

Supporting Information for:

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

Shyam Krishnan, Jeffrey T. Bagdanoff, David C. Ebner, Yeeman K. Ramtohul, Uttam K. Tambar, Brian M. Stoltz*

*The Arnold and Mabel Beckman Laboratories of Chemical Synthesis
Division of Chemistry and Chemical Engineering, California Institute of Technology
Pasadena, California 91125, U.S.A.*

Table of Contents:

1. Materials and Methods.....	S3
<u>Synthesis of (-)-aurantioclavine ((-)-1)</u>	
2. Diol (\pm)- 12	S4
3. Oxidative kinetic resolution of diol (\pm)- 12	S5
4. Azidoalcohol 24	S7
5. Sulfonamidoalcohol 11	S8
6. Bromoindole 25	S9
7. Vinylindole 26	S10
8. Diol 10	S11
9. Tricyclic alcohol 9	S12
10. Dehydration of tricyclic alcohol 9	S12
11. Dehydration of indole derivatives 25 and 26	S13
12. Bis-olefins 29 and 30	S14
13. Sulfonamidoalcohol 31	S16
14. Tricyclic indole 27	S17
15. (-)-Aurantioclavine ((-)-1).....	S17
16. Chiral HPLC assay conditions.....	S21
<u>Synthesis of (+)-amurensinine ((+)-2)</u>	
17. β -Ketoester SI2	S22
18. Diazoketoester 33	S22
19. β -Ketoester 18	S23
20. Ketoester (\pm)- 16	S24
21. Hydroxyester (\pm)- 15	S25
22. Kinetic Resolution of Hydroxyester (\pm)- 15 : Hydroxyester (-)- 15	S26
23. Lactam (+)- 34	S27
24. (+)-Amurensinine ((+)-2).....	S28
25. Lactone 35	S29
26. Alcohol (\pm)- 37	S29
27. Ketone (\pm)- 39 by Dess-Martin Periodinane Oxidation.....	S30
28. Diketone (\pm)- 38 by MnO ₂ Oxidation.....	S31
29. Diketone (\pm)- 38 by Pd-catalyzed Aerobic Oxidation.....	S32
30. Radical Inhibitor Screen in the Oxidative Kinetic Resolution of Alcohol (\pm)- 37	S32
31. Azidoalcohol (-)- 40	S34

32. Lactam (+)- 34	S35
33. (+)-Amurensinine ((+)- 2).....	S36

Synthesis of (-)-lobeline ((-)-**3**) and (-)- and (+)-sedamine ((-)- and (+)-**4**)

34. Ketone (\pm)- 42	S39
35. Alcohol (\pm)- 21	S40
36. Oxidative Kinetic Resolution of Alcohol (\pm)- 21	S42
37. (-)-Sedamine ((-)- 4).....	S43
38. (+)-Sedamine ((+)- 4).....	S43
39. TBS-ether SI4	S44
40. Aldehyde 43	S45
41. Ketone 44	S46
42. <i>N</i> -Boc, <i>O</i> -TBS-Dihydro-Lobeline SI5	S47
43. <i>meso</i> -Diol SI6	S47
44. Lobelanidine 20	S48
45. (<i>cis:trans</i>)-(-)-Lobeline ((<i>cis:trans</i>)- 3): Equation 1 Method.....	S49
46. (<i>cis:trans</i>)-(-)-Lobeline ((<i>cis:trans</i>)- 3): Equation 2 Method.....	S51
47. (<i>cis</i>)-(-)-Lobeline ((<i>cis</i>)- 3).....	S52

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.

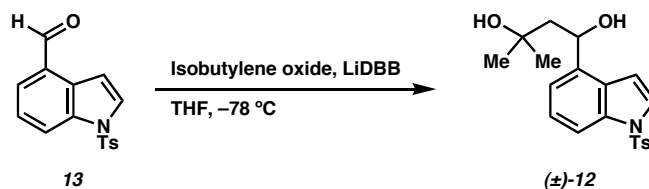
Yields of reactions refer to chromatographically and spectroscopically pure compounds. Reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with Merck silica gel 60 F₂₅₄ or aluminum oxide 60 F₂₅₄. Visualization was by the quenching of UV fluorescence ($\lambda_{max} = 254$ 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 (R_f) 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 (ν_{max}) 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 (δ_H) are quoted in ppm and are referenced to tetramethylsilane (internal). Coupling constants (J) are reported in Hertz. Data are reported as follows:

¹ Trend, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 4482.

² Wolf, H. *Org. React.* **1946**, *3*, 307.

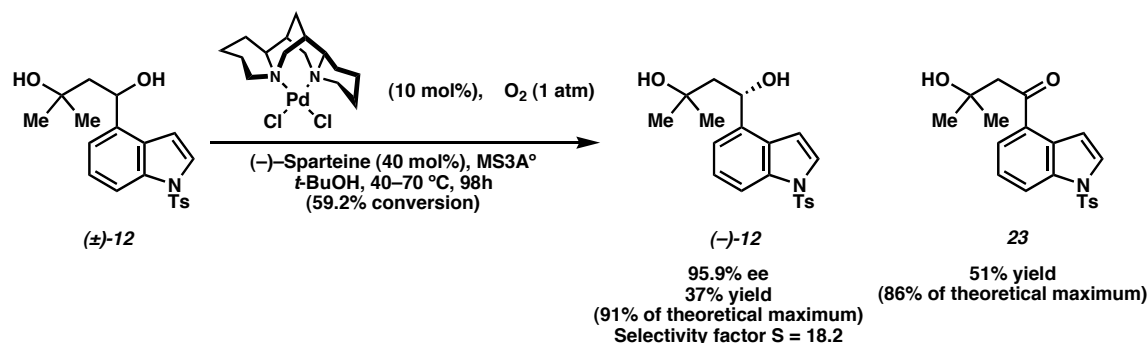
Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S4
 chemical shift, multiplicity, coupling constant(s), integration and assignment where possible. Carbon magnetic resonance spectra were recorded on Varian Mercury 300 (75 MHz) or Inova 500 (125 MHz) spectrometers. Carbon spectra assignments are supported where necessary by ^{13}C - ^1H (HMQC) correlations. Chemical shifts (δ_{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 ± 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)



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_4Cl (20 mL) was

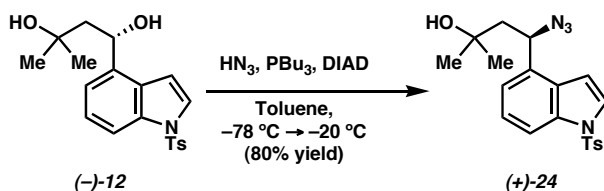
Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S5 then added, and the suspension was allowed to gradually reach 23 °C. The solution was concentrated under reduced pressure, diluted with H₂O (200 mL) and extracted with EtOAc (4 × 150 mL). The EtOAc extracts were combined, dried (Na₂SO₄), and concentrated under reduced pressure. The residue thus obtained was triturated with pentane (5 × 100 mL), and the combined pentane solutions concentrated to recover DBB. The remaining residue was purified by silica gel chromatography (2:1→3:2 hexanes:EtOAc) to yield diol (±)-**12** (8.92 g, 69% yield) as an off-white foam: *R_f* 0.24 (3:2 hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃): 7.89 (app. q, *J* = 3.0 Hz, 1H), 7.77 (app. t, *J* = 2.0 Hz, 1H), 7.74 (app. t, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 4.0 Hz, 1H), 7.28-7.22 (m, 2H), 7.15 (app. d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 4.0 Hz, 1H), 5.35 (dd, *J* = 11.0, 2.0 Hz, 1H), 4.41 (bs, 1H), 3.71 (bs, 1H) [or 3.35 (bs, 2H) also observed], 2.32 (s, 3H), 2.02 (dd, *J* = 15.0, 11.0 Hz, 1H), 1.65 (dd, *J* = 15.0, 11.0 Hz, 1H), 1.43 [s, 3H], 1.23 [s, 3H]; ¹³C NMR (75 MHz, CDCl₃): 144.9, 137.4, 135.0, 134.8, 129.7, 127.6, 126.6, 125.8, 124.5, 119.8, 112.3, 107.1, 71.5, 70.4, 49.0, 31.4, 27.3, 21.3; IR (film, cm⁻¹): 3400, 1372, 1165, 762. HRMS (FAB, *m/z*): (*M*⁺) calcd for (C₂₀H₂₃NO₄S⁺), 373.1348; found 373.1344.



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

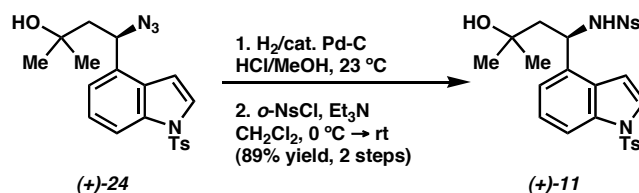
Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S6
reaction mixture that were filtered through a pad of silica gel and concentrated under reduced pressure. The temperature of the oil bath was raised by 10 °C every 24h. After 98 hours the oxidation had proceeded to 59.2% 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**: $[\alpha]_D^{25} -29.2^\circ$ (c=1.03, CHCl₃) for a sample of > 99% ee by chiral HPLC analysis.

β -hydroxyketone **21**: R_f 0.35 (3:2 Hexanes/EtOAc); ¹H 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); ¹³C 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 (C₂₀H₂₂NO₄S⁺), 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).

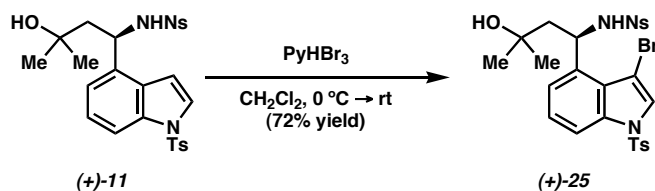


4. Azidoalcohol 24. (Caution: Hydrazoic acid is highly toxic and an explosive if concentrated!) A

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 $-78\text{ }^\circ\text{C}$ and then PBU_3 (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 $-20\text{ }^\circ\text{C}$. 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). R_f 0.51 (1:1 Hexanes/EtOAc); $^1\text{H NMR}$ (300 MHz, CDCl_3): 7.96 (d, $J = 8.5\text{ Hz}$, 1H), 7.78 (app. d, $J = 8.5\text{ Hz}$, 2H), 7.63 (d, $J = 3.5\text{ Hz}$, 1H), 7.35-7.21 (m, 4H), 6.85 (d, $J = 3.5\text{ Hz}$, 1H), 5.09 (dd, $J = 11.0, 3.0\text{ Hz}$, 1H), 2.33 (s, 3H), 2.09 (dd, $J = 14.5, 10.0\text{ Hz}$, 1H), 1.81 (dd, $J = 14.5, 3.0\text{ Hz}$, 1H), 1.30 (s, 3H), 1.27 (s, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): 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 ($\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_3\text{S}^+$), 398.1413; found 398.1425. Diol of 94.8% ee yielded azidoalcohol of 92% ee. $[\alpha]_D^{25} +94.2^\circ$ ($c=1.0$, CHCl_3) for a sample of 92.5% ee by chiral HPLC analysis.



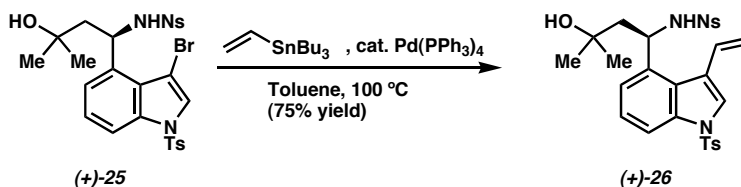
5. Sulfonamidoalcohol 11. Azidoalcohol (+)-**24** (1.59 g, 4 mmol) was dissolved in 0.3 M HCl in methanol (20 mL). 10 wt. % Pd/C (425 mg, 0.4 mmol Pd) was added and the flask evacuated and back-filled with H₂ (balloon, × 3) and the suspension stirred under an atmosphere of H₂ for 2.5 hours, then filtered 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 × 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). *R*_f 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 (C₂₆H₂₇N₃O₇S₂⁺), 557.1290; found 557.1277. [α]_D²⁵ +92.7° (c = 0.54, CHCl₃) for a sample of 92.8% ee.



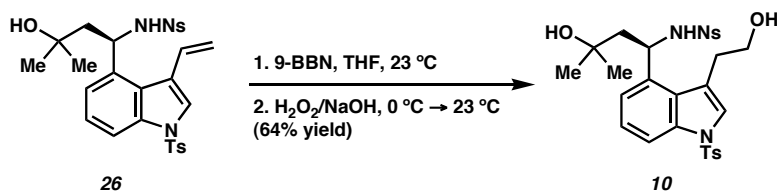
6. Bromoindole 25. Sulfonamidoalcohol (+)-**11** (2.01 g, 3.60 mmol) was dissolved in CH_2Cl_2 (35 mL) and the solution cooled to $0\text{ }^\circ\text{C}$. Pyridinium hydrobromide perbromide (PyHBr_3 , 2.30 g, 7.2 mmol) was added in small portions over 10 minutes. On completion of the addition the reaction mixture was allowed to warm to ambient temperature and stirred for 1h; then quenched with 1:1 v/v saturated aq. NaHCO_3 /1M aq. $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL). The suspension was diluted with brine (100 mL) and extracted with EtOAc ($4 \times 80\text{ mL}$). The EtOAc extracts were combined, dried (Na_2SO_4) 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. $191\text{ }^\circ\text{C}$; $^1\text{H NMR}$ (300 MHz, CDCl_3): 7.80 (app. d, $J = 8.5\text{ Hz}$, 2H, Ar-H), 7.73 (dd, $J = 8.0, 0.5\text{ Hz}$, 1H), 7.67 (s, 1H), 7.65 (dd, $J = 7.5\text{ Hz}$, 1H, 1H), 7.59 (dd, $J = 8.0, 1.0\text{ Hz}$, 1H), 7.41 (dt, $J = 7.5, 1.5\text{ Hz}$, 1H), 7.31 (m, 2H), 7.24 (m, 1H), 7.16 (dt, $J = 7.5, 1.5\text{ Hz}$, 1H), 7.09 (t, $J = 8.0\text{ Hz}$, 1H), 6.19 (td, $J = 11.0, 4.5\text{ Hz}$, 1H), 2.39 (s, 3H), 1.96 (dd, $J = 15.0, 11.0\text{ Hz}$, 1H), 1.83 (dd, $J = 15.0, 4.0\text{ Hz}$, 1H), 1.32 (s, 3H), 1.24 (s, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): 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^+ , ^{81}Br) calcd for ($\text{C}_{26}\text{H}_{26}\text{BrN}_3\text{O}_7\text{S}_2^+$), 637.0375; found 637.0365. $[\alpha]_D^{25} +5.5^\circ$ ($c = 1.16$, 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 ($4 \times 10\text{ mL}$), 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

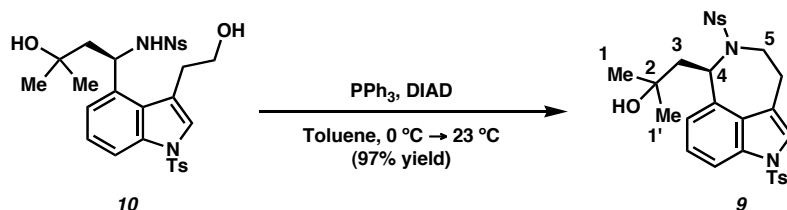
Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S10 yielded 21.6 mg of bromide (72.8% ee by chiral HPLC). The remaining residue was of low ee (ca. 5% ee).



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). *R_f* 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]_D²⁶ +40.6° (c = 1.04, CHCl₃) for a sample of 98.6% ee.



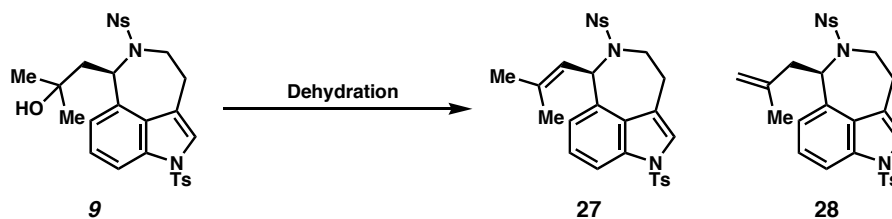
8. Diol 10. Vinyl indole **24** (127.1 mg, 0.218 mmol) was dissolved in THF (5 mL) and to the solution was added a solution of 9-BBN dimer (159.4 mg, 0.653 mmol) in THF (5 mL). The mixture was stirred at ambient temperature for 4 hours, then cooled to 0 °C. Absolute EtOH (2.0 mL) was added, followed (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). *R_f* 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 μ L, 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); ^1H NMR (300 MHz, C_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)HH'], 3.50 [m, 1H, C(5)HH'], 2.90 [m, 1H, C(6)HH'], 2.55 [dt, $J = 17.0, 4.5$ Hz, 1H, C(6)HH'], 2.04 (bs, 1H), 1.90 [dd, $J = 15.0, 10.0$ Hz, 1H, C(3)HH'], 1.67 (s, 3H, Ar-CH₃), 1.45 [dd, $J = 15.0, 3.0$ Hz, 1H, C(3)HH'], 1.13 [s, 3H, C(1')H₃], 1.09 [s, 3H, C(1)H₃]; ^{13}C NMR (75 MHz, C_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 \leftrightarrow C(5) and C(5)HH' \leftrightarrow 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 SI1. Dehydration of tricyclic alcohol **9**

Entry	Conditions	Products/Ratio 27:28	Yield
1	Martin sulfurane, PhH, 23 °C, 5h	24:76	64%
2	SOCl ₂ , Pyridine, 0 °C → 23 °C, 3h	42:58	49%
3	POCl ₃ , pyridine, 0 °C → 23 °C, 3h	31:69	69%
4	Burgess reagent, PhH, 60 °C, 3.5h	40:60	67%
5	p-TsOH.H ₂ O, Toluene, 60 °C, 10h	<5 :>95	— ^a
6	P ₂ O ₅ , PhH, 0°C → 23 °C, 3h	<5 :>95	29%
7	Ph ₃ SiOReO ₃ , Et ₂ O, 0 °C → 23 °C, 10h	21:79	42% (83%) ^b

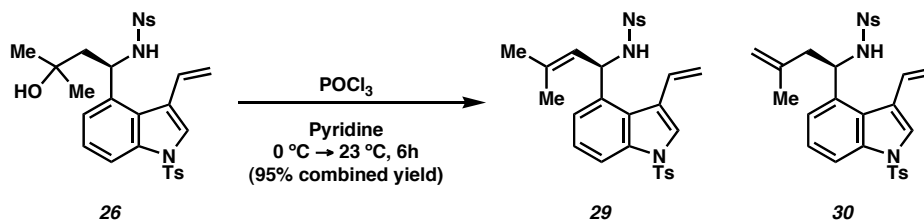
^a10% conversion; ^bBased on recovered starting material.

11. Dehydration of indole derivatives **25** and **26**.

Various dehydration conditions for the dehydration of vinylindole **26**, as well as of bromoindole **25** were examined. These are detailed in Table SI2 below.

Table S12. Dehydration of bromoindole **25** and vinylindole **26**

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



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,

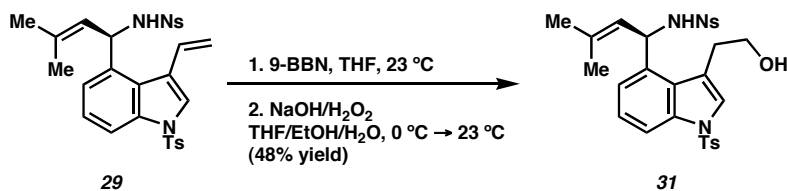
Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S15 which was purified by silica gel chromatography (Hexanes/EtOAc, 3:1) to afford a mixture of olefin isomers **29:30** = 62:38) as an off-white foam (345.5 mg, 95% combined yield). The olefin isomers could be separated 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.

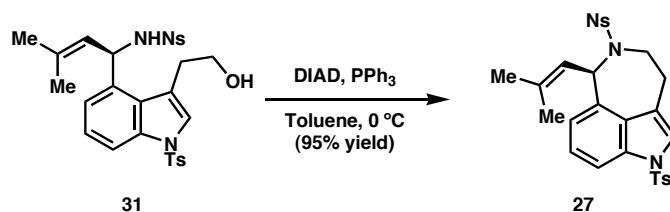
Isomer **29**: *R_f* 0.26 (2:1 Hexanes/EtOAc on SiO₂); *R_f* 0.29 (19:1 Toluene/Et₂O on SiO₂ containing 5% w/w AgNO₃); ¹H NMR (300 MHz, CDCl₃): 7.79 (app. td, *J* = 8.5, 2.0 Hz, 2H), 7.72 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.60 (d, *J* = 1.0 Hz, 1H), 7.46-7.39 (m, 2H), 7.28 (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 (C₂₈H₂₇N₃O₆S₂⁺), 565.1341; found 565.1323; [α]_D²⁶ –45.7° (c = 1.02, CHCl₃).

Isomer **30**: *R_f* 0.26 (2:1 Hexanes/EtOAc on SiO₂); *R_f* 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,

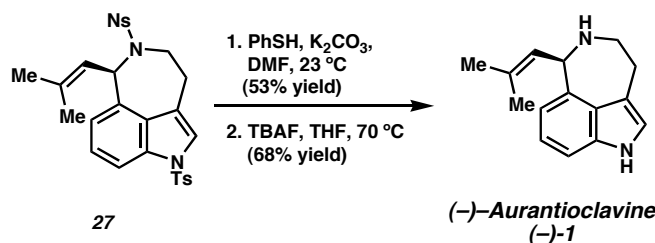
Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S16
 124.6, 123.6, 122.1, 120.8, 118.4, 115.3, 112.5, 52.3, 46.1, 21.7, 21.6; IR (film, cm^{-1}): 3340 (b,m), 1540 (s), 1364 (s), 1170 (s); HRMS (FAB, m/z): (MH^+) calcd for ($\text{C}_{28}\text{H}_{28}\text{N}_3\text{O}_6\text{S}_2^+$), 566.1420; found 566.1428; $[\alpha]_{\text{D}}^{26} +16.8^\circ$ ($c = 1.0$, CHCl_3).



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% H_2O_2 (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 (Na_2SO_4) 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_f 0.25 (6:1 Benzene/MeCN); ^1H NMR (300 MHz, CDCl_3): 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); ^{13}C NMR (75 MHz, CDCl_3): 147.0, 145.2, 139.0, 135.5, 135.0, 134.8, 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 ($\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}_7\text{S}_2^+$), 583.1447; found 583.1425; $[\alpha]_{\text{D}}^{26} -25.9^\circ$ ($c = 0.36$, CHCl_3) 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); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 (C₂₈H₂₈N₃O₆S₂⁺), 566.1420; found 566.1434; [α]_D²⁸ –93.2° (c = 1.0, CHCl₃) for a sample of 97.6% ee.

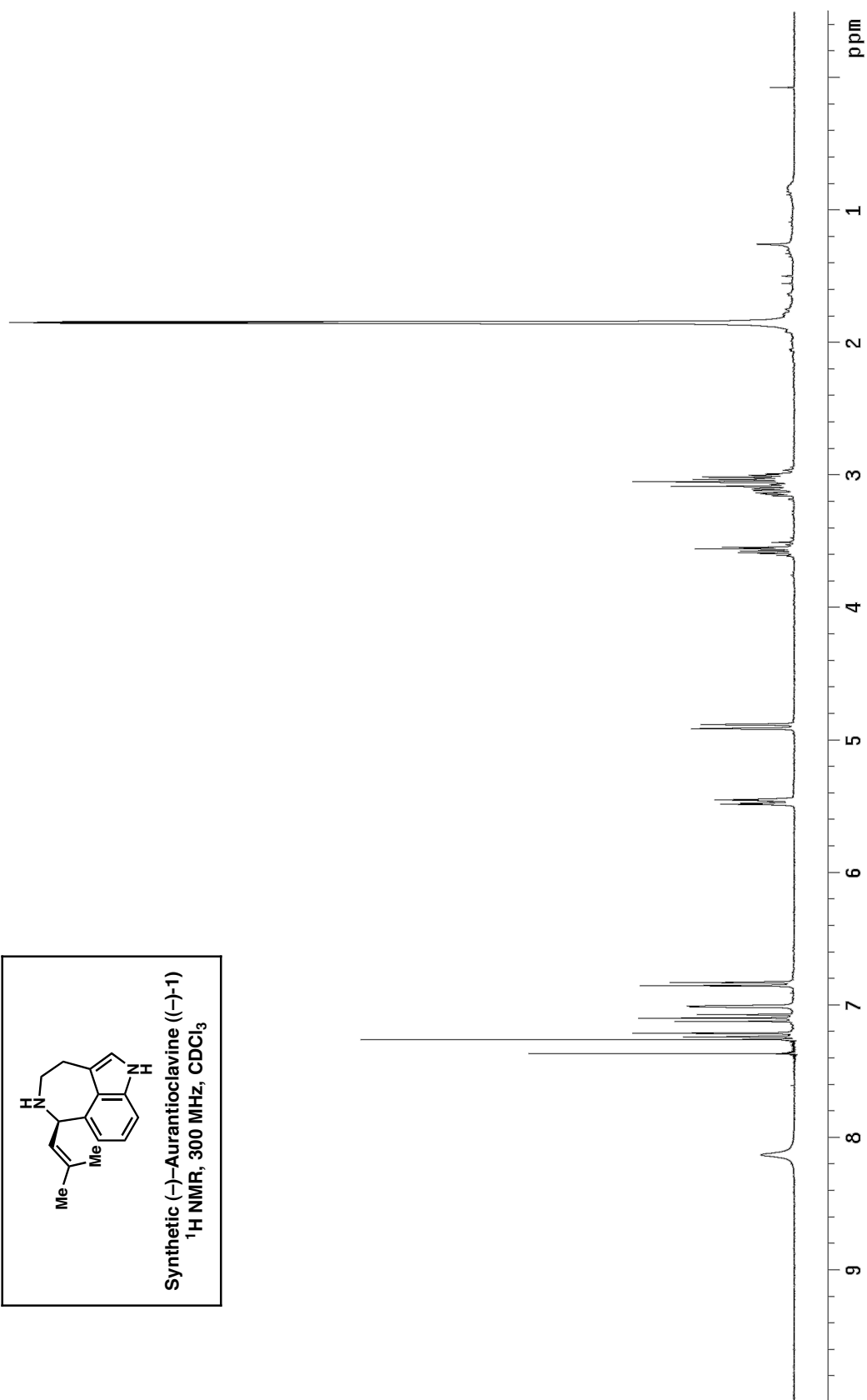
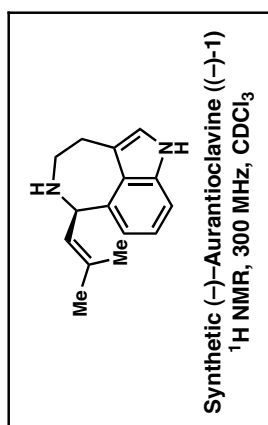


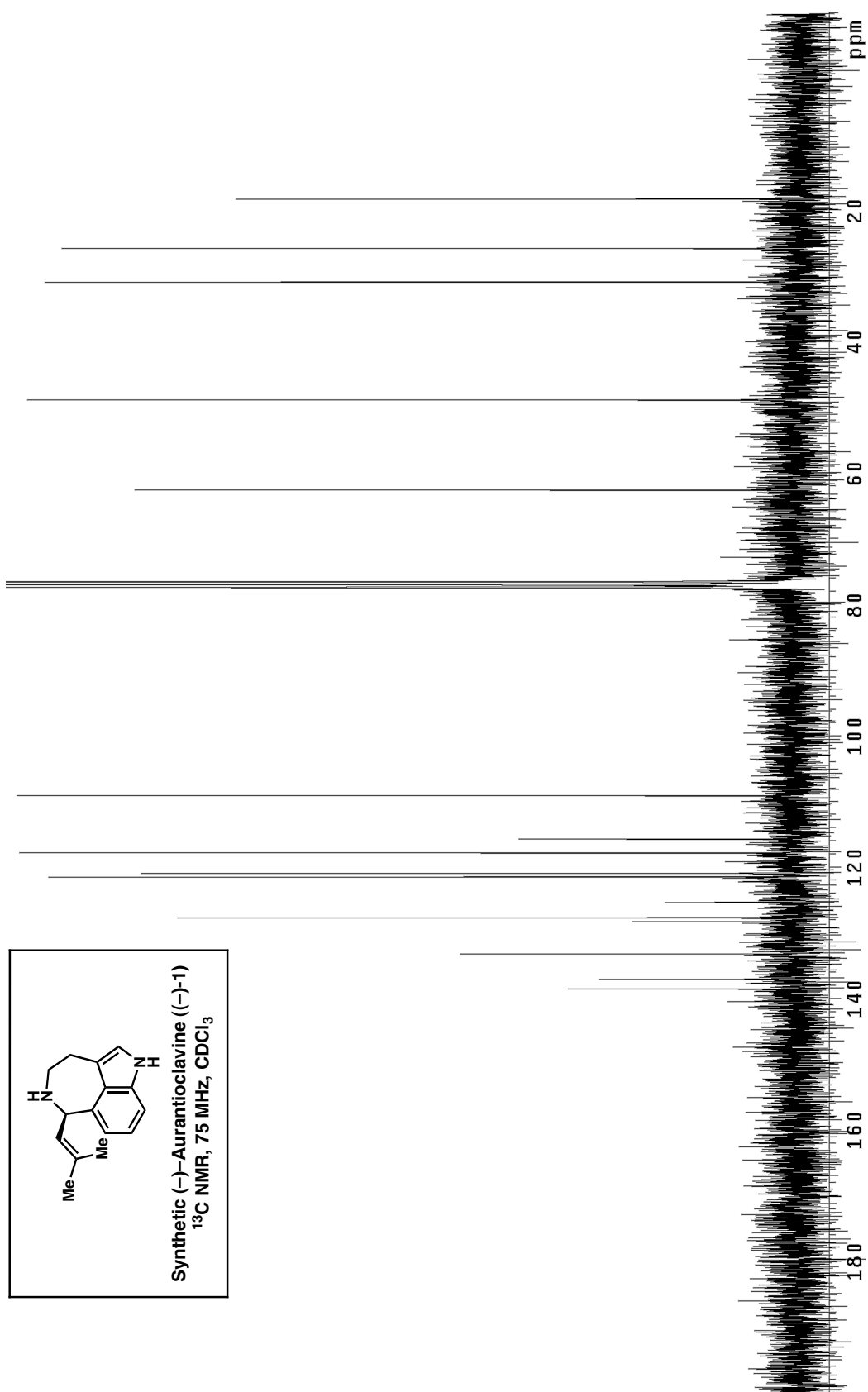
15. (R)–(–)-Aurantioclavine ((–)-1). Tricyclic indole (–)-**27** (36.8 mg, 65.1 μmol) was suspended in DMF (1 mL) with K₂CO₃ (27.0 mg, 0.195 mmol). PhSH (20 μL, 0.195 mmol) was added and the mixture stirred at ambient temperature for 12 hours, then diluted with EtOAc (100 mL) and washed with 0.5 M NaOH (4 × 30 mL), brine (1 × 50 mL), dried (K₂CO₃) and concentrated to yield a yellow

Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S18
solid, which was purified by silica gel chromatography on Et₃N-washed silica gel (Hexanes/EtOAc, 3:1
→ Hexanes/EtOAc/Et₃N, 33:17:1) to yield amine **32** as a colorless oil, 13.0 mg (53% yield). *R_f* 0.21
(Hexanes/EtOAc/Et₃N, 33:17:1 on Et₃N-washed SiO₂); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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
(C₂₂H₂₄N₂O₂S₂⁺), 380.1559; found 380.1577.

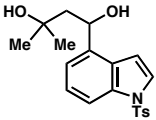
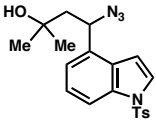
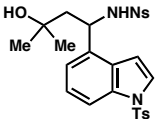
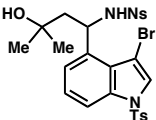
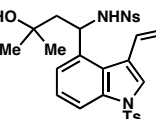
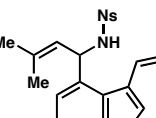
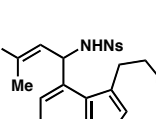
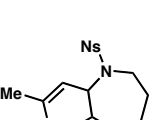
To amine **32** (21.2 mg, 56 μmol) was added TBAF (1 M in THF, 1.0 mL). The resulting solution was
heated at 70 °C for 12 hours, cooled and concentrated under reduced pressure. Saturated aqueous
NaHCO₃ (20 mL) was added and the aqueous phase extracted with EtOAc (3 × 20 mL). The extracts
were combined, dried (K₂CO₃) and concentrated under reduced pressure to afford a residue, which was
purified by silica gel chromatography on Et₃N-washed SiO₂ (Hexanes/EtOAc/Et₃N, 33:17:1) to afford
(-)-aurantioclavine ((-)-**1**) as an off-white solid, 8.6 mg (68% yield). *R_f* 0.22 (Hexanes/EtOAc/Et₃N,
25:25:1 on Et₃N-washed SiO₂); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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
¹): 3409 (b), 3292 (s), 2921 (s), 1615 (m), 1572 (m), 740 (s); HRMS (EI, *m/z*): (*M*⁺) calcd for
(C₁₅H₁₈N₂⁺), 226.1470; found 226.1472; [*α*]_D^{28.6} -30.1° (*c* = 0.38, CHCl₃) [Lit.³ [*α*]_D²²⁰ -34° (*c* = 1.25,
CHCl₃)]

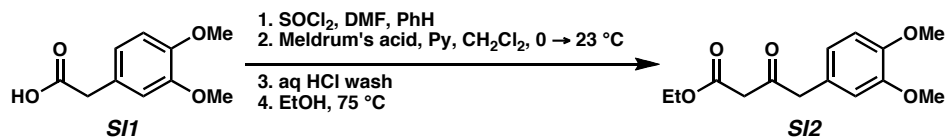
³ Kozlovskii, A.G.; Soloveva, T.F.; Sakharovskii, V.G.; Adanin, V.M. *Dokl. Akad. Nauk. SSSR* **1981**, 260, 230.



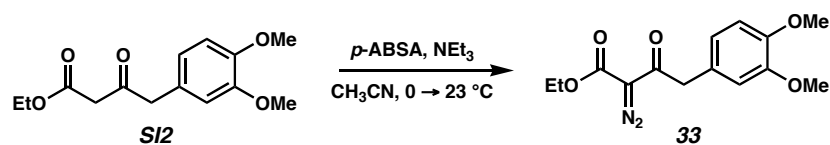


16. Table SI3. Chiral HPLC assay conditions

Compound	Conditions (flow rate = 1mL/min unless otherwise specified)			Retention times of Enantiomers
	Column	Solvent system	time	
	OD-H	5% EtOH/Hexanes	50 min	31.6 min (<i>R</i>), 38.8 min (<i>S</i>)
	OD-H	5% EtOH/Hexanes	30 min	19.1 min (<i>S</i>), 21.4 min (<i>R</i>)
	OD-H	6% EtOH/Hexanes	80 min	62.9 min (<i>S</i>), 70.9 min (<i>R</i>)
	AD	20% IPA/Hexanes	60 min	32.7 min (<i>S</i>), 47.5 min (<i>R</i>)
	AD	20% IPA/Hexanes	50 min	27.5 min (<i>S</i>), 35.0 min (<i>R</i>)
	OD-H	10% IPA/Hexanes	40 min	29.5 min (<i>R</i>), 33.0 min (<i>S</i>)
	AD	20% IPA/Hexanes	50 min	34.1 min (<i>R</i>), 39.0 min (<i>S</i>)
	OD-H	15% EtOH/Hexanes	40 min	20.4 min (<i>S</i>), 33.0 min (<i>R</i>)

Synthesis of (+)-amurensinine ((+)-2)

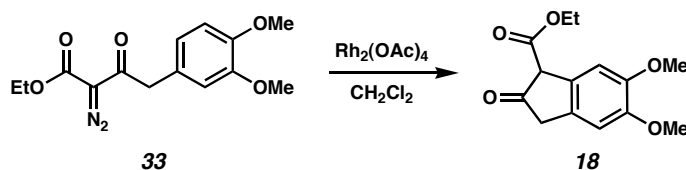
17. β -Ketoester SI2. To a solution of homoveratric acid (**SI1**, 1.0 g, 5.1 mmol, 1.0 equiv) in benzene (5 mL) was added thionyl chloride (741 μ L, 10.2 mmol, 2.0 equiv) and 4 drops of DMF. After stirring for 3 h, the reaction mixture was concentrated under reduced pressure. The resulting crude acid chloride was then dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °C. To this solution was added pyridine (825 μ L, 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



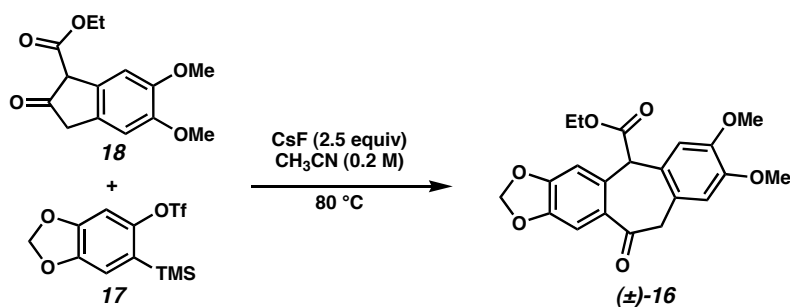
18. Diazoketoester 33. To a cooled solution (0 °C) of β -ketoester **SI2** (445 mg, 1.67 mmol, 1.0 equiv) in acetonitrile (8 mL) was added *p*-ABSA (441 mg, 1.84 mmol, 1.1 equiv) and NEt₃ (698 μ L, 5.01 mmol, 3.0 equiv). After stirring at 0 °C for 1 min, the mixture was stirred at 23 °C for 90 min. Then, the reaction was washed with 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

⁴ Capozzi, G.; Roelens, S.; Talami, S. *J. Org. Chem.* **1993**, *58*, 7932-7936.

Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S23
 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); ^1H NMR (300 MHz, C_6D_6): 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); ^{13}C NMR (75 MHz, C_6D_6): δ 190.1, 161.4, 150.4, 149.7, 127.5, 122.7, 114.5, 112.7, 75.8, 61.6, 56.0, 55.9, 45.7, 14.5; IR (thin film/NaCl): 2938, 2836, 2136, 1714, 1650, 1515, 1263, 1029 cm^{-1} ; HRMS-EI (m/z): $[\text{M}]^+$ calcd for $[\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_5]^+$, 292.1059; found, 292.1070.

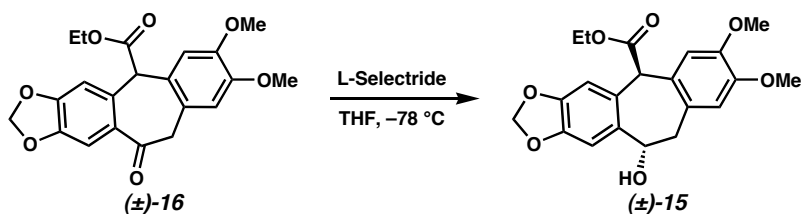


19. β -Ketoester 18. A flask equipped with an addition funnel and an N_2 inlet was charged with a catalytic amount of $\text{Rh}_2(\text{OAc})_4$ (138 mg, 0.31 mmol, 0.01 equiv) and CH_2Cl_2 (140 mL). A solution of diazoester **33** (9.12 g, 31.20 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was added dropwise over 90 min via an addition funnel. After stirring for 2.5 h at 23 $^\circ\text{C}$, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (7:3 \rightarrow 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 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3): δ 10.85 (s, 1H), 7.23 (s, 1H), 6.92 (s, 1H), 4.42 (q, $J = 7.1$ Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.52 (d, $J = 0.8$ Hz, 2H), 1.45 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 180.1, 148.7, 146.3, 132.6, 125.1, 108.6, 105.2, 105.2, 105.0, 60.7, 56.6, 56.2, 37.8, 14.6; IR (thin film/NaCl): 2976, 2833, 1650, 1602, 1494, 1469, 1305 cm^{-1} ; HRMS-FAB (m/z): $[\text{M}]^+$ calcd for $[\text{C}_{14}\text{H}_{16}\text{O}_5]^+$, 264.0998; found, 264.1003.

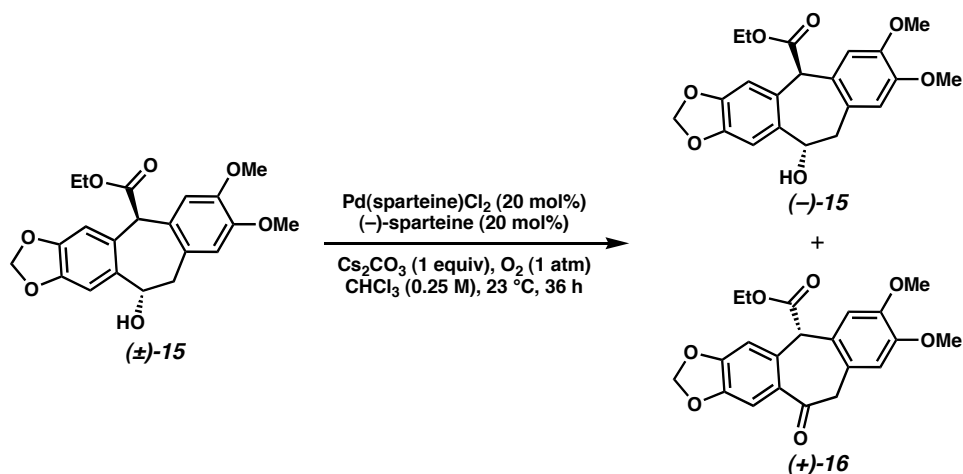


20. Ketoester (±)-16. To a solution of arylene precursor **17**⁵ (898 mg, 2.62 mmol, 1.7 equiv) in dry acetonitrile (9 mL) was added β-ketoester **18** (415 mg, 1.57 mmol, 1.0 equiv) and cesium fluoride (715 mg, 4.71 mmol, 3.0 equiv). The reaction was quickly immersed in an 80 °C oil bath and allowed 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 Et₂O (3 x 15 mL). The organic layers were combined, dried over Na₂SO₄, 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); 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.

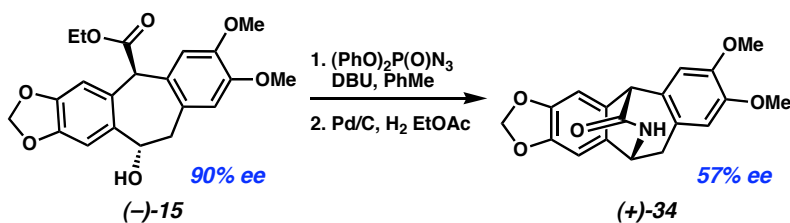
⁵ Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.



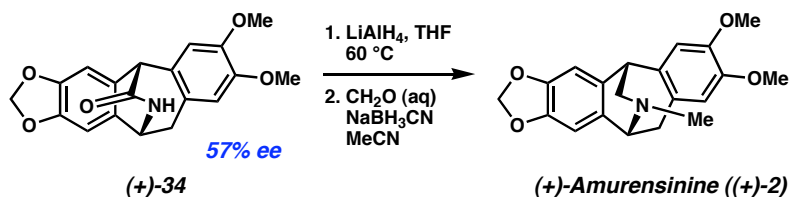
21. Hydroxyester (±)-15. To a solution of ketoester (±)-16 (52.9 mg, 0.138 mmol, 1.0 equiv) in THF (1.5 mL) at -78 °C was added dropwise a 1.0 M solution of L-Selectride in THF (200 μL , 0.206 mmol, 1.5 equiv). The resulting solution was stirred for 25 min at -78 °C and then quenched with saturated aq NH_4Cl (5 mL). After warming to 23 °C and stirring 25 min, the mixture was extracted with Et_2O (4 x 5 mL). The organics were combined, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes:EtOAc eluent) provided hydroxyester (±)-15 (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, $J = 1.5\text{ Hz}$, 1H), 5.92 (d, $J = 1.0\text{ Hz}$, 1H), 5.02-4.96 (m, 1H), 4.59 (s, 1H), 4.13 (q, $J = 7.2\text{ Hz}$, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.50 (dd, $J = 15.1, 2.4\text{ Hz}$, 1H), 2.93 (dd, $J = 15.1, 6.8\text{ Hz}$, 1H), 1.73 (d, $J = 8.3\text{ Hz}$, 1H), 1.17 (t, $J = 7.1\text{ Hz}$, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 172.6, 148.4, 147.6, 147.6, 146.9, 135.2, 129.6, 128.0, 127.3, 114.9, 114.5, 111.3, 110.7, 101.4, 69.4, 61.8, 58.5, 56.2, 56.1, 39.6, 14.3; IR (thin film/ NaCl): 3500, 2937, 1725, 1610, 1520, 1486, 1244 cm^{-1} ; HRMS-EI (m/z): $[\text{M}]^+$ calcd for $[\text{C}_{21}\text{H}_{22}\text{O}_7]^+$, 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 3 Å 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 amylenes) 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]_D²⁵ –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]_D²⁵ +19.9° (c 0.47, CHCl₃, 84.8% ee).

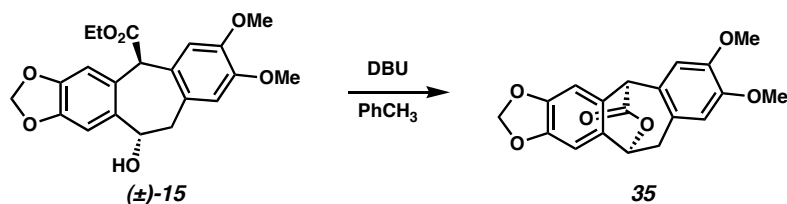


23. Lactam (+)-34. To a solution of hydroxyester (–)-**15** (9.7 mg, 0.025 mmol, 1.0 equiv) in toluene (500 μL) at 0 $^\circ\text{C}$ was added $(\text{PhO})_2\text{P(O)N}_3$ (27 μL , 0.126 mmol, 5.0 equiv) and DBU (19 μL , 0.126 mmol, 5.0 equiv). The resulting solution was stirred for 30 min at 0 $^\circ\text{C}$ and then stirred at 23 $^\circ\text{C}$ 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 , filtered, and concentrated under reduced pressure. The crude azide was passed through a short pad of SiO_2 (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 H_2 gas (1 atm) and stirred at 23 $^\circ\text{C}$ for 9 h. The reaction mixture was then passed through a short pad of Celite (Et_2O eluent) and concentrated under reduced pressure. Lactam (+)-**34** was used in the next step without further purification: R_f 0.46 (9:1 CHCl_3 :MeOH); $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.75 (s, 1H), 6.74 (s, 1H), 6.72 (s, 1H), 6.55–6.52 (m, 1H), 6.49 (s, 1H), 5.94 (d, $J = 1.5$ Hz, 1H), 5.88 (d, $J = 1.5$ Hz, 1H), 4.58–4.54 (m, 1H), 4.21 (d, $J = 2.0$ Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.28 (dd, $J = 16.8, 4.6$ Hz, 1H), 3.07 (dd, $J = 17.1, 2.4$ Hz, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 175.4, 148.8, 147.6, 147.2, 146.7, 134.1, 130.0, 128.1, 125.2, 114.7, 112.1, 106.7, 105.6, 101.4, 56.7, 56.2, 56.1, 53.6, 36.9; IR (thin film/NaCl): 3221, 2916, 1680, 1517, 1485, 1465, 1246 cm^{-1} ; HRMS-FAB (m/z): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{19}\text{H}_{18}\text{NO}_5]^+$, 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).

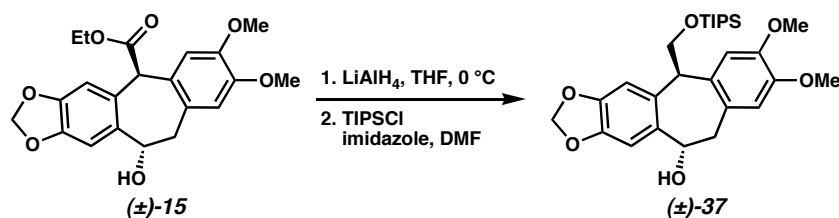


24. (+)-Amurensinine ((+)-2). To a solution of crude lactam (+)-34 in THF (1 mL) was added lithium aluminum hydride (30 mg, 0.0751 mmol, 3.0 equiv). The resulting solution was stirred for 8 h at 60 °C. The reaction mixture was then cooled to 0 °C and sequentially quenched with H₂O (30 μL), 15% aq NaOH (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 NaBH₃CN (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 (+)-amurensinine ((+)-2, 1.5 mg, 17% yield for 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.⁶ [α]_D²⁰ -145.0° (*c* 1.0, CH₂Cl₂)].

⁶ Carrillo, L.; Badía, D.; Domínguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716.

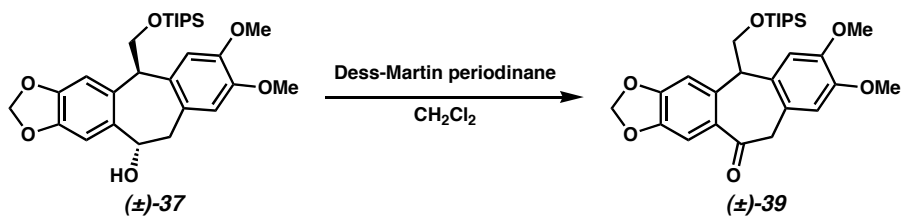


25. Lactone 35. To a solution of hydroxyester (±)-**15** (11.6 mg, 0.03 mmol, 1.0 equiv) in PhCH₃ (1 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 44.9 μL, 45.7 mg, 0.30 mmol, 10.0 equiv). After 20 h, the reaction mixture was diluted with H₂O (2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over Na₂SO₄, 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); 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.



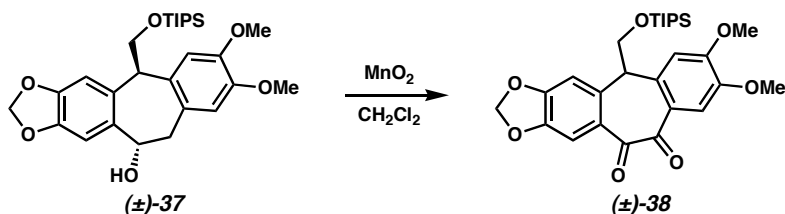
26. Alcohol (±)-37. To a solution of hydroxyester (±)-**15** (76.6 mg, 0.20 mmol, 1.0 equiv) in THF (4 mL) was added lithium aluminum hydride (37.6 mg, 0.99 mmol, 5.0 equiv) at 0 °C. After 30 min, the reaction was quenched at 0 °C by slow addition of EtOAc (5 mL) followed by 10% w/v aq sodium potassium tartrate (5 mL). After warming to 23 °C and stirring vigorously for 1 h, the biphasic mixture was diluted with H₂O (10 mL) and extracted with EtOAc (4 x 20 mL). The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude diol,

Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S30 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 , filtered, and concentrated under reduced pressure. Purification by flash chromatography (2:3 hexanes:Et₂O eluent) provided alcohol (\pm)-**37** (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.

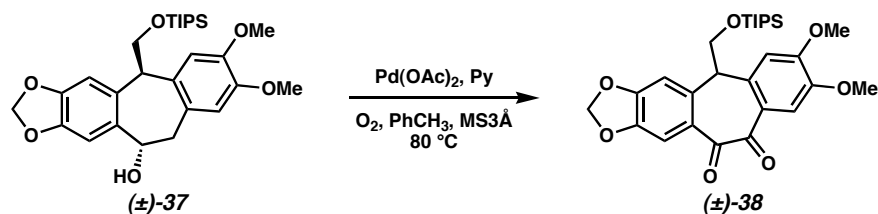


27. Ketone (\pm)-39 by Dess-Martin Periodinane Oxidation. To a solution of alcohol (\pm)-**37** (10.0 mg, 0.020 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added Dess-Martin periodinane (25.4 mg, 0.060 mmol, 3.0 equiv). After 5 min, the reaction was diluted with Et₂O (2 mL) and filtered through a short plug of

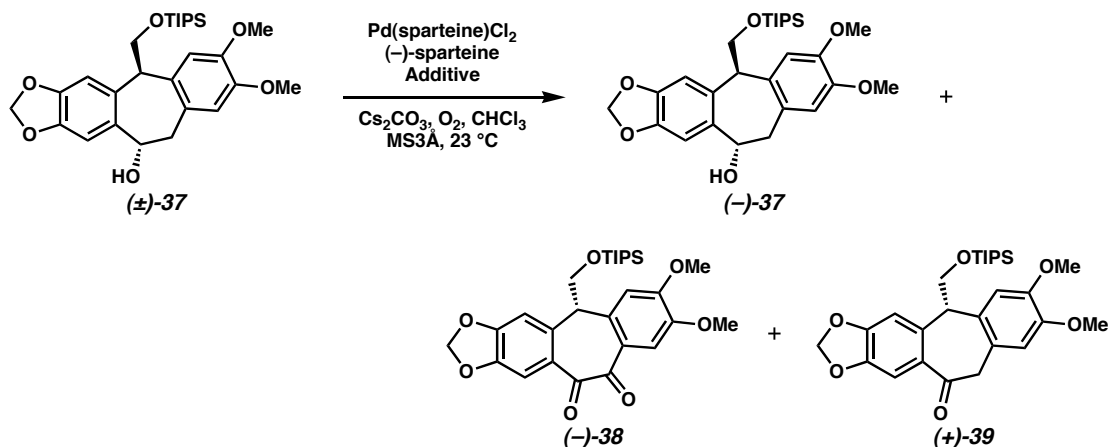
Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S31
 Celite (Et₂O eluent). The filtrate was concentrated under reduced pressure and purified by preparative TLC (7:3 hexanes:EtOAc eluent) to afford ketone (±)-**39** (7.9 mg, 79% yield) as a colorless oil: *R_f* 0.50 (3:2 hexanes:EtOAc); ¹H NMR (300 MHz, C₆D₆): 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); ¹³C NMR (75 MHz, C₆D₆): 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*): [M]⁺ calcd for [C₂₈H₃₈O₆Si]⁺, 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 CH₂Cl₂ (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 (CH₂Cl₂ 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); ¹H NMR (300 MHz, C₆D₆): 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); ¹³C NMR (75 MHz, C₆D₆): 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*): [M+H]⁺ calcd for [C₂₈H₃₇O₇Si]⁺, 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.



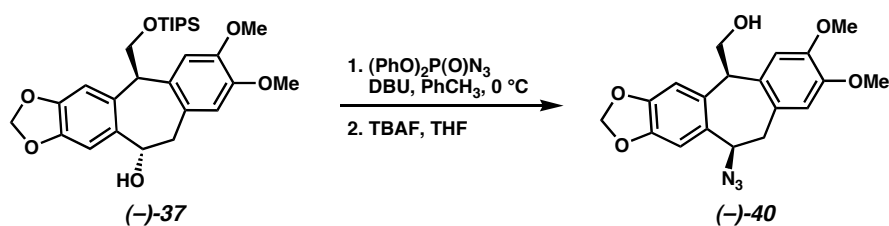
30. Radical Inhibitor Screen in the Oxidative Kinetic Resolution of Alcohol (±)-37. To a 1 dram vial with stir bar was added oven-dried powdered 3Å molecular sieves (50 mg), Pd(sparteine)Cl₂⁶ (8.2 mg, 0.02 mmol, 0.20 equiv), CHCl₃ (stabilized with amylenes, 0.5 mL), and (-)-sparteine (4.6 μL, 0.02 mmol, 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 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 (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); $[\alpha]_D^{25} -24.4^\circ$ (c 0.86, C_6H_6 , >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); $[\alpha]_D^{25} -39.9^\circ$ (c 1.21, C_6H_6 , 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); $[\alpha]_D^{25} +10.6^\circ$ (c 0.65, C_6H_6 , 76.8% ee).

Table SI4. Radical inhibitor screen in the oxidative kinetic resolution

Additive	Alcohol % yield (ee)	Diketone % yield (ee)	Ketone % 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

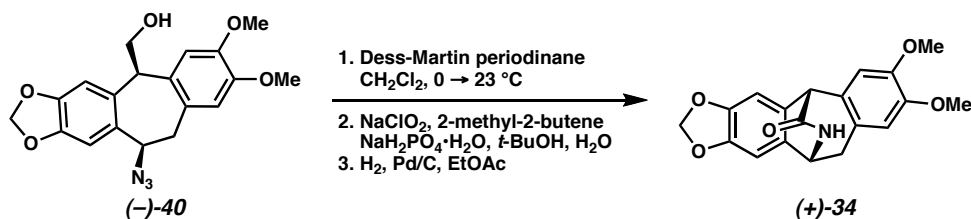
^a % Conversion determined relative to alcohol ee and diketone ee according to the equation: $C/(1-C) = ee_{\text{al}}/ee_{\text{diket}}$, where $C = \text{conversion}$. ^b Selectivity factor (*s*) determined using the equation $s = k_{\text{fast}}/k_{\text{slow}} = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$, where ee is the enantiomeric excess of recovered alcohol. ^c Reaction run for 72 h. ^d No ketone recovered.



31. Azidoalcohol (–)-40. To a solution of alcohol (–)-**37** (100.1 mg, 0.20 mmol, 1.0 equiv) in PhCH_3 (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, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S34

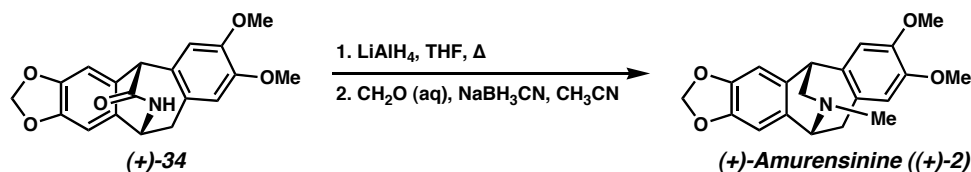
diphenylphosphoryl azide (259 μL , 1.20 mmol, 6.0 equiv) at 0 $^{\circ}\text{C}$. After stirring 6 h at 0 $^{\circ}\text{C}$, the reaction was quenched by addition of H_2O (25 mL). The mixture was then extracted with Et_2O (3 x 30 mL). The organic layers were combined, dried over Na_2SO_4 , filtered, 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 $^{\circ}\text{C}$ for 5 h. The solution was allowed to cool to 23 $^{\circ}\text{C}$ 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 , 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: 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, $J = 1.4$ 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); ^{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): $[\text{M}]^+$ calcd for $[\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_5]^+$, 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); $[\alpha]_D^{28} -70.8^{\circ}$ (c 0.91, CH_2Cl_2).



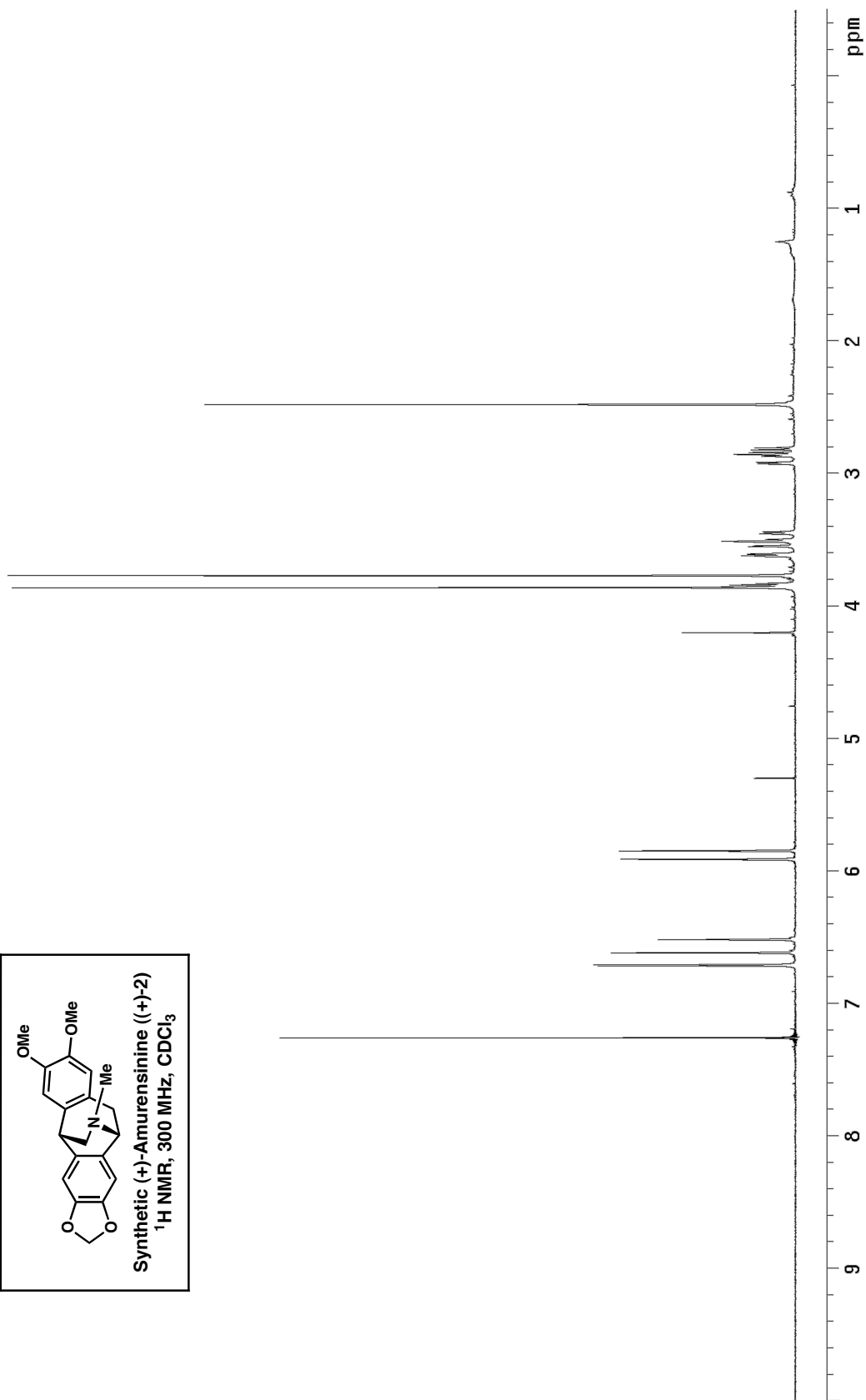
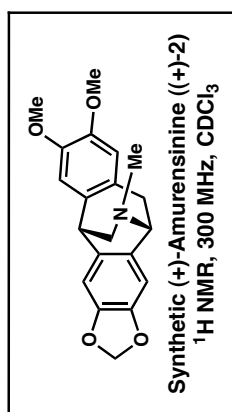
32. Lactam (+)-34. To a solution of azidoalcohol (–)-**40** (10.6 mg, 0.029 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (24.3 mg, 0.057 mmol, 2.0 equiv) at 0 $^{\circ}\text{C}$. After 30 min, the

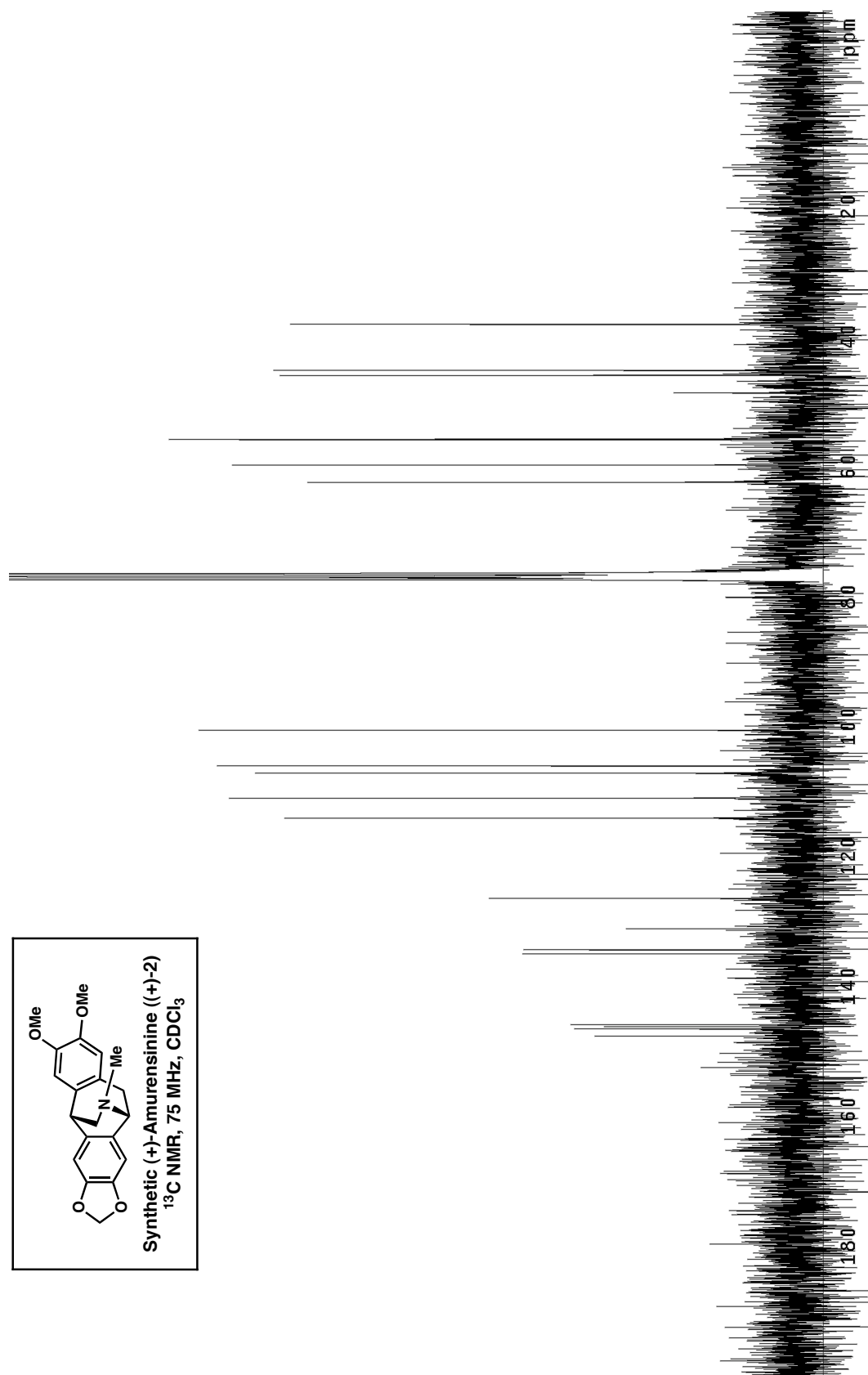
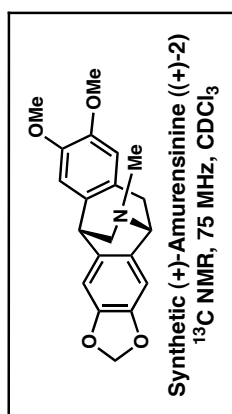
Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S35

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); ¹H NMR (300 MHz, C₆D₆): 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 *tert*-butanol (1 mL) was added 2-methyl-2-butene (182 μL, 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); 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 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; [α]_D²⁶ +3.0° (c 0.89, CH₂Cl₂).

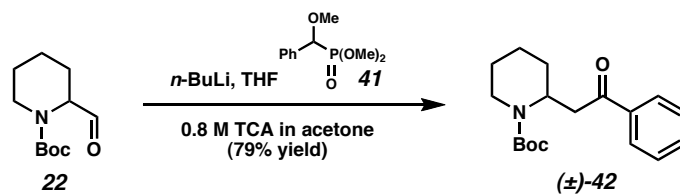


33. (+)-Amurensinine ((+)-2). To a solution of lactam (+)-34 (9.8 mg, 0.029 mmol, 1.0 equiv) in THF (1 mL) was added lithium aluminum hydride (11.0 mg, 0.29 mmol, 10.0 equiv) at 0 °C. The reaction was then heated to 65 °C for 4 h. The mixture was cooled to 0 °C and diluted with CH₂Cl₂ (1 mL). H₂O (100 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); $[\alpha]_D^{25} +125.8^\circ$ (*c* 0.49, CH₂Cl₂).



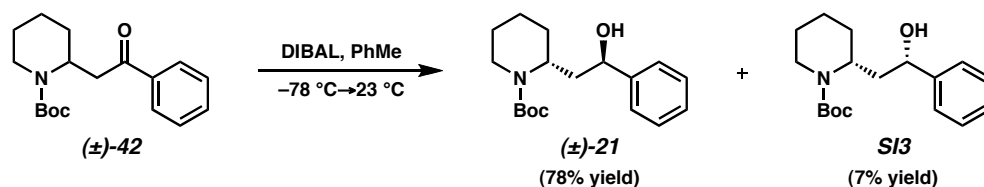


Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S39
Synthesis of (-)-lobeline ((-)-3) and (-)- and (+)-sedamine ((-)- and (+)-4)



34. Ketone (\pm)-42**.** To a $-78\text{ }^{\circ}\text{C}$ 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 **22**⁷ (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 $23\text{ }^{\circ}\text{C}$, 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 $23\text{ }^{\circ}\text{C}$ 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 (\pm)-**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

⁷ Molander, G. A.; Romero, J. A. C. *Tetrahedron* **2005**, *61*, 2631.

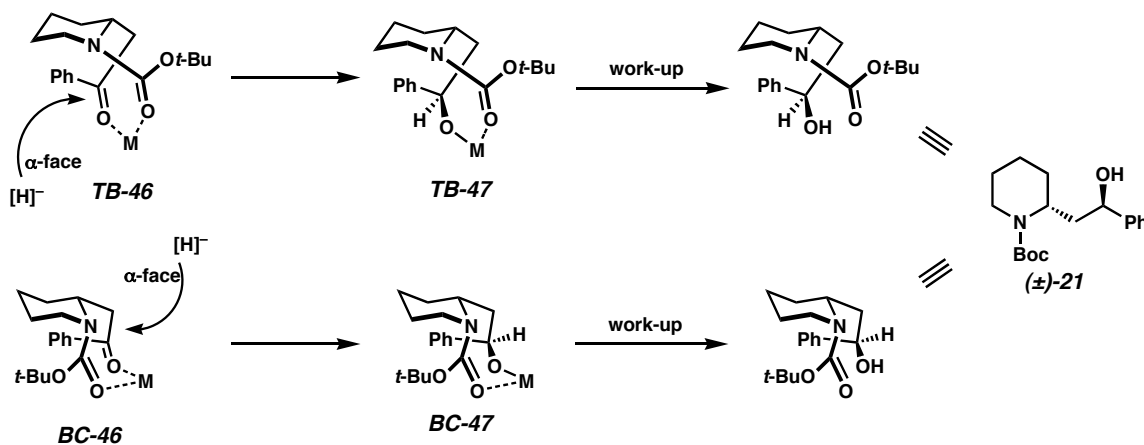


35. Alcohol (±)-21. To a $-78\text{ }^\circ\text{C}$ solution of ketone (±)-**42** (11.07 g, 36.25 mmol) in toluene (400 mL) was slowly added neat DIBAL (8.10 mL, 45.31 mmol). After 2 h, the reaction was warmed to $-42\text{ }^\circ\text{C}$ for 1 h, then warmed to $23\text{ }^\circ\text{C}$ for 1 h. At this time, the reaction was cooled to $0\text{ }^\circ\text{C}$ 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 MgSO_4 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, R_f 0.34 in 30% EtOAc:hexane) as a white waxy solid: m.p. $58\text{-}59\text{ }^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 7.40-7.18 (comp. m, 5H), 4.68 (dd, $J = 8.0, 5.4\text{ Hz}$, 1H), 4.35 (s, 1H), 3.91 (d, $J = 11.4\text{ Hz}$, 1H), 3.59 (br s, 1H), 2.77 (t, $J = 13.5\text{ Hz}$, 1H), 2.15-2.0 (m, 1H), 1.92-1.80 (m, 1H), 1.67-1.47 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) 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 $[\text{C}_{18}\text{H}_{18}\text{NO}_3]^+$: m/z 306.2069, found 306.2057.

The minor diastereomer **SI3** (0.751 g, 7% yield, R_f 0.51 30% EtOAc:hexanes) was also isolated as a white waxy solid: m.p. $55\text{-}57\text{ }^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 7.40-7.14 (comp. m, 5H), 4.78-4.52 (br s, 1H), 4.03 (d, $J = 5.7\text{ Hz}$, 1H), 2.79 (m, 1H), 2.20 (m, 1H), 1.84-1.14 (comp. m, 16H); ^{13}C NMR (75 MHz, CDCl_3) 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 $[\text{C}_{18}\text{H}_{28}\text{NO}_3]^+$: 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.⁸ 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.⁹ 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.¹⁰ 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 sterics 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.

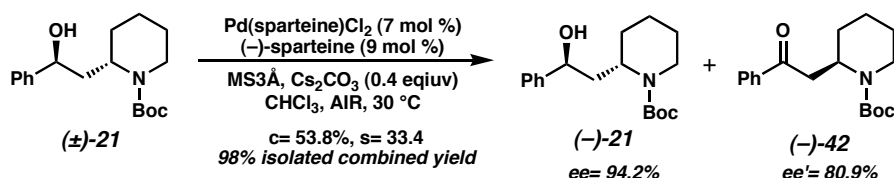
Figure 1. Stereochemical rationale for hydride addition



⁸ For a review on diastereoselective reactions involving medium rings, see: Still, W. C. *Tetrahedron* **1981**, 37, 3981.

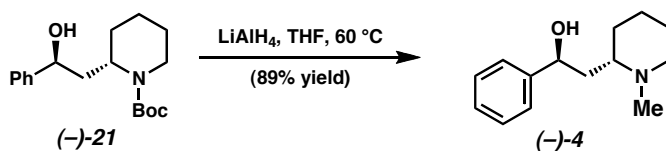
⁹ Anet, F. A. L.; Yavari, I. *J. Am. Chem. Soc.* **1977**, 99, 6986.

¹⁰ Burke, L. P.; DeBellis, A. D.; Fuhrer, H.; Meier, H.; Pastor, S. D.; Rihs, G.; Rist, G.; Rodebaugh, R. K.; Shum, S. P. *J. Am. Chem. Soc.* **1997**, 119, 8313.

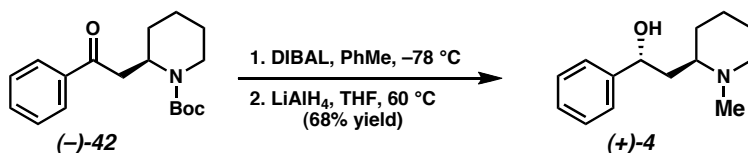


36. Oxidative Kinetic Resolution of Alcohol (±)-21. An oven dried reaction tube was charged with alcohol (±)-**21** (142 mg, 0.465 mmol), 3Å MS (250 mg), finely milled anhydrous Cs_2CO_3 (60 mg, 0.186 mmol) and chloroform (1.5 mL). To the slurry was added a solution of Pd(sparteine)Cl_2 (9.6 mg, 0.023 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 (Et_2O eluent), and the volatiles were removed under reduced pressure. The crude mixture was then purified by flash chromatography (15-25% Et_2O :pentane eluent) to provide resolved alcohol (–)-**21** (75 mg, 45% yield, R_f 0.34 in 30% EtOAc :hexane) in 94.2% ee as a white waxy solid: m.p. 58-59 $^\circ\text{C}$; $^1\text{H NMR}$ (300 MHz, CDCl_3) 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); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) 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 $[\text{C}_{18}\text{H}_{18}\text{NO}_3]^+$: m/z 306.2069, found 306.2057; $[\alpha]_{\text{D}}^{20}$ -127.5° (c 1.0, CHCl_3).

Ketone (–)-**42** (64 mg, 53% yield, R_f 0.47 in 30% Et_2O :pentane) was recovered in 80.9% ee as a clear oil: $^1\text{H NMR}$ (300 MHz, CDCl_3) 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); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) 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 $[\text{C}_{18}\text{H}_{26}\text{NO}_3]^+$: m/z 304.1913, found 304.1916; $[\alpha]_{\text{D}}^{20}$ -9.7° (c 1.0, CHCl_3).



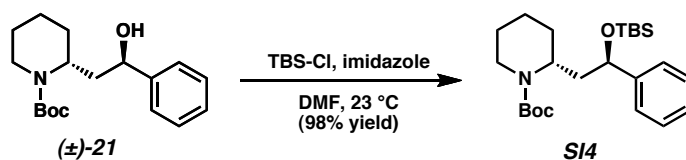
37. (-)-Sedamine ((-)-4). To a 0 °C solution of alcohol (-)-**21** (70 mg, 0.23 mmol) in THF (3 mL) was added a solution of LiAlH₄ in THF (0.92 mL, 1.0 M). The reaction was heated to 70 °C in a sealed vial for 8 h, then cooled to 0 °C and carefully quenched by the sequential addition of water (50 μL), 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 [C₁₄H₂₁NO]⁺: *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

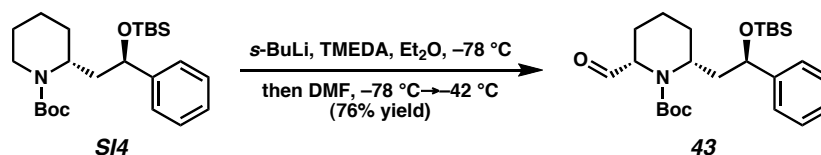
Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S44
by flash chromatography over silica (10-15% EtOAc:hexanes eluent) and used directly in the next reaction.

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_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 [C₁₄H₂₁NO]⁺: *m/z* 219.1623, found 219.1619; [α]_D²⁰ +72.2° (*c* 1, CHCl₃).

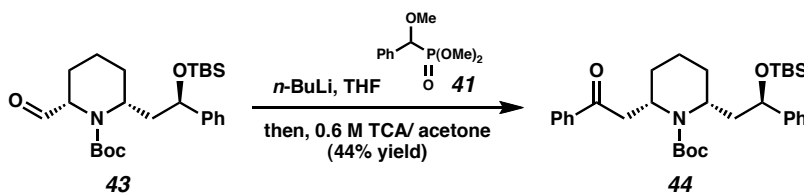


39. TBS-ether SI4. To a 23 °C solution of alcohol (±)-**21** (6.11 g, 19.88 mmol) in DMF (20 mL) was added imidazole (2.165 g, 31.80 mmol) in one portion. After 5 minutes, a solution of TBSCl (4.2 g, 27.83 mmol) in DMF (5 mL) was added to the stirred reaction mixture. 1 h later, the reaction was diluted 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_f* 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* =

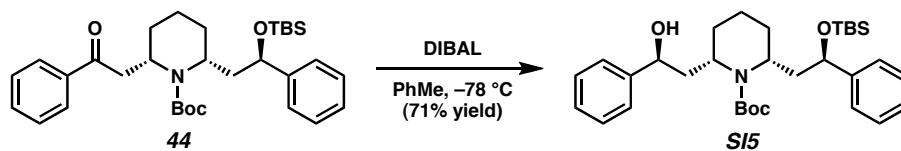
8.8 Hz, 1H), 2.04-1.84 (comp. m, 2H), 1.65-1.48 (comp. m, 5H), 1.46 (s, 9H), 0.87 (s, 9H), 0.01 (s, 3H), -0.19 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.26, 145.42, 128.35, 127.37, 126.46, 79.30, 73.25, 47.92, 40.93, 39.41, 28.79, 27.80, 26.10, 19.27, 18.39, -4.33, -4.75; IR (film) 2938, 1690, 1411, 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.



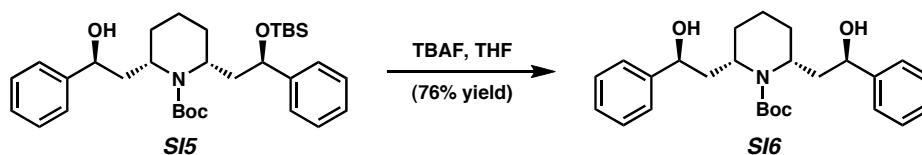
40. Aldehyde 43. To a $-78\text{ }^\circ\text{C}$ solution of TBS-ether **SI4** (4.10 g, 9.77 mmol) and TMEDA (2.65 mL, 17.59 mmol) in Et_2O (150 mL) was added slowly a 1.4 M cyclohexane solution of *s*-BuLi (12.2 mL, 17.1 mmol). After 15 minutes, the stirred solution was warmed to $-42\text{ }^\circ\text{C}$ for 45 min, then treated with DMF (1.89 mL, 24.43 mmol). The solution was maintained at $-42\text{ }^\circ\text{C}$ for 1 h, then warmed to $23\text{ }^\circ\text{C}$ for 30 min before quenching with saturated aq NH_4Cl (40 mL) and diluting with water (40 mL). The layers were separated and the aqueous layer was extracted with Et_2O (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_f 0.51 in 20% EtOAc :hexane) as a clear oil: ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $^+$) calc'd for $[\text{C}_{25}\text{H}_{42}\text{NO}_4\text{Si}]^+$: m/z 448.2883, found 448.2870.



41. Ketone 44. To a $-78\text{ }^{\circ}\text{C}$ 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 $23\text{ }^{\circ}\text{C}$, 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 $23\text{ }^{\circ}\text{C}$ for 6 h. The reaction was then neutralized by the addition of saturated aq NaHCO_3 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 MgSO_4 , then concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (5-10% Et_2O :pentane eluent) with silica to furnish ketone **44** (1.75 g, 44% yield, R_f 0.48 in 20% Et_2O :pentane) as a clear oil: ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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 $[\text{C}_{32}\text{H}_{48}\text{NO}_4\text{Si}]^+$: m/z 538.3353, found 538.3356.

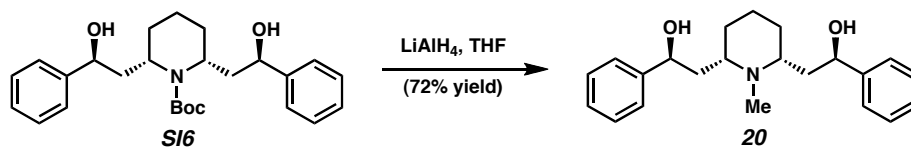


42. *N*-Boc, *O*-TBS-Dihydro-Lobeline **SI5.** To a -78 °C solution of ketone **44** (810 mg, 1.507 mmol) in toluene (30 mL) was slowly added neat DIBAL-H (296 μ L, 1.658 mmol). After 1 h, the reaction was warmed to -42 °C for 1 h, then warmed to 23 °C for 30 min. At this time, the reaction was cooled 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 MgSO_4 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, R_f 0.55 in 20% EtOAc:hexane) as a clear oil: ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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 $[\text{C}_{32}\text{H}_{50}\text{NO}_4\text{Si}]^+$: 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, R_f 0.30 in 20% EtOAc:hexane) as

a clear oil: ^1H NMR (300 MHz, CDCl_3) δ 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) δ 156.3, 145.0, 128.7, 127.6, 126.0, 129.9, 80.9, 72.6, 48.2, 28.8, 14.0; IR (film) 3393, 2937, 1653 cm^{-1} ; HRMS (FAB $^+$) calc'd for $[\text{C}_{26}\text{H}_{36}\text{NO}_4]^+$: 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 $^\circ\text{C}$ before treatment with a 1 M THF solution of LiAlH_4 (7.40 mL, 7.40 mmol). The reaction was heated to 55 $^\circ\text{C}$ in a sealed vial for 8 h, then cooled to 0 $^\circ\text{C}$ 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_3N :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 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $[\text{C}_{22}\text{H}_{30}\text{NO}_2]^+$: m/z 340.2277, found 340.2278. The relative stereochemistry of lobelanidine **20** was confirmed by x-ray crystallography (see below).

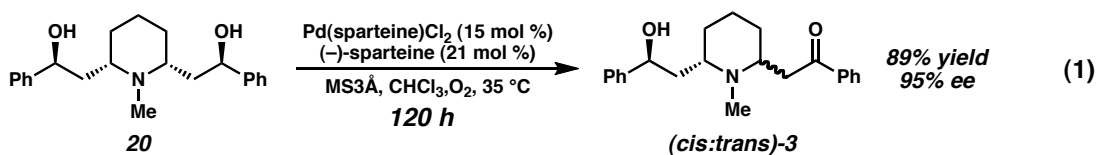
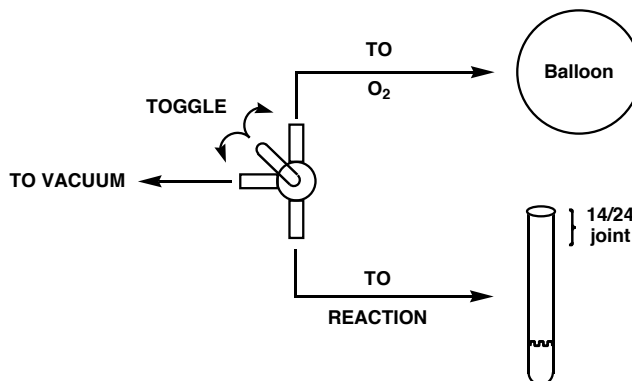


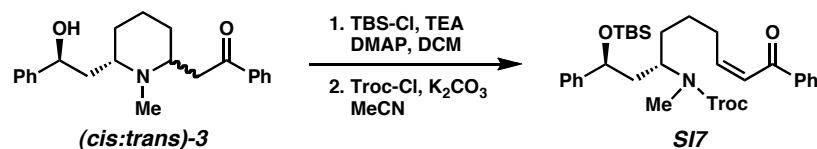
Figure 2. Experimental set-up



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 (-)-

Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S50
 lobeline as (*cis:trans*)-**3** (61 mg, 89 % yield) in a 1:1 mixture of *cis:trans* isomers as a white foam: m.p. 129-130° (130); ¹H NMR (300 MHz, CDCl₃) δ 8.01-7.97 (comp. m, 2H, *cis* isomer), 8.01-7.97 (comp. m, 2H, *trans* isomer), 7.64-7.22 (comp. m, 8H, *cis* isomer), 7.64-7.22 (comp. m, 8H, *trans* isomer), 4.97 (dd, *J* = 10.8, 2.9 Hz, 1H, *cis* isomer), 4.93 (dd, *J* = 10.7, 2.6 Hz, 1H, *trans* isomer), 3.65-3.59 (m, 1H, *cis* isomer), 3.85-3.80 (m, 1H, *trans* isomer), 3.26 (dd, *J* = 16.0, 5.0 Hz, 2H, *cis* isomer), 3.32-3.22 (comp. m, 2H, *trans* isomer), 3.0 (dd, *J* = 16.0, 8.5 Hz, 1H, *cis* isomer), 3.1 (dd, *J* = 14.9, 9.8 Hz, 1H, *trans* isomer), 2.58 (s, 3H, *trans* isomer), 2.38 (s, 3H, *cis* isomer), 2.38-2.18 (m, 1H, *trans* isomer), 2.06-1.46 (comp. m, 7H, *cis* isomer), 1.83-1.46 (comp. m, 6H, *trans* isomer), 1.29-1.18 (m, 1H, *cis* isomer); ¹³C NMR (75 MHz, CDCl₃) δ 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 [C₂₂H₂₇NO₂]⁺: *m/z* 337.2042, found 337.2027; [α]_D²⁰ -55.8° (*c* 1, CDCl₃).

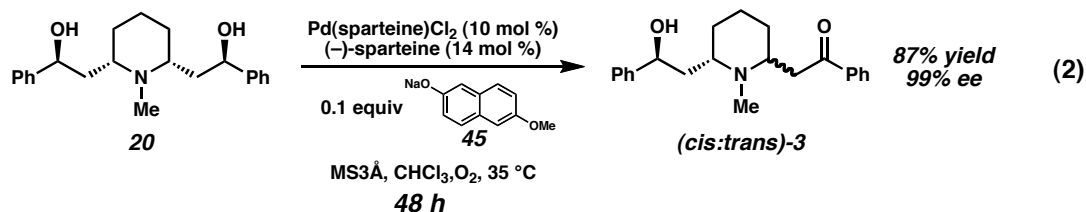
Scheme 1. Derivatization to a HPLC tractable analogue



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 (*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

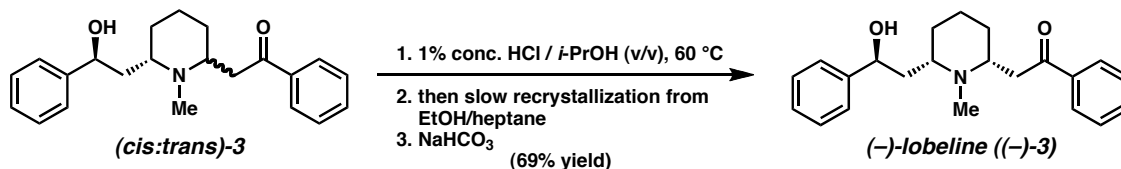
¹¹ Zheng, G.; Dwoskin, L. P.; Crooks, P. A. *J. Org. Chem.* **2004**, *69*, 8514.

Krishnan, Ramtohum, Bagdanoff, Ebner, Tambar, and Stoltz, Supporting Information, S51
 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.



46. (cis:trans)-(-)-Lobeline ((cis:trans)-3): Equation 2 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). . In a separate flask Pd(sparteine)Cl₂ (8.2 mg, 0.02 mmol) and sodium naphthaleneoxide **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(naphthaleneoxide)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 μ L). 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 NaHCO_3) 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 NaHCO_3 before concentrating the organics under reduced pressure, to provide (-)-lobeline ((-)-**3**, 40 mg, 69% yield). The ^1H NMR spectra was recorded immediately in CDCl_3 to observe exclusively the *cis* configuration, which was identical to natural (-)-lobeline: m.p. 130°; ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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 $[\text{C}_{22}\text{H}_{27}\text{NO}_2]^+$: m/z 337.2042, found 337.2043; $[\alpha]_D^{20} -41.3^\circ$ (c 1, CHCl_3).

