

Streamlined Strategy for the Scalable and Enantioselective Total Syntheses of the Eburnane Alkaloids

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Supporting Information:

Table of Contents

1	Materials and Methods.....	5
2	Previous Enantioselective Syntheses of Eburnane Alkaloids.....	6
2.1	Takano (1985): Ethyl Side Chain Eburnane Alkaloids	6
2.2	Winterfeldt (1987): (–)-Eburnamonine	7
2.3	Fuji (1987 & 1990): (–)-Eburnamonine and (–)-Dihydroeburnamenine	8
2.4	Schultz (1997): (–)-Eburnamonine.....	9
2.5	Wee (2000 & 2001): (–)-Eburnamonine	10
2.6	Okada (2004): (+)-Dihydroeburnamenine.....	11
2.7	Iwabuchi (2009): (–)-Eburnamonine	12
2.8	Prasad (2013): Eburnamonine	13
2.9	Quin (2017): Ethyl Side Chain Eburnane Alkaloids	14
2.10	Quin (2018): C18-Oxo Eburnane Alkaloids and Terengganensine B.....	15
2.11	Pandey (2017): Ethyl Side Chain Eburnane Alkaloids.....	16
2.12	Trost (2019): C19-Oxo Eburnane Alkaloids	17
2.13	Zhu (2019): Melokhanine E, Eburnamonine, Terengganensines and Larutanine	18
2.14	Stoltz (2021 & 2023): Ethyl Side Chain Eburnane Alkaloids	20
2.15	Tong (2021): (–)-Eburnamonine and (–)-Larutanine	21
2.16	Chen (2022): C18-Oxo Eburnane Alkaloids	22
3	Experimental Procedures and Characterization Data.....	23
3.1	Alkylation of γ -butyrolactone.....	23
3.2	α -Bromination of the lactone	24
3.3	Enantioconvergent cross-coupling with TMS-acetylene.....	25
3.4	Protodesilylation.....	26
3.5	Enantioconvergent cross-coupling with 1-hexyne.....	27
3.6	Ethenolysis.....	28
3.7	Lactam formation by condensation with tryptamine	29
3.8	Alcohol acetylation.....	30
3.9	Bischler-Napieralski reaction	33
3.10	Acetyl group removal	34
3.11	Oxidative lactamization	35
3.12	Lactam with n-butyl side chain.....	36

3.13	Alcohol acetylation with n-butyl side chain	37
3.14	Ethenolysis after lactam formation.....	39
3.15	Bischler-Napieralski reaction with n-butyl side chain.....	40
3.16	Acetyl group removal with n-butyl side chain	41
3.17	Oxidative lactamization with <i>n</i> -butyl side chain	42
3.18	Enantioconvergent Hiyama cross-coupling	43
3.19	(<i>-</i>)-Eburnamonine.....	44
3.20	(<i>+</i>)-Eburnamine.....	47
3.21	(<i>-</i>)-Eburnamenine.....	50
3.22	(<i>-</i>)-Dihydroeburnamenine	53
3.23	17-Oxo-eburnamonine	56
3.24	<i>epi</i> -17-OH-Eburnamonine	57
3.25	17-OH-Eburnamonine	58
3.26	(<i>+</i>)-Eburnamaline.....	59
3.27	(<i>-</i>)-19-OH-Eburnamonine	62
3.28	(<i>-</i>)-19-Oxoeburnamonine	65
3.29	(<i>-</i>)-19-OH-Eburnamonine by L-Selectride Reduction	68
3.30	(<i>+</i>)-19-OH-Eburnamine	69
3.31	(<i>+</i>)-19-Oxoeburnamine	73
3.32	(<i>-</i>)-Larutienine A	76
3.33	Hydroboration/Oxidation.....	79
3.34	Eburnaminol	80
3.35	Larutanine	83
3.36	Skeletal Rearrangement	86
3.37	(<i>-</i>)-Melokhanine E.....	88
3.38	Benzyl Protection of 3-butyn-1-ol	91
3.39	Enantioconvergent cross-coupling with benzyl protected 3-butyn-1-ol.....	91
3.40	Lactam formation for analog preparation	95
3.41	Alcohol acetylation for analog preparation	96
3.42	Bischler-Napieralski reaction for analog preparation	97
3.43	Acetyl group removal for analog preparation.....	98
3.44	Oxidative lactamization for analog.....	99
4	<i>Comparative Syntheses.....</i>	100

4.1	Comparative enantioselective synthesis of eburnamonine	100
4.2	Comparative enantioselective synthesis of eburnamine	100
4.3	Comparative enantioselective synthesis of eburnamenine	100
4.4	Comparative enantioselective synthesis of dihydroeburnamenine.....	101
4.5	Comparative enantioselective synthesis of 19-OH-eburnamonine.....	101
4.6	Comparative enantioselective synthesis of 19-OH-eburnamine.....	101
4.7	Comparative enantioselective synthesis of 19-oxoeburnamine.....	101
4.8	Comparative enantioselective synthesis of eburnaminol.....	101
4.9	Comparative enantioselective synthesis of laruteneine	102
4.10	Comparative enantioselective synthesis of melokhanine E.....	102
5	References.....	103
6	NMR Spectra	105

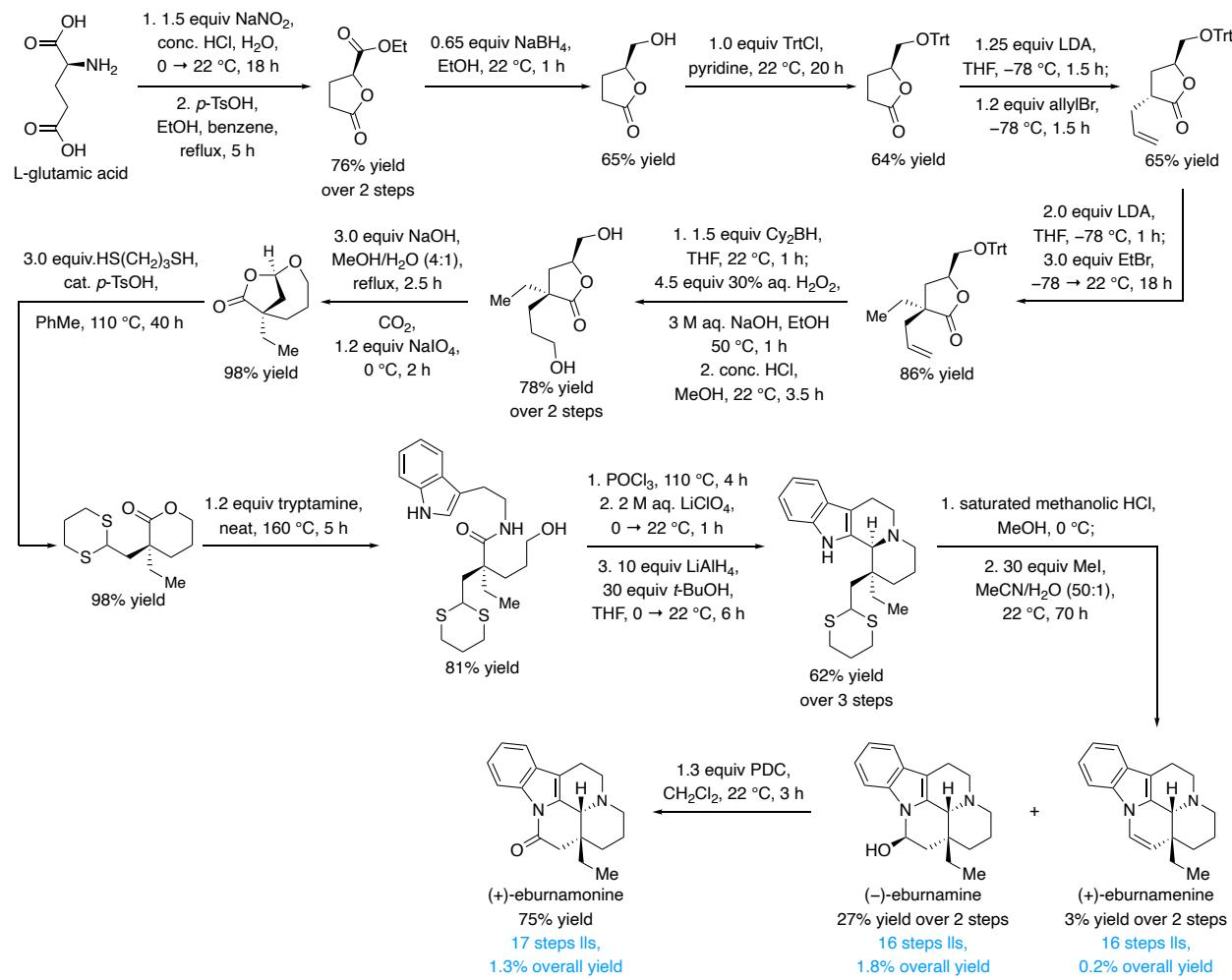
1 Materials and Methods

Reactions were performed under an inert atmosphere (dry N₂ or Ar) with freshly dried solvents utilizing standard Schlenk techniques, unless otherwise stated. Glassware was oven-dried at 120 °C for a minimum of four hours, or flame-dried utilizing a fire torch gun under high vacuum. Dry tetrahydrofuran (THF), methylene chloride (CH₂Cl₂), acetonitrile (MeCN), diethyl ether (Et₂O), 1,4-dioxane, dimethylformamide (DMF), benzene (PhH), and toluene (PhMe) were obtained by passing the previously degassed solvents through activated alumina columns. Triethylamine (Et₃N) and *N,N*-diisopropylethylamine (DIPEA) were distilled over calcium hydride prior to use. All other chemicals and solvents were purchased at the highest commercial quality and used as received, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) with Merck silica gel 60 F254 pre-coated plates (0.25 mm of thickness) using UV light as visualizing agent and *p*-anisaldehyde, vanillin, phosphomolybdic acid (PMA), basic aqueous potassium permanganate (KMnO₄), or acidic aqueous ceric ammonium molybdate (CAM) and heat as developing agents. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous material, unless otherwise stated. Flash column chromatography was performed using silica gel 60 (particle size 40–63 microns) purchased from Merck or Silicycle. NMR spectra were recorded on a Bruker Ascend™ 500 Avance NEO with Prodigy cryoprobe and were calibrated using residual non-deuterated solvent as an internal reference (CDCl₃: ¹H NMR δ = 7.26 ppm, ¹³C NMR δ = 77.16 ppm). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sex = sextet, sep = septet m = multiplet, br = broad, app = apparent. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm pathlength cell at the sodium lamp D-line wavelength (λ= 589 nm). Chiral HPLC analysis was performed on Agilent 1200 Infinity II equipped with a DAD detector. LC/MS analysis was performed on an Agilent 1200 series HPLC/MS equipped with an Agilent SB-C18 2.1 mm x 50 mm column, with mass spectra recorded on a 6120 Quadrupole mass spectrometer (API-ES), using MeCN and H₂O as the mobile phase (0.1% formic acid). LC/MS runs used the following method unless otherwise specified: flow rate of 0.5 mL/min is used, initial equilibration of 5% MeCN/H₂O with a linear gradient to 95% MeCN/H₂O over 5 minutes, then a hold at 95% MeCN/H₂O for an additional 3 minutes. HRMS were obtained from the University of Texas at San Antonio Mass Spectrometry and Proteomics Core in electrospray ionization (ESI-QTOF) mode.

2 Previous Enantioselective Syntheses of Eburnane Alkaloids

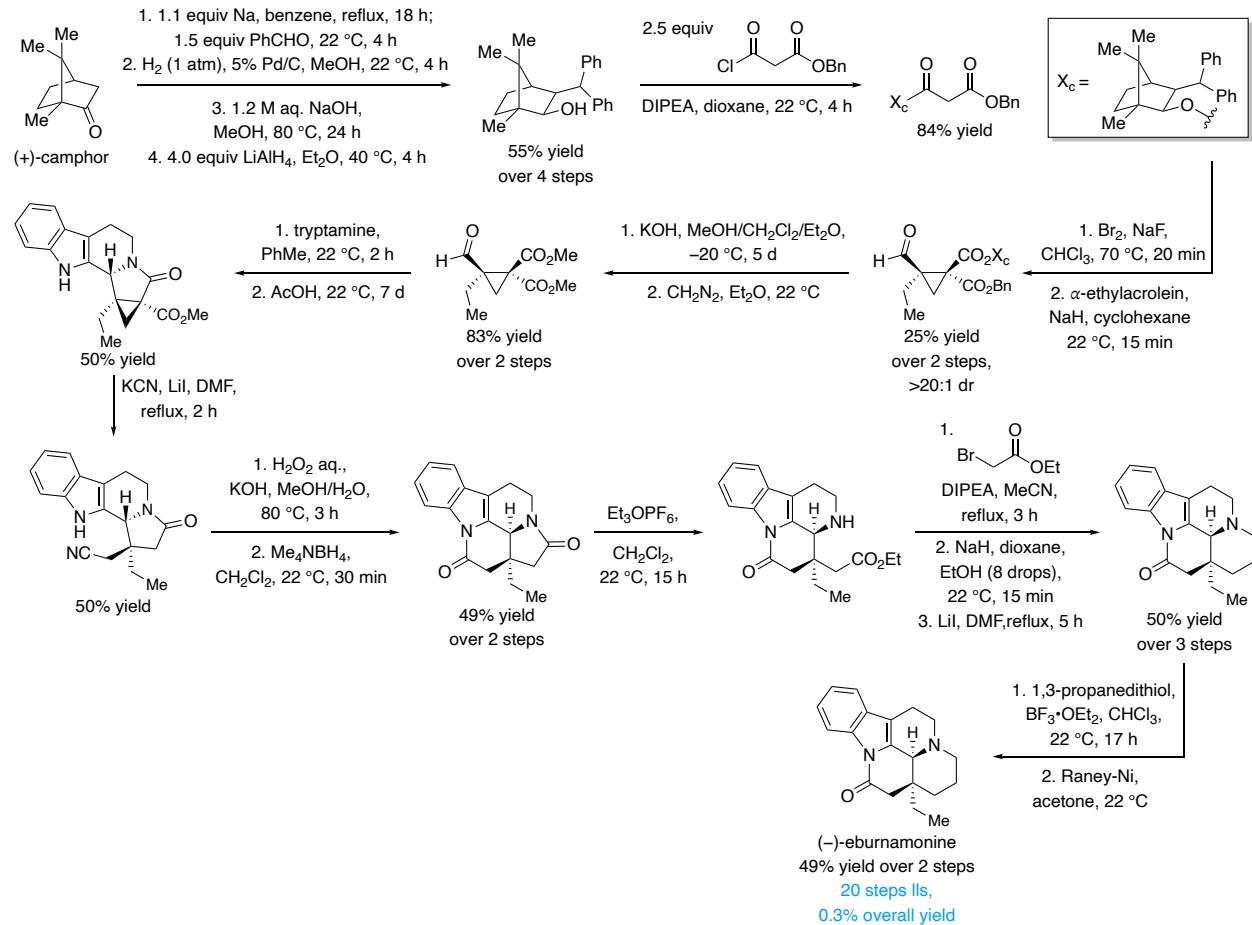
2.1 Takano (1985): Ethyl Side Chain Eburnane Alkaloids

Takano, S.; Yonaga, M.; Morimoto, M.; Ogasawara, K. Chiral Synthesis of (+)-Eburnamine, (-)-Eburnamenine, and (-)-Eburnamone. *J. Chem Perkin Trans. I* **1985**, 305–309.



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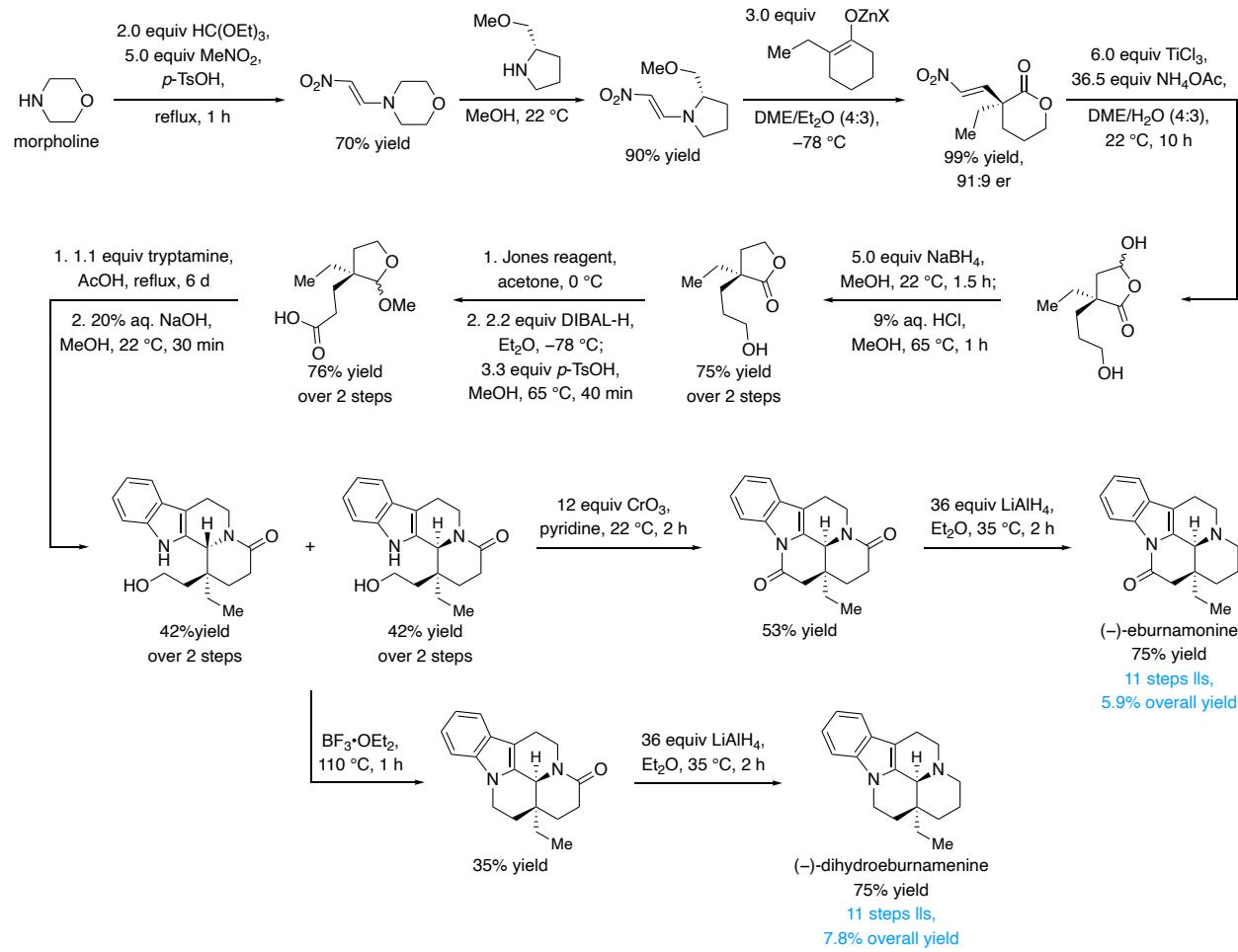
Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. Reactions with Indole Derivatives-LV. An Enantiodivergent Route to both Vincamine Enantiomers. *Tetrahedron* **1987**, *62*, 6855–6861.



2.3 Fuji (1987 & 1990): (–)-Eburnamонine and (–)-Dihydroeburnamенine

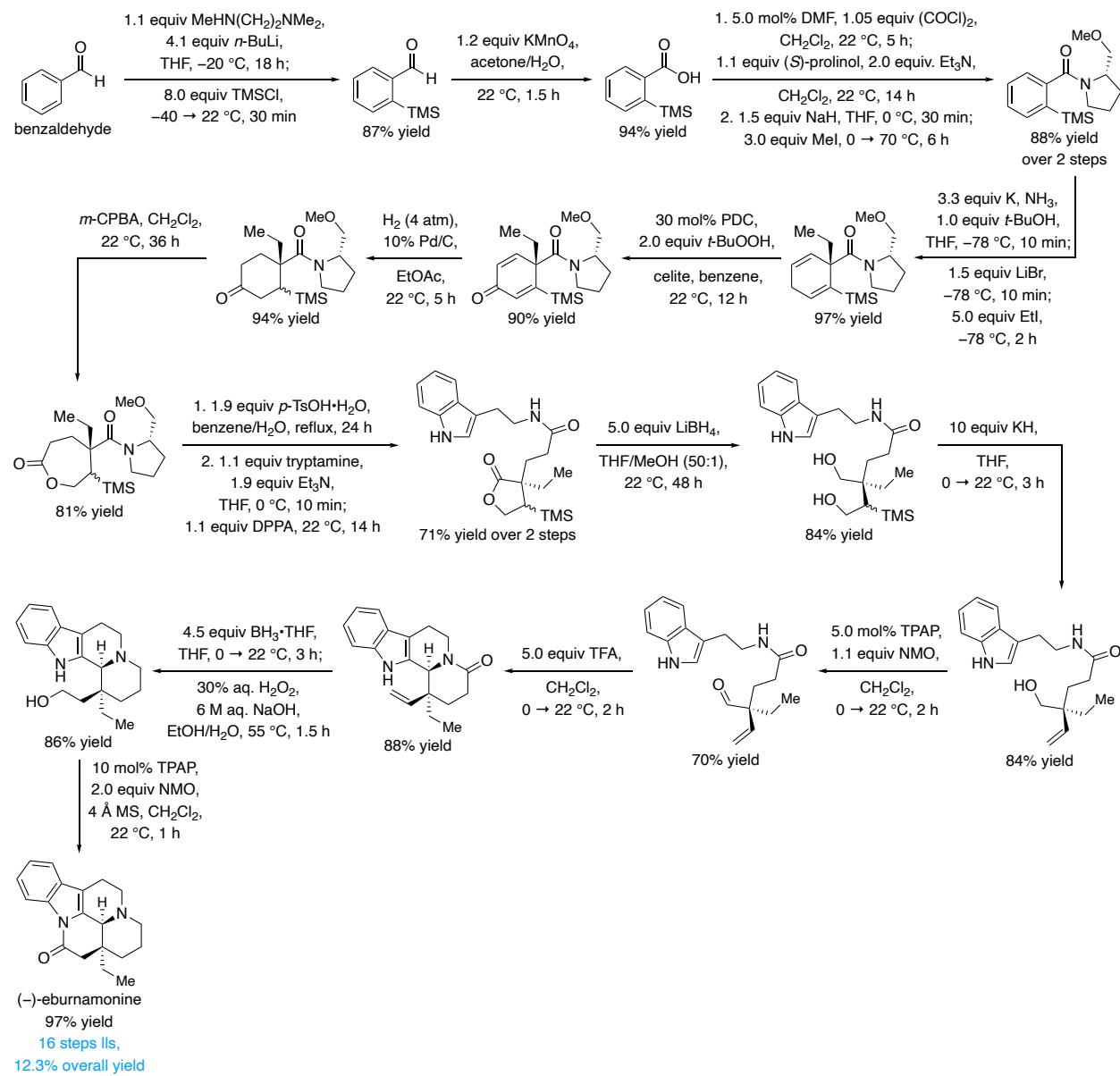
(a) Node, M.; Nagasawa, H.; Fuji, K. Expeditious Enantioselective Synthesis of Indole Alkaloids of *Aspidosperma*- and *Hunteria*-Type. *J. Am. Chem. Soc.* **1987**, *109*, 7901–7903.

(b) Node, M.; Nagasawa, H.; Fuji, K. Chiral Total Synthesis of Indole Alkaloids of the *Aspidosperma* and *Hunteria* Types. *J. Org. Chem.* **1990**, *55*, 517–521.



2.4 Schultz (1997): (-)-Eburnamone

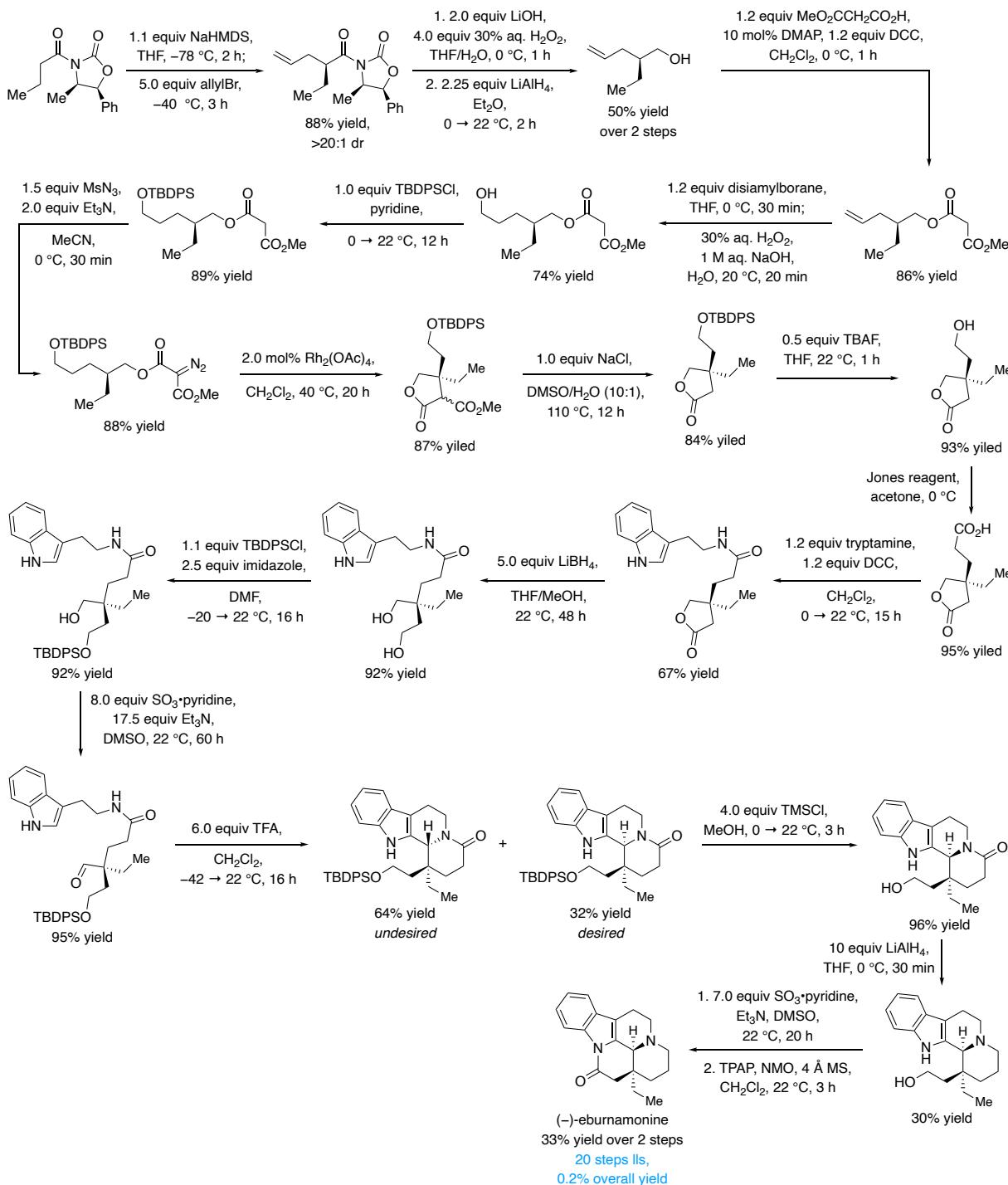
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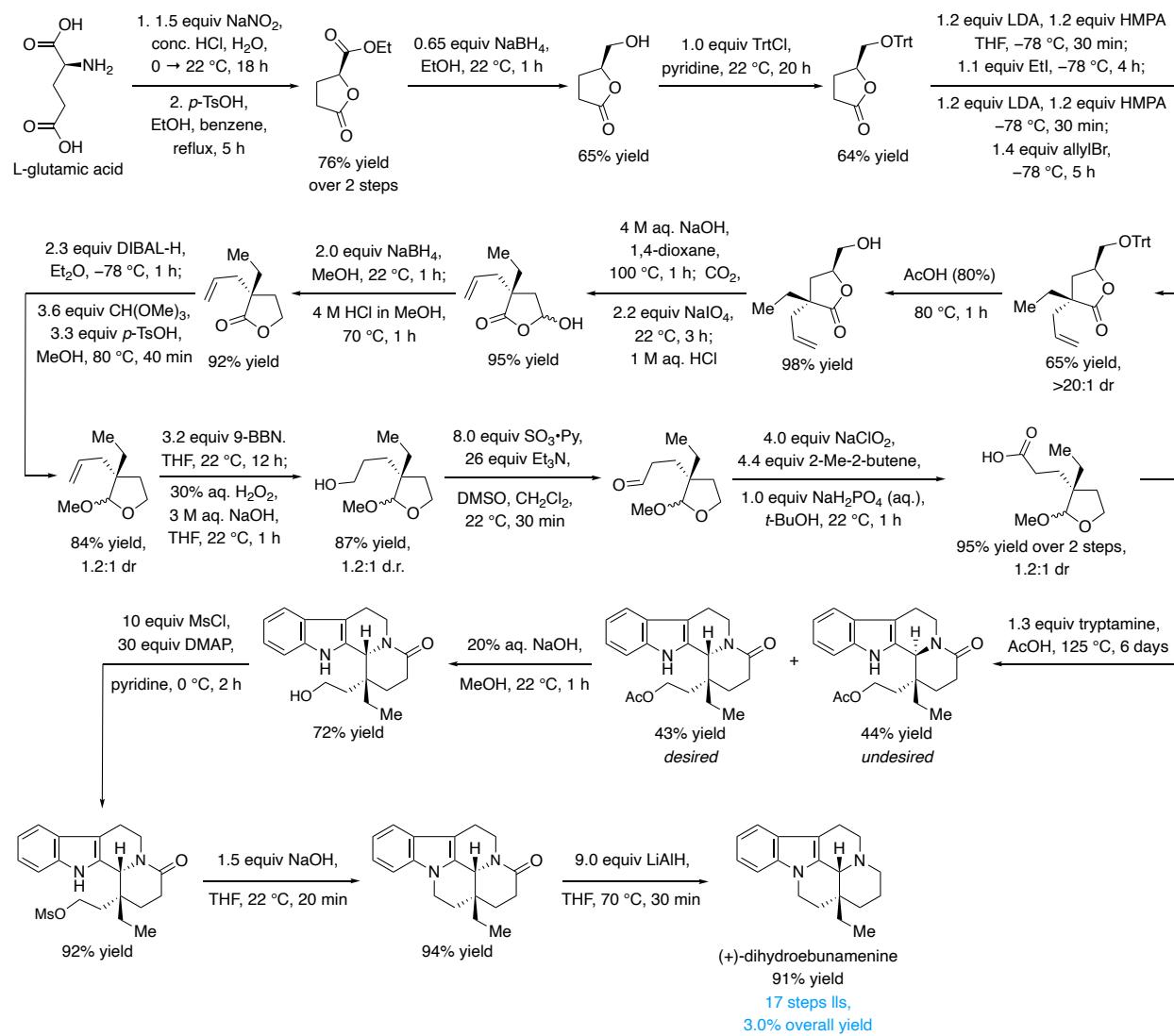
(a) Wee, A. G. H.; Yu, Q. Total Synthesis of (-)-Eburnamonine and (+)-*epi*-Eburnamonine from a Chiral Non-Racemic 4,4-Disubstituted γ -Lactone. *Tetrahedron Lett.* **2000**, *41*, 587–590.

(b) Wee, A. G. H.; Yu, Q. Asymmetric Synthesis of (-)-Eburnamonine and (+)-*epi*-Eburnamonine from (4S)-4-Ethyl-4-[2-(hydroxycarbonyl)ethyl]-2-butyrolactone. *J. Org. Chem.* **2001**, *66*, 8935–8943.



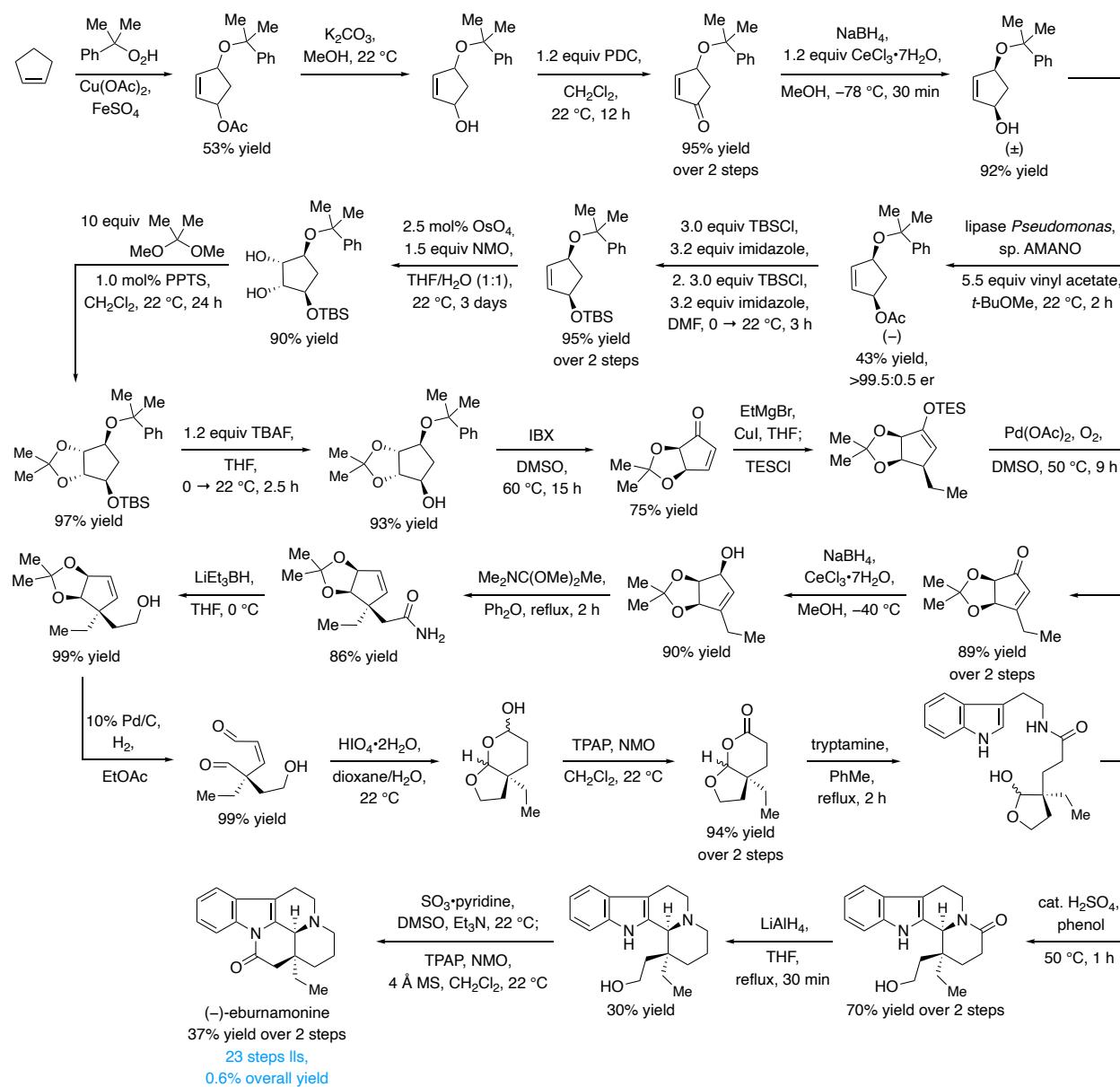
2.6 Okada (2004): (+)-Dihydroeburnamine

Tanino, H.; Fukuishi, K.; Ushiyama M.; Okada, K. Total Syntheses of (-)-Vallesamidine and Related *Aspidosperma* and *Hunteria* type Indole Alkaloids from the Common Intermediate. *Tetrahedron* **2004**, *60*, 3273–3282.



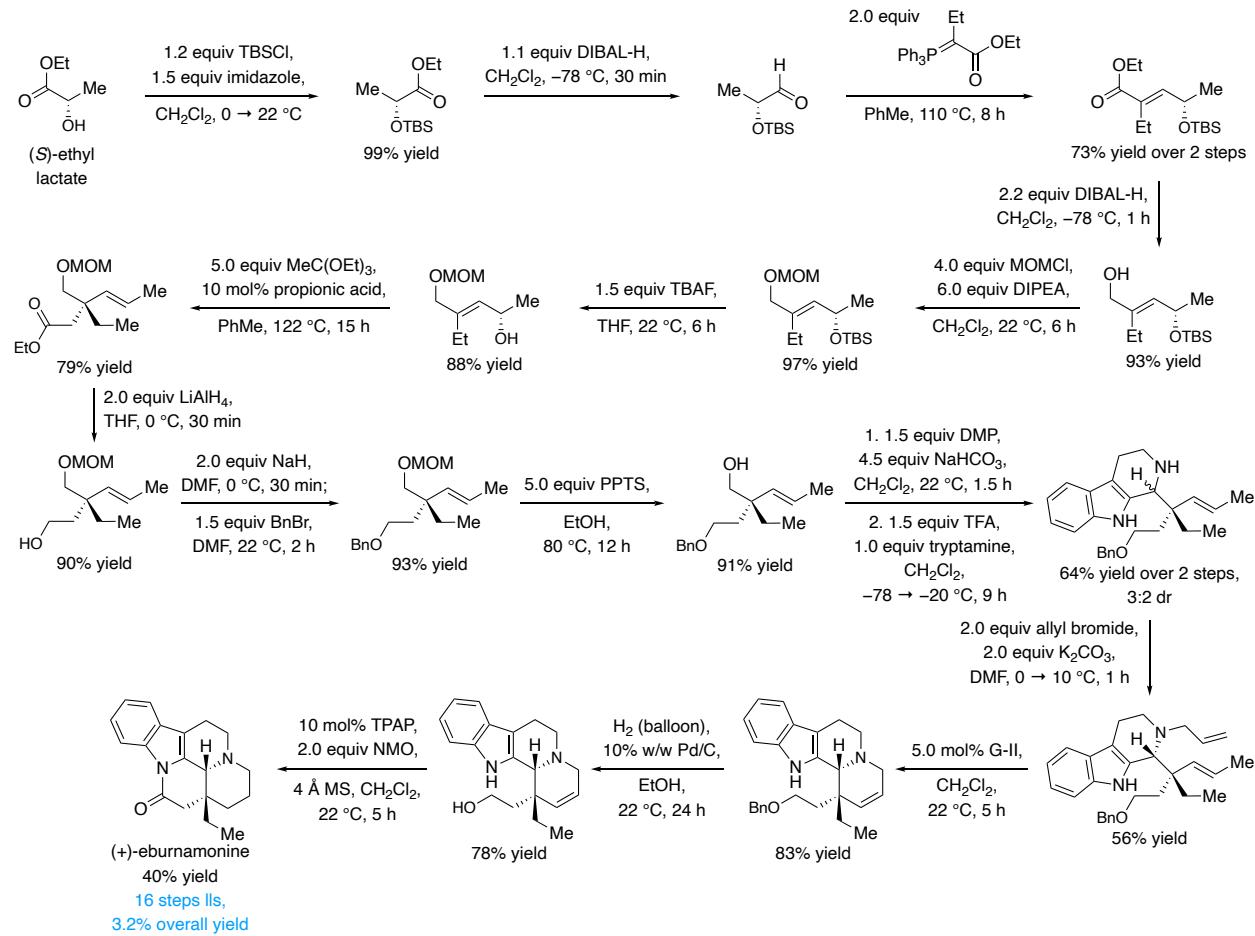
2.7 Iwabuchi (2009): (-)-Eburnamone

Hayashi, M.; Motosawa, K.; Satoh, A.; Shibuya, M.; Ogasawara, K.; Iwabuchi, Y. Flexible Access to Monoterpene Indole Alkaloids Using a Cyclopentanoid Chiral Building Block. *Heterocycles* **2009**, *77*, 855–863.



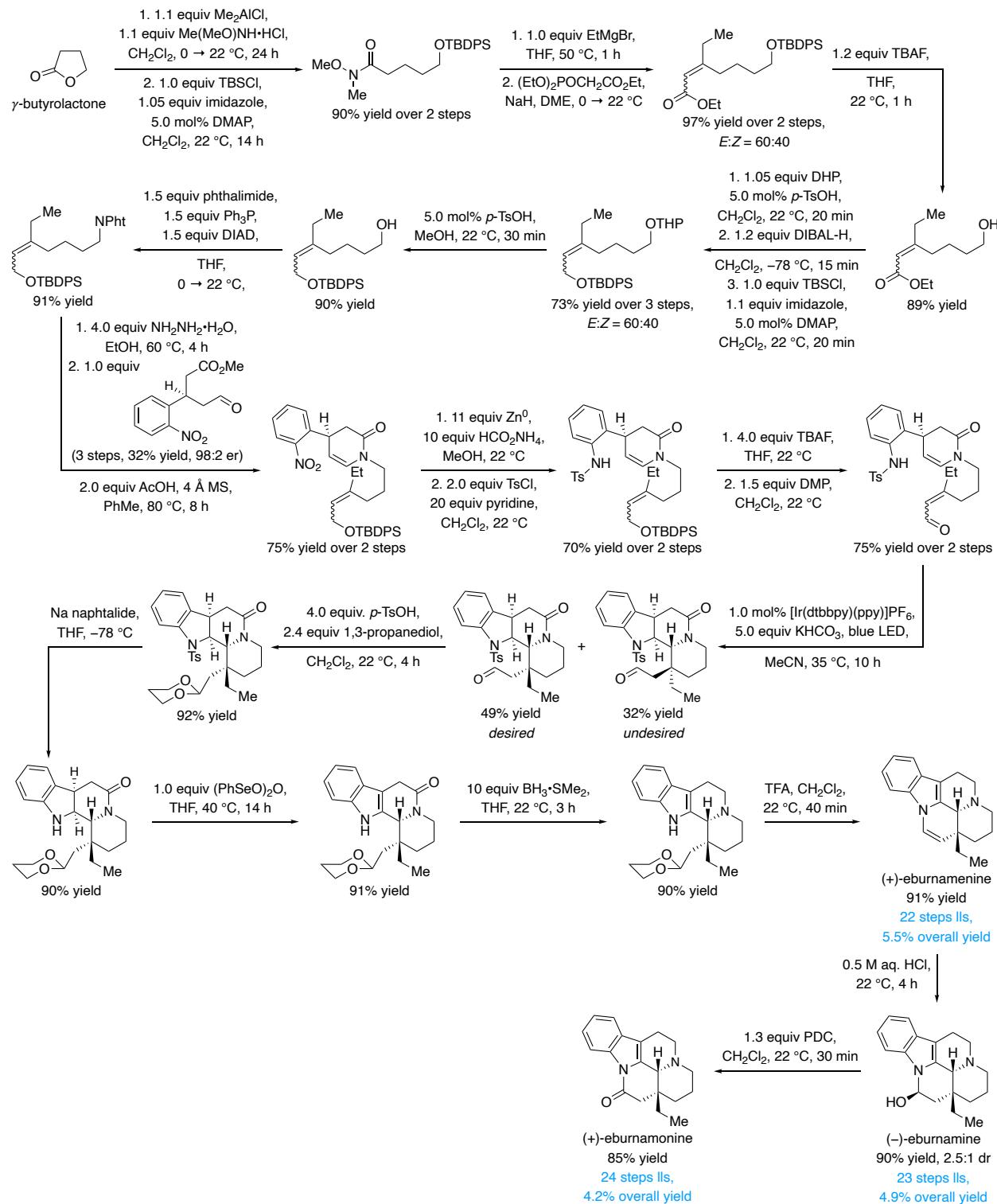
2.8 Prasad (2013): Eburnamonine

Nidhiry, J. E. Prasad, K. R. Enantiospecific Total Synthesis of Indole Alkaloids (+)-Eburnamonine, (-)-Aspidospermidine and (-)-Quebrachamine. *Tetrahedron* **2013**, *69*, 5525–5536.



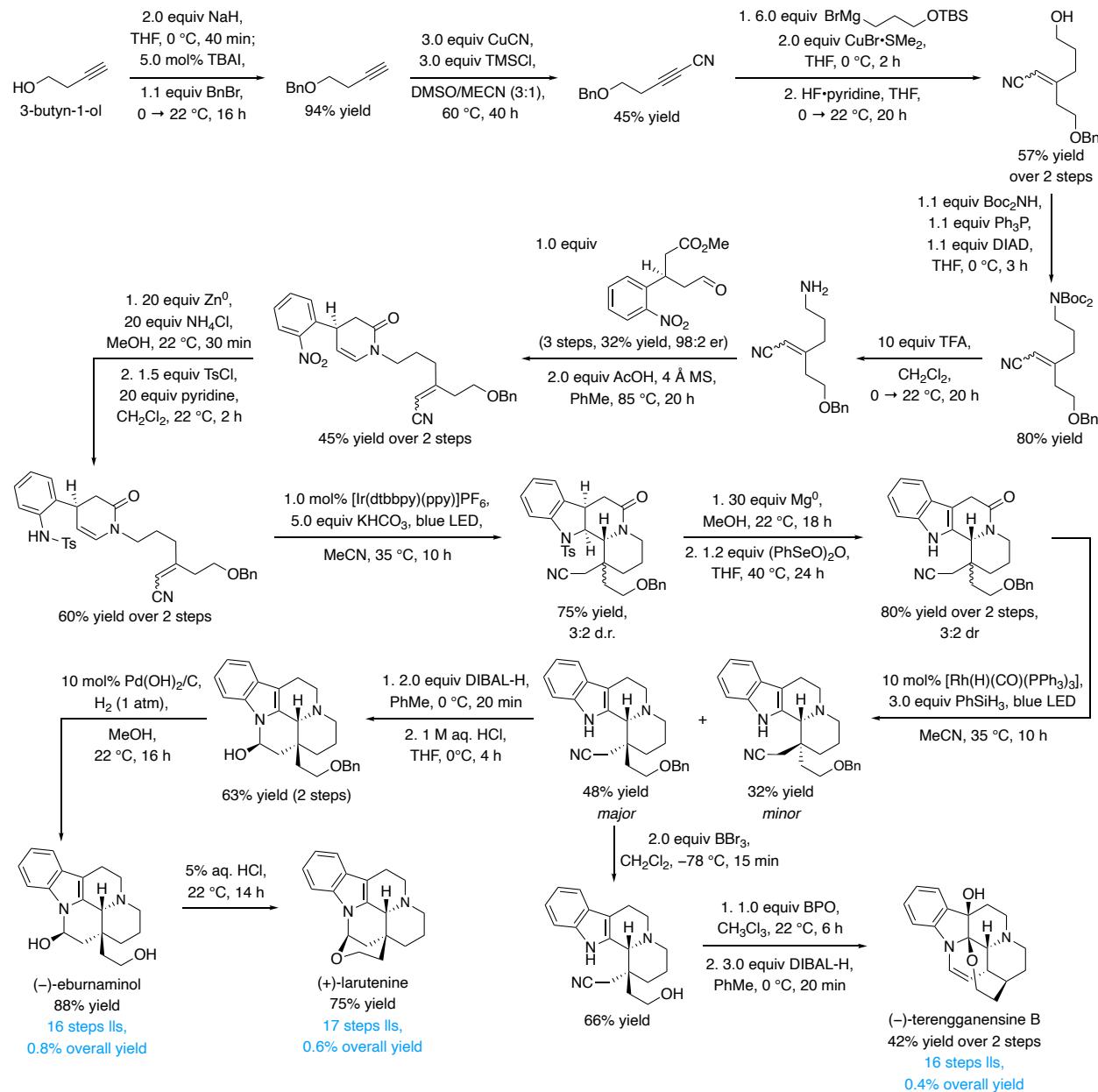
2.9 Quin (2017): Ethyl Side Chain Eburnane Alkaloids

Wang, X.; Xia, D.; Qin, W.; Zhou, R.; Zhou, X.; Zhou, Q.; Liu, W.; Dai, X.; Wang, H.; Wang, S.; Tan, L.; Zhang, D.; Song, H.; Liu, X.-L.; Qin, Y. A Radical Cascade Enabling Collective Syntheses of Natural Products. *Chem* 2017, 2, 803–816.



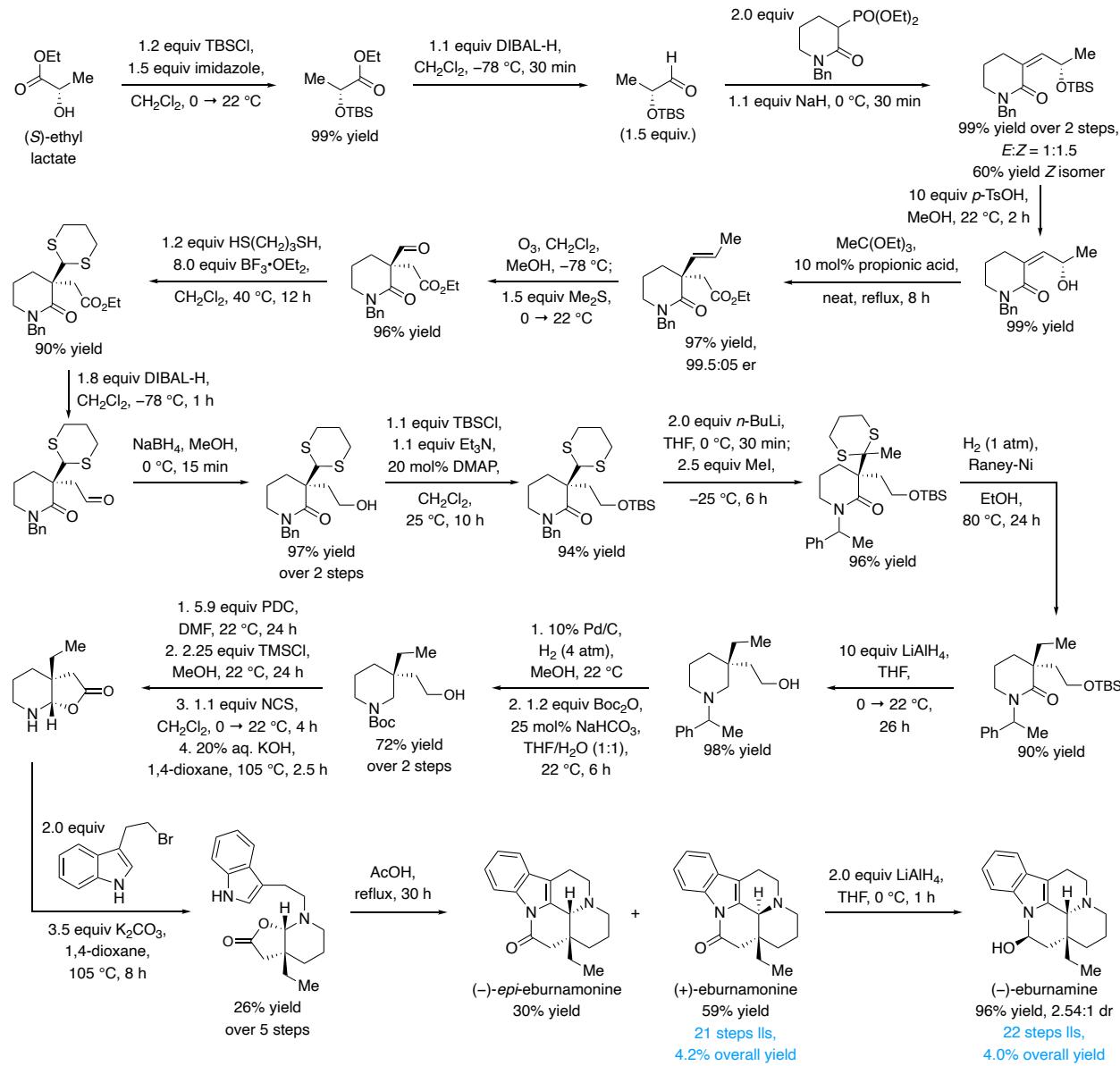
2.10 Quin (2018): C18-Oxo Eburnane Alkaloids and Terengganensine B

Zhou, Q.; Dai, X.; Song, H.; Huan He, H.; Wang, X.; Liu, X.-L.; Qin, Y. Concise Syntheses of *Eburnane* Indole Alkaloids. *Chem. Commun.* 2018, 54, 9510–9512.



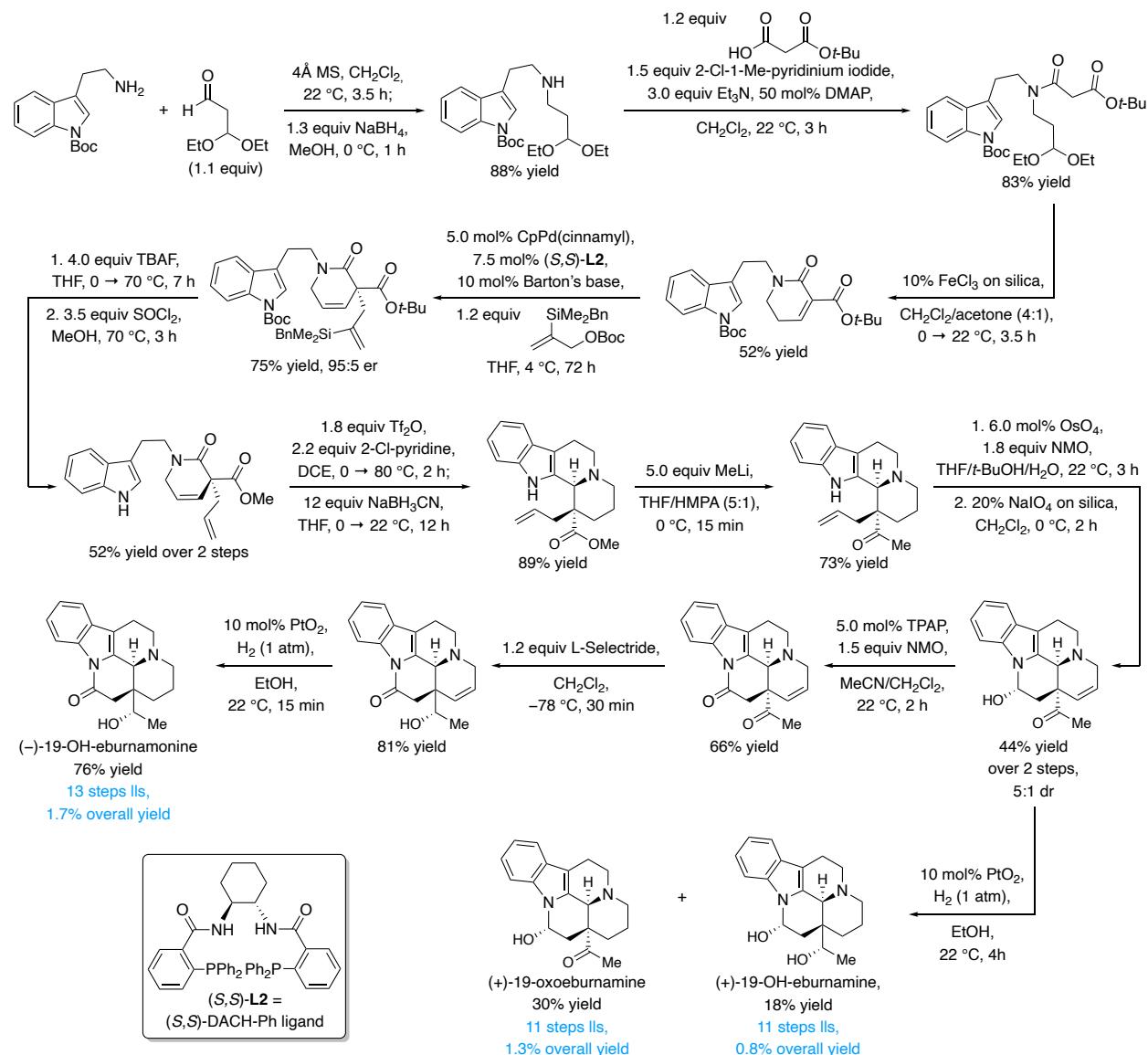
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Pandey, G.; Mishra, A.; Khamrai, J. Asymmetric Total Synthesis of Eburnamine and Eucophylline: A Biomimetic Attempt for the Total Synthesis of Leucophyllidine. *Org. Lett.* **2017**, *19*, 3267–3270.



2.12 Trost (2019): C19-Oxo Eburnane Alkaloids

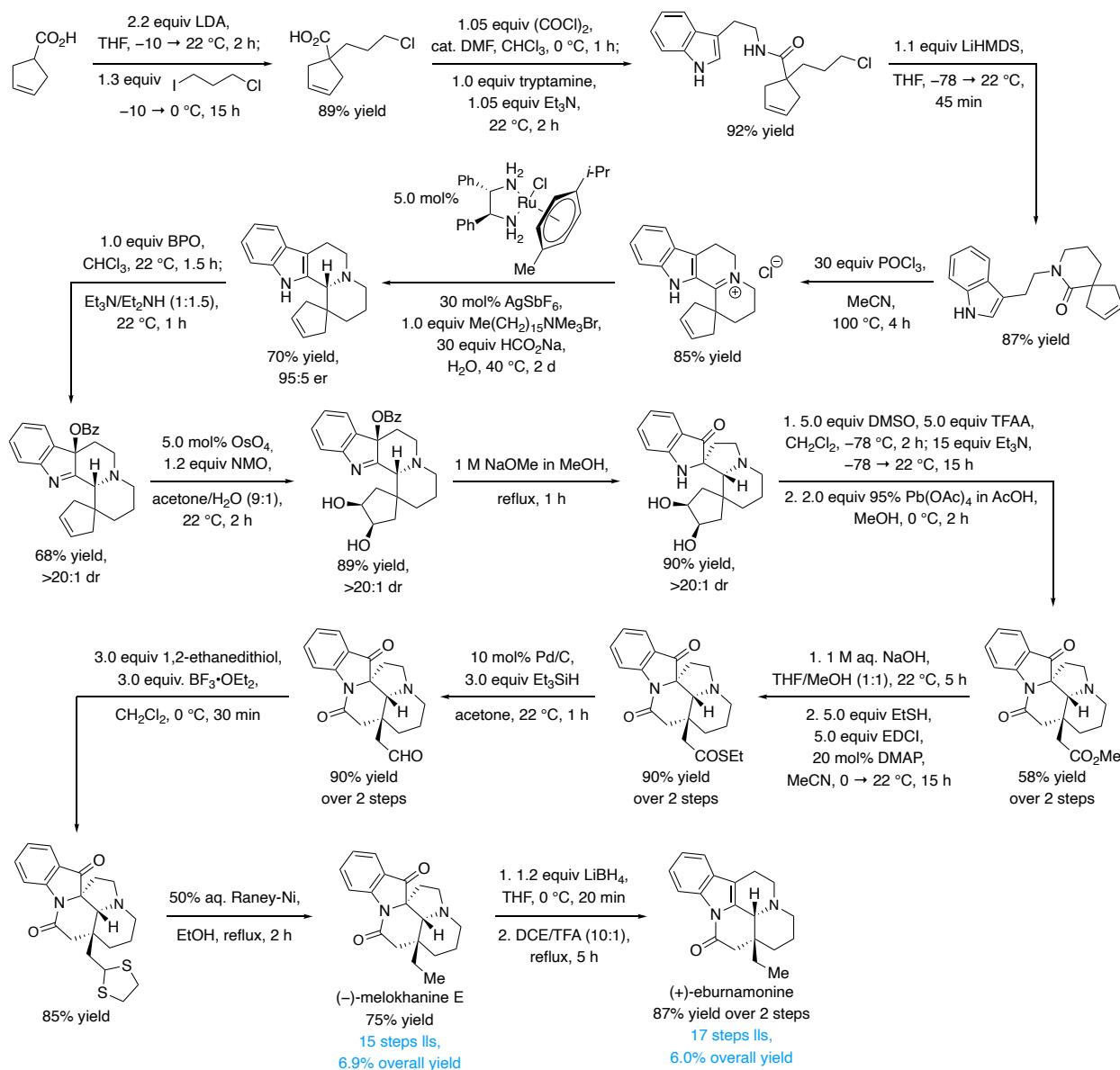
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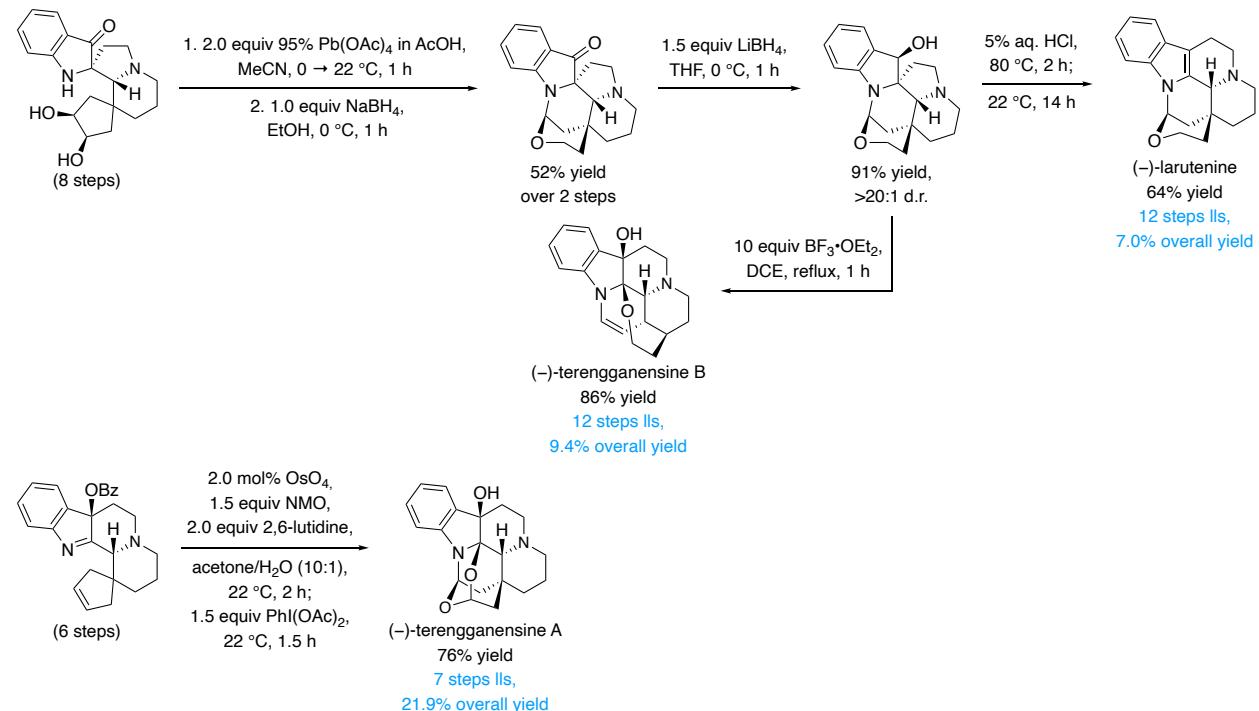
2.13 Zhu (2019): Melokhanine E, Eburnamone, Terengganensis and Laruteneine

(a) Piemontesi, C.; Wang, Q.; Zhu, J. Enantioselective Total Synthesis of (–)-Terengganensis A. *Angew. Chem., Int. Ed.* **2016**, *55*, 6556–6560.

(b) Li, G.; Piemontesi, C.; Wang, Q.; Zhu, J. Stereoselective Total Synthesis of Eburnane-Type Alkaloids Enabled by Conformation-Directed Cyclization and Rearrangement. *Angew. Chem., Int. Ed.* **2019**, *58*, 2870–2874.



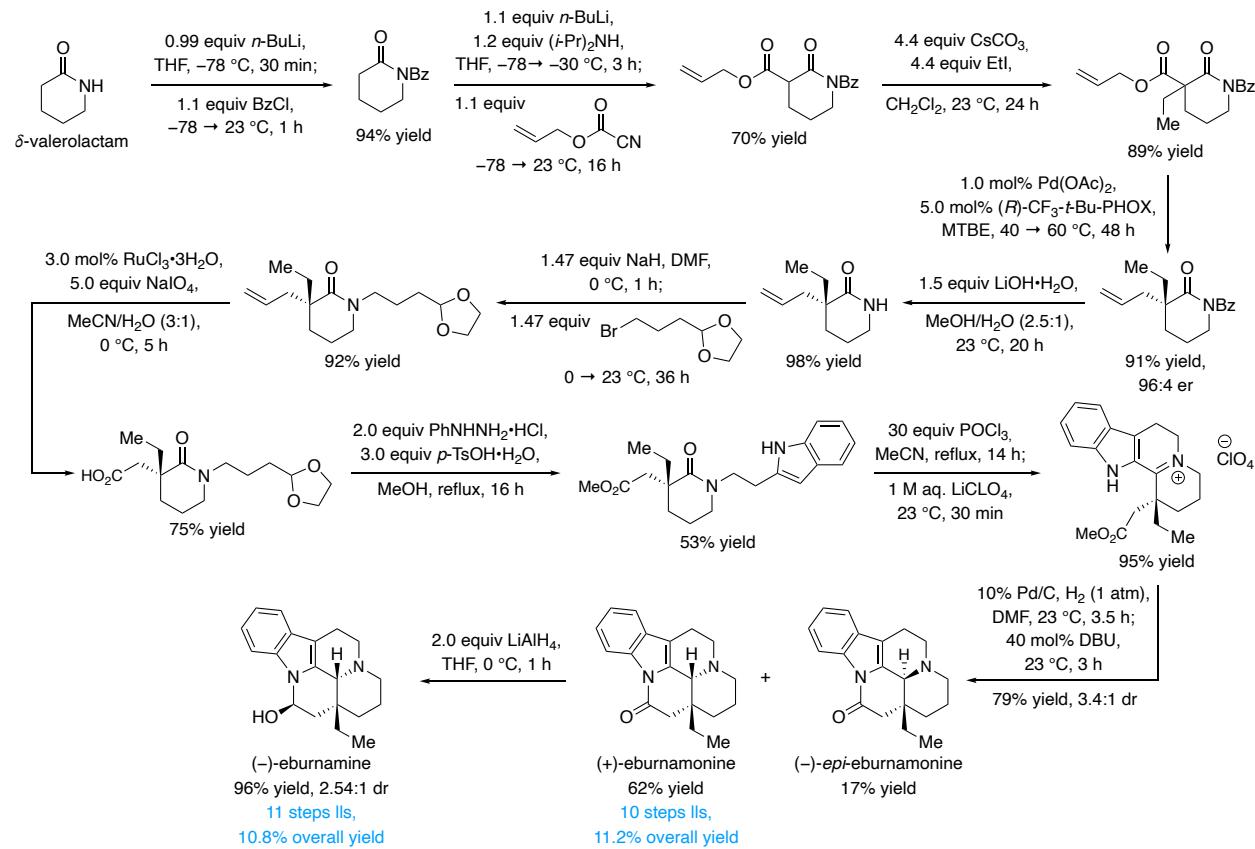
Supporting Information



2.14 Stoltz (2021 & 2023): Ethyl Side Chain Eburnane Alkaloids

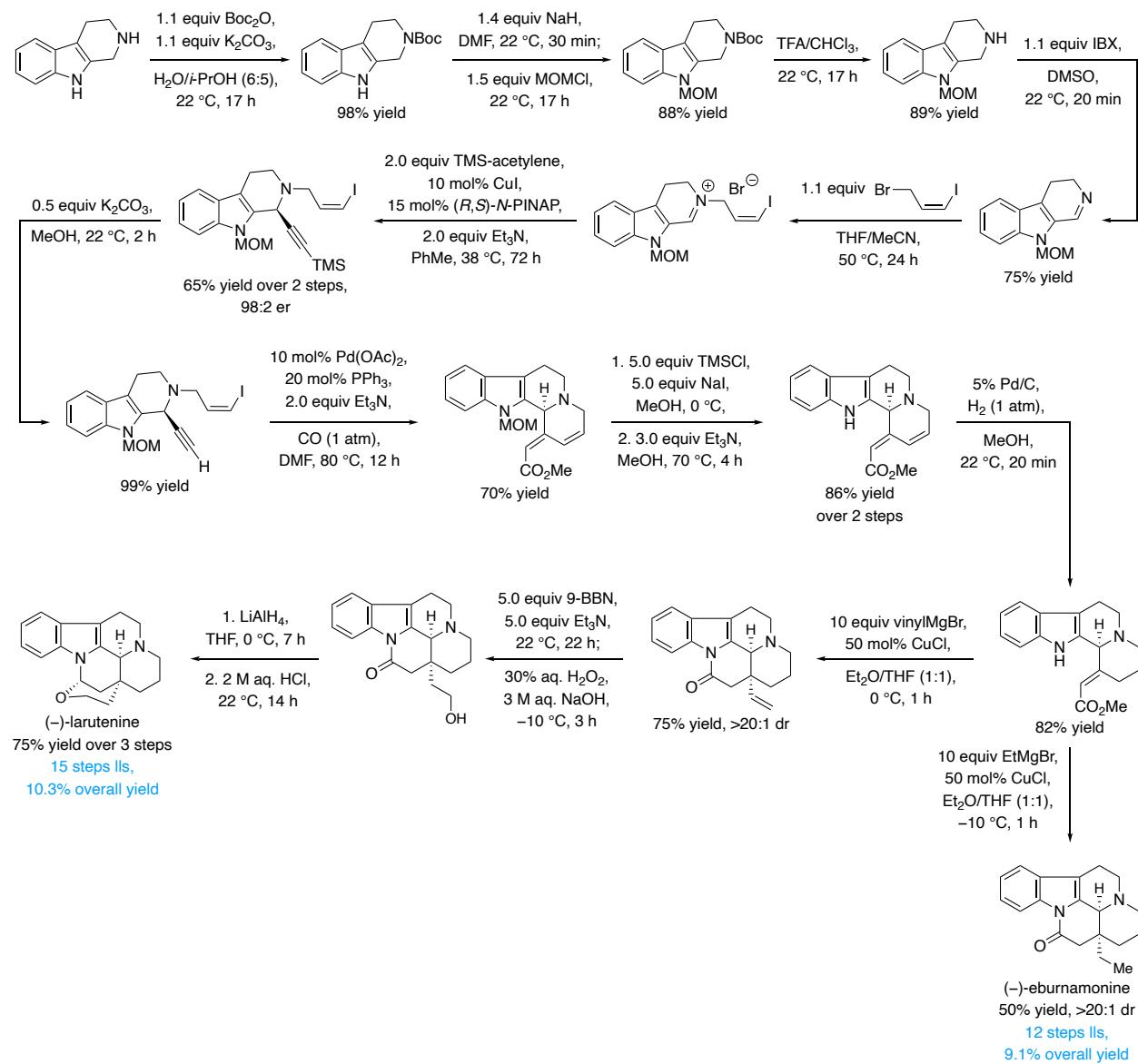
(a) Reimann, C. E.; Ngamnithiporn, A.; Hayashida, K.; Saito, D.; Korch, K. M.; Stoltz, B. M. The Enantioselective Synthesis of Eburnamonine, Eucophylline, and 16'-*epi*-Leucophyllidine. *Angew. Chem., Int. Ed.* **2021**, *60*, 17957–17962.

(b) Rand, A. W.; Gonzalez, K. J.; Reimann, C. E.; Virgil, S. C.; Stoltz, B. M. Total Synthesis of Strempeliopidine and Non-Natural Stereoisomers through a Convergent Petasis Borono–Mannich Reaction. *J. Am. Chem. Soc.* **2023**, *145*, 7278–7287.



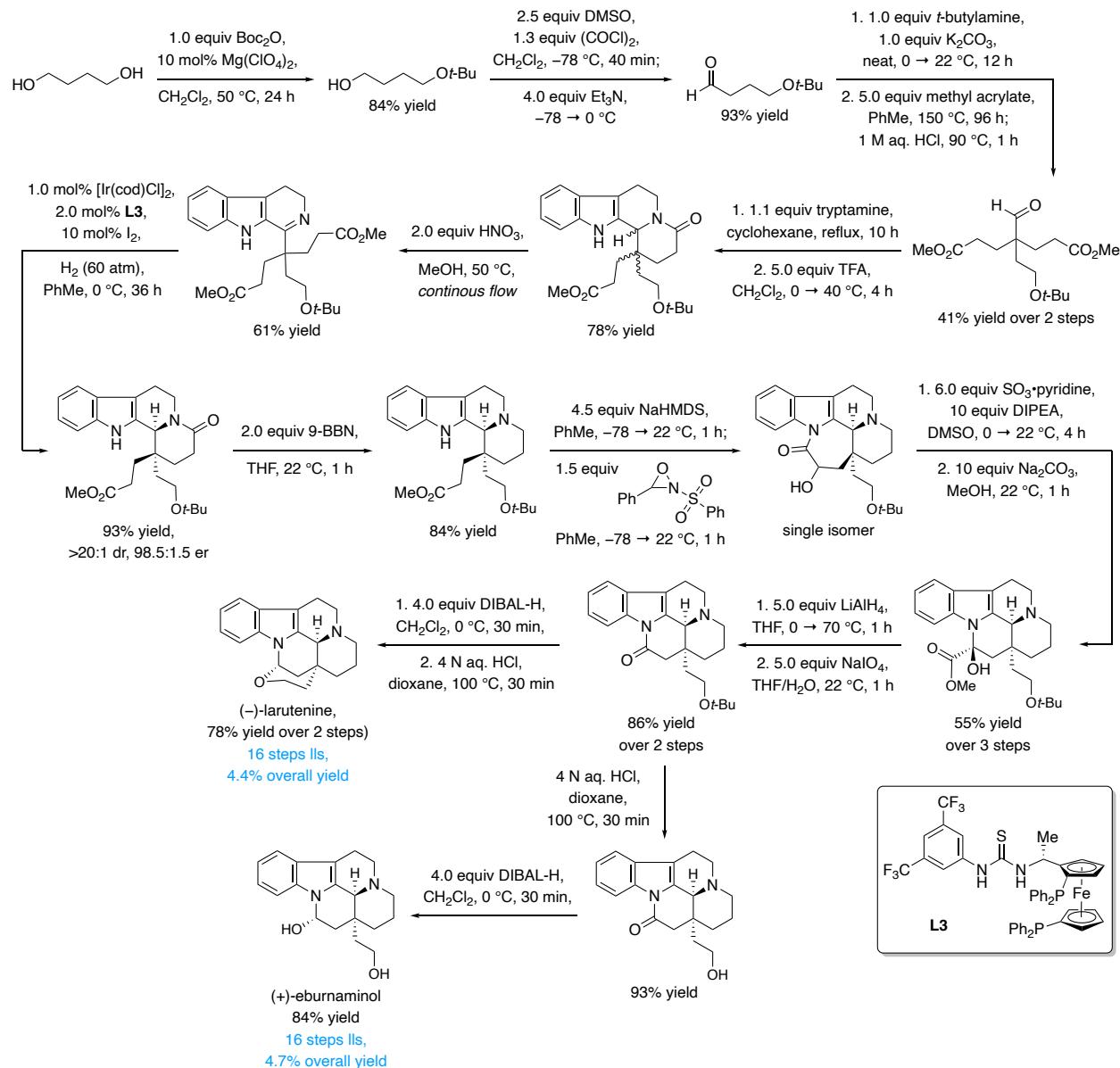
2.15 Tong (2021): (-)-Eburnamone and (-)-Larutene

Liang, L.; Zhou, S.; Zhang, W.; Tong, R. Catalytic Asymmetric Alkynylation of 3,4-Dihydro- β -carbolinium Ions Enables Collective Total Syntheses of Indole Alkaloids. *Angew. Chem., Int. Ed.* **2021**, *60*, 25135–25142.



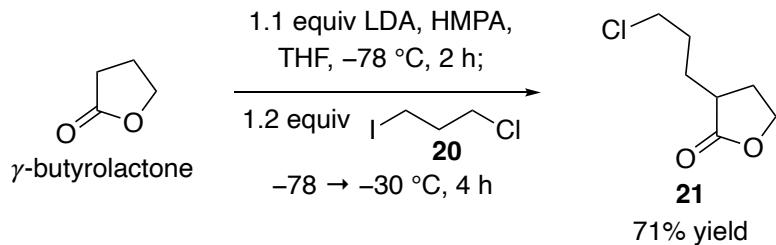
2.16 Chen (2022): C18-Oxo Eburnane Alkaloids

Zhang, W.; Wang, Z.; Lin, G.; Xue, Y.; Wu, M.; Tang, P.; Chen, F. Stereoselective Total Syntheses of C18-Oxo Eburnamine-Vincamine Alkaloids. *Org. Lett.* **2022**, *24*, 2409–2413.



3 Experimental Procedures and Characterization Data

3.1 Alkylation of γ -butyrolactone



Procedure: Compound **21** was prepared according to a reported procedure.¹

A solution of LDA in THF was prepared by addition of *n*-BuLi (76.7 mL of a 2.5 M solution in hexanes, 192 mmol, 1.1 equiv) to a solution of freshly distilled diisopropylamine (29.5 mL, 209 mmol, 1.2 equiv) in THF (300 mL) at -78°C . After addition, the solution was allowed to stir at 0°C for 30 minutes before cooling back to -78°C .

A solution of γ -butyrolactone (13.3 mL, 174 mmol, 1.0 equiv) in THF (120 mL) at -78°C was added dropwise over 1.5 h to the freshly prepared solution of LDA. Upon complete addition, the resulting mixture was allowed to stir at -78°C for an additional 30 min. A solution of 1-chloro-3-iodopropane **20** (22.5 mL, 209 mmol, 1.2 equiv) in HMPA (44 mL) was added slowly dropwise at -78°C . Upon complete addition, the reaction was warmed to -30°C and allowed to stir at this temperature for 4 h. The reaction was quenched by addition of a saturated aqueous solution of NH₄Cl (250 mL) and extracted with Et₂O (3 x 50 mL). The combined organics were washed with H₂O (200 mL) and brine (200 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (15% \rightarrow 30% EtOAc/hexanes) afforded chloride **21** (20.1 g, 124 mmol, 71% yield) as a pale-yellow oil.

Description: pale-yellow/colorless oil.

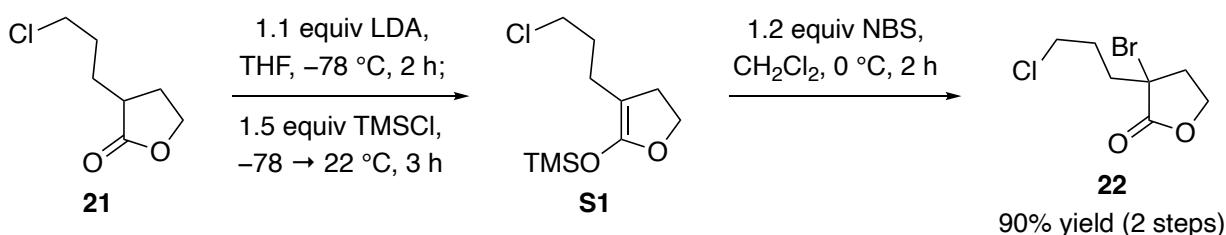
R_f: 0.48 in 50% EtOAc/hexanes (KMnO₄).

¹H NMR (500 MHz, CDCl₃): δ 4.32 (td, *J* = 8.8, 2.8 Hz, 1H), 4.17 (td, *J* = 8.8, 6.7 Hz, 1H), 3.56 (dd, *J* = 7.5, 3.6 Hz, 1H), 3.52 (dd, *J* = 7.5, 3.6 Hz, 1H), 2.58–2.48 (m, 1H), 2.39 (dtd, *J* = 12.0, 8.8, 2.8 Hz, 1H), 2.02–1.78 (m, 4H), 1.61 (dtd, *J* = 14.1, 8.8, 5.1 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 179.0, 66.5, 44.5, 38.6, 30.2, 28.7, 27.8.

HRMS: calculated for C₇H₁₂ClO₂ [M+H]⁺: 163.0520, found: 163.0522.

3.2 α -Bromination of the lactone



Procedure: A solution of LDA in THF was prepared by addition of *n*-BuLi (25.9 mL of a 2.5 M solution in hexanes, 64.8 mmol, 1.1 equiv) to a solution of freshly distilled diisopropylamine (9.97 mL, 70.6 mmol, 1.2 equiv) in THF (100 mL) at -78°C . After addition, the solution was allowed to stir at 0°C for 30 minutes before cooling back to -78°C .

A solution of lactone **21** (9.57 g, 58.9 mmol, 1.0 equiv) in THF (20 mL) was added dropwise to the freshly prepared solution of LDA at -78°C . Upon complete addition, the resulting mixture was allowed to stir at -78°C for 2 h. TMSCl (11.2 mL, 88.3 mmol, 1.5 equiv) was added dropwise and the reaction mixture was allowed to stir at -78°C for 1 h before it was allowed to slowly warm to 22°C over 2 h. The reaction was concentrated under reduced pressure and the resulting residue was diluted with hexanes (100 mL) and Et₂O (50 mL). The mixture was filtered through Celite® and the filtrate was concentrated *in vacuo* to obtain a pale-yellow residue containing silyl enol ether **S1**, which was used in the next step without further purification.

The residue was dissolved in CH₂Cl₂ (120 mL) and cooled to 0°C . NBS (12.6 g, 70.6 mmol, 1.2 equiv) was added as a solid in three portions and the resulting mixture was allowed to stir at 0°C for 2 h. The reaction was quenched by addition of a saturated aqueous solution of Na₂S₂O₃ (250 mL) and extracted with CH₂Cl₂ (3 x 80 mL). The combined organics were washed with brine (200 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (25% EtOAc/hexanes) furnished bromide **22** (12.8 g, 53.0 mmol, 90% yield) as a colorless oil.

Description: colorless oil. Became a white waxy crystalline solid upon storage at -20°C .

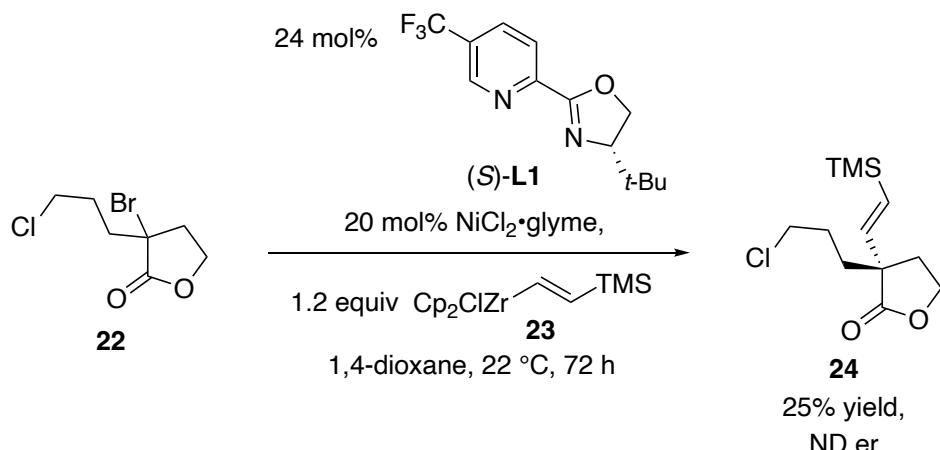
R_f: 0.35 in 25% EtOAc/hexanes (weekly UV active, KMnO₄).

¹H NMR (500 MHz, CDCl₃): δ 4.44–4.31 (m, 2H), 3.64–3.52 (m, 2H), 2.54 (ddd, *J* = 14.6, 3.9, 2.4 Hz, 1H), 2.38 (dt, *J* = 14.6, 8.9 Hz, 1H), 2.31 (ddd, *J* = 14.6, 12.0, 4.3 Hz, 1H), 2.23–2.14 (m, 1H), 2.03–1.95 (m, 1H), 1.90–1.79 (m, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 174.0, 65.8, 57.9, 44.2, 39.1, 36.3, 29.0.

HRMS: calculated for C₇H₁₁BrClO₂ [M+H]⁺: 240.9625, found: 240.9626.

3.3 Enantioconvergent cross-coupling with TMS-acetylene



Procedure: To a solution of Cp₂ZrHCl (Schwartz's reagent, 2.47 g, 9.58 mmol) in 1,4-dioxane (20 mL) at 22 °C was added TMS-acetylene (1.32 mL, 9.58 mmol) via syringe in one portion. The reaction mixture was allowed to vigorously stir at 22 °C for 1–2 h, at which time all of the white solids had been consumed and a homogeneous orange solution was obtained. The concentration of the alkenylzirconium reagent was determined to be 0.5 M in 1,4 dioxane by titration with I₂ (0.20 mmol) in THF (2 mL); at the endpoint, the solution changes from dark brown to yellow. The alkenylzirconium solution was used immediately in the enantioconvergent cross-coupling reaction.

Note: The Schwartz's reagent is moisture-sensitive and was stored inside a glovebox.

Meanwhile, NiCl₂•glyme (218 mg, 0.994 mmol, 0.10 equiv) and chiral ligand (*S*-L1² (325 mg, 1.19 mmol, 0.11 equiv) were dissolved in 1,4-dioxane (24 mL) and the resulting mixture was allowed to vigorously stir at 22 °C for 30 min furnishing a pale-yellow solution. Next, a solution of bromide **22** (2.40 g, 9.94 mmol, 1.0 equiv) in 1,4-dioxane (3 mL) was added and the resulting mixture was allowed to vigorously stir at 22 °C for 5 min. The freshly prepared solution of the alkenylzirconium reagent **23** (0.5 M in 1,4-dioxane, 23.9 mL, 11.9 mmol, 1.2 equiv) was added dropwise and the reaction was allowed to stir at 22 °C for 24 h. An additional portion of Ni-complex was prepared by dissolving NiCl₂•glyme (218 mg, 0.994 mmol, 0.10 equiv) and chiral ligand (*S*-L1 (325 mg, 1.19 mmol, 0.11 equiv) in 1,4-dioxane (4 mL) and allowing the resulting mixture to vigorously stir at 22 °C for 30 min furnishing a pale-yellow solution, and it was added to the reaction. Upon addition of the second portion of Ni-complex, the reaction mixture was allowed to stir at 22 °C for 48 h before being quenched by addition of MeOH (20 mL) and concentrated *in vacuo*. Purification by silica gel chromatography (30:1:1 hexanes/CH₂Cl₂/Et₂O → 9:1:1 hexanes/CH₂Cl₂/Et₂O) gave alkenyl-TMS **24** (560 mg, 85–90% pure, 2.49 mmol, ~25% yield) as a pale-yellow oil.

Description: pale-yellow oil.

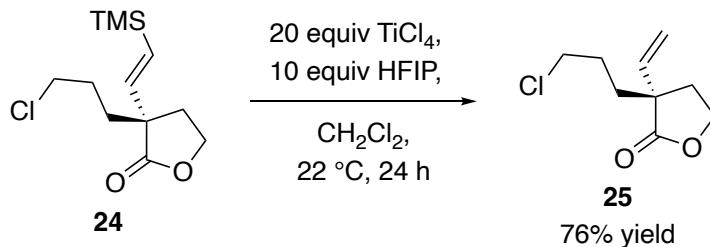
R_f: 0.52 in 3:1:1 hexanes/CH₂Cl₂/Et₂O (KMnO₄).

¹H NMR (500 MHz, CDCl₃): δ 5.94 (d, *J* = 19.0 Hz, 1H), 5.87 (d, *J* = 19.0 Hz, 1H), 4.32–4.26 (m, 1H), 4.16 (td, *J* = 9.0, 6.8 Hz, 1H), 3.53 (td, *J* = 6.3, 1.2 Hz, 2H), 2.33 (dtd, *J* = 12.7, 6.3, 2.9 Hz, 1H), 2.20 (dt, *J* = 12.7, 8.5 Hz, 1H), 1.92–1.84 (m, 2H), 1.84–1.78 (m, 1H), 1.77–1.71 (m, 1H), 1.71–1.64 (m, 1H), 0.08 (s, 9H).

¹³C NMR (126 MHz, CDCl₃): δ 178.8, 143.2, 132.3, 65.4, 51.0, 45.0, 34.0, 32.3, 27.8, –1.2.

HRMS: calculated for C₁₂H₂₂ClO₂Si [M+H]⁺: 261.1072, found: 261.1073.

3.4 Protodesilylation



Procedure: TiCl₄ (5.7 mL of a 1.0 M solution in CH₂Cl₂, 5.70 mmol, 15.0 equiv) was added dropwise to a solution of alkenyl-TMS **24** (100 mg, 0.38 mmol, 1.0 equiv) and hexafluoroisopropanol (HFIP, 800 μL, 7.60 mmol, 20.0 equiv) in CH₂Cl₂ (900 μL) at 22 °C. The resulting mixture was allowed to stir at 22 °C for 24 h then quenched by addition of a saturated aqueous solution of NaHCO₃ (20 mL) and extracted with Et₂O (3 x 10 mL). The combined organics were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10:1:1 hexanes/CH₂Cl₂/Et₂O) delivered terminal alkene **25** (54.5 mg, 0.289 mmol, 76% yield) as a colorless oil.

Description: colorless oil.

R_f: 0.21 in 9:1:1 hexanes/CH₂Cl₂/Et₂O (KMnO₄).

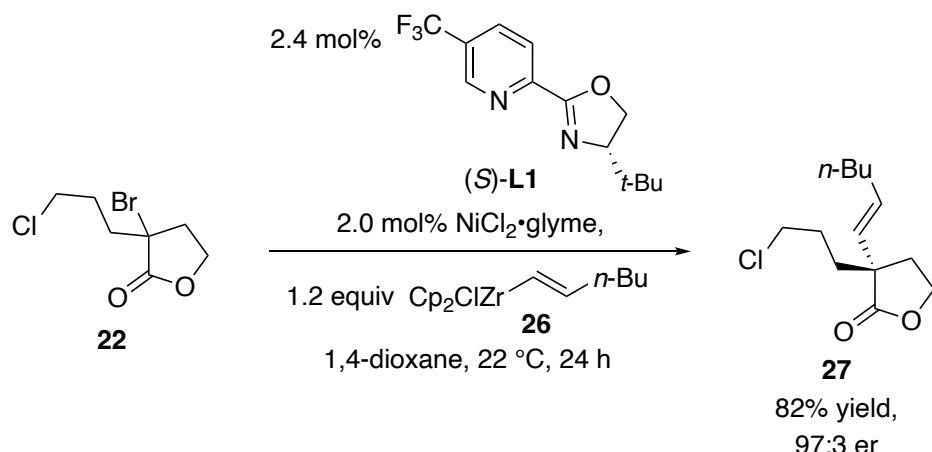
¹H NMR (500 MHz, CDCl₃): δ 5.82 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 5.22 (d, *J* = 17.2 Hz, 1H), 4.31 (td, *J* = 8.6, 3.7 Hz, 1H), 4.21 (td, *J* = 8.6, 6.7 Hz, 1H), 2.31 (ddd, *J* = 13.0, 6.7, 3.7 Hz, 1H), 2.24–2.16 (m, 1H), 1.99–1.86 (m, 2H), 1.81–1.66 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 178.6, 136.8, 116.7, 65.3, 49.3, 44.9, 34.0, 32.6, 27.7.

Optical Rotation: [α]_D¹⁹ = –42.8 (c = 1.00 in CH₂Cl₂).

HRMS: calculated for C₉H₁₃ClO₂Na [M+Na]⁺: 211.0496, found: 211.0493.

3.5 Enantioconvergent cross-coupling with 1-hexyne



Procedure: To a solution of Cp₂ZrHCl (Schwartz's reagent, 15.5 g, 60.0 mmol) in 1,4-dioxane (100 mL) at 22 °C was added 1-hexyne (6.89 mL, 60.0 mmol) via syringe in one portion. The reaction mixture was allowed to vigorously stir at 22 °C for 1–2 h, at which time all the white solids had been consumed and a homogeneous orange solution was obtained. The concentration of the alkenylzirconium reagent was determined to be 0.5 M in 1,4 dioxane by titration with I₂ (0.20 mmol) in THF (2 mL); at the endpoint, the solution changes from dark brown to yellow. The alkenylzirconium solution was used immediately in the enantioconvergent cross-coupling reaction.

Note 1: The Schwartz's reagent is moisture-sensitive and was stored inside a glovebox.

Meanwhile, NiCl₂•glyme (182 mg, 0.828 mmol, 0.02 equiv) and chiral ligand **(S)-L1**² (272 mg, 0.994 mmol, 0.024 equiv) were dissolved in 1,4-dioxane (100 mL) and the resulting mixture was allowed to vigorously stir at 22 °C for 30 min furnishing a pale-yellow solution. Next, a solution of bromide **22** (10.0 g, 41.4 mmol, 1.0 equiv) in 1,4-dioxane (10 mL) was added and the resulting mixture was allowed to vigorously stir at 22 °C for 5 min. The freshly prepared solution of the alkenylzirconium reagent **26** (0.5 M in 1,4-dioxane, 100 mL, 49.7 mmol, 1.2 equiv) was added dropwise and the reaction was allowed to stir at 22 °C for 24 h. The reaction was quenched by addition of MeOH (50 mL) and allowed to stir at 22 °C for 5 min before concentration *in vacuo*. Purification by silica gel chromatography (30:1:1 hexanes/CH₂Cl₂/Et₂O → 9:1:1 hexanes/CH₂Cl₂/Et₂O) afforded enantioenriched lactone **27** (8.33 g, 34.0 mmol, 82% yield, 97:3 er) as a colorless oil.

Note 2: When the reaction was performed with **(R)-L1** as chiral ligand on a 5.00 g scale, product **ent-27** was obtained in 82% yield (4.16 g) and 3.5:96.5 er.

Note 3: the enantiomeric purity was determined after ethenolysis, condensation with tryptamine and acetyl protection to facilitate HPLC analysis.

Description: colorless oil.

R_f: 0.30 in 9:1:1 hexanes/CH₂Cl₂/Et₂O (KMnO₄).

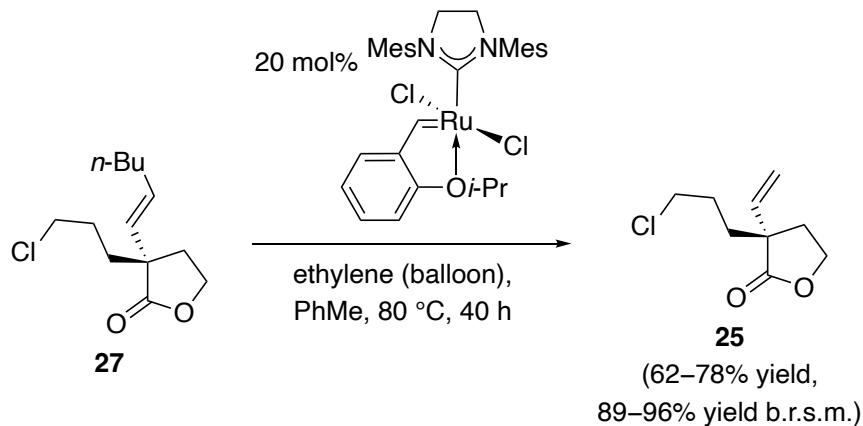
¹H NMR (500 MHz, CDCl₃): δ 5.60 (dt, *J* = 16.0, 6.7 Hz, 1H), 5.39 (dt, *J* = 16.0, 1.6 Hz, 1H), 4.28 (td, *J* = 8.5, 3.3 Hz, 1H), 4.18 (q, *J* = 8.5 Hz, 1H), 3.57–3.48 (m, 2H), 2.25 (ddd, *J* = 12.8, 6.7, 3.3 Hz, 1H), 2.17 (dt, *J* = 12.8, 8.5 Hz, 1H), 2.05 (q, *J* = 7.0 Hz, 2H), 1.97–1.82 (m, 2H), 1.75–1.66 (m, 2H), 1.38–1.23 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 179.1, 132.9, 128.3, 65.3, 48.4, 45.0, 34.4, 33.4, 32.3, 31.3, 27.8, 22.3, 14.0.

Optical Rotation: [α]_D¹⁹ = -44.5 (c = 1.00 in CHCl₃).

HRMS: calculated for C₁₃H₂₁ClO₂Na [M+Na]⁺: 267.1122, found: 267.1122.

3.6 Ethenolysis



Procedure: Hoveyda-Grubbs 2nd generation catalyst (HG-II, 1.28 g, 2.04 mmol, 0.10 equiv) and disubstituted alkene **27** (5.0 g, 20.4 mmol, 1.0 equiv) were dissolved in PhMe (1.4 L) at 22 °C. Ethylene gas was bubbled through the solution with a steady stream for 15 min. Then, the resulting mixture was heated to 80 °C and allowed to stir at this temperature for 14 h under an ethylene atmosphere (balloon). A second portion of Hoveyda-Grubbs 2nd generation catalyst (HG-II, 640 mg, 1.02 mmol, 0.05 equiv) was added to the mixture. Ethylene gas was bubbled through the solution with a steady stream for 15 min, then the resulting mixture allowed to stir at 80 °C for 12 h under an ethylene atmosphere (balloon). At this point, a third portion of Hoveyda-Grubbs 2nd generation catalyst (HG-II, 640 mg, 1.02 mmol, 0.05 equiv) was added to the mixture and the reaction was allowed to stir at 80 °C for a further 14 h. The reaction was cooled to 22 °C and MeOH (100 mL) was added. The resulting mixture was allowed to stir at 22 °C under air for 5 min, and then concentrated under reduced pressure. Purification by silica gel chromatography (25:1:1

hexanes/CH₂Cl₂/Et₂O → 8:1:1 hexanes/CH₂Cl₂/Et₂O) delivered terminal alkene **25** (3.00 g, 15.9 mmol, 78% yield) as a colorless oil, along with recovered starting material **27** (950 mg, 3.88 mmol, 19% recovery). Note: The yield range for ethenolysis seems to depend on the quality of ethylene gas. In fact, we observed variations depending on the ethylene cylinder used, but for each cylinder the yield range difference was <5%.

Description: colorless oil.

R_f: 0.21 in 9:1:1 hexanes/CH₂Cl₂/Et₂O (KMnO₄).

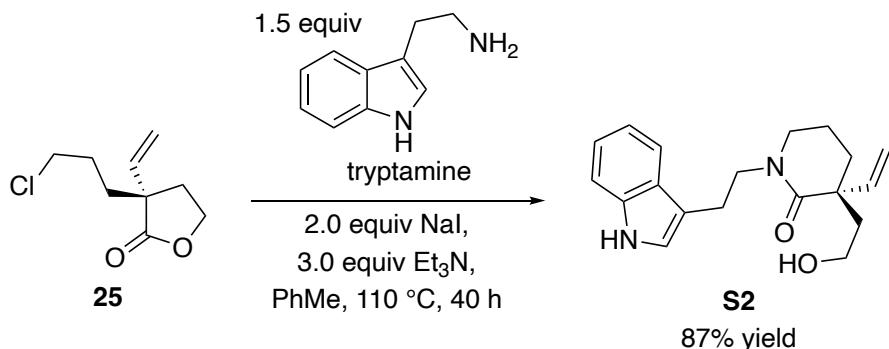
¹H NMR (500 MHz, CDCl₃): δ 5.82 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 5.22 (d, *J* = 17.2 Hz, 1H), 4.31 (td, *J* = 8.6, 3.7 Hz, 1H), 4.21 (td, *J* = 8.6, 6.7 Hz, 1H), 2.31 (ddd, *J* = 13.0, 6.7, 3.7 Hz, 1H), 2.24–2.16 (m, 1H), 1.99–1.86 (m, 2H), 1.81–1.66 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 178.6, 136.8, 116.7, 65.3, 49.3, 44.9, 34.0, 32.6, 27.7.

Optical Rotation: [α]_D¹⁹ = -42.8 (c = 1.00 in CH₂Cl₂).

HRMS: calculated for C₉H₁₃ClO₂Na [M+Na]⁺: 211.0496, found: 211.0493.

3.7 Lactam formation by condensation with tryptamine



Procedure: To a solution of lactone **25** (1.20 g, 6.36 mmol, 1.0 equiv) in PhMe (33 mL) at 22 °C were added tryptamine (1.53 g, 9.54 mmol, 1.5 equiv), NaI (1.91 g, 12.7 mmol, 2.0 equiv) and Et₃N (2.66 mL, 19.1 mmol, 3.0 equiv). The resulting mixture was heated to 110 °C and allowed to stir at this temperature for 40 h. The reaction mixture was cooled to 22 °C, quenched by addition of H₂O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (30 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (50% → 70% EtOAc/hexanes) afforded lactam **S2** (1.73 g, 5.53 mmol, 87% yield) as an off-white foam.

Description: off-white foam.

R_f: 0.23 in 70% EtOAc/hexanes (UV, purple with *p*-anisaldehyde and indigo with vanillin).

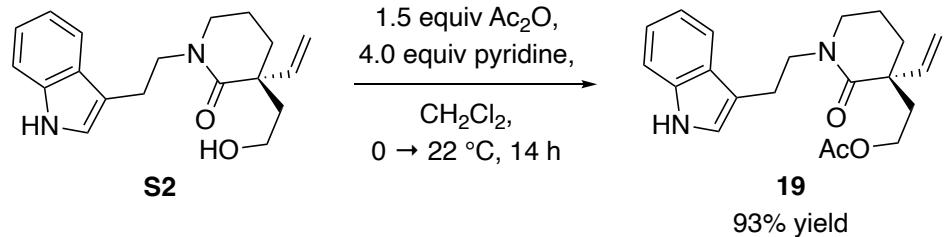
¹H NMR (500 MHz, CDCl₃): δ 8.54 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.03 (s, 1H), 5.70 (dd, *J* = 17.6, 10.7 Hz, 1H), 5.25 (d, *J* = 10.7 Hz, 1H), 5.07 (d, *J* = 17.6 Hz, 1H), 4.85 (s, 1H), 3.81 (ddd, *J* = 12.0, 9.2, 3.1 Hz, 1H), 3.71 (ddd, *J* = 12.0, 8.4, 3.8 Hz, 1H), 3.67–3.58 (m, 2H), 3.25–3.11 (m, 2H), 3.11–2.95 (m, 2H), 1.91 (ddd, *J* = 14.7, 9.2, 3.8 Hz, 1H), 1.86–1.59 (m, 5H).

¹³C NMR (126 MHz, CDCl₃): δ 173.5, 141.2, 136.4, 127.5, 122.5, 122.0, 119.4, 118.7, 116.2, 112.6, 111.4, 77.4, 58.8, 49.5, 49.2, 41.7, 33.5, 23.0, 19.1.

Optical Rotation: $[\alpha]_D^{20} = -3.6$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for $C_{19}H_{25}N_2O_2$, $[M+H]^+$: 313.1911, found: 313.1913.

3.8 Alcohol acetylation



Procedure: To a solution of alcohol **S2** (1.73 g, 5.53 mmol, 1.0 equiv) in CH₂Cl₂ (40 mL) at 0 °C was added pyridine (1.78 mL, 22.1 mmol, 4.0 equiv) and the resulting mixture was allowed to stir at 0 °C for 5 min. Ac₂O (785 µL, 8.30 mmol, 1.5 equiv) was added at 0 °C and the resulting mixture was allowed to stir at 22 °C for 14 h. The reaction was quenched by addition of H₂O (30 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were sequentially washed with 0.5 M aqueous HCl (40 mL) and brine (40 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10% → 30% EtOAc/hexanes) afforded acetylated product **19** (1.82 g, 5.14 mmol, 93% yield) as a white solid.

Description: white solid.

R_f: 0.21 in 30% EtOAc/hexanes (UV, purple with *p*-anisaldehyde).

¹H NMR (500 MHz, CDCl₃): δ 8.30 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.03 (s, 1H), 5.87 (dd, *J* = 17.6, 10.7 Hz, 1H), 5.19 (d, *J* = 10.7 Hz, 1H), 5.10 (d, *J* = 17.6 Hz, 1H), 4.15 (ddd, *J* = 11.0, 8.7, 5.8 Hz, 1H), 4.08 (ddd, *J* = 11.0, 8.7, 6.2 Hz, 1H), 3.71–3.60 (m, 2H), 3.20 (ddd, *J* = 12.2, 9.4, 4.9 Hz, 1H), 3.17–3.11 (m, 1H), 3.03 (td, *J* = 7.4, 2.7 Hz, 2H), 2.13 (ddd, *J* = 14.1, 8.7, 6.2 Hz, 1H), 2.02 (s, 3H), 1.97 (ddd, *J* = 14.1, 8.7, 5.8 Hz, 1H), 1.86–1.77 (m, 2H), 1.77–1.63 (m, 2H).

Supporting Information

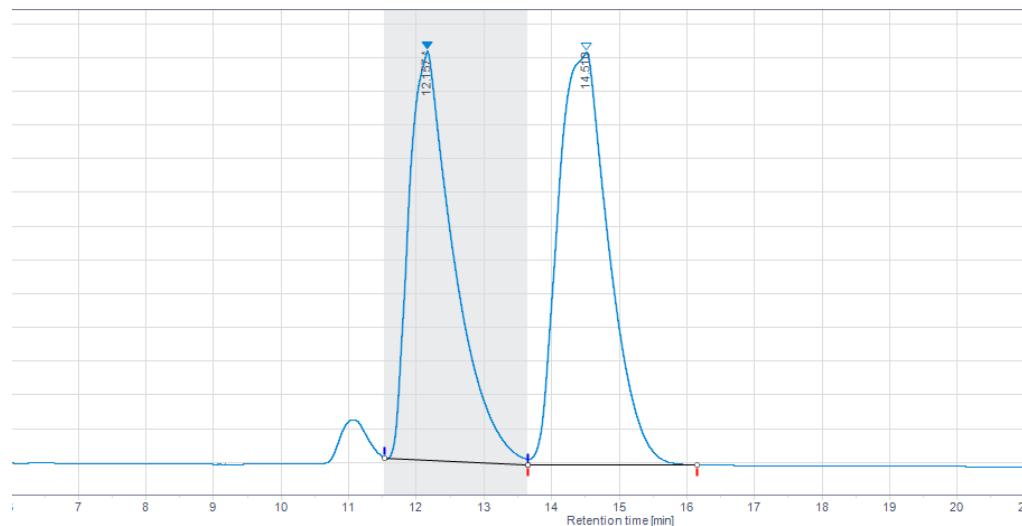
¹³C NMR (126 MHz, CDCl₃): δ 171.6, 171.3, 141.8, 136.4, 127.6, 122.3, 122.0, 119.4, 118.9, 115.0, 113.0, 111.3, 61.7, 48.8, 48.7, 47.8, 37.3, 30.3, 23.1, 21.2, 19.3.

Optical Rotation: [α]_D²⁰ = +9.4 (c = 1.00 in CHCl₃).

HRMS: calculated for C₂₁H₂₇N₂O₃ [M+H]⁺: 355.2016, found: 355.2018.

Enantiomeric purity: Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel IA-3, 9% i-PrOH/hexanes, 1.0 mL/min, 254 nm).

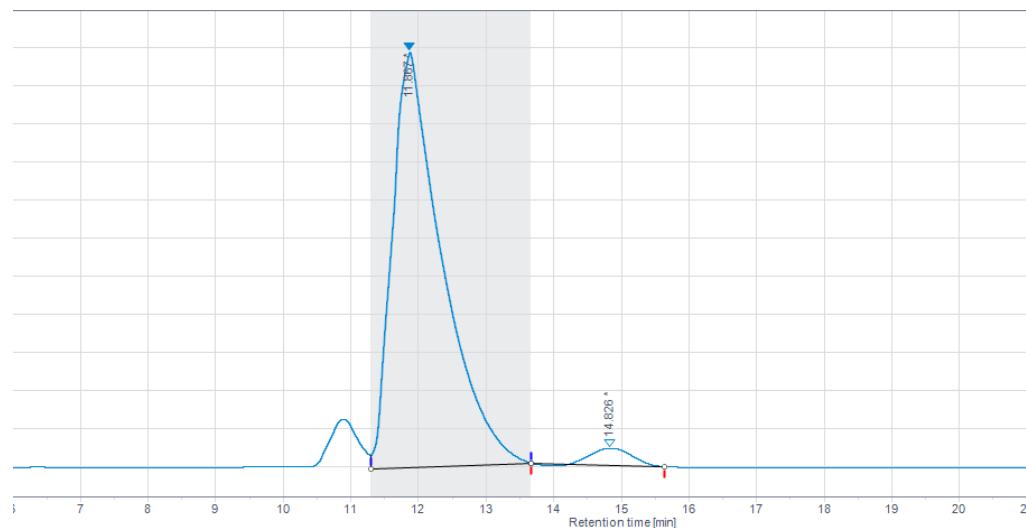
Racemic sample (obtained by performing the enantioconvergent cross-coupling with a 1:1 mixture of (*S*)-**L1** and (*R*)-**L1**)



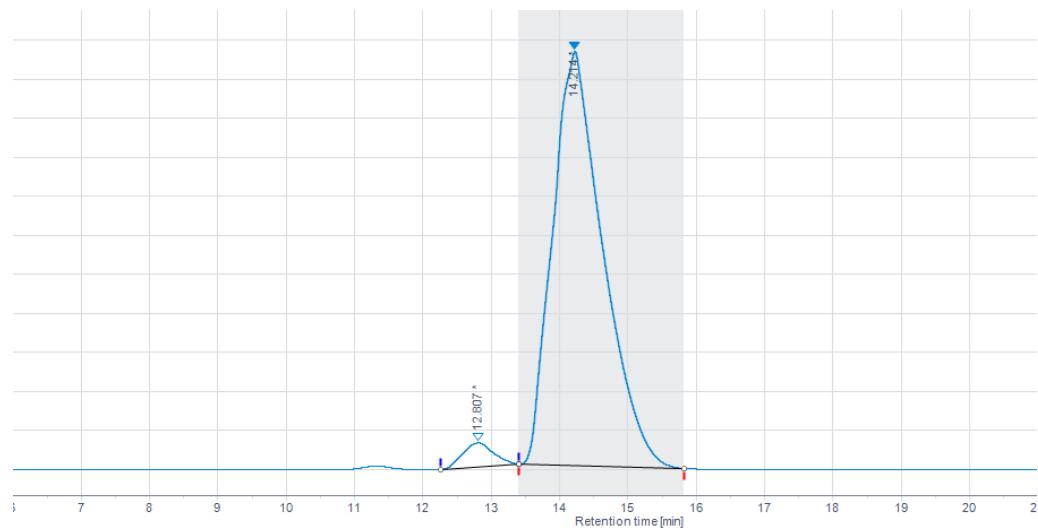
peak	RT (min)	Area (mAU·s)	Area%	Start time (min)	End time (min)
1	12.157	28008.183	46.808	11.536	13.648
2	14.510	31828.722	53.192	13.648	16.144

Supporting Information

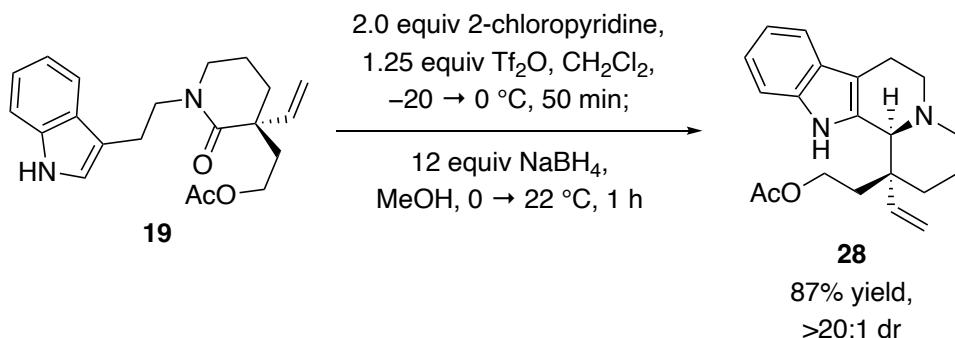
Compound **19** obtained with (*S*)-**L1**



Compound *ent*-**19** obtained with (*R*)-**L1**



3.9 Bischler-Napieralski reaction



Procedure: To a solution of amide **19** (1.70 g, 4.79 mmol, 1.0 equiv) in CH₂Cl₂ (40 mL) at -20 °C was added 2-chloropyridine (907 µL, 9.59 mmol, 2.0 equiv) and the resulting mixture was allowed to stir at -20 °C for 5 min before addition of Tf₂O (1.00 mL, 5.99 mmol, 1.25 equiv). The resulting mixture was allowed to stir at -20 °C for 30 min and then at 0 °C for a further 20 min (solution color changed from yellow to dark red). A solution of NaBH₄ (2.18 g, 57.5 mmol, 12 equiv) in MeOH (20 mL) was added at 0 °C and the resulting mixture was allowed to stir while slowly warming to 22 °C over 1 h. The reaction was quenched by addition of H₂O (50 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organics were washed with brine (40 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10% → 15% EtOAc/hexanes) gave tertiary amine **28** (1.41 g, 4.17 mmol, 87% yield, >20:1 dr) as a white solid.

Note: Acetylated compound **28** is unexpectedly unstable. Therefore, only a small amount was used for NMR characterization and the rest was immediately subjected to acetyl group removal.

Description: white solid.

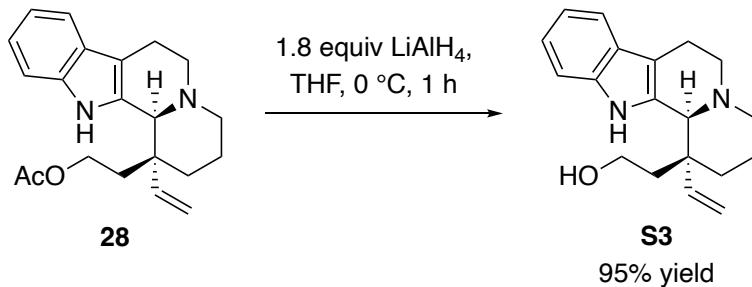
R_f: 0.43 in 30% EtOAc/hexanes (UV, purple with *p*-anisaldehyde and vanillin).

¹H NMR (500 MHz, CDCl₃): δ 8.38 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.20 (dd, *J* = 18.0, 11.1 Hz, 1H), 5.54 (d, *J* = 18.0 Hz, 1H), 5.50 (d, *J* = 11.1 Hz, 1H), 4.14 (td, *J* = 10.4, 5.2 Hz, 1H), 4.07 (td, *J* = 10.4, 6.5 Hz, 1H), 3.35 (br s, 1H), 3.10–2.86 (m, 3H), 2.63 (t, *J* = 11.4 Hz, 2H), 2.42 (q, *J* = 10.0 Hz, 2H), 1.96 (s, 3H), 1.95–1.81 (m, 1H), 1.73–1.57 (m, 3H), 1.48 (dt, *J* = 13.7, 6.9 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 171.3, 147.2, 135.5, 133.4, 126.7, 121.6, 119.3, 118.0, 115.9, 111.1, 110.9, 68.0, 61.2, 56.5, 54.0, 43.1, 4.1, 27.8, 22.2, 21.9, 21.1.

HRMS: calculated for C₂₁H₂₇N₂O₂ [M+H]⁺: 339.2067, found: 339.2069.

3.10 Acetyl group removal



Procedure: To a solution of acetylated alcohol **28** (1.23 g, 3.63 mmol, 1.0 equiv) in THF (40 mL) at 0 °C was added LiAlH₄ (248 mg, 6.54 mmol, 1.8 equiv) and the resulting mixture was allowed to stir at 0 °C for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of Na₂SO₄ (50 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (40 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10% acetone/CH₂Cl₂) furnished alcohol **S3** (1.02 g, 3.45 mmol, 95% yield) as a white foam.

Note: It is important to avoid using hexanes during chromatographic purification to prevent loss of product. We postulated this is probably due to the low solubility of alcohol **S3** in hexanes, which when used may cause loss of product for two reasons: 1) formation of aggregates that stick to silica and do not elute from the column; 2) the product crushes out from the solution.

Description: white foam.

R_f: 0.16 in 10% acetone/CH₂Cl₂ or 0.18 in 70% EtOAc/hexanes (UV, purple with *p*-anisaldehyde).

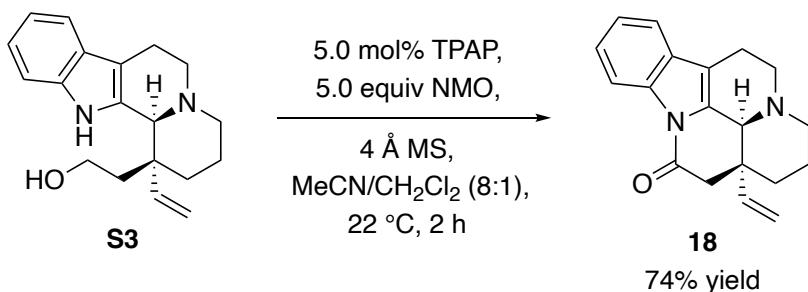
¹H NMR (500 MHz, CDCl₃): δ 8.35 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.20 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.41 (d, *J* = 11.1 Hz, 1H), 5.40 (d, *J* = 17.7 Hz, 1H), 3.80 (td, *J* = 11.1, 4.1 Hz, 1H), 3.54 (ddd, *J* = 11.1, 6.1, 4.0 Hz, 1H), 3.43 (br s, 1H), 3.09 (dt, *J* = 12.4, 6.1 Hz, 2H), 3.01 (tdd, *J* = 12.4, 5.4, 2.7 Hz, 1H), 2.73–2.64 (m, 2H), 2.46 (td, *J* = 12.0, 3.2 Hz, 1H), 2.12–2.02 (m, 1H), 1.96 (ddd, *J* = 15.9, 10.5, 6.1 Hz, 1H), 1.77–1.72 (m, 1H), 1.71–1.63 (m, 2H), 1.57 (td, *J* = 13.9, 5.2 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 149.5, 135.6, 132.5, 126.6, 121.7, 119.3, 118.2, 114.5, 110.8, 110.6, 67.4, 58.6, 56.1, 54.0, 43.8, 35.6, 34.6, 23.0, 21.4.

Optical Rotation: $[\alpha]_D^{20} = -76.9$ (c = 1.00 in CHCl_3).

HRMS: calculated for C₁₉H₂₄N₂O [M+H]⁺: 297.1961, found: 297.1961.

3.11 Oxidative lactamization



Procedure: To a solution of alcohol **S3** (1.53 g, 5.16 mmol, 1.0 equiv) in a 8:1 mixture of MeCN (40 mL) and CH₂Cl₂ (5 mL) at 22 °C were sequentially added activated 4 Å molecular sieves (1.6 g) and NMO (3.02 g, 25.8 mmol, 5.0 equiv) and the resulting mixture was allowed to stir at 22 °C for 5 min. TPAP (91.0 mg, 0.26 mmol, 0.05 equiv) was added and the resulting mixture was allowed to stir at 22 °C for 2 h. The reaction was quenched by addition of a saturated aqueous solution of Na₂SO₃ (100 mL) and extracted with EtOAc (3 x 60 mL). The combined organics were sequentially washed with brine (100 mL) and 10% aqueous CuSO₄ (100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (5% → 20% acetone/hexanes) afforded lactam **18** (1.12 g, 3.82 mmol, 74% yield) as a white solid.

Description: white solid.

R_f: 0.18 in 70% EtOAc/hexanes (UV, KMnO₄ or CAM, colorless with *p*-anisaldehyde).

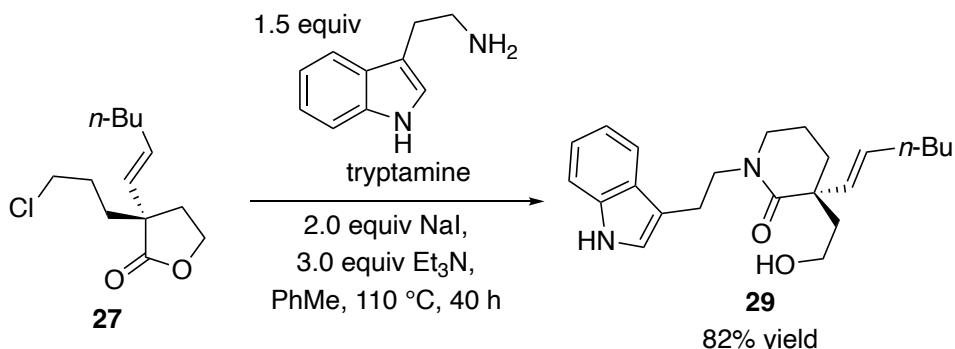
¹H NMR (500 MHz, CDCl₃): δ 8.37 (d, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.13 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.33 (d, *J* = 17.6 Hz, 1H), 5.33 (d, *J* = 10.9 Hz, 1H), 4.23 (s, 1H), 3.37 (dd, *J* = 14.0, 6.6 Hz, 1H), 3.29 (td, *J* = 14.0, 5.7 Hz, 1H), 2.92 (dddd, *J* = 16.7, 13.2, 6.6, 2.4 Hz, 1H), 2.83 (d, *J* = 16.8 Hz, 1H), 2.67–2.58 (m, 1H), 2.62 (d, *J* = 16.8 Hz, 1H), 2.51 (ddd, *J* = 16.7, 5.8, 2.4 Hz, 1H), 2.48–2.42 (m, 1H), 1.85 (qt, *J* = 13.2, 3.8 Hz, 1H), 1.61 (dd, *J* = 13.2, 3.8 Hz, 1H), 1.43 (dt, *J* = 13.2, 3.4 Hz, 1H), 1.21 (td, *J* = 13.2, 3.8 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 166.8, 142.4, 134.4, 131.2, 130.1, 124.7, 124.1, 118.3, 116.4, 115.4, 113.2, 58.0, 50.8, 46.0, 44.5, 41.4, 29.1, 21.2, 16.6.

Optical Rotation: [α]_D²⁰ = -68.0 (c = 1.00 in MeOH).

HRMS: calculated for C₁₉H₂₁N₂O [M+H]⁺: 293.1648, found: 293.1651.

3.12 Lactam with n-butyl side chain



Procedure: To a solution of lactone **27** (1.22 g, 5.0 mmol, 1.0 equiv) in PhMe (25 mL) at 22 °C were added tryptamine (1.20 g, 7.5 mmol, 1.5 equiv), NaI (1.50 g, 10.0 mmol, 2.0 equiv) and Et₃N (2.09 mL, 15.0 mmol, 3.0 equiv). The resulting mixture was heated to 110 °C and allowed to stir at this temperature for 40 h. The reaction mixture was cooled to 22 °C, quenched by addition of H₂O (25 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (25 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (50% → 70% EtOAc/hexanes) afforded lactam **29** (1.51 g, 4.10 mmol, 82% yield) as an off-white foam.

Description: off-white foam.

R_f: 0.27 in 70% EtOAc/hexanes (UV, purple with *p*-anisaldehyde and indigo with vanillin).

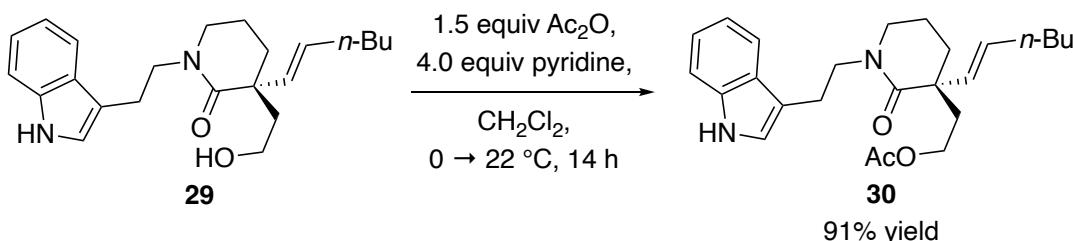
¹H NMR (500 MHz, CDCl₃): δ 8.41 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.06 (s, 1H), 5.43 (dt, *J* = 15.8, 6.8 Hz, 1H), 5.25 (d, *J* = 15.8 Hz, 1H), 3.80 (ddd, *J* = 12.0, 9.5, 2.7 Hz, 1H), 3.72–3.61 (m, 3H), 3.25–3.14 (m, 2H), 3.08 (q, *J* = 7.0 Hz, 1H), 3.02 (q, *J* = 7.0 Hz, 1H), 2.09–2.01 (m, 2H), 1.89–1.79 (m, 2H), 1.70–1.57 (m, 4H), 1.39–1.25 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 174.3, 136.4, 132.6, 132.6, 127.6, 122.5, 122.1, 119.4, 118.7, 112.6, 111.5, 58.8, 49.2, 49.2, 48.7, 41.9, 34.2, 32.5, 31.6, 22.9, 22.4, 19.1, 14.01.

Optical Rotation: [α]_D²⁰ = -3.4 (c = 1.00 in CHCl₃).

HRMS: calculated for C₂₃H₃₃N₂O₂ [M+H]⁺: 369.2537, found: 369.2536.

3.13 Alcohol acetylation with n-butyl side chain



Procedure: To a solution of alcohol **29** (1.51 g, 4.10 mmol, 1.0 equiv) in CH₂Cl₂ (30 mL) at 0 °C was added pyridine (1.32 mL, 16.4 mmol, 4.0 equiv) and the resulting mixture was allowed to stir at 0 °C for 5 min. Ac₂O (586 µL, 6.15 mmol, 1.5 equiv) was added at 0 °C and the resulting mixture was allowed to stir at 22 °C for 14 h. The reaction was quenched by addition of H₂O (25 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were sequentially washed with 0.5 M aqueous HCl (30 mL) and brine (30 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10% → 30% EtOAc/hexanes) afforded acetylated product **30** (1.53 g, 3.73 mmol, 91% yield) as a white solid.

Description: white solid.

R_f: 0.29 in 30% EtOAc/hexanes (UV, purple with *p*-anisaldehyde).

¹H NMR (500 MHz, CDCl₃): δ 8.36 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.03 (s, 1H), 5.53–5.42 (m, 2H), 4.15 (ddd, *J* = 11.0, 8.8, 5.7 Hz, 1H), 4.08 (ddd, *J* = 11.0, 8.8, 6.1 Hz, 1H), 3.24–3.12 (m, 2H), 3.07–2.97 (m, 2H), 2.10 (ddd, *J* = 14.4, 8.8, 6.1 Hz, 1H), 2.07–2.00 (m, 3H), 2.02 (s, 3H), 1.96 (ddd, *J* = 14.0, 8.8, 5.8 Hz, 1H), 1.87–1.76 (m, 2H), 1.74–1.61 (m, 2H), 1.38–1.26 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 172.2, 171.3, 136.4, 133.4, 131.0, 127.6, 122.3, 122.0, 119.3, 118.9, 113.0, 111.3, 61.9, 48.8, 48.7, 46.9, 37.8, 32.5, 31.6, 30.9, 23.1, 22.3, 21.2, 19.3, 14.1.

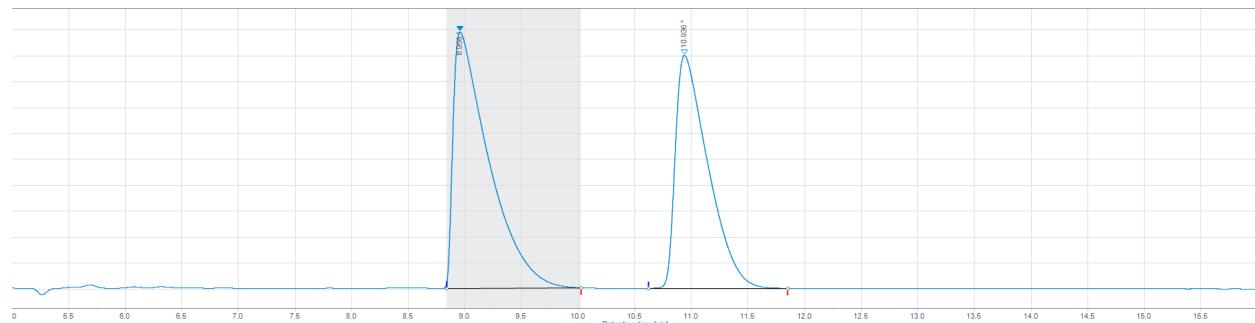
Optical Rotation: $[\alpha]_D^{20} = +8.7$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for $C_{25}H_{35}N_2O_3$ $[M+H]^+$: 411.2642, found: 411.2641.

Enantiomeric purity: Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel IA-3, 9% i-PrOH/hexanes, 1.0 mL/min, 254 nm).

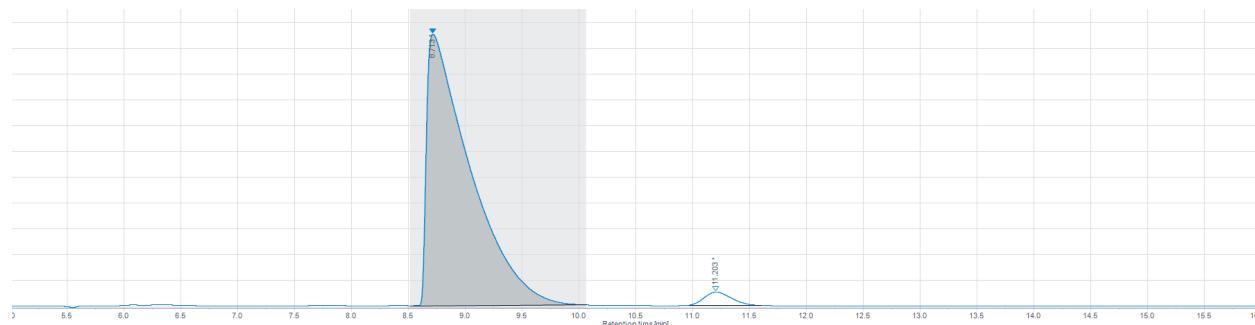
Supporting Information

Racemic sample (obtained by performing the enantioconvergent cross-coupling with a 1:1 mixture of (*S*)-**L1** and (*R*)-**L1**)



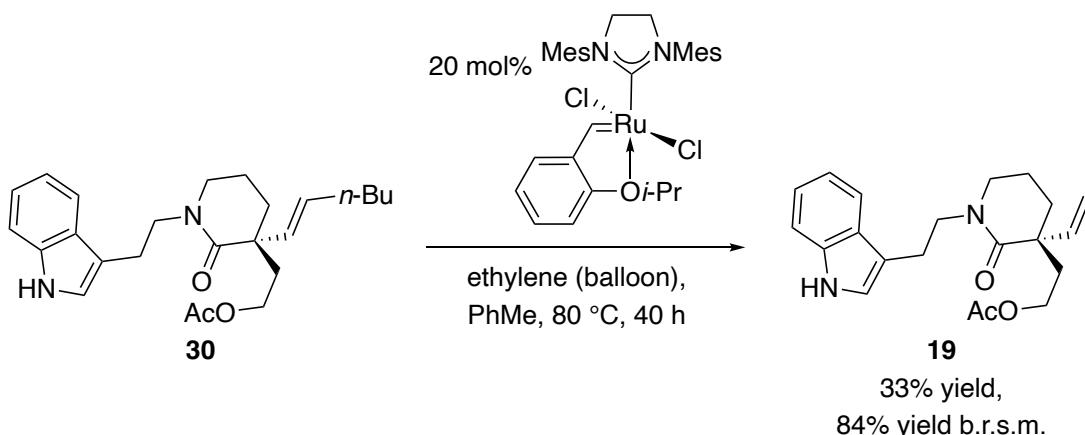
peak	RT (min)	Area (mAU·s)	Area%	Start time (min)	End time (min)
1	8.956	10164.287	51.237	8.840	10.028
2	10.936	9668.144	48.763	10.622	11.851

Compound **30** obtained with (*S*)-**L1**



peak	RT (min)	Area (mAU·s)	Area%	Start time (min)	End time (min)
1	8.713	28063.346	97.108	8.520	10.069
2	11.203	835.842	2.892	10.967	11.602

3.14 Ethenolysis after lactam formation



Procedure: Hoveyda-Grubbs 2nd generation catalyst (HG-II, 76.3 mg, 122 µmol, 0.10 equiv) and disubstituted alkene **30** (500 mg, 1.22 mmol, 1.0 equiv) were dissolved in PhMe (82 mL) at 22 °C. Ethylene gas was bubbled through the solution with a steady stream for 15 min. Then, the resulting mixture was heated to 80 °C and allowed to stir at this temperature for 14 h under an ethylene atmosphere (balloon). A second portion of Hoveyda-Grubbs 2nd generation catalyst (HG-II, 38.2 mg, 60.4 µmol, 0.05 equiv) was added to the mixture. Ethylene gas was bubbled through the solution with a steady stream for 15 min, then the resulting mixture allowed to stir at 80 °C for 12 h under an ethylene atmosphere (balloon). At this point, a third portion of Hoveyda-Grubbs 2nd generation catalyst (HG-II, 38.2 mg, 60.4 µmol, 0.05 equiv) was added to the mixture and the reaction was allowed to stir at 80 °C for a further 14 h. The reaction was cooled to 22 °C and MeOH (10 mL) was added. The resulting mixture was allowed to stir at 22 °C under air for 5 min, and then concentrated under reduced pressure. Purification by silica gel chromatography (10% → 30% EtOAc/hexanes) afforded terminal alkene **19** (142 mg, 0.40 mmol, 33% yield) as a white solid, along with recovered starting material **30** (303 mg, 0.74 mmol, 61% recovery).

Description: white solid.

R_f: 0.21 in 30% EtOAc/hexanes (UV, purple with *p*-anisaldehyde).

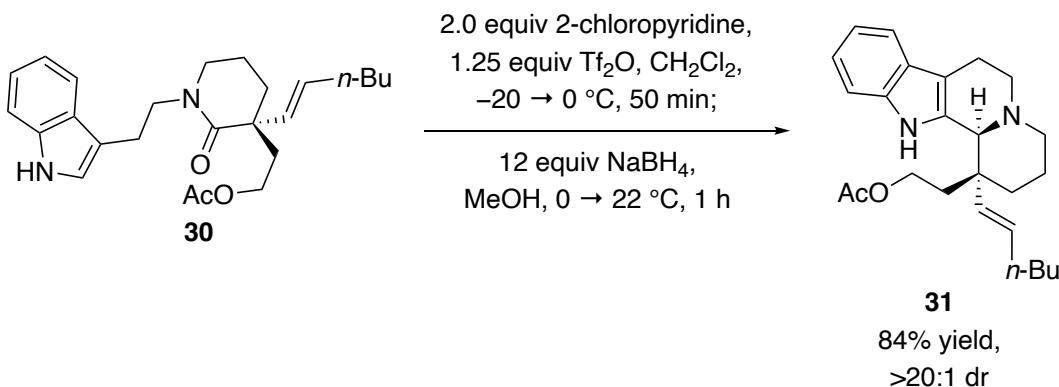
¹H NMR (500 MHz, CDCl₃): δ 8.30 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.03 (s, 1H), 5.87 (dd, *J* = 17.6, 10.7 Hz, 1H), 5.19 (d, *J* = 10.7 Hz, 1H), 5.10 (d, *J* = 17.6 Hz, 1H), 4.15 (ddd, *J* = 11.0, 8.7, 5.8 Hz, 1H), 4.08 (ddd, *J* = 11.0, 8.7, 6.2 Hz, 1H), 3.71–3.60 (m, 2H), 3.20 (ddd, *J* = 12.2, 9.4, 4.9 Hz, 1H), 3.17–3.11 (m, 1H), 3.03 (td, *J* = 7.4, 2.7 Hz, 2H), 2.13 (ddd, *J* = 14.1, 8.7, 6.2 Hz, 1H), 2.02 (s, 3H), 1.97 (ddd, *J* = 14.1, 8.7, 5.8 Hz, 1H), 1.86–1.77 (m, 2H), 1.77–1.63 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 171.6, 171.3, 141.8, 136.4, 127.6, 122.3, 122.0, 119.4, 118.9, 115.0, 113.0, 111.3, 61.7, 48.8, 48.7, 47.8, 37.3, 30.3, 23.1, 21.2, 19.3.

Optical Rotation: $[\alpha]_D^{20} = +9.4$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 355.2016, found: 355.2018.

3.15 Bischler-Napieralski reaction with n-butyl side chain



Procedure: To a solution of amide **30** (1.50 g, 3.65 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at -20°C was added 2-chloropyridine (691 μL , 7.31 mmol, 2.0 equiv) and the resulting mixture was allowed to stir at -20°C for 5 min before addition of Tf_2O (767 μL , 4.57 mmol, 1.25 equiv). The resulting mixture was allowed to stir at -20°C for 30 min and then at 0°C for a further 20 min (solution color changed from yellow to dark red). A solution of NaBH_4 (1.66 g, 43.8 mmol, 12 equiv) in MeOH (15 mL) was added at 0°C and the resulting mixture was allowed to stir while slowly warming to 22°C over 1 h. The reaction was quenched by addition of H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine (40 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10% \rightarrow 15% EtOAc/hexanes) gave tertiary amine **31** (1.21 g, 3.07 mmol, 84% yield, $>20:1$ dr) as a white solid.

Description: white solid.

R_f: 0.43 in 30% EtOAc/hexanes (UV, purple with *p*-anisaldehyde and vanillin).

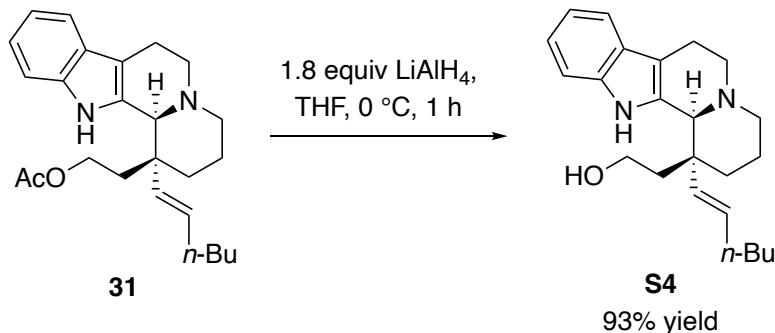
¹H NMR (500 MHz, CDCl₃): δ 8.41 (s, 1H), 7.47 (dd, $J = 7.6, 1.1$ Hz, 1H), 7.22 (dd, $J = 7.6, 1.1$ Hz, 1H), 7.14 (td, $J = 7.6, 1.1$ Hz, 1H), 7.08 (td, $J = 7.6, 1.1$ Hz, 1H), 5.89 (dt, $J = 16.4, 6.8$ Hz, 1H), 5.75 (d, $J = 16.4$ Hz, 1H), 4.13 (td, $J = 10.6, 5.4$ Hz, 1H), 4.08 (td, $J = 10.6, 6.6$ Hz, 1H), 3.31 (s, 1H), 3.08–2.91 (m, 3H), 2.69–2.59 (m, 2H), 2.46–2.36 (m, 2H), 2.27 (td, $J = 7.6, 6.4$ Hz, 2H), 1.98 (s, 3H), 1.94–1.84 (m, 1H), 1.71–1.52 (m, 5H), 1.51–1.39 (m, 3H), 1.02 (t, $J = 7.3$ Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 171.3, 138.6, 135.4, 133.6, 131.3, 126.7, 121.4, 119.2, 118.0, 110.9, 110.7, 68.3, 61.4, 56.5, 54.0, 42.2, 35.6, 33.1, 31.8, 28.1, 22.6, 22.3, 21.9, 21.1, 14.1.

Optical Rotation: $[\alpha]_D^{20} = -11.3$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 395.2693, found: 395.2692.

3.16 Acetyl group removal with n-butyl side chain



Procedure: To a solution of acetylated alcohol **31** (1.21 g, 3.07 mmol, 1.0 equiv) in THF (35 mL) at 0 °C was added LiAlH₄ (210 mg, 5.53 mmol, 1.8 equiv) and the resulting mixture was allowed to stir at 0 °C for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of Na₂SO₄ (50 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (40 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10% acetone/CH₂Cl₂) furnished alcohol **S4** (1.01 g, 2.86 mmol, 93% yield) as a white foam.

Description: white foam.

R_f: 0.21 in 10% acetone/CH₂Cl₂ or 0.26 in 70% EtOAc/hexanes (UV, purple with *p*-anisaldehyde).

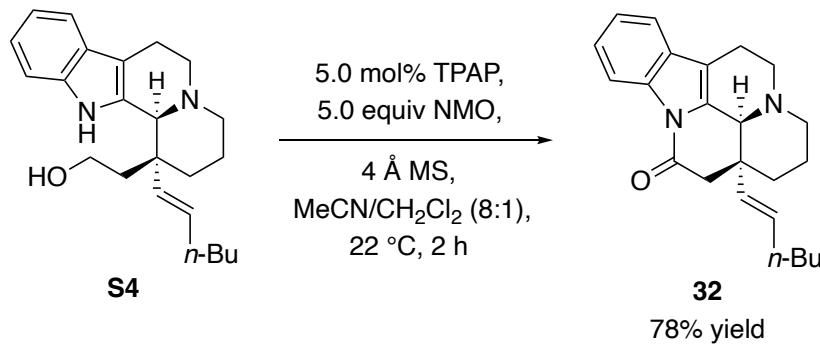
¹H NMR (500 MHz, CDCl₃): δ 8.37 (s, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 5.77 (d, *J* = 3.5 Hz, 2H), 3.81 (td, *J* = 11.1, 4.2 Hz, 1H), 3.53 (ddd, *J* = 11.7, 6.1, 3.9 Hz, 1H), 3.41 (s, 1H), 3.11 (dt, *J* = 11.2, 5.7 Hz, 2H), 3.03 (dddd, *J* = 15.7, 12.7, 5.4, 2.6 Hz, 1H), 2.69 (dq, *J* = 14.6, 3.9 Hz, 2H), 2.49–2.42 (m, 1H), 2.27–2.21 (m, 2H), 2.13–2.03 (m, 1H), 1.95 (ddd, *J* = 16.2, 10.5, 6.0 Hz, 1H), 1.75 (ddd, *J* = 14.1, 4.2, 1.9 Hz, 1H), 1.70–1.61 (m, 2H), 1.60–1.40 (m, 5H), 1.00 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 141.2, 135.5, 132.6, 130.2, 126.7, 121.7, 119.3, 118.3, 110.6, 110.5, 67.8, 58.7, 56.2, 54.2, 43.2, 36.2, 35.4, 33.0, 31.8, 23.1, 22.6, 21.3, 14.1.

Optical Rotation: $[\alpha]_D^{20} = -3.8$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for C₂₃H₃₃N₂O [M+H]⁺: 353.2587, found: 353.2589.

3.17 Oxidative lactamization with *n*-butyl side chain



Procedure: To a solution of alcohol **S4** (1.01 g, 2.86 mmol, 1.0 equiv) in a 8:1 mixture of MeCN (24 mL) and CH₂Cl₂ (3 mL) at 22 °C were sequentially added activated 4 Å molecular sieves (1.0 g) and NMO (1.68 g, 14.3 mmol, 5.0 equiv) and the resulting mixture was allowed to stir at 22 °C for 5 min. TPAP (51.0 mg, 0.14 mmol, 0.05 equiv) was added and the resulting mixture was allowed to stir at 22 °C for 2 h. The reaction was quenched by addition of a saturated aqueous solution of Na₂SO₃ (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were sequentially washed with brine (50 mL) and 10% aqueous CuSO₄ (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (5% → 20% acetone/hexanes) afforded lactam **32** (779 mg, 2.23 mmol, 78% yield) as a white solid.

Description: white solid.

R_f: 0.22 in 70% EtOAc/hexanes (UV, KMnO₄ or CAM, colorless with *p*-anisaldehyde).

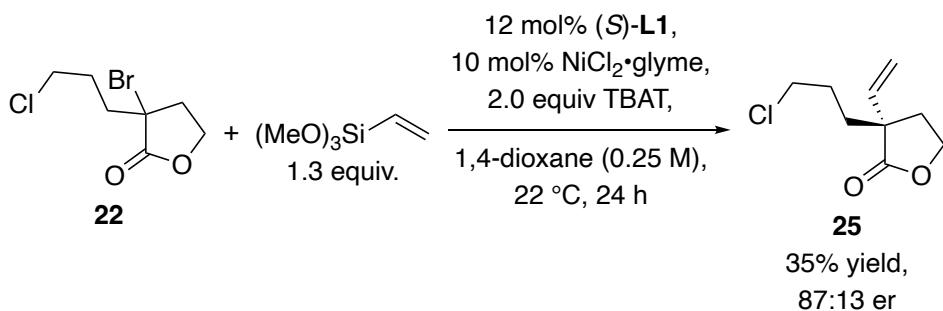
¹H NMR (500 MHz, CDCl₃): δ 8.37 (d, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.32 (td, *J* = 7.5, 1.2 Hz, 1H), 7.28 (td, *J* = 7.5, 1.2 Hz, 1H), 5.73 (t, *J* = 16.3 Hz, 1H), 5.67 (dt, *J* = 16.3, 6.6 Hz, 1H), 4.12 (s, 1H), 3.34 (dd, *J* = 13.9, 6.5 Hz, 1H), 3.26 (ddd, *J* = 13.9, 11.3, 5.8 Hz, 1H), 2.90 (dddd, *J* = 17.6, 11.4, 6.6, 2.8 Hz, 1H), 2.80 (d, *J* = 16.8 Hz, 1H), 2.59 (d, *J* = 16.8 Hz, 1H), 2.64–2.55 (m, 1H), 2.47 (ddd, *J* = 16.8, 5.7, 2.4 Hz, 1H), 2.41 (td, *J* = 12.1, 3.1 Hz, 1H), 2.11 (q, *J* = 6.8 Hz, 2H), 1.82 (qt, *J* = 13.2, 3.8 Hz, 1H), 1.55 (dd, *J* = 13.5, 3.5 Hz, 1H), 1.43–1.29 (m, 5H), 1.16 (td, *J* = 13.2, 3.7 Hz, 1H), 0.92 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 167.2, 134.3, 134.3, 131.8, 130.9, 130.2, 124.5, 124.0, 118.2, 116.4, 113.0, 58.5, 50.8, 46.8, 44.5, 40.6, 32.7, 31.7, 29.8, 22.4, 21.4, 16.6, 14.1.

Optical Rotation: $[\alpha]_D^{20} = -38.3$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for C₂₃H₂₉N₂O [M+H]⁺: 349.2274, found: 349.2276.

3.18 Enantioconvergent Hiyama cross-coupling



Procedure: $NiCl_2\text{-glyme}$ (18.2 mg, 0.083 mmol, 0.1 equiv), chiral ligand **(S)-L1** (27 mg, 0.099 mmol, 0.12 equiv) and tetrabutylammonium difluorotriphenylsilicate (TBAT, 896 mg, 1.66 mmol, 2.0 equiv) were placed in a flame dried flask under nitrogen and 1,4-dioxane (2.3 mL) was added. The resulting mixture was allowed to vigorously stir at 22 °C for 10 min furnishing a pale-yellow suspension. Next, trimethoxyvinylsilane (227 μ L, 1.08 mmol, 1.3 equiv) was added followed by addition of a solution of bromide **22** (200 mg, 0.83 mmol, 1.0 equiv) in 1,4-dioxane (1 mL). The reaction was allowed to stir at 22 °C for 24 h during which time the suspension became a dark brown solution. The reaction was quenched by addition of MeOH (1 mL) and allowed to stir at 22 °C for 5 min before concentration *in vacuo*. Purification by silica gel chromatography (18:1:1 hexanes/CH₂Cl₂/Et₂O \rightarrow 6:1:1 hexanes/CH₂Cl₂/Et₂O) afforded enantioenriched lactone **25** (56.4 mg, 0.30 mmol, 36% yield, 87:13 er) as a colorless oil.

Note: the enantiomeric purity was determined after ethenolysis, condensation with tryptamine and acetyl protection to facilitate HPLC analysis.

Description: colorless oil.

R_f: 0.21 in 9:1:1 hexanes/CH₂Cl₂/Et₂O (KMnO₄).

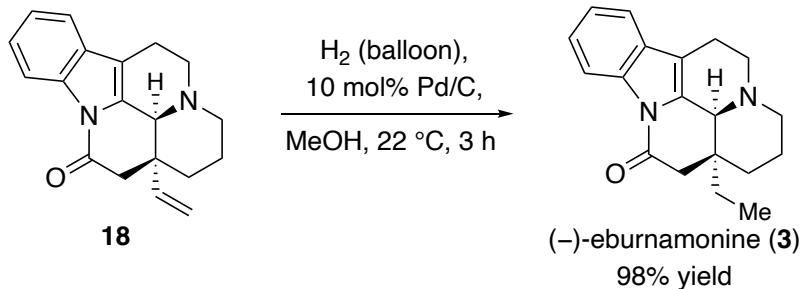
¹H NMR (500 MHz, CDCl₃): δ 5.82 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 5.22 (d, *J* = 17.2 Hz, 1H), 4.31 (td, *J* = 8.6, 3.7 Hz, 1H), 4.21 (td, *J* = 8.6, 6.7 Hz, 1H), 2.31 (ddd, *J* = 13.0, 6.7, 3.7 Hz, 1H), 2.24–2.16 (m, 1H), 1.99–1.86 (m, 2H), 1.81–1.66 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 178.6, 136.8, 116.7, 65.3, 49.3, 44.9, 34.0, 32.6, 27.7.

Optical Rotation: $[\alpha]_D^{19} = -36.5$ (*c* = 1.00 in CH₂Cl₂).

HRMS: calculated for C₉H₁₃ClO₂Na [M+Na]⁺: 211.0496, found: 211.0493.

3.19 (-)-Eburnamonine



Procedure: To a solution of alkene **18** (400 mg, 1.36 mmol, 1.0 equiv) in MeOH (13.6 mL) at 22 °C was added 10% wt. palladium on carbon (146 mg, 136 µmol with respect to Pd, 0.1 equiv), and the flask was evacuated and backfilled with hydrogen (3x). Hydrogen was bubbled through the mixture for 5 min, then the reaction was allowed to stir at 22 °C for 3 h under hydrogen atmosphere (balloon). The reaction was filtered through Celite® using EtOAc for washing. The filtrate was concentrated *in vacuo* to deliver (−)-eburnammonine **3** (394 mg, 1.34 mmol, 98% yield) as a white solid.

Description: white solid.

Rf: 0.20 in 70% EtOAc/hexanes (UV, KMnO₄ or purple with *p*-anisaldehyde).

¹H NMR (500 MHz, CDCl₃): δ 8.37 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 3.86 (br s, 1H), 3.30 (dd, *J* = 13.9, 6.4 Hz, 1H), 3.17 (ddd, *J* = 13.9, 12.7, 5.8 Hz, 1H), 2.93–2.83 (m, 1H), 2.62 (d, *J* = 16.7 Hz, 1H), 2.57 (s, 1H), 2.56 (d, *J* = 16.7 Hz, 1H), 2.46–2.33 (m, 2H), 2.03 (dq, *J* = 15.2, 7.7 Hz, 1H), 1.74 (qt, *J* = 13.3, 3.9 Hz, 1H), 1.62 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.47 (br d, *J* = 13.7 Hz, 1H), 1.36 (dt, *J* = 13.7, 3.3 Hz, 1H), 1.00 (td, *J* = 13.7, 3.9 Hz, 1H), 0.93 (t, *J* = 7.7 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 167.7, 134.3, 132.1, 130.2, 124.4, 123.9, 118.2, 116.3, 112.6, 57.7, 50.7, 44.4, 44.4, 38.5, 28.4, 27.0, 20.7, 16.6, 7.8.

Optical Rotation: $[\alpha]_D^{20} = -108.0$ (c = 1.00 in CHCl₃).

HRMS: calculated for C₁₉H₂₃N₂O [M+H]⁺: 295.1810, found: 295.1808.

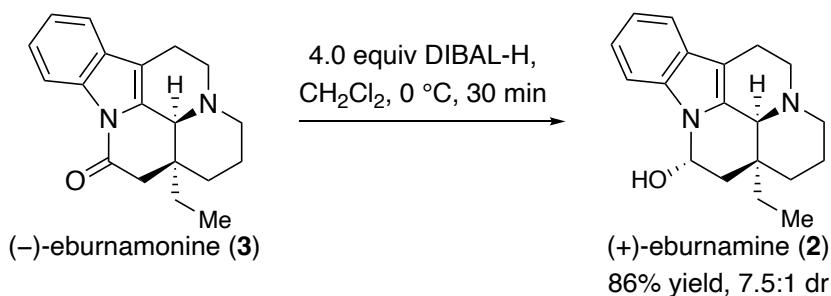
Comparison of (-)-eburnamoneine ^1H NMR peaks with previously synthesized material

This work, 500 MHz	Stoltz, 400 MHz³
8.37 (d, $J = 7.6$ Hz, 1H)	8.37 (m, 1H)
7.41 (d, $J = 7.6$ Hz, 1H)	7.44 (m, 1H)
7.31 (t, $J = 7.6$ Hz, 1H)	7.32 (m, 2H)
7.28 (t, $J = 7.6$ Hz, 1H)	
3.86 (br s, 1H)	4.05 (br s, 1H)
3.30 (dd, $J = 13.9, 6.4$ Hz, 1H)	3.38 (dd, $J = 13.9, 6.7$ Hz)
3.17 (ddd, $J = 13.9, 12.7, 5.8$ Hz, 1H)	3.29 (ddd, $J = 13.9, 11.3, 5.8$ Hz)
2.93–2.83 (m, 1H)	2.92 (dddd, $J = 16.9, 11.3, 6.7, 2.9$ Hz, 1H)
2.62 (d, $J = 16.7$ Hz, 1H)	2.69 (d, $J = 16.8$ Hz, 1H)
2.57 (s, 1H)	2.66 (br s, 1H)
2.56 (d, $J = 16.7$ Hz, 1H)	2.60 (d, $J = 16.8$ Hz, 1H)
2.46–2.33 (m, 2H)	2.50 (m, 2H)
2.03 (dq, $J = 15.2, 7.7$ Hz, 1H)	2.09 (dq, $J = 15.1, 7.6$ Hz, 1H)
1.74 (qt, $J = 13.3, 3.9$ Hz, 1H)	1.81 (qt, $J = 13.2, 3.9$ Hz, 1H)
1.62 (dq, $J = 14.8, 7.5$ Hz, 1H)	1.68 (dq, $J = 14.7, 7.4$ Hz, 1H)
1.47 (br d, $J = 13.7$ Hz, 1H)	1.51 (ddt, $J = 13.6, 3.6, 1.9$ Hz, 1H)
1.36 (dt, $J = 13.7, 3.3$ Hz, 1H)	1.42 (m, 1H)
1.00 (td, $J = 13.7, 3.9$ Hz, 1H)	1.05 (td, $J = 13.6, 3.9$ Hz, 1H)
0.93 (t, $J = 7.7$ Hz, 3H)	0.94 (t, $J = 7.6$ Hz, 3H)

Comparison of (–)-eburnamone ^{13}C NMR peaks with previously synthesized material

This work, 126 MHz	Stoltz, 101 MHz ³
167.7	167.6
134.3	134.4
132.1	131.6
130.2	130.0
124.4	124.7
123.9	124.1
118.2	118.3
116.3	116.4
112.6	112.7
57.7	57.9
50.7	50.9
44.4	44.5
44.4	44.4
38.5	38.7
28.4	28.5
27.0	26.9
20.7	20.6
16.6	16.7
7.8	7.8

3.20 (+)-Eburnamine



Procedure: To a solution of (-)-eburnamonine **3** (100 mg, 0.34 mmol, 1.0 equiv) in CH₂Cl₂ (3.4 mL) at 0 °C was added DIBAL-H (1.36 mL of a 1.0 M solution in CH₂Cl₂, 1.36 mmol, 4.0 equiv). The resulting mixture was allowed to stir at 0 °C for 30 min. The reaction was quenched by addition of 1 M aqueous NaOH (5 mL) and extracted with CH₂Cl₂ (3 x 5 mL). The combined organics were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (20% → 30% acetone/hexanes) afforded (+)-eburnamine **2** (86.6 mg, 0.29 mmol, 86% yield, 7.5:1 dr) as a white solid.

Description: white solid.

R_f: 0.20 in 5% MeOH/CH₂Cl₂ or 0.38 in 30% acetone/hexanes (UV, KMnO₄ or CAM).

¹H NMR major (500 MHz, CDCl₃): δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 5.52 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.68 (br s, 1H), 3.23 (dd, *J* = 13.6, 6.5 Hz, 1H), 3.14 (ddd, *J* = 13.6, 11.5, 5.8 Hz, 1H), 2.51–2.44 (m, 2H), 2.32–2.23 (m, 2H), 2.01 (dq, *J* = 15.3, 7.8 Hz, 1H), 1.65 (tt, *J* = 13.3, 3.9 Hz, 1H), 1.48–1.39 (m, 2H), 1.35–1.23 (m, 3H), 0.87 (t, *J* = 7.6 Hz, 3H), 0.81 (td, *J* = 13.4, 3.8 Hz, 1H).

¹³C NMR major (126 MHz, CDCl₃): δ 136.8, 132.8, 128.8, 121.4, 120.3, 118.2, 112.3, 105.7, 76.7, 58.8, 50.9, 44.4, 43.5, 36.9, 28.7, 25.2, 20.6, 16.9, 7.7.

Optical Rotation: [α]_D²⁰ = +78.9 (c = 1.00 in CHCl₃).

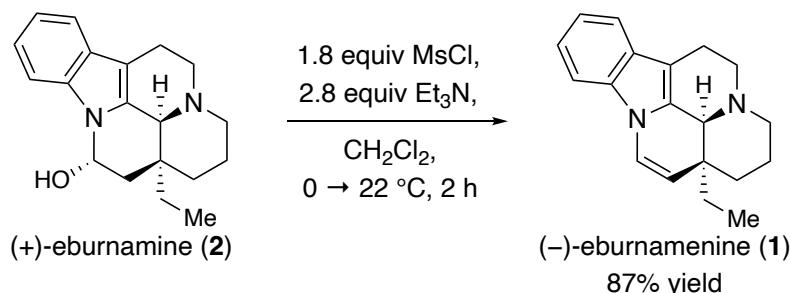
HRMS: calculated for C₁₉H₂₅N₂O [M+H]⁺: 297.1961, found: 297.1957.

Comparison of (+)-eburnamine ^1H NMR peaks with previously synthesized material

This work, 500 MHz	Qin, 400 MHz⁴
7.72 (d, $J = 7.6$ Hz, 1H)	7.72 (d, $J = 7.6$ Hz, 1H)
7.47 (d, $J = 7.6$ Hz, 1H)	7.47 (d, $J = 6.8$ Hz, 1H)
7.18 (t, $J = 7.6$ Hz, 1H),	7.21–7.11 (m, 2H)
7.15 (t, $J = 7.6$ Hz, 1H)	
5.52 (dd, $J = 9.6, 5.1$ Hz, 1H)	5.51 (dd, $J = 9.2, 4.8$ Hz, 1H)
3.68 (br s, 1H)	3.63 (s, 1H)
3.23 (dd, $J = 13.6, 6.5$ Hz, 1H)	3.21 (dd, $J = 13.6, 6.4$ Hz, 1H)
3.14 (ddd, $J = 13.6, 11.5, 5.8$ Hz, 1H)	3.16–2.87 (m, 1H)
2.51–2.44 (m, 2H)	2.52–2.40 (m, 2H)
2.32–2.23 (m, 2H)	2.31–2.21 (m, 2H)
2.01 (dq, $J = 15.3, 7.8$ Hz, 1H)	2.00 (dq, $J = 15.0, 7.6$ Hz, 1H)
1.65 (tt, $J = 13.3, 3.9$ Hz, 1H)	1.69–1.24 (m, 6H)
1.48–1.39 (m, 2H)	
1.35–1.23 (m, 3H)	
0.87 (t, $J = 7.6$ Hz, 3H)	0.86 (t, $J = 7.6$ Hz, 3H)
0.81 (td, $J = 13.4, 3.8$ Hz, 1H)	0.83–0.74 (m, 1H)

Comparison of (+)-eburnamine ^{13}C NMR peaks with previously synthesized material

This work, 126 MHz	Qin, 150 MHz ⁴
136.8	136.6
132.8	132.7
128.8	128.6
121.4	121.3
120.3	120.1
118.2	118.0
112.3	112.1
105.7	105.7
76.7	76.6
58.8	58.7
50.9	50.8
44.4	44.3
43.5	43.6
36.9	36.8
28.7	28.6
25.2	25.1
20.6	20.5
16.9	16.8
7.7	7.6

3.21 (-)-Eburnamamine

Procedure: To a solution of (+)-eburnamine **2** (83 mg, 0.28 mmol, 1.0 equiv) in CH₂Cl₂ (1 mL) at 0 °C were sequentially added Et₃N (109 µL, 0.78 mmol, 2.8 equiv) and MsCl (39 µL, 0.50 mmol, 1.8 equiv). The resulting mixture was allowed to stir at 0 °C for 30 min and then at 22 °C for 1.5 h. The reaction was quenched by addition of H₂O (5 mL) and extracted with CH₂Cl₂ (3 x 3 mL). The combined organics were washed with saturated aqueous NaHCO₃ (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (15% → 25% acetone/hexanes) afforded (-)-eburnamamine **1** (67.8 mg, 0.244 mmol, 87% yield) as a white solid.

Description: white solid.

R_f: 0.44 in 30% acetone/hexanes (UV, KMnO₄ or CAM).

¹H NMR (500 MHz, CDCl₃): δ 7.47 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.09 (d, *J* = 7.8 Hz, 1H), 4.28 (br s, 1H), 3.38 (dd, *J* = 13.6, 5.8 Hz, 1H), 3.32–3.24 (m, 1H), 3.09–3.00 (m, 1H), 2.75 (td, *J* = 11.7, 3.0 Hz, 1H), 2.69 (dtd, *J* = 11.3, 3.3, 1.6 Hz, 1H), 2.52 (ddd, *J* = 16.0, 5.3, 2.0 Hz, 1H), 2.04–1.95 (m, 1H), 1.80–1.67 (m, 2H), 1.51–1.46 (m, 1H), 1.43 (dp, *J* = 13.3, 3.3 Hz, 1H), 1.16 (td, *J* = 13.6, 3.6 Hz, 1H), 1.00 (t, *J* = 7.5 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 133.7, 130.4, 128.4, 121.7, 120.0, 119.9, 118.6, 116.9, 108.6, 107.2, 56.0, 52.3, 45.6, 37.5, 31.2, 27.7, 21.0, 16.6, 9.1.

Optical Rotation: [α]_D²⁰ = -117.0 (c = 1.00 in CHCl₃).

HRMS: calculated for C₁₉H₂₃N₂ [M+H]⁺: 279.1856, found: 279.1858.

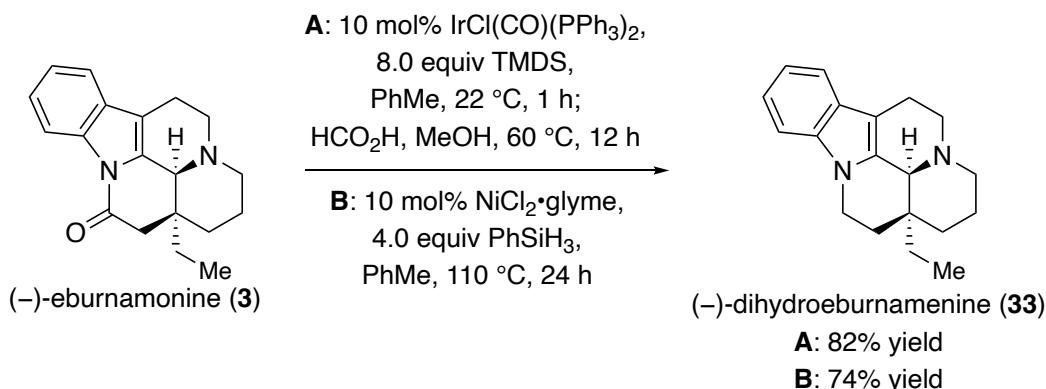
Comparison of (–)-eburnamenine ^1H NMR peaks with previously synthesized material

This work, 500 MHz	Qin, 400 MHz⁴
7.47 (d, $J = 7.6$ Hz, 1H)	7.47 (d, $J = 7.6$ Hz, 1H)
7.34 (d, $J = 7.6$ Hz, 1H)	7.34 (d, $J = 8.0$ Hz, 1H)
7.19 (t, $J = 7.6$ Hz, 1H)	7.17 (t, $J = 7.2$ Hz, 1H)
7.11 (t, $J = 7.6$ Hz, 1H)	7.11 (t, $J = 7.2$ Hz, 1H)
6.93 (d, $J = 7.8$ Hz, 1H)	6.93 (d, $J = 8.0$ Hz, 1H)
5.09 (d, $J = 7.8$ Hz, 1H)	5.08 (d, $J = 8.0$ Hz, 1H)
4.28 (br s, 1H)	4.27 (s, 1H)
3.38 (dd, $J = 13.6, 5.8$ Hz, 1H)	3.37 (dd, $J = 13.6, 6.0$ Hz, 1H)
3.32–3.24 (m, 1H)	3.33–3.22 (m, 1H)
3.09–3.00 (m, 1H)	3.11–2.97 (m, 1H)
2.75 (td, $J = 11.7, 3.0$ Hz, 1H)	2.80–2.64 (m, 2H)
2.69 (dt, $J = 11.3, 3.3, 1.6$ Hz, 1H)	
2.52 (ddd, $J = 16.0, 5.3, 2.0$ Hz, 1H)	2.52 (dd, $J = 15.6, 4.4$ Hz, 1H)
2.04–1.95 (m, 1H)	2.05–1.93 (m, 1H)
1.80–1.67 (m, 2H)	1.77–1.63 (m, 2H)
1.51–1.46 (m, 1H)	1.49–1.37 (m, 2H)
1.43 (dp, $J = 13.3, 3.3$ Hz, 1H)	
1.16 (td, $J = 13.6, 3.6$ Hz, 1H)	1.16 (td, $J = 13.6, 3.6$ Hz, 1H)
1.00 (t, $J = 7.5$ Hz, 3H)	1.00 (t, $J = 7.6$ Hz, 3H)

Comparison of (-)-eburnamenine ^{13}C NMR peaks with previously synthesized material

This work, 126 MHz	Qin, 150 MHz ⁴
133.7	133.5
130.4	130.3
128.4	128.2
121.7	121.5
120.0	119.8
119.9	119.7
118.6	118.4
116.9	116.7
108.6	108.5
107.2	107.1
56.0	55.8
52.3	52.1
45.6	45.4
37.5	37.3
31.2	31.1
27.7	27.6
21.0	20.8
16.6	16.5
9.1	9.0

3.22 (-)-Dihydroeburnamidine



Procedure A: To a solution of (-)-eburnamidine **3** (100 mg, 0.34 mmol, 1.0 equiv) and Vaska's catalyst (26.5 mg, 34.0 μmol , 0.1 equiv) in PhMe (8 mL) at 22 °C was added 1,1,3,3-tetramethyldisiloxane (TMDS) 481 μL , 2.72 mmol, 8.0 equiv). The resulting mixture was allowed to stir at 22 °C for 1 h before addition of formic acid (4 mL) to form a biphasic mixture. MeOH (4 mL) was then added dropwise (the mixture became one phase at this point) and the reaction was heated at 60 °C for 12 h. The reaction was allowed to cool to 22 °C quenched by dropwise addition of saturated aqueous K_2CO_3 until pH 10 was reached, and the resulting mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (15% → 25% acetone/hexanes) afforded (-)-dihydroeburnamidine **33** (78.2 mg, 0.28 mmol, 82% yield) as a white solid.

Procedure B: To a solution of (-)-eburnamidine **3** (100 mg, 0.34 mmol, 1.0 equiv) in PhMe (1 mL) at 22 °C was added PhSiH_3 (168 μL , 1.36 mmol, 4.0 equiv). The resulting mixture was heated to 110 °C and allowed to stir at this temperature for 24 h. The reaction was allowed to cool to 22 °C, then quenched by the addition of 1 M aqueous NaOH until pH 10 was reached and extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (15% → 25% acetone/hexanes) afforded (-)-dihydroeburnamidine **33** (70.6 mg, 0.25 mmol, 74% yield) as a white solid.

Description: white solid.

R_f: 0.42 in 30% acetone/hexanes (UV, KMnO_4 or CAM).

¹H NMR major (500 MHz, CDCl_3): δ 7.49 (d, $J = 7.6$ Hz, 1H), 7.29 (d, $J = 7.6$ Hz, 1H), 7.17 (t, $J = 7.6$ Hz, 1H), 7.11 (t, $J = 7.6$ Hz, 1H), 4.16 (ddd, $J = 11.9, 6.0, 1.5$ Hz, 1H), 3.92 (s, 1H), 3.78 (td, $J = 11.9, 5.5$ Hz, 1H), 3.37–3.24 (m, 2H), 3.05–2.93 (m, 1H), 2.67–2.55 (m, 2H), 2.47 (td, $J = 11.9, 3.1$ Hz, 1H), 2.15 (dq, $J = 15.2, 7.8$ Hz, 1H), 2.02–1.90 (m, 2H), 1.80 (qt, $J = 13.4, 4.0$ Hz, 1H), 1.56 (dq, $J = 14.8, 7.6$ Hz, 1H), 1.38 (dq, $J = 13.4, 3.2$ Hz, 1H), 1.33–1.28 (m, 1H), 1.09 (td, $J = 13.5, 4.0$ Hz, 1H), 0.93 (t, $J = 7.6$ Hz, 3H).

¹³C NMR major (126 MHz, CDCl₃): δ 136.4, 128.1, 120.7, 119.4, 118.2, 109.4, 104.4, 59.4, 51.4, 44.7, 38.6, 34.2, 32.0, 29.1, 23.9, 20.8, 17.2, 7.7.

Optical Rotation: [α]_D²⁰ = -28.6 (c = 1.00 in CHCl₃).

HRMS: calculated for C₁₉H₂₅N₂ [M+H]⁺: 281.2012, found: 281.2017.

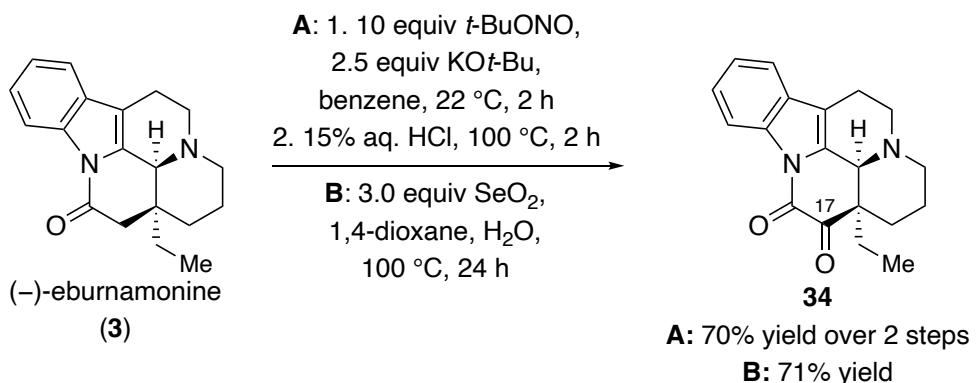
Comparison of (-)-dihydroeburnamine ¹H NMR peaks with previously synthesized material

This work, 500 MHz	Okada, 600 MHz ⁵
7.49 (d, <i>J</i> = 7.6 Hz, 1H)	7.49 (d, <i>J</i> = 7.3 Hz, 1H)
7.29 (d, <i>J</i> = 7.6 Hz, 1H)	7.29 (d, <i>J</i> = 7.3 Hz, 1H)
7.17 (t, <i>J</i> = 7.6 Hz, 1H)	7.17 (t, <i>J</i> = 7.3 Hz, 1H)
7.11 (t, <i>J</i> = 7.6 Hz, 1H)	7.11 (t, <i>J</i> = 7.3 Hz, 1H)
4.16 (ddd, <i>J</i> = 11.9, 6.0, 1.5 Hz, 1H)	4.16 (ddd, <i>J</i> = 11.7, 5.9, 1.5 Hz, 1H)
3.92 (s, 1H)	3.93 (s, 1H)
3.78 (td, <i>J</i> = 11.9, 5.5 Hz, 1H)	3.78 (td, <i>J</i> = 11.7, 5.9 Hz, 1H)
3.37–3.24 (m, 2H)	3.37–3.24 (m, 2H)
3.05–2.93 (m, 1H)	3.05–2.95 (m, 1H)
2.67–2.55 (m, 2H)	2.65–2.55 (m, 2H)
2.47 (td, <i>J</i> = 11.9, 3.1 Hz, 1H)	2.47 (td, <i>J</i> = 11.7, 2.9 Hz, 1H)
2.15 (dq, <i>J</i> = 15.2, 7.8 Hz, 1H)	2.15 (dq, <i>J</i> = 14.7, 7.3 Hz, 1H)
2.02–1.90 (m, 2H)	2.02–1.90 (m, 2H)
1.80 (qt, <i>J</i> = 13.4, 4.0 Hz, 1H)	183–1.73 (m, 1H)
1.56 (dq, <i>J</i> = 14.8, 7.6 Hz, 1H)	1.56 (dq, <i>J</i> = 14.7, 7.3 Hz, 1H)
1.38 (dq, <i>J</i> = 13.4, 3.2 Hz, 1H)	1.38 (dt, <i>J</i> = 13.9, 1.5 Hz, 1H)
1.33–1.28 (m, 1H)	1.31 (dt, <i>J</i> = 13.9, 1.5 Hz, 1H)
1.09 (td, <i>J</i> = 13.5, 4.0 Hz, 1H)	1.09 (dt, <i>J</i> = 13.9, 4.4 Hz, 1H)
0.93 (t, <i>J</i> = 7.6 Hz, 3H)	0.93 (t, <i>J</i> = 7.3 Hz, 3H)

Comparison of (-)-dihydroburnamene ^{13}C NMR peaks with previously synthesized material

This work, 126 MHz	Okada, 150 MHz⁵
136.4	136.3
128.1	127.9
120.7	120.6
119.4	119.3
118.2	118.1
109.4	109.2
104.4	104.3
59.4	59.2
51.4	51.2
44.7	44.5
38.6	38.4
34.2	34.1
32.0	31.9
29.1	28.9
23.9	23.8
20.8	20.6
17.2	17.0
7.7	7.5

3.23 17-Oxo-eburnamonine



Procedure A: To a solution of (-)-eburnamonine **3** (250 mg, 0.85 mmol, 1.0 equiv) in benzene (5 mL) at 22 °C were added tert-butyl nitrite (1.00 mL, 8.49 mmol, 10 equiv) and KO*t*-Bu (1.00 mL, 2.12 mmol, 2.5 equiv). The resulting mixture was allowed to stir at 22 °C for 2 h. The reaction was quenched by addition of a saturated aqueous solution of NH₄Cl (10 mL) and extracted with CH₂Cl₂ (3 x 8 mL). The combined organics were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was dissolved in 15% aqueous HCl (5 mL) and the resulting mixture was heated to 100 °C. The reaction was allowed to stir at 100 °C for 2 h before it was allowed to cool to 22 °C. The reaction was quenched by dropwise addition of concentrated aqueous NH₄OH until pH 10 was reached, and the resulting mixture was extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (5% EtOAc/CH₂Cl₂) afforded diketone **34** (183 mg, 0.59 mmol, 70% yield) as a white solid.

Procedure B: To a solution of (-)-eburnamonine **3** (100 mg, 0.34 mmol, 1.0 equiv) in 1,4-dioxane (7 mL) at 22 °C was added SeO₂ (113 mg, 1.02 mmol, 3.0 equiv). The resulting mixture was heated to 100 °C and allowed to stir at this temperature for 24 h. The reaction was allowed to cool to 22 °C, then filtered over a pad of Celite® using EtOAc for washing. The filtrate was washed with a saturated aqueous solution of NaHCO₃ (2 x 10 mL). The combined aqueous washing was extracted with CH₂Cl₂ (3 x 5 mL). The combined organics were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (5% EtOAc/CH₂Cl₂) afforded diketone **34** (74.3 mg, 0.24 mmol, 71% yield) as a white solid.

Description: white solid.

R_f: 0.19 in 10% EtOAc/CH₂Cl₂ (UV, KMnO₄ or CAM).

¹H NMR (500 MHz, CDCl₃): δ 8.46–8.35 (m, 1H), 7.50–7.43 (m, 1H), 7.39–7.34 (m, 2H), 4.38 (s, 1H), 3.37 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.28 (ddd, *J* = 14.0, 11.5, 5.7 Hz, 1H), 2.96 (dddd, *J* = 17.6, 11.5, 6.4, 3.1 Hz, 1H), 2.70 (dt, *J* = 11.4, 3.4 Hz, 1H), 2.63 (td, *J* = 12.0, 3.2 Hz, 1H), 2.54 (ddd, *J* = 17.0, 5.7, 2.6 Hz,

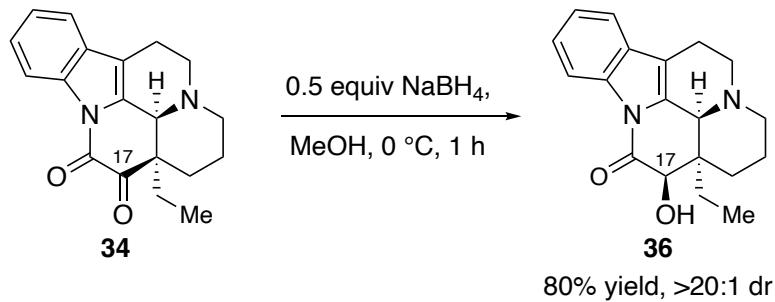
1H), 2.18 (dq, $J = 14.6, 7.4$ Hz, 1H), 2.05 (dq, $J = 14.7, 7.4$ Hz, 1H), 1.88 (qt, $J = 12.6, 4.7$ Hz, 1H), 1.56 (dp, $J = 13.4, 3.2$ Hz, 1H), 1.46–1.38 (m, 2H), 1.01 (t, $J = 7.4$ Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 194.4, 153.4, 134.2, 130.3, 129.7, 125.6, 125.3, 118.7, 117.0, 115.5, 52.8, 52.3, 50.8, 44.4, 27.6, 23.3, 20.4, 16.6, 9.23.

Optical Rotation: $[\alpha]_D^{20} = -38.0$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for $C_{19}H_{21}N_2O_2 [M+H]^+$: 309.1598, found: 309.1594.

3.24 *epi*-17-OH-Eburnamoneine



Procedure A: To a solution of diketone **34** (152 mg, 0.48 mmol, 1.0 equiv) in MeOH (2 mL) at 0 °C was added NaBH₄ (9.10 mg, 0.24 mmol, 0.5 equiv). The resulting mixture was allowed to stir at 0 °C for 1 h. The reaction was quenched by addition of AcOH (300 μL) and concentrated under reduced pressure. The resulting residue was diluted with CH₂Cl₂ (5 mL) and saturated aqueous solution of K₂CO₃ (5 mL). The phases were separated, and the aqueous phase was back extracted with CH₂Cl₂ (3 x 5 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (5% → 10% EtOAc/CH₂Cl₂) afforded alcohol **36** (128 mg, 0.41 mmol, 80% yield) as a white solid.

Description: white solid.

R_f: 0.15 in 10% EtOAc/CH₂Cl₂ (UV, KMnO₄ or CAM).

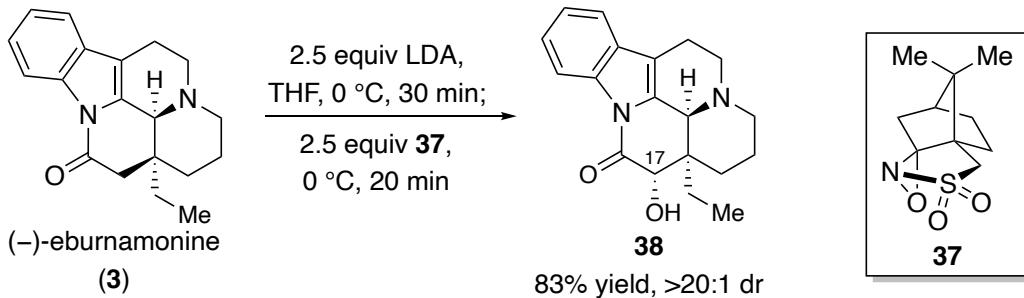
¹H NMR (500 MHz, CDCl₃): δ 8.29 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.45 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.35 (td, *J* = 7.3, 1.4 Hz, 1H), 7.30 (td, *J* = 7.3, 1.4 Hz, 1H), 4.42 (br s, 1H), 4.11 (br s, 1H), 3.56 (br s, 1H), 3.34 (dd, *J* = 14.0, 6.6 Hz, 1H), 3.26 (ddd, *J* = 14.0, 11.0, 5.8 Hz, 1H), 2.90 (dddd, *J* = 16.7, 11.0, 6.9, 2.8 Hz, 1H), 2.59 (ddt, *J* = 11.4, 3.8, 1.8 Hz, 1H), 2.50 (ddd, *J* = 16.7, 5.7, 2.7 Hz, 1H), 2.35 (td, *J* = 12.1, 3.3 Hz, 1H), 2.22 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.81–1.71 (m, 2H), 1.67 (dd, *J* = 13.4, 3.3 Hz, 1H), 1.40 (dp, *J* = 13.4, 3.1 Hz, 1H), 1.09 (t, *J* = 7.5 Hz, 3H), 0.82 (td, *J* = 13.4, 4.2 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 170.7, 134.0, 131.5, 130.6, 124.7, 124.5, 118.6, 116.1, 113.9, 73.9, 53.8, 50.7, 44.9, 43.7, 25.3, 24.8, 20.3, 16.9, 8.5.

Optical Rotation: $[\alpha]_D^{20} = -68.0$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 311.1760, found: 311.1762.

3.25 17-OH-Eburnamonine



Procedure: To a solution of $(-)$ -eburnamonine **3** (100 mg, 0.34 mmol, 1.0 equiv) in THF (5 mL) at 0 °C was added freshly prepared LDA (850 μL of a 1.0 M solution in THF, 0.85 mmol, 2.5 equiv). The resulting mixture was allowed to stir at 0 °C for 20 min before addition of a solution of $(1R)$ - $(-)$ -(10-camphorsulfonyl)oxaziridine **37** (195 mg, 0.85 mmol, 2.5 equiv) in THF (2 mL). The reaction was allowed to stir at 0 °C for 20 min, then quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 12 mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (5% → 10% EtOAc/ CH_2Cl_2) afforded alcohol **38** (87.5 mg, 0.28 mmol, 83% yield) as a white solid.

Description: white solid.

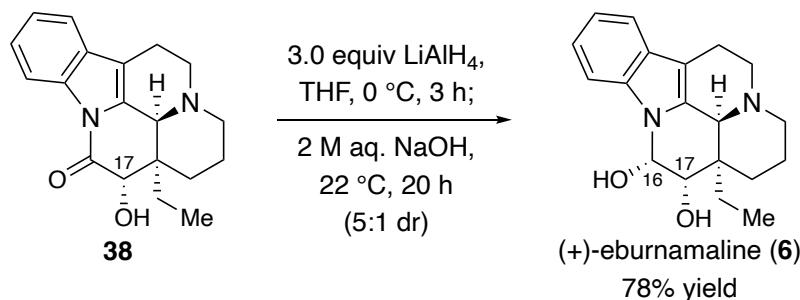
R_f: 0.11 in 10% EtOAc/ CH_2Cl_2 (UV, KMnO_4 or CAM).

¹H NMR (500 MHz, CDCl_3): δ 8.32 (dd, $J = 7.1, 1.2$ Hz, 1H), 7.43 (dd, $J = 7.1, 1.2$ Hz, 1H), 7.34–7.30 (m, 1H), 7.30–7.27 (m, 1H), 4.18 (br s, 1H), 4.17 (br s, 1H), 3.57 (br s, 1H), 3.36–3.31 (m, 1H), 3.31–3.25 (m, 1H), 2.88 (dd, $J = 16.1, 14.0, 6.3, 2.3$ Hz, 1H), 2.63 (br d, $J = 10.8$ Hz, 1H), 2.49 (dd, $J = 16.1, 6.3$ Hz, 1H), 2.40 (td, $J = 12.7, 3.2$ Hz, 1H), 2.26 (dq, $J = 15.1, 7.6$ Hz, 1H), 1.95 (dq, $J = 14.7, 7.4, 1.4$ Hz, 1H), 1.80 (qt, $J = 13.3, 4.0$ Hz, 1H), 1.52 (dd, $J = 13.7, 3.5$ Hz, 1H), 1.39 (dp, $J = 13.0, 3.1$ Hz, 1H), 0.92 (t, $J = 7.6$ Hz, 3H), 0.73 (tdd, $J = 13.4, 4.0, 1.3$ Hz, 1H).

¹³C NMR (126 MHz, CDCl_3): δ 168.2, 134.6, 131.5, 130.6, 124.6, 124.4, 118.4, 116.5, 113.2, 75.5, 55.8, 50.7, 44.9, 41.6, 23.1, 22.1, 20.2, 16.8, 7.0.

Optical Rotation: $[\alpha]_D^{20} = -121.0$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 311.1760, found: 311.1762.

3.26 (+)-Eburnamaline

Procedure: To a solution of amide **38** (84 mg, 0.27 mmol, 1.0 equiv) in THF (2.5 mL) at 0 °C was added LiAlH₄ (30.8 mg, 0.81 mmol, 3.0 equiv). The resulting mixture was allowed to stir at 0 °C for 3 h. At this point TLC analysis showed full conversion of the starting material and ¹H NMR of a small aliquot of the reaction mixture showed 1:4 dr at C16 in favor of the undesired isomer. 2.0 M aqueous NaOH (2.5 mL) was added to the reaction and the resulting mixture was allowed to stir at 22 °C for 20 h. At this point, ¹H NMR of a small aliquot of the reaction mixture showed 5:1 dr at C16 in favor of desired (+)-eburnamaline **6**. The reaction mixture was diluted with H₂O (3 mL) and extracted with CH₂Cl₂ (5 x 4 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (60% → 75% acetone/hexanes) afforded (+)-eburnamaline **6** (65.2 mg, 0.21 mmol, 78% yield) as a pale-yellow oil.

Description: pale-yellow oil.

R_f: 0.16 in 5% MeOH/CH₂Cl₂ or 0.21 70% acetone/hexanes (UV, KMnO₄ or CAM).

¹H NMR major (500 MHz, CDCl₃): δ 7.81 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.19 (td, *J* = 7.5, 1.3 Hz, 1H), 7.14 (td, *J* = 7.5, 1.3 Hz, 1H), 5.55 (d, *J* = 3.4 Hz, 1H), 4.09 (br s, 1H), 3.93 (d, *J* = 3.5 Hz, 1H), 3.21 (dd, *J* = 13.7, 6.4 Hz, 1H), 3.11 (ddd, *J* = 13.6, 11.5, 5.9 Hz, 1H), 2.89–2.80 (m, 1H), 2.54 (dt, *J* = 11.5, 3.2 Hz, 1H), 2.39–2.27 (m, 3H), 1.89–1.80 (m, 1H), 1.72 (qt, *J* = 12.7, 3.4 Hz, 1H), 1.38 (dd, *J* = 13.2, 3.4 Hz, 1H), 1.33–1.27 (m, 1H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.67 (td, *J* = 13.1, 3.5 Hz, 1H).

¹³C NMR major (126 MHz, CDCl₃): δ 137.4, 131.2, 128.7, 121.6, 120.4, 118.2, 112.6, 105.7, 77.6, 71.8, 56.1, 51.1, 44.9, 41.0, 23.0, 22.0, 20.0, 16.8, 7.0.

Optical Rotation: [α]_D²⁰ = +38.6 (c = 1.00 in CHCl₃).

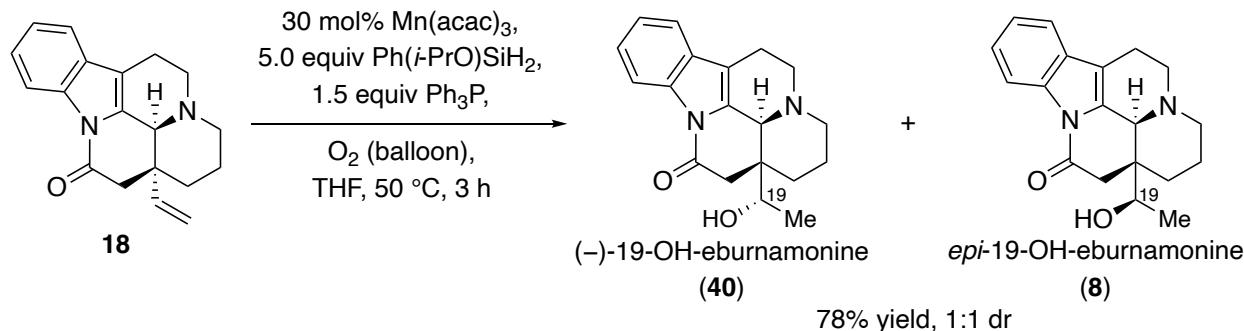
HRMS: calculated for C₁₉H₂₅N₂O₂ [M+H]⁺: 313.1911, found: 313.1914.

Comparison of (+)-eburnamaline ^1H NMR peaks with previously synthesized material

This work, 500 MHz	Natural, 400 MHz⁶
7.81 (d, $J = 7.5$ Hz, 1H)	7.79 (dd, $J = 7.0, 1.0$ Hz, 1H)
7.44 (d, $J = 7.5$ Hz, 1H)	7.45 (dd, $J = 7.0, 1.0$ Hz, 1H)
7.19 (td, $J = 7.5, 1.3$ Hz, 1H)	7.17 (td, $J = 7.0, 1.0$ Hz, 1H)
7.14 (td, $J = 7.5, 1.3$ Hz, 1H)	7.13 (td, $J = 7.0, 1.0$ Hz, 1H)
5.55 (d, $J = 3.4$ Hz, 1H)	5.54 (d, $J = 3.0$ Hz, 1H)
4.09 (br s, 1H)	4.02 (br s, 1H)
3.93 (d, $J = 3.5$ Hz, 1H)	3.90 (d, $J = 3.0$ Hz, 1H)
3.21 (dd, $J = 13.7, 6.4$ Hz, 1H)	3.22 (dd, $J = 14.0, 6.0$ Hz, 1H)
3.11 (ddd, $J = 13.6, 11.5, 5.9$ Hz, 1H)	3.14 (ddd, $J = 14.0, 12.0, 6.0$ Hz, 1H)
2.89–2.80 (m, 1H)	2.88 (dddd, $J = 16.0, 12.0, 6.0, 2.0$ Hz, 1H)
2.54 (dt, $J = 11.5, 3.2$ Hz, 1H)	2.53 (br d, $J = 13.0$ Hz, 1H)
2.39–2.27 (m, 3H)	2.42 (ddd, $J = 16.0, 6.0, 2.0$ Hz, 1H)
	2.35 (m, 1H)
	2.30 (dq, $J = 14.5, 7.7$ Hz, 1H)
1.89–1.80 (m, 1H)	1.79 (dq, $J = 14.5, 7.7$ Hz, 1H)
1.72 (qt, $J = 12.7, 3.4$ Hz, 1H)	1.70 (dt, $J = 13.0, 3.6$ Hz, 1H)
1.38 (dd, $J = 13.2, 3.4$ Hz, 1H),	1.37 (br d, $J = 13.0$ Hz, 1H),
1.33–1.27 (m, 1H)	1.29 (m, 1H)
0.91 (t, $J = 7.5$ Hz, 3H)	0.89 (t, $J = 7.7$ Hz, 3H)
0.67 (td, $J = 13.1, 3.5$ Hz, 1H)	0.66 (td, $J = 13.0, 3.6$ Hz, 1H)

Comparison of (+)-eburnamaline ^{13}C NMR peaks with previously synthesized material

This work, 126 MHz	Natural, 101 MHz⁶
137.4	137.2
131.2	131.5
128.7	128.7
121.6	121.3
120.4	120.2
118.2	118.0
112.6	112.3
105.7	105.6
77.6	77.0
71.8	71.7
56.1	55.8
51.1	50.9
44.9	44.8
41.0	40.9
23.0	22.9
22.0	21.9
20.0	20.0
16.8	16.7
7.0	6.9

3.27 (-)-19-OH-Eburnamonine

Procedure: To a solution of alkene **18** (400 mg, 1.37 mmol, 1.0 equiv) in THF (27 mL) at 22 °C were added Mn(acac)₃ (145 mg, 0.41 mmol, 0.3 equiv) and triphenylphosphine (538 mg, 2.05 mmol, 1.5 equiv). Oxygen was bubbled through the resulting mixture for 2 min. The reaction was placed under an O₂ atmosphere (balloon) and then heated to 50 °C followed by the dropwise addition of isopropoxy(phenyl)silane (1.23 mL, 6.84 mmol, 5.0 equiv). The mixture was then allowed to stir under an O₂ atmosphere (balloon) for 3 h. After completion, the reaction was cooled to 0 °C and quenched by addition of a freshly prepared 10% aqueous solution of KF (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The resulting residue was diluted with EtOAc (10 mL) and filtered through Celite® using EtOAc for washing to remove any remaining Mn salts and then concentrated under reduced pressure. Purification by silica gel chromatography (100% EtOAc → 3% MeOH/EtOAc) afforded a 1:1 mixture of **(-)-19-OH-eburnamonine 8** and **epi-19-OH-eburnamonine 40** (331 mg, 1.07 mmol, 78% yield) as a white foam.

Note: **(-)-19-OH-eburnamonine** and **epi-19-OH-eburnamonine** can only be partially separated by flash column chromatography on silica gel. However, separation can be achieved by preparative TLC (SiO₂, 5% MeOH/CH₂Cl₂, developed 3 times).

Description: white foam.

R_f: 0.14 in 1% MeOH/EtOAc (UV, KMnO₄ or CAM).

¹H NMR (-)-19-OH-eburnamonine (500 MHz, CDCl₃): δ 8.35 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 4.32 (br s, 1H), 4.08 (q, *J* = 6.5 Hz, 1H), 3.43–3.26 (m, 2H), 2.93 (dd, *J* = 17.0, 11.0, 7.2, 2.8 Hz, 1H), 2.69–2.61 (m, 1H), 2.61–2.47 (m, 4H), 2.29 (qt, *J* = 13.3, 4.6 Hz, 1H), 1.88 (br d, *J* = 14.0 Hz, 1H), 1.40 (br d, *J* = 13.3 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.05 (td, *J* = 14.0, 4.5 Hz, 1H).

¹³C NMR (-)-19-OH-eburnamonine (126 MHz, CDCl₃): δ 166.3, 134.3, 130.0, 129.9, 124.7, 124.1, 118.3, 116.3, 112.4, 77.9, 58.6, 50.4, 43.7, 43.6, 41.0, 23.9, 21.1, 17.4, 16.5.

¹H NMR epi-19-OH-eburnamonine (500 MHz, CDCl₃): δ 8.42 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 4.68 (br s, 1H), 4.62 (q, *J* = 6.5 Hz, 1H), 3.43–3.32 (m, 1H), 3.15 (d, *J* = 16.8 Hz, 1H), 3.02–2.87 (m, 1H), 2.74–2.63 (m, 1H), 2.61–2.47 (m, 4H), 1.85–1.72 (m, 1H), 1.60 (br d, *J* = 14.3 Hz, 1H), 1.40 (br d, *J* = 13.3 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.17 (td, *J* = 14.3, 4.2 Hz, 1H).

¹³C NMR epi-19-OH-eburnamonine (126 MHz, CDCl₃): δ 168.2, 134.4, 131.4, 130.2, 124.5, 124.0, 118.1, 116.4, 112.5, 65.3, 53.2, 50.6, 44.0, 43.2, 38.1, 26.8, 20.2, 17.1, 16.5.

Optical Rotation (-)-19-OH-eburnamonine: [α]_D²⁰ = -48.0 (c = 1.00 in MeCN).

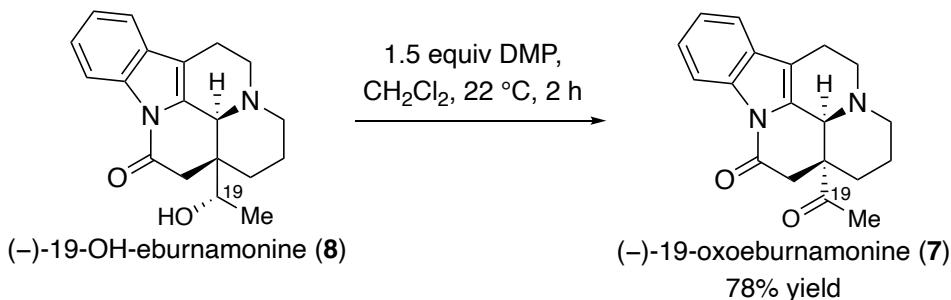
HRMS: calculated for C₁₉H₂₂N₂O₂ [M+H]⁺: 311.1754, found: 311.1750.

Comparison of (-)-19-OH-eburnamonine ¹H NMR peaks with isolated natural material

This work, 500 MHz	Natural, 500 MHz ⁷
8.35 (d, <i>J</i> = 7.5 Hz, 1H)	8.35 (dd, 7.4, 1.4 Hz, 1H)
7.44 (d, <i>J</i> = 7.5 Hz, 1H)	7.45 (dd, <i>J</i> = 7.4, 1.4 Hz, 1H)
7.34 (t, <i>J</i> = 7.5 Hz, 1H)	7.33 (td, <i>J</i> = 7.4, 1.4 Hz, 1H)
7.30 (t, <i>J</i> = 7.5 Hz, 1H)	7.31 (td, <i>J</i> = 7.4, 1.4 Hz, 1H)
4.32 (br s, 1H)	4.33 (br t, <i>J</i> = 2.8 Hz, 1H)
4.08 (q, <i>J</i> = 6.5 Hz, 1H)	4.08 (qd, <i>J</i> = 6.4, 1.4 Hz, 1H)
3.43–3.26 (m, 2H)	3.35 (ddd, <i>J</i> = 14.0, 11.0, 5.5 Hz, 1H)
	3.31 (ddd, <i>J</i> = 14.0, 7.0, 1.4 Hz, 1H)
2.93 (dddd, <i>J</i> = 17.0, 11.0, 7.2, 2.8 Hz, 1H)	2.94 (dddd, <i>J</i> = 17.0, 11.0, 7.0, 2.8 Hz, 1H)
2.69–2.61 (m, 1H)	2.65 (br dd, <i>J</i> = 11.2, 4.4 Hz, 1H)
2.61–2.47 (m, 4H)	2.56 (dddd, <i>J</i> = 17.0, 5.5, 2.8, 1.4 Hz, 1H)
	2.52 (m, 3H)
2.29 (qt, <i>J</i> = 13.3, 4.6 Hz, 1H)	2.28 (qt, <i>J</i> = 13.3, 4.6 Hz, 1H)
1.88 (br d, <i>J</i> = 14.0 Hz, 1H)	1.88 (br d, <i>J</i> = 14.0 Hz, 1H)
1.40 (br d, <i>J</i> = 13.3 Hz, 1H)	1.40 (d, <i>J</i> = 13.3 Hz, 1H)
1.23 (d, <i>J</i> = 6.4 Hz, 3H)	1.24 (d, <i>J</i> = 6.4 Hz, 3H)
1.05 (td, <i>J</i> = 14.0, 4.5 Hz, 1H)	1.06 (tdd, <i>J</i> = 14.0, 4.6, 1.4 Hz, 1H)

Comparison of (–)-19-OH-eburnamone ^{13}C NMR peaks with isolated natural material

This work, 126 MHz	Natural, 126 MHz ⁷	Trost, 126 MHz ⁸
166.3	166.3	166.3
134.3	134.3	134.3
130.0	130.1	130.1
129.9	129.9	129.9
124.7	124.7	124.7
124.1	124.1	124.1
118.3	118.3	118.3
116.3	116.3	116.3
112.4	112.4	112.4
77.9	78.1	78.1
58.6	58.7	58.7
50.4	50.4	50.4
43.7	43.7	43.7
43.6	43.6	43.7
41.0	41.0	41.0
23.9	24.0	24.0
21.1	21.2	21.1
17.4	17.4	17.5
16.5	16.5	16.5

3.28 (-)-19-Oxoeburnamonine

Procedure: To a solution of a 1:1 mixture of (–)-19-OH-eburnamonine **8** and *epi*-19-OH-eburnamonine **40** (231 mg, 0.74 mmol, 1.0 equiv) in CH₂Cl₂ (7.5 mL) at 22 °C was added Dess-Martin periodinane (DMP, 473 mg, 1.12 mmol, 1.5 equiv) and the resulting mixture was allowed to stir at 22 °C for 2 h. The reaction was quenched by addition of saturated aqueous Na₂S₂O₃ (10 mL) and saturated aqueous NaHCO₃ (10 mL). The resulting mixture was allowed to vigorously stir at 22 °C until clear (~15 min), and then extracted with CH₂Cl₂ (3 x 5 mL). The combined organics were washed with saturated aqueous NaHCO₃ (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (100% CH₂Cl₂ → 10% acetone/CH₂Cl₂) afforded (–)-19-oxoeburnamonine **7** (331 mg, 1.07 mmol, 78% yield) as a white foam.

Description: white foam.

R_f: 0.35 in 20% acetone/CH₂Cl₂ (UV, KMnO₄ or CAM).

¹H NMR (500 MHz, CDCl₃): δ 8.34 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 4.84 (br s, 1H), 3.34 (dd, *J* = 9.1, 3.2 Hz, 2H), 2.91 (dtd, *J* = 17.1, 9.1, 3.2 Hz, 1H), 2.77 (d, *J* = 16.6 Hz, 1H), 2.67 (d, *J* = 16.6 Hz, 1H), 2.61 (dt, *J* = 11.8, 3.2 Hz, 1H), 2.51 (dq, *J* = 17.1, 3.2 Hz, 1H), 2.42 (ddd, *J* = 13.3, 11.8, 3.2 Hz, 1H), 2.39 (s, 3H), 2.18 (dd, *J* = 13.3, 3.6 Hz, 1H), 1.57–1.50 (m, 1H), 1.46 (tt, *J* = 13.3, 3.6 Hz, 1H), 1.15 (td, *J* = 13.3, 4.1 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 208.5, 165.1, 134.4, 130.8, 130.2, 124.8, 124.3, 118.4, 116.3, 113.8, 53.9, 52.4, 50.6, 44.2, 42.6, 26.8, 25.7, 22.6, 16.6.

Optical Rotation: [α]_D²⁰ = –48.8 (c = 1.00 in CHCl₃); lit.⁹ [α]_D²³ = –115.0 (c = 0.09 in CHCl₃).

HRMS: calculated for C₁₉H₂₁N₂O₂ [M+H]⁺: 309.1598, found: 309.1598.

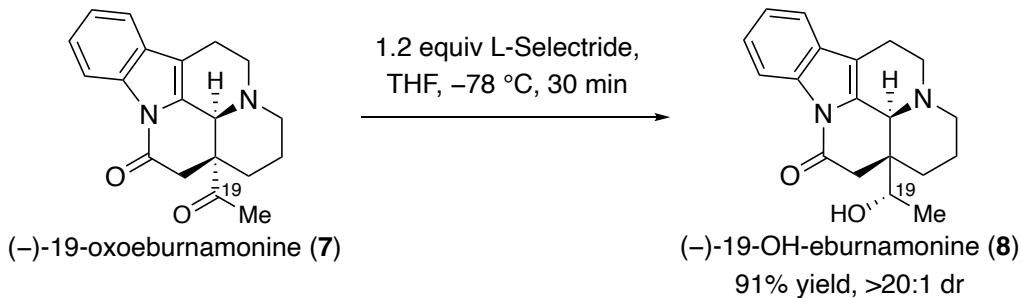
Comparison of (–)-19-oxoeburnamoneine ^1H NMR peaks with isolated natural material

This work, 500 MHz	Natural, 400 MHz⁹
8.34 (d, $J = 7.6$ Hz, 1H)	8.35 (br dd, $J = 7.5, 1.5$ Hz, 1H)
7.44 (d, $J = 7.6$ Hz, 1H)	7.46 (br dd, $J = 7.5, 1.5$ Hz, 1H)
7.33 (t, $J = 7.6$ Hz, 1H)	7.34 (td, $J = 7.5, 1.5$ Hz, 1H)
7.30 (t, $J = 7.6$ Hz, 1H)	7.31 (td, $J = 7.5, 1.5$ Hz, 1H)
4.84 (br s, 1H)	4.86 (br s, 1H)
3.34 (dd, $J = 9.1, 3.2$ Hz, 2H)	3.38–3.34 (m, 2H)
2.91 (dtd, $J = 17.1, 9.1, 3.2$ Hz, 1H)	2.92 (dddd, $J = 17.1, 10.3, 7.4, 2.8$ Hz, 1H)
2.77 (d, $J = 16.6$ Hz, 1H)	2.79 (d, $J = 16.6$ Hz, 1H)
2.67 (d, $J = 16.6$ Hz, 1H)	2.68 (d, $J = 16.6$ Hz, 1H)
2.61 (dt, $J = 11.8, 3.2$ Hz, 1H)	2.61 (br d, $J = 12.8$, 1H)
2.51 (dq, $J = 17.1, 3.2$ Hz, 1H)	2.52 (ddt, $J = 17.1, 4.6, 2.3$ Hz, 1H)
2.42 (ddd, $J = 13.3, 11.8, 3.2$ Hz, 1H)	2.44 (td, $J = 12.8, 3.2$ Hz, 1H)
2.39 (s, 3H)	2.40 (s, 3H)
2.18 (dd, $J = 13.3, 3.6$ Hz, 1H)	2.19 (br d, $J = 12.8$ Hz, 1H)
1.57–1.50 (m, 1H)	1.55 (m, 1H)
1.46 (tt, $J = 13.3, 3.6$ Hz, 1H)	1.46 (qt, $J = 12.8, 3.6$ Hz, 1H)
1.15 (td, $J = 13.3, 4.1$ Hz, 1H)	1.17 (td, $J = 12.8, 4.1$ Hz, 1H)

Comparison of (–)-19-oxoeburnamone ^{13}C NMR peaks with isolated natural material

This work, 126 MHz	Natural, 126 MHz⁹
208.5	208.5
165.1	165.0
134.4	134.3
130.8	130.7
130.2	130.1
124.8	124.6
124.3	124.2
118.4	118.2
116.3	116.2
113.8	113.7
53.9	53.9
52.4	52.3
50.6	50.6
44.2	44.1
42.6	42.5
26.8	26.8
25.7	25.6
22.6	22.6
16.6	16.4

3.29 (-)-19-OH-Eburnamone by L-Selectride Reduction



Procedure: To a solution of (-)-19-oxoeburnamone **7** (200 mg, 0.65 mmol, 1.0 equiv) in THF (6.5 mL) at -78°C was added L-Selectride (780 μL of 1.0 M solution in THF, 0.78 mmol, 1.2 equiv). The resulting mixture was allowed to stir at -78°C for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10% \rightarrow 30% acetone/ CH_2Cl_2) afforded (-)-19-OH-eburnamone **8** (183 mg, 0.59 mmol, 91% yield, $>20:1$ dr) as a white foam.

Description: white foam.

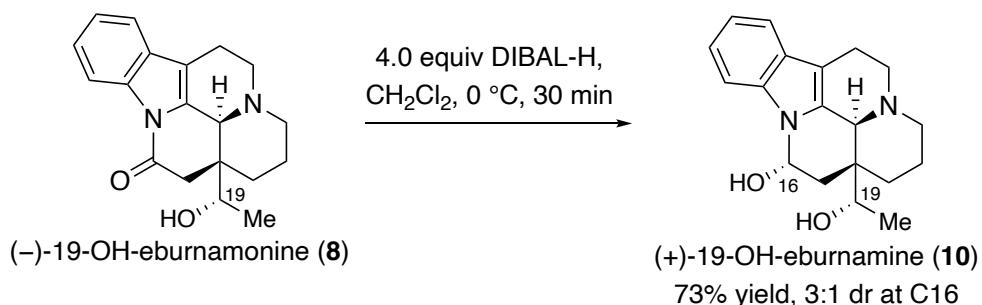
R_f: 0.14 in 1% MeOH/EtOAc (UV, KMnO_4 or CAM).

¹H NMR (500 MHz, CDCl_3): δ 8.35 (d, $J = 7.5$ Hz, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 7.5$ Hz, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 4.32 (br s, 1H), 4.08 (q, $J = 6.5$ Hz, 1H), 3.43–3.26 (m, 2H), 2.93 (dd, $J = 17.0, 11.0, 7.2, 2.8$ Hz, 1H), 2.69–2.61 (m, 1H), 2.61–2.47 (m, 4H), 2.29 (qt, $J = 13.3, 4.6$ Hz, 1H), 1.88 (br d, $J = 14.0$ Hz, 1H), 1.40 (br d, $J = 13.3$ Hz, 1H), 1.23 (d, $J = 6.4$ Hz, 3H), 1.05 (td, $J = 14.0, 4.5$ Hz, 1H).

¹³C NMR (126 MHz, CDCl_3): δ 166.3, 134.3, 130.0, 129.9, 124.7, 124.1, 118.3, 116.3, 112.4, 77.9, 58.6, 50.4, 43.7, 43.6, 41.0, 23.9, 21.1, 17.4, 16.5.

Optical Rotation: $[\alpha]_D^{20} = -48.0$ ($c = 1.00$ in MeCN).

HRMS: calculated for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$ [$\text{M}+\text{H}]^+$: 311.1754, found: 311.1750.

3.30 (+)-19-OH-Eburnamine

Procedure: To a solution of (-)-19-OH-eburnamonine **8** (180 mg, 0.58 mmol, 1.0 equiv) in CH₂Cl₂ (5.8 mL) at 0 °C was added DIBAL-H (2.32 mL of a 1.0 M solution in PhMe, 2.32 mmol, 4.0 equiv). The resulting mixture was allowed to stir at 0 °C for 30 min. The reaction was quenched by the addition of 1 M aqueous NaOH (8 mL) and extracted with CH₂Cl₂ (3 x 5 mL). The combined organics were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (1% → 15% MeOH/CH₂Cl₂) afforded (+)-19-OH-eburnamine **10** (132 mg, 0.42 mmol, 73% yield, 3:1 dr at C16) as a white foam.

Description: white foam.

R_f: 0.12 in 10% MeOH/CH₂Cl₂ (UV, KMnO₄ or CAM).

¹H NMR (500 MHz, CDCl₃) (+)-19-OH-eburnamine (major diastereoisomer): δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 5.49 (dd, *J* = 9.4, 5.1 Hz, 1H), 4.03 (br s, 1H), 3.89 (q, *J* = 6.7 Hz, 1H), 3.28 (ddd, *J* = 13.0, 11.5, 5.0 Hz, 1H), 3.19 (ddd, *J* = 13.0, 6.5, 1.5 Hz, 2H), 2.89 (dt, *J* = 17.6, 9.8 Hz, 1H), 2.61–2.43 (m, 2H), 2.36 (td, *J* = 12.2, 3.5 Hz, 1H), 2.24–2.04 (m, 2H), 1.64 (br d, *J* = 13.9 Hz, 1H), 1.42 (dd, *J* = 13.8, 9.4 Hz, 1H), 1.33 (br d, *J* = 13.1 Hz, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 0.79 (td, *J* = 13.8, 4.4 Hz, 1H).

¹³C NMR (+)-19-OH-eburnamine (major diastereoisomer, 126 MHz, CDCl₃): δ 136.8, 130.3, 128.4, 121.8, 120.4, 118.2, 112.4, 105.0, 77.8, 76.2, 59.3, 50.6, 43.8, 42.2, 39.5, 22.2, 21.0, 17.7, 16.7.

¹³C NMR (-)-19-OH-isoeburnamine (minor diastereoisomer, 126 MHz, CDCl₃): δ 135.0, 128.7, 121.7, 120.5, 118.6, 110.3, 105.0, 78.7, 74.0, 59.8, 51.0, 44.3, 39.3, 37.3, 23.4, 21.4, 17.7, 17.0.

Optical Rotation: [α]_D²⁰ = +82.3 (c = 1.00 in CHCl₃).

HRMS: calculated for C₁₉H₂₅N₂O₂ [M+H]⁺: 313.1911, found: 313.1911.

Comparison of (+)-19-OH-eburnamine (major) ^1H NMR peaks with isolated natural material

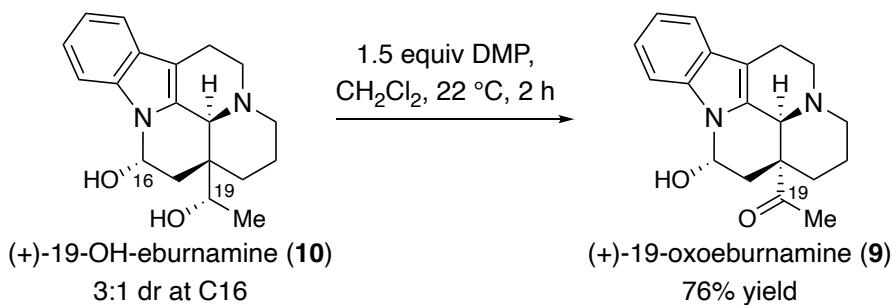
This work, 500 MHz	Natural, 400 MHz¹⁰
7.74 (d, $J = 7.6$ Hz, 1H)	7.72 (dd, $J = 7.0, 1.5$ Hz, 1H)
7.44 (d, $J = 7.6$ Hz, 1H)	7.49 (dd, $J = 7.0, 1.5$ Hz, 1H)
7.18 (t, $J = 7.6$ Hz, 1H)	7.21 (td, $J = 7.0, 1.5$ Hz, 1H)
7.15 (t, $J = 7.6$ Hz, 1H)	7.17 (td, $J = 7.0, 1.5$ Hz, 1H)
5.49 (dd, $J = 9.4, 5.1$ Hz, 1H)	5.59 (dd, $J = 10.0, 5.0$ Hz, 1H)
4.03 (br s, 1H)	4.22 (br s, 1H)
3.89 (q, $J = 6.7$ Hz, 1H)	3.98 (qd, $J = 6.5, 1.0$ Hz, 1H)
3.28 (ddd, $J = 13.0, 11.5, 5.0$ Hz, 1H)	3.33 (ddd, $J = 13.0, 11.5, 5.0$ Hz, 1H)
3.19 (ddd, $J = 13.0, 6.5, 1.5$ Hz, 1H)	3.28 (ddd, $J = 13.0, 6.5, 1.5$ Hz, 1H)
2.89 (dt, $J = 17.6, 9.8$ Hz, 1H)	2.97 (dddd, $J = 16.0, 11.5, 6.5, 2.5$ Hz, 1H)
2.61–2.43 (m, 2H)	2.57 (m, 2H)
2.36 (td, $J = 12.2, 3.5$ Hz, 1H)	2.42 (td, $J = 13.0, 4.0$ Hz, 1H)
2.24–2.04 (m, 2H)	2.25 (dd, 14.0, 5.0 Hz, 1H)
	2.19 (qt, 13.0, 4.0 Hz, 1H)
1.64 (br d, $J = 13.9$ Hz, 1H)	1.74 (br d, $J = 13.0$ Hz, 1H)
1.42 (dd, $J = 13.8, 9.4$ Hz, 1H)	1.49 (dd, $J = 14.0, 10.0$ Hz, 1H)
1.33 (br d, $J = 13.1$ Hz, 1H)	1.32 (br d, $J = 13.0$ Hz, 1H)
1.19 (d, $J = 6.5$ Hz, 3H)	1.24 (d, $J = 6.5$ Hz, 3H)
0.79 (td, $J = 13.8, 4.4$ Hz, 1H)	0.89 (tdd, $J = 13.0, 4.0, 1.0$ Hz, 1H)

Comparison of (+)-19-OH-eburnamine (major) ^{13}C NMR peaks with isolated natural material

This work, 126 MHz	Natural, 101 MHz¹⁰
136.8	136.6
130.3	130.9
128.4	128.6
121.8	121.6
120.4	120.4
118.2	118.2
112.4	112.1
105.0	105.6
77.8	78.3
76.2	76.5
59.3	59.5
50.6	50.5
43.8	43.7
42.2	43.0
39.5	39.5
22.2	22.4
21.0	21.2
17.7	17.6
16.7	16.7

Comparison of (-)-19-OH-isoeburnamine (minor) ^{13}C NMR peaks with isolated natural material

This work, 126 MHz	Natural, 101 MHz¹⁰
135.0	135.1
128.7	129.6
121.7	121.7
120.5	120.6
118.6	118.9
110.3	110.2
105.0	105.5
78.7	79.5
74.0	74.5
59.8	60.1
51.0	51.2
44.3	44.4
39.3	39.6
37.3	37.4
23.4	23.9
21.4	21.9
17.7	17.8
17.0	17.0

3.31 (+)-19-Oxoeburnamine

Procedure: To a solution of (+)-19-OH-eburnamine **10** (47 mg, 0.15 mmol, 1.0 equiv, 3:1 dr at C16) in CH₂Cl₂ (2 mL) at 22 °C was added Dess-Martin periodinane (DMP, 76 mg, 0.18 mmol, 1.5 equiv) and the resulting mixture was allowed to stir at 22 °C for 2 h. The reaction was quenched by the addition of saturated aqueous Na₂S₂O₃ (2.5 mL) and saturated aqueous NaHCO₃ (2.5 mL). The resulting mixture was allowed to vigorously stir at 22 °C until clear (~10 min), and then extracted with CH₂Cl₂ (4 x 5 mL). The combined organics were washed with saturated aqueous NaHCO₃ (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (5% → 15% acetone/hexanes) afforded (+)-19-oxoeburnamine **9** (35.4 mg, 0.114 mmol, 76% yield) as a white solid.

Description: white solid.

R_f: 0.11 in 15% acetone/hexanes (UV, CAM).

¹H NMR (500 MHz, CDCl₃): δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 5.65 (dd, *J* = 9.5, 5.3 Hz, 1H), 4.72 (br s, 1H), 3.25 (br dd, *J* = 8.4, 2.7 Hz, 2H), 2.94 (dt, *J* = 17.5, 9.2 Hz, 1H), 2.55–2.47 (m, 2H), 2.38 (s, 3H), 2.35 (q, *J* = 5.2 Hz, 1H), 2.31 (dt, *J* = 11.5, 2.7 Hz, 1H), 2.06 (br d, *J* = 13.6 Hz, 1H), 1.73 (dd, *J* = 13.6, 9.2 Hz, 1H), 1.47–1.33 (m, 2H), 0.95 (td, *J* = 13.3, 4.1 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 210.4, 136.8, 131.6, 128.8, 121.8, 120.6, 118.3, 112.2, 106.8, 76.5, 54.9, 51.9, 50.8, 44.1, 42.1, 25.7, 25.0, 22.8, 16.9.

Optical Rotation: [α]_D²⁰ = +22.3 (c = 1.00 in CHCl₃).

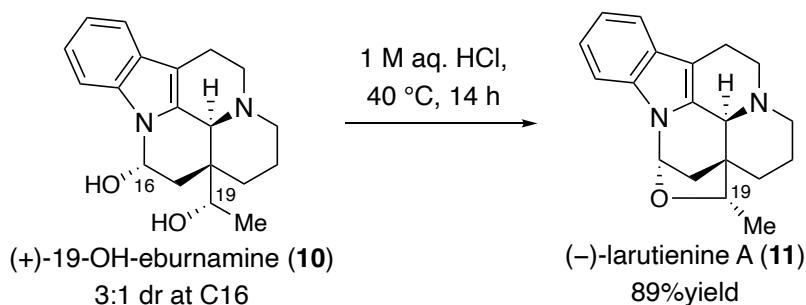
HRMS: calculated for C₁₉H₂₃N₂O₂ [M+H]⁺: 311.1754, found: 311.1756.

Comparison of (+)-19-oxoeburnamine ^1H NMR peaks with isolated natural material

This work, 500 MHz	Natural, 300 MHz ¹¹
7.71 (d, $J = 7.6$ Hz, 1H)	7.71 (dd, $J = 6.0, 2.0$ Hz, 1H)
7.49 (d, $J = 7.6$ Hz, 1H)	7.49 (dd, $J = 6.0, 2.0$ Hz, 1H)
7.20 (t, $J = 7.6$ Hz, 1H)	7.19 (m, 1H)
7.17 (t, $J = 7.6$ Hz, 1H)	7.16 (m, 1H)
5.65 (dd, $J = 9.5, 5.3$ Hz, 1H)	5.62 (dd, $J = 9.0, 5.0$ Hz, 1H)
4.72 (br s, 1H)	4.67 (br s, 1H)
3.25 (br dd, $J = 8.4, 2.7$ Hz, 2H)	3.22 (m, 2H)
2.94 (dt, $J = 17.5, 9.2$ Hz, 1H)	2.95 (m, 1H)
2.55–2.47 (m, 2H)	2.49 (m, 2H)
2.38 (s, 3H)	2.36 (s, 3H)
2.35 (q, $J = 5.2$ Hz, 1H)	2.36 (m, 1H)
2.31 (dt, $J = 11.5, 2.7$ Hz, 1H)	2.30 (m, 1H)
2.06 (br d, $J = 13.6$ Hz, 1H)	2.04 (br d, $J = 13.0$ Hz, 1H)
1.73 (dd, $J = 13.6, 9.2$ Hz, 1H)	1.70 (dd, $J = 14.0, 9.0$ Hz, 1H)
1.47–1.33 (m, 2H)	1.43 (m, 2H)
0.95 (td, $J = 13.3, 4.1$ Hz, 1H)	0.93 (br td, $J = 13.0, 5.0$ Hz, 1H)

Comparison of (+)-19-oxoeburnamine ^{13}C NMR peaks with isolated natural material

This work, 126 MHz	Natural, 76 MHz¹¹	Trost, 126 MHz⁸
210.4	210.3	210.1
136.8	136.7	136.7
131.6	131.5	131.5
128.8	128.7	128.7
121.8	121.6	121.7
120.6	120.4	120.5
118.3	118.2	118.2
112.2	112.0	112.0
106.8	106.6	106.8
76.5	76.3	–
54.9	54.8	55.0
51.9	51.7	51.8
50.8	50.6	50.8
44.1	44.0	44.1
42.1	42.0	42.2
25.7	25.6	25.6
25.0	24.9	25.0
22.8	22.6	21.1
16.9	16.8	16.8

3.32 (-)-Larutienine A

Procedure: (+)-19-OH-Eburnamine **10** (94 mg, 0.30 mmol, 1.0 equiv, 3:1 dr at C16) was dissolved in 1 M aqueous HCl (20 mL) at 22 °C, then the resulting mixture was heated to 40 °C and allowed to stir for 14 h. The mixture was cooled to 22 °C and concentrated aqueous NH₄OH was added to the reaction mixture until pH 11 was reached. The resulting mixture was extracted with CH₂Cl₂ (4 x 10 mL). The combined organics were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (20% acetone/CH₂Cl₂) afforded (-)-larutienine A **11** (79.0 mg, 0.267 mmol, 89% yield) as a white foam.

Description: white foam.

R_f: 0.19 in 20% acetone/CH₂Cl₂ (UV, KMnO₄ or CAM).

¹H NMR (500 MHz, CDCl₃): δ 7.43 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 5.93 (d, *J* = 4.0 Hz, 1H), 3.96 (q, *J* = 6.6 Hz, 1H), 3.27–3.17 (m, 1H), 3.21 (s, 1H), 3.09–2.98 (m, 1H), 2.94 (br d, *J* = 11.0 Hz, 1H), 2.86 (dd, *J* = 15.8, 6.5 Hz, 1H), 2.73 (td, *J* = 11.3, 6.5 Hz, 1H), 2.18 (td, *J* = 11.3, 2.8 Hz, 1H), 1.85 (d, *J* = 11.3 Hz, 1H), 1.81–1.64 (m, 4H), 1.58 (td, *J* = 13.4, 5.3 Hz, 1H), 1.34 (d, *J* = 6.6 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 136.5, 135.4, 128.8, 121.5, 119.8, 118.7, 109.7, 109.4, 83.4, 83.3, 60.9, 54.6, 53.5, 41.8, 41.6, 30.4, 24.0, 22.1, 15.9.

Optical Rotation: [α]_D²⁰ = -5.6 (c = 1.00 in CHCl₃); Lit:¹² [α]_D²⁵ = -5.0 (c = 0.10 in CHCl₃).

HRMS: calculated for C₁₉H₂₃N₂O [M+H]⁺: 295.1910, found: 295.1908.

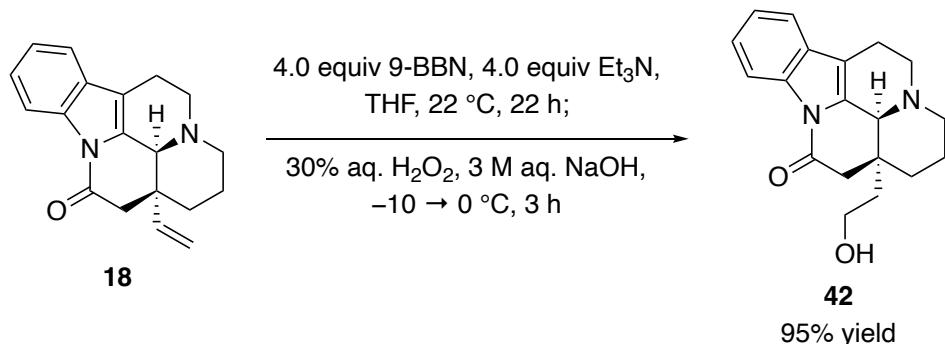
Comparison of (–)-larutienine A ^1H NMR peaks with isolated natural material

This work, 500 MHz	Natural, 400 MHz¹²
7.43 (d, $J = 7.7$ Hz, 1H)	7.42 (br d, $J = 8.0$ Hz, 1H)
7.39 (d, $J = 7.7$ Hz, 1H)	7.38 (br d, $J = 8.0$ Hz, 1H)
7.15 (t, $J = 7.7$ Hz, 1H)	7.15 (td, $J = 8.0, 1.0$ Hz, 1H)
7.06 (t, $J = 7.7$ Hz, 1H)	7.05 (td, $J = 8.0, 1.0$ Hz, 1H)
5.93 (d, $J = 4.0$ Hz, 1H)	5.92 (d, $J = 4.0$ Hz, 1H)
3.96 (q, $J = 6.6$ Hz, 1H)	3.95 (q, $J = 6.3$ Hz, 1H)
3.27–3.17 (m, 1H)	3.24 (dd, $J = 11.0, 8.0$ Hz, 1H)
3.21 (s, 1H)	3.23 (s, 1H)
3.09–2.98 (m, 1H)	3.03 (dddd, $J = 16.0, 11.0, 8.0, 2.0$ Hz, 1H)
2.94 (br d, $J = 11.0$ Hz, 1H)	2.95 (br d, $J = 11.0$ Hz, 1H)
2.86 (dd, $J = 15.8, 6.5$ Hz, 1H)	2.86 (ddd, $J = 16.0, 6.3, 2.0$ Hz, 1H)
2.73 (td, $J = 11.3, 6.5$ Hz, 1H)	2.74 (td, $J = 11.0, 6.3$ Hz, 1H)
2.18 (td, $J = 11.3, 2.8$ Hz, 1H)	2.18 (td, $J = 11.0, 3.0$ Hz, 1H)
1.85 (d, $J = 11.3$ Hz, 1H)	1.87 (d, $J = 11.0$ Hz, 1H)
1.81–1.64 (m, 4H)	1.80 (m, 1H)
	1.75 (m, 2H)
	1.67 (m, 1H)
1.58 (td, $J = 13.4, 5.3$ Hz, 1H)	1.58 (m, 1H)
1.34 (d, $J = 6.6$ Hz, 3H).	1.33 (d, $J = 6.3$ Hz, 3H)

Comparison of (–)-larutienine A ^{13}C NMR peaks with isolated natural material

This work, 126 MHz	Natural, 101 MHz¹²
136.5	136.5
135.4	135.1
128.8	128.7
121.5	121.6
119.8	119.9
118.7	118.7
109.7	109.7
109.4	109.4
83.4	83.4
83.3	83.2
60.9	60.9
54.6	54.6
53.5	53.5
41.8	41.8
41.6	41.6
30.4	30.3
24.0	23.9
22.1	22.0
15.9	16.0

3.33 Hydroboration/Oxidation



Procedure: To a solution of alkene **18** (200 mg, 0.68 mmol, 1.0 equiv) in THF (1 mL) at 22 °C were sequentially added Et₃N (379 μL, 2.72 mmol, 4.0 equiv) and 9-BBN (5.44 mL of 0.5 M solution in THF, 2.72 mmol, 4.0 equiv). The resulting mixture was allowed to stir at 22 °C for 22 h, then it was cooled to -10 °C. 3 M aqueous NaOH (9 mL) and 30% w/w aqueous H₂O₂ (3.5 mL) were added at -10 °C and the resulting mixture was allowed to vigorously stir at 0 °C for 3 h. The reaction was quenched by addition of saturated aqueous Na₂S₂O₄ (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (2% → 10% MeOH/CH₂Cl₂) afforded alcohol **42** (202 mg, 0.65 mmol, 95% yield) as a white solid.

Description: white solid.

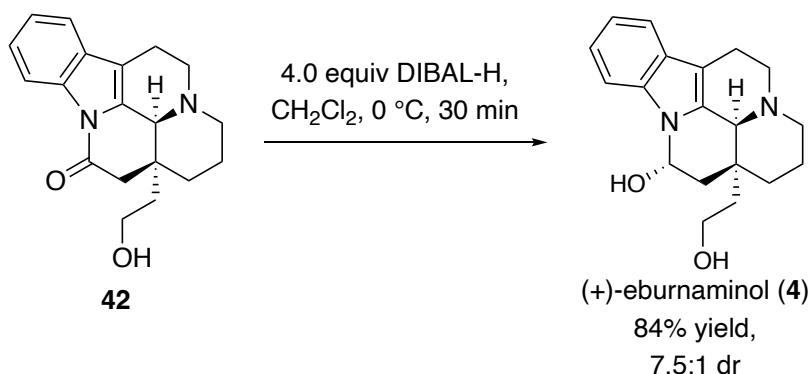
R_f: 0.23 in 10% MeOH/CH₂Cl₂ (UV, KMnO₄ or CAM).

¹H NMR (500 MHz, CDCl₃): δ 8.36 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 4.20 (s, 1H), 3.93 (ddd, *J* = 11.6, 8.3, 3.8 Hz, 1H), 3.79 (dt, *J* = 11.6, 5.3 Hz, 1H), 3.37–3.25 (m, 2H), 2.91 (dd, *J* = 17.8, 10.5, 7.2, 2.8 Hz, 1H), 2.82 (d, *J* = 16.8 Hz, 1H), 2.63 (dd, *J* = 11.4, 4.4 Hz, 1H), 2.60–2.51 (m, 1H), 2.55 (d, *J* = 16.8 Hz, 2H), 2.45 (td, *J* = 12.1, 3.4 Hz, 1H), 2.04–1.87 (m, 3H), 1.55–1.47 (m, 2H), 1.22 (td, *J* = 14.0, 5.0 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 167.0, 134.3, 130.9, 130.0, 124.8, 124.2, 118.3, 116.4, 112.7, 59.1, 57.4, 50.5, 47.5, 43.3, 43.0, 38.4, 28.8, 21.4, 16.7.

Optical Rotation: [α]_D²⁰ = -121.9 (c = 1.00 in CHCl₃).

HRMS: calculated for C₁₉H₂₃N₂O₂ [M+H]⁺: 311.1754, found: 311.1758.

3.34 Eburnaminol

Procedure: To a solution of amide **42** (200 mg, 0.64 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) at 0°C was added DIBAL-H (2.58 mL of 1.0 M solution in CH_2Cl_2 , 2.58 mmol, 4.0 equiv). The resulting mixture was allowed to stir at 0°C for 30 min, then it was quenched by addition of 1 M aqueous NaOH (9 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (5% \rightarrow 10% MeOH/ CH_2Cl_2) afforded **(+)-eburnaminol 4** (169 mg, 0.54 mmol, 84% yield, 7.5:1 dr) as a white foam.

Description: white foam.

R_f: 0.26 in 10% MeOH/ CH_2Cl_2 (UV, KMnO₄ or CAM).

¹H NMR major (500 MHz, 4% CD₃OD/CDCl₃): δ 7.72 (d, $J = 7.6$ Hz, 1H), 7.41 (d, $J = 7.6$ Hz, 1H), 7.15 (t, $J = 7.6$ Hz, 1H), 7.10 (t, $J = 7.6$ Hz, 1H), 5.53 (dt, $J = 9.0, 4.5$ Hz, 1H), 4.04 (s, 1H), 3.82–3.76 (m, 1H), 3.72–3.66 (m, 1H), 3.22 (dd, $J = 13.5, 6.4$ Hz, 1H), 3.14 (tdd, $J = 13.5, 5.9, 3.4$ Hz, 1H), 2.94–2.82 (m, 3H), 2.58–2.50 (m, 2H), 2.36 (tt, $J = 11.8, 3.4$ Hz, 1H), 2.16 (ddd, $J = 14.1, 5.2, 3.4$ Hz, 1H), 1.95–1.75 (m, 4H), 1.39–1.28 (m, 2H), 1.00 (tt, $J = 13.7, 3.9$ Hz, 1H).

¹³C NMR major (126 MHz, 4% CD₃OD/CDCl₃): δ 136.9, 130.3, 128.1, 121.7, 120.2, 118.0, 112.4, 104.7, 75.7, 58.5, 58.1, 50.5, 44.7, 43.4, 41.1, 36.5, 26.5, 20.4, 16.6.

Optical Rotation: $[\alpha]_D^{20} = +61.8$ (c = 1.00 in CHCl_3).

HRMS: calculated for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2$ [$\text{M}+\text{H}$]⁺: 313.1916, found: 313.1913.

Comparison of (+)-eburnaminol ^1H NMR peaks with previously synthesized material^a

This work, 500 MHz	Chen, 400 MHz ¹³
7.72 (d, $J = 7.6$ Hz, 1H)	7.75 (d, $J = 8.0$ Hz, 1H)
7.41 (d, $J = 7.6$ Hz, 1H)	7.44 (d, $J = 7.6$ Hz, 1H)
7.15 (t, $J = 7.6$ Hz, 1H)	7.17 (td, $J = 7.2, 1.6$ Hz, 1H)
7.10 (t, $J = 7.6$ Hz, 1H)	7.13 (td, $J = 7.6, 1.6$ Hz, 1H)
5.53 (dt, $J = 9.0, 4.5$ Hz, 1H)	5.54 (dd, $J = 9.6, 5.2$ Hz, 1H)
4.04 (br s, 1H)	3.89 (br s, 1H)
3.82–3.76 (m, 1H)	3.83–3.76 (m, 1H)
3.72–3.66 (m, 1H)	3.72–3.66 (m, 1H)
3.22 (dd, $J = 13.5, 6.4$ Hz, 1H)	3.23–3.08 (m, 2H)
3.14 (tdd, $J = 13.5, 5.9, 3.4$ Hz, 1H)	
2.94–2.82 (m, 3H including 2 x OH)	3.40–3.37 (m, 2H, 2 x OH)
	2.95–2.86 (m, 1H)
2.58–2.50 (m, 2H)	2.56–2.47 (m, 2H)
2.36 (tt, $J = 11.8, 3.4$ Hz, 1H)	2.34 (td, $J = 12.0, 3.2$ Hz, 1H)
2.16 (ddd, $J = 14.1, 5.2, 3.4$ Hz, 1H)	2.17 (dd, $J = 14.0, 5.2$ Hz, 1H)
1.95–1.75 (m, 4H)	1.86–1.75 (m, 4H)
1.39–1.28 (m, 2H)	1.40–1.29 (m, 2H)
1.00 (tt, $J = 13.7, 3.9$ Hz, 1H)	1.00 (td, $J = 13.6, 4.4$ Hz, 1H)

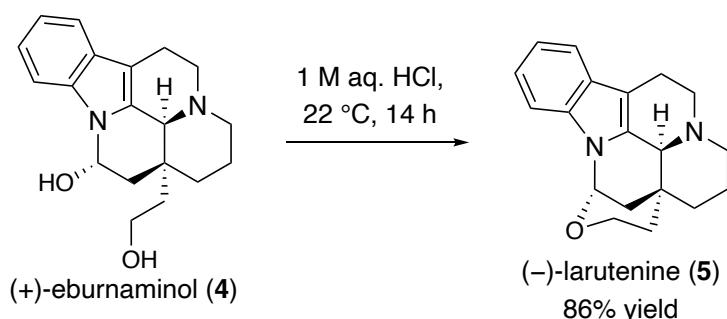
^aSome discrepancies in the NMR spectra may be due to small differences in the percentage of CD₃OD present in the sample.

Comparison of (+)-eburnaminol ^{13}C NMR peaks with previously synthesized material^a

This work, 126 MHz	Qin, 150 MHz¹⁴	Chen, 100 MHz¹³
136.9	137.0	136.6
130.3	128.3	131.0
128.1	127.5	128.1
121.7	122.1	121.2
120.2	120.4	119.9
118.0	118.0	117.8
112.4	112.4	112.1
104.7	104.1	104.8
75.7	75.4	75.6
58.5	58.3	58.3
58.1	58.0	58.0
50.5	50.6	50.3
44.7	43.5	44.9
43.4	43.3	43.2
41.1	39.3	41.4
36.5	36.4	36.3
26.5	26.2	26.4
20.4	19.4	20.7
16.6	16.2	16.6

^aSome discrepancies in the NMR spectra may be due to small differences in the percentage of CD₃OD present in the sample.

3.35 Larutanine



Procedure: (+)-Eburnaminol **4** (84.5 mg, 0.27 mmol, 1.0 equiv) was dissolved in 1 M aqueous HCl (20 mL) at 22 °C and the resulting mixture was allowed to stir at 22 °C for 14 h. Concentrated aqueous NH₄OH was added to the reaction mixture until pH 11 was reached. The resulting mixture was extracted with CH₂Cl₂ (4 x 15 mL). The combined organics were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (20% acetone/CH₂Cl₂) afforded (-)-larutanine **5** (68.5 mg, 0.23 mmol, 86% yield) as a white foam.

Description: white foam.

R_f: 0.21 in 20% acetone/CH₂Cl₂ (UV, KMnO₄ or CAM).

¹H NMR (500 MHz, CDCl₃): δ 7.46 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 5.84 (t, *J* = 3.1 Hz, 1H), 3.97 (td, *J* = 12.3, 2.8 Hz, 1H), 3.81 (dd, *J* = 12.3, 5.8 Hz, 1H), 3.24 (dd, *J* = 11.9, 7.8 Hz, 1H), 3.16 (br s, 1H), 3.07–3.00 (m, 1H), 2.97 (dt, *J* = 10.9, 5.4 Hz, 1H), 2.84 (ddd, *J* = 16.0, 6.6, 1.8 Hz, 1H), 2.70 (td, *J* = 11.3, 6.4 Hz, 1H), 2.26 (ddd, *J* = 11.2, 8.2, 4.9 Hz, 1H), 1.84 (td, *J* = 13.5, 5.9 Hz, 1H), 1.78–1.66 (m, 5H), 1.56 (br d, *J* = 13.4 Hz, 1H), 1.43 (q, *J* = 8.0 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 137.9, 136.7, 128.7, 121.7, 120.2, 118.4, 109.7, 107.9, 77.7, 63.5, 58.8, 54.4, 52.0, 40.8, 38.2, 35.7, 29.0, 21.3, 20.3.

Optical Rotation: [α]_D²⁰ = -3.2 (c = 1.00 in CHCl₃).

HRMS: calculated for C₁₉H₂₃N₂O [M+H]⁺: 295.1910, found: 295.1908.

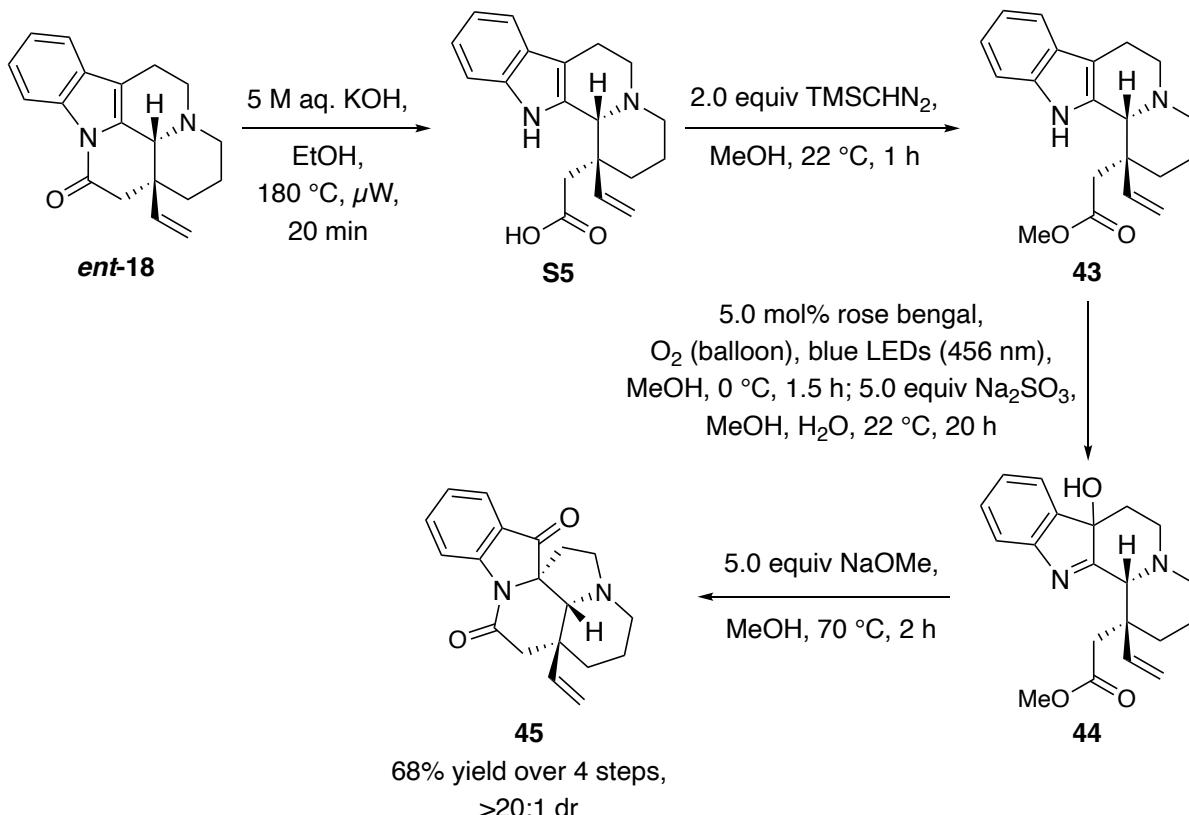
Comparison of (–)-laruteneine ^1H NMR peaks with previously synthesized material

This work, 500 MHz	Tong, 400 MHz¹⁵
7.46 (d, $J = 7.6$ Hz, 1H)	7.46 (d, $J = 7.7$ Hz, 1H)
7.41 (d, $J = 7.6$ Hz, 1H)	7.41 (d, $J = 8.1$ Hz, 1H)
7.19 (t, $J = 7.6$ Hz, 1H)	7.19 (t, $J = 7.6$ Hz, 1H)
7.12 (t, $J = 7.6$ Hz, 1H)	7.11 (t, $J = 6.9$ Hz, 1H)
5.84 (t, $J = 3.1$ Hz, 1H)	5.84 (t, $J = 2.5$ Hz, 1H)
3.97 (td, $J = 12.3, 2.8$ Hz, 1H)	3.97 (td, $J = 12.2, 2.8$ Hz, 1H)
3.81 (dd, $J = 12.3, 5.8$ Hz, 1H)	3.81 (dd, $J = 12.2, 5.2$ Hz, 1H)
3.24 (dd, $J = 11.9, 7.8$ Hz, 1H)	3.23 (dd, $J = 11.8, 7.7$ Hz, 1H)
3.16 (br s, 1H)	3.16 (s, 1H)
3.07–3.00 (m, 1H)	3.07–2.92 (m, 2H)
2.97 (dt, $J = 10.9, 5.4$ Hz, 1H)	
2.84 (ddd, $J = 16.0, 6.6, 1.8$ Hz, 1H)	2.84 (dd, $J = 15.8, 6.5$ Hz, 1H)
2.70 (td, $J = 11.3, 6.4$ Hz, 1H)	2.74–2.65 (m, 1H)
2.26 (ddd, $J = 11.2, 8.2, 4.9$ Hz, 1H)	2.31–2.20 (m, 1H)
1.84 (td, $J = 13.5, 5.9$ Hz, 1H)	1.84 (td, $J = 13.4, 5.9$ Hz, 1H)
1.78–1.66 (m, 5H)	1.74–1.65 (m, 5H)
1.56 (d, $J = 13.4$ Hz, 1H)	1.56 (d, $J = 13.4$ Hz, 1H)
1.43 (q, $J = 8.0$ Hz, 1H)	1.46–1.39 (m, 1H)

Comparison of (–)-laruteneine ^{13}C NMR peaks with previously synthesized material

This work, 126 MHz	Tong, 101 MHz¹⁵
137.9	137.7
136.7	136.6
128.7	128.5
121.7	121.6
120.2	120.1
118.4	118.3
109.7	109.6
107.9	107.8
77.7	77.6
63.5	63.4
58.8	58.6
54.4	54.3
52.0	51.9
40.8	40.7
38.2	38.1
35.7	35.6
29.0	28.8
21.3	21.1
20.3	20.1

3.36 Skeletal Rearrangement



Procedure: A microwave vial was charged with a stirring bar, lactam *ent*-18 (200 mg, 0.68 mmol, 1.0 equiv), EtOH (3 mL) and 5 M aqueous KOH (2 mL). The vial was sealed, and the reaction mixture was subjected to microwave irradiation at 180 °C for 20 min. The reaction was allowed to cool to 22 °C, then conc. HCl and 1 M aqueous HCl were added until pH 6 and the resulting mixture was extracted with CH₂Cl₂ (4 x 10 mL). The combined organics were dried over MgSO₄, filtered, and concentrated under reduced pressure to afford a brown/orange residue containing carboxylic acid **S5**, which was used directly in the next step without further purification.

The residue containing carboxylic acid **S5** was dissolved in MeOH (3 ml) at 22 °C and TMSCHN₂ (680 µL of a 2.0 M solution in hexanes, 1.36 mmol, 2.0 equiv) was added. The resulting solution was allowed to stir at 22 °C for 1 h, then concentrated under reduced pressure to afford a brown/orange residue containing methyl ester **43**, which was used directly in the next step without further purification.

The residue containing methyl ester **43** was dissolved in MeOH (4 ml) at 0 °C and rose bengal (34.6 mg, 34.0 µmol, 0.05 equiv) was added. The resulting solution was placed under atmosphere of O₂ (balloon) and irradiated with blue LEDs (456 nm) while allowed to stir at 0 °C for 1.5 h, at which point the O₂ balloon was removed, and the blue LEDs turned off. The reaction mixture was diluted with MeOH (4 mL), allowed to warm to 22 °C and a solution of Na₂SO₃ (428 mg, 3.40 mmol, 5.0 equiv) in H₂O (4 mL) was added. The

Supporting Information

resulting mixture was allowed to stir at 22 °C for 20 h, then it was diluted with H₂O (15 mL) and extracted with CH₂Cl₂ (4 x 15 mL). The combined organics were dried over MgSO₄, filtered, and concentrated under reduced pressure to afford a brown residue containing tertiary alcohol **44**, which was used directly in the next step without further purification.

Note: the ¹H NMR of the crude mixture containing alcohol **44** must be performed at -40 °C.

The residue containing tertiary alcohol **44** was dissolved in MeOH (4 ml) at 22 °C and NaOMe (184 mg, 3.40 mmol, 5.0 equiv) was added. The resulting mixture was heated at 70 °C and allowed to stir at this temperature for 2 h. The reaction mixture was allowed to cool to 22 °C, diluted with H₂O (8 mL) and extracted with CH₂Cl₂ (4 x 10 mL). The combined organics were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (20% EtOAc/hexanes) afforded spirooxiindole **45** (143 mg, 0.47 mmol, 68% yield over 4 steps, >20:1 dr) as an off-white foam.

Description: off-white foam.

R_f: 0.32 in 20% EtOAc/hexanes (UV, KMnO₄ or CAM).

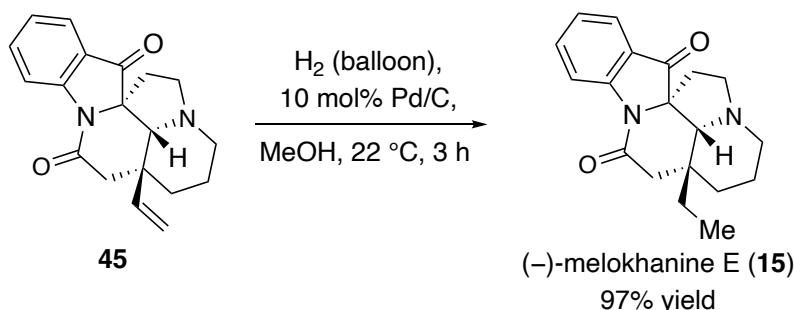
¹H NMR (500 MHz, CDCl₃): δ 8.26 (d, *J* = 7.6 Hz, 1H), 7.71 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.62 (td, *J* = 7.6, 1.4 Hz, 1H), 7.21 (td, *J* = 7.6, 1.4 Hz, 1H), 5.43 (dd, *J* = 17.8, 11.1 Hz, 1H), 4.85 (d, *J* = 17.8 Hz, 1H), 4.76 (d, *J* = 11.1 Hz, 1H), 3.60 (d, *J* = 15.5 Hz, 1H), 3.17 – 3.09 (m, 1H), 3.05 (dd, *J* = 8.8, 7.0 Hz, 1H), 2.79 (d, *J* = 2.2 Hz, 1H), 2.56 (ddd, *J* = 11.5, 8.8, 5.4 Hz, 1H), 2.36 (td, *J* = 11.5, 2.9 Hz, 1H), 2.26 (dd, *J* = 15.5, 2.2 Hz, 1H), 2.18 (dd, *J* = 12.6, 5.4 Hz, 1H), 1.92 (td, *J* = 12.0, 7.0 Hz, 1H), 1.82 – 1.71 (m, 1H), 1.66 – 1.56 (m, 2H), 1.43 (td, *J* = 13.9, 5.1 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 201.0, 170.6, 152.4, 142.0, 136.9, 124.6, 124.3, 122.4, 119.0, 115.1, 75.1, 67.4, 51.4, 50.7, 41.6, 40.8, 39.2, 35.0, 22.3.

Optical Rotation: [α]_D²⁰ = -30.6 (c = 1.00 in CHCl₃).

HRMS: calculated for C₁₉H₂₁N₂O₂ [M+H]⁺: 309.1598, found: 309.1560.

3.37 (-)-Melo Khanine E



Procedure: To a solution of alkene **45** (92 mg, 0.30 mmol, 1.0 equiv) in MeOH (3 mL) at 22 °C was added 10% wt. palladium on carbon (31.8 mg, 29.8 µmol with respect to Pd, 0.1 equiv), and the flask was evacuated and backfilled with hydrogen (3x). Hydrogen was bubbled through the mixture for 5 min, then the reaction was allowed to stir at 22 °C for 3 h under hydrogen atmosphere (balloon). The reaction was filtered through Celite® using EtOAc for washing and the filtrate was concentrated *in vacuo*. Purification by silica gel chromatography (20% EtOAc/hexanes) delivered (–)-melokhanine E **15** (89.8 mg, 0.29 mmol, 97% yield) as an off-white solid.

Description: off-white solid.

R_f: 0.30 in 20% EtOAc/hexanes (UV, KMnO₄ or CAM).

¹H NMR (500 MHz, CDCl₃): δ 8.29 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.75 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.66 (td, *J* = 7.5, 1.0 Hz, 1H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1H), 3.44 (dd, *J* = 15.4, 1.4 Hz, 1H), 3.14–3.08 (m, 1H), 3.03 (dd, *J* = 8.8, 7.0 Hz, 1H), 2.53 (d, *J* = 2.2 Hz, 1H), 2.50 (ddd, *J* = 11.6, 8.7, 5.4 Hz, 1H), 2.30 (td, *J* = 11.3, 2.9 Hz, 1H), 2.17 (dd, *J* = 12.6, 5.5 Hz, 1H), 2.11 (dd, *J* = 15.4, 2.2 Hz, 1H), 1.98–1.91 (m, 1H), 1.78–1.68 (m, 2H), 1.64–1.57 (m, 1H), 1.29–1.21 (m, 1H), 0.97–0.87 (m, 1H), 0.78–0.69 (m, 4H).

¹H NMR (500 MHz, acetone-d₆): δ 8.26 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.77–7.74 (m, 1H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 3.44 (d, *J* = 15.3 Hz, 1H), 3.16–3.10 (m, 1H), 3.06 (t, *J* = 7.8 Hz, 1H), 2.46 (br s, 1H), 2.41 (ddd, *J* = 11.6, 8.6, 5.5 Hz, 1H), 2.27 (td, *J* = 11.1, 2.8 Hz, 1H), 2.15 (dd, *J* = 12.5, 5.4 Hz, 1H), 2.04–2.01 (m, 1H), 1.99–1.92 (m, 1H), 1.80–1.70 (m, 2H), 1.64–1.58 (m, 1H), 1.29–1.25 (m, 1H), 0.94–0.86 (m, 1H), 0.73–0.66 (m, 4H).

¹³C NMR (126 MHz, CDCl₃): δ 200.8, 170.8, 152.2, 136.8, 124.9, 124.4, 122.7, 119.8, 75.4, 68.8, 51.6, 50.9, 40.8, 38.3, 38.2, 32.2, 30.0, 22.2, 7.1.

¹³C NMR (126 MHz, acetone-d₆): δ 200.9, 170.6, 153.1, 137.4, 125.6, 124.8, 123.4, 120.1, 75.9, 69.6, 52.1, 51.4, 41.2, 38.9, 38.7, 32.7, 30.5, 22.8, 7.1.

Optical Rotation: $[\alpha]_D^{20} = -48.4$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for $C_{19}H_{23}N_2O_2 [M+H]^+$: 311.1754, found: 311.1755.

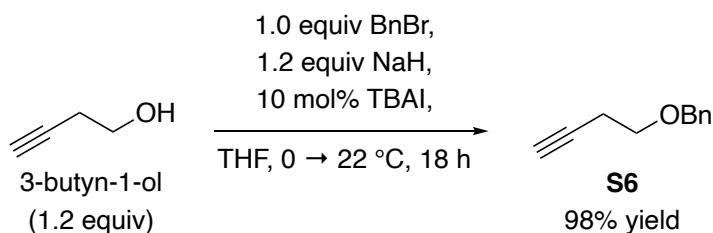
Comparison of (–)-melokhanine E ^1H NMR peaks with previously synthesized material

This work, 500 MHz	Zhu, 400 MHz¹⁶
8.26 (dd, $J = 7.4, 1.5$ Hz, 1H)	8.26 (d, $J = 8.1$ Hz, 1H)
7.77–7.74 (m, 1H)	7.77–7.70 (m, 1H)
7.73 (d, $J = 7.4$ Hz, 1H)	7.75 (d, $J = 7.6$ Hz, 1H)
7.33 (t, $J = 7.4$ Hz, 1H)	7.32 (t, $J = 7.3$ Hz, 1H)
3.44 (d, $J = 15.3$ Hz, 1H)	3.44 (dd, $J = 15.3, 1.0$ Hz, 1H)
3.16–3.10 (m, 1H)	3.17–3.10 (m, 1H)
3.06 (t, $J = 7.8$ Hz, 1H)	3.06 (dd, $J = 8.7, 7.0$ Hz, 1H)
2.46 (br s, 1H)	2.46 (d, $J = 2.2$ Hz, 1H)
2.41 (ddd, $J = 11.6, 8.6, 5.5$ Hz, 1H)	2.41 (ddd, $J = 11.5, 8.6, 5.5$ Hz, 1H)
2.27 (td, $J = 11.1, 2.8$ Hz, 1H)	2.27 (td, $J = 11.2, 2.8$ Hz, 1H)
2.15 (dd, $J = 12.5, 5.4$ Hz, 1H)	2.15 (dd, $J = 12.5, 5.4$ Hz, 1H)
2.04–2.01 (m, 1H)	2.04–2.01 (m, 1H)
1.99–1.92 (m, 1H)	1.95 (td, $J = 11.9, 7.0$ Hz, 1H)
1.80–1.70 (m, 2H)	1.82–1.68 (m, 2H)
1.64–1.58 (m, 1H)	1.65–1.56 (m, 1H)
1.29–1.25 (m, 1H)	1.29 (td, $J = 13.8, 4.2$ Hz, 1H)
0.94–0.86 (m, 1H)	0.96–0.83 (m, 1H)
0.73–0.66 (m, 4H)	0.77–0.64 (m, 4H)

Comparison of (–)-melokhanine E ^{13}C NMR peaks with previously synthesized material

This work, 126 MHz	Zhu, 101 MHz¹⁶
200.9	200.9
170.6	170.6
153.1	153.1
137.4	137.4
125.6	125.6
124.8	124.8
123.4	123.4
120.1	120.1
75.9	75.9
69.6	69.6
52.1	52.1
51.4	51.4
41.2	41.2
38.9	38.9
38.7	38.7
32.7	32.7
30.5	30.5
22.8	22.8
7.1	7.1

3.38 Benzyl Protection of 3-butyn-1-ol



Procedure: Compound **S6** was prepared according to a reported procedure.¹⁷

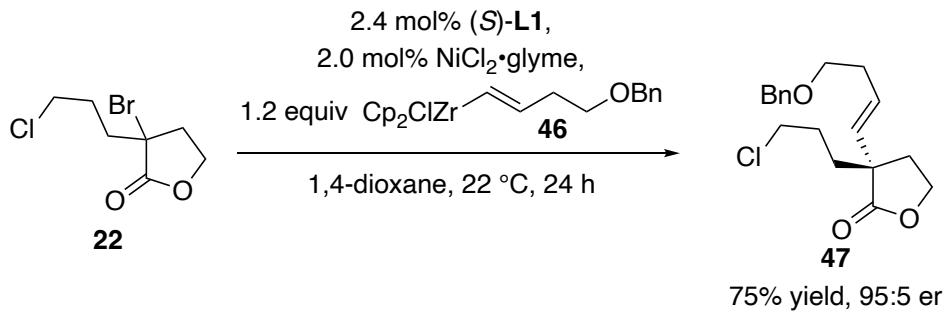
To a solution of 3-butyn-1-ol (15.0 mL, 198 mmol, 1.2 equiv) in THF (165 mL) at 0 °C were sequentially added NaH (60% in mineral oil, 7.93 g, 198 mmol, 1.2 equiv), tetrabutylammonium iodide (TBAI, 6.09 g, 16.5 mmol, 0.10 equiv) and benzyl bromide (19.6 mL, 165 mmol, 1.0 equiv). The resulting mixture was allowed to stir at 22 °C for 18 h. The reaction was quenched by addition of a saturated aqueous solution of NH₄Cl (250 mL) and extracted with Et₂O (3 x 100 mL). The combined organics were washed with H₂O (200 mL) and brine (200 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (2% EtOAc/hexanes) afforded benzyl ether **S6** (26.0 g, 162 mmol, 98% yield) as a pale-yellow oil.

Description: pale-yellow/colorless oil.

R_f: 0.80 in 20% EtOAc/hexanes (KMnO₄).

¹H NMR (500 MHz, CDCl₃): δ 7.36 (d, *J* = 4.3 Hz, 4H), 7.31 (h, *J* = 4.3 Hz, 1H), 4.58 (s, 2H), 3.62 (t, *J* = 7.0 Hz, 2H), 2.52 (td, *J* = 7.0, 2.7 Hz, 2H), 2.01 (t, *J* = 2.7 Hz, 1H); in agreement with previously reported spectroscopic data.¹⁷

3.39 Enantioconvergent cross-coupling with benzyl protected 3-butyn-1-ol



Procedure: To a solution of Cp₂ZrHCl (Schwartz's reagent, 7.74 g, 30.0 mmol) in 1,4-dioxane (50 mL) at 22 °C was added alkyne **S6** (4.81 g, 30.0 mmol) via syringe in one portion. The reaction mixture was allowed to vigorously stir at 22 °C for 1–2 h, at which time all the white solids had been consumed and a homogeneous orange solution was obtained. The concentration of the alkenylzirconium reagent was

determined to be 0.45 M in 1,4 dioxane by titration with I₂ (0.20 mmol) in THF (2 mL); at the endpoint, the solution changes from dark brown to yellow. The alkenylzirconium solution was used immediately in the enantioconvergent cross-coupling reaction.

Note 1: The Schwartz's reagent is moisture-sensitive and was stored inside a glovebox.

Meanwhile, NiCl₂•glyme (54.6 mg, 0.248 mmol, 0.02 equiv) and chiral ligand (*S*)-**L1** (81.2 mg, 0.298 mmol, 0.024 equiv) were dissolved in 1,4-dioxane (30 mL) and the resulting mixture was allowed to vigorously stir at 22 °C for 30 min furnishing a pale-yellow solution. Next, a solution of bromide **22** (3.0 g, 12.4 mmol, 1.0 equiv) in 1,4-dioxane (3 mL) was added and the resulting mixture was allowed to vigorously stir at 22 °C for 5 min. The freshly prepared solution of the alkenylzirconium reagent **46** (0.45 M in 1,4-dioxane, 33.1 mL, 14.9 mmol, 1.2 equiv) was added dropwise and the reaction was allowed to stir at 22 °C for 24 h. The reaction was quenched by addition of MeOH (20 mL) and allowed to stir at 22 °C for 5 min before concentration *in vacuo*. Purification by silica gel chromatography (30:1:1 hexanes/CH₂Cl₂/Et₂O → 9:1:1 hexanes/CH₂Cl₂/Et₂O) afforded enantioenriched lactone **47** (3.00 g, 9.32 mmol, 75% yield, 95:5 er) as a colorless oil.

Note 2: When the reaction was performed with (*R*)-**L1** as chiral ligand on a 500 mg scale, product *ent*-**47** was obtained in 74% yield (495 mg) and 5:95 er.

Description: colorless oil.

R_f: 0.25 in 9:1:1 hexanes/CH₂Cl₂/Et₂O (KMnO₄).

¹H NMR (500 MHz, CDCl₃): δ 7.38–7.26 (m, 5H), 5.66 (dt, *J* = 15.9, 6.7 Hz, 1H), 5.50 (dd, *J* = 15.9, 1.4 Hz, 1H), 4.50 (s, 2H), 4.27 (td, *J* = 8.5, 3.5 Hz, 1H), 4.18 (td, *J* = 8.5, 6.5 Hz, 1H), 3.51 (t, *J* = 6.5 Hz, 4H), 2.38 (q, *J* = 6.6 Hz, 2H), 2.26 (ddd, *J* = 13.0, 6.7, 3.6 Hz, 1H), 2.17 (dt, *J* = 12.9, 8.5 Hz, 1H), 1.95–1.82 (m, 2H), 1.77–1.64 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 179.0, 138.4, 130.4, 129.3, 128.5, 127.8, 73.0, 69.5, 65.3, 48.5, 45.0, 34.3, 33.2, 33.1, 27.8.

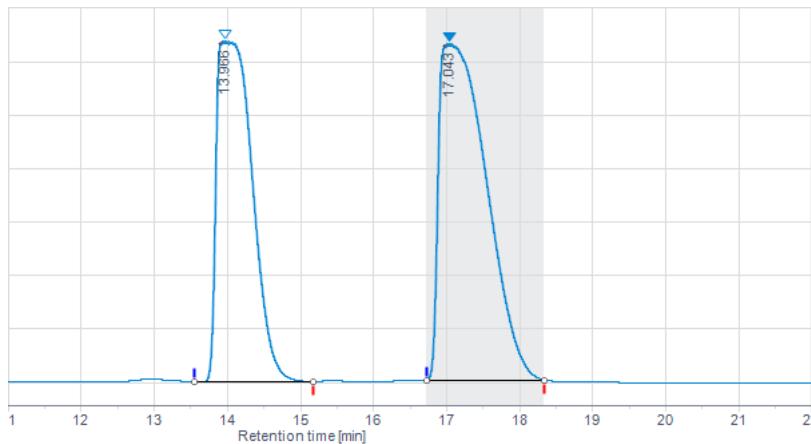
Optical Rotation: [α]_D²⁰ = -13.4 (c = 1.00 in CHCl₃).

HRMS: calculated for C₁₈H₂₃ClO₃Na [M+Na]⁺: 345.1228, found: 345.1231.

Enantiomeric purity: Enantiomeric purity was determined by HPLC analysis in comparison with authentic racemic material (Chiralcel IC-3, 10% i-PrOH/hexanes, 1.0 mL/min, 210 nm).

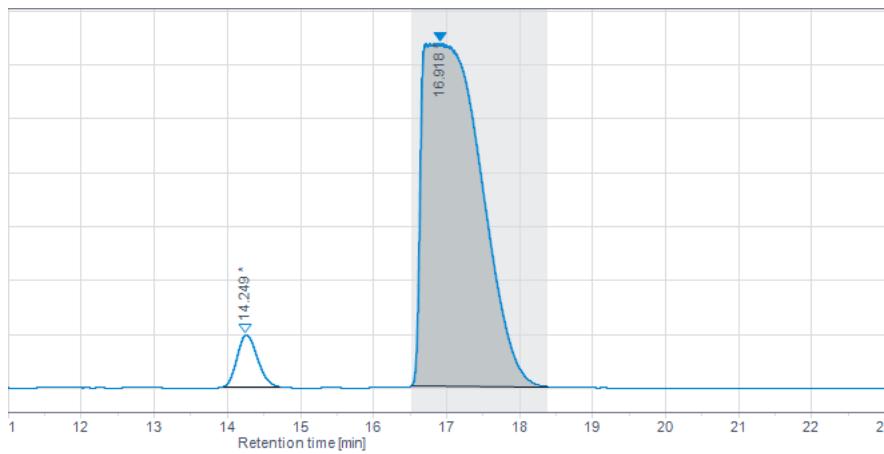
Racemic sample (obtained by performing the enantioconvergent cross-coupling with a 1:1 mixture of (*S*)-**L1** and (*R*)-**L1**)

Supporting Information



peak	RT (min)	Area (mAU·s)	Area%	Start time (min)	End time (min)
1	13.966	121779.114	49.018	13.555	15.165
2	17.043	126656.921	50.982	16.719	18.329

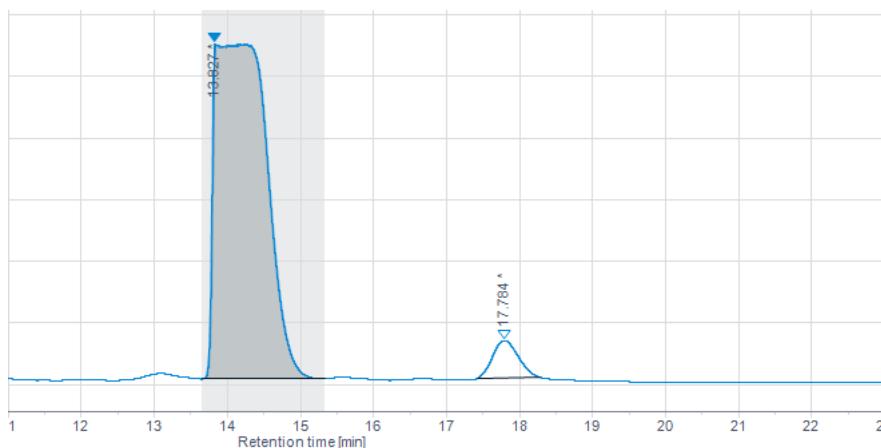
Compound 47 obtained with (S)-L1



peak	RT (min)	Area (mAU·s)	Area%	Start time (min)	End time (min)
1	14.249	9293.866	4.955	13.939	14.707
2	16.918	178270.285	95.045	16.518	18.384

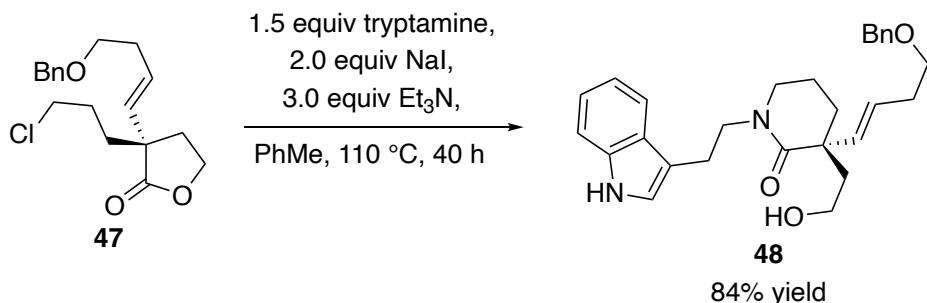
Supporting Information

Compound **ent-47** obtained with (*R*)-**L1**



peak	RT (min)	Area (mAU·s)	Area%	Start time (min)	End time (min)
1	13.827	136291.337	94.918	13.664	15.329
2	17.784	7297.323	5.082	17.430	18.277

3.40 Lactam formation for analog preparation



Procedure: To a solution of lactone **47** (2.58 g, 8.0 mmol, 1.0 equiv) in PhMe (40 mL) at 22 °C were added tryptamine (1.92 g, 12 mmol, 1.5 equiv), NaI (2.40 g, 16.0 mmol, 2.0 equiv) and Et₃N (3.35 mL, 24.0 mmol, 3.0 equiv). The resulting mixture was heated to 110 °C and allowed to stir at this temperature for 40 h. The reaction mixture was cooled to 22 °C, quenched by addition of H₂O (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (40 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (50% → 70% EtOAc/hexanes) afforded lactam **48** (3.00 g, 6.72 mmol, 84% yield) as an off-white foam.

Description: off-white foam.

R_f: 0.21 in 70% EtOAc/hexanes (UV, purple with *p*-anisaldehyde and indigo with vanillin).

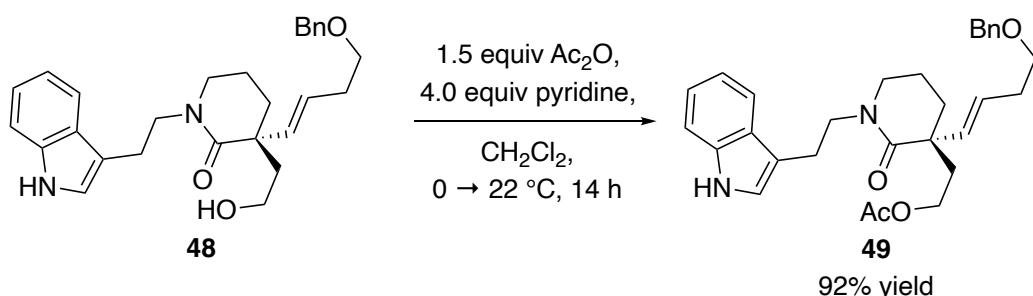
¹H NMR (500 MHz, CDCl₃): δ 8.14 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.37–.26 (m, 6H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 2.3 Hz, 1H), 5.47 (dt, *J* = 16.0, 6.4 Hz, 1H), 5.40 (d, *J* = 16.0 Hz, 0H), 4.93 (s, 1H), 4.52 (d, *J* = 13.2 Hz, 1H), 4.48 (d, *J* = 13.2 Hz, 1H), 3.84–3.73 (m, 2H), 3.64–3.59 (m, 1H), 3.56 (dd, *J* = 13.8, 7.0 Hz, 1H), 3.51 (t, *J* = 6.7 Hz, 2H), 3.15 (td, *J* = 11.4, 5.1 Hz, 1H), 3.12 – 2.97 (m, 3H), 2.38 (q, *J* = 6.6 Hz, 2H), 1.90 (ddd, *J* = 14.8, 9.1, 3.5 Hz, 1H), 1.84–1.75 (m, 1H), 1.70 (s, 3H), 1.59 (dq, *J* = 13.4, 4.3 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 173.8, 138.6, 136.4, 135.4, 128.5, 128.2, 127.8, 127.7, 127.6, 122.5, 122.0, 119.4, 118.8, 112.9, 111.3, 73.0, 70.0, 59.0, 49.1, 48.9, 48.7, 42.4, 34.0, 33.3, 23.0, 19.2.

Optical Rotation: [α]_D²⁰ = +11.6 (c = 1.00 in CHCl₃).

HRMS: calculated for C₂₈H₃₅N₂O₃ [M+H]⁺: 447.2642, found: 447.2642.

3.41 Alcohol acetylation for analog preparation



Procedure: To a solution of alcohol **48** (3.00 g, 6.72 mmol, 1.0 equiv) in CH₂Cl₂ (50 mL) at 0 °C was added pyridine (2.16 mL, 26.9 mmol, 4.0 equiv) and the resulting mixture was allowed to stir at 0 °C for 5 min. Ac₂O (953 µL, 10.1 mmol, 1.5 equiv) was added at 0 °C and the resulting mixture was allowed to stir at 22 °C for 14 h. The reaction was quenched by addition of H₂O (50 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organics were sequentially washed with 0.5 M aqueous HCl (50 mL) and brine (50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10% → 30% EtOAc/hexanes) afforded acetylated product **49** (3.02 g, 6.18 mmol, 92% yield) as a white solid.

Description: white solid.

R_f: 0.20 in 30% EtOAc/hexanes (UV, purple with *p*-anisaldehyde).

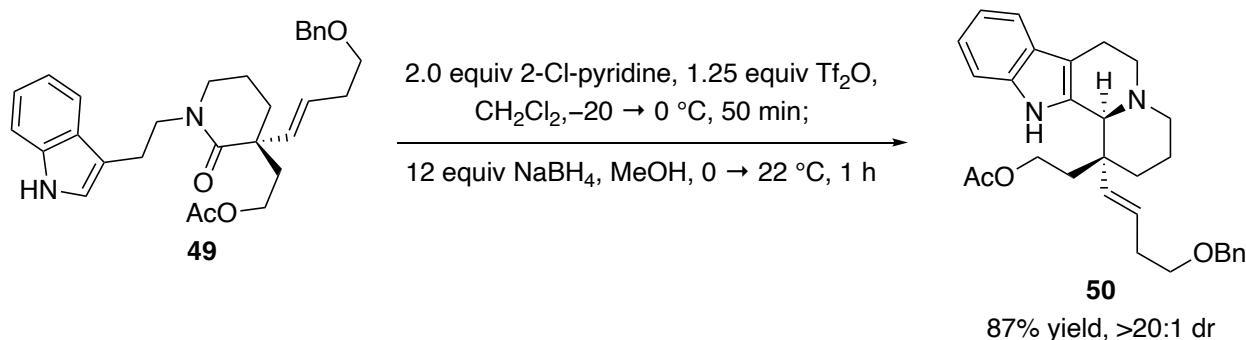
¹H NMR (500 MHz, CDCl₃): δ 8.29 (s, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.37–7.26 (m, 6H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 5.56 (d, *J* = 15.9 Hz, 1H), 5.54–5.47 (m, 1H), 4.52 (d, *J* = 13.2 Hz, 1H), 4.48 (d, *J* = 13.2 Hz, 1H), 4.15 (ddd, *J* = 11.0, 8.6, 5.6 Hz, 1H), 4.08 (ddd, *J* = 10.9, 8.6, 6.1 Hz, 1H), 3.70 (dt, *J* = 13.8, 7.1 Hz, 1H), 3.60 (dt, *J* = 13.2, 7.5 Hz, 1H), 3.51 (t, *J* = 6.7 Hz, 2H), 3.17 (td, *J* = 11.1, 5.0 Hz, 1H), 3.08 (dd, *J* = 12.1, 5.2 Hz, 1H), 3.01 (t, *J* = 7.6 Hz, 2H), 2.37 (q, *J* = 6.4 Hz, 2H), 2.10 (ddd, *J* = 14.4, 8.7, 6.2 Hz, 1H), 2.02 (s, 3H), 1.96 (ddd, *J* = 14.0, 8.7, 5.8 Hz, 1H), 1.82–1.67 (m, 3H), 1.65–1.58 (m, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 171.9, 171.2, 138.6, 136.4, 135.6, 128.5, 127.8, 127.7, 127.6, 127.1, 122.4, 121.9, 119.3, 118.8, 112.9, 111.3, 72.9, 70.0, 61.8, 48.8, 48.5, 47.0, 37.6, 33.3, 30.8, 23.0, 21.2, 19.3.

Optical Rotation: $[\alpha]_D^{20} = +13.9$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for C₃₀H₃₇N₂O₄ [M+H]⁺: 489.2748, found: 489.2744.

3.42 Bischler-Napieralski reaction for analog preparation



Procedure: To a solution of amide **49** (1.78 g, 3.65 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at -20°C was added 2-chloropyridine (691 μL , 7.31 mmol, 2.0 equiv) and the resulting mixture was allowed to stir at -20°C for 5 min before addition of Tf_2O (767 μL , 4.57 mmol, 1.25 equiv). The resulting mixture was allowed to stir at -20°C for 30 min and then at 0°C for a further 20 min (solution color changed from yellow to dark red). A solution of NaBH_4 (1.66 g, 43.8 mmol, 12 equiv) in MeOH (15 mL) was added at 0°C and the resulting mixture was allowed to stir while slowly warming to 22°C over 1 h. The reaction was quenched by addition of H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine (40 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10% \rightarrow 15% EtOAc/hexanes) gave tertiary amine **50** (1.50 g, 3.18 mmol, 87% yield, >20:1 dr) as a white solid.

Description: white solid.

R_f: 0.34 in 30% EtOAc/hexanes (UV, purple with *p*-anisaldehyde and vanillin).

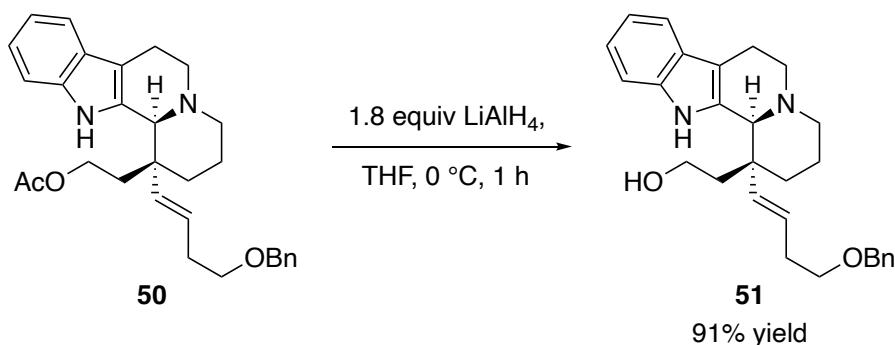
¹H NMR (500 MHz, CDCl_3): δ 9.19 (s, 1H), 7.38–7.32 (m, 1H), 7.28–7.13 (m, 5H), 7.14–7.06 (m, 1H), 7.01–6.88 (m, 2H), 5.72 (d, $J = 16.1$ Hz, 1H), 5.70–5.63 (m, 1H), 4.58 (d, $J = 12.8$ Hz, 1H), 4.54 (d, $J = 12.8$ Hz, 1H), 3.98 (t, $J = 8.0$ Hz, 2H), 3.63 (dt, $J = 10.5, 5.5$ Hz, 1H), 3.51 (dt, $J = 10.4, 5.5$ Hz, 1H), 3.25 (s, 1H), 2.98–2.88 (m, 2H), 2.88–2.81 (m, 1H), 2.60–2.49 (m, 2H), 2.43–2.27 (m, 4H), 1.86 (s, 3H), 1.85–1.74 (m, 1H), 1.58 (dd, $J = 13.8, 3.4$ Hz, 1H), 1.51–1.43 (m, 2H), 1.38 (td, $J = 13.8, 4.3$ Hz, 1H).

¹³C NMR (126 MHz, CDCl_3): δ 171.3, 140.8, 138.0, 136.0, 133.4, 128.6, 128.1, 127.9, 127.9, 126.6, 121.2, 118.8, 117.7, 111.1, 110.9, 72.6, 69.3, 68.4, 61.6, 56.7, 54.0, 42.1, 35.3, 33.6, 28.6, 22.4, 22.1, 21.2.

Optical Rotation: $[\alpha]_D^{20} = +14.5$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for $\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 473.2799, found: 473.2801.

3.43 Acetyl group removal for analog preparation



Procedure: To a solution of acetylated alcohol **50** (1.50 g, 3.18 mmol, 1.0 equiv) in THF (35 mL) at 0 °C was added LiAlH₄ (217 mg, 5.72 mmol, 1.8 equiv) and the resulting mixture was allowed to stir at 0 °C for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of Na₂SO₄ (50 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (40 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (10% acetone/CH₂Cl₂) furnished alcohol **51** (1.25 g, 2.89 mmol, 91% yield) as a white foam.

Description: white foam.

R_f: 0.13 in 10% acetone/CH₂Cl₂ or 0.18 in 70% EtOAc/hexanes (UV, purple with *p*-anisaldehyde).

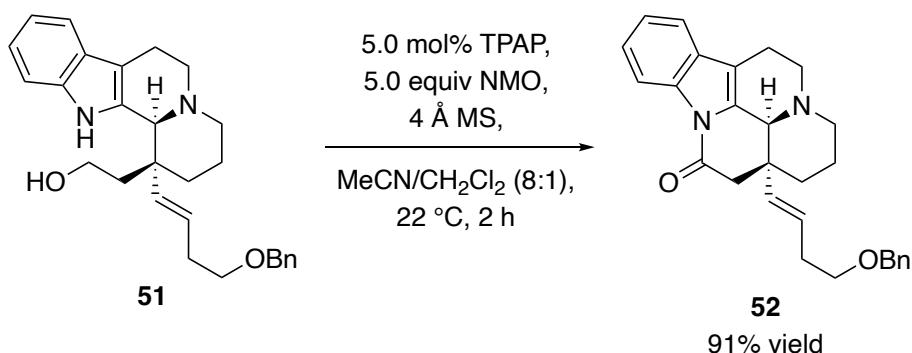
¹H NMR (500 MHz, CDCl₃): δ 9.18 (s, 1H), 7.44 (d, *J* = 7.1 Hz, 1H), 7.37–7.27 (m, 5H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.08–6.99 (m, 2H), 5.83 (d, *J* = 16.0 Hz, 1H), 5.73 (dt, *J* = 16.0, 6.6 Hz, 1H), 5.43 (s, 1H), 4.68 (d, *J* = 13.2 Hz, 1H), 4.65 (d, *J* = 13.2 Hz, 1H), 3.80 (td, *J* = 11.0, 4.4 Hz, 1H), 3.73 (ddd, *J* = 11.6, 7.9, 4.1 Hz, 1H), 3.65 (ddd, *J* = 10.2, 6.3, 4.4 Hz, 1H), 3.58–3.51 (m, 1H), 3.44 (s, 1H), 3.09 (dd, *J* = 10.7, 5.1 Hz, 2H), 3.03 (tdd, *J* = 12.7, 5.9, 2.3 Hz, 1H), 2.76–2.65 (m, 2H), 2.53–2.37 (m, 3H), 2.13–1.97 (m, 2H), 1.76 (dd, *J* = 14.0, 4.3 Hz, 1H), 1.67 (ddd, *J* = 13.6, 5.3, 2.6 Hz, 1H), 1.63–1.55 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 143.2, 138.0, 136.0, 132.6, 128.6, 128.1, 127.9, 126.8, 126.6, 121.3, 118.9, 117.9, 111.0, 110.5, 72.5, 68.4, 58.8, 56.3, 54.1, 43.0, 35.94, 35.6, 33.4, 23.1, 21.6.

Optical Rotation: [α]_D²⁰ = +6.7 (c = 1.00 in CHCl₃).

HRMS: calculated for C₂₈H₃₅N₂O₂ [M+H]⁺: 431.2693, found: 431.2696.

3.44 Oxidative lactamization for analog



Procedure: To a solution of alcohol **51** (1.23 g, 2.86 mmol, 1.0 equiv) in an 8:1 mixture of MeCN (24 mL) and CH₂Cl₂ (3 mL) at 22 °C were sequentially added activated 4 Å molecular sieves (1.0 g) and NMO (1.68 g, 14.3 mmol, 5.0 equiv) and the resulting mixture was allowed to stir at 22 °C for 5 min. TPAP (51.0 mg, 0.14 mmol, 0.05 equiv) was added and the resulting mixture was allowed to stir at 22 °C for 2 h. The reaction was quenched by addition of a saturated aqueous solution of Na₂SO₃ (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were sequentially washed with brine (50 mL) and 10% aqueous CuSO₄ (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (5% → 20% acetone/hexanes) afforded lactam **52** (1.11 g, 2.60 mmol, 91% yield) as a white solid.

Description: white solid.

Rf: 0.15 in 70% EtOAc/hexanes (UV, KMnO₄ or CAM, colorless with *p*-anisaldehyde).

¹H NMR (500 MHz, CDCl₃): δ 8.37 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.38–7.27 (m, 7H), 5.83 (d, *J* = 16.0 Hz, 1H), 5.74 (dt, *J* = 15.9, 6.5 Hz, 1H), 4.54 (s, 2H), 4.16 (s, 1H), 3.54 (t, *J* = 6.7 Hz, 2H), 3.35 (dd, *J* = 13.9, 6.6 Hz, 1H), 3.27 (td, *J* = 12.6, 5.7 Hz, 1H), 2.96–2.86 (m, 1H), 2.82 (d, *J* = 16.8 Hz, 1H), 2.63–2.57 (m, 2H), 2.53–2.39 (m, 4H), 1.81 (qt, *J* = 13.1, 3.8 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃): δ 167.1, 138.5, 136.4, 134.3, 131.7, 130.2, 128.5, 127.8, 127.7, 127.2, 124.6, 124.0, 118.3, 116.4, 113.1, 73.0, 70.0, 58.4, 50.8, 46.6, 44.5, 40.8, 33.5, 29.6, 21.4, 16.6.

Optical Rotation: $[\alpha]_D^{20} = -37.2$ ($c = 1.00$ in CHCl_3).

HRMS: calculated for C₂₈H₂₁N₂O₂ [M+H]⁺: 427.2380, found: 427.2381.

4 Comparative Syntheses

4.1 Comparative enantioselective synthesis of eburnamone

Synthesis	Year	Steps	Overall Yield	SI Section
Takano	1985	17	1.3%	2.1
Winterfeldt	1987	20	0.3%	2.2
Fuji	1987 & 1990	11	5.9%	2.3
Shultz	1997	16	12.3%	2.4
Wee	2000 & 2001	20	0.2%	2.5
Iwabuchi	2009	23	0.6%	2.7
Prasad	2013	16	3.2%	2.8
Qin	2017	24	4.2%	2.9
Pandey	2017	21	4.2%	2.11
Zhu	2019	17	6.0%	2.13
Stoltz	2021	10	11.2%	2.14
Tong	2021	12	9.1%	2.15
Romiti	2023	11	15.7%	This work

4.2 Comparative enantioselective synthesis of eburnamine

Synthesis	Year	Steps	Overall Yield	SI Section
Takano	1985	16	1.8%	2.1
Qin	2017	23	4.9%	2.9
Pandey	2017	22	4.0%	2.11
Stoltz	2021	11	10.8%	2.14
Romiti	2023	12	13.5%	This work

4.3 Comparative enantioselective synthesis of eburnamenine

Synthesis	Year	Steps	Overall Yield	SI Section
Takano	1985	16	0.2%	2.1
Qin	2017	22	5.5%	2.9
Romiti	2023	13	11.8%	This work

4.4 Comparative enantioselective synthesis of dihydroeburnamenine

Synthesis	Year	Steps	Overall Yield	SI Section
Fuji	1987 & 1990	11	7.8%	2.3
Okada	2004	17	3.0%	2.6
Romiti	2023	12	12.9%	This work

4.5 Comparative enantioselective synthesis of 19-OH-eburnamonine

Synthesis	Year	Steps	Overall Yield	SI Section
Trost	2019	13	1.7%	2.12
Romiti	2023	11	6.3%	This work

4.6 Comparative enantioselective synthesis of 19-OH-eburnamine

Synthesis	Year	Steps	Overall Yield	SI Section
Trost	2019	11	0.8%	2.12
Romiti	2023	12	4.6%	This work

4.7 Comparative enantioselective synthesis of 19-oxoeburnamine

Synthesis	Year	Steps	Overall Yield	SI Section
Trost	2019	11	1.3%	2.12
Romiti	2023	13	3.5%	This work

4.8 Comparative enantioselective synthesis of eburnaminol

Synthesis	Year	Steps	Overall Yield	SI Section
Qin	2018	16	0.8%	2.10
Chen	2022	16	4.7%	2.16
Romiti	2023	12	12.8%	This work

4.9 Comparative enantioselective synthesis of larutenine

Synthesis	Year	Steps	Overall Yield	SI Section
Qin	2018	17	0.6%	2.10
Zhu	2019	12	7.0%	2.13
Tong	2021	15	10.3%	2.15
Chen	2022	16	4.4%	2.16
Romiti	2023	13	11.0%	This work

4.10 Comparative enantioselective synthesis of melokhanine E

Synthesis	Year	Steps	Overall Yield	SI Section
Zhu	2019	15	6.9%	2.13
Romiti	2023	15	10.6%	This work

5 References

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Supporting Information

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6 NMR Spectra

