CHAPTER THREE†

The Catalytic-Enantioselective, Protecting Group-Free Total Synthesis of (+)-Dichroanone

3.1 Natural Products with a [6-5-6] Carbocyclic Skeleton

3.1.1 Tricyclic Terpenoids Isolated from Thuja standishii, Taiwania cryptomerioides, and Salvia dichroantha

There is a growing class of natural products found that share a [6-5-6] tricyclic core. Whereas the homologous abietane diterpene skeletal structure 146, which has a [6-6-6] carbocyclic scaffold, has been known for many years, this new 4a-methyltetrahydrofluorene class has only recently been uncovered (Figure 3.1). Three plant species are known to produce molecules with this tricyclic architecture. The first, Thuja standishii, yields standishinal (147), a substituted benzaldehyde.\(^1\) The second, Taiwania cryptomerioides, has yielded the largest contingent of [6-5-6] natural products to date, where each member features a highly oxidized aromatic ring.\(^2\) Finally, and most recently, natural products in this 4a-methyltetrahydrofluorene family have also been discovered in Salvia dichroantha, a flowering plant native to Turkey.\(^3\) Three 4a-methyltetrahydrofluorenes have been isolated from the root extract of this plant: dichroanal A (148), dichroanal B (149), and (−)-dichroanone ((−)-150). The biosyntheses of these compounds, though not fully understood, may begin from preformed abietanes (146). If this is true, the abietane cores may undergo oxidation and central ring restructuring, leading to rearranged 4a-methyltetrahydrofluorene diterpenoids (e.g., taiwaniaquinone D (151)).\(^2a\) Occasionally, a one-carbon excision may occur, leading to norditerpenoid variants (e.g., dichroanone ((−)-150).

†(Pages 140-189 reproduced in part from J. Am. Chem. Soc. 2006, 128, 7738; supporting information.)
Figure 3.1 [6-5-6] Natural Products

**Thuja standishii**

- Standishinal (147)
- 4a-methyltetrahydro-fluorene skeleton (152)
- Abietane Skeleton (146)

**Taiwania cryptomerioides**

- Taiwaniaquinol A (153)
- Taiwaniaquinol B (154)
- Taiwaniaquinol C (155)
- Taiwaniaquinol D (156)
- Taiwaniaquinol E (157)
- Taiwaniaquinol F (158)
- Taiwaniaquinone A (159)
- Taiwaniaquinone B (160)
- Taiwaniaquinone C (161)
- Taiwaniaquinone D (151)
- Taiwaniaquinone E (162)
- Taiwaniaquinone F (163)
- Taiwaniaquinone G (164)
- Taiwaniaquinone H (165)

**Salvia Dichroantha**

- Dichroanal A (148)
- Dichroanal B (149)
- (--) Dichroanone (--)-150
3.1.2 Biological Activity of the 4a-Methyltetrahydrofluorene Family

Little is known of the biological activity of this family of natural products. However, standishinal (147) has been found to inhibit aromatase, an enzyme involved in the biosynthesis of estrogen.\(^4\) Thus, it is believed that molecules in the family could be used to develop agents targeting estrogen-dependent carcinomas.\(^2d\) It is possible that other members of the [6-5-6] carbocyclic class might have similar biological activity to standishinal (147), and we anticipate that a general synthetic route to members of this family would allow for detailed structure-activity-relationship studies.

3.1.3 Structural Characteristics of the 4a-Methyltetrahydrofluorene Family

In addition to the unique tricyclic ring structure found in the 4a-methyltetrahydrofluorene natural products, some other features are noteworthy. The compounds each possess all-carbon quaternary stereocenters adjacent to an aromatic or quinoid ring. These highly oxidized ring systems pose another synthetic challenge. In most cases, the aromatic or quinoid ring is fully substituted, and in every case there is an isopropyl substituent at C(7) (Figure 3.1). Some members of the family display \(p\)-quinones, a potentially sensitive functional group for the synthetic chemist. The attractive features and unique [6-5-6] ring topologies of these molecules have inspired a number of total syntheses. When we initially became interested in these compounds as synthetic targets, the absolute stereochemistries of the molecules were unknown.
3.2 Synthetic Studies on [6-5-6] Carbocyclic Natural Products

3.2.1 Banerjee’s Approach to the 4a-Methyltetrahydrofluorenes

Banerjee published the first total syntheses of members of the 4a-methyltetrahydrofluorene family in 2003.\(^5\) The molecules completed in the group’s first report included \((\pm)\)-dichroanal B (149) and \((\pm)\)-dichroanone (150), but later Banerjee also published total syntheses of \((\pm)\)-taiwaniaquinol B (154) and \((\pm)\)-taiwaniaquinones H and D (151 and 154, respectively).\(^6\) Their route to these racemates was designed to handle the challenges associated with the quaternary stereocenter, while taking a convergent approach to the construction of the tricyclic core (Scheme 3.1). Two 6-membered carbocyclic fragments (166 and 167) were separately assembled and subsequently coupled to prepare the central 5-membered ring of the natural products.

Scheme 3.1 Banerjee’s Retrosynthetic Analysis

\[(\pm)\)-Dichroanone (150) \rightarrow 168 \rightarrow 166 + 167\]

Banerjee’s synthesis of the aromatic portion of the natural products began with the preparation of tetrasubstituted arene 169, according to a published method (Scheme 3.2).\(^7\) With aniline 169 in hand, Sandmeyer chemistry allowed the installation of a bromine atom. Benzylation of phenol 171 under Finkelstein conditions followed by reduction of the aldehyde functionality furnished benzylic alcohol 173. Treatment with PBr\(_3\) provided the first coupling partner, 174, in excellent yield.
Scheme 3.2 Preparation of the Aromatic Coupling Partner

The other coupling fragment 175 was then appended to the benzylic bromide 174 in an alkylation reaction (Scheme 3.3). The use of 175 as opposed to its ethyl ester variant (Hagemann’s ester) was crucial, as the attempted decarboxylation of the ethyl ester variant of 175 led to multiple products. Treatment of 177 with Gilman’s reagent installed the geminal dimethyl functionality on the cyclohexane ring of 178. Methylenation was followed by an intramolecular reductive Heck cyclization, closing the central 5-membered ring, while producing two separable diastereomers. The tricycle 180A, bearing cis-ring fusion at the C(4a) and C(9a) positions, was carried onward through the synthesis.
Scheme 3.3 Union of the Coupling Partners

The next focus of the synthesis was the installation of the isopropyl moiety. Acylation of 180A and Fries rearrangement, followed by a 4-step sequence of events, led to the acetate-protected catechol 182 (Scheme 3.4). Oxidation of the 5-membered ring with PCC gave ketone 183, which was reduced and dehydrated with SOCl₂, furnishing the styrene 184. At this point the synthesis diverged into two paths.

Scheme 3.4 Installation of the Isopropyl Moiety
(±)-Dichroanal B (149) was prepared as follows (Scheme 3.5). A portion of protected catechol 184 was converted via saponification and methylation to the veratrole 185. Chemoselective bromination of the aromatic portion of the molecule furnished 186 in excellent yield. Metal-halogen exchange was followed by DMF quench and nucleophilic demethylation with thiophenol, completing the first total synthesis of (±)-dichroanal B (149).

Scheme 3.5 Completion of (±)-Dichroanal B

Alternatively, styrene 184 could also be carried on to (±)-dichroanone (150) (Scheme 3.6). Selective bromination of 184, followed by a copper(I)-promoted methoxylation reaction, furnished the bis-(methyl)hydroquinone 188. When this molecule was treated with ceric ammonium nitrate in water and acetonitrile, (±)-dichroanone (150) was produced in 62% yield from 189.
Scheme 3.6 Total Synthesis of (±)-Dichroanone (150)

\[ 184 \xrightarrow{NBS, \text{CH}_2\text{CN}} 189 \xrightarrow{\text{MeONa, Cu, DMF}} (±)-\text{Dichroanone (150)} \]

3.2.2 Fillion’s Approach to Taiwaniaquinol B

Fillion’s group has also published a total synthesis of a 4a-methyltetrahydrofluorene diterpenoid, (±)-taiwaniaquinol B (154).\(^\text{11}\) Their synthetic design was inspired by the powerful versatility of Meldrum’s acid (190) (Scheme 3.7). It was envisioned that the tricyclic scaffold of (±)-taiwaniaquinol B (154) might be assembled in one step from the branched compound 191 via 192. It was known that Meldrum’s acid analogues, such as 191, are prone to retro [4+2] cycloadditions, leading to thermal loss of acetone. Fillion postulated that the reactive ketene generated would acylate the nearby arene, forming indanone 192. After a decarboxylation event and tert-alkylation, the final ring of the natural product could be assembled.

Scheme 3.7 Retrosynthesis of Taiwaniaquinol B

\[ (±)-\text{Taiwaniaquinol B (154)} \xrightarrow{R = \text{H or metal}} 192 \xrightarrow{\text{ROOC}} 191 \xrightarrow{\text{Meldrum's Acid (190)}} \]
The synthesis commenced with 3,5-dihydroxybenzoic acid (193) (Scheme 3.8). Regioselective bromination, followed by bis-methylation and Stille coupling of 2-propenyl stannane, furnished the styrene 195. A 5-step elaboration of 195 to the geminally substituted alkene 196 was followed by Knoevenagel condensation with Meldrum’s acid (190), affording 197.

Scheme 3.8 Beginning of the Synthesis

Chemoselective conjugate addition of MeMgBr to 197 gave the branched compound 198, poised for the key cyclization reaction (Scheme 3.9). In a unique reaction cascade, treatment of 198 with stoichiometric TMSOTf induced a Friedel-Crafts acylation, followed by decarboxylation and acid-mediated tert-alkylation of a putative enolate 199. This quickly assembled the cis-fused [6-5-6] tricyclic framework with complete diastereoselectivity. The arene 200 was readily elaborated to (±)-taiwaniaquinol B (154) after selective demethylation and oxidation to the hydroquinone oxidation state.12
Scheme 3.9 Fillion’s Total Synthesis of (±)-Taiwaniaquinol B

3.2.3 Node’s Synthesis of Dichroanal B

The Node group designed an efficient synthesis of (±)-dichroanal B (149) that employed a convergent approach.\textsuperscript{13} As Banerjee had done,\textsuperscript{5,6} Node made a key retrosynthetic disconnection across C(4a) and C(5a). A 5-\textit{exo}-intramolecular Heck cyclization was the reaction of choice for the desired C-C bond formation (Scheme 3.10). Node decided to use an endocyclic olefin at the point of cyclization (C(4a)), leading to an overall oxidatively neutral Heck cyclization. The substrate for this transformation, 201, could come from two fragments: the arene 202 and β-cyclocitral (203).\textsuperscript{14}

Scheme 3.10 Node’s Retrosynthetic Analysis
To begin the synthesis of (±)-dichroanal B (149), tetrasubstituted arene 204 was treated with MeMgBr, followed by a Lewis-acid-promoted reduction with Et₃SiH (Scheme 3.11). The two free hydroxyls of 205 were protected as isopropyl ethers, and the resulting compound was chemoselectively brominated with N-bromosuccinimide in excellent yield, furnishing 206.

Scheme 3.11 Total Synthesis of Racemic Dichroanal B

With aryl bromide 206 in hand, a lithium-halogen exchange was performed, and the resulting lithio-arene was treated with β-cyclocitral (203),¹⁴ resulting in 1,2-addition (Scheme 3.11). Chemoselective dehydration of 207 with triflic anhydride and DABCO
furnished the \( s\)-\( \textit{trans} \)-diene \( 208 \) in high yield. Selective demethylation of the aryl methyl ether in the presence of two \( i\)-Pr ethers was achieved with sodium dodecanethiolate, and the unmasked hydroxyl group was triflated, affording \( 209 \). The key intramolecular Heck cyclization proceeded as intended, and the resulting disubstituted olefin moiety was selectively hydrogenated with Wilkinson’s catalyst and \( \text{H}_2 \). The tricyclic styrene product \( 210 \) was treated with \( \text{BCl}_3 \) followed by \( \alpha,\alpha\)-dichloromethyl methyl ether, completing the total synthesis of \((\pm)\)-dicroanal B (149).\(^{15}\)

### 3.2.4 Trauner’s Synthesis of Taiwaniaquinoids

The Trauner group has also sought to address the challenges presented by the 4\( a\)-methyltetrahydrofluorene natural products.\(^{16}\) Their efforts culminated in the total syntheses of \((\pm)\)-taiwaniaquinols B and D (160 and 151), along with \((\pm)\)-taiwaniaquinone H (165) and \((\pm)\)-dichroanone (150). Their investigations demonstrated the generality of their route toward preparation of several members of this natural product family. Key to the Trauner’s retrosynthetic analysis was the possibility of building the central 5-membered ring using a Nazarov cyclization (Scheme 3.12). Like the Node’s synthesis,\(^{13}\) this one would also begin with the unification of an arene fragment (211) and \( \beta \)-cyclocitral (203).\(^{14}\)

![Scheme 3.12 Trauner’s Retrosynthetic Analysis](image)

\[ (\pm)\text{-Taiwaniaquinol B (160)} \rightarrow 212 \rightarrow (\pm)\text{-Taiwaniaquinone H (165)} \]

| (\pm)Taiwaniaquinol B (160) | 212 | \( \beta \)-Cyclocitral (203) | 211 |
To begin the syntheses, 2,6-dimethoxycumene (213) was monobrominated with \(N\)-bromosuccinimide in DMF (Scheme 3.13). Subsequent lithium halogen exchange, followed by 1,2-addition to \(\beta\)-cyclocitral (203), furnished an aryl vinyl carbinol. Oxidation with Dess-Martin periodinane gave aryl ketone 212, which was poised for the key Nazarov cyclization. Upon treatment of 212 with TMSOTf in nitromethane, followed by aqueous workup, the \(cis\)-fused product 200 was obtained in good yield as a single diastereomer. Key to the success of this reaction was the use of MeNO\(_2\) as the solvent because less polar alternatives resulted in poor conversion. Although 200 had already been prepared in Fillion’s synthesis of (±)-taiwaniaquinol B (154) (Scheme 3.9), the Trauner group published a different endgame involving monodeprotection and CAN-mediated oxidation (Scheme 3.13).

Scheme 3.13 Completion of Racemic Taiwaniaquinol B

Using alternative Lewis acids in the Nazarov cyclization was possible, ultimately leading to the completion of other natural products (Scheme 3.14). If triflic anhydride was employed in lieu of TMSOTf, along with a base, a stable enol triflate (214) could be isolated. After completion of the Nazarov triflation, Pd-catalyzed reductive detriflation
furnished the useful styrene 215, which was carried onward to (±)-dichroanone (150) and (±)-taiwaniaquinone H (165). Of note, the compound 215 could be either mono- or di-demethylated with judicious choice of Lewis acid. To install the final oxygen atom in both natural products, a cobalt(II) N,N′-bis-salicylidene-ethylenediamine catalyst (216) was used with molecular oxygen as the terminal oxidant.

Scheme 3.14 Application of the Nazarov Triflation

The enol triflate 214 was also converted to a vinyl nitrile 217 in the presence of superstoichiometric Pd(OAc)₂, P(OMe)₃, and TMSCN (Scheme 3.15). After a short series of oxidation state adjustments, the total synthesis of (±)-taiwaniaquinol D (156) was achieved. Trauner’s syntheses of these natural products showed the broad utility of the Nazarov cyclization.
3.2.5 Challenges to Address

Each group mentioned in the previous sections made great contributions toward understanding the chemistry of 4a-methyltetrahydrofluorene natural products.\(^\text{21}\) However, there was room for improvement in the syntheses of members of this class. Most of the synthetic strategies had focused attention on forming the central 5-membered ring. Although this allowed for a convergent approach to the tricyclic core, it required bringing in an aryl fragment with protecting groups. Even after the central rings were formed, there were usually numerous functional group interconversions before the total syntheses were complete. Perhaps most significant was that none of the reported methods were enantioselective. The absolute stereochemistries of these natural products was still uncertain, despite biosynthetic hypotheses.\(^\text{2b,c,22}\) We believed that using our catalytic enantioselective decarboxylative alkylation chemistry, we could address all of these matters in a concise total synthesis. Our primary target molecule would be dichroanone (150), but we envisioned that out route provide a general access to many members of the 4a-methyltetrahydrofluorene class (152, Figure 3.1).
3.3 First Retrosynthetic Analysis of Dichroanone

3.3.1 Complexities of the Dichroanone Architecture

One goal of our total synthesis was to determine the absolute stereochemistry of the natural product by using our enantioselective decarboxylative alkylation to set the all-carbon-quaternary stereocenter. The second endeavor was to design a synthesis amenable to completion of related natural products. The pioneering work of Banerjee,5-6 Fillion,11 Node,13 and Trauner16 provided a wealth of knowledge about the behavior of 4a-methyltetrahydrofluorenes. Previous syntheses had, without exception, dealt with protection of the aromatic oxygen atoms. To address this matter, we reasoned that the three oxygen atoms of dichroanone (150) could be installed at a late synthetic stage, possibly avoiding the need for protecting groups entirely. Our retrosynthesis would also need to address the challenge of selectively functionalizing the fully substituted p-quinone ring.

3.3.2 Retrosynthetic Analysis of Dichroanone

Our first retrosynthetic analysis of dichroanone (150) began with the removal of the oxygen atoms and the isopropyl group. It was reasoned that the natural product could be assembled from tricyclic hydrocarbon 218 (Scheme 3.16). This compound might arise from a simpler enone ((−)-143) via annulation. We anticipated that enone (−)-143 could be easily prepared from diketone (+)-219 using intramolecular aldol condensation. This 1,4-dicarbonyl compound could arise from allyl ketone (−)-75. Using our group’s Pd-catalyzed enantioselective alkylation chemistry, (−)-75 would originate from enol
carbonate 100. The enol carbonate would ultimately come from commercially available 2,6-dimethylcyclohexanone (220).

Scheme 3.16 First Retrosynthetic Analysis of Dichroanone

3.4 Synthesis of the Tricyclic Core

3.4.1 Preparation of a Racemic Bicyclic Enone

The first decision made during the total synthesis of (+)-dichroanone ((+)-150) was which commercially available starting material to use. 2,2,6-trimethylcyclohexanone (101) was an ideal choice, but its cost was prohibitive for use in batches larger that one gram. To facilitate the large-scale production of material, we decided to use the less-costly 2,6-dimethylcyclohexanone (220), available as a cis, trans mixture. Upon attempted methylation of 220 with iodomethane and LDA, a mixture of desired product 101, unreacted starting material 220, and bis-methylation adduct 2,2,6,6-tetramethylcyclohexanone (221) was obtained (Scheme 3.17). Initially we were encouraged because 101 was the major product of the reaction. Unfortunately, 220, 101, and 221 had very similar chromatographic properties and boiling points. Even careful fractional distillation was ineffective as a separation technique.
To address this issue and obtain large quantities of pure 101, we decided to push the methylation reaction toward overalkylation, ensuring that no unreacted starting material would remain (Scheme 3.17). Once the reaction was complete, we took advantage of the steric differences between 101 and 221. Upon treatment of the crude mixture with semicarbazide hydrochloride under basic conditions, we observed crystallization of the semicarbazone 222. Presumably, the analogous semicarbazone of 221 is unable to form due to the extreme steric hindrance by the four methyl groups, leaving unreacted 221 in the mother liquors. Acidic hydrolysis of the desired semicarbazone 222 afforded pure 2,2,6-trimethylcyclohexanone (101) after distillation. This method allowed for the production of large batches of this compound without any chromatography.

Scheme 3.17 Synthesis of 2,2,6-trimethylcyclohexanone

The 2,2,6-trimethylcyclohexanone (101) was smoothly converted to the allyl enol carbonate 100 via enolization with LiHMDS and allyl chloroformate trapping (Scheme 3.18). Conveniently, we found that if PPh₃ was employed as an achiral ligand, a
racemic Tsuji allylation\textsuperscript{26} could be conducted with as little as 0.5 mol\% Pd$_2$(dba)$_3$ and 2 mol\% PPh$_3$ ligand. Use of enantioselective conditions required low substrate concentration (0.033 M) to achieve the highest degree of enantioselectivity. Hence, large solvent volumes were needed for high material throughput. However, using the PPh$_3$-based non-enantioselective system, reactions could be performed at high concentrations (0.2 M). Although large-scale reactions could now be performed, care had to be taken during purification, as the allyl ketone (\textpm)-75 was found to be volatile.\textsuperscript{27} Initial investigations into the total synthesis would be conducted with racemic material. Once chemistry was well established, the enantioselective synthesis would be undertaken.

Scheme 3.18 Completion of the Bicyclic Enone

\[
\text{LiHMDI (1.2 equiv)} \quad \text{THF, 0 °C}
\]

then allyl chloroformate (1.3 equiv), -78 °C (86\% yield)

\[
PPh$_3$ (2 mol\%) \quad \text{Pd$_2$(dba)$_3$ (0.5 mol\%)} \quad \text{THF, 23 °C}
\]

(60\% yield)

\[
\text{PdCl$_2$ (5 mol\%)} \quad \text{Cu(OAc)$_2$+H$_2$O (25 mol\%)} \quad \text{DMA / H$_2$O (7:1), 23 °C}
\]

(77\% yield)

\[
\text{Pd$_2$(dba)$_3$ (0.5 mol\%)} \quad \text{Pd$_2$(dba)$_3$ (0.5 mol\%)} \quad \text{THF, 23 °C}
\]

(60\% yield)

\[
\text{PPh$_3$ (2 mol\%)} \quad \text{Pd$_2$(dba)$_3$ (0.5 mol\%)} \quad \text{THF, 23 °C}
\]

(60\% yield)

We believed that a Wacker oxidation would be ideal for installation of a second ketone moiety of (\textpm)-219 (Scheme 3.18).\textsuperscript{28} On small scale, this proved to be the case. However, when larger reactions were performed, catalyst lifetime was poor. Initially, we tried increasing the catalyst loadings of Pd and Cu or heating the reaction to higher temperature. These approaches met with limited success, though. We hypothesized that
inefficient catalyst turnover was due to poor reoxidation of the palladium after substrate oxidation. Without enough O\textsubscript{2} in solution, Pd\textsuperscript{0} could not be regenerated. To increase the amount of O\textsubscript{2} uptake in these Wacker oxidations, we placed the reactions on a Parr shaker under a balloon of oxygen. With the increased oxygenation and headspace-solvent interaction, our oxidation reaction became very efficient on increased scale.

Finally, an intramolecular aldol condensation of diketone (±)-219 was attempted. Conditions involving KOH and ethanol\textsuperscript{29} though capable of the transformation, were not high yielding in this case. Fortunately, if the reaction was performed in xylenes with azeotropic removal of water under Dean-Stark conditions\textsuperscript{30} bicyclic enone (±)-143 could be prepared in excellent yield.\textsuperscript{31} Employing the methods we had developed, more than 17 grams of enone (±)-143 was prepared in racemic form.

3.4.2 6π-Electrocyclization Approach to the Third Ring

With the second carbocyclic ring of the natural product in place, we began to think of methods for installing the third ring. Fallis had recently reported a 6π-electrocyclization approach toward the benzannulation of certain ketones (Scheme 3.19).\textsuperscript{32} In his method, a ketone (e.g., 223) was converted to an enol triflate 224 and coupled to a propargyl alcohol under Sonogashira conditions. When alcohol 225 was treated with vinyl magnesium halide, a directed carbomagnesiation took place. The new triene 226 could then undergo 6π-electrocyclization. The resulting diene product (227) could be treated with a proton or electrophiles such as iodine then oxidized to an aromatic system (e.g., 228).
We hoped that this benzannulation approach might be applicable to our system (Scheme 3.20). If the method succeeded, we could install both the aromatic ring of dichroanone (150) and the isopropyl group. Enone (±)-143 could be readily converted to enol triflate (±)-229 via treatment with LDA and N-phenyl triflimide. Gratifyingly, Sonogashira coupling of 2-methyl but-3-yn-2-ol (230) in the presence of Pd(PPh₃)₄ and CuI went smoothly, giving (±)-231. However, all attempts at directed carbometallation with vinyl magnesium halides were unsuccessful in our hands. Perhaps the switch from the primary propargylic alcohols typically used by Fallis (e.g., propargyl alcohol) to our tertiary one (230) was responsible in part for the difficulty with our reaction.
Scheme 3.20 Attempted Electrocyclization

\[
\begin{align*}
\text{(a)-143} & \quad \text{LDA, THF, 0 °C} \quad \text{then PhN(Tf)₂} \\
& \quad \text{then} \quad \text{(98% yield)} \\
\rightarrow & \quad \text{(a)-229} + \quad \text{230} \\
& \quad \text{THF, 75 °C} \\
& \quad \text{(62% from (a)-143)} \\
\end{align*}
\]

3.4.3 Robinson Annulation of the Enone

Enolization of bicyclic enone (±)-143 and trapping with N-phenyltriflimide had been a facile process, but when other electrophiles such as iodomethane, allyl chloroformate, or allyl bromide were used to trap the enolate, complex mixtures of products were obtained. Usually, it appeared that O-functionalization was competitive with C-functionalization. Thus, we turned toward the possibility of a two-step Robinson annulation. Fortunately, Michael addition of the lithium enolate of (±)-143 into methyl vinyl ketone (35) gave primarily one product (Scheme 3.21). Initially, the yield was low, but careful optimization of the temperature, rate of MVK (35) addition, base, and equivalents of 35 increased the yield from the low 30% range to 72% with a 10.7:1 dr. X-ray crystallographic analysis of (±)-233 revealed that the methyl group at C(4a) and the ketone chain at C(5a) in the major diastereomer possessed an anti configuration.
To complete the two-step Robinson annulation, an intramolecular aldol condensation was necessary. We turned to the conditions previously used to prepare bicyclic enone (±)-143 (Scheme 3.21). When 0.45 equivalents of KOH were used, conversion of (±)-233 to (±)-234 was limited. However, if 2.00 equivalents of KOH were employed, the final ring closure proceeded smoothly. Thus, tricyclic enone (±)-234 was isolated in 80% yield and 5.6:1 dr. Although there had been some epimerization at C(5a), we were not concerned because this stereocenter would later be removed.

3.5 Synthesis of a Dichroanone Isomer

3.5.1 α-Hydroxylation

Our next challenges included bringing the newly formed cyclohexenone ring to aromaticity and installing the isopropyl group. Direct addition of isopropylmetal species into the carbonyl of (±)-234 were met with limited success and led to complex mixtures (Scheme 3.22). To provide an extra synthetic handle, we decided to install another oxygen on the cyclohexenone ring of (±)-234.
To this end, we treated tricyclic enone \((\pm)-234\) with LDA, followed by TBSOTf, furnishing silyl enol ether \((\pm)-235\). A battery of oxidation conditions were tested for synthesizing an \(\alpha\)-hydroxylketone, including MoOPH\(^{33,34}\), Rubottom oxidation\(^3\), dimethyl dioxirane\(^3\), and methyl phenyl dioxirane\(^3\). The Davis oxaziridine\(^3\) proved most effective for this transformation, giving two partially separable diastereomeric acyloins \((\pm)-236A\) and \((\pm)-236B\) in 61% combined yield. Attempts to protect the hydroxyl groups met with limited success. Direct addition of isopropyl magnesium halide to the acyloins resulted in a complex mixture, containing traces of the hydrocarbon \((\pm)-237\). This was encouraging to us, and we thought that a further increase in the oxidation state of the starting material for the Grignard addition could potentially lead to arenes with oxygen functionality.

3.5.2 Synthesis of an Isomer of Dichroanone

To test the hypothesis regarding the increased oxygenation and its effect on Grignard addition, we treated the mixture of acyloins \((\pm)-236A\) and \((\pm)-236B\) with Dess-
Martin periodinane. The reaction became bright red, indicating the possible presence of an \( o \)-quinone such as 238 (Scheme 3.23). Unfortunately, we were unable to isolate the product in pure form, perhaps due to its high instability. Instead, we subjected the crude product to isopropyl magnesium chloride in THF at \(-78\, ^\circ\text{C}\). Gratifyingly, a reaction occurred, and the putative \( o \)-quinone 238 was consumed. Unfortunately, the product proved too unstable to isolate. We hypothesized, erroneously, that an isopropyl group had been successfully introduced at C(7) via 1,2-addition to the carbonyl, leading to a non-aromatic species 239. If this had been true, acid-mediated rearrangement and oxidation might have potentially led to \((\pm)\)-dichroanone (150).

Scheme 3.23 Synthesis of a Dichroanone Isomer

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We tested our theory by first stirring the crude Grignard product mixture with aqueous HCl, then rapidly chromatographing the resulting reaction product. The isolated species was immediately heated in the presence of Fremy’s salt (potassium nitroso
disulfonate radical), producing a product that was purified on preparative HPLC. nOe analysis revealed that an isopropyl group had indeed been added to the desired ring. However, it had undergone an overall 1,6-addition to the o-quinone 238 at C(8), ultimately leading to an isomer of dichroanone (±-240).

3.6 Second Retrosynthetic Analysis of Dichroanone

3.6.1 Lessons Learned

It was abundantly clear that an effective total synthesis of dichroanone (150) was going to require careful installation of the isopropyl group. This functionalization would need to take precedence over oxygenation of the aromatic ring of the 4a-methyltetrahydrofluorene skeleton (152). Fortunately, we had already shown it was possible to construct all of the rings in the natural product, and we were hopeful that the tricyclic enone 234 could still be an intermediate in our synthetic route.

3.6.2 Retrosynthetic Revisions

Our second-generation retrosynthetic analysis of dichroanone ((+)-150) began with the removal of the two quinoid oxygen atoms (Scheme 3.24). This simplified the system to a target phenol molecule (−)-242, which could be prepared from an arene such as (−)-237. This hydrocarbon could arise via coupling of an isopropyl metal and either an aryl or dienyl triflate (243) derived from tricyclic enone (±)-234 and a three-carbon coupling partner. The tricyclic enone (±)-234 would still be prepared from (−)-143, and from this point back, the retrosynthesis would remain largely unchanged.
3.6.3 Substrate and Catalyst Control in Pd-Catalyzed Enantioselective Alkylations

It was somewhat challenging to prepare pure 2,2,6-trimethylcyclohexanone (101), so we wondered if a Pd-catalyzed enantioselective decarboxylative alkylation could be performed with the chiral, yet racemic enol carbonate (±)-244, derived from 2,6-dimethylcyclohexanone (220) (Scheme 3.25). Assuming a 100% stereoselective, fully (R)-catalyst-controlled reaction, a 1:1 mixture of two allyl ketones 245Ba and 245Bb, each with 99% ee, would be formed. Alternatively, if the reaction were substrate controlled and/or less enantioselective, the catalyst might occasionally form the undesired diastereomers. This might lead to a mixture of four products 245Aa, 245Ab, 245Ba, and 245Bb. Upon inspection, one can see that 245Aa and 245Bb are enantiomeric, as are 245Ab and 245Ba. If the mixture of all four compounds were alkylated with LDA and iodomethane, two enantiomeric products (–)-75A and (+)-75B would be produced. However, if the (R)-PHOX ligand catalyst system were completely dominant over the substrate stereochemistry and fully enantioselective, only enantiomer (+)-75B would be seen after alkylation. This was the desired scenario.
Scheme 3.25 Substrate and Catalyst Control in a Diastereoselective Alkylation

To test the viability of this approach, racemic 244 was prepared in high yield and treated with (R)-t-Bu-PHOX (R)-69 and Pd$_2$(dba)$_3$ in THF (Scheme 3.25). A rapid reaction led to a mixture of two diastereomeric products 245A and 245B. This mixture was then treated with LDA and iodomethane, giving two enantiomers of allyl ketone (–)-75. Wacker oxidation of (+)-75 was followed by intramolecular aldol condensation. The enone (+)-143 was studied by chiral HPLC, revealing only a 53% ee. This indicated a fair degree of substrate control for this enantioselective decarboxylative alkylation. Although this method involving the enol carbonate (±)-DM32 was not enantioselective enough for application in the synthesis, insight was gained into the catalyst/substrate control bias.
3.6.4 Enantioenrichment Strategy

Using the methods described earlier in this chapter, we prepared the enol carbonate of 2,2,6_trimethylcyclohexanone, 1**00** (Scheme 3.26). Pd-catalyzed enantioselective decarboxylative allylation furnished tetrasubstituted allyl ketone (−)-7**5** in 83% yield and 91% ee, but we wanted to prepare dichroanone (+(+)**-150**) in greater than 96% ee. A crystalline intermediate (such as a semicarbazone or oxime) within our synthetic route could perhaps be recrystallized to achieve high enantioenrichment. Because 2,2,6,6-tetramethylcyclohexanone (221) had been unable to form a semicarbazone, we were concerned that tetrasubstituted allyl ketone (−)-7**5** would also be unable to do so. This meant that we would need to find some other crystalline species later in our synthesis that could be enantioenriched via recrystallization.

Scheme 3.26 Preparation of the Bicyclic Enone

Thus, we advanced material to the bicyclic enone (−)-14**3**. We thought this might be a suitable candidate for conversion to a crystalline imine analog, but we were aware that two imines (−)-24**6a** and **246b** were possible. If they both formed, this could make an
enantioenrichment recrystallization problematic. To our delight, when (−)-143 was treated with semicarbazide hydrochloride and base, a single geometric isomer of semicarbazone, (−)-246a was formed, as indicated by nOesy-1D experiments. After two recrystallizations from ethanol/water followed by acidic hydrolysis, (−)-143 was obtained in 97% ee. Using our two-step Robinson annulation, we accessed tricyclic enone (±)-234 and became ready for further investigations.

Scheme 3.27 Enantioenrichment of the Bicyclic Enone

3.7 Preparation and Manipulation of a Tricyclic Phenol

3.7.1 Attempted Aryl Triflate Synthesis

With tricyclic enone (±)-234 in hand, we thought aryl triflate 248 would be a good target. Our first goal was to increase the oxidation state of the enone ring to an aromatic level (Scheme 3.28). Treatment of racemic (±)-234 with LiHMDS, followed by PhSeCl and a hydrogen peroxide workup, appeared to yield some of the desired phenol 247. Unfortunately, the method proved difficult to optimize and was not pursued further.
Preparation of TBS enol ether (±)-235 had been facile, so we tested aromatization chemistry developed by Corey and Lazerwith. Treatment of (±)-235 with MnO$_2$ in methylcyclohexane did not affect oxidation in our hands. The Saegusa-Ito oxidation of silyl enol ethers to enones also appeared viable in this scenario. When we applied this method, it looked as though phenol 247 was present, but achieving catalyst turnover was difficult. Thus, synthesis of the aryl triflate 248 was not pursued further.

3.7.2 Kumada Coupling and Benzannulation

Considering the facile preparation of silyl enol ether (±)-235, it was not surprising that enol triflate (−)-250 was also readily accessible. We believed that coupling of an isopropenyl metal species to this compound might allow access to a tetraene 251. If this could be prepared, we anticipated that the oxidation state of the isopropenyl olefin could be transposed into the adjacent six-membered ring, affecting aromatization (Scheme 3.29). Toward this end, we attempted a Kumada coupling of enol triflate (−)-250 and
isopropenyl magnesium bromide in THF. Triflate (−)-250 was fully consumed during the reaction, but several products were observed.

Scheme 3.29 Kumada Coupling Strategy

After LCMS analysis of the crude reaction mixture was performed, three UV-active peaks were found, each bearing the mass of the desired product. Furthermore, two-dimensional TLC analysis revealed that two of the three products were unstable on silica gel. The one with the lowest retention factor (Rf) converted irreversibly to a mixture of the other two. The middle Rf compound converted irreversibly to the highest Rf product only.

Based on these observations, we reasoned that acid-promoted rearrangements were occurring, and that the two low-Rf spot were olefin isomers of 251.42 We believed the high-Rf product was the thermodynamic product of the rearrangement and, possibly, arene (−)-237. To test this hypothesis, a completed Kumada coupling reaction was quenched with 6 M aqueous HCl, and allowed to stir at 23 °C for several hours in the dark. To our delight, arene (−)-237 was formed as the only isolable product in 65%
overall yield from bicyclic enone \((\pm)-234\). This novel Kumada benzannulation achieved the installation of the aromatic ring system while placing the isopropyl group in the correct position for completion of dichroanone \((+)-150\).

3.7.3 Preparation of an Unstable Phenol

Aromatic hydrocarbon \((-)-237\) presented us with the daunting challenge of selective functionalization of the arene. Fortunately, we discovered that treatment of \((-)-237\) with TiCl\(_4\) and \(\alpha,\alpha\)-dichloromethyl methyl ether in CH\(_2\)Cl\(_2\) at low temperature produced a mixture of two separable aldehydes in a 10:1 ratio (Scheme 3.30). The major aldehyde isomer was studied using nOesy-1D experiments and found to have the structure \((-)-252\), whereas the minor one \((+)-253\) was substituted \textit{ortho} to the styrenyl vinyl group.

Scheme 3.30 Synthesis of the Two Aldehydes

Both aldehydes could be converted to their corresponding phenols \((-)-242\) and \((\pm)-254\) via Baeyer-Villiger oxidation under acidic conditions. For simplicity, we decided to carry on the major phenol \((-)-242\) (Scheme 3.31). We discovered, however, that this phenol was very unstable. It had to be prepared and used within a single day for any
practical chemistry. Careful observation of the compound by $^1$H NMR in CDCl$_3$ revealed
the formation of a new and highly unstable peroxide species (±)-255, which decomposed
over a four-hour period (in solution) to a new compound. Careful isolation and
characterization of this entity showed it to be keto-aldehyde (±)-256, which presumably
forms by retro [2 + 2] cycloaddition of the peroxide (±)-255. If (–)-242 was allowed to
stand in the solid state under ambient air, it slowly oxidized to (±)-255. This
decomposition mode has been surmised for other electron-rich styrenes found in nature.$^{43}$

Scheme 3.31 Instability of a Key Phenol

3.7.4 Protecting Group Strategies

It initially seemed wise to protect unstable phenol (–)-242. When treated with
base and iodomethane, phenol (±)-242 was transformed into methyl ether (±)-257
(Scheme 3.32). Directed $o$-lithiation of (±)-257 was unsuccessful, perhaps due to the
nearby quaternary carbon at C(4a). Formylation of the aryl ring under a variety of conditions also failed. When methyl ether (±)-257 was treated with N-bromosuccinimide in wet CH$_3$CN, bromohydrin (±)-258 was produced. Its relative stereochemical configuration was determined by nOesy-1D experiments. It was also possible to convert this bromohydrin into epoxide (±)-259. Although investigations with the methyl ether (±)-257 were not fruitful in the progression toward dichroanone ((+)-150), we believed that compounds (±)-258 and (±)-259 might eventually find use in the total synthesis of taiwaniaquinol B (154) or other bioactive molecules.

Scheme 3.32 Studies with the Methyl Ether

3.8 Total Synthesis of Dichroanone

3.8.1 Preparation of an o-Quinone

The preparation of phenol (−)-242 had become a bottleneck in the synthesis, but installation of the second oxygen atom of the aromatic system was still explorable. We made o-quinone (R)-260 our target compound (Scheme 3.33). Screening many conditions revealed a few methods capable of producing the o-quinone. The most successful reagent
for this transformation was IBX, used under a set of conditions developed by Pettus.\textsuperscript{45} We could isolate the \( o \)-quinone \((R)-260\) chromatographically, but the yield was poor because most of the compound decomposed on the flash column. Additionally, we believed that most of the starting material was forming a different oxidation byproduct \( 261,45,46\) although it could not be isolated in pure form. In order to determine the actual yield of \( o \)-quinone \((R)-260\), we turned to NMR methods.\textsuperscript{47} The maximum yield of \( o \)-quinone \((R)-260\) was found to be 36%. Any further synthetic manipulations on \((R)-260\) would need to be done in solution without direct isolation due to the extreme instability of this \( o \)-quinone. Although the yield was modest at best, we hoped that \((R)-260\) could be used as a precursor for dichroanone \((\pm)-150\).

![Scheme 3.33 Preparation of the \( o \)-Quinone](image)

3.8.2 \textit{Thiol Additions into the \( o \)-Quinone}

We began to treat the filtered chloroform solution of \( o \)-quinone \((R)-260\) (from the IBX reaction) with a variety of nucleophiles. The goal was to install a functional handle at the unsubstituted position of the \( o \)-quinone. Amongst the list of reagents tested were anhydrous HCl, MgBr\(_2\), and ethanethiol. In most cases, incomplete reaction, poor chemoselectivity, or both were encountered. When we turned to aryl thiol nucleophiles,
smoother reactions were observed. The sulfur atom appeared to undergoing a conjugate 1,4-addition into the remaining unsubstituted o-quinone ring position (Scheme 3.34).

Scheme 3.34 Nucleophilic Additions of Thiophenol

When thiophenol was used, an unstable catechol could be detected in the $^1$H NMR of a rapidly chromatographed, yet crude, product sample. Although this compound could not be isolated by itself in pure form, two broad singlets between 4 and 6 ppm in CDCl$_3$ were observed in the crude $^1$H NMR spectrum, which were possibly catechol hydroxyl protons. As we allowed a given reaction of (R)-260 with thiophenol to progress, more products began to form. It was possible that the unreacted o-quinone (R)-260 could have been oxidizing the catechol 262 as it formed (Scheme 3.34), leading to 263 and 264. Alternatively, hydride transfer from thiophenol to (R)-260 could also explain the presence of the isolated catechol. It was not possible to ascertain with full certainty the structure of the catechol observed in the crude $^1$H NMR.
Although we were not fully certain about what was happening during the thiophenol transformation, we decided to believe the theory of product 262 oxidation by starting material (R)-260. A potential solution to this hypothetical problem would have been to produce a catechol (via conjugate addition) too electron-deficient to be oxidized by unreacted (R)-260. A good thiol candidate for accomplishing this was pentafluorothiophenol (PFPSH). To our delight, when a solution of o-quinone (R)-260 was treated with this reagent, a much smoother reaction was observed as compared to the PhSH transformation (Scheme 3.35). Although we suspected the presence of catechol 265 after PFPSH addition to (R)-260, no stable product could be isolated from the reaction. Our options were now very limited.

Scheme 3.35 The Switch to Pentafluorothiophenol

3.8.3 Completion of Dichroanone

The best method for dealing with the putative catechol 265 was to simply let it oxidize. We took the completed nucleophilic addition reaction and added methanol, NaOH, and a balloon of O₂. As the bright yellow reaction was stirred, it gradually became a deep reddish-brown color. We took this as evidence that the catechol was being converted to another o-quinone 266, which was also too unstable to isolate (Scheme 3.36). The hypothesis that 266 was an o-quinone led us to make a strategic decision. 266
was not only an o-quinone, but also an activated, electron-deficient vinylogous thioester. Since NaOH was already in the reaction, we attempted a vinylogous saponification by warming the reaction.\textsuperscript{48}

Scheme 3.36 Total Synthesis of (+)-Dichroanone

The isolation chemists had indicated that dichroanone (150) was a bright red solid. Our reaction was a chalky brown color. However, when we quenched the reaction with aqueous HCl, a beautiful reaction color change to a translucent bright orange-red was observed. To our delight, aqueous workup and column chromatography on silica gel provided (+)-dichroanone ((+)-150) as a stable, bright red solid in 35% overall yield from phenol (–)-242 (Scheme 3.37). The material was identical in all respects to the natural product reported by the isolation chemists,\textsuperscript{3} with the exception of its sign of rotation. Not only was our synthesis completed in 11 steps and 4% overall yield from commercial material, but it required no protecting groups.\textsuperscript{49}
Scheme 3.37 One-Step Synthesis of Dichroanone from the Phenol

3.9 Attempts to Prepare Other Natural Products

3.9.1 Toward Taiwaniaquinone H

Taiwaniaquinone H (165) appeared to be the vinylogous methyl ester or dichroanone (150). Considering the similarity between these two natural products, we decided to try methylating 150 in an attempted synthesis of 165 (Scheme 3.38). Treatment of ethereal solutions of 150 with diazomethane gave quantitative conversion to a single compound, which we initially thought was taiwaniaquinone H (165). Closer examination of the spectral data for this species revealed some differences from the authentic natural product. Many of the $^{13}$C NMR resonances differ, and two in our sample were $> \delta$ 180 ppm, more consistent with an o-quinone moiety. The resonances in the $^1$H NMR differed as well, especially the vinylogous methyl ester CH$_3$ protons ($\delta$ 3.86 ppm in our sample, but $\delta$ 3.96 ppm for the natural product.) The carbonyls in the IR spectrum were also different. For these reasons, we believe that we have prepared (+)-267 and not taiwaniaquinone H (165).
Scheme 3.38 Preparation of a Taiwaniaquinone H Isomer.

3.9.2 Toward Taiwaniaquinol D

Treatment of dichroanone (150) first with base followed by acetyl chloride gave a single vinylogous anhydride (+)-268a (or ((+)-268b) (Scheme 3.39). It was possible to selectively oxidize the trisubstituted olefin spanning C(9) and C(9a) with m-CPBA, affording a single epoxide diastereomer (either (–)-269a or (–)-269b). Preliminary experiments have revealed that epoxide (–)-269a (or (–)-269b) may rearrange to a ketone 270a (or 270b) under thermal conditions. This product could potentially be transformed into taiwaniaquinol B (154) or E (157) after deacetylation, methylation, and reduction. The epoxide (–)-269a (or (–)-269b) might also be bioactive, as certain other oxiranyl quinones have been44.
3.10 Concluding Remarks

We have reported the first catalytic-enantioselective, protecting group-free total synthesis of (+)-Dichroanone ([+]-150), establishing the absolute stereochemistry of the natural product.\textsuperscript{49} Our synthesis has showcased the power of our enantioselective decarboxylative alkylation in the context of a total synthesis. We have developed a novel Kumada coupling-aromatization strategy, as well as a new method for generating a hydroxy $p$-benzoquinone from a phenol. Investigations were also made into synthesizing other natural products in the family.
3.11 Experimental Procedures

3.11.1 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, stabilized with ethanol, was stored in the dark over oven-dried 4Å molecular sieves. Methanol, absolute ethanol, and N,N-dimethyl acetamide were used as purchased. 2,6-dimethylcyclohexanone (220), purchased from Aldrich,\(^{24}\) was fractionally distilled from CaSO\(_4\) at ambient pressure prior to use. TMEDA, pyridine, i-Pr\(_2\)NH, and Et\(_3\)N were distilled from CaH\(_2\). All other commercially obtained reagents were used as received, unless specified otherwise. The Davis oxaziridine was prepared according to the method of Davis.\(^{38}\) IBX was prepared by the method of Santagostino.\(^{51}\) (R)- and (S)-t-BuPHOX ligands (R)-69 and (R)-69 were prepared according to known methods.\(^{52}\) 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 254 nm 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) 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 ($\delta$ 7.26 for CDCl$_3$ and $\delta$ 7.16 for C$_6$D$_6$). Data for $^1$H NMR spectra are reported as follows: chemical shift ($\delta$ ppm), multiplicity, coupling constant (Hz), and integration. $^1$H-$^1$H homodecoupling and 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. $^{13}$C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative to the residual solvent peak ($\delta$ 77.2 for CDCl$_3$ and $\delta$ 128.4 for C$_6$D$_6$). Data for $^{13}$C NMR spectra are reported in terms of chemical shift. $^{19}$F NMR spectra were recorded on a Varian Mercury 300 (at 282 MHz) and are reported in terms of chemical shift without the use of a reference peak. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer and are reported in frequency of absorption (cm$^{-1}$). IR samples were thin films deposited on sodium chloride plates by evaporation from a solvent (usually CDCl$_3$), which is recorded. Optical rotations were measured with a Jasco P-1010 polarimeter, using a 100 mm path-length cell. High-resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are measured directly during distillation and are uncorrected. UV-Vis spectra were collected on an Agilent 8453 UV-Vis spectroscopy system and are reported as follows: $\lambda_{\text{max}}$ (nm) then log($\varepsilon$) (M$^{-1}$•cm$^{-1}$). Crystallographic data for (+)-233 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 the deposition number 293604.
3.11.2 Syntheses of Compounds Related to Dichroanone

**Semicarbazone 222.** To a solution of \(i\)-Pr₂NH (16.6 mL, 119 mmol) in THF (400 mL) was added \(n\)-BuLi (44.4 mL, 2.55 M in hexanes, 113.2 mmol) in a dropwise fashion at 0 °C. After 30 min, a solution of 2,6-dimethylcyclohexanone (220) (10.0 g, 79.3 mmol, mixture of cis and trans isomers) in THF (10 mL) was added. After 1 h, Iodomethane (14.8 mL, 237.9 mmol) was added quickly, and the reaction was warmed to 23 °C. After 1 h, the reaction was poured into a round-bottom flask containing sat. aq NH₄Cl (100 mL) and H₂O (100 mL). After stirring 10 min, the reaction was diluted with H₂O (75 mL) and pentanes (75 mL). The aqueous layer was extracted with pentanes (3 x 100 mL). All organic layers were combined, washed with brine (100 mL), dried (Na₂SO₄), filtered, concentrated, and distilled under N₂ at ambient pressure, affording ketone mixture of 2,2,6-trimethylcyclohexanone (101) and 2,2,6,6-tetramethyl cyclohexanone (9.57 g) as a clear, fragrant oil, which was used without further characterization.

To a solution of this ketone mixture (9.56 g), in MeOH (160 mL), water (60 mL), and pyridine (24 mL) was added semicarbazide hydrochloride (14.0 g, 126.1 mmol). The reaction was refluxed at 105 °C for 30 min. Then, the heating was turned off, and the reaction was allowed to cool to 23 °C in the oil bath. Then, the reaction was cooled to –20 °C for 36 h. The white crystals that formed were filtered and washed with water, then dried in vacuo over P₂O₅, giving 222 (10.8 g, 69% over 2 steps from 220) as a white,
crystalline solid. R_f 0.45 (10:90 MeOH/CH_2Cl_2), (I_2/Sand, brown spot); mp 203-205 °C (water); ^1H NMR (300 MHz, CDCl_3): δ 8.39 (s, broad, 1H), 6.05 (s, broad, 1H), 5.67 (s, broad, 1H), 2.92-2.79 (m, 1H), 1.84-1.66 (m, 1H), 1.64-1.31 (m, 5H), 1.13 (s, 3H), 1.13 (d, J = 7.7 Hz, 3H), 1.12 (s, 3H), 1.11-1.08 (m, 1H); ^13C NMR (75 MHz, CDCl_3): δ 160.7, 158.8, 40.3, 38.0, 31.7, 29.6, 29.2, 28.3, 18.0, 17.1; IR (KBr): 3463, 3186, 2970, 2868, 2856, 1689, 1577, 1465, 1384, 1110, 1086 cm^{-1}; HRMS-FAB^+ (m/z): [M+H]^+ calc’d for C_{10}H_{20}N_3O, 198.1606; found, 198.1602.

2,2,6-Trimethyl Cyclohexanone (101). To a suspension of semicarbazone 222 (10.9 g, 55.0 mmol) in Et_2O (400 mL) and water (20 mL) was added 6 M aq HCl (20 mL) in a dropwise fashion. The biphasic mixture was stirred vigorously at 23 °C for 3 h. Then, sat. aq NaHCO_3 (300 mL) was added cautiously at 0 °C. After 30 min, the organic phase was collected. The aqueous phase was extracted with Et_2O (2 x 100 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was distilled at ambient pressure under N_2, affording 2,2,6-trimethylcyclohexanone (101) (6.51 g, 82% yield) as a clear, fragrant oil. R_f 0.48 (1:9 EtOAc/hexane), (p-Anisaldehyde, yellow spot); bp 178-180 °C (760 mmHg); ^1H NMR (300 MHz, CDCl_3): δ 2.54 (app. septuplet, J = 6.6 Hz, 1H), 1.99-1.88 (m, 1H), 1.77 (tdd, J_i = 26.7 Hz, J_d1 = 13.2 Hz, J_d2 = 3.8 Hz, 1H), 1.65 (app. dq, J_d = 13.2 Hz, J_q = 2.8 Hz, 1H), 1.52 (app. ddd, J = 13.7 Hz, 6.6 Hz, 4.1 Hz, 2.9 Hz, 1H), 1.42 (app. td, J_i = 13.2 Hz, J_d = 4.1 Hz, 1H), 1.19 (app. ddd, J = 26.1 Hz, 13.2
Hz, 3.9 Hz, 1H), 1.06 (s, 3H), 0.91 (s, 3H), 0.86 (d, J = 6.3 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 217.1, 45.1, 41.8, 40.7, 36.7, 25.6, 25.2, 21.5, 14.9; IR (NaCl/CDCl$_3$): 2967, 2930, 2869, 2853, 1707, 1471, 1455, 1384, 1376, 1127, 1019, 993, 957, 857 cm$^{-1}$; HRMS-El$^+$ (m/z): [M]$^+$ calc’d for C$_9$H$_{16}$O, 140.1201; found, 140.1203.

**Enol Carbonate 100.** A solution of LiHMDS (1.0 M in THF, 57.5 mL, 57.5 mmol) was added to THF (300 mL), then cooled to 0 °C. A solution of pure 2,2,6-trimethylcyclohexanone (101) (6.67 g, 47.6 mmol) in THF (10 mL) was added. The reaction was stirred at 0 °C for 1 h, then cooled to –78 °C and fitted with an addition funnel, which was charged with a solution of allyl chloroformate (6.56 mL, 61.8 mmol) in THF (200 mL). The solution was added dropwise over 30 min. Then, the reaction was warmed to 23 °C. After 13 h, the reaction was poured into a mixture of sat. aq NH$_4$Cl (100 mL), water (100 mL), and hexane (100 mL). After 10 min, the organic phase was collected and the aqueous phase extracted with Et$_2$O (3 x 75 mL). All organic layers were combined, washed with brine (100 mL), dried (Na$_2$SO$_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (2:98 Et$_2$O/hexane eluent), affording enol carbonate 100 (9.19 g, 86% yield) as a clear oil. R$_f$ 0.43 (1:9 EtOAc/hexane), (p-Anisaldehyde, blue spot); $^1$H NMR (300 MHz, CDCl$_3$): δ 5.96 (app. ddt, $J_{d1}$ = 17.1 Hz, $J_{d2}$ = 10.7 Hz, $J_t$ = 5.8 Hz, 1H), 5.38 (app. ddq, $J_{d1}$ = 17.3 Hz, $J_{d2}$ = 8.3 Hz, $J_q$ = 1.4 Hz, 1H), 5.28 (app. ddq, $J_{d1}$ = 10.5 Hz, $J_{d2}$ = 4.4 Hz, $J_q$ = 1.1 Hz, 1H),
4.65 (app. ddt, $J_{d1} = 10.2$ Hz, $J_{d2} = 5.7$ Hz, $J_{t} = 1.4$ Hz, 2H), 2.05 (t, $J = 5.5$ Hz, 2H), 1.77-1.52 (m, 4H), 1.50 (s, 3H), 1.04 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 153.5, 148.1, 131.8, 120.9, 119.1, 68.7, 39.4, 35.1, 31.4, 26.9, 19.3, 16.7; IR (NaCl/CDCl$_3$): 2965, 2934, 2868, 2838, 1759, 1459, 1363, 1271, 1238, 1138, 1025, 993, 937 cm$^{-1}$; HRMS-EI$^+$ ($m/z$): [M]$^+$ calc’d for C$_{13}$H$_{20}$O, 224.1413; found, 224.1408.

**Allyl Ketone (±)-75.** A round-bottom flask was flame-dried under argon and charged with Pd$_2$(dba)$_3$ (81.6 mg, 89.0 µmol, 0.5 mol%) and PPh$_3$ (93.6 mg, 0.357 mmol, 2.0 mol%). The system was evacuated with vacuum and back-filled with argon (3 x). Then THF (90 mL) was introduced. The red mixture was stirred vigorously for 2 min at 25 °C. Then, enol carbonate 100 (4.00 g, 17.8 mmol, 1.00 equiv) was added, and the reaction immediately turned green. After 2 h, the reaction was filtered through a plug of silica gel with the aide of THF, and the filtrate was concentrated to ~20 mL total volume. The material was transferred to a round-bottom flask and fitted with a short-path distillation head under N$_2$. The THF was distilled away at ambient pressure, then the racemic allyl ketone (±)-75 was distilled in semipure form as a yellow oil (2.40 g, 75% yield by mass, ~60% yield by $^1$H NMR). bp: 62-75 °C (8 mmHg). Other characterization data can be found on pages 40 and 41 (chapter 2).
**Enol Carbonate 244.** A round-bottom flask was charged with THF (200 mL) and \( i-\text{Pr}_2\text{NH} \) (13.33 mL, 95.2 mmol, 1.2 equiv) and cooled to 0 °C. \( n\text{-BuLi} \) (2.5 M in hexanes, 34.9 mL, 87.2 mmol, 1.1 equiv) was added dropwise. After 30 min, 2,6-dimethyl cyclohexanone (220) (cis,trans mixture) (10.0 g, 79.3 mmol, 1.0 equiv) was added along with THF (10 mL). After 1.5 h at 23 °C, the reactor was fitted with an addition funnel, which was charged with a solution of allyl chloroformate (10.1 mL, 95.2 mmol, 1.20 equiv) in THF (100 mL). The reaction was cooled to –78 °C, and the chloroformate solution was added dropwise over a 30 min period. Then, the reaction was allowed to warm to 23 °C. After 15 h, the reaction was quenched with sat. aq NH\(_4\)Cl (100 mL) and diluted with H\(_2\)O (100 mL) and hexanes (100 mL). The organic phase was collected and the aqueous layer extracted with Et\(_2\)O (2 x 100 mL). All organic layers were combined, dried (Na\(_2\)SO\(_4\)), filtered, and concentrated to an orange oil. This oil was fractionally distilled through a vacuum-jacketed Vigreux column fitted with a vacuum jacketed short path head at 8 mmHg. A forerun (~1 mL, bp 50-96 °C) was collected, followed by a main fraction (bp 96-106 °C) that contained enol carbonate 244 (13.93 g, 84% yield) as a colorless, fragrant oil. R\(_f\) 0.43 (10:90 EtOAc/hexane), (\( \rho \)-Anisaldehyde, turquoise spot); \(^1\)H NMR (300 MHz, CDCl\(_3\)) : δ 5.95 (app. ddt, \( J_{d1} = 17.3 \) Hz, \( J_{d2} = 10.4 \) Hz, \( J_t = 5.7 \) Hz, 1H), 5.37 (app. dd, \( J = 17.3 \) Hz, 1.4 Hz, 1H), 5.27 (app. dd, \( J = 10.4 \) Hz, 1.4 Hz, 1H), 4.64 (app. d, \( J = 5.7 \) Hz, 2H), 2.46 (app. d, broad, \( J = 4.7 \) Hz, 1H), 2.13 (app. dd, \( J = 6.1 \) Hz, 4.9 Hz, 2H), 1.84 (app. dddd, \( J = 12.6 \) Hz, 8.5 Hz, 5.8 Hz, 3.0 Hz, 1H), 1.72-1.48 (m,
2H), 1.55 (s 3H), 1.40 (app. dddd, \(J = 12.4\) Hz, 8.5 Hz, 6.3 Hz, 3.3 Hz, 1H), 1.00 (d, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 153.2, 146.0, 131.7, 121.1, 118.7, 68.5, 31.8, 31.3, 30.7, 20.1, 18.2, 16.1; IR (NaCl/CDCl\(_3\)): 2934, 2875, 1755, 1454, 1366, 1245, 1229, 1132, 1035 cm\(^{-1}\); HRMS-EI\(^+\) (m/z): [M]\(^+\) calc’d for \(C_{12}H_{18}O_3\), 210.1256; found, 210.1248.

**Diastereomeric Allyl Ketones 245A and 245B.** A round-bottom flask was flameddried under argon, then cycled into a glovebox. The flask was charged with Pd\(_2\)(dba)\(_3\) (54.5 mg, 0.119 mmol, 2.5 mol\% Pd), (\(R\))-t-Bu-PHOX (57.6 mg, 0.149 mmol, 6.25 mol\%), followed by THF (70 mL). After stirring for 15 min, a solution of enol carbonate 244 (500 mg, 2.38 mmol) and THF (9.0 mL) was added. The reaction went from orange to green. After 6 h at 23 °C, the reaction was cycled out of the glovebox and concentrated in vacuo (10 °C bath temperature). The resulting oil was purified by flash chromatography on silica gel (3:97 Et\(_2\)O:hexane eluent), affording 245A and 245B as a mixture of diastereomers in 7:3 dr (major diastereomer not identified) and 53% ee (as determined by derivatization to enone (+)-143 and ee assay) (384 mg total, 97% yield) as a colorless, fragrant, volatile oil. \(R_f\) 0.45 (1:9 EtOAc/hexane), (I\(_2\)/Sand, brown spot); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.80 (app. ddt, \(J_{d1} = 16.5\) Hz, \(J_{d2} = 10.7\) Hz, \(J_t = 7.2\) Hz, 0.6H), 5.60 (app. ddt, \(J_{d1} = 21.2\) Hz, \(J_{d2} = 9.6\) Hz, \(J_t = 7.4\) Hz, 1.4H), 5.08-4.86 (m, 4H), 2.62 (app. qq, \(J = 12.6\) Hz, 6.3 Hz, 1.4H), 2.53 (app. dd, \(J = 14.3\) Hz, 7.4 Hz, 0.6H), 2.26-
1.70 (m, 8H), 1.86-1.36 (m, 8H), 1.15 (s, 1.8H), 1.01 (s, 4.2H), 0.994 (d, J = 7.4 Hz, 1.8H), 0.986 (d, J = 6.3 Hz, 4.2H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 216.6, 216.3, 135.3, 133.2, 118.0, 117.5, 48.9, 47.9, 43.1, 41.9, 41.5, 41.2, 40.1, 38.8, 36.7, 36.5, 23.2, 22.6, 21.4, 21.2, 15.1, 15.0; IR (NaCl/CDCl$_3$): 3077, 2970, 2931, 2870, 2854, 1706, 1640, 1455, 1377, 1126, 999, 914 cm$^{-1}$; HRMS-El$^+$ (m/z): [M]$^+$ calc'd for C$_{11}$H$_{18}$O, 166.1358; found, 166.1357.

**Allyl Ketone (+)-75.** A round-bottom flask was charged with THF (20 mL) and i-PrNH$_2$ (556 µL, 3.97 mmol, 2.20 equiv), then cooled to 0 °C. n-BuLi (2.5 M in hexanes, 1.44 mL, 3.61 mmol, 2.05 equiv) was added dropwise, and the reaction stirred for 30 min. Then, a solution of diastereomeric allyl cyclohexanones 245A and 245B (291 mg, 1.76 mmol, 1.00 equiv) in THF (4.0 mL) was added, and the reaction was warmed to 23 °C. After 2 h, Iodomethane (561 µL, 9.00 mmol, 5.00 equiv) was introduced. After the reaction was complete, sat. aq NH$_4$Cl (5 mL) was added. 10 min later, the reaction was diluted with hexanes (10 mL) and H$_2$O (10 mL). The organic phase was collected and the aqueous layer extracted with Et$_2$O (3 x 20 mL). All organic layers were combined, dried (Na$_2$SO$_4$), filtered, and concentrated at 10 °C in vacuo. The residue was purified by flash chromatography on silica gel (hexane → Et$_2$O/hexane 4:96 eluent) affording allyl ketone (+)-75 (291 mg, 92% yield) in 53% ee as determined by derivatization to enone (+)-143
and chiral HPLC assay. Characterization data can be found on pages 40 and 41 (chapter 2).

\[
\begin{align*}
\text{Diketone (+)-219.} \quad & \text{A Parr flask was charged with PdCl}_2 (74.5 \text{ mg, } 0.420 \text{ mmol, } 5 \text{ mol%}), \\
& \text{Cu(OAc)}_2 \cdot \text{H}_2\text{O} (381 \text{ mg, } 2.10 \text{ mmol, } 25 \text{ mol%}), \text{N,N-dimethyl acetamide (17.5 mL)}, \\
& \text{and water (2.5 mL). Then allyl ketone } (-)-75 \text{ (1.51 g, 8.39 mmol, 1.0 equiv) was} \\
& \text{introduced. The system was cooled to } -78^\circ\text{C} \text{ and evacuated with vacuum and back-filled} \\
& \text{from a balloon of O}_2 (3 \times). \text{ The mixture was warmed to } 23^\circ\text{C} \text{ and placed on a Parr} \\
& \text{shaker for 24 h under a balloon of O}_2. \text{ The reaction was then directly loaded onto a silica} \\
& \text{gel column and purified by flash chromatography (15:85 Et}_2\text{O:pentane} \rightarrow \text{25:75} \\
& \text{Et}_2\text{O:pentane eluent), affording diketone (+)-219 (1.27 g, 77\% yield) as a clear oil. R}_f \\
& 0.44 (1:4 \text{ EtOAc:hexane), (KMnO}_4, \text{yellow spot);} \text{ }^1\text{H NMR (300 MHz, CDCl}_3): \delta 3.26 \\
& (\text{AB spin system, } d, J_{AB} = 18.4 \text{ Hz, } 1\text{H}), 2.32 (\text{AB spin system, } d, J_{AB} = 18.4 \text{ Hz, } 1\text{H}), \\
& 2.05 (s, 3\text{H}), 2.00-1.72 (m, 3\text{H}), 1.71-1.53 (m, 2\text{H}), 1.47 (\text{app. ddd, } J = 12.0 \text{ Hz, } 5.4 \text{ Hz,} \\
& 2.8 \text{ Hz, } 1\text{H}), 1.16 (s, 3\text{H}), 1.11 (s, 3\text{H}), 1.10 (s, 3\text{H}); \text{ }^{13}\text{C NMR (75 MHz, CDCl}_3): \delta \\
& 220.7, 206.9, 55.7, 45.0, 44.4, 38.9, 36.9, 30.2, 27.9, 27.8, 27.0, 18.2; \text{ IR (NaCl/CDCl}_3): \\
& 2965, 2943, 2924, 2868, 1715, 1694, 1463, 1394, 1379, 1360, 1147, 1034 \text{ cm}^{-1}; \text{ HRMS-} \\
& \text{EI}^+ (m/z): [M]^+ \text{calc’d for } C_{12}H_{20}O_2, 196.1463; \text{ found, } 196.1456; [\alpha]^{27}\text{D} +71.96^\circ (c 0.200,} \\
& \text{CHCl}_3), 91\% \text{ ee.}
\end{align*}
\]
**Bicyclic Enone (–)-143.** To a solution of diketone (+)–219 (1.21 g, 6.15 mmol, 1.0 equiv) in xylenes (25 mL) was added freshly powdered KOH (155 mg, 2.76 mmol, 0.45 equiv). The reactor was fitted with a Dean-Stark trap and heated to 110 °C for 11 h. The reaction was cooled to 23 °C and directly loaded onto a column of silica gel and purified by flash chromatography (pentane → 5:95 Et₂O/pentane → 50:50 Et₂O/pentane eluent), affording bicyclic enone (–)-143 (1.06 g, 96% yield) as a clear, fragrant oil, which was fully characterized after enantioenrichment (page 152 below); [α]₂₅° D –87.21° (c 0.280, CHCl₃), 91% ee.

**Bicyclic Semicarbazone (–)-246.** To a suspension of bicyclic enone (–)-143 (1.70 g, 9.51 mmol, 83% ee) in MeOH (27.1 mL), water (10.2 mL), and pyridine (4.07 mL) was added semicarbazide hydrochloride (1.91 g, 17.1 mmol). The reaction was refluxed at 105 °C for 2 h. Then, the reaction was cooled to –20 °C for 36 h. The crystals that formed were filtered and washed with water, then suspended in absolute EtOH (115 mL). The suspension was heated to 95 °C, at which point it became a solution. Water was added dropwise until cloudiness persisted for 30 seconds even with stirring (76.6 mL). EtOH (200 µL) was added to remove the clouding. Then the heat was turned off, and the
reaction was allowed to cool in the oil bath to 23 °C. After 10 h, the crystals were filtered and suspended in EtOH (100 mL). The suspension was heated to 100 °C, and water (72 mL) was added dropwise as before, followed by EtOH (200 μL). The white, flaky crystals were grown in the same way and collected by filtration, washed with water, and dried over P₂O₅ in vacuo, giving enantioenriched bicyclic semicarbazone (−)-246 (1.43 g, 64%) as a single imine geometric isomer in 97% ee as determined by chiral HPLC analysis. Rf 0.46 (10:90 MeOH/CH₂Cl₂), (UV, 254 nm); mp 227-229 °C (water); ¹H NMR (300 MHz, CDCl₃): δ 7.55 (s, broad, 1H), 5.86 (s, 1H), 5.80 (s, broad, 1H), 5.12 (s, broad, 1H), 2.42 (AB spin system, d, J₁₂ = 16.8 Hz, 1H), 2.29 (AB spin system, d, J₁₂ = 16.8 Hz, 1H), 1.89 (app. d, J = 12.9 Hz, 1H), 1.78 (app. tt, J = 13.8 Hz, 3.0 Hz, 1H), 1.61-1.48 (m, 2H), 1.37-1.30 (m, 1H), 1.28 (s, 1H), 1.29-1.23 (m, 1H), 1.17 (s, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 46.6 (broad), 44.8 (broad), 41.7, 41.0, 36.0 (broad), 31.4, 29.9, 27.7, 26.7, 19.5; IR (KBr): 3469, 3235 (broad), 3191 (broad), 3137 (broad), 2998, 2984, 2958, 2938, 2911, 2863, 1692, 1661, 1572, 1477, 1460, 1420, 1093 cm⁻¹; HRMS-FAB⁺ (m/z): [M+H]⁺ calc’d for C₁₃H₂₂N₂O, 236.1761; found, 236.1763; [α]²⁵D −103.70° (c 0.100, CHCl₃), 97% ee. ¹H-¹H nOesy-1D spectra were obtained for (−)-246 (300 MHz, CDCl₃); the results are shown below:
Enantioenriched Bicyclic Enone (−)-143. To a suspension of enantioenriched bicyclic semicarbazone (−)-246 (1.30 g, 5.53 mmol, 97% ee) in THF (120 mL) was added aqueous 6 M aq HCl (30 mL) in a dropwise fashion. After stirring vigorously for 12 h at 23 °C, the biphasic mixture was cooled to 0 °C, and sat. aq NaHCO₃ (72 mL) was added cautiously. After stirring for 10 min, the reaction was diluted with water (75 mL) and hexane (75 mL), and the organic phase was collected. The aqueous phase was extracted with Et₂O (3 x 75 mL). All organic layers were combined, washed with brine (75 mL), dried (Na₂SO₄), filtered, and concentrated, giving enantioenriched bicyclic enone (−)-143 (944 mg, 96% yield, 97% ee) as a clear, fragrant oil. Rᵣ 0.37 (1:4 EtOAc/hexane), (UV, 254 nm); mp 9-11 °C (Et₂O); ¹H NMR (300 MHz, CDCl₃): δ 5.82 (s, 1H), 2.29 (app. s, 2.29, 2H), 1.93 (app. dq, J_d = 10.5 Hz, J_q = 2.8 Hz, 1H), 1.83 (app. tt, J = 13.5 Hz, 3.3 Hz, 1H), 1.71-1.54 (m, 2H), 1.40 (app. ddd, J = 12.4 Hz, 8.0 Hz, 3.9 Hz, 1H), 1.36 (app. ddd, J = 8.0 Hz, 3.3 Hz, 2.0 Hz, 1H), 1.35 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 208.1, 194.4, 126.4, 54.7, 44.3, 41.5, 40.6, 36.5, 31.3, 27.4, 26.2, 19.1; IR (NaCl/CDCl₃): 2997, 2987, 2960, 2929, 2868, 2847, 1712, 1696, 1600, 1459, 1261, 1166 cm⁻¹; HRMS-EI⁺ (m/z): [M]⁺ calc’d for C₁₂H₁₈O, 178.1358; found, 178.1356; [α]²⁴_D −102.40° (c 0.200, CHCl₃), 97% ee.
**Dienyl Triflate (±)-229.** A round-bottom flask was charged with THF (16 mL) and freshly distilled i-Pr$_2$NH (256 µL, 1.82 mmol, 1.30 equiv) and cooled to 0 °C. n-BuLi (2.5 M in hexanes, 673 µL, 1.68 mmol, 1.20 equiv) was added dropwise. After 30 min, a solution of bicyclic enone (±)-143 (250 mg, 1.40 mmol, 1.00 equiv) in THF (2 mL) was added dropwise. Then, the reaction was warmed to 23 °C and stirred for 1.5 h. Finally, a solution of N-phenyl triflimide (651 mg, 1.82 mmol, 1.3 equiv) in THF (2 mL) was added. At 16 h, the reaction was diluted with Et$_3$N (5 mL), and the reaction was concentrated to ~5 mL total volume. Hexane (10 mL) was added, and the reaction was directly loaded onto a column of silica gel and purified by rapid flash column chromatography (5:5:90 Et$_3$N:Et$_2$O:hexane eluent), affording dienyl triflate (±)-229 (427 mg, yield not determined) as an oil. The compound was immediately used in the next reaction. R$_f$ (not determined); $^1$H NMR (300 MHz, C$_6$D$_6$): δ 5.68 (app. d, $J$ = 1.7 Hz, 1H), 5.65 (app. d, $J$ = 1.7 Hz, 1H), 1.61 (app. ddd, $J$ = 12.7 Hz, 4.7 Hz, 3.0 Hz, 1H), 1.48 (app. qt, $J_q$ = 13.6 Hz, $J_t$ = 3.3 Hz, 1H), 1.36-1.28 (m, 1H), 1.31-1.19 (m, 1H), 0.96 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.78 (app. dt, $J_d$ = 12.9 Hz, $J_t$ = 4.4 Hz, 1H), 0.72 (app. dt, $J_d$ = 12.9, $J_t$ = 4.0 Hz, 1H); $^{13}$C NMR (75 MHz, C$_6$D$_6$): δ 165.8, 147.7, 130.3, 116.9, 51.9, 42.9, 37.3, 36.0, 30.9, 24.6, 20.0, 19.6; $^{19}$F NMR (282 MHz, C$_6$D$_6$): δ −74.11, −71.69; IR: (not obtained); HRMS: (not performed).
Propargylic Alcohol (±)-231. A round-bottom flask was charged with CuI (27 mg, 0.14 mmol, 10 mol%), followed by a solution of Pd(PPh₃)₄ (80 mg, weighed in glovebox, 70 µmol, 5 mol%) in THF (10 mL) (reaction was yellow). Then, freshly distilled i-Pr₂NH (981 µL, 7.00 mmol, 5.0 equiv) was added (reaction became black), followed immediately by a solution of dienyl triflate (±)-229 (434 mg, 1.40 mmol, 1.0 equiv) in THF (10 mL) (reaction turned maroon). Finally, a solution 2-methyl-3-butyn-2-ol (230) (149 µL, 1.54 mmol, 1.1 equiv) in THF (5.0 mL) was introduced slowly (reaction became orange). The reaction was heated to 75 °C for 20 h. Then, the reaction was cooled to 23 °C and filtered through celite with the aide of hexane and Et₂O. The filtrate was concentrated, then purified by flash column chromatography on silica gel (10:90 Et₂O:hexane eluent). The product-containing fractions, which contained semipure (±)-231, were combined and concentrated. The residue was purified on a second silica gel flash column (10:90 Et₂O:hexane → 20:80 Et₂O:hexane → 50:50 Et₂O:hexane eluent), giving bicyclic enone (±)-143 (22.7 mg, 9% yield) and propargylic alcohol (±)-231 (211 mg, 62% yield over 2 steps from (±)-243) R_f (not determined); ¹H NMR (300 MHz, CDCl₃): δ 6.36 (app. s, 1H), 5.79 (app. s, 1H), 2.42-2.22 (m, 1H), 1.88 (app. d, J =13.9 Hz, 1H), 1.76 (app. t, J = 13.2 Hz, 1H), 1.60-1.48 (m, 1H), 1.54 (s, 6H), 1.18 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 0.96 (app. t, J = 11.8 Hz, 1H), 0.93 (app. t, J = 12.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 163.2, 150.8, 122.2, 121.6, 94.8, 78.9, 65.7, 54.2, 42.8, 36.8, 35.5, 31.6, 30.9, 24.7, 20.0, 19.6; IR (NaCl/CDCl₃): 3369 (broad), 3071, 2919,
2245, 1694, 1602, 1455, 1369, 1300, 1234, 1164 cm\(^{-1}\); HRMS-FAB\(^+\) (m/z): [M]\(^+\) calc’d for C\(_{17}\)H\(_{24}\)O, 244.1827; found, 244.1827.

**Keto-Enone (−)-233.** To a solution of LiHMDS (0.943M in THF, 3.27 mL, 3.09 mmol) in THF (29 mL) at 23 °C was added a solution of enantioenriched bicyclic enone (−)-143 (981 mg, 5.51 mmol) in THF (12 mL) in a dropwise fashion over 3 min. After 1 h, the reaction was cooled to −78 °C, and methyl vinyl ketone (35) (257 µL, 3.09 mmol) was added quickly. After 5 min, the reaction was quenched with a 1:1 mixture of sat. aq NH\(_4\)Cl (5 mL) and water (5mL) at −78 °C. Then, the reaction was warmed to room temperature and diluted with hexanes (20 mL) and H\(_2\)O (20 mL). After collecting the organic phase, the aqueous phase was extracted with Et\(_2\)O (3 x 15 mL). All organic layers were combined, washed with brine (20 mL), dried (Na\(_2\)SO\(_4\)), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (1:9 Et\(_2\)O/pentane → 2:8 Et\(_2\)O/pentane → 4:6 Et\(_2\)O/pentane eluent), affording starting material (−)-143 (49.3 mg, 10% yield) as a colorless oil and keto-enone (−)-233 (500 mg, 72% yield) as a colorless oil, which formed pale yellow crystals from the melt under reduced pressure. The solid was of 98% ee as determined by chiral HPLC analysis. Two separate crystals of racemic (±)-233 were analyzed by X-ray diffraction; each proved to be the same diastereomer (relative stereochemistry is depicted in the product above). R\(_f\) 0.20 (1:4 EtOAc/hexane), (UV, 254 nm); mp 67-69 °C (Et\(_2\)O/pentane) (98% ee), mp 62-64 °C (Et\(_2\)O/pentane) (83%
ee) mp 42-44 °C (Et₂O/pentane) (0% ee); ¹H NMR (300 MHz, CDCl₃), (major
diastereomer): δ 5.76 (s, 1H), 2.89 (qd, Jₚ = 9.1 Hz, Jₚ = 5.2 Hz, 1H), 2.70 (ddd, J = 18.2
Hz, 8.8 Hz, 6.6 Hz, 1H), 1.99 (dd, J = 10.7 Hz, 5.0 Hz, 1H), 2.16 (s, 3H), 1.94-1.78 (m,
2H), 1.72-1.49 (m, 4H), 1.45 (dd, J = 13.2 Hz, 3.9 Hz, 1H), 1.35 (s, 3H), 1.33 (app. dd, J
= 14.1 Hz, 4.4 Hz, 1H), 1.25 (s, 3H), 1.19 (s, 3H); ¹³C NMR (75 MHz, CDCl₃), (major
diastereomer): δ 211.0, 208.9, 193.1, 124.8, 58.1, 47.2, 41.7, 41.4, 36.7, 35.2, 31.2, 30.2,
28.3, 26.4, 21.3, 18.8; IR (KBr): 3009, 2958, 2943, 2897, 1710, 1691, 1598, 1460,
1420, 1381, 1372, 1357, 1269, 1161 cm⁻¹; HRMS-EI⁺ (m/z): [M]⁺ calc’d for C₁₆H₂₄O₂,
248.1776; found, 248.1774; [α]²⁺ D -15.79° (c 0.220, CHCl₃), 98% ee.

Tricyclic Dienone (–)-234. To a solution of keto-enone (–)-233 (457 mg, 1.60 mmol,
1.00 equiv) in xylenes (18 mL) was added freshly powdered KOH (207 mg, 3.69 mmol,
2.00 equiv). The reactor was fitted with a Dean-Stark trap and heated to 110 °C for 14 h
in the dark. The reaction was cooled to 23 °C and directly loaded onto a column of silica
gel and purified by flash chromatography (pentane → 2:8 Et₂O:pentane → 6:4
Et₂O:pentane eluent), affording tricyclic dienone (–)-234 (336 mg, 80% yield) as a
yellow oil. The product was a mixture of two diastereomers as determined by ¹H NMR.
Rf 0.28 (1:4 EtOAc/hexane), (UV, 254 nm), (first diastereomer) Rf 0.19 (1:4
EtOAc/hexane), (UV 254 nm), (second diastereomer); ¹H NMR (300 MHz, CDCl₃),
(major diastereomer): δ 6.05 (s, 1H), 5.76 (d, J = 2.5 Hz, 1H), 2.52 (app. ddd, J = 14.3
Hz, 5.5 Hz, 2.5 Hz, 1H), 2.50 (app. ddd, J = 14.9 Hz, 3.6 Hz, 2.8 Hz, 1H), 2.29 (ddd, J = 17.0 Hz, 13.5 Hz, 5.2 Hz, 1H), 1.98-1.72 (m, 4H), 1.56 (app. d, J = 12.4 Hz, 2H), 1.39-1.24 (m, 2H), 1.16 (s, 6H), (1.05 (s, 3H); ^13^C NMR (75 MHz, CDCl₃), (major diastereomer): δ 200.1, 179.3, 171.7, 122.9, 117.2, 55.3, 49.1, 41.2, 40.1, 37.9, 35.7, 31.3, 27.7, 23.9, 22.4, 19.1; IR (NaCl/CDCl₃): 2930, 2868, 2847, 1659, 1652, 1619, 1616, 1585, 1457, 1418, 1385, 1372, 1320, 1273, 1244, 1194, 1181, 970, 887 cm⁻¹; HRMS-EI⁺ (m/z): [M]^+ calc’d for C₁₆H₂₂O, 230.1671; found, 230.1668; [α]⁺²⁵ D –224.40° (c 0.550, CHCl₃), 98% ee.

**Silyl Enol Ether (±)-235.** A round-bottom flask was charged with THF (12.5 mL) and i-Pr₂NH (395 µL, 2.82 mmol, 1.3 equiv), then cooled to 0 °C. n-BuLi (2.5 M in hexanes, 1.05 mL, 2.61 mmol, 1.2 equiv) was added dropwise. After 30 min, the reaction was cooled to −78 °C, and a solution of tricyclic dienone (±)-234 (500 mg, 2.17 mmol, 1.0 equiv) in THF (2.86 mL) was added slowly. After 30 min, TBSOTf (698 µL, 3.04 mmol, 1.4 equiv) was introduced. The reaction was kept at −78 °C for 30 min, then warmed to 23 °C. Once the reaction was gauged complete, it was concentrated in vacuo to ~4 mL total volume, then diluted with hexanes (15 mL) and Et₃N (1.0 mL). The solution was directly loaded onto a column of silica gel and rapidly purified by flash column chromatography (5:5:9 Et₃N:Et₂O:hexane eluent), affording silyl enol ether (±)-235 (690 mg, 92% yield) as a bright yellow oil. R_f not determined (compound is unstable on silica gel); ^1^H NMR (300 MHz, C₆D₆)(major diastereomer only): δ 5.90 (s, 1H), 5.76 (s, 1H),
5.01-4.97 (m, 1H), 2.39 (app. dd, J = 14.0 Hz, 6.8 Hz, 1H), 2.26 (app. s, 1H), 2.01-1.93 (m, 1H), 1.74-1.08 (m, 6H), 1.08 (s, 3H), 1.07 (s, 3H), 1.02 (s, 9H), 0.98 (s, 3H), 0.20 (s, 6H); ¹³C NMR (75 MHz, C₆D₆): δ 169.1, 151.7, 150.4, 123.0, 113.9, 100.0, 51.7, 48.6, 41.4, 40.9, 35.5, 32.1, 28.2, 26.4, 23.7, 21.4, 20.0, 18.8, 3.8; IR (NaCl/neat film): 3049, 2928, 2858, 1651, 1587, 1472, 1362, 1252, 1224, 1151, 1006, 926, 839, 780 cm⁻¹; HRMS-El⁺ (m/z): [M]⁺ calc’d for C₂₂H₃₆O₅Si, 344.2536; found, 344.2532.

**Acyloins (±)-236A and (±)-236B.** A round-bottom flask containing silyl enol ether (±)-235 (600 mg, 1.74 mmol, 1.00 equiv) was charged with THF (25 mL). Then, the Davis oxaziridine (1.15 g, 2.18 mmol, 1.25 equiv) was introduced at 23 °C. Once the starting material was consumed, the reaction was concentrated in vacuo. The resulting residue was triturated with Et₂O and filtered to remove solids. The filtrate was concentrated and dissolved in THF (25 mL) and 6 M aq HCl (16 mL) was added, causing a color change from colorless to bright yellow. After 5 min, the reaction was diluted with H₂O and hexanes, and the organic phase was collected. The aqueous layer was extracted with Et₂O (3 x). 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 → 50:50 EtOAc:hexane → EtOAc eluent), giving two acyloin products, (±)-236A and (±)-236B, whose relative configurations were not assigned. The high Rf product, (±)-236A (70 mg, 17% yield), was obtained in semipure form and had
the following characteristics: R\text{f} (not measured) (UV, 254 nm); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) 6.07 (s, 1H), 5.82 (app. dd, \(J = 20.4\) Hz, 2.5 Hz, 1H), 4.12 (app. dddd, \(J = 12.7\) Hz, 5.0 Hz, 2.5 Hz, 1.9 Hz, 1H), 3.95 (s, broad, 1H), 2.70 (app. dddd, \(J = 12.7\) Hz, 6.9 Hz, 4.4 Hz, 2.8 Hz, 1H), 2.60-2.48 (m, 2H), 2.41-2.29 (m, 1H), 2.32 (app. td, \(J_1 = 16.8\) Hz, \(J_d = 5.2\) Hz, 1H), 1.93-1.51 (m, 4H), 1.17 (app. s, 6H), 1.07 (s, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) (not obtained due to modest purity of compound); IR (NaCl/CDCl\textsubscript{3}): 3460 (broad), 2931, 2868, 2847, 1655, 1613, 1582, 1459, 1320, 1212, 1182, 1107, 887 cm\textsuperscript{-1}; HRMS-EI\textsuperscript{+} (m/z): [M]+ calc’d for C\textsubscript{16}H\textsubscript{22}O, 246.1620; found, 246.1616.

The low R\text{f} product, (±)-236B (176 mg, 44% yield) was also obtained in semipure form and had the following characteristics: R\text{f} (not measured) (UV, 254 nm); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) 6.08 (s, 1H), 5.75 (app. d, \(J = 2.5\) Hz, 1H), 4.06 (app. t, \(J = 3.0\) Hz, 1H), 3.80 (s, broad, 1H), 2.97 (app. dddd, \(J = 11.3\) Hz, 4.4 Hz, 2.5 Hz, 1H), 2.10 (app. dddd, \(J = 13.5\) Hz, 4.7 Hz, 3.0 Hz, 1H), 1.90 (app. dddd, \(J = 25.0\) Hz, 13.5 Hz, 10.2 Hz, 1H), 1.90-1.70 (m, 2H), 1.60-1.50 (m, 2H), 1.40-1.17 (m, 2H), 1.16 (s, 3H), 1.15 (s, 3H), 1.05 (s, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\) 198.6, 181.2, 173.5, 123.1, 114.6, 70.5, 49.5, 49.1, 41.2, 39.7, 35.9, 31.2, 30.5, 27.8, 22.9, 19.0; IR (NaCl/CDCl\textsubscript{3}): 3386 (broad), 2960, 2927, 2868, 2848, 1643, 1612, 1582, 1459, 1327, 1164, 1058, 888 cm\textsuperscript{-1}; HRMS-EI\textsuperscript{+} (m/z): [M]+ calc’d for C\textsubscript{16}H\textsubscript{22}O, 246.1620; found, 246.1630.

\textbf{Arene (±)-237.} A vial was charged with a solution of acyloin (±)-236A (25 mg, 0.102 mmol, 1.00 equiv) and THF (2.0 mL). After cooling to –78 °C, \(i\)-PrMgCl (1.84 M in
THF, 166 µL, 3.00 equiv) was added slowly. After 10 min, the reaction was allowed to warm to 0 °C. 10 min later, the reaction was quenched with sat. aq NH₄Cl (400 µL). Then H₂O (2 mL) was added, and the material extracted with Et₂O (3 x 4 mL). All organic layers were combined, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by preparative TLC on silica gel (EtOAc/hexane 30:70 eluent), affording trace arene (±)-237 (yield not determined) as a colorless oil. Characterization data for this compound can be found on page 164 below.

**Isodichroanone (±)-240.** A solution of acyloin (±)-236B (475 mg, 1.93 mmol, 1.0 equiv) in CH₂Cl₂ (100 mL) was treated with Dess-Martin Periodinane (1.634 g, 3.86 mmol, 2.0 equiv) at 23 °C for 2 h. The reaction was then filtered through silica gel presaturated with Et₃N/CH₂Cl₂. The filtrate was adsorbed to ~3 mL of silica gel and immediately purified by flash chromatography on silica gel (20:80 EtOAc:hexane eluent), giving an orange oily product (231 mg) which was immediately used in the next reaction.

60 mg of this orange oil was concentrated several times from THF, dissolved in THF (20 mL), and cooled to −78 °C. i-PrMgCl (1.84 M in THF, 135 µL, 0.248 mmol) was then added, causing the reaction to turn from bright red to bright green. After 40 min had passed, the reaction was treated with 6 M aq HCl (3.0 mL) −78 °C, and the reaction quickly turned orange-red. The reaction was warmed to 23 °C and stirred for 3 h. Then H₂O (15 mL) was added, and organic phase was collected. The aqueous layer was
extracted with Et₂O (3 x 10 mL). All organic layers were combined, dried (Na₂SO₄),
filtered, and adsorbed to 750 μL of silica gel. The material was purified by flash column
chromatography on silica gel (10:90 EtOAc:hexane → 20:80 EtOAc:hexane eluent), and
the orange product (mass not determined) was immediately used in the next reaction.

The orange product of the grignard reaction was dissolved in THF (20 mL).
Fremy’s Salt (potassium nitroso disulfonate, radical)(424 mg, 1.61 mmol) was
introduced, and the reaction was heated to 60 °C for 5.5 h. The reaction was cooled to 23
°C and filtered through a short plug of silica gel. The filtrate was concentrated and
quickly partitioned between EtOAc (20 mL) and H₂O (20 mL). The organic layer was
collected, 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),
giving a bright red series of fractions. These fractions were combined and
concentrated. The residue was subjected to preparative HPLC (normal phase silica gel
column, 10-20 mesh)(10:90 EtOAc:hexane → 30:70 EtOAc:hexane gradient elution),
giving isodichroanone (±)-240 (~3 mg) as a red semisolid. Rf (not determined); ¹H NMR
(300 MHz, CDCl₃): δ 7.07 (s, 1H), 6.55 (s, 1H), 3.34 (septuplet, J = 6.9 Hz, 1H), 2.11
(app. d, J = 13.2 Hz, 1H), 1.96 (app. qt, J₂ = 13.6 Hz, J₁ = 3.6 Hz, 1H), 1.75-1.48 (m, 4H),
1.46 (s, 3H), 1.35 (d, J = 6.9 Hz, 6H), 1.31 (s, 3H), 1.29 (s, 3H); ¹³C NMR (125 MHz,
CDCl₃): δ 178.9, 171.4, 155.3, 151.1, 150.3, 131.2, 124.9, 121.1, 120.4, 50.1, 42.3, 38.7,
36.9, 31.1, 30.5, 29.9, 29.5, 27.4, 25.7, 25.4, 21.21, 21.17, 19.5 (4 extra carbons are
noted; compound is only semipure); IR (NaCl/CDCl₃): 3267 (broad), 2961, 2930, 2871,
1738, 1641, 1574, 1403, 1100 cm⁻¹; LRMS-El⁺ (m/z): [M]+ calc’d for C₁₉H₂₄O₃, 300;
found, 300. ¹H-¹H homodecoupling experiments (600 MHz, CDCl₃) were performed on
(±)-240: The signal at δ 3.34 (septuplet, J = 6.9 Hz, 1H) was suppressed with a decoupling current, resulting in a splitting change at δ 1.35 (d, J = 6.9 Hz, 6H → app. s, 6H). This information allowed for key nOe’s to be correctly assigned. $^1$H-$^1$H nOesy-1D spectra were obtained for (±)-240 (600 MHz, CDCl$_3$); the results are shown below:

![Diagram of chemical structure]

Tricyclic Enol Triflate (−)-250. A solution of i-Pr$_2$NH (186 µL, 1.33 mmol) in THF (17 mL) was cooled to 0 °C, and n-BuLi (2.55 M in hexanes, 482 µL, 1.23 mmol) was added dropwise. After 30 min, the reaction was cooled to −78 °C, and a solution of tricyclic dienone (−)-234 (236 mg, 1.03 mmol) in THF (3 mL) was added dropwise over 5 min. After 30 min, a solution of N-phenyl triflimide (513 mg, 1.44 mmol) in THF (6 mL) was added. 30 min later, the reaction was wrapped in foil and warmed to 23 °C. After 5 h, the reaction was diluted with Et$_3$N (5 mL) and concentrated to ~ 5 mL total volume. Then hexane (10 mL) and more Et$_3$N (2 mL) were added, and the reaction was concentrated to ~ 5 mL a second time. The reaction was filtered through a 5-inch plug of silica that had
been pre-eluted with Et₃N/Et₂O/hexane (5:20:75) and eluted with the same solvent mixture. The eluate was concentrated, giving crude, unstable tricyclic enol triflate (–)-250 (yield not determined) as an orange gel, which was immediately used in the next reaction.

¹H NMR revealed the product to be an inseparable mixture of diastereomers. R₂ 0.80 (2:8:1 EtOAc/hexane/Et₃N, TLC plate is pre-eluted), (Ceric Ammonium Molybdate, blue spot) (both diastereomers); ¹H NMR (300 MHz, C₆D₆): δ 5.66 (s, 1H), 5.58 (app. dd, J = 2.5 Hz, 2.2 Hz, 1H), 5.31 (app. dtd, J₁d = 6.6 Hz, J₂ = 2.2 Hz, J₁d₂ = 1.1 Hz, 1H), 1.95 (ddd, J = 29.2 Hz, 20.0 Hz, 2.5 Hz, 1H), 1.93 (ddd, J = 50.6 Hz, 19.8 Hz, 2.8 Hz, 1H), 1.64 (app. dt, J₁d = 14.8 Hz, J₁ = 6.9 Hz, 1H), 1.61-1.43 (m, 2H), 1.33-1.17 (m, 2H), 1.11 (app. dd, J = 12.7 Hz, 3.0 Hz, 1H), 0.97 (s, 6H), 0.96-0.80 (m, 1H), 0.77 (s, 3H); ¹³C NMR (75 MHz, C₆D₆): δ 172.7, 153.0, 149.1, 132.3, 131.4, 130.3, 122.5, 111.2, 107.7, 50.1, 48.7, 41.0, 40.2, 35.6, 31.8, 27.7, 23.1, 20.9, 19.6; ¹⁹F NMR (282 MHz, C₆D₆): δ -71.6, -74.4 (major diastereomer), -74.5 (minor diastereomer); IR (NaCl/hexane): 2961, 2931, 2868, 2848, 1649, 1579, 1445, 1420, 1246, 1209, 1144, 1096, 1059, 907, 880, 862 cm⁻¹; HRMS-EI⁺ (m/z): [M⁺] calc’d for C₁₇H₂₁F₃O₃S, 362.1164; found, 362.1166; [α]D⁻²⁵

Arene (–)-237. To a solution of crude tricyclic enol triflate (–)-250 (~371 mg, 1.03 mmol) in THF (50 mL) was added isopropenyl magnesium bromide (0.5 M in THF, 4.12 mL, 2.06 mmol), and the round-bottom flask was immediately covered in foil. Then a
solution of Pd(PPh₃)₄ (29.5 mg, 0.0515 mmol, weighed in glovebox) in THF (5 mL) was promptly added at 23 °C. After 1 h, 6 M aq HCl (5.5 mL) was added in a dropwise manner. After 16 h at 23 °C, the reaction was diluted with water (40 mL) and hexane (40 mL), and the organic phase was collected. The aqueous phase was extracted with Et₂O (3 x 30 mL). All organic layers were combined, washed with brine (30 mL), dried (Na₂SO₄), filtered, and adsorbed onto silica gel. The adsorbed product was purified by flash chromatography on silica gel (hexane eluent), affording arene (–)-237 (170 mg, 65% yield from tricyclic dienone (–)-234) as a colorless oil. Rf 0.43 (hexane), (UV 254 nm); 

1H NMR (300 MHz, CDCl₃): δ 7.21 (d, J = 1.4 Hz, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.04 (dd, J = 7.7 Hz, 1.4 Hz, 1H), 6.40 (s, 1H), 2.96 (septuplet, J = 6.9 Hz, 1H), 2.18 (ddd, J = 12.7 Hz, 4.7 Hz, 3.0 Hz, 1H), 2.00 (app. qt, J₉ = 13.8 Hz, J₈ = 4.3 Hz, 1H), 1.74-1.60 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.32 (d, J = 6.9 Hz, 6H), 1.29 (s, 3H), 1.15 (td, J₇ = 12.9 Hz, J₆ = 3.7 Hz, 1H), 1.05 (td, J₅ = 13.2 Hz, J₄ = 3.7 Hz, 1H); 

13C NMR (75 MHz, CDCl₃): δ 164.4, 152.9, 147.2, 142.4, 122.4, 121.0, 120.8, 118.6, 50.8, 42.8, 38.3, 35.7, 34.3, 31.5, 25.5, 24.54, 24.51, 23.7, 20.0; IR (NaCl/CDCl₃): 3061, 2995, 2959, 2928, 2866, 2845, 1616, 1479, 1458, 1382, 1369, 1362, 886, 820 cm⁻¹; HRMS-El⁺ (m/z): [M]+ calc’d for C₁₉H₂₆, 254.2035; found, 254.2046; [α]D²⁴ –80.74° (c 0.320, CHCl₃), 98% ee.

Aldehydes (–)-252 and (+)-253. A solution of arene (–)-237 (156 mg, 0.614 mmol) in CH₂Cl₂ (15 mL) was cooled to –78 °C and α,α-dichloromethyl, methyl ether (89.0 µL,
0.982 mmol) was introduced, followed by TiCl₄ (81.0 µL, 0.736 mmol). After 1 h, the deep red mixture was warmed to 23 °C, and 1 h later the reaction was poured onto a slurry of crushed ice (40 mL) and CH₂Cl₂ (10 mL). After stirring vigorously for 1 h, the organic phase was collected. The aqueous phase was extracted with CH₂Cl₂ (3 x 20 mL). All organic layers were combined, washed with water (20 mL), sat. aq NaHCO₃ (30 mL), and brine (30 mL), then dried (Na₂SO₄), filtered, and adsorbed onto silica gel. The adsorbed products were separated by flash chromatography on silica gel (1:99 Et₂O/hexane → 2:98 Et₂O/hexane → 5:95 Et₂O/hexane eluent), affording desired aldehyde (–)-252 (137 mg, 79% yield) as a colorless oil. Rf 0.40 (1:9 EtOAc/hexane), (UV, 254 nm); ¹H NMR (300 MHz, CDCl₃): δ 10.39 (s, 1H), 7.73 (s, 1H), 7.33 (s, 1H), 6.42 (s, 1H), 3.96 (app. septuplet, J = 6.9 Hz, 1H), 2.20 (app. d, J = 12.9 Hz, 1H), 1.96 (app. qt, Jₕ = 13.2 Hz, Jₜ = 3.3 Hz, 1H), 1.56-1.72 (m, 2H), 1.39 (s, 3H), 1.33 (d, J = 6.9 Hz, 3H), 1.32 (d, J = 6.9 Hz, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.10 (td, Jₜ = 13.2 Hz, J₆ = 3.9 Hz, 1H), 0.99 (td, Jₜ = 13.5 Hz, J₆ = 3.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 191.9, 170.2, 152.6, 151.4, 148.5, 129.2, 122.6, 121.1, 117.9, 51.3, 42.6, 37.9, 36.1, 31.3, 27.7, 25.1, 24.4, 24.3, 23.2, 19.7; IR (NaCl/CDCl₃): 3066, 2995, 2962, 2930, 2867, 2847, 2801, 2753, 2717, 2252, 1690, 1674, 1613, 1552, 1472, 1459, 1420, 1383, 1370, 1267, 1180, 1163, 906, 891 cm⁻¹; HRMS-EI⁺ (m/z): [M]⁺ calc’d for C₂₀H₂₆O, 282.1984; found, 282.1991; [α]²⁴D –109.22° (c 1.205, CHCl₃), 98% ee. ¹H-¹H nOesy-1D spectra were obtained for (–)-252 (300 MHz, CDCl₃); the results are shown below:
Undesired aldehyde (+)-253 (13.3 mg, 8% yield) was also isolated as a colorless oil. Rf 0.48 (1:9 EtOAc/hexane), (UV, 356 nm); $^1$H NMR (300 MHz, CDCl$_3$): δ 10.71 (s, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.19 (s, 1H), 7.17 (d, J = 7.7 Hz, 1H), 3.89 (septuplet, J = 6.9 Hz, 1H), 2.17 (app. dd, J = 12.9 Hz, 1.7 Hz, 1H), 1.97 (app. qt, J = 14.0 Hz, J$_t$ = 3.9 Hz, 1H), 1.74-1.58 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 1.33 (d, J = 6.9 Hz, 3H), 1.32 (d, J = 6.9 Hz, 3H), 1.26 (s, 3H), 1.11 (td, J$_t$ = 12.9 Hz, J$_d$ = 3.9 Hz, 1H), 0.96 (td, J$_t$ = 13.2 Hz, J$_d$ = 3.6 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 192.8, 169.3, 154.3, 149.7, 144.3, 125.9, 125.7, 121.6, 120.1, 50.0, 42.7, 37.9, 36.1, 31.4, 28.2, 25.2, 24.60, 24.55, 23.1, 19.8; IR (NaCl/CDCl$_3$): 2994, 2962, 2930, 2867, 2846, 2777, 2754, 1682, 1591, 1571, 1456, 1417, 1254, 1183, 1176, 1109, 882, 828 cm$^{-1}$; HRMS-EI$^+$ (m/z): [M]$^+$ calc’d for C$_{20}$H$_{26}$O, 282.1984; found, 282.1990; $[\alpha]^{26}_D$ +1.15° (c 0.665, CHCl$_3$), 98% ee. $^1$H-$^1$H nOesy-1D spectra were obtained for (+)-253 (300 MHz, CDCl$_3$); the results are shown below:
Tricyclic Phenol (±)-254. A round-bottom flask was charged with a solution of aldehyde (±)-253 (35 mg, 0.124 mmol) in THF (500 µL). MeOH (3 mL) was added, followed by 30% aq H₂O₂ (500 µL) at 23 °C. Then, conc. aq H₂SO₄ (3 drops from a glass pipet) was added. After 1 h, more 30% aq H₂O₂ (500 µL) was added. After 48 h, the reaction was added to a biphasic mixture of NaHSO₃ (1.2 g), H₂O (20 mL), CH₂Cl₂ (20 mL), and hexanes (10 mL). The organic phase was collected, and the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). All organic layers were combined, washed with brine, dried (Na₂SO₄), filtered, and adsorbed onto 1.0 mL of silica gel. The material was purified by flash chromatography on silica gel (1:99 Et₂O:hexane → 8:92 Et₂O:hexane eluent), giving tricyclic phenol (±)-254 (16.2 mg, 48% yield). R_f (not determined); ¹H NMR (300 MHz, CDCl₃): δ 7.00 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.45 (s, 1H), 4.68 (s,
1H), 3.21 (app. septuplet, $J = 6.9$ Hz, 1H), 2.12 (ddd, $J = 12.7$ Hz, 4.7 Hz, 3.0 Hz, 1H), 1.96 (app. qt, $J_q = 13.6$ Hz, $J_t = 3.9$ Hz, 1H), 1.71-1.56 (m, 2H), 1.37 (s, 3H), 1.32 (s, 3H), 1.29 (d, $J = 6.9$ Hz, 3H), 1.28 (d, $J = 6.9$ Hz, 3H), 1.25 (s, 3H), 1.12 (app. td, $J_t = 12.9$ Hz, $J_d = 3.9$ Hz, 1H), 1.01 (app. td, $J_t = 13.2$ Hz, $J_d = 3.6$ Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 163.4, 154.8, 145.7, 132.2, 128.6, 122.4, 115.4, 114.1, 51.5, 43.0, 38.4, 35.8, 31.5, 27.1, 25.6, 23.8, 23.2, 23.1, 20.0; IR (NaCl/CDCl$_3$): 3400 (broad), 2961, 2928, 2866, 2845, 1478, 1436, 1295, 1202 cm$^{-1}$; HRMS-EI$^+$ (m/z): [M]$^+$ calc’d for C$_{19}$H$_{26}$O, 270.1984; found, 270.1989.

Phenol (–)-242. To a solution of aldehyde (–)-252 (135 mg, 0.478 mmol) in THF (5.4 mL) and MeOH (13.5 mL) at 23 °C was added 30% aq H$_2$O$_2$ (2.70 mL, 23.8 mmol) immediately followed by conc. aq H$_2$SO$_4$ (245 µL). After 1 h, the reaction was cautiously added to an ice-cold mixture of NaHSO$_3$ (1.62 g, 15.6 mmol), water (54 mL), and Et$_2$O (20 mL). After 5 min, the reaction was diluted with water (10 mL) and hexane (20 mL), and the organic phase was collected. The aqueous phase was extracted with Et$_2$O (3 x 40 mL). All organic layers were combined, washed with brine (20 mL), dried (Na$_2$SO$_4$), filtered, and adsorbed on silica gel. The adsorbed product was purified by flash chromatography on silica gel (2:98 Et$_2$O/hexane → 10:90 Et$_2$O/hexane eluent), affording phenol (–)-242 (95.0 mg, 74% yield) as a white, unstable powder. R$_f$ 0.56 (1:4
EtOAc/hexane), (UV, 254 nm); mp 105-106 °C (dec.) (Et₂O/hexane); ¹H NMR (300 MHz, CDCl₃, degassed with argon): δ 7.11 (s, 1H), 6.68 (s, 1H), 6.29 (s, 1H), 4.57 (s, 1H, vanishes with D₂O addition), 3.19 (app. quintet, J = 6.9 Hz, 1H), 2.07 (app. d, J = 12.4, 1H), 1.94 (app. qt, Jₜ = 13.5 Hz, Jₚ = 3.3 Hz, 1H), 1.62 (app. s, 1H), 1.58 (app. s, 1H), 1.34 (s, 3H), 1.28 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H), 1.26 (d, J = 6.9 Hz, 3H), 1.22 (s, 3H), 1.10 (td, Jₜ = 13.2 Hz, Jₚ = 3.6 Hz, 1H), 1.01 (td, Jₜ = 13.2 Hz, Jₚ = 3.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 162.0, 154.3, 150.0, 135.5, 132.4, 120.5, 117.9, 109.4, 50.9, 42.8, 38.2, 35.5, 31.4, 27.2, 25.6, 23.8, 23.1, 20.0; IR (KBr): 3393 (broad), 3057, 2988, 2965, 2934, 2968, 2837, 1459, 1431, 1382, 1362, 1286, 1166, 1076, 1004, 894, 856 cm⁻¹; HRMS-EI⁺ (m/z): [M]+ calc’d for C₁₉H₂₆O, 270.1984; found, 270.1993; [α]²⁴D = -73.23° (c 0.080, CHCl₃), 98% ee.

**Peroxide (±)-255.** A sample of purified phenol (±)-242 (~50 mg) was dissolved in PhH (~5 mL) under an ambient air headspace (solution was colorless), then stored at < 0 °C, such that the solution froze. At 16 days, the frozen sample was found to be peach-colored. The solution was adsorbed to 750 µL of silica gel and rapidly chromatographed (8:92 Et₂O:hexane → 20:80 Et₂O:hexane eluent), giving one set of fractions containing peroxide (±)-255 (yield not determined) as a white powder. An NMR tube was charged with a solution of (±)-255 (~5 mg) and CDCl₃ (700 µL) and immediately analyzed by ¹H NMR. Rₚ (not measured, but lower than phenol (±)-242 in EtOAc:hexane 20:80); ¹H
NMR (300 MHz, CDCl₃): δ 6.62 (s, 1H), 5.90 (s, 1H), 5.06 (s, 1H), 3.19 (app. septuplet, \( J = 6.9 \) Hz, 1H), 1.76 (app. dd, \( J = 14.0 \) Hz, 3.4 Hz, 1H), 1.69 (s, 3H), 1.64-1.49 (m, 2H), 1.34 (s, 3H), 1.37-1.19 (m, 3H), 1.262 (app. d, \( J = 6.9 \) Hz, 3H), 1.261 (app. d, \( J = 6.9 \) Hz, 3H), 1.16 (s, 3H); \(^{13}\)C NMR (not measured; compound decomposed before acquisition completion); IR (not performed); HRMS (not performed). If the solution of (±)-255 was allowed to stand for an additional 4 h, noticeable conversion to keto-aldehyde (±)-256 was observable in the \(^1\)H NMR. For characterization of (±)-256, see page 170 and 171 below.

**Keto Aldehyde (±)-256.** A vial containing pure phenol (±)-242 (~5 mg, evaporated from PhH) was left open to the air for a brief period of time and stored in the dark at 23 °C for 2 yr. The vial was then opened and found to contain pure (±)-256 (~5 mg, yield not determined) as yellow-brown needles. Rf 0.22 (20:80 EtOAc/hexane), (UV, 254 nm); mp 181-185 °C (dec.); \(^1\)H NMR (300 MHz, CDCl₃): δ 9.70 (s, 1H), 7.60 (s, 1H), 6.94 (s, 1H), 5.61 (app. d, \( J = 7.1 \) Hz, 1H), 3.16 (app. septuplet, \( J = 6.9 \) Hz, 1H), 2.44 (app. td, \( J_t = 12.9 \) Hz, \( J_d = 3.9 \) Hz, 1H), 2.17 (app. td, \( J_t = 12.9 \) Hz, \( J_d = 3.6 \) Hz, 1H), 1.98 (app. qt, \( J_q = 13.7 \) Hz, \( J_i = 3.0 \) Hz, 1H), 1.76-1.64 (m, 2H), 1.62 (s, 3H), 1.60-1.52 (m, 1H), 1.29 (s, 3H), 1.27 (app. d, \( J = 6.9 \) Hz, 3H), 1.26 (app. d, \( J = 6.9 \) Hz, 3H), 1.26 (s, 3H). The signal at δ 5.61 (app. d, \( J = 7.1 \) Hz, 1H) vanishes when D₂O is shaken into the \(^1\)H NMR sample; \(^{13}\)C NMR (125 MHz, CDCl₃): δ 218.2, 191.5, 158.8, 147.1, 138.0, 132.5, 125.5, 116.2,
52.9, 44.7, 40.0, 37.9, 30.3, 27.1, 26.6, 25.5, 22.5, 22.1, 18.7; IR (NaCl/CDCl₃): 3272 (broad), 2962, 2927, 2869, 1684, 1612, 1579, 1460, 1345, 1274, 999, 909, 734 cm⁻¹; HRMS-FAB⁺ (m/z): [M+H]⁺ calc’d for C₁₉H₂₇O₃, 303.1960; found, 303.1953. \(^1\)H-\(^1\)H nOesy-1D spectra were obtained for (±)-256 (300 MHz, CDCl₃); the results are shown below:

**Aryl Methyl Ether (±)-257.** A round-bottom flask was charged with a solution of aldehyde (±)-252 (35 mg, 0.124 mmol), THF (1.0 mL), and MeOH (2.5 mL). 30% aq H₂O₂ (500 µL) was added, followed by conc. aq H₂SO₄ (3 drops from a glass pipet). After 1.2 h at 23 °C, the reaction was added slowly to a biphasic mixture of NaHSO₃ (600 mg), H₂O (20 mL), CH₂Cl₂ (20 mL), and hexanes (10 mL). The organic phase was collected, and the aqueous layer extracted with CH₂Cl₂ (3 x 15 mL). All organic layers were then combined, washed with brine (20 mL), dried (Na₂SO₄), filtered, and concentrated.
The crude product was taken up in CH₂Cl₂ (200 µL) and transferred to a Schlenk tube. Acetone (ACS grade, 800 µL) was added, followed by K₂CO₃ (155 mg, 1.12 mmol) and iodomethane (70 µL, 1.12 mmol). The tube was sealed and heated to 60 °C behind a blast shield for 20 h. Then the reaction was cooled to 23 °C and filtered over glass frits with the aide of acetone. The filtrate was adsorbed onto 750 µL of silica gel and purified by flash chromatography on silica gel (3:97 Et₂O:hexane eluent), giving aryl methyl ether (±)-257 (26.4 mg, 83% yield from (±)-252) as a white powder. R<sub>f</sub> (not determined); <sup>1</sup>H NMR (300 MHz, CDCl₃): δ 7.16 (s, 1H), 6.82 (s, 1H), 6.33 (s, 1H), 3.87 (s, 3H), 3.35 (app. septuplet, <i>J</i> = 6.9 Hz, 1H), 2.13 (app. ddd, <i>J</i> = 12.7 Hz, 4.7 Hz, 3.0 Hz, 1H), 1.98 (app. qt, <i>J</i><sub>d</sub> = 14.0 Hz, <i>J</i><sub>t</sub> = 3.9 Hz, 1H), 1.73-1.59 (m, 2H), 1.39 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 1.25 (app. d, <i>J</i> = 6.9 Hz, 3H), 1.24 (app. d, <i>J</i> = 6.9 Hz, 3H), 1.13 (app. td, <i>J</i><sub>t</sub> = 12.7 Hz, <i>J</i><sub>d</sub> = 3.9 Hz, 1H), 1.04 (app. td, <i>J</i><sub>t</sub> = 12.9 Hz, <i>J</i><sub>d</sub> = 3.6 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl₃): δ 162.0, 154.7, 153.9, 135.1, 134.8, 120.6, 117.9, 104.9, 56.1, 51.2, 43.0, 38.4, 35.6, 31.5, 26.9, 25.7, 24.0, 23.3, 23.2, 20.1; IR (NaCl/CDCl₃): 3059, 2960, 2929, 2866, 2844, 1620, 1593, 1571, 1484, 1463, 1417, 1309, 1289, 1221, 1082, 1065, 1032, 888 cm<sup>-1</sup>, HRMS-EI<sup>+</sup> (m/z): [M]<sup>+</sup> calc’d for C<sub>20</sub>H<sub>28</sub>O, 284.2140; found, 284.2131. <sup>1</sup>H-<sup>1</sup>H nOesy-1D spectra were obtained for (±)-257 (300 MHz, CDCl₃); the results are shown below:
Bromohydrin (±)-258. A round-bottom flask was charged with a solution of aryl methyl ether (±)-257 (28 mg, 99 µmol, 1.0 equiv) and CH$_3$CN (1.0 mL). To this was added a solution of N-bromo succinimide (18.4 mg, 0.103 mmol, 1.05 equiv) in CH$_3$CN (1.0 mL) at 23 °C. As time passed, the reaction went from colorless to yellow. At 16 h, the reaction was diluted with CH$_2$Cl$_2$ (20 mL) and adsorbed to 750 µL of silica gel and purified by flash chromatography on silica gel (2:98 Et$_2$O:hexane eluent), affording bromohydrin (±)-258 (8.0 mg, 21% yield). R$_f$ (not determined); $^1$H NMR (300 MHz, CDCl$_3$): δ 7.22 (s, 1H), 6.57 (s, 1H), 4.98 (app. d, $J = 12.5$ Hz, 1H), 3.83 (s, 3H), 3.28 (app. septuplet, $J = 6.9$ Hz, 1H), 2.56 (app. d, $J = 12.5$ Hz, 1H), 1.81-1.61 (m, 4H), 1.76 (s, 3H), 1.51-1.40 (m, 1H), 1.37 (s, 3H), 1.36-1.26 (m, 1H), 1.26 (s, 3H), 1.20 (app. d, $J = 6.9$ Hz, 3H), 1.19 (app. d, $J = 6.9$ Hz, 3H). The signal at δ 2.56 (app. d, $J = 12.5$ Hz, 1H) vanishes when D$_2$O is shaken into the $^1$H NMR sample; concomitantly, the signal at δ
4.98 converges: (app. d, \( J = 12.5 \) Hz, 1H → app. s, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 157.2, 148.5, 136.0, 133.1, 121.9, 110.2, 103.1, 77.2 (?), 55.7, 51.7, 41.6, 40.8, 39.4, 30.8, 28.7, 27.0, 24.7, 23.1, 22.9, 18.5; IR (NaCl/CDCl\(_3\)): 3538 (broad), 2938, 2867, 1615, 1592, 1492, 1464, 1392, 1305, 1289, 1223, 1093, 1070, 906 cm\(^{-1}\); LRMS-EI\(^+\) (m/z): [M]\(^+\) calc’d for C\(_{20}\)H\(_{29}\)O\(_2\)^{79,81}Br, 380 and 382; found, 380 and 382. \(^1\)H-\(^1\)H nOesy-1D spectra were obtained for (±)-258 (300 MHz, CDCl\(_3\)); the results are shown below:

Aryl Epoxide (±)-259. A round-bottom flask was charged with a solution of bromohydrin (±)-258 (6.2 mg, 16.3 µmol) and THF (5.0 mL) and cooled to 0 °C. (n-BuLi, 2.5 M in hexanes, 7 µL, 17.5 µmol) was added. 10 min later, the reaction was treated with D\(_2\)O (1.0 mL), then warmed to 23 °C. After 15 min, the reaction was diluted with hexanes (5 mL). The organic layer was collected, dried (Na\(_2\)SO\(_4\)), filtered, and concentrated, giving aryl epoxide (±)-259 (yield not determined) \( R_f \) (not determined); \(^1\)H
NMR (300 MHz, CDCl₃): δ 7.24 (s, 1H), 6.60 (s, 1H), 5.53 (app. d, J = 5.8 Hz, 1H), 3.85 (s, 3H), 3.28 (app. septuplet, J = 6.9 Hz, 1H), 2.26 (app. t, J = 13.4 Hz, 1H), 1.95-1.71 (m, 3H), 1.73 (s, 3H), 1.62-1.52 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 1.21 (app. d, J = 6.9 Hz, 3H), 1.20 (app. d, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 158.0, 136.2, 133.7, 122.4, 104.5, 84.7, 55.7, 40.1, 39.4, 31.7, 27.5, 27.1, 23.0, 22.8, 19.6; IR (NaCl/CDCl₃): 3434, 2959, 2933, 2873, 1615, 1492, 1464, 1376, 1308, 1226, 1058, 1018 cm⁻¹; HRMS-EI⁺ (m/z): [M+H]⁺ calc’d for C₂₀H₂₉O₂, 301.2168; found, 301.2168. ¹H-¹H homodecoupling experiments (300 MHz, CDCl₃) were performed on (±)-259: The signal at δ 6.60 (s, 1H) was suppressed with a decoupling current, resulting in no detectable splitting changes. The signal at δ 5.53 (app. d, J = 5.8Hz, 1H) was suppressed with a decoupling current, resulting in no detectable splitting changes. It is hypothesized that this signal is not really a doublet, but rather 2 singlets that arise from 2 diastereomers of (±)-259.

**o-Quinone** (±)-260. To a rapidly stirred solution of phenol (±)-242 (25 mg, 0.0925 mmol) in CHCl₃ (5 mL) wrapped in foil was added IBX (30.5 mg, 0.102 mmol) in nine portions over a 9 h period at 23 °C. After 11 h, the reaction was filtered through glass frits with the aide of CHCl₃. 80% (by volume) of the solution was carried onward; the remaining 20% was saved. The 80% of maroon filtrate to be processed was diluted with hexane (15 mL) and concentrated to ~4 mL total volume. More hexane was added (20
mL), and the solution was concentrated again to ~4 mL. This process was repeated two more times; then the solution was purified by flash chromatography on silica gel (1:9 Et₂O/hexane eluent), affording unstable o-quinone (±)-260 (4.3 mg, 20% yield based on 80% of starting material) as a purple powder. The compound was suitable for partial characterization: Rf 0.55 (1:4 EtOAc/hexane), (visible, purple spot); ¹H NMR (300 MHz, CDCl₃): δ 6.86 (s, 1H), 6.15 (s, 1H), 2.98 (app. quintet, J = 6.9 Hz, 1H), 2.41 (app. dd, J = 12.4 Hz, 1.7 Hz, 1H), 1.95-2.20 (m, 1H), 1.89 (app. qt, J_q = 13.2 Hz, J_t = 2.5 Hz, 1H), 1.72 (app. d, J = 12.7 Hz, 1H), 1.60 (s, 3H), 1.43 (s, 3H), 1.24 (s, 3H), 1.11-1.21 (m, 1H), 1.12 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H), 1.00-1.08 (m, 1H); IR (NaCl/CH₂Cl₂): 3418 (broad), 3035, 2961, 2932, 2869, 1959, 1682, 1631, 1580, 1517, 1464, 1433, 1403, 1369, 1287, 1230, 1172, 1009 cm⁻¹; HRMS-FAB⁺ (m/z): [M+H]⁺ calc’d for C₁₉H₂₅O, 285.1855; found, 285.1851. ¹H-¹H nOesy-1D spectra were obtained for (±)-260 (300 MHz, CDCl₃); the results are shown below:

The following experiment was employed for determining actual yield of (±)-260:

To a rapidly stirred solution phenol (–)-242 (25.4 mg, 0.0940 mmol) in CHCl₃ (5 mL) in the dark was added IBX (30.2 mg, 0.1018 mmol) in one portion. After 15 h, the reaction was filtered through glass frits with the aid of CHCl₃. The filtrate was partially concentrated and CDCl₃ was added; this was repeated iteratively until there was less than
2% CHCl₃ by volume and ∼3 mL total volume of solution. The solution was transferred to a 5.00 mL volumetric flask, and EtOAc (51.0 µL, 0.522 mmol, internal standard) was added. The flask was diluted to 5 mL using CDCl₃, giving a solution of unknown that was 0.0188 M in (±)-260 (assuming a 100% yield) and 0.104 M in EtOAc, with a theoretical molar ratio, Xₜ, of 1:5.55 (maximum theoretical analyte: internal standard). In a separate 2.00 mL volumetric flask, analytically pure racemic o-quinone (±)-260 (4.3 mg, 0.0151 mmol) from earlier in this procedure was dissolved in 2.0 mL of a stock solution of EtOAc (20.5 µL, 0.209 mmol, internal standard) and CDCl₃ (5.00 mL), giving a solution with a molar ratio Xₛ of 1:5.55 (analyte/internal standard). This analyte solution was serially diluted with the stock internal standard solution, giving four more solutions with molar ratios of 0.750Xₛ, 0.563Xₛ, 0.422Xₛ, and 0.211Xₛ. These four solutions, along with the original 1.000Xₛ solution, were analyzed by $^1$H NMR, and the peak integration ratios δ 6.86 (analyte): δ4.08 (internal standard) were determined. A calibration curve of molar ratio vs. integration ratio was prepared. The unknown was also analyzed by $^1$H NMR to obtain its integration ratio. The value of Xₜ (molar ratio) for the unknown was extrapolated from the equation of the least-squares best-fit line for the calibration curve, and was found to be 0.363Xₛ. This corresponds to a 36% yield of racemic o-quinone (±)-260.
Calibration Curve and Extrapolation Data for $o$-Quinone ($\pm$)-260 Yield Assay

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<th>Calibration</th>
<th>Integration δ6.86</th>
<th>Integration δ4.08</th>
<th>($\pm$)-260/Int.Std.</th>
<th>Yield ($X_\delta$)</th>
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Calibration Curve for $o$-Quinone ($\pm$)-260 Yield Assay

**Calibration Curve: Molar Ratio vs. Integration Ratio**

\[
y = 13.499x - 0.0701
\]

\[R^2 = 0.9989\]
(R)-(+)–Dichroanone ((+)-150). Phenol (–)-242 (79.8 mg, 0.295 mmol) was dissolved in CHCl₃ (16 mL) that had been degassed with argon for 10 min and shaken over oven-dry MS4Å. IBX (99.0 mg, 0.354 mmol) was added under argon with vigorous stirring in the dark at 23 °C. At 19 h, the reaction was filtered through glass frits with the aid of CHCl₃. The filtrate, which contained enantioenriched o-quinone (R)-260 (36% yield by ¹H NMR), was immediately used without further purification. To this solution was added pentafluorothiophenol (157 μL, 1.18 mmol) at 23 °C in the dark. After 2 h, the maroon reaction had become yellow-orange, and TLC revealed complete consumption of the o-quinone (R)-260. At this time, a solution of powdered NaOH (118 mg, 2.95 mmol) in MeOH (16 mL) was introduced. An O₂ balloon was attached, and the reaction became deep red over the next 2 h. Then, the mixture was refluxed under a balloon of O₂ at 75 °C in the dark for another 3 h. After cooling to 23 °C, the O₂ balloon was removed and substituted for an N₂ atmosphere. 6 M aq HCl (1.60 mL) was added dropwise and stirring was continued at 23 °C as the reaction became bright orange-red, and a white precipitate formed. After 30 min, the reaction was diluted with water (20 mL) and hexane (20 mL), and the organic phase was collected. The aqueous phase was extracted with Et₂O (3 x 20 mL). All organic layers were combined, washed with brine (20 mL), dried (Na₂SO₄), filtered, and concentrated to ~2 mL total volume. This suspension was purified by flash chromatography on silica gel (2:98 Et₂O/hexane eluent), affording semipure (+)-
dichroanone ((+)-150) as an oily, unpleasant-smelling, red solid. The residue was dissolved in hexane and adsorbed onto silica gel. The material was purified by flash chromatography on a second column of silica gel (2:98 Et₂O/hexane eluent), affording (R)-(+) -dichroanone ((+)-150) (31.0 mg, 35% yield from phenol (−)-242, 99% yield from o-quinone (R)-260) as an odorless, amorphous red solid. The product had 99.9% ee as determined by chiral HPLC. The compound had the same spectroscopic and physical properties as the natural sample and bore the opposite sense of optical rotation, establishing the absolute stereochemistry of natural dichroanone to be (S). *R* f 0.61 (1:4 EtOAc/hexane), (visible, orange-red spot); mp 119-120 °C (PhH); ¹H NMR (300 MHz, CDCl₃): δ 7.31 (s, 1H), 6.44 (s, 1H), 3.21 (septuplet, *J* = 7.2 Hz, 1H), 2.37 (app. ddd, *J* = 13.2 Hz, 5.0 Hz, 2.8 Hz, 1H), 1.92 (app. qt, *J* = 13.8 Hz, *J* = 3.3 Hz, 1H), 1.70 (app. dq, *J* = 13.2 Hz, *J* = 2.5 Hz, 1H), 1.62 (app. dddd, *J* = 14.2 Hz, 6.6 Hz, 3.9 Hz, 2.7 Hz, 1H), 1.45 (s, 3H), 1.28 (s, 3H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 1.23 (s, 3H), 1.11 (app. dt, *J* = 13.2 Hz, *J* = 4.4 Hz, 1H), 1.07 (app. dt, *J* = 13.2 Hz, *J* = 4.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 185.9, 178.4, 177.2, 152.6, 149.0, 147.9, 122.9, 118.1, 55.5, 43.5, 37.5, 37.1, 31.1, 24.9, 24.1, 20.3, 20.2, 19.2; IR (KBr): 3326, 2959, 2925, 2868, 1628, 1519, 1459, 1367, 1357, 1287, 1170, 1127, 1107, 992, 966 cm⁻¹ (NaCl/CHCl₃): 3350, 2960, 2932, 2873, 1637, 1527, 1470, 1368, 1358, 1317, 1242, 1104, 990, 966 cm⁻¹; HRMS-El⁺ (*m/z*): [M]+ calc’d for C₁₉H₂₄O₃, 300.17255; found, 300.17265; UV-Vis *λ*ₘₐₓ nm (log ε): 253(4.0), 332 (3.9); [α]_{D}^{27} +99.60° (c 0.0055, dioxane), 99.9% ee.
Comparison of Natural (S)-(−)-Dichroanone and Synthetic (R)-(+) -Dichroanone ((+)-150)

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<td>ddd, 14.2, 6.6, 3.9, 2.7</td>
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<td>1.46</td>
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<td>1.28</td>
<td>s</td>
<td>1.29</td>
<td>s</td>
</tr>
<tr>
<td>1.24</td>
<td>d, 7.2</td>
<td>1.25</td>
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<tr>
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<tr>
<td>1.23</td>
<td>s</td>
<td>1.24</td>
<td>s</td>
</tr>
<tr>
<td>1.11</td>
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<td>dt, d = 13.2, t = 4.4</td>
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1 Note that the chemical shifts of the synthetic (+)-Dichroanone ((+)-150) are uniformly 0.01 ppm upfield relative to the shifts for natural (−)-Dichroanone ((+)-150). This could be due to the reference value used by the isolation chemists. The chemical shift reference for the synthetic material was δ 7.26 ppm in accord with Cambridge Isotopes Laboratory, Inc.

2 $^1$H NMR, $^{13}$C NMR, IR, UV-Vis, and optical rotation data have been reproduced from the isolation paper. See: Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. Phytochemistry 1999, 50, 493-497.
Comparison of Natural (S)-(−)-Dichroanone and Synthetic (R)-(+) -Dichroanone ( (+)-150 )

<table>
<thead>
<tr>
<th></th>
<th>Synthetic (+), 75 MHz</th>
<th>Natural (−), 75 MHz</th>
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<tr>
<td><strong>13C NMR of Dichroanone, CDCl₃</strong></td>
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<tr>
<td><strong>Shift (ppm)</strong></td>
<td><strong>Shift (ppm)</strong></td>
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<tr>
<td>185.9</td>
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<td>178.4</td>
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<tr>
<td>-</td>
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</tr>
<tr>
<td>19.2</td>
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<table>
<thead>
<tr>
<th></th>
<th>Synthetic (+)</th>
<th>Natural (−)</th>
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<tbody>
<tr>
<td><strong>IR of Dichroanone, KBr</strong></td>
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<tr>
<td><strong>Wavenumber (cm⁻¹)</strong></td>
<td><strong>Wavenumber (cm⁻¹)</strong></td>
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<tr>
<td>3326</td>
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<td>2959</td>
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</tr>
<tr>
<td>2925</td>
<td>-</td>
<td></td>
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<tr>
<td>2868</td>
<td>-</td>
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<td>1628</td>
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<td>1519</td>
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<td>1367</td>
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<td>1170</td>
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<td>1107</td>
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<tr>
<td>992</td>
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<td>966</td>
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<table>
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<tr>
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<tbody>
<tr>
<td><strong>UV-Vis Spectrum of Dichroanone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>λmax (nm), (log ε)</strong></td>
<td><strong>λmax (nm), (log ε)</strong></td>
<td></td>
</tr>
<tr>
<td>253 (4.0)</td>
<td>253 (4.0)</td>
<td></td>
</tr>
<tr>
<td>332 (3.9)</td>
<td>332 (4.0)</td>
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<table>
<thead>
<tr>
<th></th>
<th>Synthetic (+)</th>
<th>Natural (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specific Optical Rotation of Dichroanone</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>[α]²⁷ D, (c 0.0055)</strong></td>
<td><strong>[α]⁵⁸ D, (c 0.67)</strong></td>
<td></td>
</tr>
<tr>
<td>(in dioxane, 99.9%ee)</td>
<td>(in dioxane, 100%ee)</td>
<td></td>
</tr>
<tr>
<td>+99.6°</td>
<td>-99.3°</td>
<td></td>
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</table>

³ An attempt was made to measure the specific optical rotation of synthetic (−) dichroanone ( (+)-150 ) at c = 0.67 as reported by the isolation chemists; however, due to the cell path length used (100 mm) on the polarimeter, no sodium-D (589 nm) light was transmitted through the orange-red solution, making an accurate measurement difficult. To circumvent this issue, a lower concentration was employed.
Determination of Absorption Maxima and Extinction Coefficients for (R)-(+)-Dichroanone ((+)-150). A sample of (+)-Dichroanone ((+)-150) (11.0 mg, 0.0366 mmol) was dissolved in dioxane (2.00 mL) in a volumetric flask, giving a 0.183 M solution. This solution was serially diluted to the following concentrations (10⁻⁵ M): 7.329, 4.217, and 1.925. UV-Vis spectra of the three diluted samples were obtained using a 1-cm path length quartz cuvette, and absorbances at 253 nm and 332 nm were measured. A least-squares line of absorbance vs. concentration (constrained to fit the origin) was calculated for both 253 nm and 332 nm absorbance sets. The slope of the least-squares-fit line gave the molar extinction coefficients: λ_max nm (log ε): 253(4.0), 332 (3.9).

Data Points for UV-Vis Spectra of (R)-(+) Dichroanone ((+)-150)

<table>
<thead>
<tr>
<th>Concentration (10⁻⁵M)</th>
<th>Abs at 253 nm</th>
<th>Abs at 332 nm</th>
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<tbody>
<tr>
<td>7.329</td>
<td>0.7783</td>
<td>0.5974</td>
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<tr>
<td>3.665</td>
<td>0.4217</td>
<td>0.3369</td>
</tr>
<tr>
<td>1.832</td>
<td>0.1925</td>
<td>0.1542</td>
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</table>
UV-Vis Data for \((R)-(+)\)-Dichroanone ((+)-150)

Absorbance vs. Concentration at 253 nm of \((+)-\)Dichroanone

\[
y = 0.1078x \\
R^2 = 0.995
\]

For this graph, the equation of best fit is equivalent to Beer’s Law, \(A = \varepsilon lc\), where \(l\) is a constant (1 cm, the path length of the sample in the quartz cuvette) and \(\varepsilon\) is the slope of the least squares line, constrained to run through the origin. Thus, \(\varepsilon\) is in units of \([\text{cm}^{-1} \times (10^{-5} \text{ M})^{-1}]\) or more simply, \(\varepsilon = 100000 \times \text{slope} \times \text{L} / (\text{mol} \times \text{cm})\). Hence, \(\varepsilon_{253} = 10780 \text{ L} / (\text{mol} \times \text{cm})\), and \(\log(\varepsilon_{253}) = 4.0\).

\(\varepsilon_{253} = 10780 \text{ L} / (\text{mol} \times \text{cm})\); \(\log(\varepsilon_{253}) = 4.0^4\)

\(^4\) For this graph, the equation of best fit is equivalent to Beer’s Law, \(A = \varepsilon lc\), where \(l\) is a constant (1 cm, the path length of the sample in the quartz cuvette) and \(\varepsilon\) is the slope of the least squares line, constrained to run through the origin. Thus, \(\varepsilon\) is in units of \([\text{cm}^{-1} \times (10^{-5} \text{ M})^{-1}]\) or more simply, \(\varepsilon = 100000 \times \text{slope} \times \text{L} / (\text{mol} \times \text{cm})\). Hence, \(\varepsilon_{253} = 10780 \text{ L} / (\text{mol} \times \text{cm})\), and \(\log(\varepsilon_{253}) = 4.0\).
UV-Vis Data for \((R)-(+)\)-Dichroanone (+)-150

Absorbance vs. Concentration at 332 nm of \((+)-Dichroanone\)

\[ y = 0.0836x \]
\[ R^2 = 0.9882 \]

\[ \varepsilon_{332} = 8360 \text{ L} / (\text{mol} \cdot \text{cm}) \]
\[ \log(\varepsilon_{332}) = 3.9^5 \]

^5 For this graph, the equation of best fit is equivalent to Beer’s Law, \(A = \varepsilon lc\), where \(l\) is a constant (1 cm, the path length of the sample in the quartz cuvette) and \(\varepsilon\) is the slope of the least squares line, constrained to run through the origin. Thus, \(\varepsilon\) is in units of \([\text{cm}^{-1} \cdot (10^{-5} \text{ M})^{-1}]\) or more simply, \(\varepsilon = 100000 \cdot \text{(slope)} \cdot \text{L} / (\text{mol} \cdot \text{cm})\). Hence, \(\varepsilon_{332} = 8360 \text{ L} / (\text{mol} \cdot \text{cm})\), and \(\log(\varepsilon_{332}) = 3.9\).
**O-Methyl Dichroanone (+)-267.** A vial was charged with dichroanone ((+)-150) (3.0 mg, 10 µmol), and a solution of diazomethane (2.0 M in Et₂O, 2.0 mL, 4 mmol) was added. After 1 h at 23 °C, 63 µL of silica gel was carefully added, and the reaction was adsorbed onto the silica. The reaction was then purified on a pipet flash column loaded with silica gel (10:90 Et₂O:hexane eluent), affording O-methyl dichroanone (+)-267 (3.1 mg, quantitative yield) as an orange powder. R_f 0.65 (20:80 EtOAc/hexane), (visible, orange spot); mp 85-88 °C (Et₂O/hexane); ^1H NMR (300 MHz, CDCl₃): δ 6.37 (s, 1H), 3.86 (app. d, J = 1.1 Hz, 3H), 3.25 (septuplet, J = 7.1 Hz, 1H), 2.40 (app. d, J = 13.2 Hz, 1H), 1.92 (app. qt, J_q = 13.8 Hz, J_t = 3.3 Hz, 1H), 1.70-1.60 (m, 2H), 1.44 (s, 3H), 1.27 (s, 3H), 1.23 (d, J = 7.1 Hz, 3H), 1.22 (s, 3H), 1.22 (d, J = 7.1 Hz, 3H), 1.11 (dt, J_d = 13.5 Hz, J_t = 3.9 Hz, 1H), 1.06 (dt, J_d = 13.2 Hz, J_t = 3.6 Hz, 1H); ^13C NMR (75 MHz, CDCl₃): δ 186.5, 180.0, 175.8, 157.5, 150.7, 146.0, 136.2, 116.9, 61.6, 55.8, 43.5, 37.4, 36.9, 31.1, 25.0, 24.6, 20.9, 20.3, 19.3, 15.6; IR (NaCl/CHCl₃): 2961, 2931, 2874, 1645, 1615, 1583, 1534, 1472, 1458, 1359, 1292, 1264, 1156, 1092, 1026 cm⁻¹; HRMS-EI⁺ (m/z): [M]^+ calc’d for C₂₀H₂₆O₃, 314.1882; found, 314.1868. [α]²⁵_D +68.34° (c 0.068, CHCl₃), 99.9% ee.
O-Acetyl Dichroanone (+)-268. To a solution of dichroanone ((+)-150) (5.0 mg, 16.7 µmol) in CHCl₃ (4.0 mL) was added Et₃N (100 µL), causing the solution to turn from yellow-orange to indigo. After 5 min at 23 °C, acetyl chloride (50 µL) was introduced, and the reaction became bright yellow. After 5 min, sat. aq NaHCO₃ (2.0 mL) was carefully added, followed by H₂O (2.0 mL). The organic phase was collected, and the aqueous layer was extracted with CHCl₃ (2 x 4 mL). All organic layers were combined, dried (Na₂SO₄), filtered, and adsorbed onto 125 µL of silica gel. The material was purified on a pipet silica gel flash column (5:95 Et₂O:hexane eluent), giving O-acetyl dichroanone (+)-268 (5.6 mg, 98% yield) as a yellow semisolid. Rᶠ 0.62 (20:80 EtOAc/hexane), (visible, yellow-orange spot); mp 59-61 °C (CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 6.39 (s, 1H), 3.15 (septuplet, J = 7.1 Hz, 1H), 2.42 (app. d, J = 13.2 Hz, 1H), 2.36 (s, 3H), 1.91 (app. qt, Jₐ = 13.5 Hz, Jₖ = 3.3 Hz, 1H), 1.73-1.58 (m, 2H), 1.44 (s, 3H), 1.28 (s, 3H), 1.22 (app. d, J = 6.9 Hz, 6H), 1.22 (s, 3H), 1.12 (dt, Jₐ = 13.2 Hz, 1H), 1.07 (dt, Jₐ = 12.6 Hz, Jₖ = 2.7 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 185.2, 176.6, 175.2, 168.5, 150.9, 150.4, 146.5, 138.8, 116.8, 56.0, 43.5, 36.9, 37.4, 31.1, 25.3, 25.0, 20.65, 20.61, 20.3, 19.2; IR (NaCl/CHCl₃): 2963, 2932, 2874, 1777, 1652, 1594, 1534, 1462, 1368, 1352, 1292, 1184, 1158, 1010, 921, 864 cm⁻¹; HRMS-FAB⁺ (m/z): [M+H]⁺ calc’d for C₂₁H₂₇O₄, 343.1909; found, 343.1918. [α]²⁶_D +82.61° (c 0.0280, CHCl₃), 99.5% ee.
**O-Acetyl Dichroanone Epoxide (−)-269.** A Schlenk tube was charged with *m*-CPBA (99% pure, 27.7 mg, 0.161 mmol, 10.0 equiv). A solution of *O*-acetyl dichroanone (+)-268 (5.5 mg, 16.1 µmol, 1.0 equiv) in CHCl₃ (5.0 mL) was introduced. The vessel was sealed and warmed to 40 °C for 17 h. Then, a second portion of *m*-CPBA (99% pure, 27.7 mg, 0.161 mmol, 10.0 equiv) was added. The reaction was stirred for an additional 7 h at 40 °C and concentrated. The residue was purified by flash pipet column chromatography on silica gel (5:95 Et₂O:hexane eluent), giving semipure (−)-269. This material was purified on a second flash pipet column with silica gel (5:95 Et₂O:hexane eluent), affording pure *O*-acetyl dichroanone epoxide (−)-269 (3.3 mg, 49% yield) as a single diastereomer in the form of a pale yellow oil. Rᵢ 0.55 (20:80 EtOAc/hexane), (p-Anisaldehyde, green-yellow spot); ¹H NMR (500 MHz, CDCl₃): δ 4.17 (s, 1H), 3.12 (app. quintet, *J* = 6.9 Hz, 1H), 2.32 (s, 3H), 2.26 (app. ddd, *J* = 13.2 Hz, 5.4 Hz, 2.9 Hz, 1H), 1.78 (app. qt, *J*ᵢ = 14.2 Hz, *J*ᵢ = 2.9 Hz, 1H), 1.68 (app. ddd, *J* = 13.7 Hz, 5.4 Hz, 2.9 Hz, 1H), 1.58-1.44 (m, 1H), 1.55 (s, 3H), 1.48 (s, 3H), 1.36 (app. td, *J*ᵢ = 13.7 Hz, *J*ᵢ = 3.4 Hz, 1H), 1.30 (app. td, *J*ᵢ = 13.7 Hz, *J*ᵢ = 3.9 Hz, 1H), 1.21 (app. d, *J* = 6.9 Hz, 3H), 1.20 (app. d, *J* = 6.9 Hz, 3H), 1.17 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 184.6, 178.2, 168.2, 155.9, 149.6, 145.8, 139.9, 75.2, 59.9, 49.5, 40.1, 36.8, 32.1, 28.0, 25.4, 23.8, 20.53, 20.47, 19.2, 17.5; IR (NaCl/CHCl₃): 2966, 2936, 2874, 1778, 1658, 1608, 1457,
1370, 1318, 1182, 1164, 1132, 1008, 920, 890 \text{ cm}^{-1}; \text{HRMS-FAB}^+ (m/z): [M]^+ \text{ calc'd for } C_{21}H_{26}O_5, 358.1780; \text{ found, 358.1790. } [\alpha]^{26}_D = -27.28^\circ \ (c \ 0.140, \text{ CHCl}_3), \text{ 99.5\% ee.}

3.11.3 \textit{Methods for the Determination of Enantiomeric Excess}

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<tr>
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<th>Substrate</th>
<th>Assay</th>
<th>Column</th>
<th>Method</th>
<th>Retention Time (min)</th>
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<td>Enantiomeric Excess</td>
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<td>Minor (R) 30.5</td>
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<td>Major (S) 10.2</td>
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<td>10% EtOH/Hex monitor@254nm</td>
<td>Minor (R) 9.3</td>
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<td></td>
<td>Major (S) 12.1</td>
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<td>Chiralcel AD Column</td>
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<td>4.</td>
<td>![Structure](4aS, 5aR)-233</td>
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<td>4% EtOH/Hex monitor@254nm</td>
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<td>Major Diasteromer: (4aS, 5aR)-233</td>
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<td></td>
<td></td>
<td>Major (4aR, 5aS) 28.5</td>
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<td>Chiralcel AD Column</td>
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</tr>
<tr>
<td>5.</td>
<td><img src="R" alt="Structure" />(+)-Dihydroanone(150)</td>
<td>Enantiomeric Excess</td>
<td>Chiral HPLC</td>
<td>0.3% EtOH/Hex monitor@254nm</td>
<td>Minor (S) 18.3</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Major (R) 21.1</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Chiralcel AD Column</td>
<td></td>
</tr>
</tbody>
</table>
3.12 Notes and Citations


(9) Banerjee’s longest linear sequence to Dichroanal B (149) is 28 steps from vanillin (170) with a 0.88% overall yield. Vanillin (170) costs $26 for 100 g ($0.26/g) from Aldrich.

(10) Banerjee’s longest linear sequence to dichroanone (150) is 27 steps from vanillin (170) with a 1.1% overall yield. See also reference 9.


(12) Fillion’s longest linear sequence to taiwaniaquinol B (154) is 15 steps from 3,5-dimethoxybenzoic acid (193) with a 6.4% overall yield. 3,5-dihydroxybenzoic acid (193) costs $30 for 100 g ($0.30/g) from Aldrich.


(14) β-cyclocitral (203) can be purchased from Alfa Aesar at $118 for 50 g ($2.36/g).

(15) Node’s longest linear sequence to dichroanal B (149) is 11 steps from 2’,3’-dihydroxy-4’-methoxyacetophenone (204) with a 31% overall yield. From TCI America Organic Chemicals, 2’,3’-dihydroxy-4’-methoxyacetophenone (204) costs $246 for 25 g ($9.84/g).


(17) Trauner does not specify how 2,6-dimethoxycumene (213) is prepared.

(18) Trauner’s longest linear sequence to taiwaniaquinol B (154) is 6 steps from 2,6-dimethoxycumene (213) with a 28% overall yield. See reference 17.
Taiwaniaquinone H (165) is prepared in 7 steps and 24% overall yield from 2,6-dimethoxycumene (213). Dichroanone is prepared in 7 steps and 24% overall yield from the same starting material (213). See reference 17.

Taiwaniaquinol D (156) is prepared in 8 steps and 18% overall yield from 2,6-dimethoxycumene (213). See reference 17.

Subsequent to our work, additional synthetic studies of 4a-methyltetrahydrofluorenes were presented, see: Himkus, J. M.; Majetich, G. Total synthesis of (±)-dichroanone and studies toward related diterpenoids. Abstracts, 58th Southeast Regional Meeting of the American Chemical Society, Augusta, GA, United States, November 1-4 (2006), SRM06-633.

The absolute stereochemistry of taiwaniaquinone A (159) was speculated by analogy to the abietanes in the taxodiaceae family. For information, see reference 2b. There has also been debate about how these [6-5-6] tricyclic natural products are named. As an alternative to the description “4a-methyltetrahydrofluorene” or “tawaniaquinoid”, some favor the “5(6→7)abeoabietane type” nomenclature for the diterpene members and “6-nor-5(6→7)abeoabietane type” nomenclature for the norditerpenoids. For more information, see reference 2c.

2,2,6-trimethylcyclohexanone (101) costs $48/g from Aldrich.

2,6-dimethylcyclohexanone (220), sold as a cis,trans mixture from Aldrich, costs $48 for 25 g ($1.92/g).


Typically, when solvated samples of 2-allyl-2,6,6-trimethylcyclohexanone (75) were concentrated in vacuo, the external bath temperature was kept at less than 10 °C to reduce unwanted evaporation of the compound, while still allowing distillation of the solvent.


Although xylenes do not reflux at this temperature, the xylene-water azeotrope does and can be removed. Refluxing at greater than 110 °C was avoided as it led to decomposition.


(39) The sample of bicyclic enone (–)-143 used in this recrystallization sequence was a combination of several lots of enone product and had a net ee of 83%.


(42) Two hypothetical olefin isomers corresponding to the two low-Rf species are shown below:

\[ \text{ii} \quad \text{iii} \]

(43) Luis, J. G.; Grillo, T. A. Tetrahedron, 1993, 49, 6277-6284. The authors believe that a dioxetane (vi) might explain the formation of viiia and viiib from the natural product 6,7-didehydroferruginol (iv). The compound (iv) might be enzymatically
oxidized to catechol v. In the presence of singlet dioxygen, dioxetane vi could arise. A formal $4\pi$-electrocyclic ring opening would lead to aldehyde vii, and cyclization of an aromatic hydroxyl onto the cyclohexanecarbaldehyde moiety could produce either or both of the anomers viia and viib. See below:

(44) Syper, L.; Mlochowski, J.; Kloc, K. *Tetrahedron* **1983**, *39*, 781-792. A number of oxiranyl quinones of type ix have been synthesized and evaluated for bioalkylation activity. Their mode of action is believed to begin with bioreduction to x followed by epoxide opening, generating the alkylator xi. See below:


(46) (a) The oxidation products of phenols by iodine (III) reagents has been studied computationally, see: Kurti, L.; Hurczegh, P.; Visy, J.; Simonyi, M.; Antus, S.; Pelter,

(47) A calibration curve of $^1$H NMR signal integration (ratio to EtOAc internal standard) versus mass for known amounts of pure, chromaographed $o$-quinone was prepared. Filtered product mixture from an actual IBX oxidation was doped with EtOAc, and a sample was analyzed for the integration ratio versus internal standard. The value was used to extrapolate the amount of $o$-quinone present using the calibration curve. For more details, see the experimental section.


(49) We have reported our synthesis: McFadden, R. M.; Stoltz, B. M. J. Am. Chem. Soc. 2006, 128, 7738-7739.

(50) Banerjee reported the conversion of ($\pm$)-dichroanone (150) to ($\pm$)-taiwaniaquinol-H (165) in the presence of $K_2CO_3$ and iodomethane in a 2:1 acetone/methanol solvent mixture. See reference 6 for details.


(c) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. Org. Lett. 2007, 9, 2529-2931.

(53) 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.