Highly Enantioselective Catalytic Acyl-Pictet-Spengler Reactions

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Supporting Information

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of nitrogen, unless otherwise noted. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.

Materials. Commercial reagents were purchased from Sigma Aldrich, Fluka, Alfa Aesar, or Lancaster, and used as received with the following exceptions: diethyl ether and tetrahydrofuran were distilled from sodium at 760 Torr; dichloromethane was distilled from calcium hydride at 760 Torr.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Mercury-400 (400 MHz), Inova-500 (500 MHz), or an Inova-600 (600 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl_3 : δ 7.25). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl_3 : δ 77.0). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants in Hertz (Hz). Infrared (IR) spectra were obtained using a Mattson Galaxy Series FTIR 3000 spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 370 digital polarimeter. Melting points were measured on a Mel-Temp apparatus, and are uncorrected. The mass spectroscopic data were obtained at the Harvard University mass spectrometry facility. Chiral HPLC analysis was performed on a Shimadzu VP-series instrument.

(1) Preparation of catalysts:

Catalyst **1a** was prepared according to the published procedure.¹

2-{3-[2-(2,2-Dimethyl-propionylamino)-cyclohexyl]-thioureido}-3,3,*N,N*-tetramethyl-butylamide (**1b**):

¹ Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012-10014.

Trimethylacetyl chloride (13.8 μ L, 0.112 mmol) was added dropwise by syringe to a solution of (*S,R,R*)-2-[3-(2-amino-cyclohexyl)-thioureido]-3,3,*N,N*-tetramethyl-butamide¹ (36 mg, 0.114 mmol, 1.02 equiv.) and 2,6-lutidine (13.2 μ L, 0.114 mmol, 1.02 equiv.) in diethyl ether/dichloromethane (1:1 v/v, 1.2 mL) at -78°C . The mixture was allowed to warm to 23°C over 14 hours, then concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with 3% methanol in dichloromethane, yielding the title compound as a white solid (33 mg, 0.083 mmol, 74% yield). mp = $232\text{--}235^{\circ}\text{C}$. ^1H NMR (500 MHz, CDCl_3): δ 7.51 (1H, d, $J = 9.0$ Hz), 6.94 (1H, d, $J = 9.5$ Hz), 6.90 (1H, d, $J = 7.0$ Hz), 5.67 (1H, d, $J = 10.0$ Hz), 4.50-4.40 (1H, m), 3.52-3.46 (1H, m), 3.25 (3H, s), 2.88 (3H, s), 2.06-2.02 (2H, m), 1.74-1.69 (2H, m), 1.34-1.31 (2H, m), 1.25-1.19 (2H, m), 1.10 (9H, s), 0.99 (9H, s). ^{13}C NMR (100 MHz, CDCl_3): δ 183.6, 179.0, 172.3, 59.4, 56.6, 55.8, 38.7, 38.6, 36.2, 35.8, 32.8, 32.6, 27.6, 26.9, 25.3, 24.7. IR (CH_2Cl_2 film, cm^{-1}): 3426 (br), 3055 (m), 2988 (w), 1642 (m), 1422 (w), 1265 (s). LRMS (CI): 353.6 (100%) $[\text{M}-\text{N}(\text{CH}_3)_2]^+$.

(1A) General procedure for the preparation of 2-pyrrolylcyclohexylamines.

(*R,R*)-2-(2,5-Dimethyl-pyrrol-1-yl)-cyclohexylamine:

In a round-bottomed flask equipped with reflux condenser, acetic acid (151 μ L, 2.64 mmol, 1.0 equiv.) and 2,5-hexanedione (310 μ L, 2.64 mmol, 1.0 equiv.) were added sequentially to a solution of (*R,R*)-diaminocyclohexane² (302 mg, 2.64 mmol) in methanol (13 mL). The mixture was heated to 50°C and stirred for 60 minutes, then cooled to 23°C and concentrated *in vacuo*. The residue was partitioned between dichloromethane (50 mL) and 4M aqueous sodium hydroxide (50 mL). The organic phase was separated, and the aqueous extracted twice with dichloromethane (50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica (5% methanol in dichloromethane), yielding the product as a yellow oil (409 mg, 2.13 mmol, 81% yield). ^1H NMR (500 MHz, CDCl_3): δ 5.78 (1H, br s), 5.75 (1H, br s), 3.62-3.58 (1H, m), 3.28-3.24 (1H, m), 2.36 (3H, br s), 2.23 (3H, br s), 2.07-2.04 (1H, m), 1.95-1.79 (4H, m), 1.42-1.32 (2H, m), 1.25-1.17 (1H, m), 1.02 (2H, br s). ^{13}C NMR (100 MHz, CDCl_3): δ 130.0, 127.0, 108.2, 105.5, 63.9, 53.2, 35.6, 31.6, 26.5, 25.3, 15.5, 14.0. IR (cm^{-1} , neat): 2931 (s), 2857 (w), 1601 (s), 1518 (m), 1449 (m), 1397 (s), 1292 (s). LRMS (CI): 192.8 (100%) $[\text{M}+\text{H}]^+$.

² Larrow, J.F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, 59, 1939-1942.

(*R,R*)-2-(2,5-Diphenyl-pyrrol-1-yl)-cyclohexylamine:

The general procedure described above was followed, on 1.0 mmol scale in 5:1 (v/v) methanol/toluene (6.0 mL). After 12 hours at 50°C, workup as described above and purification by chromatography on silica (5% methanol/dichloromethane) yielded the product as a pale orange solid (173 mg, 0.55 mmol, 55% yield), which was used directly in the thiourea formation reaction.

(*R,R*)-2-(2-Methyl-5-phenyl-pyrrol-1-yl)-cyclohexylamine:

The general procedure described above was followed, on a 3.13 mmol scale. After 12 hours at 50°C, workup as described above and purification by chromatography on silica (2% → 5% methanol in dichloromethane), the product was obtained as a red oil (665 mg, 2.61 mmol, 84% yield) which gradually solidified upon standing. ¹H NMR (500 MHz, CDCl₃): δ 7.38-7.30 (5H, m), 6.05 (1H, br s), 5.98 (1H, br s), 3.78-3.77 (1H, m), 3.23-3.19 (1H, m), 2.47 (3H, s), 2.03-1.95 (2H, m), 1.83-1.71 (2H, m), 1.35-1.20 (2H, m), 1.01-0.89 (4H, m). ¹³C NMR (100 MHz, CDCl₃): δ 137.4, 134.8, 129.8, 129.3, 128.6, 127.0, 109.8, 108.1, 64.8, 53.5, 35.6, 32.1, 26.2, 25.4, 15.6. IR (cm⁻¹, neat): 3366 (w), 3059 (w), 2931 (m), 2857 (m), 2236 (w), 1601 (s), 1514 (s), 1462 (s), 1385 (s), 1296 (s), 1028 (m), 910 (s). LRMS (CI): 254.5 (100%) [M]⁺, 255.1 (50%) [M+H]⁺.

(1B) General procedure for the preparation of dimethyl amide catalysts 1c-e.

(*S,R,R*)-2-{3-[2-(2,5-Dimethyl-pyrrol-1-yl)-cyclohexyl]-thioureido}-3,3,*N,N*-tetramethyl-butynamide (1c):

(*R,R*)-2-(2,5-Dimethyl-pyrrol-1-yl)-cyclohexylamine (114 mg, 0.59 mmol, 1.18 equiv.) was added to a solution of (*S*)-2-isothiocyanato-3,3,*N,N*-tetramethyl-butynamide¹ (100 mg, 0.50 mmol) in dichloromethane (5 mL) at 23°C. The resulting solution was stirred at 23°C for 48 hours, then concentrated. The residue was purified by chromatography on silica (20% → 33% ethyl acetate in hexanes), yielding the title compound as a white solid (124 mg, 0.32 mmol, 63% yield). ¹H NMR (500 MHz, CDCl₃): δ 6.34 (1H, br d, J = 8.5 Hz), 5.97 (1H, br d, J = 6.0 Hz), 5.71 (2H, br s), 5.51 (1H, br d, J = 8.5 Hz), 4.34-4.33 (1H, m), 3.86-3.80 (1H, m), 3.18 (3H, s), 2.93 (3H, s), 2.44-2.14 (6H, br m), 1.99-1.79 (4H, m), 1.46-1.21 (4H, m), 0.94 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 182.3, 172.2, 127.5, 127.5, 108.8, 106.4, 60.4, 59.5, 56.0, 38.8, 36.3, 35.9, 34.2, 32.5, 26.9, 26.4, 24.9, 15.5, 13.7. IR (cm⁻¹, CH₂Cl₂ film): 3381 (w), 3295 (w), 3055 (s), 2969 (m), 1638 (m), 1524 (m), 1422 (m), 1265 (m), 1265 (s). LRMS (CI): 192.8 (100%) [M+H]⁺.

(*S,R,R*)-2-{3-[2-(2,5-Diphenyl-pyrrol-1-yl)-cyclohexyl]-thioureido}-3,3,*N,N*-tetramethyl-butynamide (1d):

The general procedure described above was performed on 0.50 mmol scale, using 1.1 equivalents of (*R,R*)-2-(2,5-diphenyl-pyrrol-1-yl)-cyclohexylamine. After 48 hours, the reaction mixture was concentrated and the residue purified by chromatography on silica (20% □ 33% ethyl acetate in hexanes), yielding the title compound as a white foam (180 mg, 0.35 mmol, 70% yield). ¹H NMR (500 MHz, CDCl₃): □ 7.48–7.36 (10H, m), 6.20 (2H, br s), 5.90 (1H, d, *J* = 9.0 Hz), 5.51 (1H, d, *J* = 9.0 Hz), 5.34 (1H, br m), 4.01–3.96 (1H, m), 3.52 (1H, br s), 3.19 (3H, s), 2.90 (3H, s), 2.21–2.15 (2H, m), 1.92–1.84 (1H, m), 1.68–1.65 (1H, d, *J* = 13.0 Hz), 1.51 (1H, d, *J* = 13.0 Hz), 1.15–0.89 (2H, m), 1.03 (9H, s), 0.81–0.74 (1H, m).

¹³C NMR (100 MHz, CDCl₃): 182.0, 172.0, 137.4, 136.1, 135.2, 134.0, 131.6, 130.0, 129.3, 129.0, 128.8, 128.1, 112.7, 109.8, 61.0, 60.6, 56.6, 38.7, 36.0, 35.8, 34.1, 33.3, 26.9, 26.0, 24.3. IR (cm⁻¹, CH₂Cl₂ film): 3329 (w), 2938 (m), 2861 (w), 1638 (s), 1524 (s), 1398 (m), 1312 (m). LRMS (CI): 472.1 (100%) [M–Me₂N]⁺.

(*S,R,R*)-3,3,*N,N*-Tetramethyl-2-{3-[2-(2-methyl-5-phenyl-pyrrol-1-yl)-cyclohexyl]-thioureido}-butyramide (**1e**):

The general procedure described above was performed on 1.18 mmol scale, using 1.2 equivalents of (*R,R*)-2-(2-methyl-5-phenyl-pyrrol-1-yl)-cyclohexylamine. After 16 hours, the reaction mixture was concentrated and the residue purified by chromatography on silica (20% □ 33% ethyl acetate in hexanes), yielding the title compound as a pale brown foam (400 mg, 0.88 mmol, 75% yield). ¹H NMR (500 MHz, CDCl₃): □ 7.35–7.23 (5H, m), 6.24 (1H, br s), 5.92 (1H, d, *J* = 3.5 Hz), 5.81 (1H, d, *J* = 3.5 Hz), 5.59 (1H, br s), 5.52 (1H, br d, *J* = 8.5 Hz), 4.49 (1H, br s), 4.00–3.94 (1H, m), 3.12 (3H, s), 2.80 (3H, s), 2.55–2.50 (3H, m), 2.21–2.10 (3H, m), 1.83–1.80 (1H, m), 1.69–1.67 (1H, m), 1.40–1.30 (1H, m), 1.22–1.15 (1H, m), 0.98–0.90 (1H, m), 0.92 (9H, s). ¹³C NMR (100 MHz, CDCl₃):

□ 182.4, 172.0, 136.1, 134.6, 129.8, 129.8, 128.0, 110.2, 109.0, 60.1, 59.9, 56.1, 38.7, 36.5, 35.7, 33.9, 32.6, 26.9, 25.9, 24.9, 15.8. IR (cm⁻¹, CH₂Cl₂ film): 3325 (m), 3099 (w), 2938 (s), 2863 (m), 1624 (s), 1530 (s), 1398 (m), 1325 (m), 1240 (m), 1132 (m), 1072 (m). LRMS (CI): 409.9 (100%) [M–Me₂N]⁺, 409.2 (70%) [M–Me₂NH]⁺.

(*S,R,R*)-*N,N*-Diisobutyl-3,3-dimethyl-2-{3-[2-(2-methyl-5-phenyl-pyrrol-1-yl)-cyclohexyl]-thioureido}-butyramide (**1f**):

Step 1: Diisopropylethylamine (958 □L, 5.5 mmol, 2.2 equiv.), then diisobutylamine (480 □L, 2.75 mmol, 1.1 equiv.) were added to a suspension of (L)-(*S*)-Boc-*tert*-leucine

(578 mg, 2.5 mmol) and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) (1.04 g, 2.75 mmol, 1.1 equiv.) in dichloromethane (25 mL) at 23°C. The reaction was stirred for 28 hours at 23°C, then diluted with diethyl ether (50 mL), and washed twice with 1M hydrochloric acid (50 mL) then twice with saturated aqueous sodium bicarbonate (50 mL), then once with brine. After drying over sodium sulfate, the solution was concentrated, yielding the crude product (contaminated with tetramethylurea) as a foam which was used in step 2 without further purification.

Step 2: Hydrogen chloride (6 mL, 4M in dioxane, excess) was added to crude Boc-2-amino-*N,N*-diisobutyl-3,3-dimethyl-butyramide (2.5 mmol), and the resulting solution stirred at 23°C for 2 hours. The mixture was concentrated to yield (*S*)-2-amino-*N,N*-diisobutyl-3,3-dimethyl-butyramide hydrochloride (contaminated with tetramethylurea) as a foam, which was used in step 3 without further purification.

Step 3:

CAUTION! Thiophosgene is a highly toxic compound.

Saturated aqueous sodium bicarbonate (12.5 mL) was added to a solution of (*S*)-2-amino-*N,N*-diisobutyl-3,3-dimethyl-butyramide hydrochloride (2.5 mmol) in dichloromethane (12.5 mL) at 0°C. The mixture was stirred for 5 minutes, then stirring was stopped and thiophosgene (210 μ L, 2.75 mmol, 1.1 equiv.) was added to the organic (lower) phase by syringe. The resulting orange mixture was stirred at 0°C for 20 minutes.

Dichloromethane (20 mL) was added, and the organic portion separated. The aqueous was extracted twice with dichloromethane (20 mL). The combined organic extracts were dried over sodium sulfate and concentrated, yielding *N,N*-diisobutyl-2-isothiocyanato-3,3-dimethyl-butyramide (contaminated with tetramethylurea) as a solid, which was used in step 4 immediately and without further purification.

Step 4: (*R,R*)-2-(2-Methyl-5-phenyl-pyrrol-1-yl)-cyclohexylamine (820 mg, 3.22 mmol, 1.3 equiv.) was added by syringe as a dichloromethane solution (3 mL, with two 2.75 mL rinses) to a solution of *N,N*-diisobutyl-2-isothiocyanato-3,3-dimethyl-butyramide (2.5 mmol) in dichloromethane (4 mL) at 23°C. The resulting solution was stirred at 23°C for 13 hours, then concentrated. The residue was purified by chromatography on silica (5% $\square$ 10% ethyl acetate in hexanes), yielding the title compound as a white foam (1.22 g, 2.27 mmol, 91% yield). ¹H NMR (500 MHz, CDCl₃): $\square$ 7.44-7.42 (2H, m), 7.36-7.31 (3H, m), 6.07 (1H, br s), 6.02 (1H, s), 5.86 (1H, s), 5.48 (1H, br s), 4.97 (1H, m), 4.35 (1H, br s), 3.97 (1H, m), 3.80 (1H, dd, *J* = 7.0, 13.0 Hz), 3.45-3.44 (1H, m), 3.01 (1H, dd, *J* = 7.5, 14.5 Hz), 2.58 (1H, dd, *J* = 8.0, 13.5 Hz), 2.47 (m, 3H), 2.26-2.17 (3H, br s), 2.02-1.98 (2H, m), 1.88-1.86 (1H, m), 1.73-1.70 (1H, m), 1.41-1.39 (1H, m), 0.97 (9H, s), 0.93 (6H, d, *J* = 6.5 Hz), 0.89 (6H, d, *J* = 6.5 Hz), 0.85 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): $\square$ 181.4, 172.2, 136.2, 134.5, 129.8, 129.3, 129.0, 127.2, 110.4, 108.9, 60.0, 56.6, 56.1, 53.9, 37.4, 33.9, 32.6, 28.2, 27.2, 27.2, 27.0, 25.9, 24.8, 21.0, 20.8, 20.7, 19.7, 15.5. IR (cm⁻¹, CH₂Cl₂ film): 3405 (br), 3055 (m), 2988 (w), 1630 (w), 1422 (w), 1265 (s), 897 (m). LRMS (CI): 410.3 (80%) [LRMS (CI): 192.8 (100%) [M+H]⁺, 409.4 (100%) [M-*i*-Bu₂NH]⁺.

(2-Ethyl-butyldiene)-[2-(1*H*-indol-3-yl)-ethyl]-amine (**2**).

Molecular sieves (3Å spherical, 5g) were flame-dried *in vacuo*, then allowed to cool to 23°C under N₂ and suspended in dichloromethane (50 mL). Tryptamine (1.60 g, 10.0 mmol) was added, followed by 2-ethylbutanal (1.30 mL, 10.5 mmol, 1.05 equiv.)

dropwise by syringe. The resulting suspension was allowed to stand under N₂ for 7 hours, with occasional agitation by swirling the flask. The mixture was filtered and concentrated *in vacuo*. The resulting oil was suspended in hexanes and concentrated, resulting in the formation of the product as a pale brown solid, which was washed with hexanes and dried *in vacuo* (1.95g, 8.0 mmol, 80% yield). mp = 71–73°C. ¹H NMR (500 MHz, CDCl₃): δ 8.35 (1H, br s), 7.66 (1H, d, J = 7.5 Hz), 7.35 (1H, d, J = 8.5 Hz), 7.30 (1H, d, J = 7.0 Hz), 7.20 (1H, dd, J = 7.5, 7.5 Hz), 7.13 (1H, dd, J = 7.5, 8.5 Hz), 6.98 (1H, d, J = 1.5 Hz), 3.75 (2H, t, J = 7.0 Hz), 3.10 (2H, t, J = 7.0 Hz), 2.05–2.01 (1H, m), 1.47–1.33 (4H, m), 0.83 (6H, t). ¹³C NMR (100 MHz, CDCl₃): δ 169.7, 136.6, 127.7, 122.3, 122.0, 119.3, 119.2, 114.1, 111.3, 62.0, 48.4, 27.3, 25.2, 11.8. IR (CH₂Cl₂ film): 3472 (w), 3054 (m), 2965 (m), 1667 (m), 1456 (m), 1265 (s), 897 (w), 731 (s). LRMS (CI): 242.6 (M+H)⁺.

(2) General procedure for acyl-Pictet-Spengler reactions catalyzed by **1f**.

Method A. (S)-1-[1-(1-Ethyl-propyl)-1,3,4,9-tetrahydro- β -carbolin-2-yl]-ethanone (**3a**).

Molecular sieves (250 mg, 3Å spherical), were flame-dried *in vacuo* and cooled to 23°C under nitrogen. Dichloromethane (1.25 mL), then tryptamine (40 mg, 0.25 mmol, 1.0 equiv.) were added. 2-Ethylbutanal (32 μ L, 0.275 mmol, 1.0 equiv.) was added dropwise by syringe to the suspension, which was allowed to stand at 23°C for 7 hours and swirled occasionally to ensure mixing of the contents. The resulting solution was filtered by cannula transfer to a flame-dried round-bottomed flask. The dessicant was rinsed twice with dichloromethane (5 mL) and the rinses combined with the filtrate by cannula transfer. The solution was concentrated *in vacuo*, yielding the imine as a pale brown oil, which was dissolved in diethyl ether (5.0 mL). Catalyst **1f** (6.7 mg, 0.013 mmol, 5 mol%) was added, and the solution cooled to -78°C in a dry ice/acetone bath. 2,6-Lutidine (29 μ L, 0.25 mmol, 1.0 equiv.), then acetyl chloride (18 μ L, 0.25 mmol, 1.0 equiv.), were added dropwise by syringe. The mixture was stirred at -78°C for 5 minutes, then warmed to -30°C and stirred for 22 hours. The resulting heterogeneous mixture was allowed to warm to 23°C and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 20% ethyl acetate in dichloromethane, yielding the product as a white solid (46 mg, 65% yield). The enantiomeric excess was determined to be 93% by chiral HPLC ((S,S)-Whelk-01 (Pirkle), 10% ethanol/hexanes, 1.2 mL/min, 220 nm. t_r(minor): 9.9 min, t_r(major): 12.1 min.) $[\alpha]_D^{25} = +57^\circ$ (c = 0.47, methanol). mp = 156–157°C. ¹H NMR (500 MHz, CDCl₃): the compound exists as a 6:1 mixture of amide rotamers. Signals corresponding to the major rotamer: δ 7.84 (1H, br s), 7.46 (1H, d, J = 8.0 Hz), 7.33 (1H, d, J = 8.0 Hz), 7.18 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 7.10 (1H, dd, J = 8.0 Hz), 5.71 (1H, d, J = 8.5 Hz), 4.01 (1H, dd, J = 14.0, 5.5 Hz), 2.90–2.78 (2H, m), 2.22 (3H, s), 1.77–1.72 (1H, m), 1.64–1.35 (3H, m), 1.26–1.20 (1H, m), 1.00 (3H, t), 0.92 (3H, t). Representative signals corresponding to the minor rotamer: δ 7.77 (1H, br s), 7.49 (1H, d, J = 8.0 Hz), 4.95 (1H, dd, J = 13.0, 6.0 Hz), 4.68 (1H, d, J = 9.0 Hz), 3.13–3.07 (1H, m), 2.71 (1H, dd, J = 16.0, 4.5 Hz), 2.15 (3H, s), 1.91–1.88 (1H, m).

^{13}C NMR (100 MHz, CDCl_3), signals corresponding to the major rotamer: δ 170.2, 136.1, 134.5, 126.9, 121.8, 119.5, 118.0, 111.2, 108.1, 51.4, 43.4, 41.6, 22.2, 22.2, 22.1, 22.1, 11.3, 11.0. IR (CH_2Cl_2 film): 3277 (m), 3054 (m), 2965 (s), 1632 (s), 1441 (s), 1265 (s), 1018 (m), 733 (s). LRMS (CI): 284.3 (100%) $[\text{M}]^+$, 285.0 (80%) $[\text{M}+\text{H}]^+$.

Method B: (*S*)-1-(1-pentyl-1,3,4,9-tetrahydro- β -carbolin-2-yl)-ethanone (**3c**):

In a flame-dried round-bottomed flask, tryptamine (40 mg, 0.25 mmol, 1.0 equiv.) was dissolved in dichloromethane/diethyl ether (3:1 v/v, 12.5 mL). Hexanal (32 μL , 0.275 mmol, 1.05 equiv.) was added dropwise by syringe at 23°C , and the mixture was stirred at 23°C for 90 minutes. Sodium sulfate (500 mg) was added and the mixture stirred an additional 30 minutes. The resulting solution was filtered by cannula transfer to a flame-dried round-bottomed flask. The dessicant was rinsed twice with dichloromethane (5 mL) and the rinses combined with the filtrate by cannula transfer. The solution was concentrated *in vacuo*, yielding the imine as a pale brown oil which was immediately dissolved in diethyl ether (5.0 mL).³ Catalyst **1f** (13.5 mg, 0.025 mmol, 10 mol%) was added, and the solution cooled to -78°C in a dry ice/acetone bath. 2,6-Lutidine (29 μL , 0.25 mmol, 1.0 equiv.), then acetyl chloride (18 μL , 0.25 mmol, 1.0 equiv.), were added dropwise by syringe. The mixture was stirred at -78°C for 5 minutes, then warmed to -60°C and stirred for 23 hours. The resulting heterogeneous mixture was allowed to warm to 23°C and concentrated *in vacuo*. The residue was purified by chromatography on silica (33% ethyl acetate in hexanes), yielding the title compound as a white solid (47 mg, 65% yield, contaminated with 2% enamide byproduct). The enantiomeric excess was determined to be 95% by chiral HPLC (Pirkle (L)-leucine, 10% ethanol/hexanes, 1.2 mL/min, t_r (minor): 10.4 min, t_r (major): 12.3 min. $[\alpha]_D^{+92}$ ($c=0.5$, methanol). mp = $171\text{--}173^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3): the compound exists as a 4:1 mixture of amide rotamers. Signals corresponding to the major rotamer: δ 8.23 (1H, br s), 7.45 (1H, d, $J = 7.5$ Hz), 7.32 (1H, d, $J = 8.0$ Hz), 7.15 (1H, ddd, $J = 7.5, 7.5, 1.0$ Hz), 7.09 (1H, ddd, $J = 7.5, 7.5, 1.0$ Hz), 5.78 (1H, dd, $J = 9.0, 5.5$ Hz), 4.01 (1H, dd, $J = 13.5, 3.5$ Hz), 3.55–3.49 (1H, m), 2.84–2.77 (2H, m), 2.25 (3H, s), 1.92–1.85 (1H, m), 1.82–1.75 (1H, m), 1.55–1.39 (2H, m), 1.36–1.27 (4H, m), 0.89 (3H, t, $J = 6.5$ Hz). Representative signals corresponding to the minor rotamer: δ 8.01 (1H, br s), 7.50 (1H, d, $J = 8.0$ Hz), 4.96 (1H, dd, $J = 13.0, 5.0$ Hz), 4.88–4.86 (1H, m), 3.03–2.97 (1H, m), 2.71 (1H, dd, $J = 16.0, 3.5$ Hz), 2.20 (3H, s). ^{13}C NMR (100 MHz, CDCl_3), signals corresponding to the major rotamer: δ 169.9, 136.2, 135.1, 126.9, 121.9, 119.7, 118.1, 111.2, 107.6, 49.4, 41.3, 34.9, 32.2, 26.2, 22.8, 22.3, 22.2, 14.3. IR (CH_2Cl_2 film): 3271 (m), 2930 (m), 2857 (m), 1632 (s), 1451 (s). LRMS (CI): 284.6 (100%) $[\text{M}]^+$, 285.1 (30%) $[\text{M}+\text{H}]^+$.

³ Imines prepared from tryptamine and β -unbranched aldehydes are not stable to prolonged storage at 23°C as neat liquids. For best results, they should be used immediately after preparation.

1-(1-Isopropyl-1,3,4,9-tetrahydro- α -carbolin-2-yl)-ethanone (**3b**):

The reaction was performed on 0.25 mmol scale according to Method A (7 hour imine preparation time), using 10 mol% **1f** (13.5 mg) at -40°C for 65 hours. The product was obtained as a white solid after column chromatography on silica gel, eluting with 10% ethyl acetate in dichloromethane (46 mg, 67% yield). The enantiomeric excess was determined to be 85% by chiral HPLC ((*S,S*)-Whelk-01 (Pirkle), 10% ethanol/hexanes, 1.2 mL/min, 220 nm. t_r (minor): 12.9 min, t_r (major): 15.3 min.) $[\alpha]_D = +73^{\circ}$ ($c = 0.48$, methanol). mp = $199\text{--}202^{\circ}\text{C}$. ^1H NMR (500 MHz, CDCl_3): the compound exists as a 5:1 mixture of amide rotamers. Signals corresponding to the major rotamer: δ 8.30 (1H, br s), 7.46 (1H, d, $J = 8.0$ Hz), 7.33 (1H, d, $J = 8.0$ Hz), 7.16 (1H, ddd, $J = 8.0, 7.0, 1.0$ Hz), 7.09 (1H, ddd, $J = 8.0, 7.5, 1.0$ Hz), 5.47 (1H, d, $J = 8.5$ Hz), 4.02 (1H, dd, $J = 14.5, 5.0$ Hz), 3.6303.56 (1H, m), 2.89-2.77 (2H, m), 2.24 (3H, s), 2.14-2.09 (1H, m), 1.16 (3H, d, $J = 7.0$ Hz), 0.99 (3H, d, $J = 7.0$ Hz). Representative signals corresponding to the minor rotamer: δ 7.97 (1H, br s), 7.50 (1H, d, $J = 8.0$ Hz), 4.97 (1H, dd, $J = 13.0, 5.5$ Hz), 4.46 (1H, d, $J = 8.0$ Hz), 3.11-3.05 (1H, m), 2.71 (1H, dd, $J = 16.0, 4.0$ Hz), 2.16 (3H, s), 1.21 (3H, d, $J = 7.0$ Hz), 1.10 (3H, d, $J = 6.5$ Hz). ^{13}C NMR (100 MHz, CDCl_3), signals corresponding to the major rotamer: δ 170.1, 136.2, 134.3, 126.8, 121.9, 119.5, 118.1, 111.2, 107.8, 54.8, 41.6, 33.3, 22.2, 22.0, 20.3, 20.2. IR (CH_2Cl_2 film): 3468 (w), 3055 (m), 2988 (m), 1638 (m), 1424 (m), 1265 (s), 897 (m). LRMS (CI): 256.5 (100%) $[\text{M}]^+$, 257.2 (30%) $[\text{M}+\text{H}]^+$.

1-(1-Isobutyl-1,3,4,9-tetrahydro- α -carbolin-2-yl)-ethanone (**3d**):

The reaction was performed on 0.25 mmol scale according to Method B, using 10 mol% **1f** (13.5 mg) at -60°C for 22 hours. The product was obtained as a white solid after column chromatography on silica gel, eluting with 10% ethyl acetate in dichloromethane (50.5 mg, 75% yield). The enantiomeric excess was determined to be 93% by chiral HPLC (L-leucine (Pirkle), 10% ethanol/hexanes, 1.2 mL/min, 220 nm. t_r (minor): 11.9 min, t_r (major): 15.3 min.) $[\alpha]_D = +92.5^{\circ}$ ($c = 0.56$, methanol). mp = $202\text{--}204^{\circ}\text{C}$. ^1H NMR (500 MHz, CDCl_3): the compound exists as a 4.5:1 mixture of amide rotamers. Signals corresponding to the major rotamer: δ 7.79 (1H, br s), 7.45 (1H, d, $J = 7.5$ Hz), 7.32 (1H, d, $J = 7.5$ Hz), 7.16 (1H, ddd, $J = 8.0, 7.5, 1.0$ Hz), 7.10 (1H, dd, $J = 8.0, 7.5, 1.0$ Hz), 5.88 (1H, dd, $J = 9.0, 4.0$ Hz), 3.99 (1H, dd, $J = 15.0, 5.5$ Hz), 3.55-3.49 (1H, m), 2.86-2.82 (1H, m), 2.78 (1H, dd, $J = 14.0, 3.5$ Hz), 2.22 (3H, s), 1.81-1.72 (2H, m), 1.61-1.56 (1H, m), 1.09 (3H, d, $J = 6.5$ Hz), 0.99 (3H, d, $J = 7.0$ Hz). Representative signals corresponding to the minor rotamer: δ 7.74 (1H, br s), 7.49 (1H, d, $J = 7.5$ Hz), 4.91-4.91 (2H, m), 3.05-3.00 (1H, m), 2.70 (1H, dd, $J = 15.5, 3.5$ Hz), 2.19 (3H, s). ^{13}C NMR (100 MHz, CDCl_3), signals corresponding to the major rotamer: δ 170.0, 136.2, 135.5, 127.0, 121.9, 119.7, 118.6, 118.0, 111.2, 107.5, 47.5, 44.1, 40.8, 25.4, 23.6, 22.9, 22.3, 22.2. IR (CH_2Cl_2 film): 3461 (w), 3055 (m), 2988 (m), 1640 (m), 1424 (m), 1265 (s), 897 (m). LRMS (CI): 270.2 (100%) $[\text{M}]^+$, 270.9 (90%) $[\text{M}+\text{H}]^+$.

1-{1-[2-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-1,3,4,9-tetrahydro- α -carbolin-2-yl}-ethanone (**3e**):

The reaction was performed on 0.25 mmol scale, using the following modifications to Method B: 3-(*tert*-butyl-diphenyl-silanyloxy)-propionaldehyde⁴ was added as a solution in dichloromethane (2.0 mL, followed by a 1.4 mL rinse) dropwise by syringe to tryptamine in dichloromethane/diethyl ether (2:1, 9.1 mL). From this point, the procedure described in Method B was followed, using 10 mol% **1f** (13.5 mg) at -60°C for 22 hours. The product was obtained as a white solid after column chromatography on silica gel, eluting with 5% → 10% ethyl acetate in dichloromethane (96 mg, 77% yield). The enantiomeric excess was determined to be 90% by chiral HPLC (Chiralpak AD, 7% isopropanol/hexanes, 1.0 mL/min, 220 nm. *t_r*(major): 10.4 min, *t_r*(minor): 14.7 min.) $[\alpha]_D = +36^\circ$ (c = 0.52, methanol). mp = 159-163°C. ¹H NMR (500 MHz, CDCl₃): the compound exists as a 1.8:1 mixture of amide rotamers. Signals corresponding to the major rotamer: δ 8.78 (1H, br s), 7.77-7.73 (4H, m), 7.52-7.42 (7H, m), 7.18-7.10 (3H, m), 5.95 (1H, dd, J = 7.0, 7.0 Hz), 4.12-4.08 (1H, m), 4.03-3.90 (2H, m), 3.46-3.40 (1H, m), 2.91-2.74 (2H, m), 2.21 (3H, s), 2.13-2.00 (2H, m), 1.19 (9H, s). Representative signals corresponding to the minor rotamer: δ 8.26 (1H, br s), 5.26 (1H, dd, J = 7.5, 7.5 Hz), 4.97 (1H, dd, J = 12.5, 4.5 Hz), 2.94 (1H, dd, J = 11.5, 3.5 Hz), 2.72 (1H, dd, J = 15.0, 3.5 Hz), 2.24 (3H, s), 1.21 (9H, s). ¹³C NMR (125 MHz, CDCl₃), signals corresponding to both rotamers: δ 169.6, 169.3, 136.2, 136.1, 135.9, 135.8, 135.8, 134.4, 133.7, 133.4, 133.1, 132.9, 132.9, 130.6, 130.5, 130.2, 128.4, 128.3, 128.2, 128.2, 126.9, 122.3, 121.9, 119.8, 119.6, 118.6, 118.1, 111.2, 111.1, 109.7, 107.6, 62.8, 61.2, 51.1, 48.0, 41.9, 37.3, 37.0, 36.3, 27.3, 22.4, 22.2, 22.1, 21.3, 19.6, 19.5. IR (CH₂Cl₂ film): 3266 (w), 3071 (w), 2930 (m), 2857 (m), 1620 (s), 1427 (s), 1111 (s). LRMS (CI): 496.5 (100%) [M]⁺, 497.1 (70%) [M+H]⁺

(2-Ethyl-butylidene)-[2-(5-methoxy-1*H*-indol-3-yl)-ethyl]-amine (**3f**):

The reaction was performed on a 0.25 mmol scale according to Method A (5.5 hour imine preparation time), using 5 mol% **1f** (6.7 mg) at -40°C for 22 hours. The product was obtained as a white solid after chromatography on silica gel, eluting with 10% ethyl acetate in dichloromethane (64 mg, 81% yield). The enantiomeric excess was determined to be 93% by chiral HPLC ((*S,S*)-Whelk-01 (Pirkle), 10% ethanol/hexanes, 1.2 mL/min, 220 nm. *t_r*(minor): 19.1 min, *t_r*(major): 23.1 min.) $[\alpha]_D = +26^\circ$ (c = 0.50, methanol). mp = 133-135°C. ¹H NMR (500 MHz, CDCl₃): the compound exists as a 6:1 mixture of amide rotamers. Signals corresponding to the major rotamer: δ 7.75 (1H, br s), 7.21 (1H, d, J = 8.5 Hz), 6.90 (1H, d, J = 2.0 Hz), 6.82 (1H, dd, J = 8.5, 2.0 Hz), 5.68 (1H, d, J = 8.5 Hz), 4.00 (1H, dd, J = 14.0, 5.5 Hz), 3.63-3.57 (1H, m), 2.86-2.80 (1H, m), 2.75 (1H, dd, J = 15.5, 4.0 Hz), 2.21 (3H, s), 1.77-1.73 (1H, m), 1.62-1.46 (3H, m), 1.40-1.35 (1H, m), 0.98 (3H, t, J = 7.0 Hz), 0.91 (3H, t, J = 7.5 Hz). Representative signals corresponding to the minor rotamer: δ 7.67 (1H, br s), 6.93 (1H, d, J = 2.0 Hz), 2.94 (1H, dd, J = 13.0, 6.0 Hz), 4.65 (1H, d, J = 8.5 Hz), 3.12-3.06 (1H, m), 2.66 (1H, dd, J = 16.0, 4.5 Hz), 2.14 (3H, s). ¹³C NMR (100 MHz, CDCl₃), signals corresponding to the major rotamer: δ 170.2, 154.3, 135.4, 131.1, 127.3, 111.7, 111.6, 108.1, 100.4, 56.2, 51.3, 45.4, 41.6, 22.2,

⁴ Prepared according to modifications to the procedure of Baldwin (Baldwin, J. E.; Bulger, P. G.; Marquez, R. *Tetrahedron* **2002**, 58, 5441-5442), as described in: Raheem, I. T.; Goodman, S. N. Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, 126, 706-707. The aldehyde was purified by chromatography on silica (20% diethyl ether in hexanes) immediately before use.

22.2, 22.2, 22.1, 11.3, 11.0. IR (CH₂Cl₂ film): 3067 (m), 2969 (m), 1640 (m), 1424 (s), 1273 (s), 897 (s). LRMS (CI): 314.4 (100%) [M]⁺, 315.0 (50%) [M+H]⁺.

1-[1-(1-Ethyl-propyl)-6-methoxy-1,3,4,9-tetrahydro- λ -carbolin-2-yl]-ethanone (**3g**):

The reaction was performed on 0.25 mmol scale according to Method A (7.5 hour imine preparation time), using 10 mol% **1f** (13.5 mg) at -50°C for 65 hours. The product was obtained as a white solid after column chromatography on silica gel, eluting with 10% ethyl acetate in dichloromethane (60 mg, 76% yield). The enantiomeric excess was determined to be 86% by chiral HPLC ((*S,S*)-Whelk-01 (Pirkle), 10% ethanol/hexanes, 1.2 mL/min, 220 nm. *t_r*(minor): 18.0 min, *t_r*(major): 23.6 min.) $[\alpha]_D = +46^\circ$ (c = 0.48, methanol). mp = 182–185°C. ¹H NMR (500 MHz, CDCl₃): the compound exists as a 6:1 mixture of amide rotamers. Signals corresponding to the major rotamer: δ 8.00 (1H, br s), 7.31 (1H, d, J = 8.5 Hz), 6.84 (1H, s), 6.75 (1H, d, J = 8.5 Hz), 5.65 (1H, d, J = 8.5 Hz), 3.98 (1H, dd, J = 14.5, 6.0 Hz), 3.62–3.56 (1H, m), 2.85–2.79 (1H, m), 2.74 (1H, dd, J = 12.5, 4.0 Hz), 2.21 (3H, s), 1.76–1.72 (1H, m), 1.63–1.56 (1H, m), 1.55–1.45 (2H, m), 1.40–1.34 (1H, m), 0.97 (3H, t, J = 7.5 Hz), 0.90 (3H, t, J = 7.5 Hz). Representative signals corresponding to the minor rotamer: δ 7.89 (1H, br s), 7.35 (1H, d, J = 8.5 Hz), 5.60 (1H, d, J = 8.0 Hz), 4.92 (1H, dd, J = 13.5, 6.5 Hz), 4.64 (1H, d, J = 9.0 Hz), 3.09–3.08 (1H, m), 2.66 (1H, dd, J = 15.0, 4.5 Hz), 2.14 (3H, s), 1.90–1.82 (1H, m). 182–185°C. ¹³C NMR (100 MHz, CDCl₃), signals corresponding to the major rotamer: δ 170.1, 156.5, 136.9, 133.2, 121.3, 118.6, 109.2, 108.0, 95.1, 55.9, 51.3, 45.4, 41.5, 22.2, 22.2, 22.1, 22.0, 11.3, 11.0. IR (CH₂Cl₂ film): 3279 (w), 2963 (m), 2878 (w), 1624 (s), 1439 (s), 1229 (m), 1154 (s), 1032 (w). LRMS (CI): 314.3 (80%) [M]⁺, 314.9 (100%) [M+H]⁺.

(3) Recycling of catalyst **1f**.

The acyl-Pictet-Spengler reaction of tryptamine and 2-ethylbutanal to yield **3a** was performed on 0.50 mmol scale according to method A, using 5 mol% **1f** (13.5 mg). Evaporation and chromatography on silica (12 x 2 cm, eluting with 20% ethyl acetate in dichloromethane, 5 mL fraction volumes) yielded recovered **1f** in fractions 5–8 (13.5 mg, quant.) and **3a** in fractions 14–25 (103 mg, 72% yield, 93% *ee*). Recovered **1f** was transferred as a diethyl ether solution (2.0 mL with two 1.0 mL rinses) to a solution of **2** (0.50 mmol, prepared according to method A) in diethyl ether (6.0 mL). Acyl-Pictet-Spengler reaction, evaporation, and chromatography as described above yielded recovered **1f** (13.2 mg, 98% recovery), and **3a** (104 mg, 73% yield, 93% *ee*).

(4) Preparation of racemic samples for HPLC analysis.

To a solution of imine (0.10 mmol, prepared as described above) in dichloromethane (2.0 mL) at -78°C were added sequentially 2,6-lutidine (17.4 μ L, 0.15 mmol, 1.5 equiv.), and acetyl chloride (10.7 μ L, 0.15 mmol, 1.5 equiv.). The mixture was allowed to warm slowly to 4°C, then loaded directly onto a silica gel column and purified by chromatography as described above.

(5) General procedure for reductive deacetylation of products **3b and **3d**.⁵**

1-Isopropyl-2,3,4,9-tetrahydro-1*H*- β -carboline (**4b**):

A solution of diisopropylamine (101 μL , 0.72 mmol, 7.2 equiv.) in THF (0.70 mL) was cooled to -78°C . *n*-Butyllithium (321 μL , 2.15M in hexanes, 0.69 mmol, 6.9 equiv.) was added dropwise by syringe. The resulting solution was stirred at -78°C for 10 minutes, then warmed to 0°C and stirred for 10 minutes. Borane-ammonia complex (24 mg, 90% pure, 0.70 mmol, 7.0 equiv.) was added as a solid, and the suspension stirred at 0°C for 15 minutes, then warmed to 23°C and stirred for 10 minutes. After cooling to 0°C , **3b** (25.6 mg, 0.10 mmol) was added as a solid. The suspension was stirred at 0°C for 2 minutes, then warmed to 60°C over 30 minutes and stirred for 6 hours. The resulting suspension was cooled to 0°C and quenched by dropwise addition of 3M aqueous hydrochloric acid (1.7 mL), then stirred for 30 minutes. The pH of the solution was adjusted to 10 by addition of saturated aqueous sodium bicarbonate. The mixture was extracted five times with ethyl acetate (total volume 50 mL), and the combined organic extracts were dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica (10% methanol in dichloromethane), yielding the title compound as a white solid (13 mg, 0.061 mmol, 61%). $[\alpha]_D = -114^\circ$ ($c = 0.65$, methanol). [lit⁶: -65° ($c = 0.5$, methanol)]. The enantiomeric excess was determined to be 85% by acetylation as described in general procedure 5, and analysis by HPLC as **3b**.

¹H NMR (400 MHz, CDCl_3): δ 7.90 (1H, br s), 7.49 (1H, d, $J = 7.6$ Hz), 7.33 (1H, d, $J = 8.0$ Hz), 7.16 (ddd, $J = 7.6, 7.6, 1.2$ Hz), 7.11 (ddd, $J = 7.6, 7.6, 1.1, 1.2$ Hz), 4.12–4.11 (1H, m), 3.64 (1H, br s), 3.49–3.44 (1H, m), 3.09–3.02 (1H, m), 2.88–2.73 (2H, m), 2.28–2.20 (1H, m), 1.17 (3H, d, $J = 6.8$ Hz), 0.94 (3H, d, $J = 6.8$ Hz). ¹³C NMR (100 MHz, CDCl_3): δ 136.0, 134.3, 121.9, 119.7, 118.3, 111.0, 110.1, 58.4, 43.2, 31.8, 22.2, 19.7, 17.4. IR (cm^{-1} , CDCl_3 film): 3408 (w), 3183 (br), 3054 (m), 2963 (s), 2853 (m), 1454 (s), 1302 (s), 902 (s). LRMS (CI): 214.8 (5%) $[\text{M}+\text{H}]^+$, 213.2 (10%) $[\text{M}-\text{H}]^+$, 186.3 (100%) $[\text{M}-\text{C}_2\text{H}_4]^+$.

1-Isobutyl-2,3,4,9-tetrahydro-1*H*- β -carboline:

The general procedure described above was performed using 0.10 mmol **3d** (27 mg). After a reaction time of 6.5 hours at 60°C , the workup described above was followed, with the following modification: after adjusting to pH 10, the mixture was extracted three times with dichloromethane (total volume 25 mL), then twice with ethyl acetate (total volume 25 mL). After chromatography on silica (5% to 10% methanol in dichloromethane) the product was obtained as an oil that solidified upon refrigeration (17 mg, 0.074 mmol, 74%). The enantiomeric excess was determined to be 93% by acetylation according to general procedure 5, and HPLC analysis as **3d**. $[\alpha]_D = -65^\circ$ ($c =$

⁵ Myers, A. G.; Yang, B. H.; Chen, H.; McKinsty, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

⁶ Zhang, X.; Jiang, W.; Sui, Z. *J. Org. Chem.* **2003**, *68*, 4523–4526.

0.52, methanol). [lit⁷: –76.9° (c = 1.1, methanol)]. Characterization data were in good agreement with literature values.⁷

(6) Acetylation of tetrahydro-1*H*- Δ^1 -carbolines **4b and **4d** for HPLC analysis:**

A solution of 1-isopropyl-2,3,4,9-tetrahydro-1*H*- Δ^1 -carboline (6.5 mg, 0.030 mmol) in dichloromethane (0.50 mL) was cooled to 0°C. Diisopropylethylamine (26 μ L, 0.15 mmol, 5.0 equiv.) and acetyl chloride (10.7 μ L, 0.15 mmol, 5.0 equiv.), were added sequentially by syringe. The solution was stirred for 5 minutes at 0°C, then warmed to 23°C and stirred for 5 hours. The resulting mixture was concentrated, and the residue purified by passage through a short plug of silica, eluting with 10% ethyl acetate in dichloromethane, yielding **3b** as a white solid.

⁷ Pellegrini, C.; Weber, M.; Borschberg, H-J. *Helv. Chim. Acta* **1996**, 79, 151–168.

Appendix I: Methods for the preparation of enantioenriched tetrahydroisoquinolines and tetrahydro- β -carboline

A. Methods for the preparation of enantioenriched 1-substituted tetrahydroisoquinolines.

1. Enantioselective catalytic reduction of dihydroisoquinolines:

- a) Kagan, H. B.; Langlois, N.; Kang, T. P. *J. Organomet. Chem.* **1975**, 90, 353–365.
- b) Achiwa, K. *Heterocycles* **1977**, 8, 247.
- c) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, 108, 7117–7119.
- d) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, 114, 7562–7564.
- e) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, 116, 8952–8965.
- f) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, 118, 4916–4917.
- g) Morimoto, T.; Suzuki, N.; Achiwa, K. *Heterocycles* **1996**, 43, 2557–2560.
- h) Kang, J.; Kim, J. B.; Cho, K. H.; Cho, B. T. *Tetrahedron: Asymm.* **1997**, 8, 657–660.
- i) Morimoto, T.; Suzuki, N.; Achiwa, K. *Tetrahedron: Asymm.* **1998**, 9, 183–187.
- j) Mao, J.; Baker, D. C. *Organic Lett.* **1999**, 1, 841–843.
- k) Tietze, L. F.; Zhou, Y.; Töpken, E. *Eur. J. Org. Chem.* **2000**, 2247–2252.

2. Enantioselective reduction of dihydroisoquinolines with stoichiometric quantities of chiral reducing agent:

- a) Yamada, K.; Takeda, M.; Iwakuma, T. *Tetrahedron Lett.* **1981**, 22, 3869–3872.
- b) Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc., Perkin Trans.* **1983**, 265–270.
- c) Nakagawa, M.; Kawate, T.; Kakikawa, T.; Yamada, H.; Matsui, T.; Hino, T. *Tetrahedron* **1993**, 49, 1739–1748.
- d) Hajipour, A. R.; Hantehzadeh, M. *J. Org. Chem.* **64**, 8475–8478.

3. Diastereoselective alkylation of metalated tetrahydroisoquinolines bearing chiral *N*-protecting groups:

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Chrzanowaska, M.; Sokolowska, M. *Tetrahedron: Asymm.* **2001**, 12, 1435–1440.

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Ito, K.; Akashi, S. Saito, B. Katsuki, T. *Synlett* **2003**, 12, 1809–1812.

B. Methods for the preparation of enantioenriched 1-substituted tetrahydro- α -carboline.

1. Enantioselective catalytic reduction of dihydro- α -carboline:

See part A, ref. 1f, 1k.

2. Enantioselective reduction of dihydro- α -carboline with stoichiometric quantities of chiral reducing agent:

See part A, ref. 2a, 2c, 2d.

3. Diastereoselective alkylation of metalated tetrahydro- α -carboline bearing chiral *N*-protecting groups:

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For reviews:

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6. Diastereoselective Pictet-Spengler reaction of tryptamines with chiral aldehydes:

See part A, ref. 5c.

7. Enantioselective Pictet-Spengler reaction of *N*-hydroxytryptamine mediated by chiral boron reagents:

- a) Kawate, T.; Yamada, H.; Soe, T.; Nakagawa, M. *Tetrahedron: Asymm.* **1996**, *7*, 1249–1252.
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8. Diastereoselective reduction of chiral dihydro- α -carbolinium ions:

Arazny, Z.; Czarnocki, Z.; Wojtasiewicz, K.; Maurin, J. K. *Tetrahedron: Asymm.* **2000**, *11*, 2793–2800.

9. Diastereoselective addition of organometallics to chiral α -carbolinium ions:

Itoh, T.; Matsuya, Y.; Enomoto, Y.; Ohsawa, A. *Tetrahedron* **2001**, *57*, 7277–7289.

10. Enantioselective, catalytic addition of ketones to dihydro- α -carboline:

Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Organic Lett.* **2003**, *5*, 4301–4304

The chromatogram displays a baseline with two prominent peaks. The first peak is at approximately 10.5 minutes with a height of about 110 mV. The second peak is at approximately 13.5 minutes with a height of about 140 mV. A red line is drawn across the baseline at approximately 5 mV, and vertical red lines are placed at the retention times of the two peaks.

Retention Time	Area	Area Percent
10.633	3371652	50.015
13.058	3369623	49.985
Totals	6741275	100.000

Retention Time		Area	Area Percent
9.917		638234	3.636
12.058		16915789	96.364
Totals		17554023	100.000

Results

85% *ee*

Results

S - 18

Chiral HPLC: L-leucine, 10% ethanol/hexanes, 1.2 mL/min

Racemic

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
10.425	12498447	50.177
12.367	12410131	49.823
Totals	24908578	100.000

95% ee (98% pure)

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
9.783	392764	2.413
10.417	379435	2.331
12.250	15504563	95.256
Totals	16276762	100.000

Chiral HPLC: L-leucine, 10% ethanol/hexanes, 1.2 mL/min

Racemic

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
11.817	4621209	49.761
15.317	4665569	50.239
Totals	9286778	100.000

93% ee

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
11.892	202959	3.162
15.317	6215366	96.838
Totals	6418325	100.000

Chiral HPLC: Chiralpak AD, 7% isopropanol/hexanes, 1.0 mL/min

Racemic

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
10.508	12058841	50.160
14.817	11981926	49.840
Totals	24040767	100.000

90% ee

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
10.417	7469982	94.841
14.683	406369	5.159
Totals	7876351	100.000

Chiral HPLC: (S,S)-Whelk-01, 10% ethanol/hexanes, 1.2 mL/min

Racemic

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
19.517	6092684	49.961
23.842	6102213	50.039
Totals	12194897	100.000

93% ee

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
19.142	762753	3.564
23.075	20638387	96.436
Totals	21401140	100.000

Chiral HPLC: (S,S)-Whelk-01, 10% ethanol/hexanes, 1.2 mL/min

Racemic

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
17.733	4661258	49.628
23.508	4731068	50.372
Totals	9392326	100.000

86% ee

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
18.000	1033637	6.889
23.625	13970415	93.111
Totals	15004052	100.000