Supporting Information for:

**Pd-Catalyzed Enantioselective Aerobic Oxidation of Secondary Alcohols: Applications to the Total Synthesis of Alkaloids**

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1. Materials and Methods.

Except as otherwise indicated, reactions were carried out under dry argon or nitrogen with dry, freshly distilled solvents. Dry solvents were dispensed from a delivery system that passes the solvents through packed columns (tetrahydrofuran, diethyl ether, acetonitrile, and methylene chloride: dry neutral alumina; hexane, benzene, and toluene: dry neutral alumina and Q5 reactant; dimethylformamide: activated molecular sieves). Anhydrous t-BuOH was purchased from Aldrich and used as received. 4,4′-di-t-butylbiphenyl (DBB) was recrystallized from EtOH and dried in vacuo over P2O5. Pd(sparteine)Cl2 was prepared according to a previously reported procedure.1 Hydrazoic acid was prepared as a solution in toluene.2 The solution was then dried over activated 4Å molecular sieves and sparged with argon prior to use. All other reagents were purchased from commercial sources and used as received.

Yields of reactions refer to chromatographically and spectroscopically pure compounds. Reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with Merck silica gel 60 F254 or aluminum oxide 60 F254. Visualization was by the quenching of UV fluorescence (λmax = 254 nm) or by staining with ceric ammonium molybdate, p-anisaldehyde, potassium permanganate or Dragendorff’s reagent (0.08% w/v bismuth subnitrate and 2% w/v KI in 3M aq. AcOH). Retention factors (Rf) are quoted to 0.01. Melting points were obtained using a Mel-Temp II melting point apparatus and are uncorrected. Infrared spectra were recorded either as a thin film on NaCl plate or as a KBr disc on a Perkin Elmer Paragon 1000 spectrometer with internal referencing. Absorption maxima (νmax) are reported in wavenumbers (cm⁻¹). Proton magnetic resonance spectra were recorded on Varian Mercury 300 (300 MHz) or Inova 500 (500 MHz) spectrometers. Proton assignments are supported by 1H-1H COSY, HMQC and HMBC spectra where necessary. Stereochemical assignments are supported by NOESY (1D and 2D) spectra. Chemical shifts (δH) are quoted in ppm and are referenced to tetramethylsilane (internal). Coupling constants (J) are reported in Hertz. Data are reported as follows:

Chemical shift, multiplicity, coupling constant(s), integration and assignment where possible. Carbon magnetic resonance spectra were recorded on Varian Mercury 300 (75 MHz) or Inova 500 (125 MHz) spectrometers. Carbon spectra assignments are supported where necessary by $^{13}$C-$^1$H (HMBC) correlations. Chemical shifts ($\delta_C$) are quoted in ppm to the nearest 0.1 ppm and are referenced to tetramethylsilane (internal). Low resolution mass spectra were obtained with JEOL AX-505H, SX-102A (CI/EI), Micromass Platform II and LCT (APCI/ES/LCMS) spectrometers. Only molecular ions, fractions from molecular ions and other major peaks are reported. High resolution mass spectra were obtained with a Micromass LCT (ES) spectrometer, and reported mass values are within the error limits of $\pm 5$ ppm mass units. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing chiralcel OD-H, OB-H and OJ as well as chiralpak AD and AS columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries Limited with visualization at 254 nm. Optical rotations were measured using a JASCO P-1010 polarimeter at 589 nm.

**Synthesis of (−)-aurantioclavine ((−)-1)**

[Diagram of the synthesis reaction]

2. Diol (±)-12. A flame-dried 1L round-bottom flask with a magnetic stir bar was charged with lithium metal (1.21 g, 0.174 mol) and evacuated and filled with argon (3 cycles). A solution of DBB (40.9 g, 0.154 mol) in THF (250 mL) was then added and the suspension sonicated for 1 h at 23 °C. The dark blue suspension was stirred vigorously for 8 h at 23 °C, then cooled to –78 °C. Isobutylene oxide (Aldrich, 9.26 mL, 0.104 mol) was added via syringe, and the deep red solution obtained was stirred for 5 min at –78 °C. To this solution was then transferred via cannula a solution of 1-tosyl-indole-4-carboxaldehyde (13, 10.40 g, 34.7 mmol) in THF (200 mL) pre-cooled to –78 °C. After the addition was complete, the reaction solution was stirred at –78 °C for 10 min. Saturated aqueous NH$_4$Cl (20 mL) was
3. Oxidative kinetic resolution of diol (±)-12. A 250mL round-bottom flask equipped with a stir bar was charged with racemic diol 12 (1.76 g, 4.71 mmol), [Pd(−)-sparteine)Cl₂] (193.9 mg, 0.471 mmol), MS 3A° (2.355 g) and t-BuOH (50 mL). The flask was evacuated and filled with O₂ (3 x, balloon) and the suspension stirred in an oil bath maintained at 40 °C in an atmosphere of O₂ (1 atm) for 24h. The conversion of diol to ketone 23 was monitored by ¹H NMR and HPLC analysis of aliquots of the
reaction mixture that were filtered through a pad of silica gel and concentrated under reduced pressure. The temperature of the oil bath was raised by 10 °C every 24h. After 98 hours the oxidation had proceeded to 59.2% conversion. The reaction mixture was then cooled, diluted with EtOAc (100 mL) and filtered through a pad of silica gel with copious washes (EtOAc). The filtrate was concentrated under reduced pressure to yield an oil, which was purified by silica gel chromatography (2:1 to 3:2 Hexanes/EtOAc) to yield β-hydroxyketone 23 (882.7 mg, 51% yield, 86% of theoretical maximum) and enantioenriched diol (639.4 mg, 36 % yield, 91% of theoretical maximum, 95.9% ee, kinetic resolution selectivity factor = 18.2). (S)-diol (−)-12: [α]_D^{25} −29.2° (c=1.03, CHCl₃) for a sample of > 99% ee by chiral HPLC analysis.

β-hydroxyketone 21: Rₚ 0.35 (3:2 Hexanes/EtOAc); H NMR (300 MHz, CDCl₃): 8.24 (d, J = 8.5 Hz, 2H), 7.79-7.72 (m, 4H), 7.50 (d, J = 4.0 Hz, 1H), 7.37 (m, 1H), 7.21 (d, J = 8.5 Hz, 1H), 3.18 (s, 2H), 2.32 (s, 3H), 1.33 (s, 6H); C NMR (75 MHz, CDCl₃): 202.6, 145.3, 135.6, 134.9, 129.9, 129.8, 129.4, 129.0, 126.7, 125.3, 123.8, 118.6, 109.7, 70.0, 49.2, 29.5, 21.5; IR (film, cm⁻¹): 3486, 3130, 2974, 1662, 1374, 1168, 765; HRMS (FAB, m/z): (MH⁺) calcd for (C_{20}H_{22}NO₄S⁺), 372.1270; found 372.1261.

β-hydroxyketone 23 was recycled to racemic diol for further oxidative kinetic resolution as follows: β-hydroxyketone 23 (4.53 g, 12.19 mmol) was dissolved in 20 mL THF and the solution cooled to −78 °C. Lithium aluminum hydride (509 mg, 13.4 mmol) was then added in small portions over 10 minutes. After the addition was complete the reaction mixture was stirred at −78 °C for 30 minutes and EtOAc (10 mL) was added to quench excess lithium aluminum hydride; the reaction mixture was then allowed to reach ambient temperature and 15% (w/v) aqueous NaOH (7 mL) was added. The suspension was filtered and the filter cake was washed with hot EtOAc (3 × 50 mL). The filtrate and washes were combined, dried (MgSO₄) and concentrated under reduced pressure to yield an off-white foam, which was purified by silica gel chromatography (3:2 Hexanes/EtOAc) to afford the racemic diol (±)-12 as an off-white foam, 4.30 g (95% yield).
4. Azidoalcohol 24. (Caution: Hydrazoic acid is highly toxic and an explosive if concentrated!) A flame dried 250 mL round bottom flask was charged with diol (−)-12 (642.7 mg, 1.72 mmol), which was then dissolved in toluene (140 mL). The solution was sparged with Ar for 15 minutes, then hydrazoic acid (1.125 M solution in toluene, 4.6 mL, 5.16 mmol) was added. The solution was cooled to −78 ºC and then PBu₃ (0.86 mL, 3.44 mmol) was added, followed by DIAD (0.78 mL, 3.96 mmol). Once the solution was homogeneous, the flask was transferred to a freezer maintained at −20 ºC. After 30 hours, the solution was allowed to warm to ambient temperature and the reaction quenched with silica gel (10 g). The suspension was concentrated under reduced pressure and then purified by silica gel chromatography (15:1 Benzene/MeCN) to afford azidoalcohol (+)-24 (551.1 mg, 80% yield). 

**Rf** 0.51 (1:1 Hexanes/EtOAc); 

**¹H NMR** (300 MHz, CDCl₃): 7.96 (d, J = 8.5 Hz, 1H), 7.78 (app. d, J = 8.5 Hz, 2H), 7.63 (d, J = 3.5 Hz, 1H), 7.35-7.21 (m, 4H), 6.85 (d, J = 3.5 Hz, 1H), 5.09 (dd, J = 11.0, 3.0 Hz, 1H), 2.33 (s, 3H), 2.09 (dd, J = 14.5, 10.0 Hz, 1H), 1.81 (dd, J = 14.5, 3.0 Hz, 1H), 1.30 (s, 3H), 1.27 (s, 3H); 

**¹³C NMR** (75 MHz, CDCl₃): 145.1, 135.1, 135.0, 132.8, 129.9, 128.2, 126.8, 126.6, 124.6, 121.1, 113.4, 106.6, 70.2, 61.2, 47.7, 30.1, 29.1, 21.5; 

**IR** (film, cm⁻¹): 3429, 2972, 2108, 1373, 1133; 

**HRMS** (FAB, m/z): (MH⁺) calcd for (C₂₀H₂₂N₄O₃S⁺), 398.1413; found 398.1425. 

Diol of 94.8% ee yielded azidoalcohol of 92% ee. [α]D²⁵ +94.2º (c=1.0, CHCl₃) for a sample of 92.5% ee by chiral HPLC analysis.
5. Sulfonamidoalcohol 11. Azidoalcohol (+)-24 (1.59 g, 4 mmol) was dissolved in 0.3 M HCl in methanol (20 mL). 10 wt. % Pd/C (425 mg, 0.4 mmol Pd) was added and the flask evacuated and back-filled with H₂ (balloon, x 3) and the suspension stirred under an atmosphere of H₂ for 2.5 hours, then filtered through a pad of celite with methanol washes. The filtrate and washes were combined, concentrated under reduced pressure and the residue azeotroped with toluene (2 x 10 mL), then dried in vacuo to yield a white solid. This solid was suspended in CH₂Cl₂ (20 mL) in the presence of o-nitrobenzenesulfonyl chloride (1.06 g, 4.8 mmol). The suspension was cooled to 0 °C and Et₃N (2.2 mL, 15.98 mmol) was added. The reaction mixture was allowed to warm to ambient temperature and stirred for 12 hours, then poured into 0.25 M aqueous HCl (100 mL) and extracted with EtOAc (4 x 50 mL). The EtOAc extracts were combined, dried (Na₂SO₄) and concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (2:1 Hexanes/EtOAc) to afford indole derivative (+)-11 as an off-white foam, 2.05 g (92% yield, 2 steps). Rf 0.17 (3:2 Hexanes/EtOAc); ¹H NMR (300 MHz, CDCl₃): 7.77 (app. d, J = 8.5 Hz, 2H), 7.69 (app. td, J = 9.0, 4.0 Hz, 1H), 7.50 (dd, J = 8.5, 1.0 Hz, 1H), 7.44 (d, J = 4.0, 1.0 Hz, 1H), 7.28 (d, J = 8.0, 1.0 Hz, 1H), 7.23 (td, J = 7.5, 1.0 Hz, 1H), 7.08 – 7.00 (m, 3H), 6.94 (d, J = 6.0 Hz, 1H), 6.84 (td, J = 7.5, 1.0 Hz, 1H), 6.77 (d, J = 3.5 Hz, 1H), 5.13 (ddd, J = 10.5, 6.0, 4.0 Hz, 1H), 2.38 (s, 3H), 2.22 (dd, J = 15.0, 10.5 Hz, 1H), 2.01 (bs, 1H), 1.79 (dd, J = 15.0, 4.5 Hz, 1H), 1.36 (s, 3H), 1.28 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 146.9, 145.2, 135.2, 134.5, 133.8, 133.4, 132.5, 131.4, 129.94, 129.85, 128.2, 127.0, 126.1, 124.4, 124.3, 121.5, 112.6, 106.3, 71.2, 54.7, 47.7, 31.4, 28.1, 21.6; IR (film, cm⁻¹): 3533, 3349, 2974, 2928, 1596, 1538, 1360, 1165, 1130, 1089, 910, 762; HRMS (FAB, m/z): (M⁺) calcd for (C₂₉H₂₇N₃O₇S₂⁺), 557.1290; found 557.1277. [α]D 25° +92.7° (c = 0.54, CHCl₃) for a sample of 92.8% ee.
6. Bromoindole 25. Sulfonamidoalcohol (+)-11 (2.01 g, 3.60 mmol) was dissolved in CH₂Cl₂ (35 mL) and the solution cooled to 0 °C. Pyridinium hydrobromide perbromide (PyHBr₃, 2.30 g, 7.2 mmol) was added in small portions over 10 minutes. On completion of the addition the reaction mixture was allowed to warm to ambient temperature and stirred for 1 h; then quenched with 1:1 v/v saturated aq. NaHCO₃/1M aq. Na₂S₂O₃ (20 mL). The suspension was diluted with brine (100 mL) and extracted with EtOAc (4 × 80 mL). The EtOAc extracts were combined, dried (Na₂SO₄) and concentrated under reduced pressure to yield a colorless oil, which was purified by silica gel chromatography (2:1 Hexanes/EtOAc) to afford the bromoindole (+)-25 as a white solid, 1.65 g (72% yield). R_f 0.18 (3:2 Hexanes/EtOAc); m.p. 191 °C; ¹H NMR (300 MHz, CDCl₃): 7.80 (app. d, J = 8.5 Hz, 2H, Ar-H), 7.73 (dd, J = 8.0, 0.5 Hz, 1H), 7.67 (s, 1H), 7.65 (dd, J = 7.5 Hz, 1Hz, 1H), 7.59 (dd, J = 8.0, 1.0 Hz, 1H), 7.41 (dt, J = 7.5, 1.5 Hz, 1H), 7.31 (m, 2H), 7.24 (m, 1H), 7.16 (dt, J = 7.5, 1.5 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.19 (td, J = 11.0, 4.5 Hz, 1H), 2.39 (s, 3H), 1.96 (dd, J = 15.0, 11.0 Hz, 1H), 1.83 (dd, J = 15.0, 4.0 Hz, 1H), 1.32 (s, 3H), 1.24 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 147.2, 145.7, 135.9, 134.6, 134.2, 133.8, 132.9, 131.9, 130.9, 130.1, 127.2, 126.3, 125.5, 124.7, 124.1, 122.2, 112.2, 95.6, 71.6, 49.7, 48.8, 32.0, 27.5, 21.6; IR (film, cm⁻¹): 3536, 2971, 1596, 1541, 1419, 1364, 1163, 1091, 736, 705; HRMS (FAB, m/z): (M⁺, ⁸¹Br) calcd for (C₂₆H₂₆BrN₃O₂S₂)⁺, 637.0375; found 637.0365. [α]D₂⁵ +5.5° (c = 1.16, MeCN) for a sample of 98.6% ee.

Enantioenrichment of the bromide (+)-25 was readily achieved as follows. A sample of the bromide (+)-25 (394.9 mg, 82% ee) was triturated with MeOH (4 × 10 mL), the solutions combined and concentrated to yield enantioenriched bromide, 317.6 mg (80% recovery, 98.7% ee by chiral HPLC analysis). Further trituration of the residue with 5 mL MeOH followed by concentration of the solution
yielded 21.6 mg of bromide (72.8% ee by chiral HPLC). The remaining residue was of low ee (ca. 5% ee).

7. Vinylindole 26. A flame dried 25 mL Schlenk flask equipped with a stir bar was charged with bromoindole (+)-25 (185.2 mg, 0.291 mmol) and [Pd(PPh₃)₄] (67.2 mg, 0.058 mmol, 20 mol%). The flask was then evacuated and filled with N₂ (× 3). Tributylvinyltin (127 µL, 0.436 mmol) was then added, followed by toluene (10 mL). The suspension was degassed by the freeze-pump-thaw method (–196 °C to –93 °C, N₂, 3 cycles). The flask was then sealed with a teflon stopcock and then placed in an oil bath maintained at 100 °C for 12h. The reaction mixture was then cooled and diluted with EtOAc (30 mL) and filtered through a pad of silica gel with copious EtOAc washes. The filtrate and washes were combined and concentrated under reduced pressure to yield a residue, which was redissolved in MeCN (50 mL) and the resulting solution was washed with hexanes (5 × 20 mL) to remove tin-containing impurities. The MeCN solution was concentrated and the residue obtained purified by silica gel chromatography (2:1 Hexanes/EtOAc) to afford vinylindole (+)-26 as an off-white foam, 127.4 mg (75% yield). Rᵣ 0.17 (3:2 Hexanes/EtOAc); ¹H NMR (300 MHz, CDCl₃): 7.80 (app. d, J = 8.5 Hz, 2H), 7.64-7.56 (m, 3H), 7.32-7.25 (m, 3H), 7.14-7.05 (m, 2H), 6.94-6.81 (m, 3H), 5.62 (d, J = 17.5 Hz, 1H), 5.55 (m, 1H), 5.39 (d, J = 10.5 Hz, 1H), 2.40 (s, 3H), 2.05 (dd, J = 15.0, 10.5 Hz, 1H), 1.79 (dd, J = 15.0, 3.5 Hz, 1H), 1.34 (s, 3H), 1.28 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 146.9, 145.3, 135.3, 135.0, 134.8, 133.9, 132.7, 131.6, 130.4, 130.0, 129.2, 127.1, 126.2, 124.7, 124.6, 123.6, 122.2, 121.1, 118.2, 112.3, 71.3, 51.9, 49.0, 31.5, 28.2, 21.6; IR (film, cm⁻¹): 3536 (b, s), 3354 (b, s), 2971 (s), 1541 (s), 1423 (m), 1366 (s), 1169 (s), 1090 (m), 736 (s); HRMS (FAB, m/z): (M⁺) calcd for (C₂₈H₂₉N₃O₇S₂⁺), 583.1447; found 583.1465; [α]D₂⁰ +40.6° (c = 1.04, CHCl₃) for a sample of 98.6% ee.
8. Diol 10. Vinyl indole 24 (127.1 mg, 0.218 mmol) was dissolved in THF (5 mL) and to the solution was added a solution of 9-BBN dimer (159.4 mg, 0.653 mmol) in THF (5 mL). The mixture was stirred at ambient temperature for 4 hours, then cooled to 0 °C. Absolute EtOH (2.0 mL) was added, followed (simultaneously) by NaOH (3M, 2.0 mL) and 30% H₂O₂ (2.0 mL). The mixture was stirred at 0 °C for 15 minutes, then allowed to warm to ambient temperature and stirred for 2 hours, then poured into 1M HCl (30 mL) and extracted with EtOAc (4 × 50 mL). The combined EtOAc extracts were dried (Na₂SO₄) and concentrated under reduced pressure to yield a yellow oil, which was purified by silica gel chromatography (Hexanes/EtOAc, 2:3 to 1:2) to afford diol 10 as a white foam (83 mg, 64% yield). R₁ 0.20 (1:2 Hexanes/EtOAc); ¹H NMR (300 MHz, CDCl₃): 7.78 (t, J = 2.0 Hz, 1H), 7.75 (t, J = 2.0 Hz, 1H), 7.58-7.48 (m, 3H), 7.29 (s, 1H), 7.22 (td, J = 7.5, 1.5 Hz, 1H), 7.12 (dd, J = 8.0, 1.5 Hz, 1H), 6.99 (dd, J = 7.5, 1.0 Hz, 1H), 6.82 (t, J = 8.0 Hz, 1H), 6.74 (td, J = 7.5, 1.0 Hz, 1H), 6.66 (d, J = 7.5, 1.0 Hz, 1H), 5.65 (m, 1H), 3.98 (m, 2H), 3.27 (m, 2H), 2.52 (bs, 2H), 2.37 (s, 3H), 2.09 (dd, J = 15.0, 11.0 Hz, 1H), 1.86 (dd, J = 15.0, 3.0 Hz, 1H), 1.76 (bs, 1H), 1.40 (s, 3H), 1.36 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 146.6, 145.2, 135.2, 135.0, 134.0, 132.6, 131.7, 129.9, 128.3, 127.4, 127.0, 124.8, 124.6, 124.4, 121.1, 119.0, 112.4, 71.2, 62.3, 51.0, 48.9, 31.1, 30.8, 29.5, 21.6; IR (film, cm⁻¹): 3350 (b, s), 1538 (s), 1366 (s), 1159 (s); HRMS (FAB, m/z): (M⁺) calcd for (C₂₈H₃₁N₃O₈S₂)⁺, 601.1552; found 601.1541.
9. **Tricyclic alcohol 9.** Diol **10** (81.1 mg, 0.135 mmol), along with triphenylphosphine (70.7 mg, 0.269 mmol) was dissolved in toluene (12 mL). The solution was cooled to 0 °C and DIAD (53 µL, 0.269 mmol) was added. The reaction mixture was allowed to reach 23 °C, concentrated under reduced pressure and purified by silica gel chromatography (Hexanes/EtOAc, 3:2 to 1:1) to afford tricyclic alcohol **9** as a colorless oil (76.8 mg, 97% yield). \( R_f 0.30 \) (1:1 Hexanes/EtOAc); \(^1\)H NMR (300 MHz, \( CD_6D_6 \)): 8.02 (d, \( J = 8.0 \) Hz, 1H), 7.63 (m, 2H), 7.26 (d, \( J = 8.0 \) Hz, 1H), 7.18 (m, 1H), 7.01 (t, \( J = 8.0 \) Hz, 1H), 6.87 (d, \( J = 7.0 \) Hz, 1H), 6.54 (app. d, \( J = 8.0, 2.0 \) Hz, 2H), 6.49 (dd, \( J = 8.0, 1.5 \) Hz, 1H), 6.36 (td, \( J = 7.5, 1.5 \) Hz, 1H), 6.25 (td, \( J = 8.0, 1.0 \) Hz, 1H), 5.82 [dd, \( J = 10.0, 3.0 \) Hz, 1H, C(4)H′], 4.18 [dt, \( J = 15.0, 5.5 \) Hz, 1H, C(5)H′H′], 3.50 [m, 1H, C(5)H′H′], 2.90 [m, 1H, C(6)H′H′], 2.55 [dt, \( J = 17.0, 4.5 \) Hz, 1H, C(6)H′H′], 2.04 (bs, 1H), 1.90 [dd, \( J = 15.0, 10.0 \) Hz, 1H, C(3)H′H′], 1.67 (s, 3H, Ar-CH₃), 1.45 [dd, \( J = 15.0, 3.0 \) Hz, 1H, C(3)H′H′], 1.13 [s, 3H, C(1′)H₃], 1.09 [s, 3H, C(1)H₃]; \(^{13}\)C NMR (75 MHz, \( CD_6D_6 \)): 148.7, 145.1, 138.4, 136.6, 136.3, 133.5, 133.2, 130.6, 130.5, 130.2, 128.9, 127.3, 125.1, 123.7, 123.6, 122.6, 120.0, 112.7, 70.1 [C(2)], 59.6 [C(4)], 49.2 [C(3)], 43.7 [C(5)], 30.2 [C(1′)], 30.1 [C(1)], 27.1 [C(6)], 21.4 (Ar-CH₃); IR (film, cm⁻¹): 3352 (b, m), 2970 (m), 1545 (s), 1372 (s), 1165 (s), 947 (m), 748 (m); HRMS (FAB, m/z): (M⁺) calcd for \( \text{C}_{28}\text{H}_{29}\text{N}_{3}\text{O}_{7}\text{S}_{2}^+ \), 583.1447; found 583.1457. gHMBC correlations observed: C(4)H ↔ C(5) and C(5)H′H′ ↔ C(4).

10. **Dehydration of tricyclic alcohol 9**

Various dehydration conditions for the dehydration of tricyclic alcohol **9** were examined. These are detailed in Table SI1 below.
### Table S11. Dehydration of tricyclic alcohol 9

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Products/Ratio 27:28</th>
<th>Yield</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Martin sulfurane, PhH, 23 °C, 5h</td>
<td>24:76</td>
<td>64%</td>
</tr>
<tr>
<td>2</td>
<td>SOCl₂, Pyridine, 0 °C → 23 °C, 3h</td>
<td>42:58</td>
<td>49%</td>
</tr>
<tr>
<td>3</td>
<td>POCl₃, pyridine, 0 °C → 23 °C, 3h</td>
<td>31:69</td>
<td>69%</td>
</tr>
<tr>
<td>4</td>
<td>Burgess reagent, PhH, 60 °C, 3.5h</td>
<td>40:60</td>
<td>67%</td>
</tr>
<tr>
<td>5</td>
<td>p-TsOH.H₂O, Toluene, 60 °C, 10h</td>
<td>&lt;5 &gt;95</td>
<td>_a</td>
</tr>
<tr>
<td>6</td>
<td>P₂O₅, PhH, 0°C → 23 °C, 3h</td>
<td>&lt;5 &gt;95</td>
<td>29%</td>
</tr>
<tr>
<td>7</td>
<td>Ph₃SiOReO₃, Et₂O, 0 °C → 23 °C, 10h</td>
<td>21:79</td>
<td>42% (83%)_b</td>
</tr>
</tbody>
</table>

*a10% conversion; _bBased on recovered starting material.


Various dehydration conditions for the dehydration of vinylindole 26, as well as of bromoindole 25 were examined. These are detailed in Table S12 below.
Table S12. Dehydration of bromoindole 25 and vinylindole 26

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conditions</th>
<th>Products/Ratio A:B</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>POCl₃, Pyridine, 0 °C → 23 °C, 6h</td>
<td>47:53</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>vinyl</td>
<td>Burgess reagent, benzene, 60 °C, 3.5h</td>
<td>26:74</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>vinyl</td>
<td>POCl₃, Pyridine, 0 °C → 23 °C, 6h</td>
<td>62:38</td>
<td>56% (29)</td>
</tr>
<tr>
<td>4</td>
<td>vinyl</td>
<td>p-TsOH.H₂O, benzene, 60 °C, 9.5h</td>
<td></td>
<td>43%</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>Martin sulfurane, MeCN, 23 °C, 10h</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>vinyl</td>
<td>Martin sulfurane, MeCN, 23 °C, 10h</td>
<td>complex mixture</td>
<td>–</td>
</tr>
</tbody>
</table>

12. Bis-olefins 29 and 30. Vinylindole 26 (375 mg, 0.643 mmol) was dissolved in pyridine (11 mL) and the solution cooled to 0 °C. POCl₃ (180 µL, 1.928 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 15 minutes, then allowed to warm to 23 °C. After 6 hours, the reaction mixture was diluted with EtOAc (100 mL), poured into 1M HCl (100 mL) and the phases separated. The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with 1 M HCl (100 mL), brine (100 mL) dried (MgSO₄) and concentrated under reduced pressure to yield an oil,
which was purified by silica gel chromatography (Hexanes/EtOAc, 3:1) to afford a mixture of olefin isomers 29:30 = 62:38 as an off-white foam (345.5 mg, 95% combined yield). The olefin isomers could be separated for characterization using silver nitrate-impregnated silica gel as follows:

To 100 g of silica gel was added 100 mL of a 5% w/v solution of AgNO₃ in MeCN. The slurry obtained was concentrated under reduced pressure and dried in vacuo to yield AgNO₃-impregnated silica gel. Thin layer chromatography analysis was performed using glass plates precoated with Merck silica gel 60 F₂₅₄ that had been dipped in 5% w/v AgNO₃ solution in MeCN and air-dried. Visualization of compound was carried out by staining with CAM. 401.5 mg of a mixture of olefin isomers A and B (29:30 = 68:32) was purified using the silver-nitrate impregnated silica gel (3 × 20 cms column, 30:1 toluene/Et₂O) to afford (−)-29 (252.4 mg) and (+)-30 (121.6 mg) as off-white foams.

Isomer 29: Rⱼ 0.26 (2:1 Hexanes/EtOAc on SiO₂); Rⱼ 0.29 (19:1 Toluene/Et₂O on SiO₂ containing 5% w/w AgNO₃); ¹H NMR (300 MHz, CDCl₃): 7.79 (app. td, J = 8.5, 2.0 Hz, 2H), 7.72 (dd, J = 8.0, 1.0 Hz, 1H), 7.67 (dd, J = 8.0, 1.0 Hz, 1H), 7.60 (d, J = 1.0 Hz, 1H), 7.46-7.39 (m, 2H), 7.28 (app. d, J = 8.5 Hz, 2H), 7.17-6.96 (m, 4H), 5.94 (t, J = 8.5 Hz, 1H), 5.74 (d, J = 8.5 Hz, 1H), 5.61 (dd, J = 17.0, 1.5 Hz, 1H), 5.39 (dd, J = 10.5, 2.0 Hz, 1H), 5.24 (td, J = 8.5, 1.5 Hz, 1H), 2.38 (s, 3H), 1.72 (d, J = 1.5 Hz, 3H), 1.58 (d, J = 1.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): 147.0, 145.3, 138.4, 135.1, 135.0, 134.7, 134.0, 132.8, 131.8, 130.5, 130.0, 129.1, 127.0, 126.9, 124.73, 124.69, 123.5, 123.3, 122.4, 121.6, 118.0, 112.8, 52.8, 25.5, 21.6, 18.5; IR (film, cm⁻¹): 3351 (m), 1596 (m), 1540 (s), 1367 (s), 1168 (s), 1146 (s), 999 (m), 760 (m), 731 (m), 668 (s); HRMS (FAB, m/z): (M⁺) calcd for (C₂₈H₂₇N₂O₆S₂⁺), 565.1341; found 565.1323; [α]₀²⁶ = −45.7º (c = 1.02, CHCl₃).

Isomer 30: Rⱼ 0.26 (2:1 Hexanes/EtOAc on SiO₂); Rⱼ 0.32 (5:1 Toluene/Et₂O on SiO₂ containing 5% w/w AgNO₃); ¹H NMR (300 MHz, CDCl₃): 7.80 (app. d, J = 7.5 Hz, 2H), 7.67-7.58 (m, 3H), 7.37-7.27 (m, 3H), 7.11-7.08 (m, 2H), 6.98-6.86 (m, 2H), 5.82 (d, J = 7.5 Hz, 1H), 5.62 (dd, J = 17.0, 2.0 Hz, 1H), 5.37 (m, 1H), 4.82 (m, 2H), 2.44 (m, 2H), 2.39 (s, 3H), 1.62 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 147.0, 145.3, 140.3, 135.0, 134.9, 134.8, 134.0, 132.8, 131.8, 130.3, 130.0, 129.0, 127.1, 126.5, 124.7,
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124.6, 123.6, 122.1, 120.8, 118.4, 115.3, 112.5, 52.3, 46.1, 21.7, 21.6; IR (film, cm⁻¹): 3340 (b,m), 1540 (s), 1364 (s), 1170 (s); HRMS (FAB, m/z): (MH⁺) calcd for (C₂₉H₂₈N₃O₆S₂), 566.1420; found 566.1428; [α]D₂⁶ +16.8° (c = 1.0, CHCl₃).

13. Sulfonamido alcohol 31. A mixture of (−)-29 and (+)-30 (29:30 = 62:38, 345.5 mg, 0.611 mmol) was dissolved in THF (3 mL). A solution of 9-BBN dimer (447.2 mg, 1.832 mmol) in THF (5 mL) was added dropwise and the reaction mixture stirred at ambient temperature for 10 hours, then cooled to 0 °C. EtOH (1.0 mL) was added followed by (simultaneously) NaOH (3 M, 1.0 mL) and 30% H₂O₂ (1.0 mL). The reaction mixture was stirred at 0 °C for 20 minutes, then allowed to warm to 23 °C. After 4 hours, the reaction mixture was poured into 1M HCl (100 mL) and extracted with EtOAc (4 × 60 mL). The EtOAc extracts were dried (Na₂SO₄) and concentrated under reduced pressure to yield an oil, which was purified by silica gel chromatography (Hexanes/EtOAc, 3:2), then again using Benzene/MeCN (6:1) to afford the desired alcohol (−)-31 derived from (+)-29 as a white foam (106.1 mg, 48% yield). R, 0.25 (6:1 Benzene/MeCN); ¹H NMR (300 MHz, CDCl₃): 7.78-7.69 (m, 4H), 7.52 (s, 1H), 7.46-7.38 (m, 2H), 7.26 (app. d, J = 8.0 Hz, 2H), 7.08 (m, 2H), 6.97 (m, 1H), 5.99 (t, J = 8.5 Hz, 1H), 5.79 (d, J = 8.5 Hz, 1H), 5.22 (d, J = 8.5 Hz, 1H), 4.01 (t, J = 6.5 Hz, 2H), 3.26 (t, J = 6.5 Hz, 2H), 2.36 (s, 3H), 1.79 (s, 3H), 1.57 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): 147.0, 145.2, 139.0, 135.5, 134.0, 139.0, 133.7, 132.8, 132.0, 130.3, 129.9, 127.9, 126.9, 124.9, 124.8, 124.5, 123.3, 121.5, 118.8, 113.0, 62.0, 52.4, 30.6, 25.5, 21.6, 18.6; IR (film, cm⁻¹): 3351 (b,m), 2916 (m), 1595 (m), 1538 (s), 1366 (s), 1166 (s), 814 (s), 703 (s); HRMS (FAB, m/z): (M⁺) calcd for (C₂₉H₂₈N₃O₆S₂), 583.1447; found 583.1425; [α]D₂⁶ −25.9° (c = 0.36, CHCl₃) for a sample of >99% ee.
14. **Tricyclic indole 27.** Alcohol (−)-31 (111.1 mg, 0.190 mmol) and triphenylphosphine (74.9 mg, 0.286 mmol) were dissolved in Toluene (10 mL). The solution was cooled to 0 °C and DIAD (57 μL, 0.286 mmol) was added. The reaction mixture was allowed to warm to 23 °C, concentrated under reduced pressure and purified by silica gel chromatography (Hexanes/EtOAc, 9:4 and Benzene/MeCN, 20:1) to yield pure tricyclic indole (−)-27 as an off-white foam, 101.9 mg (95% yield). $R_f$ 0.54 (1:1 Hexanes/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): 7.80 (d, $J = 8.0$ Hz, 1H), 7.75 (app. d, $J = 8.5$ Hz, 2H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.47 (app. dd, $J = 6.5$, 1.5 Hz, 2H), 7.30-7.23 (m, 4H), 7.18 (t, $J = 8.0$ Hz, 1H), 6.92 (d, $J = 7.5$ Hz, 1H), 6.05 (dd, $J = 9.0$, 1.0 Hz, 1H), 5.31 (dt, $J = 9.0$, 1.5 Hz, 1H), 4.12 (dt, $J = 15.0$, 5.0 Hz, 1H), 3.72 (m, 1H), 3.18 (m, 1H), 3.05 (m, 1H), 2.37 (s, 3H), 1.66 (d, $J = 1.0$ Hz, 3H), 1.62 (d, $J = 1.0$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): 148.1, 145.0, 137.5, 136.4, 135.8, 135.2, 133.6, 133.0, 130.9, 129.9, 129.8, 127.6, 126.9, 124.4, 123.8, 122.9, 121.9, 121.7, 119.6, 112.1, 59.5, 43.9, 28.2, 25.8, 21.6, 18.3; IR (film, cm$^{-1}$): 1544 (s), 1371 (s), 1165 (s); HRMS (FAB, m/z): (MH$^+$) calcd for (C$_{28}$H$_{39}$N$_3$O$_6$S$_2$)$^+$, 566.1420; found 566.1434; [$\alpha$]$_D^{28}$−93.2º (c = 1.0, CHCl$_3$) for a sample of 97.6% ee.

15. **(R)−(−)-Aurantioclavine ((−)-1).** Tricyclic indole (−)-27 (36.8 mg, 65.1 μmol) was suspended in DMF (1 mL) with K$_2$CO$_3$ (27.0 mg, 0.195 mmol). PhSH (20 μL, 0.195 mmol) was added and the mixture stirred at ambient temperature for 12 hours, then diluted with EtOAc (100 mL) and washed with 0.5 M NaOH (4 × 30 mL), brine (1 × 50 mL), dried (K$_2$CO$_3$) and concentrated to yield a yellow
solid, which was purified by silica gel chromatography on Et$_2$N-washed silica gel (Hexanes/EtOAc, 3:1 → Hexanes/EtOAc/Et$_2$N, 33:17:1) to yield amine 32 as a colorless oil, 13.0 mg (53% yield). $R_f$ 0.21 (Hexanes/EtOAc/Et$_2$N, 33:17:1 on Et$_2$N-washed SiO$_2$); $^1$H NMR (300 MHz, CDCl$_3$): 7.87 (d, $J = 8.5$ Hz, 1H), 7.73 (d, $J = 8.5$ Hz, 2H), 7.36 (s, 1H), 7.22-7.17 (m, 3H), 6.95 (d, $J = 7.5$ Hz, 1H), 5.36 (app. dt, $J = 9.0$, 1.5 Hz, 1H), 4.80 (d, $J = 9.0$ Hz, 1H), 3.46 (m, 1H), 3.07-2.90 (m, 3H), 2.33 (s, 3H), 1.82 (d, $J = 1.0$ Hz, 3H), 1.79 (d, $J = 1.0$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): 144.6, 139.2, 136.0, 135.3, 134.1, 129.7, 128.9, 127.1, 126.8, 124.0, 122.5, 122.3, 121.9, 111.7, 62.1, 47.8, 30.7, 25.8, 21.5, 18.3; IR (film, cm$^{-1}$): 2915 (s), 1598 (s), 1368 (s), 1177 (s), 1093 (s), 758 (s); HRMS (EI, m/z): (M$^+$) calcd for (C$_{22}$H$_{30}$N$_2$O$_2$S$^+$), 380.1559; found 380.1577.

To amine 32 (21.2 mg, 56 µmol) was added TBAF (1 M in THF, 1.0 mL). The resulting solution was heated at 70 °C for 12 hours, cooled and concentrated under reduced pressure. Saturated aqueous NaHCO$_3$ (20 mL) was added and the aqueous phase extracted with EtOAc (3 × 20 mL). The extracts were combined, dried (K$_2$CO$_3$) and concentrated under reduced pressure to afford a residue, which was purified by silica gel chromatography on Et$_2$N-washed SiO$_2$ (Hexanes/EtOAc/Et$_2$N, 33:17:1) to afford (−)-aurantioclavine ((−)-I) as an off-white solid, 8.6 mg (68% yield). $R_f$ 0.22 (Hexanes/EtOAc/Et$_2$N, 25:25:1 on Et$_2$N-washed SiO$_2$); $^1$H NMR (300 MHz, CDCl$_3$): 8.13 (bs, 1H), 7.23 (td, $J = 8.0$, 1.0 Hz, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.01 (t, $J = 1.0$ Hz, 1H), 6.84 (td, $J = 7.0$, 1.0 Hz, 1H), 3.56 (m, 1H), 3.18-2.96 (m, 3H), 1.85 (d, $J = 1.5$ Hz, 3H), 1.84 (d, $J = 1.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): 138.5, 137.1, 133.2, 127.7, 125.4, 121.5, 120.9, 117.8, 115.8, 109.1, 62.6, 48.9, 31.0, 25.8, 18.3; IR (KBr, cm$^{-1}$): 3409 (b), 3292 (s), 2921 (s), 1615 (m), 1572 (m), 740 (s); HRMS (EI, m/z): (M$^+$) calcd for (C$_{15}$H$_{18}$N$_2$), 226.1470; found 226.1472; $[\alpha]_D^{28.6}$ $^{3}$−$^{30.1}$$^\circ$ (c = 0.38, CHCl$_3$) [Lit.$^3$ $[\alpha]_D^{220}$ $^{3}$−$^{34}$$^\circ$ (c = 1.25, CHCl$_3$)]

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### Table SI3. Chiral HPLC assay conditions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conditions (flow rate = 1mL/min unless otherwise specified)</th>
<th>Retention times of Enantiomers</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>Column</td>
<td>Solvent system</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>![Compound Image]</td>
<td>OD-H</td>
<td>5% EtOH/Hexanes</td>
</tr>
<tr>
<td>![Compound Image]</td>
<td>OD-H</td>
<td>5% EtOH/Hexanes</td>
</tr>
<tr>
<td>![Compound Image]</td>
<td>OD-H</td>
<td>6% EtOH/Hexanes</td>
</tr>
<tr>
<td>![Compound Image]</td>
<td>AD</td>
<td>20% IPA/Hexanes</td>
</tr>
<tr>
<td>![Compound Image]</td>
<td>AD</td>
<td>20% IPA/Hexanes</td>
</tr>
<tr>
<td>![Compound Image]</td>
<td>OD-H</td>
<td>10% IPA/Hexanes</td>
</tr>
<tr>
<td>![Compound Image]</td>
<td>AD</td>
<td>20% IPA/Hexanes</td>
</tr>
<tr>
<td>![Compound Image]</td>
<td>OD-H</td>
<td>15% EtOH/Hexanes</td>
</tr>
</tbody>
</table>
17. β-Ketoester SI2. To a solution of homoveratric acid (SI1, 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 4 drops of DMF. After stirring for 3 h, the reaction mixture was concentrated under reduced pressure. The resulting crude acid chloride was then dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °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 °C for 2 min, the mixture was stirred at 23 °C for 8 h. The reaction was then washed with 10% aq HCl (10 mL) followed by H₂O (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude mixture was then dissolved in absolute EtOH (10 mL) and refluxed at 75 °C. After 11 h, the reaction mixture was cooled to 23 °C and concentrated under reduced pressure. Purification by flash chromatography (5:1→3:1→1:1 hexanes:EtOAc eluent) provided β-ketoester SI2 (1.31 g, 96% yield) as a clear oil. The characterization data matched the data reported in the literature.⁴

18. Diazoketoester 33. To a cooled solution (0 °C) of β-ketoester SI2 (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 NEt₃ (698 µL, 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 10% aq NaOH (10 mL). The aqueous layer was then extracted with Et₂O (3 x 10 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under

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Reduced pressure. Purification by flash chromatography (4:1 hexanes:EtOAc eluent) provided diazoketoester 33 (487 mg, 99% yield) as a clear oil: $R_f$ 0.50 (1:1 hexanes:EtOAc); $^1$H NMR (300 MHz, C$_6$D$_6$): $\delta$ 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, C$_6$D$_6$): $\delta$ 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 [C$_{14}$H$_{16}$N$_2$O$_5$]$^+$, 292.1059; found, 292.1070.

19. β-Ketoester 18. A flask equipped with an addition funnel and an N$_2$ inlet was charged with a catalytic amount of Rh$_2$(OAc)$_4$ (138 mg, 0.31 mmol, 0.01 equiv) and CH$_2$Cl$_2$ (140 mL). A solution of diazoester 33 (9.12 g, 31.20 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (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 18 (7.88 g, 96% yield) as a white solid: $R_f$ 0.52 (1:1 hexanes:EtOAc); mp 117 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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, CDCl$_3$): $\delta$ 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 [C$_{14}$H$_{16}$O$_5$]$^+$, 264.0998; found, 264.1003.
20. **Ketoester (±)-16.** To a solution of aryne precursor 17\(^{5}\) (898 mg, 2.62 mmol, 1.7 equiv) in dry acetonitrile (9 mL) was added β-ketoester 18 (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 17 was consumed (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 Et\(_2\)O (3 x 15 mL). The organic layers were combined, dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes:EtOAc eluent) provided ketoester (±)-16 (348 mg, 57% yield) as a clear oil: \(R_f \) 0.23 (1:1 hexanes:EtOAc); \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)): \(\delta \) 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); \(^{13}\)C NMR (75 MHz, C\(_6\)D\(_6\)): \(\delta \) 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 [C\(_{21}\)H\(_{20}\)O\(_7\)]\(^+\), 384.1209; found, 384.1212.

21. Hydroxyester (±)-15. To a solution of ketoester (±)-16 (52.9 mg, 0.138 mmol, 1.0 equiv) in THF (1.5 mL) at –78 °C was added dropwise a 1.0 M solution of L-Selectride in THF (200 µL, 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, filtered, and concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes:EtOAc eluent) provided hydroxyester (±)-15 (51.4 mg, 97% yield) as a yellow solid: Rf 0.33 (1:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): 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): [M]+ calcd for [C₂₁H₂₂O₇]⁺, 386.1366; found, 386.1366.
22. Kinetic Resolution of Hydroxyester (±)-15: Hydroxyester (−)-15. To a 1 dram vial with stir bar was added oven-dried powdered 3Å molecular sieves (190 mg). After cooling, Pd(sparteine)Cl₂ (31.5 mg, 0.076 mmol, 0.20 equiv) followed by CHCl₃ (750 µL, stabilized with amylene) and (−)-sparteine (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 O₂ (3 ×). After allowing the mixture to warm to 23 °C, powdered anhydrous Cs₂CO₃ (124.5 mg, 0.38 mmol, 1.0 equiv) followed by a solution of hydroxyester (±)-15 (147.7 mg, 0.38 mmol, 1.0 equiv) in CHCl₃ (750 µL) were added, and the reaction was stirred vigorously under a balloon of O₂ 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 (−)-15 (56.8 mg, 39% yield) and ketoester (+)-7 (36.6 mg, 25% yield). Hydroxyester (−)-15 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); [α]$_D^{25}$ = −64.3° (c 0.78, CHCl₃, 87.9% ee). Ketoester (+)-16 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); [α]$_D^{25}$ = +19.9° (c 0.47, CHCl₃, 84.8% ee).
23. Lactam (++)-34. To a solution of hydroxyester (--)15 (9.7 mg, 0.025 mmol, 1.0 equiv) in toluene (500 μL) at 0 °C was added (PhO)₂P(O)N₃ (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 H₂O (3 mL) and extracted with Et₂O (3 x 3 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude azide was passed through a short pad of SiO₂ (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, 0.014 mmol Pd, 0.56 equiv). The reaction flask was placed under a balloon of H₂ gas (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 (++)-34 was used in the next step without further purification: Rf 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 (125 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 [C₉H₁₈NO₅]⁺ 340.1185; found, 340.1181. Lactam (++)-34 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).
24. (+)-Amurensine ((+)-2). To a solution of crude lactam (+)-34 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), 15% aq NaOH (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. To a solution of the crude secondary amine in acetonitrile (1 mL) was added NaBH₄CN (10 mg, 0.159, 6.4 equiv) and aqueous formaldehyde (37 wt %, 50 µL, 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, filtered, and concentrated under reduced pressure. Purification by preparative TLC on silica gel (0.25 mm, 9:1 CHCl₃:MeOH eluent) provided (+)-amurensine ((+)-2, 1.5 mg, 17% yield for 4 steps) as a colorless thin film: Rₜ 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 λₘₐₓ 294 nm, shoulders at 232 and 250 nm, λₘᵢₙ at 263 nm; [α]²⁵D +82.8° (c 0.035, CH₂Cl₂) [lit. ⁶ [α]²₀D −145.0° (c 1.0, CH₂Cl₂)].

25. Lactone 35. To a solution of hydroxyester (±)-15 (11.6 mg, 0.03 mmol, 1.0 equiv) in PhCH$_3$ (1 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 44.9 µL, 45.7 mg, 0.30 mmol, 10.0 equiv). After 20 h, the reaction mixture was diluted with H$_2$O (2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, concentrated under reduced pressure. The residue was purified by flash chromatography (3:2 hexanes:EtOAc) to afford lactone 35 (4.8 mg, 47% yield) as a foamy white solid: $R_f$ 0.33 (1:1 hexanes:EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) 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); $^{13}$C NMR (126 MHz, CDCl$_3$) 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 [C$_{19}$H$_{16}$O$_6$]$^+$, 340.0947; found, 340.0941.

26. Alcohol (±)-37. To a solution of hydroxyester (±)-15 (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 10% w/v aq sodium potassium tartrate (5 mL). After warming to 23 °C and stirring vigorously for 1 h, the biphasic mixture was diluted with H$_2$O (10 mL) and extracted with EtOAc (4 x 20 mL). The organic layers were combined, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford the crude diol,
which was carried on to the next step without further purification. Diol: $R_f$ 0.12 (2:3 hexanes:EtOAc); $^1$H NMR (300 MHz, $C_6D_6$): $\delta$ 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 °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 $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (2:3 hexanes:Et$_2$O eluent) provided alcohol (±)-37 (85.8 mg, 86% yield over 2 steps) as a white solid: $R_f$ 0.28 (3:2 hexanes:EtOAc); $^1$H NMR (300 MHz, $C_6D_6$): $\delta$ 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, $C_6D_6$): $\delta$ 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): [M]$^+$ calcd for $[C_{23}H_{46}O_7Si]^+$, 500.2594; found, 500.2598.

![Reaction Diagram](image_url)

27. Ketone (±)-39 by Dess-Martin Periodinane Oxidation. To a solution of alcohol (±)-37 (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$_2$O (2 mL) and filtered through a short plug of
Celite (Et₂O eluent). The filtrate was concentrated under reduced pressure and purified by preparative TLC (7:3 hexanes:EtOAc eluent) to afford ketone (±)-39 (7.9 mg, 79% yield) as a colorless oil: \( R_f \) 0.50 (3:2 hexanes:EtOAc); \(^1\)H NMR (300 MHz, \( C_6D_6 \)) \( \delta \) 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), 3.42 (s, 3H), 1.00 (comp. m, 21H); \(^13\)C NMR (75 MHz, \( C_6D_6 \)) \( \delta \) 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): [M]+ calcd for \([C_{28}H_{38}O_6Si]\)+, 498.2438; found, 498.2433.

28. Diketone (±)-38 by MnO₂ Oxidation. To a solution of alcohol (±)-37 (13.2 mg, 0.026 mmol, 1.0 equiv) in \( CH_2Cl_2 \) (1 mL) was added MnO₂ (activated, 22.9 mg, 0.26 mmol, 10.0 equiv). After 19 h, more MnO₂ (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 (7:3 hexanes:EtOAc eluent) to afford diketone (±)-38 (5.4 mg, 41% yield) as a yellow solid: \( R_f \) 0.35 (3:2 hexanes:EtOAc); \(^1\)H NMR (300 MHz, \( C_6D_6 \)) \( \delta \) 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, \( C_6D_6 \)) \( \delta \) 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): [M+H]+ calcd for \([C_{28}H_{37}O_7Si]\)+, 513.2309; found, 513.2313.
29. Diketone (±)-38 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 then pyridine (2.6 µL, 2.5 mg, 0.032 mmol, 0.80 equiv) were allowed to stir at 80 °C under O₂ atmosphere (balloon) for 10 min. Alcohol (±)-37 (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 (3:2 hexanes:EtOAc eluent) to afford diketone (±)-38 (12.1 mg, 61% yield) as a yellow solid.

30. Radical Inhibitor Screen in the Oxidative Kinetic Resolution of Alcohol (±)-37. To a 1 dram vial with stir bar was added oven-dried powdered 3Å molecular sieves (50 mg), Pd(sparteine)Cl₂ (8.2 mg, 0.02 mmol, 0.20 equiv), CHCl₃ (stabilized with amylenes, 0.5 mL), and (−)-sparteine (4.6 µL, 0.02 mmol, 0.20 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), the appropriate additive (0.020 mmol, 0.20 equiv), and a solution of alcohol (±)-37 (50.1 mg,
0.10 mmol, 1.0 equiv) in CHCl₃ (0.5 mL) were added. The reaction was stirred vigorously under a balloon of O₂ 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 (3:2 hexanes:EtOAc eluent) afforded alcohol (–)-37, diketone (–)-38, and ketone (–)-39, as shown in Table SI4. The enantiomeric excess of alcohol (–)-37 was determined by chiral HPLC (AD column, 1.0 mL/min, 5% EtOH/hexanes, major peak 13.0 min, minor peak 21.0 min); [α]²⁵D −24.4° (c 0.86, C₆H₆, >99% ee). The enantiomeric excess of diketone (–)-38 was determined by chiral HPLC (AD column, 1.0 mL/min, 5% EtOH/hexanes, major peak 63.8 min, minor peak 24.7 min); [α]²⁵D −39.9° (c 1.21, C₆H₆, 73.9% ee). The enantiomeric excess of ketone (–)-39 was determined by chiral HPLC (AD column, 1.0 mL/min, 5% EtOH/hexanes, major peak 20.6 min, minor peak 10.7 min); [α]²⁵D +10.6° (c 0.65, C₆H₆, 76.8% ee).

Table SI4. Radical inhibitor screen in the oxidative kinetic resolution

<table>
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<th>Additive</th>
<th>Alcohol % yield (ee)</th>
<th>Diketone % yield (ee)</th>
<th>Ketone % yield (ee)</th>
<th>% Conversion</th>
<th>s⁹</th>
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<td>None</td>
<td>36 (97)</td>
<td>28 (83)</td>
<td>19 (76)</td>
<td>54</td>
<td>44</td>
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<tr>
<td>BHT</td>
<td>47 (95)</td>
<td>49 (82)</td>
<td>--</td>
<td>54</td>
<td>36</td>
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<tr>
<td>Tetracyanoethylene</td>
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<td>8 (--)</td>
<td>--</td>
<td>8</td>
<td>--</td>
</tr>
<tr>
<td>2-methyl-2-butene</td>
<td>47 (99)</td>
<td>46 (79)</td>
<td>--</td>
<td>56</td>
<td>47</td>
</tr>
</tbody>
</table>

⁹ % Conversion determined relative to alcohol ee and diketone ee according to the equation: C/(1-C) = eeₐlk/eeₐlk(dikets) where C = conversion. Selectivity factor (s) determined using the equation s = kₕₐₛₜ/kₕₖₖₜ = ln[(1-C)(1-ee)/ln[(1-C)(1+ee)], where ee is the enantiomeric excess of recovered alcohol. Reaction run for 72 h. No ketone recovered.

31. Azidoalcohol (–)-40. To a solution of alcohol (–)-37 (100.1 mg, 0.20 mmol, 1.0 equiv) in PhCH₃ (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 179 µL, 1.20 mmol, 6.0 equiv) followed by
Krishnan, Ramtohul, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S34
diphenylphosphoryl azide (259 μL, 1.20 mmol, 6.0 equiv) at 0 ºC. After stirring 6 h at 0 ºC, the
reaction was quenched by addition of H₂O (25 mL). The mixture was then extracted with Et₂O (3 x 30
mL). The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated under reduced
pressure. The crude azidosilane was carried on to the next step without further purification. To a
solution of the crude azidosilane in THF (2 mL) was added tetrabutylammonium fluoride (1 M in THF,
2.0 mL, 2.0 mmol, 10.0 equiv). The reaction was warmed to 45 ºC for 5 h. The solution was allowed to
cool to 23 ºC and diluted with EtOAc (40 mL). The solution was washed with H₂O (3 x 20 mL) and
saturated aq NaCl (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure.
Purification by flash chromatography (7:3 hexanes:EtOAc eluent) followed by preparative TLC (0.5
mm, 1:1 hexanes:EtOAc eluent) afforded azidoalcohol (–)-40 (45.9 mg, 62% yield over 2 steps) as a
white foam: R₉ 0.44 (2:3 hexanes:EtOAc); ¹H NMR (300 MHz, C₅D₅); δ 7.03 (s, 1H), 6.67 (s, 1H), 6.54
(s, 1H), 6.40 (s, 1H), 5.31 (d, J = 1.4 Hz, 1H), 5.27 (d, J = 1.3 Hz, 1H), 4.27 (dd, J = 10.8, 4.6 Hz, 1H),
4.04-3.90 (comp. m, 2H), 3.86 (dd, J = 14.6, 7.3 Hz, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 3.28 (dd, J = 14.7,
11.0 Hz, 1H), 2.87 (dd, J = 14.7, 4.7 Hz, 1H), 1.10 (br s, 1H); ¹³C NMR (75 MHz, C₅D₅); 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
[C₁₉H₁₆N₄O₃]⁺, 369.1325; found, 369.1328. Azidoalcohol (–)-40 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);
[α]²⁸D −70.8° (c 0.91, CH₂Cl₂).

32. Lactam (+)-34. To a solution of azidoalcohol (–)-40 (10.6 mg, 0.029 mmol, 1.0 equiv) in CH₂Cl₂ (1
mL) was added Dess-Martin periodinane (24.3 mg, 0.057 mmol, 2.0 equiv) at 0 ºC. After 30 min, the

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mixture was diluted with Et₂O (3 mL) and filtered through a plug of Celite (Et₂O 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); \(^1\)H NMR (300 MHz, \( \text{C}_6\text{D}_6 \)): \( \delta \) 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), 2.67 (dd, \( J = 15.0, 4.1 \) Hz, 1H). To a solution of crude azidoaldehyde in tert-butanol (1 mL) was added 2-methyl-2-butene (182 \( \mu \)L, 1.71 mmol, 59.0 equiv) followed by a solution of sodium chlorite (technical grade [80%], 32.4 mg, 0.29 mmol, 10.0 equiv) and sodium phosphate monobasic monohydrate (63.1 mg, 0.46 mmol, 15.9 equiv) in water (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, filtered, and 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); \(^1\)H NMR (300 MHz, \( \text{C}_6\text{D}_6 \)): \( \delta \) 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, \( J = 14.4, 12.0, 1 \)H), 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 10% Pd/C (30.4 mg, 0.029 mmol Pd, 1.0 equiv). The suspension was stirred under a balloon of hydrogen 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 (+)-34 (4.8 mg, 49% yield over 3 steps) as a white solid. Lactam (+)-34 was found to be >99% ee by chiral HPLC; \([\alpha]^{26D}_\text{D} +3.0^\circ\) (c 0.89, CH₂Cl₂).
33. **(+)-Amurensinine ((+)-2).** To a solution of lactam (+)-34 (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), 10% w/v aq NaOH (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 10% w/v aq NaOH (2 mL), the biphasic mixture was extracted with CH₂Cl₂ (5 x 5 mL). The organic layers were combined, dried over Na₂SO₄, filtered, and 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 aqueous formaldehyde (37 wt %, 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, filtered, and concentrated under reduced pressure. Purification by preparative TLC (0.25 mm, 19:1 CHCl₃:MeOH eluent) afforded (+)-amurensinine ((+)-2, 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]₂⁵_D +125.8º (c 0.49, CH₂Cl₂).
Synthetic (+)-Amuresinidine (1+2)
$^1$H NMR, 300 MHz, CDCl$_3$
Synthetic (+)-Amurinine (1+2)

$^1$C NMR, 75 MHz, CDCl$_3$
34. **Ketone (±)-42.** To a –78 °C stirred solution of dimethyl methoxy(phenyl)methylphosphonate (41, 23.70 g, 102.95 mmol) in THF (600 mL) was slowly added n-BuLi (40.4 mL, 2.5 M in THF). After 15 min, a solution of aldehyde 227 (20.72 g, 97.13 mmol) in THF (150 mL) was introduced into the cooled reaction vessel, then stirred for 1 h with vigorous stirring. The reaction was then warmed to 23 °C, and resulting gel was carefully concentrated to 1/3 the original volume under reduced pressure. The crude mixture was then redissolved in a 0.8 M solution of trichloroacetic acid in acetone (650 mL) and stirred at 23 °C for 6 h. The reaction was then neutralized by the addition of saturated aq NaHCO₃ until gas evolution subsides and extracted into EtOAc (3 x 1500 mL). The combined organics were washed with brine solution (500 mL) and dried over MgSO₄, then concentrated under reduced pressure. Purification immediately followed by flash chromatography over silica gel (10-20% EtOAc:hexane eluent) to provide ketone (±)-42 (23.29 g, 79% yield, R_f 0.47 in 30% Et₂O:pentane) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 8.00-7.9.4 (comp. m, 2H), 7.59-7.40 (comp. m, 3H), 4.82 (m, 1H), 4.03 (d, J = 12.6 Hz, 1H), 3.00-2.17 (comp. m, 2H), 2.86 (t, J = 2.1 Hz, 1H), 1.68-1.38 (comp. m, 6H), 1.34 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 198.6, 154.9, 137.0, 133.4, 128.9, 128.5, 79.8, 48.4, 39.4, 28.5, 25.5, 19.1; IR (film) 2938, 1688, 1411 cm⁻¹; HRMS (FAB⁺) calc’d for [C₁₈H₂₆NO₃]⁺: m/z 304.1913, found 304.1916

35. Alcohol (±)-21. To a -78 °C solution of ketone (±)-42 (11.07 g, 36.25 mmol) in toluene (400 mL) was slowly added neat DIBAL (8.10 mL, 45.31 mmol). After 2 h, the reaction was warmed to -42 °C for 1 h, then warmed to 23 °C for 1 h. At this time, the reaction was cooled to 0 °C and quenched by the careful addition of saturated aq Na,K-tartrate (100 mL) and diluted with water (100 mL). The mixture was stirred vigorously for 2 h to dissipate the cloudy mixture, then the layers were separated. The aqueous layer was washed with EtOAc (3 x 200 mL) and the combined organics were washed with brine solution (200 mL) then dried over MgSO₄ and concentrated under reduced pressure. The resulting crude was purified by flash chromatography over silica (10-15% EtOAc:hexanes eluent) to yield the desired alcohol diastereomer (±)-21 (8.36 g, 78% yield, Rf 0.34 in 30% EtOAc:hexane) as a white waxy solid: m.p. 58-59 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.18 (comp. m, 5H), 4.68 (dd, J = 8.0, 5.4 Hz, 1H), 4.35 (s, 1H), 3.91 (d, J = 11.4 Hz, 1H), 3.59 (br s, 1H), 2.77 (t, J = 13.5 Hz, 1H), 2.15-2.0 (m, 1H), 1.92-1.80 (m, 1H), 1.67-1.47 (m, 1H), 1.43 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.1, 145.0, 128.5, 127.4, 126.1, 79.9, 72.6, 48.6, 40.3, 39.7, 29.2, 28.7, 25.7, 19.3; IR (film) 3412, 2933, 1688, 1416 cm⁻¹; HRMS (FAB⁺) calc’d for [C₁₈H₁₈NO₃]⁺: m/z 306.2069, found 306.2057.

The minor diastereomer S13 (0.751 g, 7% yield, Rf 0.51 30% EtOAc:hexanes) was also isolated as a white waxy solid: m.p. 55-57 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.14 (comp. m, 5H), 4.78-4.52 (br s, 1H), 4.03 (d, J = 5.7 Hz, 1H), 2.79 (m, 1H), 2.20 (m, 1H), 1.84-1.14 (comp. m, 16H); ¹³C NMR (75 MHz, CDCl₃) δ 144.3, 128.5, 127.2, 125.8, 80.6, 70.0, 46.9, 40.6, 39.8, 29.5, 28.7, 28.6, 25.7, 19.4; IR (film) 3423, 2938, 1688, 1658 cm⁻¹; HRMS (FAB⁺) calc’d for [C₁₈H₂₈NO₃]⁺: m/z 306.2069, found 306.2084.
A stereochemical rationale for the observed diastereoselectivity may be proposed based on existing models for known diastereoselective transformations involving medium rings. For this discussion, the reduction substrate 42, once chelated to a Lewis-acid, may be approximated by cis,cis-1,4-cyclooctadiene. Computational studies find that the lowest energy conformations of cis,cis-1,4-cyclooctadiene are twist-boat and boat-chair. These competing conformations were found to be of equal energy within the limits of the computational method. X-ray crystal structures of substituted medium rings bearing the same unsaturation pattern depict solid state conformations that are in good agreement with these calculations. Taking cis,cis-1,4-cyclooctadiene as a model for our ketone substrate 42 after chelation to a metal, we may consider two transition states: the twist-boat structure TB-46 and the boat-chair structure BC-46 (Figure 1). The steric of the system demand delivery of the bulky hydride source be directed from the α-face of the molecule, to provide TB-47 and/or BC-47, respectively. In either event, aqueous work-up provides the alcohol diastereomer preferred experimentally.

Figure 1. Stereochemical rational for hydride addition

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8 For a review on diastereoselective reactions involving medium rings, see: Still, W. C. *Tetrahedron* 1981, 37, 3981.
36. Oxidative Kinetic Resolution of Alcohol (±)-21. An oven dried reaction tube was charged with alcohol (±)-21 (142 mg, 0.465 mmol), 3Å MS (250 mg), finely milled anhydrous Cs₂CO₃ (60 mg, 0.186 mmol) and chloroform (1.5 mL). To the slurry was added a solution of Pd(sparteine)Cl₂ (9.6 mg, 0.023 mmol) and (−)-sparteine (7.5 μl, 0.033 mmol) in chloroform (0.5 mL). The reaction tube was fitted with a short drying tube (2”, packed with drierite) and allowed to stir open to the atmosphere. After 60 h, the reaction was filtered over a short pad of silica (Et₂O eluent), and the volatiles were removed under reduced pressure. The crude mixture was then purified by flash chromatography (15-25% Et₂O:pentane eluent) to provide resolved alcohol (−)-21 (75 mg, 45% yield, Rᵣ 0.34 in 30% EtOAc:hexane) in 94.2% ee as a white waxy solid: m.p. 58-59 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.18 (comp. m, 5H), 4.68 (dd, J = 8.0, 5.4 Hz, 1H), 4.35 (s, 1H), 3.91 (d, J = 11.4 Hz, 1H), 3.59 (br s, 1H), 2.77 (t, J = 13.5 Hz, 1H), 2.15-2.0 (m, 1H), 1.92-1.80 (m, 1H), 1.67-1.47 (m, 1H), 1.43 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.7, 145.0, 128.5, 127.4, 126.1, 79.9, 72.6, 48.6, 40.3, 39.7, 29.2, 28.7, 25.7, 19.3; IR (film) 3412, 2933, 1688, 1416 cm⁻¹; HRMS (FAB⁺) calc’d for [C₁₈H₁₆NO₃⁺]: m/z 306.2069, found 306.2057; [α]₂⁰⁻¹⁰ D 20 to −127.5° (c 1.0, CHCl₃).

Ketone (−)-42 (64 mg, 53% yield, Rᵣ 0.47 in 30% Et₂O:pentane) was recovered in 80.9% ee as a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 8.00-7.9.4 (comp. m, 2H), 7.59-7.40 (comp. m, 3H), 4.82 (m, 1H), 4.03 (d, J = 12.6 Hz, 1H), 3.00-2.17 (comp. m, 2H), 2.86 (t, J = 2.1 Hz, 1H), 1.68-1.38 (comp. m, 6H), 1.34 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 198.6, 154.9, 137.0, 133.4, 128.9, 128.5, 79.8, 48.4, 39.4, 28.5, 25.5, 19.1; IR (film) 2938, 1688, 1411 cm⁻¹; HRMS (FAB⁺) calc’d for [C₁₉H₂₆NO₃⁺]: m/z 304.1913, found 304.1916; [α]₂⁰⁻¹⁰ D 20 to −9.7° (c 1.0, CHCl₃).
37. (−)-Sedamine ((−)-4). To a 0 °C solution of alcohol (−)-21 (70 mg, 0.23 mmol) in THF (3 mL) was added a solution of LiAlH₄ in THF (0.92 ml, 1.0 M). The reaction was heated to 70 °C in a sealed vial for 8 h, then cooled to 0 °C and carefully quenched by the sequential addition of water (50 µL), 15% (w/v) aq NaOH (50 µL), then water (50 µL). The resulting mixture was filtered over a pad of celite to remove solids, rinsing with ether. The mixture was concentrated under reduced pressure and the resulting oil was purified by Kugelrohr distillation to provide (−)-sedamine ((−)-4, 45 mg, 89% yield, $R_f$ 0.33 in 10% MeOH, 1% TEA in DCM) as a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 7.42 (comp. m, 5H), 5.85 (br s, 1H), 4.87 (dd, $J = 10.5, 2.7$ Hz, 1H), 3.14-3.0 (m, 1H), 2.92-2.78 (m, 1H), 2.64-2.50 (m, 1H), 2.48 (s, 3H), 2.12 (dd, $J = 9.9, 3.9$ Hz, 1H), 1.84-1.22 (comp. m, 7H); ¹³C NMR (75 MHz, CDCl₃) δ 145.9, 128.5, 127.2, 125.8, 74.7, 61.1, 51.6, 40.2, 40.0, 26.1, 22.6, 20.8; IR (film) 3369, 2938, 1457 cm⁻¹; HRMS (EI⁺) calc'd for [C_{14}H_{21}NO]⁺: m/z 219.1623, found 219.1619; [α]D²⁰ −89.2° (c 1, CHCl₃).

38. (+)-Sedamine ((+)-4). To a −78 °C solution of ketone (−)-42 (111 mg, 0.36 mmol) in toluene (4 mL) was slowly added neat DIBAL (81 µL, 0.45 mmol). After 2 h, the reaction was warmed to −42 °C for 1 h, then warmed to 23 °C for 1 h. At this time, the reaction was cooled to 0 °C and quenched by the careful addition of saturated aq Na,K-tartrate (1 mL) and diluted with water (1 mL). The mixture was stirred vigorously for 1 h to dissipate the cloudy mixture, then the layers were separated. The aqueous layer was washed with EtOAc (3 x 2 mL) and the combined organics were washed with brine solution (2 mL) then dried over MgSO₄ and concentrated under reduced pressure. The resulting crude was purified
by flash chromatography over silica (10-15% EtOAc:hexanes eluent) and used directly in the next reaction.

To a 0 °C solution of the reduction product (75.0 mg, 0.25 mmol) in THF (3 mL) was added a solution of LiAlH₄ in THF (0.97 ml, 1.0 M). The reaction was heated to 70 °C in a sealed vial for 8 h, then cooled to 0 °C and carefully quenched by the sequential addition of water (50 µL), 15% (w/v) aq NaOH (50 µL), then water (50 µL). The resulting mixture was filtered over a pad of celite to remove solids, rinsing with ether. The mixture was concentrated under reduced pressure and the resulting oil was purified by Kugelrohr distillation to provide (+)-sedamine ((+)-4, 38.1 mg, 68% yield R, 0.33 in 10% MeOH, 1% TEA in DCM) as a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 7.42 (comp. m, 5H), 5.85 (br s, 1H), 4.87 (dd, J = 10.5, 2.7 Hz, 1H), 3.14-3.0 (m, 1H), 2.92-2.78 (m, 1H), 2.64-2.50 (m, 1H), 2.48 (s, 3H), 2.12 (dd, J = 9.9, 3.9 Hz, 1H), 1.84-1.22 (comp. m, 7H); ¹³C NMR (75 MHz, CDCl₃) δ 145.9, 128.5, 127.2, 125.8, 74.7, 61.1, 51.6, 40.2, 40.0, 26.1, 22.6, 20.8; IR (film) 3369, 2938, 1457 cm⁻¹; HRMS (El⁺) calc'd for [C₁₄H₂₁NO]⁺: m/z 219.1623, found 219.1619; [α]₀⁺ 72.2º (c 1, CHCl₃).

39. TBS-ether SI4. To a 23 °C solution of alcohol (±)-21 (6.11 g, 19.88 mmol) in DMF (20 mL) was added imidazole (2.165 g, 31.80 mmol) in one portion. After 5 minutes, a solution of TBSCl (4.2 g, 27.83 mmol) in DMF (5 mL) was added to the stirred reaction mixture. 1 h later, the reaction was diluted with water (100 mL) and extracted into hexane (4 x 100 mL). The combined organics were washed with brine solution (80 mL), dried over MgSO₄ and concentrated under reduced pressure. The resulting crude was purified by flash chromatography (5-10% Et₂O:pentane eluent) to provide the TBS-ether SI4 (8.21 g, 98% yield R, 0.66 in 20% EtOAc:hexane) as a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.20 (comp. m, 5H), 4.62 (t, J = 6.6 Hz, 1H), 4.26 (m, 1H), 3.98 (d, J = 13.5 Hz, 1H), 2.78 (t, J =
8.8 Hz, 1H), 1.65-1.48 (comp. m, 5H), 1.46 (s, 9H), 0.87 (s, 9H), 0.01 (s, 3H), –0.19 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 155.26, 145.42, 128.35, 127.37, 126.46, 79.30, 73.25, 47.92, 40.93, 39.41, 28.79, 27.80, 26.10, 19.27, 18.39, -4.33, -4.75; IR (film) 2938, 1690, 1411, 1163 cm\(^{-1}\); HRMS (FAB\(^{+}\)) calc'd for \([\text{C}_{24}\text{H}_{42}\text{NO}_{3}\text{Si}]^{+}\): \(m/z\) 420.2934, found 420.2920.

40. Aldehyde 43. To a \(-78^\circ\)C solution of TBS-ether SI4 (4.10 g, 9.77 mmol) and TMEDA (2.65 mL, 17.59 mmol) in Et\(_2\)O (150 mL) was added slowly a 1.4 M cyclohexane solution of \(s\)-BuLi (12.2 mL, 17.1 mmol). After 15 minutes, the stirred solution was warmed to \(-42^\circ\)C for 45 min, then treated with DMF (1.89 mL, 24.43 mmol). The solution was maintained at \(-42^\circ\)C for 1 h, then warmed to 23 \(^\circ\)C for 30 min before quenching with saturated aq NH\(_4\)Cl (40 mL) and diluting with water (40 mL). The layers were separated and the aqueous layer was extracted with Et\(_2\)O (2 x 100 mL). After combining all organic layers, they were washed with brine (50 mL), dried over MgSO\(_4\) and concentrated under reduced pressure. The crude oil was purified by flash chromatography over silica (5-10% EtOAc:hexane eluent), to provide aldehyde 43 (3.32 g, 76% yield, \(R\), 0.51 in 20% EtOAc:hexane) as a clear oil: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.26 (d, \(J = 2.7\) Hz, 1H), 7.42-7.14 (comp. m, 5H), 4.68 (t, \(J = 5.7\) Hz, 1H), 4.29 (br s, 1H), 3.48 (dt, \(J = 10.8, 3.3\) Hz, 1H), 2.02-1.38 (comp. m, 8H), 1.46 (s, 9H), 0.88 (s, 9H), 0.01 (s, 3H), –0.20 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 196.1, 145.0, 128.5, 128.2, 127.6, 126.1, 81.5, 73.0, 60.1, 49.4, 40.8, 28.7, 28.6, 26.3, 26.1, 25.1, 18.4, 17.4, -4.3, -4.8; IR (film) 2933, 1731, 1683, 1366 cm\(^{-1}\); HRMS (FAB\(^{+}\)) calcd for \([\text{C}_{25}\text{H}_{42}\text{NO}_{3}\text{Si}]^{+}\): \(m/z\) 448.2883, found 448.2870.
41. Ketone 44. To a –78 °C stirred solution of dimethyl methoxy(phenyl)methylphosphonate (41, 1.80 g, 7.80 mmol) in THF (60 mL) was slowly added a 2.5 M solution of n-BuLi in THF (3.06 mL, 7.66 mmol). After 15 min, a solution of aldehyde 43 (3.31 g, 7.36 mmol) in THF (15 mL) was cannulated into the cooled reaction vessel, then stirred for 1 h with vigorous stirring. At this time, the reaction was warmed to 23 °C, and resulting gel was carefully concentrated to 1/3 the original volume under reduced pressure. The crude mixture was then redissolved in a 0.6 M solution of trichloroacetic acid in acetone (75 mL) and stirred at 23 °C for 6 h. The reaction was then neutralized by the addition of saturated aq NaHCO₃ until gas evolution subsides and extracted into EtOAc (3 x 150 mL). The combined organics were washed with brine solution (100 mL) and dried over MgSO₄, then concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (5-10% Et₂O:pentane eluent) with silica to furnish ketone 44 (1.75 g, 44% yield, Rf 0.48 in 20% Et₂O:pentane) as a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 8.03 (d, J = 7.2 Hz, 2H), 7.62-7.20 (comp. m, 8H), 4.86-4.66 (comp. m, 1H), 4.4-3.8 (m, 1H), 3.54-3.08 (m, 1H), 2.36-1.84 (m, 1H), 1.78-1.56 (comp. m, 2H), 1.56-1.40 (comp. m, 9H), 0.90 (s, 9H), 0.04 (s, 3H), –0.16 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 198.9, 155.6, 155.3, 145.5, 145.3, 137.2, 137.0, 133.3, 133.2, 128.8, 128.8, 128.7, 128.5, 128.5, 128.4, 128.5, 127.4, 126.5, 126.4, 79.8, 76.6, 73.8, 73.5, 49.8, 49.0, 47.3, 45.0, 44.1, 43.7, 43.5, 28.9, 28.8, 27.9, 26.6, 26.2, 26.1, 25.9, 25.9, 25.1, 18.5, 18.4, 16.1, 14.3, -4.2, -4.3, -4.7; IR (film) 2931, 1685, 1365 cm⁻¹; HRMS (FAB⁺) calc'd for [C₃₂H₄₈NO₄Si]⁺: m/z 538.3353, found 538.3356.
42. **N-Boc, O-TBS-Dihydro-Lobeline SI5.** To a –78 °C solution of ketone 44 (810 mg, 1.507 mmol) in toluene (30 mL) was slowly added neat DIBAL-H (296 µL, 1.658 mmol). After 1 h, the reaction was warmed to –42 °C for 1 h, then warmed to 23 °C for 30 min. At this time, the reaction was cooled to 0 °C and quenched by the careful addition of saturated aq Na,K-tartrate (10 mL) and diluted with water (10 mL). The mixture was stirred vigorously for 1 h to dissipate the cloudy mixture, then the layers were separated. The aqueous layer was washed with EtOAc (20 x 3 mL) and the combined organics were washed with brine solution (20 mL) then dried over MgSO₄ and concentrated under reduced pressure. The resulting crude was purified by flash chromatography over silica (10% EtOAc:hexanes eluent) to yield the desired alcohol diastereomer SI5 (573 mg, 71% yield, Rₓ 0.55 in 20% EtOAc:hexane) as a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 7.48-7.14 (comp. m, 10H), 4.98-4.60 (comp. m, 3H), 4.52-4.30 (comp. m, 2H), 4.16-3.92 (m, 1H), 2.34-1.62 (comp. m, 10H), 1.62-1.50 (comp. m, 9H), 0.98-0.88 (comp. m, 9H), 0.10-0.03 (comp. m, 3H), -0.11-0.17 (comp. m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 156.3, 145.4, 128.5, 127.6, 127.3, 126.3, 126.0, 80.4, 80.2, 73.7, 73.5, 72.8, 50.1, 49.0, 48.3, 47.8, 46.9, 44.7, 43.9, 29.0, 26.2, 25.7, 23.7, 18.5, 14.4, 14.2, -4.1, -4.7; IR (film) 3401, 2931, 1658 cm⁻¹; HRMS (FAB⁺) calc’d for [C₃₂H₅₀NO₄Si]⁺: m/z 540.3509, found 540.3500.

43. **meso-Diol SI6.** To a stirred, 23 °C solution of ketone SI5 (352 mg, 0.653 mmol) in THF (7 mL) was added a 1 M solution of TBAF in THF (1.6 mL, 1.96 mmol). After 8 h, the reaction was concentrated under reduced pressure and purified by flash chromatography with silica gel (20% EtOAc:hexane eluent) to yield the meso-diol SI6 (210 mg, 76% yield, Rₓ 0.30 in 20% EtOAc:hexane) as
a clear oil: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.42-7.16 (comp. m, 10H), 4.62 (dd, $J$ = 10.2, 2.7 Hz, 2H), 4.37 (br s, 2H), 3.06 (s, 2H), 1.99-1.58 (comp. m, 10H), 1.54 (s, 9H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 156.3, 145.0, 128.7, 127.6, 126.0, 125.9, 80.9, 72.6, 48.2, 28.8, 14.0; IR (film) 3393, 2937, 1653 cm$^{-1}$;

HRMS (FAB$^+$) calc'd for [C$_{26}$H$_{36}$NO$_4$]$^+$: m/z 426.2644, found 426.2660.

**44. Lobelanidine 20.** A solution of the N-Boc-piperidine SI6 (630 mg, 1.48 mmol) was dissolved in THF (40 mL) and cooled to 0 °C before treatment with a 1 M THF solution of LiAlH$_4$ (7.40 mL, 7.40 mmol). The reaction was heated to 55 °C in a sealed vial for 8 h, then cooled to 0 °C before quenching by the sequential addition of water (400 µL), 15% (w/v) aq NaOH (400 µL), then water (400 µL). The crude amino diol was purified by preparatory TLC (8% MeOH/0.5% Et$_3$N:DCM eluent). The white solid was then recrystallized from benzene/heptane to give lobelanidine 20 (360 mg, 72% yield, $R_f$ 0.31 in 10% MeOH:DCM) as a white solid: m.p. 178-180 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.54-7.22 (comp. m, 10H), 4.87 (dd, $J$ = 8.6, 5.4 Hz, 2H), 4.65 (br s, 2H), 2.95 (dd, $J$ = 15.9, 10.8 Hz, 2H), 2.32 (s, 3H), 2.01 (ddd, $J$ = 14.1, 9.3, 4.5 Hz, 2H), 1.78 (br s, 1H), 1.64-1.44 (comp. m, 5H), 1.22-0.80 (comp. m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 145.1, 128.6, 127.6, 126.1, 74.3, 62.3, 41.8, 25.9, 25.2, 23.4; IR (film) 3309, 2929, 1452 cm$^{-1}$; HRMS (FAB$^+$) calc'd for [C$_{22}$H$_{30}$NO$_2$]$^+$: m/z 340.2277, found 340.2278.

The relative stereochemistry of lobelanidine 20 was confirmed by x-ray crystallography (see below).
Figure 2. Experimental set-up

\[ \text{Figure 2. Experimental set-up} \]

45. (cis:trans)-(–)-Lobeline ((cis:trans)-3): Equation 1 Method. A reaction tube (ID=1.4 cm, OD=1.8 cm, height=14 cm) equipped with a 14/24 female joint was charged with hot, oven dried (oven temp = 130 °C, >2 days) 3Å molecular sieves (100 mg). After cooling to 23 °C, the vessel was charged with crystalline amino diol 20 (68 mg, 0.20 mmol). The reaction tube was equipped with a 14/24 male joint connected by vacuum quality tubing to a valve connected differentially to a high-vacuum source and a balloon of dry O₂ (Figure 2). The reaction tube was cooled to –78 °C, then purged with dry O₂ by iteratively evacuating the reaction tube, then refilling from the balloon (3 iterations) using the toggle valve. The 14/24 joint was removed such that a stream of O₂ flows over the reaction tube while a solution of Pd(sparteine)Cl₂ (12.4 mg, 0.03 mmol) and (–)-sparteine (9.7 µl) in CHCl₃ (1.8 mL) was introduced into the cold reaction tube. The 14/24 joint was replaced and the reaction tube was again purged with O₂ by three evacuation/refilling cycles in the manner previously described. The reaction was then removed from the cooling bath and warmed to 35 °C. At 96 h, the reaction was treated with MeOH (100 µL) filtered over a plug of celite, the pad was rinsed with DCM, then the organics were concentrated under reduced vacuum. The crude material was purified by flash chromatography over Silicycle™ (pH=6.5-7.0) Ultra Pure Silica Gel (8% MeOH:0.25% TEA:DCM eluent) to yield (–)-
lobeline as \((\text{cis:trans})-3\) (61 mg, 89 % yield) in a 1:1 mixture of \(\text{cis:trans}\) isomers as a white foam: m.p. 129-130° (130); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 8.01-7.97\) (comp. m, 2H, \(\text{cis}\) isomer), 8.01-7.97 (comp. m, 2H, \(\text{trans}\) isomer), 7.64-7.22 (comp. m, 8H, \(\text{cis}\) isomer), 7.64-7.22 (comp. m, 8H, \(\text{trans}\) isomer), 4.97 (dd, \(J = 10.8, 2.9\) Hz, 1H, \(\text{cis}\) isomer), 4.93 (dd, \(J = 10.7, 2.6\) Hz, 1H, \(\text{trans}\) isomer), 3.65-3.59 (m, 1H, \(\text{cis}\) isomer), 3.85-3.80 (m, 1H, \(\text{trans}\) isomer), 3.26 (dd, \(J = 16.0, 2.9\) Hz, 1H, \(\text{cis}\) isomer), 3.32-3.22 (comp. m, 2H, \(\text{trans}\) isomer), 3.0 (dd, \(J = 16.0, 8.5\) Hz, 1H, \(\text{cis}\) isomer), 3.1 (dd, \(J = 14.9, 9.8\) Hz, 1H, \(\text{trans}\) isomer), 2.58 (s, 3H, \(\text{trans}\) isomer), 2.38 (s, 3H, \(\text{cis}\) isomer), 2.38-2.18 (m, 1H, \(\text{trans}\) isomer), 2.06-1.46 (comp. m, 7H, \(\text{cis}\) isomer), 1.83-1.46 (comp. m, 6H, \(\text{trans}\) isomer), 1.29-1.18 (m, 1H, \(\text{cis}\) isomer); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 198.4, 198.3, 145.5, 145.2, 137.1, 136.7, 133.3, 133.3, 128.8, 128.8, 128.4, 128.3, 128.2, 128.2, 127.1, 127.0, 125.6, 125.6, 75.8, 75.7, 64.6, 61.1, 59.1, 51.7, 43.8, 43.2, 38.8, 40.5, 35.8, 27.4, 24.8, 23.5, 23.5, 23.4, 23.0, 20.5; IR (film) 311, 2933, 1685 cm\(^{-1}\); HRMS (EI\(^+\)) calc’d for \([\text{C}_{22}\text{H}_{27}\text{NO}_2]\)^+: \(m/z\) 337.2042, found 337.2027; \([\alpha]_D^{20}\) –55.8° (c 1, CDCl\(_3\)).

**Scheme 1.** Derivatization to a HPLC tractable analogue

![Scheme 1](image)

Ultimately, we elected to derivatize amino alcohol 3 into a compound that was more amenable to analysis by chiral HPLC. This effort was facilitated with the aide of the report by Crooks and co-workers.\(^{11}\) According to their method, the unrecrystallized desymmetrization product \((\text{cis:trans})-3\) was silylated with TBS-Cl to form a TBS ether and subsequently treated with Troc chloride to form carbamate SI7 exclusively as the Z-olefin (Scheme 1). Carbamate SI7 was then subjected to analysis by

chiral HPLC (Chiracel OJ, 0.6% EtOH:hexane eluent @ 1.0 mL/min); major enantiomer $T_R= 14.6$ min; minor enantiomer $T_R= 28.9$ min.


A reaction tube (ID=1.4 cm, OD=1.8 cm, height=14 cm) equipped with a 14/24 female joint was charged with hot, oven dried (oven temp = 130 °C, >2 days) 3Å molecular sieves (100 mg). After cooling to 23 °C, the vessel was charged with crystalline amino diol 20 (68 mg, 0.20 mmol). In a separate flask Pd(sparteine)Cl₂ (8.2 mg, 0.02 mmol) and sodium napthaleneoxide 45 (7.9 mg, 0.04 mmol) are combined in a dry box, then diluted with CHCl₃ (1.8 mL). The catalyst solution was stirred vigorously for 1 h prior to use. After this time, the reaction tube containing the starting diol 20 was equipped with a 14/24 male joint connected by vacuum quality tubing to a valve connected differentially to a high-vacuum source and a balloon of dry O₂ (see Figure 2). The reaction tube was cooled to −78 °C, then purged with dry O₂ by iteratively evacuating the reaction tube, then refilling from the balloon (3 iterations) using the toggle valve. The 14/24 joint was removed such that a stream of O₂ flows over the reaction tube while the solution of preformed (sparteine)Pd(napthaleneoxide)₂ and (−)-sparteine (9.7 μl) was introduced into the cold reaction tube. The 14/24 joint was replaced and the reaction tube was again purged with O₂ by three evacuation/refilling cycles in the manner previously described. The reaction was then removed from the cooling bath and warmed to 35 °C. At 96 h, the reaction was treated with MeOH (100 μL) filtered over a plug of celite, the pad was rinsed with DCM, then the organics were concentrated under reduced pressure. The crude material was purified by flash chromatography over Silicycle™ (pH=6.5-7.0) Ultra
Pure Silica Gel (8% MeOH:0.25% TEA:DCM eluent) to yield (−)-lobeline ((cis:trans)-3, 59 mg, 87 % yield) in a 1:1 mixture of cis:trans isomers as a white foam.

47. (cis)-(−)-Lobeline ((cis)-3). To a solution of (1:1) (cis:trans)-3 (57 mg, 0.17 mmol) in i-PrOH (2 mL) was added conc. HCl (20 μL). The reaction was heated to 60 °C for 8 h, then cooled to 23 °C, then concentrated under a reduced pressure. 1H NMR analysis of the free base (from saturated aq NaHCO₃) revealed a 3:1 mixture of isomers favoring the cis configuration at this stage. The white foam was taken-up in EtOH (0.8 mL) and placed in a heptane vapor diffusion chamber. The chamber was maintained at 4 °C for several days to deposit white crystals. The crystals were dissolved in benzene and free based with saturated aq NaHCO₃ before concentrating the organics under reduced pressure, to provide (−)-lobeline ((−)-3, 40 mg, 69% yield). The 1H NMR spectra was recorded immediately in CDCl₃ to observe exclusively the cis configuration, which was identical to natural (−)-lobeline: m.p. 130°; 1H NMR (300 MHz, CDCl₃) δ 7.97-8.01 (comp. m, 2H), 7.64-7.22 (comp. m, 8H), 4.97 (dd, J = 10.8, 2.9 Hz, 1H), 3.65-3.59 (m, 1H), 3.26 (dd, J = 16.0, 5.0 Hz, 2H), 3.0 (dd, J = 16.0, 8.5 Hz, 1H), 2.38 (s, 3H), 2.06-1.46 (comp. m, 7H), 1.29-1.18 (m, 1H); 13C NMR (75 MHz, CDCl₃) δ 198.3, 145.2, 137.1, 133.3, 128.8, 128.3, 128.2, 127.1, 125.6, 75.8, 64.6, 59.1, 43.8, 40.5, 27.4, 24.8, 23.5, 23.4; IR (film) 3111, 2933, 1685 cm⁻¹; HRMS (EI⁺) calc'd for [C₂₂H₂₇NO₂]⁺: m/z 337.2042, found 337.2043; [α]D²⁰ = −41.3° (c 1, CHCl₃).
Synthetic (-)-Sedamine (−-4)

$^1$H NMR, 300 MHz, CDCl$_3$
Synthetic (-)-Sedamine (-4)

$^{13}$C NMR, 75 MHz, CDCl$_3$
Synthetic (-)-L-lobeline (−)-3
\textsuperscript{1}H NMR, 300 MHz, CDCl\textsubscript{3}