UNIVERSITAT DE BARCELONA

FACULTAD DE FARMACIA

DEPARTAMENTO DE FARMACOLOGÍA Y QUÍMICA TERAPÉUTICA

SÍNTESIS ESTEREOSELECTIVA DE *cis*-DECAHIDROQUINOLINAS: INTERMEDIOS AVANZADOS PARA EL ACCESO A LAS LEPADINAS

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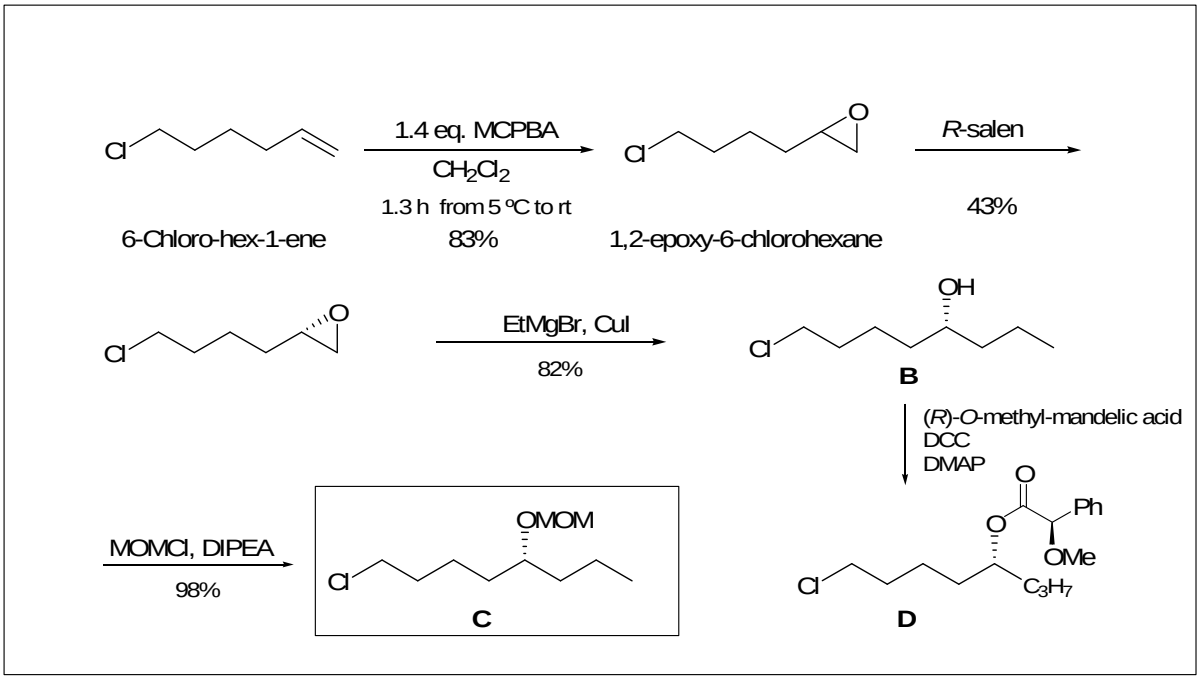
7. EXPERIMENTAL

Experimental

General. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) or Al_2O_3 (ALOX N/UV_{254}, Polygram), and the spots were located with iodoplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230-240 mesh ASTM) or Al_2O_3 (aluminium oxide 90, Merck). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or 300 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy.

CHAPTER 2. (*R*)-1-CHLORO-5-METHOXYMETHOXY-OCTANE (C)



(1*S*)-1,2-epoxy-6-chlorohexane

To a solution of (±)-1,2-epoxy-6-chlorohexane (888 mg, 6.6 mmol), which was prepared from 6-Chloro-hex-1-ene (MCPBA, DCM) by the procedure previously reported[41], the catalyst ((*R*,*R*)-Salen, 20 mg, 0.005 eq.) and AcOH (36 μL, 0.025 eq.) at 0 ºC, H_2O (66 μL, 0.55 eq.) was added in one portion. After 16 h, (1*S*)-1,2-epoxy-

6-chlorohexane (382 mg, 2.83 mmol, 43%) was isolated by distillation under reduced pressure (67 ºC, 0.1 atm). The enantiomeric purity of the recovered epoxide was determined by optical rotation.

Colourless oil. $[\alpha]^{25}_{D}$ +8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40-1.70 (m, 4H), 1.70-1.95 (m, 2H), 2.50 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.76 (dd, *J* = 5.0, 3.8 Hz, 1H), 2.86-2.98 (m, 1H), 3.56 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.4 (CH_2), 31.7 (CH_2), 32.2 (CH_2), 44.8 (CH_2), 46.9 (CH_2), 52.0 (CH).

(4*R*)-8-Chloro-octan-4-ol (B)

A mixture of CuI (11 mg, 0.06 mmol) in Et_2O (8 mL) was cooled to -78 ºC and treated with EtMgBr (3.4 mL, 3.4 mmol) 1 M in THF. After 15 min, (1*S*)-1,2-epoxy-6-chlorohexane (382 mg, 2.84 mmol) in Et_2O (1 mL) was added, and the mixture was brought to r.t. overnight. The mixture was hydrolyzed with HCl (2 mL) and extracted with Et_2O (3 x 50 mL). The resulting organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to an oil which was purified by chromatography (SiO_2, 9:1 hexane/AcOEt) to give **B** as a colourless oil (432 mg, 82%). R_f = 0.15 (SiO_2, 9:1 hexane/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.1 Hz, 3H), 1.2-1.7 (m, 6H), 1.7-1.9 (m, 2H), 3.55 (t, *J* = 6.6 Hz, 2H), 3.50-3.70 (masked, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (CH_3), 18.8 (CH_2), 23.0 (CH_2), 32.2 (CH_2), 32.6 (CH_2), 36.6 (CH_2), 39.7 (CH_2), 45.0 (CH_2), 71.4 (CH).

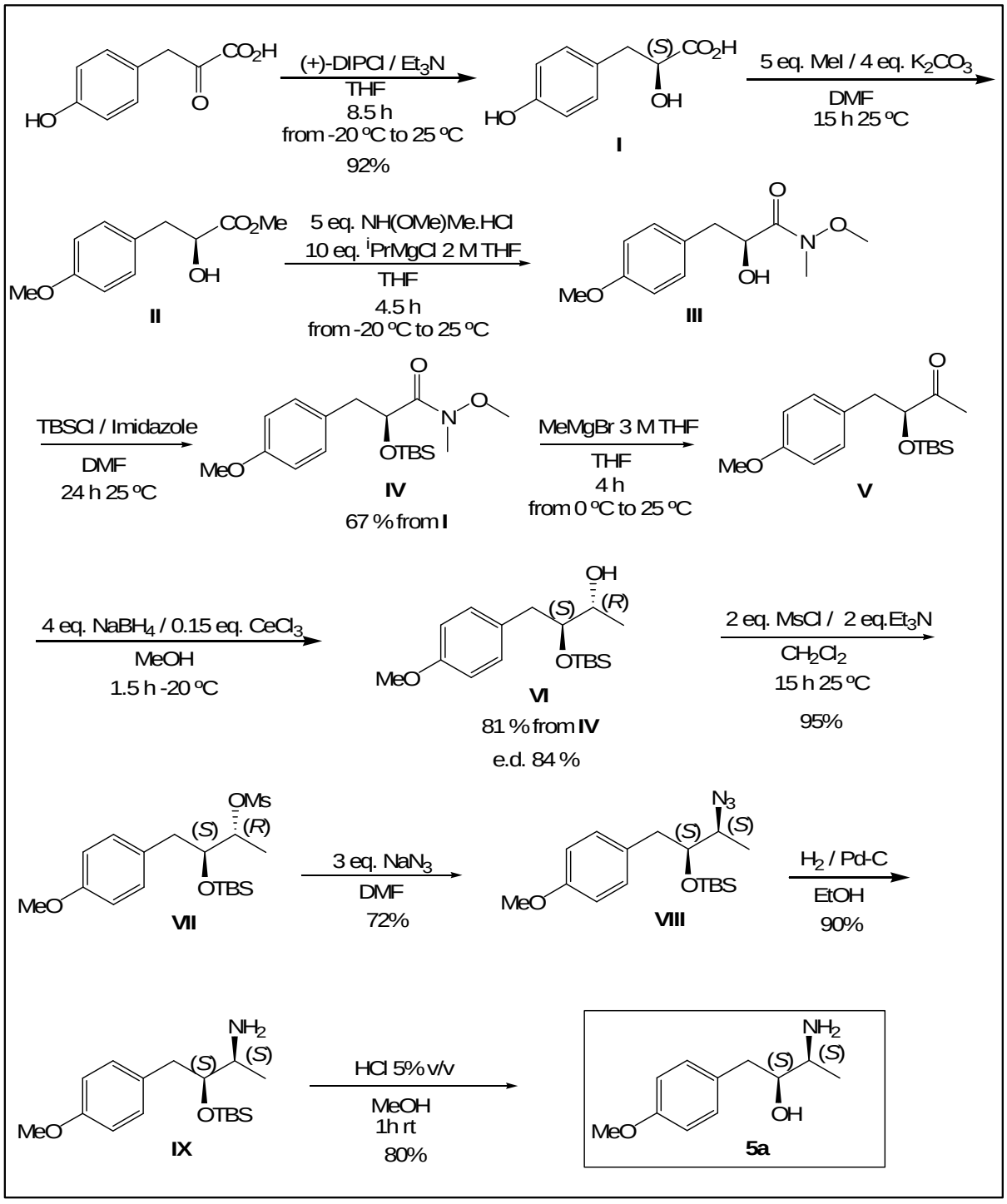
(D)

DMAP (2 mg, 0.013 mmol) was added all at once over a mixture of **B** (21 mg, 0.13 mmol), (*R*)-*O*-methylmandelic acid (22 mg, 0.13 mmol) and DCC (30 mg, 0.14 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at rt overnight. Then, the dicyclohexylurea was removed by filtration and the filter cake was washed with hexane (3 x 10 mL) and the combined filtrates were washed with HCl (2 x 10 mL), Na_2CO_3 (2 x 10 mL) and brine (2 x 10 mL), dried over Na_2SO_4 and concentrated to an oil which was purified by chromatography (SiO_2, 9:1 hexane/AcOEt) to give **D** as a single diastereoisomer (37 mg, 90%). Colourless oil. R_f = 0.26 (SiO_2, 9:1 hexane/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$) 0.72 (t, *J* = 7.0 Hz, 3H), 1.2-1.6 (m, 6H), 1.75-1.85 (m, 2H), 3.42 (s, 3H, OMe), 3.46 (t, *J* = 6.6 Hz, 2H), 4.75 (s, 1H, C<u>H</u>OMe), 4.86-4.99 (m, 1H).

(4*R*)-1-chloro-5-methoxymethoxy-octane (C)

To a solution of **B** (381 mg, 2.33 mmol) in CH_2Cl_2 (8 mL) was added diisopropylamine (8.1 mL, 46.6 mmol) followed by MOMCl (1.8 mL, 23.3 mmol). The resulting mixture was stirred at rt overnight. The reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to an oil which was purified by chromatography (SiO_2, 9:1 hexane/AcOEt) to give **C** as a colourless oil (474 mg, 98%). R_f = 0.46 (SiO_2, 9:1 hexane/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.2-1.6 (m, 6H), 1.75-1.85 (m, 2H), 3,38 (s, 3H), 3.54 (t, *J* = 6.6 Hz, 2H), 3.50-3.60 (masked, 1H), 4.65 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 18.5 (CH_2), 22.7 (CH_2), 32.7 (CH_2), 33.6 (CH_2), 36.5 (CH_2), 45.0 (CH_2), 55.5 (CH_3), 77.0 (CH), 95.4 (CH_2).

CHAPTER 4. (2*S*,3*S*)-3-AMINO-1-(4-METHOXYPHENYL)BUTAN-2-OL (5a)



(*S*)-*β*-(4-hydroxyphenyl)lactic acid [L-Hpla] (I)

A solution of *β*-(4-hydroxyphenyl)pyruvic acid (Aldrich, 901 mg, 5 mmol) in THF (18 mL) was treated with Et_3N (0.7 mL, 5 mmol) at -20 ºC. After 30 min at this temperature, a solution of (+)-DIPCl (1.9 g, 6 mmol) in THF (6 mL) was added, and the resulting solution was stirred at rt for 8 h. The reaction mixture was quenched

with 2 N aqueous NaOH (10 mL) and H_2O (5 mL). The aqueous layer was washed with *tert*-butylmethylether (2 x 20 mL) and the organic layer with H_2O (2 x 30 mL). The combined aqueous phases were acidified with HCl 2 N to pH 1 and extracted with AcOEt (4 x 50 mL), dried and concentrated to give L-Hpla **I** (846 mg, 92 %) as a white solid. The spectroscopic data were identical to its enantiomer previously reported[30]. R_f = 0.40 (SiO_2, 1:1 AcOEt/MeOH); m.p. 162-164 ºC. $[\alpha]^{25}_D$ –10.7 (*c* 0.56, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.90 (dd, *J* = 14.0, 8.0 Hz, 1H, H-3), 3.4 (br s, 1H, OH), 4.34 (dd, *J* = 7.8, 4.4 Hz, 1H, H-2), 6.75 (d, *J* = 8.4 Hz, 2H, H-6, H-8), 7.10 (d, *J* = 8.8 Hz, 2H, H-5, H-9); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.7 (C-3), 73.0 (C-2), 116.0 (C-6, C-8), 129.5 (C-4), 131.5 (C-5, C-9), 157.0 (C-7), 177.5 (C-1).

(2*S*)-2-Hydroxy-3-(4-methoxy-phenyl)-propionic acid methyl ester (II)

K_2CO_3 (558 mg, 4 mmol) was added to a solution of hydroxy acid **I** (182 mg, 1 mmol) in DMF anh. (1 mL). After the mixture had been stirred for 15 min at rt, MeI (0.32 mL, 5 mmol) was added drowise and the mixture was stirred overnight. The mixture was quenched with H_2O (20 mL) and extracted with AcOEt (3 x 20 mL). The dried organic extracts were concentrated to give **II** (210 mg) as a brown oil wich was used without further purification. The NMR data were identical to the racemic compound previously reported[79]. R_f = 0.23 (SiO_2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.40 (br s, 1H), 2.91 (dd, *J* = 14.0, 6.6 Hz, 1H), 3.06 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 4.42 (dd, *J* = 6.6, 4.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 39.6 (CH_2), 52.4 (CH_3), 55.2 (CH_3), 71.4 (CH), 113.9 (CH), 128.2 (C), 130.5 (CH), 158.6 (C), 174.5 (C).

(2*S*)-2-Hydroxy-*N*-methoxy-3-(4-methoxy-phenyl)-*N*-methyl-propionamide (III)

To a solution of ester **II** (210 mg, 1 mmol) in THF (15 mL) cooled to -20 ºC under argon atmosphere Me(MeO)NH.HCl (542 mg, 5 mmol) was added and then over 30 min a solution of ^{i}PrMgCl 2.0 M in THF (5 mL, 10 mmol) was added dropwise maintaining the temperature at -20 ℃. The mixture was stirred 2 h at -20 ℃ and 2.5 h from -20 ℃ to rt. The mixture was quenched with saturated aqueous NH_4Cl solution (50 mL). The organic layer was dried and concentrated to afford the corresponding Weinreb amide **III** (240 mg) as a yellow oil, which was used without fur

[79] Rho, H; Ko, B. *Synth. Commun.* **1999**, *29*, 2875.

ther purification: R_f = 0.29 (SiO_2, CH_2Cl_2/MeOH 99:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60 (br s, 1H), 2.81 (dd, *J* = 13.8, 7.2 Hz, 1H), 3.01 (dd, *J* = 13.9, 3.8 Hz, 1H), 3.72 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 4.55-4.65 (m, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.7 (CH_3), 40.1 (CH_2), 55.2 (CH_3), 61.4 (CH_3), 69.8 (CH), 113.8 (CH), 129.2 (C), 130.4 (CH), 158.4 (C), 168.6 (C).

(2*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-*N*-methoxy-3-(4-methoxy-phenyl)-*N*-methyl-propionamide (IV)

To a solution of Weinreb amide **III** (231 mg, 0.97 mmol) in DMF (3 mL) at rt under argon atmosphere imidazol (344 mg, 4.8 mmol) was added and then over the resulting mixture a solution of TBSCl (330 mg, 2.1 mmol) in DMF (2 mL) was added. The mixture was stirred for 18 h and then diluted with Et_2O (20 mL). The organic layer was washed with H_2O (10 mL), HCl 1 N (10 mL), $NaHCO_3$ (10 mL) and brine (10 mL), dried and concentrated to an oil which was purified by chromatography (SiO_2, CH_2Cl_2) to afford the corresponding Weinreb amide **IV** (229 mg, 67% from **I**) as a yellow oil. R_f = 0.23 (SiO_2, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ –0.14 (s, 3H), –0.10 (s, 3H), 0.81 (s, 9H), 2.76 (dd, *J* = 13.5, 8.7 Hz, 1H), 2.98 (dd, *J* = 13.4, 4.4 Hz, 1H), 3.19 (s, 3H), 3.62 (s, 3H), 3.79 (s, 3H), 4.58-4.63 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ –5.3 (CH_3), –5.2 (CH_3), 18.3 (C), 25.7 (CH_3), 29.7 (CH_3), 40.3 (CH_2), 55.3 (CH_3), 61.5 (CH_3), 71.9 (CH), 113.6 (CH), 130.1 (C), 130.7 (CH), 158.3 (C), 168.5 (C).

(3*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-(4-methoxy-phenyl)-butan-2-one (V)

To a solution of Weinreb amide **V** (222 mg, 0.63 mmol) in THF (8 mL) cooled to 0 ºC under argon atmosphere MeMgBr 3 M in Et_2O (1 mL, 3.1 mmol) was added dropwise. The reaction mixture was stirred for 4 h at 0 ºC and then it was quenched with saturated aqueous NH_4Cl solution (5 mL). The organic layer was dried and concentrated to an oil which was purified by chromatography (SiO_2, CH_2Cl_2) to afford the corresponding ketone **V** (194 mg) which was used without further purification. The crude product was cromatographed (SiO_2, CH_2Cl_2) to provide the pure ketone **V** to measure the optical rotation. R_f = 0.5 (SiO_2, CH_2Cl_2); $[\alpha]^{25}_D$ –39.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ –0.25 (s, 3H), –0.09 (s, 3H), 0.86 (s, 9H), 2.10 (s, 3H), 2.74 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.86 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.79 (s, 3H), 4.12 (dd,

J = 7.6, 4.4 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ –5.4 (CH_3), –5.3 (CH_3), 18.0 (C), 25.6 (CH_3), 25.7 (CH_3), 40.4 (CH_2), 55.3 (CH_3), 80.3 (CH), 113.7 (CH), 129.0 (C), 130.8 (CH), 158.4 (C), 212.2 (C). Anal. Calcd for $C_{17}H_{28}O_3Si$: C 66.19, H 9.15. Found: C 66.47, H 9.34.

(2*R*,3*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-(4-methoxy-phenyl)-butan-2-ol (VI)

To a solution of ketone **V** (110 mg, 0.36 mmol) in MeOH (4 mL) at rt $CeCl_3$ (14 mg, 0.05 mmol) was added. The resulting mixture was stirred for 20 min and then cooled to -20 ºC. $NaBH_4$ (56 mg, 1.43 mmol) was added and the reaction mixture was stirred for 1 h at -20 ºC. After that it was quenched with H_2O (4 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The resulting organic layer was dried and concentrated to give a mixture of alcohols **VI** and *epi*-**VI** in a 92:8 ratio according to the NMR spectrum. Purification by chromatography (SiO_2, CH_2Cl_2) gave **VI** (89 mg, 81% from **IV**) as a colourless oil. R_f = 0.35 (SiO_2, CH_2Cl_2); $[\alpha]^{25}_D$ –5.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ –0.06 (s, 3H), 0.06 (s, 3H), 0.91 (s, 9H), 1.11 (d, *J* = 6.3 Hz, 3H), 2.66 (dd, *J* = 13.4, 5.5 Hz, 1H), 2.89 (dd, *J* = 13.8, 7.5 Hz, 1H), 3.53-3-66 (m, 2H), 3.79 (s, 3H), 6.82 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ –4.6 (CH_3), –4.5 (CH_3), 18.1 (C), 20.3 (CH_3), 25.9 (CH_3), 39.4 (CH_2), 55.2 (CH_3), 67.8 (CH), 77.5 (CH), 113.7 (CH), 130.3 (C), 130.6 (CH), 158.1 (C). Anal. Calcd for $C_{17}H_{30}O_3Si$: C 65.73, H 9.74. Found: C 65.76, H 9.71.

(2*R*,3*S*)-Methanesulfonic acid 2-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-methoxy-phenyl)-1-methyl-propyl ester (VII)

To a solution of **VI** (68 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) cooled to -20 ºC and under argon atmosphere MsCl (0.035 mL, 0.44 mmol) and Et_3N (0.061 mL, 0.44 mmol) were added. The resulting solution was stirred from 0 ºC to rt for 15 h. The reaction mixture was washed with $NaHCO_3$ (2 mL), HCl 1 N (2 mL), dried and concentrated to an oil which was purified by chromatography (SiO_2, CH_2Cl_2) to give **VII** (81 mg, 95%) as a colourless oil. R_f = 0.57 (SiO_2, CH_2Cl_2); $[\alpha]^{25}_D$ –14.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ –0.38 (s, 3H), –0.03 (s, 3H), 0.85 (s, 9H), 1.44 (d, *J* = 6.6 Hz, 3H), 2.56 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.90 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.04 (s, 3H), 3.80 (s, 3H), 3.95 (dt, *J* = 8.8, 4.4 Hz, 1H), 4.71 (qd, *J* = 6.6, 4.4 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ –4.74 (CH_3),

–4.66 (CH_3), 15.0 (CH_3), 17.9 (C), 25.8 (CH_3), 36.6 (CH_3), 38.7 (CH_2), 55.3 (CH_3), 74.8 (CH), 79.7 (CH), 113.6 (CH), 130.2 (C), 130.7 (CH), 158.2 (C). Anal. Calcd for $C_{18}H_{32}O_5SSi$: C 55.63, H 8.30, S 8.25. Found: C 55.93, H 8.60, S 7.95.

(1*S*,2*S*)-[2-Azido-1-(4-methoxy-benzyl)-propoxy]-*tert*-butyl-dimethyl-silane (VIII)

To a solution of **VII** (70 mg, 0.18 mmol) in DMF (1.5 mL) under argon atmosphere Na N_3 (40 mg, 0.54 mmol) was added. The mixture was heated at 60 ºC for 6 h. Then, 3 equivalents more of NaN_3 (40 mg, 0.54 mmol) were added and the mixture was stirred for 24 h. After cooling, the mixture was poured in water (5 mL) and extracted with Et_2O (3 x 15 mL). The resulting organic layer was dried and concentrated to an oil which was purified by chromatography (SiO_2, CH_2Cl_2) to give **VIII** (43 mg, 72%) as a colourless oil. R_f = 0.86 (SiO_2, CH_2Cl_2); $[\alpha]^{25}_D$ –18.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ –0.13 (s, 3H), 0.09 (s, 3H), 0.93 (s, 9H), 1.29 (d, *J* = 6.9 Hz, 3H), 2.70 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.80 (dd, *J* = 13.6, 6.8 Hz, 1H), 3.80 (s, 3H), 3.44 (qd, *J* = 6.9, 4.4 Hz, 1H), 3.95 (td, *J* = 6.8, 4.4 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ –4.9 (CH_3), –4.7 (CH_3), 13.7 (CH_3), 18.1 (C), 25.9 (CH_3), 39.0 (CH_2), 55.3 (CH_3), 60.4 (CH), 76.3 (CH), 113.7 (CH), 130.0 (C), 130.5 (CH), 158.2 (C).

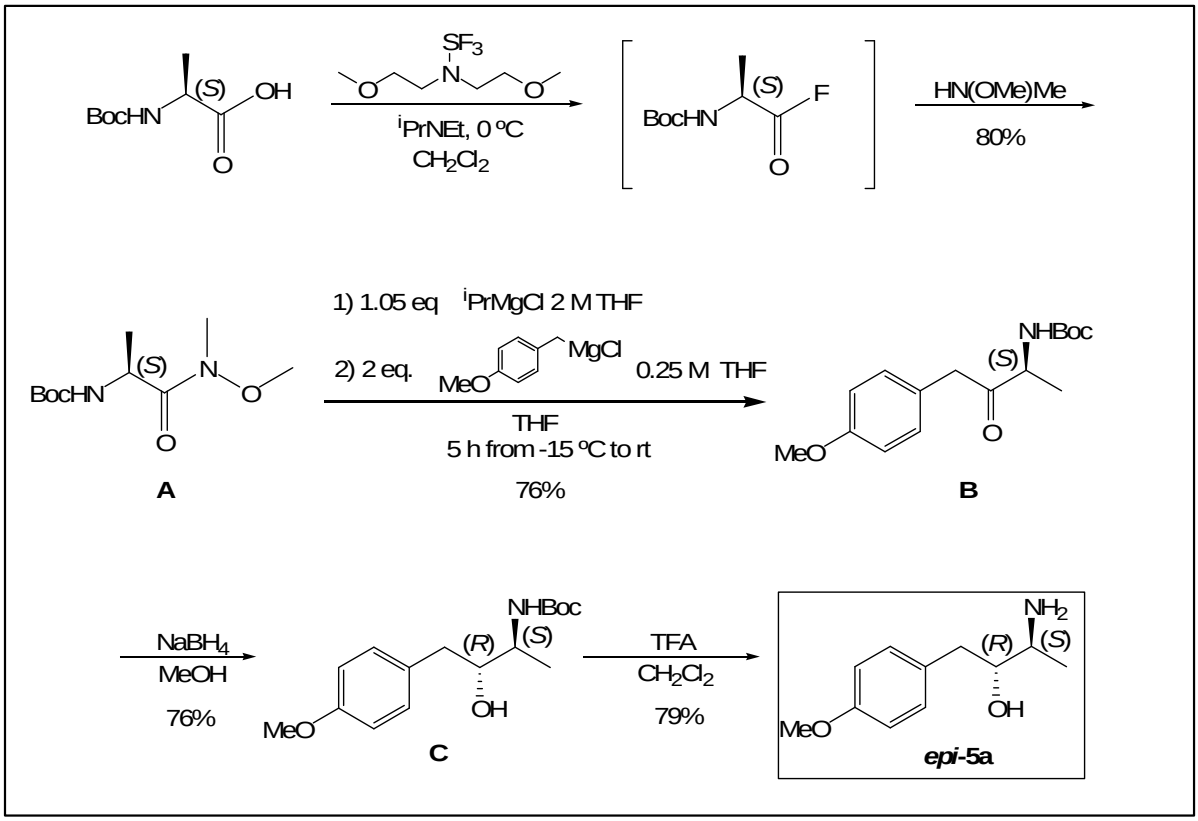
(2*S*,3*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-(4-methoxyphenyl)-2-butanamine (IX)

A suspension of **VIII** (43 mg, 0.13 mmol) and Pd/C (23 mg) in MeOH (1 mL) was stirred at room temperature under hydrogen atmosphere overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated to give an oil which was purified by chromatography (Al_2O_3, CH_2Cl_2 saturated with NH_3) to give **IX** (36 mg, 90%) as a colourless oil. R_f = 0.45 (Al_2O_3, CH_2Cl_2 saturated with NH_3); $[\alpha]^{25}_D$ –18.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ –0.30 (s, 3H), –0.06 (s, 3H), 0.84 (s, 9H), 1.11 (d, *J* = 6.6 Hz, 3H), 2.20-2.40 (br s, 2H), 2.65 (d, *J* = 6.6 Hz, 2H), 2.90-3.00 (m, 1H), 3.70-3.80 (m, 1H), 3.79 (s, 3H), 6.81 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ –4.9 (CH_3), –4.65 (CH_3), 17.9 (CH_3), 18.1 (C), 25.9 (CH_3), 37.5 (CH_2), 50.7 (CH), 55.3 (CH_3), 77.9 (CH), 113.6 (CH), 130.5 (CH), 131.0 (C), 158.0 (C). Anal. Calcd for $C_{17}H_{31}NO_2Si$: C 65.97, H 10.10, N 4.53. Found: C 65.78, H 10.21, N 4.26.

(2*S*,3*S*)-3-Amino-1-(4-methoxyphenyl)butan-2-ol (5a)

To a solution of **IX** (30 mg, 0.1 mmol) in MeOH (1 mL) was added concentrated HCl (0.05 mL, resulting in a 5% v/v solution in MeOH). The resulting solution was stirred for 1 h at rt and then saturated aqueous $NaHCO_3$ (10 mL) was added. The product was extracted with Et_2O (3 x 15 mL), dried and concentrated to an oil which was purified by chromatography (Al_2O_3, CH_2Cl_2 saturated with NH_3/MeOH 9:1) to give **5a** (15 mg, 80%) as a colourless oil. R_f = 0.3 (Al_2O_3, CH_2Cl_2 saturated with NH_3/MeOH 9:1); $[\alpha]^{25}_D$ –15.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, *J* = 6.6 Hz, 3H), 2.56 (dd, *J* = 14.0, 8.6 Hz, 1H), 2.74-2.86 (m, 2H), 3.40-3.46 (m, 1H), 3.78 (s, 3H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5 (CH_3), 39.6 (CH_2), 50.3 (CH), 54.7 (CH_2), 55.2 (CH_3), 76.4 (CH), 113.7 (CH), 130.1 (C), 130.2 (CH), 158.0 (C).

CHAPTER 4. (2*R*,3*S*)-3-AMINO-1-(4-METHOXYPHENYL)BUTAN-2-OL (*epi*-5a)



(3*S*)-3-(α-Boc)-amino-1-(4-methoxyphenyl)butan-2-one (B)

A solution of *N*-Boc-L-alanine Weinreb amide (176 mg, 0.8 mmol), which was prepared from *N*-Boc-L-alanine ([bis(2-methoxyethyl)amino]sulfur trifluoride, DIPEA, HN(OMe)Me, DCM) by the procedure previously reported[72], in dry THF (5 mL) under argon atmosphere was cooled to -15 ºC and ^{i}PrMgCl 2 M in THF (0.4 mL, 0.8 mmol) was added dropwise to afford a clear solution. Then 2-methoxybenzylmagnesium chloride 0.25 M in THF (6 mL, 1.5 mmol) was added dropwise. The reaction mixture was allowed to warm to rt over 30 min. After 5 h aged at rt, the reaction was complete. The mixture was cooled over an ice bath and aqueous HCl 1 N (5 mL) was added slowly, followed by AcOEt (5 mL). The aqueous layer was cut and the organic layer washed with H_2O (5 mL), dried and concentrated to an oil, which was purified by chromatography (SiO_2, CH_2Cl_2) to give **B** as a colourless oil (170 mg, 76%). R_f = 0.16 (SiO_2, CH_2Cl_2);. $[\alpha]^{25}_D$ +21.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (d, *J* = 7.4 Hz, 3H), 1.44 (s, 9H), 3.77 (d, *J* = 10.2 Hz, 2H), 3.79 (s, 3H), 4.4 (m, 1H), 5.2 (br s, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H); ^{13}C

NMR (50 MHz, $CDCl_3$): δ 17.9 (CH_3), 28.4 (CH_3), 45.4 (CH_2), 54.5 (CH), 55.3 (CH_3), 79.2 (C), 114.1 (CH), 125.2 (C), 130.4 (CH), 155.5 (C), 158.3 (C).

(2*R*,3*S*)-3-(α-Boc)-amino-1-(4-methoxyphenyl)butan-2-ol (C)

To a solution of ketone **B** (130 mg, 0.4 mmol) in MeOH (4 mL) cooled to -50 ºC $NaBH_4$ (30 mg, 0.74 mmol) was added and the reaction mixture was stirred for 1 h at -50 ºC. After that it was quenched with brine (4 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The resulting organic layer was dried and concentrated to give an oil which was purified by chromatography (SiO_2, CH_2Cl_2) to give **C** (100 mg, 76%) as a white solid. mp = 88-92 ºC. R_f = 0.02 (SiO_2, CH_2Cl_2); $[\alpha]^{25}_D$ –19.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (d, *J* = 6.9 Hz, 3H), 1.43 (s, 9H), 2.4 (br s, 1H), 2.50-2.75 (m, 2H), 3.60-3.80 (masked, 1H), 3.79 (s, 3H), 4.9 (br s, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.5 (CH_3), 28.4 (CH_3), 39.3 (CH_2), 50.2 (CH), 55.2 (CH_3), 75.3 (CH), 79.3 (C), 114.0 (CH), 130.1 (CH), 130.2 (C), 155.6 (C), 158.2 (C). Anal. Calcd for $C_{16}H_{25}NO_4$: C 65.06, H 8.53, N 4.74. Found: C 65.26, H 8.46, N 4.66.

(2*R*,3*S*)-3-Amino-1-(4-methoxyphenyl)butan-2-ol (*epi*-5a)

To a solution of **C** (95 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) cooled to 0 ºC under argon atmosphere trifluoroacetic acid (Aldrich, 1.2 mL, 16 mmol) was added and the mixture was stirred for 45 min at 0 ºC. The mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with $NaHCO_3$ (10 mL). The aqueous layer was extracted with $CHCl_3$/MeOH 8:2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to an oil which was purified by chromatography (Al_2O_3, CH_2Cl_2 saturated with NH_3/MeOH 9:1) to give ***epi*-5a** as a colourless oil (50 mg, 79%). R_f = 0.25 (Al_2O_3, CH_2Cl_2 saturated with NH_3/MeOH 9:1); $[\alpha]^{25}_D$ +15.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.6 Hz, 3H), 1.97 (br s, 3H), 2.50-2.80 (m, 2H), 2.82-3.00 (m, 1H), 3.55-3.65 (m, 1H), 3.77 (s, 3H), 6.83 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4 (CH_3), 38.3 (CH_2), 50.1 (CH), 55.3 (CH_3), 76.1 (CH), 114.0 (CH), 130.2 (CH), 130.3 (C), 158.1 (C).