Supporting Information

Experimental.

All reactions were carried out in oven-dried apparatus under argon unless otherwise stated. All solvents were distilled prior to use. HPLC was performed on a reverse phase analytical column, observing at 254 nm using a gradient of between 5:95 and 95:5 acetonitrile:water containing 0.1% TFA. Resin washing was performed by bubbling nitrogen through solvent-suspended resin for 5-10 minutes. Reaction vessels were shaken in an Innova water bath at 180 rpm, and vessels were sealed (to exclude water) by fitting with a ground-glass stopper. FT-IR spectroscopy was performed on a Mattson Genesis FT-IR apparatus. Proton NMR spectra were recorded on either a 250 MHz or 400 MHz Bruker instrument. Carbon NMR spectra were taken on a 400 MHz Bruker irradiating at 100 MHz. TLC was performed on silica plates observing with UV or a ceric molybdate stain.

5-Benzyloxy-2-nitrotoluene (7)

5-Hydroxy-2-nitrotoluene (20.0 g, 0.131 mol) was dissolved in DMF (200 mL) and cesium carbonate (42.6 g, 0.131 mol) was added portionwise. To this suspension, vigorously stirred, was added benzyl bromide (12.4 mL, 0.105 mmol) rapidly dropwise and then the reaction mixture was stirred at rt for 16 h, giving a mustard-coloured suspension. This was diluted with toluene (100 mL) and 1 N aqueous NaOH (100 mL) and the layers separated. The organic layer was washed with 1 N aqueous HCl (100 mL). The acidic and alkaline aqueous portions were extracted with toluene (1 × 20 mL, 3 × 20 mL respectively), and the combined organic layers were washed with water (40 mL) and brine (40 mL), dried ($MgSO_4$) then concentrated *in vacuo* to give yellow-brown needles which were recrystallised from methanol to give the benzyl-protected nitrotoluene **7** as off-white needles (25.1 g, 99%).

R_f 0.59 (EtOAc-light petroleum (bp 60-80 ^oC), 1:1); mp 68-70 ^oC (lit.[6] 70.5-71.5 ^oC); ; IR (nujol) ν/cm^{-1} 1602, 1586, 1504, 1484, 1465, 1456; ^1H NMR (400 MHz, $CDCl_3$) δ 2.62 (3H, s), 5.13 (2H, s), 6.87 (2H, m), 7.40 (5H, m), 8.07 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.68, 70.48, 112.58, 118.39, 127.49, 127.58, 128.46, 128.80, 135.72, 137.08, 142.41, 162.17; MS (EI): *m/z* (rel intens) 243.1 (21), 91 (100). HRMS: Calcd. for $C_{14}H_{13}NO_3$, 243.0892; found, 243.0888. Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39; N, 5.76; found: C, 68.97; H, 5.40; N, 5.67.

***trans*-5-Benzyloxy-β-dimethylamino-2-nitrostyrene (8)**

To 5-benzyloxy-2-nitrotoluene (22.1 g, 0.091 mol) were added DMF (25 mL) and *N,N*-dimethylformamide dimethyl acetal (18.86 mL, 0.142 mol). The flask was fitted with a Vigreux column and heated at reflux such that the methanol was gradually distilled off, requiring a bath temperature that increased from 147 ^oC to 160 ^oC over 40 h. The reaction mixture was then allowed to cool and volatile components were removed *in vacuo* to give a thick, deep red oil which was crystallised from diethyl ether-benzene (3:1) to give the enamine **8** as dark red prisms (18.6 g, 68%).

R_f (EtOAc-light petroleum (bp 60-80 ^oC), 1:4) 0.18; mp 91-93 ^oC (lit.[6] 97.5-99 ^oC); IR (CCl_4) ν/cm^{-1} 1647, 1600, 1569, 1508; ^1H NMR (400 MHz, $CDCl_3$) δ 2.91 (6H, s), 5.12 (2H, s), 6.06 (1H, d, J = 13.4 Hz), 6.59 (1H, dd, J = 9.2 & 2.7 Hz), 6.87 (1H, d, J = 13.4 Hz), 6.92 (1H, d, J = 2.7 Hz), 7.40 (5H, m), 7.97 (1H, d, J = 9.2 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 39.81, 69.96, 90.87, 107.94, 109.79, 127.80, 127.82, 128.05, 128.52, 136.82, 138.57, 139.06, 145.85, 161.94; MS (FAB): *m/z* (rel intens) 299.0 (100), 281.0 (42), 191.0 (20), 176.0 (25). HRMS: Calcd. for $C_{17}H_{18}N_2O_3$, MH^+ 299.1391; found, MH^+ 299.1408. Anal. Calcd. for $C_{17}H_{18}N_2O_3$, C, 68.44; H, 6.08; N, 9.39; found: C, 68.06; H, 6.07; N, 9.23.

5-Benzyloxy-2-nitro-α,β-dihydro-α-dimethylstyryl acetal (9)

To *trans*-5-benzyloxy-b-dimethylamino-2-nitrostyrene (17.20 g, 0.058 mol) in methanol (250 mL) was added camphor sulfonic acid (40.4 g, 0.174 mol) followed by further methanol (50 mL). This solution was heated at reflux for 16 h, and upon cooling to rt, crystals formed spontaneously. The reaction mixture was filtered, and the crystals washed with cold methanol then dried *in vacuo*. Recrystallisation from methanol gave the *acetal* **9** as orange-yellow plates (18.30 g, 100%).

R_f (EtOAc-light petroleum (bp 60-80 °C), 15:85) 0.17; mp 88-90 °C; IR (nujol) ν/cm^{-1} 1601, 1589, 1517, 1485, 1456; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.23 (2H, d, J = 5.3 Hz), 3.34 (6H, s), 4.57 (1H, t, J = 5.3 Hz), 5.13 (2H, s), 6.90 (1H, dd, J = 8.9 & 2.8 Hz), 6.94 (1H, d, J = 2.7 Hz), 7.38 (5H, m), 8.00 (1H, d, J = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.92, 54.32, 70.48, 104.52, 113.49, 119.30, 127.34, 127.49, 128.40, 128.74, 135.05, 135.68, 142.82, 161.82. MS (FAB): *m/z* (rel intens) 340.1 (4), 316.1 (8), 286.1 (100). HRMS: Calcd. for $C_{17}H_{19}NO_5$, 316.1180; found, 316.1167. Anal. Calcd. for $C_{17}H_{19}NO_5$, C, 64.34; H, 6.03; N, 4.41; found, C, 64.15; H, 6.02; N, 4.36.

5-Hydroxy-2-amino-α,β-dihydro-α-dimethylstyryl acetal (1)

10% Palladium on carbon (1.2 g) was placed under argon and then suspended in ethanol (400 mL). The flask was re-purged with argon and stirred vigorously whilst 5-benzyloxy-2-nitro-α,β-dihydro-α-dimethylstyryl acetal (1.0 g, 3.15 mmol) was introduced portionwise. The flask was subjected to 5 evacuation-then-argon cycles, followed by 5 evacuation-then-hydrogen cycles and then allowed to stir under balloon-pressure hydrogen for 16 h. The reaction mixture was then filtered through a pad of Celite on filter paper and washed through with further ethanol. The filtrate was concentrated *in vacuo* to yield an orange-brown oil. This oil was dissolved in CH_2Cl_2:hexane (1:1) at rt and left at -18 °C for 16 h. The resultant solid was filtered and washed with ice cold CH_2Cl_2:hexane (1:1) then dried *in vacuo* to give the *amino acetal* **1** as an off-white powder. The mother liquor was concentrated *in vacuo* and purified by flash column chromatography in 1:1 EtOAc-light petroleum (bp 60-80 °C) to give a further quantity of the desired *acetal* **1**. The total product yield was 435 mg (70%).

R_f (EtOAc-light petroleum (bp 60-80 °C), 1:1) 0.15; mp 69-70 °C; IR ($CDCl_3$) ν/cm^{-1} 3601, 3424 br, 3347 br, 2964, 2940, 2839, 1612, 1506, 1450 cm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (1H, br s), 2.81 (2H, d, J = 5.4 Hz), 3.37 (6H, s), 4.49 (1H, t, J = 5.37 Hz), 6.57 (3H, m); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 35.69, 53.21, 106.31, 113.92, 117.42, 117.89, 124.47, 137.58, 150.02. MS (FAB): *m/z* (rel intens) 197.1 (100), 166.1 (94). HRMS: Calcd. for $C_{10}H_{15}NO_3$, 197.1048; found, 197.1059. Anal. Calcd. for $C_{10}H_{15}NO_3$, C, 60.90; H, 7.67; N, 7.10; found, C, 60.60; H, 7.62; N, 7.03.

5-Polystyrylbenzyloxy-2-amino-α,β-dihydro-α-dimethylstyryl acetal (3)

To chloromethyl polystyrene resin (1 mmolg^{-1}, 500 mg, 0.50 mmol) swollen in DMA (5 mL) were added 5-hydroxy-2-amino-α,β-dihydro-α-dimethylstyryl acetal (300 mg, 1.5 mmol), sodium methoxide (81 mg, 1.5 mmol) and tetra-n-butyl ammonium iodide (28 mg, 5 mol%). The reaction vessel was closed and shaken at rt for 16 h. The resin was then filtered and washed with CH_2Cl_2 (2 × 5 mL), dioxane (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), DMF:water (1:1, 2 × 5 mL), CH_2Cl_2 (2 × 5 mL), CH_2Cl_2:MeOH (1:1, 2 × 5 mL), CH_2Cl_2 (2 × 5 mL), then dried *in vacuo* for 16 h to yield the *support-bound linker* **3** as a light brown powder (565 mg, 81% by mass).

IR (CH_2Cl_2 gel) ν/cm^{-1} 3431, 3355, 1629, 1615, 1505; ^{13}C NMR (100 MHz, CD_2Cl_2 gel) δ 36.49, 53.89, 70.65, 106.37, 113.87, 116.94, 118.13, 123.94, 140.08, 151.95; Anal. Found, C, 85.60; H, 7.66; N, 1.44; Cl, 0.75.

5-Polystyrylbenzyloxy-2-*N*-(4-iodobenzoyl)amino-α,β-dihydro-α-dimethylstyryl acetal (10)

To 5-polystyrylbenzyloxy-2-amino-α,β-dihydro-α-dimethylstyryl acetal **3** (approx. mmolg^{-1}, 200 mg, 0.2 mmol) swollen in CH_2Cl_2 (5 mL) were added 4-iodobenzoyl chloride (229 mg, 0.86 mmol) and pyridine (70 μL, 0.86 mmol). The reaction vessel was closed and shaken at rt for 16 h. The resin was then filtered and washed with CH_2Cl_2 (2 × 5 mL), dioxane (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), dioxane:water (1:1, 2 × 5 mL), CH_2Cl_2 (2 × 5 mL), toluene (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), then dried *in vacuo* for 16 h to give the *iodobenzamide resin* **10** as a light brown powder (250 mg, 100% by mass).

IR (CH_2Cl_2 gel) ν/cm^{-1} 3348, 1667, 1602, 1585; ^{13}C NMR (100 MHz, CD_2Cl_2 gel) δ 37.27, 54.53, 70.18, 98, 106.86, 113.10, 117.71, 137.87; Found C, 76.30; H, 6.56; N, 1.07; Cl, 0.00.

5-Polystyrylbenzyloxy-2-*N*-(5-phenylvaleroyl)amino-α,β-dihydro-α-dimethylstyryl acetal (11)

To 5-phenylvaleric acid (154 mg, 0.86 mmol) and HATU (360 mg, 0.95 mmol) dissolved in DMA (5 mL) was added pyridine (70 μL, 0.86 mmol) and this solution was allowed to stir at rt for 40 min. To this solution was then added 5-polystyrylbenzyloxy-2-amino-α,β-dihydro-α-dimethylstyryl acetal (200 mg, 0.2 mmol), the reaction vessel was closed and shaken at rt for 16 h. The resin was then filtered and washed with CH_2Cl_2 (2 × 5 mL), dioxane (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), DMF:H_2O (1:1, 2 × 5 mL), CH_2Cl_2 (2 × 5 mL), CH_2Cl_2:MeOH (1:1, 2 × 5 mL), CH_2Cl_2 (2 × 5 mL), and dried *in vacuo* for 16 h to give the *valeramide resin* **11** as a light brown powder (230 mg, 100% by mass).

IR (CH_2Cl_2 gel) ν/cm^{-1} 3351, 1678, 1602; ^{13}C NMR (100 MHz, CD_2Cl_2 gel) δ 25.41, 31.15, 35.20, 37.07, 37.40, 54.35, 70.16, 106.73, 112.96, 117.44, 142.40; Anal. Found C, 84.51; H, 7.58; N, 1.06; Cl, 0.28.

5-Polystyrylbenzyloxy-*N*-(4-iodobenzoyl)indolylamide (12)

To 5-polystyrylbenzyloxy-2-*N*-(4-iodobenzoyl)amino-α,β-dihydro-α-dimethylstyryl acetal **10** (0.9 meq., 184 mg, 0.17 mmol) swollen in toluene (4 mL) was added PPTS (5 mg, 10 mol%). The reaction vessel was closed and shaken at 50 ^{o}C for 16 h. The resin was filtered and washed with CH_2Cl_2 (2 × 5 mL), dioxane (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), DMF:H_2O (1:1, 2 × 5 mL), CH_2Cl_2 (2 × 5 mL), CH_2Cl_2:MeOH (1:1, 2 × 5 mL), CH_2Cl_2 (2 × 5 mL), then dried *in vacuo* for 16 h to give the *indolyl iodobenzamide resin* **12** as a light orange-pink powder (184 mg).

IR (CH_2Cl_2 gel) ν/cm^{-1} 1681, 1611, 1602, 1585; ^{13}C NMR (100 MHz, CD_2Cl_2 gel) δ 70.45, 104.89, 108.73, 114.14, 117.14, 137.83, 156.19; Anal. Found C, 79.23; H, 6.35; N, 1.10; Cl, 0.00.

5-Polystyrylbenzyloxy-*N*-(5-phenylvaleroyl)indolyl amide (13)

The procedure followed was that for the iodobenzamide resin **12** above, to yield the *indolylvaleramide resin* **13** as a light brown powder (no mass change).

IR (CH_2Cl_2 gel) ν/cm^{-1} 1700, 1611, 1602, 1582; ^{13}C NMR (100 MHz, CD_2Cl_2 gel) δ 24.24, 30.90, 35.30, 35.63, 70.38, 104.69, 108.48, 114.03, 117.23, 125.75, 142.22, 155.69, 170.93; Found: C, 88.34; H, 7.46; N, 1.25; Cl, 0.16.

Typical Procedure for Amide cleavage

To 5-Polystyrylbenzyloxy-*N*-(4-iodobenzoyl)indolyl-amide **12** (100 mg, 0.075 mmol) swollen in THF (2 mL) was added pyrrolidine (94 μL, 1.13 mmol). Product release began immediately as determined by TLC. The suspension was purged with Ar, sealed and shaken at room temperature for 3 days. The resin was then filtered and washed with CH_2Cl_2 (3 × 2 mL) and the combined organic filtrates were washed with 1 N aqueous HCl (3 × 5 mL). Removal of the solvent *in vacuo* gave amide **14** as a white solid (22 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (4H, m), 3.40 (2H, t, J = 6.4), 3.62 (2H, t, J = 6.8 Hz), 7.26 (2H, d, J = 8.7 Hz), 7.75 (2H, d, J = 8.8 Hz)

Typical Procedure for Ester Cleavage

To 5-Polystyrylbenzyloxy-*N*-(4-iodobenzoyl)indolyl- amide **12** (100 mg, 0.075 mmol) swollen in THF (2 mL) was added methanol (100 μL) then $NaNH_2$ (2 mg, 0.05 mmol). Product release was immediate by TLC. The vessel was purged with Ar, sealed and shaken for 30 mins. The suspension was then treated with saturated aqueous NH_4Cl solution, filtered and washed with CH_2Cl_2 (3 × 2 mL). The combined organic filtrates were concentrated *in vacuo* to give methyl ester **16** as a white solid (19 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (3H, s), 7.74 (2H, d, *J* = 6.8 Hz), 7.80 (2H, d, *J* = 6.7 Hz).

Typical Procedure for Acid Cleavage

To 5-Polystyrylbenzyloxy-*N*-(4-iodobenzoyl)indolyl- amide **12** (100 mg, 0.075 mmol) swollen in dioxane (4 mL) was added methanol (1 mL) and 1 N aqueous NaOH (800 mL). The vessel was sealed and shaken for 16 h at rt. The reaction was then quenched with 1 N aqueous HCl (5 mL) and the resin filtered and washed with CH_2Cl_2 (3 × 2 mL). The combined organic filtrates were concentrated *in vacuo* to give acid **17** as a white solid (17 mg, 91%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (2H, d, *J* = 8.6 Hz), 7.85 (2H, d, *J* = 8.6 Hz)

Comparison of Lability: Resins A and B

To two separate flasks containing resin **10** (65 mg, 0.049 mmol) and resin **12** (63 mg, 0.049 mmol) was added THF (2 ml) and pyrrolidine (61 μL, 0.73 mmol) under Ar. The vessels were sealed and shaken at rt for 5 h. After filtration, washing with 1 N aqueous HCl (3 × 2 mL) and solvent removal *in vacuo*, the organic residues were each taken up in $CDCl_3$ containing 1% TMS (500 mL). ^{1}H NMR spectra were recorded of each and the peaks known to correspond to the product were integrated with respect to the TMS internal standard set to 1.000. The sample containing the activated resin **12** integrated to 26.916 for a 2-proton peak, unactivated sample **10** gave only 0.058 for the same signal.

5-Polystyrylbenzyloxy-2-*N*-(4-phenylbenzoyl)amino-α,β-dihydro-α-dimethylstyryl acetal (22)

To 5-polystyrylbenzyloxy-2-*N*-(4-iodobenzoyl)amino-α,β-dihydro-α-dimethylstyryl acetal **10** (0.86 $mmolg^{-1}$, 251 mg, 0.216 mmol) swollen in anhydrous degassed DMF (3 mL) was added tetrakis(triphenylphosphine)palladium (0) (40mg). After 10 minutes, degassed aqueous 2 M Na_2CO_3 (1.30 ml, 12 equiv) and phenylboronic acid (132 mg, 5 equiv) were added to the suspension and a further 5 mL DMF was added to reswell the resin. The reaction vessel was closed and shaken at 50 °C for 16 h. The resin was then filtered and washed with DMF (5 mL), THF (2 × 5 mL), THF/H_2O (1:1, 2 × 5 mL), THF (2 × 5 mL), MeOH (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), then dried *in vacuo* for 16 h to give the *biarylamide resin* **22** as a light brown powder (254 mg, >100% by mass, due to palladium deposition).

IR (CH_2Cl_2 gel) *v*/cm^{-1} 3358, 1666, 1602, 1585; ^{13}C NMR (100 MHz, CD_2Cl_2 gel) δ 37.34, 54.58, 70.20, 106.95, 113.10, 117.72.

5-Polystyrylbenzyloxy-*N*-(4-iodobenzoyl)indolylamide (23)

The procedure followed was that for the iodobenzamide resin **12** above, to yield the *indolylbiarylamide resin* **23** as a light brown powder (no mass change).

IR (CH_2Cl_2 gel) *v*/cm^{-1} 1680, 1611, 1602, 1585; ^{13}C NMR (100 MHz, CD_2Cl_2 gel) δ 70.38, 104.73, 108.08, 113.90, 117.10.