CHAPTER 2[†]

Enantioselective Total Synthesis of

Cyanthiwigin Diterpenoids

2.1 INTRODUCTION

The following sections describe the structure, biological activity, and synthetic challenges associated with the cyanthiwigin family of cyathane diterpenoid molecules. This section additionally details the retrosynthetic analysis of cyanthiwigins B, F, and G.

2.1.1 STRUCTURE AND SYNTHETIC CHALLENGES

The cyanthiwigin diterpenoid natural products were originally isolated from the marine sponge *Epipolasis reiswigi*.[1] Ten years later, additional, novel cyanthiwigin molecules were found in extracts of the Jamaican sea sponge *Mermekioderma styx*.[2] To date, over 30 different examples of cyanthiwigin diterpenoids have been isolated and characterized from these two sources. The vast majority of these compounds are

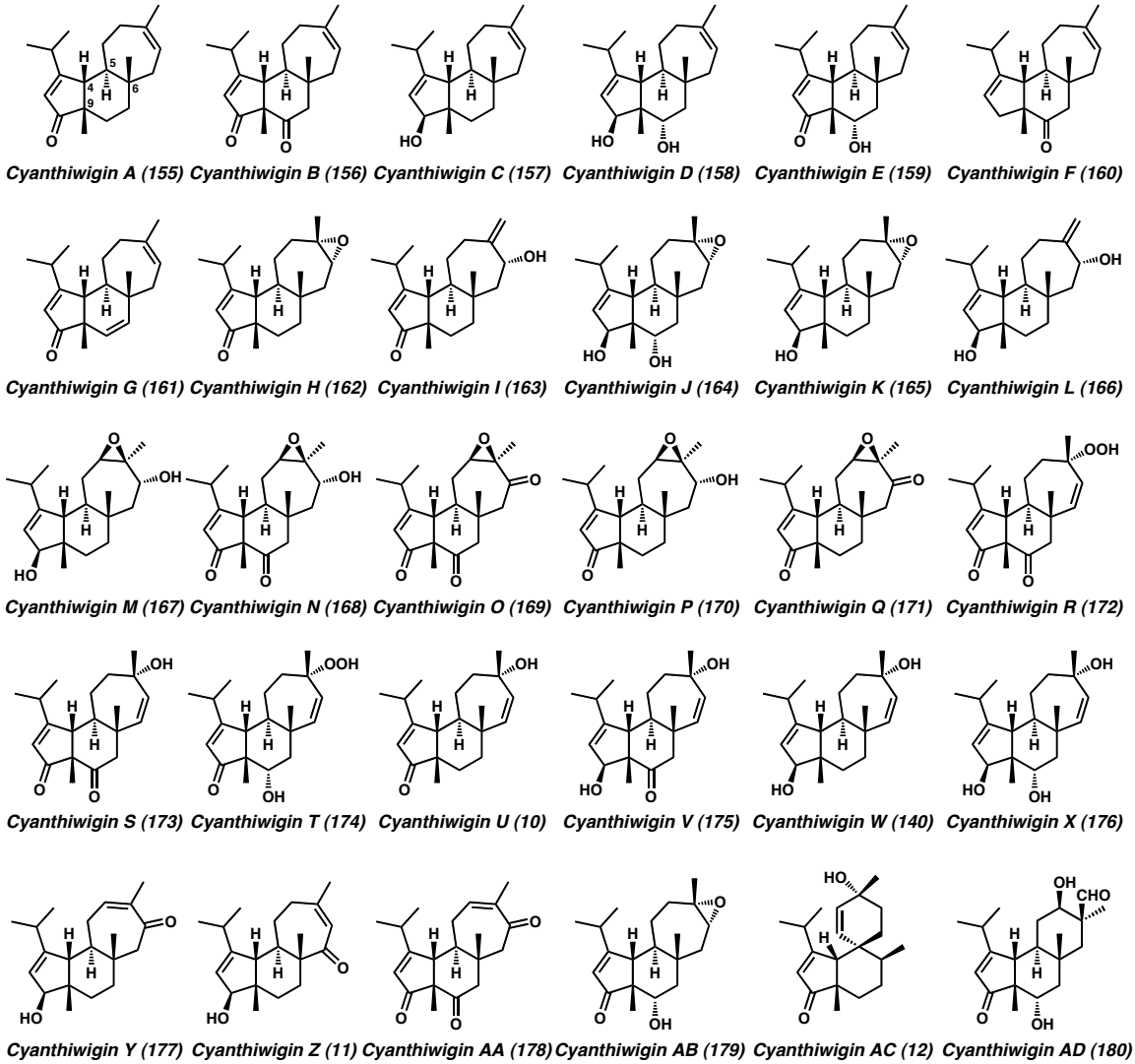
[†] Portions of this chapter have been reproduced from *Nature* **2008**, *453*, 1228–1230 and the supporting information found therein.

structurally similar, and are unified through the presence of a highly conserved tricyclic carbon scaffold (Figure 2.1). The cyanthiwigin molecules belong to a larger class of diterpene natural products known as the cyathanes. In keeping with the vast majority of other cyathane compounds, the 20 carbon atoms of the cyanthiwigins are arranged into a fused [5-6-7] tricyclic core skeleton (**155**–**180**).[3] However, in contrast to the remainder of the cyathanes, the dual all-carbon quaternary stereocenters found in the cyanthiwigin molecules at C(6) and C(9) are arranged with a *syn* relative stereochemical relationship, rather than an *anti* configuration. Furthermore, these diterpene natural products boast two additional points of stereogenicity at ring fusion carbons C(4) and C(5), structural features that establish a total of four contiguous stereocenters across the innermost bonds of the carbon scaffold. Indeed, the central ring of the cyanthiwigin [5-6-7] carbocyclic core imparts formidable challenge to the synthetic preparation of any of these natural products, due to the steric crowding surrounding and nested location of these critical stereocenters.

Structural differentiation among the members of the cyanthiwigin family is primarily manifest in variable oxidation of the peripheral carbocyclic skeleton. Oxidative diversity in the cyanthiwigins provides sparingly oxidized structures such as cyanthiwigin G (**161**), as well as more heavily oxidized examples as can be found in cyanthiwigin O (**169**). For many of the less-oxidized cyanthiwigin compounds (e.g., cyanthiwigin F (**160**)) preparative approaches toward these molecules can prove difficult owing to their sparse functionality. These minimally elaborated structures possess very few reactive handles upon which to leverage retrosynthetic planning. Because of this, synthetic routes toward the construction of less-oxygenated cyanthiwigins typically involve the installation and

subsequent removal of superfluous moieties, an often cumbersome and inefficient method due to the introduction of nonessential functionality.

Figure 2.1 The cyanthiwigin diterpenoid molecules



2.1.2 BIOLOGICAL ACTIVITY

The cyanthiwigin natural products boast a wide range of biological activities. The larger class of cyathanes in general possess a diverse set of bioactive properties, including

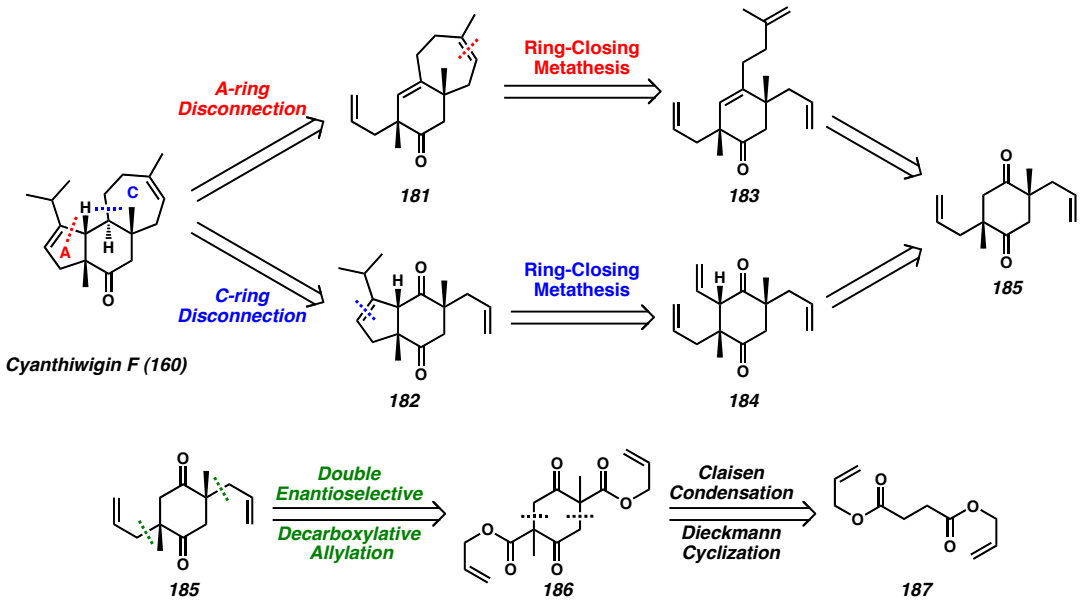
antimicrobial and antineoplastic activity, as well as κ-opioid receptor agonism.[4] Most notably, some members of the cyathane natural products possess the capacity to stimulate the synthesis of nerve growth factor (NGF), a quality that implicates their potential application as therapeutic agents for neurodegenerative diseases and spinal injuries.[5] In addition, cyanthiwigin C has shown cytotoxic activity against both A549 human lung cancer cells (IC_{50} = 4.0 μg/mL) and P-388 human leukemia cells (IC_{50} = 11.2 μg/mL).[6] Cyanthiwigin F (**160**) has displayed cytotoxic activity against human primary tumor cells (IC_{50} = 3.1 μg/mL).[2] Unfortunately, exhaustive investigation of the entire family of cyanthiwigin molecules has been impeded by a lack of sufficient material with which to perform the required biological assays. As such, synthetic preparation of these natural products has become an appealing goal.

2.1.3 RETROSYNTHETIC ANALYSIS

Because the members of the cyanthiwigin family of molecules differ from one another primarily in terms of oxygenation, we hypothesized that a synthetic route capable of rapidly preparing the carbocyclic core would provide simultaneous access to many of these marine natural products. Thus, our approach to the cyathane molecule cyanthiwigin F (**160**) was developed with a specific focus upon quickly constructing the tricyclic cyathane skeleton. In keeping with this goal, our initial retrosynthetic maneuver envisioned disconnection of either the five-membered A-ring or the seven-membered C-ring to lead back to either bicycle **181** or diketone **182**, respectively (Scheme 2.1). In either case, further simplification was anticipated via retrosynthetic opening of the remaining peripheral ring, an operation that would be addressed in the forward sense via

ring-closing metathesis. If the seven-membered C-ring were to be closed first, this strategy would lead to tetraolefin **183**. Initial closure of the five-membered A-ring would invoke triolefin precursor **184**. Regardless of the route employed, we expected that either intermediate **183** or **184** would be accessible via enantioenriched diketone **185**.

Scheme 2.1 Retrosynthetic analysis of cyanthiwigin F



In order to target diketone **185**, we envisioned the use of enantioselective alkylation technology that had been previously developed in our lab.[7] At the outset of our synthetic efforts toward the cyanthiwigin natural products, this stereoselective methodology had already proven quite reliable for the formation of α-quaternary cyclohexanone products. We predicted that by implementing this reaction on an appropriately designed substrate, that it would be possible to forge two carbon-carbon bonds with enantiocontrol, thus providing rapid access to the critical diketone **185** in a single synthetic procedure. This double stereoselective decarboxylative alkylation reaction was anticipated to employ

bis(β-ketoester) **186** as the crucial substrate, and in a forward sense, was expected to set both of the necessary all-carbon quaternary stereocenters of the natural product. Fortuitously, compounds similar to bis(β-ketoester) **186** have been known in the literature for nearly a century. As such we were confident that this material could be prepared from diallyl succinate (**187**) via an initial Claisen condensation and a subsequent Dieckmann cyclization.[8]

2.2 FORWARD SYNTHETIC EFFORTS

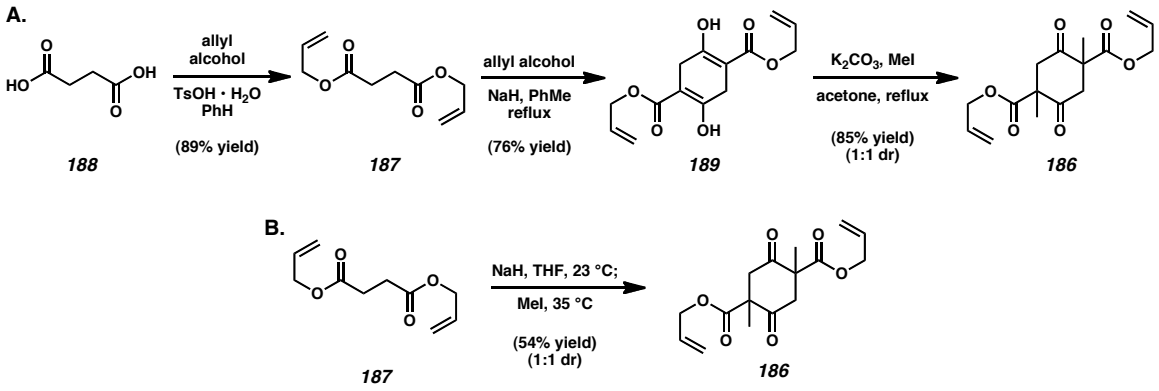
The following section describes the various reactions, routes, and experiments explored in order to synthetically prepare the cyanthiwigin marine diterpene compounds.[9]

2.2.1 DOUBLE ASYMMETRIC DECARBOXYLATIVE ALKYLATION

Studies toward the total synthesis of cyanthiwigin F commenced with the Fischer esterification of succinic acid (**188**) with allyl alcohol to afford diallylsucciniate (**187**, Scheme 2.2A). Exposure of diallyl succinate to a solution of allyl alkoxide in refluxing toluene initiated the desired Claisen condensation, a transformation immediately followed by subsequent Dieckmann cyclization to generate cyclohexadione product **189** exclusively as its bis-enol tautomer.[8] Thereafter, double methylation of bis-ester **189** under standard conditions provided access to bis(β-ketoester) **186** as a 1 : 1 mixture of racemic and *meso* diastereomers. Combination and optimization of the steps in this reaction sequence eventually facilitated the direct preparation of bis(β-ketoester) **186** from diallyl succinate (**187**). In the event, addition of diallyl succinate (**187**) to a

suspension of sodium hydride in THF at room temperature, followed by subsequent quenching with methyl iodide, allowed for the generation of bis(β-ketoester) **186** under lower temperature conditions in a single step (Scheme 2.2B).[10] While the yield of the one step procedure is nominally lower than that of the two step process, the ease of operation and facile scalability of the more direct route outweigh these minimal losses. Interestingly, the diastereomers of bis(β-ketoester) **186** were found to be separable, with each possessing distinct physical properties. While the more polar of the two diastereomers of bis(β-ketoester) **186** was always observed to be a viscous oil, the less polar diastereomer was isolated as a fluffy white solid. With cyclohexadione **186** in hand, we were poised to address the double stereoselective decarboxylative alkylation reaction.

Scheme 2.2 Preparation of the bis(β-ketoester) substrate for double allylation



Previous to these efforts, our group had developed a powerful suite of enantioselective decarboxylative catalytic alkylation reactions. Using this technology, it is possible to access enantioenriched cyclohexanone products bearing all-carbon quaternary stereocenters at the ketone α-position, starting from substrates containing an

allyl enol carbonate, silyl enol ether, or β-ketoester moiety.[7] Having attained bis(β-ketoester) **186**, we anticipated that exposure of this material to the conditions of our palladium-catalyzed alkylation would result in the formation of two independent C–C bonds, thus forging the all-carbon quaternary stereocenters corresponding to positions C(6) and C(9) of the cyanthiwigin core.

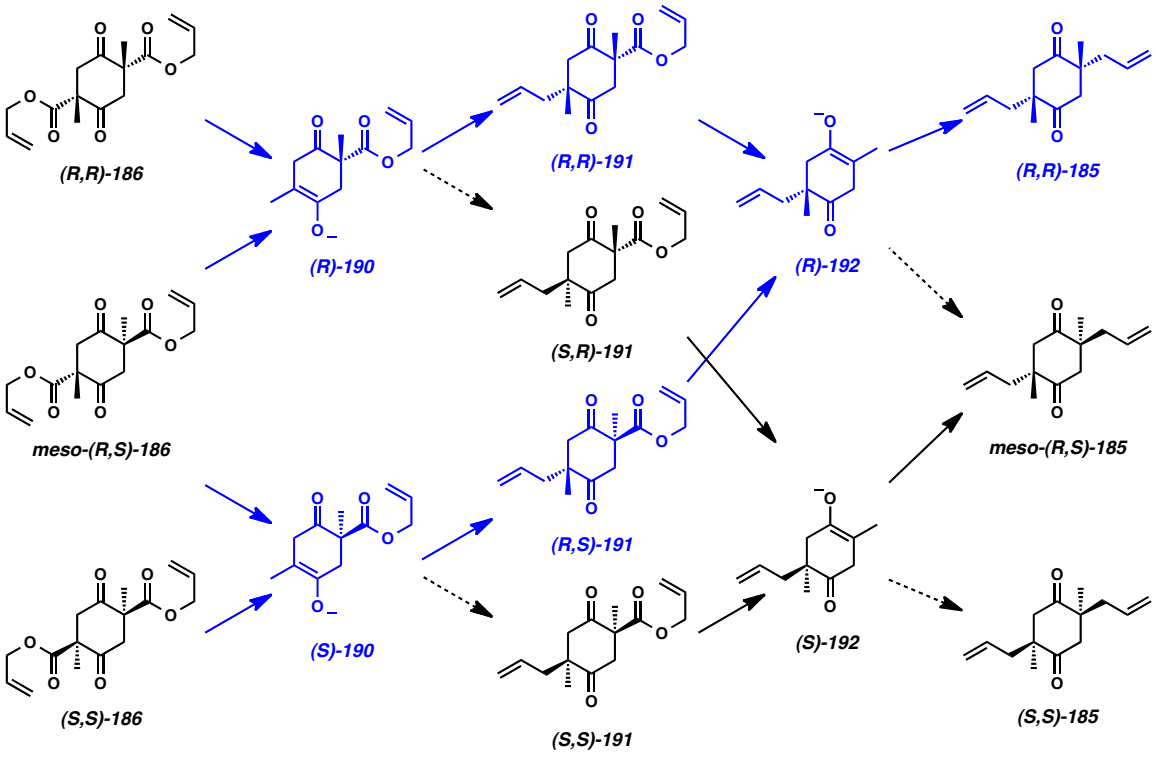
While stereoselective transformations to set more than one stereocenter have been reported in the literature prior to our efforts, the implementation of a double catalytic, stereoselective, C–C bond-forming reaction in the context of complex total synthesis has gone relatively unexplored.[11] Nevertheless, these types of transformations are both efficient and direct, as they set multiple stereocenters with a single catalytic species, and are therefore increasingly desirable for the rapid synthetic preparation of complex natural products.

Despite the potential benefits of double asymmetric transformations, it should be emphasized that the starting material (**186**) for our envisioned reaction was attained as a 1 : 1 blend of racemic and *meso* diastereomers. Exposing such a stereoisomeric mixture to an enantiopure catalyst is typically ill-advised, as the presence of pre-existing stereocenters in the substrate could interfere with inherent catalyst selectivity and afford reduced quantities of the desired product.[12] Indeed, the potential development of mismatched catalyst-substrate interactions, which would deleteriously impact yield and selectivity of the reaction, was a major concern. We were additionally mindful of the possibility for the reaction to proceed via an undesired kinetic resolution.[13]

Subjecting a diastereomeric mixture of bis(β-ketoesters) to the conditions of the stereoselective decarboxylative alkylation was a maneuver with many prospective

outcomes. In the event of diastereomeric interference between the substrate and catalyst, the potential existed for incomplete allylation or impeded decarboxylation. Even in the case of complete transformation of bis(β-ketoester) **186** into the desired diketone (**185**), the stereochemical course of the reaction was difficult to predict. The diastereomeric mixture containing three stereoisomers of starting material could possibly traverse any of 16 distinct stereodefined pathways to give any of three potential product stereoisomers (Scheme 2.3).

Scheme 2.3 Paths of the double asymmetric decarboxylative catalytic alkylation



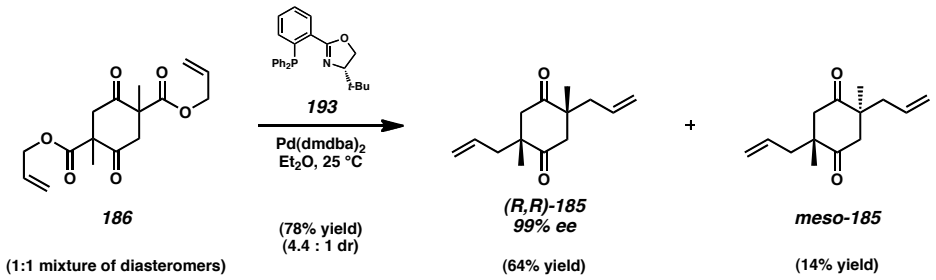
In order for the reaction to afford the desired diketone product with acceptable yield and selectivity, the catalyst employed had to meet several stringent requirements. First, initial decarboxylation of each stereoisomer of starting material ((*R*,*R*)-, *meso*-(*R*,*S*)-, or

(*S*,*S*)-**186**) to give either intermediate ketone enolate ((*R*)- or (*S*)-**190**) would need to proceed at roughly equivalent rates regardless of configuration. If a large disparity in the rate of decarboxylation existed between different stereoisomers of starting bis(β-ketoester) **186**, undesired kinetic resolution would influence the downstream stereoselective bond formation. The same requirement would be necessary for the subsequent decarboxylation of intermediates **191** to yield the transient enolates (*R*)- and (*S*)-**192**, and as such, all stereoisomers of **191** would need to react at equal rates. The second requirement envisioned was that all bond-forming reactions would occur under complete catalyst stereocontrol. This would dictate that any pre-existing or intermediately formed stereocenters present in any isomer of bis(β-ketoester) **186** or intermediate **191** should have no impact upon the selectivity of the allylation event. Third, the catalyst control in these situations would be required to be highly selective, so as to preferentially guide all of the possible ketone enolate stereoisomers ((*S*)- and (*R*)-**190**, (*S*)- and (*R*)-**192)** toward the single desired, enantioenriched product (**185**).

Despite initial uncertainty concerning the course of this reaction, we reasoned that the stereoablative nature of the stereoselective decarboxylative alkylation methodology would minimize any undesired mismatched interactions.[14] This fact, combined with the relatively distal relationship between the two reactive centers in **186**, gave us confidence in the success of our double alkylation approach. Therefore, we subjected a 1 : 1 diastereomeric mixture of racemic and *meso*-**186** to a solution of $Pd(dmdba)_2$ palladium(0) and (*S*)-*tert*-butyl phosphinooxazoline (*t*-BuPHOX, **193**) in diethyl ether (Scheme 2.4).[15] To our delight, this reaction proceeded smoothly at 25 °C to give the desired, enantioenriched diketone (*R*,*R*)-**185** in 78% yield, 99% *ee*, and a 4.4 : 1

diastereomeric ratio. This critical reaction established both of the all-carbon quaternary stereocenters necessary for completion of the cyanthiwigin molecules at an early stage of the synthesis. Creating these nested and difficult points of chirality well in advance was important to the versatility and flexibility of our route.

Scheme 2.4 Double asymmetric decarboxylative catalytic alkylation of ***186***



When considering the excellent enantioselectivity observed in the double alkylation reaction, the modest diastereoselectivity attained from this transformation was initially perplexing. Investigation of literature pertinent to double stereoselective transformations eventually revealed that the high levels of *ee* observed in diketone product (*R*,*R*)-**185** come at the expense of a reduced diastereomeric ratio.[16,17] When only a single undesired allylation event occurs while traversing the possible mechanistic pathways detailed in Scheme 2.3, an additional molecule of the undesired *meso* diastereomer is produced (*meso*-(*R*,*S*)-**185**) regardless of which alkylation occurs against preference. While this unwanted material negatively impacts the diastereomeric ratio of the isolated diketone, it nevertheless has no influence upon the *ee* of the desired product. In order to adversely affect the *ee* of cyclohexadione (*R*,*R*)-**185**, an individual molecule of bis(β-ketoester) (*R*,*R*)-**186**, *meso*-(*R*,*S*)-**186**, or (*S*,*S*)-**186** must undergo two disfavored allylation events in sequence to afford product (*S*,*S*)-**185**. Because the likelihood of two allylation errors

impacting a single substrate is very low in the presence of reasonable catalyst control, the total yield of the unwanted (*S*,*S*)-**185** stereoisomer is negligible, and thus the product *ee* is excellent. However, due to the much higher likelihood of a single alkylation event yielding the undesired configuration, the amount of diketone *meso*-(*R*,*S*)-**185** afforded through this reaction is larger than anticipated. In effect, generation of the *meso* diastereomer serves as a buffer against accumulation of undesired stereoisomer (*S*,*S*)-**185**, allowing this reaction to sacrifice some small measure of diastereomeric ratio in favor of exceptionally high levels of enantioselectivity.[18] This phenomenon (sometimes referred to as the "Horeau Principle"), was first observed and rationalized by Langenbeck in 1936, and was later elaborated into more thorough mathematical representations by Horeau, Kagan, and Rautenstrauch.[16,17]

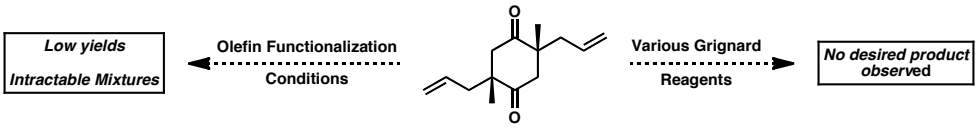
2.2.2 DIKETONE DESYMMETRIZATION AND ELABORATION

With the successful generation of enantioenriched diketone (*R*,*R*)-**185** attained, our efforts were thereafter focused on elaboration of this material via construction of the peripheral A- and C-rings of the cyathane tricycle.

At this juncture of the synthesis, advancement of diketone **185** required differentiation between the functional groups of this C_2 symmetric substrate.[19] Initial desymmetrizing efforts were attempted via careful addition of various Grignard reagents to cyclohexadione **185** in the hopes of executing a single nucleophilic addition to either ketone moiety. Disappointingly, these experiments ultimately proved unsuccessful (Scheme 2.5). The steric encumbrance imposed by the α-quaternary stereocenters of diketone **185** very likely impede approach of any incoming nucleophile toward either of

the carbonyl carbons, and thus renders this cyclohexadione intransigent to 1,2-addition conditions. An alternative desymmetrization strategy we investigated involved the attempted mono-functionalization of the pendent allyl side chains of substrate **185**. Regrettably, this approach also proved ineffective. In cases where dihydroxylation or epoxidation conditions were employed, only low yields were ever obtained, and in every case the sparing material isolated was a mixture of mono- and di-functionalized products.

Scheme 2.5 Attempts toward diketone functionalization



(*R,R*)-*185*

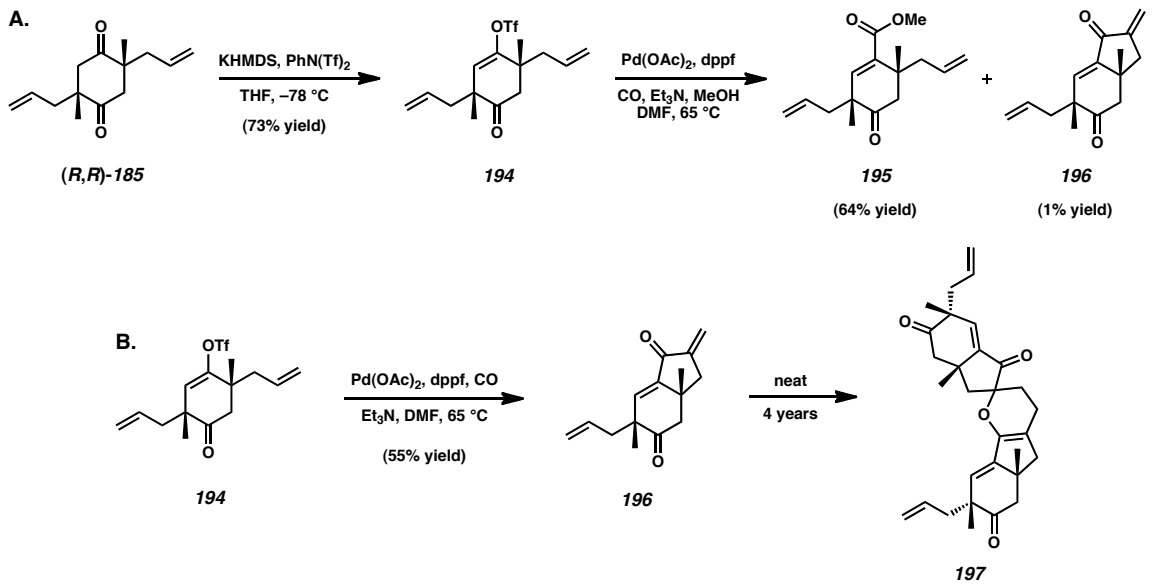
Greater selectivity and reactivity was ultimately achieved when diketone **185** was subjected to the conditions of enol triflate formation (Scheme 2.6A). Slow addition of diketone **185** to a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran allowed generation of a monoanionic ketone enolate. This intermediate was thereafter trapped via exposure to a solution of phenyl bis(trifluoromethane)sulfonimide to afford cyclohexanone **194** in reasonable yield. With this newly desymmetrized material in hand, we attempted to leverage the installed triflate to introduce functionality that would enable construction of a bicyclic structure.

By submitting enol triflate **194** to the conditions of a palladium-catalyzed carboxylation reaction in the presence of methanol, conjugated ester **195** was obtained as the major product. Unfortunately, purification of this material proved difficult, and isolates of enoate **195** were regularly contaminated with trace amounts of a strongly UV-

active impurity. Thorough and careful investigation of this contaminant eventually revealed its identity as dienone **196**, an unexpected yet intriguing byproduct of this carbonylative methodology. We suspected bicycle **196** to be the result of an intramolecular Heck-type reaction, wherein initial oxidative addition of palladium into the enol triflate bond was followed by subsequent carbon monoxide insertion and eventual olefin insertion into the pendant arm of **194**. This hypothesis was later strengthened when the methoxycarbonylation reaction was repeated in the absence of the nucleophilic cosolvent (Scheme 2.6B). Without methanol, these conditions afforded exclusively the carbonylative Heck product **196**.[20] In an additionally fascinating development, prolonged storage of neat **196** eventually generated pentacyclic spirocycle **197**, a product presumably resulting from a hetero Diels–Alder dimerization.

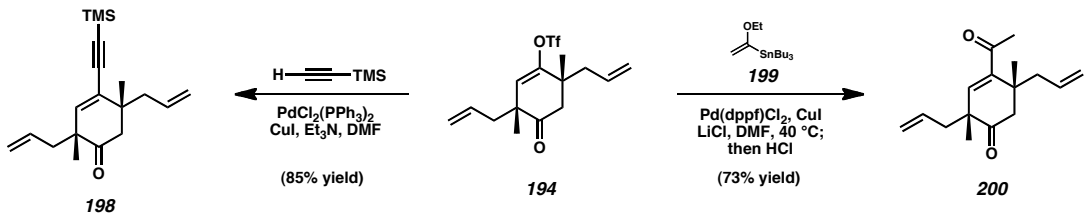
Interestingly, the structure of dienone product **196** suggests that oxidative addition and carbon monoxide incorporation occur before olefin complexation and insertion. While this phenomenon is known, typically in these reactions carbonylation occurs as the final step of the transformation, taking place only after olefin insertion.[20] This observed reversal in expected reactivity is likely due to the difficulty of olefin insertion directly following oxidative addition, a process that would require cyclobutane formation. The relatively greater ease of cyclopentanone formation provides a reasonable explanation for pre-emptive carbon monoxide incorporation. Regrettably, further elaboration of either enoate **195** or dienone **196** proved unproductive in our hands, and so alternative methods of functionalizing triflate **194** were sought.

Scheme 2.6 (A) Triflate formation and carboxylative attempts toward diketone elaboration (B) An unanticipated carbonylative Heck reaction, and subsequent dimerization



In order to better gauge the reactivity of enol triflate **194**, we executed a number of cross-coupling reactions to test the viability of sp^2-sp, sp^2-sp^2, and sp^2-sp^3 hybridized carbon-carbon bond construction. Attempts at Sonogashira coupling of ketone **194** and trimethylsilyl acetylene smoothly provided access to enyne **198** in high yield (Scheme 2.7).[21] Similarly, copper-accelerated Stille reaction of triflate **194** with enol stannane **199** proved to be very effective.[22] After acidic workup of this sp^2-sp^2 coupling reaction, enone **200** was obtained in reasonable yield.

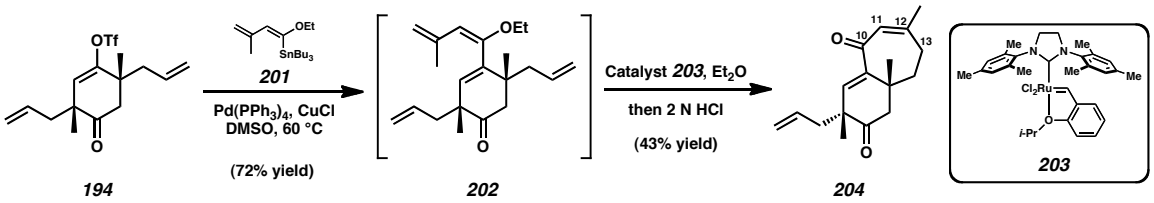
*Scheme 2.7 Palladium-catalyzed cross-coupling reactions of triflate **194***



Encouraged by the successes of the preliminary Stille coupling, we repeated this reaction while employing the more complicated enol stannane **201** in place of coupling partner **199** (Scheme 2.8).[23] This transformation progressed easily to generate cyclohexanone **202**. However, purification and manipulation of this material was difficult, due to the rapid decomposition of the enol ether upon contact with silica gel or prolonged exposure to atmospheric conditions, both of which resulted in hydrolysis to reveal the latent ketone moiety. In order to circumvent issues of instability experienced with this intermediate, enol ether **202** was immediately exposed to the Grubbs/Hoveyda generation II catalyst (**203**) in order to execute ring-closing metathesis, and this process was subsequently followed by acidic workup. This synthetic procedure successfully closed the seven-membered C-ring of the cyathane tricycle, ultimately generating bicyclic ketone **204**. While our efforts were bolstered by the successful formation of a [6,7]-bicyclic intermediate, this material nevertheless provided us with unanticipated difficulty. Formation of bicycle **204** was always accompanied by an undesired shift of the anticipated C(12)–C(13) olefin into conjugation with the newly revealed C(10) ketone.[24] If enone **204** were to be used to pursue the synthesis of the cyanthiwigin molecules, this new development would necessitate isomerization of the C(11)–C(12) olefin back into the C(12)–C(13) position, a task we regarded to be nontrivial. Furthermore, while the oxygenation present at C(10) was the result of functionality necessary for the stability of stannane **201**, this newly formed ketone was superfluous to the structure of completed natural product. Thus, removal of this moiety would be required at some later stage if enone **204** were to serve as a viable synthetic intermediate. Because of these difficulties, we opted not to pursue the further elaboration of dienone

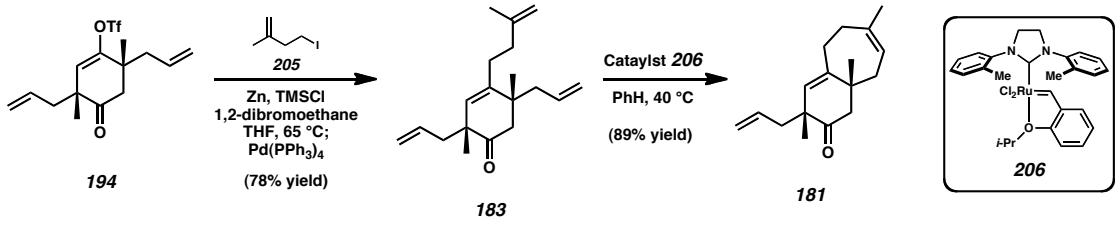
204. Instead, we chose to investigate alternative cross coupling-conditions for triflate **194**.

*Scheme 2.8 Formation, ring-closing metathesis, and acidic hydrolysis of enol ether **202***



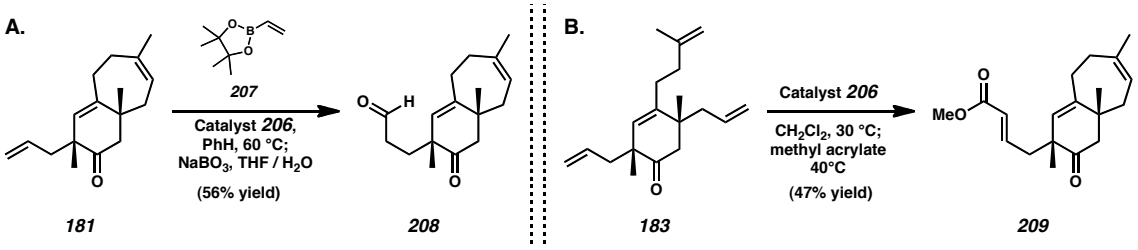
A reinvestigation of triflate **194** revealed the viability of a direct sp^2-sp^3 bond formation via a Negishi cross-coupling procedure. Zinc dust was first treated with 1,2-dibromoethane and trimethylsilyl chloride, and to this activated metal was added alkyl iodide **205**. After generation of the alkyl zinc species, a THF solution containing a palladium(0) catalyst and triflate **194** was introduced to the mixture, thus initiating Negishi cross coupling of the two fragments (Scheme 2.9).[25] After appropriate workup and purification, tetraolefin **183** was isolated as the sole product of this reaction. We were excited to find that ring-closing metathesis of cyclohexanone **183** to form the seven-membered C-ring furnished bicyclic product **181**, a structure containing two of the three rings of the cyathane skeleton. Notably, we found that this ring-forming process was both faster and higher-yielding when modified Grubbs–Hoveyda catalyst **206** was employed in place of the Grubbs/Hoveyda second-generation catalyst **203**.[26]

Scheme 2.9 Negishi cross coupling for the formation of an sp^2-sp^3 carbon-carbon bond



We anticipated that further advancement of this material toward the cyanthiwigin natural products would undoubtedly require selective functionalization of the remaining allyl side chain in the presence of the C(12)–C(13) olefin. For this reason, we turned our attention toward the possibility of using metathesis reactivity for the elaboration of the remaining terminal olefin. Cross-metathesis of vinyl boronate species **207** with newly attained bicycle **181** proved fruitful, and upon exposure to an oxidative workup involving aqueous sodium perborate, this process generated aldehyde **208** as the major product (Scheme 2.10A).[27] With the success of the ring-closing and cross-metathesis processes confirmed as independent reactions, we hypothesized that both transformations might be accomplished concurrently via the use of the same catalyst.

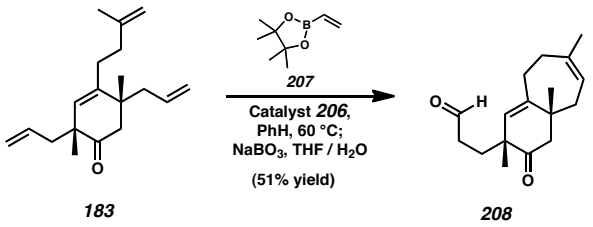
Scheme 2.10 Functionalization of the C(2)–C(3) olefin via olefin cross-metathesis



In the event, the addition of methyl acrylate to the conditions used for the ring-closing metathesis of tetraolefin **183** executed both formation of the seven-membered cyathane

C-ring and functionalization of the terminal allyl moiety (Scheme 2.10B). By employing this reaction, monocyclic starting material **183** was smoothly transformed into bicyclic enoate **209** in a single synthetic operation. Though ester **209** was not amenable to further desired transformation, the technique elucidated by its formation nevertheless aided considerably in our synthetic efforts. By subjecting tetraolefin **183** to the conditions of concurrent ring-closing and cross-metathesis in the presence of vinyl boronate **206**, and executing a subsequent oxidative workup with sodium perborate, it was possible to rapidly prepare bicyclic aldehyde **208** (Scheme 2.11).

Scheme 2.11 Ring-closing and cross-metathesis reaction to generate the bicyclic aldehyde ***208***



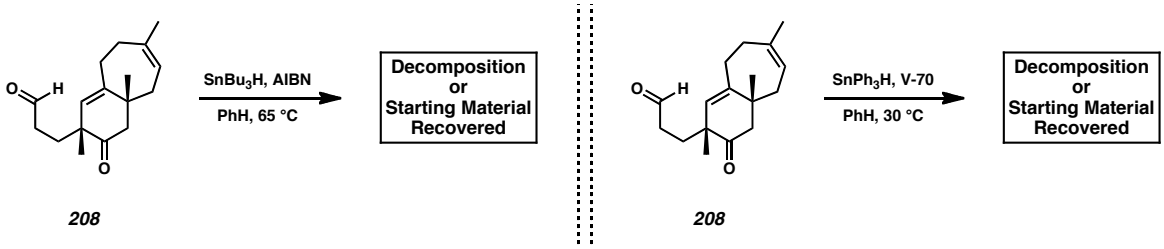
2.2.3 TRICYCLE FORMATION VIA RADICAL CYCLIZATION

At this stage in the synthesis, the synthetic challenges remaining to be addressed included the finalization of the tricyclic cyathane core via installation of the five-membered A-ring, as well as the establishment of both the C(4) and C(5) stereocenters. We hypothesized that all of these pending goals might be accomplished in tandem through the use of a radical cyclization reaction. It was envisioned that the formation of a high-energy acyl radical species via hydrogen atom abstraction from aldehyde **208** would encourage thermodynamically-controlled carbon-carbon bond formation with the C(4)–

C(5) olefin. To test this hypothesis, we turned our attention toward methods for the reliable production of acyl radical intermediates from aldehydes.[28]

Preliminary attempts to generate an acyl radical for the purpose of intramolecular cyclization were unfortunately unsuccessful. Subjecting bicyclic aldehyde **208** to tributylstannane or triphenylstannane did not yield the desired product. Both radical propagators were employed in combination with either azobisisobutyronitrile (AIBN) or 2,2'-azobis(4-methoxy-2,4-dimethyl valeronitrile) (V-70) initiators, yet in each case only unreacted substrate **208** or nonspecific decomposition were observed (Scheme 2.12).[29,30]

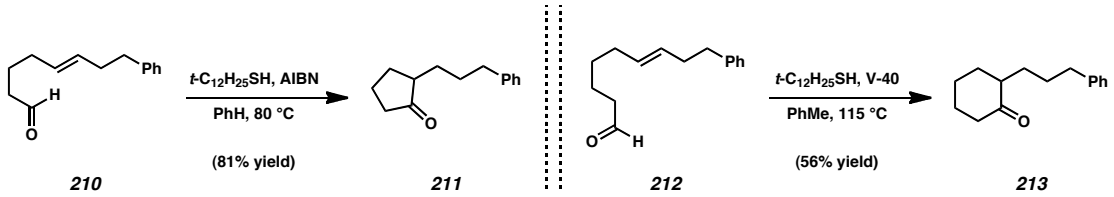
Scheme 2.12 Initial attempts at radical cyclization for A-ring formation



In light of the failure of stannane reagents to furnish the targeted tricyclic product, we sought alternative conditions for the reliable formation of acyl radical species. After a thorough investigation of the literature, we became familiarized with aldehyde-olefin cyclization methodology developed by Tomioka *et al*. in 2005.[31] By implementing a bulky thiol radical propagator and an appropriate initiator, Tomioka was able to achieve the cyclization of aldehyde functional groups onto olefins to form cyclic ketone products. By employing this reaction, it was demonstrated that in the presence of *tert*-dodecanethiol and AIBN, linear aldehyde **210** could be cyclized onto an isolated olefin moiety to be smoothly converted into cyclopentanone **211** (Scheme 2.13). Similarly,

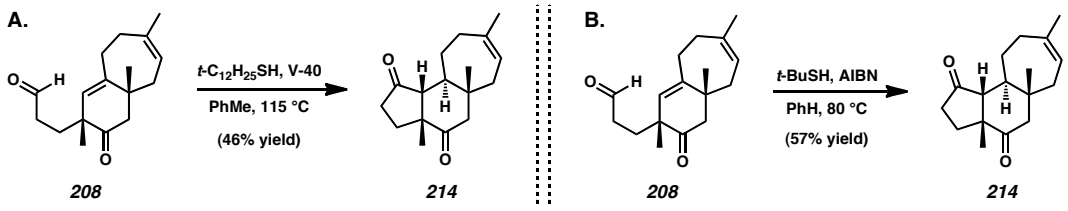
tert-dodecanethiol and 1,1'-azobis(cyclohexane-1-carbonitrile) (V-40 initiator) enabled the conversion of aldehyde **212** into cyclohexanone **213**.

Scheme 2.13 Radical cyclization conditions developed by Tomioka and coworkers[31]



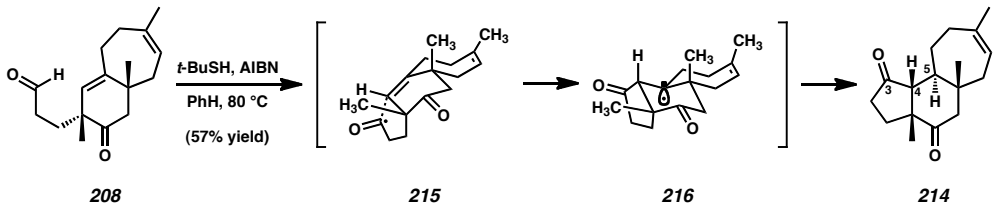
Because our work required the cyclization of an aldehyde onto an unconjugated olefin, we attempted to subject bicyclic aldehyde **208** to Tomioka's methodology with the intention of forming the required cyathane A-ring. Fortuitously, employing *tert*-dodecanethiol and V-40 initiator in the radical cyclization of **208** forged the desired cyclopentanone and provided access to fully formed cyathane tricycle **214** (Scheme 2.14A). Minor optimization of this reaction was possible under lower temperature conditions, wherein using *tert*-butylthiol as propagator and AIBN as initiator afforded slightly increased yield of the desired product (Scheme 2.14B). Regardless of the exact reagents used, both reactions afforded **214** as a single diastereomer.

Scheme 2.14 Application of Tomioka's methodology to A-ring formation



It is possible that the diastereoselectivity observed in this cyclopentanone-forming reaction is a consequence of thermodynamic control. After initial hydrogen atom abstraction from aldehyde **208**, acyl radical species **215** is formed (Scheme 2.15). Due to steric and conformational constraints, this radical species has limited access to the C(4)–C(5) olefin. Indeed, acyl radical approach and carbon-carbon bond formation may only occur from the bottom face of the bicyclic system as drawn in Scheme 2.15. Construction of this bond in line with such a trajectory establishes the desired stereochemistry at C(4), and additionally generates a rapidly equilibrating tertiary radical at C(5) (**216**). Further hydrogen atom abstraction from *tert*-butyl thiol to quench the radical found in intermediate **216** proceeds under thermodynamic control, and this affords the more stable trans-oriented [6,7] ring fusion in preference to the cis-fused alternative. Ultimately, these factors ensure that tricycle **214** is furnished as the sole stereoisomeric product of the reaction. The formation of the five-membered A-ring to construct tricyclic diketone **214** marked the completion of the cyathane core skeleton.

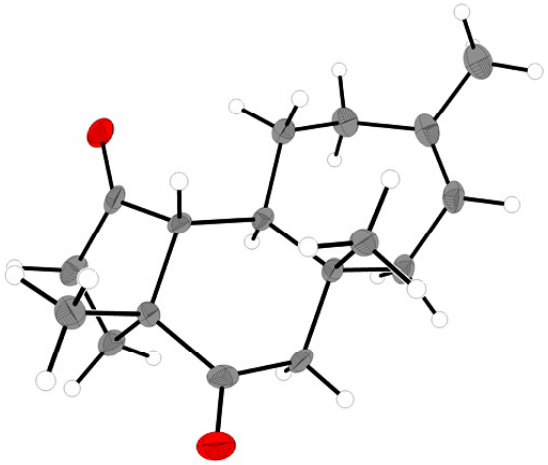
Scheme 2.15 Mechanistic hypothesis and stereochemical rationale for radical cyclization of ***214***



Attaining this material was of considerable significance to our synthetic efforts, not only because of its proximity to cyanthiwigin F (**160**), but also because we envisioned that this tricyclic diketone **214** could serve as a platform from which to access other cyanthiwigin natural products. Fortunately, solid crystals of this critical intermediate

were amenable to X-ray analysis (Figure 2.2). The data collected from X-ray crystallography on diketone **214** revealed not only the stereochemistry set by the radical cyclization reaction, but also confirmed the relative stereochemistry established by the initial double alkylation reaction as well.

*Figure 2.2 X-ray crystal structure of tricycle **214***



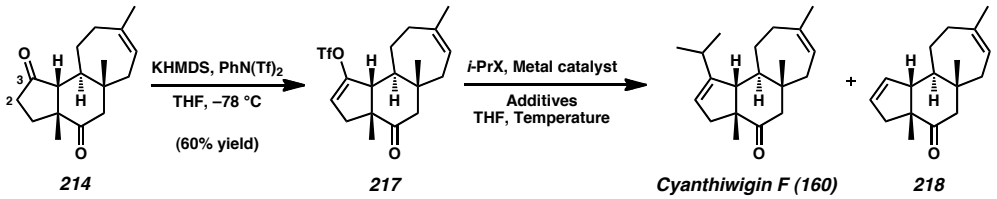
2.2.4 COMPLETION OF THE CYANTHIWIGIN NATURAL PRODUCTS

With tricyclic diketone **214** in hand, the final challenges remaining in the total synthesis of cyanthiwigin F were the installation of the C(3) isopropyl group and introduction of the C(2)–C(3) olefin. In order to address these requirements, we envisioned harnessing the reactivity of the newly installed C(3) ketone to establish a vinyl triflate suitable for transition metal-catalyzed cross-coupling reactions. In the event, selective deprotonation of diketone **214** with KHMDS and trapping with *N*-phenyl bis(trifluoromethane)sulfonimide produced vinyl triflate **217** in reasonable yield (Table 2.1). Having achieved the synthesis of tricycle **217**, we predicted that isopropyl group installation could be accomplished via a Negishi cross-coupling process similar to the one

used previously.[25] Regrettably, when these coupling conditions were employed with triflate **217** and 2-iodopropane, the only isolated material was reductive deoxygenation product **218** (Table 2.1, entry 1).

Because palladium-catalyzed cross-coupling of **217** and 2-iodopropane was met with difficulty, alternative copper-catalyzed methods to install the required three-carbon fragment were investigated. Preliminary experiments involved direct addition of isopropyl magnesium chloride to suspensions of triflate **217** and catalytic amounts of either copper iodide or copper cyanide. Disappointingly, these reactions were similarly ineffective, affording mostly the reduced tricycle **218** (Entries 2–4).[32] Use of copper bromide dimethyl sulfide complex for this direct-addition technique did yield small quantities of the natural product, but these sparing amounts of the desired compound were contaminated with larger amounts of the reduction product **218**. To rectify this issue, we endeavored to approach the coupling via the use of stoichiometric quantities of pre-generated isopropyl-cuprate reagents, using a variety of different copper sources (Entries 5–8). In all cases, we observed either low reactivity or a preference for reductive deoxygenation.

Table 2.1 Transition metal cross-coupling attempts toward cyanthiwigin F



Entry	Stoichometric *i*-PrX Reagent	Metal Catalyst	Additives	Temperature (°C)	Yield ***160*** (%)	Yield ***218*** (%)	Yield ***217*** (%)
1	*i*-PrZnI [a]	$Pd(PPh_3)_4$	1,2-dibromoethane TMSCl	65 °C	-	ND	-
2[b]	*i*-PrMgCl	CuI	-	-10 °C	-	65%	-
3[b]	*i*-PrLi	CuCN	-	–20 °C	-	-	73%
4[b]	*i*-PrMgCl	CuBr•DMS	-	–20 °C	26%	ND	57%
5[c, d]	*i*-PrMgCl + CuCN	-	-	–78 → 0 °C	-	-	99%
6[c]	*i*-PrMgCl + CuBr•DMS	-	-	–78 → –20 °C	15%, 20%	ND	-
7[c, e]	*i*-PrLi + CuCN	-	-	–78 → –20 °C	11	ND	27%
8[c, e]	*i*-PrLi + CuCN	-	BF_3•OEt_2	–20 °C	-	-	99%
9[f]	*i*-PrMgCl	$Ni(dppp)Cl_2$	-	35 °C	-	-	99%
10	*i*-PrMgCl	$Pd(PPh_3)_4$	-	–78 → 23 °C	-	ND	19%
11	*i*-PrMgCl	$Pd(dppf)Cl_2$	-	35 °C	-	ND	-
12[c,e]	*i*-PrMgCl + CuCN	$Pd(dppf)Cl_2$	-	–78 → 0 °C	41%	23%	-

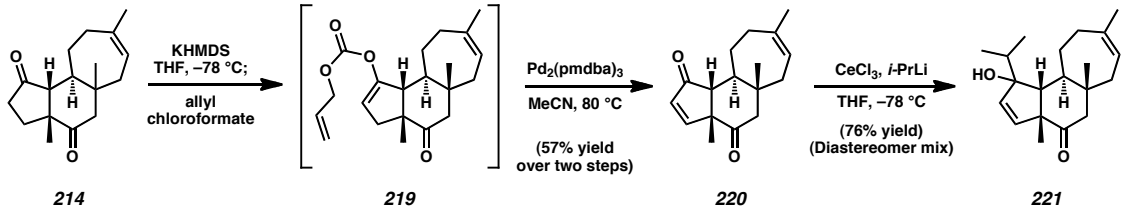
All reactions with yields listed as 'not determined' gave predominantly tricycle ***218*** as product. [a] Reagent formed via addition of *i*-PrI to activated Zn^0 metal. [b] Reaction performed via direct addition of *i*-PrX species to a suspension of the metal catalyst and ***217***. [c] Reaction involved the use of a pre-formed cuprate species. [d] A lower-order cyanocuprate was employed (1 : 1 ratio of *i*-PrX to Cu). [e] A higher-order cyanocuprate was employed (2 : 1 ratio of *i*-PrX to Cu). [f] Et_2O was employed as solvent.

Additional experiments into isopropyl cross-coupling involved employing a number of nickel and palladium catalysts in a series of Kumada-type reactions (Entries 9–11),[33] but the results overwhelmingly favored reduced product **218** in those instances where reactivity was observed. Finally, we discovered that introduction of a pre-generated, higher-order isopropyl cyanocuprate to a solution of triflate **217** and dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) gave a combined 65% yield of the natural

product (**160**) and tricycle **218**, in a 1.8 : 1 mixture favoring cyanthiwigin F (Entry 12).[34,35]

In addition to being instrumental in the total synthesis of cyanthiwigin F, it was our hope that the completed cyathane core represented by tricycle **214** would prove useful in the synthesis of other diterpenes of this natural product family. Starting from diketone **214**, deprotonation at the α-position of the C(3) ketone and trapping of the incipient enolate with allyl chloroformate provided access to enol carbonate **219**. Thereafter, treatment of this material with a catalytic quantity of palladium(0) in acetonitrile provided enone **220** in high yield (Scheme 2.16).[36] Unsaturated ketone **220** afforded an excellent opportunity for direct introduction of the C(3) isopropyl group via 1,2-addition, and so was exposed to isopropyl lithium under Luche-type activation conditions. Cerium-mediated alkyl lithium reactivity proceeded with exclusive addition to C(3), generating tertiary alcohol **221** as a mixture of inconsequential diastereomers.

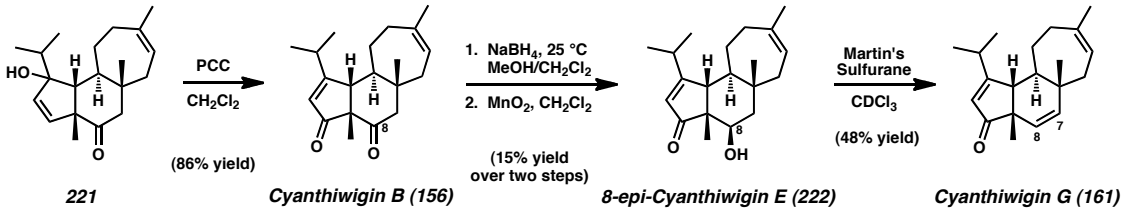
*Scheme 2.16 Advancement of tricycle **214** toward additional cyanthiwigin natural products*



The mixture of alcohols, **221**, was then subjected to PCC in dichloromethane, conditions anticipated to execute allylic oxidation with concomitant oxygen transposition. In the event, **221** was smoothly transformed into natural product **156**, thus completing the total synthesis of cyanthiwigin B (Scheme 2.17).[37] We further envisioned that cyanthiwigin B (**156**) might be additionally advanced toward other members of this

natural product family via selective carbonyl reduction at C(8).[38] Conditions reported to selectively reduce ketones in the presence of enones unfortunately provided exclusively over-reduction of both carbonyl moieties, but this difficulty was mitigated by immediate and selective reoxidation of the resulting material with manganese(IV) dioxide. This allylic oxidation process generated enone **222** as the sole product of reaction. Notably, tricycle **222** was found to be structurally identical to cyanthiwigin E, with the single exception of the configuration of the stereogenic alcohol present at C(8), which was determined to be epimeric to that found in the natural product. Nevertheless, 8-*epi*-cyanthiwigin E (**222**) served as an invaluable intermediate in the preparation of another cyanthiwigin compound. Treatment of enone **222** with Martin's sulfurane in deuterated chloroform successfully eliminated the C(8) secondary alcohol to install the C(7)–C(8) olefin, thus finalizing the total synthesis of cyanthiwigin G (**161**).[39,40]

Scheme 2.17 Completion of cyanthiwigins B and G



221 ***Cyanthiwigin B (156)*** ***8-epi-Cyanthiwigin E (222)*** ***Cyanthiwigin G (161)***

2.3 CONCLUDING REMARKS

In summary, we have developed an efficient, versatile, and enantioselective route to the cyanthiwigin natural products. Our approach toward these molecules involves a rapid synthesis of the central six-membered B-ring, with a specific focus on early installation of both the C(6) and C(9) all-carbon quaternary stereocenters. The use of a double

asymmetric decarboxylative catalytic alkylation reaction not only enables access to the critical enantioenriched cyclohexadione **185**, but this methodology has additionally proven tolerant of a diastereomeric mixture of racemic and *meso* starting materials in the same catalytic transformation. Because of the ease with which stereoisomeric mixtures of precursor bis(β-ketoester) **186** can be prepared, this stereoablative approach expedites the early phases of our synthesis considerably. Our strategy also involves an efficient, single operation ring-closing and cross-metathesis reaction to generate a bicyclic aldehyde from a monocyclic tetraolefin. Combined with a powerful radical cyclization, these techniques furnish ready and rapid access to a versatile tricyclic intermediate representing the completed cyathane core (**214**). By leveraging this core compound as a branching point toward marine natural products, our group was able to expediently prepare multiple cyanthiwigin molecules. In particular, the total synthesis of cyanthiwigin F (**160**) was accomplished in nine total steps, seven of which form carbon-carbon bonds. Of the seven carbon-carbon bond-forming transformations in our synthetic sequence, four construct more than one carbon-carbon bond simultaneously. Additionally, the synthesis is highly efficient in terms of its use of redox reactions, as only minimal oxidative or reductive processes are employed. The flexibility and modularity of our synthetic route later accommodated further extrapolation of tricyclic intermediate **214** toward additional members of the cyanthiwigin family, thus facilitating the preparation of cyanthiwigins B (**156**) and G (**161**).

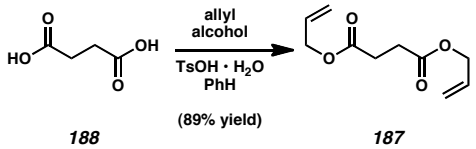
2.4 EXPERIMENTAL SECTION

2.4.1 MATERIALS AND METHODS

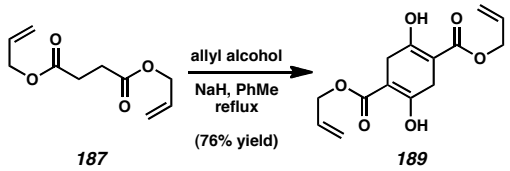
All reactions were performed at ambient temperature (22 °C) unless otherwise noted. Reactions requiring external heat were modulated to the specified temperatures indicated by using an IKAmag temperature controller. All reactions were performed in glassware flame dried under vacuum and allowed to cool under nitrogen or argon. Solvents were dried by passage over a column of activated alumina with an overpressure of argon gas. Tetrahydrofuran was distilled directly over benzophenone and sodium, or else was dried by passage over a column of activated alumina with an overpressure of argon gas. Grubbs' ruthenium catalysts **203** and **206** were donated by Materia Inc. and used without further purification. (*S*)-*t*-BuPHOX (**193**),[15,41] enol stannane **201**,[23] 4-iodo-2-methyl-1-butene (**205**),[42] and vinyl boronate ester **207**[27] were prepared according to known methods. All other chemicals and reagents were used as received. Compounds purified by flash chromatography utilized ICN silica gel (particle size 0.032–0.063 mm) or SiliCycle® Silia*Flash*® P60 Academic Silica Gel (particle size 40–63 μm; pore diameter 60 Å). Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by UV, *p*-anisaldehyde, or alkaline permanganate staining. NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR), Varian Inova 500 (at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR), or Varian Inova 600 (at 600 MHz for ^{1}H NMR only) instrument, and are reported relative to residual $CHCl_3$ (δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR) or C_6H_6 (δ 7.16 for ^{1}H NMR, δ 128.06 for ^{13}C NMR). The following format is

used for the reporting of ^{1}H NMR data: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum Paragon 1000 spectrometer, and data are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility, or else were acquired using an Agilent 6200 Series TOF mass spectrometer with an Agilent G1978A Multimode source in ESI, APCI, or MM (ESI/APCI) ionization mode. Analytical chiral gas chromatography was performed with an Agilent 6850 GC using a G-TA (30 m x 0.25 mm) column (1.0 mL/min carrier gas flow). Analytical achiral gas chromatography was performed with an Agilent 6850 GC using a DB-WAX (30 x 0.25 mm) column (1.0 mL/min carrier gas flow). Preparatory reverse-phase HPLC was performed on a Waters HPLC with Waters Delta-Pak 2 x 100 mm, 15 μm column equipped with a guard, employing a flow rate of 1 mL/min and a variable gradient of acetonitrile and water as eluent. HPLC visualization was performed by collecting 1 mL fractions after initial injection and analyzing each fraction via TLC. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using a 100 mm path-length cell.

2.4.2 PREPARATIVE PROCEDURES



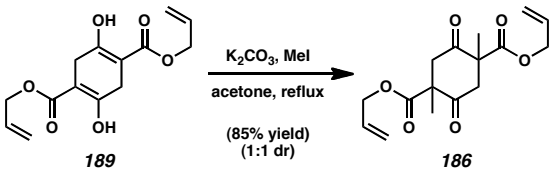
Diallyl succinate (187). To a solution of succinic acid (**188**, 40.0 g, 338.7 mmol) in benzene (300 mL) was added TsOH • H_2O (0.21 g, 1.2 mmol, 0.003 equiv). After brief mixing, allyl alcohol (70 mL, 1.01 mol, 3.00 equiv) was added to the reaction, and the flask was fitted with a Dean–Stark trap and reflux condenser under nitrogen. The reaction was heated to 105 °C and allowed to reflux over 12 h. After collection of 13 mL H_2O from the Dean–Stark trap, the reaction was allowed to cool to room temperature and was quenched by slow treatment with saturated $NaHCO_{3(aq)}$ until gas evolution halted. The phases were separated, and the organic layer was washed with saturated $NaHCO_{3(aq)}$ (2 x 40 mL) and brine (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and solvent was removed in vacuo. The resulting colorless oil was dried under high vacuum to afford diallyl succinate (**187**, 59.8 g, 89% yield). This material was carried into the next step without further purification: R_f = 0.35 (10:90 Et_2O/pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.3, 10.5, 5.6 Hz, 2H), 5.31 (ddt, *J* = 17.0, 1.6, 1.3 Hz, 2H), 5.23 (ddt, *J* = 10.4, 1.3, 1.1 Hz, 2H), 4.60 (ddd, *J* = 5.9, 1.3, 1.3 Hz, 4H), 2.67 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 132.1, 118.5, 65.5, 29.2; IR (Neat film, NaCl) 3086, 2942, 1738, 1649, 1413, 1377, 1271, 1157, 990, 932 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O_4$ $[M]^+$: 198.0892, found 198.0888.



187 ***189***

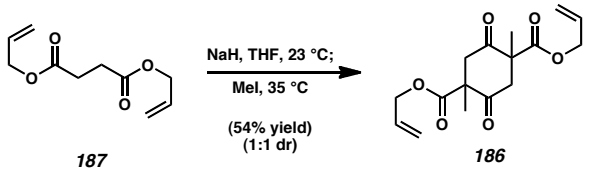
Diallyl succinylsuccinate (189).[8] To a flame dried flask under argon was added NaH (60% in mineral oil, 25.0 g, 630.6 mmol, 2.50 equiv) and toluene (125 mL). To this was added, dropwise, neat allyl alcohol (4.14 mL, 70.6 mmol, 0.28 equiv) with vigorous stirring. After gas evolution had ceased, neat diallyl succinate (**187**, 50.0 g, 252.2 mmol, 1.00 equiv) was added dropwise, and the reaction was heated to 95 °C. The reaction flask was fitted with a reflux condenser, and reaction was allowed to proceed over 10 h. After ca. 15 min, an additional portion of toluene (125.0 mL) was added to the reaction to ensure fluidity of the mixture. Once the reaction had completed by TLC, the flask was cooled to room temperature, and the solvent was removed in vacuo. The crude solid was immediately suspended in CH_2Cl_2, and then acidified by addition of 2 N $HCl_{(aq)}$ (350 mL). The biphasic mixture was allowed to stir over 2 h, after which time all solids had dissolved. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and solvent was removed in vacuo to yield a crude orange solid. The crude residue was recrystallized twice from a mixture of petroleum ether and acetone to afford diallyl succinylsuccinate (**189**) as a flaky white solid (26.9 g, 76% yield): R_f = 0.6 (15:85 ethyl acetate/hexane) ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.11 (s, 2H), 5.95 (dddd, *J* = 17.1, 10.7, 5.7, 5.7 Hz, 2H), 5.35 (ddt, *J* = 17.3, 1.6, 1.3 Hz, 2H), 5.27 (ddt, *J* = 10.4, 1.3, 1.3 Hz, 2H), 4.69 (ddd, *J* = 5.3, 1.3, 1.3 Hz, 4H), 3.22 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 168.8, 131.7, 118.4, 93.1, 65.2, 28.5; IR (Neat film, NaCl) 1666, 1647, 1684, 1451, 1389, 1329, 1219,

1204, 1133, 1061, 961, 843, 783 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{16}O_6$ $[M]^+$: 280.0947, found 280.0948.



Bis(β-ketoester) 186. Prior to use in the reaction, acetone was dried by stirring it over anhydrous calcium sulfate, and then was passing the solvent over a short plug of silica. Potassium carbonate (5.80 g, 43.9 mmol, 4.10 equiv) and diallyl succinylsuccinate (**189**, 3.00 g, 10.7 mmol, 1.00 equiv) were suspended in acetone (21.3 mL). After addition of solvent to the solids, the reaction mixture was fitted with a reflux condenser and then was heated to 50 °C. To this mixture was added methyl iodide (3.40 mL, 54.5 mmol, 5.10 equiv). The reaction was stirred vigorously to ensure completion. (Note: If reaction is not stirred, or if stirring is not efficient, potassium carbonate will collect into a solid aggregate and the reaction will halt. Breaking up these solid collections with a spatula is typically enough to reinitiate reaction, though in some cases additional methyl iodide may be required.) After 6 h, the reaction was allowed to cool and then was passed through filter paper. The remaining solids were washed with additional CH_2Cl_2 to ensure complete solvation of any precipitated product trapped within the potassium carbonate. The collected organic layers were combined and concentrated to yield an amorphous semi-solid, which was purified over silica gel using 15% → 20% ethyl acetate in hexanes as eluent. Compound **186** was afforded as two diastereomers in a 1 : 1 ratio. The less polar diastereomer (by TLC analysis with 20% ethyl acetate in hexane) was obtained as a white, fluffy solid, and the more polar diastereomer was obtained as a thick, yellow oil

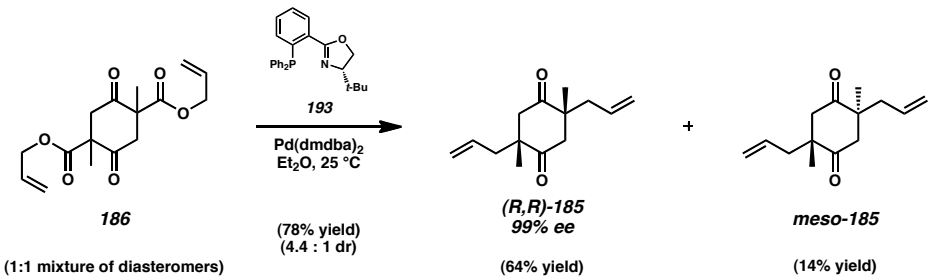
(1.4 g for each diastereomer, 2.8 g for combined diastereomers, 85% yield). **Diastereomer A**: R_f = 0.30 (20:80 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (dddd, *J* = 17.3, 10.4, 5.8, 5.8 Hz, 2H), 5.30 (app dq, *J* = 17.3, 1.3 Hz, 2H), δ 5.26 (app dq, *J* = 10.4, 1.3 Hz, 2H), δ 4.60 (app ddd, *J* = 5.9, 1.3, 1.3 Hz, 4H), δ 3.14 (d, *J* = 15.2 Hz, 2H), δ 2.80 (d, *J* = 15.2 Hz, 2H), δ 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 170.6, 131.0, 119.7, 66.8, 57.6, 48.1, 20.8; IR (Neat film, NaCl) 2988, 2940, 1749, 1708, 1420, 1375, 1281, 1227, 1132, 1076, 911, 809, 744 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{20}O_6$ [M^+]: 308.1260, found 308.1263. **Diastereomer B**: R_f = 0.20 (20:80 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 17.1, 10.4, 5.7, 5.7 Hz, 2H), δ 5.31 (app dq, *J* = 17.2, 1.5 Hz, 2H), δ 5.27 (app dq, *J* = 10.3, 1.5, 2H), δ 4.62 (app ddd, *J* = 5.4, 1.5, 1.5 Hz, 4H), δ 3.47 (d, *J* = 15.6 Hz, 2H), δ 2.63 (d, *J* = 15.9 Hz, 2H), δ 1.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 169.9, 131.1, 119.1, 66.7, 56.6, 47.1, 21.5; IR (Neat film, NaCl) 3088, 2984, 2940, 1747, 1722, 1649, 1454, 1422, 1381, 1275, 1233, 1196, 1110, 984, 934 cm^{-1}. HRMS (EI) *m/z* calc'd for $C_{16}H_{20}O_6$ [M^+]: 308.1260, found 308.1263.



187 ***186***

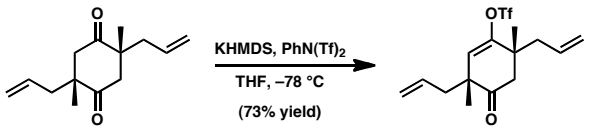
Alternative preparation of bis(β-ketoester) 186.[10] A flame dried round bottom flask was charged with NaH (60% in mineral oil, 4.44 g, 111.0 mmol, 2.2 equiv). The flask was briefly vacuum purged, and then was backfilled with argon. The solid NaH was then suspended in freshly distilled (or freshly dispensed) THF (40 mL). The

resulting suspension was cooled to 0 °C in an ice water bath. After cooling, the NaH slurry was treated with a THF solution (20 mL) of diallyl succinate (**187**, 10.0 g, 50.4 mmol) added via cannula. The reaction was allowed to gradually warm to room temperature overnight (12 h). The next morning the reaction was heated to 40 °C to encourage completion of the Claisen condensation/Dieckmann cyclization process. After 24 h at this temperature, TLC analysis revealed total consumption of diallyl succinate (**187**). The reaction was cooled to 35 °C, and then a single portion of MeI (8.16 mL, 131.2 mmol, 2.6 equiv) was introduced via syringe. After an additional 12 h at 35 °C, the reaction was quenched with saturated $NH_4Cl_{(aq)}$ (40 mL). The organic layer was separated from the aqueous layer, and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and filtered. The crude material obtained upon removal of solvent in vacuo was further purified via column chromatography over silica using 15% → 20% ethyl acetate in hexanes as eluent. Compound **186** was afforded as two diastereomers in a 1 : 1 ratio, again as both a white solid and a clear oil (2.1 g for each diastereomer, 4.2 g for combined diastereomers, 54% yield). All spectroscopic data was identical to that reported above.



Diketone 185. A flame dried round bottom flask cooled under argon was charged with bis(3,5-dimethoxydibenzylideneacetone)palladium(0) ($Pd(dmdba)_2$, 0.268 g, 0.330 mmol, 0.05 equiv) and (*S*)-*t*-BuPHOX (**193**) (0.140 g, 0.362 mmol, 0.055 equiv). The flask was purged under vacuum briefly, and then backfilled with argon. The solids were dissolved in Et_2O (500 mL), and the resulting solution was stirred at 25 °C for 30 min. After precomplexation, neat **186** (2.00 g, 6.59 mmol, 1.00 equiv) was added to the reaction. The solution was stirred vigorously at 25 °C for 10 h (Note: continual stirring is necessary due to the apparent low solubility of $Pd(dmdba)_2$ in Et_2O.), after which time the solvent was removed in vacuo. The crude oil was purified over silica gel using 3% ethyl acetate in hexanes as eluent to afford **185** as a colorless oil (1.07 g, 78% yield, 4.4 : 1 dr, 99% *ee*): R_f = 0.7 (15:85 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (dddd, *J* = 18.3, 10.2, 6.9, 6.9 Hz, 2H), 5.17–5.09 (comp. m, 3H), 5.07–5.04 (m, 1H), 2.82 (d, *J* = 14.7 Hz, 2H), 2.38 (d, *J* = 15 Hz, 2H), 2.34 (app ddt, *J* = 13.2, 6.9, 1.0 Hz, 2H), 2.09 (app ddt, *J* = 13.5, 7.8, 0.9 Hz, 2H), 1.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 132.4, 120.0, 49.4, 48.4, 43.8, 24.3; IR (Neat film, NaCl) 3078, 2978, 1712, 1640, 1458, 1378, 1252, 1129, 1101, 998, 921 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{20}O_2$ $[M]^+$: 220.1463, found 220.1466; $[\alpha]^{25}_D$ –163.1 (*c* 0.52, CH_2Cl_2). Chiral GC assay (GTA column): 100 °C isothermal method over 90 min. Retention times: 67.7 min (Major enantiomer, C_2 diastereomer, 81.7%), 74.1 min (Minor enantiomer, C_2

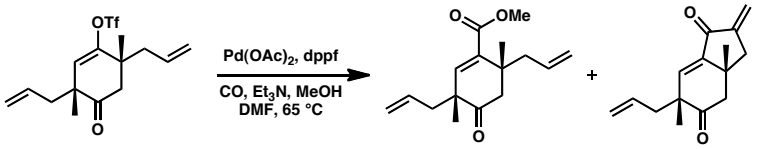
diastereomer, 0.6%), 77.4 min (*meso* diastereomer, 17.6%). Achiral GC assay (DB-Wax column): 100 °C isotherm over 2.0 min, ramp 5 °C/min to 190 °C, then 190 °C isotherm for 10.0 min. Retention times: 18.5 min (C_2 diastereomer, 81.0%), 18.7 min (*meso* diastereomer, 19.0%).



185 ***194***

Triflate 194. A flask was charged with potassium bis(trimethylsilyl)amide (1.49 g, 7.49 mmol, 1.10 equiv) in the glovebox, and then was transferred to a manifold line outside of the glovebox under argon. The solids were dissolved in THF (180 mL), and the resulting solution was stirred while being cooled to –78 °C. To this alkaline solution was added, dropwise, neat diketone **185** (1.50 g, 6.80 mmol, 1.00 equiv). The solution immediately turned yellow, and viscosity increased. Deprotonation was allowed over 30 min, after which time the anionic solution was transferred by cannula into a solution of *N*-phenyl bis(trifluoromethane)sulfonimide (2.91 g, 8.17 mmol, 1.20 equiv) in THF (60 mL) at –78 °C. Reaction was allowed to proceed at this temperature over 6 h, after which time the mixture was brought to room temperature. The anionic reaction was quenched with brine (100 mL). The phases were separated, and the aqueous layer was extracted with diethyl ether (3 x 100 mL) and ethyl acetate (1 x 100 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude oil obtained was loaded onto a silica gel column and eluted with 2% Et_2O in pentane. This afforded triflate **194** as a colorless oil (1.75 g, 73%

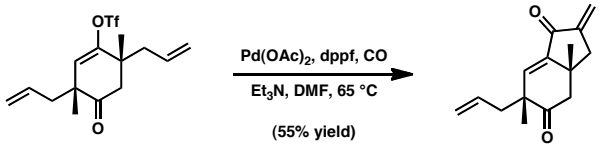
yield). R_f = 0.40 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.58 (comp. m, 2H), 5.63 (s, 1H), 5.22–5.03 (comp. m, 4H), 2.71 (d, *J* = 14.3 Hz, 1H), 2.40 (d, *J* = 14.4 Hz, 1H), 2.49–2.30 (comp. m, 2H), 2.24 (app ddt, *J* = 13.5, 6.9, 1.3 Hz, 1H), 2.09 (app ddt, *J* = 13.8, 8.24, 1.2 Hz, 1H), 1.22 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 152.0, 132.6, 132.1, 122.9, 120.6, 119.7, 49.2, 48.9, 43.8, 43.0, 42.1, 25.2, 24.6; IR (Neat film, NaCl) 3081, 2980, 2934, 1721, 1673, 1641, 1457, 1416, 1214, 1141, 1010, 923.6, 895.2, 836.2 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{19}O_4SF_3$ [M^+]: 352.0956, found 352.0949; $[\alpha]^{25}_D$ –6.5 (*c* 1.15, CH_2Cl_2).



194 ***195*** (64% yield) ***196*** (1% yield)

Enoate 195. A flame dried round bottom flask was charged with $Pd(OAc)_2$ (0.089 g, 0.397 mmol, 0.07 equiv) and dppf (0.315 g, 0.568 mmol, 0.10 equiv). The solids were briefly vacuum purged, and then the flask was backfilled with nitrogen. To the palladium and ligand were added, in sequence, DMF (67 ml), MeOH (4.6 mL), triflate **194** (2.01 g, 5.68 mmol, 1.00 equiv), and triethyl amine (2.37 mL, 17.0 mmol, 3.00 equiv). The resulting solution was sparged for 10 min with an overpressure of carbon monoxide. After this time had elapsed, the reaction was fitted with a double-walled balloon of carbon monoxide to preserve gas overpressure, and then was heated to 65 °C for 10 h. Once the reaction had completed by TLC analysis, a majority of the DMF solvent was removed in vacuo. The crude residue obtained was dissolved in CH_2Cl_2 (50 mL) and was washed with brine (30 mL). The layers were separated, and the aqueous layer was

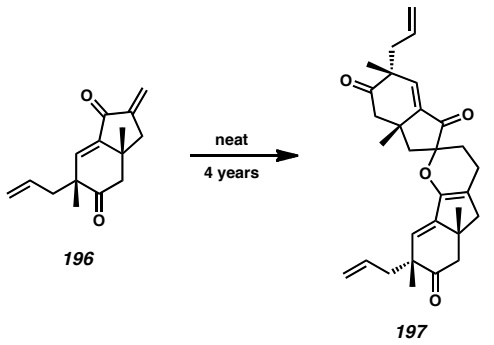
thereafter extracted with CH_2Cl_2 (4 x 30 mL). Combined organics were washed with brine (50 mL), then were dried over $MgSO_4$ and filtered. The crude product was purified via chromatography over silica gel, using 2% → 3% → 4% → 5% ethyl acetate in hexanes, followed by 100% diethyl ether, as eluent. This afforded enoate **195** (848 mg, 54% yield) and dienone **196** (17.0 mg, 1% yield), both as clear oils: Data for enoate **195** was observed as follows: R_f = 0.30 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 1H), 5.70–5.58 (m, 2H), 5.09–4.99 (m, 4H), 3.75 (s, 3H), 2.69 (dd, *J* = 13.9, 6.3 Hz, 2H), 2.36 (app ddt, *J* = 13.6, 8.1, 0.9 Hz, 1H), 2.26 (app ddt, *J* = 13.7, 6.9, 1.2 Hz, 1H), 2.15 (dd, *J* = 13.9, 7.3 Hz, 2H), 1.23 (s, 3H), 1.16, (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.5, 167.1, 144.8, 136.4, 134.1, 132.9, 119.1, 119.0, 51.8, 50.1, 49.0, 44.2, 43.9, 41.9, 27.5, 23.3; IR (Neat film, NaCl) 3077, 29.54, 2871, 1717, 1639, 1436, 1326, 1244, 1063, 995, 920 cm^{-1}; HRMS *m/z* calc'd for $C_{16}H_{22}O_3$ [M+H]: 263.1642, found 263.1649; $[\alpha]^{25}_D$ –85.9 (*c* 0.62, CH_2Cl_2).



194 *196*

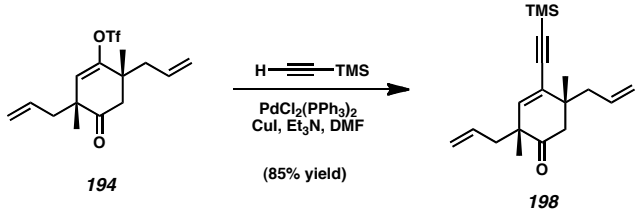
Dieneone 196. A flame dried round bottom flask was charged with $Pd(OAc)_2$ (10.0 mg, 45.0 μmol, 0.07 equiv) and dppf (31.0 mg, 56.0 μmol, 0.10 equiv). The solids were briefly vacuum purged, and then the flask was backfilled with nitrogen. To the palladium and ligand were added, in sequence, DMF (5.5 ml), triflate **194** (200 mg, 0.568 mmol, 1.0 equiv), and triethyl amine (237 μL, 1.70 mmol, 3.0 equiv). The resulting solution was sparged for 15 min with an overpressure of carbon monoxide. After this time had

elapsed, the reaction was fitted with a double-walled balloon of carbon monoxide to preserve gas overpressure, and then was heated to 65 °C for 3 h. Once the reaction had completed by TLC analysis, a majority of the DMF solvent was removed in vacuo. The crude residue obtained was dissolved in ethyl acetate (50 mL) and was washed with brine (30 mL). The layers were separated, and the aqueous layer was thereafter extracted with ethyl acetate (4 x 30 mL). The combined organics were washed with brine (30 mL), then were dried over $MgSO_4$ and filtered. The crude product was purified via chromatography over silica gel, using 2% → 3% ethyl acetate in hexanes, followed by 100% diethyl ether, as eluent. This afforded dieneone **196** as a clear oil (67 mg, 55% yield): R_f = 0.30 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.19 (ddd, *J* = 3.4, 1.6, 0.9 Hz, 1H), 5.62 (dddd, *J* = 16.8, 10.1, 8.5, 6.6 Hz, 1H), 5.52–5.49 (m, 1H), 5.05 (dddd, *J* = 16.9, 4.5, 2.3, 1.2 Hz, 2H), 2.69 (app dt, *J* = 15.8, 1.6 Hz, 1H), 2.64 (d, *J* = 13.8 Hz, 1H), 2.57 (app dt, *J* = 15.9, 3.1 Hz, 1H), 2.46 (dd, *J* = 13.8, 0.6 Hz, 1H), 2.37 (app ddt, *J* = 13.5, 8.5, 1.0 Hz, 1H), 2.27 (app ddt, *J* = 13.5, 6.5, 1.5 Hz, 1H), 1.24 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.2, 192.9, 144.9, 144.3, 137.9, 132.7, 120.3, 119.4, 52.4, 48.8, 45.6, 43.1, 39.7, 27.9, 23.2; IR (Neat film, NaCl) 2958, 2929, 1711, 1657, 1639, 1454, 1437, 1399, 1378, 1259, 1156, 1131, 929 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{18}O_2$ [M^+]: 230.1307, found 230.1313; $[\alpha]^{25}_D$ –130.8 (*c* 0.50, CH_2Cl_2).



196 *197*

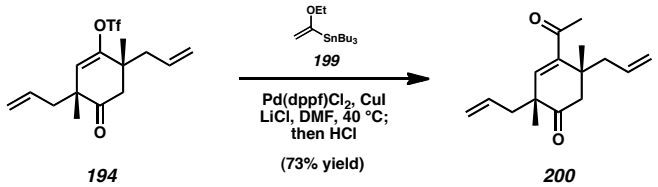
Spirocyclic dimer 197. Upon allowing dienone **196** to stand neat for ca. four years, repurification over silica using 2% ethyl acetate in hexanes as eluent afforded spirocyclic dimer **197** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 5.76–5.59 (m, 2H), 5.39 (s, 1H), 5.12–4.96 (comp. m, 4H), 2.62 (d, *J* = 13.6 Hz, 2H), 2.56–2.05 (comp. m, 6H), 2.48 (d, *J* = 10.6 Hz, 2H), 2.31 (d, *J* = 13.6 Hz, 2H), 2.10 (d, *J* = 12.3 Hz, 2H), 2.00–1.90 (m, 2H), 1.33–1.04 (m, 2H), 1.26 (s, 3H), 1.19 (s, 6H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 211.9, 201.5, 147.2, 144.8, 142.4, 140.8, 133.9, 132.4, 119.7, 118.2, 117.6, 114.4, 81.5, 53.9, 52.0, 49.0, 48.2, 47.8, 46.5, 45.4, 45.2, 41.2, 37.5, 29.3, 29.0, 28.8, 24.8, 23.1, 20.2; IR (Neat film, NaCl) 2960, 2928, 1711, 1651, 1451, 1395, 1280, 1157, 1124, 917 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{30}H_{38}O_4$ [M+H]: 461.2686, found 461.2701; $[\alpha]^{25}_{D}$ –98.6 (*c* 0.39, CH_2Cl_2).



194 *198*

Enyne 198. To a flame dried flask was added $PdCl_2(PPh_3)_2$ (59 mg, 85.0 μmol, 0.1 equiv) and CuI (10 mg, 52.0 μmol, 0.05 equiv). These solids were briefly vacuum purged, and then the flask was backfilled with nitrogen. The metal salts were thereafter

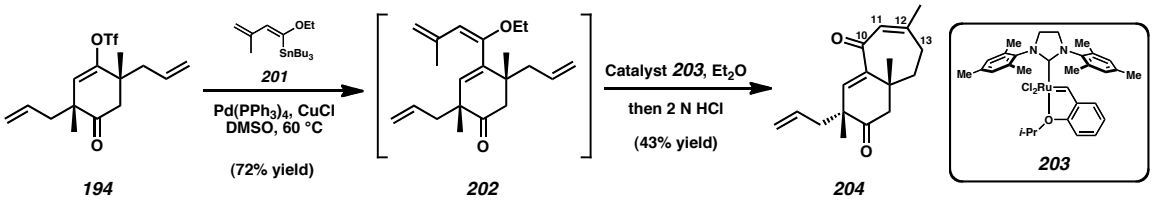
dissolved in DMF (5.1 mL), and treated with triethyl amine (356 μL, 2.55 mmol, 3.00 equiv), triflate **194** (300 mg, 0.851 mmol, 1.00 equiv), and (trimethylsilyl)acetylene (241 μL, 1.70 mmol, 2.0 equiv). The resulting solution was stirred at room temperature for 4 h, after which time the reaction had completed. The reaction was quenched by the addition of brine (10 mL), followed by extraction with diethyl ether (4 x 20 mL). The combined organics were washed with brine (10 mL), then were dried over $MgSO_4$ and filtered. The crude material isolated was purified silica gel chromatography using 2% ethyl acetate in hexanes as eluent. Enyne **198** was isolated as a clear oil (218 mg, 85% yield): R_f = 0.50 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.80 (dddd, *J* = 16.6, 10.1, 8.4, 6.3 Hz, 1H), 5.66 (dddd, *J* = 17.0, 10.2, 8.1, 6.9 Hz, 1H), 5.14–5.01 (comp. m, 4H), 2.60 (d, *J* = 13.9 Hz, 1H), 2.43 (app ddt, *J* = 13.7, 6.3, 1.3 Hz, 1H), 2.31 (app ddt, *J* = 13.7, 8.1, 1.0 Hz, 1H), 2.20 (app ddt, *J* = 13.6, 6.9, 1.3 Hz, 1H), 2.19 (d, *J* = 13.9 Hz, 1H), 2.03 (app ddt, *J* = 13.7, 8.4, 1.0 Hz, 1H), 1.12 (s, 3H), 1.10 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 141.2, 134.3, 133.3, 128.5, 118.9, 118.8, 103.2, 95.8, 49.3, 48.5, 45.3, 44.5, 42.5, 27.5, 23.6, 0.1; IR (Neat film, NaCl) 3077, 2962, 2144, 1717, 1638, 1457, 1375, 1250, 1147, 996, 843 cm^{-1}; HRMS *m/z* calc'd for $C_{19}H_{28}OSi$ [M+H]: 301.1982, found 301.1980; $[\alpha]^{25}_D$ –88.3 (*c* 0.33, CH_2Cl_2).



Enone 200. To a flame dried round bottom flask under argon was added Pd(dppf)Cl_2 (116 mg, 0.142 mmol, 0.10 equiv), CuI (27 mg, 0.142 mmol, 0.10 equiv), and LiCl (319

mg, 7.52 mmol, 5.3 equiv). These solids were briefly vacuum purged before being backfilled with argon, and then were dissolved in DMF (20 mL). The resulting solution was then treated with triflate **194** (500 mg, 1.42 mmol, 1.0 equiv) and tributylethoxyvinyl stannane (**199**, 623 μL, 1.84 mmol, 1.3 equiv). Subsequent to the addition of all reagents, the reaction was freeze-pump-thawed, and then was heated to 40 °C. After 9 h at 40 °C, the reaction was cooled to room temperature and diluted with brine (40 mL). The resulting solution was extracted with diethyl ether (3 x 40 mL), and the combined organic layers were washed with additional brine (2 x 30 mL). The combined aqueous layers were thereafter back-extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers from all extractions were dried over $MgSO_4$, filtered, and solvent was removed in vacuo. The crude material obtained after removal of solvent was then redissolved in CH_2Cl_2 (40 mL) and stirred with 2 N $HCl_{(aq)}$ (20 mL) for 2 h. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material obtained was purified via silica gel chromatography using 2% → 3% ethyl acetate in hexanes as eluent. This afforded enone **200** as a clear oil (255 mg, 73%): R_f = 0.50 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (s, 1H), 5.68 (dddd, *J* = 16.9, 10.1, 8.2, 6.9 Hz, 1H), 5.57 (app dt, *J* = 17.5, 10.2, 7.5 Hz, 1H), 5.13–4.96 (m, 4H), 2.75 (app ddt, *J* = 13.5, 7.0, 1.0 Hz, 1H), 2.69 (d, *J* = 13.8 Hz, 1H), 2.39 (app ddt, *J* = 13.6, 8.2, 0.8 Hz, 1H), 2.32 (s, 3H), 2.29 (app ddt, *J* = 13.5, 6.8, 1.3 Hz, 1H), 2.12 (d, *J* = 13.9 Hz, 1H), 2.03 (app ddt, *J* = 13.8, 7.6, 1.2 Hz, 1H), 1.22 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4, 199.8, 145.1, 145.0, 134.3, 132.8, 119.3, 118.9, 50.5, 49.1, 44.5, 43.4, 42.7, 28.1, 27.7, 23.2; IR (Neat film, NaCl) 3077, 2977, 2930, 2869, 1717, 1676, 1637,

1540, 1457, 1365, 1235, 995, 919 cm^{-1}; HRMS *m/z* calc'd for $C_{16}H_{22}O_2$ [M+H]: 247.1693, found 247.1699; $[\alpha]^{25}_D$ –60.4 (*c* 0.33, CH_2Cl_2).

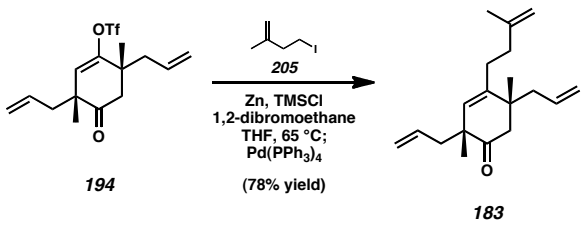


Enol ether 204. To a round bottom flask was added LiCl (64 mg, 1.50 mmol, 6.0 equiv). This flask was flame dried, backfilled with argon, and then was transferred to the glovebox. Once inside the glovebox, $Pd(PPh_3)_4$ (29 mg, 25.0 μmol, 0.1 equiv) and CuCl (124 mg, 1.25 mmol, 5.0 equiv) were added to the flask. The flask was removed from the glovebox and was transferred to a manifold line. The solids were briefly purged under vacuum, then were backfilled with argon. Afterwards, the solids were dissolved in DMSO (2.0 mL), resulting in an immediate black solution. The flask was wrapped with aluminium foil to shield from light, and then triflate **194** (88 mg, 0.250 mmol, 1.0 equiv) and enol stannane **201** (120 mg, 0.300 mmol, 1.2 equiv) were added. The solution was freeze-pump-thawed thrice, and then was heated to 60 °C. After 24 h, the reaction was cooled to room temperature and diluted with brine (4 mL). To this mixture was added ethyl acetate (5 mL), and the phases were separated. The ethyl acetate layer was separated, then was washed with brine (5 mL) and saturated $NH_4Cl_{(aq)}$ (2 x 20 mL). Combined aqueous layers were extracted with ethyl acetate (3 x 30 mL), and the resulting combined organic layers were washed with brine (40 mL). After washing, the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material obtained was purified via chromatography over silica gel, using 1% → 2% → 5% diethyl

ether in pentane. This afforded crude enol ether **202** as a clear oil. This material was carried directly into the next reaction without further purification or characterization, due to tautomeric instability.

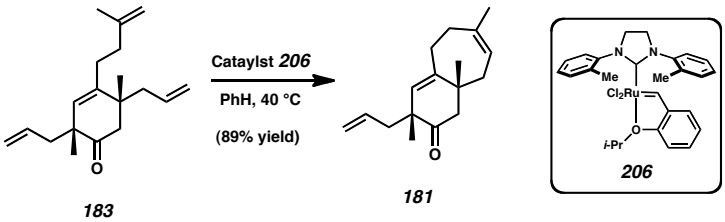
To a flame dried flask under argon was added crude **202** from the previous reaction sequence. This oil was dissolved in acetonitrile and azeotroped three times, and then was dried briefly under vacuum to remove residual solvent. The residue obtained was dissolved in diethyl ether (24 mL, **Note:** Diethyl ether was mistakenly added in this reaction, as CH_2Cl_2 was the intended solvent), and then was treated with the Grubbs–Hoveyda second-generation catalyst (**203**, 18 mg, 21.0 μmol, 0.05 equiv). The reaction was heated to 30 °C for 30 min, and then was cooled to room temperature and quenched with saturated $NaHCO_{3(aq)}$. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), then were dried over $MgSO_4$ and filtered. In order to prevent purification difficulties resulting from partial decomposition of the enol ether moiety on silica, the enol ether was pre-emptively cleaved to reveal the ketone. The crude product oil was redissolved in diethyl ether (25 mL) and was stirred with 2 N $HCl_{(aq)}$ (25 mL) for 30 min. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), then were dried over $MgSO_4$ and filtered. After concentrating in vacuo, the crude residue obtained was purified via chromatography over silica gel using 50% benzene in hexanes as eluent. This afforded bicyclic enone **204** as a clear oil, and as a mixture of diastereomers (19.7 mg, 30% yield). **Diastereomer A**: R_f = 0.30 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (s, 1H), 6.06 (dd, *J* = 2.3, 1.2 Hz, 1H), 5.66 (dddd, *J* = 17.0, 10.2,

8.2, 6.8 Hz, 1H), 5.08–5.00 (comp. m, 2H), 2.57 (dd, *J* = 13.7, 0.6 Hz, 1H), 2.49 (dddd, *J* = 7.1, 3.3, 1.3, 0.8 Hz, 1H), 2.45 (dddd, *J* = 7.0, 3.2, 1.2, 0.8 Hz, 1H), 2.39 (app ddt, *J* = 13.6, 8.2, 0.9 Hz, 1H), 2.25 (d, 13.7 Hz, 1H), 2.24 (app ddt, *J* = 13.5, 6.8, 1.2 Hz, 1H), 1.97 (app t, *J* = 0.5 Hz, 3H), 1.89 (ddd, *J* = 14.4, 9.5, 3.4 Hz, 1H), 1.69 (ddd, *J* = 14.4, 7.1, 3.7 Hz, 1H), 1.21 (s, 3H), 1.12 (app d, *J* = 0.6 Hz. 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9, 193.1, 157.9, 146.5, 140.3, 133.2, 129.9, 119.0, 52.9, 49.1, 44.9, 39.2, 38.6, 32.8, 27.2, 26.4, 23.4; IR (Neat film, NaCl) 2964, 2929, 1716, 1648, 1593, 1456, 1436, 1418, 1375, 1266 cm^{-1}. HRMS *m/z* calc'd for $C_{17}H_{22}O_2$ [M+H]: 259.1693, found 259.1694; $[\alpha]^{25}_D$ –112.6 (*c* 0.28, CH_2Cl_2). **Diastereomer B**: R_f = 0.25 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (s, 3H), 6.06 (dd, *J* = 2.4, 1.2, Hz, 1H), 5.66 (dddd, *J* = 17.2, 10.1, 7.8, 7.2 Hz, 1H), 5.08–5.02 (comp. m, 2H), 2.67 (dd, *J* = 13.5, 0.6 Hz, 1H), 2.54 (app ddt, 13.6, 7.9, 1.0 Hz, 1H), 2.47–2.34 (comp. m, 2H), 2.26 (app ddt, *J* = 13.6, 7.1, 1.2 Hz, 1H), 2.20 (d, *J* = 13.5 Hz, 1H), 1.96 (d, *J* = 1.1 Hz, 2H), 1.91 (ddd, *J* = 14.3, 9.5, 3.9 Hz, 1H), 1.68 (ddd, *J* = 14.4, 6.5, 4.1 Hz, 1H), 1.21 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.6, 192.8, 157.2, 146.2, 140.3, 133.5, 129.9, 119.0, 51.9, 49.2, 41.9, 39.4, 38.5, 33.1, 27.1, 25.9, 25.5; IR (Neat film, NaCl) 2927, 1715, 1647, 1591, 1451, 1378, 1270, 1034, 919 cm^{-1}; HRMS *m/z* calc'd for $C_{17}H_{22}O_2$ [M+H]: 259.1693, found 259.1700; $[\alpha]^{25}_D$ –35.6 (*c* 0.28, CH_2Cl_2).



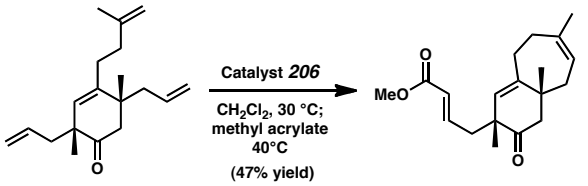
Tetraene 183. To a flame dried Schlenk flask backfilled with argon was added powdered Zn metal (3.20 g, 48.9 mmol, 7.5 equiv). After a brief vacuum purge and argon backfill, the metal was suspended in THF (45 mL). To this suspension was cannula transferred a prepared solution of 1,2-dibromoethane (0.675 mL, 7.83 mmol, 1.2 equiv) and trimethylsilyl chloride (0.271 mL, 2.13 mmol, 0.33 equiv) in THF (22.5 mL). The reaction vessel was sealed, then heated to 65 °C for 15 min. After this time had elapsed, the reaction was cooled to room temperature, and a solution of 4-iodo-2-methyl-1-butene (**205**, 1.92 g, 9.79 mmol, 1.5 equiv) in THF (22.5 mL) was cannula transferred into the suspension of activated Zn metal. The reaction vessel was sealed once again, and then was heated to 65 °C for 2 h. After this time had elapsed, the reaction was cooled to room temperature, and a prepared solution of triflate **194** (2.3 g, 6.53 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (0.377g, 0.33 mmol, 0.05 equiv) in THF (45 mL) was added to the alkyl zinc solution via cannula. The reaction was sealed and heated to 65 °C for 3 h. After reaction had completed by TLC, it was cooled to room temperature and filtered over a Celite pad with copious washing with Et_2O. The filtrate then was diluted with brine and extracted with Et_2O (4 x 100 mL). The combined organic layers were washed with brine (40 mL), followed by saturated $Na_2S_2O_{3(aq)}$ (40 mL) to removed colored impurities. The washed organic layers were dried over $MgSO_4$, filtered, and then solvent was removed in vacuo. The crude material obtained was then purified over silica gel using 0.5% → 1.0% → 1.5% → 3.0% Et_2O in petroleum ether as eluent. This afforded tetraene **183** as a

colorless oil (1.40 g, 78%): R_f = 0.50 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.61 (comp. m, 2H), 5.20 (s, 1H), 5.10–4.97 (comp. m, 4H), 4.74 (d, *J* = 8.8 Hz, 2H), 2.56 (d, *J* = 13.5 Hz, 1H), 2.40–2.13 (comp. m, 8H), 2.05–1.98 (m, 1H), 1.77 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) d 214.4, 145.5, 142.5, 134.1, 134.0, 128.6, 118.6, 117.9, 110.1, 49.5, 48.7, 44.4, 44.3, 43.2, 36.5, 28.6, 26.5, 24.7, 22.7; IR (Neat film, NaCl) 3076, 2996, 2928, 2360, 1715, 1639, 1455, 1376, 1320, 1298, 1261, 1229, 1138, 1093, 996, 916, 887 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{19}H_{28}O$ [M^+]: 272.2140, found 272.2138; $[\alpha]^{25}_D$ –72.4 (*c* 0.22, CH_2Cl_2).



Bicyclic triolefin 181. To a flame dried flask was added tetraolefin **183** (160 mg, 588 mmol, 1.00 equiv). This oil was dissolved in benzene (5 mL), and then azeotroped from this solvent. This process was repeated three times, and then the resulting residue was dissolved in benzene (28 mL) and sparged with argon for 30 min. After the sparge time had elapsed, a single portion of Grubbs–Hoveyda catalyst **206** (34.0 mg, 59.0 μmol, 0.10 equiv) was added to the solution. The reaction was then heated to 40 °C. (Note: tetraolefin **183** and bicyclic triolefin **181** are difficult to separate by TLC in a wide variety of solvent systems, and frequently are seen to co-spot. In order to afford more efficient separation via TLC, the use of silver nitrate treated silica gel TLC plates is very effective.) After 20 min at 40 °C, the reaction had completed by TLC, and so was quenched via the addition of ethyl vinyl ether (20 mL). The solvents were removed in

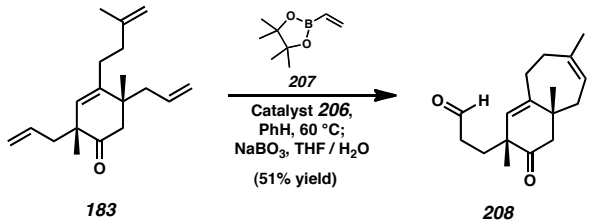
vacuo, and the resulting crude mixture was purified via chromatography over silica gel using 0.5% → 1.0% → 1.5% → 3.0% Et_2O in petroleum ether as eluent. This afforded bicyclic triene **121** as a colorless oil (128 mg, 89% yield): R_f = 0.50 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (dddd, *J* = 16.8, 10.2, 8.4, 6.5 Hz, 1H), 5.33 (dddd, *J* = 6.9, 5.4, 2.9, 1.5 Hz, 1H), 5.19 (s, 1H), 5.01–4.93 (comp. m, 2H), 2.73 (dd, *J* = 13.4, 0.6 Hz, 1H), 2.53 (dddd, *J* = 13.2, 11.7, 5.3, 0.6 Hz, 1H), 2.45–2.39 (m, 2H), 2.22–2.17 (m, 1H), 2.22 (app ddt, *J* = 13.5, 8.4, 0.9 Hz, 1H), 2.11–2.03 (m, 2H), 2.11 (app ddt, *J* = 13.5, 6.5, 1.4 Hz, 1H), 2.03 (d, *J* = 13.5 Hz, 1H), 1.65 (s, 3H), 1.10 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.6, 145.3, 138.5, 134.0, 129.2, 120.2, 117.8, 51.7, 49.0, 46.3, 44.9, 37.4, 29.5, 28.1, 25.8, 23.7; IR (Neat film, NaCl) 3076, 2961, 2927, 1711, 1639, 1452, 1372, 1225, 1163, 997, 916 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{24}O$ [M^+]: 244.1827, found 244.1821; $[\alpha]^{25}_D$ –96.7 (*c* 1.33, CH_2Cl_2).



183 *209*

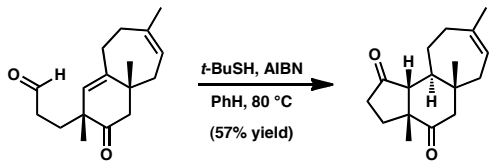
Enoate 209. To a flame dried flask under argon was added tetraolefin **183** (49.0 mg, 0.180 mmol, 1.00 equiv). This material was dissolved in benzene and azeotroped thrice, then briefly dried under high vacuum to remove residual solvent. The flask was then charged with Grubbs–Hoveyda catalyst **206** (7.0 mg, 9.0 μmol, 0.05 equiv) and CH_2Cl_2 (12 mL) and was heated to 30 °C. The reaction was allowed to stir at this temperature for 20 min, after which time TLC analysis showed complete conversion of the starting material to the ring-closed product. After 20 min had elapsed the reaction was treated

with methyl acrylate (243 μL, 2.70 mmol, 15 equiv) in a single portion, and the heat was increased to 40 °C. After 4 h, the reaction was quenched via the addition of water (20 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material obtained was purified via chromatography over silica gel using 3% → 5% ethyl acetate in hexanes as eluent. This afforded enoate **209** as a colorless oil (25.0 mg, 47% yield): R_f = 0.10 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (ddd, *J* = 15.7, 8.7, 7.1 Hz, 1H), 5.75 (app dt, *J* = 15.7, 1.3 Hz, 1H), 5.33 (dddd, *J* = 7.1, 5.6, 3.0, 1.5 Hz, 1H), 3.70 (s, 3H), 2.65 (dd, *J* = 13.6, 0.7 Hz, 1H), (2.58–2.51 (m, 1H), 2.47–2.41 (comp. m, 2H), 2.39 (dd, *J* = 8.7, 1.2 Hz, 1H), 2.37 (dd, *J* = 8.7, 1.2 Hz, 1H), 2.22 (ddd, *J* = 13.6, 7.1, 1.6 Hz, 2H), 2.12–2.02 (m, 2H), 1.68–1.62 (m, 2H), 1.66 (s, 3H), 1.15 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 166.5, 146.6, 144.3, 138.6, 128.2, 123.9, 119.9, 51.4, 49.6, 48.8, 44.8, 44.3, 37.5, 37.4, 29.5, 28.0, 25.8, 24.2; IR (Neat film, NaCl) 2954, 2879, 1725, 1657, 1436, 1374, 1332, 1271, 1200, 1151, 1039, 987, 851, 825 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{19}H_{26}O_3$ [M^+]: 302.1882, found 302.1881; $[\alpha]^{25}_D$ –106.4 (*c* 1.09, CH_2Cl_2).



Bicyclic aldehyde 208. The following reaction was preformed in a glovebox under an atmosphere of nitrogen. To a flame dried flask was added tetraene **183** (100 mg, 0.37 mmol, 1.00 equiv) and PhH (10 mL). The solution was treated with Grubbs–Hoveyda

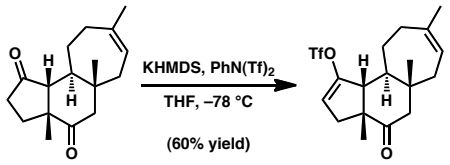
catalyst **206** (23.0 mg, 37.0 μmol, 0.10 equiv) and was heated to 40 °C for 30 min. After this time had elapsed vinyl boronate ester **207**[27] (283 mg, 1.84 mmol, 5.0 equiv) was added via syringe and the temperature was maintained at 40 °C for 20 h. The reaction was then cooled to –20 °C briefly and treated with ethyl vinyl ether (ca. 200 μL) to quench the remaining catalyst. At this stage, the reaction was removed from the glovebox. Solvent was removed in vacuo, and the crude mixture was passed over a short plug of silica gel using 20% ethyl acetate in hexanes as eluent to remove all remaining catalyst and various ruthenium byproducts. The oil obtained was then redissolved in THF (10 mL) and treated with water (10 mL). A single portion of $NaBO_3 \bullet H_2O$ (220 mg, 2.20 mmol, 6.00 equiv) was added, and the reaction was allowed to stir for 1 h. After complete consumption of the boronate was observed via TLC, the phases were separated, and the aqueous phase was extracted with ethyl acetate (4 x 20 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified over silica gel using 5.0% → 7.5% ethyl acetate in hexanes as eluent to afford bicyclic aldehyde **208** as a colorless oil (48.0 mg, 51% yield): R_f = 0.20 (10:90 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (app t, *J* = 1.3 Hz, 1H), 5.38–5.31 (m, 1H), 5.15 (s, 1H), 2.70 (d, *J* = 13.6 Hz, 1H), 2.59–2.32 (comp. m, 5H), 2.12 (d, *J* = 13.8 Hz, 1H), 2.24–2.04 (comp. m, 2 H), 1.89–1.64 (comp. m, 3 H), 1.67 (s, 3H), 1.12 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 201.6, 146.4, 138.7, 129.0, 120.1, 51.6, 47.7, 39.9, 37.6, 37.2, 33.1, 29.6, 27.8, 25.9, 23.9; IR (Neat film, NaCl) 2960, 2927, 2360, 2341, 1711–1710 (overlapping peaks), 1452, 1374, 1296, 1163 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{24}O_2$ [M^+]: 260.1776, found 260.1784; $[\alpha]^{25}_D$ –83.5 (*c* 1.09, CH_2Cl_2).



208 *214*

Tricyclic diketone 214. To a flame dried Schlenk flask was added bicyclic aldehyde **208** (600 mg, 2.32 mmol, 1.0 equiv). Dry PhH (5 mL) was added, then evaporated under vacuum. This azeotropic drying procedure was repeated two additional times, and the resulting material was then dried under high vacuum and backfilled with argon. To this was added *t*-butyl thiol (0.78 mL, 6.91 mmol, 3.0 equiv), AIBN (568 mg, 3.46 mmol, 1.5 equiv), and PhH (20 mL). The reaction was freeze-pump-thawed thrice, and afterward was backfilled with argon. The reaction vessel was sealed and the reaction was heated to 80 °C and allowed to react over 22 h. After this time, the reaction was cooled to room temperature and solvent was removed in vacuo. The crude material was purified over silica gel using a gradient of 5.0% → 7.5% → 10.0% ethyl acetate in hexanes as eluent to afford tricyclic diketone **214** as an amorphous solid (342 mg, 57% yield). An analytically pure sample was prepared via reverse-phase HPLC purification using 30% acetonitrile in water. X-ray diffraction samples were grown via diffusion crystallization of the amorphous solid from acetonitrile and water. R_f = 0.40 (10:90 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (ddq, *J* = 5.13, 5.13, 1.71 Hz, 1 H), 2.65 (d, *J* = 14.5 Hz, 1H), 2.55–2.49 (m, 1H), 2.41–2.28 (m, 2H), 2.27–2.21 (m, 1H), 2.20–2.12 (m, 1H), 2.02 (d, *J* = 14.5 Hz, 1H), 2.01–1.93 (m, 2H), 1.89 (dd, *J* = 12.2, 1.2 Hz, 1H), 1.83–1.72 (m, 3H), 1.74 (s, 3H), 1.09 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.0, 212.8, 142.6, 121.0, 63.2, 52.6, 51.0, 47.8, 42.3, 40.1, 34.4, 32.4, 31.4, 25.4, 24.1, 21.7, 17.3; IR (Neat film, NaCl) 2961, 2926, 2868, 1735, 1705, 1576, 1453, 1380, 1149 cm^{-1};

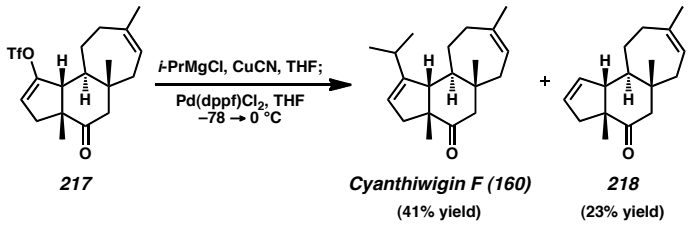
HRMS (EI) *m/z* calc'd for $C_{17}H_{24}O_2$ [M^+]: 260.1777, found 260.1776; $[\alpha]^{25}_D$ –158.6 (*c* 0.925, CH_2Cl_2); mp 94–96 °C.



214 ***217***

Tricyclic triflate 217. To a flame dried flask under argon was added tricyclic diketone **214** (250 mg, 0.960 mmol, 1.0 equiv). Dry PhH (5 mL) was added, then evaporated under vacuum. This azeotropic drying procedure was repeated two additional times, and the resulting material was then dried under high vacuum briefly, then dissolved in THF (10 mL). A separate flame dried flask under argon was charged with potassium bis(trimethylsilyl)amide (211 mg, 1.06 mmol, 1.1 equiv) and THF (10 mL). The flask containing diketone **214** was cooled to –78 °C, and the basic solution was cannula transferred into the cooled solution containing the substrate diketone via a positive pressure of argon. Deprotonation was allowed over 30 min. After this time had elapsed, a solution of *N*-phenyl bis(trifluoromethane)sulfonimide (395 mg, 1.10 mmol, 1.15 equiv) in THF (10 mL) was cannula transferred to the anionic solution under a positive pressure of argon. After 3 h, the reaction was quenched via addition of a solution of saturated $NaHCO_{3\,(aq)}$. The phases were separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed, sequentially, with 2 N $NaOH_{(aq)}$ (30 mL), 2 N $HCl_{(aq)}$ (30 mL), and brine (2 x 30 mL). The organic layers were then dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude material was purified over silica gel using 0.5% → 1.0% ethyl acetate

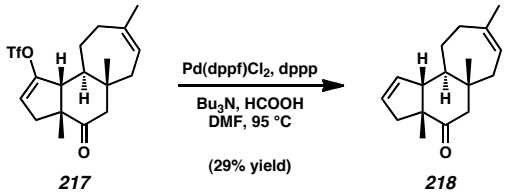
in hexanes as eluent to afford triflate **217** as a white solid (226 mg, 60% yield): R_f = 0.45 (10:90 ethyl acetate/hexane); ^{1}H NMR (500 MHz, C_6D_6) δ 5.16 (ddq, *J* = 5.1, 1.7, 1.7 Hz, 1H), 5.08 (dd, *J* = 3.0, 2.0 Hz, 1H), 2.07 (dd, *J* = 10.7, 2.2 Hz, 1H), 2.02 (br. t, *J* = 13.3 Hz, 1 H), 1.94–1.86 (m, 3H), 1.90 (s, 1H), 1.85 – 1.79 (m, 1H), 1.74 (app ddt, *J* = 14.8, 6.8, 1.5 Hz, 1H), 1.59 (s, 3H), 1.57 (d, *J* = 3.4 Hz, 1H), 1.54 (d, *J* = 3.4 Hz, 1H), 1.38–1.31 (m, 1H), 1.35 (dd, *J* = 14.4, 8.5 Hz, 1H), 1.23 (s, 3H), 0.44 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 209.8, 153.2, 141.9, 121.4, 116.0, 57.6, 54.1, 54.0, 51.2, 41.6, 38.1, 36.5, 32.5, 26.2, 25.0, 23.6, 16.8; IR (Neat film, NaCl) 2932, 1709, 1656, 1423, 1382, 1245, 1211, 1141, 1097, 927 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{23}F_3O_4S$ [M^+]: 392.1269, found 392.1273; $[\alpha]^{25}_D$ –101.9 (*c* 0.63, CH_2Cl_2).



217 ***Cyanthiwigin F (160)*** (41% yield) ***218*** (23% yield)

Cyanthiwigin F (160). To a flame dried 1 dram vial under argon was added CuCN (3.8 mg, 40.0 μmol, 1.5 equiv), followed by 0.5 mL of THF. This suspension was cooled to –78 °C, and to this was dropwise added *i*-PrMgCl (40 μL, 1.91 M solution in THF, 80.0 μmol, 3.00 equiv). After complete addition, the reaction was warmed to 0 °C and allowed to remain at this temperature until a homogeneous pale pink solution was obtained (~10 min). A separate solution was then prepared, consisting of Pd(dppf)Cl_2 (3.0 mg, 5.0 μmol, 0.15 equiv) and triflate species **217** (10.0 mg, 25.0 μmol, 1.00 equiv) dissolved in 0.5 mL of THF. The solution containing **217** was treated with the organocuprate solution via dropwise cannula addition at 0 °C. This was allowed to react

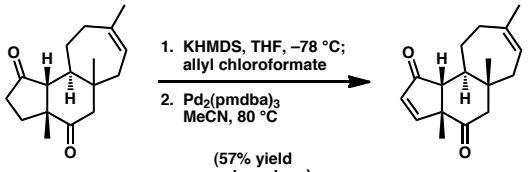
at 0 °C for 3 h, after which time the reaction was quenched with a 1 : 1 mixture of saturated $NH_4Cl_{(aq)}$ and $NH_4OH_{(aq)}$ (1 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified over silica gel using 1% Et_2O in petroleum ether as eluent to afford colorless crystals (4.4 mg, 63% yield, 1.8 : 1 mixture of **160** : **218**). An analytically pure sample of **160** was prepared via reverse-phase HPLC purification using a gradient of 15% → 30% acetonitrile in water. R_f = 0.30 (5:95 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (app q, *J* = 1.6 Hz, 1H), 5.34 (ddq, *J* = 5.1, 1.5, 1.5 Hz, 1H), 2.60 (d, *J* = 16.1 Hz, 1H), 2.50 (d, *J* = 13.7 Hz, 1H), 2.47 (app t, *J* = 6.4 Hz, 1H), 2.24 (app t, *J* = 13.3 Hz, 1H), 2.19–2.17 (m, 1H), 2.15 (d, *J* = 10.3 Hz, 1 H), 1.99 (app ddt, *J* = 14.6, 6.8, 1.5 Hz, 1H), 1.98 (d, *J* = 14.1 Hz, 1H), 1.89 (dd, *J* = 16.1, 2.4 Hz, 1H), 1.84 (app ddt, *J* = 14.2, 6.8, 2.5 Hz, 1H), 1.74 (s, 3H), 1.73 (app dd, *J* = 14.6, 8.3 Hz, 1H), 1.61 (dt, *J* = 11.0, 2.9 Hz, 1H), 1.25 (m, 1H), 1.15 (d, *J* = 6.3 Hz, 3H), 1.09 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 156.5, 141.8, 121.4, 119.9, 59.8, 55.2, 54.7, 54.3, 42.7, 42.2, 37.8, 33.2, 30.3, 26.4, 25.1, 22.8, 22.4, 21.6, 17.3; IR (Neat film, NaCl) 2961, 2924, 1703, 1444, 1380, 1294, 1144, 912, 858, 810 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{20}H_{30}O_2$ [M^+]: 286.2297, found 286.2292; $[\alpha]^{25}_D$ –125.4 (*c* 0.025, MeOH).



217 ***218***

Reduction byproduct 218. This material was obtained as a side product from the cross-coupling attempts to synthesize cyanthiwigin F (**160**), presumably as a result of reduction of the triflate moiety of **217**. Compound **218** was later synthesized directly by the following method: To a flame dried vial containing 22 mg of **217** (22 mg, 56.0 μmol, 1.00 equiv) was added dppp (7.0 mg, 17.0 μmol, 0.30 equiv) and $PdCl_2$(dppf) (5.0 mg, 6.83 μmol, 0.12 equiv). The solids were dissolved in DMF (0.5 mL), and the resulting solution was treated with 114 of Bu_3N (114 μL, 0.479 μmol, 0.009 equiv) and 11 of formic acid (11 μL, 0.292 μmol, 0.005 equiv) (Note: Upon addition of the formic acid, the reaction evolves white smoke). The reaction mixture was heated to 95 °C for 4 h, after which time all of the starting triflate was observed to be consumed by TLC. The reaction was quenched by the addition of brine (1 mL), followed by dilution with Et_2O (2 mL). The aqueous and organic phases were separated, and the aqueous phase was thereafter extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with 2 N $HCl_{(aq)}$ (5 mL) to remove any residual amine, then washed with brine (3 mL). The collected organic phases were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The resulting crude material was purified over silica gel using 2% Et_2O in petroleum ether to afford **218** as a white solid (4.0 mg, 29% yield): R_f = 0.30 (5:95 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00–5.94 (m, 1H), 5.72–5.68 (m, 1H), 5.39–5.30 (m, 1H), 2.55 (ddd, *J* = 16.6, 4.4, 2.2 Hz, 1H), 2.39 (d, *J* = 14.9 Hz, 1H), 2.23 (t, *J* = 13.5 Hz, 1H), 2.18–2.12 (comp. m, 1H), 2.08 (dd, *J* = 2.7, 1.1 Hz, 1H), 2.03 (dd, *J*

= 2.7, 1.2 Hz, 1H), 2.02 (d, *J* = 14.7 Hz, 1H), 2.01 (dddd, *J* = 14.6, 6.9, 1.5, 1.5 Hz 1H), 1.99 (d, *J* = 14.6 Hz, 1H), 1.97–1.94 (m, 1H), 1.75 (s, 3H), 1.61 (s, 1H), 1.43–1.35 (m, 1H), 1.12 (s, 3H), 0.7 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 142.0, 134.9, 128.0, 121.5, 59.4, 55.8, 54.9, 51.9, 43.8, 41.9, 37.5, 33.1, 26.6, 25.3, 23.8, 16.8; IR (Neat film, NaCl) 2961, 2927, 1702, 1559, 1441, 1380, 1293, 1257, 1140, 856, 726 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{24}O$ [M^+]: 244.1827, found 244.1821; $[\alpha]^{25}_D$ –238.4 (*c* 0.02, MeOH).

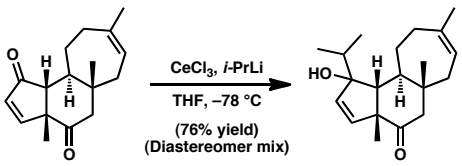


214 ***220***

Tricyclic Enone 220. A flame dried vial charged with tricyclic diketone **214** (22 mg, 77.0 μmol, 1.00 equiv), and this material was thereafter dissolved in THF (200 μL). A separate flame dried vial was backfilled with argon and cycled into a glovebox. Once inside, this vessel was charged with KHMDS (19 mg, 95.0 μmol, 1.30 equiv), and then was removed from the glovebox. Once placed on a manifold line, the KHMDS was dissolved in THF (200 μL). Both solutions were cooled to –78 °C, and then the KHMDS solution was added dropwise to the solution of diketone **214**. The mixed solutions were allowed to deprotonate at –78 °C for 30 min, after which time allyl chloroformate (10 μL, 92.0 μmol, 1.20 equiv) was added. This was allowed to react for a further 2.5 h at –78 °C. Once this time had elapsed, the reaction was warmed slowly to room temperature, and then was quenched with an excess of saturated $NH_4Cl_{(aq)}$. The phases were separated, and the aqueous layer was extracted with diethyl ether (4 x 10 mL). The combined organic layers were washed with brine (5 mL), then dried over $MgSO_4$, filtered, and

concentrated. The crude material obtained was briefly passed over a plug of silica gel using 3% ethyl acetate in hexanes as eluent. The material obtained from this rapid purification was used directly in the next reaction without further characterization.

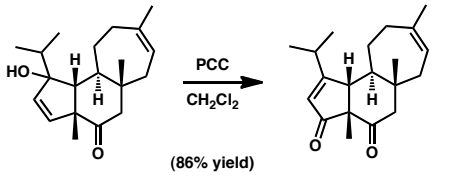
The material obtained from the silica plug above (ca. 16.6 mg) was transferred to a flame dried vial under argon, and then was azeotroped thrice from acetonitrile. The material was briefly dried under high vacuum, and then $Pd_2(pmdba)_3$ (2.8 mg, 2.0 μmol, 0.05 equiv) and acetonitrile (250 μL) were added. The reaction vial was sealed, and then the reaction was heated to 80 °C. After 2 h, the vial was cooled to room temperature, and solvent was removed in vacuo. The crude material obtained was purified via chromatography over silica using 5% ethyl acetate in hexanes as eluent. This afforded enone **220** as a colorless oil (11 mg, 57% yield): R_f = 0.60 (10:90 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 5.5 Hz, 1H), 6.09 (d, *J* = 5.5 Hz, 1H), 5.33 (dddd, *J* = 8.7, 5.2, 3.6, 1.7 Hz, 1H), 2.37 (app ddt, *J* = 14.3, 6.8, 2.2 Hz, 1H), 2.27–2.14 (m, 2H) 2.21 (dd, *J* = 15.7, 0.7 Hz, 1H), 2.15 (d, *J* = 15.7 Hz, 1H), 2.04 (d, *J* = 11.0 Hz, 1H), 2.03 (app ddt, *J* = 15.0, 6.7, 1.5 Hz, 1H) 1.75 (s, 3H), 1.77–1.67 (m, 1H), 1.35 (s, 3H), 1.27 (app dtd, *J* = 13.9, 12.1, 1.7 Hz, 1H), 1.21 (d, *J* = 15.1 Hz, 1H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 210.6, 165.9, 142.7, 131.4, 120.7, 59.1, 56.8, 55.5, 51.7, 41.7, 38.4, 32.9, 26.9, 26.0, 25.3, 17.9; IR (Neat film, NaCl) 2963, 2925, 2867, 1703, 1590, 1444, 1381, 1331, 1255, 1227, 1184, 1070, 996 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}O_2$ [M^+]: 258.1620, found 258.1622; $[\alpha]^{25}_D$ –210.9 (*c* 0.97, CH_2Cl_2).



220 ***221***

Allylic alcohol 221. To a flame dried vial was added enone **220** (29 mg, 0.112 mmol, 1.00 equiv). This material was briefly vacuum purged, and then was backfilled with argon. The vial was cycled into the glovebox, where it was charged with $CeCl_3$ (31 mg, 0.118 mmol, 1.05 equiv). The vial was then removed from the glovebox, placed under a manifold line, charged with THF (1.1 mL), and cooled to –78 °C. After reaching the desired temperature, isopropyl lithium (200 μL, 0.7 M in hexanes, 0.135 mmol, 1.20 equiv) was added to the suspension dropwise at –78 °C. The reaction was allowed to reach room temperature slowly by warming in the bath overnight. The reaction looked incomplete the next morning, and so was allowed to continue for an additional 14 h (total 22 h). The reaction was thereafter quenched with saturated $NH_4Cl_{(aq)}$ (2 mL). The phases were separated, and the aqueous layer was extracted with diethyl ether (4 x 5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material obtained was purified via chromatography over silica gel using 7% → 8% → 9% ethyl acetate in hexanes as eluent. This afforded allylic alcohol **221** as a clear oil (26 mg, isolated as two diastereomers, 76% combined yield). **Diastereomer A**: R_f = 0.40 (20:80 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (d, *J* = 5.6 Hz, 1H), 5.54 (d, *J* = 5.6 Hz, 1H), 5.33 (dddd, *J* = 8.6, 5.1, 3.4, 1.6 Hz, 1H), 2.27 (dd, *J* = 15.4, 0.9 Hz, 1H), 2.25 (m, 1H) 2.06 (d, *J* = 15.4 Hz, 1H), 2.00 (app ddt, *J* = 14.9, 6.6, 1.5 Hz, 1H), 1.99 (d, *J* = 10.6 Hz, 2H), 1.91 (app ddt, *J* = 13.6, 6.6, 2.1 Hz, 1H), 1.85 (app dt, *J* = 10.6, 2.1 Hz, 1H), 1.81–1.73 (comp. m, 3H), 1.75 (s,

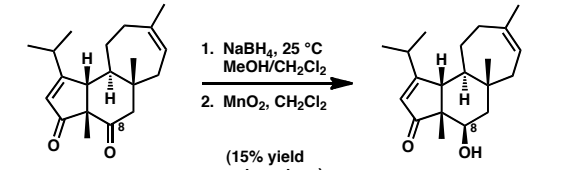
3H), 1.30 (s, 3H), 1.11 (dddd, *J* = 13.6, 12.1, 10.6, 1.6 Hz, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.6, 142.3, 137.3, 36.2, 121.2, 90.3, 59.9, 57.2, 55.1, 49.5, 42.9, 39.0, 36.6, 33.6, 28.5, 26.9, 25.5, 18.7, 18.2, 18.0; IR (Neat film, NaCl) 3494, 2968, 2923, 1694, 1456, 1382, 1286, 1249, 1137, 1110, 979 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{30}O_2$ [M$^+$]: 302.2246, found 302.2248; $[\alpha]^{25}_D$ –89.3 (*c* 0.72, CH_2Cl_2). **Diastereomer B**: R_f = 0.20 (20:80 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (d, *J* = 5.8 Hz, 1H), 5.62 (d, *J* = 5.8 Hz, 1H), 5.38–5.33 (m, 1H), 2.30 (d, *J* = 18.1 Hz, 1H), 2.27–2.20 (m, 2H), 2.10 (dd, *J* = 18.1, 0.5 Hz, 2H), 2.01 (d, *J* = 10.7, 2H), 1.86 (dd, *J* = 14.5, 8.9 Hz, 2H), 1.81–1.75 (m, 2H), 1.77 (s, 3H), 1.47 (s, 3H) 1.41–1.34 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.05 (s, 3H), 0.71 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 138.5, 121.8, 92.5, 62.8, 59.3, 54.3, 48.9, 44.4, 36.2, 33.6, 31.5, 30.3, 29.3, 25.9, 21.0, 19.9, 18.5; IR (Neat film, NaCl) 3472, 2963, 2925, 1698, 1449, 1382, 1287, 1246, 1012, 980, 795 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{30}O_2$ [M$^+$]: 302.2246, found 302.2249; $[\alpha]^{25}_D$ –67.3 (*c* 0.16, CH_2Cl_2).



221 ***Cyanthiwigin B (156)***

Cyanthiwigin B (156). To a flame dried vial was added allylic alcohol **221** (8.2 mg, 27.0 μmol, 1.00 equiv). This was dissolved in CH_2Cl_2 (275 μL), and then was treated with PCC (23 mg, 108.0 μmol, 4.00 equiv). This reaction was allowed to stir at room temperature for 14 h, and then was diluted with diethyl ether (1 mL) and passed over a

plug of celite. The celite pad was washed with additional diethyl ether (5 mL), and the collected organic solvents were concentrated to dryness. The residue obtained was purified over silica gel using 6.5% ethyl acetate in hexanes as eluent. This afforded cyanthiwigin B (**156**) as a white solid (7.0 mg, 86% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (s, 1H), 5.30–5.25 (m, 1H), 2.73 (app dt, *J* = 13.5, 6.7 Hz, 1H), 2.54 (d, *J* = 9.2 Hz, 1H), 2.20–2.12 (m, 1H), 2.10 (s, 1H), 2.09 (dd, *J* = 13.6, 0.7 Hz, 1H), 2.02 (app ddt, *J* = 15.1, 6.5, 1.6 Hz, 1H), 2.00 (d, *J* = 13.7 Hz, 1H), 1.81 (app ddt, *J* = 14.2, 6.6, 2.0 Hz, 1H), 1.71 (dd, *J* = 14.8, 8.7 Hz, 1H), 1.69 (s, 3H), 1.56 (ddd, *J* = 11.4, 9.3, 2.2 Hz, 1H), 1.47–1.39 (m, 1H), 1.24 (s, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 141.4, 123.2, 121.7, 63.7, 58.9, 56.8, 56.2, 42.6, 39.1, 33.7, 31.4, 31.2, 28.5, 25.8, 25.2, 21.9, 21.4, 18.3; IR (Neat film, NaCl) 2920, 1723, 1693, 1602, 1452, 1261, 1161, 866 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{28}O_2$ [M^+]: 300.2089, found 300.2093. $[\alpha]^{24}_D$ –215.2 (*c* 0.84, CH_2Cl_2), $[\alpha]^{25}_D$ –195.7 (*c* 0.84, MeOH).



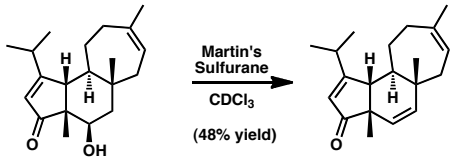
Cyanthiwigin B (156) ***8-epi-Cyanthiwigin E (222)***

8-*epi*-Cyanthiwigin E (222). To a flame dried vial was added cyanthiwigin B (**156**, 7.2 mg, 24.0 μmol, 1.00 equiv). The solids were dissolved in a 1 : 1 mixture of CH_2Cl_2 and methanol (1.0 mL). In a separate flame dried vial, $NaBH_4$ (23 mg) was dissolved in 1 : 1 mixture of CH_2Cl_2 and methanol (2.0 mL). Both solutions were cooled to –78 °C, and then a portion of the $NaBH_4$ solution (100 μL, 1.1 mg, 30.0 μmol, 1.20 equiv) was

added to the solution of cyanthiwigin B (**156**). After 1 h, no conversion was observed, and so an additional portion of the $NaBH_4$ solution was added (100 μL, 1.1 mg, 30.0 μmol, 1.2 equiv). After no conversion was observed over an additional 2.5 h period, an additional portion of the $NaBH_4$ solution was added (200 μL, 2.2 mg, 60.0 μmol, 2.40 equiv) and the temperature of reaction was warmed to –45 °C. The reaction was thereafter allowed to progress overnight. After an additional 8 h of reaction, conversion was still incomplete, and so reaction was pushed to completion by the addition of solid $NaBH_4$ (4.0 mg, 106.0 μmol, 4.40 equiv). The reaction was allowed to stir for 3 h, and then was quenched with acetone (1 mL) and 2 N $NaOH_{(aq)}$ (5 mL). The phases were separated, and the organic layer was washed immediately with brine (5 mL), and then dried over Na_2SO_4. The reaction was filtered and the solvent was removed in vacuo. The crude material obtained was purified over silica using 20% → 30% ethyl acetate in hexanes as eluent. Repurification was then executed using 7% → 10% → 20% → 50% ethyl acetate in hexanes as eluent. The material obtained as a white solid was difficult to characterize, and so was taken directly into the next reaction.

The white solid obtained above (ca. 2.2 mg) and MnO_2 (9.0 mg, 108.0 μmol, 15.0 equiv) were added to a flame dried vial. These solids were suspended in CH_2Cl_2 (0.5 mL), and were allowed to stir at room temperature for 15 h. The reaction was then passed over a plug of celite, and the plug was washed with ethyl acetate (15 mL). The solvent was removed in vacuo, and the crude material was purified via chromatography over silica using 6% ethyl acetate in hexanes as eluent. The material obtained was then repurified over silica using 4% ethyl acetate in hexanes as eluent. This afforded 8-*epi*-cyanthiwigin E (**222**) as a white solid (1.1 mg, 15% over two steps): ^{1}H NMR (500 MHz,

$CDCl_3$) δ 5.93 (s, 1H), 5.40–5.35 (m, 1H), 4.15 (ddd, *J* = 11.3, 5.0, 2.2 Hz, 1H), 2.63 (app dt, *J* = 13.6, 6.9, 1H), 2.53 (d, *J* = 2.2 Hz, 1H), 2.45 (d, *J* = 10.8 Hz, 1H), 2.29–2.20 (m, 1H), 2.12–2.04 (m, 1H), 1.98 (app ddt, *J* = 15.0, 6.3, 1.6 Hz, 1H), 1.89 (dd, *J* = 14.8, 8.8 Hz, 1H), 1.71 (s, 3H), 1.63 (dd, *J* = 13.8, 11.3 Hz, 1H), 1.57 (d, *J* = 5.1 Hz, 1H), 1.43–1.28 (comp. m, 3H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.10 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.9, 193.9, 139.4, 125.4, 123.1, 77.4, 67.4, 56.6, 55.3, 55.0, 44.8, 44.4, 35.2, 34.2, 33.5, 25.7, 25.3, 23.3, 22.1, 20.4, 19.6; IR (Neat film, NaCl) 3429, 2963, 2918, 1684, 1602, 1444, 1367, 1270, 1002 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{30}O_2$ [M^+]: 302.2246, found 302.2248; $[\alpha]^{23}_D$ –7.19 (*c* 0.16, MeOH).



8-epi-Cyanthiwigin E (222) ***Cyanthiwigin G (161)***

Cyanthiwigin G (161). To a flame dried vial was added *epi*-8-cyanthiwigin E (**222**, 1.1 mg, 4.0 μmol, 1.00 equiv). This vial was then cycled into the glovebox directly, and then was treated with Martin's sulfurane (6.2 mg, 9.0 μmol, 2.50 equiv). The vial was removed from the glovebox and transferred to a manifold line, where it was then charged with $CDCl_3$ (250 μL) and allowed to react at room temperature for 5 h. After this time had elapsed, the reaction was directly loaded onto a silica gel column and purified via chromatography using 3% ethyl acetate in hexanes as eluent. This afforded cyanthiwigin G (**161**) as a white solid (0.5 mg, 48% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (d, *J* = 0.9 Hz, 1H), 5.69 (d, *J* = 9.9 Hz, 1H), 5.54 (d, *J* = 9.9 Hz, 1H), 5.39–5.35 (m, 1H), 2.75–

2.67 (m, 1H), 2.48 (d, *J* = 10.4, 1H), 2.22–2.12 (comp. m, 2H), 1.96 (app ddt, *J* = 14.7, 6.7, 1.4 Hz, 1H), 1.89 (dd, *J* = 14.5, 8.6 Hz, 1H), 1.74 (s, 3H), 1.77–1.67 (m, 1H), 1.36–1.29 (comp. m, 2H), 1.25 (d, *J* = 6.6 Hz, 3H), 1.15 (s, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 192.1, 141.4, 140.9, 127.3, 124.4, 122.2, 58.2, 55.3, 53.8, 41.5, 37.6, 33.7, 33.4, 30.5, 28.4, 26.1, 25.2, 23.2, 20.3, 19.8; IR (Neat film, NaCl) 2962, 2921, 1706, 1601, 1444, 1366, 1261, 1156, 1091, 863, 761 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{20}H_{29}O$ [M+H]: 285.2218, found 285.2221; $[\alpha]^{25}_{D}$ –12.35 (*c* 0.10, MeOH).

2.5 NOTES AND REFERENCES

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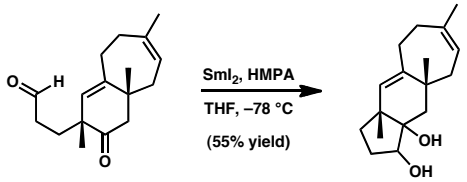
Toward this end, bicyclic aldehyde **208** was treated with a solution of samarium(II) iodide in the presence of hexamethylphosphoramide (HMPA), with the expectation that these conditions would afford an appropriate ketyl radical. Unfortunately, rather than undergo the radical-olefin cyclization process we envisaged, the ketyl radical instead engaged in an undesired intramolecular Pinacol-type coupling to yield [5-6-7] tricyclic system **C2-S1**.



208 ***C2-S1***

Diol C2-S1. To a flame dried vial was added a THF solution of aldehyde **208** (20 mg, 0.077 mmol, 1.0 equiv, in 500 μL solvent). To this solution was added HMPA (25 μL), and the vial was cooled to –78 °C. Once this temperature had been reached, SmI_2 (921 μL, 0.1 M in THF, 0.092 mmol, 1.2 equiv) was added dropwise to the reaction. After complete addition of a single portion of SmI_2, the reaction had not reached completion. A second portion of SmI_2 (921 μL, 0.1 M in THF, 0.092 mmol, 1.2 equiv) was added, and the reaction was allowed to reach 0 °C over 30 min. After this time had elapsed, the reaction was poured into a solution of brine (20 mL) that contained citric acid (770 mg). The phases were separated, and the aqueous layer was extracted with ethyl acetate (4 x 30 mL). Combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude material was purified over silica using 10% → 12% → 15% ethyl acetate in hexanes as eluent. This afforded diol **C2-S1** as a colorless oil (11 mg, 55% yield). Incomplete characterization data is as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (app t, *J* = 6.8 Hz, 1H), 5.13 (s, 1H), 3.83 (app dt, *J* = 6.8, 4.3 Hz, 1H), 2.38 (d, *J* = 4.4 Hz, 1H), 2.35–2.33 (m, 1H), 2.31 (s, 1H), 2.24–2.16 (m, 1H), 2.12 (ddd, *J* = 14.5, 6.8, 0.8 Hz, 1H), 2.03 (app dt, *J* = 14.7, 5.2 Hz, 2H), 1.95 (dddd, *J* = 14.0, 8.9, 6.8, 5.3 Hz, 1H), 1.88 (dd, *J* = 14.5, 6.8 Hz, 1H), 1.74 (ddd, *J* = 12.7, 9.1, 5.3 Hz, 1H), 1.66 (s, 3H), 1.65–1.58 (m, 1H), 1.62 (d, *J* = 4.8 Hz, 1H), 1.47 (d, *J* = 14.1 Hz, 1H), 1.44 (ddd, *J* = 12.7, 8.9, 7.2 Hz, 1H), 1.15 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 139.3, 131.5, 121.3, 79.5, 79.0, 46.4, 44.6, 40.1, 39.7, 38.4, 35.9, 30.5, 29.8, 27.7, 25.7, 23.7. IR (Neat film, NaCl) cm^{-1}.

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