Progress on Total Asymmetric Synthesis of Antifungal 8

by

Scott Garrett Greene
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<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>°C</td>
<td>Degrees Celsius</td>
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<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
<td>DHQD</td>
<td>Dihydroquinidine</td>
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<td>DHQN</td>
<td>Dihydroquinine</td>
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<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
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<tr>
<td>ee</td>
<td>Enantiomeric Excess</td>
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<tr>
<td>FB</td>
<td>Feist-Benary</td>
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<td>h</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>IFB</td>
<td>“Interrupted” Feist-Benary</td>
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<tr>
<td>LDA</td>
<td>Lithium Diisopropylamide</td>
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<tr>
<td>M</td>
<td>Molar</td>
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<td>Me</td>
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<tr>
<td>Np</td>
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<td>PS</td>
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<td>Trimethylsilyl</td>
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<td>$p$-Toluenesulfonyl chloride</td>
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ABSTRACT

Antifungal 8, which lacks a common name, has a core structure similar to GlaxoSmithKline’s griseofulvin, a potent antifungal agent, and is able to treat various systemic fungal infections in humans with compromised immune systems, livestock, and even plants (1), (2). Antifungal 8 has been previously synthesized through a stereochemically uncontrollable, photochemical intramolecular ring-forming reaction of a benzophenone derivative (3). The asymmetric total synthesis of antifungal Compound 8 involves using an organocatalyzed asymmetric reaction, “Interrupted” Feist-Benary reaction to induce chirality and preferentially yield one enantiomer of antifungal 8. Asymmetric total synthesis of both enantiomers of antifungal 8 separately permits identification of the enantiomer with the stronger antifungal properties.

The first step of the chiral synthesis of antifungal 8 involves an a-sulfonyloxy IFB reaction, a condensation reaction of a dicarbonyl compound with an a-halocarbonyl compounds to form a hydroxydihydrofuran. A chiral catalyst yielding 97% enantioselective control has been identified. The next two steps, formation of aromaticity in the right six-membered ring of the molecule and removal of the o-oxygen, allow for regioselective chlorination of the molecule. Following, the elimination of the phenol protecting group, triflation, and addition of two methyl groups to the molecule yield the desired product – antifungal 8.
1 THEORETICAL INTRODUCTION

1.1 Antifungal Agents

1.1.1. Introduction to Antifungal Agents

In much the same manner that antibacterial drugs penicillin, quinine, and others have transformed medicinal care and treatment of bacterial infections, compounds with antifungal properties have affected a similar revolution in the treatment and cure of fungal infections. In contrast to bacterial infections which have plagued medicine since time immemorial, problems with systemic and potentially life-threatening fungal infections are simultaneously a primary concern and product of modern medicine. The wide-spread introduction of antibacterial compounds to combat bacterial infections often leaves patients vulnerable to both obligate and opportunistic fungal infections, fungal infections originating from external sources and the native internal flora of the patient respectively (4).

Particularly in recent decades there are an increasing number of patients whose immune systems have been compromised due to various medical treatments and procedures. These patients include those who have been administered immunosuppressant drugs in the course of organ transplants and other medical procedures, as well as cancer patients undergoing chemotherapy (5). Perhaps most acutely, and most famously, those infected with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are at a significantly increased lifetime risk to systemic fungal infection (5). With the advance of antiviral drugs, numerous patients with HIV/AIDS have had their lifetimes far extended.
Recently, resistance to antifungal drugs has been observed by various mycoses, and thus underlines the impetus and need for the discovery and production of novel antifungal compounds. In contrast to antibacterial compounds however, there is a much more limited range of antifungal compounds known and available to treat infection. During the middle of the 20th century, only one compound, amphotericin B, which can be seen in Figure 1, was the only drug clinically approved for the systemic fungal infections (6). Since the 1980’s, and particularly since the year 2000, there has been a significant increase in the number of known antifungal compounds. However, there are still only fifteen clinically-approved antifungal agents (7). Most antifungal compounds are divided into three main categories: polyenes, allylamines, andazole-based antimycotic agents.

First discovered in the 1950’s, polyene antifungal compounds share the general structure of a macrocyclic ester ring (8). One side of the macrocycle has several conjugated carbon-carbon double bonds, while the other is substituted with multiple hydroxyl functional groups. Prominent polyenes include amphotericin B, and natamycin, as seen in Figure 1. In general, polyene antifungal compounds cause necrosis of fungal cells through interactions with a compound in the cell wall of the susceptible fungus, ergosterol (7). Amphotericin B for example, physically binds with ergosterol, creating small pores in the cell wall. This allows for the leakage of potassium ions, which then disrupts the proton gradient of the fungal cell and permits the release of necessary small molecules. This eventually leads to the death of the fungus (6). Once the frontline treatment for several types of fungal infections, today amphotericin B has been replaced by more recent, and more potent, antifungal agents.
Figure 1: Structures of the amphotericin B, natamycin, and ergosterol.

A more recent addition to known antifungal compounds is the allylamines, whose antifungal activities were first recognized in the late 1970’s and early 1980’s. Prominent examples include terbafine and naftitine, the structures of which are seen in Figure 2 (6), (9). As the name suggests, the allylamines are characterized by the presence of an allylic amine, a nitrogen in an allylic position to a double bond, in the structure of the molecule. Terbinafine is highly potent against dermatophytes, fungal infections of the epidermis layer that includes ringworm and tinea (1). Allylamines cause death of fungal cells by inhibiting the fungal enzyme squalene epoxidase. This inhibition of the epoxidation of squalene in turn inhibits the fungal cell’s production of ergosterol. However, it is not the lack of production of ergosterol that is believed to be the primary cause of fungal cell death, but rather the result of increased concentrations of squalene within the cell (9). The
high concentration of squalene within the cell is believed to cause weakening of the cell membrane, leading to disruption of various ions gradients, and eventual cell death.

**Figure 2**: Allylamines terbinafine and Nafitine HCl.

The third main group of antifungal compounds includes those based upon azole-containing structures. Examples of azole antifungals, as seen in Figure 3, include miconazole, bifonazole, and abafungin (7). All azole antifungals contain some sort of azole ring, which is a five-membered aromatic heterocyclic ring, containing at least one nitrogen and one other non-carbon element (10). Miconazole was one of the first azole-containing antifungal compound and discovery was first reported in the late 1960’s (1). The azole antifungal compounds cause cell death by interfering with the fungus’ production of ergosterol. Without the production of ergosterol, the fungal cell is unable to regulate its permeability. Thus, in a manner similar to the mechanism of polyenes, the fungal cell is able to retain essential small molecule compounds as they exit through pores in the cell membrane, ion gradients become unbalanced, and cell death occurs (11).

Though most known antifungal compounds fit within the three categories above, other antifungal compounds are known. 5-fluorocytosine is a prominent example of an antifungal compound which has a structure not described by the above three categories. The heterocyclic structure of 5-fluorocytosine can be seen in **Figure 4** (1). The compound
causes cell death by first entering the fungal cell, and is then metabolized by the cell into 5-fluorodeoxyuridylic acid \((J2)\). 5-fluorouridylic acid, the structure of which can be seen in Figure 4, is subsequently incorporated into the cell’s RNA. Once incorporated into the fungal cell’s RNA, the compound is able to inhibit DNA, RNA, and protein synthesis, causing cell death \((J2)\).

![Miconazole](image1.png)  ![Bifonazole](image2.png)  ![Abafungin](image3.png)

**Figure 3**: Azole-containing antifungals, miconazole, bifonazole, and abafungin.

![5-fluorocytosine](image4.png)  ![5-fluorodeoxyuridylic acid](image5.png)

**Figure 4**: 5-fluorocytosine and 5-fluorodeoxyuridylic acid.

### 1.1.2 Griseofulvin

Though the target of the total synthesis of the synthetic route presented within is antifungal compound 8, the structure of this molecule mimics the core of the antifungal compound griseofulvin. The compound was first isolated in 1939 by Oxford *et. al.* from
*Penicillium griseofulvum dierckx*, and antifungal properties were first reported in 1947 by Brian (2). The first total synthesis of griseofulvin was reported in 1960 by Brossi *et al.* (13). The compound is known to have fungistatic activity, meaning it inhibits growth and reproduction of the fungi without death of the fungi, against the strains *microsporum* spp., *epidermophyton floccosum*, and *trichophyton* spp (11). Griseofulvin is able to inhibit mitosis of the fungal cells, preventing reproduction, as well as intracellular microtubule formation, preventing fungal growth. The mechanism by which it inhibits growth is not known (11). Clinical trials by Goldman *et al* in 1960 showed griseofulvin’s effectiveness in treating fungal skin lesions through oral administration (2). Its primary use is in the treatment of dermatophyte fungal infections such as ringworm, and other skin and scalp infections.

![Griseofulvin](image)

**Figure 5**: Griseofulvin.

### 1.1.3 Antifungal Compound 8

The target of the synthetic route is an asymmetric total synthesis of antifungal 8. The compound lacks a common name. Similar to other benzophenone-derived compounds with a chlorine atom in the *meta* position on the right aromatic ring, a racemic mixture of antifungal 8 was found to have greater antifungal activity than griseofulvin or norfloxacin against two common fungal cultures *Aspergillus fumigatus*
and Fusarium solani. Synthesis of the compound was first reported by Khanum et. al. in 2003 (3). Antifungal 8 has been previously prepared using a photochemical intramolecular ring-forming reaction of a benzophenone derivative, which can be seen in Figure 6 (3). However, this method of photosynthesis is stereochemically uncontrollable, and a total asymmetric synthesis has not yet been reported. With a successful asymmetric synthesis of antifungal 8, testing of the antifungal activity of each enantiomer separately would be made possible, permitting the determination of which enantiomer has the stronger antifungal activity.

**Figure 6:** Literature synthesis of antifungal 8 from benzophenone (3).

![Figure 6](image_url)

**Figure 7:** (S)-antifungal 8 and (R)-antifungal 8.

**1.2 Theory of Chirality**

The characteristics, functions, and attributes of an organic molecule are dictated by the structure of the molecule. Thus, the arrangements of bonds between atoms and the spatial relationships of atoms to one another within a molecular framework is essential to
understanding both the physical and medicinal attributes of a particular compound. As predicted by Jacobus van’t Hoff and Joseph Achille Le Bel independently in 1874, and later laid down more formally in VSEPR (Valence Shell Electron Pair Repulsion) theory, a carbon with four substituents has the bonds with each of those substituents directed at the corners of a tetrahedron \((10)\). If each of these four substituents has a unique identity, meaning that each substituent is a different functional group, then the central carbon atom is identified as a chiral center, and the molecule as a whole is chiral. The term chiral is used to describe a molecule if it is asymmetric in such a way that in three dimensions the structure of the molecule and its mirror image are not superimposable \((14)\).

**Figure 8**: Tetrahedral carbon center of chirality, and its non-superimposable mirror image.

In Figure 8, no symmetry operation exists so that either chiral center could be placed in the same configuration as its mirror image reflection. The two images above are known as stereoisomers, or two molecules with atoms that are connected in the same manner, but differ only in their arrangement in space. More specifically, the two tetrahedral carbons in Figure 7 are enantiomers one another. Two objects are enantiomers of one another if one is the non-superimposable mirror image of the other. If one or more of the substituents on the molecule are identical, there exists a plane of
symmetry through a symmetry operation is possible to successfully superimpose one mirror image upon the other. If this is possible, the molecule in question is achiral.

Enantiomers for the most part, have exactly the same physical properties as one another, such as density, melting point, and boiling point, despite having different spatial orientations. Enantiomers differ in their ability to rotate plane-polarized light when placed in solution; this is known as the enantiomer’s optical activity \((10)\). Enantiomeric forms of chiral molecules will rotate plane-polarized light, light in which the electric field vector is restricted to a single plane, in equal amounts in opposite directions. One enantiomer will rotate the light clockwise, which is denoted as \((+\)) or dextrorotary, and the other will rotate light to the same extent in the counter-clockwise direction \((-\)) or levorotatory \((14)\).

Enantiomers are assigned identities, \(R\) or \(S\), based upon the three-dimensional arrangement of substituents on at a chiral center. This is known as the absolute configuration of an enantiomer. Whether a compound is assigned the identity \(R\), Latin for rectus, or \(S\), Latin for sinister, is based upon the Cahn-Ingold-Prelog notational system, also known as sequence rules \((10), (14)\). Depending upon whether the substituents on the chiral center are placed in order of descending precedence based upon the system’s rules for ranking functional groups to the left or the right, with the substituent with the lowest precedent facing away from the point of view, the enantiomer is assigned the \(S\) or \(R\) designation respectively \((14)\).
1.3 Chirality and Biological Activity

For pharmaceutical compounds and therapeutic drugs, the chirality of the compound is an important component of its biological activity and bioavailability. In order to produce the desired therapeutic effects of a compound, the compound must bind at biological receptor sites. These receptor sites are composed of proteins, and as proteins are composed of many chiral amino acids, the receptor sites themselves are chiral. Thus, if there are two enantiomers of a compound, they will form two different diastereomers upon binding with the receptor site. Diastereomers are stereoisomers that are not mirror images of one another. Diastereomers, unlike enantiomers however, have different energies and chemical properties. These diastereomer drug-receptor complexes thus have different dissociation constants, thus leading to different biological activities for each enantiomer.

Therefore, which stereoisomer of a drug is administered is very important as different stereoisomers of a single compound can have vastly different effects upon being introduced into biological processes. In recent years, a large majority of drugs approved by the FDA are chiral molecules. “In 2006, for example, more than 80% of new drugs approved by the FDA were chiral, and more than 75% of these were being produced and
marketed as a single enantiomer” (14). Sometimes, one stereoisomer of a compound will simply have a greater biological activity than the other, but both have the same qualitative effect. For two enantiomers, the more potent stereoisomer is known as the eutomer, while the less potent enantiomer is called the distomer (15). For example, the compound citalopram, the structure of which can be seen in Figure 9, was developed by the pharmaceutical company Lundbeck, was originally sold as a racemic mixture of the compound (16). However, through both in vivo and in vitro studies by Hyttel et. al found that the (S)-(+) enantiomer has a greater biological activity of greater than 167 times the (R)-(−) enantiomer (16). This enantiomeric biological activity ratio is also known as the eudismic ratio between two enantiomers.

![Figure 10: (R)-(−)-citalopram and (S)-(+)citalopram (I).](image)

Enantiomers can also have different biological effects. Sometimes, one enantiomer will not produce undesired side effects that are experienced during the use of the opposite enantiomer. The enantiomers (1R,2S)-(−)-ephedrine and (1S,2R)-(−)-ephedrine, are a good example of this. (1R,2S)-(−)-ephedrine is banned by the FDA as a dietary supplement (14). However, (1S,2R)-(+)ephedrine has been shown to be effective as a decongestant and dietary aid, without the neurological side effects of its enantiomer.
However, sometimes enantiomers can have drastically different biological effects. The compound tranylcypromine is a monoamine oxidase inhibitor used to treat patients with Parkinson’s disease (17). Though it is marketed as a racemate the effects of its enantiomers simultaneously different and complementary. The enantiomer (+)-tranylcypromine is able to improve motor control of Parkinson’s patients, while (–)-tranylcypromine assists with mental symptoms (17).

1.4 Chiral Induction, Auxiliaries and Catalysis

Prior to the development of chiral catalysis, chirality was typically induced in achiral materials through the use of chiral auxiliaries. Chiral auxiliaries are readily available chiral, optically active, compounds that are temporarily directly incorporated into the structure of the intermediate achiral synthetic compound (18). Chiral auxiliaries are commonly sourced from naturally-occurring amino acids and other optically active biological compounds. There are numerous downsides to the use of chiral auxiliaries
however. First, they must be added and removed from the main organic compound, adding at least two additional steps to a synthetic route (19). More importantly however, as they need to be incorporated into the structure of the molecule in which chiral induction is desired, stoichiometric amounts of enantiomerically pure chiral auxiliaries are required (18). Thus, the utility of chiral auxiliaries is limited during the scale-up of laboratory processes; they are nearly useless on the scale of industrial processes.

Though mostly established after the initial reports of chiral catalysis, the SAMP-/RAMP- hydrazines that were developed by Dieter Enders et al. are a good example of chiral auxiliaries (20). The SAMP-/RAMP- hydrazines are developed from the commonly available chiral material (S)-proline and (R)-glutamic acid respectively (21). The SAMP-/RAMP-hydrazines are reacted with aldehydes and ketones to form the corresponding hydrazone. The hydrazone is then deprotonated at the α-position, forming an azaenolate. The chiral auxiliary is chelated with a metal ion, forming a sterically bulky, chiral complex that permits enantioselective addition of electrophiles on only one face of the azaenolate (20). The hydrazone is then cleaved to restore the original carbonyl compound, but is now substituted asymmetrically at the α-carbon.

![Figure 13: SAMP-/RAMP-hydrazines (21).](image)

The development of catalytic methods to induce chirality in achiral starting materials was one of the most significant advances in organic chemistry and natural
product synthesis of the 20th century. Asymmetric catalysis permits the induction of chirality into a large amount of material using only a small amount of enantiomerically pure material (22). Generally, chiral catalyst loading can range from anywhere between 1 mol% of the reagent to 10 mol% of the starting reagent. Often, the chiral catalyst and/or chiral ligands can be recovered after the reaction and reused; this is a clear environmental and economic benefit. As only a catalytic amount of chiral material is needed, chiral catalysis is useful for industrial scale chemical processes and drug production. With sufficiently high catalyst turnover numbers (TON), that is the number of catalytic cycle a mole of catalyst can complete before it becomes deactivated, huge quantities of material can be brought through the asymmetric catalytic cycle using only a small amount of chiral catalyst (22).

The first example of chiral catalysis was reported by R. Noyori and H. Nozaki in 1966, who observed a stereochemically-biased reaction of styrene and ethyl diaoacetate in the presence of 1 mol% of a chiral Schiff base-Cu complex (23). The reaction yielded both cis- and trans-ethyl 2-phenylcyclopropanecarboxylate with 10% and 6% enantiomeric excess respectively (24). Though today, chiral catalysts regularly effect reactions with near complete enantiomeric excess, this was unprecedented at the time of publication (24). Nozaki would go on to develop other chiral catalysts and ligands, the chiral components of catalysts that bond dentatively to transition metal ions and provide the stereochemical control for the catalytic reactions. Nozaki would develop the incredibly versatile chiral ligand, BINAP, whose stereochemistry comes not from a chiral center, but rather the locked conformation of its aromatic rings due to steric interactions between them (25). Nozaki would later share the 2001 Nobel Prize in Chemistry with
William Knowles, another pioneer of asymmetric catalysis, for his research on asymmetric catalytic hydrogenation reactions (24).

![Catalytic Reaction](image)

**Figure 14:** Asymmetric catalytic reaction of styrene and ethyl diazoacetate (24).

![BINAP Structures](image)

**Figure 15:** (S)-BINAP and (R)-BINAP (1).

### 1.5 Organocatalysis

In recent years, examples of asymmetric organocatalytic reactions, reactions where small organic molecules play the role of the active catalyst, have been greatly expanded upon. Today, organocatalysis, in addition to biocatalysis, that is reactions with active enzymatic catalysts, organometallic catalysis, reactions catalyzed by using metal ion with chelated organic ligands, is one of the main types of asymmetric catalytic reactions. While organometallic catalysis has traditionally been the most widely applied method of catalysis in organic chemistry, organocatalysis avoids many of the problems
associated with organometallic catalysts. These problems include scarcity of rare transition metals, extremely high costs, and environmentally damaging refinement and subsequent disposal of the used catalysts. There are four main types of organocatalysts: Lewis bases, Lewis acids, Bronsted bases, and Bronsted acids (26). As would be expected, these organocatalysts operate in much the same way non-catalytic Lewis and Bronsted bases and acids function. As organocatalysts, their reactivity is the same, but it permits another reaction to proceed by means of a catalytic cycle. Lewis bases and acids add to substrates through either nucleophilic or electrophilic addition respectively, while Bronsted acids and bases protonate or deprotonate in that order (26).

A particularly good example of the potential of asymmetric organocatalysis is the one-step synthesis of the anticoagulant warfarin. Though the drug was previously administered to patients as a racemate of (S)- and (R)-warfarin, the two enantiomers have different half-lives in the body by several days; this leads to problems with dosage and concentrations of warfarin within the bloodstream (27). Through a Michael addition between in the presence of an imidazolidine-derived Lewis acid organocatalyst, warfarin was produced in a one-step synthesis with high yields and up to 82% enantiomeric excess of both the R and S enantiomer. With a subsequent recrystallization in acetone/water, both (S)-warfarin and (R)-warfarin were isolated in enantiopure forms (27). Through the use of organocatalysis, enantiopure warfarin was produced with greater atom economy and with higher yields than had been previously reported.
Figure 16: Imidazolidine-catalyzed asymmetric Michael addition synthesis of warfarin.

Asymmetric electrophilic substitution and functionalization of carbons in the α-position to ketones and aldehydes is another particularly poignant example of the utility of organocatalysis. Through the use of aminocatalysts, as is described below, one is able to asymmetrically substitute α-carbons with a large range of electrophiles asymmetrically in a single step (28). Through the use of proline-derived aminocatalysts, it is possible to asymmetrically perform amination, hydroxylation, amination, fluorination, chlorination, bromination, iodination, sulfonylation, and selenation, as well as add electron-deficient alkenes in the α-position of aldehydes with high enantiomeric excess (29). Sterics are used by the bulky substituent in the 2-position to cause preferential electrophilic attack at only one face to effect stereoinduction (28). Compare this to the use of Ender’s SAMP/RAMP hydrazines, as discussed previously, which requires a total of four steps to affect the same asymmetric substitution (21). In Figure 17 drawn with the example of the organocatalytic cycle of asymmetric α-functionalization of an aldehyde by the example catalyst α,α-diarylprolinol silyl ether catalyst (29).
Figure 17: Organocatalytic cycle of asymmetric $\alpha$-functionalization of an aldehyde by $\alpha,\alpha$-diarylprolinol silyl ether.

1.6 “Interrupted” Feist-Benary Reaction

First discovered in 1901, the Feist-Benary reaction is a cyclo-condensation reaction in which furan derivatives are created from $\beta$-keto esters and $\alpha$-halogenated carbonyl compounds (30). Traditionally, the crude product of the Feist-Benary reaction is treated with aqueous acid during work-up of the reaction mixture, yielding the furan
derivative (31). However, eliminating the acid work-up step of the reaction yields hydroxydihydrofurans, also known as the IFB, or “Interrupted” Feist-Benary product. Calter et. al. have also reported discovered that using cinchona alkaloid derivates as a catalyst for the reaction, as opposed to ammonia or pyridine, the IFB product is produced in good yields and with high enantiomeric excess (32). As opposed to traditional methods of inducing chirality, such as using chiral auxiliaries, chirality is induced in the product by the chiral catalyst. Based upon Calter et. al.’s work, Hui Chen et. al. found that cinchona alkaloid esters give comparable yields, but higher enantiomeric excess of the IFB product (33).

**Figure 18:** Example Feist-Benary and ‘Interrupted” Feist-Benary Reaction Diagram (32).

The Feist-Benary reaction is base-catalyzed. Central to the mechanism is an aldol addition between the enolate of the β-keto ester and the α-halogenated carbonyl (31). The enolate of the β-keto ester is formed through deprotonation at the α-carbon (31). Traditionally, ammonia or pyridine is used as the catalyst for the deprotonation of the β-keto ester; recent reports however have shown the use of aqueous pyridine produces a
higher yield of the furan product (30). Following deprotonation, the enolate of the β-keto ester undergoes a mixed aldol addition with the α-halogenated carbonyl (34). An enolate of a carbonyl group of the β-keto ester is then generated through proton transfer. This enolate anion removes the α-halogen from the α-halogenated carbonyl through a back-side attack, S_N2 reaction (31). Next, the acid work-up is performed, exposing the crude reaction mixture to aqueous acid; the hydroxydihydrofuran is aromatized, yielding a substituted furan derivative (31). If the acid work-up is not performed, the isolated product is a hydroxydihydrofuran derivative, the IFB product (32).

Figure 19: Generic “Interrupted” Feist-Benary Mechanism (34).

1.7 Retrosynthesis

Modern synthetic organic chemistry is based upon the concept of retrosynthetic analysis, which was devised and popularized by E.J. Corey, a giant in the field of organic chemistry and natural product synthesis. Today, nearly all, if not all, total synthetic routes are planned and developed through retrosynthetic analysis. E.J. Corey was awarded the
1990 Nobel Prize in Chemistry for “his development of the theory and methodology of organic synthesis” (35).

Prior to the work of E.J. Corey, synthetic routes were devised by first selecting commercially available starting compounds. Starting materials were chosen by selecting those compounds that had structures most similar to that of the target compounds (35). Synthetic routes were then planned from start to finish, making them highly dependent upon the starting materials. Reactions were planned so that they moved the structure of the starting material towards that of the target compound.

Corey laid out his philosophy of retrosynthesis in the journal *Pure and Applied Chemistry* in 1967 (36). Corey’s idea of retrosynthetic analysis begins the planning of a synthetic route not from the beginning, but from the end. Through discrete steps, a target compound is transformed into simpler, precursor compounds. This method does not presuppose starting materials. The result of a target molecules transformation into a simpler compound is itself transformed into simpler precursor compounds until the retrosynthetic deconstruction results in precursor compound that are commercially available (35). Reactions that are then able to complete the retrosynthetic transformations, however in the reverse direction, are either found in literature or developed in the laboratory. In Figure 20, one can see a retrosynthesis of the natural product antipathine A as proposed by the author (37).
Figure 20: Example retrosynthesis of natural product antipathine A (37).
2 ANTIFUNGAL 8 RETROSYNTHESIS AND SYNTHETIC ROUTES

2.1 Retrosynthesis and Synthetic Route of Antifungal 8

2.1.1 Retrosynthesis

The retrosynthesis of antifungal 8 was first proposed by Professor Michael A. Calter in a grant proposal to the National Institute of Health. As described in the above chapter, the retrosynthesis of antifungal 8, which can be seen in Figure 21, begins with the desired target compound moves toward simpler precursor compounds. First, the methyl groups are removed from the two aromatic rings, and replaced with a bromine substituent and a triflate substituent on the left and right aromatic rings respectively. Next, the triflate group is replaced by an alkoxide group with a primary alcohol at the end of the aliphatic chain. Then, the right aromatic group with the alkoxide group is replaced with a six-member ring substituted with an α,β-unsaturated ketone and an acetal protecting group in the position of the alkoxide. Lastly, a chiral center and a five-membered furan ring is formed by an asymmetric ring-forming reaction between nucleophile 5-(1,3-Dioxane)-1,3-cyclohexadione and electrophile α-tosyloxy-4-bromoacetophenone.

Figure 21: Retrosynthesis of antifungal 8.
2.1.2 Synthetic Route

From the retrosynthetic route, a forward-direction asymmetric synthetic route was proposed by Calter. In the first step, an asymmetric “Interrupted” Feist-Benary between 1 and 2 is used to form the substituted furan ring and induce chirality in the intermediate compound 2 discussed in Section 1.6. The reaction is asymmetrically catalyzed by a cinchona alkaloid derivative, which will be discussed in Section 2.4. In the second step, potassium tert-butoxide is used as a base to form aromaticity to the right six-membered ring, converting the α,β-unsaturated carbonyl into a phenol, and converting the acetal protecting group into an aliphatic alkoxide with a primary alcohol at the end of the chain, yielding 4. Compound 4 is then tosylated at the phenol position. The fourth step involves the nickel-catalyzed reduction of the tosyl group on compound 5 the right aromatic ring; this replaces the tosyl group with a hydrogen atom to yield 6.

Figure 22: Antifungal 8 synthetic route.
Then, the right aromatic ring on 6 is chlorinated in the ortho-position relative to the alkoxide group on the right aromatic ring to yield 7. The alkoxide group on the right aromatic ring of 7 is converted to a phenol group through oxidation; this yields compound 8. Compound 9 is formed through triflation of the phenol on 8. In the final step, a Stille Coupling is used to place methyl groups in the positions of the bromine on the left aromatic ring and the triflate on the right aromatic ring of 9, yielding the final product 10. In-depth discussion of the development, reagents, and mechanisms of each synthetic step will be discussed in the following chapter.

2.2 Nucleophile Synthesis

The compound that acts as a nucleophile in the IFB reaction, the first step of the asymmetric synthesis, 5-(1,3-Dioxane)-1,3-cyclohexadione, 2. The compound is electron-rich due to the presence of the two neighboring carbonyl compounds.

![Synthetic Route](image)

**Figure 23**: Synthetic Route for 5-(1,3-Dioxane)-1,3-cyclohexadione.
This is particularly true at the carbon on the six-membered ring between the two ketones. The synthesis of this compound was first reported by Li in her doctoral dissertation (38).

In Figure 22, one can see the synthetic route for production of, 2. The yields presented in Figure 22 are those of the author of this paper.

To yield 2, first, propylene glycol, 11, is converted to the corresponding silyl enol di-ether, 13, using TMSCl and triethylamine as a base. Then, the silyl enol ether is reacted with 12 in the presence of catalytic TMS-OTf to place an acetal protecting group upon the central ketone. This yields 14. Use of the Grignard reagent at low temperature MeMgBr converts one of the esters into the corresponding methyl ketone, yielding 15. A Dieckmann-like cyclization of 15 using LDA yields the nucleophile,

While the work performed by Li in optimizing the yields was thorough and impressive, an improvement on the methodology of the final step in the synthesis, the ring-forming intramolecular Dieckmann-like condensation reaction that converts into 15 into 2.

![Figure 24: Dieckmann-like cyclization of 15.](image)

Improvements were made upon the work-up of the reaction which greatly increased the purity of the final product of the reaction. The procedure for this reaction can be found in Chapter 4. After removing the solvent in vacuo, Li dissolved the residue in methylene chloride and 2 N acetic acid (38). The acidic acid aqueous layer would both
protonate the product of the reaction, as the product of the reaction prior to aqueous work-up is the anion of the final product, and thus improves the product’s solubility in organic solvents. This acidic aqueous layer was then washed with methylene chloride to extract the product into the organic layer. This would however also bring undesirable organic waste into the organic layer from the aqueous layer. After drying over Na$_2$SO$_4$ and removal of solvent in vacuo, a recrystallization in EtOAc/hexanes was necessary in order to yield isolated product (38).

In place of the dissolving the residue after removing the reaction solvent in 2N acetic acid and methylene chloride, the residue was diluted up in deionized water with one equivalent of HCl and methylene chloride. This would result in an aqueous layer with a pH of about 7. The organic layer would be separated away, and the unwanted organic waste from the reaction contained within. A second equivalent of hydrogen chloride dissolved in DI H$_2$O would be added to the aqueous layer and then extracted with methylene chloride. This yields a much cleaner product after drying and removal of solvent, and eliminating the necessity of recrystallization. Additional product, though of lower purity, is able to be obtained from washing the first organic layer with a basic aqueous wash, acidification of the new aqueous layer to a pH of about 1, and extracting the aqueous layer with methylene chloride.

2.3 Electrophile Synthesis

The electrophile used in the asymmetric IFB reaction is α-tosyloxy-4-bromoacetophenone. The production of the electrophile is only one step from commercially available acetophenone derivatives. The methodology for one-step
conversion of ketones to the corresponding α-tosyloxy ketone was first reported by Koser et al. (39). Use of α-tosyloxy ketones as the electrophile in organo-catalyzed asymmetric IFB reactions was reported by Calter et al (40). This method is general for substituted aryl ketones. The reaction conditions are relatively mild.

![Conversion of 4-bromoacetophenone to α-tosyloxy-4-bromoacetophenone.](image)

**Figure 25:** Conversion of 4-bromoacetophenone to α-tosyloxy-4-bromoacetophenone.

### 2.4 Chiral Catalysts and their Synthesis

The first report of enantioselective catalysts for the IFB reaction was by Calter, Phillips, and Flaschenriem. Calter *et al.* screened a number of cinchona alkaloid derivatives. Cinchona derivatives are several readily available chiral compounds ultimately derived from the *cinchona* genus of plants known for their medicinal qualities, particularly their use in fighting malaria. The cinchona alkaloid derivatives are placed on a pyrimidine framework, with either one or two cinchona groups substituted on a pyrimidine ring. Steric steering groups, such as t-butyl, phenyl, and napthyl groups, are placed in other positions of the pyrimidine ring as experimental enantiomeric excess observations suggest future catalyst synthetic directions. The active catalytic site is the nitrogen contained on the quinuclidine substructure found within cinchona derivatives. If two cinchona derivatives are placed on a pyrimidine structure, a bis-substituted catalyst, then there are two active sites on that catalyst. Various cinchona derivatives used on chiral
IFB catalysts include quinidyl (QD), quinyl (QN), dihydroquinyl (DHQN), dihydroquinidyl (DHQD). As can be expected catalysts substituted with QN or QD, and DHQD or DHQN, enantiomeric cinchona compounds yield opposite enantiomeric preference in the product of the IFB reaction. Other substituents, such as chlorine may also be placed on the pyrimidine ring as place holders in mono catalysts.

Figure 25: Bis-quinidine catalyst with phenyl, naphthy sterio groups.

Figure 27: A) quinyl, B) quinidyl, C) dihydroquinyl, D) dihydroquinidyl.

The catalysts are synthesized in two steps, starting with a Liebskind-Srogl coupling of 4,6-dichloro-2-methylthio-5-phenylpyrimidine, which is commercially
available, with various aryl boronic acids (40). A Liebeskind-Srogl coupling reaction is a carbon-carbon bond forming palladium-catalyzed, copper-mediated coupling of thiol esters with boronic acids (41). This permits the attachment of various aryl groups in the position of the methylthio group. The product of those reactions are refluxed in the presence of KOH in toluene with quinidine or quinine to yield bis(cinchona alkaloid) pyrimidine catalysts (40).

Figure 28: Two step synthesis of chiral catalysts (40).

2.5 Synthetic Step Precedents

In the synthetic route of antifungal 8, the reaction that induces the stereochemistry and enantioselectivity of the final product of the synthetic route is the Interrupted Feist-Benary reaction. The first reports of catalytic, asymmetric IFB reaction involving the condensation of α-tosyloxyacetophenones and 1,3-dicarbonyl compounds were reported by Calter et al. (40).
Various substituted acetophenones were screened in IFB reactions and produced high yields and enantiomeric excess when solvent and temperature were varied \((40)\).

Only dimedone, 5,5-dimethyl-1,3-cyclohexanedione, and 1,3-cyclohexanедione were tested as nucleophiles. The \textit{para}-bromo substituted \(\alpha\)-tosyloxyacetophenone, 1, used in this total synthesis was first used in a catalytic asymmetric IFB in the same paper by Calter \textit{et al.} \((40)\). The specific nucleophile used in the IFB reaction in the synthesis of antifungal 8, 5-(1,3-Dioxane)-1,3-cyclohexadione, was first used in an asymmetric IFB reaction by Li \((38)\).

For several of the reactions on the synthetic route after the asymmetric IFB reaction, Li also developed several similar reactions on similar substrates in her doctoral dissertation. This provided starting points for both reaction conditions and reagents when attempting to develop new reactions on the synthetic route for antifungal 8. Li developed
a reaction to induce aromaticity in her similar substrate using KOTBu in THF at 0°C (38).

This reaction is nearly analogous to the aromatization reaction that converts compound 3 into 4.

![Figure 31: Analogous aromatization (38).](image)

Li also developed tosylation and reduction reactions on substrates similar to intermediate compounds found in the total synthesis of antifungal 8.

![Figure 32: Li’s similar tosylation and reduction reactions (38).](image)
3 SYNTHETIC ROUTE DEVELOPMENT

3.1 Interrupted Feist-Benary Reaction

Reaction condition optimization for a similar IFB reaction, one using dimedone and α-tosyloxy-4-bromoacetophenone was performed by Calter et al.

![Reaction scheme](image)

**Figure 33:** Calter et al. IFB reaction (40).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp(°C)</th>
<th>Alkylation</th>
<th>% yield of IFB</th>
<th>% ee of IFB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PS</td>
<td>CH₂Cl₂</td>
<td>-42</td>
<td>1.2 : 1</td>
<td>51</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>PS</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>9.0 : 1</td>
<td>76</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>PS</td>
<td>CH₃CN</td>
<td>-28</td>
<td>1.1 : 1</td>
<td>47</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>PS</td>
<td>CH₃CN</td>
<td>0</td>
<td>3.2 : 1</td>
<td>67</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃</td>
<td>CH₂Cl₂</td>
<td>-28</td>
<td>8.9 : 1</td>
<td>73</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>K₂CO₃</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>32 : 1</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>K₂CO₃</td>
<td>CH₃CN</td>
<td>-28</td>
<td>1.2 : 1</td>
<td>50</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>K₂CO₃</td>
<td>CH₃CN</td>
<td>0</td>
<td>5.0 : 1</td>
<td>69</td>
<td>94</td>
</tr>
</tbody>
</table>

**Table 1:** Reaction condition optimization by Calter et al. (40).

This provided the framework for the initial reaction conditions of the IFB reaction between 1 and 2. The IFB was found to have the best yield of “IFB” to alkylation product and high enantiomeric excess at 0°C in methylene chloride, in the presence of potassium carbonate. Initial yields of the IFB reaction run at these conditions with 0.10 mol% of the achiral catalyst, DABCO were low, usually around a 20% yield. DABCO, or 1,4-
diazabicyclo[2.2.2]octane contains the active catalytic site without the large pyrimidine catalytic framework that provides steric bulk interactions and thus chiral control. The product resulting from an IFB reaction using catalytic amounts of DABCO is racemic. Large amounts of the c-alkylation byproduct, 17, of the reaction were yielded from the reaction. O-alkylation product, 18, was observed infrequently; and when it was observed, it was in highly limited yields. To increase reaction yield, solvent and reagent ratios were varied. The best yield in terms of both overall yield and yield of IFB product was obtained when using two equivalents of 2 in ratio to 1. The yield of the desired product and the overall mass recovery is still low however. The reaction is run overnight.

![Equation 1](image1.png)

![Equation 2](image2.png)

![Equation 3](image3.png)

**Table 2**: IFB Optimization, 17 – C-alkylation byproduct, and 18 – O-alkylation byproduct.

<table>
<thead>
<tr>
<th>Eq. of 1</th>
<th>Eq. of 2</th>
<th>Solvent</th>
<th>IFB: C : O %Yield</th>
<th>IFB : C : O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>CH₃CN</td>
<td>20 : 14 : 5</td>
<td>5.5 : 3.8 : 0.6</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>CH₂Cl₂</td>
<td>15 : 13 : 0</td>
<td>5.1 : 4.9 : 0.0</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>CH₂Cl₂</td>
<td>21 : 23 : 0.014</td>
<td>4.76 : 5.22 : 0.02</td>
</tr>
<tr>
<td>2.0</td>
<td>1.0</td>
<td>CH₂Cl₂</td>
<td>23 : 18 : 0</td>
<td>5.5 : 4.5 : 0.0</td>
</tr>
<tr>
<td>1.0</td>
<td>2.0</td>
<td>CH₂Cl₂</td>
<td>30 : 15 : 0</td>
<td>6.7 : 3.3 : 0.0</td>
</tr>
</tbody>
</table>
Catalyst screening was accomplished relatively quickly. Only two chiral catalysts were screened before a catalyst with high (>90% enantiomeric excess) was identified. Both catalysts were bis(cinchona alkaloid) pyrimidine catalysts. The bis-quinidine catalyst provided a desirable enantioselectivity, with 97% enantiomeric excess. Running the reaction at 0 °C in methylene chloride effected the desired enantiomeric control. Enantiomeric excess was determined through separation of enantiomers on AD-Chiral Pak HPLC columns and a UV/Vis detector. Integration of UV/Vis detection peaks was performed manually.

<table>
<thead>
<tr>
<th>Eq. of 1</th>
<th>Eq. of 2</th>
<th>Catalyst Y:X</th>
<th>Enantiomeric Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>QN : QN</td>
<td>75%</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>QD : QD</td>
<td>97%</td>
</tr>
</tbody>
</table>

**Table 3:** Catalyst structure and screening.

**Figure 34:** IFB reaction mechanism.
The mechanism for this IFB reaction is illustrated in Figure 34. The mechanism operates in much the same manner as the generalized IFB mechanism explained in Section 1.6.

![Figure 35: Proposed IFB transition state.](image)

In Figure 35, the proposed transition state of the asymmetric IFB reaction is illustrated. The active form of the catalyst in the reaction is not the free cinchona alkaloid derivative base, but rather the protonated version (32). The protonated form of the catalyst forms chelated hydrogen-bonding with the two carbonyls of the α-tosyloxy-4-bromoacetophenone. This simultaneously creates an ordered transition state, one that through the steric bulk of the catalyst forces preferential attack to the less hindered side of the nucleophile, and makes the tosylated compound more susceptible to electrophilic attack by the enolate of the nucleophile (32), (40).
3.2 Base-catalyzed Aromatization

As mentioned previously, Li’s work on a similar reaction on a similar substrate provided precedent for the use of KOtBu as reagent for the reaction as well as reaction conditions for the conversion of 3 into 4. The reaction proceeds quickly and cleanly. Initially allowed to react for two hours, the reaction was found to have gone to completion within one hour. After reaction, the solvent is removed \textit{in vacuo}, leaving behind a bright red oil residue that is the anion of the product. The oil is difficult to work with and is redissolved in methylene chloride and saturated NH\textsubscript{4}Cl aqueous solution. The aqueous layer protonates the product and yields the final product as a brown oil. The yield of this reaction is high, with occasional quantitative yields.

![Aromatization reaction scheme.](image1)

**Figure 36**: Aromatization reaction scheme.

![Base-catalyzed aromatization mechanism.](image2)

**Figure 37**: Base-catalyzed aromatization mechanism.
The mechanism of the aromatization reaction is illustrated in Figure 38. First, the substrate is deprotonated at the α-position to the carbonyl, forming the corresponding enolate. The oxygen-carbon double-bond reforms, thus converting the acetal protecting group into an aliphatic ether with negatively charged oxygen at the end of the aliphatic chain. Aromatization is then formed through proton-transfer to the anionic primary oxygen. The energetic stability gained through the formation of the six-membered aromatic ring is the driving force of the reaction. The reaction is completed through the protonation of the phenol oxygen during the aqueous work-up.

![Figure 38: Eliminated aromatized byproduct — 19.](image)

The product of this reaction, 4, is highly acid and heat-sensitive, and is thus prone to elimination of the tertiary alcohol group on the central heterocycle. Elimination of the tertiary alcohol forms compound 19. Elimination of the tertiary alcohol causes a loss of chirality of the substrate induced during the IFB reaction. Because of the compounds sensitivity, heat cannot be used when removing the reaction solvent in vacuo. Compound 4 was also prone to elimination when dissolved in deuterated chloroform because of the acidity of the solvent. Thus, NMR spectra of 4 were often taken in deuterated acetone. Despite this sensitivity, the $^{13}$C NMR of one of 4 was obtained in deuterated chloroform. Compound 4 would also eliminate on silica gel during flash chromatography, even in the
presence of triethylamine. Because of the instability of the 4, the compound is converted to 5 through tosylation of the phenol without isolation or purification.

### 3.3 Base-catalyzed Aromatization

**Figure 39:** Tosylation reaction.

Using tosyl chloride, 4 is converted to 5 in the presence of four equivalents of proton sponge. Proton sponge is also known as 1,8-Bis(dimethylamino)naphthalene. The protecting base is added first, and followed by tosyl chloride. The reaction proceeds to completion within two hours. Li’s tosylation of a similar substrate, of which the reaction scheme can be seen in Section 2.5, used triethylamine in place of proton sponge. Initially, four equivalents of triethylamine were used here as a base to protect the substrate from the hydrogen chloride that is formed in the course of tosylation of the phenol with tosyl chloride. However, when using triethylamine as a base for this reaction, while tosylation of the phenol was successful, only eliminated tosylated product, 20, was yielded.

**Figure 40:** Eliminated tosylated intermediate — 20.
It was found that the stereocenter of 4 was eliminating in the presence of triethylamine in methylene chloride. This was determined through comparison of $^1\text{H}$ NMR of 4 in solution in methylene chloride before and after the addition of triethylamine. Thus, during the tosylation reaction using triethylamine as the protecting base, first 20 was formed and then that compound was tosylated. A mechanism was proposed by which triethylamine was causing elimination of the stereocenter of 4. The mechanism can be seen in Figure 41.

**Figure 41**: Elimination mechanism.

First, triethylamine removes the phenolic hydrogen, and forces the elimination of the tertiary alcohol. This makes the hydrogens on the furan ring that were previously next to the stereocenter highly acidic. This is because the conjugate base of the substrate will have conjugated aromaticity across the molecule. A second equivalent of triethylamine
removes one of those protons, reforming aromaticity. This forms the anion of the 20.

Through a proton transfer from triethylamine, compound 20 is formed.

It was hypothesized that the use of a more sterically hindered base, which would be unable to remove the hydrogen of the phenol would not cause elimination of the tertiary alcohol at the stereocenter. The base, 1,8-Bis(dimethylamino)naphthalene, or proton sponge, which can be seen in Figure 42, was tried because the naphthyl group provides significant steric hinderance to the base in addition to the amines being tertiary.

![Proton sponge](image)

**Figure 42:** Proton sponge, or 1,8-Bis(dimethylamino)naphthalene.

In the presence of proton sponge, tosylation of 4 to yield 5 was successful, though some eliminated byproduct, 20 was still isolated, about 20-25% after the reaction as a minor product. Compound 5 is less sensitive to elimination than 4 because the compound is less electron-rich. This is because of the electron-withdrawing nature of the tosyl group; 5 can thus be successfully chromatographed on silica gel in the presence of triethylamine.

The mechanism for the tosylation of 4 can be seen in Figure 43. The mechanism is an Sn2 reaction of 4 and tosyl chloride. The hydrogen chloride generated during the tosylation is prevented from protonating the tertiary alcohol and causing elimination by the presence of proton sponge.
Once again, thanks to Li’s development of a nickel reduction method on a similar substrate, as shown in Section 2.5, the author had a starting point for the removal of the tosyl group on the right aromatic ring. The reaction generates Ni$^0$ in situ from the reduction of Ni(II)Cl$_2$ by lithium borohydride. This yields higher conversion of the starting material due to the short-lived nature of Ni$^0$, the active reagent, in solution in
contrast to using Ni\textsuperscript{0} directly. This is because, in part, nickel oxide forms from environmental exposure on the Ni\textsuperscript{0} particles during storage.

Despite running the reaction for five hours, more than twice as long as Li’s, the reaction has not been observed proceeding to completion. Reaction progress was monitored using \textsuperscript{1}H NMR to track the ratio of product versus starting material. After a few hours, Li would add a second equivalent of NiCl\textsubscript{2} and additional LiBH\textsubscript{4} to push the reaction towards completion. This was attempted with this substrate, as the reaction appears to stop after a few hours, however re-adding NiCl\textsubscript{2} and LiBH\textsubscript{4} did produce further reaction progress, and in fact appeared to send the reaction in reverse, decreasing the ratio between the product and the starting material in the \textsuperscript{1}H NMR spectra. Only about a 75% conversion was regularly achieved.

After the reaction and the work-up, taking a \textsuperscript{1}H NMR of the crude product was not initially possible. Despite making several \textsuperscript{1}H NMR samples, the author was unable to achieve a signal lock on two different NMR instruments. This was hypothesized to be because interference with the instrument because of the presence of Ni\textsuperscript{0} remaining the crude product. This was despite having been put through a fretted glass filter. The crude product was then filtered through a diatomaceous earth filter. This removed the remaining Ni\textsuperscript{0} and permitted \textsuperscript{1}H NMR spectra. Compound \textit{6} is able to be chromatographed on silica gel.
### 3.5 Chlorination Reaction

After the removal of the tosyl leaving group from the substrate, the next step is the aromatic chlorination of 6 to yield 7.

![Chlorination reaction scheme](image)

**Figure 45**: Chlorination reaction scheme.

In the original total synthesis proposal, Calter cited an article by Kelly *et. al.* on the total synthesis of the pyralomicinones, a class of compounds isolated from the microorganism *Microtetraspora spiralis*, that exhibit antimicrobial and antitumor activities (42). In the course of the synthesis of the pyralomicinones, the synthetic route for a number of the compounds called for the regiospecific chlorination of a substituted benzene ring, specifically, 2,4-dimethoxytoluene. The target of Kelly *et. al.* was chlorination of the aromatic ring in the *ortho* position to one of the methoxy substituents, and *meta* to the methyl substituent.

![Chlorination of 2,4-dimethoxytoluene](image)

**Figure 46**: Kelly *et. al.* chlorination of 2,4-dimethoxytoluene (42).

Kelley *et. al.* achieved the aromatic chlorination of 2,4-dimethoxytoluene by refluxing the substrate in the presence of one and a half equivalents of N-chlorosuccinimide in DMF for two hours (42). However, the author found these
conditions to be too harsh for use in the total synthesis of antifungal 8. The boiling point of DMF is 153°C, relatively high for an organic solvent (1). As many of the early intermediates compounds are very sensitive to elimination, particularly 4, more mild chlorination conditions were searched for.

An alternative aromatic chlorination reaction was found in the chemical literature. This chlorination method, detailed in a patent by Zhang et al., places the substrate in the presence of one equivalent of NCS and 5 mol% of ZrCl₄ in DCM at -78°C to room temperature (43). Clearly, the reaction conditions of this method are more mild in comparison. Zhang et al. used this method to chlorinate numerous substituted aromatic compounds, in a variety of regiospecific positions (43). It is also effective for other halogens using their halogen equivalent of NCS. N-bromosuccinimide can be used in the presence of catalytic ZrCl₄ to brominate aromatic compounds (43).

More mild conditions reactions conditions are possible because of the presence of a catalytic amount of ZrCl₄, which acts as a Lewis acid. It has been proposed that zirconium tetrachloride forms a Lewis complex with one of the carbonyls of NCS, increasing the reactivity of the haloimide compound. This is because the formation of the complex reduces the electron density of the haloimide compound, and thus stabilizes the anion formed by the transfer of the halogen to the aromatic compound.

![Figure 47: Proposed coordination of ZrCl₄ with carbonyl of haloimide (43).](image-url)
The reaction above, based on the method patented by Zhang et. al. was attempted. The reaction was tracked by $^1$H NMR aliquots of the reaction. Within thirty minutes, all of the starting material had reacted. The reaction solvent was worked up with NaHCO$_3$ as well as a brine wash. The crude reaction product was chromatographed on silica gel. After flash chromatography, none of the desired product, 7, was isolated. Instead, only the eliminated form of 6 was recovered in low yield; the compound had not been chlorinated. It was postulated that perhaps the ZrCl$_4$ caused the elimination, acting as a Lewis acid, and thus yielded the loss of chirality of the starting material.

**Figure 48**: Lewis-acid catalyzed chlorination reaction scheme.
3.6 Conclusions and Future Work

A chiral catalyst, bis-quinidine catalyst with phenyl, naphthyl steric groups, has been identified for the Interrupted Feist-Benary reaction that meets or exceeds the desired amount of chiral control (>95%). Reliable methodology has been developed and tested, creating a dependable synthesis from commercially available starting materials to compound 6, a total of nine steps, well over half of the antifungal 8 synthetic route. The known intermediate compounds on the synthetic route have been, are, or will be fully characterized. The remaining synthetic steps, aromatic chlorination, de-protection of the remaining phenol, triflation of the phenol substituent, and methylation at the bromine and triflate on the left and right aromatic rings respectively, require further methodological development and experimentation.

Once the synthetic route is completed using racemic substrate, the route can then be completed using enantiomerically enriched substrate from the IFB reaction until the final product, antifungal 8, to obtain measurements of the optical rotation of the intermediate compounds in solution. Yields could also be improved on several of the steps to increase the environmental efficiency and cost effectiveness of the synthetic route. It is hoped that the synthesis of antifungal 8 serves to show both the utility of the Interrupted Feist-Benary reaction in the asymmetric total synthesis of natural products, and that the compound antifungal 8 may one day serve as an important tool in treating fungal infections.
4 EXPERIMENTAL

General Procedures

All commercial materials were used as received unless otherwise indicated. THF, toluene, pyridine, and dichloromethane were used from a solvent purification system by filtering through an activated alumina column. Diisopropylamine was distilled over CaH$_2$ before use.

Flash column chromatography was performed on Silicycle 60 Å, 32-63 μm or Dynamic Adsorbants 60 Å, 32-63 μm silica gel, and Dynamic Adsorbants 60 Å, 32-63 μm basic alumina activity III. Thin-layer chromatography (TLC) was accomplished with SiliCycle 0.25 mm, 60 Å pore size silica gel plates or basic alumina (III) plates. TLC plates were visualized using a ceric ammonium molybdate stain or by a UV/Vis lamp.

A Varian-300 (300 Hz and 75 Hz) or Varian-400 (400 Hz and 100 Hz) NMR spectrometer was used for $^1$H and $^{13}$C spectra. Specific rotations were taken on a Perkin-Elmer 241 Polarimeter. HPLC analyses were obtained from a Thermo Separation Product Spectra Series P200 HPLC equipped with a Spectra 100 variable UV/Vis detector and a Hewlett Packard HP-3394a integrator. A Perkin Elmer 1605 149 FT-IR spectrometer was used to collect IR spectra. Elemental analyses were performed by Robertson Microlit Laboratories.
1,3-Bis-(trimethylsilyloxy)propane (13): To a solution of 1,3-propanediol (12.0 mL, 150 mmol) and NEt$_3$ (104.6 mL, 750 mmol) in 750 mL CH$_2$Cl$_2$, TMSCl (56.08 mL, 450 mmol) was added in a dropwise fashion. The mixture was stirred overnight at RT. The reaction was then quenched by the addition of sat. NaHCO$_3$ (150 mL). The aqueous layer was separated away from the organic layer, and then extracted with CH$_2$Cl$_2$ (50 mL). The combined organic phases were then washed with 1 M NaHSO$_4$ (150 mL). The aqueous layer was then separated away from the organic layer, and then extracted with CH$_2$Cl$_2$ (50 mL). The combined organic phases were then dried over Na$_2$SO$_4$, and concentrated in vacuo. This yielded 13 (32.96 g, 99%) as an clear orange oil. This compound has been characterized previously. SG-I-93 \(^{1}$$H NMR (CDCl$_3$, 300 MHz) $\delta$ 3.64 (t, $J$ = 6.0 Hz, 4H), 1.72 (q, $J$ = 6.0 Hz, 2H), 0.08 (s, 18H).

Diethyl 3-(1,3-dioxane)pentanedioate (14): TMS-OTf (4.8 mL, 26.5 mmol) was added dropwise to a solution of 12 (21.5 g, 106 mmol), and 13 (138 mmol, 30.41 g) in CH$_2$Cl$_2$ (700 mL) at -20 °C. The reaction was held at -20 °C for 10 minutes and was then warmed to RT. The reaction was then stirred at RT for 22 h. The reaction was then quenched at RT with dry pyridine (150 mL). The reaction was then washed with 1 M
NaHSO₄ (2x 200mL). The organic layer was then separated away from the aqueous layer, dried over Na₂SO₄, and concentrated *in vacuo*. This yielded 14 (28.8 g, 99%) as a yellow oil. This compound has been previously characterized. SG-II-10. \(^1\)H NMR (CDCl₃, 300 MHz) δ 4.15 (q, J = 6.9 Hz, 4H), 3.96 (t, J = 5.4 Hz, 4H), 3.09 (s, 4H), 1.73 (q, J = 5.4 Hz, 2H), 1.26 (t, J = 6.9 Hz, 6H).

**Ethyl 2-(2-(2-oxopropyl)-1,3-dioxan-2-yl)acetate (15):** Methylmagnesium bromide (3 M in diethyl ether, 23.6 mL, 70.7 mL) was added in a dropwise fashion to a solution of 14 (16.0 g, 61.5 mmol) in CH₂Cl₂ (650ml) at -78°C. The reaction was stirred at -78°C for 24 h. Following, the reaction was quenched with 125 mL of saturated NH₄Cl solution at -78°C. The reaction mixture was then warmed to room temperature and separated away from the aqueous layer. The aqueous layer was then extracted twice with CH₂Cl₂ (2 x 50 mL). The combined organic layers were then dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was then purified using flash chromatography (EtOAc, 3:7—4:6) to yield the final product 15 (6.56g, 65%) as a yellow oil. 29% of the starting material 14 was recovered. This compound has been previously characterized. SG-II-76 \(^1\)H NMR (CDCl₃, 300 MHz) δ 4.14 (m, 2H), 4.020 (m, 2H), 3.91 (m, 2H), 3.051 (s, 2H), 3.04 (s, 2H), 2.24 (s, 3H), 1.89 (m, 1H), 1.54 (m, 1H), 1.26 (m, 3H).
5-(1,3-Dioxane)-1,3-cyclohexadione (2): To a solution of diisopropylamine (1.6 mL, 11.4 mmol), was added nBuLi (1.6 M in THF, 7 mL, 11.1 mL) in THF (25 mL) at -78°C. The reaction was then warmed to RT over 30 min and added to a solution of 15 (2.43 g, 10.5 mmol) in THF (210 mL) at -78°C. The reaction mixture was warmed to RT and then heated to reflux for 3 h. The solvent was then removed in vacuo and the residue was redissolved in 150 mL of CH₂Cl₂ and 50 mL of an acidic aqueous layer (2 mL HCl per 100 mL DI H₂O). The organic layer was then separated away from the aqueous layer. The aqueous layer was then re-acidified from a pH of 7 to a pH of 1. The aqueous layer was then extracted with CH₂Cl₂ (4 x 100 mL). The organic washes were then combined, dried over Na₂SO₄, and concentrated in vacuo. This yielded the final product 2 (0.80 g, 41%) as a white solid. SG-II-13 1H NMR This compound has been previously characterized. ¹H NMR (DMSO-d₆, 300 MHz) δ 5.18 (s, 1H), 3.82 (m, 4H), 2.62 (s, 4H), 1.59 (m, 2H).

α-Tosyloxy-4-bromoacetophenone (2): Tosic acid monohydrate (15.42 g, 78.4 mmol) was added to a solution of 16 (12.04 g, 60.8 mmol) and iodosobenzene (17.15 g,
78.0 mmol) in CH\textsubscript{3}CN (300 mL) at RT. The reaction was then heated to reflux for 3 h. The reaction was then cooled and the solvent removed \textit{in vacuo}. The residue was then diluted in CH\textsubscript{3}Cl\textsubscript{2} and washed with DI H\textsubscript{2}O (2 x 125 mL). The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. The crude product was then recrystallized from toluene/hexanes to yield 1 (15.89 g, 71 \%) as a white solid. This compound has been previously characterized. SG-II-20 \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta 7.83 \) (d, \( J = 8.4 \) Hz, 2H), 7.70 (d, \( J = 8.4 \) Hz, 2H), 7.61 (d, \( J = 8.8 \) Hz, 2H), 7.34 (d, \( J = 8.4 \) Hz, 2H), 5.19 (s, 2H), 2.45 (s, 3H).

\[ \text{3-(4-bromophenyl)-3-hydroxy-3,4,5,7-tetrahydro-2H-spiro[1-benzofuran-6,2'-[1,3]dioxane-4-one (3):} \]

1,4-Diazabicyclo[2.2.2]octane (14 mg, 0.12 mmol) was added to a solution of 1 (302 mg, 1.62 mmol), 2 (301 mg, 0.82 mmol), and potassium carbonate (337 mg, 2.44 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (16 mL) at 0\textdegree C. The reaction mixture was stirred at 0\textdegree C for 46 h. The reaction solution was then washed with DI H\textsubscript{2}O. The aqueous layer was separated away from the organic layer. The organic phase was then dried over Na\textsubscript{2}SO\textsubscript{4} and the solvent removed \textit{in vacuo}. Silica gel flash chromatography (Acetonitrile/CH\textsubscript{2}Cl\textsubscript{2}, 15:85) was then used to yield 3 (92.3 mg, 30\%) as a white solid.

CHIRAL?? \([\alpha]_D^{23} = \); IR (neat) 3404, 2966, 2873, 1629, 1422, 1400, 1210; SG-II-8x IFB 82\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta 7.46 \) (dd, \( J = 2.0, 8.4 \) Hz, 2H), 7.26 (dd, \( J = 2.0, 8.8 \) Hz, 2H), 6.78 (dt, \( J = 8.8, 2.0 \) Hz, 2H), 4.96 (s, 2H), 4.20 (ddd, \( J = 10.8, 7.4, 2.0 \) Hz, 2H), 4.00 (ddd, 2H), 3.78 (s, 3H), 3.56 (s, 3H), 3.05 (t, \( J = 7.0 \) Hz, 2H), 2.80 (s, 3H), 2.57 (t, \( J = 7.0 \) Hz, 2H).
2H), 4.72 (d, J = 10.8 Hz, 1H), 4.38 (d, J = 10.8 Hz, 1H), 3.95 (m, 4H), 2.80 (m, 5H), 1.88 (m, 1H), 1.72 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 190.50, 177.50, 142.61, 131.62, 126.92, 121.69, 117.08, 99.22, 87.63, 81.65, 60.30, 44.64, 35.41, 24.95; Anal. Calcd for C$_{17}$H$_{17}$BrO$_5$: C 53.56; H 4.49. Found: C 53.40; H 4.77.

3-(4-Bromophenyl)-6-(3-hydroxypropoxy)-2,3-dihydro-1-benzofuran-3,4-diol (4): Potassium tert-butoxide (33 mg, 0.29 mmol) was added to a solution of 3 (100 mg, 0.26 mmol) in THF (5.3 mL) at 0°C. The reaction was kept at 0°C for five min and then warmed to RT. The reaction mixture was stirred at RT for 2 h. The reaction solution was removed in vacuo and the residue was diluted in CH$_2$Cl$_2$/NH$_4$Cl. The organic layer was separated away from the aqueous layer, and the aqueous layer was then extracted with CH$_2$Cl$_2$. The combined organic layers were then dried over. This yielded the product 4 as a brown oil (101 mg, 100%). SG-II-84A 1H NMR (CDCl$_3$, 400 MHz) 7.51 (d, J = 8.2 Hz, 2H), 7.38, (d, J = 8.6 Hz, 2H), 6.11 (s, 1H), 5.96 (s, 1H), 5.45 (bs, 1 H), 4.65 (d, J = 10.2 Hz, 1H), 4.43 (d, J = 10.2 Hz, 1H), 4.08 (t, J = 5.8 Hz, 2H), 3.85 (t, J = 5.6 Hz, 2H), 2.87 (bs, 1H), 2.03 (q, J = 5.8 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 217.12, 162.74, 153.72, 141.99, 131.65, 127.39, 121.75, 109.52, 96.03, 89.73, 81.72, 67.96, 65.84, 60.19, 31.86, 25.58.
3-(4-Bromophenyl)-6-(3-hydroxypropoxy)-4-(4-methylbenzenesulfonyl)-2,3-
dihydro-1-benzofuran-3-ol (5): Tosyl chloride (615 mg, 3.23 mmol) was added to a
solution of 4 (1.12 g, 2.93 mmol) and 1,8-Bis(dimethylamino)naphthalene (2.52 g, 11.76
mmol) in CH$_2$Cl$_2$ (30 mL) at 0°C. The reaction was then stirred at 0°C for 1 h. The
reaction was then quenched with 15 mL of saturated NaHCO$_3$. The aqueous layer was
extracted with 10 mL of CH$_2$Cl$_2$. The combined organic layers were then dried over
Na$_2$SO$_4$ and the solvent removed in vacuo. Silica gel flash chromatography
(Acetonitrile/CH$_2$Cl$_2$, 6:94) was then used to yield 5 (668 mg, 43%) as a red/white solid.

SG-III-15. $[\alpha]_D^{23}$ =; IR (neat) 3484, 2950, 2883, 1622, 1592, 1345, 1173; SG-II-71 2$^{nd}$
spot off column $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.45 (dd, $J$ = 2.4, 9.0 Hz, 2H), 7.40 (dd, $J$
= 2.0, 8.6 Hz, 2H), 7.39 (dd, $J$ = 1.6, 8.2 Hz, 2H), 7.27 (d, $J$ = 7.8 Hz, 2H), 6.50 (d, $J$
= 1.6 Hz, 1H), 6.05 (d, $J$ = 2.0 Hz, 1H), 4.72 (d, $J$ = 9.8 Hz, 1H), 4.34 (d, $J$ = 2.0, 9.8 Hz,
1H); 4.19 (dd, $J$ = 2.0 Hz, 1H), 4.01 (m, 2H), 3.82 (m, 2H), 2.46 (s, 3H), 2.01 (p, $J$ = 5.8
Hz, 2H); $^{13}$C NMR (CDCl$_3$, MHz) $\delta$ 163.86, 162.03, 146.00, 143.82, 141.36, 131.27,
129.73, 128.18, 127.95, 126.06, 121.65, 117.45, 102.98, 96.93, 86.89, 81.26, 65.96,
59.83, 31.71, 21.75; Anal. Calcd for C$_{24}$H$_{21}$BrO$_5$S: C 53.84; H 4.33. Found: C 53.94; H
4.37.
3-(4-bromophenyl)-6-(3-hydroxypropoxy)-2,3-dihydro-1-benzofuran-3-ol (6):

Lithium borohydride (2 M in THF, 4.0 mL, 8.10 mmol) was added dropwise to a solution of 5 (618 mg, 1.15 mmol) and nickel (II) chloride (225 mg, 1.74 mmol) in THF (115 mL) at RT. The reaction was then heated to reflux for 5 h. The reaction was then cooled to RT and quenched with 40mL of saturated NH\(_4\)Cl. The reaction mixture was then washed with CH\(_2\)Cl\(_2\) (3 x 70 mL, 2x 50 mL). The combined organic layer was then dried over Na\(_2\)SO\(_4\), and then passed through a diatomaceous earth filter. The solvent was then removed \textit{in vacuo}. Flash chromatography (Acetonitrile/CH\(_2\)Cl\(_2\), 8:92—4:6) was used to yield the final product 6 (175 mg, 50%). 26% of the starting material was recovered.

\([\alpha]_D^{23} =
\)

IR (neat) 3368, 2950, 2885, 1619, 1596, 1496, 1275, 1152; SG-II-91 G 3\(^{rd}\) spot

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.47 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 9.2 Hz, 1H), 6.49 (d, J = 9.2 Hz, 1H), 6.49 (s, 1H), 4.68 (d, J = 10.4 Hz, 1H), 4.46 (d, J = 10.4 Hz, 1H), 4.11 (t, J = 5.6 Hz, 2H), 3.85 (s, 2H), 2.38 (s, 1H), 2.04 (q, J = 4.0 Hz, 2H), 1.70 (bs, 1H);

\(^13\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 162.15, 161.56, 157.36, 141.91, 131.29, 127.93, 124.65, 124.17, 121.59, 86.95, 81.93, 65.94, 60.29, 31.86, 29.69; Anal. Calcd for C\(_{17}\)H\(_{17}\)BrO\(_4\): C 55.91; H 4.69. Found:
5 REFERENCES


37. Greene, S. Proposal for Total Synthesis of Antipathine A. **2011**.


59

6 SPECTRA
5

Br– benzene– TsO
OH
O– OH

Chemical Shift (ppm)

21.75
31.71
59.83
65.96
76.68
77.00
77.32
81.26
86.89
96.93
102.98
117.45
121.65
126.06
127.95
128.18
129.73
131.27
141.36
143.82
146.00
162.03
163.86

Chemical Shift (ppm)