A New Strategy for the Synthesis of Tetrahydroisoquinoline Alkaloids

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Supporting Information

General Experimental

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet FT-IR spectrophotometer neat unless otherwise indicated. ¹H NMR spectra were recorded on either a General Electric QE-300 spectrometer at 300 MHz or a Varian spectrometer at 500 MHz in the indicated solvent and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ¹³C NMR spectra were recorded on a General Electric QE-300 at 75 MHz or a Varian spectrometer at 126 MHz in the solvent indicated and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. Mass spectra were obtained on a VG ZAB2E or a Finnigan TSQ70. Routine monitoring of reactions was performed using Merck 60 F₂₅₄ silica gel, aluminum-backed TLC plates. The optical purities **12** and **27** were determined by HPLC analysis using an analytical chiral column (Daicel Chiralcel OD; eluent, hexane–isopropyl alcohol; flow rate, 1.0 mL/min; UV detector, 254 nm) with a Beckman Coulter System Gold 126P solvent module and Beckman Coulter System Gold 168 detector.

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Solvents and commercial reagents were purified in accordance with Perrin and Armarego or used without further purification.

Experimental Section

3-Benzyloxymethylisoquinoline **11**

To a solution of **10**¹ (3.0 g, 10.45 mmol) and propargyl benzyl ether² (1.83 g, 12.54 mmol) in triethylamine (42 mL) was added PdCl₂(Ph₃)₂ (0.147 g, 2 mol %) followed by CuI (20 mg, 1 mol %) under an atmosphere of argon at 25 °C. The mixture was warmed to 55 °C and stirred for 6 hours. The mixture was allowed to cool to 25 °C and filtered through Celite to remove the yellow precipitate which was washed with triethylamine. The filtrate was concentrated under reduced pressure, the resulting residue was dissolved in DMF (105 mL), and CuI (0.200 g, 10 mol %) was added under an atmosphere of argon at 25 °C. The mixture was heated to 100 °C and stirred for 9 h. The dark brown solution was allowed to cool to 25 °C and diluted with Et₂O (500 mL), then washed with NH₄Cl (400 mL), dried (Na₂SO₄), and filtered. The solvent was removed under reduced pressure to give a black oil, which was purified by flash column chromatography (SiO₂, 20% to 50% EtOAc in hexanes) to afford **11** as a pale yellow oil (2.2 g, 84% yield) R_f = 0.60 (100% EtOAc); IR (thin film) 3059, 3030, 2857, 1630, 1592, 1496, 1454, 1359, 1127, 1098, 747 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.24 (1 H, s), 7.95 (1 H, d, *J* = 8.1), 7.70-7.65 (2 H, m), 7.60-7.55 (2 H, m), 7.47-7.30 (5 H, m), 4.88 (2 H, s), 4.75 (2 H, s) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 152.3, 151.9, 138.3, 136.5, 130.6, 128.6, 128.0, 127.9, 127.7, 127.1, 126.8, 117.6, 73.2, 73.1 ppm; HRMS calcd. for C₁₇H₁₆NO (MH⁺) 250.1232 Da. Found 250.1239 Da.

3-Benzyloxymethyl-1-phenylsulfanylmethyl-1*H*-isoquinoline-2-carboxylic acid methyl ester **12**

A solution of *n*-butyllithium (1.95 M in hexanes, 3.25 mL, 6.46 mmol) was added dropwise within 10 min. to a degassed solution of thioanisole (0.756 mL, 6.46 mmol) and (–)-sparteine (1.48 mL, 6.46 mmol) in anhydrous THF (8.05 mL) at 0 °C under an atmosphere of argon. The cloudy, yellow solution was allowed to warm to 25 °C and was stirred for 1 h. The solution of phenylthiomethyl lithium and (–)-sparteine was added dropwise within 10 min. to a degassed solution of **11** (1.16 g, 4.61 mmol) in toluene (37 mL) at –78 °C under an atmosphere of argon. The resulting orange solution was allowed to warm to 25 °C over 15 min. The solution became black in color and methylchloroformate (1.1 mL, 13.83 mmol) was added. Upon addition the solution became pale orange. The solution was cooled to 0 °C, treated with 30 mL of saturated aqueous NaHCO₃, and then extracted with EtOAc (2 x 75 mL). The organic extracts were combined, washed with saturated aqueous NaCl (30 mL), dried (Na₂SO₄), filtered, and the solvent was removed under vacuum. The crude yellow oil was purified by flash column chromatography (SiO₂, 10%-20% EtOAc in hexanes) to provide **12** as a colorless oil (1.50 g, 75% yield). *R*_f = 0.23 (20% EtOAc in hexanes); IR (thin film) 3028, 2928, 2854, 1716, 1638, 1481, 1454, 1439, 1401, 1321, 1264, 1113, 738, 696 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.11 (14 H, m), 6.44 (1 H, s), X of ABX δ = 5.49 (1 H, bs), 4.60 (2 H, s), 4.51 (2 H, bs), 3.70 (3 H, s), A of ABX δ = 3.25 (1 H, dd, *J*_{AX} = 8.13 Hz, *J*_{AB} = 13.38 Hz), B of ABX δ = 3.04 (1 H, dd, *J*_{BX} = 6.70 Hz, *J*_{AB} = 13.68 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 154.0, 138.0, 135.9, 134.7, 132.7, 129.9, 129.0, 128.9, 128.8, 128.2, 128.0, 127.5, 127.0, 126.1, 126.0, 125.0, 113.8, 72.7, 72.3, 69.9, 55.5, 52.9, 36.4 ppm; HRMS calcd. for C₂₆H₂₆NO₃S (MH⁺) 432.1633 Da. Found 432.1619 Da. HPLC conditions: loaded 15 µl of 0.50 mg/mL sample in 1% isopropanol/hexanes, gradient 2%-5% over 15 min., enantiomers elute at 11.77 min. and 13.85 min. in a ratio of 1:1.

3-Benzylloxymethyl-1-phenylsulfanylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester 13

To a solution of **12** (1.50 g, 3.48 mmol) and triethylsilane (5.60 mL, 34.8 mmol) in CH₂Cl₂ (35.0 mL) at –20 °C was added precooled (–20 °C) trifluoroacetic acid (2.70 mL, 34.8 mmol) in one portion. The solution was allowed to warm to 25 °C and was stirred for 3 h at which point starting material could not be detected by TLC. The solution was quenched by pouring over ice, basified with 10% aqueous NaOH, then extracted with CH₂Cl₂ (2 x 50 mL). The combined extracts were washed with saturated aqueous NaCl (20 mL), dried (Na₂SO₄), filtered, and the solvent was removed under vacuum. The crude oil was purified by flash column chromatography (SiO₂, 10%-20% EtOAc in hexanes) to afford **13** as a colorless oil (1.47 g, 97% yield). *R*_f = 0.18 (20% EtOAc in hexanes); IR (thin film) 3028, 2951, 2855, 1697, 1442, 1390, 1325, 1105, 1026, 738, 697 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.55-7.25 (10 H, m), 7.22-7.18 (4 H, m), 5.55 (0.4 H, bs), 5.25 (0.6 H, bs), 4.57 (2 H, s), 4.38-4.18 (1 H, m), 3.86-3.62 (5 H, m), 3.37 (1 H, m), 3.22-3.13 (2 H, m), 3.01 (1 H, dd, *J*_{AX} = 7.15 Hz, *J*_{AB} = 16.17 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 156.8, 156.0, 138.1, 136.6, 133.4, 128.7, 128.2, 127.5, 126.9, 126.0, 125.7, 73.2, 73.1, 73.0, 72.3, 71.1, 55.1, 54.7, 52.6, 52.4, 51.8, 51.5, 39.3, 39.0, 30.2, 29.6 ppm; HRMS calcd. for C₂₆H₂₈NO₃S (MH⁺) 434.1790 Da. Found 434.1790 Da.

12-Phenylsulfanyl-11-oxa-13-aza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylic acid methyl ester **14**

To a solution of **13** (51 mg, 0.117 mmol) in chlorobenzene (0.500 mL) under an atmosphere of argon at 0 °C was added *N*-chlorosuccinimide (16 mg, 0.117 mmol). The mixture was allowed to warm to 25 °C and was stirred for 2 h, then filtered through a pad of glass wool into a dry flask under argon and washed with chlorobenzene (0.500 mL). The solution was cooled to 0 °C and SnCl₄ (3.0 M in CH₂Cl₂, 8 µL, 20 mol %) was added dropwise. The resulting yellow solution was stirred for 15 min. at 0 °C, quenched with saturated aqueous NaHCO₃ (5 mL), and extracted with EtOAc (2 x 10 mL). The combined extracts were dried (Na₂SO₄), filtered, and the solvent was removed under vacuum. The crude

residue was purified by flash column chromatography (SiO₂, 5%-10% EtOAc in hexanes) to afford **14** as a colorless oil which was crystallized from methanol to yield a white solid (30 mg, 76% yield). mp = 131-133 °C; R_f = 0.19 (25% EtOAc in hexanes); IR (thin film) 2953, 1701, 1449, 1409, 1339, 1320, 1310, 1117, 1104, 1065, 742, 692 cm⁻¹; ¹H NMR (500 MHz, toluene-*d*₈, 373 K) δ 8.61 (2 H, d, *J* = 7.23 Hz), 7.01-6.91 (4 H, m), 6.86 (1 H, t, *J* = 7.50 Hz), 6.82 (1 H, d, *J* = 7.64 Hz), 6.70 (1 H, d, *J* = 7.53 Hz), 5.32 (1 H, bs), 5.23 (1 H, s), 4.56 (1 H, dd, *J* = 3.13, 11.41 Hz), 4.25 (1 H, bs), 3.49 (3 H, s), 3.28 (1 H, d, *J* = 11.40 Hz), 3.05 (1 H, dd, *J* = 7.50, 17.27 Hz), 2.44 (1 H, d, *J* = 17.28 Hz); ¹³C NMR (126 MHz, toluene-*d*₈, 373 K) δ 155.5, 137.8, 136.4, 136.3, 131.7, 129.2, 128.9, 128.1, 128.0, 127.1, 126.7, 125.6, 125.4, 88.9, 65.7, 57.5, 52.5, 47.9, 32.0 ppm; HRMS calcd. for C₁₉H₂₀NO₃S (MH⁺) 342.1164 Da. Found 342.1159 Da.

3-Hydroxymethyl-1-phenylsulfanylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester 15

To a solution of **13** (1.05 g, 2.42 mmol) in CH₂Cl₂ (24.0 mL) under an atmosphere of argon at -78 °C was added BCl₃ (1.0 M in CH₂Cl₂, 4.84 mL, 4.84 mmol) dropwise. Upon complete addition the solution was allowed to warm to 0 °C and was stirred for 30 min., then treated with 3 mL methanol, diluted with saturated aqueous NaHCO₃ (20 mL), and extracted with CH₂Cl₂ (2 x 50 mL). The organic extracts were combined, dried (Na₂SO₄), filtered, and the solvent was removed under vacuum. The crude residue was purified by flash column chromatography (SiO₂, 20%-40% EtOAc in hexanes) to afford **15** as a colorless oil (0.806 g, 95% yield). R_f = 0.19 (50% EtOAc in hexanes); IR (thin film) 3446, 2923, 2850, 1684, 1445, 1393, 1329, 1264, 1073, 1026, 739, 690 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.41 (2 H, d, *J* = 10.2 Hz), 7.37-7.20 (7 H, m), 5.62 (0.4 H, bs), 5.34 (0.6 H, bs), 4.21-4.05 (2 H, m), 3.66 (4 H, bs), 3.43-3.02 (4 H, m), 2.98-2.90 (1 H, m) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 157.2, 136.1, 135.1, 133.6, 129.3, 128.8, 128.1, 127.8, 126.4, 126.3, 95.1, 65.7, 55.1, 52.8, 40.4, 29.2 ppm; HRMS calcd. for C₁₉H₂₂NO₃S (MH⁺) 344.1320 Da. Found 344.1317 Da.

3-Azidomethyl-1-phenylsulfanylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester 16

To a solution of **15** (0.790 g, 2.30 mmol) in THF (7.7 mL) at 0 °C under an atmosphere of argon was added triphenylphosphine (1.33 g, 5.06 mmol) and diethyl azodicarboxylate (0.797 mL, 5.06 mmol). After 2 min. a white precipitate formed and diphenylphosphoryl azide (1.09 mL, 5.06 mmol) was added. The mixture was allowed to warm to 25 °C and was stirred for 2 h, then concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 5% to 7% to 10% EtOAc in hexanes) to afford **16** as a colorless oil (0.694 g, 82% yield). *R*_f = 0.18 (20% EtOAc in hexanes); IR (thin film) 2952, 2103, 1698, 1481, 1441, 1388, 1326, 1289, 1248, 739, 690 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.39 (2 H, d, *J* = 7.61 Hz), 7.37-7.17 (7 H, m), 5.53 (0.4 H, bs), 5.24 (0.6 H, bs), 4.21-3.95 (2 H, m), 3.85-3.56 (4 H, m), 3.41 (1 H, dd, *J* = 6.77, 13.40 Hz), 3.20 (1 H, dd, *J* = 7.95, 13.44 Hz), 3.15-2.91 (2 H, m) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 156.6, 136.3, 133.0, 129.4, 129.1, 128.2, 127.9, 127.5, 126.7, 126.5, 126.3, 55.6, 54.1, 53.9, 53.3, 53.2, 53.0, 52.7, 48.1, 39.7, 30.6 ppm; HRMS calcd. For C₁₉H₂₁N₄O₂S (MH⁺) 369.1385 Da. Found 369.1380 Da.

12-Phenylsulfanyl-11,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6,11-tetraene-13-carboxylic acid methyl ester 17

To a solution of **16** (45 mg, 0.122 mmol) in chlorobenzene (0.610 mL) under an atmosphere of argon at 0 °C was added *N*-chlorosuccinimide (16 mg, 0.122 mmol). The mixture was allowed to warm to 25 °C and was stirred for 2 h, then filtered through a pad of glass wool into a dry flask under argon and washed with chlorobenzene (0.600 mL). The solution was cooled to 0 °C and SnCl₄ (3.0 M in CH₂Cl₂, 41 μL, 0.122 mmol) was added dropwise. The solution immediately became yellow, a precipitate formed, and the evolution of gas was observed. Upon complete addition no starting material could be detected by TLC. The

mixture was diluted with saturated aqueous NaHCO_3 until basic (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts were dried (Na_2SO_4), filtered, and the solvent was removed under vacuum. The crude residue was purified by flash column chromatography (SiO_2 , 10%-40% EtOAc in hexanes) to afford **17** as a yellow oil (22 mg, 49% yield). $R_f = 0.16$ (30% EtOAc in hexanes); IR (thin film) 2922, 1705, 1637, 1449, 1320, 1121, 741, 688 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.42-7.30 (5 H, m), 7.25-7.15 (4 H, m), 5.49 (0.4 H, bs), 5.33 (0.6 H, bs), 4.79 (0.4 H, m), 4.67 (0.6 H, m), 4.24-4.12 (1 H, m), 3.72 (3 H, s), 3.67 (1 H, d, $J = 18.11$ Hz), 3.41-3.33 (1 H, m), 2.71 (1 H, d, $J = 17.52$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 145.6, 134.8, 133.3, 129.5, 129.3, 129.2, 128.9, 127.8, 127.4, 126.1, 105.0, 56.6, 54.6, 53.1, 43.8, 33.9 ppm; HRMS calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$ (MH^+) 339.1167 Da. Found 339.1163 Da.

12-Oxo-11,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylic acid methyl ester 18

To a solution of **17** (22 mg, 0.060 mmol) in Et_2O (1.0 mL) was added 5% aqueous sodium hydrogen sulfate (2 mL) with vigorous stirring. After 5 min. the layers were separated and the aqueous layer was extracted with Et_2O (3 mL). The organic extracts were combined, washed with aqueous NaCl (1 mL), dried (Na_2SO_4), filtered, and the solvent was removed under vacuum. The crude oil was purified by flash column chromatography (SiO_2 , 100% EtOAc) to afford **18** as a colorless oil which was crystallized from EtOAc. (15 mg, >95% yield). mp = 211-213 $^\circ\text{C}$; $R_f = 0.17$ (100% EtOAc); IR (thin film) 3266, 2955, 1701, 1685, 1489, 1452, 1411, 1323, 1251, 1119, 746 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.39 (1 H, d, $J = 6.01$ Hz), 7.25-7.12 (3 H, m), 6.16-5.99 (1 H, m), 5.53-5.41 (1 H, m), 5.02-4.85 (1 H, m), 3.91-3.85 (1 H, m), 3.73 (3 H, s), 3.47 (1 H, dd, $J = 8.02$, 17.56 Hz), 3.23 (1 H, dd, $J = 2.57$, 11.89 Hz), 2.81 (1 H, d, $J = 17.67$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 169.0, 154.8, 132.2, 128.7, 128.0, 126.9, 126.4, 56.9, 52.9, 47.1, 42.4, 32.6 ppm; HRMS calcd. for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_3$ (MH^+) 247.1083 Da. Found 247.1082 Da.

(2-Benzyloxy-3,5-dimethoxy-4-methyl-phenyl)-methanol 22

To a stirred solution of **20**³ (7.31g, 43.5 mmol) and paraformaldehyde (1.96 g) in CH₂Cl₂ (89.0 mL) at 0 °C under an atmosphere of argon was added neat Et₂AlCl (6.27 mL, 50.0 mmol) dropwise within 15 min. The solution was stirred for 30 min. at 0 °C, and then at 25 °C for 21 h. The solution was quenched with 2 M HCl (120 mL) and quickly extracted with EtOAc (2 x 200 mL). The organic extracts were combined, washed with saturated aqueous NaCl (100 mL), dried (Na₂SO₄), filtered through Celite to remove trace precipitate, and the solvent was removed under vacuum to afford **21** as an acid sensitive yellow solid (8.6 g, 99% yield) which was shown to be free of impurities by spectrographic analysis and used immediately without further purification.

To a solution of **21** (8.6 g, 43.4 mmol) in acetone (217 mL) at 25 °C under an atmosphere of argon was added anhydrous K₂CO₃ (25.0 g, 178 mmol) and benzyl bromide (25.8 mL, 217 mmol). The mixture was heated at reflux for 4 h and then cooled to 25 °C, diluted with saturate aqueous NH₄Cl (400 mL), and extracted with EtOAc (2 x 400 mL). The combined extracts were dried (Na₂SO₄), filtered, and the solvent was removed under vacuum. The resulting brown oil was purified by flash column chromatography (SiO₂, 20% to 50% EtOAc in hexanes) to afford **22** as a burnt orange oil (11.2 g, 89% yield). *R*_f = 0.31 (40% EtOAc in hexanes); IR (thin film) 3416, 2936, 2873, 2837, 1606, 1586, 1484, 1455, 1410, 1375, 1328, 1223, 1129, 1089, 1026, 845, 755, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.46-7.35 (5 H, m), 6.63 (1 H, s), 5.01 (2 H, s), 4.55 (2 H, bs), 3.87 (3 H, s), 3.79 (3 H, s), 2.60 (1 H, bs), 2.20 (3 H, s) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 154.2, 151.6, 143.0, 137.3, 131.8, 128.4, 128.3, 128.2, 128.0, 120.0, 105.2, 75.2, 60.8, 60.3, 55.5, 8.7 ppm; HRMS calcd. for C₁₇H₂₁O₄ (MH⁺) 289.1440 Da. Found 289.1432 Da.

(2-Benzyloxy-6-iodo-3,5-dimethoxy-4-methyl-phenyl)-methanol 23

To a stirred suspension of **22** (3.60 g, 12.5 mmol) and silver trifluoroacetate (5.52 g, 25.0 mmol) at 0 °C under an atmosphere of argon in CHCl₃ (55 mL) was added I₂ (4.76 g, 18.8 mmol) as a solution in CHCl₃ (82 mL). The mixture was stirred for 1 h at 0 °C and then filtered through Celite and washed with CHCl₃. The organic solution was washed with 10% aqueous sodium thiosulfate (50 mL) and saturated aqueous NaCl (50 mL), dried (Na₂SO₄), filtered, and the solvent was removed under vacuum. The resulting yellow oil was purified by flash column chromatography (SiO₂, 10% to 25% EtOAc in hexanes) to afford **23** as a pale yellow oil (4.20 g, 82% yield). R_f = 0.46 (20% EtOAc in hexanes); IR (thin film) 3474, 2934, 2888, 2835, 1447, 1404, 1371, 1314, 1228, 1104, 1088, 1012, 965, 736, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.50-7.36 (5 H, m), 5.04 (2 H, s), 4.78 (2 H, d, *J* = 5.64 Hz), 3.86 (3 H, s), 3.76 (3 H, s), 2.31 (3 H, s) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 154.5, 152.5, 147.1, 136.8, 135.2, 128.5, 128.2, 126.1, 91.8, 76.0, 64.3, 60.3, 60.2, 10.6 ppm; HRMS calcd. for C₁₇H₁₉O₄I (M) 414.0328 Da. Found 414.0323 Da.

2-Benzyloxy-6-iodo-3,5-dimethoxy-4-methyl-benzaldehyde 24

To a stirred solution of **23** (12.9 g, 31.07 mmol) at 0 °C in CH₂Cl₂ (78.0 mL) was added pyridinium chlorochromate (20.1 g, 93.2 mmol) in small portions. The solution was allowed to warm to 25 °C and was stirred for 12 h. Silica gel was added to the mixture such that upon removal of the solvent under vacuum a fine brown powder was obtained, which was purified by flash column chromatography (SiO₂, 10% to 25% EtOAc in hexanes) to afford **24** as a pale yellow oil (12.8 g, 98% yield). R_f = 0.29 (20% EtOAc in hexanes); IR (thin film) 3031, 2935, 2870, 1699, 1445, 1392, 1362, 1304, 1255, 1238, 1105, 1017, 962, 748, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.05 (1 H, s), 7.49-7.35 (5 H, m), 5.05 (2 H, s), 3.87 (3 H, s), 3.78 (3 H, s), 2.36 (3 H, s) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 191.9, 155.2, 153.1, 150.6, 136.1, 131.9, 129.1, 128.5, 128.3, 87.4, 76.7, 60.5, 60.3, 11.1 ppm; HRMS calcd. for C₁₇H₁₇O₄I (M) 412.0171 Da. Found 412.0165 Da.

8-Benzyloxy-3-benzyloxymethyl-5,7-dimethoxy-6-methyl-isoquinoline 26

To a solution of **24** (0.490 g, 1.19 mmol) in toluene (12.5 mL) under an atmosphere of argon was added 4Å molecular sieves (ca. 2 g) and *t*-butyl amine (0.375 mL, 3.57 mmole) at 25 °C. The mixture was stirred for 3 h and was then filtered through Celite, washed with toluene, and the solvent evaporated under vacuum to afford imine **25**, which was used without further purification.

To a degassed solution of **25** (0.58 g, 1.19 mmol) and progargyl benzyl ether² (0.183 g, 1.25 mmol) in triethylamine (6.0 mL) at 25 °C under argon was added Cul (0.283, 1.49 mmol) in small portions. The mixture was stirred for 24 h and a yellow precipitate formed. The mixture was diluted with triethylamine (8.0 mL), degassed, warmed to 100 °C, and stirred for 1 h. The mixture turned dark brown and the precipitate dissolved. The solution was cooled to 25 °C, a black precipitate formed, and the mixture was filtered, washed with triethylamine, and the solvent was removed under reduced pressure to give a black oil, which was purified by flash column chromatography (SiO₂, 10% to 20% EtOAc in hexanes with 1% triethylamine) to afford **26** as a yellow oil (0.465 g, 91% yield) *R*_f = 0.43 (40% EtOAc in hexanes); IR (thin film) 2936, 2857, 1589, 1454, 1394, 1359, 1317, 1079, 1004, 735, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.45 (1 H, s), 7.91 (1 H, s), 7.54 (2 H, d, *J* = 8.01 Hz), 7.46-7.31 (8 H, m), 5.18 (2 H, s), 4.84 (2 H, s), 4.73 (2 H, s), 4.01 (3 H, s), 3.90 (3 H, s), 2.43 (3 H, s) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 150.8, 149.2, 148.9, 147.0, 143.0, 138.0, 136.7, 128.8, 128.4, 128.3, 128.2, 127.7, 127.3, 126.7, 122.3, 111.6, 75.8, 73.0, 72.6, 61.4, 60.6, 10.0 ppm; HRMS calcd. for C₂₇H₂₈NO₄ (MH⁺) 430.2018 Da. Found 430.2027 Da.

8-Benzyloxy-3-benzyloxymethyl-5,7-dimethoxy-6-methyl-1-phenylsulfanylmethyl-1*H*-isoquinoline-2-carboxylic acid methyl ester 27

A solution of *n*-butyllithium (2.10 M in hexanes, 0.551 mL, 1.16 mmol) was added dropwise within 10 min., to a degassed solution of thioanisole (0.136 mL, 1.16 mmol) and (–)-sparteine (0.266 mL, 1.16 mmol) in anhydrous THF (1.45 mL) at 0

°C under an atmosphere of argon. The yellow solution was allowed to warm to 25 °C and was stirred for 1 h. The solution of phenylthiomethyl lithium and (–)-sparteine was added dropwise within 10 min. to a degassed solution of **26** (0.166 g, 0.386 mmol) in toluene (3.10 mL) at –78 °C under an atmosphere of argon. The resulting orange solution was allowed to warm to 25 °C over 15 min. at which point the solution became black in color. To the reaction was added methylchloroformate (0.149 mL, 1.93 mmol) at 25 °C and the solution became pale orange. The solution was cooled to 0 °C, quenched with 10 mL of saturated aqueous NaHCO₃, and then extracted with EtOAc (2 x 20 mL). The organic extracts were combined, washed with saturated aqueous NaCl (10 mL), dried (Na₂SO₄), filtered, and the solvent was removed under vacuum. The crude yellow oil was purified by flash column chromatography (SiO₂, 10%-20% EtOAc in hexanes) to provide **27** as a colorless oil (0.195 g, 83% yield). R_f = 0.26 (20% EtOAc in hexanes); IR (thin film) 2951, 2936, 2857, 1715, 1463, 1454, 1439, 1414, 1327, 1295, 1122, 1070, 1027, 1005 737, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.29 (12 H, m), 7.10-7.06 (3 H, m), 6.67 (1 H, s), 5.91 (1 H, bs), 5.15 (1 H, d, *J* = 10.75 Hz), 4.90 (1 H, d, *J* = 10.82 Hz), 4.63-4.48 (4 H, m), 3.86 (3 H, s), 3.71 (3 H, s), 3.58 (3 H, bs), 3.12-2.98 (2 H, m), 2.22 (3 H, s) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 150.1, 143.4, 138.1, 137.0, 136.4, 128.6, 128.4, 128.2, 128.0, 127.9, 127.5, 127.4, 125.3, 125.1, 119.7, 119.7, 75.3, 72.3, 70.0, 61.2, 60.3, 52.6, 50.1, 34.9, 9.1 ; HRMS calcd. for C₃₆H₃₈NO₆S (MH⁺) 612.2120 Da. Found 612.2413 Da. HPLC conditions: loaded 12 µl of 0.53 mg/mL sample in 1% isopropanol/hexanes, gradient 2%-8% over 15 min., enantiomers elute at 12.43 min. and 13.12 min. in a ratio of 1:1.

8-Benzyloxy-3-benzyloxymethyl-5,7-dimethoxy-6-methyl-1-phenylsulfanylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester 28

8-Benzyloxy-5,7-dimethoxy-3,6-dimethyl-1-phenylsulfanylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester 28b

To a solution of **27** (107 mg, 0.175 mmol), triethylsilane (0.280 mL, 1.75 mmol), and benzyl alcohol (0.271 mL, 2.63 mmol) at $-20\text{ }^{\circ}\text{C}$ was added precooled ($-20\text{ }^{\circ}\text{C}$) trifluoroacetic acid (0.338 mL, 4.37 mmol) in one portion. The solution was allowed to warm to $0\text{ }^{\circ}\text{C}$ and was stirred for 16 h. The reaction was then quenched with 10 mL of saturated aqueous NaHCO_3 (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts were dried (Na_2SO_4), filtered, and the solvent was removed under vacuum. The resulting crude oil was purified by flash column chromatography (SiO_2 , 5% to 7% to 10% EtOAc in hexanes) to afford **28b** as a colorless oil (20 mg, 22% yield) and **28** as a colorless oil (76 mg, 71% yield). **28**: $R_f = 0.21$ (20% EtOAc in hexanes); IR (thin film), 2950, 2935, 2856, 1697, 1453, 1442, 1412, 1314, 1256, 1115, 1082, 1061, 1008, 738, 697 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.47-7.24 (12 H, m), 7.04 (3 H, bs), 6.08 (0.4 H, bs), 5.78 (0.6 H, bs), 5.12-4.98 (1 H, s), 4.91-4.78 (1 H, m), 4.66 (1 H, d, $J = 12.08\text{ Hz}$), 4.57 (1 H, d, $J = 12.04\text{ Hz}$), 4.23-4.08 (1 H, m), 3.85 (4 H, bs), 3.77 (1 H, dd, $J = 3.03, 9.28\text{ Hz}$), 3.69 (3 H, s), 3.55 (3 H, bs), 3.35-3.11 (3 H, m), 2.91-2.85 (1 H, m), 2.23 (3 H, s) ppm; HRMS calcd. for $\text{C}_{36}\text{H}_{40}\text{NO}_6\text{S}$ (MH^+) 614.2576 Da. Found 614.2565 Da. **28b**: $R_f = 0.44$ (40% EtOAc in hexanes); IR (thin film) 2988, 2952, 2935, 1697, 1452, 1412, 1313, 1254, 1116, 1083, 1061, 738, 698 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.47-7.28 (7 H, m), 7.13-7.08 (3 H, m), 6.07 (0.4 H, bs), 5.80 (0.6 H, bs), 5.07 (1 H, bs), 4.86 (1 H, bs), 4.13-4.01 (1 H, m), 3.85 (3 H, s), 3.69 (3 H, s), 3.67-3.43 (3 H, m), 3.31 (1 H, dd, $J = 7.28, 16.14\text{ Hz}$), 3.26-3.06 (2 H, m), 2.51 (1 H, dd, $J = 10.35, 16.10\text{ Hz}$), 2.23 (3 H, s), 1.47 (3 H, d, $J = 6.23\text{ Hz}$); ^{13}C NMR (75 MHz, CDCl_3) δ 151.6, 150.0, 144.0, 137.2, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.7, 127.6, 125.5, 125.4, 124.6, 122.5, 95.1, 75.2, 60.6, 60.3, 52.2, 48.0, 28.1, 9.2 ppm; HRMS calcd. for $\text{C}_{29}\text{H}_{34}\text{NO}_5\text{S}$ (MH^+) 508.2158 Da. Found 508.2165 Da.

8-Benzyloxy-3-hydroxymethyl-5,7-dimethoxy-6-methyl-1-phenylsulfanylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester 29

To a solution of **28** (0.133 g, 0.217 mmol) in CH₂Cl₂ (1.0 mL) at –40 °C under an atmosphere of argon was added BCl₃ (1.0 M in CH₂Cl₂, 0.434 mL, 0.434 mmol) dropwise. Upon complete addition the solution was stirred for 2 h then treated with 0.5 mL methanol, diluted with saturated aqueous NaHCO₃ (5mL), and extracted with CH₂Cl₂ (2 x 10 mL). The extracts combined extracts were dried (Na₂SO₄), filtered, and the solvent was removed under vacuum. The crude residue was purified by flash column chromatography (SiO₂, 20%-50% EtOAc in hexanes) to afford **29** as a colorless oil (0.100 g, 88% yield). R_f = 0.27 (40% EtOAc in hexanes); IR (thin film) 3448, 2936, 1697, 1412, 1396, 1349, 1315, 1257, 1115, 1056, 1006, 738, 697 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.52-7.28 (7 H, m), 7.12 (3 H, bs), 6.14 (0.4 H, bs), 5.86 (0.6 H, bs), 5.15-5.08 (1 H, m), 4.86-4.79 (1 H, m), 4.20 (1 H, dd, *J* = 2.97, 11.78 Hz), 4.06-3.98 (1 H, m), 3.86 (4 H, s), 3.75-3.70 (4 H, m), 3.68-3.46 (3 H, m), 3.27-2.82 (4 H, m), 2.24 (3 H, s) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 157.4, 151.9, 150.0, 143.7, 137.1, 135.0, 128.8, 128.6, 128.4, 128.1, 128.0, 125.7, 125.0, 124.9, 122.6, 95.0, 75.3, 65.3, 60.7, 60.3, 55.4, 52.3, 48.5, 38.3, 22.2, 9.2 ppm; HRMS calcd. for C₂₉H₃₄NO₆S (MH⁺) 524.2107 Da. Found 524.2109 Da.

3-Azidomethyl-8-benzyloxy-5,7-dimethoxy-6-methyl-1-phenylsulfanylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester 30

To a solution of **29** (0.100 g, 0.191 mmol) in THF (0.640 mL) at 0 °C under an atmosphere of argon was added triphenylphosphine (0.110 g, 0.420 mmol) and diisopropyl azodicarboxylate (83 μL, 0.420 mmol). After 2 min. a white precipitate formed and diphenylphosphoryl azide (91 μL, 0.420 mmol) was added. The mixture was allowed to warm to 25 °C and was stirred for 1.5 h. The mixture was treated with 0.400 mL of water and concentrated to a crude residue that was purified by flash column chromatography (SiO₂, 5% to 10% EtOAc in hexanes) to afford **30** as a colorless oil (89 mg, 85% yield). R_f = 0.46 (20% EtOAc in hexanes); IR (thin film) 3060, 2951, 2104, 1698, 1443, 1412, 1392, 1340, 1314,

1256, 1192, 1116, 1062, 1006, 737, 698 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.52-7.28 (7 H, m), 7.09 (3 H, bs), 6.10 (0.4 H, bs), 5.82 (0.6 H, bs), 5.15-4.98 (1 H, m), 4.78-4.91 (1 H, m), 4.04 (1 H, m), 3.86 (4 H, s), 3.82-3.70 (4 H, m), 3.50 (3 H, bs), 3.38-3.09 (3 H, m), 2.76-2.67 (1 H, m), 2.24 (3 H, s) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 156.4, 151.8, 150.1, 144.0, 137.1, 136.3, 129.2, 129.1, 129.7, 128.9, 128.7, 128.5, 128.3, 128.0, 127.9, 125.2, 124.9, 121.6, 75.2, 60.8, 60.4, 54.2, 52.5, 52.2, 48.8, 38.2, 23.3, 9.3 ppm; HRMS calcd. for $\text{C}_{29}\text{H}_{33}\text{N}_4\text{O}_5\text{S}$ (MH^+) 549.2172 Da. Found 549.2478 Da.

3-Benzyl-4,6-dimethoxy-5-methyl-12-oxo-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-13-carboxylic acid methyl ester **32**

To a solution of **30** (33 mg, 0.060 mmol) in chlorobenzene (0.300 mL) at 0 °C under an atmosphere of argon was added *N*-chlorosuccinimide (8 mg, 0.060 mmol). The mixture was allowed to warm to 25 °C and was stirred for 2 h, then filtered through a pad of glass wool into a dry flask under argon and washed with chlorobenzene (0.700 mL). The solution was cooled to 0 °C and SnCl_4 (3.0 M in CH_2Cl_2 , 71 μL , 0.060 mmole) was added dropwise. The solution immediately became orange and a precipitate formed. Upon complete addition no starting material could be detected by TLC. The mixture was diluted with saturated aqueous NaHCO_3 until basic (1 mL) and extracted with EtOAc (2 x 10 mL). The combined extracts were dried (Na_2SO_4), filtered, and the solvent was removed under vacuum. The crude residue was purified by flash column chromatography (SiO_2 , 20%-80% EtOAc in hexanes) to afford **32** as a colorless oil (13 mg, 51% yield). R_f = 0.38 (100% EtOAc); IR (thin film) 2955, 1716, 1674, 1455, 1413, 1378, 1291, 1250, 1110, 1065, 1042, 973, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.18 (1 H, s), 7.47 (2 H, d, J = 7.02 Hz), 7.43-7.39 (2 H, m), 7.37-7.34 (1 H, m), 6.60 (1 H, bs), 5.15 (1 H, 11.04 Hz), 4.97 (1 H, 11.04 Hz), 4.87-4.85 (1 H, m), 3.83-3.80 (4 H, m), 3.70 (3 H, s), 3.66 (3 H, s), 3.26 (1 H, ddd, J = 1.35, 5.30, 17.26 Hz), 3.17 (1 H, d, J = 11.54 Hz), 2.69 (1 H, dd, J = 1.01, 7.25 Hz), 2.18 (3 H, s) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.6, 153.7, 143.8, 137.25, 128.7,

128.3, 127.9, 126.3, 120.0, 75.64, 64.4, 60.5, 59.9, 53.1, 51.6, 30.1, 29.6, 9.46 ppm; HRMS calcd. for C₂₃H₂₇N₂O₆ (MH⁺) 427.1869 Da. Found 427.1867 Da.

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