CHAPTER FOUR

A Convergent Synthesis of Amurensinine Via Selective C-H and C-C Insertion Reactions[†]

4.1 Background and Introduction

4.1.1 C-H and C-C Insertion Reactions in Natural Product Synthesis

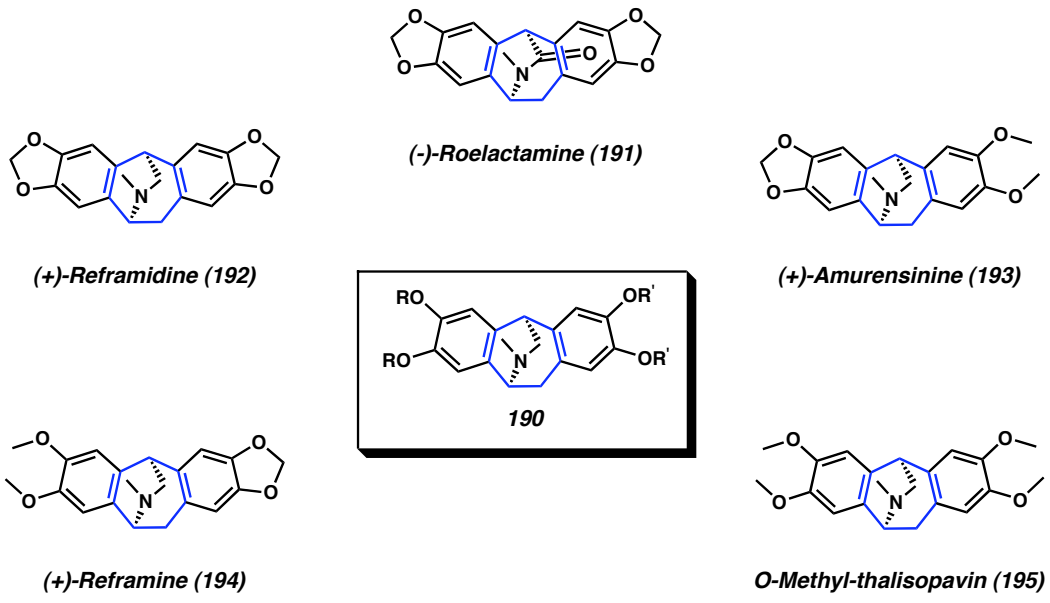
The activation of traditionally inert C-X bonds has become an important area of chemical research.[1] Unfortunately, the application of selective C-H and C-C activation reactions in the context of complex natural product synthesis has been limited because of the shear abundance of these two types of bonds in most organic molecules. The development of mild C-H[2] and C-C[3] insertion reactions may ultimately change the way synthetic chemists approach natural product synthesis by allowing efficient disconnections that would be forbidden under traditional retrosynthetic analysis. In this chapter we present a convergent and enantioselective synthesis of the natural product amurensinine that takes advantage of direct, mild, and selective C-H and C-C insertion reactions.

[†] This work was performed in collaboration with David C. Ebner, a graduate student in the Stoltz group at the California Institute of Technology.

4.1.2 Isopavine Natural Products

The synthesis of the isopavine natural products (Figure 4.1.1) and related non-natural structures has received considerable attention because of the important pharmacological properties of this family of alkaloids. Specifically, they have been shown to be promising lead structures for the treatment of neuronal disorders such as Parkinson's disease, Down's syndrome, Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's chorea.[4] All members of this group of natural products possess a tetracyclic structure containing a seven-membered benzannulated carbocycle (i.e., **190**, Figure 4.1.1). Despite the tremendous interest in the isopavines by the scientific community, few examples of the total syntheses of these natural products have been reported in the literature.[5]

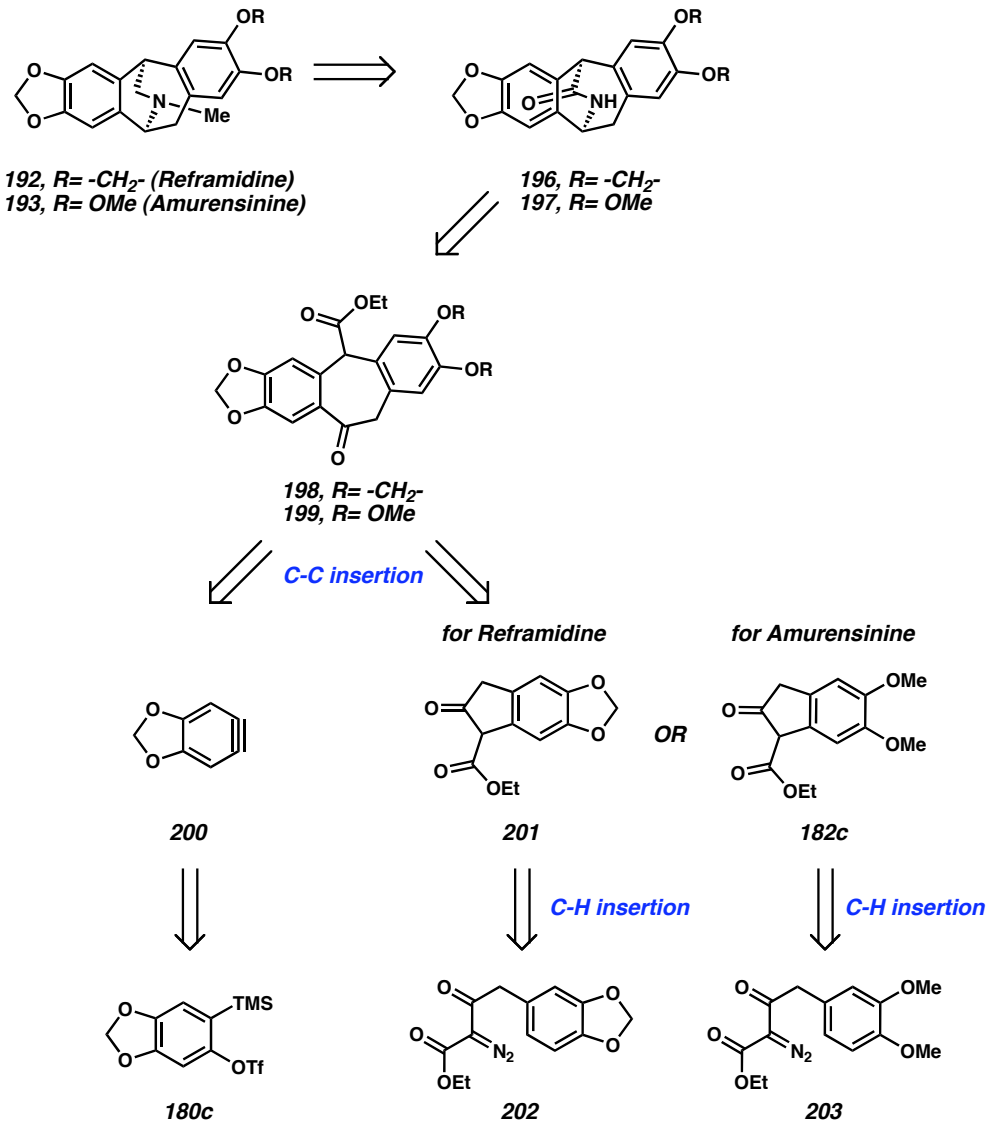
Figure 4.1.1



4.1.3 Retrosynthetic Analysis of Amurensinine and Reframidine

Reframidine (**192**) and amurensinine (**193**) are two members of the isopavine family. Our retrosynthetic strategy for the preparation of these alkaloids is shown in Scheme 4.1.1. Initial functional group interconversion of the tertiary amines in the natural products exposes lactams **196** and **197** as synthetic intermediates. We reasoned that these lactams could be accessed from ketoesters **198** and **199**, which contain seven-membered benzannulated carbocycles. These seven-membered ring structures are retrons for the direct and mild C-C insertion reaction discussed in chapter 3. Aryne **200** and β-ketoesters **201** and **182c** are then revealed as suitable substrates for the C-C insertion reaction. Aryne **200** may be generated in situ from trimethylsilyl triflate **180c**, while β-ketoesters **201** and **182c** may be synthesized by selective rhodium-catalyzed C-H insertion reactions of diazo compounds **202** and **203**, respectively.

Scheme 4.1.1

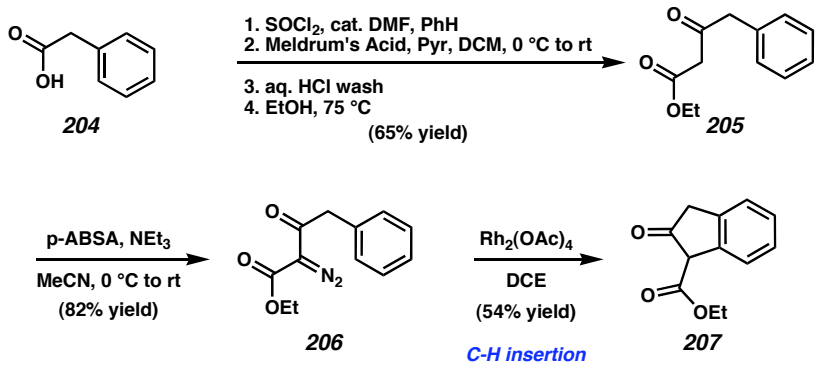

OR
OR
N
Me
O
O
192, R= -CH2- (Reframidine)
193, R= OMe (Amurensinine)
O
NH
196, R= -CH2-
197, R= OMe
OEt
198, R= -CH2-
199, R= OMe
C-C insertion
for Reframidine
for Amurensinine
OR
OMe
OEt
200
201
182c
C-H insertion
C-H insertion
TMS
OTf
N2
180c
202
203

4.2 Synthesis of Amurensinine

4.2.1 Model Studies on the C-H/C-C Insertion Strategy for the Isopavines

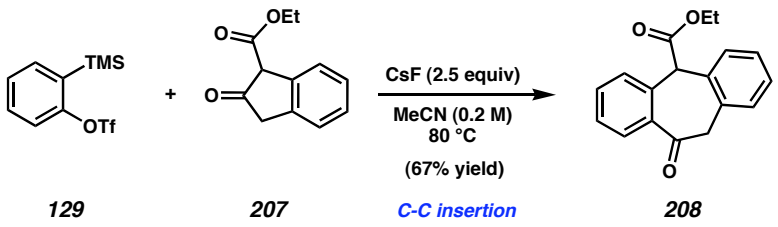
To test the viability of our strategy for synthesizing the isopavines, we commenced our efforts with the construction of a model system for ketoesters **198** and **199**. As reported in the literature for a similar substrate,[6] the unfunctionalized β-ketoester **207** was generated rapidly via a selective rhodium-catalyzed C-H insertion reaction (Scheme 4.2.1). Phenylacetic acid **204** was first converted to acyclic β-ketoester **205**, which was then diazotized to form intermediate **206**. This diazoketoester was treated with $Rh_2(OAc)_4$ in DCE, which resulted in a selective C-H insertion reaction to form cyclic β-ketoester **207**.

Scheme 4.2.1



This model β-ketoester **207** was then coupled with trimethylsilyl triflate **129** to yield the desired model ketoester **208** in 67% isolated yield (Scheme 4.2.2).

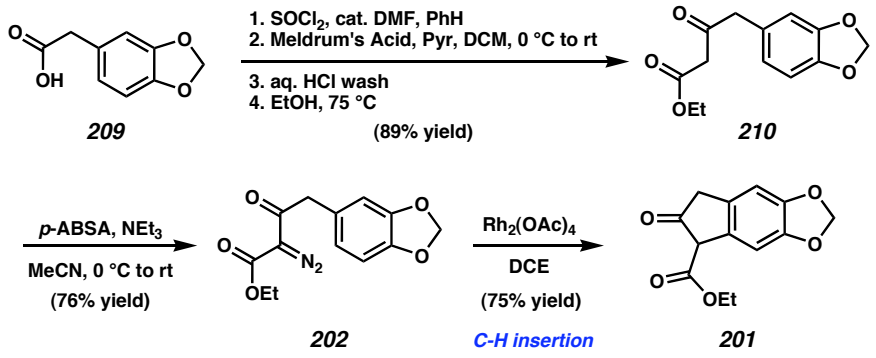
Scheme 4.2.2



4.2.2 Synthetic Efforts Toward the Synthesis of Reframidine

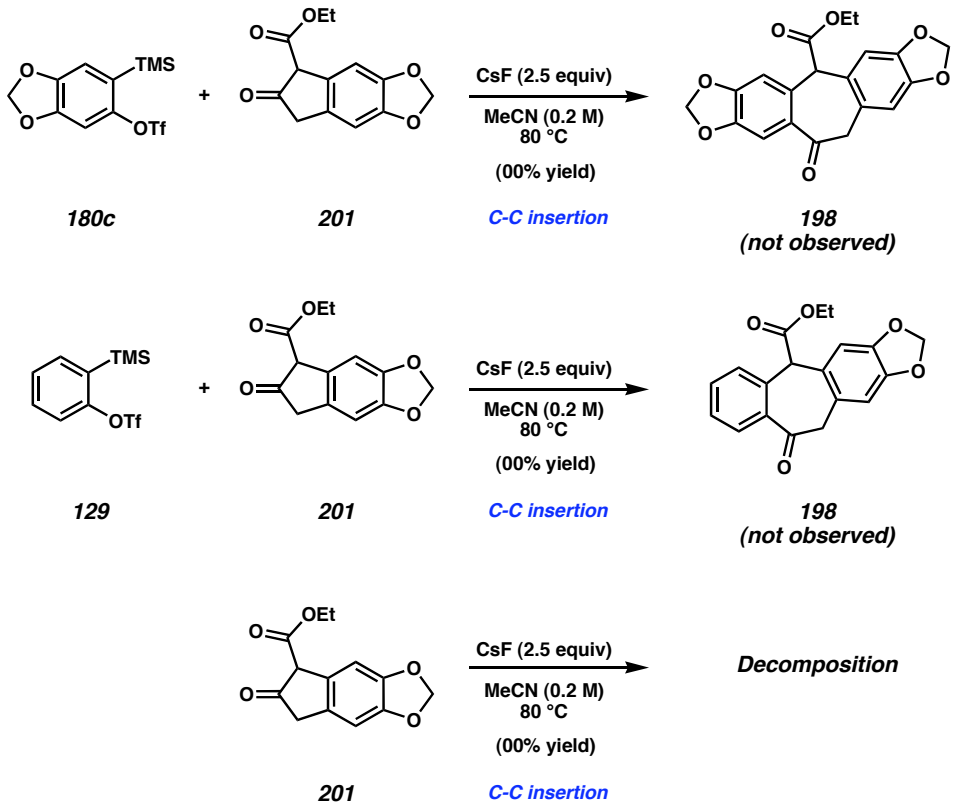
After establishing the viability of the C-H/C-C insertion strategy for synthesizing the core structure of the isopavines, we turned our attention to the synthesis of reframidiine (**192**, Figure 4.1.1). The fully functionalized β-ketoester **201** was synthesized rapidly from phenylacetic acid **209** (Scheme 4.2.3). Interestingly, diazo intermediate **202** underwent a highly position-selective C-H insertion reaction to produce the desired β-ketoester **201**.[7]

Scheme 4.2.3



Unfortunately, all attempts to couple β-ketoester **201** with trimethylsilyl triflates **180c** and **129** were unsuccessful (Scheme 4.2.4). In fact, simple exposure of β-ketoester **201** to the reaction conditions in the absence of any trimethylsilyl triflate led to decomposition. We reasoned that the methylenedioxy functionality in the β-ketoester was unstable to the conditions.

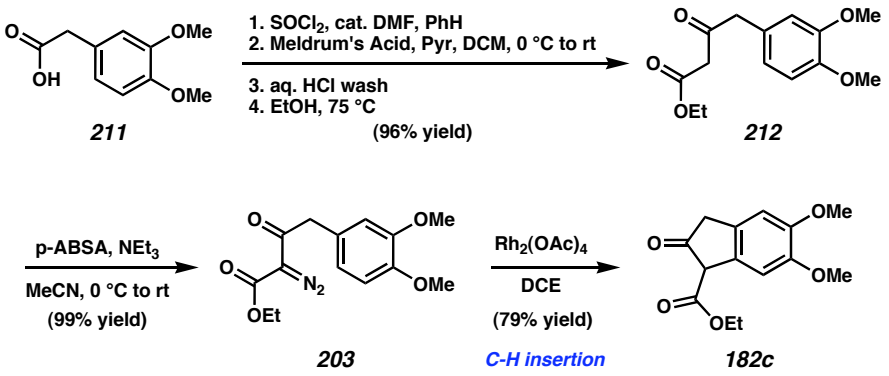
Scheme 4.2.4



4.2.3 Synthesis of the Core Structure of Amurensinine

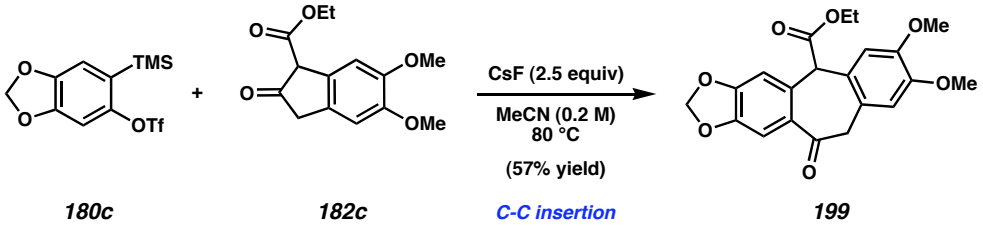
We then attempted to synthesize the core structure of amurensinine (**193**, Figure 4.1.1) by the same strategy, with the hope that the corresponding dimethoxy functionality in β-ketoester **182c** would be more stable to the reaction conditions. Phenylacetic acid **211** was easily converted to the desired β-ketoester **182c**, once again with highly position-selective C-H insertion of diazo intermediate **203** (Scheme 4.2.5).

Scheme 4.2.5



Gratifyingly, the coupling of β-ketoester **182c** and aryne precursor **180c** under our standard reaction conditions produced ketoester **199** in 57% isolated yield (Scheme 4.2.6). This transformation represents a direct and mild C-C insertion reaction to generate the polycyclic carbon framework of amurensinine (**193**).

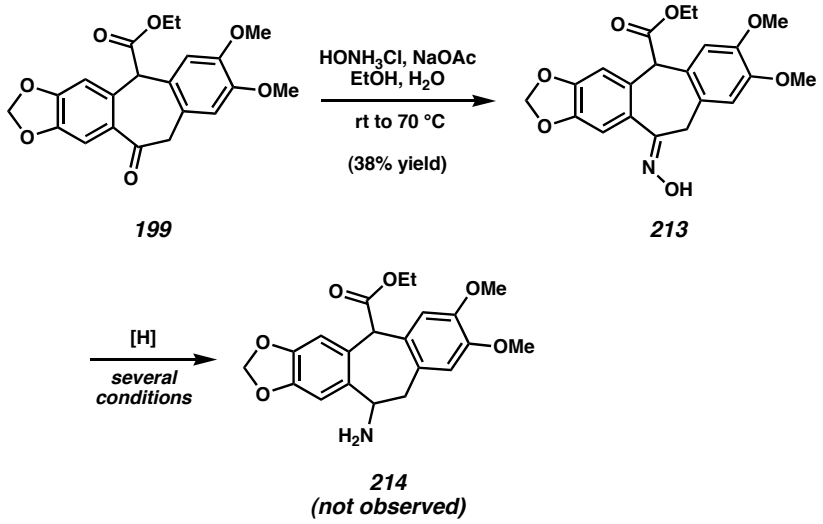
Scheme 4.2.6



4.2.4 Completion of the Total Synthesis of Amurensinine

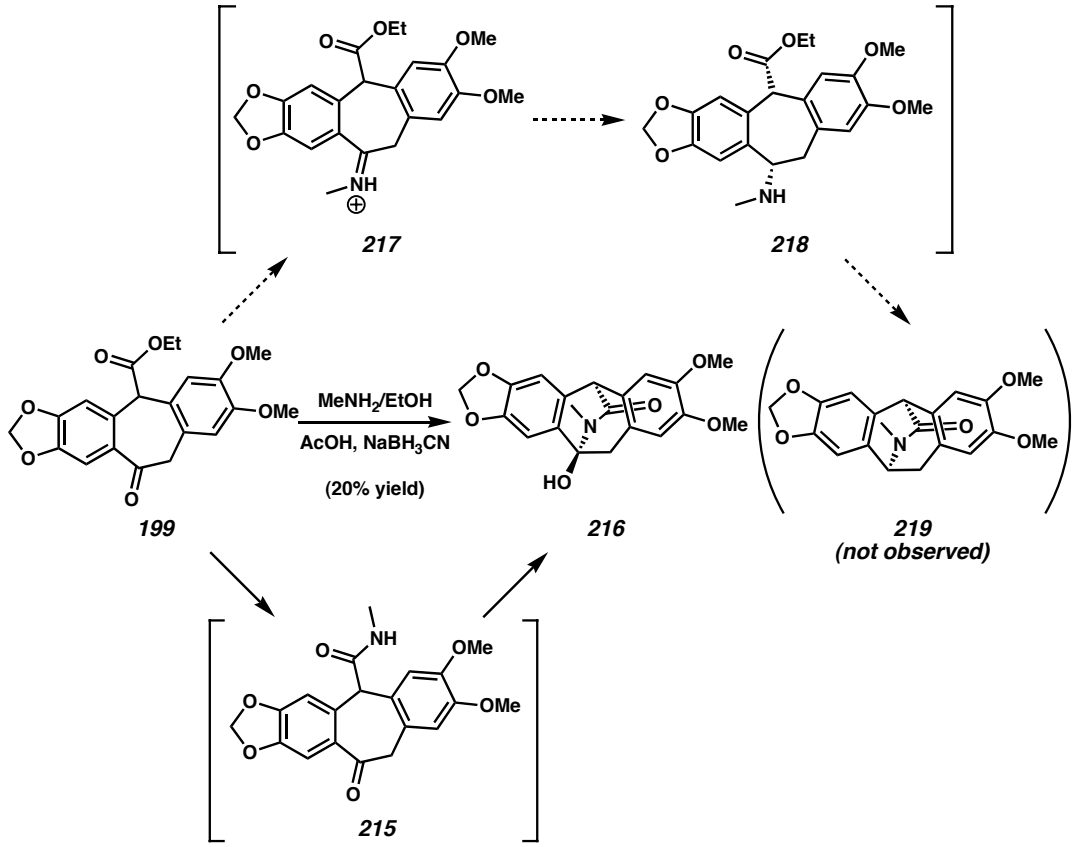
At this point, all that remained for completing the synthesis of amurensinine (**193**) was a series of functional group interconversions of ketoester **199**. Most notably, an atom of nitrogen needed to be added to the molecule. Initial efforts for nitrogen insertion focused on oximation followed by selective reduction to a primary amine (Scheme 4.2.7). Although oxime **213** was easily synthesized from ketoester **199**, the reduction of the oxime to aminoester **214** was not observed under several conditions.

Scheme 4.2.7



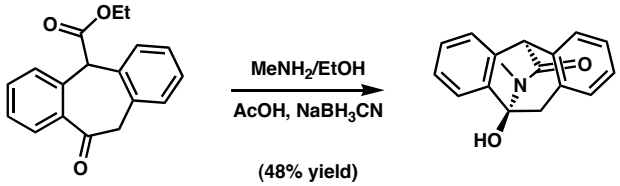
Next, we attempted to insert nitrogen into the molecule by reductive amination with methylamine (Scheme 4.2.8). Ketoester **199** was treated with excess methylamine in the presence of acetic acid and $NaCNBH_3$. Instead of observing the desired lactam **219**, we isolated aminal **216**. It seemed that amine addition into the ester was more facile than amine addition into the electronically deactivated and sterically hindered ketone of ketoester **199**.

Scheme 4.2.8



Surprisingly, a similar reaction occurred when model ketoester **208** was subjected to the reductive amination conditions (Scheme 4.2.9). Since the ketone functionality in this compound was not electronically deactivated towards nucleophillic attack, this suggested the importance of steric factors in the selective reactivity of the ester.

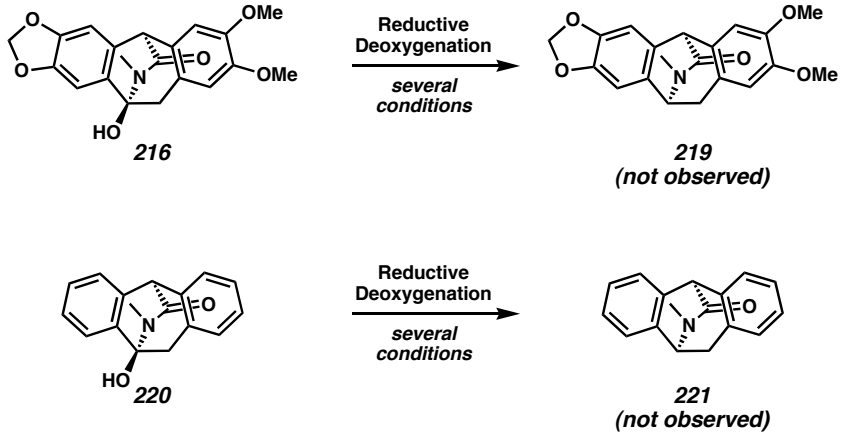
Scheme 4.2.9



208 ***220***

Unfortunately, all attempts to reductively deoxygenate aminal **216** or the model aminal **220** were unsuccessful (Scheme 4.2.10). All reported examples for the reductive deoxgenation of aminals presumably proceed through an iminium intermediate; but in our system this would lead to structures containing anti-Bredt olefins (i.e., **222** and **223**). Therefore, another strategy was needed.

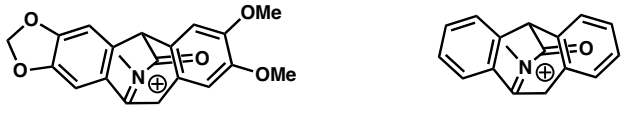
Scheme 4.2.10



216 ***219 (not observed)***

220 ***221 (not observed)***

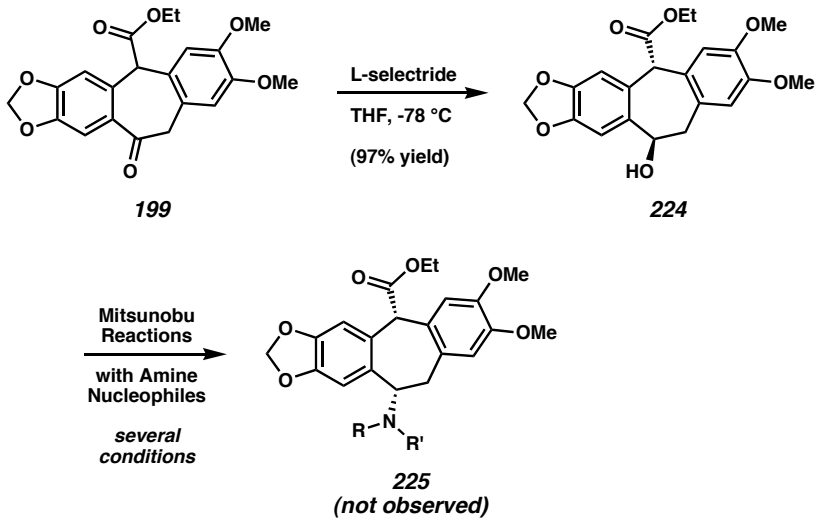
anti-Bredt Olefins (not observed):



222 ***223***

We then attempted to insert nitrogen into the molecule by a Mitsunobu reaction strategy.[8] The selective conversion of ketoester **199** to *trans*-hydroxy ester **224** was realized with L-selectride (Scheme 4.2.11).[9] Unfotunately, subjection of this alcohol to Mitsunobu conditions with amine nucleophiles led to decomposition in most cases.[10]

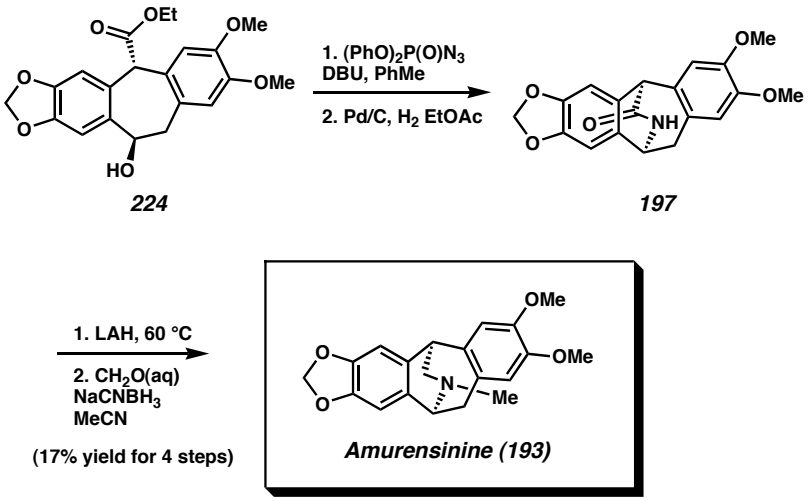
Scheme 4.2.11



Since the direct addition of an amine nucleophile into hydroxyester **224** was unsuccessful, we attempted a more indirect addition of an azide nucleophile, which would be reduced at a later stage to the corresponding amine. This two-step procedure for amine installation was realized by treating hydroxyester **224** with $(PhO)_2P(O)N_3$ in the presence of DBU,[11] followed by reduction with Pd/C under an atmosphere of H_2 (Scheme 4.2.12). To our pleasant surprise, the resulting aminoester spontaneously formed the desired lactam **197**. Simple reduction of the lactam with LAH and subsequent reductive amination of formaldehyde with the resulting secondary amine yielded the

natural product amurensinine (**193**). The spectroscopic data for synthetic amurensinine (**193**) matched the data reported in the literature.[5i]

Scheme 4.2.12



4.3 Conclusion

In summary, we have developed a convergent synthesis of amurensinine (**193**) that takes advantage of sequential C-H and C-C insertion reactions to build the core structure of the natural product in a rapid fashion. The synthesis is 14 total steps from known starting materials, with a longest linear count of only 11 steps from commercially available phenylacetic acid **211**. Our work highlights the utility of selective C-H and C-C insertion reactions in the context of natural product synthesis. Application of C-H, C-C, and other inert C-X insertion reactions toward the synthesis of related natural products is currently under investigation.

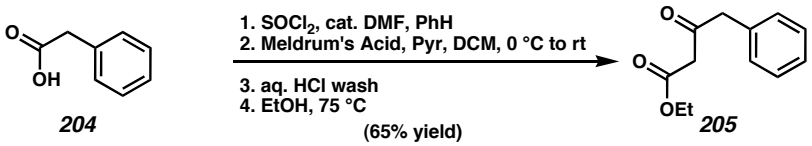
4.4 Experimental Section

4.4.1 Materials and Methods

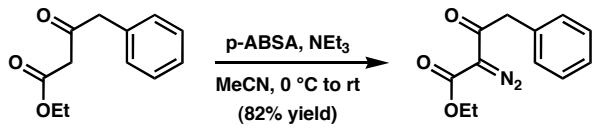
Unless stated otherwise, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using dry, deoxygenated solvents. Commercially obtained reagents were used as received. Cesium fluoride was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032 - 0.063 mm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. ^{19}F NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to CF_3COOH (δ -76.54). Data for ^{19}F NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer and are reported in terms of

frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

4.4.2 Preparative Procedures

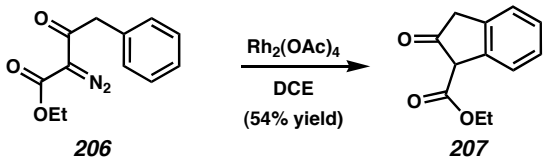


β-ketoester 205. To a solution of phenylacetic acid **204** (2.0 g, 14.7 mmol) in benzene (15 mL) was added thionyl chloride (2.14 ml, 29.4 mmol) and 10 drops of DMF. After stirring for 3 hours, the reaction mixture was concentrated under reduced pressure. The resulting crude acid chloride was then dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. To this solution was added pyridine (2.4 mL, 29.4 mmol) and Meldrum's acid (2.12 g, 14.7 mmol). After stirring at 0 °C for 2 minutes, the mixture was stirred at room temperature for 8 hours. The reaction was then extracted with 10% aqueous HCl (20 mL) and H_2O (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was then dissolved in absolute EtOH (25 mL) and refluxed at 75 °C. After 11 hours, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided β-ketoester **205** (1.96 g, 65% yield) as a clear oil. The characterization data matched the data reported in the literature.[12]

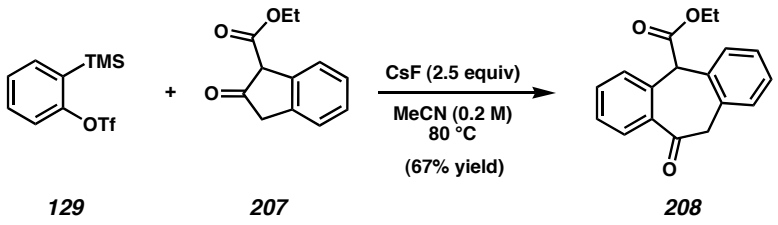


205 *206*

Diazoketoester 206. To a cooled solution (0 °C) of β-ketoester **205** (981 mg, 4.75 mmol) in acetonitrile (18 mL) was added p-ABSA (1.26 ml, 5.23 mmol) and NEt_3 (2 mL, 5.23 mmol). After stirring at 0 °C for 1 minute, the mixture was stirred at room temperature for 90 minutes. The reaction was extracted with 10% aqueous NaOH (20 mL). The aqueous layer was then washed with Et_2O (3 x 8 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided diazoketoester **206** (906 mg, 82% yield) as a clear oil. The characterization data matched the data reported in the literature.[13]

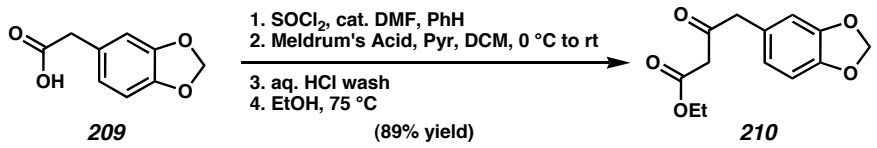


β-ketoester 207. A two-necked flask equipped with an addition funnel and an N_2 inlet was charged with a catalytic amount of $Rh_2(OAc)_4$ (80 mg, 0.18 mmol) and DCE (14 mL). A solution of diazoester **206** (837 mg, 3.60 mmol) in DCE (14 mL) was added dropwise over 1 hour via the addition funnel. After stirring for 3 hours at room temperature, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided β-ketoester **207** (398 mg, 54% yield) as a clear oil. The characterization data matched the data reported in the literature.[14]

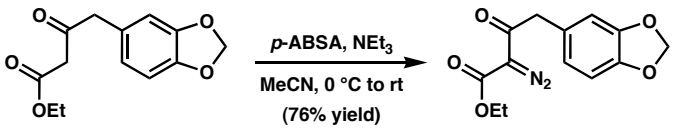


Model ketoester 208. To a flask containing acetonitrile (6.6 mL) was added β-ketoexter **207** (271 mg, 1.33 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**129**) (402 μL, 1.66 mmol) , and cesium fluoride (402 mg, 3.32 mmol). After refluxing at 80 °C for 45 minutes, the reaction mixture was cooled to room temperature and extracted with brine (10 mL). The aqueous layer was back-extracted with Et_2O (3 x 5

mL). The organics were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided model ketoester **208** (249 mg, 67% yield) as a clear oil: R_F 0.48 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.50 (td, *J* = 10.5, 3.7 Hz, 1H), (7.43-7.34 (m, 4H), 7.28-7.23 (m, 2H), 5.01 (s, 1H), 4.49 (d, *J* = 15.7 Hz, 1H), 4.28-4.10 (m, 2H), 3.87 (d, *J* = 15.7 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 171.3, 139.7, 137.5, 134.6, 133.3, 132.6, 131.4, 130.9, 130.6, 130.4, 128.5, 128.3, 127.8, 62.1, 59.9, 50.1, 14.2; IR (thin film/NaCl) 2981, 1729, 1674, 1197 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{18}H_{16}O_3]^+$: *m/z* 280.1100, found 280.1089.

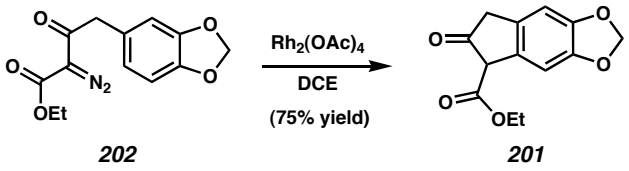


β-ketoester 210. Following the procedure for the synthesis of **205**, phenylacetic acid **209** (1 g, 5.55 mmol) was converted to acyclic β-ketoester **210**. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided β-ketoester **210** (1.24 g, 89% yield) as a clear oil: R_F 0.40 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, *J* = 7.7 Hz, 1H), 6.70-6.62 (m, 2H), 5.95 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 2H), 3.44 (s, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 167.3, 148.2, 147.2, 127.0, 123.0, 110.1, 108.8, 101.3, 61.6, 49.8, 48.3, 14.3; IR (thin film/NaCl) 2901, 1712, 1630, 1488, 1443, 1244 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{13}H_{14}O_5]^+$: 250.0841, found 250.0832.

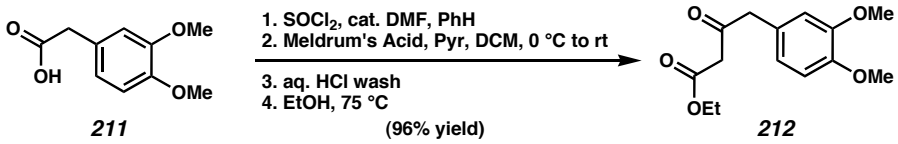


210 *202*

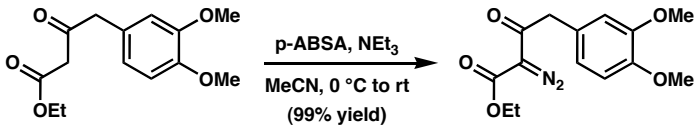
Diazoketoester 202. Following the procedure for the synthesis of **206**, β-ketoester **210** (461 mg, 1.84 mmol) was converted to diazoketoester **202**. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided diazoketoester **202** (386 mg, 76% yield) as a clear oil: R_F 0.41 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.74 (s, 2H), 5.92 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.09 (s, 2H), 1.33 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 161.4, 147.9, 146.9, 127.8, 123.0, 110. 3, 108.4, 101.1, 61.7, 45.5, 14.5; IR (thin film/NaCl) 2983, 2137, 1713, 1650, 1503, 1490, 1325, 1247 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{13}H_{13}N_2O_5]^+$: 277.0824, found 277.0820.



β-ketoester 201. Following the procedure for the synthesis of **207**, diazoketoester **202** (184 mg, 0.666 mmol) was converted to β-ketoester **201**. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided β-ketoester **201** (124 mg, 75% yield) as a white solid: R_F 0.44 (3:1 hexanes/EtOAc); mp 108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.93 (s, 1H), 7.16 (s, 1H), 6.82 (s, 1H), 5.93 (s, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.48 (s, 2H), 1.44 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 168.9, 146.9, 144.5, 133.5, 126.0, 105.6, 105.3, 102.4, 100.9, 60.8, 37.8, 14.6; IR (thin film/NaCl) 2984, 1657, 1590, 1500, 1470, 1314 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{13}H_{12}O_5]^+$: *m/z* 248.0685, found 248.0682.

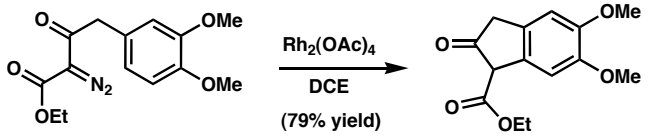


β-ketoester 212. Following the procedure for the synthesis of **205**, phenylacetic acid **211** (1 g, 5.1 mmol) was converted to β-ketoester **212**. Purification by flash chromatography (5:1→3:1→1:1 hexanes/EtOAc eluent gradient) provided β-ketoester **212** (1.31 g, 96% yield) as a clear oil. The characterization data matched the data reported in the literature.[15]



212 *203*

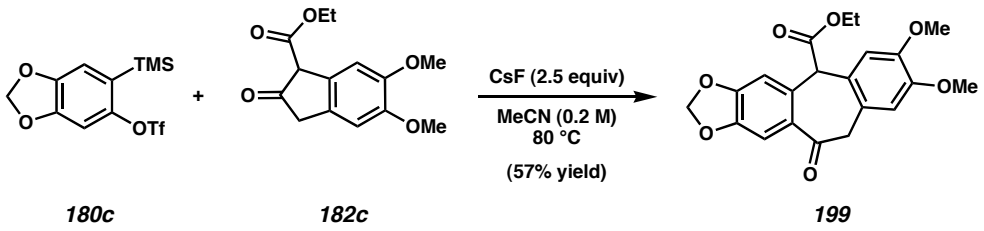
Diazoketoester 203. Following the procedure for the synthesis of **206**, β-ketoester **212** (445 mg, 1.67 mmol) was converted to diazoketoester **203**. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) provided diazoketoester **203** (487 mg, 99% yield) as a clear oil: R_F 0.50 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.00-6.94 (m, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.12 (s, 2H), 3.89 (q, *J* = 7.1 Hz, 2H), 3.51 (s, 3H), 3.43 (s, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 190.1, 161.4, 150.4, 149.7, 127.5, 122.7, 114.5, 112.7, 75.8, 61.6, 56.0, 55.9, 45.7, 14.5; IR (thin film/NaCl) 2938, 2836, 2136, 1714, 1650, 1515, 1263, 1029 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{14}H_{16}N_2O_5]^+$: *m/z* 292.1059, found 292.1070.



203 *182c*

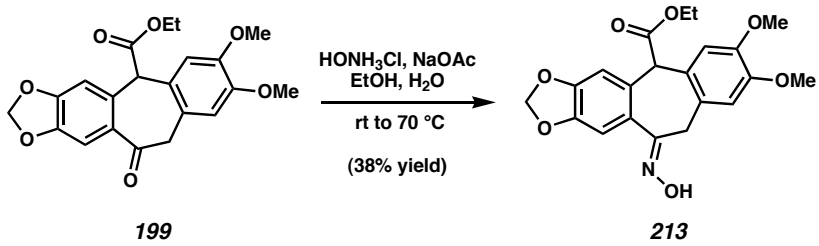
β-ketoester 182c. Following the procedure for the synthesis of **207**, diazoketoester **203** (3.64 g, 12.46 mmol) was converted to β-ketoester **182c**. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided β-ketoester **182c** (2.61 g,

79% yield) as a white solid: R_F 0.52 (1:1 hexanes/EtOAc); mp 117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.85 (s, 1H), 7.23 (s, 1H), 6.92 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.52 (d, *J* = 0.8 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 148.7, 146.3, 132.6, 125.1, 108.6, 105.2, 105.2, 105.0, 60.7, 56.6, 56.2, 37.8, 14.6; IR (thin film/NaCl) 2976, 2833, 1650, 1602, 1494, 1469, 1305 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{14}H_{16}O_5]^+$: 264.0998, found 264.1003. HRMS (FAB+) *m/z* calc'd for $[C_{14}H_{16}O_5]^+$: 264.0998, found 264.1003.



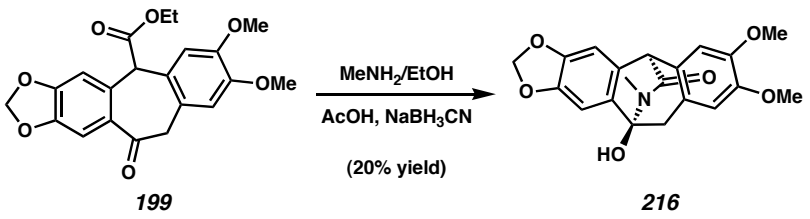
Ketoester 199. Following the procedure for the synthesis of **208**, β-ketoester **182c** (415 mg, 1.57 mmol) and aryne precursor **180c** (898 mg, 2.62 mmol) were coupled to form ketoester **199**. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided ketoester **199** (348 mg, 57% yield) as a clear oil: R_F 0.23 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 8.02 (s, 1H), 6.67 (s, 1H), 6.53 (s, 1H), 6.45 (s, 1H), 6.16 (s, 1H), 5.14 (d, *J* = 1.3 Hz, 1H), 5.10 (d, *J* = 1.3 Hz, 1H), 4.59 (d, *J* = 15.4 Hz, 1H), 4.54 (s, 1H), 3.95-3.86 (m, 2H), 3.82 (d, *J* = 15.4 Hz, 1H), 3.42 (s, 3H), 3.24 (s, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 192.4, 171.4, 151.7, 150.2, 149.1, 148.5, 137.1, 130.6, 130.5, 125.9, 115.6, 114.9, 111.4, 110.8, 102.1, 61.9, 59.7, 56.31, 55.9, 50.0, 14.4;

IR (thin film/NaCl) 2908, 1727, 1663, 1616, 1518, 1506, 1485, 1254 cm^{-1}; HRMS (EI^+) calc'd for $[C_{21}H_{20}O_7]^+$: *m/z* 384.1209, found 384.1212.

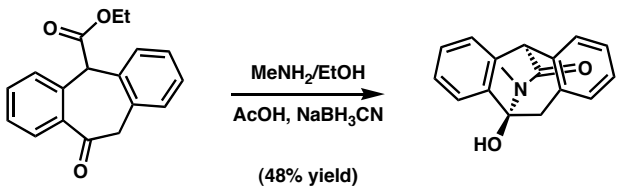


199 ***213***

Oxime 213. To a solution of ketoester **199** (81 mg, 0.21 mmol) in EtOH (2 mL) and H_2O (2 mL) was added $NaOAc•3H_2O$ (86 mg, 0.63 mmol) and $HONH_2•HCl$ (44 mg, 0.63 mmol). After stirring at 70 °C for 4.5 hours, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided oxime **213** (32 mg, 38% yield) as a clear oil: R_F 0.36 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, C_6D_6) δ 7.46 (s, 1H), 6.65 (s, 1H), 6.47 (s, 1H), 6.23 (s, 1H), 5.24 (d, *J* = 1.3 Hz, 1H), 5.18 (d, *J* = 1.3 Hz, 1H), 4.46-4.37 (m, 2H), 4.26 (d, *J* = 19.7 Hz, 1H), 4.11-3.83 (m, 2H), 3.44 (s, 3H), 3.31 (s, 3H), 1.65 (s, 1H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 171.4, 157.1, 149.8, 149.2, 148.9, 148.0, 134.5, 131.9, 127.2, 116.0, 114.9, 110.5, 109.6, 101.7, 78.1, 61.8, 58.0, 56.3, 56.0, 33.9, 14.5; IR (thin film/NaCl) 3446, 2905, 1733, 1520, 1506, 1487, 1230 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{21}H_{21}NO_7]^+$: 399.1318, found 399.1306.

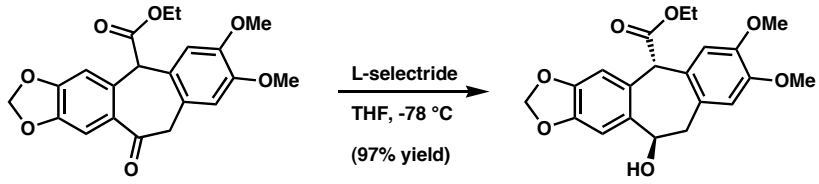


Aminal 216. To a solution of ketoester **199** (61.7 mg, 0.16 mmol) in ethanolic $MeNH_2$ (33% by wt., 2 mL) was added glacial AcOH (200 μL) and $NaBH_3CN$ (50 mg, 0.80 mmol). After stirring at room temperature for 30 minutes, the reaction mixture was extracted with saturated aqueous $NaHCO_3$ (4 mL) and Et_2O (3 x 3 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (1:3 hexanes/EtOAc eluent) provided aminal **216** (11.6 mg, 20% yield) as a clear oil: R_F 0.17 (1:3 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.74 (s, 1H), 6.67 (s, 1H), 6.45 (s, 1H), 5.95 (d, *J* = 1.3 Hz, 1H), 5.88 (d, *J* = 1.3 Hz, 1H), 4.28 (s, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.68 (s, 1H), 3.39 (d, *J* = 16.7 Hz, 1H), 3.02 (s, 3H), 3.00 (d, *J* = 16.7 Hz, 1H), 1.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 148.6, 148.0, 147.7, 147.2, 133.1, 131.4, 127.4, 124.7, 114.4, 112,0, 106.0, 103.3, 101.5, 85.5, 56.7, 56.2, 56.2, 39.9, 26.0; IR (thin film/NaCl) 2922, 1656, 1641, 1519, 1483 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{20}H_{20}NO_6]^+$: 370.1291, found 370.1295.



208 *220*

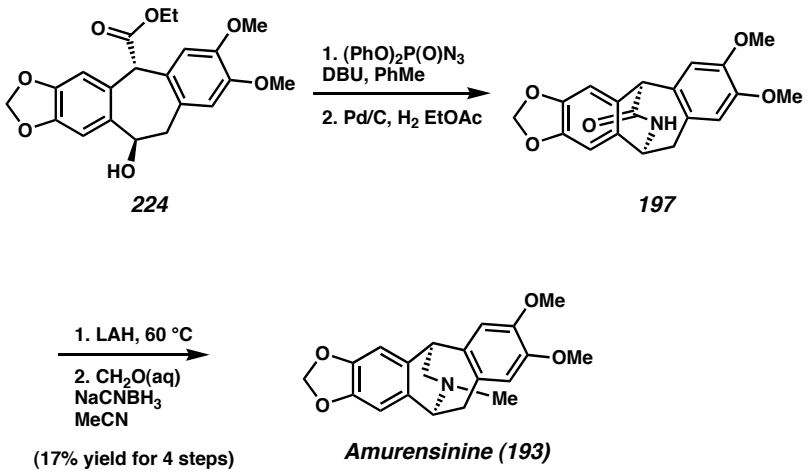
Model aminal 220. Following the procedure for the synthesis of **216**, ketoester **208** (33.4 mg, 0.12 mmol) was converted to model aminal **220**. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided model aminal **220** (31 mg, 48% yield) as a clear oil: R_F 0.38 (1:3 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.53 (m, 1H), 7.28-7.17 (m, 4H), 7.14-7.09 (m, 2H), 6.99-6.93 (m, 1H), 4.49 (s, 1H), 4.46 (s, 1H), 3.51 (d, *J* = 17.0 Hz, 1H), 3.11 (d, *J* = 17.0 Hz, 1H), 2.95 (s, 3H) 1.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 139.5, 137.1, 134.8, 133.0, 131.6, 129.2, 129.1, 127.8, 127.6, 127.2, 125.1, 121.9, 85.5, 57.6, 40.5, 25.9; IR (thin film/NaCl) 3258, 1642, 1390 cm^{-1}; HRMS (EI^+) calc'd for $[C_{17}H_{15}NO_2]^+$: *m/z* 265.1103, found 265.1113.



199 *224*

Hydroxyester 224. To a solution of ketoester **199** (52.9 mg, 0.138 mmol) in THF (1.5 mL) at –78 °C was added a 1.0 M solution of L-selectride in THF (200 μL, 0.206 mmol) in a dropwise fashion. The resulting solution was stirred for 25 minutes at –78 °C

and then quenched with saturated aqueous NH_4Cl (5 mL). After stirring at room temperature for 25 minutes, the mixture was extracted with Et_2O (4 x 5 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided aminal **224** (51.4 mg, 97% yield) as a yellow solid: R_F 0.33 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 6.69 (s, 1H), 5.94 (d, *J* = 1.5 Hz, 1H), 5.92 (d, *J* = 1.0 Hz, 1H), 5.02-4.96 (m, 1H), 4.59 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.50 (dd, *J* = 15.1, 2.4 Hz, 1H), 2.93 (dd, *J* = 15.1, 6.8 Hz, 1H), 1.73 (d, *J* = 8.3 Hz, 1H), 1.62 (s, 1H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 148.4, 147.6, 147.6, 146.9, 135.2, 129.6, 128.0, 127.3, 114.9, 114.5, 111.3, 110.7, 101.4, 69.4, 61.8, 58.5, 56.2, 56.1, 39.6, 14.3; IR (thin film/NaCl) 3500, 2937, 1725, 1610, 1520, 1486, 1244 cm^{-1}; HRMS (EI^+) calc'd for $[C_{21}H_{22}O_7]^+$: *m/z* 386.1366, found 386.1366.



Lactam 197. To a solution of hydroxyester **224** (9.7 mg, 0.025 mmol) in toluene (500 μL) at 0 °C was added $(PhO)_2P(O)N_3$ (27 μL, 0.126 mmol) and DBU (19 μL, 0.126 mmol). The resulting solution was stirred for 30 minutes at 0 °C and then stirred at room temperature for 12 hours. The reaction was then quenched with H_2O (3 mL) and extracted with Et_2O (3 x 3 mL). The organics were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude azide was passed through a short pad of SiO_2 with EtOAc eluent and concentrated under reduced pressure. To a solution of the azide in EtOAc (1.5 mL) was added Pd/C (10% by wt., 15 mg). The reaction flask was placed under a balloon of H_2 gas (1 atm) and stirred at room temperature for 9 hours. The reaction mixture was then passed through a short pad of Celite with Et_2O eluent and concentrated under reduced pressure. Lactam **197** was used in the next step without further purification: R_F 0.25 (10% MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.74 (s, 1H), 6.72 (s, 1H), 6.55-6.52 (m, 1H), 6.49 (s, 1H), 5.94 (d, *J* = 1.5 Hz, 1H), 5.88 (d, *J* = 1.5 Hz, 1H), 4.58-4.54 (m, 1H), 4.21 (d, *J* = 2.0 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.28 (dd, *J* = 16.8, 4.6 Hz, 1H), 3.07 (dd, *J* = 17.1, 2.4 Hz,

1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 148.8, 147.6, 147.2, 146.7, 134.1, 130.0, 128.1, 125.2, 114.7, 112.1, 106.7, 105.6, 101.4, 56.7, 56.2, 56.1, 53.6, 36.9; IR (thin film/NaCl) 3221, 2916, 1680, 1517, 1485, 1465, 1246 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{19}H_{18}NO_5]^+$: 340.1185, found 340.1181.

Amurensinine (193). To a solution of crude lactam **197** in THF (1 mL) was added LAH (30 mg, 0.0751 mmol). The resulting solution was stirred for 8 hours at 60 °C. The reaction mixture was then cooled to 0 °C and quenched with H_2O (30 μL), 15% aqueous NaOH (30 μL), and H_2O (90 μL). The slurry was stirred at room temperature for 25 minutes, passed through a short pad of Celite with Et_2O eluent, and concentrated under reduced pressure. To a solution of the crude secondary amine in acetonitrile (1 mL) was added $NaCNBH_3$ (10 mg, 0.159) and aqueous formaldehyde (37% by wt., 50 μL). After stirring at room temperature for 2 hours, the reaction mixture was extracted with H_2O (2 mL). The aqueous layer was back-extracted with CH_2Cl_2 (3 x 3 mL). The organics were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography on silica gel (0.25mm, 10% MeOH/$CHCl_3$ eluent) provided amurensinine **193** (1.5 mg, 17% yield for 4 steps) as a clear thin film/NaCl: R_F 0.18 (10% MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.72 (s, 1H), 6.61 (s, 1H), 6.52 (s, 1H), 5.93 (d, *J* = 1.5 Hz, 1H), 5.86 (d, *J* = 1.5 Hz, 1H), 4.00-3.91 (m, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.70-3.56 (m, 3H), 2.98-2.85 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 147.0, 146.5, 134.9, 134.2, 126.2, 114.4, 111.3, 107.7, 106.5, 101.4, 101.0, 63.1, 59.8, 56.2, 56.1, 45.8, 45.5, 37.8, 29.9; IR (thin film/NaCl) 2916, 2848, 1607, 1517, 1482, 1249 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{20}H_{21}NO_4]^+$: *m/z* 339.1471, found 339.1469.

4.5 Notes and References

(1) Gossage, R. A.; van Koten, G. A General Survey and Recent Advances in the Activation of Unreactive Chemical Bonds by Metal Complexes. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 1-8.

(2) (a) For stoichiometric reactions involving the activation of C-H bonds, see: Jones, W. D. Activation of C-H Bonds: Stoichiometric Reactions. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 9-46. (b) For catalytic reactions involving the activation of C-H bonds, see: Kakiuchi, F.; Murai, S. Activation of C-H Bonds: Catalytic Reactions. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 47-79.

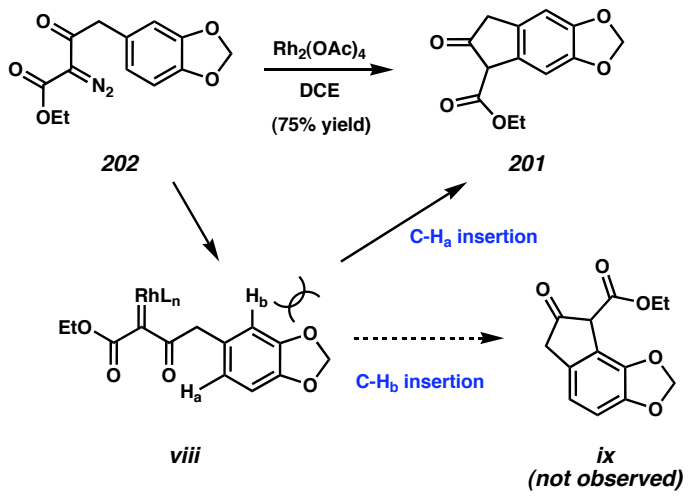
(3) Murakami, M.; Ito, Y. Cleavage of Carbon-Carbon Single Bonds by Transition Metals. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 97-129.

(4) For discussions on the biological activity of the isopavine alkaloids, see: (a) Weber, E.; Keana, J.; Barmettler, P. PCT Int. Appl. WO 12575, **1990**; *Chem. Abstr*. **1991**, *115*, 106019w. (b) Childers, W. E.; Abou-Gharbia, M. A. U.S. Patent 4940789, 1990; *Chem. Abstr*. **1990**, *113,* 191190w.

(5) For syntheses of natural and non-natural isopavines, see, for example: (a) Gozler, B. In *The Alkaloids*; Academic Press: New York, 1987; Vol. 31, pp 342-355. (b) Yasuda, M.; Hamasuna, S.; Yamano, K.; Kubo, J.; Shima, K. *Heterocycles* **1992**, *34*, 965-977. (c) Kametani, T.; Higashiyama, K.; Honda, T. *Chem. Pharm. Bull.* **1984**, *32*, 1614-1618. (d) Jung, M. E.; Miller, S. J. *J. Am. Chem. Soc*. **1981**, *103*, 1984-1992. (e) Dyke, S. F.; Kinsman, R. G.; Warren, P.; White, A. W .C. *Tetrahedron* **1978**, *34*, 241-245. (f) Dyke, S. F.;; Ellis, A. C.; Kinsman, R. G.; White, A. W .C. *Tetrahedron* **1974**, *30*, 1193-1199. (g) Rice, K. C.; Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601-607. (h) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095-5108. (i) Carrillo, L.; Badia, D.; Dominguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716-6721.

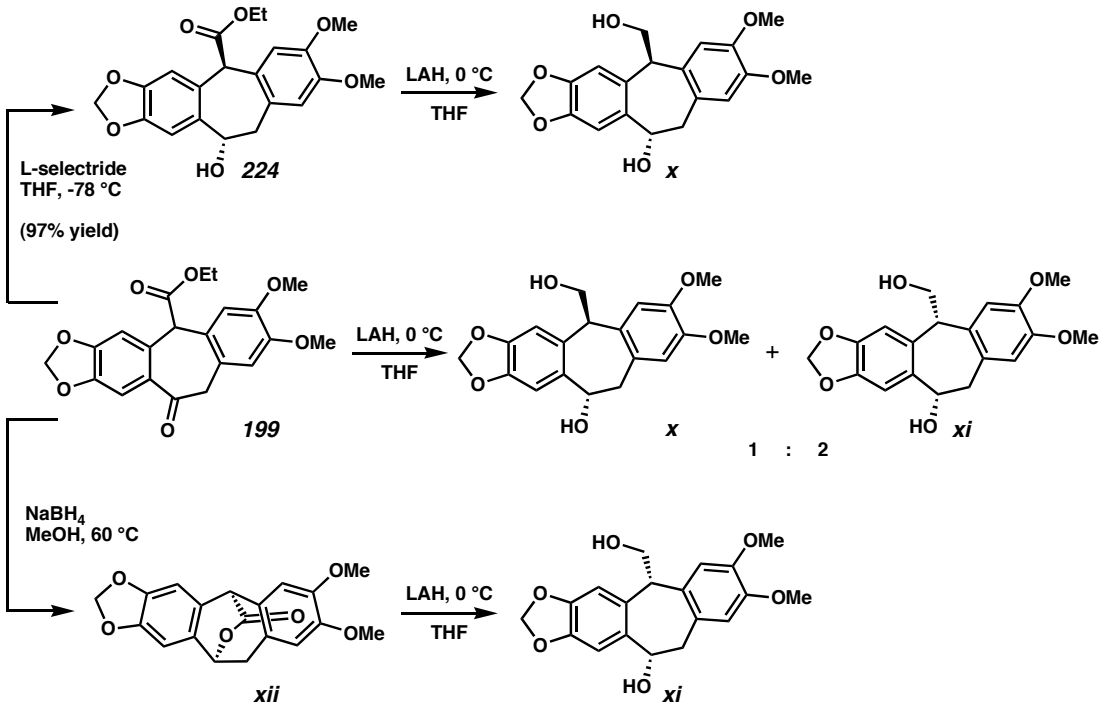
(6) Taber, D. F.; Ruckle, R. E. *J. Am. Chem. Soc*. **1986,** *108*, 7686-7693. In this paper there are no examples of C-H insertion into unsymmetrical aromatic systems such as **202** and **203**.

(7) This high position-selectivity is most likely governed by the differing steric environments of H_a and H_b in rhodium-carbneoid ***viii***:

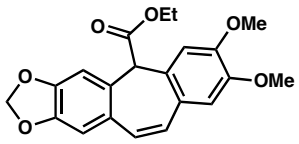


(8) For a recent review on the latest advances in amine synthesis by Mitsunobu strategies, see: Kan, T.; Fukuyama, T. *Chem. Comm.* **2004**, 353-359.

(9) Although we have no direct nOe or X-ray crystallographic evidence for the relative stereochemistry of hydroxyester **224**, we have indirect chemical evidence based on the observed products of related transformations:



(10) The decomposition products most likely involved elimination to the stilbenyl system ***xiii***:



xiii

(11) Thompson, A. S.; Humphrey,G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886-5888.

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