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Supporting Information

69451 Weinheim, Germany

The Absolute Configuration of (+)- and (−)-*erythro*-Mefloquine**

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Supporting Information

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.

1.1 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 a Lambda 2 spectrometer from Perkin-Elmer or a V-630 spectrometer from JASCO in the solvents indicated.

^{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.

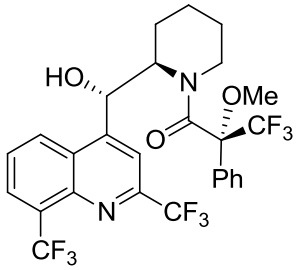
Column chromatography: Silica gel 60 (0.040–0.063 mm) from Merck was used, unless otherwise stated.

1.2 Analytical HPLC

Analytical separations were performed on a HPLC system from *Jasco* equipped with a PU-2080 solvent pump, a LG-1590-04 mixing chamber, a MD-2010 Plus multi-wavelength detector and a LC-Net II/ADC controller. In addition, an AS-2055 autosampler of the same company was installed. For monitoring, data acquisition and data analysis the Borwin PDA, HSS 2000 and Borwin Chromatography software from *Jasco* was used. A Chiralpak® IA (250 × 4.6 mm, particle size: 5 µm) column from *Daicel Chemical Industries Ltd.* was used. Solvent: 2% *iso*-propanol in *n*-hexane. Flow: 0.8 ml/min.

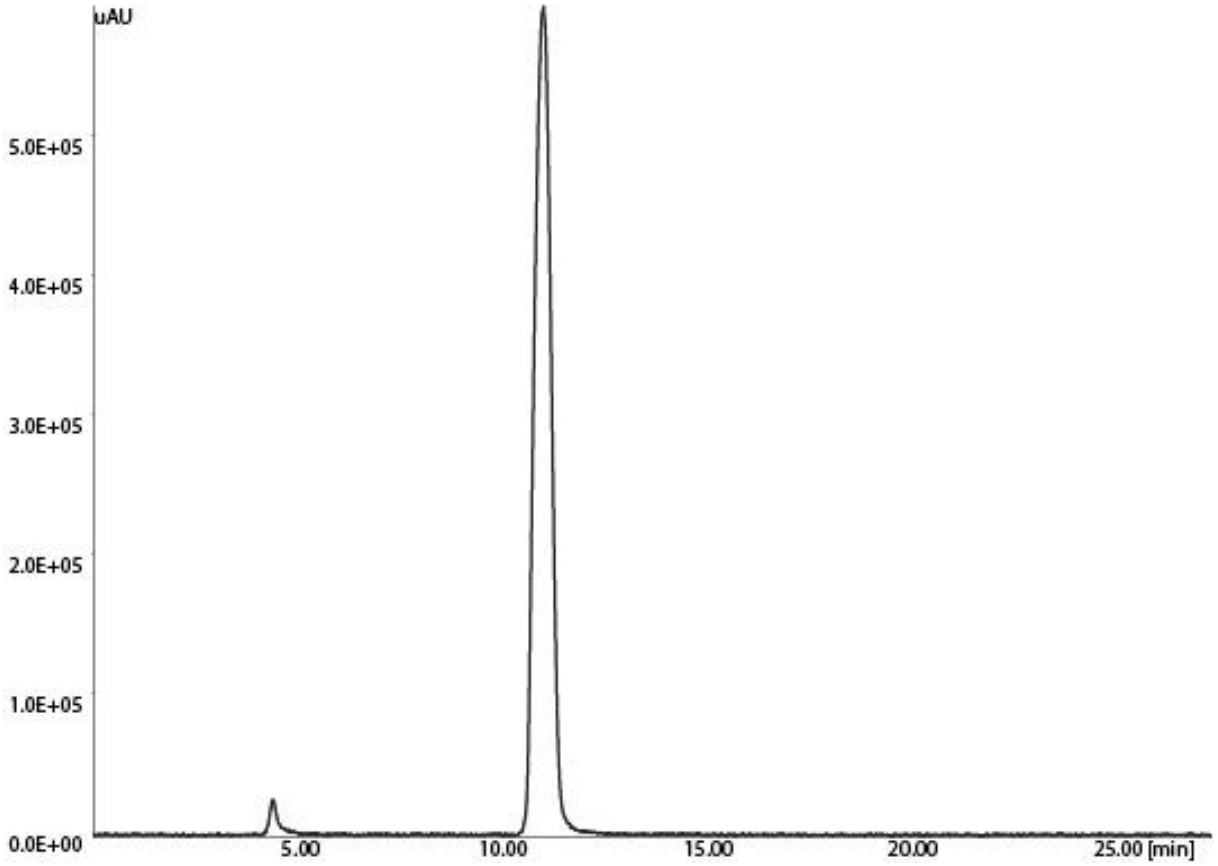
2 Synthesis of Mosher derivatives of mefloquine

2.1 (+)-(11*S*,12*R*)-Mefloquine-(*R*)-Mosher amide 3



(+)-Mefloquine hydrochloride **1** (25.0 mg, 0.066 mmol) was dissolved in CH_2Cl_2 (3.0 mL) and cooled to 0 °C. *i*-Pr_2NEt (58.0 µL, 0.33 mmol, 5.0 equiv.) and (*S*)-MTPA-Cl (13 µL, 0.066 mmol, 1.1 equiv.) were added and the solution was warmed to room temperature and stirred for 2 hours. SiO_2 (100 mg) was added and the solvent was removed under reduced pressure. Column chromatography on silica (CH_2Cl_2) gave the titled compound **3** (29.2 mg, 0.049 mmol, 74%, d.r. > 99:1) as colourless solid.
A similar reaction (compare 2.2) with the free base of (+)-mefloquine gave the titled compound that was directly crystalized from CH_2Cl_2 after column chromatography. From this batch single crystals of **3** could be obtained.

R_f = 0.31 (CH_2Cl_2); **$[\alpha]_D^{24}$** = +120.3° (c = 0.15, $CHCl_3$); **UV** (CH_3CN): λ_{max} (lg ε) = 207 nm (10.611), 220 (4.629), 290 (3.804), 316 (3.456); **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 1644.0, 1626.7, 1432.9, 1310.4, 1266.0, 1140.7, 1106.0, 1078.0, 1050.1, 990.3, 776.2, 766.6, 721.2, 700.0, 669.2; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 0.14–0.28 (m, 1 H), 0.82–0.91 (m, 2 H), 1.21–1.30 (m, 1 H), 1.49–1.61 (m, 1 H), 1.71–1.83 (m, 1 H), 2.15 (s_{br}, 1 H), 3.41 (ddd, *J* = 14.1, 12.4, 5.9 Hz, 1 H), 3.74 (s, 3 H), 3.96 (dd, *J* = 14.3, 7.1 Hz, 1 H), 4.67–4.75 (m, 1 H), 6.20 (d, *J* = 3.1 Hz, 1 H), 7.36–7.41 (m, 3 H), 7.53–7.59 (m, 2 H), 7.94 (t, *J* = 7.9 Hz, 1 H), 8.09 (s, 1 H), 8.22 (d, *J* = 7.5 Hz, 1 H), 8.98 (d, *J* = 8.7 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 18.18, 19.84, 21.10, 40.74, 55.37, 56.33, 70.94, 84.88 (q, *J* = 26.0 Hz), 114.89, 120.36 (q, *J* = 275.2), 122.52, 123.69 (q, *J* = 275.2), 125.40, 126.54, 126.72, 128.16, 128.39, 129.01 (q, *J* = 25.6), 129.37, 129.52, 134.20, 143.68, 148.17 (q, *J* = 34.7 Hz), 150.76, 166.47; **HRMS** (ESI): *m/z* calc. for $C_{27}H_{23}F_9N_2O_3$: 595.1638, found: 595.1635, $[M+H]^+$; **HPLC**: R_t = 11.00 min (conditions see 1.2).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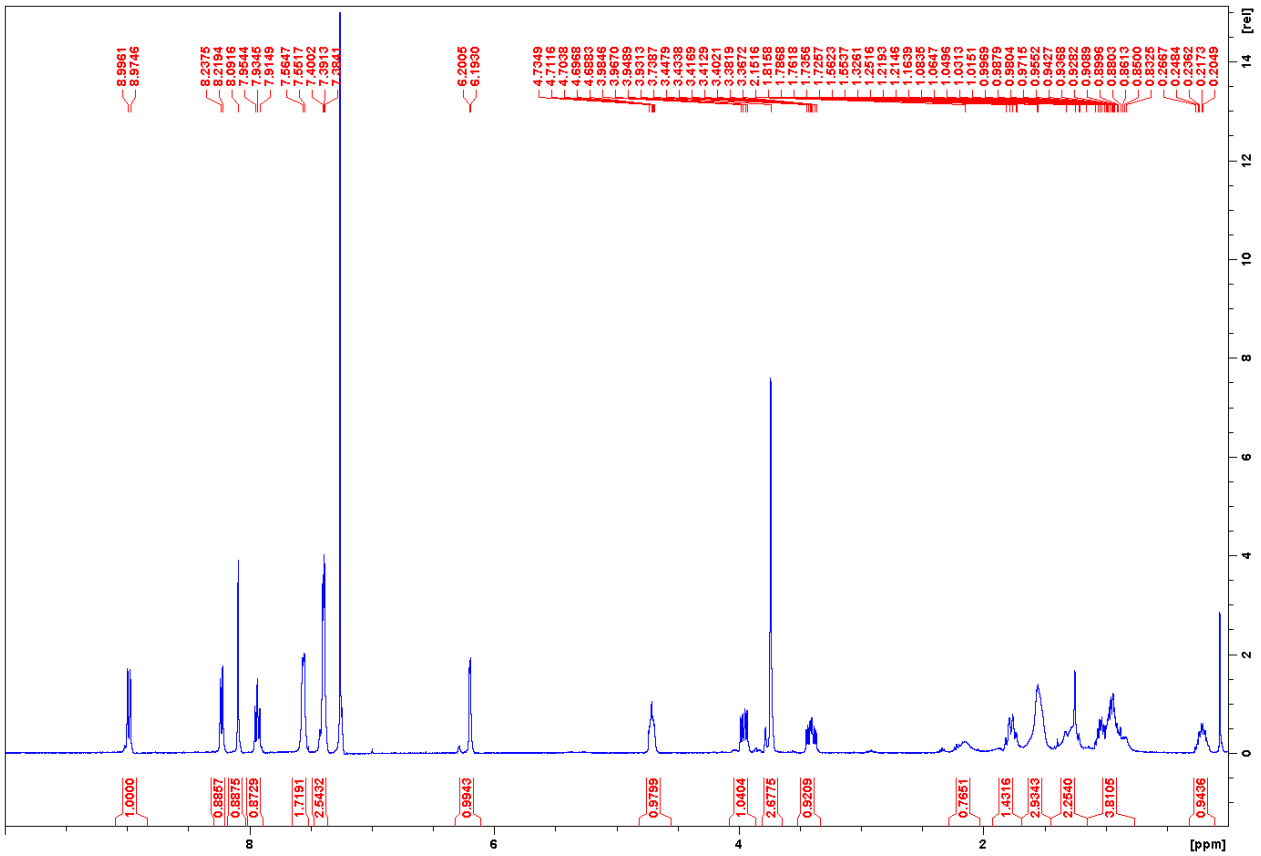
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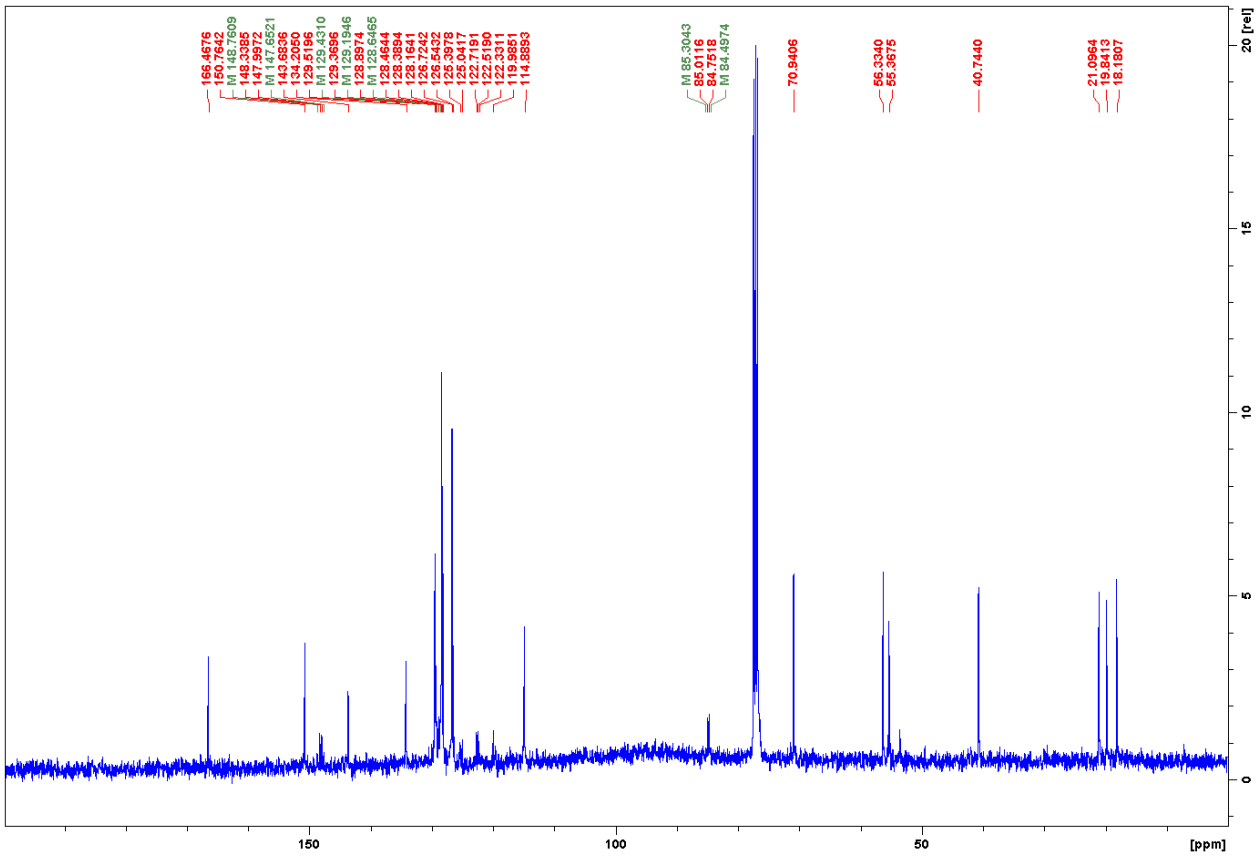
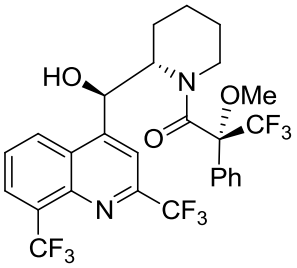
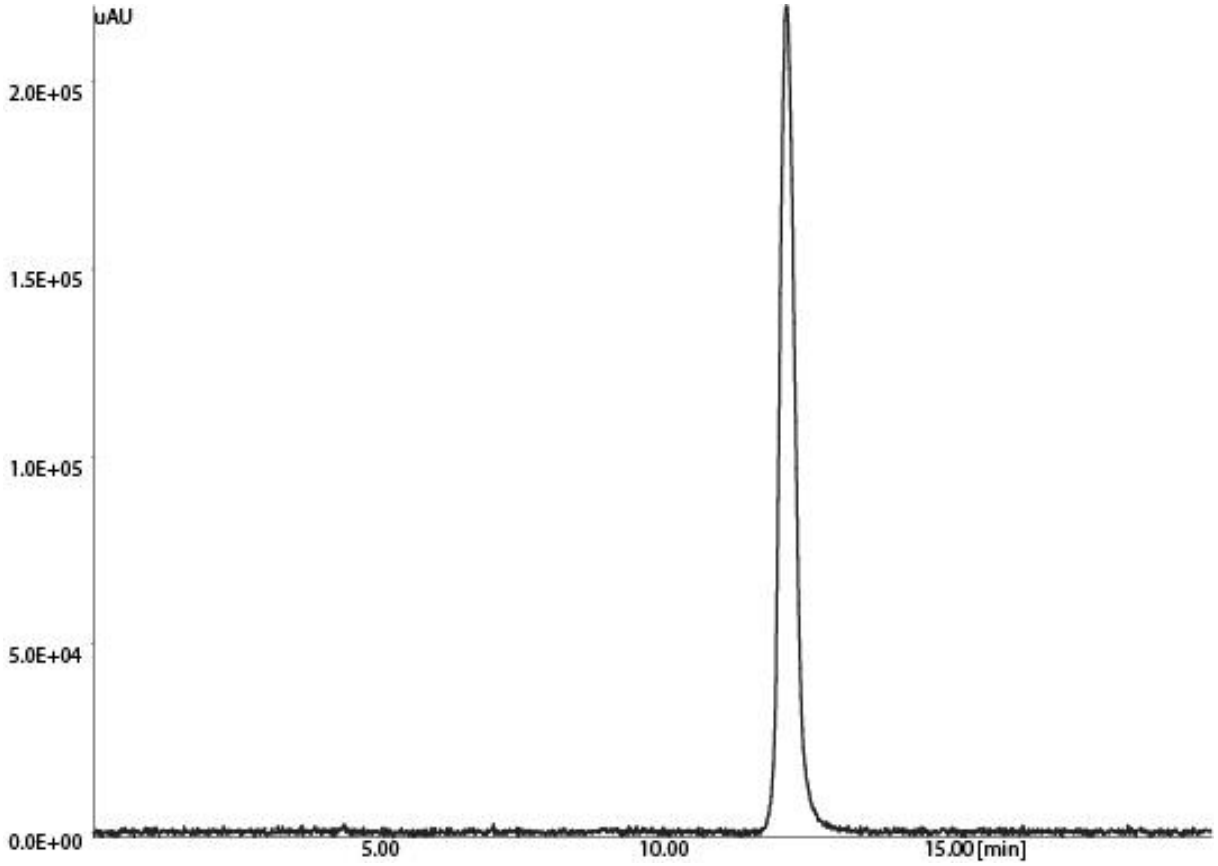


2.2 (+)-(11*R*,12*S*)-Mefloquine-(*R*)-Mosher amide 4



A solution of *rac-erythro*-mefloquine *rac*-**2** (free base, 120 mg, 0.32 mmol, 1.00 equiv.) in CH_2Cl_2 (20.0 mL) was treated at room temperature with *i*-Pr_2NEt (276 µL, 1.59 mmol, 5.00 equiv.) and and (*S*)-MTPA-Cl (65 µL, 0.35 mmol, 1.1 equiv.). After two hours SiO_2 (1 g) was added and the solvent was removed under reduced pressure. Column chromatography on silica (CH_2Cl_2/n-hexane = 2:1) gave the titled compound **4** (76.2 mg, 0.13 mmol, 41%) together with (+)-mefloquine-(R)-Mosher amide **3** (71.3 mg, 0.12 mmol, 38%), both as colourless solids. The identification as derivatives of (+)- or (–)-mefloquine was done by TLC comparison with (**3**). No single crystals could be obtained from CH_2Cl_2 and other solvents.

R_f = 0.42 (DCM); **$[\alpha]_D^{24}$** = +50.6° (c = 0.2, $CHCl_3$); **UV** (CH_3CN): λ_{max} (lg ε) = 207 nm (4.628), 219 (4.641), 290 (3.831), 316 (3.490); **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 1621.8, 1432.9, 1370.2, 1308.5, 1263.1, 1139.7, 1106.9, 1077.0, 1002.8, 983.5, 878.4, 836.0, 766.6, 733.8, 716.4, 699.1; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.08–1.18 (m, 1 H), 1.24–1.39 (m, 1 H), 1.50–1.81 (m, 4 H), 2.13 (d, *J* = 3.2 Hz, 1 H), 2.92 (ddd, *J* = 13.7, 12.0, 5.6 Hz, 1 H), 3.78 (d, *J* = 1.6 Hz, 3 H), 3.85 (ddt, *J* = 19.6, 5.85, 2.0 Hz, 1 H), 4.69 (dt, *J* = 6.9, 3.2 Hz, 1 H), 6.29 (t, *J* = 2.7 Hz, 1 H), 7.40–7.44 (m, 3 H), 7.53–7.57 (m, 2 H), 7.92 (t, *J* = 8.03 Hz, 1 H), 8.10 (s, 1 H), 8.23 (d, *J* = 7.3 Hz, 1 H), 9.01 (d, *J* = 8.6 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 19.14, 21.39, 23.92, 43.24, 55.53, 56.44, 71.61, 85.20 (q, *J* = 25.2 Hz), 115.09, 121.41 (q, *J* = 276.2 Hz), 123.74 (q, *J* = 272.9 Hz), 125.27, 126.35, 126.55, 128.18, 128.52, 128.64, 128.75, 129.35, 129.58, 134.35, 143.78, 148.25 (q, *J* = 35.0 Hz), 150.77, 166.57; **HRMS** (ESI): *m/z* calc. for $C_{27}H_{23}F_9N_2O_3$: 595.1638, found: 595.1639, $[M+H]^+$; **HPLC**: R_t = 12.15 min (conditions see 1.2).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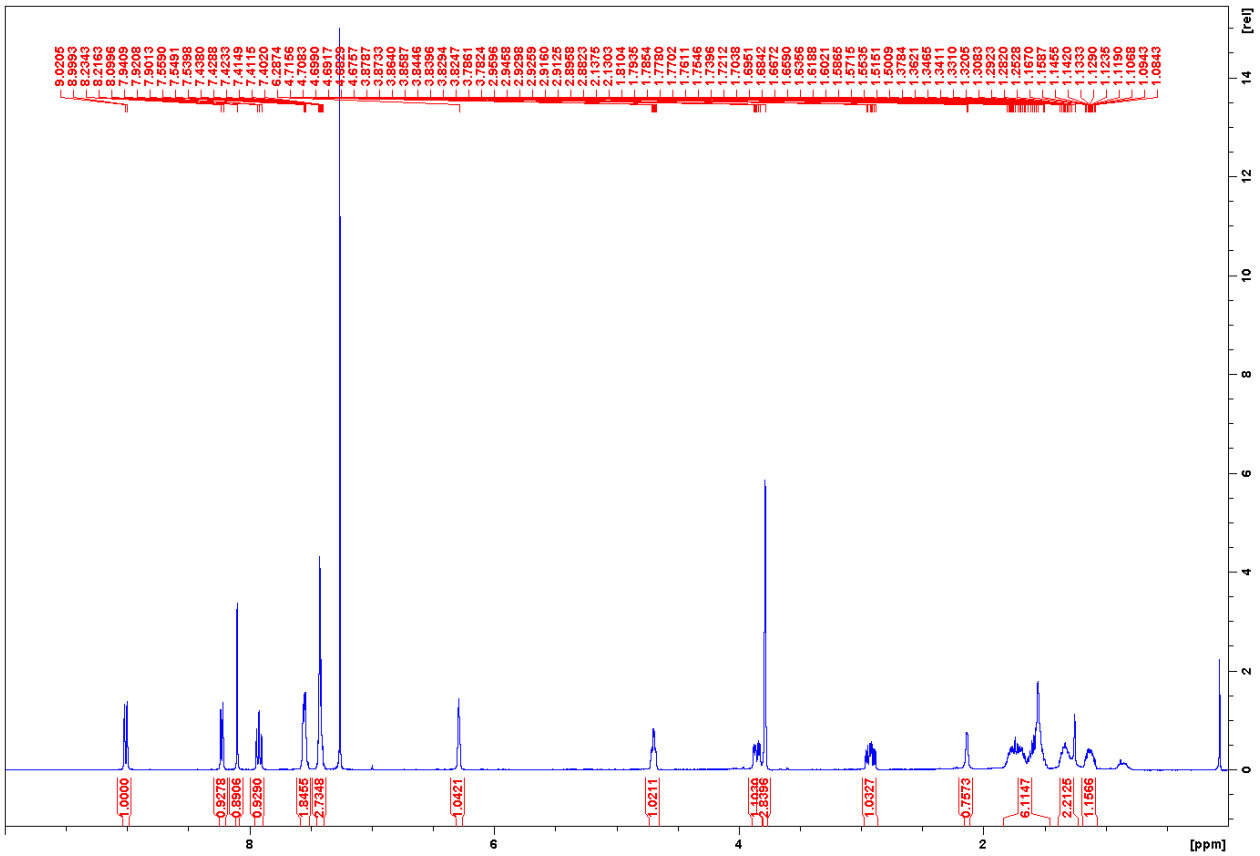
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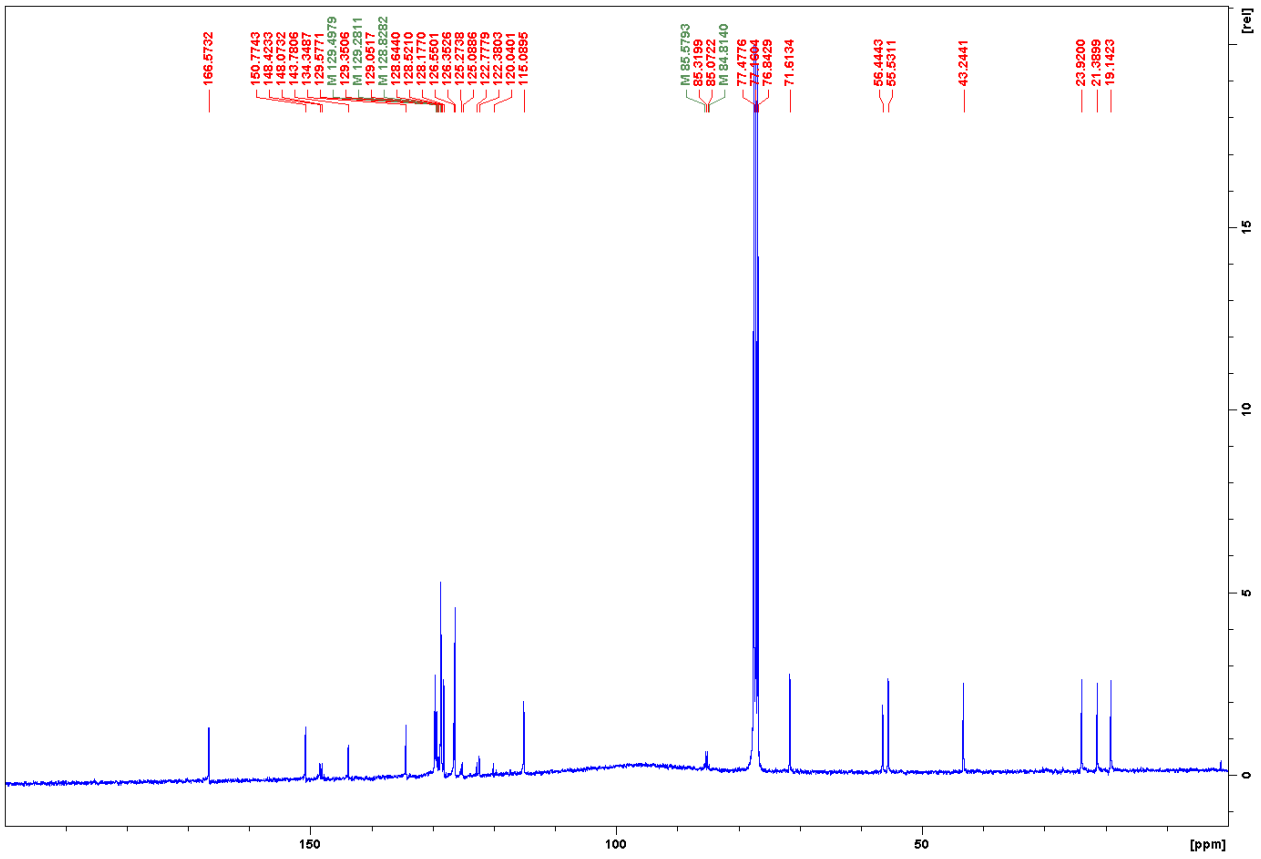
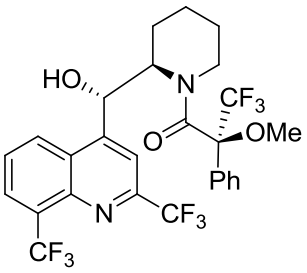
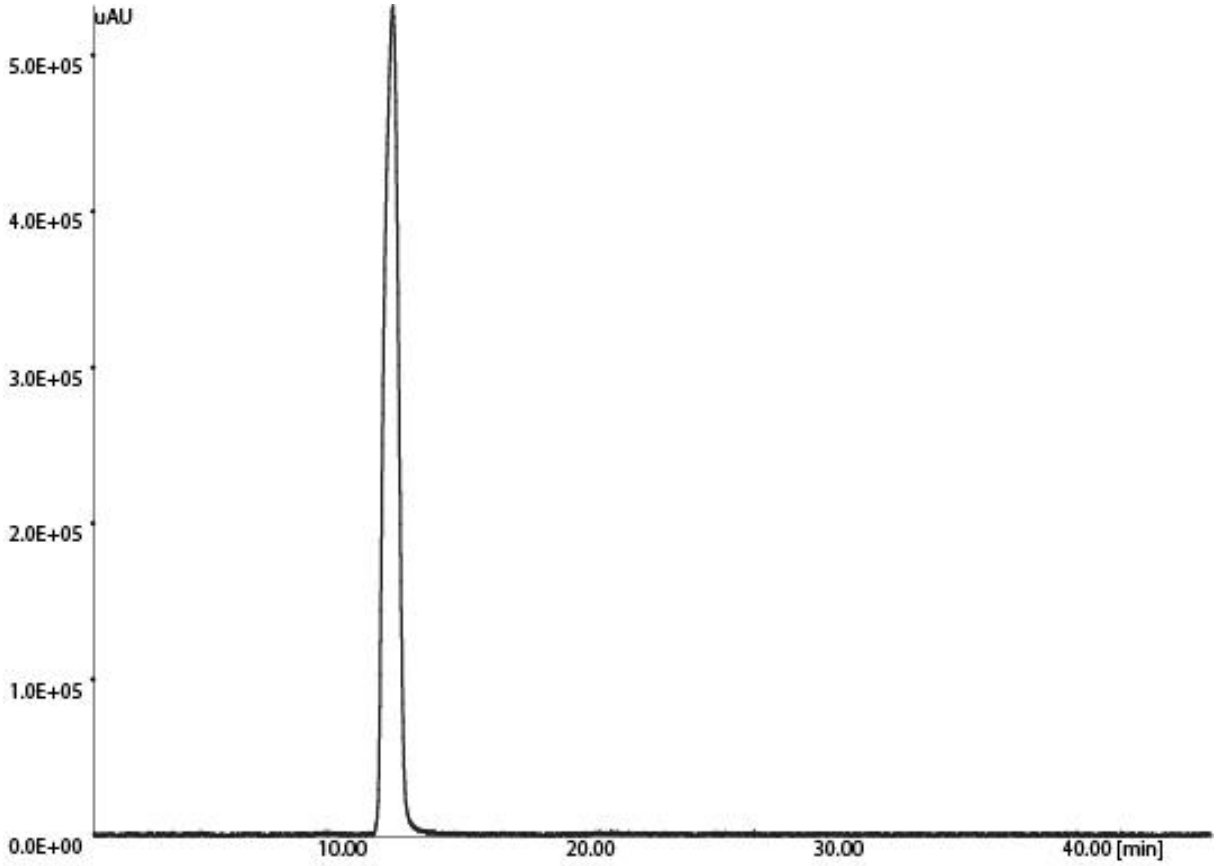


2.3 (–)-(11*S*,12*R*)-Mefloquine-(*S*)-Mosher amide *ent*-4



(+)-Mefloquine hydrochloride **1** (10.0 mg, 24.1 µmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (3.0 mL) and treated with *i*-Pr_2NEt (21 µL, 121 mmol, 5.00 equiv.) and (*R*)-MTPA-Cl (5.0 µL, 26.5 mmol, 1.10 equiv.) and stirred for 2 hours at room temperature. Then SiO_2 (100 mg) was added and the solvent was removed under reduced pressure. After column chromatography on silica (CH_2Cl_2) the titled compound *ent*-**4** (14.1 mg, 23.7 mg, 98%) was obtained as colourless solid. No single crystals could be obtained from CH_2Cl_2 or other solvents.

$[\alpha]_D^{24}$ = –45.2° (c = 0.2, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 1.02–1.16 (m, 1 H), 1.20–1.42 (m, 2 H), 1.45–1.84 (m, 5 H), 2.48 (s, 1 H), 2.90–2.98 (m, 1 H), 3.78 (s, 3 H), 3.84 (dd, *J* = 13.3, 4.1 Hz, 1 H), 4.60–4.67 (m, 1 H), 6.22 (s, 1 H), 7.36–7.46 (m, 3 H), 7.48–7.58 (m, 2 H), 7.86 (t, *J* = 7.7 Hz, 1 H), 8.08 (s, 1 H), 8.19 (d, *J* = 7.18 Hz, 1 H), 8.93 (d, *J* = 8.8 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 19.14, 21.42, 23.93, 43.29, 55.49, 56.42, 71.58, 85.20 (q, *J* = 25.3 Hz), 115.08, 121.41 (q, *J* = 276.6 Hz), 123.74 (q, *J* = 271.9 Hz), 125.28, 126.34, 126.53, 128.15, 128.47, 128.63, 128.99, 129.30, 129.57, 134.30, 143.74, 148.20 (q, *J* = 35.2 Hz), 150.87, 166.56; **HPLC**: R_t = 12.07 min (conditions see 1.2).
All other analytical data are identical to 2.2.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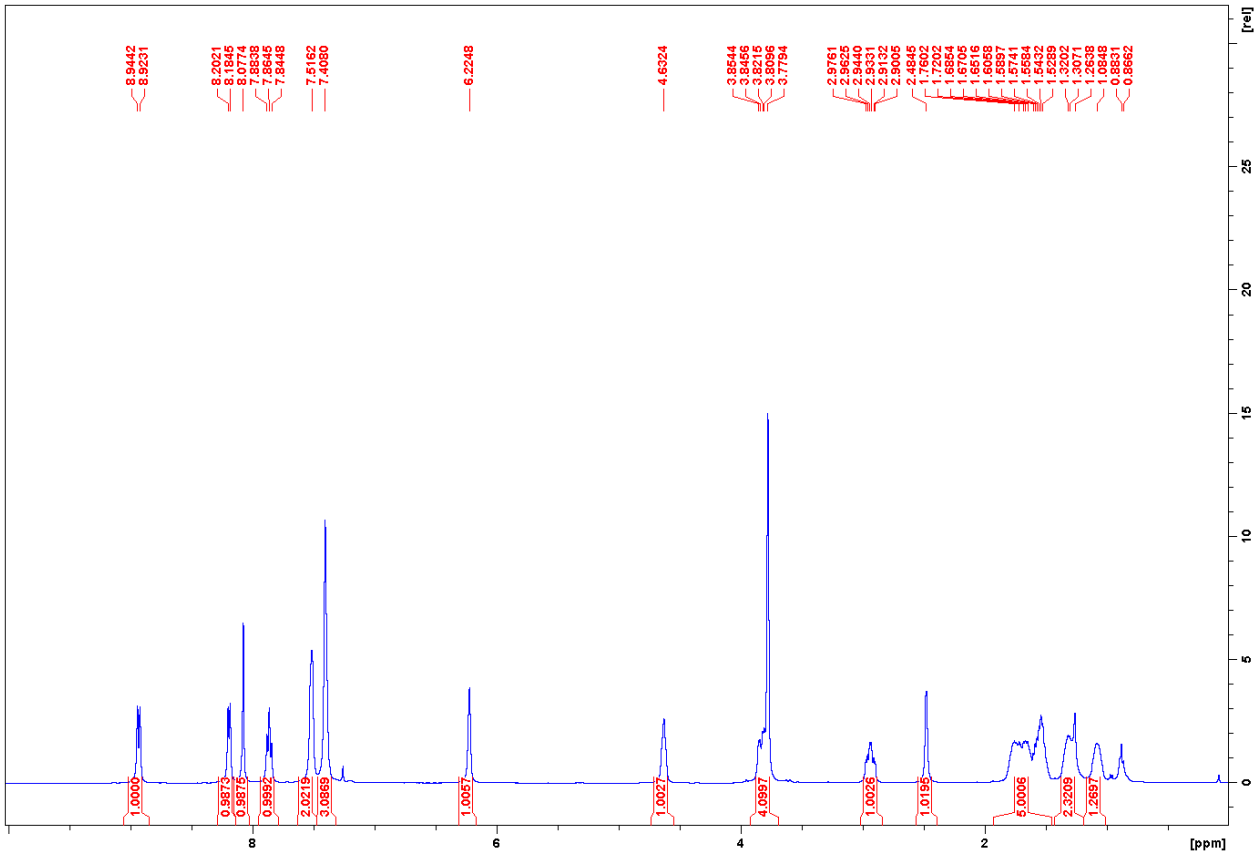
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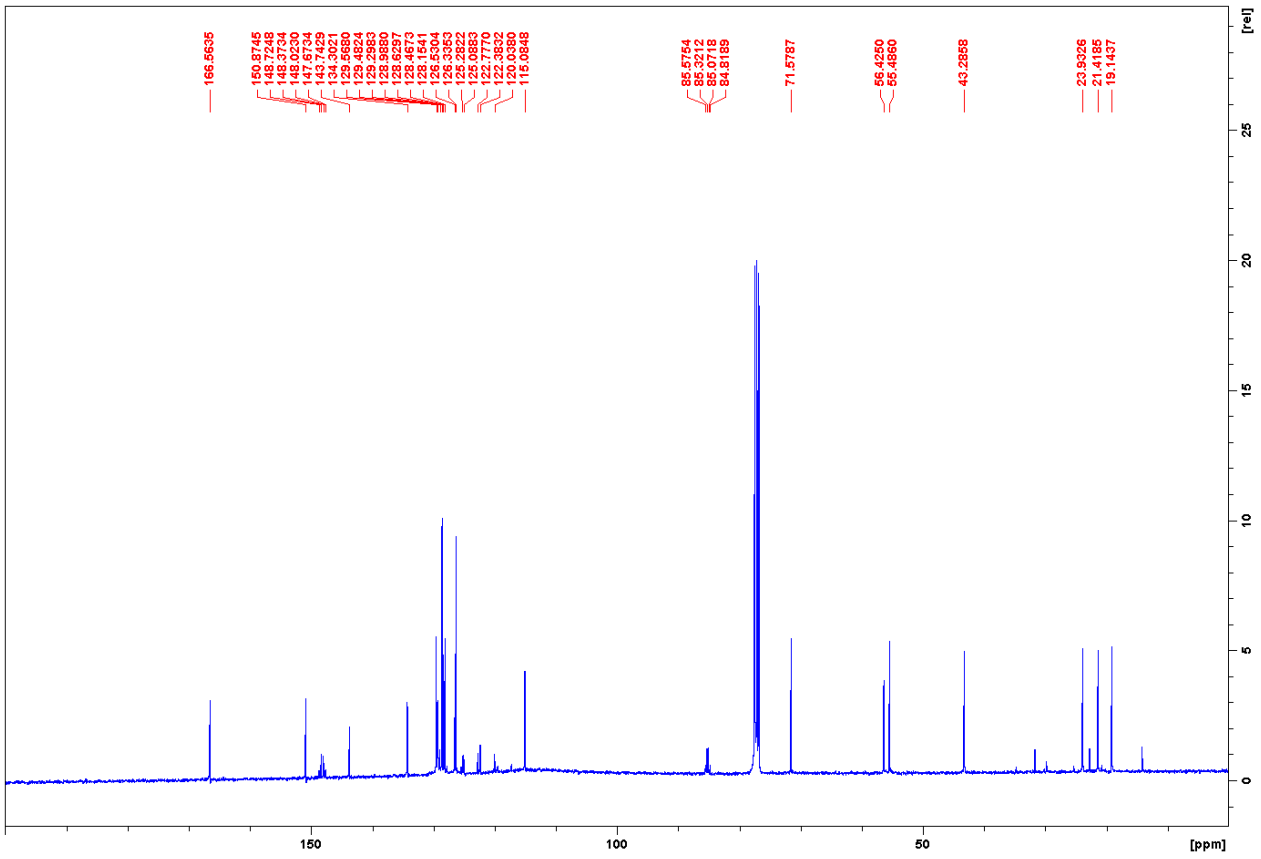
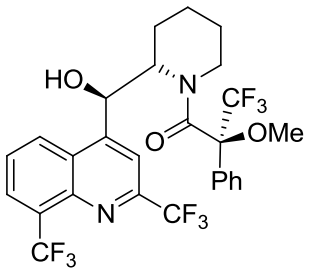
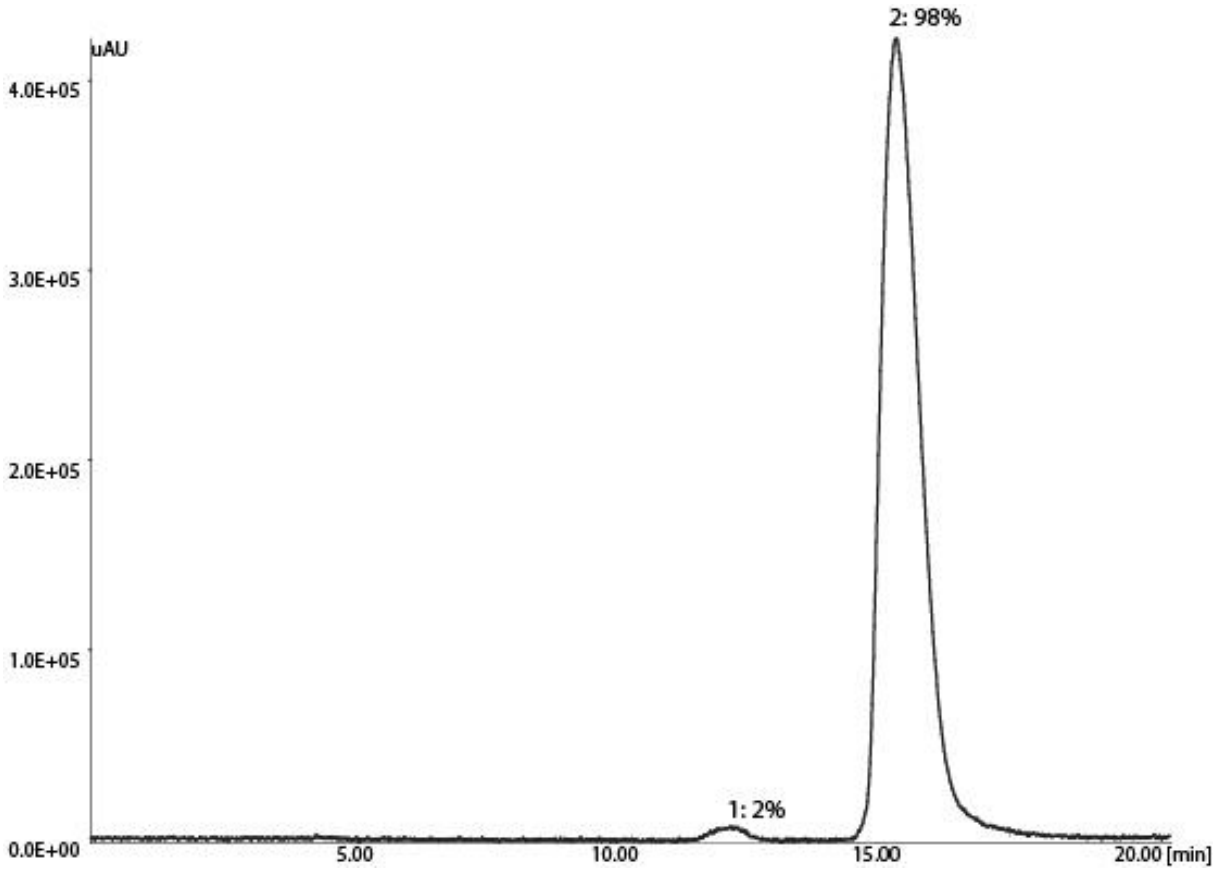


2.4 (–)-(11*R*,12*S*)-Mefloquine-(*S*)-Mosher amide *ent*-3



A solution of *rac*-erythro-mefloquine **2** (100 mg, 0.264 mmol, 1.00 equiv.) in CH_2Cl_2 (12.0 mL) was treated with *i*-Pr_2NEt (230 µL, 1.32 mmol, 5.00 equiv.) and (*R*)-MTPA-Cl (55 µL, 0.291 µmol, 1.10 equiv.) and stirred for 3 h at room temperature. SiO_2 (100 mg) was added and the solvent was removed under reduced pressure. Column chromatography on silica (CH_2Cl_2/cyclohexane = 2:1) gave the titled compound *ent*-**3** (73.6 mg, 0.124 mmol, 47%, d.r. = 98:2) and the diastereomer *ent*-**4** (67 mg, 0.113 mmol, 40%) as colourless solid each. Single crystals of *ent*-**3** could be obtained from CH_2Cl_2.

$[\alpha]_D^{24}$ = –111.9° (c = 0.15, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 0.13–0.27 (m, 1 H), 0.82–1.08 (m, 3 H), 1.43 (s, 3 H), 1.47–1.58 (m, 1 H), 1.67–1.79 (m, 1 H), 2.62 (s, 1 H), 3.39 (ddd, 14.8, 12.8, 5.4 Hz, 1 H), 3.67 (s, 3 H), 3.93 (dd, *J* = 14.4 Hz, 6.9 Hz, 1 H), 4.57–4.64 (m, 1 H), 6.03 (s, 1 H), 7.35–7.44 (m, 3 H), 7.50–7.57 (m, 2 H), 7.86 (t, *J* = 7.8 Hz, 1 H), 8.03 (s, 1 H), 8.20 (d, *J* = 6.9 Hz, 1 H), 8.83 (d, *J* = 8.5 Hz, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 18.19, 19.87, 21.12, 40.77, 55.35, 56.30, 70.94, 84.89 (q, *J* = 25.7 Hz), 114.90, 121.35 (q, *J* = 275.9 Hz), 122.52, 123.69 (q, *J* = 273.6 Hz) 125.40, 126.53, 126.72, 128.17, 128.40, 129.02 (q, *J* = 30.0 Hz), 129.34, 129.53, 134.19, 143.66, 148.16 (q, *J* = 35.4 Hz), 150.76, 166.46; **HPLC**: R_t = 15.36 min (conditions see 1.2).
All other analytical data were identical to 2.1.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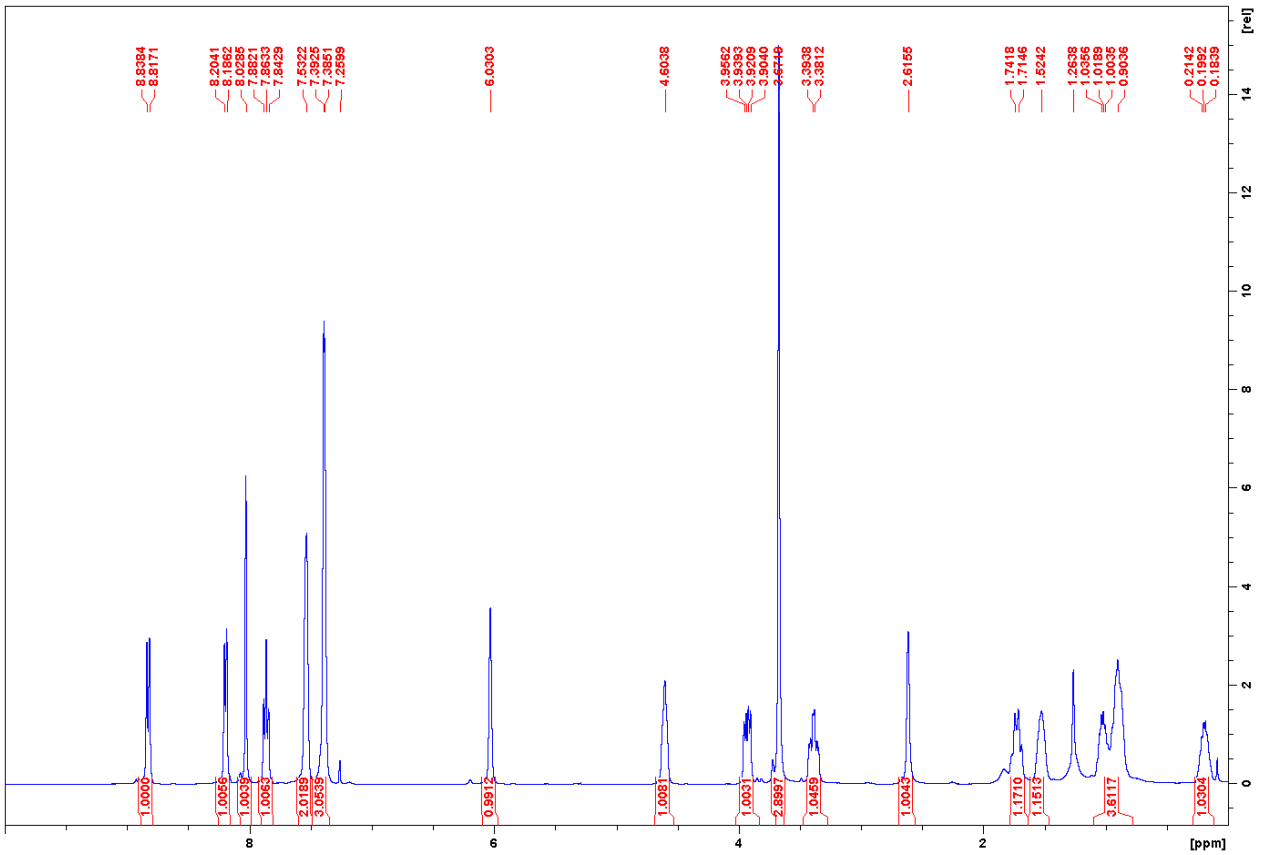
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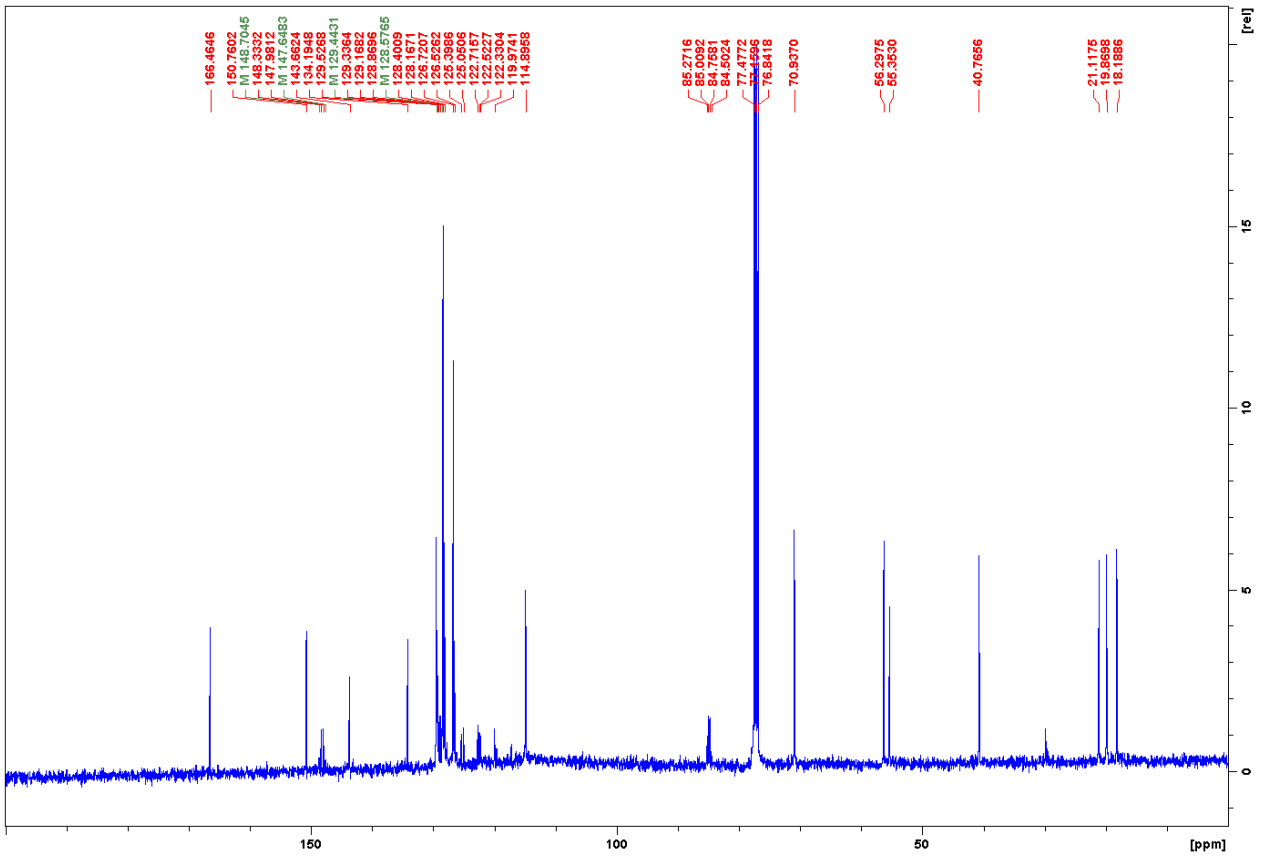
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