Stereocontrolled Syntheses of Epimeric 3-Aryl-6-Phenyl-1-Oxa-7-Aza*spiro*[4,5]decane NK-1 Receptor Antagonist Precursors

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Supplementary Material

Unless stated otherwise, all reactions were performed under a nitrogen atmosphere, using commercially available solvents and reagents without further purification. NMR spectra were recorded on Bruker AC250, DPX360, and DPX400 spectrometers with tetramethylsilane as internal standard. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and mass spectra recorded on a VG Quattro instrument. Melting points are uncorrected and were measured with a Reichert Microstar IV hot-stage apparatus. Optical purity was determined by hplc using a 250 x 4.6 mm Chiralpak AD column with detection at 210 nm. Column chromatography was performed on silica gel of particle size 40-63 µm; a Lobar® LiChroprep® Si 60 column was used for medium pressure chromatography.

(2*S*)-1-*tert*-Butoxycarbonyl-2-phenylpiperidin-3-one (5)

Dimethyl sulfoxide (2.10 mL, 2.34 g, 30 mmol) was added dropwise to a cooled (-70 °C) solution of oxalyl chloride (2.10 mL, 3.05 g, 24 mmol) in dichloromethane (75 mL). The mixture was stirred at -70 °C for 5 min., then (2*S*,3*S*)-1-*tert*-butoxycarbonyl-3-hydroxy-2-phenylpiperidine (**4**; prepared by the method described in European Patent Specification number 0 528 495-A; 5.60 g, 20 mmol) in dichloromethane (20 mL) was added dropwise. The mixture was stirred at -70 °C for 1 h. before adding triethylamine (7.00 mL, 5.05 g, 50 mmol) and allowing the mixture to warm to 0 °C over a further 1 h. The mixture was then washed with ice cold aqueous citric acid solution (5%, 2 x 75 mL) and brine (100 mL), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give **5** as a yellow oil, which was used immediately without further purification. ^{1}H NMR (250MHz, $CDCl_3$) δ 7.5-7.3 (5H, m), 5.8 (1H, br s), 4.2 (1H, br s), 3.4 (1H, m), 2.6 (2H, m), 2.0 (2H, m), and 1.54 (9H, s); MS (ES$^+$) *m/z* 276 ([M+H]$^+$), 220 ([M-*t*-butyl+2H]$^+$, 100%); hplc (1:99 ethanol/isohexane at 1.5mL/min) retention time 9.0 min for the 2*R* enantiomer, 9.8 min for the 2*S*.

(2*S*,3*R*)-1-*tert*-Butoxycarbonyl-3-(3-hydroxypropyn-1-yl)-2-phenylpiperidin-3-ol (3)

Bromoethane (1.87 mL, 2.73 g, 25 mmol) was added dropwise to magnesium turnings (0.61 g, 25 mmol) suspended in THF (60 mL) and the mixture stirred for a further 0.5 h before being cooled in an ice bath. O-Trimethylsilylpropargyl alcohol (4.25 g, 25 mmol) was added slowly and the cooling bath removed, allowing the reaction mixture to warm to room temperature over 0.5 h. After re-cooling, a pre-filtered solution of the preceding ketone in THF (15 mL) was added and stirring at room temperature resumed for 1.5 h. Aqueous ammonium chloride (satd., 25 mL), followed by water (25 mL), was added, and the mixture stirred until all of the solid had dissolved. The layers were separated, the aqueous extracted with ethyl acetate (25 mL) and the combined organic layers washed with brine (25 mL), dried ($MgSO_4$), and the solvent evaporated to leave a viscous yellow oil (9.70 g). This was dissolved in ethyl acetate (100 mL), a solution of tetrabutylammonium fluoride (1.1M in THF; 25 mL, 27.5 mmol) added, and the mixture stirred at room temperature for 1.5 h. After washing with water (2 x 50mL) and brine (50 mL), the solution was dried ($MgSO_4$) and the solvent evaporated to leave an orange oil, which on column chromatography (40% ethyl acetate in hexane) gave the desired product as a pale yellow glass (5.40 g, 82%). $[\alpha]_D$ –10.6° (c 1.1, CH_2Cl_2); ^{1}H NMR (360MHz, $CDCl_3$) δ 7.54-7.52 (2H, m), 7.34-7.24 (3H, m), 5.51 (1H, s), 4.28 (2H, s), 4.01 (1H, dd, *J* 14.7 Hz, *J* 5.2 Hz), 2.91 (1H, ddd, *J* 13.5 Hz, *J* 3.9 Hz, *J* 2.9 Hz), 2.78 (1H, br s), 2.50 (1H, br s), 2.17-2.14 (1H, m), 2.04-1.91 (2H, m), 1.74-1.64 (1H, m), and 1.40 (9H, s); ^{13}C NMR (100.6MHz, $CDCl_3$) 155.6, 137.7, 129.1, 128.2, 127.1, 88.6, 82.5, 80.2, 69.9, 62.1, 50.6, 38.7, 32.4, 28.3, 22.9; MS (ES$^+$) *m/z* 332 ([M+H]$^+$), 276 ([M-*t*-butyl+2H]$^+$, 100%); hplc (2:98 ethanol/isohexane at 1.0mL/min) retention time 12.5min for the 2*R*,3*S* enantiomer, 14.6min for the 2*S*,3*R*.

(5*R*,6*S*)-3-Tributylstannyl-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)azaspiro[4.5]dec-3-ene (7)

Tetrakis(triphenylphosphine)palladium (0) (2.30 g, 2.0 mmol) in toluene (600 mL) was added to a solution of **3** (45 g, 136 mmol) and the mixture purged with nitrogen. Tributyltin hydride (35.8 mL, 38.71 g, 133 mmol) was added dropwise over 15 min, during which time the reaction was cooled to maintain the internal temperature below 25° C. After stirring at room temperature for 1 h, the solvent was removed under reduced pressure. Analysis of the crude residue by NMR indicated a 7:1 mixture of **6a** to **6b**, as determined by integration of the C2 proton singlets (δ 5.02 and 5.07, respectively).

To a solution of the residue and triphenylphosphine (34.88 g, 133 mmol) in THF (600 mL) was added dropwise, with cooling, a solution of diethyl azodicarboxylate (20.9 mL, 23.16 g, 133 mmol) in THF (150 mL) and the resulting mixture stirred for 1 h at room temperature, before being evaporated. The residue was partitioned between acetonitrile (600 mL) and hexane (8 x 150 mL), the combined hexane layers evaporated, and the residual gum subjected to column chromatography (0-1% ethyl acetate in dichloromethane), giving **7** as a yellow oil (53.64 g, 65%). $[\alpha]_D$ –4.1° (c 1.33, CH_2Cl_2); ^{1}H NMR (360MHz, $CDCl_3$) δ 7.41-7.39 (2H, m), 7.26-7.16 (3H, m), 5.96 (1H, t, *J* 2.3 Hz), 4.93 (1H, s), 4.63 (1H, dd, *J* 12.9 Hz, *J* 2.2 Hz), 4.22 (1H, dd, *J* 12.9 Hz, *J* 2.2 Hz), 4.11 (1H, dd, *J* 13.1 Hz, *J* 6.2 Hz), 3.16-3.10 (1H, m), 1.99-1.96 (1H, m), 1.87-1.83 (1H, m), 1.76-1.72 (2H, m), 1.52-1.41 (6H, m), 1.38 (9H, s), 1.32-1.24 (6H, m), and 0.93-0.87 (15H, m); ^{13}C NMR (100.6MHz, $CDCl_3$) 155.3, 140.5, 140.2, 140.0, 128.4, 127.4, 126.3, 90.5, 81.7, 79.4, 63.3, 38.8, 31.3, 29.0, 28.3, 27.1, 22.0, 13.4, 9.5; MS (ES$^+$) *m/z* 606 ($[(^{120}Sn)M+H]^+$), 550 ($[(^{120}Sn)M$-*t*-butyl$+2H]^+$).

2-Benzyloxy-5-(trifluoromethoxy)bromobenzene (8a)

(a) *2-Bromo-4-(trifluoromethoxy)phenol.* To a cooled (0° C) solution of 4-(trifluoromethoxy)phenol (35.6 g, 0.2 mol) in chloroform (280 mL) was added dropwise a solution of bromine (32 g, 0.2 mol) in chloroform (50 mL). The solution was stirred at 0 °C for 1 h. and at room temperature for 2 h. Dichloromethane (200 mL) and water (400mL) were added and the organic phase was washed further with water (400 mL) and brine (200 mL), and dried ($MgSO_4$). The solvent was removed and the residue was purified by distillation at reduced pressure to give the title compound. ^{1}H NMR (250MHz, $CDCl_3$) δ 7.38 (1H, d, *J* 2.1 Hz), 7.13 (1H, dd, *J* 9.1 Hz, *J* 2.1 Hz), 7.03 (1H, d, *J* 9.1 Hz), and 5.53 (1H, s).

(b) *2-Benzyloxy-5-(trifluoromethoxy)bromobenzene*. 2-Bromo-4-(trifluoromethoxy)phenol (5.0 g, 20 mmol) was dissolved in *N*,*N*-dimethylformamide (60 mL), and potassium carbonate (5.4 g, 40 mmol) added, followed by benzyl bromide (3.5 mL, 30 mmol), and the reaction was stirred at ambient temperature for 15 h. The reaction was partitioned between water (150 mL) and ethyl acetate (3 x 60 mL). The combined organic fractions were washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification on silica gel, (2-5% ethyl acetate in hexane) gave **8a** as a colourless oil (6.7 g, 96%). ^{1}H NMR (360MHz, $CDCl_3$) δ 7.47-7.25 (6H, m), 7.10 (1H, dd *J* 8.2 Hz, *J* 2.9 Hz), 6.91 (1H, d, *J* 9.0 Hz), and 5.47 (2H, s).

(5*R*,6*S*)-3-(2-Benzyloxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)azaspiro-[4.5]dec-3-ene (2a)

A mixture of **8a** (3.97g, 11.43mmol), **7** (5.75 g, 9.52 mmol), tetrakis(triphenylphosphine)palladium (0) (450 mg) and lithium chloride (2.39 g, 57.1 mmol) in toluene (50 mL) was degassed with a Firestone valve, then heated under reflux for 2 days. The mixture was cooled, filtered through Celite and the solvent was evaporated under reduced pressure. The residue was dissolved in acetonitrile and washed with hexane, the acetonitrile layer evaporated under reduced pressure and the residue was dissolved in methanol. The mixture was treated with 5% methanolic potassium fluoride, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate in hexane), to give **2a** (3.88 g, 70%). ^{1}H NMR (360MHz, $CDCl_3$) δ 7.44-7.34 (7H, m), 7.27-7.17 (3H, m), 7.08 (1H, d, *J* 11.0 Hz), 6.93 (2H, m), 6.65 (1H, t, *J* 2.0 Hz), 5.14-5.06 (3H, m), 4.92 (1H, dd, *J* 12.2 Hz, *J* 2.9 Hz), 4.60 (1H, dd, *J* 12.1 Hz, *J* 2.2 Hz), 4.15-4.07 (1H, m), 3.15-3.07 (1H, m), 2.10-2.03 (1H, m), 1.81-1.72 (3H, m), and 1.33 (9H, s); MS (ES$^+$) *m/z* 582 ($[M+H]^+$, 26%), 526 ($[M$-*t*-butyl$+2H]^+$, 100%).

(3*S*,5*R*,6*S*)-3-(2-Hydroxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (1a)

Palladium hydroxide on carbon (20%, 1.00 g) was added to a solution of **2a** (3.88 g, 6.7 mmol) in ethyl acetate (15 mL) and methanol (15 mL and the suspension shaken under a hydrogen atmosphere (50 psi) for 72 h. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was purified by medium pressure chromatography on silica gel, (25% ethyl acetate in hexane) to give **1b** (191 mg, 6%) and **1a** (2.30 g, 70%), $[\alpha]_D$ +6.6° (c 1.0, CH_2Cl_2); ^{1}H NMR (360MHz, $CDCl_3$) δ 7.55 (2H, d, *J* 7.7 Hz), 7.34-7.30 (2H, m), 7.27-7.25 (1H, m), 6.96-6.93 (2H, m), 6.75 (1H, dd, *J* 8.8 Hz, *J* 0.8 Hz), 5.33 (1H, s), 4.25-4.21 (1H, m), 3.98 (1H, d, *J* 13.2 Hz), 3.93 (1H, dd, *J* 9.1 Hz, *J* 2.6 Hz), 3.65-3.59 (1H, m), 2.86-2.78 (1H, m), 2.50 (1H, dd, *J* 13.1 Hz, *J* 9.0 Hz), 2.21-2.10 (2H, m), 1.81-1.71 (3H, m) and 1.38 (9H, s); ^{13}C NMR (100.6MHz, $CDCl_3$) 155.5, 152.9, 142.2, 138.5, 129.3, 128.8, 128.1, 127.0, 121.1, 120.6 (q, *J* 255 Hz), 120.4, 116.5, 84.7, 80.4, 71.8, 62.5, 43.5, 39.2, 38.5, 30.8, 28.3, 23.1; MS (ES$^+$) *m/z* 494 ($[M+H]^+$, 29%), 438 ([M-*t*-butyl+2H]$^+$, 100%).

(5*R*,6*S*) -6-Phenyl-1-oxa-7-(*tert*-butoxycarbonyl)azaspiro[4.5]dec-3-ene (2b)

(a) *Z-(2S,3R)-1-tert-Butoxycarbonyl-3-(3-hydroxyprop-1-en-1-yl)-2-phenylpiperidin-3-ol*. Lindlar catalyst (2 g) was added to a solution of **3** (32 g, 96.6 mmol) in ethyl acetate (300 mL) and the mixture was stirred under hydrogen (1 atm.) for 4 h. The mixture was filtered and the solvent was evaporated under reduced pressure to give the desired product as an oil (32 g, 100%). ^{1}H NMR (360MHz, $CDCl_3$) δ 7.42 (2H, d, *J* 7.6 Hz), 7.35-7.25 (3H, m), 5.83 (1H, d, *J* 12.3 Hz), 5.68 (1H, dt, *J* 12.3, 6.0 Hz), 5.06 (1H, s), 4.27 (1H, m), 4.12 (2H, m), 3.32 (1H, m), 3.13 (1H, s), 2.28 (1H, t, *J* 5.9 Hz), 2.02 (1H, m), 1.92-1.78 (3H, m), and 1.32 (9H, s); ^{13}C NMR (100.6MHz, $CDCl_3$) 155.5, 140.0, 136.7, 129.8, 129.0, 128.2, 127.4, 80.0, 73.3, 63.7, 59.1, 38.8, 32.9, 28.3, 21.4; MS (ES$^+$) *m/z* 334 ($[M+H]^+$), 278 ([M-*t*-butyl+2H]$^+$, 100%).

(b) *(5R,6S)-6-Phenyl-1-oxa-7-(tert-butoxycarbonyl)azaspiro[4.5]dec-3-ene*. To a cooled (0 °C) solution of the above compound and triphenylphosphine (30.2 g, 115 mmol) in THF (700 mL) was added dropwise diethylazodicarboxylate (18.2 mL, 115 mmol) in THF (100 mL). The mixture was stirred at 0 °C for 30 min. then at room temperature for 1.5 h and the solvent removed under reduced pressure. The residue was purified by column chromatography, (5-20% ethyl acetate in hexane) to give **2b** as a colorless solid (23.4 g, 77%). M.p. 90-92 °C (hexane); $[\alpha]_D$ +70.8° (c 1.6, CH_2Cl_2); ^{1}H NMR (360MHz, $CDCl_3$) δ 7.45 (2H, d, *J* 7.4 Hz), 7.27 (2H, t, *J* 7.4 Hz), 7.20 (1H, t, *J* 7.4 Hz), 6.03 (1H, dt, *J* 6.1 Hz, *J* 2.0 Hz), 5.88 (1H, dt, *J* 6.1 Hz, *J* 2.0 Hz), 5.06 (1H, s), 4.61 (1H, dt, *J* 13.1 Hz, *J* 2.0 Hz), 4.32 (1H, dt, *J* 13.1 Hz, *J* 2.0 Hz), 4.08 (1H, dd, *J* 13.6 Hz, *J*5.3 Hz), 3.05 (1H, ddd, *J* 13.4 Hz, *J* 11.8 Hz, *J* 4.8 Hz), 2.07-2.01 (1H, m), 1.85-1.71 (3H, m), and 1.37 (9H, s); ^{13}C NMR (100.6MHz, $CDCl_3$) 155.3, 139.4, 132.1, 128.5, 127.7, 127.3, 126.6, 90.7, 79.7, 75.4, 62.7, 38.8, 31.3, 28.3, 22.4; MS (ES$^+$) *m/z* 316 ($[M+H]^+$), 260 ([M-*t*-butyl+2H]$^+$, 100%).

2-Benzyloxy-5-(trifluoromethoxy)iodobenzene (8b)

(a) *Benzyloxy-4-(trifluoromethoxy)benzene*. Benzyl bromide (66.17 mL, 95.35 g, 0.56 mol) was added to a mixture of 4-(trifluoromethoxy)phenol (90.26 g, 0.51 mol) and potassium carbonate (140.97 g, 1.2 mol) in dimethylformamide (160 mL) and the mixture was stirred at room temperature for 72 h. The mixture was poured into water (1.5 l) and extracted with ethyl acetate (3 x 500 mL). The combined organic fractions were washed with aqueous sodium carbonate (saturated, 500 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the desired product as a colorless solid (133.5 g, 99%). M.p. 57-59 °C (*iso*-hexane); ^{1}H NMR (360MHz, $CDCl_3$) δ 7.39 (5H, m), 7.14 (2H, d, *J* 9.0 Hz), 6.95 (2H, d, *J* 9.0 Hz), and 5.05 (2H, s); ^{13}C NMR (100.6MHz, $CDCl_3$) 157.3, 142.9, 136.6, 128.7, 128.2, 127.5, 122.4, 120.6 (q, *J* 256 Hz), 115.6, 70.5.

(b) *2-Benzyloxy-5-(trifluoromethoxy)iodobenzene*. Iodine (71.96 g, 0.28 mol) in chloroform (250 mL) was added dropwise to a mixture of 2-benzyloxy-5-(trifluoromethoxy)benzene (73.06 g, 0.27 mol) and silver trifluoroacetate (71.57 g, 0.32 mol) in dichloromethane (750 mL) and the mixture was stirred at room temperature for 18 h. The mixture was filtered through Celite, washed with aqueous sodium thiosulfate (5%, 2 x 2 L), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, (5% ethyl acetate in hexane), to give **8b** as a colorless oil (108.03 g), containing 11% unreacted 2-benzyloxy-5-(trifluoromethoxy)iodobenzene. ^{1}H NMR (360MHz, $CDCl_3$) δ 7.67 (1H, d, *J* 2.8 Hz), 7.40 (5H, m), 7.16 (1H, dd, *J* 8.9 Hz, *J* 2.8 Hz), 6.82

(1H, d, *J* 8.9 Hz), and 5.14 (2H, s); ^{13}C NMR (100.6MHz, $CDCl_3$) 156.2, 143.0, 136.0, 132.4, 128.7, 128.1, 127.0, 122.1, 120.5 (q, *J* 257 Hz), 112.4, 86.3, 71.4.

(3*R*,5*R*,6*S*)-3-(2-Benzyloxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (10b)

A mixture of **8b** (21.9 g, 55.6 mmol), **2b** (7.0 g, 22.2 mmol), tetra-n-butylammonium chloride (6.17 g, 22.2 mmol), lithium chloride (9.48 g, 0.22 mol), and potassium formate (5.63 g, 67.0 mmol) in dimethylformamide (100 mL) was degassed with the aid of a Firestone valve. Palladium acetate (498 mg, 2.2 mmol) was added and the mixture was stirred at 60 °C for 15 h., then further **8b** (4.32 g, 11.0 mmol), potassium formate (2.78 g, 33.5 mmol), and palladium acetate (260 mg, 1.1 mmol) were added. Stirring at 60 °C was continued for 22 h., after which the reaction was allowed to cool and filtered. The solvent was evaporated under reduced pressure, water (600 mL) was added and the mixture extracted with ethyl acetate (2 x 300 mL). The combined organic fractions were washed with brine (300 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (25-100% dichloromethane in hexane, then 5% ethyl acetate in dichloromethane, then 10-25% ethyl acetate in hexane), to give **10b** (8.61 g, 66%) as a foam, $[\alpha]_D$ -0.9° (c 1.0, CH_2Cl_2); $[\alpha]_D$ +8.7° (c 1.0, EtOH); ^{1}H NMR (360MHz, $CDCl_3$) δ 7.56 (2H, d, *J* 7.7 Hz), 7.40-7.20 (8H, m), 7.14 (1H, d, *J* 2.0 Hz), 7.00 (1H, dd, *J* 8.9 Hz, *J* 2.0 Hz), 6.88 (1H, d, *J* 8.9 Hz), 5.30 (1H, s), 5.08 (2H, s), 4.27 (1H, m), 3.97 (1H, m), 3.87 (2H, m), 2.78 (1H, m), 2.56 (1H, m), 2.15 (1H, m), 1.96 (1H, m), 1.67 (3H, m), and 1.42 (9H, s); ^{13}C NMR (100.6MHz, $CDCl_3$) 155.4, 155.1, 142.8, 139.0, 136.5, 131.9, 129.0, 128.7, 128.2, 128.0, 127.3. 126.8, 120.9, 120.6 (q, *J* 256 Hz), 120.0, 112.4, 84.4, 79.9, 72.4, 70.6, 60.6, 43.2, 39.0, 38.8, 32.5, 28.4, 23.7; MS (ES$^+$) *m/z* 584 ([M+H]$^+$, 38%), 528 ([M-*t*-butyl+2H]$^+$, 100%); *(3*S,5R,6S*)-3-(2-Benzyloxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(tert-butoxycarbonyl)aza-spiro[4.5]decane* (0.39 g, 3%), ^{1}H NMR (360MHz, $CDCl_3$) δ 7.55 (2H, d, *J* 7.4 Hz), 7.40-7.23 (8H, m), 7.14-7.02 (2H, m), 6.88 (1H, d, *J* 8.8 Hz), 5.20 (1H, s), 5.10-5.04 (2H, m), 4.24 (1H, dd, *J* 8.2, 7.3 Hz), 4.01-3.97 (1H, m), 3.87-3.78 (1H, m), 3.67 (1H, dd, *J* 8.7, 8.6 Hz), 2.88-2.82 (1H m), 2.41 (1H, dd, *J* 12.8, 8.4 Hz), 2.28-2.08 (2H, m), 1.78-1.67 (3H, m), and 1.37 (9H, s); MS (ES$^+$) *m/z* 584 ([M+H]$^+$, 32%), 528 ([M-*t*-butyl+2H]$^+$, 100%); and **11** (1.61 g, 12%), ^{1}H NMR (400MHz, CD_2Cl_2) δ 7.50-7.46 (2H, m), 7.41-7.37 (2H, m), 7.35-7.31 (4H, m), 7.29-7.20 (3H, m), 7.06 (1H, dd, *J* 8.9 Hz, *J* 3.0 Hz), 6.89 (1H, d, *J* 8.9 Hz), 6.07 (1H, dd, *J* 6.0 Hz, *J* 2.5 Hz), 5.98 (1H, dd, *J* 6.0 Hz, *J* 1.5 Hz), 5.71 (1H, s), 5.10 (1H, s), 5.06 (2H, dd, *J* 14..6 Hz, *J* 11.9 Hz), 4.12-4.07 (1H, m), 3.21-3.13 (1H, m), 2.20-2.14 (1H, m), 1.90-1.80 (3H, m), and 1.36 (9H, s); ^{13}C NMR (100.6MHz, CD_2Cl_2) 155.4, 153.8, 143.4, 140.0, 137.0, 133.1, 132.3, 130.5, 128.9, 128.3, 127.9, 127.4, 126.9, 120.8, 119.7, 112.5, 91.6, 83.1, 79.8, 70.7, 63.4, 39.2, 32.6, 28.4, 27.3, 22.4; MS (ES$^+$) *m/z* 582 ([M+H]$^+$, 32%), 526 ([M-*t*-butyl+2H]$^+$, 100%).

(3*R*,5*R*,6*S*)-3-(2-Hydroxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (1b)

Palladium on carbon (10%, 0.06 g) was added to a solution **10b** (0.66 g, 1.13 mmol) in methanol (20 mL) and the mixture was shaken under hydrogen (50 psi.) for 16 h. The mixture was filtered and the solvent was evaporated under reduced pressure. Hexane was added to the residue and the solvent re-evaporated to afford **1b** as a solid (0.55 g, 99%), m.p. 149-150 °C (hexane); $[\alpha]_D$ +2.9° (c 1.0, CH_2Cl_2); $[\alpha]_D$ +15.7° (c 1.0, EtOH); ^{1}H NMR (360MHz, $CDCl_3$) δ 7.60 (2H, d, *J* 7.3 Hz), 7.33 (2H, t, *J* 7.3 Hz), 7.26 (1H, d, *J* 7.3 Hz), 7.05 (1H, br s), 6.96 (2H, m), 6.82 (1H, d, *J* 9.4 Hz), 5.43 (1H, s), 4.29-4.25 (1H, m), 4.03-3.94 (2H, m), 3.77-3.68 (1H, m), 2.79-2.67 (2H, m), 2.33 (1H, dd, *J* 12.9 Hz, *J* 4.8 Hz), 1.87-1.58 (4H, m), and 1.50 (9H, s); ^{13}C NMR (100.6MHz, $CDCl_3$) 155.9, 153.2, 142.0, 138.1, 129.9, 128.9, 128.2, 127.0, 120.9, 120.6 (q, *J* 255 Hz), 120.3, 116.5, 85.0, 80.7, 72.0, 59.2, 43.7, 39.4, 32.3, 28.5, 23.9; MS (ES$^+$) *m/z* 494 ([M+H]$^+$, 17%), 438 ([M-*t*-butyl+2H]$^+$, 100%).