Synthesis of 3-Substituted-4-piperidinones via a one-pot Tandem Oxidation-Cyclization-Oxidation Process: Stereodivergent Reduction to 3,4-Disubstituted Piperidines

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General Procedures

Melting points were determined in open ended capillaries and are uncorrected. Chemical shifts (δ) are expressed in parts per million (ppm) downfield from tetramethylsilane (Me_4Si) in CDCl_3 unless otherwise stated and coupling constants (J) are given in Hz. The multiplicities of the spectroscopic signals are represented as follows; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and br s = broad singlet. Chemical ionisation (CI) mass spectra employed ammonia as the carrier gas. Low and high resolution Electron Spray Time-of-Flight (ES-TOF) mass spectra were run using a methanol mobile phase.

Tetrahydrofuran (THF) and toluene were dried by refluxing with benzophenone over sodium until a deep purple colour persisted. Dichloromethane (DCM) was dried by refluxing with calcium hydride (CaH_2).

All column chromatography was performed on silica gel (0.063-0.200 mm) using laboratory grade eluents. TLC plates were visualised by UV (254 nm) and potassium manganate (VII). All R_f values refer to the eluent used in purification.

All experiments were conducted under a nitrogen atmosphere in flame dried glassware unless otherwise stated.

Typical Procedure for the PCC Tandem Cyclization of the *N*-alkylated sulfonamides **1c and **1e**.** Celite (0.50 g) was added to a suspension of pyridinium chlorochromate (0.32 g, 1.5 mmol) in DCM (15 ml), which was then stirred for 5 min before cooling to 0 °C. The *N*-alkylated sulfonamide (0.6 mmol) in DCM (5 ml) was then added in one portion to the stirred suspension. After warming to room temperature and stirring for 24 h, NaHSO_4 (1.26 g) and ether (25 ml) were added to the mixture, which was then vigorously stirred for 15 min. After filtering through silica, the residue was washed with ether (200 ml), dried over MgSO_4 and concentrated *in vacuo*. Flash column chromatography of the colourless oil (silica; eluent 1:3 ethyl acetate:petroleum ether) afforded the piperidinone.

3-Cyclopent-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-one **2c**

Sulfonamide **1c** (0.20 g) afforded **2c** (0.12 g, 62%) as a white crystalline solid when subjected to the above procedure; (R_f = 0.76); mp = 94-95 °C; (Found: C, 6.95; H, 6.8; N, 4.1. $\text{C}_{17}\text{H}_{21}\text{NO}_3\text{S}$ requires C, 63.92; H, 6.63; N, 4.39%); $\nu_{\text{max}}/\text{cm}^{-1}$ 2361 (CH), 1713 (C=O), 1342 (SO_2), 1157 (SO_2), 941 (ArH); δ_{H} (400 MHz) 1.84-1.89 (2 H, m), 2.22-2.27 (2 H, m), 2.33-2.37 (2 H, m), 2.44 (3 H, s), 2.53-2.58 (2 H, m), 3.20-3.33 (3 H, m), 3.42-3.53 (2 H, m), 5.63-5.68 (1 H, m), 7.35 (2 H, d, J 8.5), 7.68 (2 H, d, J 8.5); δ_{C} (100 MHz) 19.5, 20.9, 30.5, 31.9, 37.6, 42.2, 47.7, 49.6, 125.5, 126.9, 127.8, 131.5, 137.4, 142.0, 203.4; (ES) m/z 342 (100%, $[\text{M} + \text{Na}]^+$).

3-Cyclohept-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-one 2e

Sulfonamide **1e** (0.21 g) afforded **2e** (0.14 g, 65%) as a white crystalline solid when subjected to the above procedure; (R_f = 0.58); mp = 105-106 °C; (Found: C, 65.9; H, 7.25; N, 3.95. $C_{19}H_{25}NO_3S$ requires C, 65.68; H, 7.25; N, 4.03%); ν_{max}/cm^{-1} 2916 (ArH), 2361 (CH), 1720 (C=O), 1342 (SO₂), 1165 (SO₂), 941 (ArH); δ_H (400 MHz) 1.25 -1.58 (4 H, m), 1.72-1.76 (2 H, m), 1.95-1.99 (2 H, m), 2.10-2.13 (2 H, m), 2.49 (3 H, s), 2.48-2.52 (2 H, m), 2.53-2.64 (2 H, m), 3.17-2.21 (1 H, m), 3.76-3.82 (2 H, m), 5.73 (1 H, t, J 6.6), 7.35 (2 H, d, J 8.1), 7.68 (2 H, d, J 8.1); δ_C (100 MHz) 21.5, 26.6, 26.7, 28.4, 32.1, 32.5, 40.2, 46.1, 49.8, 59.1, 127.5, 129.9, 132.0, 133.4, 139.1, 144.1, 206.1; (ES) m/z 370 (100%, $[M + Na]^+$).

Typical Procedure for the Acid Catalyzed PCC Tandem Cyclization of the *N*-alkylated sulfonamides 1a, 1b and 1d. Triflic acid (0.08 ml, 0.9 mmol) was added to a suspension of pyridinium chlorochromate (0.65 g, 3.0 mmol) in DCM (15 ml), which was then stirred for 5 min before cooling to 0 °C. The *N*-alkylated sulfonamide (0.6 mmol) in DCM (5 ml) was then added in one portion to the reaction mixture. After warming to room temperature and stirring for 24 h, NaHSO₄ (1.78 g) and ether (25 ml) were added to the mixture, which was then vigorously stirred for 15 min. After filtering through silica, the residue was washed with ether (200 ml), dried over MgSO₄ and concentrated *in vacuo*. Flash column chromatography of the colourless oil (silica; eluent 1:3 ethyl acetate:petroleum ether) afforded the piperidinone.

3-Isopropenyl-1-(toluene-4-sulfonyl)-piperidin-4-one 2a

Sulfonamide **1a** (0.18 g) afforded **2a** (0.11 g, 61%) as a white crystalline solid when subjected to the above procedure; (R_f = 0.40); mp = 82-83 °C; (Found: C, 61.3; H, 6.3; N, 4.6. $C_{15}H_{19}NO_3S$ requires C, 61.41; H, 6.53; N, 4.77%); ν_{max}/cm^{-1} 2924 (ArH), 1721 (C=O), 1598 (ArC=C), 1342 (SO₂), 1166 (SO₂); δ_H (400 MHz) 1.72 (3 H, s), 2.44 (3 H, s), 2.55-2.60 (2 H, m), 3.04-3.23 (3 H, m, CH₂CHHN, CHCHHN and CHCH₂N), 3.63-3.71 (2 H, m, CH₂CHHN and CHCHHN), 4.90 (1 H, s), 5.60-5.63 (1 H, m), 7.35 (2 H, d, J 8.1), 7.68 (2 H, d, J 8.1); δ_C (100 MHz) 22.8, 23.0, 41.2, 47.6, 50.9, 57.7, 116.5, 128.8, 131.2, 134.9, 140.9, 146.4, 206.1; (ES) m/z 316 (100%, $[M + Na]^+$).

3-(1-Ethyl-propenyl)-1-(toluene-4-sulfonyl)-piperidin-4-one 2b

Sulfonamide **1b** (0.195 g) afforded **2b** (0.13 g, 67%) as a 2:1 mixture of inseparable *E:Z* isomers, as a white crystalline solid when subjected to the above procedure; (R_f = 0.54); ν_{max}/cm^{-1} 2970 (ArH), 1718 (C=O), 1599 (ArC=C), 1358 (SO₂), 1166 (SO₂); δ_H (400 MHz) 0.87-0.97 (6 H, m, CH₂CH₃ in major and minor isomers), 1.48 (3 H, d, J 6.6, CHCH₃ in minor isomer), 1.64 (3 H, d, J 6.6, CHCH₃ in major isomer), 1.75-2.10 (4 H, m, CH₂CH₃ in major and minor isomers), 2.43 (6 H, s, CH₃ in major and minor isomers), 2.55 (2 H, t, J 5.5, CHHCH₂N in major and minor isomers), 2.63-2.83 (2 H, m, CHHCH₂N in major and minor isomers), 3.03-3.21 (6 H, m, CH₂CHHN, CHCHHN and CHCH₂N in major and minor isomers), 3.52-3.59 (1 H, m, CH₂CHHN in minor isomer), 3.63-3.69 (1 H, m, CH₂CHHN in major isomer), 3.89-3.98 (1 H, m,

CHCHHN in minor isomer), 4.01-4.11 (1 H, m, CHCHHN in major isomer), 5.37 (1 H, q, J 7.0, CCH in major isomer), 5.50 (1 H, q, J 7.0, CCH in minor isomer), 7.30 (4 H, apparent d, J 7.3, Ar CH in major and minor isomers), 7.70 (4 H, apparent d, J 7.3, Ar CH in major and minor isomers); δ_{C} (100 MHz) 12.0 (CH₃ in minor isomer), 12.2 (CH₃ in major isomer), 12.7 (CH₃ in major isomer), 13.4 (CH₃ in minor isomer), 20.9 (CH₃ in major and minor isomers), 22.5 (CH₂ in major isomer), 27.3 (CH₂ in minor isomer), 39.2 (CH₂ in major isomer), 39.7 (CH₂ in minor isomer), 44.9 (CH₂ in minor isomer), 45.7 (CH₂ in major isomer), 48.3 (CH₂ in minor isomer), 49.7 (CH₂ in major isomer), 51.6 (CH in minor isomer), 55.3 (CH in major isomer), 122.2 (CH in minor isomer), 123.0 (CH in major isomer), 126.8 (CH in minor isomer), 126.9 (CH in major isomer), 129.2 (CH in major isomer), 129.3 (CH in minor isomer), 133.2 (C⁴ in major isomer), 133.8 (C⁴ in minor isomer), 134.9 (C⁴ in minor isomer), 136.3 (C⁴ in major isomer), 143.4 (C⁴ in major and minor isomers), 204.7 (C⁴ in minor isomer), 206.2 (C⁴ in major isomer); (ES) m/z 344 (100%, [M + Na]⁺).

3-Cyclohex-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-one **2d**

Sulfonamide **1d** (0.20 g) afforded **2d** (0.12 g, 59%) as a white crystalline solid when subjected to the above procedure; (R_f = 0.53); mp = 119-120 °C; (Found: C, 65.7; H, 5.7; N, 4.0. C₁₈H₁₉NO₃S requires C, 65.63; H, 5.81; N, 4.25%); ν_{max} /cm⁻¹ 2916 (ArH), 2361 (CH), 1717 (C=O), 1342 (SO₂), 1157 (SO₂), 949 (ArH); δ_{H} (400 MHz) 1.56-1.63 (4 H, m), 1.80-1.84 (2 H, m), 2.02-2.06 (2 H, m), 2.44 (3 H, s), 2.55 (2 H, t, J 6.0), 3.07-3.18 (3 H, m), 3.58-3.63 (2 H, m), 5.60-5.63 (1 H, m), 7.35 (2 H, d, J 8.1), 7.68 (2 H, d, J 8.1); δ_{C} (100 MHz) 24.0, 24.4, 25.1, 27.7, 29.9, 42.3, 48.7, 52.0, 59.3, 129.0, 130.0, 132.3, 134.5, 135.9, 146.5, 207.5; (ES) m/z 356 (100%, [M + Na]⁺).

Typical Procedure for the L-Selectride Reduction of the Piperidinones. L-Selectride (1 M soln. in THF, 0.157 ml, 0.157 mmol) was added to the piperidinone (0.157 mmol) in THF (20 ml) at -78 °C. The reaction mixture was stirred at -78 °C for 3 h and then allowed to warm to room temperature. The reaction mixture was hydrolyzed with water (4 ml) and ethanol (15 ml); the organoborane was oxidised with 6 M NaOH (10 ml) and 30% hydrogen peroxide (15 ml) and stirring at room temperature for 1 h. The organic phase was separated and the aqueous layer was extracted with ether (3 x 20 ml). The combined organic phases were washed with brine (20 ml), dried over MgSO₄ and concentrated in vacuo. Purification by flash column chromatography (silica; eluent 2:1 petroleum ether:ethyl acetate) resulted in the (3*R**, 4*S**)-hydroxy piperidine as a white crystalline solid.

Reaction of **2a** (46 mg) according to the above reduction procedure afforded (3*R**, 4*S**)-3-isopropenyl-1-(toluene-4-sulfonyl)-piperidin-4-ol, **6a** (39 mg, 85%) as a white crystalline solid. (R_f = 0.36); mp = 89-91 °C (from petroleum ether/ethyl acetate); (Found: C, 61.0; H, 7.1; N, 4.6. C₁₅H₂₁NO₃S requires C, 60.99; H, 7.17; N, 4.74%); ν_{max} (neat)/cm⁻¹ 3519 (OH), 2920 (CH), 2904 (CH), 1651 (C=C), 1597 (ArC=C), 1447

(ArC=C), 1323 (SO₂), 1304 (SO₂), 1157 (SO₂); δ_{H} (500 MHz) 1.50 (1 H, br s), 1.77 (3 H, s), 1.81-1.95 (2 H, m), 2.37 (1 H, apparent d, J 12.1), 2.42 (3 H, s), 2.55-2.62 (2 H, m), 3.55-3.59 (2 H, m), 3.96 (1 H, apparent d, J 2.2), 4.58 (1 H, s), 4.96 (1 H, s), 7.31 (2 H, d, J 8.1), 7.64 (2 H, d, J 8.1); δ_{C} (125 MHz) 21.5, 22.8, 31.1, 40.5, 43.5, 46.7, 63.0, 112.2, 127.6, 129.6, 133.4, 143.4, 143.8; m/z (CI) 296 ([M+H]⁺, 100%), 278 (4), 257 (5), 189 (8), 143 (13), 124 (15), 105 (4), 79 (11).

Reaction of **2b** (51 mg) according to the above reduction procedure resulted in (3*R*^{*}, 4*S*^{*})-3-(1-ethylpropenyl)-1-(toluene-4-sulfonyl)-piperidin-4-ol as a 2:1 mixture of inseparable *E:Z* isomers, **6b** (42 mg, 82%) as a white crystalline solid; (R_{f} = 0.40, eluent 2:1 petroleum ether:ethyl acetate); (Found: C, 63.0; H, 7.85; N, 4.0. C₁₇H₂₅NO₃S requires C, 63.13; H, 7.79; N, 4.33%); ν_{max} (neat)/cm⁻¹ 2361 (CH), 1334 (SO₂), 1157 (SO₂); δ_{H} (300 MHz) 0.94-1.00 (4 H, m), 1.58-1.64 (4 H, m), 1.74-2.03 (3 H, m), 2.19-2.26 (1 H, m), 2.43-2.44 (4 H, m), 2.49-2.68 (2 H, m), 3.46-3.61 (2 H, m), 3.87 (1 H, m, *CHOH*, minor isomer), 3.95 (1 H, m, *CHOH*, major isomer), 5.04 (1 H, q, J 6.6, C=CH, minor isomer), 5.36 (1 H, q, J 7.0, C=CH, major isomer), 7.32 (2 H, d, J 8.5), 7.50 (2 H, d, J 8.5); δ_{C} (75 MHz) 12.8 (CH₃ minor isomer), 12.9 (CH₃ major isomer), 13.1 (CH₃ minor isomer), 13.2 (CH₃ major isomer), 21.5 (CH₃), 23.4 (CH₂ minor isomer), 26.9 (CH₂ major isomer), 31.0 (CH₂ minor isomer), 32.7 (CH₂ major isomer), 40.5 (CH₂ major isomer), 40.6 (CH₂ minor isomer), 41.7 (CH minor isomer), 41.8 (CH₂ minor isomer), 42.3 (CH₂ major isomer), 45.2 (CH major isomer), 63.1 (CH minor isomer), 67.4 (CH major isomer), 120.3 (CH minor isomer), 120.4 (CH major isomer), 127.6 (CH), 129.6 (CH), 133.5 (C⁴), 140.0 (C⁴ minor isomer), 140.5 (C⁴ major isomer), 143.4 (C⁴); m/z (ES) 346 ([M+ Na]⁺, 100%).

Reaction of **2c** (50 mg) according to the above reduction procedure generated (3*R*^{*}, 4*S*^{*})-3-cyclopent-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-ol, **6c** (44 mg, 86%) as a white crystalline solid; (R_{f} = 0.35, eluent 2:1 petroleum ether:ethyl acetate); mp = 92-93 °C (from petroleum ether/ethyl acetate); (Found: C, 63.3; H, 7.0; N, 4.15. C₁₇H₂₃NO₃S requires C, 63.52; H, 7.21; N, 4.36%); ν_{max} (neat)/cm⁻¹ 2924 (OH), 1443 (ArC=C), 1335 (SO₂), 1157 (SO₂); δ_{H} (300 MHz) 1.55 (1 H, br s), 1.76-1.96 (4 H, m), 2.19-2.37 (4 H, m), 2.43 (3 H, s), 2.55-2.66 (3 H, m), 3.54-3.62 (2 H, m), 3.95-3.97 (1 H, m), 5.41-5.43 (1 H, m), 7.31 (2 H, d, J 8.1), 7.65 (2 H, d, J 8.1); δ_{C} (75 MHz) 21.5, 22.6, 31.0, 32.7, 34.5, 40.5, 42.6, 43.7, 63.4, 126.6, 127.6, 129.7, 133.5, 142.2, 143.4; m/z (EI) 321 (M⁺, 10%), 184 (100), 155 (49), 120 (24), 91 (80), 84 (52), 42 (59).

Reaction of **2d** (52 mg) according to the above reduction procedure gave (3*R*^{*}, 4*S*^{*})-3-cyclohex-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-ol, **6d** (37 mg, 70%) as a white crystalline solid; (R_{f} = 0.62, eluent 2:1 petroleum ether:ethyl acetate); mp = 94-95 °C (from petroleum ether/ethyl acetate); (Found: C, 64.5; H, 7.8; N, 4.0. C₁₈H₂₅NO₃S requires C, 64.45; H, 7.51; N, 4.18%); ν_{max} (neat)/cm⁻¹ 2910 (OH), 2360 (CH), 1670 (C=C), 1590 (ArC=C), 1334 (SO₂), 1161 (SO₂); δ_{H} (300 MHz) 1.48-1.65 (4 H, m), 1.82-2.06 (5 H, m), 2.25-2.30 (1 H, m), 2.43 (3 H, s), 2.51-2.61 (2 H, m), 3.50-3.60 (2 H, m), 3.91-3.93 (1 H, m), 5.31 (1 H, s),

7.32 (2 H, d, *J* 8.5), 7.65 (2 H, d, *J* 8.5); δ_{C} (75 MHz) 21.5, 22.3, 22.8, 25.2, 28.6, 31.0, 40.6, 43.4, 46.9, 63.2, 123.6, 127.6, 129.7, 133.5, 136.2, 143.4; *m/z* (ES) 358 ([M+Na]⁺, 100%).

Reaction of **2e** (55 mg) according to the above reduction procedure yielded (3*R*^{*}, 4*S*^{*})-3-cyclohept-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-ol, **6e** (43 mg, 79%) as a white crystalline solid; (*R*_f = 0.51, eluent 2:1 petroleum ether:ethyl acetate); mp = 98-99 °C (from petroleum ether/ethyl acetate); (Found: C, 65.2; H, 7.7; N, 3.8. C₁₉H₂₇NO₃S requires C, 65.30; H, 7.79; N, 4.01%); ν_{max} (neat)/cm⁻¹ 2850 (OH), 2360 (CH), 1710 (C=C), 1590 (ArC=C), 1339 (SO₂), 1161 (SO₂); δ_{H} (300 MHz) 1.33-1.58 (4 H, m), 1.70-1.76 (2 H, m), 1.83-1.90 (2 H, m), 2.09-2.18 (4 H, m), 2.35-2.39 (1 H, m), 2.43 (3 H, s), 2.46-2.58 (2 H, m), 3.49-3.60 (2 H, m), 3.90-3.92 (1 H, m), 5.40 (1 H, t, *J* 6.6), 7.32 (2 H, d, *J* 8.5), 7.66 (2 H, d, *J* 8.5); δ_{C} (75 MHz) 21.5, 26.8, 27.0, 28.2, 30.0, 32.3, 32.4, 45.0, 48.6, 54.0, 68.5, 127.6, 129.7, 132.2, 133.6, 141.0, 143.5; *m/z* (ES) 372 ([M+ Na]⁺, 100%).

Preparation of DIBAOⁱPr in toluene. Isopropyl alcohol (0.81 ml, 10.5 mmol) was added dropwise to diisobutylaluminium hydride (1 M soln. in toluene, 10 ml, 10 mmol) cooled to 0 °C. After the complete evolution of hydrogen, the reagent solution was stirred at room temperature for 1 h to give a solution of DIBAOⁱPr (0.93 M) in toluene.

DIBAOⁱPr Reduction of the piperidinones. DIBAOⁱPr (0.93 M soln. in toluene, 0.169 ml, 0.157 mmol) was added to the piperidinone (0.157 mmol) in toluene (10 ml) and the reaction mixture was stirred at room temperature for 24 h. 3 M HCl (1.5 ml) and ether (10 ml) were then added and the mixture was allowed to stir for 30 min. 3 M NaOH (5 ml) was then added and the solution was allowed to stir for 1 h. The organic layer was separated and the aqueous phase was extracted with ether (3 x 20 ml). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated in vacuo. Purification by flash column chromatography (silica; eluent 2:1 petroleum ether:ethyl acetate) resulted in the (3*R*^{*}, 4*R*^{*})-hydroxy piperidine as a white crystalline solid.

Reaction of **2a** (46 mg) according to the above reduction procedure afforded (3*R*^{*}, 4*R*^{*})-3-isopropenyl-1-(toluene-4-sulfonyl)-piperidin-4-ol, **7a** (37 mg, 79%) as a white crystalline solid. (*R*_f = 0.24); mp = 149-151 °C (from petroleum ether/ethyl acetate); (Found: C, 60.1; H, 7.1; N, 4.60. C₁₅H₂₁NO₃S requires C, 60.99; H, 7.17; N, 4.74%); ν_{max} (neat)/cm⁻¹ 3391 (OH), 2920 (CH), 2904 (CH), 1647 (C=C), 1597 (ArC=C), 1458 (ArC=C), 1334 (SO₂), 1304 (SO₂), 1157 (SO₂); δ_{H} (500 MHz) 1.58-1.68 (1 H, m), 1.71 (3 H, s), 1.85 (1 H, br s), 2.01-2.06 (1 H, m), 2.17-2.27 (2 H, m), 2.37 (1 H, dt, *J* 2.8 and 12.4), 2.43 (3 H, s), 3.44 (1 H, dt, *J* 4.5 and 10.1), 3.75-3.77 (1 H, m), 3.81-3.86 (1 H, m), 4.89 (1 H, s), 5.01 (1 H, s), 7.32 (2 H, d, *J* 8.0), 7.64 (2 H, d, *J* 8.0); δ_{C} (125 MHz) 20.6, 21.5, 32.5, 45.0, 48.8, 51.6, 69.4, 114.7, 127.6, 129.7, 133.6, 142.4, 143.6; *m/z* (CI) 296 ([M+H]⁺, 100%), 278 (4), 247 (5), 189 (5), 143 (10), 124 (8), 79 (4), 69 (10).

Reaction of **2b** (51 mg) according to the above reduction procedure resulted in (3*R*^{*}, 4*R*^{*})-3-(1-ethylpropenyl)-1-(toluene-4-sulfonyl)-piperidin-4-ol as a 2:1 mixture of inseparable *E:Z* isomers, **7b** (37 mg, 74%) as a white crystalline solid; (*R*_f = 0.29); (Found: C, 63.3; H, 7.65; N, 4.1. C₁₇H₂₅NO₃S requires C, 63.13; H, 7.79; N, 4.33%); *v*_{max}(neat)/cm⁻¹ 3550 (OH), 2950 (CH), 1600 (ArC=C), 1327 (SO₂), 1157 (SO₂); δ_{H} (300 MHz) 0.76-0.90 (2 H, m), 0.94-1.10 (3 H, m), 1.63-1.69 (4 H, m), 1.79-1.95 (1 H, m), 2.00-2.20 (2 H, m), 2.29-2.40 (1 H, m), 2.43 (3 H, m), 2.73-2.81 (1 H, m, *CHOH*, minor isomer), 3.39-3.51 (1 H, m, *CHOH*, major isomer), 3.71-3.76 (1 H, m), 3.81-3.91 (1 H, m), 5.35 (1 H, q, *J* 7.0 C=CH major isomer), 5.56 (1 H, q, *J* 7.0, C=CH minor isomer), 7.26 (2 H, d, *J* 7.7), 7.64 (2 H, d, *J* 7.7); δ_{C} (75 MHz) 13.1, 13.3, 21.5, 22.7, 32.3 (CH₂ major isomer), 32.7 (CH₂ minor isomer), 45.1 (CH₂ major isomer), 45.5 (CH major isomer), 48.0 (CH₂ minor isomer), 49.9 (CH₂), 51.5 (CH major isomer), 69.1 (CH minor isomer), 69.7 (CH major isomer), 122.8 (CH major isomer), 124.0 (CH minor isomer), 127.6, 129.7, 133.6, 136.9 (C⁴ minor isomer), 138.9 (C⁴ major isomer), 143.5; *m/z* (EI) 323 (M⁺, 4%), 240 (7), 214 (19), 184 (100), 135 (52), 91 (57), 42 (48).

Reaction of **2c** (50 mg) according to the above reduction procedure generated (3*R*^{*}, 4*R*^{*})-3-cyclopent-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-ol, **7c** (35 mg, 70%) as a white crystalline solid; (*R*_f = 0.29, eluent 2:1 petroleum ether:ethyl acetate); mp = 135-136 °C (from petroleum ether/ethyl acetate); (Found: C, 63.28; H, 7.15; N, 4.15. C₁₇H₂₃NO₃S requires C, 63.52; H, 7.21; N, 4.36%); *v*_{max}(neat)/cm⁻¹ 2924 (OH), 1597 (ArC=C), 1335 (SO₂), 1157 (SO₂); δ_{H} (300 MHz) 1.57-1.92 (4 H, m), 1.99-2.07 (2 H, m), 2.17-2.24 (2 H, m), 2.31-2.38 (3 H, m), 2.44 (3 H, s), 3.39-3.47 (1 H, m), 3.69-3.81 (2 H, m), 5.60-5.62 (1 H, m), 7.33 (2 H, d, *J* 8.1), 7.63 (2 H, d, *J* 8.1); δ_{C} (75 MHz) 21.5, 23.0, 32.2, 32.3, 32.7, 44.9, 46.3, 48.4, 69.6, 127.6, 128.8, 129.7, 133.4, 141.1, 143.6; *m/z* (EI) 321 (M⁺, 8%), 240 (12), 184 (100), 155 (47), 120 (23), 91 (79), 42 (47).

Reaction of **2d** (52 mg) according to the above reduction procedure gave (3*R*^{*}, 4*R*^{*})-3-cyclohex-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-ol, **7d** (36 mg, 73%) as a white crystalline solid (*R*_f = 0.53, eluent 2:1 petroleum ether:ethyl acetate); mp = 144-145 °C (from petroleum ether/ethyl acetate) (Found: C, 64.2; H, 7.3; N, 4.0. C₁₈H₂₅NO₃S requires C, 64.45; H, 7.33; N, 4.18%); *v*_{max}(neat)/cm⁻¹ 2920 (OH), 2361 (CH), 1650 (C=C), 1590 (ArC=C), 1339 (SO₂), 1157 (SO₂); δ_{H} (300 MHz) 1.54-1.67 (5 H, m), 1.82-1.89 (2 H, m), 2.01-2.03 (1 H, m), 2.04-2.05 (2 H, m), 2.09-2.11 (1 H, m), 2.12-2.20 (1 H, m), 2.26-2.34 (1 H, m), 2.43 (3 H, s), 3.36-3.45 (1 H, m), 3.68-3.72 (1 H, m), 3.78-3.82 (1 H, m), 5.61 (1 H, s), 7.31 (2 H, d, *J* 8.5), 7.63 (2 H, d, *J* 8.5); δ_{C} (75 MHz) 21.5, 22.3, 22.7, 25.2, 26.4, 32.4, 45.1, 48.9, 52.2, 69.0, 126.6, 127.6, 129.7, 133.6, 134.4, 143.5; *m/z* (EI) 335 (M⁺, 15%), 240 (22), 184 (100), 162 (35), 155 (61), 134 (31), 108 (34), 91 (96), 79 (32), 42 (76).

Reaction of **2e** (55 mg) according to the above reduction procedure yielded (3*R*^{*}, 4*R*^{*})-3-cyclohept-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-ol, **7e** (48 mg, 87%) as a white crystalline solid; (*R*_f = 0.33, eluent 2:1 petroleum ether:ethyl acetate); mp = 134-135 °C (from petroleum ether/ethyl acetate); (Found: C, 65.2; H, 7.9; N, 4.0. C₁₉H₂₇NO₃S requires C, 65.30; H, 7.79; N, 4.01%); *v*_{max}(neat)/cm⁻¹ 2916 (OH), 2361 (CH), 1690 (C=C), 1342 (SO₂), 1157 (SO₂); δ_H(300 MHz) 1.38-1.49 (4 H, m), 1.59-1.68 (2 H, m), 1.71-1.78 (2 H, m), 2.02-2.06 (2 H, m), 2.10-2.17 (4 H, m), 2.27-2.36 (1 H, m), 2.44 (3 H, s), 3.35-3.42 (1 H, m), 3.71-3.74 (1 H, m), 3.80-3.85 (1 H, m), 5.81 (1 H, s), 7.33 (2 H, d, *J* 8.5), 7.64 (2 H, d, *J* 8.5); δ_C(75 MHz) 21.5, 26.8, 27.0, 28.2, 31.0, 32.5, 33.6, 40.6, 43.6, 48.4, 62.6, 127.6, 128.5, 129.7, 133.4, 143.1, 143.4; *m/z* (ES) 372 ([M+ Na]⁺, 100%).

3-isopropenyl-1-(toluene-4-sulfonyl)-piperidin-4-one (**2a**)

3-(1-ethylpropenyl)-1-(toluene-4-sulfonyl)-piperidin-4-one (**2b**)

3-cyclopent-1-en-1-yl-1-(toluene-4-sulfonyl)-piperidin-4-one (**2c**)

3-cyclohex-1-en-1-yl-1-(toluene-4-sulfonyl)-piperidin-4-one (**2d**)

3-cyclohept-1-enyl-1-(toluene-4-sulfonyl)-piperidin-4-one (**2e**)

3-[(3-Ethylpent-2-enyl)-(toluene-4-sulfonyl)amino]propanoic acid (**5**)

cis piperidine (**6a**)

cis piperidine (**6b**)

cis piperidine (**6c**)

cis piperidine (**6d**)

cis piperidine (**6e**)

trans piperidine (**7a**)

trans piperidine (**7b**)

trans piperidine (7c)

trans piperidine (**7d**)

trans piperidine (**7e**)

Supporting Information – HPLC traces of crude reduction products

All HPLC was performed using a C₁₈ Phenomenex Luna column, 10 µm particle size, 250x4.6 mm; gradient elution from 100:0 water:acetonitrile + 0.05% TFA to 60:40 water:acetonitrile + 0.05% TFA over 60 min, flow rate 1 mL/min.

34 PS 5 (crude)

Sample Name:	PS 5 (crude)	Injection Volume:	30.0
Vial Number:	A34	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	FOX METHOD 1ML 60MINS C	Bandwidth:	n.a.
Quantif. Method:	FOX METHOD 1ML 60MINS C	Dilution Factor:	1.0000
Recording Time:	5/2/03 22:28	Sample Weight:	1.0000
Run Time (min):	95.00	Sample Amount:	1.0000

No.	Ret.Time min	Peak Name	Height AU	Area AU*min	Rel.Area %	Amount	Type
1	49.50	n.a.	0.796	0.245	100.00	n.a.	BMB*
Total:			0.796	0.245	100.00	0.000	

trace of crude 6a tr = 49.5 min
ratio 6a:7a >99:1 (tr = 46.8 min for 7a)

3 PS 5 trans

Sample Name:	PS 5 trans	Injection Volume:	30.0
Vial Number:	A3	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	FOX METHOD 1ML 60MINS D	Bandwidth:	n.a.
Quantif. Method:	FOX METHOD 1ML 60MINS D	Dilution Factor:	1.0000
Recording Time:	6/2/03 7:25	Sample Weight:	1.0000
Run Time (min):	95.00	Sample Amount:	1.0000

No.	Ret.Time min	Peak Name	Height AU	Area AU*min	Rel.Area %	Amount	Type
1	46.80	n.a.	1.702	0.520	100.00	n.a.	BMB*
Total:			1.702	0.520	100.00	0.000	

trace of crude 7a tr = 46.8 min
ratio 7a:6a >99:1 (tr = 49.5 min for 6a)

32 PS 4 (cis)

Sample Name:	PS 4 (cis)	Injection Volume:	30.0
Vial Number:	A32	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	FOX METHOD 1ML 60MINS C	Bandwidth:	n.a.
Quantif. Method:	FOX METHOD 1ML 60MINS C	Dilution Factor:	1.0000
Recording Time:	5/2/03 19:14	Sample Weight:	1.0000
Run Time (min):	95.00	Sample Amount:	1.0000

No.	Ret.Time min	Peak Name	Height AU	Area AU*min	Ret.Area %	Amount	Type
1	58.83	n.a.	0.735	0.233	67.73	n.a.	BMb*
2	59.70	n.a.	0.358	0.111	32.27	n.a.	bMB*
Total:			1.094	0.345	100.00	0.000	

trace of crude **6b** tr = 58.8 and 59.7 min (*E* and *Z* isomers)
ratio **6b**:**7b** >99:1 (tr = 55.3 for **7b**)

33 PS 4 (trans)

Sample Name:	PS 4 (trans)	Injection Volume:	30.0
Vial Number:	A33	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	FOX METHOD 1ML 60MINS C	Bandwidth:	n.a.
Quantif. Method:	FOX METHOD 1ML 60MINS C	Dilution Factor:	1.0000
Recording Time:	5/2/03 20:51	Sample Weight:	1.0000
Run Time (min):	95.00	Sample Amount:	1.0000

No.	Ret. Time min	Peak Name	Height AU	Area AU*min	Rel. Area %	Amount	Type
1	55.30	n.a.	2.246	0.844	100.00	n.a.	BMB*
Total:			2.246	0.844	100.00	0.000	

trace of crude **7b** tr = 55.3 min

ratio **7b:6b** >99:1 [for **6b** tr = 58.8 and 59.7 min (*E* and *Z* isomers)]

22 PS 1 (crude)

Sample Name:	PS 1 (crude)	Injection Volume:	30.0
Vial Number:	A22	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	FOX METHOD 1ML 60MINS C	Bandwidth:	n.a.
Quantif. Method:	FOX METHOD 1ML 60MINS C	Dilution Factor:	1.0000
Recording Time:	4/2/03 18:41	Sample Weight:	1.0000
Run Time (min):	95.00	Sample Amount:	1.0000

No.	Ret.Time min	Peak Name	Height AU	Area AU*min	Rel.Area %	Amount	Type
1	56.67	n.a.	1.948	0.622	100.00	n.a.	BMB*
Total:			1.948	0.622	100.00	0.000	

trace of crude **6c** tr = 56.7 min
ratio **6c:7c** >99:1 (tr = 53.9 min for **7c**)

24 PS 1 (trans)

Sample Name:	PS 1 (trans)	Injection Volume:	30.0
Vial Number:	A24	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	FOX METHOD 1ML 60MINS C	Bandwidth:	n.a.
Quantif. Method:	FOX METHOD 1ML 60MINS C	Dilution Factor:	1.0000
Recording Time:	4/2/03 21:55	Sample Weight:	1.0000
Run Time (min):	95.00	Sample Amount:	1.0000

No.	Ret.Time min	Peak Name	Height AU	Area AU*min	Rel.Area %	Amount	Type
1	53.90	n.a.	1.018	0.315	86.57	n.a.	BMB*
2	56.67	n.a.	0.013	0.005	1.25	n.a.	BMB*
3	58.03	n.a.	0.104	0.033	9.05	n.a.	BMB*
4	60.47	n.a.	0.036	0.011	3.14	n.a.	BMB*
Total:			1.172	0.363	100.00	0.000	

trace of crude 7c tr = 53.9 min
ratio 7c:6c >98:2 (tr = 56.7 min for 6c)

25 PS 2 (crude)

Sample Name:	PS 2 (crude)	Injection Volume:	30.0
Vial Number:	A25	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	FOX METHOD 1ML 60MINS C	Bandwidth:	n.a.
Quantif. Method:	FOX METHOD 1ML 60MINS C	Dilution Factor:	1.0000
Recording Time:	4/2/03 23:32	Sample Weight:	1.0000
Run Time (min):	95.00	Sample Amount:	1.0000

No.	Ret.Time min	Peak Name	Height AU	Area AU*min	Rel.Area %	Amount	Type
1	60.67	n.a.	1.611	0.527	100.00	n.a.	BMB*
Total:			1.611	0.527	100.00	0.000	

trace of crude **6d** tr = 60.7 min
ratio **6d:7d** >99:1 (tr = 56.9 min for **7d**)

27 PS 2 (trans)

Sample Name:	PS 2 (trans)	Injection Volume:	30.0
Vial Number:	A27	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	FOX METHOD 1ML 60MINS C	Bandwidth:	n.a.
Quantif. Method:	FOX METHOD 1ML 60MINS C	Dilution Factor:	1.0000
Recording Time:	5/2/03 2:45	Sample Weight:	1.0000
Run Time (min):	95.00	Sample Amount:	1.0000

No.	Ret. Time min	Peak Name	Height AU	Area AU*min	Rel. Area %	Amount	Type
1	56.87	n.a.	1.358	0.427	96.15	n.a.	BMB*
2	60.70	n.a.	0.049	0.017	3.85	n.a.	BMB*
Total:			1.408	0.445	100.00	0.000	

trace of crude 7d tr = 56.9 min
ratio 7d:6d >96:4 (tr = 60.7 min for 6d)

28 PS 3 (crude)

Sample Name:	PS 3 (crude)	Injection Volume:	30.0
Vial Number:	A28	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	FOX METHOD 1ML 60MINS C	Bandwidth:	n.a.
Quantif. Method:	FOX METHOD 1ML 60MINS C	Dilution Factor:	1.0000
Recording Time:	8/2/03 4:22	Sample Weight:	1.0000
Run Time (min):	95.00	Sample Amount:	1.0000

No.	Ret.Time min	Peak Name	Height AU	Area AU*min	Rel.Area %	Amount	Type
1	41.27	n.a.	0.802	0.829	45.75	n.a.	BMB*
2	65.20	n.a.	2.491	0.984	54.25	n.a.	BMB*
Total:			3.292	1.813	100.00	0.000	

trace of crude **6e** tr = 65.2 min
ratio **6e:7e** >99:1 (tr = 56.9 min for **7e**)

30 PS 3 (trans)

Sample Name:	PS 3 (trans)	Injection Volume:	30.0
Vial Number:	A30	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	n.a.
Control Program:	FOX METHOD 1ML 60MINS C	Bandwidth:	n.a.
Quantif. Method:	FOX METHOD 1ML 60MINS C	Dilution Factor:	1.0000
Recording Time:	5/2/03 16:00	Sample Weight:	1.0000
Run Time (min):	95.00	Sample Amount:	1.0000

No.	Ret. Time min	Peak Name	Height AU	Area AU*min	Rel. Area %	Amount	Type
1	56.90	n.a.	0.297	0.093	100.00	n.a.	BMB*
Total:			0.297	0.093	100.00	0.000	

trace of crude 7e tr = 56.9 min
ratio 7e:6e >99:1 (tr = 65.2 min for 6e)