CHEMISTRY
A EUROPEAN JOURNAL

Supporting Information

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Trapped in Misbelief for Almost 40 Years: Selective Synthesis of the Four Stereoisomers of Mefloquine

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Supporting Information

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1 General

Reactions were performed in flame dried flasks under an argon atmosphere. Solvents were dried according to common laboratory techniques and freshly distilled prior to use. All reagents purchased from commercial sources were used directly without further purification.

2 Instruments

Optical rotations: Polarimeter model 241 from Perkin-Elmer and polarimeter P-2000 from JASCO. The concentration c is calculated as $c = \frac{g}{100ml}$. The optical rotation $[\alpha]_D$ is given as $[\alpha]_D = \frac{\alpha}{c \cdot l}$, while l = 1 dm.

IR spectra: An FT/IR-4100 instrument (ATR) from JASCO was used as instrument.

UV/vis-spectra: Spectra were recorded using the UV-Vis-spectrometer 8453 from Hewlett Packard.

^{1}H-NMR spectra: ^{1}H-NMR spectra were recorded on a 400 MHz Ultrashield spectrometer from Bruker at 298 K. Chemical shifts are reported in δ (ppm). Residual peaks of the deuterated solvents indicated were used as internal standards. The following abbreviations are used for characterization of the multiplicity of the signals: s (singlet), s_{br} (broad singlet), d (doublet), t (triplet), m (multiplet), m_c (centered multiplet). The spectra were interpreted according to first order. Coupling constants *J* are given in Hertz (Hz).

^{13}C-NMR spectra: ^{1}H-NMR spectra were recorded on a 400 MHz (101 MHz) Ultrashield spectrometer from Bruker at 298 K. Chemical shifts are reported in δ (ppm). Residual peaks of the deuterated solvents indicated were used as internal standards. Chemical shifts are taken from the ^{1}H broadband decoupled spectra.

Mass spectra: ESI spectra were recorded using an ion trap mass spectrometer LCQ from Finnigan or a micrOTOF from Bruker Daltronik. ESI HRMS spectra were recorded on a 7 Tesla-Fourier Transform Ion Cyclotron Resonance (FTICR)-mass spectrometer APEX IV from Bruker, equipped with an Apollo-ESI-source from Bruker and a 74900 series syringe pump from Cole-Parmer, which was operated at a pump flow of 2 µL/min. The mass/charge ratios are reported. For acquisition and analysis of the spectra the

XMASS software from Bruker was used. Alternatively, ESI HRMS spectra were recorded on a micrOTOF from Bruker Daltronik.

Thin-layer chromatography (TLC): Precoated silica gel SIL G/UV254 plates from Merck were used for TLC and vanillin in methanolic sulphuric acid (0.5 g vanillin, 3 mL conc. H_2SO_4, 85 mL methanol and 10 mL acetic acid) was used as staining agent.

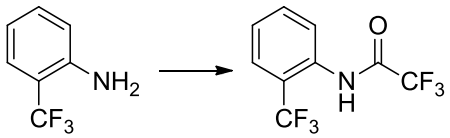
Column chromatography: Silica gel 60 (0.040–0.063 mm) from Merck was used, unless otherwise stated.

3 Analytical HPLC

Analytical separations were performed on a HPLC system from *Jasco* equipped with a PU-2080 *Plus* solvent pump, a LG-2080-04 mixing chamber, a MD-2010 *Plus* multi-wavelength detector and a LC-Net II/ADC controller. For monitoring, data acquisition and data analysis the ChromPass software from *Jasco* was used. A Chiralpak® IA-3 (250 × 4.6 mm, particle size: 3 µm) column from *Daicel Chemical Industries Ltd.* was used. The sample was injected manually via a *Rheodyne* Manual Sample Injector 7725(i) attached to a 20 µL loop.

4 Synthetic procedures

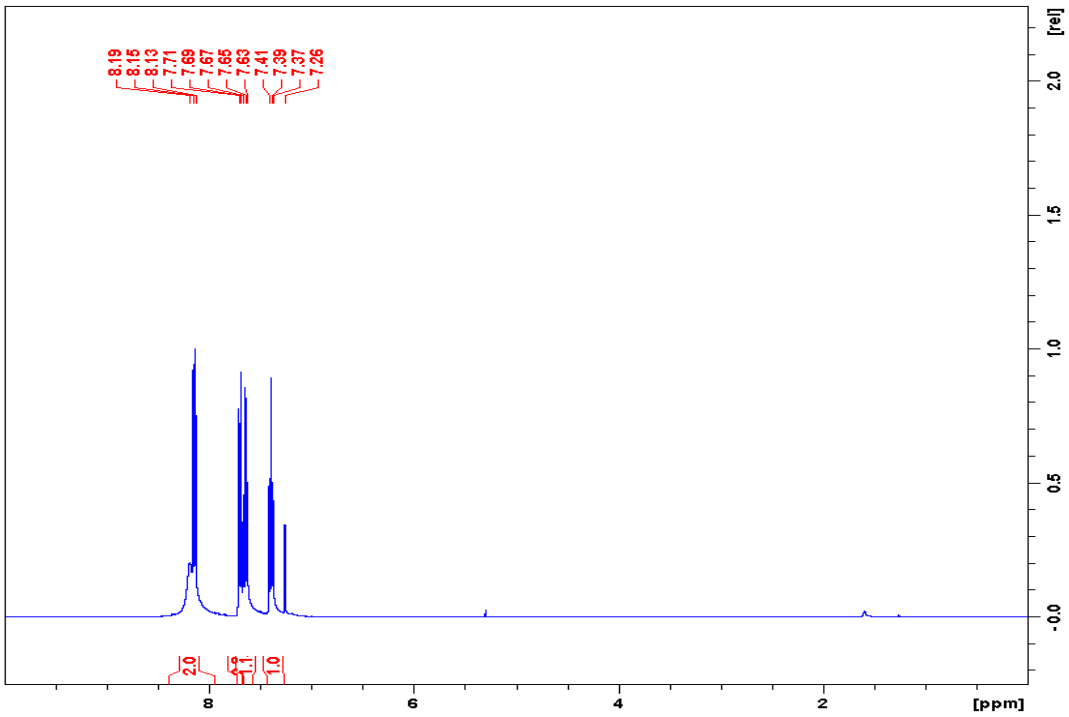
4.1 Synthesis of *N*-[2-(trifluoromethyl)phenyl]trifluoracetamide **(6)**



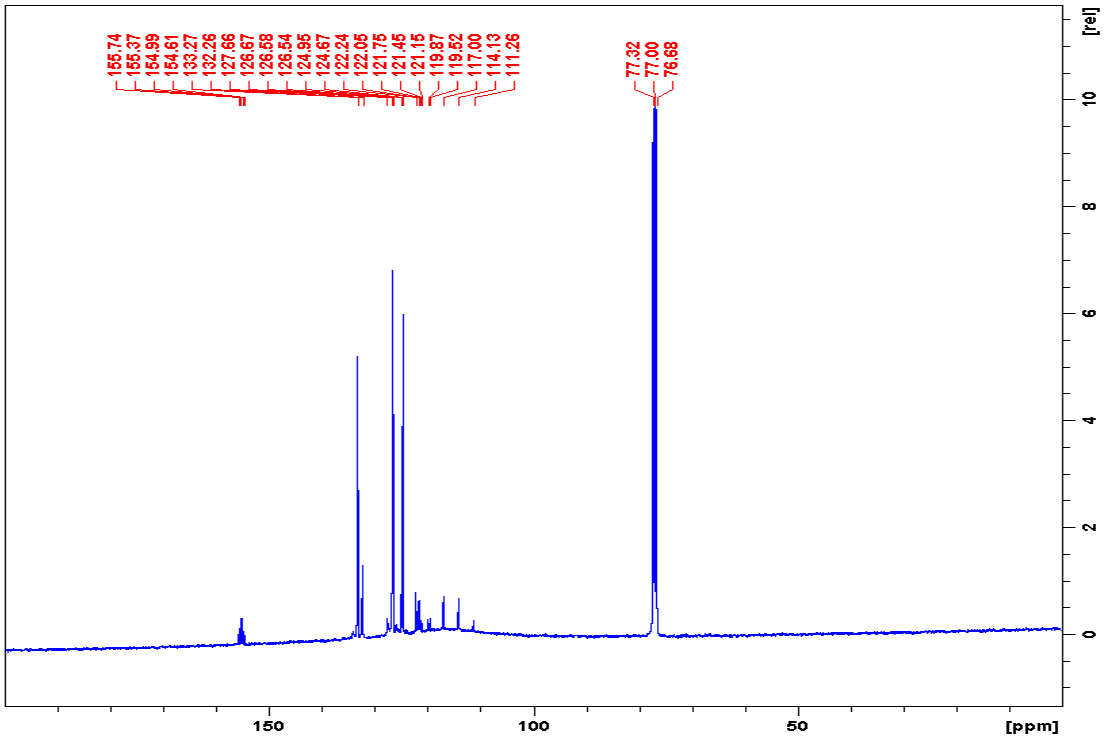
5 **6**

To a stirred solution of 2-trifluoromethylaniline (**5**) (12.4 mL, 16.1 g, 100 mmol, 1.00 equiv.), pyridine (10.1 mL, 9.89 g, 125 mmol, 1.25 equiv.), and 4-dimethylaminopyridine (146 mg, 1.20 mmol, 1.2 mol-%) in CH_2Cl_2 (100 mL) was added trifluoroacetic anhydride (15.3 mL, 23.1 g, 110 mmol, 1.10 equiv.) at 0 °C under N_2 within 30 min. The reaction mixture was stirred at 20 °C for 15 h and quenched with water (300 mL). The separated organic layer was washed with 1 N HCl (2 × 50 mL), water (50 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo to give the trifluoroacetamide **6** (25.1 g, 97.6 mmol, 98%) as a white solid.

MP: 62-65 °C; **IR** (ATR): $\tilde{\nu}$ = 1720, 1542, 1316, 1204, 1160, 1147, 1121, 1108, 1059, 1035, 920 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.39 (t, *J* = 7.7 Hz, 1 H), 7.65 (t, *J* = 7.9 Hz, 1 H), 7.70 (d, *J* = 7.9 Hz, 1 H), 8.14 (d, *J* = 8.2 Hz, 1 H), 8.19 (s_{br}, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 115.6 (q, $^1J_{CF}$ = 288.6 Hz), 121.6 (q, $^2J_{CF}$ = 30.3 Hz), 123.6 (q, $^1J_{CF}$ = 273.0 Hz), 124.7, 126.6 (q, $^3J_{CF}$ = 4.9 Hz), 126.7, 132.3, 133.3, 155.2 (q, $^2J_{CF}$ = 37.9 Hz); **HRMS** (ESI): *m/z* calc. for $C_9H_6F_6NNaO$: 280.0168, found: 280.0168, $[M+Na]^+$.

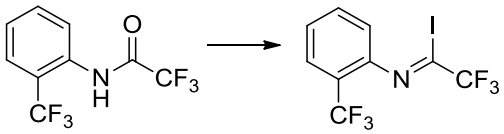


Supporting Figure 1: ^{1}H-NMR spectrum of 6



Supporting Figure 2: ^{13}C-NMR spectrum of 6

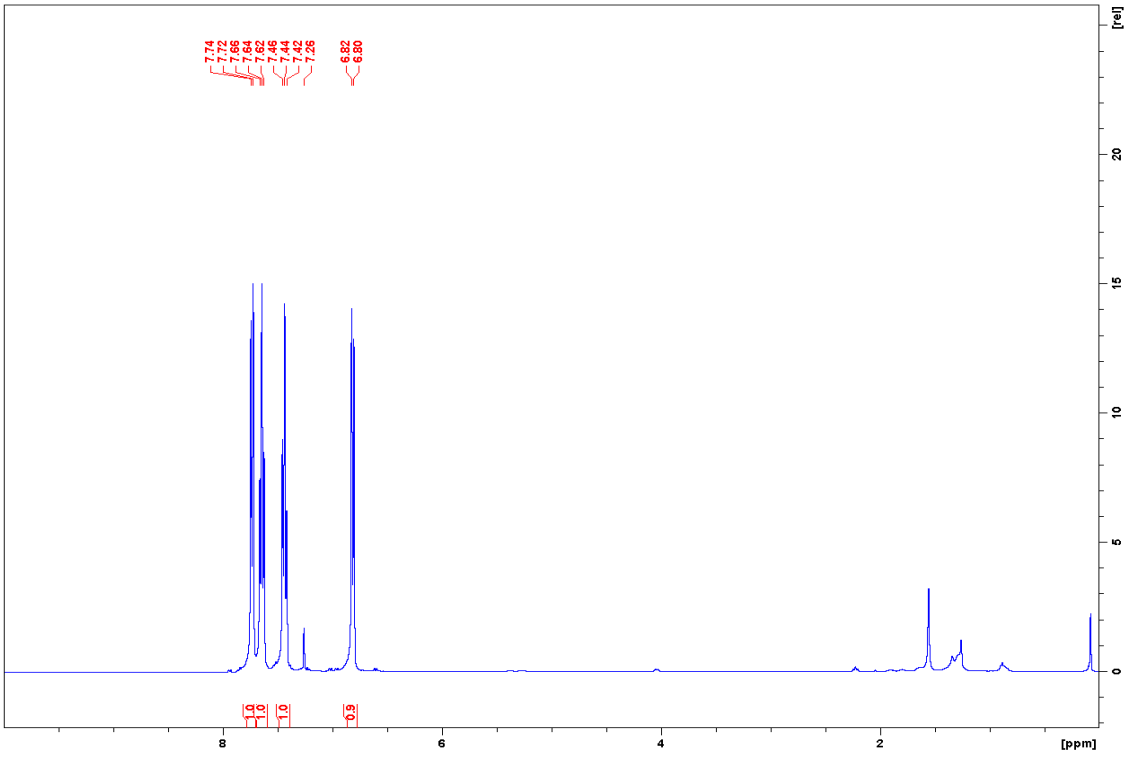
4.2 Synthesis of *N*-[2-(trifluoromethyl)phenyl]trifluoroacetimidoyl iodide **(3)**



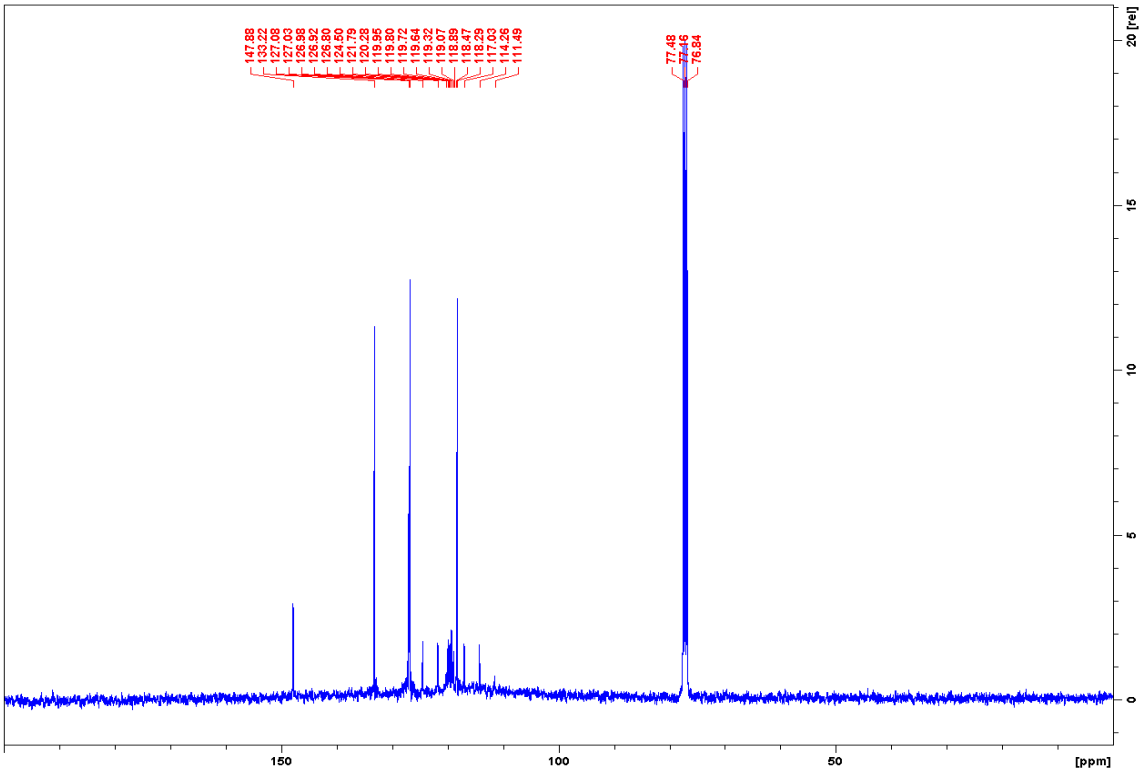
6 **3**

To a stirred solution of Ph_3P (2.62 g, 10.0 mmol, 1.00 equiv.) in toluene (40 mL) was added iodine (2.54 g, 10.0 mmol, 1.00 equiv.) at 20 °C under N_2 within 10 min. The mixture was stirred at 40 °C for 30 min until complete dissolution of iodine. Subsequently, *N*-[2-(trifluoromethyl)phenyl]trifluoracetamide **6** (2.57 g, 10.0 mmol, 1.00 equiv.) and *i*-Pr_2NEt (1.71 mL, 1.29 g, 10.0 mmol, 1.00 equiv.) were added, the resulting mixture was stirred at 80 °C for 1 h and cooled to 20 °C. *n*-Hexane (40 mL) was added and the mixture was filtered through a 1 cm silica gel plug. The filtrate was concentrated and distilled in vacuo (Kugelrohr, 110 °C, 10 mbar). The resulting product contained a little toluene and **6** was purified by flash chromatography (SiO_2, *n*-hexane) to give **3** (2.61 g, 7.10 mmol, 71%) as a yellow liquid.

TLC: R_f = 0.57 (*n*-hexane/ethyl acetate 20:1); **BP**: 110 °C (10 mbar); **IR** (ATR): $\tilde{\nu}$ = 1692, 1316, 1270, 1219, 1201, 1157, 1127, 1112, 1057, 1034, 901, 869, 837, 760, 707 cm^{-1}; **UV** (CH_3CN): λ_{max} (lg ε) = 226 (5.064), 271 (4.313) nm; **^{1}H-NMR** (400 MHz, $CDCl_3$): 6.81 (d, *J* = 8.1 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 1 H), 7.64 (t, *J* = 7.7 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 115.7 (q, $^1J_{CF}$ = 278.9 Hz), 118.3, 119.1 (q, $^2J_{CF}$ = 43.2 Hz), 119.8 (q, $^2J_{CF}$ = 31.9 Hz), 123.1 (q, $^1J_{CF}$ = 273.4 Hz), 126.8, 127.0 (q, $^3J_{CF}$ = 5.2 Hz), 133.2, 147.9; **HRMS** (EI): *m/z* calc. for $C_9H_4F_6IN$: 366.9293, found: 366.9301 $[M]^+$.

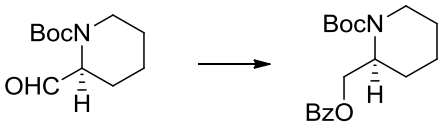


Supporting Figure 3: ^{1}H-NMR spectrum of 3



Supporting Figure 4: ^{13}C-NMR spectrum of 3

4.3 Synthesis of (*S*)-*tert*-butyl 2-[(benzoyloxy)methyl]piperidine-1-carboxylate (**7**)

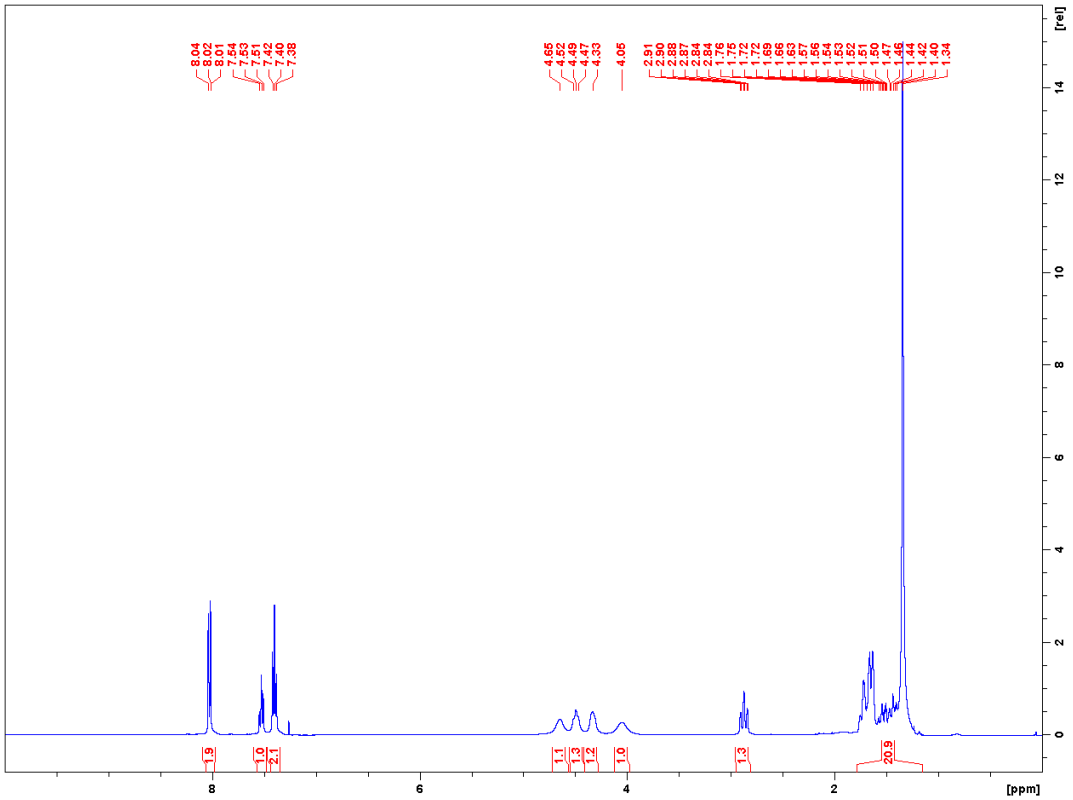


2 **7**

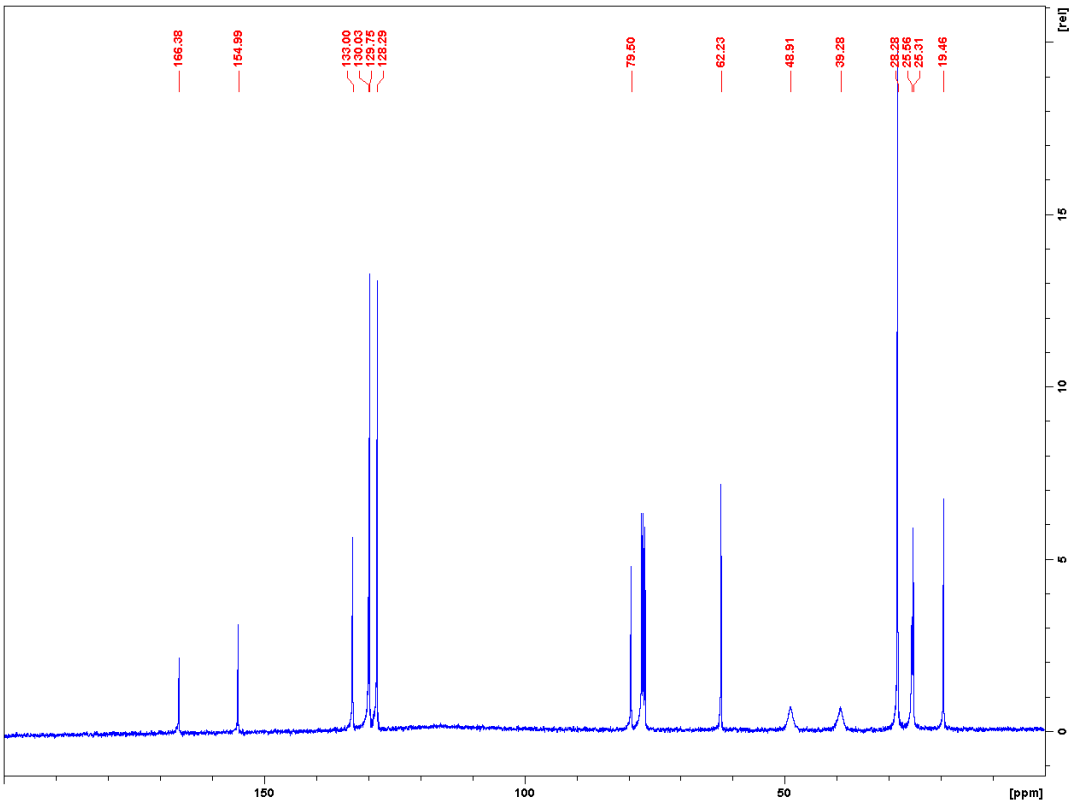
The aldehyde **2** (567 mg, 2.66 mmol) was dissolved in EtOH (5.0 mL) and added to a stirred solution of $NaBH_4$ (120 mg, 3.19 mmol, 1.20 equiv.) in EtOH (15.0 mL) at room temperature and the reaction mixture was stirred for 60 min. Afterwards the reaction mixture was diluted with Et_2O (50 mL), washed with sat. aq. NH_4Cl-solution (50 mL), brine (50 mL), sat. aq. $NaHCO_3$-solution (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude alcohol was dried for 90 min under high vacuum.

The residue was dissolved in CH_2Cl_2 (12.0 mL), 4-(dimethylamino)pyridine (16.2 mg, 133 µmol, 5 mol-%), NEt_3 (479 µL, 350 mg, 3.46 mmol, 1.30 equiv.) and benzoyl chloride (402 µL, 486 mg, 3.46 mmol, 1.30 equiv.) were added at room temperature. The reaction mixture was stirred for 12 h at room temperature. The mixture was diluted with CH_2Cl_2 (40 mL), washed with sat. aq. $NaHCO_3$-solution (3 × 50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. Column chromatography of the residue (SiO_2, *n*-hexane/ethyl acetate 19:1→9:1) gave the benzoate **7** (747 mg, 2.34 mmol, 88%) as white solid.

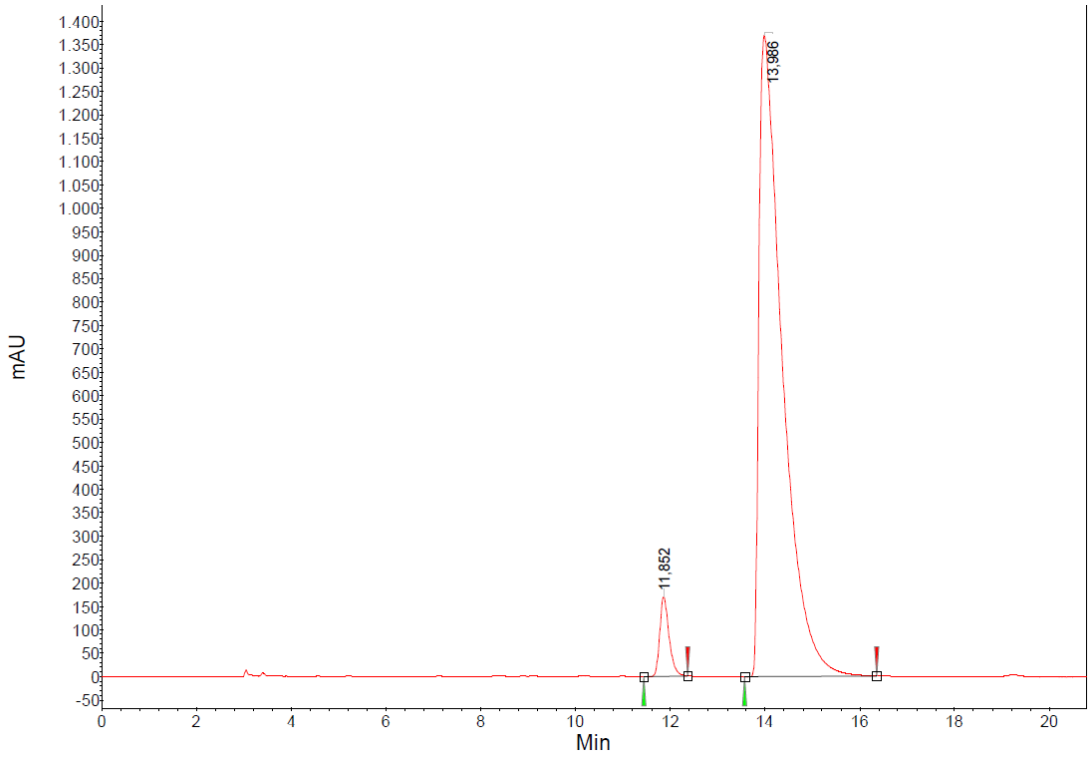
TLC: R_f = 0.35 (*n*-hexane/ acetone 4:1); **MP**: 66–67 °C; α_D^{23} = –7.10 ° (c = 0.5 in MeOH); **IR** (ATR): ṽ = 1714, 1679, 1408, 1313, 1264, 1142, 1117, 1103, 1074, 715 cm^{-1}; **UV** (CH_3CN): 229 (5.092), 273 (3.977), 280 (3.885) nm; **^{1}H-NMR** (400 MHz, $CDCl_3$): 1.34 (s, 9 H), 1.34–1.78 (m, 8 H), 2.87 (td, *J* = 13.4, 1.9 Hz, 1 H), 4.05 (s_{br}, 1 H), 4.28–4.38 (m, 1 H), 4.44–4.55 (m, 1 H), 4.65 (s_{br}, 1 H), 7.40 (t, *J* = 7.8 Hz, 1 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 8.03 (dd, *J* = 8.5, 1.4 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 19.5, 25.3, 25.6, 28.3, 39.3, 48.9, 62.2, 79.5, 128.3, 129.8, 130.0, 133.0, 155.0, 166.4; **HPLC:** Rt_{minor} = 11.9 min; Rt_{major} = 14.0 min (200:1 *n*-hexane/EtOH, flow: 1.0 mL/min; injection volume 20 µL, c = 1.0 mg/mL), *e.r.* = 95:5; **HRMS** (ESI): *m/z* calc. for $C_{18}H_{25}NO_4$: 342.1676, found: 342.1677 $[M+Na]^+$.



Supporting Figure 5: ^{1}H-NMR spectrum of 7

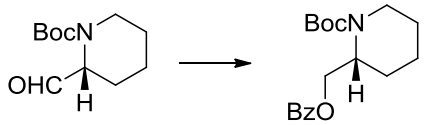


Supporting Figure 6: ^{13}C-NMR spectrum of 7



Supporting Figure 7: CHPLC chromatogram of 7

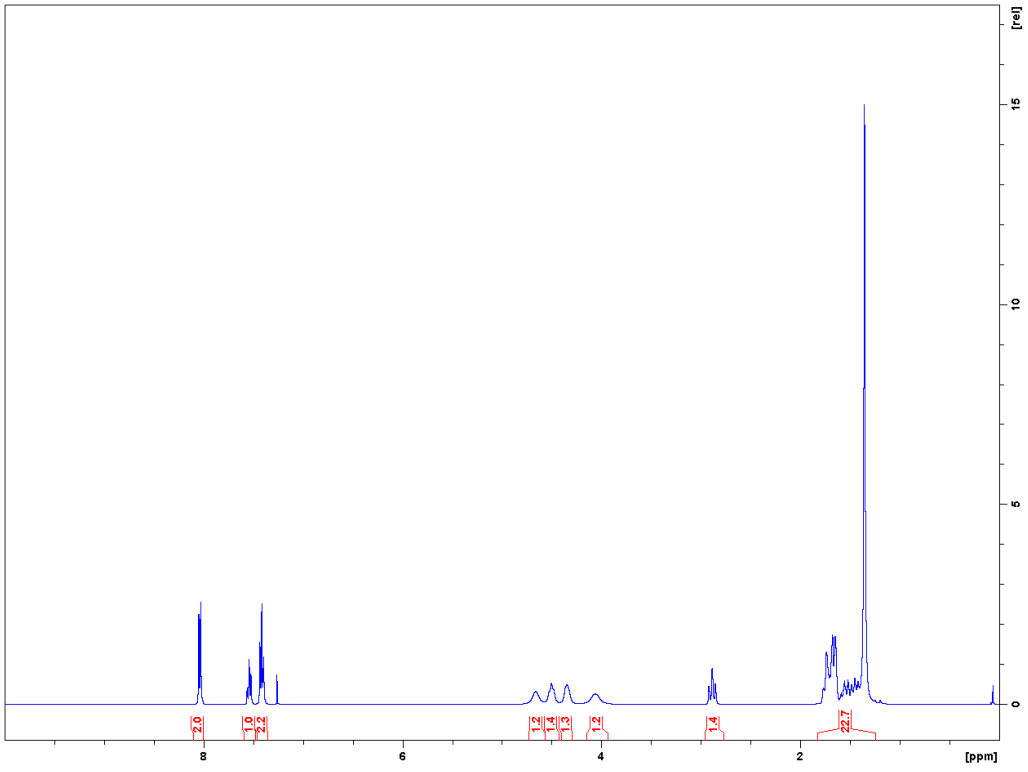
4.4 Analytical data for (*R*)-*tert*-butyl 2-[(benzoyloxy)methyl]piperidine-1-carboxylate (*ent*-**7**)



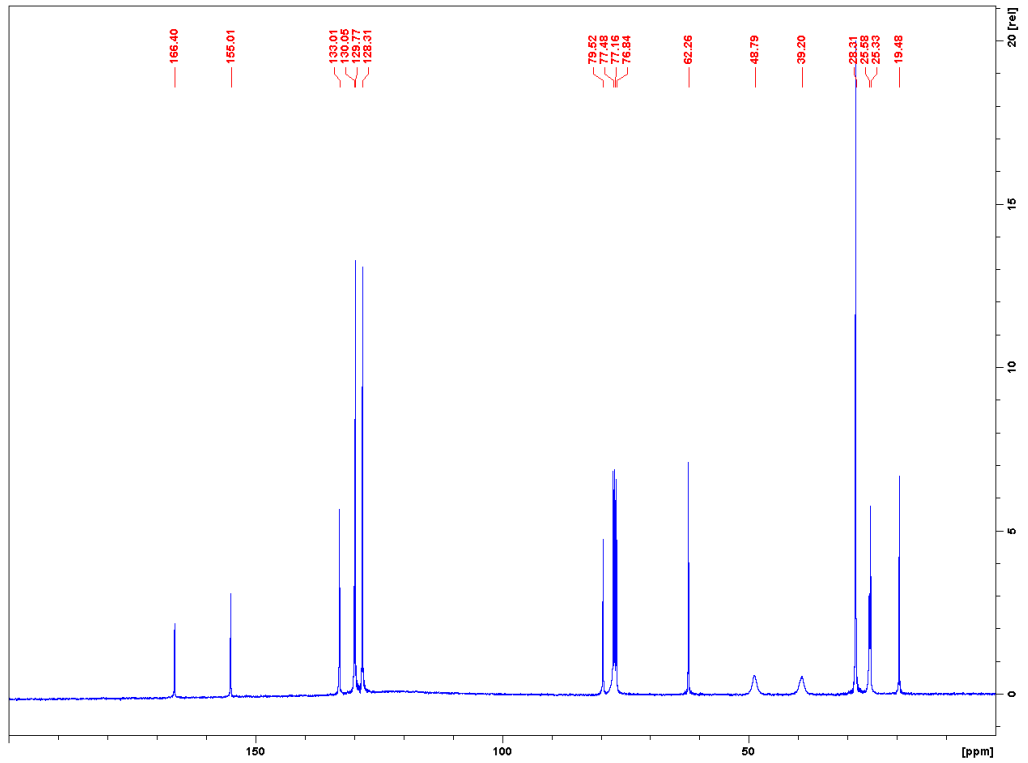
ent-**2** *ent*-**7**

The benzoate *ent*-**7** was synthesized according to 4.3.

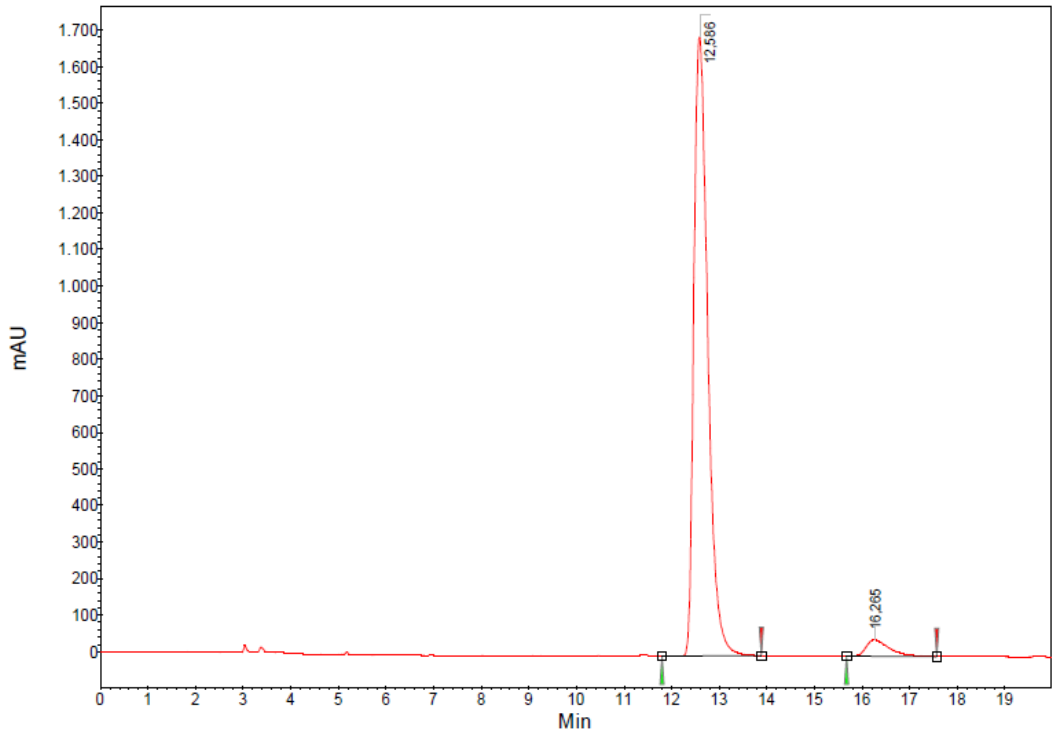
TLC: R_f = 0.35 (*n*-hexane/ acetone 4:1); **MP**: 66–67 °C; α_D^{23} = +5.42 ° (c = 0.5 in MeOH); **IR** (ATR): ṽ = 1714, 1678, 1408, 1312, 1263, 1142, 1116, 1103, 1074, 714 cm^{-1}; **UV** (CH_3CN): 229 (5.131), 273 (4.004), 280 (3.898) nm; **^{1}H-NMR** (400 MHz, $CDCl_3$): 1.35 (s, 9 H), 1.36–1.79 (m, 8 H), 2.88 (td, *J* = 13.2, 1.7 Hz, 1 H), 4.06 (s_{br}, 1 H), 4.29–4.38 (m, 1 H), 4.45–4.55 (m, 1 H), 4.66 (s_{br}, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.53 (t, *J* = 7.5 Hz, 1 H), 8.03 (dd, *J* = 8.5, 1.4 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 19.5, 25.3, 25.6, 28.3, 39.2, 48.8, 62.2, 79.5, 128.3, 129.8, 130.1, 133.0, 155.0, 166.4; **HPLC:** Rt_{major} = 12.6 min; Rt_{minor} = 16.3 min (200:1 *n*-hexane/EtOH, flow: 0.8 mL/min; injection volume 20 µL, c = 1.0 mg/mL), *e.r.* = 96:4; **MS** (ESI): m/z (%) = 320.2 (28) $[M+H]^+$, 337.0 (5) $[M+NH_4]^+$, 342.0 (26) $[M+Na]^+$, 639.1 (64) $[2M+H]^+$, 661.3 (100) $[2M+Na]^+$; **HRMS** (ESI): *m/z* calc. for $C_{18}H_{25}NO_4$: 342.1676, found: 342.1677 $[M+Na]^+$; $C_{18}H_{25}NO_4$ (319.40).



Supporting Figure 8: ^{1}H-NMR spectrum of *ent*-7

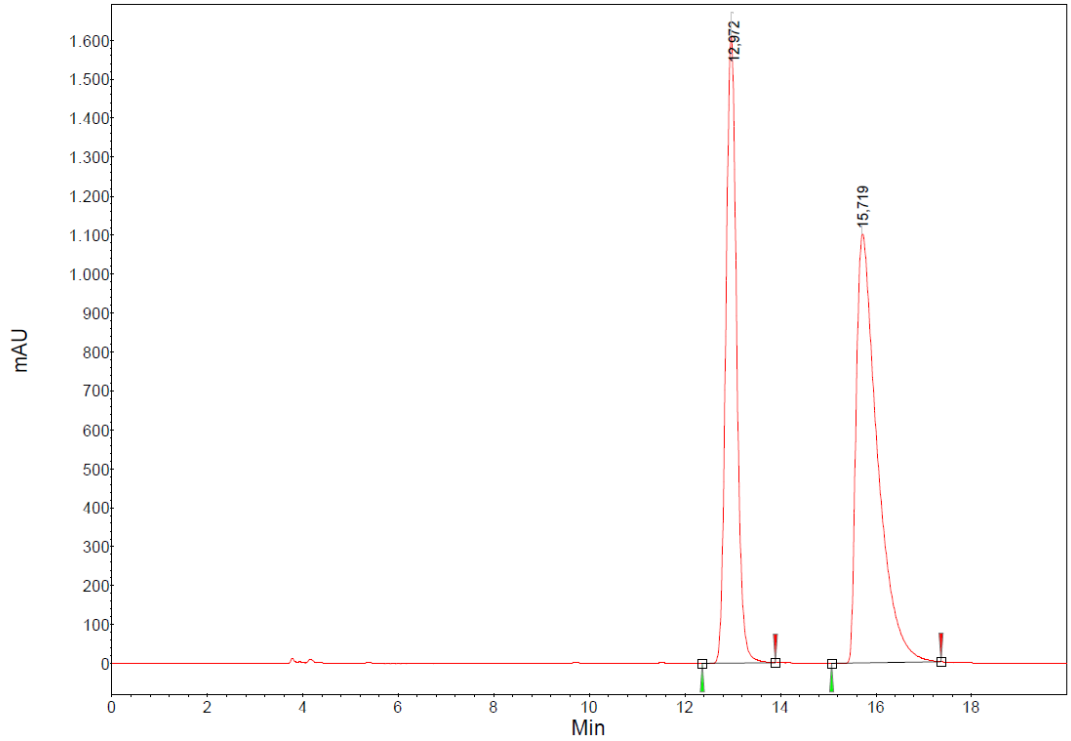


Supporting Figure 9: ^{13}C-NMR spectrum of *ent*-7



Supporting Figure 10: CHPLC chromatogram of *ent*-7

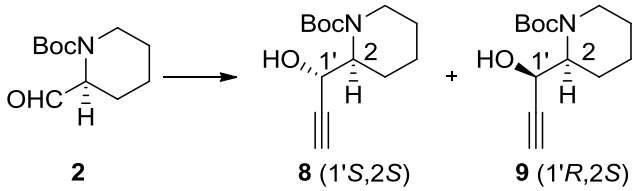
Coinjection of both enantiomers:



Supporting Figure 11: CHPLC chromatogram of 7/*ent*-7 coinjection

HPLC: Rt_1 = 12.0 min; Rt_2 = 14.4 min (200:1 *n*-hexane/EtOH, flow: 1 mL/min; injection volume 20 µL, c = 1.0 mg/mL),

4.5 Synthesis of *tert*-butyl (2*S*)-2-[(1*S*)-1-hydroxyprop-2-yn-1-yl]piperidine-1-carboxylate (**8**) and *tert*-butyl (2*S*)-2-[(1*R*)-1-hydroxyprop-2-yn-1-yl]piperidine-1-carboxylate (**9**)

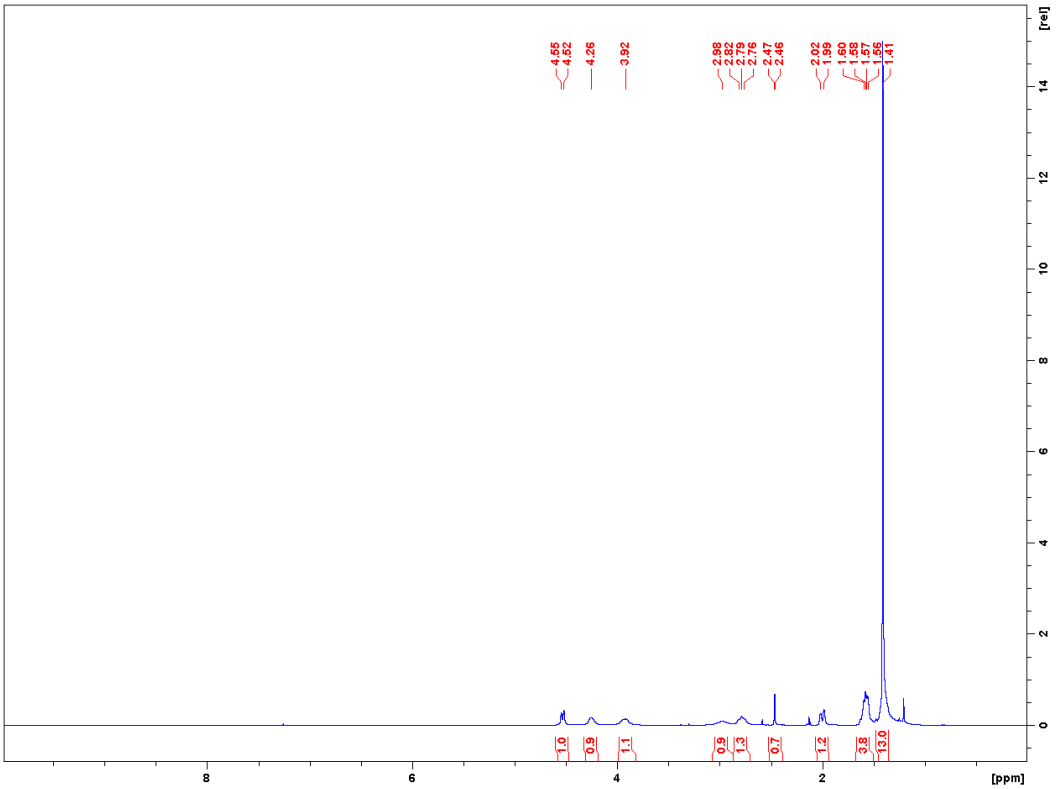


2 **8** (1'*S*,2*S*) **9** (1'*R*,2*S*)

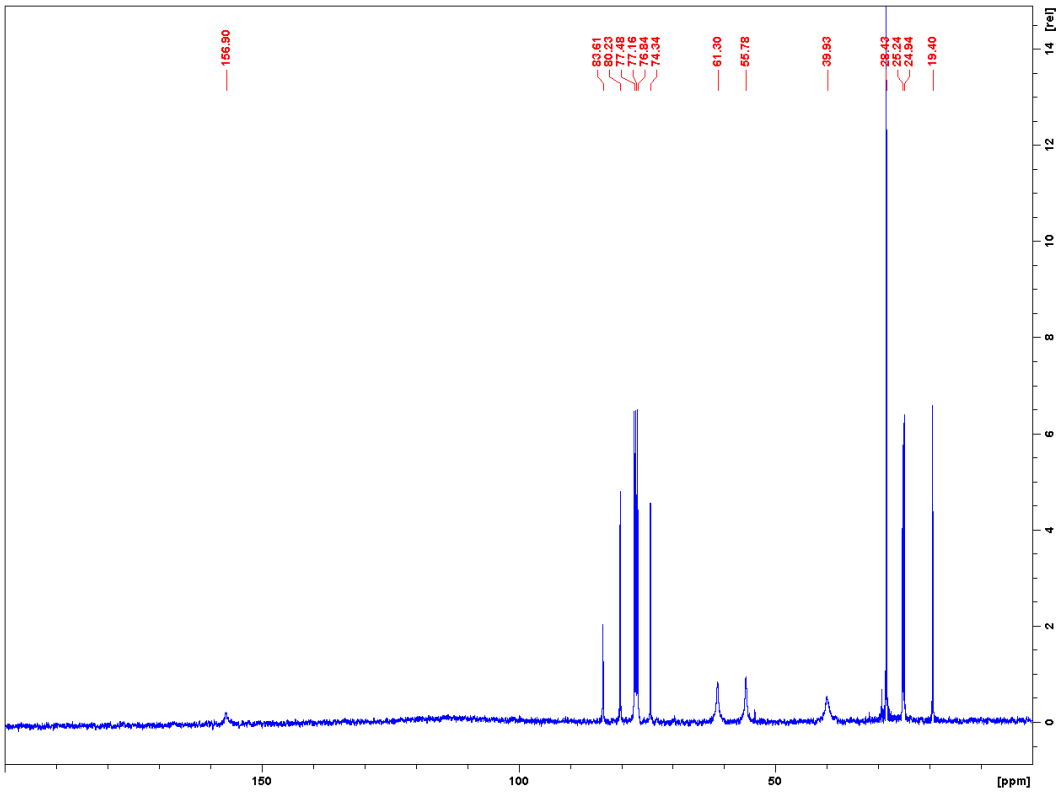
A solution of TMS-acetylene **4** (1.41 g, 14.4 mmol, 2.50 equiv.) in Et_2O (30.0 mL) was cooled to –78 °C and *n*-BuLi (1.6 M in *n*-hexane, 8.65 mL, 13.8 mmol, 2.40 equiv.) was added dropwise. Stirring was continued for 35 min. The reaction mixture is transferred via cannula at –78 °C to a solution of aldehyde **2** (1.23 g, 5.75 mmol, 1.00 equiv.) in Et_2O (20.0 mL) and the mixture was stirred for 5.5 h at –78 °C. The reaction was quenched by addition of aq. sat. NH_4Cl-solution (100 mL), the phases were separated and the aqueous layer was extracted with AcOEt (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was dissolved in MeOH (30.0 mL) and K_2CO_3 (397 mg, 2.88 mmol, 0.50 equiv.) was added at room temperature and stirred for 30 min. The reaction mixture was filtered and the solvent was removed in vacuo. Purification of the residue by column chromatography of the residue (SiO_2, *n*-hexane/acetone 4:1) yielded the diastereomeric mixture (1.07 g, 4.47 mmol, 78% over 2 steps). A second column chromatography on (SiO_2, *n*-hexane/acetone 20:1) yielded **8** (67.0 mg, 280 µmol, 5%) and **9** (847 mg, 3.54 mmol, 62%) both as colourless solids.

Analytical data for **8**:

TLC: R_f = 0.35 (*n*-hexane/ acetone 4:1); **MP**: 108–110 °C; α_D^{22} = 14.9 (*c* = 1.0 in $CHCl_3$); **IR** (ATR): $\tilde{\nu}$ = 1643, 1428, 1400, 1375, 1364, 1276, 1248, 1143, 1092, 1081, 1058, 1034, 867, 691 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$): 1.41 (s, 12 H), 1.53–1.64 (m, 3 H), 1.96–2.04 (m, 1 H), 2.47 (d, *J* = 201 Hz, 1 H), 2.73–2.85 (m, 1 H), 2.90–3.06 (m, 1 H), 3.92 (s_{br}, 1 H), 4.26 (s_{br}, 1 H), 4.54 (d, *J* = 10.0, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 19.4, 24.9, 25.2, 28.4, 39.9, 55.8, 61.3, 74.3, 80.2, 83.6, 156.9; **HRMS** (ESI): *m/z* calc. for $C_{13}H_{21}NO_3$: 262.1414, found: 262.1415 $[M+Na]^+$.



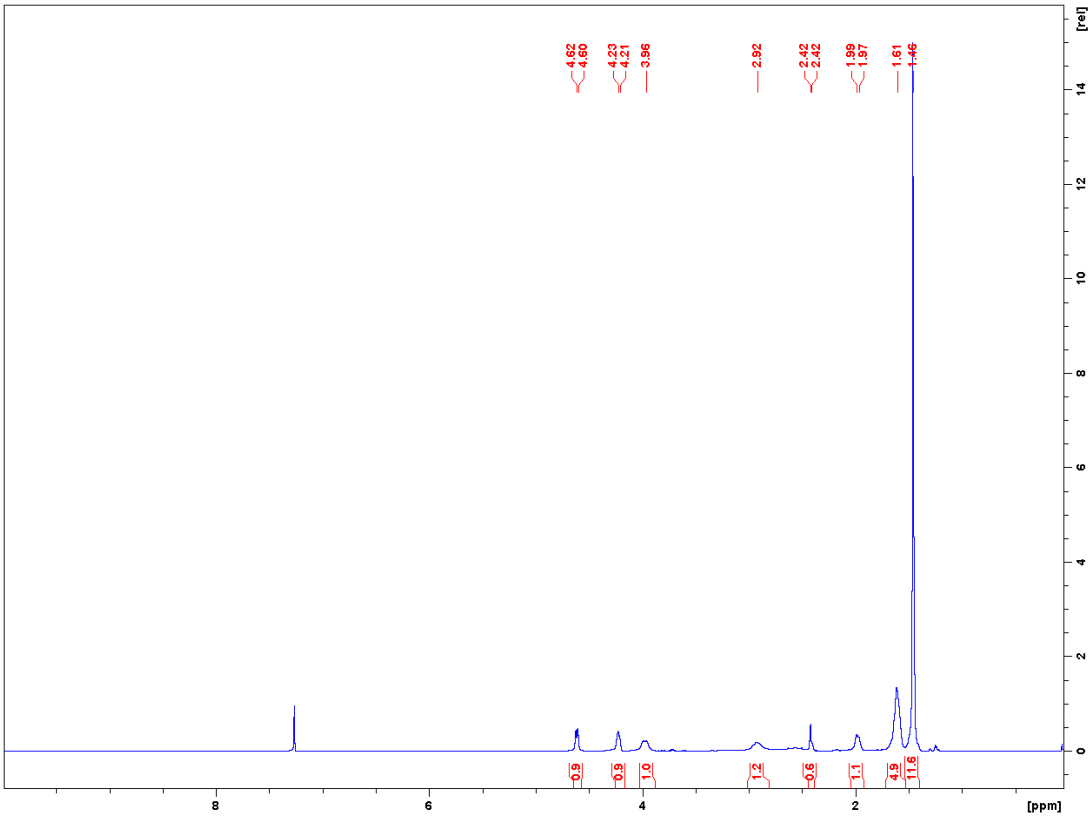
Supporting Figure 12: ^{1}H-NMR spectrum of 8



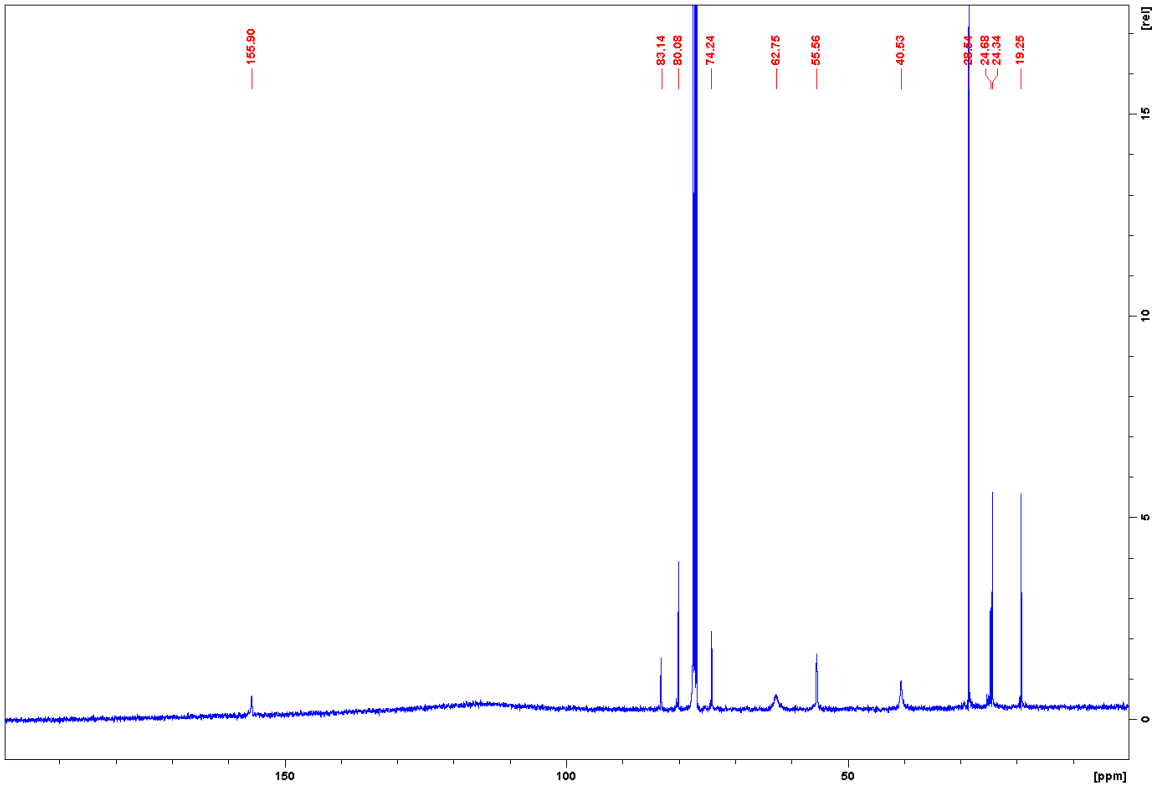
Supporting Figure 13: ^{13}C-NMR spectrum of 8

Analytical data for **9**:

TLC: R_f = 0.31 (*n*-hexane/ acetone 4:1); **MP**: 75–76 °C; α_D^{22} = –84.1 (*c* = 1.0 in $CHCl_3$); **IR** (ATR): ṽ = 1656, 1423, 1364, 1336, 1317, 1268, 1248, 1163, 1146, 1052, 1023, 945, 865, 760, 723 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$): 1.39–1.50 (m, 12 H), 1.54–1.72 (m, 3 H), 1.94–2.01 (m, 1 H), 2.42 (d, *J* = 2.1 Hz, 1 H), 2.84–2.99 (m, 1 H), 3.98 (d, *J* = 11.2 Hz, 1 H), 4.22 (t, *J* = 4.8 Hz, 1 H), 4.61 (dd, *J* = 7.1, 1.8 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 19.3, 24.3, 24.7, 28.5, 40.5, 55.6, 62.8, 74.2, 80.1, 83.1, 155.9; **MS** (ESI): m/z (%) = 501.3 (100) $[2M+Na]^+$, 278.1 (7) $[M+K]^+$, 262.2 (60) $[M+Na]^+$, 240.2 (3) $[M+H]^+$, 206.1 (6) $[M-C_4H_8+H]^+$, 184.1 (49) $[M-C_4H_8+H]^+$, 166.1 (7) $[M-C_4H_8-H_2O+H]^+$, 140.1 (15) $[M-C_5H_8O_2+H]^+$; **HRMS** (ESI): *m/z* calc. for $C_{13}H_{21}NO_3$: 262.1414, found: 262.1418 $[M+Na]^+$.

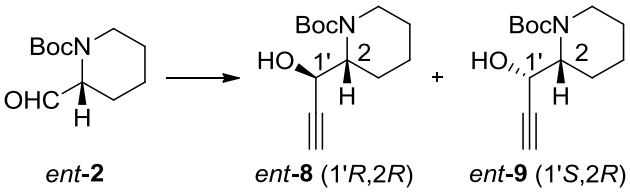


Supporting Figure 14: ^{1}H-NMR spectrum of 9



Supporting Figure 15: ^{13}C-NMR spectrum of 9

4.6 Synthesis of *t*ert-butyl (2*R*)-2-[(1*R*)-1-hydroxyprop-2-yn-1-yl]piperidine-1-carboxylate (*ent*-**8**) und *t*ert-butyl (2*R*)-2-[(1*S*)-1-hydroxyprop-2-yn-1-yl]piperidine-1-carboxylate (*ent*-**9**)



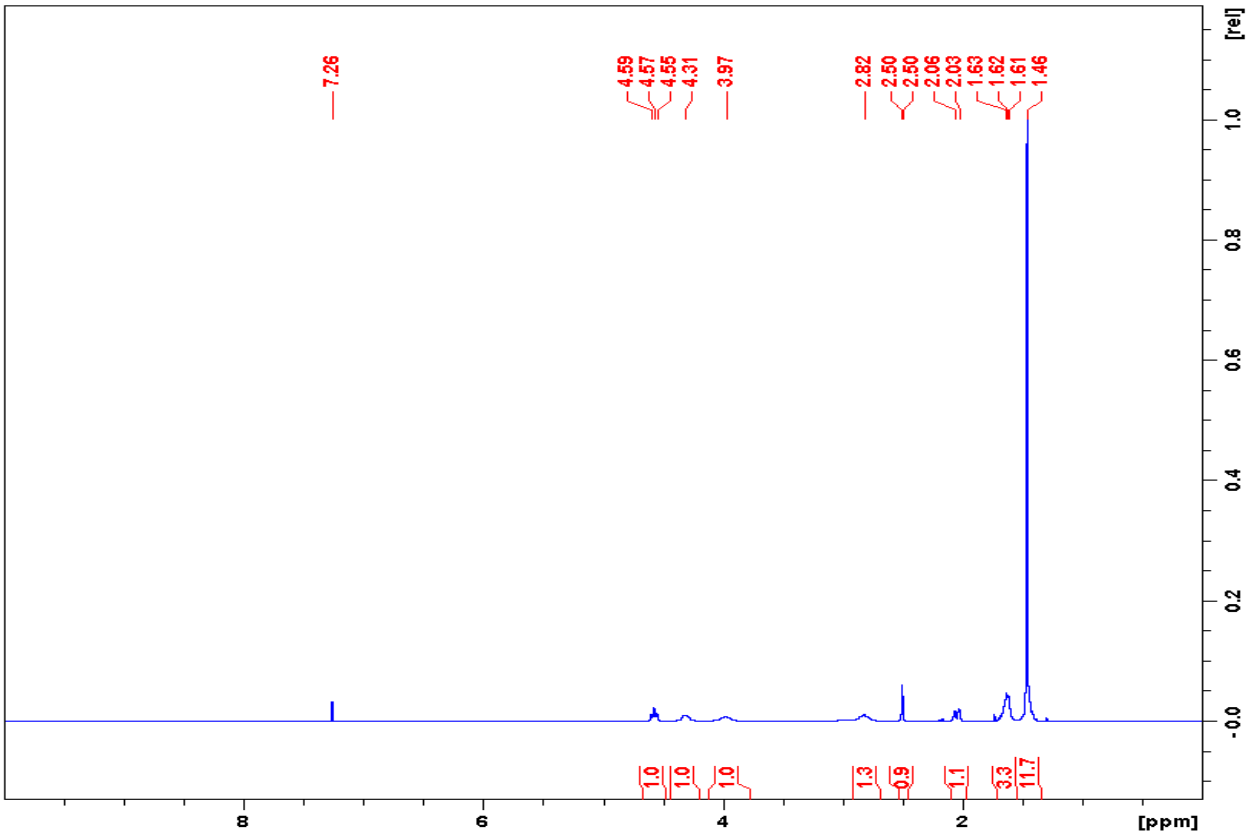
ent-**2** *ent*-**8** (1'*R*,2*R*) *ent*-**9** (1'*S*,2*R*)

A solution of TMS-acetylene **4** (5.53 mL, 3.93 g, 40.0 mmol, 2.20 equiv.) in Et_2O (60.0 mL) was cooled to 0 °C and *n*-BuLi (2.5 M, 14.6 mL, 36.4 mmol, 2.00 equiv.) was added dropwise within 10 min. Stirring was continued for 60 min and then cooled to −78 °C. A solution of (*R*)-*tert*-butyl 2-formylpiperidine-1-carboxylate *ent*-**2** (3.88 g, 18.2 mmol, 1.00 equiv.) in Et_2O (18.0 mL) was added dropwise over 10 min, and the resulting solution was stirred at −78 °C for 3 h. The reaction was quenched by addition of aq. sat. NH_4Cl-solution (40 mL), and the reaction was allowed to warm to room temperature. The phases were separated and the organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo to give the crude TMS protected propargyl alcohol. The residue was dissolved in MeOH (55.0 mL) and K_2CO_3 (5.03 g, 36.4 mmol, 2.00 equiv.) was added at room temperature and stirred for 60 min. The solids were filtered off, washed with methanol (10 mL), and the solvent was

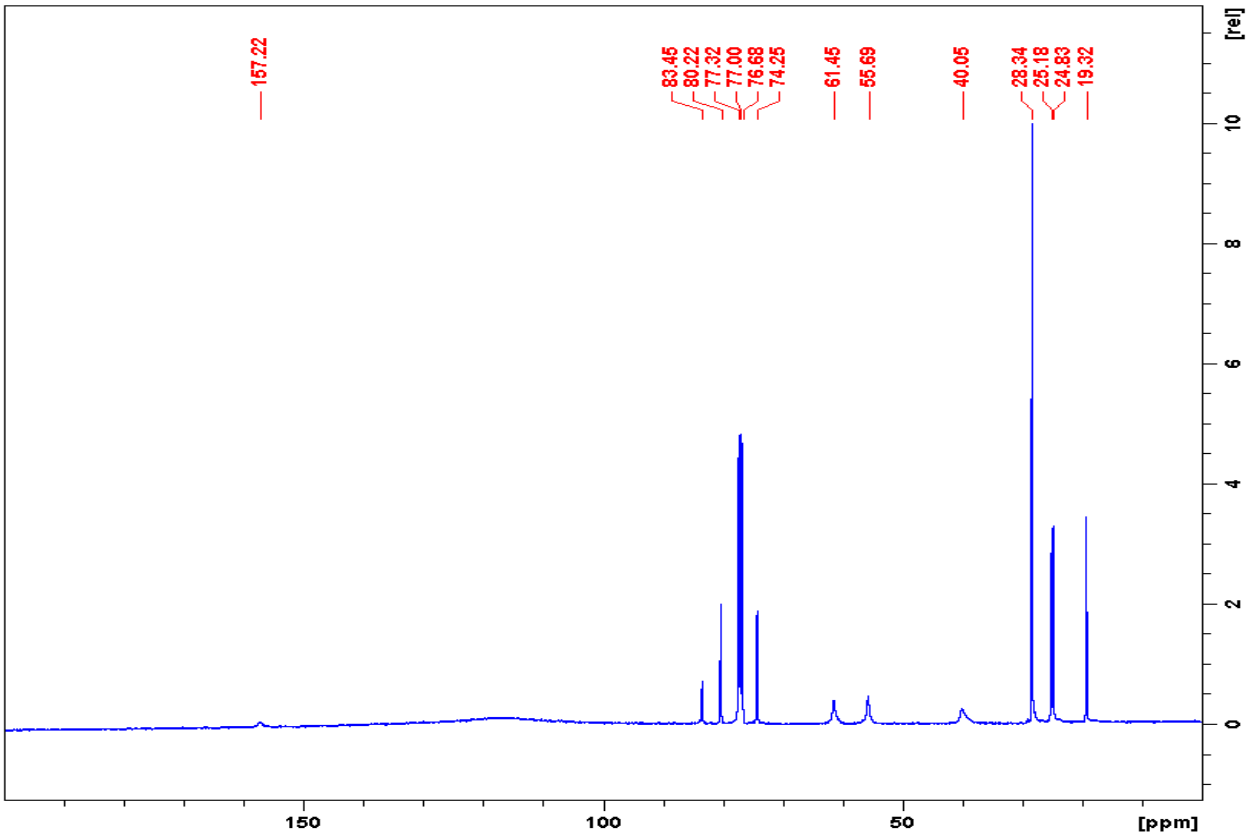
removed in vacuo. The filtrate was concentrated, dissolved in Et_2O (100 mL), washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo to give an oil, which contained a mixture of epimers. Purification of the residue by column chromatography (SiO_2, *n*-hexane/acetone 4:1) afforded 3.51 g of the diastereomeric mixture as a white solid. The solid was recrystallized from 11 mL of *n*-hexane/CH_2Cl_2 10:1 to afford pure *ent*-**9** (2.65 g) as a white solid. The mother liquor after crystallisation was concentrated in vacuo and purified by flash chromatography (SiO_2, *n*-hexane/acetone 8:1) to give *ent*-**8** (185 mg, 0.77 mmol, 4%) and *ent*-**9** (200 mg; total yield 2.85 g, 11.9 mmol, 65%) as white solids.

Analytical data for *ent*-**8**:

R_f = 0.35 (*n*-hexane/acetone 4:1); mp 108-110 °C; **$[\alpha]_D^{23}$ =** –19.8° (c = 0.5, $CHCl_3$); **IR** (ATR): $\tilde{\nu}$ = 3413, 2982, 1665, 1417, 1299, 1186, 1097, 973, 868 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.46 (s, 12 H), 1.55–1.71 (m, 3 H), 2.05 (d_{br}, *J* = 14.0 Hz, 1 H), 2.50 (d, *J* = 1.8 Hz, 1 H), 2.82 (m, 1 H), 3.97 (s_{br}, 1 H), 4.31 (s_{br}, 1 H), 4.57 (t, *J* = 8.7 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 19.3, 24.8, 25.2, 28.3, 40.1, 55.7, 61.5, 74.3, 80.2, 83.5, 157.2; **HRMS** (ESI): *m/z* calc. for $C_{13}H_{22}NO_3$: 240.1595, found: 240.1596 $[M+H]^+$.



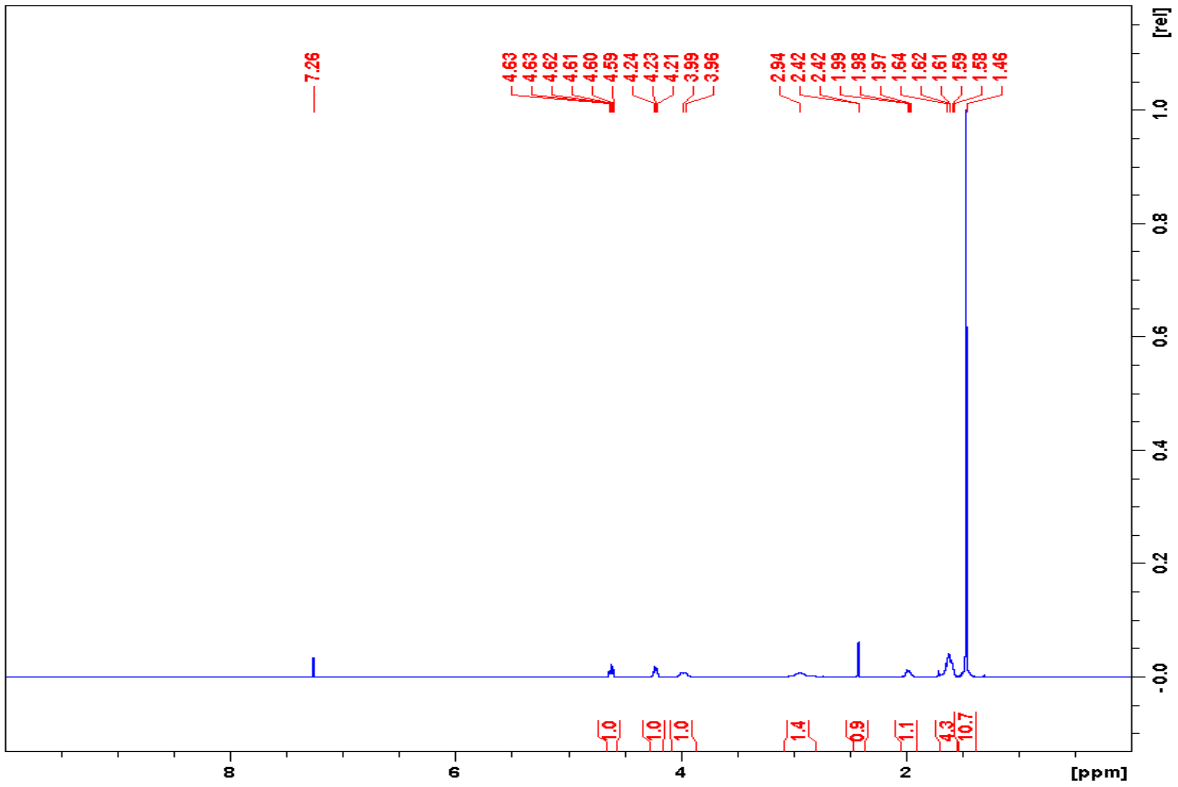
Supporting Figure 16: ^{1}H-NMR spectrum of *ent*-8



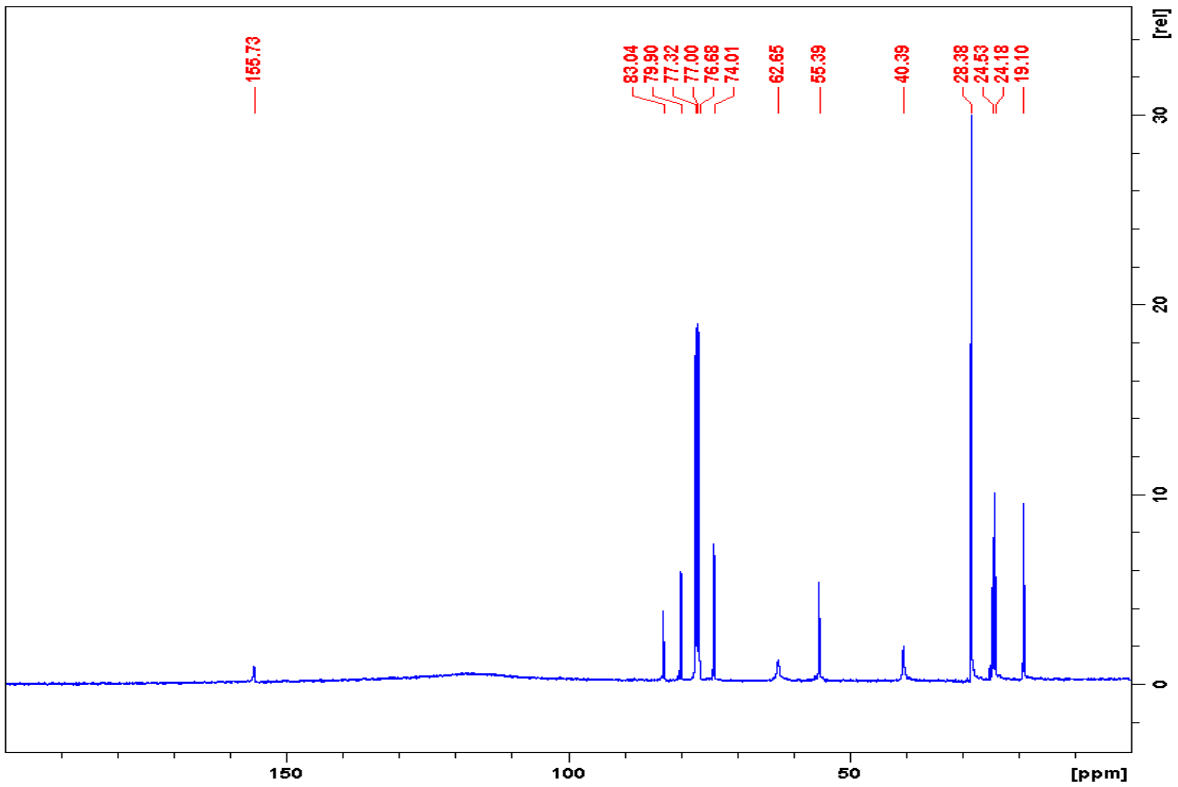
Supporting Figure 17: ^{13}C-NMR spectrum of *ent*-8

Analytical data for *ent*-**9**:

R_f = 0.31 (*n*-hexane/acetone 4:1); mp 78-79 °C; **$[\alpha]_D^{23}$ =** +88.3 ° (c = 0.5, $CHCl_3$); **IR** (ATR): $\tilde{\nu}$ = 3387, 2932, 1660, 1415, 1364, 1276, 1249, 1162, 1030, 866 cm $^{-1}$; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.46 (s, 11 H), 1.55–1.73 (m, 4 H), 1.91–2.05 (m, 1 H), 2.42 (d, *J* = 2.1 Hz, 1 H), 2.94 (m, 1 H), 3.98 (d_{br}, *J* = 11.4 Hz, 1 H), 4.16–4.28 (m, 1 H), 4.61 (dt, *J* = 7.0, 2.1 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 19.1, 24.2, 24.5, 28.4, 40.4, 55.4, 62.7, 74.0, 79.9, 83.0, 155.7; **HRMS** (ESI): *m/z* calc. for $C_{13}H_{22}NO_3$: 240.1595, found: 240.1595 $[M+H]^+$.

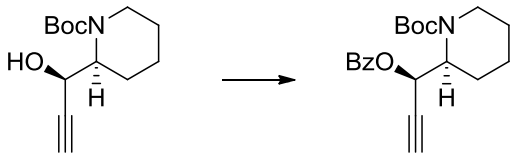


Supporting Figure 18: ^{1}H-NMR spectrum of *ent*-9



Supporting Figure 19: ^{13}C-NMR spectrum of *ent*-9

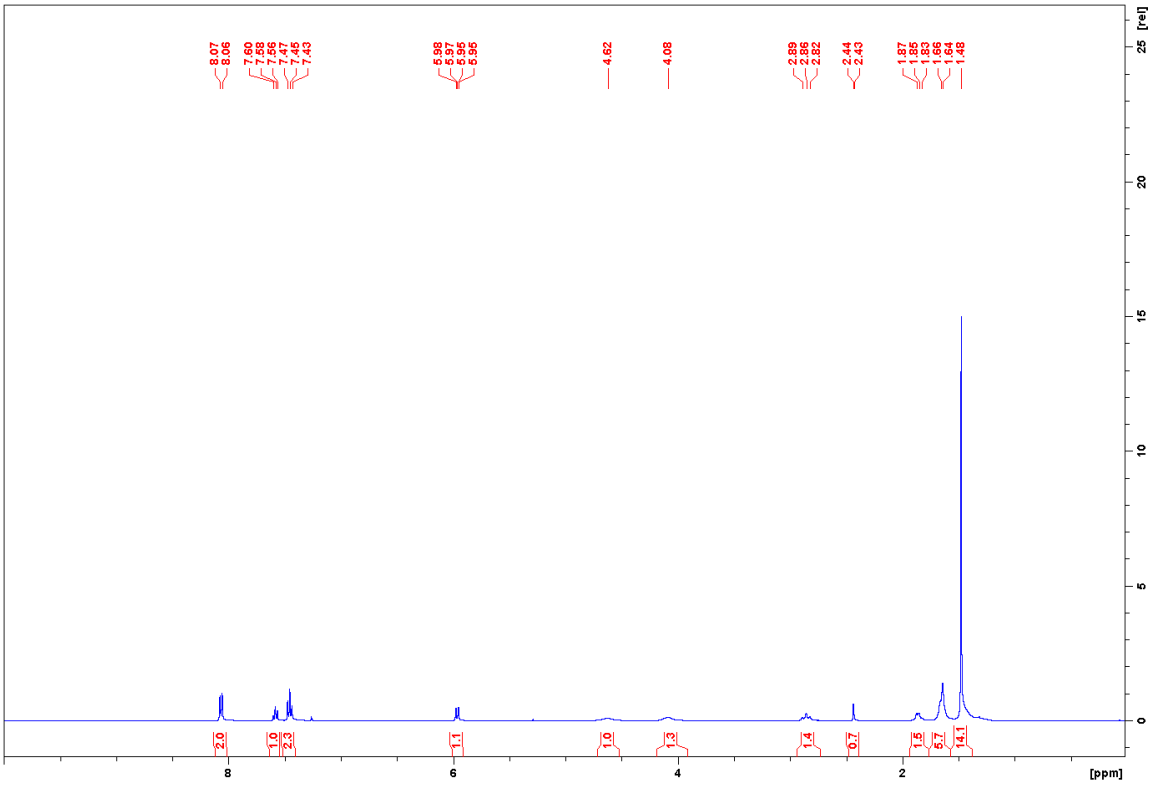
4.7 Synthesis of *tert*-butyl (2*S*)-2-[(1*R*)-1-(benzoyloxy)prop-2-yn-1-yl]piperidine-1-carboxylate (**12**)



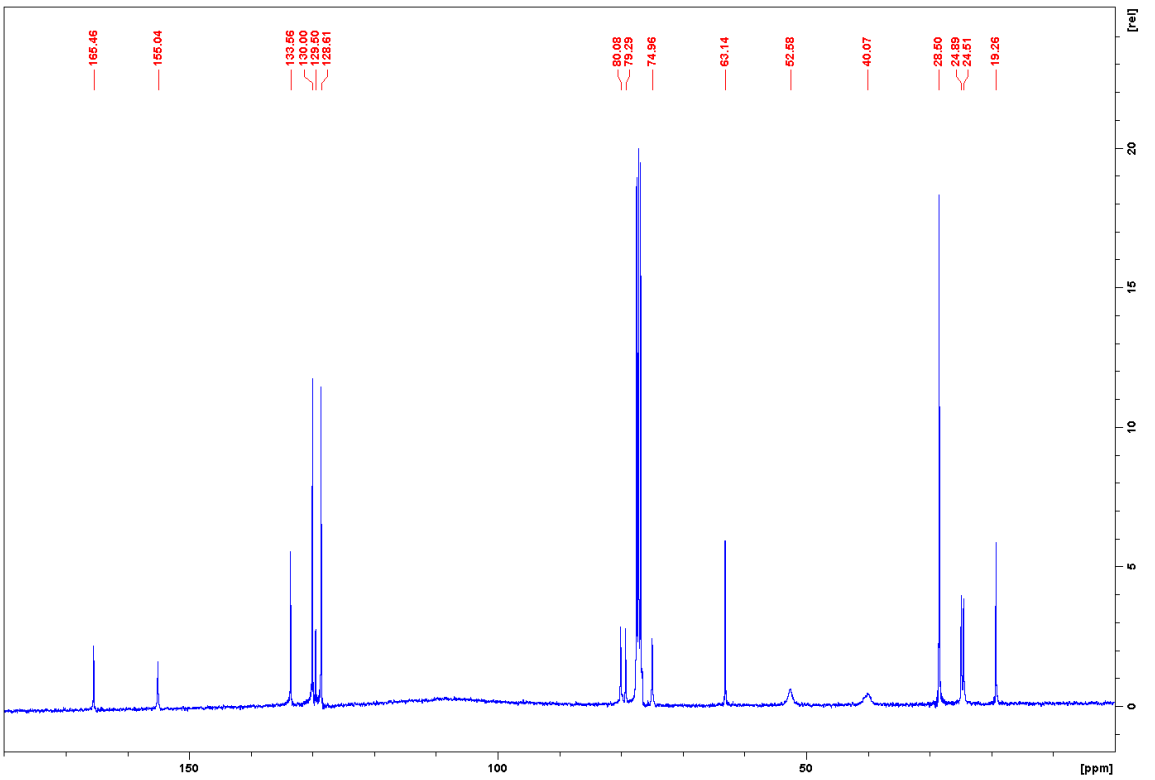
9 **12**

To a solution of alcohol **9** (627 mg, 2.62 mmol, 1.00 equiv.) in CH_2Cl_2 (12.0 mL) was added at room temperature NEt_3 (345 mg, 472 µL, 3.41 mmol, 1.30 equiv.), BzCl (368 mg, 304 µL, 3.41 mmol, 1.30 equiv.), and DMAP (16.0 mg, 131 µmol, 5.0 mol-%). The reaction mixture was stirred for 2 h at. room temperature. The reaction was quenched by addition of imidazole (53.8 mg, 0.79 mmol) and the mixture was stirred for additional 30 min at room temperature. The organic phase was washed with saturated aq. $NaHCO_3$-solution (3 × 5.0 mL) and 5% aq. citric acid (2 × 5.0 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. Column chromatography (SiO_2, hexane/acetone 4:1) yielded benzoate **12** (890 mg, 2.59 mmol, 99%) as clear, viscous oil.

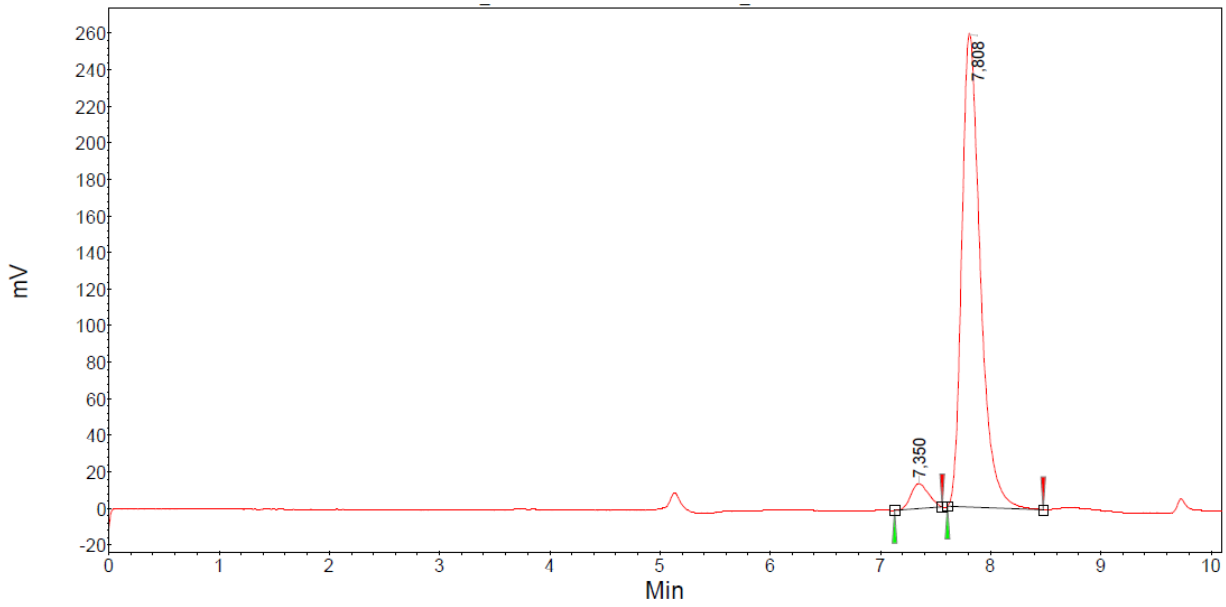
TLC: R_f = 0.37 (*n*-hexane/ acetone 4:1), α_D^{23} = –72.9 ° (c = 1.0 in $CHCl_3$), **IR** (ATR): $\tilde{\nu}$ = 1686, 1411, 1364, 1265, 1250, 1166, 1147, 1091, 1067, 1025, 709, 686 cm^{-1}, **UV** (CH_3CN): λ_{max} (lg ε) = 230 (4.387), 274 (3.252) nm, **^{1}H-NMR** (400 MHz, $CDCl_3$): 1.48 (s, 10 H), 1.59–1.71 (m, 4 H), 1.83–1.89 (m, 1 H), 2.43 (d, *J* = 2.2 Hz, 1 H), 2.86 (t, *J* = 13.1 Hz, 1 H), 4.08 (s_{br}, 1 H), 4.62 (s_{br}, 1 H), 5.96 (dd, *J* = 8.7, 2.2 Hz, 1 H), 7.45 (t, *J* = 7.7 Hz, 2 H), 7.58 (t, *J* = 7.7 Hz, 1 H), 8.06 (d, *J* = 7.7 Hz, 2 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 19.3, 24.5, 24.9, 28.5, 40.1, 52.6, 63.1, 75.0, 79.3, 80.1, 128.6, 129.5, 130.0, 133.6, 155.0, 165.5; **MS** (ESI): m/z (%) = 709.4 (42) $[2M+Na]^+$, 366.2 (39) $[M+Na]^+$, 344.2 (14) $[M+H]^+$, 288.1 (24) $[M-C_4H_8+H]^+$, 244.1 (100) $[M-C_5H_8O_2+H]^+$; **HPLC:** Rt_{minor} = 7.4 min (*ent*-**12**); Rt_{major} = 7.8 min (**12**) (200:1 *n*-hexane/EtOH, flow: 0.8 mL/min; injection volume 20 µL, c = 1.0 mg/mL) *e.r.* = 95:5; **HRMS** (ESI): *m/z* calc. for $C_{13}H_{21}NO_3$: 366.1676, found: 366.1673 $[M+Na]^+$.



Supporting Figure 20: ^{1}H-NMR spectrum of 12

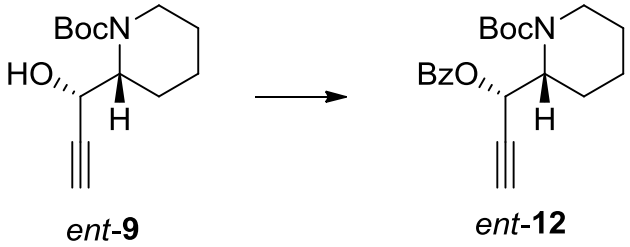


Supporting Figure 21: ^{13}C-NMR spectrum of 12



Supporting Figure 22: CHPLC chromatogram of 12

4.8 Synthesis of *tert*-butyl (2*R*)-2-[(1*S*)-1-(benzoyloxy)prop-2-yn-1-yl)]piperidine-1-carboxylate (*ent*-**12**)

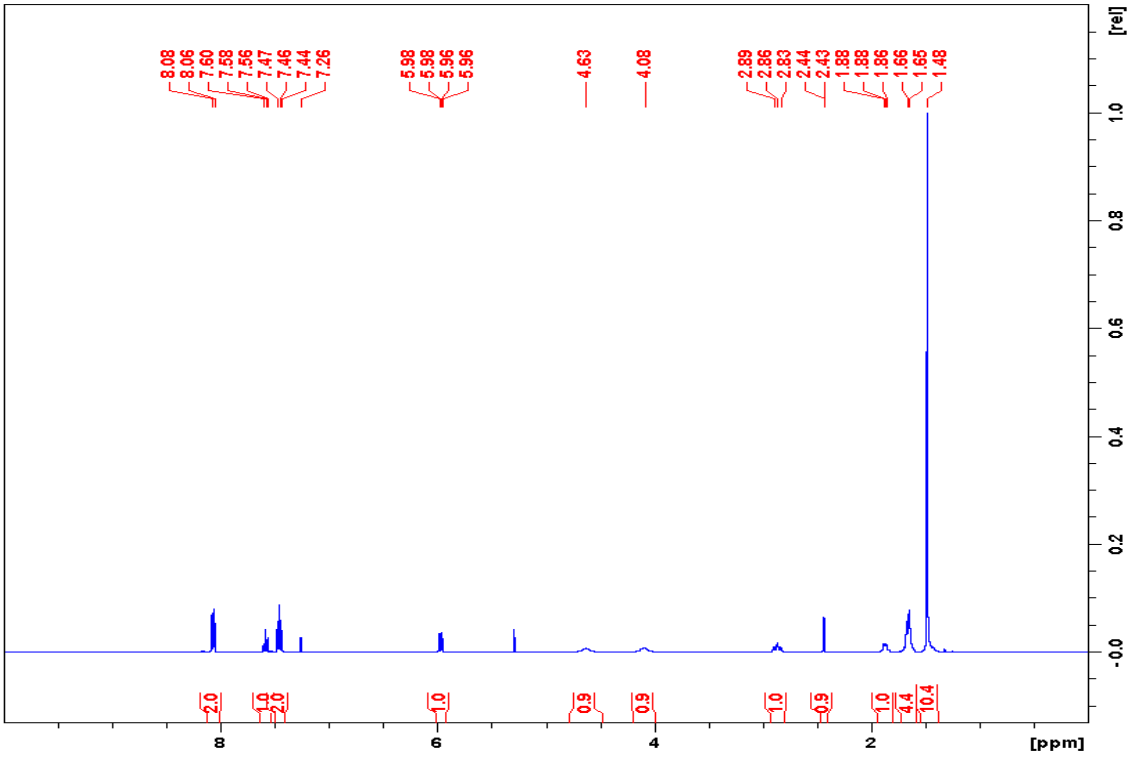


ent-**9** *ent*-**12**

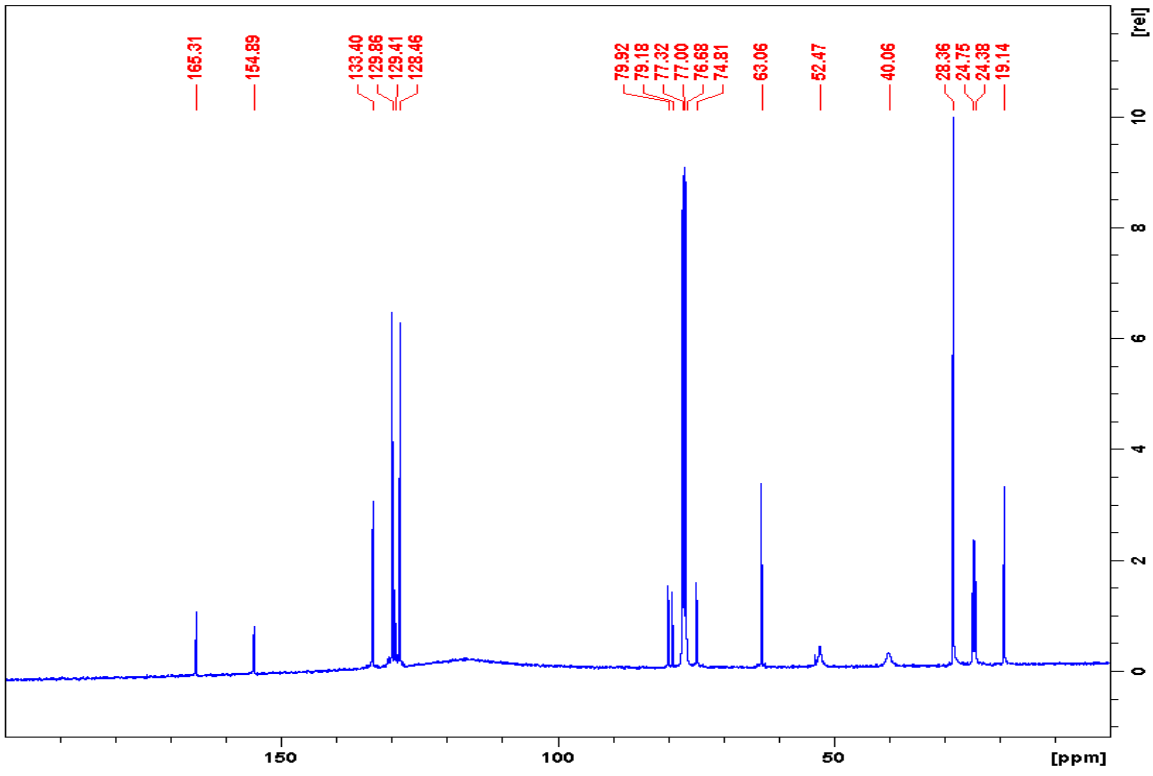
To a stirred solution of *ent*-**9** (1.20 g, 5.01 mmol, 1.00 equiv.), Et_3N (906 µL, 658 mg, 6.50 mmol, 1.30 equiv.), and 4-dimethylaminopyridine (31.0 mg, 0.25 mmol, 5.0 mol-%) in CH_2Cl_2 (25 mL) was added benzoyl chloride (754 µL, 914 mg, 6.50 mmol, 1.30 equiv.). The reaction mixture was stirred at 20 °C for 2 h and imidazole (102 mg, 1.50 mmol, 30 mol-%) was added to quench the excess of benzoyl chloride. The reaction was stirred additionally for 30 min, washed with 5% aq. $NaHCO_3$-solution (3 × 10 mL), 10% aq. citric acid solution (2 × 10 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (SiO_2, *n*-hexane/acetone 4:1) to give of *ent*-**12 (**1.71 g 4.98 mmol, 99%) as a clear, viscous oil.

TLC: R_f = 0.37 (hexane/ acetone 4:1), α_D^{23} = –66.2 ° (c = 1.0 in $CHCl_3$), **IR** (ATR): $\tilde{\nu}$ = 2938, 1724, 1686, 1411, 1364, 1266, 1250, 1147, 1091, 1067, 1025, 709 cm^{-1}, **UV** (CH_3CN): λ_{max} (lg ε) = 231 (4.201), 274 (3.039) nm, **^{1}H-NMR** (400 MHz, $CDCl_3$): 1.48 (s, 10 H), 1.58–1.73 (m, 4 H), 1.80-1.93 (m, 1 H), 2.43 (d, *J* = 2.1 Hz, 1 H), 2.86 (t_{br}, *J* = 13.0 Hz, 1 H), 4.08 (s_{br}, 1 H), 4.63 (s_{br}, 1 H), 5.97 (dd, *J* = 8.5, 2.1 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 2 H), 7.58 (t, *J* = 7.4 Hz, 1 H), 8.07 (d, *J* = 7.4 Hz, 2 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 19.1, 24.4,

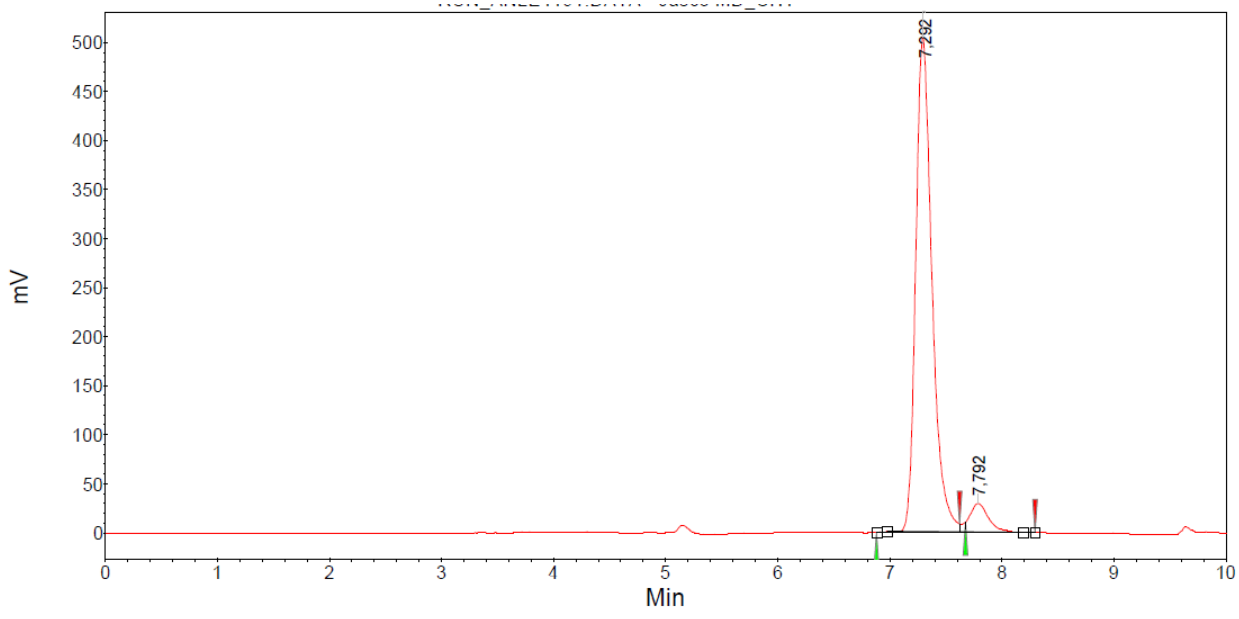
24.8, 28.4, 40.1, 52.5, 63.1, 74.8, 79.2, 79.9, 128.5, 129.4, 129.9, 133.4, 154.9, 165.3; **HPLC:** Rt_{major} = 7.4 min; Rt_{minor} = 7.8 min (200:1 *n*-hexane/EtOH, flow: 0.8 mL/min; injection volume 20 µL, c = 1.0 mg/mL), *e.r.* = 94:6; **HRMS** (ESI): *m/z* calc. for $C_{13}H_{21}NO_3$: 344.1857, found: 344.1856 $[M+H]^+$.



Supporting Figure 23: ^{1}H-NMR spectrum of *ent*-12

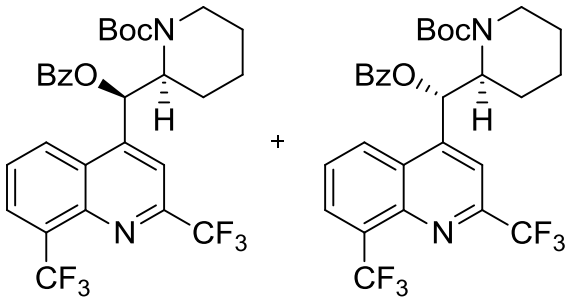


Supporting Figure 24: ^{13}C-NMR spectrum of *ent*-12



Supporting Figure 25: CHPLC chromatogram of *ent*-12

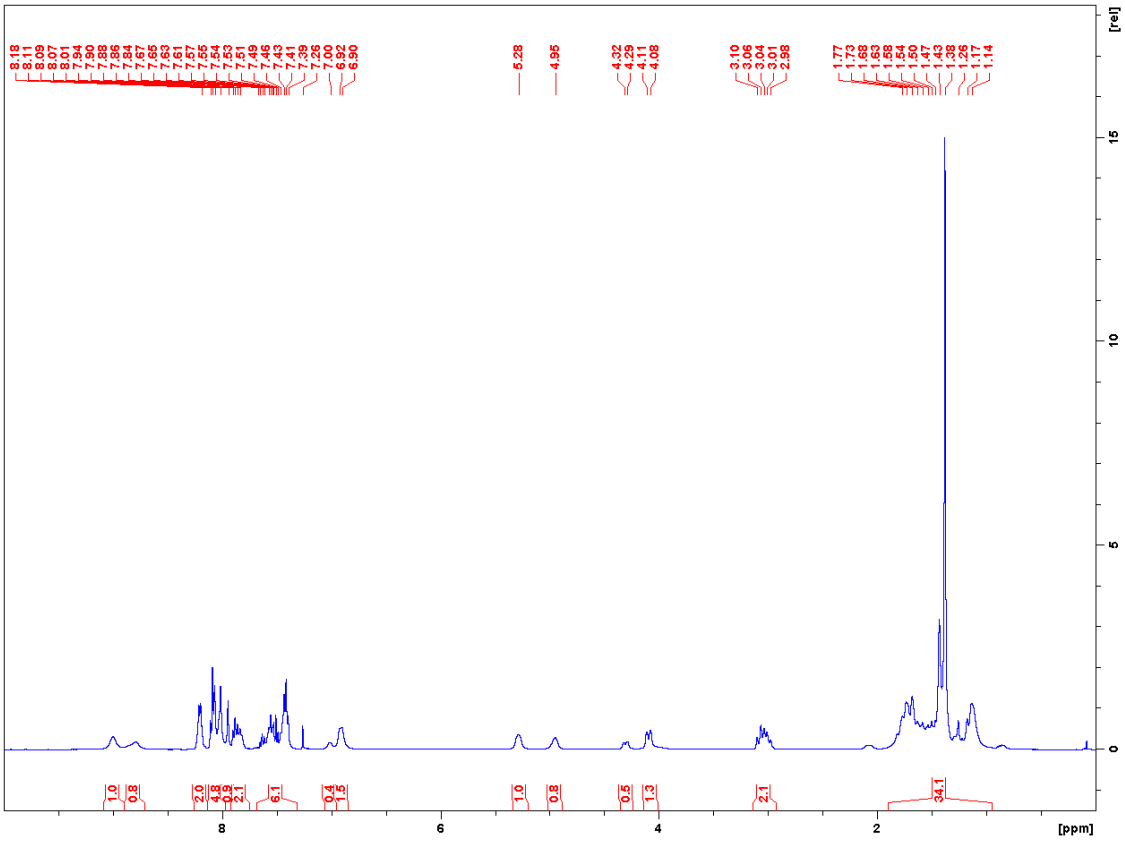
4.9 Synthesis of *tert*-butyl (2*S*)-2-[(*R*)-[2,8-bis(trifluoromethyl)quinolin-4-yl](benzoyloxy)methyl]piperidine-1-carboxylate (*N*-Boc-*O*-Bz-(–)-*erythro*-mefloquine) (**13a**) and *tert*-butyl (2*S*)-2-[(*S*)-[2,8-bis(trifluoromethyl)quinolin-4-yl](benzoyloxy)methyl]piperidine-1-carboxylate (*N*-Boc-*O*-Bz-(+)-*threo*-mefloquine) (**13b**)



13a **13b**

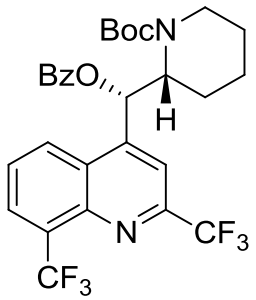
To a degassed solution of iodide **3** (1.04 g, 2.82 mmol, 1.00 equiv.) and alkyne **12** (969 mg, 2.82 mg, 1.00 equiv) in NEt_3 (12.0 mL) was added in one portion $Pd(PPh_3)_2Cl_2$ (99.0 mg, 141 µmol, 5.00 mol-%) and CuI (26.9 mg, 141 µmol, 5.00 mol%). The reaction was stirred for 90 min at 75 °C. After complete conversion the reaction mixture was cooled to room temperature, filtered through a pad of celite, and the solvent was removed in vacuo. The residue was dissolved in AcOEt (60 mL), washed with 5% aqueous citric acid-solution (2 × 15 mL), and brine (15 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. Column chromatography of the residue on SiO_2 (*n*-hexane/ethyl acetate 5:1) yielded the titled compound as yellow foam (1.41 g, 2.42 mmol, 86%) containing an inseparable mixture of epimers **13a** and **13b** in a ratio ca. **13a**:**13b** = 1:3.6 (^{1}H-NMR).

TLC: R_f = 0.33 (*n*-hexane/ethyl acetate 5:1); **IR** (ATR): $\tilde{\nu}$ = 1686, 1309, 1264, 1141, 1109, 1092, 1068, 1039, 1027, 769, 710 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$): 1.14–1.77 (m, 30 H), 2.94–3.12 (m, 2 H), 4.09 (d, *J* = 13.1 Hz, 1 H), 4.30 (d, *J* = 13.0 Hz, 1 H), 4.95 (s_{br}, 1 H), 5.28 (s_{br}, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 7.01 (d, *J* = 6.4 Hz, 1 H), 7.37–7.66 (m, 6 H), 7.79–7.92 (m, 2 H), 7.92–8.14 (m, 4 H), 8.16–8.25 (m, 2 H), 8.79 (s_{br}, 1 H), 9.00 (s_{br}, 1 H); **MS** (ESI): m/z (%) = 605 (35) $[M+Na]^+$, 583 (100) $[M+H]^+$; **HRMS** (ESI): *m/z* calc. for $C_{29}H_{29}F_6N_2O_4$: 583.2026, found: 583.2021 $[M+H]^+$.

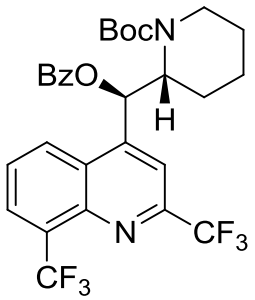


Supporting Figure 26: ^{1}H-NMR spectrum of the diastereomeric mixture of 13a and 13b

4.10 Synthesis of *tert*-butyl (2*R*)-2-[(*S*)-[2,8-bis(trifluoromethyl)quinolin-4-yl](benzoyloxy)methyl]piperidine-1-carboxylate (*N*-Boc-*O*-Bzl-(+)-*erythro*-mefloquine) (*ent*-**13a**) and *tert*-butyl (2*R*)-2-[(*R*)-[2,8-bis(trifluoromethyl)quinolin-4-yl](benzoyloxy)methyl]piperidine-1-carboxylate (*N*-Boc-*O*-Bzl-(–)-*threo*-mefloquine) (*ent*-**13b**)



ent-**13a**

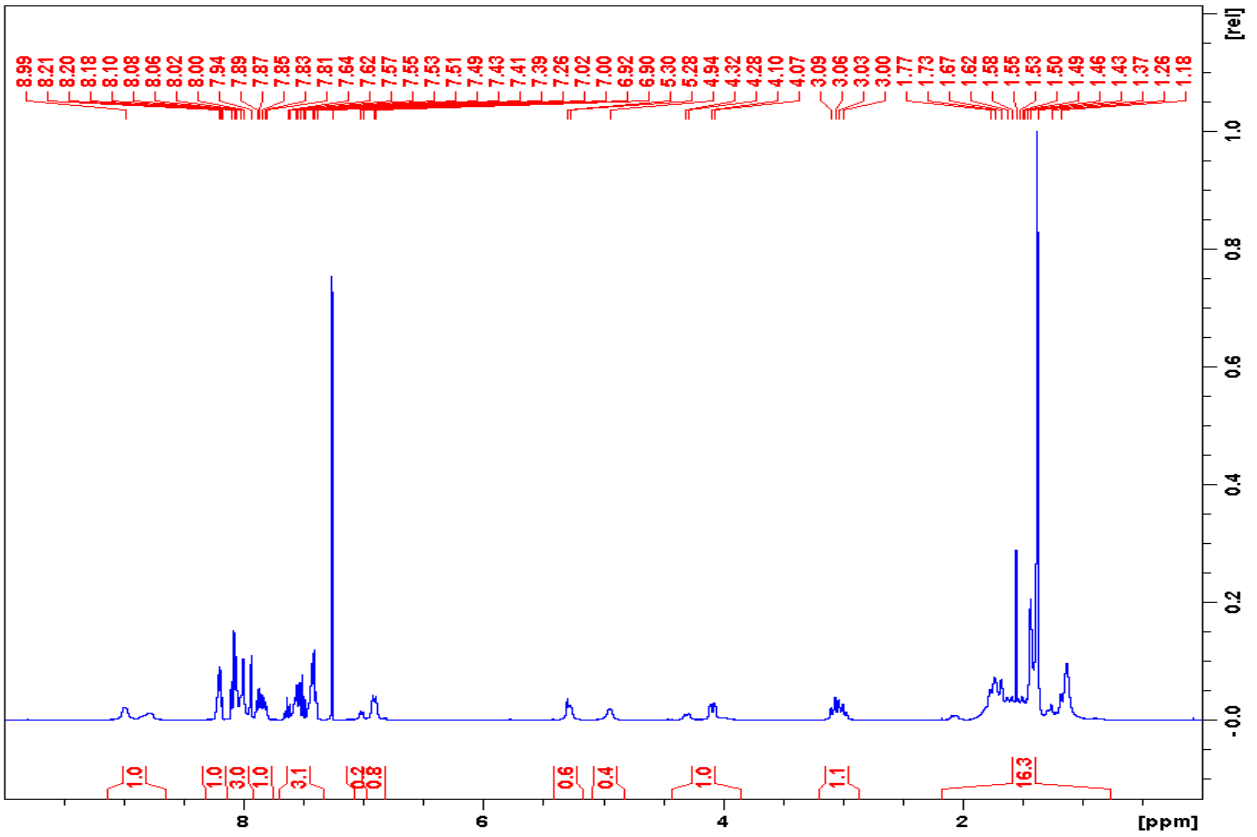


ent-**13b**

A solution of *ent*-**12** (343 mg, 1.00 mmol, 1.00 equiv.) in anhydrous Et_3N (4.0 mL) in an oven dried Schlenk-tube containing a Teflon-coated stir bar was saturated with N_2 within 30 min. Subsequently, imidoyl iodide **3** (367 mg, 1.00 mmol, 1.00 equiv.), $PdCl_2(Ph_3P)_2$ (35.0 mg, 50.0 µmol, 5.00 mol-%) and CuI

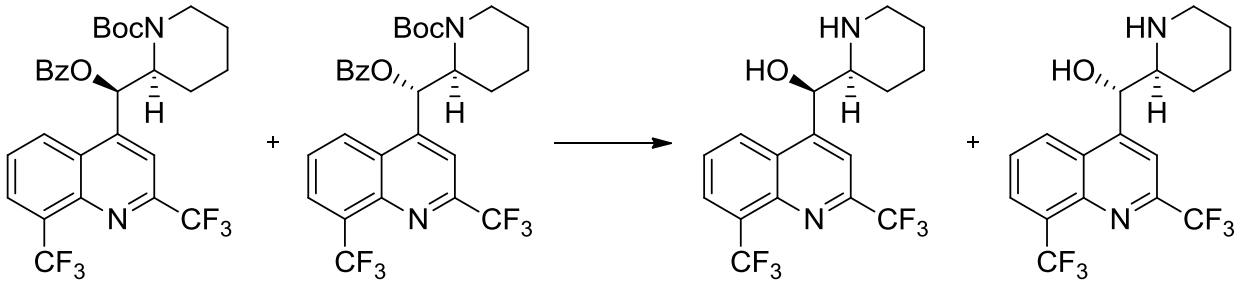
(10 mg, 50.0 µmol, 5.00 mol-%) were added, the Schlenk tube was sealed, and then evacuated and backfilled with N_2 (three cycles). The reaction was stirred at 75 °C for 1.5 h, cooled to room temperature, filtered, and the solvent was removed in vacuo. The residue was dissolved in EtOAc (20 mL), washed with 10% aq. citric acid solution (2 × 5 mL), sat. aq. NH_4Cl-solution (5 mL), brine (5 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (SiO_2, *n*-hexane/ethyl acetate 5:1) to give the product (465 mg, 798 µmol, 80%) as white foam containing an inseparable mixture of epimers *ent*-**13a** and *ent*-**13b** in a ratio ca. *ent*-**13a**: *ent*-**13b** = 1:3.6 (^{1}H-NMR).

TLC: R_f = 0.33 (*n*-hexane/ethyl acetate 5:1); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 0.77–2.17 (m, 15 H), 2.87–3.19 (m, 1 H), 4.08 and 4.30 (2 × d, *J* = 12.9 and 13.4 Hz, 1 H), 4.94 and 5.28 (2 × s_{br}, 1 H), 6.91 and 7.01 (2 × d, *J* = 9.5 and 7.9 Hz, 1 H), 7.34–7.70 (m, 3 H), 7.75–7.92 (m, 1 H), 7.92–8.14 (m, 3 H), 8.14–8.30 (m, H), 8.78 and 8.99 (2 × s_{br}, 1 H); **HRMS** (ESI): *m/z* calc. for $C_{29}H_{29}F_6N_2O_4$: 583.2027, found: 583.2027 $[M+H]^+$.



Supporting Figure 27: ^{1}H-NMR spectrum of the diastereomeric mixture of *ent*-13a and *ent*-13b

4.11 Synthesis of (*R*)-[2,8-bis(trifluoromethyl)quinolin-4-yl][(2*S*)-piperidin-2-yl]methanol ((–)-*erythro*-mefloquine) (**1a**) and (*S*)-[(2,8-bis(trifluoromethyl)quinolin-4-yl][(2*S*)-piperidin-2-yl]methanol ((+)-*threo*-mefloquine) (**1b**)

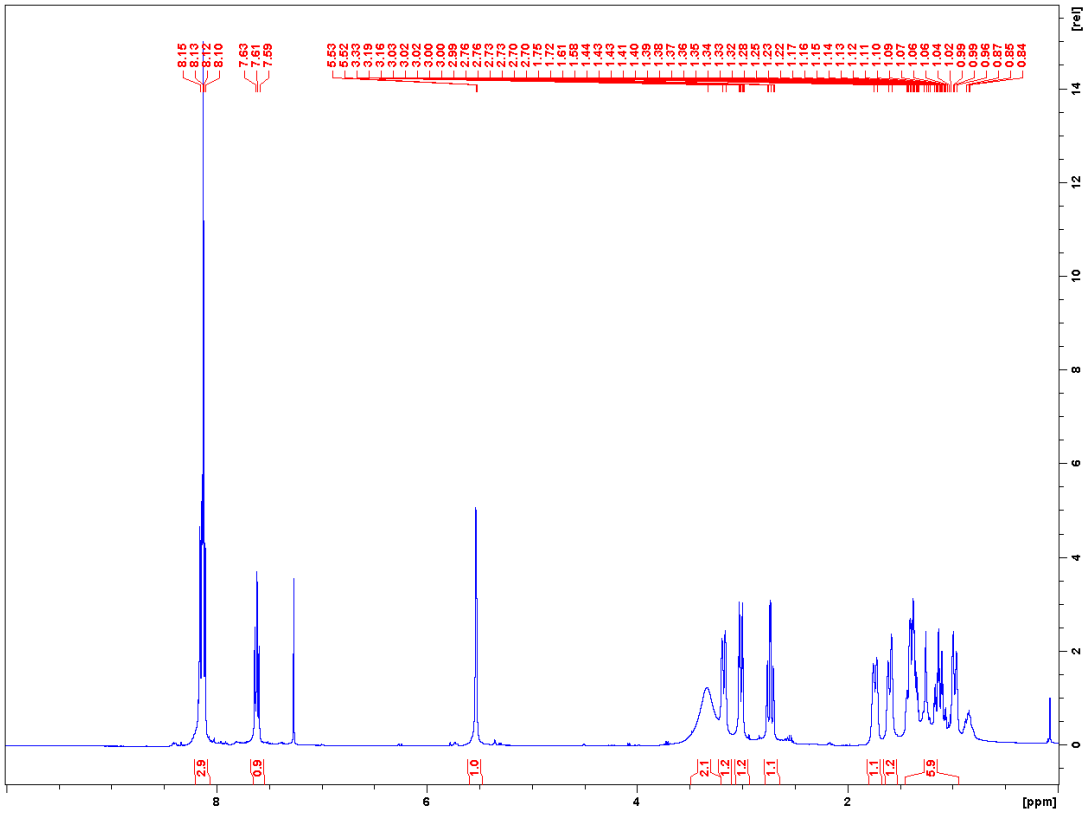


13a **13b** **1a** **1b**

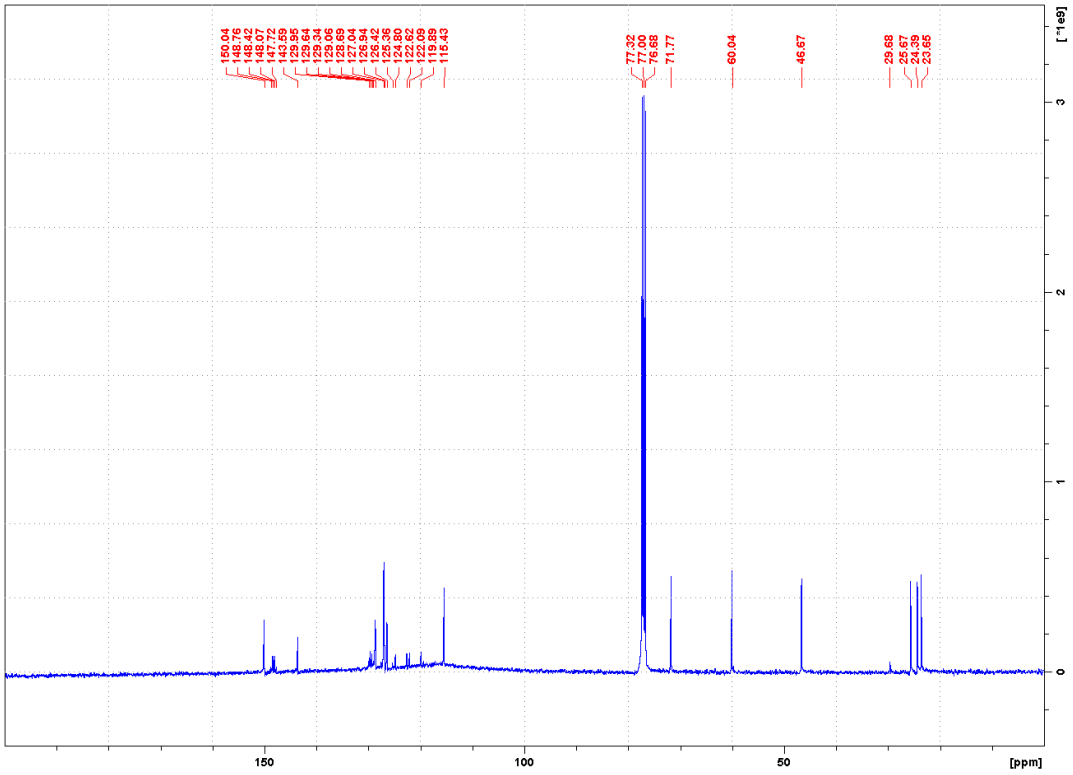
To a solution of Bz-ester (1.30 g, 2.23 mmol, 1.00 equiv.) in MeOH (80.0 mL) was added at 0 °C $LiOH·H_2O$ (187 mg, 4.46 mmol, 2.00 equiv.). It was stirred for 1 h at room temperature and afterwards the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL), the organic phase was washed with sat. aq. $NaHCO_3$-sol. (3 × 20 mL), dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The Boc-protected mefloquine was dissolved in CH_2Cl_2 (30.0 mL) and TFA (3.0 mL) was added at room temperature. The reaction mixture was stirred for 1 h and afterwards the solvent was removed in vacuo. Column chromatography (SiO_2, $CHCl_3$/MeOH/25% aq. NH_4OH 100:10:1) yielded **1b** (521 mg, 1.38 mmol, 62%) and (–)-*erythro*-mefloquine **1a** (147 mg, 388 µmol, 17%) both as white solids.

Analytical data for (–)-*erythro*-mefloquine (**1a**)

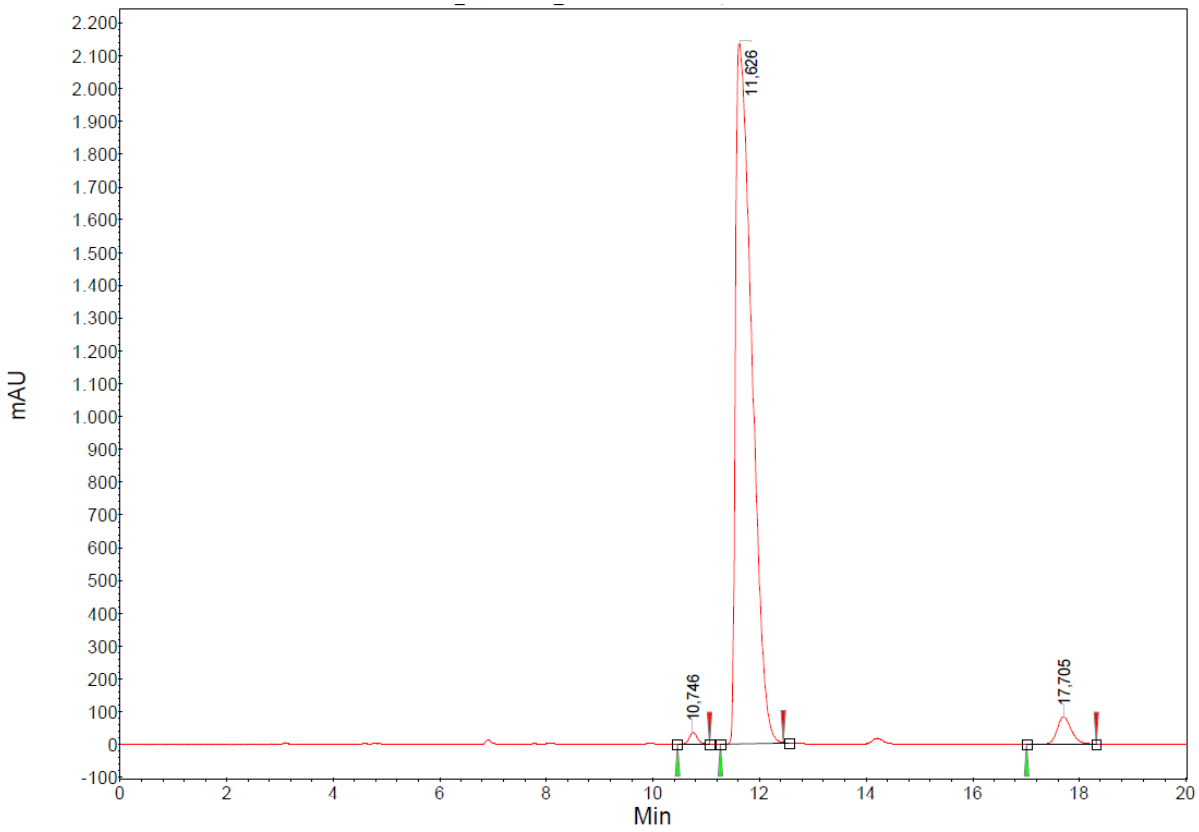
TLC: R_f = 0.11 ($CHCl_3$/MeOH/25% aq. NH_4OH 100:10:1); **MP**: 160–162 °C; **IR**: (ATR): ṽ = 1145, 1129, 1103, 1090, 1054, 1004, 937, 836, 764, 670 cm^{-1}; **UV**: 221 (4.643), 284 (3.780), 316 (3.478) nm, **^{1}H-NMR** (400 MHz, $CDCl_3$): 1.07–1.44 (m, 4 H), 1.60 (d, *J* = 13.3 Hz, 1 H), 1.74 (d, *J* = 13.3 Hz, 1 H), 2.55 (td, *J* = 12.3, 2.7 Hz, 1 H), 3.01 (dt, *J* = 12.3, 2.7 Hz, 1 H), 3.17 (dt, *J* = 12.0, 1.8 Hz, 1 H), 3.33 (s_{br}, 2 H), 5.53 (d, *J* = 5.8 Hz, 1 H), 7.61 (t, *J* = 7.9 Hz, 1 H), 8.12 (s, 1 H), 8.11 (d, *J* = 7.9 Hz, 1 H), 8.18 (d, *J* = 8.8 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 23.7, 24.4, 25.8, 46.8, 60.2, 71.9, 115.6, 121.4 (q, $^1J_{CF}$ = 276.0 Hz), 123.6 (q, $^1J_{CF}$ = 274.7 Hz), 126.6, 127.1, 127.2, 128.8 (q, $^3J_{CF}$ = 5.4 Hz), 129.7 (q, $^2J_{CF}$ = 30.4 Hz), 143.8, 148.4 (q, $^2J_{CF}$ = 35.5 Hz), 150.2; **HPLC**: Rt_{minor} = 10.7 min (this peak belongs to (+)-*threo*-mefloquine), Rt_{major} = 11.6 min ((–)-*erythro*-mefloquine), Rt_{minor} = 17.7 min ((+)-*erythro*-mefloquine), *e.r.* = 96:4 (199:1 hexane/EtOH + 0.05% ethylenediamine; flow: 1.0 mL/min; injection volume 20 µL, c = 1.0 mg/mL); **HRMS** (ESI): *m/z* calc. for $C_{17}H_{16}F_6N_2O$: 379.1240, found: 379.1242 $[M+H]^+$; A sample of **1a** was converted to its hydrochloride salt **1a**·HCl with EtOH and concentrated HCl followed by concentration and drying in vacuo. The analytical sample prepared by recrystallization from a CH_2Cl_2/hexane followed by drying at 110 °C had **$[\alpha]_D^{23}$ =** –32.83° (c = 0.4, MeOH) [lit.[15] **$[\alpha]_D^{25}$ =** –33.0° (c = 0.306, MeOH)].



Supporting Figure 28: ^{1}H-NMR spectrum of 1a



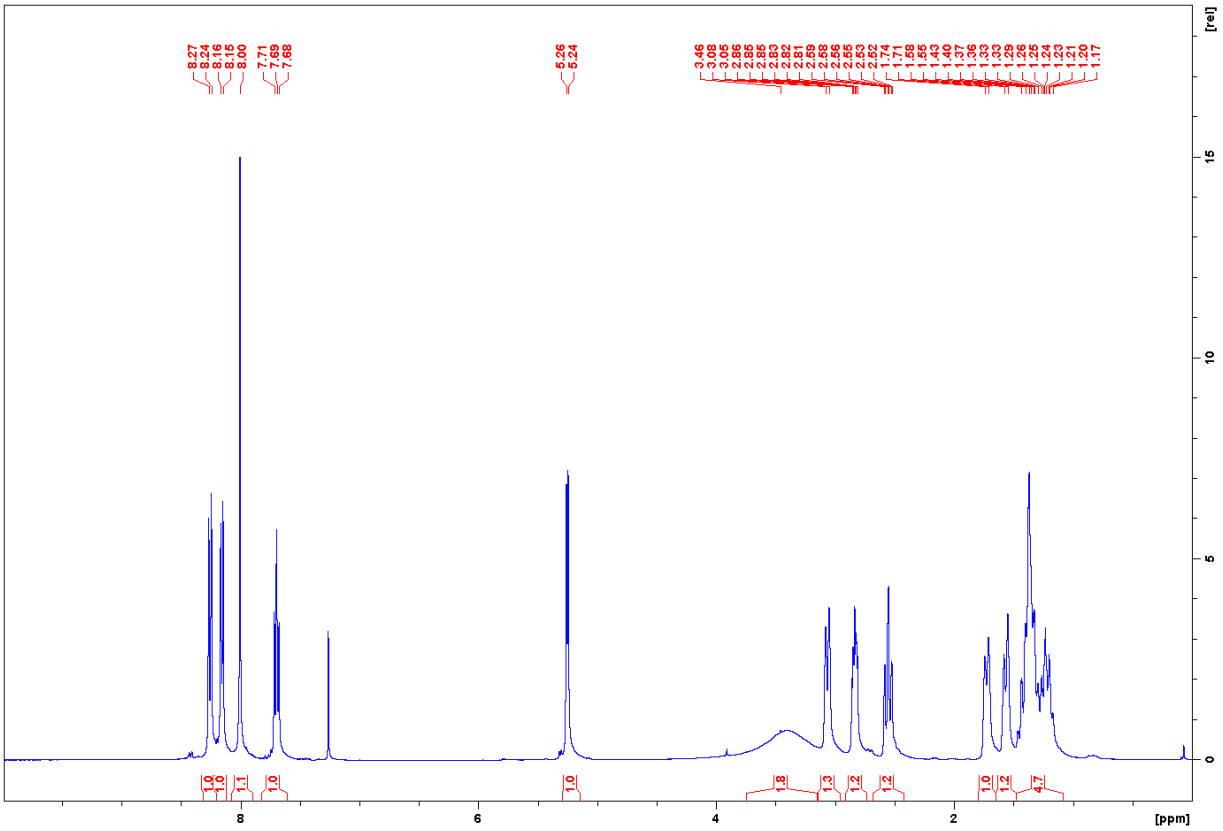
Supporting Figure 29: ^{13}C-NMR spectrum of 1a



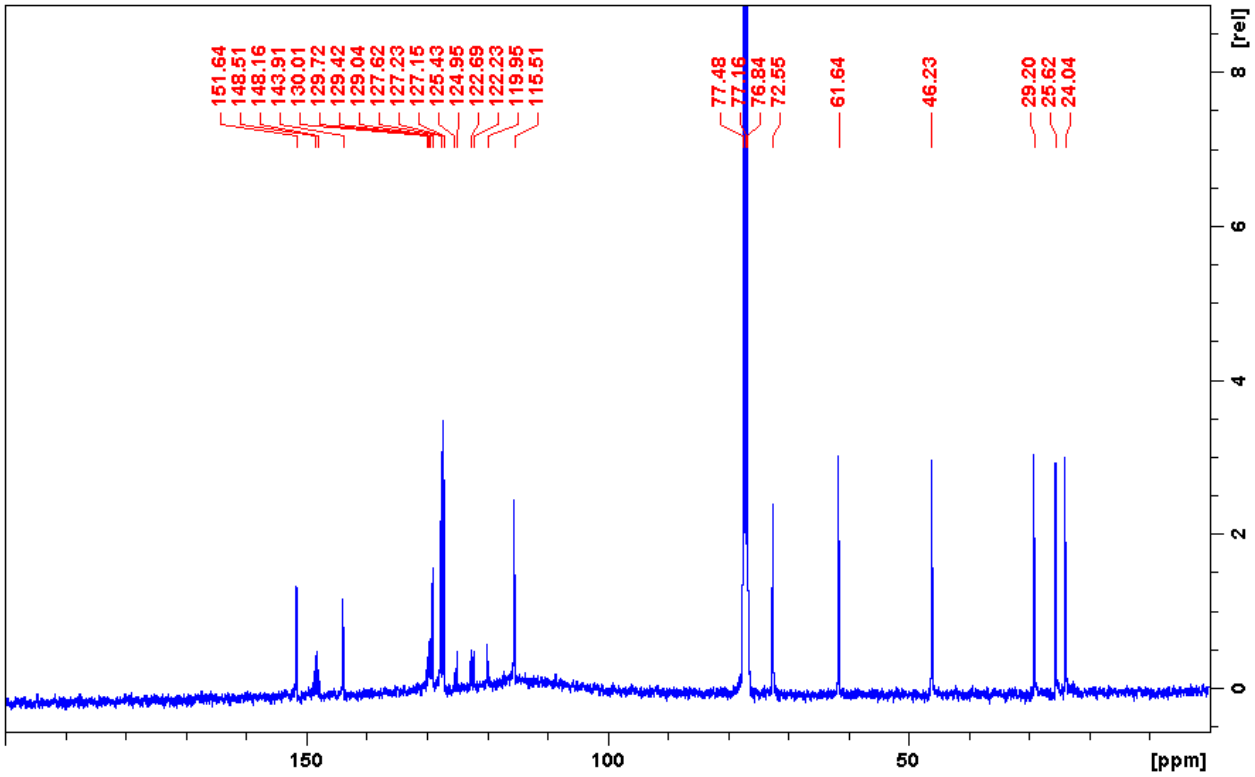
Supporting Figure 30: CHPLC chromatogram of 1a

Analytical data for (+)-*threo*-mefloquine (**1b**)

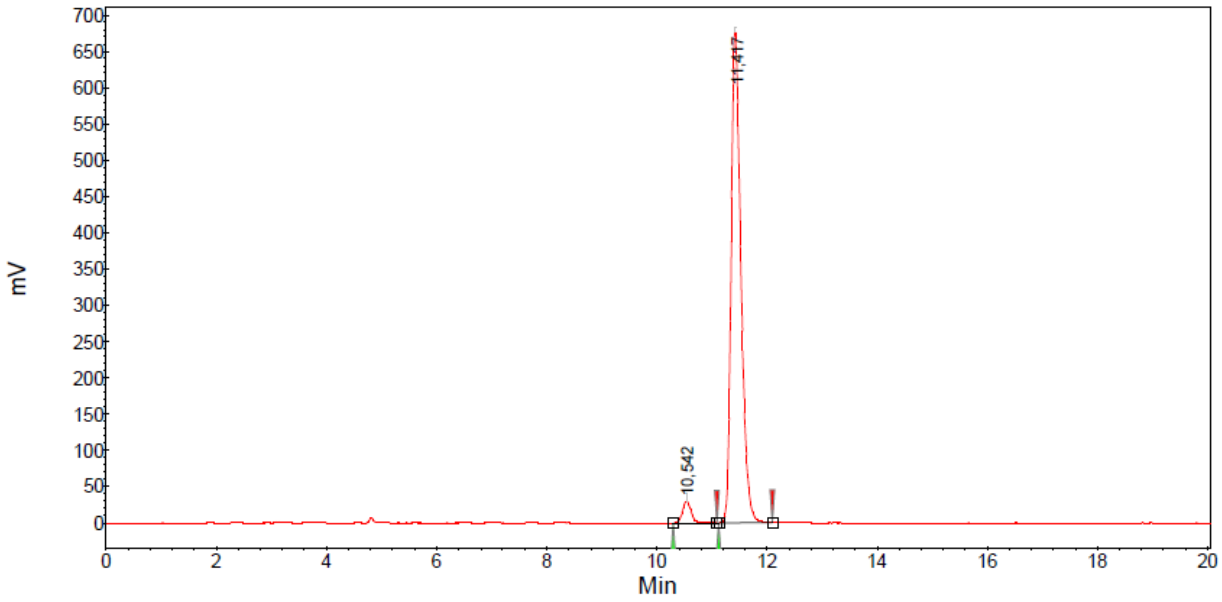
TLC: R_f = 0.19 ($CHCl_3$/MeOH/25% aq. NH_4OH 100:10:1); **MP**: 170–172 °C; **IR** (ATR): ṽ = 1300, 1295, 1190, 1144, 1130, 1106, 1074, 1059, 934, 761, 675 cm^{-1}; **UV**: 221 (4.785), 284 (3.926), 316 (3.619) nm;**^{1}H-NMR** (400 MHz, $CDCl_3$): 1.14–1.45 (m, 4 H), 1.57 (d, *J* = 13.0 Hz, 1 H), 1.73 (d, *J* = 13.0 Hz, 1 H), 2.55 (td, *J* = 11.9, 2.5 Hz, 1 H), 2.78–2.88 (m, 1 H), 3.07 (d, *J* = 12.0 Hz, 1 H), 3.46 (s_{br}, 2 H), 5.25 (d, *J* = 5.8 Hz, 1 H), 7.69 (t, *J* = 8.1 Hz, 1 H), 8.00 (s, 1 H), 8.16 (d, *J* = 7.2 Hz, 1 H), 8.26 (d, *J* = 8.7 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 24.0, 25.6, 29.2, 46.2, 61.6, 72.6, 115.5, 122.7 (q, $^1J_{CF}$ = 275.9 Hz), 123.6 (q, $^1J_{CF}$ = 273.6 Hz), 127.2, 127.2, 127.6, 129.0 (q, $^3J_{CF}$ = 5.0 Hz), 129.6 (q, $^2J_{CF}$ = 29.0 Hz), 143.9, 148.3 (q, $^2J_{CF}$ = 35.2 Hz), 151.6; **HPLC**: Rt_{minor} = 10.5 min ((–)-*threo*-mefloquine), Rt_{major} = 11.4 min ((+)-*threo*-mefloquine) (199:1 hexane/EtOH + 0.05% ethylenediamine; flow: 1.0 mL/min; injection volume 20 µL, c = 1.0 mg/mL), *e.r.* = 96:4; **HRMS** (ESI): *m/z* calc. for $C_{17}H_{16}F_6N_2O$: 379.1240, found: 379.1240 $[M+H]^+$; A sample of **1b** was converted to its hydrochloride salt **1b**·HCl with EtOH and concentrated HCl followed by concentration and drying in vacuo. The analytical sample prepared by recrystallization from a CH_2Cl_2/CH_3CN mixture followed by drying at 110 °C had **$[\alpha]_D^{23}$ =** +51.85° (c = 0.4, MeOH) [lit.[15] **$[\alpha]_D^{24}$ =** +55.27° (c = 0.431, MeOH)].



Supporting Figure 31: ^{1}H-NMR spectrum of 1b

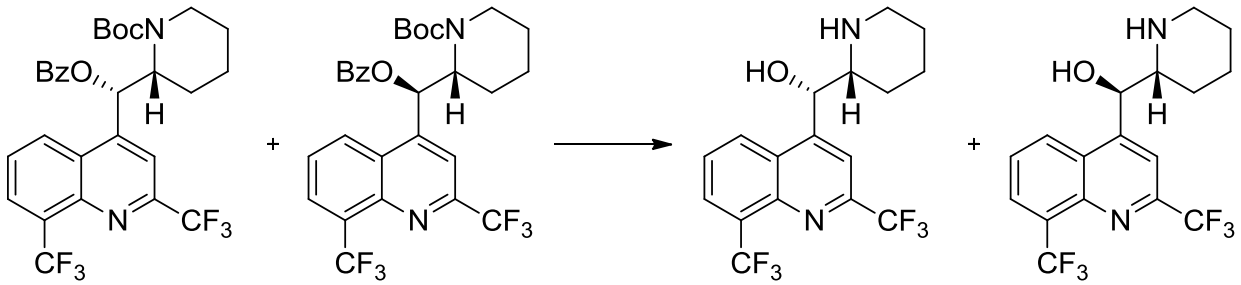


Supporting Figure 32: ^{13}C-NMR spectrum of 1b



Supporting Figure 33: CHPLC chromatogram of 1b

4.12 Synthesis of (*S*)-[2,8-bis(trifluoromethyl)quinolin-4-yl][(2*R*)-piperidin-2-yl]methanol ((+)-*erythro*-mefloquine) (*ent*-**1a**) and (*R*)-[(2,8-bis(trifluoromethyl)quinolin-4-yl][(2*R*)-piperidin-2-yl]methanol ((–)-*threo*-mefloquine) (*ent*-**1b**)

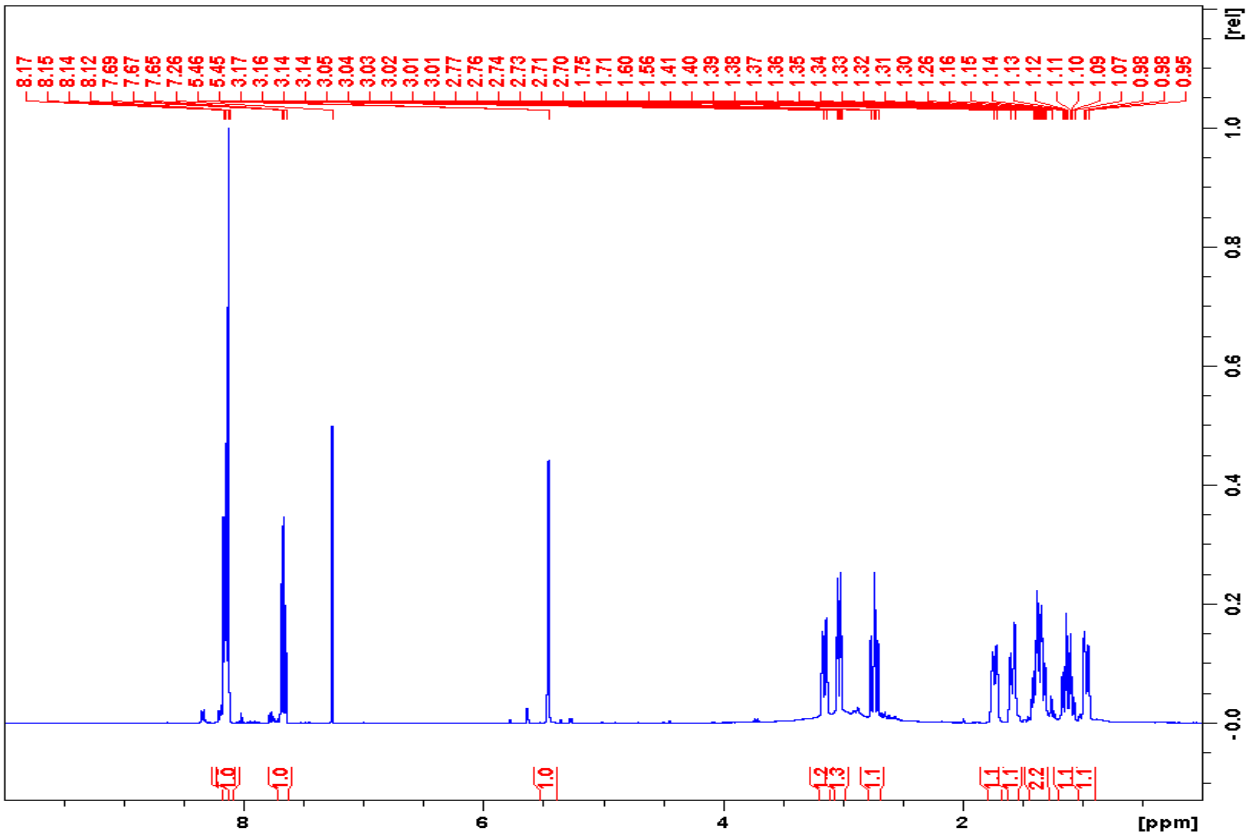


ent-**13a** *ent*-**13b** *ent*-**1a** *ent*-**1b**

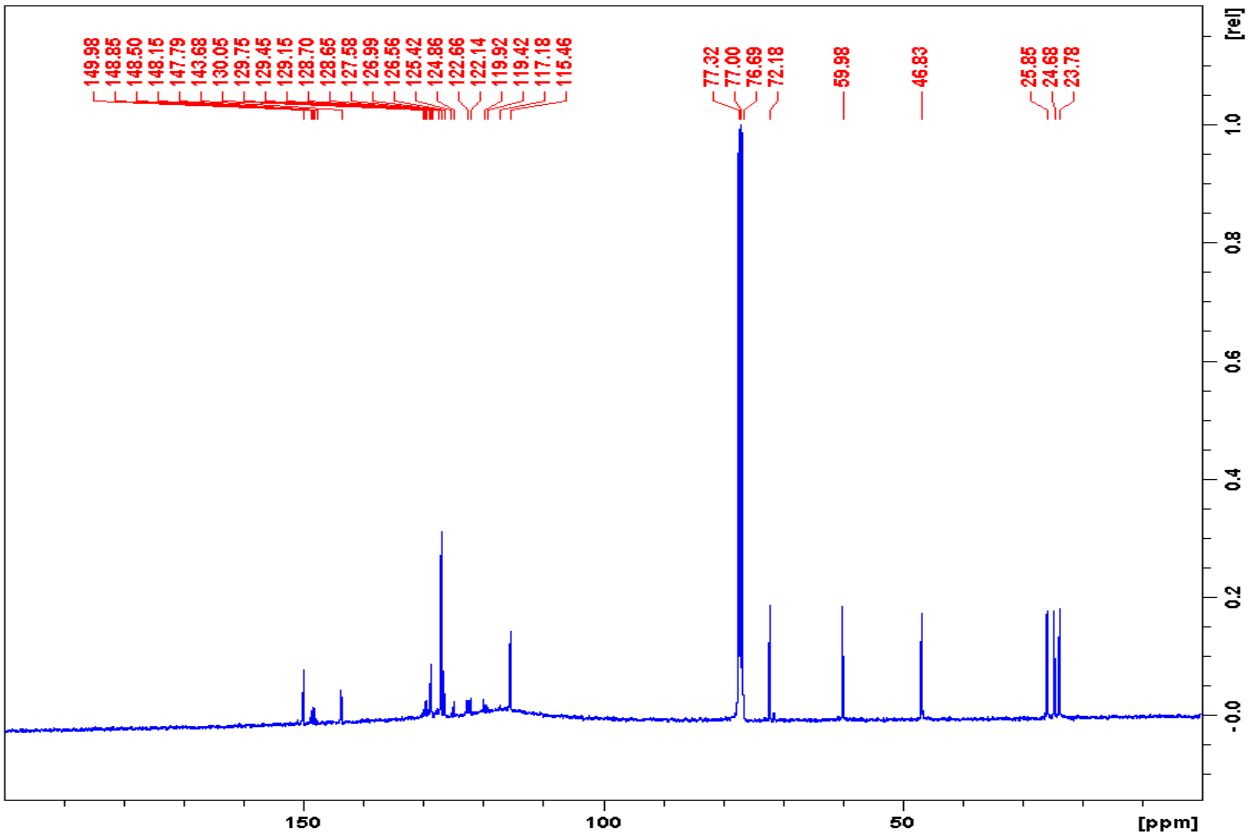
To a solution of the mixture of epimers *ent*-**13a** and *ent*-**13b** (400 mg, 687 µmol, 1.00 equiv.) in MeOH (25 mL) was added $LiOH \cdot H_2O$ (58.0mg, 1.37 mmol, 2.00 equiv.). The reaction mixture was stirred at 20 °C for 1 h and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (30 mL), washed with 5% aq. $NaHCO_3$-solution (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), treated with trifluoroacetic acid (1.0 mL), stirred at 20 °C for 1 h and the solvents were removed in vacuo. The residue was taken up in CH_2Cl_2 (25 mL) and washed with 1 N aq. NaOH-solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (SiO_2, chloroform/methanol/25% NH_4OH_{aq} 100:10:1) to give (–)-*threo*-mefloquine *ent*-**1b** (169 mg, 446 µmol, 65%) and (+)-*erythro*-mefloquine *ent*-**1a** (46 mg, 122 µmol, 18%) as white solids.

Analytical data for (+)-*erythro*-mefloquine (*ent*-**1a**):

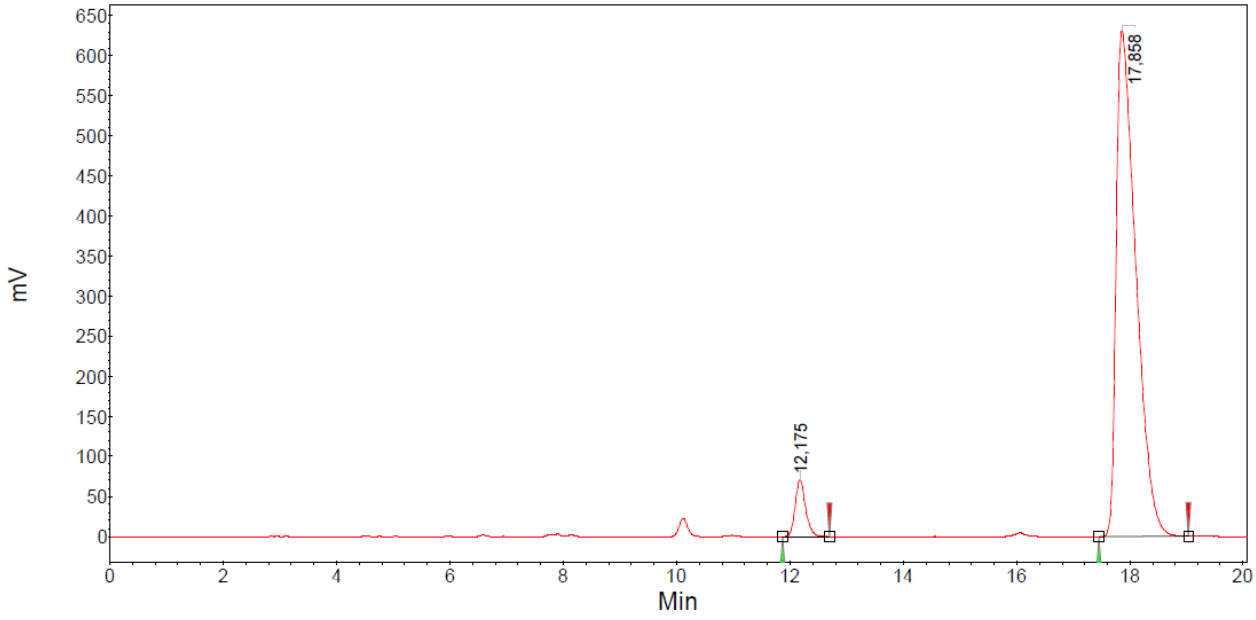
TLC: R_f = 0.11 ($CHCl_3$/MeOH/25% aq. NH_4OH 100:10:1); **MP**: 160–165 °C; **IR** (ATR): $\tilde{\nu}$ = 2942, 1601, 1585, 1431, 1314, 1146, 1129, 1104, 937, 764 cm^{-1}; **UV**: (4.672), 285 (3.816), 316 (3.518) nm; **^{1}H-NMR** (400 MHz, $CDCl_3$): 0.92-1.01 (m, 1 H), 1.12 (tq, *J* = 13.0, 3.7 Hz, 1 H), 1.29-1.43 (m, 2 H), 1.58 (d_{br}, *J* = 13.2 Hz, 1 H), 1.73 (d_{br}, *J* = 13.0 Hz, 1 H), 2.73 (dt, *J* = 12.1, 2.7 Hz, 1 H), 3.03 (td, *J* = 11.2, 3.1 Hz, 1 H), 3.15 (d_{br}, *J* = 11.8 Hz, 1 H), 5.46 (d, *J* = 3.4 Hz, 1 H), 7.67 (t, *J* = 7.9 Hz, 1 H), 8.12 (s, 1 H), 8.15 (m, 2 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): 23.8, 24.7, 25.9, 46.8, 60.0, 72.2, 115.5, 121.3 (q, $^1J_{CF}$ = 275.6 Hz), 123.5 (q, $^1J_{CF}$ = 273.7 Hz), 126.6, 127.0 (2C), 128.7 (q, $^3J_{CF}$ = 5.0 Hz), 129.6 (q, $^2J_{CF}$ = 30.2 Hz), 143.7, 148.3 (q, $^2J_{CF}$ = 35.0 Hz), 150.0; **HPLC**: Rt_{minor} = 10.6 min (this peak belongs to (–)-*threo*-mefloquine), Rt_{minor} = 12.2 min ((–)-*erythro*-mefloquine), Rt_{major} = 17.9 min ((+)-*erythro*-mefloquine) (199:1 hexane/EtOH + 0.05% ethylenediamine; flow: 1.0 mL/min; injection volume 20 µL, c = 1.0 mg/mL), *e.r.* = 94:6; **HRMS** (ESI): *m/z* calc. for $C_{17}H_{16}F_6N_2O$: 379.1240, found: 379.1240 $[M+H]^+$; A sample of *ent*-**1a** was converted to its hydrochloride salt *ent*-**1a**·HCl with EtOH and concentrated HCl followed by concentration and drying in vacuo. The analytical sample prepared by recrystallization from a CH_2Cl_2/hexane followed by drying at 110 °C had **$[\alpha]_D^{23}$ =** +26.01° (c = 0.4, MeOH) [lit.[15] **$[\alpha]_D^{22}$ =** +33.90° (c = 0.280, MeOH)].



Supporting Figure 34: ^{1}H-NMR spectrum of *ent*-1a



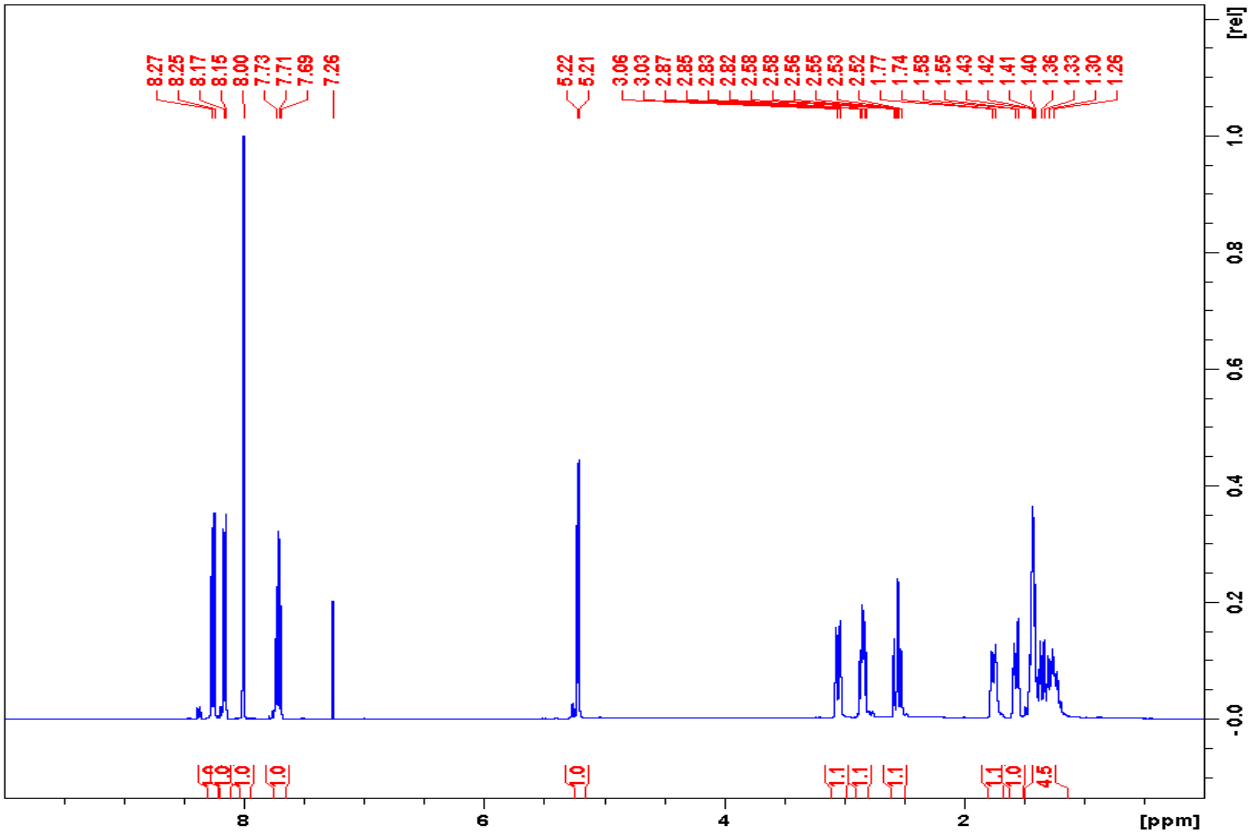
Supporting Figure 35: ^{13}C-NMR spectrum of *ent*-1a



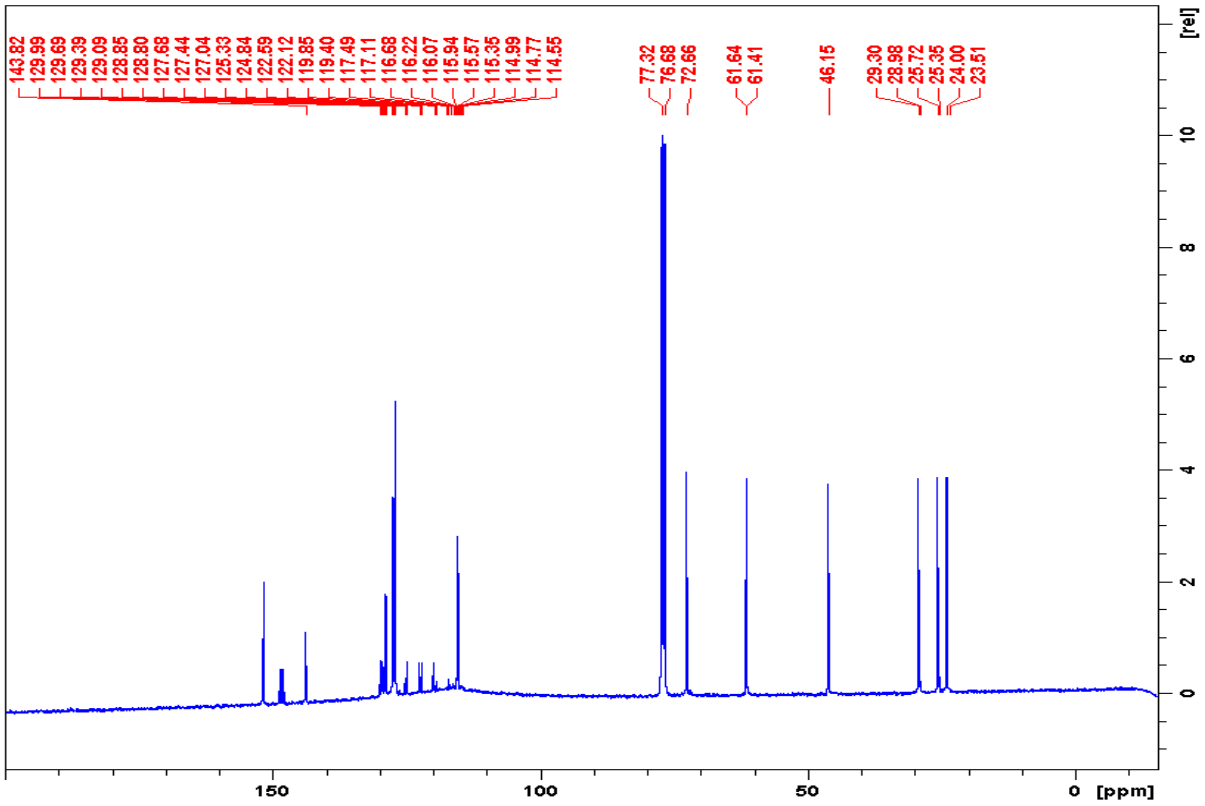
Supporting Figure 36: CHPLC chromatogram of *ent*-1a

Analytical data for (–)-*threo*-mefloquine (*ent*-**1b**)

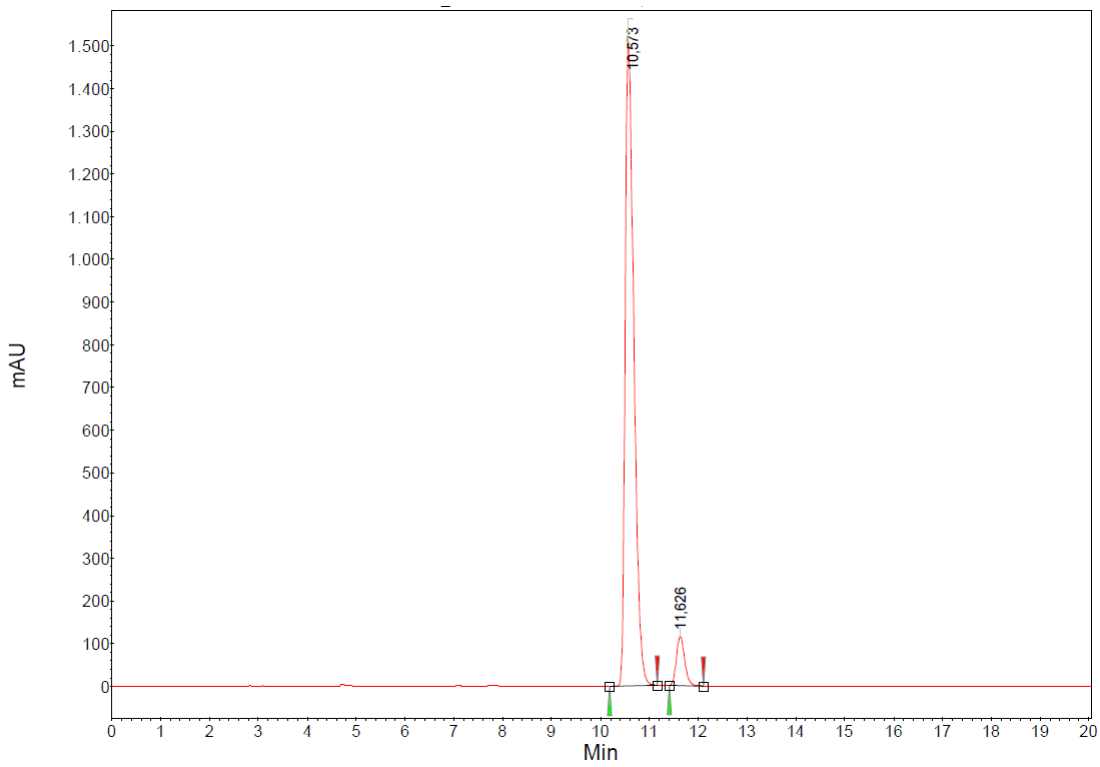
TLC: R_f = 0.19 ($CHCl_3$/MeOH/25% NH_4OH_{aq} 100:10:1); **MP** 170-175 °C; **IR** (ATR): $\tilde{\nu}$ (cm $^{-1}$) = 2939, 1601, 1584, 1429, 1313, 1135, 1107, 1076, 837, 768; **UV** (CH_3CN): λ_{max} (lg ε) = 221 (4.652), 284 (3.788), 316 (3.478) nm; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.15–1.50 (m, 4 H), 1.51–1.62 (m, 1 H), 1.67-1.81 (m, 1 H), 2.55 (dt, *J* = 11.6, 2.4 Hz, 1 H), 2.80–2.90 (m, 1 H), 3.05 (d_{br}, *J* = 12.0 Hz, 1 H), 5.21 (d, *J* = 5.5 Hz, 1 H), 7.71 (t, *J* = 7.9 Hz, 1 H), 8.00 (s, 1 H), 8.16 (d, *J* = 7.2 Hz, 1 H), 8.25 (d, *J* = 8.6 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 24.0, 25.7, 29.3, 46.1, 61.4, 72.7, 115.3, 121.2 (q, $^1J_{CF}$ = 275.6 Hz), 123.5 (q, $^1J_{CF}$ = 273.7 Hz), 127.0 (2C), 127.4, 128.8 (q, $^3J_{CF}$ = 5.0 Hz), 129.5 (q, $^2J_{CF}$ = 30.2 Hz), 143.8, 148.2 (q, $^2J_{CF}$ = 35.3 Hz), 151.6; **HPLC:** Rt_{major} ((–)-*threo*-mefloquine) = 10.6 min; Rt_{minor} ((+)-*threo*-mefloquine) = 11.6 min (200:1 *n*-hexane/EtOH + 0.05% ethylenediamine; flow: 1.0 mL/min; injection volume 20 µL, c = 1.0 mg/mL), *e.r.* = 93:7; **HRMS** (ESI): *m/z* calc. for $C_{17}H_{17}F_6N_2O$: 379.1240, found: 379.1240, $[M+H]^+$; A sample of ***ent*-1b** was converted to its hydrochloride salt ***ent*-1b**·HCl with EtOH and concentrated HCl followed by concentration and drying in vacuo. The analytical sample prepared by recrystallization from a CH_2Cl_2/CH_3CN mixture followed by drying at 110 °C had **$[\alpha]_D^{23}$ =** –50.49° (c = 0.4, MeOH) [lit.[15] **$[\alpha]_D^{25}$ =** –53.37° (c = 0.308, MeOH)].



Supporting Figure 37: ^{1}H-NMR spectrum of *ent*-1b

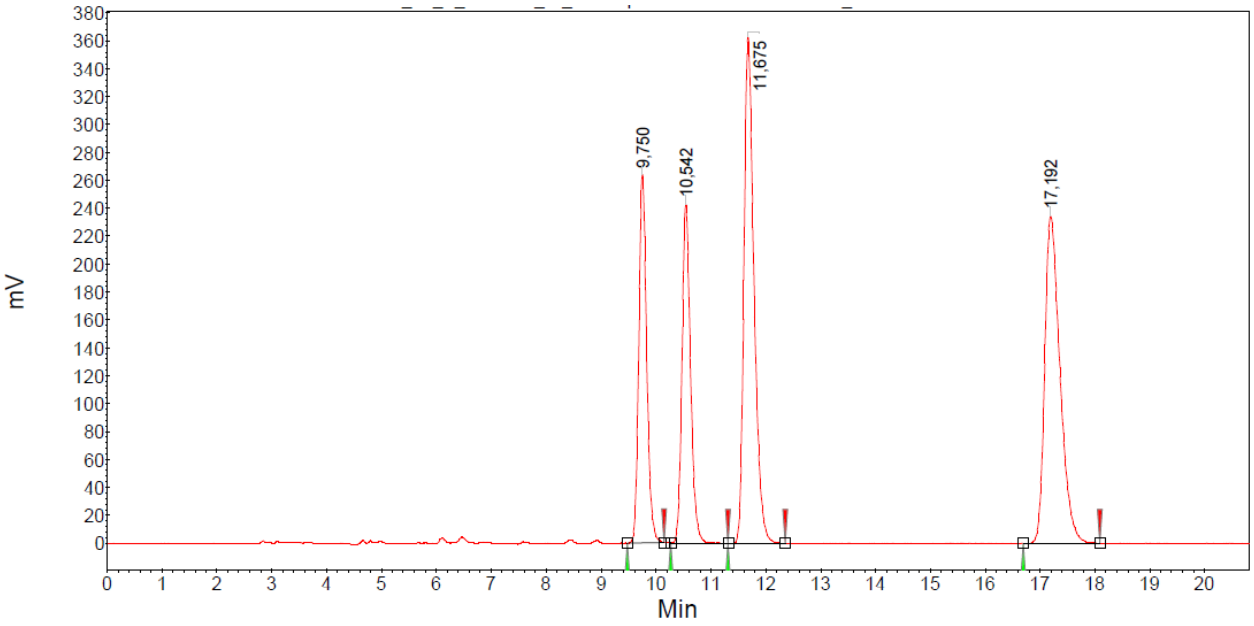


Supporting Figure 38: ^{1}H-NMR spectrum of *ent*-1b



Supporting Figure 39: CHPLC chromatogram of *ent*-1b

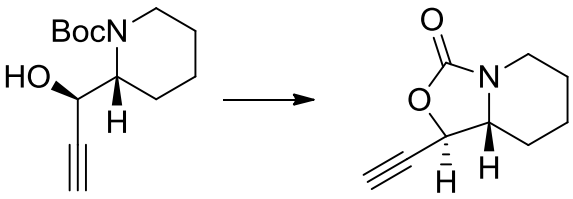
HPLC: All four stereoisomers of mefloquine



Supporting Figure 40: CHPLC chromatogram: Coinjection of Lariam (*rac-erythro*-mefloquine) and commercially available *rac-threo*-mefloquine

HPLC of the mixture of commercial racemic (±)-*erythro*- and (±)-*threo*-mefloquine in a ratio 1:1: *Rt* ((–)–*threo*-mefloquine) = 9.8 min; *Rt* ((+)–*threo*-mefloquine) = 10.5 min; *Rt* ((–)-*erythro*-mefloquine) = 11.7 min; *Rt* ((+)-*erythro*-) = 17.2 min (199:1 hexane/EtOH + 0.05% ethylenediamine; flow: 1.0 mL/min; injection volume 20 µL, c = 1.0 mg/mL).

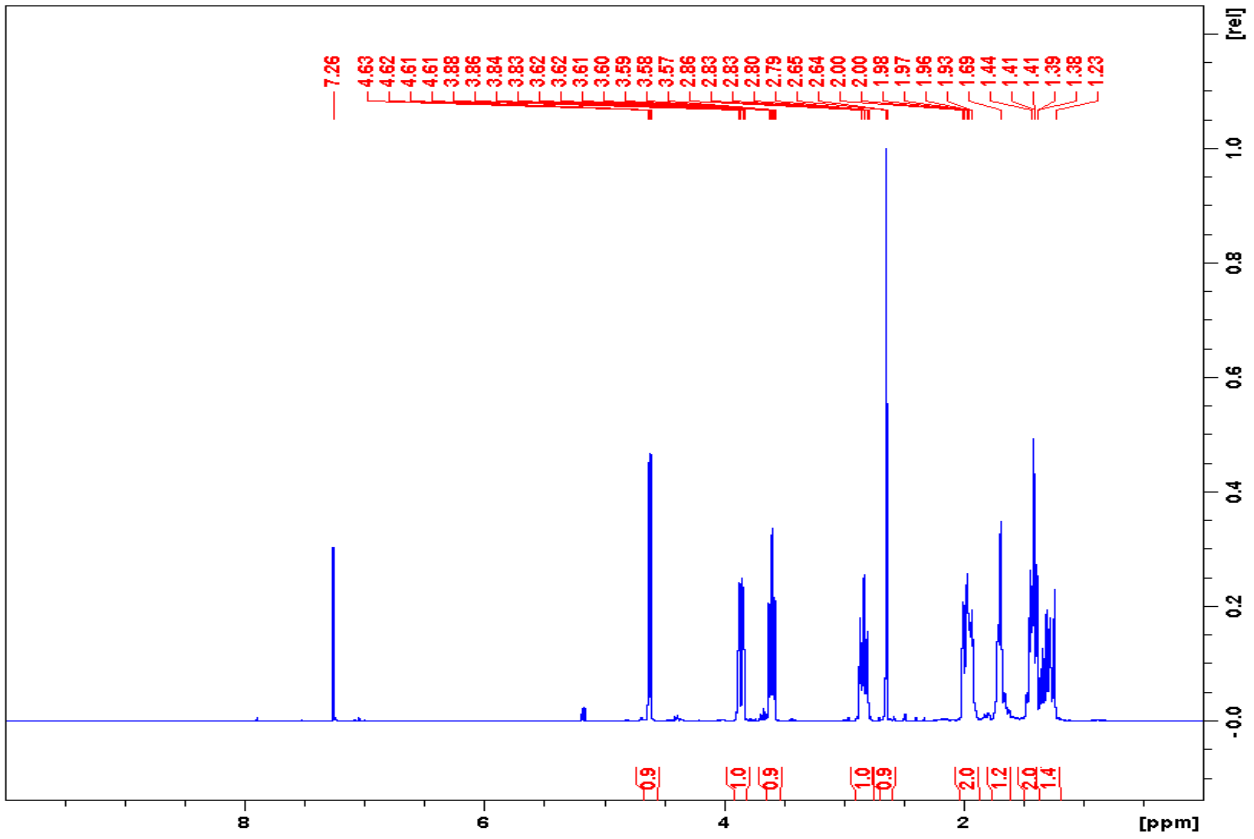
4.13 Synthesis of (1*R*,8a*R*)-1-ethynylhexahydro[1,3]oxazolo[3,4-a]pyridin-3-one (*ent*-**10**)



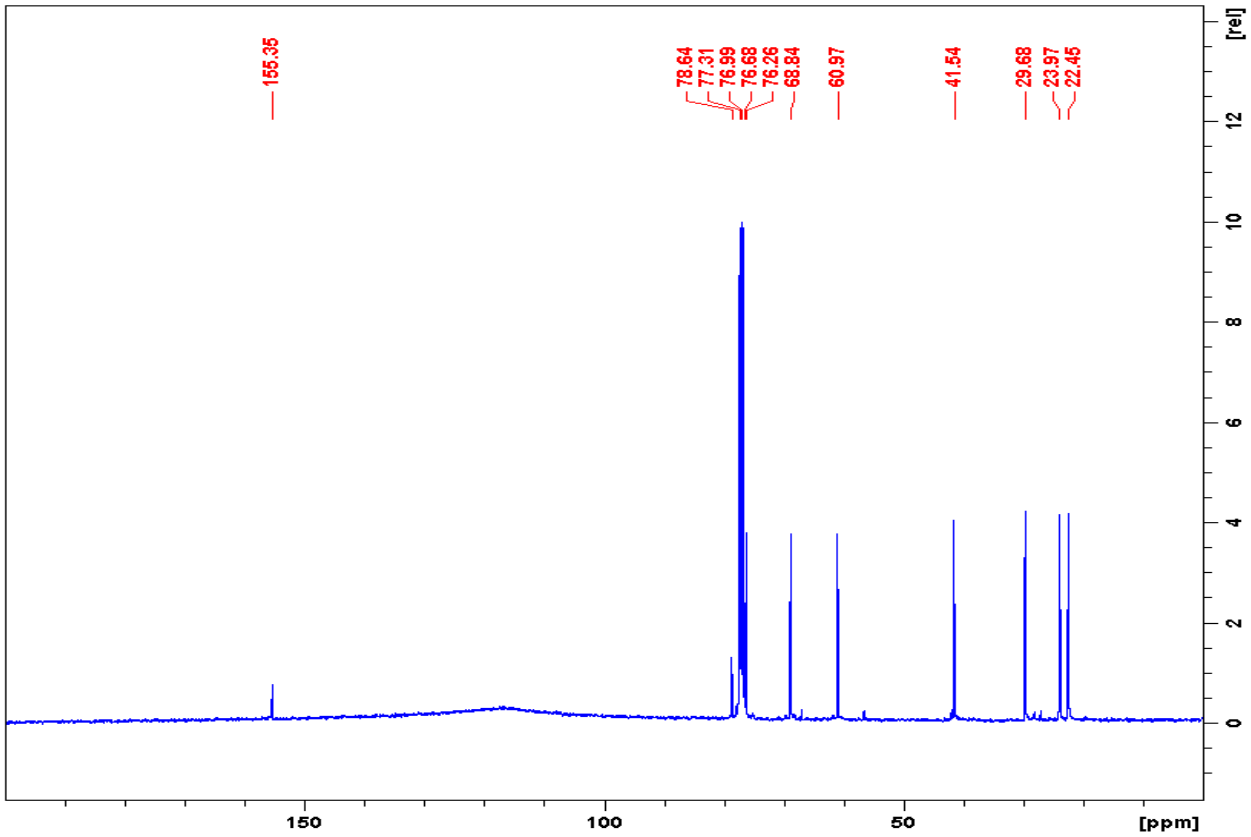
ent-**8** *ent*-**10**

Compound *ent*-**8** (239 mg, 1.00 mmol) was dissolved in a 1 M solution of HCl in ethyl acetate (6 mL) (prepared by bubbling dry HCl gas into dry ethyl acetate). The reaction mixture was stirred at 20 °C for 24 h and the solvent was removed in vacuo. The residue was suspended in CH_2Cl_2 (10 mL) and Et_3N (153 µL, 111 mg, 1.10 mmol) and *N*,*N*′-carbonyldiimidazole (324 mg, 2.00 mmol) were added. The reaction mixture was stirred at 20 °C for 5 h and the solvent was removed in vacuo. The residue was purified by flash chromatography (SiO_2, chloroform/methanol 95:5) to give *ent*-**10** (160 mg, 0.97 mmol, 97%) as a white solid.

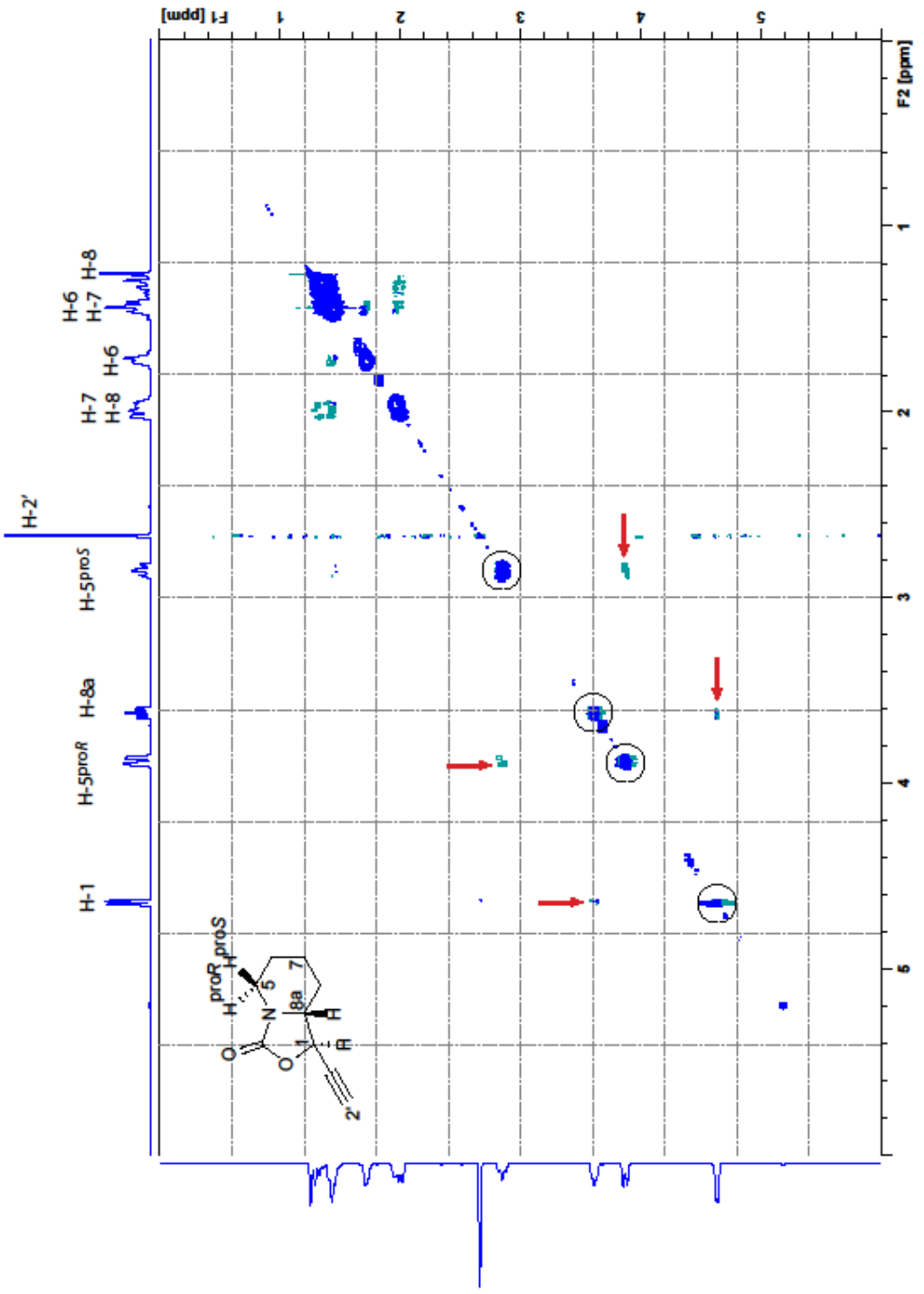
TLC: R_f = 0.85 (chloroform/methanol 95:5); **MP:** 63-65 °C; $[\alpha]_D^{23}$ = +43.4° (c = 0.5, $CHCl_3$); **IR** (ATR): $\tilde{\nu}$ = 2946, 2865, 2123, 1738, 1444, 1425, 1293, 1248, 1026, 1012, 956, 924 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.19–1.37 (m, 1 H), 1.37–1.50 (m, 2 H), 1.61–1.77 (m, 1 H), 1.87–2.04 (m, 2 H), 2.64 (d, *J* = 2.1 Hz, 1 H), 2.83 (dt, *J* = 12.7, 3.5 Hz, 1 H), 3.60 (ddd, *J* = 10.8, 6.9, 3.6 Hz, 1 H), 3.85 (dd, *J* = 13.2, 4.4 Hz, 1 H), 4.62 (dd, *J* = 6.9, 2.1 Hz, 1 H);**^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 22.5, 24.0, 29.7, 41.5, 61.0, 68.9, 76.3, 78.6, 155.4; **HRMS** (ESI): *m/z* calc. for $C_9H_{12}NO_2$: 166.0863, found: 166.0863 $[M+H]^+$.



Supporting Figure 41: ^{1}H-NMR spectrum of *ent*-10



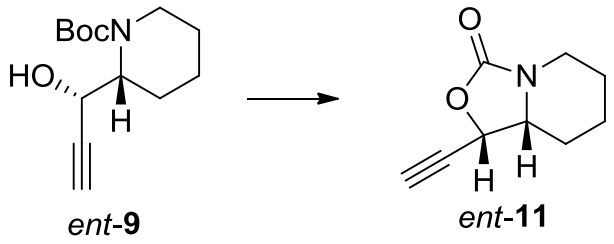
Supporting Figure 42: ^{13}C-NMR spectrum of *ent*-10



Supporting Figure 43: 2D NOESY NMR spectrum of *ent*-10

2D NOESY NMR experiments according to Thrippleton and Keeler[41] were carried out using a solution of 15 mg *ent*-**10** in 550 µL $CDCl_3$ at 298 K with DS = 32, NS = 16, TD1 = 800, TD2 = 4k, SW1 = SW2 = 2400 Hz. A mixing time of 500 ms was used with a relaxation delay of 2 s. Zero-quantum suppression was achieved through the use of an adiabatic-pulse/gradient pair during the mixing time. Both dimensions were processed using a sine-squared function with a $\pi/2$ phase shift and SI1 = 1k, SI2 = 4k.

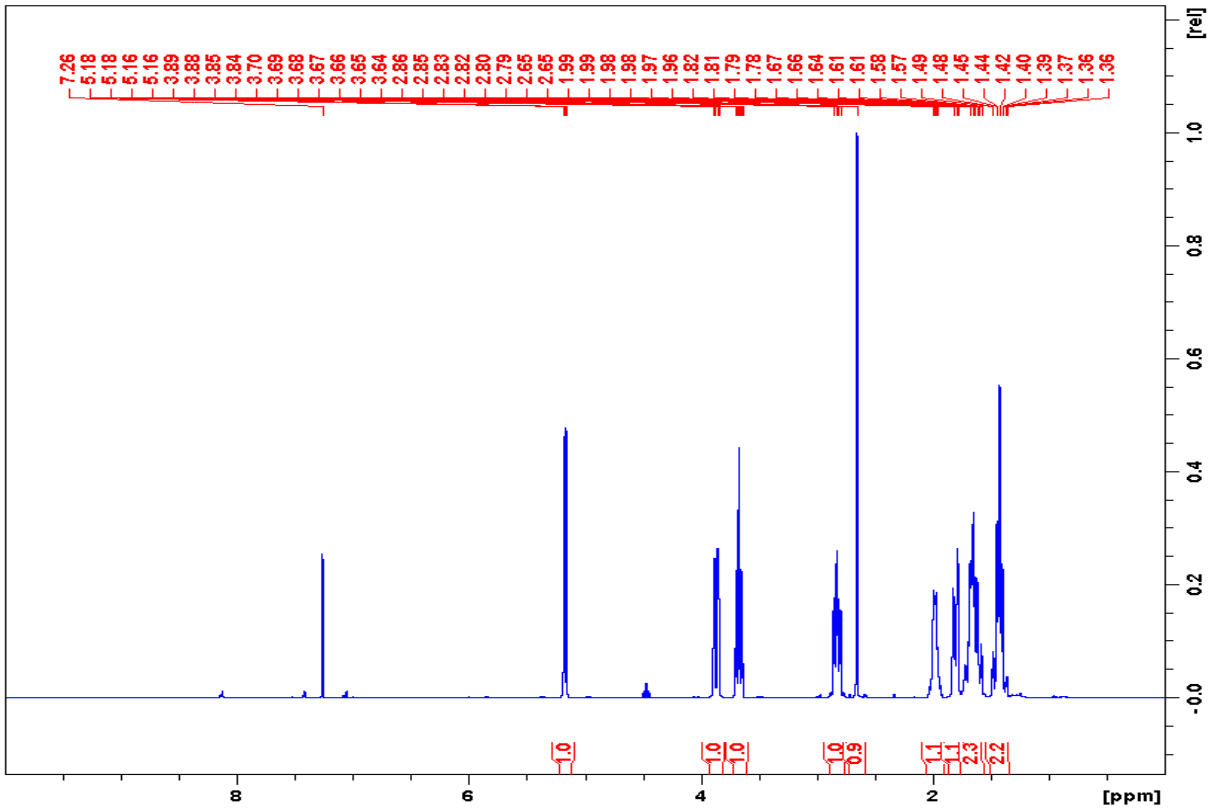
4.14 Synthesis of (1*S*,8a*R*)-1-ethynylhexahydro[1,3]oxazolo[3,4-a]pyridin-3-one (*ent*-**11**)



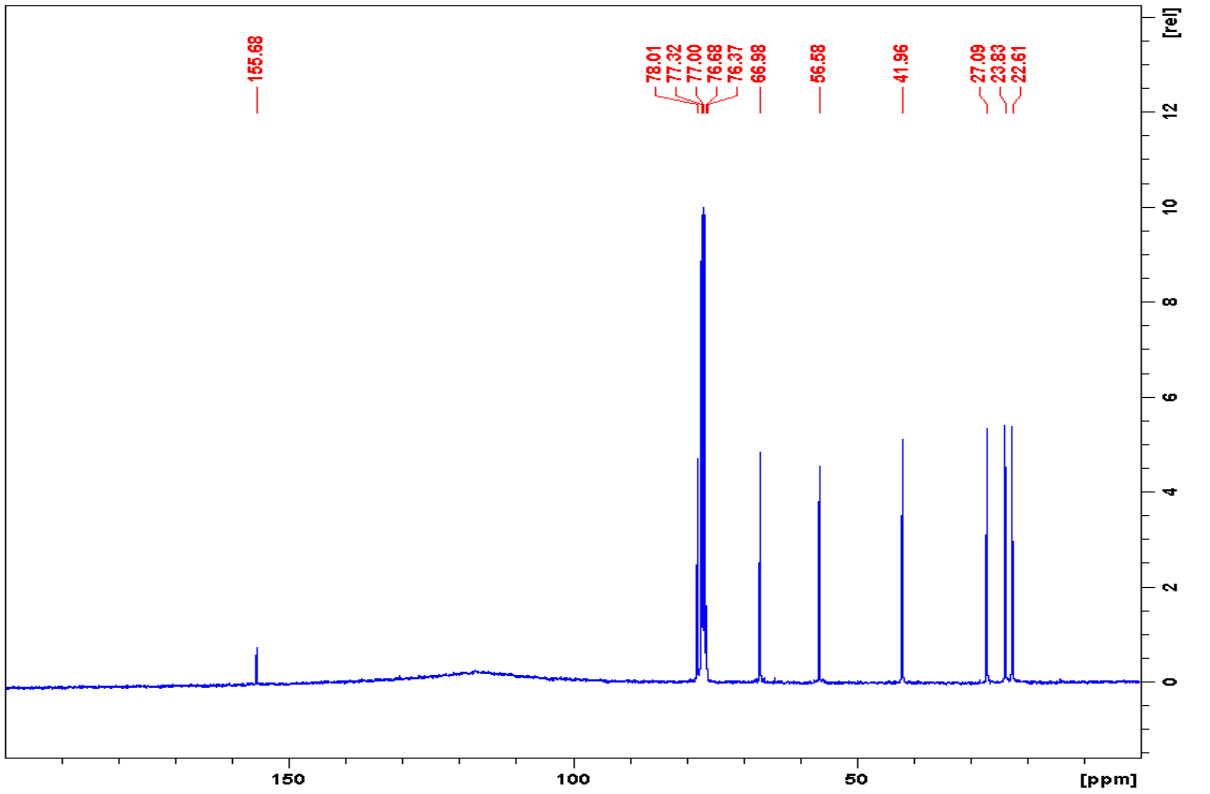
ent-**9** *ent*-**11**

Compound *ent*-**9** (239 mg, 1.00 mmol, 1.00 equiv.) was dissolved in a 1 M solution of HCl in ethyl acetate (6 mL; prepared by bubbling dry HCl gas into dry ethyl acetate). The reaction mixture was stirred at 20 °C for 24 h and the solvent was removed in vacuo. To the residue was suspended in CH_2Cl_2 (10 mL) Et_3N (153 µL, 111 mg, 1.10 mmol, 1.10 equiv.) and *N*,*N*′-carbonyldiimidazole (324 mg, 2.00 mmol, 2.00 equiv.) were added. The reaction mixture was stirred at 20 °C for 5 h and the solvent was removed in vacuo. The residue was purified by flash chromatography (SiO_2, chloroform/methanol 95:5) followed by second flash chromatography (SiO_2, hexane/ethyl acetate 1:1) to give of *ent*-**11** (152 mg, 0.92 mmol, 92%) as a white solid.

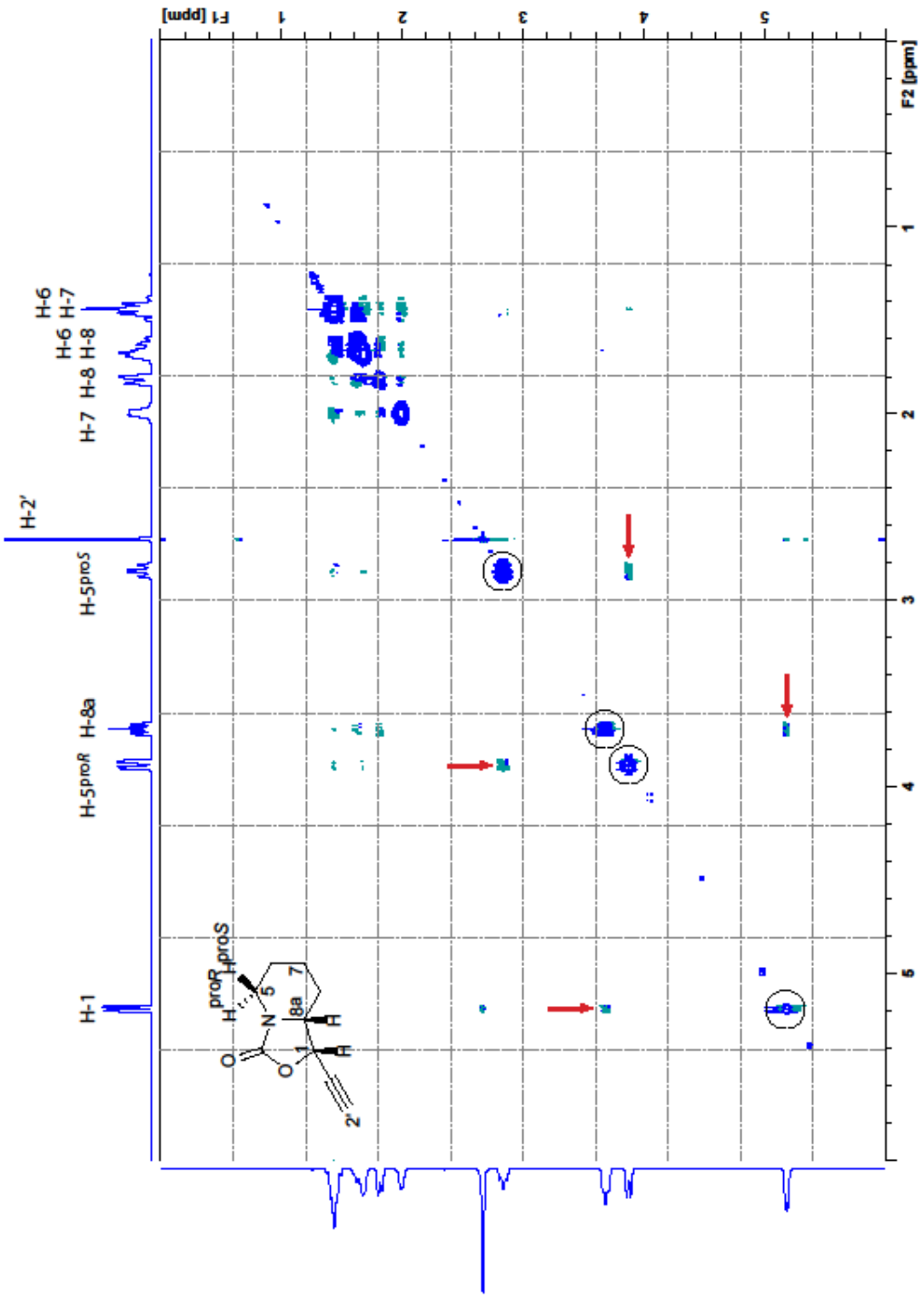
TLC: R_f = 0.75 (chloroform/methanol 95:5), R_f = 0.5 (hexane/ethyl acetate 1:1); **MP:** 61-63 °C; $[\alpha]_D^{23}$ = –49.2° (c = 0.5, $CHCl_3$); **IR** (ATR): $\tilde{\nu}$ (cm $^{-1}$) = 2948, 2859, 2120, 1742, 1417, 1275, 1028, 995, 940; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.34–1.51 (m, 2 H), 1.56–1.75 (m, 2 H), 1.76–1.87 (m, 1 H), 1.91–2.06 (m, 1 H), 2.65 (d, *J* = 2.2 Hz, 1 H), 2.82 (dt, *J* = 12.7, 3.5 Hz, 1 H), 3.67 (ddd, *J* = 11.6, 8.0, 3.6 Hz,1 H), 3.87 (dd, *J* = 13.2, 4.4 Hz, 1 H), 5.17 (dd, *J* = 8.0, 2.2 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 22.6, 23.8, 27.1, 42.0, 56.6, 67.0, 76.4, 78.0, 155.7; **HRMS** (ESI): *m/z* calc. for $C_9H_{12}NO_2$: 166.0863, found: 166.0863 $[M+H]^+$.



Supporting Figure 44: ^{1}H-NMR spectrum of *ent*-11



Supporting Figure 45: ^{13}C-NMR spectrum of *ent*-11



Supporting Figure 46: 2D NOESY NMR spectrum of *ent*-11

2D NOESY NMR experiments according to Thrippleton and Keeler[41] were carried out using a solution of 15 mg *ent*-**11** in 550 µL $CDCl_3$ at 298 K with DS = 32, NS = 16, TD1 = 800, TD2 = 4k, SW1 = SW2 = 2400 Hz. A mixing time of 500 ms was used with a relaxation delay of 2 s. Zero-quantum suppression was achieved through the use of an adiabatic-pulse/gradient pair during the mixing time. Both dimensions were processed using a sine-squared function with a $\pi/2$ phase shift and SI1 = 1k, SI2 = 4k.