CHAPTER THREE†

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

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

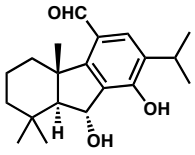
3.1.1 *Tricyclic Terpenoids Isolated from Thuja standishii, Taiwania cryptomerioides, and Salvia dichroantha*

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 diterpenpoids (e.g., taiwaniaquinone D (**151**)).[2a] Occasionally, a one-carbon excision may occur, leading to norditerpenoid variants (e.g., dichroanone (**(–)-150**).

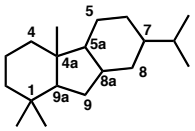
†(Pages 140-189 reproduced in part from *J. Am. Chem. Soc.* **2006**, *128*, 7738; supporting information.)

Figure 3.1 [6-5-6] Natural Products

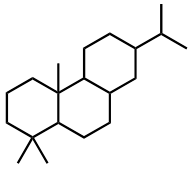
Thuja standishii



Standishinal *(147)*

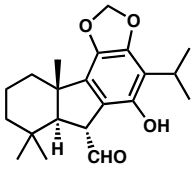


4a-methyltetrahydro-*fluorene skeleton (152)*

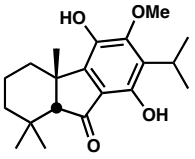


Abietane Skeleton *(146)*

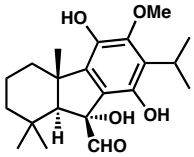
Taiwania cryptomerioides



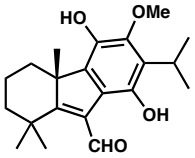
Taiwaniaquinol A *(153)*



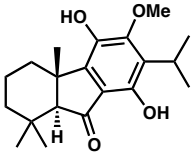
Taiwaniaquinol B *(154)*



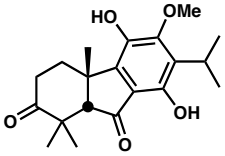
Taiwaniaquinol C *(155)*



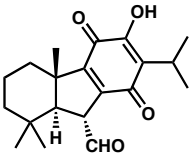
Taiwaniaquinol D *(156)*



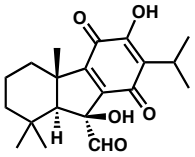
Taiwaniaquinol E *(157)*



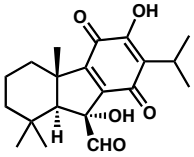
Taiwaniaquinol F *(158)*



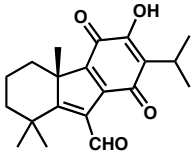
Taiwaniaquinone A *(159)*



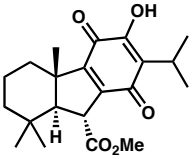
Taiwaniaquinone B *(160)*



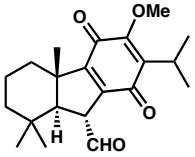
Taiwaniaquinone C *(161)*



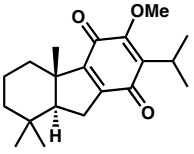
Taiwaniaquinone D *(151)*



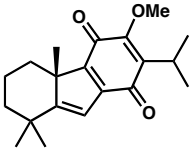
Taiwaniaquinone E *(162)*



Taiwaniaquinone F *(163)*

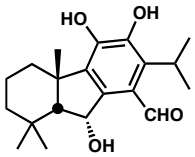


Taiwaniaquinone G *(164)*

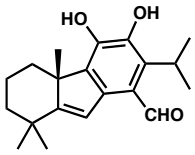


Taiwaniaquinone H *(165)*

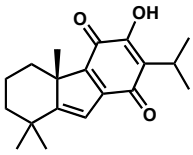
Salvia Dichroantha



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*

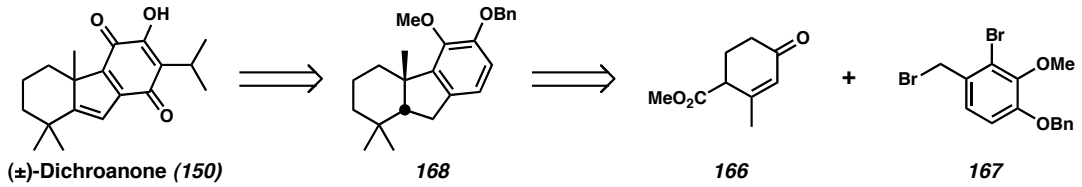
In addition to the unique tricyclic ring structure found in the 4a-methyltetrahydrofluorene natural products, some other features are noteworthy. The compounds each possess all-carbon quaternary stereocenters adjacent to an aromatic or quinoid ring. These highly oxidized ring systems pose another synthetic 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 (±)-dichroanal B (**149**) and (±)-dichroanone (**150**), but later Banerjee also published total syntheses of (±)-taiwaniaquinol B (**154**) and (±)-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.

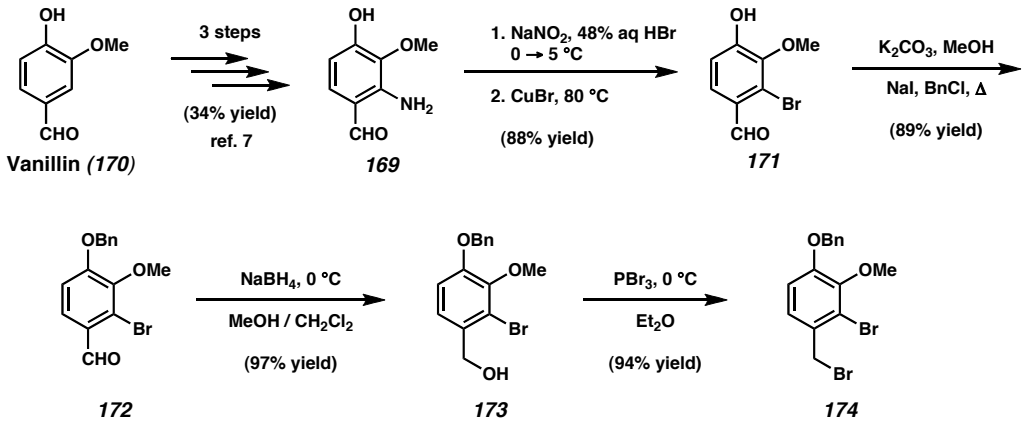
Scheme 3.1 Banerjee's Retrosynthetic Analysis



(±)-Dichroanone *(150)* *168* *166* *167*

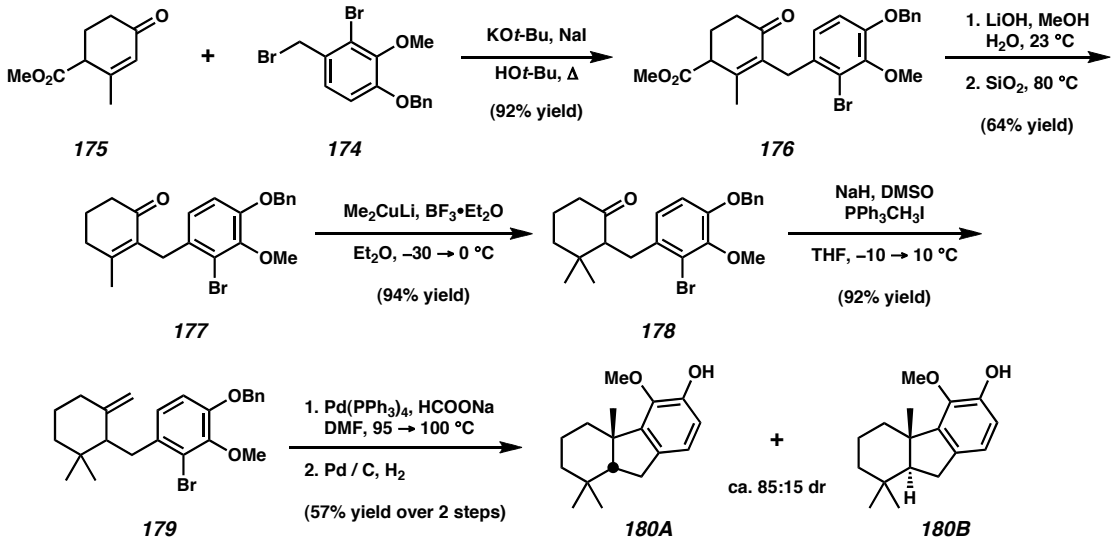
Banerjee's synthesis of the aromatic portion of the natural products began with the preparation of tetrasubstituted arene **169**, according to a published method (Scheme 3.2).[7] With aniline **169** in hand, Sandmeyer chemistry allowed the installation of a bromine atom. Benzylation of phenol **171** 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



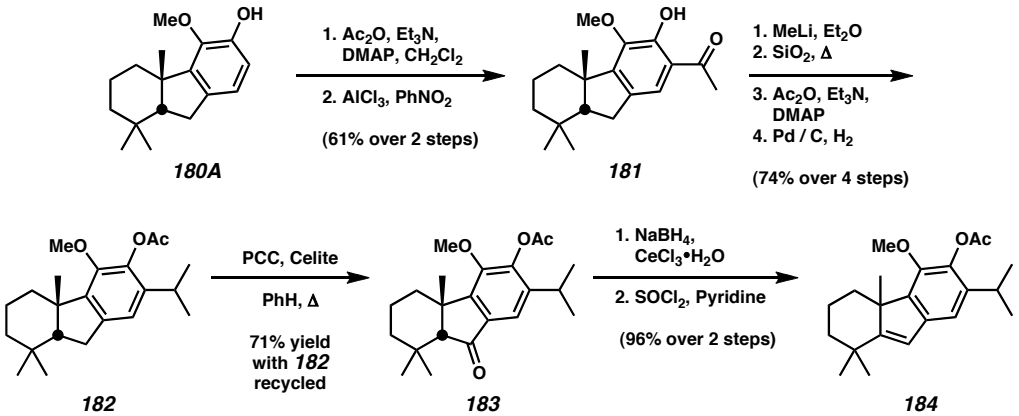
The other coupling fragment **175** was then appended to the benzylic bromide **174** in an alkylation reaction (Scheme 3.3). The use of **175** as opposed to its ethyl ester variant (Hagemann's ester) was crucial, as the attempted decarboxylation of the ethyl ester variant of **175** led to multiple 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



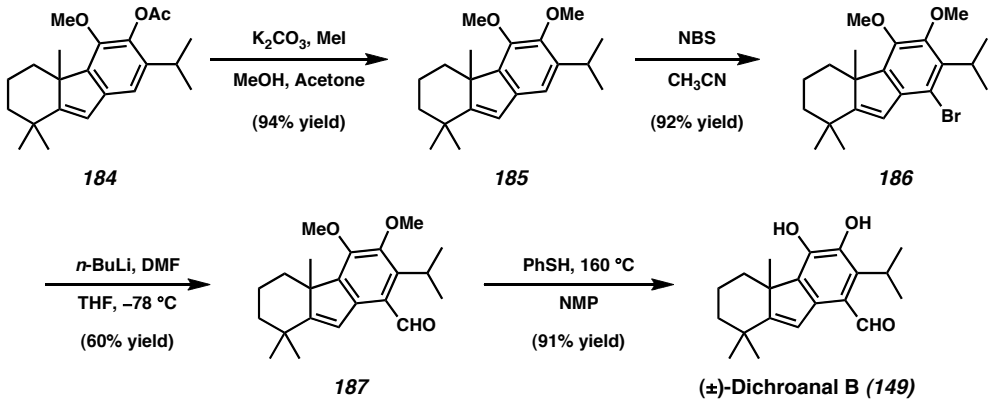
The next focus of the synthesis was the installation of the isopropyl moiety. Acylation of **180A** and Fries rearrangement,[8] followed by a 4-step sequence of events, led to the acetate-protected catechol **182** (Scheme 3.4). Oxidation of the 5-membered ring with PCC gave ketone **183**, which was reduced and dehydrated with $SOCl_2$, furnishing the styrene **184**. At this point the synthesis diverged into two paths.

Scheme 3.4 Installation of the Isopropyl Moiety



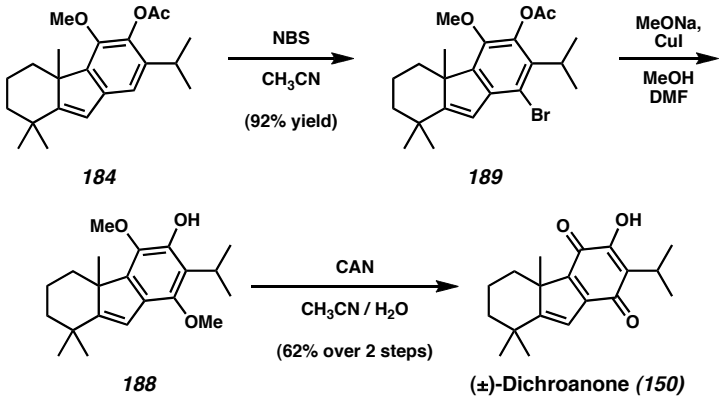
(±)-Dichroanal B (**149**) was prepared as follows (Scheme 3.5). A portion of protected catechol **184** was converted via saponification and methylation to the veratrole **185**. Chemoselective bromination of the aromatic portion of the molecule furnished **186** in excellent yield. Metal-halogen exchange was followed by DMF quench and nucleophilic demethylation with thiophenol, completing the first total synthesis of (±)-dichroanal B (**149**).[9]

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**.[10]

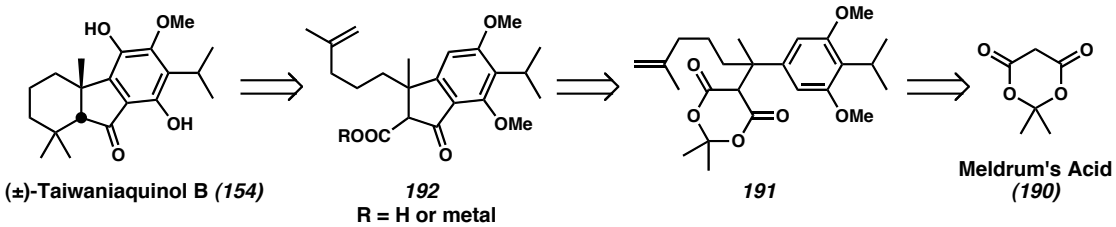
Scheme 3.6 Total Synthesis of (±)-Dichroanone (**150**)



3.2.2 *Fillion's Approach to Taiwaniaquinol B*

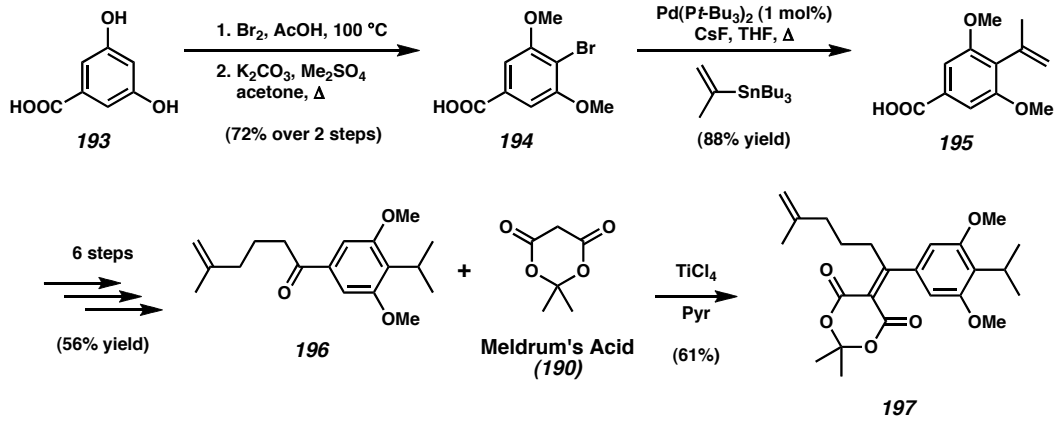
Fillion's group has also published a total synthesis of a 4a-methyltetrahydrofluorene diterpenoid, (±)-taiwaniaquinol B (**154**).[11] Their synthetic design was inspired by the powerful versatility of Meldrum's acid (**190**) (Scheme 3.7). It was envisioned that the tricyclic scaffold of (±)-taiwaniaquinol 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



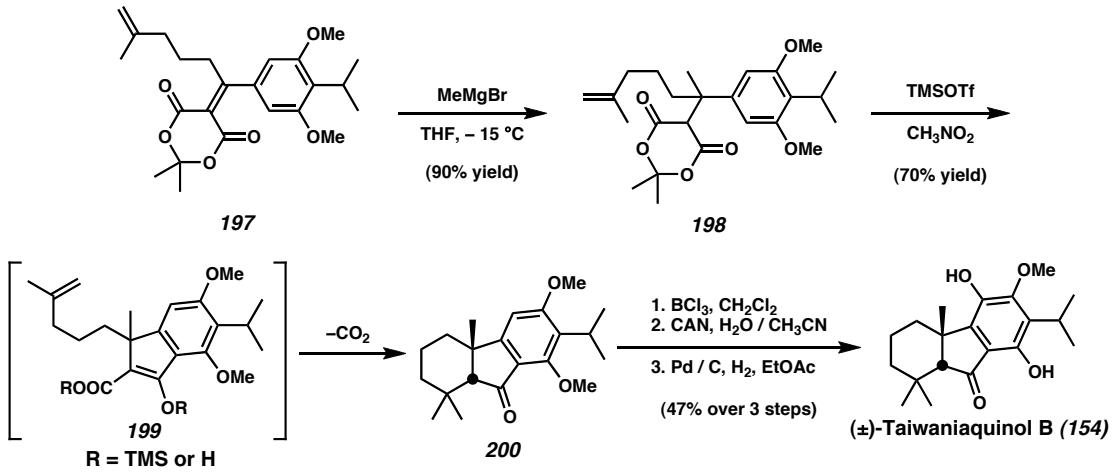
The synthesis commenced with 3,5-dihydroxybenzoic acid (**193**) (Scheme 3.8). Regioselective bromination, followed by bis-methylation and Stille coupling of 2-propenyl stannane, furnished the styrene **195**. A 5-step elaboration of **195** to the geminally substituted alkene **196** was followed by 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]

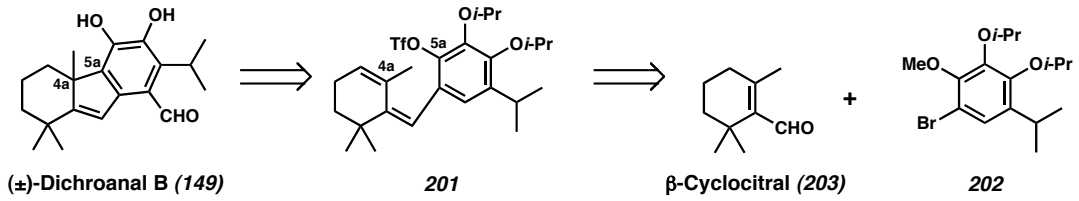
Scheme 3.9 Fillion's Total Synthesis of (±)-Taiwaniaquinol B



3.2.3 *Node's Synthesis of Dichroanal B*

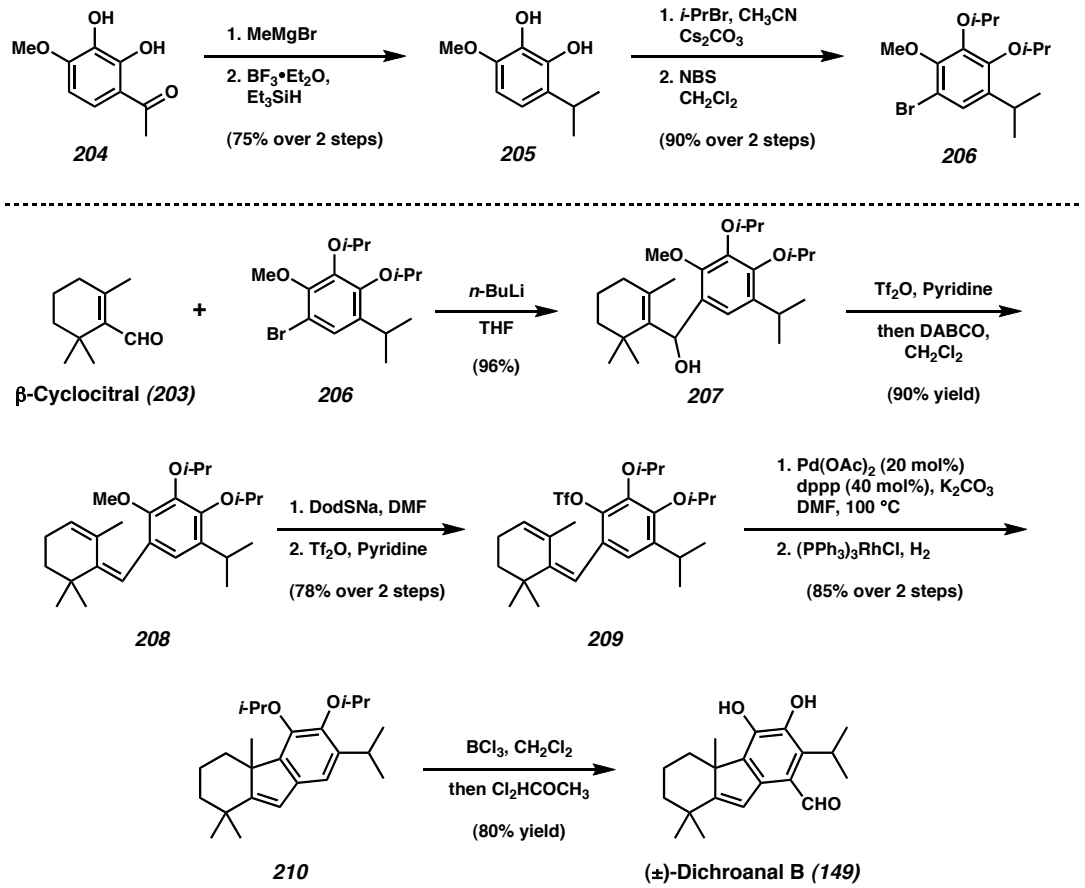
The Node group designed an efficient synthesis of (±)-dichroanal B (**149**) that employed a convergent approach.[13] As Banerjee had done,[5,6] Node made a key retrosynthetic disconnection across C(4a) and C(5a). A 5-*exo*-intramolecular Heck cyclization was the reaction of choice for the desired C-C 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**).[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 Et_3SiH (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



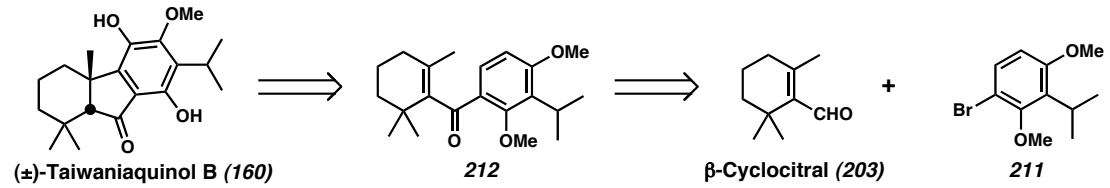
With aryl bromide **206** in hand, a lithium-halogen exchange was performed, and the resulting lithio-arene was treated with β-cyclocitral (**203**),[14] resulting in 1,2-addition (Scheme 3.11). Chemoselective dehydration of **207** with triflic anhydride and DABCO

furnished the *s-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 disubstuted olefin moiety was selectively hydrogenated with Wilkinson's catalyst and H_2. The tricyclic styrene product **210** was treated with BCl_3 followed by α,α-dichloromethyl methyl ether, completing the total synthesis of (±)-dichroanal B (**149**).[15]

3.2.4 *Trauner's Synthesis of Taiwaniaquinoids*

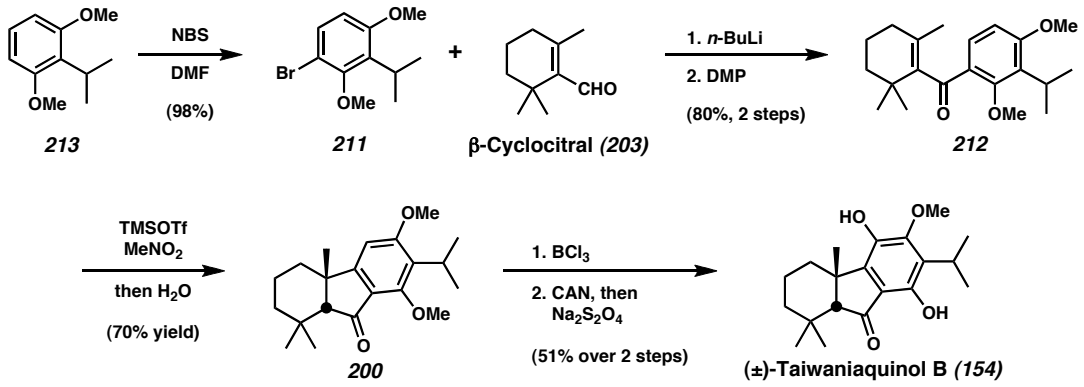
The Trauner group has also sought to address the challenges presented by the 4a-methyltetrahydrofluorene natural products.[16] Their efforts culminated in the total syntheses of (±)-taiwaniaquinols B and D (**160** and **151**), along with (±)-taiwaniaquinone H (**165**) and (±)-dichroanone (**150**). 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 β-cyclocitral (**203**).[14]

Scheme 3.12 Trauner's Retrosynthetic Analysis



To begin the syntheses, 2,6-dimethoxycumene (**213**)[17] was monobrominated with *N*-bromosuccinimide in DMF (Scheme 3.13). Subsequent lithium halogen exchange, followed by 1,2-addition to β-cyclocitral (**203**),[14] 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),[11] the Trauner group published a different endgame involving monodeprotection and CAN-mediated oxidation (Scheme 3.13).[18]

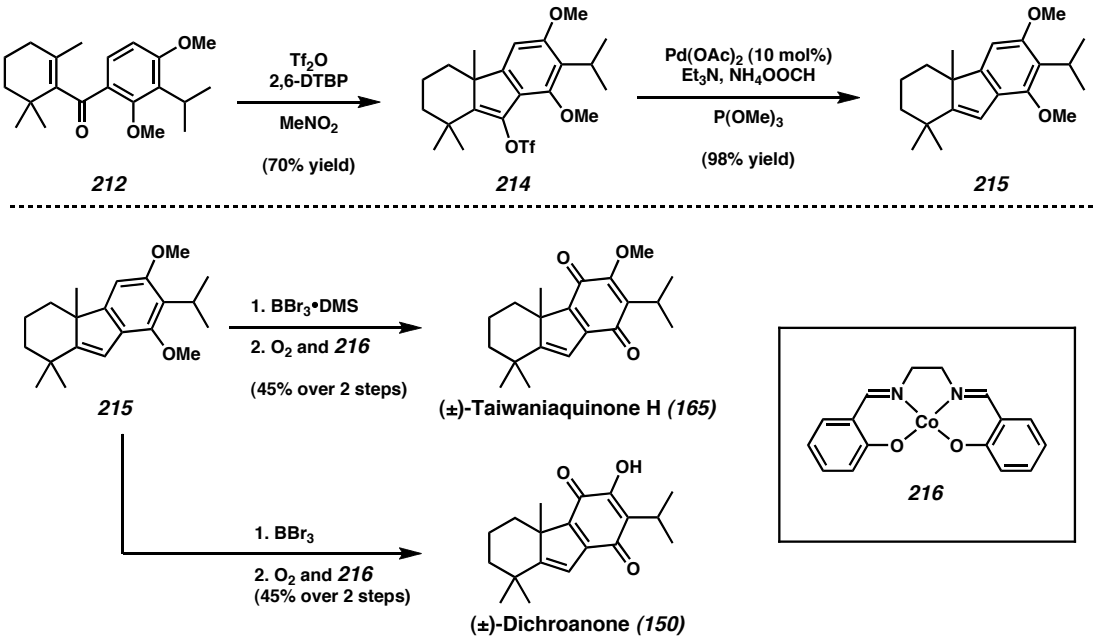
Scheme 3.13 Completion of Racemic Taiwaniaquinol B



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

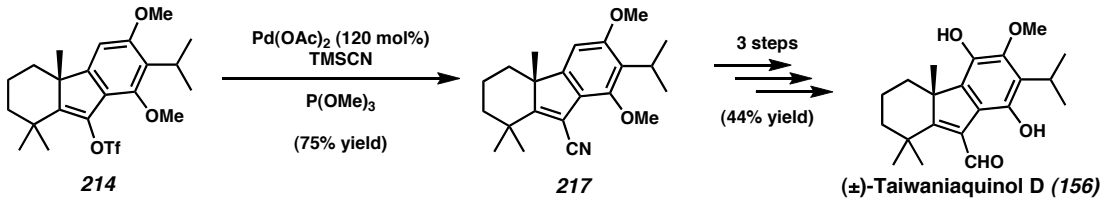
furnished the useful styrene **215**, which was carried onward to (±)-dichroanone (**150**) and (±)-taiwaniaquinone H (**165**). Of note, the compound **215** could be either mono- or di-demethylated with judicious choice of Lewis acid. To install the final oxygen atom in both natural products,[19] a 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.[20] Trauner's syntheses of these natural products showed the broad utility of the Nazarov cyclization.

Scheme 3.15 Total Synthesis of Racemic Taiwaniaquinol D



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.[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.[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*

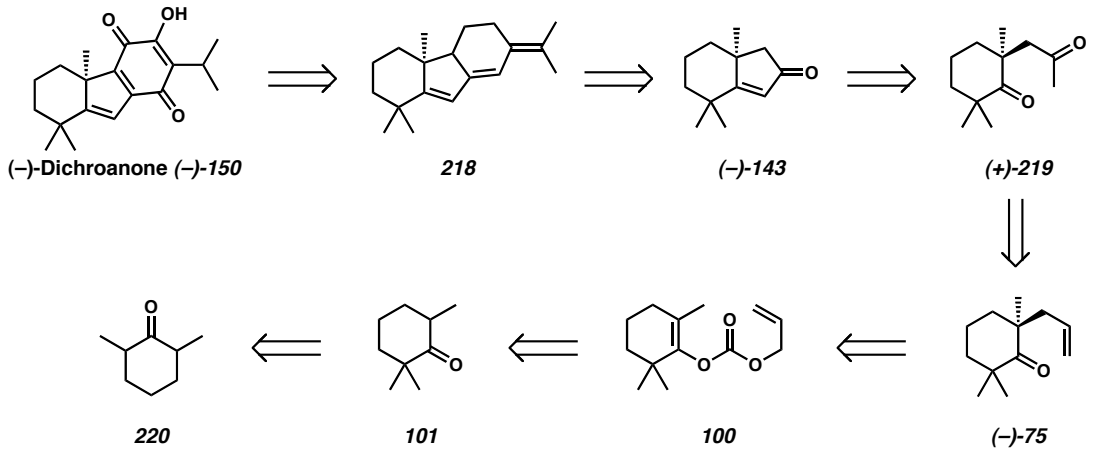
One goal of our total synthesis was to determine the absolute stereochemistry of the natural product by using our enantioselective decarboxylative alkylation to set the all-carbon-quaternary stereocenter. The second endeavor was to design a synthesis amenable to completion of related natural products. The pioneering work of Banerjee,[5,6] Fillion,[11] Node,[13] and Trauner[16] 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



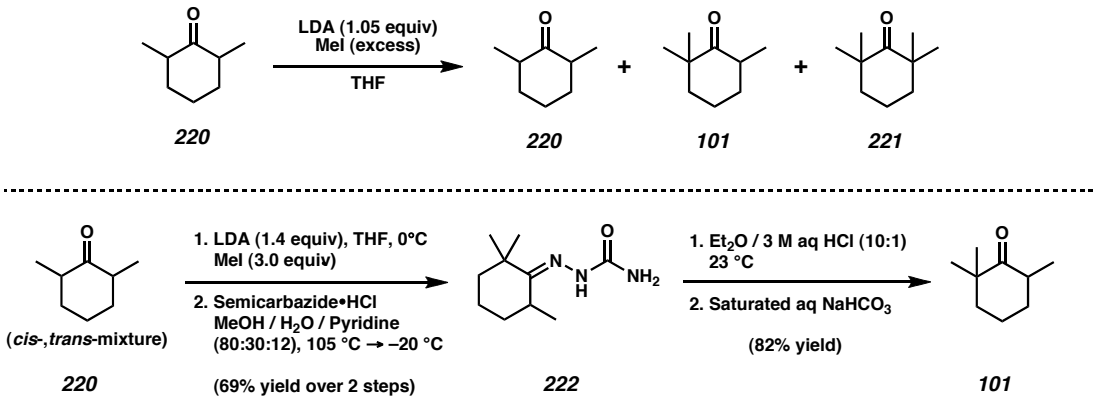
3.4 Synthesis of the Tricyclic Core

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.[23] 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.[24] 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.

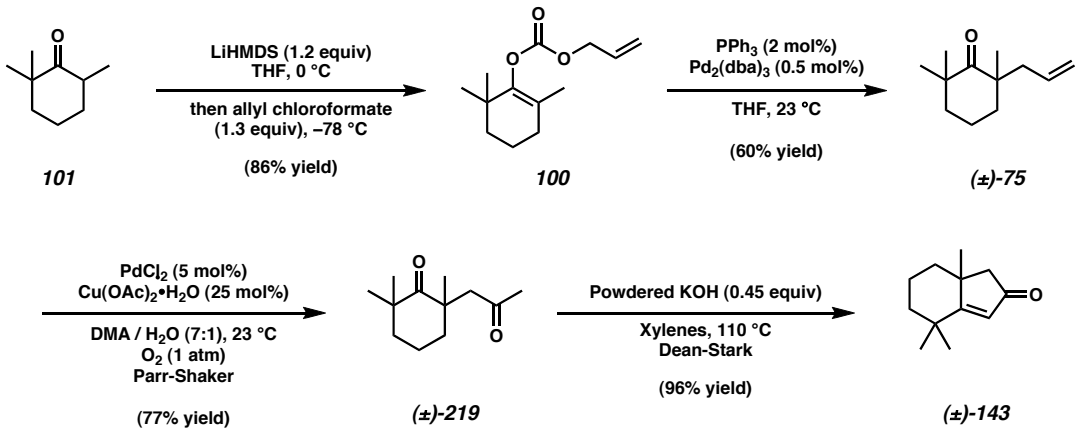
Scheme 3.17 Synthesis of 2,2,6-trimethylcyclohexanone



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).[25] Conveniently, we found that if PPh_3 was employed as an achiral ligand, a

racemic Tsuji allylation[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 **(±)-75** was found to be volatile.[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



We believed that a Wacker oxidation would be ideal for installation of a second ketone moiety of **(±)-219** (Scheme 3.18).[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

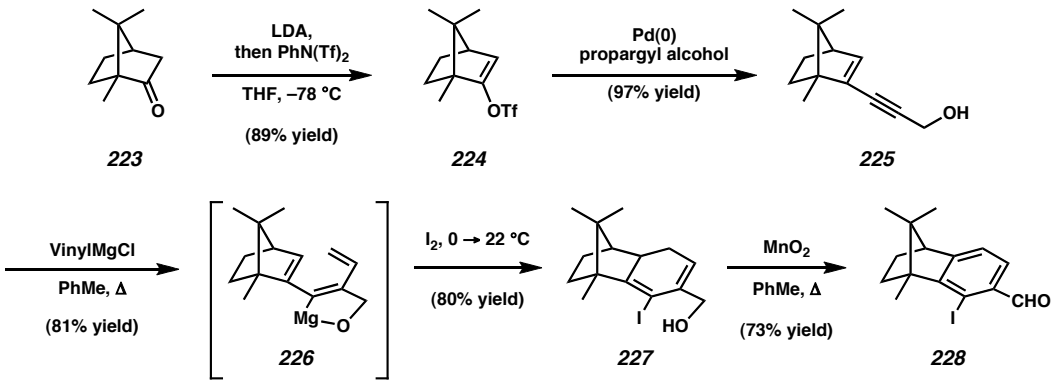
inefficient catalyst turnover was due to poor reoxidation of the palladium after substrate oxidation. Without enough O_2 in solution, Pd^0 could not be regenerated. To increase the amount of O_2 uptake in these Wacker oxidations, we placed the reactions on a Parr shaker under a balloon of oxygen. With 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,[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,[30] bicyclic enone **(±)-143** could be prepared in excellent yield.[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*

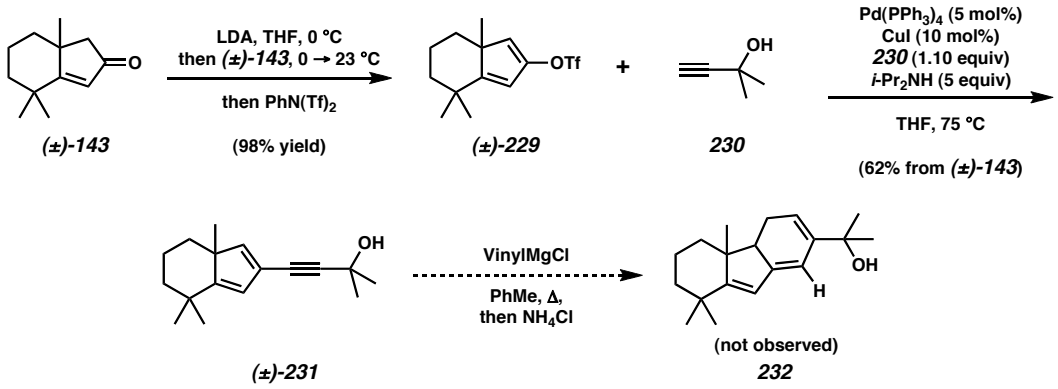
With the second carbocyclic ring of the natural product in place, we began to think of methods for installing the third ring. Fallis had recently reported a 6π-electrocyclization approach toward the benzannulation of certain ketones (Scheme 3.19).[32] In his method, a ketone (e.g., **223**) was converted 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**).

Scheme 3.19 Fallis' Benzannulation



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 $Pd(PPh_3)_4$ 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.

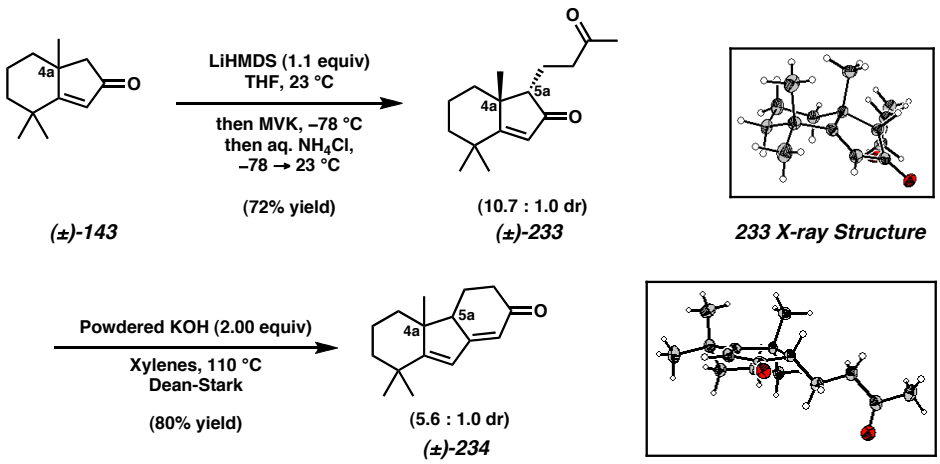
Scheme 3.20 Attempted Electrocyclization



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 enoalte, 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.

Scheme 3.21 Robinson Annulation Approach



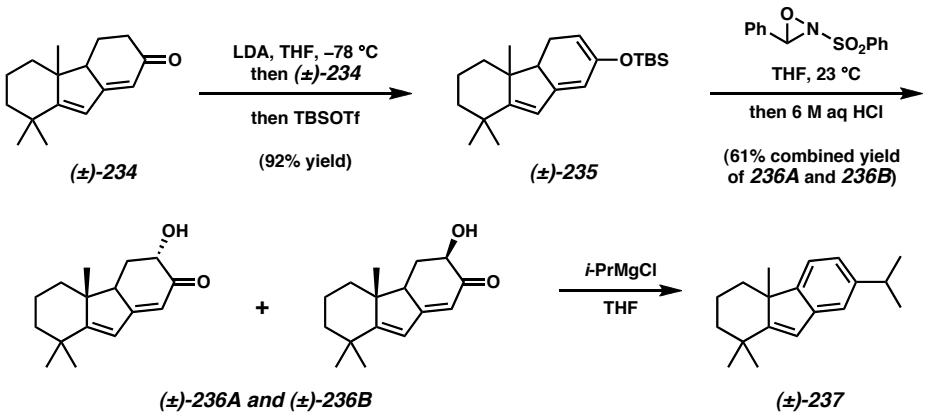
To complete the two-step Robinson annulation, an intramolecular aldol condensation was necessary. We turned to the conditions previously used to prepare bicyclic enone **(±)-143** (Scheme 3.21). When 0.45 equivalents of KOH were used, conversion of **(±)-233** to **(±)-234** was limited. However, if 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**.

Scheme 3.22 Installing an Extra Oxygen Atom



(±)-234 *(±)-235* ***(±)-236A and (±)-236B*** *(±)-237*

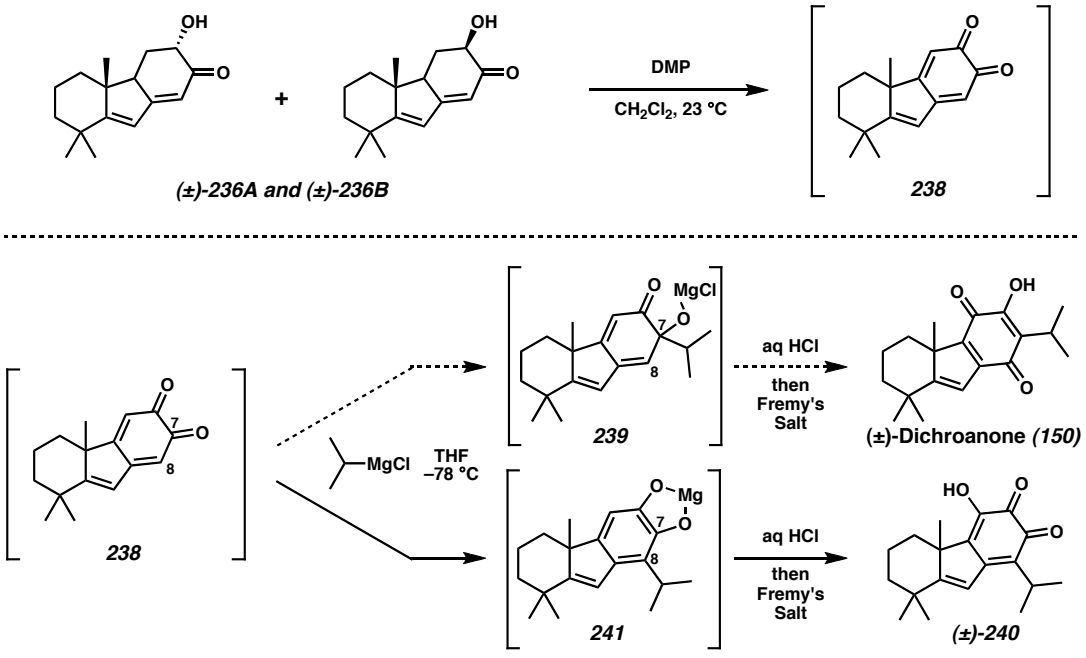
To this end, we treated tricyclic enone **(±)-234** with LDA, followed by TBSOTf, furnishing silyl enol ether **(±)-235**. A battery of oxidation conditions were tested for synthesizing an α-hydroxylketone, including MoOPH,[33,34] Rubottom oxidation,[35] dimethyl dioxirane,[36] and methyl phenyl dioxirane.[37] The Davis oxaziridine[38] proved most effective for this transformation, giving two partially separable diastereomeric acyloins **(±)-236A** and **(±)-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 **(±)-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 **(±)-236A** and **(±)-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 °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 (±)-dichroanone (**150**).

Scheme 3.23 Synthesis of a Dichroanone Isomer



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

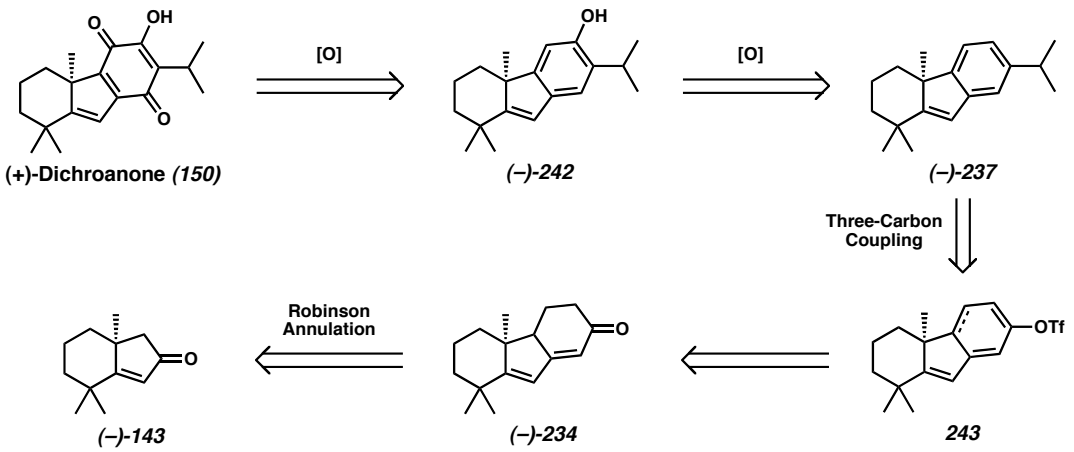
3.6.1 *Lessons Learned*

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.

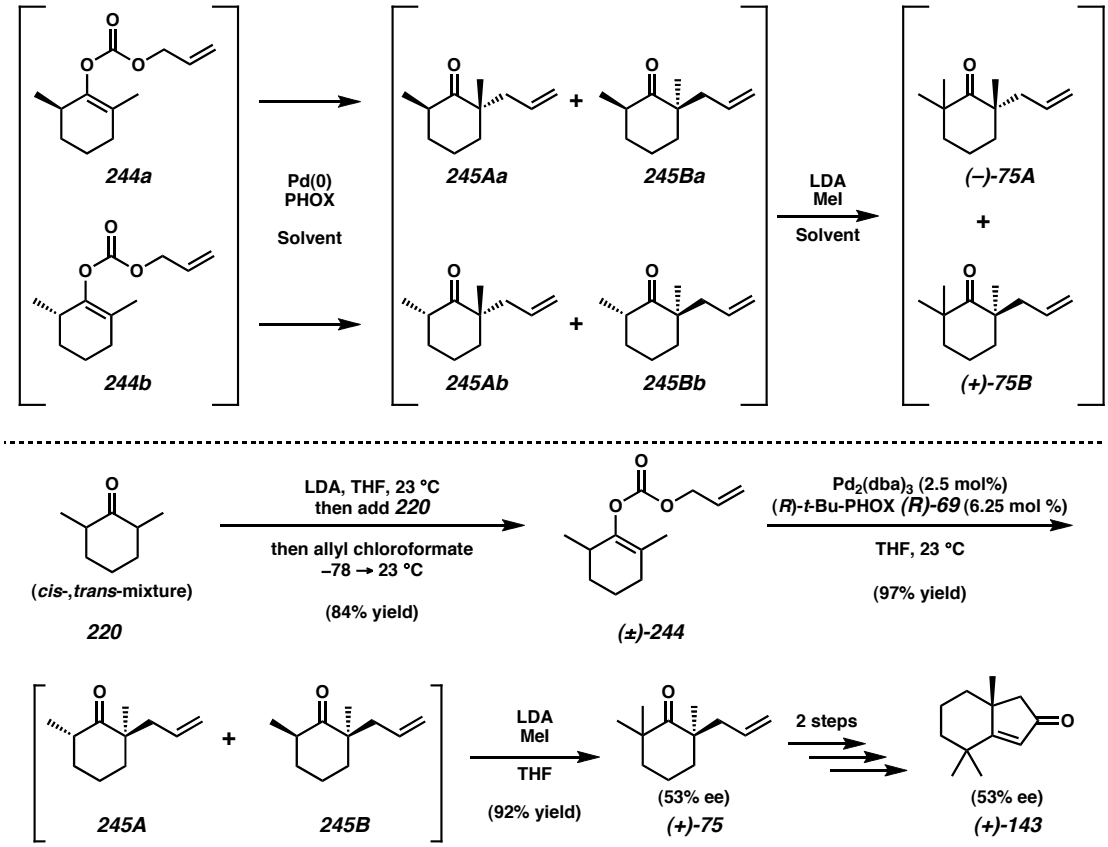
Scheme 3.24 Second Retrosynthetic Analysis of Dichroanone



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

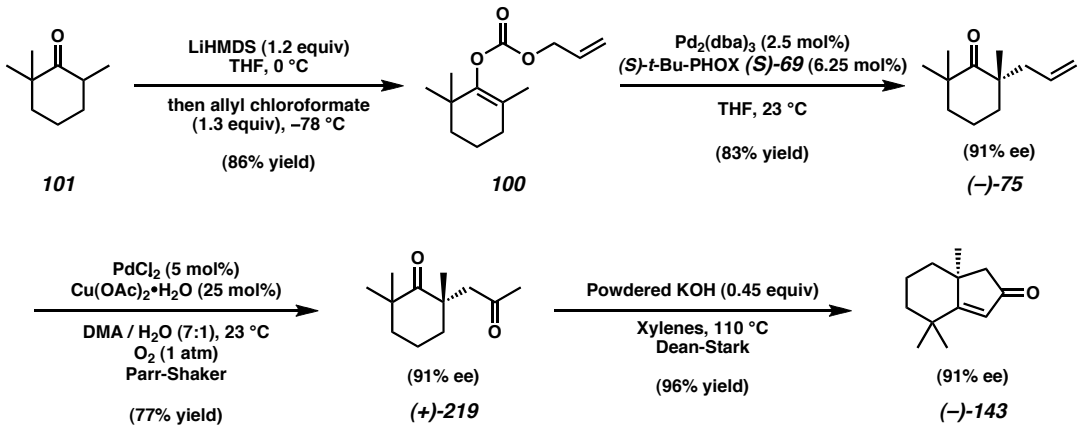


To test the viability of this approach, racemic **244** was prepared in high yield and treated with (*R*)-*t*-Bu-PHOX ***(R)*-69** and $Pd_2(dba)_3$ in THF (Scheme 3.25). A rapid reaction led to a mixture of two diastereomeric products **245A** and **245B**. This mixture was then treated with LDA and 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 gainied 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, **100** (Scheme 3.26). Pd-catalyzed enantioselective decarboxylative allylation furnished tetrasubstituted allyl ketone **(–)-75** 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 **(–)-75** 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.

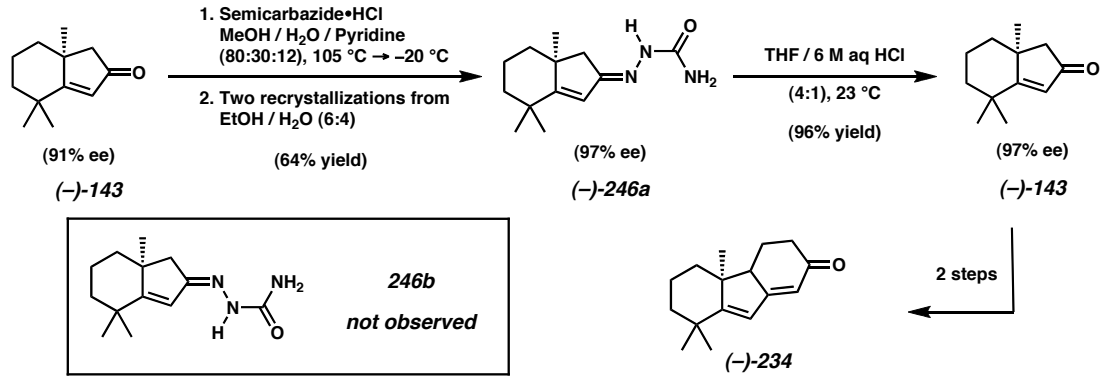
Scheme 3.26 Preparation of the Bicyclic Enone



Thus, we advanced material to the bicyclic enone **(–)-143**. We thought this might be a suitable candidate for conversion to a crystalline imine analog, but we were aware that two imines **(–)-246a** 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[39] 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

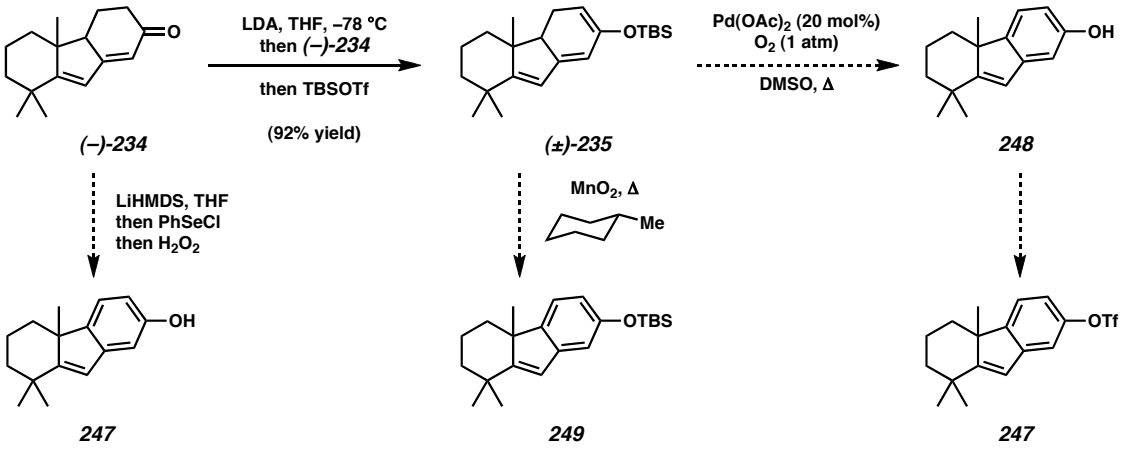


3.7 Preparation and Manipulation of a Tricyclic Phenol

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.

Scheme 3.28 Proposed Routes to the Aryl Triflate



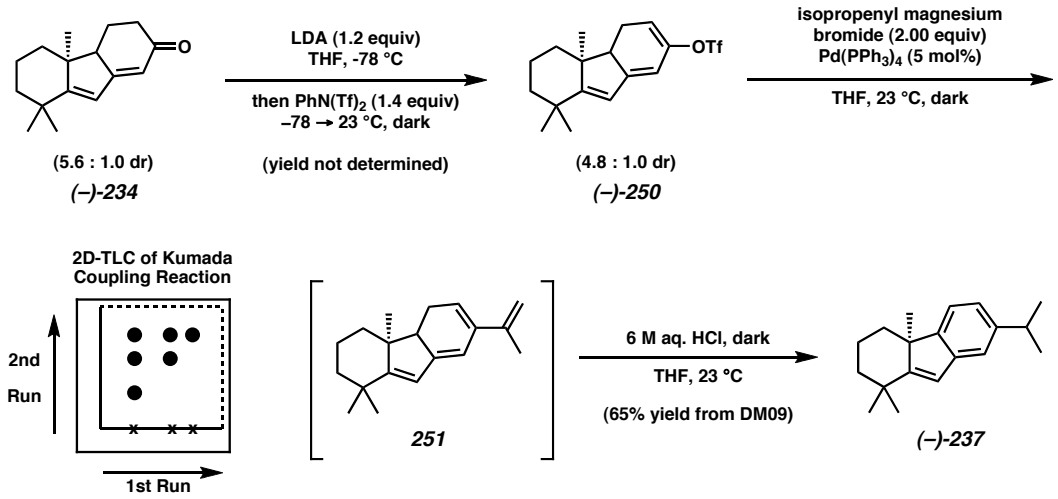
Preparation of TBS enol ether **(±)-235** had been facile, so we tested aromatization chemistry developed by Corey and Lazerwith.[40] Treatment of **(±)-235** with MnO_2 in methylcyclohexane did not affect oxidation in our hands. The Saegusa-Ito oxidation of silyl enol ethers to enones also appeared viable in this scenario.[41] 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 (R_f) converted irreversibly to a mixture of the other two. The middle R_f compound converted irreversibly to the highest R_f product only.

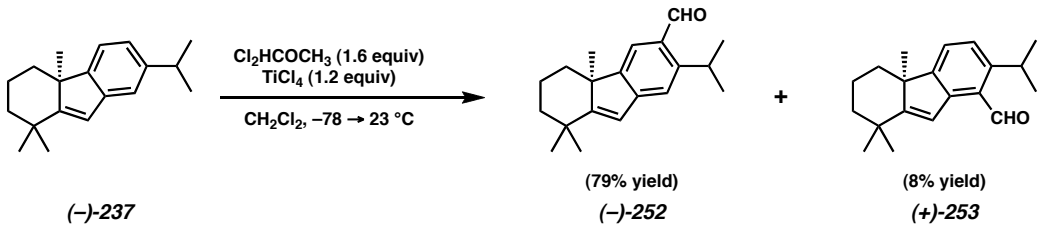
Based on these observations, we reasoned that acid-promoted rearrangements were occurring, and that the two low-R_f spot were olefin isomers of **251**.[42] We believed the high-R_f product was the thermodynamic product of the rearrangement and, possibly, arene **(–)-237**. To test this hypothesis, a 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 **(±)-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 α,α-dichloromethyl methyl ether in CH_2Cl_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 *ortho* to the styrenyl vinyl group.

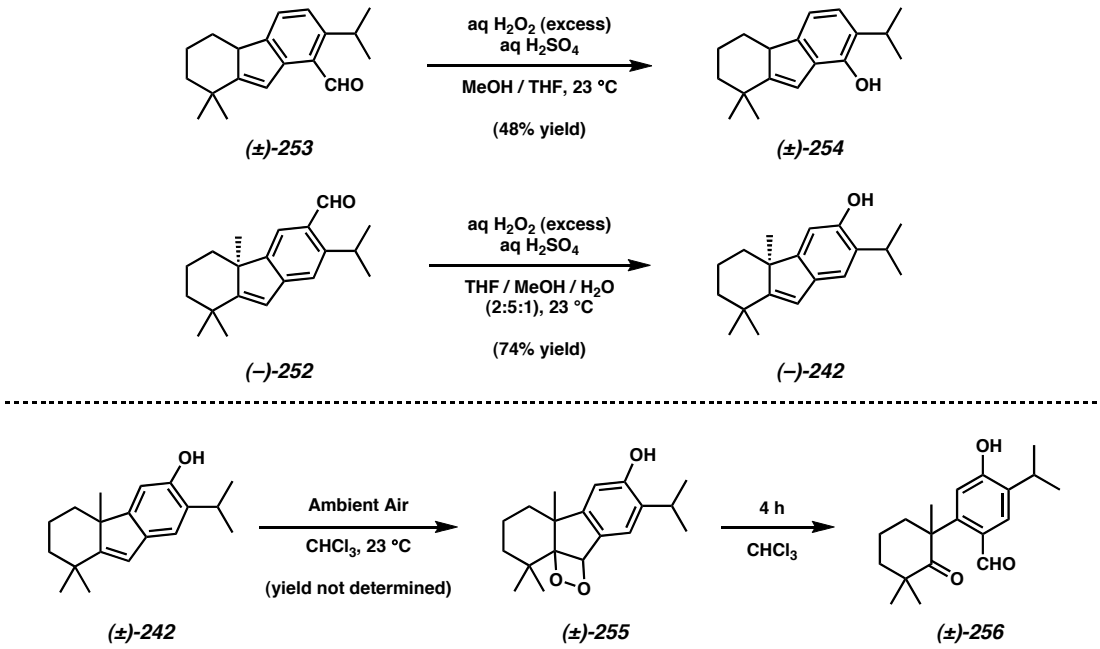
Scheme 3.30 Synthesis of the Two Aldehydes



Both aldehydes could be converted to their corresponding phenols **(–)-242** and **(±)-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

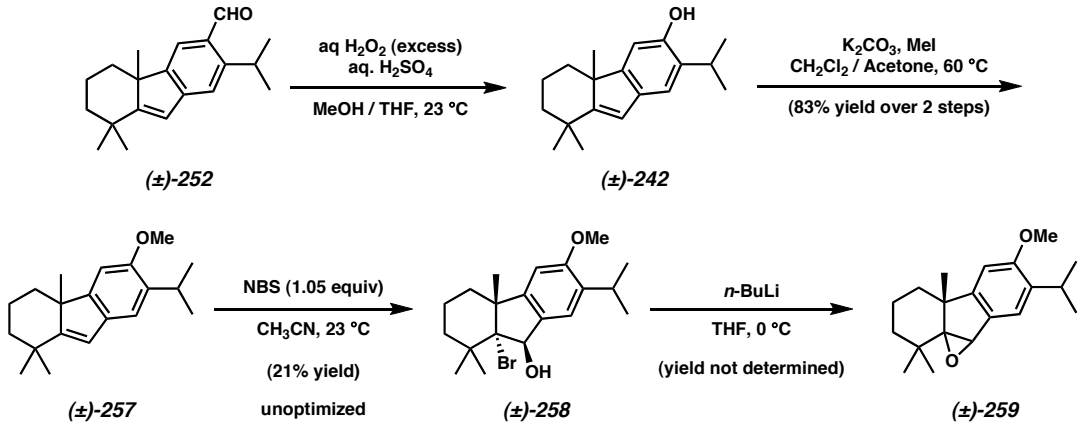


3.7.4 *Protecting Group Strategies*

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_3CN, 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.[44]

Scheme 3.32 Studies with the Methyl Ether



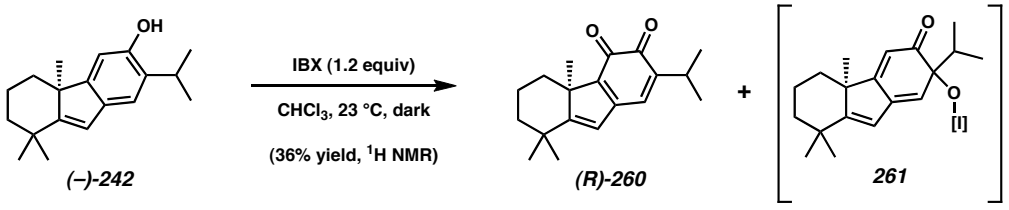
3.8 Total Synthesis of Dichroanone

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.[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.[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 (**(+)-150**).

Scheme 3.33 Preparation of the *o*-Quinone

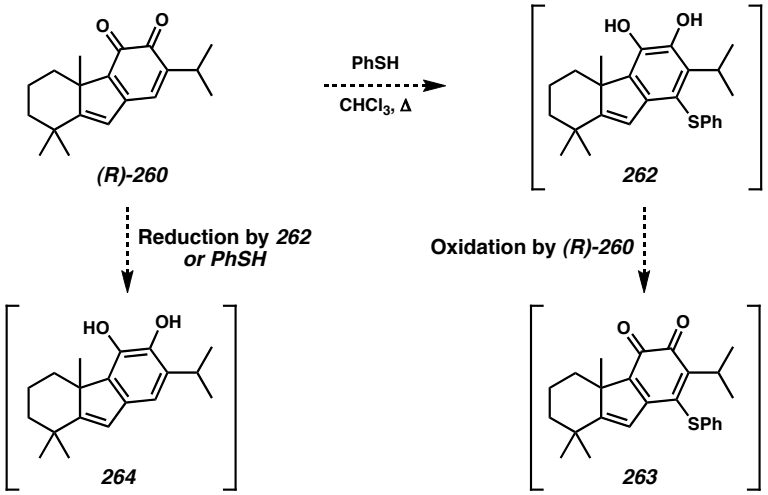


3.8.2 *Thiol Additions into the o-Quinone*

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).

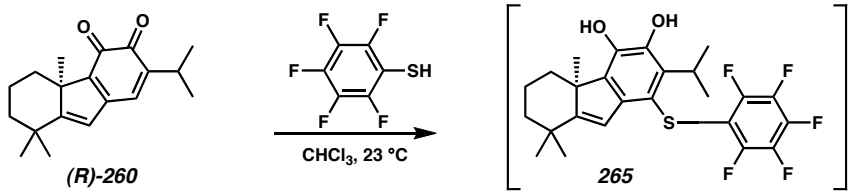
Scheme 3.34 Nucleophilic Additions of Thiophenol



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

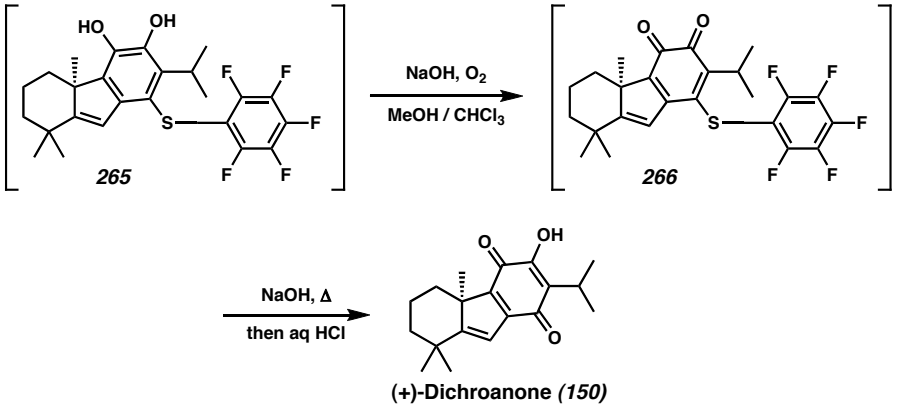


3.8.3 *Completion of Dichroanone*

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 O_2. 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**

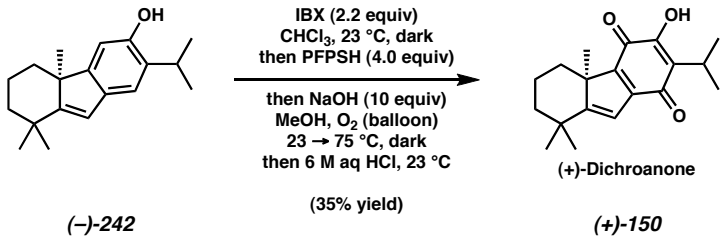
was not only an *o*-quinone, but also an activated, electron-deficient vinylogous thioester. Since NaOH was already in the reaction, we attempted a vinylogous saponification by warming the reaction.[48]

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,[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.[49]

Scheme 3.37 One-Step Synthesis of Dichroanone from the Phenol

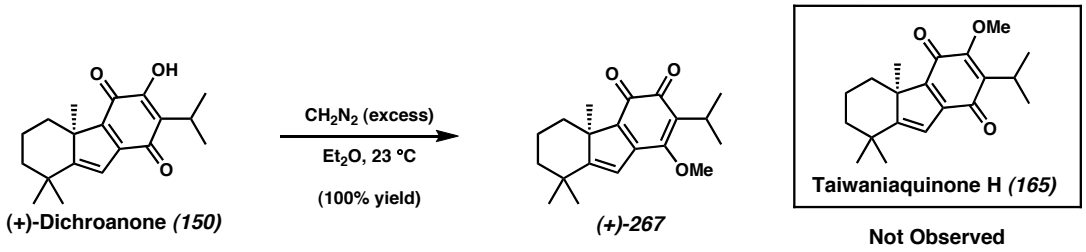


3.9 Attempts to Prepare Other Natural Products

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.[2d] Many of the ^{13}C NMR resonances differ, and two in our sample were > δ 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 (δ 3.86 ppm in our sample, but δ 3.96 ppm for the natural product.) The carbonyls in the IR spectum were also different. For these reasons, we believe that we have prepared **(+)-267** and not taiwaniaquinone H (**165**).[6,50]

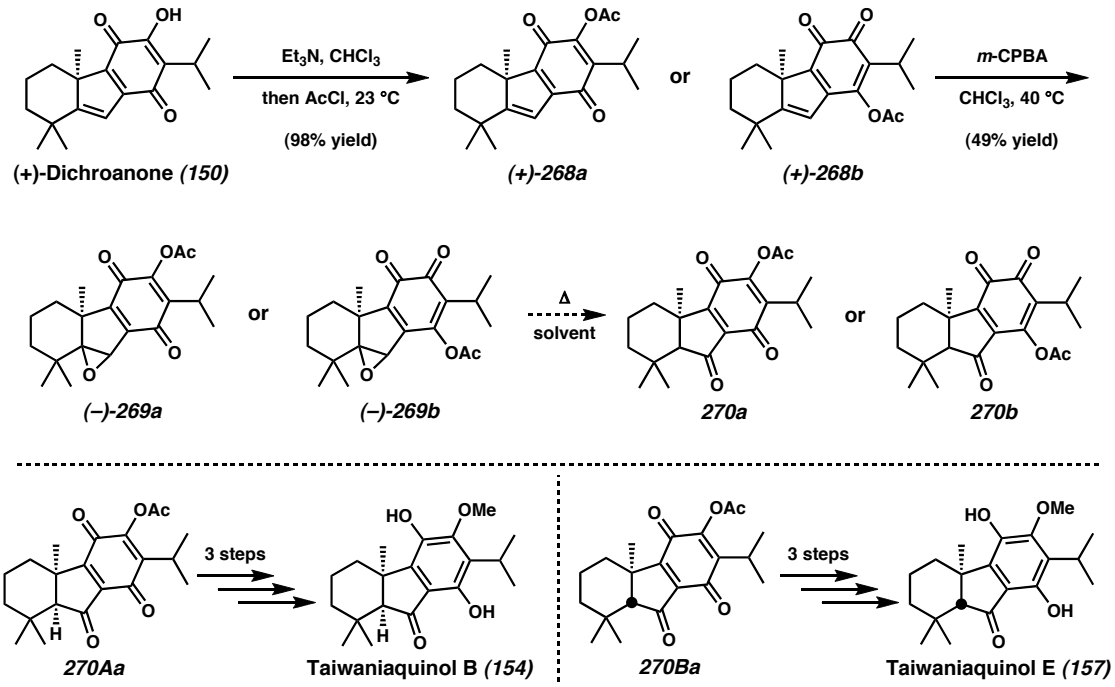
Scheme 3.38 Preparation of a Taiwaniaquinone H Isomer.



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 been.[44]

Scheme 3.39 A Potential Route to Taiwaniaquinol B or E



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.[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.

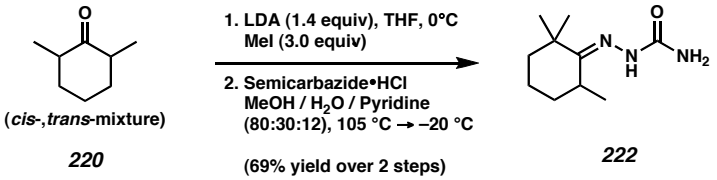
3.11 Experimental Procedures

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_2NH, and Et_3N 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*-Bu-PHOX 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 (δ 7.26 for $CDCl_3$ and δ 7.16 for C_6D_6). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz),[53] 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 (δ 77.2 for $CDCl_3$ and δ 128.4 for C_6D_6). Data for ^{13}C NMR spectra are reported in terms of chemical shift. ^{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: λ_{max} (nm) then log(ε) (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.

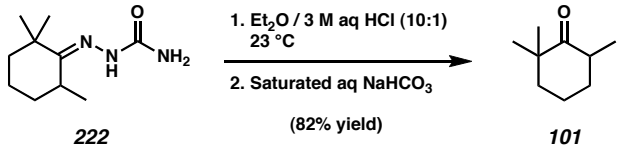
3.11.2 *Syntheses of Compounds Related to Dichroanone*



Semicarbazone 222. To a solution of *i*-Pr_2NH (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 NH_4Cl (100 mL) and H_2O (100 mL). After stirring 10 min, the reaction was diluted with H_2O (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 (Na_2SO_4), filtered, concentrated, and distilled under N_2 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 (14.0g, 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 P_2O_5, giving **222** (10.8 g, 69% over 2 steps from **220**) as a white,

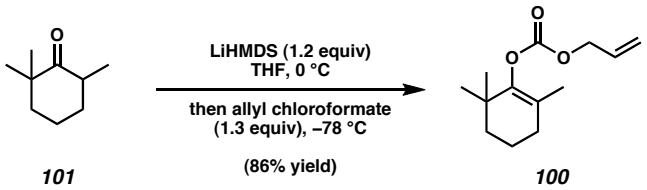
crystalline solid. R_f 0.45 (10:90 MeOH/CH_2Cl_2), (I_2/Sand, brown spot); mp 203-205 °C (water); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (s, broad, 1H), 6.05 (s, broad, 1H), 5.67 (s, broad, 1H), 2.92-2.79 (m, 1H), 1.84-1.66 (m, 1H), 1.64-1.31 (m, 5H), 1.13 (s, 3H), 1.13 (d, J = 7.7 Hz, 3H), 1.12 (s, 3H), 1.11-1.08 (m, 1H); ^{13}C 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, 2931, 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.



222 ***101***

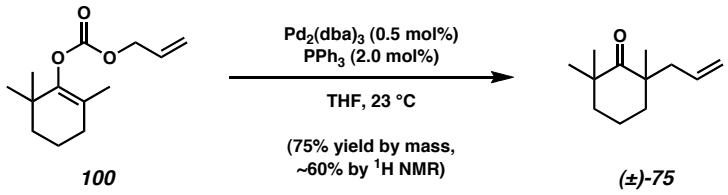
2,2,6-Trimethyl Cyclohexanone (101). To a suspension of semicarbazone **222** (10.9 g, 55.0 mmol) in Et_2O (400 mL) and water (20 mL) was added 6 M aq HCl (20 mL) in a dropwise fashion. The biphasic mixture was stirred vigorously at 23 °C for 3 h. Then, sat. aq $NaHCO_3$ (300 mL) was added cautiously 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); ^{1}H 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_t = 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. dddd, J = 13.7 Hz, 6.6 Hz, 4.1 Hz, 2.9 Hz, 1H), 1.42 (app. td, J_t = 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-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_9H_{16}O$, 140.1201; found, 140.1203.

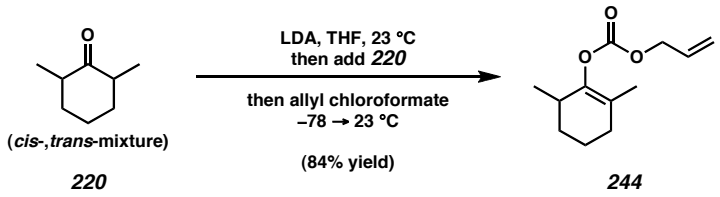


Enol Carbonate 100. A solution of LiHMDS (1.0 M in THF, 57.5 mL, 57.5 mmol) was added to THF (300 mL), then cooled to 0 °C. A solution of pure 2,2,6-trimethylcyclohexanone (**101**) (6.67 g, 47.6 mmol) in THF (10 mL) was added. The reaction was stirred at 0 °C for 1 h, then cooled to –78 °C and fitted 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_4Cl (100 mL), water (100 mL), and hexane (100 mL). After 10 min, the organic phase was collected and the aqueous phase extracted with Et_2O (3 x 75 mL). All organic layers were combined, washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (2:98 Et_2O/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.

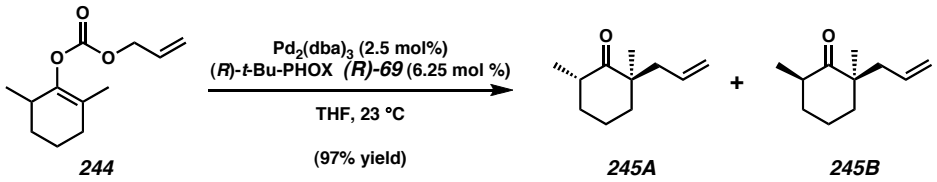


Allyl Ketone (±)-75. A round-bottom flask was flame-dried under argon and charged with $Pd_2(dba)_3$ (81.6 mg, 89.0 μmol, 0.5 mol%) and PPh_3 (93.6 mg, 0.357 mmol, 2.0 mol%). The system was evacuated with vacuum and back-filled with argon (3 x). Then THF (90 mL) was introduced. The red mixture was stirred 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).



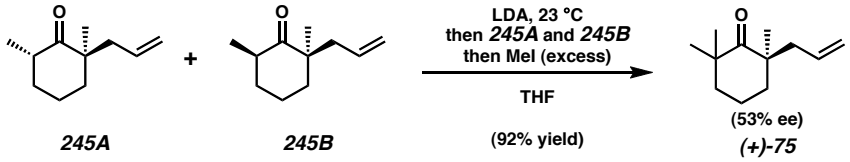
Enol Carbonate 244. A round-bottom flask was charged with THF (200 mL) and *i*-Pr_2NH (13.33 mL, 95.2 mmol, 1.2 equiv) and cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 34.9 mL, 87.2 mmol, 1.1 equiv) was added dropwise. After 30 min, 2,6-dimethyl cyclohexanone (**220**) (*cis*,*trans* mixture) (10.0 g, 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_4Cl (100 mL)and diluted with H_2O (100 mL) and hexanes (100 mL). The organic phase was collected and the aqueous layer extracted with Et_2O (2 x 100 mL). All organic layers were combined, dried (Na_2SO_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), (*p*-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, $CDCl_3$): δ 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.



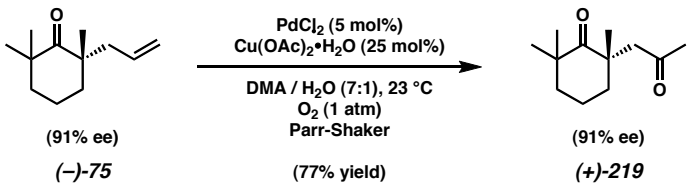
Diastereomeric Allyl Ketones 245A and **245B**. A round-bottom flask was flamedried under argon, then cycled into a glovebox. The flask was charged with $Pd_2(dba)_3$ (54.5 mg, 0.119 mmol, 2.5 mol%, 5 mol% Pd), (*R*)-*t*-Bu-PHOX (57.6 mg, 0.149 mmol, 6.25 mol%), followed by THF (70 mL). After stirring 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_2O: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, $CDCl_3$): δ 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-EI$^+$ (*m/z*): [M]$^+$ calc'd for $C_{11}H_{18}O$, 166.1358; found, 166.1357.

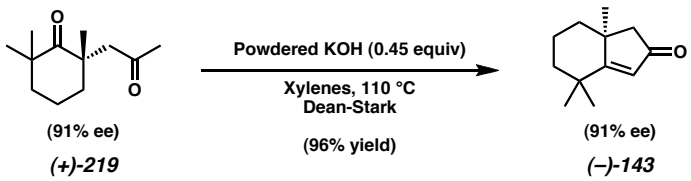


Allyl Ketone (+)-75. A round-bottom flask was charged with THF (20 mL) and *i*-PrNH_2 (556 μL, 3.97 mmol, 2.20 equiv), then cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 1.44 mL, 3.61 mmol, 2.05 equiv) was added dropwise, and the reaction stirred for 30 min. Then, a solution of diastereomeric allyl cyclohexanones **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_4Cl (5 mL) was added. 10 min later, the reaction was diluted with hexanes (10 mL) and H_2O (10 mL). The organic phase was collected and the aqueous layer extracted with Et_2O (3 x 20 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated at 10 °C in vacuo. The residue was purified by flash chromatography on silica gel (hexane → Et_2O/hexane 4:96 eluent) affording allyl ketone **(+)-75** (291 mg, 92% yield) in 53% ee as determined by derivatization to enone **(+)-143**

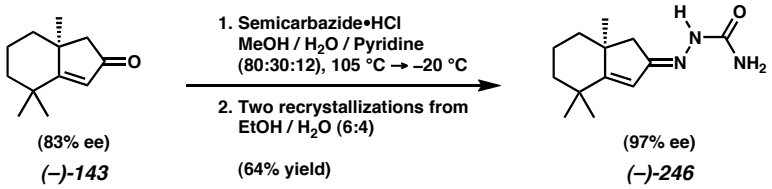
and chiral HPLC assay. Characterization data can be found on pages 40 and 41 (chapter 2).



Diketone (+)-219. A Parr flask was charged with $PdCl_2$ (74.5 mg, 0.420 mmol, 5 mol%), $Cu(OAc)_2 \bullet H_2O$ (381 mg, 2.10 mmol, 25 mol%), *N*,*N*-dimethyl acetamide (17.5 mL), and water (2.5 mL). Then allyl ketone **(–)-75** (1.51 g, 8.39 mmol, 1.0 equiv) was introduced. The system was cooled to –78 °C and evacuated with vacuum and back-filled from a balloon of O_2 (3 x). The mixture was warmed to 23 °C and placed on a Parr shaker for 24 h under a balloon of O_2. The reaction was then directly loaded onto a silica gel column and purified by flash chromatography (15:85 Et_2O:pentane → 25:75 Et_2O:pentane eluent), affording diketone **(+)-219** (1.27 g, 77% yield) as a clear oil. R_f 0.44 (1:4 EtOAc:hexane), ($KMnO_4$, yellow spot); ^1H NMR (300 MHz, $CDCl_3$): δ 3.26 (AB spin system, d, J_{AB} = 18.4 Hz, 1H), 2.32 (AB spin system, d, J_{AB} = 18.4 Hz, 1H), 2.05 (s, 3H), 2.00-1.72 (m, 3H), 1.71-1.53 (m, 2H), 1.47 (app. ddd, J = 12.0 Hz, 5.4 Hz, 2.8 Hz, 1H), 1.16 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.7, 206.9, 55.7, 45.0, 44.4, 38.9, 36.9, 30.2, 27.9, 27.8, 27.0, 18.2; IR (NaCl/$CDCl_3$): 2965, 2943, 2924, 2868, 1715, 1694, 1463, 1394, 1379, 1360, 1147, 1034 cm^{-1}; HRMS-EI^+ (*m/z*): $[M]^+$ calc'd for $C_{12}H_{20}O_2$, 196.1463; found, 196.1456; $[\alpha]^{27}_D$ +71.96° (*c* 0.200, $CHCl_3$), 91% ee.

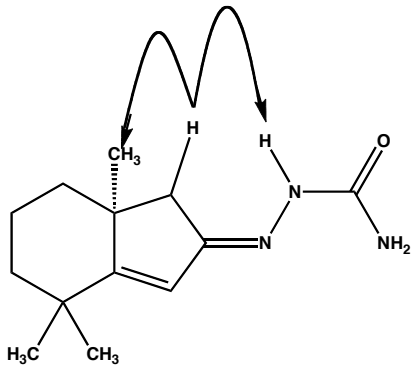


Bicyclic Enone (–)-143. To a solution of diketone **(+)-219** (1.21 g, 6.15 mmol, 1.0 equiv) in xylenes (25 mL) was added freshly powdered KOH (155 mg, 2.76 mmol, 0.45 equiv). The reactor was fitted with a Dean-Stark trap and heated to 110 °C for 11 h. The reaction was cooled to 23 °C and directly loaded onto a column of silica gel and purified by flash chromatography (pentane → 5:95 Et_2O/pentane → 50:50 Et_2O/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); $[\alpha]^{25}_D$ –87.21° (*c* 0.280, $CHCl_3$), 91% ee.

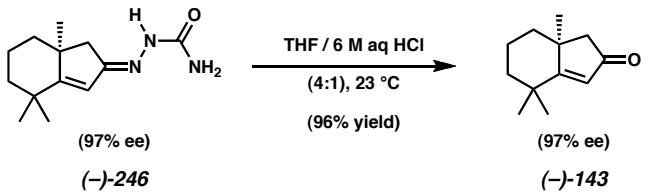


Bicyclic Semicarbazone (–)-246. To a suspension of bicyclic enone **(–)-143** (1.70 g, 9.51 mmol, 83% ee) in MeOH (27.1 mL), water (10.2 mL), and pyridine (4.07 mL) was added semicarbazide hydrochloride (1.91 g, 17.1 mmol). The reaction was refluxed at 105 °C for 2 h. Then, the reaction was cooled to –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

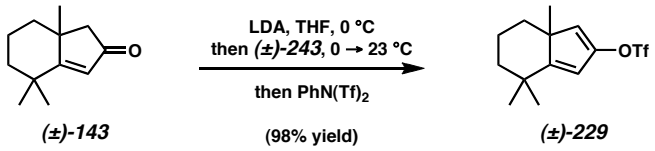
reaction was allowed to cool in the oil bath to 23 °C. After 10 h, the crystals were filtered and suspended in EtOH (100 mL). The suspension was heated to 100 °C, and water (72 mL) was added dropwise as before, followed by EtOH (200 μL). The white, flaky crystals were grown in the same way and collected by filtration, washed with water, and dried over P_2O_5 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. R_f 0.46 (10:90 MeOH/CH_2Cl_2), (UV, 254 nm); mp 227-229 °C (water); ^{1}H NMR (300 MHz, $CDCl_3$): 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, J_{AB} = 16.8 Hz, 1H), 2.29 (AB spin system, d, J_{AB} = 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{13}H_{22}N_3O$, 236.1761; found, 236.1763; $[\alpha]^{25}_D$ –103.70° (*c* 0.100, $CHCl_3$), 97% ee. ^{1}H-^{1}H nOesy-1D spectra were obtained for **(–)-246** (300 MHz, $CDCl_3$); the results are shown below:



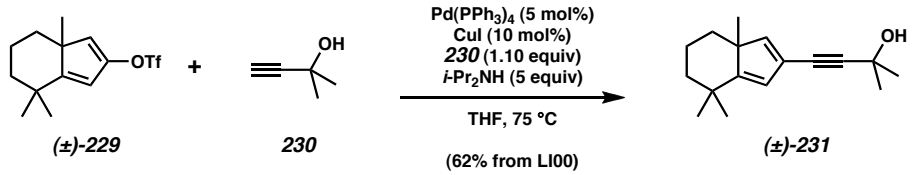
nOe's detected for *(–)-246*



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 $NaHCO_3$ (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 Et_2O (3 x 75 mL). All organic layers were combined, washed with brine (75 mL), dried (Na_2SO_4), filtered, and concentrated, giving enantioenriched bicyclic enone **(–)-143** (944 mg, 96% yield, 97% ee) as a clear, fragrant oil. R_f 0.37 (1:4 EtOAc/hexane), (UV, 254 nm); mp 9-11 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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/$CDCl_3$): 2997, 2987, 2960, 2929, 2868, 2847, 1712, 1696, 1600, 1459, 1261, 1166 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{12}H_{18}O$, 178.1358; found, 178.1356; $[\alpha]^{24}_D$ –102.40° (*c* 0.200, $CHCl_3$), 97% ee.

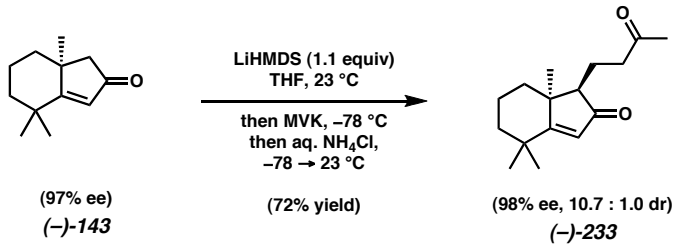


Dienyl Triflate (±)-229. A round-bottom flask was charged with THF (16 mL) and freshly distilled *i*-Pr_2NH (256 μL, 1.82 mmol, 1.30 equiv) and cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 673 μL, 1.68 mmol, 1.20 equiv) was added dropwise. After 30 min, a solution of bicyclic enone **(±)-143** (250 mg, 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_3N (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_3N:Et_2O: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); ^1H NMR (300 MHz, C_6D_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_6D_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_6D_6): δ −74.11, −71.69; IR: (not obtained); HRMS: (not performed).



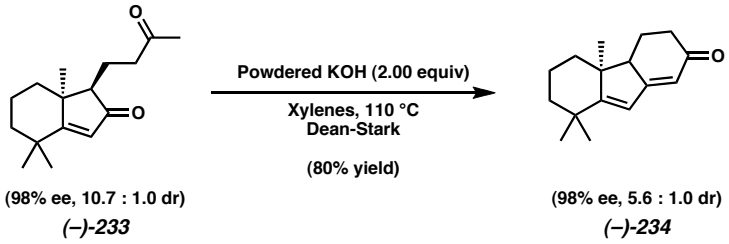
Propargylic Alcohol (±)-231. A round-bottom flask was charged with CuI (27 mg, 0.14 mmol, 10 mol%), followed by a solution of $Pd(PPh_3)_4$ (80 mg, weighed in glovebox, 70 μmol, 5 mol%) in THF (10 mL) (reaction was yellow). Then, freshly distilled *i*-Pr_2NH (981 μL, 7.00 mmol, 5.0 equiv) was added (reaction 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 Et_2O. The filtrate was concentrated, then purified by flash column chromatography on silica gel (10:90 Et_2O: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 Et_2O:hexane → 20:80 Et_2O:hexane → 50:50 Et_2O: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, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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/$CDCl_3$): 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.



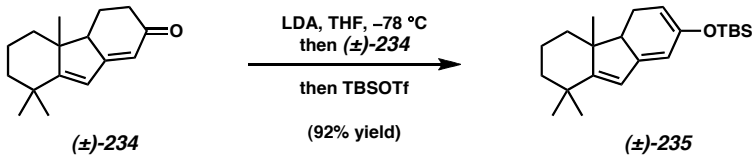
Keto-Enone (–)-233. To a solution of LiHMDS (0.943M in THF, 3.27 mL, 3.09 mmol) in THF (29 mL) at 23 °C was added a solution of enantioenriched bicyclic enone **(–)-143** (981 mg, 5.51 mmol) in THF (12 mL) in a dropwise fashion over 3 min. After 1 h, the reaction was cooled to –78 °C, and methyl vinyl 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_4Cl (5 mL) and water (5mL) at –78 °C. Then, the reaction was warmed to room temperature and diluted with hexanes (20 mL) and H_2O (20 mL). After collecting the organic phase, the aqueous phase was extracted with Et_2O (3 x 15 mL). All organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (1:9 Et_2O/pentane → 2:8 Et_2O/pentane → 4:6 Et_2O/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_2O/pentane) (98% ee), mp 62-64 °C (Et_2O/pentane) (83%

ee) mp 42-44 °C (Et_2O/pentane) (0% ee); ^1H NMR (300 MHz, $CDCl_3$), (major diastereomer): δ 5.76 (s, 1H), 2.89 (qd, J_q = 9.1 Hz, J_d = 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); ^{13}C NMR (75 MHz, $CDCl_3$), (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, 2871, 1710, 1691, 1598, 1460, 1420, 1381, 1372, 1357, 1269, 1161 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{16}H_{24}O_2$, 248.1776; found, 248.1774; $[\alpha]^{27}_D$ –15.79° (*c* 0.220, $CHCl_3$), 98% ee.



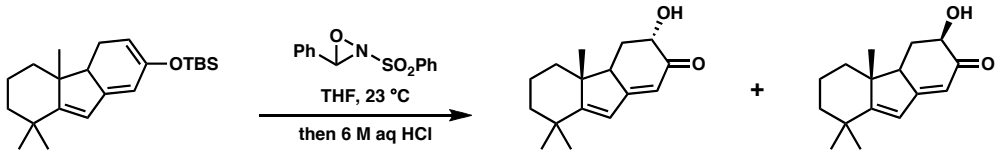
Tricyclic Dienone (–)-234. To a solution of keto-enone **(–)-233** (457 mg, 1.60 mmol, 1.00 equiv) in xylenes (18 mL) was added freshly powdered KOH (207 mg, 3.69 mmol, 2.00 equiv). The reactor was fitted with a Dean-Stark trap and heated to 110 °C for 14 h in the dark. The reaction was cooled to 23 °C and directly loaded onto a column of silica gel and purified by flash chromatography (pentane → 2:8 Et_2O:pentane → 6:4 Et_2O: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. R_f 0.28 (1:4 EtOAc/hexane), (UV, 254 nm), (first diastereomer) R_f 0.19 (1:4 EtOAc/hexane), (UV 254 nm), (second diastereomer); ^1H NMR (300 MHz, $CDCl_3$), (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 = 12.4H, 2H), 1.39-1.24 (m, 2H), 1.16 (s, 6H), (1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), (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/$CDCl_3$): 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 $C_{16}H_{22}O$, 230.1671; found, 230.1668; $[\alpha]^{25}_D$ –224.40° (*c* 0.550, $CHCl_3$), 98% ee.



Silyl Enol Ether (±)-235. A round-bottom flask was charged with THF (12.5 mL) and *i*-Pr_2NH (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 Et_3N (1.0 mL). The solution was directly loaded onto a column of silica gel and rapidly purifed by flash column chromatography (5:5:9 Et_3N:Et_2O: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, C_6D_6)(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); ^{13}C NMR (75 MHz, C_6D_6): 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-EI$^+$ (*m/z*): [M]$^+$ calc'd for $C_{22}H_{36}OSi$, 344.2536; found, 344.2532.

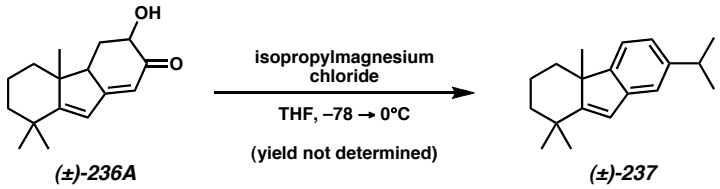


(±)-235 *(±)-236A and (±)-236B*

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 Et_2O 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 H_2O and hexanes, and the organic phase was collected. The aqueous layer was extracted with Et_2O (3 x). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (10:90 EtOAc:hexane → 20:80 EtOAc:hexane → 50:50 EtOAc:hexane → EtOAc eluent), giving two acyloin products, **(±)-236A** and **(±)-236B**, whose relative configurations were not assigned. The high R_f product, **(±)-236A** (70 mg, 17% yield), was obtained in semipure form and had

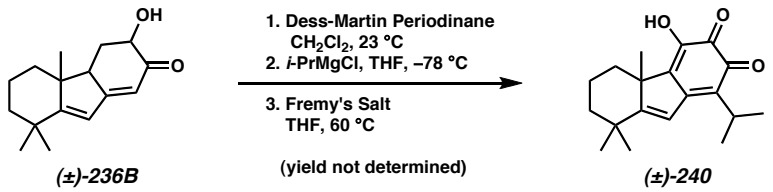
the following characteristics: R_f (not measured) (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.07 (s, 1H), 5.82 (app. dd, J = 20.4 Hz, 2.5 Hz, 1H), 4.12 (app. dddd, J = 12.7 Hz, 5.0 Hz, 2.5 Hz, 1.9 Hz, 1H), 3.95 (s, broad, 1H), 2.70 (app. dddd, J = 12.7 Hz, 6.9 Hz, 4.4 Hz, 2.8 Hz, 1H), 2.60-2.48 (m, 2H), 2.41-2.29 (m, 1H), 2.32 (app. td, J_t = 16.8 Hz, J_d = 5.2 Hz, 1H), 1.93-1.51 (m, 4H), 1.17 (app. s, 6H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (not obtained due to modest purity of compound); IR (NaCl/$CDCl_3$): 3460 (broad), 2931, 2868, 2847, 1655, 1613, 1582, 1459, 1320, 1212, 1182, 1107, 887 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{16}H_{22}O$, 246.1620; found, 246.1616.

The low R_f product, **(±)-236B** (176 mg, 44% yield) was also obtained in semipure form and had the following characteristics: R_f (not measured) (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 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. ddd, J = 11.3 Hz, 4.4 Hz, 2.5 Hz, 1H), 2.10 (app. ddd, J = 13.5 Hz, 4.7 Hz, 3.0 Hz, 1H), 1.90 (app. ddd, 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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/$CDCl_3$): 3386 (broad), 2960, 2927, 2868, 2848, 1643, 1612, 1582, 1459, 1327, 1164, 1058, 888 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{16}H_{22}O$, 246.1620; found, 246.1630.



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 NH_4Cl (400 μL). Then H_2O (2 mL) was added, and the material extracted with Et_2O (3 x 4 mL). All organic layers were combined, dried (Na_2SO_4), 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.



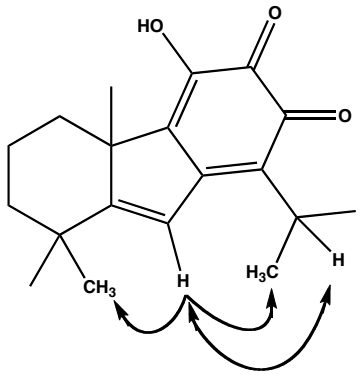
Isodichroanone (±)-240. A solution of acyloin **(±)-236B** (475 mg, 1.93 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was treated with Dess-Martin Periodinane (1.634 g, 3.86 mmol, 2.0 equiv) at 23 °C for 2 h. The reaction was then filtered through silica gel presaturated with Et_3N/CH_2Cl_2. The filtrate was 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 H_2O (15 mL) was added, and organic phase was collected. The aqueous layer was

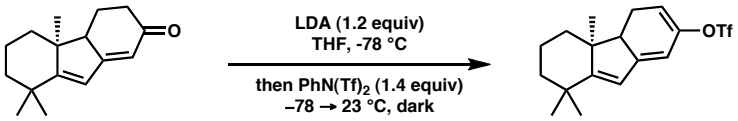
extracted with Et_2O (3 x 10 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and adsorbed to 750 μL of silica gel. The material was purified by flash column chromatography on silica gel (10:90 EtOAc:hexane → 20:80 EtOAc:hexane eluent), and the orange product (mass not determined) was 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 H_2O (20 mL). The organic layer was collected, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5:95 EtOAc:hexane → 20:80 EtOAc:hexane eluent), 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. R_f (not determined); ^{1}H NMR (300 MHz, $CDCl_3$): 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, J_q = 13.6 Hz, J_t = 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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/$CDCl_3$): 3267 (broad), 2961, 2930, 2871, 1738, 1641, 1574, 1403, 1100 cm^{-1}; LRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{19}H_{24}O_3$, 300; found, 300. ^{1}H-^{1}H homodecoupling experiments (600 MHz, $CDCl_3$) 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:



nOe's detected for *(±)-240*



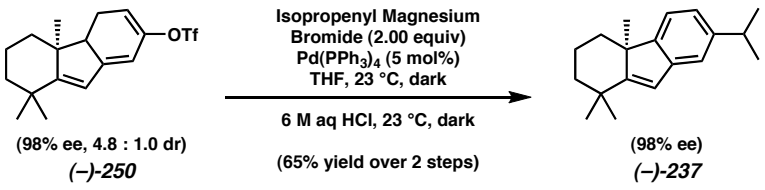
(98% ee, 5.6 : 1.0 dr)
(–)-234

(yield not determined)

(98% ee, 4.8 : 1.0 dr)
(–)-250

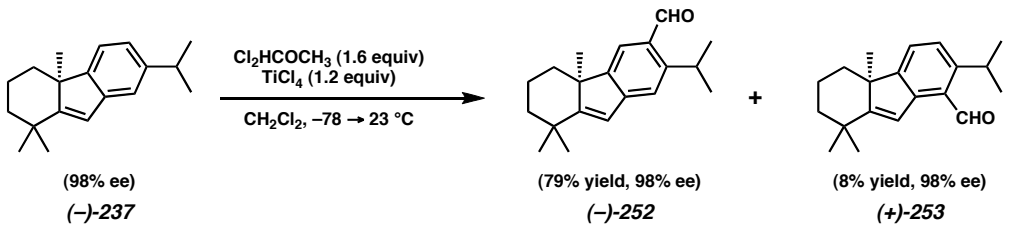
Tricyclic Enol Triflate (–)-250. A solution of *i*-Pr_2NH (186 μL, 1.33 mmol) in THF (17 mL) was cooled to 0 °C, and *n*-BuLi (2.55 M in hexanes, 482 μL, 1.23 mmol) was added dropwise. After 30 min, the reaction was cooled to –78 °C, and a solution of tricyclic dienone **(–)-234** (236 mg, 1.03 mmol) 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_3N (5 mL) and concentrated to ~ 5 mL total volume. Then hexane (10 mL) and more Et_3N (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 Et_3N/Et_2O/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. ^{1}H NMR revealed the product to be an inseparable mixture of diastereomers. R_f 0.80 (2:8:1 EtOAc/hexane/Et_3N, TLC plate is pre-eluted), (Ceric Ammonium Molybdate, blue spot) (both diastereomers); ^{1}H NMR (300 MHz, C_6D_6): δ 5.66 (s, 1H), 5.58 (app. dd, J = 2.5 Hz, 2.2 Hz, 1H), 5.31 (app. dtd, J_{d1} = 6.6 Hz, J_t = 2.2 Hz, J_{d2} = 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, J_d = 14.8 Hz, J_t = 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); ^{13}C NMR (75 MHz, C_6D_6): 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; ^{19}F NMR (282 MHz, C_6D_6): 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 $C_{17}H_{21}F_3O_3S$, 362.1164; found, 362.1166; $[\alpha]^{25}_D$ –11.24° (*c* 0.700, hexane), 98% ee.



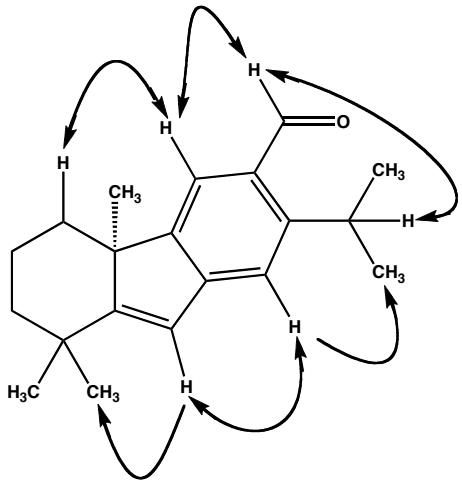
Arene (–)-237. To a solution of crude tricyclic enol triflate **(–)-250** (~371 mg, 1.03 mmol) in THF (50 mL) was added isopropenyl magnesium bromide (0.5 M in THF, 4.12 mL, 2.06 mmol), and the round-bottom flask was immediately covered in foil. Then a

solution of $Pd(PPh_3)_4$ (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 Et_2O (3 x 30 mL). All organic layers were combined, washed with brine (30 mL), dried (Na_2SO_4), 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. R_f 0.43 (hexane), (UV 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): 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, J_q = 13.8 Hz, J_t = 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, J_t = 12.9 Hz, J_d = 3.7 Hz, 1H), 1.05 (td, J_t = 13.2 Hz, J_d = 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 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/$CDCl_3$): 3061, 2995, 2959, 2928, 2866, 2845, 1616, 1479, 1458, 1382, 1369, 1362, 886, 820 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{19}H_{26}$, 254.2035; found, 254.2046; $[\alpha]^{24}_D$ –80.74° (*c* 0.320, $CHCl_3$), 98% ee.



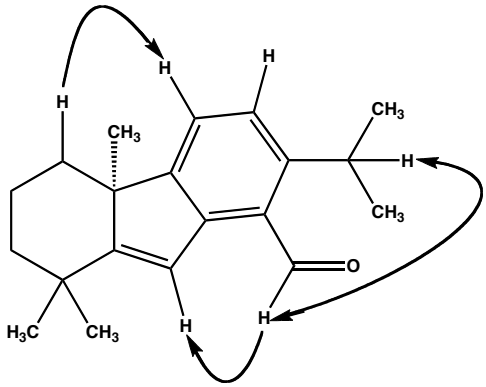
Aldehydes (–)-252 and **(+)-253**. A solution of arene **(–)-237** (156 mg, 0.614 mmol) in CH_2Cl_2 (15 mL) was cooled to –78 °C and α,α-dichloromethyl, methyl ether (89.0 μL,

0.982 mmol) was introduced, followed by $TiCl_4$ (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 CH_2Cl_2 (10 mL). After stirring vigorously for 1 h, the organic phase was collected. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). All organic layers were combined, washed with water (20 mL), sat. aq $NaHCO_3$ (30 mL), and brine (30 mL), then dried (Na_2SO_4), filtered, and adsorbed onto silica gel. The adsorbed products were separated by flash chromatography on silica gel (1:99 Et_2O/hexane → 2:98 Et_2O/hexane → 5:95 Et_2O/hexane eluent), affording desired aldehyde **(–)-252** (137 mg, 79% yield) as a colorless oil. R_f 0.40 (1:9 EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): 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, J_q = 13.2 Hz, J_t = 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, J_t = 13.2 Hz, J_d = 3.9 Hz, 1H), 0.99 (td, J_t = 13.5 Hz, J_d = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 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/$CDCl_3$): 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 $C_{20}H_{26}O$, 282.1984; found, 282.1991; $[\alpha]^{24}_D$ –109.22° (*c* 1.205, $CHCl_3$), 98% ee. ^{1}H-^{1}H nOesy-1D spectra were obtained for **(–)-252** (300 MHz, $CDCl_3$); the results are shown below:

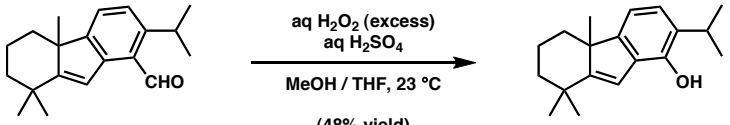


nOe's detected for *(–)-252*

Undesired aldehyde **(+)-253** (13.3 mg, 8% yield) was also isolated as a colorless oil. R_f 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_q = 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:



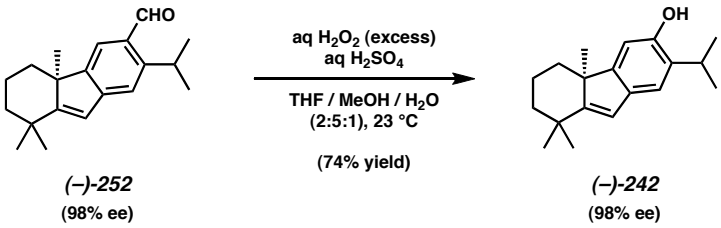
nOe's detected for *(+)-253*



(±)-253 ***(±)-254***

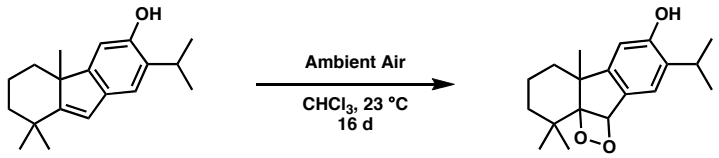
Tricyclic Phenol (±)-254. A round-bottom flask was charged with a solution of aldehyde **(±)-253** (35 mg, 0.124 mmol) in THF (500 μL). MeOH (3 mL) was added, followed by 30% aq H_2O_2 (500 μL) at 23 °C. Then, conc. aq H_2SO_4 (3 drops from a glass pipet) was added. After 1 h, more 30% aq H_2O_2 (500 μL) was added. After 48 h, the reaction was added to a biphasic mixture of $NaHSO_3$ (1.2 g), H_2O (20 mL), CH_2Cl_2 (20 mL), and hexanes (10 mL). The organic phase was collected, and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). All organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and adsorbed onto 1.0 mL of silica gel. The material was purified by flash chromatography on silica gel (1:99 Et_2O:hexane → 8:92 Et_2O:hexane eluent), giving tricyclic phenol **(±)-254** (16.2 mg, 48% yield). R_f (not determined); ^1H NMR (300 MHz, $CDCl_3$): 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_2O_2 (2.70 mL, 23.8 mmol) immediately followed by conc. aq H_2SO_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_2O (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_2O (3 x 40 mL). All organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), filtered, and adsorbed on silica gel. The adsorbed product was purified by flash chromatography on silica gel (2:98 Et_2O/hexane → 10:90 Et_2O/hexane eluent), affording phenol **(–)-242** (95.0 mg, 74% yield) as a white, unstable powder. R_f 0.56 (1:4

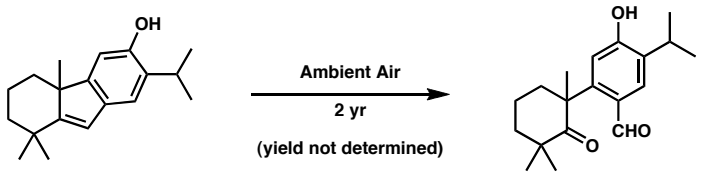
EtOAc/hexane), (UV, 254 nm); mp 105-106 °C (dec.) (Et_2O/hexane); ^{1}H NMR (300 MHz, $CDCl_3$, degassed with argon): δ 7.11 (s, 1H), 6.68 (s, 1H), 6.29 (s, 1H), 4.57 (s, 1H, vanishes with D_2O addition), 3.19 (app. quintet, J = 6.9 Hz, 1H), 2.07 (app. d, J = 12.4, 1H), 1.94 (app. qt, J_q = 13.5 Hz, J_t = 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, J_t = 13.2 Hz, J_d = 3.6 Hz, 1H), 1.01 (td, J_t = 13.2 Hz, J_d =3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 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, 2909, 2868, 2837, 1459, 1431, 1382, 1362, 1286, 1166, 1076, 1004, 894, 856 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{19}H_{26}O$, 270.1984; found, 270.1993; $[\alpha]^{24}_D$ –73.23° (*c* 0.080, $CHCl_3$), 98% ee.



(±)-242 *(±)-255*

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 Et_2O:hexane → 20:80 Et_2O: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 $CDCl_3$ (700 μL) and immediately analyzed by ^{1}H NMR. R_f (not measured, but lower than phenol **(±)-242** in EtOAc:hexane 20:80); ^{1}H

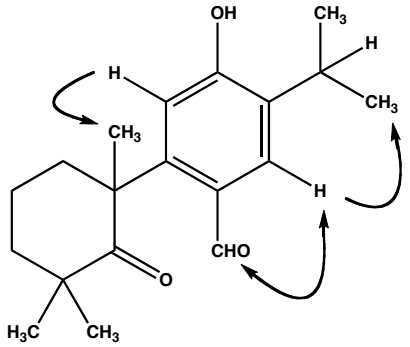
NMR (300 MHz, $CDCl_3$): δ 6.62 (s, 1H), 5.90 (s, 1H), 5.06 (s, 1H), 3.19 (app. septuplet, J = 6.9 Hz, 1H), 1.76 (app. dd, J = 14.0 Hz, 3.4 Hz, 1H), 1.69 (s, 3H), 1.64-1.49 (m, 2H), 1.34 (s, 3H), 1.37-1.19 (m, 3H), 1.262 (app. d, J = 6.9 Hz, 3H), 1.261 (app. d, J = 6.9 Hz, 3H), 1.16 (s, 3H); ^{13}C NMR (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 ^1H NMR. For characterization of **(±)-256**, see page 170 and 171 below.



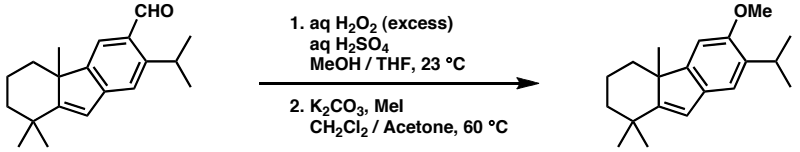
(±)-242 *(±)-256*

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. R_f 0.22 (20:80 EtOAc/hexane), (UV, 254 nm); mp 181-185 °C (dec.); ^1H NMR (300 MHz, $CDCl_3$): 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_t = 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 D_2O is shaken into the ^1H NMR sample; ^{13}C NMR (125 MHz, $CDCl_3$): 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 ($NaCl/CDCl_3$): 3272 (broad), 2962, 2927, 2869, 1684, 1612, 1579, 1460, 1425, 1345, 1274, 999, 909, 734 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M+H]^+$ calc'd for $C_{19}H_{27}O_3$, 303.1960; found, 303.1953. ^1H-^1H nOesy-1D spectra were obtained for **(±)-256** (300 MHz, $CDCl_3$); the results are shown below:



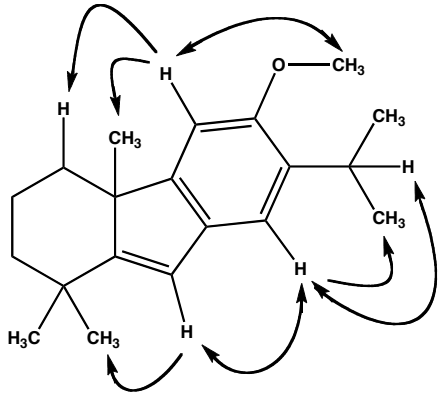
nOe's detected for *(±)-256*



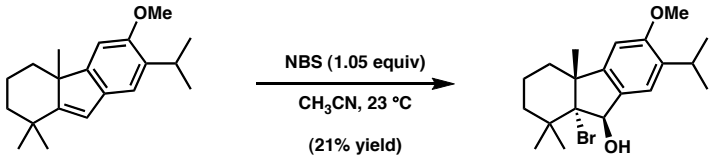
(±)-252 *(±)-257*

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 H_2O_2 (500 μL) was added, followed by conc. aq H_2SO_4 (3 drops from a glass pipet). After 1.2 h at 23 °C, the reaction was added slowly to a biphasic mixture of $NaHSO_3$ (600 mg), H_2O (20 mL), CH_2Cl_2 (20 mL), and hexanes (10 mL). The organic phase was collected, and the aqueous layer extracted with CH_2Cl_2 (3 x 15 mL). All organic layers were then combined, washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated.

The crude product was taken up in CH_2Cl_2 (200 μL) and transferred to a Schlenk tube. Acetone (ACS grade, 800 μL) was added, followed by K_2CO_3 (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 Et_2O:hexane eluent), giving aryl methyl ether **(±)-257** (26.4 mg, 83% yield from **(±)-252**) as a white powder. R_f (not determined); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (s, 1H), 6.82 (s, 1H), 6.33 (s, 1H), 3.87 (s, 3H), 3.35 (app. septuplet, J = 6.9 Hz, 1H), 2.13 (app. ddd, J = 12.7 Hz, 4.7 Hz, 3.0 Hz, 1H), 1.98 (app. qt, J_q = 14.0 Hz, J_t = 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, J = 6.9 Hz, 3H), 1.24 (app. d, J = 6.9 Hz, 3H), 1.13 (app. td, J_t = 12.7 Hz, J_d = 3.9 Hz, 1H), 1.04 (app. td, J_t = 12.9 Hz, J_d = 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 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/$CDCl_3$): 3059, 2960, 2929, 2866, 2844, 1620, 1593, 1571, 1484, 1463, 1417, 1309, 1289, 1221, 1082, 1065, 1032, 888 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{20}H_{28}O$, 284.2140; found, 284.2131. ^{1}H-^{1}H nOesy-1D spectra were obtained for **(±)-257** (300 MHz, $CDCl_3$); the results are shown below:



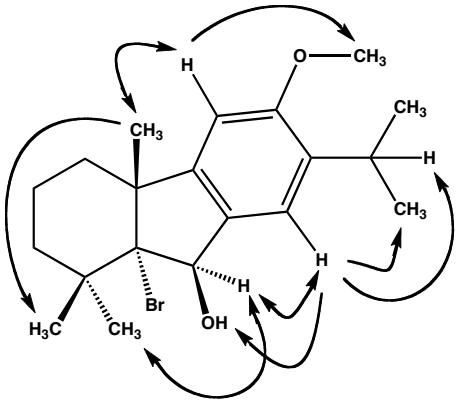
nOe's detected for *(±)-257*



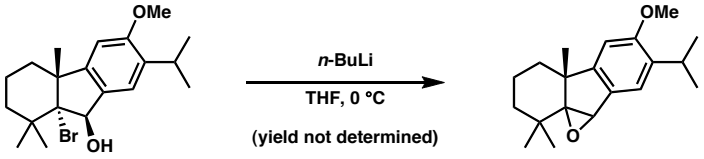
(±)-257 ***(±)-258***

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_3CN (1.0 mL). To this was added a solution of *N*-bromo succinimide (18.4 mg, 0.103 mmol, 1.05 equiv) in CH_3CN (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_2Cl_2 (20 mL) and adsorbed to 750 μL of silica gel and purified by flash chromatography on silica gel (2:98 Et_2O: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_2O 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, $CDCl_3$): δ 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:



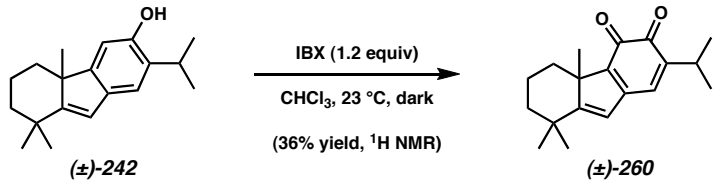
nOe's detected for *(±)-258*



(±)-258 ***(±)-259***

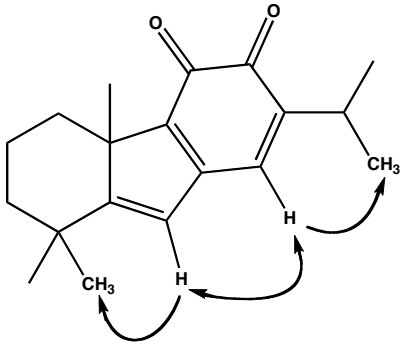
Aryl Epoxide (±)-259. A round-bottom flask was charged with a solution of bromohydrin **(±)-258** (6.2 mg, 16.3 μmol) and THF (5.0 mL) and cooled to 0 °C. (*n*-BuLi, 2.5 M in hexanes, 7 μL, 17.5 μmol) was added. 10 min later, the reaction was treated with D_2O (1.0 mL), then warmed to 23 °C. After 15 min, the reaction was diluted with hexanes (5 mL). The organic layer was collected, dried (Na_2SO_4), filtered, and concentrated, giving aryl epoxide **(±)-259** (yield not determined) R_f (not determined); ^{1}H

NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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/$CDCl_3$): 3434, 2959, 2933, 2873, 1615, 1492, 1464, 1376, 1308, 1226, 1058, 1018 cm^{-1}; HRMS-EI^+ (*m/z*): $[M+H]^+$ calc'd for $C_{20}H_{29}O_2$, 301.2168; found, 301.2168. ^1H-^1H homodecoupling experiments (300 MHz, $CDCl_3$) 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 $CHCl_3$ (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 $CHCl_3$. 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 Et_2O/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: R_f 0.55 (1:4 EtOAc/hexane), (visible, purple spot); ^{1}H NMR (300 MHz, $CDCl_3$): 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, IH), 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/CH_2Cl_2): 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 $C_{19}H_{25}O$, 285.1855; found, 285.1851. ^{1}H-^{1}H nOesy-1D spectra were obtained for **(±)-260** (300 MHz, $CDCl_3$); the results are shown below:



nOe's detected for *(±)-260*

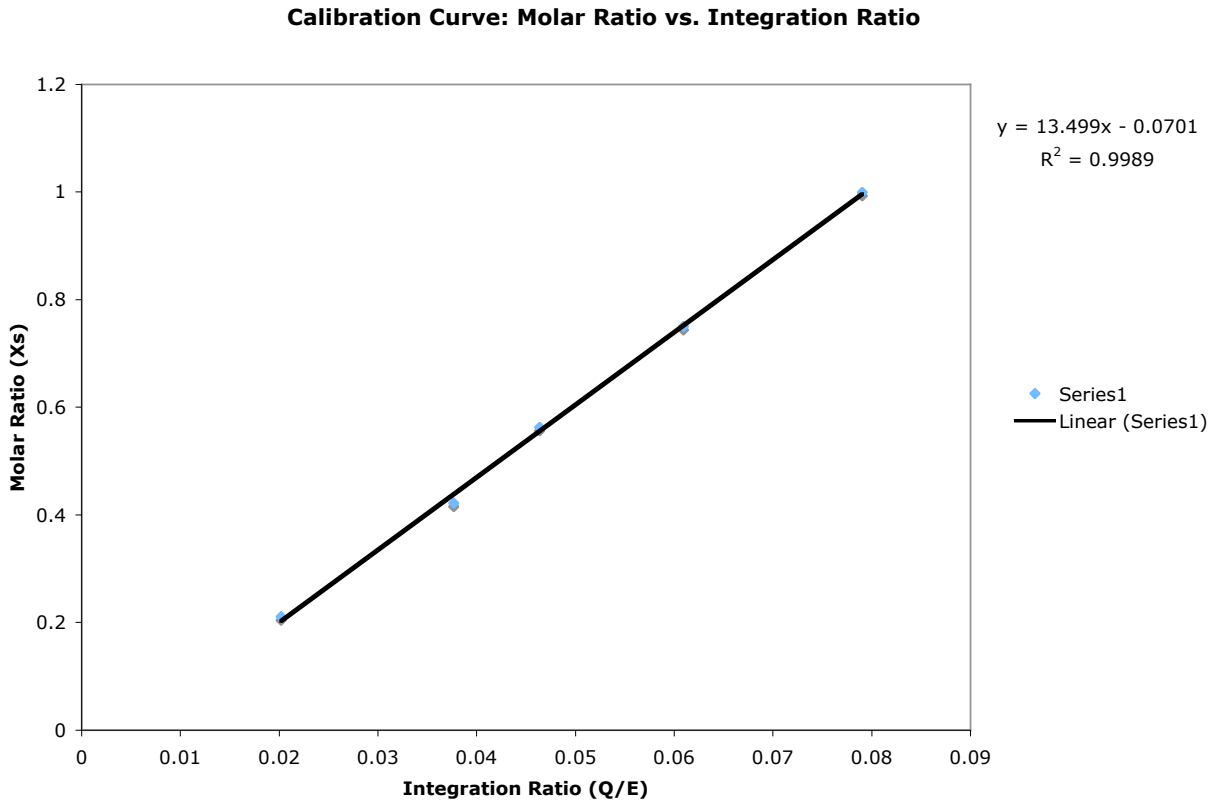
The following experiment was employed for determining actual yield of **(±)-260**: To a rapidly stirred solution phenol (–)-242 (25.4 mg, 0.0940 mmol) in $CHCl_3$ (5 mL) in the dark was added IBX (30.2 mg, 0.1018 mmol) in one portion. After 15 h, the reaction was filtered through glass frits with the aid of $CHCl_3$. The filtrate was partially concentrated and $CDCl_3$ was added; this was repeated iteratively until there was less than

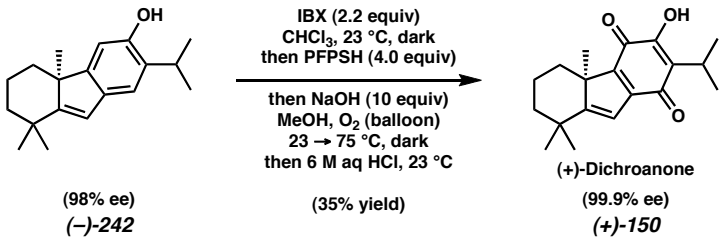
2% $CHCl_3$ by volume and ~3 mL total volume of solution. The solution was transferred to a 5.00 mL volumetric flask, and EtOAc (51.0 μL, 0.522 mmol, internal standard) was added. The flask was diluted to 5 mL using $CDCl_3$, giving a solution of unknown that was 0.0188 M in **(±)-260** (assuming a 100% yield) and 0.104 M in EtOAc, with a theoretical molar ratio, X_T, 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 $CDCl_3$ (5.00 mL), giving a solution with a molar ratio X_S 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 $0.750X_S$, $0.563X_S$, $0.422X_S$, and $0.211X_S$. These four solutions, along with the original $1.000X_S$ 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 X_T (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 $0.363X_S$. This corresponds to a 36% yield of racemic *o*-quinone **(±)-260**.

Calibration Curve and Extrapolation Data for *o*-Quinone **(±)-260** Yield Assay

	(±)-260	**Int. Std.**	**Q/E Ratio**	
Calibration	Integration δ6.86	Integration δ4.08	(±)-260/Int.Std.	Yield (X_S)
	5.37	67.95	0.0790	1.00
	4.46	73.20	0.0609	0.750
	3.62	78.07	0.0464	0.563
	2.99	79.35	0.0377	0.422
	1.72	85.11	0.0202	0.211
Extrapolation	Unknown	Internal Std.	Unknown/Int.Std.	Yield (X_T)
	2.50	78.00	0.0321	0.363

Calibration Curve for *o*-Quinone **(±)-260** Yield Assay





(*R*)-(+)-Dichroanone ((+)-150). Phenol **(–)-242** (79.8 mg, 0.295mmol) was dissolved in $CHCl_3$ (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 $CHCl_3$. The filtrate, which contained enantioenriched *o*-quinone ***(R)*-260** (36% yield by ^{1}H 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 O_2 balloon was attached, and the reaction became deep red over the next 2 h. Then, the mixture was refluxed under a balloon of O_2 at 75 °C in the dark for another 3 h. After cooling to 23 °C, the O_2 balloon was removed and substituted for an N_2 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 Et_2O (3 x 20 mL). All organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated to ~2 mL total volume. This suspension was purified by flash chromatography on silica gel (2:98 Et_2O/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 Et_2O/hexane eluent), affording (*R*)-(+)-dichroanone (**(+)-150**) (31.0 mg, 35% yield from phenol **(–)-242**, 99% yield from *o*-qunione ***(R)*-260**) as an odorless, amorphous red solid. The product had a 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); ^{1}H NMR (300 MHz, $CDCl_3$): 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_q = 13.8 Hz, J_t = 3.3 Hz, 1H), 1.70 (app. dq, J_d = 13.2 Hz, J_q = 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_d = 13.2 Hz, J_t = 4.4 Hz, 1H), 1.07 (app. dt, J_d = 13.2 Hz, J_t = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 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/$CHCl_3$): 3350, 2960, 2932, 2873, 1637, 1527, 1470, 1368, 1358, 1317, 1242, 1104, 990, 966 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{19}H_{24}O_3$, 300.17255; found, 300.17265; UV-Vis λ_{max} nm (log ε): 253(4.0), 332 (3.9); $[\alpha]^{27}_D$ +99.60° (*c* 0.0055, dioxane), 99.9% ee.

Comparison of Natural (*S*)-(–)-Dichroanone and Synthetic (*R*)-(+)-Dichroanone (**(+)-150**)

^{1}H NMR of Dichroanone, $CDCl_3$[1]			
Synthetic (+), 300 MHz		**Natural (–), 300 MHz**[2]	
Shift (ppm)	**Multiplicity/Coupling (Hz)**	**Shift (ppm)**	**Multiplicity/Coupling (Hz)**
7.31	s	7.31	s
6.44	s	6.45	s
3.21	septet, 7.2	3.22	septet, 7.0
2.37	ddd, 13.2, 5.0, 2.8	2.38	br. dd, ca. 13, ca. 2
1.92	qt, q= 13.8, t = 3.3	1.93	m
1.7	dq, d = 13.2, q = 2.5	1.71	ddd, 7.5, 2.5, 2.5
1.62	dddd, 14.2, 6.6, 3.9, 2.7	ca. 1.6	m
1.45	s	1.46	s
1.28	s	1.29	s
1.24	d, 7.2	1.25	d, 7.0
1.23	d, 7.2	1.24	d, 7.0
1.23	s	1.24	s
1.11	dt, d = 13.2, t = 4.4	ca. 1.1	m
1.07	dt, d = 13.2, t = 4.4	ca. 1.1	m

[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**)

^{13}C NMR of Dichroanone, $CDCl_3$	
Synthetic (+), 75 MHz	**Natural (–), 75 MHz**
Shift (ppm)	**Shift (ppm)**
185.9	185.8
178.4	178.3
177.2	177.3
152.6	152.6
149.0	149.0
147.9	148.0
122.9	123.0
118.1	118.1
55.5	55.5
43.5	43.6
37.5	37.5
37.1	37.1
31.1	31.0
24.9	24.9
24.1	24.1
20.3	20.3
20.2	20.2
-	20.2
19.2	19.2

IR of Dichroanone, KBr	
Synthetic (+)	**Natural (–)**
Wavenumber (cm^{-1})	**Wavenumber (cm^{-1})**
3326	3324
2959	2958
2925	-
2868	-
1628	1627
1519	1520
1459	1457
1367	-
1357	-
1287	1288
1170	-
1127	-
1107	-
992	-
966	-

UV-Vis Spectrum of Dichroanone	
Synthetic (+)	**Natural (–)**
λ_{max} (nm), (log ε)	**λ_{max} (nm), (log ε)**
253 (4.0)	253 (4.0)
332 (3.9)	332 (4.0)

Specific Optical Rotation of Dichroanone	
Synthetic (+)	**Natural (–)**
$[\alpha]^{27}_D$, (c 0.0055)	**$[\alpha]^{25}_D$, (c 0.67)[3]**
(in dioxane, 99.9%ee)	(in dioxane, 100%ee)
+99.60°	–99.3°

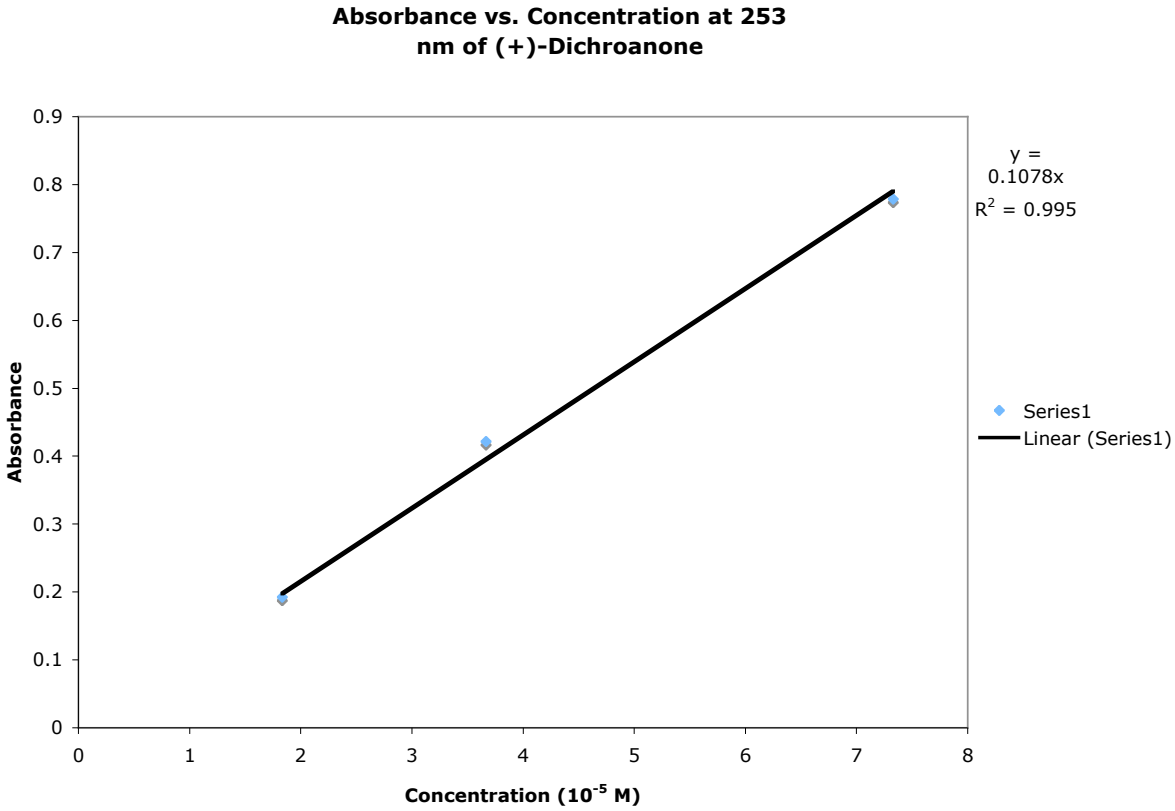
[3] An attempt was made to measure the specific optical rotation of synthetic (–) dichroanone (**(+)-150**) at c = 0.67 as reported by the isolation chemists; however, due to the cell path length used (100 mm) on the polarimeter, no sodium-D (589 nm) light was transmitted through the orange-red solution, 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**)

Concentration (10^{-5}M)	**Abs at 253 nm**	**Abs at 332 nm**
7.329	0.7783	0.5974
3.665	0.4217	0.3369
1.832	0.1925	0.1542

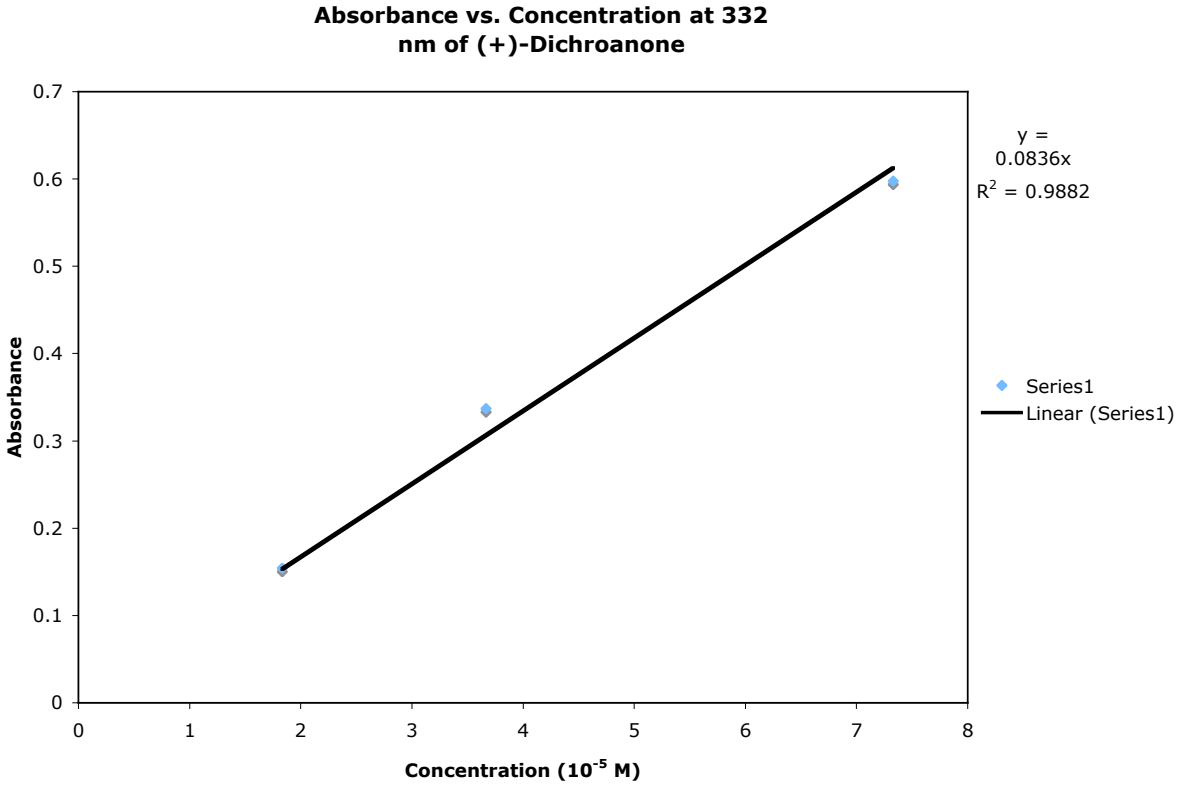
UV-Vis Data for (*R*)-(+)-Dichroanone (**(+)-150**)



ε_{253} = 10780 L / (mol • cm); log (ε_{253}) = 4.0[4]

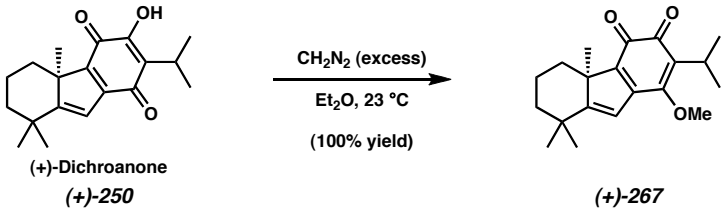
[4] For this graph, the equation of best fit is equivalent to Beer's Law, A = εlc, where l is a constant (1 cm, the path length of the sample in the quartz cuvette) and ε is the slope of the least squares line, constrained to run through the origin. Thus, ε is in units of [cm^{-1} • (10^{-5} $M)^{-1}$]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

UV-Vis Data for (*R*)-(+)-Dichroanone **(+)-150**



ε_{332} = 8360 L / (mol • cm); log (ε_{332}) = 3.9[5]

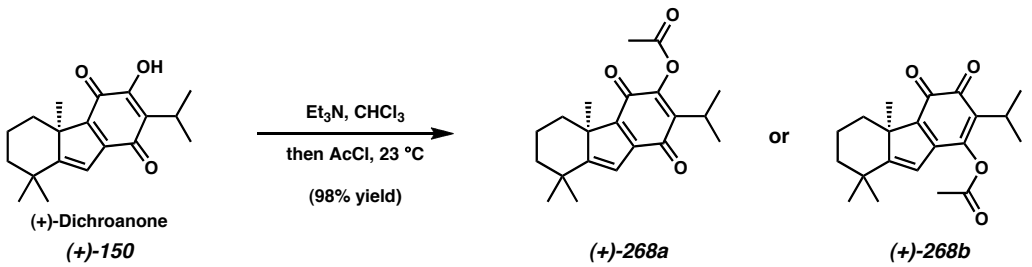
[5] For this graph, the equation of best fit is equivalent to Beer's Law, A = εlc, where l is a constant (1 cm, the path length of the sample in the quartz cuvette) and ε is the slope of the least squares line, constrained to run through the origin. Thus, ε is in units of [cm^{-1} • (10^{-5} $M)^{-1}$] or more simply, ε = 100000 • (slope) • L / (mol • cm). Hence, ε_{332} = 8360 L / (mol • cm), and log(ε_{332}) = 3.9.



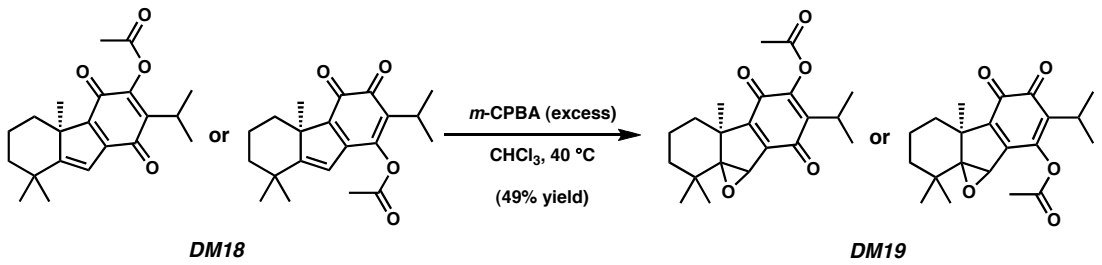
(+)-Dichroanone
(+)-250

(+)-267

***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 Et_2O, 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 Et_2O: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 (Et_2O/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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/$CHCl_3$): 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 $C_{20}H_{26}O_3$, 314.1882; found, 314.1868. $[\alpha]^{25}_D$ +68.34° (*c* 0.068, $CHCl_3$), 99.9% ee.



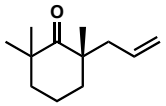
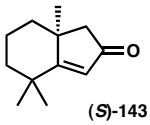
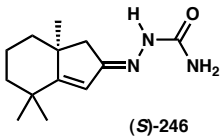
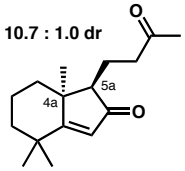
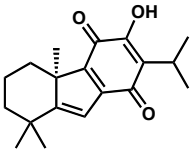
***O*-Acetyl Dichroanone (+)-268**. To a solution of dichroanone (**(+)-150**) (5.0 mg, 16.7 μmol) in $CHCl_3$ (4.0 mL) was added Et_3N (100 μL), causing the solution to turn from yellow-orange to indigo. After 5 min at 23 °C, acetyl chloride (50 μL) was introduced, and the reaction became bright yellow. After 5 min, sat. aq $NaHCO_3$ (2.0 mL) was carefully added, followed by H_2O (2.0 mL). The organic phase was collected, and the aqueous layer was extracted with $CHCl_3$ (2 x 4 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and adsorbed onto 125 μL of silica gel. The material was purified on a pipet silica gel flash column (5:95 Et_2O:hexane eluent), giving *O*-acetyl dichroanone **(+)-268** (5.6 mg, 98% yield) as a yellow semisolid. R_f 0.62 (20:80 EtOAc/hexane), (visible, yellow-orange spot); mp 59-61 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 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, J_q = 13.5 Hz, J_t = 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, J_d = 13.2 Hz, 1H), 1.07 (dt, J_d = 12.6 Hz, J_t = 2.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 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/$CHCl_3$): 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 $C_{21}H_{27}O_4$, 343.1909; found, 343.1918. $[\alpha]^{26}_D$ +82.61° (*c* 0.0280, $CHCl_3$), 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 $CHCl_3$ (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 Et_2O:hexane eluent), giving semipure **(–)-269**. This material was purified on a second flash pipet column with silica gel (5:95 Et_2O: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. R_f 0.55 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, green-yellow spot); ^{1}H NMR (500 MHz, $CDCl_3$): 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_q = 14.2 Hz, J_t = 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_t = 13.7 Hz, J_d = 3.4 Hz, 1H), 1.30 (app. td, J_t = 13.7 Hz, J_d = 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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/$CHCl_3$): 2966, 2936, 2874, 1778, 1658, 1608, 1457,

1370, 1318, 1182, 1164, 1132, 1008, 920, 890 cm^{-1}; HRMS-FAB$^+$ (*m/z*): $[M]^+$ calc'd for $C_{21}H_{26}O_5$, 358.1780; found, 358.1790. $[\alpha]^{26}_D$ –27.28° (*c* 0.140, $CHCl_3$), 99.5% ee.

3.11.3 *Methods for the Determination of Enantiomeric Excess*

Entry	Substrate	Assay	Column	Method	Retention Time (min)	
1.	 (***S***)-75	*Enantiomeric Excess*	Chiral GC	80 °C isotherm	Major (***S***)	29.1
			Agilent GT-A Column	40 min	Minor (***R***)	30.5
2.	 (***S***)-143	*Enantiomeric Excess*	Chiral HPLC	3%EtOH/Hex monitor@254nm	Minor (***R***)	9.1
			Chiralcel AD Column	20 min	Major (***S***)	10.2
3.	 (***S***)-246	*Enantiomeric Excess*	Chiral HPLC	10%EtOH/Hex monitor@254nm	Minor (***R***)	9.3
			Chiralcel AD Column	20 min	Major (***S***)	12.1
4.	**10.7 : 1.0 dr**  **Major Diasteromer: (4a*S*, 5a*R*)-233**	*Enantiomeric Excess*	Chiral HPLC	4%EtOH/Hex monitor@254nm	Minor (**4a*S*, 5a*R***)	17.6
			Chiralcel AD Column	40 min	Major (**4a*R*, 5a*S***)	28.5
5.	 (***R***)-(+)-Dichroanone-(150)	*Enantiomeric Excess*	Chiral HPLC	0.3%EtOH/Hex monitor@254nm	Minor (***S***)	18.3
			Chiralcel AD Column	30 min	Major (***R***)	21.1

3.12 Notes and Citations

(1) For the isolation of standishinal, see: Ohtsu, H.; Iwamoto, M.; Ohishi, H.; Matsunaga, S.; Tanaka, R.; *Tetrahedron Lett.* **1999**, *40*, 6419-6422.

(2) Several isolations of 4a-methyltetrahydrofluorene natural products from *Taiwania cryptomerioides* have been reported: (a) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1995**, *40*, 871-873. (b) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1996**, *42*, 1657-1663. (c) Chang, C.-I.; Chien, S.-C.; Lee, S.-M.; Kuo, Y.-H. *Chem. Pharm. Bull.* **2003**, *51*, 1420-1422. (d) Chang, C.-I.; Chang, J.-Y.; Kuo, C.-C.; Pan, Y.-H.; Kuo, W.-Y. *Planta Med.* **2005**, *71*, 72-76.

(3) For isolations of 4a-methyltetrahydrofluorene natural products from *Salvia dichroantha*, see: Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493-497.

(4) (a) Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Med. Chem.* **2001**, *9*, 1911-1921. (b) Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742-745.

(5) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. Kr. *Org. Lett.* **2003**, *5*, 3931-3933.

(6) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. Kr. *J. Org. Chem.* **2006**, *71*, 2787-2796.

(7) Burger, A. P. N.; Brandt, E. V.; Roux, D. G. *Phytochemistry* **1983**, *22*, 2813-2817.

(8) (a) Blatt, A. H. *Org. React.* **1942**, *1*, 342-369. (b) Gammill, R. B. *Tetrahedron Lett.* **1985**, *26*, 1385-1388.

(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.

(11) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144-13145.

(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.

(13) Planas, L.; Mogi, M.; Takita, H.; Kajimoto, T.; Node, M. *J. Org. Chem.* **2006**, *71*, 2896-2898.

(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).

(16) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022-11023.

(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.

(19) 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.

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

(21) 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.

(22) 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.

(23) 2,2,6-trimethylcyclohexanone (**101**) costs $48/g from Aldrich.

(24) 2,6-dimethylcyclohexanone (**220**), sold as a *cis*,*trans* mixture from Aldrich, costs $48 for 25 g ($1.92/g).

(25) Aboulhoda, S. J.; Hénin, F.; Muzart, J.; Thorey, C. *Tetrahedron Lett.* **1995**, *36*, 4795-4796.

(26) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793-1796.

(27) 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.

(28) Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765-8768.

(29) These conditions worked well for a similar substrate. See: Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045.

(30) 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.

(31) Thomas, A. F.; Ozainne, M.; Guntz-Dubini, R. *Can. J. Chem.* **1980**, *58*, 1810-1820.

(32) Tessier, P. E.; Nguyen, N.; Clay, M. D.; Fallis, A. G. *Org. Lett.* **2005**, *7*, 767-770.

(33) For the use of MoOPH in the synthesis of α-hydroxylketones, see: Vedejs, E.; Engler, D. A.; Teclschow, J. E. *J. Org. Chem.* **1978**, *43*, 188-196.

(34) (a) For the preparation of the DMPU analogue of MoOPH, see: Daniewski, A. R.; Wojciechowska, W. *Synth. Commun.* **1986**, *16*, 535-536. (b) For application of the aforementioned analogue toward α-hydroxylketone synthesis, see: Anderson, J. C.; Smith, S. C. *Synlett* **1990**, 107-108.

(35) (a) Rubottom, G. M.; Juve, H. D., Jr. *J. Org. Chem.* **1983**, *48*, 422-425. (b) Katsumura, S.; Isoe, S. *Chem. Lett.* **1982**, 1689-1692.

(36) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800-2803.

(37) Nakamura, N.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* **1987**, *109*, 4969-4973.

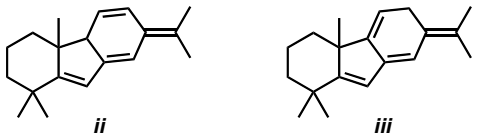
(38) (a) Davis, F. A.; Lamendola, J., Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000-2005. (b) For use of the Davis oxaziridine in preparation of α-hydroxylketones, see: Davis, F. A.; Sheppard, A. C. *J. Org. Chem.* **1987**, *52*, 955-957. (c) A practical synthesis of the Davis oxaziridine using Oxone® has been reported: Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087-2089.

(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%.

(40) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777-12782.

(41) Ito, Y.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011-1013.

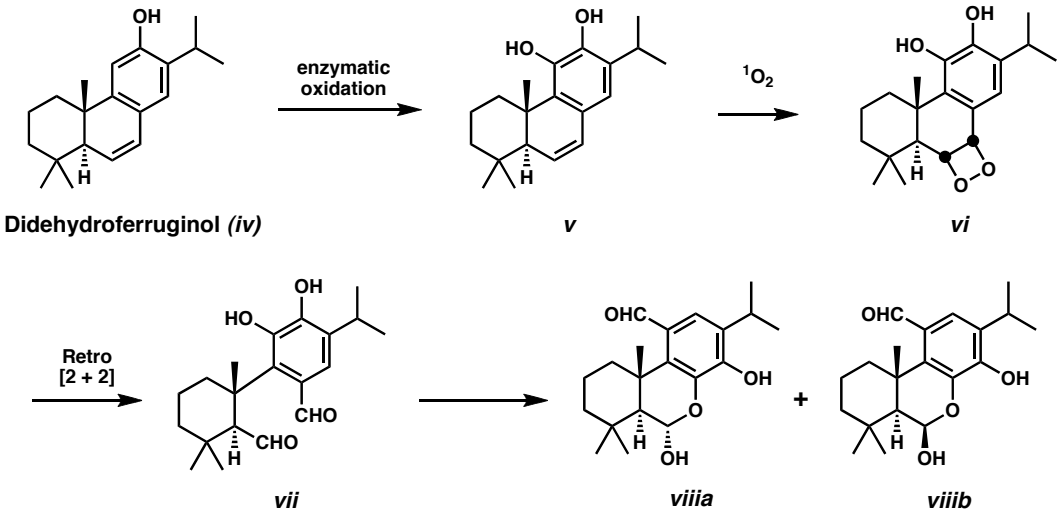
(42) Two hypothetical olefin isomers corresponding to the two low-R_f species are shown below:



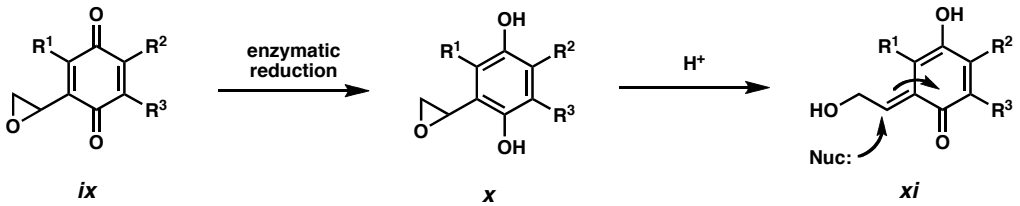
ii *iii*

(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 *4π*-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 **viiia** and **viiib**. 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:



(45) Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285-288.

(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,

A. *J. Chem. Soc., Perkin Trans. 1: Organic and Bio-Organic Chemistry* **1999**, *4*, 379-380. (b) phenolic oxidative dearomatization has been used in the total synthesis of aquaticol: Gagnepain, J.; Castet, F.; Quideau, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1533-1535.

(47) A calibration curve of ^{1}H NMR signal intergration (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.

(48) For a discussion about quinoid vinylogous esters and vinylogous anhydride hydrolysis during synthetic investigations on analogues of the natural product asteriquinone, see: Kaji, A.; Saito, R.; Hata, Y.; Kiriyama, N. *Chem. Pharm. Bull.* **1999**, *47*, 77-82.

(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 (±)-dichroanone (**150**) to (±)-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.

(51) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537-4538.

(52) (a) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Riech, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547-7583. (b) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045.

(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.