Supplementary Material (ESI) for Chemical Communications

Hemi-aminals as substrates for sulfur ylides+ Direct asymmetric syntheses of functionalised pyrrolidines and piperidines

Christoforos G. Kokotos, and Varinder K. Aggarwal*

School of Chemistry, Bristol University, Cantock's Close, Bristol, UK BS8 1TS.
E-mail: v.aggarwal@bristol.ac.uk; Fax: +44 (0)117 929 8611; Tel: +44 (0)117 954 6315

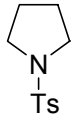
Supplementary Information

General Methods

Flash chromatography was performed on silica gel (SiO_2, Merck Kiesegel 60, 230-400 mesh). TLC was performed on aluminium backed silica plates ($60F_{254}$, 0.2 mm) which were visualised using: UV fluorescence (254 and 366 nm), phosphomolybdic acid/Δ, anisaldehyde/Δ. Melting points were determined on a Kofler hot stage. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer, only selected absorbencies (ν_{max}) are reported. ^{1}H NMR spectra were recorded at 270 or 400 MHz on Jeol Delta GX/270 or Jeol Delta GX/400 instruments, respectively. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to TMS, *J* values are given in Hz. ^{13}C NMR spectra were recorded at 67 or 101 MHz on Jeol Delta GX/270 or Jeol Delta GX/400 instruments, respectively. Chemical shifts (δ_C) are quoted in parts per million (ppm), referenced to the appropriate residual solvent. Degenerate peaks are prefixed by the number of carbons. Low resolution mass spectra (m/z) were recorded on a Micromass Analytical Autospec spectrometer, with only molecular ions (M^+ or MH^+) and major peaks being reported with intensities quoted as percentages of the base peak. High-resolution mass spectra were recorded on a Micromass Analytical Autospec Spectrometer. All chemicals were purchased from Aldrich, Fluka, Lancaster or Strem and used as received unless otherwise mentioned. Anhydrous THF, CH_2Cl_2, and acetonitrile were obtained from a purification column composed of activated alumina (A-2).[1] Other anhydrous solvents were used as obtained from Aldrich. All reactions were performed in dry glassware under an inert atmosphere of either argon or nitrogen. Enantioselectivities were measured by chiral HPLC utilising Chiralcel OD, OJ or ODH columns eluting with different ratios of hexane and 2-propanol.

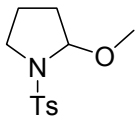
Experimental procedures

1-[(4-Methylphenyl)sulfonyl]pyrrolidine[2]



To a solution of pyrrolidine (10.0 g, 0.141 mol), triethylamine (33.77 g, 0.242 mmol) in chloroform (20 mL) at 0 °C under nitrogen was added a solution of *p*-toluenesulfonyl chloride (29.55 g, 0.155 mmol) in chloroform (25 mL) dropwise over 10 minutes. After 1 h the reaction mixture was warmed to room temperature and stirred for a further 18 h and quenched with aqueous $NaHCO_3$ (5%, 50 mL). The reaction mixture was extracted with EtOAc (80 mL). The organic layer was washed with aqueous citric acid (5%, 2 × 40 mL), H_2O (2 × 40 mL), aqueous $NaHCO_3$ (5%, 2 × 40 mL) and brine (1 × 40 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuum to give the product as a white solid [2] (30.5 g, 96%); mp 123 °C [lit., [2] 122-124 °C]; δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, *J* 8.0 Hz, ArH), 7.32 (2H, d, *J* 8.0 Hz, ArH), 3.23 (4H, m, 2 × CH_2), 2.43 (3H, s, CH_3), 1.74 (4H, m, 2 × CH_2); δ_c (100.5 MHz, $CDCl_3$) 143.2, 134.2, 129.6, 127.6, 47.9, 25.3, 21.5.

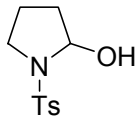
2-Methoxy-1-[(4-methylphenyl)sulfonyl]pyrrolidine[3]



This experiment is based on an electrochemical oxidation described by Ban[4]. To a solution of 1-[(4-Methylphenyl)sulfonyl]pyrrolidine (5.00 g, 22.00 mmol) in anhydrous methanol (25 mL) and acetonitrile (25 mL) was added tetraethylammonium *p*-toluenesulfonate (0.19 g, 0.63 mmol) and was electrochemically oxidised (10 V, 0.1 A) using carbon electrodes for 8.5 h at room temperature. The reaction mixture was then concentrated in vacuo and the residue was purified by flash chromatography, eluting with 1:4 EtOAc : pet.ether followed by 1:3 EtOAc : pet.ether to give the product as a colourless oil [3] (4.89 g, 87%); δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, *J* 8.0 Hz, ArH), 7.29 (2H, d, *J* 8.0 Hz, ArH), 5.10 (1H, d, *J* 5.5 Hz, NCH), 3.41 (3H, s, OCH_3), 3.40 (1H, td, *J* 10.0 and 2.5 Hz, NC*H*H), 3.13 (1H, td, *J* 10.0 and 7.5 Hz, NC*H*H), 2.42 (3H, s, CH_3), 2.00 (1H, m, C*H*H), 1.85 (1H, ddd, *J*

13.0, 7.0 and 1.5 Hz, C*H*H), 1.74 (1H, m, C*H*H), 1.37 (1 H, tdd, *J* 13.0, 13.0, 8.0 and 5.0 Hz, C*H*H); δ_c (100.5 MHz, $CDCl_3$) 143.5, 136.1, 129.7, 127.4, 91.7, 55.3, 47.3, 32.7, 23.2, 21.5.

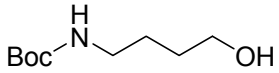
1-[(4-Methylphenyl)sulfonyl]-2-pyrrolidinol (3)[3]



3

To a solution of 2-methoxy-1-[(4-methylphenyl)sulfonyl]pyrrolidine (1.0 g, 3.92 mmol) in deionised water (6 mL) and acetonitrile (8 mL) was added pyridinium *p*-toluenesulfonate (0.1 g, 0.39 mmol) at room temperature under nitrogen. The reaction mixture was then stirred for 18 h. The reaction mixture was then concentrated in vacuo and the residue partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (1 × 20 mL) and dried ($MgSO_4$). The organic layers were then concentrated in vacuo and the residue purified by flash chromatography, eluting with 1:4 EtOAc : pet. ether followed by 3:7 EtOAc : pet. ether to give the product as a white solid[3] (0.73 g, 77 %); mp 59-61 °C; δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.5 Hz, ArH), 7.32 (2H, d, *J* 8.5 Hz, ArH), 5.44 (1H, m, NC*H*OH), 3.56 (1H, ddd, *J* 10.0, 8.0 and 2.5 Hz, NC*H*H), 3.16 (1H, dd, *J* 3.0 and 1.0 Hz, OH), 3.06 (1H, td, *J* 10.0 and 6.5 Hz, NC*H*H), 2.43 (3H, s, CH_3), 2.16-2.04 (1H, m), 1.95-1.87 (1H, m), 1.81-1.67 (2H, m); δ_c (100.5 MHz, $CDCl_3$) 143.7, 136.0, 127.6, 127.2, 84.0, 47.6, 33.9, 23.0, 21.5.

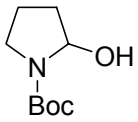
***tert*-Butyl-*N*-(4-hydroxybutyl) carbamate**[5]



To a solution of 4-amino-butanol (0.5 g, 5.6 mmol), triethylamine (3.9 mL, 28.0 mmol) in methanol (20 mL) was added Boc anhydride (1.8 g, 8.4 mmol) at 0 ^oC. Once the reaction was judged complete by TLC, the solvent was removed and CH_2Cl_2 (20 mL) and H_2O (20 mL) were added. The layers were separated and the organic layer was consecutively washed with H_2O (20 mL), $NaHCO_3$ (20 mL), water (20 mL), and dried ($MgSO_4$). The

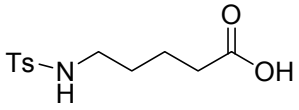
solvents were removed in vauo to give the product as a colourless oil[5] which was used without further purification (0.76 g, 72 %); δ_H (400 MHz, $CDCl_3$) 5.09 (1H, br s, NH), 3.69 (1H, br s, OH), 3.40 (2H, t, *J* 6.5 Hz, C*H*$_2$OH), 2.91 (2H, m, CH_2N), 1.45-1.31 (4H, m, CH_2CH_2), 1.22 (9H, s, 3 × CH_3); δ_c (100.5 MHz, $CDCl_3$) 156.2, 78.5, 61.7, 40.2, 29.6, 28.5, 28.3.

tert-Butyl 2-hydroxy-1-pyrrolidinecarboxylate[6]



To a solution of oxalyl chloride (0.25 ml, 2.86 mmol) in anhydrous CH_2Cl_2 (10 ml) at -78 ^oC anhydrous DMSO (0.37 ml, 5.20 mmol) was then added drop-wise over a period of 5 min and the reaction mixture was stirred at -78 ^oC for 10 min. A solution of *tert*-butyl-*N*-(4-hydroxybutyl) carbamate (0.50 g, 2.60 mmol) in CH_2Cl_2 (20 ml) was added drop-wise over 5 min and a pale yellow precipitate was formed. The reaction mixture was then warmed until the precipitate dissolved, cooled to -78 ^oC and stirred for 10 min. Triethylamine (1.81 ml, 13.00 mmol) was then added, and the reaction was warmed to room temperature. H_2O (20 mL) was then added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layers were dried ($MgSO_4$) and the solvents were removed in vacuo. The resulting product was purified by column chromatography, eluting with 7:3 pet. ether : EtOAc to give the product as a colourless oil[6] (0.38 g, 71 %); δ_H (400 MHz, $CDCl_3$) 5.48-5.21 (1H, m, NC*H*OH), 3.80 (1H, br s, OH), 3.58-3.42 (1H, m, NCH*H*), 3.35-3.12 (1H, m, NC*H*H), 2.16-1.72 (4H, m, CH_2CH_2), 1.50 (9H, s, 3 × CH_3); δ_c (100.5 MHz, $CDCl_3$) 154.9, 81.7, 79.9, 45.9, 32.7, 28.5, 21.8.

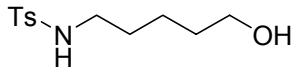
5-(Toluene-4-sulfonylamino)-pentanoic acid[7]



To a solution of 5-aminovaleric acid (14.0 g, 0.12 mol) in water (150 mL), was added solid NaOH (10.0 g, 0.28 mol) followed by tosyl chloride (23.0 g, 0.12 mol) into portions over 15 minutes. The reaction mixture was then heated to 90 ^oC and stirred for 3 h. After

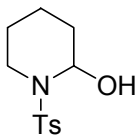
cooling to room temperature, the pH was adjusted to 5 with HCl (6N). The resulting precipitate was then filtered, washed with water, and dried to afford the product as a white solid [6] (30.5 g, 94%); mp 91-93 °C [lit., [7] 95 °C]; δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.3 Hz, ArH), 7.21 (2H, d, *J* 8.3 Hz, ArH), 4.95 (1H, t, *J* 6.5 Hz, NH), 2.96 (2H, q , *J* 6.5 Hz, NCH_2), 2.46 (3H, s, CH_3), 2.34 (2H, t, *J* 7.0 Hz, CH_2CO_2H), 1.66-1.59 (2H, m, CH_2), 1.57-1.50 (2H, m, CH_2).

_N_-(5-Hydroxy-pentyl)-4-methyl-benzenesulfonamide[8]



To a solution of 5-(toluene-4-sulfonylamino)-pentanoic acid (0.70 g, 2.6 mmol) in THF (15 mL) at -10 °C was added triethylamine (0.36 mL, 2.6 mmol) followed by ethyl chloroformate (0.25 mL, 2.6 mmol).[8] After 10 min, $NaBH_4$ (294 mg, 7.8 mmol) was added in one portion followed by MeOH (30 mL) dropwise to the reaction mixture over 10 min at 0 °C. The solution was stirred for additional 10 min and then neutralised with HCl (1N). The solvent was evaporated and the product was extracted with EtOAc (3 × 20 mL). The organic layer was washed consecutively with HCl (1N, 20 mL), H_2O (20 mL), $NaHCO_3$ (5%, 20 mL), H_2O (20 mL) and the organic layer was dried ($MgSO_4$). The solvent was evaporated to yield the product as a yellow oil [8] (0.45 g, 68%): δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.3 Hz, ArH), 7.35 (2H, d, *J* 8.3 Hz, ArH), 5.91 (1H, t, *J* 6.5 Hz, NH), 3.59 (2H, t, *J* 6.5 Hz, CH_2OH), 3.10 (1H, br s, OH), 2.73 (2H, q , *J* 6.5 Hz, NCH_2), 2.44 (3H, s, CH_3), 1.56-1.47 (4H, m, 2 × CH_2), 1.43-1.34 (2H, m, CH_2); δ_c (100.5 MHz, $CDCl_3$) 143.1, 137.1, 129.6, 129.6, 62.0, 43.0, 31.9, 29.1, 22.7, 21.4.

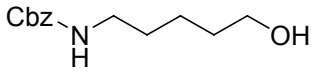
1-(Toluene-4-sulfonyl)-piperidin-2-ol



To a solution of oxalyl chloride (0.11 ml, 1.16 mmol) in anhydrous CH_2Cl_2 (5 ml) at -78 ° C was added anhydrous DMSO (0.08 ml, 2.10 mmol) drop-wise over 5 min. The reaction mixture was then stirred at -78 °C for 10 min. *N*-(5-Hydroxy-pentyl)-4-methyl-

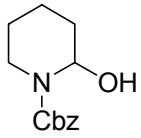
benzenesulfonamide (0.27 g, 1.05 mmol) dissolved in CH_2Cl_2 (10 ml) was then added drop-wise over 5 min and a pale yellow precipitate then formed. The reaction mixture was warmed until the precipitate dissolved, then cooled to -78 ^{o} C and stirred for 10 min. Triethylamine (0.77 ml, 5.50 mmol) was added and the reaction was warmed to room temperature. H_2O was added and the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography, eluting with 6:4 pet. ether : EtOAc to give product as an oil (0.19 g, 72%); δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.3 Hz, ArH), 7.30 (2H, d, *J* 8.3 Hz, ArH), 5.56 (1H, m, NCH), 3.57 (1H, ddd, J 12.2, 4.5 and 2.5 Hz, NC*H*H), 3.11 (1H, td, *J* 12.2 and 2.9 Hz, NC*H*H), 2.54 (1H, dd, *J* 3.5 and 1.5 Hz, OH), 2.44 (3H, s, CH_3), 1.79-1.67 (2H, m, CH_2), 1.66-1.46 (4H, m, 2 × CH_2); δ_c (100.5 MHz, $CDCl_3$) 143.6, 137.0, 129.8, 127.3, 77.1, 40.1, 31.4, 24.9, 21.6, 17.3.

_N_-Benzyloxycarbonyl-5-aminopentan-1-ol[10]



To a solution of 5-aminopentan-1-ol (4.00 g, 39.0 mmol) in aqueous NaOH (1 N, 43.0 mmol) at 0 ^{o}C was added benzylchloroformate (6.14 ml, 43.0 mmol) drop-wise. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. After the solvents were removed in vacuo, the crude product was recrystallised from EtOAc and pet. Ether[10] (7.59 g, 82%); mp 43-44 ^{0}C [Lit.,[9] mp 45-46 ^{0}C (Pet. ether, EtOAc)]; δ_H (400 MHz, $CDCl_3$) 7.39-7.26 (5H, m, ArH), 5.07 (2H, s, CH_2Ph), 4.78 (1H, br s, NH), 3.58 (2H, t, *J* 6.5 Hz, C*H*$_2$OH), 3.16 (2H, m, NHC*H*$_2$), 2.48 (1H, br s, OH), 1.58-1.36 (6H, m, $CH_2CH_2CH_2$).

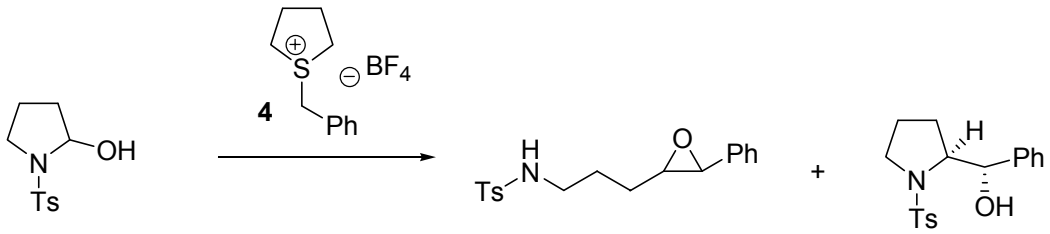
_N_-Benzyloxycarbonyl-2-hydroxypiperidine[10]



To a solution of oxalyl chloride (0.61 ml, 6.95 mmol) in CH_2Cl_2 (25 ml) at -78 ^{o}C was added anhydrous DMSO (0.90 ml, 12.60 mmol) drop-wise over 5 min. The reaction mixture was stirred at -78 ^{o}C for 10 min. *N*-Benzyloxycarbonyl-5-aminopentan-1-ol (1.50 g, 6.32

mmol) in CH_2Cl_2 (60 ml) was added drop-wise over 5 min and a pale yellow precipitate formed. The reaction mixture was warmed until the precipitate dissolved and then cooled to -78 ^{o} C and stirred for 10 min. Triethylamine (4.41 ml, 31.60 mmol) was added, the reaction was warmed to room temperature and H_2O (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were removed in vacuo. The crude product was purified by column chromatography, eluting with 6:4 pet. ether : EtOAc to give the product as an oil[10] (1.04 g, 70%); δ_H (400 MHz, $CDCl_3$) 7.28-7.17 (5H, m, Ar*H*), 5.70 (1H, m, C*H*OH), 5.03 (2H, s, CH_2Ph), 3.81 (1H, br d, CHO*H*), 3.10 (2H, t, *J* 10.5 Hz, NCH_2), 1.79-1.30 (6H, m, $CH_2CH_2CH_2$); δ_C (101 MHz; $CDCl_3$) 154,.3, 136.4, 128.6, 127.8, 127.7, 74.5, 62.1, 45.9, 31.8, 24.5, 18.3.

Reaction of hemiaminal 3 with achiral sulfonium salt 4



3 **6** **7**

To a solution of 1-[(4-methylphenyl)sulfonyl]-2-pyrrolidinol **3** (0.15 g, 0.62 mmol) and 1-benzyl-tetrahydro-thiophenium tetrafluoroborate **4** (0.18 g, 0.68 mmol) in CH_2Cl_2 (3 mL) at 0 ^{o}C was added P_2 base (0.41 mL, 1.24 mmol). The reaction mixture was then stirred for 3 hours at 0 ^{o}C. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), and dried ($MgSO_4$). The solvents were removed in vacuo and the resultant residue was purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to give:

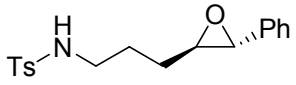
4-methyl-*N*-[3-(3-phenyl-oxiranyl)-propyl]-benzenesulfonamide **(6)** as white solid (111 mg, 54 %); R_f (EtOAc : pet. ether, 4:6) 0.50; mp 74-75 °C; IR (film) 3276, 3058, 1496, 1328, 1157, 815 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.3 Hz, ArH), 7.35-7.21 (5H, m, ArH), 7.19 (2H, dd, *J* 8.3 and 1.5 Hz, ArH), 5.06 (1H, t, *J* 6.0 Hz, NH), 3.57 (1H, d, *J* 1.9 Hz, OCHPh), 3.01 (2H, m, NCH_2), 2.88 (1H, ddd, *J* 6.3, 4.4 and 1.9 Hz, C*H*OCHPh), 2.40 (3H, s, CH_3), 1.80 (1H, m, C*H*HCH_2), 1.69-1.59 (2H, m, C*H*HC*H*H), 1.57 (1H, m, C*H*HCH_2); δ_c

(100.5 MHz, $CDCl_3$) 143.4, 137.4, 137.3, 129.8, 128.5, 128.2, 127.1, 125.6, 62.2, 58.9, 42.8, 29.3, 26.2, 21.5;MS (CI): *m*/*z* (%) 332 (MH^+, 32%), 314 (M^+-H_2O, 74%), 161 (M^+-Tos-O, 100%) and 155 (Tos, 10 %); HRMS (CI) found 332.1320. $C_{18}H_{22}NO_3S$ requires 332.1320 (Found: C, 65.10%; H, 6.51%; N, 4.21%. $C_{18}H_{21}NO_3S$ requires C, 65.23%; H, 6.39%; N, 4.23%).

Depending on the reaction conditions a mixture of *trans*: *cis* epoxides was sometimes isolated; *cis* isomer: δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.3 Hz, ArH), 7.35-7.21 (5H, m, ArH), 7.21-7.19 (2H, m, ArH), 4.61 (1H, t, *J* 6.3 Hz, NH), 4.06 (1H, d, *J* 4.3 Hz, OCHPh), 3.17 (1H, ddd, *J* 6.8, 5.8 and 4.3 Hz, C*H*OCHPh), 2.89 (2H, m, NCH_2) 2.41 (3H, s, CH_3), 1.70-1.50 (4H, m, CH_2CH_2); δ_c (100.5 MHz, $CDCl_3$) 143.4, 137.4, 137.3, 129.8, 128.5, 128.2, 127.1, 125.6, 58.5, 57.5, 42.7, 26.2, 24.2, 21.5.

Phenyl-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]-methanol **(7)** as a colourless oil (37 mg, 18 %); R_f (EtOAc : pet. ether, 4:6) 0.46; IR (film) 3495, 1494, 1334, 1154, 816 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.3 Hz, ArH), 7.47-7.23 (7H, m, ArH), 4.65 (1H, dd, *J* 8.0 and 2.4 Hz, C*H*OH), 3.87 (1H, d, *J* 2.4 Hz, OH), 3.82 (1H, td, *J* 8.0 and 2.5 Hz, NC*H*CHOH), 3.47-3.26 (2H, m, NCH_2), 2.44 (3H, s, CH_3), 1.56-1.42 (2H, m, CH_2), 1.40-1.10 (2H, m, CH_2); δ_c (100.5 MHz, $CDCl_3$) 143.8, 140.8, 134.0, 129.9, 128.4, 127.7, 127.4, 125.6, 76.2, 66.2, 49.8, 28.0, 24.1, 21.6; MS (CI) *m*/*z* (%) 332 (MH^+, 18%), 314 (M^+-H_2O, 100%), 224 (M^+-Tos-H_2O, 67%) and 176 (M^+-Tos, 20 %); HRMS (CI) found 332.1324. $C_{18}H_{22}NO_3S$ requires 332.1320; (Found: C, 65.10%; H, 6.52%; N, 4.17%. $C_{18}H_{21}NO_3S$ requires C, 65.23%; H, 6.39%; N, 4.23%).

(*R*,*R*)-4-methyl-*N*-[3-(3-phenyl-oxiranyl)-propyl]-benzenesulfonamide (6)

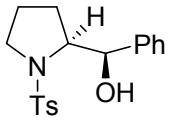


6

To a solution of 1-[(4-methylphenyl)sulfonyl]-2-pyrrolidinol **3** (0.15 g, 0.62 mmol) and chiral sulfonium salt **10** (0.29 g, 0.68 mmol) in CH_2Cl_2 (3 mL) at 0 ^oC was added P_2 base (0.41 mL, 1.24 mmol). The reaction mixture was then stirred for 3 hours at 0 ^oC. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), and dried ($MgSO_4$). The solvents were removed in vacuo and the resultant residue was purified by column chromatography, eluting with 3:2 pet.

ether : EtOAc to give **6** as white solid (111 mg, 54 %); R_f (EtOAc : pet. ether, 4:6) 0.50; mp 77-79 °C; IR (film) 3276, 3058, 1496, 1328, 1157, 815 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.3 Hz, ArH), 7.35-7.21 (5H, m, ArH), 7.19 (2H, dd, *J* 8.3 and 1.5 Hz, ArH), 5.06 (1H, t, *J* 6.0 Hz, NH), 3.57 (1H, d, *J* 1.9 Hz, OCHPh), 3.01 (2H, m, NCH_2), 2.88 (1H, ddd, *J* 6.3, 4.4 and 1.9 Hz, C*H*OCHPh), 2.40 (3H, s, CH_3), 1.80 (1H, m, C*H*HCH_2), 1.69-1.59 (2H, m, C*H*HC*H*H), 1.57 (1H, m, C*H*HCH_2); δ_c (100.5 MHz, $CDCl_3$) 143.4, 137.4, 137.3, 129.8, 128.5, 128.2, 127.1, 125.6, 62.2, 58.9, 42.8, 29.3, 26.2, 21.5;MS (CI): *m*/*z* (%) 332 (MH^+, 32%), 314 (M^+-H_2O, 74%), 161 (M^+-Tos-O, 100%) and 155 (Tos, 10 %); HRMS (CI) found 332.1320. $C_{18}H_{22}NO_3S$ requires 332.1320 (Found: C, 65.10%; H, 6.51%; N, 4.21%. $C_{18}H_{21}NO_3S$ requires C, 65.23%; H, 6.39%; N, 4.23%); $[\alpha]_D^{23}$ + 180 (*c*. 0.2, CH_2Cl_2). The *ee* for the chiral compound (94% *ee*) was measured by chiral HPLC using a Chiralcel OJ chiral column eluting with 95:5 hexane:isopropanol with a flow rate of 1 ml/min at room temperature (t_{RR} (major= 18.8 min, t_{SS} (minor)= 26.3 min).

Phenyl-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]-methanol (8)



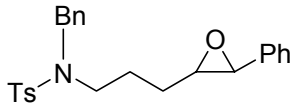
To a solution of 1-[(4-methylphenyl)sulfonyl]-2-pyrrolidinol **3** (0.15 g, 0.62 mmol) and 1-benzyl-tetrahydro-thiophenium tetrafluoroborate **4** (0.18 g, 0.68 mmol) in THF (3 mL) at 0 °C was added P_2 base (0.41 mL, 1.24 mmol). The reaction mixture was left stirring for 18 h at 0 °C. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude material was purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to give the product as white solid (0.18 g, 89 %), R_f (EtOAc : pet. ether, 4:6) 0.43; mp 123-124 °C, IR (film) 3337, 1466, 1378, 1160, 816 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.3 Hz, ArH), 7.42-7.30 (5H, m, ArH), 7.29-7.24 (2H, m, ArH), 5.24 (1H, dd, *J* 5.3 and 4.2 Hz, C*H*OH), 3.81 (1H, ddd, *J* 8.2, 5.3 and 2.6 Hz, NC*H*CHOH), 3.38-3.24 (2H, m, NCH_2), 3.06 (1H, d, *J* 4.2 Hz, OH), 2.44 (3H, s, CH_3), 1.91-1.81 (1H, m, C*H*H), 1.61-1.53 (1H, m, C*H*HCH_2), 1.36-1.18 (2H, m, CH*H*); δ_c (100.5 MHz, $CDCl_3$) 143.9, 140.7, 133.9, 129.9, 128.3, 127.7, 127.4, 126.2, 75.0, 66.0, 50.6, 25.8, 24.5, 21.6; Ms (CI) *m*/*z* (%) 332 (MH^+, 16 %), 314 (M^+-H_2O, 100 %), 161 (M^+-Tos-O, 100 %) and 155 (Tos, 10 %); HRMS

(CI) found 332.1318. $C_{18}H_{22}NO_3S$ requires 332.1320; (Found: C, 65.12%; H, 6.48%; N, 4.15%. $C_{18}H_{21}NO_3S$ requires C, 65.23%; H, 6.39%; N, 4.23%).

(*S*)-*α*-(*R*)-Phenyl-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]-methanol (8)

To a solution of 1-[(4-methylphenyl)sulfonyl]-2-pyrrolidinol **3** (0.15 g, 0.62 mmol) and chiral sulfonium salt **10** (0.29 g, 0.68 mmol) in THF (3 mL) at 0 ^oC was added P_2 base (0.41 mL, 1.24 mmol). The reaction mixture was left stirring for 18 h at 0 ^oC. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude material was purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to give the product as white solid (0.16 g, 79 %), R_f (EtOAc : pet. ether, 4:6) 0.43; mp 120-121 °C, IR (film) 3337, 1466, 1378, 1160, 816 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.3 Hz, ArH), 7.42-7.30 (5H, m, ArH), 7.29-7.24 (2H, m, ArH), 5.24 (1H, dd, *J* 5.3 and 4.2 Hz, C*H*OH), 3.81 (1H, ddd, *J* 8.2, 5.3 and 2.6 Hz, NC*H*CHOH), 3.38-3.24 (2H, m, NCH_2), 3.06 (1H, d, *J* 4.2 Hz, OH), 2.44 (3H, s, CH_3), 1.91-1.81 (1H, m, C*H*H), 1.61-1.53 (1H, m, C*H*HCH$_2$), 1.36-1.18 (2H, m, CH*H*); δ_c (100.5 MHz, $CDCl_3$) 143.9, 140.7, 133.9, 129.9, 128.3, 127.7, 127.4, 126.2, 75.0, 66.0, 50.6, 25.8, 24.5, 21.6; Ms (CI) *m*/*z* (%) 332 (MH^+, 16 %), 314 (M^+-H_2O, 100 %), 161 (M^+-Tos-O, 100 %) and 155 (Tos, 10 %); HRMS (CI) found 332.1318. $C_{18}H_{22}NO_3S$ requires 332.1320; (Found: C, 65.12%; H, 6.48%; N, 4.15%. $C_{18}H_{21}NO_3S$ requires C, 65.23%; H, 6.39%; N, 4.23%); $[\alpha]_D^{23}$ - 116 (*c*. 1.0, CH_2Cl_2). The *ee* for the chiral compound (94% *ee*) was measured by chiral HPLC using a Chiralcel OJ chiral column eluting with 90:10 hexane:isopropanol with a flow rate of 1 ml/min at room temperature (t_{SR} (major)= 19.2 min, t_{RS} (minor)= 27.8 min).

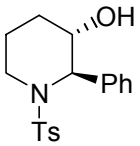
***N*-Benzyl-4-methyl-N-[3-(3-phenyl-oxiranyl)-propyl]-benzenesulfonamide (9)**



By-products of the epoxidation reaction, isolated as mixtures of *trans* : *cis* (2:1) R_f (EtOAc : pet. ether, 4:6) 0.69; IR (film)/ 3056, 1496, 1336, 1158, 815 cm^{-1} ; <u>*trans* isomer</u> : δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.3 Hz, ArH), 7.40-7.20 (10H, m, ArH), 7.15 (2H, d, *J* 8.3 Hz, ArH), 4.32 (1H, d, *J* 14.6 Hz, NC*H*HPh), 4.28 (1H, d, *J* 14.6 Hz, NC*H*HPh), 3.42 (1H, d,

J 1.9 Hz, OCHPh), 3.15 (2H, t, *J* 5.9 Hz, NCH_2), 2.71 (1H, td, *J* 5.4 and 1.9 Hz, C*H*OCHPh), 2.44 (3H, s, CH_3), 1.66-1.20 (4H, m, 2 × CH_2); δ_c (100.5 MHz, $CDCl_3$) 143.9, 137.9, 136.2, 136.0, 129.8, 128.6, 128.6, 128.5, 128.4, 128.1, 127.2, 125.6, 62.2, 58.3, 52.2, 48.1, 29.5, 24.7, 21.7; <u>*cis* isomer</u> : δ_H (400 MHz, $CDCl_3$) 7.69 (2H, d, *J* 8.3 Hz, ArH), 7.40-7.20 (10H, m, ArH), 7.15 (2H, d, *J* 8.3 Hz, ArH), 4.21 (1H, d, *J* 14.6 Hz, NC*H*HPh), 4.13 (1H, d, *J* 14.6 Hz, NC*H*HPh), 3.97 (1H, d, *J* 3.9 Hz, OCHPh), 2.98 (3H, m, NCH_2 and C*H*OCHPh), 2.44 (3H, s, CH_3), 1.66-1.20 (4H, m, 2 × CH_2); δ_c (100.5 MHz, $CDCl_3$) 143.9, 137.9, 136.2, 136.0, 129.8, 128.6, 128.6, 128.5, 128.4, 128.1, 127.2, 125.6, 58.4, 57.3, 51.9, 47.8, 29.5, 24.6, 21.7.

trans-2-Phenyl-1-(toluene-4-sulfonyl)-piperidin-3-ol (12)



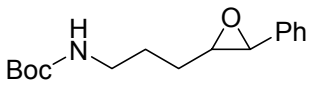
To a solution of 4-methyl-N-[3-(3-phenyl-oxiranyl)-propyl]-benzenesulfonamide **6** (0.070 g, 0.70 mmol) in CH_2Cl_2 (3 mL) at room temperature was added trimethylsilyl trifluoromethanesulfonate (0.040 g, 0.70 mmol). After 48 h the reaction was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 10 mL). The combined organic layers were washed with brine (920 mL), dried ($MgSO_4$) and the solvents were removed in vacuo. The crude product purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to give the product as white solid (67 mg, 98 %), R_f (EtOAc : pet. ether, 4:6) 0.32; mp 152-153 °C; IR (film) 1595, 1496, 1338, 1159, 815 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.3 Hz, ArH), 7.48-7.16 (7H, m, ArH), 5.18 (1H, br s, NCHPh), 4.43 (1H, m, C*H*OH), 3.75 (1H, m, NC*H*H), 3.15 (1H, td, *J* 12.7 and 3.2 Hz, NC*H*H), 2.44 (3H, s, CH_3), 2.25 (1H, d, *J* 6.6 Hz, OH), 1.87-1.71 (1H, m, C*H*H), 1.70-1.60 (2H, m, C*H*HC*H*H), 1.59-1.50 (1H, m, C*H*H); δ_c (100.5 MHz, $CDCl_3$) 143.9, 138.2, 137.9, 129.5, 128.7, 128.6, 127.3, 126.8, 67.5, 62.3, 41.7, 25.7, 21.5, 18.5; MS (CI) *m*/*z* (%) 332 (MH^+, 92%), 314 (M^+-H_2O, 100%), 176 (M^+-Tos, 92%) and 161 (M^+-Tos-O, 98%); HRMS (CI) found 332.1324. $C_{18}H_{22}NO_3S$ requires 332.1320.

(*2R, 3S*)-2-Phenyl-1-(toluene-4-sulfonyl)-piperidin-3-ol (12)

To a solution of (*R, R*)-4-methyl-N-[3-(3-phenyl-oxiranyl)-propyl]-benzenesulfonamide **6** (0.070 g, 0.70 mmol) in CH_2Cl_2 (3 mL) at room temperature was added trimethylsilyl trifluoromethanesulfonate (0.040 g, 0.70 mmol). After 48 h the reaction

was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 10 mL). The combined organic layers were washed with brine (920 mL), dried ($MgSO_4$) and the solvents were removed in vacuo. The crude product purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to give the product as white solid (69 mg, 100 %), R_f (EtOAc : pet. ether, 4:6) 0.32; mp 156-158 °C; IR (film) 1595, 1496, 1338, 1159, 815 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.3 Hz, ArH), 7.48-7.16 (7H, m, ArH), 5.18 (1H, br s, NCHPh), 4.43 (1H, m, C*H*OH), 3.75 (1H, m, NC*H*H), 3.15 (1H, td, *J* 12.7 and 3.2 Hz, NC*H*H), 2.44 (3H, s, CH_3), 2.25 (1H, d, *J* 6.6 Hz, OH), 1.87-1.71 (1H, m, C*H*H), 1.70-1.60 (2H, m, C*H*HC*H*H), 1.59-1.50 (1H, m, C*H*H); δ_c (100.5 MHz, $CDCl_3$) 143.9, 138.2, 137.9, 129.5, 128.7, 128.6, 127.3, 126.8, 67.5, 62.3, 41.7, 25.7, 21.5, 18.5; MS (CI) *m*/*z* (%) 332 (MH^+, 92%), 314 (M^+-H_2O, 100%), 176 (M^+-Tos, 92%) and 161 (M^+-Tos-O, 98%); HRMS (CI) found 332.1324. $C_{18}H_{22}NO_3S$ requires 332.1320; $[\alpha]_D^{23}$ – 33 (*c*. 0.6, CH_2Cl_2). The *ee* for the chiral compound (93% *ee*) was measured by chiral HPLC using a Chiralcel OD chiral column eluting with 96.5:3.5 hexane:isopropanol with a flow rate of 1 ml/min at room temperature (t_{SR} (minor)= 45.8 min, t_{RS} (major)= 62.3 min).

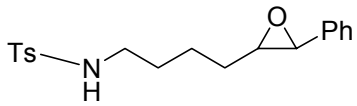
[3-(3-Phenyl-oxiranyl)-propyl]-carbamic acid *tert*-butyl ester



To a solution of *tert*-butyl 2-hydroxy-1-pyrrolidinecarboxylate (0.15 g, 0.80 mmol) and 1-benzyl-tetrahydro-thiophenium tetrafluoroborate (0.23 g, 0.88 mmol) in CH_2Cl_2 (4 mL) at 0 ^oC was added P_2 base (0.53 mL, 1.60 mmol). The reaction mixture was monitored by TLC and after completion the reaction was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and the solvents were removed in vacuo. The crude product was then purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to give the product as a mixture of *trans*:*cis* mixture (5:1) in the form of a colourless oil (31 mg, 14 %), R_f (EtOAc : pet. ether, 4:6) 0.55; IR (film) 2253, 1686, 1393, 1367, 1253, 903 cm^{-1}; *trans* isomer : δ_H (400 MHz, $CDCl_3$) 7.39-7.22 (5H, m, ArH), 4.65 (1H, br s, NH), 3.63 (1H, d, *J* 2.0 Hz, OCHPh), 3.31-3.20 (2H, m, NCH_2), 2.96 (1H, td, *J* 4.4 and 2.0 Hz, C*H*OCHPh), 2.00-1.63 (4H, m, CH_2CH_2), 1.45 (9H, s, 3 × CH_3); δ_c (100.5 MHz, $CDCl_3$) 156.0, 137.6, 128.5, 128.1, 125.1, 80.2, 62.6, 58.6, 40.2, 29.6, 28.6, 28.5; *cis* isomer: δ_H (400 MHz, $CDCl_3$) 7.39-7.22 (5H, m,

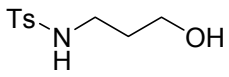
ArH), 4.40 (1H, br s, NH), 4.05 (1H, d, *J* 4.2 Hz, OCHPh), 3.10-2.97 (3H, m, NCH_2 and C*H*OCHPh), 2.00-1.63 (4H, m, CH_2CH_2), 1.45 (9H, s, 3 × CH_3); δ_c (100.5 MHz, $CDCl_3$) 156.0, 135.8, 128.5, 128.1, 125.1, 79.8, 58.9, 57.9, 40.2, 29.6, 28.6, 28.5; MS (CI) *m*/*z* (%) 278 (MH^+, 23%), 222 (M^+- $C(CH_3)_3$, 55%), 178 (M^+- Boc, 29%) and 170 (M^+- $PhCH_2O$, 100%); HRMS (CI) found 278.1746. $C_{16}H_{24}NO_3$ requires 278.1756.

4-Methyl-N-[4-(3-phenyl-oxiranyl)-butyl]-benzenesulfonamide



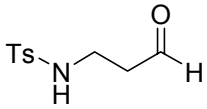
To a solution of 1-(toluene-4-sulfonyl)-piperidin-2-ol (0.13 g, 0.51 mmol) and 1-benzyl-tetrahydro-thiophenium tetrafluoroborate (0.15 g, 0.56 mmol) in THF (2 mL) at 0 ^oC was added P_2 base (0.34 mL, 1.02 mmol). After completion the reaction was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and the solvents were removed in vacuo. The crude material was then purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to give the product as a *trans* : *cis* mixture (1.5:1) in the form of a colourless oil (58 mg, 33 %), R_f (EtOAc : pet. ether, 4:6) 0.52; <u>*trans* isomer</u> : δ_H (400 MHz $CDCl_3$) 7.74 (2H, d, *J* 8.3 Hz, ArH), 7.39-7.17 (7H, m, ArH), 4.92 (1H, t, *J* 6.3 Hz, NH), 3.56 (1H, d, *J* 2.0 Hz, OCHPh), 2.96 (2H, q, *J* 6.3 Hz, NCH_2), 2.85 (1H, td, *J* 6.3 and 2.0 Hz, C*H*OCHPh), 2.44 (3H, s, CH_3), 1.72-1.45 (4H, m, 2 × CH_2), 1.42-1.34 (2H, m, CH_2); δ_c (100.5 MHz, $CDCl_3$) 143.9, 137.8, 137.4, 129.7, 128.5, 128.1, 127.1, 126.4, 62.7, 58.5, 43.0, 31.7, 29.3, 23.0, 21.6; <u>*cis* isomer</u>: δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.3 Hz, ArH), 7.39-7.17 (7H, m, ArH), 4.72 (1H, t, *J* 6.3 Hz, NH), 4.04 (1H, d, *J* 4.4 Hz, OCHPh), 3.12 (1H, td, *J* 5.9 and 4.4 Hz, C*H*OCHPh), 2.83-2.76 (2H, m, NCH_2) 2.44 (3H, s, CH_3), 1.72-1.45 (6H, m, 3 × CH_2); δ_c (100.5 MHz, $CDCl_3$) 143.9, 138.7, 135.7, 129.7, 128.1, 127.1, 126.4, 125.6, 59.1, 57.4, 42.9, 29.3, 26.1, 23.0, 21.6.

N-1-(3-Hydroxypropyl)-4-methyl-1-benzenesulfonamide[11]



To a solution of 3-aminopropan-1-ol (5.00 g, 66.0 mmol), triethylamine (18.56 g, 133.0 mmol) in $CHCl_3$ (10 mL) at 0 °C under nitrogen was added a solution of *p*-toluenesulfonyl chloride (13.84 g, 72.6 mmol) in $CHCl_3$ (15 mL) drop-wise over 10 min. After 1 h the reaction mixture warmed to room temperature and stirred for a further 18 h. The reaction was quenched with aqueous $NaHCO_3$ (5%, 25 mL) and EtOAc (50 mL) was added. The organic layer was separated and washed with aqueous citric acid solution (5%, 2 × 20 mL), H_2O (2 × 20 mL), aqueous $NaHCO_3$ (5%, 2 × 20 mL) and brine (1 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to give the product as a colourless oil [11] (13.76 g, 91%); IR (film) 3500, 3276, 2948, 2881, 1317,1151 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.0 Hz, ArH), 7.31 (2H, d, *J* 8.0 Hz, ArH), 5.23 (1H, t, *J* 6.0 Hz, NH), 3.72 (2H, q, *J* 6.0 Hz, NCH_2), 3.08 (2H, q, *J* 6.0 Hz, CH_2OH), 2.42 (3H, s, CH_3), 2.13 (1H, t, *J* 6.0 Hz, OH), 1.70 (2H, quin., *J* 6.0 Hz, CH_2).

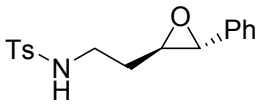
N-1-(3-Oxopropyl)-4-methyl-1-benzenesulfonamide (13)



To a solution of oxalyl chloride (1.66 g, 13.1 mmol) in anhydrous CH_2Cl_2 (6 mL) at − 78 °C under nitrogen was added anhydrous DMSO (3.10 mL, 43.7 mmol) in CH_2Cl_2 (2 mL) drop-wise over 3 min and the reaction mixture stirred for a further 30 min at −78 °C. A solution of *N*-1-(3-hydroxypropyl)-4-methyl-1-benzenesulfonamide (2.00 g, 8.7 mmol) in anhydrous CH_2Cl_2 (8 mL) was then added drop-wise over 3 min and stirred for a further 50 min. Diisopropylamine (10.6 mL, 61.0 mmol) was then added and the reaction mixture was allowed to warm to 0 °C over 30 min. The reaction was acidified with saturated aqueous citric acid (pH 5) and extracted with 1:1 Et_2O: EtOAc (3 × 30 mL). The combined organic layers were then washed with H_2O (2 × 30 mL), aqueous $NaHCO_3$ (2 × 30 mL) and brine (1 × 30 mL), and then dried ($MgSO_4$). The organic layers were then concentrated in vacuo and the residue was purified by column chromatography, eluting with 1:2 EtOAc : pet. ether followed

by 1:1 EtOAc : pet. ether to give the product as a yellow oil (1.26 g, 65%); IR (film) 1719, 1322, 1154 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.72 (1H, s, CHO), 7.74 (2H, d, *J* 8.0 Hz, ArH), 7.31 (2H, d, *J* 8.0 Hz, ArH), 5.11 (1H, m, NH), 3.20 (2H, q, *J* 6.0 Hz, NCH_2), 2.74 (2H, t, *J* 6.0 Hz, CH_2), 2.43 (3H, s, CH_3); δ_c (100.5 MHz, $CDCl_3$) 200.7, 143.7, 137.0, 129.9, 127.1, 43.7, 36.9, 21.5.

trans-4-Methyl-N-[2-(3-phenyl-oxiranyl)-ethyl]-benzenesulfonamide (14)



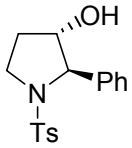
To a solution of *N*-1-(3-oxopropyl)-4-methyl-1-benzenesulfonamide **13** (0.15 g, 0.66 mmol) and 1-benzyl-tetrahydro-thiophenium tetrafluoroborate **4** (0.19 g, 0.72 mmol) in THF (3 mL) at 0 ^oC was added P_2 base (0.41 mL, 1.22 mmol). The reaction mixture was then stirred for 7 h at 0 ^oC, diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude material was purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to give the product as white solid (44 mg, 21 %), R_f (EtOAc : pet. ether, 4:6) 0.51; mp 123-124 °C; IR (film) 3343, 1496, 1378, 1160, 951, 896, 815 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.3 Hz, ArH), 7.38-7.27 (5H, m, ArH), 7.22-7.16 (2H, m, ArH), 4.95 (1H, t, *J* 6.3 Hz, NH), 3.59 (1H, d, *J* 2.4 Hz, OCHPh), 3.17 (2H, q, *J* 6.3 Hz, NCH_2), 2.95 (1H, ddd, *J* 6.3, 3.9 and 2.4 Hz, C*H*OCHPh), 2.44 (3H, s, CH_3), 2.12-1.97 (1H, m, C*H*H), 1.78-1.63 (1H, m, C*H*H); δ_c (100.5 MHz, $CDCl_3$) 143.6, 136.8, 136.8, 129.8, 128.6, 128.4, 127.2, 125.6, 60.8, 58.0, 40.5, 31.7, 21.6; MS (CI) *m*/*z* (%) 318 (MH^+, 64%), 300 (M^+-H_2O, 100%), 162 (M^+-Tos, 72%) and 155 (Tos, 10%); HRMS (CI) found 318.1171. $C_{17}H_{20}NO_3S$ requires 318.1163.

(*R, R*)-4-Methyl-N-[2-(3-phenyl-oxiranyl)-ethyl]-benzenesulfonamide (14)

To a solution of *N*-1-(3-oxopropyl)-4-methyl-1-benzenesulfonamide **13** (0.15 g, 0.66 mmol) and chiral sulfonium salt **10** (0.31 g, 0.72 mmol) in THF (3 mL) at 0 ^oC was added P_2 base (0.41 mL, 1.22 mmol). The reaction mixture was then stirred for 7 h at 0 ^oC, diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude

material was purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to give the product as white solid (44 mg, 21 %), R_f (EtOAc : pet. ether, 4:6) 0.51; mp 127-130 °C; IR (film) 3343, 1496, 1378, 1160, 951, 896, 815 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.3 Hz, ArH), 7.38-7.27 (5H, m, ArH), 7.22-7.16 (2H, m, ArH), 4.95 (1H, t, *J* 6.3 Hz, NH), 3.59 (1H, d, *J* 2.4 Hz, OCHPh), 3.17 (2H, q, *J* 6.3 Hz, NCH_2), 2.95 (1H, ddd, *J* 6.3, 3.9 and 2.4 Hz, C*H*OCHPh), 2.44 (3H, s, CH_3), 2.12-1.97 (1H, m, C*H*H), 1.78-1.63 (1H, m, C*H*H); δ_c (100.5 MHz, $CDCl_3$) 143.6, 136.8, 136.8, 129.8, 128.6, 128.4, 127.2, 125.6, 60.8, 58.0, 40.5, 31.7, 21.6; MS (CI) *m*/*z* (%) 318 (MH^+, 64%), 300 (M^+-H_2O, 100%), 162 (M^+-Tos, 72%) and 155 (Tos, 10%); HRMS (CI) found 318.1171. $C_{17}H_{20}NO_3S$ requires 318.1163; $[\alpha]_D^{23}$ + 29 (*c*. 0.4, CH_2Cl_2).The *ee* for the chiral compound (91% *ee*) was measured by chiral HPLC using a Chiralcel OD chiral column eluting with 97.5:2.5 hexane:isopropanol with a flow rate of 1 ml/min at room temperature (t_{RR} (major)= 127.5 min, t_{SS} (minor)= 138.3 min).

trans-2-Phenyl-1-(toluene-4-sulfonyl)-pyrrilidin-3-ol (15)

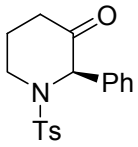


To a solution of *N*-1-(3-oxopropyl)-4-methyl-1-benzenesulfonamide **13** (0.15 g, 0.66 mmol) and 1-benzyl-tetrahydro-thiophenium tetrafluoroborate **4** (0.19 g, 0.72 mmol) in THF (3 mL) at 0 ^oC was added P_2 base (0.41 mL, 1.22 mmol). The reaction mixture was stirred for 8 h and then heated to reflux for 12 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude material was then purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to afford the product as white solid (149 mg, 71 %), R_f (EtOAc : pet. ether, 4:6) 0.40; mp 117-119 °C; IR (film) 1495, 1337, 1158, 1058, 814 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.3 Hz, ArH), 7.45-7.10 (7H, m, ArH), 4.67 (1H, br s, NCHPh), 4.13 (1H, m, C*H*OH), 3.71 (1H, td, *J* 9.5 and 2.4 Hz, NC*H*H), 3.51 (1H, dt, *J* 9.5 and 6.8 Hz, NC*H*H), 2.44 (3H, s, CH_3), 2.08-1.93 (1H, m, C*H*H), 1.84-1.66 (2H, m, C*H*H and OH); δ_c (100.5 MHz, $CDCl_3$) 143.5, 140.0, 134.1, 129.6, 128.5, 127.8, 127.5, 126.2, 78.7, 72.0, 46.9, 31.2, 21.6; MS (CI) *m*/*z* (%) 318 (MH^+, 62%), 300 (M^+-H_2O, 100%), 162 (M^+-Tos, 69%); HRMS (CI) found 318.1167. $C_{17}H_{20}NO_3S$ requires 318.1163.

(*2R, 3S*)-2-Phenyl-1-(toluene-4-sulfonyl)-pyrrilidin-3-ol (15)

To a solution of *N*-1-(3-oxopropyl)-4-methyl-1-benzenesulfonamide **13** (0.15 g, 0.66 mmol) and chiral sulfonium salt **10** (0.31 g, 0.72 mmol) in THF (3 mL) at 0 ^{o}C was added P_2 base (0.41 mL, 1.22 mmol). The reaction mixture was stirred for 8 h and then heated to reflux for 12 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude material was then purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to afford the product as white solid (149 mg, 71 %), R_f (EtOAc : pet. ether, 4:6) 0.40; mp 115-116 °C; IR (film) 1495, 1337, 1158, 1058, 814 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.3 Hz, ArH), 7.45-7.10 (7H, m, ArH), 4.67 (1H, br s, NCHPh), 4.13 (1H, m, C*H*OH), 3.71 (1H, td, *J* 9.5 and 2.4 Hz, NC*H*H), 3.51 (1H, dt, *J* 9.5 and 6.8 Hz, NC*H*H), 2.44 (3H, s, CH_3), 2.08-1.93 (1H, m, C*H*H), 1.84-1.66 (2H, m, C*H*H and OH); δ_c (100.5 MHz, $CDCl_3$) 143.5, 140.0, 134.1, 129.6, 128.5, 127.8, 127.5, 126.2, 78.7, 72.0, 46.9, 31.2, 21.6; MS (CI) *m*/*z* (%) 318 (MH^+, 62%), 300 (M^+-H_2O, 100%), 162 (M^+-Tos, 69%); HRMS (CI) found 318.1167. $C_{17}H_{20}NO_3S$ requires 318.1163; $[\alpha]_D^{23}$ - 256 (*c*. 0.25, CH_2Cl_2).

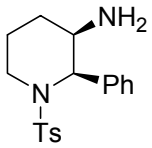
2-Phenyl-1-(toluene-4-sulfonyl)-piperidin-3-one (17)



To a solution of 2-phenyl-1-(toluene-4-sulfonyl)-piperidin-3-ol **12** (72 mg, 0.22 mmol) in CH_2Cl_2 (2.2 mL) at room temperature was added Dess Martin periodinane (0.420 g, 0.99 mmol) and the reaction mixture was stirred for 4 h. The reaction was quenched with aqueous $NaHCO_3$ (10 %, 5 mL) and the organic layer was separated. The aqueous layer was further extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and the solvents were removed in vacuo. The crude material was purified by column chromatography, eluting with 3:2 pet. ether : EtOAc to give the product as white solid (62 mg, 85 %); mp 152-154 ° C; IR (film) 1603, 1495, 1720, 1160, 815 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.3 Hz, ArH), 7.41-7.24 (7H, m, ArH), 5.57 (1H, s, NCHPh), 3.85 (1H, dt, *J* 14.0 and 5.0 Hz, NC*H*H), 3.46 (1H, ddd, *J* 14.0, 9.6 and 4.3 Hz, NC*H*H), 2.44

(3H, s, CH_3), 2.42-2.29 (2H, m, CH_2), 1.80-1.59 (2H, m, CH_2); δ_c (100.5 MHz, $CDCl_3$) 204.5, 143.9, 137.2, 134.1, 130.0, 129.2, 128.2, 127.1, 125.8, 66.8, 41.2, 36.8, 23.6, 21.6; MS (CI) *m*/*z* (%) 330 (MH^+, 100%), 252 (M^+-Ph, 19%), 174 (M^+-Tos, 100%) and 158 (M^+-Tos-NH_2, 46%); HRMS (CI) found 330.1165. $C_{18}H_{20}NO_3S$ requires 330.1164.

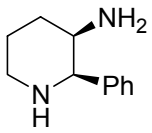
(*2R, 3R*)-3-Amino-2-Phenyl-1-(toluene-4-sulfonyl)-piperidine (19)



To a solution of 2-phenyl-1-(toluene-4-sulfonyl)-piperidin-3-one **17** (55 mg, 0.17 mmol) in pyridine (3.0 mL) at room temperature was added methoxyamine hydro chlorite (25 mg, 0.20 mmol) and the reaction mixture was stirred for 6 h. The reaction was quenched with aqueous NH_4Cl (10 %, 5 mL), and the resulting mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and the solvents were removed in vacuo. The residue was dissolved in THF (3 mL) and a solution of $BH_3.Me_2S$ (1 M, 1 mL) was added. The reaction mixture was heated to reflux for 15 h. MeOH (5 mL) was carefully added drop-wise followed by a solution of Et_2O.HCl (1 M, 3 mL). The reaction mixture was heated to reflux for 1 h and the solvents were removed in vacuo. The residue was dissolved in an aqueous solution of HCl (1 N, 15 mL) and extracted with Et_2O (3 × 15 mL). Ammonia in water was then added to the aqueous layer (~pH =12) and was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and the solvents were removed in vacuo. This afforded the product as a colourless oil (47 mg, 77 %); IR (film) 2986, 1495, 1151, 815 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30-7.14 (7H, m, ArH), 6.99 (2H, d, *J* 8.3 Hz, ArH), 5.11 (1H, d, *J* 6.2 Hz, NCHPh), 3.81 (1H, ddd, *J* 12.6, 3.3 and 2.0 Hz, NHC*H*H), 3.16 (1H, ddd, *J* 12.1, 6.2 and 4.1 Hz, C*H*NH_2), 3.09 (1H, td, *J* 12.6 and 3.5 Hz, NHC*H*H), 2.44 (3H, s, CH_3), 1.94-1.85 (1H, m, C*H*H), 1.84-1.70 (2H, m, C*H*HC*H*H), 1.65-1.55 (1H, m, C*H*H); δ_c (100.5 MHz, $CDCl_3$) 142.5, 136.7, 136.5, 130.0, 129.0, 128.2, 127.7, 127.0, 62.2, 51.3, 41.3, 28.3, 24.5, 21.4; MS (CI) *m*/*z* (%) 331 (MH^+, 78%), 314 (M^+-NH_2, 100%), 175 (M^+-Tos, 69%) and 160 (MH^+-Tos-NH_2, 47%); HRMS (CI) found 331.1479. $C_{18}H_{23}N_2O_2S$ requires 331.1480; $[\alpha]_D^{23}$ - 71 (*c*. 0.16, CH_2Cl_2). The *ee* for the chiral compound (89% *ee*) was measured by chiral HPLC using a Chiralcel OD

chiral column eluting with 98:2 hexane:isopropanol with a flow rate of 1 ml/min at room temperature (t_{SS} (minor)= 180.4 min, t_{RR} (major)= 195.2 min).

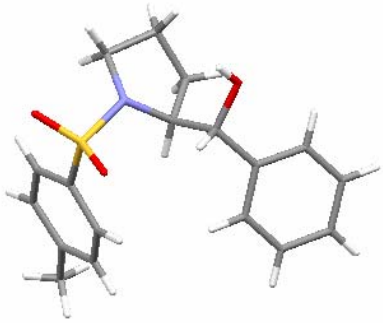
cis-3-Amino-2-Phenyl-piperidine (20)[12]



To a solution of naphthalene (0.52 g, 3.96 mmol) in 1,2-dimethoxy-ethane (5 mL) at room temperature was added finely chopped sodium metal (0.09 g, 3.60 mmol). The reaction was stirred for 2 h, during which a dark green solution appeared. 3-Amino-2-phenyl-1-(toluene-4-sulfonyl)-piperidine **19** (0.06 g, 0.18 mmol) in 1,2-dimethoxy-ethane (1.0 mL) was cooled to -78 ^{o}C. The Na-naphthalenide solution was added drop-wise to this reaction using a syringe, until a dark green colour persisted for 5 min. The reaction mixture was then left stirring for 1 h. The reaction was quenched at – 78 ^{o} C with 1-2 drops of water (to discharge the green colour) and diluted with Et_2O (15 mL). This afforded a cloudy suspension which was dried ($MgSO_4$), filtered and concetrated. Purification by column chromatography, eluting with 200 : 9 : 1 $CHCl_3$: MeOH : NH_3 gave the product as a colourless oil[12] (28 mg, 89 %); δ_H (400 MHz, $CDCl_3$) 7.34-7.21 (5H, m, ArH), 3.81 (1H, d, *J* 2.9 Hz, NCHPh), 3.17 (1H, m), 2.95 (1H, br dd, *J* 5.1 and 2.6 Hz), 2.74 (1H, td, *J* 11.7 and 2.9 Hz), 1.92 (1H, m,), 1.82-1.73 (2H, m), 1.60-1.40 (4H, m, CH_2CH_2); δ_c (100.5 MHz, $CDCl_3$) 143.2, 127.0, 126.9, 126.7, 65.2, 51.0, 47.8, 32.6, 20.0; MS (CI) *m*/*z* (%) 177 (MH^+, 3%), 160 (MH^+-NH_3, 5%), 97 (M^+-Ph, 100%) and 82 (MH^+-Ph-NH_3, 47%).

Supplementary information: X-ray Crystallography

Compound **8**



An x-ray diffraction experiment on compound **8** was carried out at 100 K on a Bruker PROTEUM diffractometer using Cu-Kα X-radiation (λ = 1.54178 Å) and a CCD area-detector, from a single crystal coated in paraffin oil mounted on a glass fibre. Intensities were integrated[i] from several series of exposures, each exposure covering 0.3° in ω. Absorption corrections were based on equivalent reflections using SADABS V2.10,[ii] and structures were refined against all F_o^2 data with hydrogen atoms riding in calculated positions using SHELXTL[iii] Crystal and refinement data are given in Table 1.

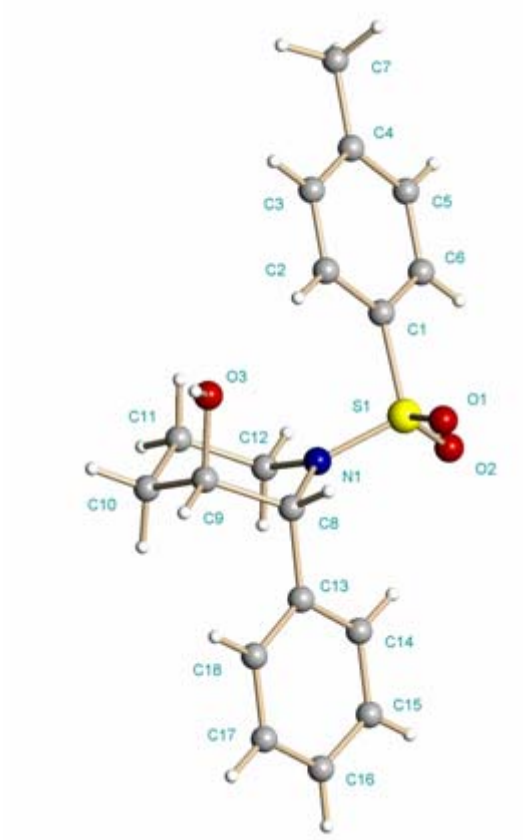
Table 1 : Crystal and refinement data for compound **8**

Colour, habit	colourless block
Empirical Formula	$C_{18}H_{21}NO_3S$
M	331.42
Crystal system	monoclinic
Space group	*P* $2_{1/n}$
a/Å	9.4610(19)
b/Å	18.6300(4)
cÅ	10.0330(2)
α°	90
β°	112.92
γ°	90
V/Å^{-3}	1628.78
Z	4

μ/mm^{-1}	0.213
T/K	100
Reflections: total/independent/R_{int}	3722/3386/0.0334
Final R_1 and wR_2	0.0443, 0.1040

[1] SAINT integration software, Siemens Analytical X-ray Instruments Inc., Madison, WI, 1994.
[1] SADABS V2.10, Sheldrick, G.M., University of Göttingen, 2003.
[1] SHELXTL program system version 6.14; Bruker Analytical X-ray Instruments Inc., Madison, WI, 2000-2003.

Compound **12**



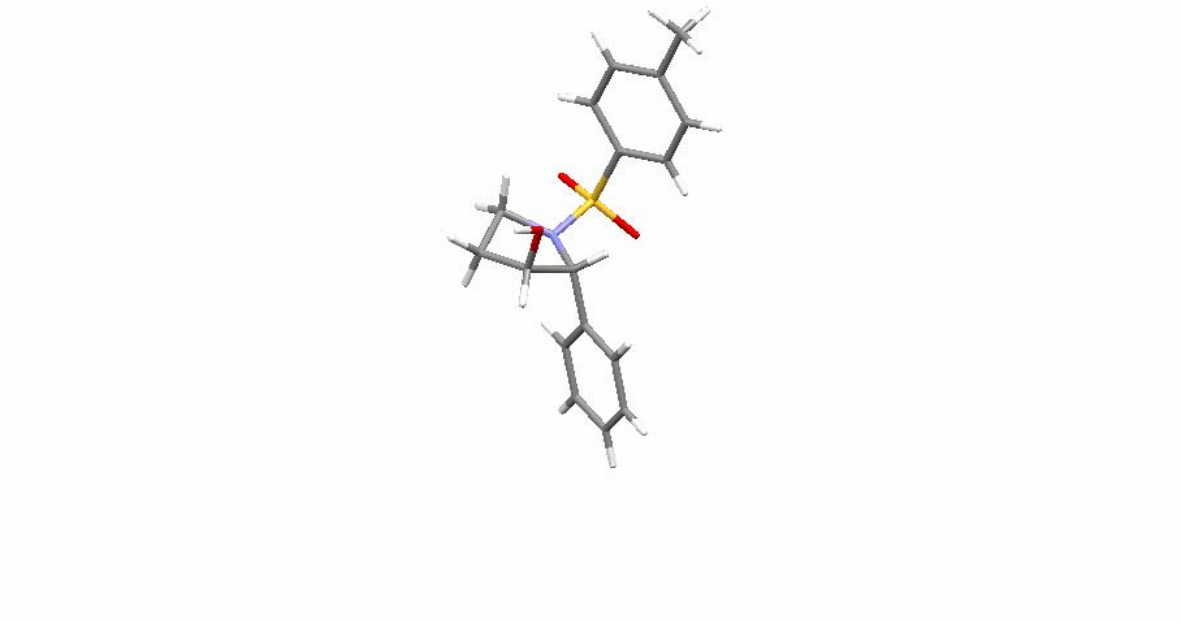
An x-ray diffraction experiment on compound **12** was carried out at 100 K on a Bruker PROTEUM diffractometer using Cu-Kα X-radiation (λ = 1.54178 Å) and a CCD area-detector, from a single crystal coated in paraffin oil mounted on a glass fibre. Intensities were integrated[iv] from several series of exposures, each exposure covering 0.3° in ω. Absorption corrections were based on equivalent reflections using SADABS V2.10,[v] and structures were refined against all F_o^2 data with hydrogen atoms riding in calculated positions using SHELXTL[vi] Crystal and refinement data are given in Table 2.

Table 2 : Crystal and refinement data for compound **12**

Colour, habit	colourless block
Empirical Formula	$C_{18}H_{21}NO_3S$
M	331.42
Crystal system	orthorhombic
Space group	*P b c a*
a/Å	8.0828(3)
b/Å	18.1324(5)
cÅ	22.0830(7)
α°	90
β°	90
γ°	90
V/Å^{-3}	3236.50(18)
Z	8
μ/mm^{-1}	1.9
T/K	100
Reflections: total/independent/R_{int}	3033/2491/0.0649
Final R_1 and wR_2	0.0524, 0.1568

[1] SAINT integration software, Siemens Analytical X-ray Instruments Inc., Madison, WI, 1994.
[1] SADABS V2.10, Sheldrick, G.M., University of Göttingen, 2003.
[1] SHELXTL program system version 6.14; Bruker Analytical X-ray Instruments Inc., Madison, WI, 2000-2003.

Compound **15**



An x-ray diffraction experiment on compound **15** was carried out at 100 K on a Bruker PROTEUM diffractometer using Cu-Kα X-radiation (λ = 1.54178 Å) and a CCD area-detector, from a single crystal coated in paraffin oil mounted on a glass fibre. Intensities were integrated[vii] from several series of exposures, each exposure covering 0.3° in ω. Absorption corrections were based on equivalent reflections using SADABS V2.10,[viii] and structures were refined against all F_o^2 data with hydrogen atoms riding in calculated positions using SHELXTL[ix] Crystal and refinement data are given in Table 3.

Table 3 : Crystal and refinement data for compound **15**

Colour, habit	colourless needle
Empirical Formula	$C_{17}H_{19}NO_3S$
M	317.39
Crystal system	monoclinic
Space group	$P\ 2_{1/C}$
a/Å	7.7097(15)
b/Å	18.1324(5)
cÅ	19.5460(4)
α°	90
β°	94.63
γ°	90
V/Å^{-3}	1563.75
Z	4
μ/mm^{-1}	0.219
T/K	100
Reflections: total/independent/R_{int}	3578/2953/0.0442
Final R_1 and wR_2	0.0437, 0.1054

[1] SAINT integration software, Siemens Analytical X-ray Instruments Inc., Madison, WI, 1994.
[1] SADABS V2.10, Sheldrick, G.M., University of Göttingen, 2003.
[1] SHELXTL program system version 6.14; Bruker Analytical X-ray Instruments Inc., Madison, WI, 2000-2003.

References:

1 A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, 1996, **15**, 1518.

2 S. Zhu, G. Jin and Y. Xu, *Tetrahedron*, 2003, **59**, 4389-4394.

3 J. Ahman and P. Somfai, *Tetrahedron*, 1992, **48**, 9537-9544.

4 M. Mori, Y. Washioka, T. Urayama, K. Yoshiura, K. Chiba and Y. Ban, *J. Org. Chem.*, 1983, **48**, 4058-4067.

5 W. Hu, E. Reder and M. Hesse, *Helv. Chim. Acta*, 1996, **79**, 2137-2151.

6 R. K. Dieter and R. R. Sharma, *J. Org. Chem.*, 1996, **61**, 4180 -4184.

7 M. W. Hosseini, J. Comarmond and J. M. Lehn, *Helv. Chim. Acta*, 1989,***726***, 1066-1077.

8 N. Katagiri, M. Muto, M. Nomura, T. Higaskikawa and C. Kaneko, *Chem. Pharm. Bull*, 1991, **39**, 1112-1122.

9 G. Kokotos, *Synthesis*, 1990, 299-301.

10 O. Okitsu, R. Suzuki and S. Kobayashi, *J. Org. Chem.,* 2001, **66**, 809-823.

11 T. R. Bailey, R. S. Garigipati, J. A. Morton and S. M. Weinreb, *J. Am. Chem. Soc*., 1984, **106**, 3240-3245.

12 T. J. Rosen, *US 5686615*, 1997.