APPENDIX 4

Additional Studies Related to Chapter 2: Progress toward the Total Synthesis of Scandine and the Melodinus *Alkaloids*

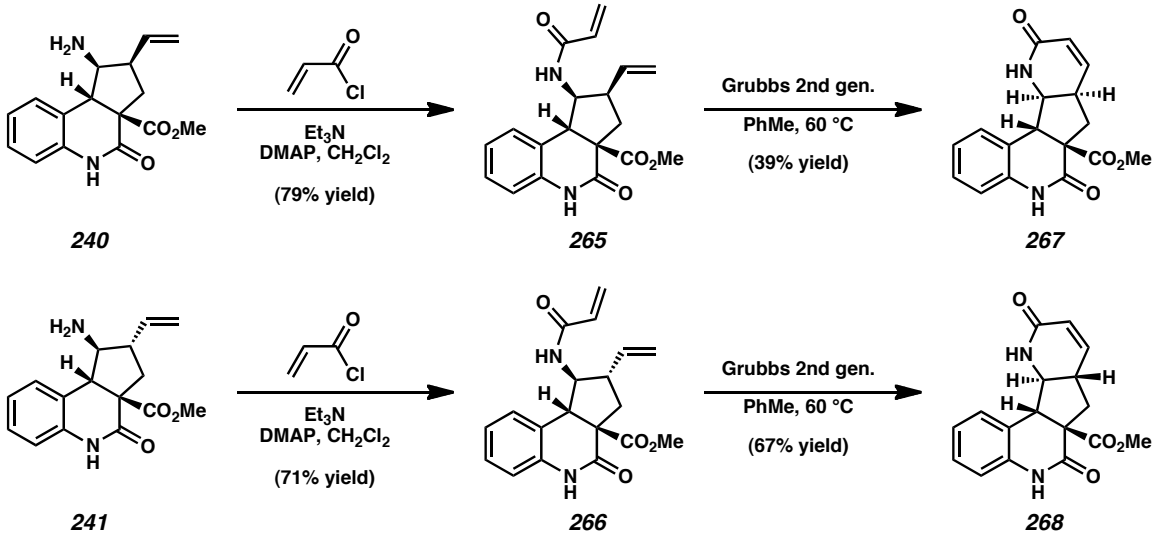
A4.1 ALTERNATIVE APPROACHES TO D-RING RCM

A4.1.1 ACRYLAMIDE RING-CLOSING METATHESIS APPROACH

Our initial approach to the D-ring of the *Melodinus* alkaloids involved conversion of primary amine **240** to the acrylamide followed by ring-closing metathesis (Scheme A4.1.1). In the event, treatment of either diastereomer (**240** or **241**) of the primary amine with acryloyl chloride resulted in clean conversion to the corresponding acrylamides (**265** and **266**). Although Grubbs' first-generation catalyst did not successfully accomplish ring-closure in refluxing dichloromethane, the use of the second-generation catalyst at higher temperatures in toluene afforded tetracycles **267** and **268** in moderate yield. Notably, under the unoptimized conditions, the 5-6 *trans* system was formed in a higher yield than the corresponding *cis* compound. This route offers the possibility of γ-

alkylation of the α,β-unsaturated lactam, which could provide an avenue for epimerizing the undesired diastereomer; however, selective reduction of the lactam to the dehydropiperidine system would be necessary in this case.

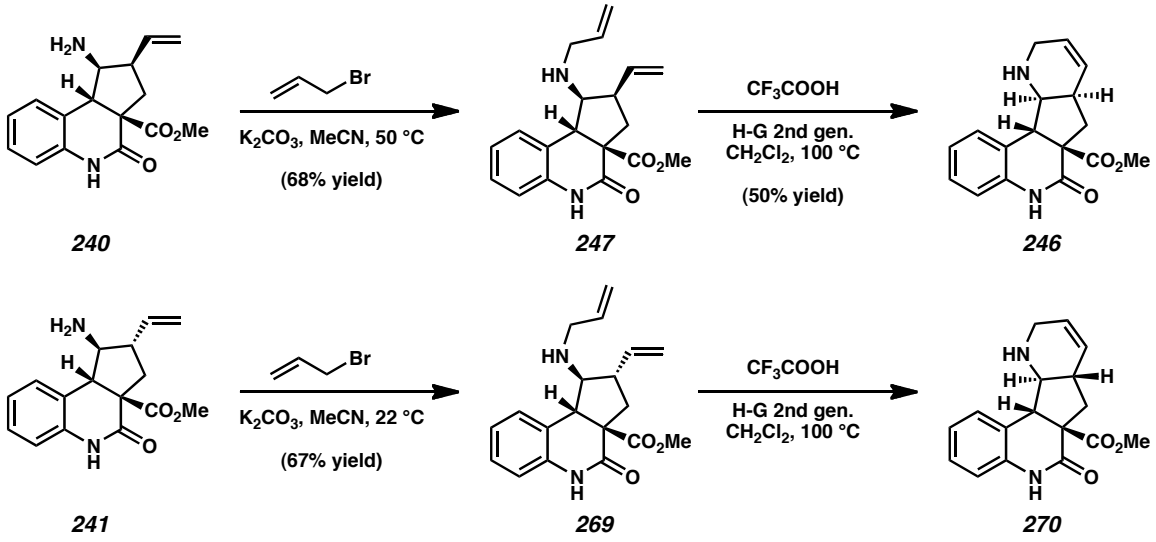
Scheme A4.1.1. Acylation/RCM sequence for D-ring synthesis.



A4.1.2 ALLYLAMINE RING-CLOSING METATHESIS APPROACH

We also examined an analogous approach to the tetracyclic framework of the natural product family using an amine allylation approach to install the D-ring in the correct oxidation state. Whereas reductive amination with acrolein could not be accomplished, we found that either diastereomer of the tricyclic primary amine (**240** or **241**) could be monoalkylated in moderate yield with allyl bromide (Scheme A4.1.2). Ring-closing metathesis could then be accomplished by treatment of the secondary amines (**247** or **269**) with trifluoroacetic acid followed by reaction with Hoveyda–Grubbs second generation catalyst. In the event, free secondary amines **246** and **270** were formed, though further optimization is necessary.

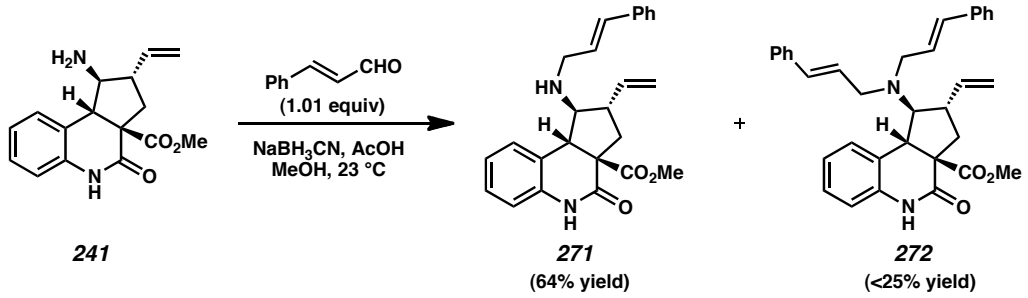
*Scheme A4.1.2. Allylation and RCM of primary amines **240** and **241**.*



A4.1.3 DEVELOPMENT OF REDUCTIVE AMINATION CONDITIONS

In our effort to improve the yield of the amine alkylation/ring-closing metathesis sequence, we examined the reductive amination of amine **241** with cinnamaldehyde (Scheme A4.1.3). Using an excess of aldehyde (1.6 equiv), we observed mixtures of mono- and bis-cinnamylated amine by LCMS (**271** and **272** respectively), and reducing the quantity of aldehyde under these conditions still resulted in mixtures.

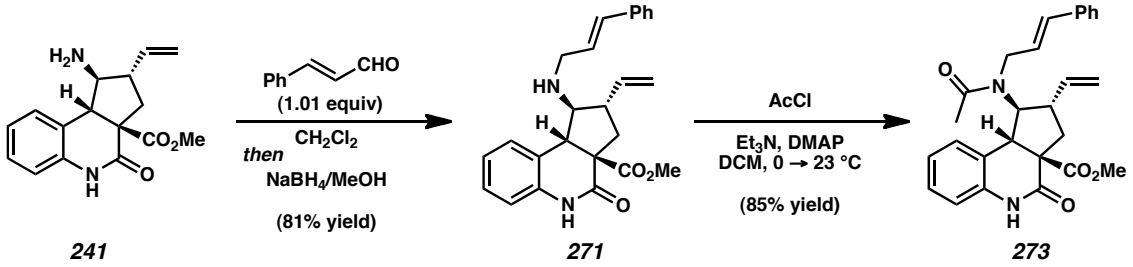
Scheme A4.1.3. Initial reductive amination attempt with cinnamaldehyde



Gratifyingly, we found that preforming the imine followed by reduction with sodium borohydride afforded the desired cinnamylamine (**271**) in 81% yield, and acetylation of

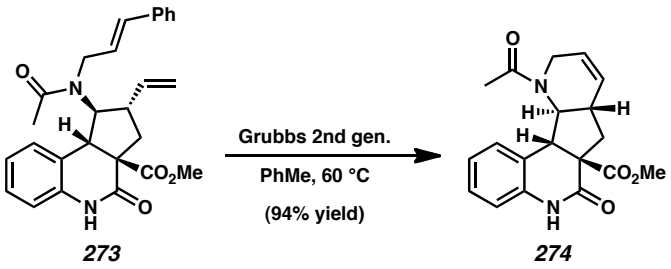
the secondary amine proceeded cleanly (Scheme A4.1.4). Notably, the conditions that were effective in the RCM of free allylamines **247** and **269** surprisingly gave no product when applied to secondary cinnamylamine **271.**

*Scheme A4.1.4. Reductive amination and acetylation of amine **241***



Ring-closing metathesis of the protected secondary amine (**273**) was successful, and the tetracyclic product (**274**) precipitated from the reaction mixture with excellent purity (Scheme A4.1.5). It is worth noting that both the acetylation and RCM steps of the reaction needed re-optimization for the *cis* diastereomer (**242**). Under the same acetylation conditions as above, a doubly acetylated compound was formed as a side product.[1] Furthermore, the corresponding RCM substrate (**243**, Chapter 2) was insoluble in toluene and the desired reaction did not proceed under the same conditions; the conditions described in Chapter 2 were effective for this transformation.

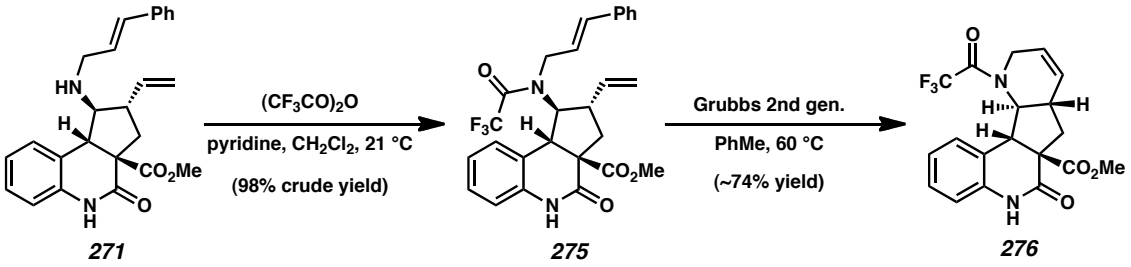
*Scheme A4.1.5. Ring-closing metathesis of cinnamylamine **273***



A4.1.4 TRIFLUOROACETAMIDE-PROTECTED RCM SUBSTRATE

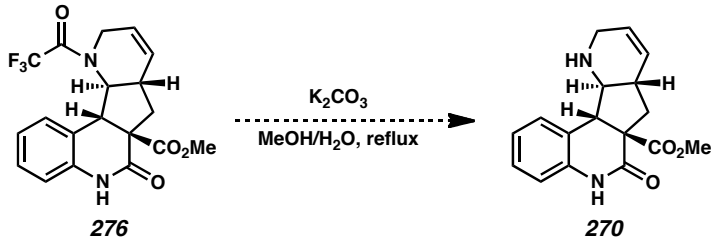
Due to the difficulty in directly converting the tetracyclic acetamide (**245**, Chapter 2) to the desired diazoacetamide, we considered the use of a trifluoroacetamide as an easily cleaved nitrogen protecting group toward the free tetracyclic secondary amine. We first investigated this sequence with **242**; the protection step proceeded cleanly, providing trifluoroacetamide **275** in 98% crude yield, and ring-closing metathesis provided tetracycle **276** (Scheme A4.1.6).

Scheme A4.1.6. Ring-closing metathesis of TFA protected amine



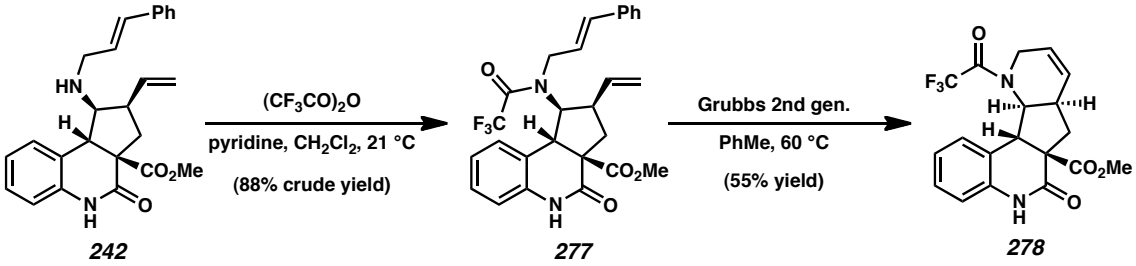
Only a single attempt has been made to cleave the trifluoroacetamide group from tetracycle **276** (Scheme A4.1.7). While promising by LCMS, the product (**270**) was not successfully isolated.

*Scheme A4.1.7. Attempt to cleave TFA group from tetracycle **276***



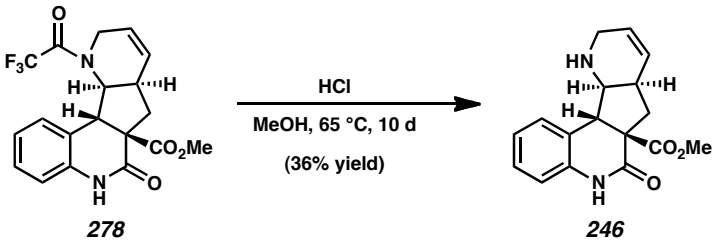
Application of the same protection/RCM sequence to the *cis* cinnamylamine diastereomer was equally effective, but lower yielding, likely due to loss of material during a filtration step (Scheme A4.1.8).

Scheme A4.1.8. TFA protection/RCM Sequence with cis*-diastereomer* ***242***



Cleavage of the trifluoroacetate group from tetracycle **278** under the conditions attempted with the *trans*-[5,6] tetracycle (**276**) was ineffective, and only methyl ester hydrolysis and decarboxylation was observed by LCMS. Several other conditions were attempted, including sodium borohydride reduction, and lithium hydroxide mediated hydrolysis failed to cleanly convert the trifluoroacetamide **278** to the free secondary amine **246**. However, preliminary efforts using methanolic hydrochloric acid performed the desired amine deprotection cleanly, albeit slowly (Scheme A4.1.9). Starting material could be recovered, however further optimization may be necessary improve the efficiency of this transformation.

Scheme A4.1.9. Amine deprotection under acidic conditions



A4.1.5 SUMMARY

Our studies on the assembly of the *Melodinus* alkaloid D-ring revealed that the chemistry of the *trans*-5,6-fused system typically was well-behaved compared to the *cis*-5,6-fused system that is found in the natural product. Firstly, the reactivity of the *trans*

system did not always translate well to the *cis* system, and often required reoptimization. Direct conversion of the secondary cinnamyl amine (**242**) to the corresponding tetracycle by RCM would shorten the synthetic sequence by avoiding protection and deprotection steps. However, the most reliable approach would likely be via the trifluoroacetamide, if the deprotection step can be optimized.

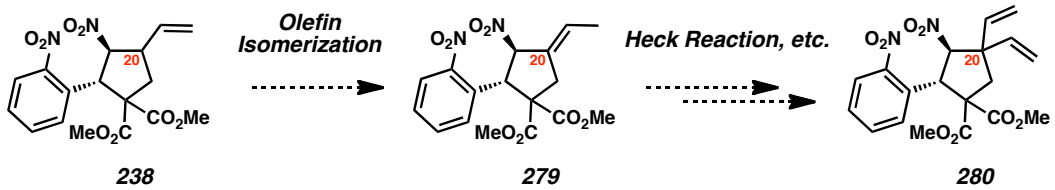
A4.2 INITIAL EFFORTS FOR C(20) FUNCTIONALIZATION

Prior to our collaborative efforts with the Davies group, we examined several methods to functionalize the C(20) position of the natural product scaffold.

A4.2.1 OLEFIN ISOMERIZATION

We examined the reactivity of the (3 + 2) cycloaddition adduct (**238**) with an array of catalysts known to perform olefin isomerization, envisioning the formation of trisubstituted olefin **279**, which could be used as a handle for installing the quaternary center at C(20) by a Heck reaction.[2] Unfortunately under none of these conditions did we observe the desired transformation (Scheme A4.2.1).

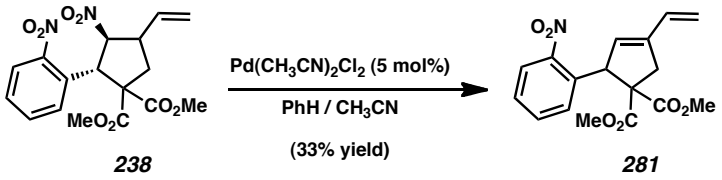
Scheme A4.2.1. Olefin Isomerization approach to C(20) functionalization.



Catalysts: $Pd(CH_3CN)_2Cl_2$, $RhCl_3 \cdot 3H_2O$, Grubbs II/MeOH, $RuCl_3/Ph_3P$

Interestingly, with bis(acetonitrile)dichloropalladium(II), we observed an elimination of nitrous acid to form diene **281** (Scheme A4.2.2).

*Scheme A4.2.2. Unexpected elimination of HNO_2 to form diene **281***

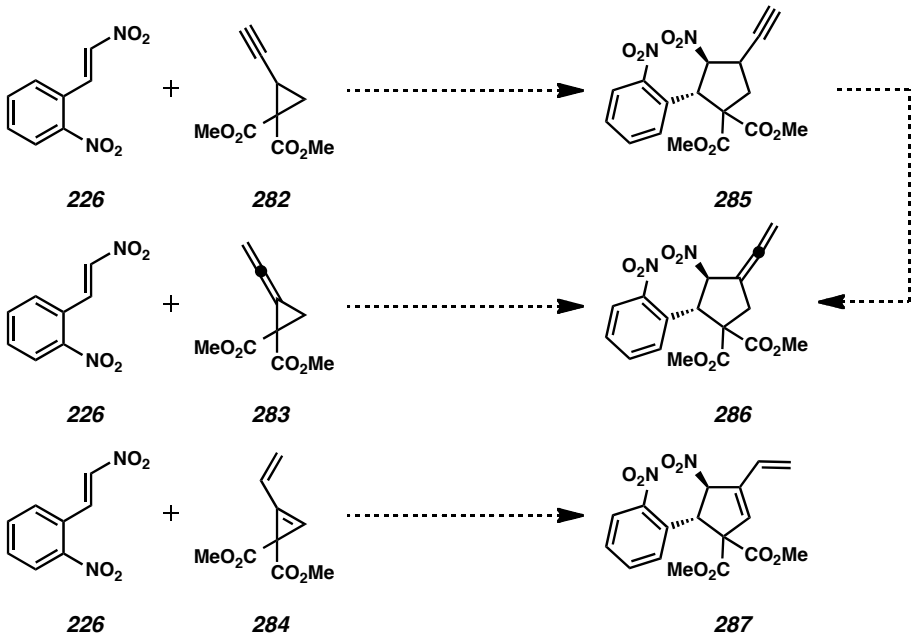


238 ***281***

A4.2.2 ALTERNATIVE CYCLOPROPANES

We also considered installing an additional unit of unsaturation on the cyclopropane, prior to (3 + 2) cycloaddition (Scheme A4.2.3). Accordingly application of a alkynyl- or vinylidenecyclopropane (**282** and **283** respectively) or a vinylcyclopropene (**284**) would provide access to cyclopentane derivatives (**285**, **286**, **287**) with an additional functional handle.

Scheme A4.2.3. Proposed application of doubly unsaturated cyclopropanes



226 ***282*** ***285***

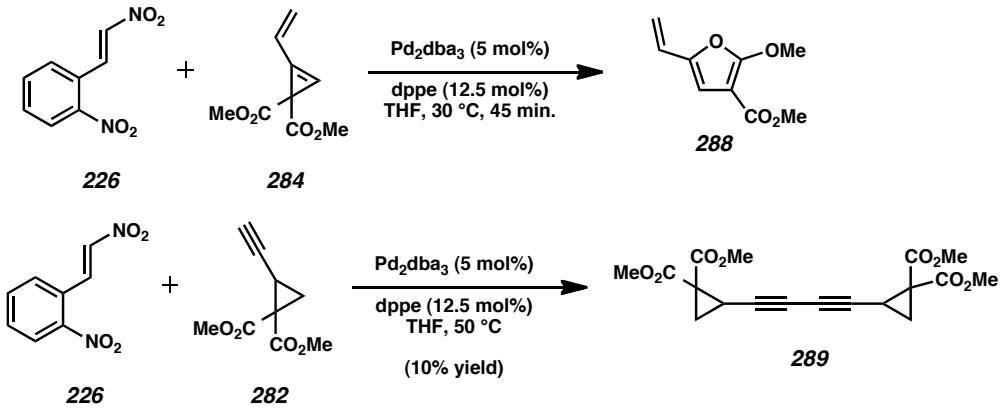
226 ***283*** ***286***

226 ***284*** ***287***

Unfortunately, none of these cyclopropane derivatives underwent the desired (3 + 2) cycloaddition with nitrostyrene **226**. Vinylidenecyclopropane **283** was unreactive under

standard conditions, alkynylcyclopropane **282** underwent a Glaser-type coupling in low yield, and vinylcyclopropene **284** isomerized rapidly to furan **288**.

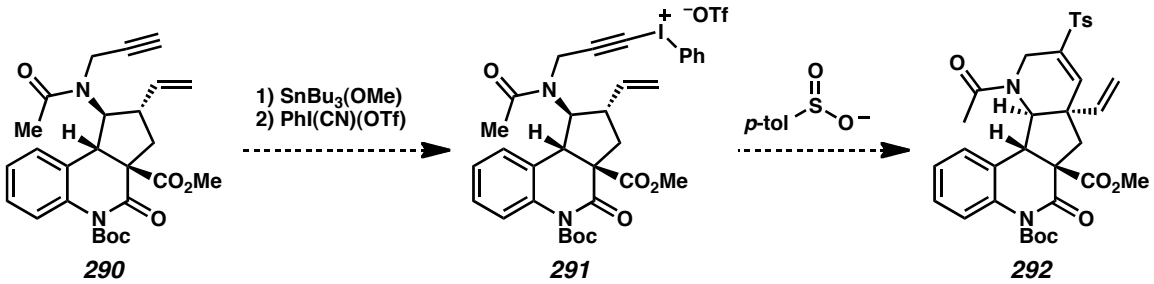
*Scheme A4.2.4. Reactions of cyclopropane derivatives **282** and **284***



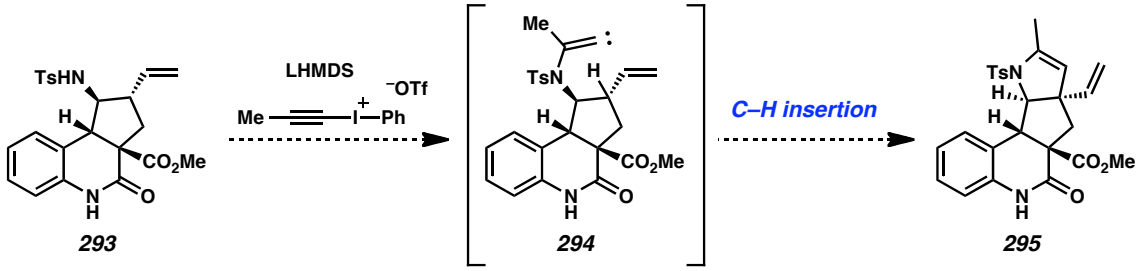
A4.3 C(20) FUNCTIONALIZATION VIA C–H INSERTION

Prior to the preliminary studies on intermolecular C–H vinylation, we examined an approach to the D-ring by means of an intramolecular alkylidene carbene or vinylidene carbenoid C–H insertion reaction.[3] Preliminary examinations of this approach were unsuccessful. Two methods examined involved reaction of alkynyl iodonium triflate **291** with *para*-toluene sulfinate (Scheme A4.3.1) and reaction of toluenesulfonamide **293** with propynyl iodonium triflate (Scheme A4.3.2).

*Scheme A4.3.1. Attempted formation and reaction of alkynyliodonium triflate **291**.*



Scheme A4.3.2. Attempted formal (3 + 2) cycloaddition of toluenesulfonamide ***293***

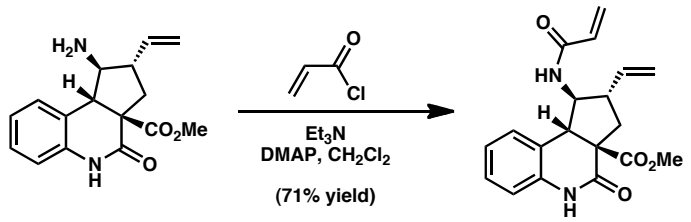


A4.4 EXPERIMENTAL SECTION

A4.4.1 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).[4] 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.

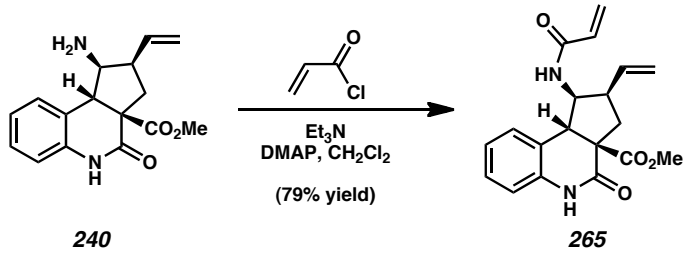
A4.4.2 PREPARATIVE PROCEDURES



241 *266*

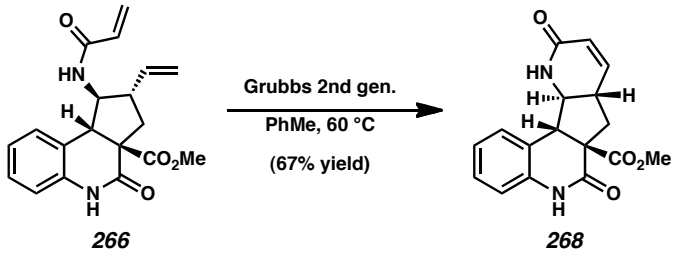
Acrylamide 266. To a flame-dried round-bottom flask were added amine **241** (53.9 mg, 0.19 mmol, 1 equiv) and 4-(*N*,*N*-dimethylamino)pyridine (1.9 mg, 0.02 mmol, 0.1 equiv). The flask was sealed with a rubber septum and placed under an inert atmosphere. The flask was charged with dichloromethane (1 mL, 0.2 M) and upon dissolution of the solids with stirring, the flask was cooled in an ice-water bath. To the cooled solution was added triethylamine (0.034 mL, 0.24 mmol, 1.3 equiv) followed by acryloyl chloride (0.018 mL, 0.22 mmol, 1.2 equiv). The cooling bath was removed and the reaction mixture was allowed to warm to ambient temperature. After 5 hours, complete conversion was observed by LCMS. The volatiles were removed in vacuo and the residue was purified by column chromatography on SiO_2 (20:1 $CHCl_3$:MeOH) to afford acrylamide **266** (45.4 mg, 71% yield) as an off-white powder: ^{1}H NMR (500 MHz, 1:1 CD_3OD:$CDCl_3$, referenced to residual CHD_2OD peak at 3.31 ppm) δ 8.19 (d, *J* = 9.3 Hz, 1H), 7.15 (td, *J* = 7.7, 1.5 Hz, 1H), 7.04 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.90 (td, *J* = 7.5, 1.2 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.19–6.05 (m, 2H), 5.66 (ddd, *J* = 17.0, 10.2, 7.8 Hz, 1H), 5.59 (dd, *J* = 9.9, 1.9 Hz, 1H), 5.06 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.02–4.94 (m, 1H), 4.02–3.94 (m, 1H), 3.61 (s, 4H), 3.40 (dd, *J* = 11.4, 1.8 Hz, 1H), 2.77 (dd, *J* = 13.7, 9.7 Hz, 1H), 2.69 (p, *J* = 9.1 Hz, 1H), 2.46 (dd, *J* = 13.7, 8.8 Hz, 1H); ^{13}C NMR (126 MHz, 1:1 CD_3OD:$CDCl_3$, referenced to $^{13}CD_3OD$ peak at 49.0 ppm) δ 173.1, 170.0,

138.6, 136.1, 131.1, 131.0, 128.9, 126.9, 123.7, 121.2, 116.7, 116.1, 60.5, 55.7, 53.4, 52.3, 52.2, 37.4; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{21}N_2O_4$ $[M+H]^+$: 341.1496, found 341.1479.



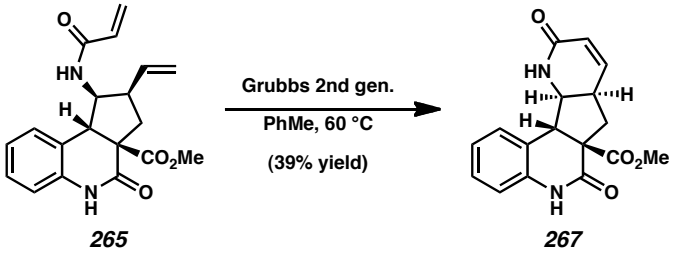
240 ***265***

Acrylamide 265. Prepared according to the same procedure as above. Full conversion was observed by LCMS after 5 hours, and after similar purification, acrylamide **265** (49.8 mg, 79% yield) was obtained: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.21 (td, *J* = 7.7, 1.5 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.99 (td, *J* = 7.5, 1.1 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.20 (dd, *J* = 17.0, 1.3 Hz, 1H), 6.06 (dd, *J* = 17.0, 10.3 Hz, 1H), 5.85 (ddd, *J* = 17.7, 10.4, 7.8 Hz, 1H), 5.70–5.61 (m, 2H), 5.29–5.15 (m, 1H), 4.51–4.41 (m, 1H), 3.66 (s, 3H), 3.53–3.42 (m, 2H), 3.05 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.98 (dt, *J* = 15.4, 7.9 Hz, 1H), 2.51 (dd, *J* = 13.8, 6.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 168.0, 165.1, 136.3, 135.3, 130.6, 128.7, 127.1, 123.8, 121.1, 118.7, 115.6, 115.4, 57.9, 56.5, 53.5, 52.5, 43.3, 37.4.



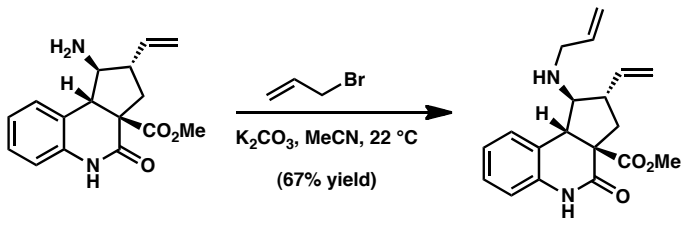
266 ***268***

Tetracycle 268. A flame-dried 5 mL conical flask was charged with acrylamide **266** (20.7 mg, 0.059 mmol, 1 equiv) and Grubbs' first-generation catalyst (2.4 mg, 0.003 mmol, 0.05 equiv). The flask was sealed with a septum, evacuated, and back-filled with argon. A separate flame-dried flask was charged with dichloromethane and sparged with argon gas. Dichloromethane (1.2 mL) was transferred into the first flask, and the septum was quickly swapped for a cold-finger water condenser. The solution was heated to reflux for 10 hours, and little conversion was observed by LCMS. The reaction mixture was concentrated in vacuo, and Grubbs second-generation catalyst (4.2 mg, 0.005 mmol, 0.1 equiv) was added, followed by degassed (sparging with $Ar_{(g)}$) toluene. The resulting solution was heated to 60 °C and monitored by LCMS for conversion. Upon complete consumption of starting material, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography on SiO_2 (30:1 $CHCl_3$:MeOH) to afford tetracycle **268** (12.7 mg, 67% yield) as a maroon-brown solid. Trituration with d_6-acetone affords a white solid. ^{1}H NMR (500 MHz, 1:1 CD_3OD:$CDCl_3$, referenced to residual CHD_2OD peak at 3.31 ppm) δ 7.56 (s, 1H), 7.30–7.22 (m, 2H), 7.08 (td, *J* = 7.5, 1.2 Hz, 1H), 6.93 (d, *J* = 7.3 Hz, 1H), 6.87 (dd, *J* = 9.6, 1.9 Hz, 1H), 5.87 (dd, *J* = 9.6, 2.9 Hz, 1H), 3.65 (s, 3H), 3.39 (d, *J* = 11.5 Hz, 1H), 3.27 (d, *J* = 11.5 Hz, 1H), 2.98 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.90–2.78 (m, 1H), 2.26 (dd, *J* = 13.6, 12.2 Hz, 1H); 13C NMR (126 MHz, 1:1 CD_3OD:$CDCl_3$, referenced to $^{13}CD_3OD$ peak at 49.0 ppm) δ 172.5, 170.0, 169.7, 145.0, 136.1, 129.6, 129.0, 126.0, 124.3, 119.3, 116.7, 62.4, 57.1, 53.7, 51.2, 42.1, 34.6.



265 ***267***

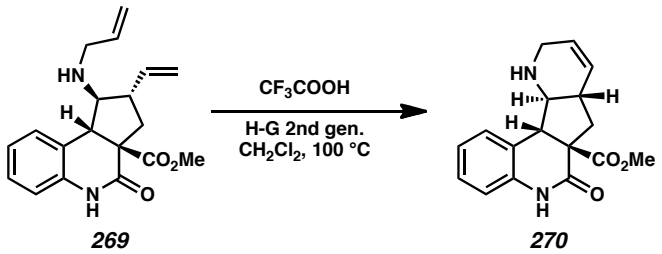
Tetracycle 267. Prepared according to the above procedure: Grubbs first-generation catalyst gave no conversion in dichloromethane, the solution was filtered through celite prior to resubjecting the material with Grubbs second-generation catalyst in toluene (full conersion was observed by LCMS after 13 hours). No trituration after the chromatographic purification was recorded, and tetracycle **267** (7.3 mg, 39% yield) was obtained. ^{1}H NMR (300 MHz, 1:1 CD_3OD:$CDCl_3$, referenced to residual CHD_2OD peak at 3.31 ppm) δ 7.24 (td, *J* = 7.7, 1.6 Hz, 1H), 7.17 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.04 (td, *J* = 7.5, 1.2 Hz, 1H), 6.92 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.54 (ddd, *J* = 10.1, 2.6, 1.0 Hz, 1H), 5.87 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.66–3.50 (app m, 5H), 3.26 (d, *J* = 9.8 Hz, 1H), 3.19 – 3.08 (m, 1H), 2.45 (dd, *J* = 13.4, 4.7 Hz, 1H); HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{17}N_2O_4$ $[M+H]^+$: 313.1183, found 313.1175.



241 ***269***

Allylamine 269. A flame-dried flask was charged with amine **241** (67.1 mg, 0.23 mmol, 1 equiv) and potassium carbonate (33 mg, 0.24, 1.02 equiv), then sealed with a rubber septum and placed under an inert atmosphere. Acetonitrile (2 mL) was added,

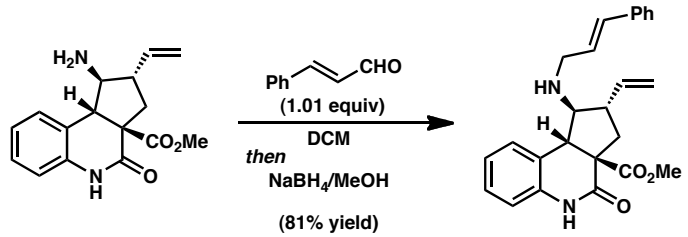
followed by allyl bromide (0.021 mL, 0.24 mmol, 1.04 equiv), and the mixture was stirred at ambient temperature overnight. The reaction mixture was filtered through celite, washing with dichloromethane, and the volatiles were removed in vacuo. The residue was purified by column chromatography on SiO_2 (150:1 $CHCl_3$:MeOH) to afford allylamine **269** (51.3 mg, 67% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.31 –7.15 (m, 2H), 7.04 (td, *J* = 7.5, 1.2 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 5.79–5.58 (m, 2H), 5.19–4.87 (m, 4H), 3.61 (s, 3H), 3.34 (d, *J* = 10.7 Hz, 1H), 3.27–3.07 (m, 1H), 3.06–2.95 (m, 1H), 2.81–2.48 (m, 4H). HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{23}N_2O_3$ $[M+H]^+$: 327.1703, found 327.1692.



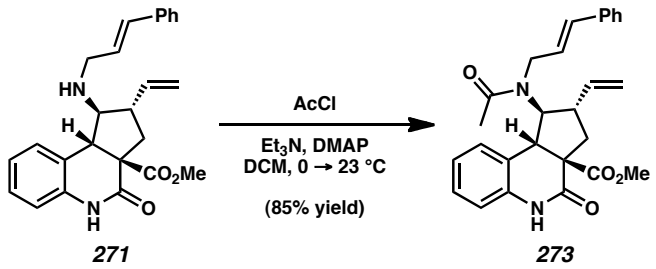
269 ***270***

Tetracycle 270. A flame-dried microwave vial (2-5 mL capacity), equipped with a magnetic stir bar, was charged with allylamine **269** (11.5 mg, 0.035 mmol, 1 equiv) then sealed with a rubber septum, placed under an inert atmosphere and charged with dichloromethane (4.5 mL). To a flame-dried flask was added trifluoroacetic acid (0.1 mL) and toluene (0.9 mL), and 0.027 mL of this solution was added to the microwave vial. Finally, the septum was removed and Hoveyda-Grubbs second-generation catalyst (2.2 mg, 0.0035 mmol, 0.1 equiv) was added quickly, and the microwave vial was sealed with a microwave cap. The reaction mixture was heated to 100 °C in a microwave reactor for 1 hour. Additional catalyst (1.0 mg) was added to the reaction mixture and the

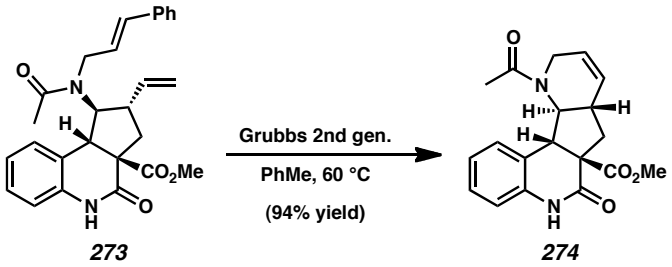
vial was re-sealed and subjected to microwave heating for an additional hour. The volatiles were removed in vacuo and the residue was purified by preparatory TLC (10:1 $CHCl_3$:MeOH; R_F SM = 0.44, Prod: 0.50) to afford tetracycle **270** (yield was not recorded). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.18–7.08 (m, 2H), 7.00 (t, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.84 (d, *J* = 11.1 Hz, 1H), 5.55 (ddd, *J* = 10.2, 6.0, 3.1 Hz, 1H), 3.60 (s, 3H), 3.47 (ddd, *J* = 17.6, 5.3, 2.6 Hz, 1H), 3.34 (ddd, *J* = 17.2, 6.0, 2.5 Hz, 1H), 3.13 (d, *J* = 11.1 Hz, 1H), 2.85 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.53–2.28 (m, 1H), 2.07–1.91 (m, 1H).



Cinnamylamine 271. Prepared by an analogous method as that reported for the synthesis of **242**, Chapter 2, using amine **241** (302.4 mg, 1.04 mmol, 1 equiv), cinnamaldehyde (0.138 mL, 1.10 mmol, 1.05 equiv) and sodium borohydride (47 mg, 1.25 mmol, 1.2 equiv) to obtain cinnamylamine **271** (343.1 mg, 81% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.35–7.17 (m, 9H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.78 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.26 (d, *J* = 16.0 Hz, 1H), 6.01 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.73 (ddd, *J* = 16.9, 10.0, 8.3 Hz, 1H), 5.16 (d, *J* = 17.0 Hz, 1H), 5.07 (dd, *J* = 10.1, 1.6 Hz, 1H), 3.61 (s, 3H), 3.40–3.27 (m, 2H), 3.19 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.83–2.73 (m, 2H), 2.67 (dt, *J* = 16.9, 8.6 Hz, 1H), 2.58 (dd, *J* = 13.2, 7.3 Hz, 1H).

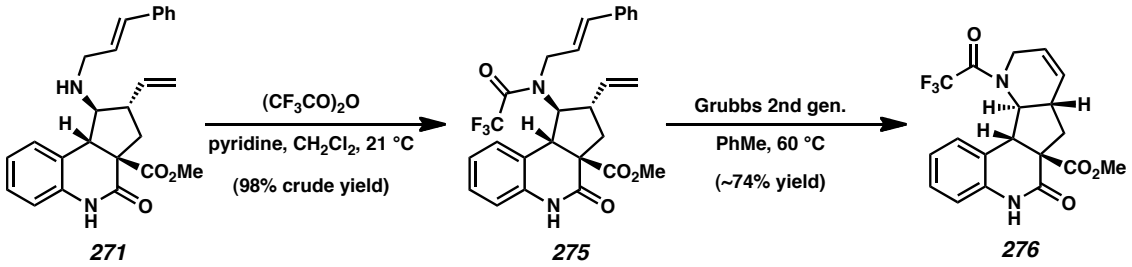


Acetamide 273. A flame-dried round-bottom flask, equipped with a magnetic stir bar, was charged with amine **271** (149.8 mg, 0.37 mmol, 1 equiv) and 4-(*N*,*N*-dimethylamino)pyridine (4.9 mg, 0.037 mmol, 0.1 equiv), sealed with a rubber septum and placed under an inert atmosphere. To the flask was added dichloromethane (3 mL) and triethylamine (0.065 mL, 0.45 mmol, 1.2 equiv). The flask was cooled in an ice-water bath, then acetyl chloride (0.030 mL, 0.41 mmol, 1.1 equiv) was added. The cooling bath was removed, and the reaction was monitored by LCMS. Upon complete consumption of starting material, the reaction mixture was dry-loaded onto SiO_2 (~2 mL) and purified by column chromatography on SiO_2 (2:1 → 1:1 hexanes:EtOAc) to afford acetamide **273** (140.7 mg, 85% yield).



Tetracycle 274. A flame-dried Schlenk tube, equipped with a stir bar, was charged with Grubbs' second-generation catalyst (3.8 mg, 0.0045 mmol, 0.1 equiv), then sealed with a rubber septum, and evacuated and backfilled with argon. In a separate flame-dried flask, acetamide **273** (20 mg, 0.045 mmol, 1 equiv) was dissolved in toluene (0.9 mL)

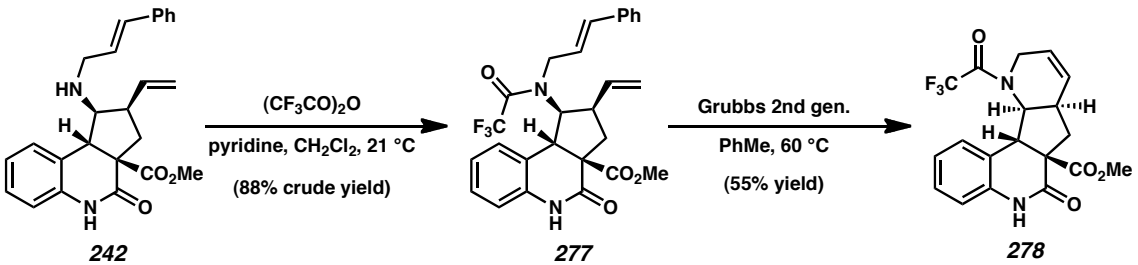
which was degassed by sparging with argon gas. The acetamide solution was transferred via syringe to the Schlenk tube, and the resulting solution was heated to 60 °C in an oil bath. After one hour, a brown suspension was observed, and after five hours (total), the suspension was filtered, washing with a small amount of toluene (ambient temperature) to afford tetracycle **274** (14.4 mg, 94% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.27–7.13 (m, 1H), 7.02 (td, *J* = 7.5, 1.2 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.98 (d, *J* = 9.6 Hz, 1H), 5.62 (d, *J* = 9.7 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 4.05 (d, *J* = 18.0 Hz, 1H), 3.74 (d, *J* = 17.5 Hz, 1H), 3.64 (s, 3H), 2.98 (q, *J* = 8.4 Hz, 2H), 2.79 (t, *J* = 11.0 Hz, 1H), 2.10 (app m, 4H).



Trifluoroacetamide 276. An oven-dried vial, equipped with a magnetic stir bar, was charged with amine **271** (141.3 mg, 0.35 mmol, 1 equiv), sealed with a cap fitted with a Teflon septum, and placed under an inert atmosphere. To the vial were added sequentially dichloromethane (0.72 mL), trifluoroacetic anhydride (0.250 mL, 1.76 mmol, 5 equiv), and freshly distilled pyridine (0.18 mL, 2.23 mmol, 6.4 equiv). The reaction was allowed to stir at ambient temperature for 6 hours, then was quenched by addition of saturated aqueous copper(II) sulfate (exothermic!). The biphasic mixture was extracted with dichloromethane, then the combined organics were dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was filtered through a short plug

of SiO_2 (1:1 hexanes:EtOAc), and concentrated in vacuo to afford crude acetamide **275** (172.0 mg, 98% yield) as a yellow-ish foam after concentrating from hexanes. The material was found to be clean by LCMS and was carried forward directly to the next stage of the sequence.

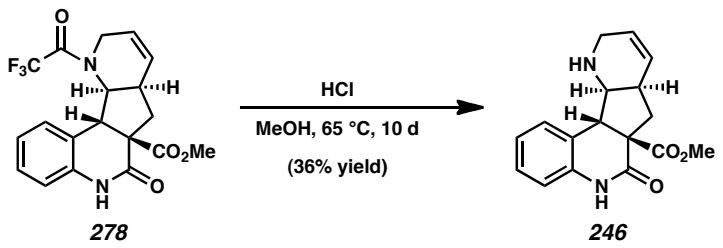
A flame-dried Schlenk flask, equipped with a magnetic stir bar, was charged with Grubbs' second generation catalyst (29.8 mg, 0.035 mmol, 0.1 equiv), then sealed with a rubber septum, evacuated and backfilled with argon. To the flask was then added benzene (4 mL). Crude acetamide **275** (172.0 mg, 0.345 mmol, 1 equiv) was then added to the Schlenk flask as a solution in benzene (3 mL). The reaction mixture was heated to 60 °C in an oil bath with stirring for 17 hours, then dry-loaded onto SiO_2 and purified by column chromatography (3:1 hexanes:EtOAc) to afford trifluoroacetamide **276** (102.9 mg, 74% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.04 (d, *J* = 8.9 Hz, 1H), 5.67 (d, *J* = 10.6 Hz, 1H), 5.03 (d, *J* = 11.9 Hz, 1H), 4.29 (d, *J* = 18.7 Hz, 1H), 3.82 (d, *J* = 16.8 Hz, 1H), 3.68 (s, 3H), 3.15 – 2.93 (m, 3H), 2.20 (dd, *J* = 12.9, 10.2 Hz, 1H).



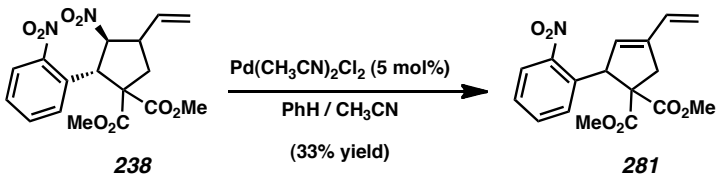
Trifluoroacetamide 277. Acylation of secondary amine **242** (506.1 mg, 1.26 mmol, 1 equiv) was performed exactly as above, using trifluoroacetic anhydride (0.89 mL, 6.29

mmol, 5 equiv), pyridine (0.63 mL), and dichloromethane (2.5 mL) to afford crude trifluoroacetamide **278** (548.9 mg, 88% yield) as a yellow-brown foam which was carried forward without further purification.

Ring-closing metathesis of crude trifluoroacetamide **278** (548.9 mg, 1.1 mmol, 1 equiv) was performed as above, using Grubbs' second generation catalyst (93 mg, 0.11 mmol, 0.1 equiv) and benzene (22 mL, 0.05 M), with modifications: after 16 hours, additional catalyst (50 mg, 0.059 mmol) was added, and complete consumption of starting material was observed by LCMS after an additional 2 hours. The volatiles were removed in vacuo, and the solid residue was triturated with diethyl ether—some material was likely lost in this stage—to afford trifluoroacetate **278** (240.8 mg, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ~ 1:1 mixture of amide bond rotamers) δ 8.22 (s, 0.45H), 8.11 (s, 0.55H), 7.30–7.18 (m, 1H), 7.01 (app qd, *J* = 8.4, 8.0, 1.1 Hz, 1H), 6.92 (t, *J* = 6.1 Hz, 1H), 6.81 (dd, *J* = 7.9, 5.3 Hz, 1H), 5.89–5.82 (m, 1H), 5.78 – 5.70 (m, 1H), 5.00 (dd, *J* = 11.9, 7.9 Hz, 0.45H), 4.79–4.65 (m, 0.55H), 4.35 (d, *J* = 17.9 Hz, 0.55H), 4.24–4.05 (m, 1H), 3.89–3.69 (m, 1H), 3.64–3.61 (m, 3H), 3.58 (d, *J* = 11.9 Hz, 0.45H), 3.22 (ddd, *J* = 19.7, 14.4, 9.6 Hz, 1H), 2.93 (s, 1H), 2.33 (td, *J* = 14.9, 3.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.6, -69.8.

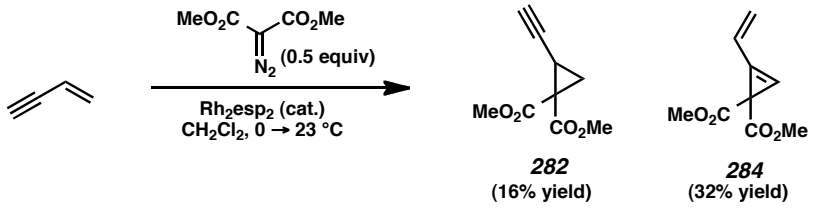


Secondary amine 246. A flame-dried round-bottom flask, equipped with a stir-bar, sealed with a rubber septum, and under an inert atmosphere, was charged with methanol (10 mL), which was freshly distilled from $Mg(OMe)_2$, and cooled in an ice-water bath. Acetyl chloride (0.25 mL, 3.5 mmol, 6.7 equiv) was added to the flask, dropwise, then the cooling bath was removed. The rubber septum was removed, acetamide **278** (206.7 mg, 0.524 mmol, 1 equiv) was added quickly, and the septum was replaced. The flask was heated to 65 °C in an oil bath with stirring. After heating for 4 days, the reaction flask was cooled to room temperature, additional acetyl chloride (0.05 mL) was added, and the flask was reheated to 65 °C for 4 days. The flask was cooled to ambient temperature, and stirred for an additional 2 days. The volatiles were removed in vacuo and the residue was partitioned between water and diethyl ether, with a small amount of acetone to solubilize remaining solids. The phases were separated, and the aqueous layer was extracted once with diethyl ether and twice with ethyl acetate. The aqueous layer was then basified to pH = ~ 11 with aqueous sodium hydroxide (3 M, 1 mL) and extracted with an unrecorded solvent. Upon concentration of the combined basic extracts, the residue was purified by column chromatography (30:1 → 15:1 $CHCl_3$:MeOH) to afford secondary amine **246** (56.8 mg, 36% yield). The characterization data matches those reported in Chapter 2.



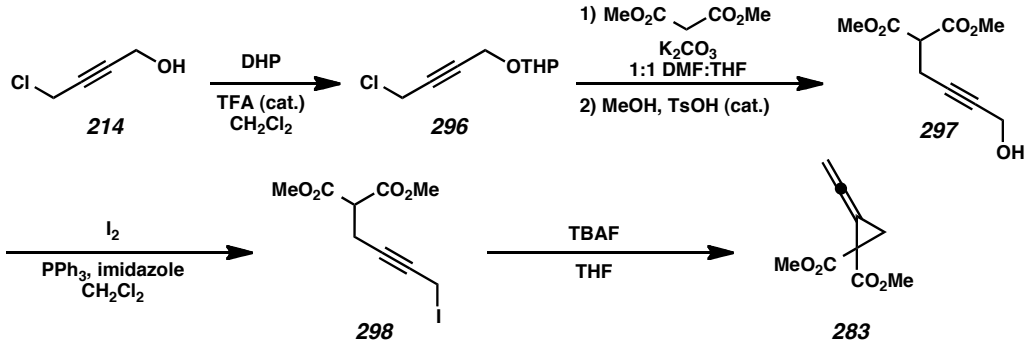
238 *281*

Diene 281. A flame-dried Schlenk tube, equipped with a magnetic stir bar, was charged with cyclopentane **238** (50 mg, 0.13 mmol, 1 equiv) and bis(acetonitrile)dichloropalladium(II) (2.1 mg, 0.007 mmol, 0.05 equiv). The tube was sealed with a rubber septum, and evacuated and backfilled with argon. To the Schlenk were added toluene (1.3 mL, 0.1 M) and acetonitrile (0.020 mL). The reaction mixture was heated, with stirring, at 75 °C in an oil bath for 12 hours. The volatiles were removed and the residue was purified by column chromatography on SiO_2 (6:1 → 3:1 hexanes:EtOAc) to afford diene **281** (14.4 mg, 33% yield) and recovered starting material (23.0 mg, 46% recovery). **281**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H), 7.38–7.32 (m, 1H), 7.19 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.60 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.70 (d, *J* = 45.0 Hz, 1H), 5.27 (d, *J* = 5.7 Hz, 1H), 5.24 (s, 1H), 3.76 (s, 3H), 3.64 (d, *J* = 17.1 Hz, 1H), 3.17 (s, 3H), 2.93 (d, *J* = 17.1 Hz, 1H).

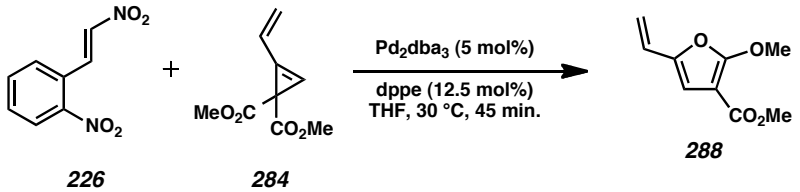


Alkynylcyclopropane 282 and Vinylcyclopropene 284. A 25 mL conical side-arm flask—with a line drawn with a marker indicating 1 mL volume—was fitted with a magnetic stir bar and a dry-ice cold-finger condenser. The joints on the condensor and flask side-arm were sealed with rubber septa, the system was flame-dried under vacuum, and allowed to cool under a positive pressure of nitrogen. The conical flask was charged with bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] (2.2 mg, 0.0029 mmol, 0.04 mol%) and after reattaching the condenser, the entire system was evacuated

and backfilled with argon. The condenser was charged with dry ice and acetone and the conical flask was lowered into an ice-water bath, then gaseous vinylacetylene (b.p. = 0–6 °C) was introduced into the system with a needle, through the condenser septum until the condensate reached the 1 mL line drawn on the side-arm flask (15 mmol, ~ 2 equiv). The flask was then charged, via the side-arm, with dichloromethane (8.0 mL, 1 M) and diazodimethylmalonate (1.00 mL, 7.98 mmol, 1 equiv), and the cooling bath was removed. After 3.5 hours, a spatula tip of catalyst was added quickly via the side-arm and additional bubbling was observed. After complete conversion of the diazomalonate, the volatiles were removed and the residue was purified by column chromatography on SiO_2 (6:1 → 3:1 hexanes:Et_2O) to afford alkynylcyclopropane **282** (239.7 mg, 16% yield) as a clear oil and vinylcyclopropene **284** (468.0 mg, 32% yield) as an oil which solidifies upon refrigeration. **282**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.75 (s, 3H), 2.47 (ddd, *J* = 9.4, 7.3, 2.2 Hz, 1H), 1.97 (d, *J* = 2.2 Hz, 1H), 1.86 (dd, *J* = 7.3, 4.7 Hz, 1H), 1.59 (dd, *J* = 9.3, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 79.6, 68.6, 53.0, 52.9, 35.8, 21.9, 16.3. **284**: 1H NMR (400 MHz, $CDCl_3$) δ 6.68–6.66 (m, 1H), 6.47 (dd, *J* = 17.0, 10.3 Hz, 1H), 5.82–5.71 (m, 2H), 3.66 (s, 6H).

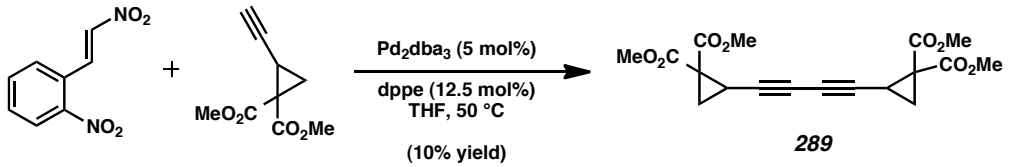


Vinylidenecyclopropane 283. Prepared according to the method of Johnson and coworkers.[5]



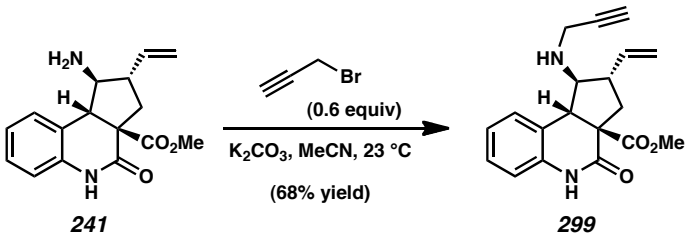
226 ***284*** ***288***

Furan 288. Set up under standard (3 + 2) conditions (see compound **238**, chapter 2). Complete conversion of the cyclopropane was observed in less than 45 minutes. The reaction mixture was dry-loaded onto SiO_2 and purified by column chromatography (20:1 → 10:1 hexanes:EtOAc) to afford furan **288** (no yield was obtained): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (d, *J* = 1.4 Hz, 1H), 6.32 (ddd, *J* = 17.4, 11.4, 1.4 Hz, 1H), 5.47 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 11.3 Hz, 1H), 4.15 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 161.6, 143.0, 124.0, 110.9, 109.6, 92.6, 58.0, 51.3.

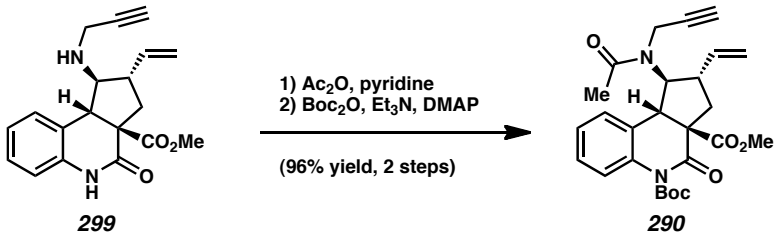


226 ***282*** ***289***

Diyne 289. Setup under standard (3 + 2) conditions (see compound **238**, chapter 2). No conversion was observed at 30 °C over 3 hours. Heated to 50 °C for an additional 1.5 hours. Reaction halted and purified by column chromatography in spite of incomplete conversion of cyclopropane to afford diyne **289**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 6H), 3.75 (s, 6H), 2.49 (dd, *J* = 9.2, 7.2 Hz, 2H), 1.87 (dd, *J* = 7.2, 4.8 Hz, 2H), 1.61 (dd, J = 9.2, 4.7 Hz, 2H).



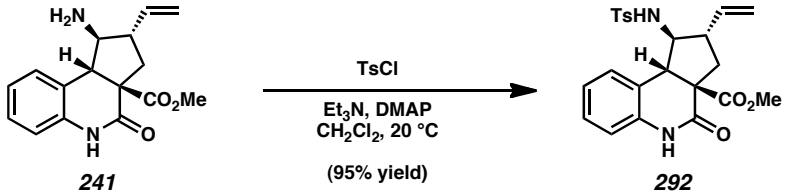
Propargylamine 299. An oven-dried vial equipped with a magnetic stir bar was charged with amine **241** (100.7 mg, 0.35 mmol, 1.67 equiv) and potassium carbonate (49.3 mg, 0.35 mmol, 1.67 equiv). The vial was sealed with a cap lined with a Teflon septum, and placed under an inert atmosphere. Acetonitrile (0.70 mL) was added, followed by propargyl bromide (0.024 mL, 80 wt% in toluene, 0.21 mmol, 1 equiv), and the resulting reaction mixture was stirred at ambient temperature for 5.5 hours. The reaction mixture was filtered through Celite, dry-loaded onto SiO_2 (~1 mL), and purified by column chromatography on SiO_2 (5:3 hexanes:EtOAc until product eluted, then 20:1 $CHCl_3$) to afford recovered amine **241** (53.6 mg, 53% rsm) and propargyl amine **299** (46.9 mg, 68% yield, 41% of **241**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 2.8 Hz, 1H), 7.21–7.13 (m, 2H), 6.96 (td, *J* = 7.5, 1.2 Hz, 1H), 6.81 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.68 (ddd, *J* = 16.9, 10.0, 8.5 Hz, 1H), 5.10 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.99 (dd, *J* = 10.1, 1.6 Hz, 1H), 3.52 (s, 3H), 3.27 (d, *J* = 10.5 Hz, 1H), 3.21 (dd, *J* = 17.1, 2.4 Hz, 1H), 3.11 (dd, *J* = 17.1, 2.4 Hz, 1H), 2.83 (dd, *J* = 10.5, 9.1 Hz, 1H), 2.77–2.67 (m, 1H), 2.60–2.48 (m, 2H), 1.99 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 170.1, 140.1, 135.6, 129.0, 128.6, 123.6, 121.8, 116.7, 115.9, 82.1, 71.6, 66.4, 56.0, 54.0, 53.2, 49.1, 37.6, 37.0.



299 ***290***

Propargyl acetamide 290. An oven-dried vial equipped with a magnetic stir bar was charged with propargyl amine **299** (14.7 mg, 0.046 mmol, 1 equiv), sealed with a cap lined with a Teflon septum, and placed under an inert atmosphere. To the vial were added dichloromethane (0.100 mL), pyridine (0.037 mL, 0.46 mmol, 10 equiv), and acetic anhydride (0.022 mL, 0.23 mmol, 5 equiv). After 24 hours of stirring, toluene was added to and evaporated from the solution twice to remove excess pyridine. Hexanes was added, and a white precipitate was observed. The solvent was then removed in vacuo to afford a crude acetate which was carried forward without further purification.

A vial was charged with the crude acetate, di-*tert*-butyl dicarbonate (14.3 mg, 0.054 mmol, 1.2 equiv), 4-(*N*,*N*-dimethylamino)pyridine (unspecified), dichloromethane (0.200 mL), and triethylamine (0.012 mL, 0.068 mmol, 1.5 equiv). Complete consumption of starting material was observed after 90 minutes, and the reaction mixture was dry-loaded onto SiO_2 and purified by column chromatography (3:1 hexanes:EtOAc) to afford propargyl acetamide **290** (20.3 mg, 96% yield, two steps).



241 ***292***

Toluenesulfonamide 292. An oven-dried 1 dram vial, equipped with a magnetic stir bar, was charged with amine **241** (100.4 mg, 0.35 mmol, 1 equiv), tosyl chloride (79.8 mg, 0.38 mmol, 1.1 equiv) and 4-(*N*,*N*-dimethylamino)pyridine (4.5 mg, 0.038 mmol, 0.1 equiv). The vial was sealed with a cap lined with a Teflon septum, and placed under nitrogen atmosphere. Dichloromethane (1.8 mL) was added to the vial, followed by freshly distilled triethylamine (0.08 mL, 0.5 mmol, 1.5 equiv), and the reaction mixture was stirred for 6.5 hours. The reaction mixture was dry-loaded onto SiO_2 (~1.5 mL) and purified by column chromatography on SiO_2 (3:1 hexanes:EtOAc until excess TsCl eluted, then 1:1 hexanes:EtOAc) to afford toluenesulfonamide **292** (146.2 mg, 95% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 3H), 7.20 (td, *J* = 7.7, 1.4 Hz, 1H), 7.14–7.08 (m, 2H), 6.87 (td, *J* = 7.5, 1.1 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 5.39 (ddd, *J* = 17.2, 9.9, 7.3 Hz, 1H), 4.92 (d, *J* = 17.0 Hz, 1H), 4.82–4.72 (m, 2H), 3.63 (s, 3H), 3.43–3.36 (m, 1H), 3.32 (d, *J* = 11.0 Hz, 1H), 2.77–2.67 (m, 1H), 2.62–2.51 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 168.4, 143.1, 138.2, 136.8, 134.8, 129.8, 129.4, 128.5, 126.8, 123.7, 119.7, 117.0, 115.0, 64.2, 54.9, 53.3, 53.2, 49.0, 36.0, 21.5.

A4.5 NOTES AND REFERENCES

(1) Observed via LCMS

(2) An intramolecular Heck reaction would be the most likely method to successfully install the quaternary center at this position. This approach has been employed in several natural product syntheses. See: (a) Overman, L. E. *Pure & Appl. Chem.* **1994**, *66*, 1423–1430. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. MacMillan used a similar intramolecular Heck reaction in the total synthesis of aspidospermidine: (c) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183–188.

(3) (a) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795–3849. (b) Stang, P. J. *Acc. Chem. Res.* **1982**, *15*, 348–354. (c) Stang, P. J. *Acc. Chem. Res.* **1978**, *11*, 107–114. (d) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383–405. (d) Barluenga, J.; Sigüeiro, R.; Vicente, R.; Ballesteros, A.; Tomás, M.; Rodríguez, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 10377–10381. (e) Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525–16528. (f) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440–5452. (g) Feldman, K. S.; Wrobleski, M. L. *Org. Lett.* **2000**, *2*, 2603–2605.

(4) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

(5) Campbell, M. J.; Pohlhaus, P. D.; Min, G.; Ohmatsu, K.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 9180–9181. (b) THP protected precursor to **297** was

prepared according to the method described in: Deslongchamps, P.; Lamothe, S.; Lin, H.-S. *Can. J. Chem.* **1984**, *62*, 2395–2398.