CHAPTER 2

Progress toward the Total Synthesis of Scandine and the Melodinus *Alkaloids*[†]

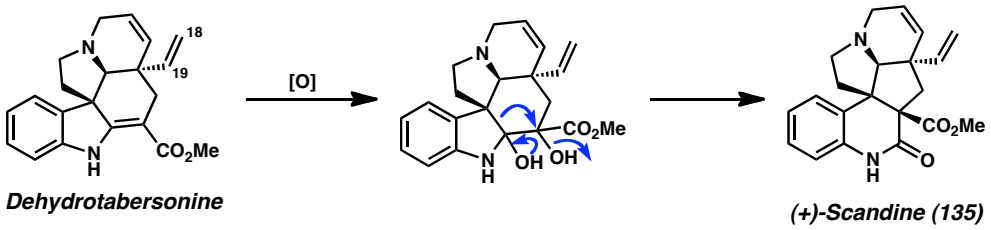
2.1 INTRODUCTION AND SYNTHETIC STRATEGY

2.1.1 INTRODUCTION

The *Melodinus* alkaloids are a family of dihydroquinolinone natural products originally isolated over 40 years ago from *Melodinus scandens* Forst and are structurally related to the *Aspidosperma* alkaloids by means of an oxidative rearrangement of 18,19-dehydrotabersonine (Scheme 2.1.1).[1,2] Although no biological activity has been directly attributed to any member of this class of compounds to date, some species of the *Melodinus* genus are used in Chinese folk medicine to treat meningitis in children and rheumatic disease.[3,4]

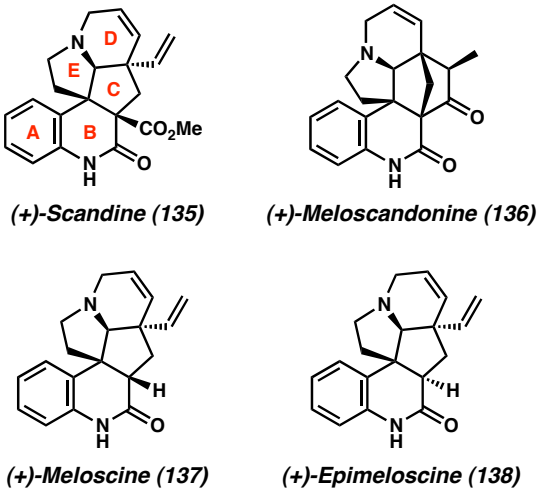
[†] Later aspects of this work were performed in collaboration with Nicholas R. O'Connor, a graduate student in the Stoltz group. A portion of this work was published. See: Goldberg, A. F. G.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 4474–4476.

Scheme 2.1.1. Proposed Biosynthesis of the Melodinus *Alkaloids.*



Despite the lack of known biological activity, we were intrigued by their structural complexity and interested in the prospects of preparing non-natural derivatives for biological evaluation (Figure 2.1.1). The *Melodinus* alkaloids feature a congested cyclopentane core, bearing four contiguous stereocenters; in the case of (+)-scandine (**135**),[1] (+)-meloscandonine (**136**),[5] and others,[6] three of these are quaternary stereocenters. Indeed, construction of this highly substituted C ring constitutes a formidable challenge, and the only members of the family to have been synthesized to date are meloscine (**137**) and its C(16) epimer, epimeloscine (**138**).[7,8,9]

Figure 2.1.1. Representative examples of the Melodinus *Alkaloids*



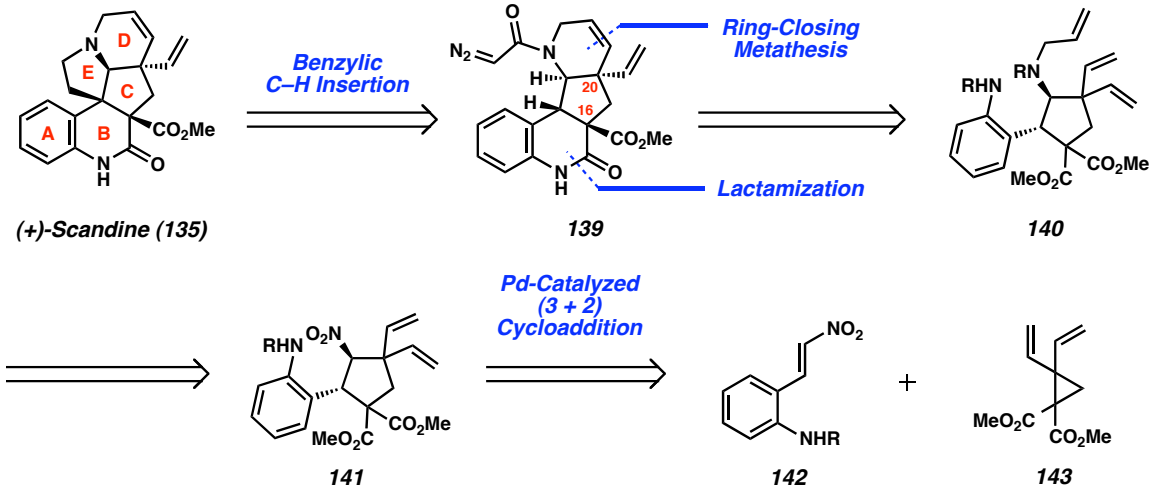
2.1.2 ORIGINAL RETROSYNTHETIC ANALYSIS

The parent of the natural product family, (+)-scandine (**135**), is believed to be the biosynthetic precursor to the 13 other known members of the family. In the long-term interest of a general route to the Melodinus alkaloids, we sought a strategy for the rapid assembly of scandine (**135**); other members of the *Melodinus* alkaloids would then be prepared from this natural product, or by a similar approach.

Through our synthetic strategy, we chose to exploit elements of symmetry found within the target natural product. In particular, the quaternary stereocenter at C(20) bears two olefinic substituents, and C(16) bears two carbon substituents in the carboxylic acid oxidation state.

Accordingly, after disconnection of the E ring via benzylic C–H insertion, we envisioned that the D and B rings of **139** could be formed by ring-closing metathesis (RCM) and lactamization respectively of divinylcyclopentane **140** (Scheme 2.1.2). Notably, the C(20) and C(16) quaternary carbons in this proposed intermediate are not stereogenic; the vinyl groups and the methyl esters are diastereotopic, and the stereochemistry at these carbons would be set by the RCM and lactamization steps, controlled by the neighboring stereocenters. This intermediate could arise, in turn, from nitrocyclopentane (**141**), the product of a transition metal catalyzed, intermolecular formal (3 + 2) cycloaddition between a *trans*-β-nitrostyrene (**142)** and divinylcyclopropane **143**.[10]

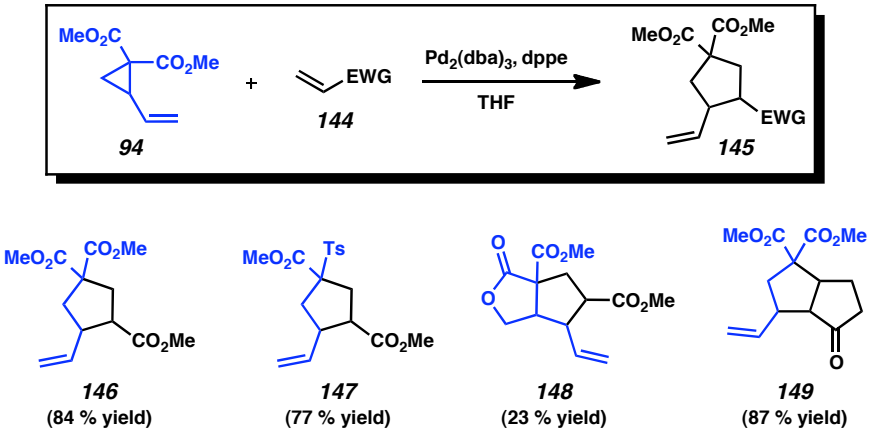
*Scheme 2.1.2. Retrosynthetic analysis of scandine (**135**).*



2.1.2.1 METAL-CATALYZED CYCLOPROPANE (3 + 2) CYCLOADDITIONS

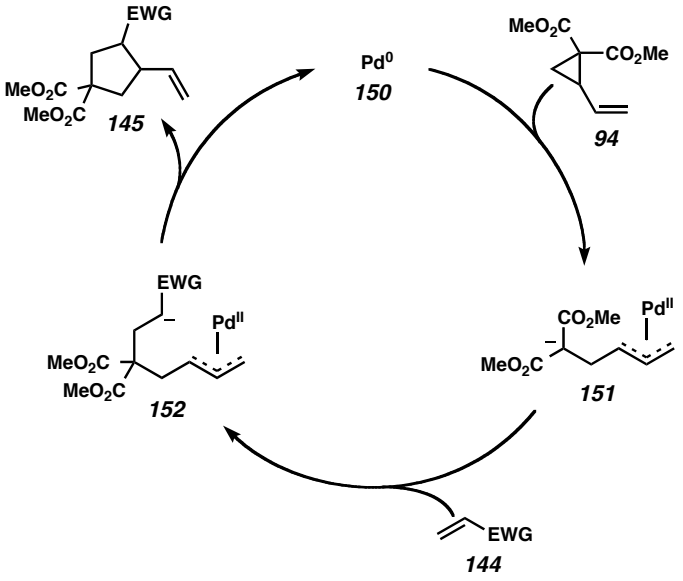
In 1985, Tsuji and coworkers reported a palladium-catalyzed (3 + 2) cycloaddition of vinylcyclopropane-1,1-diesters with a range of conjugate acceptors. In particular, α,β-unsaturated ketones and esters afforded cyclopentane products (**146**–**149**, Scheme 2.1.3). All of the products were isolated as mixtures of diastereomers.[10]

Scheme 2.1.3. Tsuji's palladium-catalyzed (3 + 2) cycloaddition of vinylcyclopropanes



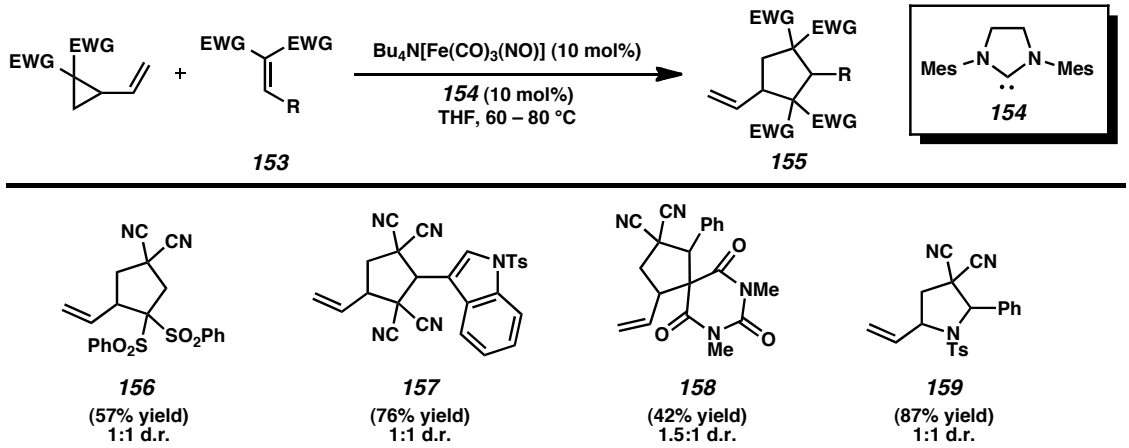
The mechanism of the reaction is believed to proceed via palladium mediated C–C bond cleavage of vinylcyclopropane **94** to form a palladium(II) allyl species with a pendent malonate anion (**151**, Scheme 2.1.4). The malonate moiety then reacts with the conjugate acceptor (**144**) to form anion **152**, which undergoes a 5-exo ring-closure to generate the vinylcyclopentane product **145** and regenerate the palladium(0) catalyst.

Scheme 2.1.4. Proposed mechanism of the palladium-catalyzed (3 + 2) cycloaddition



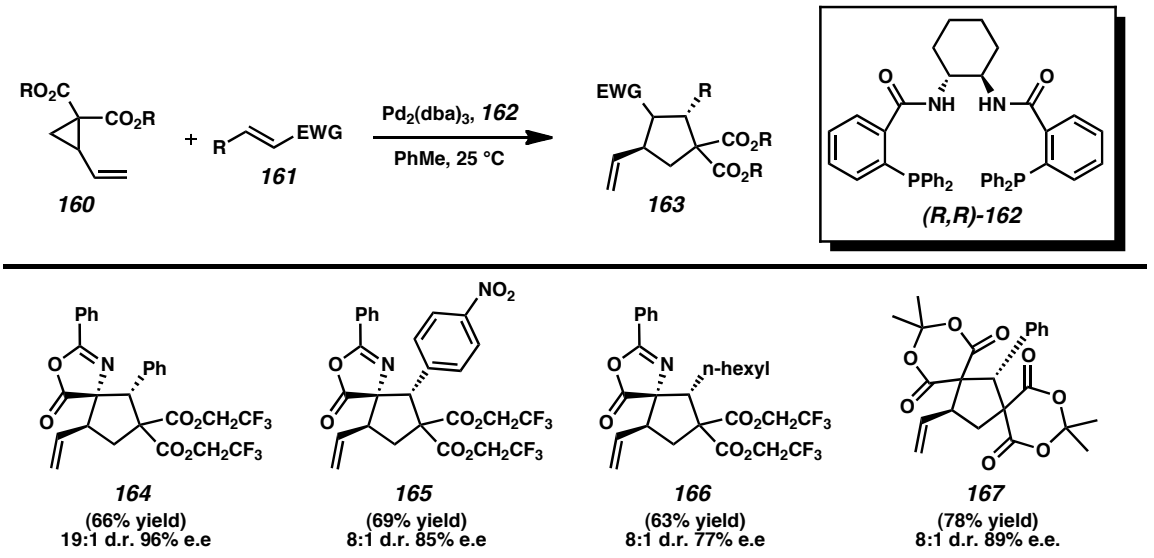
More recently, an iron-catalyzed variant of this reaction was reported by Plietker in 2012, which expanded the substrate scope to some degree, but suffered from the same problems with diastereoselectivity as the original system (Scheme 2.1.5).[11] Notably, the reaction was amenable to the use of nitrogen-containing cyclopropanes and conjugate acceptors.

Scheme 2.1.5. Iron-catalyzed (3 + 2) cycloaddition of vinylcyclopropanes



During the course of our studies, in 2011, Trost and coworkers disclosed the enantio- and diastereoselective variant of this reaction (Scheme 2.1.6).[12] In this case, vinylcyclopropanes with highly electron-deficient ester groups were reacted with conjugate acceptors to afford cyclopentanes (**155**) with high stereoselectivity. The electron-deficiency of the cyclopropane diester functionality was critical to the enantioselectivity, as it rendered reversible the non-stereoselective conjugate addition step of the reaction mechanism (*vide supra*, Scheme 2.1.4).

Scheme 2.1.6. Enantio- and diastereoselective palladium-catalyzed (3 + 2) cycloaddition

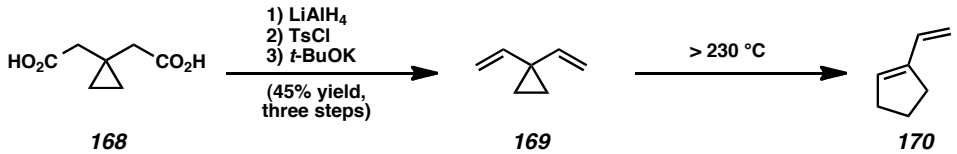


From the literature precedent, it was not clear whether this reaction would be compatible with vinylcyclopropanes bearing quaternary centers. We therefore began a research program to synthesize and examine the reactivity of such a cyclopropane toward the ultimate goal of applying it to the synthesis of the *Melodinus* alkaloids.

2.1.2.2 KNOWN 1,1-DIVINYLCYCLOPROPANES

At the outset of this project, only two 1,1-divinylcyclopropanes were known in the literature,[13,14] prompting some concern that the desired cyclopropane would be too unstable to isolate. First, in 1972, Dolbier and Alonso reported the synthesis of 1,1-divinylcyclopropane (**169**), by a three-step procedure from diacid **169** (Scheme 2.1.7).[13] In their studies, they found that this compound underwent quantitative rearrangement to cyclopentene **170** at 230 °C; notably, the activation barrier was 12–13 kcal/mol lower than the corresponding monovinylcyclopropane. The proposed mechanism is concerted or biradical in nature, so while this example is illustrative of potential stability issues that may arise in the synthesis of the desired diester analogue (**143**), that cyclopropane would likely react via a polar mechanism.

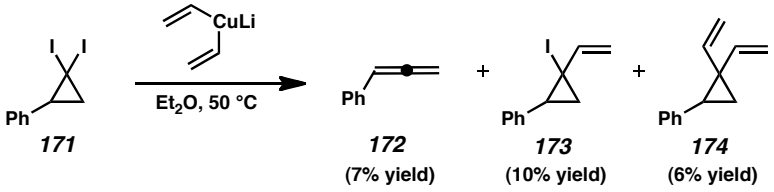
*Scheme 2.1.7. Synthesis and properties of 1,1-divinylcyclopropane (**169**)*



The other 1,1-divinylcyclopropane known at the time was prepared by Mathias and Weyerstahl through vinylation of a 1,1-dihalocyclopropane (**171**, Scheme 2.1.8).[14] Treatment of this cyclopropane with divinyl cuprate afforded a low-yielding mixture of

three compounds, including phenylallene (**172**), a monovinylated cyclopropane (**173**) and the divinylcyclopropane of interest (**174**).

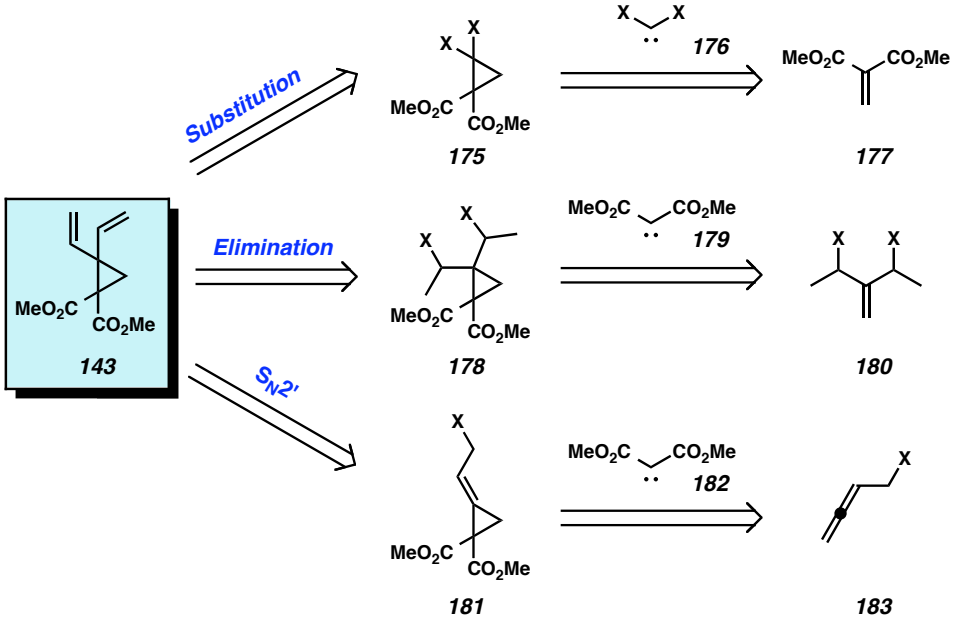
*Scheme 2.1.8. Synthesis of 2-phenyl-1,1-divinylcyclopropane (**174**)*



2.1.2.3 DIVINYLCYCLOPROPANE RETROSYNTHESIS

We examined several possible approaches toward the synthesis of the desired divinylcyclopropane (**143**, Scheme 2.1.9). First, a substitution approach analogous to Weyerstahl's may be possible from a 1,1-dihalocyclopropane (**175**), which would be generated in turn from methylidene dimethylmalonate (**177**).[15] Alternatively, the two vinyl groups could be formed by elimination of cyclopropane **178**, synthesized by cyclopropanation with a malonate-derived carbenoid (**179**). Finally, the last route that we studied involved S_N2' displacement of alkylidene cyclopropane **181** with a vinyl nucleophile. This cyclopropane could be derived by cyclopropanation of allene **183**.

Scheme 2.1.9. Retrosynthesis of divinylcyclopropane ***143***

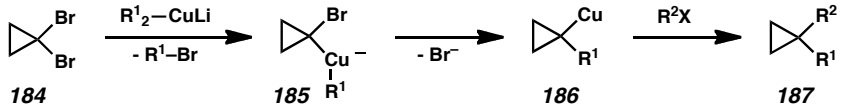


2.2 TOWARD THE SYNTHESIS OF A DIVINYLCYCLOPROPANE

2.2.1 GEM-DIHALOCYCLOPROPANE SUBSTITUTION ROUTE

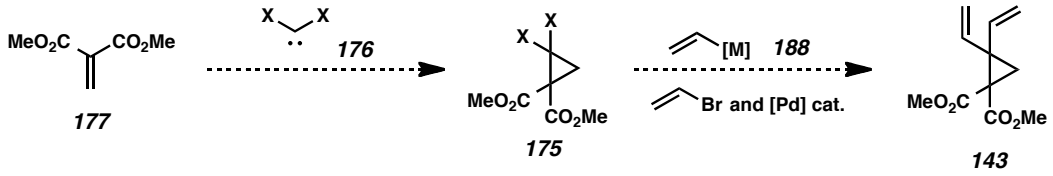
We first examined the use of a 1,1-dihalocyclopropane toward the desired divinylcyclopropane (**143**). The synthesis and reactions of 1,1-dihalocyclopropanes has been extensively researched and an excellent literature review on this topic was published by Fedorynski in 2003.[15] Fedorynski describes reactions of 1,1-dihalocyclopropanes with dialkyl cuprates,[16] trialkyl zincates,[17] manganates,[18] or magnesates[19] that yield alkylated cyclopropylmetals (**186**), which can react with an electrophile to deliver products with geminal substitution (**187**, Scheme 2.2.1). Furthermore, the cyclopropylmetal intermediates can be used in metal-catalyzed cross-coupling reactions with vinyl halides to deliver vinylcyclopropanes.

Scheme 2.2.1. Dialkylation of dihalocyclopropanes with dialkylcuprates



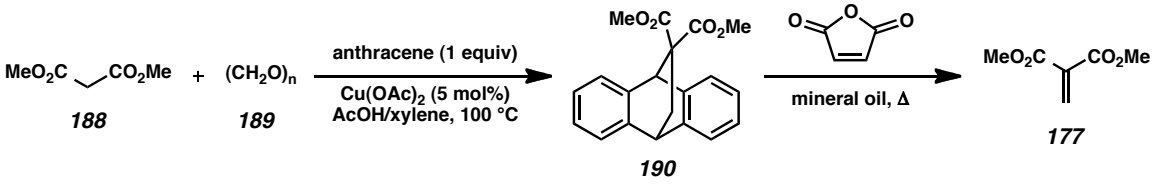
Accordingly, cyclopropanation of methylidene dimethylmalonate (**177**) followed by substitution could conceivably provide a rapid route to the desired 1,1-divinylcyclopropane (**143**, Scheme 2.2.2)

Scheme 2.2.2. Proposed gem*-dihalocyclopropane route toward 1,1-divinylcyclopropane* ***143***



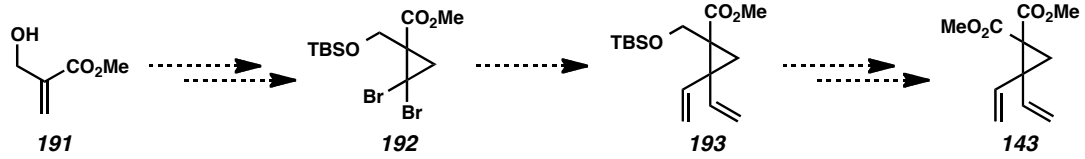
Methylidene dimethylmalonate (**177**), from a technical standpoint, is notoriously difficult to synthesize and handle.[20] It is particularly prone to anionic polymerization, which can easily occur under the reaction conditions by which it is synthesized, typically by condensation of dimethylmalonate (**188**) and formaldehyde (**189**). De Keyser and coworkers succeeded in the development of a scalable route to its synthesis (Scheme 2.2.3).[20] Their method involves an in situ trapping of the condensation product via a Diels–Alder reaction with anthracene to afford a crystalline adduct (**190**), which can easily be separated without chromatography from the reaction mixture. Following recrystallization, the anthracene adduct (**190**) is thermolyzed in the presence of maleic anhydride—used to trap the anthracene and drive the reaction forward—and the methylidene dimethylmalonate (**177**) is purified by distillation.

*Scheme 2.2.3. De Keyser's synthesis of methylene dimethylmalonate (**177**)*



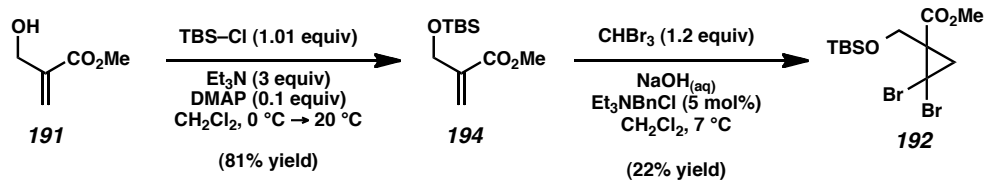
Due to the highly reactive nature of methylidene dimethylmalonate (**177**), we sought to first examine the vinylation of *gem*-dihalocyclopropanes using a model substrate (**192**). Acrylate **191** was chosen as a suitable cyclopropane precursor because of its relative ease of preparation, its structural resemblance to the desired acrylate, and the potential for conversion to the 1,1-diester following successful vinylation (Scheme 2.2.4). Studies on this substrate could later be applied to methylidene dimethylmalonate (**177**) to shorten the synthetic sequence.

*Scheme 2.2.4. Proposed conversion of model cyclopropane **192** to desired (3 + 2) substrate **143***



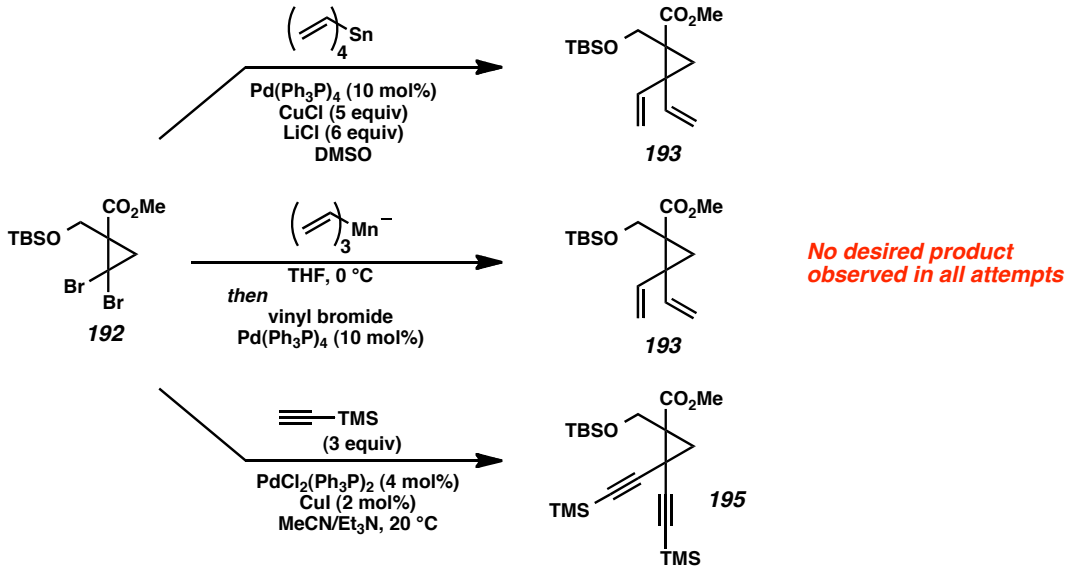
Accordingly, acrylate derivative **191** was prepared by a known procedure, and protected as a silyl ether (**194**, Scheme 2.2.5).[21] The product (**194**) was then cyclopropanated by phase-transfer catalysis to afford the *gem*-dibromocyclopropane (**192**).

Scheme 2.2.5. Synthesis of a model gem*-dihalocyclopropane (**192**)*



Unfortunately, efforts to doubly substitute cyclopropane **192** failed (Scheme 2.2.6). Attempted procedures included Stille and Sonogashira cross-couplings, as well as a substitution with a trialkylmanganate with in situ palladium-catalyzed cross coupling to vinyl bromide.[18b] Since no desired substitution products observed with this substrate, we did not pursue this route further and we shifted our focus to an alternative approach.

Scheme 2.2.6. Efforts to vinylate dibromocyclopropane ***192***

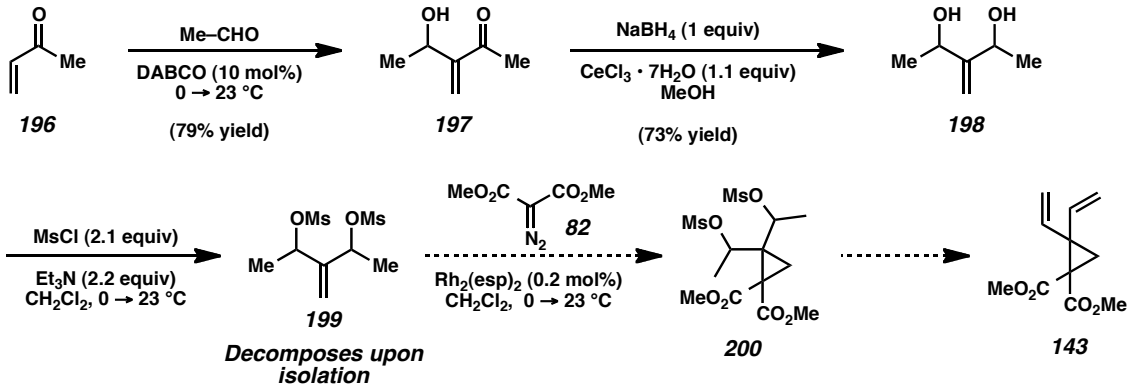


2.2.2 DOUBLE ELIMINATION ROUTE

We turned our attention toward the formation of the desired vinyl groups by elimination of two leaving groups. In this vein, we set out to prepare dimesylate **200** as a divinyl cyclopropane precursor (Scheme 2.2.7). Baylis–Hilman reaction of methyl vinyl ketone (**19**) with acetaldehyde by a known procedure furnished adduct **197** which was then reduced to afford diol **198** as a mixture of diastereomers.[22] Although this substrate underwent mesylation cleanly, the product (**199**) was unstable as a neat oil, and underwent spontaneous, violent decomposition.[23] Furthermore, when the dimesylate was

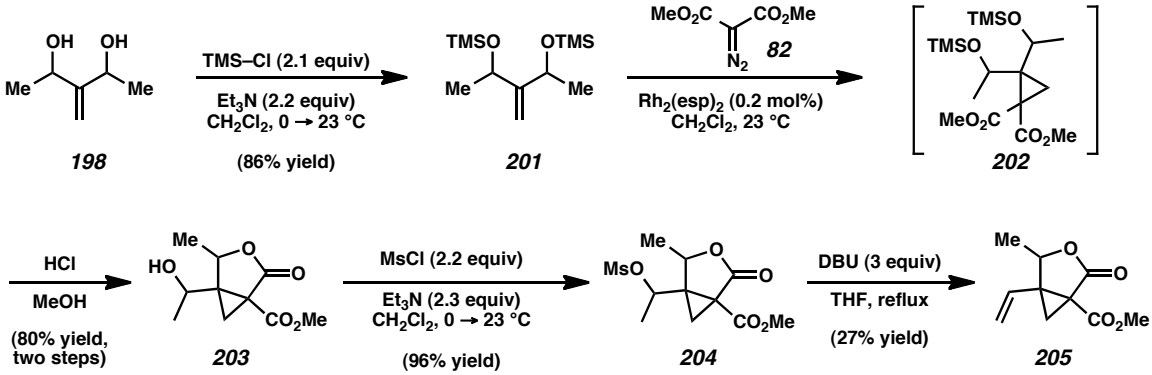
subjected as a solution in dichloromethane directly to cyclopropanation with diazodimethylmalonate, a complex reaction mixture was observed and no desired cyclopropane product (**200**) could be isolated.

Scheme 2.2.7. Synthetic approach to elimination substrate precursor



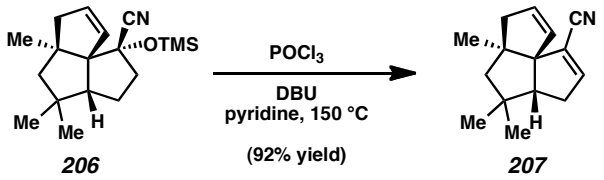
To avoid problems of substrate stability, we opted to protect diol **198** as a disilyl ether (**201**), and this substrate was cyclopropanated efficiently using Du Bois' catalyst to give cyclopropane **202**, which was immediately subjected to alcohol deprotection under acidic conditions.[24] In the event, one free hydroxyl underwent an undesired, in situ lactonization to give bicyclic lactone **203**. This product could however be mesylated and eliminated to yield a vinylcyclopropane (**205**).

*Scheme 2.2.8. Vinylcyclopropane synthesis via a protected diol (**201**).*



We attempted to avoid the undesired lactonization by directly eliminating the silyl ethers under an array of conditions. In particular, a report by Paquette and coworkers detailed the elimination of a silylated cyanohydrin (**206**) to give an unsaturated nitrile (**207**, Scheme 2.2.9).[25] The stability of the unsaturated nitrile (**207**) likely aided the elimination of the silyl ether in Paquette's system. Unfortunately, our efforts with this and numerous other methods to directly convert silyl ethers to olefins were unsuccessful.

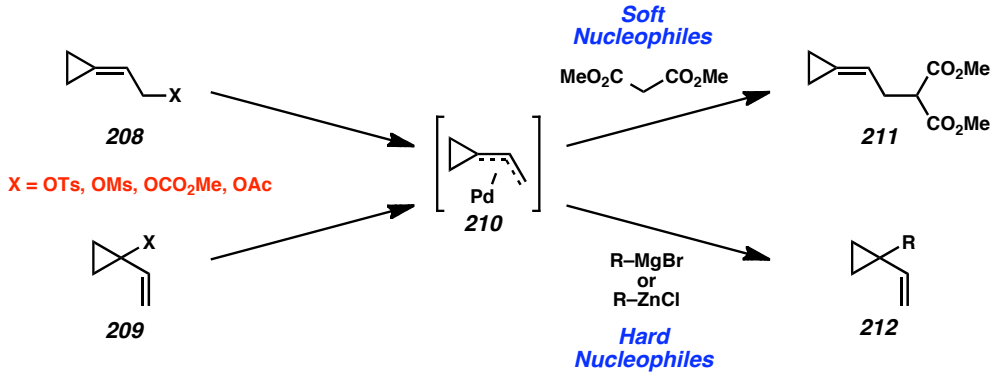
*Scheme 2.2.9. Direct elimination of a silyl ether (**206**) to form an unsaturated nitrile (**207**)*



2.2.3 ALKYLIDENECYCLOPROPANE ROUTE

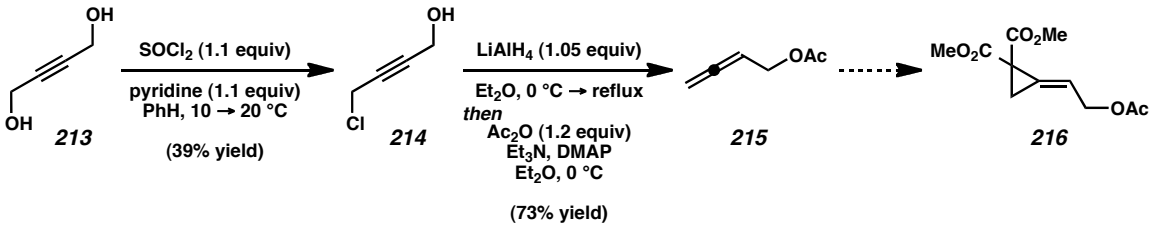
Finally, we examined a route to the divinylcyclopropane by S_N2' displacement of a substituted alkylidenecyclopropane. De Meijere and coworkers have studied the allylic alkylation of cyclopropane derivatives with carbon nucleophiles under palladium catalysis.[26] In their study, they demonstrated that both vinylcyclopropanes (**209**) and methylenecyclopropanes (**208**) with allylic leaving groups will react with the palladium catalyst to form a common palladium allyl intermediate (**210**), which is then alkylated by soft nucleophiles (*i.e.* malonates) at the terminal position or by hard nucleophiles (*i.e.* organozinc or Grignard reagents) at the branched position to afford substituted methylene cyclopropanes (**211**) or vinyl cyclopropanes (**212**) respectively.

Scheme 2.2.10. Allylic alkylation of cyclopropane derivatives



We sought to prepare an analogous alkylidenecyclopropane bearing the necessary methyl ester functionalities, and envisioned its preparation using a known homoallenyl acetate (**215**, Scheme 2.2.11).[27]

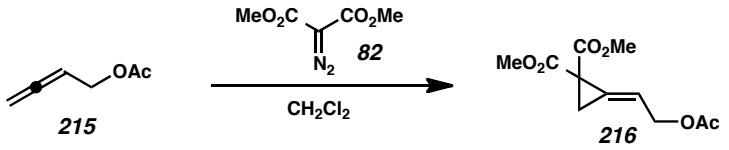
*Scheme 2.2.11. Synthetic approach to alkylidenecyclopropane **216***



Conditions were screened for cyclopropanation of allene **215** with diazodimethylmalonate (**82**), examining several catalysts, carbenoid precursor equivalents, and addition times (Table 2.2.1). On our first attempt (entry 1), we were able to isolate the desired alkylidenecyclopropane (**216**) in 42% yield; however, this required an excess of the allene starting material (**215**), which required several steps to prepare. When the excess reagent was inverted, the yield decreased (entry 2), however, increasing the catalyst loading and the diazo equivalence improved the yield to 58% (entry 3). Increasing or decreasing the slow addition time of the diazo reagent had a detrimental effect on the yield (entries 4-5). Changing the catalyst ligand to electron poor

trifluoroacetate resulted in a complex product mixture (entry 6), and electron-rich caprolactam was poorly reactive under similar conditions (entry 7). Microwave heating of a neat mixture of the reaction components (entry 8) afforded considerably shortened reaction times, however, the yield was not improved. Finally, the use of Du Bois' catalyst gave the highest isolated yield, with a short reaction time, low catalyst loading, and no need for slow addition of the diazodimethylmalonate (**82**).[28]

Table 2.2.1. Optimization of allene cyclopropanation

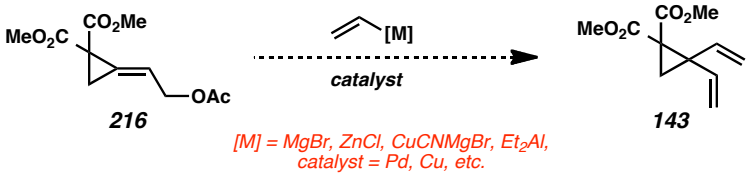


entry	diazo equiv	catalyst	temperature	addition time	yield (%)[a]
1	0.3	$Rh_2(OAc)_4$ (0.25 mol%)	reflux	8 h	42[b]
2	2	$Rh_2(OAc)_4$ (0.25 mol%)	reflux	6 h	28[b]
3	3	$Rh_2(OAc)_4$ (1 mol%)	reflux	6 h	58
4	3	$Rh_2(OAc)_4$ (1 mol%)	reflux	12 h	37
5	3	$Rh_2(OAc)_4$ (1 mol%)	reflux	3 h	38
6	3	$Rh_2(tfa)_4$ (1 mol%)	reflux	3 h	18
7	3	$Rh_2(cap)_4$ (1 mol%)	reflux	3 h	22[c]
8	1.3	$Rh_2(OAc)_4$ (0.4 mol%)	100 °C[d]	3 h	51
9	1.3	$Rh_2(esp)_2$ (0.1 mol%)	0 → 23 °C	–	80[b]

[a] ^{1}H NMR yield (pentachlorobenzene as internal standard). [b] Isolated yield. [c] 55% recovered starting material. [d] Microwave heating, solvent-free, 15 minute reaction time.

With the desired alkylidene cyclopropane (**216**) in hand, we examined an array of allyllic substitution conditions with vinyl nucleophiles, including those reported by de Meijere, as well as other catalytic systems with vinyl alanes, and cuprates (Scheme 2.2.12). Unfortunately, in all cases, none of the desired divinylcyclopropane **143** was observed, and only ring-opened products could be observed.[29,30]. It is possible that the diester functionality on the methylenecyclopropane serves to weaken the distal bond of the methylenecyclopropane, favoring ring-opening rather than substitution.

Scheme 2.2.12. Attempted S_N2' displacement with vinyl nucleophiles

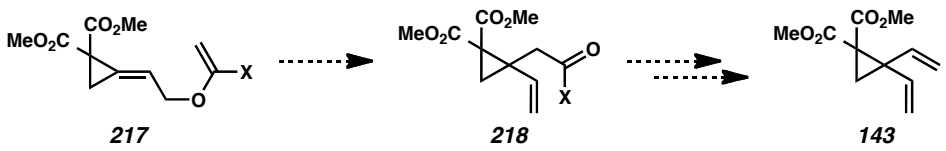


It is possible that a broader screen may find a compatible leaving group for this transformation to out-compete the ring-opening process; however, we turned our attention at this point to other possible approaches to install the necessary vinyl group from this alkylidenecyclopropane substrate.

2.2.4 CLAISEN REARRANGEMENT ROUTE

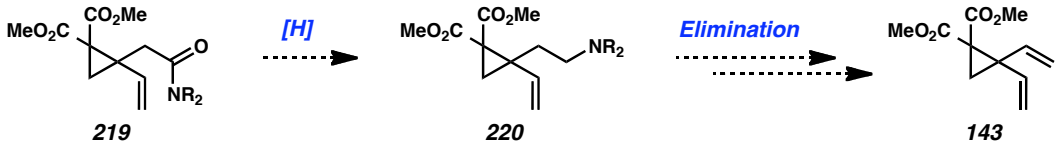
At this stage, we considered that the use of a Claisen rearrangement may offer an alternative pathway to install the desired quaternary carbon on the cyclopropane (Scheme 2.2.13).[31] The use of Claisen rearrangements to install vicinal quaternary centers is well precedented, and the intramolecular nature of the reaction could aid the efficiency of the carbon-carbon bond formation. However, we envisioned potential chemoselectivity and side-reactivity problems in the conversion of the Claisen product (**218**) to the desired divinylcyclopropane (**143**). Particularly, conditions would be necessary that could reduce the product carbonyl in the presence of the methyl esters, and lactonization of any intermediate alcohol with the ester functionalities would also present a challenge.

Scheme 2.2.13. Proposed Claisen-rearrangement approach to cyclopropane ***143***



Accordingly, we turned to the Eschenmoser–Claisen reaction variant, since numerous examples exist in the literature for chemoselective reduction of amides in the presence of esters,[32] the product tertiary amines (**220**) would not be expected to react with the pendent ester functionalities and can be eliminated to form olefins by means of the Cope[33] or Hofmann[34] elimination (Scheme 2.2.14).

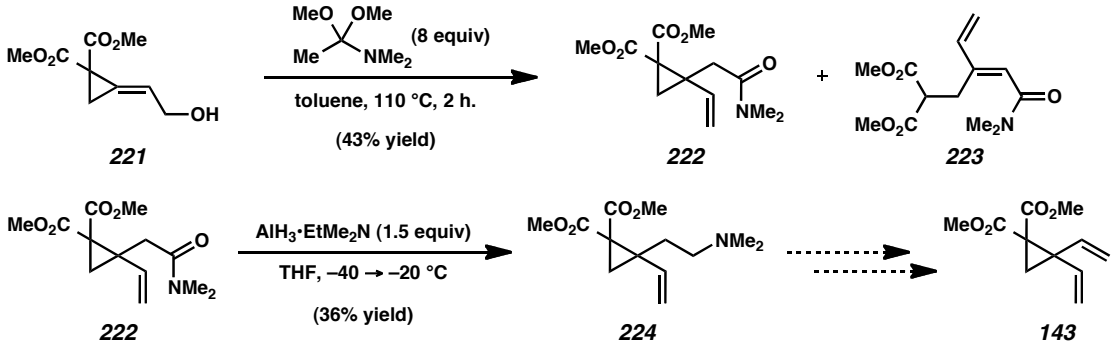
*Scheme 2.2.14. Proposed selective derivatization of an Eschenmoser–Claisen product (**219**)*



219 **220** **143**

We therefore treated alcohol **221** under typical reaction conditions with dimethylacetamide dimethyl acetal, and observed the formation of amide **222** in moderate yield (Scheme 2.2.15).[35] The main side product of the reaction was conjugated amide (**223**), likely formed by base-promoted ring opening of the desired product. Unfortunately, extensive screening of reaction temperatures and times could not improve the yield of the desired vinylcyclopropane (**222**); nevertheless, sufficient material could be rendered to examine the later stages of the synthesis. Therefore, the amide (**222**) was reduced in 36% yield to the dimethylamine (**224**) using alane. Efforts to eliminate the amine (**224**) to form the desired divinylcyclopropane (**143**) have been unsuccessful to date. Fortunately, our efforts to this point provided three unique vinylcyclopropanes (**205**, **222**, and **224**) which we could examine in the palladium-catalyzed (3 + 2) reaction.

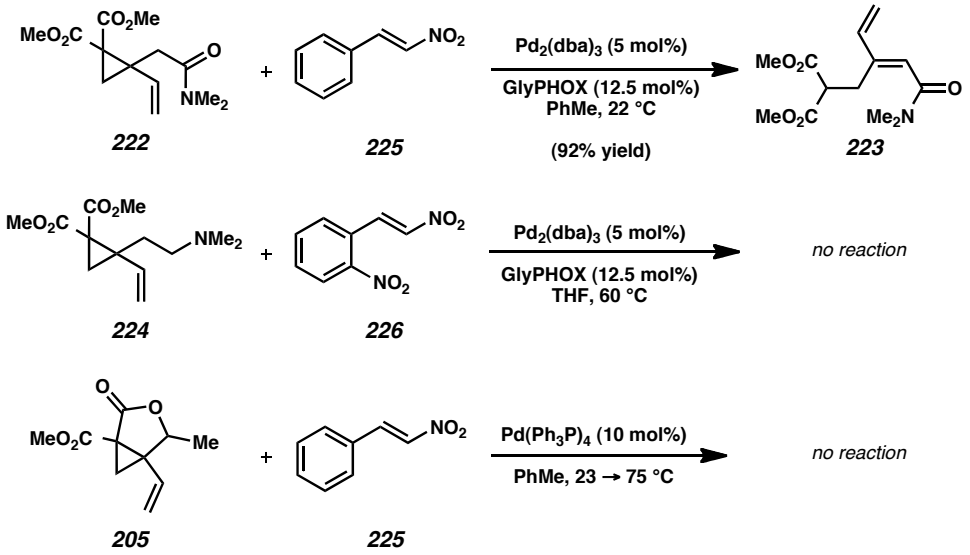
Scheme 2.2.15. Eschenmoser–Claisen rearrangement of alkylidenecyclopropane ***221***



2.3 INVESTIGATION OF (3 + 2) CYCLOADDITION

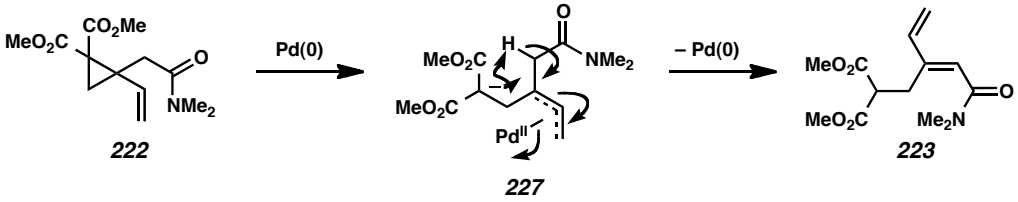
With three functionalized vinyl cyclopropanes in hand, we set out to determine their compatibility with palladium-catalyzed (3 + 2) cycloaddition conditions originally developed by Tsuji. Under an array of conditions, no cyclopentane products could be isolated (Scheme 2.3.1). In the case of the dimethylamide substituted cyclopropane (**222**), the starting material was isomerized in high yield to conjugated amide **223** as a mixture of olefin isomers. With the dimethylamine analogue (**224**) and bicyclic vinylcyclopropane **205**, the starting material remained unreacted, even at elevated temperatures.

Scheme 2.3.1. Attempted (3 + 2) cycloadditions of vinyl cyclopropanes with nitrostyrenes



The isomerization of dimethylamide **222** is attributed to the presence of acidic protons on the substrate: upon formation of the palladium(II) allyl species (**227**), the pendant malonate acts as a base, eliminating Pd(0) via deprotonation of the α-proton of the dimethylamide to give conjugated amide **223** (Scheme 2.3.2).

*Scheme 2.3.2. Mechanism for cyclopropane ring-opening isomerization of dimethylamide **222***



As for vinylcyclopropanes **205** and **224**, we propose that the lack of reactivity results from a demanding allylation step of the mechanistic cycle (Scheme 2.3.3). Whereas hard nucleophiles such as Grignard reagents will typically react under palladium catalysis via an inner-sphere mechanism, at the allyl terminus with greater substitution, soft-nucleophiles often proceed by outer-sphere attack at the least-substituted position. In the case of an unsubstituted vinyl cyclopropane (3 + 2) cycloaddition (*i.e.* **228**, R = H,

Scheme 2.3.3), conformational effects in the ring-closure presumably override the innate selectivity for terminal vs. branched alkylation; however, in the case of our substituted vinylcyclopropanes (*i.e.* R ≠ H), the steric demand is likely too high to form the desired cyclopentane ring (**229**).

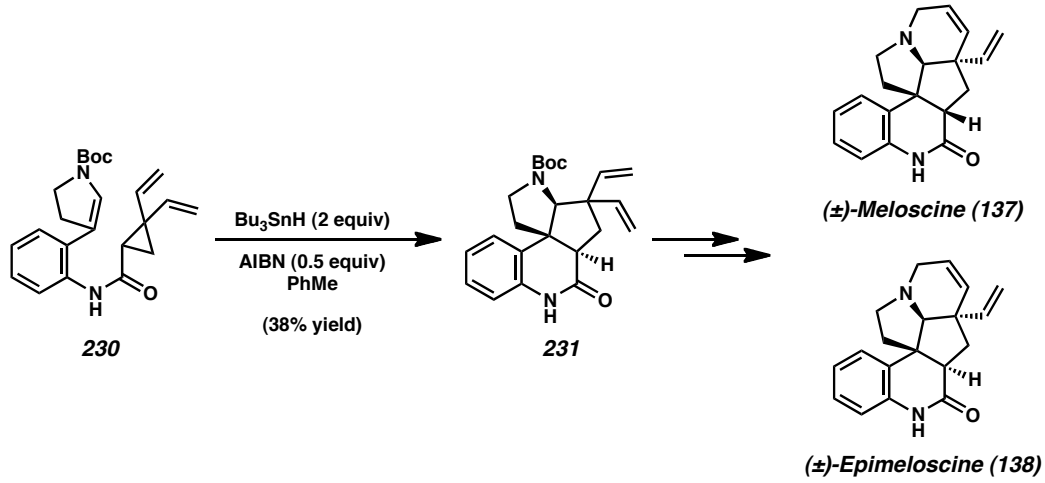
Scheme 2.3.3. Mechanistic reasoning for cycloaddition failure

228 ***229***

2.4 REVISED RETROSYNTHESIS

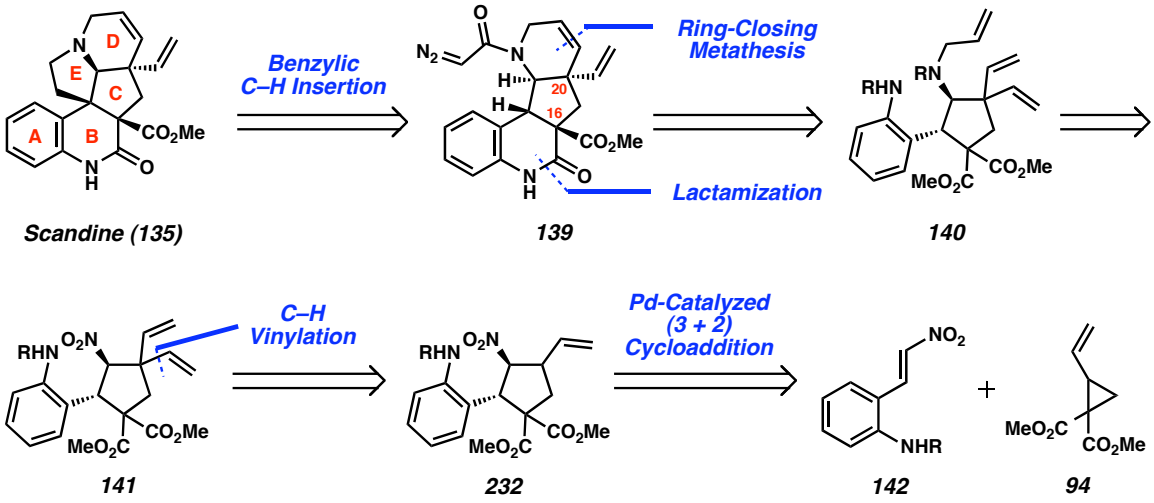
In the course of our studies, Curran and Zhang reported the total syntheses of (±)-meloscine (**137**) and (±)-epimeloscine (**138**) by a similar route to our own original proposed synthesis (Scheme 2.4.1).[7d] Their synthesis relied on an intramolecular, radical-mediated cycloaddition of a divinylcyclopropane with a pendent dihydropyrrole to provide tetracycle **231** which was quickly advanced to both natural products, using a diastereoselective ring-closing metathesis to complete the final ring. Scandine (**135**), the parent of the natural product family, was not accessed via this route, and the radical-mediated cycloaddition offered no obvious pathway for an enantioselective total synthesis; nevertheless, the similarity of their route to our own original pathway, as well as the challenges we faced in effecting a transition metal catalyzed intermolecular (3 + 2) cycloaddition encouraged us to modify our synthetic plan.

*Scheme 2.4.1. Summary of Curran's synthesis of (±)-meloscine (**137**) and (±)-epimeloscine (**138**)*



The primary revision to our synthetic plan involves using a monovinylcyclopropane (**94**) in the palladium-catalyzed (3 + 2) cycloaddition, and appending the second vinyl group at a later stage by C–H functionalization. While the (3 + 2) cycloaddition step is better supported by literature precedent, no published approach to direct C–H vinylation exists to date.

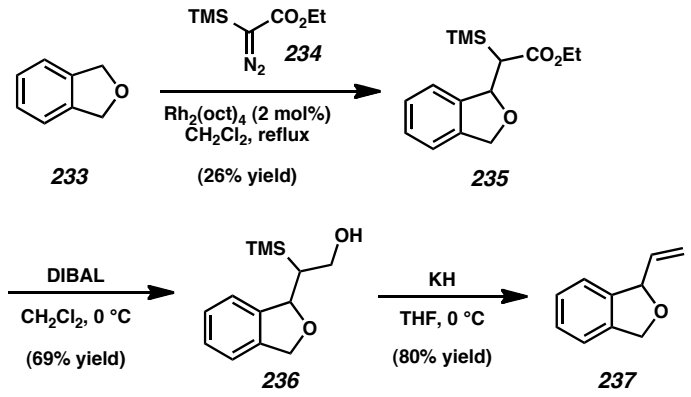
*Scheme 2.4.2. Revised retrosynthesis for scandine (**135**)*



Inspired by our synthetic proposal, Davies and coworkers have set out to develop conditions for C–H vinylation, based on their vast expertise with donor–acceptor

carbenoids.[36] In preliminary efforts, Davies found that a trimethylsilyl group on diazo **234** can serve as a moderately effective electron-donating group for C–H insertion with phthalan (**233**).[37] After reduction of the ethyl ester (**235**) with DIBAL, Peterson-type elimination of silyl alcohol **236** delivers the vinylated product (**237**) in a moderate overall yield. Efforts are currently ongoing to improve the yield of this process and apply it to more complex and synthetically relevant structures; application of this method to the natural product synthesis will require an orthogonal approach for formation of the β-hydroxysilane in the presence of the ester functionalities on the natural product. [38]

Scheme 2.4.3. Davies' preliminary C–H vinylation results

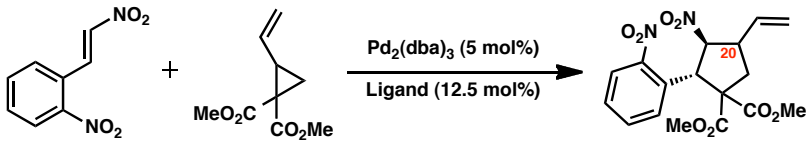


2.5 CONSTRUCTION OF THE ABCD RING SYSTEM

Our initial efforts via this route focused on examining the palladium catalyzed (3 + 2) cycloaddition with commercially available β-2-dinitrostyrene **226** and we examined several ligands, solvents and reaction temperatures (Table 2.5.1). In particular, the conservation of the *trans* relationship between the aryl ring and the styrenyl nitro group was critical, whereas the diastereoselectivity at the allylic position could prove inconsequential, upon installation of the second vinyl group at a later stage. Indeed, in all cases, we observed the formation of only two product diastereomers, and the relative

stereochemistry of each was established after reduction of the nitro groups (*vide infra*); the two products formed were differentiated only by the stereochemistry at C(20). In the course of our optimizations, we found that elevated reaction temperatures improved the reaction yield (entries 1–2). A screen of several solvents (entries 2–5) revealed THF to be optimal. The use of monodentate triphenylphosphine provided poor yields of the cyclopentane product (entry 6) and the use of dppe, a ligand originally used in Tsuji's study, offered comparable yields to GlyPHOX (entry 7). Finally, reducing the temperature from 60 °C to 40 °C proved beneficial (entry 8). Unfortunately, the catalyst loading could not be reduced without lowering the yield (entry 9), potentially due to catalyst oxidation by the nitro functionalities on the starting material and product.

Table 2.5.1. Optimization of (3 + 2) cycloaddition



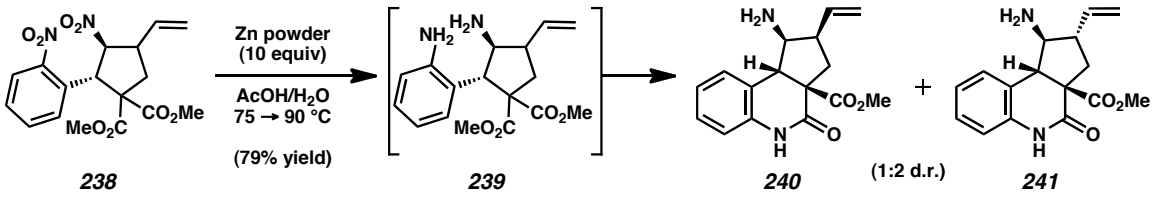
226 ***94*** ***238***

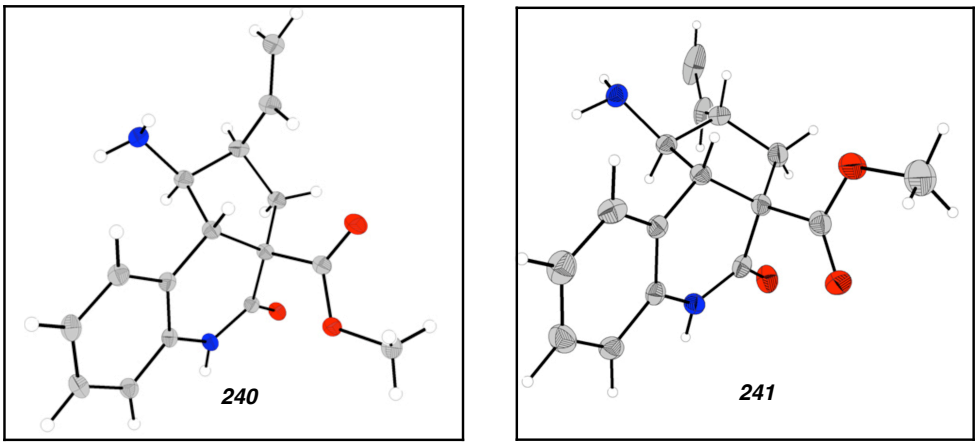
entry[a]	solvent	ligand	temperature	yield (%)[b]
1	PhMe	GlyPHOX	23 °C	21[c]
2	PhMe	GlyPHOX	60 °C	38
3	dioxane	GlyPHOX	60 °C	58
4	EtOAc	GlyPHOX	60 °C	60
5	THF	GlyPHOX	60 °C	73
6	THF	PPh_3[d]	60 °C	26
7	THF	dppe	60 °C	70
8	THF	dppe	40 °C	81 (60[c])
9	THF	dppe[e]	40 °C	19[c]

[a] 1 equiv of **226** and **94** used in each reaction. [b] ^{1}H NMR yield (hexamethylcyclotrisiloxane as internal standard). [c] Isolated yield. [d] 22.5 mol% of ligand used. [e] 2.5 mol% Pd and 6.25 mol% ligand used.

Having developed an effective method to prepare vinylcyclopentane **238**, we next examined the reduction of the nitro functionalities on the molecule. Treatment of the diastereomeric mixture of vinylcyclopentanes (**238**) with zinc in acetic acid performed the desired transformation, and the nascent aniline underwent diastereoselective lactamization to generate tricycles **240** and **241**; their structures were confirmed unambiguously by single crystal X-ray diffraction (Scheme 2.5.1).

*Scheme 2.5.1. Reduction of cyclopentane **238** to diastereomeric tricyclic lactams **240** and **241***

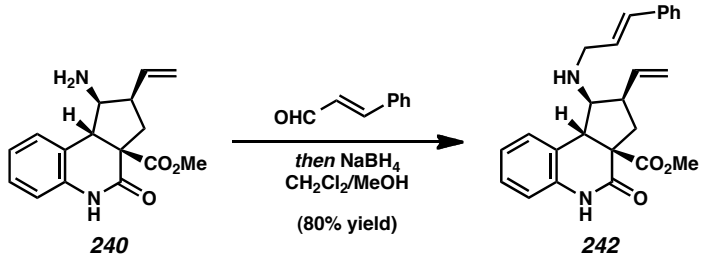




Following construction of the ABC ring system, we turned our attention to the installation of the D ring by ring-closing metathesis, using tricyclic primary amine **240** to this end. Monoalkylation of the primary amine proved non-trivial, yielding mixtures of bisalkylated product when treated with allylic electrophiles or under standard reductive amination conditions. Fortunately, preforming the cinnamaldimine, followed by dilution

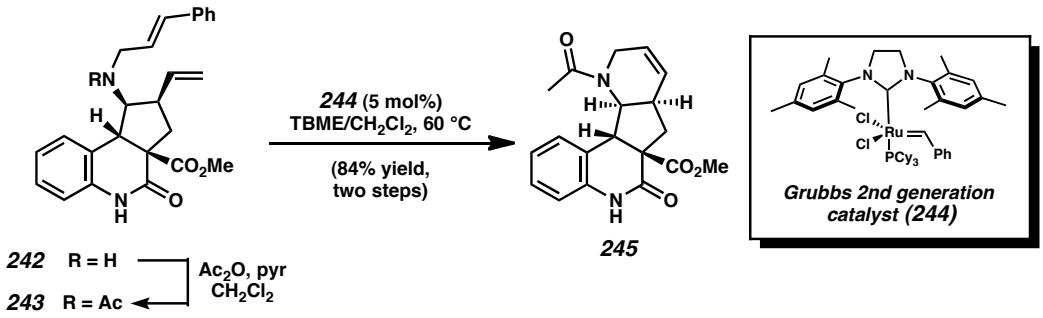
and reduction with sodium borohydride yielded secondary cinnamyl amine **242** exclusively (Scheme 2.5.2).

*Scheme 2.5.2. Reductive amination of primary amine **240***



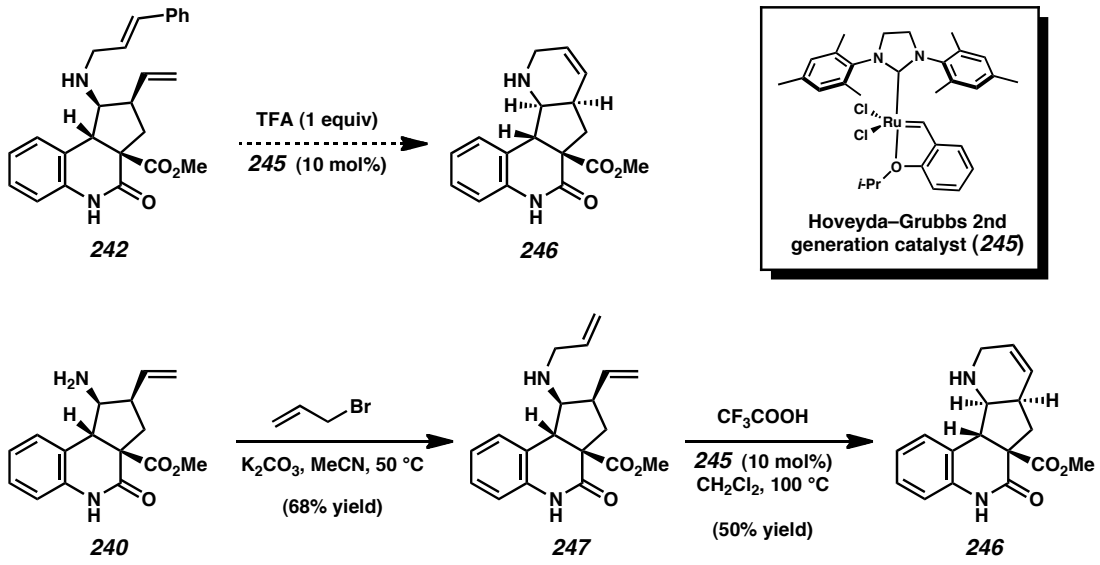
Secondary amine **242** was treated with acetic anhydride to generate acetamide **243**, which precipitated cleanly from the reaction mixture and could be advanced to the ring-closing metathesis step without additional purification. We encountered solubility issues in the following stage; acetamide **243** was found to be insoluble in several organic solvents commonly employed in olefin metathesis. Conveniently, we found that at elevated temperatures, acetamide **243** was soluble in a 1:1 mixture of *tert*-butyl methyl ether and dichloromethane. Therefore, a suspension of the metathesis substrate in a solution of Grubbs 2nd generation catalyst (**244**) in this solvent system became homogeneous at the desired reaction temperature; upon cooling, the metathesis product (**245**) precipitated from the reaction mixture with > 95% purity based on NMR analysis.

*Scheme 2.5.3. Ring-closing metathesis of cinnamyl amine **242***



Efforts are ongoing to complete the pentacyclic framework of the *Melodinus* alkaloids by benzylic C–H activation. Attempts to directly diazotize acetamide **245** were unsuccessful, as were our efforts to cleave the acetate, so we turned instead to examining the ring-closing metathesis on an unprotected secondary amine, then appending the diazoacetamide fragment separately. It has previously been demonstrated that protonation of secondary amines can serve to prevent their coordination to metathesis catalysts, allowing for an in situ protection of the amine.[39] This approach was unsuccessful for conversion of cinnamyl amine **242** to the desired tetracyclic secondary amine (**246**). Nevertheless, allyl amine **247** was a competent substrate for this transformation albeit in low overall yield (Scheme 2.5.4).[40]

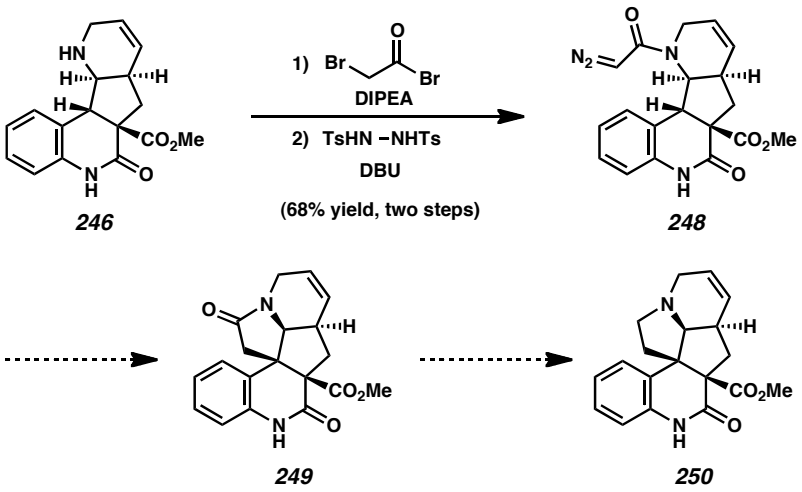
*Scheme 2.5.4. Synthesis of tetracyclic secondary amine **246***



The free tetracyclic secondary amine (**246**) could then be converted to the diazoacetamide (**248**) by a two-step procedure reported by Fukuyama.[41] Unfortunately, efforts to date to perform the desired benzylic C–H insertion have produced only complex product mixtures, and we have not isolated the desired pentacyclic core (**249**) of

the natural product family to date. When this transformation is accomplished, reduction of the tertiary lactam in the presence of the methyl ester and quinolinone moieties will afford the pentacyclic skeleton of scandine (**250**), absent the C(20) vinyl group. We predict that the presence of two alkyl substituents on the tertiary lactam will improve its reactivity with Lewis acidic reductants, compared to the secondary, quinolinone lactam, which is also adjacent to a quaternary center.[42]

*Scheme 2.5.5. Synthesis of diazoacetamide (**248**), proposed C–H insertion and lactam reduction*



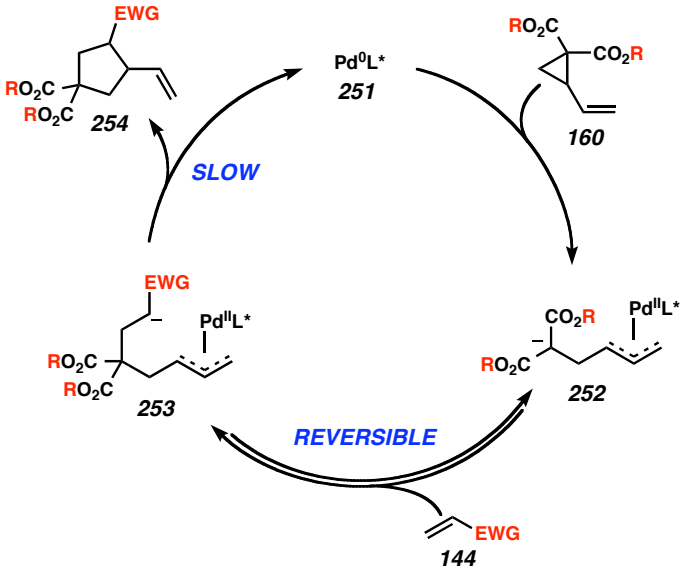
2.6 OUTLOOK

The remaining challenges to overcome in the synthesis of the scandine (**135**) include the benzylic C–H insertion of diazoacetamide **248**, installation of the C(20) vinyl group, and rendering the synthesis enantioselective. Finally, the derivatization of scandine (**135**) to other members of the natural product family will be examined; a strategy to this end will be discussed in this section.

2.6.1 ENANTIOSELECTIVE TOTAL SYNTHESIS

With the goal of rendering the synthesis of the *Melodinus* alkaloids enantioselective, we will draw on the studies by Trost and co-workers on the enantioselective vinylcyclopropane (3 + 2) cycloaddition.[12] The unifying feature of their system is the use of an electron-withdrawing diester component on the cyclopropane (**160**), and an electron-poor conjugate acceptor (**144**, Scheme 2.6.1). These two components, together, contribute to the reversibility of the conjugate addition step of the catalytic cycle; an electron-poor diester makes for a good leaving group in the retro-Michael reaction, and an electron-poor conjugate acceptor likely slows the ring-closing allylation step.

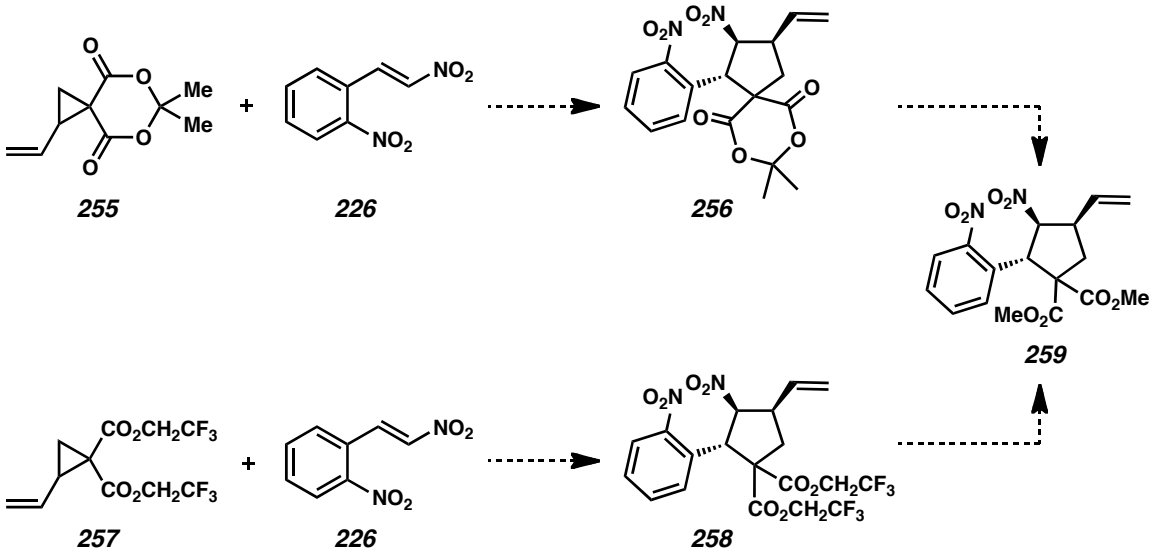
Scheme 2.6.1. Mechanism of Trost's enantioselective (3 + 2) cycloaddition.



We envision that nitrostyrene **226** may be a suitable partner in an enantioselective (3 + 2) cycloaddition with Meldrum's acid derived cyclopropane **255** or bis(trifluoroethyl)malonate derivative **257** (Scheme 2.6.2). Although the pKa of a nitroalkane (~10)[43] is higher than that of a Meldrum's acid derivative (~5)[44] or an azlactone (~9),[45] it is conceivable that the reversibility of the conjugate addition will be

aided by the extended conjugation of the dinitrostyrene conjugate acceptor (**226**). The cyclopentane product of either (3 + 2) cycloaddition could be converted to dimethyl ester **259** using procedures reported by Trost in the same account.

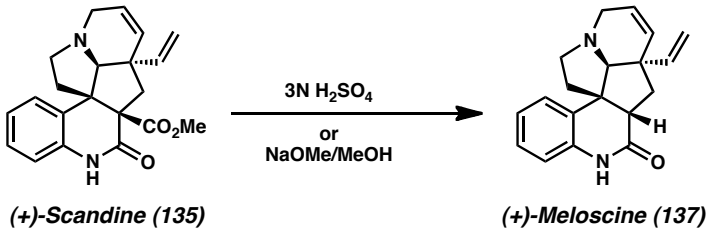
*Scheme 2.6.2. Proposed enantioselective (3 + 2) cycloaddition with nitrostyrene (**226**)*



2.6.2 DERIVATIZATION OF SCANDINE TO OTHER NATURAL PRODUCTS

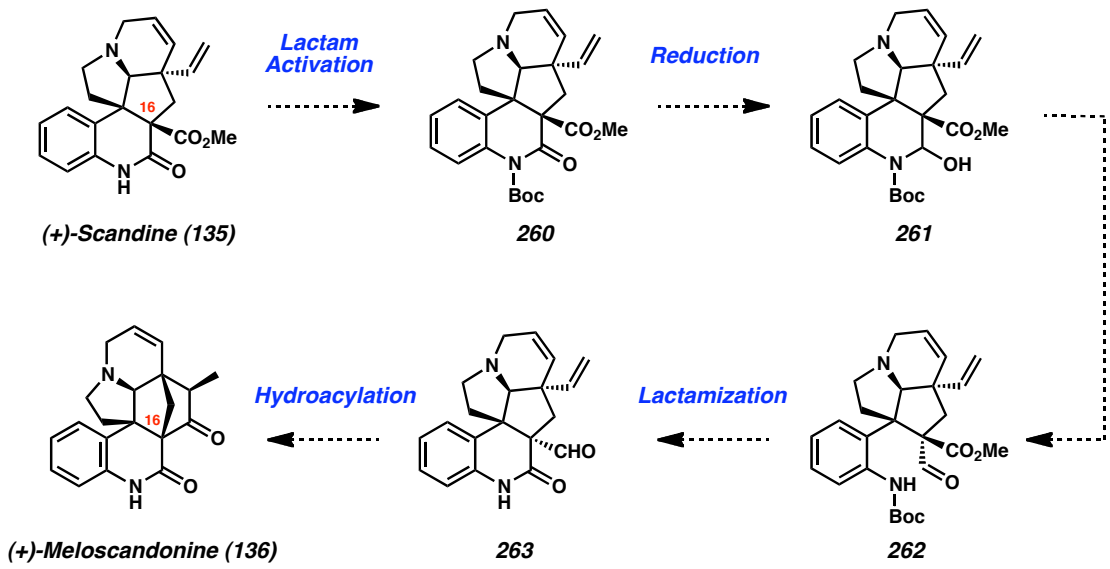
The conversion of scandine (**135**) to meloscine (**137**) was demonstrated by Bernauer and coworkers in 1969 (Scheme 2.6.3).[1b] However, the synthesis of any other member of the natural product family from scandine has not been accomplished to our knowledge.

*Scheme 2.6.3. Conversion of scandine (**135**) to meloscine (**137**)*



We propose the synthesis of meloscandonine (**136**) from scandine (**135**) by means of an inversion of the stereochemistry at C(16), followed by C–C bond formation with the C(20) vinyl group (Scheme 2.6.4). Envisioned is an activation of the quinolinone carbonyl by forming Boc imide **260** followed by reduction to hemiaminal **261**. The stereochemistry at C(16) could be inverted by reversible ring-opening of the hemiaminal, followed by irreversible lactamization with the methyl ester, with loss of methanol, to form aldehyde **263**. Finally, intramolecular hydroacylation of the C(20) vinyl group would complete the synthesis of meloscandonine (**136**).[46]

*Scheme 2.6.4. Proposed synthesis of meloscandonine (**136**) from scandine (**135**)*



2.7 CONCLUSION

In summary, efforts to synthesize and apply a 1,1-divinylcyclopropane toward the total synthesis of scandine are described. Furthermore, we have applied a monovinylcyclopropane toward the preparation of a tetracyclic precursor to scandine

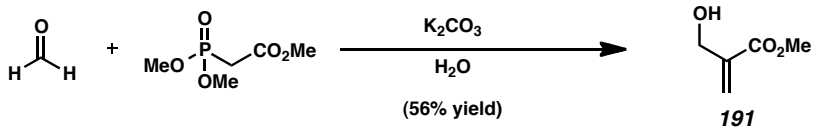
(**135**) via palladium-catalyzed (3 + 2) cycloaddition with a nitrostyrene (**226**) followed by ring-closing metathesis. Efforts are currently underway to complete the total synthesis by sequential C–H activation of the benzylic and allylic positions.

2.8 EXPERIMENTAL SECTION

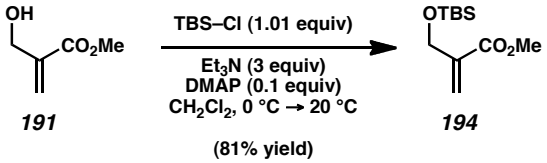
2.8.1 MATERIALS AND METHODS

Unless stated otherwise, reactions were performed under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).[47] Commercially obtained reagents were used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, or potassium permanganate, iodine, or anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz respectively), Varian 400 (at 400 MHz and 100 MHz, respectively) or on a Varian Mercury 300 (at 300 MHz) and are reported relative to $CHCl_3$ (δ 7.26 & 77.16 respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

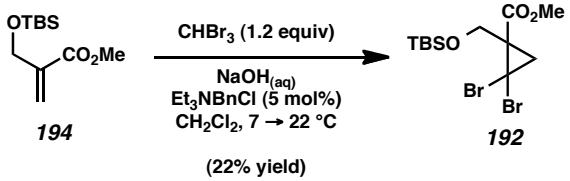
2.8.2 PREPARATIVE PROCEDURES



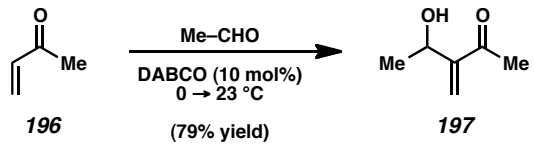
Acrylate 191. Synthesized by a method adapted from Villieras and Rambaud.[21] To a round-bottom flask were added trimethyl phosphonoacetate (9.1 mL, 63 mmol, 1 equiv) and formaldehyde (20.5g, 37% in water, 252 mmol, 4 equiv). The flask was lowered into a room-temperature water bath. To the mixture was added a saturated solution of potassium carbonate in water (15.3 g, 110 mmol, 1.75 equiv) dropwise via addition funnel over the course of one hour, and stirring was continued for an additional hour. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride (30 mL), then extracted three times with diethyl ether. The combined organics were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Methyl acrylate, produced as a side-product, was mostly removed by azeotropic distillation with methanol. The residue was purified by vacuum distillation (~0.5 torr, 44 °C) to afford acrylate **191** as a clear oil (4.07 g, 56% yield) with minor impurities which were carried forward to the next reaction. The characterization data matched those reported in the literature.[48]



Silyl ether 194. To a flame-dried round-bottom flask equipped with a stir bar were added *tert*-butyl dimethyl silyl chloride (5.34 g, 35.4 mmol, 1.01 equiv), 4-(*N*,*N*-dimethylamino)pyridine (430 mg, 3.5 mmol, 0.1 equiv), and the flask was sealed with a rubber septum and placed under an inert atmosphere. Dichloromethane (75 mL, 0.48 M) was added and the solution was cooled in an ice-water bath. Acrylate **191** (4.0711 g, 35.0 mmol, 1 equiv) was added to the solution, followed by a dropwise addition of triethylamine (15 mL, 105.2 mmol, 3 equiv) to give a cloudy suspension. The reaction mixture was allowed to warm slowly to ambient temperature (23 °C) and TLC analysis showed complete conversion after 11 hours. The reaction mixture was vacuum filtered through a fritted funnel to remove ammonium salts, and washed with cold, aqueous hydrochloric acid (1N, 75 mL). The aqueous layer was back-extracted with dichloromethane (3 x 10 mL, 1 x 20 mL). The combined organics were washed with saturated aqueous sodium bicarbonate (70 mL) and the aqueous layer was back-extracted with dichloromethane (3 x 10 mL). The combined organics were washed with brine (40 mL) and the aqueous layer was back-extracted with dichloromethane (2 x 10 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (30:1 hexanes:EtOAc) to afford silyl ether **194** (6.5294 g, 81% yield) as a clear oil. The characterization data matched those reported in the literature.[49]

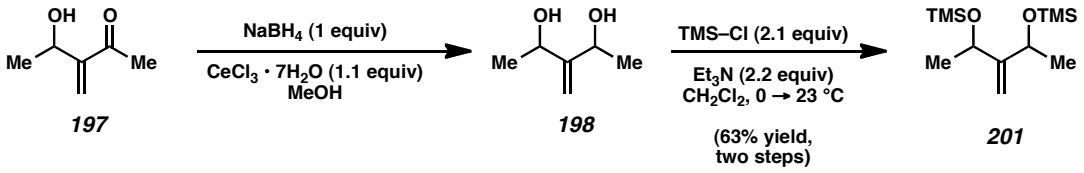


Cyclopropane 192. To a round-bottom flask were added silyl ether **194** (2.0 g, 8.7 mmol, 1 equiv), bromoform (0.91 mL, 10.4 mmol, 1.2 equiv), and triethylbenzylammonium chloride (100 mg, 0.43 mmol, 0.05 equiv). The reaction mixture was cooled in a 7 °C bath, and sodium hydroxide (1.6 mL, 50% in water) was added dropwise; a brown precipitate was observed upon addition of base. The reaction mixture was slowly warmed to ambient temperature (22 °C) and stirred for 18 hours. The reaction mixture was quenched by addition of sulfuric acid (7 mL, 5% in water), diluted with water (20 mL), and extracted with dichloromethane (3 x 30 mL); on the second wash, an emulsion formed, and was homogenized by addition of brine (15 mL). The combined organics were washed with brine (20 mL). The combined aqueous layers was acidified with sulfuric acid (20 mL, 5% in water) and extracted with ethyl acetate (2 x 50 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (30:1 → 5:1 hexanes:EtOAc) to afford dibromocyclopropane **192**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 (d, *J* = 10.5 Hz, 1H), 3.79 (s, 3H), 3.56 (d, *J* = 10.4 Hz, 1H), 2.40 (d, *J* = 8.0 Hz, 1H), 1.87 (d, *J* = 8.1 Hz, 1H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 66.5, 52.9, 40.7, 30.7, 25.8, 18.3, -5.2, -5.4; IR (NaCl/film) 2953, 2859, 1748, 1434, 1251, 1160, 1100, 836, 777 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{23}O_3Si^{79}Br_2$ $[M+H]^+$: 400.9778, found 400.9776.



196 *197*

Hydroxyketone 197. Prepared according to the procedure of Koert et al.[22] 1,4-Diazabicyclo[2.2.2]octane (5.98 g, 50 mmol, 0.1 equiv) and acetaldehyde (27.40 mL, 465 mmol, 1 equiv) were added to a round-bottom flask, which was cooled in an ice-water bath. Methyl vinyl ketone (40 mL, 480 mmol, 1 equiv) was added dropwise via addition funnel over 8 hours with stirring, and the resulting solution was stirred at this temperature for an additional 2 hours, then warmed to ambient temperature (23 °C), and stirred for an additional 11 hours. The reaction mixture was partitioned between diethyl ether (300 mL) and aqueous hydrochloric acid (50 mL, 1N), and the resulting biphasic mixture was separated. The aqueous layer was extracted with diethyl ether (2 x 100 mL). The combined organics were washed with saturated aqueous sodium bicarbonate, and the aqueous layer was back-extracted with diethyl ether (2 x 100 mL). The combined organics were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by vacuum distillation (5.4 torr, 71 °C; lit: 6 torr, 80 °C) to afford hydroxyketone **197** (42.18 g, 79% yield) as a colorless oil. The spectral data matched those reported by Koert et al.

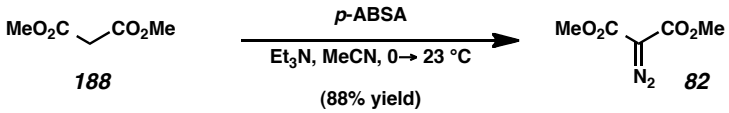


Disilylether 201. To a round-bottom flask, equipped with a magnetic stir bar, were added hydroxyketone **197** (5.00 g, 43.8 mmol, 1 equiv), cerium trichloride heptahydrate (18.0 g, 48.2 mmol, 1.1 equiv) and undistilled methanol (220 mL, 0.2 M). The flask was lowered into an ice-water bath, and sodium borohydride (1.66 g, 43.8 mmol, 1 equiv) was

added in portions. Upon consumption of starting material, as observed by TLC, acetone (10 mL) was added, and the reaction mixture was concentrated in vacuo. The residue was partitioned between ethyl acetate (150 mL) and a saturated solution of sodium potassium tartrate (150 mL), and stirred overnight; the aqueous phase became a creamy yellow suspension. To the biphasic mixture was added saturated aqueous ammonium chloride (50 mL) and deionized water (100 mL), and the phases were separated. The aqueous layer was extracted with dichloromethane (150 mL); a emulsion resulted, which was clarified by addition of brine (50 mL). The combined organics were dried over sodium sulfate, filtered and concentrated in vacuo to afford crude diol **198** (3.7031 g, 73% yield).

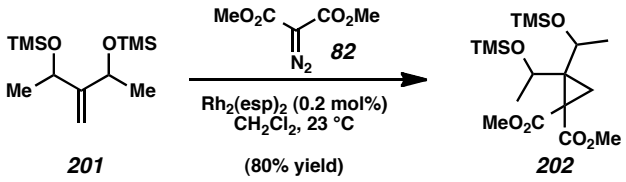
To a flame-dried round-bottom flask was added crude diol **198** (1.000 g, 8.61 mmol, 1 equiv). The flask was sealed with a rubber septum and placed under an inert atmosphere. Dichloromethane (86 mL, 0.1 M) and freshly distilled triethylamine (2.7 mL, 18.9 mmol, 2.2 equiv) were added, and the flask was cooled in an ice-water bath with stirring. To the stirring solution was added freshly distilled trimethylsilyl chloride (2.3 mL, 18.1 mmol, 2.1 equiv) dropwise over 15 minutes, and the reaction mixture was warmed to ambient temperature. Upon consumption of starting material, as observed by TLC, the reaction mixture was poured into an aqueous solution of sodium bicarbonate (100 mL, 10%), and the phases were separated. The aqueous layer was extracted with dichloromethane (50 mL). The combined organics were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (2:1 hexanes:diethyl ether) to afford a mixture of diastereomeric silyl ethers **201** (1.9228 g, 86%, 63% over two steps) as a

clear oil: R_f = 0.56 (9:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 5.11 (t, *J* = 1.1 Hz, 2H), 4.28 (qt, *J* = 6.4, 1.1 Hz, 2H), 1.27 (d, *J* = 6.4 Hz, 6H), 0.11 (s, 18H); ^{1}H NMR (400 MHz, $CDCl_3$, minor diastereomer) δ 5.07 (t, *J* = 0.8 Hz, 2H), 4.37 (q, *J* = 6.3 Hz, 2H), 1.28 (d, *J* = 6.6 Hz, 6H), 0.11 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, major diastereomer) δ 157.0, 107.7, 68.5, 25.0, 0.2; ^{13}C NMR (101 MHz, $CDCl_3$, minor diastereomer) δ 156.5, 108.5, 68.4, 24.4, 0.3; IR (NaCl/film) 2963, 1652, 1449, 1370, 1249, 1100, 972, 838 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{29}O_2Si_2$ $[M+H]^+$: 261.1701, found 261.1703.



Diazodimethylmalonate 82. According to the method of Tullis and Helquist, with minor modifications.[50] To a flame-dried round-bottom flask were sequentially added *p*-acetamidobenzenesulfonyl azide[51] (34.72 g, 144.6 mmol, 1.01 equiv), acetonitrile (500 mL), and freshly distilled triethylamine (21.4 mL, 153.6 mmol, 1.07 equiv), and the resulting homogeneous mixture was cooled in an ice-water bath. To the stirring solution was added dimethylmalonate (16.4 mL, 143.4 mmol, 1 equiv) dropwise over approximately 5 minutes; over the course of the addition, the solution become yellow. The ice-water bath was removed and the reaction mixture was stirred for 17 hours. After this time, a thick slurry was observed, which was vacuum-filtered through a fritted funnel, washing the filter cake with 1:1 hexanes:diethyl ether (400 mL). The solution was concentrated in vacuo, and a thick slurry resulted. The slurry was passed through the same filter cake, washing with 1:1 hexanes:diethyl ether (> 500 mL, the yellow color was

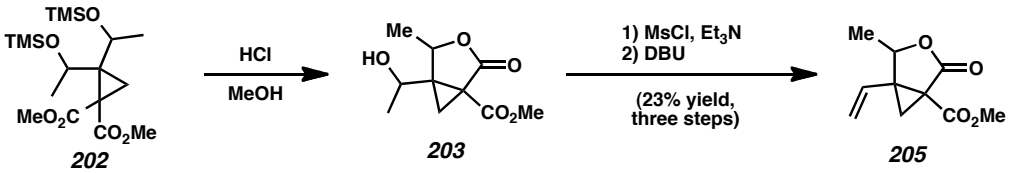
mostly removed from the filter cake). The solution was concentrated in vacuo and the residue was purified by vacuum distillation (62 °C, 1.84 torr, *CAUTION*)[52] to afford diazodimethylmalonate **82** (19.9 g, 88% yield) as a yellow oil.



201 *202*

Cyclopropane 202. To a flame-dried round-bottom flask, equipped with a magnetic stir bar, were added olefin **201** (689.0 mg, 2.6 mmol, 1 equiv), bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] (2.0 mg, 2.5 μmol, 0.001 equiv), and dichloromethane (2.5 mL). The flask was sealed and placed under an inert atmosphere. To a separate, flame-dried flask was added diazodimethylmalonate (0.33 mL, 2.6 mmol, 1 equiv) and dichloromethane (2.5 mL) under an inert atmosphere. This mixture was taken up in a syringe and transferred by syringe pump to the first flask, over 3 hours. The reaction mixture was concentrated in vacuo, and filtered through a short plug of SiO_2 (3:1 hexanes:EtOAc). The crude product was then purified by column chromatography on SiO_2 (25:1 hexanes:EtOAc) to afford cyclopropane **202** (458.8 mg, 80% yield) as a 20:12:3 mixture of diastereomers: R_f = 0.41 (9:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, integration referenced to major diastereomer) δ 4.24 (q, *J* = 6.5 Hz, 1H) 4.20 (q, *J* = 6.4 Hz, 1.2H), 4.04 (q, *J* = 6.4 Hz, 0.37H), 3.92 (q, *J* = 6.5 Hz, 1H), 3.73 – 3.64 (m, 10.7H), 1.67 – 1.59 (m, 1.5H), 1.45 – 1.33 (m, 8.3H), 1.29 – 1.20 (m, 3.5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 169.3, 168.9, 168.5, 70.3, 68.2, 66.9, 66.9, 52.8, 52.5, 52.4, 52.3, 46.1, 45.2, 38.2, 37.3, 23.1, 23.0, 22.3, 22.2, 21.5, 21.4, 20.6, 0.7, 0.4, 0.3, 0.2; IR

(NaCl/film) 2958, 2903, 1733, 1434, 1251, 1100, 982, 841 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{34}O_6Si_2$ $[M+H]^+$: 391.1967, found 391.1981.

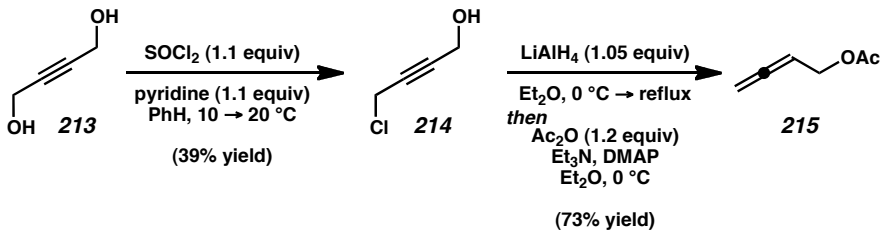


Vinylcyclopropane 205. To a solution of silyl ether **202** (249.3 mg, 0.64 mmol, 1 equiv) in methanol (6.4 mL) was added a drop of aqueous hydrochloric acid (1 N). After 15 minutes, the reaction mixture was diluted with deionized water (30 mL) and dichloromethane (10 mL). The phases were separated and the aqueous phase was washed with dichloromethane (4 x 20 mL). The combined organics were washed with brine (20 mL) and the aqueous phase was back-extracted with dichloromethane (20 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated to afford crude alcohol **203** (157.5 mg, 99% yield) as a complex mixture of diastereomers which was carried forward without further purification.

A flame-dried round-bottom flask was charged with alcohol **203** (385.4 mg, 1.8 mmol, 1 equiv), sealed with a rubber septum, and placed under an inert atmosphere. To the flask were added dichloromethane (10 mL, 0.2 M) and mesyl chloride (155 μL, 1.98 mmol, 1.1 equiv), then the flask was cooled in an ice bath and stirred. Triethylamine (0.38 mL, 2.16 mmol, 1.2 equiv) was added dropwise to the stirring solution and warmed to room temperature. The reaction was quenched after 10 minutes with water (3 mL) and saturated aqueous ammonium chloride (3 mL), the phases were separated, and the aqueous layer was extracted with additional dichloromethane (10 mL). The combined

organics were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (1:1 hexanes:EtOAc) to afford mesylate **204** as a complex mixture of diastereomers.

A round-bottom flask was charged with mesylate **204**, THF (6 mL, 0.25 M) and DBU (0.67 mL, 4.5 mmol, 3 equiv), and fitted with a reflux condenser. The solution was heated in an oil bath to reflux, and stirred for 15 hours. Upon completion, the solvent was evaporated and the residue was purified by column chromatography (5:1 hexanes:EtOAc) to afford vinylcyclopropane **205** (82.9 mg, 23% yield over two steps): ^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ 5.78 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.42 – 5.26 (m, 2H), 4.83 (q, *J* = 6.3 Hz, 1H), 3.79 (s, 3H), 2.19 (d, *J* = 5.3 Hz, 1H), 1.59 (d, J = 5.4 Hz, 1H), 1.36 (d, *J* = 6.3 Hz, 3H); ^{1}H NMR (300 MHz, $CDCl_3$, minor diastereomer) δ 5.96 (dd, *J* = 17.1, 10.1 Hz, 1H), 5.45 – 5.37 (m, 2H), 4.52 (q, *J* = 6.5 Hz, 1H), 3.78 (s, 3H), 2.32 (d, *J* = 5.0 Hz, 1H), 1.51 (d, *J* = 4.8 Hz, 1H), 1.47 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, major diastereomer) δ 170.3, 165.5, 130.2, 119.7, 76.1, 53.1, 45.0, 38.1, 21.1, 16.3; IR (NaCl/film) 3087, 2993, 2948, 1780, 1731, 1441, 1365, 1221, 1098, 1041, 940 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{12}O_4Na$ $[M+Na]^+$: 219.0628, found 219.0631.

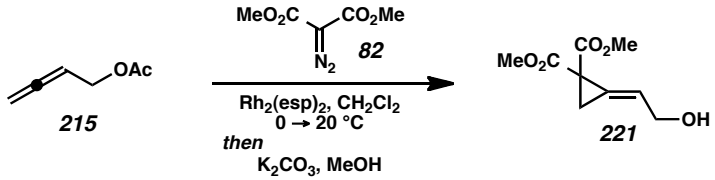


Allene 215. Synthesized by a procedure adapted from the literature.[27] A round-bottom flask containing 2-butyne-1,4-diol (86.0 g, 1.00 mol, 1 equiv), pyridine (89.0 mL, 1.1 mol, 1.1 equiv) and benzene (100 mL) was cooled in a 10 °C bath and stirred. Thionyl chloride (80.2 g, 1.1 mol, 1.1 equiv) was added dropwise by addition funnel over 4.5 hours, and the reaction mixture was allowed to warm slowly to ambient temperature (20 °C), and stirred overnight. Throughout the addition, a biphasic mixture was observed as well as a precipitate. The reaction mixture was poured into ice-cold water (250 mL) and the phases were separated. The aqueous layer was extracted with diethyl ether (4 x 100 mL). The combined organics were washed with water (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL), then dried over magnesium sulfate, filtered, and concentrated in vacuo to afford a brown oil. The residue was purified by fractional distillation (1.30–1.05 torr, 47–57 °C), and redistilled (1.3 torr, 56–60 °C) to afford alkyne **214** as a clear oil (41.0 g, 39% yield). Spectral data matched those reported in the literature.[27a]

To a 1 L, 3-neck flask, equipped with a reflux condenser, addition funnel, and a magnetic stirrer was added lithium aluminum hydride (8.39 g, 210 mmol, 1.05 equiv). The system was then sealed with rubber septa, purged with inert gas, freshly distilled diethyl ether (250 mL) was added, and the flask was cooled in an ice-water bath. Alkyne **214** (20.89 g, 200 mmol, 1 equiv) and diethyl ether (150 mL) were added to the addition funnel, and the resulting solution was added at such a rate to allow the receiving solution to reflux and evolve hydrogen gas gently; the alkyne addition proceeded over 1.25 hours. Complete consumption of starting material was observed after an additional 1 hour of stirring. The reaction was quenched by careful, dropwise addition of water (8.4 mL) via

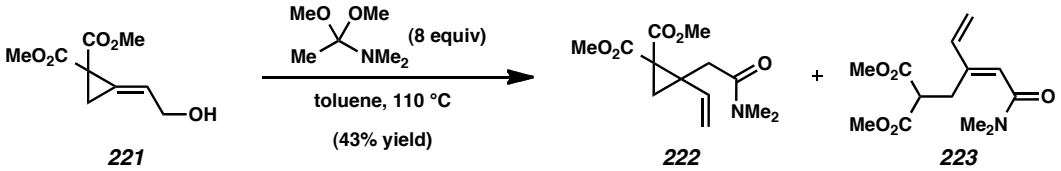
the addition funnel, followed by aqueous sodium hydroxide (8.4 mL, 15%), then additional water (25.2 mL). Finally, anhydrous magnesium sulfate was added to the stirring mixture, and the entire suspension was vacuum filtered through a plug of celite on a fritted filter, directly into a second 1 L flask, washing with diethyl ether.

To the resulting solution were added 4-(*N*,*N*-dimethylamino)pyridine (2.45 g, 20 mmol, 0.1 equiv) and freshly distilled triethylamine (36 mL, 260 mmol, 1.3 equiv), and the flask was sealed with a rubber septum, placed under an inert atmosphere and cooled in an ice-water bath. Acetic anhydride (22.6 mL, 240 mmol, 1.2 equiv) was added dropwise to the solution, and TLC analysis following the addition revealed complete conversion to the desired acetate. The reaction mixture was diluted to a volume of approximately 500 mL with diethyl ether, and was washed with 10% aqueous hydrochloric acid (4 x 75 mL). The combined aqueous layers were washed once with diethyl ether (75 mL). The combined organics were washed with brine and dried over magnesium sulfate, filtered, and concentrated carefully in vacuo (*volatile product!*). The residue was purified by vacuum distillation (110–85 torr, 90 °C) to afford allene **215** as a colorless oil (22.4 g, 73% yield), which should be kept in a –20 °C freezer for prolonged storage—becomes discolored over time at room temperature: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (app p, J = 6.8 Hz, 1H), 4.85 (d, J = 6.6 Hz, 2H), 4.57 (d, J = 7.0 Hz, 2H); 2.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.8, 170.8, 86.4, 76.6, 62.2, 20.9; IR (NaCl/film) 2948, 1956, 1736, 1436, 1377, 1362, 1229, 1029, 853 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_6H_8O_2$ $[M+H]^+$: 112.0524, found 112.0517.



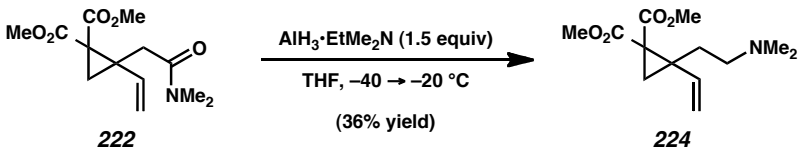
Alkylidenecyclopropane 221. A flame-dried 250 mL round-bottom flask, equipped with a magnetic stir bar, was charged with bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] (6.4 mg, 8.4 μmol, 0.0002 equiv) and sealed with a rubber septum. The flask was evacuated and backfilled with argon three times, then charged with dichloromethane (30 mL) and allene **215** (4.00 mL, 34.8 mmol, 1 equiv), and cooled in an ice-water bath. To a separate, flame-dried flask was added diazodimethylmalonate **82** (5.66 mL, 45.2 mmol, 1.3 equiv) and dichloromethane (30 mL). The diazo solution was transferred to the first flask by syringe over 10 minutes. The resulting mixture was stirred for ten minutes, then warmed to ambient temperature with continued stirring. After 4.5 hours, the solvent was evaporated in vacuo, and redissolved in methanol (150 mL). To the resulting solution was added potassium carbonate (500 mg, 3.6 mmol, 0.1 equiv), and this mixture was stirred for 1 hour. At this time, additional potassium carbonate (400 mg, 2.9 mmol) was added, and the mixture was stirred for an additional hour. The mixture was then poured into a 1 L round-bottom flask containing water (75 mL) and saturated aqueous ammonium chloride (75 mL). Methanol was evaporated *in vacuo*, then the remaining aqueous solution was extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine (75 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (6:5 hexanes/EtOAc) to provide alkylidenecyclopropane **221** (5.97 g, 94% yield). $R_f = 0.28$ (1:1 hexanes/Et_2O); ^1H NMR (300 MHz, $CDCl_3$, major

diastereomer) δ 6.21 (tt, *J* = 5.6, 2.7 Hz, 1H), 4.36 (d, *J* = 5.6 Hz, 2H), 3.74 (s, 6H), 2.29 – 2.21 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 123.1, 120.3, 61.9, 52.9, 30.7, 18.0; IR (Neat Film/NaCl) 3469, 2953, 1731, 1439, 1315, 1266, 1105 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_{12}O_5Na$ [M]$^+$: 223.0577; found 223.0586.



Vinylcyclopropane 222. A flame-dried 250 mL round-bottom flask, equipped with a magnetic stir bar, was charged with alcohol **221** (801.8 mg, 4 mmol, 1 equiv), toluene (50 mL), and dimethylacetamide dimethyl acetal (5 mL, 34 mmol, 8.5 equiv). The flask was then fitted with a reflux condenser and a rubber septum, placed under a positive pressure of nitrogen gas, and heated to reflux in a preheated oil bath. The reaction was stirred for two hours, then cooled to room temperature. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (3:2 → 1:1 → 2:3 hexanes:EtOAc) to afford vinylcyclopropane **222** (460.0 mg, 43% yield) and conjugated amide **223** (as a mixture of olefin isomers). **222**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 17.2, 10.5 Hz, 1H), 5.10 (d, *J* = 10.5 Hz, 1H), 5.06 (d, *J* = 17.2 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.01 (d, *J* = 16.7 Hz, 1H), 2.98 (s, 3H), 2.93 (s, 3H), 2.83 (d, *J* = 16.5 Hz, 1H), 1.99 (d, *J* = 5.6 Hz, 1H), 1.64 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 169.7, 168.1, 137.1, 116.3, 52.9, 52.8, 39.7, 37.2, 35.5, 35.5, 35.2, 24.4; IR (NaCl/film) 3474, 2948, 1728, 1652, 1434, 1301, 1263, 1224, 1110 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{20}NO_5$ [M+H]$^+$: 270.1336, found 270.1363. **223**: ^{1}H NMR (400 MHz,

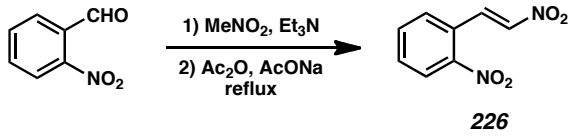
$CDCl_3$, olefin isomer 1) δ 6.30 (dd, *J* = 17.5, 10.9 Hz, 1H), 6.10 (s, 1H), 5.47 (d, *J* = 17.5 Hz, 1H), 5.27 (d, *J* = 10.9, 1H), 3.81 (t, *J* = 7.6 Hz, 1H), 3.68 (s, 6H), 3.17 (d, *J* = 7.7 Hz, 2H), 3.01 (s, 3H), 2.98 (s, 3H); 1H NMR (400 MHz, $CDCl_3$, olefin isomer 2) δ 6.83 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.97 (s, 1H), 5.45 (d, *J* = 18.1 Hz, 1H), 5.31 (d, *J* = 11.1 Hz, 1H), 3.73 (s, 6H), 3.67 (t, *J* = 7.5 Hz, 1H), 2.98 – 2.90 (app m, 8H).



222 ***224***

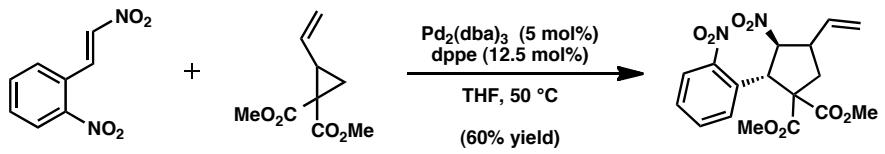
Amine 224. A flame-dried round-bottom flask, equipped with a magnetic stir bar, was charged with amide **222** (53.3 mg, 0.2 mmol, 1 equiv), sealed with a rubber septum, and placed under an inert atmosphere. THF (3 mL, 0.2 M) was added, and the reaction mixture was cooled to –40 °C. Alane was added dropwise as a 0.5 M solution in toluene (0.4 mL, 0.2 mmol, 1 equiv), and the solution was stirred for one hour, slowly allowing the cooling bath to warm to –20 °C. Upon completion, methanol (100 μL) was added to quench unreacted alane, and the reaction mixture was partitioned between ethyl acetate and water. The phases were separated and the aqueous phase was extracted with ethyl acetate (3x). The combined organics were washed with brine, dried over anhydrous sodium sulfate, decanted, and concentrated in vacuo. The residue was purified by column chromatography (20:1 $CHCl_3$:MeOH with 0.1% Et_3N) to afford dimethyl amine **224** (18.3 mg, 36% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (dd, *J* = 17.2, 10.5 Hz, 1H), 5.18 (dd, *J* = 10.5, 0.9 Hz, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 2.43 (ddd, *J* = 9.9, 5.7, 3.8 Hz, 2H), 2.28 (s, 6H), 2.04 (ddd, *J* = 13.9, 10.5, 6.0 Hz, 1H),

1.85 (d, J = 5.5 Hz, 1H), 1.80 (ddd, J = 13.5, 10.0, 6.4 Hz, 1H), 1.58 (d, J = 5.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 167.8, 135.9, 117.6, 57.0, 52.9, 52.7, 45.2, 40.7, 37.2, 29.2, 23.7; IR (NaCl/film) 2953, 2764, 1731, 1437, 1298, 1224, 1108 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{13}H_{22}NO_4$ $[M+H]^+$: 256.1543, found 256.1548.



226

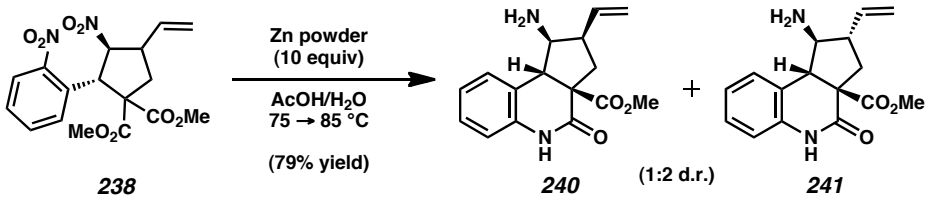
β-2-dinitrostyrene 226. Prepared by a modified procedure from Solomonovici et al.[53] To a round-bottom flask equipped with a magnetic stir bar were added 2-nitrobenzaldehyde (40.00 g, 265 mmol, 1 equiv), nitromethane (22 mL, 406.0 mmol, 1.6 equiv) and triethylamine (0.24 mL, 1.7 mmol, 0.006 equiv), and the resulting homogeneous mixture was stirred for 24 hours. At this point, acetic anhydride (240 mL) and sodium acetate (12.8 g, 156 mmol, 0.6 equiv) were added, and the mixture was heated to reflux and stirred for an hour. The reaction mixture was then poured into deionized water (2.4 L) and stirred until the red oil became a crystalline orange solid. The orange solid was filtered through a Büchner funnel, washed with additional deionized water, and air-dried on the funnel. The crude solid was purified by recrystallization from toluene to afford β-2-dinitrostyrene **226** (37.46 g, 73% yield) as gold-colored crystals.



226 ***94*** ***238***

Cyclopentane 238. To a flame-dried schlenk-tube was added $Pd_2(dba)_3$ (147 mg, 0.160 mmol) and dppe (147 mg, 0.369 mmol). The Schlenk tube was evacuated and backfilled twice with argon. In a separate, flame-dried, conical flask, THF was sparged with argon for 20 minutes. After this period, THF (25 mL) was added to the Schlenk tube, and the resulting purple solution was heated at 40 °C until the solution became bright orange, at which point, it was allowed to cool to ambient temperature. To a separate, flame-dried conical flask was added β-2-dinitrostyrene (**226**) (575 mg, 2.96 mmol, 1 equiv), THF (5 mL) and vinylcyclopropane **94** (500 μl, 2.96 mmol, 1 equiv). The latter solution was transferred via cannula to the Schlenk tube, and the reaction mixture became red. The solution was heated to 40 °C and stirred for 14 hours. Upon completion, the reaction mixture was concentrated in vacuo and purified by flash chromatography (100 mL SiO2, 10:1→5:1 hexanes:ethyl acetate), yielding a yellow solid which was further purified by trituration with diethyl ether to afford **238** (670.9 mg, 60% yield), a white solid, as a mixture of diastereomers: R_f = 0.17 (3:1 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 7.89–7.84 (m, 1H), 7.60–7.52 (m, 1H), 7.49–7.41 (m, 1H), 7.40–7.35 (m, 1H), 5.90 (dtd, *J* = 18.2, 8.8, 8.0 Hz, 1.4 Hz, 1H), 5.53 (d, *J* = 10.7 Hz, 1H), 5.33–5.19 (m, 2H), 5.10 (td, *J* = 10.5, 1.4 Hz, 1H), 3.85–3.76 (m, 1H) 3.75 (app d, *J* = 1.4 Hz, 3H), 3.27 (app d, *J* = 1.5 Hz, 3H), 2.76–2.67 (m, 1H), 2.65–2.56 (m, 1H); ^{1}H NMR (400 MHz, $CDCl_3$, minor diastereomer) δ 7.89–7.84 (m, 1H), 7.60–7.52 (m, 1H), 7.49–7.41 (m, 1H), 7.40–7.35 (m, 1H), 5.76–5.61 (m, 2H), 5.43 (ddd, *J* = 8.7, 7.1, 1.3 Hz, 1H), 5.33–5.19 (m, 2H), 3.71 (app d, *J* = 1.6 Hz, 3H), 3.42–3.30 (m, 1H), 3.34 (app d, *J* = 1.4 Hz, 3H), 2.79 (ddd, *J* = 13.7, 6.9, 1.3 Hz, 1H), 2.39 (ddd, *J* = 13.8, 10.6, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.4, 170.0,

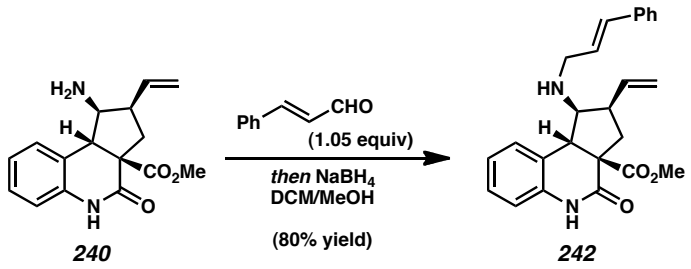
169.9, 134.7, 132.9, 132.5, 132.4, 130.6, 129.5, 129.4, 129.2, 125.4, 125.4, 120.3, 119.4, 94.9, 93.4, 64.7, 62.9, 53.7, 53.5, 52.9, 52.8, 48.2, 46.6, 46.3, 38.6, 37.4; IR (NaCl/film) 3002, 2955, 1733, 1557, 1532, 1436, 1358, 1282, 1263, 1219, 1173, 932 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{19}N_2O_8$ $[M+H]^+$: 379.1136, found 379.1144.



238 ***240*** ***241***

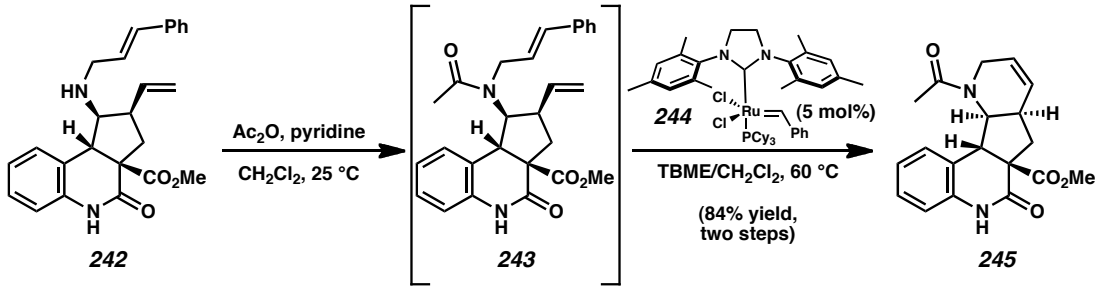
Lactams 240 and 241. A suspension of cyclopentane **238** (5.2206 g, 13.8 mmol, 1 equiv) in acetic acid (85% in H_2O, 70 mL, 0.2 M) was stirred in an open flask, heated in a 75 °C oil bath until completely homogeneous. Zinc powder (9.0130 g, 138 mmol, 10 equiv) was added to the heated solution in portions, maintaining an internal temperature lower than 90 °C. Vigorous bubbling was observed over the course of the zinc addition. Upon completion of the addition, the temperature was allowed to stabilize at 75 °C and the reaction progress was monitored by TLC. Upon consumption of starting material, the flask was removed from the oil bath and allowed to cool to room temperature, during which time, white solids precipitated from solution. The heterogeneous mixture was filtered through celite, and washed with 100 mL of ethyl acetate. The solution was basified with saturated $NaHCO_3$(aq) and solid Na_2CO_3. The phases were separated and the aqueous phase was extracted exhaustively with ethyl acetate. The combined organics were washed with saturated $NaHCO_3$(aq) and brine, dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by flash chromatography (800 mL SiO_2, 150:1:0.25 $CHCl_3$:MeOH:Et_3N) to afford **240** (1.7434 g, 44% yield) as a white

solid and a 3.5:1 mixture of **241:240** (1.3768g, 35% yield) which could be repurified under the same conditions to yield **241** as a single diastereomer. **240**: R_f = 0.30 (10:1 chloroform:methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.22–7.11 (m, 2H), 7.01–6.95 (m, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 5.59 (ddd, *J* = 16.8, 10.0, 8.4 Hz, 1H), 5.15–4.98 (m, 2H), 3.54 (s, 3H), 3.05 (d, *J* = 10.8 Hz, 1H), 2.77 (dd, *J* = 14.3, 9.8, 1H), 2.67 (t, *J* = 10.4 Hz, 1H), 2.50 (dd, *J* = 14.3, 9.2 Hz), 2.44–2.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 169.2, 138.2, 134.4, 121.7, 127.4, 122.5, 120.6, 116.0, 114.8, 61.2, 54.6, 54.6, 52.2, 50.0, 36.33; IR (NaCl/film) 3233, 1734, 1675, 1595, 1496, 1383, 1248, 919, 758 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{19}N_2O_3$ $[M+H]^+$: 287.1390, found 287.1392. **241**: R_f = 0.26 (10:1 chloroform:methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.23–7.04 (m, 2H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 5.86 (dt, *J* = 18.1, 9.5 Hz, 1H), 5.21–5.08 (m, 2H), 3.55 (s, 3H), 3.03 (m, 3H), 2.76 (dt, *J* = 14.3, 7.6 Hz, 1H), 2.37 (dd, *J* = 13.9, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.5, 137.5, 135.6, 128.8, 128.3, 123.5, 122.4, 117.9, 115.8, 60.3, 56.5, 54.8, 53.2, 45.2, 37.2; IR (NaCl/film) 3210, 3074, 1730, 1672, 1595, 1496, 1384, 1272, 1250, 1213, 924, 758 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{19}N_2O_3$ $[M+H]^+$: 287.1390, found 287.1393.



Cinnamyl amine 242. A flame-dried Schlenk tube was charged with primary amine **240** (200.6 mg, 0.70 mmol, 1 equiv), and CH_2Cl_2 (1.4 mL, 0.5M). To this suspension, at ambient temperature (21 °C) was added freshly distilled *trans*-cinnamaldehyde (92 μL, 0.73 mmol, 1.05 equiv). After three minutes, the mixture becomes completely homogeneous. The progress of the reaction was monitored by TLC (imine R_f = 0.47, 10:1 chloroform:methanol), and after consumption of the primary amine was observed (approximately one hour), the solution was cooled to 0 °C in an ice bath, and methanol (7 mL) was added. The solution was stirred for one minute, sodium borohydride (34.9 mg, 0.91 mmol, 1.3 equiv) was added in one portion under high flow of argon, and vigorous bubbling was observed. The Schlenk tube was removed from the ice bath, and after 5 minutes, LCMS indicated complete consumption of the imine. After an additional 10 minutes of stirring, the solution was cooled again to 0 °C, and water (1 mL) was added dropwise. The reaction mixture was concentrated *in vacuo*, partitioned between diethyl ether (20 mL) and water (5 mL), and the phases were separated. The aqueous phase was extracted with diethyl ether (2 x 15 mL), then the combined organics were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (30 mL SiO_2, 3:1 → 1:1 hexanes:ethyl acetate) to afford **242** (225.2 mg, 80% yield) as a white solid: R_f = 0.46 (1:1 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.23–7.06 (m, 7H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.20 (d, *J* = 15.9 Hz, 1H), 6.02–5.88 (m, 2H), 5.18–5.08 (m, 2H), 3.53 (s, 3H), 3.34 (d, *J* = 10.5 Hz, 1H), 3.26 (dd, *J* = 13.7, 6.5 Hz, 1H), 3.06 (dd, *J* = 14.2, 6.2 Hz, 1H), 3.01–2.92 (m, 2H), 2.89–2.76 (m, 1H), 2.38 (dd, *J* = 14.2, 4.6 Hz, 1H) 1.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 169.6, 137.8, 137.1, 135.6, 131.0,

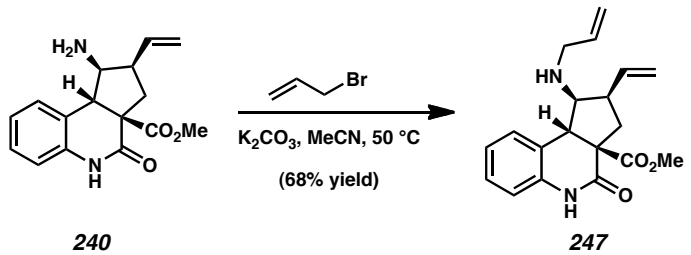
129.4, 128.6, 128.3, 128.2, 127.4, 126.3, 123.5, 122.4, 117.1, 115.7, 65.6, 56.5, 53.2, 52.2, 50.0, 43.8, 37.5; IR (NaCl/film) 3207, 3060, 1733, 1677, 1596, 1494, 1384, 1247, 1104, 753 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{25}H_{27}N_2O_3$ $[M+H]^+$: 403.2016, found 403.2018.



Tetracycle 245. An oven-dried scintillation vial was charged with secondary amine **242** (60.3 mg, 0.150 mmol, 1 equiv) and sealed with a screw-cap fitted with a teflon septum. Dichloromethane (0.3 mL) was added, followed by acetic anhydride (71 μL, 77 mg, 0.75 mmol, 5 equiv), then pyridine (0.12 mL, 118 mg, 1.5 mmol, 10 equiv). The vial was lowered into a 25 °C oil bath and stirred for 14 hours. Over the course of the reaction, a white precipitate formed. Upon completion, the reaction mixture was diluted with diethyl ether (2 mL) and the precipitate was collected by filtration, washed further with diethyl ether and air-dried to afford crude acetamide **243** (58.9 mg, 88% crude yield) which was used without further purification in the next reaction.

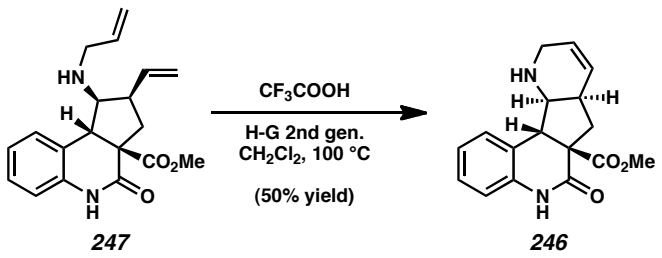
A flame-dried Schlenk bomb was charged with crude **243** (58.9 mg, 0.133 mmol, 1 equiv) and Grubbs 2nd generation catalyst (**244**) (5.8 mg, 0.0068 mmol, 0.05 equiv). The bomb was evacuated and backfilled with argon three times. In a separate, flame-dried conical flask, a 1:1 mixture of dichloromethane and *tert*-butyl methyl ether was degassed

by sparging with argon for 20 minutes, then 2.7 mL of this solvent mixture was added to the schlenk bomb under high argon flow. The bomb was sealed and heated in a 60 °C oil bath, and the heterogeneous mixture was stirred for 100 minutes, monitoring by LCMS. Upon completion, the reaction mixture was concentrated in vacuo, and the residue was triturated with toluene to yield tetracycle **245** (45.1 mg, 95% yield, 84% over two steps), in greater than 95% purity, as a grey solid which exists as a 3:1 mixture of rotamers in chloroform: R_f = 0.26 (10:1 $CHCl_3$:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (br s, 0.33H), 8.19 (br s, 1H), 7.29–7.23 (m, 1H), 7.23–7.17 (m, 0.33H), 7.03 (td, *J* = 7.5, 1.2 Hz, 1H), 6.98–6.91 (m, 1.33H), 6.87–6.77 (m, 1.66H), 5.83–5.70 (m, 2.66H), 5.16 (dd, *J* = 11.9, 7.8 Hz, 0.33H), 4.75–4.66 (m, 1H), 4.16–3.98 (m, 1.66H), 3.64–3.56 (m, 5.66H), 3.48 (d, *J* = 11.9 Hz, 0.33H), 3.23–3.13 (m, 1.33H), 2.89 (br s, 1H), 2.80 (br s, 0.33 H), 2.35 (dd, *J* = 14.4, 3.3 Hz, 1H), 2.27 (dd, *J* = 14.3, 3.3 Hz, 0.33 H), 1.99 (s, 1H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 171.5, 170.3, 169.8, 169.0, 168.8, 135.7, 135.4, 130.6, 129.2, 128.9, 128.5, 128.4, 127.9, 124.2, 123.2, 121.8, 121.1, 120.6, 120.4, 116.0, 115.6, 60.9, 55.6, 55.5, 54.7, 53.5, 53.3, 47.3, 46.7, 41.6, 38.0, 37.1, 34.6, 33.8, 34.6, 33.8, 22.1, 20.7; IR (NaCl/film) 3215, 2917, 1734, 1680, 1639, 1624, 1597, 1493, 1430, 1372, 1271, 1246, 1214, 1115, 758 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{21}N_2O_4$ $[M+H]^+$: 341.1496, found 341.1498.



240 ***247***

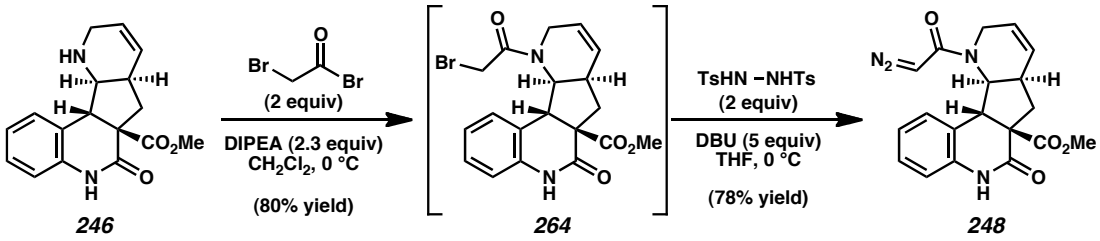
Allylamine 247. A flame-dried flask was charged with amine **240** (51.5 mg, 0.17 mmol, 1 equiv) and potassium carbonate (27.2 mg, 0.19 mmol, 1 equiv), then sealed with a rubber septum and placed under inert atmosphere. Acetonitrile (0.6 mL) was added, followed by allyl bromide (0.017 mL, 0.19 mmol, 1.1 equiv), and the mixture was stirred at ambient temperature for one hour, 40 °C for 3 hours, and 50 °C for 5 hours. At this stage additional allyl bromide (0.005 mL, 0.058 mmol, 0.34 equiv) was added, and the reaction mixture was stirred at 50 °C for an additional 14 hours. The reaction mixture was filtered through celite, and volatiles were removed in vacuo. The residue was purified by column chromatography (150:1 → 50:1 $CHCl_3$:MeOH) to afford allylamine **247** (40.2 mg, 68% yield) as a white powder after lyophilization from benzene, with minor impurities detected by NMR: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.24 – 7.19 (m, 2H), 7.03 (td, *J* = 7.5, 1.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.99 (ddd, *J* = 17.0, 10.2, 8.9 Hz, 1H), 5.72 – 5.60 (m, 1H), 5.24 – 5.13 (m, 2H), 4.99 – 4.91 (m, 2H), 3.61 (s, 3H), 3.40 (d, *J* = 10.4 Hz, 1H), 3.20 – 3.12 (m, 1H), 3.06 – 2.94 (m, 3H), 2.88 (qd, *J* = 8.4, 4.7 Hz, 1H), 2.44 (dd, *J* = 14.3, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 169.5, 136.6, 135.5, 129.4, 128.3, 123.5, 122.4, 117.1, 115.8, 115.5, 65.4, 56.6, 53.2, 52.1, 50.5, 43.7, 37.5; IR (NaCl/film) 3225, 3082, 2978, 1731, 1676, 1597, 1496, 1382, 1246, 915 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{23}N_2O_3$ $[M+H]^+$: 327.1703, found 327.1713.



247 ***246***

Tetracycle 246. A flame-dried microwave vial (2–5 mL capacity), equipped with a magnetic stir bar, was charged with allylamine **247** (21.3 mg, 0.065 mmol, 1 equiv), then sealed with a microwave cap and evacuated and back-filled with argon. Dichloromethane was degassed by sparging with argon in a separate flame-dried conical flask, and added (3 mL) to the microwave vial. To the resulting solution was added neat trifluoroacetic acid (0.005 mL, 0.065 mmol, 1 equiv). A separate, flame-dried conical flask was charged with Hoveyda-Grubbs 2nd generation catalyst (4 mg, 0.064 mmol, 0.1 equiv), sealed with a rubber septum, and evacuated and backfilled with argon. To this flask was added degassed dichloromethane (1–2 mL), and the resulting solution was transferred to the microwave vial via syringe. The reaction mixture was heated to 100 °C for 1 hour. Upon cooling, saturated aqueous sodium bicarbonate (2 mL) was added and the phases were separated. The aqueous layer was extracted with dichloromethane (2 x 2 mL) and the combined organics were dried over anhydrous sodium sulfate, decanted and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (150:1 → 30:1 $CHCl_3$:MeOH) to afford tetracycle **246** (9.8 mg, 50% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.85 (d, *J* = 10.5 Hz, 1H), 5.76 (d, *J* = 10.4 Hz, 1H), 3.61 (s, 3H), 3.55 (d, *J* = 9.8 Hz, 1H) 3.51 (d, *J* = 17.4 Hz, 1H), 3.31 (d, *J* = 17.3 Hz, 1H), 3.23 (dd, *J* = 9.7, 7.8 Hz, 1H), 3.09 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.71 – 2.64 (br

m, 1H), 2.15 (dd, J = 13.6, 6.7 Hz, 1H), 1.70 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 168.7, 135.3, 129.1, 128.7, 128.0, 125.4, 123.6, 123.0, 115.4, 61.8, 56.6, 53.1, 48.2, 40.2, 37.7, 34.7; IR (NaCl/film) 3211, 3062, 2913, 1733, 1676, 1597, 1491, 1432, 1377, 1244, 1105, 912 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{17}H_{19}N_2O_3$ $[M+H]^+$: 299.1390, found 299.1401.



Diazoacetamide 248. A flame-dried round-bottom flask, fitted with a magnetic stir bar, was charged with secondary amine **246** (51.3 mg, 0.172 mmol, 1 equiv) and sealed with a rubber septum. Dichloromethane (2 mL, 0.1 M) and Diisopropylethylamine (0.070 mL, 0.395 mmol, 2.3 equiv) were added, the flask was lowered into an ice-water bath, and stirring was initiated. Bromoacetyl bromide (30 μL, 3.44 mmol, 2 equiv) was added dropwise, and the starting material was consumed within 5 minutes (LCMS). The reaction mixture was directly dry-loaded onto silica gel (~1.5 mL) and purified by column chromatography on SiO_2 (1:1 hexanes:EtOAc) to afford bromoacetamide **264** (57.8 mg, 80%) which was carried forward directly to the next step.

A flame-dried round-bottom flask, fitted with a magnetic stir bar, was charged with bromoacetamide **264** (57.8 mg, 0.138 mmol, 1 equiv), and N,N'-ditosylhydrazide (95.3 mg, 0.276 mmol, 2 equiv). The flask was sealed with a rubber septum, and THF (0.4 mL, 0.4 M) was added. The flask was lowered into an ice-water bath, and stirring

was initiated. 1,8-Diazabicycloundec-7-ene (100 μL, 0.689 mmol, 5 equiv) was then added dropwise, and the reaction was monitored by LCMS. Upon completion, the reaction mixture was dry-loaded onto SiO_2 and purified by column chromatography (2:1 →4:1→1:0 EtOAc:hexanes), and repurified (35:1 CH_2Cl_2:MeOH) to afford diazoacetamide **248** (39.3 mg, 78% yield) as a yellow solid, and observed to be a mixture of rotamers by NMR: ^{1}H NMR (500 MHz, d6-DMSO, 80 °C) δ 10.32 (s, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.98 – 6.92 (m, 2H), 6.92 – 6.87 (m, 1H), 5.77 (d, *J* = 11.9 Hz, 1H), 5.72 (d, *J* = 10.3 Hz, 1H), 5.41 (br s, 1H), 3.82 (d, *J* = 18.3 Hz, 1H), 3.56 – 3.49 (m, 4H), 3.45 (d, *J* = 11.5 Hz, 1H), 2.96 (dd, *J* = 14.2, 9.4 Hz, 1H), 2.74 (br s, 2H), 2.19 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR (126 MHz, d6-DMSO, 80 °C) δ 188.4, 187.2, 171.6, 171.3, 167.5, 167.1, 163.8, 137.4, 137.0, 129.0, 122.8, 121.0, 120.0, 115.7, 58.3, 55.3, 53.3, 47.5, 46.7, 46.2, 41.4, 41.2, 38.0, 36.8, 33.8. IR (NaCl/film) 3216, 3092, 2918, 2104, 1733, 1681, 1597, 1493, 1427, 1377, 1241, 1209, 1167, 1110 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{19}N_4O_4$ $[M+H]^+$: 367.1401, found 367.1414.

2.9 NOTES AND REFERENCES

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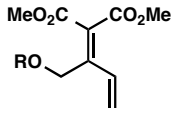

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