

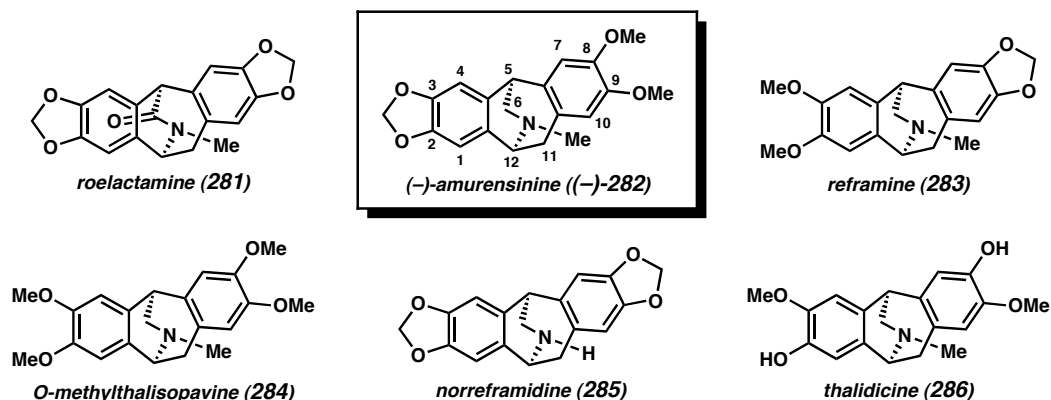
CHAPTER 5

**A Convergent Total Synthesis of (+)-Amurensinine and Formal Synthesis of (-)-
Amurensinine via Oxidative Kinetic Resolution[†]**

5.1 Background and Introduction**5.1.1 Isopavine Natural Products**

The isopavines are a class of natural products originally isolated from plants in the family Papaveraceae (Figure 5.1.1).^{1,2} These alkaloids have a characteristic tetrahydroisoquinoline core structure consisting of a doubly benzannulated azabicyclo[3.2.2]nonane. The isopavines and non-natural analogues have displayed important biological activity for the treatment of neurological disorders such as Parkinson's disease, Down's syndrome, Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's chorea.³

Figure 5.1.1 Representative isopavine natural products.

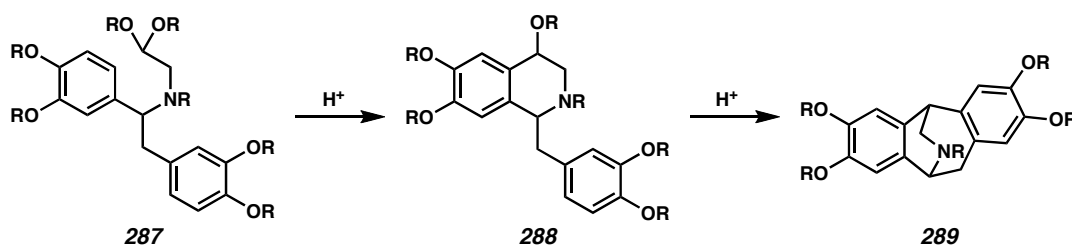


[†] This work was performed in collaboration with Uttam K. Tambar (Ph.D. 2005), a graduate student in the Stoltz group at California Institute of Technology.

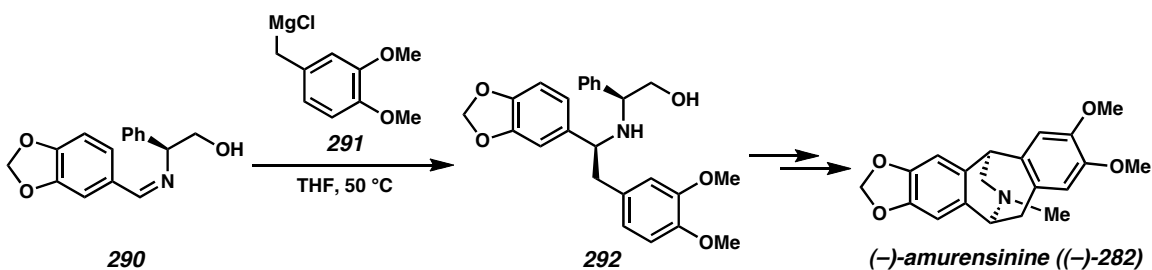
5.1.2 Previous Isopavine Syntheses

Despite the potential medicinal applications of the isopavines and related non-natural structures, relatively few total syntheses of these natural products have been reported. The majority of these syntheses involve intramolecular acid-promoted cyclizations to form the azabicyclo[3.2.2]nonane core of the isopavines (Scheme 5.1.1).⁴ Enantioselective syntheses have been even rarer. Badía and Domínguez reported the only enantioselective synthesis of (–)-amurensinine ((–)-**282**), based on a chiral auxiliary and acid-promoted cyclization approach (Scheme 5.1.2).⁵ Recently, a number of non-natural isopavine analogues have been prepared by [1,2]- and [2,3]-Stevens rearrangements.⁶

Scheme 5.1.1 Classical approach to isopavine synthesis.



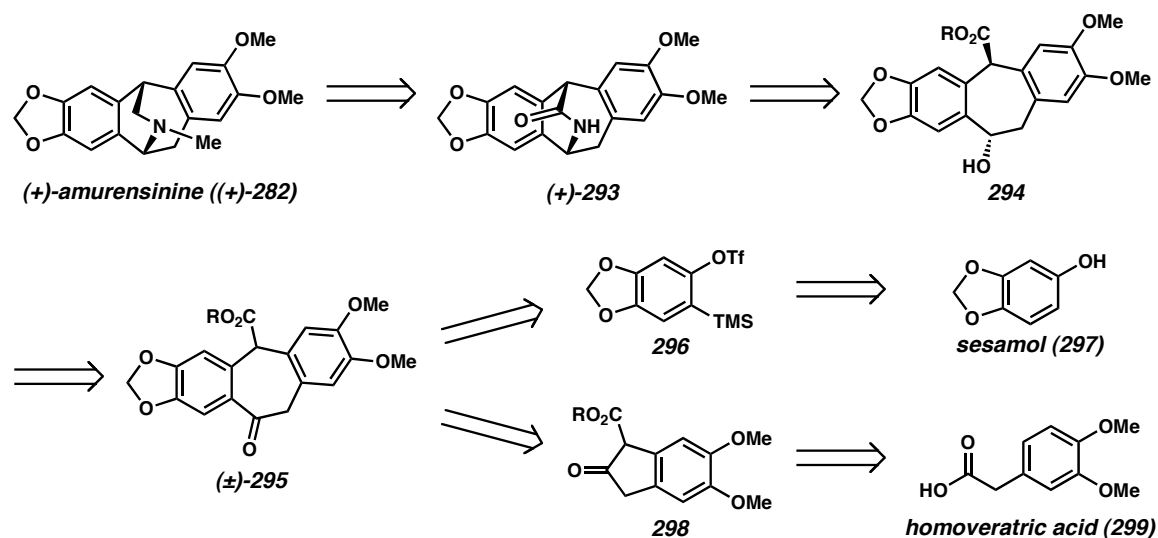
Scheme 5.1.2 Auxiliary-based synthesis of (–)-amurensinine.



5.1.3 Retrosynthetic Analysis of Amurensinine

We looked to develop a novel approach to the isopavine core and utilize our oxidative kinetic resolution methodology to provide a catalytic enantioselective synthesis of (+)-amurensinine. Our approach to the isopavines, and specifically to amurensinine, is depicted in Scheme 5.1.3.⁷ The tertiary amine of the natural product could be obtained from amide (+)-**293**. Disconnection of the bridging amide reveals hydroxyester **294**. This benzylic alcohol potentially could be resolved utilizing our oxidative kinetic resolution methodology, providing access to an enantioselective synthesis. Hydroxyester **294** could be derived from ketoester (\pm)-**295**, which we envisioned arising from arylsilyl triflate **296** and β -ketoester **298** via aryne insertion methodology developed in our laboratories.⁸ Arylsilyl triflate **296** could be readily prepared from sesamol (**297**), and β -ketoester **298** could be derived from homoveratric acid (**299**).

Scheme 5.1.3 Retrosynthesis of (+)-amurensinine.

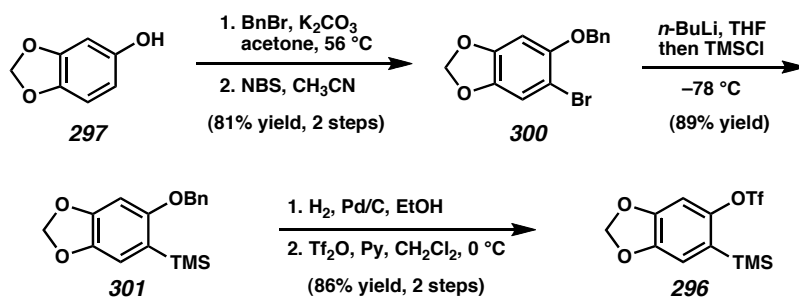


5.2 Total Synthesis of (+)-Amurensinine

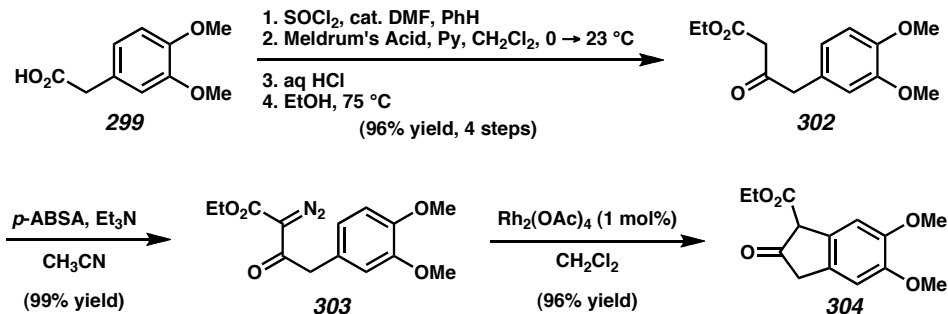
5.2.1 Initial Route

The synthesis of amurensinine commenced with benzylation and bromination of sesamol (**297**, Scheme 5.2.1).⁹ Lithiation of aryl bromide **300** followed by trapping of the aryl anion with chlorotrimethylsilane afforded arylsilane **301**. Benzyl group removal and reaction of the resulting phenol with triflic anhydride provided arylsilyl triflate **296** in good overall yield from sesamol (**297**).

Scheme 5.2.1 Synthesis of aryne precursor **296**.

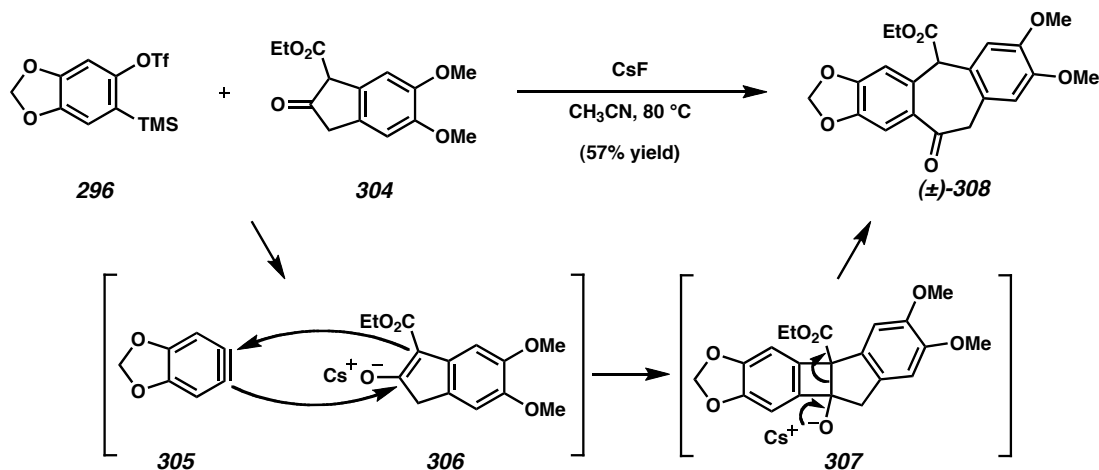


The β -ketoester coupling partner (**304**) was synthesized starting from homoveratric acid (**299**). Acid chloride formation and treatment with Meldrum's acid, followed by acidic aqueous washing and heating in absolute ethanol afforded β -ketoester **302** in excellent yield (Scheme 5.2.2). Ketoester **302** was diazotized with *p*-ABSA to produce diazoketoester **303**. A highly regioselective rhodium(II)-catalyzed C–H insertion generated the desired β -ketoester **304** in 96% yield.¹⁰

Scheme 5.2.2 Synthesis of β -ketoester **304**.

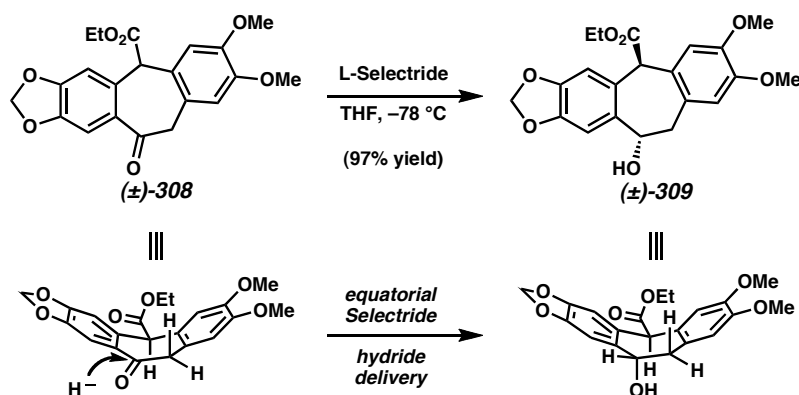
The feasibility of the key bond-forming aryne insertion reaction was then investigated. Treatment of β -ketoester **304** with arylsilyl triflate **296** under standard aryne generation conditions with cesium fluoride in dry acetonitrile¹¹ formed aryne **305**, which then underwent a formal [2+2] cycloaddition with cesium enolate **306** (Scheme 5.2.3). Retro-aldol reaction then opened the cyclobutene to provide observed ketoester (\pm)-**308**. Importantly, in a single step from readily available precursors, the entire carbocyclic framework of amurensinine was produced, including all of the carbons present in the natural product.

Scheme 5.2.3 Aryne insertion.

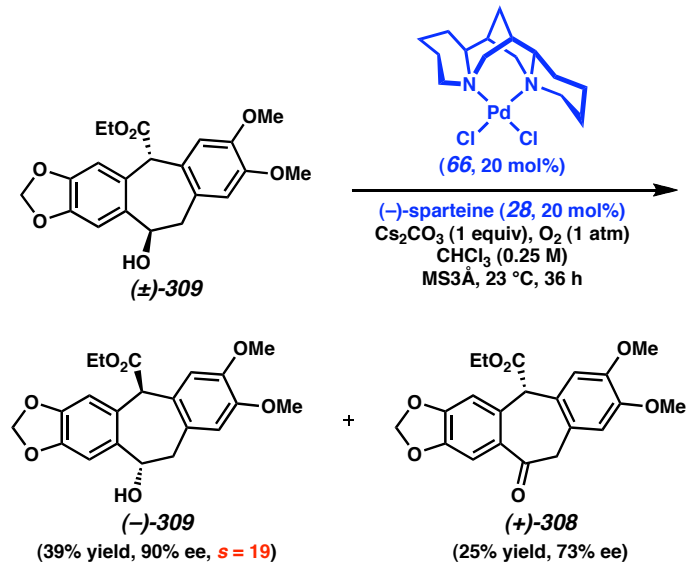


Selective reduction of the ketone of (\pm)-**308** with L-Selectride generated hydroxyester (\pm)-**309**. While a variety of other reduction protocols gave mixtures of products, a single diastereomer was observed in this transformation. The excellent observed selectivity potentially is due to preferential equatorial delivery of hydride from the bulky Selectride reagent to the ketone.

Scheme 5.2.4 Diastereoselective ketone reduction of hydroxyester (\pm)-**308**.

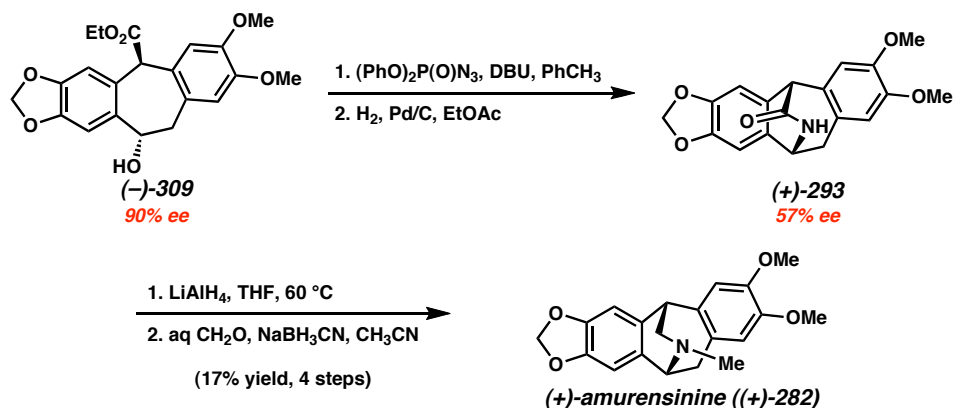


Next, we looked to apply our oxidative kinetic resolution methodology to this hydroxyester.¹² Conditions at 23 °C in chloroform proved best for the resolution of this alcohol, promoting good rate and selectivity¹³ under modified conditions with elevated catalyst loadings (Scheme 5.2.5). While overall mass recovery from the resolution was moderate, substantial quantities of enantioenriched hydroxyester ($-$)-**309** could be accessed from this reaction.

Scheme 5.2.5 Resolution of hydroxyester (\pm)-**309**.

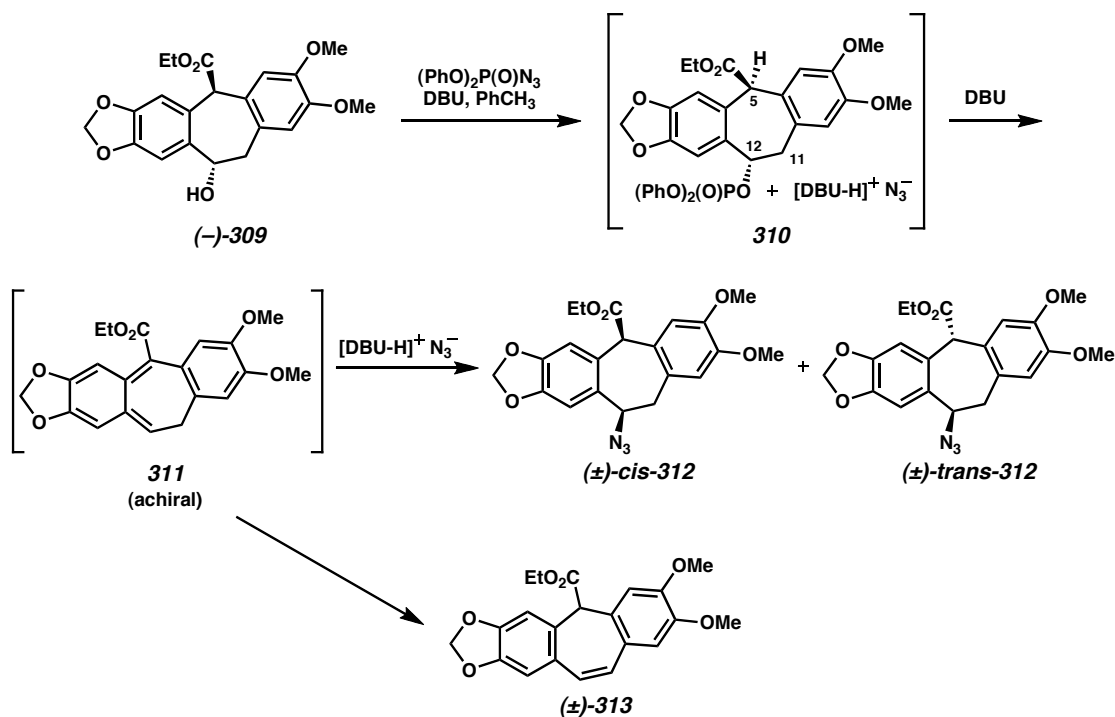
Installation of the amine required for amurensinine proved challenging. Mitsunobu protocols with many common *N*-nucleophiles led either to no reaction or elimination to form a stilbene system. Installation of an azide was achieved by treatment of hydroxyester ($-$)-**309** with DPPA in a procedure developed specifically for electron-rich benzylic alcohols by Thompson (Scheme 5.2.6).¹⁴ After reduction of the resulting azide, lactam ($+$)-**293** was formed directly. Amide reduction and reductive methylation afforded amurensinine ($(+)$ -**282**) in 17% yield over 4 steps.

Scheme 5.2.6 Initial route to complete (+)-amurensinine.

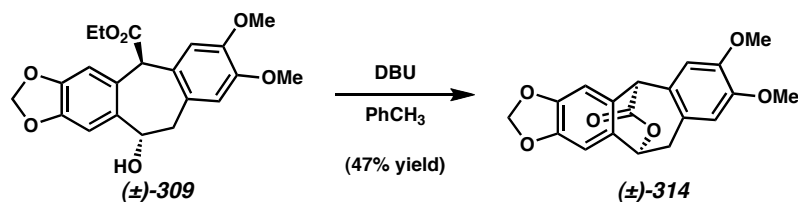


The low yield for this four-step sequence, primarily due to the production of a number of side products, was problematic. Even more disconcerting, lactam (+)-**293** was produced in only 57% ee. This partial racemization required two stereocenters to be inverted in the azide installation reaction, C(5) and C(12),¹⁵ potentially by an intermediate such as **311** (Scheme 5.2.7). Achiral intermediate **311** could lead to four possible azidoester products (\pm)-*cis*-**312** and (\pm)-*trans*-**312**, only two of which have the necessary cis configuration for cyclization subsequent to the azide reduction. Furthermore, rearomatization of achiral ester **311** would produce one of the observed byproducts, stilbene (\pm)-**313**.

Scheme 5.2.7 Possible racemization mechanism.



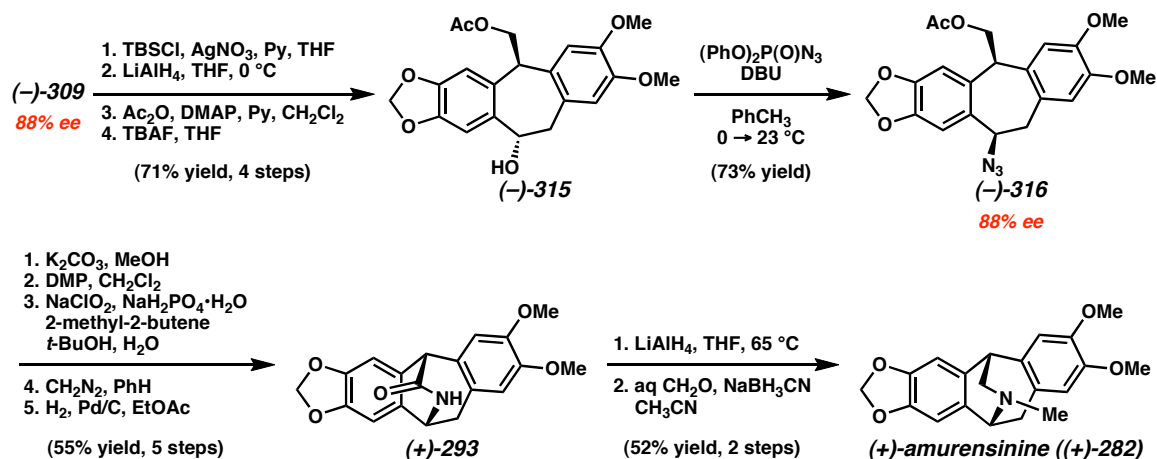
Alternatively, the inversion of the two stereocenters could be independent. Epimerization of C(5) could accompany competing $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ displacements at C(12) by azide. To demonstrate the propensity of C(5) toward epimerization, hydroxyester (\pm)-**309** was exposed to DBU without DPPA. Lactone (\pm)-**314** was generated, presumably via epimerization followed by base-promoted lactonization.

Scheme 5.2.8 Lactonization by epimerization of hydroxyester (\pm)-**309**.

5.2.2 Alternate End Sequence

To circumvent the issues associated with epimerization of C(5), an alternate route to amurensinine was devised. Protection of the benzylic alcohol of hydroxyester (–)-**309** as a silyl ether, ester reduction to the primary alcohol, alcohol acetylation, and silyl ether cleavage afforded hydroxyacetate (–)-**315** in 71% overall yield. This benzylic alcohol was anticipated to be much less prone to epimerization at C(5). Indeed, treatment of hydroxyacetate (–)-**315** with DPPA and DBU afforded a 73% yield of azidoacetate (–)-**316**. Importantly, azidoacetate (–)-**316** of 88% ee was obtained from hydroxyester (–)-**309** of 88% ee, demonstrating that the stereochemistry of C(5) was maintained. Furthermore, clean inversion was observed in the azide displacement, indicating no competing S_N1 processes. Azidoacetate (–)-**316** was next transformed to lactam (+)-**293** by a five-step sequence. Acetate cleavage, two-step oxidation, and esterification with diazomethane afforded an azidoester, which was reduced to generate lactam (+)-**293** in 55% yield over five steps. Reduction and amine methylation provided (+)-amurensinine ((+)-**282**).

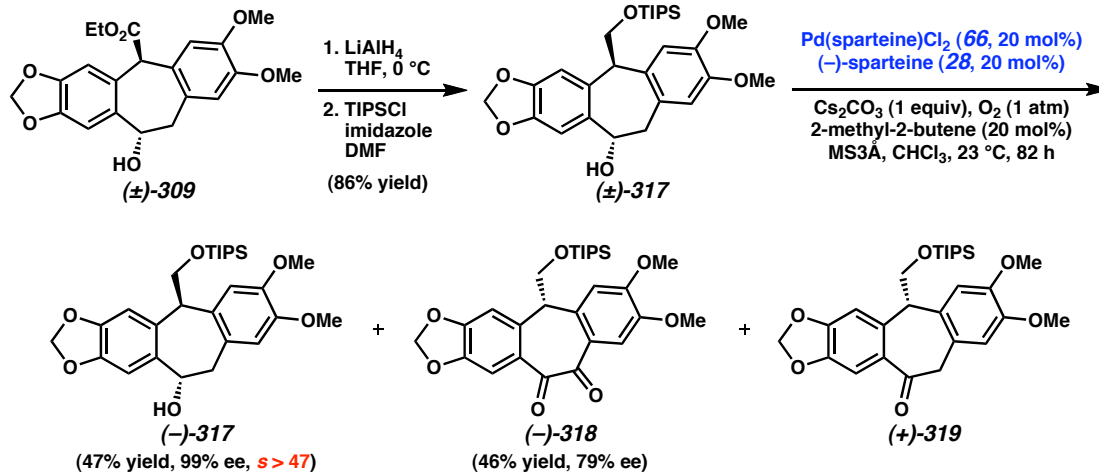
Scheme 5.2.9 Long route to complete (+)-amurensinine.



5.2.3 Final Route to (+)-Amurensinine

Further improvements of the synthesis were investigated. While the racemization issues in the azide displacement had been addressed, the route was much longer. Furthermore, the oxidative kinetic resolution proved to be a problematic step in the sequence. In addition to poor mass recovery, this reaction rarely provided enantioenriched hydroxyester (–)-**309** in over 90% ee. Thus, an alternate oxidative kinetic resolution substrate was pursued.

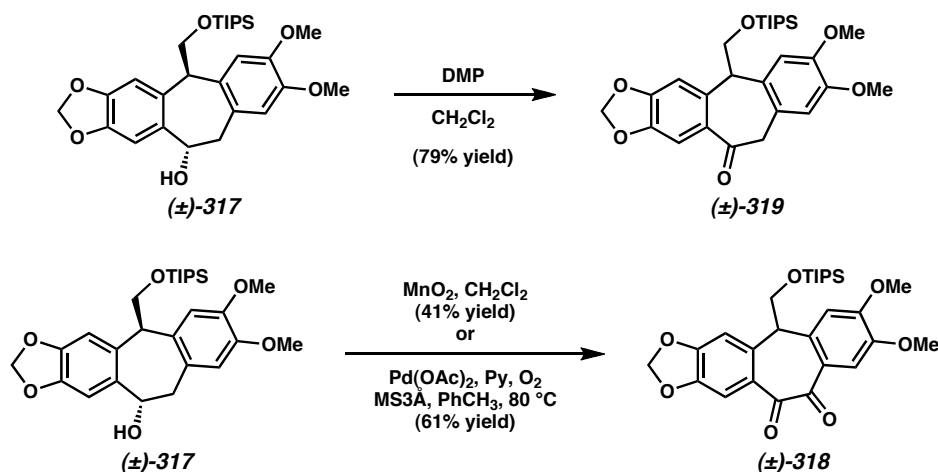
To this end, hydroxyester (±)-**309** was reduced with lithium aluminum hydride to afford a diol, which was selectively silylated on the primary alcohol to yield hydroxysilane (±)-**317** (Scheme 5.2.10). This selective procedure was a substantial improvement over the previous four-step procedure involving protection/deprotection to obtain hydroxyacetate (–)-**315**, while still decreasing the acidity of C(5) from hydroxyester (–)-**309**. Gratifyingly, oxidative kinetic resolution of this alcohol proved highly selective, providing enantioenriched hydroxysilane (–)-**317** in high ee with excellent mass recovery. Reactions conducted under ambient air atmosphere instead of pure oxygen provided comparable results.

Scheme 5.2.10 Hydroxysilane (\pm)-**317** oxidative kinetic resolution.

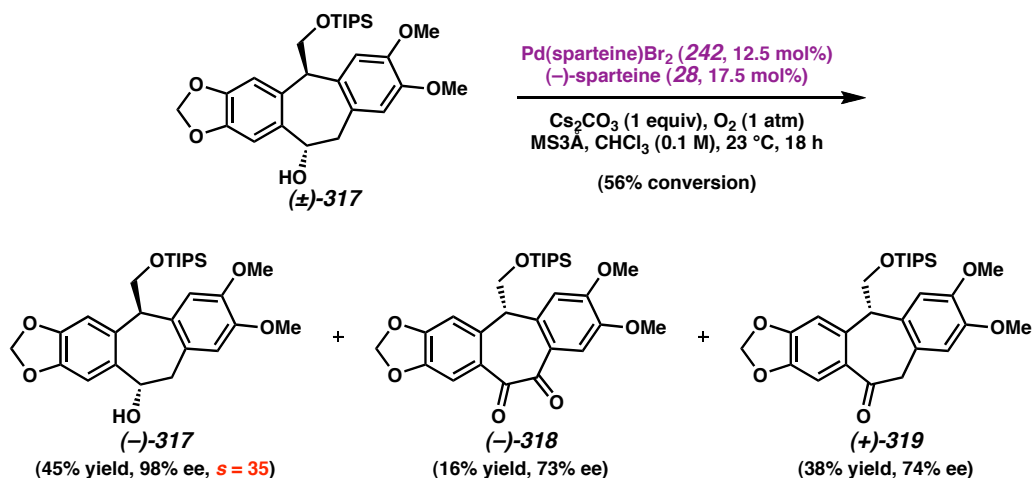
Interestingly, resolutions allowed to proceed to high ee of $(-)$ -**317** did not afford any expected ketosilane $(+)$ -**319**. Instead, diketosilane $(-)$ -**318** was formed in good yield and enantiomeric excess. Monitoring the reactions by TLC and ^1H NMR demonstrated that ketosilane $(+)$ -**319** was being generated; however, it slowly underwent further oxidation to the diketosilane. In fact, isolated samples of ketosilane **319** slowly oxidized to diketosilane **318** in C_6D_6 . Handling of this ketosilane under argon delayed this decomposition. We hypothesized that ketosilane $(+)$ -**319** was reacting with molecular oxygen in situ via a radical pathway to lead to the diketosilane. This theory was supported by experiments with non-enantioselective oxidations. Treatment of hydroxysilane (\pm) -**317** with Dess-Martin periodinane cleanly provided ketosilane (\pm) -**319** (Scheme 5.2.11). However, conditions with MnO_2 , an oxidant thought to react with alcohols via radical pathways, and palladium(II) with molecular oxygen both formed diketosilane (\pm) -**318**. Thus, various radical inhibitors were added to kinetic resolutions of hydroxysilane (\pm) -**317**. While BHT had little effect, tetracyanoethylene led to little alcohol oxidation. 2-Methyl-2-butene also did not suppress ketosilane overoxidation;

however, incorporation of even catalytic quantities provided improved mass recovery in the kinetic resolution. Efforts to elucidate the role of 2-methyl-2-butene in the resolution are ongoing.

Scheme 5.2.11 Non-enantioselective oxidations of hydroxysilane (\pm)-**317**.

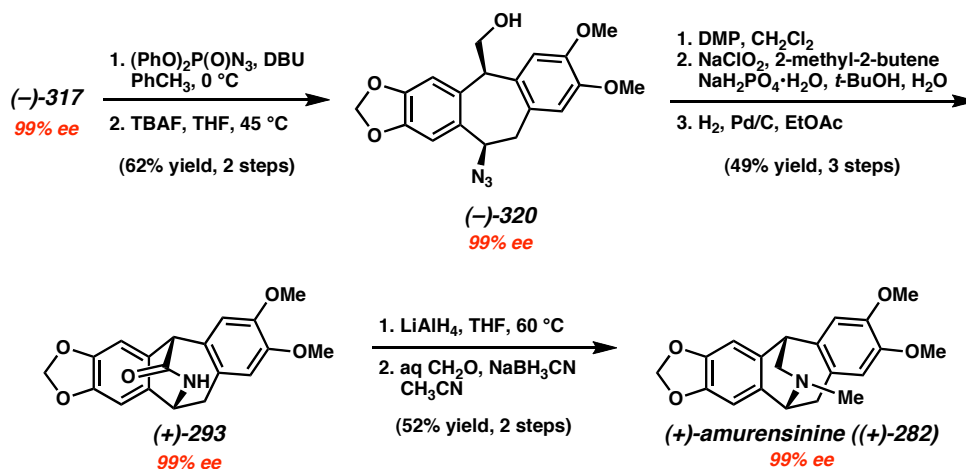


Ongoing catalyst development studies in the oxidative kinetic resolution led to the discovery of Pd(sparteine)Br₂ (**242**) as a catalyst promoting more rapid oxidation with comparable selectivity for a range of secondary alcohol substrates as compared to Pd(sparteine)Cl₂ (**66**).¹⁶ This effect was also explored in the context of the total synthesis of amurensinine. Hydroxysilane (\pm)-**317** was exposed to modified conditions with dibromide complex **242** in chloroform at 23 °C. Much more rapid resolution was observed, even at decreased catalyst loadings relative to Pd(sparteine)Cl₂ conditions. While these conditions did not completely suppress overoxidation of ketosilane (+)-**319** to diketosilane (–)-**318**, significant quantities of the ketosilane at moderate ee were obtained. Most importantly, hydroxysilane (–)-**317** was produced in 98% ee and in excellent yield.

Scheme 5.2.12 Rate enhancement with Pd(sparteine)Br₂.

Having substantial quantities of highly enantioenriched alcohol (-)-**317**, we next sought to install the necessary nitrogen of the natural product. Use of Thompson's conditions¹⁴ followed by exposure to TBAF to effect desilylation provided azidoalcohol (-)-**320** (Scheme 5.2.13). Gratifyingly, this azide was obtained with clean inversion in 99% ee. Two-step oxidation provided an intermediate azidoacid. Azide reduction led directly to bridged amide (+)-**293** in 99% ee, without requiring intermediate esterification. Reduction and methylation as before afforded (+)-amurensinine ((+)-**282**).

Scheme 5.2.13 Final route to complete (+)-amurensinine.



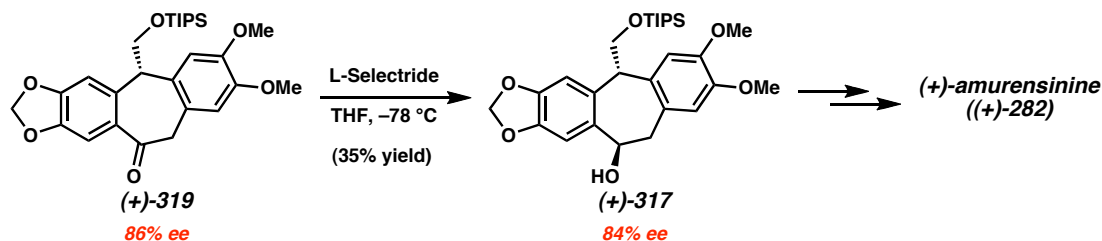
5.3 Formal Synthesis of (–)-Amurensinine

5.3.1 Enantioenriched Ketosilane Reduction

With the completion of the total synthesis of the non-natural enantiomer of amurensinine, efforts were undertaken to access natural (–)-amurensinine ((–)-**282**). When the enantiomer of alcohol desired is opposite to that produced in an enantioselective process, a Mitsunobu inversion protocol is a common method to obtain the desired stereochemistry. However, inversion of the benzylic alcohol stereocenter of hydroxysilane (–)-**317** would provide a diastereomer and not the desired enantiomeric alcohol (+)-**317** due to the C(5) stereocenter. Because this stereochemical information is preserved in the stereoablative oxidative kinetic resolution,¹⁷ ketosilane (+)-**319** has the stereochemistry at C(5) needed for natural enantiomer (–)-**282**.

Thus, an enantiodivergent approach to both enantiomers of amurensinine based on the oxidative kinetic resolution was envisioned. Enantioenriched hydroxysilane (–)-**317** was transformed into non-natural (+)-amurensinine, while (–)-amurensinine could potentially be derived from the oxidation product, ketosilane (+)-**319**. In the event, reduction of ketosilane (+)-**319** with L-Selectride proceeded selectively to desired hydroxysilane (+)-**317**, constituting a formal total synthesis of (+)-amurensinine via the route described for hydroxysilane (–)-**317** (Scheme 5.3.1). However, the low yield for this transformation, the instability of ketosilane (+)-**319** to oxidation, and the moderate enantiomeric excess of the ketone made this route unfeasible for accessing (–)-amurensinine ((–)-**282**).

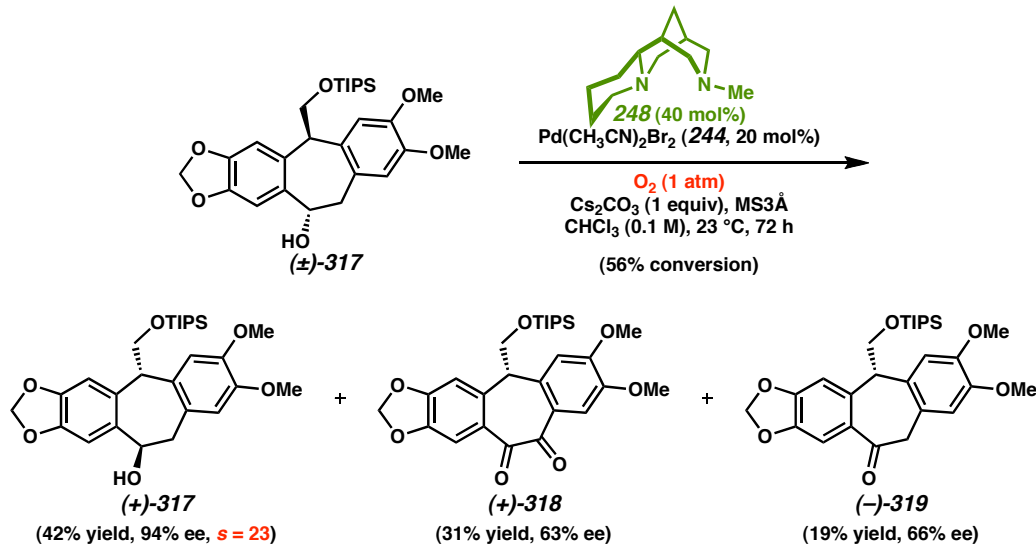
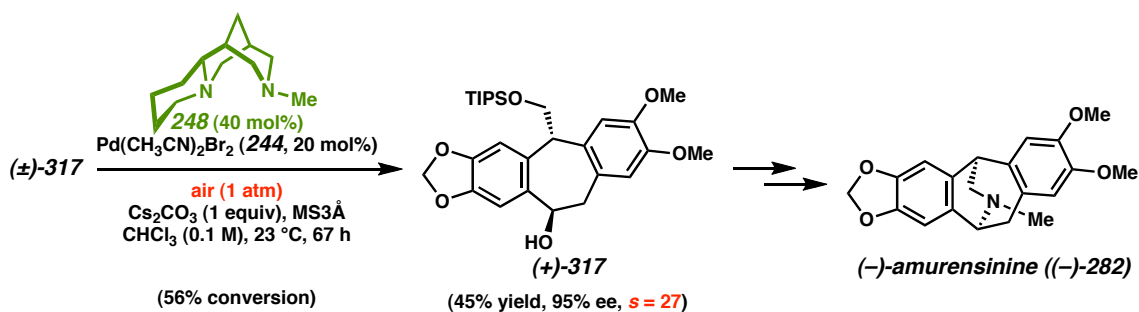
Scheme 5.3.1 Diastereoselective ketosilane reduction.



5.3.2 Preparation of Enantioenriched Hydroxysilane by Resolution

An alternate approach to a formal synthesis of (–)-amurensinine would involve the production of hydroxysilane **(+)-317** directly from the oxidative kinetic resolution. Oxidation of the opposite enantiomer of the alcohol would require the (+)-enantiomer of the chiral ligand, sparteine (**28**). While the use of diamine *ent*-(+)-**28** in the oxidation is impractical due to its inaccessibility,¹⁸ recent developments in the use of alternate ligands in the palladium-catalyzed resolution have demonstrated the utility of diamine **248** as a (+)-sparteine surrogate.¹⁶

In the oxidative kinetic resolution of hydroxysilane (±)-**317**, diamine **248** proved to be a competent ligand for selective oxidation with a dibromide complex. At 23 °C in chloroform under an atmosphere of molecular oxygen, hydroxysilane **(+)-317** was recovered in high ee with good yield and excellent corresponding selectivity (Scheme 5.3.2). Ketosilane (–)-**319** and diketosilane **(+)-318** could also be obtained from the resolutions in modest enantiomeric excess. Additionally, these resolutions could be conducted with ambient air as oxidant with no detrimental effects (Scheme 5.3.3). This resolution of (±)-**317** constitutes a formal synthesis of (–)-amurensinine ((–)-**282**).

Scheme 5.3.2 Resolution with diamine **248** under O₂.Scheme 5.3.3 Resolution with diamine **248** under ambient air.

5.4 Conclusion

A novel route to both enantiomers of amurensinine has been developed. The core of the natural product has been constructed in a rapid and convergent manner by aryne insertion methodology developed in these laboratories. A highly selective oxidative kinetic resolution with (-)-sparteine (**28**) has provided an enantioenriched alcohol intermediate in high enantiomeric excess. Synthetic investigations have led to a stereocontrolled method for incorporation of the amine found in the natural product, leading to a highly enantio- and diastereoselective synthesis of (+)-amurensinine.⁷

Further efforts based on recent advances in the oxidative kinetic resolution utilizing alternate diamine **248** have provided a formal total synthesis of (–)-amurensinine.^{16b} These syntheses are readily amenable to modifications to provide other members of the isopavine family of natural products, as well as non-natural derivatives. Finally, the described approaches to amurensinine establish the aryne insertion and oxidative kinetic resolution methodologies as highly applicable and flexible tools for modern synthesis.

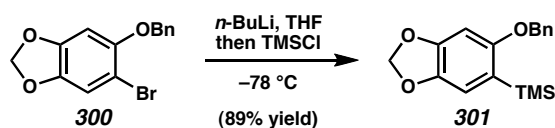
5.5 Experimental Section

5.5.1 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 purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI and were used as received. Pyridine, Et₃N, and TMSCl were distilled over CaH₂. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Powdered 3Å activated molecular sieves were stored in a 120 °C drying oven until immediately prior to use. Reaction temperatures were controlled using an IKA Mag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 or 0.5 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 32-63 μm) or SiliCycle SiliaFlash P60 Academic silica gel (particle size 40-63 μm; pore diameter 60 Å) was used for flash column chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD, Chiralcel OD-H, or Chiralcel OJ column (each is 4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Semi-preparative achiral HPLC was performed on a Waters 600 system with a 15-20 μm particle size Waters μPorasil column with peak detection at 254 nm. ¹H 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 Me₄Si (δ 0.0). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ¹³C NMR spectra were

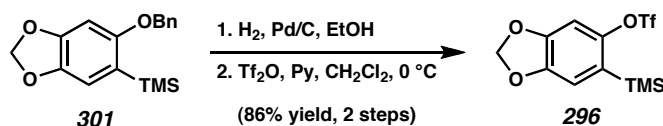
recorded on a Varian Mercury 300 (at 75 MHz) or Varian Inova 500 (at 126 MHz) and are reported relative to Me₄Si (δ 0.0). Data for ¹³C NMR spectra are reported in terms of chemical shift. ¹⁹F NMR spectra were recorded on a Varian Mercury 300 instrument (at 282 MHz) and are reported relative to external F₃CCO₂H standard (δ -76.53). Data for ¹⁹F NMR spectra are reported in terms of chemical shift (δ ppm). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using a 100 mm path-length cell. IR spectra were recorded on a Perkin Elmer Paragon 1000 or Spectrum BX II spectrometer and are reported in terms of frequency of absorption (cm⁻¹). UV-Vis spectra were collected on an Agilent 8453 UV-Vis spectrometer and are reported in terms of wavelength of absorption (nm). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

5.5.2 Preparative Procedures



Arylsilane 301. A solution of aryl bromide **300**⁹ (325 mg, 1.06 mmol, 1.0 equiv) in THF (3.5 mL) was cooled to -78 °C. *n*-Butyllithium (2.5 M in hexanes, 634 μ L, 1.59 mmol, 1.5 equiv) was added dropwise. After 15 min, TMSCl (200 μ L, 1.59 mmol, 1.5 equiv) was added dropwise at -78 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C and stirred for 15 min. Saturated aq NH₄Cl (5 mL) was added, and the mixture was extracted with Et₂O (3 x 5 mL). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. Purification by flash chromatography (10:1 hexanes:EtOAc eluent) provided arylsilane **301** (282 mg, 89% yield) as a clear oil: *R*_f 0.57 (3:1 hexanes:EtOAc); ¹H NMR (300

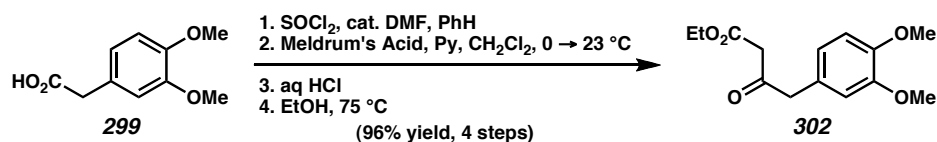
MHz, CDCl₃): δ 7.45-7.29 (comp. m, 5H), 6.85 (s, 1H), 6.53 (s, 1H), 5.91 (s, 2H), 5.01 (s, 2H), 0.23 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 159.2, 149.6, 141.5, 137.3, 128.7, 128.0, 127.5, 119.3, 113.7, 101.3, 95.2, 71.0, -0.5; IR (thin film/NaCl): 2953, 2894, 1606, 1502, 1473, 1410, 1386, 1243, 1177, 1042 cm⁻¹; HRMS-EI (*m/z*): [M]⁺ calcd for [C₁₇H₂₀O₃Si]⁺, 300.1182; found, 300.1187.



Arylsilyl Triflate 296. To a solution of arylsilane **301** (4.90 g, 16.3 mmol, 1.0 equiv) in absolute EtOH (300 mL) was added Pd/C (10% w/w, 1.74 g, 1.63 mmol Pd, 0.10 equiv). The reaction was wrapped in aluminum foil to exclude light. The reaction was allowed to proceed under a balloon of H₂ (1 atm) for 12 h. The mixture was then filtered in the dark over Celite (Et₂O eluent). The filtrate was evaporated under reduced pressure to afford a crude phenol, which was used in the next step without further purification.

A solution of the crude phenol in CH₂Cl₂ (95 mL) was cooled to 0 °C in the dark. Pyridine (3.26 mL, 40.4 mmol, 2.5 equiv) was added. A solution of Tf₂O (4.07 mL, 24.2 mmol, 1.5 equiv) in CH₂Cl₂ (65 mL) was added dropwise by addition funnel over 30 min. After allowing the reaction to stir 2.5 h in the dark at 0 °C, saturated aq NaHCO₃ (150 mL) was added. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 150 mL). The organic layers were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (97:3 hexanes:CH₂Cl₂ eluent) to provide arylsilyl triflate **296** (4.80 g,

86% yield over 2 steps) as a clear oil: R_f 0.54 (3:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3): δ 6.88 (s, 1H), 6.84 (s, 1H), 6.03 (s, 2H), 0.33 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3): δ 149.7, 148.8, 147.1, 125.1, 113.4, 113.4, 102.6, 102.5, -0.5; ^{19}F NMR (282 MHz, CDCl_3) δ -74.63; IR (thin film/NaCl): 2960, 2903, 1479, 1422, 1247, 1216, 1141, 984, 843 cm^{-1} ; HRMS-EI (m/z): $[\text{M}]^+$ calcd for $[\text{C}_{11}\text{H}_{13}\text{O}_5\text{F}_3\text{SiS}]^+$, 342.0205; found, 342.0211.

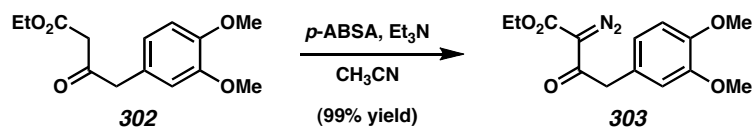


β -Ketoester 302. To a solution of homoveratric acid (**299**, 1.0 g, 5.1 mmol, 1.0 equiv) in benzene (5 mL) was added thionyl chloride (741 μL , 10.2 mmol, 2.0 equiv) and DMF (40 μL , 0.52 mmol, 0.1 equiv). After stirring for 3 h, the reaction mixture was concentrated under reduced pressure to afford the crude acid chloride.

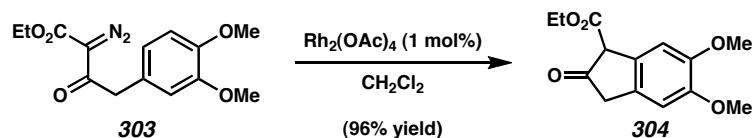
The resulting crude acid chloride was then dissolved in CH_2Cl_2 (10 mL) and cooled to 0 $^\circ\text{C}$. To this solution was added pyridine (825 μL , 10.2 mmol, 2.0 equiv) and Meldrum's acid (735 mg, 5.1 mmol, 1.0 equiv). After stirring at 0 $^\circ\text{C}$ for 2 min, the mixture was stirred at 23 $^\circ\text{C}$ for 8 h. The reaction was then washed with aq HCl (10% w/v, 10 mL) followed by H_2O (10 mL). The organic layer was dried over MgSO_4 and filtered, and the filtrate was concentrated under reduced pressure to afford the crude β -ketoacid.

The crude β -ketoacid was dissolved in absolute EtOH (10 mL) and refluxed at 75 $^\circ\text{C}$. After 11 h, the reaction mixture was cooled to 23 $^\circ\text{C}$ and concentrated under reduced pressure. Purification by flash chromatography (5:1 \rightarrow 3:1 \rightarrow 1:1 hexanes:EtOAc eluent)

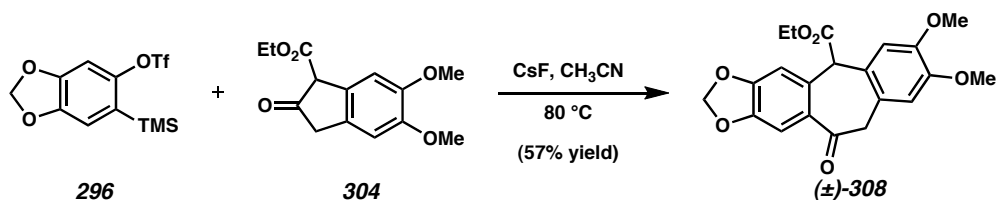
provided β -ketoester **302** (1.31 g, 96% yield over 4 steps) as a clear oil. The characterization data matched the data reported in the literature.¹⁹



Diazoketoester 303. To a cooled (0 °C) solution of β -ketoester **302** (445 mg, 1.67 mmol, 1.0 equiv) in acetonitrile (8 mL) was added *p*-ABSA (441 mg, 1.84 mmol, 1.1 equiv) and Et₃N (698 μ L, 5.01 mmol, 3.0 equiv). After stirring at 0 °C for 1 min, the mixture was stirred at 23 °C for 90 min. Then, the reaction was washed with aq NaOH (10% w/v, 10 mL). The aqueous layer was then extracted with Et₂O (3 x 10 mL). The organic layers were combined, dried over MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (4:1 hexanes:EtOAc eluent) to provide diazoketoester **303** (487 mg, 99% yield) as a clear oil: *R*_f 0.50 (1:1 hexanes:EtOAc); ¹H NMR (300 MHz, C₆D₆): δ 7.00-6.94 (comp. 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); ¹³C NMR (75 MHz, C₆D₆): 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 (*m/z*): [M]⁺ calcd for [C₁₄H₁₆N₂O₅]⁺, 292.1059; found, 292.1070.

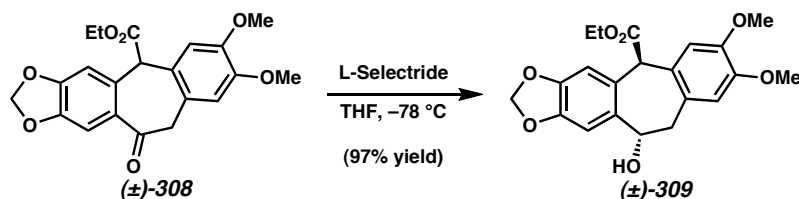


β -Ketoester 304. A flask equipped with an addition funnel and an N₂ inlet was charged with Rh₂(OAc)₄ (138 mg, 0.31 mmol, 0.01 equiv) and CH₂Cl₂ (140 mL). A solution of diazoketoester **303** (9.12 g, 31.2 mmol, 1.0 equiv) in CH₂Cl₂ (100 mL) was added dropwise over 90 min via an addition funnel. After stirring for 2.5 h at 23 °C, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (7:3→1:1 hexanes:EtOAc eluent) provided β -ketoester **304** (7.88 g, 96% yield) as a white solid: *R_f* 0.52 (1:1 hexanes:EtOAc); mp 117 °C; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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*): [*M*]⁺ calcd for [C₁₄H₁₆O₅]⁺, 264.0998; found, 264.1003.



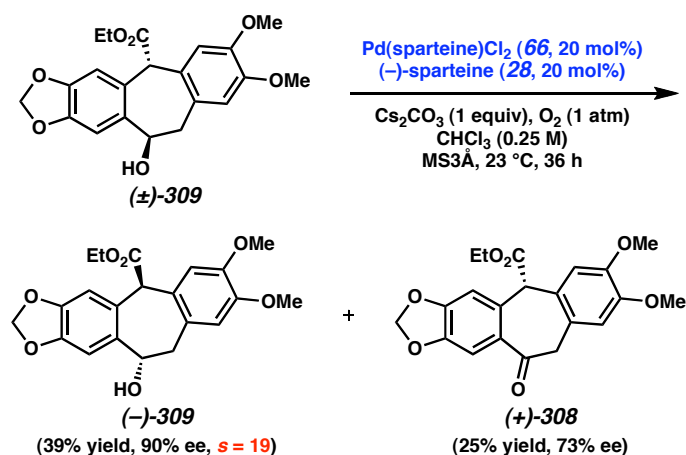
Ketoester (\pm)-308. To a solution of arylsilyl triflate **296** (898 mg, 2.62 mmol, 1.7 equiv) in acetonitrile (9 mL) was added β -ketoester **304** (415 mg, 1.57 mmol, 1.0 equiv) and cesium fluoride (715 mg, 4.71 mmol, 3.0 equiv). The reaction was quickly immersed in an 80 °C oil bath and allowed to reflux until arylsilyl triflate **296** was consumed (determined by TLC, 2 h). The reaction mixture was then cooled to 23 °C and washed

with saturated aq NaCl (15 mL). The aqueous layer was back-extracted with Et₂O (3 x 15 mL). The organic layers were combined, dried over Na₂SO₄, and filtered, and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes:EtOAc eluent) provided ketoester (\pm)-**308** (348 mg, 57% yield) as a clear oil: *R_f* 0.23 (1:1 hexanes:EtOAc); ¹H NMR (300 MHz, C₆D₆): δ 8.03 (s, 1H), 6.67 (s, 1H), 6.53 (s, 1H), 6.44 (s, 1H), 5.13 (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), 3.90 (dq, *J* = 7.1, 2.0 Hz, 2H), 3.83 (d, *J* = 15.3 Hz, 1H), 3.41 (s, 3H), 3.24 (s, 3H), 0.84 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆): 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, 56.3, 55.9, 50.0, 14.4; IR (thin film/NaCl): 2908, 1727, 1663, 1616, 1518, 1506, 1485, 1254 cm⁻¹; HRMS-EI (*m/z*): [M]⁺ calcd for [C₂₁H₂₀O₇]⁺, 384.1209; found, 384.1212.



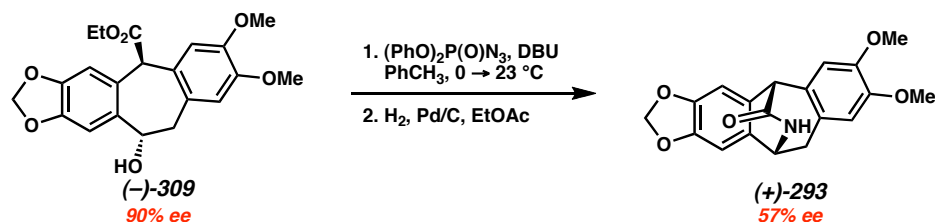
Hydroxyester (\pm)-309. To a solution of ketoester (\pm)-**308** (52.9 mg, 0.138 mmol, 1.0 equiv) in THF (1.5 mL) at -78 °C was added dropwise L-Selectride (1.0 M in THF, 200 μ L, 0.206 mmol, 1.5 equiv). The resulting solution was stirred for 25 min at -78 °C and then quenched with saturated aq NH₄Cl (5 mL). After warming to 23 °C and stirring 25 min, the mixture was extracted with Et₂O (4 x 5 mL). The organics were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (1:1 hexanes:EtOAc eluent) to provide

hydroxyester (\pm)-**309** (51.4 mg, 97% yield) as a yellow solid: R_f 0.33 (1:1 hexanes:EtOAc); $^1\text{H NMR}$ (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), 1.17 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (126 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 (m/z): $[\text{M}]^+$ calcd for $[\text{C}_{21}\text{H}_{22}\text{O}_7]^+$, 386.1366; found, 386.1366.



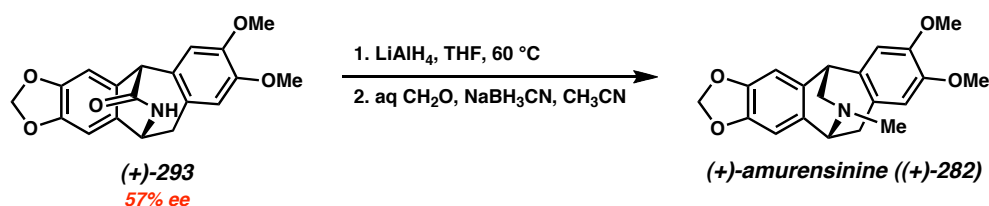
Kinetic Resolution of Hydroxyester (\pm)-309: Hydroxyester ($-$)-309. To a 1 dram vial with stir bar was added oven-dried powdered 3Å molecular sieves (190 mg). After cooling, Pd(sparteine)Cl_2 ²⁰ (**66**, 31.5 mg, 0.076 mmol, 0.20 equiv) followed by CHCl_3 (750 μL)²¹ and $(-)\text{-sparteine}$ (**28**, 17.6 μL , 0.076 mmol, 0.20 equiv) were added. The mixture was then cooled to -78 °C and alternately evacuated and backfilled with O_2 (3 \times). After allowing the mixture to warm to 23 °C, powdered anhydrous Cs_2CO_3 (124.5 mg, 0.38 mmol, 1.0 equiv) followed by a solution of hydroxyester (\pm)-**309** (147.7 mg,

0.38 mmol, 1.0 equiv) in CHCl_3 (750 μL) were added, and the reaction was stirred vigorously under a balloon of O_2 for 36 h. The reaction mixture was then filtered through a short plug of silica gel (EtOAc eluent) and evaporated under reduced pressure. Purification by flash chromatography (3:1 hexanes:EtOAc eluent) afforded hydroxyester (–)-**309** (56.8 mg, 39% yield) and ketoester (+)-**308** (36.6 mg, 25% yield). Hydroxyester (–)-**309** was found to be 90.4% ee by chiral HPLC (AD column, 0.55 mL/min, 60% EtOH/hexanes, major peak 16.3 min, minor peak 26.7 min); $[\alpha]_D^{25} -64.3^\circ$ (*c* 0.78, CHCl_3 , 87.9% ee). Ketoester (+)-**308** was found to be 73.0% ee by chiral HPLC (AD column, 0.55 mL/min, 60% EtOH/hexanes, major peak 46.6 min, minor peak 20.5 min); $[\alpha]_D^{25} +19.9^\circ$ (*c* 0.47, CHCl_3 , 84.8% ee).



Lactam (+)-293. To a solution of hydroxyester (–)-**309** (9.7 mg, 0.025 mmol, 1.0 equiv) in toluene (500 μL) at 0 °C was added DPPA (27 μL , 0.126 mmol, 5.0 equiv) and DBU (19 μL , 0.126 mmol, 5.0 equiv). The resulting solution was stirred for 30 min at 0 °C and then stirred at 23 °C for 12 h. The reaction was then quenched with H_2O (3 mL) and extracted with Et_2O (3 x 3 mL). The combined organics were dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude azide was passed through a short pad of silica gel (EtOAc eluent), concentrated under reduced pressure, and used in the next step without further purification.

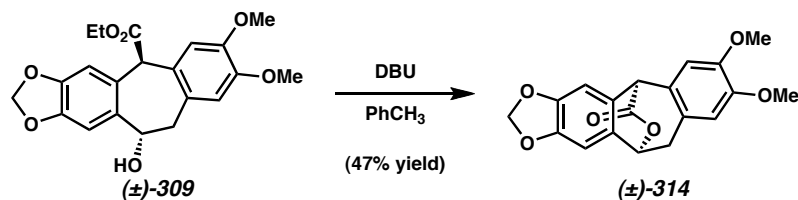
To a solution of the azide in EtOAc (1.5 mL) was added Pd/C (10% w/w, 15 mg, 0.014 mmol Pd, 0.56 equiv). The reaction flask was placed under a balloon of H₂ (1 atm) and stirred at 23 °C for 9 h. The reaction mixture was then passed through a short pad of Celite (Et₂O eluent) and concentrated under reduced pressure. Lactam (+)-**293** was used in the next step without further purification: *R_f* 0.46 (9:1 CHCl₃:MeOH); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (126 MHz, CDCl₃): 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*): [M+H]⁺ calcd for [C₁₉H₁₈NO₅]⁺, 340.1185; found, 340.1181. Lactam (+)-**293** was found to be 57.0% ee by chiral HPLC (OD-H column, 1.0 mL/min, 15% EtOH/hexanes, major peak 29.0 min, minor peak 45.1 min).



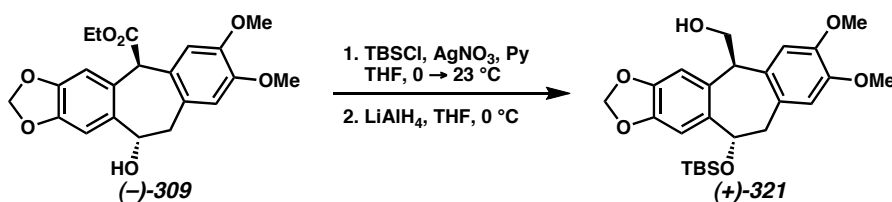
(+)-Amurensinine ((+)-282). To a solution of crude lactam (+)-**293** in THF (1 mL) was added lithium aluminum hydride (30 mg, 0.0751 mmol, 3.0 equiv). The resulting solution was stirred for 8 h at 60 °C. The reaction mixture was then cooled to 0 °C and sequentially quenched with H₂O (30 μL), aq NaOH (15% w/v, 30 μL), and H₂O (90 μL). The slurry was stirred at 23 °C for 25 min, passed through a short pad of Celite

(Et₂O eluent), and concentrated under reduced pressure to afford the crude secondary amine, which was used in the next step without further purification.

To a solution of the crude secondary amine in acetonitrile (1 mL) was added NaBH₃CN (10.0 mg, 0.159 mmol, 6.4 equiv) and aq formaldehyde (37% w/w, 50 μ L, 0.67 mmol, 26.9 equiv). After stirring at 23 °C for 2 h, the reaction mixture was washed with H₂O (2 mL). The aqueous layer was back-extracted with CH₂Cl₂ (3 x 3 mL). The organics were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and purified by preparative TLC (0.25 mm, 9:1 CHCl₃:MeOH eluent) to provide (+)-amurensinine ((+)-**282**, 1.5 mg, 17% yield over 4 steps) as a colorless thin film: *R_f* 0.18 (9:1 CHCl₃:MeOH); ¹H NMR (300 MHz, CDCl₃): δ 6.72 (s, 1H), 6.71 (s, 1H), 6.62 (s, 1H), 6.52 (s, 1H), 5.91 (d, *J* = 1.4 Hz, 1H), 5.85 (d, *J* = 1.4 Hz, 1H), 3.86 (s, 3H), 3.84 (dd, *J* = 3.7, 3.7 Hz, 1H), 3.77 (s, 3H), 3.62 (dd, *J* = 4.5, 1.5 Hz, 1H), 3.53 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.48 (dd, *J* = 17.0, 4.1 Hz, 1H), 2.90 (dd, *J* = 17.3, 3.5 Hz, 1H), 2.83 (dd, *J* = 10.6, 4.6 Hz, 1H), 2.48 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 147.7, 146.6, 146.3, 145.9, 135.1, 134.5, 131.2, 126.5, 114.2, 111.1, 107.2, 106.1, 100.6, 62.5, 59.9, 56.0, 55.9, 46.0, 45.3, 38.2; IR (thin film/NaCl): 2916, 2848, 1607, 1517, 1482, 1249 cm⁻¹; HRMS-EI (*m/z*): [M]⁺ calcd for [C₂₀H₂₁NO₄]⁺, 339.1471; found, 339.1469; UV-Vis λ_{max} 294 nm, shoulders at 232 and 250 nm, λ_{min} at 263 nm; [α]_D²⁵ +82.8° (*c* 0.035, CH₂Cl₂) [lit.²² [α]_D²⁰ -145.0° (*c* 1.0, CH₂Cl₂)].



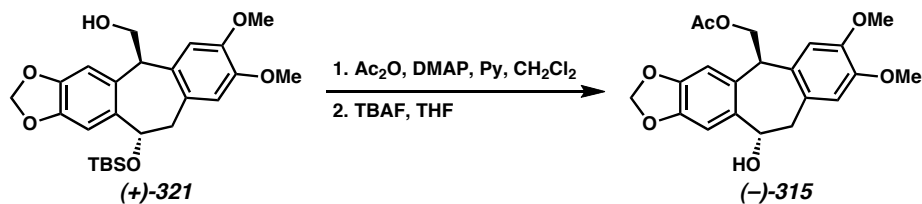
Lactone (±)-314. To a solution of hydroxyester (±)-**309** (11.6 mg, 0.030 mmol, 1.0 equiv) in PhCH₃ (1 mL) was added DBU (44.9 μL, 45.7 mg, 0.30 mmol, 10.0 equiv). After 20 h, the reaction mixture was diluted with H₂O (2 mL) and extracted with EtOAc (3 x 3 mL). The organic layers were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (3:2 hexanes:EtOAc) to afford lactone (±)-**314** (4.8 mg, 47% yield) as a foamy white solid: *R_f* 0.33 (1:1 hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 6.77 (s, 1H), 6.73 (s, 1H), 6.72 (s, 1H), 6.52 (s, 1H), 5.97 (d, *J* = 1.4 Hz, 1H), 5.91 (d, *J* = 1.4 Hz, 1H), 5.55 (dd, *J* = 4.5, 2.4 Hz, 1H), 4.43 (s, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 3.59 (dd, *J* = 17.8, 4.5 Hz, 1H), 3.15 (dd, *J* = 17.9, 2.4 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 171.9, 149.0, 148.0, 147.8, 147.1, 132.1, 127.1, 126.4, 124.3, 113.9, 111.4, 106.1, 105.6, 101.4, 78.7, 56.0, 55.9, 54.0, 35.8; IR (thin film/NaCl) 2904, 1746, 1519, 1252 cm⁻¹; HRMS-EI (*m/z*): [M]⁺ calcd for [C₁₉H₁₆O₆]⁺, 340.0947; found, 340.0941.



Hydroxysilane (+)-321. A solution of hydroxyester (-)-**309** (375.2 mg, 0.97 mmol, 1.0 equiv) in THF (19 mL) was cooled to 0 °C. AgNO₃ (660 mg, 3.89 mmol, 4.0 equiv), pyridine (628 μL, 7.76 mmol, 8.0 equiv), and then TBSCl (585 mg, 3.89 mmol,

4.0 equiv) were added. The cloudy mixture was allowed to warm to 23 °C and stirred 14 h. The mixture was filtered through a short plug of Celite (Et₂O eluent). The filtrate was washed with H₂O (40 mL). The aqueous layer was extracted with Et₂O (3 x 40 mL). The organic layers were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford the crude silylester, which was used in the next step without further purification.

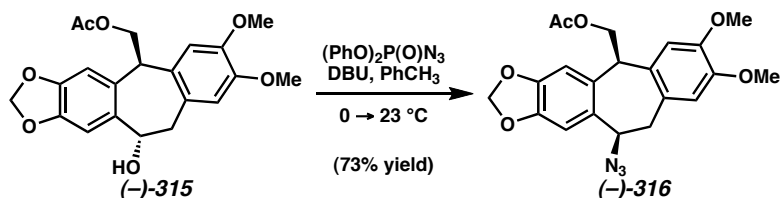
A solution of the crude silylester in THF (19 mL) was cooled to 0 °C. Lithium aluminum hydride (184 mg, 4.85 mmol, 5.0 equiv) was added. The mixture was allowed to stir at 0 °C for 30 min. H₂O (200 μL), then aq NaOH (10% w/v, 200 μL), then H₂O (400 μL) were sequentially added. The mixture was allowed to warm to 23 °C and stir 30 min before filtration through a short plug of Celite (Et₂O eluent). The filtrate was concentrated under reduced pressure and purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford hydroxysilane (+)-**321** as a white foam: *R_f* 0.20 (1:1 hexanes:EtOAc); ¹H NMR (300 MHz, C₆D₆) δ 7.53 (s, 1H), 6.72 (s, 1H), 6.61 (s, 1H), 6.44 (s, 1H), 5.53 (dd, *J* = 10.2, 2.4 Hz, 1H), 5.39 (app. s, 1H), 5.37 (app. s, 1H), 4.11-3.84 (comp. m, 4H), 3.47 (s, 3H), 3.39 (s, 3H), 3.31-3.08 (comp. m, 2H), 0.98 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ¹³C NMR (75 MHz, C₆D₆) δ 148.7, 148.2, 147.4, 146.6, 138.4, 129.6, 129.2, 128.7, 116.0, 115.4, 111.7, 106.2, 100.9, 70.1, 67.8, 57.5, 55.7, 55.5, 44.3, 26.0, 18.4, -4.8, -4.8; IR (thin film/NaCl) 3512, 2930, 1521, 1484, 1040 cm⁻¹; HRMS-FAB (*m/z*): [M-H]⁺ calcd for [C₂₅H₃₃O₆Si]⁺, 457.2046; found, 457.2049. Hydroxysilane (+)-**321** was found to be 86.8% ee by chiral HPLC (AD column, 1.0 mL/min, 10% EtOH/hexanes, major peak 8.1 min, minor peak 12.1 min); [α]_D²⁵ +66.9° (*c* 0.71, C₆H₆).



Hydroxyacetate (–)-315. To a solution of hydroxysilane (+)-**321** in CH_2Cl_2 (12 mL) was added pyridine (672 μL , 8.3 mmol, 10.0 equiv), DMAP (101 mg, 0.83 mmol, 1.0 equiv), and acetic anhydride (785 μL , 8.3 mmol, 10.0 equiv). After 5 min, saturated aq NaCl (15 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, dried over Na_2SO_4 , and filtered. The filtrate was evaporated under reduced pressure. Heptane (200 mL) was added, followed by concentration under reduced pressure. Then, PhCH_3 (100 mL) was added, and the solution was concentrated under reduced pressure to azeotrope excess reagents. The crude silylacetate was used in the next step without further purification.

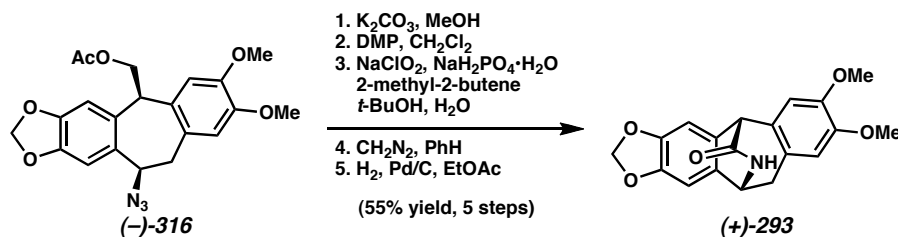
To a solution of crude silylacetate in THF (8 mL) was added TBAF (1.0 M in THF, 2.40 mL, 2.40 mmol, 3.0 equiv). After 10 min, the reaction was diluted with EtOAc (50 mL), washed with H_2O (2 x 10 mL) and saturated aq NaCl (10 mL), dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (3:2 hexanes:EtOAc) to afford hydroxyacetate (–)-**315** (219 mg, 71% yield over 4 steps) as a white foam: R_f 0.19 (1:1 hexanes:EtOAc); ^1H NMR (300 MHz, C_6D_6) δ 7.13 (s, 1H), 6.70 (s, 1H), 6.62 (s, 1H), 6.46 (s, 1H), 5.36-5.32 (comp. m, 2H), 4.87 (d, $J = 7.5$ Hz, 1H), 4.60-4.46 (comp. m, 2H), 4.15 (t, $J = 8.1$ Hz, 1H), 3.46 (s, 3H), 3.37 (s, 3H), 3.27 (dd, $J = 15.2, 8.1$ Hz, 1H), 2.86 (dd, $J = 15.3, 8.1$ Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 170.4, 149.5, 148.8, 147.9, 147.4, 137.2,

130.5, 130.2, 128.9, 116.4, 116.0, 111.5, 110.4, 101.5, 70.2, 67.6, 56.2, 55.9, 53.3, 41.8, 20.8; IR (thin film/NaCl) 3506, 2935, 1736, 1487, 1242, 1038 cm^{-1} ; $[\alpha]_{\text{D}}^{25} -11.9^{\circ}$ (c 1.14, C_6H_6).



Azidoacetate (–)-316. A solution of hydroxyacetate (–)-**315** (101.8 mg, 0.26 mmol, 1.0 equiv) in PhCH_3 (5.2 mL) was cooled to 0 °C. DPPA (118 μL , 0.55 mmol, 7.5 equiv) and DBU (82 μL , 0.55 mmol, 7.5 equiv) were added. The reaction was stirred and allowed to warm to 23 °C. After 15 h, H_2O (15 mL) was added. The mixture was extracted with Et_2O (3 x 20 mL). The organics were combined, dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (4:1→7:3 hexanes:EtOAc) to afford azidoacetate (–)-**316** (79.5 mg of (–)-**316**, 73% yield of (–)-**316**, contaminated with trace byproducts) as a colorless oil. Further purification by preparative HPLC (1:0→4:1 hexanes:EtOAc) provided an analytically pure sample of azidoacetate (–)-**316**: R_f 0.64 (2:3 hexanes:EtOAc); ^1H NMR (300 MHz, C_6D_6) δ 7.00 (s, 1H), 6.67 (s, 1H), 6.56 (s, 1H), 6.37 (s, 1H), 5.29 (dd, $J = 1.4$, 0.6 Hz, 1H), 5.24 (dd, $J = 1.4$, 0.5 Hz, 1H), 4.76 (dd, $J = 11.0$, 8.2 Hz, 1H), 4.62 (dd, $J = 11.0$, 7.6 Hz, 1H), 4.27 (dd, $J = 10.7$, 4.8 Hz, 1H), 4.16 (t, $J = 7.9$ Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 3.28 (dd, $J = 14.6$, 10.9 Hz, 1H), 2.89 (dd, $J = 15.0$, 4.8 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 170.4, 149.6, 149.2, 148.0, 147.8, 132.7, 131.9, 131.1, 128.9, 115.4, 113.8, 110.7, 110.2, 101.7, 66.9, 62.9, 56.2, 56.1, 50.1, 38.5, 20.8; IR (thin

film/NaCl) 2934, 2099, 1737, 1236 cm^{-1} ; HRMS-EI (m/z): $[M]^+$ calcd for $[\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_6]^+$, 411.1430; found, 411.1423. Azidoacetate (–)-**316** was found to be 88.3% ee by chiral HPLC (AD column, 1.0 mL/min, 10% EtOH/hexanes, major peak 45.2 min, minor peak 41.4 min); $[\alpha]_D^{25}$ -58.8° (c 0.61, C_6H_6).



Lactam (+)-293. To a solution of azidoacetate (–)-**316** (20.0 mg, 0.049 mmol, 1.0 equiv) in MeOH (2 mL) was added K_2CO_3 (67 mg, 0.49 mmol, 10.0 equiv). After 25 min, the reaction was diluted with saturated aq NH_4Cl (5 mL) and H_2O (5 mL). The mixture was then extracted with EtOAc (3 x 10 mL). The organics were combined, dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure to afford a crude azidoalcohol, which was used in the next step without further purification.

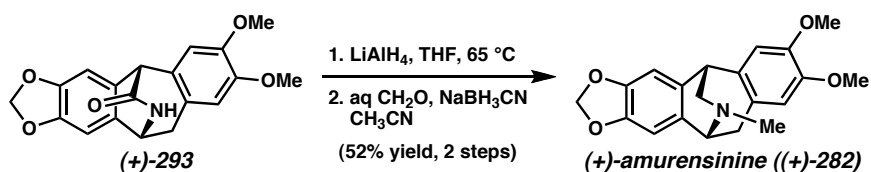
To a solution of crude azidoalcohol in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane²³ (62.0 mg, 0.15 mmol, 3.0 equiv). After 2 h, the mixture was filtered through a short plug of Celite (CH_2Cl_2 eluent). The filtrate was concentrated under reduced pressure to afford a crude azidoaldehyde, which was used in the next step without further purification.

To a solution of crude azidoaldehyde in *t*-BuOH (1.6 mL) was added 2-methyl-2-butene (154 μL , 1.45 mmol, 30.0 equiv) followed by a solution of NaClO_2 (technical grade [80%], 22.0 mg, 0.24 mmol, 5.0 equiv) and $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (53.0 mg, 0.39 mmol, 8.0 equiv) in H_2O (800 μL). After stirring vigorously for 2 h, the mixture was diluted

with saturated aq NaCl (4 mL) and extracted with EtOAc (4 x 4 mL). The organics were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford a crude azidoacid, which was used in the next step without further purification.

To a solution of crude azidoacid in PhH (3 mL) was added CH₂N₂ (0.2 M in Et₂O, 2 mL) until yellow color persisted. After 5 min, the reaction was concentrated under reduced pressure and purified by preparative TLC (0.5 mm, 3:2 hexanes:EtOAc eluent) to afford an azidoester, which was used in the next step without further purification.

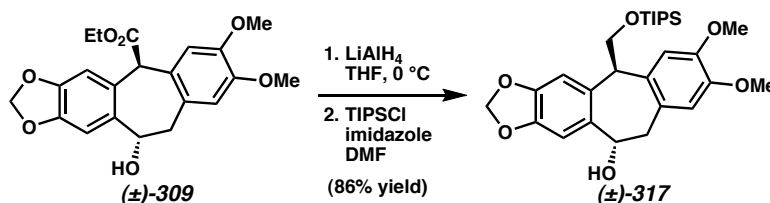
To a solution of azidoester in EtOAc (4.7 mL) was added Pd/C (10% w/w, 50 mg, 0.049 mmol Pd, 1.0 equiv). The reaction flask was placed under a balloon of H₂ (1 atm) and stirred at 23 °C for 15 h. The reaction mixture was then filtered through a short plug of Celite (EtOAc eluent), concentrated under reduced pressure, and purified by preparative TLC (0.25 mm, 9:1 CHCl₃:MeOH) to afford lactam (+)-**293** (9.1 mg, 55% yield over 5 steps).



(+)-Amurensinine ((+)-282). To a solution of lactam (+)-**293** (9.8 mg, 0.029 mmol, 1.0 equiv) in THF (1 mL) was added lithium aluminum hydride (11.0 mg, 0.29 mmol, 10.0 equiv) at 0 °C. The reaction was then heated to 65 °C for 4 h. The mixture was cooled to 0 °C and diluted with CH₂Cl₂ (1 mL). H₂O (100 μL), aq NaOH (10% w/v, 100 μL), and H₂O (200 μL) were added sequentially dropwise. The biphasic mixture was warmed to 23 °C and stirred vigorously for 1 h. The reaction was then filtered through a

short plug of Celite (CH₂Cl₂ eluent) to remove suspended solids. After dilution with H₂O (2 mL) and aq NaOH (10% w/v, 2 mL), the biphasic mixture was extracted with CH₂Cl₂ (5 x 5 mL). The organic layers were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford the crude secondary amine, which was carried on to the next step without further purification.

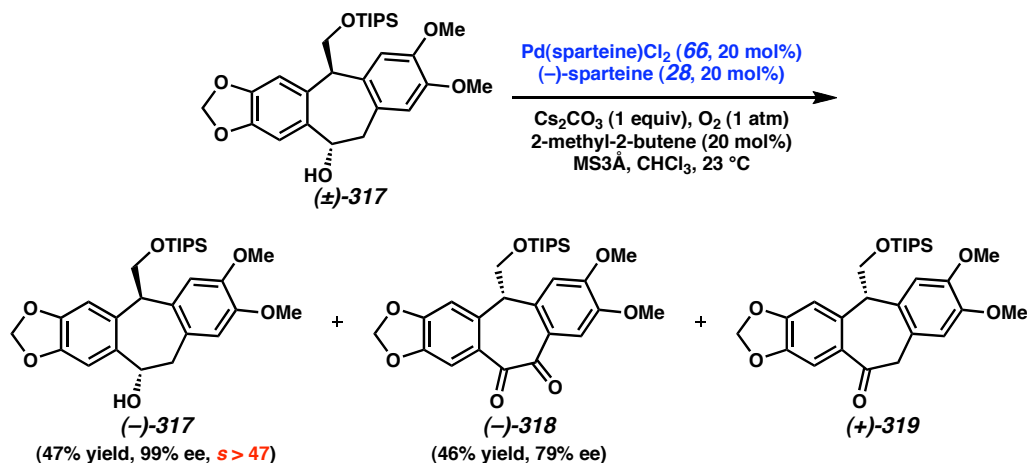
To a solution of crude secondary amine in acetonitrile (1 mL) was added sodium cyanoborohydride (24.7 mg, 0.40 mmol, 13.8 equiv) followed by aq formaldehyde (37% w/w, 110 μL, 1.48 mmol, 51.0 equiv). After stirring for 5.5 h at 23 °C, the reaction was diluted with H₂O (2 mL) and extracted with CH₂Cl₂ (4 x 2 mL). The organic layers were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and purified by preparative TLC (0.25 mm, 19:1 CHCl₃:MeOH eluent) to afford (+)-amurensinine ((+)-**282**, 5.1 mg, 52% yield over 2 steps) as a colorless thin film.



Hydroxysilane (±)-317. To a solution of hydroxyester (±)-**309** (76.6 mg, 0.20 mmol, 1.0 equiv) in THF (4 mL) was added lithium aluminum hydride (37.6 mg, 0.99 mmol, 5.0 equiv) at 0 °C. After 30 min, the reaction was quenched at 0 °C by slow addition of EtOAc (5 mL) followed by aq sodium potassium tartrate (10% w/v, 5 mL). After warming to 23 °C and stirring vigorously for 1 h, the biphasic mixture was diluted with H₂O (10 mL) and extracted with EtOAc (4 x 20 mL). The organic layers were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced

pressure to afford a crude diol, which was carried on to the next step without further purification. Diol: R_f 0.12 (2:3 hexanes:EtOAc); ^1H NMR (300 MHz, C_6D_6): δ 7.10 (s, 1H), 6.69 (s, 1H), 6.56 (s, 1H), 6.49 (s, 1H), 5.36 (dd, $J = 1.4, 0.5$ Hz, 1H), 5.34 (dd, $J = 1.4, 0.6$ Hz, 1H), 4.82 (br d, $J = 6.8$ Hz, 1H), 3.86-3.78 (comp. m, 3H), 4.15 (s, 1H), 3.44 (s, 3H), 3.40 (s, 3H), 3.21 (dd, $J = 15.0, 2.6$ Hz, 1H), 2.83 (dd, $J = 15.0, 7.9$ Hz, 1H), 1.37 (br s, 1H), 1.03 (br s, 1H).

To a solution of crude diol in DMF (4 mL) was added imidazole (40.5 mg, 0.60 mmol, 3.0 equiv) then tri-isopropylchlorosilane (63.7 μL , 0.30 mmol, 1.5 equiv). After stirring 12 h at 23 $^\circ\text{C}$, the solution was quenched by addition of H_2O (20 mL). The mixture was then extracted with EtOAc (4 x 30 mL). The organic layers were combined, dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (2:3 hexanes:Et₂O eluent) to provide hydroxysilane (\pm)-**317** (85.8 mg, 86% yield over 2 steps) as a white solid: R_f 0.28 (3:2 hexanes:EtOAc); ^1H NMR (300 MHz, C_6D_6): δ 7.11 (s, 1H), 6.86 (s, 1H), 6.74 (s, 1H), 6.55 (s, 1H), 5.37 (d, $J = 1.3$ Hz, 1H), 5.34 (d, $J = 1.3$ Hz, 1H), 4.93 (ddd, $J = 7.9, 7.9, 1.9$ Hz, 1H), 4.18-4.15 (comp. m, 2H), 4.09 (dd, $J = 15.5, 8.1$ Hz, 1H), 3.53 (s, 3H), 3.41 (s, 3H), 3.41 (dd, $J = 14.8, 2.2$ Hz, 1H), 2.91 (dd, $J = 14.9, 7.6$ Hz, 1H), 1.36 (d, $J = 8.4$ Hz, 1H), 1.01 (comp. m, 21H); ^{13}C NMR (75 MHz, C_6D_6): δ 149.0, 148.5, 147.3, 147.1, 136.4, 132.0, 131.3, 116.6, 116.3, 112.2, 110.5, 101.1, 70.4, 68.2, 57.9, 55.9, 55.7, 41.5, 18.2, 12.3; IR (thin film/NaCl): 2941, 2865, 1520, 1487, 1240, 1098, 1041 cm^{-1} ; HRMS-FAB (m/z): $[\text{M}]^+$ calcd for $[\text{C}_{28}\text{H}_{40}\text{O}_6\text{Si}]^+$, 500.2594; found, 500.2598.

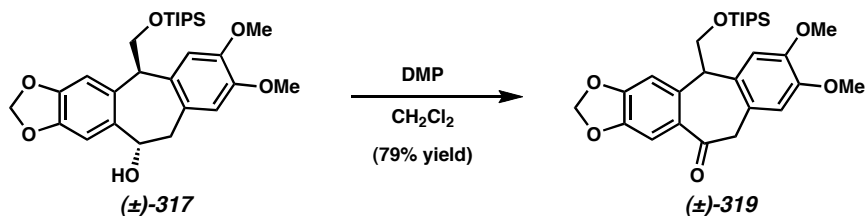


Oxidative Kinetic Resolution of Hydroxysilane (\pm)-**317**: Hydroxysilane ($-$)-

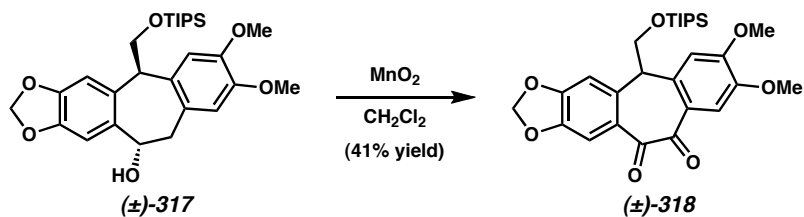
317. To a 1 dram vial with stir bar was added oven-dried powdered 3Å molecular sieves (50 mg), Pd(sparteine)Cl_2 (**66**, 8.2 mg, 0.02 mmol, 0.20 equiv), CHCl_3 (0.5 mL),²¹ and ($-$)-sparteine (**28**, 4.6 μL , 0.02 mmol, 0.20 equiv). The mixture was cooled to -78 °C and alternately evacuated and backfilled with O_2 (3x). After allowing the mixture to warm to 23 °C, powdered anhydrous Cs_2CO_3 (32.6 mg, 0.10 mmol, 1.0 equiv), 2-methyl-2-butene (2.1 μL , 0.02 mmol, 0.20 equiv), and a solution of hydroxysilane (\pm)-**317** (50.1 mg, 0.10 mmol, 1.0 equiv) in CHCl_3 (0.5 mL) were added. The reaction was stirred vigorously under a balloon of O_2 for 82 h. The reaction mixture was filtered through a short plug of silica gel (EtOAc eluent) and evaporated under reduced pressure. Purification by preparative TLC (0.5 mm, 3:2 hexanes:EtOAc eluent) afforded hydroxysilane ($-$)-**317** (23.7 mg, 47% yield) and diketosilane ($-$)-**318** (23.4 mg). Hydroxysilane ($-$)-**317** was found to be $>99\%$ ee by chiral HPLC (AD column, 1.0 mL/min, 5% EtOH/hexanes, major peak 13.0 min, minor peak 21.0 min); $[\alpha]_D^{25} -24.4^\circ$ (c 0.86, C_6H_6 , $>99\%$ ee). Reactions stopped earlier than 82 h afforded another product in addition to hydroxysilane ($-$)-**317** and diketosilane ($-$)-**318**. This compound was revealed to be ketosilane ($+$)-**319**, which gradually oxidized to the diketone in the presence of O_2 .

Diketosilane (–)-318. R_f 0.35 (3:2 hexanes:EtOAc); ^1H NMR (300 MHz, C_6D_6): δ 7.61 (s, 1H), 7.58 (s, 1H), 6.59 (s, 1H), 6.48 (s, 1H), 5.16 (s, 2H), 3.97 (d, $J = 5.9$ Hz, 2H), 3.79 (t, $J = 5.7$ Hz, 1H), 3.39 (s, 3H), 3.26 (s, 3H), 0.94 (comp. m, 21H); ^{13}C NMR (75 MHz, C_6D_6): δ 186.8, 185.8, 153.6, 151.6, 149.6, 147.9, 138.8, 136.8, 131.0, 114.5, 112.9, 111.5, 109.9, 101.9, 71.9, 58.9, 55.3, 18.1, 12.2; IR (thin film/NaCl): 2942, 2866, 1659, 1597, 1517, 1485, 1251 cm^{-1} ; HRMS-FAB (m/z): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{28}\text{H}_{37}\text{O}_7\text{Si}]^+$, 513.2309; found, 513.2313. Diketosilane (–)-**318** was found to be 79.1% ee by chiral HPLC (AD column, 1.0 mL/min, 5% EtOH/hexanes, major peak 63.8 min, minor peak 24.7 min). The kinetic resolution therefore has a selectivity factor $s > 47$.¹³ $[\alpha]_{\text{D}}^{25} -39.9^\circ$ (c 1.21, C_6H_6 , 73.9% ee).

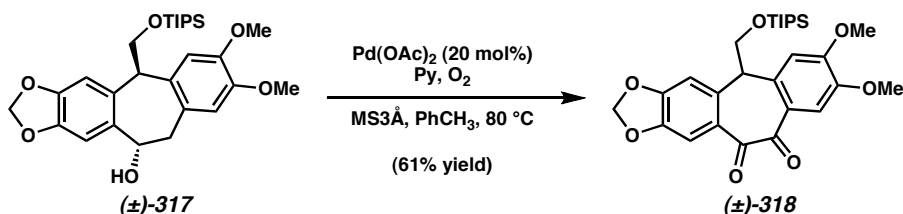
Ketosilane (+)-319. R_f 0.50 (3:2 hexanes:EtOAc); ^1H NMR (300 MHz, C_6D_6): δ 8.03 (s, 1H), 6.82 (s, 1H), 6.71 (s, 1H), 6.48 (s, 1H), 5.21 (d, $J = 1.4$ Hz, 1H), 5.17 (d, $J = 1.2$ Hz, 1H), 4.42 (d, $J = 14.5$ Hz, 1H), 4.37-4.26 (m, 2H), 4.24-4.13 (m, 1H), 3.83 (d, $J = 14.9$ Hz, 1H), 3.49 (s, 3H), 3.29 (s, 3H), 1.00 (comp. m, 21H); ^{13}C NMR (75 MHz, C_6D_6): δ 192.8, 151.3, 149.5, 148.7, 147.6, 139.9, 132.1, 130.8, 125.1, 115.2, 114.6, 110.9, 110.2, 101.7, 65.8, 56.0, 55.6, 50.3, 18.2, 12.2; IR (thin film/NaCl): 2941, 2865, 1665, 1516, 1484, 1102 cm^{-1} ; HRMS-FAB (m/z): $[\text{M}]^+$ calcd for $[\text{C}_{28}\text{H}_{38}\text{O}_6\text{Si}]^+$, 498.2438; found, 498.2433. Ketosilane (+)-**319** was found to be 76.8% ee by chiral HPLC (AD column, 1.0 mL/min, 5% EtOH/hexanes, major peak 20.6 min, minor peak 10.7 min); $[\alpha]_{\text{D}}^{25} +10.6^\circ$ (c 0.65, C_6H_6 , 76.8% ee).



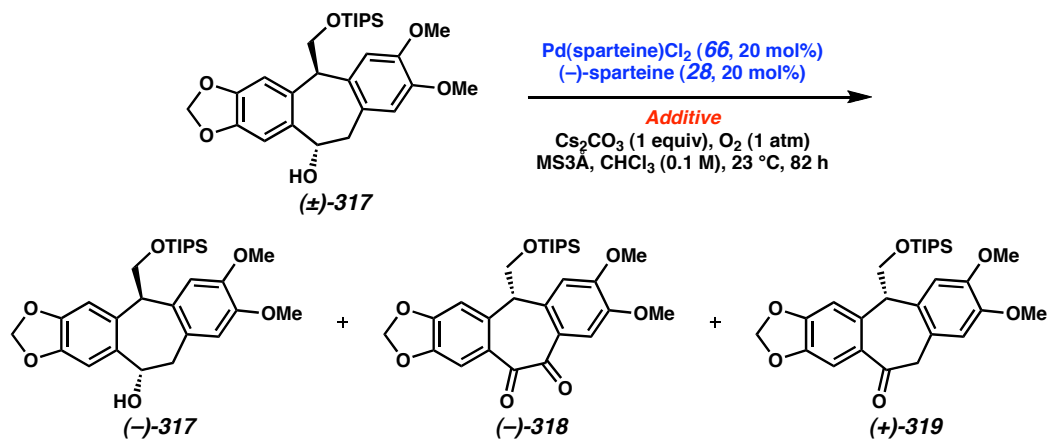
Ketosilane (±)-319 by Dess-Martin Periodinane Oxidation. To a solution of hydroxysilane (±)-**317** (10.0 mg, 0.020 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added Dess-Martin periodinane (25.4 mg, 0.060 mmol, 3.0 equiv). After 5 min, the reaction was diluted with Et_2O (2 mL) and filtered through a short plug of Celite (Et_2O eluent). The filtrate was concentrated under reduced pressure and purified by preparative TLC (0.25 mm, 7:3 hexanes:EtOAc eluent) to afford ketosilane (±)-**319** (7.9 mg, 79% yield) as a colorless oil.



Diketosilane (±)-318 by MnO_2 Oxidation. To a solution of hydroxysilane (±)-**317** (13.2 mg, 0.026 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added MnO_2 (activated, 22.9 mg, 0.26 mmol, 10.0 equiv). After 19 h, more MnO_2 (45.8 mg, 0.52 mmol, 20.0 equiv) was added. After 115 h, the reaction was filtered through a short plug of Celite (CH_2Cl_2 eluent). The filtrate was concentrated under reduced pressure and purified by preparative TLC (0.25 mm, 7:3 hexanes:EtOAc eluent) to afford diketosilane (±)-**318** (5.4 mg, 41% yield) as a yellow solid.



Diketosilane (±)-318 by Pd-catalyzed Aerobic Oxidation. Palladium acetate (1.8 mg, 0.008 mmol, 0.20 equiv), oven-dried 3Å molecular sieves (20 mg), PhCH₃ (0.5 mL), and pyridine (2.6 μL, 0.032 mmol, 0.80 equiv) were allowed to stir at 80 °C under O₂ atmosphere (balloon) for 10 min. Hydroxysilane (±)-**317** (20.0 mg, 0.040 mmol, 1.0 equiv) was added, and the reaction was allowed to stir at 80 °C under O₂ atmosphere for 23 h. After cooling to 23 °C, the mixture was diluted with EtOAc (2 mL) and filtered through a short plug of Celite (EtOAc eluent). The filtrate was concentrated under reduced pressure and purified by preparative TLC (0.25 mm, 3:2 hexanes:EtOAc eluent) to afford diketosilane (±)-**318** (12.1 mg, 61% yield) as a yellow solid.



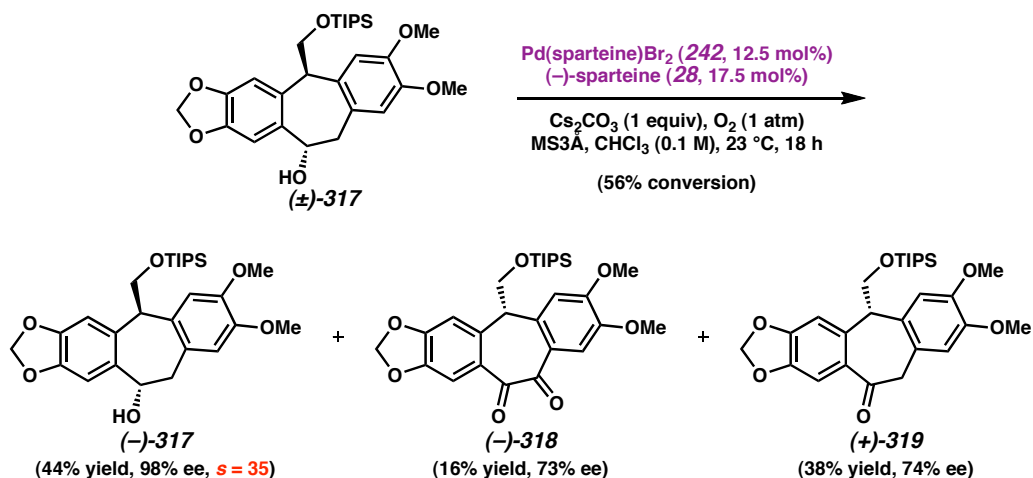
Radical Inhibitor Screen in the Oxidative Kinetic Resolution of Hydroxysilane (±)-317: Hydroxysilane (-)-317. To a 1 dram vial with stir bar was added oven-dried powdered 3Å molecular sieves (50 mg), Pd(sparteine)Cl₂ (**66**, 8.2 mg, 0.02 mmol, 0.20 equiv), CHCl₃ (0.5 mL),²¹ and (-)-sparteine (**28**, 4.6 μL, 0.02 mmol,

0.20 equiv). The mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and alternately evacuated and backfilled with O_2 (3x). After allowing the mixture to warm to $23\text{ }^{\circ}\text{C}$, powdered anhydrous Cs_2CO_3 (32.6 mg, 0.10 mmol, 1.0 equiv), the appropriate additive (0.020 mmol, 0.20 equiv), and a solution of hydroxysilane (\pm)-**317** (50.1 mg, 0.10 mmol, 1.0 equiv) in CHCl_3 (0.5 mL) were added. The reaction was stirred vigorously under a balloon of O_2 for 82 h. The reaction mixture was filtered through a short plug of silica gel (EtOAc eluent) and evaporated under reduced pressure. Purification by preparative TLC (0.25 mm, 3:2 hexanes:EtOAc eluent) afforded hydroxysilane (–)-**317**, diketosilane (–)-**318**, and ketosilane (+)-**319**, as shown in Table 5.5.1.

Table 5.5.1 Radical inhibitor screening.

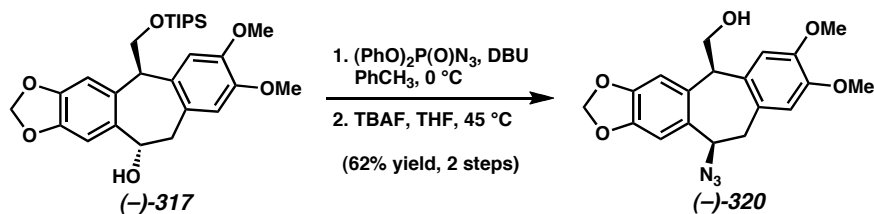
| additive | hydroxysilane % yield (ee) | diketosilane % yield (ee) | ketosilane % yield (ee) | % conversion ^a | <i>s</i> ^b |
|--------------------|-------------------------------|------------------------------|----------------------------|---------------------------|-----------------------|
| none ^c | 36 (97) | 28 (83) | 19 (76) | 54 | 44 |
| BHT | 47 (95) | 49 (82) | -- ^d | 54 | 36 |
| tetracyanoethylene | 92 (< 5) | 8 (--) | -- ^d | 8 | -- |
| 2-methyl-2-butene | 47 (99) | 46 (79) | -- ^d | 56 | 47 |

^a % Conversion determined relative to hydroxysilane ee and diketosilane ee, see ref 13. ^b Selectivity factor (*s*) determined according to ref 13. ^c Reaction run for 72 h. ^d No ketosilane recovered.



Oxidative Kinetic Resolution of Hydroxysilane (\pm)-**317** with Dibromide

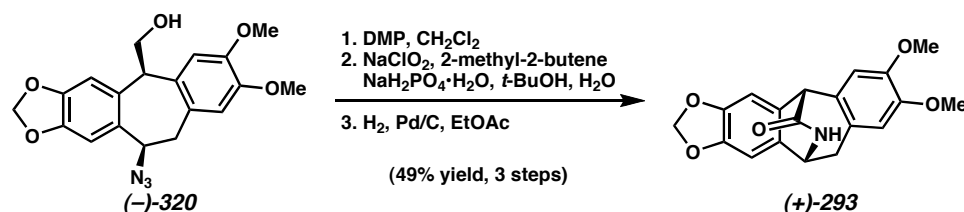
Complex 242: Hydroxysilane ($-$)-317**.** To a 1 dram vial with stir bar was added oven-dried powdered 3Å molecular sieves (125 mg), Pd(sparteine)Br_2 ¹⁶ (**242**, 6.3 mg, 0.0125 mmol, 0.125 equiv), CHCl_3 (0.5 mL),²¹ and ($-$)-sparteine (**28**, 4.0 μL , 0.0175 mmol, 0.175 equiv). The mixture was cooled to -78 °C and alternately evacuated and backfilled with O_2 (3x). After allowing the mixture to warm to 23 °C, powdered anhydrous Cs_2CO_3 (32.6 mg, 0.10 mmol, 1.0 equiv) and a solution of hydroxysilane (\pm)-**317** (50.1 mg, 0.10 mmol, 1.0 equiv) and 1,4-bis(trimethylsilyl)benzene (internal ^1H NMR standard, 4.4 mg, 0.020 mmol, 0.20 equiv) in CHCl_3 (0.5 mL) were added. The reaction was stirred vigorously under a balloon of O_2 for 18 h. The reaction mixture was filtered through a short plug of silica gel (EtOAc eluent) and evaporated under reduced pressure. Conversion was determined to be 55.8% based on ^1H NMR of remaining starting hydroxysilane relative to internal standard. Purification by flash chromatography (7:3→1:1 hexanes:Et₂O eluent) afforded hydroxysilane ($-$)-**317** (22.7 mg, 45% yield, 98.0% ee, $s = 35$), diketosilane ($-$)-**318** (8.3 mg, 73.3% ee), and ketosilane ($+$)-**319** (19.0 mg, 73.7% ee).



Azidoalcohol (–)-320. To a solution of hydroxysilane (–)-**317** (100.1 mg, 0.20 mmol, 1.0 equiv) in PhCH_3 (5 mL) was added DBU (179 μL , 1.20 mmol, 6.0 equiv) followed by DPPA (259 μL , 1.20 mmol, 6.0 equiv) at $0\text{ }^\circ\text{C}$. After stirring 6 h at $0\text{ }^\circ\text{C}$, the reaction was quenched by addition of H_2O (25 mL). The mixture was then extracted with Et_2O (3 x 30 mL). The organic layers were combined, dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure to afford a crude azidosilane, which was carried on to the next step without further purification.

To a solution of crude azidosilane in THF (2 mL) was added TBAF (1.0 M in THF, 2.0 mL, 2.0 mmol, 10.0 equiv). The reaction was warmed to $45\text{ }^\circ\text{C}$ for 5 h. The solution was allowed to cool to $23\text{ }^\circ\text{C}$ and diluted with EtOAc (40 mL). The solution was washed with H_2O (3 x 20 mL) and saturated aq NaCl (20 mL), dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (7:3 hexanes: EtOAc eluent) followed by preparative TLC (0.5 mm, 1:1 hexanes: EtOAc eluent) to afford azidoalcohol (–)-**320** (45.9 mg, 62% yield over 2 steps) as a white foam: R_f 0.44 (2:3 hexanes: EtOAc); ^1H NMR (300 MHz, C_6D_6): δ 7.03 (s, 1H), 6.67 (s, 1H), 6.54 (s, 1H), 6.40 (s, 1H), 5.31 (d, $J = 1.4\text{ Hz}$, 1H), 5.27 (d, $J = 1.3\text{ Hz}$, 1H), 4.27 (dd, $J = 10.8, 4.6\text{ Hz}$, 1H), 4.04–3.90 (comp. m, 2H), 3.86 (dd, $J = 14.6, 7.3\text{ Hz}$, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 3.28 (dd, $J = 14.7, 11.0\text{ Hz}$, 1H), 2.87 (dd, $J = 14.7, 4.7\text{ Hz}$, 1H), 1.10 (br s, 1H); ^{13}C NMR (75 MHz, C_6D_6): δ 149.1, 148.8, 147.6, 147.3, 133.1,

132.5, 130.6, 115.1, 114.2, 110.5, 110.4, 101.3, 66.3, 62.8, 55.9, 55.9, 54.4, 38.2; IR (thin film/NaCl): 3492, 2935, 2099, 1517, 1487, 1236 cm^{-1} ; HRMS-FAB (m/z): $[M]^+$ calcd for $[\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_5]^+$, 369.1325; found, 369.1328. Azidoalcohol (–)-**320** was found to be >99% ee by chiral HPLC (AD column, 1.0 mL/min, 30% EtOH/hexanes, major peak 17.0 min, minor peak 15.3 min); $[\alpha]_{\text{D}}^{28} -70.8^\circ$ (c 0.91, CH_2Cl_2).

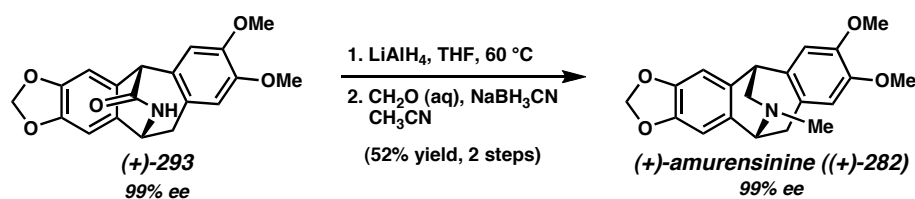


Lactam (+)-293. To a solution of azidoalcohol (–)-**320** (10.6 mg, 0.029 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (24.3 mg, 0.057 mmol, 2.0 equiv) at 0 °C. After 30 min, the mixture was diluted with Et_2O (3 mL) and filtered through a plug of Celite (Et_2O eluent). Concentration under reduced pressure afforded crude azidoaldehyde, which was used in the next step without further purification: R_f 0.77 (2:3 hexanes:EtOAc); ^1H NMR (300 MHz, C_6D_6): δ 9.63 (s, 1H), 6.83 (s, 1H), 6.43 (s, 1H), 6.38 (s, 1H), 6.32 (s, 1H), 5.30 (d, $J = 1.3$ Hz, 1H), 5.23 (d, $J = 1.3$ Hz, 1H), 4.00 (dd, $J = 10.6, 4.2$ Hz, 1H), 3.84 (s, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.12 (dd, $J = 15.0, 10.7$ Hz, 1H), 2.67 (dd, $J = 15.0, 4.1$ Hz, 1H).

To a solution of crude azidoaldehyde in $t\text{-BuOH}$ (1 mL) was added 2-methyl-2-butene (182 μL , 1.71 mmol, 59.0 equiv) followed by a solution of NaClO_2 (technical grade [80%], 32.4 mg, 0.29 mmol, 10.0 equiv) and $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (63.1 mg, 0.46 mmol, 15.9 equiv) in H_2O (1 mL). The biphasic mixture was stirred vigorously for 90 min. After diluting with saturated aq NaCl (4 mL), the mixture was extracted with EtOAc (5 x

4 mL). The organic layers were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford the crude azidoacid, which was used in the next step without purification: *R_f* 0.40 (9:1 CHCl₃:MeOH); ¹H NMR (300 MHz, C₆D₆): δ 6.89 (s, 1H), 6.53 (s, 1H), 6.51 (s, 1H), 6.35 (s, 1H), 5.26 (d, *J* = 1.4 Hz, 1H), 5.17 (d, *J* = 1.3 Hz, 1H), 4.32 (s, 1H), 4.07 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.67 (dd, *J* = 14.4, 12.0, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 2.78 (dd, *J* = 14.4, 5.1 Hz, 1H).

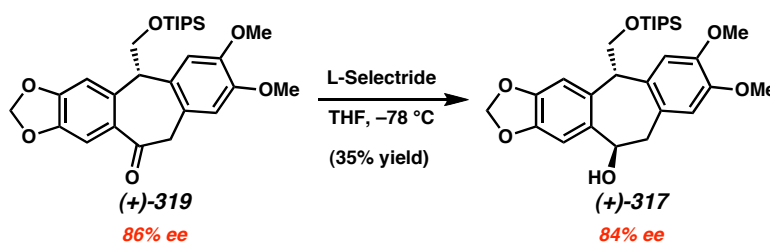
To a solution of crude azidoacid in EtOAc (1 mL) was added Pd/C (10% w/w, 30.4 mg, 0.029 mmol Pd, 1.0 equiv). The suspension was stirred under a balloon of H₂ (1 atm) for 12 h, after which it was filtered through a plug of Celite (MeOH eluent). Concentration under reduced pressure followed by purification by preparative TLC (0.25 mm, EtOAc eluent) afforded lactam (+)-**293** (4.8 mg, 49% yield over 3 steps) as a white solid. Lactam (+)-**293** was found to be >99% ee by chiral HPLC; [α]_D²⁶ +3.0° (*c* 0.89, CH₂Cl₂).



(+)-Amurensinine ((+)-282). To a solution of lactam (+)-**293** (9.8 mg, 0.029 mmol, 1.0 equiv) in THF (1 mL) was added lithium aluminum hydride (11.0 mg, 0.29 mmol, 10.0 equiv) at 0 °C. The reaction was then heated to 65 °C for 4 h. The mixture was cooled to 0 °C and diluted with CH₂Cl₂ (1 mL). H₂O (100 μL), aq NaOH (10% w/v, 100 μL), and H₂O (200 μL) were added sequentially dropwise. The biphasic mixture was warmed to 23 °C and stirred vigorously for 1 h. The reaction was then filtered through a

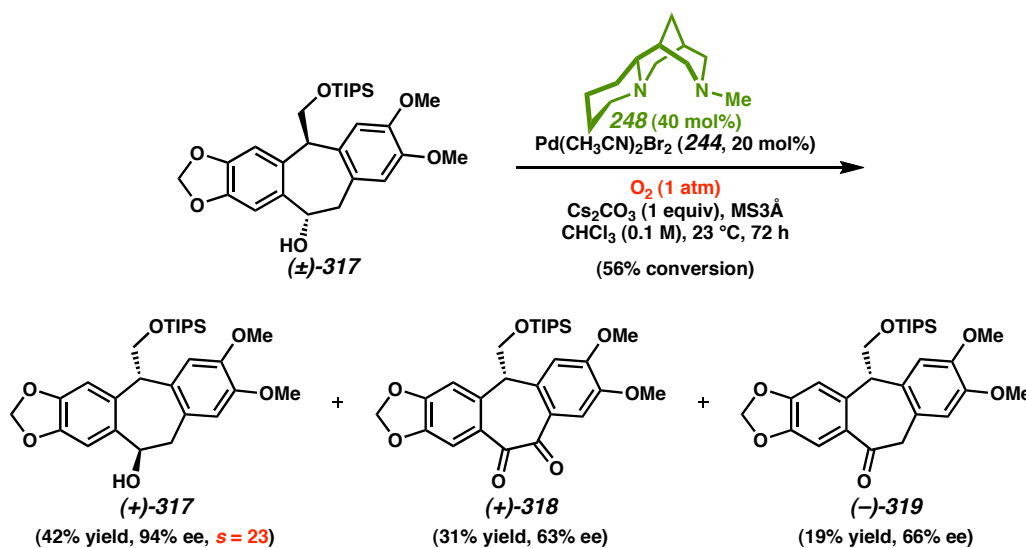
short plug of Celite (CH₂Cl₂ eluent) to remove suspended solids. After dilution with H₂O (2 mL) and aq NaOH (10% w/v, 2 mL), the biphasic mixture was extracted with CH₂Cl₂ (5 x 5 mL). The organic layers were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford the crude secondary amine, which was carried on to the next step without further purification.

To a solution of crude secondary amine in acetonitrile (1 mL) was added sodium cyanoborohydride (24.7 mg, 0.40 mmol, 13.8 equiv) followed by aq formaldehyde (37% w/w, 110 μL, 1.48 mmol, 51.0 equiv). After stirring for 5.5 h at 23 °C, the reaction was diluted with H₂O (2 mL) and extracted with CH₂Cl₂ (4 x 2 mL). The organic layers were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and purified by preparative TLC (0.25 mm, 19:1 CHCl₃:MeOH eluent) to afford (+)-amurensinine ((+)-**282**, 5.1 mg, 52% yield over 2 steps) as a colorless thin film. (+)-Amurensinine was found to be 99.0% ee by chiral HPLC (OJ column, 0.8 mL/min, 30% EtOH/hexanes, major peak 28.2 min, minor peak 20.5 min); [α]_D²⁵ +125.8° (c 0.49, CH₂Cl₂).



Hydroxysilane (+)-317. A solution of ketosilane (+)-**319** (12.7 mg, 0.025 mmol, 1.0 equiv, 85.9% ee by HPLC) in THF (0.5 mL) was cooled to -78 °C. L-Selectride (1.0 M in THF, 204 μL, 0.20 mmol, 8.0 equiv) was added dropwise. After stirring 15 min at -78 °C, saturated aq NH₄Cl (1 mL) was added. The mixture was allowed to warm to 23

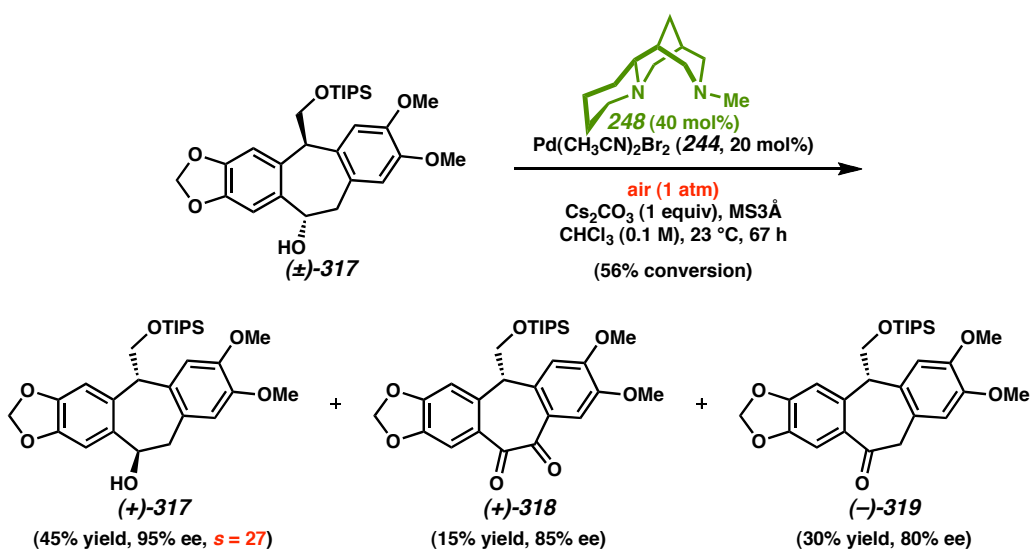
°C and was diluted with H₂O (1 mL). The mixture was extracted with EtOAc (4 x 2 mL). The organic layers were combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and purified by preparative TLC (0.25 mm, 3:2 hexanes:EtOAc eluent) to afford hydroxysilane (+)-**317** (4.5 mg, 35% yield, 83.7% ee by HPLC).



Oxidative Kinetic Resolution of Hydroxysilane (±)-**317** with Pd(CH₃CN)₂Br₂

(**244**), Diamine **248**, and O₂: Hydroxysilane (+)-**317**. To a 1 dram vial with stir bar was added oven-dried powdered 3Å molecular sieves (125 mg), Pd(CH₃CN)₂Br₂¹⁶ (**244**, 7.0 mg, 0.020 mmol, 0.20 equiv), CHCl₃ (0.5 mL),²¹ and diamine **248**²⁴ (7.8 mg, 0.040 mmol, 0.40 equiv). The mixture was cooled to -78 °C and alternately evacuated and backfilled with O₂ (3x). After allowing the mixture to warm to 23 °C, powdered anhydrous Cs₂CO₃ (32.6 mg, 0.10 mmol, 1.0 equiv) and a solution of hydroxysilane (±)-**317** (50.1 mg, 0.10 mmol, 1.0 equiv) and 1,4-bis(trimethylsilyl)benzene (internal ¹H NMR standard, 4.4 mg, 0.020 mmol, 0.20 equiv) in CHCl₃ (0.5 mL) were added. The reaction was stirred vigorously under a balloon of O₂ for 72 h. The reaction mixture was filtered through a

short plug of silica gel (EtOAc eluent) and evaporated under reduced pressure. Conversion was determined to be 56.3% based on ^1H NMR of remaining starting hydroxysilane relative to internal standard. Purification by flash chromatography (7:3→1:1 hexanes:Et₂O eluent) afforded hydroxysilane (+)-**317** (20.9 mg, 42% yield, 94.3% ee, $s = 23$), diketosilane (+)-**318** (16.0 mg, 62.9% ee), and ketosilane (–)-**319** (9.5 mg, 65.8% ee).



Oxidative Kinetic Resolution of Hydroxysilane (±)-**317** with Pd(CH₃CN)₂Br₂

(**244**), Diamine **248**, and Air: Hydroxysilane (+)-**317**. To a 1 dram vial with stir bar was added oven-dried powdered 3Å molecular sieves (125 mg), Pd(CH₃CN)₂Br₂ (**244**, 7.0 mg, 0.020 mmol, 0.20 equiv), CHCl₃ (0.5 mL),²¹ and diamine **248** (7.8 mg, 0.040 mmol, 0.40 equiv). Powdered anhydrous Cs₂CO₃ (32.6 mg, 0.10 mmol, 1.0 equiv) and a solution of hydroxysilane (±)-**317** (50.1 mg, 0.10 mmol, 1.0 equiv) and 1,4-bis(trimethylsilyl)benzene (internal ^1H NMR standard, 4.4 mg, 0.020 mmol, 0.20 equiv) in CHCl₃ (0.5 mL) were added. The reaction was stirred vigorously open to air for 67 h. The reaction mixture was filtered through a short plug of silica gel (EtOAc eluent) and

evaporated under reduced pressure. Conversion was determined to be 55.6% based on ^1H NMR of remaining starting hydroxysilane relative to internal standard. Purification by flash chromatography (7:3→1:1 hexanes:Et₂O eluent) followed by preparative TLC (0.25 mm, 3:2 hexanes:EtOAc eluent) afforded hydroxysilane (+)-**317** (22.4 mg, 45% yield, 95.3% ee, $s = 27$), diketosilane (+)-**318** (7.5 mg, 84.8% ee), and ketosilane (–)-**319** (15.0 mg, 80.3% ee).

5.6 Notes and References

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$$\frac{ee_{alc}}{ee_{ket}} = \frac{conv}{1 - conv} \quad \text{and} \quad s = \frac{\ln[(1 - conv)(1 - ee_{alc})]}{\ln[(1 - conv)(1 + ee_{alc})]}$$
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