Relaying stereochemistry through aromatic ureas: 1,9 and 1,15 remote stereocontrol

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SUPPORTING INFORMATION

General Information

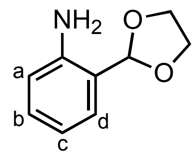
NMR spectra were recorded on a Varian XL 300 or a Bruker Ultrashield 300, 400 or 500 spectrometer. The chemical shifts (δ) are reported in ppm downfield of trimethylsilane and coupling constants (J) reported in hertz and rounded to 0.5 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or a combination of these. Solvents were used as internal standard when assigning NMR spectra (δ_H: $CDCl_3$ 7.27 ppm; δ_C: $CDCl_3$ 77.0 ppm; δ_H: DMSO-d_6 2.50 ppm; δ_C: DMSO-d_6 39.4 ppm; δ_H: CD_3OD 3.31 ppm; δ_C: CD_3OD 49.0 ppm;).

Low and high resolution mass spectra were recorded by staff at the University of Manchester. EI and CI spectra were recorded on a Fisons VG Trio 2000; and high resolution mass spectra (HRMS) were recorded on a Kratos Concept-IS mass spectrometer, and are accurate to ± 0.001. Infrared spectra were recorded on an Ati Matson Genesis Series FTIR spectrometer as a film on a sodium chloride plate. Absorptions reported are sharp and strong unless otherwise stated as broad (br), medium (m), or weak (w), only absorption maxima of interest are reported. Melting points (mpt) were determined on a Gallenkamp apparatus and are uncorrected.

Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel alugram Sil G/$_{UV254}$) and visualised with UV light at 254 nm or phosphomolybdic acid dip (5 % in ethanol). Flash chromatography was carried out using Fluorochem Davisil 40-63u 60 Å.

All reactions were conducted under an atmosphere of dry nitrogen in oven dried glassware. Tetrahydrofuran (THF) was distilled under nitrogen from sodium using benzophenone as indicator. Dichloromethane and toluene were obtained by distillation from calcium hydride under nitrogen. Petrol refers to the fraction of light petroleum ether boiling between 40-65 °C. All other solvents and commercially obtained reagents were used as received or purified using standard procedures.

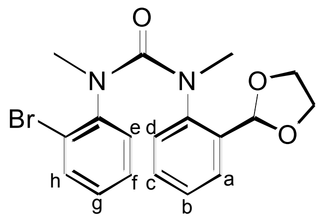
***2-(1,3-Dioxolan-2-yl)benzenamine*, 4**



2-Nitrobenzaldehyde (15.0 g, 100 mmol) was dissolved in toluene (200 cm^3) at room temperature, ethylene glycol (30 cm^3) and PTSA (0.20 g, 1.2 mmol) were added, the mixture heated to reflux temperature and maintained at this temperature for 18 h. Cooled to room temperature, CH_2Cl_2 (200 cm^3) and saturated $NaHCO_3$ (50 cm^3) added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 cm^3), the combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 1 % Et_3N in petrol to 1 % Et_3N, 10 % EtOAc in petrol) to give *2-(2-nitrophenyl)-1,3-dioxolane* (19.1 g, 99 %), as a yellow oil; R_f (20 % EtOAc in petrol) 0.29; υ_{max} (film)/cm^{-1} 1533 (NO_2); δ_H (300 MHz; $CDCl_3$) 7.94 (1 H, dd, *J* 8.0 and 1.5, CH-a), 7.85 (1 H, dd, *J* 8.0 and 1.5, CH-d), 7.67 (1 H, ddd, *J* 8.0, 8.0 and 1.5, CH-c), 7.55 (1 H, ddd, *J* 8.0, 8.0 and 1.5, CH-b), 6.54 [1 H, s, (CHO_2)] and 4.13-4.06 [4 H, m, (CH_2) × 2]; δ_C (75 MHz; $CDCl_3$) 149.1 (C), 133.5 (C), 133.2 (CH), 129.9 (CH), 127.9 (CH), 124.7 (CH), 99.8 (CH) and 65.6 [(CH_2) × 2]; m/z (CI) 213 (100 %, M+NH_4^+); (Found: M+NH_4^+, 213.0870, $C_9H_{13}N_2O_4$ requires *M+H*, 213.0870).

The 2-(2-nitrophenyl)-1,3-dioxolane (18.0 g, 92.0 mmol) was dissolved in IPA (200 cm^3), triethylamine (50 cm^3, 36 mmol), 10 % palladium on carbon (0.98 g, 0.92 mmol) added and the suspension stirred under a hydrogen atmosphere for 18 h. The suspension was filtered through celite and the filtrate dissolved in CH_2Cl_2 (100 cm^3). The organic layer was washed with saturated $NaHCO_3$ (2 × 50 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 1 % Et_3N in petrol to 1 % Et_3N, 10 % EtOAc in petrol) to give *2-(1,3-dioxolan-2-yl)benzenamine* **4** (15.2 g, 98 %), as a yellow oil; R_f (20 % EtOAc in petrol) 0.25; υ_{max} (film)/cm^{-1} 3490, 3389 and 1623 (N–H); δ_H (300 MHz; $CDCl_3$) 7.36 (1 H, dd, *J* 8.0 and 1.5, CH-d), 7.22 (1 H, ddd, *J* 8.0, 8.0 and 1.5, CH-b), 6.82 (1 H, ddd, *J* 8.0, 8.0 and 1.5, CH-c), 6.77 (1 H, dd, *J* 8.0 and 1.5, CH-a), 5.88 [1 H, s, (CHO_2)] and 4.20-4.07 [4 H, m, (CH_2) × 2]; δ_C (75 MHz; $CDCl_3$) 145.5 (C), 130.3 (CH), 127.8 (CH), 121.5 (C), 118.2 (CH), 116.8 (CH), 103.6 (CH), and 65.1 [(CH_2) × 2]; m/z (CI) 166 (100 %, M+H^+); (Found: M+H^+, 166.0864, $C_9H_{12}NO_2$ requires *M+H*, 166.0863).

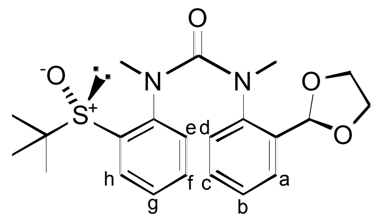
***1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-(2-bromophenyl)-1,3-dimethylurea*, 5**



2-(1,3-Dioxolan-2-yl)benzenamine **4** (0.50 g, 3.0 mmol) was dissolved in CH_2Cl_2 at room temperature, 2-bromophenylisocyanate (0.36 cm^3, 3.0 mmol) added dropwise and stirred for 18 h. The precipitate was isolated to give *1-(2-(1,3-dioxolan-2-yl)phenyl)-3-(2-bromophenyl)urea* (1.05g, 97 %), as colourless cubes, m.p. 195-198 ºC (from EtOAc-pentane); R_f (EtOAc) 0.50; υ_{max} (film)/cm^{-1} 3435 (NH), 1686 (C=O) and 759 (C-Br); δ_H (300 MHz; d_6-DMSO) 8.67 [2 H, s, (NH) × 2], 7.91 (1 H, dd, *J* 8.0 and 1.5, CH-e), 7.71 (1 H, dd, *J* 8.0 and 1.5, CH-d), 7.61 (1 H, dd, *J* 8.0 and 1.5, CH-h), 7.45 (1 H, dd, *J* 8.0 and 1.5, CH-a), 7.35 (1 H, td, *J* 8.0 and 1.5, CH-f), 7.31 (1 H, td, *J* 8.0 and 1.5, CH-c), 7.11 (1 H, td, *J* 8.0 and 1.5, CH-b), 6.99 (1 H, td, *J* 8.0 and 1.5, CH-g), 5.88 [1 H, s, (CHO_2)], 4.13-4.03 [2 H, m, (OCH_2CH_2O)] and 4.03-3.93 [2 H, m, (OCH_2CH_2O)]; δ_C (75 MHz; d_6-DMSO) 153.5 (C=O), 137.8 (C), 137.6 (C), 133.2 (CH), 129.9 (CH), 129.1 (C), 128.7 (CH), 127.6 (CH), 125.3 (CH), 124.6 (CH), 124.5 (CH), 124.0 (CH), 115.1 (C), 100.9 (CH) and 65.5 [(CH_2) × 2]; m/z (ES^+) 363 (100 %, $M+H^+$); (Found: $M+H^+$, 363.0349, $C_{16}H_{15}N_2O_3$ requires *M+H*, 363.0345).

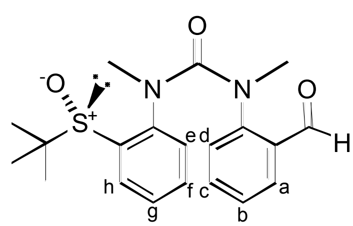
The 1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-(2-bromophenyl)urea (2.0 g, 5.5 mmol) was dissolved in THF (40 cm^3) and cooled to 0 ºC. Sodium hydride (0.66 g, 16 mmol) was added portionwise and stirred at room temperature for 1 h. Methyl iodide (1.05 cm^3, 16 mmol) was added and stirred at room temperature for 19 h. Water (50 cm^3) was added and extracted with EtOAc (3 × 30 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 10 % EtOAc and 2 % Et_3N in petrol) to give *1-(2-(1,3-dioxolan-2-yl)phenyl)-3-(2-bromophenyl)-1,3-dimethylurea* **5** (2.10 g, 98 %), as colourless cubes, m.p. 202-204 ºC (from EtOAc-pentane); R_f (50 % EtOAc in petrol) 0.24; υ_{max} (film)/cm^{-1} 1711 (C=O) and 733 (C-Br); δ_H (300 MHz; $CDCl_3$) 7.40-7.30 (2 H, m, CH-d and CH-e), 7.11-6.93 (2 H, m, CH-a and CH-h), 6.91-6.80 (2 H, m, CH-c and CH-f), 6.86-6.56 (2 H, m, CH-b and CH-g), 5.70 [1 H, s, (CHO_2)], 4.18-4.11 [2 H, m, (OCH_2CH_2O)], 4.10-3.98 [2 H, m, (OCH_2CH_2O)], 3.25 [3 H, s, $(NCH_3)_A$] and 3.17 [3 H, s, $(NCH_3)_B$]; δ_C (75 MHz; $CDCl_3$) 157.5 (C=O), 143.9 (C), 143.1 (C), 133.3 (CH), 130.2 (CH), 130.0 (CH), 128.3 (C), 127.9 (CH), 127.7 (CH), 127.3 (CH), 126.9 (CH), 126.8 (CH), 110.0 (C), 99.7 (CH), 65.5 (CH_2), 64.0 (CH_2), 40.7 $(NCH_3)_A$ and 39.1 (NCH_3); m/z (ES^+) 391 (100 %, $M+H^+$); (Found: $M+H^+$, 391.0660, $C_{18}H_{19}N_2O_3S$ requires *M+H*, 391.0658).

***1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-(2-(tert-butylsulfinyl)phenyl)-1,3-dimethylurea*, 6**



1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-(2-bromophenyl)-1,3-dimethylurea **5** (2.0 g, 5.2 mmol) was dissolved in THF (90 cm^3) and cooled to –90 ºC. *n*-Butyllithium (2.40 cm^3, 5.72, 2.38 mmol in hexanes) was added dropwise and stirred for 1 min at –90 ºC. After this time, (*S*)-*tert*-Butyl 2-methylpropane-2-sulfinothioate [1.13 g, 5.72 mmol in THF (10 cm^3)][1] was added in one portion and stirred at –90 ºC for 5 min. After warming to room temperature over 18 h, saturated aqueous ammonium chloride (10 cm^3) and water (20 cm^3) were added and the aqueous layer extracted with EtOAc (3 × 50 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 20 % EtOAc and 2 % Et_3N in petrol) to give *1-(2-(1,3-dioxolan-2-yl)phenyl)-3-(2-(tert-butylsulfinyl)phenyl)-1,3-dimethylurea* **6** (1.41 g, 65 %), as colourless cubes, m.p. 232-234 ºC (from EtOAc-pentane); $[\alpha]_D^{22} = -36.0$ (c = 0.5 in CH_2Cl_2); R_f (EtOAc) 0.15; υ_{max} (film)/cm^{-1} 1648 (C=O) and 1069 (S=O); δ_H (300 MHz; $CDCl_3$) 7.40-7.30 (1 H, d, *J* 8.0, CH-d), 7.35 (1 H, br., CH-e), 7.20-6.66 (4 H, br., CH-a, CH-c, CH-f and CH-h), 6.66-6.30 (2 H, br., CH-b and CH-g), 5.68 [1 H, br., (CHO_2)], 4.34-3.84 [4 H, br., (OCH_2CH_2O)], 3.27 [3 H, s, $(NCH_3)_A$], 3.23 [3 H, s, $(NCH_3)_B$] and 1.20 [9 H, s, (CH_3) × 3]; δ_C (75 MHz; $CDCl_3$) 159.7 (C=O), 144.3 (C), 143.2 (C), 131.9 (CH), 131.0 (C), 130.3 (CH), 130.1 (CH), 129.3 (CH), 129.2 (CH), 127.1 (CH), 126.4 (CH), 125.6 (CH), 110.0 (C), 99.4 (CH), 65.4 [(CH_2) × 2], 56.0 (C), 40.4 $(NCH_3)_A$, 39.7 $(NCH_3)_B$ and 11.7 [(CH_3) × 3]; m/z (ES^+) 431 (100 %, $M+H^+$); (Found: $M+H^+$, 418.1929, $C_{22}H_{29}N_2O_4S$ requires *M+H*, 418.1927).

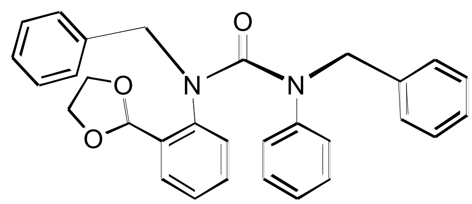
***1-(2-(tert-Butylsulfinyl)phenyl)-3-(2-formylphenyl)-1,3-dimethylurea*, 7**



1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-(2-(*tert*-butylsulfinyl)phenyl)-1,3-dimethylurea **6** (0.90 g, 2.2 mmol) was dissolved in THF (40 cm^3), 1 N aqueous hydrochloric acid (30 cm^3) added and stirred at room temperature for 16 h. The aqueous layer was extracted with EtOAc (3 × 20 cm^3), the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 40 % EtOAc in petrol) to give *1-(2-(tert-butylsulfinyl)phenyl)-3-(2-formylphenyl)-1,3-dimethylurea* **7**

(0.79 g, 98 %), as colourless cubes, m.p. 224-226 ºC (from EtOAc-pentane); $[\alpha]_D^{24}$ = – 40.0 (c = 0.2 in $CDCl_3$); R_f (EtOAc) 0.12; υ_{max} (film)/cm^{-1} 1687 (HC=O), 1660 (C=O) and 1034 (S=O); δ_H (300 MHz; $CDCl_3$) 10.05 (1 H, s, CH=O), 7.68 (1 H, dd, *J* 8.0 and 1.5, CH-d), 7.61 (1 H, dd, *J* 8.0 and 1.5, CH-a), 7.22 (1 H, br., CH-c), 7.15-7.03 (2 H, m, CH-g and CH-f), 6.94 (1 H, td, *J* 8.0 and 1.5, CH-b), 6.87 (1 H, br., CH-e) 6.35 (1 H, dd, *J* 8.0 and 1.5, CH-h), 3.43 [3 H, s, $(NCH_3)_A$], 3.25 [3 H, s, $(NCH_3)_B$ and 1.21 [9 H, s, $(CH_3) \times 3$]; δ_C (75 MHz; $CDCl_3$) 190.0 (HC=O), 160.3 (C=O), 143.5 (C), 139.2 (C), 138.1 (C), 134.9 (CH), 132.2 (CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 126.6 (CH), 126.4 (CH), 125.9 (CH), 56.3 (C), 39.3 $(NCH_3)_A$, 39.0 $(NCH_3)_B$ and 23.1 [$(CH_3) \times 3$]; m/z (ES$^+$) 374 (100 %, M+H$^+$); (Found: M+H$^+$, 374.1667, $C_{20}H_{25}N_2O_3S$ requires *M+H*, 374.1665).

***1-(2-(1,3-Dioxolan-2-yl)phenyl)-1,3-dibenzyl-3-phenylurea*, 8**

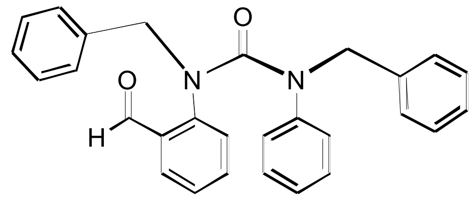


2-(1,3-Dioxolan-2-yl)benzenamine **4** (1.64 g, 10.0 mmol) was dissolved in CH_2Cl_2 (50 cm^3). Phenyl isocyanate (10.9 cm^3, 10.0 mmol) was added dropwise, stirred for 60 h and concentrated under reduced pressure. The residue was recrystallised from CH_2Cl_2-petrol to give *1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-phenylurea* (2.69 g, 95 %) as white cubes, m.p. 167-169 ºC (from CH_2Cl_2-petrol); R_f (2 % Et_3N, 49 % EtOAc in petrol) 0.50; υ_{max} (film)/cm^{-1} 3584 (N–H) and 1710 (C=O); δ_H (300 MHz; $CDCl_3$) 9.39 [1 H, s, $(NH)_A$], 8.06 [1 H, s, $(NH)_B$], 7.87 (1 H, dd, *J* 8.0 and 1.0, CH-a), 7.55-7.44 (3 H, m, CH-d and CH-e), 7.42-7.27 (3 H, m, CH-c and CH-f), 7.11 (1 H, ddd, *J* 8.0, 7.5 and 1.0, CH-b), 7.01 (1 H, tt, *J* 8.0 and 1.0, CH-g), 5.87 [1 H, s, (CHO_2)], 4.18-4.09 [2 H, m, (OCH_2CH_2O)] and 4.09-4.00 [2 H, m, (OCH_2CH_2O)]; δ_C (75 MHz; $CDCl_3$) 153.3 (C=O), 140.6 (C), 138.0 (C), 130.0 (CH), 129.5 (CH), 127.7 (CH), 127.6 (C), 123.6 (CH), 123.3 (CH), 122.5 (CH), 119.0 (CH), 101.7 (CH) and 65.5 [$(CH_2) \times 2$]; m/z (ES$^+$) 307 (100 %, M+Na$^+$); (Found: M+Na$^+$, 307.1056, $C_{16}H_{16}N_2O_3Na$ requires *M+Na*, 307.1053).

The 1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-phenylurea (1.60 g, 5.65 mmol) was dissolved in THF (57 cm^3) and cooled to 0 ºC. Sodium hydride (0.90 g, 23 mmol) was added portionwise and stirred at room temperature for 2 h. Benzyl bromide (2.74 cm^3, 23.0 mmol) was added dropwise and stirred at room temperature for 19 h. Water (50 cm^3) was added and extracted with EtOAc (3 × 40 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 2 % Et_3N, 10 % EtOAc in petrol) to give *1-(2-(1,3-dioxolan-2-yl)phenyl)-1,3-dibenzyl-3-phenylurea* **8** (1.33 g, 51 %) as a colourless oil, R_f (2 % Et_3N, 49 % EtOAc in petrol) 0.31; υ_{max} (film)/cm^{-1} 1715 (C=O); δ_H (300 MHz; $CDCl_3$) 7.54-7.34 (10 H, m, Ar), 7.10 (1 H, dd, *J* 7.5 and 7.0, Ar), 7.04-6.96 (2 H, br., Ar), 6.87 (1 H, dd, *J* 8.0 and 7.5, Ar), 6.76-6.67 (2 H, br., Ar), 6.35 (1 H, d, *J* 8.0, Ar), 5.66 [1 H, s, (CHO_2)], 5.10-

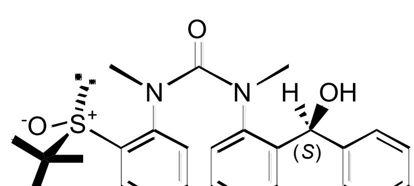
4.70 [4 H, br., (NCH_2Ar) × 2], 4.20-4.05 [2 H, br., (OCH_2CH$_2$O)] and 4.04-3.80 [2 H, br., (OCH$_2$CH_2O)]; δ_C (75 MHz; $CDCl_3$) 161.5 (C=O), 143.8 (C), 142.8 (C), 138.8 (C), 138.6 (C), 135.0 (C), 129.6 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.4 (CH), 126.8 (CH), 126.0 (CH), 125.6 (CH), 99.9 (CH), 65.6 [(CH_2) × 2], 56.4 (N*C*H$_2$Ar)$_A$ and 56.1 (N*C*H$_2$Ar)$_B$; m/z (ES^+) 487 (100 %, M+Na^+); (Found: M+Na^+, 487.2001, $C_{30}H_{28}N_2O_3Na$ requires *M+Na*, 487.1998).

***1,3-Dibenzyl-1-(2-formylphenyl)-3-phenylurea*, 9**



1-(2-(1,3-Dioxolan-2-yl)phenyl)-1,3-dibenzyl-3-phenylurea **8** (1.30 g, 2.80 mmol) was dissolved in THF (28 cm^3), 1 N aqueous hydrochloric acid (30 cm^3) added and stirred at room temperature for 16 h. The aqueous layer was extracted with EtOAc (3 × 20 cm^3), the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 40 % EtOAc in petrol) to give *1,3-dibenzyl-1-(2-formylphenyl)-3-phenylurea* **9** (1.18 g, 99 %) as a colourless oil, R_f (2 % Et_3N, 49 % EtOAc in petrol) 0.76; υ_{max} (film)/cm^{-1} 1715 (C=O) and 1655 (C=O); δ_H (400 MHz; $CDCl_3$) 9.59 (1 H, s, CHO), 7.54 (1 H, dd, *J* 8.0 and 2.0, Ar), 7.30-7.23 (10 H, m Ar), 7.19 (1 H, ddd, 8.0, 8.0 and 2.0, Ar), 7.11 (1 H, dd, *J* 7.5 and 7.0, Ar), 6.95-6.89 (3 H, m, Ar), 6.63 (1 H, dd, *J* 8.0 and 1.0, Ar), 6.54-6.47 (2 H, m, Ar), 4.91 [2 H, s, (NCH_2Ar)$_A$] and 4.77 [2 H, s, (NCH_2Ar)$_B$]; δ_C (100 MHz; $CDCl_3$) 189.4 (CHO), 161.1 (C=O), 145.7 (C), 142.8 (C), 137.5 (C), 136.6 (C), 134.0 (CH), 132.2 (C), 129.5 (CH), 129.4 (CH), 129.2 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 126.5 (CH), 125.9 (CH), 56.4 (N*C*H$_2$Ar)$_A$ and 55.8 (N*C*H$_2$Ar)$_B$; m/z (ES^+) 423 (100 %, M+Na^+); (Found: M+Na^+, 423.1742, $C_{28}H_{24}N_2O_2Na$ requires *M+Na*, 423.1730).

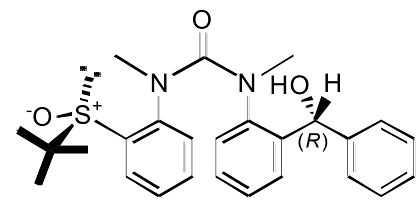
***(S,S)-1-(2-(tert-Butylsulfinyl)phenyl)-3-(2-(hydroxy(phenyl)methyl)phenyl)-1,3-dimethylurea)* 10a** (Nu = Ph)



1-(2-(*tert*-Butylsulfinyl)phenyl)-3-(2-formylphenyl)-1,3-dimethylurea **7** (0.10 g, 0.27 mmol) was dissolved in THF (5 cm^3), cooled to –78 °C and DMPU (0.10 cm^3, 1.0 mmol) added. PhMgBr (0.54 cm^3, 0.54 mmol, 1.0 M in hexanes) was added dropwise and stirred at –78 °C for 4 h. MeOH (5 cm^3) was added, warmed to room temperature and water (10 cm^3) added. The aqueous layer was extracted with EtOAc (3 × 20 cm^3) and the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; Pentane to EtOAc) and recrystallisation to give *1-(2-(tert-butylsulfinyl)phenyl)-3-(2-(hydroxy-(phenyl)methyl) phenyl) -1,3-dimethylurea* **10a** (Nu = Ph) (0.115 g, 95 %), as colourless cubes, m.p. 189-191 ºC (from EtOAc-pentane); $[\alpha]_D^{24} = -353$ (c = 0.2 in CH_2Cl_2); R_f (EtOAc) 0.48; υ_{max} (film)/cm^{-1} 3390 (OH) and 1648 (C=O); δ_H (400 MHz; $CDCl_3$) 7.62 (1 H, d, *J* 8.0, Ar), 7.32-6.40 (12 H, m, Ar), 5.89, [1 H, s, Ar(C*H*)OHAr], 3.28 [3 H, s, $(NCH_3)_A$], 2.91 [3 H, s, $(NCH_3)_B$] and 1.15 [9 H, s, $(CH_3) \times 3$]; δ_C (100 MHz; $CDCl_3$) 159.8 (C=O), 144.8 (C), 144.4 (C), 140.7 (C), 137.8 (C), 137.7 (C), 132.2 (CH), 129.3 (CH), 128.5 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.5 (CH), 125. 9 (CH), 125.6 (CH), 71.1 (CH), 56.0 (C), 40.0 $(NCH_3)_A$, 39.7 $(NCH_3)_B$ and 23.1 [$(CH_3) \times 3$]; m/z (ES$^+$) 451 (100 %, M+H$^+$); (Found: M+H$^+$, 451.2044, $C_{26}H_{30}N_2O_3S$ requires *M+H*, 451.2050).

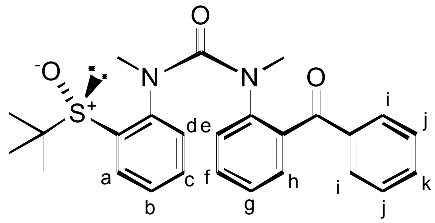
This procedure was repeated as above at different temperatures, using different reaction conditions and with different Grignard reagents as described in Chapter 2.

***(S,R)-1-(2-(tert-Butylsulfinyl)phenyl)-3-(2-(hydroxy(phenyl)methyl)phenyl)-1,3-dimethylurea*, 10b** (Nu = Ph)



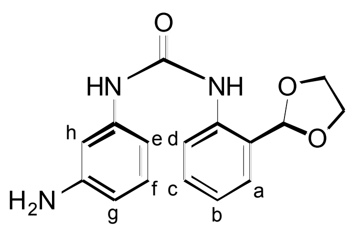
1-(2-(*tert*-Butylsulfinyl)phenyl)-3-(2-(benzoyl)phenyl)-1,3-dimethylurea **11** (0.10 g, 0.22 mmol) was dissolved in CH_2Cl_2 (5 cm^3) and cooled to –78 °C. DibalH (0.44 cm^3, 0.44 mmol, 1.0 M in hexanes) was added dropwise and stirred at –78 °C for 8 h. MeOH (5 cm^3) was added, warmed to room temperature and water (10 cm^3) added. The aqueous layer was extracted with EtOAc (3 × 20 cm^3) and the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; Pentane to EtOAc) and recrystallisation to give *1-(2-(tert-butylsulfinyl)phenyl)-3-(2-(hydroxy-(phenyl)methyl) phenyl) -1,3-dimethylurea* **10b** (Nu = Ph) (0.115 g, 95 %), as colourless cubes, m.p. 189-191 ºC (from EtOAc-pentane); $[\alpha]_D^{24} = +80$ (c = 0.2 in CH_2Cl_2); R_f (EtOAc) 0.48; υ_{max} (film)/cm^{-1} 3390 (OH) and 1648 (C=O); δ_H (400 MHz; $CDCl_3$) 7.62 (1 H, d, *J* 8.0, Ar), 7.32-6.40 (12 H, m, Ar), 5.81, [1 H, s, Ar(C*H*)OHAr], 3.28 [3 H, s, $(NCH_3)_A$], 2.91 [3 H, s, $(NCH_3)_B$] and 1.15 [9 H, s, $(CH_3) \times 3$]; δ_C (100 MHz; $CDCl_3$) 159.8 (C=O), 144.8 (C), 144.4 (C), 140.7 (C), 137.8 (C), 137.7 (C), 132.2 (CH), 129.3 (CH), 128.5 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.5 (CH), 125. 9 (CH), 125.6 (CH), 71.1 (CH), 56.0 (C), 40.0 $(NCH_3)_A$, 39.7 $(NCH_3)_B$ and 23.1 [$(CH_3) \times 3$]; m/z (ES$^+$) 451 (100 %, M+H$^+$); (Found: M+H$^+$, 451.2044, $C_{26}H_{30}N_2O_3S$ requires *M+H*, 451.2050).

***1-(2-(tert-Butylsulfinyl)phenyl)-3-(2-(benzoyl)phenyl)-1,3-dimethylurea*, 11**



PCC (0.10 g, 0.50 mmol) was dissolved in CH_2Cl_2 (10 cm^3) at room temperature, 1-(2-(*tert*-Butylsulfinyl)phenyl)-3-(2-(hydroxy(phenyl)methyl)phenyl)-1,3-dimethylurea **10**(Nu = Ph) (0.15 g, 0.35 mmol) in CH_2Cl_2 (5 cm^3) added dropwise and stirred for 2 h. Diethyl ether (30 cm^3) was added, the precipitate isolated, washed with ether (3 × 30 cm^3) and the combined organics concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; Pentane to EtOAc) and precipitation to give *1-(2-(tert-butylsulfinyl)phenyl)-3-(2-(benzoyl)phenyl)-1,3-dimethylurea* **11** (0.14 g, 98 %), as a colourless foam, m.p. 165-167 ºC (from EtOAc-pentane); $[\alpha]_D^{24} = -18.0$ (c = 0.5 in CH_2Cl_2); R_f (EtOAc) 0.46; υ_{max} (film)/cm^{-1} 1686 (C=O) and 1650 (C=O); δ_H (400 MHz; $CDCl_3$) 7.62 (2 H, dd, *J* 8.0 and 2.0, CH-i), 7.58 (2 H, m, CH-a and CH-b) 7.46 (2 H, m, CH-e and CH-k), 7.21 (1 H, m, CH-f), 6.96 (4 H, m, CH-c, CH-g and CH-j), 6.79 (1 H, d, *J* 8.0, CH-d), 6.71 (1 H, d, *J* 8.0, CH-h), 3.02 [3 H, s, $(NCH_3)_A$], 2.99 [3 H, s, $(NCH_3)_B$] and 1.05 [9 H, s, $(CH_3) \times 3$] ; δ_C (100 MHz; $CDCl_3$) 197.1 (C=O), 158.1 (C=O), 144.0 (C), 143.0 (C), 138.0 (C), 137.0 (C), 136.0 (C), 133.7 (CH), 132.0 (CH), 131.8 (CH), 131.0 (CH), 129.7 (CH), 129.2 (CH), 128.5 (CH), 127.8 (CH), 127.0 (CH), 126.5 (CH), 125.5 (CH), 56.0 (C), 39.5 $(NCH_3)_A$, 38.6 $(NCH_3)_B$ and 22.9 [$(CH_3) \times 3$]; m/z (ES^+) 449 (50 %, M+H^+); (Found: M+H^+, 449.1892, $C_{26}H_{28}N_2O_3S$ requires *M+H*, 449.1894).

***1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-(3-aminophenyl)urea*, 12**

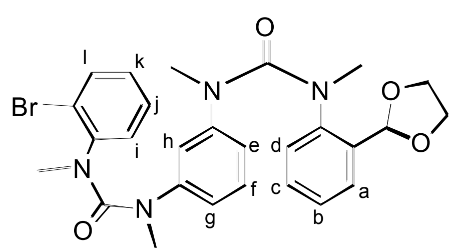


2-(1,3-Dioxolan-2-yl)benzenamine **4** (4.1 g, 25 mmol) was dissolved in THF (150 cm^3). 3-Nitrophenyl isocyanate (4.1 g, 25 mmol) was added portionwise and stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure and the residue purified by recrystallisation from CH_2Cl_2/petrol to give *1-(2-(1,3-dioxolan-2-yl)phenyl)-3-(3-nitrophenyl)urea* (7.22 g, 88 %) as pale yellow cubes, m.p. 191-193 ºC (from CH_2Cl_2-petrol); R_f (2% Et_3N, 48 % EtOAc in petrol) 0.22; υ_{max} (film)/cm^{-1} 3438 (NH), 1663 (C=O), 1551 and 1351 (NO_2); δ_H (300 MHz; d_6-DMSO) 9.91 [1 H, s, $(NH)_A$], 9.50 [1 H, s, $(NH)_B$], 8.58 (1 H, ddd, *J* 2.0, 2.0 and 2.0, CH-h), 7.88 (1 H, dd, *J* 8.0 and 1.0, CH-a), 7.80 (1 H, ddd, *J* 8.0, 2.0 and 1.0, CH-g), 7.76 (1 H, ddd, *J* 8.0, 2.0 and 1.0, CH-e), 7.60 (1 H, ddd, *J* 8.0, 8.0 and 2.0, CH-f), 7.47 (1 H, dd, *J* 8.0 and 2.0, CH-d), 7.40 (1 H, ddd,

J 8.0, 8.0 and 2.0, CH-b), 7.14 (1 H, ddd, J 8.0, 8.0 and 1.0, CH-c), 5.87 [1 H, s, (CHO_2)], 4.19-4.09 [2 H, m, (OCH_2CH_2O)] and 4.09-4.00 [2 H, m, (OCH_2CH_2O)]; δ_C (75 MHz; d_6-DMSO) 153.2 (C=O), 148.9 (C), 141.9 (C), 141.4 (C), 137.4 (C), 130.9 (CH), 130.0 (CH), 128.0 (CH), 125.4 (CH), 124.9 (CH), 123.9 (CH), 117.0 (CH), 112.8 (CH), 101.8 (CH) and 65.5 [(CH_2) × 2]; m/z (ES^+) 330 (100 %, $M+H^+$); (Found: $M+H^+$, 330.1091, $C_{16}H_{16}N_3O_5$ requires $M+H$, 330.1084).

The 1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-(3-nitrophenyl)urea (4.4 g, 15 mmol) was dissolved in THF (100 cm^3), IPA (100 cm^3), triethylamine (2.7 cm^3, 20 mmol), 10 % palladium on carbon (0.16 g, 0.15 mmol) added and the suspension stirred under a hydrogen atmosphere for 18 h. The suspension was filtered through celite and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 1 % Et_3N, 49 % EtOAc in petrol) to give *1-(2-(1,3-dioxolan-2-yl)phenyl)-3-(3-aminophenyl)urea* **12** (3.62 g, 80 %), as white plates, m.p. 189-191 ºC (from EtOAc-petrol); R_f (2 % Et_3N in EtOAc) 0.18; υ_{max} (film)/cm^{-1} 3351 (N–H) and 1672 (C=O); δ_H (300 MHz; d_6-DMSO) 8.97 [1 H, s, $(NH)_A$], 7.94 [1 H, s, $(NH)_B$], 7.87 (1 H, dd, J 8.0 and 1.0, CH-a), 7.41 (1 H, dd, J 8.0 and 1.0, CH-d), 7.30 (1 H, ddd, J 8.0, 8.0 and 1.0, CH-b), 7.02 (1 H, ddd, J 8.0, 8.0 and 1.0, CH-c), 6.90 (1 H, dd, J 8.0 and 8.0, CH-f), 6.85 (1 H, dd, J 2.0 and 2.0, CH-h), 6.60 (1 H, ddd, J 8.0, 2.0 and 1.0, CH-e), 6.24 (1 H, ddd, J 8.0, 2.0 and 1.0, CH-g), 5.82 [1 H, s, (CHO_2)], 4.76 [2 H, s, (NH_2)] and 4.15-4.08 [2 H, m, (OCH_2CH_2O)] and 4.07-3.97 [2 H, m, (OCH_2CH_2O)]; δ_C (75 MHz; d_6-DMSO) 153.2 (C=O), 149.4 (C), 141.0 (C), 138.1 (C), 129.7 (CH), 129.6 (CH), 127.5 (CH), 127.2 (C), 123.4 (CH), 122.8 (CH), 109.1 (CH), 107.6 (CH), 105.2 (CH), 101.9 (CH) and 65.4 [(CH_2) × 2]; m/z (ES^+) 300 (100 %, $M+H^+$); (Found: $M+H^+$, 300.1339, $C_{16}H_{18}N_3O_3$ requires $M+H$, 300.1343).

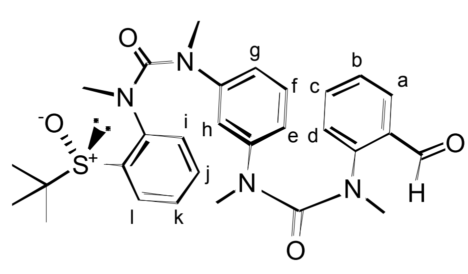
***1-(2-(1,3-Dioxolan-2-yl)phenyl)-1,3-dimethyl-3-(3-(3-(2-bromophenyl)-1,3-dimethyl-ureido)phenyl)urea*, 13**



1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-(3-aminophenyl)urea **12** (1.0 g, 3.3 mmol) was dissolved in THF (50 cm^3), 2-bromophenylisocyanate (0.41 cm^3, 3.3 mmol) added dropwise, stirred for 18 h and concentrated. The residue was purified by recrystallisation from CH_2Cl_2-petrol to give *1-(2-(1,3-dioxolan-2-yl)phenyl)-3-(3-(3-(2-bromophenyl)ureido)phenyl)urea* (1.59 g, 97 %) as colourless prisms, m.p. 106-108 ºC (from CH_2Cl_2-petrol); R_f (2 % Et_3N, 49 % EtOAc in petrol) 0.70; υ_{max} (film)/cm^{-1} 3412 and 3312 (N–H), 1738 and 1715 (C=O) and 747 (C-Br); δ_H (300 MHz; d_6-DMSO) 9.56 (1 H, s, NH), 9.44 (1 H, s, NH), 8.15 (1 H, s, NH), 8.13 (1 H, dd, J 8.0 and 1.5, CH-l), 8.05 (1 H, s, NH), 7.88 (1 H, dd, J 8.0 and 1.5, CH-a), 7.80 (1 H, t, J 1.5, CH-h), 7.64 (1 H, dd, J 8.0 and 1.5, CH-i), 7.45 (1 H, dd, J 8.0 and 1.5, CH-d), 7.37 (2 H, m, CH-e and CH-g), 7.25-7.05 (4 H, m, CH-c, CH-f, CH-j and CH-k), 6.99 (1 H, ddd, *J* 8.0, 8.0 and 1.5, CH-b), 5.87 [1 H, s, (CHO_2)] and 4.19-3.99 [4 H, m, (OCH_2CH_2O)]; δ_C (75 MHz; d_6-DMSO) 153.2 (C=O), 152.8 (C=O), 141.1 (C), 140.7 (C), 138.0 (C), 137.8 (C), 133.2 (CH), 129.9 (CH), 128.8 (CH), 127.7 (C), 127.5 (CH), 124.7 (CH), 124.4 (CH), 123.5 (CH), 123.2 (CH), 122.7 (CH), 113.6 (C), 112.8 (CH), 112.4 (CH), 108.7 (CH), 101.7 (CH), and 65.5 [(CH_2) × 2]; m/z (ES^+) 519 (100 %, $M+Na^+$); (Found: $M+Na^+$, 519.0642, $C_{23}H_{21}N_4O_4BrNa$ requires *M+Na*, 519.0638).

The 1-(2-(1,3-Dioxolan-2-yl)phenyl)-3-(3-(3-(2-bromophenyl)ureido)phenyl)urea (1.58 g, 3.18 mmol) was dissolved in DMF (50 cm^3) and cooled to 0 ºC. Sodium hydride (0.64 g, 16.0 mmol) was added portionwise and stirred at room temperature for 1 h. Methyl iodide (1.12 cm^3, 18.0 mmol) was added and stirred at room temperature for 21 h. Water (50 cm^3) was added and extracted with EtOAc (3 × 40 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 10 % EtOAc and 2 % Et_3N in petrol) to give *1-(2-(1,3-dioxolan-2-yl)phenyl)-1,3-dimethyl-3-(3-(3-(2-bromophenyl)-1,3-dimethyl-ureido)phenyl)urea* **13** (1.65 g, 94 %), as colourless cubes, m.p. 190-192 ºC (from EtOAc-pentane); R_f (2 % Et_3N, 49 % EtOAc in petrol) 0.35; υ_{max} (film)/cm^{-1} 1738 and 1716 (C=O) and 735(C-Br); δ_H (300 MHz; $CDCl_3$) 7.33 (1 H, dd, *J* 8.0 and 1.5, CH-l), 7.06 (1 H, td, *J* 8.0 and 1.5, CH-j), 7.00 (1 H, td, *J* 8.0 and 1.5, CH-k), 6.94 (1 H, td, *J* 8.0 and 1.5, CH-b), 6.85 (1 H, dd, *J* 8.0 and 1.5, CH-i), 6.79 (1 H, t, *J* 8.0, CH-f) 6.78 (1 H, td, *J* 8.0 and 1.5, CH-c), 6.69 (1 H, dd, *J* 8.0 and 1.5, CH-d), 6.58 (1 H, dd, *J* 8.0 and 1.5, CH-a), 6.51 (1 H, m, CH-e or CH-g), 6.44 (1 H, m, CH-g or CH-e), 6.11 (1 H, d, *J* 1.5 and 1.5, CH-h), 5.58 [1 H, s, (CHO_2)], 4.18-3.97 [4 H, m, (OCH_2CH_2O)], 3.17 [3 H, s, $(NCH_3)_A$], 3.13 [3 H, s, $(NCH_3)_B$], 3.03 [3 H, s, $(NCH_3)_C$] and 2.98 [3 H, s, $(NCH_3)_D$]; δ_C (75 MHz; $CDCl_3$) 161.4 (C=O), 160.5 (C=O), 146.0 (C), 145.8 (C), 144.2 (C), 144.0 (C), 134.7 (C), 133.4 (CH), 130.2 (CH), 129.8 (CH), 129.2 (CH), 128.4 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 126.8 (CH), 123.7 (CH), 123.4 (CH), 123.3 (CH), 122.9 (C), 99.7 (CH), 65.5 [(CH_2) × 2], 40.5 $(NCH_3)_A$, 40.0 $(NCH_3)_B$, 39.9 $(NCH_3)_C$ and 38.8 $(NCH_3)_D$ m/z (ES^+) 575 (100 %, $M+Na^+$); (Found: $M+Na^+$, 575.1269, $C_{27}H_{29}N_4O_4BrNa$ requires *M+Na*, 575.1264).

***1-(2-(tert-Butylsulfinyl)phenyl)-1,3-dimethyl-3-(3-(3-(2-formylphenyl)-1,3-dimethyl-ureido)phenyl)urea*, 14**

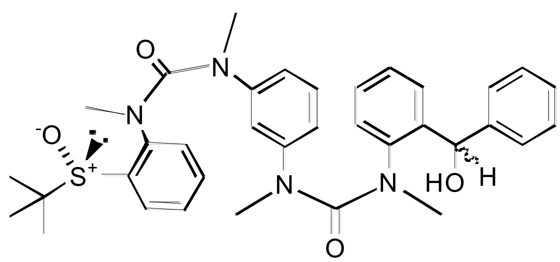


1-(2-(1,3-Dioxolan-2-yl)phenyl)-1,3-dimethyl-3-(3-(3-(2-bromophenyl)-1,3-dimethyl-ureido)phenyl)urea **13** (1.10 g, 1.99 mmol) was dissolved in THF (100 cm^3) and cooled to –90 ºC. *n*-Butyllithium (1.19 cm^3, 2.28 mmol, 1.92 M in hexanes) was added dropwise and stirred for 1 min at –90 ºC. After this time, (*S*)-*tert*-Butyl 2-methylpropane-2-sulfinothioate[1] [0.59 g, 2.99 mmol in THF (6.0 cm^3)] was added in one portion and stirred at –

90 ºC for 5 min. After warming to room temperature over 18 h, saturated aqueous ammonium chloride (10 cm^3) and water (20 cm^3) were added and the aqueous layer extracted with EtOAc (3 × 30 cm^3). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 20 % EtOAc and 2 % Et_3N in petrol to 2 % Et_3N in EtOAc) to give *1-(2-(1,3-dioxolan-2-yl)phenyl)-1,3-dimethyl-3-(3-(3-(2-(tert-butylsulfinyl)phenyl)-1,3-dimethyl-ureido)phenyl)urea* (0.68 g, 61 %), as colourless cubes, m.p. 245-247 ºC (from EtOAc-petrol); $[\alpha]_D^{22}$ = + 47.2 (c = 0.5 in CH_2Cl_2); R_f (2 % Et_3N in EtOAc) 0.32; υ_{max} (film)/cm^{-1} 1724 (C=O), 1655 (C=O) and 1072 (S=O); δ_H (300 MHz; $CDCl_3$) 7.56 (1 H, dd, *J* 8.0 and 2.0, CH-l), 7.27 (1 H, dd, *J* 8.0 and 2.0, CH-i), 7.05-6.78 (4 H, m, CH-b, CH-c, CH-j and CH-k), 6.65 (1 H, d, *J* 8.0, CH-d), 6.39 (1 H, dd, 8.0 and 1.0, CH-a), 6.35 (2 H, dd, *J* 8.0 and 2.0, CH-e and CH-g), 6.03 (1 H, dd, *J* 2.0 and 2.0, CH-h), 5.47 [1 H, s, (CHO_2)], 4.14-3.82 [4 H, m, (OCH_2CH_2O)], 3.18 [3 H, s, $(NCH_3)_A$], 3.09 [3 H, s, $(NCH_3)_B$], 3.01 [3 H, s, $(NCH_3)_C$], 2.91 [3 H, s, $(NCH_3)_D$] and 1.08 [9 H, s, (CH_3) × 3]; δ_C (75 MHz; $CDCl_3$) 161.4 (C=O), 159.8 (C=O), 145.8 (C), 144.1 (C), 143.9 (C), 137.8 (C), 134.6 (C), 131.6 (CH), 129.8 (CH), 129.1 (CH), 128.3 (C), 127.4 (CH), 127.2 (CH), 126.8 (CH), 126.7 (CH), 125.4 (CH), 123.3 (CH), 123.1 (CH), 123.0 (CH), 122.9 (CH), 99.7 (CH), 65.5 [(CH_2) × 2], 56.0 (C), 40.5 $(NCH_3)_A$, 39.7 $(NCH_3)_B$, 39.6 $(NCH_3)_C$, 39.2 $(NCH_3)_D$ and 23.0 [(CH_3) × 3]; m/z (ES^+) 601 (100 %, M+Na^+); (Found: M+Na^+, 601.2454, $C_{31}H_{38}N_4O_5NaS$ requires *M+Na*, 601.2455). *1-(2-(1,3-Dioxolan-2-yl)phenyl)-1,3-dimethyl-3-(3-(3-phenyl)-1,3-dimethyl-ureido)phenyl)urea* (0.33 g, 36 %) was also obtained as colourless cubes, m.p. 230-232 ºC (from EtOAc-petrol); R_f (2 % Et_3N in EtOAc) 0.50; υ_{max} (film)/cm^{-1} 1710 (C=O), 1651 (C=O) and 1072 (S=O); δ_H (300 MHz; $CDCl_3$) 7.33 (1 H, dd, *J* 8.0 and 2.0, CH-a), 7.08-6.58 (4 H, m, Ar), 6.89 (1 H, tt, 7.0 and 1.0, CH-k), 6.75 (1 H, dd, *J* 8.0 and 8.0, CH-f), 6.72 (2 H, dd, *J* 7.0 and 1.0, CH-i), 6.57 (1 H, dd, *J* 8.0 and 1.0, CH-d), 6.49 (1 H, ddd, *J* 8.0, 2.0 and 1.0, CH-e), 6.38 (1 H, ddd, *J* 8.0, 2.0 and 1.0, CH-g), 6.06 (1 H, dd, *J* 2.0 and 2.0, CH-h), 5.53 [1 H, s, (CHO_2)], 4.17-4.03 [2 H, m, (OCH_2CH_2O)], 4.02-3.93 [2 H, m, (OCH_2CH_2O)], 3.16 [3 H, s, $(NCH_3)_A$], 3.14 [3 H, s, $(NCH_3)_B$], 3.00 [3 H, s, $(NCH_3)_C$] and 2.94 [3 H, s, $(NCH_3)_D$]; No ^{13}C spectrum was recorded; m/z (ES^+) 497 (100 %, M+Na^+); (Found: M+Na^+, 497.2159, $C_{27}H_{30}N_4O_4Na$ requires *M+Na*, 497.2154).

The 1-(2-(1,3-Dioxolan-2-yl)phenyl)-1,3-dimethyl-3-(3-(3-(2-(*tert*-butylsulfinyl)phenyl)-1,3-dimethyl-ureido)phenyl)urea (0.65 g, 1.12 mmol) was dissolved in THF (20 cm^3), 1 N aqueous hydrochloric acid (20 cm^3) added and stirred at room temperature for 16 h. The aqueous layer was extracted with EtOAc (3 × 20 cm^3), the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 50 % EtOAc in petrol) to give *1-(2-(tert-butylsulfinyl)phenyl)-1,3-dimethyl-3-(3-(3-(2-formylphenyl)-1,3-dimethyl-ureido)phenyl)urea* **14** (0.59 g, 98 %), as colourless cubes, m.p. 215-217 ºC (from EtOAc-pentane); $[\alpha]_D^{23}$ = + 40.0 (c = 0.4 in CH_2Cl_2); R_f (50 % EtOAc in petrol) 0.50; υ_{max} (film)/cm^{-1} 1691 (HC=O), 1654 (C=O) and 1032 (S=O); δ_H (300 MHz; $CDCl_3$) 9.79 (1 H, s, CH=O), 7.62 (1 H, dd, *J* 8.0 and 1.5, CH-a), 7.53 (1 H, dd, *J* 8.0 and 1.5, CH-d), 7.31 (1 H, ddd, *J* 8.0, 8.0 and 1.5, CH-c), 7.12 (1 H, ddd, *J* 8.0, 8.0 and 1.5, CH-j), 7.03 (1 H, ddd, *J* 8.0, 8.0 and 1.5, CH-b), 6.95 (1 H, td, *J* 8.0 and 1.5, CH-k), 6.85 (1 H, d, *J* 8.0,CH-l), 6.69 (1 H, t, *J* 8.0,CH-f), 6.47-6.30 (3 H, m, CH-e, CH-g and CH-i), 5.98 (1 H, dd, *J* 1.5 and 1.5, CH-h), 3.23 [3 H, s, $(NCH_3)_A$], 3.22 [3 H, s, $(NCH_3)_B$, 3.00 [3 H, s, $(NCH_3)_C$], 2.99 [3 H, s, $(NCH_3)_D$] and 1.13 [9 H, s, $(CH_3) \times 3$]; δ_C (75 MHz; $CDCl_3$) 189.4 (HC=O), 161.2 (C=O), 159.5 (C=O), 147.9 (C), 146.0 (C), 145.2 (C), 143.8 (C), 137.8 (C), 134.6 (CH), 131.7 (CH), 131.2 (C), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.2 (CH), 127.2 (CH), 126.9 (CH), 126.6 (CH), 125.5 (CH), 123.4 (CH), 123.2 (CH), 56.0 (C), 41.2 $(NCH_3)_A$, 39.6 $(NCH_3)_B$, 39.5 $(NCH_3)_C$, 39.2 $(NCH_3)_D$ and 23.0 [$(CH_3) \times 3$]; m/z (ES^+) 535 (100 %, $M+H^+$); (Found: $M+H^+$, 535.2379, $C_{29}H_{35}N_4O_4S$ requires *M+H*, 535.2374).

***1-(2-(tert-Butylsulfinyl)phenyl)-1,3-dimethyl-3-(3-(3-(2-(hydroxy-(phenyl)methyl)phenyl)-1,3-dimethylureido)phenyl)urea*, 15**



Method 1

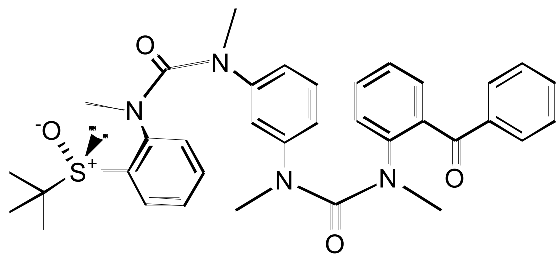
1-(2-(*tert*-Butylsulfinyl)phenyl)-1,3-dimethyl-3-(3-(3-(2-formylphenyl)-1,3-dimethyl-ureido)phenyl)urea **14** (0.10 g, 0.18 mmol) was dissolved in THF (5 cm^3), cooled to –78 °C and DMPU (0.24 cm^3, 1.8 mmol) added. PhMgBr (0.54 cm^3, 0.54 mmol, 1.0 M in hexanes) was added dropwise and stirred at –78 °C for 5 h. MeOH (5 cm^3) was added, warmed to room temperature and water (10 cm^3) added. The aqueous layer was extracted with EtOAc (3 × 20 cm^3) and the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; petrol to EtOAc) to give a mixture of inseparable diastereoisomers of *1-(2-(tert-butylsulfinyl)phenyl)-1,3-dimethyl-3-(3-(3-(2-(hydroxy-(phenyl)methyl)phenyl)-1,3-dimethylureido)phenyl)urea* **15** (0.102 g, 90 %), as colourless cubes, m.p. 254-256 ºC (from EtOAc-petrol); $[\alpha]_D^{23} = -8.1$ (c = 0.3 in CH_2Cl_2); R_f (EtOAc) 0.27; υ_{max} (film)/cm^{-1} 3387 (OH), 1654 (C=O), 1636 (C=O) and 1032 (S=O); δ_H (300 MHz; $CDCl_3$) 7.65-7.53 (2 H, m, $Ar^{maj\ and\ min}$), 7.52-7.41 (2 H, m, $Ar^{maj\ and\ min}$), 7.36-7.16 (8 H, m, $Ar^{maj\ and\ min}$), 7.13-6.75 (12 H, m, $Ar^{maj\ and\ min}$), 7.65 (2 H, dd, *J* 8.0 and 8.0, $Ar^{maj\ and\ min}$), 6.58-6.31 (6 H, m, $Ar^{maj\ and\ min}$), 6.17 (2 H, dd, *J* 2.0 and 2.0, $Ar^{maj\ and\ min}$), 5.71 [1 H, s, $(Ar(C\mathit{H})OHAr)^{maj}$], 5.66 [1 H, s, $(Ar(C\mathit{H})OHAr)^{min}$], 3.21 [3 H, s, $(NCH_3)_A{}^{maj\ and\ min}$], 3.06 [3 H, s, $(NCH_3)_B{}^{maj\ and\ min}$], 2.91 [3 H, s, $(NCH_3)_C{}^{maj\ and\ min}$], 2.88 [3 H, s, $(NCH_3)_D{}^{maj\ and\ min}$] and 1.14-1.02 [18 H, s, $\{(CH_3) \times 3\}^{maj\ and\ min}$]; δ_C (75 MHz; $CDCl_3$) 161.4 $(C{=}O)^{maj}$, 160.8 $(C{=}O)^{min}$, 159.8 $(C{=}O)^{maj}$, 159.5 $(C{=}O)^{min}$, 147.8 $(C)^{maj}$, 146.5 $(C)^{min}$, 146.3 $(C)^{maj}$, 146.1 $(C)^{min}$, 145.9 $(C)^{maj}$, 145.2 $(C)^{min}$, 143.9 $(C)^{maj}$, 143.4 $(C)^{min}$, 142.8 $(C)^{maj}$, 142.6 $(C)^{min}$, 141.1 $(C)^{maj}$, 137.7 $(C)^{min}$, 137.4 $(C)^{maj}$, 134.6 $(C)^{min}$, 131.8 $(CH)^{maj}$, 131.7 $(CH)^{min}$, 131.2 $(CH)^{maj}$, 129.2 $(CH)^{min}$, 129.1 $(CH)^{maj}$, 129.0 $(CH)^{min}$, 128.5 $(CH)^{maj}$, 128.4 $(CH)^{maj}$, 128.2 $(CH)^{min}$, 127.7 $(CH)^{maj}$, 127.6 $(CH)^{min}$, 127.4

$(CH)^{maj}$, 127.3 $(CH)^{min}$, 127.22 $(CH)^{maj}$, 127.17 $(CH)^{min}$, 126.9 $(CH)^{maj}$, 126.6 $(CH)^{min}$, 125.6 $(CH)^{maj}$, 125.5 $(CH)^{min}$, 123.4 $(CH)^{maj}$, 123.1 $(CH)^{min}$, 122.81 $(CH)^{maj}$, 122.80 $(CH)^{min}$, 71.2 $(CH)^{maj}$, 71.0 $(CH)^{min}$, 56.0 $(C)^{maj}$, 55.8 $(C)^{min}$, 40.2 $(NCH_3)_A{}^{maj}$, 40.1 $(NCH_3)_A{}^{min}$, 39.8 $(NCH_3)_B{}^{maj}$, 39.7 $(NCH_3)_B{}^{min}$, 39.6 $(NCH_3)_C{}^{maj}$, 39.5 $(NCH_3)_C{}^{min}$, 39.2 $(NCH_3)_D{}^{maj}$, 39.1 $(NCH_3)_D{}^{min}$, 23.0 $[(CH_3) \times 3^{maj}]$ and 22.9 $[(CH_3) \times 3]^{min}$; m/z (ES^+) 635 (100 %, $M+Na^+$); (Found: $M+Na^+$, 635.2660, $C_{35}H_{40}N_4O_4NaS$ requires *M*+*Na*, 635.2662).

Method 2

1-(2-(*tert*-Butylsulfinyl)phenyl)-1,3-dimethyl-3-(3-(3-(2-(benzoyl)phenyl)-1,3-dimethylureido)phenyl)urea **16** (0.13 g, 0.22 mmol) was dissolved in CH_2Cl_2 (5 cm^3) and cooled to –78 °C. DibalH (0.44 cm^3, 0.44 mmol, 1.0 M in hexanes) was added dropwise and stirred at –78 °C for 8 h. MeOH (5 cm^3) was added, warmed to room temperature and water (10 cm^3) added. The aqueous layer was extracted with EtOAc (3 × 20 cm^3) and the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; 20 % EtOAc in petrol) to give a mixture of inseparable diastereoisomers of *1-(2-(tert-butylsulfinyl)phenyl)-1,3-dimethyl-3-(3-(3-(2-(hydroxy-(phenyl)methyl)phenyl)-1,3-dimethylureido)phenyl)urea* **15** (0.102 g, 90 %), as colourless cubes, m.p. 254-256 ºC (from EtOAc-petrol); $[\alpha]_D{}^{23} = -9.4$ (c = 0.4 in CH_2Cl_2); R_f (50 % EtOAc in petrol) 0.27; υ_{max} (film)/cm^{-1} 3387 (OH), 1654 (C=O), 1636 (C=O) and 1032 (S=O); δ_H (300 MHz; $CDCl_3$) 7.65-7.53 (2 H, m, $Ar^{maj\ and\ min}$), 7.52-7.41 (2 H, m, $Ar^{maj\ and\ min}$), 7.36-7.16 (8 H, m, $Ar^{maj\ and\ min}$), 7.13-6.75 (12 H, m, $Ar^{maj\ and\ min}$), 7.65 (2 H, dd, *J* 8.0 and 8.0, $Ar^{maj\ and\ min}$), 6.58-6.31 (6 H, m, $Ar^{maj\ and\ min}$), 6.17 (2 H, dd, *J* 2.0 and 2.0, $Ar^{maj\ and\ min}$), 5.71 [1 H, s, $(Ar(C\mathit{H})OHAr)^{maj}$], 5.66 [1 H, s, $(Ar(C\mathit{H})OHAr)^{min}$], 3.21 [3 H, s, $(NCH_3)_A{}^{maj\ and\ min}$], 3.06 [3 H, s, $(NCH_3)_B{}^{maj\ and\ min}$], 2.91 [3 H, s, $(NCH_3)_C{}^{maj\ and\ min}$], 2.88 [3 H, s, $(NCH_3)_D{}^{maj\ and\ min}$] and 1.14-1.02 [18 H, s, $\{(CH_3) \times 3\}^{maj\ and\ min}$]; δ_C (75 MHz; $CDCl_3$) 161.4 $(C{=}O)^{maj}$, 160.8 $(C{=}O)^{min}$, 159.8 $(C{=}O)^{maj}$, 159.5 $(C{=}O)^{min}$, 147.8 $(C)^{maj}$, 146.5 $(C)^{min}$, 146.3 $(C)^{maj}$, 146.1 $(C)^{min}$, 145.9 $(C)^{maj}$, 145.2 $(C)^{min}$, 143.9 $(C)^{maj}$, 143.4 $(C)^{min}$, 142.8 $(C)^{maj}$, 142.6 $(C)^{min}$, 141.1 $(C)^{maj}$, 137.7 $(C)^{min}$, 137.4 $(C)^{maj}$, 134.6 $(C)^{min}$, 131.8 $(CH)^{maj}$, 131.7 $(CH)^{min}$, 131.2 $(CH)^{maj}$, 129.2 $(CH)^{min}$, 129.1 $(CH)^{maj}$, 129.0 $(CH)^{min}$, 128.5 $(CH)^{maj}$, 128.4 $(CH)^{maj}$, 128.2 $(CH)^{min}$, 127.7 $(CH)^{maj}$, 127.6 $(CH)^{min}$, 127.4 $(CH)^{maj}$, 127.3 $(CH)^{min}$, 127.22 $(CH)^{maj}$, 127.17 $(CH)^{min}$, 126.9 $(CH)^{maj}$, 126.6 $(CH)^{min}$, 125.6 $(CH)^{maj}$, 125.5 $(CH)^{min}$, 123.4 $(CH)^{maj}$, 123.1 $(CH)^{min}$, 122.81 $(CH)^{maj}$, 122.80 $(CH)^{min}$, 71.2 $(CH)^{maj}$, 71.0 $(CH)^{min}$, 56.0 $(C)^{maj}$, 55.8 $(C)^{min}$, 40.2 $(NCH_3)_A{}^{maj}$, 40.1 $(NCH_3)_A{}^{min}$, 39.8 $(NCH_3)_B{}^{maj}$, 39.7 $(NCH_3)_B{}^{min}$, 39.6 $(NCH_3)_C{}^{maj}$, 39.5 $(NCH_3)_C{}^{min}$, 39.2 $(NCH_3)_D{}^{maj}$, 39.1 $(NCH_3)_D{}^{min}$, 23.0 $[(CH_3) \times 3^{maj}]$ and 22.9 $[(CH_3) \times 3]^{min}$; m/z (ES^+) 635 (100 %, $M+Na^+$); (Found: $M+Na^+$, 635.2660, $C_{35}H_{40}N_4O_4NaS$ requires *M*+*Na*, 635.2662).

***1-(2-(tert-Butylsulfinyl)phenyl)-1,3-dimethyl-3-(3-(3-(2-(benzoyl)phenyl)-1,3-dimethylureido)phenyl)urea*, 16**



PCC (0.36 g, 1.8 mmol) was dissolved in CH_2Cl_2 (18 cm^3) at room temperature, 1-(2-(*tert*-Butylsulfinyl)phenyl)-1,3-dimethyl-3-(3-(3-(2-(hydroxy-(phenyl)methyl)phenyl)-1,3-dimethylureido)phenyl)urea **15** (1.1 g, 1.8 mmol) in CH_2Cl_2 (18 cm^3) added dropwise and stirred for 12 h. Diethyl ether (60 cm^3) was added, the precipitate isolated, washed with ether (3 × 30 cm^3) and the combined organics concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; EtOAc to 10 % MeOH in EtOAc) to give a 1:1 ratio of inseparable rotamers of *1-(2-(tert-butylsulfinyl)phenyl)-1,3-dimethyl-3-(3-(3-(2-(benzoyl)phenyl)-1,3-dimethylureido)phenyl)urea* **16** (0.70 g, 60 %), as colourless cubes, m.p. 262-264 ºC (from EtOAc-MeOH); $[\alpha]_D^{23}$ = + 18.4 (c = 0.5 in CH_2Cl_2); R_f (EtOAc:MeOH; 9:1) 0.35; υ_{max} (film)/cm^{-1} 1716 (C=O), 1700 (C=O), 1651 (C=O) and 1086 (S=O); δ_H (500 MHz; $CDCl_3$) 7.62 (1 H, d, *J* 7.5, Ar^{maj}), 7.58 (1 H, d, *J* 7.5, Ar^{min}), 7.53 (2 H, dd, *J* 7.0 and 7.0, $Ar^{maj\ and\ min}$), 7.41 (1 H, dd, *J* 7.5 and 7.5, Ar^{maj}), 7.38 (1 H, dd, *J* 7.5 and 7.5, Ar^{min}), 7.29-7.12 (6 H, m, $Ar^{maj\ and\ min}$), 7.09-6.98 (2 H, m, $Ar^{maj\ and\ min}$), 6.98-6.87 (4 H, m, $Ar^{maj\ and\ min}$), 6.82 (1 H, dd, *J* 7.5 and 7.5, Ar^{maj}), 6.76 (1 H, dd, *J* 7.5 and 7.5, Ar^{min}), 6.59-6.52 (3 H, m, Ar^{maj}), 6.52-6.37 (4 H, m, Ar^{min}), 6.33 (2 H, dd, *J* 7.5 and 7.5, 2 × Ar^{maj} and Ar^{min}], 6.25 (2 H, d, *J* 7.5, Ar^{min}), 6.14 (2 H, br., Ar^{maj}), 3.18 [3 H, s, $(NCH_3)_A{}^{min}$], 3.15 [3 H, s, $(NCH_3)_A{}^{maj}$], 3.06 [3 H, s, $(NCH_3)_B{}^{maj}$], 3.02 [3 H, s, $(NCH_3)_B{}^{min}$], 2.97 [3 H, s, $(NCH_3)_C{}^{maj}$], 2.92-2.85 [3 H, m, $(NCH_3)_C{}^{min}$], 2.68 [3 H, s, $(NCH_3)_D{}^{maj}$], 2.66-2.61 [3 H, s, $(NCH_3)_D{}^{min}$] and 1.06 [18 H, s, $\{(CH_3) \times 3\}^{maj\ and\ min}$]; δ_C (75 MHz; $CDCl_3$) 195.3 (ketone C=O)$^{maj\ and\ min}$ 159.6 (urea C=O)$^{maj\ and\ min}$, 159.4 (urea C=O)$^{maj\ and\ min}$, 145.3 (C)$^{maj\ and\ min}$, 143.7 (C)$^{maj\ and\ min}$, 143.5 (C)$^{maj\ and\ min}$, 143.3 (C)$^{maj\ and\ min}$, 137.5 (C)$^{maj\ and\ min}$, 137.2 (C)$^{maj\ and\ min}$, 135.3 (C)$^{maj\ and\ min}$, 133.4 (CH)$^{maj\ and\ min}$, 131.4 (CH)$^{maj\ and\ min}$, 131.1 (CH)$^{maj\ and\ min}$, 129.8 (CH)$^{maj\ and\ min}$, 129.6 (CH)$^{maj\ and\ min}$, 128.7 (CH)$^{maj\ and\ min}$, 128.4 (CH)$^{maj\ and\ min}$, 128.3 (CH)$^{maj\ and\ min}$, 127.1 (CH)$^{maj\ and\ min}$, 127.0 (CH)$^{maj\ and\ min}$, 126.4 (CH)$^{maj\ and\ min}$, 125.3 (CH)$^{maj\ and\ min}$, 125.2 (CH)$^{maj\ and\ min}$, 121.8 (CH)$^{maj\ and\ min}$, 121.6 (CH)$^{maj\ and\ min}$, 55.7 (C)$^{maj\ and\ min}$, 39.4 $(NCH_3)_A{}^{maj\ and\ min}$, 39.3 $(NCH_3)_B{}^{maj\ and\ min}$, 38.9 $(NCH_3)_C{}^{maj\ and\ min}$, 38.3 $(NCH_3)_D{}^{maj\ and\ min}$ and 22.8 $(CH_3)^{maj\ and\ min}$; m/z (ES^+) 633 (100 %, M+Na^+) and 611 (60 %, M+H^+); (Found: M+H^+, 611.2692, $C_{35}H_{39}N_4O_4S$ requires *M+H*, 611.2687).

[1] D. J. Weix and J. A. Ellman, *Org. Lett.*, 2003, **5**, 1317.