

Supplementary Materials

Total Synthesis of Floyocidin B: 4,5-regioselective functionalization of 2-chloropyridines

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1. Synthesis and compound characterization

General information:

All chemicals and solvents/anhydrous solvents were commercially supplied and used without further purification. For heating of reaction mixtures, aluminum flask carriers in different sizes from IKA were used. Reactions were monitored using thin layer chromatography (TLC) or using one of the following LCMS systems: 1100 HPLC (Agilent) with DAD and ELSD equipped with MSD (Agilent) ESI quadrupole MS, 1100 HPLC (Agilent) with DAD equipped with Amazon (Bruker) ESI trap MS, 1290 UPLC (Agilent) with DAD or ELSD equipped with micrOTOF (Bruker) ESI TOF MS or 1290 UPLC (Agilent) with DAD and ELSD equipped with maXis II (Bruker) ESI TOF MS. TLC was performed on pre-coated silica gel glass plates (Merck TLC Silica gel 60 F254) and compounds were detected under UV light (254 nm) and/or by staining with an aqueous solution of KMnO_4 with K_2CO_3 and NaOH or an aqueous solution of phosphomolybdic acid, cerium(IV) sulfate, and H_2SO_4 followed by heating with a heat gun. Products were purified by flash column chromatography using silica gel 60 M (Macherey-Nagel) or by using an automated flash column chromatography system (Biotage® SP4 with ISOLUTE® Flash SI II) equipped with ISOLUTE® Flash SI II columns of different sizes from Biotage, PF-15SIHC flash columns of different sizes from Interchim or Götec GX flash columns of different sizes from Götec-Labortechnik (eluants are given in parentheses). NMR spectra were recorded on a Bruker AVANCE II WB spectrometer (400 MHz), a AVANCE III HD spectrometer (400 MHz) or a AVANCE III HD spectrometer (600 MHz) with CDCl_3 , CD_3OD or DMSO-d_6 as solvent with chemical shifts (δ) quoted in parts per million (ppm) and referenced to the solvent signal ($\delta^1\text{H}/^{13}\text{C}$: CDCl_3 7.26/77.1, CD_3OD 3.31/49.0), $\delta^1\text{H}/^{13}\text{C}$: DMSO-d_6 2.50 / 39.5 or TMS ($\delta = 0$ ppm in CDCl_3). Assignment was confirmed based on COSY, HSQC, HMBC, ROESY, and NOESY correlations. High resolution mass spectrometry was performed on the maXis II (Bruker) ESI TOF MS. Specific rotation was measured by a polarimeter (P 3000 series) from Krüss.

4-Chloro-3-phenylfuro[3,4-c]pyridin-1(3H)-one (12):

The reaction was carried out in moisture-free glassware under inert atmosphere. To a solution of TMP (1.60 mL, 9.52 mmol, 3.00 eq.) in anhydrous THF (6 mL), *n*-BuLi (2.5 M in hexane, 5.00 mL, 12.7 mmol, 4.00 eq.) was added at -78 °C. The reaction mixture was warmed up to -30 °C and kept at this temperature for a few minutes before cooling -60 °C. A suspension of 2-chloroisonicotinic acid (**7**, 0.500 g, 3.17 mmol, 1.00 eq.) in anhydrous THF (9 mL) was added slowly at -60 °C and the reaction mixture was then stirred at -25 °C for 30 min. After this time, the mixture was cooled to -78 °C and benzaldehyde (2.00 mL, 20.6 mmol, 6.50 eq.) was added. The reaction mixture stirred at -78 °C for 2 h, was then diluted with 1 M aqueous HCl (10 mL) and acidified with further 1 M aqueous HCl (10 mL) to pH = 4 at room temperature. After extraction with ethyl acetate (90 mL and 60 mL), the combined organic layers were washed with saturated aqueous NaCl (60 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. For a complete lactone formation, the crude product was coevaporated twice with CH_2Cl_2 , dissolved in CH_2Cl_2 (15 mL) and kept on the rotary evaporator for 2 h at 200 mbar and 50 °C. Concentration under reduced pressure and purification *via* flash column chromatography (0–30% ethyl acetate in *n*-heptane) yielded **12** (0.491 g, 2.00 mmol, 63%) as yellow oil, which crystallized after a few days.

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): $\delta = 8.53$ (dd, 1H, $J = 4.9, 0.7$ Hz, N-CH), 7.66 (d, 1H, $J = 4.9$ Hz, N-CH=CH), 7.30–7.21 (m, 3H, Ar-H), 7.10–7.05 (m, 2H, Ar-H), 6.32 (s, 1H, O-CH); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): $\delta = 167.4$ (C=O), 151.1 (N-CH), 147.3 (CO-C_q), 141.8 (Cl-C_q), 137.0 (Cl-C_q), 132.8 (Ar-C_q), 130.2 (Ar-CH), 129.1 (Ar-CH), 118.1 (N-CH-CH), 82.6 (O-CH); **HRMS (ESI)** m/z calcd. for $\text{C}_{13}\text{H}_9\text{ClNO}_2$: 246.0316 (M+H)⁺; found: 246.0318 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 2:1): 0.46.

(E)-2-(Pent-1-en-1-yl)isonicotinic acid (14):

To a solution of **13** (1.50 g, 8.74 mmol, 1.00 eq.) in 1,4-dioxane/ H_2O (8:1; 40 mL/5.0 mL), *trans*-1-penten-1-ylboronic acid pinacol ester (1.99 g, 17.5 mmol, 2.00 eq.) and Cs_2CO_3 (8.54 g, 26.2 mmol, 3.00 eq.) were added. The solution was degassed with argon for 15 min and APhos Pd G3 (0.278 g, 0.44 mmol, 0.05 eq.) as well as APhos (0.116 g, 0.44 mmol, 0.05 eq.) were added. The reaction solution was stirred overnight at 100 °C. After cooling to room temperature, saturated

aqueous NH₄Cl (70 mL) was added. The mixture was extracted with ethyl acetate (1 x 200 mL and 2 x 100 mL) and the combined organic layers were washed with saturated aqueous NaCl (120 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0–30% ethyl acetate in *n*-heptane) to give the methyl ester of **14** (1.60 g, 7.78 mmol, 89%) as yellow oil. The methyl ester (1.60 g, 7.78 mmol, 1.00 eq.) was dissolved in THF/H₂O 10:1 (50 mL/5.0 mL). LiOH · H₂O (1.42 g, 33.9 mmol, 5.00 eq.) was added and the reaction solution stirred 3 h at room temperature and 2 h at 40 °C, until LC-MS indicated complete conversion. The reaction mixture was acidified with 1 M aqueous HCl (38 mL) to pH = 4 and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (60 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure to yield **14** (1.46 g, 7.63 mmol, 98% from methyl ester, 87% over two steps) as colorless solid, which was used in the next stage without further purification.

¹H-NMR (DMSO-*d*₆, 400 MHz): δ = 13.62 (s, br, 1H, COOH), 8.66 (d, 1H, *J* = 4.9 Hz, N-CH), 7.77 (t, 1H, *J* = 1.4 Hz, pentenyl-C_q-CH), 7.60 (dd, 1H, *J* = 4.9, 1.4 Hz, N-CH=CH), 6.84 (dt, 1H, *J* = 15.6, 7.1 Hz, CH₂-CH=CH), 6.59 (dt, 1H, *J* = 15.7, 1.3 Hz, CH₂-CH=CH), 2.22 (m, 2H, CH₂-CH=CH), 1.49 (m, 2H, CH₃-CH₂), 0.93 (t, 3H, *J* = 7.4 Hz, CH₃-CH₂); **¹³C-NMR** (DMSO-*d*₆, 100 MHz): δ = 166.2 (COOH), 156.3 (N-CH), 150.2 (N-C_q), 138.7 (C_q-COOH), 136.3 (CH₂-CH=CH), 129.3 (CH₂-CH=CH), 120.6 (pyridine-CH), 119.8 (pyridine-CH), 34.1 (CH₂-CH=CH), 21.6 (CH₃-CH₂), 13.6 (CH₃-CH₂); **¹H-NMR** (CD₃OD, 400 MHz): δ = 8.59 (dd, 1H, *J* = 4.8, 0.3 Hz, N-CH), 7.95 (t, 1H, *J* = 1.3 Hz, pentenyl-C_q-CH), 7.72 (dd, 1H, *J* = 4.8, 1.5 Hz, N-CH=CH), 6.82 (dt, 1H, *J* = 15.8, 7.0 Hz, CH₂-CH=CH), 6.58 (dt, 1H, *J* = 15.8, 1.4 Hz, CH₂-CH=CH), 2.29 (m, 2H, CH₂-CH=CH), 1.57 (m, 2H, CH₃-CH₂), 1.00 (t, 3H, *J* = 7.4 Hz, CH₃-CH₂); **¹³C-NMR** (CD₃OD, 100 MHz): δ = 167.8 (COOH), 158.3 (N-CH), 150.4 (N-C_q), 141.3 (C_q-COOH), 139.1 (CH₂-CH=CH), 130.0 (CH₂-CH=CH), 122.3 (N-CH-CH), 121.5 (pentenyl-C_q-CH), 36.0 (CH₂-CH=CH), 23.2 (CH₃-CH₂), 14.0 (CH₃-CH₂); **HRMS (ESI)** *m/z* calcd. for C₁₁H₁₄NO₂: 192.1019 (M+H)⁺; found: 192.1019 (M+H)⁺; **R_f** (ethyl acetate): 0.11.

(E)-6-(Pent-1-en-1-yl)-3-phenylfuro[3,4-c]pyridin-1(3H)-one (15):

Compound **15** (0.351 g, 1.26 mmol, 49%) was synthesized analogously to **12** starting from **14** (0.492 g, 2.57 mmol, 1.00 eq.) and was obtained as colorless solid after purification by flash column chromatography (0–100% ethyl acetate in *n*-heptane).

¹H-NMR (CDCl₃, 400 MHz): δ = 8.64 (s, 1H, N-CH), 7.74 (d, 1H, *J* = 0.8 Hz, CO-C_q-CH), 7.44–7.36 (m, 3H, Ar-H), 7.32–7.25 (m, 2H, Ar-H), 6.88 (dt, 1H, *J* = 15.6, 7.1 Hz, CH₂-CH=CH), 6.62 (dt, 1H, *J* = 15.7, 1.6 Hz, CH₂-CH=CH), 6.52 (s, 1H, O-CH), 2.29 (m, 2H, CH₂-CH=CH), 1.56 (m, 2H, CH₃-CH₂), 0.98 (t, 3H, *J* = 7.4 Hz, CH₃-CH₂); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 169.1 (C=O), 157.7 (N-C_q), 145.2 (N-CH), 140.8 (CO-C_q), 138.8 (CH₂-CH=CH), 135.5 (Ar-C_q), 134.4 (CO-C_q-C_q), 129.9 (Ar-CH), 129.3 (Ar-CH), 129.0 (CH₂-CH=CH), 127.1 (Ar-CH), 115.3 (N-C_q-CH), 82.4 (O-CH), 35.0 (CH₂-CH=CH), 22.2 (CH₃-CH₂), 13.9 (CH₃-CH₂); **HRMS (ESI)** *m/z* calcd. for C₁₈H₁₈NO₂: 280.1332 (M+H)⁺; found: 280.1330 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 2:1): 0.39.

1-(5-Bromo-2-chloropyridin-4-yl)-5-methylhex-4-en-1-one (24):

The reaction was carried out in moisture-free glassware under inert atmosphere. To a solution of LDA (2 M in THF/*n*-heptane/ethylbenzene, 7.00 mL, 14.0 mmol, 2.00 eq.) in anhydrous THF (32 mL) 5-bromo-2-chloropyridine (**9**, 2.69 g, 14.0 mmol, 2.00 eq.) was added in portions at –78 °C. After stirring for 1 h 10 min at –78 °C, Weinreb amide **21** (1.20 g, 6.98 mmol, 1.00 eq.) dissolved in anhydrous THF (8 mL) was added. The reaction mixture was stirred for 1 h 10 min at –78 °C and was then diluted with saturated aqueous NH₄Cl (30 mL). After extraction with ethyl acetate (2 x 100 mL), the combined organic layers were washed with saturated aqueous NaCl (75 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (0–30% ethyl acetate in *n*-heptane) yielded **24** (1.72 g, 5.68 mmol, 81%) as colorless oil.

¹H-NMR (CDCl₃, 400 MHz): δ = 8.55 (s, 1H, N-CH), 7.23 (s, 1H, Cl-CH), 5.09 (m, 1H, Me₂C=CH), 2.90 (t, 2H, *J* = 7.2 Hz, CO-CH₂), 2.39 (q, 2H, *J* = 7.2 Hz, Me₂C=CH-CH₂), 1.69 (s, 3H, E-CH₃), 1.61 (s, 3H, Z-CH₃); **¹³C-NMR** (CDCl₃, 100

MHz): δ = 201.1 (C=O), 152.7 (N-CH), 151.0 (CO-C_q), 151.0 (Cl-C_q), 134.0 (C_qMe₂), 122.7 (ClC-CH), 121.8 (CH=CMe₂), 114.6 (CBr), 42.7 (CO-CH), 25.8 (E-CH₃), 22.5 (CH₂-CH=CMe₂), 17.9 (Z-CH₃); **HRMS (ESI)** m/z calcd. for C₁₂H₁₄BrClNO: 301.9942 (M+H)⁺; found: 301.9942 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.60.

2-Allyl-1-(5-bromo-2-chloropyridin-4-yl)-5-methylhex-4-en-1-one (25):

Compound **25** was synthesized analogously to **24** starting from **9** (1.86 g, 9.65 mmol, 2.00 eq.) and Weinreb amide **22** (1.02 g, 4.83 mmol, 1.00 eq.). Purification *via* flash column chromatography (0–20% ethyl acetate in *n*-heptane) yielded **25** (1.27 g, 3.69 mmol, 76%) as colorless oil.

¹H-NMR (CDCl₃, 400 MHz): δ = 8.54 (d, 1H, *J* = 0.3 Hz, N-CH), 7.18 (d, 1H, *J* = 0.4 Hz, ClC-CH), 5.75 (ddt, 1H, *J* = 17.1, 10.1, 7.1 Hz, CH₂=CH), 5.14–4.99 (m, 3H, CH₂=CH and Me₂C=CH), 3.24 (quintett, 1H, *J* = 6.6 Hz, CO-CH), 2.60–2.19 (m, 2H, Me₂C=CH-CH₂), 2.60–2.19 (m, 2H, CH₂=CH-CH₂), 1.67 (s, 3H, E-CH₃), 1.58 (s, 3H, Z-CH₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 203.7 (C=O), 152.8 (N-CH), 160.0 (CO-C_q or Cl-C_q), 150.8 (Cl-C_q or CO-C_q), 135.1 (C_qMe₂), 134.9 (CH=CH₂), 123.2 (ClC-CH), 120.3 (CH=CMe₂), 118.0 (CH=CH₂), 115.2 (CBr), 50.9 (CO-CH), 34.6 (CH₂-CH=CMe₂), 29.2 (CH₂=CH-CH₂), 25.9 (E-CH₃), 18.0 (Z-CH₃); **HRMS (ESI)** m/z calcd. for C₁₅H₁₈BrClNO: 342.0255 (M+H)⁺; found: 342.0256 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.63.

tert-Butyl 3-(5-bromo-2-chloroisonicotinoyl)-6-methylhept-5-enoate (26):

Compound **26** was synthesized analogously to **24** starting from **9** (0.135 g, 0.702 mmol, 2.00 eq.) and Weinreb amide **23** (0.100 g, 0.350 mmol, 1.00 eq.). Purification *via* flash column chromatography (0–20% ethyl acetate in *n*-heptane) yielded **26** (0.080 g, 0.19 mmol, 55%) as colorless oil and recovered starting material **23** (0.032 g, 0.11 mmol, 32%).

¹H-NMR (CDCl₃, 400 MHz): δ = 8.56 (s, 1H, N-CH), 7.57 (s, 1H, ClC-CH), 4.99 (m, 1H, Me₂C=CH), 3.54 (m, 1H, CO-CH), 2.80 (dd, 1H, *J* = 17.2, 9.5 Hz, CH₂-CO₂*t*-Bu), 2.45 (dd, 1H, *J* = 17.2, 4.4 Hz, CH₂-CO₂*t*-Bu), 2.39–2.08 (m, 2H, Me₂C=CH-CH₂), 1.66 (s, 3H, E-CH₃), 1.56 (s, 3H, Z-CH₃), 1.43 (s, 9H, C(CH₃)₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 202.4 (CO-CH), 171.6 (CO₂*t*-Bu), 152.8 (N-CH), 151.0 (CO-C_q or ClC), 150.3 (ClC or CO-C_q), 135.8 (C_qMe₂), 123.7 (ClC-CH), 119.7 (CH=CMe₂), 115.6 (CBr), 81.4 (C(CH₃)₃), 47.4 (CH-CO), 35.7 (CH₂-CO₂*t*-Bu), 29.0 (Me₂C=CH-CH₂), 28.2 (C(CH₃)₃), 25.9 (E-CH₃), 18.0 (Z-CH₃); **HRMS (ESI)** m/z calcd. for C₁₈H₂₄BrClNO₃: 416.0623 (M+H)⁺; found: 416.0625 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 5:1): 0.53.

3-Chloro-6-(3-methylbut-2-en-1-yl)-8-methylene-7,8-dihydroisoquinolin-5(6*H*)-one (27) and 3-chloro-8-methyl-6-(3-methylbut-2-en-1-yl)isoquinolin-5-ol (28):

Under argon atmosphere, NEt₃ (0.081 mL, 0.58 mmol, 2.00 eq.) and Pd(PPh₃)₂Cl₂ (0.010 g, 0.014 mmol, 0.05 eq.) were added to a solution of **25** (0.100 g, 0.292 mmol, 1.00 eq.) in anhydrous MeCN (20 mL). The reaction mixture was refluxed for 24 h. After this time, LC-MS indicated only a low conversion. For structure elucidation of the formed products, the reaction was stopped prematurely by cooling down to room temperature. The reaction mixture was concentrated *in vacuo* and the residue loaded on silica. Purification *via* flash column chromatography (0–15% ethyl acetate in *n*-heptane) yielded **27** (0.003 g, 0.01 mmol, 4%) as colorless oil and **28** (0.003 g, 0.01 mmol, 4%) as colorless solid as well as recovered starting material **25** (0.056 g, 0.16 mmol, 56%). In a second experiment, complete conversion of **25** was achieved by using DMF instead of MeCN as solvent and by stirring at 120 °C for 16 h. Traces of **27** were detected by LC-MS and **28** (0.039 g, 0.15 mmol, 51%) was obtained as main product after purification *via* flash column chromatography.

For **27**: **¹H-NMR** (CDCl₃, 400 MHz): δ = 8.79 (d, 1H, *J* = 0.6 Hz, N-CH), 7.79 (d, 1H, *J* = 0.6 Hz, ClC-CH), 5.77 (s, 1H, C_q=CH₂), 5.39 (s, 1H, C_q=CH₂), 5.11 (m, 1H, Me₂C=CH), 2.89 (dd, 1H, *J* = 12.7, 3.5, CH₂-C_q=CH₂), 2.77–2.55 (m, 2H, CH₂-C_q=CH₂ and CO-CH), 2.55–2.19 (m, 2H, Me₂C=CH-CH₂), 1.73 (s, 3H, E-CH₃), 1.61 (s, 3H, Z-CH₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 197.9 (CO), 151.7 (ClC), 147.8 (N-CH), 138.2 (C_q-CO), 137.0 (CH₂=C_q), 134.9 (C_qMe₂), 132.9 (N-CH-C_q), 120.4 (ClC-CH), 120.4 (CH=CMe₂), 114.3 (CH₂=C_q), 48.5 (CO-CH), 36.7 (CH₂-C_q=CH₂), 28.2 (Me₂C=CH-CH₂), 26.0 (E-CH₃), 18.1 (Z-CH₃); **HRMS (ESI)** m/z calcd. for C₁₅H₁₇ClNO: 262.0993 (M+H)⁺; found: 262.0989 (M+H)⁺; **R_f** (*n*-

heptane/ethyl acetate 4:1): 0.50. For **28**: **¹H-NMR** (CDCl₃, 400 MHz): δ = 9.10 (d, 1H, *J* = 0.9 Hz, N-CH), 8.00 (d, 1H, *J* = 0.7 Hz, ClC-CH), 7.09 (s, 1H, Ar-H), 5.93 (s, br, 1H, OH), 5.36 (m, 1H, Me₂C=CH), 3.50 (d, 2H, *J* = 7.3 Hz, Me₂C=CH-CH₂), 2.65 (d, 3H, *J* = 0.8 Hz, Ar-CH₃), 1.85 (s, 3H, Z-CH₃), 1.82 (d, 3H, *J* = 1.2 Hz, E-CH₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 149.3 (N-CH), 146.8 (MeC_q), 145.3 (ClC), 137.1 (C_qMe₂), 130.6 (Ar-CH), 130.5 (C_q-OH), 127.2 (ClC-CH-C_q), 126.1 (N-CH-C_q), 125.1 (CH₂-C_q), 120.7 (CH=CMe₂), 114.7 (ClC-CH), 30.8 (Me₂C=CH-CH₂), 26.0 (E-CH₃), 18.2 (Z-CH₃), 17.8 (Ar-CH₃); **HRMS (ESI)** *m/z* calcd. for C₁₅H₁₇ClNO: 262.0993 (M+H)⁺; found: 262.0993 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.37.

tert-Butyl 3-((5-bromo-2-chloropyridin-4-yl)((triisopropylsilyl)oxy)methyl)-6-methylhept-5-enoate (29):

To a solution of **26** (0.944 g, 2.27 mmol, 1.00 eq.) in anhydrous THF (4 mL) LiBH₄ (0.049 g, 2.3 mmol, 2.00 eq.) was added at 0 °C. After stirring for 10 min at 0 °C, LC-MS indicated complete conversion of the starting material. Saturated aqueous NH₄Cl (30 mL) was added and the reaction mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (75 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (0–20% ethyl acetate in *n*-heptane) yielded secondary alcohols derived from **26** (0.560 g, 1.34 mmol, 59%, inseparable mixture of diastereomers) as colorless oil. To the resulting diastereomeric mixture (0.100 g, 0.239 mmol, 1.00 eq.) dissolved in anhydrous CH₂Cl₂ (5 mL), 2,6-lutidine (0.111 mL, 0.960 mmol, 4.00 eq.) followed by TIPSOTf (0.128 mL, 0.480 mmol, 2.00 eq.) were added at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After this time, the TLC showed remaining starting material. Therefore a second portion of 2,6-lutidine (4.00 eq.) and TIPS triflate (2.00 eq.) were added at 0 °C and the reaction mixture stirred for 5 h. To complete conversion a third portion of 2,6-lutidine (4.00 eq.) and TIPS triflate (2.00 eq.) were added at 0 °C. After stirring at room temperature for additional 1 h at room temperature, the TLC showed a complete conversion. Saturated aqueous NH₄Cl (10 mL) was added. The mixture was extracted with ethyl acetate (2 x 30 mL) and the combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was prepurified by flash column chromatography (0–10% ethyl acetate in *n*-heptane) to give **39** (0.081 g, 0.14 mmol, 59% from alcohol intermediate, 35% over two steps, inseparable mixture of diastereomers, *dr* > 3:1 (The relative stereochemistry of the two diastereomers in the mixture was not assigned.)) as a colorless oil.

¹H-NMR (CDCl₃, 400 MHz): Diastereomer 1: δ = 8.42 (s, 1H, N-CH), 7.50 (s, 1H, ClC-CH), 5.21 (d, 1H, *J* = 3.5 Hz, CH-OTIPS), 4.96 (m, 1H, Me₂C=CH), 2.44 (dd, 1H, *J* = 15.4, 6.9 Hz, CH₂-CO₂*t*-Bu), 2.39–1.92 (m, 3H, Me₂C=CH-CH₂ and CH-CH₂-CO₂*t*-Bu), 2.20 (dd, 1H, *J* = 15.4, 6.0 Hz, CH₂-CO₂*t*-Bu), 1.63 (s, 3H, E-CH₃), 1.53 (s, 3H, Z-CH₃), 1.43 (s, 9H, C(CH₃)₃), 1.09–0.97 (m, 21H, TIPS-H); Diastereomer 2: δ = 8.40 (s, 1H, N-CH), 7.47 (s, 1H, ClC-CH), 5.25–5.16 (m, 1H, Me₂C=CH), 5.18 (d, 1H, *J* = 2.3 Hz, CH-OTIPS), 2.39–1.92 (m, 5H, CH₂-CO₂*t*-Bu, Me₂C=CH-CH₂ and CH-CH₂-CO₂*t*-Bu), 1.70 (s, 3H, E-CH₃), 1.61 (s, 3H, Z-CH₃), 1.34 (s, 9H, C(CH₃)₃), 1.09–0.97 (m, 21H, TIPS-H); **¹³C-NMR** (CDCl₃, 100 MHz): Diastereomer 1: δ = 172.1 (CO₂*t*-Bu), 155.0 (BrC-C_q), 151.6 (N-CH), 150.3 (ClC), 133.8 (C_qMe₂), 125.1 (ClC-CH), 122.0 (CH=CMe₂), 118.8 (CBr), 80.5 (C(CH₃)₃), 75.0 (CH-OTIPS), 41.6 (CH-CH₂-CO₂*t*-Bu), 36.8 (CH₂-CO₂*t*-Bu), 28.3 (C(CH₃)₃), 26.9 (Me₂C=CH-CH₂), 26.0 (E-CH₃), 17.9 (Z-CH₃), 18.2 (CH(CH₃)₂), 12.8 (CH(CH₃)₂); Diastereomer 2: δ = 172.2 (CO₂*t*-Bu), 155.3 (BrC-C_q), 151.5 (N-CH), 150.5 (ClC), 134.4 (C_qMe₂), 124.4 (ClC-CH), 121.9 (CH=CMe₂), 118.8 (CBr), 80.5 (C(CH₃)₃), 74.6 (CH-OTIPS), 41.3 (CH-CH₂-CO₂*t*-Bu), 33.8 (CH₂-CO₂*t*-Bu), 30.7 (Me₂C=CH-CH₂), 28.1 (C(CH₃)₃), 26.0 (E-CH₃), 18.2 (Z-CH₃), 17.9 (CH(CH₃)₂), 12.9 (CH(CH₃)₂); **HRMS (ESI)** *m/z* calcd. for C₂₇H₄₆BrClNO₃Si: 574.2113 (M+H)⁺; found: 574.2113 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 10:1): 0.63.

(5R,6S)-3-Chloro-6-(3-methylbut-2-en-1-yl)-5-((triisopropylsilyl)oxy)-6,7-dihydroisoquinolin-8(5H)-one (31) and tert-butyl 3-((2-chloropyridin-4-yl)((triisopropylsilyl)oxy)methyl)-6-methylhept-5-enoate (30):

The halogen-lithium exchange was carried out in a moisture-free glassware under argon atmosphere. To a solution of ester **29** (0.069 g, 0.12 mmol, 1.00 eq.) in anhydrous THF (5 mL) prediluted *n*-BuLi solution (0.12 mmol, 1.00 eq.) was added at –100 °C (A 2.5 M solution of *n*-BuLi in hexane from a commercial supplier was diluted by a factor of four at –78 °C with anhydrous THF for a better handling. For the –100 °C cooling bath a mixture of ethanol and liquid N₂ was used.). The obtained yellow solution was stirred at –100 °C for 25 min and was then diluted with saturated aqueous NH₄Cl (10

mL). The mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0–20% ethyl acetate in *n*-heptane) to give desired product **31** (0.011 g, 0.026 mmol, 22%) (Compound **31** was obtained as a single diastereomer and the relative stereochemistry was assigned by NOE experiment) as well as uncyclized **30** (0.031 g, 0.062 mmol, 52%, *dr* = 2:1) as colorless oils.

For **31**: ¹H-NMR (CDCl₃, 400 MHz): δ = 8.95 (s, 1H, N-CH), 7.30 (s, 1H, ClC-CH), 5.05 (m, 1H, Me₂C=CH), 4.76 (d, 1H, *J* = 3.5 Hz, CH-OTIPS), 3.21 (dd, 1H, *J* = 17.4, 4.9 Hz, Me₂C=CH-CH₂), 2.52–2.38 (m, 1H, Me₂C=CH-CH₂), 2.49–2.38 (m, 1H, CH-CHOTIPS), 1.88 (t, 2H, *J* = 7.4 Hz, CO-CH₂), 1.68 (s, 3H, E-CH₃), 1.39 (s, 3H, Z-CH₃), 1.09–0.98 (m, 21H, TIPS-H); ¹³C-NMR (CDCl₃, 100 MHz): δ = 196.3 (C=O), 156.0 (ClC), 153.2 (N-CH-C_q), 149.7 (N-CH), 134.9 (C_qMe₂), 125.3 (ClC-CH-C_q), 124.1 (ClC-CH), 120.7 (CH=CMe₂), 70.8 (CH-OTIPS), 42.4 (CH-CHOTIPS), 38.8 (Me₂C=CH-CH₂), 30.2 (CO-CH₂), 25.8 (E-CH₃), 17.9 (Z-CH₃), 18.2/18.1 (CH(CH₃)₂), 12.7 (CH(CH₃)₂); HRMS (ESI) *m/z* calcd. for C₂₃H₃₇ClNO₂Si: 422.2277 (M+H)⁺; found: 422.2277 (M+H)⁺; R_f (*n*-heptane/ethyl acetate 4:1): 0.38. For **30**: ¹H-NMR (CDCl₃, 400 MHz): Diastereomer 1: δ = 8.31 (d, 1H, *J* = 5.4 Hz, N-CH), 7.25 (m, 1H, ClC-CH), 7.17 (dd, 1H, *J* = 5.2, 1.2 Hz, N-CH-CH), 5.09 (m, 1H, Me₂C=CH), 4.97 (d, 1H, *J* = 3.8 Hz, CH-OTIPS), 2.60 (dd, 1H, *J* = 15.8, 5.4 Hz, CH₂-CO₂*t*-Bu), 2.40–2.19 (m, 1H, CH-CH₂-CO₂*t*-Bu), 2.07–1.97 (m, 1H, Me₂C=CH-CH₂), 1.81–1.65 (m, 2H, CH₂-CO₂*t*-Bu and Me₂C=CH-CH₂), 1.70 (s, 3H, E-CH₃), 1.57 (s, 3H, Z-CH₃), 1.43 (s, 9H, C(CH₃)₃), 1.10–0.96 (m, 21H, TIPS-H); Diastereomer 2: δ = 8.32 (d, 1H, *J* = 5.4 Hz, N-CH), 7.31 (m, 1H, ClC-CH), 7.21 (dd, 1H, *J* = 5.4, 1.1 Hz, N-CH-CH), 5.03 (m, 1H, Me₂C=CH), 4.92 (d, 1H, *J* = 4.0 Hz, CH-OTIPS), 2.40–2.19 (m, 3H, CH-CH₂-CO₂*t*-Bu, CH₂-CO₂*t*-Bu and Me₂C=CH-CH₂), 1.97–1.84 (m, 1H, CH₂-CO₂*t*-Bu), 1.55–1.48 (m, 1H, Me₂C=CH-CH₂), 1.67 (s, 3H, E-CH₃), 1.50 (s, 3H, Z-CH₃), 1.46 (s, 9H, C(CH₃)₃), 1.10–0.96 (m, 21H, TIPS-H); ¹³C-NMR (CDCl₃, 100 MHz): Diastereomer 1: δ = 172.5 (CO₂*t*-Bu), 155.5 (C_q-OTIPS), 151.5 (ClC), 149.2 (N-CH), 134.2 (C_qMe₂), 122.5 (ClC-CH), 121.9 (CH=CMe₂), 120.9 (N-CH-CH), 80.6 (C(CH₃)₃), 73.9 (CH-OTIPS), 44.0 (CH-CH₂-CO₂*t*-Bu), 35.2 (CH₂-CO₂*t*-Bu), 28.2 (C(CH₃)₃), 28.0 (Me₂C=CH-CH₂), 25.9 (E-CH₃), 18.1 (Z-CH₃), 18.1 (CH(CH₃)₂), 12.5 (CH(CH₃)₂); Diastereomer 2: δ = 172.3 (CO₂*t*-Bu), 155.2 (C_q-OTIPS), 151.5 (ClC), 149.2 (N-CH), 134.1 (C_qMe₂), 122.9 (ClC-CH), 121.8 (CH=CMe₂), 121.3 (N-CH-CH), 80.8 (C(CH₃)₃), 74.5 (CH-OTIPS), 43.9 (CH-CH₂-CO₂*t*-Bu), 36.0 (CH₂-CO₂*t*-Bu), 28.0 (C(CH₃)₃), 27.1 (Me₂C=CH-CH₂), 26.0 (E-CH₃), 18.1 (CH(CH₃)₂), 18.0 (Z-CH₃), 12.4 (CH(CH₃)₂); HRMS (ESI) *m/z* calcd. for C₂₇H₄₇ClNO₃Si: 496.3014 (M+H)⁺; found: 496.3008 (M+H)⁺; R_f (*n*-heptane/ethyl acetate 4:1): 0.53.

4,5-Dibromo-2-chloropyridine (10):

Sandmeyer reaction under water-free conditions: To a suspension of copper(II) bromide (6.46 g, 28.9 mmol, 1.20 eq.) in MeCN (70 mL), *t*-BuONO (90%, 4.80 mL, 36.2 mmol, 1.50 eq.) was added slowly. The suspension was stirred at room temperature for 15 min and was then cooled to 0 °C. Amine **35** (5.00 g, 24.1 mmol, 1.00 eq.), dissolved in MeCN (50 mL) by gentle warming, was added at 0 °C. After stirring at 0 °C for 1 h, the mixture was allowed to warm to room temperature and stirred overnight. After concentration *in vacuo* (Due to beginning sublimation of the product at low pressure, careful concentration *in vacuo* (≥ 200 mbar) is necessary), aqueous ammonia solution (50 mL) was added. The mixture was extracted with CH₂Cl₂ (3 x 100 mL) and the combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure.⁴ The crude product was purified by flash column chromatography (petroleum ether/CH₂Cl₂ 2:1; 100% CH₂Cl₂) to give product **10** (6.32 g, 23.3 mmol, 97%) as colorless solid. For Sandmeyer reaction in aqueous medium see chapter 1.3.

¹H-NMR (CDCl₃, 400 MHz): δ = 8.51 (s, 1H, N-CH), 7.64 (s, 1H, ClC-CH); ¹³C-NMR (CDCl₃, 100 MHz): δ = 151.7 (N-CH), 150.5 (C-Cl), 136.8 (ClC-CH=CBr), 128.8 (ClC-CH), 122.6 (N-CH=CBr); HRMS (ESI) *m/z* calcd. for C₅H₃Br₂ClN: 269.8315 (M+H)⁺; found: 269.8320 (M+H)⁺; R_f (*n*-heptane/ethyl acetate 4:1): 0.73, (PE/CH₂Cl₂ 2:1): 0.39.

(4-Bromopyridin-3-yl)(phenyl)methanol (34) and (3-bromopyridin-4-yl)(phenyl)methanol (33):

The reaction was carried out in a moisture-free glassware under argon atmosphere. To a solution of **32** (0.300 g, 1.27 mmol, 1.00 eq.) in anhydrous THF (5 mL) *i*-PrMgCl (2.0 M in THF, 0.63 mL, 1.27 mmol, 1.00 eq.) was added dropwise. After stirring at room temperature for 1 h, benzaldehyde (0.129 mL, 1.27 mmol, 1.00 eq.) was added. The reaction mixture was stirred at room temperature overnight and was then diluted with saturated aqueous NH₄Cl (15 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0–70% ethyl acetate in *n*-heptane) to give addition products **34** (0.147 g, 0.557 mmol, 44%) and **33** (0.094 g, 0.36 mmol, 28%) as colorless solids.

For **34**: **¹H-NMR** (DMSO-*d*₆, 400 MHz): δ = 8.74 (s, 1H, N-CH-C_q), 8.31 (d, 1H, *J* = 5.4 Hz, N-CH-CH), 7.65 (d, 1H, *J* = 5.2 Hz, N-CH-CH), 7.39–7.30 (m, 4H, phenyl-*H*), 7.28–7.23 (m, 1H, phenyl-*H*), 6.30 (d, 1H, *J* = 4.4 Hz, OH), 5.97 (d, 1H, *J* = 4.4 Hz, CH-OH); **¹³C-NMR** (DMSO-*d*₆, 100 MHz): δ = 149.6 (N-CH-C_q), 149.1 (N-CH-CH), 142.8 (phenyl-C_q), 139.5 (N-CH-C_q), 132.0 (BrC_q), 128.3 (phenyl-CH), 127.5 (N-CH-CH), 127.4 (phenyl-CH), 126.8 (phenyl-CH), 71.8 (CH-OH); **HRMS (ESI)** *m/z* calcd. for C₁₂H₁₁BrNO: 264.0019 (M+H)⁺; found: 264.0023 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 1:1): 0.26. For **33**: **¹H-NMR** (CDCl₃, 400 MHz): δ = 8.53 (s, 1H, N-CH-C_q), 8.46 (d, 1H, *J* = 5.1 Hz, N-CH-CH), 7.68 (d, 1H, *J* = 5.0 Hz, N-CH-CH), 7.41–7.27 (m, 5H, phenyl-*H*), 6.05 (s, 1H, CH-OH), 3.20 (s, br, 1H, OH); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 141.7 (N-CH-C_q), 151.7 (BrC-C_q), 148.4 (N-CH-CH), 140.8 (phenyl-C_q), 128.9 (phenyl-CH), 128.5 (phenyl-CH), 127.5 (phenyl-CH), 122.9 (N-CH-CH), 120.9 (BrC_q), 74.1 (CH-OH); **HRMS (ESI)** *m/z* calcd. for C₁₂H₁₁BrNO: 264.0019 (M+H)⁺; found: 264.0018 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 1:1): 0.37.

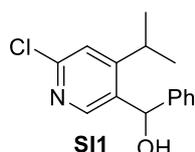
(4-Bromo-6-chloropyridin-3-yl)(phenyl)methanol (37) and (5-bromo-2-chloropyridin-4-yl)(phenyl)methanol (36):

Condition 1: General procedure for functionalization by halogen-magnesium exchange: The reaction was carried out in a moisture-free glassware under argon atmosphere. To a solution of **10** (0.080 g, 0.30 mmol, 1.00 eq.) in anhydrous THF (2 mL) *i*-PrMgCl (2.0 M in THF, 0.15 mL, 0.30 mmol, 1.00 eq.) was added dropwise. After stirring at room temperature for 1 h, benzaldehyde (0.030 mL, 0.30 mmol, 1.00 eq.) was added. The reaction mixture was stirred at room temperature overnight and was then diluted with saturated aqueous NH₄Cl (15 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0–20% ethyl acetate in *n*-heptane) to give addition product **37** (0.016 g, 0.054 mmol, 18%) as colorless oil and **36** (0.033 g, 0.11 mmol, 38%) as colorless solid. Model studies on the regioselectivity of the halogen-magnesium exchange were performed analogously by variation of reaction temperature and reaction time starting from **10** or **39**. In one reaction (scheme 5, condition g), *i*-PrMgCl (2.0 M in THF) was replaced by *i*-PrMgCl · LiCl (1.3 M in THF). LC-MS analysis of a test reaction at room temperature (scheme 5, condition c) uncovered the formation of a side product. To investigate this side product, the reaction was repeated with two equivalents of *i*-PrMgCl (2.0 M in THF) and longer reaction time (the reaction mixture was stirred for 2 h before addition of benzaldehyde). After purification *via* flash column chromatography isopropyl-substituted product **SI1** (0.017 g, 0.065 mmol, 14%) was isolated as a single regioisomer and its regiochemistry was unambiguously elucidated by NMR analyses (Main products remained **37** and **36** in a ratio of 1:1.77, which ratio was determined by LC-MS from the crude. **37** and **36** were not isolated). **SI1** was obtained as colorless oil. A hypothesized mechanism of the formation of side product **SI1** is shown in chapter 1.4 (Scheme S3).

Condition 2: Synthesis of 36 as reference sample by ortho-lithiation: The reaction was carried out in moisture-free glassware under inert atmosphere. To a solution of LDA (2 M in THF/*n*-heptane/ethylbenzene, 1.40 mL, 2.83 mmol, 2.00 eq.) in anhydrous THF (5 mL) 5-bromo-2-chloropyridine (**9**, 0.544 g, 2.83 mmol, 2.00 eq.) was added in portions at –78 °C. After stirring at –78 °C for 1 h 10 min, benzaldehyde (0.144 mL, 1.41 mmol, 1.00 eq.) was added. The reaction mixture was stirred at –78 °C for 1 h and was then diluted with saturated aqueous NH₄Cl (20 mL). After extraction with ethyl acetate (2 x 30 mL), the combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (0–20% ethyl acetate in *n*-heptane) yielded **36** (0.205 g, 0.688 mmol, 49%) as single product.

For **37**: **¹H-NMR** (CDCl₃, 400 MHz): δ = 8.61 (s, 1H, N-CH), 7.52 (s, 1H, ClC-CH), 7.40–7.29 (m, 5H, phenyl-H), 6.10 (s, 1H, CH-OH), 2.39 (s, br, 1H, OH); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 150.9 (ClC), 149.3 (N-CH), 140.9 (phenyl-C_q), 137.5 (BrC-C_q), 134.5 (BrC), 129.0 (phenyl-CH), 128.6 (phenyl-CH), 127.7 (ClC-CH), 127.3 (phenyl-CH), 73.5 (CH-OH); **HRMS (ESI)** m/z calcd. for C₁₂H₁₀BrClNO: 297.9629 (M+H)⁺; found: 297.9629 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.21. For **36**: **¹H-NMR** (CDCl₃, 400 MHz): δ = 8.37 (s, 1H, N-CH), 7.76 (s, 1H, ClC-CH), 7.38–7.33 (m, 5H, phenyl-H), 6.00 (s, 1H, CH-OH), 2.49 (s, br, 1H, OH); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 154.1 (ClC), 151.6 (N-CH), 151.2 (BrC-C_q), 140.0 (phenyl-C_q), 129.1 (phenyl-CH), 129.0 (phenyl-CH), 127.7 (phenyl-CH), 123.4 (ClC-CH), 119.1 (BrC), 74.3 (CH-OH); **HRMS (ESI)** m/z calcd. for C₁₂H₁₀BrClNO: 297.9629 (M+H)⁺; found: 297.9628 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.29.

(6-Chloro-4-isopropylpyridin-3-yl)(phenyl)methanol (SI1):



¹H-NMR (CDCl₃, 400 MHz): δ = 8.43 (s, 1H, N-CH), 7.40–7.23 (m, 5H, phenyl-H), 7.19 (s, 1H, ClC-CH), 6.05 (s, 1H, CH-OH), 3.12 (septett, 1H, *J* = 6.8 Hz, CHMe₂), 2.79 (s, br, 1H, OH), 1.11 (d, 3H, *J* = 6.8 Hz, CH₃), 0.96 (d, 3H, *J* = 6.8 Hz, CH₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 159.4 (Me₂CH-C_q), 151.3 (ClC), 148.8 (N-CH), 142.4 (phenyl-C_q), 134.8 (N-CH-C_q), 128.9 (phenyl-CH), 128.2 (phenyl-CH), 127.0 (phenyl-CH), 121.5 (ClC-CH), 71.8 (CH-OH), 28.8 (CHMe₂), 23.1 (CH₃), 22.9 (CH₃);

HRMS (ESI) m/z calcd. for C₁₅H₁₇ClNO: 262.0993 (M+H)⁺; found: 262.0995 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.18.

4-Bromo-5-((R)-((2R,3S)-3-(((tert-butyl)diphenylsilyloxy)methyl)-3-(3-methylbut-2-en-1-yl)oxiran-2-yl))((triisopropylsilyloxy)methyl)-2-chloropyridine (43):

2,6-Lutidine (0.677 mL, 5.84 mmol, 6.00 eq.) and then TIPSOTf (0.784 mL, 2.92 mmol, 3.00 eq.) were added to a solution of alcohol **41** (0.585 g, 0.973 mmol, 1.00 eq.) in anhydrous CH₂Cl₂ (20 mL) at 0 °C. After 3 h and 7 h, additional portions of 2,6-lutidine (6.00 eq.) and TIPSOTf (3.00 eq.) were added to drive the reaction to complete conversion. After stirring at room temperature overnight, the TLC showed complete conversion. Saturated aqueous NH₄Cl (30 mL) was added. The mixture was extracted with ethyl acetate (2 x 75 mL) and the combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0–10% ethyl acetate in *n*-heptane) to give **43** (0.507 g, 0.669 mmol, 69%) as colorless oil.

¹H-NMR (CDCl₃, 400 MHz): δ = 8.47 (s, 1H, N-CH), 7.75–7.64 (m, 4H, Ar-H), 7.75–7.64 (m, 7H, ClC-CH, Ar-H), 5.09 (m, 1H, Me₂C=CH), 4.85 (d, 1H, *J* = 7.5 Hz, CH-OTIPS), 4.10 (d, 1H, *J* = 11.1 Hz, TBDPSO-CH₂), 3.76 (d, 1H, *J* = 11.1 Hz, TBDPSO-CH₂), 2.99 (d, 1H, *J* = 7.5 Hz, epoxy-CH), 2.92 (dd, 1H, *J* = 14.6, 8.1 Hz, Me₂C=CH-CH₂), 2.16 (dd, 1H, *J* = 14.7, 6.8 Hz, Me₂C=CH-CH₂), 1.70 (s, 3H, E-CH₃), 1.64 (s, 3H, Z-CH₃), 1.10 (s, 9H, ^tBu-CH₃), 0.91–0.84 (m, 21H, TIPS-H); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 150.9 (Cl-C), 150.2 (N-CH), 137.2 (C-Br or C_qMe₂), 136.0/135.8 (Ar-C), 135.3 (C_qMe₂ or C-Br), 134.0 (N-CH-C_q), 133.4/133.0 (Ar-C_q), 129.9 (Ar-C), 127.9/127.9 (Ar-C), 127.3 (ClC-CH), 118.2 (CH=CMe₂), 68.2 (CH-OTIPS), 65.8 (epoxy-C_q), 65.7 (epoxy-CH), 64.4 (TBDPSO-CH₂), 30.9 (Me₂C=CH-CH₂), 27.0 (^tBu-CH₃), 26.0 (E-CH₃), 19.4 (^tBu-C_q), 18.2 (Z-CH₃), 17.9/17.8 (CH(CH₃)₂), 12.2 (CH(CH₃)₂); **HRMS (ESI)** m/z calcd. for C₃₉H₅₈BrClNO₃Si₂: 756.2665 (M+H)⁺; found: 756.2666 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.71; **Specific rotation** [α]_D^{24.7} = -6.0 (c = 1.20; CHCl₃).

4-Bromo-5-((S)-((2R,3S)-3-(((tert-butyl)diphenylsilyloxy)methyl)-3-(3-methylbut-2-en-1-yl)oxiran-2-yl))((triisopropylsilyloxy)methyl)-2-chloropyridine (49):

Compound **49** (0.421 g, 0.556 mmol, 90%) was synthesized in analogous manner to **43** starting from **42** (0.371 g, 0.617 mmol) and was obtained as colorless oil.

¹H-NMR (CDCl₃, 400 MHz): δ = 8.37 (s, 1H, N-CH), 7.69–7.60 (m, 4H, Ar-H), 7.46–7.33 (m, 7H, ClC-CH, Ar-H), 4.87 (m, 1H, Me₂C=CH), 4.77 (d, 1H, *J* = 7.5 Hz, CH-OTIPS), 3.69 (d, 1H, *J* = 11.4 Hz, TBDPSO-CH₂), 3.57 (d, 1H, *J* = 11.1 Hz, TBDPSO-CH₂), 3.21 (d, 1H, *J* = 7.7 Hz, epoxy-CH), 2.87 (dd, 1H, *J* = 14.7, 8.1 Hz, Me₂C=CH-CH₂), 2.06 (dd, 1H, *J* = 14.7, 6.5 Hz, Me₂C=CH-CH₂), 1.62 (s, 3H, E-CH₃), 1.54 (s, 3H, Z-CH₃), 1.06 (s, 9H, ^tBu-CH₃), 1.04–0.87 (m, 21H, TIPS-H); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 150.9 (Cl-C), 150.4 (N-CH), 136.4 (C-Br), 135.9/135.8 (Ar-C), 135.2 (C_qMe₂), 133.5 (N-CH-

C_q), 133.1/133.0 (Ar-C_q), 129.9/129.8 (Ar-C), 127.8 (Ar-C), 127.5 (ClC-CH), 118.1 (CH=CMe₂), 71.1 (CH-OTIPS), 66.1 (epoxy-CH), 65.7 (TBDPSO-CH₂), 65.1 (epoxy-C_q), 31.0 (Me₂C=CH-CH₂), 26.9 (tBu-CH₃), 25.8 (E-CH₃), 19.4 (tBu-C_q), 18.2 (Z-CH₃), 17.9/17.9 (CH(CH₃)₂), 12.3 (CH(CH₃)₂); **HRMS (ESI)** m/z calcd. for C₃₉H₅₆BrClNO₃Si₂: 756.2665 (M+H)⁺; found: 756.2669 (M+H)⁺; R_f (*n*-heptane/ethyl acetate 4:1): 0.77; **Specific rotation** [α]_D^{24.7} = -11.0 (c = 1.68; CHCl₃).

((2S,3R)-3-((R)-(4-Bromo-6-chloropyridin-3-yl)((triisopropylsilyl)oxy)methyl)-2-(3-methylbut-2-en-1-yl)oxiran-2-yl)methanol (44) and **(R)-(4-bromo-6-chloropyridin-3-yl)((2R,3S)-3-(hydroxymethyl)-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)methanol (45)**:

In a 50 mL falcon tube NH₄F (0.085 g, 2.3 mmol, 10.00 eq.) was added to a solution of **43** (0.174 g, 0.230 mmol, 1.00 eq.) in MeOH/THF (9 mL/1 mL). Because the TLC showed little conversion of the starting material at room temperature, the reaction was stirred at 40 °C for 6 h 30 min. The reaction was stopped by addition of saturated aqueous NaHCO₃ (20 mL) and H₂O (20 mL). The mixture was extracted twice with ethyl acetate (75 mL and 100 mL) and the combined organic layers were washed with saturated aqueous NaCl (60 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0–50% ethyl acetate in *n*-heptane) to give the desired product **44** (0.033 g, 0.064 mmol, 28%) as colorless solid, undesired product **45** (0.045 g, 0.12 mmol, 53%) as colorless oil, and recovered starting material **43** (0.010 g, 0.010 mmol, 6%). The analytical data of **44** were in complete accordance to the previous reported ones [6].

For **45**: **¹H-NMR** (CDCl₃, 400 MHz): δ = 8.53 (s, 1H, N-CH), 7.55 (s, 1H, ClC-CH), 5.14–5.06 (m, 2H, CH-OH, Me₂C=CH), 4.29 (s, br, 1H, CH₂-OH), 4.07 (d, 1H, *J* = 11.6 Hz, CH₂-OH), 3.79 (d, 1H, *J* = 11.6 Hz, CH₂-OH), 3.08 (s, br, 1H, CH-OH), 3.06 (d, 1H, *J* = 7.6 Hz, epoxy-CH), 2.45 (dd, 1H, *J* = 15.1, 7.4 Hz, Me₂C=CH-CH₂), 2.39 (dd, 1H, *J* = 15.0, 7.6 Hz, Me₂C=CH-CH₂), 1.70 (s, 3H, E-CH₃), 1.62 (s, 3H, Z-CH₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 151.1 (Cl-C), 149.2 (N-CH), 136.5 (C_qMe₂), 136.1 (N-CH-C_q), 134.7 (C-Br), 127.9 (ClC-CH), 117.1 (CH=CMe₂), 69.5 (CH-OH), 64.7 (epoxy-CH), 63.9 (epoxy-C_q), 63.6 (CH₂-OH), 32.4 (Me₂C=CH-CH₂), 25.9 (E-CH₃), 18.1 (Z-CH₃); **HRMS (ESI)** m/z calcd. for C₁₄H₁₈BrClNO₃: 362.0153 (M+H)⁺; found: 362.0154 (M+H)⁺; R_f (*n*-heptane/ethyl acetate 1:1): 0.34; **Specific rotation** [α]_D^{27.6} = +7.2 (c = 1.56; CHCl₃).

((2S,3R)-3-((S)-(4-Bromo-6-chloropyridin-3-yl)((triisopropylsilyl)oxy)methyl)-2-(3-methylbut-2-en-1-yl)oxiran-2-yl)methanol (50):

50 (0.049 g, 0.094 mmol, 17%) was synthesized in analogous manner to **44** starting from **49** (0.420 g, 0.555 mmol). **50**, undesired product **51** (0.122 g, 0.336 mmol, 61%), (Diol **51** was identified by LC-MS. Since it was of no synthetic value, it was not fully characterized and discarded.) and recovered starting material **49** (0.019 g, 0.025 mmol, 5%) were obtained as colorless oils. The analytical data of **50** were in complete accordance to the previous reported ones (Diol **51** was identified by LC-MS. Since it was of no synthetic value, it was not fully characterized and discarded.).

(2R,3R)-3-((R)-(4-Bromo-6-chloropyridin-3-yl)((triisopropylsilyl)oxy)methyl)-2-(3-methylbut-2-en-1-yl)oxirane-2-carbaldehyde (46):

Alcohol **44** (0.356 g, 0.686 mmol, 1.00 eq.) was dissolved in CH₂Cl₂ (17 mL) and DMP (15% in CH₂Cl₂, 2.85 mL, 1.37 mmol, 2.00 eq.) was added. After stirring at room temperature for 2 h, the TLC showed complete conversion of the starting material. The reaction mixture was filtered through a short silica column (100% CH₂Cl₂, 20 g silica). The product containing fractions were concentrated *in vacuo* to give aldehyde **46** (0.328 g, 0.634 mmol, 92%) as colorless oil.

¹H-NMR (CDCl₃, 400 MHz): δ = 9.79 (s, 1H, CHO), 8.41 (s, 1H, N-CH), 7.54 (s, 1H, ClC-CH), 5.49 (d, 1H, *J* = 4.2 Hz, CH-OTIPS), 4.99 (m, 1H, Me₂C=CH), 3.26 (d, 1H, *J* = 4.2 Hz, epoxy-CH), 2.98 (dd, 1H, *J* = 15.2, 7.5 Hz, Me₂C=CH-CH₂), 2.37 (dd, 1H, *J* = 15.3, 7.4 Hz, Me₂C=CH-CH₂), 1.65 (s, 3H, E-CH₃), 1.51 (s, 3H, Z-CH₃), 1.11–0.92 (m, 21H, TIPS-H); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 199.3 (CHO), 151.6 (Cl-C), 150.3 (N-CH), 136.9 (C_qMe₂), 135.7 (C-Br or N-CH-C_q), 133.5 (N-CH-C_q or C-Br), 127.4 (ClC-CH), 116.1 (CH=CMe₂), 68.4 (CH-OTIPS), 67.0 (epoxy-CH), 66.7 (epoxy-C_q), 28.9 (Me₂C=CH-CH₂), 25.9 (E-CH₃), 18.0 (Z-CH₃), 17.9/17.8 (CH(CH₃)₂), 12.2 (CH(CH₃)₂); **HRMS (ESI)** m/z calcd. for C₂₃H₃₆BrClNO₃Si: 519.1313 (M+H)⁺; found: 519.1313 (M+H)⁺; R_f (*n*-heptane/ethyl acetate 4:1): 0.77; **Specific rotation** [α]_D^{24.7} = -11.0 (c = 1.68; CHCl₃).

516.1331 (M+H)⁺; found: 516.1327 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.68; **Specific rotation** $[\alpha]_D^{23.8} = -2.2$ (c = 0.91; CHCl₃).

(2*R*,3*R*)-3-((*S*)-(4-Bromo-6-chloropyridin-3-yl))((triisopropylsilyl)oxy)methyl)-2-(3-methylbut-2-en-1-yl)oxirane-2-carbaldehyde (52):

Compound **52** (0.450 g, 0.871 mmol, 95%) was synthesized in analogous manner to **46** starting from **50** (0.480 g, 0.925 mmol) and was obtained as colorless oil.

¹H-NMR (CDCl₃, 400 MHz): δ = 9.52 (s, 1H, CHO), 8.53 (s, 1H, N-CH), 7.52 (s, 1H, Cl-CH), 5.32 (d, 1H, *J* = 6.8 Hz, CH-OTIPS), 4.95 (m, 1H, Me₂C=CH), 3.47 (d, 1H, *J* = 6.7 Hz, epoxy-CH), 2.54 (dd, 1H, *J* = 15.3, 7.4 Hz, Me₂C=CH-CH₂), 2.41 (dd, 1H, *J* = 15.3, 7.4 Hz, Me₂C=CH-CH₂), 1.65 (s, 3H, *E*-CH₃), 1.54 (s, 3H, *Z*-CH₃), 1.16–0.93 (m, 21H, TIPS-*H*); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 198.2 (CHO), 151.6 (Cl-C), 150.4 (N-CH), 136.7 (C_qMe₂), 135.3 (C-Br or N-CH-C_q), 132.9 (N-CH-C_q or C-Br), 127.5 (Cl-CH), 116.0 (CH=CMe₂), 69.8 (CH-OTIPS), 67.7 (epoxy-C_q), 67.3 (epoxy-CH), 28.2 (Me₂C=CH-CH₂), 25.8 (*E*-CH₃), 18.1 (*Z*-CH₃), 17.9/17.9 (CH(CH₃)₂), 12.2 (CH(CH₃)₂); **HRMS (ESI)** *m/z* calcd. for C₂₃H₃₆BrClNO₃Si: 516.1331 (M+H)⁺; found: 516.1331 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.67; **Specific rotation** $[\alpha]_D^{23.8} = +35.9$ (c = 1.06; CHCl₃).

(1*aR*,2*R*,7*aR*)-5-Chloro-7*a*-(3-methylbut-2-en-1-yl)-2-((triisopropylsilyl)oxy)-1*a*,7*a*-dihydrooxireno[2,3-g]isoquinolin-7(2*H*)-one (5), (1*aR*,2*R*,7*S*,7*aS*)-5-chloro-7*a*-(3-methylbut-2-en-1-yl)-2-((triisopropylsilyl)oxy)-1*a*,2,7,7*a*-tetrahydrooxireno[2,3-g]isoquinolin-7-ol (47), and (5*aS*,6*aR*,7*R*,11*bS*)-10-chloro-3-methyl-7-((triisopropylsilyl)oxy)-2,5,7,11*b*-tetrahydro-6*aH*-oxepino[2,3-f]oxireno[2,3-g]isoquinoline (48):

Aldehyde **46** (0.082 g, 0.16 mmol, 1.00 eq.) was dissolved in toluene (8 mL). After addition of Cs₂CO₃ (0.154 g, 0.473 mmol, 3.00 eq.), the solution was degassed with argon for 15 min. PdCl₂(PPh₃)₂ (0.011 g, 0.016 mmol, 0.10 eq.) was added and the reaction mixture was refluxed for 2 d, whereby a second portion of PdCl₂(PPh₃)₂ (0.10 eq.) was added after 24 h reaction time. Since prolonged reaction times led to significant side product formation, the reaction was stopped by cooling to room temperature before complete conversion of the starting material was monitored by LC-MS. Saturated aqueous NH₄Cl (14 mL) was added. The mixture was extracted with ethyl acetate (2 x 30 mL) and the combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0–20–25% ethyl acetate in *n*-heptane) to give **5** (0.012 g, 0.026 mmol, 16%) as a colorless oil. Additionally, side products **47** (0.011 g, 0.025 mmol, 15%) and **48** (0.007 g, 0.02 mmol, 10%) were obtained as slightly yellow oils. The analytical data of **5** were in complete accordance to the previous reported ones [6].

For **47**: **¹H-NMR** (CDCl₃, 600 MHz): δ = 8.64 (s, 1H, N-CH), 7.17 (s, 1H, Cl-CH), 5.42 (s, br, 1H, CH-OTIPS), 5.23 (m, 1H, Me₂C=CH), 4.88 (d, 1H, *J* = 2.2 Hz, CH-OH), 3.46 (s, 1H, epoxy-CH), 2.83 (dd, 1H, *J* = 15.1, 8.1 Hz, Me₂C=CH-CH₂), 2.48 (dd, 1H, *J* = 15.2, 7.2 Hz, Me₂C=CH-CH₂), 2.18 (d, 1H, *J* = 3.7 Hz, OH), 1.77 (s, 3H, *E*-CH₃), 1.70 (s, 3H, *Z*-CH₃), 1.31–1.13 (m, 21H, TIPS-*H*); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 150.8 (C_q-CH-OH), 148.9 (N-CH), 146.0 (Cl-C), 136.9 (C_qMe₂), 130.4 (N-CH-C_q), 123.2 (Cl-CH), 117.1 (CH=CMe₂), 70.8 (CH-OH), 67.3 (CH-OTIPS), 60.4 (epoxy-C_q), 59.4 (epoxy-CH), 29.8 (Me₂C=CH-CH₂), 25.9 (*E*-CH₃), 18.2 (*Z*-CH₃), 18.3/18.2 (CH(CH₃)₂), 12.8 (CH(CH₃)₂); **HRMS (ESI)** *m/z* calcd. for C₂₃H₃₇ClNO₃Si: 438.2226 (M+H)⁺; found: 438.2228 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.24; **Specific rotation** $[\alpha]_D^{18.8} = +37.1$ (c = 1.08; CHCl₃). For **48**: **¹H-NMR** (CDCl₃, 400 MHz): δ = 8.52 (s, 1H, N-CH), 7.45 (s, 1H, Cl-CH), 5.36 (d, 1H, *J* = 4.4 Hz, CH-OTIPS), 5.12 (s, br, 1H, O-CH₂), 4.96 (s, br, 1H, O-CH₂), 4.90 (CH₂-O-CH), 4.53 (dd, 1H, *J* = 8.1, 7.8 Hz, MeC=CH), 3.65 (d, 1H, *J* = 3.8 Hz, epoxy-CH), 2.43 (dd, 1H, *J* = 13.2, 9.4 Hz, C_q-CH₂-CH), 2.23 (dd, 1H, *J* = 13.2, 6.7 Hz, C_q-CH₂-CH), 1.84 (s, 3H, C_q-CH₃), 1.27–1.07 (m, 21H, TIPS-*H*); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 151.0 (Cl-C), 150.4 (N-CH), 145.6 (Cl-CH-C_q), 143.7 (MeC_q), 130.8 (N-CH-C_q), 123.3 (Cl-CH), 112.1 (O-CH₂), 80.9 (MeC-CH), 73.0 (CH₂-O-CH), 67.8 (epoxy-C_q), 65.3 (CH-OTIPS), 59.3 (epoxy-CH), 34.6 (C_q-CH₂-CH), 18.0 (C_q-CH₃), 18.2/18.2 (CH(CH₃)₂), 12.8 (CH(CH₃)₂); **HRMS (ESI)** *m/z* calcd. for C₂₃H₃₅ClNO₃Si: 436.2069 (M+H)⁺; found: 436.2070 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.40; **Specific rotation** $[\alpha]_D^{20.4} = +39.3$ (c = 0.85; CHCl₃).

(1aR,2S,7aR)-5-Chloro-7a-(3-methylbut-2-en-1-yl)-2-((triisopropylsilyloxy)-1a,7a-dihydrooxireno[2,3-g]isoquinolin-7(2H)-one (53) and (1aR,2S,7S,7aS)-5-chloro-7a-(3-methylbut-2-en-1-yl)-2-((triisopropylsilyloxy)-1a,2,7,7a-tetrahydrooxireno[2,3-g]isoquinolin-7-ol (54):

Compound **53** (0.119 g, 0.273 mmol, 42%) was synthesized in analogous manner to **5** starting from **52** (0.338 g, 0.654 mmol). A second portion of PdCl₂(PPh₃)₂ (0.10 eq.) was added after 9 h reaction time and the reaction was stopped after 24 h. **53** and side product **54** (0.041 g, 0.10 mmol, 15%) were obtained as colorless oils. No formation of tetracyclic side product was observed (see synthesis of **5**). The analytical data of **53** were in complete accordance to the previous reported ones [6].

For **54**: **¹H-NMR** (CDCl₃, 600 MHz): δ = 8.20 (s, 1H, N-CH), 7.63 (s, 1H, ClC-CH), 5.24 (d, 1H, *J* = 3.3 Hz, CH-OTIPS), 5.21 (m, 1H, Me₂C=CH), 5.03 (d, 1H, *J* = 10.5 Hz, CH-OH), 3.49 (d, 1H, *J* = 3.3 Hz, epoxy-CH), 3.11 (dd, 1H, *J* = 14.8, 8.8 Hz, Me₂C=CH-CH₂), 2.21 (dd, 1H, *J* = 14.9, 6.3 Hz, Me₂C=CH-CH₂), 2.14 (d, 1H, *J* = 10.8 Hz, OH), 1.74 (s, 3H, E-CH₃), 1.73 (s, 3H, Z-CH₃), 1.14–0.95 (m, 21H, TIPS-H); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 152.2 (Cl-C), 149.6 (N-CH), 149.6 (C_q-CH-OH), 136.6 (C_qMe₂), 129.2 (N-CH-C_q), 121.9 (ClC-CH), 117.4 (CH=CMe₂), 68.0 (CH-OH), 67.1 (CH-OTIPS), 60.6 (epoxy-C_q), 59.0 (epoxy-CH), 30.5 (Me₂C=CH-CH₂), 26.0 (E-CH₃), 18.2 (Z-CH₃), 18.2/18.0 (CH(CH₃)₂), 12.6 (CH(CH₃)₂); **HRMS (ESI)** *m/z* calcd. for C₂₃H₃₇ClNO₃Si: 438.2226 (M+H)⁺; found: 438.2225 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.28; **Specific rotation** [α]_D²⁵ = -20.3 (*c* = 0.20; CHCl₃).

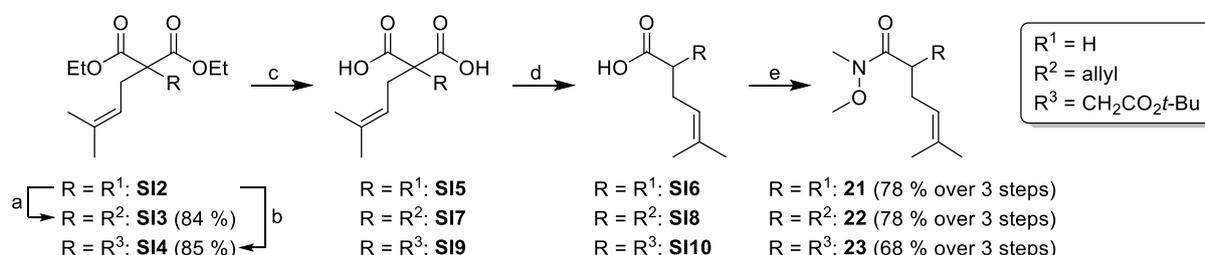
(1aR,2R,7aR)-7a-(3-Methylbut-2-en-1-yl)-5-((E)-pent-1-en-1-yl)-2-((triisopropylsilyloxy)-1a,7a-dihydrooxireno[2,3-g]isoquinolin-7(2H)-one (55), (5S,6R)-2,2-dimethyl-9-((E)-pent-1-en-1-yl)-6-((triisopropylsilyloxy)-5,6-dihydro-2H-pyrano[2,3-f]isoquinolin-5-ol (56), and (E)-2,2-dimethyl-9-(pent-1-en-1-yl)-6-((triisopropylsilyloxy)-2H-pyrano[2,3-f]isoquinoline (57):

The reaction was carried out under argon atmosphere. Compound **5** (0.074 g, 0.17 mmol) was dissolved in 1,4-dioxane/H₂O 8:1 (15.0 mL/1.88 mL). *trans*-1-Penten-1-ylboronic acid pinacol ester (0.077 g, 0.67 mmol, 4.00 eq.) as well as Cs₂CO₃ (0.165 g, 0.506 mmol, 3.00 eq.) were added and the solution was degassed by bubbling a stream of argon through the solution for 15 min. Then APPhos Pd G3 (0.005 g, 0.008 mmol, 0.10 eq.) was added. The resulting mixture was stirred at 100 °C for 6 h, then the reaction mixture was allowed to cool to room temperature, diluted with saturated aqueous NH₄Cl (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0–40% ethyl acetate in *n*-heptane) to give **55** (0.003 g, 0.01 mmol, 4%) as colorless oil as well as side products **56** (0.021 g, 0.045 mmol, 27%) and **57** (0.009 g, 0.02 mmol, 12%) as yellow oils. The yield of **55** could be increased by carefully monitoring of the reaction by LC-MS measurement [6]. The analytical data of **55** were in complete accordance to the previous reported ones [6].

For **56**: (**56** was isolated with approx. 10–15% impurities) **¹H-NMR** (CDCl₃, 400 MHz): δ = 8.89 (s, 1H, N-CH), 7.93 (d, 1H, *J* = 12.5 Hz, Me₂C-CH=CH), 7.75 (s, 1H, pentenyl-C_q-CH), 6.81 (dt, 1H, *J* = 15.0, 7.3 Hz, CH₂-CH=CH), 6.56 (dt, 1H, *J* = 15.8, 1.6 Hz, CH₂-CH=CH), 6.37 (d, br, 1H, *J* = 12.5 Hz, Me₂C-CH=CH), 5.19 (d, br, 1H, *J* = 2.9 Hz, CH-OTIPS), 5.15 (d, br, 1H, *J* = 3.1 Hz, CH-OH), 2.56 (s, br, 1H, OH), 2.26 (m, 2H, CH₂-CH=CH), 2.03 (s, 3H, C(CH₃)₂), 2.00 (s, 3H, C(CH₃)₂), 1.54 (m, 2H, CH₃-CH₂), 1.39–1.07 (m, 21H, TIPS-H), 0.96 (t, 3H, *J* = 7.3 Hz, CH₃-CH₂); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 185.5 (C_q-C_q-O), 156.8 (N-C_q), 153.6 (C_qMe₂), 148.8 (N-CH), 139.8 (Me₂C-CH=CH), 138.4 (pentenyl-C_q-CH-C_q), 137.0 (CH₂-CH=CH), 132.3 (N-CH-C_q), 129.7 (CH₂-CH=CH), 129.0 (C_q-C_q-O), 120.2 (Me₂C-CH=CH), 116.5 (pentenyl-C_q-CH), 70.2 (CH-OTIPS), 68.9 (CH-OH), 35.1 (CH₂-CH=CH), 27.8 (C(CH₃)₂), 22.3 (CH₃-CH₂), 19.6 (C(CH₃)₂), 18.3/18.2 (CH(CH₃)₂), 12.7 (CH(CH₃)₂), 13.9 (CH₃-CH₂); **HRMS (ESI)** *m/z* calcd. for C₂₈H₄₄NO₃Si: 470.3085 (M+H)⁺; found: 470.3083 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.28. For **57**: **¹H-NMR** (CDCl₃, 400 MHz): δ = 9.46 (s, 1H, N-CH), 7.66 (s, 1H, pentenyl-C_q-CH), 6.90 (dt, 1H, *J* = 14.8, 7.4 Hz, CH₂-CH=CH), 6.62 (dt, 1H, *J* = 15.6, 1.1 Hz, CH₂-CH=CH), 6.50 (s, 1H, C_qOTIPS-CH), 6.33 (d, 1H, *J* = 9.8 Hz, Me₂C-CH=CH), 5.72 (d, 1H, *J* = 9.6 Hz, Me₂C-CH=CH), 2.28 (m, 2H, CH₂-CH=CH), 1.57 (m, 2H, CH₃-CH₂), 1.49 (s, 6H, C(CH₃)₂), 1.43–1.31 (m, 3H, CH(CH₃)₂), 1.31–1.11 (m, 19H, CH(CH₃)₂), 0.99 (t, 3H, *J* = 7.4 Hz, CH₃-CH₂); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 149.9 (N-C_q), 148.1 (N-CH), 146.9 (N-CH-C_q), 141.1 (Me₂C-O-C_q),

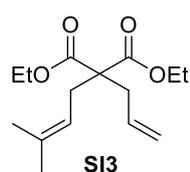
134.6 (CH₂-CH=CH), 132.2 (Me₂C-CH=CH), 130.3 (CH₂-CH=CH), 129.4 (C_q-OTIPS), 122.7 (Me₂C-CH=CH), 121.6 (pentenyl-C_q-CH-C_q), 119.5 (Me₂C-CH=CH-C_q), 111.4 (pentenyl-C_q-CH), 110.9 (C_q(OTIPS)-C_q), 76.7 (C_qMe₂), 35.2 (CH₂-CH=CH), 27.8 (C(CH₃)₂), 22.5 (CH₃-CH₂), 18.2 (CH(CH₃)₂), 14.0 (CH₃-CH₂), 13.1 (CH(CH₃)₂); **HRMS (ESI)** m/z calcd. for C₂₈H₄₂NO₂Si: 452.2979 (M+H)⁺; found: 452.2981 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 8:1): 0.51.

1.1. Weinreb amides **21**, **22**, and **23**



Scheme S1. Synthesis of the Weinreb amides **21**, **22**, and **23**. Conditions: (a) NaH, THF, 40 °C; R²-Br; (b) NaH, THF, 40 °C; R³-Br; (c) KOH, EtOH, H₂O; (d) pyridine/H₂O 30:1, 100 °C to 120 °C; (e) EDC · HCl, Oxyma, NEt₃, NHMe(OMe) · HCl, CH₂Cl₂.

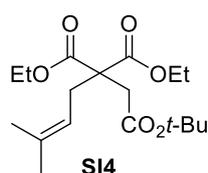
Diethyl 2-allyl-2-(3-methylbut-2-en-1-yl)malonate (**SI3**):



SI2 was synthesized according to a literature known procedure [36]. To a solution of **SI2** (2.00 g, 8.77 mmol, 1.00 eq.) in anhydrous THF (30 mL) NaH (60% in mineral oil, 0.527 g, 13.2 mmol, 1.50 eq.) was added at 0 °C. After stirring at room temperature for 30 min, allyl bromide (1.15 mL, 13.2 mmol, 1.50 eq.) was added. The suspension was stirred at room temperature for 48 h and was then diluted with saturated aqueous NH₄Cl (30 mL). The mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with saturated aqueous NaCl (60 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0–5% ethyl acetate in *n*-heptane) to give **SI3** (1.97 g, 7.35 mmol, 84%) as colorless oil.

¹H-NMR (CDCl₃, 400 MHz): δ = 5.66 (m, 1H, CH₂=CH), 5.10 (m, 1H, CH₂=CH), 5.06 (m, 1H, CH₂=CH), 4.97 (m, 1H, Me₂C=CH), 4.17 (m, 4H, CH₂-CH₃), 2.65–2.57 (m, 4 H, CH-CH₂ and CH-CH₂), 1.69 (d, 1H, *J* = 1.0 Hz, 3H, *E*-CH₃), 1.61 (s, 3H, *Z*-CH₃), 1.24 (t, 6H, *J* = 7.1 Hz, CH₂-CH₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 171.3 (C=O), 135.6 (C_qMe₂), 132.9 (CH=CH₂), 119.0 (CH=CH₂), 117.8 (CH=CMe₂), 61.3 (CH₂-CH₃), 57.8 (C_q-CO₂Et), 36.9 (CH₂=CH-CH₂), 31.1 (Me₂C=CH-CH₂), 26.2 (*E*-CH₃), 18.2 (*Z*-CH₃), 14.2 (CH₂-CH₃); **HRMS (ESI)** m/z calcd. for C₁₅H₂₅O₄: 269.1747 (M+H)⁺; found: 269.1751 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 10:1): 0.35.

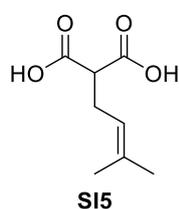
1-(*tert*-Butyl) 2,2-diethyl 5-methylhex-4-ene-1,2,2-tricarboxylate (**SI4**):



SI4 was synthesized analogously to **SI3** starting from **SI2** (3.00 g, 13.2 mmol, 1.00 eq.) and NaH (60% in mineral oil, 0.284 g, 11.9 mmol, 0.90 eq.) and by stirring overnight with *tert*-butyl bromoacetate (2.90 mL, 19.7 mmol, 1.50 eq.). **SI4** (3.45 g, 10.1 mmol, 85%) was obtained as colorless oil.

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 4.97 (m, 1H, $\text{Me}_2\text{C}=\text{CH}$), 4.18 (m, 4H, $\text{CH}_2\text{-CH}_3$), 2.86 (s, 2H, $\text{CH}_2\text{-CO}_2t\text{-Bu}$), 2.73 (d, 2H, J = 7.6 Hz, CH-CH_2), 1.69 (s, 3H, $E\text{-CH}_3$), 1.59 (s, 3H, $Z\text{-CH}_3$), 1.42 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.24 (t, 6H, J = 7.1 Hz, $\text{CH}_2\text{-CH}_3$); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 170.5 (CO_2Et), 169.9 ($\text{CO}_2t\text{-Bu}$), 136.3 (C_qMe_2), 117.9 ($\text{CH}=\text{CMe}_2$), 81.1 ($\text{C}(\text{CH}_3)_3$), 61.5 ($\text{CH}_2\text{-CH}_3$), 55.7 ($\text{C}_q\text{-CO}_2\text{Et}$), 38.3 ($\text{CH}_2\text{-CO}_2t\text{-Bu}$), 31.9 ($\text{Me}_2\text{C}=\text{CH-CH}_2$), 28.1 ($\text{C}(\text{CH}_3)_3$), 26.2 ($E\text{-CH}_3$), 18.0 ($Z\text{-CH}_3$), 14.2 ($\text{CH}_2\text{-CH}_3$); **HRMS (ESI)** m/z calcd. for $\text{C}_{18}\text{H}_{30}\text{O}_6\text{Na}$: 365.1935 ($\text{M}+\text{Na}$) $^+$; found: 365.1936 ($\text{M}+\text{Na}$) $^+$; R_f (*n*-heptane/ethyl acetate 10:1): 0.29.

2-(3-Methylbut-2-en-1-yl)malonic acid (**SI5**):

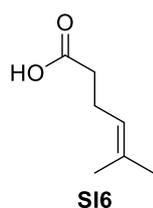


To a solution of **SI2** (2.23 g, 9.77 mmol, 1.00 eq.) in ethanol (30 mL) and a few drops of water, KOH (4.49 g, 80.0 mmol, 8.00 eq.) was added and the solution was allowed to stir overnight until LC-MS indicated complete conversion of the starting material. The reaction mixture was concentrated *in vacuo*, diluted with 1 M aqueous HCl (60 mL) and was then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (80 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure to yield **SI5** as colorless solid, which was used in

the next stage without further purification.

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 10.51 (s, br, 1H, COOH), 5.10 (m, 1H, $\text{Me}_2\text{C}=\text{CH}$), 3.45 (t, 1H, J = 7.4 Hz, CH-COOH), 2.65 (t, 2H, J = 7.3 Hz, $\text{CH}_2\text{-CH}$), 1.71 (s, 3H, $E\text{-CH}_3$), 1.64 (s, 3H, $Z\text{-CH}_3$); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 174.8 ($\text{C}=\text{O}$), 136.2 (C_qMe_2), 118.9 ($\text{CH}=\text{CMe}_2$), 51.9 (CH-COOH), 27.7 (CH_2), 25.9 ($E\text{-CH}_3$), 17.9 ($Z\text{-CH}_3$); **HRMS (ESI)** m/z calcd. for $\text{C}_8\text{H}_{13}\text{O}_4$: 173.0808 ($\text{M}+\text{H}$) $^+$; found: 173.0807 ($\text{M}+\text{H}$) $^+$; R_f (*n*-heptane/ethyl acetate 1:1): 0.18.

5-Methylhex-4-enoic acid (**SI6**):



The reaction was carried out according to slightly modified literature-known procedure [36]. Dicarboxylic acid **SI5** (9.77 mmol, 1.00 eq.) dissolved in pyridine (6 mL) and H_2O (0.2 mL) was stirred at 100 °C overnight. To complete conversion, which was monitored by LC-MS, the solution was stirred at 120 °C for further 2 h. The reaction mixture was concentrated *in vacuo* and the residue was diluted with 1 M aqueous HCl, acidified with 1 M aqueous HCl (35 mL) to pH = 1 and extracted with ethyl acetate (3 x 100 mL and 1 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl (80 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure to yield **SI6** as colorless oil, which was used in the next stage without further purification.

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 9.45 (s, br, 1H, COOH), 5.10 (m, 1H, $\text{Me}_2\text{C}=\text{CH}$), 2.41–2.28 (m, 4H, CH_2), 1.69 (d, 3H, J = 1.0 Hz, $E\text{-CH}_3$), 1.63 (s, 3H, $Z\text{-CH}_3$); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 179.5 ($\text{C}=\text{O}$), 133.6 (C_qMe_2), 122.2 ($\text{CH}=\text{CMe}_2$), 34.3 (CO-CH_2), 25.8 ($\text{CH}_2\text{-CH}$), 23.5 ($E\text{-CH}_3$), 17.8 ($Z\text{-CH}_3$); **HRMS (ESI)** m/z calcd. for $\text{C}_7\text{H}_{13}\text{O}_2$: 129.0910 ($\text{M}+\text{H}$) $^+$; found: 129.0909 ($\text{M}+\text{H}$) $^+$; R_f (*n*-heptane/ethyl acetate 1:1): 0.57.

N-Methoxy-*N*,5-dimethylhex-4-enamide (**21**):

To crude **SI6** (9.77 mmol, 1.00 eq.) dissolved in CH_2Cl_2 (20 mL) NEt_3 (4.50 mL, 32.5 mmol, 3.50 eq.) and Oxyma (1.98 g, 13.9 mmol, 1.50 eq.) followed by EDC · HCl (2.67 g, 13.9 mmol, 1.50 eq.) as well as $\text{NHMe}(\text{OMe}) \cdot \text{HCl}$ (1.09 g, 11.1 mmol, 1.20 eq.) were added. After stirring for 2.5 h, LC-MS indicated full conversion. Saturated aqueous NaHCO_3 (75 mL) was added and the mixture was extracted with ethyl acetate (200 mL). The organic layer was separated and washed with another portion of saturated aqueous NaHCO_3 (75 mL), aqueous citric acid (solution 10%, 2 x 75 mL) and saturated

aqueous NaCl (75 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (0–40% ethyl acetate in *n*-heptane) yielded **21** (1.31 g, 7.67 mmol, 78% over three steps) as a colorless oil.

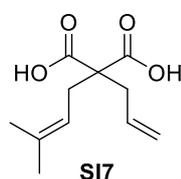
¹H-NMR (CDCl₃, 400 MHz): δ = 5.13 (m, 1H, Me₂C=CH), 3.67 (s, 3H, O-CH₃), 3.18 (s, 3H, N-CH₃), 2.44 (t, 2H, *J* = 7.5 Hz, CO-CH₂), 2.31 (q, 2H, *J* = 7.4 Hz, CH-CH₂), 1.69 (s, 3H, *E*-CH₃), 1.63 (s, 3H, *Z*-CH₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 132.8 (C_qMe₂), 123.2 (CH=CMe₂), 61.3 (O-CH₃), 32.3 (N-CH₃), 32.3 (CO-CH₂), 25.8 (*E*-CH₃), 23.4 (CH-CH₂), 17.8 (*Z*-CH₃); **HRMS (ESI)** *m/z* calcd. for C₉H₁₈NO₂: 172.1332 (M+H)⁺; found: 172.1330 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 2:1): 0.37.

2-Allyl-*N*-methoxy-*N*,5-dimethylhex-4-enamide (**22**):

Weinreb amide **22** (1.19 g, 5.62 mmol, 78% over three steps) was synthesized in analogous manner to **21** starting from **SI3** (1.97 g, 7.33 mmol, 1.00 eq.) and was obtained as colorless oil. Intermediates **SI7** and **SI8** were obtained as colorless oils (The saponification was stirred at room temperature for 48 h and the decarboxylation was stirred at 100 to 120 °C for 36 h until complete conversion was detected by LC-MS.).

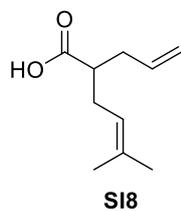
¹H-NMR (CDCl₃, 400 MHz): δ = 5.75 (ddt, 1H, *J* = 17.1, 10.2, 7.0 Hz, CH₂=CH), 5.13–4.98 (m, 3H, CH₂=CH and Me₂C=CH), 3.65 (s, 3H, O-CH₃), 3.17 (s, 3H, N-CH₃), 2.91 (s, br, 1H, CH-CO), 2.42–2.11 (m, 4H, CH₂ and CH₂), 1.68 (s, 3H, *E*-CH₃), 1.60 (s, 3H, *Z*-CH₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 176.7 (C=O), 136.4 (CH=CH₂), 133.7 (C_qMe₂), 121.7 (CH=CMe₂), 116.5 (CH=CH₂), 61.6 (O-CH₃), 41.3 (CH-CO), 36.3 (CH₂=CH-CH₂), 32.3 (N-CH₃), 30.8 (Me₂C=CH-CH₂), 25.9 (*E*-CH₃), 17.9 (*Z*-CH₃); **HRMS (ESI)** *m/z* calcd. for C₁₂H₂₂NO₂: 212.1645 (M+H)⁺; found: 212.1646 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.27.

2-Allyl-2-(3-methylbut-2-en-1-yl)malonic acid (**SI7**):



¹H-NMR (CD₃OD, 400 MHz): δ = 5.69 (ddt, 1H, *J* = 17.2, 10.0, 7.3 Hz, CH₂=CH), 5.11–5.00 (m, 3H, CH₂=CH and Me₂C=CH), 2.60–2.52 (m, 4H, CH₂, CH₂), 1.70 (s, 3H, *E*-CH₃), 1.63 (s, 3H, *Z*-CH₃); **¹³C-NMR** (CD₃OD, 100 MHz): δ = 175.5 (C=O), 136.2 (C_qMe₂), 134.4 (CH=CH₂), 119.5 (CH=CMe₂), 118.9 (CH=CH₂), 58.6 (C_q-COOH), 38.6 (CH₂=CH-CH₂), 32.8 (Me₂C=CH-CH₂), 26.2 (*E*-CH₃), 18.2 (*Z*-CH₃); **HRMS (ESI)** *m/z* calcd. for C₁₁H₁₇O₄: 213.1121 (M+H)⁺; found: 213.1120 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 1:1): 0.21.

2-Allyl-5-methylhex-4-enoic acid (**SI8**):



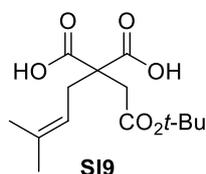
¹H-NMR (CDCl₃, 400 MHz): δ = 5.78 (ddt, 1H, *J* = 17.2, 10.1, 6.9 Hz, CH₂=CH), 5.13–5.02 (m, 3H, CH₂=CH and Me₂C=CH), 2.55–2.18 (m, 5H, CH₂, CH₂, and CH-CH₂), 1.70 (s, 3H, *E*-CH₃), 1.61 (s, 3H, *Z*-CH₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 181.5 (C=O), 135.4 (CH=CH₂), 134.4 (C_qMe₂), 120.7 (CH=CMe₂), 117.2 (CH=CH₂), 45.6 (CH-COOH), 35.6 (CH₂=CH-CH₂), 30.1 (Me₂C=CH-CH₂), 25.9 (*E*-CH₃), 18.0 (*Z*-CH₃); **HRMS (ESI)** *m/z* calcd. for C₁₀H₁₇O₂: 169.1223 (M+H)⁺; found: 169.1222 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 1:1): 0.79.

tert-Butyl 3-(methoxy(methyl)carbamoyl)-6-methylhept-5-enoate (23):

Weinreb amide **23** (1.95 g, 6.82 mmol, 68% over three steps) was synthesized in analogous manner to **21** starting from **SI4** (3.46 g, 10.1 mmol, 1.00 eq.) and was obtained as colorless oil. Intermediate **SI9** was obtained as colorless oil and **SI10** as yellow oil. (The saponification was stirred at room temperature for 48 h and the decarboxylation was stirred at 100 °C for 9 h until complete conversion was detected by LC-MS).

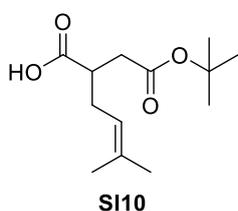
¹H-NMR (CDCl₃, 400 MHz): δ = 5.09 (m, 1H, Me₂C=CH), 3.76 (s, 3H, O-CH₃), 3.19 (s, br, 4H, N-CH₃ and CH-CO), 2.68 (dd, 1H, *J* = 16.6, 10.0 Hz, CH₂-CO₂*t*-Bu), 2.32 (dd, 1H, *J* = 16.6, 4.5 Hz, CH₂-CO₂*t*-Bu), 2.30–2.05 (m, 2H, Me₂C=CH-CH₂), 1.69 (s, 3H, *E*-CH₃), 1.60 (s, 3H, *Z*-CH₃), 1.42 (s, 9H, C(CH₃)₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 176.0 (CO₂*t*-Bu), 172.1 (CO-NMe), 134.4 (C_qMe₂), 121.0 (CH=CMe₂), 80.5 (C(CH₃)₃), 37.9 (CH-CO), 36.6 (CH₂-CO₂*t*-Bu), 32.4 (N-CH₃), 30.5 (Me₂C=CH-CH₂), 28.3 (C(CH₃)₃), 25.9 (*E*-CH₃), 18.3 (*Z*-CH₃); **HRMS (ESI)** *m/z* calcd. for C₁₅H₂₇NO₄Na: 308.1832 (M+Na)⁺; found: 308.1837 (M+Na)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.20.

2-(2-(tert-Butoxy)-2-oxoethyl)-2-(3-methylbut-2-en-1-yl)malonic acid (SI9):



¹H-NMR (CDCl₃, 400 MHz): δ = 5.04 (m, 1H, Me₂C=CH), 3.02 (s, 2H, CH₂-CO₂*t*-Bu), 2.63 (d, 2H, *J* = 7.8 Hz, CH-CH₂), 1.72 (s, 3H, *E*-CH₃), 1.60 (s, 3H, *Z*-CH₃), 1.42 (s, 9H, C(CH₃)₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 175.6 (COOH), 170.6 (CO₂*t*-Bu), 138.4 (C_qMe₂), 116.0 (CH=CMe₂), 82.7 (C(CH₃)₃), 54.6 (C_q-COOH), 40.8 (CH₂-CO₂*t*-Bu), 35.8 (Me₂C=CH-CH₂), 28.0 (C(CH₃)₃), 26.1 (*E*-CH₃), 18.0 (*Z*-CH₃); **HRMS (ESI)** *m/z* calcd. for C₁₄H₂₂O₆Na: 309.1309 (M+Na)⁺; found: 309.1305 (M+Na)⁺; **R_f** (*n*-heptane/ethyl acetate 1:1): 0.03.

2-(2-(tert-Butoxy)-2-oxoethyl)-5-methylhex-4-enoic acid (SI10):

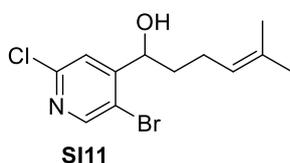


SI10
acetate 1:1): 0.79.

¹H-NMR (CDCl₃, 400 MHz): δ = 5.08 (m, 1H, Me₂C=CH), 2.92–2.78 (m, 1H, CH-COOH), 2.58 (dd, 1H, *J* = 16.7, 9.3 Hz, CH-CH₂), 2.46–2.20 (m, 3H, CH-CH₂, CH₂-CO₂*t*-Bu), 1.70 (s, 3H, *E*-CH₃), 1.61 (s, 3H, *Z*-CH₃), 1.43 (s, 9H, C(CH₃)₃); **¹³C-NMR** (CDCl₃, 100 MHz): δ = 180.1 (COOH), 171.6 (CO₂*t*-Bu), 135.2 (C_qMe₂), 120.0 (CH=CMe₂), 81.2 (C(CH₃)₃), 41.7 (CH₂-CO₂*t*-Bu), 36.5 (CH-CO), 30.2 (Me₂C=CH-CH₂), 28.3 (C(CH₃)₃), 26.1 (*E*-CH₃), 18.1 (*Z*-CH₃); **HRMS (ESI)** *m/z* calcd. for C₁₀H₁₇O₂: 169.1223 (M+H)⁺; found: 169.1222 (M+H)⁺; **R_f** (*n*-heptane/ethyl

1.2. Reduction of 24 with LDA

1-(5-Bromo-2-chloropyridin-4-yl)-5-methylhex-4-en-1-ol (SI11):



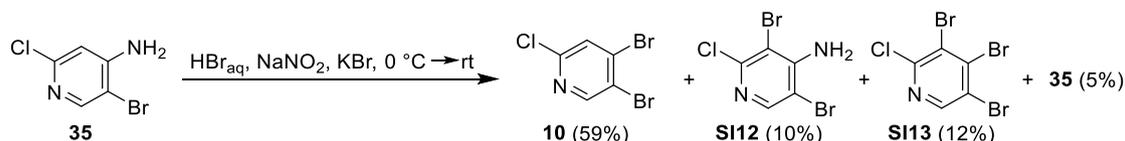
SI11
The reaction was carried out in moisture-free glassware under inert atmosphere. LDA (2 M in THF/*n*-heptane/Ethylbenzol, 0.181 mL, 0.361 mmol, 1.10 eq.) was added to ketone **24** (0.099 g, 0.33 mmol, 1.00 eq.) in anhydrous THF (8 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and was then diluted with saturated aqueous NH₄Cl (15 mL). After extraction with ethyl acetate (30 mL), the organic layer was washed with saturated aqueous NaCl (15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (0–30% ethyl acetate in *n*-heptane) yielded **SI11** (0.032 g, 0.11 mmol, 32%) as colorless solid and reisolated **24** (0.013 g, 0.043 mmol, 13%).

An attempt of trapping of the lithiated species with *tert*-butyl bromoacetate (2.00 eq.) as electrophile did not result the desired product **26** but **SI11** (0.026 g, 0.085 mmol, 51%) after aqueous work-up and purification *via* flash column chromatography.

¹H-NMR (CDCl₃, 400 MHz): δ = 8.39 (s, 1H, N-CH), 7.56 (s, 1H, Cl-CH), 5.18 (m, 1H, Me₂C=CH), 4.95 (dd, 1H, *J* = 8.9, 2.9 Hz, CH-OH), 2.30–2.10 (m, 3H, Me₂C=CH-CH₂, OH), 1.88–1.77 (m, 1H, HO-CH-CH₂), 1.71 (s, 3H, *E*-CH₃), 1.65 (s,

3H, *Z*-CH₃), 1.66–1.54 (m, 1H, HO-CH-CH₂); ¹³C-NMR (CDCl₃, 100 MHz): δ = 155.9 (BrC-C_q), 151.3 (N-CH), 151.1 (Cl-C_q), 133.7 (C_qMe₂), 123.0 (CH=CMe₂), 122.9 (ClC-CH), 118.2 (CBr), 72.1 (CH-OH), 36.9 (HO-CH-CH₂), 25.9 (*E*-CH₃), 24.5 (CH₂-CH=CMe₂), 17.9 (*Z*-CH₃); **HRMS (ESI)** m/z calcd. for C₁₂H₁₆BrClNO: 304.0098 (M+H)⁺; found: 304.0101 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.32.

1.3. Sandmeyer reaction in aqueous medium



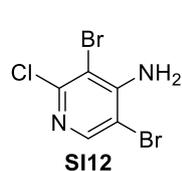
Scheme S2. Sandmeyer reaction in aqueous medium.

4,5-Dibromo-2-chloropyridine (**10**):

Amine **35** (4.30 g, 20.7 mmol, 1.00 eq.) was sonicated at 40 °C in aqueous HBr solution (48%, 100 mL). After the suspension was diluted with water (100 mL), NaNO₂ (2.43 g, 35.2 mmol, 1.70 eq.) in water (15 mL) was added dropwise at 0 °C over a period of 1 h. The reaction mixture was stirred at 0 °C for further 5 min and after addition of KBr (2.71 g, 22.8 mmol, 1.10 eq.) the mixture was stirred at room temperature overnight. The suspension was alkalinized at 0 °C with aqueous NaOH (50%, 46 mL) to pH = 10. The aqueous layer was extracted with Et₂O (2 x 200 mL) and the combined organic layers were washed with saturated aqueous NaCl (150 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure (Due to beginning sublimation of the product at low pressure, careful concentration *in vacuo* (≥ 200 mbar) is necessary). The crude product was purified by flash column chromatography (petroleum ether/CH₂Cl₂ 8:1 → 2:1 then 100% CH₂Cl₂ then CH₂Cl₂/ethyl acetate 4:1) to give **10** (3.32 g, 12.2 mmol, 59%) as well as side products **SI12** (0.565 g, 1.97 mmol, 10%) and **SI13** (0.861 g, 2.48 mmol, 12%) as colorless solids. Additionally, starting material **35** (0.202 g, 0.974 mmol, 5%) was recovered.

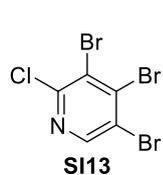
¹H-NMR (CDCl₃, 400 MHz): δ = 8.51 (s, 1H, N-CH), 7.64 (s, 1H, ClC-CH); ¹³C-NMR (CDCl₃, 100 MHz): δ = 151.7 (N-CH), 150.5 (C-Cl), 136.8 (ClC-CH=CBr), 128.8 (ClC-CH), 122.6 (N-CH=CBr); **HRMS (ESI)** m/z calcd. for C₅H₃Br₂ClN: 269.8315 (M+H)⁺; found: 269.8320 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.73 and (petroleum ether/CH₂Cl₂ 2:1): 0.39.

3,5-Dibromo-2-chloropyridin-4-amine (**SI12**):



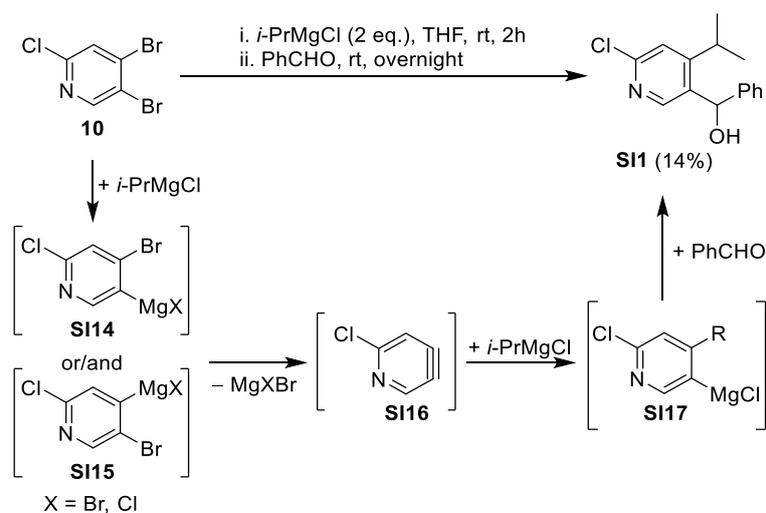
¹H-NMR (CDCl₃, 400 MHz): δ = 8.12 (s, 1H, CH), 5.29 (s, br, 2H, NH₂); ¹³C-NMR (CDCl₃, 100 MHz): δ = 150.3 (CH or C-Cl), 150.0 (C-Cl or CH), 148.0 (C-NH₂), 104.7 (CBr), 104.6 (CBr); **HRMS (ESI)** m/z calcd. for C₅H₄Br₂ClN₂: 284.8424 (M+H)⁺; found: 284.8427 (M+H)⁺; **R_f** (*n*-heptane/ethyl acetate 4:1): 0.31.

3,4,5-Tribromo-2-chloropyridine (**SI13**):



H-NMR (CDCl₃, 400 MHz): δ = 8.45 (s, 1H, CH); ¹³C-NMR (CDCl₃, 100 MHz): δ = 150.8 (CCl), 148.9 (CH), 140.2 (CBr=CBr-CBr), 124.9 (ClC-CBr or N-CH=CBr), 122.9 (N-CH=CBr or ClC-CBr); **HRMS (ESI)** m/z calcd. for C₅H₂Br₃ClN: 247.7420 (M+H)⁺; found: 247.7413 (M+H)⁺; **R_f** (petroleum ether/CH₂Cl₂ 2:1): 0.41.

1.4. Hypothesized mechanism of the formation of side product **SI1**



Scheme S3. Hypothesized mechanism of the formation of side product **SI1**.

As a plausible mechanism of the formation of **SI1** (Scheme S3), we hypothesized that the initially formed magnesium species **SI14** and **SI15** resulted in heteroaryne **SI16**, which has been described by Sundalam *et al.* [37]. After regioselective reaction with an excess of the Grignard reagent, the resulting magnesium-species **SI17** is trapped by benzaldehyde. Regioselective transformation of **10** to a higher functionalized product such as **SI0** would be of general synthetic value provided that the formation of the heteroaryne **SI16** could be increased. However, no attempts to optimize this transformation were performed.

2. NMR Spectra

Figure S1. 4-Chloro-3-phenylfuro[3,4-c]pyridin-1(3H)-one (**12**) (^1H - and ^{13}C -NMR).

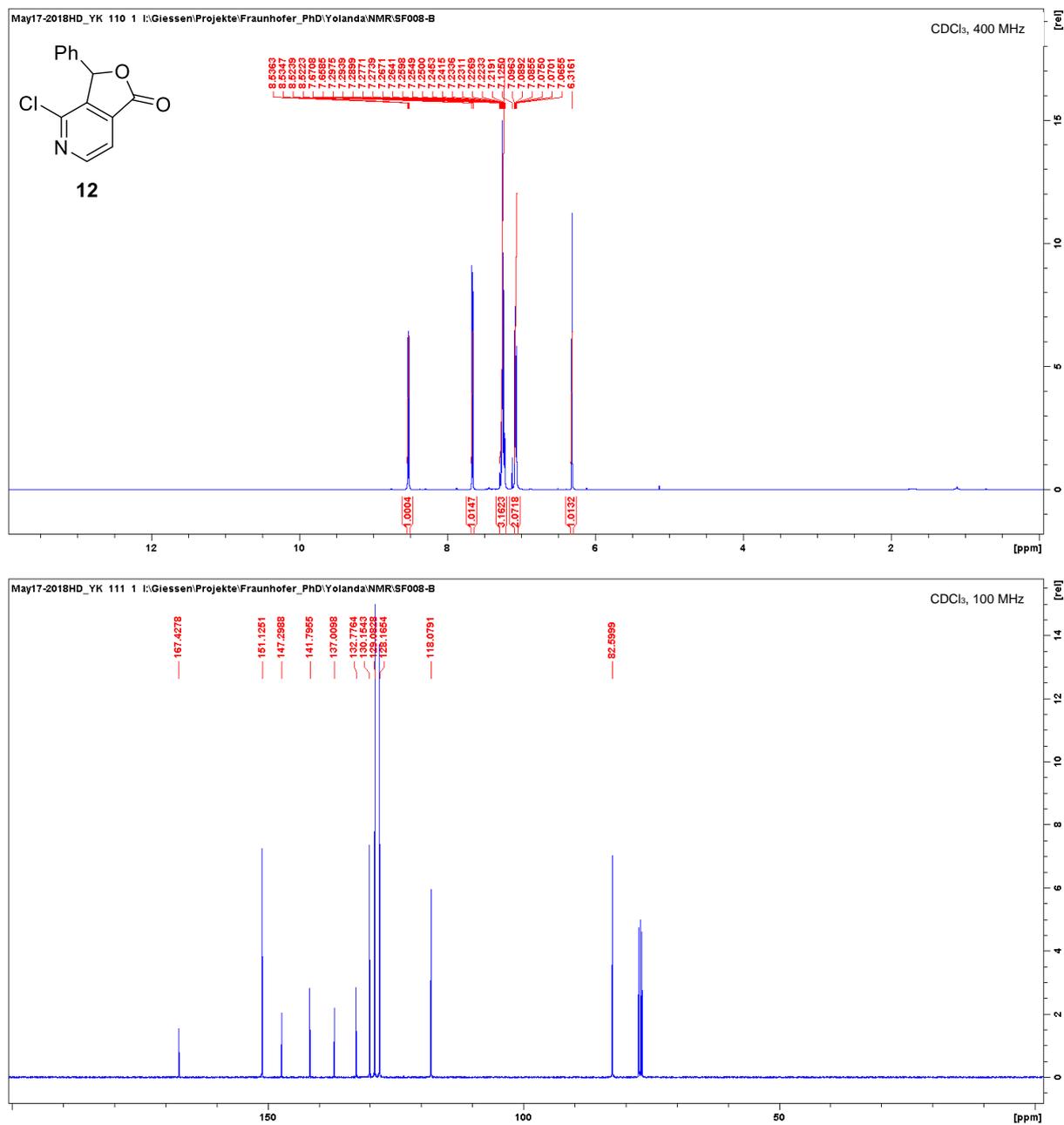


Figure S2. (*E*)-2-(Pent-1-en-1-yl)isonicotinic acid (**14**) (^1H - and ^{13}C -NMR in $\text{DMSO-}d_6$).

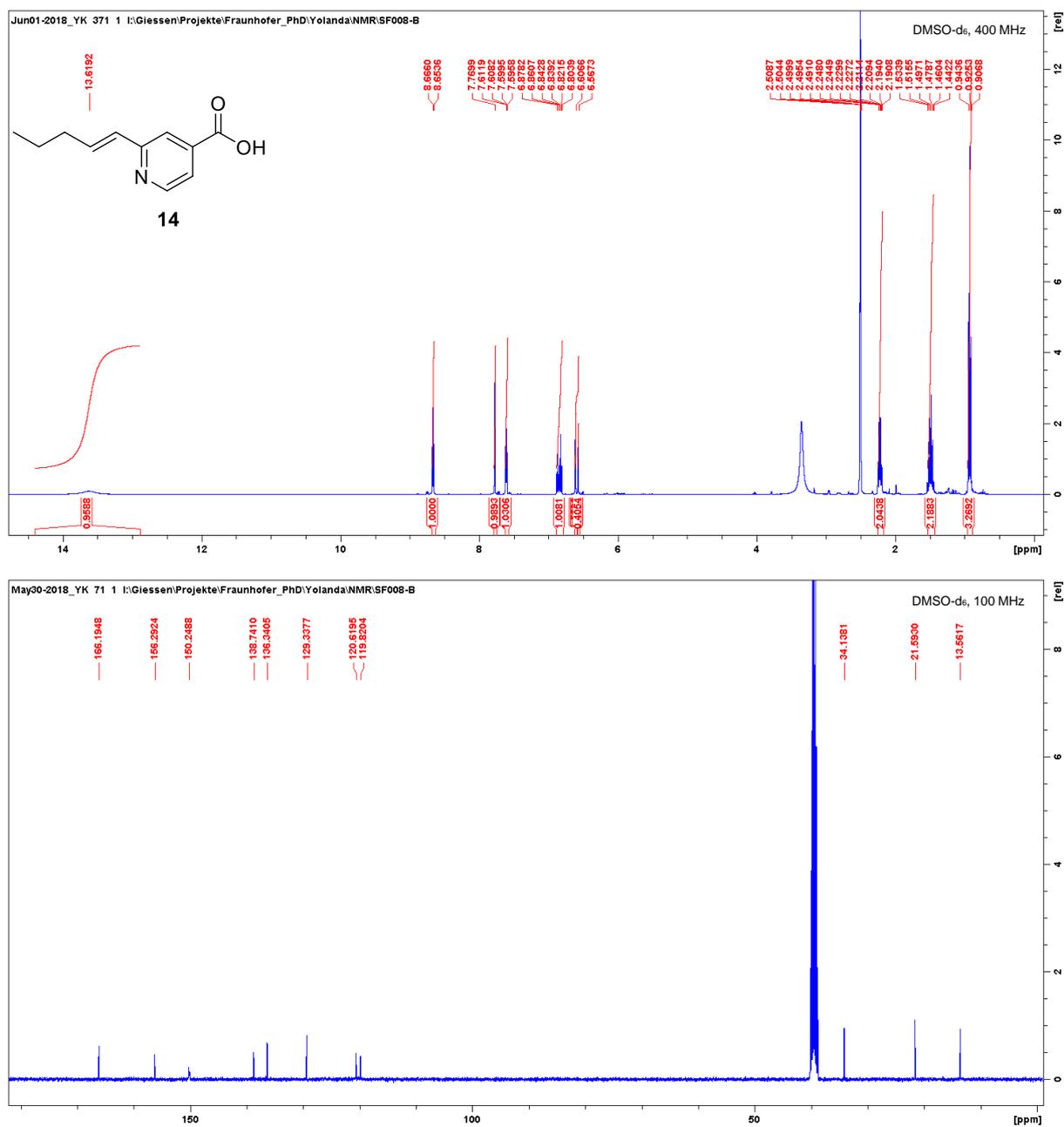


Figure S3. (*E*)-2-(Pent-1-en-1-yl)isonicotinic acid (**14**) (¹H- and ¹³C-NMR in CD₃OD).

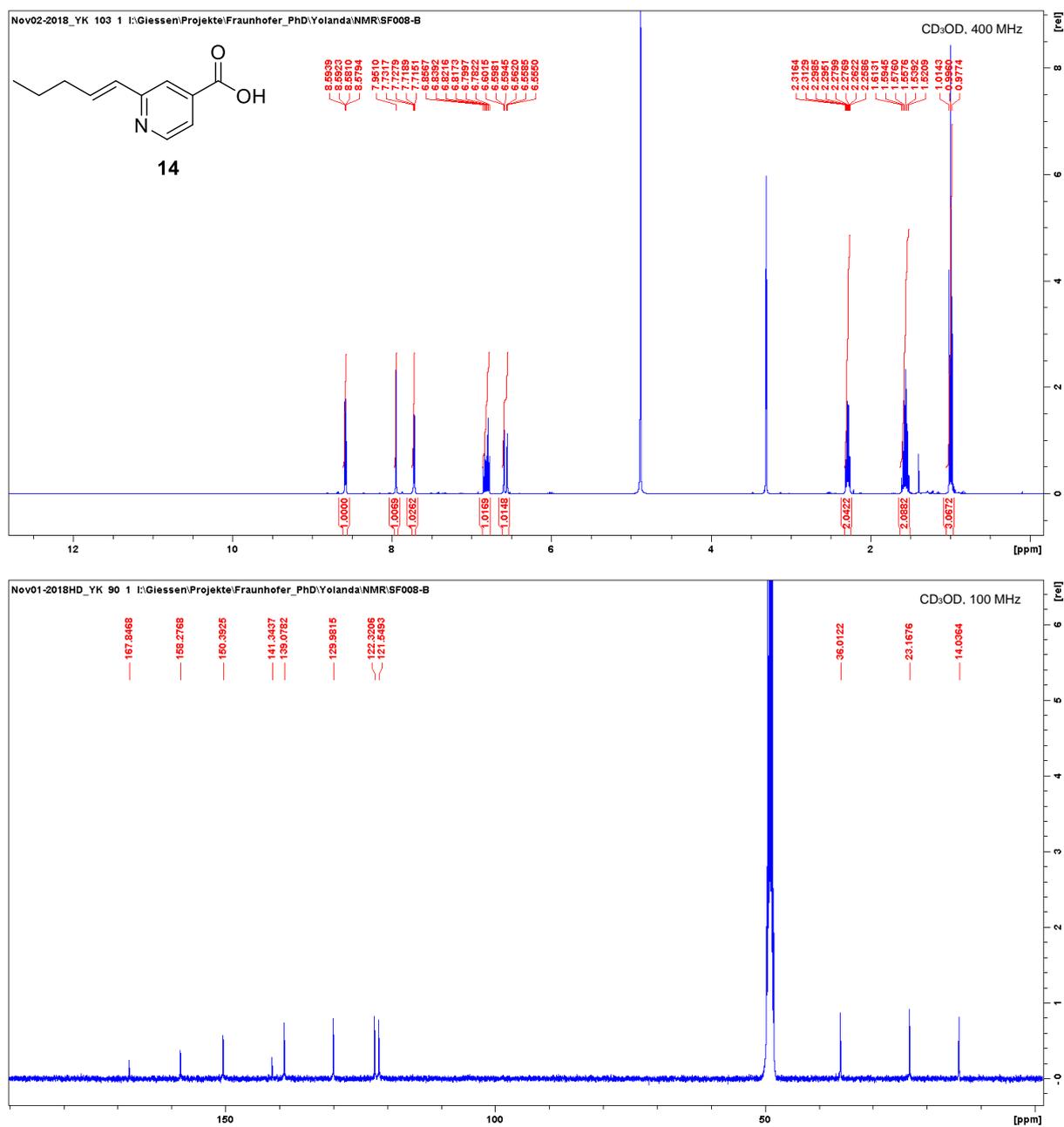


Figure S4. (*E*)-6-(Pent-1-en-1-yl)-3-phenylfuro[3,4-c]pyridin-1(3*H*)-one (**15**) (¹H- and ¹³C-NMR).

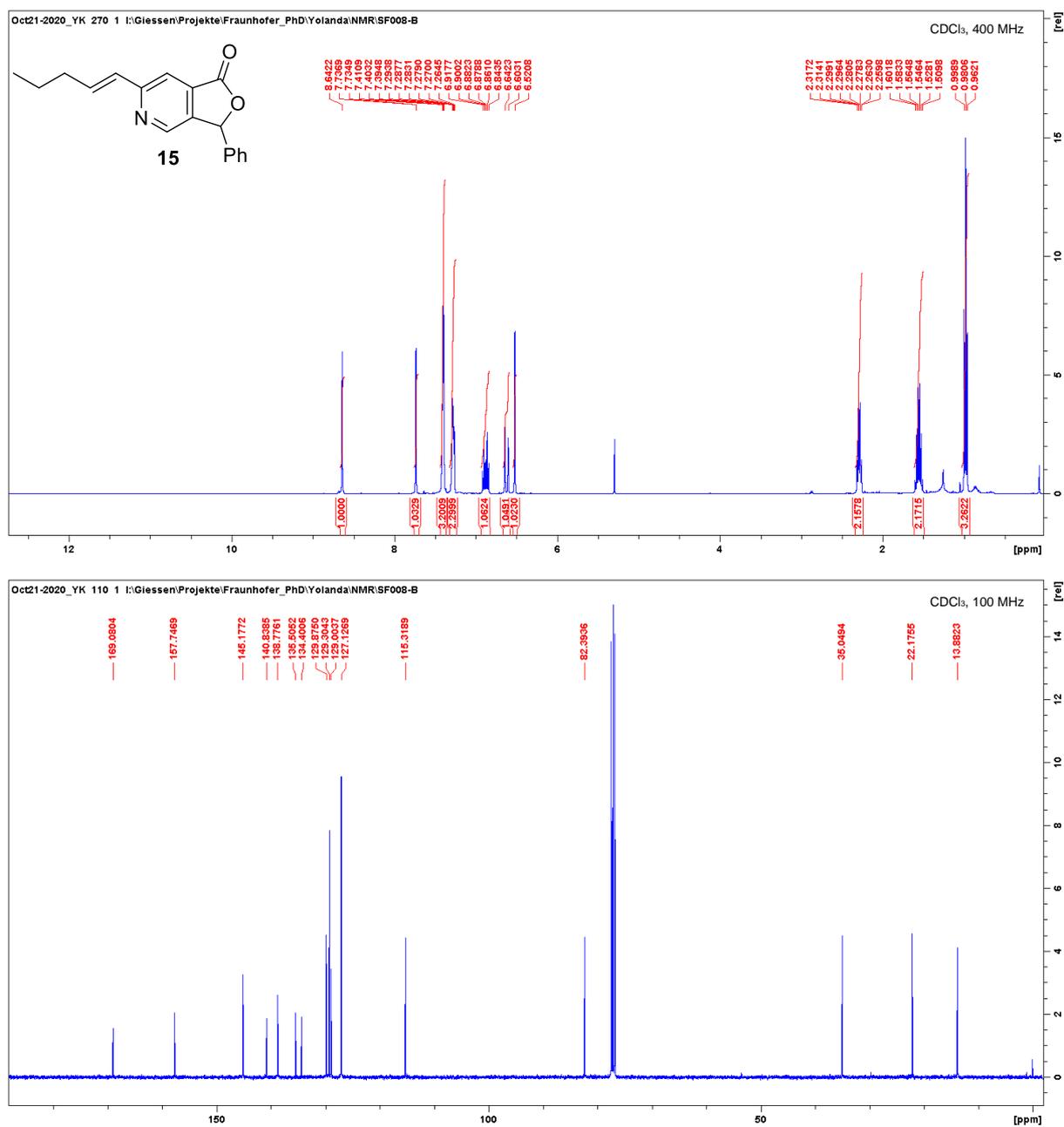


Figure S5. Diethyl 2-allyl-2-(3-methylbut-2-en-1-yl)malonate (**SI3**) (¹H- and ¹³C-NMR).

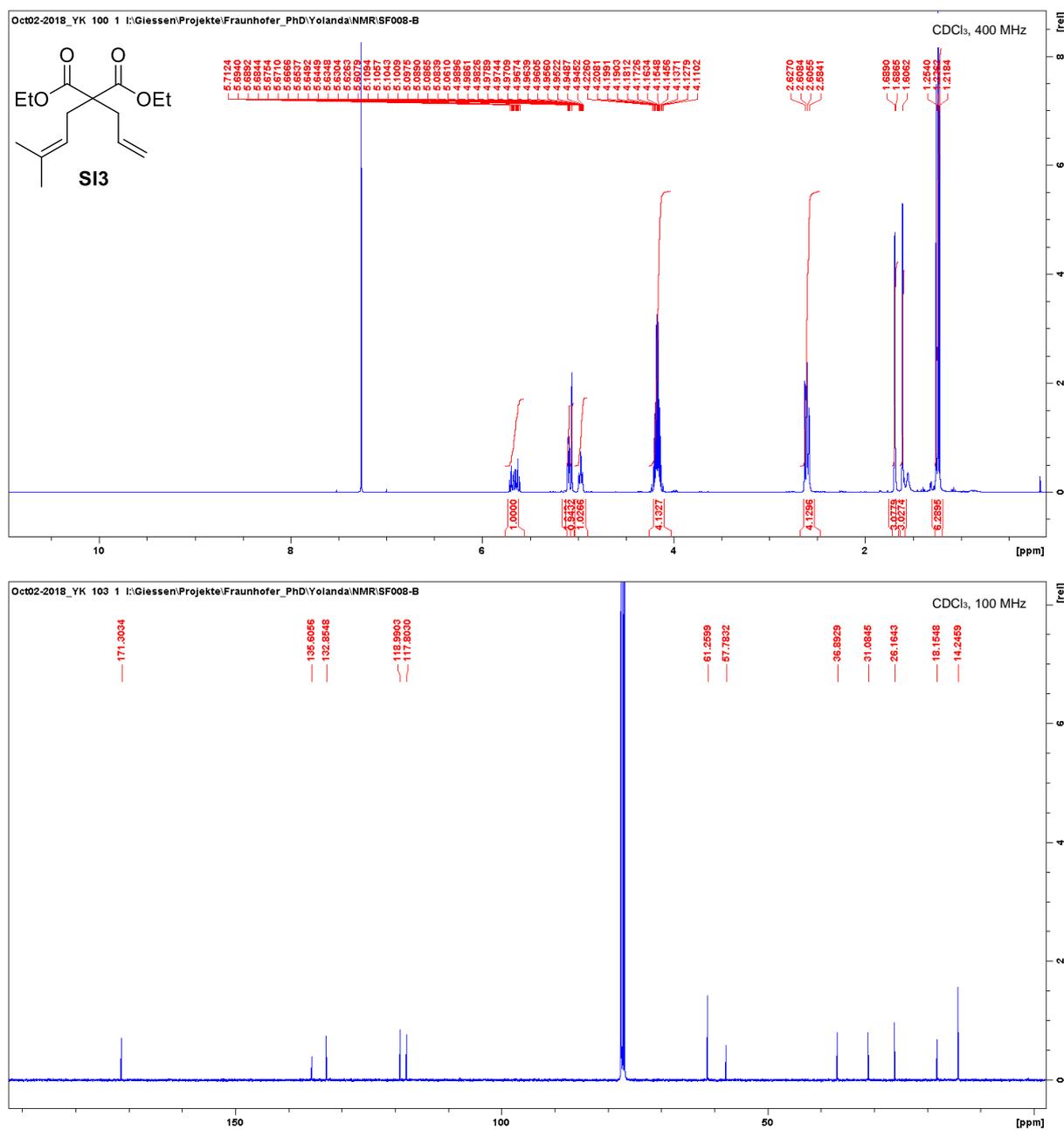


Figure S6. 1-(*tert*-Butyl) 2,2-diethyl 5-methylhex-4-ene-1,2,2-tricarboxylate (**SI4**) (^1H - and ^{13}C -NMR).

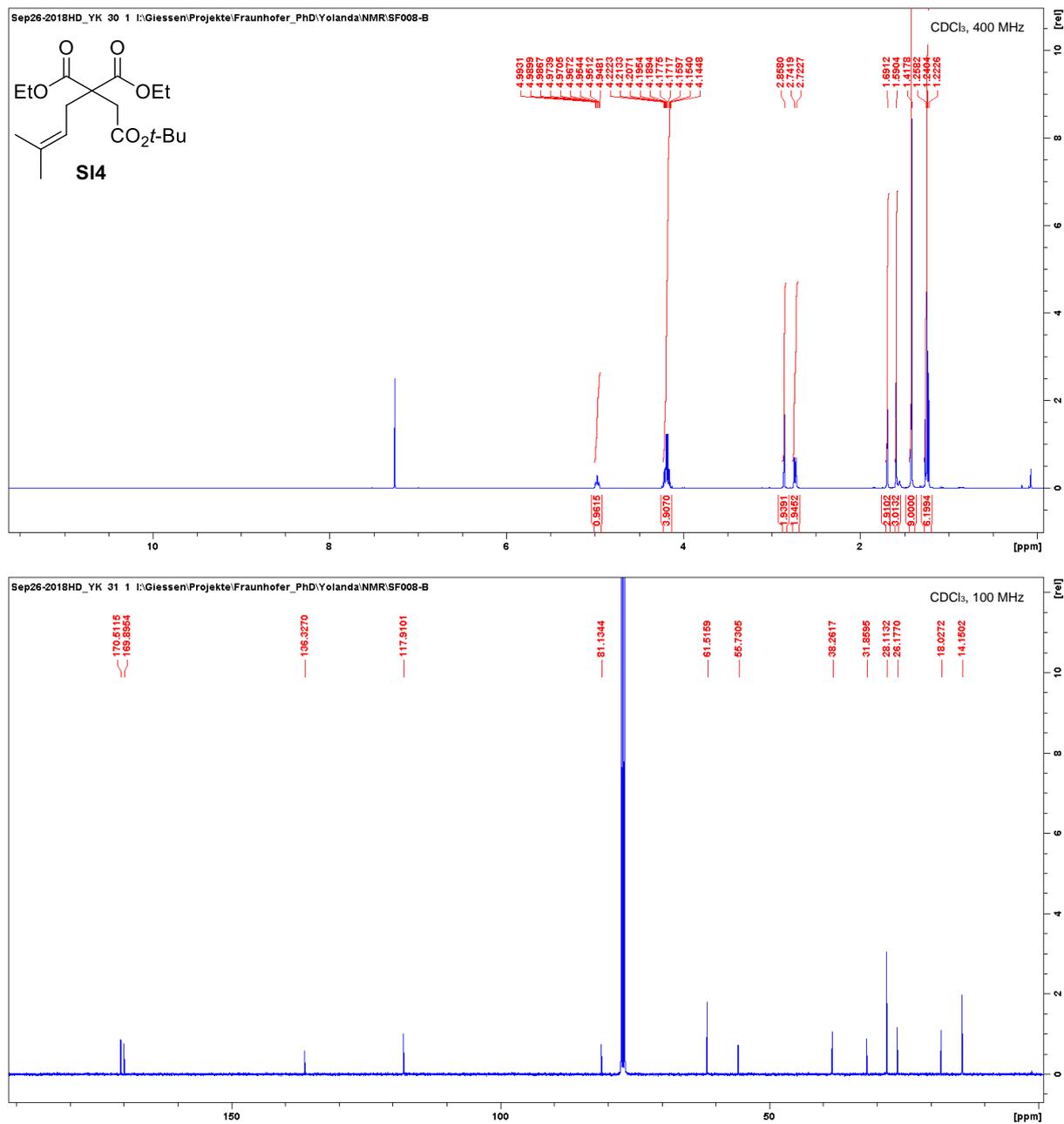


Figure S7. 2-(3-Methylbut-2-en-1-yl)malonic acid (**SI5**) (¹H- and ¹³C-NMR).

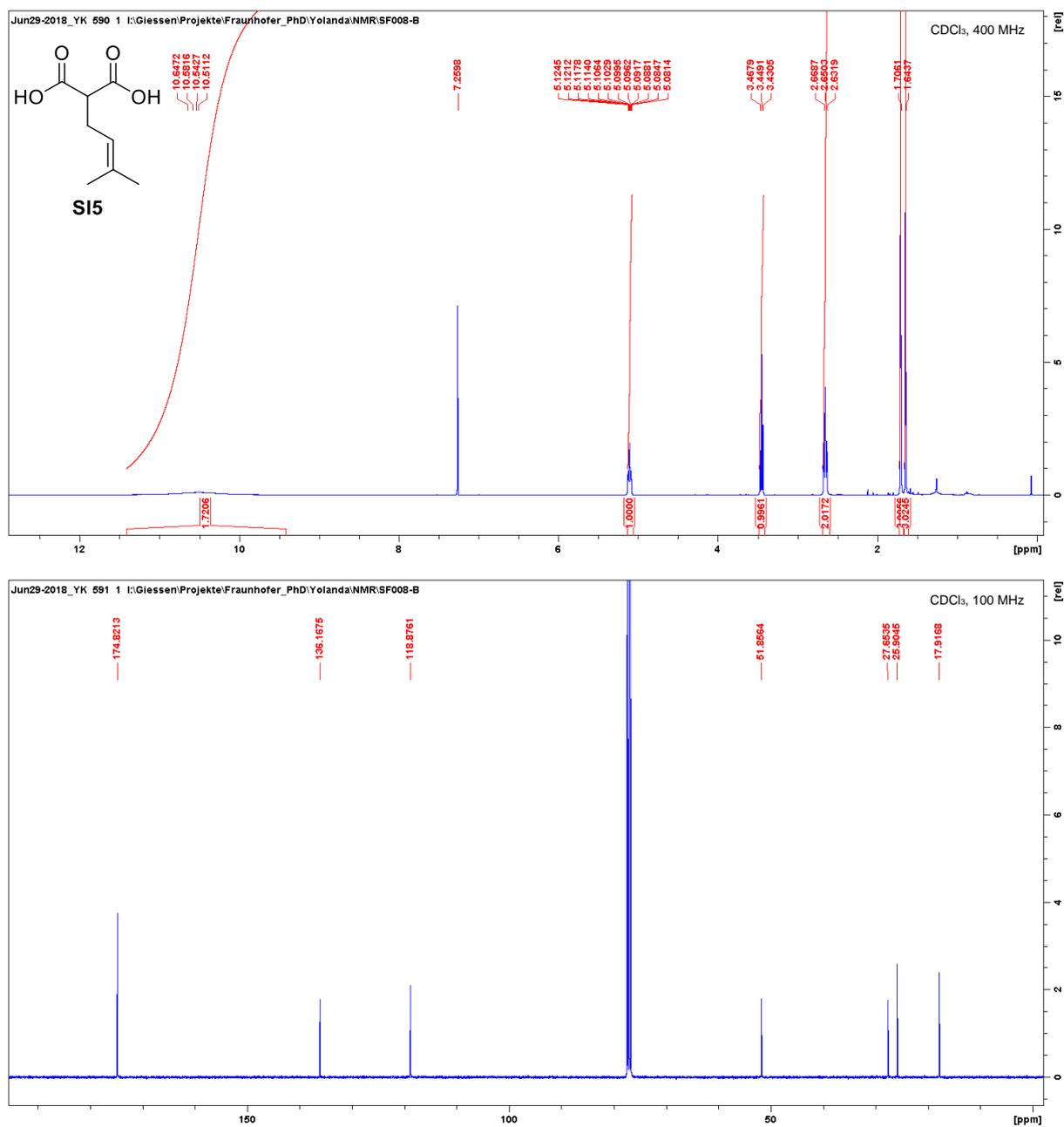


Figure S8. 5-Methylhex-4-enoic acid (**SI6**) (^1H - and ^{13}C -NMR).

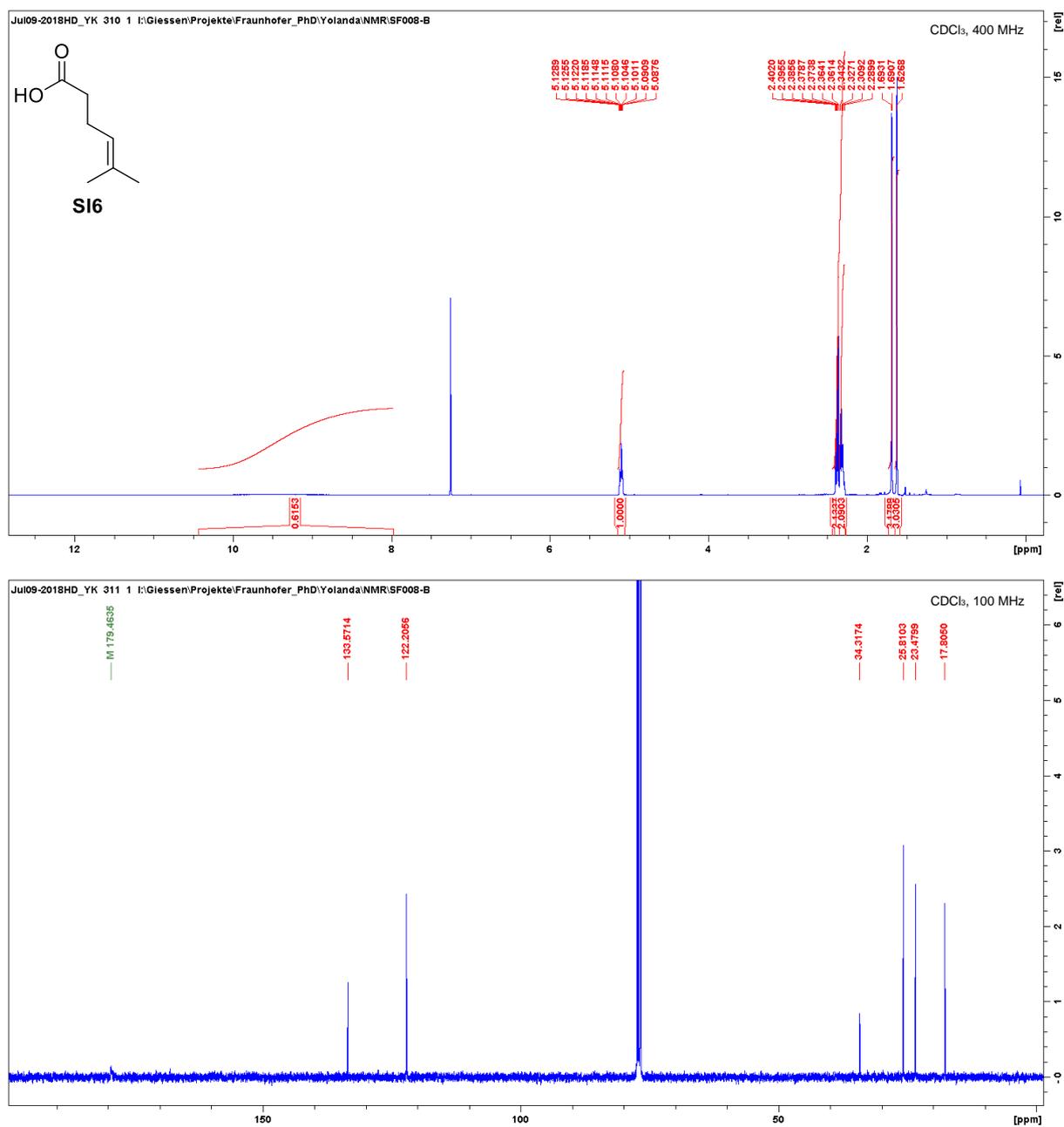


Figure S9. *N*-Methoxy-*N*,5-dimethylhex-4-enamide (**21**) (^1H - and ^{13}C -NMR).

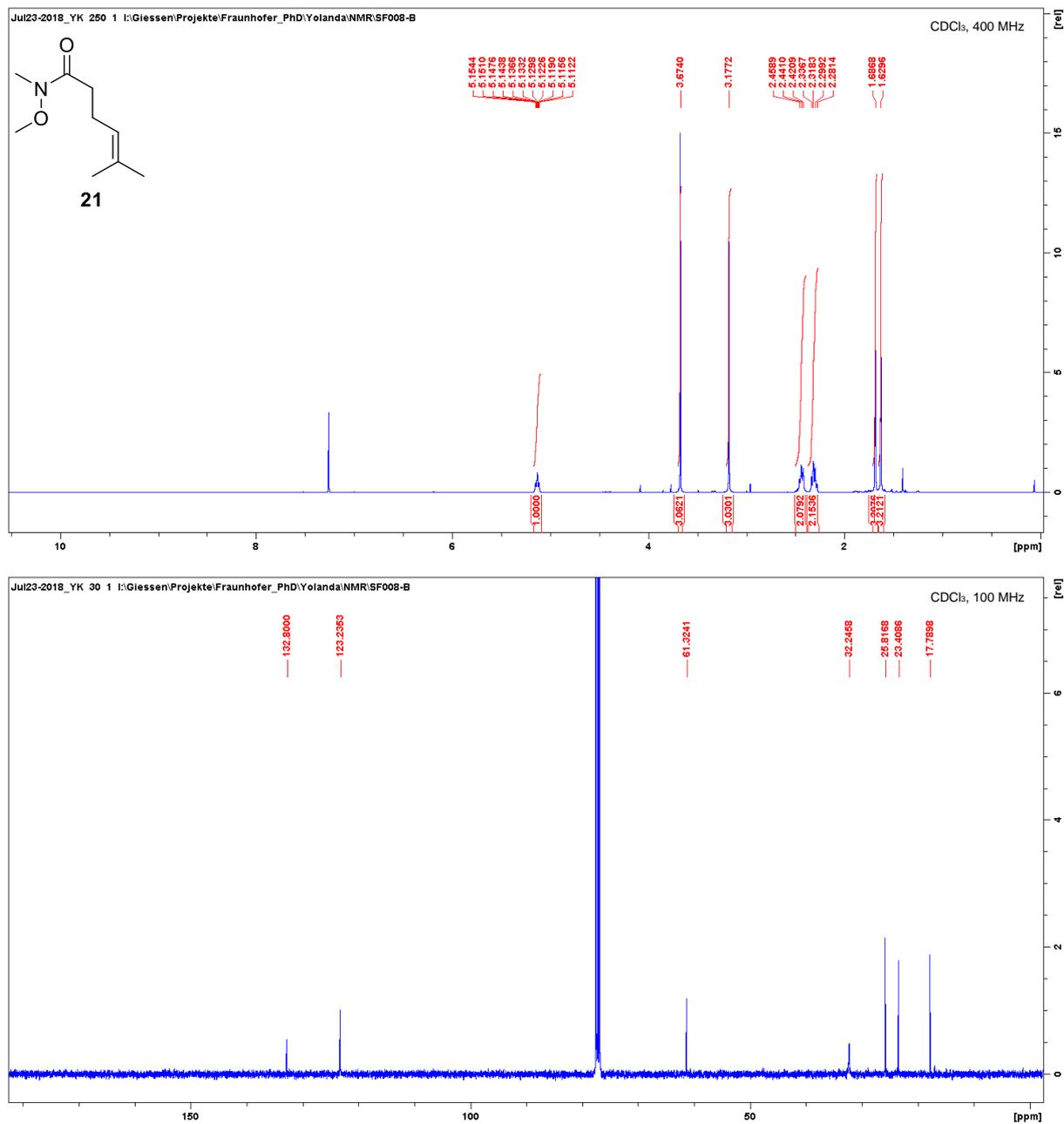


Figure S10. 2-Allyl-*N*-methoxy-*N*,5-dimethylhex-4-enamide (**22**) (¹H- and ¹³C-NMR).

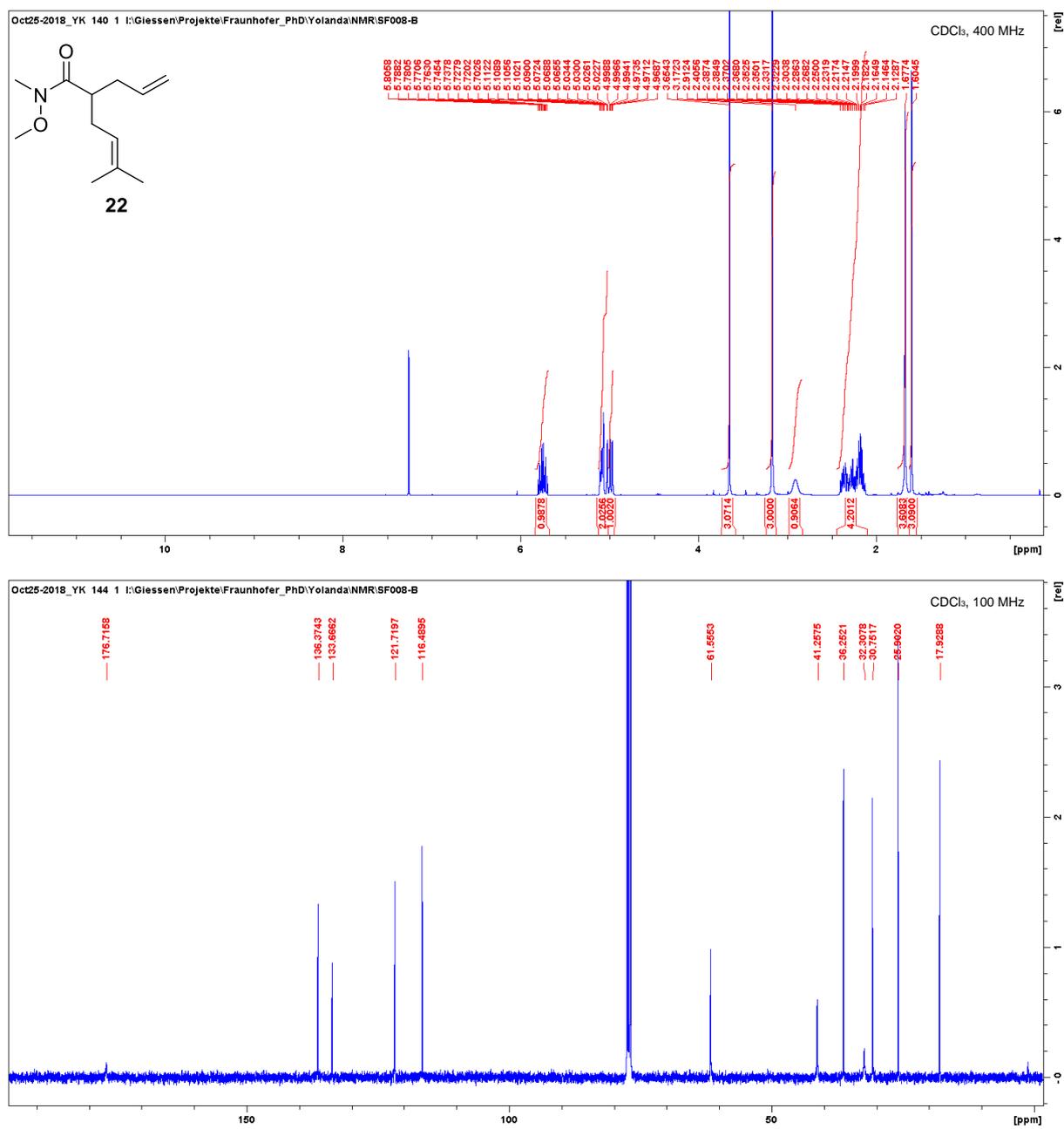


Figure S11. 2-Allyl-2-(3-methylbut-2-en-1-yl)malonic acid (**S17**) (¹H- and ¹³C-NMR).

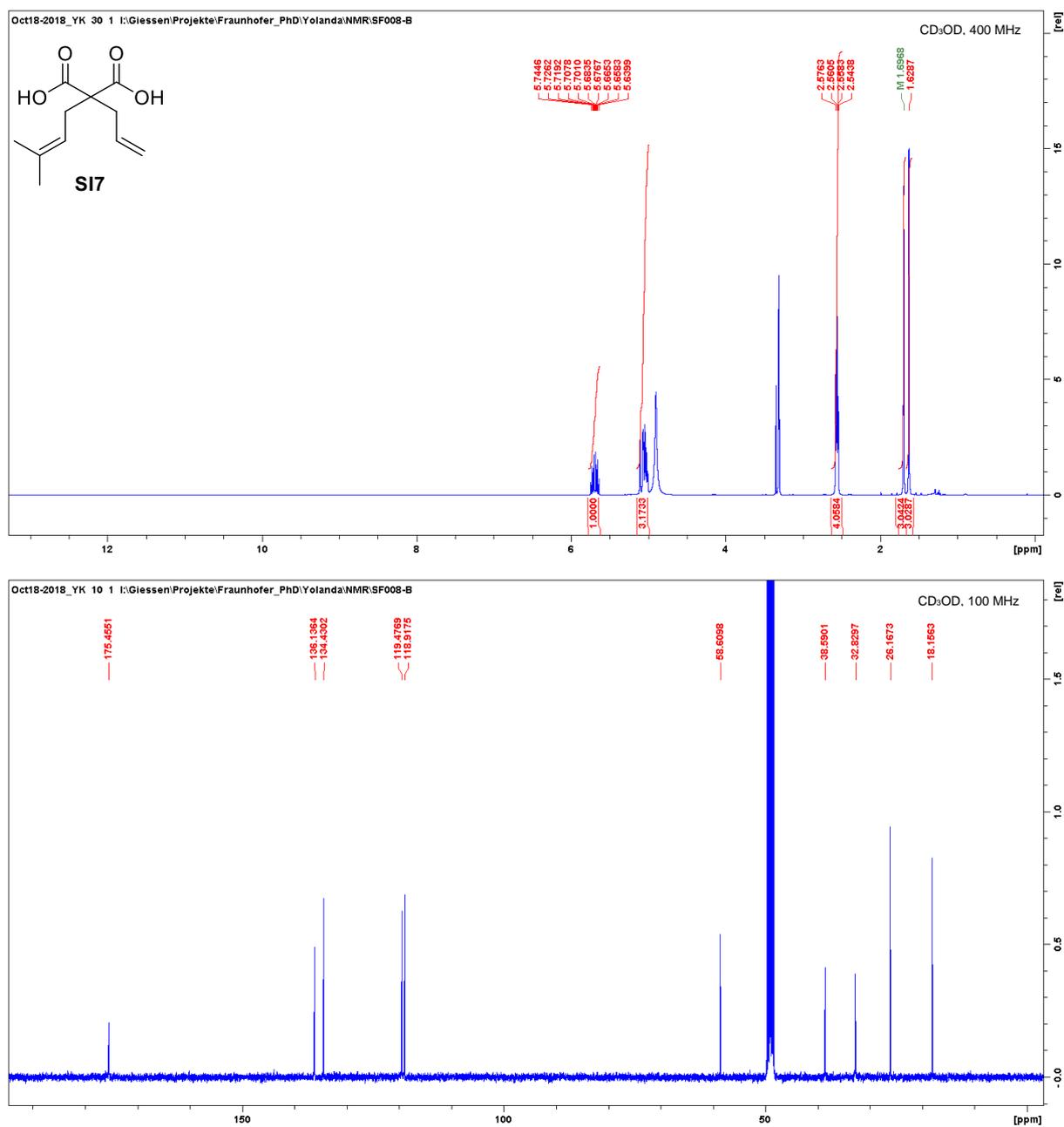


Figure S12. 2-Allyl-5-methylhex-4-enoic acid (**SI8**) (^1H - and ^{13}C -NMR).

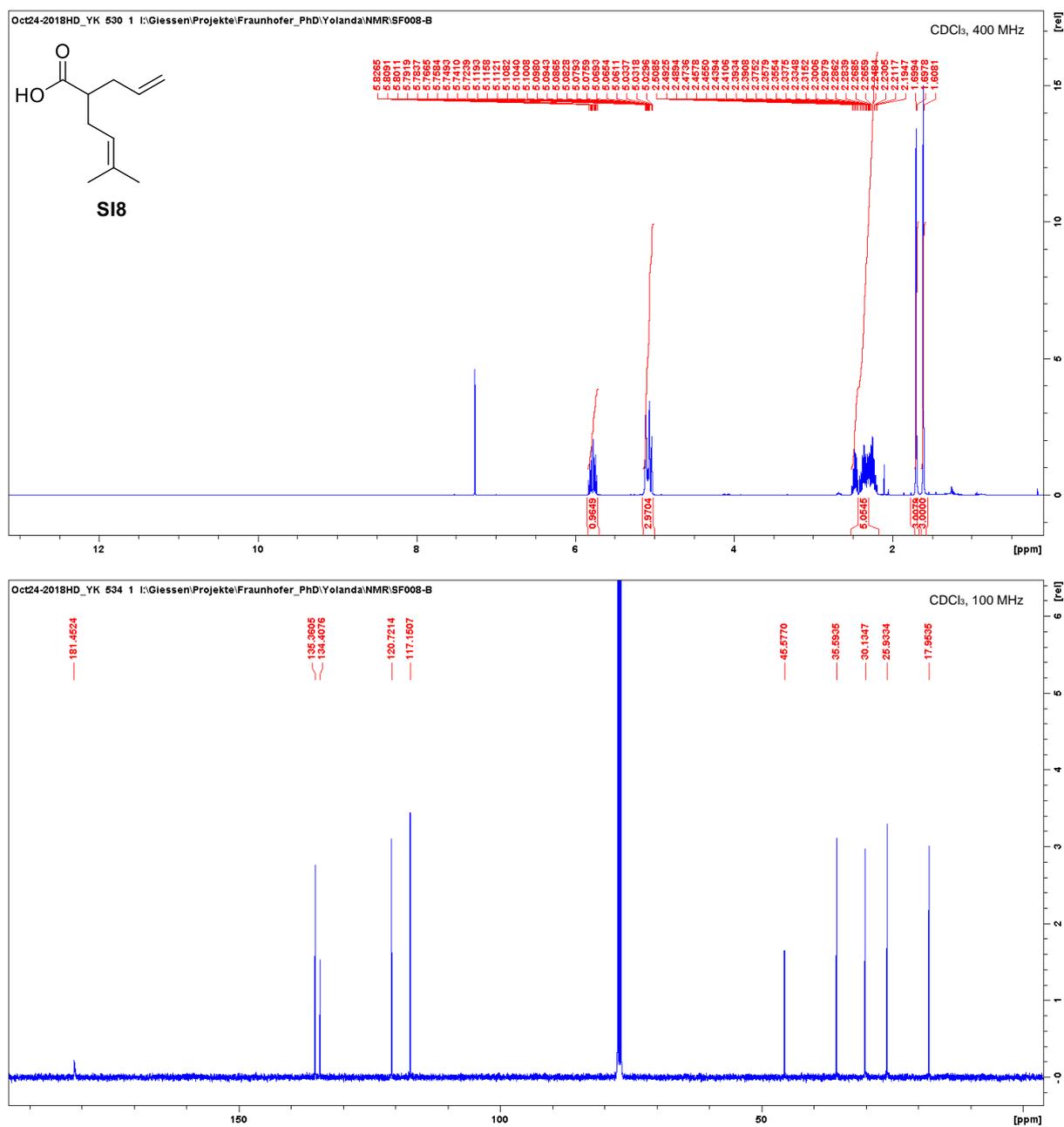


Figure S13. *tert*-Butyl 3-(methoxy(methyl)carbamoyl)-6-methylhept-5-enoate (**23**) (¹H- and ¹³C-NMR).

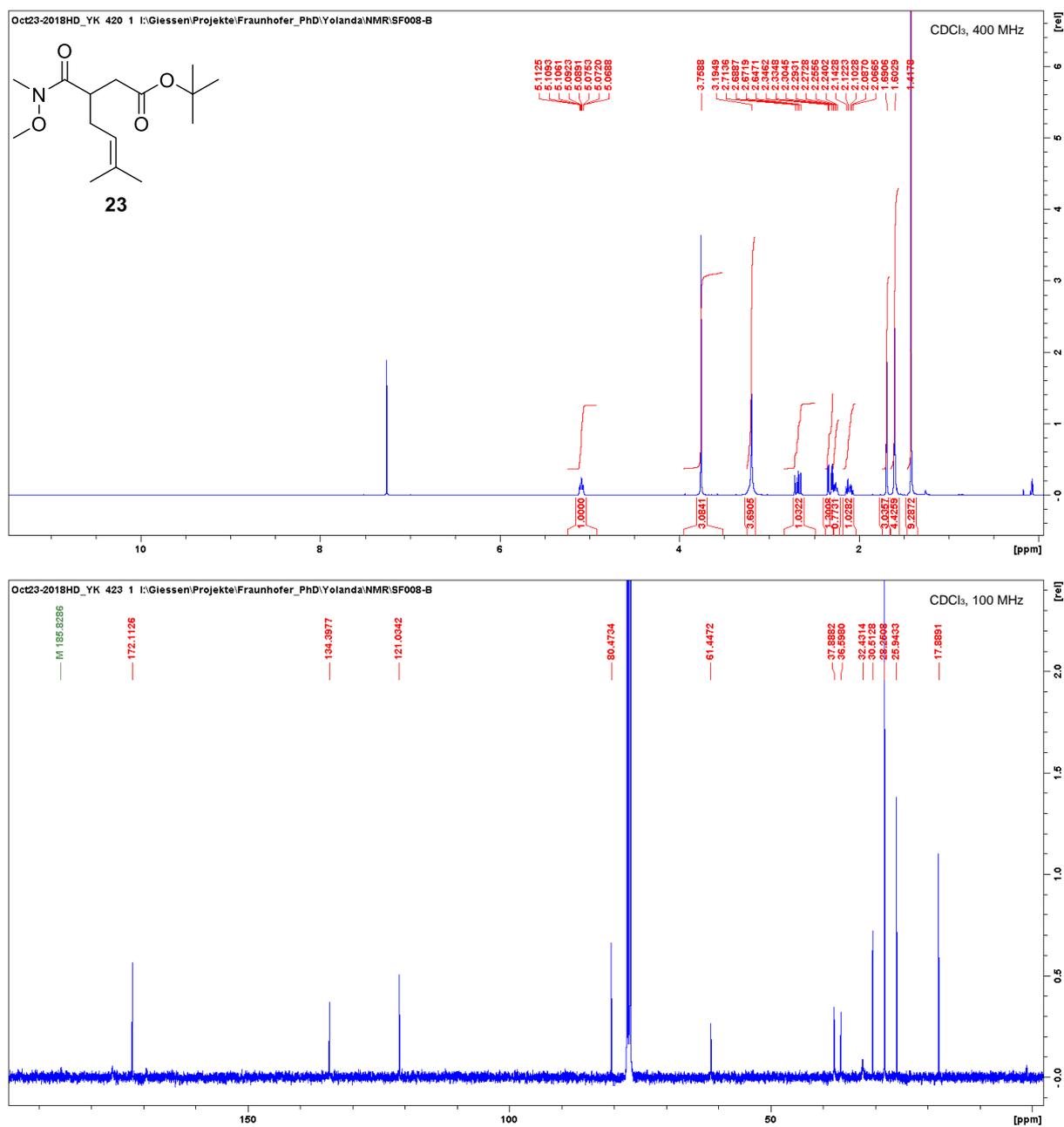


Figure S14. 2-(2-(*tert*-Butoxy)-2-oxoethyl)-2-(3-methylbut-2-en-1-yl)malonic acid (**S19**) (^1H - and ^{13}C -NMR).

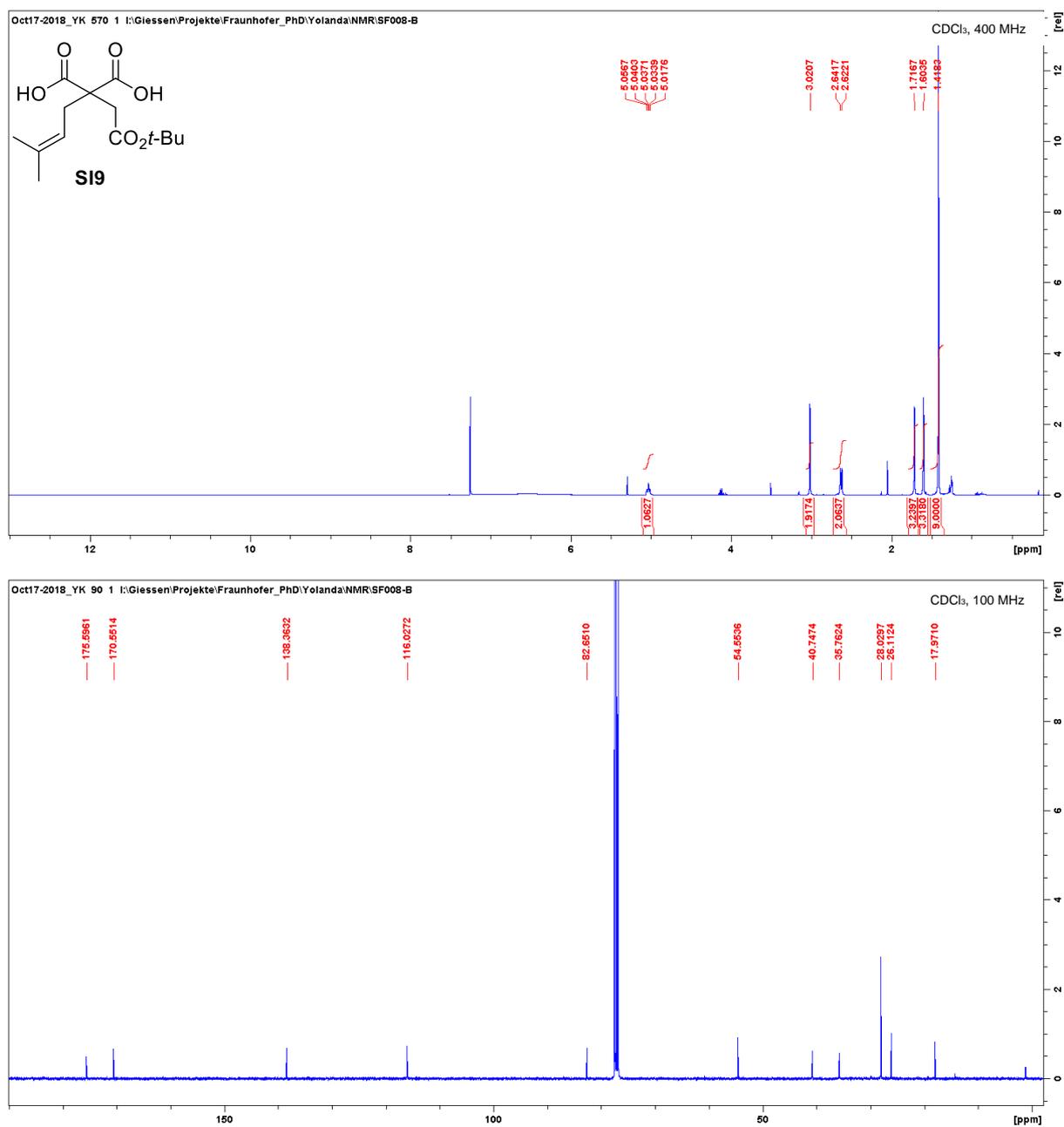


Figure S15. 2-(2-(*tert*-Butoxy)-2-oxoethyl)-5-methylhex-4-enoic acid (**SI10**) (¹H- and ¹³C-NMR).

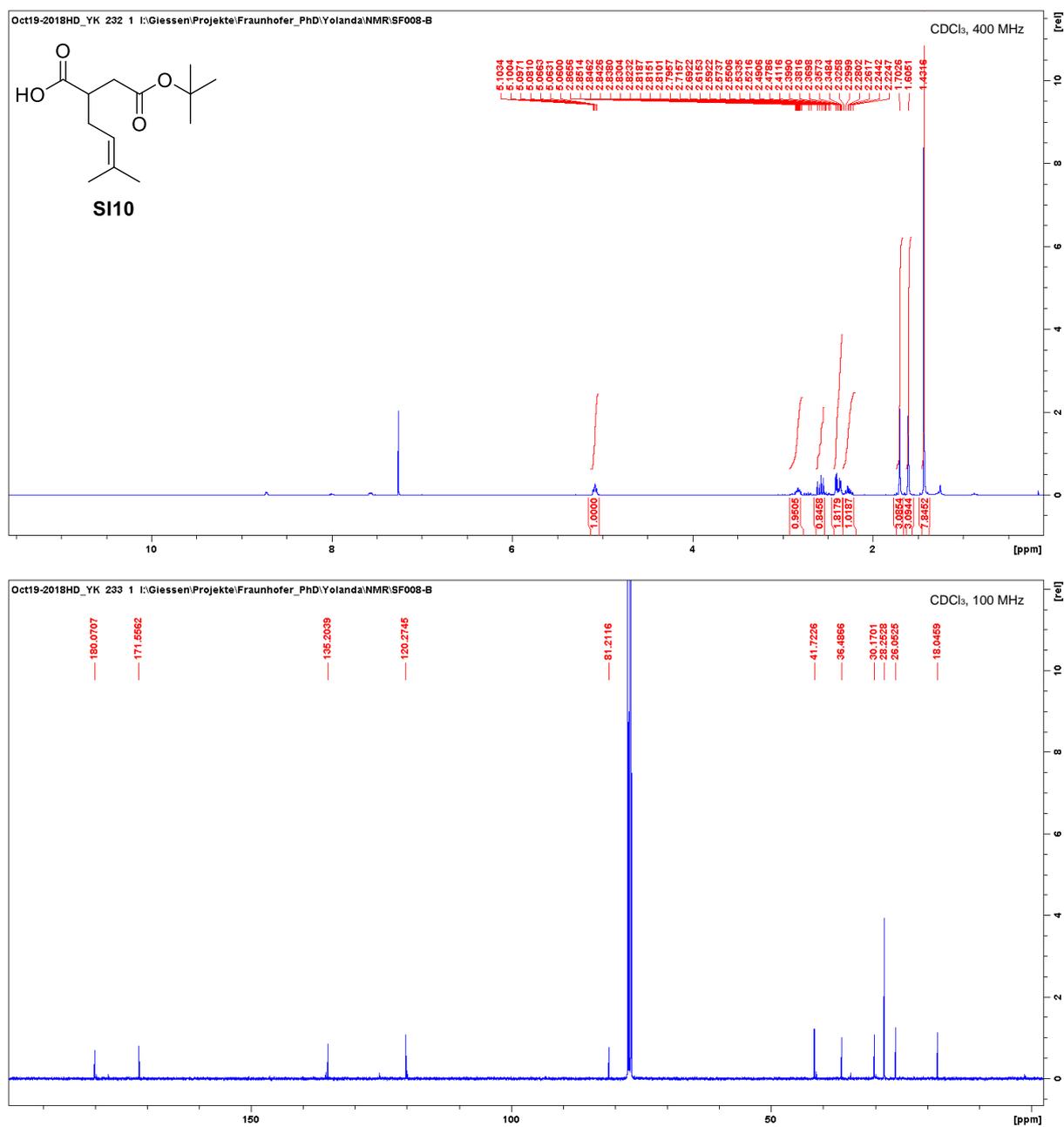


Figure S16. 1-(5-Bromo-2-chloropyridin-4-yl)-5-methylhex-4-en-1-one (**24**) (¹H- and ¹³C-NMR).

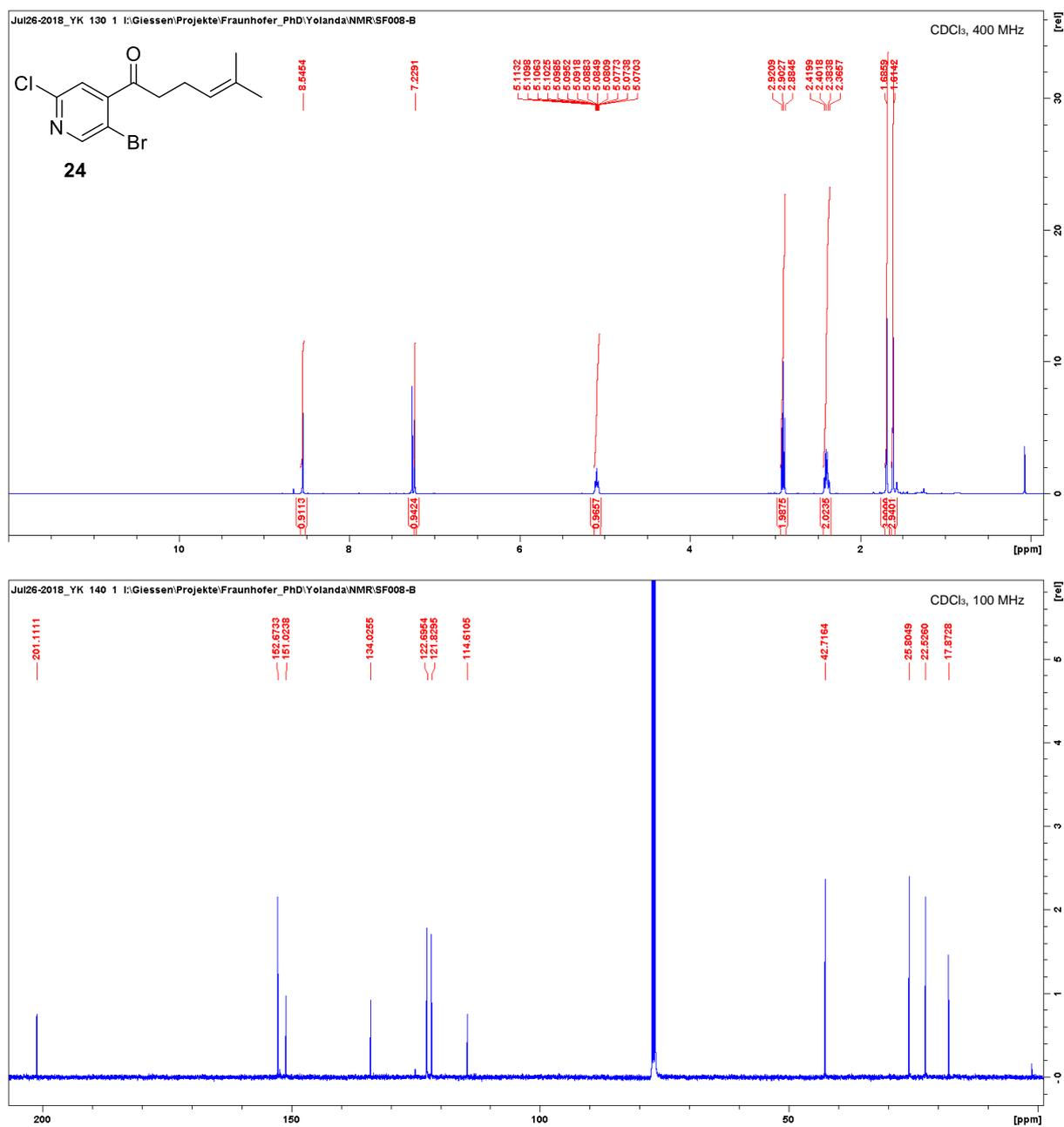


Figure S17. 2-Allyl-1-(5-bromo-2-chloropyridin-4-yl)-5-methylhex-4-en-1-one (**25**) (¹H- and ¹³C-NMR).

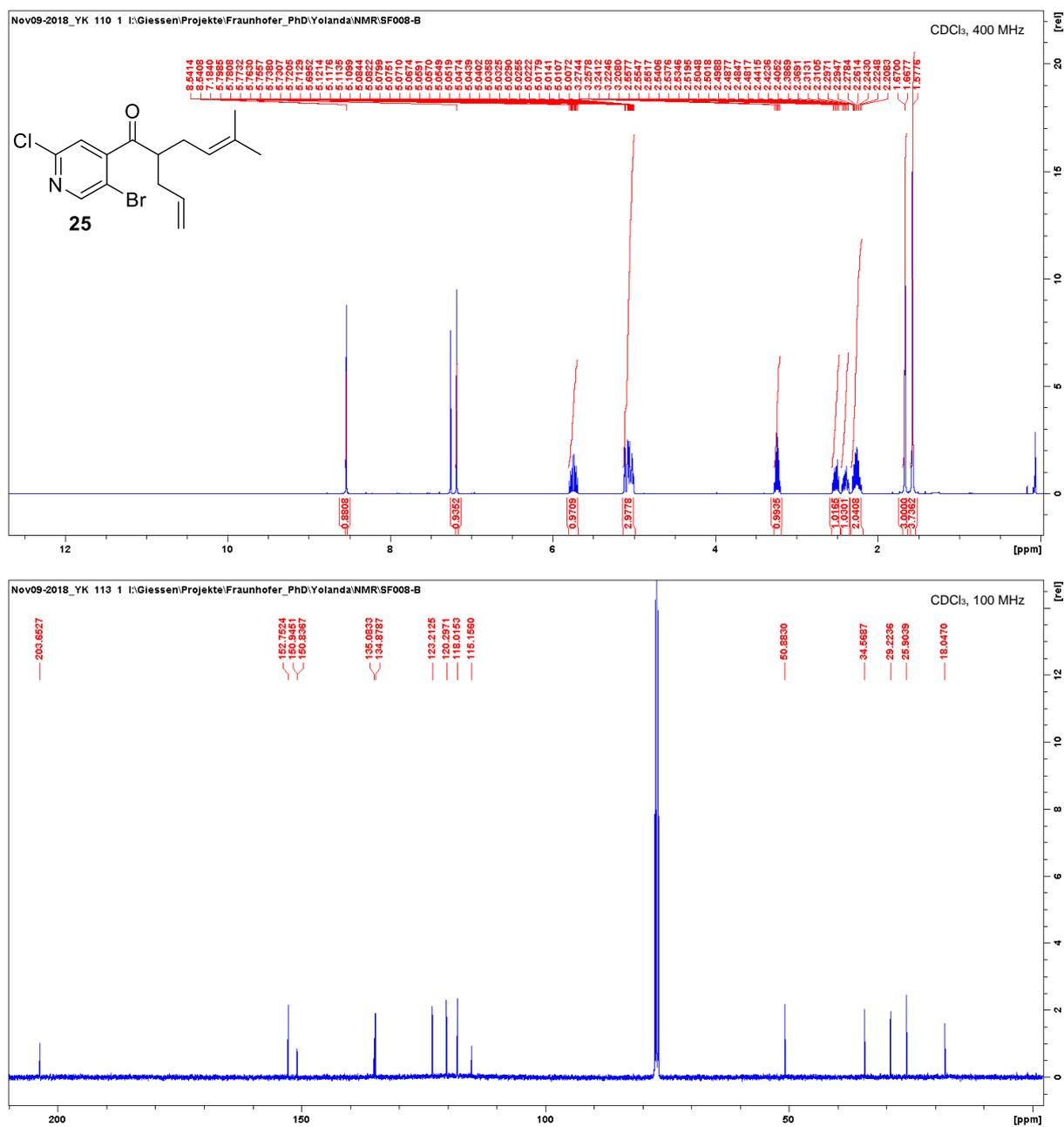


Figure S18. *tert*-Butyl 3-(5-bromo-2-chloroisonicotinoyl)-6-methylhept-5-enoate (**26**) (¹H- and ¹³C-NMR).

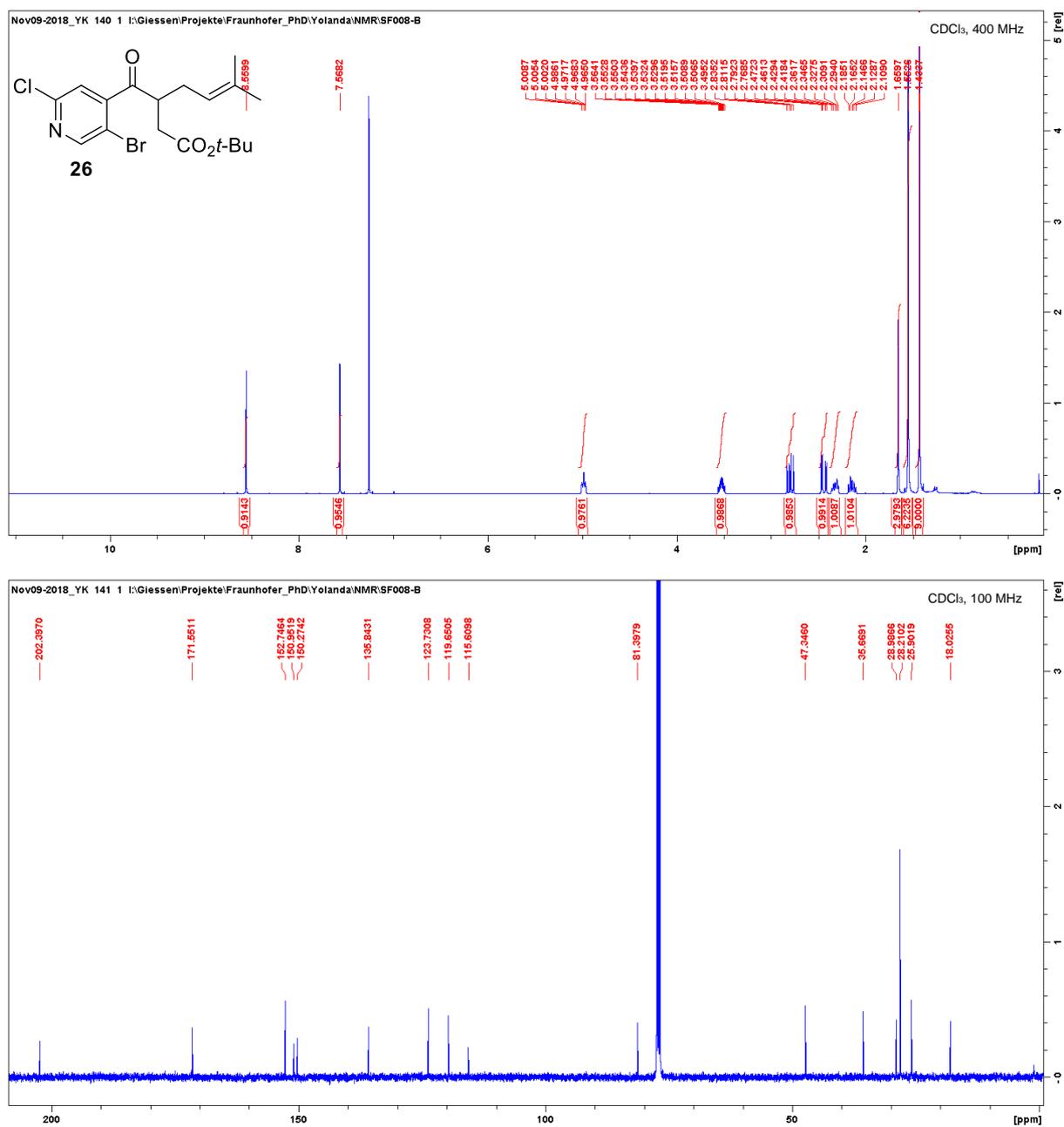


Figure S19. 3-Chloro-6-(3-methylbut-2-en-1-yl)-8-methylene-7,8-dihydroisoquinolin-5(6*H*)-one (**27**) (¹H- and ¹³C-NMR).

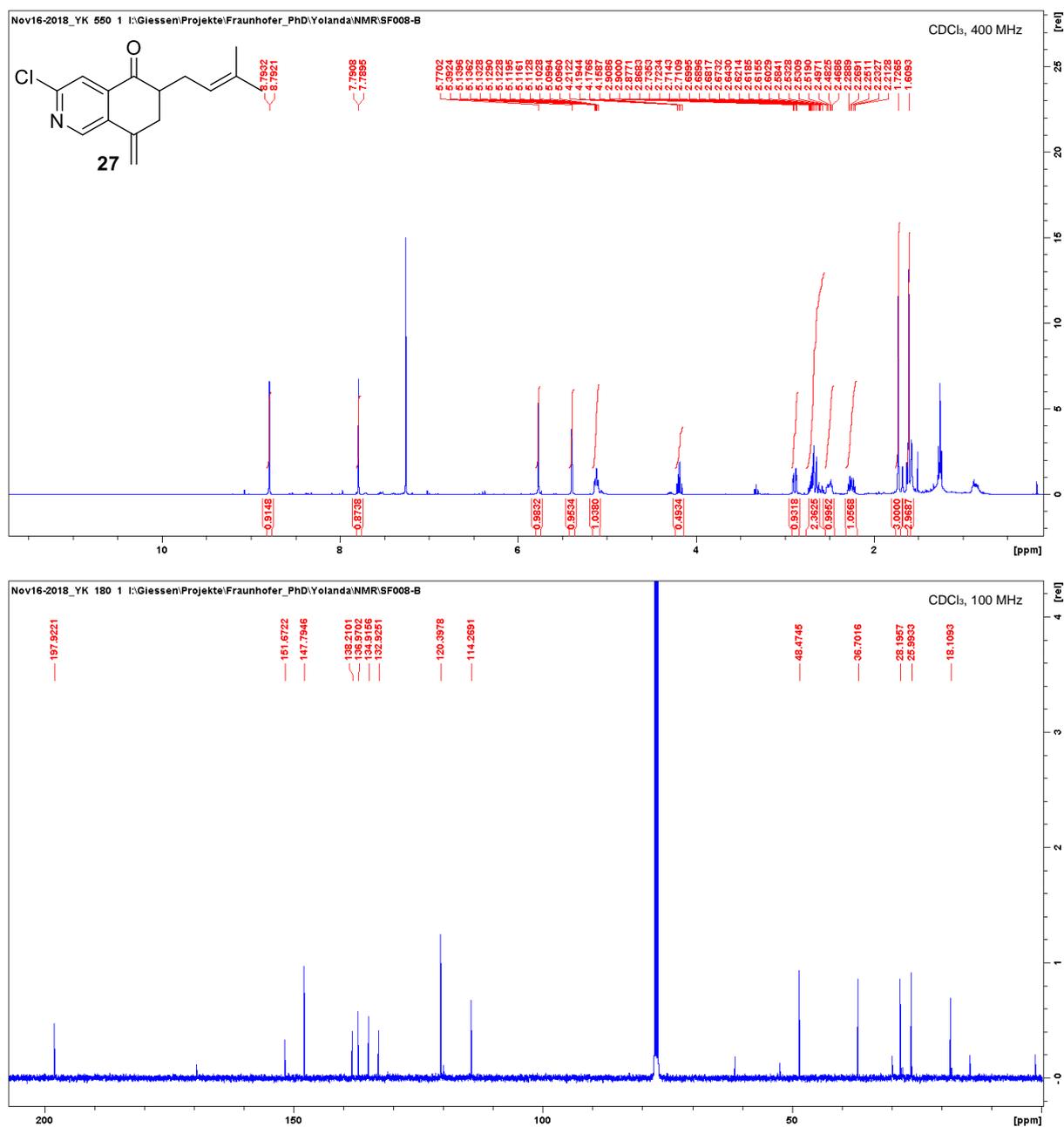


Figure S20. 3-Chloro-8-methyl-6-(3-methylbut-2-en-1-yl)isoquinolin-5-ol (**28**) (^1H - and ^{13}C -NMR).

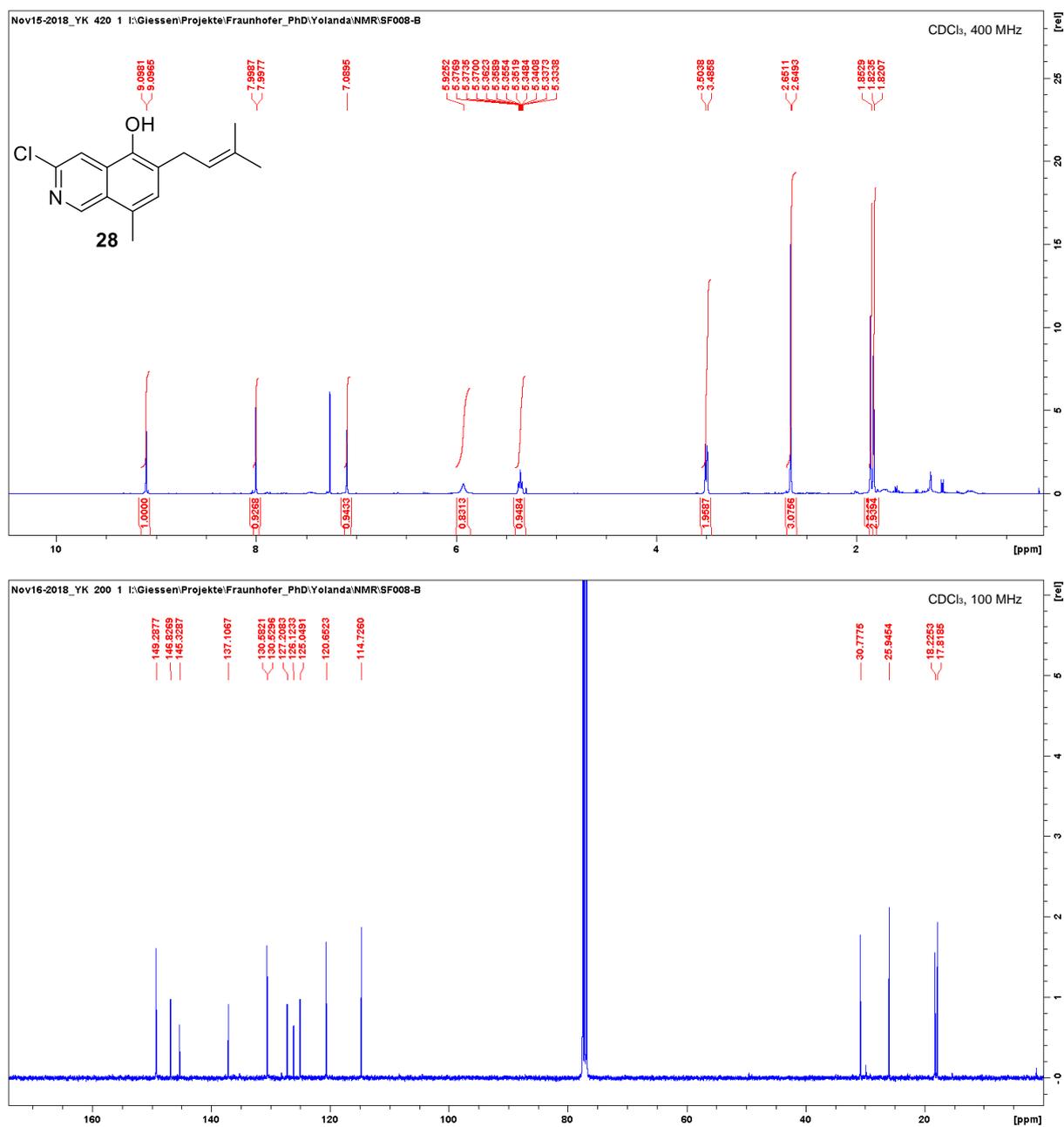


Figure S22. (5*R*,6*S*)-3-Chloro-6-(3-methylbut-2-en-1-yl)-5-((triisopropylsilyl)oxy)-6,7-dihydroisoquinolin-8(5*H*)-one (**31**) (¹H- and ¹³C-NMR).

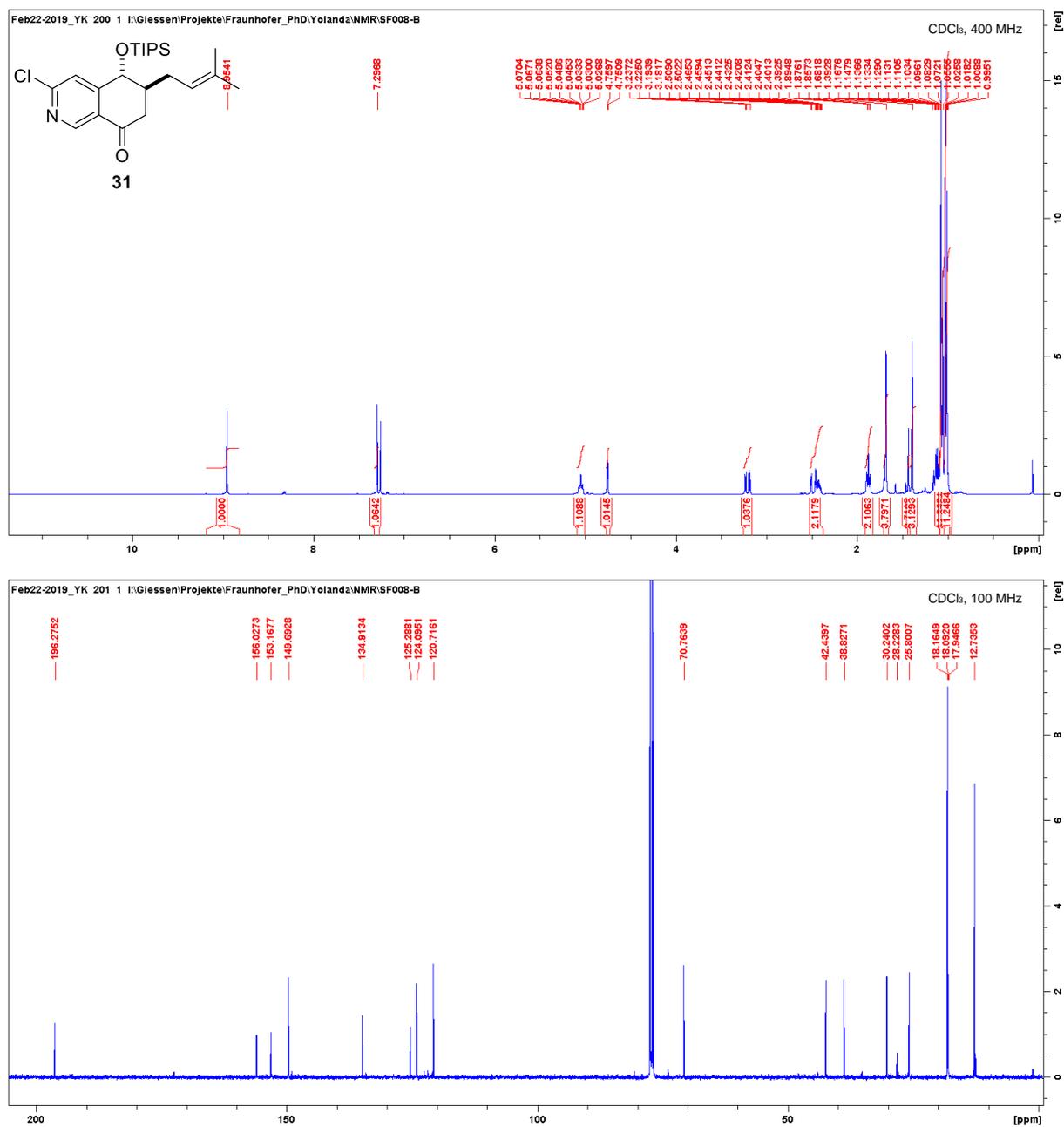


Figure S23. *tert*-Butyl 3-((2-chloropyridin-4-yl)((triisopropylsilyl)oxy)methyl)-6-methylhept-5-enoate (**30**) (¹H- and ¹³C-NMR).

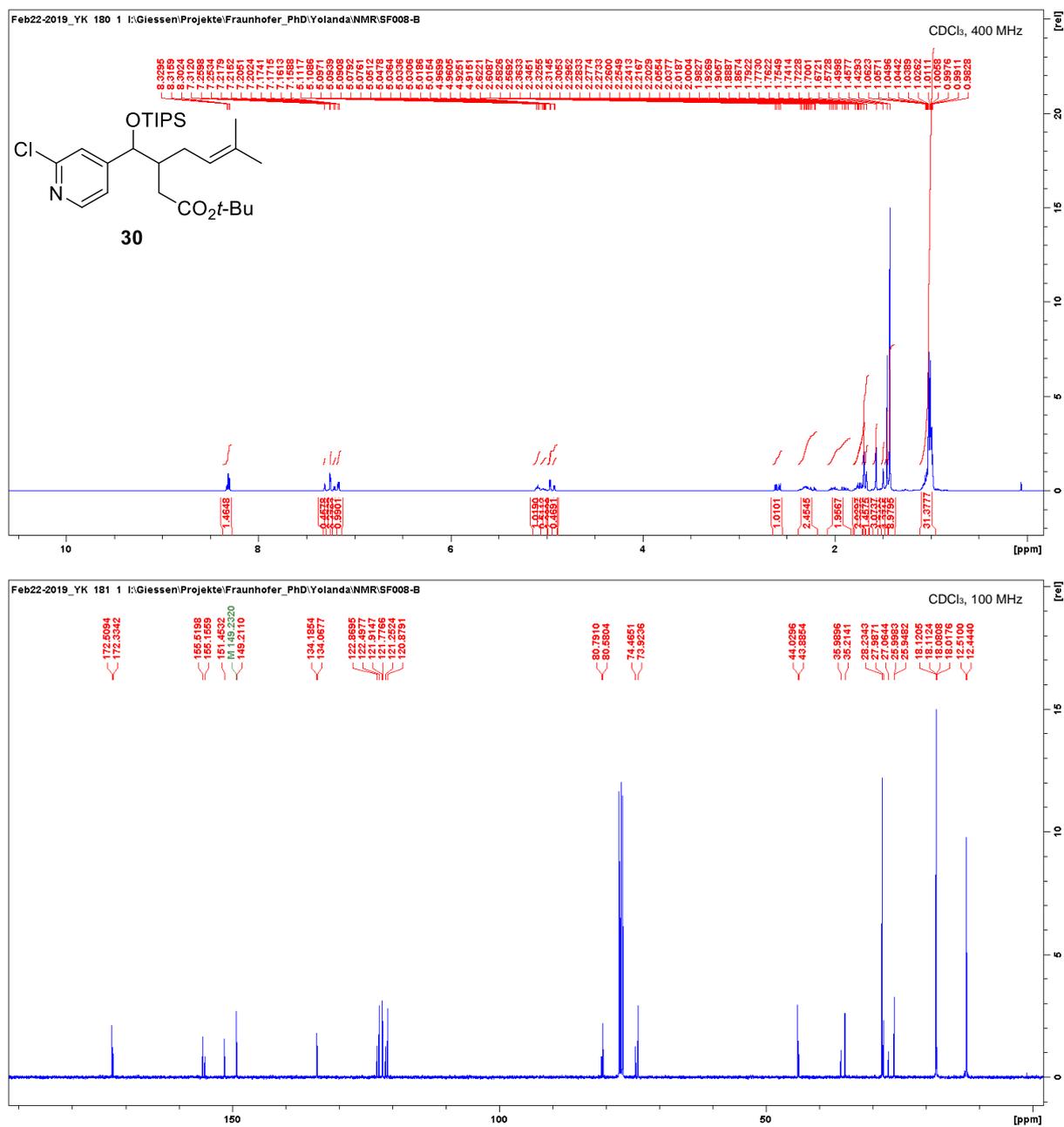


Figure S24. 1-(5-Bromo-2-chloropyridin-4-yl)-5-methylhex-4-en-1-ol (SI11) (¹H- and ¹³C-NMR).

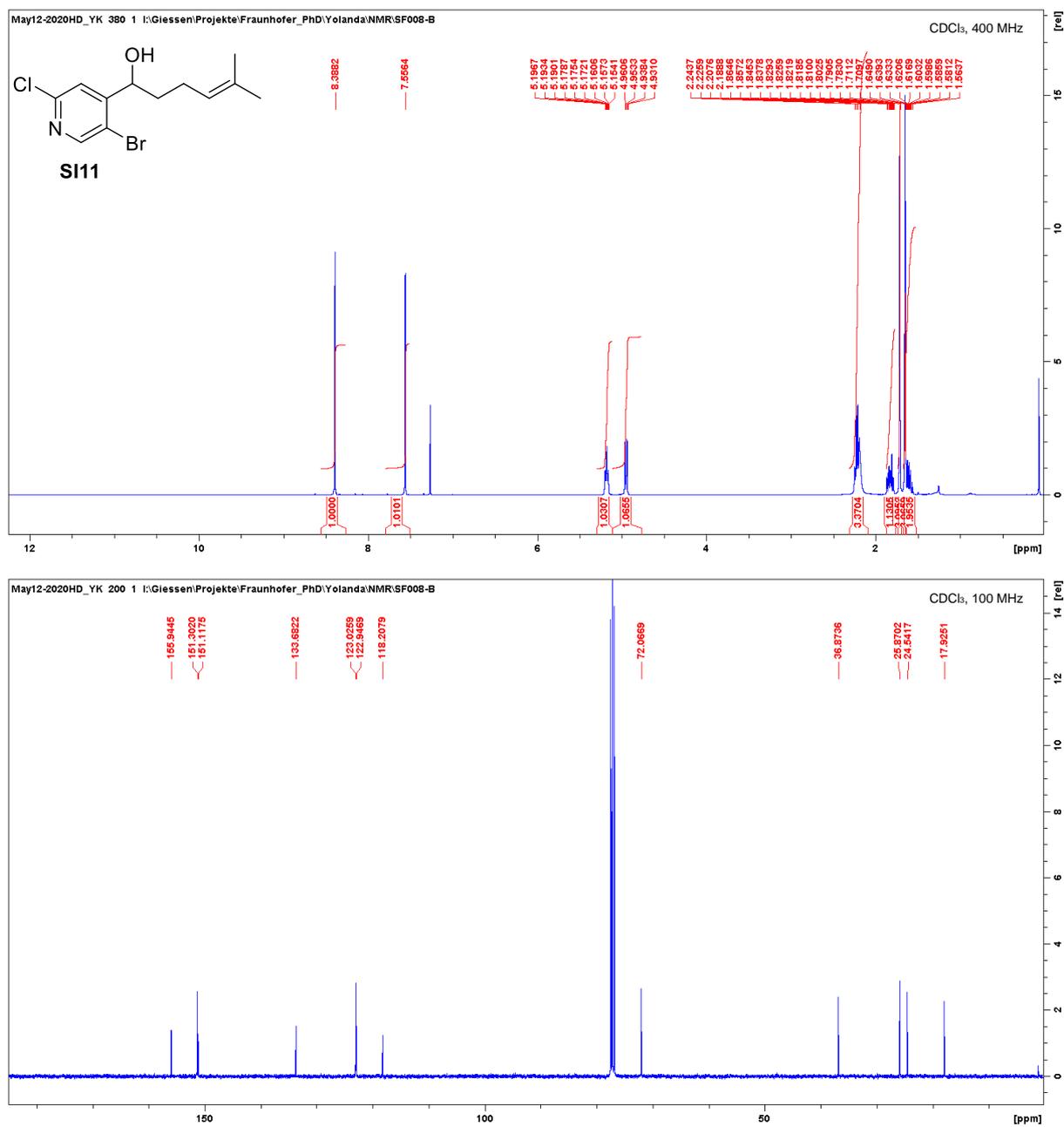


Figure S25. 4,5-Dibromo-2-chloropyridine (**10**) (^1H - and ^{13}C -NMR).

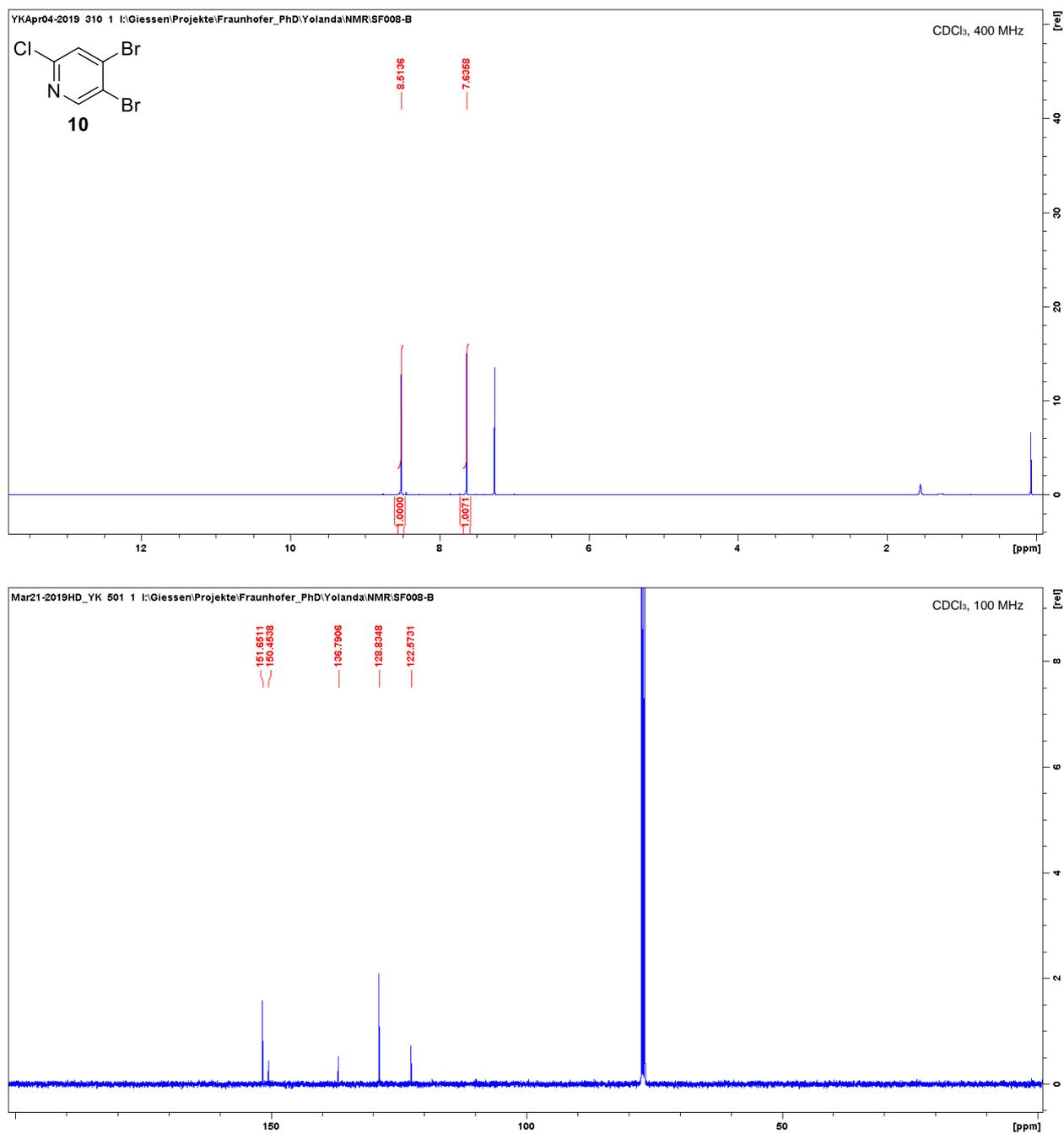


Figure S26. 3,5-Dibromo-2-chloropyridin-4-amine (**SI12**) (^1H - and ^{13}C -NMR).

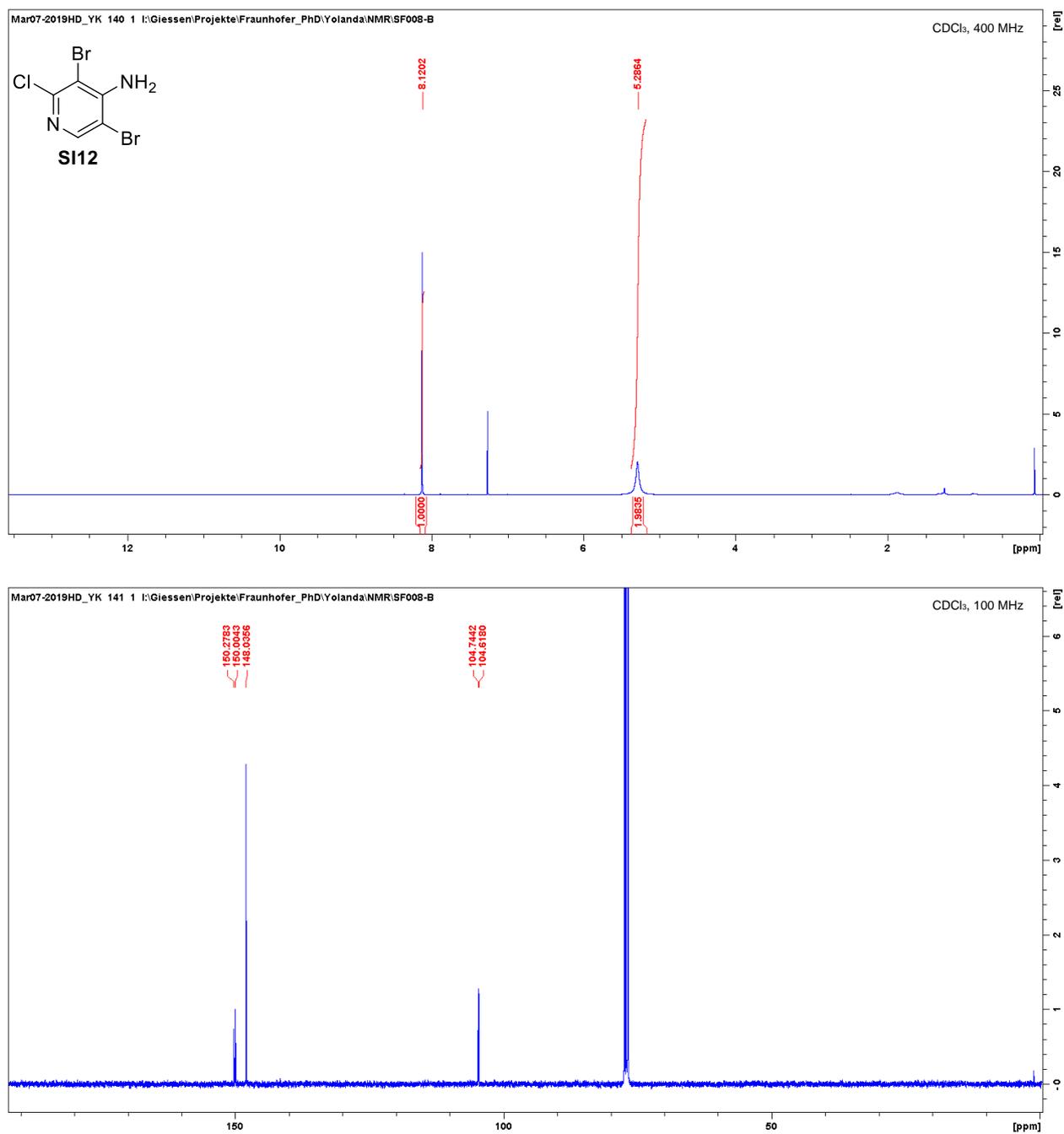


Figure S27. 3,4,5-Tribromo-2-chloropyridine (**SI13**) (^1H - and ^{13}C -NMR).

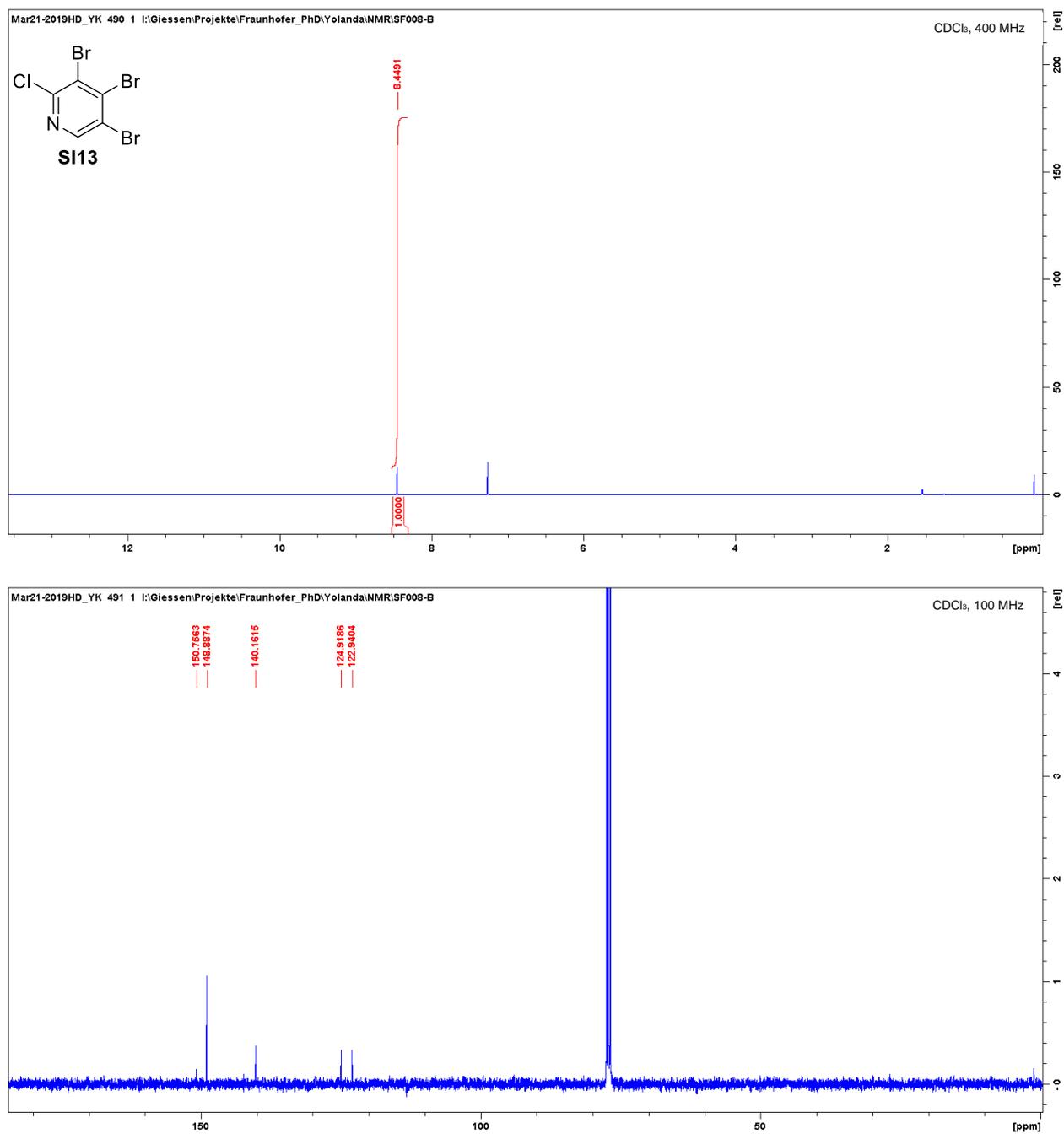


Figure S28. (4-Bromopyridin-3-yl)(phenyl)methanol (**34**) (¹H- and ¹³C-NMR).

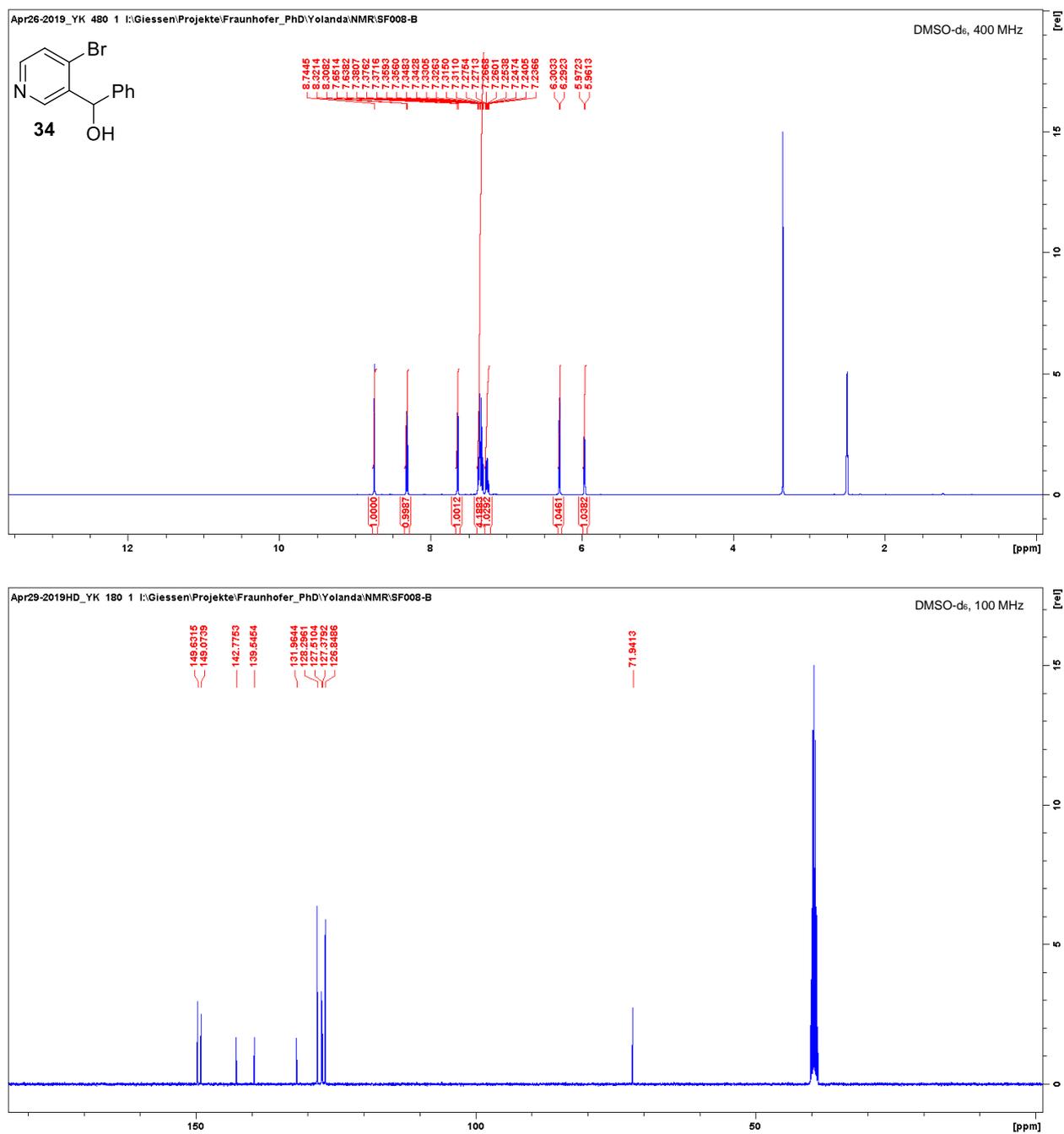


Figure S29. (3-Bromopyridin-4-yl)(phenyl)methanol (**33**) (¹H- and ¹³C-NMR).

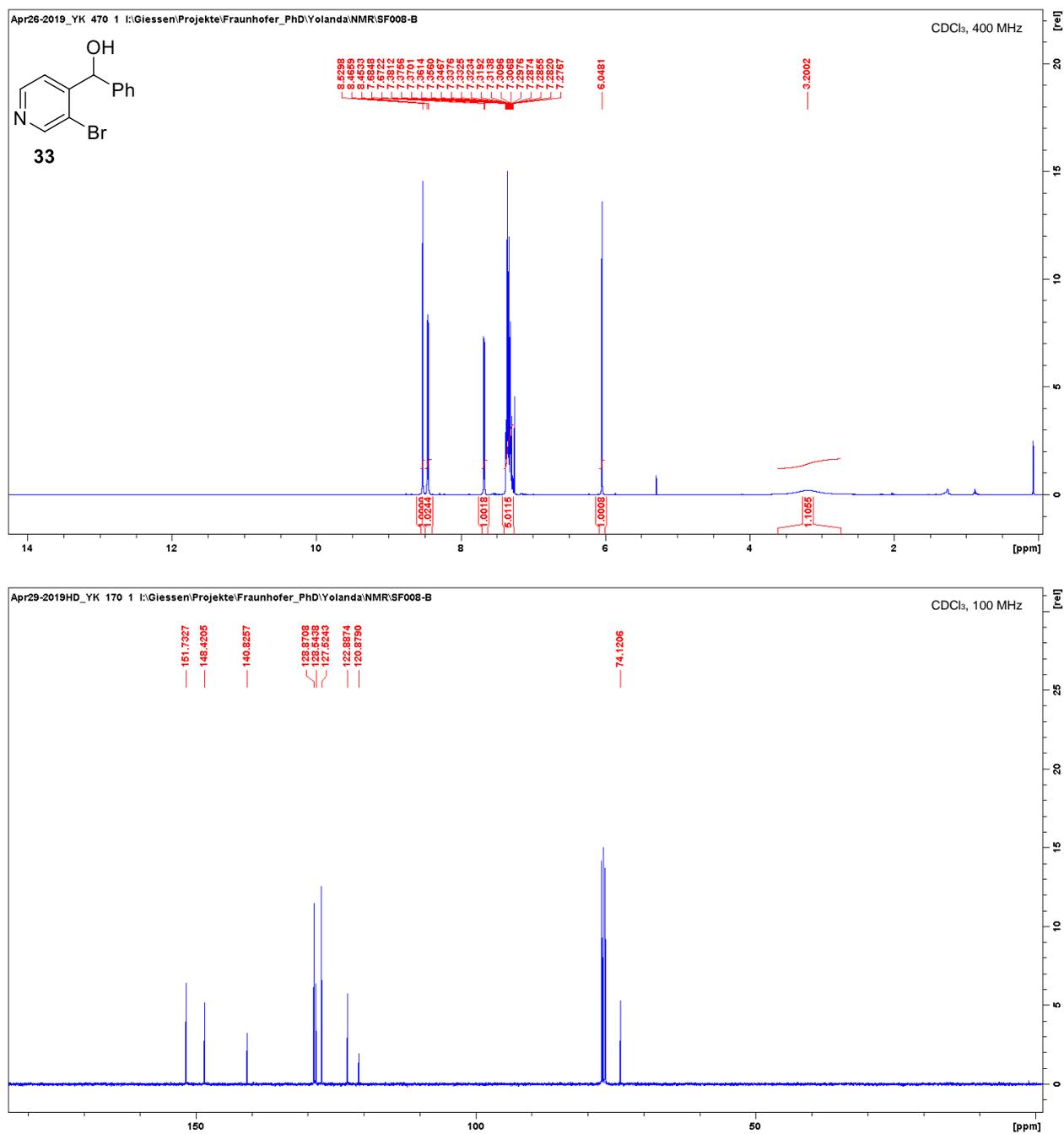


Figure S30. (4-Bromo-6-chloropyridin-3-yl)(phenyl)methanol (**37**) (^1H - and ^{13}C -NMR).

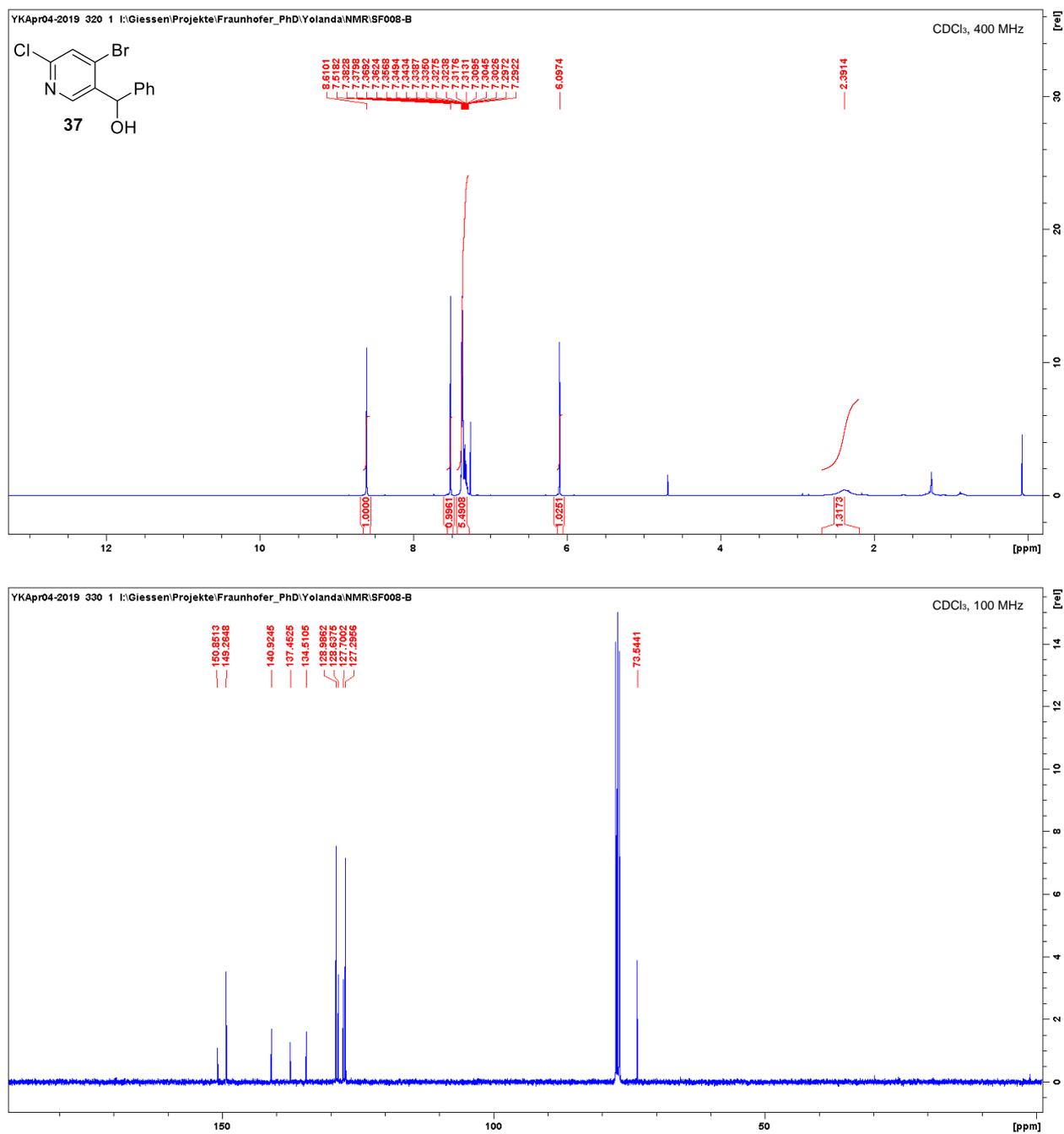


Figure S31. (5-Bromo-2-chloropyridin-4-yl)(phenyl)methanol (**36**) (^1H - and ^{13}C -NMR).

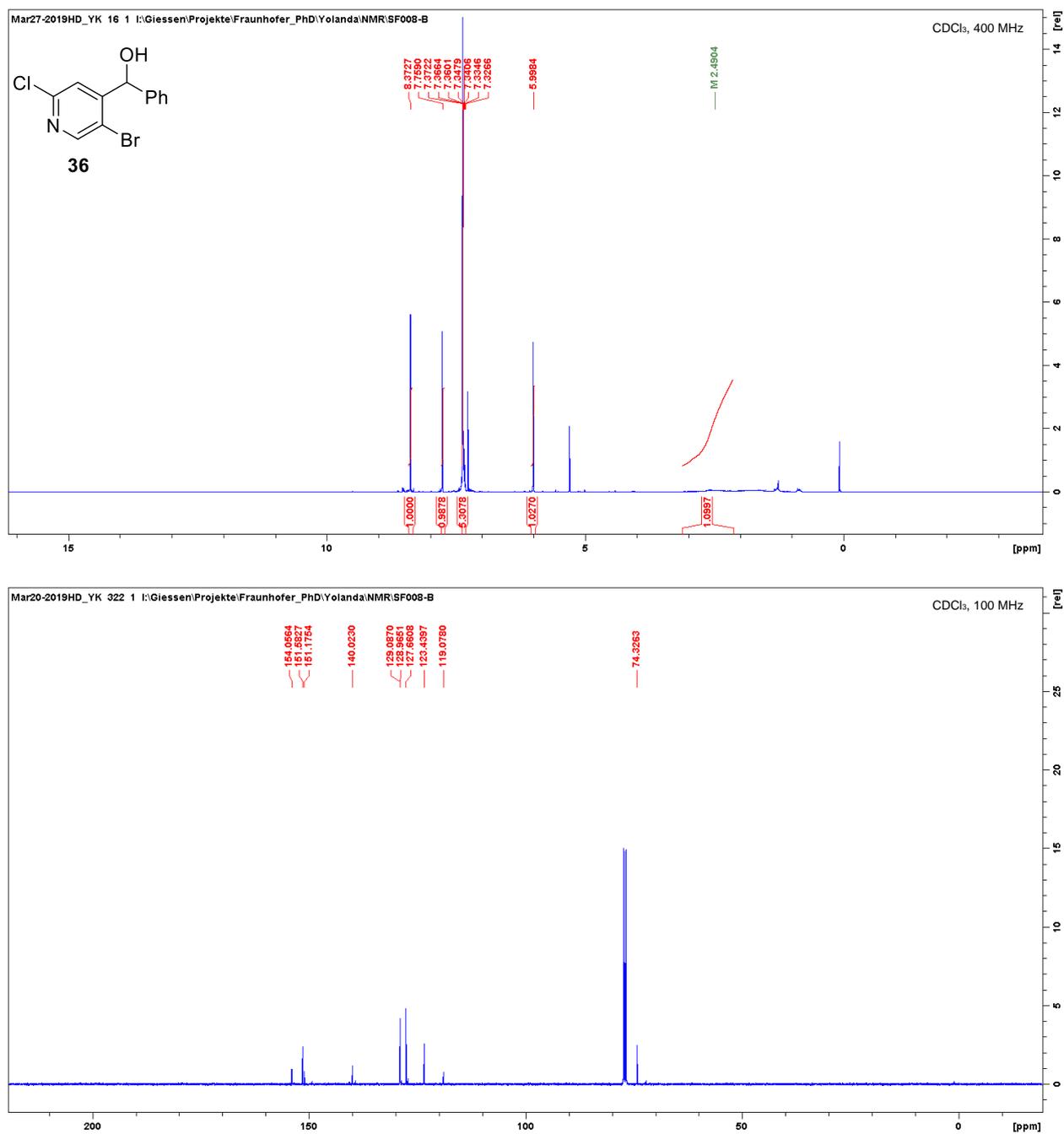


Figure S33. 4-Bromo-5-((*R*)-((2*R*,3*S*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)((triisopropylsilyloxy)methyl)-2-chloropyridine (**43**) (^1H - and ^{13}C -NMR).

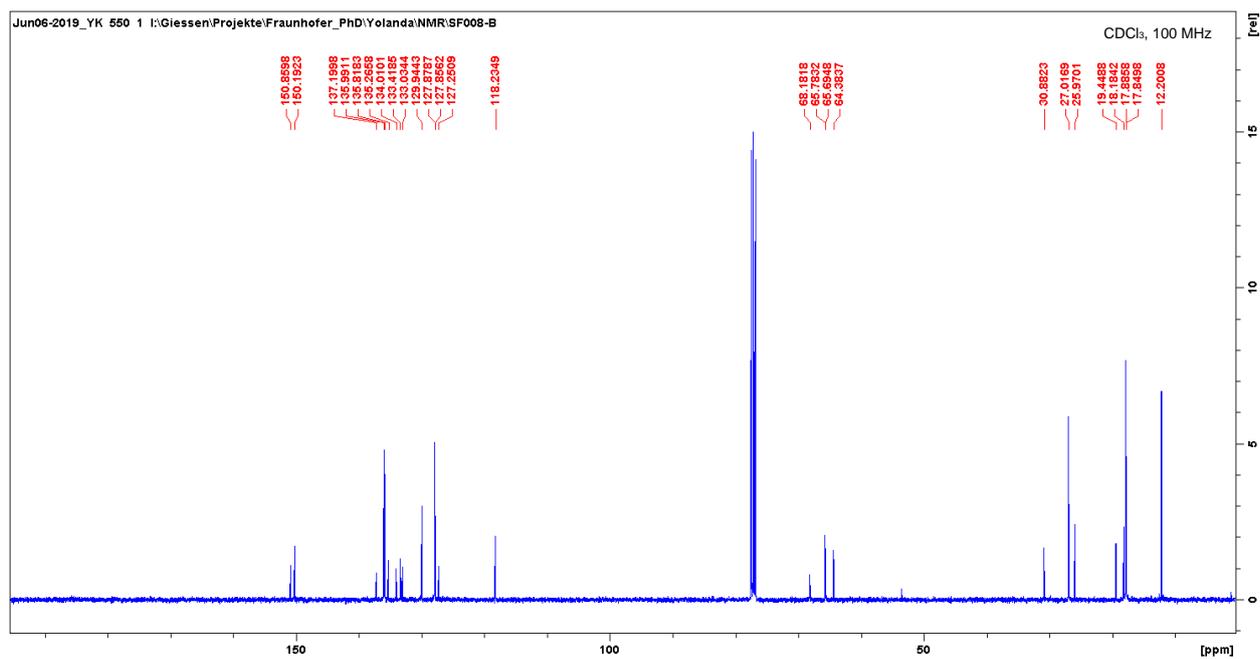
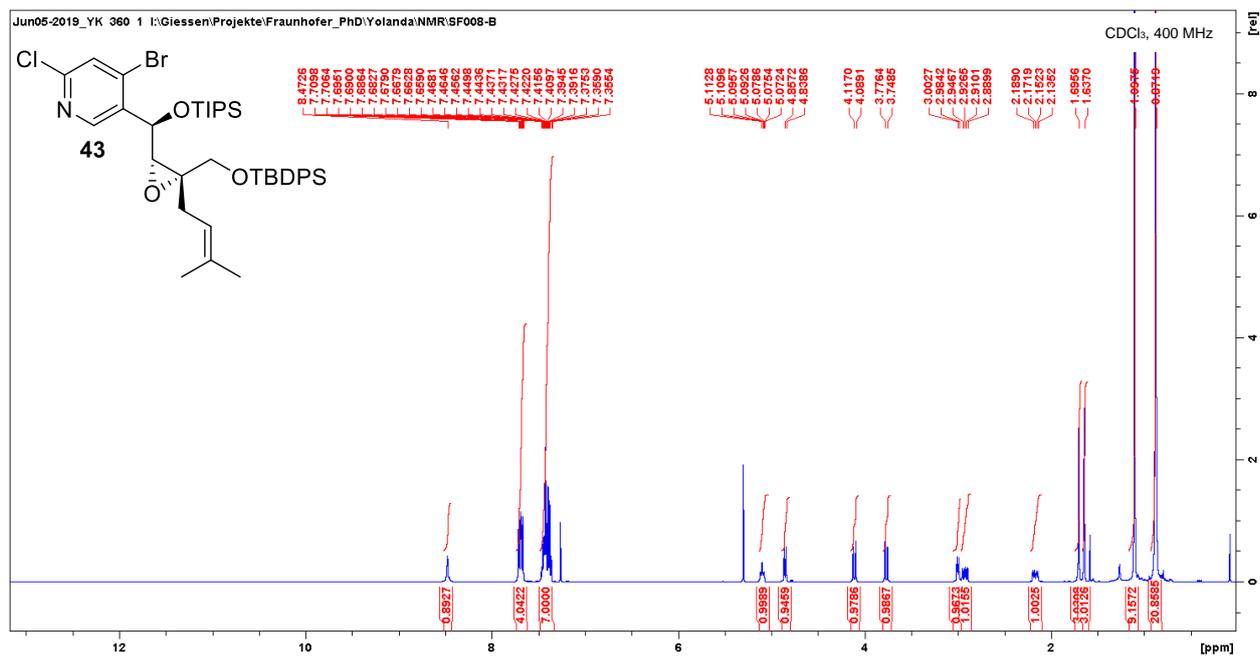


Figure S34. 4-Bromo-5-((S)-((2R,3S)-3-((*tert*-butyldiphenylsilyloxy)methyl)-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)((triisopropylsilyloxy)methyl)-2-chloropyridine (**49**) (^1H - and ^{13}C -NMR).

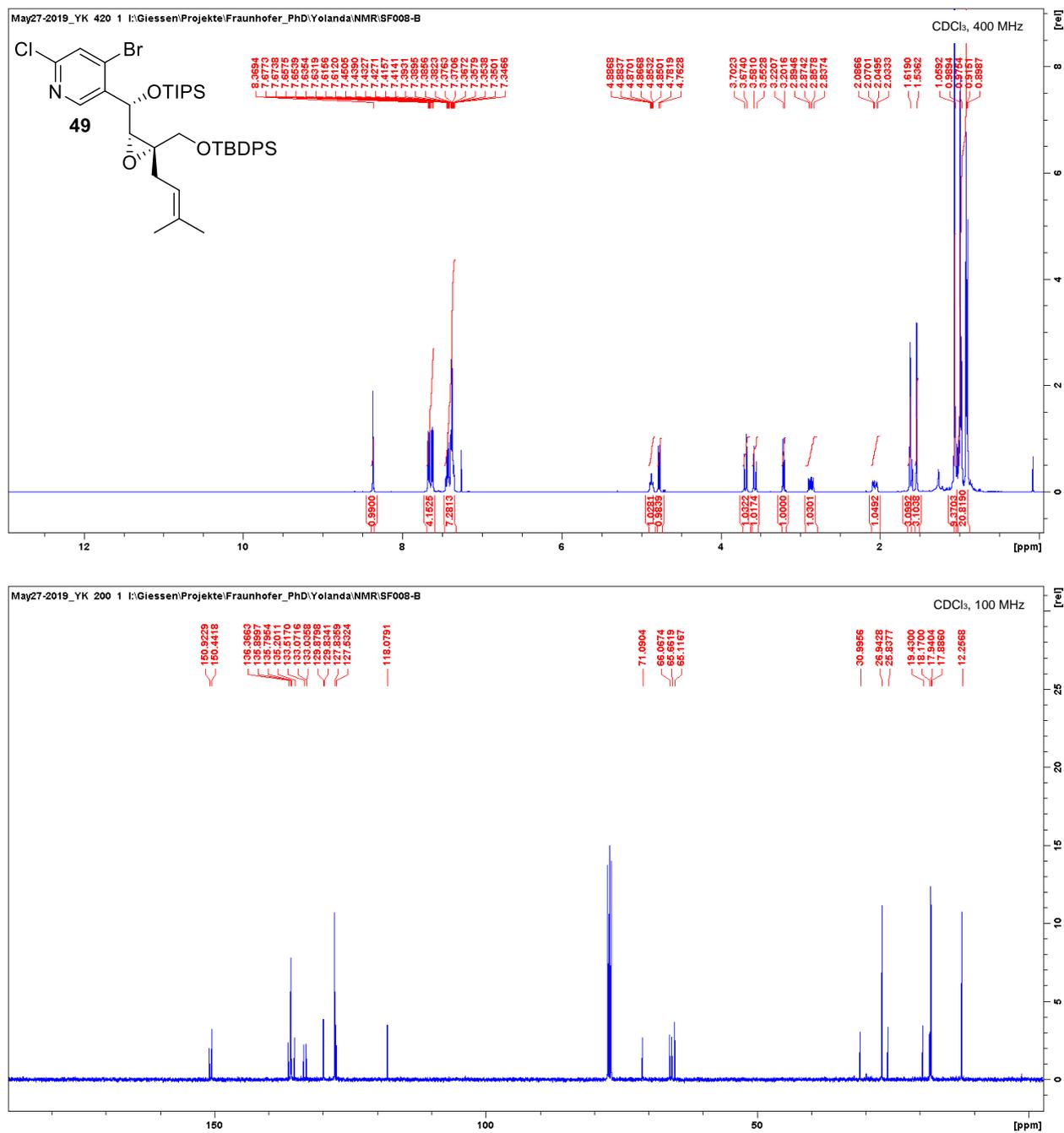


Figure S35. (*R*)-(4-Bromo-6-chloropyridin-3-yl)((*2R,3S*)-3-(hydroxymethyl)-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)methanol (**45**) (¹H- and ¹³C-NMR).

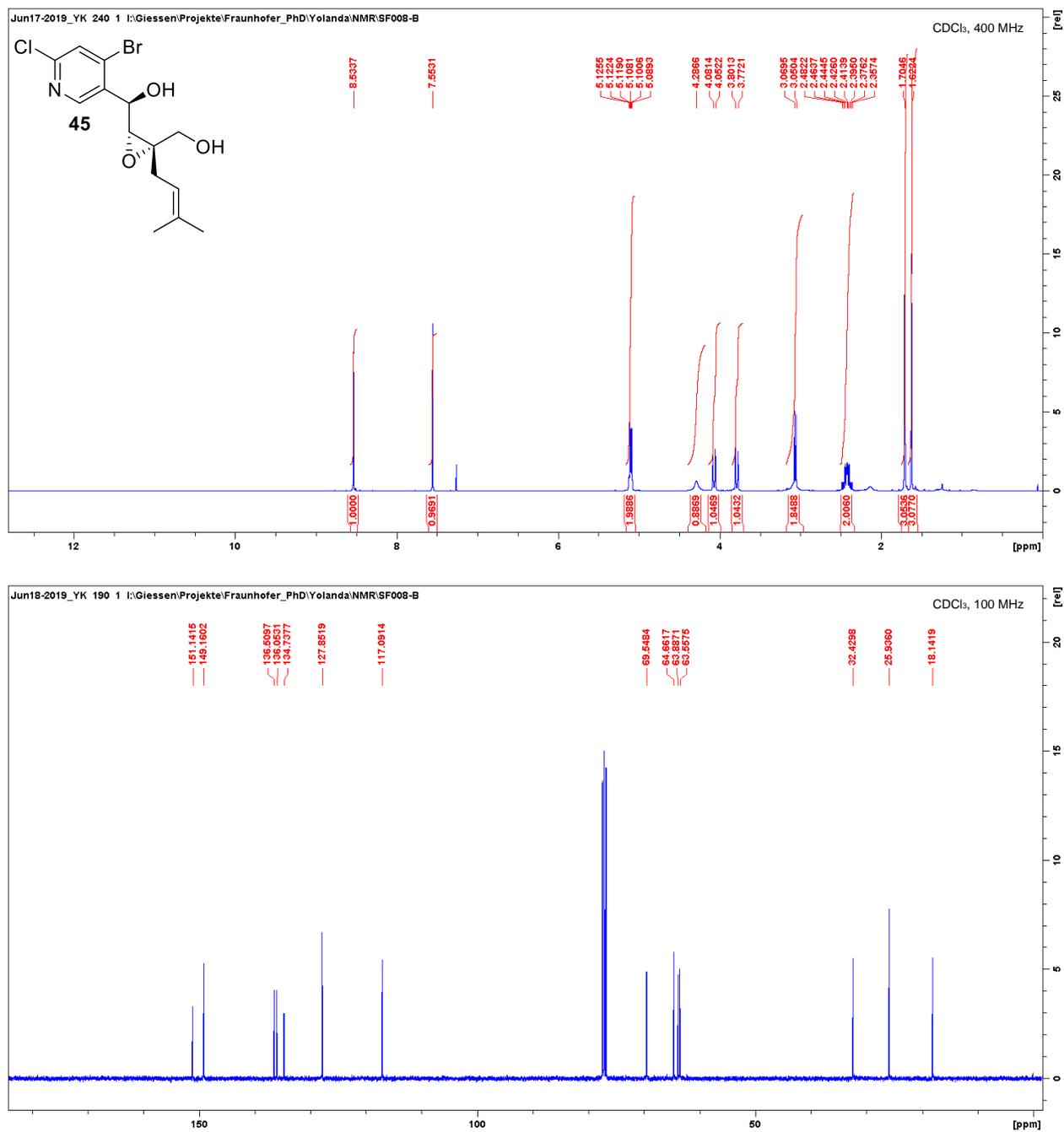


Figure S36. (2*R*,3*R*)-3-((*R*)-(4-Bromo-6-chloropyridin-3-yl)((triisopropylsilyl)oxy)methyl)-2-(3-methylbut-2-en-1-yl)oxirane-2-carbaldehyde (**46**) (¹H- and ¹³C-NMR).

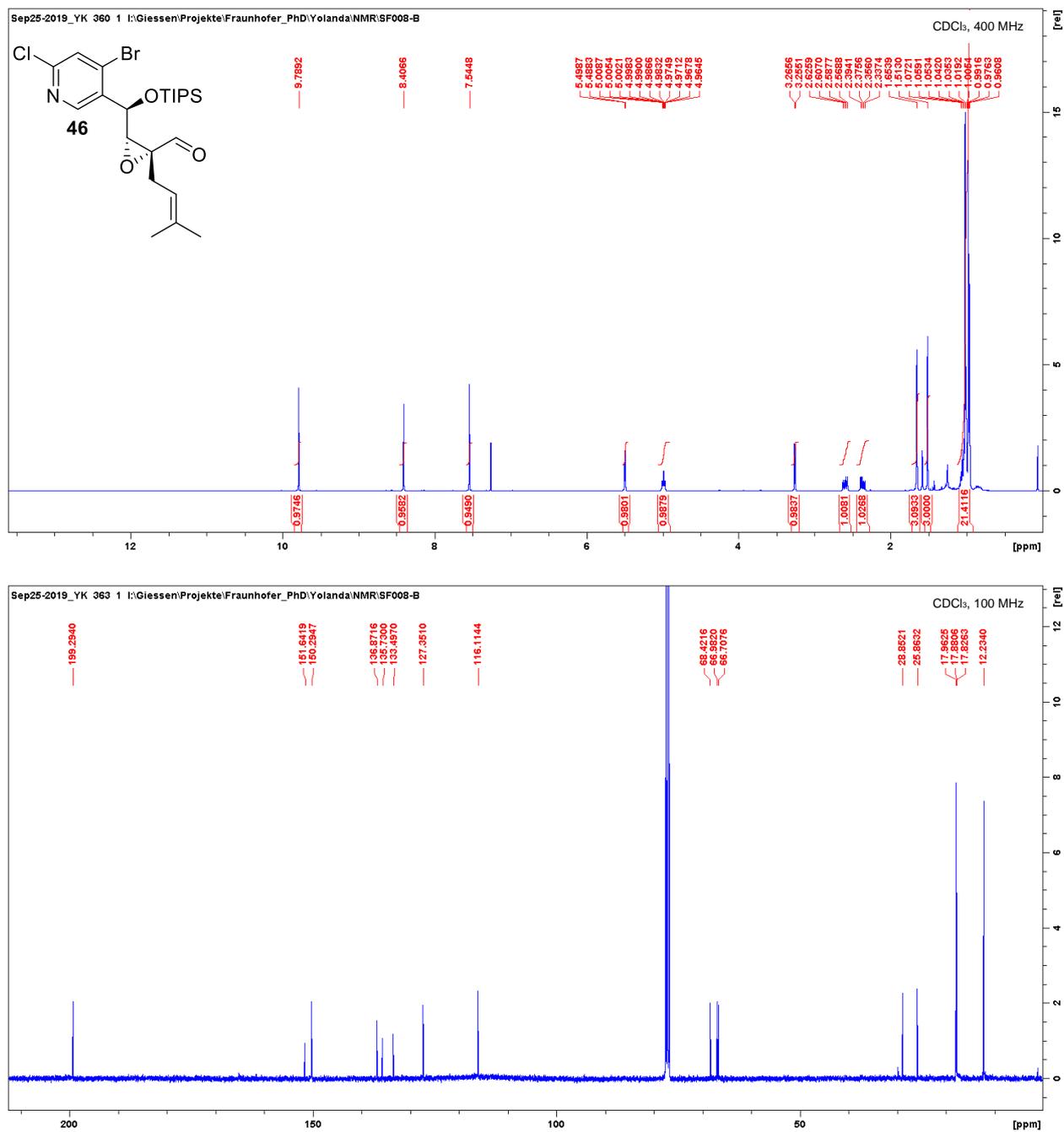


Figure S37. (2*R*,3*R*)-3-((*S*)-(4-Bromo-6-chloropyridin-3-yl)((triisopropylsilyl)oxy)methyl)-2-(3-methylbut-2-en-1-yl)oxirane-2-carbaldehyde (**52**) (¹H- and ¹³C-NMR).

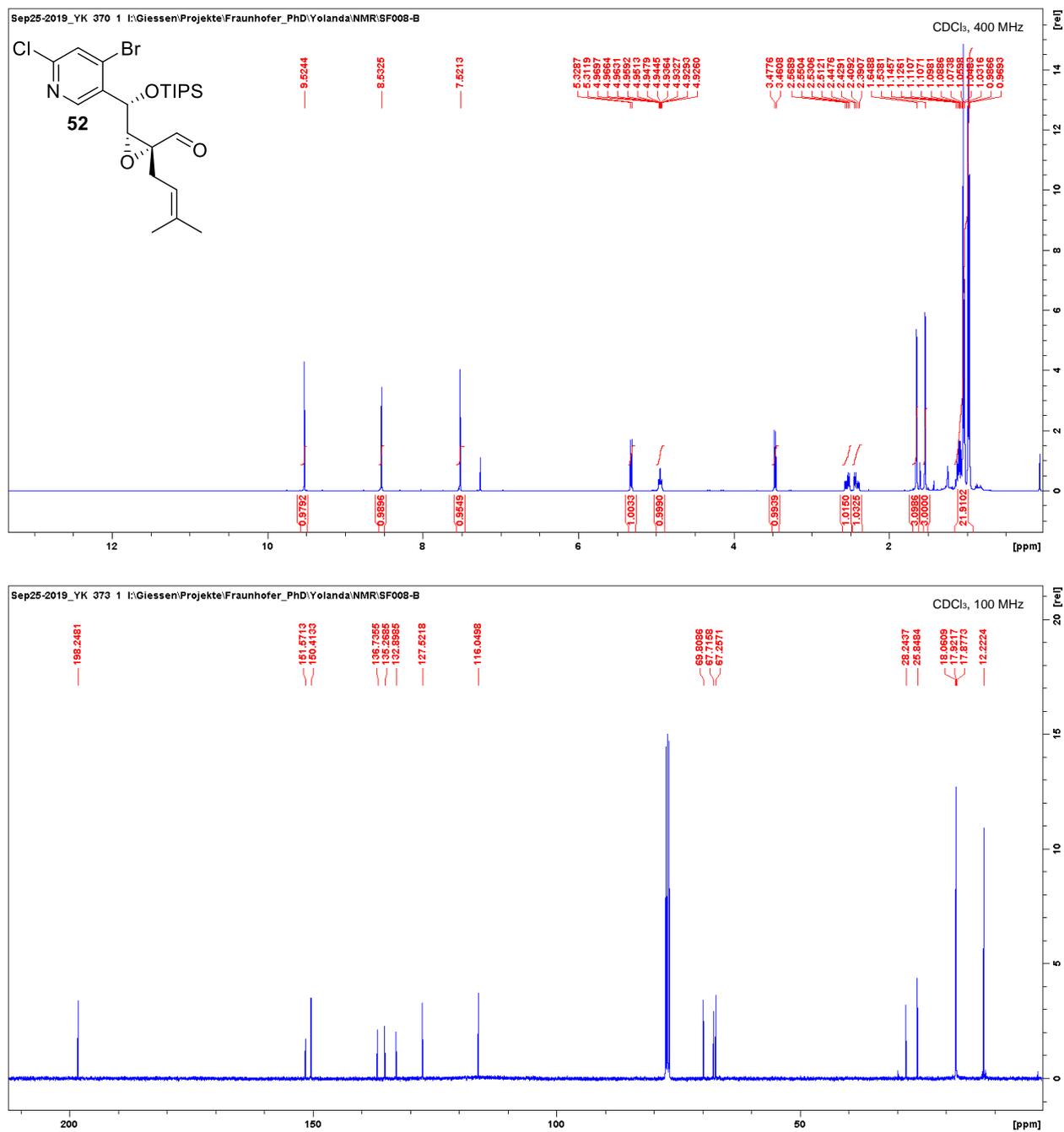


Figure S38. (1*aR*,2*R*,7*S*,7*aS*)-5-Chloro-7*a*-(3-methylbut-2-en-1-yl)-2-((triisopropylsilyl)oxy)-1*a*,2,7,7*a*-tetrahydrooxireno[2,3-*g*]isoquinolin-7-ol (**47**) (¹H- and ¹³C-NMR).

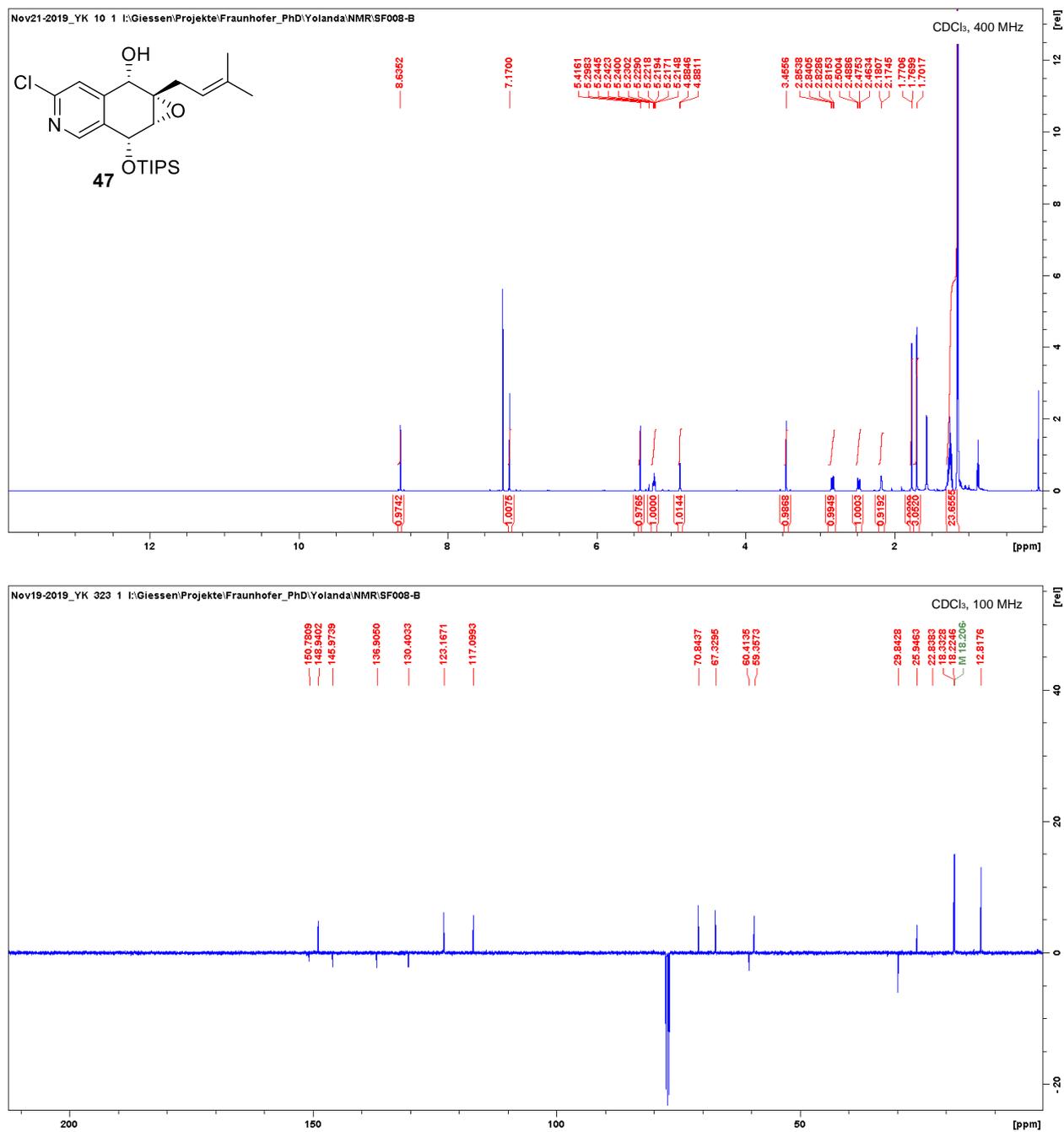


Figure S39. (5*a*S,6*a*R,7*R*,11*b*S)-10-Chloro-3-methyl-7-((triisopropylsilyloxy)-2,5,7,11*b*-tetrahydro-6*a*H-oxepino[2,3-*f*]oxireno[2,3-*g*]isoquinoline (**48**) (¹H- and ¹³C-NMR).

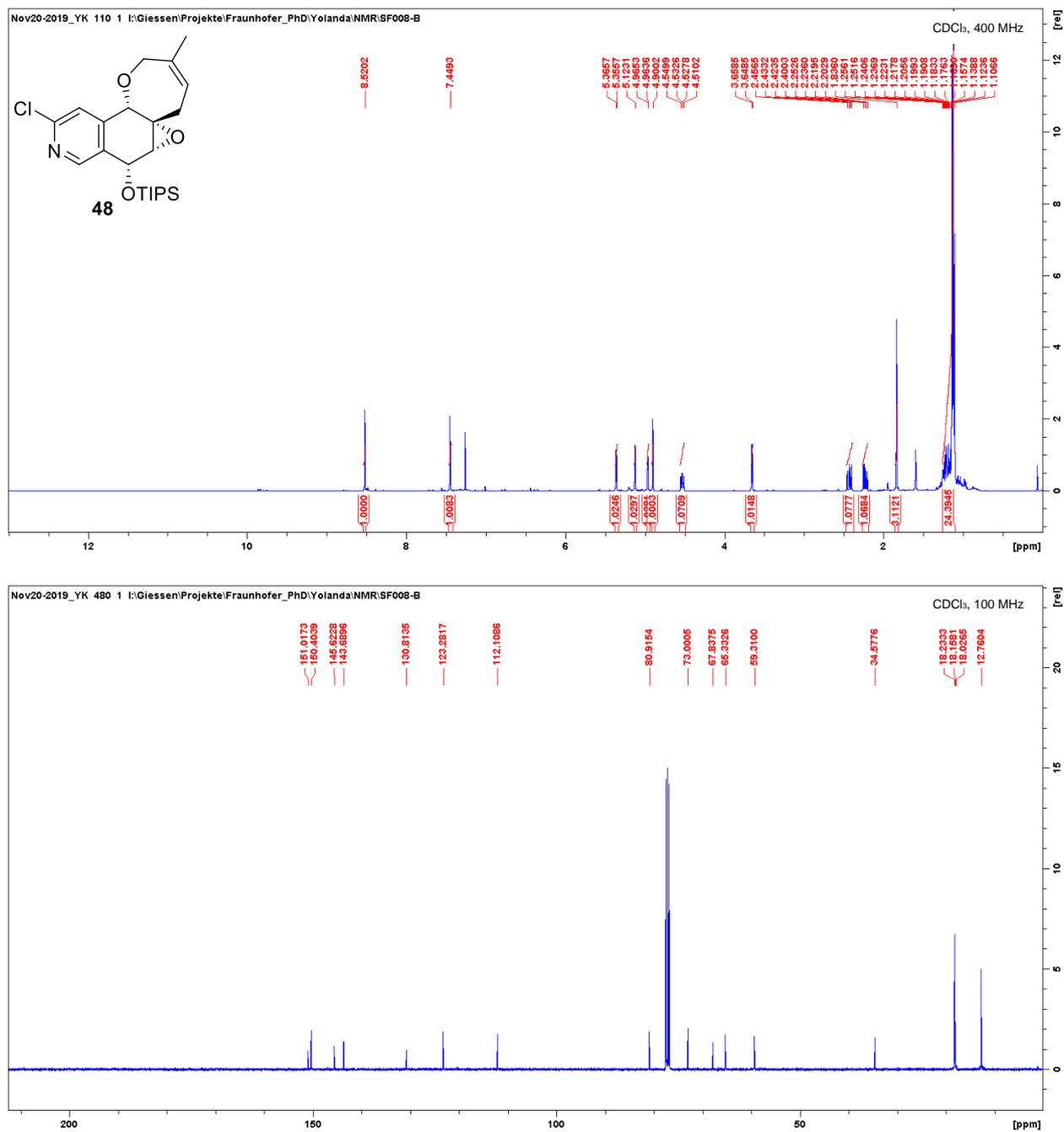


Figure S40. (1*aR*,2*S*,7*S*,7*aS*)-5-Chloro-7*a*-(3-methylbut-2-en-1-yl)-2-((triisopropylsilyl)oxy)-1*a*,2,7,7*a*-tetrahydrooxireno[2,3-*g*]isoquinolin-7-ol (**54**) (¹H- and ¹³C-NMR).

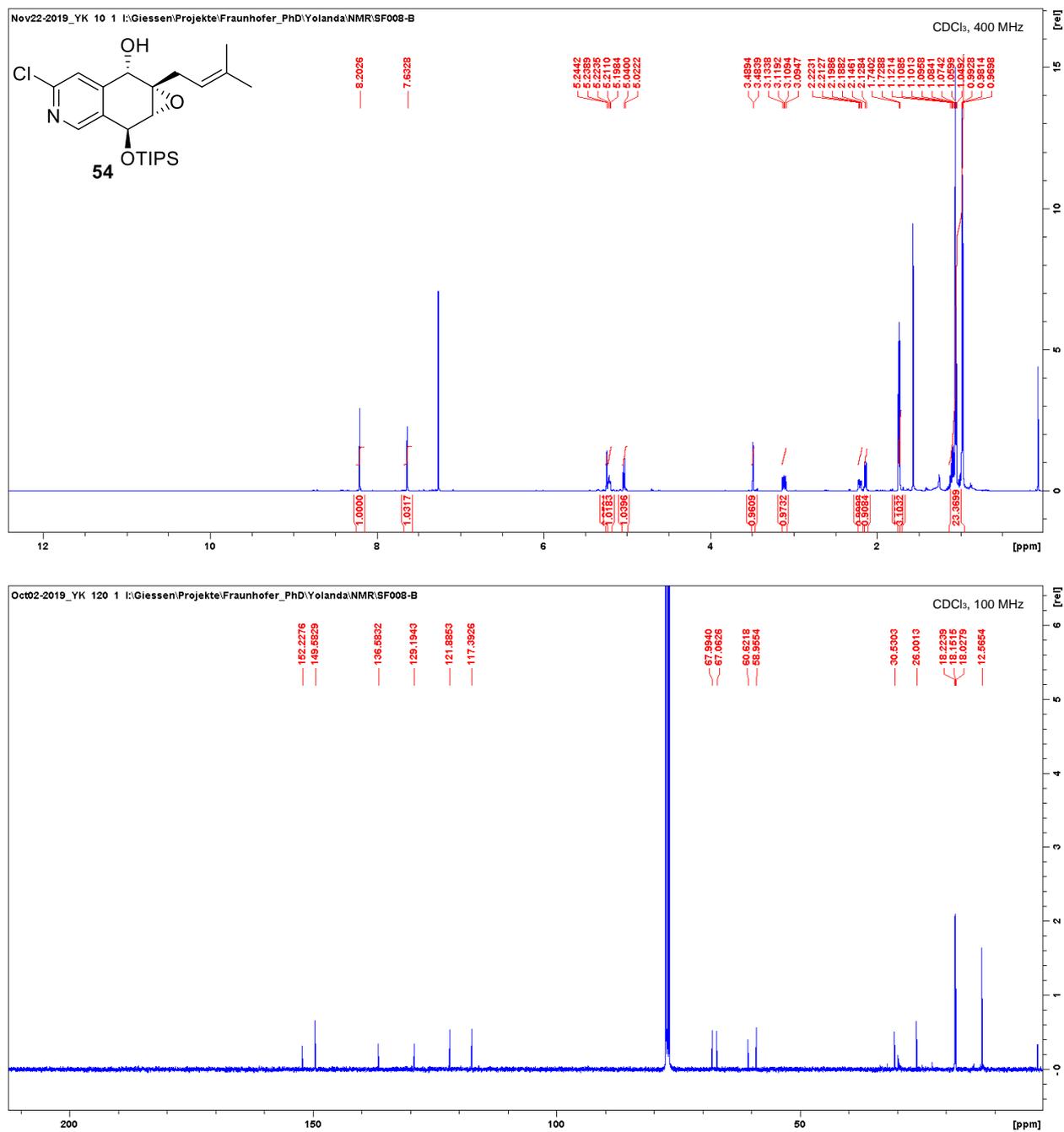


Figure S41. (5*S*,6*R*)-2,2-Dimethyl-9-((*E*)-pent-1-en-1-yl)-6-((triisopropylsilyl)oxy)-5,6-dihydro-2*H*-pyrano[2,3-*f*]isoquinolin-5-ol (**56**) (¹H- and ¹³C-NMR).

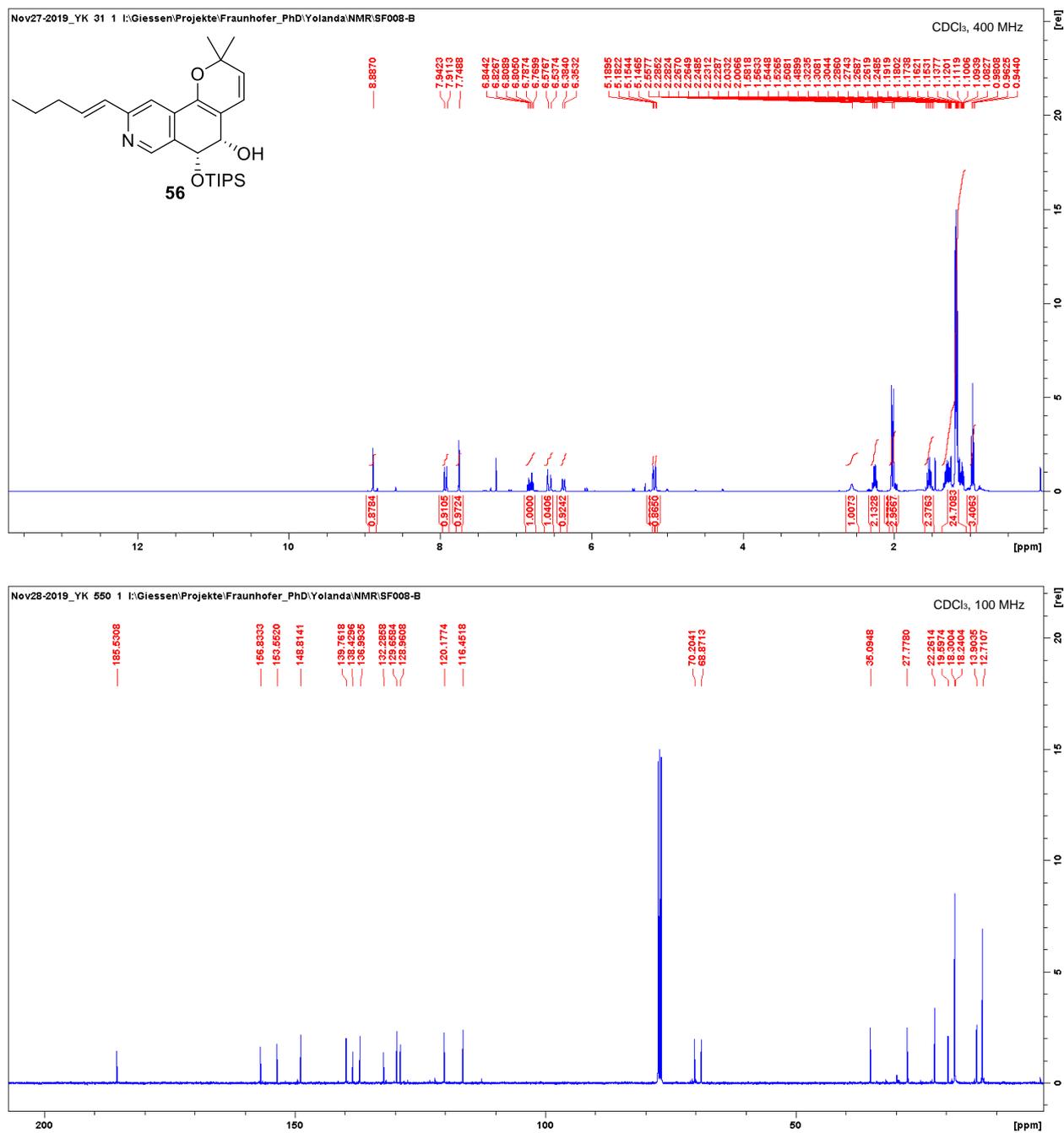


Figure S42. (*E*)-2,2-Dimethyl-9-(pent-1-en-1-yl)-6-((triisopropylsilyl)oxy)-2*H*-pyrano[2,3-*f*]isoquinoline (**57**) (¹H- and ¹³C-NMR).

