

## Supplementary data for:

### Synthesis of 5-hydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-ones; selective antagonists of muscarinic (M<sub>3</sub>) receptors

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## Experimental

### General

Flash column chromatography was performed using Merck silica gel (60H; 40-60 $\mu$ , 230-240 mesh). Light petroleum was redistilled before use and refers to the fraction boiling between 40 and 60 °C. Tetrahydrofuran was dried over sodium-benzophenone and was distilled prior to use. Dichloromethane was dried over CaH<sub>2</sub> and was distilled before use. Ether refers to diethyl ether. Reactions under non-aqueous conditions were carried out under an atmosphere of nitrogen or argon.

Electron impact (EI) or chemical ionisation using ammonia (CI) mass spectra were recorded using a Fisons VG Trio 200 spectrometer and high resolution mass spectra on a Kratos Concept IS spectrometer. Infra-red spectra were measured using a Genesis FTIR spectrometer on NaBr plates, either neat or as evaporated films unless otherwise stated. Nuclear magnetic resonance spectra were recorded in deuteriated chloroform unless otherwise indicated on either a Varian Unity 500 (500 MHz), Varian INOVA 300 (300 MHz), or a Varian Gemini 200 (200 MHz) spectrometer. Coupling constants (*J*) are given in Hertz (Hz) and chemical shifts relative to tetramethylsilane.

### 2-(*tert*-Butoxycarbonylaminoethyl)-1,3-dithiane **5**

1,3-Propanedithiol (2 cm<sup>3</sup>, 19.92 mmol) then boron trifluoride diethyl etherate (11 cm<sup>3</sup>, 89.44 mmol) were added to 2,2-diethoxyethylamine **8** (3 g, 22.52 mmol) in dichloromethane (50 cm<sup>3</sup>). After 15 h,

aqueous sodium hydroxide (2.5 M, 100 cm<sup>3</sup>) was added and the mixture stirred vigorously for 1 h. The aqueous layer was extracted with dichloromethane (3 x 50 cm<sup>3</sup>) and the combined organic extracts washed with brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). After concentration under reduced pressure, the residue was dissolved in dichloromethane (50 cm<sup>3</sup>) then Boc-anhydride (5.4 g, 24.74 mmol) and triethylamine (3.5 cm<sup>3</sup>, 25.11 mmol) in dichloromethane (10 cm<sup>3</sup>) were added. After 2 days, water (50 cm<sup>3</sup>) and aqueous hydrogen chloride (1 M, 25 cm<sup>3</sup>) were added, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 50 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography using light petroleum : ethyl acetate (5 : 1) as eluent gave the carbamate **5** as a white solid (3.54 g, 63%), further purified by recrystallisation from hexane, m.p. 71 °C (lit.<sup>5</sup> 75-76 °C);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.36 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.85 and 1.99 (each 1 H, m, CH), 2.67 (2 H, ddd, *J* 3, 9, 14), 2.82 (2 H, ddd, *J* 3, 7, 14), 3.43 (2 H, t, *J* 6.5, CH<sub>2</sub>), 3.92 (1 H, t, *J* 6.5, CH) and 4.92 (1 H, br. s, NH); *m/z* (CI) 250 (M<sup>+</sup>+1, 10%), 211 (50), 150 (75) and 119 (100).

### **2-*tert*-Butyldimethylsilyloxymethyl-*N*-methoxy-*N*-methylbenzamide **6****

Trimethylaluminium (2 M in hexane, 32 cm<sup>3</sup>, 64.5 mmol) was added at 0 °C dropwise over *ca.* 0.25 h to a suspension of *N,O*-dimethylhydroxylamine hydrochloride (6.29 g, 64.5 mmol) in dichloromethane (60 cm<sup>3</sup>). During the addition a vigorous gas evolution ensued. The mixture was stirred for 1 h at 0 °C, phthalide (4.32 g, 32.2 mmol) in dichloromethane (20 cm<sup>3</sup>) was added and the stirring was continued for 7 h. The mixture was allowed to warm to room temperature before saturated aqueous sodium potassium tartrate (100 cm<sup>3</sup>) was added. After extraction with dichloromethane (2 x 100 cm<sup>3</sup>), the organic extracts were washed with brine (100 cm<sup>3</sup>), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 cm<sup>3</sup>) and *tert*-butyldimethylsilyl chloride (4.9 g, 32.2 mmol) and imidazole (4.4 g, 64.5 mmol) were added. After stirring for 15 h, water (100 cm<sup>3</sup>) and dichloromethane (50 cm<sup>3</sup>) were added. The organic extracts were dried (MgSO<sub>4</sub>) then concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (5:1 → 3:1) gave the *title compound* **6** (5.93 g, 60%) as a clear liquid (Found: M<sup>+</sup>+H, 310.1835. C<sub>16</sub>H<sub>28</sub>NO<sub>3</sub>Si requires *M*, 310.1838);  $\nu_{\text{max}}$  3064, 1650, 1463, 1416, 1383, 1257, 1119 and 1081 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 0.00 (6 H, s, 2 x SiCH<sub>3</sub>), 0.84 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 3.19 (3 H, s, OCH<sub>3</sub>), 3.44 (3 H, br. s, NCH<sub>3</sub>), 4.69 (2 H, s, OCH<sub>2</sub>), 7.16-7.22 (2 H, m, ArH), 7.31 (1 H, dt, *J* 2.5, 7.5, ArH) and 7.45 (1 H, d, *J* 7.5, ArH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) -5.40, 18.39, 25.92, 33.64, 61.00, 62.54, 126.43, 126.86, 129.38, 132.70, 138.80 and 169.71; *m/z* (CI) 310 (M<sup>+</sup>+1, 100%).

**2-(tert-Butoxycarbonylamino)methyl-2-[(2-tert-butyltrimethylsilyloxymethyl)phenyl]cyclobutylhydroxymethyl-[1,3]-dithiane 10**

*n*-Butyllithium (1.35 M in hexanes, 2.65 cm<sup>3</sup>, 3.58 mmol) was added to the dithiane **5** (446 mg, 1.79 mmol) in THF (9 cm<sup>3</sup>) under argon at -40 °C and the solution stirred for 2 h gradually being warmed to -20 °C. *N,N*-Dimethylpropyleneurea (DMPU) (0.76 cm<sup>3</sup>, 6.26 mmol) was added and the mixture stirred for 1 h at -78 °C then transferred *via* cannula into a solution of the cyclobutyl ketone **7** (247 mg, 0.895 mmol) in THF (4.5 cm<sup>3</sup>) at -78 °C gradually being warmed to room temperature. After 15 h, saturated aqueous ammonium chloride (25 cm<sup>3</sup>) was added and the mixture was extracted with ethyl acetate (3 x 25 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate as eluent (9 : 1) gave recovered ketone **7** (127 mg, 51%) and the *title compound 10* (209 mg, 42%) as a clear viscous oil (Found: M<sup>+</sup>, 553.2716. C<sub>28</sub>H<sub>47</sub>NO<sub>4</sub>S<sub>2</sub>Si requires *M*, 553.2716);  $\nu_{\max}$  3435, 3361, 3060, 1712, 1495, 1365, 1255, 1171, 1029 and 839 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 0.04 and 0.21 (each 3 H, s, SiCH<sub>3</sub>), 0.87 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.32-1.41 (2 H, m), 1.38 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.46-1.58 (2 H, m), 1.71 (1 H, sex, *J* 9, CH), 1.79 and 1.95 (each 1 H, m), 2.15 (1 H, dt, *J* 4.5, 14.5, CH), 2.37-2.52 (2 H, m), 2.79 (1 H, ddd, *J* 3.5, 10.5, 14, SCH), 2.92 (1 H, ddd, *J* 3, 11, 14, SCH), 3.52 (1 H, dd, *J* 3, 14.5, CHN), 3.53 (1 H, pent, *J* 9), 3.76 (1 H, dd, *J* 8, 14.5, CHN), 4.41 and 5.44 (each 1 H, d, *J* 10.5, CHO), 5.91 (1 H, m, NH), 6.08 (1 H, s, OH), 7.06 (1 H, dd, *J* 2, 7.5, ArH), 7.11-7.20 (2 H, m, ArH) and 7.58 (1 H, dd, *J* 1.5, 7.5, ArH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) -5.42, -4.97, 17.54, 24.03, 24.61, 24.73, 25.66, 25.76, 26.72, 28.38, 42.83, 44.77, 68.66, 78.64, 85.98, 126.94, 127.37, 130.61, 131.70, 138.51, 140.42 and 156.60; *m/z* (EI) 553 (M<sup>+</sup>, 2%), 422 (5), 305 (20), 173 (100) and 119 (50).

**2-(tert-Butoxycarbonylamino)methyl-2-(2-hydroxymethylphenyl)cyclobutylhydroxymethyl-[1,3]-dithiane 11**

Tetra-*n*-butylammonium fluoride in THF (1 M, 0.23 cm<sup>3</sup>, 0.230 mmol) was added to the silyl ether **10** (125 mg, 0.227 mmol) in THF (2 cm<sup>3</sup>) at 0 °C. After 15 min, ether (15 cm<sup>3</sup>) and water (15 cm<sup>3</sup>) were added and the aqueous layer extracted with ether (15 cm<sup>3</sup>). The organic extracts were washed with brine (15 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (3:1 → 1:1) as eluent gave the *title compound 11* (71 mg, 71%) as a clear viscous oil (Found: M<sup>+</sup>+H, 440.1919. C<sub>22</sub>H<sub>34</sub>NO<sub>4</sub>S<sub>2</sub> requires *M*, 440.1929);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.31 (1 H, m), 1.35 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.41-1.74 (4 H, m), 1.78-1.85 (2 H, m), 2.28 (1 H, dt, *J* 4.5, 14.5), 2.40 (1 H, m), 2.49 (1 H, dt, *J* 4, 14.5), 2.71 (1 H, ddd, *J* 3.5, 10, 14), 2.84 (1 H, ddd, *J* 3.5,

11, 14.5), 3.52 (1 H, pent,  $J$  8), 3.55-3.71 (2 H, m, CH<sub>2</sub>N), 4.49 (1 H, dd,  $J$  6.5, 11.5, OCH), 5.26 (1 H, dd,  $J$  5.5, 11.5, OCH), 5.39 (1 H, br. s, NH), 5.51 (1 H, s, OH), 7.09-7.22 (3 H, m, ArH) and 7.55 (1 H, dd,  $J$  1.5, 7.5, ArH);  $m/z$  (CI) 440 ( $M^{+}+1$ , 30%), 340 (25) and 173 (100).

### **2-(*tert*-Butoxycarbonylamino)methyl-2-[2-(*tert*-butyldimethylsilyloxymethyl)benzoyl]-[1,3]-dithiane 12**

Following the procedure described above for the preparation of the dithiane **10**, the amide **6** (451 mg, 1.46 mmol) in THF (6 cm<sup>3</sup>) and dithiane **5** (727 mg, 2.92 mmol) in THF (6 cm<sup>3</sup>), deprotonated using *n*-butyllithium (1.6 M in hexanes, 3.65 cm<sup>3</sup>, 5.84 mmol), gave the *title compound* **12** (501 mg, 69%), as a colourless oil, after chromatography using light petroleum : ethyl acetate (5 : 1) as eluent (Found:  $M^{+}+H$ , 498.2160. C<sub>24</sub>H<sub>40</sub>NO<sub>4</sub>S<sub>2</sub>Si requires  $M$ , 498.2168);  $\nu_{\max}$  3438, 1714, 1681, 1497, 1366, 1249, 1168, 1124, 1079, 840 and 777 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 0.06 (6 H, s, 2 x SiCH<sub>3</sub>), 0.84 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.34 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.84-1.97 (2 H, m), 2.78-2.94 (4 H, m), 3.69 (2 H, d,  $J$  6.5, NCH<sub>2</sub>), 4.66 (2 H, s, OCH<sub>2</sub>), 5.08 (1 H, m, NH), 7.16 (1 H, t,  $J$  7.5, ArH), 7.35 (1 H, t,  $J$  7.5, ArH), 7.52 (1 H, d,  $J$  7.5, ArH) and 8.01 (1 H, d,  $J$  7.5, ArH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) -5.32, 18.40, 23.75, 25.98, 26.76, 28.25, 45.72, 59.95, 62.82, 79.48, 125.91, 127.06, 128.03, 130.62, 135.25, 140.24, 156.15 and 200.4;  $m/z$  (CI) 498 ( $M^{+}+1$ , 10%), 442 (20), 369 (40), 145 (80), 133 (80), 106 (95) and 91 (100).

### **2-(*tert*-Butyldimethylsilyloxymethyl)benzyl chloride 14**

2-*tert*-Butyldimethylsilyloxymethylbenzyl alcohol **13**<sup>14</sup> (19.5 g, 0.077 mol) in dichloromethane (50 cm<sup>3</sup>) and pyridine (9.5 cm, 0.118 mol) in dichloromethane (50 cm<sup>3</sup>) were added simultaneously to thionyl chloride (8.5 cm<sup>3</sup>, 0.117 mol) in dichloromethane (250 cm<sup>3</sup>) at 0 °C. After 0.5 h, water (150 cm<sup>3</sup>) and aqueous hydrogen chloride (1 M, 35 cm<sup>3</sup>) were added. The aqueous layer was extracted with dichloromethane (100 cm<sup>3</sup>) and the organic extracts washed with brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). After concentration under reduced pressure, chromatography using light petroleum : ethyl acetate (19:1) gave the *title compound* **14** (9.7 g, 53%) as a yellow oil (Found:  $M^{+}+H$ , 271.1298. C<sub>14</sub>H<sub>24</sub>OClSi requires  $M$ , 271.1285);  $\nu_{\max}$  3438, 1714, 1681, 1497, 1366, 1249, 1168, 1124, 1079, 840 and 777 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 0.00 (6 H, s, 2 x SiCH<sub>3</sub>), 0.85 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 4.62 and 4.80 (each 2 H, s, CH<sub>2</sub>), 7.16-7.24 (3 H, m, ArH) and 7.29 (1 H, d,  $J$  7.5, ArH);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) -5.31, 18.33, 25.91, 43.65, 62.63, 127.52, 127.64, 128.79, 129.92, 134.59 and 139.74;  $m/z$  (CI) 288, 290 ( $M^{+}+18$ , 60 and 20%) and 271, 273 ( $M^{+}+1$ , 100, 33).

### **2-(*tert*-Butoxycarbonylamino)methyl-2-(2-*tert*-butyldimethylsilyloxymethylphenyl)methyl-[1,3]-dithiane 15**

Following the procedure described above for the preparation of the dithiane **10** with deprotonation of the dithiane **5** (975 mg, 3.92 mmol) in THF (50 cm<sup>3</sup>) using *n*-butyllithium (1.6 M in hexanes, 4.9 cm<sup>3</sup>, 7.84 mmol) and DMPU (1.5 cm<sup>3</sup>, 12.41 mmol), the chloride **14** (677 mg, 2.84 mmol) in THF (5 cm<sup>3</sup>) gave, after 30 min at -78 °C and chromatography using light petroleum : ethyl acetate (5:1), the *title compound 15* (919 mg, 67%) as a colourless oil (Found: M<sup>+</sup>+H, 484.2353. C<sub>24</sub>H<sub>42</sub>O<sub>3</sub>SiS<sub>2</sub> requires *M*, 484.2375);  $\nu_{\max}$  2950, 2850, 1600, 1500, 1450, 1380, 1250, 1100, 1050, 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, 100;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 0.02 (6 H, s, 2 x SiCH<sub>3</sub>), 0.82 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.36 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.65 and 1.88 (each 1 H, m, 5-H), 2.46 (2 H, dt, *J* 3.5, 14.5, 2 x SCH), 2.89 (2 H, dd, *J* 12, 14.5, 2 x SCH), 2.98 (2 H, s, ArCH<sub>2</sub>), 3.56 (2 H, d, *J* 6, CH<sub>2</sub>N), 4.79 (2 H, s, OCH<sub>2</sub>), 4.90 (1 H, br d, *J* 6, NH), 7.08-7.21 (2 H, m, ArH) and 7.26 and 7.33 (each 1 H, d, *J* 7, ArH); *m/z* (CI) 484 (M<sup>+</sup>+1, 10%), 352 (60), 296 (85), 252 (100) and 146 (95)

### **2-(*tert*-Butoxycarbonylamino)methyl-2-(2-hydroxymethylphenyl)methyl-[1,3]-dithiane 16**

Following the procedure outlined for the synthesis of the alcohol **11**, the silyl ether **15** (1.1 g, 2.28 mmol) in THF (40 cm<sup>3</sup>) with tetra-*n*-butylammonium fluoride (1 M in THF, 2.25 cm<sup>3</sup>, 2.25 mmol), after chromatography using light petroleum : ethyl acetate (1:1), gave the *title compound 16* (746 mg, 89%) as a viscous oil (Found: C, 58.95; H, 7.55; N, 3.85; S, 17.4%; M<sup>+</sup>, 369.1433. C<sub>18</sub>H<sub>27</sub>NO<sub>3</sub>S<sub>2</sub> requires C, 58.5; H, 7.3; N, 3.8; S, 17.3%; *M*, 369.1432);  $\nu_{\max}$  3400, 3000, 2950, 2850, 1600, 1500, 1450, 1380, 1250, 1100, 1050, 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, 100;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.45 [9 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.82 and 2.05 (each 1 H, m, 5-H), 2.38 (1 H, br. s, OH), 2.62 (2 H, dt, *J* 4, 14.5, 2 x SCH), 3.03 (2 H, dd, *J* 13, 14.5, 2 x SCH), 3.18 (2 H, s, ArCH<sub>2</sub>), 3.70 (2 H, d, *J* 6, NCH<sub>2</sub>), 4.83 (2 H, s, OCH<sub>2</sub>), 5.20 (1 H, m, NH), 7.26-7.35 (2 H, m, ArH) and 7.42-7.50 (2 H, m, ArH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 24.26, 26.35, 28.32, 39.84, 44.79, 53.80, 63.11, 79.80, 127.36, 127.62, 129.30, 132.04, 132.94, 140.20 and 164.55; *m/z* (EI) 369 (M<sup>+</sup>, 60%), 308 (50) and 124 (100).

### **2-(*tert*-Butoxycarbonylamino)methyl-2-(2-formylphenyl)methyl-[1,3]-dithiane 17**

Pre-activated manganese dioxide (5.9 g, 67.82 mmol) was added to the alcohol **16** (5 g, 12.55 mmol) in dichloromethane (125 cm<sup>3</sup>) and the mixture stirred for 24 h at room temperature then filtered through Celite<sup>®</sup>. The solid residue was washed with dichloromethane (2 x 50 cm<sup>3</sup>) and, after concentration of the extracts under reduced pressure, chromatography of the residue using light petroleum : ethyl acetate (3:1) gave the *title compound 17* (3.5 g, 70%) as a viscous oil (Found: M<sup>+</sup>, 367.1282. C<sub>18</sub>H<sub>25</sub>NO<sub>3</sub>S<sub>2</sub> requires *M*, 367.1276);  $\nu_{\max}$  3420, 3067, 1700, 1506, 1426, 1368, 1254 and 1166;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 300

MHz) 1.41 [9 H, s, C(CH<sub>3</sub>)], 1.65 and 1.95 (each 1 H, m, 5-H), 2.48 (2 H, dt, *J* 4, 14.5, 2 x SCH), 2.90 (2 H, dd, *J* 12, 14.5, 2 x SCH), 3.45 (2 H, s, ArCH<sub>2</sub>), 3.51 (2 H, d, *J* 6, NCH<sub>2</sub>), 5.18 (1 H, m, NH), 7.32-7.51 (3 H, m, ArH), 7.81 (1 H, d, *J* 7.5, ArH) and 10.22 (1 H, s, CHO);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 24.04, 26.20, 28.30, 38.75, 45.12, 53.73, 79.60, 127.80, 131.28, 132.88, 133.77, 135.40, 136.72, 156.20 and 192.25; *m/z* (CI) 385 (M<sup>++</sup>18, 15%), 368 (M<sup>++</sup>1, 20), 350 (75), 329 (79), 312 (70), 268 (55), 250 (100) and 237 (52). Starting alcohol **16** (524 mg, 11%) was then eluted off the column.

#### 4,4-Propylenedithio-2,3,4,5-tetrahydro-[1H]-2-benzazepine **19**

Aqueous hydrogen chloride (4.5 M, 14 cm<sup>3</sup>, *ca.* 65 mmol) in ethyl acetate (10 cm<sup>3</sup>) was added to the aldehyde **17** (2.4 g, 6.54 mmol) in ethyl acetate (150 cm<sup>3</sup>). After 5 h, ether (150 cm<sup>3</sup>) and water (100 cm<sup>3</sup>) were added, and the mixture basified using aqueous sodium hydroxide (1 M) to *ca.* pH 11. Following extraction with ether (3 x 150 cm<sup>3</sup>), the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the imine **18**;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.85-2.12 (2 H, m, CH<sub>2</sub>), 2.79 (2 H, m, 2 x SCH), 2.92-3.05 (2 H, m, 2 x SCH), 2.97 (2 H, s, 5-H<sub>2</sub>), 3.80 (2 H, br. s, 3-H<sub>2</sub>), 7.19-7.38 (4 H, m, ArH) and 8.68 (1 H, br. s, 1-H). Sodium cyanoborohydride (1.23 g, 19.6 mmol) and concentrated aqueous hydrogen chloride (*ca.* 0.5 cm<sup>3</sup>) were added to the imine **18** (*ca.* 6.54 mmol) in methanol (100 cm<sup>3</sup>) and the mixture stirred for 2 h. Ether (100 cm<sup>3</sup>), water (100 cm<sup>3</sup>) and aqueous sodium hydroxide (1 M) were added until the pH was *ca.* 10. The aqueous layer was extracted with ether (3 x 100 cm<sup>3</sup>) and the ethereal extracts were dried (MgSO<sub>4</sub>) then concentrated under reduced pressure. Chromatography of the residue using ether containing triethylamine (1%) gave the *title compound* **19** (1.2 g, 73%) as a viscous yellow oil (Found: M<sup>+</sup>, 251.0798. C<sub>13</sub>H<sub>17</sub>NS<sub>2</sub> requires *M*, 251.0802);  $\nu_{\text{max}}$  3395, 3065, 1462, 1382 and 1095;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.89 and 2.10 (each 1 H, m, 5'-H), 2.40 (1 H, s, NH), 2.60-2.72 and 2.80-2.95 (each 2 H, m, 2 x SCH), 3.36, 3.55 and 3.99 (each 2 H, s, CH<sub>2</sub>), 7.11 (1 H, m, ArH) and 7.18-7.25 (3 H, m, ArH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 25.27, 26.08, 47.62, 50.66, 53.39, 54.45, 59.98, 126.99, 127.28, 127.69, 130.98, 135.31 and 142.24; *m/z* (EI) 251 (M<sup>+</sup>, 60%) and 145 (100).

#### 2-*tert*-Butoxycarbonyl-4,4-propylenedithio-2,3,4,5-tetrahydro-[1H]-2-benzazepine **20**

Boc-anhydride (1.00 g, 4.58 mmol) was added to the tetrahydrobenzazepine **19** (1.03 g, 4.10 mmol) and triethylamine (0.9 cm<sup>3</sup>, 6.46 mmol) in dichloromethane (25 cm<sup>3</sup>) and the mixture stirred at room temperature for 18 h before ether (100 cm<sup>3</sup>) and water (100 cm<sup>3</sup>) were added. The aqueous layer was extracted with ether (3 x 100 cm<sup>3</sup>) and the organic extracts were dried (MgSO<sub>4</sub>) then concentrated under

reduced pressure. Chromatography using light petroleum : ethyl acetate (5:1) as eluent gave the *title compound 20* (1.45 g, 100%) as a colourless solid recrystallised from ethyl acetate, m.p. 96-98 °C (Found: C, 61.65; H, 7.95; N, 4.0; S, 18.1%;  $M^+$ , 351.1330.  $C_{18}H_{25}NO_2S_2$  requires C, 61.5; H, 7.1; N, 4.0; S, 18.2%;  $M$ , 351.1327);  $\nu_{\max}$  3065, 1693, 1456, 1410, 1367, 1246, 1167 and 1140;  $\delta_H$  (300 MHz,  $CDCl_3$ ; spectrum poorly resolved due to rotamers) 1.50 [9 H, br. s,  $C(CH_3)_3$ ], 1.84 and 2.10 (each 1 H, m, 5'-H), 2.49-2.75 (2 H, m, 2 x SCH), 2.91-3.32 (4 H, m), 3.86-4.52 (4 H, m) and 7.14-7.35 (4 H, m, ArH);  $m/z$  (EI) 351 ( $M^+$ , 10%), 295 (20), 250 (30) and 146 (100).

### **2-(4-Methylphenylsulfonyl)-4,4-propylenedithio-2,3,4,5-tetrahydro-[1H]-2-benzazepine 21**

Toluene *p*-sulfonyl chloride (835 mg, 4.38 mmol) was added to the tetrahydrobenzazepine **19** (1.00 g, 3.98 mmol) in pyridine (35  $cm^3$ ) and the mixture stirred for 24 h before being concentrated under reduced pressure. Ether (100  $cm^3$ ) and aqueous hydrogen chloride (3.45 M, 100  $cm^3$ ) were added and the aqueous layer extracted with ether (3 x 100  $cm^3$ ). The organic extracts were dried ( $MgSO_4$ ) and concentrated under reduced pressure. Recrystallisation of the residue from methanol gave the *title compound 21* (1.09 g, 68%) as a colourless solid, m.p. 146-147 °C (Found: C, 59.15; H, 6.1; N, 3.45; S, 23.9%;  $M^+$ , 405.0894.  $C_{20}H_{23}NO_2S_3$  requires C, 59.3; H, 5.7; N, 3.5; S, 23.7%;  $M$ , 405.0891);  $\nu_{\max}$  3062, 1693, 1450, 1342, 1163 and 1092;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 1.79 and 2.06 (each 1 H, m, 5'-H), 2.35 (3 H, s,  $CH_3$ ), 2.57 (2 H, dt,  $J$  14.5, 4, 2 x SCH), 2.99 (2 H, ddd,  $J$  2.5, 12, 14.5, 2 x SCH), 3.14 (2 H, s, 5-H<sub>2</sub>), 3.86 (2 H, br. s, 3-H<sub>2</sub>), 4.21 (2 H, s, 1-H<sub>2</sub>), 6.96 (1 H, d,  $J$  6.5, ArH), 7.08-7.14 (3 H, m, ArH), 7.22 (2 H, d,  $J$  8, ArH) and 7.69 (2 H, d,  $J$  8, ArH);  $\delta_C$  (75 MHz,  $CDCl_3$ ) 21.46, 24.93, 26.47, 46.78, 49.52, 53.02, 57.80, 127.29, 127.61, 127.93, 128.46, 129.61, 131.05, 135.20, 136.40, 136.80 and 143.80;  $m/z$  (CI) 423 ( $M^{+18}$ , 80%) and 406 ( $M^{+1}$ , 100).

### **2-Phenylmethyl-4,4-propylenedithio-2,3,4,5-tetrahydro-[1H]-2-benzazepine 22**

Sodium triacetoxyborohydride (157 mg, 0.741 mmol) was added to the tetrahydrobenzazepine **19** (62 mg, 0.247 mmol) and benzaldehyde (28  $\mu L$ , 0.276 mmol) in tetrahydrofuran (5  $cm^3$ ) at room temperature and the mixture stirred for 24 h before ether (25  $cm^3$ ) was added. After washing with sodium hydroxide (1 M, 25  $cm^3$ ), the aqueous layer was re-extracted with ether (3 x 25  $cm^3$ ) and the extracts were dried ( $MgSO_4$ ) then concentrated under reduced pressure. Preparative TLC of the residue using light petroleum : ethyl acetate (1:1) gave the *title compound 22* (55 mg, 66%) as a yellow oil (Found:  $M^+$ , 341.1275.  $C_{20}H_{23}NS_2$  requires  $M$ , 341.1272);  $\nu_{\max}$  3065, 3028, 1494, 1454, 1426, 1261, 1149 and 1101;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 1.87 (2 H, pent,  $J$  6, 5'-H<sub>2</sub>), 2.55-2.75 (4 H, m, 2 x SCH<sub>2</sub>), 3.35,

3.44, 3.74 and 3.81 (each 2 H, s, CH<sub>2</sub>), 6.90 (1 H, m, ArH) and 7.08-7.31 (8 H, m, ArH);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 25.41, 26.41, 46.24, 51.64, 58.17, 60.16, 66.83, 126.91, 127.02, 127.08, 128.23, 128.78, 129.19, 130.36, 136.68, 139.49 and 139.66;  $m/z$  (EI) 341 (M<sup>+</sup>, 15%), 250 (50) and 91 (100).

### **2-*tert*-Butoxycarbonyl-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-one 23**

Boron trifluoride diethyletherate (5.3 cm<sup>3</sup>, 41.82 mmol), red mercuric oxide (4.37 g, 20.18 mmol) and water (8.5 cm<sup>3</sup>) were added to the dithiane **20** (2.98 g, 8.49 mmol) in THF (85 cm<sup>3</sup>) at room temperature. The mixture was stirred for 2 h then ether (250 cm<sup>3</sup>) and saturated aqueous sodium bicarbonate (250 cm<sup>3</sup>) were added. The aqueous layer was extracted with ether (4 x 150 cm<sup>3</sup>) and organic extracts were washed with brine (250 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>) then concentrated under reduced pressure. Recrystallisation using ether gave the *title compound* **23** (1.90 g, 86%) as a colourless crystalline solid, m.p. 82-83 °C (Found: C, 69.25; H, 7.25; N, 5.35%. C<sub>15</sub>H<sub>19</sub>NO<sub>3</sub> requires C, 69.0; H, 7.3; N, 5.4%. Found: M<sup>+</sup>+NH<sub>4</sub>, 279.1713. C<sub>15</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> requires *M*, 279.1708);  $\nu_{\text{max}}$  (CHCl<sub>3</sub>) 3010, 1725, 1694, 1421, 1396, 1368, 1265, 1160, 910 and 733 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>; major and minor rotamers, ratio 60 : 40) 1.37 [3.6 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.41 [5.4 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 3.77 (2 H, s, 5-H<sub>2</sub>), 3.98 (1.2 H, s, 3-H<sub>2</sub>), 4.06 (0.8 H, s, 3-H<sub>2</sub>), 4.71 (0.8 H, s, 1-H<sub>2</sub>), 4.86 (1.2 H, s, 1-H<sub>2</sub>) and 6.98-7.23 (4 H, m, ArH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 28.15, 28.22, 29.59, 30.20, 48.36, 48.47, 51.08, 51.76, 55.66, 56.24, 81.00, 81.19, 127.38, 127.53, 127.59, 127.70, 128.00, 129.69, 139.96, 131.18, 134.75, 135.13, 154.65, 155.32, 206.45 and 206.93;  $m/z$  (CI) 279 (M<sup>+</sup>+18, 65%), 262 (M<sup>+</sup>+1, 30) and 223 (100). Chromatography of the concentrated mother liquor after the recrystallisation of **23** using light petroleum : ethyl acetate (5:1) as eluent gave more tetrahydrobenzazepin-4-one **23** (90 mg, 4%).

### **2-(4-Methylphenyl)sulfonyl-2,3,4,5-tetrahydro-[1H]-2-benzazepine-4-one 24**

Following the procedure outlined for the synthesis of **23**, dithiane **21** (783 mg, 1.93 mmol) was treated with boron trifluoride diethyl etherate (1.2 cm<sup>3</sup>, 9.47 mmol) and red mercuric oxide (994 mg, 4.59 mmol) in aqueous THF (20 cm<sup>3</sup>; THF : water, 10:1) to give the *title compound* **24** (438 mg, 72%) as a colourless solid after recrystallisation from ethyl acetate and petroleum ether (40:60), m.p. 138-140 °C (Found: C, 64.45; H, 5.15; N, 4.50; S, 10.35%; M<sup>+</sup>, 315.0932. C<sub>17</sub>H<sub>17</sub>NO<sub>3</sub>S requires C, 64.8; H, 5.4; N, 4.4; S, 10.2%; *M*, 315.0929);  $\nu_{\text{max}}$  (CHCl<sub>3</sub>) 3055, 1728, 1349, 1265 and 1164 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 2.38 (3 H, s, CH<sub>3</sub>), 3.88, 3.91 and 4.61 (each 2 H, s, CH<sub>2</sub>), 6.96-7.09 and 7.14-7.19 (each 2 H, m, ArH) and 7.23 and 7.62 (each 2 H, d, *J* 8, ArH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 21.62, 48.36, 52.71, 57.06,



126.98, 127.63, 127.93, 128.09, 129.92, 130.17, 131.07, 132.94, 135.11, 143.99 and 204.24;  $m/z$  (CI) 333 ( $M^{++18}$ , 15%), 316 ( $M^{++1}$ , 5) and 162 (100).

### **2-Phenylmethyl-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-one 25**

Following the procedure outlined for the synthesis of ketone **23**, the dithiane **22** (62 mg, 0.182 mmol) was treated with boron trifluoride diethyletherate (0.11 cm<sup>3</sup>, 0.868 mmol) and red mercuric oxide (93 mg, 0.429 mmol) in THF (2 cm<sup>3</sup>) and water (0.2 cm<sup>3</sup>) to give after 5 h and preparative TLC using light petroleum : ethyl acetate (1:1) containing triethylamine (1%) as eluent, the *title compound* **25** (38 mg, 84%) as a viscous yellow oil (Found:  $M^{++H}$ , 252.1388. C<sub>17</sub>H<sub>18</sub>NO requires  $M$ , 252.1388);  $\nu_{\max}$  (CDCl<sub>3</sub>) 3054, 1719, 1422, 1265, 909 and 745 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 3.32, 3.59, 4.01 and 4.03 (each 2 H, s, CH<sub>2</sub>), 6.93 (1 H, m, ArH), 7.03-7.14 (3 H, m, ArH) and 7.17-7.29 (5 H, m, ArH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 49.58, 60.05, 60.56, 65.43, 126.94, 127.35, 127.37, 128.40, 128.76, 128.80, 130.39, 131.09, 136.14, 137.95 and 206.85;  $m/z$  (CI) 252 ( $M^{++1}$ , 100%).

### **2-tert-Butoxycarbonyl-4-triethylsilyloxy-2,3-dihydro-[1H]-2-benzazepine 26**

The ketone **23** (654 mg, 2.51 mmol), triethylamine (0.73 cm<sup>3</sup>, 5.24 mmol) and triethylsilyl trifluoromethanesulfonate (0.68 cm<sup>3</sup>, 3.01 mmol) were stirred at room temperature in dichloromethane (25 cm<sup>3</sup>) for 15 h. Ether (50 cm<sup>3</sup>) and saturated aqueous sodium bicarbonate (50 cm<sup>3</sup>) were added and the aqueous layer extracted with ether (3 x 50 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (9 : 1) containing triethylamine (0.5%) as eluent gave the enol ether **26** (612 mg, 65%) as a clear oil;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>; a mixture of rotamers, ratio 60 : 40) 0.55 (2.4 H, q,  $J$  8, 3 x SiCH<sub>2</sub>), 0.81 (3.6 H, q,  $J$  8, 3 x SiCH<sub>2</sub>), 0.97 (3.6 H, t,  $J$  8, 3 x CH<sub>3</sub>), 1.06 (5.4 H, t,  $J$  8, 3 x CH<sub>3</sub>), 1.36 [5.4 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.43 [3.6 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 4.29 (2 H, s, CH<sub>2</sub>), 4.34 (1.2 H, s, CH<sub>2</sub>), 4.36 (0.8 H, s, CH<sub>2</sub>), 5.95 (0.6 H, s, 5-H), 5.98 (0.4 H, s, 5-H) and 7.05-7.28 (4 H, m, ArH);  $m/z$  (CI) 393 ( $M^{++18}$ , 25%), 376 ( $M^{++1}$ , 30), 337 (40), 320 (50) and 132 (100).

### **2-(4-Methylphenylsulfonyl)-4-triethylsilyloxy-2,3-dihydro-[1H]-2-benzazepine 27**

The ketone **24** (34 mg, 0.108 mmol), triethylamine (17  $\mu$ L, 0.122 mmol) and triethylsilyl trifluoromethanesulfonate (27  $\mu$ L, 0.119 mmol) were heated in dichloromethane (2 cm<sup>3</sup>) under reflux for 15 min. Ether (10 cm<sup>3</sup>) and saturated aqueous sodium bicarbonate (10 cm<sup>3</sup>) were added and the aqueous layer extracted with ether (3 x 10 cm<sup>3</sup>). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) then

concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (9:1) containing triethylamine (1%) gave the enol ether **27** (31 mg, 67%) as a colourless oil (Found:  $M^+$ , 429.1794.  $C_{23}H_{31}NO_3SSi$  requires  $M$ , 429.1793);  $\delta_H$  (300 MHz,  $CDCl_3$ ) 0.58 (6 H, q,  $J$  8, 3 x  $SiCH_2$ ), 0.99 (9 H, t,  $J$  8, 3 x  $CH_3$ ), 2.34 (3 H, s,  $ArCH_3$ ), 4.23 and 4.48 (each 2 H, s,  $CH_2$ ), 5.65 (1 H, s, 5-H), 6.76 (1 H, dd,  $J$  1.5, 7,  $ArH$ ), 7.01 (2 H, d,  $J$  8,  $ArH$ ), 7.07-7.17 (2 H, m,  $ArH$ ), 7.21 (1 H, dd,  $J$  2, 7,  $ArH$ ) and 7.30 (2 H, d,  $J$  8,  $ArH$ );  $m/z$  (EI) 429 ( $M^+$ , 25%) and 273 (100).

### ***N*-(2-Ethenylphenylmethyl)prop-2-enylamine 30**

Prop-2-enylamine (0.32  $cm^3$ , 4.34 mmol) and magnesium sulfate (2 g) were added to 2-ethenylbenzaldehyde **29** (520 mg, 3.94 mmol) in dichloromethane (25  $cm^3$ ) and the solution stirred at room temperature for 18 h, then filtered and the solvent removed under reduced pressure. The residue was taken up in methanol (20  $cm^3$ ) and sodium borohydride (150 mg, 3.97 mmol) was added. The mixture was stirred for 1 h before the volume was reduced to approximately half under reduced pressure and ether (50  $cm^3$ ) and aqueous sodium hydroxide (1 M, 50  $cm^3$ ) were added. The aqueous layer was extracted with ether (3 x 50  $cm^3$ ) and the organic extracts were dried ( $MgSO_4$ ). Concentration under reduced pressure gave the amine **30** (410 mg, 61%) as an oil which was used without purification;  $\nu_{max}$  3325, 3069, 3016, 1639, 1627, 1482, 1450 and 1414  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 3.35 (2 H, dd,  $J$  1, 6.5, 1- $H_2$ ), 3.91 (2 H, s,  $ArCH_2$ ), 5.16-5.28 (2 H, m, 3- $H_2$ ), 5.39 (1 H, d,  $J$  11, 2''-H), 5.78 (1 H, d,  $J$  17, 2''-H'), 5.99 (1 H, m, 2-H), 7.10 (1 H, dd,  $J$  11, 17, 1''-H), 7.22-7.40 (3 H, m,  $ArH$ ) and 7.53-7.61 (1 H, m,  $ArH$ );  $m/z$  (CI) 174 ( $M^++1$ , 100%).

### ***N*-(2-Ethenylphenyl)methyl-*N*-prop-2-enyl 2-nitrobenzene sulfonamide 32**

2-Nitrophenylsulfonyl chloride (0.71 g, 3.20 mmol) was added to the amine **30** (0.53 g, 3.06 mmol), triethylamine (0.64  $cm^3$ , 4.59 mmol) and 4-dimethylaminopyridine (*ca.* 4 mg) in dichloromethane (35  $cm^3$ ) and the solution stirred at room temperature for 1.5 h. Silica (*ca.* 3 g) was added and the mixture concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (3:1) as eluent gave the *title compound* **32** (924 mg, 85%) as a colourless viscous oil (Found:  $M^++NH_4$ , 376.1337.  $C_{18}H_{22}N_3O_4S$  requires  $M$ , 376.1331);  $\nu_{max}$  3089, 3024, 1543, 1372, 1353, 1163, 1126, 1065, 916, 852 and 774;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 3.92 (2 H, d,  $J$  6,  $NCH_2$ ), 4.65 (2 H, s,  $ArCH_2$ ), 5.03-5.16 (2 H, m, 3- $H_2$ ), 5.31 (1 H, d,  $J$  11, 2''-H), 5.60 (1 H, d,  $J$  17, 2''-H'), 5.62 (1 H, m, 2-H), 6.98 (1 H, dd,  $J$  11, 17, 1''-H), 7.21-7.34 (3 H, m,  $ArH$ ), 7.47 (1 H, d,  $J$  7.5,  $ArH$ ), 7.61-7.76 (3 H, m,  $ArH$ ) and 7.98 (1 H, d,  $J$  7.5,  $ArH$ );  $\delta_C$  (75 MHz,  $CDCl_3$ ) 48.13, 49.56, 116.89, 119.35, 124.09, 126.26, 127.80,

128.06, 129.03, 131.00, 131.58, 131.92, 133.36, 133.57, 133.83, 137.48 and 147.78;  $m/z$  (CI) 376 ( $M^{++18}$ , 60%), 359 ( $M^{++1}$ , 30), 172 (80) and 117 (100).

### **2,3-Dihydro-[1H]-2-benzazepine 35**

Potassium carbonate (233 mg, 1.69 mmol), thiophenol (60  $\mu$ L, 0.584 mmol) and 18-crown-6 (trace) added to the *N*-(2-nitrophenylsulfonyl)dihydrobenzazepine **34** (171 mg, 0.518 mmol, 1 eq.) in *N,N*-dimethylformamide (6  $\text{cm}^3$ ) and the mixture stirred for 4 h. Ethyl acetate (25  $\text{cm}^3$ ) and water (25  $\text{cm}^3$ ) were added and the aqueous layer was extracted with ethyl acetate (4 x 25  $\text{cm}^3$ ). The organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (5:1) containing triethylamine (1%) gave the *title compound* **35** (63 mg, 84%) as a clear oil (Found:  $M^+$ , 145.0889.  $\text{C}_{10}\text{H}_{11}\text{N}$  requires  $M$ , 145.0891);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.90 (1 H, br. s, NH), 3.78 (2 H, m, 3- $\text{H}_2$ ), 4.01 (2 H, s, 1- $\text{H}_2$ ), 5.94 (1 H, dt,  $J$  12.5, 3.5, 4-H), 6.48 (1 H, dt,  $J$  12.5, 2.5, 5-H) and 7.02-7.33 (4 H, m, ArH);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 52.99, 54.60, 126.64, 126.95, 127.58, 129.17, 131.06, 134.65, 135.72 and 141.90;  $m/z$  (CI) 163 ( $M^{++18}$ , 5%) and 146 ( $M^{++1}$ , 100).

### **(4SR,5RS)-4,5-Dihydroxy-2-(4-methylphenyl)sulfonyl-2,3-dihydro-[1H]-2-benzazepine 36**

*N*-Methylmorpholine-*N*-oxide (41 mg, 0.350 mmol) and osmium tetroxide (2 mg,  $7.9 \times 10^{-3}$  mmol, 2.5 mol%) were added to the dihydrobenzazepine **33** (95 mg, 0.318 mmol) in acetone (2  $\text{cm}^3$ ) and water (2  $\text{cm}^3$ ). The reaction mixture was stirred for 24 h at room temperature before dichloromethane (25  $\text{cm}^3$ ) and water (25  $\text{cm}^3$ ) were added. The aqueous layer was extracted with dichloromethane (2 x 25  $\text{cm}^3$ ) and the organic extracts dried ( $\text{MgSO}_4$ ). After concentration under reduced pressure, chromatography using light petroleum : ethyl acetate (1:1  $\rightarrow$  1:2) gave the *title compound* **36** (61 mg, 58%) as a colourless solid (Found:  $M^+$ , 333.1027.  $\text{C}_{17}\text{H}_{19}\text{NO}_4\text{S}$  requires  $M$ , 333.1035);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 2.36 (3 H, s,  $\text{CH}_3$ ), 3.53 (1 H, dd,  $J$  8, 13.5, 3-H), 3.61 (1 H, dd,  $J$  3.5, 13.5, 3-H'), 3.82 (1 H, m, 4-H), 4.31 and 4.53 (each 1 H, d,  $J$  15, 1-H), 4.80 (1 H, m, 5-H), 7.11-7.34 (6 H, m, ArH) and 7.53 (2 H, d,  $J$  8, ArH);  $m/z$  (CI) 351 ( $M^{++18}$ , 5%), 333 ( $M^+$ , 10), 316 (10), 178 (40) and 160 (100).

### **(4RS,5SR)-4,5-Dihydroxy-2-(2-nitrophenyl)sulfonyl-2,3,4,5-tetrahydro-[1H]-2-benzazepine 37**

Following the procedure described for the synthesis of diol **36**, the dihydrobenzazepine **34** (7.16 g, 21.7 mmol), *N*-methylmorpholine-*N*-oxide (3.00 g, 25.6 mmol) and osmium tetroxide (110 mg, 0.43 mmol, 2 mol%) gave, after washing with saturated aqueous sodium sulfite (50  $\text{cm}^3$ ) and chromatography using light petroleum : ethyl acetate (1:1  $\rightarrow$  1:2), the *title compound* **37** (6.50 g, 82%) as a light brown syrup

which solidified gradually (Found:  $M^+ + NH_4$ , 382.1072.  $C_{16}H_{20}N_3O_6S$  requires  $M$ , 382.1072);  $\nu_{max}$  ( $CH_2Cl_2$ ) 3496, 3055, 1546, 1371, 1265 and 1165  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 2.41 (1 H, d,  $J$  7.5, OH), 2.60 (1 H, m, OH), 3.71-3.82 (2 H, m, 3- $H_2$ ), 4.13 (1 H, m, 4-H), 4.52 and 4.75 (each 1 H, d,  $J$  15.5, 1-H), 5.05 (1 H, m, 5-H), 7.28-7.45 (4 H, m, ArH), 7.62-7.77 (3 H, m, ArH) and 7.98 (1 H, d,  $J$  8, ArH);  $m/z$  (CI) 382 ( $M^+ + 18$ , 20%) and 180 (100).

### **2-Butyl-4,5-dihydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepine 39**

Following the procedure outlined for the preparation of the tetrahydrobenzazepine **35**, the 2-(2-nitrophenyl)sulfonyltetrahydrobenzazepine **37** (819 mg, 2.25 mmol) potassium carbonate (1.01 g, 7.31 mmol) and thiophenol (0.26  $cm^3$ , 2.53 mmol) in acetonitrile (30  $cm^3$ ) after stirring for 15 h gave the dihydroxytetrahydrobenzazepine **38**. This was dissolved in THF (15  $cm^3$ ) and butyraldehyde (0.30  $cm^3$ , 3.40 mmol), sodium triacetoxyborohydride (715 mg, 3.37 mmol) and glacial acetic acid (64  $\mu L$ , 1.12 mmol) were added. After stirring for 24 h, ether (20  $cm^3$ ) and water (25  $cm^3$ ) were added and the aqueous layer was basified to pH 10 using sodium hydroxide (2.5 M). The aqueous phase was extracted with ether (3 x 25  $cm^3$ ) and the organic extracts were dried ( $MgSO_4$ ). After concentration under reduced pressure, chromatography of the residue using light petroleum : ethyl acetate (1:2) containing triethylamine (1%) gave the *title compound* **39** (242 mg, 46%) as a colourless solid recrystallised as plates from ether (Found: C, 71.0; H, 8.0; N, 5.95%.  $C_{14}H_{21}NO_2$  requires C, 71.5; H, 8.2; N, 6.0%. Found:  $M^+ + H$ , 236.1653.  $C_{14}H_{22}NO_2$  requires  $M$ , 236.1650);  $\nu_{max}$  ( $CDCl_3$ ) 3368, 3072, 3024, 1545, 1454 and 1378  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 0.96 (3 H, t,  $J$  7.5, 4'- $H_3$ ), 1.36 (2 H, sex,  $J$  7.5, 3'- $H_2$ ), 1.57 (2 H, pent,  $J$  7.5, 2'- $H_2$ ), 2.49-2.65 (2 H, m, 1'- $H_2$ ), 2.98 and 3.19 (each 1 H, dd,  $J$  3.5, 13.5, 3-H), 3.64 (1 H, d,  $J$  15, 1-H), 3.99 (1 H, m, 4-H), 4.09 (1 H, d,  $J$  15, 1-H'), 4.83 (1 H, d,  $J$  2, 5-H), 7.17 (1 H, m, ArH), 7.22-7.36 (2 H, m, ArH) and 7.43 (1 H, m, ArH);  $m/z$  (CI) 236 ( $M^+ + 1$ , 100%).

### **(2-tert-Butyldimethylsilyloxymethylphenyl)cyclobutylcarbinol 42**

*tert*-Butyldimethylsilyl chloride (0.79 g, 5.24 mmol) in *N,N*-dimethylformamide (2.1  $cm^3$ ) was added to the diol **41** (1.00 g, 5.21 mmol) and imidazole (0.53 g, 7.78 mmol) in *N,N*-dimethylformamide (5.2  $cm^3$ ) at  $-10^\circ C$  over a period of 20 min. The mixture was stirred for 2 h at  $-10^\circ C$  then deionised water (50  $cm^3$ ) was added and the aqueous phase extracted with ethyl acetate (3 x 100  $cm^3$ ). The organic extracts were washed with deionised water (3 x 50  $cm^3$ ), brine (50  $cm^3$ ) and dried ( $Na_2SO_4$ ). After concentration under reduced pressure, chromatography eluting with light petroleum : ethyl acetate (9 : 1) gave the *title compound* **42** (1.27 g, 80%) as an oil (Found:  $M^+ + H$ , 307.2099.  $C_{18}H_{31}O_2Si$  requires  $M$ , 307.2093);

$\nu_{\max}$  3065, 3028, 1472, 1255, 1071, 838 and 776;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 0.02 and 0.06 (each 3 H, s,  $\text{SiCH}_3$ ), 0.82 [9 H, s,  $\text{C}(\text{CH}_3)_3$ ], 1.56-1.88 (4 H, m), 1.94-2.18 (2 H, m), 2.79 (1 H, sex,  $J$  8, CH), 2.84 (1 H, br. s, OH), 4.62 (1 H, d,  $J$  12, OHCH), 4.74 (1 H, d,  $J$  8, 1-H), 4.85 (1 H, d,  $J$  12, OHCH) and 7.10-7.27 (4 H, m, ArH);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ) -5.31, -5.23, 17.89, 18.25, 24.69, 25.30, 25.86, 39.77, 64.20, 74.35, 126.28, 127.34, 127.90, 128.70, 138.29 and 141.09;  $m/z$  (CI) 324 ( $\text{M}^{++18}$ , 1%), 307 ( $\text{M}^{++1}$ , 2), 289 (20) and 157 (100).

#### 2-(1-Cyclobutylethenyl)phenylmethanol 44

Tetra-*n*-butylammonium fluoride (1 M, 0.9  $\text{cm}^3$ , 0.90 mmol) was added to a solution of the silyl ether **43** (269 mg, 0.89 mmol) in THF (10  $\text{cm}^3$ ) at room temperature and the mixture stirred for 2 h. Ether (15  $\text{cm}^3$ ) and water (25  $\text{cm}^3$ ) were added and the aqueous layer extracted with ether (2 x 25  $\text{cm}^3$ ). The ethereal extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (19:1  $\rightarrow$  5:1) afforded the *title compound* **44** (139 mg, 83%) as a clear oil (Found:  $\text{M}^+\text{+H}$ , 189.1277.  $\text{C}_{13}\text{H}_{17}\text{O}$  requires  $M$ , 189.1279);  $\nu_{\max}$  3335, 3065, 3023, 1634, 1446, 1194, 1034, 901 and 763;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.55-1.67 (1 H, m), 1.71-2.01 (5 H, m), 3.13 (1 H, pent,  $J$  8, CH), 4.54 (2 H, s,  $\text{OCH}_2$ ), 4.83 and 5.11 (each 1 H, d,  $J$  1, 2'-H), 6.99 (1 H, d,  $J$  7, ArH), 7.11-7.22 (2 H, m, ArH) and 7.36 (1 H, d,  $J$  7, ArH);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 17.58, 27.93, 42.10, 63.16, 112.42, 127.07, 127.10, 128.00, 128.47, 137.65, 141.75 and 152.23;  $m/z$  (CI) 206 ( $\text{M}^+\text{+18}$ , 15%), 188 ( $\text{M}^+$ , 20) and 171 (100).

#### 2-(1-Cyclobutylethenyl)benzaldehyde 45

A suspension of manganese dioxide (4.40 g, 50.61 mol) and alcohol **44** (1.90 g, 10.11 mol) in dichloromethane (60  $\text{cm}^3$ ) was stirred at room temperature for 48 h then filtered through Celite<sup>®</sup> and the residue was washed with dichloromethane (2 x 50  $\text{cm}^3$ ). After concentration under reduced pressure, chromatography of the residue using light petroleum : ethyl acetate (19:1) as the eluent gave the *title compound* **45** (1.75 g, 93%) as a clear liquid (Found:  $\text{M}^+\text{+H}$ , 187.1121.  $\text{C}_{13}\text{H}_{15}\text{O}$  requires  $M$ , 187.1122);  $\nu_{\max}$  3084, 1694, 1596, 1479, 1446, 1391, 1261 and 1195  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.66-1.77 (1 H, m), 1.79-2.13 (5 H, m), 3.31 (1 H, pent,  $J$  8, CH), 4.96 and 5.37 (each 1 H, d,  $J$  1.5, 2'-H), 7.25 (1 H, d,  $J$  7.5, ArH), 7.37 and 7.52 (1 H, t,  $J$  7.5, ArH), 7.93 (1 H, d,  $J$  7.5, ArH) and 10.18 (1 H, s, CHO);  $\delta_{\text{C}}$  (75 M,  $\text{CDCl}_3$ ) 17.59, 27.75, 42.26, 115.66, 127.21, 127.35, 128.94, 133.25, 133.70, 146.34, 149.20 and 192.41;  $m/z$  (CI) 204 ( $\text{M}^+\text{+18}$ , 15%), 187 ( $\text{M}^+\text{+1}$ , 60), 186 ( $\text{M}^+$ , 70) and 169 (100).

### ***N*-[2-(1-Cyclobutylethenyl)phenyl]methyl prop-2-enylamine **46****

Prop-2-enylamine (0.45 cm<sup>3</sup>, 6.00 mmol) was added to the aldehyde **45** (540 mg, 2.90 mmol) and magnesium sulfate (*ca.* 5 g) in dichloromethane (30 cm<sup>3</sup>) at room temperature. The mixture was stirred for 24 h then filtered and concentrated under reduced pressure. The residue was dissolved in methanol (20 cm<sup>3</sup>) and sodium borohydride (164 mg, 4.33 mmol) was added. After stirring for 2 h, dichloromethane (50 cm<sup>3</sup>) and water (50 cm<sup>3</sup>) were added and the mixture basified to pH 10 using aqueous sodium hydroxide (2.5 M). The aqueous phase was extracted with dichloromethane (3 x 50 cm<sup>3</sup>) and the organic extracts were dried (MgSO<sub>4</sub>). Concentration under reduced pressure gave the *title compound* **46** (600 mg, 91%) as a yellow oil (Found: M<sup>+</sup>+H, 228.1746. C<sub>16</sub>H<sub>22</sub>N requires *M*, 228.1747);  $\nu_{\max}$  3323, 3070, 1682, 1633, 1455, 1445, 900 and 762;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.45 (1 H, br. s, NH), 1.73 (1 H, m), 1.87-2.11 (5 H, m), 3.21 (1 H, pent, *J* 8, CH), 3.25 (2 H, dt, *J* 6.5, 0.5, 1-H<sub>2</sub>), 3.75 (2 H, s, ArCH<sub>2</sub>), 4.93 (1 H, s, 2''-H), 5.07-5.25 (2 H, m, 3-H<sub>2</sub>), 5.19 (1 H, s, 2''-H'), 5.93 (1 H, m, 2-H), 7.06 (1 H, m, ArH), 7.16-7.29 (2 H, m, ArH) and 7.41 (1 H, m, ArH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 17.61, 28.04, 42.19, 50.63, 51.85, 112.01, 115.64, 126.27, 126.78, 128.59, 128.69, 136.94, 137.03, 141.83 and 152.70; *m/z* (CI) 288 (M<sup>+</sup>+1, 100).

### ***N*-[2-(1-Cyclobutylethenyl)phenyl]methyl-*N*-prop-2-enyl toluene *p*-sulfonamide **47****

The amine **46** (87 mg, 0.383 mmol), triethylamine (80  $\mu$ L, 0.574 mmol), toluene *p*-sulfonyl chloride (80 mg, 0.421 mmol) and 4-dimethylaminopyridine (*ca.* 1 mg) in dichloromethane (5 cm<sup>3</sup>) were stirred at room temperature for 4 h. Ether (15 cm<sup>3</sup>) and water (15 cm<sup>3</sup>) were added and the aqueous layer extracted with ether (2 x 15 cm<sup>3</sup>). The ethereal extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the *title compound* **47** (140 mg, 96%) (Found: M<sup>+</sup>+H, 382.1847. C<sub>23</sub>H<sub>28</sub>NO<sub>2</sub>S requires *M*, 382.1841);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.60 (1 H, m), 1.68-1.99 (5 H, m), 2.38 (3 H, s, CH<sub>3</sub>), 3.01 (1 H, pent, *J* 8.5, CH), 3.67 (2 H, d, *J* 6.5, 1-H<sub>2</sub>), 4.28 (2 H, s, ArCH<sub>2</sub>), 4.74 (1 H, t, *J* 1.5, 2''-H), 4.82-4.93 (2 H, m, 3-H<sub>2</sub>), 5.06 (1 H, t, *J* 1.5, 2''-H'), 5.41 (1 H, m, 2-H), 6.95 (1 H, dd, *J* 1.5, 7, ArH), 7.09-7.21 (2 H, m, ArH), 7.24 (2 H, d, *J* 8, ArH), 7.39 (1 H, dd, *J* 1.5, 7.5, ArH) and 7.67 (2 H, d, *J* 8, ArH); *m/z* (CI) 382 (M<sup>+</sup>+1, 20%), 228 (50) and 171 (100).

### ***N*-Phenylmethyl-*N*-prop-2-enyl 2-nitrobenzene sulfonamide **58**<sup>35</sup>**

2-Nitrophenylsulphonyl chloride (1.43 g, 6.45 mmol) was added to *N*-(phenylmethyl)prop-2-enylamine **57** (950 mg, 6.46 mmol), triethylamine (1.8 cm<sup>3</sup>, 12.91 mmol) and 4-dimethylaminopyridine (*ca.* 2 mg) in dichloromethane (20 cm<sup>3</sup>) and the mixture stirred for 3 h before water (50 cm<sup>3</sup>) and ether (50 cm<sup>3</sup>)

were added. The aqueous phase was extracted with ether (2 x 50 cm<sup>3</sup>) and the organic extracts were dried (MgSO<sub>4</sub>). After concentration under reduced pressure, chromatography of the residue using light petroleum : ethyl acetate (5:1) as eluent gave the *title compound* **58** (1.63 g, 76%) as a viscous clear oil (Found: M<sup>+</sup>+NH<sub>4</sub>, 350.1176. C<sub>16</sub>H<sub>20</sub>N<sub>3</sub>O<sub>4</sub>S requires *M*, 350.1174); δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 3.77 (2 H, d, *J* 6.5, 1-H<sub>2</sub>), 4.45 (2 H, s, ArCH<sub>2</sub>), 4.95-5.08 (2 H, m, 3-H<sub>2</sub>), 5.50 (1 H, ddd, *J* 6.5, 10, 17, 2-H), 7.19-7.25 (5 H, m, ArH), 7.51-7.65 (3 H, m, ArH) and 7.93 (1 H, d, *J* 7.5, ArH); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 49.15, 50.31, 119.63, 124.15, 127.81, 128.30, 128.57, 130.90, 131.70, 131.75, 133.46, 133.96 and 135.30; *m/z* (CI) 350 (M<sup>+</sup>+18, 100%).

### ***N*-Benzyl-*N*-formylmethyl 2-nitrobenzene sulfonamide **59****

A steady stream of ozone was passed through a solution of the alkene **58** (1.11 g, 3.34 mmol) in dichloromethane (25 cm<sup>3</sup>) at -78 °C until no starting material remained (tlc, *ca.* 0.5 h). The excess of ozone was purged by a flow of oxygen and then dimethyl sulfide (4.0 cm<sup>3</sup>, 54.47 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 15 h. After concentration under reduced pressure, chromatography using light petroleum : ethyl acetate (1:1) as eluent gave the *title compound* **59** (1.04 g, 92 %) as a colourless solid recrystallised from ethyl acetate and light petroleum, m.p. 105-108 °C (decomp.) (Found: C, 53.6; H, 4.45; N, 8.4; S, 9.65%. C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>S requires, C, 53.9; H, 4.2; N, 8.4; S, 9.6%); ν<sub>max</sub> (CDCl<sub>3</sub>) 3055, 1735, 1546, 1371, 1266 and 1166 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 4.11 (2 H, s, CH<sub>2</sub>), 4.65 (2 H, s, CH<sub>2</sub>), 7.25-7.38 (5 H, m, ArH), 7.65-7.74 (3 H, m, ArH), 8.11 (1 H, d, *J* 7.5, ArH) and 9.39 (1 H, s, CHO); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 52.60, 55.51, 124.30, 128.56, 128.70, 128.94, 130.90, 131.88, 132.98, 133.78, 134.09, and 196.42; *m/z* (ES) 690 (90%).

### ***N*-(3-Hydroxypropyl)-*N*-naphth-2-ylmethyl 2-nitrobenzene sulfonamide **61****

3-Aminopropanol (4.81 g, 64.03 mmol) was added to naphth-2-aldehyde **60** (5 g, 32.01 mmol) and magnesium sulphate (60 g) in dichloromethane (320 cm<sup>3</sup>) and the mixture stirred at room temperature for 48 h. The reaction mixture was then filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in methanol (213 cm<sup>3</sup>), sodium cyanoborohydride (2.01 g, 32.01 mmol) was added and the reaction mixture was stirred at room temperature for one hour. Ether (100 cm<sup>3</sup>) and deionised water (200 cm<sup>3</sup>) were added and the aqueous layer was extracted with ether (2 x 100 cm<sup>3</sup>). The aqueous layer was basified with aqueous sodium hydroxide (2 M) and extracted with dichloromethane (3 x 200 cm<sup>3</sup>). The dichloromethane extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to afford 3-(naphth-2-ylmethyl)propan-1-ol<sup>36</sup> (5.15 g, 75%) as a waxy solid

(Found:  $M^+ + H$ , 216.1385.  $C_{14}H_{18}NO$  requires  $M$ , 216.1383);  $\delta_H$  (300 MHz,  $CDCl_3$ ) 2.02 (2 H, pent,  $J$  7, 2- $H_2$ ), 3.90 (2 H, t,  $J$  7, 1- $H_2$ ), 3.92-4.00 (4 H, m, 2 x  $CH_2$ ), 7.42-7.60 (3 H, m, ArH, NH) and 7.78-8.06 (5 H, m, ArH);  $m/z$  (CI) 214 ( $M^+ - 1$ , 100%).

Sodium carbonate (2.79 g, 26.35 mmol) in deionised water (16  $cm^3$ ) and tetra-*n*-butylammonium iodide was added to the aminoalcohol **60** (5.15 g, 23.95 mmol) in acetone (24  $cm^3$ ). After the mixture was cooled to 0 °C, 2-nitrophenylsulfonyl chloride (5.31 g, 23.95 mmol) in acetone (8  $cm^3$ ) was added dropwise and the reaction mixture was stirred at room temperature for four hours. Deionised water (200  $cm^3$ ) was added and the aqueous phase was extracted with dichloromethane (3 x 200  $cm^3$ ). The organic extracts were dried ( $Na_2SO_4$ ) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (1 : 1  $\rightarrow$  1 : 4) gave the *title compound* **61** (6.72 g, 68%) as an oil (Found:  $M^+ + H$ , 401.1173.  $C_{20}H_{21}N_3O_5S$  requires  $M$ , 401.1171);  $\nu_{max}$  3562, 3360, 1545, 1345, 1162, 1127, 781 and 750;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 1.59 (2 H, pent,  $J$  7, 2- $H_2$ ), 2.00 (1 H, br. s, OH), 3.42-3.56 (4 H, m, 2 x  $CH_2$ ), 4.64 (2 H, s,  $ArCH_2$ ), 7.39 (1 H, m, ArH), 7.46-7.53 (2 H, m, ArH), 7.54-7.71 (4 H, m, ArH), 7.73-7.85 (3 H, m, ArH) and 7.97 (1 H, m, ArH);  $\delta_C$  (75.5 MHz,  $CDCl_3$ ) 30.70, 44.96, 52.16, 59.12, 124.38, 125.98, 126.44, 126.57, 127.48, 127.85, 127.91, 128.84, 130.91, 131.92, 133.09, 133.24, 133.51, 133.76, 142.01 and 148.08;  $m/z$  (CI) 418 ( $M^+ + 18$ , 5%), 399 (10), 278 (65), 261 (85) and 214 (100).

#### ***N*-Naphth-2-ylmethyl-*N*-(3-oxopropyl)-2-nitrobenzene sulfonamide **62****

Dess-Martin periodinane (5.30 g, 12.5 mmol) was added to the alcohol **61** (2.50 g, 6.25 mmol) in dichloromethane (32  $cm^3$ ) and the reaction mixture stirred at room temperature until complete (tlc). Aqueous sodium hydroxide (1.3 M, 150  $cm^3$ ) was added and the aqueous phase was extracted with ether (5 x 100  $cm^3$ ). The organic extracts were washed with aqueous sodium hydroxide (1.3 M, 150  $cm^3$ ) and deionised water (150  $cm^3$ ), then dried ( $Na_2SO_4$ ) and concentrated under reduced pressure to give the aldehyde **62** (1.03 g, 2.58 mmol, 41%) as an oil used without further purification (Found:  $M^+ + NH_4$ , 402.1127.  $C_{19}H_{20}N_3O_5S$  requires  $M$ , 402.1123);  $\nu_{max}$  3096, 1735, 1543, 1353 and 1164;  $\delta_H$  (500 MHz,  $CDCl_3$ ) 2.50 (2 H, t,  $J$  7, 2- $H_2$ ), 3.54 (2 H, t,  $J$  7, 3- $H_2$ ), 4.60 (2 H, s,  $ArCH_2N$ ), 7.3-7.43 (3 H, m, ArH), 7.50-7.65 (4 H, m, ArH), 7.65-7.78 (3 H, m, ArH) and 7.95 (1 H, m, ArH).

#### ***N*-(6-Methylnaphth-2-yl)methyl-3-hydroxypropylamine **64****

3-Aminopropanol (88.2 mg, 1.18 mmol) was added to 2-methyl-6-naphthaldehyde **63**<sup>37</sup> (0.1 g, 0.59 mmol) and magnesium sulphate (1.5 g) in dichloromethane (6  $cm^3$ ) and the reaction mixture stirred at



room temperature for 24 h then filtered and concentrated under reduced pressure. The residue was dissolved in methanol (4 cm<sup>3</sup>) and sodium cyanoborohydride (37 mg, 0.59 mmol) was added. The reaction mixture was then stirred at room temperature for 1 h and ether (50 cm<sup>3</sup>) and deionised water (50 cm<sup>3</sup>) were added. The aqueous layer was extracted with ether (2 x 50 cm<sup>3</sup>) then basified with aqueous sodium hydroxide (2.5 M) and extracted with dichloromethane (3 x 100 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to afford the *title compound 64* (78 mg, 58%) as a solid, m.p. 74-76 °C (Found: M<sup>+</sup>+H, 230.1538. C<sub>15</sub>H<sub>20</sub>NO requires *M*, 230.1539);  $\nu_{\max}$  3294, 1608, 1450, 1068, 878 and 815;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.78 (2 H, pent, *J* 7, 2-H<sub>2</sub>), 2.55 (3 H, s, CH<sub>3</sub>), 2.96 (2 H, t, *J* 7, 1-H<sub>2</sub>), 3.11 (2 H, br. s, NH, OH), 3.86 (2 H, t, *J* 7, 3-H<sub>2</sub>), 3.96 (2 H, s, ArCH<sub>2</sub>), 7.35 and 7.43 (each 1 H, dd, *J* 8.5, 1.5, ArH), 7.63 (1 H, s, ArH) and 7.71-7.77 (3 H, m, ArH);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 21.69, 30.80, 49.39, 54.11, 64.39, 126.41, 126.48, 126.67, 127.50, 127.62, 128.40, 131.59, 132.91, 135.36 and 136.06; *m/z* (CI) 228 (M<sup>+</sup>, 1%), 172 (100) and 155 (81).

#### ***N*-(6-Methylnaphth-2-yl)methyl-*N*-(3-hydroxypropyl) 2-nitrobenzene sulfonamide 65**

Sodium carbonate (0.15 g, 1.42 mmol) in deionised water (1 cm<sup>3</sup>) and tetra-*n*-butylammonium iodide were added to the aminoalcohol **64** (295 mg, 1.29 mmol) in acetone (3 cm<sup>3</sup>) and the reaction mixture was cooled to 0 °C before a solution of 2-nitrophenylsulfonyl chloride (285 mg, 1.29 mmol) in acetone (1 cm<sup>3</sup>) was added. The reaction mixture was stirred at room temperature for 4 h then deionised water (30 cm<sup>3</sup>) was added and the aqueous phase extracted with dichloromethane (3 x 100 cm<sup>3</sup>). The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (1 : 1 → 1 : 4) as eluent gave the *title compound 65* (0.41 g, 77%) as a solid, m.p. 115.5-117.5 °C (Found: M<sup>+</sup>+Na, 437.1141. C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>NaS requires *M*, 437.1142); 3399, 1543, 1344 and 1161;  $\delta_{\text{H}}$  (200 MHz; CDCl<sub>3</sub>) 1.55-1.65 (2 H, m, 2-H<sub>2</sub>), 1.81 (1 H, m, OH), 2.51 (3 H, s, CH<sub>3</sub>), 3.43-3.54 (4 H, m, 2 x CH<sub>2</sub>), 4.66 (2 H, s, ArCH<sub>2</sub>), 7.33-7.37 (2 H, m, ArH), 7.57-7.73 (7 H, m, ArH) and 7.98 (1 H, m, ArH);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 21.71, 30.59, 44.74, 52.10, 58.96, 124.25, 125.93, 126.70, 127.17, 127.57, 128.06, 128.72, 130.89, 131.35, 131.70, 132.02, 133.20, 133.49, 133.54, 136.10 and 148.00; *m/z* (CI) 432 (M<sup>+</sup>+18, 5%), 391 (20) and 256 (100).

#### ***N*-(6-Methylnaphth-2-yl)methyl-*N*-(3-oxopropyl) 2-nitrobenzene sulfonamide 66**

The Dess-Martin periodinane (462 mg, 1.09 mmol) was added to the aminoalcohol **65** (410 mg, 0.99 mmol) in dichloromethane (5 cm<sup>3</sup>) and the reaction mixture stirred at room temperature until complete (tlc). Aqueous sodium hydroxide (1.3 M, 25 cm<sup>3</sup>) was added and the aqueous phase extracted with ether

(5 x 50 cm<sup>3</sup>). The organic extracts were washed with aqueous sodium hydroxide (1.3 M, 150 cm<sup>3</sup>), deionised water (150 cm<sup>3</sup>), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give the *title compound 66* (397 mg, 97%) as an oil used without further purification (Found: M<sup>+</sup>+H, 413.1158. C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub>S requires *M*, 413.1166);  $\nu_{\max}$  1723, 1545, 1370 and 1163;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 2.43 (3 H, s, CH<sub>3</sub>), 2.48 (2 H, t, *J* 7, 2-H<sub>2</sub>), 3.53 (2 H, t, *J* 7, 1-H<sub>2</sub>), 4.57 (2 H, s, ArCH<sub>2</sub>), 7.25 and 7.32 (each 1 H, dd, *J* 8.5, 1.5, ArH), 7.50-7.68 (7 H, m, ArH), 7.93 (1 H, m, ArH) and 9.43 (1 H, s, CHO);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 20.68, 40.35, 42.15, 52.01, 123.29, 124.87, 125.70, 126.23, 126.59, 127.24, 127.78, 129.97, 130.34, 130.78, 130.88, 131.97, 132.25, 132.72, 135.19, 147.02 and 198.66; *m/z* (ES) 413 (M<sup>+</sup>+1, 100%).

**(4*SR*,5*RS*)-5-Cyclobutyl-4,5-dihydroxy-2-[3-(*N*-naphth-2-ylmethyl-*N*-2-nitrophenylsulfonyl-amino)propyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 73**

The tetrahydrobenzazepine **52** (250 mg, 1.07 mmol) in methanol (5 cm<sup>3</sup>) was added to the aldehyde **65** (1.03 g, 2.58 mmol) suspended in methanol (10 cm<sup>3</sup>), followed by sodium cyanoborohydride (68 mg, 1.07 mmol) and concentrated hydrochloric acid (2 drops). The reaction mixture, which briefly became homogeneous although a precipitate separated out after 10 min, was stirred for 12 h. Deionised water (30 cm<sup>3</sup>) was added and the aqueous layer extracted with ether (3 x 50 cm<sup>3</sup>). The ether extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (1 : 1 → 1 : 4) containing triethylamine (1%) gave the *title compound 73* (212 mg, 0.35 mmol, 32%) (Found: M<sup>+</sup>+H, 616.2487. C<sub>34</sub>H<sub>38</sub>N<sub>3</sub>O<sub>6</sub>S requires *M*, 616.2481);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.53-1.82 (7 H, m), 2.12-2.25 (2 H, m), 2.40 and 2.54 (each 1 H, m, 1'-H), 2.70-2.79 (2 H, m), 2.86 (1 H, ddd, *J* 13, 5, 2, 3-H'), 2.97 (1 H, br. s, OH), 3.34 (2 H, t, *J* 7, 3'-H<sub>2</sub>), 3.41 (1 H, dd, *J* 13, 1.5, 1-H), 3.59 (2 H, m, 1-H' and 4-H), 4.62 and 4.77 (each 1 H, d, *J* 15, NHCHPh), 6.86 (1 H, d, *J* 7, ArH), 7.12 (1 H, t, *J* 7, ArH), 7.30 (1 H, m, ArH), 7.43 (1 H, dd, *J* 8, 1.5, ArH), 7.50-7.54 (2 H, m, ArH), 7.59 (1 H, m, ArH), 7.67-7.70 (3 H, m, ArH), 7.75-7.88 (4 H, m, ArH) and 7.98 (1 H, d, *J* 8, ArH); *m/z* (ES) 616 (M<sup>+</sup>+1, 100%) and 582 (12).

**(4*SR*,5*RS*)-5-Cyclobutyl-4,5-dihydroxy-2-[3-(*N*-6-methylnaphth-2-ylmethyl-*N*-2-nitrophenyl-sulfonylamino)propyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 74**

The tetrahydrobenzazepine **52** (84 mg, 0.36 mmol) in methanol (2.5 cm<sup>3</sup>) was added to a suspension of the aldehyde **66** (90 mg, 0.22 mmol) in methanol (1.5 cm<sup>3</sup>) followed by sodium cyanoborohydride (14 mg, 0.22 mmol) and concentrated aqueous hydrogen chloride (2 drops). The reaction mixture became

homogeneous and a precipitate separated out after 10 minutes. The reaction mixture was stirred overnight, then deionised water (10 cm<sup>3</sup>) was added. The aqueous layer was extracted with ether (3 x 25 cm<sup>3</sup>) and the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (1 : 1 → 1 : 4) containing triethylamine (1%) as the eluent gave the *title compound 74* (43 mg, 31%) as an oil (Found: M<sup>+</sup>+H, 630.2637. C<sub>35</sub>H<sub>40</sub>N<sub>3</sub>O<sub>6</sub>S requires M, 630.2632);  $\nu_{\max}$  3467, 3054, 1543, 1372, 1348, 1161 753 and 736;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.3 (1 H, m), 1.53-1.79 (6 H, m), 2.12-2.24 (2 H, m, 2'-H<sub>2</sub>), 2.40 and 2.50 (each 1 H, m, 1'-H), 2.54 (3 H, s, CH<sub>3</sub>), 2.71 (1 H, d, *J* 13, 1-H), 2.76 (1 H, m, 3-H), 2.84 (1 H, ddd, *J* 13, 5, 2, 3-H'), 3.30 (1 H, br. s, OH), 3.33 (2 H, t, *J* 8, 3'-H<sub>2</sub>), 3.42 (1 H, d, *J* 1.5, 4-H), 3.58 (1 H, br. s, OH), 3.59 (1 H, d, *J* 13, 1-H'), 4.57 and 4.59 (each 1 H, d, *J* 15, NHCHPh), 6.84 (1 H, d, *J* 8, ArH), 7.12 (1 H, t, *J* 8, ArH), 7.29-7.41 (3 H, m, ArH), 7.58-7.73 (7 H, m, ArH) and 7.81 and 7.97 (each 1 H, d, *J* 8, ArH);  $\delta_{\text{C}}$  (75.5 MHz, CDCl<sub>3</sub>) 17.63, 21.63, 23.52, 26.29, 29.62, 39.47, 46.07, 52.01, 56.47, 58.88, 59.31, 72.90, 79.32, 124.12, 125.86, 126.62, 126.98, 127.08, 127.17, 127.49, 128.01, 128.62, 128.93, 130.05, 130.82, 130.98, 131.58, 132.25, 133.27, 133.38, 134.92, 136.01, 141.15, 141.78 and 147.90; *m/z* (ES) 630 (M<sup>+</sup>+1, 100%).

### **5-Cyclobutyl-5-hydroxy-2-[3-(*N*-naphth-2-ylmethylamino)propyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 76**

Dess-Martin periodinane (63 mg, 0.15 mmol) was added to the dihydroxytetrahydrobenzazepine **73** (70 mg, 0.114 mmol) in dichloromethane (1.5 cm<sup>3</sup>) and the reaction mixture stirred for two hours at room temperature. Aqueous sodium hydroxide (1.3 M, 20 cm<sup>3</sup>) was added and the aqueous phase was extracted with dichloromethane (3 x 30 cm<sup>3</sup>). The organic extracts were washed with aqueous sodium hydroxide (1.3 M, 50 cm<sup>3</sup>) and deionised water (50 cm<sup>3</sup>) then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give the crude hydroxyketone **75** (59.4 mg, 0.10 mmol, 85%) which was dissolved in *N,N*-dimethylformamide (1.0 cm<sup>3</sup>). Thiophenol (14 mg, 0.13 mmol) and potassium carbonate (47 mg, 0.34 mmol) were added and the reaction mixture stirred for 12 h. Deionised water (15 cm<sup>3</sup>) was added and the *pH* adjusted to *pH* 12 using aqueous sodium hydroxide (2 M). The aqueous phase was extracted with ethyl acetate (5 x 25 cm<sup>3</sup>) and the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (4 : 1 → □ : 1) containing triethylamine (1%) gave the *title compound 76* (17 mg, 41%);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.51-1.79 (5 H, m, CH<sub>2</sub>), 1.87 (1 H, m), 2.19-2.30 (2 H, m, 2'-H<sub>2</sub>), 2.39-2.51 (2 H, m, 3'-H<sub>2</sub>), 2.62-2.70 (2 H, m, 1'-H<sub>2</sub>), 3.51 (1 H, m), 3.51 and 3.72 (each 1 H, d, *J* 12, 1-H), 3.90 (1 H, d, *J* 16, 3-H), 3.91 (2 H, s,

NCH<sub>2</sub>Ph), 4.18 (1 H, d, *J* 16, 3-H'), 7.01 (1 H, dd, *J* 8, 1.5, ArH), 7.15 and 7.23 (each 1 H, dt, *J* 8, 1.5, ArH), 7.39-7.46 (3 H, m, ArH) and 7.70-7.80 (5 H, m, ArH).

### **5-Cyclobutyl-5-hydroxy-2-[3-(*N*-6-methylnaphth-2-ylmethylamino)propyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 78**

Dess-Martin periodinane (142 mg, 0.334 mmol) was added to the dihydroxytetrahydrobenzazepine **74** (140 mg, 0.223 mmol) in dichloromethane (1.2 cm<sup>3</sup>) and the reaction mixture stirred for 2 h at room temperature. Aqueous sodium hydroxide (1.3 M, 50 cm<sup>3</sup>) was added and the aqueous phase was extracted with dichloromethane (3 x 50 cm<sup>3</sup>). The organic extracts were washed with aqueous sodium hydroxide (1.3 M, 50 cm<sup>3</sup>) and deionised water (50 cm<sup>3</sup>) then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give the crude hydroxyketone **77** (111 mg, 0.18 mmol, 80%);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.53-1.64 (4 H, m, 2 x CH<sub>2</sub>), 1.71-1.89 (3 H, m), 2.17-2.27 (3 H, m), 2.55 (3 H, s, CH<sub>3</sub>), 3.25-3.40 (5 H, m, 1-H, 1'-H<sub>2</sub> and 3'-H<sub>2</sub>), 3.64 and 3.69 (each 1 H, d, *J* 16, 1-H and 3-H), 4.04 (1 H, d, *J* 16, 3-H'), 4.66 (2 H, s, ArCH<sub>2</sub>N), 6.79 (1 H, d, *J* 7.5, ArH), 7.13 (1 H, t, *J* 7.5, ArH), 7.25 (1 H, d, *J* 7.5, ArH), 7.36 and 7.41 (each 1 H, d, *J* 8, ArH), 7.57-7.75 (8 H, m, ArH) and 7.99 (1 H, d, *J* 8, ArH).

Thiophenol (2.15 mg, 0.02 mmol) and potassium carbonate (7.2 mg, 0.052 mmol) were added to the crude 2-nitrophenylsulfonamide **77** (10 mg, 0.016 mmol) in *N,N*-dimethylformamide (0.5 cm<sup>3</sup>) and the mixture stirred overnight at room temperature. Deionised water (10 cm<sup>3</sup>) was added and the pH adjusted to pH 12 using aqueous sodium hydroxide (2 M). The aqueous phase was extracted with ethyl acetate (5 x 25 cm<sup>3</sup>) and the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (4 : 1 → 2 : 1) containing triethylamine (1%) as eluent gave the *title compound* **78** (7 mg, 97%) (Found: M<sup>+</sup>+H, 443.2700. C<sub>29</sub>H<sub>35</sub>N<sub>2</sub>O<sub>2</sub> requires *M*, 443.2698);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.51-1.74 (5 H, m), 1.78-1.88 (2 H, m), 2.19 (2 H, m, 2'-H<sub>2</sub>), 2.35-2.42 (5 H, m, CH<sub>3</sub> and CH<sub>2</sub>), 2.61 (2 H, t, *J* 7, CH<sub>2</sub>), 3.45 (1 H, m), 3.47 (1 H, d, *J* 16, 1-H), 3.69 (1 H, d, *J* 16, 1-H'), 3.82 (2 H, s, NCH<sub>2</sub>Ph), 3.84 and 4.12 (each 1 H, d, *J* 16, 3-H), 6.95 (1 H, d, *J* 8, ArH), 7.06-7.23 (3 H, m, ArH), 7.29 (1 H, dd, *J* 8, 1.5, ArH), 7.50 (1 H, s, ArH) and 7.67 (4 H, m, ArH); *m/z* (CI) 443 (M<sup>+</sup>+1, 8%) and 425 (2).

### ***N*-(3-Hydroxypropyl)-*N*-phenylmethyl-2-nitrobenzene sulfonamide 80<sup>38</sup>**

Sodium carbonate (3.67 g, 34.59 mmol) in deionised water (21 cm<sup>3</sup>) and tetra-*n*-butylammonium iodide (trace) were added to 3-(*N*-phenylmethyl)aminopropanol **79** (5.19 g, 31.45 mmol) in acetone (32 cm<sup>3</sup>) and the mixture cooled to -10 °C. 2-Nitrophenylsulfonyl chloride (6.97 g, 31.45 mmol) in acetone (10.5

cm<sup>3</sup>) was added dropwise over a period of 40 min and the reaction mixture was stirred at room temperature for 2 h. Deionised water (200 cm<sup>3</sup>) was added and the aqueous phase was extracted with dichloromethane (3 x 200 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (1 : 1 → 1 : 4 containing triethylamine (1%) as eluent gave the sulfonamide **80**<sup>38</sup> (8.63 g, 78%) as an oil (Found: M<sup>+</sup>+H, 351.1005. C<sub>16</sub>H<sub>19</sub>N<sub>2</sub>O<sub>5</sub>S requires M, 351.1009); ν<sub>max</sub> 3562, 3399, 3092, 3031, 1669, 1589, 1543, 1371, 1344, 1161, 781, and 739; δ<sub>H</sub> (200 MHz, CDCl<sub>3</sub>) 1.59 (2 H, pent, J 6, 2-H<sub>2</sub>), 1.81 (1 H, br. s, OH), 3.43 (2 H, t, J 6, 3-H<sub>2</sub>), 3.55 (2 H, br. t, J 6, 1-H<sub>2</sub>), 4.53 (2 H, s, PhCH<sub>2</sub>), 7.21-7.37 (5 H, m, ArH), 7.65-7.77 (3 H, m, ArH) and 7.98 (1 H, m, ArH); δ<sub>C</sub> (75.5 MHz, CDCl<sub>3</sub>) 30.59, 44.77, 51.90, 59.10, 124.40, 128.21, 128.43, 128.87, 130.92, 131.93, 133.54, 133.74, 135.73, 142.20 and 148.02; m/z (ES) 351 (M<sup>+</sup>+1, 100%).

### 3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)aminopropanoic acid **81**

Dess-Martin periodinane (1.8 g, 4.26 mmol) was added to the 3-sulfonylaminoalcohol **80** (0.75 g, 2.13 mmol) in dichloromethane (11 cm<sup>3</sup>) and the reaction mixture was stirred for 2 h at room temperature. Aqueous sodium hydroxide (1.3 M, 30 cm<sup>3</sup>) was added and the aqueous phase was extracted with dichloromethane (3 x 30 cm<sup>3</sup>). The organic extracts were washed with aqueous sodium hydroxide (1.3 M, 30 cm<sup>3</sup>) and deionised water (50 cm<sup>3</sup>) then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to leave crude 3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)aminopropanal (0.7 g, 95%).

2-Methyl-2-butene (10.06 cm<sup>3</sup>, 20.11 mmol), sodium chlorite (1.13 g, 12.57 mmol) and sodium dihydrogen phosphate (2.41 g, 20.11 mmol) were added to the 3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)aminopropanal (0.7 g, 2.01 mmol) in 2,2-dimethylpropanol and water (1 : 1, 50.3 cm<sup>3</sup>) and the reaction mixture was stirred for 12 h. Brine (60 cm<sup>3</sup>) and ethyl acetate (60 cm<sup>3</sup>) were added and the aqueous phase was extracted with ethyl acetate (3 x 75 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the *title compound* **81** (0.63 g, 81%) (Found: M<sup>+</sup>+H, 365.0804. C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>O<sub>6</sub>S requires M, 365.0808); ν<sub>max</sub> 2600-3600, 1712, 1543, 1369, 1349, 1163, 941, 771 and 738; δ<sub>H</sub> (200 MHz, CDCl<sub>3</sub>) 2.46 (2 H, t, J 8, 2-H<sub>2</sub>) 3.55 (2 H, t, J 8, 3-H<sub>2</sub>), 4.56 (2 H, s, PhCH<sub>2</sub>), 7.24-7.37 (5 H, m, Ar-H), 7.63-7.75 (3 H, m, Ar-H) and 8.04 (1 H, m, Ar-H); δ<sub>C</sub> (75.5 MHz, CDCl<sub>3</sub>) 33.25, 43.06, 52.31, 124.53, 128.39, 129.02, 131.03, 132.11, 132.61, 133.18, 134.03, 135.49, 148.04 and 176.22; m/z (CI) 382 (M<sup>+</sup>+18, 50%), 365 (M<sup>+</sup>+1, 8) and 178 (100).

**(4*RS*,5*SR*)-5-Cyclobutyl-4,5-dihydroxy-2-[3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)amino-  
propanoyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 84**

*N*-Methylmorpholine-*N*-oxide (26 mg, 0.23 mmol) and osmium tetroxide (5 mg, 0.021 mmol) were added to the dihydrobenzazepine **83** (111.4 mg, 0.21 mmol) in acetone (3.4 cm<sup>3</sup>), 2,2-dimethylpropan-2-ol (3.4 cm<sup>3</sup>) and deionised water (1.6 cm<sup>3</sup>) and the reaction mixture stirred for 12 h. Ethyl acetate (20 cm<sup>3</sup>) was added followed by deionised water (20 cm<sup>3</sup>) and the aqueous phase was extracted with ethyl acetate (3 x 25 cm<sup>3</sup>). The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (1 : 1) → □□□□□□□□□□ → ethyl acetate : methanol (20 : 1) all containing triethylamine (1%) as eluent gave the *title compound* **84** (118.14 mg, 0.21 mmol, 99%) as a solid (Found: M<sup>+</sup>+H, 580.2127. C<sub>30</sub>H<sub>34</sub>N<sub>3</sub>O<sub>7</sub>S requires *M*, 580.2118); ν<sub>max</sub> 3416, 1634, 1543, 1455, 1372, 1344, 1162 and 735; δ<sub>H</sub> (300 MHz, dimethyl sulfoxide-*d*<sub>6</sub>, 150 °C) 1.29 (1 H, m) 1.73-1.60 (2 H, m), 1.88-1.77 (1 H, m), 2.06 (1 H, m), 2.19 (1 H, m), 2.50 (3 H, m), 3.51 (2 H, t, *J* 7.5, 3'-H<sub>2</sub>), 3.55 (1 H, m, 3-H), 3.68 (1 H, dd, *J* 15, 3, 3-H'), 3.79 (1 H, m, 4-H), 4.17 (2 H, br. s, 2 x OH), 4.28 (1 H, d, *J* 15, 1-H), 4.51 (2 H, s, PhCH<sub>2</sub>N), 4.76 (1 H, d, *J* 15, 1-H'), 7.03 (1 H, m, ArH), 7.11 and 7.20 (each 1 H, t, *J* 6, ArH), 7.29 (5 H, m, ArH), 7.66 (1 H, d, *J* 9, ArH), 7.76 (1 H, m, ArH), 7.84 (2 H, m, ArH) and 7.96 (1 H, d, *J* 9, ArH); *m/z* (CI) 580 (M<sup>+</sup>+1, 45%), 393 (27) and 106 (100).

**(4*RS*,5*SR*)-5-Cyclobutyl-4,5-dihydroxy-2-[3-(*N*-phenylmethyl)aminopropanoyl]-2,3,4,5-  
tetrahydro-[1*H*]-2-benzazepine 85**

Thiophenol (29 mg, 0.27 mmol) and potassium carbonate (99 mg, 0.72 mmol) were added to the 2-nitrobenzene sulfonamide **84** (118 mg, 0.21 mmol) in *N,N*-dimethylformamide (5.12 cm<sup>3</sup>) and the mixture stirred for 12 h. Deionised water (40 cm<sup>3</sup>) was added and the *pH* adjusted to *pH* 12 using aqueous sodium hydroxide (2 M). The aqueous phase was extracted with ethyl acetate (5 x 40 cm<sup>3</sup>) and the organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (1 : 1 → 1 : 4) containing triethylamine (1%) as eluent gave the *title compound* **85** (76 mg, 94%) as an oil (Found: M<sup>+</sup>+H, 395.2338. C<sub>24</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub> requires *M*, 395.2335); ν<sub>max</sub> 3390, 3059, 3023, 1631, 1455, 1207, 1097, 1026, 997, 734 and 699; δ<sub>H</sub> (300 MHz, dimethyl sulfoxide-*d*<sub>6</sub>, 150 °C) 1.30 (1 H, m) 1.67-1.75 (2 H, m), 1.85 (1 H, m), 2.08 (1 H, m), 2.23 (1 H, m), 2.54 (2 H, m), 2.81 (2 H, br. s, CH<sub>2</sub>), 3.72 (2 H, s, CH<sub>2</sub>), 3.85 (3 H, m), 4.15 (1 H, m), 4.43 and 4.92 (each 1 H, d, *J* 15, 1-H), 7.05-7.35 (8 H, m, ArH) and 7.70 (1 H, d, *J* 7, ArH); δ<sub>C</sub> (75.5 MHz, dimethyl sulfoxide-*d*<sub>6</sub>, 150 °C) 16.45, 21.20, 21.35, 32.19, 44.30, 50.73, 52.21, 72.52, 77.98, 78.46,

125.64, 125.79, 125.88, 127.27, 127.38, 128.08, 128.66, 133.82, 139.93, 141.91 and 170.52;  $m/z$  (CI) 395 ( $M^{+}+1$ , 43%), 288 (28) and 108 (100).

### **2-(2-Bromophenylmethoxy)tetrahydro-[2H]-pyran 88**

Dihydropyran (2.25 g, 26.7 mmol) and toluene *p*-sulfonic acid (102 mg, 0.535 mmol) were added to the 2-bromobenzyl alcohol **87** (1.0 g, 5.35 mmol) in dichloromethane (20 cm<sup>3</sup>) at 0 °C. The reaction was allowed to warm to room temperature and was stirred for 3 h. Dichloromethane (20 cm<sup>3</sup>) was added and the solution washed with saturated aqueous sodium bicarbonate (3 x 20 cm<sup>3</sup>) and brine (2 x 10 cm<sup>3</sup>). The organic phase was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 4) gave the *title compound* **88** (1.42 g, 98%) as a colourless oil (Found:  $M^{+}+NH_4$ , 288.0597. C<sub>12</sub>H<sub>19</sub>BrNO<sub>2</sub> requires  $M$ , 288.0594);  $\nu_{max}$  1569, 1440, 1348, 1201, 1124 and 1024 cm<sup>-1</sup>;  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 1.52-1.71 (3 H, m) 1.70-1.90 (2 H, m), 1.95 (1 H, m), 3.62 (1 H, m, 6-H), 3.96 (1 H, m, 6-H'), 4.60 (1 H, d,  $J$  13, ArCHH), 4.93 (1 H, t,  $J$  3.5, 2-H), 4.87 (1 H, d,  $J$  13 ArCHH), 7.19 (1 H, m, ArH), 7.36 (1 H, dt,  $J$  1.5, 8, ArH) and 7.55-7.60 (2 H, m, Ar-H);  $\delta_C$  (75 MHz; CDCl<sub>3</sub>) 19.73, 25.85, 30.92, 62.58, 68.98, 98.81, 123.13, 127.74, 129.17, 129.44, 132.88 and 138.24;  $m/z$  (CI) 288, 290 ( $M^{+} + 18$ , 1.5%) and 102 (100).

### **Cyclopentanoyl 2-(tetrahydro-[2H]-pyran-2-yloxymethyl)benzene 89**

*tert*-Butyllithium (0.56 cm<sup>3</sup>, 1.6 M in pentane) was added to 2-(2-bromophenylmethoxy)tetrahydro-[2H]-pyran **88** (100 mg, 0.44 mmol) at -78 °C in tetrahydrofuran (2 cm<sup>3</sup>) and the solution stirred for 15 min. Cyclopentylcarboxaldehyde (45 mg, 0.46 mmol) in tetrahydrofuran (1 cm<sup>3</sup>) was added and the mixture stirred for 30 min. before saturated aqueous ammonium chloride (1 cm<sup>3</sup>) was added. The mixture was extracted with ethyl acetate (3 x 10 cm) and the organic extracts dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 9) as eluent gave yield cyclopentyl 2-(tetrahydro-[2H]-pyran-2-yloxymethyl)phenyl carbinol (113 mg, 89%), a 50 : 50 mixture of diastereoisomers, as a colourless oil (Found:  $M^{+}+H$ , 291.1954. C<sub>18</sub>H<sub>27</sub>O<sub>3</sub> requires  $M$ , 291.1955);  $\nu_{max}$  3436, 1453, 1119, 1024, 905 and 760 cm<sup>-1</sup>;  $\delta_H$  (500 MHz; CDCl<sub>3</sub>) 0.84 (1 H, m), 1.00 (1 H, m), 1.30-1.80 (11 H, m), 1.92 (1 H, m), 2.37 (1 H, sext,  $J$  8), 2.70 (1 H, br. s, OH), 3.48 and 3.80 (each 1 H, m), 4.43 (0.5 H, d,  $J$  10, ArHCHO), 4.54-4.68 (2.5 H, m), 4.74 and 4.93 (each 0.5 H, d,  $J$  10, ArHCHO), 7.17 (1 H, m, ArH), 7.24-7.28 (2 H, m, ArH) and 7.41 (1 H, d,  $J$  8, ArH);  $\delta_C$  (125 MHz; CDCl<sub>3</sub>) 19.44, 19.46, 25.63, 25.90, 25.92, 26.03, 29.03, 29.96, 29.98, 30.41, 30.60, 30.77, 45.36, 45.51, 62.36, 62.43, 67.73, 67.92, 75.08, 75.29, 98.02, 98.15, 127.30, 127.61, 128.79, 128.81, 130.31, 130.40, 135.53, 135.62, 143.49 and 144.39;  $m/z$  (CI) 308 ( $M^{+}+18$ , 10%) and 187 (100).

Pyridine (126 mg, 1.56 mmol) was added to the Dess Martin periodinane (113 mg, 0.26 mmol) in dichloromethane (4 cm<sup>3</sup>). After 20 min, cyclopentyl 2-(tetrahydro-[2H]-pyran-2-yloxymethyl)phenyl carbinol (70 mg, 0.24 mmol) in dichloromethane (2 cm<sup>3</sup>) was added and the solution was stirred for 4 h. Saturated aqueous sodium sulfite (5 cm<sup>3</sup>) was added and the mixture was stirred vigorously for 1 h then extracted with dichloromethane (3 x 15 cm<sup>3</sup>). The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate : light petroleum (1 : 9) gave the *title compound* **89** (67 mg, 98%) as a colourless oil (Found: M<sup>+</sup>+H, 289.1794. C<sub>18</sub>H<sub>25</sub>O<sub>3</sub> requires *M*, 289.1798);  $\nu_{\max}$  1769, 1678, 1599, 1573, 1451, 1352, 1219, 1200, 1129 and 1035 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>), 1.51-1.84 (10 H, m), 1.90-1.94 (4 H, m), 3.53 (1 H, m), 3.61 (1 H, quin, *J* 8, CHCO), 3.93 (1 H, m), 4.75 (1 H, t *J* 4, OCHO), 4.87 and 5.03 (each 1 H, d, *J* 14, OHCH), 7.39 and 7.52 (each 1 H, dt, *J* 1.5, 8, ArH) and 7.71 (2 H, d, *J* 8, ArH);  $\delta_{\text{C}}$  (75 MHz; CDCl<sub>3</sub>) 19.80, 25.72, 26.50, 26.52, 30.03, 30.12, 30.85, 49.27, 62.58, 67.50, 98.77, 127.18, 128.54, 128.60, 131.45, 137.63, 139.29 and 207.12; *m/z* (CI) 289 (M<sup>+</sup>+1, 1%) and 187 (100).

### **(1-Cyclopentylethenyl)-2-(tetrahydro-[2H]-pyran-2-yloxymethyl)benzene 90**

*n*-Butyllithium (207  $\mu$ L, 0.33 mmol) was added to a solution of methyltriphenylphosphonium bromide (124 mg, 0.35 mmol) in tetrahydrofuran (2 cm<sup>3</sup>) and the solution stirred for 30 min before the ketone **89** (40 mg, 0.14 mmol) was added and the mixture stirred for 18 h. Saturated aqueous ammonium chloride (1 cm<sup>3</sup>) was added and the mixture extracted using ethyl acetate (3 x 4 cm<sup>3</sup>). The organic extracts were washed with a saturated aqueous sodium bicarbonate (2 x 5 cm<sup>3</sup>) and brine (1 x 5 cm<sup>3</sup>), then dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 4) as eluent gave the *title compound* **90** (35 mg, 80%) as a colourless oil (Found: M<sup>+</sup>+H, 287.2011. C<sub>19</sub>H<sub>27</sub>O<sub>2</sub> requires *M*, 287.2006);  $\nu_{\max}$  3066, 3024, 1633, 1453, 1350, 1201, 1118. 1026, 905 and 766 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 1.41-1.98 (14 H, m), 2.75, 3.58 and 3.96 (each 1 H, m), 4.51 (1 H, d, *J* 12, OCHH), 4.75 (1 H, t, *J* 3.5, OCHO), 4.80 (1 H, d, *J* 12, OCHH), 4.92 (1 H, d *J* 1.5, 2'-H), 5.22 (1 H, t, *J* 2, 2'-H), 7.15 (1 H, dd, *J* 2, 7, ArH), 7.34-7.24 (2 H, m, ArH) and 7.54 (1 H, m, ArH);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 19.64, 24.80, 25.79, 30.92, 31.75, 31.80, 47.75, 62.28, 67.12, 98.41, 112.66, 127.01, 127.12, 128.71, 135.59, 143.44 and 151.99; *m/z* (CI) 314 (M<sup>+</sup>+178, 3%), 287 (M<sup>+</sup>+1, 4) and 102 (100).

### **2-(1-Cyclopentylethenyl)phenylmethanol 91**

Toluene *p*-sulfonic acid (14 mg, 0.07 mmol) was added to the tetrahydropyranyl ether **90** (100 mg, 0.35 mmol) in methanol (2 cm<sup>3</sup>) and the solution stirred for 4 h. Water (4 cm<sup>3</sup>) was added and the mixture extracted with ether (3 x 10 cm<sup>3</sup>). The organic extracts were washed with a saturated aqueous sodium



hydrogen carbonate ( $2 \times 10 \text{ cm}^3$ ) then dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum ether (3 : 7) as eluent gave the *title compound 91* (61 mg, 86%) as a colourless oil (Found:  $\text{M}^+$ , 202.1351.  $\text{C}_{14}\text{H}_{18}\text{O}$  requires  $M$ , 202.1352);  $\nu_{\text{max}}$  3368, 3067, 1633, 1480, 1456, 1195, 1031, 901 and  $765 \text{ cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz;  $\text{CDCl}_3$ ) 1.22-1.32, 1.41-1.48, 1.52-1.57 and 1.62-1.68 (each 2 H, m), 2.55 (1 H, m, CH), 4.53 (2 H, s,  $\text{OCH}_2$ ), 4.76 and 5.11 (each 1 H, t,  $J$  1, 2'-H) and 6.97, 7.12, 7.16 and 7.33 (each 1 H, m, ArH);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 24.81, 31.91, 47.87, 63.31, 112.82, 127.33, 127.47, 128.21, 128.89, 138.03, 142.94 and 152.48;  $m/z$  (CI) 220 ( $\text{M}^+ + 18$ , 15%), 202 ( $\text{M}^+$ , 20) and 185 (100).

### **2-(1-Cyclopentylethenyl)benzaldehyde 92**

Dess-Martin periodinane (415 mg, 0.98 mmol) was added to the alcohol **91** (180 mg, 0.89 mmol) in dichloromethane ( $6 \text{ cm}^3$ ) and the mixture stirred at room temperature for 2 h then poured into a rapidly stirred aqueous sodium sulfite ( $25 \text{ cm}^3$ ). After 20 min, the mixture was extracted with dichloromethane ( $3 \times 10 \text{ cm}^3$ ) and the organic extracts dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. Chromatography of the residue using ether : petroleum ether (1 : 4) gave the *title compound 92* (155 mg, 86%) as a colourless oil (Found:  $\text{M}^+ + \text{H}$ , 201.1274.  $\text{C}_{14}\text{H}_{17}\text{O}$  requires  $M$ , 201.1274);  $\nu_{\text{max}}$  3382, 1719, 1705, 1596, 1251, 1195, 906 and  $771 \text{ cm}^{-1}$ ;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 1.44-1.89 (8 H, m), 2.92 (1 H, m), 4.96 and 5.45 (each 1 H, t,  $J$  1, 2'-H), 7.40 (1 H, dd,  $J$  1.5, 8, ArH), 7.45 (1 H, dt,  $J$  1, 7.5, ArH), 7.55 (1 H, dt,  $J$  1.5, 8, ArH), 7.97 (1 H, dd,  $J$  1.5, 8, Ar-H) and 10.26 (1 H, d,  $J$  0.5, CHO);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 24.73, 31.68, 48.17, 115.94, 127.46, 127.59, 129.49, 133.58, 133.97, 148.14, 149.48 and 192.83;  $m/z$  (CI) 218 ( $\text{M}^+ + 18$ , 30%), 201 ( $\text{M}^+ + 1$ , 100) and 183 (95).

### **N-[2-(1-Cyclopentylethenyl)phenylmethyl] prop-2-enyl amine 93**

Magnesium sulfate (1.4 g) and prop-2-enylamine (86 mg, 1.5 mmol) were added to 2-(1-cyclopentylethenyl)benzaldehyde **92** (150 mg, 0.75 mmol) in dichloromethane ( $10 \text{ cm}^3$ ) and the solution stirred for 24 h then filtered and concentrated under reduced pressure. The residue was dissolved in methanol ( $8 \text{ cm}^3$ ) and sodium borohydride (42 mg, 1.125 mmol) was added. The mixture was stirred for 3 h then concentrated under reduced pressure and the residue dissolved in ethyl acetate ( $15 \text{ cm}^3$ ). This solution was washed with aqueous hydrogen chloride (1 M,  $5 \text{ cm}^3$ ) and brine ( $10 \text{ cm}^3$ ), dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Chromatography of the residue using dichloromethane as eluent gave the *title compound 93* (164 mg, 91%) as a colourless oil (Found:  $\text{M}^+ + \text{H}$ , 242.1908.  $\text{C}_{17}\text{H}_{24}\text{N}$  requires  $M$ , 242.1903);  $\nu_{\text{max}}$  1632, 1540, 1439, 1371, 1165, 1126, 913 and  $772 \text{ cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz;  $\text{CDCl}_3$ ) 1.34, 1.48, 1.61 and 1.72 (each 2 H, m), 2.57 (1 H, m), 3.16 (2 H, dt,  $J$  6, 1.5, 1-

H<sub>2</sub>), 4.58 (2 H, s, ArCH<sub>2</sub>), 4.79 (1 H, m, vinylic H), 5.00-5.16 (3 H, m, vinylic H), 5.80 (1 H, m, 2-H), 6.98 (1 H, dd, *J* 1, 7, ArH), 7.11 and 7.16 (each 1 H, dt, *J* 1.5, 7.5, ArH) and 7.31 (1 H, dd, *J* 1, 7.5, ArH);  $\delta_{\text{C}}$  (75 MHz; CDCl<sub>3</sub>) 24.98, 32.03, 47.98, 51.08, 52.32, 112.50, 116.26, 126.73, 127.44, 128.34, 129.02, 129.11, 137.36, 143.80 and 153.22; *m/z* (EI) 242 (M<sup>+</sup>+1, 10%), 200 (15), 169 (28), 131 (60) and 115 (65).

#### ***N*-[2-(1-cyclopentylethenyl)phenylmethyl]-*N*-prop-2-enyl 2-nitrobenzenesulfonamide **94****

4-Dimethylaminopyridine (50 mg), triethylamine (3.71 cm<sup>3</sup>, 2.66 mmol) and 2-nitrobenzenesulfonyl chloride (4.51 g, 20.4 mmol) were added to [2-(1-cyclopentylethenyl)phenylmethyl]prop-2-enylamine **93** (4.27 g, 17.7 mmol) in dichloromethane (215 cm<sup>3</sup>) and the solution was stirred for 20 min at room temperature. The reaction mixture was then washed with water (100 cm<sup>3</sup>) and brine (2 x 100 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using dichloromethane as eluent gave the *title compound* **94** (6.9 g, 92%) as a colourless oil (Found: M<sup>+</sup>+ Na, 449.1510. C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>SNa requires *M*, 449.1505);  $\nu_{\text{max}}$  3082, 1634, 1540, 1371, 1165, 1126, 914 and 774 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz; CDCl<sub>3</sub>) 1.40, 1.60, 1.73 and 1.79 (each 2 H, m), 2.60 (1 H, m), 3.92 (2 H, d, *J* 6, 1-H<sub>2</sub>), 4.62 (2 H, s, ArCH<sub>2</sub>), 4.83 (1 H, s, 2"-H), 5.00-5.06 (2 H, m, 3-H<sub>2</sub>), 5.24 (1 H, t, *J* 1.5, 2"-H), 5.70 (1 H, m, 2-H), 7.07 (1 H, m, ArH), 7.21 (2 H, m, ArH), 7.36 (1 H, dd, *J* 3, 6, ArH), 7.63-7.74 (3 H, m, ArH) and 8.03 (1 H, dd, *J* 1.5, 8, Ar-H);  $\delta_{\text{C}}$  (125 MHz; CDCl<sub>3</sub>) 24.89, 32.04, 47.93, 48.65, 50.00, 113.17, 119.42, 124.54, 124.57, 127.23, 127.49, 129.26, 131.54, 132.07, 132.48, 132.66, 133.81, 134.58, 143.74, 148.27 and 152.14; *m/z* (ES) 465 (100%) and 449 (M<sup>+</sup>+23, 30).

#### **5-Cyclopentyl-2-[3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)aminopropanoyl]-2,3-dihydro-[1*H*]-2-benzazepine **97****

Potassium carbonate (60 mg, 0.44 mmol) and thiophenol (17  $\mu$ L, 0.23 mmol) were added to the *N*-nosyldihydrobenzazepine **95** (48 mg, 0.23 mmol) in *N,N*-dimethylformamide (1 cm<sup>3</sup>) and the solution stirred for 24 h. Water (3 cm<sup>3</sup>) was added, and the mixture extracted with ethyl acetate (3 x 5 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give 5-cyclopentyl-2,3-dihydro-[1*H*]-2-benzazepine **96** as a yellow oil;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 1.37, 1.56, 1.68 and 1.80 (each 2 H, m), 2.94 (3 H, m, 3-H<sub>2</sub> and CH), 3.16 (1 H, br. s, NH), 3.61 (2 H, s, 1-H<sub>2</sub>), 5.89 (1 H, dt, *J* 1.5, 7, 4-H) and 7.15-7.33 (4 H, m, ArH);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 25.14, 32.53, 42.44, 45.37, 49.26, 119.92, 126.34, 127.63, 127.83, 129.43, 138.06, 142, 65 and 149.68.

TBTU (81 mg, 0.25 mmol) and di-isopropylethylamine (80  $\mu$ L, 0.46 mmol) were added to 3-[*N*-(2-nitrobenzyl)sulfonyl-*N*-phenylmethyl]aminopropanoic acid **81** (83 mg, 0.23 mmol) in

dichloromethane (2 cm<sup>3</sup>) at 0 °C and the mixture was stirred for 15 min. 5-Cyclopentyl-2,3-dihydro-[1*H*]-2-benzazepine **96** (48 mg, 0.23 mmol), prepared as outlined above, in dichloromethane (2 cm<sup>3</sup>) was added and the solution stirred at room temperature for 16 h. Dichloromethane (10 cm<sup>3</sup>) was added and the solution washed using saturated aqueous ammonium chloride (3 x 15 cm<sup>3</sup>). The organic layer was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate in light petroleum (3 : 7) gave the *title compound* **97** (117 mg, 91%), a mixture of rotamers, as a colourless oil (Found: M<sup>+</sup>+H, 560.2226. C<sub>31</sub>H<sub>34</sub>N<sub>3</sub>O<sub>5</sub>S requires *M*, 560.2214); ν<sub>max</sub> 1636, 1540, 1438, 1370, 1163 and 733 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz; CDCl<sub>3</sub>) 1.25, 1.49, 1.58 and 1.72 (each 2 H, m), 2.27 (1.2 H, t, *J* 7, 2'-H<sub>2</sub>), 2.39 (0.8 H, t, *J* 7, 2'-H<sub>2</sub>), 2.87 (1 H, m, 1''-H), 3.18 (1.2 H, d, *J* 7.5, 3-H<sub>2</sub>), 3.38-3.54 (2.8 H, m, 3-H<sub>2</sub> and 3'-H<sub>2</sub>), 3.87 (0.8 H, s, PhCH<sub>2</sub>), 4.14 (1.2 H, s, PhCH<sub>2</sub>), 4.43 (1.2 H, s, 1-H<sub>2</sub>), 4.45 (0.8 H, s, 1-H<sub>2</sub>), 5.67 (0.6 H, t, *J* 7.5, 4-H), 5.72 (0.4 H, t, *J* 7.5, 4-H), 7.05-7.30 (9 H, m, ArH), 7.45-7.60 (3 H, m, ArH) and 7.83 (1 H, m, ArH); *m/z* (ES) 582 (M<sup>+</sup>+23, 100%) and 560 (45).

### 2-Bromo-5-fluorophenylmethanol **106**<sup>40</sup>

2-Bromo-5-fluorobenzyl bromide **105**<sup>39</sup> (5.0 g, 18.66 mmol) was added to a suspension of calcium carbonate (7.5 g) in dioxane - water (1:1.5, 150 cm<sup>3</sup>) and the mixture heated at 100 °C for 24 h. The reaction mixture was allowed to cool then was extracted with ether. The organic extracts were dried (NaSO<sub>4</sub>) and concentrated under reduced pressure. Trituration with cold hexane gave the alcohol **106**<sup>40</sup> (3.78 g, 99%) as a colourless solid, m.p. 92-94 °C (lit.<sup>41</sup>: 92-94 °C) (Found: M<sup>+</sup>, 203.9583. C<sub>7</sub>H<sub>6</sub>OBrF requires *M*, 203.9586); ν<sub>max</sub> 3298, 3202, 1579, 1464, 1440, 1410, 1361, 1266, 1219, 1148, 1065, 1025 and 809 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 2.05 (1 H, t, *J* 6, OH) 4.77 (2 H, d, *J* 6, CH<sub>2</sub>), 6.93 (1 H, td, *J* 3, 8.5, 4-H), 7.32 (1 H, dd, *J* 3, 9, 6-H) and 7.53 (1 H, dd, *J* 5, 8.5, 3-H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 64.38, 115.29 and 115.65 (d, <sup>2</sup>*J*<sub>C-F</sub> 27), 115.65, 115.69 and 115.92 (d, <sup>2</sup>*J*<sub>C-F</sub>, 18), 133.49 and 133.59 (d, <sup>3</sup>*J*<sub>C-F</sub> 8), 141.90 and 141.98 (d, <sup>3</sup>*J*<sub>C-F</sub> 7), and 163.58 and 160.86 (d, <sup>1</sup>*J*<sub>C-F</sub> 246); *m/z* (CI) 204 (M<sup>+</sup>+1, 30%), 142 (50), 124 (25), 123 (50), 107 (50) and 96 (100).

### 1-Bromo-4-fluoro-2-[(4-methoxyphenyl)methoxymethyl]benzene **107**

The bromoalcohol **106** (11.0 g, 53.66 mmol) in tetrahydrofuran (50 cm<sup>3</sup>) was added to a suspension of sodium hydride (60% dispersion; 4.3 g) in tetrahydrofuran – *N,N*-dimethylformamide (1:2, 150 cm<sup>3</sup>) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature over 2 h and 4-methoxybenzyl chloride (7.43 cm<sup>3</sup>) was added slowly. After the reaction was complete (tlc), water and ether were added and the mixture extracted into ether. The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 :

9) as eluent gave the *title compound 107* (16.39 g, 94%) as colourless oil (Found:  $M^+$ , 324.0159.  $C_{15}H_{14}O_2BrF$  requires  $M$ , 324.0162);  $\nu_{\max}$  3000, 1612, 1582, 1514, 1467, 1249, 1174, 1150, 1112, 1088, 1033 and 812  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 3.87 (3 H, s,  $CH_3$ ), 4.59 and 4.63 (each 2 H, s,  $CH_2$ ), 6.86-7.00 and 7.28-7.42 (each 3 H, m, ArH) and 7.52 (1 H, dd,  $J$  9, 6, ArH);  $\delta_C$  (75 MHz,  $CDCl_3$ ) 55.22, 70.69, 72.58, 113.83, 115.49 and 115.64 (d,  $^2J_{C-F}$  11), 115.88 and 115.92 (d,  $^4J_{C-F}$  3), 115.79 and 115.96 (d,  $^2J_{C-F}$  13), 129.37, 129.75, 133.36 and 133.46 (d,  $^3J_{C-F}$  7.5), 140.15 and 140.25 (d,  $^3J_{C-F}$  7.5), 159.32, and 160.51 and 163.78 (d,  $^1J_{C-F}$  246);  $m/z$  (CI) 342 ( $M^++18$ , 20%), 324 ( $M^+$ , 40) and 121 (100).

#### **4-Fluoro-2-[(4-methoxyphenyl)methoxymethyl]cyclobutanoylbenzene 109**

A crystal of iodine followed by 1,2-dibromoethane (2 drops) were added to magnesium turnings (312 mg, 13 mmol) in tetrahydrofuran (3  $cm^3$ ) and the mixture stirred under nitrogen for 10 min. Bromobenzene **107** (3.25 g, 10 mmol) in tetrahydrofuran (10  $cm^3$ ) was added and the mixture heated under reflux for 3 h. After cooling to room temperature, *N*-methoxy-*N*-methylcyclobutylcarboxamide **108** (1.861 g, 13 mmol) was added dropwise and the mixture stirred for 12 h. Saturated aqueous ammonium chloride was added and the mixture extracted with ether. The organic extracts were dried ( $NaSO_4$ ) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 9) as eluent afforded the *title compound 109* (1.94 g, 60%) as colourless oil (Found:  $M^++H$ , 329.0552.  $C_{20}H_{22}O_3F$  requires  $M$ , 329.0553);  $\nu_{\max}$  1675, 1609, 1583, 1513, 1248, 1225, 1114, 1081, 1036, 975 and 821  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 1.82-2.48 (6 H, m, 3 x  $CH_2$ ), 3.84 (3 H, s,  $OCH_3$ ), 3.94 (1 H, pent,  $J$  8.5, 1'-H), 4.64 and 4.95 (each 2 H, s,  $OCH_2$ ), 6.94 (2 H, d,  $J$  8.5, ArH), 7.02 (1 H, td,  $J$  8, 2.5, ArH), 7.37 (2 H, d,  $J$  8.5, ArH), 7.58 (1 H, dd,  $J$  10.5, 2.5, ArH) and 7.70 (1 H, dd,  $J$  8.5, 5.5, ArH);  $\delta_C$  (75 MHz,  $CDCl_3$ ) 17.84, 25.11, 43.56, 55.19, 69.82, 72.60, 113.01 and 113.31 (d,  $^2J_{C-F}$  22.5), 113.75, 114.59 and 114.91 (d,  $^2J_{C-F}$  24), 129.25, 129.98 and 129.94 (d,  $^4J_{C-F}$  3), 130.17, 131.49 and 131.62 (d,  $^3J_{C-F}$  10), 144.94 and 145.05 (d,  $^3J_{C-F}$  8), 159.16, 163.15 and 165.51 (d,  $^1J_{C-F}$  252), and 202.33;  $m/z$  (CI) 329 ( $M^++1$ , 15%), 241 (52), 221 (50), 191 (45) and 121 (100).

#### **1-(1-Cyclobutylethenyl)-4-fluoro-2-[(4-methoxyphenyl)methoxymethyl]benzene 110**

$Cp_2TiMe_2$  (25.78 mmol, 5.37 g) in THF (20  $cm^3$ ) was added dropwise to the ketone **109** (3.68 g, 11.21 mmol) in THF (100  $cm^3$ ) at 0 °C under nitrogen and the mixture was heated at 65 °C for 15 h then concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 20) as eluent gave the *title compound 110* (3.40 g, 93%) as pale yellow oil (Found:  $M^++NH_4$ , 344.2033.  $C_{21}H_{27}O_2FN$  requires  $M$ , 344.2026);  $\nu_{\max}$  3078, 3035, 1611, 1586, 1513, 1493, 1301, 1249, 1178, 1151, 1067, 1037, 961, 906, 875 and 823  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 1.60-2.14 (6 H, m, 3 x  $CH_2$ ), 3.18 (1 H,

m, 1''-H), 3.86 (3 H, s, OCH<sub>3</sub>), 4.52 and 4.55 (each 2 H, s, ArCH<sub>2</sub>), 4.92 and 5.20 (each 1 H, s, 2'-H), 6.91-7.01 (3 H, m, ArH), 7.08 (1 H, dd, *J* 8.5, 5.5, ArH), 7.29 (1 H, dd, *J* 9.5, 3, ArH) and 7.35 (2 H, d, *J* 8.5, ArH);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 17.60, 27.89, 42.03, 55.19, 69.05, 72.21, 112.81, 113.51 and 113.77 (d,  $^2J_{C-F}$  19.5), 113.77, 114.58 and 114.88 (d,  $^2J_{C-F}$  22.5), 129.35, 129.66 and 129.76 (d,  $^3J_{C-F}$  7.5), 130.17, 137.06 and 137.10 (d,  $^4J_{C-F}$  3), 137.86 and 137.96 (d,  $^3J_{C-F}$  7.5), 150.99, 159.23, and 160.22 and 163.47 (d,  $^1J_{C-F}$  244); *m/z* (CI) 344 (M<sup>+</sup>+18, 20%), 309 (40), 205 (45), 138 (65) and 121 (100).

### 2-(1-Cyclobutylethenyl)-5-fluorophenylmethanol 111

Dichlorodicyanoquinone (1.81 g, 7.96 mmol) was added to the 4-methoxybenzyl ether **110** (2.16 g, 6.63 mmol) in dichloromethane and water (10:1, 99 cm<sup>3</sup>) and the mixture stirred for 2 h at room temperature. Water (50 cm<sup>3</sup>) was added, the mixture extracted using dichloromethane and the organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 1) as eluent gave the *title compound 111* (1.284 g, 94%) after distillation, b.p. 70 °C at 0.1 mmHg as a colourless oil (Found: M<sup>+</sup>, 206.1107. C<sub>13</sub>H<sub>15</sub>OF requires *M*, 206.1107);  $\nu_{\max}$  3340, 1635, 1606, 1586, 1491, 1266, 1230, 1147, 1031, 905, 874 and 823 cm<sup>-1</sup>;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 1.64-2.16 (7 H, m, 3 x CH<sub>2</sub>, OH), 3.20 (1 H, m, 1''-H), 4.65 (2 H, d, *J* 6, CH<sub>2</sub>O), 4.92 and 5.23 (each 1 H, s, 2'-H), 6.95 (1 H, td, *J* 8, 2.5, ArH), 7.07 (1 H, dd, *J* 8.5, 5.5, ArH) and 7.24 (1 H, dd, *J* 10, 2.5, ArH);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 17.55, 27.87, 42.03, 62.21, 112.98, 113.51 and 113.78 (d,  $^2J_{C-F}$  20), 113.95 and 114.24 (d,  $^2J_{C-F}$  22), 129.80 and 129.90 (d,  $^3J_{C-F}$  7.5), 136.50 and 136.55 (d,  $^4J_{C-F}$  4), 140.07 and 140.16 (d,  $^3J_{C-F}$  7.5), 151.21, and 163.50 and 160.25 (d,  $^1J_{C-F}$  244); *m/z* (EI) 206 (M<sup>+</sup>, 40%), 189 (100), 177 (65), 163 (58), 159 (50), 149 (35), 147 (55), 137 (38) and 133 (40).

### 2-(1-Cyclobutylethenyl)-5-fluorobenzaldehyde 112

Dess-Martin periodinane (9.00 g, 21.23 mmol) was added to the benzyl alcohol **111** (3.43 g, 16.73 mmol) in dichloromethane (50 cm<sup>3</sup>) at room temperature under nitrogen and mixture stirred for 12 h. Water (20 cm<sup>3</sup>) and aqueous sodium hydroxide (1.3 M, 20 cm<sup>3</sup>) were added, and the mixture extracted with dichloromethane (3 x 50 cm<sup>3</sup>), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 19) as eluent gave the *title compound 112* (2.9 g, 85%) as a colourless oil (Found: M<sup>+</sup>, 204.0948. C<sub>13</sub>H<sub>13</sub>OF requires *M*, 204.0950);  $\nu_{\max}$  1692, 1604, 1489 and 1413 cm<sup>-1</sup>;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 1.68-2.18 (6 H, m, 3 x CH<sub>2</sub>), 3.29 (1 H, m, 1''-H), 4.99 (1 H, t, *J* 1, 2'-H), 5.42 (1 H, t, *J* 1.5, 2'-H'), 7.07 (2 H, m, ArH), 7.63 (1 H, ddd, *J* 9, 2, 12, ArH) and 10.14 (1 H, d, *J* 3, CHO);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 17.54, 27.69, 42.28, 113.18 and 113.47 (d,  $^2J_{C-F}$  22),

116.29, 120.35 and 120.64 (d,  $^2J_{C-F}$  22), 130.82 and 130.91 (d,  $^3J_{C-F}$  7), 135.33 and 135.42 (d,  $^3J_{C-F}$  7), 142.27 and 142.31 (d,  $^4J_{C-F}$  3), 148.22, 160.06, and 163.35 (d,  $^1J_{C-F}$  247) and 191.01;  $m/z$  (CI) 222 ( $M^+ + 18$ , 50%), 206 (20), 205 (100), 187 (55) and 176 (68).

### [2-(1-Cyclobutylethenyl)-5-fluorophenyl]methyl(prop-2-enyl)amine **113**

Anhydrous magnesium sulfate (6.1 g, 50.68 mmol) was added to the aldehyde **112** (2.4 g, 11.76 mmol) and prop-2-enylamine (3.6 cm<sup>3</sup>, 47.92 mmol) in dichloromethane (50 cm<sup>3</sup>) at room temperature and the reaction stirred for 24 h, then filtered and concentrated under reduced pressure. Sodium borohydride (670 mg, 17.72 mmol) was added to the residue in methanol (20 cm<sup>3</sup>) and the mixture stirred for 2 h, then concentrated under reduced pressure and diluted with water (30 cm<sup>3</sup>). The mixture was extracted with dichloromethane (5 x 30 cm<sup>3</sup>) and the organic extracts dried (NaSO<sub>4</sub>) and concentrated under reduced pressure to afford the *title compound* **113** (2.88 g, 99%) as a yellow oil (Found:  $M^+$ , 245.1571. C<sub>16</sub>H<sub>20</sub>NF requires  $M$ , 245.1580);  $\nu_{\max}$  3079, 1638, 1606, 1585, 1491, 1447, 1266, 1227, 1149 and 905 cm<sup>-1</sup>;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 1.50-2.04 (6 H, m, 3 x CH<sub>2</sub>), 3.06 (1 H, m, CH), 3.17 (2 H, d,  $J$  5.5, 1'-H<sub>2</sub>) 3.64 (2 H, s, ArCH<sub>2</sub>N-), 4.81 (1 H, t,  $J$  1.5, 2''-H), 5.03 (1 H, dd,  $J$  10, 1.8, 3-H), 5.10, (1 H, t,  $J$  1.5, 2''-H'), 5.12 (1 H, dd,  $J$  17, 2, 3-H'), 5.84 (1 H, m, 2-H), 6.80 (1 H, td,  $J$  8, 2.5, ArH), 6.92 (1 H, dd,  $J$  8.5, 6, ArH) and 7.08 (1 H, dd,  $J$  10, 2.5, ArH);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 17.57, 27.95, 42.15, 50.21, 51.75, 112.59, 112.83 and 113.11 (d,  $^2J_{C-F}$  21), 114.85 and 115.13 (d,  $^2J_{C-F}$  21), 115.81, 129.88 and 129.98 (d,  $^3J_{C-F}$  7.5), 136.73, 137.41 and 137.45 (d,  $^4J_{C-F}$  3), 139.62 and 139.71 (d,  $^3J_{C-F}$  7), 151.79, and 160.18 and 163.42 (d,  $^1J_{C-F}$  243);  $m/z$  (EI) 246 ( $M^+ + 1$ , 30%), 217 (30), 204 (25), 176 (30), 162 (40), 147 (60), 133 (40) and 41 (100).

### *N*-[2-(1-cyclobutylethenyl)-5-fluorophenyl]methyl-*N*-prop-2-enyl 2-nitrophenylsulfonamide **114**

2-Nitrophenylsulfonyl chloride (2.40 g, 10.83 mmol), triethylamine (4 cm<sup>3</sup>) and 4-dimethylaminopyridine (*ca.* 5 mg) were added to the amine **113** (2.19 g, 8.92 mmol) in dichloromethane (80 cm<sup>3</sup>) at room temperature under nitrogen and the mixture stirred for 12 h. Ether (250 cm<sup>3</sup>) and water (250 cm<sup>3</sup>) were added and the aqueous layer extracted with ether (2 x 150 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>) then concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1:1) as eluent gave the *title compound* **114** (3.30 g, 86%) (Found:  $M^+ + NH_4$ , 448.1695. C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>SF requires  $M$ , 448.1706);  $\nu_{\max}$  3083, 1608, 1586, 1545, 1491, 1440, 1369, 1357, 1270, 1164, 1126, 914 and 778 cm<sup>-1</sup>;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 1.60-2.16 (6 H, m, 3 x CH<sub>2</sub>), 3.13 (1 H, m, CH), 3.95 (2 H, d,  $J$  6, 1-H<sub>2</sub>), 4.59 (2 H, s, ArCH<sub>2</sub>N-), 4.88 (1 H, t,  $J$  1.5, 2''-H), 5.06 (1 H, dd,  $J$  17, 1, 3-H),

5.11 (1 H, dd,  $J$  10, 1, 3-H<sup>1</sup>), 5.24 (1 H, t,  $J$  1.5, 2''-H<sup>1</sup>), 5.61 (1 H, m, 2-H), 6.91 (1 H, td,  $J$  8, 2.5, ArH), 6.99-7.14 (2 H, m, ArH), 7.62-7.80 (3 H, m, ArH) and 8.06 (1 H, dd,  $J$  8, 1, ArH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 17.55, 27.95, 41.98, 47.95, 49.87, 113.41 and 113.65 (d,  $^2J_{\text{C-F}}$  18), 113.65 and 113.92 (d,  $^2J_{\text{C-F}}$  20.5), 113.96, 119.31, 124.15, 130.15 and 130.26 (d,  $^3J_{\text{C-F}}$  7.5), 130.98, 131.68, 131.78, 133.60, 133.76, 135.03 and 135.12 (d,  $^3J_{\text{C-F}}$  7), 137.45 and 137.49 (d,  $^4J_{\text{C-F}}$  3), 147.76, 150.75, and 160.33 and 163.59 (d,  $^1J_{\text{C-F}}$  244.5);  $m/z$  (CI) 448 (M<sup>+</sup>+18, 20%), 401 (40), 246 (100), 244 (90) and 189 (90).

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