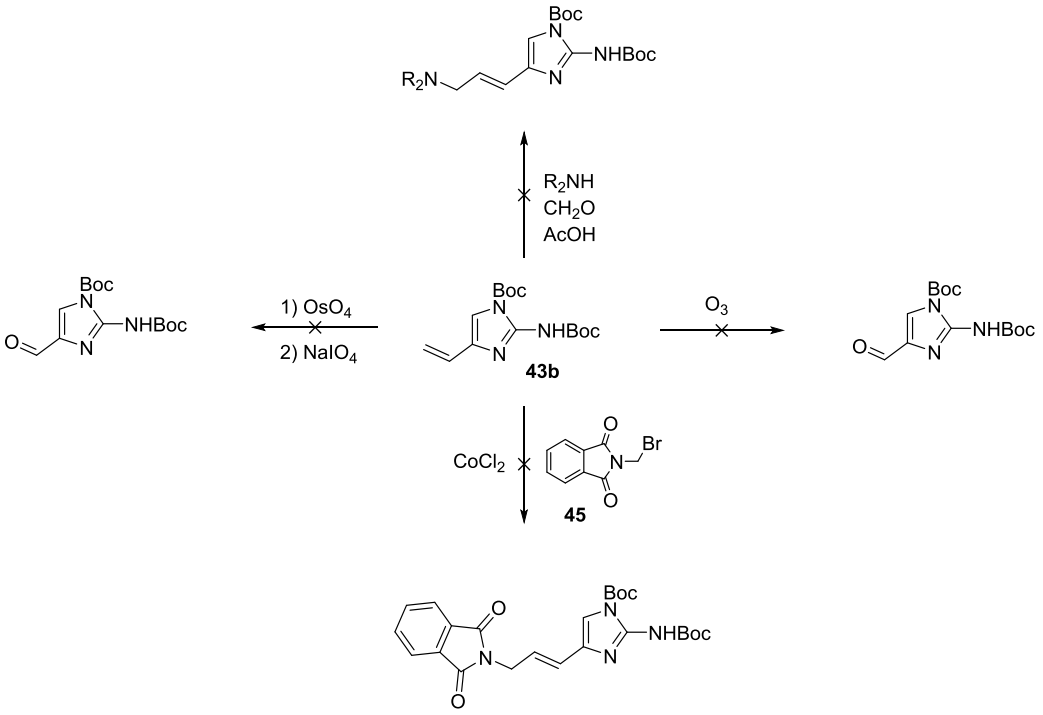
undergo an S_N2 reaction with an amine to give a compound which would be equivalent to the advanced intermediate in most of the published syntheses towards oroidin. (Scheme 17). Compound **44** proved to be unstable to column chromatography and attempts to react it with ammonia or potassium phthalimide were unsuccessful.



Scheme 17. Metathesis with cis-1,4-dichloro-2-butene

With metathesis seemingly an ineffective route, we decided to try to functionalize the exocyclic double bond of **43b** instead. The Ando synthesis[32] uses the 2-amino-4-formylimidazole as an advanced intermediate, therefore getting to this compound would constitute a formal synthesis. Many logical reactions on carbon-carbon double bonds were attempted. Ozonolysis, followed by a reductive workup, or dihydroxylation with osmium tetraoxide followed by oxidative cleavage with sodium periodate[44] were unsuccessful (Scheme 18). A Heck-type reaction using cobalt(II) to generate free-radicals allows for alkyl halides where a traditional Heck reaction has problems due to β-elimination of the intermediate palladium species.[45] Attempts to perform this transformation using commercially available N-(bromomethyl)phthalimide

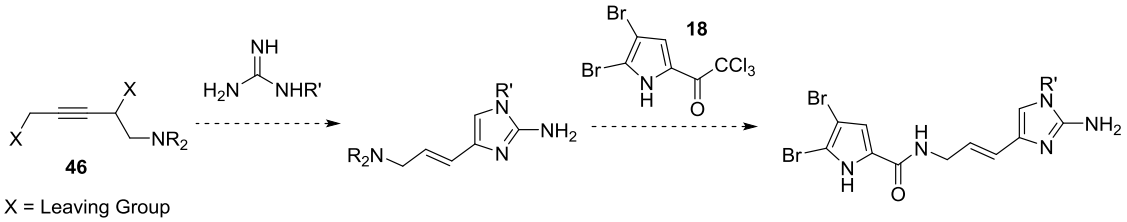
(**45**) also proved problematic. Finally, we attempted an aminomethylation using paraformaldehyde, acetic acid and a secondary amine.[46] Diallylamine, and dibenzylamine were employed with **43b** but were met with the same difficulties as before. We believe that standard chemistry has been unsuccessful on this double bond due to the ring being electron-rich, making the 5-position reactive and possibly more reactive than the double bond. The instability of the Boc groups to harsh reaction conditions could also have been contributing to the problems, considering the potentially free amino groups can be reactive and also increase the water solubility of the deprotected imidazole intermediates.



Scheme 18. Attempts to functionalize **43b**

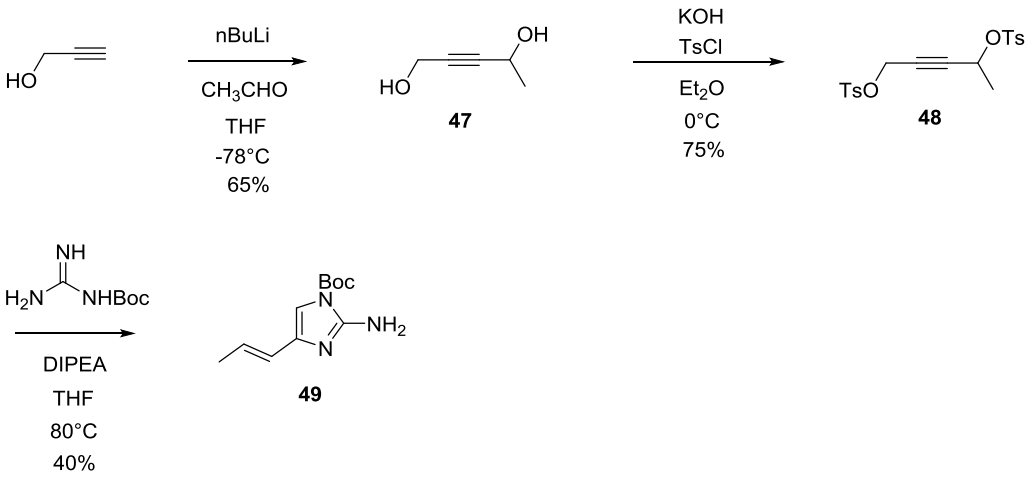
Without any success modifying the vinylimidazole, we then turned our thinking towards installing the required functionality before the imidazole cyclization reaction. If

the aminomethyl group we attempted to install previously was already attached to the alkyne (**46**), we would be able to cyclize to the desired intermediate which could be coupled to pyrrole **18** to give the core structure of oroidin (Scheme 19).



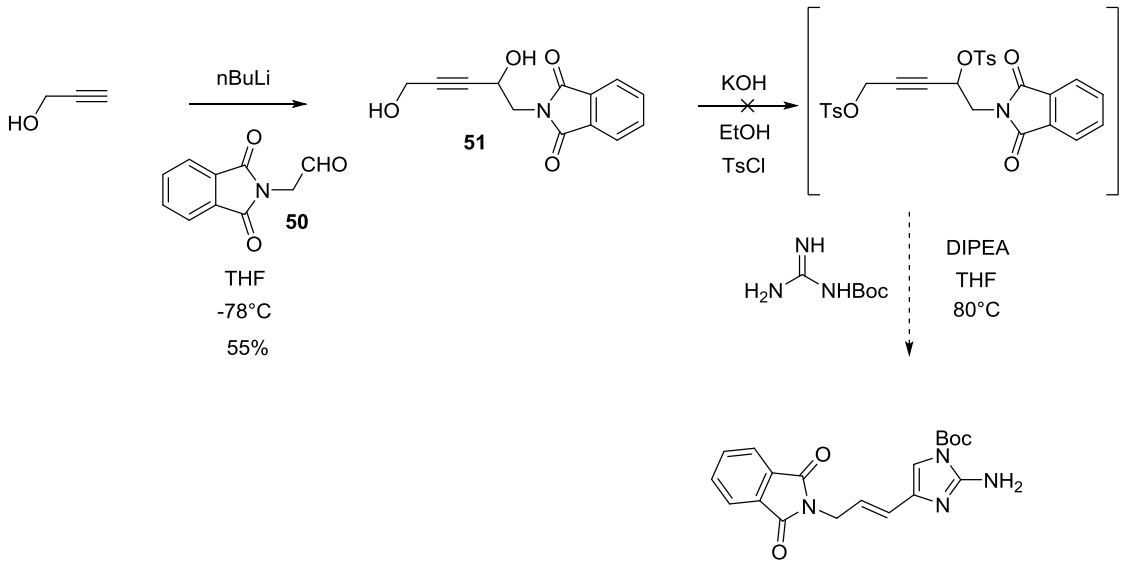
Scheme 19. Cyclization to core structure of **1**

We originally looked toward a model system to see if additional functionality could be tolerated on the alkyne during cyclization. Propargyl alcohol was treated with 2 equivalents of *n*-butyllithium and reacted with acetaldehyde[47] to give diol **47** which was ditosylated to give cyclization precursor **48** (Scheme 20). We chose tosylates as our leaving groups because the reaction conditions were milder than synthesizing the dibromide. Our standard conditions afforded the imidazole product (**49**) with an additional methyl group in moderate yield.



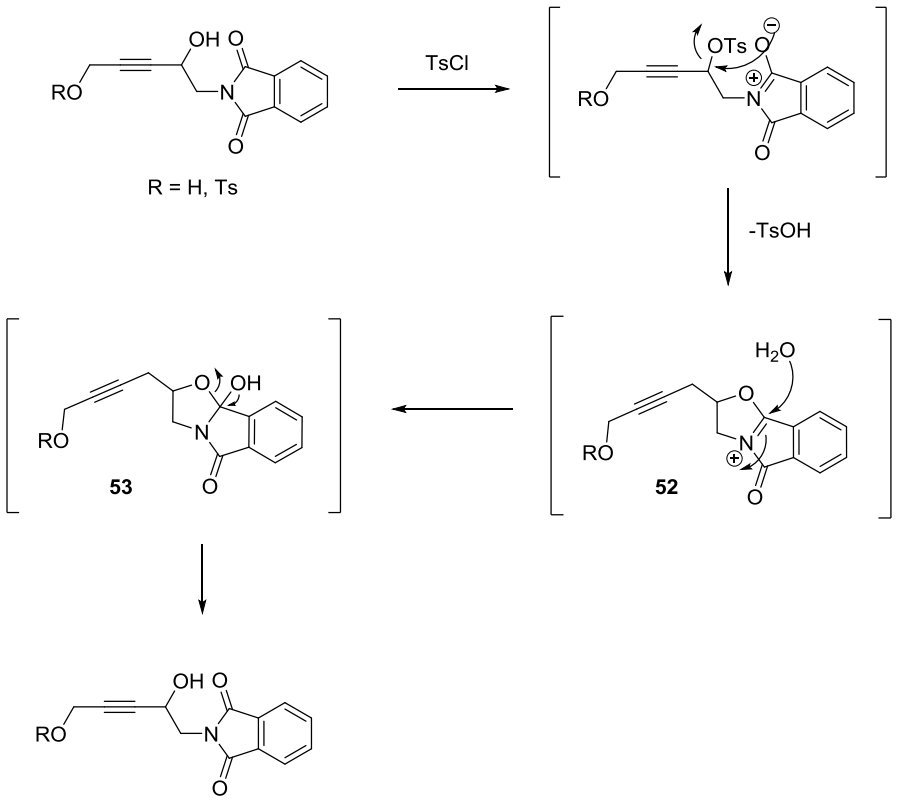
Scheme 20. Synthesis of model compound **49**

With this success, we went after the desired compound with a protected aminomethyl group attached to the alkyne. We chose N-(formylmethyl)phthalimide (**50**) due to its ease of synthesis[48] and stability. Similarly, reaction of the dianion of propargyl alcohol with **50** gave diol **51** with the protected aminomethyl group installed in 55% yield (Scheme 21). Attempted ditosylation gave a monotosylated product and returned starting diol. We reasoned that the neighboring phthalimide participated in keeping the internal alcohol ultimately unprotected.



Scheme 21. Attempted cyclization to imidazole

We believe the zwitterionic form of the phthalimide group allows an intramolecular S_N2 displacement of the internal tosylate through a 5-membered ring transition state as it forms (Scheme 22). The resulting imine (**52**) can be hydrolyzed during the aqueous workup to give a hemiketal (**53**) which falls apart back to the unprotected alcohol.

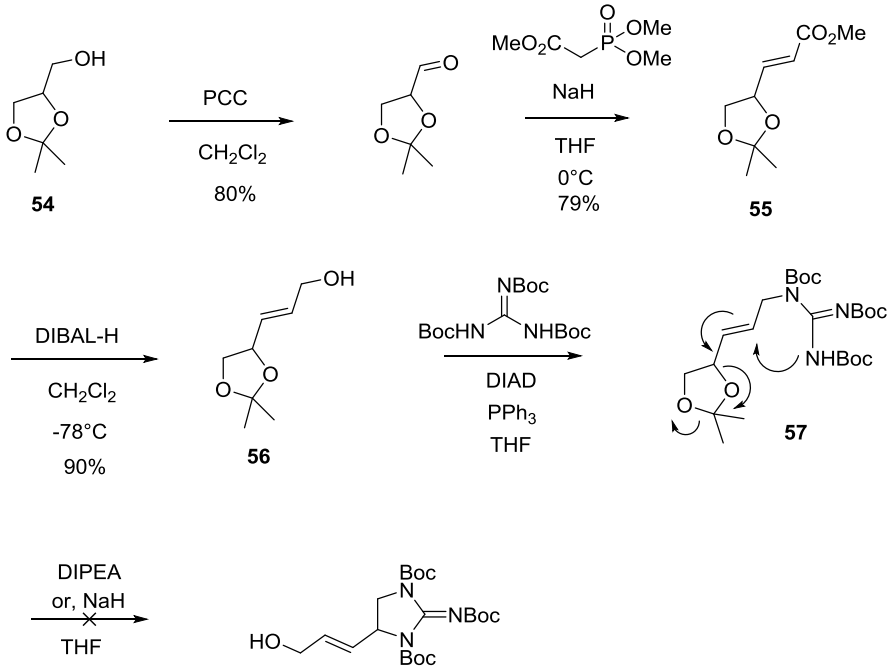


Scheme 22. Phthalimide participation

After seeing little success working towards the fully oxidized imidazole system, we decided to move towards the dihydroimidazole instead. During the cyclization processes of the more complex compounds of the oroidin alkaloids, the imidazole ring frequently loses its aromaticity. Since these compounds, such as axinellamines A (**10**) and B (**11**) and palau'amine (**14**) show promising biological activity, dihydrooroidin analogues would be interesting to study as well.

Our original work into the dihydro series began with commercially available 1,2-isopropylideneglycerol (**54**). Oxidation of the alcohol to an aldehyde followed by Horner-Wadsworth-Emmons olefination gave unsaturated ester **55** in good yields (Scheme 23).[49] Reduction of the ester with diisobutylaluminum hydride gave allylic

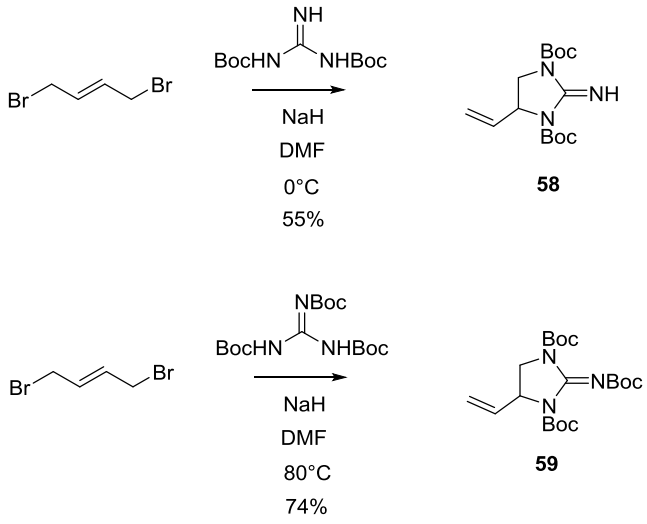
alcohol **56** which underwent a Mitsonobu reaction with tri-Boc protected guanidine, diisopropyl azodicarboxylate and triphenylphosphine to give **57**,[50] which was set up for intramolecular cyclization to give the dihydroimidazole. Unfortunately, the Mitsonobu reaction gave a low yield and the following cyclization step was unsuccessful using N,N-diisopropylethylamine or sodium hydride as base. The product was not observed at temperatures lower than 60 °C, while at 80 °C, the isopropylidene acetal was opened to the diol.



Scheme 23. Attempt towards dihydroimidazole intermediate

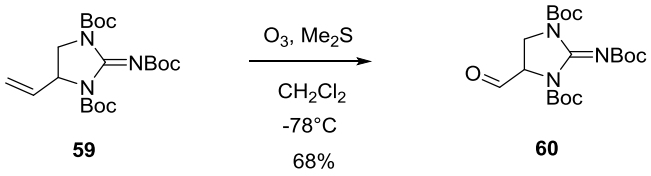
We then decided to modify our imidazole cyclization procedure in an attempt to make 2-amino-4-vinyldihydroimidazoles. Since we believe the electrophilicity of the aminoimidazole ring plays a role in the limited reactivity of the exocyclic double bond, we should be able to functionalize the double bond on the dihydro version. Employing

similar chemistry as for forming the imidazole, we used *trans*-1,4-dibromo-2-butene which reacted with di-Boc guanidine to give the dihydro product **58** in 55% yield (Scheme 24). When tri-Boc guanidine[51] was employed, 74% of the product (**59**) was obtained at an optimized temperature of 80 °C. The standard conditions for imidazole cyclization were not successful for either system. Dimethylformamide and sodium hydride were necessary for these reactions.



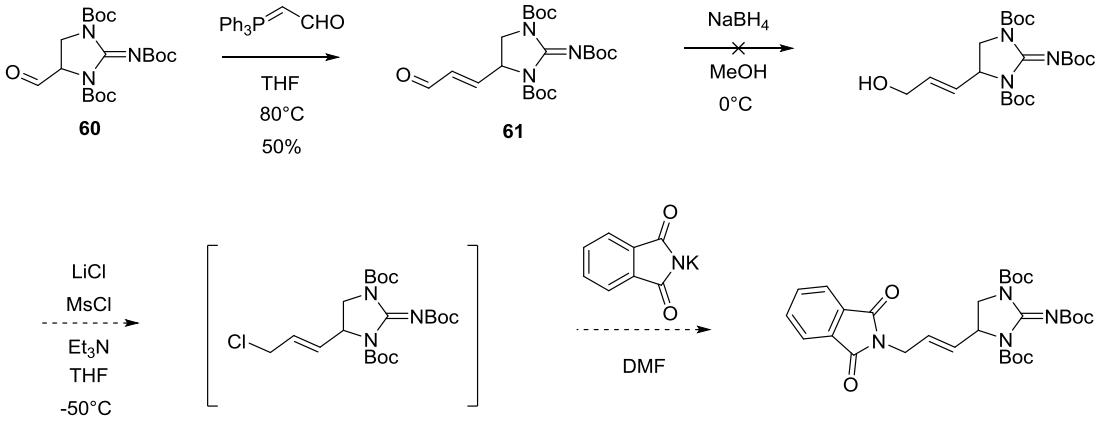
Scheme 24. Dihydroimidazole synthesis

With the dihydroimidazole compounds in hand, we attempted some of the reactions to functionalize the double bond. Since we optimized the reaction and will have to deprotect the Boc groups anyways, we decided to use compound **59** for further elaboration. While cross metathesis using the same conditions and catalysts was unsuccessful, we were able to form the aldehyde (**60**) through ozonolysis (Scheme 25). The crystalline product was suitable for reaction without further purification.



Scheme 25. Ozonolysis of **59**.

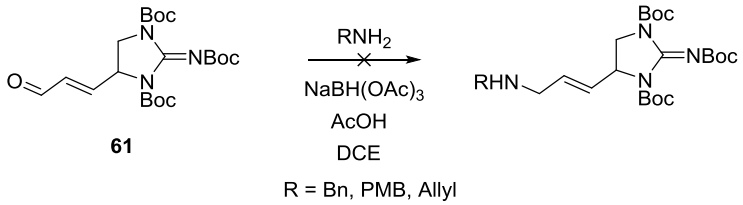
With the aldehyde now available, we thought to employ parts of the Romo synthesis[31] to get to the key allylic amine intermediate towards oroidin. Compound **60** underwent a Wittig reaction with commercially available (triphenylphosphoranylidene)acetaldehyde to give unsaturated aldehyde **61** (Scheme 26).[52] The Wittig reaction was sluggish at room temperature, but reaction in refluxing tetrahydrofuran afforded the desired product in 50% yield.. Attempts to reduce the aldehyde to the allylic alcohol[53] were surprisingly wrought with difficulties related to the loss of Boc groups.



Scheme 26. Towards key dihydro intermediate

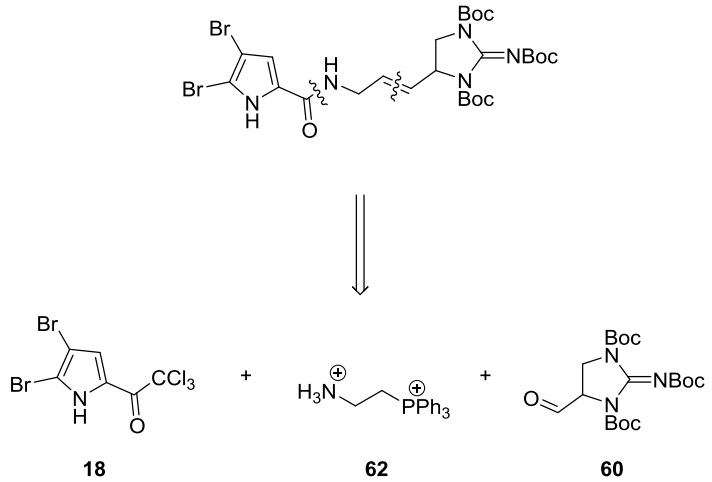
This result led us to try to get to the allylic amine directly from the unsaturated aldehyde (**61**). A successful reductive amination on this aldehyde would give the necessary protected allylic amine. Reductive amination has been shown to generate

allylic amines using sodium triacetoxyborohydride[54] and allylic aldehydes[55] under acidic conditions in dichloroethane (DCE). We employed allylamine, benzylamine and *p*-methoxybenzylamine (PMB) to react with **61**, but the transformation to the allylic amine was unsuccessful in all three cases (Scheme 27).



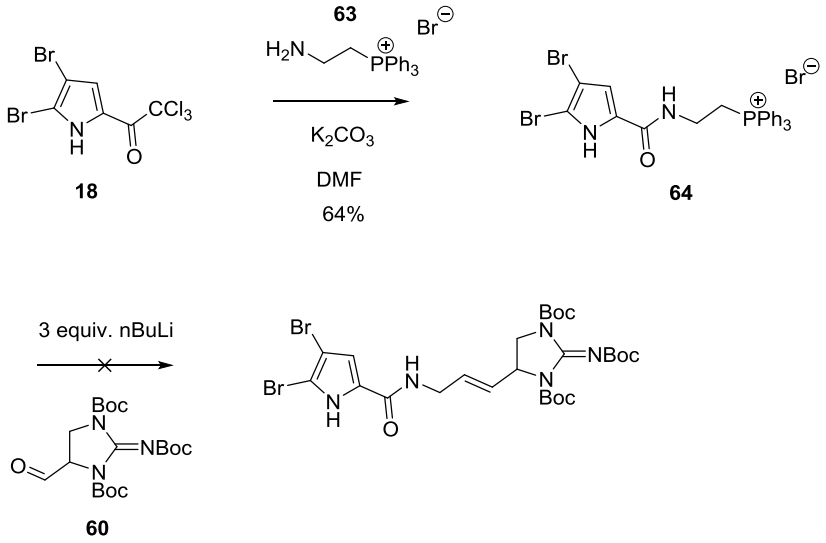
Scheme 27. Attempted reductive amination of **61**

We then started looking at putting together the dihydro compound with three components (Scheme 28); pyrrole **18**, phosphonium salt **62**, and our dihydroimidazole aldehyde **60**. The question became in which order to form the key amide bond and carbon-carbon double bond. Unfortunately, it turned out that the Wittig reaction between compounds **62** and **60** was unsuccessful.



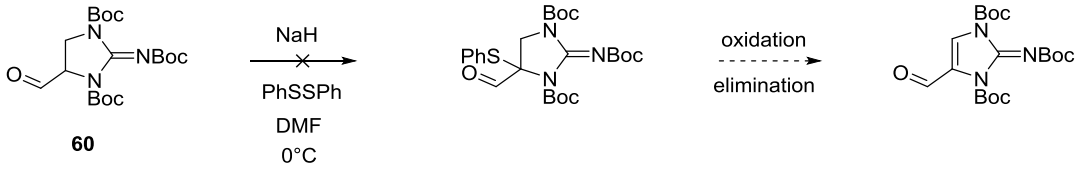
Scheme 28. Three-part approach retrosynthesis

We were then left with forming the amide bond first. Condensation of **18** with **63**,[39] which came from commercially available 2-bromoethylamine hydrobromide and triphenylphosphine,[56] gave phosphonium salt **64**[57] in 64% yield. This compound was set up for a trianion Wittig reaction with aldehyde **60**. To our dismay, this similar combination of aliphatic aldehyde and unstabilized Wittig reagent proved to be an unproductive route towards our desired product.



Scheme 29. Trianion Wittig reaction

With these attempts to transform the dihydroimidazole aldehyde (**60**) ultimately not getting us to the final dihydrooroidin product, we needed to look back at oxidizing **60** to the imidazole aldehyde represented in Ando's synthesis of oroidin.[32] We attempted a reaction published by the Kraus group[58] which installs a phenylsulfide group alpha to the carbonyl which can then be oxidized and eliminated to the unsaturated carbonyl compound (Scheme 30). This reaction did not show promise on our system either.

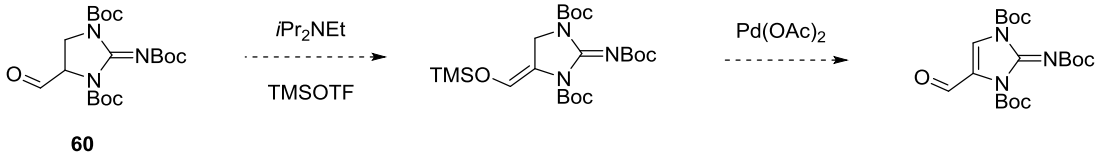


Scheme 30. Direct oxidation of aldehyde **60**.

Conclusion

We have devised and attempted many different approaches towards oroidin (**1**) and dihydrooroidin. We have explored ultimately unsuccessful routes but have developed new chemistry along the way and have gained more understanding on how the intermediate compounds toward this important marine alkaloid react. This knowledge should lead to improved syntheses of **1** in the near future.

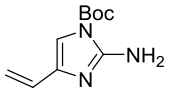
One idea we are still currently working on is oxidation of **60** to the imidazole aldehyde. Saegusa oxidation conditions have been used extensively to convert enol silyl ethers to unsaturated aldehydes using palladium(II) acetate.[59] We believe we can oxidize **60** by pre-forming the enol silyl ether using an excess of diisopropylethylamine and trimethylsilyl triflate (TMSOTf). This intermediate should be able to be oxidized by stoichiometric amounts of palladium(II) to the desired aldehyde (Scheme 31) to intercept Ando's oroidin synthesis. Our contributions to this work are in developing a novel method to form 2-amino-4-vinylimidazoles and dihydroimidazoles.



Scheme 31. Saegusa oxidation

Experimental

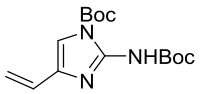
All NMR spectra were obtained on a Varian VXR spectrometer, operating at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR instrument. Thin-layer chromatography was performed using commercially available 250 micron silica gel plates (Analtech). Preparative thin-layer chromatography was performed using commercially available 1000 micron silica get plates (Analtech). Visualization of TLC plates was effected with short wavelength ultraviolet light (254 nm) or a potassium permanganate stain. All reagents were used as obtained commercially unless otherwise noted. High resolution mass spectra were recorded on an Agilent 6540 QTOF using EI, ESI, or ACPI. All reagents were used directly as obtained from commercial suppliers unless otherwise noted.



***tert*-Butyl 2-amino-4-vinyl-*1H*-imidazole-1-carboxylate (43a):**

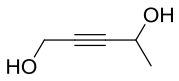
To a solution of N-Boc-guanidine (3 equiv) in tetrahydrofuran was added 1,4-dibromo-2-butyne (1 equiv) and N,N-diisopropylethylamine (3 equiv) sequentially. The mixture was refluxed for 12 h, and then cooled to rt and quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product which was purified *via* flash column chromatography (hexanes:EtOAc) to give **43a** in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.63 (s,

1H), 6.31 (dd, J = 10.8, 17.4 Hz, 1H), 6.20 (br s, 2H), 5.61 (dd, J = 1.8, 17.4 Hz, 1H), 5.05 (dd, J = 1.8, 10.8 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 149.4, 136.5, 127.8, 113.5, 108.7, 84.8, 28.0.



***tert*-Butyl 2-((*tert*-butoxycarbonyl)amino)-4-vinyl-*1H*-imidazole-1-carboxylate (43b):**

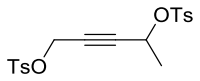
To a solution of **43a** in THF was added Boc_2O (1.2 equiv) and then a solution of NaHMDS (1.0 M, 1.1 equiv) in THF dropwise at 0 °C. After warming to rt overnight, the solution was quenched with sat. aq. NH_4Cl and extracted with EtOAc, washing with brine. The combined organic phases were dried over $MgSO_4$, and concentrated to give **43b** in 73% yield after flash chromatography (hexanes:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.15 (br s, 1H), 6.90 (s, 1H), 6.46 (dd, J = 11.1, 17.4 Hz, 1H), 5.94 (dd, J = 1.9, 17.3 Hz, 1H), 5.23 (dd, J = 1.5, 12.3 Hz, 1H), 1.53 (s, 9H), 1.50 (s, 9H).



Pent-2-yne-1,4-diol (47):

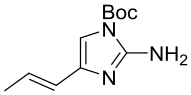
To a solution of propargyl alcohol in THF was added *n*BuLi (2.2 equiv) at -78 °C. After stirring 30 min, acetaldehyde (1.1 equiv) was added, stirred for 1 h at -78 °C and quenched with sat. aq. NH_4Cl. The crude mixture was extracted with Et_2O, washed with brine and dried over $MgSO_4$, followed by filtration and concentration. The residue was purified *via* flash chromatography (hexanes:EtOAc) to give **47** in 65% yield. ^{1}H NMR

(300 MHz, $CDCl_3$): δ = 4.57 (q, J = 6.3 Hz, 1H), 4.29 (s, 2H), 3.93 (br s, 1H), 3.86 (br s, 1H), 1.44 (d, J = 6.6 Hz, 3H).



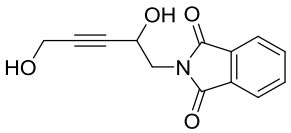
Pent-2-yne-1,4-diyl bis(4-methylbenzenesulfonate) (48):

Following the procedure for compound **47**, instead of quenching with NH_4Cl, TsCl (2.2 equiv) was added and allowed to warm to rt overnight. After diluting with hexanes, the solid was filtered and the residue was purified by flash chromatography (hexanes:EtOAc) to give **48** as a dark yellow liquid in 22% from propargyl alcohol. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, J = 7.8 Hz, 4H), 7.34 (d, J = 6.6 Hz, 4H), 5.02 (q, J = 6.9 Hz, 1H), 4.48 (d, J = 0.9 Hz, 2H), 2.43 (s, 6H), 1.37 (d, J = 6.6 Hz, 3H).



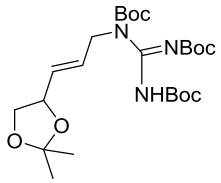
***tert*-Butyl 2-amino-4-(prop-1-en-1-yl)-*1H*-imidazole-1-carboxylate (49):**

Following the same procedure as for cyclization to **43a**, **48** was employed to give **49** in 40% yield as a clear oil after flash chromatography (hexanes:EtOAc). ^1H HMR (300 MHz, $CDCl_3$): δ = 6.72 (s, 1H), 6.32-6.22 (m, 1H), 6.07 (d, J = 12 Hz, 1H), 5.82 (br s, 2H), 1.94 (dd, J = 1.2, 7.2 Hz, 3H), 1.59 (s, 9H).



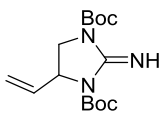
2-(2-5-Dihydroxypent-3-yn-1-yl)isoindoline-1,3-dione (51):

Following the procedure for **47**, the dianion of propargyl alcohol was quenched with N-(formylmethyl)phthalimide (**50**) to give **51** in 55% yield after flash chromatography (hexanes:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (dd, J = 3.3, 5.4 Hz, 2H), 7.75 (dd, J = 3.0, 5.4 Hz, 2H), 4.84-4.74 (m, 1H), 4.26 (s, 2H), 4.06 (dd, J = 6.3, 14.7 Hz, 1H), 3.95 (dd, J = 4.5, 14.4 Hz, 1H).



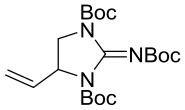
4,5-Isopropylidene-1-(tri(*tert*-butoxycarbonyl)guanidyl)-pent-2-ene (57):

To a solution of allylic alcohol **56** and tri-Boc-guanidine (3 equiv) in THF was added PPh_3 (1.5 equiv). At -15 °C, DIAD (1.5 equiv) was added dropwise and stirred at 0 °C for 1 h. The reaction was concentrated and the residue was purified *via* flash chromatography to give **57** in 45% yield. The product contained unreacted DIAD which was difficult to fully purify. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90-5.80 (m, 1H), 5.68-5.59 (m, 1H), 4.64 (br s, 1H), 4.52-4.40 (m, 1H), 4.37 (d, J = 6 Hz, 1H), 4.10 (d, J = 7.2 Hz, 1H), 4.05 (t, J = 7.2 Hz, 1H), 3.55 (t, J = 7.8 Hz, 1H), 1.49 (s, 9H), 1.48 (s, 9H), 1.47 (s, 9H), 1.45 (s, 3H), 1.43 (s, 3H). HRMS: *m/z* calcd for $C_{24}H_{41}N_3O_8$ [M^+]: 500.2913; found: 500.2971.



Di-*tert*-butyl 2-imino-4-vinylimidazolidine-1,3-dicarboxylate (58):

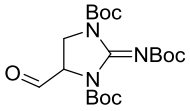
To a slurry of NaH (2 equiv) in DMF was added 1,3-bis(*tert*-butoxycarbonyl)guanidine (1 equiv) at 0 °C. After vigorous bubbling, *trans*-1,4-dibromo-2-butene was added in one portion. The reaction was allowed to warm to rt overnight, quenched with sat. aq. NH_4Cl and extracted with EtOAc, washing with brine. After drying over $MgSO_4$, filtering and concentrating *in vacuo*, the residue was purified with flash chromatography (hexanes:EtOAc) to give **58** in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81-5.72 (m, 1H), 5.19 (d, J = 16.2 Hz, 1H), 5.10 (d, J = 10.2 Hz, 1H), 4.32 (q, J = 7.5 Hz, 1H), 3.87 (t, J = 9.9 Hz, 1H), 3.39 (dd, J = 6.9, 10.5 Hz, 1H), 1.41 (s, 9H), 1.38 (s, 9H).



Di-*tert*-butyl 2-((*tert*-butyoxycarbonyl)imino)-4-vinylimidazolidine-1,3 dicarboxylate (59):

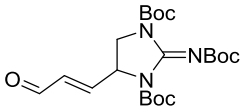
To a slurry of NaH (2 equiv) in DMF was added N, N', N''-tri-Boc-guanidine (1 equiv) at 0 °C. After 30 mins, *trans*-1,4-dibromo-2-butene was added in one portion. The reaction was warmed to rt, then heated to 80 °C for 12 h. After cooling, the reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc and brine, dried over $MgSO_4$, filtered and concentrated to give crude **59** in 74% yield, which was sufficiently pure for use in the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.82-5.71 (m, 1H), 5.39 (d, J = 16.8 Hz, 1H), 5.23 (d, J = 10.2 Hz, 1H), 4.55 (t, J = 6.3 Hz, 1H), 3.82 (dd, J = 8.4, 10.5 Hz, 1H), 3.57 (dd, J = 2.1, 10.8 Hz, 1H), 1.48 (s, 9H), 1.46 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2, 149.6, 149.3, 143.5, 134.6, 117.5, 83.3, 83.2, 80.0,

56.0, 48.6, 28.4, 28.2, 28.1. HRMS: *m/z* calcd for $C_{20}H_{33}N_3O_6$ [M^+]: 412.2413; found: 412.2440.



Di-*tert*-butyl 2-((*tert*-butoxycarbonyl)imino)-4-formylimidazolidine-1,3-dicarboxylate (60):

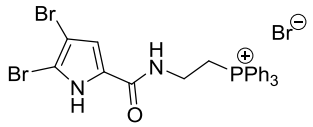
To a solution of **59** in CH_2Cl_2 was passed O_3 at -78 °C until the solution persists a blue color. The mixture was purged with argon until clear again, and Me_2S was added at -78 °C. After warming to rt over 24 h, the solution was quenched with water, extracted with CH_2Cl_2, washed with copious amounts of water and brine (to remove DMSO), dried over $MgSO_4$, filtered and concentrated. A slightly off-white solid is obtained in 68% and is sufficiently pure for further reactions. Attempts to purify the crude solid by flash chromatography lead to loss of the imine Boc group. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.59 (d, J = 1.5 Hz, 1H), 4.54-4.45 (m, 1H), 3.85 (dd, J = 6.0, 17.4 Hz, 1H), 3.75 (dd, J = 4.5, 11.1 Hz, 1H), 1.47 (s, 9H), 1.46 (s, 9H), 1.45 (s, 9H).



Di-tert-butyl 2-((tert-butoxycarbonyl)imino)-4-(3-oxoprop-1-en-1-yl)imidazolidine-1,3-dicarboxylate (61):

Compound **60** and (triphenylphosphoranylidene)acetaldehyde (1.1 equiv) in THF were heated to 80 °C for 5 h. The mixture was cooled, concentrated and purified by flash

chromatography (3:1 – 1:1 hexanes:EtOAc) to give **61** in 50% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.57 (d, J = 7.5 Hz, 1H), 6.80-6.68 (m, 1H), 6.21 (dd, J = 7.5, 15.9 Hz, 1H), 4.80 (dt, J = 3.0, 9.6 Hz, 1H), 3.94 (t, J = 10.8 Hz, 1H), 3.56 (dd, J = 3.3, 11.1 Hz, 1H), 1.49 (s, 9H), 1.47 (s, 9H), 1.42 (s, 9H). HRMS: *m/z* calcd for $C_{21}H_{33}N_3O_7$ [M^+]: 440.2332; found: 440.2396.



4,5-Dibromo-*N*-(2-(triphenylphosphanyl)ethyl)-*1H*-pyrrole-2-carboxamide bromide (64):

To a solution of **63** in DMF was added K_2CO_3 (2.2 equiv). After stirring 5 min, **18** (1.1 equiv) was added and stirred 16 h. The crude mixture was quenched with water, extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified with flash chromatography (10:1 – 5:1 hexanes:EtOAc) to give **64** as a white solid in 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.39 (br s, 1H), 7.92-7.57 (m, 15H), 6.81 (s, 1H), 3.87-3.78 (m, 2H), 3.56-3.48 (m, 2H).

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GENERAL CONCLUSIONS

The biorenewable synthesis of an important industrial compound, as well as the synthesis and study of heterocyclic natural products have been described in this dissertation. Chapter 1 focused on the development of a renewable synthesis of terephthalic acid, a precursor to food and beverage containers, produced worldwide in over 50 million tons a year. Malic acid, readily available from fruits and fermentation processes, was converted in high yields to coumalic acid using a strong acid as catalyst. Coumalic acid has been shown as the platform chemical for our novel one-pot Diels-Alder-decarboxylation-aromatization sequence which gives disubstituted aromatic compounds, such as terephthalic acid.

Chapter 2 discussed the Kraus indole synthesis and its application to natural products. A phosphonium salt was employed as the leaving group in the key six-electron ring closure step. Starting materials were chosen that would yield indoles which have the required functionality to further elaborate to natural product systems with diverse biological activities. Isocryptolepine, as well as the parent structure of the indolo[2,1-*a*]isoquinoline series of compounds have been prepared in good yields using our novel route to indoles.

Chapter 3 described our efforts towards the synthesis of the marine alkaloid oroidin. Recent discovery of its antibiofilm activity make this compound an important target for synthesis, along with structural analogues. We initially approached the compound with a cross metathesis reaction to link the 2-aminoimidazole head and

bromopyrrole tail of the molecule. We developed a key cyclization of a protected guanidine with 1,4-dibromo-2-butyne to give 2-amino-4-vinylimidazole products. We also pursued routes towards the dihydroimidazole analogue, seeking new compounds for study. Using 1,4-dibromo-2-butene and the guanidine furnished the dihydro structure. Based on the poor reactivity of the vinylimidazole system, we focused on pursuing an oxidation of the dihydro compound to the imidazole which would intersect with previous syntheses of the compound.