Development of a Stepwise [3+3] Annulation to Functionalised Piperidines

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General experimental methods have been reported elsewhere¹. Compounds **8**, **11**, **17**, **23** have been described previously.¹

Preparation of the Grignard reagent

To BuLi (4 mL, 2.2M, 3 eq.) at 0°C were added dry ether (4 mL), TMEDA (1.2 mL, 2.6 eq) and methallyl alcohol (dropwise, 0.25 mL, 1 eq.). The resulting yellow mixture was stirred at 0°C for 1 h, then warmed to room temperature and stirred for a further hour. To this was added magnesium bromide (1.4 g, 2.6 eq.) at 0°C and the suspension warmed to room temperature and stirred for 1h. After this time, the Grignard reagent was titrated according to the method shown below, and 0.2 eq. aziridine in THF added to the remainder.

Titration of the Grignard reagent²

To menthol (31 mg, 0.2 mmol) in dry THF (1.5 mL) was added 1,10-phenanthroline (4 mg). The Grignard reagent to be assayed was added dropwise by syringe until a distinct violet or burgundy colour persisted for longer than one minute.

Concentration = (mol. menthol x 1000)/vol. Grignard added

General procedure for the Grignard addition reaction

After adding aziridine to the Grignard reagent, the colourless suspension was stirred at room temperature until TLC indicated that the reaction had gone to completion (c.a. 2 h). The remaining organometallic reagent was quenched by the slow addition of 1M HCl, and product extracted into ethyl acetate, washed with brine and the solvent removed *in vacuo*. The ring opened material was isolated by column chromatography (solvent 2:1 petroleum ether: ethyl acetate).

¹ Hedley, S.J.; Moran, W.J.; Price, D.A.; Harrierty, J.P.A. *J. Org. Chem.* **2003**, 68, 4286.

² Lin H.S., Paquette L.A., *Synth. Commun.*, **1994**, 24, 2503

Synthesis of *N*-(1-benzyl-4-hydroxymethyl-pent-4-enyl)-4-methyl-benzenesulfonamide (7**)**

According to the general procedure, 2-benzyl-1-(toluene-4-sulfonyl)-aziridine **6** (0.102 g, 0.36 mmol) yielded 0.112 g of *N*-(1-benzyl-4-hydroxymethyl-pent-4-enyl)-4-methyl-benzenesulfonamide **7** (87%). $[\alpha]_D = -18$ ($c = 1.12$ CH₂Cl₂). ¹H NMR (250 MHz in CDCl₃): δ 1.42 – 1.73 (2H, m), 1.89 – 2.17 (2H, m), 2.40 (3H, s), 2.63 (2H, d, $J = 6.5$ Hz), 3.35 – 3.51 (1H, m), 3.94 (2H, s), 4.69 (1H, s), 4.89 (1H, d, $J = 8.0$ Hz), 4.96 (1H, s), 6.93 – 7.01 (2H, m), 7.14 – 7.28 (5H, m), 7.64 (2H, d, $J = 8.5$ Hz); ¹³C NMR (62.9 MHz in CDCl₃): δ 21.5, 28.5, 32.2, 41.3, 54.9, 65.6, 109.8, 126.5, 127.0, 128.5, 129.4, 129.6, 137.4, 137.9, 143.1, 148.0; FTIR (film): 3490 (b), 3284 (b), 2926 (m), 1654 (w), 1599 (w), 1496 (w), 1454 (m), 1323 (s), 1304 (s) cm⁻¹; HRMS (ES) Calcd for C₂₀H₂₅NO₃S: 360.1633. Found: 360.1647.

Synthesis of 2-benzyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine (8**)¹**

A flame dried flask was charged with 4Å molecular sieves (20 mg), palladium acetate (4 mg, 0.017 mmol, 10 mol%), triphenylphosphine (17 mg, 0.066 mmol, 40 mol%) and toluene (0.5 mL). To this were added allylic alcohol **7** (59 mg, 0.165 mmol, 1 eq) in toluene (1 mL) and titanium isopropoxide (12 μ L, 0.041 mmol, 25 mol%). The flask was fitted with a condenser and put in a oil bath preheated to 110°C for 2 h. After cooling, 1M HCl was added and the reaction mixture was extracted into ethyl acetate. The aqueous layer was then basified by the addition of 1M NaOH and extracted into ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and the solvent removed *in vacuo*. The residue was purified by flash chromatography using 10:1 hexanes: ethyl acetate to yield 2-benzyl-5-

methylene-1-(toluene-4-sulfonyl)-piperidine **8** as a colourless solid (56 mg, 100%) Mp 88 - 89 °C (Lit. mp 85 – 86 °C); ¹H NMR (250 MHz in CDCl₃): δ 1.25 – 1.54 (2H, m), 1.98 (1H, dt, *J* = 14.5, 4.0 Hz), 2.27 (1H, m), 2.38 (3H, s), 2.94 (2H, d, *J* = 7.6 Hz), 3.74 (1H, d, *J* = 15.0 Hz), 4.10 – 4.21 (1H, m), 4.25 (1H, d, *J* = 15.0 Hz), 4.71 (1H, s), 4.81 (1H, s), 7.15 – 7.33 (7H, m), 7.63 (2H, d, *J* = 8.0 Hz); ¹³C NMR (62.9 MHz in CDCl₃): δ 21.5, 26.4, 27.1, 36.9, 46.8, 54.3, 110.6, 126.5, 127.3, 128.6, 129.2, 129.5, 137.7, 138.2, 141.0, 143.0.

Synthesis of *N*-(1-methyl-4-hydroxymethyl-pent-4-enyl)-4-methyl-benzenesulfonamide (**10**)

Following representative procedure, 117 mg 2-methyl-1-(toluene-4-sulfonyl) aziridine **9** (0.55 mmol, 0.2 eq) yielded *N*-(1-methyl-4-hydroxymethyl-pent-4-enyl)-4-methyl-benzenesulfonamide **10** as a colourless oil (146 mg, 93%). [α]_D = -20 (*c* = 0.86, CH₂Cl₂). ¹H NMR (250 MHz in CDCl₃): δ 0.93 (3H, d, *J* = 6.5 Hz), 1.48 (2H, dd, *J* = 14.5, 7.5 Hz), 1.96 (2H, dd, *J* = 15.5, 7.5 Hz), 2.35 (3H, s), 3.17 – 3.34 (1H, m), 3.93 (2H, s), 4.70 (1H, br), 4.84 (1H, d, *J* = 8.0 Hz), 4.92 (1H, br), 7.23 (2H, d, *J* = 8.5 Hz), 7.69 (2H, d, *J* = 8.5 Hz); ¹³C NMR (62.9 MHz in CDCl₃): δ 21.5, 29.8, 35.4, 49.7, 65.8, 109.9, 127.0, 129.7, 138.2, 143.3, 148.0; FTIR (film): 3278 (br), 2929 (m), 1654 (w), 1598 (w), 1495 (w), 1432 (m), 1321 (m), 1159 (s), 1092 (m), 1021 (m) cm⁻¹; HRMS (ES) Calcd for C₁₄H₂₁NO₃Na S 306.1140. Found: 306.1125.

Synthesis of 2-methyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine¹

Following representative procedure, 76 mg *N*-(1-methyl-4-hydroxymethyl-pent-4-enyl)-4-methyl-benzenesulfonamide **10** (0.27 mmol) 6 mg Pd(OAc)₂, 28 mg PPh₃ and

20 μL $\text{Ti}(\text{O}^i\text{Pr})_4$ yielded 2-methyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine **11** as a colourless solid (48 mg, 67%). Mp $75 - 77^\circ\text{C}$ (Lit. mp $68 - 69^\circ\text{C}$) ^1H NMR (250 MHz in CDCl_3): δ 1.12 (3H, d, $J = 7.0$ Hz), 1.31 – 1.55 (2H, m), 1.95 (1H, dt, $J = 14.5, 4.0$ Hz), 2.12 – 2.29 (1H, m), 2.33 (3H, s), 3.61 (1H, d, $J = 14.5$ Hz), 4.04 – 4.15 (2H, m), 4.63 (1H, br), 4.72 (1H, br), 7.18 (2H, d, $J = 8.5$ Hz), 7.62 (2H, d, $J = 8.5$ Hz); ^{13}C NMR (62.9 MHz in CDCl_3): δ 16.2, 21.5, 27.0, 30.5, 46.2, 48.4, 110.4, 127.2, 129.5, 137.8, 141.3, 142.9.

Synthesis of 2-methyl-1-(2-trimethylsilanyl-ethansulfonyl) aziridine (**12**)

To a solution of 2-amino-propan-1-ol (0.2 g, 2.7 mmol, 1 eq.) in DMF (1mL) at 0°C was added triethylamine (2.2 mL, 15.98 mmol, 6 eq.). 2-trimethylsilanylethanesulfonyl chloride (1.08 g, 5.9 mmol, 2.2 eq.) in DMF (1 mL) was then added via cannula. The resulting solution was stirred at 0°C for 1h then warmed to room temperature overnight. It was then partitioned between water and ethyl acetate, dried over magnesium sulphate and the solvent removed *in vacuo*. This was purified by column chromatography (15:1 petroleum ether: ethyl acetate elution solvent) to yield a mixture of 2-trimethylsilanyl-ethanesulfonic acid 2-(2-trimethylsilanyl-ethanesulfonylamino)-propyl ester (291 mg, 27 %) and 2-methyl-1-(2-trimethylsilanyl-ethansulfonyl) aziridine **12** (272 mg, 46 %).

Data for 2-trimethylsilanyl-ethanesulfonic acid 2-(2-trimethylsilanyl-ethanesulfonylamino)-propyl ester: $[\alpha]_D = -11$ ($c = 1.0$, CH_2Cl_2). ^1H NMR (250 MHz, CDCl_3): δ 0.02 (9H, s), 0.00 (9H, s), 0.90 – 1.08 (4H, m), 1.26 (3H, d, $J = 6.5$ Hz), 2.85 – 2.96 (2H, m), 2.97 – 3.07 (2H, m), 3.67 – 3.80 (1H, m), 4.02 – 4.19 (2H, m), 4.55 (1H, d, $J = 8.5$ Hz); ^{13}C NMR (62.9 MHz in CDCl_3) δ 2.1, -2.0, 10.3, 10.6, 18.7, 47.2, 49.1, 50.4, 72.3; FTIR (film): 2954 (m), 1423 (m), 1354 (s), 1323 (s), 1251 (s), 1178 (s), 1141 (s), 1014 (m), 976 (m) cm^{-1} ; HRMS (ES) Calcd for $\text{C}_{13}\text{H}_{34}\text{NO}_5\text{Si}_2\text{S}_2$ 404.1417. Found: 404.11434.

Data for **12**: M.p. 33-35 °C. $[\alpha]_D^{25} = 29$ (c 0.89, CH_2Cl_2). ^1H NMR (250 MHz, CDCl_3): δ 0.07 (9H, s), 1.08-1.17 (2H, m), 1.33 (3H, d), 2.05 (1H, d, $J=5.0$ Hz), 2.60 (1H, d, $J=7.0$ Hz), 2.72-2.85 (1H, m), 3.01-3.12 (2H, m); ^{13}C NMR (62.9 MHz, CDCl_3): δ -2.0, 9.7, 17.0, 34.1, 34.9, 48.9; FTIR (CH_2Cl_2): 2958 (w), 1400 (w), 1322 (s), 1251 (m), 1141 (m), 854 (s) cm^{-1} ; m/z (CI): 222 (MH^+ , 100%), 206 (15%), 101 (10%), 73 (57%), 56 (66%); Anal. Calcd. For $\text{C}_8\text{H}_{19}\text{NO}_2\text{SSi}$: C, 43.40; H, 8.65; N, 6.38. Found: C, 43.17; H, 8.66; N, 6.38.

2-Trimethylsilylanyl-ethanesulfonic acid 2-(2-trimethylsilylanyl-ethanesulfonylamino)-propyl ester (209 mg) could then be transformed to **12** by treatment with sodium hydride (60% in mineral oil; 31 mg, 0.78 mmol, 1.5 eq.) in THF (5 mL) at room temperature for 1 h. Water was added, and this was extracted into ethyl acetate, dried over magnesium sulphate and the solvent removed *in vacuo*. The residue was columned using 10:1 petroleum ether: ethyl acetate to yield **12** as a colourless oil (109 mg, 95%).

Synthesis of 2-trimethylsilylanyl-ethanesulfonic acid (1-methyl-4-hydroxymethyl-pent-4-enyl)-amide (**13**)

Following the representative procedure, 130 mg 2-methyl-1-(2-trimethylsilylanyl-ethanesulfonyl)-aziridine **12** yielded 2-trimethylsilylanyl-ethanesulfonic acid (1-methyl-4-hydroxymethyl-pent-4-enyl)-amide **13** as a colourless oil (105 mg, 81 %). $[\alpha]_D = -8$ (c = 1.0, CH_2Cl_2). ^1H NMR (250 MHz in CDCl_3): δ 0.0 (9H, s), 0.91 – 1.03 (2H, m), 1.19 (3H, d, J = 6.5 Hz), 1.56 – 1.73 (2H, m), 2.08 – 2.19 (2H, m), 2.82 – 2.92 (2H, m), 3.37 – 3.51 (1H, m), 4.04 (2H, s), 4.12 (1H, d, J = 9.0 Hz), 4.84 (1H, br), 5.01 (1H, br); ^{13}C NMR (62.9 MHz in CDCl_3): δ -2.0, 10.7, 22.4, 29.0, 35.8, 49.9, 49.9, 65.8, 110.1, 148.0; FTIR (film): 3462 (br), 3281 (br), 2954 (s), 1654 (w), 1432 (m), 1380 (w), 1313 (s), 1283 (w), 1264 (m), 1251 (s), 1167 (m), 1132 (s), 1089 (m), 1030 (m) cm^{-1} ; HRMS (ES) Calcd for $\text{C}_{12}\text{H}_{27}\text{NO}_3\text{NaSSi}$ 316.1379. Found: 316.1385.

Synthesis of 2-methyl-5-methylene-1-(2-trimethylsilyanyl-ethansulfonyl)-piperidine (14)

Following the representative procedure above, 115 mg of 2-trimethylsilyanyl-ethanesulfonic acid (1-methyl-4-hydroxymethyl-pent-4-enyl)-amide **13**, 9 mg $\text{Pd}(\text{OAc})_2$, 41 mg PPh_3 and 29 μl $\text{Ti}(\text{O}^i\text{Pr})_4$ yielded 2-methyl-5-methylene-1-(2-trimethylsilyanyl-ethansulfonyl)-piperidine **14** as a colourless solid (67 mg, 62%). Mp 53 – 55 °C. $[\alpha]_D = -10$ ($c = 0.98$, CH_2Cl_2). ^1H NMR (250 MHz in CDCl_3): δ 0.00 (9H, s), 0.85 – 1.10 (2H, m), 1.32 (3H, d, $J = 7.0$ Hz), 1.56 – 1.69 (1H, m), 1.69 – 1.86 (1H, m), 2.23 (1H, dt, $J = 14.0, 4.0$ Hz), 2.29 – 2.46 (1H, m), 2.81 (2H, dd, $J = 9.5, 8.5$ Hz), 3.72 (1H, d, $J = 15.0$ Hz), 3.97 (1H, d, $J = 15.0$ Hz), 4.06 – 4.19 (1H, m), 4.79 (1H, br), 4.81 (1H, br); ^{13}C NMR (62.9 MHz in CDCl_3): δ -2.0, 10.4, 17.0, 27.3, 31.5, 46.3, 48.3, 48.9, 110.2, 142.3. FTIR (film): 2951 (s), 1654 (w), 1461 (w), 1437 (w), 1419 (w), 1382 (w), 1336 (s), 1264 (m), 1250 (m), 1166 (m), 1140 (s), 1112 (w), 1047 (w), 1016 (m) cm^{-1} ; HRMS (ES) Calcd for $\text{C}_{12}\text{H}_{25}\text{NO}_2\text{NaSSi}$ 298.1273. Found: 298.1281.

Synthesis of *N*-(4-hydroxymethyl-1-phenyl-pent-4-enyl)-4-methyl-benzenesulfonamide and *N*-(4-hydroxymethyl-2-phenyl-pent-4-enyl)-4-methyl-benzenesulfonamide (16)

Following the representative procedure, 92 mg 2-phenyl-1-(toluene-4-sulfonyl) aziridine yielded a 8:1 mixture of regioisomers (in favour of *N*-(4-hydroxymethyl-2-phenyl-pent-4-enyl)-4-methyl-benzenesulfonamide **16**) as a colourless solid (95 mg, 81 %). Data for **16** (major regioisomer): Mp 98 – 100 °C. ^1H NMR (250 MHz in CDCl_3): δ 2.16 – 2.45 (2H, m), 2.35 (3H, s), 2.78 -3.00 (2H, m), 3.11 – 3.28 (1H, m),

2.85 (2H, s), 4.37 (1H, br), 4.68 (1H, s), 4.93 (1H, s), 6.93 – 7.03 (2H, m), 7.12 – 7.28 (5H, m), 7.57 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (62.9 MHz in CDCl_3): δ 21.5, 37.0, 43.8, 48.1, 65.7, 112.6, 127.1, 127.2, 127.7, 128.9, 129.7, 136.8, 141.2, 143.4, 145.7; FTIR (film): 3282 (br), 2924 (m), 1652 (w), 1598 (w), 1495 (w), 1453 (m), 1324 (s), 1158 (s), 1094 (m) cm^{-1} ; HRMS (ES) Calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_3\text{S}$ 346.1477. Found: 346.1488.

Synthesis of 3-methylene-5-phenyl-1-(toluene-4-sulfonyl)-piperidine (17) and 5-methylene-2-phenyl-1-(toluene-4-sulfonyl)-piperidine¹

Following the representative procedure above, 95 mg of an 8:1 mixture of *N*-(4-hydroxymethyl-2-phenyl-pent-4-enyl)-4-methyl-benzenesulfonamide **16** and *N*-(4-hydroxymethyl-1-phenyl-pent-4-enyl)-4-methyl-benzenesulfonamide, 6 mg $\text{Pd}(\text{OAc})_2$, 29 mg PPh_3 and 20 μL $\text{Ti}(\text{O}^i\text{Pr})_4$ yielded a 8:1 mixture of 3-methylene-5-phenyl-1-(toluene-4-sulfonyl)-piperidine **17** and 5-methylene-2-phenyl-1-(toluene-4-sulfonyl)-piperidine as a colourless solid (68 mg, 76 %). Mp 131 – 133 $^\circ\text{C}$ (mixture). Major regioisomer: ^1H NMR (250 MHz in CDCl_3): δ 1.45 – 1.69 (1H, m) 2.04 – 2.19 (1H, m), 2.36 (3H, s), 2.40 – 2.51 (1H, m), 2.83 (1H, tt, $J = 12.0, 3.5$ Hz), 2.90 (1H, d, $J = 13.0$ Hz), 3.77 – 3.88 (1H, m), 4.16 (1H, d, $J = 12.0$ Hz), 4.83 (1H, br), 4.93 (1H, br), 7.05 – 7.14 (2H, m), 7.16 – 7.30 (5H, m), 7.58 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (62.9 MHz in CDCl_3): δ 21.6, 39.0, 42.6, 52.0, 52.2, 112.6, 127.1, 127.2, 127.8, 128.7, 129.7, 133.2, 139.9, 141.7, 143.6.

Synthesis of *N*-[2-(2-hydroxymethyl-allyl)-cyclohexyl]-4-methyl-benzenesulfonamide (22)

Following representative procedure, 100 mg 7-(toluene-4-sulfonyl)-7-aza-bicyclo[4.1.0]heptane **21** (0.4 mmol, 0.2 eq) yielded *N*-[2-(2-hydroxymethyl-allyl)-

cyclohexyl]-4-methyl-benzenesulfonamide **22** as a colourless solid (102 mg, 79%). Mp 126 – 128 °C; ^1H NMR (250 MHz in CDCl_3): δ 0.67 – 1.37 (6H, m), 1.40 – 1.55 (2H, m), 1.56 – 1.66 (1H, m), 1.68 – 1.82 (1H, m), 2.35 (3H, s), 2.44 – 2.58 (1H, m), 2.68 – 2.86 (1H, m), 3.95 (2H, s), 4.71 (1H, s), 4.94 (1H, s), 5.18 (1H, d, $J = 8.5$ Hz), 7.22 (2H, d, $J = 8.0$ Hz), 7.69 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (62.9 MHz in CDCl_3): δ 21.5, 24.9, 25.1, 31.2, 34.4, 36.5, 41.1, 57.8, 65.7, 111.3, 126.9, 129.6, 138.6, 143.2, 146.9; FTIR (film): 3278 (br), 2930 (s), 2857 (m), 1654 (w), 1599 (w), 1495 (w), 1448 (m), 1321 (s), 1158 (s), 1093 (m), 1045 (m) cm^{-1} ; HRMS (ES) Calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_3\text{S}$ 324.1633. Found: 324.1620.

Synthesis of 3-methylene-1-(toluene-4-sulfonyl)-decahydro-quinoline (**23**)¹

Following the representative procedure above, 50 mg *N*-[2-(2-hydroxymethyl-allyl)-cyclohexyl]-4-methyl-benzenesulfonamide **22**, 3.5 mg $\text{Pd}(\text{OAc})_2$, 16 mg PPh_3 and 11 μL $\text{Ti}(\text{O}^i\text{Pr})_4$ yielded 3-methylene-1-(toluene-4-sulfonyl)-decahydro-quinoline **23** as a colourless solid (41 mg, 87%). Mp 91 – 93 °C (Lit. mp 92 – 93 °Cⁱ). ^1H NMR (250 MHz in CDCl_3): δ 0.77 (1H, m), 1.08 – 1.51 (8H, m), 2.04 (1H, dd, $J = 15.5, 3.0$ Hz), 2.22 (1H, dd, $J = 12.5, 3.0$ Hz), 2.34 (3H, s), 2.73 (1H, dt, $J = 11.0, 3.5$ Hz), 3.89 (1H, d, $J = 16.0$ Hz), 4.04 (1H, dq, $J = 16.0, 1.5$ Hz), 4.55 (1H, s), 4.71 (1H, s), 7.17 (2H, d, $J = 8.0$ Hz), 7.62 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (62.9 MHz in CDCl_3): δ 21.5, 25.6, 25.7, 33.0, 33.4, 36.4, 39.5, 49.1, 62.9, 109.8, 127.6, 129.3, 136.7, 142.3, 143.0.

Synthesis of *N*-[2-(2-Hydroxymethyl-allyl)-cycloheptyl]-4-methyl-benzenesulfonamide (**25**)

Following the representative procedure, 79 mg of 8-(toluene-4-sulfonyl)-8-azabicyclo[5.1.0]octane **24** yielded *N*-[2-(2-hydroxymethyl-allyl)-cycloheptyl]-4-methyl-

benzenesulfonamide **25** as a colourless solid (76 mg, 76%). Mp 78 – 80 °C. ^1H NMR (250 MHz in CDCl_3): δ 1.05 – 1.70 (11H, m), 2.16 (2H, d, J = 13.0 Hz), 2.35 (3H, s), 2.88 - 3.05 (1H, m), 3.94 (2H, s), 4.68 (1H, s), 4.93 (1H, s), 5.18 (1H, d, J = 7.5 Hz), 7.22 (2H, d, J = 8.5 Hz), 7.69 (2H, d, J = 8.5 Hz); ^{13}C NMR (62.9 MHz in CDCl_3): δ 21.5, 23.2, 26.3, 28.7, 29.3, 33.4, 37.7, 43.4, 59.7, 65.6, 111.6, 127.1, 129.6, 138.1, 143.2, 147.1; FTIR (film): 3283 (br), 2927 (s), 2858 (m), 1654 (w), 1599 (w), 1495 (w), 1446 (m), 1323 (s), 1158 (s), 1094 (m), 1056 (m) cm^{-1} ; HRMS (ES) Calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_3\text{S}$ 338.1790. Found: 338.1778.

Synthesis of 3-methylene-1-(toluene-4-sulfonyl)-decahydro-cyclohepta[*b*]pyridine (**26**)

Following the representative procedure above, 47 mg *N*-[2-(2-hydroxymethyl-allyl)-cycloheptyl]4-methyl-benzenesulfonamide **25**, 3 mg $\text{Pd}(\text{OAc})_2$, 15 mg PPh_3 and 10 μL $\text{Ti}(\text{O}^i\text{Pr})_4$ yielded 3-methylene-1-(toluene-4-sulfonyl)-decahydro-quinoline **26** as a colourless solid (34 mg, 77%). Mp 73 – 75 °C. ^1H NMR (250 MHz in CDCl_3): δ 0.89 – 1.11 (2H, m), 1.35 - 1.77 (9H, m), 1.85 (1H, dd, J = 15.5, 3.0 Hz), 2.00 – 2.17 (1H, m), 2.40 (3H, s), 3.49 (1H, td, J = 9.5, 4.5 Hz), 3.75 (1H, dq, J = 17.5, 2.5 Hz), 4.31 (1H, d, J = 17.5 Hz), 4.60 (1H, s), 4.72 (1H, s), 7.23 (2H, d, J = 8.5 Hz), 7.67 (2H, d, J = 8.5 Hz); ^{13}C NMR (62.9 MHz in CDCl_3): δ 21.5, 25.2, 25.6, 27.8, 34.7, 35.1, 36.4, 38.3, 44.8, 60.3, 107.6, 127.1, 129.4, 131.8, 142.8, 143.3; FTIR (film): 2926 (s), 2856 (m), 1597 (w), 1494 (w), 1448 (m), 1341 (s), 1305 (m), 1287 (m), 1154 (s), 1092 (m), 1059 (m) cm^{-1} ; HRMS (ES) Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2\text{S}$ 320.1684. Found: 320.1681.

Synthesis of 6-*tert*-butyl-1-(toluene-4-sulfonyl)-1-aza-spiro[2.5]octane (**27**)

To a solution of 4-*tert*-butyl-1-methylenecyclohexane³ (1 g, 6.6 mmol, 1 eq.) in dry acetonitrile (120 mL) were added chloramine-T (1.5 g, 6.6 mmol, 1 eq.) and N-bromosuccinimide (0.23 g, 1.3 mmol, 0.2 eq.) and the resulting suspension stirred overnight at room temperature. The reaction was quenched with water, extracted into ethyl acetate and the organic extracts washed with brine and dried over magnesium sulphate. The solution was concentrated *in vacuo* and the residue purified by column chromatography (10:1 petroleum ether : ethyl acetate) and recrystallised to yield 6-*tert*-butyl-1-(toluene-4-sulfonyl)-1-aza-spiro[2.5]octane **27** as a colourless crystalline solid, (0.73 g, 34%)⁴. Mp 150-151 °C. ¹H NMR (250 MHz, CDCl₃): δ0.85 (9H, s), 1.03 – 1.23 (3H, m), 1.67 – 1.80 (2H, m), 1.82 – 2.09 (4H, m), 2.38 – 2.47 (2H, m), 2.42 (3H, s), 7.30 (2H, d, *J*=8.0 Hz), 7.92 (2H, d, *J*=8.0 Hz); ¹³C NMR (62.9 MHz, CDCl₃): δ21.6, 26.7, 27.6, 32.3, 33.1, 41.2, 47.0, 53.6, 127.3, 129.5, 138.0, 143.7; FTIR (CH₂Cl₂): 2950 (m), 2856 (w), 1598 (w), 1549 (w), 1319 (m), 1156 (S), 1094 (m) cm⁻¹. *m/z* (EI): 321 (M⁺, 2%), 166 (100%), 91 (18 %). Anal. calcd. for C₁₈H₂₇NO₂S: C, 67.25; H, 8.47; N, 4.36. Found: C, 67.26; H, 8.68; N, 4.29.

Synthesis of *N*-[4-*tert*-butyl-1-(3-hydroxymethyl-but-3-enyl)-cyclohexyl]-4-methyl-benzenesulfonamide (**28**)

Following the representative procedure 106 mg of 6-*tert*-butyl-1-(toluene-4-sulfonyl)-1-aza-spiro[2.5]octane **27** yielded *N*-[4-*tert*-butyl-1-(3-hydroxymethyl-but-3-enyl)-

³ Olah, G.A., Reddy, V.P., Prakash, G.K.S. *Synthesis*, **1991**, 29

⁴ The relative stereochemistry in **27** was established by X-ray crystallography: S.J. Hedley, Ph.D. thesis, University of Sheffield, 2003

cyclohexyl]-4-methyl-benzenesulfonamide **28** as a colourless solid (97 mg, 75%). Mp 73 – 75 °C. ^1H NMR (250 MHz in CDCl_3): δ 0.77 (9H, s), 0.83 – 1.12 (4H, m), 1.29 – 1.45 (2H, m), 1.47 – 1.60 (2H, m), 1.74 – 1.87 (3H, m), 2.01 – 2.12 (2H, m), 2.40 (3H, s), 4.08 (2H, s), 4.82 (1H, s), 4.89 (1H, s), 4.99 (1H, s), 7.26 (2H, d, $J = 8.0$ Hz), 7.76 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (62.9 MHz in CDCl_3): δ 21.5, 23.0, 26.1, 27.4, 31.7, 32.2, 36.3, 47.0, 59.8, 65.8, 110.0, 126.9, 129.5, 140.9, 142.8, 148.8; FTIR (film): 3278 (br), 2950 (s), 2869 (s), 1650 (w), 1599 (w), 1453 (m), 1367 (m), 1330 (m), 1240 (w), 1156 (s), 1095 (m), 1047 (m) cm^{-1} ; HRMS (ES) Calcd for $\text{C}_{22}\text{H}_{36}\text{NO}_3\text{S}$: 394.2416. Found: 394.2427.

Synthesis of 9-*tert*-butyl-3-methylene-1-(toluene-4-sulfonyl)-1-aza-spiro[5.5]undecane (29)

Following the representative procedure above, 100 mg *N*-[4-*tert*-butyl-1-(3-hydroxymethyl-but-3-enyl)-cyclohexyl]-4-methyl-benzenesulfonamide **28**, 6 mg $\text{Pd}(\text{OAc})_2$, 27 mg PPh_3 and 19 μL $\text{Ti}(\text{O}^i\text{Pr})_4$ yielded 3-methylene-1-(toluene-4-sulfonyl)-decahydro-quinoline **29** as a colourless solid (60 mg, 63 %). Mp 113 – 115 °C. ^1H NMR (250 MHz in CDCl_3): δ 0.73 (9H, s), 0.89 – 1.05 (3H, m), 1.47 – 1.64 (4H, m), 1.76 – 1.87 (2H, m), 1.93 – 2.08 (2H, m), 2.12 – 2.22 (2H, m), 2.32 (3H, s), 4.14 (2H, s), 4.74 (1H, br), 4.82 (1H, br), 7.16 (2H, d, $J = 8.0$ Hz), 7.61 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (62.9 MHz in CDCl_3): δ 21.5, 23.5, 27.3, 27.5, 31.0, 32.3, 33.5, 46.8, 48.3, 61.9, 109.7, 126.7, 129.3, 141.5, 142.3, 142.9; FTIR (film): 2945 (s), 2868 (m), 1657 (w), 1598 (w), 1460 (m), 1367 (m), 1324 (m), 1156 (s), 1093 (m), 1050 (w), 1016 (w) cm^{-1} ; HRMS (ES) Calcd for $\text{C}_{22}\text{H}_{34}\text{NO}_2\text{S}$: 376.2310. Found: 376.2325.

Synthesis of *N*-[1-benzyl-4-(1-hydroxy-ethyl)-pent-4-enyl]4-methyl-benzenesulfonamide (32**)**

To BuLi (4.0 mL, 2.2M, 8.81 mmol, 3 eq.) at 0°C were added dry Et₂O (4 mL), TMEDA (1.15 mL, 7.64 mmol, 2.6 eq) and alcohol **31** in 1 mL ether (dropwise, 0.25 g, 2.3 mmol, 1 eq.). The resulting yellow mixture was stirred at 0°C for 1 h, then warmed to room temperature and stirred for a further hour. To this was added magnesium bromide (1.4 g, 7.64 mmol, 2.6 eq.) at 0°C and the suspension warmed to room temperature and stirred for 1h. 2-benzyl-1-(toluene-4-sulfonyl)-aziridine **6** (169 mg, 0.59 mmol, 0.2 eq) in THF (1 mL) was added to the remaining solution and the reaction mixture stirred at room temperature for 2 h. The remaining organometallic was quenched by the slow addition of 1M HCl, and product extracted into ethyl acetate, washed with brine and solvent removed *in vacuo*. The ring-opened material was isolated by column chromatography (solvent 2:1 petroleum ether: ethyl acetate) to yield *N*-[1-benzyl-4-(1-hydroxy-ethyl)-pent-4-enyl]4-methyl-benzenesulfonamide **32** as a yellow oil (198 mg, 90 %). ¹H NMR (250 MHz in CDCl₃): δ1.18 (3H, d, *J* = 6.5 Hz), 1.41 – 1.74 (2H, m), 1.79 – 2.16 (2H, m), 2.39 (3H, s), 2.61 – 2.69 (2H, m), 3.36 – 3.54 (1H, m), 4.06 – 4.19 (1H, m), 4.60 (1H, d, *J* = 7.0 Hz), 4.90 (0.5H, d, *J* = 8.0 Hz), 4.91 (0.5H, d, *J* = 8.0 Hz), 4.96 (1H, s), 6.93 – 7.04 (2H, m), 7.14 – 7.30 (5H, m), 7.66 (2H, m); ¹³C NMR (62.9 MHz in CDCl₃): δ21.5, 22.1, 26.8, 27.3, 32.4, 32.6, 41.4, 41.4, 70.8, 71.0, 108.8, 108.8, 126.6, 127.0, 128.5, 129.4, 129.7, 137.2, 137.8, 137.8, 143.2, 152.0, 152.1; FTIR (film): 3490 (br), 3284 (br), 2973 (m), 2927 (m), 1648 (w), 1599 (w), 1496 (m), 1454 (m), 1323 (s), 1304 (m), 1289 (m), 1157 (s), 1089 (s), 1031 (w) cm⁻¹; HRMS (ES) Calcd for C₂₁H₂₈NO₃S: 374.1780. Found: 374.1782.

Synthesis of 6-benzyl-2-methyl-3-methylene-1-(toluene-4-sulfonyl)-piperidine (33)

To a solution of *N*-[1-benzyl-4-(1-hydroxy-ethyl)-pent-4-enyl]4-methylbenzenesulfonamide **32** (198 mg, 0.53 mmol, 1 eq.) in THF (6 mL) were added diisopropylazodicarboxylate (133 μ L, 0.68 mmol, 1.2 eq.) and triphenylphosphine (193 mg, 0.13 mmol, 1.3 eq.). The resulting solution was stirred at room temperature for 16 h. THF was then removed *in vacuo*, the residue dry-loaded onto silica and purified chromatographically in 10:1 hexanes: ethyl acetate, yielding 6-benzyl-2-methyl-3-methylene-1-(toluene-4-sulfonyl)-piperidine **33** as a colourless oil (178 mg, 94%), 1:1 mixture of diastereomers at C2. ^1H NMR (250 MHz in CDCl_3): δ 1.09 – 1.31 (2H, m), 1.38 (3H, d, $J = 7.0$ Hz), 1.43 – 1.65 (2H, m), 1.53 (3H, d, $J = 7.0$ Hz), 1.69 – 1.84 (2H, m), 2.30 – 2.51 (2H, m), 2.37 (3H, s), 2.39 (3H, s), 2.71 (1H, dd, $J = 13.0, 10.5$ Hz), 3.00 (1H, dd, $J = 13.0, 11.5$ Hz), 3.13 (1H, dd, $J = 13.5, 4.5$ Hz), 3.25 (1H, dd, $J = 13.0, 3.5$ Hz), 3.89 – 4.10 (2H, m), 4.53 (1H, q, $J = 7.0$ Hz), 4.67 (1H, br), 4.71 (1H, q, $J = 7.0$ Hz), 4.74 (1H, br), 4.85 (1H, br), 4.97 (1H, br), 7.13 – 7.35 (10H, m), 7.66 (2H, d, $J = 8.0$ Hz), 7.68 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (62.9 MHz in CDCl_3): δ 21.2, 21.5, 24.6, 24.8, 24.8, 25.3, 25.4, 26.1, 39.5, 42.9, 54.8, 55.3, 56.2, 56.3, 109.4, 110.9, 126.4, 126.5, 126.8, 127.0, 128.5, 128.5, 129.2, 129.3, 129.5, 129.5, 138.0, 139.0, 139.2, 140.0, 142.8, 142.8, 145.6, 145.9; FTIR (film): 3027 (w), 2939 (m), 1652 (w), 1599 (w), 1496 (m), 1327 (s), 1304 (m), 1231 (w), 1162 (s), 1104 (m), 1086 (m), 1040 (w) cm^{-1} ; HRMS (ES) Calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_2\text{S}$: 365.1684 Found: 356.2679.

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 7

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 10

**$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 2-trimethylsilyl-ethanesulfonic acid
2-(2-trimethylsilyl-ethanesulfonylamino) - propyl ester**

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 12

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 13

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 14

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 16

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 22

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 25

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 26

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 27

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 28

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 29

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 32

$^1\text{H}/^{13}\text{C}$ NMR Spectrum of 33