

# CHAPTER 3

*Progress toward the Asymmetric*

*Total Synthesis of Variecolin<sup>†</sup>*

## 3.1 INTRODUCTION AND SYNTHETIC STRATEGY

### 3.1.1 INTRODUCTION

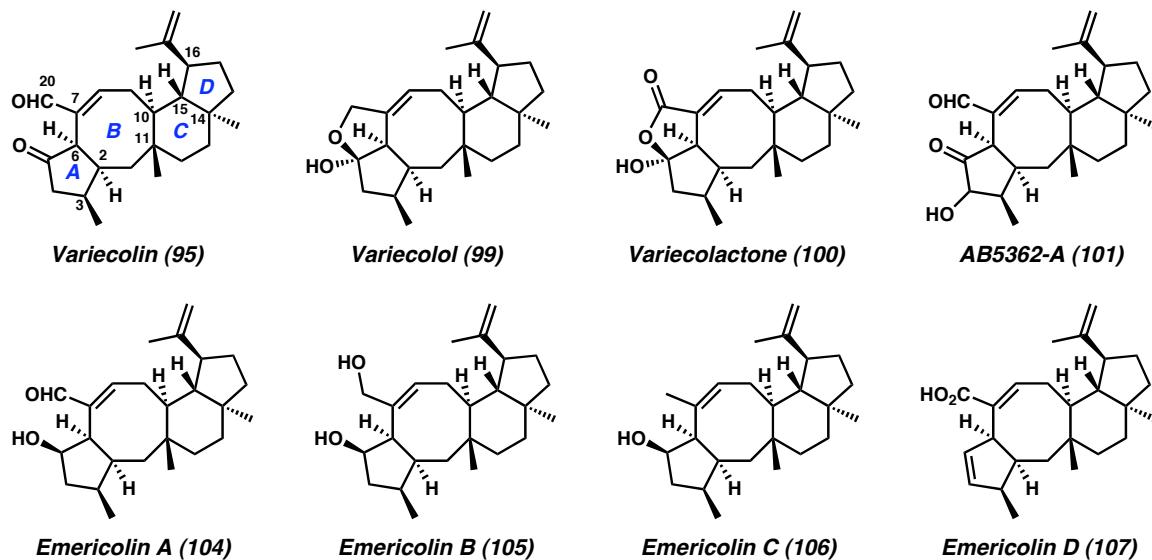
Variecolin (**95**) is a complex sesterterpenoid isolated from extracts of the fungi *Asperigillus* sp. and *Emericella* sp.<sup>1</sup> It belongs to a growing class of sesterterpene natural products defined by a tetracyclic core possessing a central eight-membered ring, comprising variecolol (**99**), variecolactone (**100**),<sup>2</sup> AB5362-A (**101**), and emericolins A–D (**104–107**) (Figure 3.1.1). This family exhibits an array of biological activities, including antihypertensive,<sup>1a,2</sup> anti-HIV,<sup>1f</sup> immunosuppressive,<sup>1e</sup> and antifungal<sup>1c</sup> properties. Our interest in the pursuit of an effective and general synthetic strategy toward these bioactive natural products focused on variecolin, as it represents the most widely studied and biologically relevant member. The inherent synthetic challenges

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<sup>†</sup> This work was performed in collaboration with Thomas Jensen, a visiting scholar from the Technical University of Denmark, and Dr. Chris Henry, a postdoctoral scholar in the Stoltz group.

posed by the complex tetracyclic core representative of this sesterterpene family provide inspiration to utilize and expand the state of the art in catalysis and synthetic methodology.

Figure 3.1.1. Variecolin family of sesterterpenes.



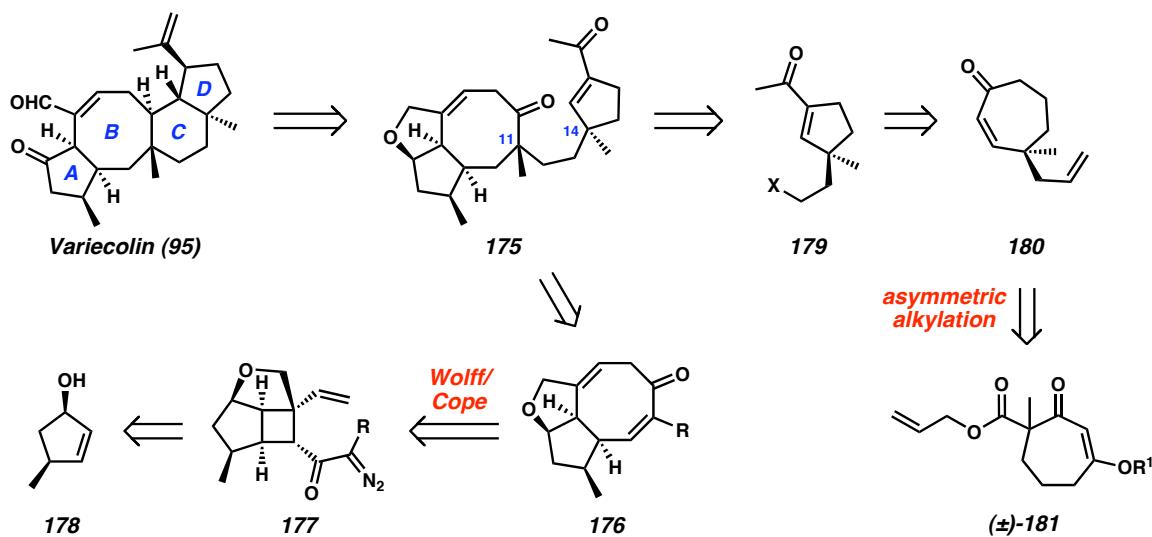
The 25-carbon tetracyclic core of variecolin (**95**) consists of a central eight-membered ring and possesses eight stereocenters, including two all-carbon quaternary stereocenters at C(11) and C(14)<sup>3</sup> of the B–C and C–D ring fusions, respectively.<sup>1a,e,f</sup> Synthetic control of the relative and absolute stereochemistry of these trans-fused rings poses a significant challenge for the design of critical bond-forming reactions. Herein we present a convergent approach to variecolin that harnesses methods developed in our laboratories to construct these key structural features and provides opportunities to explore new reactivity. At the outset of our investigations, two laboratories had published efforts

toward variecolin, although all members of this family have thus far continued to elude chemical synthesis.<sup>4</sup>

### 3.1.2 RETROSYNTHETIC ANALYSIS

Our retrosynthetic approach toward variecolin (**95**) focused on the construction of the central eight-membered ring and two all-carbon quaternary stereocenters,<sup>5</sup> with the intention of improving synthetic efficiency through the coupling of two highly substituted fragments. We envisioned a critical C-ring disconnection, through bisketone **175**, to AB ring fragment **176** and D-ring fragment **179** (Scheme 3.1.1). Our laboratory recently developed a powerful tandem Wolff/Cope rearrangement for the facile generation of functionalized fused bicyclic cycloheptadienones from vinyl cyclopropyl diazo ketones.<sup>6</sup> Using this technology, we anticipated that AB ring synthon **176** could be accessed through a Wolff/Cope rearrangement of highly functionalized cyclobutane **177**, which may in turn be assembled via a tethered cycloaddition of alcohol **178**. We surmised that the crucial all-carbon quaternary stereocenter of D-ring synthon **179** could be installed through an enantioselective Pd-catalyzed alkylation of in situ-generated cyclic enolates recently developed in our laboratories.<sup>7</sup> Accordingly, **179** could originate from a ring contraction of cycloheptenone **180**, which itself would arise from the asymmetric palladium-catalyzed alkylation of racemic vinylogous  $\beta$ -ketoester ( $\pm$ )-**181**.

Scheme 3.1.1. Retrosynthetic analysis of variecolin



### 3.2 A WOLFF/COPE APPROACH TO THE AB RING SYSTEM

Eight-membered rings are common structural motifs that occur in widely diverse terrestrial plants, insects, marine organisms, and fungi. The theoretical and synthetic intrigue of these medium-sized carbocyclic structures has stimulated the development of various strategies for their preparation, many of which have been applied toward the synthesis of complex molecular targets.<sup>8</sup> Inasmuch as we are restricted by the limitations of reaction scope in the state of the art, the selective preparation of eight-membered rings remains a noteworthy and continuing challenge to modern chemical methods.<sup>9</sup>

The design of tandem reaction sequences for the rapid generation of molecular complexity is an area of constant investigation in our laboratory.<sup>10</sup> We have recently developed a tandem Wolff/Cope rearrangement for the facile construction of functionalized seven-membered rings.<sup>6</sup> A critical component to the success of this method was the identification of photochemical or silver-catalyzed sonochemical

conditions to allow direct access to a variety of  $[n-7]$  fused bicyclic systems in excellent yields. In drawing inspiration from this efficient process, a primary objective of the devised synthetic plan toward variecolin (**95**) is the development of a tandem Wolff/Cope rearrangement to forge fused carbocyclic eight-membered ring systems. Application of this key transformation for the construction of the central B ring of **95** would expand the reaction scope, and furthermore, could provide new tools and strategies for the general preparation of natural and nonnatural substances containing this eight-membered ring motif.

### **3.2.1 MODEL STUDIES OF THE WOLFF/COPE REARRANGEMENT TOWARD CONSTRUCTION OF THE EIGHT-MEMBERED AB RING**

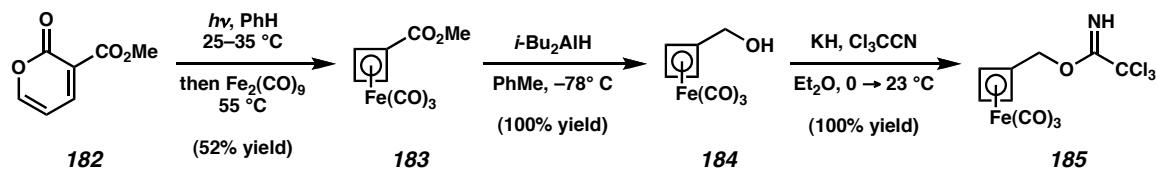
In order to investigate the tandem Wolff/Cope rearrangement toward eight-membered AB ring fragment (**176**), we sought an expedient, stereoselective synthesis of a highly substituted cyclobutane substrate (e.g., **177**). During the course of our efforts, we elected to use an exceedingly effective cyclobutadiene–olefin cycloaddition for the rapid construction of this cyclobutane moiety.<sup>11</sup> Model studies pursued toward this goal provided insight into the physical properties and identification of reaction intermediates using a readily available cyclopentenol analogue.

#### **3.2.1.1 MODEL WOLFF/COPE SUBSTRATE SYNTHESIS**

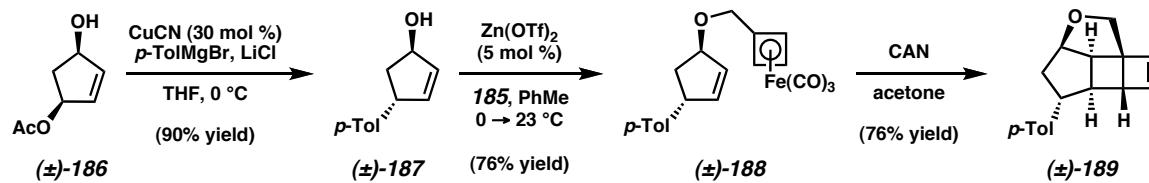
We initiated investigations toward an AB ring model system by preparing a suitable tricarbonyliron-cyclobutadiene derivative with sufficient electrophilicity to enable

alcohol alkylations under mild conditions.<sup>12</sup> Conversion of pyrone **182** into tricarbonyliron-cyclobutadiene complex **183**,<sup>13</sup> followed by ester reduction produced alcohol **184** (Scheme 3.2.1). Alkoxide generation using KH and exposure to trichloroacetonitrile effectively formed trichloroacetimidate **185** in quantitative yield.

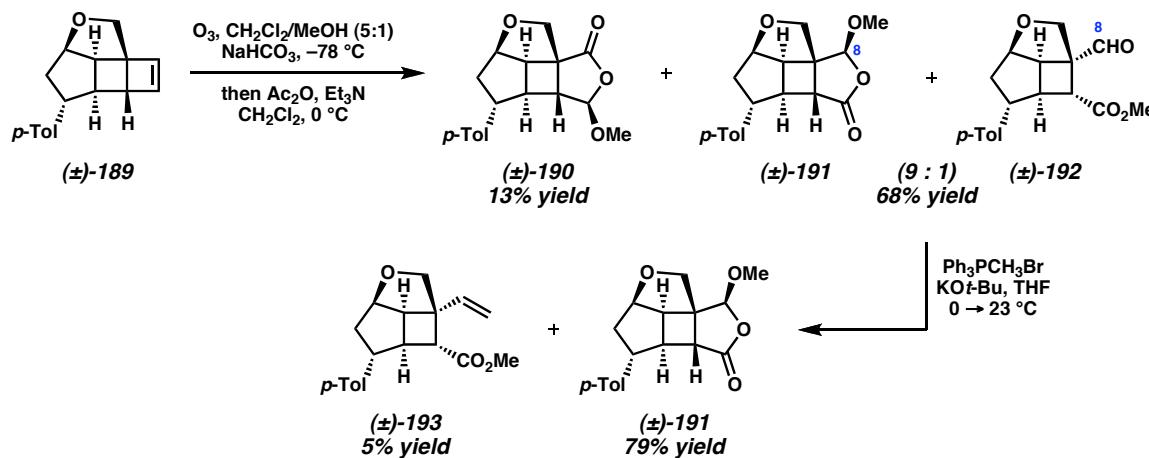
Scheme 3.2.1. Preparation of trichloroacetimidate **185**



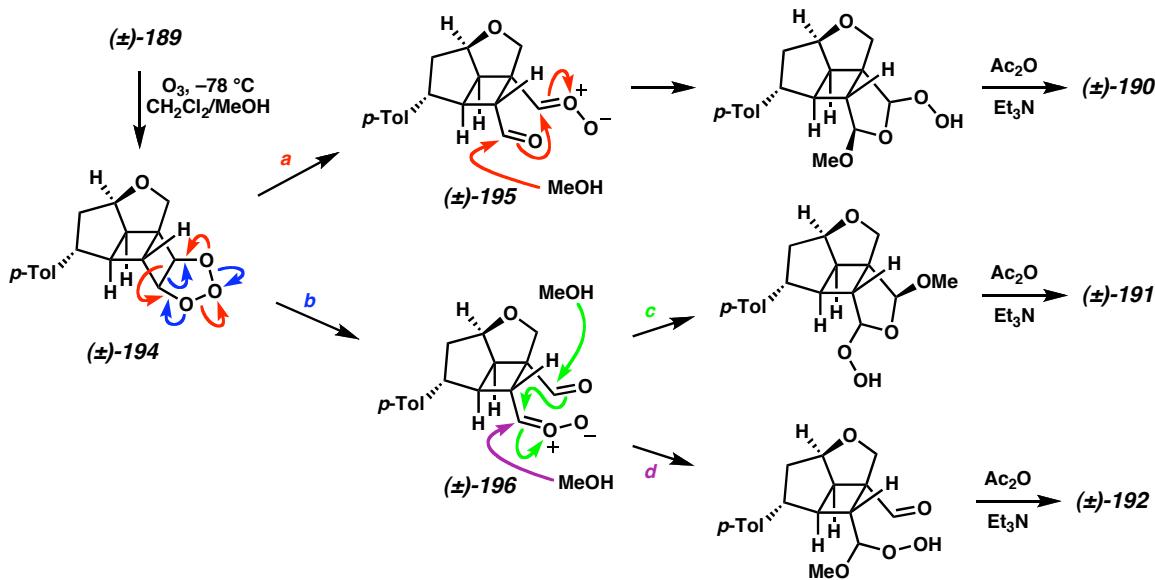
The stereoselective synthesis of a chiral cyclopentenol was achieved utilizing precedented cuprate chemistry.<sup>14</sup> Readily available *anti*-cyclopentenol ( $\pm$ )-**187**<sup>14b</sup> was prepared from monoacetate ( $\pm$ )-**186**<sup>15</sup> by a copper(I) cyanide-catalyzed S<sub>N</sub>2 displacement using *p*-tolylmagnesium bromide (Scheme 3.2.2). Zinc(II)-catalyzed alkylation<sup>16</sup> of *anti*-cyclopentenol **187** with trichloroacetimidate **185** afforded the requisite intramolecular cycloaddition substrate **188** in 76% yield.<sup>12</sup> Oxidative liberation of cyclobutadiene promoted by ceric ammonium nitrate (CAN), with subsequent olefin cycloaddition rapidly assembled the desired cyclobutene **189** in 76% yield, establishing the stereoselective preparation of a model for our highly substituted cyclobutane intermediate.

Scheme 3.2.2. Tethered cycloaddition of alcohol  $(\pm)$ -187

We next considered regioselective functionalization of the cyclobutene moiety via construction of cycloadduct **189** en route to a Wolff/Cope substrate. To this end, we explored a method for the ozonolytic cleavage of olefins to terminally differentiated products in  $\text{CH}_2\text{Cl}_2$  and methanol popularized by Schreiber.<sup>17,18</sup> Exposure of cycloadduct **189** to typical reaction conditions provided a mixture of compounds including undesired acetal **190** in 13% yield and an inseparable 9:1 mixture of acetal **191** and desired aldehyde **192** in 68% yield (Scheme 3.2.3). Direct Wittig methylation of the mixture afforded pure acetal **191** in addition to minor quantities of desired olefin **193**.

Scheme 3.2.3. Termini-differentiating ozonolysis of cyclobutene **189**

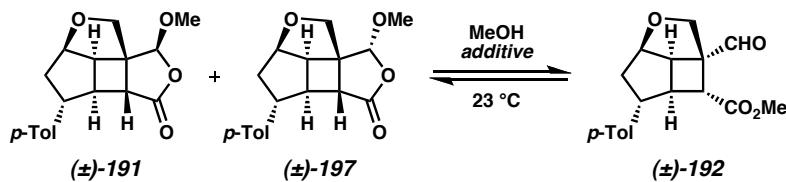
The production of acetals **190** and **191** from this unsymmetrical ozonolysis indicates diverging reaction pathways (Scheme 3.2.4). Cycloaddition of ozone to cyclobutene **189** generates primary ozonide **194**, which fragments in one of two ways. Cleavage of the primary ozonide to **195** (path *a*) positions the carbonyl oxide on the fully substituted carbon. Subsequent addition of methanol to this intermediate and dehydration with  $\text{Ac}_2\text{O}/\text{Et}_3\text{N}$  generates acetal **190**. Conversely, primary ozonide cleavage in the opposite manner produces **196** (path *b*) with the carbonyl oxide positioned on the less-substituted carbon. This intermediate further reacts by another of two possible pathways: (1) addition of methanol from the reaction medium (path *c*) and dehydration to generate acetal **191**, or (2) methanol addition to the carbonyl oxide (path *d*) and dehydration to furnish aldehyde **192**. Although desired aldehyde **192** is a minor component of this reaction, the selectivity for the cleavage of primary ozonide **194** via the desired path *b* is favored in an approximate 3:1 ratio, and is presumably the result of steric influences of the cyclobutene moiety.<sup>19</sup>

Scheme 3.2.4. Proposed ozonolytic cleavage of cyclobutene **189**

The isolation of aldehyde **192** as a minor product from the unsymmetrical ozonolysis of cyclobutene **189** hindered progress toward a model Wolff/Cope substrate. Fortunately, we recognized that acetal **191** and aldehyde **192** arise from the same fragmentation pathway (path *b*, Scheme 3.2.4) and thus possess the same aldehyde oxidation state at C(8)<sup>3</sup> (cf. Scheme 3.2.3). To exploit this result, we explored potential equilibration conditions to determine the propensity for formation of aldehyde **192** from the isomeric aldehyde/acetal mixture (Table 3.2.1). Our primary investigations revealed that solvation of pure acetal **191** in methanol effected the equilibration to favor aldehyde **192** and produced minor quantities of acetal diastereomer **197** (entries 1 and 2). A survey of various Lewis acids identified the proficiency of divalent triflate salts in shifting the equilibrium to further favor **192** (entries 3–6).<sup>20</sup> Similarly, molecular sieves and combinations thereof with Lewis acids proved to be efficient for the conversion to **192** (entries 7–10). As a result of this screen of conditions, we elected to proceed in the

synthesis using 4 Å MS in our optimal conditions because they provide a nearly 3:1 ratio of **192**:**191** + **197** and enhanced operational efficiency.<sup>21</sup>

Table 3.2.1. Equilibration of acetal **191**



entry <sup>a</sup>	additive <sup>b</sup>	<b>191</b> + <b>197</b> : <b>192</b> <sup>c</sup>
1	—	66 : 34
2	— <sup>d</sup>	39 : 61
3	CuCl <sub>2</sub>	75 : 25
4	ZnCl <sub>2</sub>	41 : 59
5	Cu(OTf) <sub>2</sub>	36 : 64
6	Zn(OTf) <sub>2</sub>	30 : 70
7	3 Å MS	32 : 68
8	4 Å MS	29 : 71
9	4 Å MS/Zn(OTf) <sub>2</sub>	27 : 73
10	4 Å MS/Cu(OTf) <sub>2</sub>	28 : 72

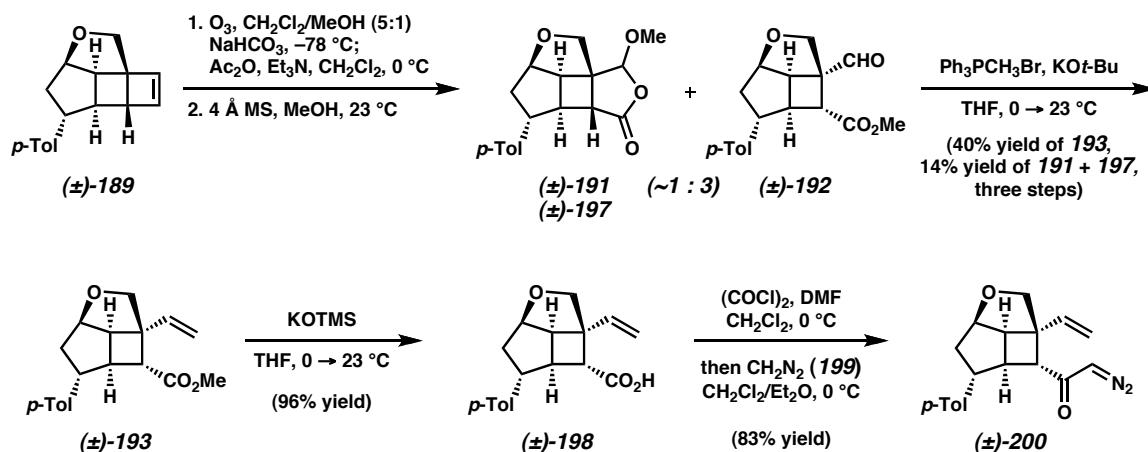
<sup>a</sup> Each entry started from pure acetal **191**. <sup>b</sup> Lewis acids were used in 20 mol %; molecular sieves were used in 0.5 g/mmol. <sup>c</sup> Ratio determined by <sup>1</sup>H NMR analysis of crude reaction filtrate after 20–24 h. <sup>d</sup> At 50 °C.

The equilibration of acetal **191** to desired aldehyde **192** considerably improved the overall reaction sequence for the preparation of a Wolff/Cope  $\alpha$ -diazoketone substrate (e.g., **177**). In the event, the unsymmetrical ozonolysis of cyclobutene **189** followed by equilibration with 4 Å MS in methanol afforded a ~1:3 ratio of acetals **191** + **197** and aldehyde **192** (Scheme 3.2.5). Wittig methylenation of this mixture produced the desired olefin **193** in 40% yield over three steps, while the recovery of acetals **191** and **197** in 14% yield enabled recycling of material.<sup>22</sup> Hydrolysis of ester **193** with KOTMS and

conversion to  $\alpha$ -diazoketone **200** by way of an acid chloride and diazomethane (**199**)

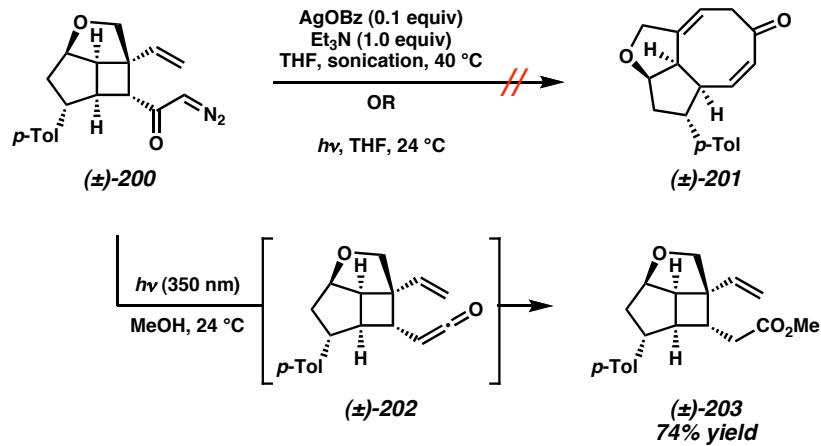
proceeded in excellent yield.

Scheme 3.2.5. Optimized synthesis of  $\alpha$ -diazoketone **200**



### 3.2.1.2 MODEL WOLFF/COPE REARRANGEMENT INVESTIGATIONS

The synthesis of  $\alpha$ -diazoketone **200** enabled the examination of our key Wolff/Cope rearrangement toward the eight-membered B ring of variecolin. Thorough investigations of this transformation utilizing various photochemical or silver(I)-catalyzed sonochemical conditions afforded only intractable mixtures (Scheme 3.2.6). The lack of useful information acquired from these initial experiments required us to examine the tandem process in a stepwise manner. Accordingly, irradiation of  $\alpha$ -diazoketone **200** in methanol with a 350 nm light induced the photochemical Wolff rearrangement to form homologated<sup>23</sup> ester **203** as the sole product, confirming the intermediacy of ketene **202**. We were thus able to conclude that the ketene vinyl cyclobutane rearrangement does not readily occur under the conditions surveyed.

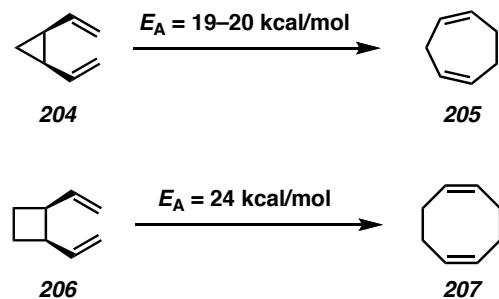
Scheme 3.2.6. Initial Wolff/Cope studies on  $\alpha$ -diazoketone 200

To rationalize the difficulty of the *cis*-ketene vinyl cyclobutane rearrangement of **202**, we considered the analogous *cis*-divinyl cyclobutane rearrangement.<sup>24</sup> A comparison of the experimental activation energy ( $E_A$ ) for a strain-releasing Cope rearrangement of *cis*-divinyl cyclopropane (**204**) to that of *cis*-divinyl cyclobutane (**206**) reveals a higher activation barrier of the latter by roughly 4–5 kcal/mol (Figure 3.2.1).<sup>25</sup> The related decrease in reaction rate constant is consistent with the slightly elevated reaction temperatures known to be required for *cis*-divinyl cyclobutane rearrangements. This difference, when coupled with our observations that the ketene vinyl cyclopropane rearrangement to afford substituted cycloheptadienones occurs under mild conditions,<sup>6</sup> suggested that thermolysis of the intermediate ketene should facilitate the rearrangement. In the event, a photochemical Wolff rearrangement with subsequent thermolysis at 80 °C provided cyclooctenone **201** in 59% yield (Scheme 3.2.7).

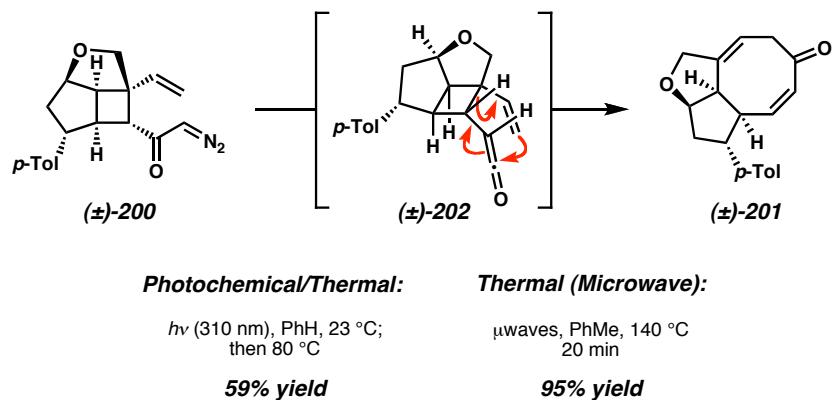
With the success of this tandem reaction, we recognized that the high reactivity of a ketene intermediate and the time between photolysis/thermolysis could account for the

moderate yield of **201** and furthermore might hinder material throughput. In our search for alternative conditions, we investigated reports harnessing microwave irradiation to promote Wolff rearrangements, where we anticipated that the surplus energy could facilitate the Cope rearrangement.<sup>26</sup> Indeed, microwave irradiation for 20 minutes at 140 °C in toluene afforded cyclooctadienone **201** in 95% yield. These model system results thereby confirm the Wolff/Cope strategy for the synthesis of the AB fragment of variecolin (**95**), and provide new tools for the construction of substituted eight-membered rings

Figure 3.2.1 Comparison of the strain-releasing Cope rearrangements of **204** and **206**.



Scheme 3.2.7. Successful Wolff/Cope rearrangement of  $\alpha$ -diazoketone **200**

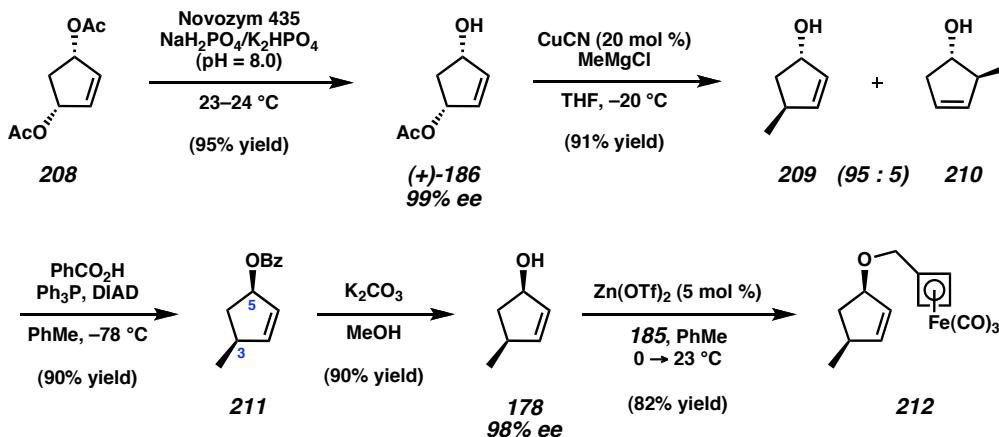


### 3.2.2 ASYMMETRIC SYNTHESIS OF THE AB RING FRAGMENT OF VARIECOLIN EMPLOYING THE WOLFF/COPE REARRANGEMENT

Having established a viable route toward the AB ring system of variecolin through model system studies, we then pursued an asymmetric synthesis of this fragment.

#### 3.2.2.1 ASYMMETRIC SYNTHESIS OF WOLFF/COPE SUBSTRATE TOWARD VARIECOLIN

The application of our proven intramolecular cycloaddition strategy for an asymmetric synthesis of the AB ring fragment (i.e., **176**, Scheme 3.1.1) originated from a chiral cyclopentenol possessing syn stereochemistry. An enzymatic desymmetrization of *meso*-bisacetate **208** provided monoacetate (+)-**186** in excellent yield and 99% ee (Scheme 3.2.8).<sup>27</sup> Copper(I) cyanide-catalyzed S<sub>N</sub>2 displacement using methylmagnesium chloride with monoacetate **186** afforded a 95:5 mixture of alcohols **209** and **210** in 91% yield.<sup>14a</sup> Mitsunobu inversion of this alcohol mixture using benzoic acid produced allylic benzoate **211**, possessing the desired syn stereochemistry between C(3) and C(5).<sup>3,28</sup> Benzoate methanolysis and zinc(II)-catalyzed coupling<sup>16</sup> with tricarbonyliron-cyclobutadiene trichloroacetimidate **185** gave the requisite intramolecular cycloaddition substrate (**212**).

Scheme 3.2.8. Asymmetric synthesis of intramolecular cycloaddition substrate **212**

Efforts toward the intramolecular cyclobutadiene–olefin cycloaddition of **212** promoted by CAN resulted in low yields and complex mixtures of products, presumably the result of competing intermolecular dimerization reactions. Snapper has established that the rapid oxidative decomplexation of tricarbonyliron-cyclobutadiene complexes using CAN provides sufficient access to cycloadducts of substrates predisposed for the intramolecular cycloaddition (e.g., **188**).<sup>11f</sup> Oxidations using trimethylamine-*N*-oxide, however, enact a slow release of cyclobutadiene to enable access to cycloadducts of substrates with a lower reactivity for this process (e.g., **212**). The gradual liberation of the highly reactive intermediate favors an intramolecular cycloaddition process by disfavoring intermolecular reaction pathways. Application of trimethylamine-*N*-oxide to facilitate the oxidative decomplexation of **212** in refluxing acetone smoothly generated cycloadduct **213** (Scheme 3.2.9).<sup>29,30</sup> Subsequent unsymmetrical ozonolysis of **213**, acetal equilibration promoted by 4 Å MS in refluxing methanol and Wittig methylenation afforded a 2.7:1 ratio olefins **216** and **217**, in addition to acetals **214** and **215**. This reaction sequence provided desired olefin **216** in 16% yield over four steps, together with

17% yield of recyclable acetal **214**.<sup>31</sup> Critically, acetal **215** was sufficiently crystalline to enable X-ray analysis, providing further confirmation of the desired relative stereochemistry of this polycyclic fragment (Figure 3.2.2).<sup>32</sup>

Scheme 3.2.9. Cycloaddition, ozonolysis, and olefination toward an asymmetric Wolff/Cope substrate

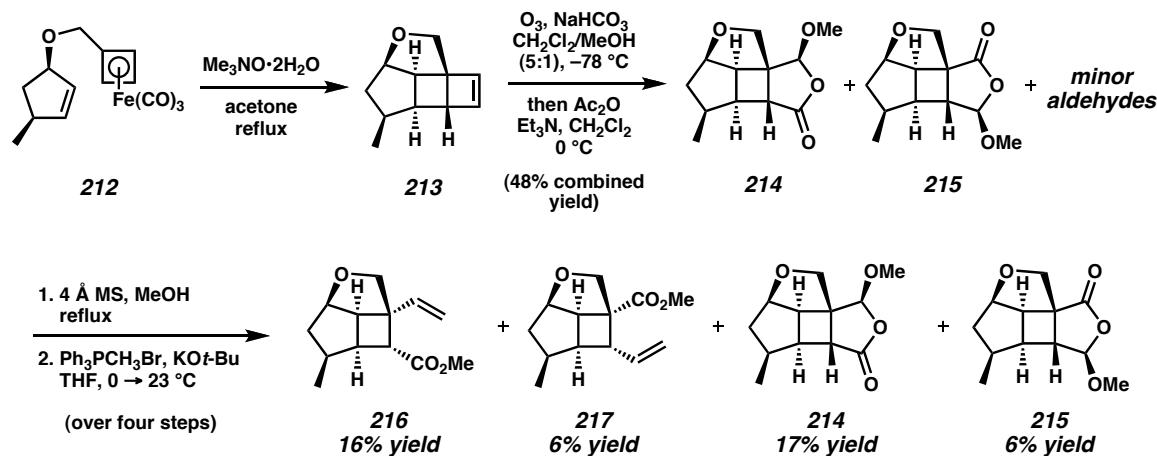
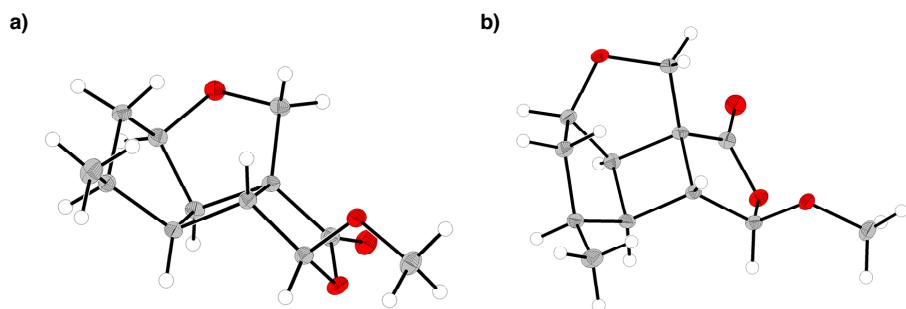


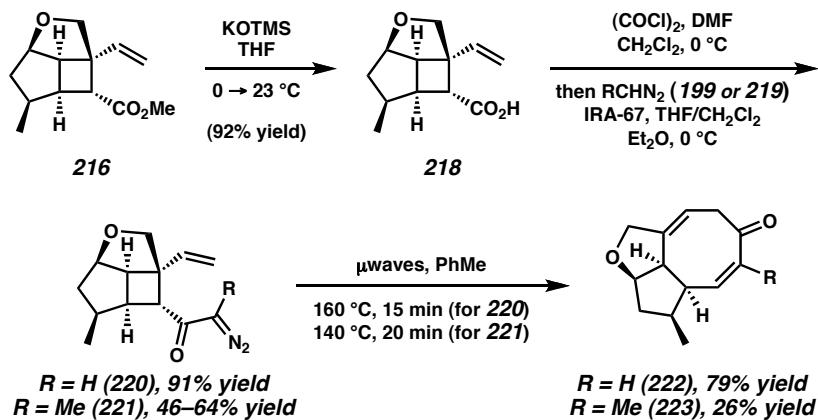
Figure 3.2.2. X-ray crystal structure of acetal **215**. The molecular structure is shown with 50% probability ellipsoids. a) Side view. b) Top view.



### 3.2.2.2 $\alpha$ -DIAZOKETONE SYNTHESIS AND WOLFF/COPE STUDIES

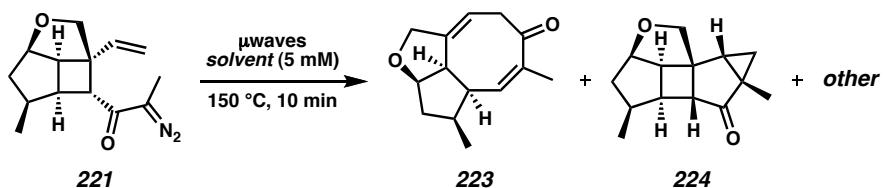
In the synthesis of our asymmetric AB ring fragment, we desired cyclooctadienone products **176** where  $R = H$ , Me, or alkyl (Scheme 3.1.1). Model studies have demonstrated the tandem rearrangement where  $R = H$  (i.e., **200**  $\rightarrow$  **201**, see subsection 3.2.1.2). However, alkyl substitution had not yet been explored for the Wolff/Cope rearrangement and thus represented an unprecedented extension of the methodology. Advancing to the target  $\alpha$ -diazoketones, hydrolysis of ester **216** to acid **218** and conversion to the acid chloride and treatment with either diazomethane (**199**,  $R = H$ ) or diazoethane (**219**,  $R = Me$ ) produced  $\alpha$ -diazoketones **220** and **221**, respectively (Scheme 3.2.10). Although diazomethane generated **220** in 91% yield, we were surprised by the inconsistent and lower-yielding results obtained using diazoethane.<sup>33</sup> Despite extensive efforts toward optimization, however, improvements in yield could not be realized.<sup>34</sup> Nonetheless, the microwave-promoted tandem Wolff/Cope rearrangement of both substrates resulted in the successful construction of their respective cyclooctadienones (**222** and **223**).

Scheme 3.2.10.  $\alpha$ -Diazoketone synthesis and Wolff/Cope rearrangement



The notably low yield of  $\alpha$ -substituted cyclooctadienone **223** using microwave irradiation is a direct result of the formation of numerous byproducts.<sup>35</sup> Inspection of these various compounds revealed that cyclopropane **224** is a major side product (~1:1 ratio of **223**:**224**) of this reaction, formed through a carbene intermediate. Two mechanisms have been proposed for the Wolff rearrangement: 1) a concerted group migration with nitrogen expulsion to a ketene or 2) the stepwise loss of nitrogen to generate an  $\alpha$ -carbonyl carbene intermediate that can either undergo the desired Wolff rearrangement to a ketene or participate in other intra- or intermolecular reactions.<sup>36</sup> A complicating factor in our analysis of the rearrangement of **221** is that the two mechanisms often operate competitively with high substrate dependence. However, we noted the influence of solvent toward substrate conformation (**224**) and its impact on the mechanistic pathway,<sup>37</sup> and thus posited that solvent variation might facilitate an increase in the production of our targeted cyclooctadienone **223** (Table 3.2.2).<sup>38</sup> We observed that high-polarity solvents such as acetonitrile or 1,2-dichloroethane favored cyclopropane formation decidedly over the Wolff rearrangement (entries 1 and 2). Less-polar solvents, such as THF, ethyl acetate, and toluene, reversed the selectivity and improved the formation of desired product **223** (entries 3–6). Furthermore, the nonpolar solvents methylcyclohexane and heptane reversed the reaction selectivity to favor the desired **223** as a major product, in a 3:1 ratio (entries 7 and 8). Although solvent polarity roughly reflects product selectivity, in which less-polar solvents favor the Wolff rearrangement, the complex reaction profile makes it difficult to conclusively correlate solvent polarity to reaction pathway.

Table 3.2.2. Wolff/Cope solvent studies of  $\alpha$ -diazoketone 221

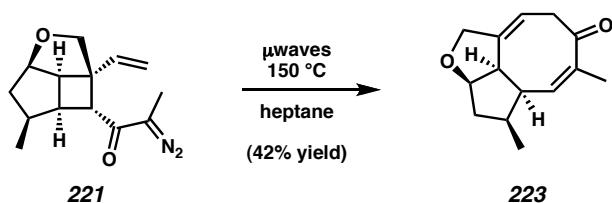


entry <sup>a</sup>	solvent	dielectric constant ( $\epsilon$ )	223 : 224 <sup>b</sup>
1	acetonitrile	37.5	1 : 4
2	DCE	10.4	1 : 2.8
3	THF	7.58	1 : 1.1
4	EtOAc	6.02	1 : 1.3
5	toluene	2.38	1.1 : 1
6	1,4-dioxane	2.21	1 : 1.7
7	methylcyclohexane	2.02	3 : 1
8	heptane	1.92	3 : 1

<sup>a</sup> Starting material was consumed in all reactions. <sup>b</sup> Ratios determined by <sup>1</sup>H NMR analysis of crude reaction mixtures.

The application of these optimized reaction conditions with heptane enabled the microwave-promoted rearrangement of **221** to produce  $\alpha$ -methyl cyclooctadienone **223** in 42% isolated yield (Scheme 3.2.11). The success of this rearrangement is significant as it represents the first example of the tandem Wolff/Cope rearrangement of a substrate possessing  $\alpha$ -alkyl functionality. Moreover, the combined results from all substrates in this study (i.e., **200**, **220**, and **221**) highlight the utility of microwave energy to facilitate tandem rearrangements and expand the collection of eight-membered rings available by this method. This Wolff/Cope approach to variecolin AB ring systems **222** and **223** provided advanced material to support fragment coupling studies toward completion of the natural product.

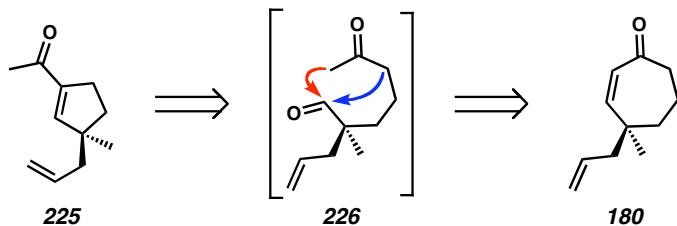
Scheme 3.2.11. Optimized rearrangement of  $\alpha$ -diazoketone **221** to  $\alpha$ -methyl cyclooctadienone **223**



### 3.3 CATALYTIC ASYMMETRIC SYNTHESIS OF A D-RING FRAGMENT

D-ring fragment **179** presents an all-carbon quaternary stereocenter contained within the cyclopentene core as the key synthetic challenge. Literature reports of approaches to similar quaternary acylcyclopentenes are remarkably limited,<sup>39</sup> and thus we sought a novel route to construct these potentially useful substances. Structures analogous to **179** have been assembled both from five-membered rings<sup>40</sup> and as the products of six-membered ring contractions.<sup>41,42</sup> In our design of a synthetic route to D-ring fragment **225** we envisioned the contraction of cycloheptenone **180** via a retro-aldol/aldol sequence<sup>43</sup> to enable the direct formation of a cyclopentene intermediate (Scheme 3.3.1).

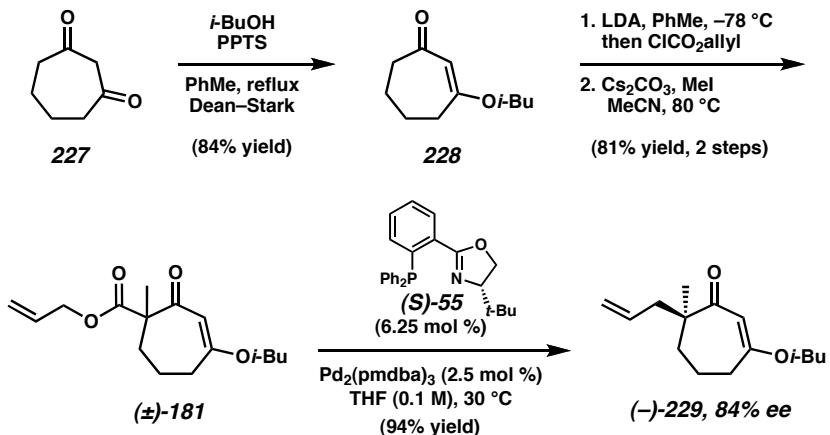
Scheme 3.3.1. Proposed ring contraction approach to acylcyclopentene **225**



The palladium-catalyzed enantioselective alkylation of unstabilized, prochiral ketone enolates has been an area of intense investigation in our laboratory.<sup>7</sup> This technology has enabled the preparation of a wide variety of cyclic carbonyl compounds possessing adjacent quaternary stereocenters with high levels of selectivity and excellent yields. To explore this ring contraction pathway, we pursued the enantioselective construction of the C(14) quaternary stereocenter via the asymmetric alkylation of racemic vinylogous<sup>44</sup>  $\beta$ -ketoester ( $\pm$ )-**181**.

### 3.3.1        ***OPTIMIZATION OF THE Pd-CATALYZED ASYMMETRIC ALKYLATION OF CYCLIC SEVEN-MEMBERED VINYLOGOUS $\beta$ -KETOESTERS***

The synthesis of a suitable  $\beta$ -ketoester substrate initiated with the production of vinylogous ester **228** from cycloheptane-1,3-dione (**227**)<sup>45</sup> (Scheme 3.3.2). Ketone enolization and acylation with allyl chloroformate formed an intermediate  $\beta$ -ketoester that was subsequently alkylated with methyl iodide to produce racemic  $\beta$ -ketoester ( $\pm$ )-**181**. In the presence of our standard alkylation conditions employing a catalyst complex generated *in situ* from  $\text{Pd}_2(\text{pmdba})_3$  and (*S*)-*t*-Bu-PHOX ((*S*)-**55**) in THF at 30 °C, vinylogous  $\beta$ -ketoester was transformed to  $\alpha$ -quaternary ketone (−)-**229** in 94% yield and 84% ee.

Scheme 3.3.2. Vinylogous  $\beta$ -ketoester substrate synthesis and Pd-catalyzed asymmetric alkylation

Although allyl ketone **229** was produced in excellent yield, we sought to improve the enantioselectivity of the process. A survey of common solvents afforded similar yields of allyl ketone **229** with a distinct enhancement of enantioselectivity (Table 3.3.1). Ethereal solvents enabled a modest selectivity increase to 86% ee in  $\text{Et}_2\text{O}$  (entries 1–3), while aromatic solvents provided a more substantial improvement to 88% ee in toluene (entries 4 and 5). In addition, we altered the electronics of our ligand, using fluorinated derivative **230**<sup>46</sup> to produce allyl ketone **229** in 90% ee, albeit with diminished yield at higher catalyst loading (entry 6). Since the diminished reactivity<sup>47</sup> of the electronically deficient palladium complex derived from **230** required increased catalyst loadings and resulted in lower yields, we elected to use the standard *t*-Bu-PHOX ligand (**55**) in toluene to carry out our asymmetric alkylation. The large-scale application of this method was facilitated by lower catalyst loadings (2.4 mol %) and increased reaction concentrations (0.2 M) to smoothly form allyl ketone **229** in 98% yield and 88% ee, a critical result that enhanced the practicality of the transformation (Scheme 3.3.3). Moreover, the optimal conditions for this class of cyclic vinylogous esters provide us with a new variety of

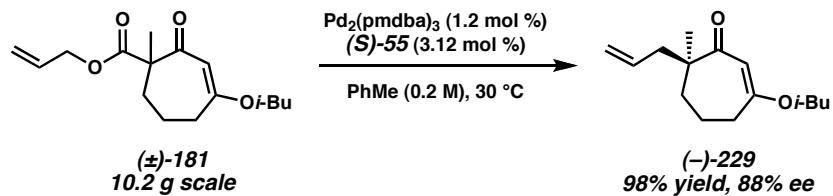
substrates for our asymmetric alkylation methodology as we continue to seek new synthetic applications for this chemistry.

Table 3.3.1. Asymmetric alkylation screen of vinylogous  $\beta$ -ketoester ( $\pm$ )-181

entry <sup>a</sup>	ligand	solvent	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	55 ( $R = H$ , $Ar = Ph$ )	THF	94	84
2	55 ( $R = H$ , $Ar = Ph$ )	TBME	88	85
3	55 ( $R = H$ , $Ar = Ph$ )	Et <sub>2</sub> O	93	86
4	55 ( $R = H$ , $Ar = Ph$ )	benzene	84	86
5	55 ( $R = H$ , $Ar = Ph$ )	toluene	91	88
6 <sup>d</sup>	230 ( $R = CF_3$ , $Ar = 4-CF_3-C_6H_4$ )	benzene	57	90

<sup>a</sup> pmdba = bis(4-methoxybenzylidene)acetone. <sup>b</sup> Isolated yield. <sup>c</sup> Enantiomeric excess determined by chiral HPLC. <sup>d</sup> 5 mol % Pd<sub>2</sub>(pmdba)<sub>3</sub> and 12.5 mol % **230** were used to reach complete conversion.

Scheme 3.3.3. Large-scale enantioselective alkylation of  $\beta$ -ketoester ( $\pm$ )-181

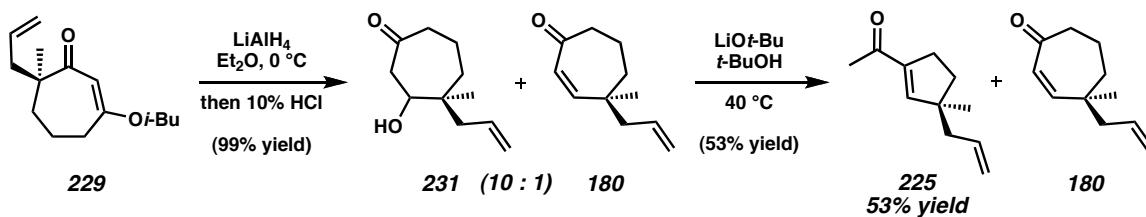


### 3.3.2 RING CONTRACTION INVESTIGATIONS AND DETERMINATION OF THE ABSOLUTE STEREOCHEMISTRY

A scalable and efficient asymmetric preparation of allyl ketone **229** enabled our pursuit of the targeted D-ring fragment **179**. Reduction of vinylogous ester **229** with

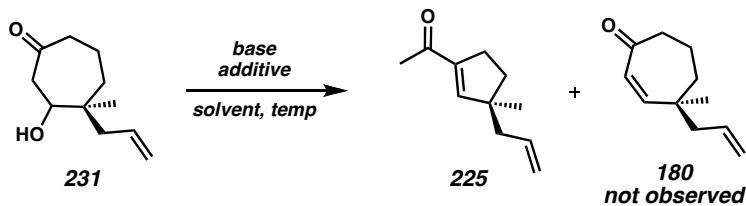
acidic workup furnished a 10:1 mixture of  $\beta$ -hydroxyketone **231** and enone **180** in 99% overall yield (Scheme 3.3.4). Exposure of this crude mixture to aldol conditions using LiOt-Bu in *t*-BuOH produced the desired ring-contracted acylcyclopentene **225** in 53% yield. Our isolation of the desired product in greater than 10% yield indicated to us that  $\beta$ -hydroxyketone **231** is readily converted to **225**, whereas the minor cycloheptenone **180** remained in the reaction after consumption of **231**. Since  $\beta$ -hydroxyketone **231** is equivalent to the first step of the retro-aldol/aldol sequence (through water addition to the enone) and is available as the major product from the reduction of **229**, it thus provided us with an ideal substrate on which to pursue further studies.<sup>48</sup>

Scheme 3.3.4. Reduction of ketone **229** and preliminary ring contraction



Our subsequent efforts to maximize the efficiency of this transformation focused on the ring contraction of the major reduction product,  $\beta$ -hydroxyketone **231**. Given our early result using LiOt-Bu (Scheme 3.3.4), we examined numerous aldol conditions that consisted of a variety of non-nucleophilic bases (Table 3.3.2).<sup>49</sup> We observed that several *t*-butoxides in *t*-BuOH and THF effected substrate conversion to the desired product (**225**) in good yields (entries 1–4), noting that the rate of product formation was comparatively slower with LiOt-Bu than that of Na- and KOt-Bu. The use of various hydroxides revealed a similar trend, where NaOH and KOH generated **225** in 4 hours

with improved yields over their respective *t*-butoxides (entries 5 and 6). In contrast, the reactivity of LiOH was comparatively sluggish, providing **225** in low yield with the formation of various intermediates (entry 7).<sup>50</sup> To harness the mild reactivity of LiOH while improving the yield of **225**, we investigated the effect of alcohol additives to modulate the efficacy of the transformation. The combination of *t*-BuOH and LiOH in THF increased the yield of **225** to a similar level as that observed with LiOt-Bu, although the reaction continued to proceed at a slow rate (entry 8). Application of more acidic, non-nucleophilic alcohols such as trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP)<sup>51</sup> demonstrated exceptional reactivity with LiOH to efficiently produce **225** in high yields (entries 9 and 10).<sup>52</sup> This is reflective of the recently reported use of fluorinated lithium alkoxides to promote Horner–Wadsworth–Emmons olefinations of sensitive substrates and underscores their mild reactivity and efficacy.<sup>53</sup> The data from our study further recognize the unique properties of these mild bases and suggest their application may be examined in a broader context. While a number of bases are effective in the production of **225** in good yields, we selected the combination of LiOH and TFE as our optimal conditions for scale-up efforts. Importantly, none of the conditions surveyed for the ring contraction studies generated the  $\beta$ -elimination product, cycloheptenone **180**, providing further validation that  $\beta$ -hydroxyketone **231** is an ideal substrate for this transformation.<sup>54</sup>

Table 3.3.2. Ring contraction investigations of **231**

entry <sup>a,b</sup>	base	additive	solvent	temp (°C)	t (h)	conversion (%) <sup>c</sup>	yield (%) <sup>c</sup>
1	LiOt-Bu	—	t-BuOH	40	9	100	71
2	LiOt-Bu	—	THF	40	8	100	60
3	NaOt-Bu	—	THF	40	5	100	81
4	KOt-Bu	—	THF	40	5	100	85
5	NaOH	—	THF	60	4	100	89
6	KOH	—	THF	60	4	100	87
7	LiOH	—	THF	60	24	78	19 <sup>d</sup>
8	LiOH	t-BuOH	THF	60	24	98	78
9	LiOH	TFE	THF	60	12.5	99	96
10	LiOH	HFIP	THF	60	12.5	99	87

<sup>a</sup> TFE = 2,2,2-trifluoroethanol; HFIP = hexafluoro-2-propanol. <sup>b</sup> Reactions performed with 1.5 equiv each of base and additive at 0.1 M in solvent. <sup>c</sup> Determined by GC analysis using an internal standard. <sup>d</sup> Several intermediates observed by TLC and GC analysis.

The reduction of allyl ketone **229** with acidic workup furnished  $\beta$ -hydroxyketone **231** in 90% yield and 1:1.5 dr (Scheme 3.3.5). Application of the devised ring contraction conditions consisting of LiOH and TFE in THF at 60 °C facilitated the preparation of desired acylcyclopentene **225** in 96% yield, and enabled access to multigram quantities of this important intermediate. The production of allyl ketone **229** in 88% ee from the asymmetric allylic alkylation reaction was satisfactory for our synthetic efforts, but we were interested in identifying an appropriate crystalline derivative to enhance the optical purity of our material. We thus pursued the derivatization of acylcyclopentene **225** by conversion to semicarbazone **232** in 92% yield and with a marginal increase in ee to 91%.<sup>55</sup> Recrystallization of this material provided semicarbazone **232** in 98% ee, which was readily cleaved under acidic conditions to reveal the desired acylcyclopentene (**225**). Further functionalization of semicarbazone **232** with 4-iodobenzyl amine furnished **233**,

and enabled X-ray crystal structure analysis to confirm the absolute stereochemistry of the asymmetric alkylation (Figure 3.3.1).<sup>56</sup>

Scheme 3.3.5. Scale-up, derivatization, and enantioenrichment of acylcyclopentene **225**

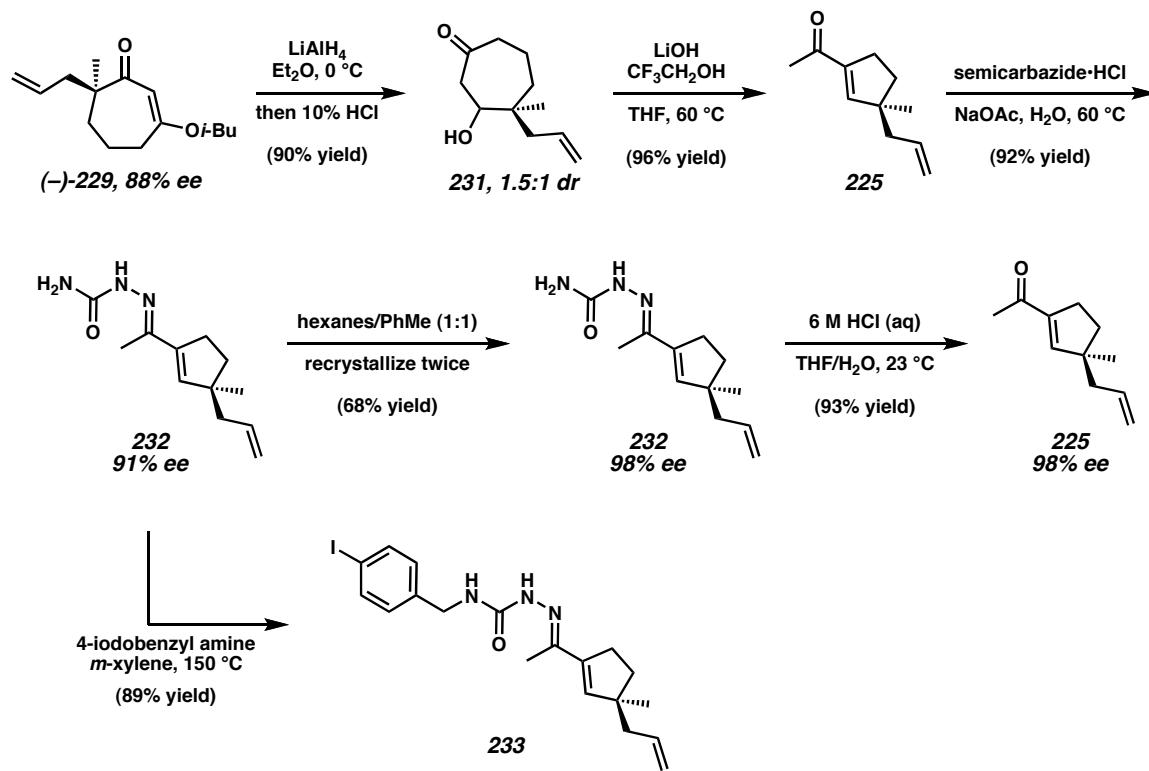
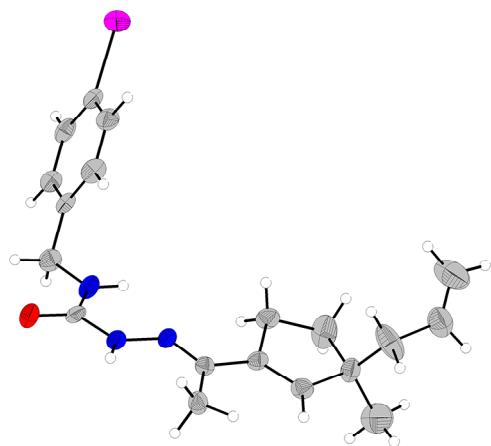
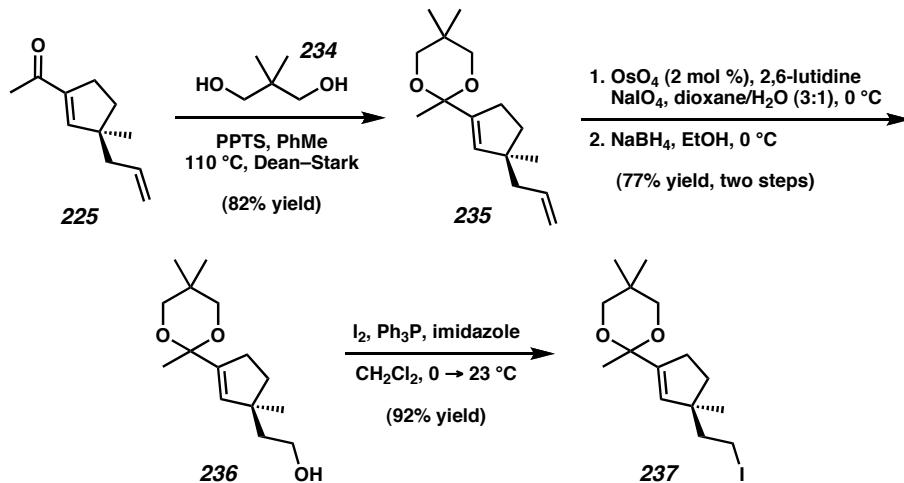


Figure 3.3.1. X-ray crystal structure of semicarbazone **233**. The molecular structure is shown with 50% probability ellipsoids.



### 3.3.3 COMPLETION OF THE D-RING FRAGMENT

The completion of a viable D-ring fragment required protection of the carbonyl as acetal **235** (Scheme 3.3.6).<sup>57</sup> Oxidative cleavage of the allyl group using modified Lemieux–Johnson conditions<sup>58</sup> with reduction of the resulting aldehyde generated alcohol **236**, a useful intermediate for further derivatization. Conversion to iodide **237** was readily achieved with iodine/Ph<sub>3</sub>P, completing the synthesis of the devised D-ring component to enable fragment-coupling studies with AB ring intermediates **222** and **223** toward the synthesis of variecolin (**95**).

Scheme 3.3.6. Completion of D-ring fragment **237**

### 3.4 STUDIES TOWARD THE FRAGMENT COUPLING OF THE AB AND D-RING FRAGMENTS TOWARD VARIECOLIN

The asymmetric syntheses of AB ring fragments **222** and **223** and D-ring fragment **237** allowed the evaluation of C-ring annulation strategies toward completion of the target. We envisioned that construction of the final two bonds of the tetracyclic core of variecolin could be achieved by a convergent, strategic operation from these advanced intermediates. An important characteristic of the cyclooctadienones generated by the Wolff/Cope rearrangement is the ability of the enone functionality to provide regiocontrol for the reductive generation of nonsymmetrical ketone enolates.<sup>59</sup> We planned to harness this regiospecific enolate generation to carry out a diastereoselective C(11)<sup>3</sup> alkylation of D-ring iodide **237** to produce a derivative of coupled diketone **175** (Scheme 3.1.1). With the fusion of fragments **223** and **237** to produce a derivative of diketone **175**, we envisioned that the final C-ring closure would occur via radical addition

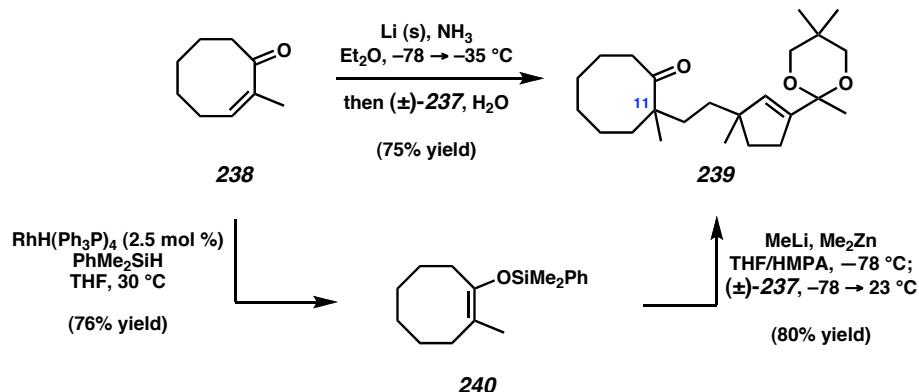
to the conjugated enone. Toward this end, we examined model compounds to determine the feasibility of this convergent approach for the construction of the C ring.

### **3.4.1 MODEL STUDIES FOR FRAGMENT COUPLING AND C-RING ANNULATION**

#### **3.4.1.1 MODEL REDUCTIVE ENONE ALKYLATION AND HYDROSILYLATION/ALKYLATION**

The availability of 2-methyl cyclooctenone (**238**) as a model  $\alpha$ -substituted eight-membered enone allowed us to evaluate various reductive methods to install the C(11) all-carbon quaternary stereocenter of variecolin (**95**). This can be readily accomplished with **238** in a one-pot dissolving metal (Li/NH<sub>3</sub>) reductive alkylation procedure<sup>60</sup> to generate an intermediate lithium enolate that was subsequently alkylated with D-ring iodide **237** to construct ketone **239** in 75% yield as a mixture of diastereomers (Scheme 3.4.1). An alternative two-step method used a rhodium(I)-catalyzed hydrosilylation of enone **238** with PhMe<sub>2</sub>SiH to produce isolable enol silane **240**.<sup>61</sup> This was next exposed to Noyori's<sup>62</sup> alkylation conditions with D-ring iodide **237** to furnish the desired quaternary ketone (**239**) in 61% yield over two steps. The results of this model study establish a reasonable precedent for the construction of the C(11) quaternary stereocenter via alkylation, and importantly underscore the reactivity of D-ring iodide **237** with a congested lithium enolate (derived from **238**).

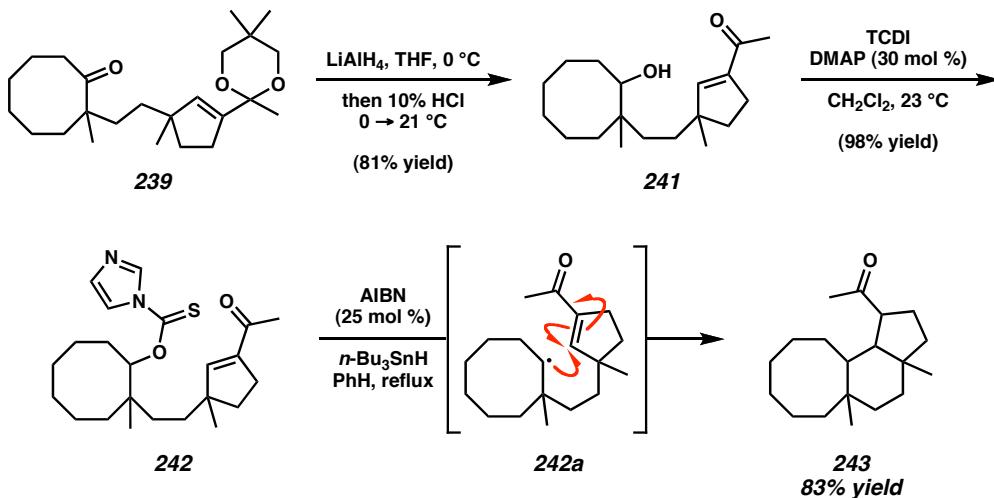
Scheme 3.4.1. Model studies for B-D ring coupling



### 3.4.1.2 MODEL C-RING RADICAL CYCLIZATION

With a plausible unification of the model fragments to form BD ring ketone **239** established, we pursued a radical-mediated formation of the final C–C bond to complete the C-ring annulation.<sup>63</sup> The requisite substrate was prepared from  $\text{LiAlH}_4$  reduction of ketone **239** with acidic workup to effect protecting group cleavage and reveal cyclopentene **241** as a mixture of four diastereomers (Scheme 3.4.2). Conversion of the alcohol into imidazoyl thiocarbonate **242** followed by the AIBN-initiated radical cyclization with slow addition of tri-*n*-butyltin hydride formed the final C–C bond of our model BCD ring core (i.e., **243**) for the variecolin sesterterpenes. This significant result provides firm precedent for the C-ring annulation approach for completion of the tetracyclic core of this family, although information concerning the stereochemistry of our model cyclization product could not be conclusively discerned from this system owing to the number of diastereomers present in the starting material and product mixtures.

Scheme 3.4.2. Model radical cyclization for annulation of the C ring



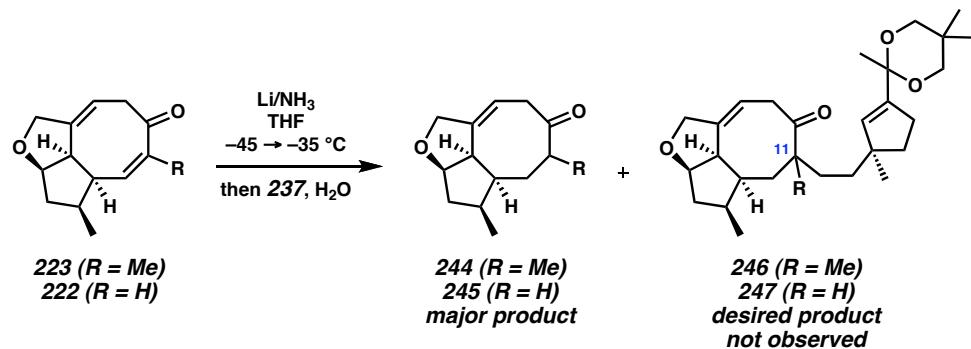
### 3.4.2 COUPLING STUDIES REGARDING THE ASYMMETRIC AB RING FRAGMENT OF VARIECOLIN

#### 3.4.2.1 ENONE REDUCTIVE ALKYLATION OF THE ASYMMETRIC AB RING FRAGMENT

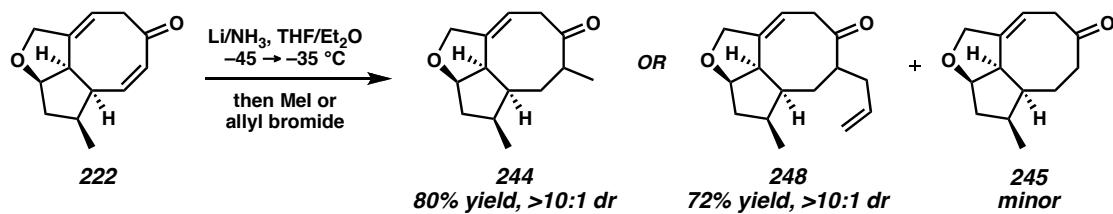
The confirmation of our model alkylation/radical cyclization sequence to form the C ring of variecolin prompted application toward the total synthesis. The direct formation of the C(11) quaternary stereocenter was initially examined using the one-pot reductive alkylation procedure. In the event, dissolving metal reduction of  $\alpha$ -substituted cyclooctadienone intermediate **223** and exposure to an excess of D-ring iodide **237** resulted in a number of products, with saturated ketone **244**—the 1,4-reduction product of **223**—as the major component (Scheme 3.4.3). Unfortunately, the desired  $\alpha$ -quaternary ketone **246** was not observed. Further investigation of this direct reductive alkylation of

AB ring fragment **222** yielded similar results, thus indicating that D-ring iodide **237** is not sufficiently reactive toward enolates derived from **222** and **223**.

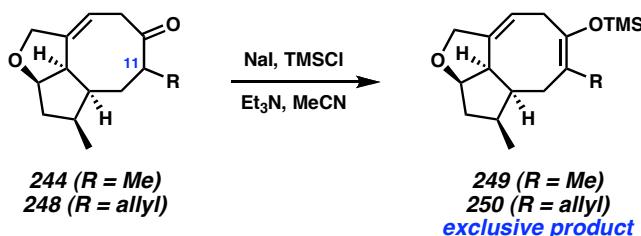
*Scheme 3.4.3. Efforts toward the direct reductive alkylation of enones **222** and **223** with iodide **237***



To understand the reactivity difference of the alkylation model system (**238**) and AB ring nucleophiles (**222** and **223**) toward the D-ring iodide (**237**), we explored more reactive electrophiles. Interestingly, the reductive alkylation of enone **222** using either methyl iodide or allyl bromide produced the desired  $\alpha$ -tertiary ketones **244** and **248** in good yield and diastereoselectivity with only minor quantities of reduced ketone **245** (Scheme 3.4.4).<sup>64</sup> These observations provide further evidence that D-ring iodide **237** is not sufficiently reactive toward AB ring nucleophiles derived from **222** and **223**. Due to limited quantities of  $\alpha$ -substituted cyclooctadienone **223**, we are currently unable to assess the potential of a direct reductive alkylation with reactive electrophiles (e.g., allyl bromide) to generate the C(11) quaternary stereocenter.

Scheme 3.4.4. Diastereoselective reductive alkylation of **222** with methyl iodide or allyl bromide

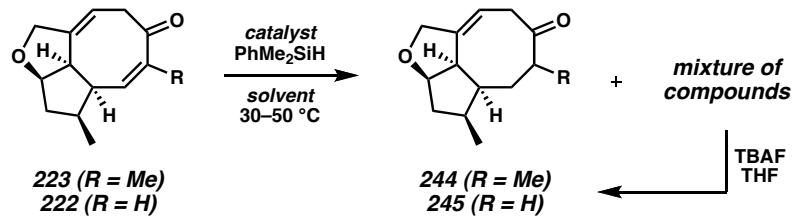
Although we are currently unable to construct the C(11) quaternary stereocenter using a direct reductive alkylation of D-ring iodide **237**, the availability of saturated  $\alpha$ -substituted ketones **244** and **248** encouraged us to determine the plausibility for regioselective enolate formation for this alkylative step. Soft enolization conditions employing  $\text{TMSI}/\text{Et}_3\text{N}^{65}$  smoothly transformed ketones **244** and **248** to tetrasubstituted enol silanes **249** and **250**, respectively, as the exclusive reaction products (Scheme 3.4.5). The preparation of various latent enolate equivalents thus expands our investigations to include a host of enolate alkylation conditions that will promote the formation of the C(11) all-carbon quaternary stereocenter.

Scheme 3.4.5. Soft enolization of ketones **244** and **248**

### 3.4.2.2 ENONE HYDROSILYLATION OF THE ASYMMETRIC AB RING FRAGMENT

After identifying an effective two-step procedure to generate substituted enol silanes in model studies (see subsection 3.4.1.1), we explored a potential one-step transformation using a transition-metal catalyzed hydrosilylation reaction. We applied conditions optimized using model studies to  $\alpha$ -substituted enone **223** that provided a number of compounds by TLC analysis, including saturated ketone **244** (Scheme 3.4.6).<sup>66</sup> We were unable to determine if any of the remaining products were the desired silyl enol ether due to difficulties encountered during purification of the side products. Purification of **244** and exposure of the mass balance to TBAF provided **244**, suggesting that some of the products formed under the reaction conditions are isomeric to the desired enol silane. The use of enone **222**, which does not possess  $\alpha$ -substitution, yielded similar results, demonstrating a unique conformational preference for the fused [5–5–8] system that inhibits the desired reactivity observed in the model system. The inability to generate a pure enol silane product and isolation difficulties halted further hydrosilylation efforts.

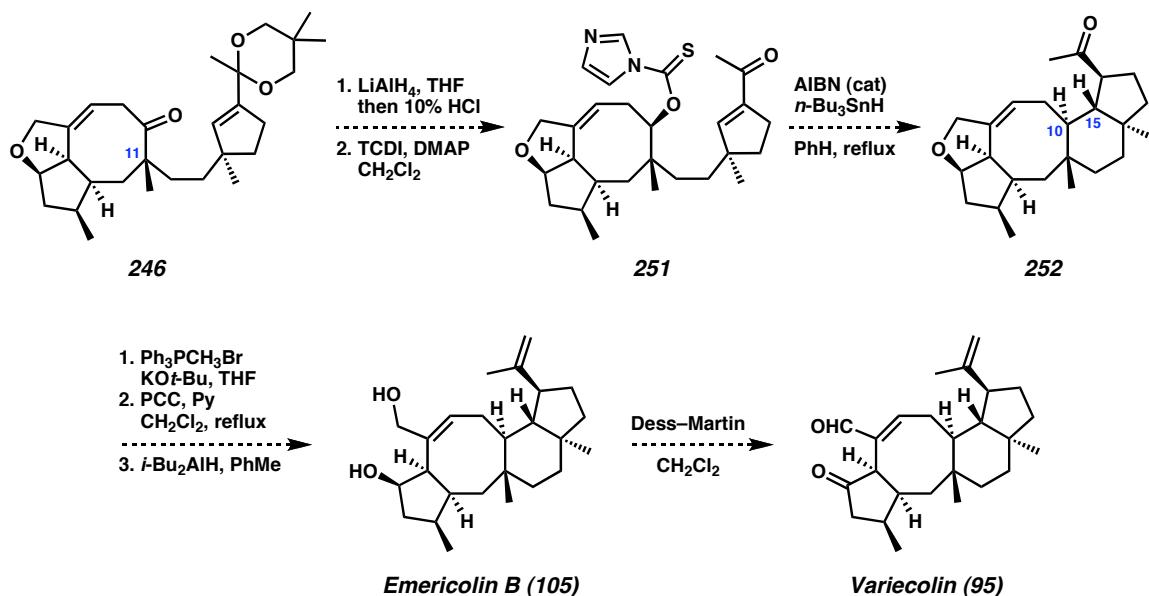
Scheme 3.4.6. Hydrosilylation investigations of enones **222** and **223**



### 3.5 PROPOSED COMPLETION OF VARIECOLIN

The regioselective preparation of enol silane **249** provides optimism for advancing the AB and D-ring fragments toward variecolin (**95**). Potential access to a variety of D-ring derivatives through our synthetic route, and the observed stereoselective alkylation (**222** → **244**, Scheme 3.4.4) are key elements that predict the success of this strategy. In the event of the desired C(11) alkylation with a suitable D-ring fragment to form ketone **246**, we anticipate that the following transformations will enable the rapid completion of the total synthesis (Scheme 3.5.1). Reduction of ketone **246** and acylation with thiocarbonyldiimidazole (TCDI) should form the imidazoyl thiocarbonate **251**. Radical generation and diastereoselective cyclization should accomplish the C(10)–C(15) ring closure to complete the tetracyclic core of variecolin (i.e., **252**). Carbonyl methylenation, allylic ether oxidation with PCC/pyridine,<sup>4b,13</sup> and lactone reduction with *i*-Bu<sub>2</sub>AlH will produce emericolin B (**105**). Diol oxidation using Dess–Martin periodinane<sup>67</sup> will then furnish variecolin (**95**).

Scheme 3.5.1. Proposed end game strategy for completion of variecolin



### 3.6 CONCLUSION

In summary, we have achieved significant progress toward a general, convergent asymmetric approach for the total synthesis of the variecolin sesterterpenoids. Our critical disconnection bisected variecolin into two highly substituted fragments containing the central eight-membered ring and an important all-carbon quaternary stereocenter. The AB ring preparation features an intriguing regioselective cleavage of a fused cyclobutene to terminally differentiated products en route to several advanced  $\alpha$ -diazoketones, and set the stage for a key tandem Wolff/Cope rearrangement to construct the eight-membered ring. Importantly, our investigations revealed the proficiency of microwave energy to promote this tandem process, and provided first examples of  $\alpha$ -substituted cyclooctadienones to further expand the collection of eight-membered rings available by this method. Our synthetic route to the D ring features a

palladium-catalyzed enantioselective alkylation of racemic vinylogous  $\beta$ -ketoester **( $\pm$ )-181** for the construction of the C(14) quaternary stereocenter. The efficient, large-scale preparation of ketone **229** enabled our development of a new strategy for the synthesis of enantioenriched quaternary cyclopentenes that harnesses the exceptional reactivity of fluorinated lithium alkoxides, and moreover, provides a new variety of substrates for our Pd-catalyzed asymmetric alkylation methodology. We believe that the results achieved from this synthetic endeavor highlight intriguing reactivity and expand synthetic methods that can be of general use for the preparation of natural and non-natural substances. Studies directed toward the coupling of these highly substituted AB and D-ring fragments for the final C-ring annulation and completion of the synthesis are ongoing.

### 3.7 EXPERIMENTAL SECTION

#### 3.7.1 MATERIALS AND METHODS

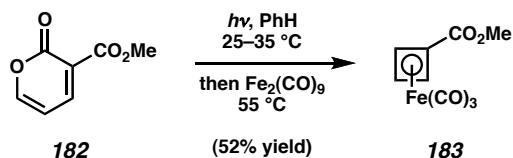
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reagent grade acetone was used as received. Water (18 MΩ) used as reaction medium was obtained from a Millipore MiliQ water purification system. All starting materials were purchased from commercial sources and used as received, unless otherwise stated. Liquids and solutions were transferred via syringe or positive-pressure cannulation. Brine solutions refer to saturated aqueous sodium chloride solutions. Diiron nonacarbonyl was stored and handled in a glove box. Triethylamine, diisopropylamine, and *t*-BuOH were distilled from CaH<sub>2</sub> prior to use. The following liquids were purified by distillation and stored in a Schlenk tube under nitrogen: acetic acid (from CrO<sub>3</sub>), hexamethylphosphoramide (from CaH<sub>2</sub>), and oxalyl chloride. Zinc dust was activated over 1% HCl. Solutions of *n*-BuLi, MeLi, *p*-TolMgBr, and MeMgCl were titrated prior to use. Molecular sieves were dried and stored in a 115 °C oven. Anhydrous granular LiOH was pulverized using a mortar and pestle. Lithium wire was stored over mineral oil and washed with hexanes, then methanol, then hexanes prior to use. Previously reported methods were used to prepare Pd<sub>2</sub>(pmdba)<sub>3</sub>,<sup>68</sup> (*S*)-*t*-Bu-PHOX ((*S*)-**55**),<sup>69</sup> fluorinated PHOX ligand **230**,<sup>46</sup> and RhH(Ph<sub>3</sub>P)<sub>4</sub>.<sup>70</sup> Diazomethane (**199**) was freshly prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) as a solution in Et<sub>2</sub>O using a Diazald kit. Diazoethane (**219**) was freshly prepared from *N*-ethyl-*N*-nitrosourea<sup>71</sup> as a solution in Et<sub>2</sub>O using a

Diazald kit. Diazoalkane solutions were dried over KOH pellets for ca. 30 min at or below 0 °C and cannula (Teflon) transferred under nitrogen to a dry Erlenmeyer flask prior to use. Reaction temperatures were controlled by an IKAmag temperature modulator. Ozonolysis reactions were performed with an OzoneLab OL80 Desktop ozone generator. Photochemical irradiation was performed in septum sealed quartz tubes with a Luzchem Photochemical reactor or with a water-cooled Hanovia 450 W medium pressure mercury-vapor immersion lamp. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz. Thin-layer chromatography was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, potassium permanganate, or ceric ammonium molybdate staining. SiliCycle SiliaFlash P60 Academic Silica Gel (particle size 40–63 µm; pore diameter 60 Å) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiraldex OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with 1 mL/min mobile phase and visualization at 254 nm. Analytical achiral GC was performed on an Agilent 6850 GC with FID detector using an Agilent DB-WAX (30.0 m x 0.25 mm) column at 1.0 mL/min He carrier gas flow. Chiral GC was performed on an Agilent 6850 GC with FID detector using a Chiraldex GTA column (30.0 m x 0.25 mm, purchased from Bodman Industries) at 1.0 mL/min He carrier gas flow. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using spectrophotometric grade solvents. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), Varian Inova 500 (at 500 MHz and 126 MHz, respectively) or Varian Inova 600 (at 600 MHz), and are reported relative to Me<sub>4</sub>Si (δ 0.0

ppm).<sup>72</sup> Data for <sup>1</sup>H NMR spectra are reported as follows: chemical shift ( $\delta$  ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm<sup>-1</sup>). Melting points were acquired using a Buchi Melting Point B-545 instrument and the values are uncorrected. High-resolution mass spectra were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in ESI, APCI, or MM (ESI/APCI) ionization mode, in addition to the Caltech Mass Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

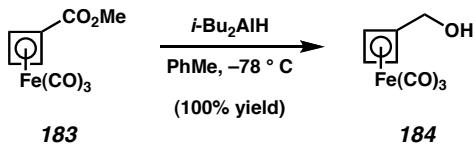
### 3.7.2 PREPARATIVE PROCEDURES

#### 3.7.2.1 TRICARBONYLIRON-CYCLOBUTADIENE FRAGMENTS



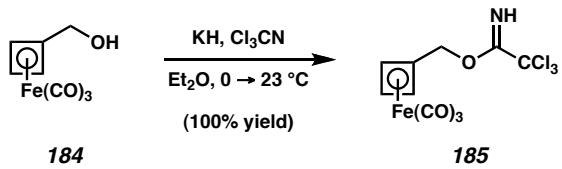
**Tricarbonyliron-cyclobutadiene methyl ester 183.**<sup>13b</sup> Pyrone **182** (5.086 g, 33.00 mmol, 1.0 equiv) was dissolved in spectrophotometric grade benzene (1 L, 0.033 M) in a flame-dried 1 L photochemical reactor containing a stir bar, the reactor and lamp were assembled and the solution was sparged with N<sub>2</sub> for 30 min. The resulting degassed solution was irradiated with a Hanovia medium-pressure mercury-vapor lamp affixed with a pyrex filter until consumption of pyrone **182** by TLC (5:1 CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, typically requires 20 h to 5 d; T<sub>internal</sub> = 25–35 °C). The lamp was removed from the reactor and the solution was transferred to a dry 3 L flask containing a stir bar, washing the photoreaction with excess benzene (2 x 30 mL). Fe<sub>2</sub>(CO)<sub>9</sub> (14.4 g, 39.6 mmol, 1.2 equiv) was weighed into a glass jar in a glove box, transferred out of the box, and added to the reaction. The resulting suspension was warmed to 50 °C (internal) in an oil bath (T = 55–60 °C) and after 2 h at 50 °C, a second portion of Fe<sub>2</sub>(CO)<sub>9</sub> (2.40 g, 6.60 mmol, 0.2 equiv) was added to the reaction. After another 1 h, the turbid reaction was cooled to room temperature and filtered through a plug of basic alumina (5 x 8 cm) capped with Celite (5 x 16 cm) washing with excess Et<sub>2</sub>O (ca. 400 mL) until the eluent was colorless. The dark yellow solution was concentrated under reduced pressure to a turbid, yellow/brown oil. The crude material was purified by flash chromatography on SiO<sub>2</sub> (2.5

x 24 cm, 15:1 → 9:1 → 4:1 hexanes/Et<sub>2</sub>O) to afford tricarbonyliron-cyclobutadiene methyl ester **183** (4.2585 g, 17.03 mmol, 52% yield) as a dark yellow/brown oil that solidified in a -20 °C freezer.  $R_f$  = 0.54 (2:1 hexanes/EtOAc); <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 3.84 (s, 2H), 3.22 (s, 3H), 3.20 (s, 1H). All other spectral data are consistent with reported values.



**Hydroxymethyl cyclobutadiene 184.** To a solution of cyclobutadiene ester **183** (9.066 g, 36.27 mmol, 1.0 equiv) in PhMe (120 mL, 0.3 M) at -78 °C was added neat *i*-Bu<sub>2</sub>AlH (14.54 mL, 81.60 mmol, 2.25 equiv) dropwise over 15 min with vigorous stirring. Upon consumption of **183** by TLC analysis (typically as last of *i*-Bu<sub>2</sub>AlH is added), EtOAc (3.54 mL, dried over MgSO<sub>4</sub>, 1.0 equiv) was added and after 5 min the reaction was placed in a 0 °C ice bath. After 30 min the reaction was slowly quenched with a 1 M solution of Na/K tartrate (100 mL) with vigorous stirring. After 5 min, the cooling bath was removed and EtOAc (50 mL) was added to the thick suspension. When the layers became homogeneous (typically 5–8 h), the layers were separated and the aq phase was extracted with Et<sub>2</sub>O (2 x 50 mL). The combined organic layers were dried with MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The thick oil was dried under high vacuum until a constant mass was achieved to afford hydroxymethyl cyclobutadiene **184** (8.105 g, 36.51 mmol, 100% yield) as a pale brown solid.  $R_f$  = 0.29 (2:1 hexanes/EtOAc); <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 3.37 (s, 3H), 3.34 (s, 1H), 3.26 (s, 1H), 0.62 (t, *J* = 5.9 Hz, 1H); <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 214.9, 85.0, 63.9, 62.2, 58.0; IR

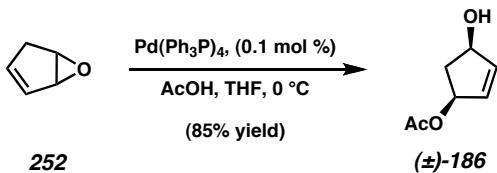
(Neat Film NaCl) 3326 (br), 2932, 2872, 2046, 1963, 1448, 1297, 1070, 997, 822, 613  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_8\text{H}_6\text{O}_4\text{Fe} [\text{M}]^+$ : 221.9616, found 221.9615.



**Cyclobutadiene trichloroacetimidate 185.** To a round-bottom flask charged with KH (41 mg, 1.0 mmol, 0.057 equiv) and  $\text{Et}_2\text{O}$  (43 mL) at 0 °C was added a solution of hydroxymethyl cyclobutadiene **184** (3.86 g, 17.4 mmol, 1.0 equiv) in  $\text{Et}_2\text{O}$  (43 mL, 0.2 M total) by cannula. After 10 min, trichloroacetonitrile (8.7 mL, 87 mmol, 5.0 equiv) was added to the light orange solution dropwise by syringe. Over the course of the addition, the reaction turned dark brown. After 15 min, the ice bath was removed and the reaction was allowed to warm to room temperature. Upon reaching ambient temperature the volatiles were removed in *vacuo* and the remaining dark brown oil was taken up in hexane (20 mL, from solvent column) with *vigorous* shaking. This solution was filtered through a pad of Celite, and the reaction flask was washed with an additional portion of hexane (20 mL) and filtered. The combined filtrate was concentrated in *vacuo* to afford trichloroacetimidate **185** (6.38 g, 17.4 mmol, 100% yield) as a clear, pale red oil. This oil was immediately used in the next step without further purification and is not stable to prolonged storage.  $R_f$  = *unstable to SiO<sub>2</sub>*;  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  8.22 (br s, 1H), 4.25 (s, 2H), 3.49 (s, 2H), 3.30 (s, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  214.5, 162.6, 92.0, 76.8, 65.7, 64.9, 64.5; IR (Neat Film NaCl) 3344, 2049, 1971, 1666, 1449, 1368, 1304,

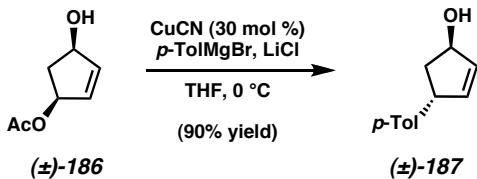
1288  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_9\text{H}_6\text{Cl}_3\text{FeNO}_3$  [ $\text{M} - \text{CO}$ ] $^+$ : 336.8763, found 336.8769.

### 3.7.2.2 AB RING MODEL SYSTEM FRAGMENTS

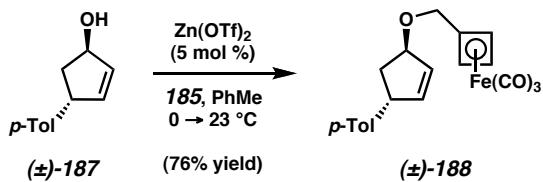


**Monoacetate 186.**<sup>15</sup> A 1 L 3-neck flask fitted with an addition funnel was charged with  $\text{Pd}(\text{Ph}_3\text{P})_4$  (595 mg, 0.515 mmol, 0.001 equiv) and dissolved in THF (258 mL, 2 M). The catalyst solution was cooled to 0 °C and a solution of epoxide **252** (42.29 g corrected, 515.1 mmol, 1.0 equiv) in THF (86 mL) was transferred to the addition funnel via cannulation. To the catalyst solution was added AcOH (29.5 mL, 515.1 mmol, 1.0 equiv) via syringe, followed by the solution of **252** via addition funnel over 20 min. Upon consumption by TLC (reaction turns orange in color when complete) the solution was transferred to a flask washing with EtOAc and concentrated in vacuo. The crude material was purified by flash chromatography on  $\text{SiO}_2$  (7 x 5 cm, dry load onto  $\text{SiO}_2$ , flush with  $\text{Et}_2\text{O}$  until product elutes by TLC) to afford monoacetate  $(\pm)\text{-186}$  as a yellow semisolid. This was diluted with heptane (100 mL), concentrated and dried under high vacuum to afford a pale yellow semisolid (62.30 g, 438.3 mmol, 85.1% yield) that completely solidified in a -20 °C freezer.  $R_f = 0.33$  (1:1 hexanes/EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.12 (ddd,  $J = 5.61, 2.07, 1.30$  Hz, 1H), 5.99 (ddd,  $J = 5.57, 2.04, 1.06$  Hz, 1H), 5.52–5.47 (m, 1H), 4.76–4.69 (m, 1H), 2.81 (app dt,  $J = 14.7, 7.4$  Hz, 1H),

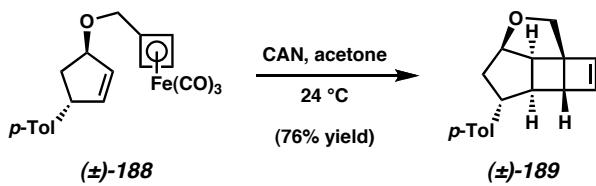
2.06 (s, 3H), 1.72 (br s, 1H), 1.66 (app dt,  $J$  = 14.6, 3.8 Hz, 1H). All other spectral data are consistent with reported values.



**Aryl cyclopentenol 187.**<sup>14b</sup> A flask was charged with LiCl (896.4 mg, 21.1 mmol, 4.0 equiv), flame-dried under vacuum and cooled under nitrogen. To this was added CuCN (142 mg, 1.59 mmol, 0.3 equiv) and the solids were partially dissolved in THF (20 mL) and cooled to 0 °C. To this suspension was added a solution *p*-TolMgBr (15.9 mL, 15.9 mmol, 1 M in Et<sub>2</sub>O). After 5 min, a solution of monoacetate **(±)-186** (751.5 mg, 5.29 mmol, 1.0 equiv) in THF (15 mL) over 5 min via cannulation and the flask was washed with additional THF (2 x 1 mL) for a quantitative transfer. Upon consumption of **186** by TLC (ca. 1.5 h), the reaction was slowly quenched with sat aq NH<sub>4</sub>Cl (10 mL) and water (5 mL) and stirred vigorously for 30 min. The homogeneous phases were separated, the aq layer was extracted with EtOAc (3 x 30 mL), and the combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on SiO<sub>2</sub> (6:1 → 3:1 → 1:1 hexanes/Et<sub>2</sub>O) to afford aryl cyclopentenol **187** (829.7 mg, 4.76 mmol, 90% yield) as a pale yellow oil.  $R_f$  = 0.63 (1:1 hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.10 (d,  $J$  = 7.83, 2H), 7.03 (d,  $J$  = 8.0 Hz, 2H), 6.04–6.01 (comp m, 2H), 5.05 (d,  $J$  = 5.1 Hz, 1H), 4.13–4.10 (m, 1H), 2.32 (s, 3H), 2.27 (ddd,  $J$  = 14.1, 8.0, 2.7 Hz, 1H), 2.09 (ddd,  $J$  = 14.1, 7.0, 5.5, 1H). All other spectral data are consistent with reported values.

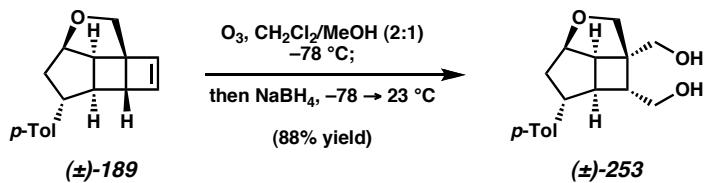


**Aryl cyclopentenol ether 188.** To a round-bottom flask charged with zinc(II) triflate (14.9 mg, 0.041 mmol, 5 mol %) and PhMe (0.2 mL) at 0 °C was added aryl cyclopentenol **187** (151.3 mg, 0.868 mmol, 1.0 equiv) by syringe. To this suspension was added a solution of cyclobutadiene trichloroacetimidate **185** (370 mg, 1.01 mmol, 1.2 equiv) in PhMe (0.2 mL) by cannula transfer, with further washing by additional PhMe (0.2 mL). A yellow precipitate was observed at the beginning of the addition, and this turned into a thick slurry upon completion of the addition. The ice bath was allowed to expire over 1.5 h and the reaction was stirred for an additional 6 h at ambient temperature. The crude reaction mixture was transferred directly onto a 5 g silica gel loading cartridge and purified with a Teledyne ISCO CombiFlash system using a 40 g silica column (1:0 → 9:1 hexanes/EtOAc) to afford ether **188** (250.8 mg, 0.663 mmol, 76% yield) as a pale yellow oil.  $R_f$  = 0.56 (4:1 hexanes/EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.00 (d,  $J$  = 7.8 Hz, 2H), 6.94 (d,  $J$  = 7.9 Hz, 2H), 5.88–5.85 (m, 1H), 4.45–4.44 (m, 1H), 3.96–3.94 (m, 1H), 3.55 (d,  $J$  = 1.2 Hz, 2H), 3.46 (s, 2H), 3.33 (s, 1H), 2.28 (ddd,  $J$  = 13.8, 6.9, 5.4 Hz, 1H), 2.14 (s, 3H), 1.86 (ddd,  $J$  = 13.7, 6.9, 5.4 Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  215.0, 142.3, 140.1, 135.9, 131.6, 129.5, 127.4, 84.9, 82.5, 64.6 (two lines), 64.0, 62.3, 50.1, 41.2, 21.0; IR (Neat Film NaCl) 2863, 2044, 1959, 1513, 1075, 1048, 613  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{20}\text{H}_{18}\text{O}_4\text{Fe}$  [M] $^+$ : 378.0554, found 378.0551.



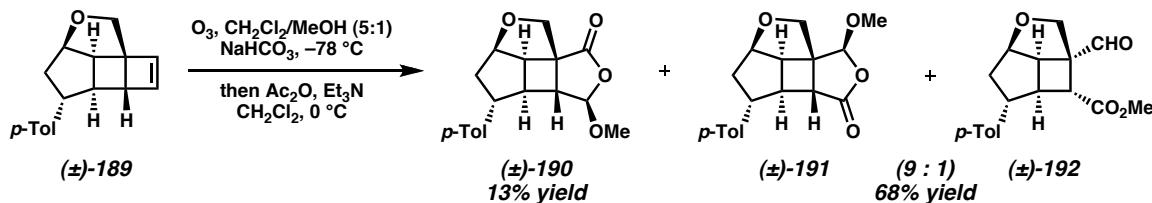
**Aryl cyclobutene 189.** To a vigorously stirring solution of aryl cyclopentenol ether **188** (683 mg, 1.806 mmol, 1.0 equiv) in acetone (1.81 mL, 1 mM) was added CAN (1.98 g, 3.61 mmol, 2.0 equiv) under ambient atmosphere. After 15 min, a second portion of CAN (1.98 g, 3.61 mmol, 2.0 equiv) was added. After 5 min, TLC showed consumption of **188** (4:1 hexanes/Et<sub>2</sub>O, developed twice) and the reaction was quenched by addition of sat aq NaHCO<sub>3</sub> (50 mL). After 15 min, stirring was ceased, the solids were allowed to settle and the supernatant was decanted into a flask (to prevent bumping) and concentrated in vacuo to ca. 50 mL. This slurry and the remnants of the flask were transferred to a separatory funnel with minimal acetone, diluted with brine (10 mL) and pentane (200 mL). The layers were separated, the organic phase was washed with water (2 x 100 mL), and the combined aq layers were extracted with 1:1 hexanes/Et<sub>2</sub>O (200 mL). The combined organic layers were concentrated to ca. 25 mL, transferred to a sep funnel and diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and brine (25 mL). The layers were separated, the aq was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 30 mL), the organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to a dark orange oil. The crude material was purified by flash chromatography on SiO<sub>2</sub> (2.5 x 21 cm, 15:1 → 9:1 hexanes/Et<sub>2</sub>O, slow gradient) to afford aryl cyclobutene **189** (326.2 mg, 1.37 mmol, 76% yield) as a colorless oil that solidified in a -20 °C freezer. *R*<sub>f</sub> = 0.54 (4:1 hexanes/Et<sub>2</sub>O, developed twice); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.11 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.35 (d, *J* = 2.1

Hz, 1H), 6.31 (d,  $J$  = 2.3 Hz, 1H), 4.71–4.69 (m, 1H), 3.91 (d,  $J$  = 9.8 Hz, 1H), 3.87 (d,  $J$  = 9.8 Hz, 1H), 3.27 (ddd,  $J$  = 8.6, 8.6, 3.9 Hz, 1H), 3.06 (app t,  $J$  = 3.1 Hz, 1H), 2.94 (s, 1H), 2.46 (ddd,  $J$  = 13.8, 7.0, 2.3 Hz, 1H), 2.35 (app t,  $J$  = 4.8 Hz, 1H), 2.32 (s, 3H), 2.03 (ddd,  $J$  = 13.8, 8.8, 4.9 Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  142.9, 140.3, 138.4, 135.6, 129.3, 127.2, 84.1, 71.2, 59.6, 54.9, 52.6, 50.3, 46.5, 44.6, 21.1; IR (Neat Film) NaCl) 3025, 2949, 1514, 1074, 1041, 1025, 811, 744  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{17}\text{H}_{17}\text{O} [\text{M} + \text{H} - \text{H}_2]^+$ : 237.1279, found 237.1271.



**Diol 253.** To a solution of aryl cyclobutene **189** (18.0 mg, 75.5  $\mu$ mol, 1.0 equiv) in a 2:1 mixture of  $\text{CH}_2\text{Cl}_2$  (1.0 mL) and MeOH (0.5 mL) was added a solution of Sudan Red 7b (25  $\mu$ L of a 0.05 wt % in MeOH) and cooled to  $-78$   $^{\circ}\text{C}$ . The resulting pink solution was sparged with a gentle stream of oxygen for  $\sim$ 1 min, then ozonolyzed until consumption of **189** by TLC (indicator typically turned colorless just prior to completion). The solution was sparged with oxygen for another 1 min, and  $\text{NaBH}_4$  (28.8 mg, 0.76 mmol, 10 equiv) was added and the bath was removed. When the reaction reached room temperature,  $\text{CH}_2\text{Cl}_2$  (2 mL) was added followed by quenching with 10% HCl (1 mL). The layers were separated, the aq extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 2 mL), the organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on  $\text{SiO}_2$  to afford diol **253** (18.2 mg, 66.3  $\mu$ mol, 88% yield) as a colorless oil.  $R_f$  = 0.31 (3:1 hexanes/EtOAc);  $^1\text{H}$  NMR (300 MHz,

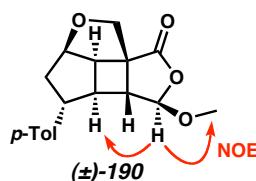
$\text{CDCl}_3$ )  $\delta$  7.09 (d,  $J$  = 8.1 Hz, 2H), 7.00 (d,  $J$  = 8.0 Hz, 2H), 4.60 (app t,  $J$  = 4.3 Hz, 1H), 4.24 (d,  $J$  = 11.5 Hz, 1H), 4.10 (d,  $J$  = 9.2 Hz, 1H), 3.88–3.78 (comp m, 2H), 3.69 (d,  $J$  = 9.2 Hz, 1H), 3.55 (d,  $J$  = 11.5 Hz, 1H), 3.42 (ddd,  $J$  = 10.6, 7.1, 3.8 Hz, 1H), 3.09 (br s, 2H), 2.82 (dd,  $J$  = 8.5, 5.3 Hz, 1H), 2.58 (dd,  $J$  = 14.0, 7.2 Hz, 1H), 2.36 (dd,  $J$  = 11.0, 5.4 Hz, 1H), 2.31 (s, 3H), 1.99 (app dt,  $J$  = 8.7, 4.4 Hz, 1H), 1.73 (ddd,  $J$  = 13.9, 10.5, 3.4 Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.1, 135.7, 129.3, 127.0, 86.2, 80.6, 63.5, 63.4, 51.4, 50.8, 50.7, 49.1, 44.8, 42.2, 21.1; IR (Neat Film NaCl) 3332 (br), 2922, 1514, 1436, 1100, 1037, 811  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{17}\text{H}_{21}\text{O}_3$  [ $\text{M} + \text{H} - \text{H}_2$ ] $^+$ : 273.1491, found 273.1485.



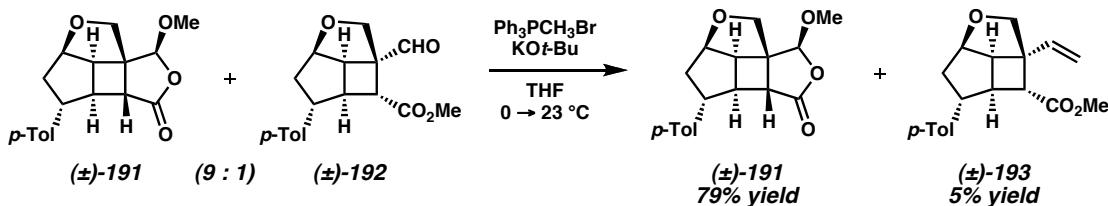
**Ozonolysis of cyclobutene 189 to form acetals 190 and 191, along with aldehyde 192.** To a solution of aryl cyclobutene **189** (49.6 mg, 0.208 mmol, 1.0 equiv) in a 5:1 mixture of  $\text{CH}_2\text{Cl}_2$  (1.75 mL) and MeOH (0.35 mL, 0.1 M total) was added  $\text{NaHCO}_3$  (5.2 mg, 63  $\mu\text{mol}$ , 0.3 equiv) and a solution of Sudan Red 7b (75  $\mu\text{L}$  of a 0.05 wt % solution in MeOH). The resulting pink-colored solution was cooled to  $-78^\circ\text{C}$ , sparged with a stream of oxygen for 1 min, then ozonolyzed until consumption of **189** by TLC (typically just as indicator turns colorless). The solution was sparged with oxygen for 1 min, the gas inlet was removed and the flask was fitted with a drying tube and warmed to room temperature. The crude reaction was filtered through a cotton plug with  $\text{CH}_2\text{Cl}_2$  (2 x 1 mL) and benzene (1 mL). The filtrate was concentrated to ca. 0.5 mL in vacuo,

diluted with 5 mL of benzene, and further concentrated to ca. 0.5 mL. This crude was dissolved in  $\text{CH}_2\text{Cl}_2$  (2.1 mL), cooled to 0 °C, and  $\text{Ac}_2\text{O}$  (58.5  $\mu\text{L}$ , 0.624 mmol, 3 equiv) and  $\text{Et}_3\text{N}$  (37.7  $\mu\text{L}$ , 0.270 mmol, 1.3 equiv) were added. After 5 min the bath was removed and the reaction was stirred at room temperature for 5 h, at which point the reaction was diluted with  $\text{CH}_2\text{Cl}_2$  (25 mL), washed with 5%  $\text{H}_2\text{SO}_4$  (3 x 5 mL), sat aq  $\text{NaHCO}_3$  (3 x 5 mL), brine, and dried over  $\text{Na}_2\text{SO}_4$ . The crude pale yellow oil was purified by flash chromatography on  $\text{SiO}_2$  (4:1  $\rightarrow$  3:1  $\rightarrow$  1:1 hexanes/EtOAc) to furnish acetal **190** (8.3 mg, 27.6  $\mu\text{mol}$ , 13% yield) as a colorless oil and an inseparable 9:1 mixture of acetal **191** and aldehyde **192** (42.6 mg, 0.142 mmol, 68% yield) as a pale yellow oil.

**Acetal 190.**  $R_f$  = 0.52 (1:2 hexanes/Et<sub>2</sub>O); <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.13 (d,  $J$  = 7.8 Hz, 2H), 7.05 (d,  $J$  = 8.1 Hz, 2H), 5.36 (s, 1H), 4.75 (dd,  $J$  = 5.2, 4.0 Hz, 1H), 4.13 (d,  $J$  = 9.7 Hz, 1H), 4.01 (d,  $J$  = 9.7 Hz, 1H), 3.56 (app t,  $J$  = 6.3 Hz, 1H), 3.49 (s, 3H), 3.48–3.45 (m, 1H), 2.58–2.52 (comp m, 3H), 2.33 (s, 3H), 1.80 (ddd,  $J$  = 14.4, 10.9, 3.7 Hz, 1H); <sup>13</sup>C NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  175.5, 141.3, 136.3, 129.5, 127.2, 109.0, 85.9, 73.0, 56.8, 55.5, 51.9, 51.3, 51.2, 44.5, 44.2, 21.1; IR (Neat Film NaCl) 2927, 1773, 1515, 1353, 1182, 1143, 1118, 1018, 990, 930, 814  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{18}\text{H}_{21}\text{O}_4$  [M + H]<sup>+</sup>: 301.1440, found 301.1448. Relative stereochemistry determined by NOE interactions shown below.



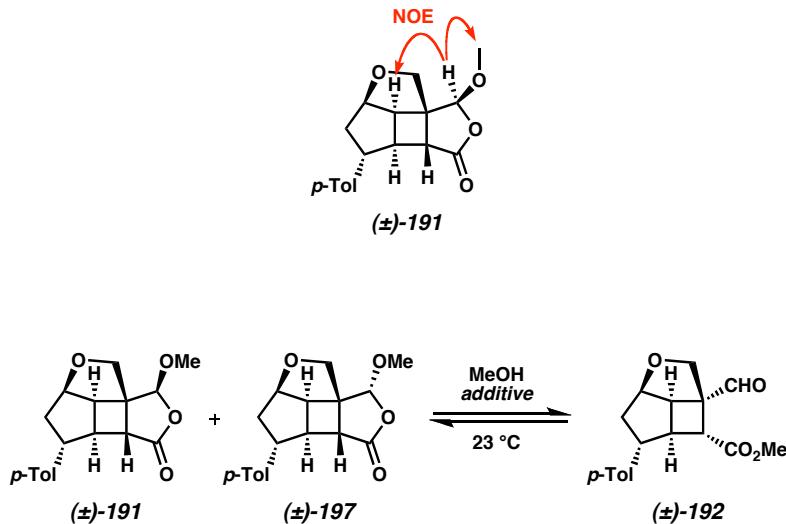
**Mix of acetal 191 and aldehyde 192.** Aldehyde **192** was difficult to isolate as a pure compound, as it usually contained varying quantities of acetal **191**. It has the following spectrum:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.76 (s, 1H), 7.10 (d,  $J$  = 8.3 Hz, 2H), 7.04 (d,  $J$  = 8.2 Hz, 2H), 4.69 (dd,  $J$  = 4.5, 3.9 Hz, 1H), 4.10 (d,  $J$  = 9.6 Hz, 1H), 3.91 (d,  $J$  = 9.7 Hz, 1H), 3.70 (s, 3H), 3.59 (dd,  $J$  = 8.3, 5.3 Hz, 1H), 3.45 (ddd,  $J$  = 10.7, 7.1, 3.7 Hz, 1H), 3.06–2.97 (comp m, 2H), 2.63 (dd,  $J$  = 14.2, 7.3 Hz, 1H), 2.31 (s, 3H), 1.81 (ddd,  $J$  = 14.1, 10.6, 3.4 Hz, 1H).



**Wittig methylenation to form olefin **193** and recover acetal **191**.** To a suspension of methyltriphenylphosphonium bromide (23.6 mg, 66  $\mu\text{mol}$ , 0.58 equiv) in  $\text{THF}$  (0.4 mL) at  $0^\circ\text{C}$  was added  $\text{KO}t\text{-Bu}$  (6.4 mg, 57  $\mu\text{mol}$ , 0.5 equiv) in one portion. The white suspension immediately turned bright yellow in color and was stirred for 15 min, at which point a solution of a ~9:1 mixture acetal **191** and aldehyde **192** (34.2 mg, 114  $\mu\text{mol}$ , 1.0 equiv) in  $\text{THF}$  (0.2 mL) was quantitatively transferred via cannulation. After 30 min, the reaction was quenched with 0.5 mL water and diluted with  $\text{CH}_2\text{Cl}_2$  (3 mL). The layers were separated, the aq layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 2 mL), the organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The crude material was purified by preparative TLC on  $\text{SiO}_2$  (2:1 hexanes/EtOAc) to give olefin **193** (1.8 mg, 6.0  $\mu\text{mol}$ , 5% yield) as a colorless oil and recovered acetal **191** (27.1 mg, 90.2  $\mu\text{mol}$ , 79% yield) as a colorless oil.

**Olefin 193.**  $R_f = 0.62$  (2:1 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.09 (d,  $J = 8.0$  Hz, 2H), 7.05 (d,  $J = 8.2$  Hz, 2H), 5.94 (dd,  $J = 17.5, 10.8$  Hz, 1H), 5.18 (dd,  $J = 10.8, 1.1$  Hz, 1H), 5.14 (dd,  $J = 17.5, 1.1$  Hz, 1H), 4.64 (app t,  $J = 4.3$  Hz, 1H), 4.03 (d,  $J = 9.2$  Hz, 1H), 3.62 (s, 3H), 3.57 (d,  $J = 9.2$  Hz, 1H), 3.40 (ddd,  $J = 10.7, 7.3, 3.8$  Hz, 1H), 3.26 (dd,  $J = 8.5, 5.2$  Hz, 1H), 3.04–3.01 (m, 1H), 2.98 (d,  $J = 5.5$  Hz, 1H), 2.64 (dd,  $J = 14.1, 7.3$  Hz, 1H), 2.31 (s, 3H), 1.78 (ddd,  $J = 14.0, 10.5, 3.3$  Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.3, 142.6, 135.6, 134.7, 129.2, 127.1, 116.3, 86.5, 78.9, 55.2, 53.0, 51.6, 51.2, 51.1, 45.0, 40.8, 21.1; IR (Neat Film NaCl) 2952, 2922, 1733, 1515, 1435, 1210, 1158, 1055, 1037, 919, 812  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{19}\text{H}_{22}\text{O}_3$  [M] $^+$ : 298.1569, found 298.1580.

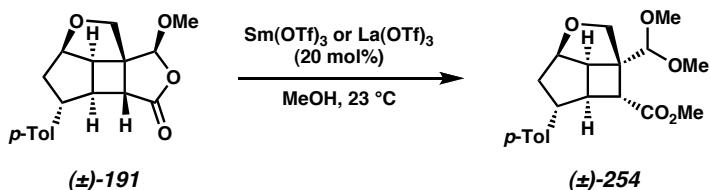
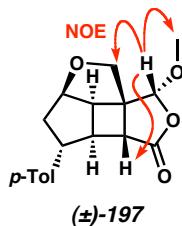
**Acetal 191.**  $R_f = 0.33$  (1:2 hexanes/Et<sub>2</sub>O);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.09 (d,  $J = 8.0$  Hz, 2H), 7.06 (d,  $J = 8.1$  Hz, 2H), 5.40 (s, 1H), 4.71 (dd,  $J = 5.4, 3.1$  Hz, 1H), 4.08 (d,  $J = 10.5$  Hz, 1H), 3.78 (d,  $J = 10.5$  Hz, 1H), 3.55 (app pentet,  $J = 6.1$  Hz, 1H), 3.48 (s, 3H), 3.31 (dd,  $J = 7.4, 5.7$  Hz, 1H), 2.89 (d,  $J = 2.4$  Hz, 1H), 2.66 (ddd,  $J = 7.6, 5.2, 2.4$  Hz, 1H), 2.53 (dd,  $J = 13.8, 6.7$  Hz, 1H), 2.31 (s, 3H), 1.76 (ddd,  $J = 13.9, 11.7, 3.2$  Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.7, 140.1, 136.1, 129.4, 127.1, 106.3, 85.7, 71.8, 56.8, 55.0, 51.1, 50.0, 47.9, 46.2, 43.9, 21.1; IR (Neat Film NaCl) 2925, 2847, 1772, 1516, 1352, 1207, 1168, 1144, 1108, 1042, 943, 814, 729, 705  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{18}\text{C}_{21}\text{O}_4$  [M + H] $^+$ : 301.1440, found 301.1444. Relative stereochemistry determined by NOE interactions shown below.



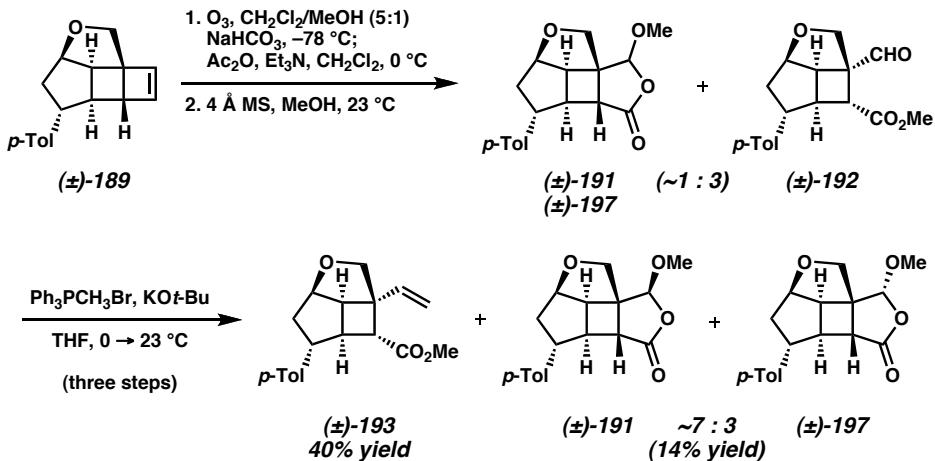
**Equilibration of acetal 191.** To a solution of pure acetal **191** in MeOH (25 mM) as added the appropriate additive (MS = 0.5 mg/μmol; Lewis acid = 20 mol %). The reaction atmosphere was purged with nitrogen, capped and stirred at ambient temperature. After 20–24 h the reaction was diluted with Et<sub>2</sub>O, filtered through a small plug of SiO<sub>2</sub> and concentrated in vacuo. The crude filtrate was then analyzed by <sup>1</sup>H NMR analysis. In addition to acetal **191** and aldehyde **192**, acetal diastereomer **197** was identified as a minor product.

**Acetal 197.**  $R_f$  = 0.19 (1:2 hexanes/Et<sub>2</sub>O); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.1 (d,  $J$  = 8.0 Hz, 2H), 7.06 (d,  $J$  = 8.1 Hz, 2H), 5.30 (s, 1H), 4.68 (dd,  $J$  = 5.6, 3.3 Hz, 1H), 4.07 (d,  $J$  = 9.5 Hz, 1H), 3.72 (dd, 7.2, 6.2 Hz, 1H), 3.69 (d,  $J$  = 9.5 Hz, 1H), 3.63 (s, 3H), 3.52–3.47 (m, 1H), 2.85 (d,  $J$  = 2.7 Hz, 1H), 2.66 (ddd,  $J$  = 7.7, 5.0, 2.7 Hz, 1H), 2.54 (dd,  $J$  = 13.9, 6.8 Hz, 1H), 2.31 (s, 3H), 1.79 (ddd,  $J$  = 14.0, 11.5, 3.3 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  175.8, 140.8, 136.1, 129.4, 127.1, 104.0, 86.0, 72.7, 58.7, 54.5, 50.2 (two lines), 47.7, 44.8, 44.0, 21.1; IR (Neat Film NaCl) 2922, 1770, 1515, 1450, 1386, 1209, 1170, 1106, 1041, 995, 942, 813 cm<sup>-1</sup>; HRMS (MM: ESI/APCI)  $m/z$  calc'd for

$C_{18}H_{21}O_4$   $[M + H]^+$ : 301.1434, found 301.1432. Relative stereochemistry determined by NOE analysis as shown below.



**Dimethyl acetal 254.** To a solution of acetal **191** (1.0 equiv) in MeOH (25 mM) was added either La(OTf)<sub>3</sub> or Sm(OTf)<sub>3</sub> (20 mol %). The reaction was stirred until complete conversion by TLC, diluted with Et<sub>2</sub>O, filtered through a plug of Celite, and concentrated in vacuo. The crude <sup>1</sup>H NMR showed dimethyl acetal **254** as the exclusive product.  $R_f$  = 0.36 (1:2 hexanes/Et<sub>2</sub>O); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.08 (d,  $J$  = 7.9 Hz, 2H), 7.04 (d,  $J$  = 8.1 Hz, 2H), 4.69 (s, 1H), 4.58 (dd,  $J$  = 4.8, 3.8 Hz, 1H), 3.88 (d,  $J$  = 9.2 Hz, 1H), 3.86 (d,  $J$  = 9.2 Hz, 1H), 3.67 (s, 3H), 3.51 (s, 3H), 3.39 (s, 3H), 3.36 (ddd,  $J$  = 10.7, 7.4, 3.8 Hz, 1H), 3.23 (dd,  $J$  = 8.7, 5.3 Hz, 1H), 2.93 (ddd,  $J$  = 9.1, 5.6, 3.8 Hz, 1H), 2.82 (d,  $J$  = 5.7 Hz, 1H), 2.60 (dd,  $J$  = 14.1, 7.4 Hz, 1H), 2.30 (s, 3H), 1.75 (ddd,  $J$  = 14.0, 10.3, 3.5 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  174.1, 142.7, 135.6, 129.2, 127.1, 105.0, 85.8, 75.0, 58.3, 56.6, 54.5, 52.1, 51.7, 51.4, 49.4, 45.0, 42.4, 21.1; IR (Neat Film NaCl) 2952, 1727, 1515, 1435, 1362, 1210, 1069, 1042, 977, 813 cm<sup>-1</sup>; HRMS (FAB+) *m/z* calc'd for C<sub>20</sub>H<sub>25</sub>O<sub>5</sub> [M + H - H<sub>2</sub>]<sup>+</sup>: 345.1702, found 345.1701.



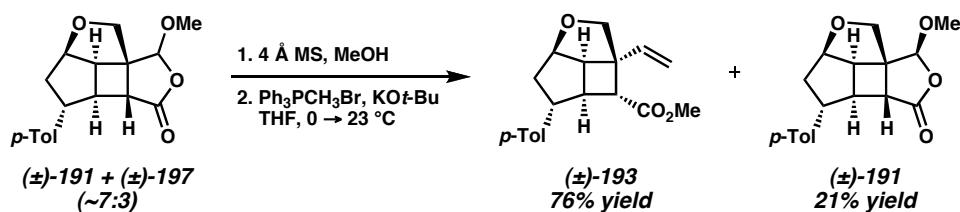
### Conversion of cyclobutene **189** over three steps to olefin **193** and acetals **191** and **197**.

A solution of cyclobutene **189** (326.2 mg, 1.369 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (5:1, 27.4 mL, 0.05 M) containing  $\text{NaHCO}_3$  (34.5 mg, 0.411 mmol, 0.3 equiv) and Sudan Red 7b (150  $\mu\text{L}$  of a 0.05 wt % solution in MeOH) at  $-78^\circ\text{C}$  was sparged with a stream of oxygen for  $\sim 1$  min and ozonolyzed until consumption by TLC analysis (typically as indicator turned colorless). After sparging with oxygen for an additional 3 min, the reaction was capped with a drying tube and warmed to room temperature. The solution was filtered through a cotton plug, washing with benzene (3 mL). The reaction was concentrated in vacuo to  $\sim 2$  mL, and to this flask was added a stir bar, septum, and the flask was evacuated/purged briefly (3x). To the crude was added  $\text{CH}_2\text{Cl}_2$  (13.7 mL), the solution was cooled to  $0^\circ\text{C}$ , and to this was added  $\text{Ac}_2\text{O}$  (387  $\mu\text{L}$ , 4.11 mmol, 3.0 equiv) and  $\text{Et}_3\text{N}$  (286  $\mu\text{L}$ , 2.05 mmol, 1.5 equiv). The bath was removed and the reaction was stirred at room temperature for 8 h, diluted with  $\text{CH}_2\text{Cl}_2$  (25 mL), washed with 2% HCl (10 mL), then 10% NaOH (10 mL), dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo to a pale yellow oil. The crude oil was purified by flash chromatography on  $\text{SiO}_2$  (2.5 x 8 cm, 4:1  $\rightarrow$  1:1 hexanes/ $\text{Et}_2\text{O}$ ) to afford acetal **190** (61.5 g, 0.205 mmol, 15%

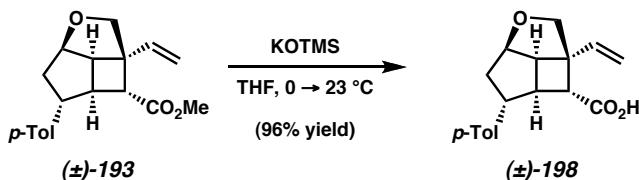
yield) and a mixture of aldehyde **192** and acetals **191** and **197** (293.5 mg, 0.977 mmol, 71% yield).

The mixture of desired isomers (293.5 mg) was dissolved in MeOH (19.5 mL, 0.05 M) and to this was added oven-dried 4 Å MS (489 mg, 0.5 g/mmol). After 24 h at room temperature, the reaction was diluted with EtOAc (20 mL), filtered through a plug of Celite, and concentrated to a turbid yellow oil. This was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and passed through a small SiO<sub>2</sub> plug and concentrated in vacuo to afford a pale yellow oil (312.1 mg).

To a solution of methyltriphenylphosphonium bromide (390 mg, 1.09 mmol, 1.05 equiv) at 0 °C was added KO*t*-Bu (105 mg, 0.935 mmol, 0.9 equiv). The resulting bright yellow solution was stirred for 1 h, and a solution of aldehyde **192** and acetals **191** and **197** (312.1 mg) in THF (2 mL) was quantitatively transferred via cannulation. After 10 min, the bath was removed and at 5 h the reaction was quenched with water (5 mL) and diluted with Et<sub>2</sub>O (5 mL). The layers were separated, the aq was extracted with Et<sub>2</sub>O (2 x 10 mL), the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo to a pale yellow oil. The crude material was purified by flash chromatography on SiO<sub>2</sub> (2.5 x 15 cm, 9:1 → 1:1 hexanes/Et<sub>2</sub>O) to afford olefin **193** (162.2 mg, 0.544 mmol, 40% yield over three steps) and a ~7:3 mixture of acetals **191** and **197** (59.5 mg, 0.198 mmol, 14% yield over three steps).

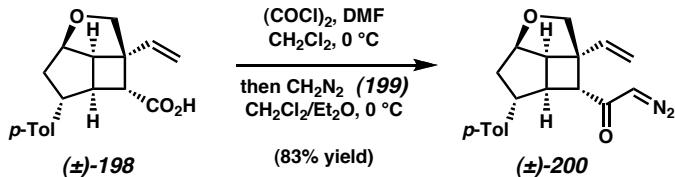


**Recycling of acetals **191** and **197**.** A ~7:3 mixture of acetals **191** and **197** (60.7 mg, 0.202 mmol) were equilibrated in MeOH with 4 Å MS to ~3:1 mixture of aldehyde **192** and acetals **191** and **197**, and the resulting crude was olefinated as detailed above with methyltriphenylphosphonium bromide (1.5 equiv) and KOT-Bu (1.25 equiv) and purified by flash chromatography on SiO<sub>2</sub> to provide olefin **193** (46.2 mg, 0.155 mmol, 76% yield over two steps) and acetal **191** (13.0 mg, 0.432 mmol, 21% yield over two steps).



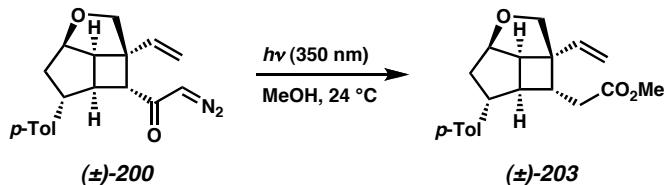
**Acid **198**.** To a solution of olefin **193** (162.2 mg, 0.544 mmol, 1.0 equiv) in THF (10.9 mL, 0.05 M) at 0 °C was added KOTMS (698 mg, 5.44 mmol, 10 equiv) in one portion. The cooling bath was removed and the reaction was stirred until consumption of **193** by TLC analysis (typically 5–6 h). The reaction was cooled to 0 °C and slowly quenched with 1 N HCl (10 mL), diluted with EtOAc (20 mL) and brine (5 mL). The layers were separated, the aq was extracted with EtOAc (3 x 20 mL), the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to a pale yellow semisolid. The crude material was purified by flash chromatography on SiO<sub>2</sub> (1:1 hexanes/EtOAc) to give acid **198** (148.7 mg, 0.523 mmol, 96% yield) as a white solid.  $R_f$  = 0.23 (2:1 hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.09 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.00 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.21 (dd, *J* = 10.8, 1.1 Hz, 1H), 5.17 (dd, *J* = 17.6, 1.2 Hz, 1H), 3.64 (dd, *J* = 4.7, 3.7 Hz, 1H), 4.04 (d, *J* = 9.3 Hz, 1H), 3.57 (d, *J* = 9.3

Hz, 1H), 3.40 (ddd,  $J = 10.6, 7.3, 3.6$  Hz, 1H), 3.26 (dd,  $J = 8.2, 5.2$  Hz, 1H), 3.00–2.95 (comp m, 2H), 2.64 (d,  $J = 14.2, 7.3$  Hz, 1H), 2.31 (s, 3H), 1.78 (ddd,  $J = 14.0, 10.5, 3.3$  Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.7, 142.6, 135.7, 134.4, 139.3, 127.7, 116.6, 86.6, 79.0, 54.9, 53.2, 51.1 (two lines), 44.9, 40.8, 21.1; IR (Neat Film NaCl) 2923, 1729, 1700, 1515, 1418, 1223, 1053, 992, 918, 812  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{18}\text{H}_{21}\text{O}_3$  [M + H] $^+$ : 285.1491, found 285.1495.



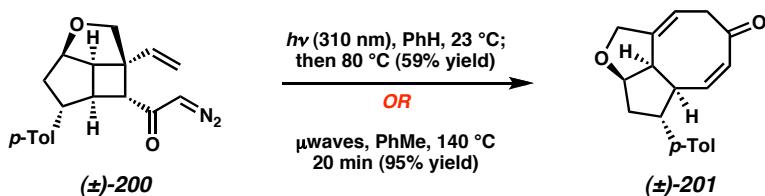
**$\alpha$ -Diazoketone 200.** To a solution of acid **198** (14.7 mg, 51.7  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (2 mL, 0.025 M) at 0  $^\circ\text{C}$  was added a solution of oxalyl chloride (107  $\mu\text{L}$  of a 1.45 M solution in  $\text{CH}_2\text{Cl}_2$ , 155  $\mu\text{mol}$ , 3.0 equiv), followed by 1 drop of DMF. The reaction was stirred for 1 h, at which point the stir bar was removed and the volatiles were removed on a rotovap purged with argon. The septum and stir bar were replaced and the crude material was further dried under high vacuum for 10 min. The resulting crude semisolid was partially dissolved in  $\text{CH}_2\text{Cl}_2$  (1 mL) and transferred quantitatively via Teflon cannula to a vigorously stirring solution of excess diazomethane (**199**, 5–8 mL) at 0  $^\circ\text{C}$ . After 30 min the cooling bath was removed, and after a further hour the diazomethane was pulled off via water aspirator. The pale yellow solution was filtered through a small  $\text{SiO}_2$  plug ( $\text{Et}_2\text{O}$ ) and concentrated in vacuo. The crude material was purified by flash chromatography on  $\text{SiO}_2$  (9:1  $\rightarrow$  3:1 hexanes/EtOAc) to afford  $\alpha$ -diazoketone **200** (13.2 mg, 42.8  $\mu\text{mol}$ , 83% yield) as a bright yellow oil that solidified

in a  $-20$  °C freezer.  $R_f$  = 0.31 (2:1 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.07 (d,  $J$  = 7.9 Hz, 2H), 7.03 (d,  $J$  = 7.9 Hz, 2H), 6.01 (dd, 17.5, 10.8 Hz, 1H), 5.17 (d,  $J$  = 10.8 Hz, 1H), 5.11–5.06 (br m, 2H), 4.64 (app t,  $J$  = 4.0 Hz, 1H), 3.97 (br d,  $J$  = 9.1 Hz, 1H), 3.66 (br d,  $J$  = 8.6 Hz, 1H), 3.36 (ddd,  $J$  = 10.6, 7.7, 3.5 Hz, 1H), 3.19 (br s, 1H), 3.11 (br s, 1H), 2.92 (br s, 1H), 2.64 (dd,  $J$  = 14.2, 7.3 Hz, 1H), 2.30 (s, 3H), 1.78 (ddd,  $J$  = 13.7, 10.5, 3.0 Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  193.6, 142.5, 135.7, 134.9, 129.3, 127.1, 116.0, 86.5, 78.6, 60.8, 55.3, 53.6, 51.4, 44.9, 40.5, 30.4, 21.1; IR (Neat Film NaCl) 2955, 2921, 2100, 1633, 1514, 1370, 1352, 1048, 812  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{19}\text{H}_{21}\text{O}_2\text{N}_2$  [M + H] $^+$ : 309.1603, found 309.1619.



**Homologated ester 203.** A solution of  $\alpha$ -diazoketone **200** (3.2 mg, 104  $\mu\text{mol}$ ) in  $\text{MeOH}$  (5.2 mL, 2 mM) in a dried quartz tube was irradiated in a Luzchem rayonette ( $\lambda$  = 350 nm) for 1.5 h. The solution was concentrated in vacuo and revealed homologated ester **203** as the sole product by crude  $^1\text{H}$  NMR. An analytical sample was obtained from purification by preparative TLC on  $\text{SiO}_2$  (2:1 hexanes/EtOAc) to give **203** (2.4 mg, 7.7  $\mu\text{mol}$ , 74% yield) as a colorless oil.  $R_f$  = 0.43 (2:1 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.07 (d,  $J$  = 7.5 Hz, 2H), 7.02 (d,  $J$  = 7.5 Hz, 2H), 5.89 (dd,  $J$  = 16.9, 10.2 Hz, 1H), 5.22 (d,  $J$  = 10.7 Hz, 1H), 5.13 (d,  $J$  = 17.5 Hz, 1H), 4.64 (app t,  $J$  = 3.9 Hz, 1H), 3.97 (d,  $J$  = 8.7 Hz, 1H), 3.51 (s, 3H), 3.50 (d,  $J$  = 8.7 Hz, 1H), 3.46–3.42 (m, 1H), 3.23 (dd,  $J$  = 7.9, 5.8 Hz, 1H), 2.61 (dd,  $J$  = 14.1, 7.3 Hz, 1H), 2.54–2.36 (comp

m, 3H), 2.30 (s, 3H), 2.11 (app dt,  $J$  = 7.7, 3.8 Hz, 1H), 1.78 (ddd,  $J$  = 12.7, 10.4, 2.1 Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.1, 143.6, 135.5, 135.3, 129.2, 127.1, 116.4, 86.7, 79.2, 52.4, 51.9, 51.6, 50.1, 47.0, 46.9, 45.0, 37.2, 21.1; IR (Neat Film NaCl) 2951, 2922, 1736, 1514, 1435, 1207, 1163, 1041, 916, 808  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{20}\text{H}_{24}\text{O}_3$  [M] $^+$ : 312.1726, found 312.1725.

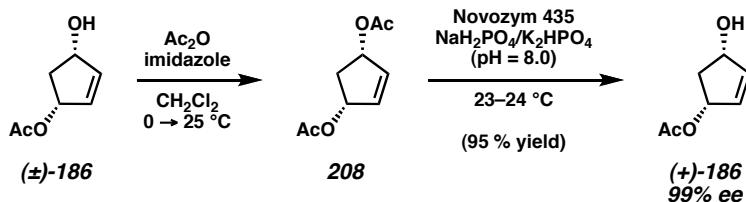


**Cyclooctadienone 201.** *Photochemical/Thermal:* A solution of  $\alpha$ -diazoketone **200** (3.5 mg, 11.4  $\mu\text{mol}$ ) in PhH (5.7 mL, 2 mM) in a dried quartz tube was irradiated in a Luzchem photochemical reactor ( $\lambda$  = 310 nm) for 10 min, and then the lamp was turned off and the quartz tube was placed in an 80 °C oil bath for 2 h. The reaction was concentrated in vacuo and purified by preparative TLC on  $\text{SiO}_2$  (1:1 hexanes/Et<sub>2</sub>O, developed twice) to give cyclooctadienone **201** (1.9 mg, 6.8  $\mu\text{mol}$ , 59% yield) as a colorless oil.

*Microwave (thermal):* A solution of  $\alpha$ -diazoketone **200** (2.3 mg, 7.5  $\mu\text{mol}$ ) in PhMe (1.5 mL, 5 mM) was prepared in a nondried microwave vial containing a stir bar under ambient atmosphere. The vial was sealed and irradiated in a Biotage Initiator microwave reactor at 400 W until the temperature reached 140 °C, and the temperature was maintained for 20 min. The vial was cooled to room temperature, the seal was removed, and the contents were concentrated in vacuo. Reaction conversion was monitored by crude  $^1\text{H}$  NMR analysis ( $\text{C}_6\text{D}_6$ ). The crude material was purified by preparative TLC on

$\text{SiO}_2$  (2:1 hexanes/EtOAc) to give **201** (2.0 mg, 7.1  $\mu\text{mol}$ , 95% yield) as a colorless oil that solidified in a  $-20\text{ }^\circ\text{C}$  freezer.  $R_f = 0.32$  (3:1 hexanes/EtOAc);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.17–7.13 (comp m, 4H), 5.80–5.73 (comp m, 2H), 5.63–5.59 (m, 1H), 4.76 (d,  $J = 5.2$  Hz, 1H), 3.66 (dd,  $J = 10.8, 5.9$  Hz, 1H), 3.41 (dd,  $J = 14.7, 8.1$  Hz, 1H), 3.23 (app t,  $J = 11.3$  Hz, 1H), 3.13–3.05 (comp m, 2H), 2.34 (s, 3H), 2.30 (dd,  $J = 13.8, 5.9$  Hz, 1H), 1.93 (ddd,  $J = 13.8, 12.1, 4.6$  Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  203.3, 146.8, 139.7, 138.4, 136.9, 129.7, 129.2, 127.9, 144.2, 85.3, 72.2, 53.9, 50.6, 48.1, 45.4, 41.4, 21.2;  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.99 (d,  $J = 7.7$  Hz, 2H), 6.86 (d,  $J = 6.9$  Hz, 2H), 5.78–5.75 (m, 1H), 5.55 (d,  $J = 13.6$  Hz, 1H), 5.11–5.08 (m, 1H), 4.35 (app t,  $J = 5.13$  Hz, 1H), 4.24 (d,  $J = 13.1$  Hz, 1H), 4.11 (d,  $J = 13.2$  Hz, 1H), 3.04–2.89 (comp m, 4H), 2.70 (app t,  $J = 11.3$  Hz, 1H), 2.20 (dd,  $J = 13.6, 5.9$  Hz, 1H), 2.15 (s, 3H), 1.53–1.46 (m, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  201.9, 147.2, 139.2, 138.6, 136.8, 130.1, 130.0, 128.7, 114.4, 85.5, 72.5, 53.8, 51.2, 48.3, 45.9, 41.9, 21.3; IR (Neat Film NaCl) 3015, 2922, 1693, 1661, 1516, 1435, 1318, 1208, 1062, 1030, 817  $\text{cm}^{-1}$ ; HRMS (MM: ESI/APCI)  $m/z$  calc'd for  $\text{C}_{19}\text{H}_{19}\text{O}_2$  [ $\text{M} - \text{H}$ ] $^+$ : 279.1319, found 279.1384.

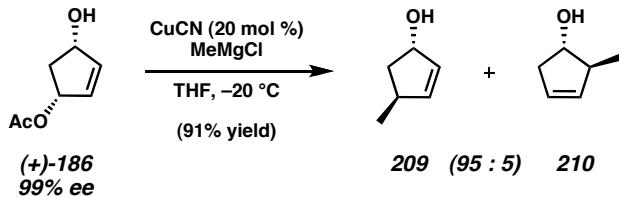
### 3.7.2.3 AB RING ASYMMETRIC FRAGMENTS



**Monoacetate (+)-186.**<sup>27</sup> To a solution of monoacetate ( $\pm$ )-**186** (40.43 g, 284.4 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (47 mL, 6 M) was added imidazole (21.11 g, 310 mmol, 1.09 equiv), and after the contents were completely dissolved, the solution was cooled to 0 °C and  $\text{Ac}_2\text{O}$  (29.3 mL, 310 mmol, 1.09 equiv) was added over 5–7 min via syringe. After 10 min, the bath was removed and the solution was stirred for 22 h at room temperature, at which  $\text{EtOAc}$  (150 mL) was added and the contents were poured into ice-cold 1 N HCl (150 mL). The layers were separated and the aq layer was saturated with NaCl (s) and extracted with  $\text{Et}_2\text{O}$  (2 x 100 mL, 1 x 50 mL). The combined organics were washed with sat. aq  $\text{NaHCO}_3$  (100 mL), this aq layer was saturated with NaCl (s) and extracted with  $\text{Et}_2\text{O}$  (2 x 100 mL). The combined organics were dried over  $\text{MgSO}_4$ , filtered, concentrated, and dried under high vacuum to afford *meso*-bisacetate **208** (50.88 g, 276.2 mmol, 97% yield) as a pale yellow oil. This material could be used in subsequent reactions as is, or can be purified by short-path distillation (bp = 74–98 °C, ~0.8 torr) to give **208** as a colorless oil in 89% yield.  $R_f$  = 0.75 ( $\text{Et}_2\text{O}$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.09 (d,  $J$  = 0.9 Hz, 2H), 5.54 (ddd,  $J$  = 7.6, 3.8, 0.9 Hz, 2H), 2.88 (app dt,  $J$  = 15.1, 7.6 Hz, 1H), 2.06 (s, 6H), 1.74 (app dt,  $J$  = 15.0, 3.8 Hz, 1H). All other spectral data are consistent with reported values.<sup>27c</sup>

*meso*-Bisacetate **208** (33.15 g, 180.0 mmol, 1.0 equiv) was added to a purified water triple-rinsed 1 L Erlenmeyer flask containing a stir bar and partially dissolved in aq  $\text{NaH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$  buffer (0.05 M, pH = 8.0). To this solution was added Novozym 435 (4.0 g), the flask was covered with parafilm and stirred gently to at room temperature until consumption of **208** by TLC analysis (5–8 h). The contents were vacuum filtered and the supported enzyme was washed with water (150 mL) and  $\text{EtOAc}$  (2 x 150 mL).

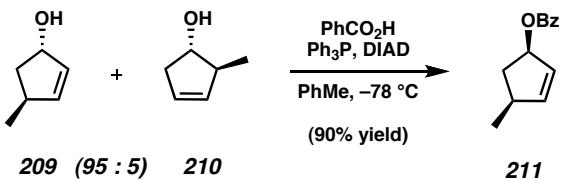
The filtrate layers were separated and the aq layer was saturated with NaCl (200 g), extracted with EtOAc (5 x 200 mL, follow by TLC), and the combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The crude oil was dissolved in Et<sub>2</sub>O (150 mL) and heptane was added (150 mL), followed by concentration in vacuo to afford a white semisolid. This was repeated one more time and the solid was dried under high vacuum to provide monoacetate (+)-**186** (24.36 g, 171 mmol, 95% yield) as a white semisolid. The crude material is >95% pure by <sup>1</sup>H NMR, but can be purified by flash chromatography on SiO<sub>2</sub> (1:2 hexanes/Et<sub>2</sub>O, dry load onto SiO<sub>2</sub>) to provide **186** in 89% yield. The material displayed the same spectral properties as above;<sup>27a,b</sup> mp = 45–49 °C; [α]<sub>D</sub><sup>22.5</sup> +61.2° (c 1.28, CHCl<sub>3</sub>, 99% ee). GC conditions: 100 °C isothermal, GTA column, *t*<sub>R</sub> (min): major = 30.5, minor = 27.6. We have reused the recovered Novozym 435 up to four times and observed slightly lower activity for each subsequent use with identical selectivities.



**anti-Cyclopentenols 209 and 210.** A 2 L 3-neck flask was charged with CuCN (2.01 g, 112.2 mmol, 0.2 equiv) and THF (280 mL), and the suspension was cooled to ca. -20 °C (internal) using a cryocool. To this was added a solution of MeMgCl (109 mL, 337 mmol of a 3.1 M solution in THF) and the internal temperature warmed to -14 °C. After 30 min at -20 °C, a solution of monoacetate (+)-**186** (15.95 g, 112.2 mmol, 1.0 equiv) in THF (40 mL) was slowly transferred (quantitative) via cannulation at such a

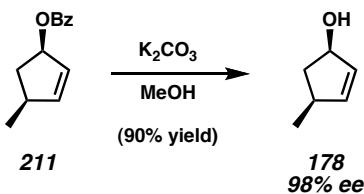
rate that the temperature does not rise above  $-10\text{ }^{\circ}\text{C}$  (requires  $\sim 1\text{ h}$ ). After 30 min the reaction was slowly quenched with sat. aq  $\text{NH}_4\text{Cl}$  (100 mL), 50% sat. brine (100 mL), the cooling bath was removed and the viscous suspension was stirred vigorously for several hours. Additional water (200 mL) and 3% HCl (100 mL) was added and the layers were separated. The aq layer was extracted with  $\text{Et}_2\text{O}$  (3 x 200 mL), the combined organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated carefully (water bath =  $5\text{ }^{\circ}\text{C}$ , down to 30 torr) to a pale yellow oil. The crude material was purified by short path distillation (bp = 88–92  $^{\circ}\text{C}$ , 40 torr) to afford a 95:5 mixture of *anti*-cyclopentenols **209** and **210** (8.847 g, 90.2 mmol, 80% yield). The early distillation fractions and washing from the apparatus were combined and purified by flash chromatography on  $\text{SiO}_2$  (2.5 x 27 cm, 6:1  $\rightarrow$  1:1 pentane/ $\text{Et}_2\text{O}$ ) to provide another 1.049 g of **209** and **210**. The combined yield obtained was 9.996 g, 101.9 mmol, 91% yield.  $R_f$  (**210**) = 0.35 (1:1 hexanes/ $\text{EtOAc}$ );  $R_f$  (**209**) = 0.29 (1:1 hexanes/ $\text{EtOAc}$ ); bp = 88–92  $^{\circ}\text{C}$  (40 torr).

An analytical sample of **209** was obtained from the column conditions above.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.89 (dd,  $J$  = 5.5, 1.9 Hz, 1H), 5.79 (ddd,  $J$  = 4.6, 2.2, 2.2 Hz, 1H), 4.88–4.86 (m, 1H), 2.99–2.91 (m, 1H), 1.96 (ddd,  $J$  = 14.0, 7.5, 2.6 Hz, 1H), 1.71 (ddd,  $J$  = 14.0, 7.1, 5.2 Hz, 1H), 1.48 (br s, 1H), 1.03 (d,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  142.0, 132.1, 77.6, 42.7, 38.5, 21.0; IR (Neat Film NaCl) 3338 (br), 2956, 2870, 1354, 1088, 1017, 982, 742  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_6\text{H}_{10}\text{O}$  [M] $^+$ : 98.07317, found 98.07171;  $[\alpha]_D^{21} -272.2^{\circ}$  ( $c$  0.39,  $\text{CHCl}_3$ , 99% ee). GC conditions: 45  $^{\circ}\text{C}$  isothermal, GTA column,  $t_R$  (min): major = 37.7, minor = 36.7.



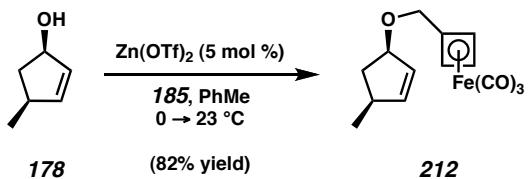
**syn-Benzoate 211.** To a suspension of  $\text{Ph}_3\text{P}$  (13.41 g, 51.12 mmol, 1.2 equiv) and benzoic acid (6.243 g, 51.12 mmol, 1.2 equiv) in  $\text{PhMe}$  (237 mL) at  $-75^\circ\text{C}$  (internal) was added DIAD (10.1 mL, 51.12 mmol, 1.2 equiv) dropwise, neat over 15 min. The resulting yellow suspension was stirred vigorously for 30 min, at which point a solution of **209** and **210** (4.1806 g, 42.60 mmol, 1.0 equiv) in  $\text{PhMe}$  (47 mL, 0.15 M total) was transferred via cannula quantitatively over 30 min (observed maximum temperature increase to  $-70^\circ\text{C}$ ). When  $\sim 1/3$  of this solution was added, the reaction mixture turned homogeneous. After complete addition of **209** and **210**, the reaction was stirred for an additional 30 min (white precipitate has formed) and quenched with sat. aq  $\text{NaHCO}_3$  (100 mL) and water (100 mL) and the contents were warmed to room temperature. The layers were separated, the aq was extracted with  $\text{Et}_2\text{O}$  (2 x 50 mL), and the combined organics were shaken with 3% aq  $\text{H}_2\text{O}_2$  until TLC showed disappearance of  $\text{Ph}_3\text{P}$ . The layers were separated, the aq was extracted with  $\text{Et}_2\text{O}$  (1 x 50 mL), and the combined organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated to a pale yellow solid. The crude material was purified by flash chromatography on  $\text{SiO}_2$  (7 x 7.5 cm, 1:0  $\rightarrow$  24:1 hexanes/ $\text{Et}_2\text{O}$ , dry loaded onto  $\text{SiO}_2$ ) to give *syn*-benzoate **211** (7.792 g, 38.53 mmol, 90% yield) as a pale yellow oil.  $R_f = 0.57$  (3:1 hexanes/ $\text{EtOAc}$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.04 (dd,  $J = 8.2, 1.2$  Hz, 2H), 7.56–7.53 (m, 1H), 7.43 (app t,  $J = 7.8$  Hz, 2H), 6.03 (dd,  $J = 4.4, 2.0$  Hz, 1H), 5.90–5.86 (comp m, 2H), 2.80–2.73 (m, 1H), 2.65 (ddd,  $J = 14.0, 7.8, 7.8$  Hz, 1H), 1.51 (ddd,  $J = 14.0, 4.4, 4.4$  Hz, 1H), 1.16 (d,  $J = 7.0$  Hz, 3H);

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 166.6, 142.9, 132.9, 130.8, 129.7, 128.6, 128.4, 80.9, 38.9, 38.7, 21.7; IR (Neat Film NaCl) 2961, 1716, 1451, 1340, 1315, 1272, 1110, 711 cm<sup>-1</sup>; HRMS (EI+) *m/z* calc'd for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub> [M]<sup>+</sup>: 202.0994, found 202.0957; [α]<sub>D</sub><sup>25.7</sup> +123.8° (c 1.175, CHCl<sub>3</sub>, 98–99% ee). For a chiral analytical assay, see *syn*-diol **178**.



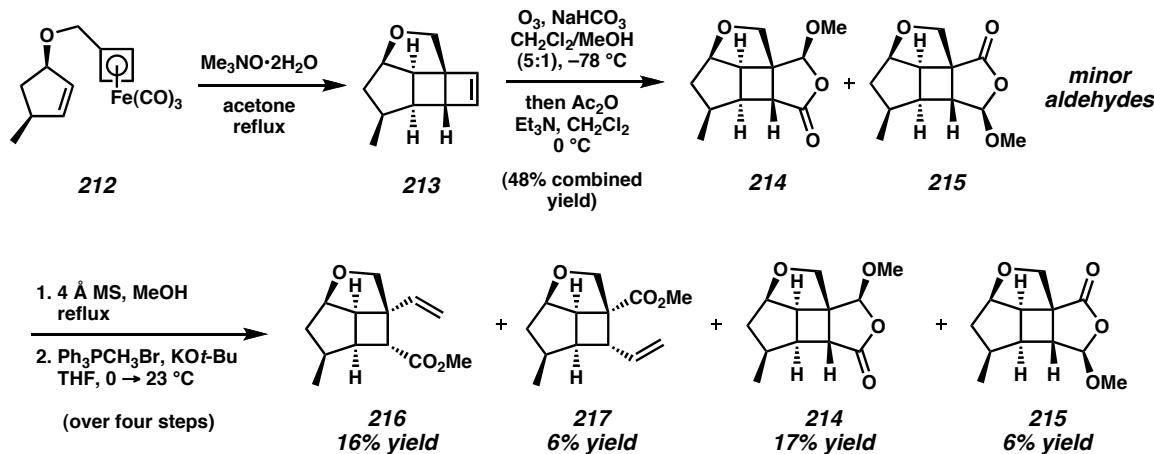
***syn*-Cyclopentenol 178.** To a solution of benzoate **211** (6.255g, 30.93 mmol, 1.0 equiv) in MeOH (62 mL, 0.5 M) was added K<sub>2</sub>CO<sub>3</sub> (8.549 g, 61.85 mmol, 2.0 equiv) in one portion. After completion as judged by TLC analysis (3 h, 3:1 hexanes/EtOAc), the reaction was concentrated carefully in vacuo to a slurry (~5–10 mL). The white slurry was diluted with brine (25 mL) and extracted with Et<sub>2</sub>O (4 x 25 mL, follow by TLC), the organics were dried over MgSO<sub>4</sub>, filtered, and concentrated carefully in vacuo. The crude material was purified by flash chromatography on SiO<sub>2</sub> (5 x 12 cm, 6:1 → 1:1 pentane/Et<sub>2</sub>O) and concentrated down to 100 torr until <sup>1</sup>H NMR analysis revealed the absence of solvent to afford *syn*-cyclopentenol **178** (2.728 g, 27.79 mmol, 90% yield) as a colorless oil. *R*<sub>f</sub> = 0.25 (3:1 hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.82 (app dt, *J* = 5.5, 1.5 Hz, 1H), 5.73 (app dt, *J* = 5.5, 2.0 Hz, 1H), 4.79 (br s, 1H), 2.66–2.59 (m, 1H), 2.52 (ddd, *J* = 13.4, 7.6, 7.6 Hz, 1H), 1.79 (br s, 1H), 1.17 (app dt, 13.4, 5.4 Hz, 1H), 1.09 (d, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 140.4, 132.8, 77.8, 42.6, 39.0, 22.0; IR (Neat Film NaCl) 3338 (br), 3048, 2959, 2870, 1456, 1356, 1322, 1115,

1051, 755  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_6\text{H}_{10}\text{O}$  [M] $^+$ : 98.07317, found 98.06857;  $[\alpha]_D^{27} -23.0^\circ$  ( $c$  0.475,  $\text{CHCl}_3$ , 98.2% ee). GC conditions: 50  $^\circ\text{C}$  isothermal, GTA column,  $t_{\text{R}}$  (min): major = 21.2, minor = 20.7.



**Cyclobutadiene-iron ether complex 212.** To a round-bottom flask containing zinc(II) triflate (271 mg, 0.745 mmol, 5 mol%) and PhMe (3.7 mL) at 0  $^\circ\text{C}$  was added cyclopentenol **178** (1.45 g, 14.8 mmol, 1.0 equiv) by syringe. To this suspension was added a solution of cyclobutadiene trichloroacetimidate **185** (6.38 g, 17.4 mmol, 1.2 equiv) in PhMe (2.0 mL) by cannula transfer, with further washing by PhMe (1.7 mL). A yellow precipitate was observed at the beginning of the addition, and this turned into a viscous slurry upon completion of the addition. The ice bath was allowed to expire over 1.5 h and the reaction was stirred for an additional 0.5 h at ambient temperature. The crude reaction mixture was transferred directly onto a 25 g silica gel loading cartridge and purified with a Teledyne ISCO CombiFlash system using a 125 g silica column (1:0  $\rightarrow$  19:1 hexanes/EtOAc) to afford cyclobutadiene-ether complex **212** (3.65 g, 12.2 mmol, 82% yield) as a pale yellow oil.  $R_f = 0.73$  (4:1 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.72 (app dt,  $J = 5.6, 1.9$  Hz, 1H), 5.66 (app dt,  $J = 5.6, 1.6$  Hz, 1H), 4.27–4.24 (m, 1H), 3.54 (d,  $J = 9.1$  Hz, 1H), 3.52 (d,  $J = 9.1$  Hz, 1H), 3.48 (s, 2H), 3.32 (s, 1H), 2.43–2.39 (m, 1H), 2.15 (app dt,  $J = 13.3, 7.6$  Hz, 1H), 1.26 (ddd,  $J = 17.0, 11.2, 6.9$  Hz, 1H), 0.98 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  215.0, 140.5, 130.5,

85.2, 82.6, 64.6 (two lines), 64.0, 62.2, 39.1, 38.9, 21.6; IR (Neat Film NaCl) 2961, 2871, 2046, 1965, 1359, 1076, 1055, 757  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{14}\text{H}_{14}\text{FeO}_4$  [M] $^+$ : 302.0242, found 302.0244;  $[\alpha]_D^{25} +22.7^\circ$  ( $c$  0.86, hexane, 98% ee).



**Cycloaddition to cyclobutene **213**.** A solution of ether **212** (2.3582 g, 7.806 mmol, 1.0 equiv) dissolved in acetone (780 mL, 10 mM) in a 1 L round-bottom flask fitted with a reflux condenser was warmed in a  $70^\circ\text{C}$  oil bath. When the solution approached reflux, the condenser was momentarily removed and  $\text{Me}_3\text{NO} \cdot 2\text{H}_2\text{O}$  (8.77 g, 78.9 mmol, 10 equiv) was added in a single portion. The solution was allowed to reflux and within 10 min the reaction vessel was filled with a rust colored precipitate. After 4 h a second portion of  $\text{Me}_3\text{NO} \cdot 2\text{H}_2\text{O}$  (4.35 g, 45.9 mmol, 5.8 equiv) was added. The solution was heated at reflux for an additional 17 h after which the reaction was judged to be complete by TLC analysis (4:1 hexanes/EtOAc). The solution was cooled to room temperature and poured directly onto a  $\text{SiO}_2$  column (25 x 5 cm) packed in pentane. The column was washed with 0  $\rightarrow$  10%  $\text{Et}_2\text{O}$  in pentane, and all fractions containing cyclobutene **213** were combined and concentrated carefully to a volume of  $\sim$ 30 mL by atmospheric

pressure distillation. This solution was purified by flash chromatography on SiO<sub>2</sub> (pack with pentane, elute with 20:1 pentane/Et<sub>2</sub>O). The fractions containing product were combined and concentrated to a volume of ~10 mL by atmospheric pressure distillation. This pale yellow cyclobutene solution in pentane was used directly in the following reaction. An analytical sample of cyclobutene **213** could be prepared by further chromatography and exhaustive distillation of solvent.  $R_f = 0.39$  (3:1 hexanes/Et<sub>2</sub>O); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.27 (d,  $J = 2.2$  Hz, 1H), 6.22 (s, 1H), 4.84 (dd,  $J = 14.4$ , 7.1 Hz, 1H), 4.04 (d,  $J = 9.1$  Hz, 1H), 3.94 (d,  $J = 8.6$  Hz, 1H), 3.00 (s, 1H), 2.89 (dd,  $J = 19.7$ , 13.8 Hz, 1H), 2.27–2.18 (m, 1H), 2.10–2.05 (comp m, 2H), 1.37 (ddd,  $J = 13.0$ , 13.0, 7.0 Hz, 1H), 0.97 (d,  $J = 6.7$  Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  140.2, 138.4, 84.7, 70.3, 57.9, 52.0, 47.8, 44.8, 39.0, 37.3, 14.3; IR (Neat Film NaCl) 2955, 2865, 1458, 1334, 1089, 1075, 1057, 1032, 931, 740 cm<sup>-1</sup>; HRMS (EI+) *m/z* calc'd for C<sub>11</sub>H<sub>14</sub>O [M]<sup>+</sup>: 162.1045, found 162.1026; an optical rotation was not obtained due to the volatility of this compound. Cyclobutene **213** was found to possess an optical purity (ee) of 98% by chiral GC analysis; GC conditions: 110 °C isothermal, GTA column,  $t_R$  (min): major = 13.6, minor = 13.3.

**Ozonolysis, equilibration, and methylenation to olefins **216** and **217**, and acetals **214** and **215**.** In a 250 mL round-bottom flask, the cyclobutene solution prepared above was diluted with CH<sub>2</sub>Cl<sub>2</sub> (130 mL) and methanol (26 mL, 5:1, 0.05 M total). To this was added NaHCO<sub>3</sub> (205.2 mg, 2.44 mmol, 0.3 equiv) and a few drops of Sudan Red (0.05 wt % in MeOH) until the solution became a persistent pink color (ca. 10 drops). The reaction vessel was cooled to -78 °C and the solution was sparged with O<sub>2</sub> gas (0.5 L/min) for 2 min. The reaction was then ozonolyzed (setting the ozone generator to

“5” with an O<sub>2</sub> flow rate of 0.5 L/min) for 60 min, at which point the pink color of the solution had disappeared and the reaction was judged to be complete by TLC analysis. The ozone was sparged with O<sub>2</sub> gas (1 L/min) through the solution for 2 min, and the pale yellow solution was warmed to room temperature and filtered through a cotton plug to remove the solid NaHCO<sub>3</sub>. The cotton plug was washed with PhH (10 mL) and the filtrate was concentrated to a small volume (ca. 3–4 mL). The resulting crude yellow oil was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (78 mL), cooled to 0 °C, and to this was added Et<sub>3</sub>N (1.63 mL, 11.7 mmol, 1.5 equiv) and Ac<sub>2</sub>O (2.21 mL, 23.4 mmol, 3.0 equiv) dropwise via syringe. After 6 h, the reaction was quenched by the addition of 2 M HCl (25 mL), the organic layer was separated and washed with 2 M NaOH (25 mL), and the combined aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 x 25 mL). The organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to afford a pale brown oil which was passed through a SiO<sub>2</sub> plug eluting with EtOAc, and concentrated to afford a pale yellow oil (0.8504 g, 3.8 mmol, three steps, 48% crude yield) containing mostly acetals **214** and **215**.

The crude pale yellow oil prepared above was azeotroped from PhH (2 x 10 mL) in a 250 mL round-bottom flask and dissolved in MeOH (76 mL, 0.05 M). To this was added oven dried 4 Å MS (1.90 g, 0.5 g/mmol) and the flask was fitted with a reflux condenser and heated to reflux using an 80 °C oil bath. After 6 h, a reaction aliquot was judged complete by <sup>1</sup>H NMR analysis and the reaction was cooled to room temperature. Most of the 4 Å MS were removed by filtration through Celite eluting with EtOAc. The filtrate was concentrated and the resultant turbid oil was further purified by filtration through a SiO<sub>2</sub> plug with EtOAc. This filtrate was concentrated to afford a yellow oil (0.8420 g)

containing mostly aldehydes derived from **214** and **215** with acetals **214** and **215**.

This was used directly in the following reaction.

A flask containing  $\text{Ph}_3\text{PCH}_3\text{Br}$  (1.62 g, 4.54 mmol, 1.2 equiv) was partially dissolved with THF (15 mL) and cooled to 0 °C. To this was added  $\text{KO}t\text{-Bu}$  (423 mg, 3.77 mmol, 1.0 equiv) in one portion, and the solution immediately displayed a bright yellow color. The crude yellow oil of aldehydes/acetals (0.8420 g, ~3.7 mmol) prepared above was azeotroped from PhH (2 x 10 mL), dissolved in THF (7.5 mL), cooled to 0 °C, and transferred dropwise via positive pressure cannulation into the solution of phosphorane over ca. 10 min. The flask was then washed with a second portion of THF (7.5 mL) to ensure quantitative transfer. The reaction was gradually allowed to warm to room temperature. After 18 h the reaction was quenched by the addition of  $\text{H}_2\text{O}$  (25 mL) and extracted with  $\text{Et}_2\text{O}$  (4 x 20 mL) then  $\text{EtOAc}$  (2 x 20 mL). The combined organics were dried with  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The crude yellow residue was purified flash chromatography on  $\text{SiO}_2$  (15 x 2 cm, 20:1 → 4:1 hexanes/EtOAc) to afford olefins **216** and **217** (384.4 mg, 1.729 mmol, 2.7:1 ratio, 22.2% yield over four steps from ether **212**) as a colorless oil and acetals **214** and **215** (400.5 mg, 1.786 mmol; 2.7:1 ratio, 22.9% yield over four steps from ether **212**) as pale yellow oil. Olefins **216** and **217** could be separated by further flash chromatography on  $\text{SiO}_2$  (20:1 → 9:1 hexanes/EtOAc), and acetals **214** and **215** could be separated by further flash chromatography on  $\text{SiO}_2$  (3:1 → 1:1 hexanes/EtOAc).

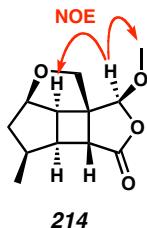
**Olefin 216.**  $R_f$  = 0.46 (9:1 hexanes/EtOAc, developed thrice);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.95 (dd,  $J$  = 17.5, 10.8 Hz, 1H), 5.15 (dd,  $J$  = 10.8, 1.2 Hz, 1H), 5.11 (dd,  $J$  = 17.5, 1.2 Hz, 1H), 4.59 (ddd,  $J$  = 6.3, 6.3, 1.5 Hz, 1H), 3.99 (d,  $J$  = 9.0 Hz, 1H), 3.64 (s,

3H), 3.54 (d,  $J$  = 9.0 Hz, 1H), 3.16 (d,  $J$  = 7.1 Hz, 1H), 3.02 (app t, 7.1 Hz, 1H), 2.95 (dd,  $J$  = 7.5, 7.4 Hz, 1H). 2.43–2.34 (m, 1H), 2.18 (ddd,  $J$  = 14.7, 10.4, 5.7 Hz, 1H), 1.71 (ddd,  $J$  = 14.6, 6.3, 1.7 Hz, 1H), 1.02 (d,  $J$  = 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.6, 134.9, 115.9, 87.1, 78.7, 52.6, 51.6, 51.4, 44.8, 42.5, 38.9, 37.2, 17.2; IR (Neat Film NaCl) 2954, 1736, 1436, 1363, 1236, 1206, 1162, 1042, 920  $\text{cm}^{-1}$ ; HRMS (MM: ESI/APCI)  $m/z$  calc'd for  $\text{C}_{13}\text{H}_{18}\text{O}_3$  [M + H] $^+$ : 223.13287, found 223.13255;  $[\alpha]_D^{16.8} -4.73^\circ$  ( $c$  1.18,  $\text{CH}_2\text{Cl}_2$ , 98% ee).

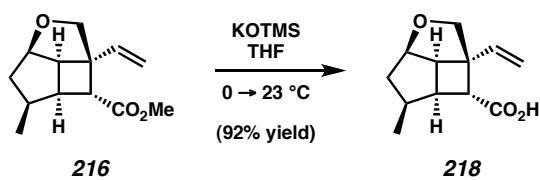
**Olefin 217.**  $R_f$  = 0.39 (9:1 hexanes/EtOAc, developed thrice);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.86 (ddd,  $J$  = 17.0, 10.3, 7.8 Hz, 1H), 5.05 (ddd,  $J$  = 17.1, 1.5, 1.5 Hz, 1H), 5.02 (ddd,  $J$  = 10.3, 1.4, 1.4 Hz, 1H), 4.67 (ddd,  $J$  = 6.6, 6.6, 2.8 Hz, 1H), 4.02 (d,  $J$  = 9.4 Hz, 1H), 3.88 (d,  $J$  = 9.4 Hz, 1H), 3.68 (s, 3H), 3.30 (app t,  $J$  = 7.2 Hz, 1H), 3.00 (app t,  $J$  = 7.2 Hz, 1H), 2.54 (app q, 7.16 Hz, 1H), 2.35 (d septuplets,  $J$  = 9.6, 7.1 Hz, 1H), 2.18 (ddd,  $J$  = 14.5, 9.7, 6.3 Hz, 1H), 1.67 (ddd,  $J$  = 14.5, 7.7, 2.8 Hz, 1H), 1.01 (d,  $J$  = 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.3, 137.9, 115.9, 87.1, 76.0, 55.8, 51.7, 48.9, 44.9, 43.6, 41.8, 38.0, 16.2; IR (Neat Film NaCl) 2953, 5873, 1731, 1436, 1295, 1207, 1041, 917  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{13}\text{H}_{18}\text{O}_3$  [M] $^+$ : 222.1256, found 222.1216;  $[\alpha]_D^{15.1} -0.49^\circ$  ( $c$  0.72,  $\text{CH}_2\text{Cl}_2$ , 98% ee).

**Acetal 214.**  $R_f$  = 0.29 (2:1 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.39 (s, 1H), 4.80 (ddd,  $J$  = 6.5, 6.5, 4.5 Hz, 1H), 4.00 (d,  $J$  = 10.6 Hz, 1H), 3.98 (d,  $J$  = 10.7 Hz, 1H), 3.48 (s, 3H), 3.13 (app t,  $J$  = 6.7 Hz, 1H), 2.89 (d,  $J$  = 3.3 Hz, 1H), 2.61 (ddd,  $J$  = 6.9, 6.9, 3.3 Hz, 1H), 2.39–2.30 (m, 1H), 2.06 (ddd,  $J$  = 14.4, 8.4, 6.3 Hz, 1H), 1.60 (ddd,  $J$  = 13.3, 8.5, 4.5 Hz, 1H), 1.11 (d,  $J$  = 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  179.0, 107.4, 86.7, 70.9, 56.8, 52.4, 51.5, 44.7, 40.8, 38.6, 37.2, 16.9; IR (Neat Film NaCl)

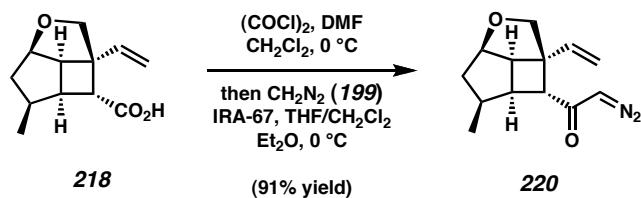
2961, 2877, 1772, 1353, 1150, 1128, 1100, 1062, 936, 710  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{12}\text{H}_{16}\text{O}_4$   $[\text{M}]^+$ : 224.1049, found 224.1052;  $[\alpha]_D^{18.3} +73.0^\circ$  ( $c$  1.13,  $\text{CH}_2\text{Cl}_2$ , 98% ee). Relative stereochemistry determined by NOE interactions shown below.



**Acetal 215.**  $R_f = 0.19$  (2:1 hexanes/EtOAc); mp = 151.5–153  $^\circ\text{C}$  ( $\text{Et}_2\text{O}$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.30 (s, 1H), 4.89 (dd,  $J = 12.9, 7.2$  Hz, 1H), 4.19 (d,  $J = 9.6$  Hz, 1H), 4.11 (d,  $J = 9.6$  Hz, 1H), 3.49 (s, 3H), 3.33 (dd,  $J = 7.0, 6.3$  Hz, 1H), 2.58 (d,  $J = 4.0$  Hz, 1H), 2.40 (ddd,  $J = 10.0, 6.0, 4.1$  Hz, 1H), 2.30–2.22 (m, 1H), 2.16 (ddd,  $J = 14.5, 7.4, 7.4$  Hz, 1H), 1.55 (ddd,  $J = 14.0, 11.1, 5.7$  Hz, 1H), 1.03 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.2, 108.4, 86.6, 73.2, 56.5, 55.5, 50.1, 42.8, 41.2, 38.7, 38.2, 15.3; IR (Neat Film NaCl) 2934, 1766, 1460, 1359, 1199, 1171, 1143, 1130, 1115, 1063, 1045, 916, 904, 691  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{12}\text{H}_{16}\text{O}_4$   $[\text{M}]^+$ : 224.1049, found 224.1044;  $[\alpha]_D^{17.9} -56.7^\circ$  ( $c$  0.62,  $\text{CH}_2\text{Cl}_2$ , 98% ee). Crystals suitable for X-ray analysis were obtained by slow evaporation from  $\text{Et}_2\text{O}$ . See Appendix 3 for the crystallography report.

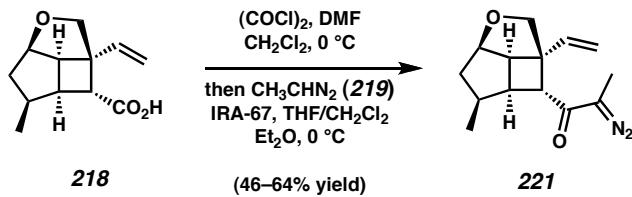


**Acid 218.** To a solution of olefin **216** (41.0 mg, 0.184 mmol, 1.0 equiv) in THF (3.7 mL, 0.05 M) cooled to 0 °C was added KOTMS (236 mg, 1.84 mmol, 10 equiv) in one portion. After 5 min the reaction was warmed to room temperature and monitored by TLC. At 12 h the reaction was cooled to 0 °C and slowly quenched with 10% HCl (4 mL) and diluted with brine (4 mL) and EtOAc (10 mL). The layers were separated and the aq layer was extracted with EtOAc (3 x 10 mL), the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to a pale yellow oil. The crude was purified by flash chromatography on SiO<sub>2</sub> (6:1 → 3:1 hexanes/EtOAc, CH<sub>2</sub>Cl<sub>2</sub> load) to afford acid **218** (35.2 mg, 0.169 mmol, 92% yield) as a white solid.  $R_f$  = 0.21 (2:1 hexanes/EtOAc); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 6.04 (dd,  $J$  = 17.5, 10.8 Hz, 1H), 5.20 (dd,  $J$  = 10.8, 1.2 Hz, 1H), 5.17 (dd,  $J$  = 17.5, 1.2 Hz, 1H), 4.61 (ddd,  $J$  = 6.4, 6.4, 1.6 Hz, 1H), 4.02 (d,  $J$  = 9.1 Hz, 1H), 3.54 (d,  $J$  = 9.1 Hz, 1H), 3.22 (d,  $J$  = 7.3 Hz, 1H), 3.05 (app t,  $J$  = 7.1 Hz, 1H), 2.91 (app q,  $J$  = 7.6 Hz, 1H), 2.40 (d septuplets,  $J$  = 10.4, 7.0 Hz, 1H), 2.20 (ddd,  $J$  = 14.7, 10.4, 5.8 Hz, 1H), 1.73 (ddd,  $J$  = 14.7, 6.3, 1.7 Hz, 1H), 1.05 (d,  $J$  = 7.1 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 178.6, 134.5, 116.2, 87.2, 78.8, 52.8, 51.2, 44.7, 42.5, 39.0, 37.2, 17.2; IR (Neat Film NaCl) 3085 (br), 2958, 2930, 1731, 1704, 1418, 1283, 1241, 1086, 1041, 996, 921 cm<sup>-1</sup>; HRMS (EI+) *m/z* calc'd for C<sub>12</sub>H<sub>16</sub>O<sub>3</sub> [M]<sup>+</sup>: 208.1100, found 208.1094;  $[\alpha]_D^{15.3}$  +28.3° (*c* 0.97, CH<sub>2</sub>Cl<sub>2</sub>, 98% ee).

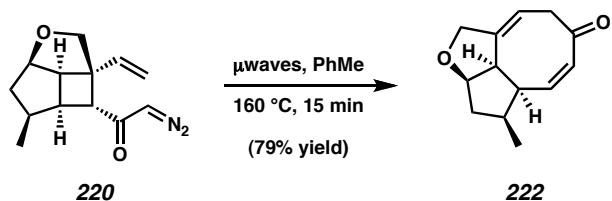


**Diazoketone 220.** To a solution of acid **218** (62.5 mg, 0.300 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (6.0 mL, 0.05 M) at 0 °C was added a solution of oxalyl chloride (353  $\mu\text{L}$  of a 1.7 M solution in  $\text{CH}_2\text{Cl}_2$ , 0.600 mmol, 2.0 equiv), followed by 1 drop of DMF. The reaction was stirred for 45 min at 0 °C, at which point the stir bar was removed, PhMe was added (6 mL), and the volatiles were removed on a rotovap purged with argon. The septum and stir bar were replaced and the crude material was further dried under high vacuum for 10 min. The resulting crude semisolid was partially dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and THF (4 mL) and transferred quantitatively via Teflon cannula to a vigorously stirring solution of excess diazomethane (**199**, ca. 30 mL) containing IRA-67 (161 mg, ca. 0.9 mmol, 3.0 equiv) at 0 °C. The flask was further washed with  $\text{CH}_2\text{Cl}_2$  (4 mL) and THF (2 mL) and quantitatively transferred. After 3.5 h the cooling bath was removed and the diazomethane was pulled off via water aspirator. The pale yellow solution was filtered through a small  $\text{SiO}_2$  plug ( $\text{Et}_2\text{O}$ ) and concentrated in vacuo. The crude material was purified by flash chromatography on  $\text{SiO}_2$  (6:1 → 2:1 hexanes/ $\text{Et}_2\text{O}$ ) to afford  $\alpha$ -diazoketone **220** (63.2 mg, 0.272 mmol, 91% yield) as a bright yellow oil that solidifies in a –20 °C freezer.  $R_f$  = 0.24 (3:1 hexanes/ $\text{EtOAc}$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.01 (dd,  $J$  = 17.5, 10.8 Hz, 1H), 5.15 (d,  $J$  = 10.9 Hz, 1H), 5.10 (br s, 1H), 5.05 (d,  $J$  = 17.5 Hz, 1H), 4.59 (app t,  $J$  = 6.1 Hz, 1H), 3.92 (d,  $J$  = 9.0 Hz, 1H), 3.63 (d,  $J$  = 9.0 Hz, 1H), 3.11 (br d,  $J$  = 14.8, 2H), 2.96 (app t,  $J$  = 6.9 Hz, 1H), 2.44–2.35 (m, 1H), 2.20 (ddd,  $J$  = 15.4, 10.5, 5.8 Hz, 1H), 1.70 (dd,  $J$  = 14.7, 6.3 Hz, 1H), 0.99 (d,  $J$  = 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  193.7, 134.9, 115.7, 87.2, 78.3, 54.8, 53.3, 51.9, 50.4, 42.6, 38.3, 37.3, 17.2; IR (Neat Film NaCl) 3081, 2956, 2100, 1635, 1373,

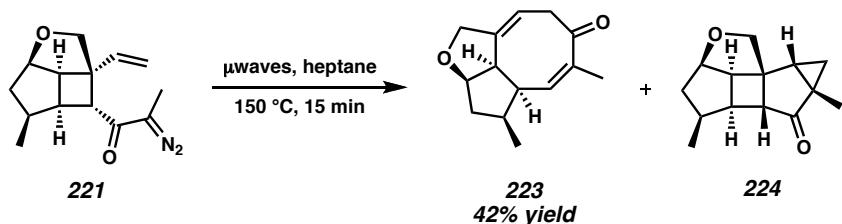
1047, 919  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 233.1290, found 233.1296;  $[\alpha]_{\text{D}}^{20.2} -66.3^\circ$  ( $c$  0.99,  $\text{CH}_2\text{Cl}_2$ , 98% ee).



**Diazoketone 221.**  $\alpha$ -Diazoketone was prepared by the same procedure as described for diazoketone **220** using acid **218** (17.3 mg, 83.1  $\mu$ mol, 1.0 equiv), but with freshly prepared and KOH-dried diazoethane (**219**, ca. 20 mL). After 4 h at 0 °C the excess diazoethane was removed via water aspirator. The pale orange solution was filtered through a small  $\text{SiO}_2$  plug ( $\text{Et}_2\text{O}$ ) and concentrated in vacuo. The crude material was purified by flash chromatography on  $\text{SiO}_2$  (6:1 → 4:1 hexanes/ $\text{Et}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$  load) to afford  $\alpha$ -diazoketone **221** (13.0 mg, 52.8  $\mu$ mol, 64% yield) as a bright yellow oil.  $R_f$  = 0.38 (2:1 hexanes/ $\text{Et}_2\text{O}$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.95 (dd,  $J$  = 17.5, 10.9 Hz, 1H), 5.10 (d,  $J$  = 10.8 Hz, 1H), 5.05 (d,  $J$  = 17.6 Hz, 1H), 4.57 (app t,  $J$  = 5.7 Hz, 1H), 3.86 (d,  $J$  = 9.3 Hz, 1H), 3.66 (d,  $J$  = 9.3 Hz, 1H), 3.34 (d,  $J$  = 6.8 Hz, 1H), 3.28 (dd,  $J$  = 14.9, 7.5 Hz, 1H), 2.93 (app t,  $J$  = 6.9 Hz, 1H), 2.45–2.36 (m, 1H), 2.16 (ddd,  $J$  = 15.1, 10.6, 5.7 Hz, 1H), 1.94 (s, 3H), 1.70 (dd,  $J$  = 14.5, 5.9 Hz, 1H), 0.98 (d,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  14.3, 134.8, 115.5, 87.0, 77.3, 53.0, 52.5, 47.7, 42.3, 36.7, 36.3, 17.3, 8.3; IR (Neat Film NaCl) 2957, 2926, 2064, 1631, 1286, 1050  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{14}\text{H}_{19}\text{O}_2\text{N}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 247.1447, found 247.1457;  $[\alpha]_D^{19.9} +71.6^\circ$  ( $c$  0.57,  $\text{CH}_2\text{Cl}_2$ , 98% ee).



**Cyclooctadienone 222.** A solution of  $\alpha$ -diazoketone **220** (69.2 mg, 0.271 mmol) in PhMe (54 mL, 5 mM) was partitioned equally into three nondried 20 mL microwave reaction vessels containing a stir bar under ambient atmosphere. Each vial was sealed and irradiated in a Biotage Initiator microwave reactor at 400 W until the temperature reached 160 °C, and the temperature was maintained for 15 min. The vial was cooled to room temperature, the seal was removed, and the contents were concentrated in vacuo. Reaction conversion was monitored by crude  $^1\text{H}$  NMR analysis ( $\text{CDCl}_3$ ). The crude material was purified by flash chromatography on  $\text{SiO}_2$  (9:1  $\rightarrow$  6:1  $\rightarrow$  3:1 hexanes/EtOAc) to give **222** (43.9 mg, 0.215 mmol, 79% yield) as a colorless oil that solidifies in a -20 °C freezer.  $R_f$  = 0.35 (3:1 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.08 (dd,  $J$  = 12.4, 6.5 Hz, 1H), 5.93 (app dt,  $J$  = 12.4, 1.9 Hz, 1H), 5.54 (dtd,  $J$  = 4.8, 3.2, 2.6, 1.7 Hz, 1H), 4.59 (dd,  $J$  = 14.1, 6.9 Hz, 1H), 4.38 (d,  $J$  = 12.1 Hz, 1H), 4.32 (d,  $J$  = 12.2 Hz, 1H), 3.44 (ddd,  $J$  = 9.4, 2.2, 1.0 Hz, 1H), 3.28 (dd,  $J$  = 14.3, 9.8 Hz, 1H), 3.18–3.13 (m, 1H), 2.99 (ddd,  $J$  = 14.3, 6.2, 1.2 Hz, 1H), 2.41–2.32 (m, 1H), 2.18 (dd,  $J$  = 13.1, 7.1, 6.1, 1.2 Hz, 1H), 1.44 (ddd,  $J$  = 13.2, 13.2, 5.9 Hz, 1H), 1.11 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  204.4, 146.1, 139.2, 131.6, 114.2, 85.1, 74.6, 52.9, 47.8, 40.1, 38.9, 15.0; IR (Neat Film NaCl) 2958, 2874, 1691, 1666, 1116, 1064, 1032, 974, 867  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{13}\text{H}_{17}\text{O}_2$  [M + H] $^+$ : 205.1229, found 205.1223;  $[\alpha]_D^{20.4}$  -642° (c 1.38,  $\text{CH}_2\text{Cl}_2$ , 98% ee).

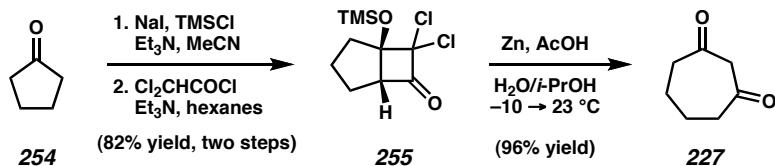


**Wolff/Cope rearrangement for cyclooctadienone 223 and cyclopropane 224.** A solution of  $\alpha$ -diazoketone **221** (17.7 mg, 71.9  $\mu$ mol) in heptane (14.4 mL, 5 mM) was prepared in a nondried 20 mL microwave reaction vessel under ambient atmosphere and sealed. The contents were irradiated in a Biotage Initiator microwave reactor at 400 W until the temperature reached 150 °C, and the temperature was maintained for 10 min. The reaction was cooled to room temperature and TLC analysis showed consumption of **221**. The solution was concentrated in vacuo and purified by preparative TLC on  $\text{SiO}_2$  (3:1 hexanes/EtOAc, develop twice) to afford  $\alpha$ -methyl cyclooctadienone **223** (6.6 mg, 30.2  $\mu$ mol, 42% yield) as a colorless oil and cyclopropane **224** as a single diastereomer.

**Cyclooctadienone 223.**  $R_f = 0.41$  (3:1 hexanes/EtOAc);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.80 (app dq,  $J = 7.2, 1.3$  Hz, 1H), 5.52–5.48 (m, 1H), 4.58 (ddd,  $J = 7.3, 7.3, 6.2$  Hz, 1H), 4.38 (d,  $J = 12.1$  Hz, 1H), 4.31 (ddd,  $J = 10.7, 3.0, 1.6$  Hz, 1H), 3.36 (dddd,  $J = 9.3, 8.1, 2.4, 1.1$  Hz, 1H), 3.24 (dd,  $J = 15.6, 9.5$  Hz, 1H), 3.02–2.98 (comp m, 2H), 2.36–2.14 (m, 1H), 2.16 (ddd,  $J = 13.2, 7.1, 1.0$  Hz, 1H), 1.84 (app t,  $J = 1.5$  Hz, 3H), 1.47 (ddd,  $J = 13.3, 13.3, 5.9$  Hz, 1H), 1.08 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  207.6, 146.6, 137.2, 132.5, 113.7, 85.1, 74.5, 53.3, 47.0, 46.8, 40.3, 38.9, 20.8, 15.0; IR (Neat Film NaCl) 2956, 2923, 2874, 1693, 1667, 1452, 1375, 1076, 1045, 1020, 973, 873, 838  $\text{cm}^{-1}$ ; HRMS (MM: ESI/APCI)  $m/z$  calc'd for  $\text{C}_{14}\text{H}_{19}\text{O}_2$  [M + H] $^+$ : 219.1380, found 219.1379;  $[\alpha]_{\text{D}}^{25} -573^\circ$  ( $c$  0.35,  $\text{CHCl}_3$ , 98% ee)

**Cyclopropane 224.**  $R_f = 0.36$  (3:1 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.80 (ddd,  $J = 7.2, 7.2, 6.0$  Hz, 1H), 3.94 (d,  $J = 9.3$  Hz, 1H), 3.84 (d,  $J = 9.3$  Hz, 1H), 2.86 (d,  $J = 1.8$  Hz, 1H), 2.84 (dd,  $J = 7.4, 5.8$  Hz, 1H), 2.25 (d,  $J = 2.9$  Hz, 1H), 2.16 (dddd,  $J = 10.5, 10.5, 8.6, 4.1$  Hz, 1H), 2.12–2.07 (m, 1H), 2.04 (ddd,  $J = 9.0, 4.6, 1.8$  Hz, 1H), 1.56–1.54 (comp m, 2H), 1.49 (ddd,  $J = 13.6, 10.9, 5.8$  Hz, 1H), 1.22 (s, 3H), 0.96 (d,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  198.7, 86.3, 74.3, 67.1, 57.9, 51.0, 49.7, 46.7, 43.1, 38.8, 37.4, 32.7, 15.2, 9.4; IR (Neat Film NaCl) 2953, 2923, 2868, 1776, 1449, 1073, 1015, 937  $\text{cm}^{-1}$ ; HRMS (MM: ESI/APCI)  $m/z$  calc'd for  $\text{C}_{14}\text{H}_{19}\text{O}_2$  [M + H] $^+$ : 219.1380, found 219.1382;  $[\alpha]_D^{25} +46.1^\circ$  ( $c$  0.38,  $\text{CHCl}_3$ , 98% ee)

### 3.7.2.4 D-RING FRAGMENTS



**Cycloheptane-1,3-dione (227).**<sup>45</sup> NaI (156.74 g, 1.046 mol, 1.25 equiv) was placed in a 3 L 3-neck flask and dried under high vacuum at 90 °C for 12 h and then cooled to ambient temperature under  $\text{N}_2$ .  $\text{CH}_3\text{CN}$  (1.3 L, 0.65 M) was added to dissolve the NaI and to the resulting solution was added cyclopentanone (254, 70.7 g, 74.3 mL, 0.840 mol, 1.0 equiv) followed by  $\text{Et}_3\text{N}$  (106.25 g, 146.3 mL, 1.050 mol, 1.25 equiv). The flask was fitted with an oven-dried addition funnel and was charged with TMSCl (104.03 g, 122 mL, 0.958 mol, 1.15 equiv), which was added dropwise over 30 min. The resulting suspension was stirred for an additional 1 h at ambient temperature. Pentane (1.0 L) was

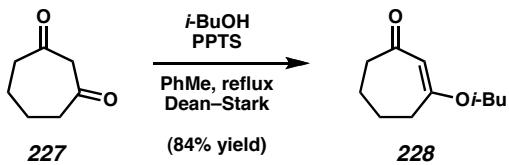
added and the biphasic system was stirred vigorously for 10 min. The layers were separated and the  $\text{CH}_3\text{CN}$  layer was extracted with pentane (3 x 400 mL). The combined pentane extracts were washed with  $\text{H}_2\text{O}$  (2 x 500 mL), brine (500 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and carefully concentrated under reduced pressure (down to 100 torr) to afford the desired silyl enol ether (131.4 g, 0.840 mol, quantitative yield) as a colorless oil. This material was used directly in the following reaction without further purification.  $R_f = 0.83$  (4:1 hexanes/EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.78 (dt,  $J = 3.9, 2.0$  Hz, 1H), 2.45–2.33 (comp m, 4H), 1.89–1.79 (comp m, 2H), 0.27 (s, 9H). All other spectral data are consistent with reported values.

The obtained silyl enol ether (89.7 g, 0.574 mol, 1.0 equiv) was placed in a 3 L 3-neck round-bottom flask fitted with a stopper, an addition funnel, and an overhead stirrer. Hexanes (900 mL) were added followed by  $\text{Et}_3\text{N}$  (80.7 g, 111.2 mL, 0.798 mol, 1.4 equiv). Dichloroacetyl chloride (101.70 g, 66.4 mL, 0.690 mol, 1.2 equiv) was dissolved in hexanes (400 mL), transferred to the closed addition funnel, and added dropwise to the reaction over 9.5 h with vigorous stirring. After 18 h of stirring at 23 °C, the brown suspension was vacuum filtered through a coarse sintered-glass funnel. The filter cake was thoroughly rinsed with EtOAc (3 x 500 mL) while agitating the precipitate with a stirring rod. The clear brown solution was concentrated under reduced pressure and then filtered through a pad of  $\text{Al}_2\text{O}_3$  (neutral, 7 x 18 cm) eluting with EtOAc. The resulting solution was concentrated under reduced pressure to afford dichlorocyclobutanone **255** (124.7 g, 0.467 mol, 82% yield) as a dark brown oil that crystallized in a –20 °C freezer. This material was used directly in the next reaction without further purification.  $R_f = 0.58$  (6:1 hexanes/EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

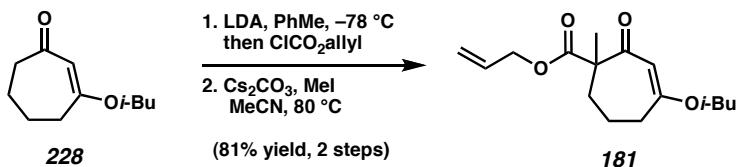
$\delta$  3.66 (9d,  $J$  = 8.4 Hz, 1H), 2.55 (dd,  $J$  = 13.3, 6.8 Hz, 1H), 2.12–1.84 (comp m, 4H), 1.64–1.51 (m, 1H), 0.25 (s, 9H). All other spectral data are consistent with reported values.

The above dichlorocyclobutanone **255** (53.4 g, 0.200 mol, 1.0 equiv) was placed in a 3 L 3-neck round-bottom flask fitted with a thermometer, an addition funnel and an overhead stirrer. This material was dissolved in *i*-PrOH and purified water (170 mL each). The suspension was cooled to –10 °C (internally) in a MeOH/ice bath. To this cooled solution was added Zn dust (58.8 g, 0.899 mol, 4.5 equiv) in four portions (5 min between each). The addition funnel was charged with a solution of AcOH (66.1 g, 63 mL, 1.10 mol, 5.5 equiv) dissolved in purified water (130 mL) and this solution was added to the reaction in a dropwise manner at such a rate to keep the internal temperature below 0 °C (typically added over 1.5 h). Upon complete addition, the suspension was stirred for an additional 30 min at –10 °C (internal) and then the cooling bath was removed and the reaction was allowed to warm to ambient temperature. After 8.5 h, the reaction mixture was filtered through a coarse sintered-glass funnel and rinsed with *i*-PrOH (100 mL). The filtrate was cooled to 0 °C and slowly neutralized by portionwise addition of  $\text{K}_2\text{CO}_3$  (74.6 g, 0.54 mol, 2.7 equiv) with vigorous stirring (overhead stirrer). The viscous suspension was filtered and rinsed with  $\text{H}_2\text{O}$  (100 mL) and EtOAc (300 mL). The biphasic system was concentrated under reduced pressure to ~200 mL to remove a large portion of the *i*-PrOH and extracted with  $\text{CH}_2\text{Cl}_2$  (100 mL portions until TLC clear). The combined organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to afford cycloheptane-1,3-dione (**227**) (24.2 g, 0.192 mol, 96% yield) as a pale orange oil.  $R_f$  = 0.16 (4:1 hexanes/EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.59 (s, 2H),

2.60–2.56 (comp m, 4H), 2.02–1.94 (comp m, 4H). All other spectral data are consistent with reported values.



**Vinylogous ester 228.** To a solution of **227** (35.8 g, 0.284 mol, 1.0 equiv) in toluene (280 mL, 1 M) in a flask fitted with a Dean–Stark trap and reflux condenser was added *i*-BuOH (168.3 g, 208 mL, 2.27 mol, 8.0 equiv) and PPTS (1.07 g, 4.26 mmol, 0.0015 equiv). The solution was immersed into an oil bath at 130 °C and monitored by TLC. Upon consumption of the starting material (typically within 4–6 h), the reaction was allowed to cool to room temperature and the resulting dark orange solution was washed with sat. aq NaHCO<sub>3</sub> (200 mL). The aqueous phase was extracted with EtOAc (3 x 150 mL), the combined organics were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to afford a thick dark orange oil. The crude oil was flushed through a plug of silica gel (7 x 9 cm SiO<sub>2</sub>, 1:4 → 3:7 → 1:1 hexanes/Et<sub>2</sub>O) to afford the vinylogous ester **228** (43.5 g, 0.239 mol, 84% yield) as a pale orange oil. *R*<sub>f</sub> = 0.22 (2:1 hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.37 (s, 1H), 3.49 (d, *J* = 6.6 Hz, 2H), 2.60–2.56 (comp m, 4H), 2.00 (septuplet, *J* = 6.6 Hz, 1H), 1.88–1.77 (comp m, 4H), 0.96 (d, *J* = 6.8 Hz, 6H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 202.5, 176.6, 106.0, 75.0, 41.9, 33.1, 27.9, 23.7, 21.5, 19.3; IR (Neat Film NaCl) 2958, 2872, 1646, 1607, 1469, 1237, 1190, 1174 cm<sup>-1</sup>; HRMS (EI+) *m/z* calc'd for C<sub>11</sub>H<sub>18</sub>O<sub>2</sub> [M]<sup>+</sup>: 182.1307; found 182.1310.



**Vinylogous  $\beta$ -ketoester ( $\pm$ )-181.**

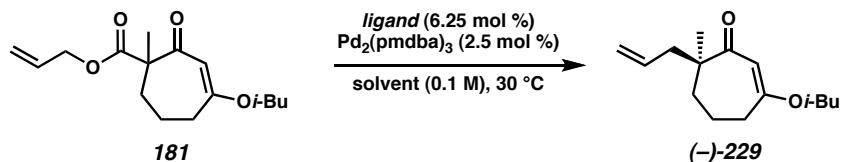
To a solution of *i*-Pr<sub>2</sub>NH (3.06 mL, 21.9 mmol, 2.05 equiv) in PhMe (75 mL) cooled to  $-78$  °C was added a solution of *n*-BuLi (8.36 mL, 21.3 mmol, 2.0 equiv; 2.55 M in hexane) via syringe. The flask was placed in a 0 °C ice bath for 10 min, and then cooled back to  $-78$  °C at which point a solution of **228** (1.9434 g, 10.7 mmol, 1.0 equiv) in PhMe (7 mL) was added dropwise via cannula. The flask was washed with extra PhMe (5 mL) to ensure complete transfer. After 30 min, allyl chloroformate (1.25 mL, 11.7 mmol, 1.1 equiv) was added dropwise and the cooling bath was removed. After 1 h at room temperature the reaction was quenched with 1 N KHSO<sub>4</sub> (25 mL) and the layers were separated. The aq layer was extracted with Et<sub>2</sub>O (2 x 40 mL) and the combined organics were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to a viscous yellow oil.

The crude oil was dissolved in MeCN (43 mL, 0.25 M) and to this was added Cs<sub>2</sub>CO<sub>3</sub> (4.34 g, 13.3 mmol, 1.25 equiv) and MeI (2.0 mL, 32.0 mmol, 3.0 equiv). The flask was fitted with a reflux condenser and placed in an 80 °C oil bath with vigorous stirring. After 6–8 h the reaction was warmed to room temperature, diluted with EtOAc (50 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on SiO<sub>2</sub> (9:1 → 6:1 → 3:1 hexanes/EtOAc, PhMe load) to give vinylogous  $\beta$ -ketoester ( $\pm$ )-**181** (2.4416 g, 8.71 mmol, 81% yield over two steps) as a pale yellow oil.  $R_f$  = 0.43 (4:1 hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.86

(dddd,  $J = 17.1, 10.7, 5.6, 5.6$  Hz, 1H), 5.39 (s, 1H), 5.29 (ddd,  $J = 17.1, 2.9, 1.5$  Hz, 1H), 5.20 (app d,  $J = 10.5$  Hz, 1H), 4.59 (dddd,  $J = 19.0, 13.2, 5.6, 1.2$  Hz, 2H), 3.50 (dd,  $J = 9.3, 6.8$  Hz, 1H), 3.47 (dd,  $J = 9.3, 6.6$  Hz, 1H), 2.59 (ddd,  $J = 17.8, 9.8, 3.9$  Hz, 1H), 2.45–2.38 (comp m, 2H), 2.02–1.94 (m, 1H), 1.84–1.75 (m, 1H), 1.70 (ddd,  $J = 14.4, 7.3, 4.4$  Hz, 1H), 1.43 (s, 3H), 0.94 (d,  $J = 6.6$  Hz, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  199.1, 174.0, 173.5, 132.0, 118.4, 105.2, 74.8, 65.8, 59.1, 34.3, 33.9, 27.9, 24.2, 21.4, 19.3; IR (Neat Film NaCl) 2959, 2936, 2875, 1734, 1650, 1613, 1456, 1384, 1233, 1170, 1115, 994  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{16}\text{H}_{24}\text{O}_4$  [M] $^+$ : 280.1675; found 280.1686.

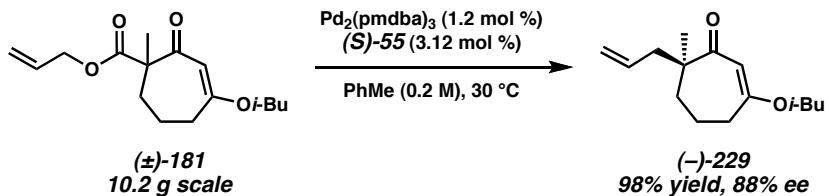
*Alternative procedure using allyl cyanoformate.* To a solution of *i*-Pr<sub>2</sub>NH (4.66 g, 6.46 mL, 46.1 mmol, 1.2 equiv) in THF (180 mL) cooled to 0 °C in a 500 mL round-bottom flask was added *n*-BuLi (17.2 mL, 44.2 mmol, 2.57 M in hexanes, 1.15 equiv) dropwise over 15 min by use of syringe pump. After 15 min stirring at 0 °C, the mixture was cooled to –78 °C and a solution of vinylogous ester **228** (7.01 g, 38.4 mmol, 1.0 equiv) dissolved in THF (20 mL) and added in a dropwise manner over 20 min by use of a syringe pump. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (4.69 g, 4.60 mL, 42.2 mmol, 1.1 equiv) was added in a dropwise manner over 10 min. The mixture was stirred at –78 °C for 2.5 h and quenched with 50% sat. aq NH<sub>4</sub>Cl (60 mL) and allowed to warm to ambient temperature. The reaction mixture was diluted with Et<sub>2</sub>O (100 mL) and the phases were separated. The aq phase was extracted with Et<sub>2</sub>O (2 x 100 mL) and the combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to afford a pale orange oil (10.5 g, >100%, some allyl cyanoformate left).

The crude oil was converted to vinylogous  $\beta$ -ketoester **181** as above using CH<sub>3</sub>CN (130 mL, 0.3 M), MeI (16.35 g, 7.2 mL, 115 mmol, 3.0 equiv), and Cs<sub>2</sub>CO<sub>3</sub> (16.76 g, 49.9 mmol, 1.3 equiv). Purification by flash chromatography on SiO<sub>2</sub> (19:1  $\rightarrow$  9:1, hexanes/EtOAc, dry-loaded using Celite) afforded vinylogous  $\beta$ -ketoester ( $\pm$ )-**181** (8.51 g, 30.4 mmol, 79% yield over two steps) as a pale yellow oil.

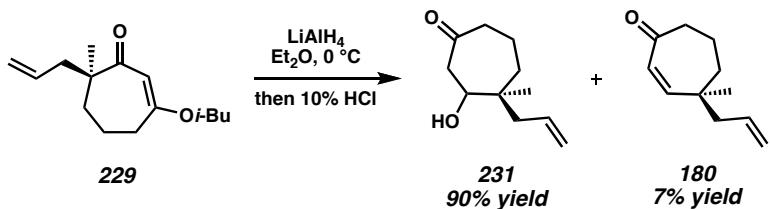


**Screen for ketone (-)-229.** To a dry flask was added Pd<sub>2</sub>(pmdba)<sub>3</sub> (2.5 mol %) and ligand (6.25 mol %) and the contents were evacuated/purged 3x with N<sub>2</sub>. To this was added solvent (0.1 M, most of it) and the contents were stirred for 30 min in a 30 °C oil bath, at which point a solution of ( $\pm$ )-**181** (1.0 equiv) in remaining solvent was transferred via cannula. When judged complete by TLC analysis, the reaction was filtered through a small plug of SiO<sub>2</sub> eluting with Et<sub>2</sub>O and concentrated in vacuo. Purification by flash chromatography (15:1  $\rightarrow$  9:1 hexanes/EtOAc) or preparative TLC (4:1 hexanes/EtOAc) provided ketone **229** for analytical analysis.  $R_f$  = 0.31 (3:1 hexanes/Et<sub>2</sub>O); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.72 (dd,  $J$  = 16.6, 10.5, 7.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.05–5.00 (m, 2H), 3.50 (dd,  $J$  = 9.3, 6.6 Hz, 1H), 3.47 (dd,  $J$  = 9.3, 6.6 Hz, 1H), 2.53–2.42 (m, 2H), 2.38 (dd,  $J$  = 13.7, 7.1 Hz, 1H), 2.20 (dd,  $J$  = 13.7, 7.8 Hz, 1H), 1.98 (app septuplet,  $J$  = 6.6 Hz, 1H), 1.86–1.70 (comp m, 3H), 1.62–1.56 (m, 1H), 1.14 (s, 3H), 0.95 (app d,  $J$  = 6.6 Hz, 6H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  206.7, 171.3, 134.6, 117.9, 105.0, 74.5, 51.5, 45.4, 36.1, 35.2, 28.0, 25.2, 19.9, 19.3, 19.3; IR (Neat Film NaCl) 2960, 2933, 2873,

1614, 1470, 1387, 1192, 1171, 998, 912  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{15}\text{H}_{24}\text{O}_2$  [M]<sup>+</sup>: 236.1776; found 236.1767. HPLC conditions: 1% *i*-PrOH in hexanes, OD-H column,  $t_{\text{R}}$  (min): major = 6.3, minor = 7.3.



**Scale-up of ketone (-)-229.**  $\text{Pd}_2(\text{pmdba})_3$  (496 mg, 0.453 mmol, 0.0125 equiv) and ligand *(S)*-55 (439 mg, 1.13 mmol, 0.0312 equiv) were placed in a 500 mL round-bottom flask and the flask was evacuated and backfilled with  $\text{N}_2$  (3 cycles with 10 min evacuation per cycle). Toluene (150 mL, sparged with  $\text{N}_2$  for 1 h immediately prior to use) was added and the dark purple suspension was immersed into a 30 °C oil bath. After 30 min stirring the solution had changed to a dark orange color and vinylogous  $\beta$ -ketoester  $(\pm)\text{-181}$  (10.16 g, 36.24 mmol, 1.0 equiv) dissolved in toluene (31 mL sparged with  $\text{N}_2$  immediately before use) was added via positive pressure cannulation. Upon addition of  $(\pm)\text{-181}$ , the dark orange catalyst solution immediately turned olive green. The reaction mixture was stirred at 30 °C for 21 h (consumption by TLC), allowed to cool to ambient temperature, filtered through a small plug of  $\text{SiO}_2$  (5.5 x 2 cm,  $\text{Et}_2\text{O}$  eluent) and concentrated under reduced pressure. Purification by flash chromatography on  $\text{SiO}_2$  (5 x 15 cm, 19:1 hexanes/EtOAc, dry-loaded on  $\text{SiO}_2$ ) afforded ketone  $(-)\text{-229}$  (8.38 g, 35.46 mmol, 98% yield) as a pale yellow oil.  $[\alpha]_D^{25.6} -69.04^\circ$  (*c* 1.08,  $\text{CHCl}_3$ , 88% ee).

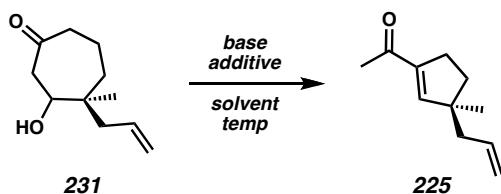


**Reduction of ketone (-)-229.** To a flask charged with Et<sub>2</sub>O (15 mL) cooled to 0 °C was added LiAlH<sub>4</sub> (71.2 mg, 1.88 mmol, 0.55 equiv) in one portion. After 10 min, a solution of ketone **229** (806.1 mg, 3.41 mmol, 1.0 equiv) in Et<sub>2</sub>O (2 mL) was added via cannula, washing the transfer flask with excess Et<sub>2</sub>O to ensure quantitative transfer. After consumption of **229** by TLC analysis (1 h), the reaction was quenched by slow addition of 10% HCl (10 mL). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 8–15 h. The layers were separated and the aq phase was extracted with Et<sub>2</sub>O (3 x 20 mL). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was azeotroped with toluene (3 x 5 mL) and purified by flash chromatography on SiO<sub>2</sub> (9:1 → 3:1 hexanes/EtOAc) to afford β-hydroxyketone **231** (558.8 mg, 3.07 mmol, 90% yield) as a colorless oil that forms a semisolid in a –20 °C freezer and cycloheptenone **180** (40.8 mg, 0.248 mmol, 7% yield) as a colorless oil.

**$\beta$ -Hydroxyketone 231.**  $R_f = 0.23$  (7:3 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  **major diastereomer:** 5.88 (dddd,  $J = 15.1, 9.0, 7.6, 7.6$  Hz, 1H), 5.12–5.08 (m, 2H), 3.70 (dd,  $J = 4.9, 3.9$  Hz, 1H), 2.86 (dd,  $J = 15.6, 1.7$  Hz, 1H), 2.65 (dd,  $J = 15.6, 7.3$  Hz, 1H), 2.54–2.43 (m, 2H), 2.24 (dd,  $J = 13.7, 7.8$  Hz, 1H), 2.07 (dd,  $J = 13.4, 7.3$  Hz, 1H), 1.99 (dd,  $J = 15.9, 4.4$  Hz, 1H), 1.82–1.69 (comp m, 2H), 1.45–1.41 (m, 1H), 0.96 (s, 3H); **minor diastereomer:** 5.83 (dddd,  $J = 14.9, 10.3, 7.6, 7.6$  Hz, 1H), 5.12–5.06 (m, 2H), 3.68 (dd,  $J = 4.1, 2.4$  Hz, 1H) 2.80 (dd,  $J = 15.4, 2.4$  Hz, 1H), 2.74 (dd,  $J =$

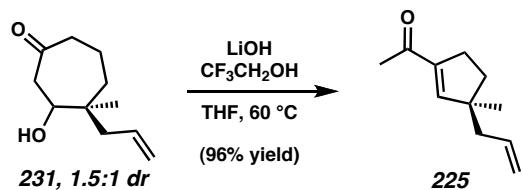
15.4, 8.1 Hz, 1H), 2.46–2.38 (m, 2H), 2.18 (dd,  $J$  = 13.9, 7.3 Hz, 1H), 2.09 (dd,  $J$  = 12.9, 7.8 Hz, 1H), 1.82–1.65 (comp m, 3H) 1.50–1.47 (m, 1H), 1.02 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  **major diastereomer:** 213.2, 135.0, 118.1, 72.9, 46.7, 44.9, 44.2, 41.0, 36.3, 21.9, 18.9; **minor diastereomer:** 212.6, 134.2, 118.3, 73.3, 47.2, 42.8, 41.0, 35.9, 22.6, 18.7 one peak overlapping; IR (Neat Film NaCl) 3436 (br), 3074, 2932, 1692, 1638, 1443, 1403, 1380, 1352, 1318, 1246, 1168, 1106, 1069, 999, 913, 840  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{11}\text{H}_{18}\text{O}_2$  [M] $^+$ : 182.1307; found 182.1313;  $[\alpha]_D^{22.8} -57.1^\circ$  ( $c$  2.56,  $\text{CHCl}_3$ , 1.5:1 dr and 88% ee).

**Cycloheptenone 180.**  $R_f = 0.54$  (7:3 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.04 (dd,  $J$  = 12.9, 0.7 Hz, 1H), 5.82 (d,  $J$  = 12.9 Hz, 1H), 5.75 (dd,  $J$  = 17.1, 10.3, 7.8, 7.1 Hz, 1H), 5.10 (dd,  $J$  = 10.3, 1.2, 1.2, 1.2 Hz, 1H), 5.08–5.03 (m, 1H), 2.65–2.52 (m, 2H), 2.19 (app dd,  $J$  = 13.7, 6.8 Hz, 1H), 2.11 (app dd,  $J$  = 13.7, 8.1 Hz, 1H), 1.84–1.76 (m, 3H), 1.68–1.63 (m, 1H), 1.10 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  204.7, 152.5, 133.8, 128.6, 118.6, 47.2, 45.1, 42.7, 38.2, 27.1, 18.4; IR (Neat Film NaCl) 3076, 3011, 2962, 2934, 2870, 1659, 1454, 1402, 1373, 1349, 1335, 1278, 1208, 1172, 997, 916, 874, 822, 772  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{11}\text{H}_{16}\text{O}$  [M] $^+$ : 164.1201; found 164.1209;  $[\alpha]_D^{21.0} -9.55^\circ$  ( $c$  1.07,  $\text{CHCl}_3$ , 88% ee).



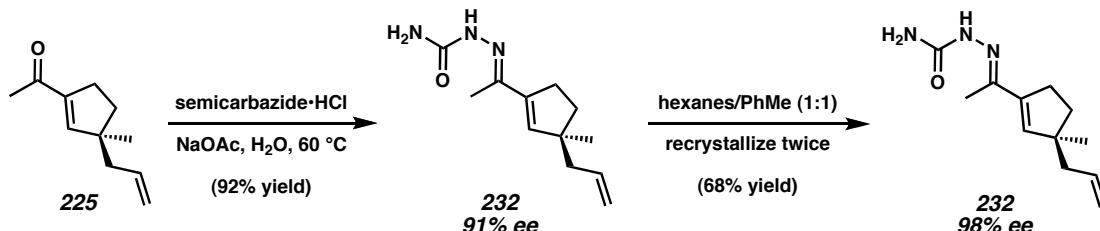
**Ring contraction screen to produce acylcyclopentene 225.** A benzene solution of  $\beta$ -hydroxyketone **231** was transferred to a dry 1-dram vial and concentrated in vacuo to

obtain a starting mass. To this vial was added a stir bar, 1,4-diisopropylbenzene (by mass, as internal standard), and the contents were solvated in either *t*-BuOH or THF (0.1 M). After complete solvation, an appropriate additive (*t*-BuOH, TFE, or HFIP; 1.5 equiv) followed by a base (1.5 equiv) were added, the head space of the vial was purged with nitrogen, and the vial was capped with a teflon-lined cap and placed on the appropriate heating block (40 or 60 °C). Reaction progress was initially followed by TLC analysis, and when necessary aliquots were removed and flushed through a small SiO<sub>2</sub> plug with EtOAc for GC analysis. GC conditions: 90 °C isothermal for 5 min, then ramp 10 °C/min to 250 °C, DB-WAX column, *t*<sub>R</sub> (min): 1,4-diisopropylbenzene = 5.3, acylcyclopentene **225** = 9.3, β-hydroxyketone **231** = 17.1 and 17.2 (two diastereomers).



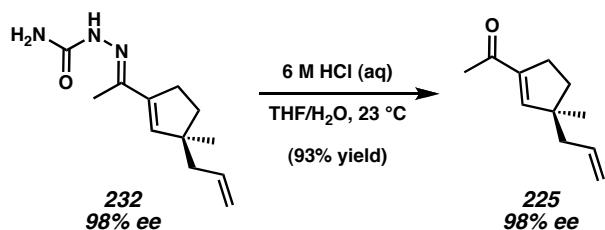
**Scale-up of acylcyclopentene 225.** To a solution of β-hydroxyketone **231** (6.09 g, 33.4 mmol, 1.0 equiv) dissolved in THF (334 mL, 0.1 M) in a 500 mL flask was added 2,2,2-trifluoroethanol (5.04 g, 3.67 mL, 50.1 mmol, 1.5 equiv) and LiOH (1.20 g, 50.1 mmol, 1.5 equiv). The flask was fitted with a reflux condenser, purged with a stream of N<sub>2</sub>, and placed in a 60 °C oil bath. After 18 h the suspension was allowed to cool to ambient temperature, diluted with Et<sub>2</sub>O (150 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (30 min stirring), filtered, and concentrated carefully under vacuum allowing for a film of ice to form on the outside of the flask. The crude product was purified by flash chromatography on SiO<sub>2</sub> (5 x 15 cm, 15:1 hexanes/Et<sub>2</sub>O) and concentrated carefully to afford

acylcyclopentene **225** (5.29 g, 32.2 mmol, 96% yield) as a colorless fragrant oil.  $R_f$  = 0.67 (4:1 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.45 (app t,  $J$  = 1.7 Hz, 1H), 5.76 (dddd,  $J$  = 16.4, 10.7, 7.3, 7.3 Hz, 1H), 5.07–5.03 (comp m, 2H), 2.59–2.48 (comp m, 2H), 2.21–2.14 (comp m, 2H), 2.30 (s, 3H), 1.85 (ddd,  $J$  = 12.9, 8.3, 6.3 Hz, 1H), 1.64 (ddd,  $J$  = 6.1, 8.5, 12.9 Hz), 1.11 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  197.5, 151.9, 143.8, 134.9, 117.8, 50.0, 45.3, 36.0, 29.7, 26.8, 25.6; IR (Neat Film NaCl) 3077, 2956, 2863, 1668, 1635, 1616, 1454, 1435, 1372, 1366, 1309, 1265, 1213, 1177, 993, 914, 862  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{11}\text{H}_{16}\text{O}$  [M] $^+$ : 164.1201; found 164.1216;  $[\alpha]_D^{21.4}$  +17.3° ( $c$  0.955,  $\text{CHCl}_3$ , 88% ee). GC conditions: 80 °C isothermal, GTA column,  $t_R$  (min): major = 54.7, minor = 60.2.

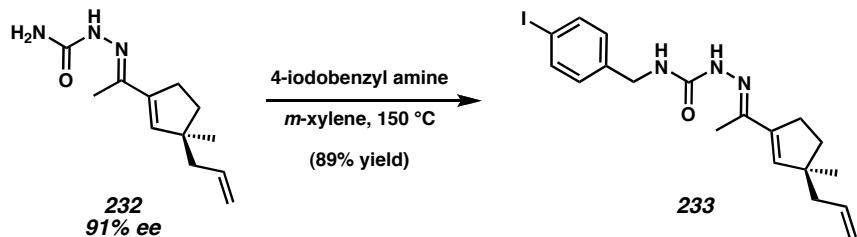


**Semicarbazone 232.** A 15 mL round-bottom flask was charged with sodium acetate (150 mg, 1.83 mmol, 1.2 equiv), and semicarbazide hydrochloride (204 mg, 1.83 mmol, 1.2 equiv). The solids were dissolved in purified water (1.7 mL). Acylcyclopentene **225** (250 mg, 1.52 mmol, 1.0 equiv) was added neat and the mixture was heated to 60 °C for 4 h. The slurry was allowed to cool to ambient temperature while stirring and vacuum filtered (water aspirator). The white solid was dried under reduced pressure to afford semicarbazone **232** (311 mg, 1.41 mmol, 92% yield). The *ee* of **232** at this point was found to be 91% (measured by hydrolysis to acylcyclopentene **225**). Semicarbazone **232**

(300 mg, 1.36 mmol) was transferred to a round-bottom flask, the solids were suspended in toluene/hexanes (1:1), and the mixture was heated to 90 °C with stirring. After a few minutes stirring, the solids had dissolved completely to afford a clear, colorless solution. Heating was discontinued and the stirring mixture was allowed to cool to 23 °C while still immersed in the oil bath. After 10 h had elapsed, the slurry was vacuum filtered to afford **232** (246 mg, 1.11 mmol, 82% yield). The *ee* at this point was found to be 94.5% (measured by hydrolysis to **225** and chiral GC analysis). A second recrystallization following the above procedure (241 mg, 1.09 mmol) afforded **232** (201 mg, 0.908 mmol, 83% yield). The *ee* at this point was found to be 97.9% (measured by hydrolysis to **225**).  $R_f$  = 0.30 (9:1 CHCl<sub>3</sub>/MeOH); mp = 145–146 °C (1:1 toluene/hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.52 (br s, 1H), 6.06 (br s, 1H), 5.85 (app t, *J* = 1.6 Hz, 1H), 5.76 (dddd, *J* = 16.7, 9.3, 7.4, 7.4 Hz, 1H), 5.47 (br s, 1H), 5.06–4.98 (comp m, 2H), 2.67–2.49 (m, 2H), 2.15–2.12 (m, 2H), 1.98 (s, 3H), 1.82 (ddd, *J* = 12.8, 8.2, 6.9 Hz, 1H), 1.62 (ddd, *J* = 12.8, 8.5, 6.4 Hz, 1H), 1.07 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 158.1, 145.0, 141.7, 141.2, 135.6, 117.2, 49.2, 45.9, 36.2, 30.8, 26.3, 12.8; IR (Neat Film NaCl) 3473, 3266, 3189, 2946, 2858, 1698, 1579, 1478, 1437, 1377, 1349, 1321, 1130, 1109, 993, 910, 845, 768 cm<sup>-1</sup>; HRMS (TOF MS ES+) *m/z* calc'd for C<sub>12</sub>H<sub>20</sub>N<sub>3</sub>O [M + H]<sup>+</sup>: 222.1606; found: 222.1610;  $[\alpha]_D^{21.5}$  +39.8° (*c* 0.84, CHCl<sub>3</sub>, 97.9% *ee*).

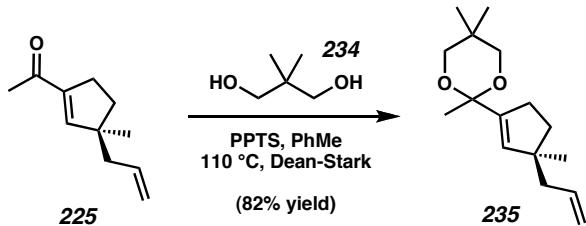


**Hydrolysis to acylcyclopentene 225.** Semicarbazone **232** (191.8 mg, 0.867 mmol) was dissolved in THF (1.92 mL) and aq HCl (3.84 mL, 6 M) was added. The resulting biphasic mixture was stirred vigorously at 23 °C for 30 h. The reaction mixture was diluted with Et<sub>2</sub>O (10 mL), the phases were separated, and the aqueous phase was extracted with Et<sub>2</sub>O (2 x 10 mL). The combined organics were dried over MgSO<sub>4</sub>, filtered and concentrated carefully under vacuum allowing for a film of ice to form on the outside of the flask. The residue was filtered through a short pad of SiO<sub>2</sub> (4:1 hexanes/Et<sub>2</sub>O) to afford **225** (132.6 mg, 0.81 mmol, 93% yield);  $[\alpha]_D^{21.2} +19.6^\circ$  (*c* 1.035, CHCl<sub>3</sub>, 97.9% ee).



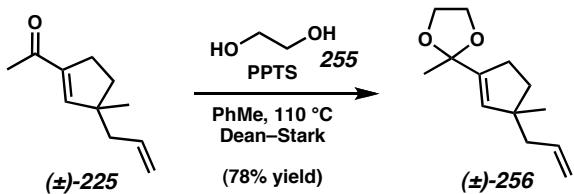
**Iodoarene 233.** To a solution of semicarbazone **232** (50 mg, 0.23 mmol, 91% ee, 1.0 equiv) in *m*-xylene (2.2 mL) was added 4-iodobenzylamine (63 mg, 0.27 mmol, 1.2 equiv). The resulting pale yellow solution was immersed in a 150 °C oil bath. After 9 h, the mixture was allowed to cool to ambient temperature and concentrated under reduced pressure to afford a pale yellow solid. The crude solid was purified by flash chromatography on SiO<sub>2</sub> (9:1 → 7:3 hexanes/EtOAc) to afford iodoarene **233** (88 mg, 0.20 mmol, 89% yield) as a white solid. X-ray-quality crystals were obtained by slow vapor diffusion of pentane into a chloroform solution of **233**.  $R_f = 0.52$  (9:1 CHCl<sub>3</sub>/MeOH); mp = 123–124°C (CHCl<sub>3</sub>/*n*-pentane); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.88

(s, 1H), 7.66–7.64 (m, 2H), 7.08 (d,  $J$  = 8.5 Hz, 2H), 6.50 (t,  $J$  = 6.1 Hz, 1H), 5.86 (app t,  $J$  = 1.5 Hz, 1H), (dddd,  $J$  = 16.9, 9.0, 7.6, 7.6 Hz, 1H), 5.04–5.01 (comp m, 2H), 4.46 (d,  $J$  = 6.3 Hz, 2H), 2.60–2.49 (comp m, 2H), 2.18–2.10 (comp m, 2H); 1.95 (s, 3H), 1.82 (ddd,  $J$  = 12.9, 8.5, 6.3 Hz, 1H), 1.62 (ddd,  $J$  = 12.9, 8.5, 6.1 Hz, 1H), 1.07 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  156.3, 144.5, 141.5, 141.4, 139.2, 137.8, 135.6, 129.4, 117.2, 92.6, 49.3, 45.9, 43.2, 36.2, 30.9, 26.3, 12.5; IR (Neat Film NaCl) 3411, 3194, 3075, 2946, 2920, 2863, 1677, 1528, 1486, 1401, 1323, 1259, 1142, 1114, 1057, 1000, 913, 845  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{19}\text{H}_{25}\text{N}_3\text{OI}$  [M + H] $^+$ : 438.1043; found 438.1036;  $[\alpha]_D^{22.2}$  +31.4° ( $c$  0.385,  $\text{CHCl}_3$ , 91% ee).



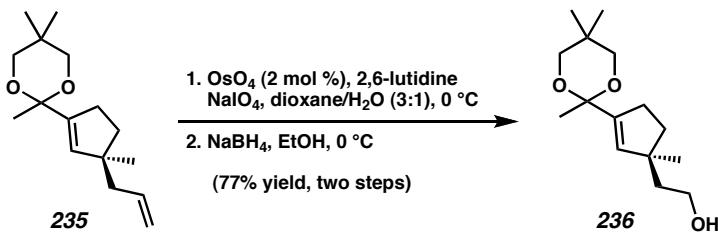
**Acetal 235.** To a solution of acylcyclopentene **225** (5.29 g, 32.2 mmol, 1.0 equiv) in toluene (322 mL) in a 1 L round-bottom flask was added neopentyl glycol (**234**) (20.1 g, 193.2 mmol, 6.0 equiv) and PPTS (809 mg, 3.22 mmol, 0.1 equiv). The flask was fitted with a Dean–Stark trap and a condenser and the mixture was placed in a 135 °C oil bath and heated to reflux. After 25 h the mixture was allowed to cool to ambient temperature, diluted with  $\text{Et}_2\text{O}$  (250 mL), and poured into sat. aq  $\text{NaHCO}_3$  (100 mL). The aq phase was extracted with  $\text{Et}_2\text{O}$  (2 x 100 mL) and the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to afford a white semisolid. The crude product was purified by flash chromatography on  $\text{SiO}_2$  (1:0 → 99:1 → 98:2 hexanes/EtOAc) to afford acetal **235** (6.59 g, 26.3 mmol, 82% yield) as a pale yellow oil.

$R_f = 0.62$  (7:3 hexanes/EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.80 (dddd,  $J = 16.7, 9.3, 7.4, 7.4$  Hz, 1H), 5.52 (app t,  $J = 1.8$  Hz, 1H), 5.06–4.99 (comp m, 2H), 3.59 (dd,  $J = 11.2, 0.8$  Hz, 1H), 3.51 (dd,  $J = 11.2, 0.8$  Hz, 1H), 3.31 (d,  $J = 11.2$  Hz, 2H), 2.37–2.19 (m, 2H), 2.13 (app dt,  $J = 7.4, 1.1$  Hz, 2H), 1.853 (ddd,  $J = 12.8, 8.2, 6.4$  Hz, 1H), 1.63 (ddd,  $J = 12.8, 8.8, 6.1$  Hz, 1H), 1.41 (s, 3H), 1.17 (s, 3H), 1.07 (s, 3H), 0.69 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  141.1, 138.2, 136.1, 116.9, 98.8, 71.8, 71.7, 49.0, 46.2, 36.4, 31.4, 29.8, 27.8, 26.9, 22.8, 22.2; IR (Neat Film NaCl) 3075, 2952, 2906, 2868, 1640, 1472, 1455, 1182, 1118, 1041, 996, 950, 911, 862  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{16}\text{H}_{27}\text{O}_2$   $[\text{M} + \text{H}]^+$ : 251.2011; found 251.2011;  $[\alpha]_D^{20.9} +11.5^\circ$  ( $c$  1.01,  $\text{CHCl}_3$ , 88% ee).



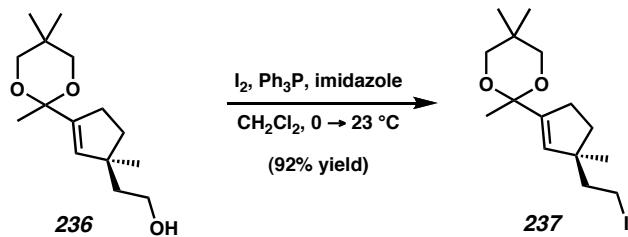
**Dioxolane 256.** To a solution of **225** (388.1 mg, 2.36 mmol, 1.0 equiv) in benzene (11.8 mL) in a 25 mL round-bottom flask was added ethylene glycol (**255**) (880 mg, 791  $\mu\text{L}$ , 14.2 mmol, 6.0 equiv) and PPTS (59.4 mg, 0.24 mmol, 0.1 equiv). The flask was fitted with a condenser and a Dean–Stark trap and immersed into a 115  $^\circ\text{C}$  oil bath and heated to reflux. After 18 h at reflux, the mixture was allowed to cool to ambient temperature, diluted with  $\text{Et}_2\text{O}$  (50 mL), and washed with brine (10 mL). The aq phase was extracted with  $\text{Et}_2\text{O}$  (2 x 10 mL) and the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a colorless oil. The crude product was purified by flash chromatography on  $\text{SiO}_2$  (15:1  $\rightarrow$  9:1 hexanes/EtOAc) to afford dioxolane **256** (381.4 mg, 1.83 mmol, 78% yield) as a colorless

oil.  $R_f = 0.49$  (7:3 hexanes/EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.76 (dddd,  $J = 17.1, 9.3, 7.6, 7.6$  Hz, 1H), 5.50, (br s, 1H), 5.02–4.99 (comp m, 4H), 3.98–3.84 (comp m, 2H), 2.36 (dddd,  $J = 10.3, 8.1, 5.9, 1.7$  Hz, 1H), 2.30 (dddd,  $J = 10.3, 8.1, 6.1, 1.7$  Hz, 1H), 2.09 (d,  $J = 7.3$  Hz, 2H), 1.82 (ddd,  $J = 12.9, 8.5, 6.1$  Hz, 1H), 1.62 (ddd,  $J = 12.7, 8.8, 5.9$  Hz, 1H), 1.48–1.47 (m, 3H), 1.03 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  142.9, 136.0, 135.7, 116.8, 107.4, 64.7, 64.7 (two lines), 48.4, 46.1, 36.8, 30.6, 26.5, 24.0; IR (Neat Film NaCl) 2951, 2888, 1454, 1372, 1192, 1108, 1043, 996, 946, 912, 858  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{12}\text{H}_{17}\text{O}_2$  [ $\text{M} - \text{CH}_3$ ] $^+$ : 193.1229; found 193.1232.



**Alcohol 236.** To a solution of acetal **235** (1.51 g, 6.03 mmol, 1.0 equiv) in 1,4-dioxane (45 mL) and purified  $\text{H}_2\text{O}$  (15 mL) was added 2,6-lutidine (1.29 g, 1.40 mL, 12.0 mmol, 2.0 equiv). The mixture was cooled to 0 °C and  $\text{NaIO}_4$  (5.13 g, 24.0 mmol, 4.0 equiv) was added followed by  $\text{OsO}_4$  (30.5 mg, 0.120 mmol, 0.02 equiv). The resulting suspension was stirred for 4.5 h at 0 °C and then vacuum filtered, rinsing with EtOAc (100 mL). The aq phase was separated and extracted with EtOAc (2 x 25 mL), the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to afford the desired product 1.82 g (>100%, contains some 2,6-lutidine) as a clear brown oil. This material was used in the subsequent step without purification.

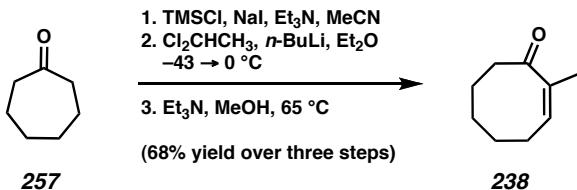
The crude product was dissolved in EtOH (7.5 mL) and cooled to -21 °C by use of a MeOH/ice bath. A solution of NaBH<sub>4</sub> (227.0 mg, 6.00 mmol, 1.0 equiv) dissolved in EtOH (7.5 mL) and precooled to 0 °C was added dropwise over 25 min to the reaction mixture via positive pressure cannulation. After an additional 1 h stirring at -21 °C, the reaction was quenched by slow addition of H<sub>2</sub>O (4.5 mL). The reaction mixture was allowed to warm to 0 °C, concentrated under reduced pressure to ca. 10 mL and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford a pale brown oil. The crude material was purified by flash chromatography on SiO<sub>2</sub> (19:1 → 9:1 → 4:1 hexanes/EtOAc) to afford alcohol **236** (1.18 g, 4.64 mmol, 77% yield over two steps) as a pale yellow oil.  $R_f$  = 0.38 (7:3 hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.57 (app t, *J* = 1.7 Hz, 1H), 3.71 (ddd, *J* = 7.3, 7.3, 5.4 Hz, 2H), 3.52 (app t, *J* = 11.0 Hz, 2H), 3.34 (11.0 Hz, 2H), 2.38–2.26 (comp m, 2H), 1.88 (ddd, *J* = 12.9, 8.5, 6.1 Hz, 1H), 1.71 (t, *J* = 7.3 Hz, 2H), 1.69 (ddd, *J* = 12.9, 8.5, 5.9 Hz, 1H), 1.42 (s, 3H), 1.21 (t, *J* = 5.1 Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H). 0.71 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 141.1, 138.1, 98.6, 71.7, 60.2, 47.5, 44.1, 36.9, 31.1, 29.7, 27.4, 27.1, 22.7, 22.2; IR (Neat Film NaCl) 3428 (br), 3041, 2951, 2868, 1472, 1456, 1396, 1370, 1353, 1321, 1259, 1242, 1181, 1117, 1082, 1040, 1015, 950, 911, 862, 809, 793 cm<sup>-1</sup>; HRMS (FAB+) *m/z* calc'd for C<sub>15</sub>H<sub>27</sub>O<sub>3</sub> [M + H]<sup>+</sup>: 255.1960; found 255.1951; [α]<sub>D</sub><sup>19.9</sup> -3.25° (*c* 0.99, CHCl<sub>3</sub>, 88% ee).



**Iodide 237.** A 25 mL flask was charged with PPh<sub>3</sub> (881.3 mg, 3.36 mmol, 1.5 equiv) and imidazole (457.5 mg, 6.72 mmol, 3.0 equiv) and the flask was evacuated and backfilled with Ar (3x). The solids were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL, typically solvated within 10 min). The flask was wrapped in aluminum foil and I<sub>2</sub> (869.6 mg, 3.36 mmol, 1.5 equiv) was added. After 10 min, the mixture was cooled to 0 °C and a solution of alcohol **236** (571.2 mg, 2.24 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added via syringe. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to 23 °C. After an additional 3 h stirring, hexanes (11 mL) was added and the resulting slurry was filtered through a plug of Celite (5 x 1 cm) eluting with hexanes/Et<sub>2</sub>O (1:1, 100 mL). The filtrate was concentrated under reduced pressure, resuspended in hexanes (50 mL), filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on SiO<sub>2</sub> (1:0 → 99:1 → 98:2 → 90:10 hexanes/Et<sub>2</sub>O, dry-loaded on Celite) to afford iodide **237** (753 mg, 2.07 mmol, 92% yield) as a colorless oil. *R*<sub>f</sub> = 0.71 (7:3 hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.51 (s, 1H), 3.50 (app t, 11.5 Hz, 2H), 3.34 (d, *J* = 11.2 Hz, 2H), 3.19–3.06 (comp m, 2H), 2.38–2.25 (comp m, 2H), 2.12–2.02 (comp m, 2H), 1.84 (ddd, *J* = 13.2, 8.8, 5.9 Hz, 1H), 1.67 (ddd, *J* = 13.2, 8.8, 5.6 Hz, 1H), 1.41 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 0.71 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 142.5, 136.6, 98.6, 71.9, 71.9 (two lines), 51.2, 46.8, 36.1, 31.4, 29.8, 27.5, 26.4, 22.8, 22.3, 1.1; IR (Neat Film NaCl) 3039, 2956, 2863, 1470, 1450, 1390, 1365, 1315, 1254,

1173, 1119, 1083, 1039, 1011, 944, 915, 866, 814  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $\text{C}_{15}\text{H}_{26}\text{O}_2\text{I} [\text{M} + \text{H}]^+$ : 365.0978; found 365.0980;  $[\alpha]_D^{20,3} +31.2^\circ$  ( $c$  1.03,  $\text{CHCl}_3$ , 88% ee).

### 3.7.2.5 MODEL FRAGMENT COUPLING AND C-RING ANNULATION



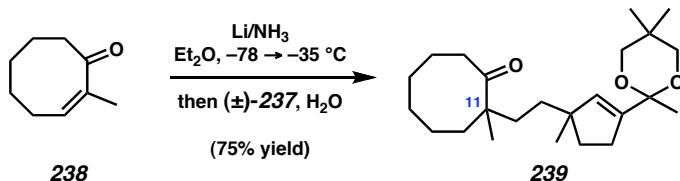
**2-Methyl cyclooctenone (238).** A 500 mL round-bottom flask was charged with  $\text{NaI}$  (18.74 g, 125 mmol, 1.25 equiv),  $\text{MeCN}$  (140 mL) was added, and the system was evacuated and backfilled with Ar. Cycloheptanone (257) (11.2 g, 11.8 mL, 100 mmol, 1.0 equiv) was added followed by  $\text{Et}_3\text{N}$  (16.7 g, 17.4 mL, 125 mmol, 1.25 equiv) and dropwise addition of  $\text{TMSCl}$  (12.4 g, 14.6 mL, 114 mmol, 1.14 equiv). The resulting suspension was stirred at 23 °C for 30 min and then petroleum ether (100 mL) was added. The biphasic system was stirred vigorously for 10 min, the petroleum ether layer was decanted, and the  $\text{MeCN}$  layer was extracted with petroleum ether (3 x 50 mL). The combined petroleum ether layers were washed with  $\text{H}_2\text{O}$  (2 x 50 mL), brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude oil was purified by short path distillation (8.7 torr, bp = 75–81 °C) to afford the desired silyl enol ether (18.4 g, 99.8 mmol, 99.8% yield) as a colorless oil.

A solution of the above silyl enol ether (8.20 g, 44.5 mmol) in  $\text{Et}_2\text{O}$  (22.8 mL) and 1,1-dichloroethane (17.8 g, 15.1 mL, 180 mmol, 4.0 equiv) in a 250 mL round-bottom flask was cooled to –40 °C by use of a  $\text{MeCN}/\text{CO}_{2(s)}$  bath. To this was added  $n\text{-BuLi}$

(58.7 mL, 135 mmol, 2.3 M in hexanes, 3.0 equiv) in a dropwise manner over 3 h by use of a syringe pump. The resulting mixture was stirred for an additional 1 h at  $-40\text{ }^{\circ}\text{C}$ , at which time the reaction was warmed to  $0\text{ }^{\circ}\text{C}$  for 2 h, quenched with  $\text{H}_2\text{O}$  (20 mL) and allowed to warm to ambient temperature. The phases were separated and the organic phase was washed with  $\text{H}_2\text{O}$  (4 x 20 mL) until the aqueous phase showed neutral pH. The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to afford the desired cyclopropane (11.1 g, 45.0 mmol, quantitative) as a clear, pale yellow oil. This material was used in the following reaction without further purification.

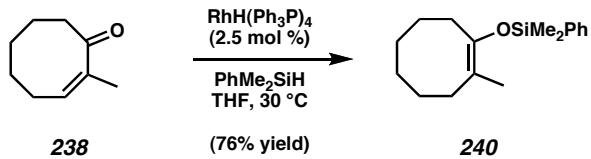
To a solution of the above cyclopropane (11.1 g, 45.0 mmol, 1.0 equiv) in  $\text{MeOH}$  (136 mL) was added  $\text{Et}_3\text{N}$  (41.0 g, 56 mL, 405 mmol, 9.0 equiv). The flask was fitted with a condenser and the mixture was immersed into a  $85\text{ }^{\circ}\text{C}$  oil bath and heated to reflux. After 65 h, the mixture was allowed to cool to ambient temperature and concentrated carefully under reduced pressure (the compound is somewhat volatile). The residue was suspended in pentane (50 mL), filtered, and concentrated under reduced pressure. The final traces of  $\text{Et}_3\text{N}$  were removed by dissolving the residue in  $\text{Et}_2\text{O}$  (100 mL) and washing with  $\text{KHSO}_4$  (20 mL, 1.0 M). The organic phase was dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on  $\text{SiO}_2$  (1:0  $\rightarrow$  19:1 hexanes/ $\text{Et}_2\text{O}$ ) to 2-methyl cyclooctenone (**239**) (4.21 g, 30.5 mmol, 68% yield over three steps) as a colorless oil.  $R_f$  = 0.43 (4:1 hexanes/ $\text{Et}_2\text{O}$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.09 (app tq,  $J$  = 6.9, 1.5 Hz, 1H), 2.65–2.61 (comp m, 2H), 2.42–2.35 (comp m, 2H), 1.86–1.77 (comp m, 3H), 1.84 (q,  $J$  = 1.4 Hz, 2H), 1.64–1.49 (comp m, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  208.9,

137.5, 135.0, 42.9, 28.6, 25.9, 23.3, 22.8, 21.1; IR (Neat Film NaCl) 2928, 1685, 1654, 1452, 1377, 1099, 850  $\text{cm}^{-1}$ ; HRMS (MM: ESI/APCI)  $m/z$  calc'd for  $\text{C}_9\text{H}_{15}\text{O}$  [M + H]<sup>+</sup>: 139.1117, found 139.1114.

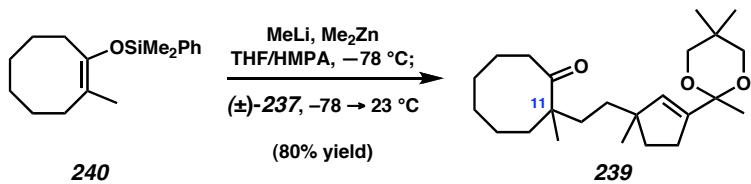


**Ketone 239.** Ammonia (ca. 5 mL) was condensed into a 2-neck round-bottom flask fitted with a septum, an argon inlet, and a glass-coated stir bar at  $-78^\circ\text{C}$ , and to this was added lithium wire (9.3 mg, 1.3 mmol, 3.0 equiv). The solution turned dark blue. The mixture was stirred for 20 min, at which point a solution of 2-methyl cyclooctenone (**238**, 60.2 mg, 0.436 mmol, 1.0 equiv) in a 0.21 M  $\text{H}_2\text{O}$  solution in  $\text{Et}_2\text{O}$  (2 mL, prepared by dissolving  $\text{H}_2\text{O}$  (94  $\mu\text{L}$ ) in  $\text{Et}_2\text{O}$  (25 mL) in a flame-dried round-bottom flask under argon) was added via cannula transfer. The vial was further washed and transferred with a portion of anhydrous  $\text{Et}_2\text{O}$  (1 mL). The bright blue color remained after addition and the solution was stirred for 10 min, at which point a solution of iodide  $(\pm)\text{-237}$  (324 mg, 0.980 mmol, 2.0 equiv) in  $\text{Et}_2\text{O}$  (2 mL) was added dropwise via cannula. During the addition of iodide  $(\pm)\text{-237}$ , the color of the solution changed from blue to colorless and stirring was continued in the acetone/ $\text{CO}_{2(s)}$  bath. After 2 h, the cooling bath was replaced with a  $\text{MeCN}/\text{CO}_{2(s)}$  cooling bath held between  $-45$  and  $-35^\circ\text{C}$ . The mixture was stirred for an additional 2 h, at which point solid  $\text{NH}_4\text{Cl}$  (523 mg) was added, the cooling bath was removed, and the reaction was allowed to reach room temperature. After most of the ammonia had evaporated, the reaction was diluted with  $\text{H}_2\text{O}$  (10 mL)

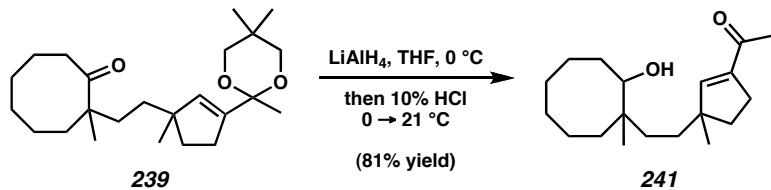
and Et<sub>2</sub>O (25 mL). The aqueous layer was extracted with Et<sub>2</sub>O (5 x 15 mL) and the combined organics were washed with brine (10 mL), dried with MgSO<sub>4</sub>, filtered, and concentrated. The crude residue was purified by flash chromatography on SiO<sub>2</sub> (95:5 hexanes/EtOAc) to afford desired ketone **239** (122.9 mg, 0.326 mmol, 75% yield) as 1:1.2 mixture of diastereomers.  $R_f$  = 0.70 (3:7 hexanes/Et<sub>2</sub>O); <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  **major diastereomer:** 5.58 (app t,  $J$  = 1.7 Hz, 1H), 3.55 (d,  $J$  = 11.0 Hz, 1H), 3.48 (d,  $J$  = 11.0 Hz, 1H), 3.31 (d,  $J$  = 11.0 Hz, 2H), 2.40–2.36 (comp m, 3H), 2.03 (ddd,  $J$  = 10.7, 7.1, 3.4 Hz, 1H), 1.81–1.69 (comp m, 3H), 1.62 (s, 3H), 1.60–1.50 (comp m, 3H), 1.42–1.22 (comp m, 8H), 1.19 (s, 3H), 1.18–1.10 (comp m, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.53 (s, 3H); **minor diastereomer:** 5.56 (app t,  $J$  = 1.7 Hz, 1H), 3.52 (d,  $J$  = 11.0 Hz, 1H), 3.48 (d,  $J$  = 10.7 Hz, 1H), 3.30 (d,  $J$  = 11.0 Hz, 2H), 2.40–2.36 (comp m, 3H), 2.02 (ddd,  $J$  = 10.7, 7.1, 3.4 Hz, 1H), 1.81–1.69 (comp m, 3H), 1.62 (s, 3H), 1.62 (s, 3H), 1.60–1.50 (comp m, 3H), 1.42–1.22 (comp m, 8H), 1.19 (s, 3H), 1.18–1.10 (comp m, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.52 (s, 3H); <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  **mixture of two diastereomers:** 218.1 (two lines), 142.4 (two lines), 137.9, 137.8, 98.9 (two lines), 71.9, 71.8 (three lines), 49.8 (two lines), 48.7 (two lines), 36.9, 36.8, 36.5 (two lines), 35.9, 35.8, 34.6, 34.5, 34.2, 34.1, 31.9 (two lines), 30.4 (two lines), 29.7, 28.1, 28.0, 27.2, 27.1, 26.2, (two lines), 25.3 (two lines), 24.5, 22.9, 22.2, 22.1, 19.2, 19.1; IR (Neat Film NaCl) 2932, 2858, 1698, 1469, 1448, 1396, 1368, 1254, 1239, 1180, 1117, 1083, 1040, 950, 911, 863, 810, 793 cm<sup>-1</sup>; HRMS (FAB+) *m/z* calc'd for C<sub>24</sub>H<sub>41</sub>O<sub>3</sub> [M + H]<sup>+</sup>: 377.3056; found 377.3043.



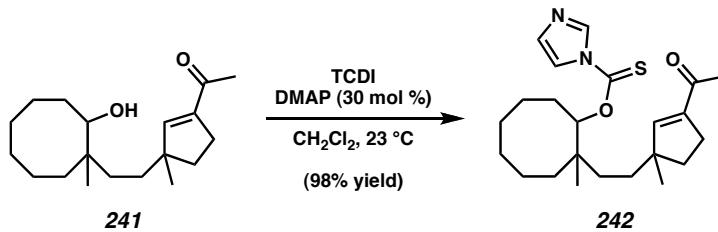
**Silyl enol ether 240.** Enone **238** (100 mg, 0.724 mmol, 1.0 equiv) was placed in a 1-dram vial, evacuated and backfilled with N<sub>2</sub> (3x), and solvated in THF (350 μL). A separate flask containing RhH(PPh<sub>3</sub>)<sub>4</sub> (20.9 mg, 0.0181 mmol, 0.025 equiv) was evacuated and backfilled with N<sub>2</sub> (3 cycles with 5 min evacuation per cycle) and then THF (1.1 mL) was added. A separate vial containing an excess of PhMe<sub>2</sub>SiH was degassed by evacuation/backfilling with N<sub>2</sub> (3x). The required amount of PhMe<sub>2</sub>SiH (631 mg, 720 μL, 4.63 mmol, 6.4 equiv) was added to the catalyst suspension via syringe and the resulting clear orange solution was immersed in a 30 °C oil bath. After 10 min, the THF solution of enone **238** was added via positive pressure cannulation. After 25 h the reaction was allowed to cool to ambient temperature, filtered through a plug of SiO<sub>2</sub> (2 x 1 cm, Et<sub>2</sub>O) and concentrated under reduced pressure to afford a pale orange oil. The crude material was purified by flash chromatography on SiO<sub>2</sub> (99:1 → 98:2 hexanes/PhH) to afford silyl enol ether **240** (150.2 mg, 0.547 mmol, 76% yield) as a colorless oil.  $R_f$  = 0.52 (hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.65–7.61 (comp m, 2H), 7.42–7.34 (comp m, 3H), 2.18–2.14 (comp m, 2H), 2.06–2.02 (comp m, 2H), 1.59 (s, 3H), 1.55–1.38 (comp m, 8H), 0.44 (s, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 145.1, 138.7, 133.5, 129.6, 127.9, 113.9, 31.9, 31.6, 29.0, 28.7, 26.8, 26.5, 16.1, –0.4; IR (Neat Film NaCl) 3075, 2951, 2863, 1638, 1468, 1450, 1393, 1370, 1254, 1241, 1179, 1117, 1080, 1037, 1011, 995, 949, 910, 861, 809 cm<sup>–1</sup>; HRMS (FAB+) *m/z* calc'd for C<sub>17</sub>H<sub>26</sub>OSi [M]<sup>+</sup>: 274.1753; found 274.1752.



**Ketone 239.** Silyl enol ether **240** (39.7 mg, 0.145 mmol, 1.0 equiv) was placed in a 10 mL round-bottom flask, the flask was evacuated and backfilled with N<sub>2</sub> (3x), solvated in THF (1.45 mL, 0.1 M) and cooled to 0 °C. To this solution was added MeLi (57 µL, 0.152 mmol, 2.66 M in dimethoxymethane, 1.05 equiv) was added dropwise over 5 min. After an additional 1 h stirring at 0 °C, HMPA (260 mg, 252 µL, 1.45 mmol) was added in a dropwise manner over 5 min, at which point the reaction was cooled in a dry ice/acetone bath to -78 °C. The resulting clear solution mixture was stirred for 10 min followed by dropwise addition of Me<sub>2</sub>Zn (145 µL, 0.145 mmol, 1.0 M in heptane, 1.0 equiv). After an additional 10 min, a solution of iodide (±)-**237** (63.4 mg, 0.0174 mmol) in THF (200 µL) was added dropwise over 2 min. After 1 h at -78 °C, the reaction was allowed to gradually warm to ambient temperature. After a further 21 h at 23 °C, the reaction mixture was diluted with Et<sub>2</sub>O and washed with H<sub>2</sub>O (10 mL). The aqueous phase was extracted with Et<sub>2</sub>O (2 x 10 mL) and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography on SiO<sub>2</sub> (99:1 → 98:2 → 95:5 → 90:10 hexanes/Et<sub>2</sub>O) to afford ketone **239** (43.9 mg, 0.117 mmol, 80% yield) as a 1:1.25 mixture of diastereomers.

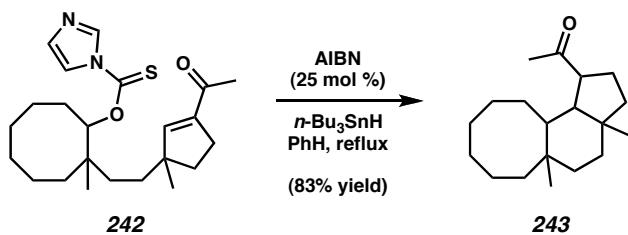


lines), 26.8, 26.6 (two lines), 26.0, 25.8, 25.6 (two lines), 25.5, 25.4, 23.7, 22.7, 22.2 (two lines), 19.3; IR (Neat Film NaCl) 3468, 3039, 2925, 2853, 1667, 1618, 1468, 1447, 1377, 1365, 1305, 1269, 1204, 1044, 964, 944, 871  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{19}\text{H}_{32}\text{O}_2$  [M] $^+$ : 292.2402; found 292.2401.



**Imidazoyl thiocarbonate 242.** To a solution of ketoalcohol **241** (66.0 mg, 0.226 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (4.7 mL) was added DMAP (8.28 mg, 0.068 mmol, 0.3 equiv) and 1,1'-thiocarbonyldiimidazole (TCDI) (201.4 mg, 1.13 mmol, 5.0 equiv). The resulting yellow solution was stirred at 23 °C. After 29 h, the reaction mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography on  $\text{SiO}_2$  (9:1 → 4:1 hexanes/EtOAc) to afford imidazoyl thiocarbonate **242** (89.2 mg, 0.222 mmol, 98% yield) as a viscous colorless oil.  $R_f$  = 0.19 (7:3 hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  **major set of diastereomers:** 8.32 (s, 1H), 8.30 (s, 1H), 7.60 (s, 2H), 7.03 (s, 2H), 6.37 (s, 1H), 6.34 (s, 1H), 5.65 (app d,  $J$  = 8.5 Hz, 2H), 2.63–2.53 (comp m, 2H), 2.53–2.42 (comp m, 2H), 2.23 (s, 3H), 2.21 (s, 3H), 2.09–2.03 (comp m, 2H), 1.84–1.22 (comp m, 34 H), 1.03 (s, 6H), 1.02 (two lines, s, 3H each); **minor set of diastereomers:** 8.30 (s, 1H), 8.29 (s, 1 H), 7.59 (s, 1H), 7.55 (s, 1H), 7.03 (s, 2H), 6.45 (s, 1H), 6.44 (s, 1H), 5.77 (app d,  $J$  = 9.3 Hz, 2H), 2.63–2.53 (comp m, 2H), 2.53–2.42 (comp m, 2H), 2.31 (two lines, s, 3H each), 2.09–2.03 (comp m, 2H), 1.84–1.22 (comp m, 34 H), 1.13 (two lines, s, 3H each), 0.95 (s, 3H), 0.94 (s, 3H each).

3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  mixture of four diastereomers: 197.5, 197.4 (two lines), 184.1, 152.0, 151.9 (two lines), 151.8, 143.8, 143.7, 143.6 (two lines), 136.8, 136.7, 130.9 (two lines), 118.0, 117.9, 117.8, 91.7, 91.6, 91.3, 91.2 50.0, 49.9, 49.7 (two lines), 40.2 (two lines), 39.9 (two lines), 36.3, 36.1 (two lines), 36.0, 35.2, 34.8, 34.7, 34.6, 34.5, 34.4, 32.5, 32.4, 32.3, 31.3, 30.5 (two lines), 29.9, 29.8, 29.7, 29.6, 28.7, 28.6, 27.6, 27.4 (two lines), 26.8 (two lines), 26.7, 26.4, 26.2, 25.7, 25.6, 25.3 (two lines), 25.1 (two lines), 23.3 (two lines), 22.6 (two lines), 22.1 (two lines), 21.5, 21.4; IR (Neat Film NaCl) 3158, 3121, 2930, 2853, 1664, 1618, 1530, 1460, 1383, 1328, 1282, 1228, 1099, 1037, 1013, 967, 889, 871, 830, 734  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_2\text{S} [\text{M}]^+$ : 402.2341; found 402.2354.



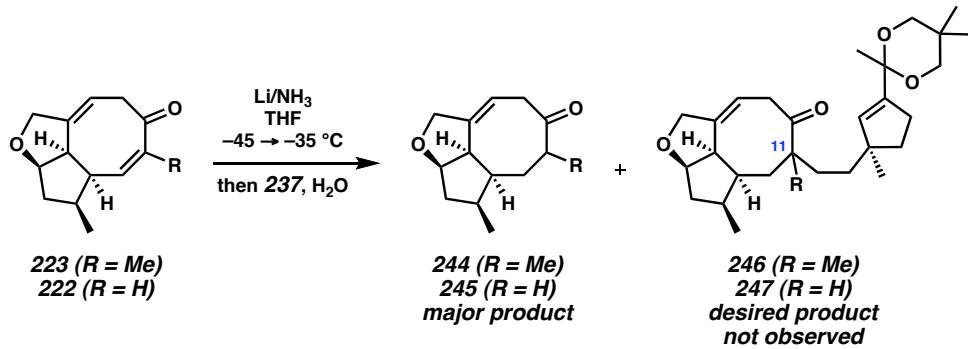
**Ketone 243.** Imidazoyl thiocarbonate **242** (41.2 mg, 0.102 mmol, 1.0 equiv) was placed in a 50 mL round-bottom 2-neck flask fitted with a condenser, solvated in PhH (18.4 mL), and the solution was sparged with  $\text{N}_2$  for 1 h. The reaction mixture was immersed into an 85  $^{\circ}\text{C}$  oil bath and heated to reflux. A separate flask was charged with AIBN (4.19 mg, 0.026 mmol, 0.25 equiv), evacuated and backfilled with  $\text{N}_2$  (3x), and PhH (2.0 mL, sparged with  $\text{N}_2$  for 1 h prior to use) was added followed by  $n\text{-Bu}_3\text{SnH}$  (59.4 mg, 54  $\mu\text{L}$ , 0.204 mmol, 2.0 equiv). The solution of AIBN/ $n\text{-Bu}_3\text{SnH}$  was added dropwise to substrate **242** over 5 h via syringe pump. The reaction was stirred for an additional 12 h at reflux, allowed to cool to ambient temperature, and concentrated under

reduced pressure to afford a pale yellow oil. The crude oil was purified by flash chromatography on  $\text{SiO}_2$  impregnated with  $\text{AgNO}_3$  (hexanes eluent) to afford a mixture of diastereomers of the desired ketone **243** (23.4 mg, 0.0846 mmol, 83% yield) as a colorless oil. Samples of sufficient purity for characterization were obtained by flash chromatography (1:0  $\rightarrow$  99:1  $\rightarrow$  98:1 hexanes/ $\text{Et}_2\text{O}$ ) and subsequent preparative TLC on  $\text{SiO}_2$  (20 x 20 cm, PhMe, developed thrice) of the fractions containing mainly the desired set of diastereomers.

**Major diastereomer.**  $R_f$  = 0.52 (4:1 hexanes/ $\text{Et}_2\text{O}$ );  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  3.27 (ddd,  $J$  = 10.8, 7.3, 7.3 Hz, 1H), 2.38 (app dt,  $J$  = 7.0, 1.2 Hz, 1H), 2.27–2.22 (m, 1H), 2.20 (s, 3H), 1.78–1.74 (m, 2H), 1.67–1.10 (comp m, 12H), 0.98 (s, 3H), 0.96 (s, 3H), 0.89–0.81 (comp m, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  210.3, 56.9, 49.5, 42.7, 42.0, 37.9, 36.4, 34.6, 31.7, 31.6, 31.5, 30.9, 30.4, 26.8, 26.0, 25.6, 23.3, 23.0, 22.4; IR (Neat Film NaCl) 2920, 2853, 1708, 1460, 1377, 1199, 1179  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{19}\text{H}_{32}\text{O}$  [M] $^+$ : 276.2453; found 276.2450.

**Minor set of diastereomers.**  $R_f$  = 0.58 (4:1 hexanes/ $\text{Et}_2\text{O}$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.90 (ddd,  $J$  = 10.0, 8.3, 5.6 Hz, 1H), 2.71–2.64 (m, 1H), 2.35 (app t,  $J$  = 7.3 Hz, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 2.07–1.85 (comp m, 4H), 1.76–1.06 (comp m, 33H), 1.04 (s, 3H), 1.03 (s, 3H), 1.00–0.82 (comp m, 6H), 0.77 (s, 3H), 0.76 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  211.5, 211.2, 58.8, 55.9, 44.6, 44.5, 41.3, 40.9 (two lines), 39.6, 36.4, 35.2, 34.6, 34.0, 33.1, 32.1, 32.0, 30.7, 29.9 (two lines), 29.5, 29.4, 29.2, 29.0, 28.8, 28.7, 27.9, 27.2, 26.4, 26.2, 25.8, 25.4, 24.6, 24.5, 24.3, 22.8, 22.1, 19.8; IR (Neat Film NaCl) 2919, 2848, 1737, 1711, 1460, 1383, 1352, 1261, 1173  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $\text{C}_{19}\text{H}_{32}\text{O}$  [M] $^+$ : 276.2453; found 276.2441.

### 3.7.2.6 ASYMMETRIC AB RING AND D-RING FRAGMENT COUPLING



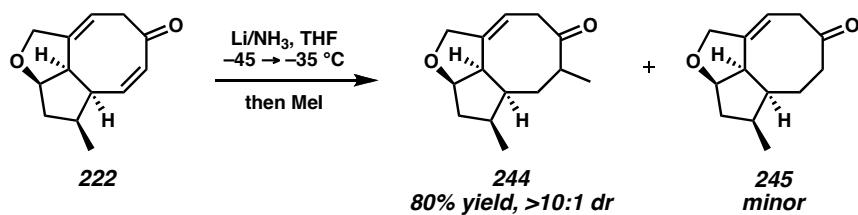
#### Attempted reductive alkylation of the asymmetric AB and D-ring systems.

Reductive alkylations of cyclooctadienones **223** and **222** were attempted using the Li/NH<sub>3</sub> conditions with a large excess of iodide **237** described above to afford the enolate protonation product ketones **244** and **245**, respectively, as the only products.

**α**-Methyl cyclooctanone **244**. <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 4.84–4.80 (m, 1H), 4.42–4.39 (m, 1H), 4.25 (dm, *J* = 12.5 Hz, 1H), 4.08 (dm, *J* = 12.5 Hz, 1H), 3.07 (dm, *J* = 16.5 Hz, 1H), 2.98 (br m, 1H), 2.61–2.54 (m, 1H), 2.39–2.32 (m, 1H), 1.79–1.76 (m, 3H), 1.66–1.58 (m, 1H), 1.44–1.38 (m, 1H), 1.15 (dm, *J* = 14.0 Hz, 1H), 0.88 (d, *J* = 7.5 Hz, 3H), 0.86 (d, *J* = 3H).

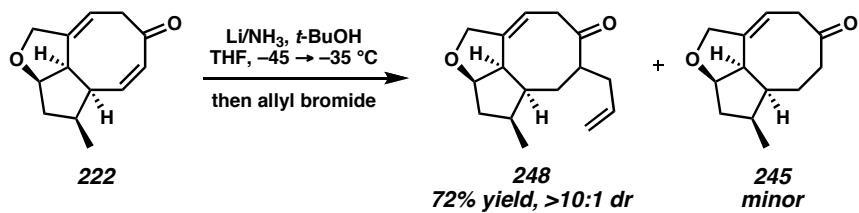
**Cyclooctanone 245.** *R*<sub>f</sub> = 0.28 (3:1 hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.39–5.35 (m, 1H), 4.64 (ddd, *J* = 6.5, 3.1, 3.1 Hz, 1H), 4.43 (d pentets, *J* = 12.6, 1.9 Hz, 1H), 4.27–4.22 (m, 1H), 3.47–3.41 (m, 1H), 3.16–3.14 (m, 1H), 2.98–2.92 (m, 1H), 2.72 (ddd, *J* = 13.6, 5.3, 2.7 Hz, 1H), 2.38–2.32 (m, 1H), 2.20–2.04 (comp m, 3H), 1.83–1.78 (m, 1H), 1.77–1.75 (comp m, 2H), 0.91 (d, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

$\delta$  213.8, 143.3, 112.6, 88.5, 73.3, 48.9, 47.4, 46.0, 44.6, 40.4, 38.1, 24.1, 16.5; IR (Neat Film NaCl) 2952, 2918, 1707, 1432, 1246, 1145, 1074  $\text{cm}^{-1}$ ; HRMS (MM: ESI/APCI)  $m/z$  calc'd for  $\text{C}_{13}\text{H}_{17}\text{O}_2$  [M – H] $^+$ : 205.1234, found 205.1225;  $[\alpha]_D^{25} -4.35^\circ$  ( $c$  0.953,  $\text{CHCl}_3$ , 98% ee).



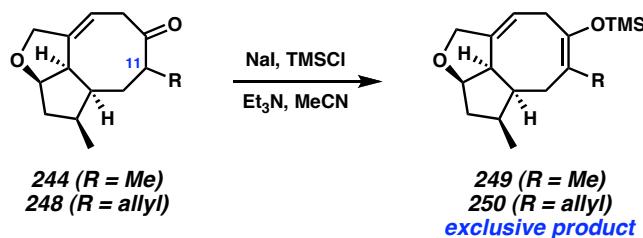
**$\alpha$ -Methyl cyclooctanone 244.** Ammonia (ca. 5 mL) was condensed into a 2-neck round-bottom flask fitted with a septum, an argon inlet, and a glass-coated stir bar cooled to  $-78^\circ\text{C}$ , and to this was added lithium wire (3.3 mg, 0.5 mmol, 11 equiv). The solution turned dark blue. The cooling bath was replaced with a  $\text{MeCN}/\text{CO}_{2(s)}$  bath held between  $-45$  and  $-35^\circ\text{C}$ . The mixture was stirred for 20 minutes, at which point cyclooctadienone **22** (9.3 mg, 0.045 mmol, 1.0 equiv) in  $\text{THF}$  (1 mL) was added dropwise via cannula transfer. The vial was further washed and transferred with a portion of anhydrous  $\text{THF}$  (1 mL). The bright blue color remained after addition. As quickly as possible,  $\text{MeI}$  (100  $\mu\text{L}$ , 1.61 mmol, 35 equiv) was added to the stirred solution by syringe, and the reaction color changed from blue to clear. After 1 h, solid  $\text{NH}_4\text{Cl}$  (100 mg) was added to the reaction, the cooling bath was removed, and the reaction was allowed to reach room temperature. After most of the ammonia had evaporated, the reaction was diluted with  $\text{H}_2\text{O}$  (10 mL) and  $\text{Et}_2\text{O}$  (25 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (5 x 15 mL) and the combined organics were washed with brine (2 x 10 mL), dried with  $\text{MgSO}_4$ , filtered and concentrated. The crude residue was purified by

flash chromatography on  $\text{SiO}_2$  (2 x 10 cm, 25:1  $\rightarrow$  10:1 hexanes/EtOAc) to afford  $\alpha$ -methyl cyclooctanone **244** (8.0 mg, 36  $\mu\text{mol}$ , 80% yield) as a single major diastereomer with a minor amount of cyclooctanone **245**.



**$\alpha$ -Allyl cyclooctenone 248.** Ammonia (ca. 7 mL) was condensed into a 2-neck round-bottom flask fitted with a septum, an argon inlet, and a glass-coated stir bar cooled to  $-78$   $^\circ\text{C}$ , and to this was added lithium wire (5.6 mg, 0.81 mmol, 45 equiv). The solution turned dark blue. The cooling bath was replaced with a MeCN/CO<sub>2(s)</sub> bath held between  $-40$  and  $-35$   $^\circ\text{C}$ . The mixture was stirred for 20 minutes, at which point cyclooctadienone **222** (3.7 mg, 0.018 mmol, 1.0 equiv) dissolved in a 0.009 M *t*-BuOH solution in THF (2 mL, prepared by dissolving *t*-BuOH (21.5  $\mu\text{L}$ ) in THF (25 mL) in a flamed dried round-bottom flask under argon) was transferred dropwise via cannula. The bright blue color remained after addition and the solution was stirred for 30 s, after which allyl bromide (200  $\mu\text{L}$ , 2.31 mmol, 128 equiv) was added by syringe. Stirring was continued for 30 min after which the cold bath was removed, NH<sub>4</sub>Cl (420 mg) was added in a single portion and the reaction was allowed to reach room temperature. The reaction was diluted with H<sub>2</sub>O (5 mL) and extracted with Et<sub>2</sub>O (5 x 20 mL). The combined organics were washed with H<sub>2</sub>O (5 mL) then brine (5 mL), dried with MgSO<sub>4</sub>, and concentrated in vacuo. The crude residue was purified by flash chromatography on  $\text{SiO}_2$  (15:1  $\rightarrow$  4:1 hexanes/EtOAc) to afford  $\alpha$ -allyl cyclooctanone **248** (3.2 mg, 13  $\mu\text{mol}$ , 72%

yield) as a single major diastereomer with a minor amount of cyclooctanone **245**.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.66–5.58 (m, 1H), 5.31–5.29 (m, 1H), 5.01–4.96 (m, 2H), 4.58–4.56 (m, 1H), 4.36 (d m,  $J$  = 11 Hz, 1H), 4.17 (m,  $J$  = 11 Hz, 1H), 3.44 (d m,  $J$  = 15.5 Hz, 1H), 3.07 (br m, 1H), 2.76–2.70 (m, 1H), 2.52–2.38 (m, 1H), 2.28–2.23 (m, 2H), 2.08–1.97 (m, 2H) 1.87–1.79 (m, 2H), 1.70–1.64 (m, 2H), 0.82 (d,  $J$  = 7.5 Hz, 3H).



**Representative procedure for the soft enolization to silyl enol ethers **249** and **250**.**

To a solution of sodium iodide (1.2 mg, 0.008 mmol, 2 equiv) and  $\alpha$ -allyl cyclooctanone **248** (1.0 mg, 0.004 mmol, 1 equiv) in MeCN (0.5 mL) was added  $\text{Et}_3\text{N}$  (162  $\mu\text{L}$  of a 0.05 M solution in MeCN, 0.008 mmol, 2 equiv) followed by TMSCl (121  $\mu\text{L}$  of a 0.05 M solution in MeCN, 0.006 mmol, 1.5 equiv). After 1.5 h the solution was diluted with pentane (1 mL) and stirred for several minutes. The pentane was removed by pipette and the acetonitrile was further extracted with pentane (4 x 1 mL). The combined pentane extracts were dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to afford crude silyl enol ether **250** (2.0 mg) as a single isomer by  $^1\text{H}$  NMR analysis. This compound was used directly in subsequent reactions.  $R_f = \text{unstable to SiO}_2$ .

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(12) The preparation of tricarbonyliron-cyclobutadiene ether complexes of allylic alcohols is typically accomplished with bromide **258** (see ref. 11e). In our hands, this procedure was variable and furnished only modest yields of ether **188**.

CC1=CC(O)C=C1.[Fe(CO)3]CBr>>CC1=CC(O[Fe(CO)3])C=C1

(41–69% yield)

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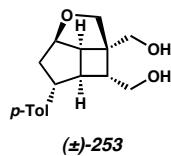
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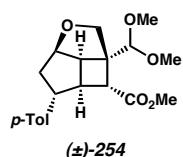
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(18) We also investigated the group-selective differentiation of diol **253** without success.



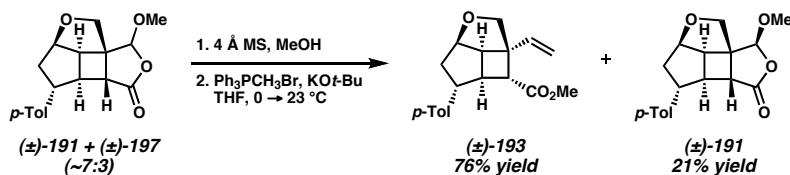
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(20) The Lewis acids  $\text{La}(\text{OTf})_3$  or  $\text{Sm}(\text{OTf})_3$  effect the conversion of acetal **191** to dimethyl acetal **254** as the sole product.



(21) Our equilibration results suggest that the formation of acetal **191** is the kinetic product of the unsymmetrical ozonolysis, and is apparently due to the proximity of substituents attached to the cyclobutane ring.

(22) The recycling of acetals **191** and **197** via this equilibration/olefination sequence provides olefin **193** and recovered acetal **191** in excellent yield over two steps.



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(28) Alcohol isomer **210** is not reactive under these Mitsunobu conditions.

(29) TLC analysis of the reaction progress indicated cycloadduct **213** as the major product, however, we are thus far unable to obtain isolated yields due to the volatility of this compound and its challenging isolation from a large volume of acetone.

(30) The reactivity differences observed for this substrate (**212**) and the model system (**188**) underline the difference in the C(3) stereochemistry and its impact on the cycloaddition.

(31) The reaction yield for the two steps post cycloaddition/ozonolysis is excellent (94%), indicating the low overall yield for the four steps is the result of either problematic cycloaddition or ozonolysis procedures. The difficulties we have encountered with the volatility and purification of cycloadduct **213** are suggestive of the major limitation of this reaction sequence.

(32) The absolute stereochemistry of acetal **215** could not be determined from the X-ray diffraction data. See Appendix 3 for details.

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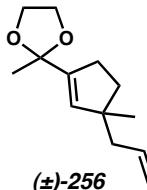
(48) The remarkable stability of  $\beta$ -hydroxyketone **231** is likely the result of transannular interactions or some other form of ring strain. This is comparable to the observation that cycloheptane-1,3-dione (**227**) exists exclusively in the diketo-

form in solution, and contrasts with propensity for six-membered analogue cyclohexane-1,3-dione to be completely enolized in solution. See ref 45b.

- (49) Preliminary investigations employing sodium methoxide/methanol conditions produced minor quantities of conjugate addition adducts of cycloheptenone **180**.
- (50) A number of intermediates are possible for the proposed retro-aldol/aldol sequence, such as ketoaldehyde **226** and several diastereomeric aldol addition adducts.  $^1\text{H}$  NMR analysis of crude reaction filtrates exhibit a characteristic aldehyde peak, along with numerous other compounds. Addition of TFE to reactions containing these compounds facilitated the conversion to the desired acylcyclopentene **225**, further supporting their role as intermediates in the transformation.
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**(±)-256**

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