CHAPTER 3

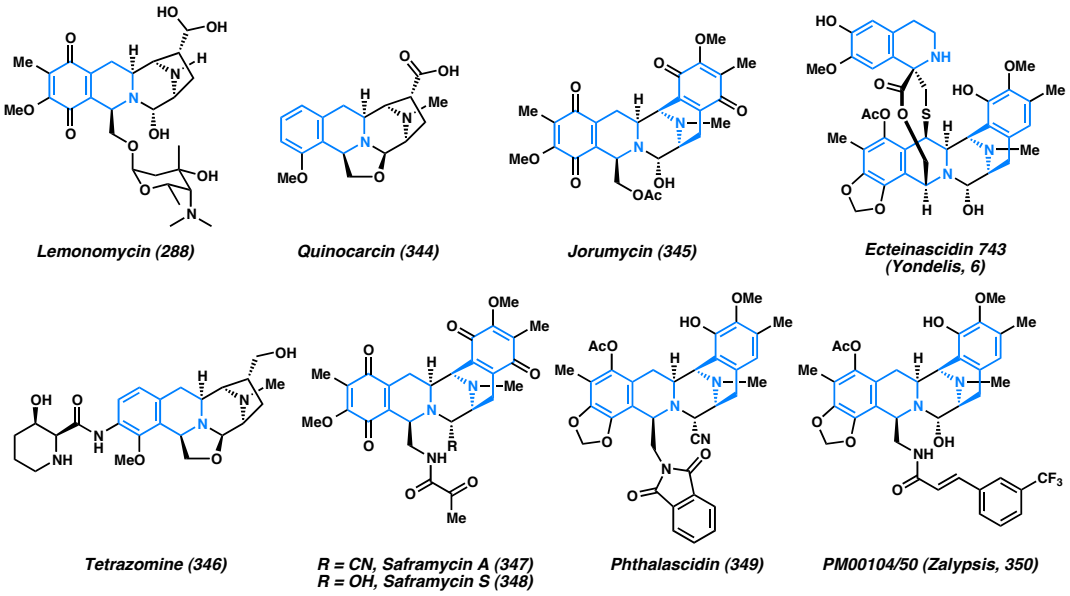
Progress Toward the Total Synthesis of Jorumycin

3.1 INTRODUCTION

The tetrahydroisoquinoline (THIQ) alkaloids have garnered attention from the chemical, biological and medicinal communities over the last three decades as a result of their complex molecular architectures, novel biochemical modes of action, and potent biological activity.[1] The THIQ alkaloid family—containing more than 60 naturally occurring members—includes a remarkable array of structural diversity that is paralleled by the many antibiotic anticancer properties that these molecules consistently display (Figure 3.1). For example, saframycins A (**347**) and S (**348**) display nanomolar cytotoxicity toward L1210 leukemia cell lines (IC_{50} = 5.6, 5.3 nM, respectively).[2] Jorumycin (**345**) inhibits the growth of A549 human lung carcinoma and HT29 human colon carcinoma cell lines at extremely low concentrations (IC_{50} = 0.24 nM).[3] Lemonomycin (**288**) shows activity against colon cancer HCT 116 (IC_{50} = 0.65 μM).[4] KW2152 (the citrate salt of quinocarcin, **344**) has been clinically tested against non-small cell lung cancer,[5] P-388 leukemia (IC_{50} = 0.11 μM),[6] and several types of melanoma.[7] The members that have advanced through human clinical trials and entered the

oncologist's arsenal for the war on cancer best convey the therapeutic potential of these molecules. Ecteinascidin 743 (Trabectedin, Yondelis, **6**) is approved in Europe, Russia, South Korea and Japan for the treatment of soft tissue sarcomas and has obtained orphan drug status within the U.S. as a treatment for relapsed ovarian cancer.[8] The synthetic ecteinascidin analog PM00104/50 (Zalypsis, **350**) is currently in Phase II trials to treat solid tumors.[9] In addition to their various anticancer properties, the THIQ alkaloids also possess broad-spectrum antibiotic activity against the Gram-positive and Gram-negative bacterial strains responsible for infectious diseases such as meningitis, pneumonia, strep throat, and diphtheria.[10] Furthermore, these compounds provide promising leads for alternatives to current drugs such as vancomycin and methicillin in cases of bacterial drug resistance.[4]

Figure 3.1. *Representative THIQ antitumor antibiotics*

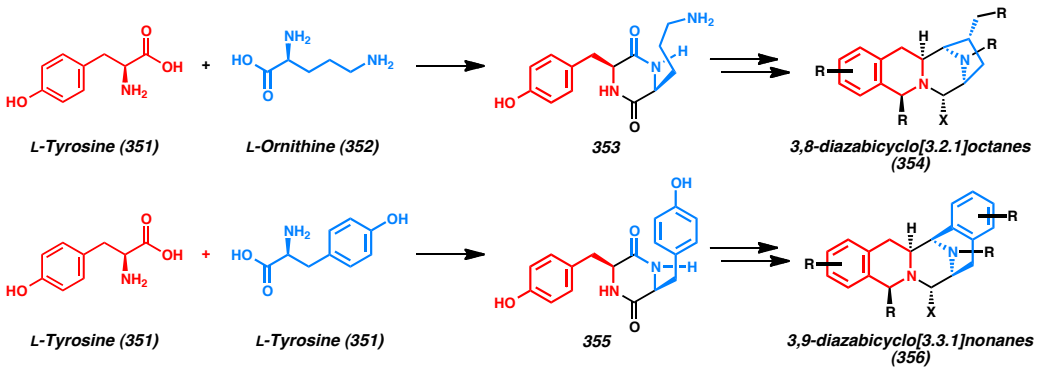


While the noteworthy biological properties of the THIQ alkaloids make them ideal targets for pharmaceutical development, the isolation of material from natural sources is often expensive and low yielding.[1] Fortunately, in these cases, chemical synthesis can provide an alternative means to produce the quantities necessary for clinical testing. It is therefore of critical importance to develop synthetic methods that assemble these important molecules in a concise and efficient manner. In pursuit of this goal, we have developed a general strategy to rapidly construct the core structures of the THIQ alkaloids while providing avenues to introduce the varying peripheral functionality that create the diversity within this large class of natural products.

3.1.1 Biosynthetic Origins

The THIQ alkaloids can be divided into two structural subclasses based on the nature of the central diazabicycle: those featuring a 3,8-diazabicyclo[3.2.1]octane (**354**) biosynthetically derived from the condensation of the amino acids tyrosine (**351**) and ornithine (**352**);[11] and those featuring a 3,9-diazabicyclo[3.3.1]nonane (**356**) derived from two equivalents of tyrosine (**351**) (Scheme 3.1).[12] These two groups of natural products can be further distinguished by the presence of either one (as in the 3,8-diazabicyclo[3.2.1]octanes) or two (as in the 3,9-diazabicyclo[3.3.1]nonanes) embedded tetrahydroisoquinolines.

Scheme 3.1. *Biosynthetic origins of the THIQ alkaloids*

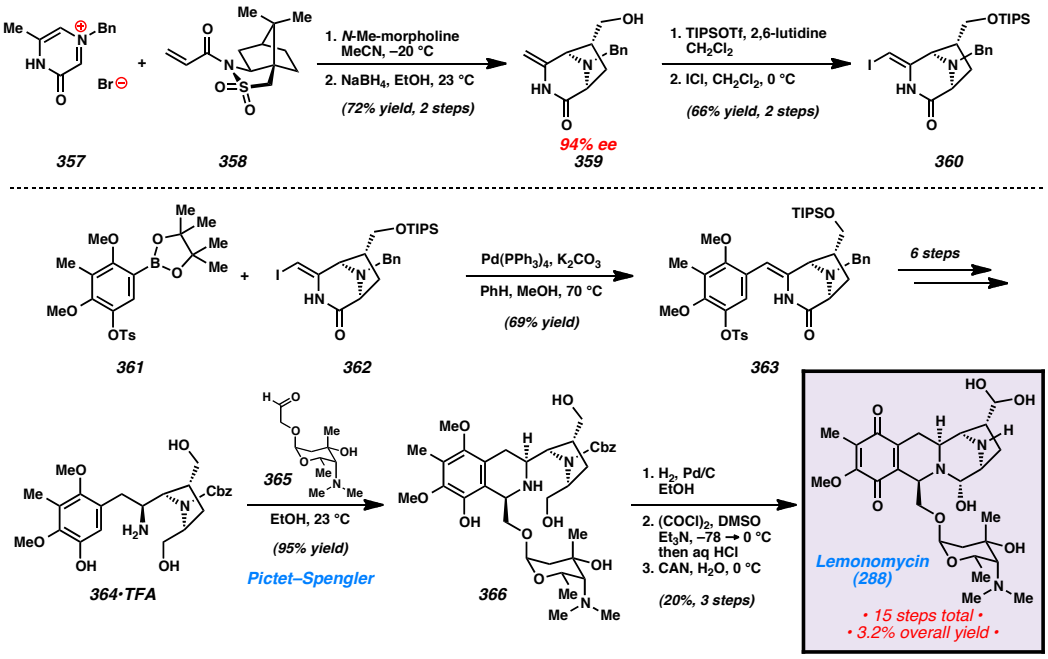


3.1.2 The Enantioselective Total Synthesis of (–)-Lemonomycin[†,13]

Focusing on the mono-THIQ alkaloids, our group reported the first total synthesis of (–)-lemonomycin,[14,4] a compound that has demonstrated potent activity against both *Staphylococcus aureus* and *Bacillus subtilis* in addition to its antitumor properties. We initiated our efforts by investigating an auxiliary-controlled diastereoselective dipolar cycloaddition between oxidopyrazinium bromide **357**[15] and the acrylamide of Oppolzer's sultam (**358**) (Scheme 3.2).[16] Following reductive removal of the auxiliary, alcohol **359** was isolated in 94% ee, thus establishing the absolute stereochemistry. Silylation and iodination provided iodoenamide **360**, which was then coupled with boronic ester **361** under Suzuki–Miyaura conditions. This intermediate was carried forward to aminotriol **364**, at which point the tetrahydroisoquinoline ring system was generated by a highly diastereoselective Pictet–Spengler cyclization with aldehyde **365**, simultaneously introducing the fully elaborated glycoside. Protecting group removal, ring closure, and oxidation provided (–)-lemonomycin (**288**), completing the first, and to date only, total synthesis of this natural product in a total of 15 linear steps.[17]

[†] The total synthesis of (–)-lemonomycin was completed by Dr. Eric Ashley, a former graduate student in the Stoltz lab.

Scheme 3.2. *The total synthesis of (–)-lemonomycin (**288**)*



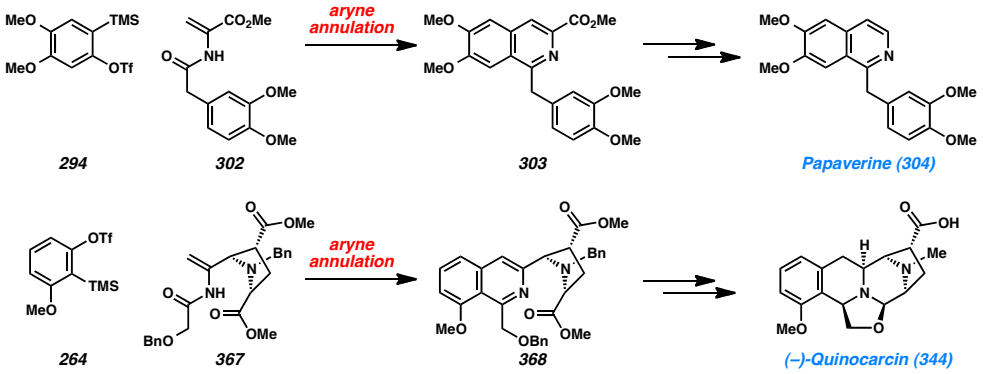
3.1.3 An Aryne Annulation in the Synthesis of Isoquinolines[18] and the Total Synthesis of (–)-Quinocarcin[19,†]

Following the successful completion of our first target within the 3,8-diazabicyclo[3.2.1]octane subclass, we began exploring other methods with the potential for general applicability to the assembly of the THIQ architecture. Specifically, we designed a route toward the THIQ scaffold that exploits the highly convergent nature of our aryne annulation methodology.[18,20] We had previously demonstrated the utility of this method in the rapid total synthesis of papaverine (**304**),[21] a clinically used non-narcotic antispasmotic agent that is a biosynthetic precursor of several pavine alkaloids and one of the four major constituents of opium (Scheme 3.3).[22,23,24] Targeting a THIQ through a

† The total synthesis of (–)-quinocarcin was completed by Dr. Kevin M. Allan, a former graduate student in the Stoltz lab.

similar isoquinoline intermediate (e.g., **303**) is a novel approach to these molecules. We found ourselves particularly intrigued by the complete regioselectivity of *ortho*-methoxy arynes generated from silyl aryl triflate **264**.[25] To explore this method, we devised a synthetic route toward an asymmetric total synthesis of (–)-quinocarcin (**344**) using this aryne annulation approach via intermediate pyrrolidinyl isoquinoline **368**.[19,26]

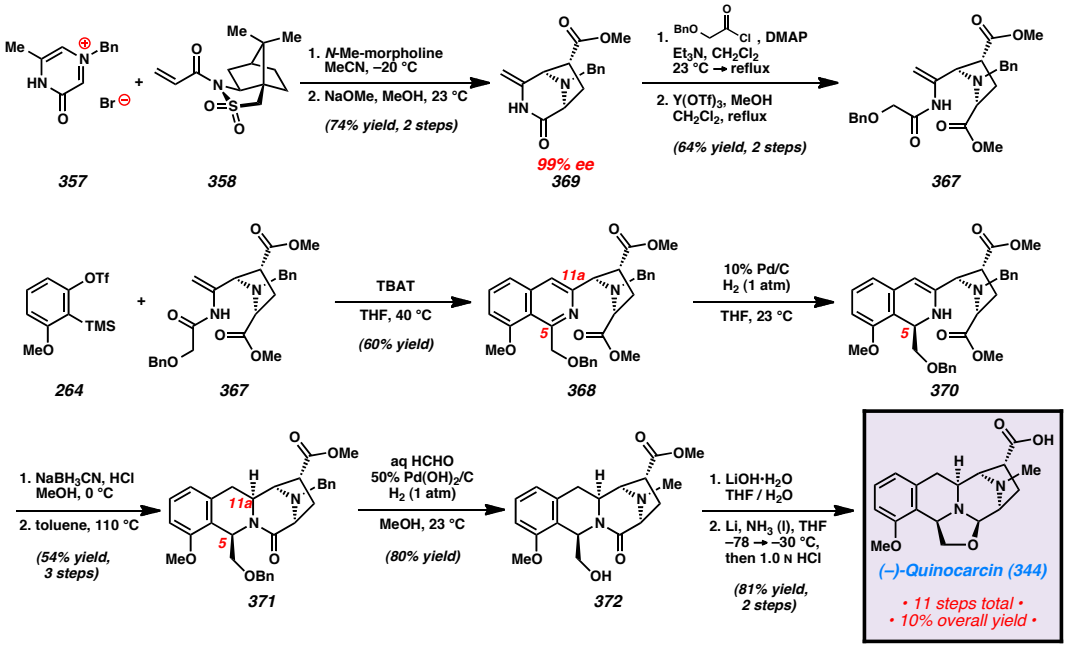
Scheme 3.3. *Aryne annulation approach to isoquinoline natural products*



Drawing from our experience with (–)-lemonomycin, we chose once again to build the bridged bicycle of quinocarcin using an auxiliary-controlled diastereoselective dipolar cycloaddition between oxidopyrazinium salt **357** and chiral acrylamide **358** (Scheme 3.4). After separation of the major diastereomer, the auxiliary was removed via basic methanolysis to provide diazabicycle **369** in 99% ee. This compound was then acylated and selectively methanolyzed at the lactam carbonyl to generate *N*-acyl enamine **367**, the substrate for the key aryne annulation. To our delight, simple treatment of a mixture of silyl aryl triflate **264**[27] and enamine **367** with TBAT resulted in the formation of isoquinoline **368**. Thus, in only 5 steps, we had constructed an intermediate comprising the entire carbon skeleton of quinocarcin (**344**).

Next, a two-step reduction was employed to convert isoquinoline **368** to a tetrahydroisoquinoline. First, 1,2-hydrogenation of the isoquinoline ring system formed a 3.3:1 mixture of diastereomeric dihydroisoquinolines (**370** being the major diastereomer). Based on the stereochemistry at C(5), reduction using sodium cyanoborohydride proceeded diastereoselectively to produce an equivalent ratio of tetrahydroisoquinolines with syn disposed C(5) and C(11a) substituents. The major diastereomer was purified and heated in toluene to close the lactam, generating tetracycle **371**. The sequence was completed by benzyl group hydrogenolysis, *N*-methylation, saponification, and dissolving metal reduction to furnish (–)-quinocarcin (**344**) in 10% overall yield through 11 linear steps, the shortest route reported to date.[28,29,30]

Scheme 3.4. *The total synthesis of (–)-quinocarcin (**344**)*

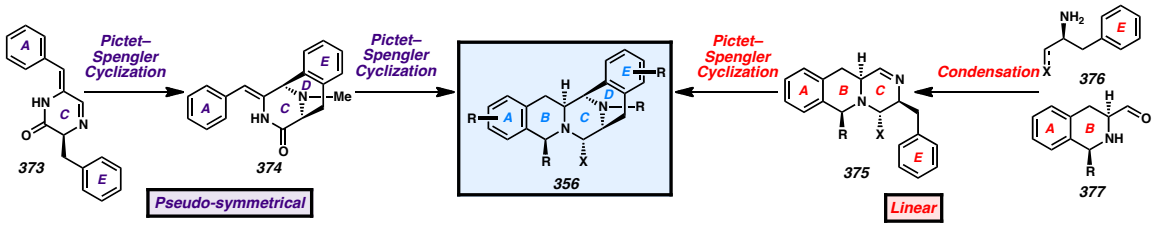


3.2 PROGRESS TOWARD THE TOTAL SYNTHESIS OF JORUMYCIN

3.2.1 Strategic overview of bis-THIQ synthesis

With two completed members of the 3,8-diazabicyclo[3.2.1]octane subclass, we have directed our efforts toward extending this isoquinoline-based synthetic strategy to THIQ alkaloids featuring the 3,9-diazabicyclo[3.3.1]nonane framework. Unlike lemonomycin (**288**) and quinocarcin (**344**), these natural products contain a second tetrahydroisoquinoline ring system embedded within a pentacyclic core. The majority of reported synthetic approaches to this bis-THIQ scaffold have employed one of two retrosynthetic disconnections (Scheme 3.5). The first takes advantage of the pseudosymmetry of the core by attaching the A and E rings to a central piperazine C-ring (**373**) and subsequently performing successive Pictet–Spengler cyclizations.[31] The second, more linear strategy joins the A–B tetrahydroisoquinoline (**377**) to an E-ring-containing fragment (**376**) through condensation before cyclizing the D–E tetrahydroisoquinoline to close the [3.3.1]-diazabicycle (**375**).[32] Notably, both of these strategies make heavy use of the Pictet–Spengler reaction, which requires electron-rich aromatic rings and, in some cases, suffers from poor regio- and stereoselectivity.

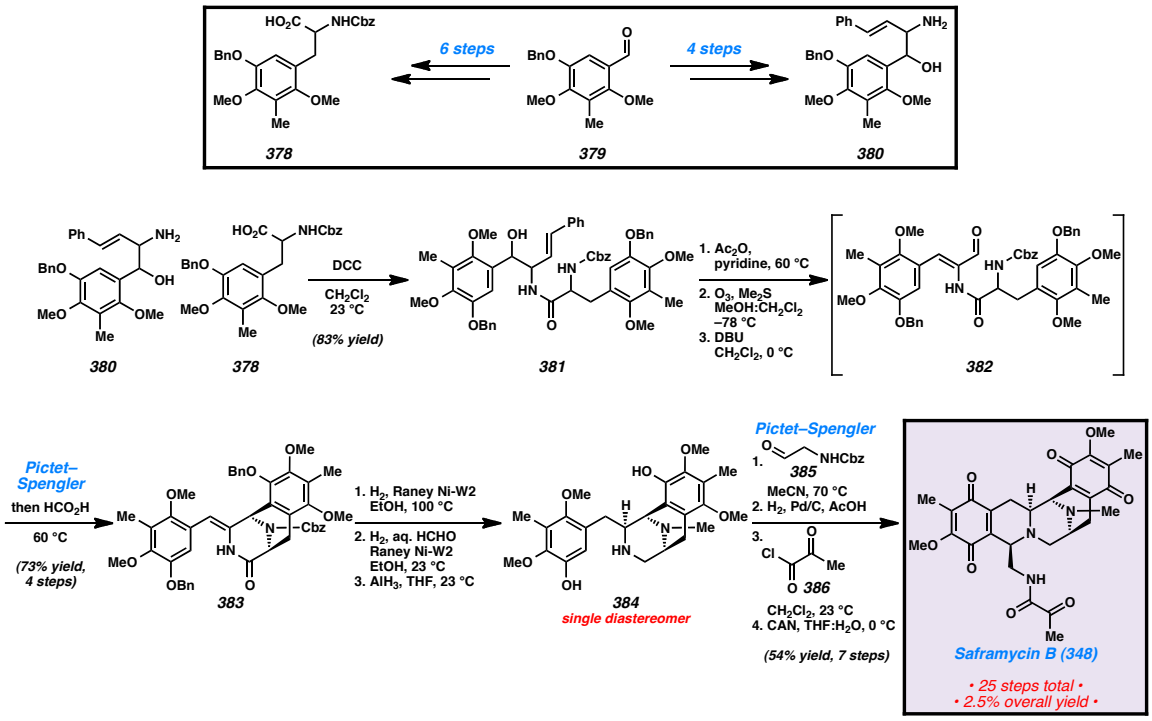
Scheme 3.5. *Strategic approaches to the bis-THIQ, 3,9-diazabicyclo[3.3.1]nonane framework*



Two classical syntheses illustrate both the strategic concerns and the state of the art for bis-THIQ natural product synthesis. The initial total synthesis of a member of this

family was completed by Fukuyama in 1982, where a variation of the pseudo symmetrical strategy was used to construct saframycin B (**348**, Scheme 3.6).[33] This convergent approach employed a coupling of two tyrosine fragments (**378** and **380**) derived from the same advanced aryl aldehyde (**379**). Both the C ring piperazine and the D–E THIQ were constructed using a single Pictet–Spengler reaction (**381→382→383**) with these partners (**378** and **380**). Next, the synthesis was advanced to a second such Pictet–Spengler cyclization that closed the A–B THIQ to ultimately furnish the natural product (**348**). This impressive first synthesis of any member of the saframycin family afforded saframycin B in 2.5% total yield in a 25-step synthesis.

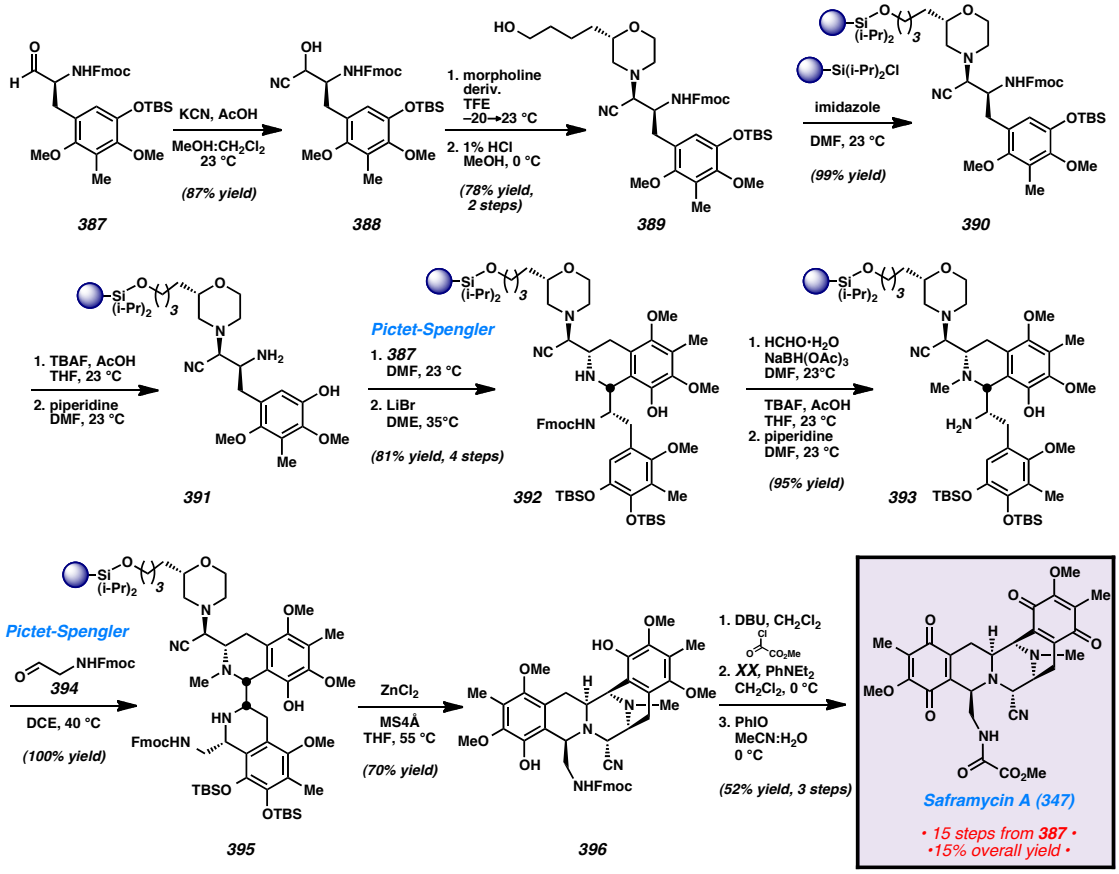
Scheme 3.6. *Fukuyama's total synthesis of (±)-saframycin B (**348**)*



In 2002, Myers completed (–)-saframycin A (**347**) by employing a concise, linear strategy to accommodate a solid phase synthetic approach (Scheme 3.7).[34] Initially, this route was similar to Fukuyama's due to Myers' use of a tyrosine derivative as a universal

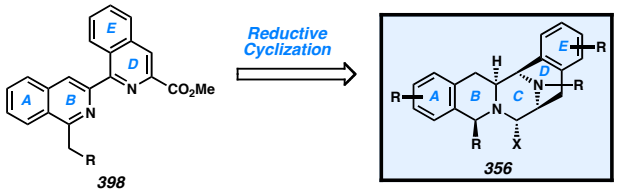
synthetic precursor, amino aldehyde **387**. He was able to generate the A–B THIQ (**392**) through a fragment-coupling step by performing a Pictet–Spengler reaction between solid-supported amine **391** (from **387**) and the amino aldehyde (**387**). Advancement of this isoquinoline provided the substrate for a second Pictet–Spengler reaction and afforded bis-THIQ **395**. Cleavage of this intermediate from the solid support using $ZnCl_2$ revealed the pentacyclic bis-THIQ saframycin core (**396**) in a single step. Side chain functionalization and arene oxidation produced saframycin A (**347**) in 15 total steps and 15% overall yield from amino aldehyde **387**, marking the shortest synthetic approach to any member of the 3,9-diazabicyclo[3.3.1]nonane class of THIQ natural products.

Scheme 3.7. *Myers' total synthesis of (–)-saframycin A (**347**)*



In contrast to these approaches, we plan to intercept a highly functionalized bis-isoquinoline intermediate (**398**) using our recently developed aryne annulation methodology.[18] Stereoselective reduction of bis-isoquinoline **398** followed by lactamization will generate the pentacyclic core (**356**), setting four of the five stereocenters of the bis-THIQ in the process. Furthermore, unlike Pictet–Spengler-based strategies, the application of the aryne annulation to the synthesis of bis-isoquinoline **398** will allow modular incorporation of a range of electronically diverse A and E ring fragments. Due to the versatility and flexibility offered by this aryne approach, we are planning to target several members of the renieramycins, saframycins, and ecteinascidins in a way that maximizes diversity and requires few changes to the central strategy. As a demonstration of this concept, we have targeted (–)-jorumycin (**345**) as a representative member of the bis-THIQ class of alkaloids.

Scheme 3.8. *A new approach to bis-THIQ core* ***356*** *by reductive cyclization of bis-isoquinoline* ***398***

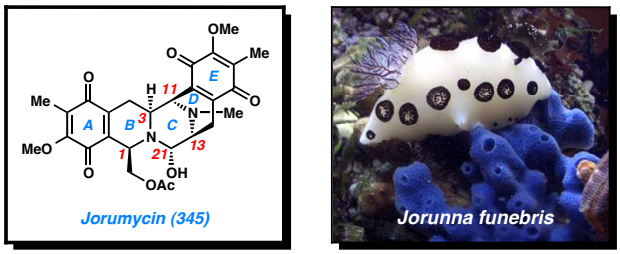


3.2.2 Isolation, Biological Activity, and Mechanism of Action of Jorumycin

Jorumycin (**345**) was isolated in 2000 from the mantle and mucus of the Pacific nudibranch *Jorunna funebris* (Figure 3.2).[3a] Primary oncology assays on jorumycin have indicated activity against NIH 3T3 tumor cells (100% of inhibition at 50 ng/mL). More detailed investigations demonstrated that jorumycin (**345**) is cytotoxic (IC_{50} = 12.5 ng/mL) at very low concentrations against several different tumor cell lines, such as P388

mouse lymphoma, A549 human lung carcinoma, HT29 human colon carcinoma, and MEL28 human melanoma cells. Additionally, jorumycin inhibits the growth of various Gram-positive bacteria, including *Bacillus subtilis* and *Staphylococcus aureus*, at concentrations lower than 50 ng/mL.

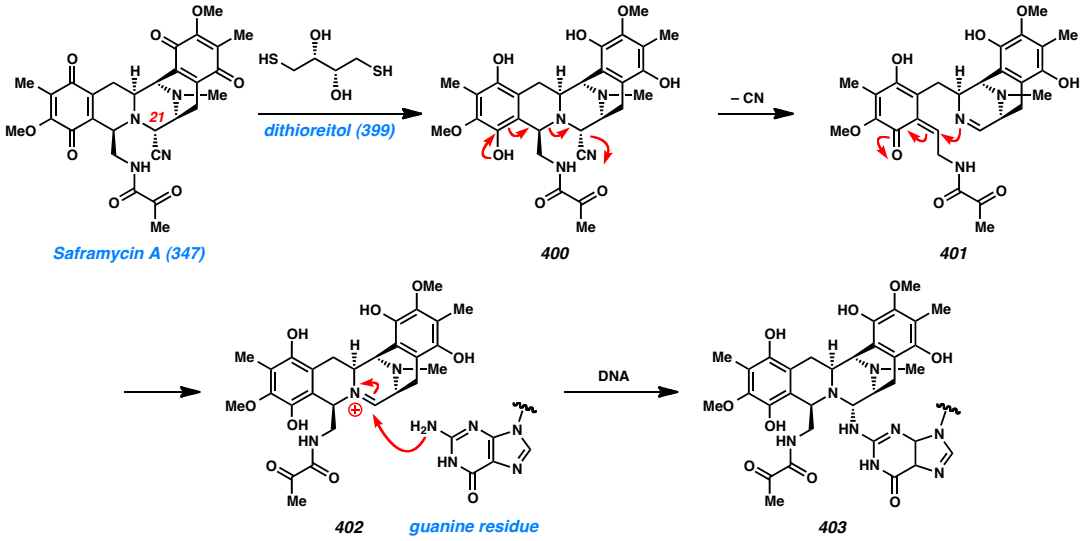
Figure 3.2. *Jorumycin (**345**), isolated from the Pacific nudibranch Jorunna funebris*[35]



Although the mechanism of action of jorumycin (**345**) has not been studied explicitly, it is likely similar to its saframycin and renieramycin relatives. The antitumor activity of these compounds is derived from their ability to alkylate DNA in the minor groove by forming an intermediate iminium ion (**402**) (Scheme 3.9). According to the mechanism proposed by Hill and Remers[36] for alkylation of DNA by saframycin A (**347**), cellular reductants such as dithiothreitol (DTT) (**399**) initially reduce the quinone moieties to the corresponding hydroquinones (**400**). This reduction is essential for DNA alkylation. After reduction, ejection of the axially disposed cyanide and C–N bond scission within the A–B THIQ is assisted by the newly formed phenol to form imino *ortho*-quinone methide **401**. Addition of the imine into the *ortho*-quinone methide generates an activated iminium (**402**) that can alkylate guanine-rich sequences of DNA (**403**).[37] Experimental support for this mechanism was obtained by ^{14}C labeling studies in which ^{14}C-labeled saframycin was incorporated into DNA in the presence of DTT.[38]

Similar structures bearing C(21) hydroxyl, acetate and ether groups in place of the nitrile functionality show comparable activity and are believed to operate by the same mechanism.[39] The common, reactive iminium (**402**) helps explain why the C(21) functional diversity found across the spectrum of THIQ and bis-THIQ natural products is mirrored by consistently high cytotoxicity in spite of these significant structural differences at the active site.

Scheme 3.9. *Proposed mechanism for DNA alkylation by the saframycins*



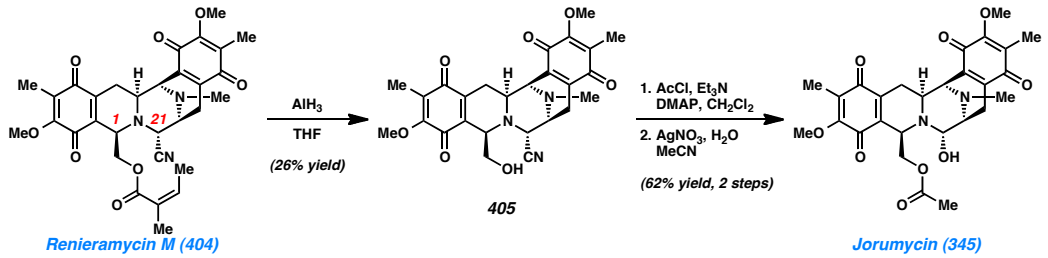
The broad bioactivity of the bis-THIQ alkaloids, like jorumycin (**345**), can also be attributed to aerobic oxidative mechanisms in addition to DNA alkylation. There is evidence for the formation of superoxide and hydroxyl radicals in the presence of saframycins in their hydroquinone forms (e.g., **400**), leading to eventual DNA cleavage under aerobic conditions.[40]

3.2.3 Previous Total Syntheses of Jorumycin

The bis-THIQ alkaloids have been the subject of intense synthetic study since their original isolation and structural determinations. Indeed, there have been hundreds of efforts directed at their synthesis reported in the literature; these accounts have been reviewed in detail elsewhere[1] and are beyond the scope of this report. Since its isolation, jorumycin (**345**) has been synthetically prepared twice by total synthesis and once by semisynthesis from renieramycin M (**404**).

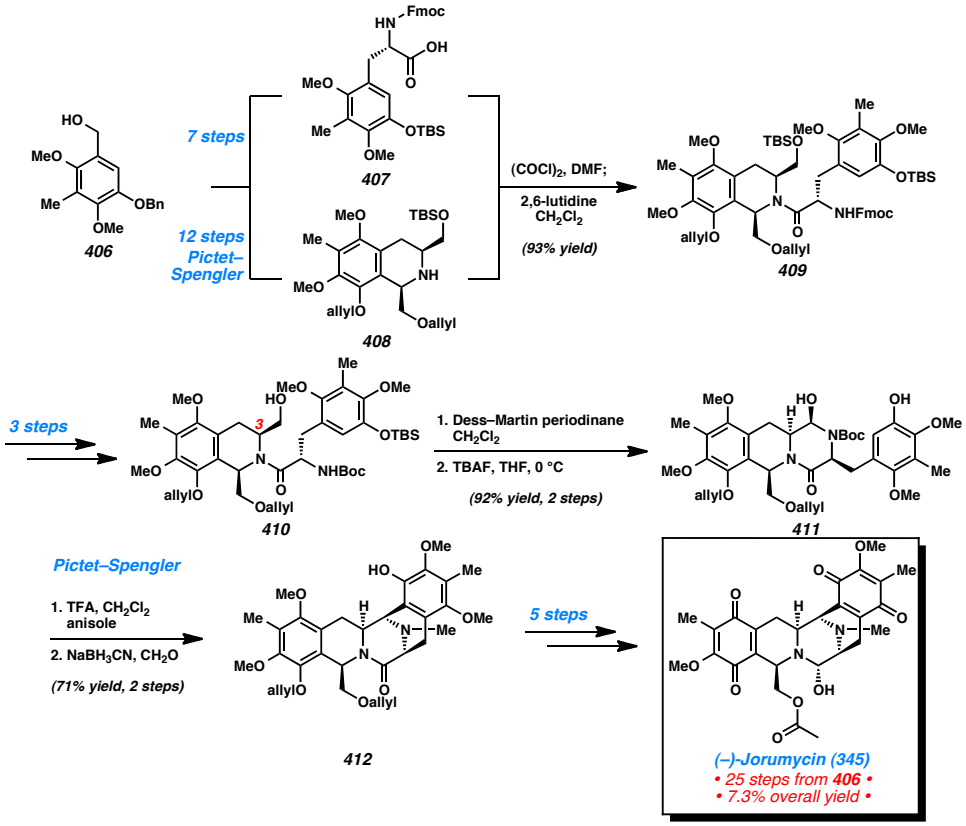
The first synthetic effort to construct jorumycin (**345**) was reported by Saito in 2004 as a semisynthesis from renieramycin M (**404**), which is isolable in gram quantities from *Xestospongia sp*.[41] Structurally, the critical distinctions between jorumycin (**345**) and renieramycin M (**404**) are the identity of the ester group appended to C(1), as well as the C(21) substituent (Scheme 3.10). The conversion of renieramycin M (**404**) to jorumycin (**345**) begins with angelate ester cleavage by alane reduction, unveiling the alcohol (**405**). Acetylation the primary alcohol (**405**) was followed by exchange of the C(21) nitrile for a hydroxyl to make jorumycin (**345**) in a total of three steps from renieramycin M (**404**).

Scheme 3.10. *Saito's semisynthesis of jorumycin (**345**) from renieramycin M (**404**)*



The next year, Williams reported the first enantioselective total synthesis of jorumycin by using a linear strategy (Scheme 3.11).[42] Both arene components of jorumycin are introduced from a common benzyl alcohol (**406**), and advanced by chiral auxiliary-assisted alkylations to tetrahydroisoquinoline **408** and tyrosine analogue **407**. These two components were coupled to form amide **409**, which was was advanced over three steps to an intermediate bearing a primary alcohol at C(3) (**410**) (Scheme 3.8). Oxidation of this position to the aldehyde and subsequent cleavage of the silyl ether revealed tricyclic aminal **411**. The A–B isoquinoline appended to the piperazine C ring was next treated with trifluoroacetic acid to close the D–E isoquinoline via Pictet–Spengler cyclization (**412**). At this point, the pentacyclic core of jorumycin (**412)** was converted over five additional steps to one enantiomer of the natural product (**345**). Overall, jorumycin was completed in 7.3% total yield in a longest linear sequence of 25 steps beginning from arene **406**.[43]

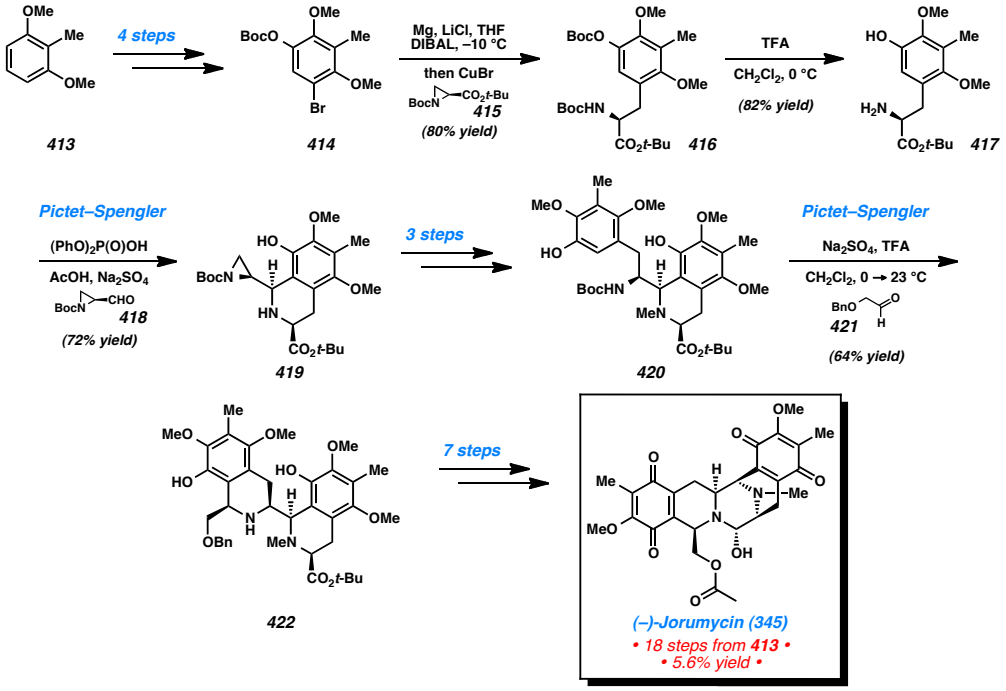
Scheme 3.11. *Williams' total synthesis of (–)-jorumycin (**345**)*



Zhu reported the most recent synthesis of (–)-jorumycin (**345**) in 2009.[44] This strategy relied upon iterative aziridine ring-opening reactions to build the pentacyclic core (Scheme 3.12). In a similar overall approach to the one used by Williams, Zhu constructed the two individual tetrahydroisoquinolines of jorumycin by Pictet–Spengler cyclizations. The effort initiated with the four-step synthesis of aryl bromide **413** from commercially available 2,6-dimethoxytoluene (**413**). Formation of a benzylic organomagnesium reagent from **414** allowed nucleophilic ring-opening addition to aziridine **415**, and produced protected amino acid **416**. Following Boc group cleavage, a Pictet–Spengler reaction of the resultant aminophenol (**417**) with another aziridine bearing an aldehyde (**418**) furnished the first tetrahydroisoquinoline (**419**). The

heterocycle (**419**) was advanced over three steps to phenol **420** in preparation for a second Pictet–Spengler cyclization to generate bis-THIQ **422**. Finally, tetracyclic bis-THIQ **422** was converted to (–)-jorumycin (**345**) over seven additional steps. Zhu was able to construct (–)-jorumycin (**345**) in 5.6% overall yield and 18 total linear steps from commercially available compounds (**413**).

Scheme 3.12. *Zhu's total synthesis of (–)-jorumycin (**345**)*

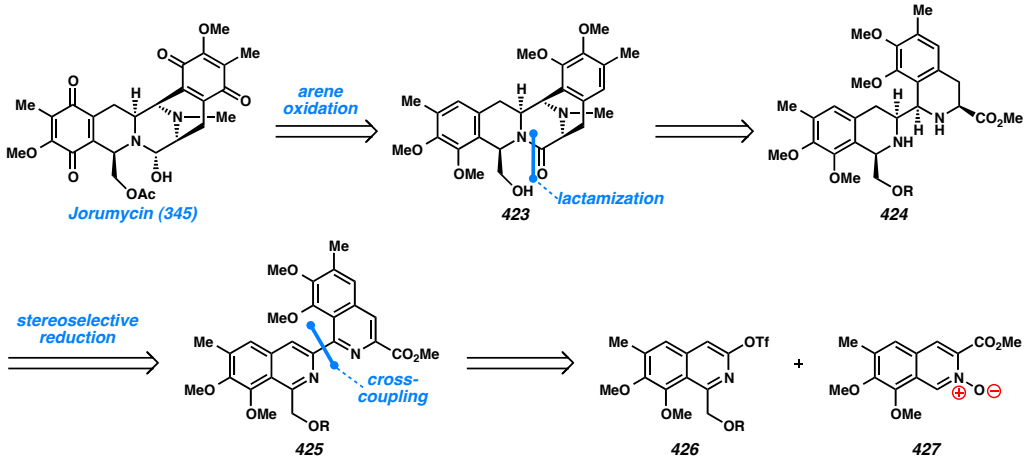


3.2.4 Retrosynthetic Analysis of Jorumycin

In considering our synthetic strategy toward jorumycin (**345**), we sought an approach that would maximize convergency while simultaneously allowing us to target its myriad relatives and unprecedented non-natural analogs through the same pathway (Scheme 3.13). The pentacyclic bis-THIQ framework (**423**) of jorumycin (**345**) will be accessed by reduction of functionalized bis-isoquinoline **425** via tetracyclic bis-THIQ

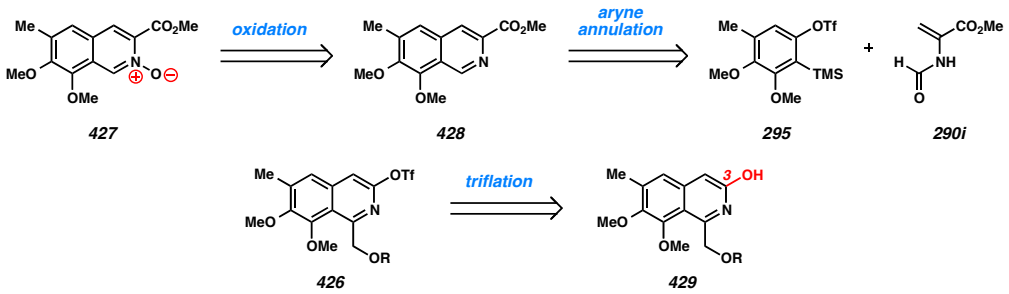
424. This key intermediate (**425**) will be disconnected along the central carbon–carbon bond linking the two discrete isoquinolines to an isoquinoline triflate (**426**) and an isoquinoline *N*-oxide (**427**). We plan to couple triflate **426** and *N*-oxide **427** by a palladium-catalyzed C–C bond forming reaction by directed C–H functionalization methods such as those developed by Fagnou and co-workers.[45]

Scheme 3.13. *Retrosynthetic analysis of jorumycin (**345**)*



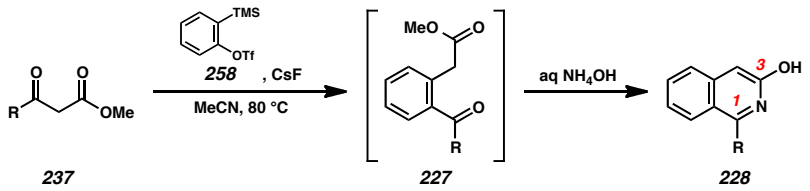
Each of these building blocks (**426** and **427**) will be prepared by aryne-based methodologies developed in our group. Importantly, the symmetry inherent to jorumycin (**435**) can be exploited, requiring only a single aryne precursor to prepare each coupling partner. Retrosynthetically, the isoquinoline *N*-oxide (**427**) can be derived from the parent isoquinoline (**428**), which will in turn be constructed by aryne annulation of silyl aryl triflate **295** with formyl enamide **290i** (Scheme 3.14). Isoquinoline triflate **426** will be most directly prepared from 3-hydroxyisoquinoline **429**. Unfortunately, isoquinolines bearing heteroatoms at the C(3) position are inaccessible by our aryne annulation protocol described in Chapter 2.

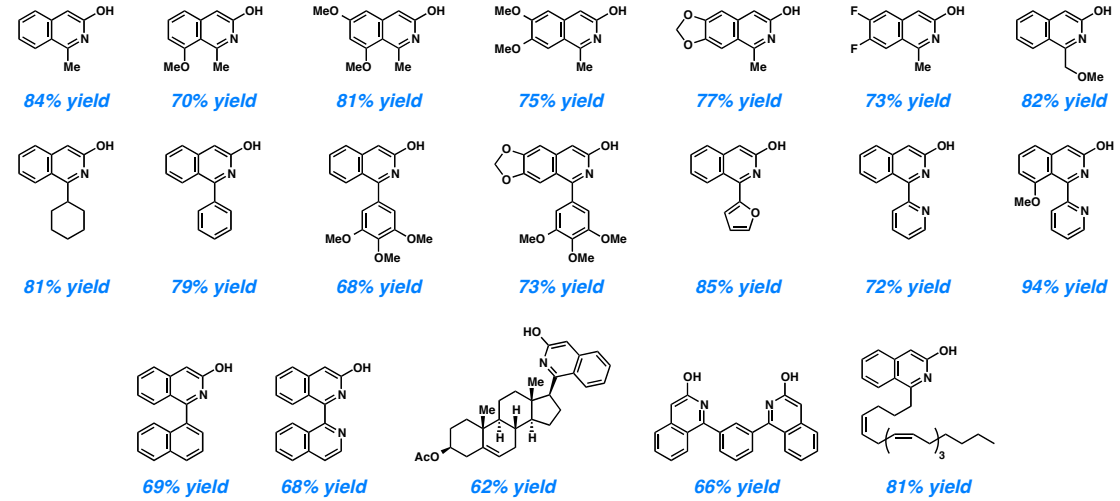
Scheme 3.14. *Retrosynthetic analysis of isoquinoline N-oxide* ***427*** *and isoquinoline triflate* ***426***



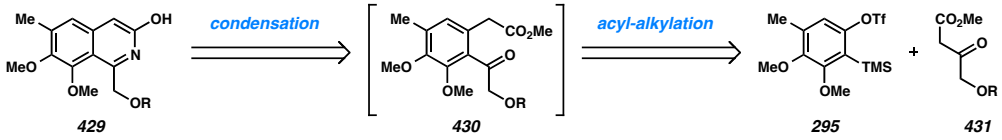
Concurrent with these efforts, we developed a one-pot protocol for the synthesis of 3-hydroxyisoquinolines (**228**) by a known condensation of ammonia[46] with ketoester products of our previously reported aryne insertion methodology (**227**, Table 3.1).[47] This extension of the acyl-alkylation reaction directly generates a variety of C(1)-substituted 3-hydroxyisoquinolines from silyl aryl triflate (e.g., **256**) and β-ketoester (e.g., **237**) starting materials.[48] In this manner, we planned to construct 3-hydroxyisoquinoline intermediate **429** in order to pursue a cross-coupling strategy in the synthesis of jorumycin (**345**). This coupling partner can be prepared from silyl aryl triflate **295** and β-ketoester **431** (Scheme 3.15).

Table 3.1. *C(1)-functionalized 3-hydroxyisoquinolines by one-pot acyl-alkylation/condensation*





Scheme 3.15. *Retrosynthetic analysis of 3-hydroxyisoquinoline* ***429***



3.2.5 A Jorumycin Model System for Cross-Coupling and Reduction[†]

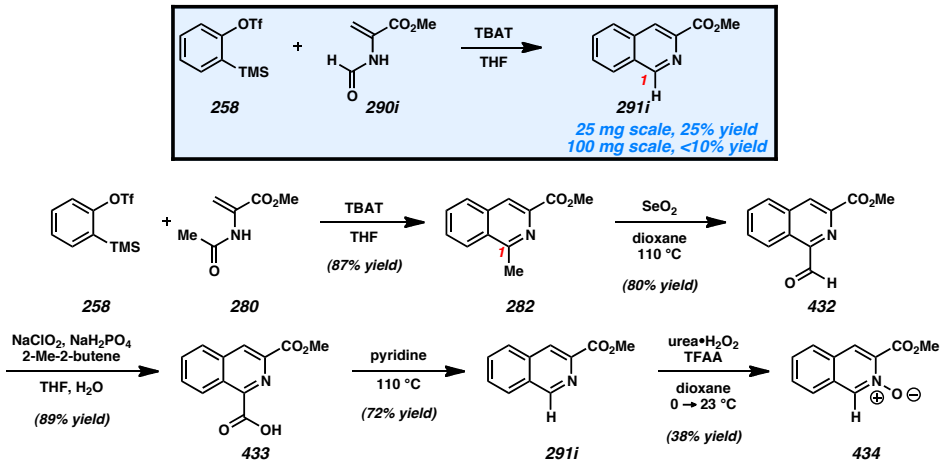
We set about testing our synthetic strategy for isoquinoline cross-coupling and bis-isoquinoline reduction in a model system lacking functionality on the silyl aryl triflate before beginning the synthesis of jorumycin (**345**). To our dismay, initial attempts to

[†] This synthetic work was performed in collaboration with Dr. Pamela M. Tadross, a fellow graduate student in the Stoltz lab.

prepare model compounds of both 3-hydroxyisoquinoline **429** and 1-*H*-isoquinoline **428** were met with significant difficulty.

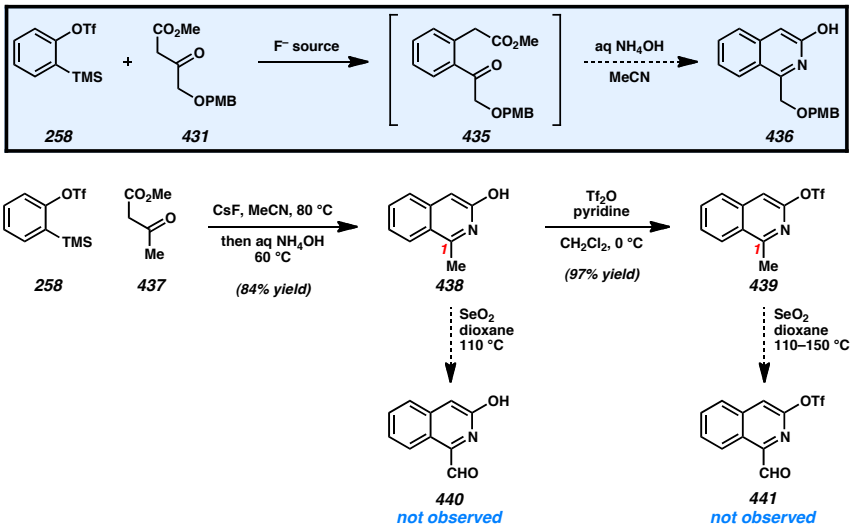
The synthesis of 1-*H*-isoquinoline **291i** by aryne annulation of formyl enamide **290i** with silyl aryl triflate **258** was hindered by amidoacrylate polymerization, resulting in very low yielding reactions on preparative scale (Scheme 3.16). As a consequence, several alternative procedures were investigated to incorporate a hydrogen at C(1). The highest yielding and most operationally straightforward of these methods begins with isoquinoline **282**, which is the product of aryne annulation between silyl aryl triflate **258** and methyl 2-acetamidoacrylate (**280**). Oxidation of the C(1) methyl group was readily accomplished by treatment of isoquinoline **282** with selenium dioxide in dioxane,[49] yielding aldehyde **432**. Pinnick oxidation followed by thermal decarboxylation then afforded 1-*H*-isoquinoline **291i** in excellent yield. Finally, isoquinoline **291i** was oxidized to the corresponding *N*-oxide (**434**) upon treatment with urea•H_2O_2 and trifluoroacetic anhydride (TFAA).[50]

Scheme 3.16. *Synthesis of 1-H-isoquinoline* ***291i*** *and isoquinoline N-oxide* ***434***



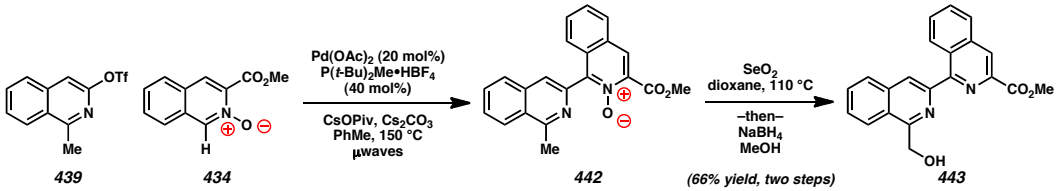
For the synthesis of hydroxyisoquinoline **436**, the acyl-alkylation step with β-ketoesters bearing γ-alkoxy substituents (e.g., **431**) proved challenging (Scheme 3.17). Separating the acyl-alkylation/condensation process into two steps indicated that, while aryne C–C insertion to form ketoester **435** is viable, the subsequent condensation with ammonia rapidly decomposes to a complex mixture containing low yields of the desired hydroxyisoquinoline (**436**). Fortunately, the selective selenium dioxide oxidation of the isoquinoline C(1) methyl group should circumvent this problem. We next prepared 3-hydroxyisoquinoline **438** from aryne precursor **258** and methyl acetoacetate (**437**) in very good yield and advanced this material to the corresponding triflate (**439**). Attempts to oxidize the C(1) methyl group of both the 3-hydroxyisoquinoline (**438**) and the isoquinoline triflate (**439**) failed. Treatment of 3-hydroxyisoquinoline **438** with selenium dioxide resulted in rapid decomposition, and isoquinoline triflate **439** failed to react at all, even under more forcing conditions. These negative results caused us to alter our overall synthetic plan, as C(1) methyl group oxidation could be performed immediately following cross-coupling of isoquinoline *N*-oxide **434** and isoquinoline triflate **439**, which more closely resembles isoquinoline **436**.

Scheme 3.17. *Synthesis of isoquinoline triflate* ***439*** *and failed C(1) methyl group oxidations*



In practice, palladium-catalyzed cross coupling of isoquinoline *N*-oxide **434** and isoquinoline triflate **439** afforded bis-isoquinoline **442** in good yield (Scheme 3.18).[45] Oxidation of bis-isoquinoline **442** with SeO_2 and subsequent reduction with sodium borohydride yields the bis-isoquinoline bearing the required hydroxymethyl group at C(1) (**443**). However, before investigating this step, we were interested in testing the key reduction of bis-isoquinoline **443** to the corresponding bis-THIQ.

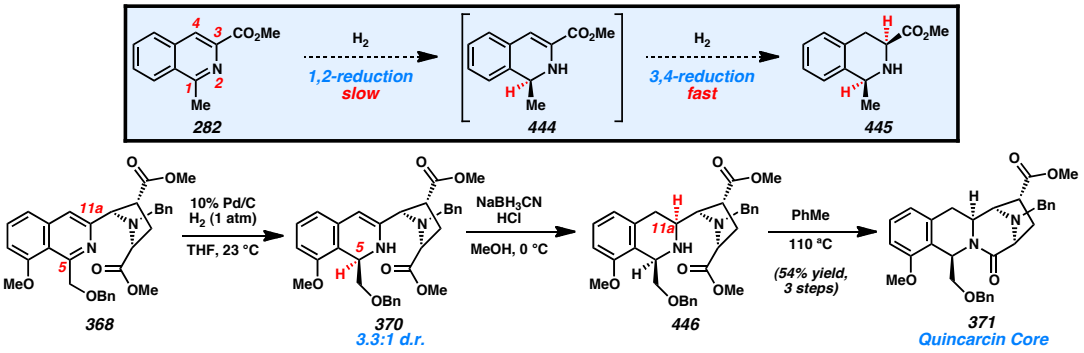
Scheme 3.18. *Cross-coupling of isoquinoline triflate* ***439*** *and isoquinoline N-oxide* ***434*** *with subsequent C(1) methyl group oxidation*



With bis-isoquinoline **443** in hand, we turned our attention to the key reduction of this intermediate to a tetracyclic bis-THIQ.[51,52,19] Generally, the reduction of isoquinolines

is known to proceed by 1,2-reduction to yield an enamine (**282→444**), which then undergoes rapid reduction of the C(3)–C(4) bond (**444→445**) (Scheme 3.19).[53,54,51b] Furthermore, the stereochemical outcome of the initial 1,2-reduction is known to strongly influence the stereoselectivity of the subsequent 3,4-reduction,[55,51b,54c] furnishing THIQ products bearing substituents at C(1) and C(3) with cis relative stereochemistry. In the total synthesis of quinocarcin, this reactivity was exploited in an all-syn, three-step reductive cyclization to construct the tetracyclic core structure (**371**). Initial Pd-catalyzed hydrogenation of the isoquinoline C(1) position (**368**) to the corresponding 1,2-dihydroisoquinoline **370** proceeds in a 3.3:1 diastereomeric ratio. Secondary reduction of this intermediate to its THIQ counterpart proceeds to exclusively form the syn-disposed THIQ **446**. We believe that this characteristic of isoquinoline reduction can be exploited to effect the all-cis reduction required for the synthesis of a tetracyclic bis-THIQ.

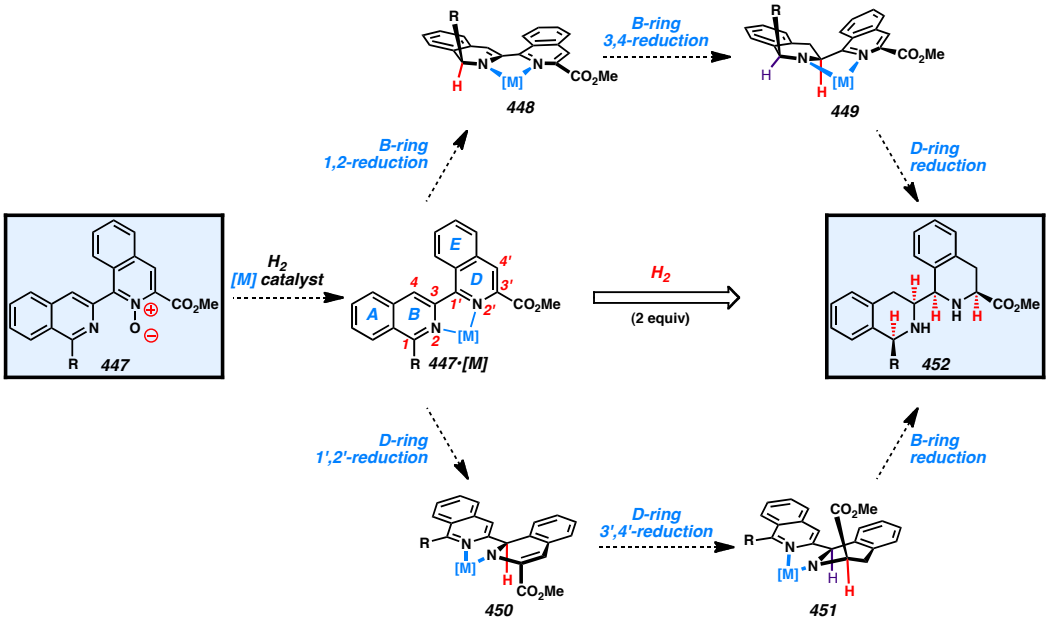
Scheme 3.19. *Proposed reduction pathway for jorumycin isoquinolines, inspired by quinocarcin reductive cyclization*



Upon exposure of bis-isoquinoline **442** to a metal catalyst (homogeneous or heterogeneous) and hydrogen gas, two potential reduction pathways can lead to the

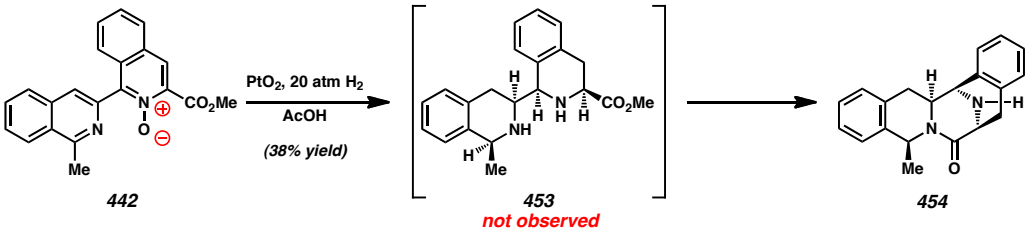
desired bis-THIQ (**452**) (Scheme 3.20). Each pathway can be initiated by reduction of the *N*-oxide and complexation of the bis-isoquinoline to the metal catalyst. This will serve to constrain the substrate in a conformation conducive to reduction with the preferred stereoselectivity. In an achiral sense, a reduction cascade can be initiated by 1,2-reduction on either of the two discrete isoquinoline units. If initial 1,2-reduction occurs on the B-ring (**447→448**), we expect that the newly formed stereocenter at C(1) would impart a concavity on the system, leading to fast 3,4-reduction in a syn fashion (**448→449**). Importantly, the increased concavity of THIQ **448** will further predispose the system toward D-ring reduction from the convex face to produce all-syn bis-THIQ **452**. In this way, the stereochemistry of the C(1)-position can be relayed to the other three stereocenters formed during this reduction process. An alternative pathway would begin with 1,2-reduction of the D-ring, proceeding through intermediates **450** and **451** en route to bis-THIQ **452**. Importantly, in an achiral reduction of bis-isoquinoline **447**, initiation of the reduction cascade on either the B- or D-ring will lead to bis-THIQ **452** with the same relative (all-syn) stereochemistry.

Scheme 3.20. *Obtaining syn stereoselectivity in the reduction of bis-isoquinoline* ***447***



While there have been few reported reductions of isoquinolines to THIQs, several heterogeneous catalysts and a recently disclosed Crabtree iridium catalyst have performed the desired transformation.[56,51] In our initial efforts, treatment of bis-isoquinoline **442** with Adams' catalyst under 20 atm H_2 at 60 °C yielded not the expected tetracyclic bis-THIQ **453**, but instead afforded the pentacyclic core of the bis-THIQ alkaloids (**454**) directly (Scheme 3.21). Pentacycle **454** is believed to arise by full reduction of the bis-isoquinoline, as anticipated, followed by in situ lactamization of the all-syn tetracyclic bis-THIQ (**453**). With this proof-of-principle result in hand, we turned our attention to preparation of the fully functionalized bis-isoquinoline required for the synthesis of jorumycin.

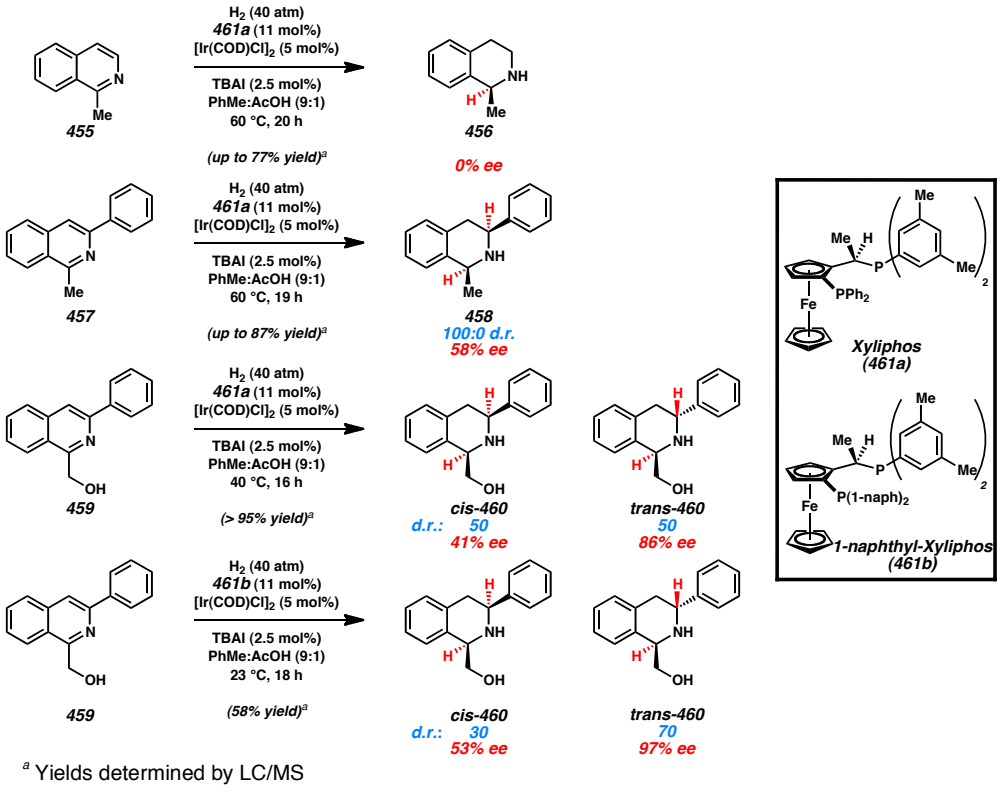
Scheme 3.21. *Reductive cyclization of bis-isoquinoline* ***442*** *to core analog* ***454***



More recently, we have investigated several conditions for the reduction of model, single isoquinoline substrates.[†] We found that moderate enantiomeric excesses of tetrahydroisoquinolines are obtainable in reasonable conversions with homogenous iridium-phosphine catalysts and high pressures of hydrogen (Scheme 3.22). Interestingly, isoquinolines bearing C(α)-hydroxyl substituents (**459**) appear to react under more mild hydrogenation conditions, to produce diastereomeric mixtures of tetrahydroisoquinolines (**cis-** and **trans-460**). The role of this hydroxyl group is not fully understood, but it likely assists in organizing an isoquinoline complex with the cationic iridium hydride complex in interacting with the C(1)–N double bond for hydride addition. This directing effect might be responsible for the favored *trans*-THIQ products (**trans-460**).

[†] Isoquinoline reduction work was performed in collaboration with Dr. Christian Grünanger, a post-doctoral researcher in our lab. Data regarding this project is contained in his post-doctoral research summary.

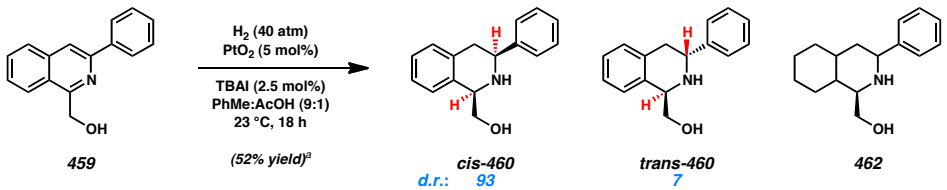
Scheme 3.22. *Homogeneous reduction conditions for isoquinolines*[a]



[a] Yields determined by LC/MS

Interestingly, using Adam's catalyst (PtO_2) under similar reaction conditions, the C(α)-hydroxylated isoquinoline (**459**), underwent reduction to the corresponding *cis*-THIQ product (**cis-460**) with a high degree of diastereoselectivity (Scheme 3.23). Further development of this catalyst system is needed, as a common side product of these reactions is the overreduction of the isoquinoline aromatic ring (**462**).

Scheme 3.23. *Diastereoselective, heterogeneous reduction of isoquinoline* ***459*** *with* PtO_2

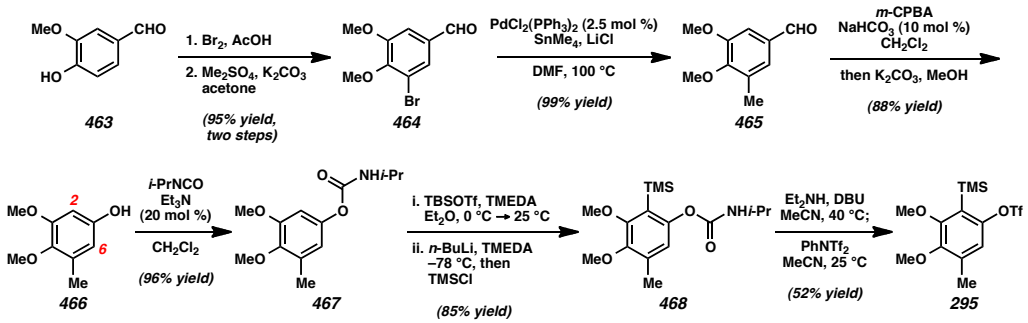


[a] Yields determined by LC/MS

3.2.6 Synthesis of the Jorumycin Aryne Precursor[57]

Prior to obtaining the key bis-isoquinoline desired for the synthesis of jorumcyin, we requireds a rapid and scalable synthesis of the functionalized silyl aryl triflate (**295**) aryne precursor. To accomplish this goal, we began with a regioselective bromination of vanillin (**463**) to provide 5-bromo vanillin, which was methylated, yielding bromo dimethoxy benzaldehyde **464** (Scheme 3.24).[58] Next, Stille coupling of the bromoarene (**464**) with tetramethyltin enabled the introduction of the 5-methyl substituent to generate arene **465**.[59] Further elaboration of this intermediate by one-pot Baeyer–Villiger oxidation and cleavage of the resultant formate ester yielded intermediate phenol **466**. All attempts to install a bromide selectively at C(2) of phenol **466** failed, instead resulting in exclusive bromination at C(6). In order to selectively functionalize phenol **466**, we turned to a recently disclosed 3-step procedure for the general synthesis of *ortho*-silyl aryl triflates by Garg.[60] This account suggested that conversion of the phenol to a carbamate might facilitate silylation at C(2) over C(6). Application of the sequence to our intermediate (**466**) allowed the direct *ortho*-silylation of carbamate **467**, exclusively producing the 2-silyl carbamate (**468**). Subsequent cleavage of the carbamate and triflation of the resulting phenoxide furnished the desired aryne precursor (**295**) in 5 steps from known aldehyde **464**.

Scheme 3.24. *Synthesis of the jorumycin aryne precursor (**295**)*

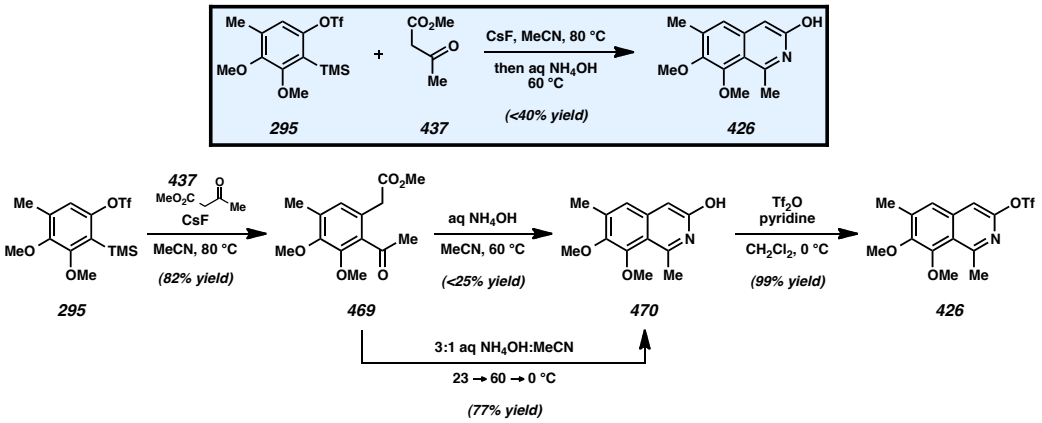


3.2.7 Construction of a Functionalized Bis-Isoquinoline

With silyl aryl triflate **295** in hand, we turned our attention toward the preparation of a bis-isoquinoline appropriately functionalized for the synthesis of jorumycin (**345**). Throughout these efforts we encountered several subtle differences in reactivity stemming from silyl aryl triflate **295** instead of the unsubstituted model system aryne precursor (**258**).

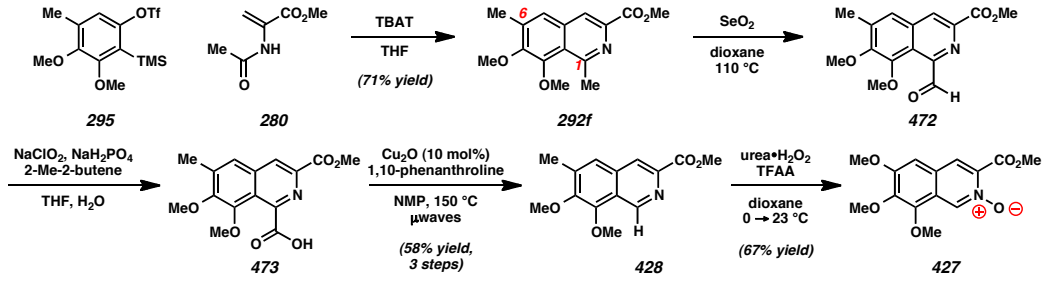
Our synthesis of the bis-isoquinoline commenced with preparation of the isoquinoline triflate (**426**) and isoquinoline *N*-oxide (**427**) coupling partners. Isoquinoline triflate **426** was targeted by a one-pot acyl-alkylation/condensation with silyl aryl triflate **295** and methyl acetoacetate (**437**) (Scheme 3.25).[48] However, despite significant effort to optimize this reaction, yields could not be increased above 40%. Attempts to perform the hydroxyisoquinoline formation in a stepwise manner showed that the acyl-alkylation reaction routinely occurred in 82% yield while the condensation step was the problematic one. Gratifyingly, purified acyl-alkylation product **469**, in a 3:1 mixture of ammonium hydroxide in acetonitrile, undergoes the condensation reaction when heated to 60 °C for 1 hour, and the desired 3-hydroxyisoquinoline (**470**) rapidly precipitates from solution upon cooling to 0 °C in good yield. Finally, triflation of hydroxyisoquinoline **470** with triflic anhydride and pyridine furnished isoquinoline triflate **426**.

Scheme 3.25. *Synthesis of substituted isoquinoline triflate* ***426***



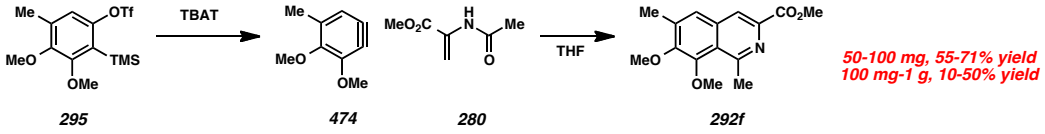
Synthesis of the isoquinoline *N*-oxide coupling partner (**427**) began with aryne annulation of silyl aryl triflate **295** and methyl 2-acetamidoacrylate (**280**) in lower yields than those observed for the corresponding model system (i.e., **258** and **280**, vide supra) (Scheme 3.26). However, the directed C(1) methyl group oxidation of isoquinoline **471** with selenium dioxide proceeded with perfect selectivity, leaving the C(6) methyl group untouched. Pinnick oxidation and decarboxylation were followed by *N*-oxide formation to yield the desired isoquinoline *N*-oxide (**427**).

Scheme 3.26. *Synthesis of substituted isoquinoline* N*-oxide* ***427***



While the synthesis of 1-*H*-isoquinoline **428** was successful by this route, producing multi-gram quantities of the coupling partner was exceedingly problematic, as a result of poor scalability in the aryne annulation reactions. On a small scale, the reaction proceeds with consistent, moderate yields. However, increasing the scale of the reaction severely curbs the product output (Scheme 3.27). A direct explanation for this dependency on scale is not clear. The stability of methyl-2-acetamidoacrylate (**280**) is notoriously suspect in these aryne annulation reaction. The purity of large quantities of this material–even when freshly prepared—cannot be verified. Throughout our exploration of the reaction using many different arynes, even after rigorous exclusion of known acrylate polymerization intiators like light and oxygen, small quantities of polymerized starting material are found in reaction mixtures, leading to yields that vary more widely with larger reaction scales.

Scheme 3.27. *Reaction scale concerns in aryne annulation forming 1-methyl isoquinoline* ***292f***

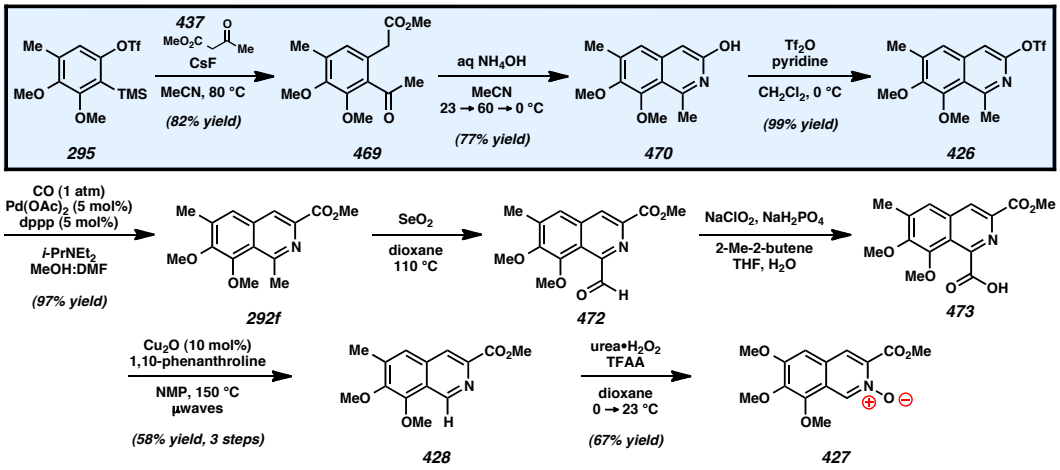


295 *474* *280* *292f*

Because the acyl-alkylation/condensation provided consistently good yields of the isoquinoline triflate cross-coupling partner (**426**), we adapted this approach to our synthesis of the isoquinoline *N*-oxide (**427**, Scheme 3.28). Carboxymethylation of the triflate (**426**) using a protocol developed by Merck allows us to generate 1-methyl-3-carboxymethyl isoquinoline **471**.[61] Shepherding this intermediate along the previously

disclosed C(1) functionalization path we had previously developed provided us with multigram quantities of the *N*-oxide (**427**) for advacement of the synthesis.

Scheme 3.28. *Alternative approach to isoquinoline* N*-oxide* ***427*** *via acyl-alkylation/condensation*

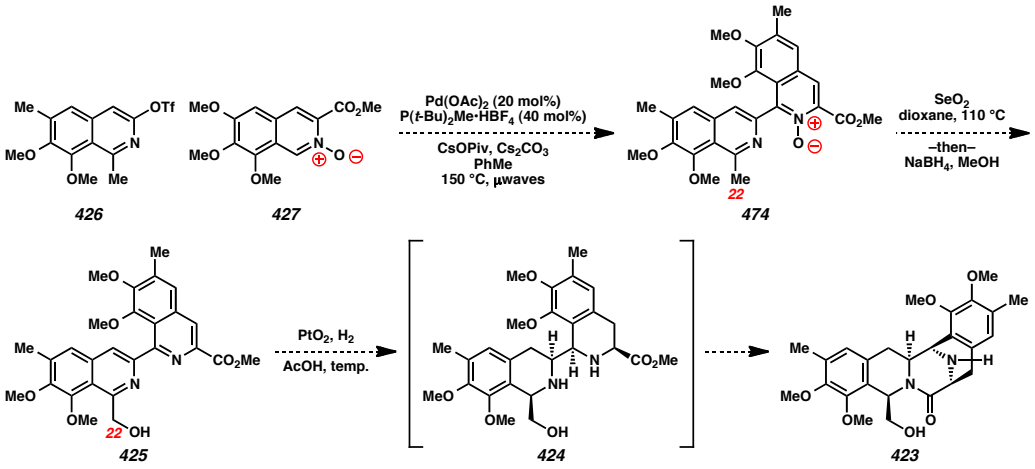


3.2.8 Strategy for the Completion of Jorumycin

We will soon be poised to investigate the key cross-coupling of isoquinoline *N*-oxide **427** and isoquinoline triflate **426** en route to the core of the natural product (Scheme 3.29). By using the conditions developed for our model system cross-coupling (vide supra) we anticipate producing the desired bis-isoquinoline (**474**). Chemoselective selenium dioxide oxidation of the bis-isoquinoline C(22) position will reveal, after reductive workup, the hydroxy-bis-isoquinoline (**425**). Finally, we plan to reduce bis-isoquinoline **425** to pentacyclic bis-THIQ **423** via tetracyclic intermediate **424** after treatment with Adams' catalyst under a hydrogen atmosphere. This process will establish the relative chemistry of four of the five stereocenters present in jorumycin (**345**) in a single operation. Furthermore, in only two steps the simple isoquinoline triflate (**426**)

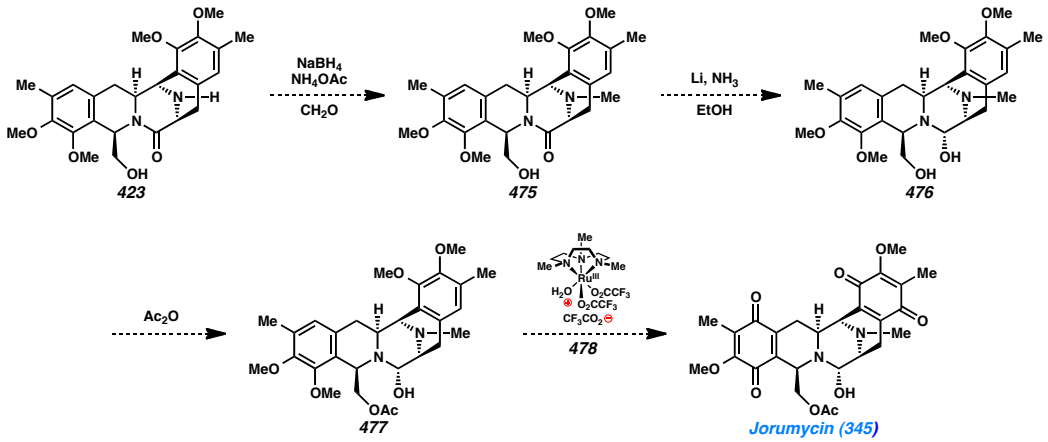
and isoquinoline *N*-oxide (**427**) will be stereoselectively transformed into the pentacyclic core of jorumycin (**245**) and other bis-THIQ alkaloids.

Scheme 3.29. *Proposed route for advancement to jorumycin core (**423**)*



Completion of jorumycin (**345**) can be accomplished from pentacylic bis-THIQ **423** in as few as four synthetic transformations (Scheme 3.30). First, reductive methylation will install the *N*-methyl group on the secondary amine of **423**, yielding *N*-methyl pentacycle **475**. Next, the amide (**475**) will be diastereoselectively reduced under dissolving metal conditions, as in many prior syntheses of alkaloids in this class, to the aminal (**476**).[62,29a,b,e] We anticipate that acetylation of pentacycle **476** will occur selectively at the primary alcohol, leaving the aminal untouched. Finally, oxidation of the arenes to their corresponding quinones using ruthenium catalyst **478** will afford jorumycin (**345**).[63] In total, the route described here will furnish jorumycin (**345**) in only 12 linear steps from silyl aryl triflate (**295**) through a highly convergent strategy.

Scheme 3.30. *Strategy for the completion of jorumycin (**345**)*



3.3 CONCLUDING REMARKS

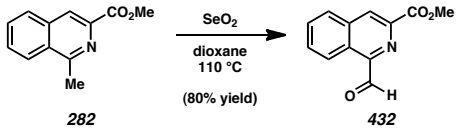
In designing our route to jorumycin we have focused on the development of a highly convergent strategy capable of generating significant complexity in a rapid fashion. Implementation of an aryne-based approach to the synthesis of simple isoquinoline coupling partners has facilitated our progress toward jorumycin, allowing synthesis of the core of the natural product in just three steps from these building blocks. Furthermore, a reduction cascade of bis-isoquinolines intermediates sets the relative stereochemistry of four of the five stereocenters in jorumycin in a single operation. Given the success of the reduction of bis-isoquinolines to the pentacyclic bis-THIQ core of these alkaloids, we are confident that jorumycin will be completed in due course. Finally, we anticipate that this strategy will be a general one, amenable to the synthesis of many members of the bis-THIQ family of alkaloids as well as non-natural analogs for biological studies.

3.4 EXPERIMENTAL SECTION

3.4.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

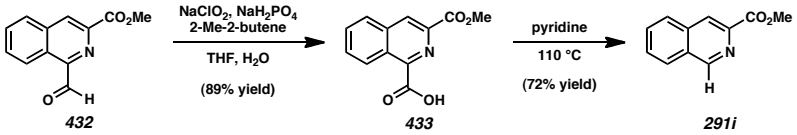
3.4.2 Preparative Procedures and Spectroscopic Data



282 *432*

Aldehyde 432

Selenium dioxide (206 mg, 1.86 mmol) was added to a solution of isoquinoline **282** (93.5 mg, 0.465 mmol) in dioxane (5 mL). The reaction was sealed and heated to 100 °C, at which temperature it was maintained with stirring until isoquinoline **282** had been completely consumed by TLC analysis. Following this time, the reaction was cooled, filtered, and concentrated under vacuum. The crude residue was purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield aldehyde **432** (80 mg, 80% yield): $R_f = 0.16$ (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.43 (s, 1H), 9.33 (dd, J = 8.3, 1.2 Hz, 1H), 8.73 (s, 1H), 8.02 (dd, J = 7.2, 1.6 Hz, 1H), 7.94–7.73 (m, 2H), 4.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.00, 165.39, 149.75, 140.95, 136.90, 132.23, 131.59, 128.41, 128.39, 127.26, 126.10, 53.15; IR (NaCl/film) 2946, 2829, 1751, 1719, 1708, 1452, 1372, 1332, 1299, 1255, 1213, 1150, 1112, 1056, 985, 914, 793, 749 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{12}H_{10}O_3N$ $[M+H]^+$: 216.0655, found 216.0659.

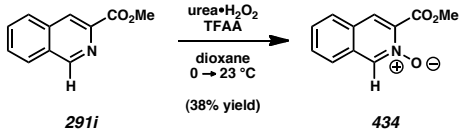


432 ***433*** ***291i***

Isoquinoline 291i

A solution of $NaClO_2$ (336 mg, 3.72 mmol) and $NaH_2PO_4 \bullet H_2O$ (928 mg, 5.95 mmol) in H_2O (3.7 mL) was added to a suspension of aldehyde **432** (80 mg, 0.372 mmol) and 2-methyl-2-butene (2.36 mL, 22.3 mmol) in *t*-BuOH (3.7 mL). The biphasic suspension was then maintained at room temperature with vigorous stirring until aldehyde **432** was fully consumed by TLC analysis. Following this time, the reaction was diluted with brine (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under vacuum. The crude product (**433**, 76 mg, 89% yield) was used without further purification.

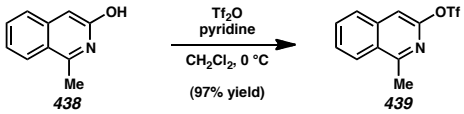
Acid **433** (76 mg, 0.330 mmol) was taken up in pyridine (2 mL) and heated to 110 °C. The solution was maintained at 110 °C until acid **433** had been fully consumed by TLC analysis. At that time, the reaction was cooled to room temperature, diluted with ethyl acetate, and washed sequentially with water (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (1:1 hexanes:ethyl acetate eluent) to yield isoquinoline **291i** (45 mg, 72% yield): R_f = 0.16 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.52 (s, 1H), 8.05–7.94 (m, 1H), 7.94–7.82 (m, 1H), 7.69 (m, 2H), 3.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.36, 152.74, 141.54, 135.53, 131.27, 130.01, 129.71, 128.09, 127.77, 124.14, 52.96; IR (NaCl/film) 2994, 2951, 1726, 1577, 1497, 1452, 1387, 1328, 1291, 1228, 1202, 1139, 1095, 970, 901, 795, 769 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 188.0706, found 188.0709.



291i *434*

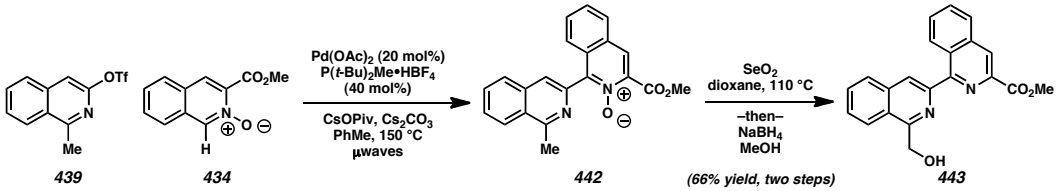
Isoquinoline *N*-oxide 434

Urea•H_2O_2 (108 mg, 1.14 mmol) and K_2CO_3 (316 mg 2.28 mmol) were combine in dioxane (11 mL) and maintained at room temperature with stirring for 1 hour. Following this time, the suspension was cooled to 0 °C in an ice bath with vigorous stirring. Trifluoroacetic anhydride (161.4 μL, 1.14 mmol) was added and, after 10 minutes at 0 °C, the reaction was allowed to warm to room temperature over 30 minutes. At that time, isoquinoline **291i** (21.4 mg, 0.114 mmol) was added and the reaction was heated to 50 °C. The suspension was maintained with vigorous stirring at 50 °C for 24 hours, at which point it was cooled to room temperature and concentrated under vacuum. The crude residue was diluted with CH_2Cl_2 (25 mL) and washed with water (20 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (1:2:0.15 hexanes:ethyl acetate:Et_3N eluent) to yield isoquinoline *N*-oxide **434** (8.7 mg, 38% yield): R_f = 0.30 (5% Et3N in ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.03 (s, 1H), 7.83 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.75–7.71 (m, 1H), 7.67 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.62 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.25, 139.05, 137.36, 130.82, 130.11, 129.41, 127.77, 127.42, 125.69, 124.70, 53.40; IR (NaCl/film) 2952, 1742, 1630, 1601, 1559, 1439, 1320, 1290, 1208, 1180, 1135, 1077, 918, 796, 754 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_3N$ $[M+H]^+$: 204.0655, found 204.0647.



Isoquinoline triflate 439

A suspension of 3-hydroxyisoquinoline **438** (250 mg, 1.57 mmol) in CH_2Cl_2 (16 mL) was cooled to 0 °C. Pyridine (1.27 mL, 15.7 mmol) was added, followed by Tf_2O (528 μL, 3.14 mmol). The reaction was maintained at 0 °C until 3-hydroxyisoquinoline **438** was fully consumed by TLC analysis. At that time, the reaction was quenched at 0 °C by the addition of a saturated solution of $NaHCO_3$ (6 mL) and then allowed to warm to room temperature. The reaction was then diluted with diethyl ether (25 mL) and washed sequentially with water (25 mL), saturated NH_4Cl (25 mL), and brine (25 mL). The organics were dried with Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (25:1 hexanes:ethyl acetate eluent) to yield isoquinoline triflate **439** (441.3 mg, 97% yield): R_f = 0.45 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.76 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.66 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.41 (s, 1H), 2.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.12, 151.16, 138.40, 131.34, 128.01, 127.61, 127.47, 125.98, 118.77 (q, J = 320.5 Hz), 108.82, 21.99; IR (NaCl/film) 3073, 2961, 2927, 1624, 1600, 1562, 1506, 1421, 1327, 1213, 1139, 1116, 988, 957, 890, 833, 741 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{11}H_9O_3NSF_3$ $[M+H]^+$: 292.0250, found 292.0261.

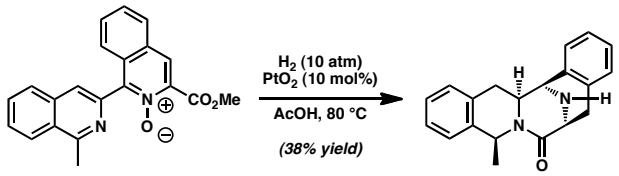


Bis-isoquinoline alcohol 443

Palladium acetate (0.9 mg, 0.004 mmol) was added to a flame-dried microwave vial containing cesium carbonate (23 mg, 0.07 mmol), cesium pivalate (7 mg, 0.03 mmol) and di-*tert*-butylmethylphosphonium tetrafluoroborate (2 mg, 0.008 mmol). The vessel was sealed, and then evacuated and backfilled with an atmosphere of argon three times. Next, toluene (4 mL) was added to the reaction vial, which was subsequently heated to 50 °C in an oil bath. The suspension was maintained at this temperature for 30 minutes with vigorous stirring. Concomitant to this step, isoquinoline triflate **439** (6 mg, 0.02 mmol) was added to a flask containing isoquinoline *N*-oxide **434** (12 mg, 0.06 mmol). This flask was sealed with a rubber septum, and evacuated and backfilled with an atmosphere of argon three times. Toluene (2 mL) was added to the flask under an argon atmosphere. After the palladium suspension had stirred for 30 minutes at 50 °C, the solution had turned from clear to pale yellow. Upon cooling to room temperature, the isoquinoline solution was added via syringe to the microwave vessel, with care given to prevent exposure to the air. Next, the microwave vial was heated in the microwave at 150 °C for 5 hours. At the completion of this step, the contents filtered over a short plug of celite. The crude residue was purified by flash chromatography to yield bis-isoquinoline **442**.

Bis-isoquinoline **442** was dissolved in dioxane (5 mL) and transferred to a Schlenck tube containing selenium dioxide (4.4 mg, 0.04 mmol). The vessel was flushed with N_2 and sealed before being heated to 110 °C for 2 hours. The flask was cooled to

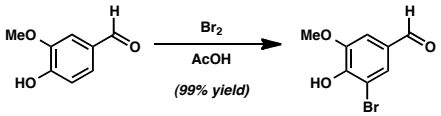
room temperature, and methanol (2 mL) was added. The contents of the tube were filtered over a short celite plug, washing with methanol (4 mL), and the eluent was collected in a round-bottom flask. This flask was placed under an atmosphere of N_2 and cooled in an ice bath to 0 °C, at which point sodium borohydride (3 mg, 0.08 mmol) was added at once. The reaction was allowed to stir at 0 °C for 30 minutes, and allowed to warm to room temperature over 1 hour. Once at room temperature, 1.0 M aqueous sodium hydroxide (6 mL) was added to quench the reductant. The mixture was partitioned with ethyl acetate (15 mL) and brine (25 mL) was added. The aqueous was extracted with ethyl acetate (3 x 25 mL), and the organic fractions were combined, and dried over sodium sulfate. After filtration and concentration, the residue was purified by flash chromatography (30% → 50% EtOAc:hexanes) to yield bis-isoquinoline alcohol **443** (5.5mg 66% yield), which was isolated as a white solid: $R_f = 0.37$ (50% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.58 (d, J = 8.3 Hz, 1H), 8.41 (s, 1H), 8.05 (q, J = 10.2 Hz, 3H), 7.81 (q, J = 7.2 Hz, 2H) 7.73 (t, J = 9.0 Hz, 2H), 5.37 (d, J = 3.31, 2H), 4.91 (s, 1H), 4.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.41, 158.14, 156.58, 149.15, 140.63, 136.93, 136.90, 130.91, 130.86, 129.82, 128.50, 128.45, 128.44, 128.42, 128.10, 124.60, 124.51, 123.17, 122.60, 61.61, 52.94; IR (NaCl/film) 1720, 1559, 1448, 1397, 1340, 1300, 1246, 1214, 1204, 1147, 1080, 1009, 886, 779, 742 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{17}N_2O_3$ $[M+H]^+$: 345.1239, found 345.1242.



442 *454*

Pentacycle 454

Bis-isoquinoline **442** (1 mg, 0.003 mmol) was dissolved in acetic acid (1 mL), and transferred into a test tube for the multiwell H_2 autoclave with a stir bar, and purged with N_2 for 5 minutes. The reaction was then charged with Adams' catalyst (0.1 mg, 0.0003 mmol), and placed inside the autoclave. Upon sealing, the bomb was pressurized to 5 atm, and the pressure was released to purge the bomb of oxygen. This process was repeated 3 times before the autoclave was pressurized to 10 atm of H_2 and warmed to 80 °C for 72 hours. Upon cooling, the crude reaction mixture was purified on preparatory TLC (EtOAc as eluent). The characterization of structure **454** is tentative, based on clear mass spectral assignment.

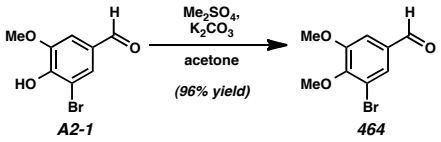


463 *A2-1*

3-Bromovanillin (A2-1)

The following procedure was adopted from a literature report by Rao and Stuber.[58] A single-neck, 2 L round-bottom flask was charged with vanillin (**463**, 50 g, 328.6 mmol). Glacial acetic acid was added (1.1 L, 3.0 M). Following this, a mechanical stirrer was affixed to the flask through the neck and, with vigorous but even stirring, the vanillin dissolved to form a pale yellow solution. At this point, neat bromine (16.84 mL, 361.5 mmol) was added in a rapid dropwise fashion to the stirring solution through the

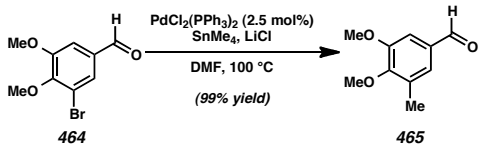
flask neck to produce a deep red-orange solution. Following addition, the reaction was maintained with vigorous stirring for 90 minutes, after which time TLC analysis indicated formation of the product (R_f = 0.32, 15% ethyl acetate in hexanes). The reaction also results in the formation of a bright orange-yellow precipitate when nearing completion. Upon completion of the reaction, the mechanical stirrer was disengaged and the contents of the reaction flask were poured onto chilled deionized water (0 °C, 600 mL), resulting in further precipitation of a pale yellow solid from the bright orange aqueous layer. The reaction flask was washed into this flask with more chilled water. While still cooled, the contents of the 1 L Erlenmeyer flask were filtered over a glass frit to separate the desired solid product. The isolated solid product (**A2-1**, 75.25 g, 99% yield) was transferred to a flask and dried under vacuum for a period of 8 hours.



3-bromo-4,5-dimethoxy benzaldehyde (464)

To a 1 L round-bottom flask was added anhydrous K_2CO_3 (113.56 g, 821.6 mmol), followed by a solution of bromobenzaldehyde **A2-1** (75.25 g, 325.66 mmol) in reagent grade acetone (700 mL). A mechanical stirrer was affixed to the reaction flask, and vigorous stirring was required to generate an evenly distributed, maroon suspension. To this stirring mixture was added Me_2SO_4 (77.74 mL, 821.69 mmol) over 1 minute via funnel. The reaction was left to stir vigorously at 25 °C for 8 hours, at which point TLC analysis confirmed the conversion of phenol **A2-1** to a less polar product. The reaction contents were then vacuum filtered over a glass frit to separate residual solid K_2CO_3. The

filtered solid was washed with acetone (2 x 100 mL) and methanol (100 mL). The organic filtrate was concentrated to an orange oil and purified by flash chromatography (5% → 50% ethyl acetate in hexanes eluent) to yield bromobenzaldehyde **464** (76.6 g, 96% yield), which was isolated as a white powder: R_f = 0.56 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.67 (d, J = 1.80 Hz, 1H), 7.40 (d, J = 1.85 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.83, 154.17, 151.81, 133.03, 128.77, 117.92, 110.09, 60.83, 56.25; IR (NaCl/film) 2945, 2860, 1692, 1588, 1566, 1486, 1469, 1452, 1420, 1393, 1380, 1312, 1281, 1240, 1212, 1144, 1133, 1048, 993, 855, 840 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_9BrO_3$ $[M]^+$: 243.9735, found 243.9731.

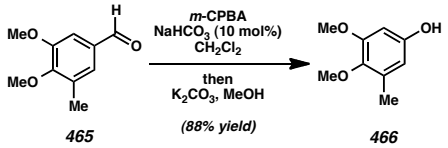


464 *465*

3,4-dimethoxy-5-methylbenzaldehyde (465)

A 250 mL round-bottom flask was charged with lithium chloride (4.32 g, 102.00 mmol) and then flame dried. To this flask was added a solution of benzaldehyde **464** (5.0 g, 20.40 mmol) in *N*,*N*-dimethylformamide (200 mL) that had been rigorously sparged with argon. Next, $PdCl_2(PPh_3)_2$ (0.358 g, 0.51 mmol) was added to the stirring mixture, producing a bright yellow-orange solution that was stirred vigorously. A reflux condenser was affixed to the top of the reaction flask before adding, dropwise, neat tetramethyltin (7.06 mL, 51.0 mmol). The reaction vessel was sealed under an argon atmosphere and heated to reflux in 100 °C oil bath. The reaction was maintained at reflux for 3 hours; during this period the color of the solution changed to dark red-

orange.[64] TLC analysis of the reaction after this period showed full consumption of the starting material. The reaction was cooled to room temperature and then quenched by the addition of H_2O (200 mL). The aqueous layer was thoroughly extracted with ethyl acetate (5 x 200 mL), and the combined organic layers were washed with brine (150 mL). The organic extract was dried over $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5% ethyl acetate in hexanes eluent) to furnish benzaldehyde **465** as a colorless oil (3.63 g, 99% yield): $R_f = 0.42$ (10% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.17 (d, J = 1.71 Hz, 1H), 7.16 (d, J = 0.60 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.14, 153.02, 152.70, 126.95, 108.79, 60.05, 55.65, 15.75; IR (NaCl/film) 2939, 2833, 1693, 1586, 1491, 1465, 1422, 1387, 1329, 1299, 1233, 1140, 1096, 1003, 856 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{12}O_3$ $[M]^+$: 180.0786, found 180.0779.

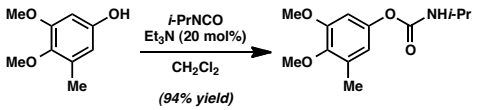


465 466

3,4-dimethoxy-5-methylphenol (466)

A 250 mL round-bottom flask was charged with anhydrous $NaHCO_3$ (0.467 g, 0.56 mmol). To this, was added a solution of benzaldehyde **465** (1.00 g, 5.55 mmol) in CH_2Cl_2 (11 mL). This mixture was vigorously stirred until the $NaHCO_3$ fully dissolved. At this point, *m*-CPBA (1.92 g, 11.10 mmol) was added as a solid in a single portion to the pale yellow solution. Immediately, the solution turned bright yellow, and was maintained with stirring at 25 °C under an atmosphere of N_2. Notable accumulation of precipitate resulted in increasing turbidity of the solution, and after 6 hours, TLC analysis

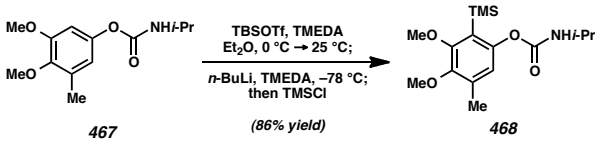
indicated formation of a new product (R_f = 0.22, hexanes) and consumption of benzaldehyde **465**. At this time, methanol (110 mL) and anhydrous K_2CO_3 (2.30 g, 16.65 mmol) were added, and the solution turned maroon in color. The reaction was maintained at 25 °C for 12 hours, resulting in formation of a new polar product. The reaction was stopped by concentration under vacuum to yield a dark maroon solid. This solid was dissolved in H_2O (100 mL), and then neutralized with concentrated aqueous HCl (6 mL). **Warning:** vigorous gas evolution. The resulting suspension was extracted with CH_2Cl_2 (5 x 100 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 200 mL) to remove benzoate byproducts. The organic layers were dried with Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (30% ethyl acetate in hexanes eluent) to provide phenol **466** (0.822 g, 4.89 mmol, 88% yield) as a white solid: R_f = 0.30 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (d, J = 2.80 Hz, 1H), 6.20 (d, J = 2.80 Hz, 1H), 4.53 (s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.36, 151.78, 141.12, 132.41, 108.36, 98.17, 60.35, 55.69, 15.85; IR (NaCl/film) 3272, 2957, 1614, 1483, 1463, 1440, 1430, 1348, 1268, 1226, 1219, 1196, 1181, 1154, 1096, 1001, 854, 772, 737 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_9H_{12}O_3$ $[M]^+$: 168.0786, found 168.0753.



466 *467*

Isopropyl carbamate 467

This procedure was adopted from the literature procedure reported by Bronner, et al.[60] A 100 mL round-bottom flask was charged with a solution of phenol **467** (1.696 g, 10.08 mmol) in CH_2Cl_2 (35 mL). The solution was stirred at 25 °C under an atmosphere of N_2 before neat isopropyl isocyanate (1.483 mL, 15.12 mmol) was added via syringe. The solution turned orange, and after 5 minutes of stirring, freshly distilled Et_3N (0.281 mL, 2.02 mmol) was added via syringe to effect the formation of a dark purple solution. The reaction was maintained with stirring for 18 hours at 25 °C. Following this period, TLC analysis showed conversion of phenol **466** to a single product. The reaction was concentrated to an orange-brown residue and purified by flash chromatography (5% ethyl acetate in hexanes eluent) to provide isopropyl carbamate **467** as a clear, pale yellow oil (2.404 g, 94% yield): R_f = 0.48 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (d, J = 2.65 Hz, 1H), 6.54 (d, J = 2.65 Hz, 1H), 2.79 (s, 1H), 3.87 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.24 (s, 3H), 1.23 (d, J = 7.25 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.92, 152.87, 146.66, 144.62, 115.29, 104.21, 60.15, 55.78, 43.44, 22.93, 15.91; IR (NaCl/film) 3326, 2972, 2936, 1715, 1604, 1529, 1490, 1466, 1422, 1332, 1220, 1190, 1175, 1142, 1095, 1050, 1009, 936, 854, 773 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{13}H_{19}NO_4$ $[M]^+$: 253.1314, found 253.1319.

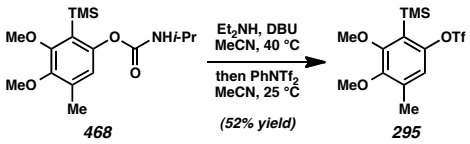


467 ***468***

TMS carbamate 468

This procedure was adopted from the literature procedure reported by Bronner, et al.[60] To a 25 mL round-bottom flask was added a solution of isopropyl carbamate **467** (2.404 g, 9.49 mmol) in diethyl ether (94 mL), followed by freshly distilled TMEDA (1.56 mL, 10.44 mmol) via syringe. The solution was cooled to 0 °C in an ice water bath. Upon temperature equilibration (15 minutes), neat distilled TBSOTf (2.398 mL, 10.44 mmol) was added. The resulting solution was maintained for 10 minutes at 0 °C and then the flask was allowed to warm to 23 °C over 30 minutes. At this point, TLC analysis showed formation of a less polar product (R_f = 0.81, 15% ethyl acetate in hexanes) corresponding to the *N*-silylated intermediate. Additional TMEDA was added to the mixture via syringe (5.688 mL, 37.964 mmol). The reaction was then cooled to –78 °C in a dry ice and acetone bath with vigorous stirring to avoid aggregation of triflate salts. Next, *n*-BuLi solution (2.32 M in hexanes, 16.36 mL, 37.96 mmol) was added dropwise down the side of the flask of the cold solution. The solution was maintained with stirring at –78 °C for 4 hours, after which time freshly distilled TMSCl (8.432 mL, 66.437 mmol) was added dropwise to the flask. The reaction vessel, in the cold bath, was allowed to warm to 23 °C over the course of two hours. At this point, TLC analysis indicated the presence of a single, new product. Saturated aqueous $NaHSO_4$ solution (50 mL) was added and stirred with the reaction mixture for 1 hour. The layers were separated and the organic layer was washed with an additional 50 mL of the $NaHSO_4$ solution. The combined aqueous layers were then extracted with diethyl ether (3 x 50mL). The

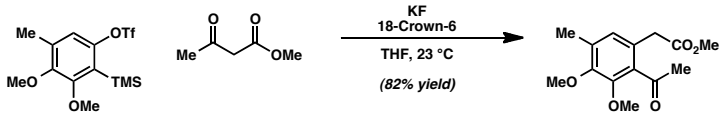
combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, and then concentrated under vacuum to a colorless crystalline solid. Purification via flash chromatography (5% → 20% ethyl acetate in hexanes eluent) provided pure TMS carbamate **468** (2.63 g, 86% yield): R_f = 0.63 (15% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62, 4.69 (d, J = 7.08 Hz, 1H), 3.89 (m, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.23 (s, 3H), 1.23 (d, J = 6.75, 6H), 0.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.69, 153.00, 149.33, 147.28, 133.33, 121.79, 118.88, 59.19, 58.54, 42.27, 21.88, 14.83, 0.13; IR (NaCl/film) 3326, 2971, 2937, 1710, 1601, 1530, 1464, 1384, 1370, 1324, 1247, 1220, 1193, 1179, 1080, 1026, 987, 844, 810, 759 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{27}NO_4Si$ $[M+H]^+$: 326.1734, found 326.1725.



Silyl aryl triflate 295

This procedure was adopted from the literature procedure reported by Bronner, et al.[60] A 250 mL round-bottom flask was charged with a solution of TMS carbamate **468** (2.63 g, 8.10 mmol) in acetonitrile (80 mL). To this was added diethylamine (1.01 mL, 9.71 mmol), followed by DBU (1.82 mL, 12.14 mmol). The reaction was carefully monitored by TLC as it was heated to 40 °C in an oil bath. After 10 minutes, TLC anaylsis indicated complete consumption of the starting material and conversion to two spots (R_{f1} = 0.78 and R_{f2} = 0.60).[65] The reaction was immediately removed from the oil bath and a solution of $PhNTf_2$ (4.34 g, 12.14 mmol) in acetonitrile (24 mL) was added via syringe. The reaction was maintained with stirring for 12 hours at 23 °C, after which point the

reaction solution was washed with saturated aqueous $NaHSO_4$ (2 x 50 mL) and brine (100 mL). The organic extract was dried over $MgSO_4$, concentrated under vacuum to an orange oil, and purified via flash chromatography (5% ethyl acetate in hexanes eluent) to yield silyl aryl triflate **295** (1.57 g, 52% yield) as a pale yellow oil: R_f = 0.68 (15% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.27 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.72, 150.74, 149.21, 135.84, 117.49 (q, J = 320 Hz), 124.53, 117.96, 60.79, 60.03, 16.43, 1.41; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.10; IR (NaCl/film) 2956, 2858, 1600, 1464, 1420, 1383, 1368, 1292, 1248, 1213, 1179, 1142, 1068, 1023, 982, 930, 873, 846, 764 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{19}F_3O_5SSi$ $[M]^+$: 372.0675, found 372.0674.

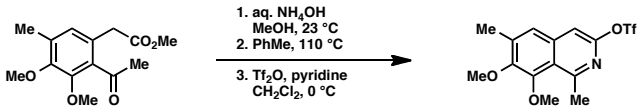


295 *431* *469*

Ketoester 469

Silyl aryl triflate **295** (500 mg, 1.34 mmol) was added to a solution of methyl acetoacetate (**431**, 132 μL, 1.22 mmol), KF (160 mg, 2.74 mmol) and 18-crown-6 (758 mg, 2.86 mmol) in THF (15 mL) at 23 °C. The reaction was maintained at this temperature for 16 hours, at which time TLC analysis indicated complete consumption of both silyl aryl triflate **295** and methyl acetoacetate (**431**). The solution was diluted with diethyl ether (50 mL) and washed with saturated aqueous sodium chloride (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated to a yellow oil. Purification of this residue by flash chromatography (10% EtOAc in hexanes eluent) furnished ketoester **469**

(295 mg, 82% yield) as a clear, colorless oil: R_f = 0.49 (4:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.61 (s, 2H), 2.55 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.50, 172.03, 150.77, 150.33, 134.38, 134.07, 128.57, 126.65, 61.17, 60.08, 52.00, 37.76, 32.26, 15.89; IR (NaCl/film) 2951, 2849, 1740, 1692, 1604, 1568, 1484, 1451, 1437, 1400, 1351, 1306, 1269, 1200, 1167, 1147, 1078, 1040, 1012 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 267.1227, found 267.1233.



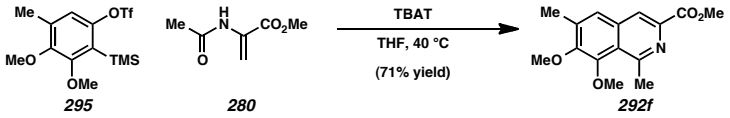
469 ***426***

Isoquinoline triflate 426

Ketoester **469** (50 mg, 0.188 mmol) was dissolved in MeOH (2 mL) in a Schlenk flask with a sealable top. To this was added 28–30% aqueous ammonium hydroxide (10 mL, 80 mmol), and the flask was sealed. The reaction was maintained at 23 °C with vigorous stirring for 30 min. At this point, TLC analysis indicated the complete consumption of the starting material, and the reaction was stopped by concentration under vaccuum. The resulting orange-yellow residue was taken up in PhMe (10 mL) and heated to 110 °C for 18 hours. The reaction was then cooled and concentrated under vaccuum. The crude product was used without further purification in the next step.

The crude starting material was dissolved in dry CH_2Cl_2 (8 mL). To this solution, was added pyridine (1.75 mL, 18.80 mmol), and the reaction was cooled to 0 °C in an ice bath under an atmosphere of nitrogen. Triflic anhydride (63 μL, 0.376 mmol) was added

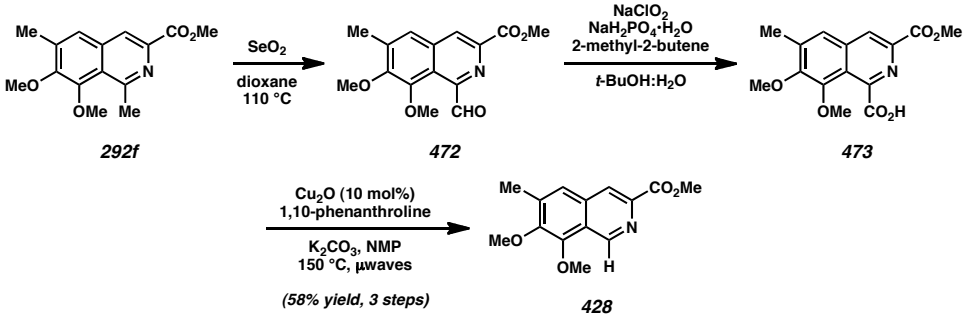
dropwise to the cold solution, which was maintained at 0 °C for 30 minutes. At this time, TLC analysis indicated complete consumption of the starting material. The reaction was quenched at 0 °C by the addition of saturated aqueous $NaHCO_3$ (10 mL) followed by warming to 23 °C. The mixture was extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated under vaccuum. The resulting residue was purified by flash chromatography (10% ethyl acetate in hexanes eluent) to furnish isoquinoline triflate **426** (38 mg, 56% yield, 3 steps): $R_f = 0.83$ (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.21 (s, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.07 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ158.61, 151.01, 150.42, 149.87, 139.22, 136.77, 123.56, 122.86, 118.73 (q, J = 320 Hz), 107.60, 60.73, 60.13, 26.63, 16.93; IR (NaCl/film) 2961, 2924, 2853, 1604, 1552, 1452, 1413, 1377, 1352, 1332, 1260, 1208, 1094, 1059, 1016, 966, 940, 799, 699 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 366.0618, found 366.0637.



Isoquinoline 292f

To a round-bottomed flask containing methyl-2-acetamidoacrylate (**280**, 50 mg, 0.349 mmol) and TBAT (141 mg, 0.262 mmol) stirring in THF (35 mL) at 23 °C was added silyl aryl triflate **295** (66 mg, 0.175 mmol) via syringe. The flask was maintained at 23 °C for 8 hours until amidoacrylate **280** had been fully consumed by TLC analysis. At this point, the reaction was stopped by dilution with methanol (20 mL) and adsorption of the resultant mixture onto silica gel (1 g) under vacuum. The resulting powder was

purified by flash chromatography (2.5% → 10% ethyl acetate in CH_2Cl_2 eluent) to furnish isoquinoline **292f** (34 mg, 71% yield) as an off-white powder: R_f = 0.35 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.51 (s, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.09 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.62, 157.80, 152.53, 149.72, 139.37, 138.12, 133.88, 125.11, 124.12, 122.20, 60.82, 60.19, 52.80, 27.49, 16.92; IR (NaCl/film) 2948, 2852, 1735, 1715, 1617, 1559, 1487, 1450, 1437, 1396, 1355, 1328, 1261, 1218, 1194, 1131, 1091, 1057, 1010, 998, 907, 874, 782 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ [M+H]$^+$: 276.1230, found 276.1245.



Isoquinoline 428

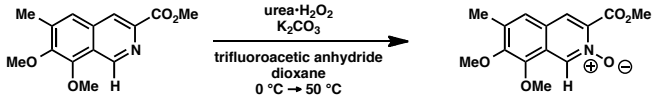
A solution of isoquinoline **292f** (20 mg, 0.073 mmol) in dioxane (1 mL) was added to selenium dioxide (16 mg, 0.146 mmol) in a flame-dried round-bottomed flask containing a stir bar. A reflux condenser was attached, and the colorless suspension was vigorously stirred while heating to reflux (110 °C) under a nitrogen atmosphere. The reaction was maintained for 30 minutes at reflux, by which time the reaction had turned red-orange and appeared complete by TLC analysis. The flask was then cooled to room temperature and diluted with ethyl acetate (20 mL). The suspension was filtered through a short plug of celite to remove residual solids and the concentrated under vacuum. This

crude mixture was purified by flash chromatography (25% ethyl acetate in hexanes eluent) to yield aldehyde **472** (19 mg, 88% yield) as a clear oil: R_f = 0.28 (1:1 ethyl acetate:hexanes).

Aldehyde **472** (19 mg, 0.064 mmol) was suspended in a mixture of *t*-BuOH (1.3 mL) and 2-methyl-2-butene (0.406 mL, 3.840 mmol). To this suspension was added a solution of $NaH_2PO_4 \bullet H_2O$ (141 mg, 1.024 mmol) and $NaClO_2$ (58 mg, 0.640 mmol) in H_2O (1.3 mL). The biphasic solution was vigorously stirred for 28 hours, after which time TLC analysis indicated complete consumption of aldehyde **472**. The reaction was diluted with ethyl acetate (100 mL), and washed with water (150 mL). The aqueous layer was extracted with ethyl acetate (5 x 100 mL), until the persistent yellow color of the aqueous layer disappeared. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to provide isoquinoline carboxylic acid **473** (18 mg, 94% yield), which was used without further purification.

A solution of isoquinoline carboxylic acid **473** (18 mg, 0.060 mmol) in *N*-methyl pyrrolidinone (1 mL) was added to a microwave vial containing cuprous oxide (1 mg, 0.006 mmol), 1,10-phenanthroline (2 mg, 0.012 mmol), and K_2CO_3 (17 mg, 0.120 mmol). The vial was sealed and heated to 150 °C at a maximum power of 400 W for 30 minutes. The resulting brown suspension was diluted with ethyl acetate (10 mL) and filtered through a silica plug. The filtrate was added to brine (25 mL) and extracted with ethyl aetate (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to provide a brown residue. Purification via flash chromatography (30% ethyl acetate in hexanes eluent) yielded isoquinoline **428** (11 mg, 70% yield): R_f = 0.32 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (s,

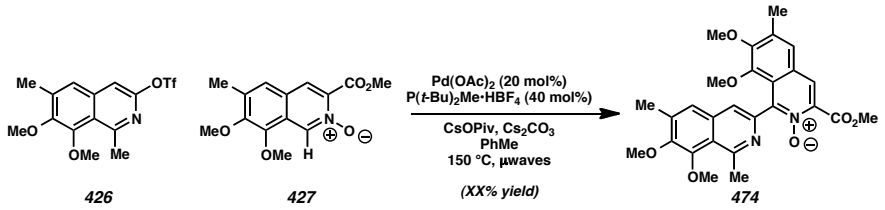
1H), 8.44 (s, 1H), 7.52 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 4.01 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.55, 147.46, 147.16, 140.85, 139.20, 132.70, 124.82, 124.09, 123.04, 109.98, 61.59, 60.48, 52.81, 17.36; IR (NaCl/film) 2949, 2855, 1738, 1717, 1620, 1570, 1483, 1456, 1418, 1386, 1321, 1285, 1257, 1196, 1141, 1105, 1085, 1006, 984, 906, 818, 802, 777cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 262.1074, found 262.1070.



Isoquinoline *N*-oxide 427

To a flame-dried round-bottomed flask with a large stirring bar containing urea•H_2O_2 (288 mg, 3.06 mmol) and K_2CO_3 (530 mg, 3.82 mmol) was added dioxane (7.5 mL). The suspension was stirred at 23 °C for 15 minutes before being cooled to 0 °C in an ice/water bath. To this suspension, trifluoroacetic anhydride (0.425 mL, 3.060 mmol) was added dropwise to maintain a consistent internal temperature. The reaction was maintained with stirring for 1 hour at 0 °C before transferring to an oil bath at 50 °C. After maintaining the suspension at 50 °C for 30 minutes, a solution of 1-*H*-isoquinoline **428** (40 mg, 0.153 mmol) in dioxane (7.5 mL) was added, and the reaction was maintained at 50 °C for 12 hours. After this time, TLC analysis indicated complete consumption of the isoquinoline, and the reaction was stopped by dilution with CH_2Cl_2 (100 mL). Water (50 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to a yellow oil. Purification by flash chromatography (1:10:10 NEt_3:ethyl

acetate:hexanes eluent) provided the isoquinoline *N*-oxide **427** (28 mg, 67% yield): R_f = 0.12 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.88 (s, 1H), 7.36 (s, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.48, 151.85, 144.27, 137.25, 133.10, 125.59, 124.99, 124.95, 123.53, 61.35, 60.48, 53.33, 30.96, 17.21; IR (NaCl/film) 2951, 2850, 1742, 1623, 1607, 1558, 1475, 1447, 1418, 1374, 1277, 1258, 1209, 1144, 1100, 1073, 1002, 958, 936, 828 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 278.1028, found 278.1034.



Bis-isoquinoline 474

Palladium acetate (0.7 mg, 0.003 mmol) was added to a flame-dried microwave vial containing cesium carbonate (24 mg, 0.075 mmol), cesium pivalate (9 mg, 0.0375 mmol) and di-*tert*-butylmethylphosphonium tetrafluoroborate (2.5 mg, 0.010 mmol). The vessel was sealed, and then evacuated and backfilled with an atmosphere of argon three times. Next, toluene (1.5 mL) was added to the reaction vial, which was subsequently heated to 50 °C in an oil bath. The suspension was maintained at this temperature for 30 minutes with vigorous stirring. Concomitant to this step, isoquinoline triflate **426** (5 mg, 0.013 mmol) was added to a flask containing isoquinoline *N*-oxide **427** (7 mg, 0.025 mmol). This flask was sealed with a rubber septum, and evacuated and backfilled with an atmosphere of argon three times. Toluene (1.0 mL) was added to the flask under an argon atmosphere. After the palladium suspension had stirred for 30

minutes at 50 °C, the solution had turned from clear to pale yellow. Upon cooling to room temperature, the isoquinoline solution was added via syringe to the microwave vessel, with care given to prevent exposure to the air. Next, the microwave vial was heated in the microwave at 150 °C for 8 hours. At the completion of this step, the contents filtered over a short plug of celite. The crude residue was purified by flash chromatography (5% MeOH in CH_2Cl_2 as eluent) to yield bis-isoquinoline **474** (5 mg, 78% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.62 (s, 1H), 7.59 (s, 1H), 7.40 (s, 1H), 4.00 (s, 6H), 3.99 (s, 3H), 3.81 (s, 3H), 3.39 (s, 3H), 3.13 (s, 3H), 2.47 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 150.9, 147.5, 147.2, 140.9, 139.2, 132.7, 124.8, 124.1, 123.0, 61.6, 60.5, 52.8, 17.4; IR (NaCl/film) 2924, 2850, 1734, 1717, 1616, 1558, 1486, 1455, 1398, 1318, 1261, 1122, 1095, 1010, 915, 802, 736 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{27}H_{29}N_2O_7$ $[M+H]^+$: 493.1964, found 493.2012.

4.5 NOTES AND REFERENCES

(1) Scott. J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.

(2) a) Arai, T.; Takahashi, K.; Ishiguro, K.; Yazawa, K. *J. Antibiot.* **1980**, *33*, 951-960. b) Mikami, Y.; Yokoyama, K.; Tabeta, H.; Nakagaki, K.; Arai, T. *J. Pharmacobiodyn.* **1981**, *4*, 282-286.

(3) a) Fontana, A.; Cavaliere, P.; Wahidulla, S.; Naik, C. G.; Cimino, G. *Tetrahedron* **2000**, *56*, 7305-7308. b) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684-12690.

(4) He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067-2071.

(5) a) Jett, J. R.; Saijo, N.; Hong, W.-S.; Sasaki, Y.; Takahashi, H.; Nakano, H.; Nakagawa, K.; Sakurai, M.; Suemasu, K.; Tesada, M. *Investig. New Drugs* **1987**, *5*, 155-159. b) Chiang, C. D.; Kanzawa, F.; Matsushima, Y.; Nakano, H.; Nakagawa, K.; Takahashi, H.; Terada, M.; Morinaga, S.; Tsuchiya, R.; Sasaki, Y. *J. Pharmacobiodyn.* **1987**, *10*, 431-435.

(6) Inaba, S.; Shimoyama, M. *Cancer Res.* **1988**, *48*, 6029-6032.

(7) Plowman, J.; Dykes, D. J.; Narayanan, V. L.; Abbott, B. J.; Saito, H.; Hirata, T.; Grever, M. R. *Cancer Res.* **1995**, *55*, 862-867.

(8) a) Verschraegen, C. F.; Glover, K. *Curr. Opin. Investig. Drugs* **2001**, *2*, 1631-1638. b) Ryan, D. P.; Supko, J. G.; Eder, J. P.; Seiden, M. V.; Demetri, G.; Lynch, T. J.; Fischman, A. J.; Davis, J.; Jimeno, J.; Clark, J. W. *Clin. Cancer Res.* **2001**, *7*, 231-242.

(9) a) Elices, M.; Grant, W.; Harper, C. *AACR Meeting Abstr.* **2005**, 147-14a. b) LePage, D.; Sasak, H.; Maria, J. *AACR Meeting Abstr.* **2007**, C62. c) LePage, D.; Sasak, H.; Cheney, L. *AACR Meeting Abstr.* **2007**, 1519. d) Greiner, T.; Maier, A.; Bausch, N. *AACR Meeting Abstr.* **2007**, C60. e) Gallerani, E.; Yap, T. A.; Lopez, A.; Coronado, C.; Shaw, H.; Florez, A.; de las Heras, B.; Cortés-Funes, H.; de Bono, J.; Paz-Ares, L. *J. Clin. Oncol., ASCO Meeting Abstr.* **2007**, *25,* 2517.

(10) a) Asaoka, T.; Yazawa, K.; Mikami, Y.; Arai, T.; Takahashi, K. *J. Antibiot.* **1982**, *35*, 1708-1710. b) Tomita, F.; Takahashi, K.; Shimizu, K.-I. *J. Antibiot.* **1983**, *36*, 463-467. c) Frincke, J. M.; Faulkner, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 265-269. d) Ikeda, Y.; Shimada, Y.; Honjo, K.; Okumoto, T.; Munakata, T. *J. Antibiot.* **1983**, *36*, 1290-1294.

(11) Zmijewski, M. J.; Mikolajczak, M.; Viswanatha, V.; Hruby, V. J. *J. Am. Chem. Soc.* **1982**, *104*, 4969–4971.

(12) a) Mikami, Y.; Takahashi, K.; Yazawa, K.; Arai, T.; Namikoshi, M.; Iwasaki, S.; Okuda, S. *J. Biol. Chem.* **1985**, *260*, 344–348. b) Jeedigunta, S.; Krenisky, J. M.; Kerr, R. G. *Tetrahedron* **2000**, *56*, 3303–3307.

(13) Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000–15001.

(14) Whaley, H. A.; Patterson, E. L.; Dann, M.; Shay, A. J.; Porter, J. N. *Antimicrob. Agents Chemother.* **1964**, *14*, 83–86.

(15) Karmas, G.; Spoerri, P. E. *J. Am. Chem. Soc.* **1952**, *74*, 1580–1584.

(16) a) Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, *28*, 2187–2190. b) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893–5903. c) Yates, N. D.; Peters, D. A.; Allway, P. A.; Beddoes, R. L.; Scopes, D. I. C.; Joule, J. A. *Heterocycles* **1995**, *40*, 331–347.

(17) For synthetic work toward lemonomycin, see: a) Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12476–12477. b) Rikimaru, K.; Mori, K.; Kan, T.; Fukuyama, T. *Chem. Commun.* **2005**, 394–396. c) Courturier, C.; Schlama, T.; Zhu, J. *Synlett* **2006**, 1691–1694. d) Vincent, G.; Chen, Y.; Lane, J. W.; Williams, R. M. *Heterocycles* **2007**, *72*, 385–398. e) Siengalewicz, P.; Brecker, L.; Mulzer, J. *Synlett* **2008**, 2443–2446. f) Wu, Y.-C.; Bernadat, G.; Masson, G.; Couturier, C.; Schlama, T.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 2046–2052.

(18) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559.

(19) Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270–17271.

(20) Shortly after our report, Blackburn and Ramtohul disclosed a preparation of both isoquinolines and benzocyclobutanes using CsF as the fluoride source. See: Blackburn, T.; Ramtohul, Y. K. *Synlett* **2008**, 1159–1164.

(21) For the isolation of papaverine, see: Merck, G. *Liebigs Ann. Chem.* **1848**, *66*, 125–128.

(22) a) Bentley, K. W. In *The Isoquinoline Alkaloids*; Ravindranath, B., Ed.; Harwood Academic Publishers: Amsterdam, 1998; pp 107–122. b) Bentley, K. W. *Nat. Prod. Rep.* **2005**, *22*, 249–268.

(23) For previous total syntheses of papaverine, see: a) Pictet, A.; Finkelstein, M. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 1979–1989. b) Rosenmund, K. W.; Nothnagel, M.; Riesenfeldt, H. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 392–398. c) Mannich, C.; Walther, O. *Arch. Pharm.* **1927**, *265*, 1–11. d) Galat, A. *J. Am. Chem. Soc.* **1951**, *73*, 3654–3656. e) Wahl, H. *Bull. Soc. Chim. Fr.* **1950**, *17*, 680. f) Popp, F. D.; McEwen, W. E. *J. Am. Chem. Soc.* **1957**, *79*, 3773–3777. g) Hirsenkorn, R. *Tetrahedron Lett.* **1991**, *32*, 1775–1778.

(24) For our account of the papaverine synthesis, see Chapter 2 of this thesis.

(25) a) Xin, H. Y.; Biehl, E. R. *J. Org. Chem.* **1983**, *48*, 4397-4399. b) Han, Y. X.; Jovanovic, M. V.; Biehl, E. R. *J. Org. Chem.* **1985**, *50*, 1334–1337. c) Biehl, E. R.; Razzuk, A.; Jovanovic, M. V.; Khanapure, S. P. *J. Org. Chem.* **1986**, *51*, 5157–5160.

(26) a) Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, *36*, 468–470. b) Tomita, F.; Takahashi, K.; Tamaoki, T. *J. Antibiot.* **1984**, *37*, 1268–1272.

(27) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827–5828.

(28) For the synthesis of (±)-quinocarcin, see: Fukuyama, T.; Nunes, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 5196–5198.

(29) For asymmetric syntheses of (–)-quinocarcin, see: a) Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1992**, *114*, 2767–2768. b) Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1993**, *115*, 10742–10753. c) Katoh, T.; Kirihara, M.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6239–6258. d) Kwon, S.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 16796–16797. e) Wu, Y.-C.; Liron, M.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 7148–7152.

(30) For synthetic work toward quinocarcin, see: a) Danishefsky, S. J.; Harrison, P. J.; Webb, R. R., II; O'Neill, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421–1423. b) Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *28*, 4065–4068. c) Lessen, T. A.; Demko, D. M.; Weinreb, S. M. *Tetrahedron Lett.* **1990**, *31*, 2105–2108. d) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett.* **1990**, *31*, 4781–4782. e) Saito, S.; Tamura, O.; Kobayashi, Y.; Matsuda, F.; Katoh, T.; Terashima, S. *Tetrahedron* **1994**, *50*, 6193–6208. f) Saito, S.; Tanaka, K.; Nakatani, K.; Matsuda, F.; Katoh, T.; Terashima, S. *Tetrahedron* **1994**, *50*, 6209–

6220. g) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6221–6238. h) Katoh, T.; Kirihara, M.; Yoshino, T.; Tamura, O.; Ikeuchi, F.; Nakatani, K.; Matsuda, F.; Yamada, K.; Gomi, K.; Ashizawa, T.; Terashima, S. *Tetrahedron* **1994**, *50*, 6259–6270. i) Flanagan, M. E.; Williams, R. M. *J. Org. Chem.* **1995**, *60*, 6791–6797. j) McMills, M. C.; Wright, D. L.; Zubkowski, J. D.; Valente, E. J. *Tetrahedron Lett.* **1996**, *37*, 7205–7208. k) Koepler, O.; Laschat, S.; Baro, A.; Fischer, P.; Miehlich, B.; Hotfilder, M.; le Viseur, C. *Eur. J. Org. Chem.* **2004**, 3611–3622. l) Schneider, U.; Pannecoucke, X.; Quirion, J.-C. *Synlett* **2005**, 1853–1856.

(31) a) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957–4958. b) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712-3713. c) Kubo, A.; Saito, N.; Yamauchi, R.; Sakai, S.-i. *Chem. Pharm. Bull.* **1987**, *35*, 2158–2160. d) Kubo, A.; Saito, N.; Yamato, H.; Kawakami, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2525–2532. e) Kubo, A.; Saito, N.; Nakamura, M.; Ogata, K.; Sakai, S. *Heterocycles* **1987**, *26*, 1765–1771. f) Kubo, A.; Saito, N.; Yamato, H.; Yamauchi, R.; Hiruma, K.; Inoue, S. *Chem. Pharm. Bull.* **1988**, *26*, 2607–2614. g) Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295–4310. h) Shawe, T. T.; Liebeskind, L. S. *Tetrahedron* **1991**, *47*, 5643–5666. i) Fukuyama, T.; Linton, S. D.; Tun, M. M. *Tetrahedron Lett.* **1990**, *31*, 5989–5992.

(32) a) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828–10829. b) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322–3327. c) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401–8402. d) Martinez, E. J.; Corey, E. J.

Org. Lett. **1999**, *1*, 75–78. e) Zhou, B.; Edmondson, S.; Padron, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2039–2041. f) Zhou, B.; Guo, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2043–2046.

(33) T. Fukuyama, R. A. Sachleben *J. Am. Chem. Soc.* **1982**, *104*, 4957–4958.

(34) (a) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828–10829. (b) Myers, A. G.; Lanman, B. *J. Am. Chem. Soc.* **2002**, *124*, 12969–12970.

(35) Tserada, C. © 2005 (Feb. 9) *Jorunna funebris* in aquarium. [Message in] Sea Slug Forum. Australian Museum, Sydney. Available from http://seaslugforum.net/find/12966.

(36) Hill, G. C.; Remers, W. A. *J. Med. Chem.* **1991**, *34*, 1990–1998.

(37) a) Rao, K. E.; Lown, J. W. *Chem. Res. Toxicol.* **1990**, *3*, 262–267. b) Rao K. E.; Lown, J. W. *Biochemistry* **1992**, *31*, 12076–12082.

(38) Ishiguro, K.; Takahashi, K.; Yazawa, K.; Sakiyama, S.; Arai, T. *J. Biol. Chem.* **1981**, *256*, 2162–2167.

(39) Ortin, I.; Gonzalez, J. F.; de la Cuesta, E.; Manguan-Garcia, C.; Perona, R.; Avendano, C. *Bioorg. Med. Chem. Lett.* **2009**, *17*, 8040–8047.

(40) Lown, J. W.; Joshua, A. V.; Lee, J. S. *Biochemistry* **1982**, *21*, 419–428.

(41) Saito, N.; Tanaka, C.; Koizumi, Y.-i.; Suwanborirux, K.; Amnuoypol, S.; Pummangura, S.; Kubo, A. *Tetrahedron* **2004**, *60*, 3873–3881.

(42) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684–12690.

(43) Arene **406** was previously prepared in seven steps. See ref. 33a.

(44) Wu, Y.-C.; Zhu, J. *Org. Lett.* **2009**, *11*, 5558–5561.

(45) For the development, substrate scope, and mechanistic investigations of C–H functionalization reactions of azine *N*-oxides by Fagnou, see: (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021. (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781–7786. (c) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267. (d) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelesky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276–3277. (e) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155–3164. (f) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977–4983. (g) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357–1360. (h) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306. (i) Sun, H.-Y.; Gorelesky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180–8189. (j) Tan, Y.; Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, ASAP.

(46) Bentley, H. R.; Dawson, W.; Spring, F. S. *J. Chem. Soc.* **1952**, 1763–1768.

(47) a) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341. b) Ebner, D. C.; Tambar, U. K.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 161–171.

(48) Allan, K. M.; Hong, B. D.; Stoltz, B. M. *Org. Biomol. Chem.* **2009**, *7*, 4960–4964.

(49) For examples of directed oxidation of substrates similar to isoquinoline **885**, see: a) Jampilek, J.; Dolezal, M.; Kunes, J.; Buchta, V.; Silva, L.; Kralova, K. *Med. Chem.* **2005**, *1*, 591–599. b) Contour-Galcéra, M.-O.; Sidhu, A.; Plas, P.; Roubert, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3555–3559.

(50) a) Rong, D.; Phillips, V. A.; Rubio, R. S.; Castro, M. Á.; Wheelhouse, R. T. *Tetrahedron Lett.* **2008**, *49*, 6933–6935. b) Rong, D.; Phillips, V. A.; Rubio, R. S.; Castro, M. Á.; Wheelhouse, R. T. *Tetrahedron Lett.* **2009**, *50*, 4394.

(51) For reviews on asymmetric hydrogenations of aromatic heterocycles, see: (a) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171–4175. (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357–1366.

(52) a) Ginos, J. Z. *J. Org. Chem.* **1975**, *40*, 1191–1195. b) Brooks, D. J.; Dowell, D. S.; Minter, D. E.; Villarreal, M. C. *J.* Org. *Chem.* **1984**, *49*, 130–133. c) Bharathi, P.; Comins, D. L. *Org. Lett.* **2008**, *10*, 221–223.

(53) Yurovskaya, M. A.; Karchava, A. V. *Tetrahedron: Asymm.* **1998**, *9*, 3331–3352.

(54) a) Fleurant, A.; Célérier, J. P.; Lhommet, G. *Tetrahedron: Asymm.* **1993**, *4*, 1429–1433. b) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178–5189. c) Takayama, H.; Maeda, M.; Ohbayashi, S.; Kitajima, M.; Sakai, S.-i.; Aimi, N. *Tetrahedron Lett.* **1995**, *36*, 9337–9342.

(55) a) Ishida, A.; Fujii, H.; Nakamura, T.; Oh-ishi, T.; Aoe, K.; Nishibata, Y.; Kinumaki, A. *Chem. Pharm. Bull.* **1986**, *34*, 1994–2006. b) Youte, J.-J.; Barbier, D.; Al-Mourabit, A.; Gnecco, D.; Marazano, C. *J. Org. Chem.* **2004**, *69*, 2737–2740.

(56) Voutchkova, A. M.; Gnanamgari, D.; Jakobsche, C. E.; Butler, C.; Miller, S. J.; Parr, J.; Crabtree, R. H. *J. Organomet. Chem.* **2008**, *693*, 1815–1821.

(57) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224–1227.

(58) Rao, D. V.; Stuber, F. A. *Synthesis* **1983**, 308.

(59) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203.

(60) Bronner, S. M.; Garg, N. K. *J. Org. Chem.* **2009**, *74*, 8842–8843.

(61) Grimm, J. B.; Wilson, K. J.; Witter, D. J. *Tetrahedron Lett.* **2007**, *48*, 4509–4513.

(62) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2478–2479.

(63) Cheung, W.-H.; Yip, W.-P.; Yu, W.-Y.; Che, C.-M. *Can. J. Chem.* **2005**, *83*, 521–526.

(64) Cessation of the reaction occurs when exposed to air, and large amounts of Pd(0) black deposits result in a grey solution and reduced yields.

(65) R_{f1} corresponds to the 2-TMS phenol, the desired cleavage product. R_{f2} corresponds to undesired des-TMS phenol **466**.