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 multidimensional NMR techniques, later confirming the structural assignment via racemic total synthesis.\(^1\) When Andersen isolated the molecule, he named its unprecedented 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

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 because there are numerous kinases in the human genome. 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. Selective inhibitors of individual isoforms of these enzymes would allow for the targeting of specific diseases spanning cancer, cardiovascular disease, and autoimmune disorders. 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). 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.\textsuperscript{1,5,6} Though somewhat selective, molecules such as LY294002 (275) lack the potency of liphagal (271).\textsuperscript{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 PI3K$\alpha$

4.1.4 Biosynthetic Proposals

Andersen proposed that liphagal (271) could have one of several biosynthetic origins.\textsuperscript{1} One of the first hypotheses discussed was the natural product’s potential origination from siphonodictyval 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
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.
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-bromosalicylaldehyde (291) in modest yield (Scheme 4.4). Protection of the free phenol with TBSCI 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.

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.
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 $\text{BI}_3$ at $-78 \, ^\circ\text{C}$ then completed Andersen’s total synthesis of ($\pm$)-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 biological 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).

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 Pd2(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 liphalg (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\(_2\)Cl\(_2\) 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. Coordination of the carbonyl by a Lewis acid would develop a partial positive charge on carbon. The developing cyclobutyl carbiny l 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. 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). 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. 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.

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. 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 BF₃•Et₂O in CH₂Cl₂, clean conversion to a single diastereomer of (+)–312 was observed (Scheme 4.12). 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 BF₃•Et₂O, obtaining diastereopure (+)-312.

Scheme 4.12 Reversion of the Bicyclobutane to the Cyclobutene

\[ \text{(-)-313} \xrightarrow{\text{BF}_3\text{-Et}_2\text{O, CH}_2\text{Cl}_2, 77\% \text{ yield}} \text{(+)312} \]

4.4.4 Formal $4\pi$ Electroyclic Ring Expansion

Heating a sample of unseparated (±)-312 and (±)-313 that had been treated with BF₃•Et₂O 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 $4\pi$-electroyclic ring-opening.²⁴

Scheme 4.13 Ring Opening of the Cyclobutene

\[ \text{(±)-312} + \text{(±)-313} \xrightarrow{\text{BF}_3\text{-Et}_2\text{O, CH}_2\text{Cl}_2, 50 \degree \text{C, sealed}} \text{(±)-312} + \text{(±)-318} \]

\[ \text{(±)-312} \xrightarrow{\text{BF}_3\text{-Et}_2\text{O (0.5 equiv.), CH}_2\text{Cl}_2, 50 \degree \text{C, sealed}} \text{(±)-318} \]
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. 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.

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

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](image)

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. TiCl₄ 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,\textsuperscript{29} producing the unstable \textit{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.\textsuperscript{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 Br\text{"o}nsted bases. It was also surprisingly difficult to functionalize the vinylogous acid oxygen of 340. Thus, we discontinued the use of this complex \textit{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). When other methods, such as hard enolization with silyl triflate quench or soft enolization, were used, (±)-342 was never observed in the product mixture. 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). The reactions were typically run “on water” 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. Gratifyingly, upon heating (+)-143 and 4-bromoveratrole (347) in the presence of NaOt-Bu, Pd(OAc)₂, and P(t-Bu)₃, aryl ketone (±)-348 was produced in good yield.

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. 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.
4.6.2 Attempted Arylation of the Dienone

Compound (±)-318 displayed the necessary characteristics we were searching for during the retrosynthetic revisions. Given the sp² 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 NaOt-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 NaOt-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.

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 sp² 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 sp³ 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. 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
stoiochermistry 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 Electroyclic Opening
Mechanistically, the transformation from (+)-369 to (±)-370 happens by a series of concerted C–C bond migrations. 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 AlCl₃ in CHCl₃, 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 \((\pm)-373\) was the result of an intramolecular Friedel-Crafts cyclization of \((\pm)-356\). This gave us some insight into the conformational preferences of aryl ketone \((\pm)-356\). Apparently, the electron-rich veratrole moiety sits directly underneath the olefinic \(\pi\)-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 \((\pm)-356\) in hand, we tested our hydrogenation reaction developed for the transformation of \((\pm)-318\) to \((\pm)-305\). A reaction occurred, but the product, \((\pm)-374\), 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 \(\alpha\) face is believed to prevent hydrogenation.

We hoped that this olefin could be reduced stereoselectively on the \(\alpha\) 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-Bu)_4N 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 Br2 in CHCl3, leading to (+)-379 in good yield and excellent chemoselectivity (Scheme 4.35). To our delight, when bromoveratrole-substituted cyclobutene (+)-379 was treated with AlCl3 in CHCl3, 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 Li⁰ 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\textsubscript{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 H2O 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 Pd2(db)3 in dioxane/H2O 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).
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/H₂O³³ we obtained dihydrobenzofuran 391 as the exclusive product. Finally, the fourth ring the liphagane skeleton (272, Figure 4.1) was in place.
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.
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.\(^{46}\)
4.8.4 Proposed Endgame for the Total Synthesis of Liphagal

If the preparation of 303 were possible, chloromethylation of the benzofuran followed by oxidation 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$_2$NH 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. 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 CDCl₃ and δ 7.16 for C₆D₆). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), 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. ¹³C 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 CDCl₃ and δ 128.4 for C₆D₆). Data for ¹³C 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 CDCl₃), 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

![Chemical Structure](image)

**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$_2$O:pentane → 8:92 Et$_2$O:pentane eluent), giving allyl ketone (+)-75 (2.23 g, 94% yield) as a colorless oil in 84% ee as determined by chiral HPLC. [$\alpha$]$^D_{25}$ +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)$_2$•H$_2$O (227 g, 12.2 mmol), followed by H$_2$O (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 Et₂O:hexane eluent), giving diketone \((-\text{219})\) (3.51 g, 73% yield) in 84% ee as determined by chiral HPLC. \(\left[\alpha\right]_{D}^{26} -70.3^\circ\ (c 0.970, \text{CHCl}_3), 84\%\ \text{ee}\). 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 \((-\text{219})\) (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 \(\rightarrow\) 40:60 Et₂O:hexane eluent), giving bicyclic enone \((+\text{-143})\) (3.06 g, 97% yield) in 84% ee as determined by chiral HPLC. \(\left[\alpha\right]_{D}^{26} +90.7^\circ\ (c 0.865, \text{CHCl}_3), 84\%\ \text{ee}\). 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 \((+\text{-143})\) (3.04 g, 17.06 mmol, 1.00 equiv, 84% ee) was charged with MeOH (48.6 mL), H₂O (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 H₂O, dried in the air, and transferred to a new round-bottom flask. Absolute EtOH (200 mL) was added gradually at 100 °C. H₂O (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. The crystals were filtered and redissolved in EtOH (180 mL) at 100 °C. H₂O (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 P₂O₅, 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 CH₂Cl₂ (3 x 30 mL) followed by with EtOAc (3 x 30 mL). All organic layers were combined, dried (Na₂SO₄), 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.
[α]$_D^{25}$ +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$_2$Cl$_2$ (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$_2$O:pentane → 50:50 Et$_2$O: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\textsubscript{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\textsubscript{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\textsuperscript{-1}; HRMS-EI\textsuperscript{+} (m/z): [M]\textsuperscript{+} calc’d for C\textsubscript{14}H\textsubscript{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\textsubscript{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. Rf 0.45 (1:4 EtOAc/hexane), (p-Anisaldehyde, red spot); $^1$H NMR (300 MHz, C$_6$D$_6$): 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$_6$D$_6$): 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-El$^+$ (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$_6$H$_6$), 95% ee. Unreacted starting material (±)-143 (146.8 mg, 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$_2$Cl$_2$ (5 ml) was treated with BF$_3$•Et$_2$O (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$_2$Cl$_2$ (20 mL). The organic layer was collected, and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 x). The organic layers were combined, dried (Na$_2$SO$_4$), 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. Rf 0.58 (1:4 EtOAc/hexane), (p-Anisaldehyde, red spot); mp 54-139 °C (amorphous), sublimation point, sp: < 23 °C (3 mmHg); 1H NMR (300 MHz, C6D6): 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, JAB = 16.0 Hz, 1H), 1.58 (AB spin system, app. dd, JAB = 16.0 Hz, JB = 1.7 Hz, 1H), 1.36 (app. ddt, Jd1 = 27.2 Hz, Jd2 = 12.7 Hz, Jt = 3.0 Hz, 1H), 0.85 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H); 13C NMR (75 MHz, C6D6): δ 2123.0, 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/CHCl3): 3130, 3040, 2925, 2870, 2845, 1733, 1456, 141, 1388, 1378, 1212, 1160, 754, 726 cm−1; HRMS-EI+(m/z): [M]+ calc’d for C14H20O, 204.1514; found, 204.1523; [α]26D +694.99° (c 1.232, C6H6), 95% ee.

The crude mixture of cyclobutene (+)-312 and (−)-313 prepared above (excluding the pure isolated (−)-313) was dissolved in CH2Cl2 (50 mL) and treated with BF3 • Et2O (86 µL) at 23 °C for 10 min. The reaction was added dropwise to a rapidly stirred suspension of brine (50 mL), sat. aq NaHCO3 (50 mL), and CH2Cl2 (50 mL). The organic layer was collected, and the aqueous phase was extracted with CH2Cl2 (2 x). The organic layers were combined, dried (Na2SO4), 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 1H NMR). A contaminant (with a structure similar to the product) with a mass of 265 mg was also present, as determined by 1H NMR. The semipure cyclobutene (+)-312 was used in subsequent reactions without further purification.
Cycloheptadienone (±)-318. A flamedried Schlenk tube under N₂ was charged with a solution of cyclobutene (+)-312 (125 mg, 0.600 mmol) and CH₂Cl₂ (20 mL). Then, BF₃•Et₂O (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. Rᵣ 0.52 (20:80 EtOAc/hexane), (ρ-Anisaldehyde, rose spot, UV, 254 nm); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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/CDCl₃): 3030, 2961, 2932, 2867, 1660, 1571, 1461, 1420, 1372, 1312, 1233, 986 cm⁻¹; HRMS-FAB⁺ (m/z): [M+H]⁺ calc’d for C₁₄H₂₁O, 205.1592; found, 205.1583.

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 H₂ (1 atm) at 23 °C for 4 h. The reaction was sparged with argon, then filtered through celite with the aide of Et₂O. The filtrate was concentrated and purified by flash chromatography on silica gel (Et₂O:hexane 10:90 eluent), affording cycloheptanone (±)-305 (536 mg, 91% yield) as a colorless oil. Rf 0.58 (20:80 EtOAc/hexane), (p-Anisaldehyde, yellow spot); 

1H NMR (300 MHz, CDCl₃): 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); 13C NMR (75 MHz, CDCl₃): 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/CDCl₃): 2929, 1696, 1457, 1258 cm⁻¹; HRMS-EI⁺ (m/z): [M⁺] calc’d for C₁₄H₂₄O, 208.1827; found, 208.1824.

**Methylcycloheptanone (±)-304.** A flamedried round-bottom flask was charged with THF (7.7 mL) and i-Pr₂NH (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 NH₄Cl (5 mL) followed by H₂O (10 mL). Hexanes (10 mL) and Et₂O (15 mL) were added. The organic layer was collected, and the
aqueous layer was extracted with Et$_2$O (3 x 15 mL). All organic layers were combined, washed with brine (15 mL), dried (Na$_2$SO$_4$), filtered, and concentrated. The residue 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-El$^+$ (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$_2$O (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$_2$O, CHCl$_3$, and H$_2$O. The suspension was extracted with Et$_2$O (3 x). Organic layers were combined, dried (Na$_2$SO$_4$), 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); ^1H 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); ^13C 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.

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 NH₄Cl (8 mL). 5 min later, H₂O and hexanes were added. The reaction was extracted with EtOAc (3 x 20 mL). Organic layers were combined, dried (Na₂SO₄), 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 (CDCl₃); ¹H NMR (300 MHz, CDCl₃): 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, 6.0 Hz, 2H), 2.35 (app. dd, J = 6.6 Hz, 6.0 Hz, 2H), 1.80-1.60 (m, 6H); ¹³C NMR (75 MHz, CDCl₃): 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/CDCl₃): 2927, 2860, 2224, 1645, 1601, 1572, 1501, 1449, 1238, 1214, 1162, 892, 836 cm⁻¹; HRMS-EI⁺ (m/z): [M]+ calc’d for C₁₃H₁₄N₂O, 214.1106; found, 214.1104.

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 H₂O and CH₂Cl₂. The organic layer was collected and the aqueous layer extracted with CH₂Cl₂ (1 x). Organic layers were combined, dried (Na₂SO₄), 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); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 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\(_4\)Cl (5 mL) and diluted with hexane (10 mL) and H\(_2\)O (5 mL). The suspension was extracted with Et\(_2\)O (3 x 15 mL). All organic layers were combined, washed (brine, 10 mL), dried (Na\(_2\)SO\(_4\)), 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\(_3\)): \( \delta \) 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$_3$): $\delta$ 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-El$^+$ (m/z): [M]$^+$ calc’d for C$_{22}$H$_{30}$N$_2$O, 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$_2$Cl$_2$ (10 mL) and cooled to $-78$ °C. Then, a solution of TiCl$_4$ (82 µL, 0.746 mmol) and CH$_2$Cl$_2$ (1.6 mL) was slowly introduced, followed by a solution of benzoquinone (330) (40.4 mg, 0.373 mmol, 1 equiv) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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 H2O and hexanes. The suspension was extracted with CH2Cl2 (2 x). All organic layers were combined and washed with brine. The combined aqueous layers were back-extracted with CH2Cl2 (3 x). All organic layers were combined, dried (Na2SO4), 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. Rf 0.19 (20:80 EtOAc/hexane), (p-Anisaldehyde, purple spot, UV, 254 nm); 1H NMR (300 MHz, CDCl3): 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, Jsext = 6.9 Hz, Jd = 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); 13C NMR (75 MHz, CDCl3): 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/CDCl3): 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 C13H15O2, 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-\textit{t}-butyl-4-methyl pyridine (309 mg, 1.50 mmol, 4 equiv) and CH\textsubscript{2}Cl\textsubscript{2} (10 mL) and cooled to \(-78^\circ\)C. Then, a solution of TiCl\textsubscript{4} (83 \(\mu\)L, 0.751 mmol)) and CH\textsubscript{2}Cl\textsubscript{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\textsubscript{2}Cl\textsubscript{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\textsubscript{2}Cl\textsubscript{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 \(-78^\circ\)C, and the reaction was warmed to 23 \(^\circ\)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 \(^\circ\)C overnight. The reaction was cooled to 23 \(^\circ\)C and diluted with H\textsubscript{2}O and hexanes. The suspension was extracted with Et\textsubscript{2}O (3 x 20 mL). All organic layers were combined and washed with brine. The combined aqueous layers were back-extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 x). All organic layers were combined, dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane \(\rightarrow\) EtOAc:hexane 5:95 eluent), affording 5-hydroxy-6-methoxybenzofuran 334 (28.3 mg, 30% yield based on 2-methoxybenzoquinone (333)) white powder. R\textsubscript{f} 0.40 (20:80 EtOAc/hexane), \((p\text{-Anisaldehyde, blue spot, UV, 254 nm); mp 127-129 \(^\circ\)C (CHCl\textsubscript{3}); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \delta 6.99 (s, 1H), 6.92 (s, 1H), 5.52 (s, 1H), 3.91 (s, 3H), 2.94 (app. d of sextuplet,
$J_{\text{sext}} = 6.9$ 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$_3$): $\delta$ 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.

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$_2$O 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$_2$SO$_4$), 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.$^{51}$
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 CHCl₃ (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 CHCl₃ (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

2,3,6-Triacetoxy-methylbenzoate (338). A round-bottom flask was charged with acetic anhydride (98%, 5 mL), and 10 drops of conc. aq H₂SO₄ 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-benzoquinone (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 H₂O (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 (Na₂SO₄), 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). Rₛ 0.55 (3:97 MeOH/DCM), (UV, 254 nm); mp 68-70 °C (CHCl₃); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): 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/CDCl₃): 2955, 1774, 1733, 1479, 1455, 1372, 1281, 1188, 1040, 1018, 902, 878 cm⁻¹; HRMS-EI⁺ (m/z): [M]+ calc’d for C₁₄H₁₄O₈, 310.0688; found, 310.0683.

![Chemical Structure](image)

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 H₂O (80 mL) and extracted with CH₂Cl₂ (3 x 40 mL). All organic layers were combined, dried (Na₂SO₄), filtered, and concentrated, giving 2,3,6-trihydroxy-methylbenzoate (339) (595 mg, 100% yield) as a pale yellow powder. Rₛ 0.49 (50:50 EtOAc/hexane), (UV, 254 nm); mp 132-134 °C (CHCl₃); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): δ 170.0, 153.1, 146.7, 137.7, 122.4, 107.5, 100.1,
53.2; IR (NaCl/CDCl₃): 3434 (br), 1680, 1460, 1325, 1283, 1192, 1165, 1127, 1031, 996, 834, 811, 792 cm⁻¹; HRMS-EI⁺ (m/z): [M]⁺ calc’d for C₈H₈O₅, 184.0372; found, 184.0375.

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 CHCl₃ (10 mL, stabilized with amylene). 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). Rf 0.30 (50:50 EtOAc/hexane), (visible red spot), (compound is unstable on silica gel); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): δ 181.7, 180.7, 171.1, 165.1, 139.2, 133.3, 132.5(?), 107.6(?), 53.8(?), 53.7(?); IR (NaCl/CDCl₃/CHCl₃): 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 C₈H₆O₅, 182.0215; found, 182.0223.
**Silyl Enol Ether** (±)-342. A flamedried round-bottom flask was charged with THF (6.0 mL) and i-Pr₂NH (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 Et₃N (500 µL), followed by sat. aq NaHCO₃ (1.0 mL). The reaction was allowed to thaw to 25 °C. The reaction was diluted with H₂O (10 mL) and hexanes (5 mL). The suspension was extracted with Et₂O (3 x 10 mL). The organic layers were collected and the aqueous layer was extracted with Et₂O (3 x 15 mL). All org layers were combined, washed with water (20 mL) followed by brine (10 mL), dried (K₂CO₃), 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 Et₃N/hexane), (p-Anisaldehyde, purple spot); ^1^H NMR (300 MHz, C₆D₆): 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, 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, C₆D₆): 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.
Aryl Enone (±)-348. In the glovebox, a vial was charged with NaOt-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$_4$Cl (1.0 mL). After 5 min, the reaction was diluted with H$_2$O and hexane, then extracted with EtOAc (4 x 8 mL). All organic layers were combined, washed with brine, dried (Na$_2$SO$_4$), 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.

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$_2$O and extracted with CHCl$_3$ (3 x). All organic layers were combined, dried (Na$_2$SO$_4$), filtered, and concentrated. The residue was purified on a flash pipet column (2:98 EtOAc:hexane $\rightarrow$ 5:95 EtOAc:hexane $\rightarrow$ 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); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_8$H$_7$O$_5$Br, 261.9477; found, 261.9474.
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•H₂O (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. Rf 0.72 (50:50 EtOAc/hexane), (p-Anisaldehyde, pink spot); mp 78-80 °C (PhH); ¹H NMR (300 MHz, C₆D₆): 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); ¹³C NMR (75 MHz, C₆D₆): 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 C₁₁H₁₂O₅, 224.0685; found, 224.0690.

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 Me₂SO₄ (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 H₂O and extracted with Et₂O (4 x). All organic layers were combined, dried (Na₂SO₄), filtered, and concentrated from CH₂Cl₂. 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); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): δ166.6, 150.7, 147.2, 147.0, 119.4, 114.5, 106.4, 61.6, 56.7, 56.4, 52.6; IR (NaCl/CDCl₃): 3002, 2947, 2908, 2839, 1736, 1591, 1493, 1465, 1285, 1257, 1212, 1190, 1167, 1141, 1098, 1062, 1014 cm⁻¹; HRMS-El⁺ (m/z): [M]⁺ calc’d for C₁₁H₁₄O₅, 226.0841; found, 226.0840.

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 CH₃CN (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); ^1H 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); ^13C 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.

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 NaOt-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$_6$D$_6$): $\delta$ 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$_6$D$_6$): $\delta$ 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$_2$Cl$_2$): 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:

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$_6$D$_6$): $\delta$ 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$_6$D$_6$): $\delta$ 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$_2$Cl$_2$): 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.
Vinyllogous 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 CH₂Cl₂ (10 mL). NaOt-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 Et₂O 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, Et₃N (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. Rₚ 0.57 (20:80 EtOAc/hexane), (KMnO₄, yellow spot); ¹H NMR (300 MHz, C₆D₆): 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, JAB = 12.6 Hz, 1H), 2.25 (AB spin system, d, JAB = 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); ¹³C NMR (75 MHz, C₆D₆): 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/CH₂Cl₂): 3058, 2930, 2866, 1671, 1561, 1480, 1441, 1321, 1209, 1195, 750 cm⁻¹; HRMS-FAB⁺ (m/z): [M+H]⁺ calc’d for C₂₁H₂₅SO, 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 NH₄Cl (1 mL) and diluted with H₂O (5 mL) and hexane (3 mL). The biphasic mixture was extracted with EtOAc (3 x 8 mL). All organic layers were combined, dried (Na₂SO₄), 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 NH₄Cl (3.0 mL) and diluted with H₂O and hexanes. The biphasic mixture was extracted with EtOAc (3 x 20 mL). All organic layers were combined, dried (Na₂SO₄), 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 mixture of tautomers (±)-361A, (±)-361B, and (±)-361C in the form of a pale yellow oil. Rf (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); ¹H NMR (300 MHz, CDCl₃) ((±)-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, Jₐₖ = 13.5 Hz, 1H), 1.90 (AB spin system, Jₐₖ = 13.5 Hz, 1H), 1.77 (app. dd, J = 13.5 Hz, 7.7 Hz, 1H), 1.62 (app. qt, Jₕ = 13.9 Hz, Jₗ = 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); ¹³C NMR (75 MHz, CDCl₃) ((±)-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-EL$^+$ (m/z): [M]$^+$ calc’d for C$_{17}$H$_{28}$O$_3$, 280.2038; found, 280.2031.

α-Methyl-β-Ketoester (±)-362. A vial was charged with anhydrous Cs$_2$CO$_3$ (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$_3$CN (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$_2$SO$_3$. The washing was back-extracted with CHCl$_3$ (2 x). All organic layers were combined, dried (Na$_2$SO$_4$), 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, 2H), 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, CDCl₃): 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/CDCl₃): 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 C₁₈H₃₀O₃, 294.2195; found, 294.2182.

Silyl Enol Ether (±)-363. A flame-dried round-bottom flask was charged with THF (8.0 mL) and i-Pr₂NH (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, Et₃N (1.0 mL) was added, followed by sat. aq NaHCO₃ (2.5 mL). The reaction was warmed to 23 °C, then diluted with H₂O and hexanes. The organic phase was collected, and the aqueous layer was extracted with Et₂O (2 x). All organic layers were combined, dried (K₂CO₃), filtered, and concentrated. The residue was concentrated several times from PhMe to remove residual H₂O 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. Rf 0.74 (2:20:80 Et₃N/EtOAc/hexane), (I₂/Sand, white spot); ¹H NMR (300 MHz, C₆D₆): 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\(_6\)D\(_6\)): \(\delta\) 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);

**Aryl Cyclobutene (+)-369.** In the glovebox, a round-bottom flask was charged with NaOt-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$_4$Cl (12.0 mL) and diluted with H$_2$O (25 mL) and hexane (15 mL). The suspension was extracted with EtOAc (3 x 40 mL). All organic layers were combined, dried (Na$_2$SO$_4$), 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. Rf 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\(_6\)D\(_6\)): 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\(_6\)D\(_6\)): 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\(_2\)Cl\(_2\) (52 mL). BF\(_3\)•Et\(_2\)O (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 NaHCO₃ (25 mL), and CH₂Cl₂ (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 CH₂Cl₂ (2 x 30 mL). All organic layers were combined, dried (Na₂SO₄), 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); ¹H NMR (500 MHz, C₆D₆): 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); ¹³C NMR (125 MHz, C₆D₆): 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/CHCl₃): 2924, 1645, 1573, 1516, 1463, 1419, 1264, 1236, 1148, 1028 cm⁻¹; HRMS-El⁺ (m/z): [M]+ calc’d for C₂₂H₂₈O₃, 340.2039; found, 340.2038.

In addition to (±)-356, several fractions containing a second compound in semipurse 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 CH₂Cl₂:PhH → 10:50:50 EtOAc:CH₂Cl₂: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), \((p\text{-Anisaldehyde, brown spot, UV, 254 nm)}\); mp 116-118 °C \((\text{C}_6\text{D}_6)\); \(^1\text{H NMR} \) \((500 \text{ MHz, C}_6\text{D}_6)\); \( \delta \) 6.79 (app. d, \( J = 8.3 \text{ Hz, 1H} \), 6.78 (app. s, 1H), 6.57 (app. d, \( J = 8.3 \text{ Hz, 1H} \), 6.32 (app. dd, \( J = 7.1 \text{ Hz, 3.9 Hz, 1H} \), 6.20 (app. dd, \( J = 7.1 \text{ Hz, 1.2 Hz, 1H} \), 3.54 (s, 3H), 3.44 (s, 3H), 2.83 (app. dd, \( J = 3.9 \text{ Hz, 0.7 Hz, 1H} \), 2.23 (s, 1H), 2.04 (app. td, \( J_t = 13.4 \text{ Hz, } J_d = 3.9 \text{ Hz, 1H} \), 1.47 (app. qt, \( J_q = 13.7 \text{ Hz, } J_t = 3.2 \text{ Hz, 1H} \), 1.35 (app. d, \( J = 14.2 \text{ Hz, 1H} \), 1.32-1.13 (m, 2H), 1.29 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.74 (app. d, \( J = 13.9 \text{ Hz, 1H} \)); \(^{13}\text{C NMR} \) \((125 \text{ MHz, C}_6\text{D}_6)\); \( \delta \) 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 \((\text{NaCl/CHCl}\text{_3})\): 2995, 2934, 2867, 2834, 1772, 1518, 1464, 1267, 1254, 1241, 1147, 1030, 750 cm\(^{-1}\); HRMS-EI \((m/z)\): \([M]^+\) calc’d for \( \text{C}_{22}\text{H}_{28}\text{O}_3 \), 340.2039; found, 340.2034.

**Friedel-Crafts Adduct (±)-373.** A solution of aryl cyclobutene (+)-369 \((50 \text{ mg, 0.147 mmol, 1.0 equiv})\) in CHCl\(_3\) (15.0 mL) was treated with AlCl\(_3\) \((98.0 \text{ mg, 0.735 mmol, 5.0 equiv, weighed in the glovebox})\). 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 \((\text{Na}_2\text{SO}_4)\), filtered, and oncentrated to \(~500 \mu\text{L} \) 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. Rf 0.24 (20:80 EtOAc/hexane), (UV, 254 nm); mp 152-155 °C (CHCl₃); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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/CDCl₃): 2932, 1659, 1605, 1504, 1464, 1402, 1295, 1206, 1096, 1036, 914, 857, 755 cm⁻¹; HRMS-EI⁺ (m/z): [M]⁺ calc’d for C₂₂H₂₈O₃, 340.2039; found, 340.2039. ¹H-nOesy-1D spectra were obtained for (±)-373 (300 MHz, CDCl₃); the results are shown below:
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\(_6\)D\(_6\)): 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\(_6\)D\(_6\)): 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-El\(^{+}\) (m/z): [M]\(^+\) calc’d for C\(_{22}\)H\(_{30}\)O\(_3\), 342.2195; found, 342.2183.
γ,δ-Unsaturated Methyl Aryl Cycloheptanone (±)-375. A round-bottom flask was charged with THF (4.2 mL) and i-Pr₂NH (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 NH₄Cl (4 mL) and diluted with H₂O and hexanes. The suspension was extracted with EtOAc (3 x 20 mL). All organic layers were combined, dried (Na₂SO₄), 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. Rf 0.48 (25:75 EtOAc/hexane), (p-Anisaldehyde, blue spot, UV, 254 nm); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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/CHCl₃): 2933, 1714, 1694, 1515, 1464, 1374, 1261, 1236, 1145, 1030, 757 cm⁻¹; HRMS-EI⁺ (m/z): [M]+ calc’d for C₂₃H₃₂O₃, 356.2352; found, 356.2352. ¹H-¹H gCOSY experiments (300 MHz, CDCl₃), were performed on (±)-375. The following spin systems were observed:

<table>
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<td>H¹⁸</td>
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<td>δ 2.03, m</td>
<td>H¹⁹</td>
<td>H¹⁰, H¹⁸, H¹³</td>
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<tr>
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<td>H²E</td>
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<td>H²Z</td>
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</table>

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, CDCl₃); the results are shown below:
**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 CH₃CN (12 mL) and treated with n-Bu₄N Br₃ (106.2 mg, 0.220 mmol) at 23 °C in the dark. After 16 h, the pale yellow reaction was diluted with CH₂Cl₂ (20 mL) and sat. aq NaHCO₃ (10 mL), and the reaction became colorless. The organic phase was collected, and the aqueous and the aqueous layer was extracted with CH₂Cl₂ (2 x). All organic layers were combined, dried (Na₂SO₄), 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. Rf 0.40 (20:80 EtOAc/hexane), (p-Anisaldehyde, blue spot, UV, 254 nm); mp 159-161 °C (MeOH); 1H NMR (300 MHz, CDCl₃): 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_l = 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); 13C NMR (75 MHz, CDCl₃): 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/CHCl₃): 2954, 2868, 2837, 1723, 1515, 1464, 1375, 1273, 1254, 1238, 1145, 1029, 756 cm⁻¹; HRMS-FAB⁺ (m/z): [M]+ calc’d for C₂₂H₂₉BrO₃, 420.1308; found, 420.1300. 1H-1H homodecoupling
experiments (300 MHz, CDCl₃) 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. ¹H-nOesy-1D spectra were obtained for (±)-376 (300 MHz, CDCl₃); the results are shown below:
**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 Br₂ (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 H₂O (30 mL) and CHCl₃ (30 mL). The organic phase was carefully treated with sat. aq NaHCO₃ (20 mL). The organic layer was then collected, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1:50:50 MeOH:CH₂Cl₂:PhH eluent), giving bromoarene (±)-377 (28.6 mg, 48% yield) as a white semisolid. Rᵣ 0.47 (20:80 EtOAc/hexane), (UV, 254 nm); mp 163-165 °C (dec.); ¹H NMR (300 MHz, CDCl₃): 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, Jᵣ = 12.4 Hz, Jₜ = 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); ¹³C NMR (75 MHz, CDCl₃): 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/CDCl₃): 2953, 2936, 2869, 2846, 1723, 1661, 1508, 1463, 1440, 1368, 1350, 1213, 1166, 1031, 912, 732 cm⁻¹; HRMS-FAB⁺ (m/z): [M]⁺ calc’d for C₂₂H₂₈Br₂O₃, 500.0385; found, 500.0382.
Bromoaryl Cyclobutene (+)-379. A round-bottom flask containing aryl cyclobutene (+)-369 (652 mg, 1.92 mmol, 1.0 equiv) in CHCl\textsubscript{3} (35 mL) was treated with Br\textsubscript{2} (460 mg, 2.87 mmol, 1.5 equiv) in CHCl\textsubscript{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\textsubscript{2}SO\textsubscript{3} (17.5 mL) and sat. aq NaHCO\textsubscript{3} (17.5 mL) was added. After 10 min, the organic phase was collected, and the aqueous layer was extracted with CHCl\textsubscript{3} (3 x 30 mL). All organic layers were combined, dried (Na\textsubscript{2}SO\textsubscript{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\textsubscript{f} 0.39 (20:80 EtOAc/hexane), (UV, 254 nm); mp 215-217 °C (EtOAc/hexane)(racemate), mp 240-242 °C (95% ee); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{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); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{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\textsubscript{3}): 2931, 2870, 2844, 1732, 1603, 1571, 1508, 1464, 1379, 1258, 1211, 1166, 1032, 914, 845, 735 cm\textsuperscript{-1}; HRMS-FAB\textsuperscript{+} (m/z): [M+H]\textsuperscript{+} calc’d for C\textsubscript{22}H\textsubscript{27}O\textsubscript{3}\textsuperscript{81}Br, 420.1123; found, 420.1119. [α]\textsuperscript{23}\textsubscript{D} +527.47° (c 1.82, CHCl\textsubscript{3}), 95% ee.
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 CHCl₃ (36 mL). The reaction was degassed with argon for 10 min. Then, AlCl₃ (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 NaHCO₃ (35 mL), and CHCl₃ (35 mL). The organic layer was collected, and the aqueous phase was extracted with CHCl₃ (3 x 35 mL). All organic layers were combined, dried (Na₂SO₄), 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. Rf 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); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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/CDCl₃): 2934, 1644, 1572, 1509, 1463, 1440, 1377, 1267,
1248, 1230, 1205, 1159, 1030, 837 cm\(^{-1}\); HRMS-El\(^{+}\) \((m/z): [M]^{+}\) calc’d for C\(_{22}\)H\(_{27}\)BrO\(_{3}\), 418.1144; found, 418.1158. \([\alpha]^{24}_{D} -437.31^\circ (c 0.985, \text{CHCl}_3), 95\% \text{ ee.}\)

\(\gamma,\delta\)-Unsaturated Aryl Cycloheptanone \((\pm)\)-374. A 3-neck round-bottom flask fitted with a cold finger condenser, argon inlet, and mineral oil bubbler was cooled to \(-78 \, ^{\circ}\text{C}\). The cold finger was charged with dry ice and acetone, and the system placed under a continuous flow of argon. Ammonia gas was flushed through the system until the condensed volume of liquid NH\(_3\) was \(\sim\)10 mL. A solution of bromoaryl cycloheptadienone \((\pm)\)-380 (10 mg, 23.8 \(\mu\text{mol}\)), \text{tert} amyl alcohol (10.5 mg, 0.118 mmol), and THF (2 mL) was added. Lithium wire (1.2 mm diameter \(\times\) 5 mm length, \(\sim\) 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\(_4\)Cl (3.0 mL). The reaction became colorless and was carefully warmed to 0 \({}^{\circ}\text{C}\). Once all of the ammonia had evaporated, the reaction was diluted with H\(_2\)O and hexanes and thawed to 23 \({}^{\circ}\text{C}\). The organic phase was collected. The aqueous layer was extracted with EtOAc (1 \(\times\)). All organic layers were combined, dried (Na\(_2\)SO\(_4\)), filtered, and concentrated. The residue was purified by preparative TLC on silica gel (EtOAc:hexane 20:80 eluent), giving \(\gamma,\delta\)-Unsaturated Aryl Cycloheptanone \((\pm)\)-374 (yield was not determined). Characterization data for this compound can be found on page 367 above.
**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 NaOt-Bu (8.5 mg, 88.1 μmol, 6 mol%). The reactor was cycled out of the glovebox and charged with PPh₃ (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/cm³, 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/cm³, high viscosity, ~1 g) was added to aide conversion. Additionally, a solution of CuCl (7.4 mg, 73.4 μmol, 5 mol%), NaOt-Bu (8.5 mg, 88.1 μmol, 6 mol%), PPh₃ (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 NH₄Cl (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 (Na₂SO₄), 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.

**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, PtO₂ (43.2 mg, 0.190 mmol, 20 mol%) was carefully added. The reaction was cooled to –78 °C, then evacuated/backfilled (vacuum/H₂ (1 atm)) (3 x). With vigorous stirring, the reaction was warmed to 23 °C under H₂ (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. Rf 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); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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/CDCl₃): 2936, 2845, 1716, 1699, 1600, 1567,
1506, 1463, 1440, 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 \(\gamma,\delta\)-Unsaturated Cycloheptanones (+)-382 and 383.** A flame-dried round-bottom flask was charged with THF (8.0 mL) and \(i\)-Pr\(_2\)NH (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-\(\gamma,\delta\)-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\(_4\)Cl (5.0 mL). Then, H\(_2\)O (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\(_2\)SO\(_4\)), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (5:95 EtOAc:hexane \(\rightarrow\) 20:80 EtOAc:hexane eluent), giving 4 main fractions. The first contained bromoaryl methyl \(\gamma,\delta\)-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$_3$):

$\delta$ 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, $J_I = 6.0$ 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, $J_I = 12.6$ 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$_3$): $\delta$ 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$_3$Br, 436.1436; found, 436.1437. $[\alpha]_{D}^{25} +37.00^\circ$ (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:

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spin systems found for (+)-382
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:

![Diagram](image)

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$_3$Br, 436.1436; found, 436.1422.

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

**α-Hydroxyketone (±)-385.** A vial (open to the air) was charged with KOt-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$_4$Cl (2.0 mL) and H$_2$O (1.0 mL). The reaction was diluted with more H$_2$O (4 mL), then extracted with CHCl$_3$ (3 x 8 mL). All organic layers were combined, dried (Na$_2$SO$_4$), 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, $J_{AB} = 16.6$ Hz, $J_a = 6.6$ Hz, 1H), 1.73 (app. qt, $J_q = 13.2$ Hz, $J_r = 3.6$ 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.

**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$_2$O (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$_2$O (1 mL) and extracted with CHCl$_3$ (3 x 1 mL). All organic layers were combined, dried (Na$_2$SO$_4$), 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. Rf 0.37 (20:80 EtOAc/hexane), (p-Anisaldehyde, blue spot); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 $\delta$ 5.32 (app. t, $J$ = 6.0 Hz, 1H) was suppressed with a decoupling current, resulting in a splitting change at $\delta$ 2.18 (app. d, $J$ = 6.0 Hz, 2H $\rightarrow$ app. s, 2H). The signal at $\delta$ 2.18 (app. d, $J$ = 6.0 Hz, 2H) was suppressed with a decoupling current, resulting in a splitting change at $\delta$ 5.32 (app. t, $J$ = 6.0 Hz, 1H $\rightarrow$ 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:
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 H₂O (25 mL) and extracted with PhH (3 x 30 mL). All organic layers were combined, dried (Na₂SO₄), 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. Rₗ 0.24 (20:80 EtOAc/hexane), (p-Anisaldehyde, blue spot, UV, 254 nm); ¹H NMR (300 MHz, CDCl₃): 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, J₁ = 9.3 Hz, J₂ = 6.9 Hz, J₃ = 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); ¹³C NMR (75 MHz, CDCl₃): 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/CDCl₃): 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 C₂₂H₂₉O₃⁸¹Br, 422.1280; found,
422.1283. $^1$H-nOesy-1D spectra were obtained for (±)-389 (300 MHz, CDCl$_3$); the results are shown below:

![Chemical Structure](image)

**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$_2$SO$_4$), 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.) Rr 0.45 (1:9 MeOH/DCM), (I2/Sand); mp 203-205 °C (water); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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, 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\(_3\)Br, 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:

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spin systems found for (+)-390
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:

![Diagram of chemical structure]

nOe’s detected for (+)-390

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**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$_2$O (5.0 mL). The suspension was degassed with argon for 10 min and Cul (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$_2$O (50 mL). The suspension was then extracted with CH$_2$Cl$_2$ (3 x 25 mL). All organic layers
were combined, dried (Na$_2$SO$_4$), 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. [α]$^2$$_D$−59.10° (c 1.385, CHCl$_3$), 95% ee.

**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$_3$): $\delta$ 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$_3$): $\delta$ 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.

**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$_3$): $\delta$ 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), 1.07 (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, 1198, 1138, 1044 cm$^{-1}$; HRMS-El$^+$ (m/z): [M]$^+$ calc'd for C$_{23}$H$_{32}$O$_3$, 356.2352; found, 356.2351.

**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 ºC. The reaction turned yellow. 37% aq formaldehyde (100 µL) was introduced, followed by HCl gas (generated via slow addition of conc. aq H$_2$SO$_4$ to NaCl), which was bubbled in steadily for 3 min. The reaction became yellow-orange. The vessel was sealed and heated to 50 ºC for 30 min followed by 80 ºC for 30 min, during which time the reaction turned maroon. The vessel was cooled to 23 ºC 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 (Na₂SO₄), 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:
Benzaldehyde 396. A vial containing benzo furan 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 H₂SO₄ 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 CHCl₃ (1 mL). The reaction was stirred vigorously for 10 min, and the organic phase was collected. The aqueous layer was extracted with CHCl₃ (2 x 1 mL). All organic layers were combined, carefully washed with sat. aq NaHCO₃ (1 x 500 µL), dried (Na₂SO₄), and filtered through a pipet of silica with the aide of CHCl₃. 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 CaH₂, 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. Rf 0.46 (20:80 EtOAc/hexane), (UV, 356 nm, yellow spot, and UV, 254 nm); ¹H NMR (500 MHz, CDCl₃): 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); 13C
NMR (75 MHz, CDCl3): 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/CDCl3): 2930, 2864, 1689, 1605, 1464, 1386, 1363,
1327, 1297, 1238, 1139, 1057, 979, 732 cm⁻¹; HRMS-El⁺ (m/z): [M]⁺ calc’d for C24H32O4, 384.2301;
found, 384.2306.

4.11.3 Methods for the Determination of Enantiomeric Excess

<table>
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<th>Entry</th>
<th>Substrate</th>
<th>Assay</th>
<th>Column</th>
<th>Method</th>
<th>Retention Time (min)</th>
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<td>Chiral GC</td>
<td>80 °C isotherm</td>
<td>Minor (S) 29.1</td>
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4.12 Notes and Citations


Williams, O.; Loewith, R.; Stokoe, D.; Balla, A.; Toth, B.; Balla, T. Weiss, W. A.;
Williams, R. L.; Shokat, K. M. Cell, 2006, 125, 733-737.

(6) (a) Robertson, A. J.; Jackson, S.; Kenche, V.; Yaip, C.; Parbaharan, H.; Thompson, P.
US 6403588, 2002. (c) Sadhu, C.; Masinovsky, B.; Dick, K.; Sowell, G. C.; Staunton,

(7) Andersen prepared liphagal (271) in 5.6% yield over a 12 step longest linear sequence
from 2,4,5-trimethoxybenzaldehyde (290), which can be purchased from Aldrich for
$1.34/g ($134/100 g).


(11) Our synthesis of bicyclic enone (+)-143 constitutes a formal total synthesis of nat-
(–)-dichroanone ((–)-150); see chapter three and reference 8 for details.

(12) For investigations of the stereochemistry of [2+2] cycloadditions of alkenes to
enones, see: (a) Shih, C.; Fritzen, E. L.; Swenton, J. S. J. Org. Chem. 1980, 45, 4462-

(13) For examples of ethylene photoadditions, see: (a) Eaton, P. E.; Nyi, K. J. Am. Chem.
Soc. 1971, 93, 2786-2788. (b) Cargill, R. L.; Wright, B. W. J. Org. Chem. 1975, 40,
120-122. (c) Tsutsumi, K.; Nakano, H.; Furutani, A.; Endou, K.; Merpuge, A.;


(17) A small sample of solid cyclobutene (±)-312 evaporated during attempted solvent removal under high vacuum.


(22) A related bicyclobutane rearrangement to a cyclobutene mediated by AlBr₃ has been reported: Razin, V. V.; Mostova, M. I.; D’yakonov, I. *Zh. Organish. Khim.* **1968**, *4*, 535.

(23) For studies of transition metal-catalyzed rearrangements of bicyclobutanes, see:


(24) For studies regarding 4π-electrocyclic ring openings, see:


(25) For excellent discussion on the Fischer indole synthesis, see:


(b) Robinson, B. In *The Fischer Indole Synthesis*. John


(32) Although the products from these reactions were not fully characterized, $^1$H NMR data suggested they had the structure below:

![Structure](structure-image)


(34) For an excellent theoretical discussion of “on-water” chemical phenomena, see:


(37) The relative stereochemistry of the major diastereomer was not assigned.


(39) A beautiful application of the Cargill rearrangement in the total synthesis of verrucarol has been detailed. The authors noted dramatic substituent effects when attempting the key cyclobutene opening. See: White, J. D.; Kim, N.-S.; Hill, D. E.; Thomas, J. A. *Synthesis* **1998**, 619-626.


(44) See the experimental section for details.


(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:

(47) We have initiated a collaboration with Lewis Cantley, a pioneer in the field of PI3K biology, to investigate the structure activity relationship of liphaganes. Appendix nine gives a detailed list of compounds to be investigated.


(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.

(50) Allowing the recrystallization to cool below 23 °C led to crystals having less enantioenrichment.