

One-pot formation of nitrogen-containing heterocyclic ring systems using a one-pot deprotection/cyclisation/asymmetric reduction sequence.

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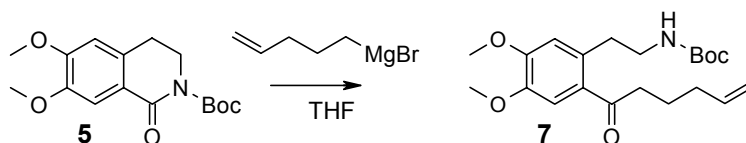
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Supporting Information

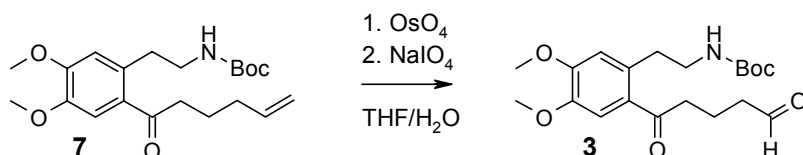
All reactions, unless otherwise stated, were run under an atmosphere of nitrogen at ambient temperature (18-22 °C). 0 °C refers to an ice/water slush bath and -78 °C refers to a dry ice-acetone bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by TLC using aluminium backed silica gel 60 (F254) plates, visualised using UV 254 and 2,4-dinitrophenylhydrazine, ninhydrin and potassium permanganate dips as appropriate. Flash column chromatography was carried out routinely using 60 Å silica gel (Merck). Reagents were used as received from commercial sources apart from the following exceptions, THF was distilled from sodium benzophenone ketyl, triethylamine was distilled from calcium hydride and formic acid was distilled from phthalic anhydride. NMR spectra were recorded on a Bruker DPX (300 or 400 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million downfield from TMS. Coupling constants (J) are measured in hertz. IR spectra were recorded on a Perkin-Elmer spectrum One FT-IR Golden Gate. Mass spectra were recorded on a 7070E VG mass spectrometer. Melting points were recorded on a Stuart Scientific SMP 1 instrument and are uncorrected.

Synthesis of *t*-butyl-2-(4,5-dimethoxy-2-hex-5-oxoylphenyl)-ethylcarbamate (7)



To a suspension of Mg turnings (0.29 g, 11.2 mmol) in THF (5 mL) was added a solution of 5-bromopent-1-ene (1.36 g, 9.1 mmol) in THF (5 mL) followed by a single crystal of iodine, the mixture was heated under reflux for 2 h and then cooled to rt. The Grignard solution was added to a solution of *t*-butyl-6,7-dimethoxy-1-oxo-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.0 g, 6.5 mmol) in THF (40 mL) in one portion at rt. The resulting mixture was stirred for 1 h, 2 M HCl was added to acidify (pH 1-2) and the phases separated, the aqueous phase was further extracted with DCM (3 × 30 mL). The organics were combined, dried (Na₂SO₄) and evaporated under reduced pressure to afford a yellow oil which was purified by flash column chromatography (SiO₂, EtOAc-Hexanes 15:85) to afford *t*-butyl-2-(4,5-dimethoxy-2-hex-5-oxoylphenyl)-ethylcarbamate (1.75 g, 71 %) as a white solid; mp 42-44 °C; (Found: C, 66.78; H, 8.29; N, 3.80. C₂₁H₃₁NO₅ requires C, 66.82; H, 8.28; N, 3.71 %); ν_{\max} (neat)/cm⁻¹ 3364, 2938, 1673, 1516 and 1128; δ_{H} (300 MHz; CDCl₃; Me₄Si) 7.17 (1 H, s, ArH), 6.76 (1 H, s, ArH), 5.81 (1 H, ddt, *J* 17.1, 9.5 and 7.2, CH=CH₂), 5.10 (1 H, br s, NH), 5.04 (1 H, dq, *J* 17.1 and 1.5, HC=CH_{trans}H_{cis}), 5.00 (1, dq, *J* 9.5 and 1.1, HC=CH_{trans}H_{cis}), 3.93 (3 H, s, OCH₃), 3.91 (3 H, s, OCH₃), 3.37 (2 H, q, *J* 6.8, NCH₂), 2.96 (2 H, t, *J* 6.8, ArCH₂), 2.89 (2 H, t, *J* 7.2, COCH₂), 2.14 (2 H, q, *J* 7.2, COCH₂CH₂), 1.82 (2 H, quintet, *J* 7.2 H₂C=CHCH₂) and 1.42 (9 H, s, *t*-Bu); δ_{C} (75 MHz; CDCl₃) 203.1 (C_q), 156.5 (C_q), 151.9 (C_q), 141.1 (C_q), 138.4 (CH), 134.5 (C_q), 130.4 (C_q), 115.7 (CH₂), 114.6 (CH), 112.6 (CH), 79.3 (C_q), 56.6 (CH₃), 56.4 (CH₃), 42.6 (CH₂), 40.7 (CH₂), 34.2 (CH₂), 33.5 (CH₂), 28.8 (CH₃), and 23.9 (CH₂); *m/z* (EI⁺) 377.2202 (C₂₁H₃₁NO₅ requires 377.2214), 377 (1 %), 303 (15), 260 (40), 205 (42), 78 (90) and 62 (100).

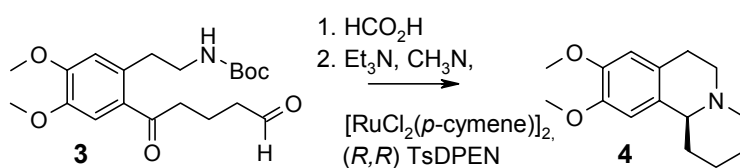
Synthesis of *t*-butyl-2-[4,5-dimethoxy-2-(5-oxopentanoyl)phenyl]-ethylcarbamate (3)



To a solution of *t*-butyl-2-(4,5-dimethoxy-2-hex-5-oxoylphenyl)-ethylcarbamate (2.19 g, 5.8 mmol) in dioxane/water (43.8 mL / 13.1 mL) under nitrogen was added

osmium tetroxide (37 mg, 0.14 mmol), the solution was stirred for 20 minutes, NaIO₄ (2.48 g, 1.2 mmol) was added portion-wise over 1 h and the resulting mixture stirred for 1 h. The white precipitate was filtered and washed with DCM (2 x 100 mL). The phases separated and the aqueous phase was further extracted with DCM (2 x 100 mL). The combined organics were dried (Na₂SO₄) and the solvent removed under reduced pressure to afford a brown oil which was purified by flash column chromatography (SiO₂, EtOAc-Hexanes 50:50) to afford *t*-butyl-2-[4,5-dimethoxy-2-(5-oxopentanoyl)phenyl]-ethylcarbamate (1.85 g, 85 %) as an off white solid; mp 49-51 °C; ν_{\max} (neat)/cm⁻¹ 3371, 2970, 1707, 1674, 1513, 1263 and 1127; δ_{H} (300 MHz; CDCl₃; Me₄Si) 9.82 (1 H, t, *J* 1.3, HCO), 7.22 (1 H, s, ArH), 6.75 (1 H, s, ArH), 5.03 (1 H, br s, NH), 3.93 (6 H, s, 2 x OCH₃), 3.86 (2 H, q, *J* 6.8, NCH₂), 2.99 (2 H, t, *J* 6.8, ArCH₂), 2.96 (2 H, t, *J* 7.1, COCH₂), 2.59 (2 H, dt, *J* 7.1 and 1.3, HCOCH₂), 2.05 (2 H, quintet, *J* 7.1, COCH₂CH₂) and 1.42 (9 H, s, *t*-Bu); δ_{C} (75 MHz; CDCl₃) 202.4 (CH), 201.9 (C_q), 156.5 (C_q), 152.1 (C_q), 147.2 (C_q), 134.8 (C_q), 129.8 (C_q), 114.8 (CH), 112.7 (CH), 79.3 (C_q) 56.6 (CH₃), 56.4 (CH₃), 43.5 (CH₂), 42.6 (CH₂), 40.2 (CH₂), 34.5 (CH₂), 28.8 (CH₃) and 17.3 (CH₂); *m/z* (EI+) 379.1994 (C₂₀H₂₉NO₆ requires 379.1977), 379 (15 %), 305 (15), 280 (35), 262 (100), and 179 (65).

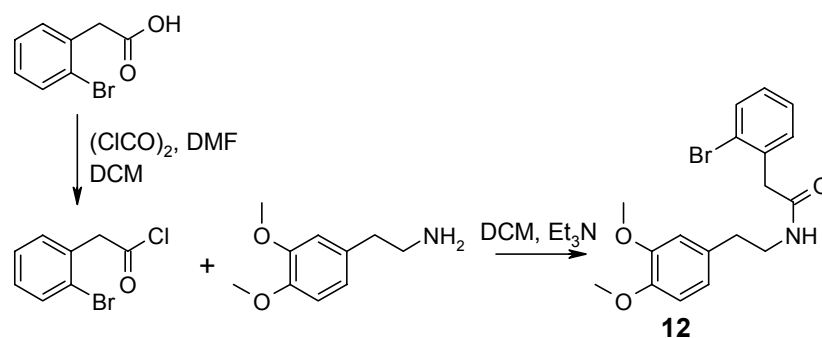
Synthesis of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1- α]isoquinoline (4)



t-Butyl-2-[4,5-dimethoxy-2-(5-oxopentanoyl)phenyl]-ethylcarbamate (0.10 g, 0.26 mmol) was stirred in freshly distilled formic acid (0.9 mL) for 1 h. The flask was then sealed and cooled to 0 °C; triethylamine (0.15 mL) was added cautiously with vigorous shaking until all gas had redissolved. In a separate flask a mixture of (*p*-cymene) ruthenium (II) chloride dimer (0.4 mg, 0.25 mol %) and (*1R,2R*)-TsDPEN (0.5 mg, 0.5 mol %), triethylamine (1 drop) and anhydrous acetonitrile (0.5 mL) were stirred at 40 °C for 40 minutes. The catalyst solution was transferred to the formic acid

/ triethylamine solution and the mixture stirred at 28°C for 3 h. The mixture was made basic (pH 9-10) with saturated Na₂CO₃ solution and extracted with DCM (3 x 25 mL). The combined organics were dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (SiO₂, DCM-MeOH, 97:3) to afford the 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1- α] isoquinoline (42 mg, 64 %) ¹ as a pale brown oil; $[\alpha]_D^{22}$ -39.4 ($c = 0.36$ in CHCl₃); ν_{\max} (neat)/cm⁻¹ 2918, 2746, 1509, 1258 and 1005; δ_H (300 MHz; CDCl₃; Me₄Si) 6.68 (1 H, s, ArH), 6.57 (1 H, s, ArH), 3.85 (6 H, s 2 x OCH₃), 3.19-3.01 (2 H, m, CH and ArCH_aH_b), 3.04-2.95 (2 H, m, CH_aH_bNCH_aH_b), 2.62 (1 H, dd, J 15.6 and 3.9, ArCH_aH_b), 2.54 (1 H, dt, J 11.5 and 3.9, ArCH₂CH_aH_b), 2.36 (1 H, dt, 11.1 and 4.5, NCH_aH_b), 2.45-2.30 (1 H, m, CHCH_aH_b), 1.96-1.91 (1 H, m, CHCH₂CH_aH_b), 1.76-1.67 (2 H, m, NCH₂CH₂) and 1.56-1.44 (2 H, m CHCH₂CH_aH_b and CHCH_aH_b); δ_C (75 MHz; CDCl₃; Me₄Si) 147.8 (C_q), 147.5 (C_q), 130.3 (C_q), 126.9 (C_q), 111.8 (CH), 108.4 (CH), 63.5 (CH), 57.0 (CH₂), 56.3 (CH₃), 56.2 (CH₃), 53.0 (CH₂), 31.6 (CH₂), 29.2 (CH₂), 25.6 (CH₂) and 25.3 (CH₂); m/z (EI+) 246.1495 (C₁₅H₂₀NO₂ requires 246.1494), 247 (15 %), 245 (100), 217 (42), and 190 (35).

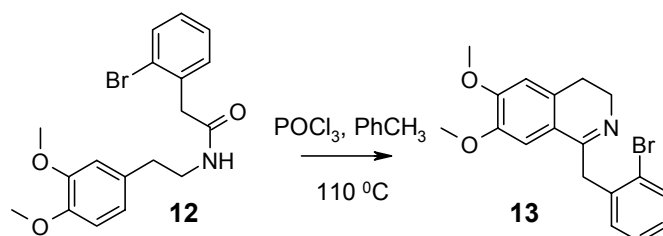
Synthesis of 2-(2-bromophenyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (12)



To a stirred solution of 2-bromophenylacetic acid (20.0 g, 93 mmol) and oxalyl chloride (12.3 g, 8.37 mL, 98 mmol) in DCM (200 mL) was added DMF (2 drops). The reaction was stirred until NMR had shown complete consumption of the 2-bromophenylacetic acid, the solvent was then removed under reduced pressure to afford a pink solid which was redissolved in DCM (30 mL) and added dropwise to a cooled (0 °C) stirred solution of 3,4- dimethoxyphenylethylamine (16.7 g, 92.5 mmol)

and Et₃N (11.3 g, 15.5 mL, 110 mmol) in DCM (168 mL) over a period of 30 minutes. The resulting suspension was stirred for 1 h then washed with 1 M HCl (30 mL), saturated NaHCO₃ (30 mL), brine (30 mL), dried (Na₂SO₄). The solvent was removed *in vacuo* to afford 2-(2-bromophenyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (33.0 g, 94 %) as a white solid; mp 124-126 °C; (Found: C, 57.07; H, 5.32; N, 3.63. C₁₈H₂₀NO₃Br requires C, 57.16; H, 5.33; N, 3.70 %); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3303, 2937, 1643, 1547, 1233 and 1024; δ_{H} (400 MHz; CDCl₃; Me₄Si) 7.54 (1 H, d, *J* 8.0, Ar*H*), 7.30-7.22 (2 H, m, 2 x Ar*H*), 7.17-7.09 (1 H, m, Ar*H*), 6.72 (1 H, d, *J* 8.0, Ar*H*), 6.65-6.57 (2 H, m, Ar*H*), 5.53 (1 H, br s, NH), 3.84 (3 H, s, OCH₃), 3.82 (3 H, s, OCH₃), 3.65 (2 H, s, ArCH₂), 3.45 (2 H, q, *J* 7.0, NCH₂) and 2.70 (2 H, t, *J* 7.0, ArCH₂); (100 MHz; CDCl₃) 169.5 (C_q), 149.0 (C_q), 147.6 (C_q), 134.8 (C_q), 133.1 (CH), 131.6 (CH), 131.1 (C_q), 129.1 (CH), 127.9 (CH), 124.9 (C_q), 120.6 (CH), 111.8 (CH), 111.4 (CH), 55.9 (CH₃), 55.8 (CH₃), 44.0 (CH₂), 40.9 (CH₂) and 40.8 (CH₂); *m/z* (EI⁺) 377.0612 (C₁₈H₂₀NO₃⁷⁹Br requires 377.0626) 376/378 (30 %), 164 (100) and 151 (74).

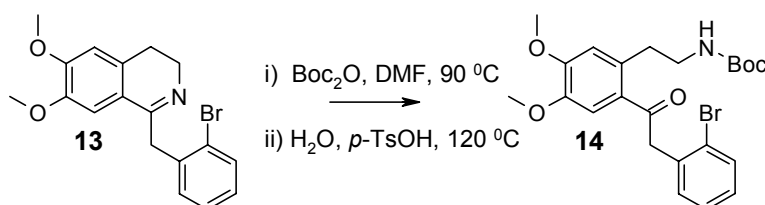
Synthesis of 1-(2-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (13)



A suspension of 2-(2-bromophenyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (32.0 g, 0.85 mol) and POCl₃ (13.0 g, 7.9 mL, 0.85 mol) in toluene (320 mL) was heated at reflux for 12 h. The reaction was cooled to rt and diluted with EtOAc (500 mL) and washed with saturated NaHCO₃ (3 × 50 mL) and brine (50 mL). The organic phase was dried (Na₂SO₄) and the solvent removed under reduced pressure to give a yellow oil. The oil was redissolved in EtOAc and 1-(2-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (28.7 g, 94 %) was precipitated by the addition of hexanes as a pale yellow powder; mp 85-87 °C; $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3008, 2359, 2341, 1514, 1142 and 746; δ_{H} (400 MHz; CDCl₃; Me₄Si) 7.57 (1 H, dd, *J* 8.0 and 1.8, Ar*H*), 7.26 (1 H, dd, *J* 7.4 and 1.6, Ar*H*), 7.18 (1 H, td, *J* 7.4 and 1.6, Ar*H*), 7.05 (1 H, td, *J*

8.0 and 1.8, *ArH*), 6.91 (1 H, s, *ArH*), 6.66 (1 H, s, *ArH*), 4.20 (2 H, s, *CH*₂), 3.88 (3 H, s, *OCH*₃), 3.79 (3 H, s, *OCH*₃), 3.73 (2 H, t, *J* 7.5, *NCH*₂) and 2.67 (2 H, t, *J* 7.5, *ArCH*₂); δ_{C} (100 MHz; *CDCl*₃) 165.1 (*C*_q), 150.7 (*C*_q), 147.4 (*C*_q), 137.7 (*C*_q), 132.8 (*CH*), 131.8 (*C*_q), 130.2 (*CH*), 128.2 (*CH*), 127.6 (*CH*), 124.5 (*C*_q), 121.5 (*C*_q), 110.2 (*CH*), 109.2 (*CH*), 56.2 (*CH*₃), 55.9 (*CH*₃), 47.4 (*CH*₂), 42.6 (*CH*₂) and 25.8 (*CH*₂); *m/z* (*EI*⁺) 358.0427 (*C*₁₈*H*₁₇*NO*₂⁷⁹*Br* requires 358.0443) 357/359 (45 %), 280 (100) and 264 (28).

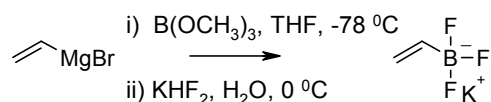
Synthesis of *t*-butyl-2-{2-[(2-bromophenyl)acetyl]-4,5-dimethoxy phenyl}ethylcarbamate (**14**)



Boc_2O (4.31 g, 19.8 mmol) was added to a solution of 1-(2-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (4.75 g, 13.2 mmol) in DMF (38 mL) and heated to 90 °C for 1.5 h. Water (9.5 mL) and *p*-TsOH (50 mg) were added carefully and the reaction heated to 130 °C for 12 h. The solution was cooled to rt, diluted with EtOAc (200 mL) and washed with water (4 x 50 mL), brine (20 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a brown solid which was purified by flash column chromatography (SiO_2 , EtOAc-hexanes, 20:80) to afford *t*-butyl-2-{2-[(2-bromophenyl)acetyl]-4,5-dimethoxy phenyl}ethylcarbamate (4.4 g, 70 %) as a white solid; mp 94-95 °C; (Found: C, 57.65; H, 5.88; N, 2.72. $\text{C}_{23}\text{H}_{28}\text{NO}_5\text{Br}$ requires C, 57.75; H, 5.90; N, 2.93 %); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3367, 2859, 1676, 1661, 1516 and 1215; δ_{H} (400 MHz; *CDCl*₃; Me_4Si) 7.59 (1 H, dd, *J* 8.0 and 1.0, *ArH*), 7.34 (1 H, s, *ArH*), 7.33-7.25 (2 H, m, 2 x *ArH*), 7.18-7.13 (1 H, m, *ArH*), 6.77 (1 H, br s, *ArH*), 4.95 (1 H, br s, *NH*), 4.37 (2 H, s, *COCH*₂), 3.93 (3 H, s, *OCH*₃), 3.92 (3 H, s, *OCH*₃), 3.36 (2 H, q, *J* 6.6, *NCH*₂), 2.99 (2 H, t, *J* 6.6, *ArCH*₂), and 1.40 (9 H, s, *t*-Bu); (75 MHz; *CDCl*₃) 198.0 (*C*_q), 155.9 (*C*_q), 151.6 (*C*_q), 146.5 (*C*_q), 135.2 (*C*_q), 134.7 (*C*_q), 132.9 (*CH*), 131.5 (*CH*), 128.8 (*C*_q), 128.6 (*CH*), 127.4 (*CH*), 124.7 (*C*_q), 114.2 (*CH*), 112.3 (*CH*), 78.6 (*C*_q), 56.0 (*CH*₃), 55.8 (*CH*₃), 48.1 (*CH*₂), 41.9 (*CH*₂), 33.8 (*CH*₂) and 28.2

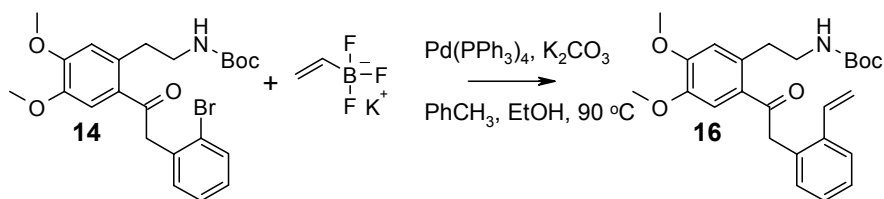
(CH₃); *m/z* (LSIMS+) 476.1059 (C₂₃H₂₇NO₅⁷⁹Br requires 476.1073) 477/479 (20 %), 377/379 (55), 359/361 (45) and 207 (100).

Synthesis of potassium vinyltrifluoroborate



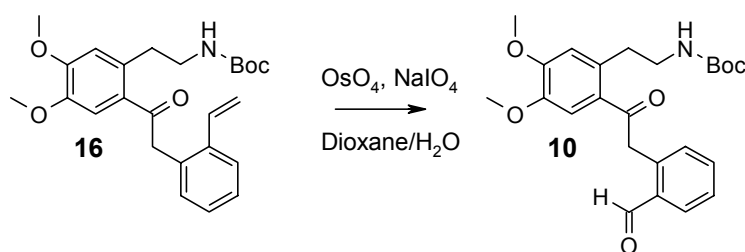
To a solution of trimethylborate (6.96 g, 0.067 mol) in THF (45 mL) at -78 °C was added dropwise a 1 M solution of vinylmagnesium bromide (54 mL). The solution was stirred at -78 °C for 20 minutes and warmed to rt. KHF₂ (20.91 g, 0.16 mol) was added followed by water (35 mL). The suspension was warmed to rt and stirred for a further 30 minutes. The reaction was concentrated under reduced pressure. The residue was slurried in hot acetone (100 mL) and filtered, the filtrate was concentrated under reduced pressure to give a white solid which was dissolved in hot acetone (50 mL) and filtered, Et₂O (100 mL) was added and the white precipitate collected by filtration to afford potassium vinyltrifluoroborate (5.07 g, 71 %) as a white powder; mp 223 °C (decomp) (lit.² 225 °C decomp); $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3052, 2958, 1620, 1418, 1098 and 1020; δ_{H} (300 MHz; acetone) 5.82 (1 H, ddq, *J* 20.1, 13.8 and 4.3, *BCH*), 5.45-5.20 (1 H, m, CH=CH_aH_b) and 5.19-5.03 (1 H, m, C=CH_aH_b); δ_{C} (75 MHz; acetone) 124.4 (d, *J* 5.0, CH₂) and CH (not observed), δ_{F} (282 MHz; acetone) -142.9 (q, *J* 47.1); *m/z* (LSIMS-) 96 (94 %).

Synthesis of *t*-butyl-2-{3,4-dimethoxy-2-[(2-vinylphenyl)acetyl]phenyl}ethylcarbamate (16)



To a stirred suspension of *t*-butyl-2-{2-[(2-bromophenyl)acetyl]-4,5-dimethoxyphenyl}ethylcarbamate (3.77 g, 8.2 mmol) and K₂CO₃ (1.58 g, 11.5 mmol) in toluene / EtOH (30 mL / 7.5 mL) was added tetrakis (triphenylphosphine) palladium (0.28 g, 0.25 mmol) followed by potassium vinyltrifluoroborate (1.63 g, 12.3 mmol). The mixture was heated at 80 °C for 12 h, cooled to rt and filtered through celite. Removal of the solvent under reduced pressure gave a brown oil which was purified by flash column chromatography (SiO₂, EtOAc-hexanes, 15:85) to afford *t*-butyl-2-{3,4-dimethoxy-2-[(2-vinylphenyl)acetyl]phenyl}ethylcarbamate (2.7 g, 80 %) as a white solid; mp 121-122 °C; (Found: C, 70.41; H, 7.34; N, 3.23. C₂₅H₃₁NO₅ requires C, 70.57; H, 7.34; N, 3.29 %); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3360, 2968, 1667, 1662, 1518 and 1126; δ_{H} (400 MHz; CDCl₃; Me₄Si) 7.52 (1 H, dd, *J* 7.7 and 2.2, Ar*H*), 7.29-7.20 (3 H, m, 3 x Ar*H*), 7.16 (1 H, dd, *J* 6.8 and 1.2, Ar*H*), 6.82 (1 H, dd, *J* 17.3 and 11.2 CH₂=CH), 6.75 (1 H, br s, Ar*H*), 5.63 (1 H, dd, *J* 17.3 and 1.4, CH=CH_{trans}H_{cis}), 5.28 (1 H, dd, *J* 11.2 and 1.4, CH=CH_{trans}H_{cis}), 4.96 (1 H, br s, NH), 4.29 (2 H, s, COCH₂), 3.91 (3 H, s, OCH₃), 3.87 (3 H, s, OCH₃), 3.32 (2 H, q, *J* 7.0, NCH₂), 2.93 (2 H, t, *J* 7.0, ArCH₂), and 1.40 (9 H, s, *t*-Bu); (100 MHz; CDCl₃) 199.4 (C_q), 156.1 (C_q), 151.8 (C_q), 146.7 (C_q), 137.4 (C_q), 134.9 (C_q), 134.4 (CH), 132.6 (C_q), 130.7 (CH), 129.1 (C_q), 128.0 (CH), 127.6 (CH), 126.3 (CH), 116.7 (CH₂), 114.5 (CH), 112.5 (CH), 78.8 (C_q), 56.2 (CH₃), 56.0 (CH₃), 45.9 (CH₂), 42.1 (CH₂), 33.9 (CH₂) and 28.4 (CH₃); *m/z* (EI⁺) 425 (3 %), 306 (35), 292 (100) and 208 (80).

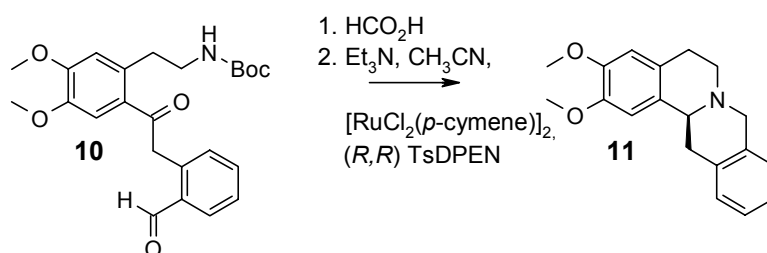
Synthesis of *t*-butyl-2-{2-[(2-formylphenyl)acetyl]-3,4-dimethoxyphenyl}ethylcarbamate (**10**)



To a stirred solution of *t*-butyl-2-{3,4-dimethoxy-2-[(2-vinylphenyl)acetyl]phenyl}ethylcarbamate (2.70 g, 6.35 mol) and OsO₄ (40 mg, 0.16 mmol) in dioxane (40 mL) and water (13.5 mL) was added in small portions

sodium periodate (2.87 g, 13.3 mol) over a period of 1 h. The resulting suspension was stirred for 2 h then diluted with EtOAc (50 mL) and washed with water (3 × 10 mL), the organic phase was dried (MgSO₄) and the solvent removed under reduced pressure to give a brown oil which was purified by flash column chromatography (SiO₂, EtOAc-hexanes, 25:75) to afford *t*-butyl-2-{2-[(2-formylphenyl)acetyl]-3,4-dimethoxyphenyl}ethylcarbamate (2.2 g, 82 %) as a white solid; mp 40-41 °C; ν_{max} (neat)/cm⁻¹ 3366, 2972, 1687 (broad), 1512, 1263 and 1122; δ_{H} (400 MHz; CDCl₃; Me₄Si) 10.03 (1H, s, CHO), 7.86 (1 H, dd, *J* 7.5 and 1.4, ArH), 7.60 (1 H, td, *J* 7.5 and 2.0, ArH), 7.54 (1 H, td, *J* 7.5 and 1.4, ArH), 7.48 (1 H, s, ArH), 7.31 (1 H, d, *J* 7.5, ArH), 6.78 (1 H, br s, ArH), 4.96 (1 H, br s, NH), 4.65 (1 H, s, COCH₂), 3.96 (3 H, s, OCH₃), 3.93 (3 H, s, OCH₃), 3.33 (2 H, q, *J* 6.8, NCH₂), 2.94 (2 H, t, *J* 6.8, ArCH₂), and 1.39 (9 H, s, *t*-Bu); (100 MHz; CDCl₃) 199.1 (C_q), 193.0 (CH), 156.1 (C_q), 151.6 (C_q), 146.8 (C_q), 136.4 (C_q), 135.5 (CH), 134.4 (C_q), 134.4 (C_q), 133.7 (CH), 132.9 (CH), 129.8 (C_q), 127.8 (CH), 114.3 (CH), 112.5 (CH), 78.8 (C_q), 56.2 (CH₃), 55.9 (CH₃), 46.2 (CH₂), 42.0 (CH₂), 33.7 (CH₂) and 28.4 (CH₃); *m/z* (LSIMS⁺) 427.1995 (C₂₄H₂₉NO₆ requires 427.1995) 427 (10 %), 410 (100), 354 (25) and 310 (35).

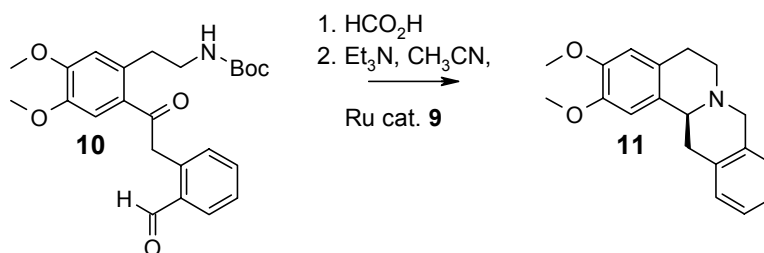
Synthesis of 2,3-dimethoxyberbine (11)



t-Butyl-2-{2-[(2-formylphenyl)acetyl]-3,4-dimethoxyphenyl}ethylcarbamate (0.10 g, 0.23 mmol) was stirred in freshly distilled formic acid (0.9 mL) for 1 h. The flask was then sealed and cooled to 0 °C; triethylamine (0.15 mL) was added cautiously with vigorous shaking until all gas had redissolved. In a separate flask a mixture of (*p*-cymene) ruthenium (II) chloride dimer (0.7 mg, 0.5 mol %) and (1*R*,2*R*)-TsDPEN (0.9 mg, 1 mol %), triethylamine (1 drop) and anhydrous acetonitrile (0.6 mL) were stirred at 40 °C for 40 minutes. The catalyst solution was transferred to the formic acid

/ triethylamine solution and the mixture stirred at 28 °C for 48 h. The mixture was made basic (pH 9-10) with saturated Na₂CO₃ solution and extracted with DCM (3 × 25 mL). The combined organics were dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (SiO₂, EtOAc-hexanes, 40:60) to afford 2,3-dimethoxyberbine (45 mg, 70 %) as a pale yellow oil which crystallised on standing; mp 210-217 °C (lit.³ 236-238 °C) [α]_D²² -17.5 (*c* = 0.01 in CHCl₃); ν_{\max} (neat)/cm⁻¹ 2907, 1509, 1257, and 1136; δ_{H} (400 MHz; CDCl₃; Me₄Si) 7.17-7.13 (3 H, m, 3 x ArH), 7.09-7.05 (1 H, m, ArH), 6.75 (1 H, s, ArH), 6.62 (1 H, s, ArH), 4.02 (1 H, d, *J* 15.0, NCH_aH_bAr), 3.89 (3 H, s, OCH₃), 3.86 (3 H, s, OCH₃), 3.73 (1 H, d, NCH_aH_bAr), 3.62 (1 H, dd, *J* 11.0 and 4.4 ArCH), 3.33 (1 H, dd, *J* 16.8 and 4.4, ArCHCH_aH_bAr), 3.19-3.10 (2 H, m, ArCH_aH_bCH_aH_bN), 2.91 (1 H, dd, 16.8 and 11.0, ArCHCH_aH_bAr) and 2.70-2.59 (2 H, m, ArCH_aH_bCH_aH_bN); δ_{C} (100 MHz; CDCl₃) 147.5 (C_q), 147.4 (C_q), 134.5 (C_q), 134.4 (C_q), 129.7 (C_q), 128.7 (CH), 126.2 (C_q), 126.3 (CH), 126.2 (CH), 125.8 (CH), 111.4 (CH), 108.6 (CH), 59.6 (CH), 58.6 (CH₂), 56.1 (CH₃), 55.8 (CH₃), 51.4 (CH₂), 36.8 (CH₂) and 29.1 (CH₂); *m/z* (EI⁺) 294.1510 (C₁₉H₂₀NO₂ requires 294.1494), 294 (100 %), 190 (40), and 105 (45).

HPLC conditions; Chiracel OD column, 0.5 mL min⁻¹, EtOH / *c*-hexane / Et₂NH (9 : 90 : 1), 12.40 min (55 %) and 16.99 min (45 %)

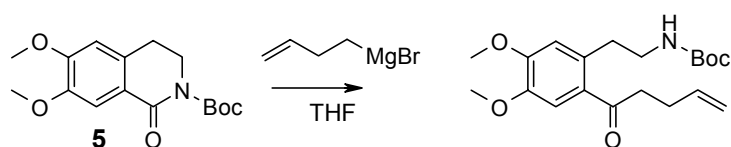


t-Butyl-2-{2-[(2-formylphenyl)acetyl]-3,4-dimethoxyphenyl}ethylcarbamate (0.10 g, 0.23 mmol) was stirred in freshly distilled formic acid (0.9 mL) for 1 h. The flask was then sealed and cooled to 0 °C; triethylamine (0.15 mL) was added cautiously with vigorous shaking until all gas had redissolved. Acetonitrile (0.6 mL) and the Ruthenium catalyst **9** (1 mol %) was added and the reaction stirred until complete by NMR (typically 2-3 h). The mixture was made basic (pH 9-10) with saturated Na₂CO₃ solution and extracted with DCM (3 x 25 mL). The combined organics were

dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (SiO₂, EtOAc-hexanes, 40:60) to afford 3,4-dimethoxyberbine (48 mg, 73 %) as a pale yellow oil; $[\alpha]_D^{22}$ -122.6 ($c = 0.035$ in 5 mL CHCl₃).

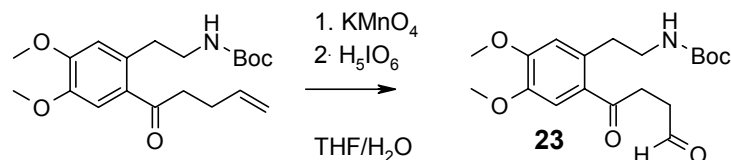
HPLC conditions; Chiracel OD column, 0.5 mL min⁻¹, EtOH / *c*-hexane / Et₂NH (9 : 90 : 1), 12.40 min (75 %) and 16.99 min (25 %)

Synthesis of *t*-butyl-2-(4,5-dimethoxy-2-pent-4-enoylphenyl)-ethylcarbamate



A solution of 4-butenylmagnesium bromide (0.99 g, 6.5 mmol) in THF (7.3 mL) was added to a solution of *t*-butyl-6,7-dimethoxy-1-oxo-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.6 g, 5.2 mmol) in THF (32 mL) in one portion at rt. The resulting mixture was stirred for 1 h, 2 M HCl was added to acidify (pH 1-2) and the phases separated, the aqueous phase was further extracted with DCM (3 x 25 mL). The organics were combined, dried (Na₂SO₄) and evaporated under reduced pressure to afford a yellow oil which was purified by flash column chromatography (SiO₂, EtOAc-Hexanes, 15:85) to afford *t*-butyl-2-(4,5-dimethoxy-2-pent-4-enoylphenyl)-ethylcarbamate (1.48 g, 80 %) as a white solid; mp 49-51 °C (Found: C, 66.07; H, 8.06; N, 3.77. C₂₀H₂₉NO₅ requires C, 66.09; H, 8.04; N, 3.85 %); ν_{\max} (neat)/cm⁻¹ 3365, 2975, 2359, 1749, 1673 and 1514; δ_{H} (300 MHz; CDCl₃; Me₄Si) 7.19 (1 H, s, ArH), 6.76 (1 H, s, ArH), 5.88 (1 H, ddt, J 17.1, 10.4 and 7.0, H₂C=CH), 5.07 (1 H, dd, J 17.1 and 1.6, C=CH_{trans}H_{cis}), 5.05 (1H, br s, NH), 5.02 (1, dd, J 10.4 and 1.6, C=CH_{trans}H_{cis}), 3.93 (3 H, s, OCH₃), 3.91 (3 H, s, OCH₃), 3.37 (2 H, q, J 6.6, NCH₂), 2.99 (2 H, t, J 7.0, ArCH₂), 2.97 (2 H, t, J 6.0, COCH₂), 2.46 (2 H, q, J 7.0, H₂C=CHCH₂) and 1.42 (9 H, s, *t*-Bu); δ_{C} (75 MHz; CDCl₃) 202.2 (C_q), 156.5 (C_q), 151.9 (C_q), 147.2 (C_q), 137.6 (CH), 134.6 (C_q), 130.2 (C_q), 115.8 (CH₂), 114.7 (CH), 112.6 (CH), 79.3 (C_q), 56.6 (CH₃), 56.4 (CH₃), 42.6 (CH₂), 40.7 (CH₂), 34.3 (CH₂), 29.9 (CH₂), and 28.8 (CH₃); m/z (EI⁺) 363.2046 (C₂₀H₂₉NO₅ requires 363.2050), 364 (35 %), 363 (30), 308 (35), 290 (45), 247 (75), 208 (75), 132 (40) and 84 (100).

Synthesis of *t*-butyl-2-[4,5-dimethoxy-2-(4-oxobutanoyl)phenyl]-ethylcarbamate (23)



To a stirred solution of *t*-butyl-2-(4,5-dimethoxy-2-pent-4-enylphenyl)-ethylcarbamate (1.0 g, 2.7 mmol) in THF (27 mL) was added dropwise a solution of KMnO_4 (0.87 g, 5.5 mmol) in water (20 mL) over a period of 30 minutes. Periodic acid (0.68 g, 3.0 mmol) was added in 1 portion and the suspension stirred for 1 h. The mixture was filtered through a pad of celite, the filtrate was diluted with brine (5 mL) and the phases separated, the aqueous phase was further extracted with DCM (3 × 25 mL), the organics were combined, dried (Na_2SO_4) and evaporated under reduced pressure to afford a yellow oil which was purified by flash column chromatography (SiO_2 , EtOAc-Hexanes, 15:85) to afford *t*-butyl-2-[4,5-dimethoxy-2-(4-oxobutanoyl)phenyl]-ethylcarbamate (0.71 g, 71 %) as a white solid; mp 65-66 °C; (Found: C, 62.29; H, 7.45; N, 3.78. $\text{C}_{19}\text{H}_{27}\text{NO}_6$ requires C, 62.45; H, 7.45; N, 3.83 %); ν_{max} (neat)/ cm^{-1} 3365, 2970, 1674, 1711, 1518 and 1129; δ_{H} (300 MHz; CDCl_3 ; Me_4Si) 9.90 (1 H, s, HCO), 7.28 (1 H, s, ArH), 6.76 (1 H, s, ArH), 4.98 (1 H, br s, NH), 3.93 (6 H, s, 2 × OCH_3), 3.35 (2 H, q, J 7.0, NCH_2), 3.32 (2 H, t, J 5.9, ArCOCH_2), 2.97 (2 H, t, J 7.0, NCH_2CH_2), 2.92 (2 H, t, J 5.9, HCOCH_2), 1.41 (9 H, s, *t*-Bu); δ_{C} (75 MHz; CDCl_3) 201.2 (CH), 200.3 (C_q), 156.5 (C_q), 152.2 (C_q), 147.2 (C_q), 134.8 (C_q), 129.7 (C_q), 114.7 (CH), 112.7 (CH), 79.3 (C_q), 56.6 (CH_3), 56.4 (CH_3), 42.4 (CH_2), 38.5 (CH_2), 34.4 (CH_2), 33.8 (CH_2) and 29.8 (CH_3); m/z (EI⁺) 366 (10 %), 310 (20), 266 (35), 248 (100), 179 (45) and 55 (35).

Synthesis of 5,6-dihydro-8,9-dimethoxypyrrole[2,1- α]isochinolin (**24**)



t-Butyl-2-[4,5-dimethoxy-2-(4-oxobutanoyl)phenyl]-ethylcarbamate (0.10 g, 0.20 mmol) was stirred in TFA (1 mL) for 1 h, 2 M NaOH was added to adjust pH to 8-9, the resulting precipitate was filtered off and washed with hexane (2 mL). The solids were recrystallised from EtOAc / hexanes to afford 5,6-dihydro-8,9-dimethoxypyrrole[2,1- α]isochinolin (62 mg, 99 %) as colourless plates; mp 130-132°C (lit.⁴ 132-133 °C); (Found: C, 73.32; H, 6.70; N, 5.93. C₁₄H₁₅NO₂ requires C, 73.34; H, 6.59; N, 6.11 %); ν_{\max} (neat)/cm⁻¹ 3102, 2953, 2558, 1552 and 1504; δ_{H} (300 MHz; CDCl₃; Me₄Si) 7.02 (1 H, s, ArH), 6.70 (1 H, s, ArH), 6.64 (1 H, dd, *J* 2.6 and 1.7, pyrrole *H*), 6.39 (1 H, dd, *J* 3.6 and 1.7, pyrrole *H*), 6.20 (1 H, dd, *J* 3.6 and 2.6, pyrrole *H*), 4.04 (2 H, t, *J* 6.6, ArCH₂), 3.91 (3 H, s, OCH₃), 3.88 (3 H, s, OCH₃) and 2.97 (2 H, t, *J* 6.6, NCH₂); δ_{C} (75 MHz; CDCl₃) 148.6 (C_q), 147.6 (C_q), 130.3 (C_q), 123.2 (C_q), 122.9 (C_q), 120.8 (CH), 111.7 (CH), 108.7 (CH), 106.3 (CH), 102.7 (CH), 56.4 (2 x CH₃), 44.7 (CH₂) and 29.5 (CH₂); *m/z* (EI+) 229 (100 %) and 214 (45).

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