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

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2006
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$_2$O$_3$ (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$_2$O$_3$ (aluminium oxide 90, Merck). Drying of organic extracts during workup of reactions was performed over anhydrous Na$_2$SO$_4$. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter. $^1$H 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$_4$Si. All new compounds were determined to be >95% pure by $^1$H NMR spectroscopy.

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

![Chemical structure](image)

*(1S)-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 °C, H$_2$O (66 µL, 0.55 eq.) was added in one portion. After 16 h, *(1S)-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. \([\alpha]^{25}_D +8 \ (c \ 1.0, \ \text{CHCl}_3)\); \(^1\text{H NMR} \ (200 \text{ MHz}, \ \text{CDCl}_3): \ \delta \ 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}\text{C NMR} \ (50 \text{ MHz}, \ \text{CDCl}_3): \ \delta \ 23.4 \ (\text{CH}_2), \ 31.7 \ (\text{CH}_2), \ 32.2 \ (\text{CH}_2), \ 44.8 \ (\text{CH}_2), \ 46.9 \ (\text{CH}_2), \ 52.0 \ (\text{CH}).

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

A mixture of CuI (11 mg, 0.06 mmol) in Et\(_2\)O (8 mL) was cooled to -78 ºC and treated with EtMgBr (3.4 mL, 3.4 mmol) 1 M in THF. After 15 min, \((1S)-1,2\)-epoxy-6-chlorohexane (382 mg, 2.84 mmol) in Et\(_2\)O (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\(_2\)O (3 x 50 mL). The resulting organic layer was washed with brine (20 mL), dried over Na\(_2\)SO\(_4\) 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 \ (\text{SiO}_2, \ 9:1 \ \text{hexane/AcOEt}); \ ^1\text{H NMR} \ (200 \text{ MHz}, \ \text{CDCl}_3) \ \delta \ 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}\text{C NMR} \ (50 \text{ MHz}, \ \text{CDCl}_3): \ \delta \ 14.1 \ (\text{CH}_3), \ 18.8 \ (\text{CH}_2), \ 23.0 \ (\text{CH}_2), \ 32.2 \ (\text{CH}_2), \ 32.6 \ (\text{CH}_2), \ 36.6 \ (\text{CH}_2), \ 39.7 \ (\text{CH}_2), \ 45.0 \ (\text{CH}_2), \ 71.4 \ (\text{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\(_2\)Cl\(_2\) (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\(_2\)CO\(_3\) (2 x 10 mL) and brine (2 x 10 mL), dried over Na\(_2\)SO\(_4\) 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 \ (\text{SiO}_2, \ 9:1 \ \text{hexane/AcOEt}); \ ^1\text{H NMR} \ (200 \text{ MHz}, \ \text{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, \ \text{OMe}), \ 3.46 \ (t, \ J = 6.6 \ Hz, \ 2H), \ 4.75 \ (s, \ 1H, \ \text{CHOMe}), \ 4.86-4.99 \ (m, \ 1H).
Experimental

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

To a solution of B (381 mg, 2.33 mmol) in CH₂Cl₂ (8 mL) was added diisopropylamine (8.1 mL, 46.6 mmol) followed by MOMCI (1.8 mL, 23.3 mmol). The resulting mixture was stirred at rt overnight. The reaction was quenched with H₂O. The aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to an oil which was purified by chromatography (SiO₂, 9:1 hexane/AcOEt) to give C as a colourless oil (474 mg, 98%). Rᵣ = 0.46 (SiO₂, 9:1 hexane/AcOEt); ¹H NMR (200 MHz, CDCl₃): 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); ¹³C NMR (50 MHz, CDCl₃): δ 14.3 (CH₃), 18.5 (CH₂), 22.7 (CH₂), 32.7 (CH₂), 33.6 (CH₂), 36.5 (CH₂), 45.0 (CH₂), 55.5 (CH₃), 77.0 (CH), 95.4 (CH₂).
(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$_3$N (0.7 mL, 5 mmol) at -20 °C. 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...
Experimental

with 2 N aqueous NaOH (10 mL) and H₂O (5 mL). The aqueous layer was washed with tert-butylmethyl ether (2 x 20 mL) and the organic layer with H₂O (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. *R* = 0.40 (SiO₂, 1:1 AcOEt/MeOH); m.p. 162-164 °C. [α]²⁵D −10.7 (c 0.56, CHCl₃); ¹H NMR (200 MHz, CDCl₃) 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); ¹³C NMR (50 MHz, CDCl₃): 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).

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

K₂CO₃ (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, Mel (0.32 mL, 5 mmol) was added dropwise and the mixture was stirred overnight. The mixture was quenched with H₂O (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 which was used without further purification. The NMR data were identical to the racemic compound previously reported. *R* = 0.23 (SiO₂, CH₂Cl₂); ¹H NMR (200 MHz, CDCl₃) δ 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); ¹³C NMR (50 MHz, CDCl₃): δ 39.6 (CH₂), 52.4 (CH₃), 55.2 (CH₃), 71.4 (CH), 113.9 (CH), 128.2 (C), 130.5 (CH), 158.6 (C), 174.5 (C).

(2S)-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 °C under argon atmosphere Me(MeO)NH.HCl (542 mg, 5 mmol) was added and then over 30 min a solution of iPrMgCl 2.0 M in THF (5 mL, 10 mmol) was added dropwise maintaining the temperature at -20 °C. The mixture was stirred 2 h at -20 °C and 2.5 h from -20 °C to rt. The mixture was quenched with saturated aqueous NH₄Cl 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.

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ther purification: \( R_f = 0.29 \) (SiO\(_2\), CH\(_2\)Cl\(_2\)/MeOH 99:1). \( ^1\)H NMR (200 MHz, CDCl\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 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).

\((2S)-2-(\text{tert-Butyl-dimethyl-silanyloxy})-N\text{-methoxy-3-(4-methoxy-phenyl)-N-methyl-propionamide (IV)}\)

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\(_2\)O (20 mL). The organic layer was washed with H\(_2\)O (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\(_2\)Cl\(_2\)) to afford the corresponding Weinreb amide IV (229 mg, 67% from I) as a yellow oil. \( R_f = 0.23 \) (SiO\(_2\), CH\(_2\)Cl\(_2\)). \( ^1\)H NMR (200 MHz, CDCl\(_3\)): \( \delta \) −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\(_3\)): \( \delta \) −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).

\((3S)-3-(\text{tert-Butyl-dimethyl-silanyloxy})-4-(4-methoxy-phenyl)-butan-2-one (V)\)

To a solution of Weinreb amide V (222 mg, 0.63 mmol) in THF (8 mL) cooled to 0 °C under argon atmosphere MeMgBr 3 M in Et\(_2\)O (1 mL, 3.1 mmol) was added dropwise. The reaction mixture was stirred for 4 h at 0 °C and then it was quenched with saturated aqueous NH\(_4\)Cl solution (5 mL). The organic layer was dried and concentrated to an oil which was purified by chromatography (SiO\(_2\), CH\(_2\)Cl\(_2\)) to afford the corresponding ketone V (194 mg) which was used without further purification. The crude product was chromatographed (SiO\(_2\), CH\(_2\)Cl\(_2\)) to provide the pure ketone V to measure the optical rotation. \( R_f = 0.5 \) (SiO\(_2\), CH\(_2\)Cl\(_2\)); [\( \alpha \)]\(^{25}_D\) −39.5 (c 1.2, CHCl\(_3\)).

\( ^1\)H NMR (200 MHz, CDCl\(_3\)): \( \delta \) −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,
Experimental

$J = 7.6, 4.4$ 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$_3$Si: C 66.19, H 9.15. Found: C 66.47, H 9.34.

(2R,3S)-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 $-20$ °C. NaBH$_4$ (56 mg, 1.43 mmol) was added and the reaction mixture was stirred for 1 h at $-20$ °C. After that it was quenched with H$_2$O (4 mL) and extracted with CH$_2$Cl$_2$ (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$_2$Cl$_2$) gave VI (89 mg, 81% from IV) as a colourless oil. $R_f = 0.35$ (SiO$_2$, CH$_2$Cl$_2$); $[\alpha]^{25}_D -5.8$ (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, $2H$); $^{13}C$ 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$_3$Si: C 65.73, H 9.74. Found: C 65.76, H 9.71.

(2R,3S)-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$_2$Cl$_2$ (2 mL) cooled to $-20$ °C and under argon atmosphere MsCl (0.035 mL, 0.44 mmol) and Et$_3$N (0.061 mL, 0.44 mmol) were added. The resulting solution was stirred from 0 °C to rt for 15 h. The reaction mixture was washed with NaHCO$_3$ (2 mL), HCl 1 N (2 mL), dried and concentrated to give VII (81 mg, 95%) as a colourless oil. $R_f = 0.57$ (SiO$_2$, CH$_2$Cl$_2$); $[\alpha]^{25}_D -14.9$ (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$_3$),
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−4.66 (CH₃), 15.0 (CH₃), 17.9 (C), 25.8 (CH₃), 36.6 (CH₃), 38.7 (CH₂), 55.3 (CH₃), 74.8 (CH), 79.7 (CH), 113.6 (CH), 130.2 (C), 130.7 (CH), 158.2 (C). Anal. Calcd for C₁₈H₃₂O₅Si: C 55.63, H 8.30, S 8.25. Found: C 55.93, H 8.60, S 7.95.

(1S,2S)-[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 N₃ (40 mg, 0.54 mmol) was added. The mixture was heated at 60 °C for 6 h. Then, 3 equivalents more of NaN₃ (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 Et₂O (3 x 15 mL). The resulting organic layer was dried and concentrated to an oil which was purified by chromatography (SiO₂, CH₂Cl₂) to give VIII (43 mg, 72%) as a colourless oil. Rᵣ = 0.86 (SiO₂, CH₂Cl₂); [α]²⁵ₒ −18.6 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): δ −4.9 (CH₃), −4.7 (CH₃), 13.7 (CH₃), 18.1 (C), 25.9 (CH₃), 39.0 (CH₂), 55.3 (CH₃), 60.4 (CH), 76.3 (CH), 113.7 (CH), 130.0 (C), 130.5 (CH), 158.2 (C).

(2S,3S)-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 (Al₂O₃, CH₂Cl₂ saturated with NH₃) to give IX (36 mg, 90%) as a colourless oil. Rᵣ = 0.45 (Al₂O₃, CH₂Cl₂ saturated with NH₃); [α]²⁵ₒ −18.6 (c 1.2, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): δ −4.9 (CH₃), −4.65 (CH₃), 17.9 (CH₃), 18.1 (C), 25.9 (CH₃), 37.5 (CH₂), 50.7 (CH), 55.3 (CH₃), 77.9 (CH), 113.6 (CH), 130.5 (CH), 131.0 (C), 158.0 (C). Anal. Calcd for C₁₇H₃₁NO₂Si: C 65.97, H 10.10, N 4.53. Found: C 65.78, H 10.21, N 4.26.
(2S,3S)-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 NaHCO₃ (10 mL) was added. The product was extracted with Et₂O (3 x 15 mL), dried and concentrated to an oil which was purified by chromatography (Al₂O₃, CH₂Cl₂ saturated with NH₃/MeOH 9:1) to give 5a (15 mg, 80%) as a colourless oil. $R_f = 0.3$ (Al₂O₃, CH₂Cl₂ saturated with NH₃/MeOH 9:1); $[\alpha]_{D}^{25} = -15.0$ (c 1.0, CHCl₃); $^1$H NMR (300 MHz, CDCl₃): $\delta$ 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, CDCl₃): $\delta$ 20.5 (CH₃), 39.6 (CH₂), 50.3 (CH), 54.7 (CH₂), 55.2 (CH₃), 76.4 (CH), 113.7 (CH), 130.1 (C), 130.2 (CH), 158.0 (C).
CHAPTER 4. (2R,3S)-3-AMINO-1-(4-METHOXYPHENYL)BUTAN-2-OL (epi-5a)

(3S)-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\(^\text{72}\), in dry THF (5 mL) under argon atmosphere was cooled to -15 °C and \(^1\)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 washed with H\(_2\)O (5 mL), dried and concentrated to an oil, which was purified by chromatography (SiO\(_2\), CH\(_2\)Cl\(_2\)) to give B as a colourless oil (170 mg, 76%). \(R_f = 0.16\) (SiO\(_2\), CH\(_2\)Cl\(_2\)); \([\alpha]^{25}_D +21.4\) (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
Experimental

NMR (50 MHz, CDCl₃): δ 17.9 (CH₃), 28.4 (CH₃), 45.4 (CH₂), 54.5 (CH), 55.3 (CH₃), 79.2 (C), 114.1 (CH), 125.2 (C), 130.4 (CH), 155.5 (C), 158.3 (C).

(2R,3S)-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 °C NaBH₄ (30 mg, 0.74 mmol) was added and the reaction mixture was stirred for 1 h at -50 °C. After that it was quenched with brine (4 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The resulting organic layer was dried and concentrated to give an oil which was purified by chromatography (SiO₂, CH₂Cl₂) to give C (100 mg, 76%) as a white solid. mp = 88-92 °C. Rᵣ = 0.02 (SiO₂, CH₂Cl₂); [α]²⁵D -19.8 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (50 MHz, CDCl₃): δ 14.5 (CH₃), 28.4 (CH₃), 39.3 (CH₂), 50.2 (CH), 55.2 (CH₃), 75.3 (CH), 79.3 (C), 114.0 (CH), 130.1 (CH), 130.2 (C), 155.6 (C), 158.2 (C). Anal. Calcd for C₁₆H₂₅NO₄: C 65.06, H 8.53, N 4.74. Found: C 65.26, H 8.46, N 4.66.

(2R,3S)-3-Amino-1-(4-methoxyphenyl)butan-2-ol (epi-5a)
To a solution of C (95 mg, 0.32 mmol) in CH₂Cl₂ (3 mL) cooled to 0 °C under argon atmosphere trifluoroacetic acid (Aldrich, 1.2 mL, 16 mmol) was added and the mixture was stirred for 45 min at 0 °C. The mixture was diluted with CH₂Cl₂ (10 mL) and the organic layer was washed with NaHCO₃ (10 mL). The aqueous layer was extracted with CHCl₃/MeOH 8:2 (2 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to an oil which was purified by chromatography (Al₂O₃, CH₂Cl₂ saturated with NH₃/MeOH 9:1) to give epi-5a as a colourless oil (50 mg, 79%). Rᵣ = 0.25 (Al₂O₃, CH₂Cl₂ saturated with NH₃/MeOH 9:1); [α]²⁵D +15.7 (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃): δ 17.4 (CH₃), 38.3 (CH₂), 50.1 (CH), 55.3 (CH₃), 76.1 (CH), 114.0 (CH), 130.2 (CH), 130.3 (C), 158.1 (C).