CHAPTER FOUR

Progress Toward the Catalytic Enantioselective Total Synthesis of Liphagal

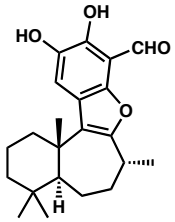
4.1 Background

4.1.1 *Isolation of the First Liphagane Natural Product, Liphagal*

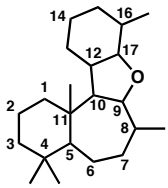
Liphagal (**271**), a tetracyclic meroterpenoid natural product, was recently isolated from the sponge *Aka coralliphaga*, native to Dominica (Figure 4.1).[1] Anderson, who isolated the natural product, assigned its structure and relative stereochemistry using multidimentional NMR techniques, later confirming the structural assignment via racemic total synthesis.[1] When Andersen isolated the molecule, he named its unprecented framework, hallmarked by its unusual [6-7-5-6] tetracyclic core, the "liphagane" skeleton (**272)**. To the best of our knowledge, no other liphaganes have been reported to date.

Figure 4.1 The Structure of Liphagal

Aka coralliphaga



Liphagal *(271)*



Liphagane Skeleton *272*

4.1.2 *Biological Activity of Liphagal*

Liphagal (**271**) was isolated via bioactivity-guided extraction and reverse-phase chromatography. In particular, the isolation chemists were searching for potent inhibitors of phosphatidylinositol 3-kinase α (PI3Kα) using a fluorescence polarization assay developed in SF9 insect cells.[1] Liphagal (**271**) was found to have an IC_{50} value of 100

nM against PI3Kα in this primary assay. Secondary assays of the compound revealed substantial cytotoxicity toward various cancer cell lines. Against LoVo (human colon) cells, liphagal (**271**) displayed an IC_{50} of 0.58 μM, and against another cell line, CaCo (human colon), the IC_{50} value was 0.67 μM. Additionally, some cytotoxicity toward a breast cancer cell line, MDA-468 was observed (IC_{50} = 1.58 μM). Without a doubt, this natural product has significant biological activity and could be useful as a lead structure for chemotherapeutics development.

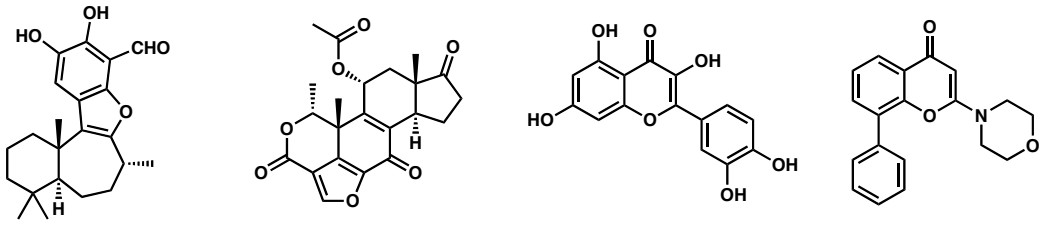
4.1.3 *Phosphatidylinositol 3-Kinases and their Biology*

Potentially the most significant finding about liphagal (**271**) is its selective inhibition of PI3Kα relative to other PI3K's[1] because there are numerous kinases in the human genome.[2] The PI3K family of enzymes is intimately involved in numerous cellular pathways spanning proliferation, survival, adhesion, movement, differentiation, membrane trafficking, glucose transport, neurite outgrowth, and superoxide production in cells.[3] Selective inhibitors of individual isoforms of these enzymes would allow for the targeting of specific diseases spanning cancer, cardiovascular disease, and autoimmune disorders.[3,4] Liphagal (**271**) has an IC_{50} of 100 nM against PI3Kα and is at least 10-fold more potent against this isoform of the enzyme compared to any other PI3K.

Many natural product and synthetic inhibitors of PI3K's are known, but selective inhibition of an individual isoform is rare. Although the natural product wortmannin (**273**) shows an IC_{50} of 12 nM toward PI3Kα, it has nearly equal potency against several other related enzymes (Figure 4.2).[1,5] Quercitin (**274**) and other molecules have already

been used in chemical genetics studies to understand the roles of certain PI3K's in cell signaling. Second generation synthetic molecules designed to mimic natural products (e.g., LY294002 (**275**)) have been developed and studied by the pharmaceutical industry.[1,5,6] Though somewhat selective, molecules such as LY294002 (**275**) lack the potency of liphagal (**271**).[1] With its unique biological activity and potentially novel mode of action, liphagal (**271**) promises to be useful in the development of new therapeutics and as a chemical tool for studying cellular signaling and disease states.

Figure 4.2 Selected Inhibitors of PI3Kα

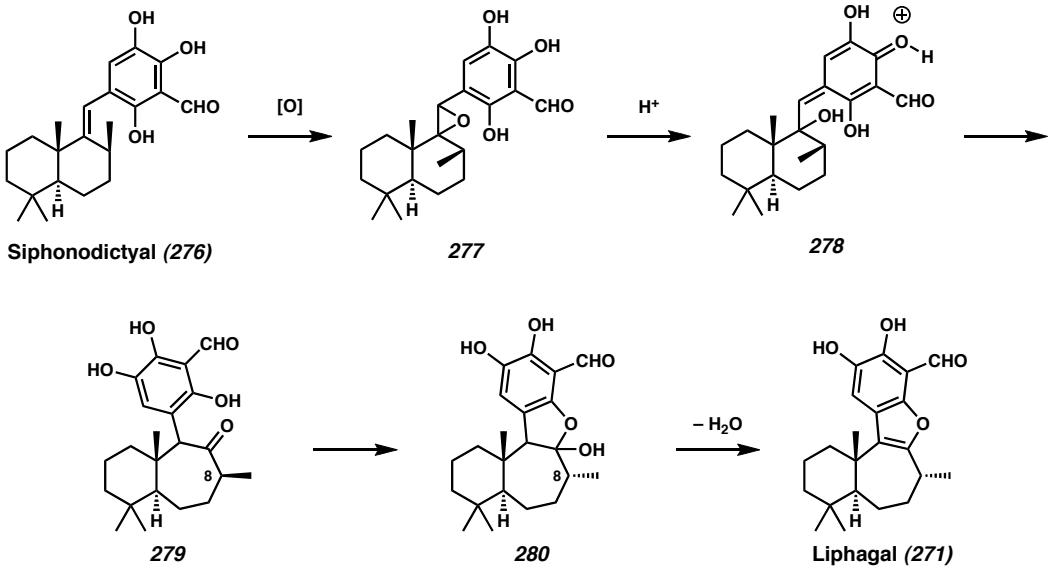


Liphagal ***(271)*** **Wortmannin** ***(273)*** **Quercitin** ***(274)*** **LY294002** ***(275)***

4.1.4 *Biosynthetic Proposals*

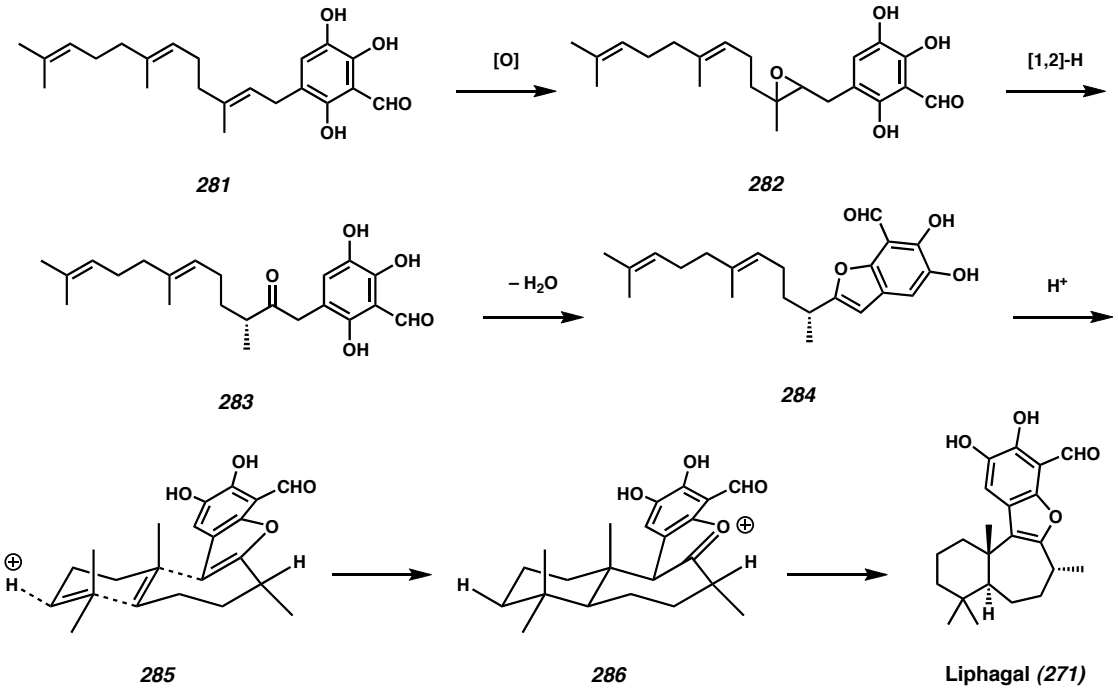
Andersen proposed that liphagal (**271**) could have one of several biosynthetic origins.[1] One of the first hypotheses discussed was the natural product's potential origination from siphonodictyal B (**276**) (Scheme 4.1). Oxidation of the trisubstituted olefin of **276** could be followed by an epoxide fragmentation-triggered ring expansion, generating the 7-membered ring of **279**. Epimerization of the C(8) stereocenter and phenolic condensation might ultimately lead to liphagal (**271**).

Scheme 4.1 Possible Biosynthesis of Liphagal from Siphonodictyal



Alternatively, the biosynthesis of **271** could begin with the polyisoprenylated arene **281** (Scheme 4.2). Oxidation of the olefin proximal to the electron-rich aromatic core, followed by a formal [1,2] H-shift, would lead to ketone **283**. A dehydrative cyclization might lead to the substituted benzofuran **284**, poised for an acid-induced polyene cyclization cascade. If a diastereoselective series of ring closures occurs, liphagal (**271**) could arise. It was this latter theory that inspired Andersen to complete the first and only total synthesis of liphagal (**271**) reported to date.[1]

Scheme 4.2 Alternative Cationic Cyclization Proposal

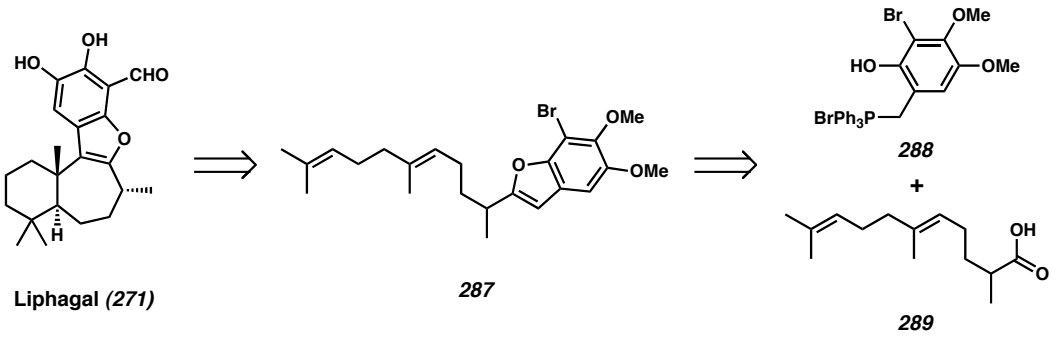


4.2 Andersen's Racemic Total Synthesis of Liphagal

4.2.1 *Retrosynthetic Analysis*

Andersen designed his retrosynthesis for the natural product based on the polyene cyclization cascade biosynthetic hypothesis.[1] Accordingly, liphagal (**271**) could arise from a diolefinic precursor **287** containing an electron-rich benzofuran moiety (Scheme 4.3). This aromatic system would serve as the terminating nucleophile in a biomimetic, acid-mediated polyene cyclization cascade. Retrosynthetically, **287** could be prepared from two fragments, a substituted phenol **288** and a carboxylic acid **289,** that could be unified via Wittig cyclization.

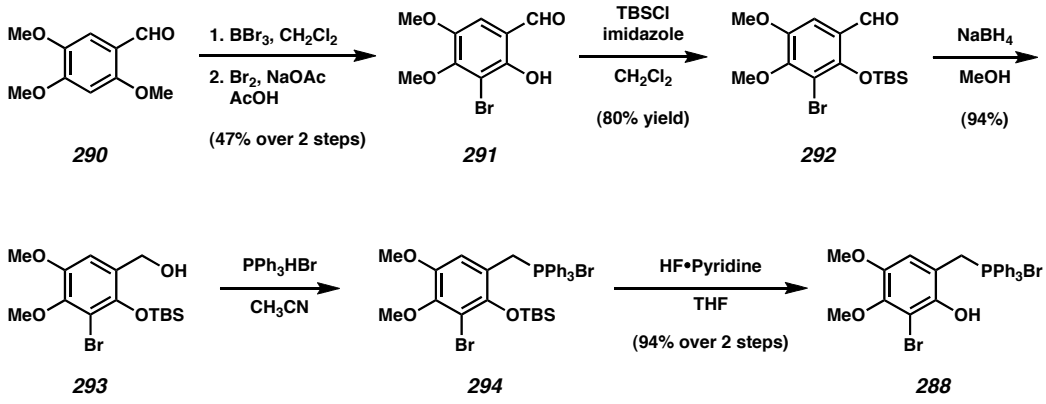
Scheme 4.3 Andersen's Retrosynthesis of Liphagal



4.2.2 *Preparation of the Fragments*

To begin the synthesis, the known aldehyde **290** was selectively demethylated and treated with bromine in buffered acetic acid to furnish 4,5-dimethoxy-3-bromo-salicylaldehyde (**291**) in modest yield (Scheme 4.4). Protection of the free phenol with TBSCl and reduction of the benzaldehyde moiety led to the benzylic alcohol **293**. Treatment of **293** with triphenylphosphonium bromide in acetonitrile installed a quaternary phosphonium salt, giving **288** after treatment with HF•pyridine.

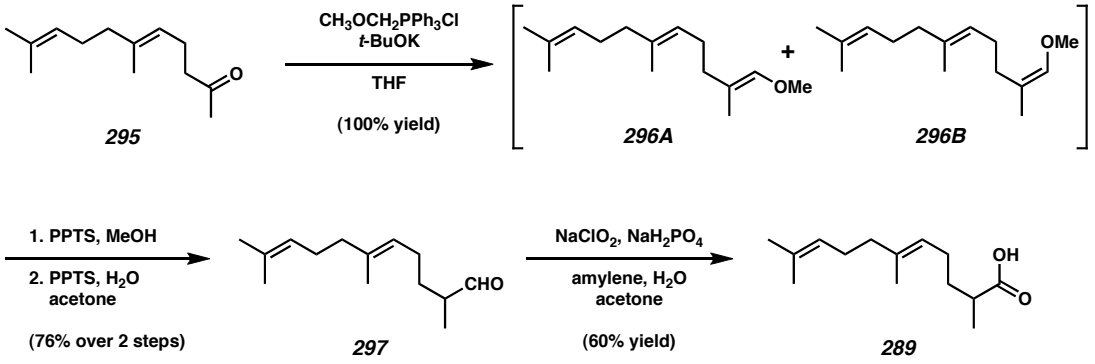
Scheme 4.4 Synthesis of the Aromatic Piece



The synthesis of the second fragment began with geranylacetone (**295**). When treated with methoxymethylene triphenylphosphonium chloride and base, **295** was

transformed to a mixture of methyl vinyl ethers **296A** and **296B** (Scheme 4.5). Conversion to the dimethyl acetal and hydrolysis afforded aldehyde **297** in good yield. Upon oxidation of **297** with buffered sodium chlorite, the requisite carboxylic acid **289** was complete.

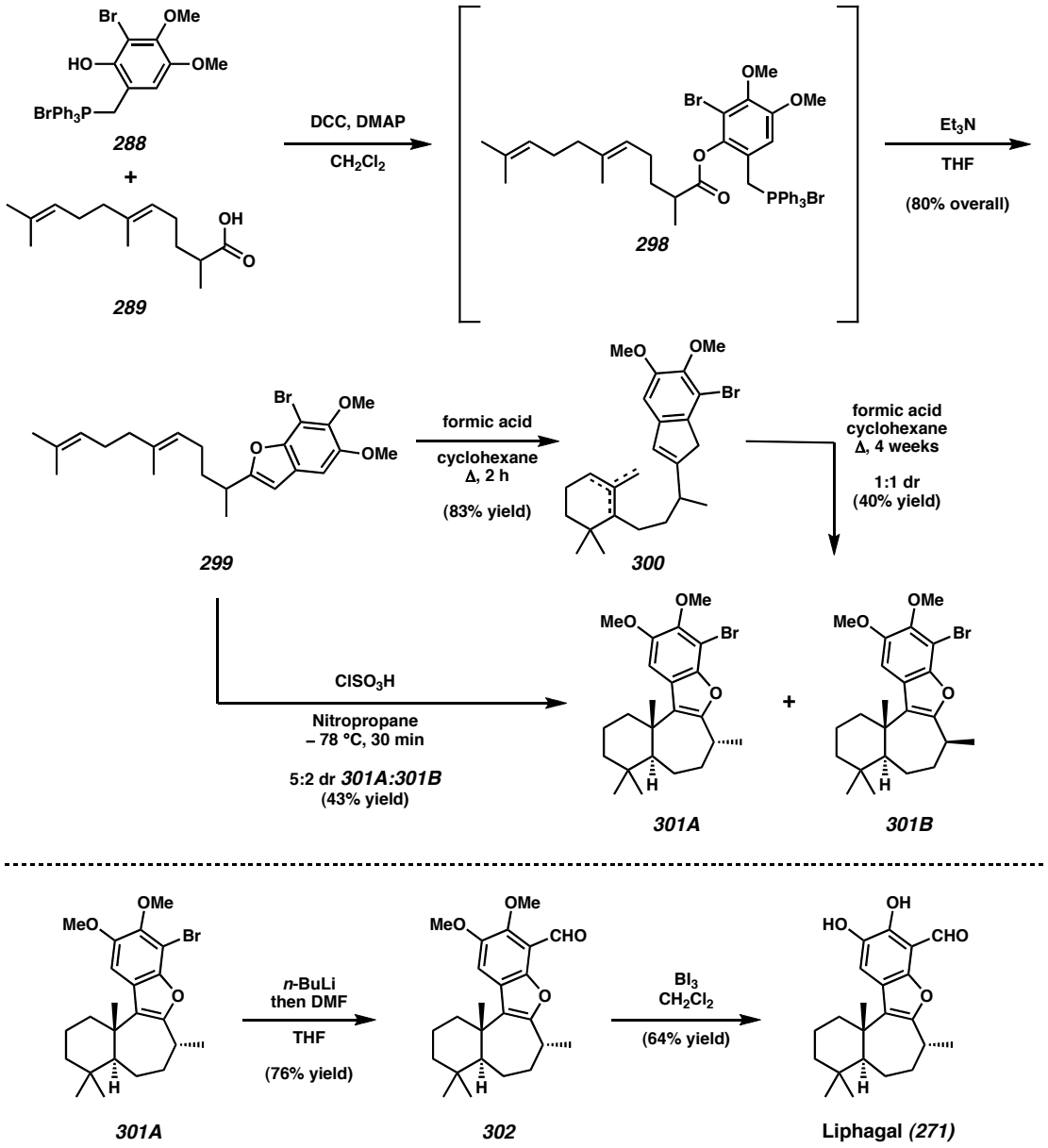
Scheme 4.5 Preparation of the Carboxylic Acid Coupling Partner



4.2.3 *Completion of Racemic Liphagal*

Once coupling partners **288** and **289** were complete, they were linked together using DCC and DMAP (Scheme 4.6). The intermediate **298** was not isolated, but rather subjected to mildly basic conditions, affecting an intramolecular Wittig cyclization of the resulting benzyl phosphonium ylide onto the carbonyl of the ester. The outcome was the completion of benzofuran **299**. Initially, the polyene cyclization approach was tested with formic acid as the promoter. Although the 6-membered ring cyclization to **300** readily occurred within two hours, more forcing conditions were necessary to close the 7-membered ring of the natural product. Unfortunately, the final ring closure had occurred with poor diastereoselectivity and modest conversion even over a four-week period.

Scheme 4.6 Completion of the Natural Product



Ultimately, these challenges were surmounted when the precursor **299** was treated with chlorosulfonic acid in nitropropane (as opposed to formic acid) at low temperature. In this case both requisite ring closures occurred during a thirty-minute timeframe, favoring the correct diastereomer **301A** in 5:2 dr for completion of the synthesis. Metal halogen exchange followed by DMF quench was used to install the aldehyde of **302**.

Didemethylation with BI_3 at –78 °C then completed Andersen's total synthesis of (±)-liphagal (**271**).[7]

4.3 First Retrosynthetic Analysis of Liphagal

4.3.1 *Challenges for Synthesizing Liphagal*

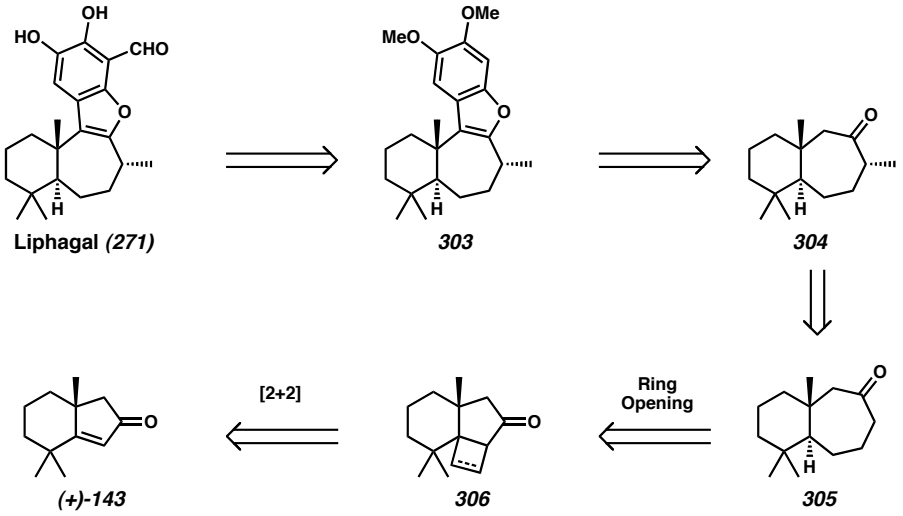
We became interested in liphagal (**271**) as a synthetic target for several reasons. First, the molecule has a unique carbocyclic architecture including a highly oxidized benzofuran ring system, saturated *trans*-fused [6-7] bicyclic domain, and three stereocenters. One of these is an all-carbon quaternary stereocenter. When we began the endeavor of synthesizing liphagal (**271**), the absolute stereochemistry of the natural product was unknown, but we anticipated that our enantioselective decarboxylative alkylation could be used to set the quaternary stereocenter, eventually determining the absolute stereochemistry of the natural product. Finally, our total synthesis would also serve to develop and apply new synthetic methods, while gaining insight about the chemistry of [6-7] bicyclic systems.

Andersen's synthesis employed a biosynthetic approach to the molecule in an elegant manner.[1] However, in light of the natural product's significant biologoical activity, we wanted an approach more amenable to the synthesis of analogues. Having derivatives in hand, we could probe the structure-activity-relationship of the natural product with respect to PI3K's, determining which moieties are necessary pharmacophores for activity.

4.3.2 *Retrosynthetic Analysis*

Examination of liphagal (**271**) revealed potentially sensitive catechol and aldehyde moieties; thus we opted to install them toward the end of the synthesis. Therefore, we thought liphagal (**271**) could arise from a protected benzofuran (**303**) (Scheme 4.7). We anticipated that the benzofuran might originate from the bicyclic ketone **(±)-304** via an annulation sequence. By installing the benzofuran at a late synthetic stage, there would be flexibility for variation of the aromatic ring for analog studies. Bicyclic methyl ketone **(±)-304** might be accessible from the simpler cycloheptanone **(±)-305**, which could be synthesized from an angularly-fused [6-5-4] cyclobutane or cyclobutene **306** via ring opening. The 4-membered ring of **306** could arise from photoaddition of ethylene or acetylene to a bicyclic enone **(+)-143**. We decided to prepare the enantiomer of the enone **(–)-143** present in the dichroanone synthesis since we thought that liphagal (**271**) belonged to the same enantiomeric series as natural (–)-dichroanone (**(–)-150**).[8]

Scheme 4.7 First Retrosynthetic Analysis of Liphagal

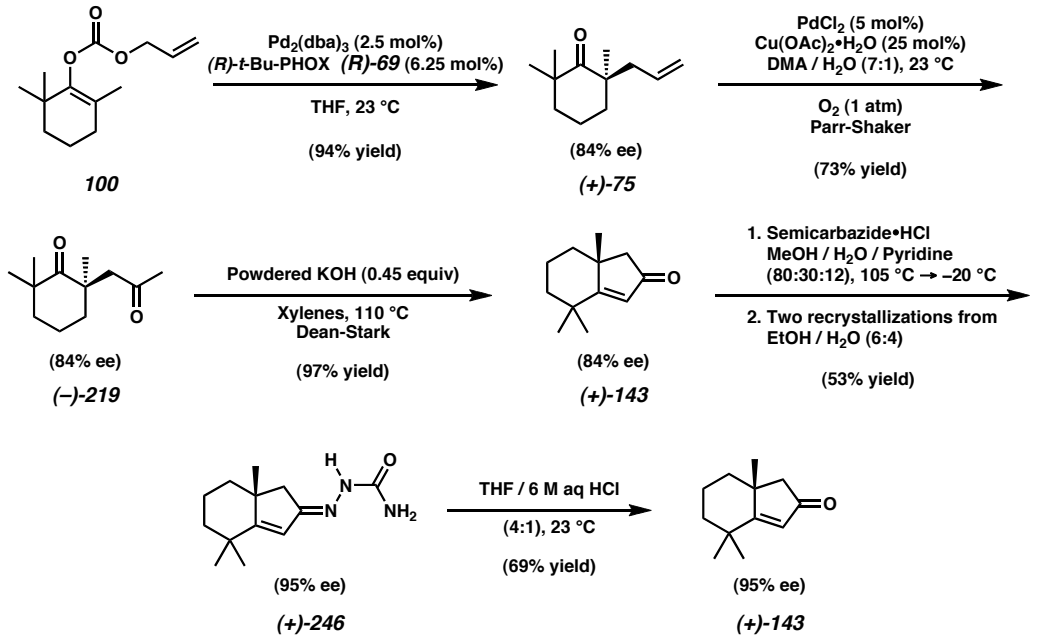


4.4 A Photochemical Approach to the [6-7] Ring System

4.4.1 *Synthesis of the Bicyclic Enone Antipode*

Our total synthesis effort commenced with enol carbonate **100**, prepared during our dichroanone synthesis.[8] Treatment of **100** with catalytic *(R)-t*-Bu-PHOX ***(R)-69*** and $Pd_2(dba)_3$ resulted in the preparation of allyl ketone **(+)-75** in 84% ee (Scheme 4.8). Wacker oxidation of **(+)-75** led to the 1,4-diketone **(–)-219** in good yield.[9] This compound was cyclized under aldol condensation conditions, furnishing the bicyclic enone **(+)-143** in high yield.[10] After transformation to the semicarbazone **(+)-246** followed by recrystallization, the ee was elevated to 95%. Hydrolysis under acidic conditions gave the enantioenriched bicyclic enone **(+)-143**, which would be used to investigate the preparation of the 7-membered ring of liphagal (**271**).[11]

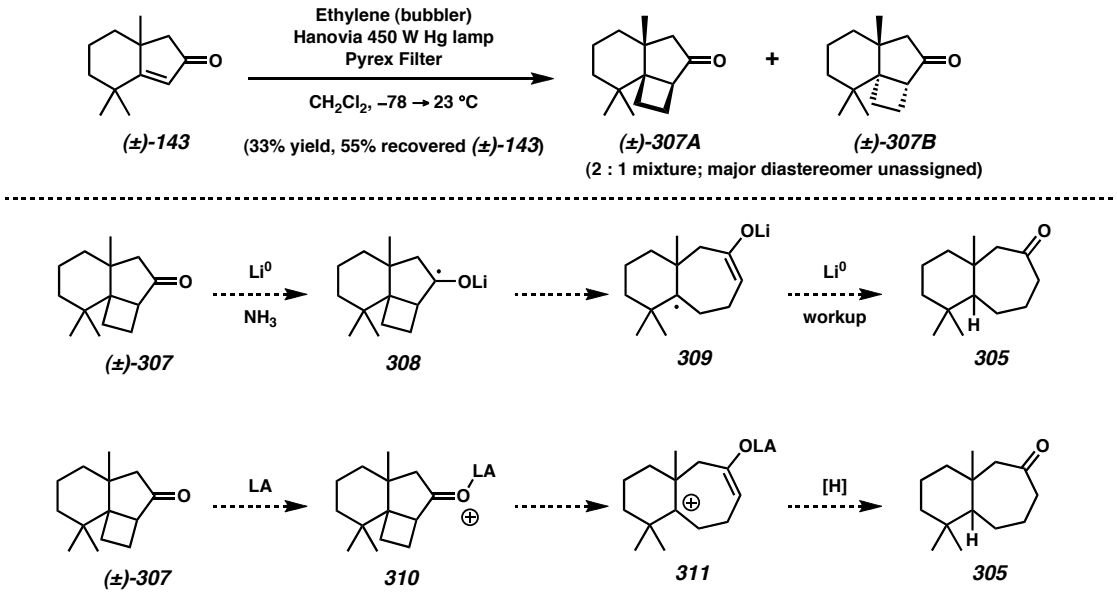
Scheme 4.8 Preparation of the Bicyclic Enone



4.4.2 *Photochemical Investigations*

To build a 7-membered ring compound from our [6-5] bicyclic enone, a 2-carbon spacer would need to be inserted. We hoped that photoaddition of ethylene in a [2 + 2] sense to our bicyclic enone **(+)-143** would accomplish this goal.[12,13] To this end, a solution of **(±)-143** in CH_2Cl_2 was saturated with ethylene gas at low temperature and irradiated with light from a medium-pressure mercury lamp. To our delight, a slow but productive cycloaddition occurred, and two diastereomeric, angularly fused cyclobutanes **(±)-307A** and **(±)-307B** were obtained in a modest yield (Scheme 4.9).

Scheme 4.9 Angularly-Fused Cyclobutanes

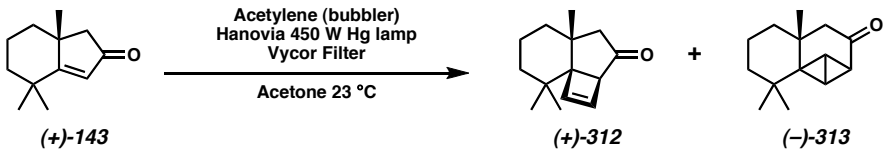


We believed that a reductive ring opening of the 4-membered rings of **(±)-307A** and **(±)-307B** could be achieved. One might envision reduction of the ketone to a cyclobutyl carbinyl radical **308**, possibly prone to cyclobutane ring fragmentation. A second 1-electron reduction of **309** and protonations might lead to the desired **(±)-305**. However, when we treated the cyclobutanes **(±)-307A** and **(±)-307B** with Li^0 in liquid

ammonia, none of the desired ring-opening product **(±)-305** could be isolated. An alternative approach was Lewis acid-mediated ring expansion of the 4-membered ring.[14] Coordination of the carbonyl by a Lewis acid would develop a partial positive charge on carbon. The developing cyclobutyl carbinyl cation **310** might rearrange with C–C bond fragmentation. However, we found no conditions effective for this transformation.

We hypothesized that switching from a cyclobutane to a more strained cyclobutene would facilitate ring opening.[15] To this end, we bubbled acetylene gas through a solution of the bicyclic enone **(+)-143** in acetone while irradiating the reaction through a vycor filter (Scheme 4.10).[16] Gratifyingly, the starting material was almost completely consumed in less than 12 hours. TLC analysis revealed the presence of at least two products. One was a single diastereomer of the desired angularly-fused cyclobutene **(+)-312**, a chromatographically stable, yet volatile solid.[17] At the time, we did not know which cyclobutene diastereomer had formed, but later investigations would reveal its identity. The second major product of the photoreaction was bicyclobutane **(–)-313**, a compound isolable in pure form, yet unstable to silica gel.[18,19]

Scheme 4.10 Photoadducts from the Acetylene [2 + 2]

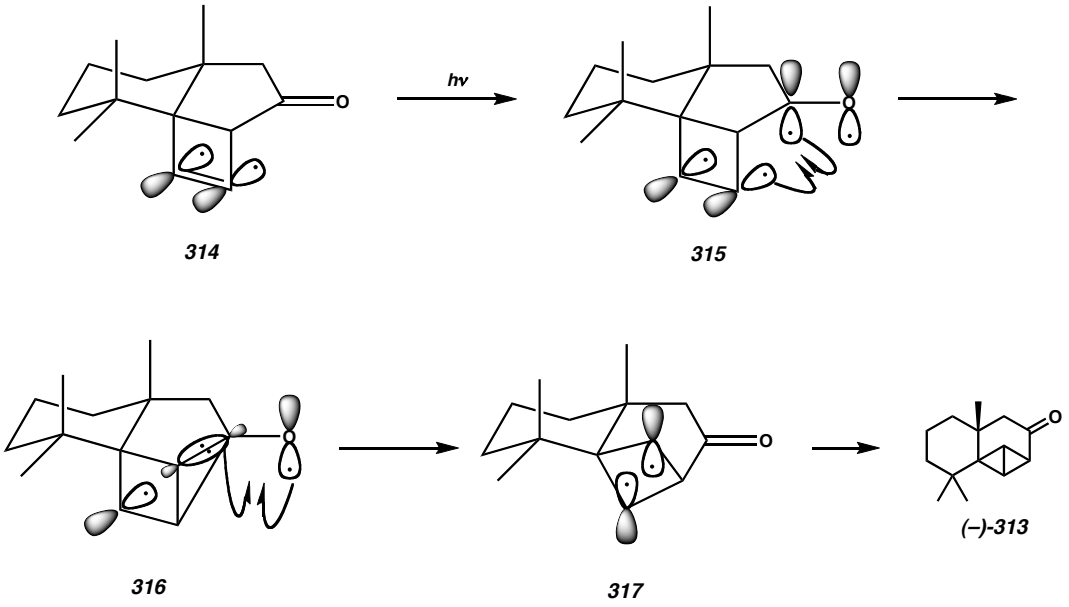


4.4.3 *A Photochemical Rearrangement Pathway*

Cyclobutanes bearing an olefin β,γ relative to a ketone can undergo an oxa-di-π-methane rearrangement under photochemical conditions.[20,21] The mechanism is believed

to begin with excitation of the carbonyl chromophore **314** (Scheme 4.11). Diradical **315** will then combine with the π-system of the olefin, leading to another diradical **316**. One of the bonds in the newly formed cyclopropane ring can then rupture, with concomitant regeneration of the carbonyl C–O π-bond. Once **317** has formed, the 1,3-diradical collapses, forming bicyclo[1.1.0]butane **(–)-313**.

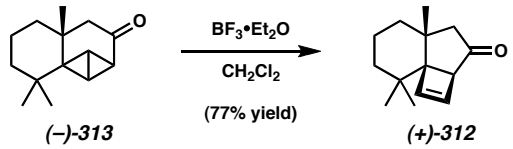
Scheme 4.11 Mechanism of the Oxa-Di-π-Methane Rearrangement



A significant portion of the mass balance in our acetylene photoaddition was bicyclobutane **(–)-313**, making our reaction somewhat unattractive as an early synthetic step in a total synthesis. Gratifyingly, when pure **(–)-313** was treated with BF_3•Et_2O in CH_2Cl_2, clean conversion to a single diastereomer of **(+)-312** was observed (Scheme 4.12).[22,23] This cyclobutene had the same relative configuration as the one directly isolated from the acetylene photoaddition, meaning our [2 + 2] method could effectively install vicinal all-carbon quaternary stereocenters in greater than 99:1 dr. Operationally,

we could perform the photoaddition, chromatograph the crude products, then treat the mixture of **(+)-312** and **(–)-313** with BF_3•Et_2O, obtaining diastereopure **(+)-312**.

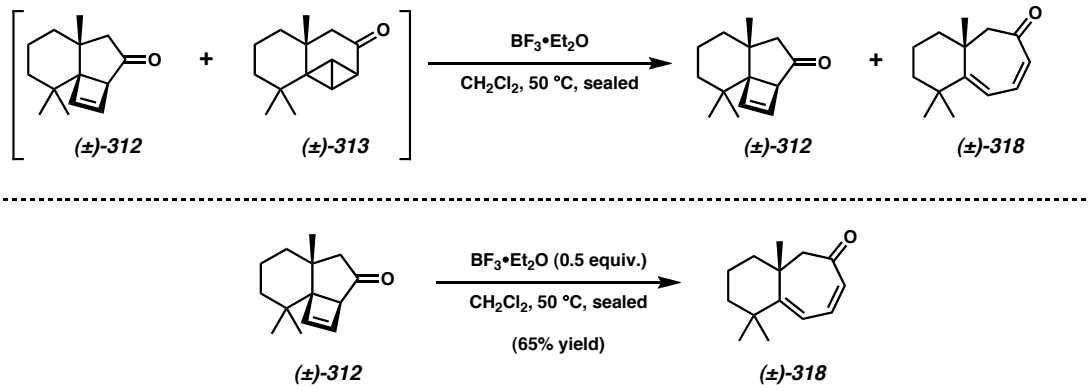
Scheme 4.12 Reversion of the Bicyclobutane to the Cyclobutene



4.4.4 *Formal 4π Electrocyclic Ring Expansion*

Heating a sample of unseparated **(±)-312** and **(±)-313** that had been treated with BF_3•Et_2O led to the formation of a new product (Scheme 4.13). Careful isolation showed that it was a doubly unsaturated, bicyclic ketone **(±)-318**. This serendipitous discovery allowed for the streamlined synthesis of the [6-7] carbocyclic framework we needed. Later we learned that **(±)-318** could be prepared directly from the cyclobutene **(+)-312**, in what constituted a formal 4π-electrocyclic ring-opening.[24]

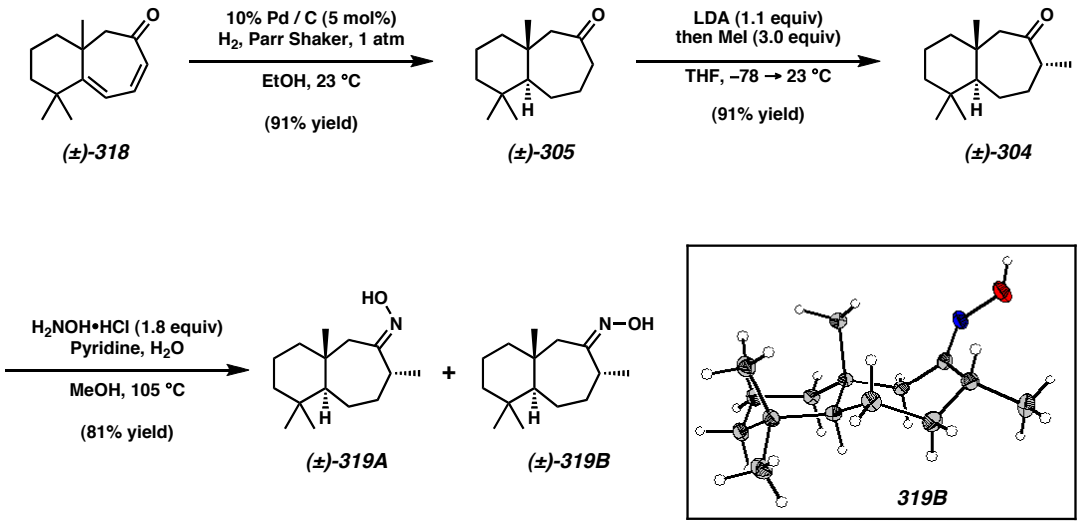
Scheme 4.13 Ring Opening of the Cyclobutene



4.4.5 *Elaboration of the [6-7] Core*

The bicyclic dienone **(±)-318** could be readily hydrogenated to the fully saturated cycloheptanone **(±)-305** in good yield (Scheme 4.14). Fortunately, a single diastereomer was produced during this transformation. At the time, we were unable to assign the relative stereochemistry of the compound because it was recalcitrant to nOe analysis. We attempted methylation of the carbonyl using LDA and iodomethane trapping, which produced methyl ketone **(±)-304** as a single diastereomer in high yield. This compound was then converted to a mixture of two oxime isomers **(±)-319A** and **(±)-319B**, one of which was obtained in crystalline form suitable for X-ray crystallographic analysis. The structural data revealed that all stereochemistry present was analogous to that of the natural product. Our next major task was installation of the benzofuran present in liphagal (**271**).

Scheme 4.14 Functionalization of the [6-7] Ring System



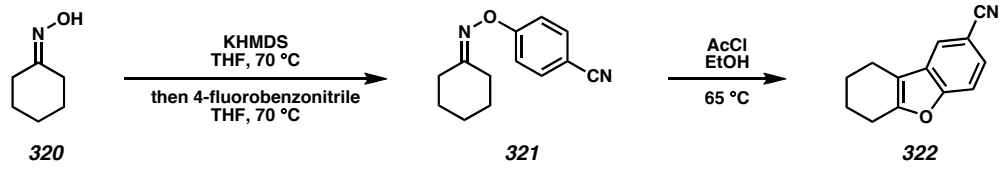
4.5 Attempts to Install the Benzofuran Moiety of Liphagal

4.5.1 *An Aryloxime Model System*

We had a number of systems designed to model benzofuran installation. The first concept we explored was based on the Fischer indole synthesis.[25] In a Fischer indole synthesis, an aryl hydrazone undergoes a [3,3] sigmatropic rearrangement, ultimately leading to an indole. There were a few examples of the analogous transformation with a *O*-aryloximes.[26,27]

As a model study, we deprotonated the oxygen atom of cyclohexanoxime (**320**) with KHMDS and added 4-fluorobenzonitrile, furnishing the desired *O*-aryloxime **321** (Scheme 4.15). The choice and number of equivalents of base in this transformation were both crucial. Weaker bases led to complex product mixtures, as did excess base.

Scheme 4.15 Aryloxime Cyclization Reaction



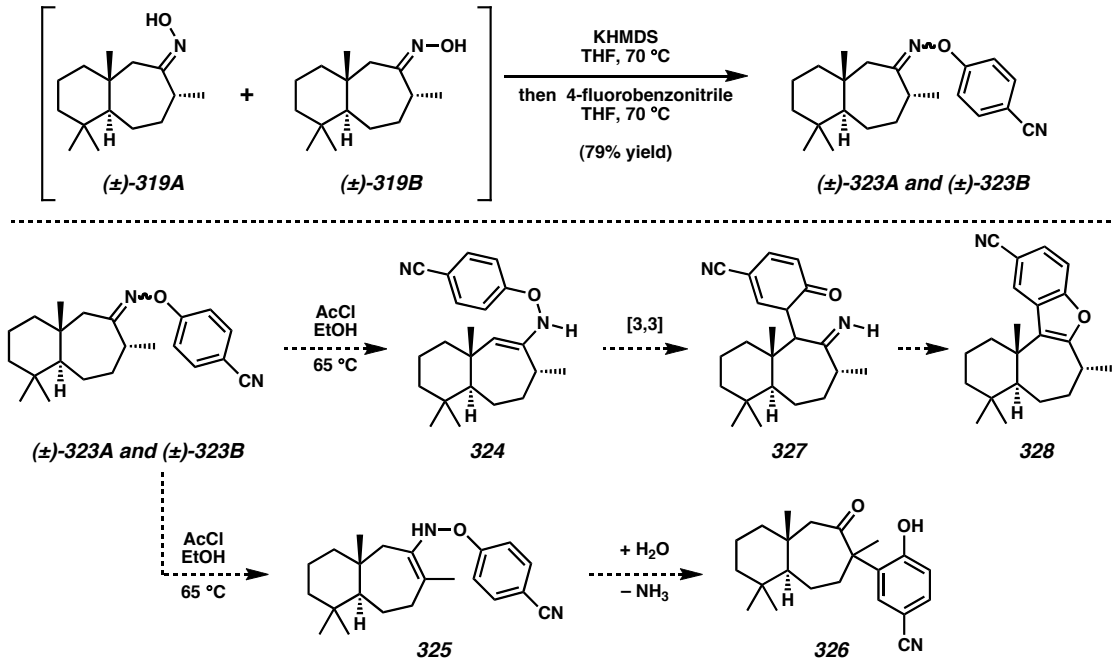
320 *321* *322*

With model *O*-aryloxime **321** in hand, we screened several conditions for the benzofuran synthesis. Ultimately, we found very mild conditions that could achieve the desired transformation. When **321** was added to a pre-stirred solution of acetyl chloride in ethanol and warmed to 65 °C, an acid-promoted sequence of events led to the desired benzofuran **322**. With a working reaction in hand, we began investigation in the context of the liphagane framework.

4.5.2 *An Aryloxime Approach to Liphagal*

We took the readily prepared mixture of oximes **(±)-319A** and **(±)-319B** and synthesized aryloximes **(±)-323A** and **(±)-323B**, without separation. We believed the favored enehydroxylamine tautomer **324** would be formed when **(±)-323A** and **(±)-323B** were treated with acid (Scheme 4.16). Although we realized the difficulty of making a C–C bond near an all-carbon quaternary stereocenter, we anticipated that an intramolecular [3,3] sigmatropic cyclization mode would overcome this challenge. Unfortunately, there was no desired C–C bond formation at the desired position under acidic conditions. We speculated that an alternative enehydroxylamine tautomer **325** formed during the reaction, and [3,3] sigmatropic rearrangement led to a product **326** incapable of forming a benzofuran. Despite our efforts, we were unable to prepare the desired benzofuran **328** using the aryloxime methodology.

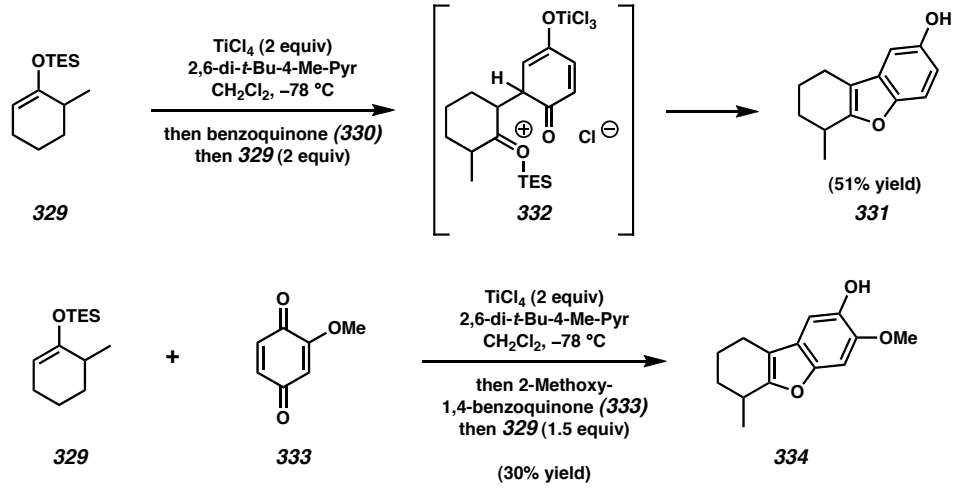
Scheme 4.16 Failed Attempts to Prepare a Benzofuran Using an *O*-Aryloxime



4.5.3 *A Mukaiyama Michael-Based Benzofuran Synthesis*

The problem of regioselective C–C bond formation necessary for the benzofuran installation merited attention. We thought that regioselectivity in the bond-forming event might be possible using a preformed enolate. A model system to test this hypothesis was designed. We anticipated that silyl enol ether **329** might undergo conjugate addition into 1,4-benzoquinone (**330**) in the presence of Lewis acid (Scheme 4.17). After the initial C–C bond formation, a condensation would lead to a substituted benzofuran **331**. To the best of our knowledge, this type of reaction was unexplored in the literature.

Scheme 4.17 Benzoquinone Mukaiyama Michael Model System

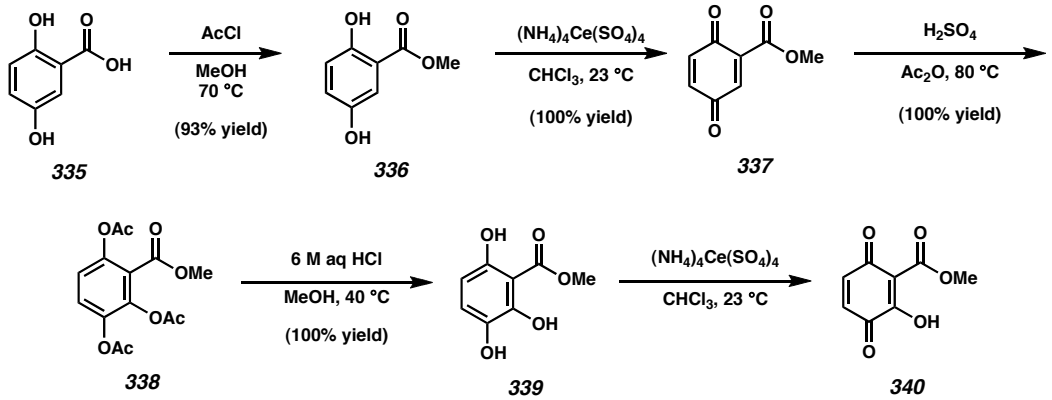


We prepared the known silyl enol ether **329** and screened its reactivity with 1,4-benzoquinone (**330**) in the presence of various acid promoters. We discovered that little or no productive reaction occurred in the absence of base, but when 2,6-di-*t*-Bu-4-methyl pyridine was employed for this transformation, it appeared to have no interaction with the Lewis acid used. One could envision the propensity of intermediate **332** toward

rearomatization. If this happened, an equivalent of HX would be generated. In the absence of base, the acid could desilylate the starting material; often we saw 2-methylcyclohexanone during these reactions. $TiCl_4$ emerged as a superior promoter for the overall transformation, and optimization revealed 2.0 equivalents of the Lewis acid relative to the benzoquinone (**330**) to be ideal. Under fully optimized conditions, hydroxybenzofuran **331** was accessible in 51% isolated yield from benzoquinone.

Other more complex quinone acceptors could be envisioned. 2-Methoxy-1,4-benzoquinone (**333**) also underwent a productive reaction with **329** in 30% yield based on benzoquinone. Of interest, **334** was the only benzofuran isolated, an indication that the 5-position of **333** was the most electrophilic. Based on this observation, we began to prepare more complex benzoquinones for this chemistry during our initial optimization stage (Scheme 4.18). With the right substrate design, the Mukaiyama Michael product could contain functionality similar to liphagal (**271**) (Scheme 4.19).

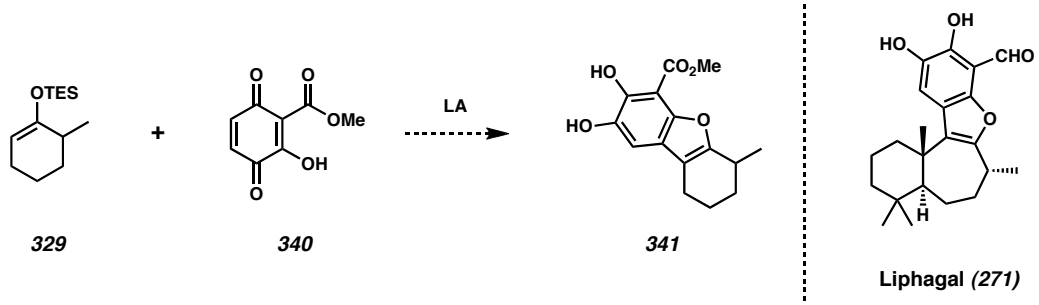
Scheme 4.18 Synthesis of a More Substituted Quinone



To this end, commercially available gentisic acid (**335**) was esterified in acidic methanol, furnishing **336** in high yield.[28] A chloroform solution of the methyl ester **336**

was stirred with solid ceric ammonium sulfate,[29] producing the unstable *p*-quinone **337** in near-quantitative yield after a filtration workup. Thiele-Winter acetoxylation of the solid quinone in acetic anhydride with sulfuric acid gave a remarkably clean conversion to triacetate **338**.[30] Acidic hydrolysis of the three acetates led to trihydroxyarene **339** in excellent yield. When **339** was stirred with ceric ammonium sulfate in chloroform, **340** became available. One could envision that addition of silyl enol ether **229** into the most electrophilic carbon of **340** (the 6-position) might ultimately lead to a substituted benzofuran **341** remarkably similar to liphagal (**271**) (Scheme 4.19). However, we were unable to prepare **341** using **340** presumably due to the instability of **340** in the presence of both Lewis acids and BrØnstead bases. It was also surprisingly difficult to functionalize the vinylogous acid oxygen of **340**. Thus, we discontinued the use of this complex *p*-benzoquinone for obtaining a benzofuran.

Scheme 4.19 A Complex Quinone Model System

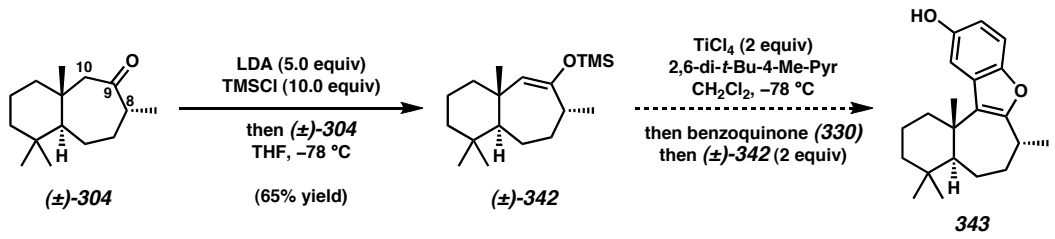


4.5.4 *Mukaiyama Michael Approach to Liphagal*

Although the complex benzoquinone **340** was not amendable to our model system, the success we had with **330** and **333** was encouraging. Thus, we began to synthesize a silyl enol ether appropriate for the synthesis of liphagal (**271**). When methyl

ketone **(±)-304** was added to a preformed mixture of TMSCl and LDA at –78 °C, silyl enol ether **(±)-342** was isolated as the major product (Scheme 4.20).[31] When other methods, such as hard enolization with silyl triflate quench or soft enolization, were used, **(±)-342** was never observed in the product mixture.[32] As we had observed with the aryl oximes **(±)-323A** and **(±)-323B**, there seemed to be a strong tendency toward generation of an olefin between C(8) and C(9) in these systems.

Scheme 4.20 Attempted Mukaiyama Michael Reaction

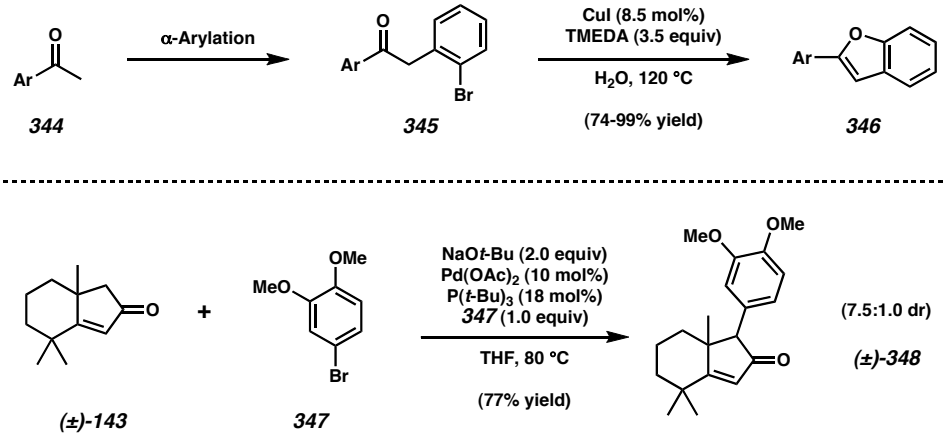


With silyl enol ether **(±)-342** in hand, we tested our benzoquinone Mukaiyama Michael strategy with *p*-benzoquinone (**330**). Unfortunately, we never observed C–C bond formation at the correct position. Usually, desilylated ketone **(±)-304** was the major product isolated. Qualitatively, we observed that **(±)-342** was much more acid-labile than the corresponding silyl enol ether **329** (Scheme 4.19). We tested different Lewis acids, silyl groups, and ingredient addition orders, but we never obtained the desired benzofuran **343**. Perhaps the transition state for C–C bond formation was too sterically hindered, or maybe transannular strain within the 7-membered ring was responsible for the lack of desired reactivity.

4.5.5 *α-Arylation Strategy*

In addition to our aryloxime and Mukaiyama Michael concepts for benzofuran synthesis, we had another model. Recently, SanMartin and Domínguez demonstrated that α-aryl ketones bearing *ortho* halogenation (e.g., **345**) could undergo a smooth transformation to benzofurans such as **346** (Scheme 4.21).[33] The reactions were typically run "on water"[34] using catalytic CuI and superstoichiometric TMEDA. We found that this chemistry was readily duplicated on simple compounds, but we needed a method for installing an analogous aromatic ring in the real system. Hence, we investigated α-arylations of a model ketone **(+)-143** using standard Buchwald-Hartwig conditions.[35] Gratifyingly, upon heating **(+)-143** and 4-bromoveratrole (**347**) in the presence of NaO*t*-Bu, $Pd(OAc)_2$, and P(*t*-Bu)$_3$, aryl ketone **(±)-348** was produced in good yield.

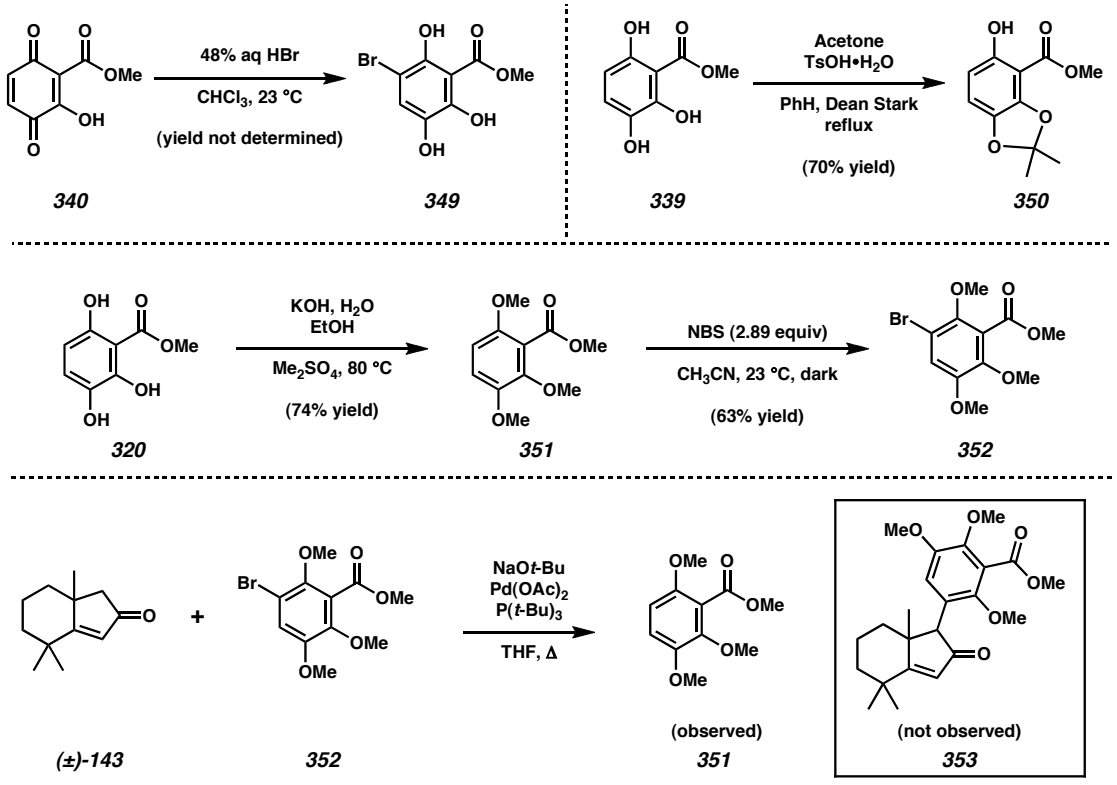
Scheme 4.21 Arylation/CuI Cyclization Strategy



With this initial result using **(±)-143**, we wanted to test more substituted aryl halide partners related to **349** in the Buchwald-Hartwig coupling. To this end, we treated the quinone **340** prepared earlier from gentisic acid (**335**) with HBr, achieving

chemoselective bromination of the arene. (Scheme 4.22). Although the transformation worked, the compound **349** was chromatographically unstable and unsuitable for further synthetic manipulation. Protection of the hydroxy groups would be necessary to improve compound stability. Triol **339** could be converted to its acetonide **350** in 70% yield, but the chemistry was hard to reproduce on larger scale. The best method for installation of bromide functionality began with global methylation of **339**. This transformation was challenging because use of strong bases led to decomposition during the protection. Nevertheless, carefully controlled use of KOH in dimethyl sulfate and ethanol furnished **351** in 74% yield from **339**. This compound was regioselectively brominated with excess *N*-bromosuccinimide in acetonitrile, giving the desired **352**.

Scheme 4.22 Synthesis of a Complex Aryl Halide

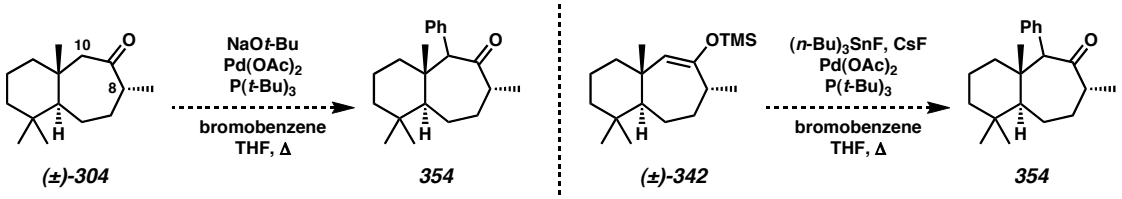


With aryl bromide **352** in hand, we tried to α-arylate **(+)-143** under conditions previously utilized to prepare **(±)-348**. Unfortunately, only dehalogenated arene **351** was observed under the conditions tested. Although this indicated that oxidative addition was possible, the steric demand for later steps in the catalytic cycle had become too great. Although minor optimizations were tested for preparation of **353**, we could not achieve arylation of **(+)-143** with **352**.

4.5.6 *α-Arylation Attempts on the [6-7] Bicyclic System*

The next step in our investigation was the attempted arylation of methyl ketone **(±)-304**, a substatrate further along the synthetic route to liphagal (**271**). Test reactions did not lead to any of the desired C–C bonded product **354** (Scheme 4.23). We speculated that α-arylation of C(8) was perhaps competing with the desired pathway. Attempts were made using modified conditions for α-arylation of silyl enol ethers.[36] However, when **(±)-342** was tested using these methods, only **(±)-304** was observed. Considering the difficulty encountered with the requisite benzofuran C–C bond formation on our [6-7] systems, our retrosynthesis needed revision.

Scheme 4.23 Attempted Arylation of the [6-7] System

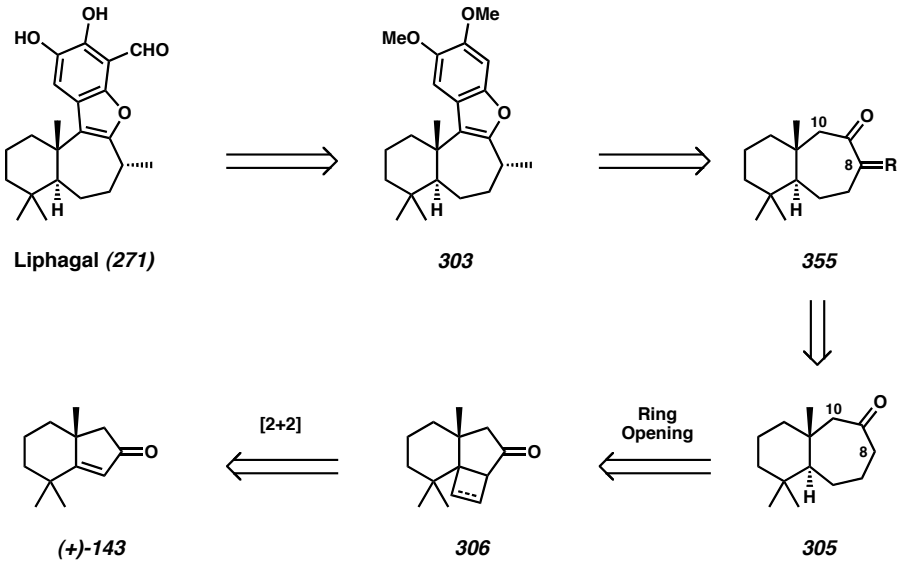


4.6 Positional Blocking Strategies Applied to the Key Benzofuran Synthesis

4.6.1 *Retrosynthetic Revisions*

Our previous experiments on the [6-7] ring system had demonstrated the difficulty of forming an exocyclic C–C bond at C(10) (Scheme 4.24). One reason for this observation could be competitive reactivity at C(8). We hypothesized that mitigation of unwanted C(8) chemistry would be achieved by completely blocking the position, forcing chemistry at C(10). Modifying the previous retrosynthesis, the benzofuran **303** could arise from a C(8)-blocked species **355**. This carbonyl-containing entity could be prepared from **(±)-305**. Once the key carbon bond at C(10) was established, the functionality at C(8) could be altered for installation of the requisite methyl group. Otherwise, our retrosynthetic analysis would remain unchanged.

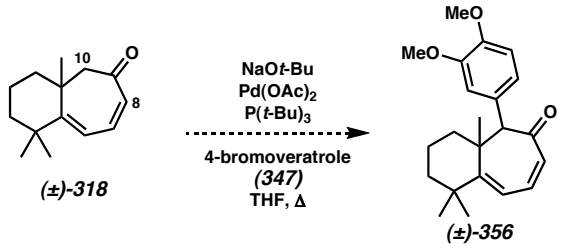
Scheme 4.24 Second Retrosynthesis of Liphagal



4.6.2 *Attempted Arylation of the Dienone*

Compound **(±)-318** displayed the necessary characteristics we were searching for during the retrosynthetic revisions. Given the sp^2 hybridization at C(8), enolization should occur selectively at C(10). Thus, we attempted Buchwald-Hartwig α-arylation of **(±)-318** using 4-bromoveratrole (Scheme 4.25). A productive reaction occurred; however, the purified product was not arylated at C(10). Control reactions in the absence of Pd and phosphine ligand revealed that **(±)-318** was unstable in the presence of NaO*t*-Bu. The product of the attempted arylation did contain a veratrole group, but its location on the [6-7] framework could not be unambiguously assigned. Hence, we discontinued arylation studies with **(±)-318**.

Scheme 4.25 Attempted Dienone Arylation

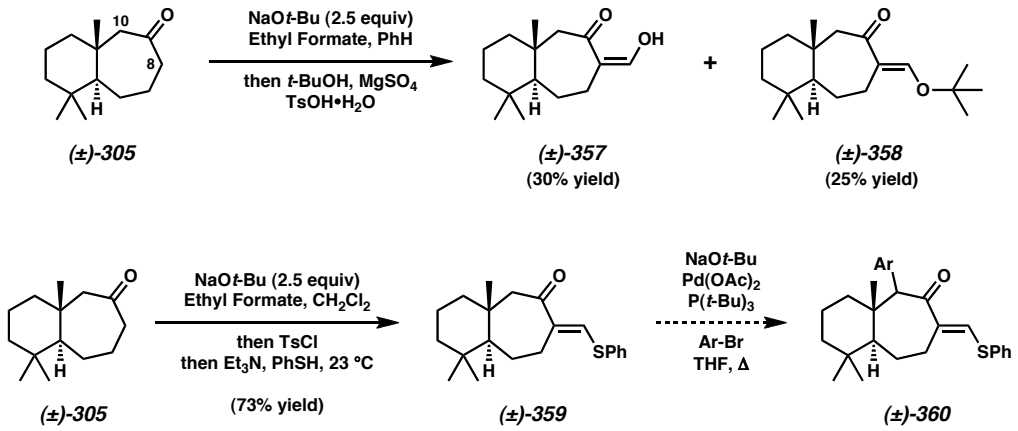


4.6.3 *Exocyclic Olefin Substrates*

Although substrate **(±)-318** was not amenable to arylation, we anticipated that an exocyclic olefin could efficiently block C(8). Ketone **(±)-305** was subjected to excess ethyl formate and NaO*t*-Bu, followed by an attempted vinylogous esterification using *t*-BuOH (Scheme 4.26). We were pleased to observe both the vinylogous acid **(±)-357** and the vinylogous ester **(±)-358**, each in modest yield. Conceptually, one could envision conversion of the exocyclic methylene of **(±)-357** or **(±)-358** to a methyl group (Scheme

4.26) via reduction. Since the vinylogous acid **(±)-357** was not ideal for α-arylation, and conversion to **(±)-358** was difficult, we targeted a vinylogous thioester **(±)-359**.

Scheme 4.26 Vinylogous Substrates



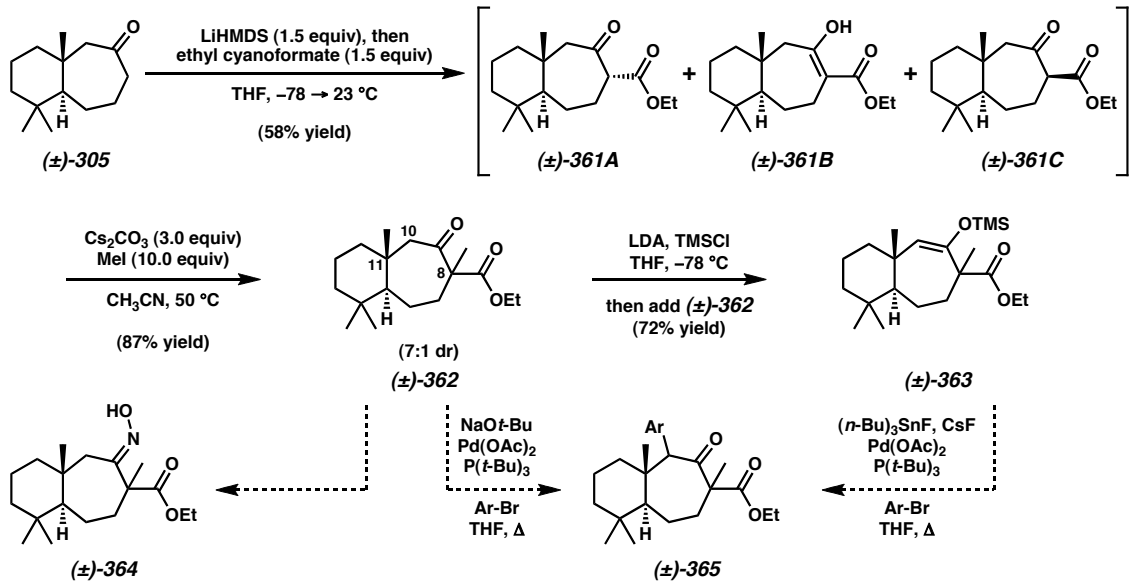
The vinylogous acid **(±)-357** was treated with TsCl, and the intermediate vinylogous mixed anhydride underwent conjugate addition/elimination with thiophenol. Thus, in a one-pot sequence, **(±)-305** could be rapidly transformed into **(±)-359**. When α-arylation of vinylogous thioester **(±)-359** was attempted, we observed no C–C bond formation at C(10), but rather vinylogous saponification to give **(±)-358**. To remedy this situation, we tried to prepare an *N*-methyl, *N*-phenyl vinylogous amide, but efforts to do so were fruitless. Considering these results, we decided to develop an alternative blocking strategy.

4.6.4 *Quaternization of C(8)*

Observing that sp^2 hybridization of C(8) was not a viable method for achieving arylation of C(10), we decided to transform C(8) into a non-enolizable, quaternary sp^3 carbon. Treatment of bicyclic ketone **(±)-305** with LiHMDS followed by ethyl

cyanoformate at low temperature gave a tautomeric mixture of the β-ketoesters **(±)-361A**, **(±)-361B**, and **(±)-361C** (Scheme 4.27). This crude isolate was immediately methylated in acetonitrile, furnishing quaternized **(±)-362** in high dr.[37] We attempted α-arylation of **(±)-362**, but did not observe any bond formation at C(10).

Scheme 4.27 Quaternized Substrates



At this point, we questioned whether enolization was even possible. Looking at **(±)-362** we could see that transannular strain might develop between substituents at C(8) and C(11) during an enolization. Despite this, silyl enol ether **(±)-363** was readily obtained when **(±)-362** was treated with a preformed mixture of LDA and TMSCl.[31] We also tested the Hartwig-modified conditions for α-arylation of **(±)-363**,[36] but these efforts were fruitless. The silyl enol ether was also screened with our benzoquinone Mukaiyama Michael conditions, yet no C–C bonded product could be isolated. Perhaps most surprising of all, when we attempted several conditions for oxime formation on β-

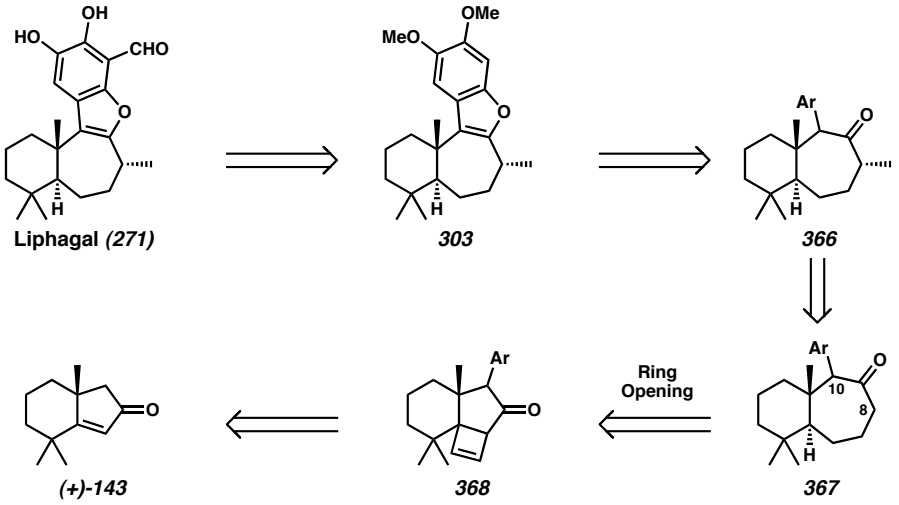
ketoester **(±)-362** at C(9), no condensation was realized. This meant that we could not access an *O*-aryloxime for a [3,3] sigmatropic rearrangement. Based on all of these observations, we concluded that the environment around C(10) was not conducive to C–C bonding, so more retrosynthetic revisions were in order.

4.7 Approaches Based on Arylation of [6-5] Systems

4.7.1 *Retrosynthetic Revisions*

A somewhat significant retrosynthetic revision was required to address the necessary C(10) exocyclic C–C bond construction. The most efficacious strategic adjustment might be to arylate a [6-5] carbocyclic species and subsequently perform the ring expansion (Scheme 4.28). This meant that the arene would be carried through many synthetic steps prior to benzofuran closure. We were unsure of what effects this would have on later stereoselective transformations but believed that previously developed chemistry would be applicable to this new strategy.

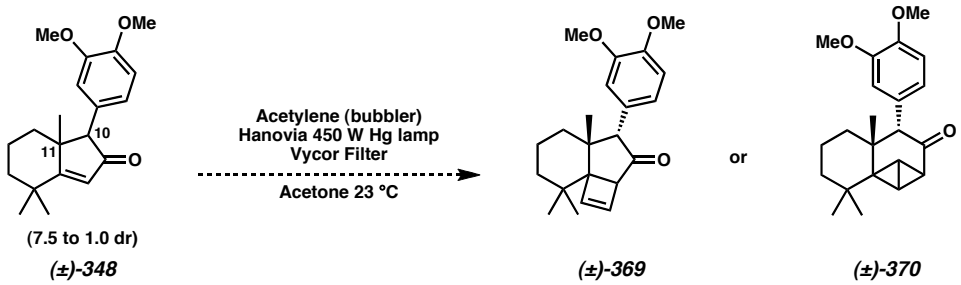
Scheme 4.28 A New Retrosynthesis



4.7.2 *Attempted Photoaddition to an Aryl Enone*

The aryl enone **(±)-348** previously prepared in the context of a model system appeared to be a good starting point for further investigations (Scheme 4.29). Although we did not know which diastereomer of **(±)-348** was the major one, it likely had an *anti* relationship between the aryl group at C(10) and the axial methyl at C(11). This assumption was made based on the crystallographic data observed for Michael adduct **233** from the dichroanone synthesis, which existed in a 10.7:1.0 dr.[8] Results obtained later in the synthesis would further support our hypothesis. We ran an acetylene [2 + 2] photocyclization with **(±)-348** under conditions similar to those used for **(+)-312**, but never observed a productive reaction.

Scheme 4.29 Photochemistry of the Aryl Enone



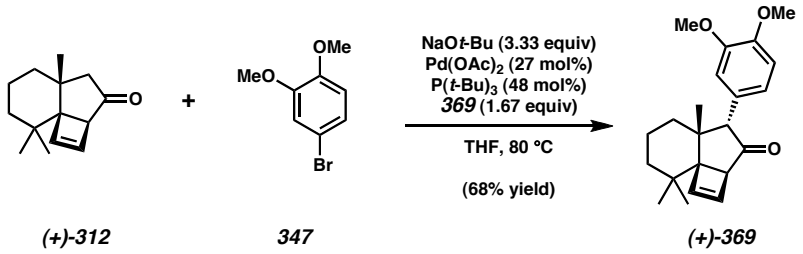
Two theories might explain the lack of reactivity, the first of which is a steric argument. Given the relative stereochemistry described, the aryl group of **(±)-348** would sit directly beneath the olefin moiety. This might block the α-face, preventing the first photoaddition step. The axial quaternary methyl groups would potentially hinder the β-face of the olefin as well. Another argument for the lack of reactivity could be a photophysical one. Presumably, the first step of the net [2 + 2] cycloaddition is an

excitation of the enone chromophore. The nearby aryl group of **(±)-348** has a significant absorption cross section in the UV and lies physically close to the enone. Thus, a fluorescent resonant energy transfer from the excited enone to the aryl group could induce a new state incapable of exciplex formation with acetylene.

4.7.3 *Successful Arylation of the Keto-Cyclobutene*

Our only other option for C–C bond formation at C(10) was to α-arylate the angularly-fused cyclobutene **(+)-312**. We were delighted to find that **(+)-312** reacted cleanly with 4-bromoveratrole under the Buchwald-Hartwig conditions, furnishing a single diastereomer of **(+)-369** (Scheme 4.30). At the time, we did not know the relative stereochemistry of the aryl ketone **(+)-369**, but a serendipitous discovery would later elucidate this matter. The arylation, though clean, required a slight excess of 4-bromoveratrole, elevated catalyst loadings, and longer reaction times in part due to steric demands. Nonetheless, we were pleased to finally have the C–C bond necessary for the benzofuran moiety of liphagal (**271**).

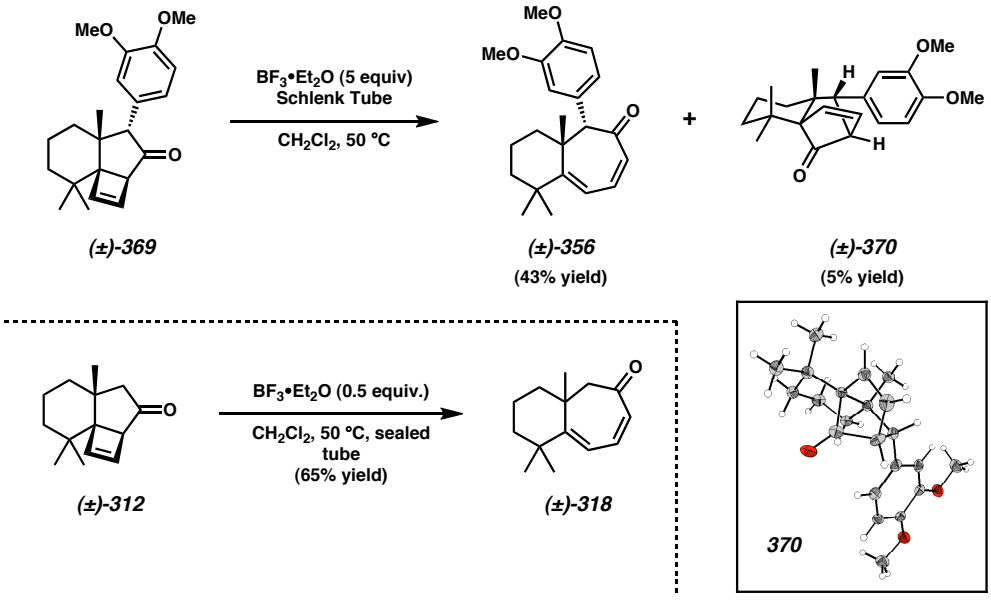
Scheme 4.30 Arylation of the Cyclobutene



4.7.4 *Changes In the Ring Expansion*

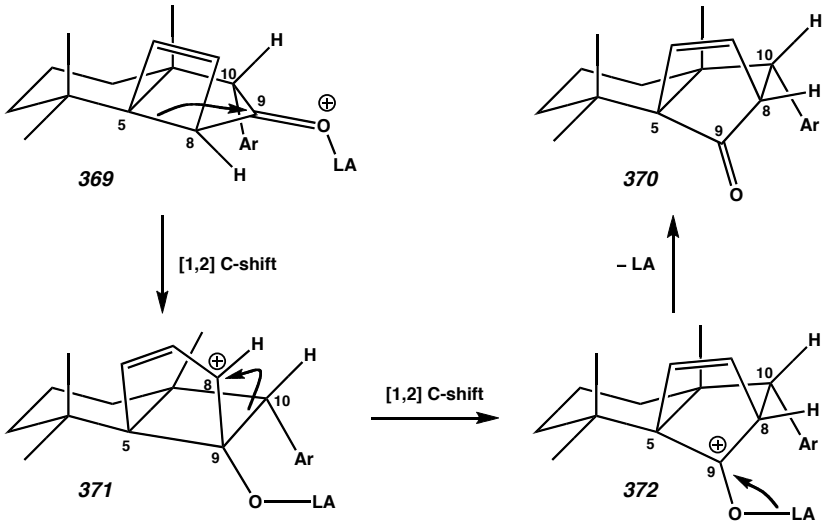
Once we had formed the requisite C–C bond at C(10), we tested our formal retro 4π electrocyclization chemistry using **(+)-369**. Gratifyingly, we could advance material through to **(±)-356** without loss of stereochemical information at C(10) (Scheme 4.31). Despite this, we noticed a substantial drop in yield for this reaction compared to the analogous transformation (lacking the aryl group) from **(+)-312** to **(±)-318**. Noticeable quantities of an unusual side product, **(±)-370**, were now also present. Fortuitously, X-ray quality crystals of the polycyclic ketone **(±)-370** could be obtained, and its relative stereochemistry was established. We had encountered a rearrangement mode of cyclobutene-containing ketones described by Cargill.[38] Clearly, small changes to our cyclobutene (*c.f.* **(+)-312** and **(+)-369**) could have dramatic effects upon its reactivity.[39]

Scheme 4.31 Side Product Formation During the Electrocyclic Opening



Mechanistically, the transformation from **(+)-369** to **(±)-370** happens by a series of concerted C–C bond migrations.[38] Activation of the carbonyl with Lewis acid induces development of a partial positive charge at C(9) (Scheme 4.32). The bond between C(5) and C(8) of **369** undergoes a [1,2] C-shift, generating an allylic carbocation **371**. The bond between C(9) and C(10) of the resulting cyclobutane then migrates via [1,2] C-shift into the carbocation at C(8), generating homoallylic carbocation **372** centered at C(9). Lewis acid dissociation quenches the carbocation, giving **(±)-370**. Based on the relative stereochemistry of **(±)-370**, we could backtrack through this mechanism, determining the relative configuration of **(+)-369**, **(±)-318**, and by analogy, **(±)-348** (Scheme 4.29).

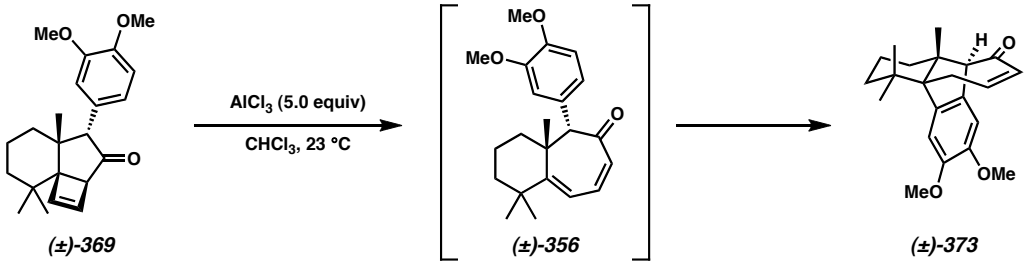
Scheme 4.32 Mechanism of the Cargill Rearrangement



It was worthwhile to screen other Lewis acids for the electrocyclic ring opening. Many others we tested led to the Cargill product **(±)-370**. Curiously, when we treated **(±)-369** with $AlCl_3$ in $CHCl_3$, no Cargill product **(±)-370** was observed. However, a new species **(±)-373** was noticed instead of the desired **(±)-356** (Scheme 4.33). After

confirmation of its relative stereochemistry and structure, we could see that **(±)-373** was the result of an intramolecular Friedel-Crafts cyclization of **(±)-356**. This gave us some insight into the conformational preferences of aryl ketone **(±)-356**. Apparently, the electron-rich veratrole moiety sits directly underneath the olefinic π-system. When the carbonyl is activated, a 1,6-addition of the arene into the doubly unsaturated system may occur.

Scheme 4.33 Observation of Friedel-Crafts Chemistry



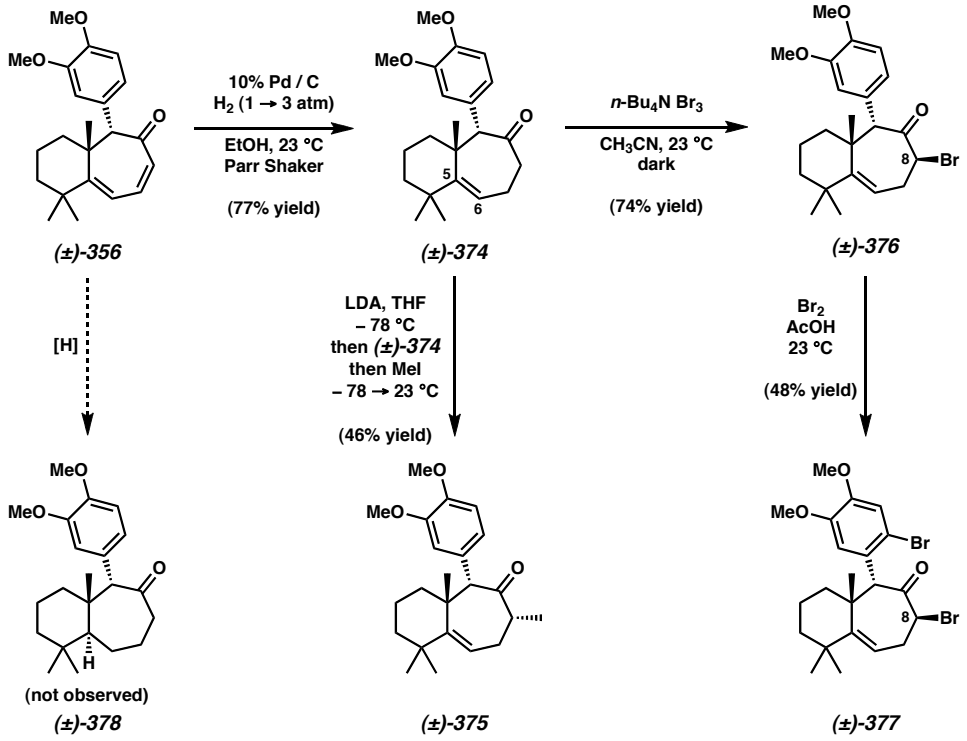
4.7.5 *Effects of the Aryl Group on Subsequent Chemistry*

The observation of the Friedel-Crafts chemistry presaged some of the discoveries we would later make. With arylated dienone **(±)-356** in hand, we tested our hydrogenation reaction developed for the transformation of **(±)-318** to **(±)-305**. A reaction occurred, but the product, **(±)-374**, still contained the trisubstituted olefin spanning C(5) and C(6) (Scheme 4.34). More forcing conditions were attempted to reduce this alkene, but all were unsuccessful. The close proximity of the sterically large arene and C(5)–C(6) olefin α face is believed to prevent hydrogenation.

We hoped that this olefin could be reduced stereoselectively on the α face once the benzofuran moiety of the liphagane skeleton was installed. To this end, we tested

some of our other previously developed chemistry. **(±)-374** was treated with LDA and iodomethane, furnishing **(±)-375** in 46% yield and 3:1 dr with a 38% recovery of unreacted **(±)-374**. nOesy-1D analysis of **(±)-375** revealed that the major diastereomer possessed correct relative stereochemistry at C(8).

Scheme 4.34 The Chemistry of the Aryl Dienone



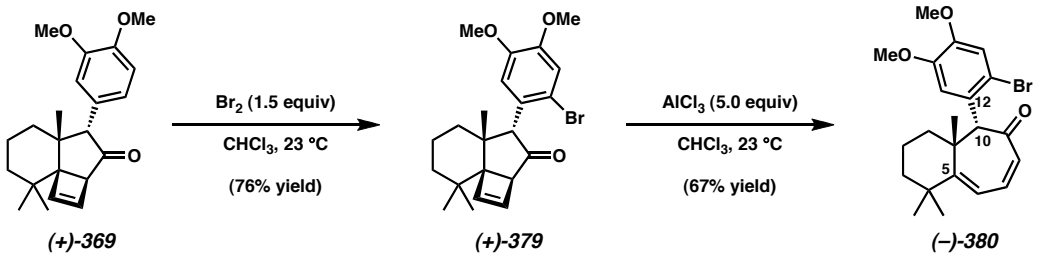
We anticipated that an aryl bromide handle would be useful for closure to a benzofuran later in the synthesis. Treatment of **(±)-374** with $(n\text{-Bu})_4\text{N Br}_3$ in CH_3CN led to bromination of only C(8), whereas stronger conditions applied to **(±)-376** could also chemoselectively brominate the aromatic ring, furnishing dibromide **(±)-377**. Although we had halogenated the arene, we now had an unwanted alkyl bromide at C(8).

Bromination of the arene prior to ring expansion of the cyclobutene could potentially avoid this problem.

4.7.6 *Optimized Electrocyclic Ring Expansion*

We believed that the electron-rich nature of the veratrole moiety in **(±)-369** was responsible for conversion of **(±)-356** to **(±)-373** during the Lewis acid-promoted ring expansion. We also wanted a bromine atom on our aromatic ring for the eventual benzofuran synthesis. Bromination of the arene **(±)-356** could attenuate the unwanted Friedel-Crafts pathway by making the aromatic ring less electron-rich. The bromide might also change the dihedral angle about C(10)–C(12), precluding a conformation requisite for nucleophilic attack on C(5) (Scheme 4.35).

Scheme 4.35 Bromination Solution for Ring Expansion

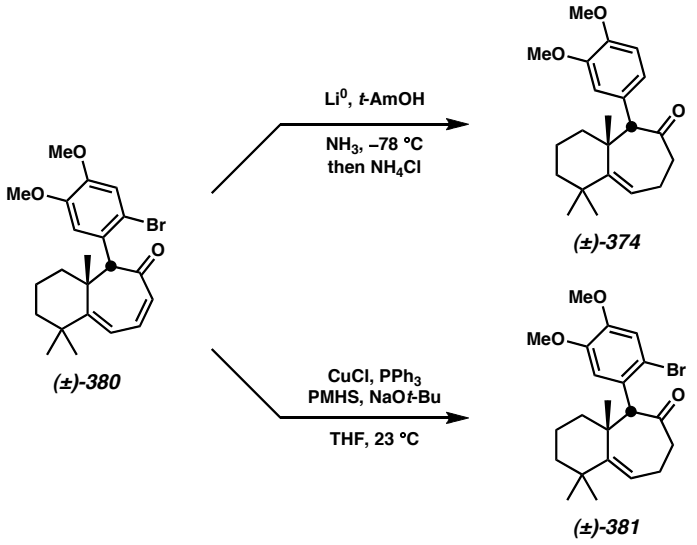


To test our hypotheses, **(+)-369** was treated with Br_2 in $CHCl_3$, leading to **(+)-379** in good yield and excellent chemoselectivity (Scheme 4.35). To our delight, when bromoveratrole-substituted cyclobutene **(+)-379** was treated with $AlCl_3$ in $CHCl_3$, a very clean rearrangement to **(–)-380** occurred devoid of both Friedel-Crafts and Cargill rearrangement side products.

4.7.7 *Functionalization of the Dienone*

We needed to reduce the two alkenes within the 7-membered ring of **(±)-380**, and hoped that a dissolving metal reduction might efficiently reduce both olefins. However, when **(±)-380** was treated with Li^0 and *t*-AmOH in liquid ammonia, only 1,4 reduction and dehalogenation were observed (Scheme 4.36). We realized that conjugation of the γ,δ olefin to the other π-systems was somewhat limited. Even if we could suppress dehalogenation, it would be difficult to achieve 1,6-reduction using dissolving metal reductions.

Scheme 4.36 Early Reduction Methods

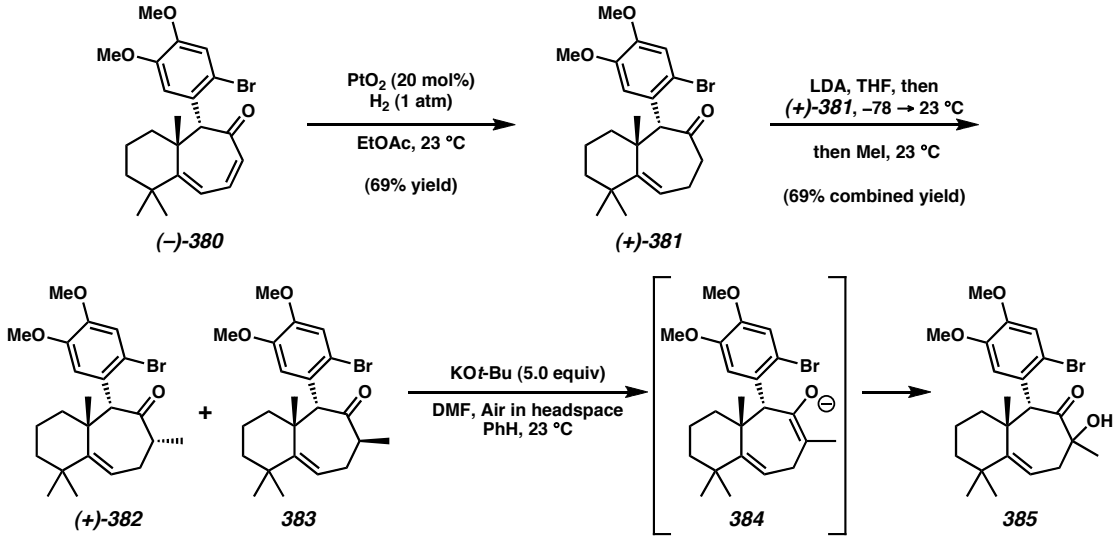


One method that was useful initially was a copper hydride conjugate reduction of **(±)-380** to **(±)-381**.[40] The advantage of this approach was its high chemoselectivity; no debromination was ever observed. One of the disadvantages of this method was its poor

reproducibility. Although many reaction variables were screened, yields ranged from 0-56%. It was too risky to use this procedure during scale-up.

Ultimately, the best means for reduction of **(–)-380** proved to be hydrogenation with Adams' catalyst in EtOAc (Scheme 4.37). The choice of solvent was critical, as substantial debromination was observed in EtOH when PtO_2 was used. In no instance was reduction of the γ,δ olefin observed, consistent with previous data obtained.

Scheme 4.37 Methylation and Epimerization Studies



Now that the dienone had been reduced, methylation of **(+)-381** was tested. Gratifyingly, treatment of **(+)-381** with LDA, followed by iodomethane, installed the methyl group of **(+)-382** in 5:2 dr, favoring the desired diastereomer (Scheme 4.37). Although conversion in this reaction was generally incomplete, the two diastereomers **(+)-382** and **383** were fully separable, and most of the unreacted starting material could be recovered. We made a significant discovery when we tried to epimerize **383** to the

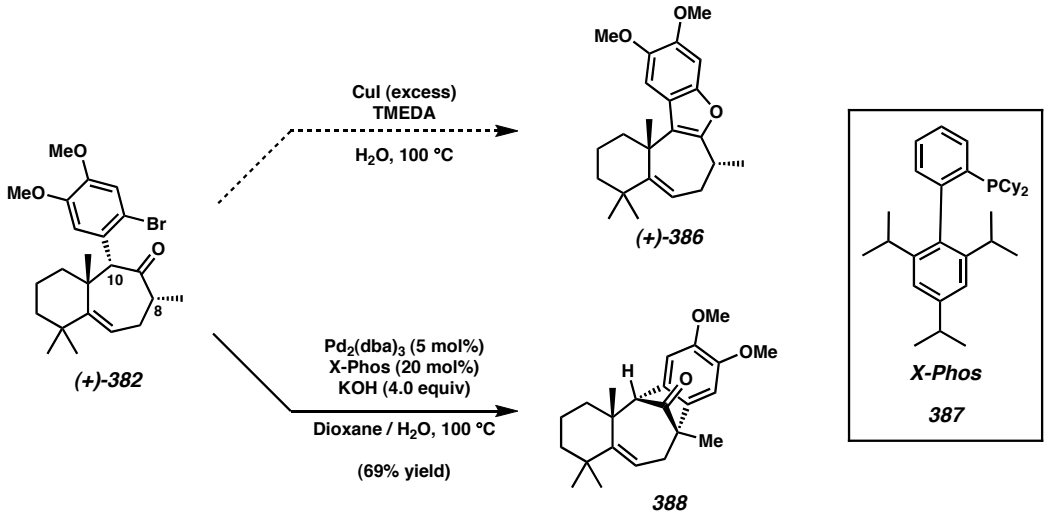
desired **(+)-382**. The enolate **384** was presumably very unstable because we could never reisolate any **(+)-382** or **383**. Instead, the only discernable product from any epimerization attempt was the acyloin **385**. The relative configuration of this species was not determined.

4.8 Completion of the Benzofuran Ring

4.8.1 *Preparation of a Dihydrobenzofuran*

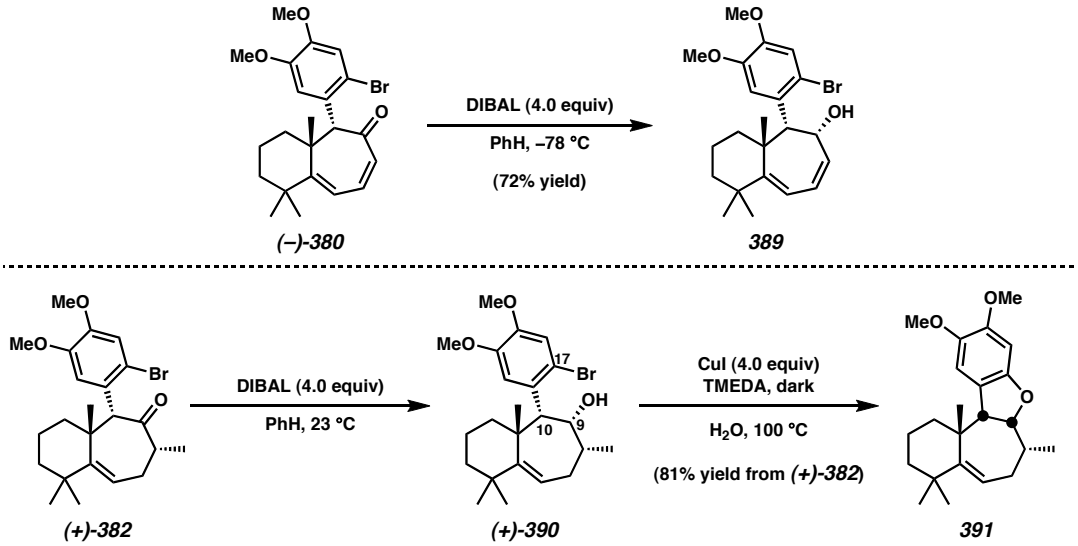
With the bromoveratrole **(+)-382** in hand, we were finally ready to close the benzofuran. **(+)-382** was treated with excess CuI in TMEDA and H_2O rigorously degassed with argon (Scheme 4.38).[33] Unfortunately, but not surprisingly, in light of the enolate instability of **384**, we never observed any C–O bond formation or **(+)-386**. We turned instead to an alternative method described by Buchwald. When certain aryl halides are heated in the presence X-Phos ligand **387** and $Pd_2(dba)_3$ in dioxane/H_2O with KOH, conversion of the aryl halide to a phenol is observed.[41] We hoped to access a phenol, which upon dehydrative cyclization might lead to benzofuran **(+)-386**. We were excited when we observed full conversion of **(+)-382** to a single, stable product. To our surprise, the product **388** was the result of a clean intramolecular α-arylation. This reactivity again highlights the strong preference of our [6,7] carbocyclic ketone systems toward enolization at C(8) compared to C(10).

Scheme 4.38 Failed Attempts to Prepare the Benzofuran



We needed a creative way to make the C(17)-O bond while avoiding unwanted reactions at C(8). During another study, dienone **(–)-380** could be diastereoselectively reduced to allylic alcohol **389** in good yield, so we believed it would be possible to perform the analogous transformation on **(+)-382** (Scheme 4.39). To our delight, treatment of **(+)-382** with DIBAL in benzene at 23 °C gave complete conversion to **(+)-390** as a single diastereomer. The relationship between the protons at C(9) and C(10) was *syn*, so we anticipated that cyclization of the C(9) oxygen of **(+)-390** onto C(17) would be possible. When we treated **(+)-390** with excess CuI in TMEDA/H_2O[33] we obtained dihydrobenzofuran **391** as the exclusive product. Finally, the fourth ring the liphagane skeleton (**272**, Figure 4.1) was in place.

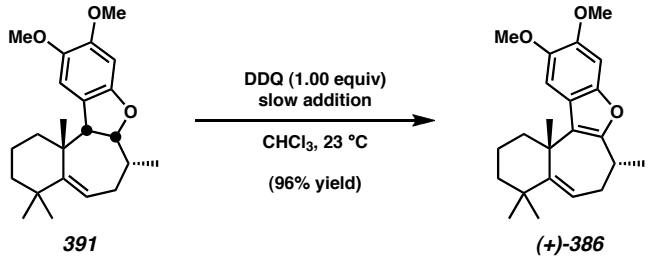
Scheme 4.39 Making the Necessary C–O Bond



4.8.2 *Controlled Oxidation of the Dihydrobenzofuran*

At last we were poised for the installation of the benzofuran. Treatment of dihydrobenzofuran **391** in high dilution with one equivalent of DDQ over a three-hour timeframe at 23 °C gave a 96% yield of benzofuran **(+)-386** (Scheme 4.40). The methods developed for this reaction were critical. If more than one equivalent of DDQ was used or the addition was too rapid, overoxidation byproducts were observed.

Scheme 4.40 Careful Oxidation to the Benzofuran

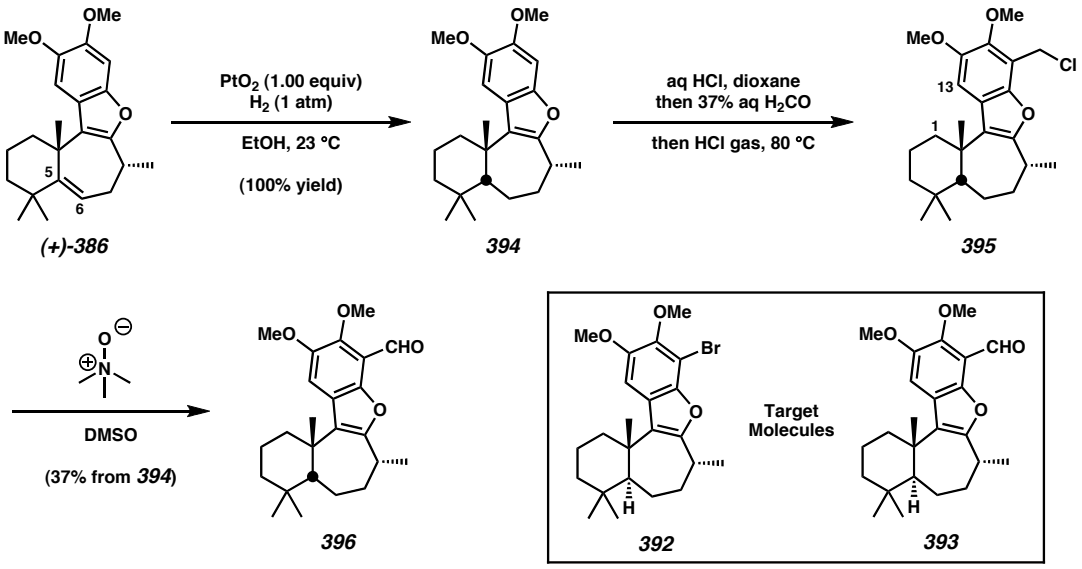


4.8.3 *Installation of the Aldehyde Functionality*

Although all of the rings in the natural product were present, we still needed to install the aldehyde functionality. We hoped to intercept a compound reported in Andersen's racemic total synthesis, either aryl bromide **392** or aldehyde **393**.[1] We tried a few conditions for hydrogenation of the C(5)–C(6) double bond, and quickly discovered that PtO_2 / H_2 reduction at 1 atm in EtOH produced a single diastereomeric product **394** (Scheme 4.41). At the time, we could not tell which diastereomer we had produced. We were hopeful that *trans* ring fusion across C(5) and C(11) was achieved based on similar reactions with [6-6] carbocycles.[42] Literature examples of more relevant [6-7] systems were nearly scarce,[43] but we anticipated stereoselection in our hydrogenation might follow the same trends seen for [6-6] systems.

With our hydrogenated 7-membered ring benzofuran **394**, we targeted **392**. Under all conditions tested, we failed to observe any bromination of our arene. Instead, oxidation of the 7-membered ring was more common. Undaunted, we decided to pursue **393**. We tested many methods of direct formylation or cyanation, but had limited success. Instead, we came to rely upon a two-step sequence. Condensation of **394** with aqueous formaldehyde in HCl-saturated dioxane produced a single isomer of benzyl chloride **395**, which was partially characterized (Scheme 4.41). Most importantly, a key nOe was observed between the aryl proton at C(13) and a proton on C(1).[44] This confirmed the position of the benzylic chloride moiety. To our delight, when **395** was treated with trimethylamine *N*-oxide in DMSO,[45] benzaldehyde **396** was the major product in 37% yield from **394**. However, we had prepared the C(5) epimer of Andersen's aldehyde **393**.[46]

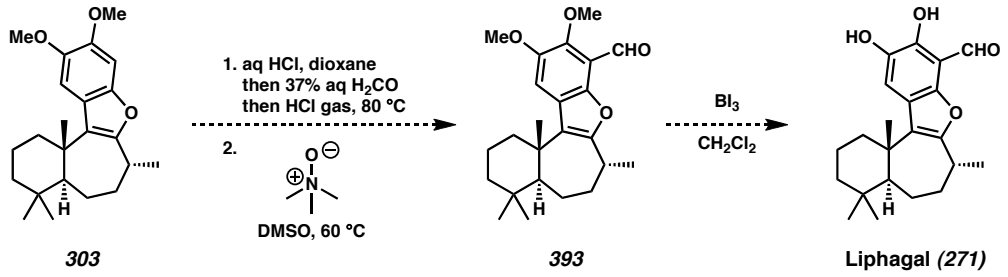
Scheme 4.41 Further Functionalizations



4.8.4 *Proposed Endgame for the Total Synthesis of Liphagal*

If the preparation of **303** were possible, chloromethylation of the benzofuran followed by oxidization using the Taylor-Ganem modification of the Kornblum oxidation[45] would lead to Andersen's aldehyde **393** (Scheme 4.42). This would constitute a formal total synthesis of **271**. Didemethylation of **393** with BI_3 at low temperature[1] would then complete the catalytic enantioselective total synthesis of liphagal (**271**).

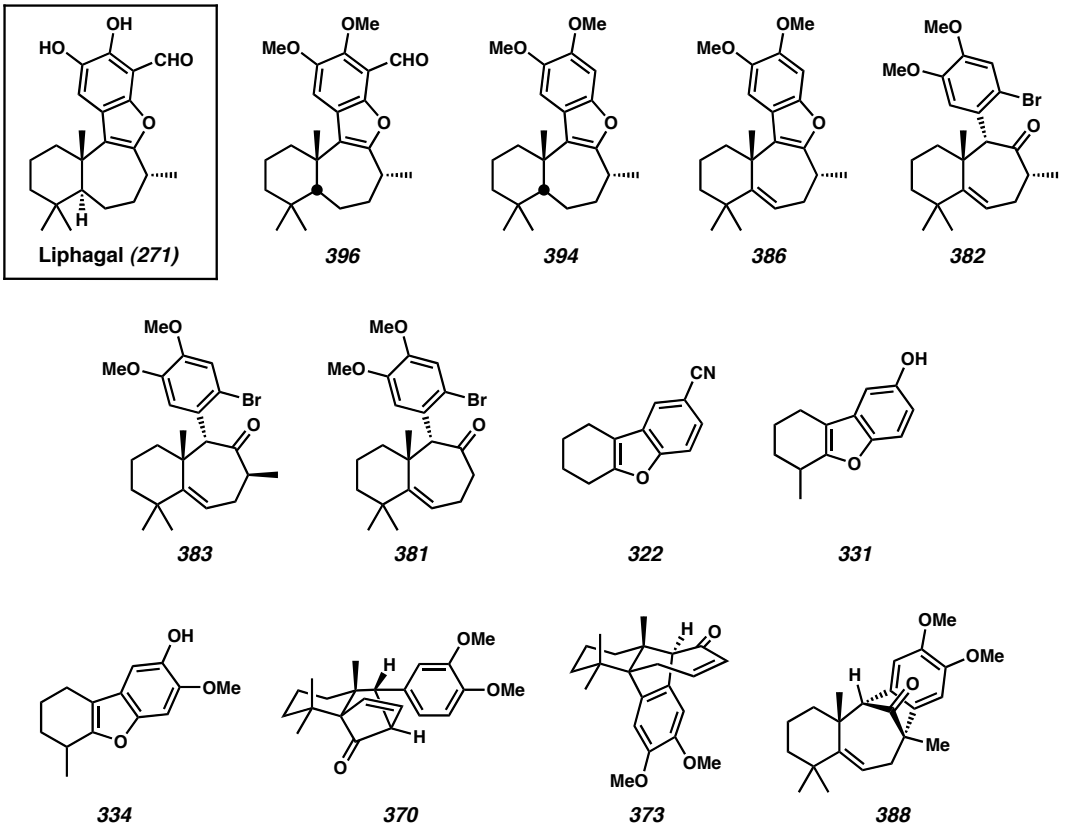
Scheme 4.42 Proposed Total Synthesis of Liphagal



4.9 Analogues for PI3K Biological Screening

A large number of potential candidates for PI3K biological screening have been prepared during our synthetic investigations toward liphagal (**271**). Many of these molecules could be used for structure-activity-relationship studies (Figure 4.3). Specifically, we can probe the functional groups of our compounds that are mandatory for biological activity.

Figure 4.3 Selected Molecules For PI3K Biological Activity Studies



Screening of aldehyde **396** may determine if the catechol pharmacophore is necessary for liphagal's potency and selectivity in PI3Kα inhibition assays (Figure 4.3). Liphaganes including **396**, **394**, and **386** could ascertain the effect of aldehyde

functionality (or lack thereof) on biological activity. The importance of the benzofuran could be studied using compounds **382**, **383**, **381**, and others. Furthermore, the biological significance of the [6-7] carbocyclic system of the liphaganes (**272**, Figure 4.1) might be understood using model compounds **322**, **331**, and **334**. Additional structure activity relationship data may be garnered from the polycyclic compounds **370**, **373**, and **388**. A large collection of molecules prepared during this synthesis will be sent for biological screening against PI3K enzymes.[47]

4.10 Concluding Remarks

Herein we have reported significant progress toward the catalytic enantioselective total synthesis of the meroterpenoid liphagal (**271**). Our route displays the utility of the enantioselective decarboxylative alkylation chemistry developed in our laboratory and sets the absolute stereochemistry of the natural product. We have also developed a powerful method for expanding [5-4] cyclobutene ring systems into 7-membered rings. The photoaddition of acetylene to a bicyclic enone sets vicinal quaternary stereocenters in a very congested molecule with high diastereoselectivity. These synthetic endeavors toward liphagal (**271**) have done much to elucidate the stereochemical proclivities of [6-7] carbocyclic frameworks. Furthermore, our synthesis of the benzofuran portion of the natural product demonstrated a creative solution to the problems posed by the inherent 7-membered ring chemistry. Importantly, many interesting compounds have been prepared during this synthetic investigation that could help elucidate the structure-activity-relationship between liphaganes (**272**) and PI3K enzymes.

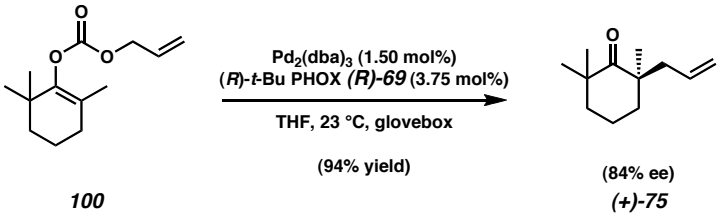
4.11 Experimental Procedures

4.11.1 *Materials and Methods*

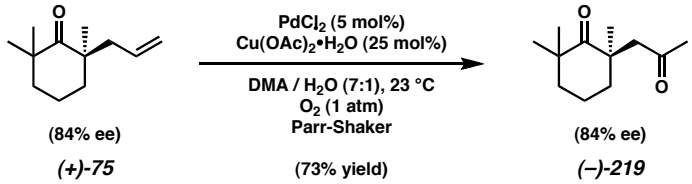
Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). Chloroform was stabilized with ethanol and stored in the dark unless indicated otherwise. Methanol and *N,N*-dimethyl acetamide were used as purchased. TMEDA and *i*-Pr_2NH were distilled from CaH_2. 2,6-dimethylcyclohexanone (**220**) was fractionally distilled from $CaSO_4$ at ambient pressure prior to use. Dimethyl sulfate was fractionally distilled through a Vigreux column prior to use. All other commercially-obtained reagents were used as received, unless specified otherwise. (*R*)-*t*-Bu-PHOX ligand ***(R)*-69** was prepared according to known methods.[48] Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using UV at 254nm or 356 nm, *p*-anisaldehyde, ceric ammonium molybdate, potassium permanganate, and iodine vapor over sand. TLC data include R_f, eluent, and method of visualization. ICN silica gel (particle size 0.032-0.063 mm) or SilliaFlash P60 Academic silica gel (0.040-0.063 mm) was used for flash column chromatography. Analytical chiral HPLC analyses were performed with an Agilent 1100 Series HPLC using a chiralcel AD normal-phase column (250 x 4.6 mm) employing 2.0-3.0% ethanol in hexane isocratic elution and a flow rate of 0.1 mL/min with visualization at 254nm. Analytical chiral GC analysis was performed with an Agilent 6850 GC using a GT-A column (0.25m x 30.00m) employing an 80 °C isotherm and a flow rate of 1.0 mL/min. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a

Varian Inova 500 (at 500 MHz) and are reported relative to the residual solvent peak (δ 7.26 for $CDCl_3$ and δ 7.16 for C_6D_6). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz),[49] and integration. ^1H-^1H nOesy 1D experiments were conducted at 300 MHz. In nOe drawings, the tail of the arrow denotes the proton being saturated, and the head the proton receiving spin transfer energy. ^1H-^1H gCOSY experiments were performed at 300 MHz or 500 MHz. ^1H-^1H homodecoupling experiments were performed at 300 MHz. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative the residual solvent peak (δ 77.2 for $CDCl_3$ and δ 128.4 for C_6D_6). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer and are reported in frequency of absorption (cm^{-1}). IR samples were usually thin films deposited on sodium chloride plates by evaporation from a solvent (usually $CDCl_3$), which is recorded. Optical rotations were measured with a Jasco P-1010 polarimeter, using a 100 mm path-length cell. High-resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are measured directly during distillation and are uncorrected. Sublimation points are measured directly. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Copies can be obtained on request, free of charge, by quoting the publication citation and either deposition number 606034 for **(±)-319** or 634511 for **(±)-370**.

4.11.2 *Syntheses of Compounds Related to Liphagal*

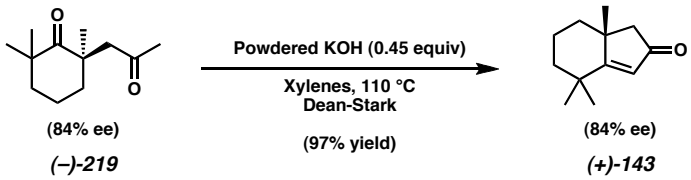


Allyl Ketone (+)-75. In the glovebox, a flamedried round-bottom flask was charged with $Pd_2(dba)_3$ (181 mg, 0.198 mmol) and (*R*)-*t*-Bu-PHOX ***(R)*-69** (192 mg, 0.495 mmol). Dry THF (390 mL) was added at 23 °C. After 30 min, a solution of enol carbonate **100** in THF (10 mL) was added. After 24 h, the reaction was removed from the glovebox and concentrated in vacuo at < 10 °C (product is volatile). The residue was purified by flash chromatography on silica gel (pentane → 4:96 Et_2O:pentane → 8:92 Et_2O:pentane eluent), giving allyl ketone **(+)-75** (2.23 g, 94% yield) as a colorless oil in 84% ee as determined by chiral HPLC. $[\alpha]^{25}_D$ +36.0° (*c* 0.855, $CHCl_3$), 84% ee. Other characterization data for this compound can be found on pages 40 and 41 (chapter 2).

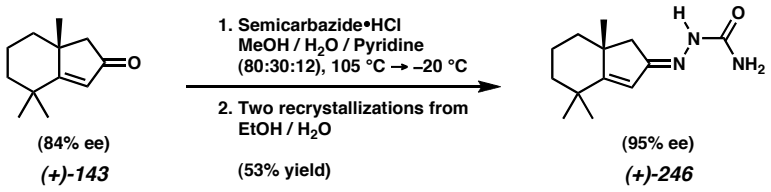


Diketone (–)-219. A Parr flask was charged with $PdCl_2$ (432 mg, 2.44 mmol) and $Cu(OAc)_2 \bullet H_2O$ (2.27 g, 12.2 mmol), followed by H_2O (6.0 mL). A solution of allyl ketone **(+)-75** (4.39 g, 24.4 mmol) in DMA (42.0 mL) was introduced. The reaction was cooled to –78 °C, then evacuated/backfilled (vacuum/O_2) (3 x). The reaction was warmed to 23 °C and placed on a Parr Shaker under 1 atm of O_2 for 28 h. The reaction was

directly loaded onto a column of silica gel and purified by flash chromatography (20:80 Et_2O:hexane eluent), giving diketone **(–)-219** (3.51 g, 73% yield) in 84% ee as determined by chiral HPLC. $[\alpha]^{26}_D$ –70.3° (*c* 0.970, $CHCl_3$), 84% ee. Other characterization data for this compound can be found on page 149 (chapter 3).

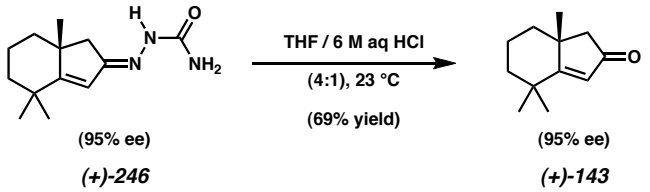


Bicyclic Enone (+)-143. A round-bottom flask was charged with a solution of diketone **(–)-219** (3.48 g, 17.7 mmol) in xylenes (75 mL). Powdered KOH (448 mg, 7.98 mmol) was added. The reaction was fitted with a Dean-Stark trap and reflux condenser, then heated to 110 °C for 22 h. Then, the reaction was cooled to 23 °C. It was directly loaded onto a column of silica gel and purified by flash chromatography (hexane → 40:60 Et_2O:hexane eluent), giving bicyclic enone **(+)-143** (3.06 g, 97% yield) in 84% ee as determined by chiral HPLC. $[\alpha]^{26}_D$ +90.7° (*c* 0.865, $CHCl_3$), 84% ee. Other characterization data for this compound can be found on page 152 (chapter 3).



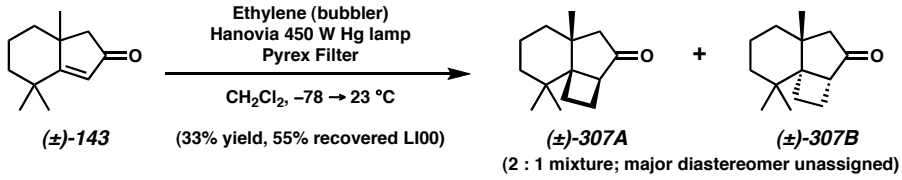
Bicyclic Semicarbazone (+)-246. A round-bottom flask containing the scalemic bicyclic enone **(+)-143** (3.04 g, 17.06 mmol, 1.00 equiv, 84% ee) was charged with MeOH (48.6 mL), H_2O (18.2 mL), and pyridine (7.30 mL). Semicarbazide hydrochloride (3.42 g, 30.7

mmol, 1.80 equiv) was added. The reaction was heated to 105 °C for 4 h and cooled to –20 °C overnight. The white crystals that formed were filtered, washed with H_2O, dried in the air, and transferred to a new round-bottom flask. Absolute EtOH (200 mL) was added gradually at 100 °C. H_2O (160 mL) was gradually added. A persistent cloudiness developed, but had cleared by 2 min. The heat was turned off, and the flask allowed to cool to gradually to 23 °C overnight.[50] The crystals were filtered and redissolved in EtOH (180 mL) at 100 °C. H_2O (130 mL) was added as before. The heating bath was turned off, and the system allowed to cool to 23 °C. The crystals were collected after 2 days via filtration. They were dried in vacuo over P_2O_5, giving **(+)-246** (2.45 g, 53% yield) in 95% ee as determined by chiral HPLC. Other characterization data for this compound can be found on page 151 (chapter 3).



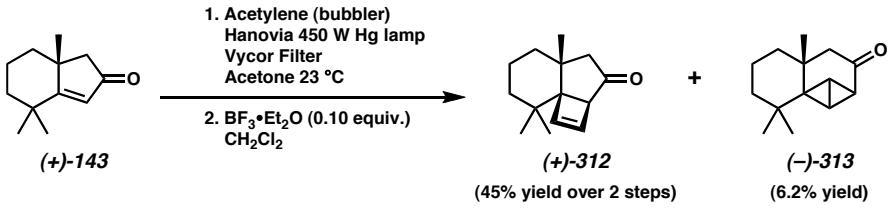
Bicyclic Enone (+)-143. A round-bottom flask containing the bicyclic semicarbazone **(+)-246** (2.37 g, 10.1 mmol, 95% ee) was charged with THF (50 mL) and 6 M aq HCl (20 mL). The reaction was stirred vigorously at 23 °C for 18 h. It was diluted with hexanes (20 mL), and the organic phase was collected. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) followed by with EtOAc (3 x 30 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (20:80 EtOAc:hexane eluent), giving enantioenriched bicyclic enone **(+)-143** (3.06 g, 69% yield) in 95% ee as determined by chiral HPLC.

$[\alpha]^{25}_{D}$ +107.5° (*c* 1.415, $CHCl_3$), 95% ee. Other characterization data for this compound can be found on page 152 (chapter 3).



Cyclobutenes (±)-307A and (±)-307B. A 500 mL glass photoreactor was charged with a solution of racemic bicyclic enone **(±)-143** (950 mg, 5.33 mmol) in CH_2Cl_2 (240 mL). The solution was degassed with argon for 10 min. A quartz cooling jacket was inserted into the reactor. A hanovia medium pressure 450 W mercury lamp, jacketed with a pyrex filter, was inserted into the quartz cooling jacket. The reactor was cooled externally to −78 °C and internally with water circulation in the quartz cooling jacket. The reaction was kept under a positive pressure of N_2. Ethylene gas was bubbled through steadily using a needle for 10 min. Then, the bubbling was stopped and the solution irradiated. More ethylene was bubbled in every hour for 10 min time intervals until 2 hours had passed. Seeing that not much starting material had converted to product, the external temperature was carefully elevated to 23 °C, and ethylene was bubbled through steadily for another 2 hours. The reaction was concentrated. Benzene was added, and the reaction was concentrated a second time. The residue was then taken up in benzene and wet-loaded onto a silica gel column then purified by flash chromatography (20:80 Et_2O:pentane → 50:50 Et_2O:pentane eluent), affording an inseparable mixture of cyclobutenes **(±)-307A** and **(±)-307B** (368 mg, 33% yield, 2:1 dr, major diastereomer not identified) as a waxy white semisolid. R_f 0.55 (1:4 EtOAc/hexane), (*p*-Anisaldehyde, red

spot); mp 203-205 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.91 (AB spin system, d, J_{AB} = 16.5 Hz , 1.33H), 2.78 (AB spin system, d, J_{AB} = 16.8 Hz , 0.67H), 2.53 (app. d, J = 12.2 Hz, 0.67H), 2.49 (app. d, J = 8.0 Hz, 1.33H), 2.32-1.90 (m, 6H), 1.79 (AB spin system, d, J_{AB} = 16.8 Hz, 0.67H), 1.76 (AB spin system, d, J_{AB} = 16.5 Hz, 1.33H), 1.70-1.16 (m, 14H), 1.08 (s, 4H), 1.01 (s, 2H), 1.00 (s, 2H), 0.97 (s, 4H), 0.95 (s, 4H), 0.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ220.8, 220.4, 57.8, 55.2, 54.2, 54.0, 48.3, 45.3, 43.5, 41.1, 36.3, 35.7, 34.7, 34.3, 33.4, 30.1, 29.6, 28.3, 27.2, 24.6, 24.2, 22.3, 22.0, 20.1, 19.9; IR (KBr): 2931, 1736, 1466, 1390, 1269, 1156 cm^{-1}; HRMS-EI$^+$ (*m/z*): [M]$^+$ calc'd for $C_{14}H_{22}O$, 206.1671; found, 206.1669. In addition, unreacted **(±)-143** (527 mg, 55% yield) was also recovered.



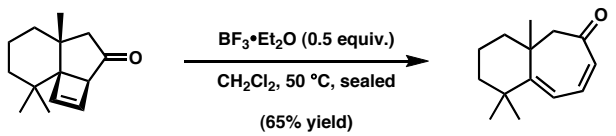
Cyclobutene (+)-312 and Bicyclobutane (–)-313. A 1.5 L glass photoreactor was charged with a solution of bicyclic enone **(+)-143** (1.207 g, 6.77 mmol) in acetone (ACS grade)(1.0L). The solution was degassed with argon for 10 min. A quartz cooling jacket was inserted into the reactor. A hanovia medium pressure 450 W mercury lamp, jacketed with a vycor filter, was inserted into the quartz cooling jacket. The reactor was cooled externally to 0 °C and internally with water circulation in the quartz cooling jacket. The reactor was also fitted with a reflux condenser with circuated ethylene glycol/water at a temperature of 5 °C, and the reaction was kept under a positive pressure of N_2. Acetylene gas was bubbled through steadily using a needle as the solution was

irradiated for 10 h. The reaction was concentrated. The residue was then taken up in benzene and wet-loaded onto a silica gel column then purified by flash chromatography (5:95 EtOAc:hexane → 20:80 EtOAc:hexane eluent), affording a crude mixture of cyclobutene **(+)-312** and bicyclobutane **(–)-313**, which was carried on to the next reaction. Additionally, an analytically pure sample of bicyclobutane **(–)-313** (85.2 mg, 6.2% yield) was obtained as a pale yellow oil, which was unstable on silica gel. R_f 0.45 (1:4 EtOAc/hexane), (*p*-Anisaldehyde, red spot); ^{1}H NMR (300 MHz, C_6D_6): δ 2.48 (app. dd, *J* = 3.9 Hz, 2.5 Hz, 1H), 1.80 (app. d *J* = 16.3 Hz, 1H), 1.75 (app. d, *J* = 16.3, 1H), 1.68 (app. dd, *J* = 9.9 Hz, 2.5 Hz, 1H), 1.59 (app. dd, *J* = 9.9 Hz, 3.9 Hz, 1H), 1.31-1.15 (m, 6H), 0.94 (s, 3H), 0.85 (s, 3H), 0.52 (s, 3H) ; ^{13}C NMR (75 MHz, C_6D_6): δ 208.5, 60.4, 55.8, 48.3, 41.7, 40.7, 36.9, 33.4, 29.1, 28.3, 27.0, 18.6, 16.7, 14.9; IR (NaCl/neat film): 3092, 2927, 1713, 1456, 1390, 1377, 1276, 1226, 1041, 979, 812, 797 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{14}H_{20}O$, 204.1514; found, 204.1519. $[\alpha]^{25}_D$ –22.04° (*c* 1.65, C_6H_6), 95% ee. Unreacted starting material **(±)-143** (146.8mg, 12% yield) was also recovered.

An analytically pure sample of cyclobutene **(+)-312** was obtained in the following manner. A round-bottom flask containing analytically pure bicyclobutane **(–)-313** (80.0 mg, 0.392 mmol) in CH_2Cl_2 (5 ml) was treated with BF_3•Et_2O (5 μL) at 23 °C. After 10 min, the reaction was added dropwise to a rapidly stirred suspension of brine (10 mL), sat. aq $NaHCO_3$ (10 mL), and CH_2Cl_2 (20 mL). The organic layer was collected, and the aqueous phase was extracted with CH_2Cl_2 (2 x). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was taken up in benzene and purified by flash chromatography on silica gel (5:95 EtOAc:hexane eluent), affording cyclobutene

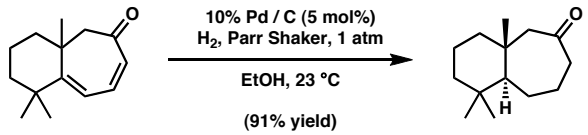
(+)-312 (61.6 mg, 77% yield) as a waxy white, volatile semisolid. R_f 0.58 (1:4 EtOAc/hexane), (*p*-Anisaldehyde, red spot); mp 54-139 °C (amorphous), sublimation point, sp: < 23 °C (3 mmHg); ^{1}H NMR (300 MHz, C_6D_6): δ 6.00 (app. dd, J = 2.8 Hz, 0.6 Hz, 1H), 5.93 (app. dd, J = 2.8 Hz, 1.4 Hz, 1H), 3.00 (app. s, 1H), 2.87 (AB spin system, d, J_{AB} = 16.0 Hz, 1H), 1.58 (AB spin system, app. dd, J_{AB} = 16.0 Hz, J = 1.7 Hz, 1H), 1.36 (app. ddt, J_{d1} = 27.2 Hz, J_{d2} = 12.7 Hz, J_t = 3.0 Hz, 1H), 1.23-0.95 (m, 5H), 0.85 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ2123.0, 142.8, 138.4, 65.4, 58.9, 52.2, 39.0, 37.3, 36.1, 33.6, 28.5, 25.4, 22.2, 18.9; IR (NaCl/$CHCl_3$): 3130, 3040, 2925, 2870, 2845, 1733, 1456, 141, 1388, 1378, 1212, 1160, 754, 726 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{14}H_{20}O$, 204.1514; found, 204.1523; $[\alpha]^{26}_D$ +694.99° (*c* 1.232, C_6H_6), 95% ee.

The crude mixture of cyclobutene **(+)-312** and **(–)-313** prepared above (excluding the pure isolated **(–)-313**) was dissolved in CH_2Cl_2 (50 mL) and treated with $BF_3 \bullet Et_2O$ (86 μL) at 23 °C for 10 min. The reaction was added dropwise to a rapidly stirred suspension of brine (50 mL), sat. aq $NaHCO_3$ (50 mL), and CH_2Cl_2 (50 mL). The organic layer was collected, and the aqueous phase was extracted with CH_2Cl_2 (2 x). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was taken up in benzene and purified by flash chromatography on silica gel (5:95 EtOAc:hexane eluent), affording semipure cyclobutene **(+)-312** (578 mg, 45% yield over 2 steps as determined by ^{1}H NMR). A contaminant (with a structure similar to the product) with a mass of 265 mg was also present, as determined by ^{1}H NMR. The semipure cyclobutene **(+)-312** was used in subsequent reactions without further purification.



(±)-312 *(±)-318*

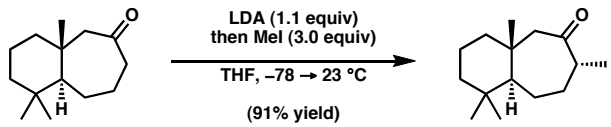
Cycloheptadienone (±)-318. A flamedried Schlenk tube under N_2 was charged with a solution of cyclobutene **(+)-312** (125 mg, 0.600 mmol) and CH_2Cl_2 (20 mL). Then, BF_3•Et_2O (38 μL, 0.300 mmol) was added. The tube was sealed, and the yellow solution was heated to 50 °C for 9 h. The reaction was cooled to 23 °C and concentrated to ~5 mL. The solution was directly loaded onto a silica gel column and purified by flash chromatography (8:92 EtOAc:hexane eluent), affording cycloheptadienone **(±)-318** (81.8 mg, 65% yield) as a pale yellow oil. R_f 0.52 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, rose spot, UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60 (dd, J = 11.8 Hz, 8.8 Hz, 1H), 6.10 (d, J = 8.8 Hz, 1H), 6.00 (app. dd, J = 11.8 Hz, 1.9 Hz, 1H), 2.79 (AB spin system, d, J_{AB} = 14.0 Hz, 1H), 2.16 (AB spin system, app. dd, J_{AB} = 14 Hz, J = 1.9 Hz, 1H), 1.80-1.30 (m, 6H), 1.20 (s, 3H), 1.12 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.7, 169.7, 139.4, 129.1, 119.4, 56.7, 41.9, 39.5, 38.2, 35.5, 32.9, 31.8, 20.4, 18.0; IR (NaCl/$CDCl_3$): 3030, 2961, 2932, 2867, 1660, 1571, 1461, 1420, 1372, 1312, 1233, 986 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M+H]^+$ calc'd for $C_{14}H_{21}O$, 205.1592; found, 205.1583.



(±)-318 *(±)-305*

Cycloheptanone (±)-305. A Parr flask was charged with 10% w/w Pd/C (150 mg, 0.142 mmol), followed by a solution of cycloheptadienone **(±)-318** (580 mg, 2.84 mmol) and

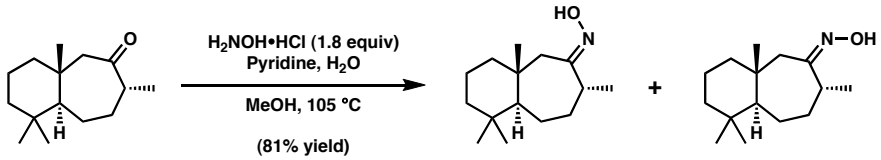
absolute ethanol (120 mL). The reaction was placed on a Parr shaker under H_2 (1 atm) at 23 °C for 4 h. The reaction was sparged with argon, then filtered through celite with the aide of Et_2O. The filtrate was concentrated and purified by flash chromatography on silica gel (Et_2O:hexane 10:90 eluent), affording cycloheptanone **(±)-305** (536 mg, 91% yield) as a colorless oil. R_f 0.58 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, yellow spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (AB spin system, d, J_{AB} = 12.4 Hz, 1H), 2.45 (app. dt, J_d = 18.4 Hz, J_t = 3.6 Hz, 1H), 2.24 (app. ddd, J = 19.2 Hz, 13.2 Hz, 4.1 Hz, 1H), 2.06 (AB spin system, J_{AB} = 12.4 Hz, 1H), 2.02-1.86 (m, 2H), 1.68-1.46 (m, 2H), 1.44-1.30 (m, 3H), 1.30-1.10 (m, 4H), 0.91 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 214.9, 61.6, 59.2, 43.4, 43.3, 42.4, 36.5, 34.7, 33.8, 26.1, 24.8, 21.7, 19.3, 19.1; IR (NaCl/$CDCl_3$): 2929, 1696, 1457, 1258 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{14}H_{24}O$, 208.1827; found, 208.1824.



(±)-305 *(±)-304*

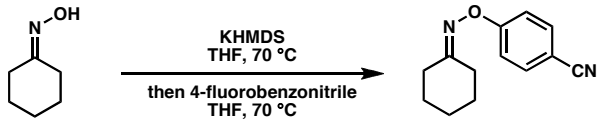
Methylcycloheptanone (±)-304. A flamedried round-bottom flask was charged with THF (7.7 mL) and *i*-Pr_2NH (130 μL, 0.922 mmol) and cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 338 μL, 0.845 mmol) was added dropwise. After 30 min, the reaction was cooled to −78 °C. THF (5.7 mL) was added, followed by a solution of cycloheptanone **(±)-305** (160 mg, 0.768 mmol) in THF (2.0 mL). After 1 h, MeI (144 μL, 2.31 mmol) was added. After another hour had passed, the reaction was warmed to 23 °C and stirred for 1 h. The reaction was quenched with sat. aq NH_4Cl (5 mL) followed by H_2O (10 mL). Hexanes (10 mL) and Et_2O (15 mL) were added. The organic layer was collected, and the

aqueous layer was extracted with Et_2O (3 x 15 mL). All organic layers were combined, washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated. The resuidue was purified by flash chromatography on silica gel (EtOAc:hexane 8:92 eluent), affording methylcycloheptanone **(±)-304** (147 mg, 86% yield) as a yellow oil. R_f 0.61 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, purple spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (AB spin system, d, J_{AB} = 11.6 Hz, 1H), 2.28-2.14 (m, 1H), 1.96 (AB spin system, d, J_{AB} = 11.6 Hz, 1H), 1.93 (app. d, J = 8.6 Hz, 1H), 1.87 (app. d, J = 8.6 Hz, 1H), 1.58 (app. ddt, J_{d1} = 14.3 Hz, J_{d2} = 13.5 Hz, J_t = 3.6 Hz, 1H), 1.43-1.30 (m, 3H), 1.30-1.12 (m, 3H), 1.16-0.88 (m, 2H), 1.01 (d, J = 7.4 Hz, 3H), 0.88 (s, 3H), 0.84 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.9, 59.3, 59.2, 47.9, 43.0, 42.3, 36.6, 34.6, 34.2, 33.7, 24.9, 21.6, 19.6, 19.5, 19.2; IR (NaCl/$CDCl_3$): 2927, 2868, 2846, 1697, 1458, 1385, 1367, 1274, 971 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{15}H_{26}O$, 222.1984; found, 222.1979.



Methylcycloheptanoximes (±)-319A and (±)-319B. A vial containing methylcyclohexanone **(±)-304** (70 mg, 0.315 mmol) in MeOH (882 μL) was treated with H_2O (329 μL) and pyridine (133 μL). Then hydroxylamine hydrochloride (39.4 mg, 0.567 mmol) was introduced. The vial was sealed and heated to 105 °C. After 11 h, the residue was diluted with Et_2O, $CHCl_3$, and H_2O. The suspension was extracted with Et_2O (3 x). Organic layers were combined, dried (Na_2SO_4), filtered, and concentrated, giving methylcycloheptanoxime (2 imine geometric isomers) **(±)-319A** and **(±)-319B** (61 mg,

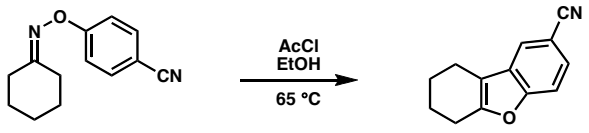
81% yield) as a white powder. R_f 0.25 (3:97 MeOH/DCM), ($KMnO_4$, yellow spot); mp 153-155 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) (major imine geometric isomer **(±)-319A**): δ 8.62 (s, broad, 1H), 3.04 (app. sept, J_{sept} = 6.9 Hz, 1H), 2.16 (AB spin system, d, J_{AB} = 12.9 Hz, 1H), 1.98-1.82 (m, 1H), 1.85 (AB spin system, d, J_{AB} = 12.9 Hz, 1H), 1.75 (app. dd, J = 12.9 Hz, 9.1 Hz, 1H), 1.61 (app. tt, J = 13.5 Hz, 3.6 Hz, 1H), 1.46-1.40 (m, 1H), 1.38 (app. d, J = 13.2 Hz, 2H), 1.28-1.10 (m, 3H), 1.16 (d, J = 6.9 Hz, 3H), 0.99 (app. d, J = 10.2 Hz, 1H), 0.95 (app. d, J = 10.2 Hz, 1H), 0.89 (s, 3H), 0.84 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (major imine geometric isomer **(±)-319A**): δ 165.6, 60.7, 48.3, 43.0, 42.3, 37.4, 36.3, 34.6, 34.1, 33.9, 24.0, 21.7, 19.6, 19.5, 18.6; IR (NaCl/$CDCl_3$) (major imine geometric isomer **(±)-319A**) : 3233 (broad), 2927, 1457, 1382, 1363, 994, 979, 962, 881 cm^{-1}; HRMS-EI$^+$ (*m/z*): [M]$^+$ calc'd for $C_{15}H_{27}ON$, 237.2093; found, 237.2087. X-Ray-quality crystals of the minor imine geometric isomer **(±)-319B** were obtained by taking the **(±)-319A**/**(±)-319B** mixture and dissolving it in heptane. The solution was allowed to undergo negative vapor diffusion within a sealed chamber containing heavy mineral oil.



320 *321*

***O*-Aryloxime 321.** In the glovebox, a flamedried round-bottom flask under argon was charged with KHMDS (484.1 mg, 2.43 mmol) and removed from the glovebox. A solution of cyclohexanoxime (**320**) (250 mg, 2.21 mmol) in THF (20 mL) was added. The reaction was fitted with a reflux condenser and heated to 70 °C for 1 h. Then, a solution of 4-fluorobenzonitrile (267.7 mg, 2.21 mmol) in THF (5 mL) was added.

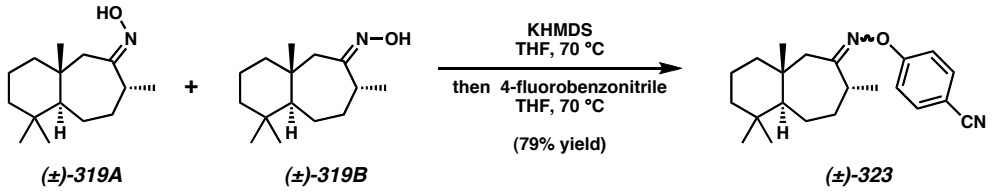
Heating at 70 °C was continued for 4 h. The reaction was cooled to 23 °C and quenched with sat. aq NH_4Cl (8 mL). 5 min later, H_2O and hexanes were added. The reaction was extracted with EtOAc (3 x 20 mL). Organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The compound was purified by flash chromatography on silica gel (5:95 EtOAc:hexane eluent), affording **321** (yield not determined) as a white semisolid. R_f 0.59 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, red spot); mp 66-68 °C ($CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (app. ddd, *J* = 9.1 Hz, 2.5 Hz, 2.1 Hz, 2H), 7.24 (app. ddd, *J* = 8.8 Hz, 2.5 Hz, 1.9 Hz, 2H), 2.65 (app. dd, *J* = 6.6 Hz, 6.0Hz, 2H), 2.35 (app. dd, *J* = 6.6 Hz, 6.0 Hz, 2H), 1.80-1.60 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 162.8, 133.9, 119.6, 115.1, 104.6, 32.2, 27.1, 26.4, 26.0, 25.7; IR (NaCl/$CDCl_3$): 2927, 2860, 2224, 1645, 1601, 1572, 1501, 1449, 1238, 1214, 1162, 892, 836 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{13}H_{14}N_2O$, 214.1106; found, 214.1104.



321 ***322***

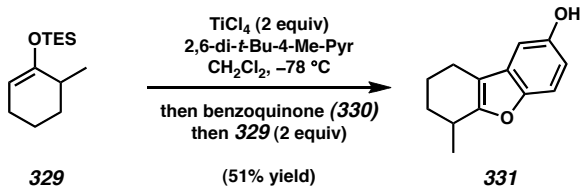
Cyanobenzofuran 322. A vial containing *O*-aryloxime **321** (20 mg, 93.3 μmol) was treated with a preformed solution of acetyl chloride (100 μL, 1.41 mmol) and absolute EtOH (1.0 mL). The vial was sealed and heated to 65 °C for 4.5 h. After cooling to 23 °C, the reaction was concentrated, and the residue immediately diluted with H_2O and CH_2Cl_2. The organic layer was collected and the aqueous layer extracted with CH_2Cl_2 (1 x). Organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified on a preparative thin layer plate of silica gel (20:80 EtOAc:hexane

eluent), affording **322** (yield not determined) as a white powder. R_f 0.58 (20:80 EtOAc/hexane), (UV, 254 nm); mp 99-101 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (app. s, 1H), 7.48 (dd, *J* = 8.5 Hz, 1.7 Hz, 1H), 7.44 (app. dd, *J* = 8.5 Hz, 0.8 Hz, 1H), 2.76 (app. tt, *J* = 6.0 Hz, 2.0 Hz, 2H), 2.62 (app. tt, *J* = 6.0 Hz, 2.0 Hz, 2H), 2.01-1.91 (m, 2H), 1.91-1.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 129.8, 127.1, 123.5, 120.0, 113.2, 112.0, 106.1, 23.5, 22.8, 22.5, 20.3; IR (NaCl/$CDCl_3$): 2940, 2862, 2220, 1638, 1462, 1440, 1295, 1228, 1106, 876, 810 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{13}H_{11}NO$, 197.0841; found, 197.0843.



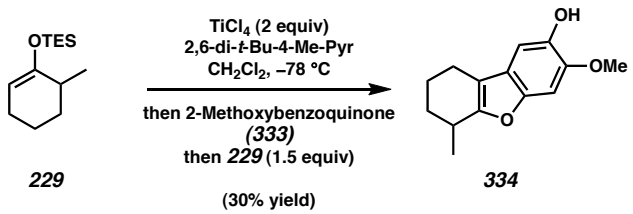
Aryloxime (±)-323. A solution of the two methylcyclohexanoximes **(±)-319A** and **(±)-319B** (59 mg total, 2.49 mmol) and THF (25 mL) was treated with KHMDS (52 mg, 2.61 mmol, weighed in glovebox). The reaction was heated to 70 °C for 1 h. 4-Fluorobenzonitrile (30.1 mg, 2.49 mmol) was introduced, and the heating at 70 °C was continued for 4 h. The reaction was quenched with sat. aq NH_4Cl (5 mL) and diluted with hexane (10 mL) and H_2O (5 mL). The suspension was extracted with Et_2O (3 x 15 mL). All organic layers were combined, washed (brine, 10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane → 5:95 EtOAc:hexane eluent), affording **(±)-323** as a 3 : 1 mixture of imine geometric isomers (66.2 mg, 79% yield) as a colorless oil. R_f 0.67 (20:80 EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (app. ddd, *J* = 9.1 Hz, 2.2 Hz, 1.7 Hz, 4H), 7.22

(app. ddd, J = 8.8 Hz, 1.9 Hz, 1.7 Hz, 4H), 3.18 (app. septet, J_{sept} = 6.9 Hz, 1.5H), 2.85 (AB spin system, d, J_{AB} = 12.4 Hz, 0.5H), 2.67 (app. d of septet, J_d = 11.0 Hz, J_{sept} = 6.9 Hz, 0.5H), 2.28 (AB spin system, d, J_{AB} = 12.7 Hz, 1.5H), 2.01 (AB spin system, d, J_{AB} = 12.7 Hz, 1.5H), 2.11-1.87 (m, 2H), 1.98 (AB spin system, d, J_{AB} = 12.4 Hz, 0.5H), 1.46-1.38 (m, 6H), 1.32-1.20 (m, 8H), 1.16 (d, J = 6.9 Hz, 1.5H), 1.11 (d, J = 6.9 Hz, 4.5H), 1.18-0.86 (m, 2H), 0.93 (s, 1.5H), 0.91 (s, 4.5H), 0.90 (s, 4.5H), 0.89 (s, 1.5H), 0.77 (s, 1.5H), 0.76 (s, 4.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 169.9, 162.9, 162.7, 133.9 (2C), 119.6, 115.3, 115.2, 104.6, 60.7, 60.3, 47.8, 43.0, 42.8, 42.3, 42.2, 42.0, 39.7, 38.0, 37.3, 36.2, 35.9, 35.3, 34.7, 34.6, 33.8, 33.7, 23.9, 23.8, 22.5, 21.7, 21.6, 19.8, 19.6, 19.50, 19.45, 19.1; IR (NaCl/$CDCl_3$): 2928, 2868, 2224, 1601, 1576, 1501, 1458, 1311, 1242, 1161, 941, 911, 880, 836 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{30}N_2O$, 338.2358; found, 338.2363.



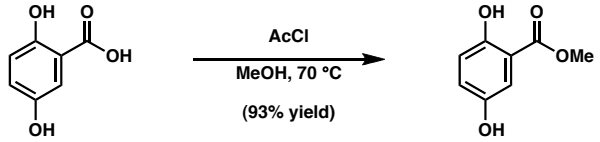
Hydroxybenzoquinone 331. A flamedried round-bottom flask under argon was charged with a solution of 2,6-di-*t*-butyl-4-methyl pyridine (307 mg, 1.49 mmol, 4 equiv) and CH_2Cl_2 (10 mL) and cooled to −78 °C. Then, a solution of $TiCl_4$ (82 μL, 0.746 mmol)) and CH_2Cl_2 (1.6 mL) was slowly introduced, followed by a solution of benzoquinone (**330**) (40.4 mg, 0.373 mmol, 1 equiv) in CH_2Cl_2 (10 mL). The reaction turned an orange-brown color. Then, a solution of silyl enol ether **229** (170 mg, 0.746 mmol, 2 equiv) in CH_2Cl_2 (5 mL) was added via syringe pump over a 3 h period, and the reaction became

maroon. Once the addition was complete, 6 M aq HCl (5 mL) was added at −78 °C, and the reaction was warmed to 23 °C, becoming pale yellow. After 3 h, MeOH (25 mL) was added, and the reaction was refluxed overnight. The reaction was cooled to 23 °C, then diluted with H_2O and hexanes. The suspension was extracted with CH_2Cl_2 (2 x). All organic layers were combined and washed with brine. The combined aqueous layers were back-extracted with CH_2Cl_2 (3 x). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane → EtOAc:hexane 5:95 eluent), affording hydroxybenzofuran **331** (41.8 mg, 51% yield based on benzoquinone (**330**)) as a colorless oil. R_f 0.19 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, purple spot, UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.71 (dd, J = 8.8 Hz, 2.5 Hz, 1H), 4.99 (s, 1H), 2.96 (app. d of sextuplet, J_{sext} = 6.9 Hz, J_d = 1.4 Hz, 1H), 2.55 (app. dd, J = 5.2 Hz, 1.9 Hz, 1H), 2.52 (app. dd, J = 5.2 Hz, 1.9 Hz, 1H), 2.00 (app. dddd, J = 34.7 Hz, 12.9 Hz, 5.8 Hz, 2.8 Hz, 1H), 1.99 (app. dddd, J = 32.2 Hz, 12.9 Hz, 5.5 Hz, 2.5 Hz, 1H), 1.69 (app. dddd, J = 63.8 Hz, 20.4 Hz, 10.2 Hz, 2.8 Hz, 1H), 1.68 (app. dddd, J = 56.9 Hz, 15.7 Hz, 7.7 Hz, 2.5 Hz, 1H), 1.31 (d, J = 6.9 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 151.2, 149.5, 129.9, 112.4, 111.3, 104.2, 32.2, 29.5, 21.5, 20.9, 18.9; IR (NaCl/$CDCl_3$): 3338 (br), 2962, 2932, 2854, 1619, 1596, 1456, 1395, 1377, 1336, 1283, 1191, 1152, 1125, 931, 800 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M+H]^+$ calc'd for $C_{13}H_{15}O_2$, 203.1072; found, 203.1079.



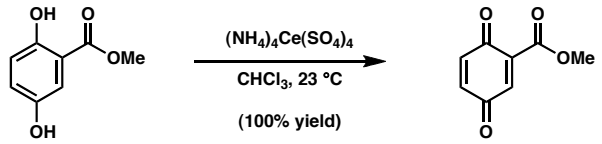
5-Hydroxy-6-Methoxybenzoquinone 334. A flamedried round-bottom flask under argon was charged with a solution of 2,6-di-*t*-butyl-4-methyl pyridine (309 mg, 1.50 mmol, 4 equiv) and CH_2Cl_2 (10 mL) and cooled to −78 °C. Then, a solution of $TiCl_4$ (83 μL, 0.751 mmol)) and CH_2Cl_2 (1.6 mL) was slowly introduced, followed by a solution of 2-methoxybenzoquinone (**333**) (51.9 mg, 0.373 mmol, 1 equiv) in CH_2Cl_2 (8.0 mL). The reaction turned a red-brown color. Then, a solution of silyl enol ether **229** (128 mg, 0.563 mmol, 1.5 equiv) in CH_2Cl_2 (5 mL) was added via syringe pump over a 2 h period, and the reaction became violet. Once the addition was complete, 6 M aq HCl (5 mL) was added at −78 °C, and the reaction was warmed to 23 °C, becoming orange-brown. THF (20 mL) was added, and the reaction was concentrated in vacuo to ~25 mL. More THF (20 mL) and 6 M aq HCl (3 mL) were added, and the pink reaction was heated to 65 °C overnight. The reaction was cooled to 23 °C and diluted with H_2O and hexanes. The suspension was extracted with Et_2O (3 x 20 mL). All organic layers were combined and washed with brine. The combined aqueous layers were back-extracted with CH_2Cl_2 (2 x). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane → EtOAc:hexane 5:95 eluent), affording 5-hydroxy-6-methoxybenzofuran **334** (28.3 mg, 30% yield based on 2-methoxybenzoquinone (**333**)) white powder. R_f 0.40 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, blue spot, UV, 254 nm); mp 127-129 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (s, 1H), 6.92 (s, 1H), 5.52 (s, 1H), 3.91 (s, 3H), 2.94 (app. d of sextuplet,

J_{sext} = 6.9 Hz, J_d = 1.9 Hz, 1H), 2.56 (app. dd, *J* = 5.5 Hz, 1.9 Hz, 1H), 2.53 (app. dd, *J* = 5.5 Hz, 1.9 Hz, 1H), 2.00 (app. dddd, *J* = 34.7 Hz, 12.9 Hz, 5.8 Hz, 2.8 Hz, 1H), 1.99 (app. dddd, *J* = 32.2 Hz, 12.9 Hz, 5.5 Hz, 2.5 Hz, 1H), 1.69 (app. dddd, *J* = 63.8 Hz, 20.4 Hz, 10.2 Hz, 2.8 Hz, 1H), 1.68 (app. dddd, *J* = 56.9 Hz, 15.7 Hz, 7.7 Hz, 2.5 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 148.4, 144.2, 142.2, 121.7, 112.3, 103.0, 94.9, 56.6., 32.3, 29.5, 21.6, 21.0, 19.0; IR (NaCl/$CDCl_3$): 3436 (br), 2959, 2928, 2854, 1623, 1595, 1491, 1445, 1374, 1343, 1318, 1189, 1136 cm^{-1}; LRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{14}H_{16}O_3$, 232.1; found, 232.1106.



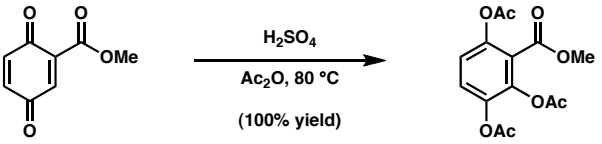
335 ***336***

2,5 Dihydroxy Methylbenzoate (336). A round-bottom flask containing MeOH (40 mL) was treated slowly with AcCl (460 μL) at 23 °C. Then, gentisic acid (**335**) (5.00 g, was added, and the reaction was heated to 70 °C for 21 h. Then, more AcCl (690 μL) was cautiously added to facilitate conversion. Heating to 70 °C was continued for 2 d. $KHCO_3$ and H_2O were added to quench the acid. The reaction was extracted with EtOAc (3 x 50 mL). Organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was concentrated from PhH, taken up in EtOAc:PhH (1:1), then purified via flash column chromatography on silica gel (EtOAc:hexane 30:70 eluent), giving 2,5 dihydroxy methylbenzoate (**336**) (5.06 g, 93% yield). Characterization data for this compound was identical to previously reported data.[51]



336 *337*

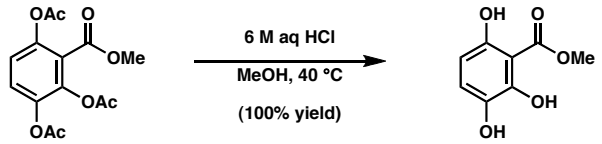
2-Methoxycarbonyl-1,4-benzoquinone (337). A round-bottom flask containing 2,5-dihydroxy methylbenzoate (**336**) (5.06 g, 30.1 mmol, 1.0 equiv) was charged with ceric ammonium sulfate (54.0 g, 90.3 mmol, 3.0 equiv) and $CHCl_3$ (stabilized with amylenes, 200 mL). The reaction was stirred vigorously for 20 h at 23 °C. It was then filtered over glass frits with the aide of $CHCl_3$ (stabilized with amylenes). The filtrate was concentrated in vacuo, giving 2-methoxycarbonyl-1,4-benzoquinone (**337**) (5.04 g, 100% yield). Characterization data for this compound was identical to previously reported data.[52]



337 *338*

2,3,6-Triacetoxy-methylbenzoate (338). A round-bottom flask was charged with acetic anhydride (98%, 5 mL), and 10 drops of conc. aq H_2SO_4 were cautiously added (reaction tends to exotherm) from a glass pipet. Then, this solution was added slowly (exothermic reaction begins) to another round-bottom flask containing 2-Methoxycarbonyl-1,4-benzozoquione (**337**) (427 mg, 2.57 mmol). The flask was capped and warmed slowly to 60 °C and kept at this temperature for 3 h. The reaction was cooled to 23 °C and added slowly to a rapidly stirred suspension of H_2O (30 mL) and EtOAc (30 mL). The reaction was stirred vigorously for 15 min and the organic phase was collected. The aqueous layer

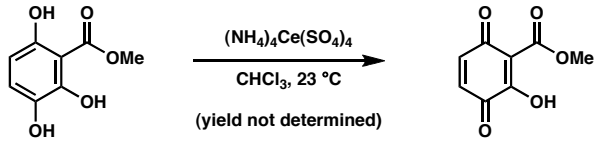
was extracted with EtOAc (2 x 20 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated multiple times from toluene (to remove residual acetic acid), giving 2,3,6-triacetoxy-methylbenzoate (**338**) as a viscous orange-yellow oil, which solidified to a tan solid in vacuo (820 mg, 100% yield). R_f 0.55 (3:97 MeOH/DCM), (UV, 254 nm); mp 68-70 °C ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 9.0 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 2.278 (s, 3H), 2.276 (s, 3H), 2.274 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 168.0, 167.7, 163.1, 147.0, 141.7, 141.0, 126.2, 121.4, 121.0, 52.8, 20.9, 20.8, 20.5; IR (NaCl/$CDCl_3$): 2955, 1774, 1733, 1617, 1479, 1455, 1372, 1281, 1188, 1040, 1018, 902, 878 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{14}H_{14}O_8$, 310.0688; found, 310.0683.



338 *339*

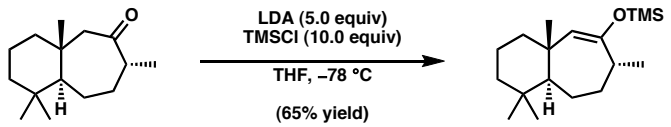
2,3,6-Trihydroxy-methylbenzoate (339). A round-bottom flask was charged with 2,3,6-triacetoxy-methylbenzoate (**338**) (1.00 g, 3.22 mmol), MeOH (40 mL), and 6 M aq HCl (8 mL). The reaction was warmed to 40 °C for 21 h. The reaction was then poured into H_2O (80 mL) and extracted with CH_2Cl_2 (3 x 40 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated, giving 2,3,6-trihydroxy-methylbenzoate (**339**) (595 mg, 100% yield) as a pale yellow powder. R_f 0.49 (50:50 EtOAc/hexane), (UV, 254 nm); mp 132-134 °C ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.89 (s, broad, 1H), 9.81 (s, broad, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.42 (d, *J* = 8.5 Hz, 1H), 5.22 (s, broad, 1H), 4.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 153.1, 146.7, 137.7, 122.4, 107.5, 100.1,

53.2; IR (NaCl/$CDCl_3$): 3434 (br), 1680, 1460, 1325, 1283, 1192, 1165, 1127, 1031, 996, 834, 811, 792 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_8H_8O_5$, 184.0372; found, 184.0375.



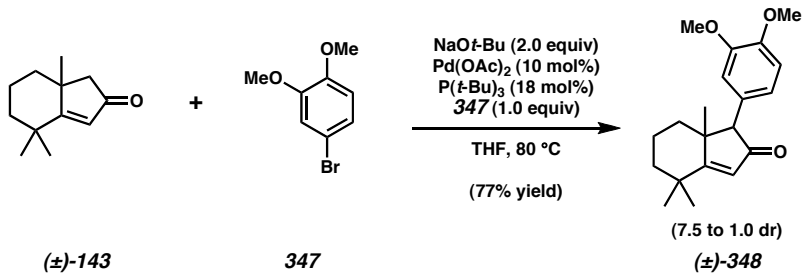
339 ***340***

2-Methoxycarbonyl-3-hydroxy-1,4-benzoquinone (340). A round-bottom flask was charged with 2,3,6-trihydroxy-methylbenzoate (**339**) (50 mg, 0.271 mmol) and ceric ammonium sulfate (487 mg, 0.814 mmol, 3 equiv), followed by $CHCl_3$ (10 mL, stabilized with amylenes). The reaction was stirred vigorously at 23 °C for 6 h, during which time the solvent became very orange-red. After the reaction was complete, it was filtered over glass frits, and the filtrate was concentrated, giving 2-methoxycarbonyl-3-hydroxy-1,4-benzoquinone (**340**) (yield not determined). R_f 0.30 (50:50 EtOAc/hexane), (visible red spot), (compound is unstable on silica gel); ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.40 (s, broad, 1H), 6.79 (d, *J* = 10.2 Hz, 1H), 6.72 (d, *J* = 10.2 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.7, 180.7, 171.1, 165.1, 139.2, 133.3, 132.5(?), 107.6(?), 53.8(?), 53.7(?) ; IR (NaCl/$CDCl_3$/$CHCl_3$): 3300 (br), 1734, 1682, 1662, 1575, 1449, 1393, 1356, 1325, 1249, 1210, 1117, 1030, 980, 850 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_8H_6O_5$, 182.0215; found, 182.0223.



(±)-304 *(±)-342*

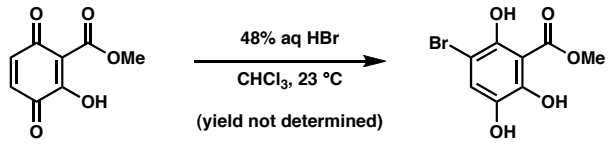
Silyl Enol Ether (±)-342. A flamedried round-bottom flask was charged with THF (6.0 mL) and *i*-Pr_2NH (240 μL, 1.71 mmol) and cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 624 μL, 1.56 mmol) was added dropwise. After 30 min, the reaction was cooled to –78 °C, and TMSCl (395 μL, 3.11 mmol, freshly distilled) was added. 5 min later, a solution of methylcycloheptanone **(±)-304** (69.3 mg, 0.311 mmol), and THF (2.0 mL) was introduced dropwise over a 10 min period. 20 min later, the reaction was quenched at –78 °C via addition of Et_3N (500 μL), followed by sat. aq $NaHCO_3$ (1.0 mL). The reaction was allowed to thaw to 25 °C. The reaction was diluted with H_2O (10 mL) and hexanes (5 mL). The suspension was extracted with Et_2O (3 x 10 mL). The organic layers were collected and the aqueous layer was extracted with Et_2O (3 x 15 mL). All org layers were combined, washed with water (20 mL) followed by brine (10 mL), dried (K_2CO_3), filtered, and concentrated. The residue was evaporated 3x from PhH to remove residual water and TMSOH, giving **(±)-342** (59.2 mg, 65% yield) as a colorless oil. R_f 0.53 (10:90 Et_3N/hexane), (*p*-Anisaldehyde, purple spot); ^{1}H NMR (300 MHz, C_6D_6): δ 4.75 (s, 1H), 2.45 (app. qdd, J_q = 7.2 Hz, J_{d1} = 7.2 Hz, J_{d2} = 2.5 Hz, 1H), 1.98-1.74 (m, 3H), 1.62-1.22 (m, 8H), 1.18 (d, J = 7.2 Hz, 3H), 1.11 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 155.1, 124.1, 51.9, 45.9, 43.6, 38.4, 37.1, 34.8, 33.9, 33.2, 24.5, 22.5, 21.5, 19.7, 18.0, 1.1(3C); IR (NaCl/neat film): 2929, 2868, 2846, 1685, 1655, 1645, 1460, 1384, 1375, 1251, 1168, 1150, 1131, 892, 841 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{18}H_{34}OSi$, 294.2379; found, 294.2365.



(±)-143 *347* *(±)-348*

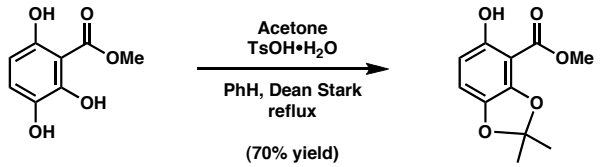
Aryl Enone (±)-348. In the glovebox, a vial was charged with NaO*t*-Bu (50.4 mg, 0.524 mmol), $Pd(OAc)_2$ (5.9 mg, 26.2 μmol), and a solution of P(*t*-Bu)$_3$ (9.5 mg, 47.2 μmol) in THF (1.0 mL). Then, a solution of the enone **(±)-143** (47 mg, 0.262 mmol), 4-bromoveratrole (**347**) (56.9 mg, 0.262 mmol), and THF (1.0 mL) was introduced. The vial was cycled out of the glovebox, sealed, and heated to 80 °C for 24 h. Then, the reaction was cooled to 23 °C and quenched with sat. aq NH_4Cl (1.0 mL). After 5 min, the reaction was diluted with H_2O and hexane, then extracted with EtOAc (4 x 8 mL). All organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane → 7:93 EtOAc:hexane → 15:85 EtOAc:hexane → 30:70 EtOAc:hexane eluent), affording aryl enone **(±)-348** (63.7 mg, 77% yield) as a yellow powder in 7.5:1.0 dr (major diastereomer not identified). R_f 0.57 (50:50 EtOAc/hexane), (UV, 254 nm); mp 132-136 °C ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)(Major Diastereomer Only): δ 6.83 (app. d, *J* = 8.1 Hz, 1H), 6.64 (app. d, *J* = 8.1 Hz, 1H), 6.59 (s, 1H), 6.00 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.49 (s, 1H), 1.98 (app. d, *J* = 12.7 Hz, 1H), 1.83 (app. dd, *J* = 27.6 Hz, 13.7 Hz, 1H), 1.71-1.50 (m, 3H), 1.46 (app. dd, *J* = 13.4 Hz, 11.9 Hz, 1H), 1.27 (s, 3H), 1.25 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)(Major Diastereomer Only): δ 207.5, 192.1, 148.8, 148.3, 128.9, 125.9, 122.8, 113.6, 111.3, 68.6, 56.1, 56.0, 49.1, 41.1, 39.9, 36.3, 31.4, 27.4, 25.1, 18.9; IR (KBr): 3082, 2965, 2939, 2915, 2838, 1692, 1602,

1520, 1470, 1255, 1235, 1165, 1143, 1028 cm^{-1}; HRMS-EI^+ (*m/z*): $[M]^+$ calc'd for $C_{20}H_{26}O_3$, 314.1882; found, 314.1875.



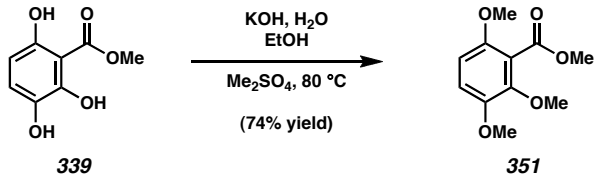
340 *349*

5-Bromo-2,3,6-trihydroxy-methylbenzoate (349). A vial was charged with 2-methoxycarbonyl-3-hydroxy-1,4-benzoquinone (**340**) (9 mg, 49.3 μmol) as a solution in $CHCl_3$ (1.0 mL, stabilized with amylenes). 48% aq HBr (200 μL) was added, causing the reaction to turn from yellow to red. Once the reaction was complete, it was diluted with H_2O and extracted with $CHCl_3$ (3 x). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified on a flash pipet column (2:98 EtOAc:hexane → 5:95 EtOAc:hexane → 10:90 EtOAc:hexane eluent), affording 5-bromo-2,3,6-trihydroxy-methylbenzoate (**349**) (yield was not determined) as a white powder. R_f 0.41 (50:50 EtOAc/hexane), (visible yellow spot); ^1H NMR (500 MHz, $CDCl_3$): δ 9.84 (s, 1H), 9.46 (s, 1H), 7.34 (s, 1H), 5.24 (s, 1H), 4.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 149.4, 146.4, 138.3, 125.4, 100.7, 99.5, 53.7; IR (NaCl/$CDCl_3$): 3427 (br), 3116, 2960, 2917, 2849, 1680, 1630, 1474, 1438, 1398, 1367, 1308, 1278, 1181 cm^{-1}; HRMS-EI^+ (*m/z*): $[M]^+$ calc'd for $C_8H_7O_5Br$, 261.9477; found, 261.9474.



339 *350*

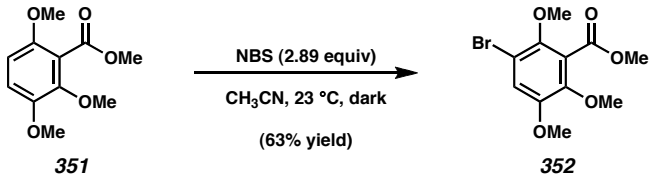
Acetonide 350. A round-bottom flask was charged with 2,3,6-trihydroxy-methylbenzoate (**339**) (100 mg, 0.543 mmol), PhH (10 mL), acetone (10 mL, Aldrich), and TsOH•H_2O (10.3 mg, 0.543 mmol, 1.0 equiv). The reactor was fitted with a Dean-Stark trap and heated to reflux (90 °C) for 20 h. Then, the reaction was cooled to 23 °C and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane → 10:90 EtOAc:hexane eluent), giving acetonide **350** (85.6 mg, 70% yield) as a yellow-white powder. R_f 0.72 (50:50 EtOAc/hexane), (*p*-Anisaldehyde, pink spot); mp 78-80 °C (PhH); ^{1}H NMR (300 MHz, C_6D_6): δ 10.99 (s, 1H), 6.59 (d, J = 8.5 Hz, 1H), 6.45 (d, J = 8.5 Hz, 1H), 3.38 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 170.4, 156.6, 148.7, 141.1, 119.7, 114.9, 107.9, 99.8, 52.2, 26.0 (2C); IR (KBr): 3110, 2994, 2953, 1810, 1683, 1634, 1490, 1468, 1440, 1390, 1376, 1358, 1223, 1124, 1099, 1029, 1010, 802 cm^{-1}; HRMS-EI$^+$ (*m/z*): [M]$^+$ calc'd for $C_{11}H_{12}O_5$, 224.0685; found, 224.0690.



339 *351*

2,3,6-Trimethoxy-methylbenzoate (351). A vial containing 2,3,6-trihydroxy-methylbenzoate (**339**)(50 mg, 0.271 mmol) was charged with absolute EtOH (1.0 mL) and Me_2SO_4 (500 μL, fractionally distilled at ambient pressure). The reaction was

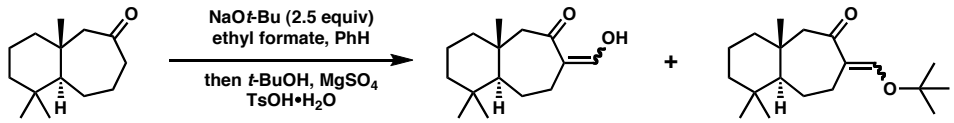
warmed until all solids had dissolved, then conc. aq KOH (500 μL) was added dropwise (there was a mild exotherm, and each drop caused a slight reddening of the reaction which quickly faded). Once the addition was complete, the reaction was sealed and heated to 80 °C. A precipitate gradually formed. At 3 h, the reaction was diluted with H_2O and extracted with Et_2O (4 x). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated from CH_2Cl_2. The residue was purified by flash column chromatography on silica gel (hexane → 10:90 EtOAc:hexane → 30:70 EtOAc:hexane eluent), affording 2,3,6-trimethoxy-methylbenzoate (**351**) (45.4 mg, 74% yield) as a colorless liquid. R_f 0.55 (50:50 EtOAc/hexane), (*p*-Anisaldehyde, pink spot); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (d, *J* = 9.0 Hz, 1H), 6.58 (d, *J* = 9.0 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ166.6, 150.7, 147.2, 147.0, 119.4, 114.5, 106.4, 61.6, 56.7, 56.4, 52.6; IR (NaCl/$CDCl_3$): 3002, 2947, 2908, 2839, 1736, 1591, 1493, 1465, 1285, 1257, 1212, 1190, 1167, 1141, 1098, 1062, 1014 cm^{-1}; HRMS-EI$^+$ (*m/z*): [M]$^+$ calc'd for $C_{11}H_{14}O_5$, 226.0841; found, 226.0840.



351 *352*

5-Bromo-2,3,6-trimethoxy-methylbenzoate (352). A vial was charged with a solution of 2,3,6-trimethoxy-methylbenzoate (**351**) (110 mg, 0.486 mmol) and CH_3CN (1.0 mL). *N*-bromosuccinimide (250 mg, 1.40 mmol) was added in one portion. The vial was sealed, and the reaction was stirred in the dark for 44 h. The reaction was then adsorbed directly onto silica gel, which was dried-loaded onto a silica gel column. The material was purified by flash column chromatography (10:90 EtOAc:hexane eluent), affording 5-

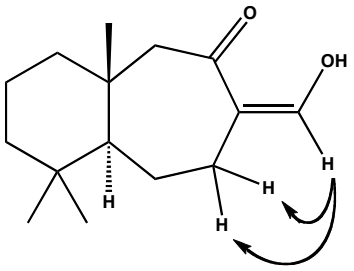
bromo-2,3,6-trimethoxy-methylbenzoate (**352**) (94.2 mg, 63% yield) as a colorless oil. R_f 0.39 (20:80 EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (s, 1H), 3.97 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 149.8, 147.6, 146.0, 125.3, 117.9, 110.9, 62.4, 61.7, 56.6, 52.7; IR (NaCl/$CHCl_3$): 3090, 3002, 2946, 2841, 1737, 1594, 1571, 1481, 1423, 1281, 1224, 1080, 1059, 1000, 937 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M+H]^+$ calc'd for $C_{11}H_{14}O_5Br$, 305.0024; found, 305.0030.



(±)-305 *(±)-357* (30% yield) *(±)-358* (25% yield)

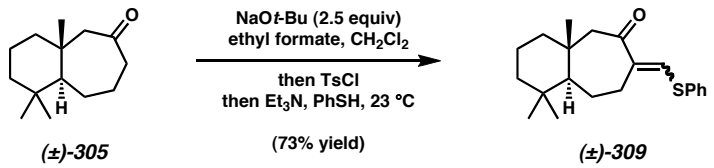
Vinylogous Acid (±)-357 and **Vinylogous Ester (±)-358**. A round-bottom flask was charged with a solution of cycloheptanone **(±)-305** (40 mg, 0.192 mmol, 1 equiv) in PhH (4.0 mL). Ethyl formate (78 μL, 0.960 mmol, 5 equiv) was introduced, followed by NaO*t*-Bu (46 mg, 0.480 mmol, 2.5 equiv). The reaction immediately turned yellow and was stirred vigorously at 23 °C for 30 min. The reaction was concentrated to a thick residue and *t*-BuOH (4.0 mL) was added along with $MgSO_4$ (231 mg, 1.92 mmol, 10 equiv), followed by TsOH•H_2O (128 mg, 0.672 mmol, 3.75 equiv). The vessel was closed and warmed to 65 °C for 48 h. Then, the reaction was cooled to 23 °C, diluted with PhH, and filtered through celite over glass frits with the aide of PhH. The filtrate was concentrated and evaporated from PhH several times to remove residual *t*-BuOH. The residue was then purified by flash chromatography on silica gel (hexane → 2:98 EtOAc:hexane → 8:92 EtOAc:hexane → 20:80 EtOAc:hexane eluent), giving vinylogous acid **(±)-357** (13.4 mg, 30% yield) as yellow oil. R_f 0.63 (20:80 EtOAc/hexane),

($KMnO_4$, yellow spot, UV, 254 nm); ^{1}H NMR (300 MHz, C_6D_6): δ 7.38 (app. d, J = 8.6 Hz, 1H), 2.21 (AB spin system, d, J_{AB} = 13.0 Hz, 1H), 2.00 (AB spin system, d, J_{AB} = 13.0 Hz, 1H), 1.84-1.78 (m, 2H), 1.64-1.54 (m, 1H), 1.41 (app. qt, J_q = 13.2 Hz, J_t = 3.6 Hz, 1H), 1.26-1.18 (m, 2H), 1.15 (app. d, J = 14.6 Hz, 1H), 1.08-0.82 (m, 3H), 0.89-0.75 (m, 1H), 0.82 (s, 3H), 0.78 (s, 3H), 0.66 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 201.9, 171.5, 114.8, 59.7, 59.3, 43.8, 42.9, 36.4, 34.8, 33.9, 29.3, 26.4, 22.1, 19.5, 18.9; IR ($NaCl/CH_2Cl_2$): 2929, 2867, 2845, 1642, 1586, 1446, 1272, 1209, 1089, 978 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{15}H_{24}O_2$, 236.1776; found, 236.1780. ^{1}H-nOesy-1D spectra were obtained for **(±)-357** (300 MHz, $CDCl_3$); the results are shown below:



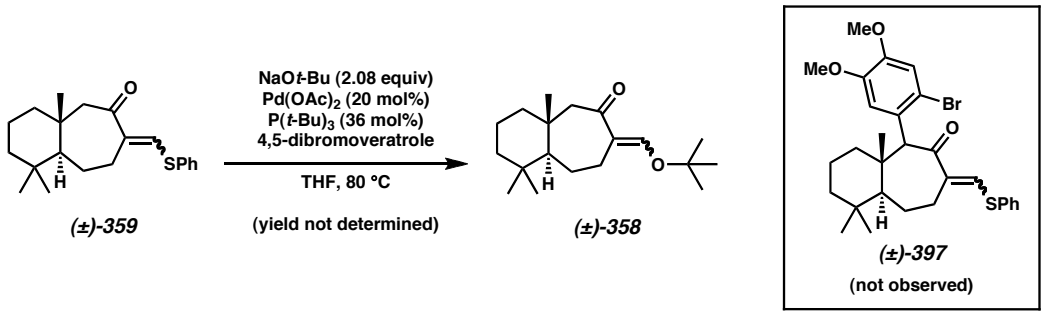
nOe's detected for *(±)-357*

Additionally, vinylogous ester **(±)-358** (14.2 mg, 25% yield) was obtained as a yellow oil. R_f 0.43 (20:80 EtOAc/hexane), ($KMnO_4$, yellow spot); ^{1}H NMR (300 MHz, C_6D_6): δ 7.90 (s, 1H), 3.24 (app. dd, J = 14.8 Hz, 7.4 Hz, 1H), 2.56 (AB spin system, d, J_{AB} = 12.4 Hz, 1H), 2.31 (AB spin system, d, J_{AB} = 12.4 Hz, 1H), 1.96-1.80 (m, 2H), 1.57-1.37 (m, 1H), 1.32-1.20 (m, 4H), 1.16-0.88 (m, 3H), 1.02 (s, 3H), 1.00 (s, 9H), 0.82 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 201.1, 150.1, 120.1, 79.1, 62.2, 59.7, 44.2, 43.1, 36.7, 34.8, 34.1, 28.3 (3C), 26.9, 25.2, 22.1, 19.8, 19.2; IR ($NaCl/CH_2Cl_2$): 2968, 2936, 2868, 2845, 1678, 1594, 1464, 1370, 1265, 1210, 1165 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{19}H_{32}O_2$, 292.2402; found, 292.2410.

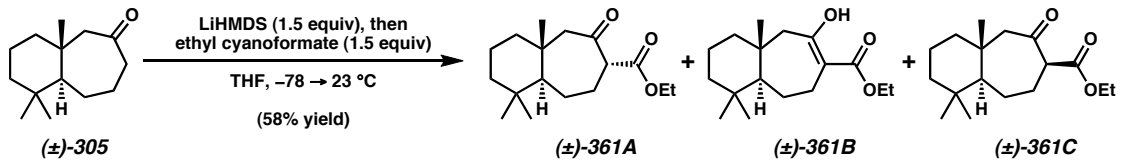


(±)-305 *(±)-309*

Vinylogous Thioester (±)-359. A round-bottom flask was charged with a solution of cycloheptanone **(±)-305** (100 mg, 0.48 mmol, 1.0 equiv), ethyl formate (200 μL, 2.4 mmol, 5 equiv), and CH_2Cl_2 (10 mL). NaO*t*-Bu (92 mg, 0.960 mmol, 2.0 equiv, weighed in glovebox) was then added, and the yellow reaction was stirred for 3.5 h at 23 °C. Then TsCl (recrystallized from Et_2O at –78 °C) (183 mg, 0.960 mmol, 2.0 equiv) was introduced, and the reaction was stirred at 23 °C for 5 min. Finally, Et_3N (1.0 mL) was added, followed by thiophenol (100 μL, 0.960 mmol, 2.0 equiv). After 4 h at 23 °C, the reaction was directly loaded onto a silica gel column and subjected to flash chromatography (5:95 EtOAc:hexane eluent). Semipure **(±)-359** thus obtained was repurified via flash column chromatography on silica gel (2:98 EtOAc:hexane eluent), affording pure vinylogous thioester **(±)-359** (114.7 mg, 73% yield) as a yellow oil. R_f 0.57 (20:80 EtOAc/hexane), ($KMnO_4$, yellow spot); ^{1}H NMR (300 MHz, C_6D_6): δ 7.94 (s, 1H), 7.32-7.23 (m, 2H), 6.94-6.86 (m, 3H), 2.88 (app. dd, J = 14.8 Hz, 7.4 Hz, 1H), 2.41 (AB spin system, d, J_{AB} = 12.6 Hz, 1H), 2.25 (AB spin system, d, J_{AB} = 12.6 Hz, 1H), 2.19 (app. dd, J = 13.4 Hz, 13.2 Hz, 1H), 1.83 (app. dd, J = 14.3 Hz, 7.7 Hz, 1H), 1.46-1.36 (m, 1H), 1.28-1.16 (m, 4H), 1.10-0.80 (m, 3H), 0.88 (s, 3H), 0.80 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 197.4, 137.8, 137.0, 134.7, 131.5, 130.9 (2C), 130.0 (2C), 61.0, 59.3, 44.0, 42.9, 37.0, 34.8, 34.0 30.7, 26.1, 22.0, 19.6, 19.2; IR ($NaCl/CH_2Cl_2$): 3058, 2930, 2866, 1671, 1561, 1480, 1441, 1321, 1209, 1195, 750 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M+H]^+$ calc'd for $C_{21}H_{29}SO$, 329.1939; found, 329.1933.

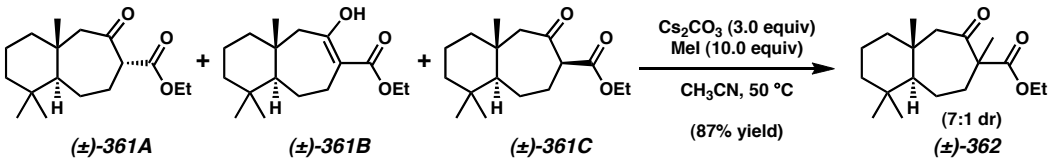


Attempted α-Arylation of (±)-359. In the glovebox, a vial was charged with P(*t*-Bu)$_3$ (7.5 mg, 36 μmol, 36 mol%), Pd(OAc)$_2$ (4.5 mg, 20 μmol, 20 mol%), and NaO*t*-Bu (20.0 mg, 0.208 mmol, 2.08 equiv). The vial was removed from the glovebox and charged with a solution of vinylogous thioester **(±)-359** (32.8 mg, 0.100 mmol, 1.00 equiv), 4,5-dibromoveratrole (29.7 mg, 0.100 mmol, 1.00 equiv), and THF (1.0 mL). The vial was sealed and heated to 80 °C for 22 h. The reaction was cooled to 23 °C and quenched with sat. aq NH_4Cl (1 mL) and diluted with H_2O (5 mL) and hexane (3 mL). The biphasic mixture was extracted with EtOAc (3 x 8 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane → 2:98 EtOAc:hexane → 5:95 EtOAc:hexane → 8:92 EtOAc:hexane → 20:80 EtOAc:hexane eluent), giving vinylogous ester **(±)-358** (yield was not determined). No α-aryl vinylogous ester **(±)-397** was observed. Characterization data for **(±)-358** can be found on page 356 above.



Ethyl β-Ketoester (as tautomers **(±)-361A**, **(±)-361B**, and **(±)-361C**). In the glovebox, a flamedried flask was charged with LiHMDS (77.1 mg, 0.461 mmol, 1.5 equiv) and removed from the glovebox. THF (10 mL) was introduced at 23 °C, followed by a solution of cycloheptanone **(±)-305** (64 mg, 0.307 mmol, 1.0 equiv) in THF (2.0 mL). After 30 min, the reaction was cooled to –78 °C, and ethyl cyanoformate (45.5 μL, 0.461 mmol, 1.5 equiv) was introduced. The reaction was allowed to warm to 23 °C and stirred for 16 h. Then, the reaction was quenched with sat. aq NH_4Cl (3.0 mL) and diluted with H_2O and hexanes. The biphasic mixture was extracted with EtOAc (3 x 20 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (3:97 EtOAc:hexane eluent), giving the ethyl β-Ketoester (50.1 mg, 58% yield) as a mixtute of tautomers **(±)-361A**, **(±)-361B**, and **(±)-361C** in the form of a pale yellow oil. R_f (3 tautomers): 0.66 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, sharp green spot), 0.64 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, sharp red spot), 0.64 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, broad yellow spot); ^{1}H NMR (300 MHz, $CDCl_3$) (**(±)-361B** only): δ 12.58 (s, 1H), 4.19 (q, J = 7.0 Hz, 1H), 4.18 (q, J = 7.0 Hz, 1H), 2.88 (app. dd, J = 15.4 Hz, 6.6 Hz, 1H), 2.44 (AB spin system, J_{AB} = 13.5 Hz, 1H), 1.90 (AB spin system, J_{AB} = 13.5 Hz, 1H), 1.77 (app. dd, J = 13.5 Hz, 7.7 Hz, 1H), 1.62 (app. qt, J_q = 13.9 Hz, J_t = 3.3 Hz, 1H), 1.46-1.34 (m, 3H), 1.30 (t, J = 7.0 Hz, 3H), 1.32-1.14 (m, 5H), 0.94, (s, 3H), 0.88 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (**(±)-361B** only): δ 176.9, 172.8, 101.4, 60.4, 60.2, 52.8,

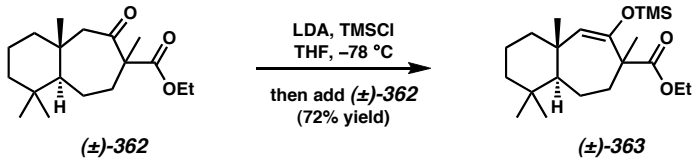
43.2, 42.7, 35.1, 34.6, 33.6, 25.3, 23.6, 21.8, 19.3, 18.2, 14.5; IR (NaCl/$CDCl_3$): 2931, 2867, 2845, 1742, 1703, 1644, 1614, 1463, 1401, 1379, 1306, 1276, 1247, 1216, 1178, 1047, 976, 861 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{17}H_{28}O_3$, 280.2038; found, 280.2031.



(±)-361A *(±)-361B* *(±)-361C* ***(±)-362***

α-Methyl-β-Ketoester (±)-362. A vial was charged with anhydrous Cs_2CO_3 (174 mg, 0.535 mmol, 3.0 equiv), followed by a solution of β-Ketoester (50 mg, 0.178 mmol, 1.0 equiv) (as a tautomeric mixture of **(±)-361A**, **(±)-361B**, and **(±)-361C**), MeI (111 μL, 1.78 mmol, 10.0 equiv), and CH_3CN (2.0 mL). The vessel was sealed and heated to 50 °C for 16 h. The reaction was then cooled to 23 °C and filtered over glass frits. The filtrated was concentrated in vacuo, then taken up in $CHCl_3$ and filtered through silica gel with the aide of $CHCl_3$. The pink filtrate was washed with sat. aq Na_2SO_3. The washing was back-extracted with $CHCl_3$ (2 x). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated, giving α-methyl-β-ketoester **(±)-362** as a mixture of diastereomers (>7:1 dr, major diastereomer unidentified) (45.5 mg, 87% yield) in the form of a colorless oil. R_f 0.57 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, pink spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.15 (app. q, J = 7.1 Hz, 2H), 2.46 (AB spin system, d, J_{AB} = 11.5 Hz, 1H), 2.23 (app. ddd, J = 14.7 Hz, 8.1 Hz, 2.1 Hz, 1H), 2.19 (AB spin system, d, J_{AB} = 11.5 Hz, 1H), 1.84-1.66 (m, 2H), 1.66-1.48 (m, 2H), 1.45-1.31 (m, 3H), 1.26 (s, 3H), 1.30-1.08 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 0.96 (s, 3H), 0.88 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (75

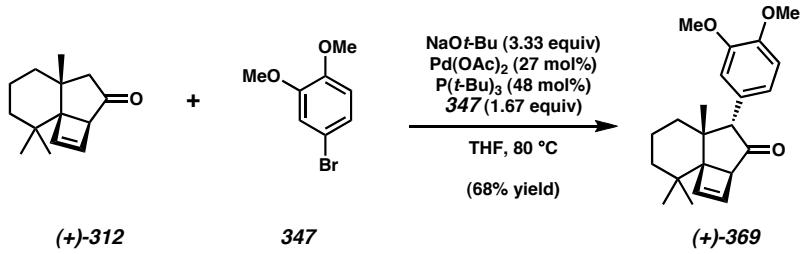
MHz, $CDCl_3$): δ 210.7, 173.6, 61.1, 28.9, 58.2, 57.9, 42.6, 37.23, 37.19, 34.7, 33.5, 23.3, 22.1, 21.6, 20.0, 19.2, 14.1; IR (NaCl/$CDCl_3$): 2930, 2869, 2847, 1738, 1703, 1460, 1389, 1311, 1261, 1180, 1102, 1057, 1035, 1018, 862 cm^{-1}; HRMS-EI^+ (*m/z*): $[M]^+$ calc'd for $C_{18}H_{30}O_3$, 294.2195; found, 294.2182.



(±)-362 *(±)-363*

Silyl Enol Ether (±)-363. A flamedried round-bottom flask was charged with THF (8.0 mL) and *i*-Pr_2NH (137 μL, 0.979 mmol, 6.0 equiv) and cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 326 μL, 0.816 mmol, 5.0 equiv) was added dropwise. After 30 min, the reaction was cooled to −78 °C, and TMSCl (186 μL, 1.47 mmol, 9.0 equiv, freshly distilled) was added. After 5 min, a solution of α-Methyl-β-Ketoester (>7:1 dr, major diastereomer unidentified) **(±)-362** (>7:1 dr, major diastereomer unidentified) **(**48 mg, 0.163 mmol, 1.0 equiv) in THF (2.0 mL) was added. After 1 h, Et_3N (1.0 mL) was added, followed by sat. aq $NaHCO_3$ (2.5 mL). The reaction was warmed to 23 °C, then diluted with H_2O and hexanes. The organic phase was collected, and the aqueous layer was extracted with Et_2O (2 x). All organic layers were combined, dried (K_2CO_3), filtered, and concentrated. The residue was concentrated several times from PhMe to remove residual H_2O and TMSOH, giving silyl enol ether **(±)-363** (43.2 mg, 72% yield) as a diastereomeric mixture (> 7:1 dr, major diastereomer not identified) in the form of a pale yellow oil. R_f 0.74 (2:20:80 Et_3N/EtOAc/hexane), (I_2/Sand, white spot); ^1H NMR (300 MHz, C_6D_6): δ 4.71 (s, 1H), 4.04 (app. q, *J* = 7.1 Hz, 2H), 2.53 (app. ddd, *J* = 13.5 Hz, 10.7 Hz, 4.1 Hz, 1H), 1.83-

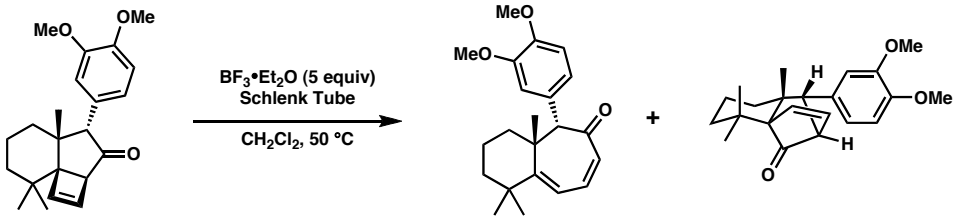
1.69 (m, 1H), 1.69-1.55 (m, 1H), 1.54 (s, 3H), 1.52-1.24 (m, 8H), 1.12 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H), 0.83 (s, 3H), 0.81 (s, 3H), 0.22 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 175.5, 151.9, 124.7, 60.7, 52.2, 52.0, 45.9, 43.3, 37.4, 35.7, 34.8, 33.6, 23.1, 22.2, 21.91, 21.88, 19.7, 14.7, 1.0 (3C); IR (NaCl/CH_2Cl_2): 2933, 2905, 2868, 2847, 1738, 1655, 1461, 1384, 1251, 1172, 1141, 1093, 878, 842 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M+H]^+$ calc'd for $C_{21}H_{39}O_3Si$, 367.2669; found, 367.2676.



(+)-312 ***347*** ***(+)-369***

Aryl Cyclobutene (+)-369. In the glovebox, a round-bottom flask was charged with NaO*t*-Bu (913 mg, 9.50 mmol, 3.33 equiv), $Pd(OAc)_2$ (171 mg, 0.760 mmol, 27 mol%), and P(*t*-Bu)$_3$ (277 mg, 1.37 mmol, 48 mol%). The vessel was removed from the glovebox, and THF (27 mL) was added. The reaction was stirred at 23 °C for 15 min (solution was bright orange-red) and a solution of semipure cyclobutene **(+)-312** (75% pure by mass, 776 mg total mass, (2.85 mmol pure cyclobutene, 582 mg pure cyclobutene)), 4-bromoveratrole (**347**) (1.031 g, 4.75 mmol, 1.67 equiv), and THF (10 mL) was added. The reaction was fitted with a condenser and heated to 80 °C for 30 h. Reaction went from bright red to chalky reddish-brown. Then the reaction was cooled to 23 °C and quenched with sat. aq NH_4Cl (12.0 mL) and diluted with H_2O (25 mL) and hexane (15 mL). The suspension was extracted with EtOAc (3 x 40 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5:95 EtOAc:hexane → 20:80

EtOAc:hexane eluent), affording aryl cyclobutene **(+)-369** (655 mg, 68% yield based on pure cyclobutene **(+)-312**) as a white powder. R_f 0.28 (20:80 EtOAc/hexane), (UV, 254 nm); mp 154-156 °C (EtOAc/hexane) (racemate), 145-147 °C (EtOAc/hexane) (95% ee); ^{1}H NMR (500 MHz, C_6D_6): δ 6.80 (d, *J* = 2.2 Hz, 1H), 6.74 (dd, *J* = 8.3 Hz, 2.2 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.15 (app. dd, *J* = 2.9 Hz, 0.9 Hz, 1H), 6.05 (app. dd, *J* = 2.9 Hz, 1.5 Hz, 1H), 4.35 (s, 1H), 3.54 (s, 3H), 3.46 (s, 3H), 3.12 (app. dd, *J* = 1.5 Hz, 0.9 Hz, 1H), 1.37-1.18 (m, 3H), 1.09 (app. ddd, *J* = 13.7 Hz, 3.7 Hz, 3.4 Hz, 1H), 1.08-1.02, (m, 1H), 1.07 (app. ddd, *J* = 12.9 Hz, 3.7 Hz, 3.2 Hz, 1H), 1.02 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 212.8, 149.93, 149.92, 142.6, 140.4, 126.9, 125.1, 117.1, 112.3, 63.1, 60.7, 57.1, 56.3, 56.0, 40.5, 39.3, 34.0, 33.6, 28.7, 25.9, 20.7, 18.6; IR (NaCl/$CHCl_3$): 2930, 2871, 2842, 1732, 1608, 1588, 1517, 1464, 1253, 1146, 1030, 739 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{28}O_3$, 340.2039; found, 340.2040. $[\alpha]^{25}_D$ +575.36° (*c* 0.620, $CHCl_3$), 95% ee.

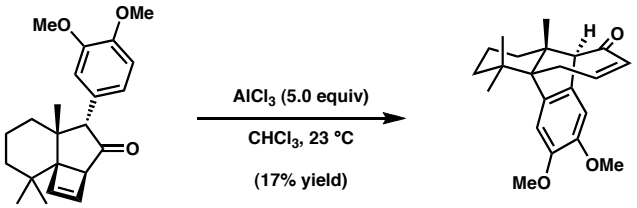


Aryl Cycloheptadienone (±)-356 and **Cargill Rearrangement Adduct (±)-370**. A Schlenk flask was charged with a solution of aryl cyclobutene **(±)-369** (563 mg, 1.65 mmol) and CH_2Cl_2 (52 mL). BF_3•Et_2O (1.05 mL, 8.27 mmol) was then introduced. The vessel was sealed and heated with stirring to 50 °C behind a blast shield for 20 h. The

reaction was cooled to 23 °C and added slowly to a suspension of brine (25 mL), sat. aq $NaHCO_3$ (25 mL), and CH_2Cl_2 (25 mL). After addition was complete, the reaction was stirred vigorously for 5 min. The organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane → 20:80 EtOAc:hexane → 30:70 EtOAc:hexane → 40:60 EtOAc:hexane eluent), affording aryl cycloheptadienone **(±)-356** (242 mg, 43% yield) as a yellow oil. R_f 0.61 (50:50 EtOAc/hexane), (*p*-Anisaldehyde, green spot, UV, 254 nm); ^{1}H NMR (500 MHz, C_6D_6): δ 7.01 (app. d, J = 2.0 Hz, 1H), 6.95 (app. dd, J = 8.3 Hz, 2.0 Hz, 1H), 6.53 (d, J = 8.3 Hz, 1H), 6.17 (d, J = 6.8 Hz, 1H), 6.16 (d, J = 2.0 Hz, 1H), 5.91 (dd, J = 6.8 Hz, 2.0 Hz, 1H), 3.55 (s, 1H), 3.48 (s, 3H), 3.38 (s, 3H), 1.82 (app. td, J_t = 13.2 Hz, J_d = 5.1 Hz, 1H), 1.53-1.43 (m, 1H), 1.29-1.16 (m, 2H), 1.24 (s, 3H), 1.13-1.00 (m, 2H), 1.00 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 198.5, 166.8, 150.1, 150.0, 137.0, 129.8, 129.5, 123.1, 121.0, 114.8, 112.3, 70.6, 56.1, 55.9, 41.0, 38.6, 38.3, 36.8, 33.6, 31.7, 25.2, 17.9; IR (NaCl/$CHCl_3$): 2924, 1645, 1573, 1516, 1463, 1419, 1264, 1236, 1148, 1028 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{28}O_3$, 340.2039; found, 340.2038.

In addition to **(±)-356**, several fractions containing a second compound in semipure form were collected from the flash column above. These fractions were combined and concentrated. The residue was purified by flash column chromatography on silica gel (50:50 CH_2Cl_2:PhH → 10:50:50 EtOAc:CH_2Cl_2:PhH), affording pure Cargill rearrangement adduct **(±)-370** (28.1 mg, 5.0% yield) as colorless crystals. One of these crystals was suitable for X-Ray analysis, allowing for determination of the relative

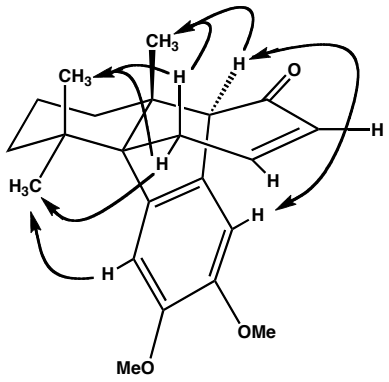
stereochemistry of the compound. R_f 0.74 (50:50 EtOAc/hexane), (*p*-Anisaldehyde, brown spot, UV, 254 nm); mp 116-118 °C (C_6D_6); ^{1}H NMR (500 MHz, C_6D_6); δ 6.79 (app. d, *J* = 8.3 Hz, 1H), 6.78 (app. s, 1H), 6.57 (app. d, *J* = 8.3 Hz, 1H), 6.32 (app. dd, *J* = 7.1 Hz, 3.9 Hz, 1H), 6.20 (app. dd, *J* = 7.1 Hz, 1.2 Hz, 1H), 3.54 (s, 3H), 3.44 (s, 3H), 2.83 (app. dd, *J* = 3.9 Hz, 0.7 Hz, 1H), 2.23 (s, 1H), 2.04 (app. td, J_t = 13.4 Hz, J_d = 3.9 Hz, 1H), 1.47 (app. qt, J_q = 13.7 Hz, J_t = 3.2 Hz, 1H), 1.35 (app. d, *J* = 14.2 Hz, 1H), 1.32-1.13 (m, 2H), 1.29 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.74 (app. d, *J* = 13.9 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6): δ 206.5, 150.2, 149.4, 134.6, 134.4, 134.1, 121.0, 113.2, 112.5, 64.0, 56.1, 56.0, 53.4, 40.2, 37.1, 34.3, 32.5, 32.4, 28.1, 26.9, 26.6, 19.6; IR ($NaCl/CHCl_3$): 2995, 2934, 2867, 2834, 1772, 1518, 1464, 1267, 1254, 1241, 1147, 1030, 750 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{28}O_3$, 340.2039; found, 340.2034.



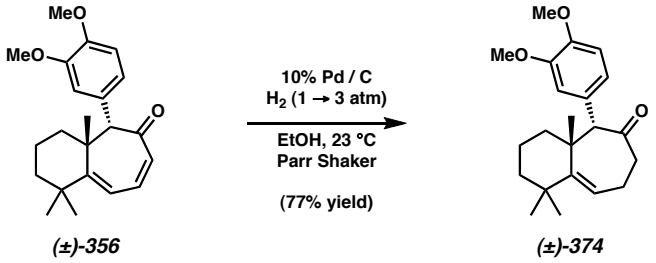
(±)-369 *(±)-373*

Friedel-Crafts Adduct (±)-373. A solution of aryl cyclobutene **(+)-369** (50 mg, 0.147 mmol, 1.0 equiv) in $CHCl_3$ (15.0 mL) was treated with $AlCl_3$ (98.0 mg, 0.735 mmol, 5.0 equiv, weighed in the glovebox). As the reaction stirred for 48 h, it went from peach-colored to maroon. After the reaction was complete, it was added dropwise to a solution of brine (20 mL) and sat. aq $NaHCO_3$ (20 mL) at 23 °C. The suspension was then extracted with $CHCl_3$ (2 x 20 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and oncentrated to ~500 μL total volume. The brown oil was purified by

preparative TLC (20:80 EtOAc:hexane eluent), affording the Friedel-Crafts adduct **(±)-373** (8.3 mg, 17% yield) as a yellow powder. R_f 0.24 (20:80 EtOAc/hexane), (UV, 254 nm); mp 152-155 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (s, 1H), 6.64 (s, 1H), 6.04 (app. ddd, *J* = 12.6 Hz, 5.5 Hz, 3.6 Hz, 1H), 5.66 (app. dd, broad, *J* = 12.6 Hz, 1.9 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.33 (app. d, broad, *J* = 1.6 Hz, 1H), 2.84 (app. d, broad, *J* = 1.9 Hz, 1H), 2.84 (app. dd, *J* = 9.0 Hz, 1.6 Hz, 1H), 1.72-1.58 (m, 1H), 1.54-1.26 (m, 4H), 1.43 (s, 3H), 1.26 (s, 3H), 1.24-1.00 (m, 1H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8, 148.4, 142.9, 139.5 135.5, 128.7, 110.2, 107.6, 73.1, 57.5, 56.3, 55.9, 46.4, 40.8, 39.9, 38.9, 37.5, 29.6, 26.9, 20.7, 18.4; IR (NaCl/$CDCl_3$): 2932, 1659, 1605, 1504, 1464, 1402, 1295, 1206, 1096, 1036, 914, 857, 755 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{28}O_3$, 340.2039; found, 340.2039. ^{1}H-nOesy-1D spectra were obtained for **(±)-373** (300 MHz, $CDCl_3$); the results are shown below:

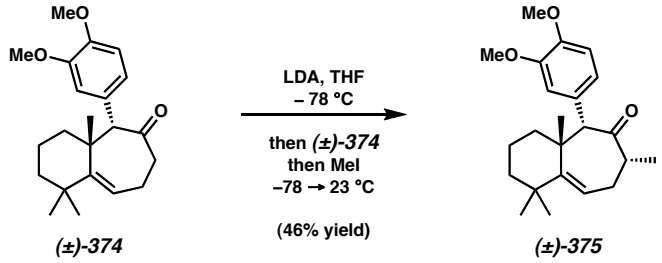


nOe's detected for *(±)-373*



(±)-356 *(±)-374*

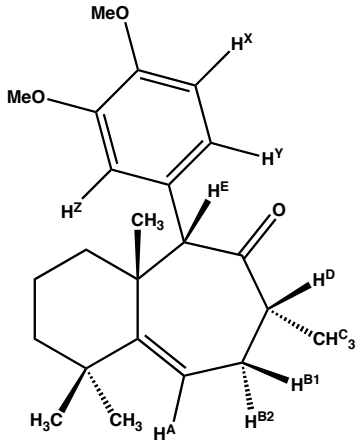
γ,δ-Unsaturated Aryl Cycloheptanone (±)-374. A Parr flask was charged with 10% w/w Pd/C (38 mg, 35.3 μmol, 5 mol%), followed by a solution of aryl cycloheptadienone **(±)-356** (240 mg, 0.705 mmol) in absolute EtOH (40 mL). The reaction was placed under H_2 (1 atm) at 23 °C on a Parr shaker for 40 h. At this time, more 10% w/w Pd/C (114 mg, 0.106 mmol, 15 mol%) was carefully added. The reaction was continued under H_2 (now 3 atm) for 20 h. Once the reaction was complete, it was filtered through celite over glass frits with the aide of EtOAc. The filtrate was concentrated and purified by flash chromatography on silica gel (hexane → 20:80 EtOAc:hexane eluent), giving γ,δ-unsaturated aryl cycloheptanone **(±)-374** (188 mg, 77% yield) as a colorless oil. R_f 0.31 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, blue spot); ^{1}H NMR (300 MHz, C_6D_6): δ 7.17 (app. d, J = 2.1 Hz, 1H), 7.09 (app. dd, J = 8.2 Hz, 2.1 Hz, 1H), 6.59 (app. d, J = 8.2 Hz, 1H), 5.77 (dd, J = 8.2 Hz, 5.2 Hz, 1H), 3.85 (s, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 2.60 (app. td, J_t = 13.8 Hz, J_d = 4.7 Hz, 1H), 2.30-1.86 (m, 5H), 1.60-1.42 (m, 1H), 1.36-1.20 (m, 1H), 1.27 (s, 3H), 1.16 (s, 3H0, 1.01 (s, 3H), 0.98-0.68 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6): δ 210.0, 153.5, 150.1, 149.7, 130.5, 123.6, 123.5, 115.3, 112.3, 71.8, 56.2, 55.9, 42.0, 41.0, 40.2, 37.8 (2C), 33.8, 33.7, 28.4, 23.7, 18.6; IR (NaCl/$CHCl_3$): 2933, 1695, 1603, 1588, 1515, 1464, 1379, 1252, 1146, 1029, 756 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{30}O_3$, 342.2195; found, 342.2183.



(±)-374 *(±)-375*

γ,δ-Unsaturated Methyl Aryl Cycloheptanone (±)-375. A round-bottom flask was charged with THF (4.2 mL) and *i*-Pr_2NH (29 μL, 0.209 mmol, 1.2 equiv), then cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 77 μL, 0.192 mmol, 1.1 equiv) was added dropwise. After 30 min, the reaction was cooled to −78 °C, and a solution of γ,δ-unsaturated aryl cycloheptanone **(±)-374** (60 mg, 0.174 mmol, 1 equiv) in THF (2.8 mL) was added dropwise via syringe pump over 1 h. Then, iodomethane (65 μL, 1.04 mmol, 6.0 equiv) was added swiftly. The reaction was kept at −78 °C for 6 h, then warmed to 23 °C and stirred for 16 h. Reaction gradually went from yellow to colorless. The reaction was quenched with sat. aq NH_4Cl (4 mL) and diluted with H_2O and hexanes. The suspension was extracted with EtOAc (3 x 20 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane → 5:95 EtOAc:hexane → 12:88 EtOAc:hexane eluent), giving unreacted starting material (**(±)-374**) (22.6 mg, 38% yield) and γ,δ-unsaturated methyl aryl cycloheptanone **(±)-375** (29.0 mg, 46% yield) as a colorless oil. R_f 0.48 (25:75 EtOAc/hexane), (*p*-Anisaldehyde, blue spot, UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, *J* = 1.9 Hz, 1H), 6.99 (dd, *J* = 8.3 Hz, 1.9 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 5.84 (app. t, *J* = 7.3 Hz, 1H), 4.37 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.90-2.70 (m, 2H), 2.08-1.88 (m, 2H), 1.68-1.28 (m, 4H), 1.31 (s, 3H), 1.16 (s, 3H), 1.12 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.00-0.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.6,

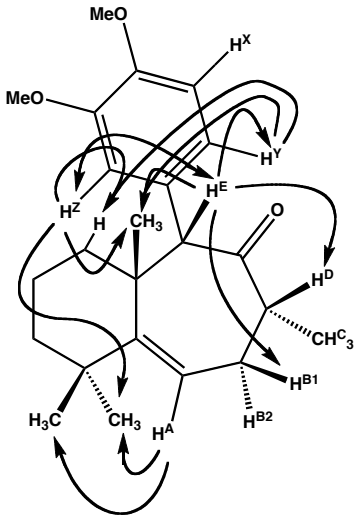
153.8, 148.1, 148.0, 128.2, 123.3, 21.1, 114.0, 110.2, 65.0, 56.0, 55.9, 49.0, 43.0, 40.2, 37.7, 35.4, 34.1, 32.2, 30.4, 28.1, 18.3, 15.5; IR ($NaCl/CHCl_3$): 2933, 1714, 1694, 1515, 1464, 1374, 1261, 1236, 1145, 1030, 757 cm^{-1}; HRMS-EI^+ (*m/z*): $[M]^+$ calc'd for $C_{23}H_{32}O_3$, 356.2352; found, 356.2352. ^1H-^1H gCOSY experiments (300 MHz, $CDCl_3$), were performed on **(±)-375**. The following spin systems were observed:



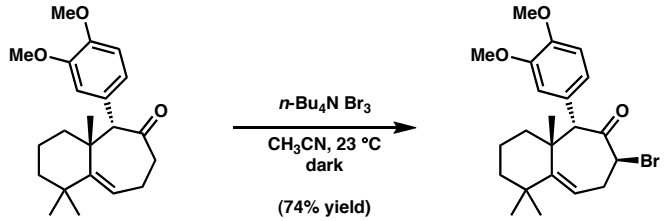
spin systems found for *(±)-375*

Resonance	Proton	Coupled Proton Spins
δ 5.84, t	H^A	H^{B1}, H^{B2}
δ 2.85, m	H^{B1}	H^A, H^{B2}, H^D
δ 2.03, m	H^{B2}	H^A, H^{B1}, H^D
δ 1.04, d	$3H^C$	H^D
δ 2.75, m	H^D	H^{B1}, H^{B2}, $3H^C$
δ 4.37, s	H^E	NONE
δ 6.75, d	H^X	H^Y
δ 6.99, dd	H^Y	H^X, H^Z
δ 7.32, d	H^Z	H^Y

Using the data from the gCOSY experiments along with proton assignments allowed for the assignments of some nOe's. ^1H-nOesy-1D spectra were obtained for **(±)-375** (300 MHz, $CDCl_3$); the results are shown below:



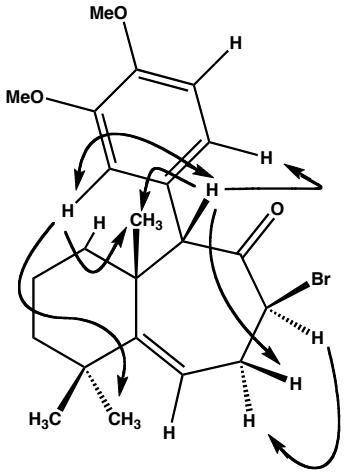
nOe's detected for*(±)-375*



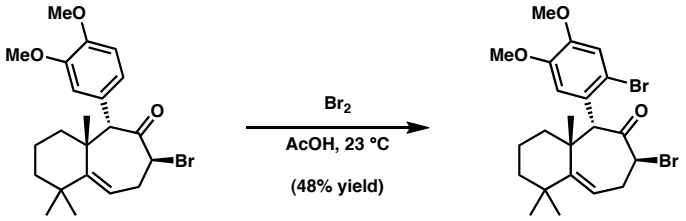
(±)-374 *(±)-376*

α-Bromo Aryl Ketone (±)-376. A round-bottom flask containing γ,δ-unsaturated aryl cycloheptanone **(±)-374** (75.4 mg, 0.220 mmol) was charged with CH_3CN (12 mL) and treated with *n*-Bu_4N Br_3 (106.2 mg, 0.220 mmol) at 23 °C in the dark. After 16 h, the pale yellow reaction was diluted with CH_2Cl_2 (20 mL) and sat. aq $NaHCO_3$ (10 mL), and the reaction became colorless. The organic phase was collected, and the aqueous and the aqueous layer was extracted with CH_2Cl_2 (2 x). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane → 8:92 EtOAc:hexane eluent), affording α-Bromo aryl ketone **(±)-376** (68.5 mg, 74% yield) as a white powder. R_f 0.40 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, blue spot, UV, 254 nm); mp 159-161 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 1.5 Hz, 1H), 7.03 (dd, J = 8.2 Hz, 1.5 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.79 (dd, J = 9.3 Hz, 5.8 Hz, 1H), 4.58 (s, broad, 1H), 4.22 (app. s, broad, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.09-2.93 (m, 1H), 2.79 (app. ddd, J = 15.1 Hz, 9.3 Hz, 5.8 Hz, 1H), 1.80 (app. td, J_t = 12.4 Hz, J_d = 5.8 Hz, 1H), 1.58-1.22 (m, 4H), 1.31 (s, 3H), 1.14 (s, 3H), 1.18-1.06 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.8, 148.4, 148.1, 128.2, 123.6, 119.2, 114.5, 110.3, 56.1, 55.9, 45.0 (broad), 39.5, 38.1, 34.8, 33.8, 33.0, 32.4, 26.6, 22.8, 18.0, 14.3; IR (NaCl/$CHCl_3$): 2954, 2868, 2837, 1723, 1515, 1464, 1375, 1273, 1254, 1238, 1145, 1029, 756 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{29}BrO_3$, 420.1308; found, 420.1300. ^{1}H-^{1}H homodecoupling

experiments (300 MHz, $CDCl_3$) were performed on **(±)-376**: The signal at δ 2.79 (app. ddd, *J* = 15.1 Hz, 9.3 Hz, 5.8 Hz, 1H) was suppressed with a decoupling current, resulting in a splitting change at δ 5.79 (dd, *J* = 9.3 Hz, 5.8 Hz, 1H → app. d, *J* ~9 Hz, broad, 1H). The signal at δ 3.09-2.93 (m, 1H) was suppressed with a decoupling current, resulting in splitting changes at δ 5.79 (dd, *J* = 9.3 Hz, 5.8 Hz, 1H → app. d, *J* ~9 Hz, broad, 1H) and δ 2.79 (app. ddd, *J* = 15.1 Hz, 9.3 Hz, 5.8 Hz, 1H → app. dd, *J* ~15 Hz, ~6 Hz, broad, 1H). The signal at δ 4.22 (app. s, broad, 1H) was suppressed with a decoupling current, resulting in splitting changes at δ 3.09-2.93 (m, 1H → m, 1H: lineshape change only) and δ 2.79 (app. ddd, *J* = 15.1 Hz, 9.3 Hz, 5.8 Hz, 1H → app. dd, *J* ~15 Hz, ~9 Hz, broad, 1H). The signal at δ 4.57 (s, 1H) was suppressed with a decoupling current, resulting no noticeable splitting changes. This information allowed for key nOe's to be correctly assigned. ^{1}H-nOesy-1D spectra were obtained for **(±)-376** (300 MHz, $CDCl_3$); the results are shown below:

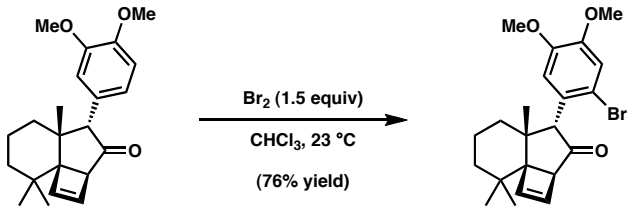


nOe's detected for *(±)-376*



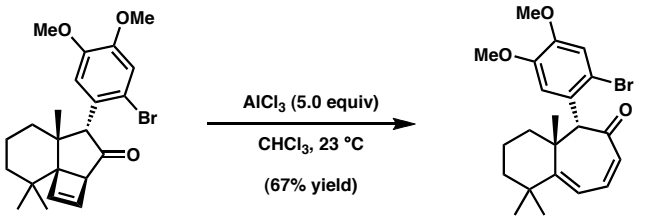
(±)-376 *(±)-377*

Bromoarene (±)-377. α-Bromo aryl ketone **(±)-376** (50 mg, 0.119 mmol) was dissolved in glacial AcOH (3.0 mL), and the solution was treated with a solution of Br_2 (19 mg, 0.119 mmol) in glacial AcOH (500 μL) at 23 °C. After 6 h, the reaction was added dropwise to a suspension of H_2O (30 mL) and $CHCl_3$ (30 mL). The organic phase was carefully treated with sat. aq $NaHCO_3$ (20 mL). The organic layer was then collected, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1:50:50 MeOH:CH_2Cl_2:PhH eluent), giving bromoarene **(±)-377** (28.6 mg, 48% yield) as a white semisolid. R_f 0.47 (20:80 EtOAc/hexane), (UV, 254 nm); mp 163-165 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.04 (s, 1H), 5.83 (app. dd, J = 9.6 Hz, 5.8 Hz, 1H), 5.55 (s, 1H), 4.15 (app. dd, J = 11.6 Hz, 5.8 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.21 (app. ddd, J = 14.6 Hz, 11.8 Hz, 5.8 Hz, 1H), 2.80 (app. ddd, J = 15.4 Hz, 9.6 Hz, 6.0 Hz, 1H), 1.88 (app. td, J_t = 12.4 Hz, J_d = 5.2 Hz, 1H), 1.63-1.39 (m, 3H), 1.34 (s, 3H), 1.27-1.21 (m, 2H), 1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.5, 158.3, 148.8, 147.3, 126.5, 119.2, 117.5, 116.0, 115.3, 56.3, 56.2, 55.1 (broad), 50.3, 47.3, 39.7, 38.3, 34.6, 34.1, 32.9, 32.0, 27.0, 18.0; IR (NaCl/$CDCl_3$): 2953, 2936, 2869, 2846, 1723, 1661, 1508, 1463, 1440, 1368, 1316, 1255, 1213, 1166, 1031, 912, 732 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{28}Br_2O_3$, 500.0385; found, 500.0382.



(+)-369 *(+)-379*

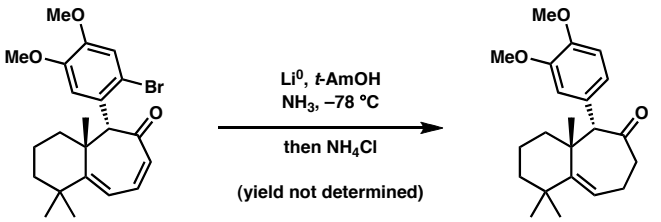
Bromoaryl Cyclobutene (+)-379. A round-bottom flask containing aryl cyclobutene **(+)-369** (652 mg, 1.92 mmol, 1.0 equiv) in $CHCl_3$ (35 mL) was treated with Br_2 (460 mg, 2.87 mmol, 1.5 equiv) in $CHCl_3$ at 23 °C over a 3 min period of slow addition. Once the addition was complete, the reaction was stirred for 1.5 h at 23 °C. Then, a mixture of sat. aq Na_2SO_3 (17.5 mL) and sat. aq $NaHCO_3$ (17.5 mL) was added. After 10 min, the organic phase was collected, and the aqueous layer was extracted with $CHCl_3$ (3 x 30 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (15:85 EtOAc:hexane eluent), affording bromoaryl cyclobutene **(+)-379** (610 mg, 76% yield) as a white solid. R_f 0.39 (20:80 EtOAc/hexane), (UV, 254 nm); mp 215-217 °C (EtOAc/hexane)(racemate), mp 240-242 °C (95% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (s, 1H), 6.65 (s, 1H), 6.57 (app. dd, *J* = 2.7 Hz, 0.8 Hz, 1H), 6.52 (app. dd, *J* = 2.7 Hz, 1.6 Hz, 1H), 5.21 (s, 1H), 3.84 (app. s, 6H), 3.13 (app. s, 1H), 1.60-1.40 (m, 3H), 1.34 (app. dd, *J* = 12.9 Hz, 3.8 Hz, 1H), 1.28-1.04 (m, 2H), 1.19 (s, 3H), 1.11 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.8, 148.7, 147.5, 142.7, 140.2, 125.0, 118.2, 115.9, 115.4, 62.9, 58.6, 56.3, 56.21, 56.18, 42.0, 39.0, 33.8, 33.5, 28.4, 25.6, 20.7, 17.9; IR (NaCl/$CDCl_3$): 2931, 2870, 2844, 1732, 1603, 1571, 1508, 1464, 1379, 1258, 1211, 1166, 1032, 914, 845, 735 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M+H]^+$ calc'd for $C_{22}H_{27}O_3{}^{81}Br$, 420.1123; found, 420.1119. $[\alpha]^{23}_D$ +527.47° (*c* 1.82, $CHCl_3$), 95% ee.



(+)-379 *(–)-380*

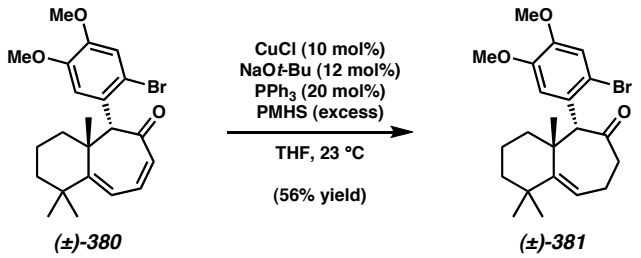
Bromoaryl Cycloheptadienone (–)-380. A round-bottom flask was charged with a solution of bromoaryl cyclobutene **(+)-379** (605 mg, 1.44 mmol, 1.0 equiv) and $CHCl_3$ (36 mL). The reaction was degassed with argon for 10 min. Then, $AlCl_3$ (959 mg, 7.20 mmol, 5.0 equiv, weighed in glovebox) was added at 23 °C, and the reaction went from pale yellow to deep maroon. After 24 h, the reaction was added at 0 °C to a rapidly stirred suspension of brine (35 mL), sat. aq $NaHCO_3$ (35 mL), and $CHCl_3$ (35 mL). The organic layer was collected, and the aqueous phase was extracted with $CHCl_3$ (3 x 35 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (10:90 EtOAc:hexane → 20:80 EtOAc:hexane eluent), affording bromoaryl cycloheptadienone **(–)-380** (404 mg, 67% yield) as a yellow soild. R_f 0.28 (20:80 EtOAc/hexane), (visible yellow spot, UV, 254 nm); mp 146-147 °C (EtOAc/hexane)(racemate), mp 144-147 °C (EtOAc/hexane)(95% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.03 (s, 1H), 6.70 (dd, J = 12.4 Hz, 8.8 Hz, 1H), 6.30 (d, J = 8.8 Hz, 1H), 6.08 (d, J = 12.4 Hz, 1H), 4.16 (s, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 1.75-1.33 (m, 5H), 1.37 (s, 3H), 1.21 (s, 3H), 1.22-1.04 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.7, 168.4, 148.4, 148.0, 137.6, 129.5, 128.1, 120.4, 118.0, 115.8, 112.4, 66.3, 56.1, 55.8, 42.8, 38.4, 37.9, 35.4, 33.5, 31.5, 25.3, 17.0; IR (NaCl/$CDCl_3$): 2934, 1644, 1572, 1509, 1463, 1440, 1377, 1267,

1248, 1230, 1205, 1159, 1030, 837 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{27}BrO_3$, 418.1144; found, 418.1158. $[\alpha]^{24}_D$ –437.31° (*c* 0.985, $CHCl_3$), 95% ee.



(±)-380 *(±)-374*

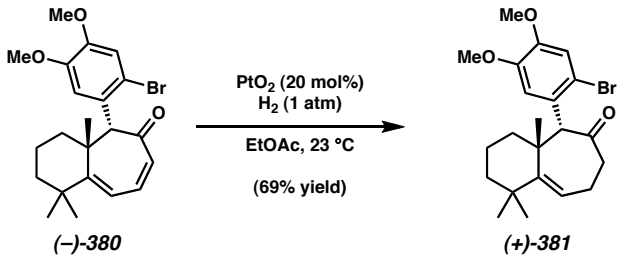
γ,δ-Unsaturated Aryl Cycloheptanone (±)-374. A 3-neck round-bottom flask fitted with a cold finger condenser, argon inlet, and mineral oil bubbler was cooled to –78 °C. The cold finger was charged with dry ice and acetone, and the system placed under a contiuous flow of argon. Ammonia gas was flushed through the system until the condensed volume of liquid NH_3 was ~10 mL. A solution of bromoaryl cycloheptadienone **(±)-380** (10 mg, 23.8 μmol), *tert* amyl alcohol (10.5 mg, 0.118 mmol), and THF (2 mL) was added. Lithium wire (1.2 mm diameter x 5 mm length, ~ 50 mg) was introduced. A deep blue coloration developed, and the reaction was stirred for 15 min. While the system was still under a steady flow of argon, more THF (10 mL) was added, followed by dropwise addition of sat. aq NH_4Cl (3.0 mL). The reaction became colorless and was carefully warmed to 0 °C. Once all of the ammonia had evaporated, the reaction was diluted with H_2O and hexanes and thawed to 23 °C. The organic phase was collected. The aqueous layer was extracted with EtOAc (1 x). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by preparative TLC on silica gel (EtOAc:hexane 20:80 eluent), giving γ,δ-Unsaturated Aryl Cycloheptanone **(±)-374** (yield was not determined). Characterization data for this compound can be found on page 367 above.



(±)-380 *(±)-381*

Bromoaryl–γ,δ–Unsaturated Cycloheptanone (±)-381. In the glovebox, a flamedried round-bottom flask was charged with CuCl (7.4 mg, 73.4 μmol, 5 mol%) and NaO*t*-Bu (8.5 mg, 88.1 μmol, 6 mol%). The reactor was cycled out of the glovebox and charged with PPh_3 (38.6 mg, 0.147 mmol, 10 mol%). THF (5.0 mL) was added, and the reaction was stirred for 20 min. PMHS (1.006 g/cm^3, high viscosity, 447 mg, 4.00 hydride equivalents) was introduced, immediately followed by a solution of bromoaryl cycloheptadienone **(±)-380** (617 mg, 1.47 mmol) in THF (5.0 mL). After 2 h, more PMHS (1.006 g/cm^3, high viscosity, ~1 g) was added to aide conversion. Additionally, a solution of CuCl (7.4 mg, 73.4 μmol, 5 mol%), NaO*t*-Bu (8.5 mg, 88.1 μmol, 6 mol%), PPh_3 (38.6 mg, 0.147 mmol, 10 mol%), and THF (1.0 mL) was added. Within 2 h, the reaction had become a thick, brown suspension. Sat. aq NH_4Cl (10 mL) was introduced, followed by 6 M aq HCl (5.0 mL). EtOAc (30 mL) was then added, and the polyphasic mixture was extracted with EtOAc (3 x 20 mL). The EtOAc-containing phases were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (5:95 EtOAc:hexane → 30:70 EtOAc:hexane → EtOAc eluent), giving semipure bromoaryl–γ,δ–unsaturated cycloheptanone **(±)-381**. The material was purified on a second silica gel flash column (5:95 EtOAc:hexane → 10:90 EtOAc:hexane eluent), giving pure bromoaryl–γ,δ–unsaturated cycloheptanone **(±)-381**

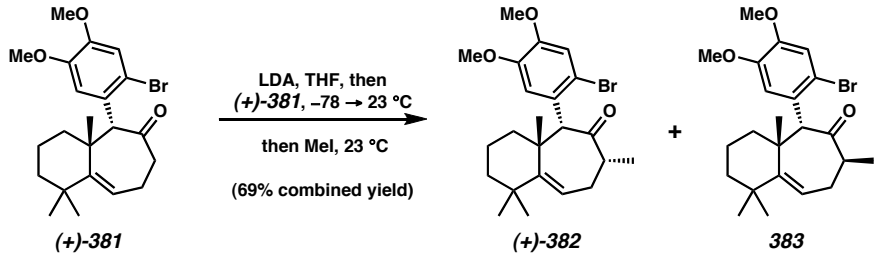
(365 mg, 56% yield) and unreacted starting material **(±)-380** (200 mg, 32% yield). Characterization data for **(+)-381** can be found on pages 377 and 378 below.



(–)-380 *(+)-381*

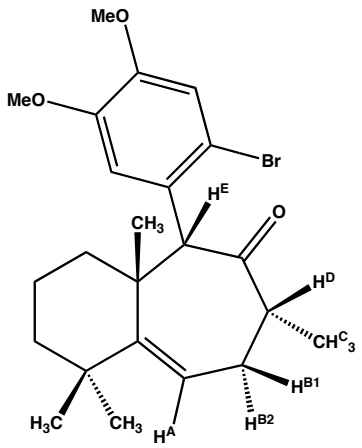
Bromoaryl–γ,δ–Unsaturated Cycloheptanone (+)-381. A round-bottom flask containing bromoaryl cycloheptadienone **(–)-380** (400 mg, 0.952 mmol) in EtOAc (ACS grade, 50 mL) was degassed with argon for 5 min. Then, PtO_2 (43.2 mg, 0.190 mmol, 20 mol%) was carefully added. The reaction was cooled to –78 °C, then evacuated/backfilled (vacuum/H_2 (1 atm)) (3 x). With vigorous stirring, the reaction was warmed to 23 °C under H_2 (1 atm). After 30 min, the reaction was concentrated, and the residue was taken up in PhH. It was purified by flash chromatography on silica gel (10:90 EtOAc:hexane eluent), giving bromoaryl–γ,δ–unsaturated cycloheptanone **(+)-381** (277 mg, 69% yield) as a white solid. R_f 0.41 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, blue spot, UV, 254 nm); mp 114-116 °C (EtOAc/hexane)(racemate), mp 121-123 °C (EtOAc/hexane)(95% ee) ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.02 (s, 1H), 6.00 (dd, *J* = 9.9 Hz, 4.4 Hz, 1H), 4.68 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.71-2.49 (m, 2H), 2.43-2.32 (m, 2H), 1.79-1.57 (m, 2H), 1.51-1.39 (m, 2H), 1.36-1.24 (m, 2H), 1.28 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.0, 153.8, 148.6, 147.8, 128.2, 122.7, 118.4, 115.6, 115.0, 66.0, 56.7, 56.2, 43.9, 41.5, 39.7, 37.8, 36.4, 33.7, 33.3, 27.5, 23.4, 17.9; IR (NaCl/$CDCl_3$): 2936, 2845, 1716, 1699, 1600, 1567,

1506, 1463, 1440, 1374, 1254, 1212, 1159, 1030, 732 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{29}BrO_3$, 420.1300; found, 420.1303. $[\alpha]^{25}_D$ +162.47° (*c* 1.250, $CHCl_3$), 95% ee.



Bromoaryl Methyl γ,δ–Unsaturated Cycloheptanones (+)-382 and **383**. A flamedried round-bottom flask was charged with THF (8.0 mL) and *i*-Pr_2NH (129 μL, 0.920 mmol, 1.2 equiv) and cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 338 μL, 0.844 mmol, 1.1 equiv) was added dropwise. After 30 min, the reaction was cooled to −78 °C. A solution of bromoaryl–γ,δ–unsaturated cycloheptanone **(+)-381** (324 mg, 0.767 mmol, 1.0 equiv) in THF (6.0 mL) was added, and the reaction gradually went from colorless to yellow. After 30 min, the reaction was warmed to 23 °C for 30 min. MeI (143 μL, 2.30 mmol, 3.0 equiv) was added. After 2 h had passed, the reaction was quenched with sat. aq NH_4Cl (5.0 mL). Then, H_2O (20 mL), hexanes (10 mL), and EtOAc (20 mL) were added. The organic layer was collected, and the aqueous layer was extracted with EtOAc (2 x 20 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (5:95 EtOAc:hexane → 20:80 EtOAc:hexane eluent), giving 4 main fractions. The first contained bromoaryl methyl γ,δ–unsaturated cycloheptanone **(+)-382** (130 mg, 39% yield) in pure enough form for characterization. The compound was a white solid. R_f 0.49 (20:80 EtOAc/hexane), (*p*-

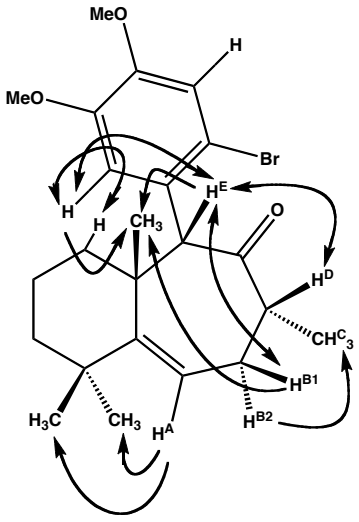
Anisaldehyde, blue spot); mp 53-57 °C (EtOAc)(racemate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (s, 1H), 6.97 (s, 1H), 5.87 (dd, J = 9.3 Hz, 6.0 Hz, 1H), 5.55 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.29 (app. dt, J_d = 15.1 Hz, J_t = 6.0 Hz, 1H), 2.77 (app. dq, J_d = 8.2 Hz, J_q = 6.6 Hz, 1H), 2.07 (app. ddd, J = 15.1 Hz, 9.3 Hz, 1.9 Hz, 1H), 1.91 (app. td, J_t = 12.6 Hz, J_d = 4.9 Hz, 1H), 1.61-1.19 (m, 5H), 1.27 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 1.03 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.6, 154.5, 148.4, 147.1, 126.9, 121.7, 117.8, 116.1, 114.8, 58.1, 56.02, 55.98, 50.4, 40.0, 37.8, 34.4, 34.2, 31.8, 29.9, 27.2, 18.1, 14.1; IR (NaCl/$CDCl_3$): 2934, 2869, 2846, 1716, 1601, 1569, 1506, 1464, 1440, 1370, 1302, 1255, 1212, 1163, 1032, 915, 733 cm^{-1}; HRMS-FAB^{+} (*m/z*): $[M]^{+}$ calc'd for $C_{23}H_{31}O_3{}^{81}Br$, 436.1436; found, 436.1437. $[\alpha]^{25}_{D}$ +37.00° (*c* 0.885, $CHCl_3$), 95% ee. ^{1}H-^{1}H gCOSY experiments (300 MHz, $CDCl_3$), were performed on **(+)-382**. The following spin systems were observed:



spin systems found for *(+)-382*

Resonance	Proton	Coupled Proton Spins
δ 5.87, dd	H^A	H^{B1}, H^{B2}
δ 3.29, dt	H^{B1}	H^A, H^{B2}, H^D
δ 2.07, ddd	H^{B2}	H^A, H^{B1}
δ 1.03, d	$3H^C$	H^D
δ 2.77, dq	H^D	H^{B1}, $3H^C$
δ 5.55, s	H^E	NONE

Using the data from the gCOSY experiments along with proton assignments allowed for the assignments of some nOe's. ^{1}H-nOesy-1D spectra were obtained for **(+)-382** (300 MHz, $CDCl_3$); the results are shown below:

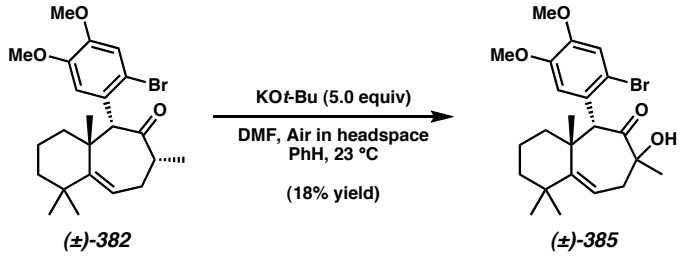


nOe's detected for *(+)-382*

The second fraction contained a mixture of **(+)-382** and **383** (52.4 mg, 16% yield). The third fraction contained bromoaryl methyl γ,δ−unsaturated cycloheptanone **383** (47.8 mg, 14% yield) in pure enough form for characterization. The compound was a white semisolid. R_f 0.44 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, blue spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.02 (s, 1H), 5.93 (dd, J = 9.6 Hz, 5.2 Hz, 1H), 4.89 (s, broad, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 2.70 (app. septet, J = 5.2 Hz, 1H), 2.42-2.20 (m, 1H), 2.24 (app. ddd, J = 14.8 Hz, 9.6 Hz, 5.2 Hz, 1H), 1.77 (app. ddd, J = 25.5 Hz, 12.9 Hz, 4.4 Hz, 1H), 1.64 (app. qt, J_q = 12.1 Hz, J_t = 3.3 Hz, 1H), 1.55-1.37 (m, 2H), 1.36-1.04 (m, 2H), 1.26 (s, 3H), 1.16 (app. s, 6H), 0.99 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.3 (broad), 153.8, 148.5, 147.5, 128.0 (broad), 122.0, 117.9, 115.6 (broad), 115.3, 56.6, 56.1, 44.5 (broad), 40.0, 37.8, 35.9 (broad), 33.9, 32.8, 31.9, 27.2, 18.1, 16.7; IR (NaCl/$CDCl_3$): 2933, 2869, 1716, 1600, 1569, 1505, 1463, 1440, 1374,

1254, 1213, 1160, 1031, 732; HRMS-FAB$^+$ (*m/z*): $[M]^+$ calc'd for $C_{23}H_{31}O_3{}^{81}Br$, 436.1436 ; found, 436.1422.

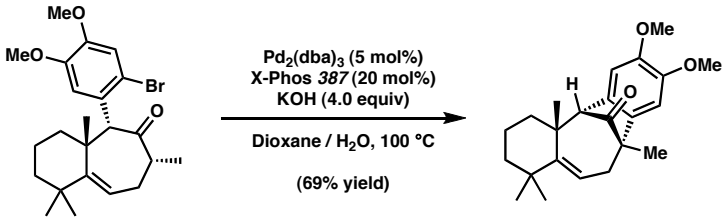
The fourth fraction contained unreacted starting material **(+)-381** (40.0 mg, 12% yield).



(±)-382 *(±)-385*

α-Hydroxyketone (±)-385. A vial (open to the air) was charged with KO*t*-Bu (28.0 mg, 0.229 mmol, 5.0 equiv) and dry, argon-degassed DMF (500 μL). The vial was then capped with air in the headspace, and a solution of bromoaryl methyl γ,δ–unsaturated cycloheptanone **(+)-382** (20.0 mg, 45.8 μmol, 1.0 equiv) in PhH (660 μL) was added at 23 °C. After 48 min, the reaction was quenched with sat. aq NH_4Cl (2.0 mL) and H_2O (1.0 mL). The reaction was diluted with more H_2O (4 mL), then extracted with $CHCl_3$ (3 x 8 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified on a 0.5 mm silica preparative TLC plate (20:80 EtOAc:hexane eluent), affording α-hydroxyketone **(±)-385** (3.8 mg, 18% yield) as a white semisolid. (The relative stereochemistry of the hydroxyl stereocenter was not determined, but it was entirely one epimer.) R_f 0.34 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, purple spot, UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 1H), 6.97 (s, 1H), 5.65 (app. dd, J = 6.6 Hz, 1.9 Hz, 1H), 4.00 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.76 (AB spin system, app. dd, J_{dAB} = 16.6 Hz, J_d = 1.9 Hz, 1H), 2.12 (s, 3H), 2.11 (app. td, J_t = 12.1 Hz, J_d = 3.8 Hz,

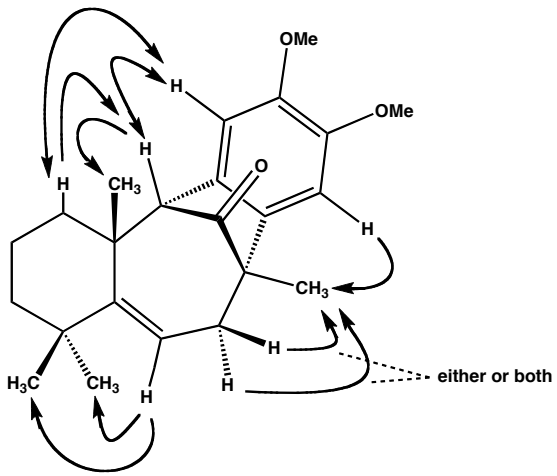
1H), 1.97 (AB spin system, app. dd, J_{dAB} = 16.6 Hz, J_d = 6.6 Hz, 1H), 1.73 (app. qt, J_q = 13.2 Hz, J_t = 3.6 Hz, 1H), 1.58-1.20 (m, 4H), 1.31 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H), 1.10-1.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.8, 151.3, 148.5, 147.6, 129.3, 117.7, 115.4, 114.83, 114.80, 81.4, 56.1, 53.2, 43.1, 42.3, 37.8, 37.5, 35.7, 34.2, 28.9, 27.8, 24.4, 19.3; IR (NaCl/$CDCl_3$): 3437 (broad), 2930, 1704, 1602, 1505, 1464, 1251, 1211, 1162, 1103, 1029, 913, 731 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M]^+$ calc'd for $C_{23}H_{31}BrO_4$, 450.1406; found, 450.1401.



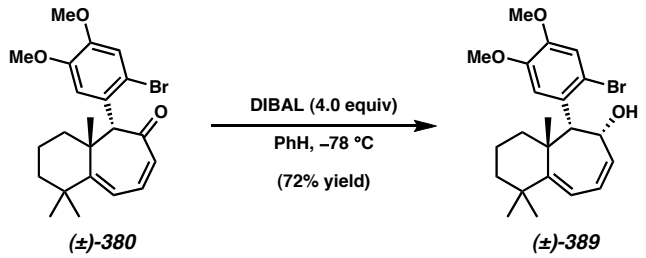
(±)-382 *(±)-388*

Tetracyclic Ketone (±)-388. In the glovebox, a vial was charged with $Pd_2(dba)_3$ (0.5 mg, 0.575 μmol, 5 mol%), X-Phos (**387**) (1.1 mg, 2.30 μmol, 20 mol%), and anhydrous, powdered KOH (2.6 mg, 46 μmol, 4.0 equiv). The vessel was cycled out, and a solution of bromoaryl methyl γ,δ−unsaturated cycloheptanones **(±)-382** (5.0 mg, 11.5 μmol, 1.0 equiv) in dioxane (250 μL) was added, followed by degassed H_2O (250 μL). The vial was sealed and heated to 100 °C. With time, the reaction went from colorless to yellow, but by 3.5 h, there was Pd black observed, and the reaction was once again colorless. At this time, the reaction was cooled to 23 °C and treated with 6 M aq HCl (50 μL) and diluted with H_2O (1 mL) and extracted with $CHCl_3$ (3 x 1 mL). All organic layers were combined, dried (Na_2SO_4), and concentrated to ~300 μL. The residue purified on a silica gel preparative TLC plate (20:80 EtOAc:hexane eluent), affording tetracyclic ketone **(±)-**

388 (2.8 mg, 69% yield) as a colorless oil. R_f 0.37 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, blue spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.64 (s, 1H), 5.32 (app. t, J = 6.0 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.80 (s, 1H), 2.23 (app. td, J_t = 12.6 Hz, J_d = 6.0 Hz, 1H), 2.18 (app. d, J = 6.0 Hz, 2H), 1.84-1.68 (m, 1H), 1.68-1.18 (m, 4H), 1.36 (s, 3H), 1.20 (s, 3H), 0.99 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.9, 150.9, 149.3, 148.2, 137.3, 131.7, 119.1, 108.6, 105.2, 64.3, 56.6, 56.2, 52.0, 43.1, 40.5, 38.6, 37.3, 37.2, 32.9, 32.6, 25.5, 18.5, 17.7; IR (NaCl/$CDCl_3$): 2928, 1747, 1608, 1500, 1464, 1310, 1244, 1058 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{23}H_{30}O_3$, 354.2195; found, 354.2183. ^{1}H-^{1}H homodecoupling experiments (300 MHz, $CDCl_3$) were performed on **(±)-388**: The signal at δ 5.32 (app. t, J = 6.0 Hz, 1H) was suppressed with a decoupling current, resulting in a splitting change at δ 2.18 (app. d, J = 6.0 Hz, 2H → app. s, 2H). The signal at δ 2.18 (app. d, J = 6.0 Hz, 2H) was suppressed with a decoupling current, resulting in a splitting change at δ 5.32 (app. t, J = 6.0 Hz, 1H → app. s, broad, 1H). This information allowed for key nOe's to be correctly assigned. ^{1}H-nOesy-1D spectra were obtained for **(±)-388** (300 MHz, $CDCl_3$); the results are shown below:



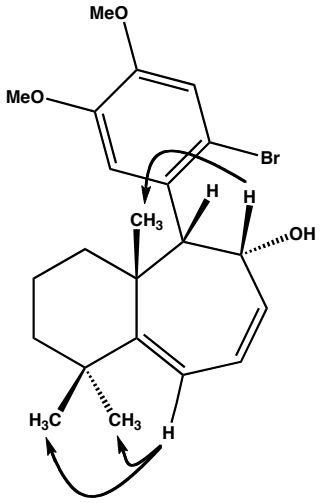
nOe's detected for *(±)-388*



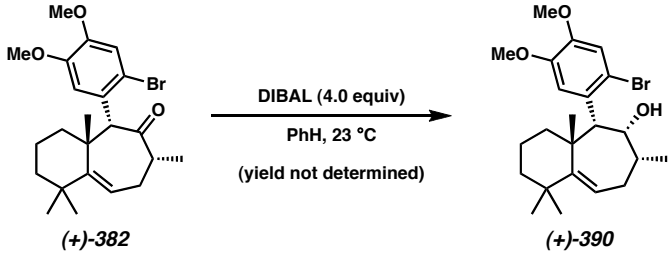
(±)-380 *(±)-389*

Bromoaryl Cycloheptadienol (±)-389. A flamedried round-bottom flask was charged with a solution of bromoaryl cycloheptadienone **(±)-380** (50 mg, 0.119 mmol, 1.0 equiv) and PhMe (10 mL), then cooled to –78 °C. DIBAL (0.67 M in PhMe, 721 μL, 0.476 mmol, 4.0 equiv) was added dropwise. After 15 min, the reaction was quenched at –78 °C with 1.0 M aq sodium, potassium tartrate (5.0 mL). Then, the reaction was warmed to 23 °C. The biphasic mixture was diluted with H_2O (25 mL) and extracted with PhH (3 x 30 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane → 5:95 EtOAc:hexane eluent), affording bromoaryl cycloheptadienol **(±)-389** (36.2 mg, 72% yield) as an off-white semisolid. R_f 0.24 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, blue spot, UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (s, 1H), 7.03 (s, 1H), 6.08 (d, J = 8.5 Hz, 1H), 5.93 (app. ddd, J = 12.1 Hz, 8.5 Hz, 2.7 Hz, 1H), 5.72 (app. d, broad, J = 12.1 Hz, 1H), 4.89 (app. ddt, J_{d1} = 9.3 Hz, J_{d2} = 6.9 Hz, J_t = 2.7 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.62 (app. dd, J = 6.9 Hz, 1.4 Hz, 1H), 1.78-1.62 (m, 1H), 1.43-1.32 (m, 4H), 1.33 (s, 3H), 1.17 (s, 3H), 1.11-1.00 (m, 1H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 148.1, 147.8, 135.3, 130.8, 123.1, 120.0, 119.7, 115.0, 114.1, 71.4, 56.1, 55.7, 53.5, 44.0, 38.8, 37.6, 36.5, 33.7, 32.6, 29.9, 17.4; IR (NaCl/$CDCl_3$): 3516 (broad), 2934, 2866, 1601, 1571, 1506, 1463, 1440, 1371, 1259, 1204, 1172, 1031, 912, 856, 793, 731 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{22}H_{29}O_3{}^{81}Br$, 422.1280; found,

422.1283. ^{1}H-nOesy-1D spectra were obtained for **(±)-389** (300 MHz, $CDCl_3$); the results are shown below:



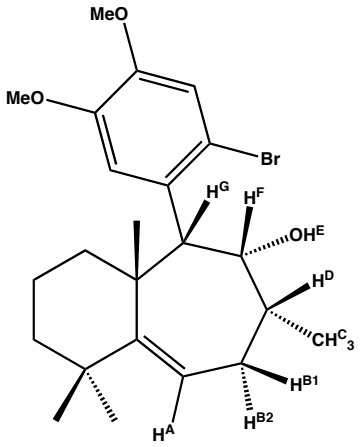
nOe's detected for *(±)-389*



(+)-382 *(+)-390*

Bromoaryl Methyl Cycloheptanol (+)-390. A round-bottom flask containing bromoaryl methyl γ,δ−unsaturated cycloheptanone **(+)-382** (128.0 mg, 0.293 mmol, 1.0 equiv) in PhH (10.0 mL) was treated with DIBAL (0.67 M in PhMe, 1.78 mL, 1.17 mmol, 4.0 equiv) at 23 °C. After 15 min, the reaction was added slowly to a rapidly stirred suspension of 1.0 M aq sodium, potassium tartrate (20.0 mL) and PhH (20.0 mL). After 90 min, the organic phase was collected. The aqueous layer was extracted with PhH (3 x 30 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated, giving bromoaryl methyl cycloheptanol **(+)-390** (135.8 mg, app. 106% yield) as a white

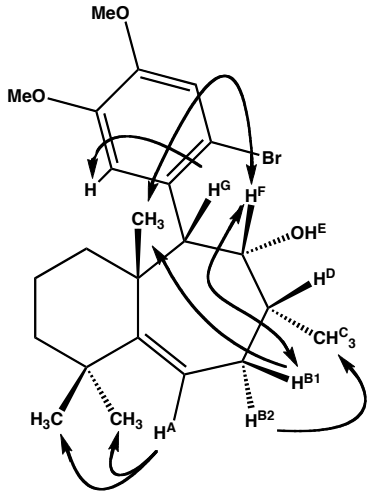
semisolid, which was immediately carried on to the next reaction. (The material was sufficiently pure for characterization.) R_f 0.45 (1:9 MeOH/DCM), (I_2/Sand); mp 203-205 °C (water); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 1H), 6.95 (s, 1H), 6.10 (dd, J = 8.8 Hz, 6.3 Hz, 1H), 4.01 (app. dd, J = 9.6 Hz, 8.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.88 (app. dt, J_d = 14.3 Hz, J_t = 6.9 Hz, 1H), 2.43 (d, J = 12.1 Hz, 1H), 2.23 (app. td, J_t = 13.7 Hz, J_d = 6.9 Hz, 1H), 1.95 (app. td, J_t = 12.9 Hz, J_d = 4.4 Hz, 1H), 1.83 (app. dd, J = 14.3 Hz, 9.1 Hz, 1H), 1.65-1.55 (m, 1H), 1.44-1.28 (m, 4H), 1.41 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 1.05 (d, J = 7.4 Hz, 3H), 0.92 (d, broad, J = 12.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 148.0, 136.5, 124.3, 115.8, 115.2, 114.5, 80.4, 56.5, 56.2, 56.1, 43.5, 39.8, 39.7, 38.8, 37.8, 34.6, 33.4, 30.1, 28.5, 18.6, 16.8; IR (NaCl/$CDCl_3$): 3552 (broad), 2928, 1602, 1504, 1464, 1376, 1244, 1209, 1161, 1031 cm^{-1}; HRMS-ESI$^+$ (*m/z*): $[M+H]^+$ calc'd for $C_{23}H_{34}O_3Br$, 437.1691; found, 437.1678. $[\alpha]^{25}_D$ +14.21° (*c* 2.00, $CHCl_3$), 95% ee. ^{1}H gCOSY experiments (300 MHz, $CDCl_3$) were performed on **(+)-390**. The following spin systems were observed:



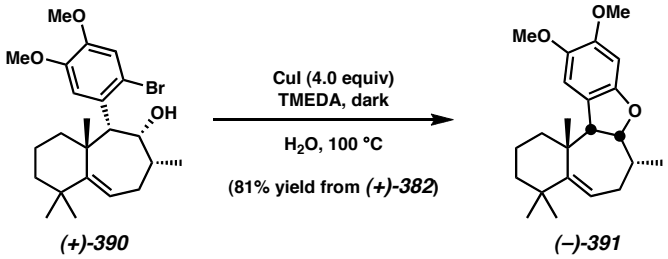
spin systems found for *(+)-390*

Resonance	Proton	Coupled Proton Spins
δ 6.10, dd	H^A	H^{B1}, H^{B2}
δ 2.88, dt	H^{B1}	H^A, H^{B2}
δ 1.83, dd	H^{B2}	H^A, H^{B1}
δ 1.05, d	$3H^C$	H^D
δ 2.23, td	H^D	$3H^C$
uncertain	H^E	uncertain
δ 4.01, dd	H^F	H^G
δ 2.34, d	H^G	H^F

Using the data from the gCOSY experiments along with proton assignments allowed for the assignments of some nOe's. ^{1}H-nOesy-1D spectra were obtained for **(+)-390** (300 MHz, $CDCl_3$); the results are shown below:



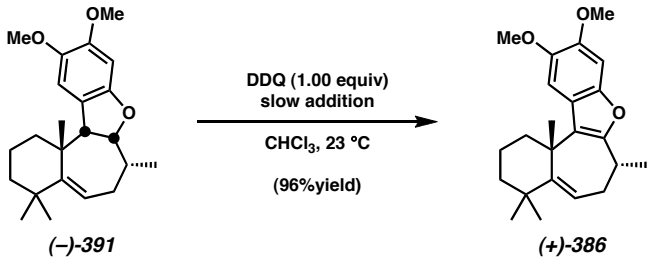
nOe's detected for *(+)-390*



(+)-390 *(–)-391*

Dihydrobenzofuran (–)-391. A round-bottom flask containing bromoaryl methyl cycloheptanol **(+)-390** (~128 mg (from the previous reaction), 0.293 mmol (estimated), 1.0 equiv) was charged with freshly distilled TMEDA (5.0 mL) and H_2O (5.0 mL). The suspension was degassed with argon for 10 min and CuI (223 mg, 1.17 mmol, 4.0 equiv) was introduced. The reactor was fitted with a reflux condenser and heated to 100 °C in the dark under N_2 for 18 h. The reaction was cooled to 23 °C and diluted with H_2O (50 mL). The suspension was then extracted with CH_2Cl_2 (3 x 25 mL). All organic layers

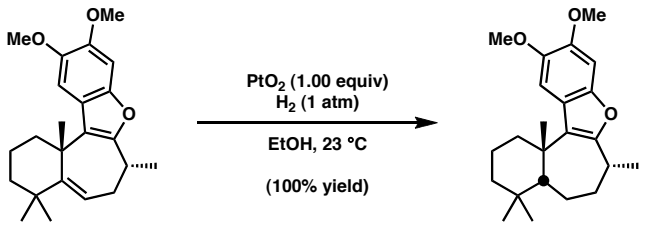
were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5:95 EtOAc:hexane eluent), affording dihydrobenzofuran **(–)-391** (85.7 mg, 81% over 2 steps from **(+)-382**) as a yellow oil. R_f 0.48 (20:80 EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H), 6.29 (s, 1H), 5.29 (dd, J = 5.2 Hz, 4.9 Hz, 1H), 4.71 (dd, J = 8.9 Hz, 3.6 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.54 (d, J = 8.9 Hz, 1H), 2.30 (app. ddd, J = 14.3 Hz, 6.9 Hz, 3.6 Hz, 1H), 2.19 (app. td, J_t = 13.5 Hz, J_d = 4.4 Hz, 1H), 1.82 (app. qt, J_q = 12.2 Hz, J_t = 4.4 Hz, 1H), 1.60 (app. dd, J = 6.9 Hz, 5.8 Hz, 1H), 1.62-1.34 (m, 4H), 1.43 (s, 3H), 1.18-0.95 (m, 1H), 1.04 (s, 3H), 1.00 (s, 3H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 148.9, ,141.7, 128.4, 123.7, 120.5, 110.8, 93.8, 88.4, 58.6, 57.1, 56.0, 41.7, 41.2, 39.8, 36.8, 35.7, 34.1, 32.9, 32.4, 30.5, 18.6, 18.3; IR (NaCl/$CDCl_3$): 2933, 2970, 2841, 1618, 1494, 1454, 1377, 1303, 1210, 1165, 1097, 996, 976, 908, 832 cm^{-1}; HRMS-ESI$^+$ (*m/z*): $[M+H]^+$ calc'd for $C_{23}H_{33}O_3$, 357.2430; found, 357.2419. $[\alpha]^{27}_D$ –59.10° (*c* 1.385, $CHCl_3$), 95% ee.



(–)-391 *(+)-386*

Benzofuran (+)-386. A round-bottom flask containing dihydrobenzofuran (–)-**391** (27.7 mg, 77.7 μmol) was charged with $CHCl_3$ (9.0 mL). A solution of DDQ (17.6 mg, 77.7 μmol) in $CHCl_3$ (5.0 mL) was added via syringe pump over a 5 h period at 23 °C. Then the reaction was filtered through a short plug of silica gel with the aide of $CHCl_3$, giving benzofuran **(+)-386** (26.6 mg, 96% yield) as a white semisolid. R_f 0.50 (20:80

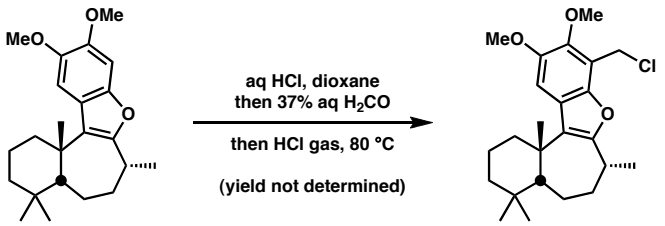
EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (s, 1H), 6.94 (s, 1H), 5.95 (app. dd, J = 9.6 Hz, 5.8 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.13 (app. qt, J_q = 6.9 Hz, J_t = 3.4 Hz, 1H), 2.70-2.60 (m, 2H), 2.20 (app. ddd, J = 14.0 Hz, 9.6 Hz, 4.4 Hz, 1H), 1.90-1.75 (m, 2H), 1.75-1.53 (m, 2H), 1.63 (s, 3H), 1.47-1.33 (m, 1H), 1.30 (d, J = 6.9 Hz, 3H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 154.2, 148.2, 146.9, 144.9, 121.9, 121.4, 120.5, 106.1, 95.1, 57.2, 56.3, 40.6, 38.6, 37.8, 37.6, 34.0, 33.8, 33.5, 31.7, 27.1, 18.7, 18.4; IR (NaCl/$CDCl_3$): 3056, 2930, 2868, 2832, 1624, 1489, 1464, 1440, 1313, 1276, 1213, 1198, 1165, 1124, 1002, 733 cm^{-1}; HRMS-EI$^+$ (*m/z*): [M]$^+$ calc'd for $C_{23}H_{30}O_3$, 354.2195; found, 354.2199.



(+)-386 *394*

Benzofuran 394. A round-bottom flask containing benzofuran **(+)-386** (5.0 mg, 14.1 μmol, 1.0 equiv) was charged with absolute EtOH (2.0 mL). The solution was degassed with argon for 5 min. Then, PtO_2 (3.0 mg, 14.1, μmol, 1.0 equiv) was introduced. The reaction was cooled to –78 °C and purged/backfilled with vacuum and H_2 (1 atm) (3 x). Then, the reaction was warmed to 23 °C and stirred vigorously under H_2 (1 atm) for 20 h. The reaction was then concentrated and taken up in EtOAc. The mixture was filtered through silica gel with the aide of EtOAc. The filtrate was concentrated, affording benzofuran **394** (5.0 mg, 100% yield) as a white semisolid. R_f 0.48 (20:80 EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H), 6.98 (s, 1H),

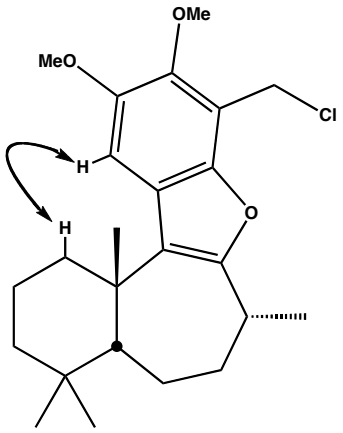
3.901 (s, 3H), 3.896 (s, 3H), 3.19-3.10 (m, 1H), 2.80-2.68 (m, 1H), 2.27-2.15 (m, 1H), 1.98 (app. q, J = 12.7 Hz, 1H), 1.80 (app. q, J = 12.4 Hz, 1H), 1.67-1.59 (m, 1H), 1.41 (d, J = 6.8 Hz, 3H), 1.50-0.80 (m, 6H), 1.31 (s, 3H), 0.97 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.2, 146.5, 145.3, 120.4, 104.7, 95.0, 56.7, 56.2, 54.2 (broad), 45.7 (broad), 41.8 (broad), 38.8 (broad), 35.8, 35.1 (broad), 32.7, 32.5 (broad), 30.6, 29.8, 26.6, 21.5, 18.8; IR (NaCl/$CDCl_3$): 2944, 2863, 1622, 1489, 1383, 1322, 1294, 1217, 1198, 1138, 1044 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{23}H_{32}O_3$, 356.2352; found, 356.2351.



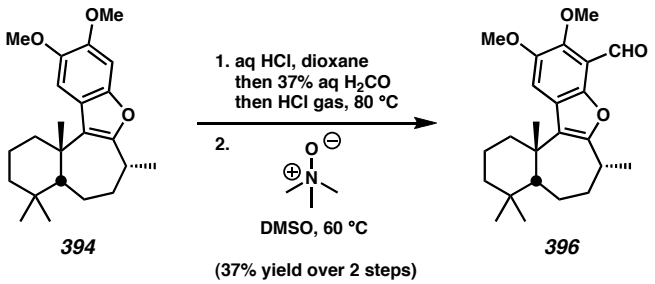
394 ***395***

Benzyl Chloride 395. A vial containing benzofuran **394** (4.0 mg, 11.2 μmol) and dioxane (degassed with argon, 100 μL) was treated dropwise with conc. aq HCl (100 μL) at 23 °C. The reaction turned yellow. 37% aq formaldehyde (100 μL) was introduced, followed by HCl gas (generated via slow addition of conc. aq H_2SO_4 to NaCl), which was bubbled in steadily for 3 min. The reaction became yellow-orange. The vessel was sealed and heated to 50 °C for 30 min followed by 80 °C for 30 min, during which time the reaction turned maroon. The vessel was cooled to 23 °C and 6 M aq HCl (1 mL) was added along with $CHCl_3$ (1 mL). The reaction was stirred vigorously for 10 min, then the organic phase was collected. The aqueous layer was extracted with $CHCl_3$ (2 x 1 mL). All organic layers were combined, carefully washed with sat. aq $NaHCO_3$ (2 x 1 mL),

dried (Na_2SO_4), filtered, and concentrated. The residue was purified on a pipet flash column containing silica gel (10:90 EtOAc:hexane eluent), giving semipure benzyl chloride **395** (yield not determined) as a yellow oil. R_f 0.60 (20:80 EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (s, 1H), 4.933 (app. s, 1H), 4.929 (app. s, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.24-3.08 (m, 1H), 2.70 (app. d, broad, *J* = 14.1 Hz, 1H), 2.32-2.12 (m, 2H), 1.71-1.59 (m, 2H), 1.48-1.05 (m, 6H), 1.45 (d, *J* =7.1 Hz, 3H), 1.26 (s, 3H), 0.98 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (not performed); IR (not performed); LCMS-APCI$^+$ (*m/z*): $[M+H]^+$ calc'd for $C_{24}H_{34}O_3{}^{35,37}Cl$, 404, 406; found, 404, 406, and 369 $(M+H-{}^{35,37}Cl)^+$. ^{1}H-nOesy-1D spectra were obtained for **395** (300 MHz, $CDCl_3$); the results are shown below:



nOe's detected for *395*

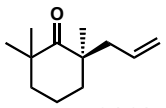
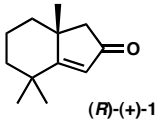
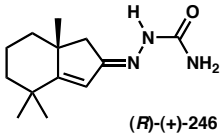


Benzaldehyde 396. A vial containing benzofuran **394** (4.0 mg, 11.2 μmol) and dioxane (degassed with argon, 100 μL) was treated dropwise with conc. aq HCl (100 μL) at 23 °C. The reaction turned yellow. 37% aq formaldehyde (100 μL) was introduced, followed by HCl gas (generated via slow addition of conc. aq H_2SO_4 to NaCl), which was bubbled in steadily for 3 min. The reaction became yellow-orange. The vessel was sealed and heated to 80 °C for 50 min, during which time the reaction turned maroon. The vessel was cooled to 23 °C and 6 M aq HCl (1 mL) was added along with $CHCl_3$ (1 mL). The reaction was stirred vigorously for 10 min, and the organic phase was collected. The aqueous layer was extracted with $CHCl_3$ (2 x 1 mL). All organic layers were combined, carefully washed with sat. aq $NaHCO_3$ (1 x 500 μL), dried (Na_2SO_4), and filtered through a pipet of silica with the aide of $CHCl_3$. The filtrate, which contained benzyl chloride **395**, was concentrated and immediately used in the next reaction.

The benzyl chloride **395** was treated with DMSO (distilled from CaH_2, 200 μL), followed by trimethylamine *N*-oxide (4.2 mg, 5.60 mmol, 5.0 equiv relative to **394**). The vessel was sealed and heated to 60 °C for 20 min. The reaction was purified on an preparative TLC plate (20:80 EtOAc:hexane eluent), giving benzaldehyde **396** (1.6 mg, 37% yield from **394**) as a yellow oil. R_f 0.46 (20:80 EtOAc/hexane), (UV, 356 nm, yellow spot, and UV, 254 nm); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.59 (s, 1H), 7.51 (s, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.23-3.10 (m, 1H), 2.70 (app. d, broad, J = 11.0 Hz, 1H),

2.28-2.16 (m, 2H), 1.91 (app. q, J = 11.1 Hz, 1H), 1.89-1.75 (m, 1H), 1.69-1.62 (m, 2H), 1.50 (d, J = 6.8 Hz, 3H), 1.43-1.22 (m, 4H), 1.30 (s, 3H), 0.98 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.7, 149.2, 148.5, 125.2, 115.0, 63.0, 57.0, 35.7, 29.9, 26.4, 21.5, 18.7; IR (NaCl/$CDCl_3$): 2930, 2864, 1689, 1605, 1464, 1386, 1363, 1327, 1297, 1238, 1139, 1057, 979, 732 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{24}H_{32}O_4$, 384.2301; found, 384.2306.

4.11.3 *Methods for the Determination of Enantiomeric Excess*

Entry	Substrate	Assay	Column	Method	Retention Time (min)	
1.	 (***R***)-(+)-75	*Enantiomeric Excess*	Chiral GC	80 °C isotherm	Minor (***S***)	29.1
			Agilent GT-A Column	40 min	Major (***R***)	30.5
2.	 (***R***)-(+)-143	*Enantiomeric Excess*	Chiral HPLC	3%EtOH/Hex monitor@254nm	Major (***R***)	9.1
			Chiralcel AD Column	20 min	Minor (***S***)	10.2
3.	 (***R***)-(+)-246	*Enantiomeric Excess*	Chiral HPLC	10%EtOH/Hex monitor@254nm	Major (***R***)	9.3
			Chiralcel AD Column	20 min	Minor (***S***)	12.1

4.12 Notes and Citations

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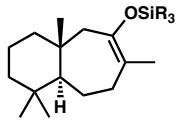

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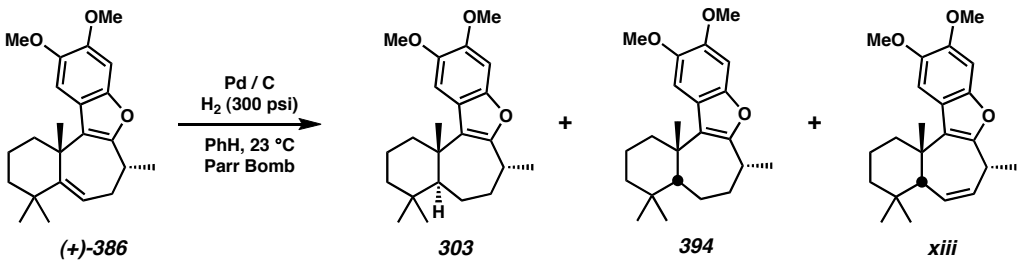
(46) A variety of hydrogenation conditions were tested on **(+)-386** in an attempt to produce **303**. One reaction produced an apparent 2:1:2 mixture of **303**, **394**, and **xiii**. See below:



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(49) When a subscript is shown with the coupling constant, it indicates what type of splitting the constant is associated with. For example (td, J_t = 5.0 Hz, J_d = 3.3 Hz, 1H) indicates that the triplet splitting has a 5.0 Hz coupling constant and the doublet has a 3.3 Hz coupling constant.

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