Enantioselective Catalysis Coupled with Stereodivergent Cyclization Strategies Enables Rapid Syntheses of (+)-Limaspermidine and (+)-Kopsihainanine A

Beau P. Pritchett*, Etienne J. Donckele*, and Brian M. Stoltz*

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Materials and Methods

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially available reagents were used as received. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or p-anisaldehyde staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 40-63 nm) was used for flash chromatography. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively) and are reported in terms of chemical shift relative to CHCl$_3$ ($\delta$ 7.26 and 77.16, respectively). Data for $^1$H NMR spectra are reported as follows: chemical shift ($\delta$ ppm) (multiplicity, coupling constant (Hz), integration). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm$^{-1}$). Analytical chiral SFC was performed with a Mettler SFC supercritical CO$_2$ analytical chromatography system with Chiralpak (AD-H) or Chiracel (OD-H) columns obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or from the Caltech Center for Catalysis and Chemical
Synthesis using an Agilent 6200 series TOF with an Agilent G1978A Multimode source in mixed (Multimode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm.

Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Bis(cyclopentadienyl) zirconium chloride hydride was purchased from Strem Chemicals and stored at room temperature in a N₂-filled glovebox. Hydroxylamine-O-sulfonic acid was purchased from Sigma Aldrich and stored at −30°C in the glovebox freezer. MeOH was distilled from magnesium methoxide immediately prior to use. Triethylamine was distilled from calcium hydride immediately prior to use. (S)-(CF₃)₅-t-BuPHOX (L1), ² tris(4,4′-methoxydibenzylideneacetone)dipalladium(0) Pd₂(pmdba)₃,³ allyl cyanoformate,⁴ and (2-benzzyloxy)ethyl iodide (15)⁵ were prepared by known methods.

**List of Abbreviations:**

DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene, TBD – 1,5,7-triazabicyclo[4.4.0]dec-5-ene,
TBME – tert-butyl methyl ether, ee – enantiomeric excess, LHMDS – lithium bis(trimethylsilyl)amide, SFC – supercritical fluid chromatography, TFA – trifluoroacetic acid, THF – tetrahydrofuran, TLC – thin-layer chromatography
Experimental Procedures

**Allyl 6-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-7-carboxylate (S1):** A flame-dried round bottom flask was charged with LHMDS (3.34 g, 20.0 mmol, 2.0 equiv) and a magnetic stirring bar in a N₂-filled glove box. The flask was sealed, removed from the glovebox, fitted with an argon line, and suspended in a dry ice/acetone bath. THF (50 mL) was added slowly to the flask and allowed to stir until the LHMDS had been completely dissolved. A solution of heteroarene 14 (1.84 g, 10.0 mmol, 1.0 equiv) in THF (7 mL) was added dropwise, and the reaction was allowed to stir for 30 min at −78 °C. Allyl cyanoformate (1.32 mg, 12.0 mmol, 1.2 equiv) was then added dropwise, and the reaction mixture was allowed to warm slowly to 0 °C over 4 h. Once the cooling bath temperature reached 0 °C, saturated aqueous NH₄Cl (200 mL) was then added slowly and the mixture stirred for 20 min before being extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. Flash column chromatography (SiO₂, 15% acetone in hexanes) afforded tertiary β-amidoester S5 (2.56 g, 96% yield) as a faintly yellow oil which solidified to an off-white amorphous solid upon storage at −30 °C: Rᵣ = 0.35 (4:1 hexanes:acetone eluent); ¹H NMR (500 MHz, CDCl₃) δ 8.45–8.42 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.24 (m, 2H), 6.36 (td, J = 1.4, 0.7 Hz, 1H), 5.93 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.35 (dq, J = 17.2, 1.5 Hz, 1H), 5.26 (dq, J = 10.4, 1.2 Hz, 1H), 4.77–4.67 (m, 2H), 3.83 (dd, J = 8.0, 5.0 Hz, 1H), 3.11 (dddd, J = 16.4, 8.1, 4.5, 1.4 Hz, 1H), 2.98...
(dddd, J = 16.4, 8.5, 4.6, 1.5 Hz, 1H), 2.55–2.46 (m, 1H), 2.38–2.29 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 169.0, 165.2, 137.0, 135.1, 131.5, 129.9, 124.51, 124.48, 120.0, 119.1, 116.7, 105.8, 66.5, 51.1, 25.3, 21.8; IR (Neat Film, NaCl) 3085, 3051, 2946, 2850, 1732, 1690, 1577, 1454, 1381, 1356, 1301, 1213, 1177, 1148, 1021, 977, 932, 802, 742 cm$^{-1}$; HRMS (FAB+) m/z calc'd for C$_{16}$H$_{16}$NO$_3$ [M+H]$^+$: 270.1130, found 270.1140.

**Allyl 7-(2-(benzyloxy)ethyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-7-carboxylate (16):** To a solution of β-amidoester S1 (727 mg, 2.70 mmol, 1.0 equiv) in DMF (9 mL) were added K$_2$CO$_3$ (522 mg, 3.78 mmol, 1.4 equiv) and iodide 15$^5$ (990 mg, 3.78 mmol, 1.4 equiv) at 23 °C with stirring. The reaction mixture was placed in a pre-heated 50 °C oil bath. After 4 h, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH$_4$Cl (50 mL) was added, followed by extraction with EtOAc (3 x 100 mL). The combined organic layers were washed with H$_2$O (50 mL), brine (50 mL), dried over Na$_2$SO$_4$, and concentrated. Flash column chromatography (SiO$_2$, 25% Et$_2$O in hexanes) afforded quaternary β-amidoester 16 (903 mg, 83% yield) as a clear colorless oil: R$_f$ = 0.32 (7:3 hexanes:Et$_2$O eluent); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.49–8.43 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.22 (m, 2H), 7.23–7.18 (m, 5H), 6.31 (dt, J = 1.8, 0.9 Hz, 1H), 5.81 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.21 (dq, J = 17.2, 1.5 Hz, 1H), 5.16 (dq, J = 10.5, 1.3 Hz, 1H), 4.64–4.56 (m, 2H), 4.46 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 3.74 (t, J = 6.3 Hz, 2H), 3.07 (ddt, J = 16.7, 4.7, 1.1 Hz, 1H), 2.96 (dddd, J = 16.6, 11.7, 4.6, 1.8 Hz, 1H), 2.59–2.49 (m, 2H), 2.41 (dt, J = 14.3, 6.1 Hz, 1H), 2.27 (ddd, J = 13.5, 11.8, 4.7 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.2, 167.9, 138.2, 137.2, 135.4, 131.4, 130.2, 128.4, 127.64, 127.62, 124.30, 124.28, 119.9, 118.9, 116.8, 105.3, 73.1, 66.8, 66.4, 55.3, 34.7, 30.3, 20.9; IR (Neat Film,
NaCl) 3066, 3032, 2930, 2855, 1728, 1701, 1597, 1577, 1451, 1353, 1333, 1301, 1171, 1093, 1026, 973, 798, 733, 695 cm⁻¹; HRMS (ESI/APCI) m/z calc’d for C₂₅H₂₆NO₄ [M+H]⁺: 404.1856, found 404.1865.

(S)-7-allyl-7-(2-(benzyloxy)ethyl)-8,9-dihydropyrido[1,2-a]indol-6(7H)-one (17): A flame-dried 100 mL Schlenk Flask was charged with Pd₂(pmdba)₃ (56 mg, 51.1 µmol, 0.05 equiv), (S)-(CF₃)₃-t-BuPHOX (L₁, 77 mg, 0.13 mmol, 0.125 equiv), and a magnetic stirring bar in a N₂-filled glove box. The flask was then charged with TBME (28 mL) and stirred at 23 °C for 30 minutes, generating a dark purple solution. To the preformed catalyst solution was added a solution of 16 (417 mg, 1.03 mmol, 1.0 equiv) in TBME (3 mL, including washings). The flask was sealed, removed from the glovebox, and placed in a preheated 60 °C oil bath with stirring. Full consumption of starting material was achieved after 8 h, as determined by TLC analysis. The crude reaction mixture was stripped onto silica gel, and purified by flash column chromatography (SiO₂, 12% Et₂O → 25% Et₂O in hexanes) to afford α-quaternary DHPI 17 (305 mg, 82% yield) as a faintly yellow oil: R_f = 0.5 (7:3 hexanes:Et₂O eluent); 94% ee, [α]D²⁵ +22.6 (c 1.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.49–8.46 (m, 1H), 7.49–7.46 (m, 1H), 7.30–7.25 (m, 2H), 7.25–7.20 (m, 5H), 6.30 (q, J = 1.3 Hz, 1H), 5.82 (ddt, J = 16.0, 11.2, 7.4 Hz, 1H), 5.15 (t, J = 1.1 Hz, 1H), 5.14–5.11 (m, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 3.69 (dt, J = 9.6, 6.9 Hz, 1H), 3.62 (ddd, J = 9.6, 7.2, 5.7 Hz, 1H), 3.05
(dd, $J = 7.5, 5.9, 1.3$ Hz, 2H), 2.66 (ddt, $J = 13.9, 7.0, 1.3$ Hz, 1H), 2.49–2.42 (m, 1H), 2.29 (dt, $J = 14.2, 7.1$ Hz, 1H), 2.12–2.03 (m, 2H), 1.99 (ddd, $J = 14.2, 6.9, 5.7$ Hz, 1H);

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.5, 138.3, 137.7, 135.3, 133.2, 130.2, 128.4, 127.62, 127.59, 124.02. 123.96, 119.8, 119.3, 116.7, 104.7, 73.2, 66.7, 45.6, 40.9, 35.4, 29.5, 19.9; IR (Neat Film, NaCl) 3062, 3028, 2930, 2856, 1693, 1639, 1595, 1574, 1451, 1433, 1355, 1299, 1181, 1097, 1026, 1001, 915, 797, 733, 695 cm$^{-1}$; HRMS (ESI/APCI) $m/z$ calc’d for C$_{24}$H$_{26}$NO$_2$ [M+H]$^+$: 360.1958, found 360.1962; SFC conditions: 15% $i$-PrOH, 2.5 mL/min, Chiralcel OD-H column, $\lambda = 210$ nm, $t_R$ (min): major = 8.83, minor = 9.71.

(4a$R$,11c$R$)-4a-(2-(Benzyloxy)ethyl)-2,3,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazole (19): A flame-dried round bottom flask was charged with $\alpha$-quaternary DHPI 17 (98 mg, 0.273 mmol, 1.0 equiv), THF (1.4 mL), and a magnetic stirring bar in a N$_2$-filled glovebox. To this solution was added bis(cyclopentadienyl) zirconium chloride hydride (84 mg, 0.325 mmol, 1.2 equiv), and the mixture was stirred at 23 °C for 30 min. A second portion of bis(cyclopentadienyl) zirconium chloride hydride (14 mg, 54 µmol, 0.2 equiv) was added, and the reaction mixture was stirred for an additional 30 min at which point a brown solution was observed. Hydroxylamine-$O$-sulfonic acid (46 mg, 0.406 mmol, 1.5 equiv) was added, the vial was sealed and removed from the glovebox, and stirring was resumed at 23 °C in a fume hood for an additional 10 min. The reaction mixture was then cooled to 0 °C and LiAlH$_4$ (0.82 mL, 1.0 M in THF, 0.82 mmol, 3.0 equiv) was added over five minutes. The reaction was stirred at 0 °C for 15 minutes
before careful quenching with H₂O (2.2 mL) and AcOH (6.6 mL). Stirring was continued at 23 °C for 12h, at which point complete equilibration to the desired Pictet–Spengler product (19) was observed by LCMS. The mixture was basified with 2N NaOH until pH > 12, and was extracted with CH₂Cl₂ (3 x 75 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford crude cis-fused tetracycle 19 (96 mg), which was carried on without further purification.

An analytical sample of 19 was obtained after flash column chromatography (SiO₂, 2% Et₃N in EtOAc): off-white foam; Rₜ = 0.45 (19:1 EtOAc:Et₃N eluent); [α]D₂⁵ = −23.1 (c 0.22, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.94 (br s, 1H), 7.56 (d, J = 7.3 Hz, 1H), 7.35–7.24 (m, 6H), 7.14–7.01 (m, 2H), 4.45 (s, 2H), 3.75 (s, 1H), 3.61–3.54 (m, 2H), 3.01 (d, J = 12.2 Hz, 1H), 2.80–2.72 (m, 3H), 2.36 (app q, J = 10.2 Hz, 1H), 1.85–1.75 (m, 2H), 1.65–1.43 (m, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 138.7, 136.3, 134.1, 128.5, 127.60, 127.57, 127.5, 121.0, 119.3, 117.6, 112.1, 110.6, 73.0, 66.9, 56.7, 46.3, 36.7, 35.1, 34.4, 25.4, 22.8, 20.3; IR (Neat Film, NaCl) 3401, 3295, 3147, 3057, 3030, 2926, 2854, 1622, 1588, 1495, 1466, 1452, 1364, 1328, 1101, 1028, 1011, 806, 739, 697 cm⁻¹; HRMS (ESI/APCI) m/z calc’d for C₂₄H₂₉N₂O [M+H]⁺: 361.2274, found 361.2287.

**Ethanolamine 209**: To a solution of crude cis-fused tetracycle 19 (96 mg, 0.266 mmol, 1.0 equiv) in EtOH (8.9 mL) were added 2-bromoethanol (0.15 mL, 2.11 mmol, 8.0 equiv), K₂CO₃ (295 mg, 2.11 mmol, 8.0 equiv) and a magnetic stirring bar. The suspension was heated to 80 °C and stirred for 4 h, at which point full consumption of
starting material was observed by TLC analysis. The suspension was concentrated to dryness, partitioned between H₂O (75 mL) and EtOAc (75 mL), and extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. Flash column chromatography (SiO₂, 1% Et₃N in EtOAc) gave ethanolamine 20 (68 mg, 62% yield in two steps from 17) as tan foam: Rₜ = 0.5 (19:1 EtOAc:Et₃N eluent); [α]D²⁵ = +17.8 (c 1.28, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.90 (br s, 1H), 7.42–7.38 (m, 1H), 7.32–7.28 (m, 2H), 7.27–7.22 (m, 4H), 7.12–7.05 (m, 2H), 4.40 (d, J = 11.9 Hz, 1H), 4.37 (d, J = 11.9 Hz, 1H), 3.56–3.42 (m, 3H), 3.24 (s, 1H), 3.17–3.07 (m, 3H), 2.87–2.72 (m, 3H), 2.26–2.17 (m, 2H), 1.89–1.74 (m, 2H), 1.66–1.51 (m, 3H), 1.48–1.41 (m, 1H), 1.30 (ddd, J = 14.1, 8.3, 5.8 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 138.6, 136.2, 135.4, 129.9, 128.5, 127.62, 127.57, 121.1, 119.6, 117.8, 110.6, 110.5, 73.0, 67.0, 63.2, 58.0, 54.2, 52.3, 36.84, 36.82, 35.8, 25.2, 22.1, 20.5; IR (Neat Film, NaCl) 3406, 3212, 3178, 3107, 3060, 3031, 2943, 2871, 1619, 1584, 1496, 1452, 1366, 1329, 1305, 1246, 1187, 1104, 1075, 1038, 983, 903, 870, 741, 697 cm⁻¹; HRMS (ESI/APCI) m/z calc’d for C₂₆H₃₃N₂O₂ [M+H]: 405.2537, found 405.2541.

**O-Benzyl Limaspermidine (22):** To a solution of primary alcohol 20 (64 mg, 158 µmol, 1.0 equiv) and N,N-diisopropylethylamine (DIPEA, 36 µL, 206 µmol, 1.3 equiv) in CH₂Cl₂ (3.1 mL) was added methanesulfonyl chloride (MsCl, 12.5 µL, 161 µmol, 1.02 equiv) dropwise at −15 °C (ice/MeOH bath). After stirring at −15 °C for 45 min, KOt-Bu (0.79 mL, 0.5 M in THF, 0.395 mmol, 2.5 equiv) was added and the reaction mixture was
allowed to warm to 0 °C over a period of 2 h. The reaction mixture was quenched with brine (25 mL), and extracted with EtOAc (5 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude residue was dissolved in EtOH (4.8 mL) and the resulting solution cooled to 0 °C. NaBH₄ (30 mg, 0.79 mmol, 5.0 equiv) was added in three equal portions over 10 min. After stirring at 0 °C for 15 additional min, the reaction mixture was removed from the ice bath and stirring was continued for a further 3 h. Sodium citrate dihydrate (233 mg, 0.79 mmol, 5.0 equiv) and H₂O (5 mL) were added, and the mixture was stirred at 23 °C for 30 min. The reaction mixture was partitioned between H₂O (20 mL) and EtOAc (20 mL), and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Flash column chromatography (SiO₂, 8% MeOH in CH₂Cl₂) gave O-benzyl 10imaspermidine (22, 44.6 mg, 73% yield) as faint yellow oil: Rf = 0.22 (19:1 CH₂Cl₂:MeOH eluent); [α]D₂5 +10.0 (c 0.44, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.30 (dd, J = 8.0, 6.5 Hz, 2H), 7.27–7.23 (m, 1H), 7.22–7.19 (m, 2H), 7.08 (d, J = 7.4 Hz, 1H), 7.02 (td, J = 7.6, 1.3 Hz, 1H), 6.74 (td, J = 7.3, 1.0 Hz, 1H), 6.64 (d, J = 7.7 Hz, 1H), 4.36 (d, J = 12.0 Hz, 1H), 4.32 (d, J = 12.0 Hz, 1H), 3.51 (dd, J = 11.0, 6.2 Hz, 1H), 3.44 (ddd, J = 9.6, 8.1, 5.9 Hz, 1H), 3.40–3.35 (m, 1H), 3.15–3.10 (m, 1H), 3.05 (d, J = 11.0 Hz, 1H), 2.35–2.22 (m, 2H), 2.27 (s, 1H), 2.08–1.93 (m, 2H), 1.86 (ddd, J = 14.5, 8.3, 6.5 Hz, 1H), 1.80–1.70 (m, 1H), 1.66 (ddt, J = 13.0, 6.4, 3.1 Hz, 2H), 1.54–1.42 (m, 3H), 1.31–1.19 (m, 2H), 1.08–1.03 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 149.6, 138.6, 135.4, 128.4, 127.7, 127.5, 127.4, 123.0, 119.4, 110.4, 72.8, 71.0, 66.2, 65.6, 53.9, 53.6, 53.0, 38.7, 36.9, 35.6, 35.5, 28.4, 24.4, 21.9; IR (Neat Film, NaCl) 3361, 3027, 2928, 2857, 2779, 2722, 1606, 1481, 1462, 1363, 1332, 1259, 1176, 1095, 1026,
740, 697 cm⁻¹; HRMS (ESI/APCI) m/z calc’d for C_{26}H_{33}N_{2}O [M+H]^+: 389.2587, found 389.2592.

(+)-Limaspermidine (2): To a solution of O-benzyl 11imaspermidine (22, 21 mg, 54 µmol, 1.0 equiv) in EtSH (1.8 mL) was added BF₃•Et₂O (133 µL, 1.07 mmol, 20 equiv) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was transferred to a pre-heated 30 °C oil bath and stirred for an additional 4 h. After cooling to 23 °C and quenching with saturated aqueous NHCO₃ (5 mL) and H₂O (5 mL), the mixture was stirred for an additional 2 h, then extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Flash column chromatography (SiO₂, 8% MeOH in CH₂Cl₂) furnished (+)-limaspermidine (2, 13.5 mg, 84% yield) as an off-white amorphous solid: Rᶠ = 0.27 (9:1 CH₂Cl₂:MeOH eluent); [α]D{sup 25} +22.6 (c 0.17, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.08 (dd, J = 7.4, 1.2 Hz, 1H), 7.01 (td, J = 7.6, 1.3 Hz, 1H), 6.73 (td, J = 7.4, 1.0 Hz, 1H), 6.64 (d, J = 7.7 Hz, 1H), 3.63 (td, J = 10.0, 5.4 Hz, 1H), 3.58–3.48 (m, 2H), 3.16–3.10 (m, 1H), 3.04 (app dt, J = 10.9, 2.2 Hz, 1H), 2.34–2.22 (m, 3H), 2.06 (td, J = 13.8, 3.5 Hz, 1H), 1.99 (ddd, J = 12.4, 10.9, 2.9 Hz, 1H), 1.81–1.67 (m, 3H), 1.65 (d, J = 13.5 Hz, 1H), 1.54–1.44 (m, 3H), 1.27 (td, J = 13.4, 4.6 Hz, 1H), 1.19 (ddd, J = 14.2, 9.3, 5.4 Hz, 1H), 1.04 (dd, J = 13.7, 3.8 Hz, 1H), 0.92 (br s, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 149.6, 135.4, 127.5, 122.9, 119.3, 110.6, 70.8, 65.5, 58.8, 53.9, 53.6, 53.0, 40.6, 38.7, 35.62, 35.55, 28.4, 24.4, 21.9; IR (Neat Film, NaCl) 3308, 3149, 2930, 2858, 2816, 2793, 1607, 1466, 1320, 1256, 1216, 1166,
1041, 1015, 900, 749 cm⁻¹; HRMS (ESI/APCI) m/z calc'd for C₁₉H₂₇N₂O [M+H]⁺: 299.2118, found 299.2114.

**Allyl 7-(3-methoxy-3-oxopropyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-7-carboxylate (23):** To a solution of β-amidoester S1 (530 mg, 1.96 mmol, 1.0 equiv) in MeCN (13.1 mL) were added methyl acrylate (0.36 mL, 3.92 mmol, 2.0 equiv) and DBU (15 µL, 98 µmol, 0.05 equiv) at 23 °C with stirring. After 90 min, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH₄Cl (100 mL) was added, followed by extraction with EtOAc (3 x 150 mL). The combined organic layers were washed with H₂O (100 mL), brine (100 mL), then dried over Na₂SO₄, filtered and concentrated. Flash column chromatography (SiO₂, 25% acetone in hexanes) afforded quaternary β-amidoester 23 (670 mg, 96% yield) as a light yellow oil: Rf = 0.33 (3:1 hexanes:acetone eluent); ¹H NMR (500 MHz, CDCl₃) δ 8.47–8.44 (m, 1H), 7.47–7.45 (m, 1H), 7.31–7.24 (m, 2H), 6.32 (dt, J = 1.7, 0.9 Hz, 1H), 5.83 (ddt, J = 17.2, 10.4, 5.7 Hz, 1H), 5.24 (dq, J = 17.2, 1.6 Hz, 1H), 5.19 (dq, J = 10.5, 1.3 Hz, 1H), 4.65 (dt, J = 5.7, 1.4 Hz, 2H), 3.67 (s, 3H), 3.09 (ddt, J = 16.8, 4.9, 1.1 Hz, 1H), 2.96 (dddd, J = 16.7, 11.5, 4.8, 1.8 Hz, 1H), 2.68 (ddd, J = 15.8, 9.3, 6.5 Hz, 1H), 2.55 – 2.47 (m, 2H), 2.44 (ddd, J = 10.7, 5.6, 3.9 Hz, 2H), 2.13 (ddd, J = 13.4, 11.4, 4.7 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 173.4, 170.9, 167.5, 136.8, 135.3, 131.2, 130.1, 124.44, 124.42, 120.0, 119.2, 116.8, 105.6, 66.5, 55.6, 52.0, 30.6, 30.0, 29.9, 20.8; IR (Neat Film, NaCl) 2951, 2854, 1738, 1704, 1600, 1577, 1455, 1375, 1357, 1315, 1227, 1176, 1087, 1034,
Methyl 3-(7-allyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indol-7-yl)propanoate (24): A flame-dried 250 mL Schlenk Flask was charged with Pd$_2$(pmdba)$_3$ (90 mg, 82.1 µmol, 0.05 equiv), (S)-(CF$_3$)$_3$-t-BuPHOX (L1, 120 mg, 0.202 mmol, 0.125 equiv), and a magnetic stirring bar in a N$_2$-filled glove box. The flask was then charged with TBME (42 mL) and stirred at 23 °C for 30 minutes, generating a dark purple solution. To the preformed catalyst solution was added a solution of 23 (580 mg, 1.63 mmol, 1.0 equiv) in TBME (7 mL, including washings). The flask was sealed, removed from the glovebox, and placed in a preheated 60 °C oil bath with stirring. Full consumption of starting material was achieved after 12 h, as determined by TLC analysis. The crude reaction mixture was stripped onto silica gel, and purified by flash column chromatography (SiO$_2$, 25% Et$_2$O in hexanes) to afford α-quaternary DHPI 24 (456 mg, 90% yield) as a yellow oil: R$_f$ = 0.29 (7:3 hexanes:Et$_2$O eluent); 92% ee, [α]$_D^{25}$ = -4.2 (c 0.89, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.47–8.43 (m, 1H), 7.47–7.44 (m, 1H), 7.29–7.22 (m, 2H), 6.30 (td, J = 1.4, 0.7 Hz, 1H), 5.85–5.75 (m, 1H), 5.18–5.16 (m, 1H), 5.15–5.14 (m, 1H), 3.64 (s, 3H), 3.07 (td, J = 6.7, 1.4 Hz, 2H), 2.63 (ddt, J = 14.1, 7.1, 1.2 Hz, 1H), 2.53–2.39 (m, 3H), 2.18–2.03 (m, 3H), 2.01–1.91 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.8, 172.9, 137.4, 135.3, 132.8, 130.2, 124.14, 124.11, 119.9, 119.6, 116.7, 105.0, 51.9, 45.8, 40.2,
30.5, 29.6, 29.2, 19.7; IR (Neat Film, NaCl) 3459, 3376, 3077, 2948, 2865, 1731, 1694, 1639, 1597, 1575, 1452, 1358, 1310, 1258, 1176, 1101, 1031, 996, 920, 879, 800, 757, 644 cm⁻¹; HRMS (ESI/APCI) m/z calc’d for C₁₉H₂₂NO₃ [M+H]+: 312.1594, found 312.1584; SFC conditions: 7% i-PrOH, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, tᵣ (min): major = 15.71, minor = 14.34.

**Primary alcohol 25:** To a solution of DHPI 24 (1.2 g, 3.85 mmol, 1.0 equiv) in THF (38 mL) were added RhCl(PPh₃)₃ (176 mg, 0.19 mmol, 0.05 equiv) and catecholborane (7.6 mL, 1.0 M in THF, 7.6 mmol, 2.0 equiv) sequentially at 23 °C. After stirring at 23 °C for 30 min, H₂O (10 mL) and NaBO₂•4H₂O (2.9 g, 18.8 mmol, 5.0 equiv) were added. The reaction mixture was transferred to a pre-heated 85 °C oil bath and stirred for 15 min. After cooling to 23 °C, the resulting suspension was filtered. The filter cake was washed with THF, and the filtrate was concentrated to dryness. The residue was partitioned between CH₂Cl₂ (40 mL) and H₂O (40 mL), and the aqueous layer was extracted with CH₂Cl₂ (40 mL). The combined organic layers were washed with 1N aq. NaOH (3 x 40 mL) and brine (40 mL), dried over Na₂SO₄, filtered and concentrated. Flash column chromatography (SiO₂, 20% Et₂O in CH₂Cl₂) afforded alcohol 25 as a yellow oil (1.09 g, 86%): Rₚ = 0.21 (4:1 CH₂Cl₂:Et₂O eluent); [α]D²⁵ +10.9 (c 1.23, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.44–8.41 (m, 1H), 7.47–7.44 (m, 1H), 7.29–7.21 (m, 2H), 6.29 (app q, J = 1.1 Hz, 1H), 3.66–3.61 (m, 2H), 3.64 (s, 3H), 3.07 (ddt, J = 7.2, 5.8, 1.3, 2H), 2.52–2.36 (m, 2H), 2.17–2.02 (m, 3H), 2.00–1.88 (m, 2H), 1.77–1.69 (m, 2H), 1.66–1.59 (m,
\( ^{13} \text{C} \) NMR (126 MHz, CDCl\(_3\)) \( \delta \) 173.9, 173.4, 137.3, 135.2, 130.2, 124.13, 124.10, 119.9, 116.7, 105.1, 62.8, 51.9, 45.6, 31.6, 30.6, 29.7, 29.2, 27.1, 19.7; IR (Neat Film, NaCl) 3449, 2948, 2869, 1736, 1695, 1598, 1575, 1454, 1379, 1356, 1335, 1311, 1181, 1056, 1024, 819, 802, 758 cm\(^{-1}\); HRMS (ESI/APCI) \( m/z \) calc’d for C\(_{19}\)H\(_{24}\)NO\(_4\) [M+H]\(^+\): 330.1700, found 330.1705.

**Azide 26:** To a solution of alcohol 25 (1.1 g, 3.33 mmol, 1.0 equiv) and Et\(_3\)N (1.5 mL, 10.76 mmol, 3.2 equiv) in CH\(_2\)Cl\(_2\) (24 mL) was added methanesulfonyl chloride (MsCl, 0.28 mL, 3.62 mmol, 1.09 equiv) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, then was quenched with sat. aq. NaHCO\(_3\) (10 mL). After stirring for an additional 15 min, the aqueous layer was separated and extracted with CH\(_2\)Cl\(_2\) (2 x 20 mL). The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated. The crude product was dissolved in DMF (24 mL), and NaN\(_3\) (240 mg, 3.69 mmol, 1.1 equiv) was added. The suspension was stirred at 60 °C for 1 h, at which point complete consumption of starting material was determined by TLC analysis. The reaction mixture was cooled to 23 °C, diluted with H\(_2\)O (20 mL), and extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with H\(_2\)O (2x20 mL) and brine (20 mL), dried over Na\(_2\)SO\(_4\) and concentrated. Flash column chromatography (SiO\(_2\), 20% EtOAc in hexanes) afforded azide 26 as a yellow oil (1.04 g, 88% over two steps): \( R_f = 0.33 \) (3:1 hexanes:EtOAc eluent); \([\alpha]_d^{25} = -65.7 \) (c 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.45-8.41 (m, 1H), 7.49-7.43 (m, 1H), 7.31-7.21 (m, 2H), 6.31 (app q, \( J = 1.3 \) Hz, 1H).
Hz, 1H), 3.65 (s, 3H), 3.32 (td, J = 6.4, 1.3 Hz, 2H), 3.09 (dddd, J = 7.2, 5.7, 4.4, 1.5 Hz, 2H), 2.50–2.37 (m, 2H), 2.18–2.06 (m, 2H), 2.06–1.96 (m, 2H), 1.95–1.84 (m, 1H), 1.77–1.61 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.7, 172.8, 137.1, 135.3, 130.2, 124.23, 124.19, 119.9, 116.7, 105.2, 52.0, 51.8, 45.6, 32.7, 30.5, 29.8, 29.1, 23.7, 19.7; IR (Neat Film, NaCl) 2949, 2868, 2096, 1736, 1694, 1597, 1575, 1454, 1380, 1356, 1336, 1312, 1302, 1262, 1179, 1027, 1000, 819, 803, 758 cm$^{-1}$; HRMS (ESI/APCI) m/z calc’d for C$_{19}$H$_{23}$N$_4$O$_3$ [M+H]$^+$: 355.1765, found 355.1767.

Methyl ®-3-(3-(2-(1H-indol-2-yl)ethyl)-2-oxopiperidin-3-yl)propanoate (27): To a solution of azide 26 (700 mg, 1.97 mmol, 1.0 equiv) in THF (20 mL) and H$_2$O (4 mL) was added polymer-bound PPh$_3$ (1.31 g, ~3 mmol/g loading, 3.94 mmol, 2.0 equiv) in one portion. The reaction mixture was placed in a pre-heated oil bath and stirred at 65 °C for 4 h. After cooling to 23 °C, the reaction mixture filtered, washing with EtOAc, and the filtrate was concentrated to dryness. Flash column chromatography (SiO$_2$, 4% MeOH in CH$_2$Cl$_2$) afforded δ-lactam 27 as a light yellow foam (525 mg, 81%): $R_f$ = 0.27 (19:1 CH$_2$Cl$_2$:MeOH eluent); $[\alpha]_D^{25}$ = -21.4 (c 0.4, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.37 (br s, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.30–7.27 (m, 1H), 7.10 (ddd, J = 8.1, 7.1, 1.3 Hz, 1H), 7.04 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 6.21 (s, 1H), 5.85 (br s, 1H), 3.66 (s, 3H), 3.32 (td, J = 5.7, 2.1 Hz, 2H), 2.86 (ddd, J = 14.6, 11.1, 5.8 Hz, 1H), 2.69 (ddd, J = 15.0, 11.0, 4.5 Hz, 1H), 2.42 (h, J = 8.5 Hz, 2H), 2.16 (ddd, J = 13.7, 11.2, 4.6 Hz, 1H), 2.01 (t, J = 8.2 Hz, 2H), 1.91–1.80 (m, 4H), 1.77–1.68 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$)
δ 176.0, 174.1, 139.5, 136.2, 128.7, 121.1, 119.8, 119.5, 110.7, 99.4, 51.9, 44.3, 42.8, 37.5, 33.2, 30.2, 29.4, 23.6, 19.5; IR (Neat Film, NaCl) 3287, 3054, 2949, 2870, 1731, 1645, 1551, 1489, 1456, 1417, 1289, 1173, 1094, 1061, 1012, 910, 782, 748 cm\(^{-1}\); HRMS (ESI/APCI) \(m/z\) calc’d for C\(_{19}\)H\(_{25}\)N\(_2\)O\(_3\) [M+H]\(^+\): 329.1860, found 329.1868.

**Trans-fused tetracycle 28:** To a solution of δ-lactam 27 (111 mg, 0.338 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (8.4 mL) were added 2-chloropyridine (39 µL, 0.405 mmol, 1.2 equiv) and triflic anhydride (63 µL, 0.372 mmol, 1.1 equiv) at –20 °C (dry ice in H\(_2\)O/MeOH (7:3) bath). After 15 min, the reaction mixture was removed from the cooling bath and stirring continued for a further 15 min. At this time, the reaction mixture was cooled back to –20 °C and a solution of NaBH\(_4\) (64 mg, 1.69 mmol, 5.0 equiv) in MeOH (8.4 mL) was added dropwise over a period of two minutes. The reaction was diluted with CH\(_2\)Cl\(_2\) and quenched by the addition of saturated aqueous NaHCO\(_3\) (10 mL). The biphasic mixture was poured into H\(_2\)O (25 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated. Flash column chromatography (SiO\(_2\), 1% MeOH → 8% MeOH in CH\(_2\)Cl\(_2\)) afforded trans-fused tetracycle 28 (89 mg, 84% yield) as a yellow foam: R\(_f\) = 0.22 (9:1 CH\(_2\)Cl\(_2\):MeOH eluent); \([\alpha]_D^{25}\) +21.3 (c 0.5, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.89 (d, \(J = 7.9\) Hz, 1H), 7.82 (br s, 1H), 7.25 (d, \(J = 7.2\) Hz, 1H), 7.07 (ddd, \(J = 8.1, 7.1, 1.4\) Hz, 1H), 7.01 (ddd, \(J = 8.2, 7.1, 1.2\) Hz, 1H), 3.96 (app t, \(J = 2.0\) Hz, 1H), 3.61 (s, 3H), 3.33–3.26 (m, 1H), 2.91 (td, \(J = 12.9, 3.8\) Hz, 1H), 2.75 (dddd, \(J = 20.2, 11.8, 6.2, 3.1\) Hz, 1H), 2.65 (ddt, \(J =
16.7, 6.4, 1.4 Hz, 1H), 2.30 (ddd, \( J = 14.8, 12.1, 5.5 \) Hz, 1H), 2.20 (ddd, \( J = 14.8, 11.9, 4.8 \) Hz, 1H), 1.98 (td, \( J = 13.4, 12.7, 5.3 \) Hz, 1H), 1.78–1.69 (m, 3H), 1.62–1.42 (m, 3H), 1.35–1.23 (m, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 174.9, 136.1, 133.1, 127.2, 120.9, 120.5, 119.2, 110.8, 110.4, 64.1, 51.8, 47.2, 35.5, 33.6, 32.0, 29.0, 22.5, 20.6, 20.3; IR (Neat Film, NaCl) 3395, 3177, 3054, 2926, 2856, 1731, 1619, 1579, 1465, 1435, 1317, 1250, 1198, 1174, 1142, 1014, 875, 856, 739, 693 cm\(^{-1}\); HRMS (ESI/APCI) \( m/z \) calc’d for C\(_{19}\)H\(_{25}\)N\(_2\)O\(_2\) [M+H]\(^{+}\): 313.1911, found 313.1905.

**Pentacyclic lactam 29:** In an N\(_2\)-filled glovebox, an oven-dried scintillation vial was charged with a magnetic stirring bar, trans-fused tetracycle 28 (56 mg, 0.179 mmol, 1.0 equiv), toluene (2.2 mL), THF (0.44 mL), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 25 mg, 0.179 mmol, 1.0 equiv) at 23 °C. The vial was sealed and removed from the glovebox and placed in a pre-heated 80 °C heating block. After stirring for 5 h at 80 °C, the reaction mixture was cooled to 23 °C and stripped onto silica gel. Flash column chromatography (SiO\(_2\), 2% MeOH in CH\(_2\)Cl\(_2\)) afforded lactam 29 (32.5 mg, 65% yield) as a white amorphous solid: \( R_f = 0.32 \) (19:1 CH\(_2\)Cl\(_2\):MeOH eluent); recrystallized by slow evaporation from absolute ethanol; \( [\alpha]_D^{25} -17.5 \) (c 0.38, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.87 (br s, 1H), 7.72–7.67 (m, 1H), 7.26 (dt, \( J = 8.1, 0.9 \) Hz, 1H), 7.11 (ddd, \( J = 8.2, 7.1, 1.3 \) Hz, 1H), 7.02 (ddd, \( J = 8.1, 7.1, 1.1 \) Hz, 1H), 4.41 (dd, \( J = 12.9, 5.6 \) Hz, 1H), 4.33 (app t, \( J = 2.0 \) Hz, 1H), 3.15 (td, \( J = 12.8, 3.3 \) Hz, 1H), 3.02 (dddd, \( J = 13.6, 11.1, 6.6, 3.2 \) Hz, 1H), 2.76 (ddt, \( J = 17.2, 5.8, 1.7 \) Hz, 1H), 2.11–2.04 (m, 2H), 2.01–
1.83 (m, 4H), 1.73–1.67 (m, 2H), 1.59–1.48 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 186.1, 136.3, 133.2, 125.1, 121.9, 120.3, 119.8, 111.2, 110.4, 64.4, 53.8, 39.9, 37.0, 35.0, 34.6, 27.8, 22.5, 19.8; IR (Neat Film, NaCl) 3273, 3059, 2924, 2853, 1657, 1464, 1409, 1328, 1245, 1163, 1131, 1075, 910, 846, 804, 738 cm$^{-1}$; HRMS (ESI/APCI) $m/z$ calc’d for C$_{18}$H$_{21}$N$_2$O [M+H]$^+$: 281.1648, found 281.1649.

Dunitz–Winkler Distortion Parameters for Bridgehead Lactam 29

Single crystal X-ray diffraction enabled the calculation of amide distortion parameters ($\chi_C$, $\chi_N$, and $\tau$) for strained lactam 29. We calculated a pyramidalization parameter $\chi_N$ of 50.5°. The carbonyl carbon was found to exhibit a slight deviation from planarity with a distortion parameter $\chi_C$ of 6.5°. The torsion angle about the C–N bond, $\tau$, was determined to be 23.5°.
$^1$HNMR Data Comparison of Synthetic (+)-Limaspermidine (2) (Table S1)

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\( ^{13} \text{CNMR Data Comparison of Synthetic (+)-Limaspermidine (2) (Table S2)} \)

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Notes and References


2. McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M.


5. Procedure adapted from: King, B. W. Lactam Derivatives as Inhibitors of Matrix

6. For the definition of amide bond deformation, see: Dunitz, J. D.; Winkler, F. K.

$^1$H NMR (500 MHz, CDCl$_3$) of compound 16.
Infrared spectrum (Thin Film, NaCl) of compound 16.

$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 16.
$^1$H NMR (500 MHz, CDCl$_3$) of compound 17.
Infrared spectrum (Thin Film, NaCl) of compound 17.

$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 17.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 19.
Infrared spectrum (Thin Film, NaCl) of compound 19.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 19.
\(^1\text{H NMR} (500 \text{ MHz, CDCl}_3)\) of compound 20.
13C NMR (126 MHz, CDCl₃) of compound 20.

Infrared spectrum (Thin Film, NaCl) of compound 20.
$^1$H NMR (500 MHz, CDCl$_3$) of compound 22.
Infrared spectrum (Thin Film, NaCl) of compound 22.

$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 22.
$^1$H NMR (500 MHz, CDCl$_3$) of (+)-Limaspermidine (2).
Infrared spectrum (Thin Film, NaCl) of (+)-Limaspermidine (2).

$^{13}$C NMR (126 MHz, CDCl$_3$) of (+)-Limaspermidine (2).
$^1$H NMR (500 MHz, CDCl$_3$) of compound 23.
Infrared spectrum (Thin Film, NaCl) of compound 23.

$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 23.
\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) of compound 24.
Infrared spectrum (Thin Film, NaCl) of compound 24.

$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 24.
$^{1}$H NMR (500 MHz, CDCl$_3$) of compound 25.
Infrared spectrum (Thin Film, NaCl) of compound 25.

$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 25.
\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) of compound 26.
Infrared spectrum (Thin Film, NaCl) of compound 26.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 26.
$^{1}$H NMR (500 MHz, CDCl$_3$) of compound 27.
Infrared spectrum (Thin Film, NaCl) of compound 27.

$^{13}$C NMR (126 MHz, CDCl$_3$) of compound 27.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 28.
Infrared spectrum (Thin Film, NaCl) of compound 28.

$^{13}$C NMR (101 MHz, CDCl$_3$) of compound 28.
$^{1}$H NMR (400 MHz, CDCl$_3$) of compound 29.
Infrared spectrum (Thin Film, NaCl) of compound 29.

$^{13}\text{C}$ NMR (101 MHz, CDCl$_3$) of compound 29.