STUDIES TOWARDS THE TOTAL SYNTHESIS OF HAPLOSCLERIDAMINE AND CERATINADIN B

by

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Abstract

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In Chapter 1, we discuss the synthesis of haploscleridamine. Haploscleridamine is a novel tryptamine-derived alkaloid isolated from a sponge of the order Haplosclerida. This alkaloid inhibits cathepsin K, a cysteine protease, which is involved in the catabolism of elastin, collagen, and gelatin allowing the breakdown of bone and cartilage. Cathepsin K “blockers” show great potential in the treatment of osteoporosis. Building off earlier studies, we adopted a novel application of the Buchwald indole synthesis instead of a traditional Fischer indole synthesis to construct the β-carboline fragment. Starting from L-histidine, after several steps including a ring closing metathesis, a cyclohexanone was formed, which is the key precursor for indole formation. In chapter 2, we introduce a novel indole synthesis: a modified Buchwald indole synthesis, which provided mono tosyl protected haploscleridamine. Following deprotection of tosyl group, the natural product haploscleridamine was formed. Because of separation problem, the overall yield was not determined.

Ceratinadin B, a quinolone-imidazole-containing alkaloid, was isolated from the marine sponge of a species of Oceanopia. This alkaloid was first discovered in 2001 by researchers at the NIH as a possible inhibitor of a key enzyme in the detoxification cycle of Mycobacterium tuberculosis and other Mycobacterium.
In Chapter 3, we briefly introduce tuberculosis, which is currently the second highest cause of death worldwide. New strategies for treating the disease, such as those offered by the alkaloid described above are of special interest because they attack unique enzymatic pathways of the bacterium species that is not found in the human host.

Chapter 4 of this dissertation describes a synthetic route to this marine alkaloid which is predicated on the assembly and union of two key fragments: a spiroisoxazoline and an imidazole-quinolone. The spiroisoxazoline fragment was synthesized by using a novel asymmetric palladium-catalyzed dearomatizing spirocyclization instead of chiral auxiliary supported methods reported in the literature. The preparation of the 2-amino-4,5-disubstituted imidazole fragment started from an α-bromoketone and a monoacetylguanidine derivative. A modified Meldrum’s acid derivative permitted access to the 3-Cbz protected quinolone derivative utilizing Gould–Jacobs quinoline synthesis. The Cbz, acetyl and phthalimidoyl groups were deprotected by hydrazine in one pot. Excess BBr₃ was added to deprotect the two methyl groups attached to benzene ring. Finally, the two fragments, the isoxazoline and the imidazole-quinolone could be coupled to form ceratinadin B.
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Chapter 1

Total Synthesis of Haploscleridamine

1.1 Natural Products

Organic compounds from terrestrial and marine organisms have seen extensive use in the treatment of many diseases and serve as compounds of interest both in their natural form and as templates for synthetic modification.\(^1\) In recent years, however, marine organisms such as sponges, tunicates, shell-less mollusks, and others are increasingly attracting attention due to their production of structurally unique and pharmacologically active compounds (Figure 1.1).

![Chemical structures of natural products](image)

Figure 1.1 Some Marine Natural Products

The chemistry and biology of indole, annulated indole and carbazole alkaloids containing an imidazole ring derived from marine sources is a steadily growing and is a
very promising source for the development of pharmacologically active compounds.\textsuperscript{2} Indole alkaloids have been extensively investigated for a wide variety of pharmacological effects, including anti-tumor, anti-inflammatory, anti-malarial, anti-HIV, contraceptive and bactericidal activities, as well as for stimulatory action on the central nervous systems.\textsuperscript{1a} To date, more than 2000 different compounds of this class have been isolated and are one of the most studied classes of alkaloids due to their CNS related activity, their anti-cancer activity, and their potential use as anti-addiction agents.\textsuperscript{1a–c}
1.2 Importance of Natural Products as Drugs

In early times, all drugs and medicinal agents were derived from natural substances, and most of these remedies were obtained from plants. Today, many new chemotherapeutic agents are synthetically derived, based on “rational” drug design. However, many clinically used drugs can trace their origins either directly or indirectly to natural products. The study of natural products has advantages over de novo drug design is that it often leads to materials having new structural features with novel biological activities. Nature continues to be one of the most important sources of pharmacologically active compounds in the quest for drugs against life-threatening diseases such as microbial infections, diseases of the heart, the circulatory system, cancer, and others. Almost 40% of the top selling pharmaceutical drugs are natural products or natural product derivatives even though compounds from nature, constitute less than 1% of the molecules structurally known today.

Natural products (their derivatives and analogs) still represent over 40% of all drugs in clinical use, with higher plant-derived natural products representing ca. 25% of the total. The World Health Organization estimates that 80% of people in developing countries of the world rely on traditional medicine for their primary health care, and about 85% of traditional medicine involves the use of plant extracts. This means that about 3.5 to 4 billion people in the world rely on plants as sources of drugs.

Conservative estimates suggest that there are more than 250,000 species of plants existing on this planet, and only a very small percentage of plants have been exhaustively studied for their potential value as a source of drugs. Obviously, natural products will continue to be extremely important as sources of medicinal agents. Remarkably, despite these compelling arguments large pharmaceutical industry has mostly exited from investigating natural products in drug discovery efforts. In addition to
the natural products which have found direct medicinal application as drug entities, many others can serve as chemical models or templates for the design, synthesis, and semisynthesis of novel substances for treating disease. Although there are some new approaches to drug discovery, such as combinatorial chemistry, fragment based screening and computer-based molecular modeling design, it has not been shown that they can replace the important role of natural products in drug discovery and development.

Alkaloids are (in a chemical sense) basic natural products occurring primarily in plants that in most cases, are nitrogen-containing heterocyclic which exhibit pronounced physiological activities. By 2008, over 12,000 alkaloids of various structural types have been identified. The biogenesis of alkaloids involves the derivatization of amino acids especially ornithine, lysine, phenylalanine, tyrosine and tryptophan. Akin to other natural products, the micro-scale occurrence of alkaloids in nature makes their isolation and their broad scale pharmacological evaluation difficult. Furthermore, preparing derivatives of natural products which aid in the identification of pharmacophore (i.e., the minimal active moiety), becomes a tedious task with a limited amount of material and chemoselectivity issues. The total synthesis of natural products can provide sufficient material to enable a complete pharmacological evaluation. An additional benefit is that total synthesis can allow the preparation of a number of structural analogs, which may play a crucial role in identifying the active pharmacophore. Once the active parts of the natural products are determined, structure-activity relationships can be established, and possibly a mechanism of action. This information in turn can provide an opportunity to develop a novel therapeutic agent.
1.3 β-Carboline Imidazole Alkaloids

A large number of alkaloids containing imidazole rings have been isolated from natural sources which are different in structure and origin (Figure 1.2). These compounds have been found in plants (e.g., Cactaeae, Euphorbiaceae, and Orchidacea), in bacteria (e.g., Aspergillus species), in fungi (e.g., Streptomyces and Penicillium species), and in animal sources (mainly marine sponges).

![Chemical structures of alkaloids](image)

Figure 1.2 β-Carboline Imidazole Alkaloids Villagorgin A and B

Many of these systems are found to exhibit pronounced biological activity, including antimicrobial, antitumor and antiviral activities. Villagorgin A (9) and villagorgin B (10) were isolated from the gorgonian Villagorgia rubra found in New Caledonia. Ricardo and coworkers focused their attention on the gorgonian Villagorgia rubra, which was selected for study because the methanol extracts were very active in the guinea-pig ileum contraction test. V. rubra is a rich source of nitrogenous metabolites that were isolated from the butanolic fraction and identified as caffeine, the simple indoles, tryptamine, 1,2,3,4-tetrahydro-β-carboline and two new complex indole alkaloids named villagorgin A (9) and villagorgin B (10). The structure and absolute configuration of the villagorgins were deduced by extensive use of 2D-NMR, FABMS and HREIMS, and CD
data. It was further determined that villagorgin A (9) has calmodulin-related antagonist activity. Calmodulin is a calcium–binding protein that is involved in the regulation of various cellular functions including inflammation, metabolism, muscle contraction, intracellular movement, short-term and long-term memory, nerve growth and the immune response.18

A Closely related alkaloid is haploscleridamine (11), a novel tryptamine derived alkaloid from a sponge of the order Haplosclerida.19,20 This alkaloid inhibits cathepsin K, a cysteine protease, which is involved in the catabolism of elastin, collagen, and gelatin allowing the breakdown of bone and cartilage. Cathepsin K “blockers” show great potential in the treatment of osteoporosis.19

All of these molecules are chiral but appear to have lost their optical activity during isolation and purification (Figure 1.3).26

From a biosynthetic perspective, lessoclin C 15 is formally obtained from condensation of 6-bromotryptamine with C2 rather than C1 of 4-imidazolopyruvic acid, probably derived by transamination from histidine, followed by the loss of C1 carboxylate.
Lessoclin C 15 is chiral, but the optical activity of the isolated natural product was almost zero. Both the specific rotation and circular dichroism spectrum (CD) of the TFA salt of Lessoclin C 15 were negligible; thus indicating the compound was nearly racemic. Brossi and Cook have pointed out that C1-substituted tetrahydro-β-carbolines readily racemize in acidic solution,\textsuperscript{26} a property that is enhanced with substitution of C6 (indole numbering) with electron-donating groups. Although the mechanism of racemization is not clear, a possible explanation for loss of optical activity lessoclin C 15 would involve protonation of the piperidine ring followed by reversible ring opening to the achiral intermediate 16, stabilized by electron donating from 7-bromo substituent (Scheme 1.1).\textsuperscript{26}

![Scheme 1.1 Possible Mechanism for Loss of Optical Activity](image-url)
1.4 Reported Synthesis on Villagorgin

Villagorgin A (9) and villagorgin B (10) are attractive synthetic targets due to their biological properties and their novel structure. However, since their isolation in 1993, these alkaloids have not attracted substantial synthetic attention. Kuehne and coworkers have been the only group so far to publish a synthetic approach to these two natural products, leading to racemic material. Their synthetic route involved a reduction, followed by a Pictet-Spengler-like cyclization of an indolylethylimidazopyridium salt. Subsequent oxidation of villagorgin A (9) with mercuric acetate gave villagorgin B (10) (Scheme 1.2).21

Scheme 1.2 Synthesis of Racemic Villagorgin

A previous Lovely group member, Ms. Koda began working on an asymmetric approach toward the total synthesis of haploscleridamine and villagorgin A. Details of the synthesis will be discussed in the subsequent chapter of this thesis. However, prior to the development of this route, an alternative approach was explored.
1.5 Initial Retrosynthetic Analysis of Villagorgin

The planned synthesis of these imidazole derivatives employed the well-known Pictet-Spengler\textsuperscript{22-25} and Fischer indole reactions;\textsuperscript{24} these transformations have been extensively used with imidazole containing substrate and in particular in total synthesis endeavors. A potentially versatile and attractive route for the synthesis of imidazolyl β-carboline ring systems using the amino acid \textit{L}-histidine as starting material was designed (Scheme 1.3)

All together three different routes to access villagorgin A were explored by our lab. Koda attempted to assemble the key intermediate either from a Dieckmann cyclization\textsuperscript{27, 28} or through ring-closing metathesis of the appropriate diene (Scheme 1.3, 1.4 and 1.5).

![Scheme 1.3 Retrosynthetic Analysis (Route I) for Villagorgin A](image-url)
Scheme 1.4 Retrosynthetic Analysis (Route II) for Villagorgin A

Two different retrosynthetic routes, involving a Dieckmann condensation were proposed (Scheme 1.3 and 1.4). In route I, the retrosynthetic approach employs a Pictet-Spengler reaction early in the sequence followed by Fischer indole synthesis, whereas in route II, the Pictet-Spengler reaction will be employed in the later stages of the synthesis. Route II, is also synthetically appealing because it potentially gives access to haploscleridamine which is structurally related to villagorgin A, except it is devoid of the D-ring. This sequence of disconnections will allow the synthesis of non-racemic villagorgin A via haploscleridamine. In addition, if the Fischer indole synthesis is carried out under non-acidic conditions, it should be possible to obtain both antipodes of haploscleridamine starting from either enantiomer of histidine.

Initial attempts to employ the Dieckmann route were unsuccessful as difficulties were encountered in the construction of molecules related to 23. Furthermore, the Dieckmann condensation is a potentially risky step in these two approaches, due to the presence of acidic protons in the substrate which means that it can potentially undergo racemization. In order to avoid racemization we investigated another approach towards
villagorgin A, a second generation approach involving – ring closing metathesis (RCM) (Scheme 1.5).

Scheme 1.5 Second Generation Approach – RCM

In our second generation synthesis of haploscleridine and villagorgin A, we adopted second generation Grubbs’ catalyst to construct the key α,β-unsaturated ketone via ring-closing metathesis. After reduction of conjugated double bond by hydrogenation, the saturated cyclohexanone was obtained. However, after repeating Ms. Koda’s Heck-type indole synthesis, we were surprised to find that there were intramolecular annulations reactions, not the indolization (see Scheme 2.15). We believe that the basic conditions were not appropriate for indolization, because C4-H on imidazole is relatively active under basic conditions while N-H on imidazole was protected by strong electron-withdrawing group such as Ts group. Thus indole synthesis under acidic condition is the
best choice. It is known that the Fischer Indole synthesis is usually carried out acidic conditions with reagents such as PPA (polyphosphoric acid), sulfuric acid, HCl (aq), and even some Lewis acids etc. So, we designed a new approach to the indole fragment synthesis from an acyclic ketone (third generation synthesis)
1.6 Fischer Indole Synthesis

1.6.1 Fischer Indole Synthesis Introduction

The cyclization of aryl hydrazones to form indoles, known as the Fischer Indole synthesis, is based on the discovery of the reaction a century ago by Emil Fischer. This reaction has become one of the most versatile and widely studied reactions in organic chemistry. The reaction of a (substituted) phenyl hydrazine with an aldehyde or ketone initially forms a phenyl hydrazone which isomerizes to the corresponding enamine (ene-hydrazine). After protonation, a [3,3]-sigmatropic rearrangement occurs producing an imine. The resulting imine forms a cyclic aminoacetal (or aminal), which under acid catalysis eliminates NH₃, resulting in the energetically favorable aromatic indole (Scheme 1.6).

Scheme 1.6 Fischer Indole Synthesis Mechanism
Initial attempts to perform Fischer indole synthesis in the context of our project by using either an acyclic or cyclic ketone under strongly acidic condition such as PPA, TsOH, concentrated HCl, even ZnCl₂ were not successful. We found that there were two major drawbacks with the traditional Fischer indole reaction; the yields were low with numerous byproducts being formed and reactions involving unsymmetrical hydrazines or ketones often give products of mixed regioselectivity, which results in separation difficulties.³⁰-³⁶

1.6.2 Buchwald Indole Synthesis (Fischer Indole Synthesis Transformation)

Using palladium chemistry developed at MIT by Stephen Buchwald, the Fischer indole synthesis can be accomplished using aryl bromides as starting materials to generate the corresponding indole.³⁷ In contrast to simple hydrazones derived from nonaromatic ketones, N-arylbenzophenone hydrazones could typically be stored for weeks on the bench top without significant decomposition.³⁸ This transformation was discovered during attempts to affect the hydrolysis of these compounds afforded the desired N-aryl hydrazine in low yield, along with the corresponding aniline side-product resulting from N-N bond cleavage of the aryl hydrazine. Based on this observation, Buchwald group developed a modified approach. The hydrolysis of hydrazones can generally be promoted by trapping the liberated hydrazine with an excess of an aldehyde or ketone.³⁹ In the case of N-aryl benzophenone hydrazones, the hydrolysis in the presence of a ketone could produce an enolizable hydrazone that would undergo Fischer indolization under the acidic reaction conditions.⁴⁰ This strategy is advantageous from two perspectives. First, it would obviate the need to prepare or isolate potentially sensitive aryl hydrazines. Second, it would provide a potentially very general means to the N-aryl hydrazones precursors for Fischer indolization from a single, commercially available precursor. They found that the best results were obtained using p-
toluenesulfonic acid monohydrate (p-TsOH·H₂O). In this way a 95% yield of 3-chloro-6,7,8,9-tetrahydro-5H-carbazole was realized. They found that the p-TsOH·H₂O generally provides sufficient water to effect hydrolysis of the N-aryl benzophenone hydrazone. Although THF was found to be a satisfactory solvent in this procedure, protocols which utilized ethanol were frequently found to be preferable.

\[
\begin{align*}
\text{R} & \quad + \quad \text{H₂N}N\text{PhPh} \quad \xrightarrow{[\text{Pd}]} \quad \text{R} \quad + \quad \text{NH₂NPhPh} \\
\text{R} & \quad \text{Ph} \quad \text{NH} \quad \quad \quad \text{Ph} \\
\text{N} & \quad + \quad \text{O} \quad \quad \quad \text{Ph} \quad \quad \quad \text{R} \quad \text{O} \\
\text{R} & \quad \text{Br} \quad \text{N} \quad \quad \quad \text{Ph} \quad \quad \quad \text{R} \quad \text{R}^1 \quad \text{R}^2 \\
\text{N} & \quad \text{NH} \quad \quad \quad \text{Ph} \quad \quad \quad \text{R} \quad \text{R}^1 \quad \text{R}^2
\end{align*}
\]

\[\text{Scheme 1.7 Buchwald Indole Syntheses}\]

As shown in Scheme 1.7, aryl hydrazone 37 and ketone 38 are in dynamic equilibrium. Hydrazone 37, however, is irreversibly consumed in the Fischer indolization process, thus driving the reaction to completion.

Regioselectivity with respect to the ketone component was consistent with rate-limiting sigmatropic rearrangement of the more substituted ene-hydrazone. In all cases
where unsymmetrical ketones were employed, only one regioisomer of the product was observed. Based on these considerations, it appears that the Buchwald indole synthesis is the best choice for synthesis of haploscleridamine, since a nonsymmetric ketone is to be used.
1.7 Olefin Ring-Closing Metathesis Reactions

Ring-closing metathesis (RCM) is an extremely powerful method for the formation of carbon-carbon bonds in the construction of unsaturated cyclic systems from acyclic dienes. According to the generally accepted mechanism, the reaction proceeds via a sequence of [2+2] cycloaddition/cycloreversion reactions and is mainly driven by entropy gained by release of ethylene or other volatile side products (Scheme 1.8).\textsuperscript{41-44}
Chapter 2

Result and Discussions

2.1 First Generation Approach – Palladium catalyzed Indole synthesis

The synthesis of cyclohexanone 43 has been described previously by Karuna Koda in our lab; however, several improvements were implemented to make product separation more convenient resulting in higher yield. Her initial forward synthesis is shown below: (Scheme 2.1).

Scheme 2.1 Ms. Koda’s Forward Synthesis
2.1.1 Preparation of Histidine Methyl Ester

There are many conditions to prepare L-histidine methyl ester. Previously, our group used methanol as solvent with addition of a catalytic amount of concentrated sulfuric acid. However, the reaction did not always go to completion, which accorded workup difficulties because histidine and its methyl ester are both soluble in water. As a result, it is very difficult to extract the desired product from water. Accordingly, we revised the procedure and used saturated HCl/MeOH with refluxing, overnight. After concentration, we could obtain the pure L-histidine methyl ester as the dihydrochloride salt, which can be then used directly for next step without purification (Scheme 2.2).

![Scheme 2.2 Synthesis of L-histidine methyl ester](image)

2.1.2 Protection of Histidine Methyl Ester

Installing a blocking group which protects the N-position of imidazole moiety against racemization of the histidine at the α-carbon center, an electron-withdrawing group was used to protect N1 in the imidazole to decrease the basicity of N3. Treatment of histidine methyl ester with four equivalents of triethylamine in dichloromethane and two equivalents of tosyl chloride provided the histidine ditosylate 29 in 86% yield (Scheme 2.3). After repeating Koda’s experiment, we found that histidine ditosylate 29 has poor solubility in DCM, EtOAc and other common solvents, thus, it is very hard to extract it from reaction mixture. Based on its solubility, we revised the procedure: after the reaction is as complete as monitored by TLC, water is added to the
reaction mixture, vacuum filtration delivers a white solid. After washing the white solid with water and hexanes several times, subsequent drying affords the pure product. The NMR spectra show no indication of the formation of mixtures of isomers (i.e. N-3 derivatives) and the spectra are consistent with the literature data.\(^4\)

2.1.3 Allylation

Reaction of ditosylated intermediate 29 with two equivalents of allyl bromide in the presence of two equivalents of K\(_2\)CO\(_3\) at room temperature yielded the N-allylated ester 30 (Scheme 2.4).\(^5\) This reaction is very clean reaction and product can be used directly for next step without purification.

2.1.4 Oxidation of Cyclic Allylic Alcohol

Following Koda’s procedure, allylic alcohol 32 was obtained from 29. To oxidize the allylic alcohol, 1.1 equivalents of IBX were added to an acetone solution of the alcohol. After 1 h under reflux condition, the reaction was complete as monitored by TLC
(scheme 2.5). It was observed that the reaction was slow if ethyl acetate was used as the solvent. A possible explanation for this observation is that IBX has higher solubility in acetone than in ethyl acetate. Meanwhile, the workup of this reaction is very easy: after concentration, addition of a small amount of ethyl acetate to tritrate the residue, then vacuum filtration to afford the pure product.

![Scheme 2.5 Oxidation of Allyl Alcohol](image)

**Scheme 2.5 Oxidation of Allyl Alcohol**

### 2.1.5 Heck Reaction to Construct the Indole Ring

Starting from saturated cyclic ketone 43 and 2-bromoaniline, a Heck-like reaction was carried out following Larsen's procedure. After carefully checking the side product $^1$H NMR spectra, we found that instead of a Heck reaction, intramolecular annulation occurred as depicted in scheme 2.6 according to the mass spectrum. From the structure of ditosyl protected saturated ketone, we can see that the proton attached to C-5 of imidazole is relatively acidic. The pKa of chiral proton and methylene proton attached to N$_3$ is close, thus, the regioselectivity is similar. Presumably nucleophilic attack by C-5 on the cyclic ketone forms the tertiary alcohol, then dehydration to provide 44 and 45 with almost equal ratio.
Scheme 2.6 Heck Reaction

2.2 Third Generation Approach – Buchwald Indole Synthesis

The following two schemes describe the third generation retrosynthesis and forward synthesis route separately.

Scheme 2.7 Third Generation Retrosynthesis
2.2.1 N-Benzyl protection of sulfonamide

Reaction of tosylated product 29 with two equivalents of benzyl bromide in the presence of two equivalents of K₂CO₃ at room temperature yielded the N-allylated ester 46. This reaction is a very clean reaction. The product can be used directly for next step without further purification.
2.2.2 Methyl ester reduction

With the benzyl protected methyl ester 46 in hand, the next step was selective reduction of the methyl ester group. The ester group was reduced selectively to the aldehyde by using Dibal-H at -78 °C and dichloromethane as solvent. The identity of the product obtained 47 was confirmed through 1H NMR spectroscopy analysis as distinct aldehyde peak at δ 9.35 and was observed along with the disappearance of the methyl ester peak at δ 3.4. (Scheme 2.10)

2.2.3 Preparation of Alcohol

Aldehyde 47, on treatment with 3-benzyloxypropanoyl magnesium bromide Grignard reagent, afforded allylic alcohol 48 with an overall yield of 89%. The experiment was conducted at -78 °C in THF and the Grignard reagent was prepared by treating magnesium turnings with 1-((3-chloropropoxy)methyl)benzene (Scheme 2.11).
2.2.4 Oxidation of Alcohol

At this point, we investigated the preparation of the indole synthesis precursor: acyclic ketone 49. To obtain the ketone, several methods to oxidize this chiral alcohol were screened. IBX oxidation using DMSO as solvent and the TPAP/NMO oxidation were tested, but these methods failed to provide the desired ketone with good yield. Eventually, the Swern oxidation was tested. Fortunately, this method successfully provided the desired acyclic ketone; this reaction is very clean. After workup and concentration, the residue can be used directly for next step without purification (Scheme 2.12).

2.2.5 Buchwald Indolization starting from acyclic Ketone 49

Since the Buchwald group has already tested different aryl hydrazones, we believe that this kind of indole synthesis would be effective for non-substituted benzyl hydrazone. Firstly, we conducted the experiment with 1 equivalent of hydrazine 52, one
equivalent linear ketone 49 and 3 equivalents \( p\)-TsOH\( \cdot \)H\(_2\)O. We found that the yield was low and there was still unreacted hydrazone and a high percentage of mono-tosyl protected ketone recovered. Thus, we increased the amount of hydrazine to 3 equivalents and \( p\)-TsOH\( \cdot \)H\(_2\)O to 5 equivalents and one equivalent linear ketone. After refluxing for four days, most of the ketone was consumed and a very small ratio of the benzyl group was deprotected. Because indole intermediate 50 is hard to separate by column chromatography, we decided to continue to the next step without purification. We attempted to use general hydrogenolysis condition to deprotects OBn. However, we were surprised to discover that only reduction of the C2-C3 bond was occurred according to \(^1\)H NMR. In the \(^1\)H NMR spectrum of the crude reaction product, the chemical shift of the methylene group attached to the indole ring is a multiplet around 2.5. After reduction, these peaks disappeared. In the chemical shift 1.2 area, new peaks appeared. Based on this observation, indole ring reduction could be proved. Meanwhile, according to the \(^1\)H NMR spectrum, the benzyl group attached to oxygen was retained. But the benzyl group attached to the sulfonamide moiety was deprotected because its characteristic peak disappeared in the \(^1\)H NMR spectrum (Scheme 2.13).
Since the deprotection of benzyl group using general hydrogenation conditions clearly failed, there are two possible ways to circumvent the problems: one way is to protect NH attached to indole; an alternative approach is to use cyclic ketone as Buchwald indole synthesis precursor. If we were to adopt the first way, we would have to increase the number of protection groups, which would increase the number of synthetic steps, therefore, the second choice appears to be better. As a result we decided to go back to Ms. Koda’s former route. We hypothesized that if we use a cyclic ketone, we could avoid the OBn deprotection problem and potentially simplify the synthetic route.

2.2.6 Indole Moiety Insertion: Buchwald Indole Synthesis (cyclic ketone)

Following the first generation synthetic route, the cyclic ketone was obtained. By using the same Buchwald Indole synthesis conditions, mono-tosyl protected haploscleridamine 53 was obtained based on its mass spectrum and $^1$HNMR. Treating mono-tosyl protected haploscleridamine with magnesium in methanol could deprotect the
tosyl group with good conversion. However, until now, because of purification problems, we have yet to obtain the exact final yield. (Scheme 2.14)

Scheme 2.14 Synthesis of Haploscleridamine by Using Buchwald Indolization

While running the column by adding Et₃N as eluent, we are surprised to find that haploscleridamine appears to be oxidized. After checking the ¹H NMR spectrum the crude product, we found that the signal of one of the methylene groups attached to indole ring disappeared. After checking the IR spectrum, we found there is a new carbonyl peak at 1710 cm⁻¹. One possibility is hydrolysis via a retro Pictec-Spengler or another possibility is the Winterfeldt oxidation. Dr. Jiang has reported the preparation of optically pure pyrroloquinolones from a Winterfeldt oxidation of the β-carbolines without epimerization as depicted in Scheme 2.15.⁵⁷

Scheme 2.15 Jiang’s Synthesis of Dihydropyrrolo[3,2-b]-quinolones
In 2012, Prof. Zhu reported the synthesis of dihydropyrrolo[3,2-b]-quinolone from Winterfeldt oxidation of the γ-1,2,3,4-tetrahydro-carboline (Scheme 2.16). He also postulated the oxidation mechanism as following (Scheme 2.17):
Because haploscleridamine has an imidazole and a β-carboline fragment, while exposed in air, the possible Winterfeldt oxidation will take place at basic condition. Also, without protection of β-carboline, the oxidation is very complicated. So, from the Winterfeldt oxidation condition, we can see that this reaction needs oxygen or air and base. While running regular column, usually small an amount of triethylamine was added to eluent to neutralize the silica gel. Meanwhile, it takes long time to finish running regular silica gel column. Gradually, Winterfeldt oxidation would take place. Maybe that is the possible reason for failure for regular column separation. To succeed in separation, there are two possible ways: one way is to add some formic acid to eluent; an alternative way is to use HPLC.
Chapter 3

Total Synthesis of Ceratinadin B

This part of the dissertation discusses the synthetic approaches towards ceratinadin B (a quinolone-imidazole-containing alkaloid), derived from the marine sponge species Oceanapia.\textsuperscript{59,60} This alkaloid was first discovered in 2001 by Bewley at the NIH as a possible inhibitor of a key enzyme in the detoxification cycle of Mycobacterium tuberculosis and isolated more recently a second time by Kobayashi.\textsuperscript{61,62}

Chapter 3 provides a brief introduction of tuberculosis, which is currently the second highest cause of death worldwide. New treatments are desperately needed and the alkaloid described above is of special interest because it exerts its activity through a unique enzymatic pathway in the bacterium that is not found in the human host.\textsuperscript{61}

Chapter 4 of this dissertation describes a potential synthetic route to this marine alkaloid which is predicated on the assembly and union of two key fragments: a spiro-isoxazoline and an imidazole-quinolone. The spiro-isoxazoline fragment was synthesized by using a novel palladium-catalyzed Wacker-type oxidation instead of initially proposed chiral auxiliary supported asymmetric dearomatization strategy. The imidazole fragment was formed by using a classical synthetic method for the synthesis of 2-amino-4,5-disubstituted imidazole derivative. The quinolone fragment could be obtained by using Gould–Jacobs quinoline synthesis.\textsuperscript{62} After formation of imidazole-quinolone fragment, there are problems with respect to protection strategies, which will be discussed later.
3.1 Background Introduction

3.1.1 TB and Anti-TB Drugs

Tuberculosis, MTB, or TB (short for tubercle bacillus) is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis*. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air. Most infections are asymptomatic and latent, but about one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those so infected.

Globally, there are 2 billion people, one third of the world’s population, infected with the bacterium that causes the lung disease tuberculosis (TB), with at least 15 million active TB cases in the US. According to a 2006 report from the Center for Disease Control (CDC), there are 4.6 cases of active TB per 100,000 people in the United States. Among the US-born population, there are 2.3/100,000, and 22.0/100,000 for the foreign-born population. Less than 1% of all cases have primary drug resistance to the two main anti-TB drugs, isoniazid (INH) and rifampin (RIF). Only 3 cases were considered extremely drug resistant to INH, RIF and several second-line drugs. 48% of all cases in the United States occurred in California, New York, Texas and Florida. 13% of cases among 25-44 year olds were dually infected with HIV.

Since TB cases in the US were rapidly decreasing in the 1970’s, much federal TB funding was eliminated. There was almost a 30 year period in which no new drugs for TB had been developed. During this time, primary drug resistance was seen in all first-line anti-TB drugs, and in many second-line drugs.
One main issue keeping TB drugs from being developed is drug companies. TB is considered an orphan disease; too few people are infected in developed nations to create the market needed to fuel the drug development. Drug companies often sell drugs for more in industrialized countries so they can subsidize the costs in poorer countries. With few patients in richer countries, TB drugs are not an attractive target for pharmaceutical companies. In the US, treatment for a full course of anti-TB drugs costs $900, whereas in developing countries, only $11.

Since there is existing resistance to all first and second-line anti-TB drugs, researchers are looking at new pathways for fighting the disease. Jachak and Jain reviewed the recent literature about anti-mycobacterial agents. Many of the newly discovered natural products were being tested on new enzymatic pathways that targeted the synthesis of the antimycobacterial cell wall component mycolic acid or antibiotic detoxification. The waxy outer layer of the bacteria is made mostly of mycolic acids, which control the permeability and fluidity of the cell wall. These drugs are attractive towards both the treatment of drug-resistant strains of *M. tuberculosis* and emerging mycobacterium pathogens, such as *M. avium* complex.

3.1.2 Inhibitors of Mycothiol S-Conjugate Amidase (MCA)

From 2001-2003, Bewley et al. published a description of a series of natural product MCA inhibitors that were isolated from the marine sponge species *Oceanapia* and *Pseudoceratina* (Figure 3.6). The products were screened using a fluorescence-detected assay for MCA inhibition by measuring the extent of cleavage of mycothiol bimane (MSmB). Included in this group of inhibitors were several bromotyrosine-derived natural products which contained three common structure elements: a central amide bond, an oxyimine on the carboxy side of the amide, and polar substituents on the amino
side. Some time later, Kobayashi and coworkers reported the isolation of the same compound from an *Okinanan* sponge *Pseudoceratina*, which they termed ceratinadin B 63. In addition to the 63, Kobayashi’s lab reported two other closely related molecules, ceratinadin A 62 and C 64.

Further studies confirmed that the distinct structures led to different modes of inhibition for some of the molecules. Molecules that contained the three functional groups described above were determined to be competitive inhibitors, while simpler structures were determined to be non-competitive inhibitors, interacting with both free enzyme and the enzyme-substrate complex.

![Chemical structures of ceratinadins A, B, and C](image)

**Figure 3.1 MCA inhibitors**

3.1.3 *First generation retrosynthesis of Mycothiol S-Conjugate amidase (MCA) inhibitor*

On the basis of the promising activity of these natural products against MCA and due to an uncommon linkage between imidazole and quinolone fragments, our group
determined that ceratinatin B would be an exciting synthetic target. The first generation retrosynthesis is shown in Figure 3.2:

![Figure 3.2 First generation retrosynthesis](image_url)

The natural product can be broken into three fragments: a spiroisoxazoline 67, a 2-aminoimidazole 68, and a quinolone 69. The spiroisoxazoline 67 and the imidazole amine 68 can be combined using a condensation reaction. The connection between the imidazole and the quinolone is quite unique in natural products and its construction is the key step to the total synthesis. Dr. Schmid was able to prepare fragments related to 68 and 69, however, attempts to construct the aryl-imidazole fragment by using transition metal catalyzed cross coupling strategies failed.
3.1.4 Truncated Analogs

As part of this project we wanted to establish a structure activity relationship (SAR), Dr. Schmid in our group proposed to synthesize a number of truncated analogs en route to the total synthesis of the natural product. As stated above, the Bewley work suggested that three common elements are needed for activity: (1) a central amide bond; (2) an oxyimine moiety on the carboxyl side; and (3) polar substituent on the amino side.

To simplify the synthesis and produce materials that are likely more stable, there are three elements we wished to explore during the SAR investigation. Since the spiroisoxazoline fragment may not be needed for activity, Dr. Schmid removed that fragment and replaced it with a less complicated and commercially available or easily prepared heterocyclic ring. Lastly, the degree of oxidation on the quinolone ring may be reduced. Examples of proposed truncated analogs are shown in Figure 3.3. However, if primary ethanamine was protected by amide, there is a problem of deprotection. Thus, to avoid this, we decide to synthesize intermediate HCl or HBr salt instead of amide.

![Figure 3.3 Proposed truncated analogs](image-url)
Chapter 4
Results and Discussion

Based on difficulties encountered in the first generation synthesis towards ceratinadin B 63, we redesigned the retrosynthetic route as depicted below in Scheme 4.1; the amide coupling is a very obvious way to join the two heterocyclic fragments. However, as Dr. Schmid found the cross-coupling between the imidazole and quinolone fragments was difficult.

![Scheme 4.1 Second generation retrosynthesis towards ceratinadin B](image)

We found that the cross coupling between imidazole and benzene derivatives are very challenging after we tried many times. Meanwhile, the synthesis of a protected 5-(2-aminoethyl)-imidazole fragment is rather long. Rather than using a linear and protecting group intensive route to fragment B, we elected to redesign the structure of the
heterocyclic intermediates. The retrosynthetic for this approach is depicted below (scheme 3.2):

Scheme 4.2 Retrosynthesis of Fragment B of Ceratinadin B
4.1 Synthesis of 2-amino-4,5-disubstituted imidazole derivatives

Previously, Dr. Schmid attempted to construct the aryl-imidazole C-C bond by using palladium-catalyzed cross-coupling starting from pre-exist imidazole derivatives and benzene derivatives. However, before cross-coupling, the reactive groups such as the amino group require protection. For our particular substrates, transition-metal catalyzed cross coupling is challenging. Therefore, we decided to evaluate more classical 2-amino-4,5-disubstituted imidazole synthesis methods.

4.1.1 Synthesis of 2-amino-4,5-disubstituted imidazole from 1,2-diketone

In 1979, Prof. Nishimura reported the synthesis of 2-amino-4,5-diaryl-4-hydroxy-4H-imidazole 84 obtained by the reaction of substituted benzils with guanidine in methanol at room temperature. Catalytic hydrogenation of the resulting 4-hydroxy-4H-imidazoles produced 2-amino-4,5-diarylimidazoles in excellent yields. In the case of 1-phenyl-1,2-propanedione and butane-2,3-dione, the intermediate 4-hydroxy-4H-imidazoles could not be isolated and the reaction mixtures were hydrogenated directly to yield the corresponding 2-aminoimidazoles. 1,1-Dimethylguanidine and benzils also produced the corresponding 4H-imidazoles in excellent yields. These compounds were quantitatively converted to 2-(dimethylamino)-5,5-diarylimidazolin-4-ones by heating.

Based on this precedent, we decided to prepare and evaluate an appropriate 1,2-diketone.
Starting from aryl bromide 89 and alkyne 90, after Sonogoshira coupling, alcohol 91 was obtained with high yield. Protection of alcohol 91 with TBDPS provided silyl ether 92. After Wacker type oxidation of alkyne 92, diketone 93 was provided in very high yield. However, diketone 93 is not stable. It mainly exists in enol ketone 94 according to IR (3423 cm$^{-1}$). While diketone 93 was in hand, we tested the reaction conditions reported by Nishiyama. After checking $^1$H NMR spectrum of the reaction mixture, we were surprised to find that signals due to two methoxy groups disappeared (Scheme 4.4).

While the mechanism is still not clear, we assume a quinone is formed from the electron rich aromatic system, although this was not established unequivocally.
4.1.2  Synthesis of 2-amino-4,5-disubstituted imidazole from α–bromo ketone

4.1.2.1  Background Introduction

In 1994, Webber and coworkers attempted to synthesize 2-amino-4(5)-phenylimidazole by the reaction of α-bromoacetophenone with mono-acetylguanidine. In their initial trials, the free base of guanidine was liberated in situ from its hydrochloride (HCl) salt with sodium hydroxide (NaOH) in ethanol (EtOH) followed by the addition of the bromide. Variations made to the reaction conditions were all unsuccessful. Generally, these experiments yielded intractable mixtures of compounds. A mixture of products was
observed by thin layer chromatography (TLC) when attempts were made to treat α-bromoacetophenone with the free base in anhydrous dimethyl sulfoxide (DMSO), DMF, or EtOH.

By substituting guanidine with an excess of \( N \)-acetylguanidine,\(^{83, 84} \) they observed a clean reaction when α-bromoacetophenone was stirred at room temperature in anhydrous DMF. The bromide was completely consumed after 96 h as indicated by TLC. The DMF solution was poured into water (\( H_2O \)) whereupon a precipitate formed which was collected and washed with cold \( H_2O \). This method gave relatively clean material by TLC but a 20-30% loss in mass resulted. They were able to avoid this loss by slightly modifying the workup. Instead of pouring the DMF solution into \( H_2O \), they first removed the solvent completely under high vacuum and then washed the resulting solid. The product was recrystallized from \( MeOH \) and shown to be 4-phenyl-\( N \)-(4-imidazol-2-yl)acetamide, (58%), by NMR spectroscopy and elemental analysis. An additional product, which was originally seen by TLC while monitoring the reaction, completely disappeared (scheme 5.5).

\[
\begin{array}{c}
\text{Ph} & \text{O} & \text{Br} & + & \text{H}_2\text{N} & \text{NHAc} & \xrightarrow{\text{DMF}} & \text{Ph} & \text{N} & \text{N} & \text{NH} & \text{NHAc} & \xrightarrow{\text{H}_2\text{NNH}_2} & \text{Ph} & \text{N} & \text{N} & \text{NH} & \text{NH}_2 \\
95 & & & & 96 & & & & 97 & & & & 98
\end{array}
\]

Scheme 4.5 Synthesis of 2-amino-4-phenylimidazole

4.1.2.2. Revised Synthesis towards 2-acetylamino-4,5-disubstituted imidazole

Starting from 1,4-dimethoxybenzene 99, by monobromination with NBS, 2-bromo-1,4-dimethoxybenzene (100) could be obtained in high yield (scheme 4.6).\(^71\) Next, treating the aryl bromide 100 with nitric acid by using glacial acetic acid as solvent,
delivered the expected 1-bromo-2,5-dimethoxy-4-nitrobenzene 101 in almost quantitative yield. Reduction of nitro group with iron powder and 25% ammonium chloride solution produced 4-bromo-2,5-dimethoxyaniline 102 with high yield. Protection of amino group with benzyl groups results in the dibenzylaniline 79. We observed that aniline 79 is not especially stable, it appears to undergo debromination and thus the aniline 79 was used immediately. Treating 4-bromodibenzylaniline 79 with magnesium to prepare the Grignard reagent followed by addition of aldehyde 80 produces secondary alcohol 78. Oxidation of alcohol 78 by using Swern conditions failed, resulting in formation of the alkene via elimination instead of forming the required ketone. However, oxidation of this alcohol using IBX in acetone provided ketone 103 quantitatively. The next challenge was to prepare the α-bromoketone, this was finally accomplished by treating ketone 103 with 1.1 equivalents of TMSOTf and addition of triethylamine as base to form the TMS-enol ether. To synthesize the α-bromoketone, we initially used sodium bicarbonate as base according to the literature, however, an intractable mixture of products was formed. We reasoned that the solubility of base might be the problem. At last, we evaluated an organic base—triethylamine; the TMS-enol ether was added to 2 equivalents of NBS and excess triethylamine. After workup, the α-bromoketone 77 was formed and could be used directly for next step without additional purification. With α-bromoketone in hand, the next step was to prepare the 2-aminoimidazole derivative. When the solvent was anhydrous DMF, the reaction was very slow. Only a very small amount of α-bromoketone was consumed, even after stirring at room temperature for more than one week. Raising the temperature did not result in an appreciable change in conversion. Following another report, acetonitrile was tested as solvent. Addition of 3 equivalents of monoacetylguanidine to α-bromoketone 77 acetonitrile solutions, after heating to reflux overnight, results in the formation of the imidazole 76 with very high yield (scheme 4.6).
Next, deprotection of dibenzyl groups by hydrogenation provided aniline 75. At this stage, we decided to evaluate strategies for introduction of the quinolone moiety.
Scheme 4.6 synthesis towards N-(4-(4-amino-2,5-dimethoxyphenyl)-5-(2-(1,3-dioxoisooindolin-2-yl)ethyl)-1H-imidazol-2-yl)acetamide 75
4.2 Introduction for Synthesis of Quinolones Intermediate

4.2.1 Different Approaches to Quinoline Compounds

Initially, we considered an approach to the 3-hydroxyquinolone derivative by using Ru-catalyzed 1,2-diketonization\(^8\) of a 1,2-dihydroquinoline derivative, which would be provided by reduction of quinoline derivative.

Prior to describing this chemistry, we briefly review some classical approaches to quinoline. Quinoline derivatives represent an important class of heterocycles as the quinoline ring system occurs in various natural products. The quinoline skeleton is often used for the design of synthetic compounds with diverse biological activities even as potential drugs. One of the best known examples of naturally-occurring quinoline derivatives is quinine 104. Prior to 1820, the bark was first dried, ground to a fine powder, and then mixed into a liquid (commonly wine) which was then drunk. Large-scale use of quinine as a prophylaxis started around 1850. Despite its relatively low efficacy and tolerability, quinine still plays an important role in the treatment of multiresistant malaria.\(^76\) This molecule was very important in organic chemistry as a target for structural determination and total synthesis have been described,\(^77\) and recently both stereoselective\(^78\) and enantioselective total syntheses have been reported.\(^79\) Chimanine alkaloids, simple quinolines (104-108), isolated from the bark of *Galipea longiflora* trees,\(^80-82\) are effective against the parasites *Leishmania* sp., which are the causative agents of *Leishmaniasis*, a protozoan disease of the tropical areas in South America. Cryptolepine (109) is an indoloquinoline alkaloid found in the West African climbing shrub *Cryptolepis sanguinolenta* and also an antimalarial drug with cytotoxic properties. It is used as an anticancer drug as it is able to intercalate into DNA at the cytosine-cytosine sites.\(^95\) Enediyne dynemicin A (110) and streptonigrin (111) are useful anti-cancer drugs whose
syntheses are based on the utilization of quinoline derivatives. They display properties which illustrate promise as innovative cancer treatments, but still requires further research. 8-(Diethylaminohexylamino)-6-methoxy-4-methylquinoline (112) has been shown to be highly effective against Leishmania donovani in hamsters and 2-(2-methylquinolin-4-ylamino)-N-phenylacetamide (113) was found to significantly more active than the standard antileishmanial drug sodium antimony gluconate (Figure 4.1).

Figure 4.1 Quinoline derivatives with diverse pharmacological properties.

The core structure of quinoline has generally been synthesized by application of diverse name reactions such as the Skraup, Doebner-von Miller,
Friedländer,\textsuperscript{90} Pfitzinger,\textsuperscript{91} Conrad-Limpach,\textsuperscript{92} Combes\textsuperscript{93} syntheses etc. These syntheses are still frequently applied for the preparation of pharmaceutical agents, ligands and functional materials which have a quinoline skeleton.\textsuperscript{94} However, current methods for quinoline synthesis often have large limitations with respect to diversity and substitution on the quinoline ring system.\textsuperscript{95} Recent developments in the syntheses of quinoline derivatives have demonstrated that new metal-catalyzed coupling cyclizations or acid catalyzed cycloaddition of appropriate precursors provide more choice for the efficient and rapid construction of the quinoline.

The important and general approaches to quinoline compounds are mostly based on the use of non-heterocyclic precursors. Analysis of the structure of the quinoline ring indicates two general synthetic routes: one is the utilization of mono-substituted anilines; the second is the use of ortho-substituted anilines. In several of the classical synthetic methods, substituted enamines and azomethines are intermediates which are usually not isolated. It is not surprising that various organic chemists have postulated the basic idea to exploit the chemistry of ald(ket)imines to construct the quinoline nucleus. This “new” possibility was resulted in a renewed impetus to chemical research on quinoline syntheses (Scheme 4.7).

![Scheme 4.7 Possible synthetic routes towards quinoline](image-url)

The Skraup, Doebner-von Miller, Combes and Conrad-Limpach syntheses employs aromatic primary amines as the nucleophilic nitrogen donating component as
the C-C-N unit and an electrophilic three-carbon unit, usually carbonyl compounds (Route A, Scheme 4.7).

Actually, both the classical Skraup and Doebner-von Miller syntheses are very similar in that they all use acrolein. However, they also have slight differences: the former involves heating anilines with acrolein, generated in situ from glycerol and a strong acid, whereas the latter method is based on using a substituted acrolein. The Combes quinoline synthesis involves the condensation of unsubstituted or substituted anilines with β-diketones to form substituted quinolines (Scheme 4.8).

Even though these syntheses have relative generality, versatility and simplicity, there are still considerable drawbacks, including harsh reaction conditions and strong acid. Moreover, the regioselectivity is not good for the reactions of meta- or 3,4-disubstituted anilines, which also leads to separation problem. In the case of the Combes synthesis, the regioselectivity can be poor when unsymmetrical 1,3-diketones are used.

Due to these synthetic drawbacks, it is still necessary to develop mild, regioselective and practical syntheses for these quinoline derivatives. In the last years, due to great biological importance of substituted quinolines, some interesting modification
to these methods have been developed resulting in the extension of the scope of these reactions.

Microwave-assisted reactions between anilines and alkyl vinyl ketones or 1,3-diketones on the surface of diverse absorbents proceeded smoothly to give new substituted quinolines. A simple and efficient procedure, described by Ranu and co-workers, consists of a one-pot reaction of anilines with methyl vinyl ketone or its analogs on the surface of silica gel impregnated with InCl₃ under microwave irradiation in the absence of any solvent. This method was used in the synthesis of 6-aminoquinoline derivatives used as potential antimalarial agents. Alumina-supported synthesis of antibacterial quinolines by using microwaves was also reported. The reaction time in both of these methods has been shortened from hours to seconds with improved yield as compared to conventional heating methods. The coupling of microwaves with solvent-free conditions modernizes and simplifies these classical procedures, in addition to avoiding volatile and toxic organic solvents, and corrosive mineral acids. Environmentally friendly vapor state synthesis of alkyl quinolines from 2-ethylaniline and ethylene glycol in the presence of montmorillonite K10 was described. A variety of 2, 2, 4-trisubstituted 1, 2-dihydroquinolines were synthesized by the reaction of substituted anilines with ketones in good yield by using lanthanide catalyst (Sc(OTf)₃) under microwave irradiative. This modified Skraup reaction can be readily applied to the general synthesis of combinatorial libraries of quinoline derivatives.

Fukuyama and co-workers reported a novel route to substituted quinolines from anilines through the strong acid (sulfuric acid or HBr) mediated cyclizations of 3-(N-aryl-N-sulfonylamino)propionaldehydes. The substrates in turn are prepared in a straightforward way by treatment of p-substituted anilines with p-TsCl or MsCl and pyridine in CH₂Cl₂ at room temperature, followed by Michael addition to acrolein (5
equiv.) in the presence of catalytic amount of triethylamine in methanol. Cyclization under acidic conditions and subsequent treatment of dihydroquinoline derivatives with KOH in DMSO gave the desired quinolines (Scheme 4.9).\textsuperscript{101}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_4.9.png}
\end{center}

Scheme 4.9 Fukuyama’s Synthesis of Quinone from acrolein

Recently, Ila and colleagues have developed a modified Skraup synthesis by using 3-bis(methylthio)acrolein (118) as an acrolein surrogate, which was synthesized from vinyl acetate.\textsuperscript{102,103} Cyclization of substituted anilines and acrolein (118) proceeded in refluxing AcOH (8-10 h) to provide single products (119) (Scheme 4.10).
The 2-(methylthio) functionality can be either dethiomethylated or replaced by various nitrogen and carbon nucleophiles to afford 2-substituted quinolines and thus broadens the overall reaction scope. This new quinoline synthesis protocol can also successfully be implemented for the synthesis of tri- and tetracyclic pyrido fused quinolines.\(^\text{104}\)

It was found that the Doebner-von Miller reaction of aniline with α, β-unsaturated carbonyl groups, which is biphasic, decreases the extent of polymerization of the crotonaldehyde. The reaction proceeded smoothly even in the absence of oxidants to give 2-methylquinoline derivatives (Scheme 4.11).\(^\text{105}\)

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Yield (%)</th>
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<td>OMe</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>62</td>
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Scheme 4.10 Ila’s Synthesis of Quinolone

Scheme 4.11 Doebner-von Miller reaction
This reaction also can be catalyzed by Lewis acids such as tin tetrachloride and scandium(III) triflate and Brønsted acids such as p-toluenesulfonic acid, perchloric acid, amberlite and iodine.\textsuperscript{106}

4.2.2 Dr. Schmid's first generation synthesis of quinolone derivatives

Dr. Schmidt from our group synthesized different quinolone derivatives as potential building block and as truncated ceratinadin B analogs. Starting from similar aniline starting materials 120a-c and ethyl (ethoxymethylene) cyanoacetate, after condensation, quinolinone adducts 121a-c were formed in quantitative yields (Scheme 4.12). Generally, these adducts were isolated as a mixture of the E- and Z- isomers, and were cyclized in Ph$_2$O without further purification. The E-isomer of the dimethoxy adduct 121c was isolated by recrystallization from EtOH or by chromatography, and brominated in AcOH to give 121d in 92% yield.

Cyclization in Ph$_2$O at 260 °C provided quinolones 121a-d with a 3-cyano moiety in 35-75% yield. The cyano group was then reduced with Raney nickel to the corresponding aldehyde. Higher yields were obtained when the reaction was done at elevated temperatures (69% of the aldehyde 123d at 60 °C versus 39% at room temperature). The proposed oxidation with basic H$_2$O$_2$ to give the hydroxylated quinolones was investigated that can be used in subsequent cross-coupling studies. However, preliminary attempts of this reaction were not successful (scheme 4.12).
**Scheme 4.12 Dr. Schmid’s Synthesis toward 3-hydroxyquinolone**

### 4.2.3 Dr Schmid’s approach to Introduction of the 3-Hydroxyl Group onto the 4-quinolone

It is known that the Ebb’s persulfate oxidation (Scheme 4.13) can be used to introduce the 3- hydroxyl group on several quinolone derivatives. Even though the reported literature yields of this reaction were quite low (20-40%), but it was the only known oxidation that would introduce the functional group at the 3-position of the quinolone.

---

120a. \( R_1 = R_2 = R_3 = H \)
120b. \( R_1 = R_3 = H, \ R_2 = Br \)
120c. \( R_1 = R_3 = OMe, \ R_2 = H \)

121a. \( R_1 = R_2 = R_3 = H, \text{ Quant} \)
121b. \( R_1 = R_3 = H, \ R_2 = Br, \text{ Quant} \)
121c. \( R_1 = R_3 = OMe, \ R_2 = H, \text{ Quant} \)
121d. \( R_1 = R_3 = OMe, \ R_2 = Br, \text{ Quant} \)

122a. \( R_1 = R_2 = R_3 = H, \ 40\% \)
122b. \( R_1 = R_3 = H, \ R_2 = Br, \ 66\% \)
122c. \( R_1 = R_3 = OMe, \ R_2 = H, \ 35\% \)
122d. \( R_1 = R_3 = OMe, \ R_2 = Br, \ 75\% \)

123a. \( R_1 = R_2 = R_3 = H, \ 25\% \)
123b. \( R_1 = R_3 = OMe, \ R_2 = Br, \ 69\% \ (60 ^\circ C) \)

124a. \( R_1 = R_2 = R_3 = H \)
123d. \( R_1 = R_3 = OMe, \ R_2 = Br, \)

54
When the simple quinoline 125a was treated with potassium persulfate in aqueous KOH, a (2:1) mixture of the 3-hydroxylated product 126 and recovered starting material was isolated in approximately 42% yield. A lower conversion occurred with the functionalized quinolone 125d. A (1:2) mixture of the 3-hydroxylated product 127 and starting material were recovered in approximately 60% yield. Although the literature report suggested the 3-hydroxylated compounds should crystallize out of solution, only mixtures were recovered. The polarity of the compounds rendered purification using silica gel was difficult and as a result the hydroxylated compounds 126 and 127 could not be purified from the starting material (scheme 4.13).

![Scheme 4.13 Introduction of the 3-Hydroxyl Group in Quinolones](image)

<table>
<thead>
<tr>
<th>Quinolone</th>
<th>Ratio of Hydroxylated Product: Recovered Starting Material</th>
<th>Total Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>125a</td>
<td>2:1</td>
<td>42</td>
</tr>
<tr>
<td>125d</td>
<td>1:2</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 4.1 Comparison of Introduction of 3-Hydroxy Group in different Quinolones

The postulated mechanism was reported as following (scheme 4.14): 125
Based on these experiences, even though the Ebb's persulfate oxidation could introduce 3-hydroxy group, it is a poor choice in the present context because of its low yield and separation problem.

4.2.4 Modified Synthesis towards on 6-bromo-5, 8-dimethoxyquinoline

As a result of these early studies, we decided to synthesize fragment B starting from 6-bromo-5,8-dimethoxyquinoline. We proposed that after Grignard or lithium exchange with the aryl bromide, the addition of the appropriate aldehyde will provide the desired secondary alcohol we need. A concise synthesis of 5,8-dimethoxyquinoline was described in the literature in 2011. Kim’s group prepared 5,8-dimethoxyquinoline from commercially available 2,5-dimethoxyaniline by a Skraup reaction. However, the reported yield is very low. Since 5,8-dimethoxyquinoline would serve as our starting material, an improved yield was desired. The reaction was heated to 80 °C and maintained for overnight, concentrated to provide brown foam. The main component of the brown foam is 5,8-quinolinequinone according to $^1$H NMR spectrum. Since 5,8-quinolinequinone is provided, reduction of quinone by using sodium thiosulfate, then addition of sodium hydroxide and dimethylsulfate in sequence thus providing the corresponding quinoline.
Scheme 4.15 Revised Synthesis of 5,8-dimethoxyquinoline

In 2002, Dr. Ham reported the synthesis of 6-bromo-5,8-dimethoxyquinoline. 5,8-dimethoxyquinoline was submitted to reaction with NBS (2 equivalents) at room temperature for 2 h in different solvents.\textsuperscript{108} When a solvent chosen from CCl\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2} and CH\textsubscript{3}CN was used, a mixture of regioisomers was formed without notable selectivity. The apparently lower reactivity in the case of CCl\textsubscript{4} may be a consequence of low solubility of NBS in CCl\textsubscript{4}. Surprisingly, a substantial increase in the regioselectivity (6.1:1) for C(7) over C(6) and moderate isolation yields (79\%) of 130 was observed using THF as a solvent under otherwise identical conditions. In this case, the minimum amount of NBS relative to the substrate was found to be 2 equiv., and neither di-bromo nor \textit{p}-quinone products were formed significantly. Moreover, in terms of reaction times, the bromination was slower in THF than in either CH\textsubscript{2}Cl\textsubscript{2} or CH\textsubscript{3}CN (scheme 4.16).

Scheme 4.16 Bromination of Quinoline

From the above, we can see that the bromination regioselectivity is not optimal good, which brings difficulty in separation for large scale. To solve this problem, we
decided to start from 4-bromo-2,5-dimethoxyaniline by using Skraup synthesis (Scheme 4.17).

![Scheme 4.17 Synthesis of 6-bromo-5,8-dimethoxyquinoline](image)

Unfortunately, treating 6-bromo-5,8-dimethoxyquinoline 130 with n-BuLi then adding aldehyde did not form the desired secondary alcohol. According to the $^1$H NMR spectra, there is no bromine-lithium exchange. EtMgBr was also tested; however, there is no Grignard exchange, only starting material was recovered. Thus, starting from 6-bromo-5,8-dimethoxyquinoline is not effective.

Whereas 6-bromo-5,8-dimethoxyquinoline is not suitable as a starting point, we knew that the corresponding quinolone could be obtained with high yield starting from Meldrum’s acid and aniline. However, the shortcoming of this approach is that after formation of quinolone, it is hard to introduce a hydroxyl group to position 3. To introduce the 3-hydroxyl group to quinolone, we came up with an idea to the Meldrum’s acid by preinstalling the 3-hydroxy unit (scheme 4.18). Treatment of commercially available Meldrum’s acid 132 sodium ethoxide provides the corresponding sodium salt 133. Stirring a mixture of salt 133 and dibenzylperoxydicarbonate at room temperature for 2 hours provided benzylcarbonate 134. At -78 °C, addition of LDA to a solution of carbonate 134, then ethyl formate provided aldehyde hydrate 135.
We found that if ethyl formate was replaced with DMF, only starting material was recovered. However, even with ethyl formate as electrophile, the desired aldehyde was not obtained but only benzyl 5-(dihydroxymethyl)-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl carbonate 135 was obtained. Fortunately, it was useful in the synthesis of 3-hydroxy-quinolone. With aniline 75 in hand, we continued to obtain 3-OCbz quinolone 74 after condensation, rearrangement and cyclization (scheme 4.19). We assume that the imine is formed which upon decarboxylation and loss of acetone affords the ketene. Next electrophilic substitution delivers the imidazolyl-quinolone 74.
Treating **75** with hydrazine at 70 °C without solvent, the acetyl and phthalimido group were deprotected to provide primary amine **136** (scheme 4.20).
The final step is to deprotect two methyl groups attached to quinolone benzene ring. Treating 136 with excess BBr₃ at -78 °C, results in deprotection of the two methyl groups were deprotected. After workup, fragment B 73 was obtained as the HBr (scheme 4.21).

Scheme 4.21 Deprotection of Methyl Groups
4.3 Synthesis of Spiro-Isoxazoline Fragment A

Although there are several publications describing the synthesis of the spiroisoxazoline fragment A,\textsuperscript{112-117} Dr. Schimd attempted to follow a combination of Spilling’s work\textsuperscript{114} with Nishiyama’s work\textsuperscript{117} to synthesize the spiroisoxazoline fragment A, resulting in the formation of the racemic spiroisoxazoline. However, we wanted to accomplish an asymmetric total synthesis and therefore an asymmetric spiroisoxazoline was necessary. Two methods have been reported in the literature involving either resolution or an auxiliary-based approach.\textsuperscript{118} Thus, we redesigned the synthetic route for spiroisoxazoline fragment. We initially evaluated a route involving a chiral camphorsulfonyl auxiliary (Oppolzer chemistry); however, problems with hydrolysis of an amide were encountered and thus we abandoned the approach. Based on our knowledge of enolate-palladium catalyzed methodology and the Wacker oxidation,\textsuperscript{116} we postulated that there is palladium-enolate species formed after deprotonation of phenol, then possible dearomatization would take place. Thus, we decided to investigate a novel palladium catalyzed method to solve this problem. Following the literature synthesis of the spiroisoxazoline fragment,\textsuperscript{118-123} oxime E-143 was obtained as depicted in scheme 4.23. Starting from commercially available resorcinol 137, after Vilsmeier–Haack reaction,\textsuperscript{119} aldehyde 138 was obtained with good yield. Then, chemoselective methylation provided 2-hydroxy-4-methoxybezaldehyde 139.\textsuperscript{120} After treating aldehyde 139 with two equivalents of NBS, dibromobenzaldehyde 140 was formed with almost quantitative yield,\textsuperscript{121} which was used directly for next step without purification. After MOM protection of phenol 140,\textsuperscript{122} aldehyde 141 was obtained with high yield and used directly for next step without purification. Following Spilling’s report, E-oxime 143 was obtained.\textsuperscript{124}
Scheme 4.22 Synthesis of Oxime 143

With oxime 143 was in hand, after screening many conditions (Table 4.4), we developed palladium-catalyzed oxidative dearomatizing spirocyclization as following (scheme 4.23).

Scheme 4.23 Palladium-Catalyzed Dearomatization Spirocyclization
Table 4.2: Screening of Different Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Yield of 144 (1H NMR)\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>Phl(OAc)\textsubscript{2}</td>
<td>MeCN</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>NBS</td>
<td>DMF</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>3\textsuperscript{a}</td>
<td>PdBr\textsubscript{2}</td>
<td>CuBr\textsubscript{2}</td>
<td>O\textsubscript{2}</td>
<td>1,4-dioxane</td>
<td>40%</td>
</tr>
<tr>
<td>4\textsuperscript{b}</td>
<td>-</td>
<td>CuBr\textsubscript{2}</td>
<td>O\textsubscript{2}</td>
<td>1,4-dioxane</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>CuBr\textsubscript{2}</td>
<td>O\textsubscript{2}</td>
<td>1,4-dioxane</td>
<td>5%</td>
</tr>
<tr>
<td>6</td>
<td>PdBr\textsubscript{2}</td>
<td>CuBr\textsubscript{2}</td>
<td>O\textsubscript{2}</td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>PdBr\textsubscript{2}</td>
<td>CuBr\textsubscript{2}</td>
<td>O\textsubscript{2}</td>
<td>DMSO</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>PdBr\textsubscript{2}</td>
<td>-</td>
<td>BQ</td>
<td>1,4-dioxane</td>
<td>5%</td>
</tr>
<tr>
<td>9\textsuperscript{c}</td>
<td>PdBr\textsubscript{2}</td>
<td>CuBr\textsubscript{2}</td>
<td>BQ</td>
<td>1,4-dioxane</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
<td>BQ</td>
<td>1,4-dioxane</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>CuBr</td>
<td>BQ</td>
<td>1,4-dioxane</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>CuBr\textsubscript{2}</td>
<td>BQ</td>
<td>1,4-dioxane</td>
<td>10%</td>
</tr>
</tbody>
</table>

- a: part of CH\textsubscript{2} group was oxidized to ketone;  
- b: the reaction is run overnight;  
- c: reaction was conducted for 6 h at 0.025 M in solvent with 1.0 equiv of benzoquinone, 5 mol% palladium catalyst, and 10 mol% additive  
- d: use CH\textsubscript{2}Br\textsubscript{2} as internal standard.

From the table above (Table 4.2), we followed the literature to obtain racemic spiroketone with high yield (entry 1 & 2).\textsuperscript{122} Then, we adopted classical Wacker oxidation conditions and the desired ketone was formed. However, the yield was low and the possible reason is competitive oxidation of methylene group which prevented the dearomatizing spirocyclization. Results of different solvents indicates that 1,4-dioxane is optimal (entry 6,7 and 9). Thus, we can see that PdBr\textsubscript{2}/CuBr\textsubscript{2}/BQ/1,4-dioxane conditions are optimal. To test the asymmetric catalyzed reaction, different ligands: (-)-sparteine and (S)-BINAP were screened. We were surprised to get 90% (ee) and 87% (ee). Hereby, the next problem is to improve the ee value. We postulated that during dearomatizing
spirocyclization CuBr₂ may also participated in the reaction. To fully understand the possible mechanism, general Wacker oxidation mechanism is shown as follows

(Figure 4.2):
From the general mechanism of Wacker oxidation, we proposed a possible mechanism as depicted in Figure 4.3. We assume that after deprotonation of phenol, there is palladium-enolate species formation. After another deprotonation of oxime, cyclization could provide the spiroketone 144. As we know that there are many reports about copper enolate, after deprotonation, E-oxime 143 could form enolate copper complex. Next, cyclization could provide the racemic spiroketone 144. Also, from entry 4 of table 4.2, CuBr$_2$ itself can provide the dearomatizing spirocyclization. Since
CuBr$_2$ participated in the dearomatizing spirocyclization and led to low ee value. To improve ee, we added CuBr instead of CuBr$_2$ as additive. Fortunately, we obtained the chiral ketone with ee above 99% (scheme 4.24). Corresponding HPLC spectra are shown in figure 4.4. However, the exact mechanism of this reaction is still not quite clear. We will conduct further investigation.

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Yield of 145 ($^1$H NMR)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>CuBr$_2$</td>
<td>BQ</td>
<td>1,4-dioxane</td>
<td>&gt;99%</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>CuBr$_2$</td>
<td>BQ</td>
<td>1,4-dioxane</td>
<td>&gt;99%</td>
<td>79</td>
</tr>
<tr>
<td>3$^a$</td>
<td>A</td>
<td>CuBr</td>
<td>BQ</td>
<td>1,4-dioxane</td>
<td>&gt;99%</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

a: The reaction was conducted at 0.0125 M; Reaction 1 and 2 were conducted at 0.025 M.
b: The reaction was conducted at 0.25 M; Pd catalyst (2.5 mol%).
c: use CH$_3$Br$_2$ as internal standard.

A: Pd[(-)-Sparteine]Br$_2$; B: PdBr$_2$ and (S)-BINAP;

Scheme 4.24 Asymmetric Palladium-Catalyzed Dearomatizing Spirocyclization

As Nishiyama reported, the achiral spiro-ketone 131 was reduced with Zn(BH$_4$)$_2$, followed by a work-up with MgSO$_4$, provided the highest yields of the cis (146, 39%) and trans (147, 41%) products (Scheme 4.25).
Scheme 4.25 Nishiyama Ketone Reduction

Figure 4.4 HPLC of Starting Material (A), Racemic Product (B) and Chiral Product (C)
First time application of Buchwald indolization led to successful total synthesis of haploscleridamine. However, the separation of haploscleriamine should be investigated. Classical 2-amino-4,5-disubstituted imidazole derivative synthesis made the synthesis of fragment B of ceratinadin B concise and avoided the complicated protection problem. Meanwhile, a novel 3-hydroxyquinolone synthesis methodology simplified the synthesis of fragment B of ceratinadin B, which brought us more choice for the synthesis of complicated 3-hydroxyquinolone. Novel palladium-catalyzed 1,2-dearomatization spirocyclization led to a revolutionary synthesis of asymmetric spiroketone. Since, fragments A and B of ceratinadin B are in hand, the next step is to synthesize ceratinadin B by using very common condensation as following (scheme 4.26):

![Scheme 4.26 Synthesis of Ceratinadin B](image-url)
Chapter 5

Experimental

General methods:

All of the reagents were purchased from commercial suppliers and were used without purification otherwise specified. All reactions involving air- or water-sensitive compounds were conducted in oven-dried (overnight) glassware under atmosphere of dry nitrogen. All the solvents were purified by Innovative Technology's Pure-Solve solvent purification system.

NMR spectra were recorded on JEOL Eclipse+ 500 MHz spectrometers. The $^1$H NMR spectra were recorded in CDCl$_3$ (unless otherwise indicated) at a spectrometer frequency of 500.13 MHz using residual CHCl$_3$ ($\delta = 7.26$) as reference. The $^{13}$C spectra were recorded in CDCl$_3$ (unless otherwise indicated) at a spectrometer frequency of 125.76 MHz using residual CDCl$_3$ ($\delta = 77.2$) as internal reference.

Melting points were recorded on a Laboratory Devices Inc. Melt. Temp apparatus and are uncorrected.

Infrared (IR) spectra were obtained on a Bruker Vector 22 FT-IR spectrometer, using KBr pellets for solid or neat films between NaCl for liquids and oils, and Bruker ALPHA FT-IR Spectrometer using neat samples. All spectra are reported in cm$^{-1}$.

Mass spectra were recorded by the Department of Chemistry and Biochemistry, University of Florida and Shimadzu Center in University of Texas at Arlington, Gainesville by electrospray ionization (HR-ESIMS) unless otherwise indicated. All mass spectral data are reported as m/z (relative intensity).

Analytical thin layer chromatography (TLC) was performed on Whatman silica gel 60F254 aluminum backed precoated plates (0.25 mm layer). All liquid chromatography separation (LCS) was performed using ICN silica gel (200-400 mesh).
5.1 Total Synthesis of Haploscleridamine

(S)-Methyl 2-amino-3-(1H-imidazol-4-yl)propanoate dihydrochloride (25)

A mixture of L-histidine (47.7 g, 0.25 mol) in MeOH (500 ml) was cooled to 0 °C. Dry HCl gas (prepared by reaction of concentrated H2SO4 and NaCl) was bubbled to the mixture until the HCl/MeOH is saturated. Then the ice bath was changed to an oil bath and heated the mixture to reflux. After keeping at reflux 4 h, the mixture was cooled to room temperature, then cooled to 0 °C. Additional dry HCl gas (prepared by using concentrated H2SO4 and NaCl) was added to the mixture again until the HCl bubbles unstoppably came out. The mixture was heated to reflux. After keeping mixture at reflux overnight, concentration of the solution provided L-histidine methyl ester dihydrochloride. All of the spectroscopic data match the literature.45

(S)-Methyl 2-(4-methylphenylsulfonamido)-3-(1-tosyl-1H-imidazol-4-yl)propanoate (29)

L-Histidine methyl ester dihydrochloride 18 (24.1 g, 0.1 mol) was placed in a 500 ml three-necked round bottom flask. Dichloromethane (200 ml) and triethylamine (56 ml)
were added consecutively and stirred for 15 minutes; the mixture was cooled to 0 °C.
Tosyl chloride (38 g, 0.2 mol) was slowly added to the mixture in several portions. After the addition was complete, the reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 4 h. The reaction mixture was filtered and the resulting solid was washed with water several times. The resulting solid was dried in air to provide the product 40.5 g, (85% yield), mp: 89-90 °C (literature: mp: 90-91 °C). This product can be used directly for next step. All spectra match Ms. Koda’s.

(S)-Methyl 2-(N-benzyl-4-methylphenylsulfonamido)-3-(1-tosyl-1H-imidazol-4-yl)propanoate (46).

\[
\text{Ts}
\quad \text{CO}_2\text{Me}
\]

Tosyl protected L-histidine methyl ester (12.0 g, 25 mmol) was dissolved in DMF (30 ml) and K$_2$CO$_3$ (6.0 g, 44 mmol) was added and stirred for 15 min. Then benzyl bromide (5.4 ml, 45 mmol) was added all at once and the reaction was stirred at room temperature overnight. After filtration to remove residual solids, the solution was diluted with 500 ml ethyl acetate and an equal amount of water. The organic extract was washed with brine (3 x 30 ml) and water (3 x 30 ml). The organic extract was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated to provide the crude product. The crude product was purified by flash chromatography (silica gel, EtOAc/hexanes = 1 : 2) to afford the pure benzyl protected ditosyl L-histidine methyl ester (12.3 g, 87% yield) as a white solid: mp: 130-132 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.79 (d, 2H, J = 8.2 Hz), 7.75 (s, 1H), 7.67 (d, 2H, J = 8.2 Hz), 7.34 (d, 2H, J = 8.2 Hz), 7.26 (d, 2H, J = 8.2 Hz), 7.20 - 7.19 (m, 5H), 6.77 (s, 1H), 4.78 (dd, 1H, J = 7.5, 9.0 Hz), 4.52 (d, 1H, J = 16.0 Hz), 4.26
(d, 1H, \( J = 16.0 \) Hz), 3.39 (s, 1H), 3.01 (dd, 1H, \( J = 6.3, 15.5 \) Hz), 2.79 (dd, 1H, \( J = 6.3, 15.5 \) Hz), 2.42 (s, 3H), 2.41 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta = 170.5, 146.3, 143.7, 140.2, 137.1, 136.7, 136.0, 135.1, 134.3, 130.5, 129.6, 128.6, 128.4, 127.8, 127.6, 127.4, 115.2, 59.1, 52.1, 50.1, 29.4, 21.8, 21.6. FT-IR: 1746, 1371, 1153, 674, 604, 572, 539. HR-ESIMS (m/z): calcd. for [M+H]\(^+\) C\(_{28}\)H\(_{29}\)N\(_3\)O\(_6\)S\(_2\) 568.1571, found 568.1582.

\((S)-N\)-benzyl-4-methyl-N-(1-oxo-3-(1-tosyl-1H-imidazol-4-yl)propan-2-yl)benzenesulfonamide (47)

Benzyl protected ditosyl L-histidine methyl ester (11.36 g, 20 mmol) was dissolved in dry DCM (150 ml) and cooled to -78 ℃. A precooled (-78 ℃) solution of Dibal-H (30 ml, 30 mmol) was slowly added to the reaction solution. After stirring for 2 h at this temperature the reaction was quenched with methanol (100 ml), warmed to room temperature and the resulting mixture was stirred for 1 h with saturated K-Na-tartrate solution, then the mixture was extracted with DCM. The combined organic solutions were washed with brine (3 x 50 ml) and water (50 ml), dried over anhydrous Na\(_2\)SO\(_4\). The concentrated residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 1 : 2) to furnish the aldehyde as a colorless solid (9.35 g, 85% yield): mp: 120-121 ℃. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 9.35 \) (s, 1H), 7.74 (d, 2H, \( J = 8.0 \) Hz), 7.72 (s, 1H), 7.67 (d, 2H, \( J = 8.0 \) Hz), 7.35 (d, 2H, \( J = 8.0 \) Hz), 7.31 (d, 2H, \( J = 8.0 \) Hz), 7.29 (m, 5H), 4.50 (d, 1H, \( J = 15.0 \) Hz), 4.34 (dd, 1H, \( J = 5.0, 10.0 \) Hz), 4.11 (d, 1H, \( J = 15.0 \) Hz), 3.12 (dd, 1H,
$J = 5.0, 10.0 \text{ Hz}$), 2.70 (dd, 1H, $J = 9.0, 15.0 \text{ Hz}$), 2.49 (s, 3H), 2.43 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 197.9, 146.5, 144.2, 140.4, 137.6, 136.1, 135.7, 135.0, 130.5, 130.0, 129.1, 128.9, 128.6, 127.3, 114.9, 65.4, 51.0, 25.5, 29.4, 21.8, 21.7. FT-IR: 1723, 1378, 1330, 1155, 1072, 672. HR-ESIMS (m/z): calcd. for [M+H]$^+$ C$_{27}$H$_{27}$N$_3$O$_5$S$_2$ 538.1465, found 538.1473.

(S)-N-benzyl-N-(6-(benzyloxy)-3-hydroxy-1-(1-tosyl-1H-imidazol-4-yl)hexan-2-yl)-4-methylbenzenesulfonamide (48)

A solution of (3-(benzyloxy)propyl)magnesium chloride (ca. 1.0 M in THF, 40 mL, prepared from 1-((3-chloropropoxy)methyl)benzene (18.4 g, 100 mmol) and magnesium turnings (3.0 g, 125 mmol) was added to a solution of aldehyde 29 (10.74 g, 20 mmol) in THF (100 mL) at -78 °C, and the mixture was stirred for 2 h at same temperature. After stirring for an additional 1 h at 25 °C, a saturated solution of NH$_4$Cl (50 ml) was added to the mixture which was then extracted with EtOAc. The organic phase was washed with brine, dried (Na$_2$SO$_4$), and then evaporated to give oil. The crude product was purified by flash chromatography (silica gel, EtOAc/hexane = 50/50), to give the desired alcohol 30 (12.4 g, 90%) as a clear viscous oil: $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.75$ (d, 2H, $J = 8.0 \text{ Hz}$), 7.68 (s, 1H), 7.57 (d, 2H, $J = 8.0 \text{ Hz}$), 7.35 - 7.20 (m, 14H), 6.58 (m, 1H), 4.48 - 4.38 (m, 4H), 3.90-3.92 (m, 1H), 3.62 - 3.68 (m, 1H), 3.48 - 3.42 (m, 1H), 3.34 – 3.25 (m, 2H), 2.70 - 2.74 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 1.51 – 1.47 (m,
2H), 1.47 – 1.38 (m, 1H), 1.20 - 1.25 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 146.4, 143.5, 141.9, 138.4, 138.1, 135.8, 135.1, 130.6, 130.0, 129.8, 129.3, 129.1, 128.9, 128.5, 127.7, 127.3, 127.2, 126.0, 114.8, 72.6, 71.9, 63.3, 49.2, 32.5, 26.9, 26.2, 21.8, 21.6. FT-IR: 3400, 1596, 1494, 1454, 1172, 1088, 813, 727, 699, 671, 656. HR-ESIMS (\(m/z\)): calcd. for [M+H]\(^+\) C\(_{37}\)H\(_{41}\)N\(_3\)O\(_6\)S\(_2\) 688.2510, found 688.2534.

\((S)-N\text{-benzyl-}N\text{-}(6\text{-benzyloxoy})\text{-3-oxo-1\text{-(1-tosyl-1H-imidazol-4-yl)hexan-2-yl})-4-methylbenzenesulfonamide (49)\)

![Chemical Structure]

To a dry round bottom flask was added oxalyl chloride (4 ml), dry dichloromethane (100 ml). After cooling the solution to -78 °C, anhydrous DMSO (6 ml) was added dropwise over 10 min. After addition, the solution was stirred for 10 min. Then, N-benzyl-N-((2S)-6-(benzyloxy)-3-hydroxy-1-(1-tosyl-1H-imidazol-4-yl)hexan-2-yl)-4-methylbenzenesulfonamide (14.0 g, 20.4 mmol) in anhydrous DCM (10 ml) was added slowly over 15 min. After addition, the solution was stirred over 30 min at same temperature. Then, triethylamine (37 ml) was added over 20 min. After addition, the temperature of reaction was slowly raised to r.t. The mixture was filtered by passing through a pad of silica gel (10 g), then, washed by anhydrous diethyl ether (100 ml). The solution was concentrated to get comparably pure 3-benzyloxypropyl ketone as pale yellow viscous oil (13.97 g, >99%). The crude ketone can be used directly for next step. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.78\) (s, 1 H), 7.72 (t, 4H, \(J = 14\) Hz), 7.38 - 7.21 (m, 14.0 H), 6.54 (s, 1H), 6.58 (m, 1H), 4.56 (t, 4H, \(J = 11\) Hz), 4.42 – 4.32 (m, 3H), 4.14 (d, 1H, \(J = 11\) Hz).
= 15 Hz), 3.27 - 3.24 (m, 2H), 3.12 (dd, 1H, J = 11 Hz), 2.62 – 2.49 (m, 2H), 2.43 (s, 3H), 2.45 (s, 3H), 2.41 (s, 3H), 2.24 – 2.12 (m, 1H), 1.68 – 1.53 (m, 2H), 1.49 – 1.38 (m, 1H);

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 206.3, 146.4, 144.0, 140.8, 138.6, 137.6, 136.1, 135.9, 135.8, 135.0, 130.5, 130.0, 129.6, 129.1, 128.6, 128.5, 127.7, 127.5, 127.4, 115.0, 73.0, 69.3, 63.9, 50.4, 36.3, 26.0, 23.7, 21.8, 21.7. FT-IR: 1718, 1356, 1336, 1190, 1074, 720, 699, 671. HR-ESIMS (m/z): calcd. for [M+H]$^+$ C$_{37}$H$_{41}$N$_3$O$_6$S$_2$ 686.2353, found 686.2355.

Hydrazone 52 (11.28 g, 40.0 mmol), ketone 49 (6.85 g, 10.0 mmol), and p-TsOH·H$_2$O (9.50 g, 50 mmol), were dissolved in EtOH (60 mL) and the solution was heated at reflux for 4 days. The reaction mixture was concentrated, diluted with ethyl acetate, and neutralized with aqueous NaHCO$_3$. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and combined organic extracts were dried over anhydrous Na$_2$SO$_4$, and concentrated under vacuum. Purification of the crude product by flash column chromatography (50% EtOAc-hexane) to remove excess hydrazine 52 and byproduct benzophenone, then, (50% EtOAc-MeOH) provided the crude indole 50. Because of separation problem, the crude $^1$H NMR was obtained. Please see the attachment.
Hydrazone 52 (5.44 g, 20.0 mmol), ketone 43 (2.44 g, 5.0 mmol), and $\rho$-TsOH·$\text{H}_2\text{O}$ (4.75 g, 25 mmol), were dissolved in EtOH (30 mL) and the solution was heated at reflux for 4 days. The reaction mixture was concentrated, diluted with ethyl acetate, and neutralized with aqueous NaHCO$_3$. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and combined organic extracts were dried over anhydrous Na$_2$SO$_4$, and concentrated under vacuum. Purification of the crude product by flash column chromatography (50% EtOAc-hexane) to remove excessive hydrazine 52 and byproduct benzophenone, then, (50% EtOAc-MeOH) provided the crude indole 53. Because of separation problem, the crude $^1$H NMR (500 MHz, CDCl$_3$) was obtained. Please see the attachment.

11. Haploscleridamine

Mg (turnings) was added (0.48 g, 20 mmol) to a solution of indole 52 (0.82 g, 2 mmol) in dry MeOH (20 mL), and the mixture was sonicated until all magnesium turnings were consumed. MeOH was evaporated, acidified with concentrated HCl, and extracted with ethyl acetate (3 x 20 mL) to remove side product. The aqueous solution was basified with NaHCO$_3$ until the pH value was adjusted to 8, extracted with ethyl acetate (3 x 50 mL). The combined extracts were dried over anhydrous Na$_2$SO$_4$, concentrated to provide
crude haploscleridamine 11, the crude $^1$H NMR (500 MHz, CDCl$_3$) was obtained. Please see the attachment.
5.2 Total Synthesis of Ceratinad B

2-(4-(4-(dibenzylamino)-2,5-dimethoxyphenyl)-4-hydroxybutyl)isoindoline-1,3-dione 78

To a solution of 4-bromo-2,5-dimethoxyaniline\(^\text{72}\) (29.3 g, 150 mmol) in DMF (200 ml) was added benzyl chloride (50.6 g, 400 mmol), NaI (4.5 g, 30 mmol) and K\(_2\)CO\(_3\) (55.2 g, 400 mmol) in sequence. After refluxing for 2 hours, the reaction mixture was concentrated. The residue was washed with diethyl ether (500 ml). The ether solution was washed with water (3 X 50 ml). The solution was dried over anhydrous Na\(_2\)SO\(_4\). The solution was concentrated to provide red oil, which was used directly without further purification. Note: N,N-dibenzyl-4-bromo-2,5-dimethoxybenzenamine cannot be kept for an extended period, otherwise debromination takes place. A solution of (N,N-dibenzyl-2,5-dimethoxybenzenamine)magnesium bromide (1.0 M in THF, 100 mL, prepared from N,N-dibenzyl-4-bromo-2,5-dimethoxybenzenamine (61.8 g, 150 mmol) and magnesium turnings (4.0 g, 167 mmol)) was added to a solution of 4-(1,3-dioxoisouindolin-2-yl)butanal\(^\text{73}\) (17.4 g, 80.2 mmol) in THF (100 mL) at 0 °C, and the mixture was stirred for 2 h at same temperature. After stirring for an additional 1 h at 25 °C, a saturated solution of NH\(_4\)Cl (50 ml) was added to the mixture which was then extracted with EtOAc. The organic phase was washed with brine, dried (Na\(_2\)SO\(_4\)), and then evaporated to give viscous oil. The crude product was purified by flash chromatography (silica gel, EtOAc/hexane 1/2), to give the desired alcohol 78 (34.3 g, 78%) as a viscous oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.83 – 7.80\) (m, 2H), 7.70 – 7.67 (m, 2H), 7.30 – 7.17 (m, 10H),
6.83 (s, 1H), 6.30 (s, 1H), 4.81 (t, 1H, \( J = 8.5 \) Hz), 4.24 (s, 4H), 3.87 (s, 3H), 3.72 (t, 2H, \( J = 6.0 \) Hz), 3.54 (s, 2H), 2.67 (s, 1H), 1.89 - 1.81 (m, 2H), 1.77 - 1.69 (m, 2H); \(^{13}\)C NMR: \( \delta = 168.6, 150.5, 147.0, 139.5, 134.0, 133.2, 132.2, 128.5, 128.3, 126.9, 125.1, 123.3, 111.7, 106.0, 70.5, 56.6, 55.9, 38.0, 34.7, 25.4. \) FT-IR: 3521, 2936, 2833, 1703, 1611, 1452, 1434. HR-ESIMS (m/z): calcd. for [M+Na]\(^+\) C\(_{34}\)H\(_{34}\)N\(_2\)O\(_5\) 573.2360, found 573.2356.

2-(4-(4-dibenzylamino)-2,5-dimethoxyphenyl)-4-oxobutyloisoindoline-1,3-dione

The benzyl alcohol \( \textbf{78} \) (27.5 g, 50 mmol, 1 equiv), IBX (20 g, 75 mmol, 1.5 equiv) in acetone (200 mL) was heated at refluxing for 2 h. After cooling to room temperature, the slurry was filtered and washed with acetone. The filtrate was concentrated by rotary evaporation to provide the crude product. The crude product was washed by EtOAc and after vacuum filtration, the EtOAc solution was concentrated to provide crude ketone \( \textbf{103} \) which can be used directly for next step without purification. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.71 \) (d, 2H, \( J = 3.0 \) Hz), 7.59 (t, 2H, \( J = 3.0 \) Hz), 7.36 (s, 1H), 7.30 – 7.20 (m, 10H), 6.22 (s, 1H), 4.39 (s, 4H), 3.77 (s, 3H), 3.71 (t, 2H, \( J = 6.0 \) Hz), 3.53 (s, 3H), 2.93 (t, 2H, \( J = 4.6 \) Hz), 2.07 – 2.01 (m, 2H); \(^{13}\)C NMR: \( \delta = 198.2, 168.5, 155.0, 145.6, 145.4, 138.4, 133.9, 132.3, 128.5, 128.0, 127.1, 123.2, 118.4, 113.3, 103.8, 56.2, 55.8, 55.5, 41.1, 37.9, 23.8. \) FT-IR: 2933, 2832, 1765, 1705, 1649, 1592, 1501, 1432, 1412. HR-ESIMS (m/z): calcd. for [M+Na]\(^+\) C\(_{34}\)H\(_{32}\)N\(_2\)O\(_5\) 571.2203, found 571.2194.
2-(3-bromo-4-(4-(dibenzylamino)-2,5-dimethoxyphenyl)-4-oxobutyl)isoindoline-1,3-dione 77

To 12.9 g (23.6 mmol) of ketone 103 was added 125 mL of anhydrous benzene containing (3.6 g, 35.6 mmol) of NEt₃. Trimethylsilyl triflate (5.7 g, 25.9 mmol), was added dropwise through additional funnel over a 10 min period with stirring at room temp under argon. After 15 h, 50 mL of saturated aqueous NaHCO₃ was added and this mixture was extracted with 500 mL of ether. The organic layer was washed with 50 mL of H₂O, dried (Na₂SO₄), and evaporated. The crude silyl enol ether was dissolved in 75 mL of anhydrous THF, and 7.2 g (71.2 mmol) of NEt₃ was added while the mixture was cooled to 0 °C. To the solution was added NBS (3.87 g, 23.6 mmol) and stirring was continued for 2 h. After which time it was allowed to warm to rt and 10 mL of saturated aqueous NaHCO₃ was added. The mixture was then extracted with 500 mL of ether. The organic layer was washed with H₂O, dried (Na₂SO₄), and concentrated to give a crude 77, which was used directly for next step. ¹H NMR (500 MHz, CDCl₃): δ = 7.79 (d, 2H, J = 2.8 Hz), 7.69 (t, 2H, J = 2.8 Hz), 7.41 (s, 1H), 7.30 – 7.20 (m, 10H), 6.23 (s, 1H), 5.43 (dd, 1H, J = 3.0, 9.0 Hz), 4.49 (dd, 4H, J = 3.5, 16.0 Hz), 3.95 – 3.85 (m, 2H), 3.80 (s, 3H), 3.58 (s, 3H), 2.51 – 2.54 (m, 1H), 2.41 – 2.33 (m, 1H); ¹³C NMR: δ = 191.5, 168.2, 155.2, 146.5, 145.5, 138.3, 134.0, 132.1, 128.6, 127.9, 127.2, 123.3, 115.0, 114.1, 103.2, 56.12, 56.06, 55.5, 50.8, 36.5, 33.1. FT-IR: 2933, 2832, 1765, 1705, 1649, 1592, 1501, 1432, 1412.
HR-ESIMS (m/z): calcd. for [M+Na]+ C_{34}H_{31}N_{2}O_{5}Br^{78} and C_{34}H_{31}N_{2}O_{5}Br^{81} 649.1314 and 651.1348, found 649.1296 and 651.1283.

\(N-(4-(4-(\text{dibenzylamino})-2,5\text{-dimethoxyphenyl})-5-(2-(1,3\text{-dioxoisodolin-2-yl})\text{ethyl})-1H\text{-imidazol-2-yl})\text{acetamide} \ 76\)

\[
\begin{align*}
\text{Bn}_2\text{N} & \quad \text{OMe} \\
\text{OMe} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N=H} \\
\text{NHAc} & \quad \text{O} \\
\text{H} & \quad \text{76}
\end{align*}
\]

To 3.0 equiv of acetylguanidine (4.42 g, 43.62 mmol) in anhydrous acetonitrile 120 mL was added 1.0 equiv of the \(\alpha\)-bromoketone (9.02 g, 14.41 mmol). The reaction mixture was heated at reflux overnight whereupon it was evaporated to dryness and the residue was purified by column with chromatography (EtOAc : MeOH = 10 : 1) to provide \(76\) (8.25 g, 90%) as a deep yellow foam. \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)): \(\delta = 7.71 - 7.68\) (m, 2H), 7.59 – 7.56 (m, 2H), 7.41 (s, 1H), 7.38 – 7.18 (m, 10H), 6.91 (s, 1H), 6.34 (s, 1H), 4.31 (s, 4H), 4.0 – 3.86 (m, 5H), 3.59 (s, 3H), 3.08 (t, 2H, \(J = 6.5\) Hz), 2.03 (s, 3H); \(^{13}\text{C NMR}\): \(\delta = 170.2, 168.2, 150.2, 146.9, 141.7, 140.1, 139.0, 133.8, 132.1, 128.5, 127.1, 123.1, 113.8, 106.0, 56.6, 56.0, 55.8, 37.8, 26.2, 23.3.\) FT-IR: 2933, 2832, 1770, 1709, 1593, 1505, 1451. HR-ESIMS (m/z): calcd. for [M+H]+ C_{37}H_{38}N_{4}O_{5} 630.2706, found 630.2711.
To a solution of 76 (6.29 g, 10 mmol) in MeOH was added Pd/C (0.6 g) and several drops of concentrated HCl. The mixture was stirred at room temperature and at 50 psi of pressure of hydrogen. After stirring 12 hours, the reaction mixture was filtered. The solution was concentrated to provide crude product 75 (4.45 g, >95%), which was pure enough to be used for next step directly without purification. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.69 – 7.66\) (m, 2H), 7.61 – 7.58 (m, 2H), 7.61 – 7.56 (m, 2H), 7.38 – 7.18 (m, 10H), 6.69 (s, 1H), 6.18 (s, 1H), 3.87 (t, 2H, \(J = 6.5\) Hz), 3.79 (s, 3H), 3.74 – 3.66 (m, 5H), 3.01 (t, 2H, \(J = 6.5\) Hz), 2.11 (s, 3H); \(^1^3\)C NMR: \(\delta = 170.0, 168.2, 150.8, 144.1, 136.9, 133.6, 132.0, 123.0, 122.2, 99.3, 68.0, 56.2, 55.9, 37.8, 25.7, 23.4\). FT-IR: 3347, 2936, 1886, 1770, 1709, 1611, 1509. HR-ESIMS (m/z): calcd. for [M+Na]\(^+\) \(C_{23}H_{23}N_5O_5\) 472.1588, found 472.1591.
Aniline 75 (2.65 g, 5 mmol) and crude aldehyde hydrate 135 (1.70 g, 5 mmol) were dissolved in EtOH (20 mL). After aniline 107 was consumed completely monitored by TLC, the reaction solution was concentrated under vacuum at room temperature. The residue was added Ph$_2$O (20 mL), the reaction mixture was heated to 250 °C and maintained 1 h, then cooled to room temperature. The reaction mixture was diluted with hexanes, passed through a short pad of silica gel to remove Ph$_2$O by 50% EtOAc-Hexanes. After concentration, the residue was used directly for next step without further purification.

The mixture of quinolone 74 obtained from previous step and anhydrous hydrazine (10 mL) was heated to 70 °C, stirred overnight at same temperature, concentrated to remove hydrazine. The residue was titrated by EtOH (5 mL). The precipitate was filtered. The solution was concentrated and the residue was used directly for next step. For the
BBR₃ (5 mL, 60 mmol) was slowly added to the mixture of crude quinolone 136 obtained from previous step in dichloromethane (20 mL) at -78 °C. After stirring at -78 °C for 1 hour, the reaction temperature was slowly raised to room temperature, stirred for 1 more hour, quenched by dropwise MeOH (10 mL) at -78 °C, concentrated to provide crude fragment B 73.
Appendix A

A. $^1$H NMR AND $^{13}$C NMR Spectra of

(s)-Methyl 2-(n-benzyl-4-methylphenylsulfonamido)-3-(1-tosyl-1h-imidazol-4-yl)propanoate 46
Appendix B

$^1$H NMR AND $^{13}$C NMR spectra of

(s)-n-Benzyl-4-methyl-n-(1-oxo-3-(1-tosyl-1h-imidazol-4-yl)propan-2-yl)benzenesulfonamide 47
Appendix C

$^1$H NMR AND $^{13}$C NMR Spectra of

(s)-n-Benzyl-n-(6-(benzyloxy)-3-hydroxy-1-(1-tosyl-1h-imidazol-4-yl)hexan-2-yl)-4-methylbenzenesulfonamide 48
Appendix D

$^1$H NMR AND $^{13}$C NMR Spectra of

$(s)$-n-Benzyl-n-(6-(benzyloxy)-3-oxo-1-(1-tosyl-1$^h$-imidazol-4-yl)hexan-2-yl)-4-methylbenzenesulfonamide 49
Appendix E

$^1$H NMR AND $^{13}$C NMR Spectra of

2-(4-(4-(Dibenzylamino)-2,5-dimethoxyphenyl)-4-hydroxybutyl)isoindole-1,3-dione 78
Appendix F

$^1$H NMR AND $^{13}$C NMR Spectra of

2-(4-(4-(Dibenzylamino)-2,5-dimethoxyphenyl)-4-oxobutyl)isoindoline-1,3-dione 103
Appendix G

$^1$H NMR AND $^{13}$C NMR Spectra of

2-(3-Bromo-4-(4-(dibenzylamino)-2,5-dimethoxyphenyl)-4-oxobutyl)isoindoline-1,3-dione

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Appendix H

$^1$H NMR AND $^{13}$C NMR Spectra of

$n$-(4-(4-(Dibenzylamino)-2,5-dimethoxyphenyl)-5-(2-(1,3-dioxoisindolin-2-yl)ethyl)-1H-imidazol-2-yl)acetamide 76
Appendix I

$^1$H NMR AND $^{13}$C NMR Spectra of

$n$-(4-(4-Amino-2,5-dimethoxyphenyl)-5-(2-(1,3-dioxoisindolin-2-yl)ethyl)-1h-imidazol-2-yl)acetamide 75
APPENDIX J

$^1$H NMR Spectra of Srude

$(s)-n-(1-(3-(2-(Benzyloxy)ethyl)-1h-indol-2-yl)-2-(1h-imidazol-4-yl)ethyl)-4-

methylbenzenesulfonamide 50
Appendix K

$^1$H NMR Spectra of Crude

$(s)$-1-(((1h-Imidazol-4-y)methyl)-2-tosyl-2,3,4,9-tetrahydro-1h-pyrido[3,4-b]indole 53
Appendix L

$^1$H NMR Spectra of Crude Haploscleridamine 11
Appendix M

$^1$H NMR Spectra of Crude

6-(2-Acetamido-5-(2-(1,3-dioxoisindolin-2-yl)ethyl)-1h-imidazol-4-yl)-5,8-dimethoxy-4-
oxo-1,4-dihydroquinolin-3-yl benzyl carbonate 74
Appendix N

$^1$H NMR Spectra of Crude

6-(2-Amino-5-(2-aminoethyl)-1h-imidazol-4-yl)-3-hydroxy-5,8-dimethoxyquinolin-4(1h)-one 136
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