Stereoselective Synthesis of Densely Substituted Tetrahydroquinolines by a Conjugate Addition nitro-Mannich Reaction with Carbon Nucleophiles

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General Experimental

Unless otherwise stated, all reactions were carried out under an atmosphere of nitrogen. All glassware was flame dried under a stream of nitrogen before use. Cooling to 0 °C was effected using an ice-water bath. Reactions were monitored by thin layer chromatography (TLC) using Polygram Sil G/UV_{254} 0.25 mm silica gel precoated plastic plates with fluorescent indicator. Sheets were visualised using ultraviolet light (254 nm), ninhydrin or $KMnO_4$, as appropriate. Flash chromatography was performed using Fluorochem silica gel 60, 35-70 μM. The liquid phase was analytical grade 40-60 petroleum ether (pet. Ether) and ethyl acetate (EtOAc) unless otherwise stated.

Removal of solvents (*in vacuo*) was achieved using a Vacuubrand diaphragm pump or house vacuum and Büchi rotary evaporators.

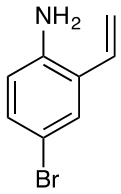
All NMR data was collected using a Bruker AMX 300 MHz, Bruker AVANCE III 400 MHz, Bruker AVANCE 500 MHz or Bruker AVANCE III 600 MHz. Data was manipulated directly using Bruker XwinNMR (version 2.6), TopSpin (version 2.1) or Mnova (version 9.1.0). Reference values for residual solvents were taken as δ = 7.26 ($CDCl_3$) and 2.51 ppm (DMSO-*d*6) for ^{1}H NMR; δ = 77.16 ppm ($CDCl_3$) for ^{13}C NMR. Multiplicities for coupled signals were denoted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, apt. = apparent and dd = double doublet *etc.* Coupling constants (*J*) are given in Hz and are uncorrected. Where appropriate, COSY, DEPT, HMBC, HMQC and NOE experiments were carried out to aid assignment. ^{1}H and ^{13}C assignments correspond to the major diastereomer only. Mass spectroscopy data was collected on a Thermo Finnigan Mat900xp (EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Infrared data

was collected using a Perkin-Elmer 1600 FTIR machine as a thin film unless otherwise stated. Elemental analysis was performed on an Exeter Analytical Inc. EA440 horizontal load analyser. Melting points are uncorrected and were recorded on a Stuart Scientific SMP3 system.

Purification of Solvents and Reagents:

Commercial solvents and reagents were used as supplied or purified in accordance with standard procedures, as described below. THF, Et_2O and Toluene were obtained from solvent towers, where the degassed solvent was passed through a 7-micron filter under 4 bar pressure. Nitrostyrenes **5a**, **5b**, **5c**, **5e, 5f** and **5g** were synthesised according to a previous report.[1] 4-bromo-2-iodoaniline was synthesised according to a previous report.[2] Et_2Zn (1.0M in Hexanes) & Me_2Zn (1.2M in PhMe) were used as supplied from Sigma Aldrich.

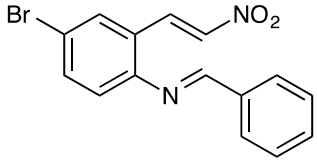
4-bromo-2-vinylaniline **9**



A solution of 4-bromo-2-iodoaniline (2.98 g, 10.0 mmol), potassium vinyltrifluoroborate (1.34 g, 10.0 mmol), K_2CO_3 (1.66 g, 12.0 mmol) and $Pd(PPh_3)_4$ (1.16 g, 10 mol%, 1.00 mmol) in DME (30 mL) was added H_2O (10 ml) and left to stir for 18 hours at 85°C. The reaction mixture was added brine (100 mL), the product was extracted with EtOAc (3 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude styrene **9** as a brown oil. Purification by column chromatography (9:1 pet. Ether:EtOAc) gave the pure styrene **9** as a low melting brown solid (980 mg, 49%); R_f = 0.23 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3413 (N-H), 1618 (C=C) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.38 (1H, d, *J* = 2.3 Hz, Ar*H*), 7.16 (1H, dd, *J* = 8.5, 2.3 Hz, Ar*H*), 6.67 (1H, dd, *J* = 17.4, 11.0 Hz, C*H*), 6.56 (1H, d, *J* = 8.5 Hz, Ar*H*), 5.63 (1H, dd, *J* = 17.4, 1.2 Hz, C*H*), 5.35 (1H, dd, *J* = 11.0, 1.2 Hz, C*H*), 3.75 (2H , s, NH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3 (Ar*C*), 131.6 (*C*H), 131.4 (*C*H),

129.9 (*C*H), 126.3 (Ar*C*), 117.9 (*C*H), 117.3 (CH_2), 111.2 (Ar*C*); m/z (ESI) 198 (100%, $M+H^+$); HRMS C_8H_9NBr calcd. 197.9913 found 197.9911.

(*E*)-*N*-(4-bromo-2-((*E*)-2-nitrovinyl)phenyl)-1-phenylmethanimine **5d**



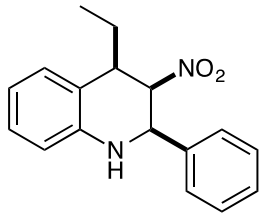
Synthesised according to previous report.[1]

9 (891 mg, 4.50 mmol) gave **5d** as a tan solid (645 mg, 43%); mp 156-158°C; R_f = 0.35 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 1618 (C=N), 1332 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.41 (s, 1H, C*H*N), 8.34 (1H, d, *J* = 13.7 Hz, C*H*), 7.95 (2H, d, *J* = 7.4 Hz, Ar*H*), 7.70 (2H, dd, *J* = 7.8, 5.8 Hz, Ar*H*), 7.63 – 7.49 (5H, m, C*H*), 6.98 (1H, d, *J* = 8.4 Hz, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0 (*C*HN), 151.1 (Ar*C*), 139.4 (Ar*C*H), 135.7 (Ar*C*H), 135.5 (Ar*C*H), 134.9 (Ar*C*H), 132.7 (Ar*C*H), 132.4 (Ar*C*H), 129.9 (Ar*C*H), 129.5 (Ar*C*H), 129.3 (Ar*C*H), 129.1 (*C*H), 126.5 (Ar*C*), 120.8 (*C*H), 119.7 (Ar*C*), 109.7 (Ar*C*); m/z (CI) 331 (100%, M^+); HRMS $C_{15}H_{12}N_2O_2Br$ calcd. 331.0077, found 331.0076.

General Experimental – Dialkylzinc Addition

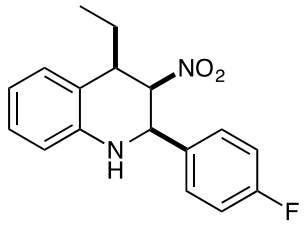
A solution of **5** (0.25 mmol) and $Cu(OTf)_2$ (5 mol%) in Et_2O (2.5 mL) was cooled to -78 °C over 30 minutes. A solution of $ZnEt_2$ (0.375 mL of a 1.0 M solution in Hexanes, 1.5 equiv.) was added and the mixture stirred for up to 1 hour and then stirred for up to 2 hours at room temperature. The resulting suspension was re-cooled to -78 °C over 30 minutes and TFA (2.5 equiv.) was added drop wise, stirred for up to 1 hour and then stirred for up to 1 hour at room temperature. The reaction was then quenched with saturated aqueous $NaHCO_3$ (50 mL), extracted with EtOAc or DCM (3 x 30 mL), the combined organic layers washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude tetrahydroquinoline **6**. Purification by column chromatography gave the pure tetrahydroquinoline.

((2*R*,3*R*,4*R*)-4-ethyl-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline **6a**



Prepared using the general procedure above using **5a**. (63 mg, 0.25 mmol) to give after column chromatography *cis*,*cis*-**6a** brown oil (44 mg, 62%); R_f = 0.33 (1:1 DCM:Hexanes); IR ν_{max} (neat) 3416 (N-H), 1545 (N-O), 1368 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32-7.45 (5H, m, Ar*H*), 7.08-7.16 (2H, m, Ar*H*), 6.82 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.68 (1H, dd, *J* = 7.9, 1.3 Hz, Ar*H*), 4.98 (1H, app. t, *J* = 2.9 Hz, C*H*NO_2), 4.76 (1H, d, *J* = 3.3 Hz, C*H*Ph), 4.25 (1H, s, N*H*), 3.20 (1H, ddd, *J* = 8.3, 5.3, 2.4 Hz, C*H*Et), 1.69 – 2.01 (2H, m, CH_2CH_3), 1.12 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 142.5 (Ar*C*). 138.1 (Ar*C*), 129.4 (Ar*C*H), 129.1 (Ar*C*H), 129.1 (Ar*C*), 127.6 (Ar*C*H), 126.8 (Ar*C*H), 121.2 (Ar*C*H), 118.8 (Ar*C*H), 114.7 (Ar*C*H), 86.8 (*C*H), 54.6 (*C*H), 41.8 (*C*HEt), 30.7 (CH_2CH_3), 11.6 (CH_2CH_3); m/z (ESI) 234 (100%, M-$H_3NO_2^+$), (45%, M+H^+); HRMS $C_{17}H_{19}N_2O_2$ calcd. 283.1447, found 283.1448.

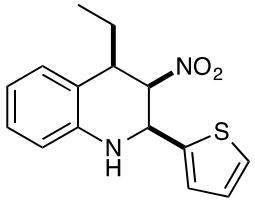
(2*R*,3*R*,4*R*)-4-ethyl-2-(4-fluorophenyl)-3-nitro-1,2,3,4-tetrahydroquinoline **6b**



Prepared using the general procedure above using **5b** (90 mg, 0.33 mmol) to give after column chromatography *cis*,*cis*-**6b** yellow wax (79 mg, 80%); R_f = 0.30 (1:1 DCM:Hexanes); IR ν_{max} (neat) 3386 (N-H), 1546 (N-O), 1367 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.30 – 7.36 (2H, m, Ar*H*), 7.07 – 7.16 (4H, m, Ar*H*), 6.81 – 6.85 (1H, m, Ar*H*), 6.68 (1H, dd, *J* = 8.0, 1.1 Hz, Ar*H*), 4.94 (1H, dd, *J* = 3.3, 2.6 Hz, C*H*NO_2), 4.75 (1H, d, *J* = 3.3 Hz, C*H*Ar), 4.21 (1H, s, N*H*), 3.20 (1H, ddd, *J* = 8.3, 5.4, 2.6 Hz, C*H*Et), 1.73 – 1.97 (2H, m, CH_2CH_3), 1.12 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 163.0 (d, *J* = 248.1 Hz, Ar*C*F), 128.6 (d, *J* = 8.4 Hz, Ar*C*H), 142.3 (Ar*C*), 133.9 (d, *J* = 3.8 Hz, Ar*C*), 129.4 (Ar*C*H), 127.7 (Ar*C*H), 121.2 (Ar*C*H), 119.0 (Ar*C*), 116.1 (d, *J* = 21.7 Hz, Ar*C*H), 114.8 (Ar*C*H), 86.9 (*C*H), 54.0 (*C*H), 41.6 (*C*HEt), 30.6

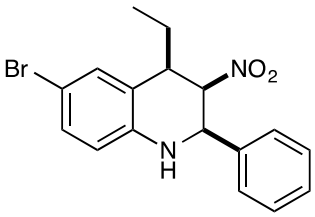
(CH_2CH_3), 11.6 (CH_2CH_3); 19F NMR ($CDCl_3$, 282 MHz) δ -112.6 (1F, s, Ar*F*); m/z (ESI) 301 (100%, $M+H^+$); HRMS $C_{17}H_{18}FN_2O_2$ calcd. 301.1352, found 301.1364.

(2*S*,3*R*,4*R*)-4-ethyl-3-nitro-2-(thiophen-2-yl)-1,2,3,4-tetrahydroquinoline **6c**



Prepared using the general procedure above using **5c** (26 mg, 0.10 mmol) to give after column chromatography *cis*,*cis*-**6c** as a brown oil (15 mg, 53%); R_f = 0.33 (1:1 DCM:Hexanes); IR ν_{max} (neat) 3400 (N-H), 1546 (N-O), 1364 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.26 – 7.28 (1H, m, Ar*H*), 7.04 – 7.16 (3H, m), 7.00 (1H, dd, *J* = 5.1, 3.6 Hz,Ar*H*), 6.85 (1H, td, *J* = 7.5, 1.2 Hz, Ar*H*), 6.68 (1H, dd, *J* = 7.9, 1.1 Hz, Ar*H*), 5.12 (1H, d, *J* = 3.6 Hz, C*H*Ph), 5.05 (1H, app. t, *J* = 3.9 Hz, C*H*NO_2), 3.37 (1H, app. dt, *J* = 8.5, 4.7 Hz, C*H*Et), 1.78 – 1.92 (2H, m, C*H*$_2$$CH_3$), 1.05 (3H, t, *J* = 7.4 Hz, CH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 141.8 (Ar*C*), 140.4 (Ar*C*), 129.2 (Ar*C*H), 127.7 (Ar*C*H), 127.2 (Ar*C*H), 126.0 (Ar*C*H), 125.9 (Ar*C*H), 121.4 (Ar*C*), 119.6 (Ar*C*H), 115.4 (Ar*C*H), 86.6 (*C*H), 51.5 (*C*H), 40.7 (*C*HEt), 29.5 (*C*H_2CH_3), 11.0 (CH_2*C*H_3); m/z (ESI) 301 (100%, $M+H^+$); HRMS $C_{15}H_{17}N_2O_2S$ calcd. 289.1011, found 289.1001.

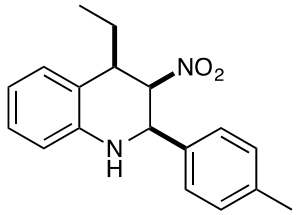
(2*R*,3*R*,4*R*)-6-bromo-4-ethyl-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline **6d**



Prepared using the general procedure above using **5d**. (83 mg, 0.25 mmol) to give after column chromatography *cis*,*cis*-**6d** yellow wax (72 mg, 80%); R_f = 0.41 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3376 (N-H), 1540 (N-O), 1334 (N-O) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.32 – 7.43 (5H, m, Ar*H*), 7.22 – 7.26

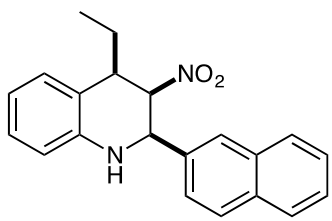
(1H, m, Ar*H*), 7.20 (1H, dd, *J* = 8.6, 2.2 Hz, Ar*H*), 6.57 (1H, d, *J* = 8.5 Hz, Ar*H*), 4.95 (1H, dd, *J* = 3.3, 2.3 Hz, C*H*NO_2), 4.73 (1H, d, *J* = 3.3 Hz, C*H*Ar), 4.28 (1H, s, N*H*), 3.16 (1H, ddd, *J* = 8.2, 5.3, 2.3 Hz, C*H*Et), 1.71 – 1.95 (2H, m, CH_2CH_3), 1.13 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 141.6 (Ar*C*), 137.6 (Ar*C*), 131.9 (Ar*C*H), 130.4 (Ar*C*H), 129.3 (Ar*C*H), 126.7 (Ar*C*H), 123.3 (Ar*C*), 116.3 (Ar*C*H), 86.3 (Ar*C*H), 79.7 (*C*H), 54.5 (*C*H), 41.7 (*C*HEt), 30.8 (CH_2CH_3), 11.6 (CH_2CH_3); m/z (ESI) 361 (100%, $M+H^+$); HRMS $C_{17}H_{18}BrN_2O_2$ calcd. 351.0552, found 361.0565.

(2*R*,3*R*,4*R*)-4-ethyl-3-nitro-2-(*p*-tolyl)-1,2,3,4-tetrahydroquinoline **6e**



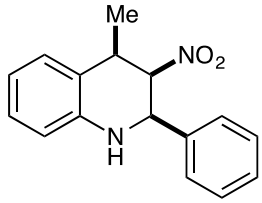
Prepared using the general procedure above using **5e** (106 mg, 0.40 mmol) to give after column chromatography *cis*,*cis*-**6e** cream wax (87 mg, 73%); R_f = 0.30 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3401 (N-H), 1542 (N-O), 1365 (N-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.18 – 7.25 (4H, m, Ar*H*), 7.09 – 7.14 (2H, m, Ar*H*), 6.79-6.82 (1H, m, Ar*H*), 6.67 (1H, dd, *J* = 7.9, 1.2 Hz, Ar*H*), 4.94 (1H, dd, *J* = 3.3, 2.4 Hz, C*H*NO_2), 4.71 (1H, d, *J* = 3.3 Hz, C*H*Ar), 4.21 (1H, s, N*H*), 3.18 (1H, ddd, *J* = 8.2, 5.3, 2.5 Hz, C*H*Et), 2.36 (3H, s, ArCCH_3), 1.73-1.96 (2H, m, CH_2CH_3), 1.11 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 142.6 (Ar*C*), 139.0 (Ar*C*), 135.0 (Ar*C*), 129.8 (Ar*C*H), 129.4 (Ar*C*H), 127.6 (Ar*C*H), 126.6 (Ar*C*H), 121.3 (Ar*C*), 118.7 (Ar*C*H), 114.7 (Ar*C*H), 86.9 (*C*HNO_2), 54.4 (*C*HAr), 41.8 (*C*HEt), 30.8 (CH_2CH_3), 21.3 (ArC*C*H_3), 11.6 (CH_2CH_3); m/z (EI) 220 (100%, M-$C_2H_6^+$), 296 (65%, M^+); HRMS $C_{18}H_{20}N_2O_2$ calcd. 296.1519, found 296.1520.

(2*R*,3*R*,4*R*)-4-ethyl-3-nitro-2-(*p*-tolyl)-1,2,3,4-tetrahydroquinoline **6f**



Prepared using the general procedure above using **5f** (92 mg, 0.30 mmol) give after column chromatography *cis*,*cis*-**6f** brown oil (86 mg, 86%); R_f = 0.25 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3366 (N-H), 1539 (N-O), 1336 (N-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.51-8.04 (6H, m, Ar*H*), 7.44 (1H, dd, *J* = 8.5, 1.8 Hz, Ar*H*), 7.13 – 7.18 (2H, m, Ar*H*), 6.85 (1H, td, *J* = 7.5, 1.2 Hz, Ar*H*), 6.74 (1H, dd, *J* = 7.9, 1.2 Hz, ArH), 5.08 (1H, dd, *J* = 3.3, 2.4 Hz, C*H*NO_2), 4.92 (1H, d, *J* = 3.3 Hz, C*H*Ar), 4.36 (1H, br. s, N*H*), 3.25 (1H, ddd, *J* = 8.2, 5.4, 2.3 Hz, C*H*Et), 1.77 – 2.01 (2H, m, C$H_2$$CH_3$), 1.16 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 134.7 (Ar*C*), 129.7 (Ar*C*), 129.5 (Ar*C*), 129.2 (Ar*C*H), 129.2 (Ar*C*H), 129.0 (Ar*C*H), 128.3 (Ar*C*H), 128.2 (Ar*C*H), 127.9 (Ar*C*H), 127.6 (Ar*C*H), 127.2 (Ar*C*H), 126.7 (Ar*C*H), 126.7 (Ar*C*H), 126.0 (Ar*C*H), 124.3 (Ar*C*H), 122.9 (Ar*C*), 118.9 (Ar*C*H), 114.8 (Ar*C*H), 86.8 (*C*H), 54.7 (*C*H), 42.0 (*C*HEt), 30.9 (*C*$H_2$$CH_3$), 11.7 ($CH_2$*C*$H_3$); m/z (ESI) 333 (100%, M+H^+); HRMS $C_{18}H_{21}N_2O_2$ calcd. 333.1603, found 333.1596.

(2*R*,3*R*,4*R*)-4-methyl-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline **6g**



Prepared using the general procedure above using **5g** (101 mg, 0.40 mmol) to give after column chromatography *cis*,*cis*-**6g** red oil (56 mg, 52%); R_f = 0.40 (9:1 pet. Ether:EtOAc); IR ν_{max} (neat) 3349 (N-H), 1544 (N-O), 1367 (N-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.28 – 7.40 (5H, m, Ar*H*), 7.18 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.12 (1H, m, Ar*H*), 6.83 (1H, td, *J* = 7.5, 1.2 Hz, Ar*H*), 6.67 (1H, dd, *J* = 8.0, 1.2 Hz, Ar*H*), 4.85 (1H, dd, *J* = 4.2, 3.6 Hz, C*H*NO_2), 4.82 (1H, d, *J* = 3.6 Hz, C*H*Ph), 3.45 (1H, qd, *J* = 7.1, 4.1 Hz, C*H*CH_3), 1.49 (3H, d, *J* = 7.1 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 142.3 (Ar*C*), 138.1 (Ar*C*), 129.1 (Ar*C*H), 129.1 (Ar*C*H), 128.8 (Ar*C*H), 127.7 (Ar*C*H), 126.8 (Ar*C*H), 122.4 (Ar*C*), 119.0 (Ar*C*H), 114.7 (Ar*C*H), 89.6 (*C*HPh), 55.0 (*C*HNO_2), 33.6 (*C*HCH_3), 22.7 (CH*C*H_3); m/z (EI) 206 (100%, M-$CH_4NO_2^+$), 268 (65%, M^+); HRMS $C_{16}H_{16}N_2O_2$ calcd. 268.1206, found 268.1206.

Refereces:

1) Anderson, J.C.; Barham, J.P.; Rundell, C.D., *Org*. *Lett.*, **2015**, 17, 4090.
2) Fra, L.; Millán, A.; Souto, J. A.; Muñiz, K., *Angew. Chem. Int. Ed.,* **2014,** *53*, 7349.