A Divergent Synthetic Route to the Vallesamidine, Strempeliopine and Schizozygine Alkaloids: Total Synthesis of (+)-Vallesamidine and (+)-14,15-Dehydrostrempeliopine

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Contents

General Experimental

Glassware was flame-dried before use. All solvents and chemicals were used as received unless stated. The anhydrous solvents diethyl ether (Et_2O), tetrahydrofuran (THF), dichloromethane (DCM), toluene and hexane were obtained from solvent purification system. Thin layer chromatography (TLC) was performed using Merck silica-aluminium plates and visualised by UV light (254 nm) and potassium permanganate or anisaldehyde stains. For column chromatography, Merck Geduran® Si 60 silica gel was used.

All ^{1}H NMR and ^{13}C NMR data were recorded using Bruker AVANCE III 400 MHz, Bruker AVANCE 500, Bruker AVANCE III 600 MHz and Bruker AVANCE NEO 700 MHz machines at 400, 500, 600 and 700 MHz for ^{1}H NMR and 101, 126, 151 and 176 MHz for ^{13}C NMR respectively. Samples were prepared as dilute solutions of $CDCl_3$, DMSO-d_6 or MeOD-d_4 and spectra were

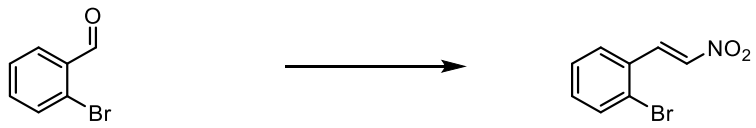
recorded at 298K, unless otherwise stated. Reference values for residual solvents were taken as δ = 7.26 ($CDCl_3$), 2.51 (DMSO-d_6), 3.30 (MeOD-d_4) ppm for ^1H NMR and δ = 77.2 ($CDCl_3$), 39.5 (DMSO-d_6), 49.0 (MeOD-d_4) ppm for ^{13}C NMR. Coupling constants (J) are given in Hz and are uncorrected and multiplicities for coupled signals were denoted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, apt. = apparent and dd = double doublet etc. COSY and DEPT experiments were carried out to aid assignment where appropriate.

Mass spectroscopy data was collected on a Thermo Finnigan Mat900xp (EI/CI), Waters LCT Premier XE (ES) and Agilent 6510 Q TOF mass spectrometers (ESI). Infrared data were collected using Bruker compact FTIR spectrometer. Melting points were uncorrected and recorded on a DigMelt MPA160-SRS machine. Optical rotations were obtained using a Bellingham+Stanley ADP430 series polarimeter. Chiral HPLC was performed using a Chiralcel OD-H 15 cm analytical column.

Experimental procedures and listing of characterisation data

Compound 15

Compound **15** is commercially available and can also be prepared using following procedure:



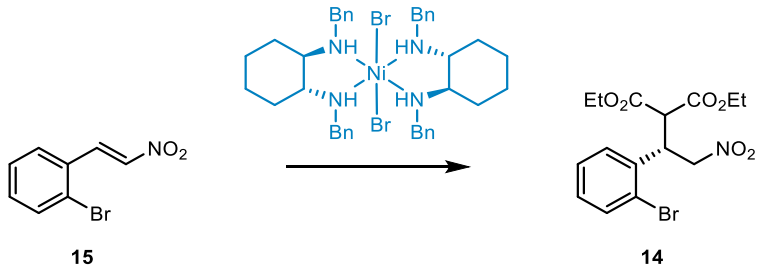
15

Procedure[1]**:** To a mixture of NH_4OAc (7.50 g, 97.0 mmol) in AcOH (150 mL) was added 2-bromobenzaldehyde (6.30 mL, 54.0 mmol) and the resulting mixture was stirred at room temperature for 10 min before nitromethane (10.0 mL) was added slowly. After addition the reaction solution was flushed with nitrogen and heated to 130 °C for 4 h with stirring. Then the orange solution was cooled to room temperature and poured into ice water (200 mL) and extracted with CH_2Cl_2 (150 mL x 2). The combined organic layers were washed with saturated aq. $NaHCO_3$ (150 mL x 2), dried (Na_2CO_3) and concentrated by rotary evaporation to give crude product as a yellow solid. Hexane (150 mL) was added to the crude product and heated to reflux and during which time diethyl ether was added slowly until most of the solid dissolved.

Then the solution was cooled to room temperature and furtherly to 0 °C to afford the recrystalised compound **15** as a microcrystalline yellow solid (9.40 g, 78%) and data was consistent with the literature.[1]

R_f (1:2 CH_2Cl_2/hexane): 0.2; m.p. 83.5 – 84.5 °C (lit. 87 – 88 °C) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (1H, d, *J* = 13.6, C*H*=CHNO$_2$), 7.70 (1H, dd, *J* = 7.9, 1.3, Ar*H*), 7.58 (1H, dd, *J* = 7.7, 1.8, Ar*H*), 7.54 (1H, d, *J* = 13.6, CH=C*H*NO$_2$), 7.39 (1H, td, *J* = 7.6, 1.3, Ar*H*), 7.35 (1H, td, *J* = 7.7, 1.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.0 (CH=*C*HNO$_2$), 137.7 (*C*H=CHNO$_2$), 134.2 (Ar*C*H), 133.0 (Ar*C*H), 130.5 (Ar*C*), 128.6 (Ar*C*H), 128.2 (Ar*C*H), 126.5 (Ar*C*).

Compound 14



15 **14**

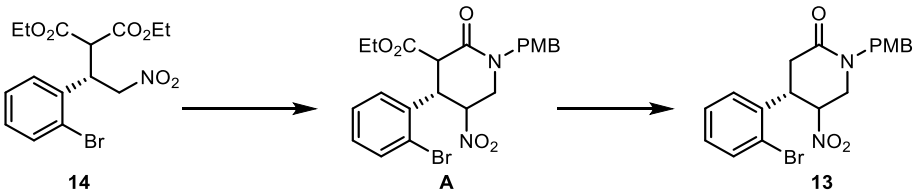
Procedure[2]**:** To a solution of nitroalkene **15** (3.80 g, 16.5 mmol) in toluene (8.5 mL) was added diethylmalonate (2.50 mL, 16.5 mmol) and catalyst[2] (133 mg, 0.16 mmol). The resulting mixture was stirred at room temperature for 3 days and then concentrated by rotary evaporation. Chromatography of the residue on silica gel, using 1:4 EtOAc/hexane, gave compound **14** as a yellow oil (5.83 g, 91%).

R_f (1:4 EtOAc/hexane): 0.29; $[\alpha]_D^{25}$ +6.42 (c 0.1, $CHCl_3$); Enantiomeric ratio (*e.r.*): 95:5 (Chiralcel OD-H column, 90:10 hexane:isopropanol, 1mL/min, 215 nm, major enantiomer t_r 7.0 min, minor enantiomer t_r 12.7 min); absolute stereochemistry was determined by analogy with literature.[2] FTIR (neat, cm^{-1}): 2979, 2934, 1726, 1551, 1369, 1285, 1225, 1022; HRMS (ESI-TOF, m/z) calcd. for $C_{15}H_{18}NO_6{}^{79}BrNa$ $[M+Na]^+$ 410.0210, found 410.0212; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (1H, dd, *J* = 8.0, 1.2 Hz, Ar*H*), 7.38–7.22 (2H, m, Ar*H*), 7.16 (ddd, 1H, *J* = 8.0, 7.1, 1.9 Hz, Ar*H*), 5.12 (1H, dd, *J* = 13.6, 8.3 Hz, *H*CHNO$_2$), 4.95 (1H, dd, *J* = 13.6, 4.4 Hz, HC*H*NO$_2$), 4.76 (1H, td, *J* = 8.3, 4.4 Hz, Ar-C*H*), 4.21 (2H, qd, *J* = 10.8, 7.2 Hz, CO$_2$C*H*$_2$), 4.12–4.08 (3H, m, CO$_2$C*H*$_2$ and C*H*(CO$_2$Et)$_2$), 1.24 (3H, t, *J* = 7.1 Hz, CO$_2$CH$_2$C*H*$_3$), 1.13 (3H, t, *J* = 7.1

Hz, $CO_2CH_2CH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5 (CO_2Et), 167.0 (CO_2Et), 135.5 (Ar*C*H), 134.0 (Ar*C*H), 129.8 (Ar*C*H), 128.6 (Ar*C*), 128.0 (Ar*C*H), 125.0 (Ar*C*), 75.9 (CH_2NO_2), 62.3 ($CO_2CH_2CH_3$), 62.2 ($CO_2CH_2CH_3$), 53.4 ($CH(CO_2Et)_2$), 41.6 (Ar-*C*H), 14.1 ($CO_2CH_2CH_3$), 13.9 ($CO_2CH_2CH_3$).

- For large scale preparation (> 10 g), the crude product could be used directly without chromatography and first chromatographic purification could be performed after Tsuji-Trost allylation.

Compound 13



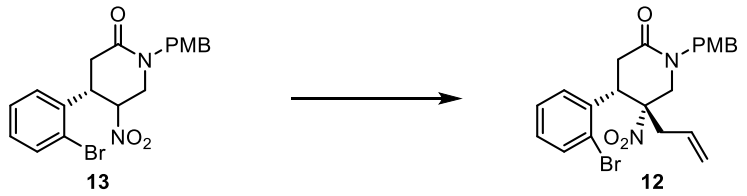
Procedure: To a solution of nitro malonate **14** (13.0 g, 33.5 mmol) in ethanol (90.0 mL) was added *p*-methoxybenzylamine (8.70 mL, 67.0 mmol) and paraformaldehyde powder (1.20 g, 36.9 mmol) and the resulting mixture was heated to 80 °C under nitrogen atmosphere for 2 hours. Reaction mixture was then cooled to room temperature and quenched with 1 M HCl aq. solution (100 mL) followed by extraction with EtOAc (150 mL x 3). Combined organic layers were dried (Na_2SO_4) and concentrated by rotary evaporation to give the crude product **A** which was put into next step directly without further purification.

Sodium chloride (11.0 g) was added to the mixture of above crude product **A** in DMSO/H_2O (36.0 mL/12.00 mL) and the resulting mixture was heated to 150 - 160 °C (heating block) under nitrogen atmosphere overnight. The reaction mixture was cooled to room temperature and diluted with water (150 mL) and extracted with EtOAc (150 x 3 mL). The combined organic layers were washed with brine (300 mL x 2), dried (Na_2SO_4) and concentrated by rotary evaporation. Chromatography of the crude product on silica gel, using 4:5 EtOAc/ hexane, gave titled compound **13** as a yellow foam (11.8 g, 84%). The proton NMR of product shows a mixture of inseparable diastereomers (*dr* 5:1, determined by ^1H NMR). A small fraction of major diastereomer was obtained for data collection.

R_f (50% EtOAc in hexane): 0.34; FTIR (neat, cm^{-1}) 2927, 2833, 1642, 1549, 1509, 1242, 1024; HRMS (EI, m/z) calcd. for $C_{19}H_{19}N_2O_4{}^{79}Br$ $[M]^{+\cdot}$ 418.05227, found 418.05232; **Major isomer**: ^1H

NMR (700 MHz, $CDCl_3$) δ 7.59 (1H, dd, *J* = 8.0 Hz, 1.3, Ar*H*), 7.27 (1H, td, *J* = 7.6, 1.3 Hz, Ar*H*), 7.22 (2H, d, *J* = 8.6 Hz, $Ar_{PMB}H$), 7.16 (1H, td, *J* = 7.7, 1.6 Hz, Ar*H*), 7.13 (1H, dd, *J* = 7.7, 1.6 Hz, Ar*H*), 6.87 (2H, d, *J* = 8.6 Hz, $Ar_{PMB}H$), 4.99 (1H, q, *J* = 5.2 Hz, C*H*NO_2), 4.85 (1H, d, *J* = 14.4 Hz, N-*H*CH), 4.43 (1H, q, *J* = 6.4 Hz, ArC-C*H*), 4.38 (1H, d, *J* = 14.3 Hz, N-HC*H*), 3.85 (1H, dd, *J* = 13.6, 5.1 Hz, *H*CH-$CHNO_2$), 3.80 (3H, s, O*Me*), 3.41 (1H, dd, *J* = 13.7, 4.6 Hz, HC*H*-$CHNO_2$), 2.97 (1H, dd, *J* = 18.2, 6.7 Hz, NC(O)*H*CH), 2.71 (1H, dd, *J* = 18.2, 6.1 Hz, NC(O)HC*H*); ^{13}C NMR (176 MHz, $CDCl_3$) δ 167.1 (*C*(O)N), 159.6 ($Ar_{PMB}C$), 137.3 (Ar*C*), 134.0 (Ar*C*H), 130.0 ($Ar_{PMB}C$), 129.9 ($Ar_{PMB}C$H x 2), 128.6 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 124.4 (Ar*C*), 114.3 ($Ar_{PMB}C$H x 2), 81.7 (*C*HNO_2), 55.4 (O*C*H_3), 49.8 (N-*C*H_2PMP), 46.3 (N-*C*H_2), 41.0 (ArC-*C*H), 34.2 (NC(O)*C*H_2).

Compound 12

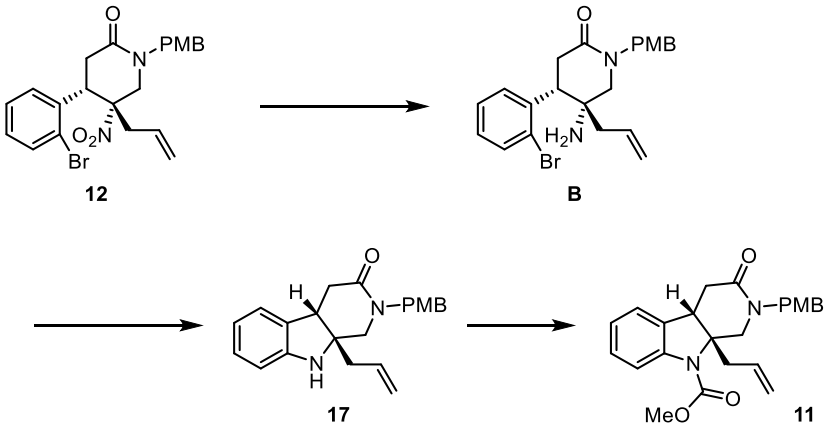


Procedure: To a cooled (0 °C) and stirred solution of **13** (11.8 g, 28.2 mmol) in CH_2Cl_2 (94.0 mL) under nitrogen was added $Pd(PPh_3)_4$ (330 mg, 0.28 mmol), allyl acetate (4.56 mL, 42.3 mmol) and DBU (6.31 mL, 42.3 mmol). The resulting solution was stirred at 0 °C for 1 hour before it was concentrated by rotary evaporation. Chromatography of the residue on silica gel, using 40% EtOAc in hexane, gave tilted compound **12** as a yellow foam (11.1 g, 86%).

R_f (50% EtOAc in hexane): 0.4; $[\alpha]_D^{25}$ +45.3 (c 0.22, $CHCl_3$); FTIR (neat, cm^{-1}) 3064, 2928, 1647, 1538, 1510, 1243, 1174, 1026; HRMS (EI, m/z) cald for $C_{22}H_{23}N_2O_4{}^{79}Br$ $[M]^{+\cdot}$ 458.08357, found 458.08358; ^1H NMR (700 MHz, $CDCl_3$) δ 7.60 (1H, dd, *J* = 8.0, 1.2 Hz, Ar*H*), 7.30–7.26 (1H, m, Ar*H*), 7.27 (2H, d, *J* = 8.5 Hz, $Ar_{PMB}H$), 7.18 (1H, td, *J* = 7.7, 1.6 Hz, Ar*H*), 6.98 (1H, dd, *J* = 8.0, 1.6 Hz, Ar*H*), 6.89 (2H, d, *J* = 8.5 Hz, $Ar_{PMB}H$), 5.41 (1H, dddd, *J* = 16.6, 10.2, 8.2, 6.1 Hz, CH_2CH=CH_2), 5.11 (1H, d, *J* = 10.1 Hz, CH=HC*H*), 5.05 (1H, dd, *J* = 16, 1.6 Hz, CH=*H*CH), 4.76 (1H, d, *J* = 14.4 Hz, C(O)N-HC*H*), 4.54 (1H, d, *J* = 14.4 Hz, C(O)N-*H*CH), 4.23 (1H, dd, *J* = 11.5, 5.6 Hz, Ar-C*H*), 3.81 (3H, s, OMe), 3.79 (1H, d, *J* = 14.3 Hz, N-HC*H*PMP), 3.47 (1H, d, *J* = 14.3 Hz, N-*H*CHPMP), 2.86–2.78 (2H, m, NC(O)*H*CH and *H*CH-CH=CH_2), 2.74 (1H, dd, *J* = 17.8, 5.7

Hz, NC(O)HC*H*), 2.62 (1H, dd, *J* = 14.7, 8.2 Hz, HC*H*-CH=CH_2); ^{13}C NMR (176 MHz, $CDCl_3$) δ 167.6 (*C*(O)N), 159.4 (Ar_{PMB}*C*), 135.4 (Ar*C*), 133.5 (Ar*C*H), 130.1 (Ar*C*H), 129.9 (Ar_{PMB}*C*H x 2), 129.3 (*C*H=CH_2), 129.0 (Ar*C*H), 128.2 (Ar*C*H), 128.0 (Ar_{PMB}*C*), 126.1 (Ar*C*), 122.1 (CH=*C*H_2), 114.3 (Ar_{PMB}*C*H x 2), 90.3 (*C*NO_2), 55.4 (O*C*H_3), 52.5 (*C*H_2-PMP), 49.6 (C(O)N*C*H_2), 44.1 (ArC-*C*H), 40.4 (allyl *C*H_2), 35.2 (NC(O)*C*H_2).

Compound 11



Procedure (B): To a cooled (0 °C) and stirred solution of **12** (3.18 g, 6.93 mmol) in EtOAc/EtOH (80.0/80.0 mL) was added zinc dust (4.5 g, 69.3 mmol) and 6M HCl aq. solution (23.0 mL, 138.6 mmol). The resulting mixture was stirred at 0 °C until all the starting material was fully consumed (typically around 30 min, checked by TLC). Reaction mixture was then poured into saturated $NaHCO_3$ aq. Solution (150 mL) at 0 °C and then the whole mixture was filtered through a pad of celite, followed by washing with EtOAc (200 mL). The organic layer was separated, and aqueous layer was extracted by another portion of EtOAc (150 mL). Combined organic layers were dried (Na_2SO_4) and concentrated by rotary evaporation to give the primary amine **B** as a grey foam (2.90 g, 98%) without further purification.

Compound B: R_f (66% EtOAc in hexane): 0.11; $[\alpha]_D^{25}$ +33.3 (c 0.27, $CHCl_3$); FTIR (neat, cm^{-1}): 3372, 3310, 3064, 2923, 1636, 1509, 1243; HRMS (EI, m/z) calcd. for $C_{22}H_{25}N_2O_2{}^{79}Br$ $[M]^{+\cdot}$ 428.10939, found 428.10940; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (1H, dd, *J* = 8.0, 1.3 Hz, ArC*H*), 7.45 (1H, dd, *J* = 7.9, 1.7 Hz, ArC*H*), 7.28–7.25 (3H, m, $Ar_{PMB}CH_2$ and ArC*H*), 7.12 (1H, td, *J* = 7.6, 1.7 Hz, ArC*H*), 6.88 (2H, d, *J* = 8.6 Hz, $Ar_{PMB}CH_2$), 5.65 (1H, ddt, *J* = 17.5, 10.1, 7.5 Hz, CH_2-C*H*=CH_2), 5.09 (1H, dd, *J* = 10.2, 1.9 Hz, CH_2-CH=HC*H*), 5.04–4.96 (1H, m, CH=*H*CH), 4.74 (1H,

d, *J* = 14.2 Hz, HC*H*-PMP), 4.42 (1H, d, *J* = 14.2 Hz, *H*CH-PMP), 3.82 (3H, s, OCH_3), 3.77 (1H, dd, *J* = 9.3, 6.3 Hz, ArC-C*H*), 3.22 (1H, d, *J* = 12.6 Hz, CH*H*NC=O), 2.93 (1H, d, *J* = 12.7 Hz, C*H*HNCO), 2.83 (1H, d, *J* = 9.3 Hz, HC*H*C(O)N), 2.73 (1H, dd, *J* = 18.2, 6.3 Hz, *H*CHC(O)N), 2.27 (1H, dd, *J* = 14.0, 7.3 Hz, HC*H*-CH=CH_2), 2.02 (1H, dd, *J* = 14.0, 7.7 Hz, *H*CH-CH=CH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.0 (N*C*=O), 159.2 (Ar_{PMB}*C*), 139.4 (Ar*C*), 133.3 (Ar*C*H), 132.1 (*C*H=CH_2), 129.9 (Ar_{PMB}*C*H X 2), 129.0 (Ar_{PMB}*C*), 129.0 (Ar*C*H), 128.8 (Ar*C*H), 128.0 (Ar*C*H), 126.4 (Ar*C*), 120.0 (CH=*C*H_2), 114.2 (Ar_{PMB}*C*H X 2), 57.5 (*C*H_2NC(O)), 55.4 (O*C*H_3), 53.0 (*C*-NH_2), 49.8 (*C*H_2-PMP), 45.0 (ArC-*C*H), 43.3 (*C*H_2CH=CH_2), 35.8 (*C*H_2C(O)N).

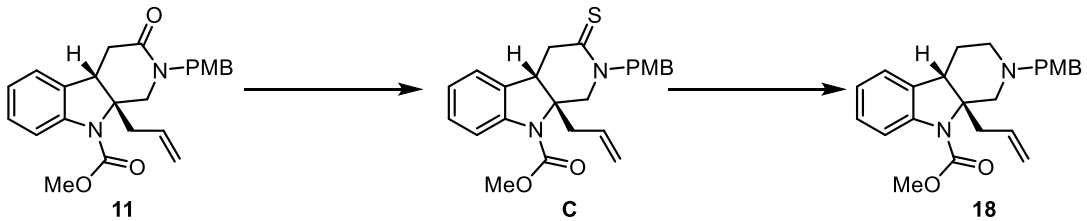
Procedure (17) [3]**:** A flame-dried, argon filled round bottom flask was added CuI (78.0 mg, 0.41 mmol), *L*-proline (94.0 mg, 0.82 mmol) and K_3PO_4 (1.70 g, 8.18 mmol), followed by addition of **B** (1.75 g, 4.09 mmol) in anhydrous DMSO (10.0 mL). The mixture was degassed and back filled with argon (repeated 3 times) and then heated to 95 °C (heating block) with stirring for 1 hour (TLC indicated all consumption of starting material). After cooling to room temperature, the reaction mixture was added water (50.0 mL) and EtOAc (50.0 mL). Aqueous layer was separated and extracted with EtOAc (50.0 mL x 2). The combined organic layers were washed with brine (100 mL x 3), dried (Na_2SO_4) and concentrated to give **17** as a brown oil (1.42 g, quant.) which was pure enough to go to next step. A small fraction was purified by chromatography (50% EtOAc/hexane) for data collection.

Compound 17: R_f (50% EtOAc in hexane): 0.21; $[\alpha]_D^{25}$ -95.1 (c 0.10, $CHCl_3$); FTIR (neat, cm^{-1}): 3330, 3079, 2908, 1646, 1608, 1511, 1486, 1244; HRMS (ESI-TOF, m/z): calcd. for $C_{22}H_{25}N_2O_2$ $[M+H]^+$ 349.1916, found 349.1911; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14–6.94 (4H, m, Ar_{PMB}C*H* and ArC*H*), 6.84 (2H, d, *J* = 8.6, Ar_{PMB}C*H*), 6.71 (1H, td, *J* = 7.4, 0.9 Hz, ArC*H*), 6.41 (1H, d, *J* = 7.8 Hz, ArC*H*), 5.66 (1H, ddt, *J* = 17.3, 10.2, 7.2 Hz, CH_2-C*H*=CH_2), 5.16–4.99 (2H, m, CH_2-CH=CH_2), 4.79 (1H, d, *J* = 14.5 Hz, HC*H*-PMP), 4.13 (1H, d, *J* = 14.5 Hz, *H*CH-PMP), 3.82 (3H, s, O*Me*), 3.45 (1H, t, *J* = 5.9 Hz, ArC-C*H*), 3.35 (1H, d, *J* = 13.6 Hz, C(O)N-HC*H*), 3.30 (1H, s, N-*H*), 3.10 (1H, d, *J* = 13.6 Hz, C(O)N-*H*CH), 2.75 (1H, dd, *J* = 15.1, 6.5 Hz, NC(O)-HC*H*), 2.66 (1H, dd, *J* = 15.0, 5.4 Hz, NC(O)-*H*CH), 2.26 (2H, d, *J* = 7.3 Hz, CH_2-CH=CH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0 (N*C*=O), 159.2 (Ar_{PMB}*C*), 149.8 (Ar*C*), 132.3 (*C*H=CH_2), 130.1 (Ar_{PMB}*C*H x 2), 129.9 (Ar*C*), 129.1 (Ar_{PMB}*C*), 128.4 (Ar*C*H), 124.5 (Ar*C*H), 119.9 (CH=CH_2), 119.2 (Ar*C*H), 114.1 (Ar_{PMB}*C*H x 2), 109.3 (Ar*C*H), 65.1 (*C*-allyl), 55.4 (O*C*H_3), 53.9 (C(O)N*C*H_2), 49.1 (PMP-*C*H_2), 46.0 (ArC-*C*H), 44.4 (*C*H_2CH=CH_2), 37.4 (*C*H_2C(O)N).

Procedure (11): To a solution of crude indoline **17** (3.60 g, 10.3 mmol) in methyl chloroformate (80 mL) was added Na_2CO_3 (11.0 g, 103 mmol) and the resulting mixture was heated to 60 °C (oil bath) under N_2 atmosphere and stirred overnight. The reaction mixture was cooled to room temperature and solid was filtered. The filtrate was concentrated via rotary evaporation and chromatography of the residue on silica gel, using 60% EtOAc in hexane, gave **11** as a yellow foam (3.70 g, 88%).

Compound 11: R_f (2:1 EtOAc:hexane): 0.26; $[\alpha]_D^{25}$ -41.7 (c 0.12, $CHCl_3$); m.p. 107.7–109.5 °C; FTIR (neat, cm^{-1}) 3003, 2953, 1696, 1660, 1511, 1484, 1365, 1202; HRMS (ESI-TOF, m/z) calcd. for $C_{24}H_{27}N_2O_4$ $[M+H]^+$ 407.1971, found 407.1962; ^1H NMR (600 MHz, $CDCl_3$) δ 7.87 – 6.78 (8H, m, Ar*H*), 5.57 – 5.47 (1H, m, CH_2-C*H*=CH_2), 5.13 – 5.00 (2H, m, CH_2-CH=C*H*$_2$), 4.90–4.74 (1H, m, HC*H*), 4.13 (1H, d, *J* = 13.9 Hz, C(O)N-HC*H*), 3.91 (1H, d, *J* = 14.6 Hz, *H*CH-PMP), 3.81 (3H, s, OC*H*$_3$), 3.66–3.58 (4H, m, ArC-C*H* and OC*H*$_3$), 3.54–3.37 (1H, m, C(O)N-*H*CH), 3.02 (1H, brs, HC*H*-CH=CH_2), 2.75 (1H, dd, *J* = 15.1, 6.0 Hz, NC(O)-*H*CH), 2.69 (1H, dd, *J* = 15.1, 5.2 Hz, NC(O)-HC*H*), 2.33–2.22 (1H, m, *H*CH-CH=CH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6 (N*C*=O), 159.0 ($Ar_{PMB}C$), 153.2 (N*C*O_2Me), 142.3 (Ar*C*), 131.5 (*C*H=CH_2), 130.8 (Ar*C*), 130.0 ($Ar_{PMB}C$H X 2), 129.2 (Ar*C*), 128.4 (Ar*C*H), 124.2 (Ar*C*H), 123.5 (Ar*C*H), 120.0 (CH=*C*H_2), 115.3 (Ar*C*H), 113.9 ($Ar_{PMB}C$H X 2), 69.7 (*C*-Allyl), 55.4 (O*C*H_3), 52.4 (N$CO_2C$$H_3$), 51.2 (C(O)N*C*$H_2$), 49.0 (*C*$H_2$-PMP), 44.0 (ArC-*C*H), 40.2 (*C*H_2-CH=CH_2), 37.1 (NC(O)*C*H_2).

Compound 18



Procedure (C): To a solution of **11** (2.50 g, 5.90 mmol) in toluene (120 mL) was added Lawesson's reagent (1.20 g, 2.96 mmol) and the resulting mixture was heated to reflux and stirred for 1 hour. The clear yellow solution was cooled to room temperature and concentrated by rotary evaporation. Chromatography of the residue on silica gel, using 30% EtOAc in hexane, gave intermediate **C** as a white foam (2.32 g, 93%).

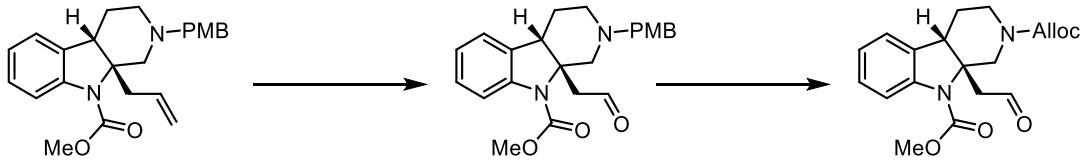
Compound C: R_f (30% EtOAc in hexane): 0.49; $[\alpha]_D^{25}$ -140.0 (c 0.22, $CHCl_3$); FTIR (neat, cm^{-1}): 3073, 2953, 1697, 1485, 1438, 1299, 1250, 1238; HRMS (ESI-TOF, m/z): calcd. for $C_{24}H_{27}N_2O_3S$ $[M+H]^+$ 423.1742, found 423.1745; ^1H NMR (700 MHz, $CDCl_3$) δ 7.84 – 6.79 (8H, m, Ar*H*), 5.65 – 5.43 (2H, m, HC*H*-PMP and CH_2-C*H*=CH_2), 5.13 – 4.98 (2H, m, CH_2-CH=C*H*$_2$), 4.69 – 4.42 (1H, m, C(S)N-*H*CH), 4.32 – 3.92 (1H, m, *H*CH-PMP), 3.82 (3H, s, OC*H*$_3$), 3.71 – 3.63 (4H, m, C(S)N-HC*H* and NCO_2CH_3), 3.60 (1H, t, *J* = 5.6 Hz, Ar-C*H*), 3.42 – 3.11 (2H, m, C*H*$_2$C(S)N), 3.05 – 2.70 (1H, m, *H*CH-CH=CH_2), 2.29 – 2.14 (1H, m, HC*H*-CH=CH_2); ^{13}C NMR (176 MHz, $CDCl_3$) δ 200.0 (*C*=S), 159.4 ($Ar_{PMB}C$), 153.2 (N*C*O$_2$Me), 142.1 (Ar*C*), 131.0 (*C*H=CH_2), 130.1 ($Ar_{PMB}C$H x 2), 129.9 ($Ar_{PMB}C$), 128.5 (Ar*C*H), 127.6 ($Ar_{PMB}C$), 124.5 (Ar*C*H), 123.6 (Ar*C*H), 120.3 (CH=*C*H$_2$), 115.4 (Ar*C*H), 114.1 ($Ar_{PMB}C$H X 2), 69.7 (*C*-allyl), 56.4 (PMP-*C*H$_2$), 55.4 (O*C*H$_3$), 53.9 (C(S)N*C*H$_2$), 52.5 (NCO_2CH_3), 47.1 (*C*H$_2$C(S)N), 44.3 (ArC-*C*H), 40.2 (*C*H$_2$-CH=CH_2).

Procedure (18): A solution of thiolactam **C** (2.40 g, 5.69 mmol) in methyl iodide (10.0 mL) was heated to reflux and stirred until the complete consumption of starting material (appx. 1 hour, monitored by TLC). Methyl iodide was distilled off (recovered) and the residue was dissolved in methanol (50.0 mL) and cooled to 0 ^oC and sodium borohydride (1.10 g, 28.5 mmol) was added portion wise. The resulting mixture was stirred at the same temperature for 1 h and then concentrated by rotary evaporation. The residue was quenched with saturated $NaHCO_3$ aq. solution (30.0 mL) and water (30.0 mL). The mixture was extracted with CH_2Cl_2 (30 mL x 3) and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to give **18** as a colourless oil which was pure without further purification (2.21 g, quant.). Chromatography on a small amount of crude product on silica gel was carried out (20% EtOAc in hexane) to give pure **18** for data collection.

Compound 18: R_f (30% EtOAc in hexane): 0.43; $[\alpha]_D^{25}$ -54.8 (c 1.04, $CHCl_3$); FTIR (neat, cm^{-1}) 3001, 2950, 1700, 1510, 1460, 1376, 1241; HRMS (ESI-TOF, m/z) calcd. for $C_{24}H_{29}N_2O_3$ $[M+H]^+$ 393.2178, found 393.2176; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, brs, Ar*H*), 7.22–7.14 (3H, m, $Ar_{PMB}H$ and Ar*H*), 7.09 (1H, dt, *J* = 7.4, 1.4 Hz, Ar*H*), 6.99 (1H, td, *J* = 7.4, 1.0 Hz, Ar*H*), 6.84 (2H, d, *J* = 8.5 Hz, $Ar_{PMB}H$), 5.78 (1H, dddd, *J* = 16.6, 10.1, 8.4, 6.1 Hz, CH_2-C*H*=CH_2), 5.14–4.96 (2H, m, CH_2-CH=C*H*$_2$), 3.81 (3H, s, OC*H*$_3$), 3.78 (3H, s, NCO_2CH_3), 3.40 (1H, d, *J* = 13.1 Hz, *H*CH-PMP), 3.38–3.35 (1H, m, ArC-C*H*), 3.31 (1H, d, *J* = 13.2 Hz, HC*H*-PMP), 3.13–2.94 (2H, m, *H*CH-CH=CH_2 and N-*H*CH-C), 2.84 (1H, dd, *J* = 14.5, 8.4 Hz, HC*H*-CH=CH_2), 2.64–2.56 (1H, m, N-*H*CHCH_2), 2.28 (1H, d, *J* = 11.6 Hz, N-HC*H*-C), 2.08–2.02 (3H, m, N-HC*H*CH_2 and N-CH_2C*H*$_2$); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 158.7 ($Ar_{PMB}C$), 154.1 (NCO_2CH_3), 142.7 (Ar*C*), 134.2 ($CH_2CH=CH_2$), 132.5 (Ar*C*), 130.8 ($Ar_{PMB}C$), 129.9 ($Ar_{PMB}CH$ x 2), 127.6 (Ar*C*H), 122.8 (Ar*C*H x 2), 118.2 ($CH_2CH=CH_2$), 115.5 (Ar*C*H), 113.6 ($Ar_{PMB}CH$ x 2), 69.5 (*C*-$CH_2CH=CH_2$), 62.0 (PMP-*C*H_2), 58.4 (N-*C*H_2-C), 55.3 (O*C*H_3), 52.2 (NCO_2CH_3), 49.4 (N-*C*H_2CH_2), 41.2 (ArC-*C*H), 39.2 (*C*$H_2CH=CH_2$), 24.3 (N-CH_2CH_2).

Compound 19



Procedure (D): To a cooled (0 °C) and stirred solution of **18** (2.20 g, 5.60 mmol) in CH_2Cl_2 (100 mL) was added TFA (1.30 mL, 16.8 mmol) and the resulting solution was stirred at this temperature for 10 min before it was cooled to -78 °C. Then ozone/oxygen flow was bubbled into the solution until a light blue colour appeared and persisted (TLC indicated all consumption of starting material). Ozone generator was stopped, and oxygen was bubbled until the blue colour disappeared and then dimethyl sulfide (4.00 mL, 56.0 mmol) was added. The mixture was stirred for 1.5 hour and triethylamine (4.00 mL, 28.0 mmol) was added to neutralise the acid. The mixture was concentrated by rotary evaporation and chromatography of the residue on silica gel, using 30% EtOAc/hexane, gave intermediate **D** as a colourless oil (1.95 g, 90%).

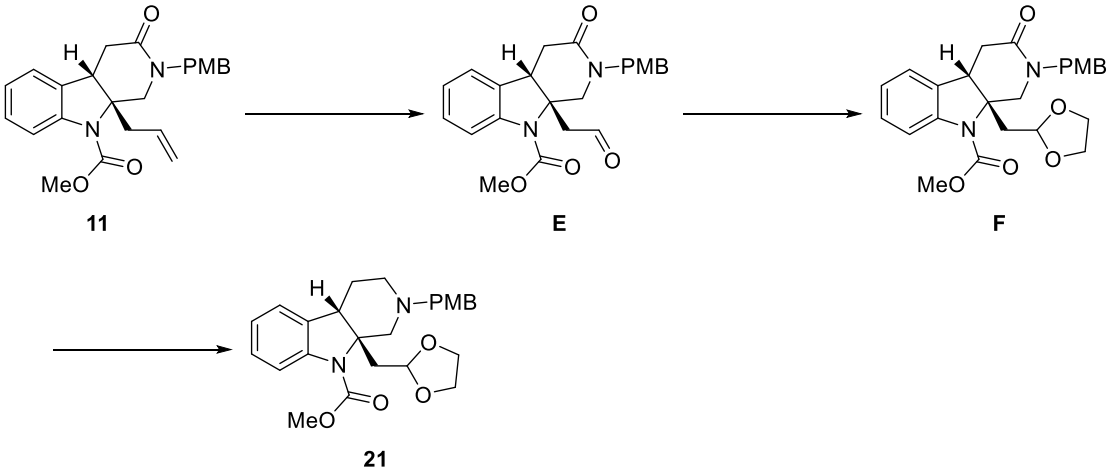
Compound D: R_f (30% EtOAc/hexane) 0.2; $[\alpha]_D^{25}$ -104.4 (c 0.12, $CHCl_3$); FTIR (neat, cm^{-1}) 2948, 2803, 1697, 1509, 1478, 1439, 1364, 1241; HRMS (ESI-TOF, m/z) calcd. for $C_{23}H_{27}N_2O_4$ $[M+H]^+$ 395.1971, found 395.1957; ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.80 (1H, t, *J* = 2.6 Hz, C*H*O), 7.66 (1H, brs, Ar*H*), 7.21 (1H, t, *J* = 7.8 Hz, Ar*H*), 7.17 (2H, d, *J* = 8.4 Hz, $Ar_{PMB}H$), 7.13 (1H, dt, *J* = 7.4, 1.4 Hz, Ar*H*), 7.04 (1H, td, *J* = 7.4, 1.0 Hz, Ar*H*), 6.85 (2H, d, *J* = 8.6 Hz, $Ar_{PMB}H$), 3.81 (6H, s, CO_2CH_3 and OCH_3), 3.43–3.31 (3H, m, ArC-C*H* and CH_2-PMP), 3.25–3.09 (3H, m, C-*H*CH-N and CH_2CHO), 2.72–2.64 (1H, m, CH_2-*H*CH-N), 2.25 (1H, d, *J* = 11.8 Hz, C-HC*H*-N), 2.13–2.02 (3H, m, CH_2-CH_2-N and CH_2-HC*H*-N); ^{13}C NMR (176 MHz, $CDCl_3$) δ 200.7 (*C*HO), 158.9 ($Ar_{PMB}C$), 153.9 (NCO_2Me), 141.8 (Ar*C*), 131.6 (Ar*C*), 130.2 ($Ar_{PMB}C$), 130.1 ($Ar_{PMB}CH$ x 2), 128.1 (Ar*C*H), 123.4 (Ar*C*H), 123.3 (Ar*C*H), 115.9 (Ar*C*H), 113.8 ($Ar_{PMB}CH$ x 2), 67.8 (*C*-CH_2-N), 61.9 (*C*H_2-PMP), 57.4 (C-*C*H_2-N),

55.4 (O*C*H_3), 52.7 (NCO_2*C*H_3), 49.2 (CH_2-*C*H_2-N), 48.7 (*C*H_2CHO), 43.7 (ArC-*C*H), 24.4 (*C*H_2-CH_2-N);

Procedure (19): To a solution of intermediate **D** (1.95 g, 4.95 mmol) in 1,2-dichloroethane (10.0 mL) was added allylchloroformate (5.3 mL, 49.5 mmol). The resulting solution was stirred at 65 ^oC for 24h and then warmed to reflux for another 24h. The reaction mixture was cooled to room temperature and concentrated by rotary evaporation. Chromatography of the residue on silica gel, using 30% EtOAc/hexane, gave **19** as a colourless oil (1.00 g, 56% yield, 77% yield brsm).

Compound 19: R_f (30% EtOAc/hexane): 0.12; $[\alpha]_D^{25}$ -73.3 (c 0.69, $CHCl_3$); FTIR (neat, cm^{-1}) 2953, 1697, 1649, 1551, 1461, 1365, 1116, 1076; HRMS (EI, m/z) calcd. for $C_{19}H_{22}N_2O_5$ $[M]^{+\cdot}$ 358.1523233, found 358.1522814; ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.70 – 9.64 (1H, m, C*H*O), 8.08–7.33 (1H, m, Ar*H*), 7.23–7.18 (1H, m, Ar*H*), 7.12 (1H, d, *J* = 7.4 Hz, Ar*H*), 7.02 (1H, t, *J* = 7.4 Hz, Ar*H*), 5.95–5.80 (1H, m, CH_2-C*H*=CH_2), 5.35–5.10 (2H, m, CH_2-CH=C*H*$_2$), 4.45 (2H, brs, OC*H*$_2$-CH=CH_2), 4.13–3.74 (5H, m, N-C-C*H*$_2$-N and NCO_2*Me*), 3.49 (1H, dt, *J* = 2.1, 5.9 Hz, N-*H*CHCH_2), 3.46 – 3.37 (1H, m, ArC-C*H*), 3.34 – 2.79 (3H, N-HC*H*-CH_2 and C*H*$_2$CHO), 2.28–2.11 (1H, m, N-CH_2-*H*CH), 2.05–1.87 (1H, m, N-CH_2-HC*H*); ^{13}C NMR (175 MHz, $CDCl_3$) δ 199.5 (*C*HO), 156.1 (N*C*O_2), 153.5 (N*C*O_2), 141.1 (Ar*C*H), 133.0 (CH_2*C*H=CH_2), 130.4 (Ar*C*), 128.7 (Ar*C*H), 124.0 (ArC*H*), 123.8 (ArC*H*), 117.7 (CH_2CH=*C*H_2), 115.5 (Ar*C*H); 67.4 (N-*C*-CH_2N), 66.3 (CO_2*C*H_2CH=CH_2), 53.0 (CO_2*C*H_3), 49.9 (*C*H_2CHO), 45.0 (N-*C*H_2-C), 44.6 (ArC-*C*H), 40.2 (N*C*H_2CH_2), 25.1 (NCH_2*C*H_2);

Compound 21



Procedure (E): To a solution of **11** (5.10 g, 12.6 mmol) in acetone/water (10:1, 110 mL) was added NMO (2.20 g, 18.8 mmol), 2,6-lutidine (3.00 mL, 25.1 mmol) and OsO_4 (4% w/w in water, 1.60 mL, 0.25 mmol). The resulting solution was stirred at room temperature for 24 h (TLC indicated all consumption of alkene) and $PhI(OAc)_2$ (6.0 g, 18.8 mmol) was added and the mixture was stirred for 0.5 h. Acetone was removed by rotary evaporation and the residue was added EtOAc (150 mL) and quenched with sat. Na_2SO_3 aq. (150 mL). The aqueous layer was separated and extracted with EtOAc (150 mL x 2). Combined organic layers were washed with brine (150 mL), dried (Na_2SO_4) and concentrated. Chromatography of the crude product on silica gel, using 3:2 to 4:1 EtOAc/hexane, gave aldehyde **E** as a colourless oil (4.01 g, 78%).

Compound E: R_f (100% EtOAc): 0.38; $[\alpha]_D^{25}$ -14.4 (c 1.22, $CHCl_3$); FTIR (neat, cm^{-1}) 2951, 2833, 1690, 1655, 1608, 1510, 1483, 1438, 1241, 751, 727; HRMS (ESI-TOF, m/z) calcd. for $C_{23}H_{25}N_2O_5$ $[M+H]^+$ 409.1764, found 409.1748; ^1H NMR (700 MHz, $CDCl_3$) δ 9.59 (1H, s, C*H*O), 7.30 (1H, brs, Ar*H*), 7.18 (1H, brs, Ar*H*), 7.15 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.02 (1H, t, *J* = 7.4 Hz, Ar*H*), 6.93 (2H, d, *J* = 8.2 Hz, $Ar_{PMB}H$), 6.78 - 6.77 (2H, m, $Ar_{PMB}H$), 4.78 (1H, brs, *H*CH-PMP), 4.10 (1H, brs, C(O)N-*H*CH), 3.90 (1H, brs HC*H*-PMP), 3.80 (3H, s, OCH_3), 3.70 (1H, t, *J* = 4.3 Hz, ArC-C*H*), 3.66 – 3.60 (4H, m, OCH_3 and C(O)N-HC*H*), 3.25 (1H, brs, *H*CH-CHO), 3.05 (1H, brs, HC*H*-CHO), 2.98 (1H, dd, *J* = 15.2, 6.1 Hz, NC(O)-*H*CH), 2.70 (1H, dd, *J* = 15.2, 4.5 Hz, NC(O)-HC*H*); ^{13}C NMR (176 MHz, $CDCl_3$) δ 199.0 (*C*HO), 170.5 (N*C*=O), 159.1 ($Ar_{PMB}C$), 153.3 (NCO_2Me), 141.5 (Ar*C*), 130.3 (Ar*C*), 130.0 ($Ar_{PMB}C$H X 2), 129.0 ($Ar_{PMB}C$), 128.7 (Ar*C*H), 124.4 (Ar*C*H), 124.0 (Ar*C*H), 115.3 (Ar*C*H), 114.0 ($Ar_{PMB}C$H X 2), 67.6 (*C*-CH_2CHO), 55.4 (O*C*H_3), 52.6 (O*C*H_3), 50.1 (NCO_2CH_3), 49.5 (C(O)N*C*H_2), 48.9 (*C*H_2-PMP), 45.5 (ArC-*C*H), 37.0 (*C*H_2CHO).

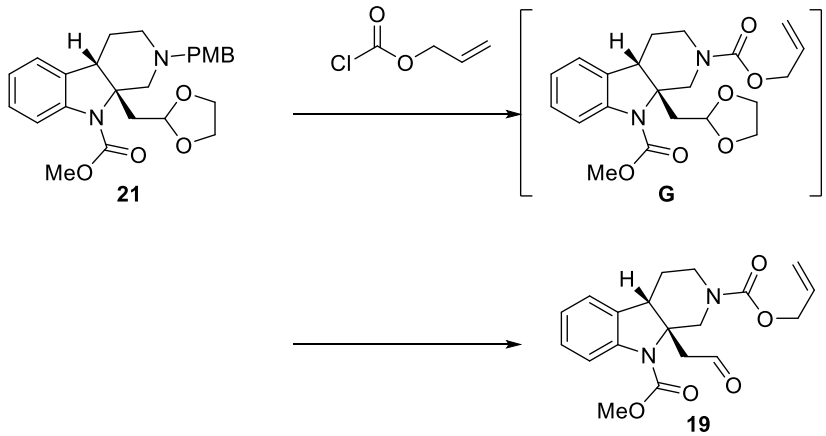
Procedure (F): To a cooled (-78 °C) and nitrogen filled round bottom flask charged with aldehyde **E** (1.755 g, 4.30 mmol) in CH_2Cl_2 (40.0 mL) was added $(CH_2OTMS)_2$ (1.10 mL, 4.5 mmol) and TMSOTf (0.08 mL, 0.43 mmol). The resulting solution was stirred at -78 °C for 10 min and then warmed to room temperature and stirred for 1 hour. Saturated $NaHCO_3$ aq (40 mL) was added to quench the reaction and the mixture was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were dried (Na_2SO_4) and concentrated by rotary evaporation to give compound **F** as a colourless oil (1.95 g, quant.) which was pure to go to next step without further purification. A small amount of sample was purified by column chromatography (silica gel, 80% EtOAc in hexane) for data collection.

Compound F: R_f (80% EtOAc in hexane): 0.29; $[\alpha]_D^{25}$ -22.5 (c 0.63, $CHCl_3$); FTIR (neat, cm^{-1}) 2995, 2885, 1696, 1662, 1510, 1483, 1440, 1357, 1243, 751; HRMS (ESI-TOF, m/z) calcd. for $C_{25}H_{29}N_2O_6$ $[M+H]^+$ 453.2026, found 453.2031; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.94—7.27 (1H, brs x 2, Ar*H*), 7.23 – 7.10 (2H, m, Ar*H*), 6.99 (1H, t, *J* = 7.3 Hz, Ar*H*), 6.95 (2H, d, *J* = 8.8 Hz, $Ar_{PMB}H$), 6.77 (2H, brs, $Ar_{PMB}H$), 4.78 (2H, brs, *H*C(O,O) and *H*CH-PMP), 4.14 (1H, brs, (O)N-*H*CH-C), 4.04 – 3.88 (1H, m, HC*H*-PMP), 3.98 (1H, t, *J* = 5.4 Hz, Ar-C*H*), 3.86 – 3.69 (5H, m, OCH_3 and OCH_2CH_2O), 3.69 – 3.56 (5H, OCH_3 and OCH_2CH_2O), 3.56 – 3.34 (1H, m, (O)N-HC*H*-C), 2.76 (1H, dd, *J* = 15.0, 6.3 Hz, *H*CHC(O)N), 2.66 (1H, dd, *J* = 15.1, 4.9, HC*H*C(O)N), 2.43 (1H, brs, *H*CH-CH(O,O)), 1.95 (1H, dd, *J* = 14.5, 4.5 Hz, HC*H*-CH(O,O)); ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.7 (*C*(O)N), 159.0 ($Ar_{PMB}C$), 153.3 (NCO_2Me), 142.2 (Ar*C*), 131.0 (Ar*C*), 129.9 ($Ar_{PMB}C$H X 2), 129.3 (Ar*C*), 128.3 (Ar*C*H), 124.3 (Ar*C*H), 123.5 (Ar*C*H), 115.4 (Ar*C*H), 113.9 ($Ar_{PMB}C$H X 2), 101.6 (H*C*(O,O)), 68.2 ((O)N-CH_2-*C*), 64.8 (OCH_2CH_2O), 64.6 (OCH_2CH_2O), 55.4 (OCH_3), 52.4 (NCO_2CH_3), 51.5 (C(O)NCH_2), 49.0 (CH_2-PMP), 44.4 (ArC-*C*H), 39.2 (CH_2CH(O,O)), 37.0 (CH_2C(O)N);

Procedure (21): To a solution of lactam **F** (364 mg, 0.80 mmol) in THF (3.00 mL) under nitrogen was added $Mo(CO)_6$ (21.0 mg, 0.08 mmol) and phenylsilane (0.26 mL, 2.08 mmol) and the resulting mixture was heated to 75 °C and stirred for 6 to 8 h. The reaction solution was cooled to 0 °C and quenched with 1 M NaOH aq. slowly until gas evolution ceased. Water (10.0 mL) and EtOAc (10.0 mL) were added and the aqueous layer was separated and extracted with EtOAc (10.0 mL). Combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel, using 30% EtOAc in hexane, gave the compound **21** as a colourless oil (267 mg, 76%).

Compound 21: R_f (80% EtOAc in hxane): 0.63; $[\alpha]_D^{25}$ -42.8 (c 0.72, $CHCl_3$); FTIR (neat, cm^{-1}) 2948, 2881, 2798, 1699, 1509, 1477, 1439, 1476, 1359, 1242, 1125; HRMS (ESI-TOF, m/z) cald. for $C_{25}H_{31}N_2O_5$ $[M+H]^+$ 439.2233, found 439.2221; ^1H NMR (700 MHz, $CDCl_3$) δ 7.75 (1H, brs, Ar*H*), 7.18 (1H, t, *J* = 7.8 Hz, Ar*H*), 7.15 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.09 (1H, *J* = 7.3 Hz, Ar*H*), 6.99 (1H, *J* = 7.1 Hz, Ar*H*), 6.82 (2H, d, *J* = 8.6 Hz, Ar*H*), 4.98 (1H, dd, *J* = 6.0, 3.1 Hz, *H*C(O,O)), 3.96 – 3.88 (2H, m, OC*H*$_2$CH$_2$O), 3.80 (3H, s, OC*H*$_3$), 3.77 (3H, brs, OCH_3), 3.76 – 3.73 (2H, m, OCH_2CH_2O), 3.68 (1H, t, *J* = 4.0 Hz, Ar-C*H*), 3.37 (1H, d, *J* = 13.1 Hz, N-*H*CH-C), 3.30 (1H, d, *J* = 13.2 Hz, N-HC*H*-C), 2.98 (1H, d, *J* = 10.0 Hz, N-*H*CH-C), 2.74 (1H, brs, C-*H*CH-CH(O,O)), 2.63 – 2.59 (1H, m, N-*H*CH-CH$_2$), 2.52 (1H, dd, *J* = 15.2, 6.0 Hz, C-HC*H*-CH(O,O)), 2.24 (1H, d, *J* = 11.4, N-HC*H*-C), 2.11 – 2.00 (3H, m, N-HC*H*-CH$_2$ and N-CH-C*H*$_2$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.7 ($Ar_{PMB}C$), 154.4 (NCO_2Me), 142.7 (Ar*C*), 132.4 (Ar*C*), 130.9 ($Ar_{PMB}C$), 129.9 ($Ar_{PMB}C$H x 2), 127.7 (Ar*C*H), 122.9 (Ar*C*H), 122.8 (Ar*C*H), 115.6 (Ar*C*H), 113.7 ($Ar_{PMB}C$H x 2), 102.5 (*C*H(O,O)), 68.0 (N-CH$_2$-*C*), 65.0 (OCH_2CH_2O), 64.4 (OCH_2CH_2O), 62.1 (N-*C*H$_2$-PMP), 58.8 (N-*C*H$_2$-C), 55.4 (OCH_3), 52.4 (OCH_3), 49.3 (N-*C*H$_2$CH$_2$), 41.8 (ArC-*C*H), 38.4 (C-*C*H$_2$CH(O,O)), 24.2 (N-CH$_2$*C*H$_2$).

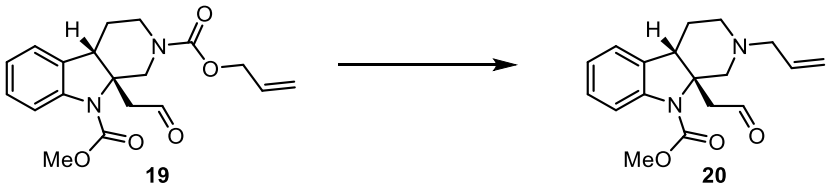
Compound 19



Procedure: To a stirred solution of **21** (4.78 g, 10.9 mmol) in $ClCH_2CH_2Cl$ (55.0 mL) under N_2 atmosphere was added allyl chloroformate (5.60 mL, 54.6 mmol), and $NaHCO_3$ (4.6 g, 54.6 mmol) and the resulting mixture was heated to 80 ^oC for 1 h. After cooling to room temperature, the $NaHCO_3$ was filtered and filtrate was concentrated by rotary evaporation and dried on high vacuum for 6 h. This crude dioxolane product **G** was then dissolved in THF (7.00 mL), followed by addition of acetic acid AcOH (14.0 mL) and H_2O (7.00 mL). The resulting

mixture was the stirred at 90 °C until full consumption of dioxolane (24 h). The reaction mixture was cooled to room temperature, diluted with EtOAc (100 mL) and washed successfully with H_2O (100 mL x 2) and sat. $NaHCO_3$ aq. solution (100 mL x 3). The combined organic layers were dried (Na_2SO_4) and concentrated by rotary evaporation. Chromatography of the residue on silica gel, using 30% EtOAc in hexane, gave aldehyde **19** as a colourless oil (2.82 g, 72% over two steps).

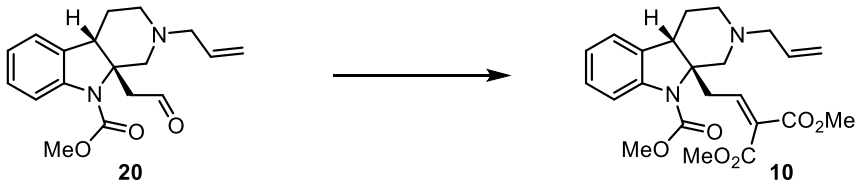
Compound 20



Procedure: To a solution of **19** (3.06 g, 8.54 mmol) in dichloromethane (80.0 mL) under N_2 atmosphere was added $Pd(PPh_3)_4$ (246 mg, 2.50 mol%) and the resulting yellow solution was stirred at room temperature for 1 hour. The solution was then concentrated by rotary evaporation and flash chromatography of the residue on silica gel, using 30% EtOAc/hexane, gave **20** as a yellow oil (2.47 g, 92% yield).

R_f (3:7 EtOAc/hexane): 0.28; $[\alpha]_D^{25}$ -36.7 (c 0.15, $CHCl_3$); FTIR (neat, cm^{-1}) 2914, 2853, 2806, 1711, 1479, 1462, 1154, 1074; HRMS (ESI-TOF, m/z) calcd. for $C_{18}H_{23}N_2O_3$ $[M+H]^+$ 315.1703, found 315.1707; ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.86 (1H, brs, C*H*O), 7.68 (1H, brs, Ar*H*), 7.21 (1H, t, *J* = 7.8 Hz, Ar*H*), 7.13 (1H, d, *J* = 7.4 Hz, Ar*H*), 7.03 (1H, t, *J* = 7.5 Hz, Ar*H*), 5.77 (1H, ddd, *J* = 14.7, 11.0, 7.0 Hz, CH_2-C*H*=CH_2), 5.15 – 5.09 (2H, m, CH_2-CH=C*H*$_2$), 3.85 (3H, s, NCO_2*Me*), 3.38 (1H, brs, ArC-C*H*), 3.29 – 3.10 (3H, m, C*H*$_2$CHO and N-C-HC*H*-N), 2.96 (1H, dd, *J* = 13.7, 6.3 Hz, HC*H*-CH=CH_2), 2.90 (1H, dd, *J* = 13.7, 6.6 Hz, *H*CH-CH=CH_2), 2.75–2.69 (1H, m, N-HC*H*-CH_2), 2.21 (1H, d, J = 11.9 Hz, N-C-*H*CH-N), 2.13–2.02 (3H, m, N-*H*CH-CH_2 and N-CH_2-C*H*$_2$); ^{13}C NMR (176 MHz, $CDCl_3$) δ 200.4 (*C*HO), 154.0 (N*C*O_2Me), 141.9 (Ar*C*), 134.9 (CH_2-*C*H=CH_2), 131.6 (Ar*C*), 128.2 (Ar*C*H), 123.5 (Ar*C*H), 123.3 (Ar*C*H), 118.1 (CH_2-CH=*C*H_2), 115.9 (Ar*C*H), 67.8 (N-*C*-CH_2N), 61.2 (N-*C*H_2CH=CH_2), 57.3 (N-C-*C*H_2N), 52.7 (NCO_2*C*H_3), 49.4 (N*C*H_2CH_2), 48.7 (*C*H_2CHO), 43.6 (ArC-*C*H), 24.5 (NCH_2*C*H_2).

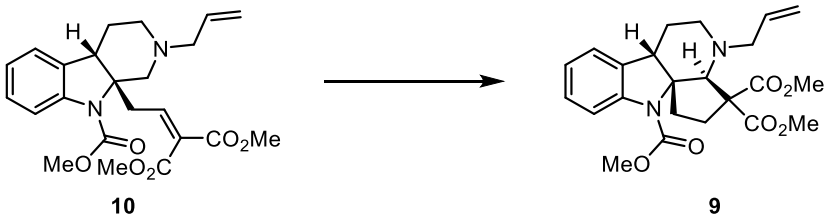
Compound 10



Procedure: To a solution of aldehyde **20** (2.47 g, 7.87 mmol) in DMSO (80.0 mL) was added dimethyl malonate (2.69 mL, 23.6 mmol) and *L*-proline (1.36 g, 11.8 mmol). The resulting mixture was stirred at room temperature overnight. Water (200 mL) was added and the mixture was extracted with EtOAc (150 mL x 3). Combined organic layers were washed with brine (500 mL x 3), dried (Na_2SO_4) and concentrated by rotary evaporation. Flash chromatography of the residue on silica gel, using 30% EtOAc in hexane, gave **10** as a colourless oil (3.24 g, 96% yield).

R_f (30% EtOAc/hexane) 0.12; $[\alpha]_D^{25}$ -54.2 (c 0.12, $CHCl_3$); FTIR (neat, cm^{-1}) 2952, 1707, 1481, 1439, 1363, 1249; HRMS (ESI-TOF, m/z) calcd. for $C_{23}H_{29}N_2O_6$ $[M+H]^+$ 429.2020, found 429.2017; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.72 (1H, brs, Ar*H*), 7.19 (1H, t, *J* = 7.8 Hz, Ar*H*), 7.13–7.10 (2H, m, C*H*=C$(CO_2Me)_2$ and Ar*H*), 7.02 (1H, t, *J* = 7.4 Hz, Ar*H*), 5.78 (1H, ddt, *J* = 16.7, 10.2, 6.3 Hz, CH_2CH=CH_2), 5.14–5.06 (2H, m, CH_2CH=CH_2), 3.85 (6H, brs, CO_2CH_3 and N-CO_2CH_3), 3.73 (3H, s, CO_2CH_3), 3.34 – 3.15 (3H, m, ArC-C*H* and CH_2-CH=C$(CO_2Me)_2$), 3.09 (1H, d, *J* = 11.1 Hz, N-*H*CH-C), 2.94–2.86 (2H, m, CH_2-CH=CH_2), 2.69–2.66 (1H, m, N-*H*CHCH_2), 2.19 (1H, d, *J* = 11.7, N-HC*H*-C), 2.09–1.97 (3H, m, N-HC*H*-CH_2 and N-CH_2CH_2); ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.0 (CO_2Me), 164.2 (CO_2Me), 154.2 (N-CO_2Me), 145.5 (*C*H=C$(CO_2Me)_2$), 142.3 (Ar*C*), 135.3 (CH_2CH=CH_2), 131.9 (Ar*C*), 129.8 (CH=*C*$(CO_2Me)_2$), 128.0 (Ar*C*H), 123.3 (Ar*C*H), 123.1 (Ar*C*H), 117.7 (CH_2CH=*C*H_2), 115.9 (Ar*C*H), 69.3 (N-*C*CH_2N), 61.4 (N-*C*H_2CH=CH_2), 58.2 (N-C*C*H_2N), 52.7, 52.53 and 52.48 (*C*O_2Me x 2 and N-*C*O_2Me), 49.6 (N-*C*H_2CH_2), 42.2 (ArC-*C*H), 35.2 (*C*H_2CH=C$(CO_2Me)_2$), 24.3 (N-CH_2*C*H_2).

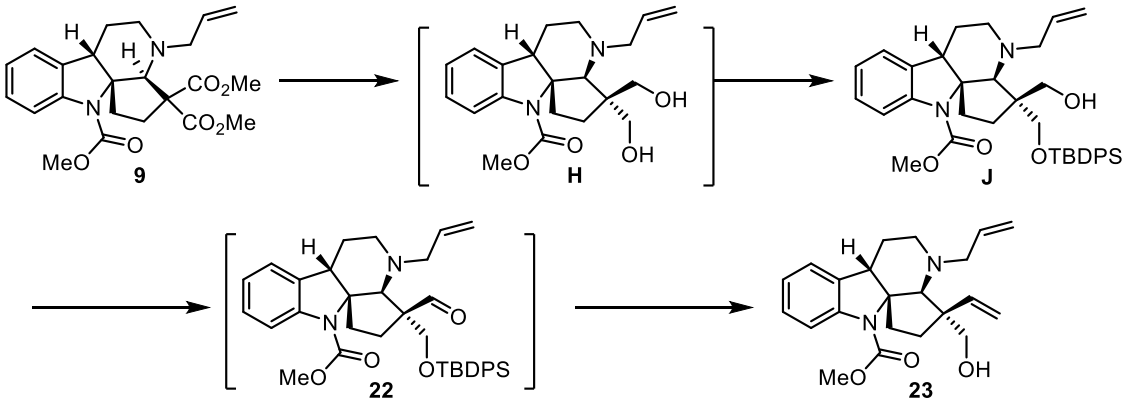
Compound 9



Procedure: To a solution of **10** (3.24 g, 7.57 mmol) in anhydrous toluene (150 mL) under N_2 atmosphere was added $Yb(OTf)_3$ (469 mg, 0.76 mmol) and the resulting mixture was heated to 110 ^oC and stirred for 4 h. The reaction mixture was cooled to room temperature and concentrated by rotary evaporation. Flash chromatography of the crude material on silica gel, using 30% EtOAc in hexane, gave **9** as a colourless oil (2.59 g, 80% yield).

R_f (30% EtOAc/hexane) 0.39; $[\alpha]_D^{25}$ +34.4 (c 0.1, $CHCl_3$); FTIR (neat, cm^{-1}) 2951, 1730, 1705, 1484, 1438, 1370, 1260; HRMS (ESI-TOF, m/z) calcd. for $C_{23}H_{29}N_2O_6$ $[M+H]^+$ 429.2020, found 429.2018; ^1H NMR (700 MHz, $CDCl_3$) δ 7.78 (1H, s, Ar*H*), 7.18 (1H, td, *J* = 7.9, 0.8 Hz, Ar*H*), 7.11 (1H, d, *J* = 7.4 Hz, Ar*H*), 6.99 (1H, td, *J* = 7.4, 1.0 Hz, Ar*H*), 5.63 (1H, dddd, *J* = 17.2, 10.1, 7.2, 5.8 Hz, NCH_2CH=CH_2), 5.42 (1H, s, N-C-C*H*-C), 5.09 – 4.99 (2H, m, NCH_2CH=CH_2), 3.86 (3H, s, CO_2CH_3), 3.78 (3H, s, CO_2CH_3), 3.72 (3H, s, CO_2CH_3), 3.30 – 3.24 (2H, m, NCH_2CH=CH_2), 3.21 (1H, dd, *J* = 6.6, 3.3 Hz, ArC-C*H*), 2.69 (1H, td, *J* = 13.6, 6.4 Hz, C-*H*CHCH$_2$C), 2.52 (1H, ddd, *J* = 11.1, 5.4, 3.5 Hz, N-*H*CHCH$_2$), 2.40 (1H, td, *J* = 12.8, 6.6 Hz, C-HC*H*CH$_2$C), 2.27 – 2.18 (2H, m, C-CH$_2$-*H*CH-C and N-HC*H*CH$_2$), 2.16 – 2.07 (1H, m, N-CH$_2$-*H*CH), 1.68 (1H, ddt, *J* = 13.7, 5.6, 2.9 Hz, N-CH$_2$-HC*H*), 1.61 (1H, ddd, *J* = 12.6, 6.4, 1.9 Hz, C-CH$_2$-HC*H*-C); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.0 (*C*O$_2$Me), 171.1 (*C*O$_2$Me), 153.7 (N*C*O$_2$Me), 142.4 (Ar*C*), 135.4 (NCH_2CH=CH_2), 133.4 (Ar*C*), 127.9 (Ar*C*H), 124.0 (Ar*C*H), 123.1 (Ar*C*H), 117.3 (NCH_2CH=CH_2), 115.4 (Ar*C*H), 74.8 (*C*(CO$_2$Me)$_2$), 65.4 (N-*C*-CHN), 64.9 (N-C-*C*HN), 60.0 (N-*C*H$_2$CH=CH$_2$), 53.0 (CO_2CH_3), 52.6 (CO_2CH_3), 52.4 (CO_2CH_3), 45.5 (ArC-*C*H), 42.1 (N-*C*H$_2$CH$_2$), 35.0 (N-CH$_2$*C*H$_2$), 30.0 (C-*C*H$_2$CH$_2$-C), 29.9 (C-CH$_2$*C*H$_2$-C);

Compound 23



Procedure (J): To a cooled (0 °C) and stirred solution of **9** (216 mg, 0.59 mmol) in THF (10.0 mL) was added $LiAlH_4$ (1.0 M in THF, 2.40 mmol, 2.40 mmol) under N_2. Cooling bath was then removed, and the solution was stirred at room temperature (22 °C) for 15 min. The reaction solution was cooled back to 0 °C and quenched by dropwise addition of H_2O (0.30 mL) and 15% NaOH aq. (0.30 mL). EtOAc(15.0 mL) was added and the resulting mixture was stirred at room temperature for 15 min. Anhydrous Na_2SO_4 was then added and stirring was continued for another 30 min before the precipitates were filtered through a pad of celite. The resulting filtrate was concentrated, and the residue was simply purified by a short silica column (5 cm), eluted by 80% EtOAc in hexane, to remove any non-polar side products. The diol **H** obtained (178 mg, 61% yield), with acceptable purity, was put into next step directly without further purification.

To a cooled (0 °C) and stirred solution of diol **H** (160 mg, 0.43 mmol) in CH_2Cl_2 (4.00 mL) was added Et_3N (0.13 mL, 0.86 mmol), DMAP (16.0 mg) and TBDPSCl (0.13 mL, 0.47 mmol). The resulting mixture was stirred at 0 °C for 10 min and then warmed to room temperature and stirred until all consumption of starting material. The reaction solution was diluted with CH_2Cl_2 (15.0 mL) and washed with water (10.0 mL x 2). The organic layer was dried (Na_2SO_4) and concentrated by rotary evaporation. Chromatography of the residue on silica gel, using 20% EtOAc in hexane, gave intermediate **J** (220 mg, 84%, 51% over 2 steps) as a white foam.

Compound J: R_f (20% EtOAc in hexane): 0.29; $[\alpha]_D^{25}$ +45.2 (c 0.87, $CHCl_3$); FTIR (neat, cm^{-1}) 3485, 2928, 2853, 1698, 1480, 1439, 1360, 1108, 1063, 751, 702; HRMS (ESI-TOF, m/z) calcd. for $C_{37}H_{47}N_2O_4Si$ $[M+H]^+$ 611.3300, found 611.3310; ^1H NMR (700 MHz, $CDCl_3$) δ 7.74—7.71 (4H, m, Si*Ph*$_2$-t-Bu), 7.66 (1H, brs, Ar*H*), 7.47—7.39 (6H, m, Si*Ph*$_2$-t-Bu), 7.15 (1H, td, *J* = 7.4,

1.3 Hz, Ar*H*), 7.04 (1H, d, *J* = 7.3 Hz, Ar*H*), 6.96 (1H, td, *J* = 7.4, 0.8 Hz, Ar*H*), 5.69 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, NCH_2-C*H*=CH_2), 5.05 (1H, dd, *J* = 10.0, 1.3 Hz, NCH_2-CH=*H*CH), 4.99 (1H, dd, *J* = 17.1, 1.4 Hz, NCH_2-CH=HC*H*), 4.39 (1H, s, N-C*H*-C-N), 4.08 (1H, d, *J* = 10.1 Hz, *H*CH-OTBDPS), 3.97 (1H, d, *J* = 10.3 Hz, *H*CH-OH), 3.86 (3H, s, NCO_2CH_3), 3.80 (1H, d, *J* = 10.2 Hz, HC*H*-OH), 3.61 (1H, d, *J* = 10.0 Hz, HC*H*-OTBDPS), 3.21 (1H, ddt, *J* = 13.9, 6.5, 1.3 Hz, N-*H*CH-CH=CH_2), 3.10 (1H, ddt, *J* = 14.0, 6.7, 1.3 Hz, N-HC*H*-CH=CH_2), 2.67 (1H, t, *J* = 6.9 Hz, Ar-C*H*), 2.42—2.31 (2H, m, N-CH_2-CH_2), 2.19 (1H, dt, *J* = 14.5, 7.9 Hz, C-*H*CH-CH_2-C), 1.75 (1H, dt, *J* = 13.4, 7.0 Hz, C-CH_2-*H*CH-C), 1.63 (1H, dt, *J* = 13.0, 7.6 Hz, C-CH_2-HC*H*-C), 1.46 (1H, dt, *J* = 13.3, 6.7 Hz, C-HC*H*-CH_2-C), 1.42—1.34 (2H, m, N-CH_2-CH_2); ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.3 (N*C*O_2Me), 141.8 (Ar*C*, weak signal, confirmed by HMBC), 136.1 (NCH_2-*C*H=CH_2), 136.0 (ArC*H*, TBDPS), 135.9 (ArC*H*, TBDPS), 134.2 (Ar*C*), 133.5 (Ar*C*, TBDPS), 133.4 (Ar*C*, TBDPS), 123.0 (Ar*C*H, TBDPS), 129.9 (Ar*C*H, TBDPS), 127.9 (Ar*C*H, TBDPS), 127.9 (Ar*C*H, TBDPS), 127.7 (Ar*C*H), 123.8 (Ar*C*H), 123.1 (Ar*C*H), 117.7 (NCH_2-CH=*C*H_2), 115.6 (Ar*C*H), 72.8 (N-*C*-CH-N), 70.3 (*C*H_2OH), 66.8 (*C*H_2OTBDPS), 64.1 (N-C-*C*H-N), 60.4 (N-*C*H_2-CH=CH_2), 52.4 (NCO_2CH_3), 50.9 (*C*(CH_2O)), 47.6 (ArC-*C*H), 44.6 (N-*C*H_2CH_2), 36.4 (C-*C*H_2CH_2-C), 27.8 (N-CH_2*C*H_2), 27.6 (C-CH_2*C*H_2-C), 27.1 (C(*C*H_3)$_3$, TBDPS), 19.4 (*C*(CH_3)$_3$, TBDPS).

Procedure (22): To a stirred solution of alcohol **J** (327 mg, 0.54 mmol) in EtOAc (10.0 mL) was added IBX (450 mg, 1.61 mmol) and the resulting mixture was stirred at 80 °C for 2 h. After cooling to room temperature, solids were filtered, and filtrate was concentrated by rotary evaporation. The residue was dissolved in CH_2Cl_2 (10.0 mL), followed by addition of silica gel (3.00 g) and the mixture was stirred at room temperature for 2 h. Silica gel was filtered, and the filtrate was concentrated by rotary evaporation to give **22** (296 mg, 92%, 93:7 *dr* by ^{1}H NMR) as a colourless oil which was used directly without purification.

Compound 22: R_f (20% EtOAc in hexane): 0.63; ^{1}H NMR (700 MHz, $CDCl_3$) **major** δ 9.69 (1H, s, C*H*O), 7.70—7.61 (5H, m, Si*Ph*$_2$-t-Bu), 7.48—7.35 (6H, m, Si*Ph*$_2$-t-Bu and Ar*H*), 7.21—7.05 (2H, m, Ar*H*), 6.98 (1H, td, *J* = 7.3, 1.0 Hz, Ar*H*), 5.68—5.51 (1H, m, NCH_2-C*H*=CH_2), 5.04—4.87 (2H, m, NCH_2-CH=CH_2), 4.34 (1H, brs, N-C*H*-C-N), 4.23 (1H, d, *J* = 10.2 Hz, *H*CH-OTBDPS), 3.73 (1H, d, *J* = 10.6 Hz, HC*H*-OTBDPS), 3.63 (3H, s, NCO_2CH_3), 3.13 (1H, dd, *J* = 13.9, 6.7 Hz, N-*H*CH-CH=CH_2), 3.09—3.02 (2H, m, N-HC*H*-CH=CH_2 and ArC-C*H*), 2.53 (1H, ddd, *J* = 12.2, 8.9, 2.8 Hz, N-*H*CH-CH_2), 2.32—2.24 (2H, m, N-HC*H*-CH_2 and C-*H*CH-CH_2-C), 2.12—1.98 (1H, m, C-HC*H*-

CH_2-C), 1.75—1.60 (2H, m, C-CH_2-*H*CH-C and N-CH_2-*H*CH), 1.58—1.46 (2H, m, C-CH_2-HC*H*-C and N-CH_2-HC*H*), 1.04 (9H, s, $SiPh_2$-*t-Bu*);

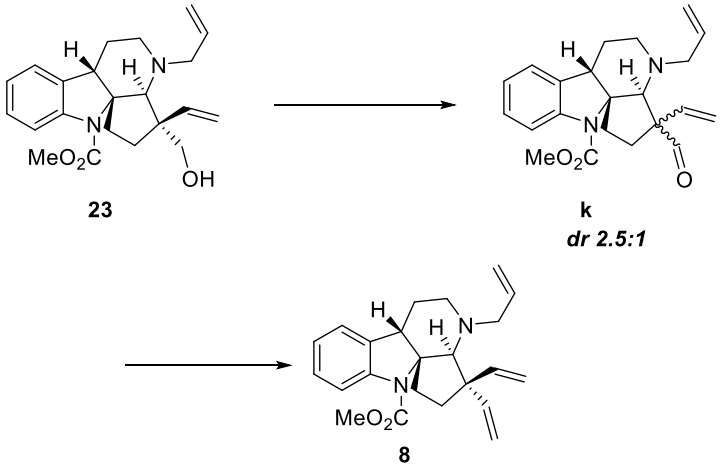
Procedure (23): To a round bottom flask charged with aldehyde **22** (915 mg, 1.50 mmol) under N_2 atmosphere was added Petasis reagent (13.5% w/w, 12.0 mL) and the resulting solution was stirred at 80 °C in dark until full consumption of starting material (checked by TLC). After cooling to 60 °C, aq. MeOH (MeOH:H_2O 9:1, 5.00 mL) was added the resulting mixture stirred at 60 °C for 2 h to decompose excess Petasis reagent. The brown precipitates were filtered through a pad of silica gel and then washed with EtOAc (30.0 mL x 2). The filtrate was concentrated by rotary evaporation and the crude alkene product was put into next step directly.

A solution of TBAF (1.0 M, 15.0 mL) was added to above crude alkene and the resulting solution was stirred at 70 °C for 3 h. After cooling to room temperature, THF was removed by rotary evaporation and the residue was added $NaClO_4$ aq. and stirred for 5 min before extraction with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to ~10 mL. Then 20% EtOAc in hexane (100 mL) was added and the resulting precipitates (*n*-Bu4N$^+$X$^-$) was filtered and the filtrate was concentrated. Chromatography of the residue on silica gel, using 20% EtOAc in hexane, gave alcohol **23** as a yellow oil (361 mg, 65%). ^{1}H NMR indicated a mixture of epimers (*dr* 94:6).

Compound 23: R_f (20% EtOAc in hexane) 0.22; FTIR (neat, cm^{-1}) 3465, 2947, 2867, 1699, 1481, 1440, 1361, 1060, 915; HRMS (ESI-TOF, m/z) calcd. for $C_{22}H_{29}N_2O_3$ $[M+H]^+$ 369.2173, found 369.2172; ^{1}H NMR (700 MHz, $CDCl_3$): mixture of diastereomers, dr 94:6; **major isomer**: δ 7.70 (1H, brs, Ar*H*), 7.18 (1H, td, *J* = 7.8, 1.4 Hz, Ar*H*), 7.12 (1H, dt, *J* = 7.4, 0.7 Hz, Ar*H*), 6.99 (1H, td, *J* = 7.3, 1.0 Hz, Ar*H*), 6.33 (1H, dd, *J* = 17.9, 11.0 Hz, C-C*H*=CH_2), 5.76 (1H, dddd, *J* = 17.0, 10.1, 6.8, 6.1 Hz, NCH_2-C*H*=CH_2), 5.28 (1H, dd, *J* = 10.9, 1.6 Hz, C-CH=*H*CH), 5.17 (1H, dd, *J* = 17.9, 1.7 Hz, C-CH=HC*H*), 5.13—4.98 (2H, m, NCH_2-CH=CH_2), 4.34 (1H, s, N-C*H*-C-N), 3.87 (3H, s, OCH_3), 3.61 (1H, d, *J* = 10.4 Hz, C-*H*CH-OH), 3.45 (1H, d, *J* = 10.4 Hz, C-HC*H*-OH), 3.32 (1H, ddt, *J* = 13.8, 6.8, 1.3 Hz, N-*H*CH-CH=CH_2), 3.19 (1H, ddt, *J* = 13.8, 6.1, 1.5 Hz, N-HC*H*-CH=CH_2), 3.01 (1H, dd, *J* = 8.6, 6.2 Hz, Ar-C*H*), 2.88 (1H, ddd, *J* = 13.0, 10.0, 3.0 Hz, N-*H*CH-CH_2), 2.57 (1H, brs, O*H*), 2.46 (1H, ddd, *J* = 12.9, 6.3, 3.5 Hz, N-HC*H*-CH_2), 2.35—2.25 (1H, m, C-*H*CH-CH_2-C), 1.93 (1H, ddd, *J* = 12.0, 7.6, 3.3 Hz, C-CH_2-*H*CH-C), 1.74—1.61 (3H, m, C-HC*H*-CH_2-C, C-CH_2-

HC*H*-C and N-CH_2-*H*CH), 1.51 (1H, dddd, *J* = 13.8, 9.9, 8.6, 3.5 Hz, N-CH_2-HC*H*); ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.3 (N*C*O_2Me), 142.8 (C-*C*H=CH_2), 142.0 (Ar*C*), 137.0 (NCH_2-*C*H=CH_2), 134.3 (Ar*C*), 127.7 (Ar*C*H), 123.9 (Ar*C*H), 123.1 (Ar*C*H), 117.2 (NCH_2-CH=*C*H_2), 115.7 (Ar*C*H), 114.5 (C-CH=*C*H_2), 72.4 (N-*C*-CH-N), 69.3 (C-*C*H_2OH), 64.2 (N-*C*H-C-N), 59.7 (N-*C*H_2CH=CH_2), 52.5 (*C*-CH_2OH), 52.1 (NCO_2*C*H_3), 46.4 (ArC-*C*H), 44.4 (N-*C*$H_2$$CH_2$), 34.1 (C-*C*$H_2$$CH_2$-C), 27.6 (C-$CH_2$*C*$H_2$-C), 26.4 (N$CH_2$*C*$H_2$).

Compound 8



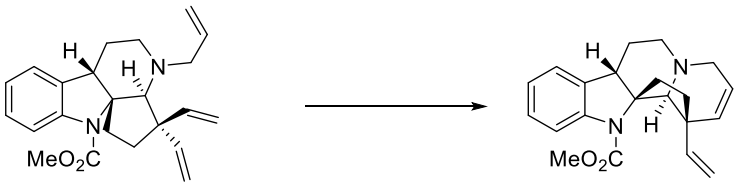
Procedure: To a cooled (-78 °C) and stirred solution of DMSO (0.25 mL, 3.58 mmol) in CH_2Cl_2 (5.00 mL) was added $(COCl)_2$ (0.15 mL, 1.79 mmol) dropwise and the resulting solution was stirred -78 °C for 30 min. Then a solution of **23** (150 mg, 0.407 mmol) in CH_2Cl_2 (3.00 mL) was added dropwise and the mixture was stirred at -78 °C for 30 min before Et_3N (0.60 mL, 14.07 mmol) was added dropwise and the mixture was slowly warmed to 0 °C during which time the TLC indicated full consumption of starting material. The reaction mixture was quenched with sat. NH_4Cl aq. (20.0 mL) and aqueous layer was separated and extracted with CH_2Cl_2 (15.0 mL). Combined organic layers were dried (Na_2SO_4) and concentrated to give aldehyde **K** as a mixture of epimers (2.5:1, checked by ^{1}H NMR) which was put into next step directly.

To a cooled (-78 °C) and stirred suspension of Ph_3PCH_3Br (2.00 g, 5.60 mmol) in THF (7.50 mL) under N_2 atmosphere was added NaHMDS (2.0 M in THF, 2.50 mL) and the resulting yellow mixture was stirred at -78 °C for 1.5 h and the solution of crude aldehyde **K** in THF (2.50 mL) was then added. The mixture was slowly warmed to room temperature and stirred for

another 1 h. Saturated NH_4Cl aq. solution (20.0 mL) was added to quench the reaction at 0 ^oC and the mixture was extracted with EtOAc (15.0 mL x 3). Combined organic layers were dried (Na_2SO_4) and concentrated by rotary evaporation. Chromatography of residue on silica gel, using 10% EtOAc in hexane, gave **8** (112 mg, 76% over 2 steps) as a pale-yellow oil.

R_f (10% EtOAc in hexane): 0.43; $[\alpha]_D^{25}$ +112 (c 0.10, $CHCl_3$); FTIR (neat, cm^{-1}) 3068, 2947, 2926, 1699, 1480, 1438, 1359, 1108, 749, 702; HRMS (ESI-TOF, m/z) calcd. for $C_{23}H_{29}N_2O_2$ $[M+H]^+$ 365.2229, found 365.2231; ^1H NMR (700 MHz, $CDCl_3$) δ 7.70 (1H, brs, Ar*H*), 7.17 (1H, td, *J* = 7.7, 1.4 Hz, Ar*H*), 7.10 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.98 (1H, td, *J* = 7.4, 1.0 Hz, Ar*H*), 6.32 (1H, dd, *J* = 17.9, 10.9 Hz, C-C*H*=CH_2), 6.08 (1H, dd, *J* = 17.0, 10.9 Hz, C-C*H*=CH_2), 5.72 (1H, ddt, *J* = 16.8, 10.5, 6.4 Hz, NCH_2-C*H*=CH_2), 5.20 (1H, dd, *J* = 10.9, 1.5 Hz, C-CH=*H*CH), 5.09 (1H, dd, *J* = 17.9, 1.5 Hz, C-CH=HC*H*), 5.05—4.97 (4H, m, C-CH=C*H*$_2$ and NCH_2-CH=C*H*$_2$), 4.47 (1H, s, N-C*H*-C-N), 3.86 (3H, s, NCO_2CH_3), 3.29 (1H,dd, *J* = 14.2, 6.3 Hz, N-*H*CH-CH=CH_2), 3.20 (1H, dd, *J* = 14.0, 6.5 Hz, N-HC*H*-CH=CH_2), 3.05 (1H, t, *J* = 6.5 Hz, ArC-C*H*), 2.83 (1H, ddd, *J* = 11.8, 8.1, 3.3 Hz, N-*H*CH-CH_2), 2.40 (1H, ddd, *J* = 11.9, 8.1, 3.3 Hz, N-HC*H*-CH_2), 2.36—2.27 (1H, m, C-*H*CH-CH_2-C), 2.06—1.98 (1H, m, C-HC*H*-CH_2-C), 1.96—1.85 (2H, m, C-CH_2-*H*CH-C and NCH_2-*H*CH), 1.78 (1H, dt, *J* = 13.1, 7.2 Hz, C-CH_2-HC*H*-C), 1.53 (1H, dddd, *J* = 13.9, 8.1, 6.8, 3.4 Hz, NCH_2-HC*H*); ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.3 (N*C*O_2Me), 146.8 (C-*C*H=CH_2), 142.5 (C-*C*H=CH_2), 142.1 (Ar*C*), 136.9 (NCH_2-*C*H=CH_2), 134.4 (Ar*C*), 127.6 (Ar*C*H), 123.80 (Ar*C*H), 123.0 (Ar*C*H), 116.7 (C-CH=*C*H_2), 115.5 (Ar*C*H), 112.5 (C-CH=*C*H_2), 111.6 (NCH_2-CH=*C*H_2), 73.4 (N-*C*-CH-N)), 68.7 (N-C-*C*H-N), 60.7 (N*C*H_2-CH=CH_2), 54.5 (*C*(CH=CH_2)$_2$), 52.3 (NCO_2CH_3), 47.7 (ArC-*C*H), 44.1 (N*C*H_2CH_2), 36.9 (C-*C*H_2CH_2-C), 30.6 (C-CH_2*C*H_2-C), 28.1 (NCH_2*C*H_2).

Compound 7



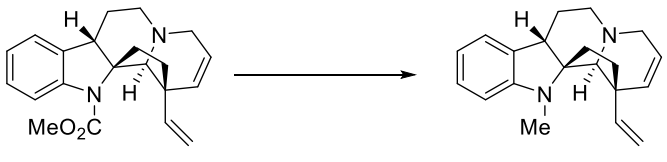
8 **7**

Procedure: To a stirred solution of **8** (100 mg, 0.27 mmol) in PhMe (5.00 mL) under N_2 was added Hoveyda-Grubbs catalyst (17.0 mg, 0.027 mmol). The resulting solution was degassed

and backed filled with N_2 and then stirred at 80 °C for 1 h. After cooling to 35~40 °C, DMSO (50 eq. to catalyst, 0.10 mL) was added and the mixture was stirred at this temperature for 4 h. The solvent was removed by rotary evaporation and chromatography of the residue on silica gel, using 30% EtOAc in hexane, gave **7** as a colourless oil (70.0 mg, 76%).

R_f (20% EtOAc in hexane) 0.20; $[\alpha]_D^{25}$ +174 (c 0.07, $CHCl_3$); FTIR (neat, cm^{-1}) 2932, 2847, 1705, 1477, 1459, 1437, 1367, 1356, 1321, 1229, 1116, 754; HRMS (ESI-TOF, m/z) calcd. for $C_{21}H_{25}N_2O_2$ $[M+H]^+$ 337.1916, found 337.1913; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.56 (H, d, *J* = 8.0 Hz, Ar*H*), 7.19 (1H, tt, *J* = 8.2, 1.1 Hz, Ar*H*), 7.13—7.10 (1H, m, Ar*H*), 7.06 (1H, td, *J* = 7.4, 1.0 Hz, Ar*H*), 5.95 (1H, dd, *J* = 17.6, 10.7 Hz, C-*C*H=CH_2), 5.58 (1H, ddd, *J* = 9.8, 5.5, 1.6 Hz, NCH_2-C*H*=CH-C), 5.54—5.50 (1H, m, NCH_2-CH=C*H*-C), 4.97 (1H, dd, *J* = 17.9, 0.9 Hz, C-CH=*H*CH), 4.93 (1H, dd, *J* = 10.7, 0.9 Hz, C-CH=HC*H*), 3.73 (3H, s, NCO_2CH_3), 3.34 (1H, t, *J* = 4.4 Hz, ArC-C*H*), 3.02 (1H, dd, *J* = 16.0, 5.6 Hz, N-*H*CH-CH=CH), 2.79 (1H, ddd, *J* = 13.3, 8.3, 3.4 Hz, C-*H*CH-CH_2-C), 2.70 —2.56 (3H, m, N-C*H*-C-N, N-HC*H*-CH=CH and N-*H*CH-CH_2), 2.50 (1H, dt, *J* = 12.8, 7.9 Hz, C-CH_2-*H*CH-C), 2.42 (1H, ddd, *J* = 13.5, 10.6, 6.8 Hz, C-HC*H*-CH_2-C), 2.28—2.21 (1H, m, NCH_2-*H*CH), 2.19—2.14 (1H, m, N-*H*CH-CH_2), 2.12—2.08 (1H, m, NCH_2-HC*H*), 1.98 (1H, ddd, *J* = 12.7, 10.7, 3.8 Hz, C-CH_2-HC*H*-C); ^{13}C NMR (176 MHz, $CDCl_3$) δ 153.5 (N*C*O_2Me), 146.4 (C-*C*H=CH_2), 143.5 (Ar*C*), 134.6 (Ar*C*), 134.5 (NCH_2-CH=*C*H-C), 127.3 (Ar*C*H), 123.7 (Ar*C*H), 122.5 (Ar*C*H), 120.1 (NCH_2-*C*H=CH-C), 118.7 (Ar*C*H), 111.4 (C-CH=*C*H_2), 80.5 (N-CH-*C*-N), 72.4 (N-*C*H-C-N), 52.9 (N-*C*H_2-CH=CH-C), 52.1 (NCO_2CH_3), 50.4 (*C*-CH=CH_2), 49.0 (N-*C*H_2CH_2), 44.2 (ArC-*C*H), 36.5 (C-*C*H_2CH_2-C), 29.9 (C-CH_2*C*H_2-C), 24.0 (NCH_2*C*H_2).

Compound 24



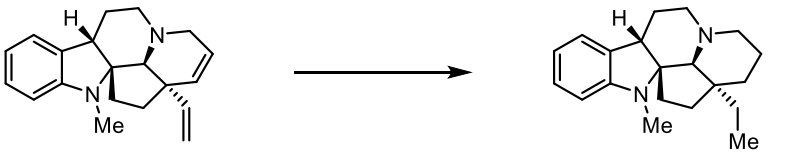
7 **24**

Procedure: To a cooled (0 °C) and stirred solution of **7** (15.0 mg, 0.045 mmol) in THF (1.00 mL) was added $LiALH_4$ (1.0 M in THF, 0.13 mL) and the mixture was heated to 65 °C for 30 min. After cooling back to 0 °C, the reaction mixture was quenched with water (3 drops) and 15% NaOH aq. (3 drops). Stirring was continued for 10 min and EtOAc (5.00 mL) and Na_2SO_4 were

added with another 10 min stirring. Precipitates were filtered and the filtrate was concentrated by rotary evaporation and chromatography (pipet) of the residue on silica gel, using 20% EtOAc in hexane, gave compound **24** (10.2 mg, 80%) as a colourless oil.

Mol. Formula: $C_{20}H_{24}N_2$; R_f (20% EtOAc/hexane): 0.2; $[\alpha]_D^{25}$ +130.8 (c 0.13, $CHCl_3$); FTIR (neat, cm^{-1}) 2954, 2922, 2851, 1668, 1483, 1462; HRMS (ESI-TOF, m/z) calcd. for $C_{20}H_{25}N_2[M+H]^+$ 293.2012, found 293.2008; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.07 (1H, td, *J* = 7.6, 1.3 Hz, Ar*H*) 7.02 (1H, d, *J* = 7.1 Hz, Ar*H*), 6.67 (1H, td, *J* = 7.3, 1.0 Hz, Ar*H*), 6.42 (1H, d, *J* = 7.7 Hz, Ar*H*), 5.89 (1H, dd, *J* = 17.5, 10.6 Hz, C*H*=CH_2), 5.76 (1H, ddd, *J* = 9.9, 5.8, 2.0 Hz, CH_2C*H*=CH), 5.56 (1H, ddd, *J* = 9.9, 2.7, 0.8 Hz, N-CH_2CH=C*H*), 5.12 (1H, dd, *J* = 17.5, 0.9 Hz, CH=HC*H*), 5.09 (1H, dd, *J* = 10.6, 0.9 Hz, CH=*H*CH), 3.13 (1H, ddd, *J* = 16.5, 5.8, 0.8 Hz, N-*H*CH-CH=CH), 3.00 (1H, t, *J* = 8.0 Hz, ArC-C*H*), 2.87 – 2.0 (2H, m, HC*H*-CH=CH_2 and N-*H*CHCH_2), 2.78 (1H, s, N-C*H*), 2.71 (3H, s, N*Me*), 2.29 (1H, ddd, *J* = 11.4, 7.5,6.1 Hz, N-HC*H*CH_2), 2.06 (1H, dq, *J* = 14.1, 7.1 Hz, NCH_2-*H*CH), 2.00 (1H, dddd, *J* = 12.6, 6.7, 3.0, 1.2 Hz, C-*H*CHCH_2-C), 1.88 (1H, ddd, *J* = 12.6, 10.6, 6.5, C-CH_2-*H*CH-C), 1.81 (1H, ddd, *J* = 12.6, 10.6, 7.3 C-HC*H*CH_2-C), 1.72–1.65 (2H, m, NCH_2-HC*H* and C-CH_2-HC*H*-C); ^{13}C NMR (176 MHz, $CDCl_3$) δ 152.0 (Ar*C*), 145.6 (*C*H=CH_2), 134.6 (Ar*C*), 133.5 (CH_2CH=*C*H), 127.5 (Ar*C*H), 122.9 (Ar*C*H), 122.9 (CH_2*C*H=CH), 117.8 (Ar*C*H), 112.6 (CH=*C*H_2), 108.0 (Ar*C*H), 77.9 (N-*C*-CH-N), 72.1 (N-C-*C*H-N), 52.9 (*C*H_2CH=CH), 49.8 (*C*-CH=CH_2), 49.7 (N-*C*H_2CH_2), 44.6 (ArC-*C*H), 33.4 (C-*C*H_2CH_2-C), 31.3 (N-*C*H_3), 28.2 (C-CH_2*C*H_2-C), 27.3 (N-CH_2*C*H_2).

(+)-vallesamidine 1



24 **1 (+)-vallesamidine**

Procedure: To a round bottom flask charged with **24** (8.00 mg, 0.027 mmol) was added Pd/C (10% w/w, 5.00 mg) and methanol (4.00 mL) under N_2. The system was degassed and back-filled with H_2 (balloon) and the mixture was stirred in H_2 atmosphere for 3 hours. The Pd/C was filtered through a pad of celite and the filtrate was concentrated by rotary evaporation. Chromatography of the residue on silica gel, eluted with acetone, to give **(+)-vallesamidine (1)** as a slightly yellow oil (6.20 mg, 77%).

R_f (50% EtOAc/hexane): 0.18; $[\alpha]_D^{25}$ +72.7 (c 0.22, $CHCl_3$), Literature data for (-)-vallesamidine: $[\alpha]_D^{20}$ = −81.5 (c 0.33, $CHCl_3$)[4]; $[\alpha]_D^{20}$ −76.6 (c 0.25, $CHCl_3$)[5]; FTIR (neat, cm^{-1}) 2936, 2855, *2796, 2750 (Bohlman-Wenkert bands)*, 1607, 1481; HRMS (ESI-TOF, m/z) calcd. for $C_{20}H_{29}N_2$ $[M+H]^+$ 297.2325, found 297.2325; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.06 (1H, t, *J* = 7.6 Hz, Ar*H*), 7.02 (1H, d, *J* = 7.1 Hz, Ar*H*), 6.65 (1H, t, *J* = 7.3 Hz, Ar*H*), 6.42 (1H, d, *J* = 7.7 Hz, Ar*H*), 2.91–2.84 (2H, m, ArC-C*H* and N-*H*CHCH$_2$), 2.83–2.76 (4H, m, N*Me* and N-*H*CHCH$_2$CH$_2$), 2.29–2.17 (3H, m, N-C*H*, N-HC*H*CH$_2$ and N-HC*H*CH$_2$CH$_2$), 1.93–1.86 (1H, m, N-CH$_2$-*H*CH), 1.84–1.74 (2H, m, N-CH$_2$-*H*CH-CH$_2$ and C-*H*CHCH$_2$-C), 1.67–1.59 (3H, m, C-HC*H*CH$_2$-C, C-CH$_2$-*H*CH-C and *H*CH-CH$_3$), 1.58–1.44 (5H, m, N-CH$_2$CH$_2$C*H$_2$*, N-CH$_2$-HC*H*CH$_2$ and N-CH$_2$-HC*H* and HC*H*CH$_3$), 1.43–1.38 (1H, m, C-CH$_2$-HC*H*-C), 0.89 (3H, t, *J* = 7.4 Hz, CH$_2$C*H$_3$*); ^{13}C NMR (176 MHz, $CDCl_3$) δ 151.5 (Ar*C*), 135.0 (Ar*C*), 127.3 (Ar*C*H), 123.0 (Ar*C*H), 117.7 (Ar*C*H), 107.7 (Ar*C*H), 79.1 (N-*C*-CH-N), 73.2 (N-C-*C*H-C), 50.6 (N-*C*H$_2$CH$_2$), 50.0 (N-*C*H$_2$CH$_2$CH$_2$), 44.6 (*C*-CH$_2$CH$_3$), 44.4 (ArC-*C*H), 35.6 (C-CH$_2$-*C*H$_2$-C), 31.4 (N-*C*H$_3$), 31.2 (*C*H$_2$CH$_3$), 30.4 (C-*C*H$_2$CH$_2$-C), 27.7 (N-CH$_2$*C*H$_2$), 26.6 (N-CH$_2$CH$_2$*C*H$_2$), 18.5 (N-CH$_2$*C*H$_2$CH$_2$), 9.3 (CH$_2$*C*H$_3$).

Table 1 Comparison of ^{1}H NMR data of **(+)-1** with literatures

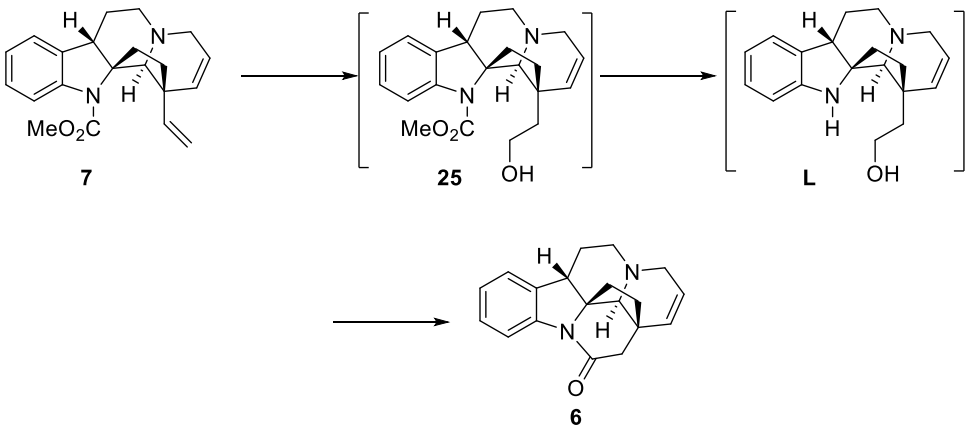
Lit. data 1 (600 MHz, $CDCl_3$)[5]	Lit. data 2 (600 MHz, $CDCl_3$)[4]	Our data (700 MHz, $CDCl_3$)	Error Δ δ/ppm (1/2)
7.07 (1H, t, 7.3)	7.07 (1H, t, 7.2)	7.06 (1H, t, 7.6)	-0.01/-0.01
7.03 (1H, d, 7.3)	7.02 (1H, d, 7.2)	7.02 (1H, d, 7.1)	-0.01/0
6.67 (1H, t, 7.3)	6.66 (1H, t, 7.2)	6.65 (1H, t, 7.3)	-0.02/-0.01
6.44 (1H, d, 7.3)	6.42 (1H, d, 7.8)	6.42 (1H, d, 7.7)	-0.02/0
3.00 – 2.70 (3H, m)	2.94 – 2.78 (3H, m)	2.91 – 2.76 (3H, m)	-
2.78 (3H, s)	2.78 (3H, s)	2.78 (3H, s)	0
2.50 – 2.25 (3H, m)	2.32 -2.24 (3H, m)	2.29 – 2.17 (3H, m)	-
2.15 – 1.35 (12H, m)	1.95 – 1.38 (12H, m)	1.93 – 1.38 (12H, m)	-
0.90 (3H, t, 7.3)	0.90(3H, t, 7.8)	0.89 (3H, t, 7.4)	-0.01/-0.01

Table 2 Comparison of ^{13}C NMR data of **(+)-1** with literature

Lit. data 1 (150 MHz, $CDCl_3$)[5]	Lit. data 2 (150 MHz, $CDCl_3$)[4]	Our data (176 MHz, $CDCl_3$)	Error Δ δ/ppm (1/2)
151.3	151.3	151.5	0.2/0.2

134.6	134.8	135.0	0.4/0.2
127.3	127.1	127.3	0/0.2
122.9	122.8	123.0	0.1/0.2
117.7	117.5	117.7	0/0.2
107.6	107.5	107.7	0.1/0.2
78.6	78.9	79.1	0.5/0.2
72.6	72.9	73.2	0.6/0.3
50.1	50.3	50.6	0.5/0.3
49.6	49.8	50.0	0.4/0.2
44.4	44.4	44.6	0.2/0.2
44.0	44.2	44.4	0.4/0.2
35.4	35.4	35.6	0.2/0.2
31.2	31.2	31.4	0.2/0.2
31.0	31.1	31.2	0.2/0.1
30.1	30.2	30.4	0.3/0.2
27.3	27.4	27.7	0.4/0.3
26.4	26.5	26.6	0.2/0.1
18.1	18.3	18.5	0.4/0.2
9.1	9.1	9.3	0.2/0.2

(+)-14,15-dehydrostrempeliopine (6)



Preparation of c-Hex$_2$BH: To a round bottom flask charged with anhydrous THF (5.50 mL) under N_2 was added $BH_3{\cdot}Me_2S$ (5.0 M in Et_2O, 0.38 mL) and cooled to 0^{o}C. Cyclohexene (0.42 mL) was added slowly and the resulting mixture was stirred at 0 ^{o}C for 15 min and then 1 h at room temperature to give c-Hex$_2$BH as a white suspension which was ready to use (ca. 0.3 M).

Hydroboration/oxidation (25): To a cooled (0°C) and stirred solution of **7** (10.0 mg, 0.03 mmol) in anhydrous THF (0.50 mL) was added freshly prepared c-Hex_2BH solution (0.3 M, 0.50 mL, 0.15 mmol) dropwise. The mixture was slowly warmed to room temperature and stirred for 30 min. Solid $NaBO_3 \cdot H_2O$ (60.0 mg, 0.60 mmol) and water (0.50 mL) was added and the resulting mixture was stirred at room temperature for 2.5 h. Water (10.0 mL) was added and the mixture was extracted with CH_2Cl_2 (5.00 mL x 3). The combined organic layers were dried (Na_2SO_4) and concentrated by rotary evaporation. Chromatography of the residue on 20 x 20 TLC plate, gave compound **25** (8.00 mg, 75%) as a colourless oil with acceptable purity (*due to the high polarity, the obtained compound **25** contained some impurities which was difficult to purify. Further purification was not performed, and this intermediate was put into next step directly*).

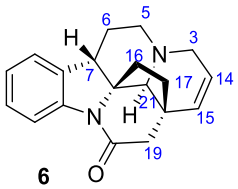
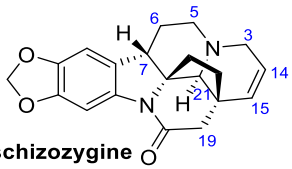
Compound 25: R_f (5% MeOH in CH_2Cl_2): 0.14; FTIR (neat, cm^{-1}) 3362, 2934, 1697, 1478, 1459, 1438, 1354, 1321, 1228, 1042, 727; HRMS (ESI-TOF, m/z) calcd for. $C_{21}H_{27}N_2O_3$ $[M+H]^+$ 355.2022, found 355.2010; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 8.2 Hz, Ar*H*), 7.19—7.15 (1H, m, Ar*H*), 7.15—7.11 (1H, m, Ar*H*), 7.01 (1H, td, *J* = 7.4, 1.0 Hz, Ar*H*), 5.82 (1H, dt, *J* = 10.0, 3.6 Hz, NCH_2-C*H*=CH-C), 5.54 (1H, d, *J* = 10.1 Hz, NCH_2-CH=C*H*-C), 3.84 (3H, s, NCO_2*Me*), 3.72 (1H, ddd, *J* = 11.3, 9.2, 4.9 Hz, CH_2-*H*CH-OH), 3.65 (1H, ddd, *J* = 11.3, 5.8, 4.4 Hz, CH_2-HC*H*-OH), 3.16 (1H, d, *J* = 16.5 Hz, N-*H*CH-CH=CH-C), 3.07—2.98 (2H, m, N-HC*H*-CH=CH-C and ArC-C*H*), 2.90—2.80 (1H, m, N-*H*CH-CH_2), 2.61 (1H, s, N-C*H*-C-N), 2.55—2.48 (1H, m, N-HC*H*-CH_2), 2.30—1.50 (8H, m, C*H*$_2$-CH_2OH, NCH_2CH_2, C-CH_2CH_2-C).

Hydrolysis (L): To a solution of **25** (8.00 mg, 22.6 μmol) in MeOH was added 3M KOH aq. solution and the resulting mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the mixture was added water (5.00 mL) and extracted with CH_2Cl_2 (10.0 mL x 3). Combined organic layers were dried (Na_2SO_4) and concentrated to give crude **L** (5.30 mg, 79% crude yield) which was put into next step directly.

Oxidative cyclisation: To a solution to **L** (3.00 mg, 10 mmol) in CH_2Cl_2 (0.50 mL) was added NMO (0.2M in CH_2Cl_2, 0.1 mL) and TPAP (0.01M in CH_2Cl_2, 0.1 mL) and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was passed through a short pad of silica gel and the filtrated was concentrated and preparative TLC on the residue, using 40% EtOAc in hxane, gave **6** (1.87 mg, 60% yield, 36% overall yield from **7**) as a colourless oil.

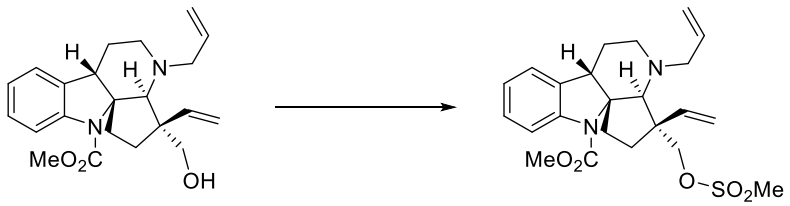
(+)-14,15-dehydrostrempeliopine: R_f (40% EtOAc in hexane) 0.2; $[\alpha]_D^{25}$ +19.3 (c 0.09, $CHCl_3$); FTIR (neat, cm^{-1}) 2922, 2851, 1656, 1597, 1476, 1459, 1387, 1370, 1260, 754; HRMS (ESI-TOF, m/z) calcd. for $C_{19}H_{21}N_2O$ $[M+H]^+$ 293.1654, found 293.1649; ^1H NMR (700 MHz, $CDCl_3$) δ 8.04 (1H, dt, *J* = 8.1, 0.5 Hz, Ar*H*), 7.24—7.21 (1H, m, Ar*H*), 7.18 (1H, dt, 7.5, 1.3 Hz, Ar*H*), 7.07 (1H, td, *J* = 7.4, 1.1 Hz, Ar*H*), 5.74 (1H, ddd, *J* = 10.0, 2.9, 1.9 Hz, NCH_2-CH=C*H*-C), 5.58 (1H, ddd, *J* = 10.0, 4.5, 1.9 Hz, NCH_2-C*H*=CH-C), 3.40 (1H, ddd, *J* = 16.8, 4.4, 1.9 Hz, N-*H*CH-CH=CH), 3.31 (1H, t, *J* = 6.6 Hz, ArC-C*H*), 3.06 (1H, ddd, *J* = 11.5, 7.2, 5.2 Hz, N-*H*CH-CH_2), 2.80 (1H, ddd, *J* = 16.7, 2.9, 2.0 Hz, N-HC*H*-CH=CH), 2.70 (1H, d, *J* = 18.0 Hz, NC(O)-*H*CH-C), 2.54 (1H, dd, *J* = 18.0, 2.8 Hz, NC(O)-HC*H*-C), 2.37—2.34 (2H, m, C-C*H*$_2$-CH_2-C), 2.29 (1H, ddd, *J* = 12.0, 7.1, 4.8 Hz, N-HC*H*-CH_2), 2.27 (1H, s, N-C*H*-C-N), 2.16—2.06 (3H, m, N-CH_2-C*H*$_2$ and C-CH_2-*H*CH-C), 1.90 (1H, ddd, *J* = 13.0, 8.5, 5.6 Hz, C-CH_2-HC*H*-C); ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.8 (N-*C*=O), 142.7 (Ar*C*), 132.6 (Ar*C*), 130.2 (N-CH_2-CH=*C*H-C), 128.3 (Ar*C*H), 124.0 (Ar*C*H), 123.8 (NCH_2-*C*H=CH-C), 123.6 (Ar*C*H), 115.9 (Ar*C*H), 71.9 (N-CH-*C*-N), 68.5 (N-*C*H-C-N), 53.5 (N-*C*H_2-CH=CH-C), 50.3 (N-*C*H_2CH_2), 47.2 (NC(O)-*C*H_2-C), 44.7 (N-CH_2-CH=CH-*C*), 42.1 (ArC-*C*H), 38.5 (C-*C*H_2-CH_2-C), 37.7 (C-CH_2-*C*H_2-C), 25.5 (NCH_2-*C*H_2).

Table 3. Spectra data comparison of **(+)-6** with **schizozygine**

^1H NMR comparison		
H-19	2.70 (d, 18.0)	2.61 (d, 18.0)
H-19’	2.54 (dd, 18.0, 2.8)	2.45 (dd, 18.0, 2.8)
H-21	2.27 (s)	2.25 (s)
H-14	5.57 (ddd, 10.0, 4.5, 2.0)	5.57 (ddd, 10.0, 4.4, 2.0)
H-15	5.73 (dt, 9.8, 2.2)	5.73 (dt, 9.9, 2.2)
H-7	3.31 (t, 6.6)	3.20 (t, 6.6)
H5	2.29 (ddd, 12.0, 7.1, 4.8),	2.27 (m)
H5’	3.06 (ddd, 11.5, 7.2, 5.2)	3.03 (brs)
H6/6’/17’	2.16—2.06 (m)	2.04 (m)
H-17	1.90 (ddd, 13.0, 8.5, 5.6)	1.86 (ddd, 12.8, 8.6, 5.3)
^{13}C NMR comparison		
C3	53.5	53.5
C5	50.3	50.1
C6	25.5	25.8

C7	42.1	42.1
C2	71.9	72.6
C21	68.5	68.0
C20	44.7	44.7
C19	47.2	46.9
C18	169.8	168.9
C14	123.8	123.8
C15	130.2	130.2
C16	38.5	38.6
C17	37.7	37.6

Compound 26

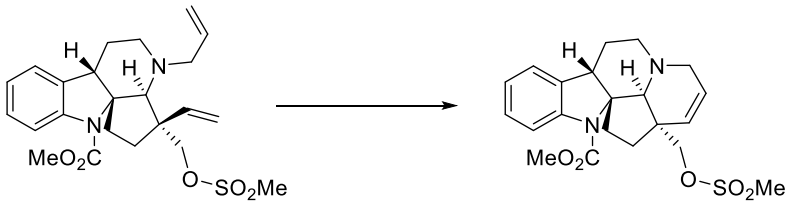


To a cooled (0 °C) and stirred solution of alcohol **23** (100 mg, 0.27 mmol) in CH_2Cl_2 (10.0 mL) under N_2 atmosphere was added Et_3N (41 mL, 0.40 mmol) and MsCl (37 mL, 0.40 mmol). Cooling bath was left but not recharged and the stirring was continued until full consumption of starting material (1.5 h, checked by TLC). Saturated NH_4Cl aq. Solution (10 mL) was added and organic layer was separated, dried (Na_2SO_4) and concentrated by rotary evaporation to give **26** (122 mg, quant.) which was pure enough to go to next step. A small amount of crude product from initial attempt was purified by chromatography (silica gel, 20% EtOAc in hexane) for data collection.

R_f (100% CH_2Cl_2) 0.4; $[\alpha]_D^{25}$ +52.0 (c 0.2, $CHCl_3$); FTIR (neat, cm^{-1}) 2952, 2932, 1699, 1481, 1442, 1357, 1329, 1174, 954, 757; HRMS (ESI-TOF, m/z) calcd. for $C_{23}H_{31}N_2O5_S$ $[M+H]^+$ 447.1954, found 447.1947; ^1H NMR (700 MHz, $CDCl_3$) δ 7.69 (1H, brs, Ar*H*), 7.18 (1H, t, *J* = 7.8 Hz, Ar*H*), 7.11 (1H, d, *J* = 6.7 Hz, Ar*H*), 6.99 (1H, td, *J* = 7.4, 1.0 Hz, Ar*H*), 6.26 (1H, dd, *J* = 17.8, 11.0 Hz, C-C*H*=CH_2), 5.73 (1H, ddt, *J* = 16.8, 10.6, 6.4 Hz, NCH_2-C*H*=CH_2), 5.27 (1H, dd, *J* = 10.9, 1.2 Hz, C-CH=*H*CH), 5.16 (1H, dd, *J* = 17.9, 1.3 Hz, C-CH=HC*H*), 5.09—5.00 (2H, m, NCH_2-CH=CH_2), 4.39 (1H, s, N-C*H*-C-N), 4.18 (1H, d, *J* = 9.2 Hz, C-*H*CH-OMs), 4.14 (1H, d, *J* = 9.1 Hz, C-HC*H*-OMs), 3.87 (3H, s, NCO_2*Me*), 3.28 (1H, dd, *J* = 14.1, 6.6 Hz, N-*H*CH-CH=CH_2), 3.19 (1H, dd, *J* = 13.9,

6.4 Hz, N-HC*H*-CH=CH_2) 3.03 (3H, s, CH_2OSO_2*Me*), 3.00 (1H, t, *J* = 6.8 Hz, ArC-C*H*), 2.80 (1H, ddd, *J* = 12.2, 8.8, 3.2 Hz, N-*H*CH-CH_2), 2.45—2.33 (2H, m, N-HC*H*-CH_2 and C-*H*CH-CH_2-C), 1.90 (1H, dd, *J* = 9.1, 5.2 Hz, C-CH_2-*H*CH-C), 1.81—1.49 (4H, m, N-CH_2-C*H*$_2$, C-HC*H*-CH_2-C and C-CH_2-HC*H*-C); ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.1 (N*C*O_2Me), 141.9 (C-*C*H=CH_2), 141.1 (Ar*C*), 136.7 (NCH_2-*C*H=CH_2), 133.9 (Ar*C*), 127.8 (Ar*C*H), 123.9 (Ar*C*H), 123.1 (Ar*C*H), 117.1 (NCH_2-CH=*C*H_2), 115.6 (Ar*C*H), 115.0 (C-CH=*C*H_2), 75.2 (N-*C*-CH-N), 72.9 (C-*C*H_2OMs), 63.2 (N-*C*H-C-N), 60.0 (N-*C*H_2CH=CH_2), 52.7 (*C*-CH_2OMs), 52.5 (NCO_2*C*H_3), 50.4 (C-CH_2OSO_2*Me*), 46.5 (ArC-*C*H), 44.2 (N-*C*H_2CH_2), 37.5 (C-*C*H_2CH_2-C), 27.7 (C-CH_2*C*H_2-C), 27.0 (NCH_2*C*H_2).

Compound 27

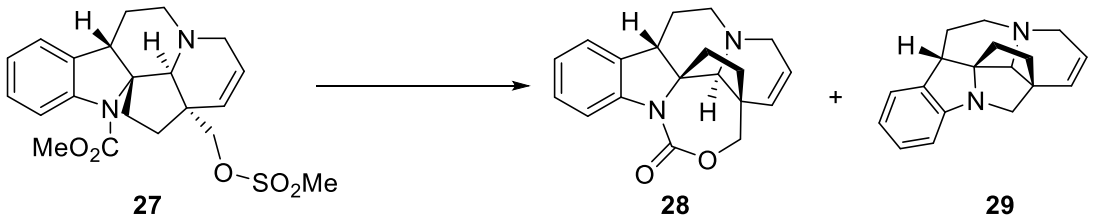


Procedure: To a solution of **26** (122 mg, 0.24 mmol) in PhMe (12.0 mL) under N_2 atmosphere was added Hoveyda-Grubbs 2nd generation catalyst (7.7 mg, 0.024 mmol). The mixture was then stirred at 60 ^{o}C for 4 h. After cooling to room temperature, solvent was removed by rotary evaporation and chromatography of residue on silica gel, using pure Et_2O gave **27** as a light brown oil (80 mg, 80%).

R_f (100% Et_2O) 0.16; $[\alpha]_D^{25}$ +50.5 (c 0.19, $CHCl_3$); FTIR (neat, cm^{-1}) 2929, 2851, 1701, 1481, 1462, 1441, 1354, 1328, 1175, 955; HRMS (ESI-TOF, m/z) calcd. for $C_{21}H_{27}N_2O_5S$ 419.1641, found 419.1649; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.20 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.13 (1H, d, *J* = 7.5 Hz, Ar*H*, 7.08 (td, *J* = 7.4, 1.0 Hz, Ar*H*), 5.83 (1H, ddd, *J* = 10.1, 5.7, 1.8 Hz, NCH_2-C*H*=CH-C), 5.74 (1H, dd, *J* = 10.1, 2.5 Hz, NCH_2-CH=C*H*-C), 4.32 (1H, d, *J* = 9.4 Hz, *H*CH-OMs), 4.17 (1H, d, *J* = 9.5 Hz, HC*H*-OMs), 3.80 (3H, s, NCO_2*Me*), 3.28 (1H, brs, ArC-C*H*), 3.03 (1H, dd, *J* = 16.1, 5.8 Hz, N-*H*CH-CH=CH-C), 3.00 (3H, s, CH_2OSO_2*Me*), 2.93 (1H, brs, N-C*H*-C-N), 2.76 (1H, d, *J* = 16.2 Hz, N-HC*H*-CH=CH-C), 2.66—2.58 (2H, m, N-*H*CH-CH_2 and C-*H*CH-CH_2-C), 2.37—2.14 (4H, m, N-HC*H*-CH_2, C-HC*H*-CH_2-C, C-CH_2-*H*CH-C, N-CH_2-*H*CH), 2.02—1.95 (1H, m, NCH_2-HC*H*), 1.85—1.76 (1H, m, C-CH_2-HC*H*-C); ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.1

(N*C*O$_2$Me), 142.6 (Ar*C*), 134.8 (Ar*C*), 131.7 (NCH$_2$-CH=*C*H-C), 127.4 (Ar*C*H), 124.8 (NCH$_2$-*C*H=CH-C), 124.2 (Ar*C*H), 122.8 (Ar*C*H), 119.4 (Ar*C*H), 79.9 (N-CH-*C*-N) 74.9 (*C*H$_2$OMs), 67.1 (N-*C*H-C-N), 52.7 (NCO$_2$*Me*), 52.5 (N-*C*H$_2$CH=CH-C), 48.3 (N-*C*H$_2$CH$_2$), 47.6 (*C*-CH$_2$OMs) 45.3 (ArC-*C*H), 37.4 (CH$_2$OSO$_2$*Me*), 32.7 (C-CH$_2$-*C*H$_2$-C), 30.4 (C-*C*H$_2$-CH$_2$-C), 25.7 (N-CH$_2$*C*H$_2$).

Compound 28 and 29



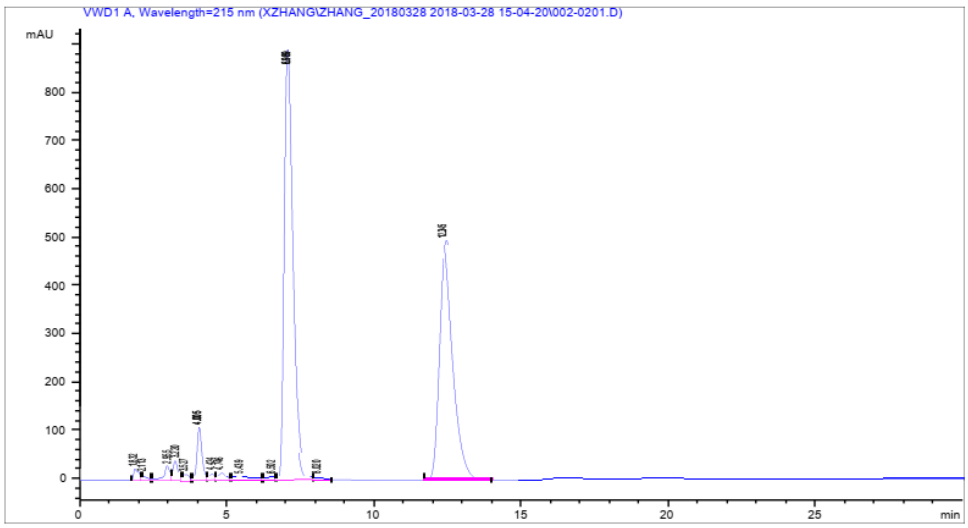
Procedure: To a stirred solution of **27** (50.0 mg, 0.12 mmol) in DMSO (2.50 mL) was added KCN (65.0 mg) and the resulting mixture was stirred at 100 ^{o}C for 24 h. After cooling to room temperature, the reaction mixture was added EtOAc (15.0 mL) and water (15.0 mL). Aqueous layer was extracted with EtOAc (15.0 mL x 2) and combined organic layers were washed with brine (20.0 mL x 2), dried (Na$_2$SO$_4$) and concentrated by rotary evaporation. ^{1}H NMR indicated a 1:1 mixture of two compounds. Chromatography of crude material on silica gel, using 10% acetone in hexane, gave **28** (12.0 mg, 32%) and **29** (10.0 mg, 31%) as colourless oil.

Compound 28: R$_f$ (30% EtOAc in hexane): 0.3; [α]$_D^{25}$ -24.5 (c 0.22, CHCl$_3$); FTIR (neat, cm^{-1}) 3024, 2931, 1701, 1478, 1459, 1396, 1358, 1221, 1061, 1025, 752; HRMS (ESI-TOF, m/z) clacd. For C$_{19}$H$_{21}$N$_2$O$_2$ [M+H]$^+$ 309.15976, found 309.15975; ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.77 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.25—7.22 (1H, m, Ar*H*), 7.15 (1H, dt, *J* = 7.3, 1.5 Hz, Ar*H*), 7.07 (1H, td, *J* = 7.4, 1.0 Hz, Ar*H*), 5.74 (1H, ddd, *J* = 10.0, 4.9, 1.8 Hz, NCH$_2$-C*H*=CH-C), 5.43 (1H, ddd, *J* = 10.0, 2.9, 1.6 Hz, NCH$_2$-CH=C*H*-C), 4.02 (1H, d, *J* = 12.1 Hz, NCO$_2$-*H*CH-C), 3.88 (1H, dd, *J* = 12.1, 1.5 Hz, NCO$_2$-HC*H*-C), 3.46 (1H, d, *J* = 6.0 Hz, ArC-C*H*), 3.24 (1H, ddd, *J* = 16.7, 4.9, 1.6 Hz, N-*H*CH-CH=CH-C), 2.70—2.63 (2H, m, N-HC*H*-CH=CH-C and N-*H*CH-CH$_2$), 2.55 (1H, ddd, *J* = 14.8, 9.8, 7.0 Hz, C-*H*CH-CH$_2$-C), 2.40 (1H, ddd, *J* = 15.1, 12.0, 3.3 Hz, C-HC*H*-CH$_2$-C), 2.32—2.28 (1H, m, NCH$_2$-*H*CH), 2.25—2.15 (2H, m, C-CH$_2$-*H*CH and NCH$_2$-HC*H*), 2.10—1.99 (3H, m, N-C*H*-C-N, C-CH$_2$-HC*H*-C and N-HC*H*-CH$_2$); ^{13}C NMR (176 MHz, CDCl$_3$) δ 154.7 (N*C*O$_2$), 142.3 (Ar*C*), 131.5 (Ar*C*), 128.3 (Ar*C*H), 127.1 (NCH$_2$-CH=*C*H-C), 127.0 (NCH$_2$-*C*H=CH-C), 123.8 (Ar*C*H), 122.4 (Ar*C*H), 115.4 (Ar*C*H), 77.8 (NCO$_2$*C*H$_2$), 75.6 (N-CH-*C*-N), 73.7 (N-*C*H-C-N), 53.6 (N-*C*H$_2$-CH=CH-

C), 50.3 (NCO_2-CH_2-*C*), 48.7 (N-*C*H_2CH_2), 43.4 (ArC-*C*H), 36.5 (C-*C*H_2CH_2-C), 34.4 (C-CH_2*C*H_2-C), 23.1 (NCH_2*C*H_2).

Compound 29: R_f (30% EtOAc in hexane): 0.4; $[\alpha]_D^{25}$ -9.7 (c 0.10, $CHCl_3$); FTIR (neat, cm^{-1}) 2925, 2853, 1698, 1669, 1602, 1449, 1285, 1239, 1099, 756, 746; HRMS (ESI-TOF, m/z) calcd. for $C_{18}H_{21}N_2$ $[M+H]^+$ 265.1699, found 265.1701; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.13—7.07 (2H, m, Ar*H*), 6.82 (1H, td, *J* = 7.4, 1.0 Hz, Ar*H*), 6.59 (1H, dt, *J* = 7.4, 1.0 Hz, Ar*H*), 5.96 (1H, ddd, *J* = 9.9, 3.1, 1.9 Hz, NCH_2-C*H*=CH-C), 5.47 (1H, ddd, *J* = 9.9, 4.0, 2.1 Hz, NCH_2-CH=C*H*-C), 3.55 (1H, d, *J* = 9.1 Hz, N-*H*CH-C), 3.48 (1H, ddd, *J* = 16.9, 4.1, 1.9, N-*H*CH-CH=CH-C), 3.20 (1H, dd, *J* = 5.2, 1.9 Hz, ArC-C*H*), 2.94 (1H, ddd, *J* = 11.3, 5.1, 2.2 Hz, N-*H*CH-CH_2), 2.90 (1H, dd, *J* = 9.1, 3.0 Hz, N-HC*H*-C), 2.43 (1H, ddd, *J* = 16.8, 3.1, 2.2, N-HC*H*-CH=CH-C), 2.36 (1H, td, *J* = 12.2, 4.5 Hz, C-*H*CH-CH_2-C), 2.29—2.15 (2H, m, NCH_2C*H*$_2$), 2.04—1.97 (1H, m, C-CH_2-*H*CH-C), 1.94—1.79 (3H, m, N-HC*H*-CH_2, C-HC*H*-CH_2-C and C-CH_2-HC*H*-C), 1.60 (1H, s, N-C*H*-C-N); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.8 (Ar*C*), 134.5 (Ar*C*), 128.1 (NCH_2-*C*H=CH-C), 127.9 (Ar*C*H), 126.1, (NCH_2-CH=*C*H-C) 124.3 (Ar*C*H), 120.1 (Ar*C*H), 112.4 (Ar*C*H), 76.3 (N-*C*-CH-N), 70.3 (N-C-*C*H-C), 64.7 (N-*C*H_2-C), 54.2 (N-*C*H_2-CH=CH-C), 53.5 (N-*C*H_2CH_2), 49.0 (N-CH_2-*C*), 37.8 (ArC-*C*H), 36.3 (C-CH_2-*C*H_2-C), 29.0 (C-*C*H_2-CH_2-C), 25.1 (NCH_2*C*H_2).

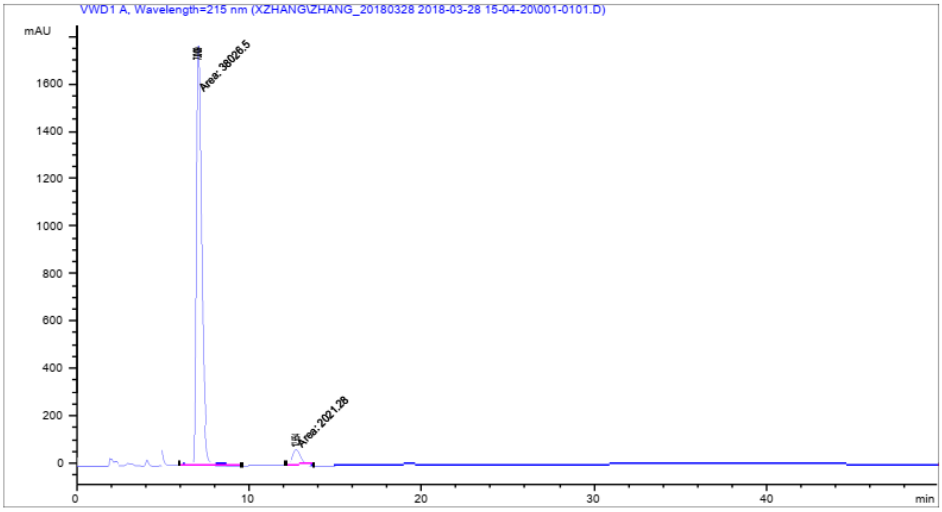
Chiral HPLC chromatogram of **14**



Signal 1: VWD1 A, Wavelength=215 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.832	BV	0.1586	217.26871	18.14535	0.5553
2	2.113	VV	0.1778	109.09632	8.01330	0.2788
3	2.955	VV	0.1852	362.41397	27.35223	0.9263
4	3.220	VV	0.1602	399.82538	37.22874	1.0219
5	3.527	VV	0.2134	147.43463	9.18994	0.3768
6	4.005	VV	0.1656	1160.18066	104.73870	2.9653
8	4.746	VV	0.2521	212.96925	11.83874	0.5443
9	5.439	VV	0.5738	179.82901	3.95790	0.4596
10	6.502	VV	0.3245	71.86116	3.00128	0.1837
11	6.989	VV	0.3098	1.80113e4	886.71130	46.0353
12	8.020	VB	0.3973	82.05363	2.95011	0.2097
13	12.345	BB	0.5649	1.80503e4	491.99304	46.1350
Totals :				3.91250e4	1615.02747	

Figure 1 Chiral HPCL of racemic **14**



Signal 1: VWD1 A, Wavelength=215 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.009	MM	0.3601	3.80265e4	1760.21899	94.9528
2	12.654	MM	0.5807	2021.27979	58.01327	5.0472
Totals :				4.00478e4	1818.23226	

Figure 2 Chiral HPCL of enantioenriched **14**

Crystallographic analyses of **11**

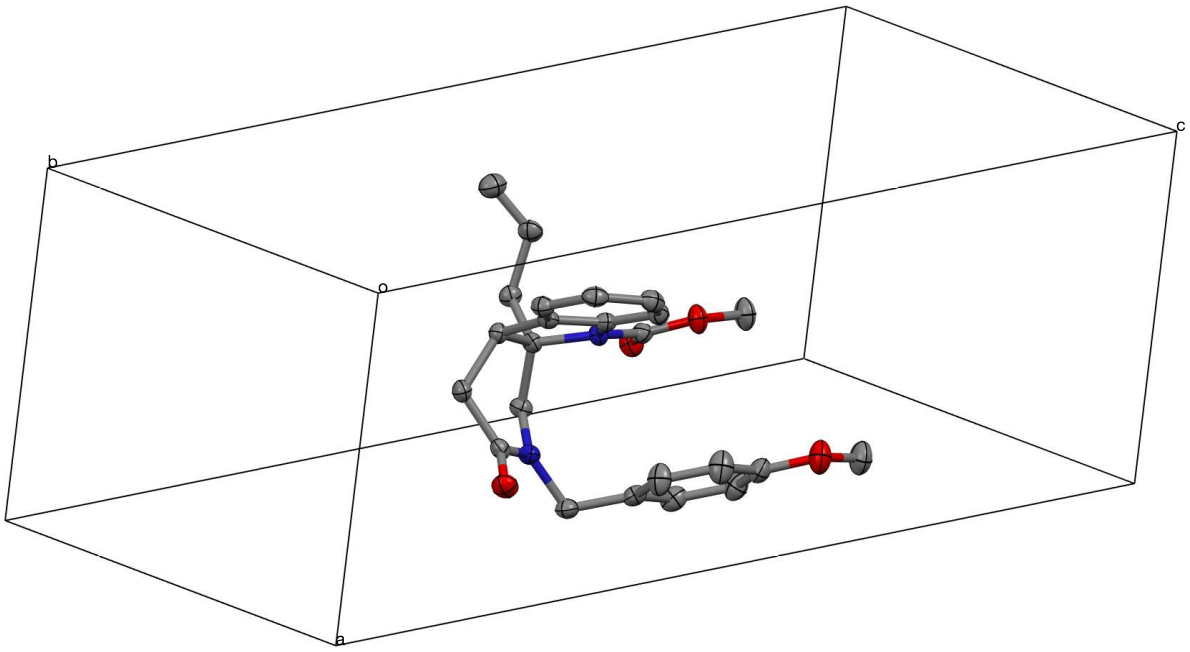


Figure 3 Asymmetric unit of the crystal structure of compound **11**. The thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms and atom labels are omitted for clarity. Colour scheme: carbon – grey, nitrogen – blue, oxygen – red.

All diffraction data for compound **11** were collected on a four-circle *Agilent SuperNova* (Dual Source) single crystal X-ray diffractometer using a micro-focus CuKα X-ray beam (λ = 1.54184 Å) and an *Atlas* CCD detector. The crystal temperature was controlled with an *Oxford Instruments* cryojet. Unit cell determination, data reduction and analytical numeric absorption correction were carried out using the *CrysAlis*^{Pro} programme.[1] The crystal structures were solved with the *ShelXT* programme[2] and refined by least squares on the basis of F^2 with the *ShelXL* programme.[3] All non-hydrogen atoms were refined anisotropically by the full-matrix least-squares method. Hydrogen atoms associated with carbon and oxygen atoms were refined isotropically [U_{iso}(H) = 1.2 U_{eq} (C)] in geometrically constrained positions. The crystallographic and refinement parameters for compound 11 are shown in Table 3.

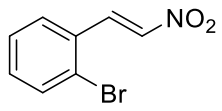
Table 3. Crystallographic and refinement parameters of 11.

Compound **11**	
Empirical formula	$C_{24}H_{26}N_2O_4$
Formula weight	406.47
Temperature/K	151(2)

Crystal system	orthorhombic
Space group	$P2_12_12_1$
a / Å	8.0488(1)
b / Å	9.8870(1)
c / Å	25.9184(3)
α / °	90
β / °	90
γ / °	90
V / Å^3	2062.55(4)
Z	4
ρ_{calc} / g cm^{-3}	1.309
μ / mm^{-1}	0.725
F(000)	864.0
Crystal size / mm^3	0.272 × 0.134 × 0.104
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection / °	6.82 to 133.184
Index ranges	$-9 \le h \le 9$ $-11 \le k \le 11$ $-30 \le l \le 30$
Number of collected reflections	68536
Number of unique reflections	3650 [I > 2σ(I)]
Data/Restraints/¨arameters	3650/0/284
Goodness-of-fit on F^2	1.057
R_{int}	0.0446
R (F), $F > 2\sigma(F)$	0.0280
wR (F^2), $F > 2\sigma(F)$	0.0690
R (F), all data	0.0289
wR (F^2), all data	0.0698
Δ_r (max., min.) e Å^{-3}	0.15/−0.18
Flack parameter	−0.08(4)
CCDC number	1904992

References: 1) *CrysAllisPro*. *Agilent Technologies*, Inc. (2014). 2) Sheldrick, G. M. A short history of *SHELX*. *Acta Crystallogr.*, 2008, **A64***,* 112–122. DOI: 10.1107/S0108767307043930. 3) Sheldrick, G. M. Crystal structure refinement with *SHELXL*. *Acta Crystallogr.*, 2015, **C71***,* 3–8. DOI:1107/S2053229614024218

^{1}H and ^{13}C NMR spectra for all compounds



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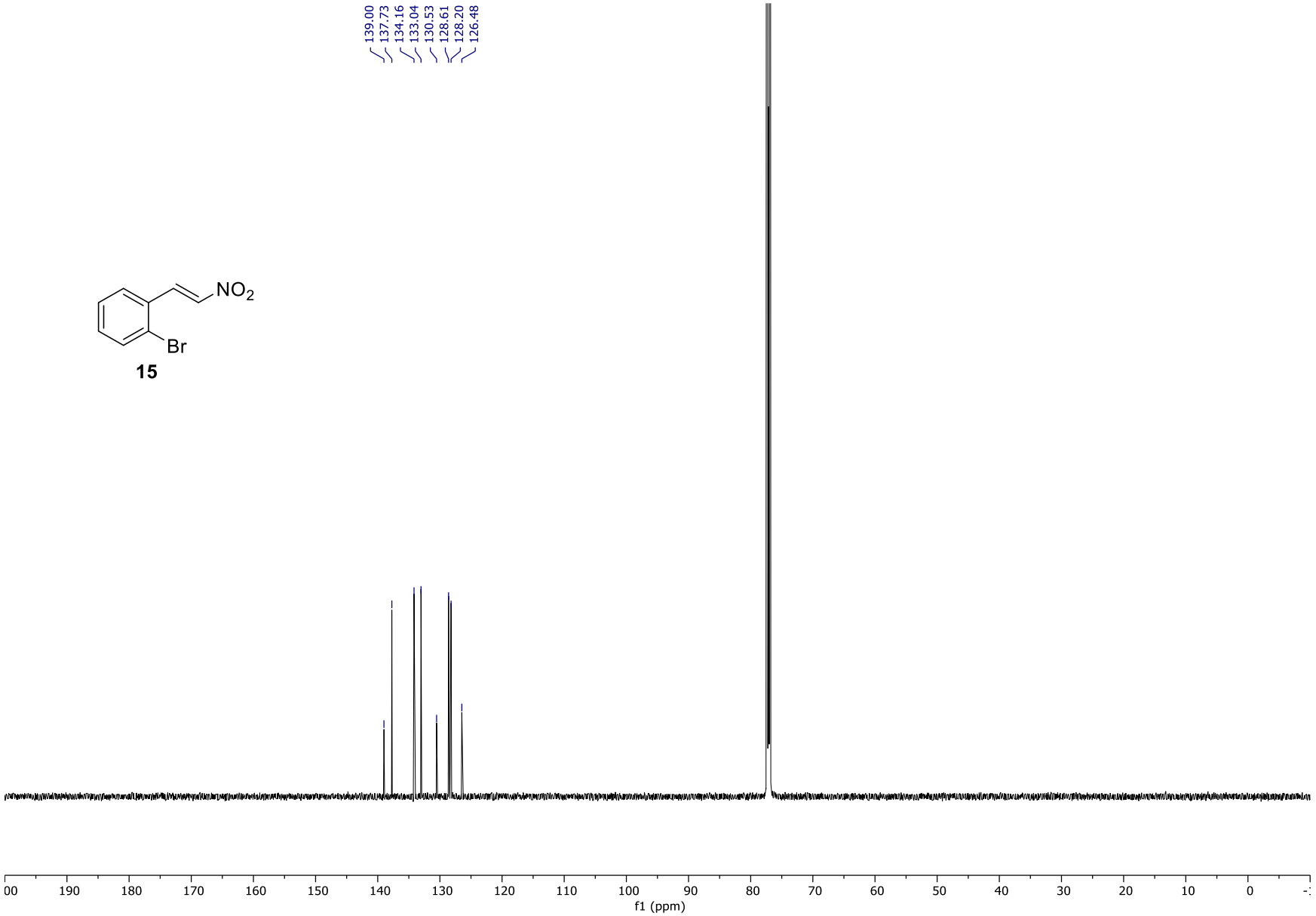
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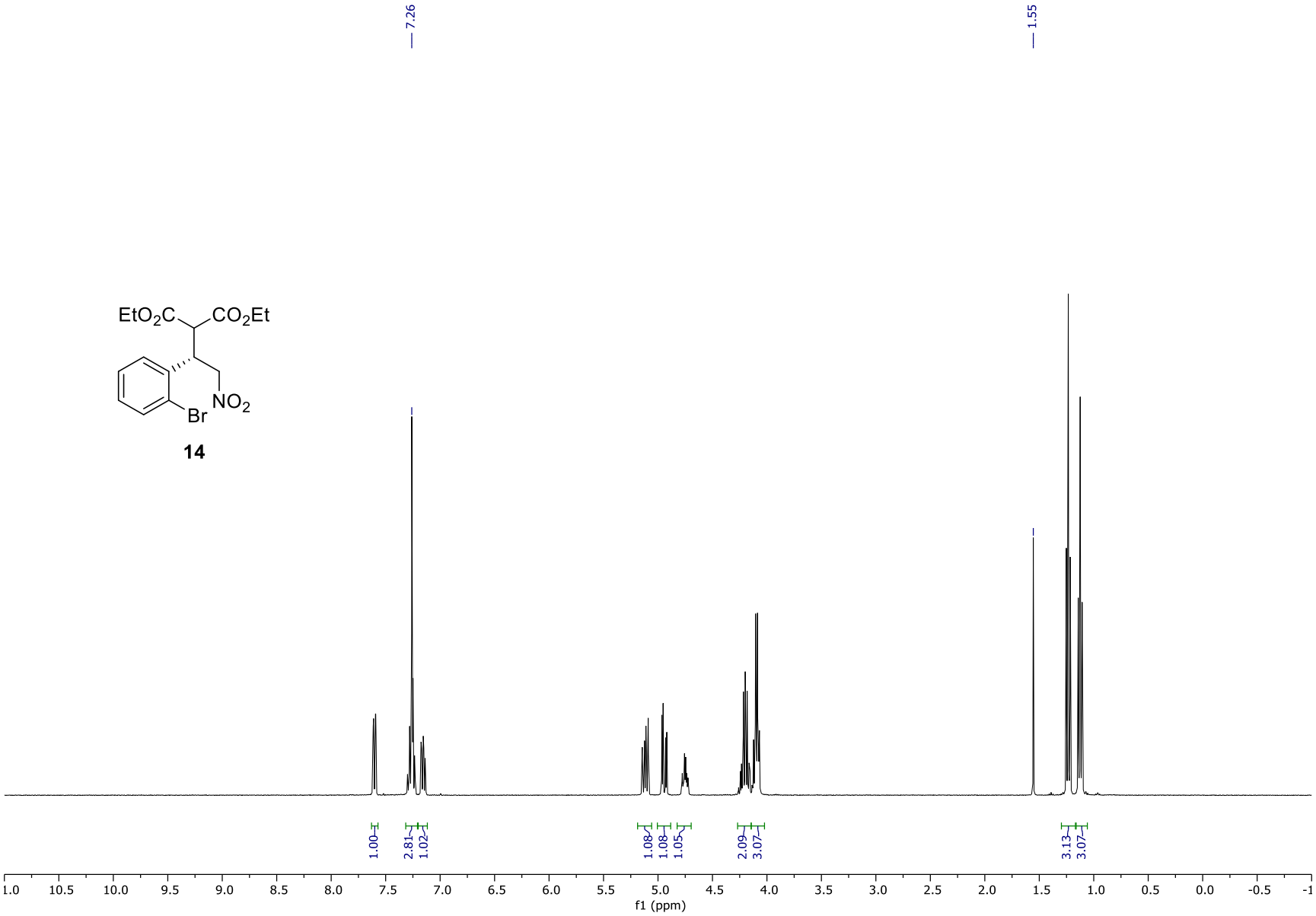
134.16
133.04
130.53
128.61
128.20
126.48
NO2
Br
15
f1 (ppm)


7.26
1.55
EtO2C
CO2Et
NO2
Br
14
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2.81
1.02
1.08
1.08
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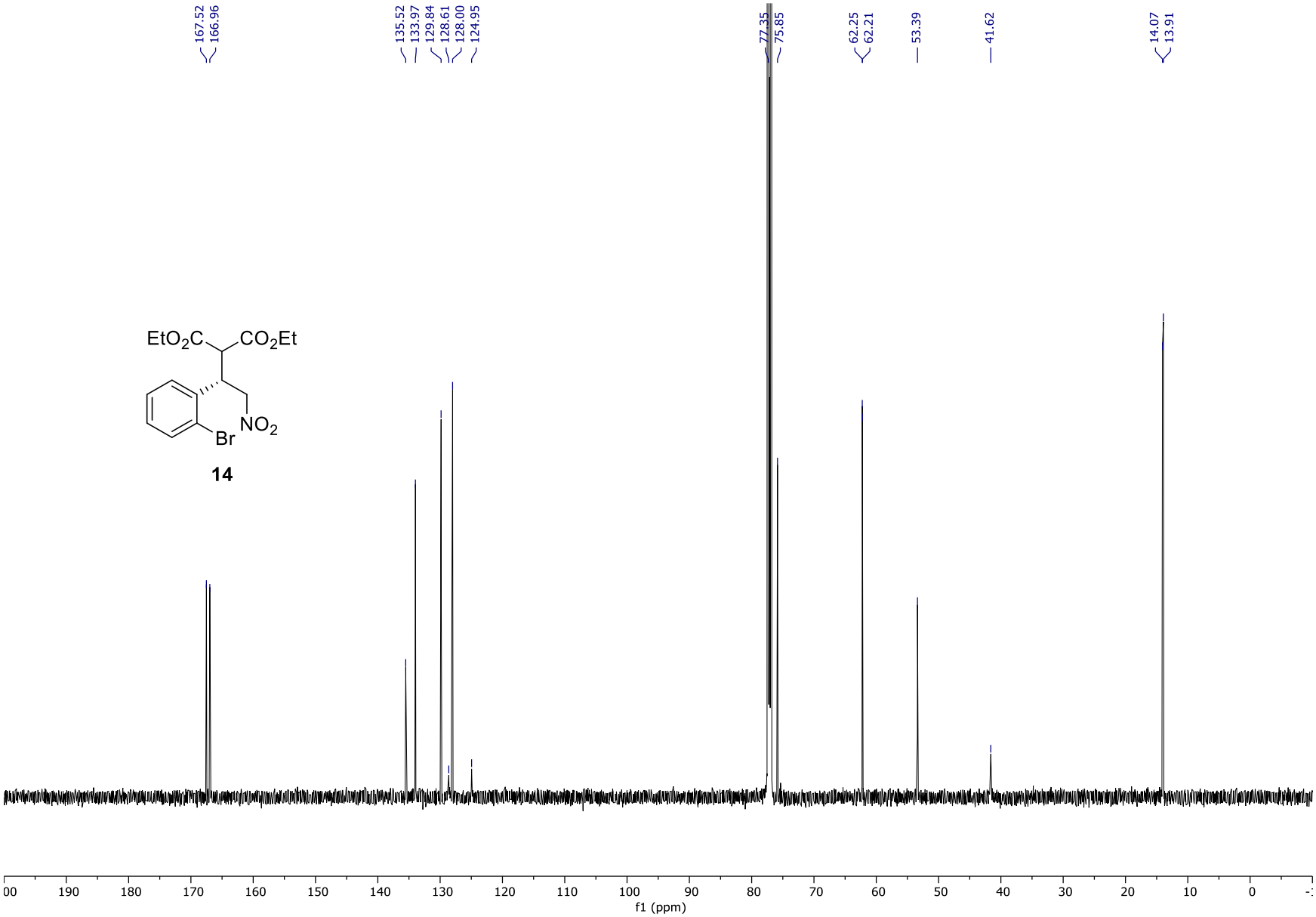
2.09
3.07
3.13
3.07
f1 (ppm)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166.96
135.52
133.97
129.84
128.61
128.00
124.95
77.35
75.85
62.25
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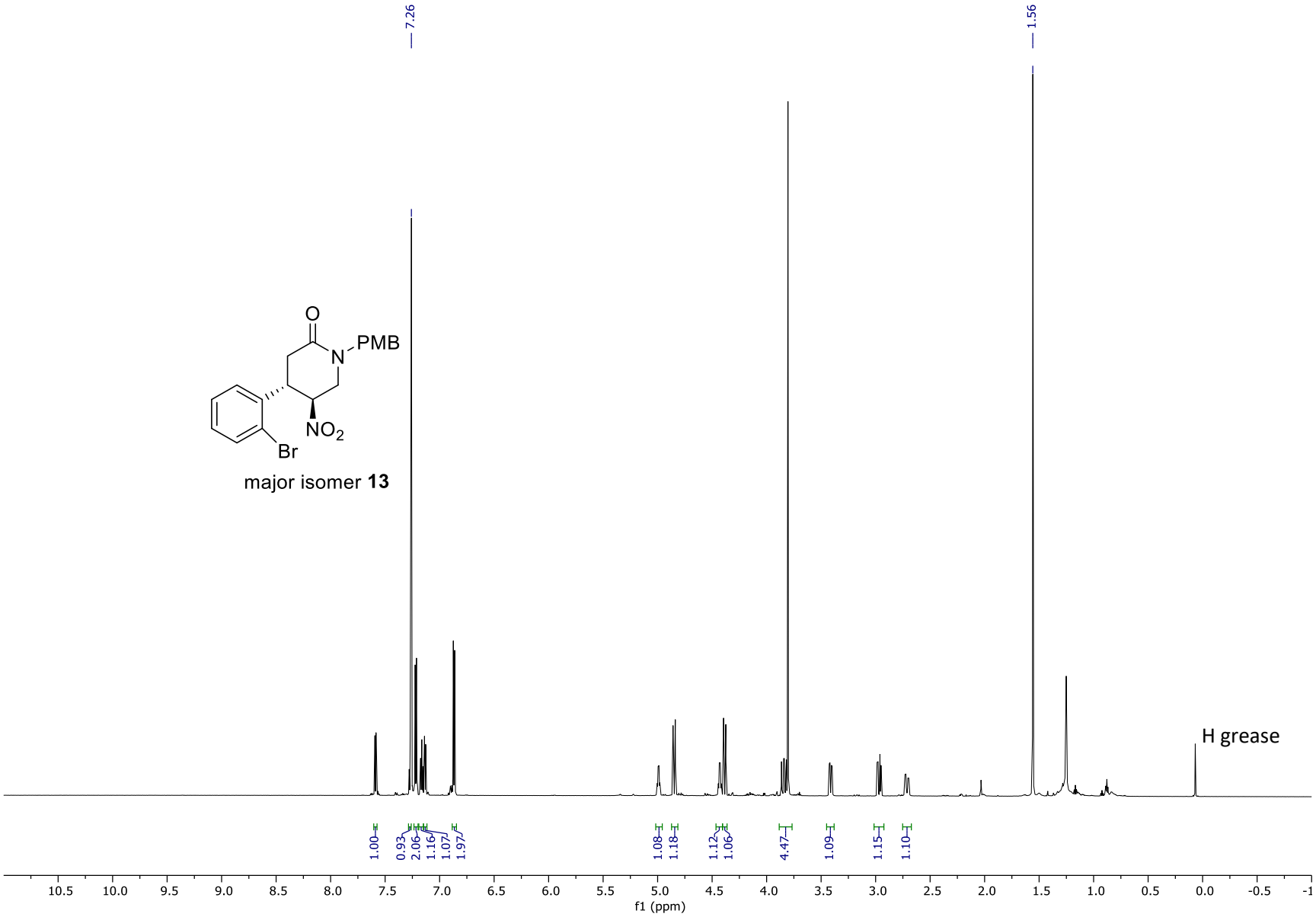
53.39
41.62
14.07
13.91
EtO2C
CO2Et
NO2
Br
14
f1 (ppm)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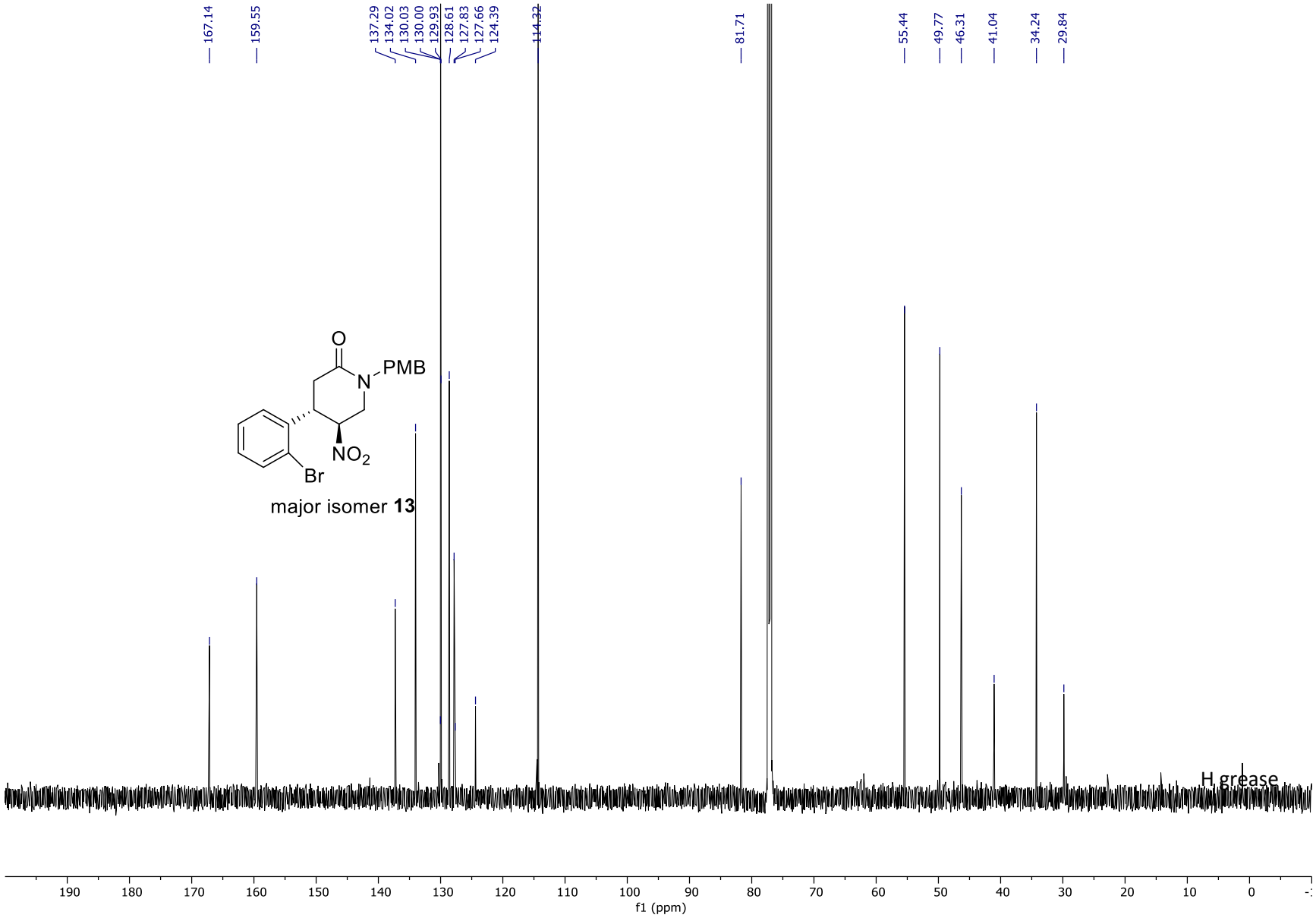
1.56
O
N
PMB
NO2
Br
major isomer 13
H grease
1.00
0.93
2.06
1.16
1.07
1.97
1.08
1.18
1.12
1.06
4.47
1.09
1.15
1.10
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)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130.03
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129.93
128.61
127.83
127.66
124.39
114.32
81.71
55.44
49.77
46.31
41.04
34.24
29.84
O
N
PMB
NO2
Br
major isomer 13
H grease
190
180
170
160
150
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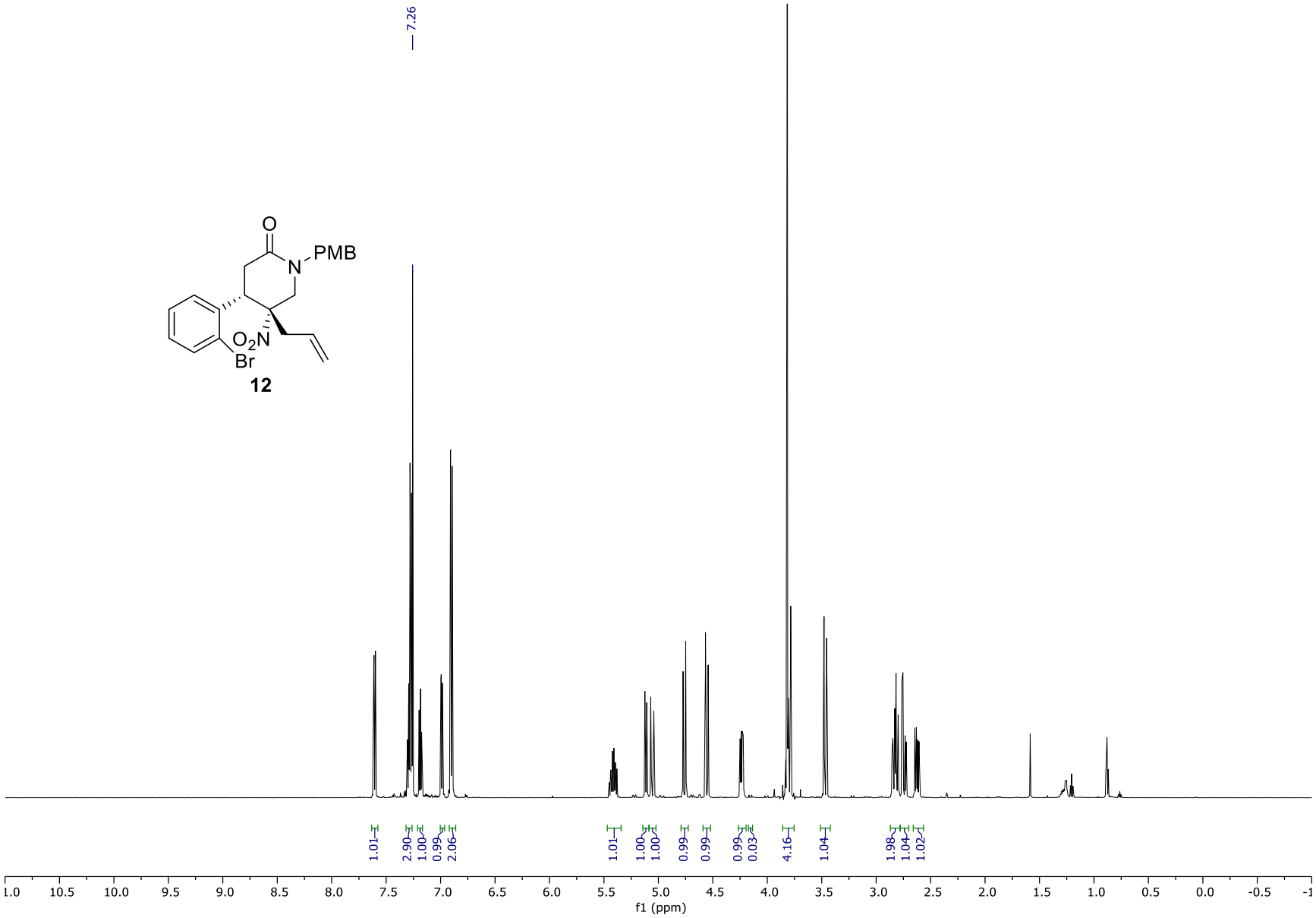
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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PMB
N
O_2N
Br
12
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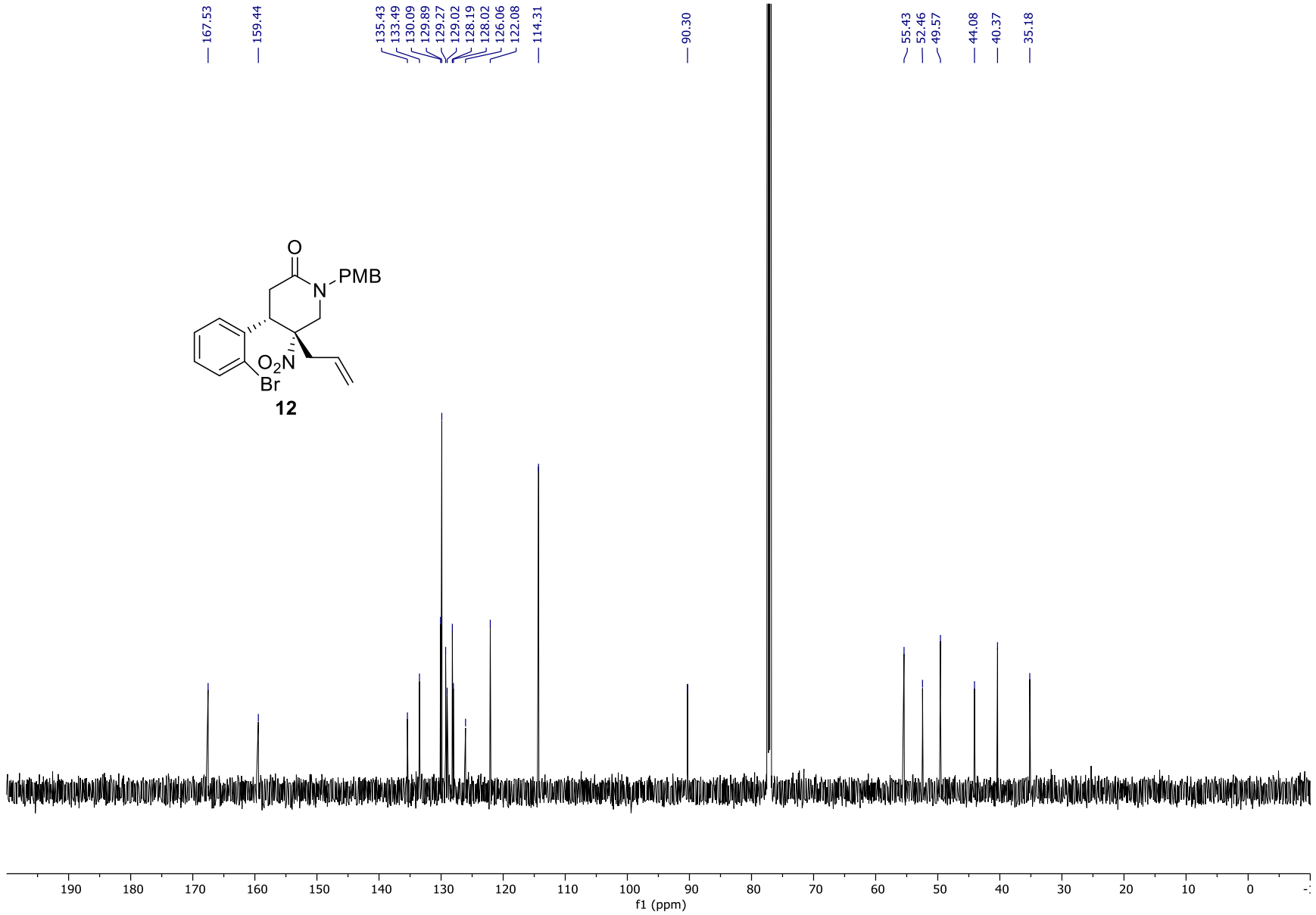
1.98
1.04
1.02
f1 (ppm)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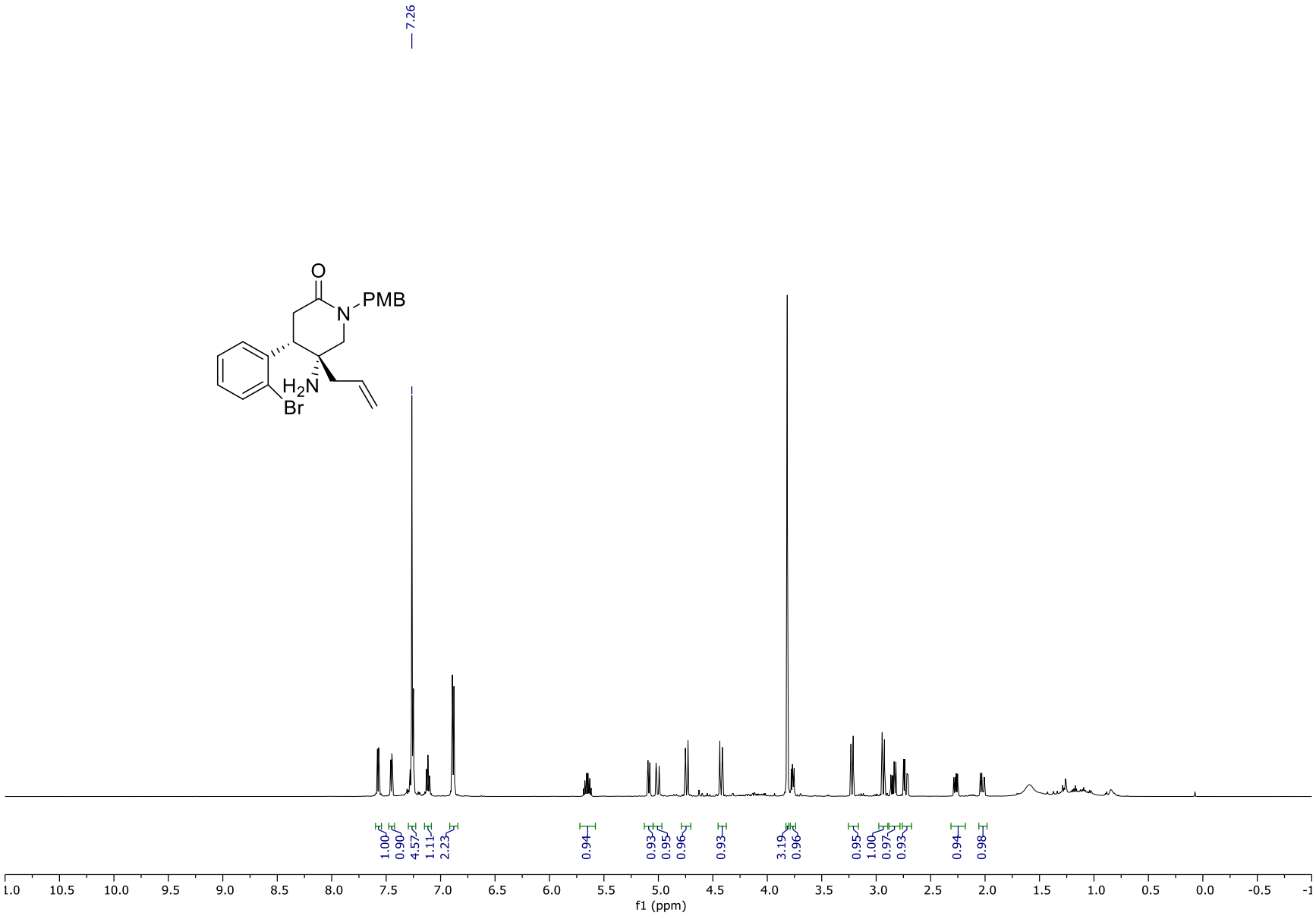
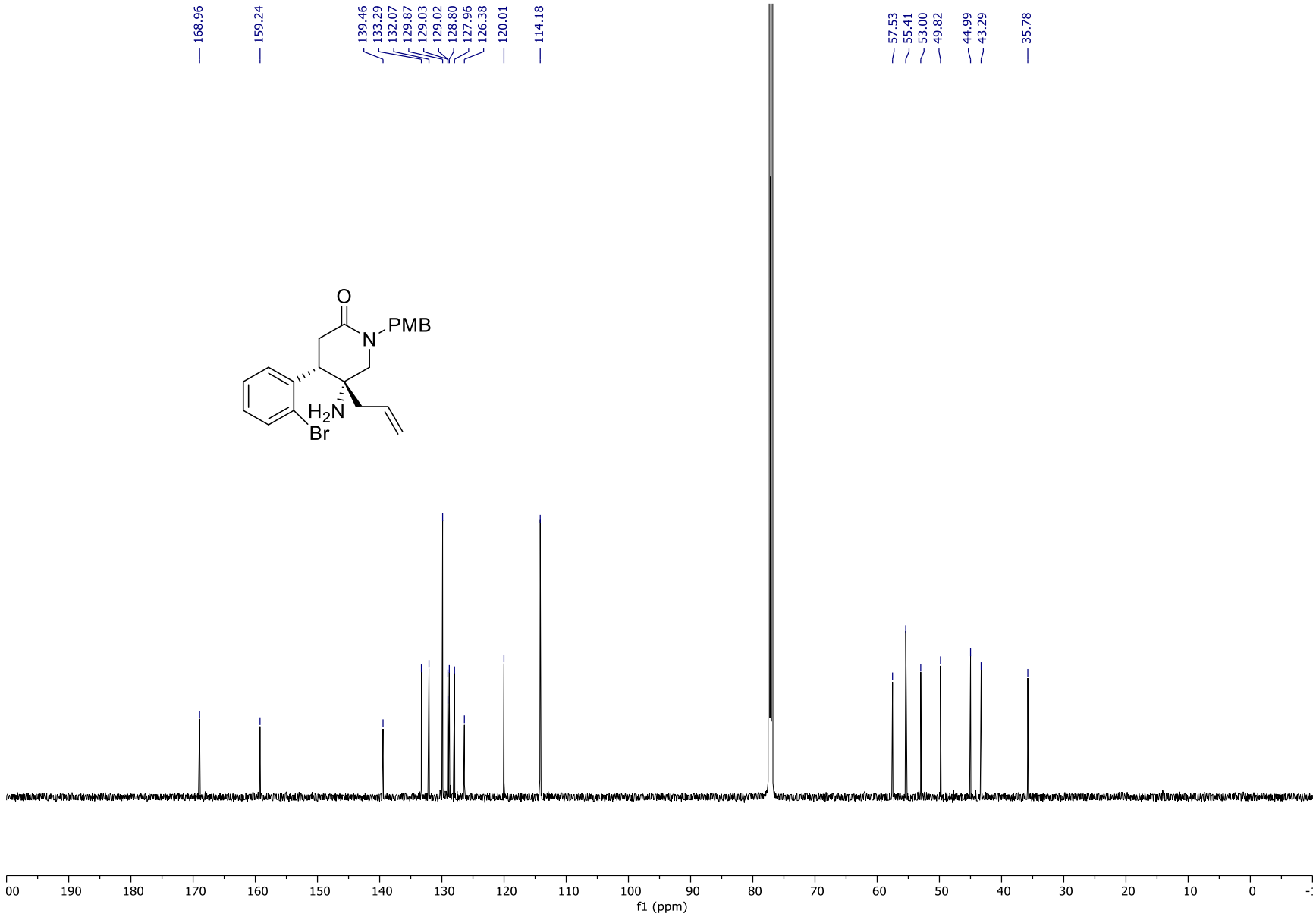
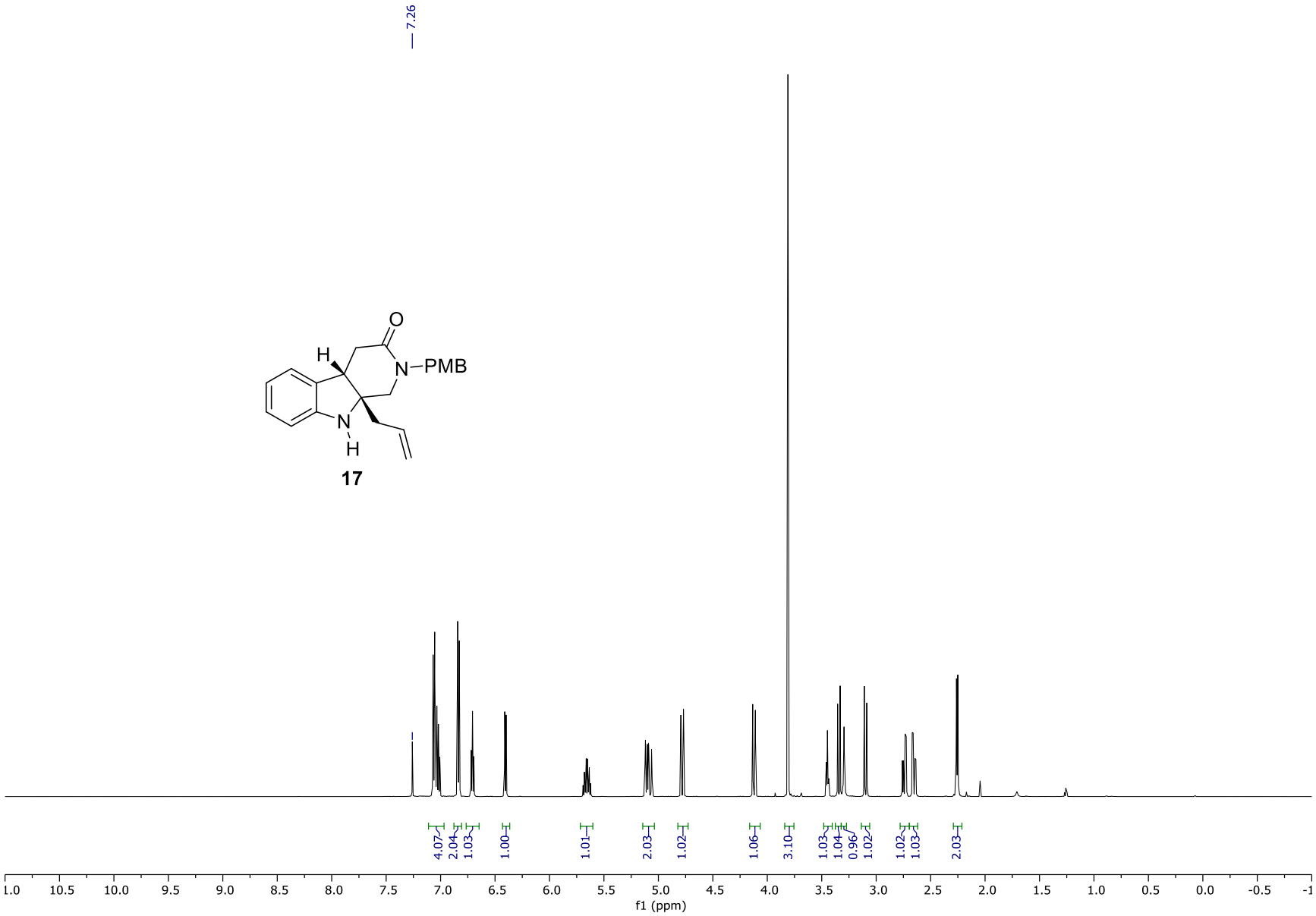
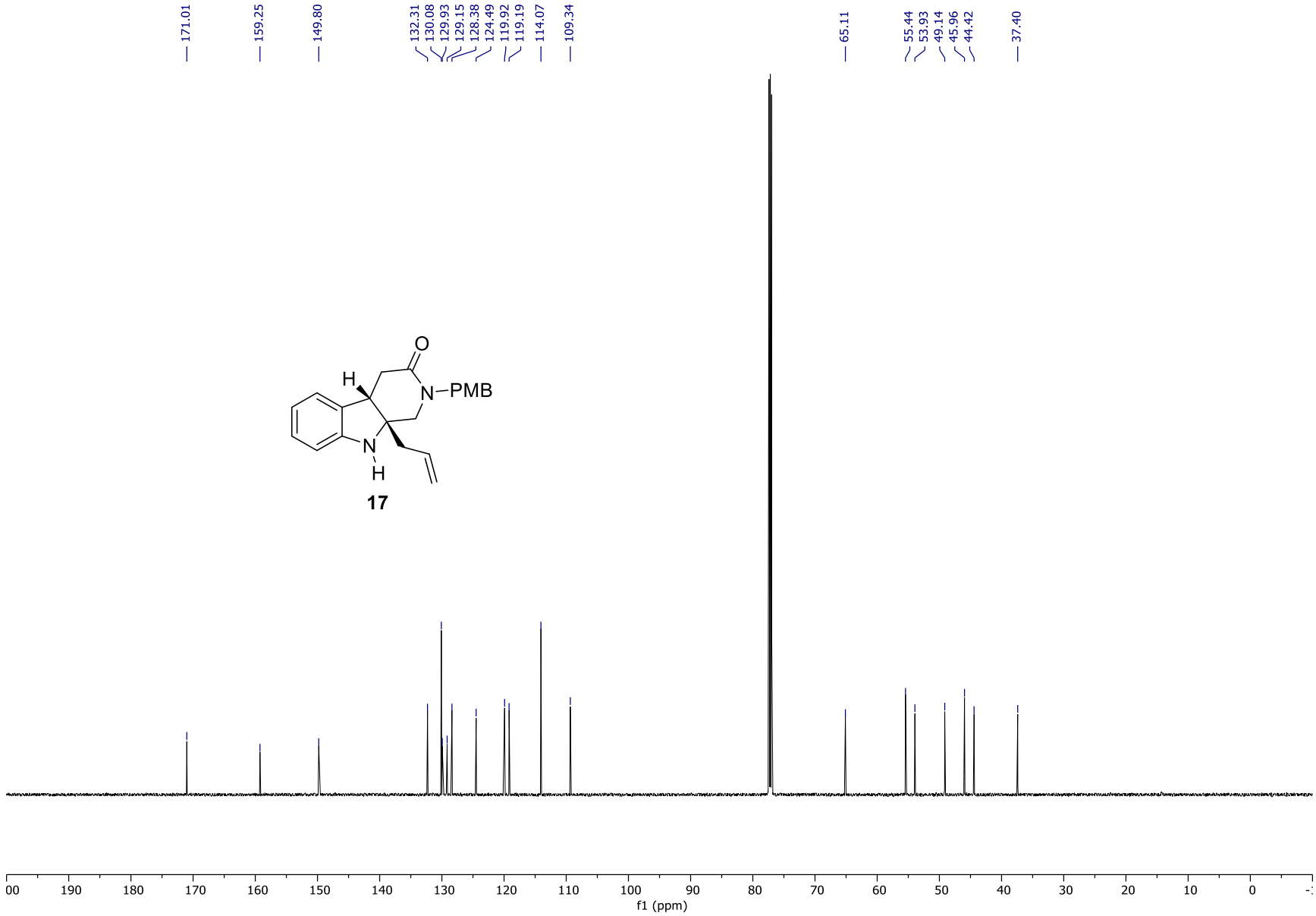
129.89
129.27
129.02
128.19
128.02
126.06
122.08
114.31
90.30
55.43
52.46
49.57
44.08
40.37
35.18
O
N
PMB
O2N
Br
12
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.26
O
N
PMB
H2N
Br
1.00
0.90
4.57
1.11
2.23
0.94
0.93
0.95
0.96
0.93
3.19
0.96
0.95
1.00
0.97
0.93
0.94
0.98
f1 (ppm)


168.96
159.24
139.46
133.29
132.07
129.87
129.03
129.02
128.80
127.96
126.38
120.01
114.18
57.53
55.41
53.00
49.82
44.99
43.29
35.78
O
N
PMB
H2N
Br
f1 (ppm)


7.26
O
H
N–PMB
N
H
17
4.07
2.04
1.03
1.00
1.01
2.03
1.02
1.06
3.10
1.03
1.04
0.96
1.02
1.02
1.03
2.03
f1 (ppm)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129.15
128.38
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119.92
119.19
114.07
109.34
65.11
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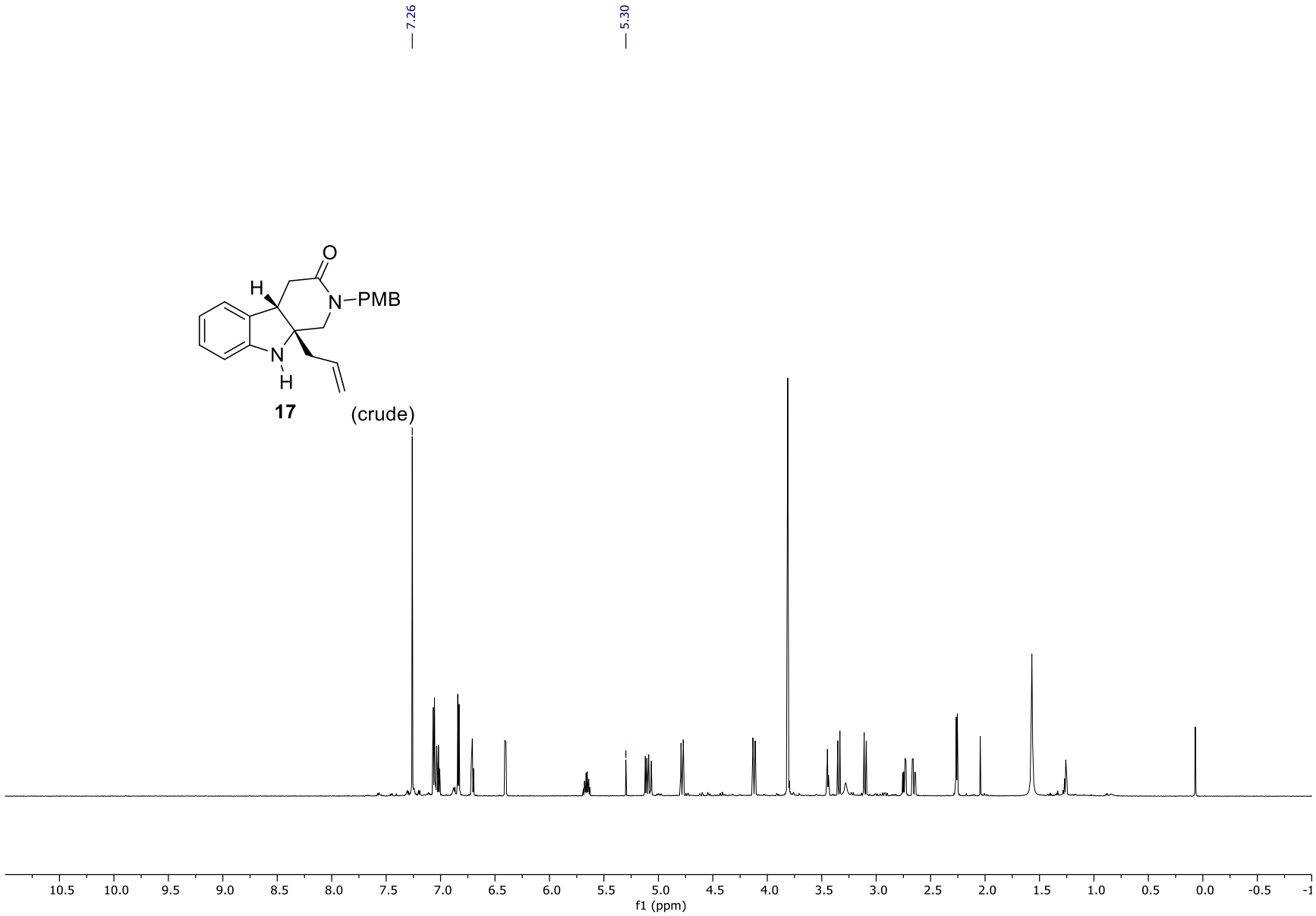
53.93
49.14
45.96
44.42
37.40
O
H
N–PMB
N
H
17
f1 (ppm)


7.26
5.30
O
H
N–PMB
N
H
17
(crude)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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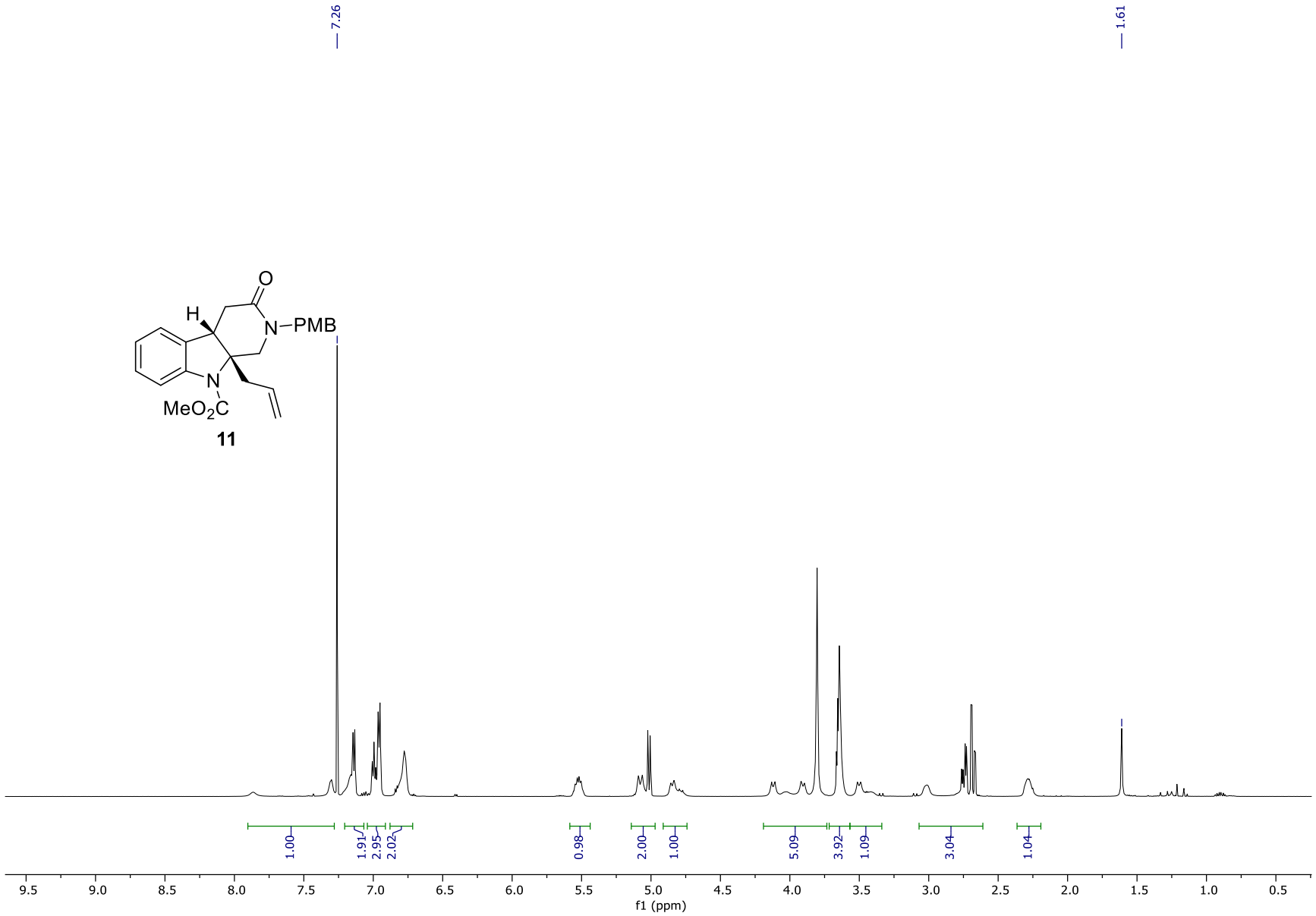
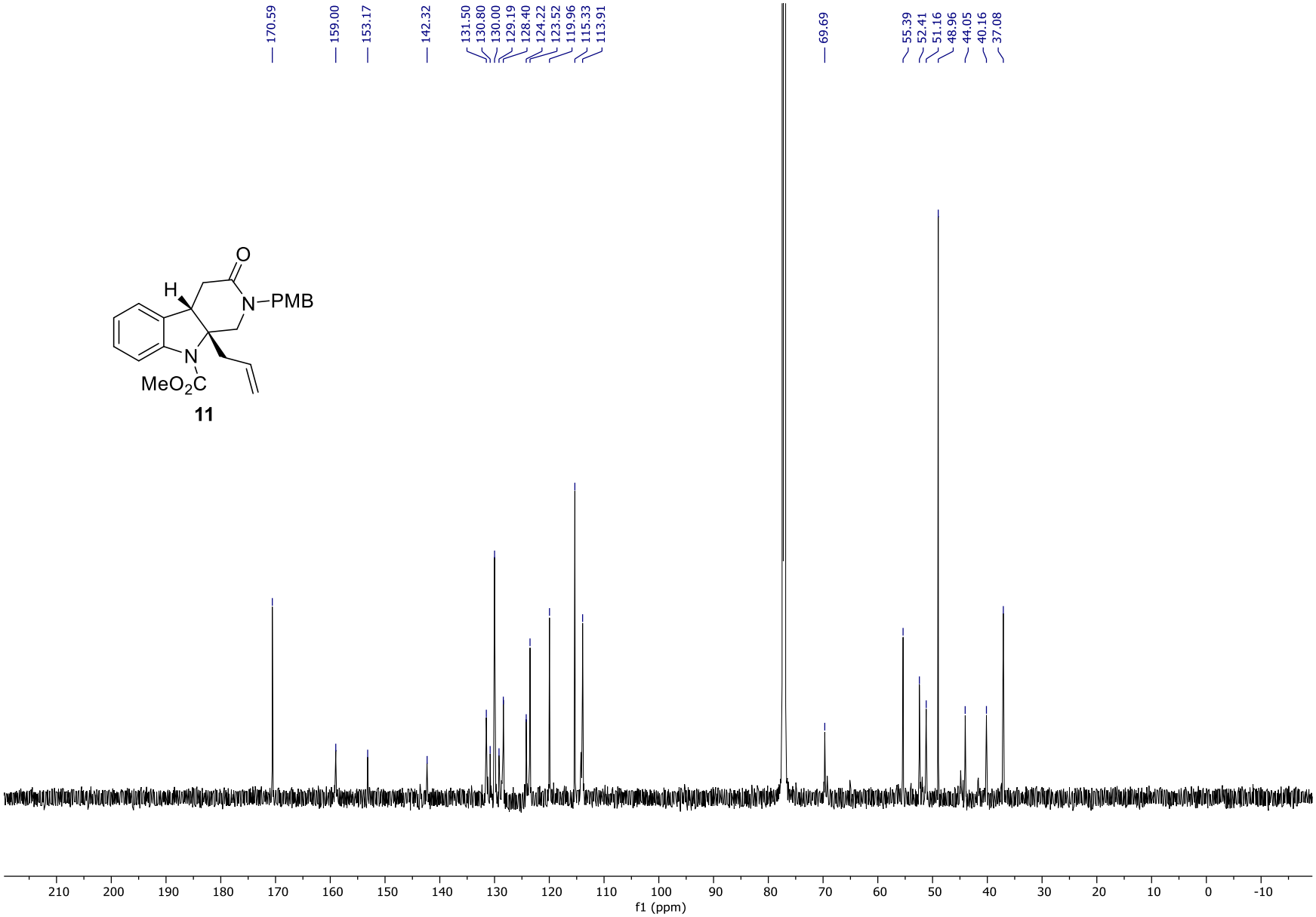
-1
f1 (ppm)


7.26
1.61
O
H
N–PMB
N
MeO2C
11
1.00
1.91
2.95
2.02
0.98
2.00
1.00
5.09
3.92
1.09
3.04
1.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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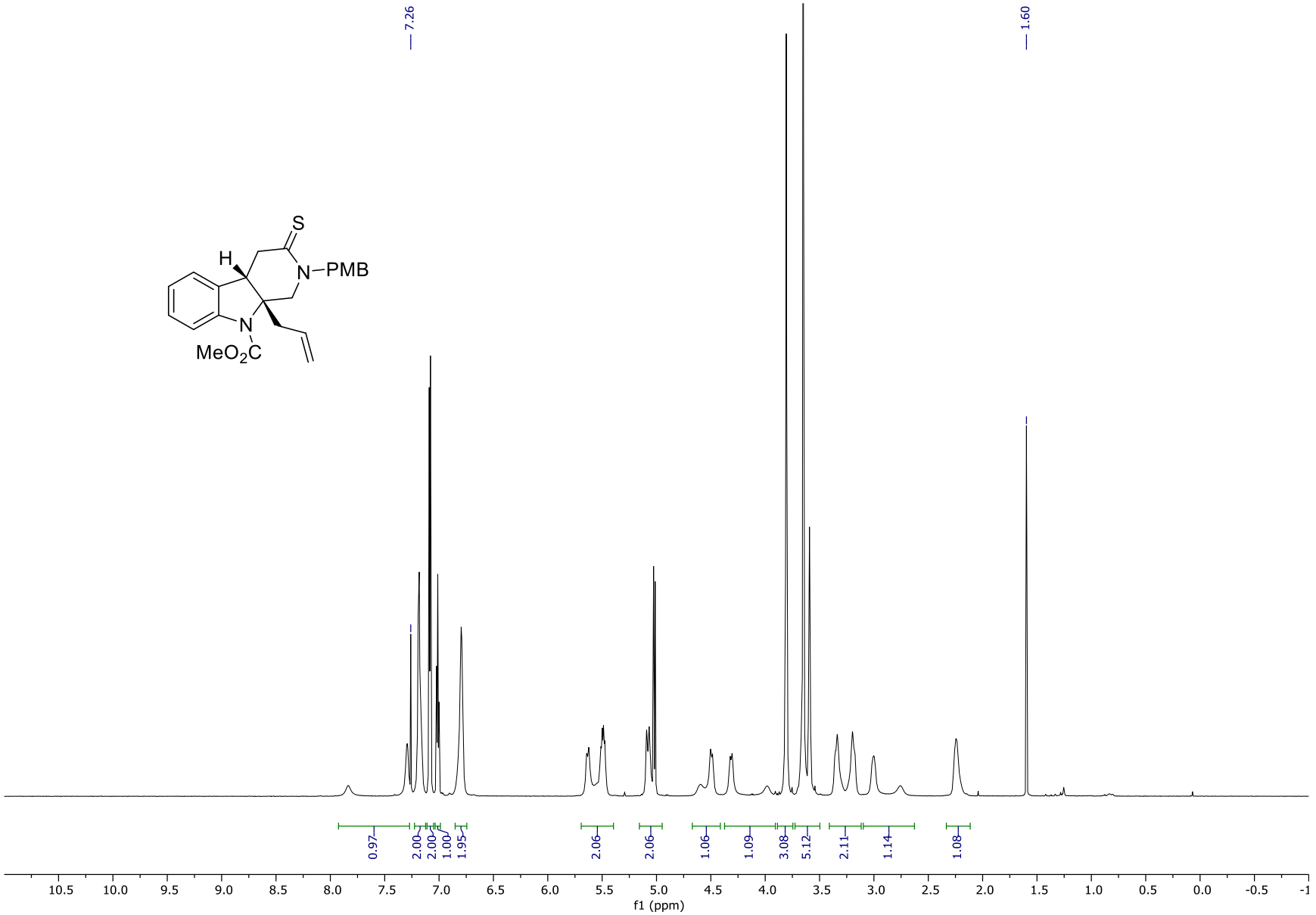
124.22
123.52
119.96
115.33
113.91
69.69
55.39
52.41
51.16
48.96
44.05
40.16
37.08
O
H
N–PMB
N
MeO2C
11
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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1.60
S
H
N–PMB
N
MeO2C
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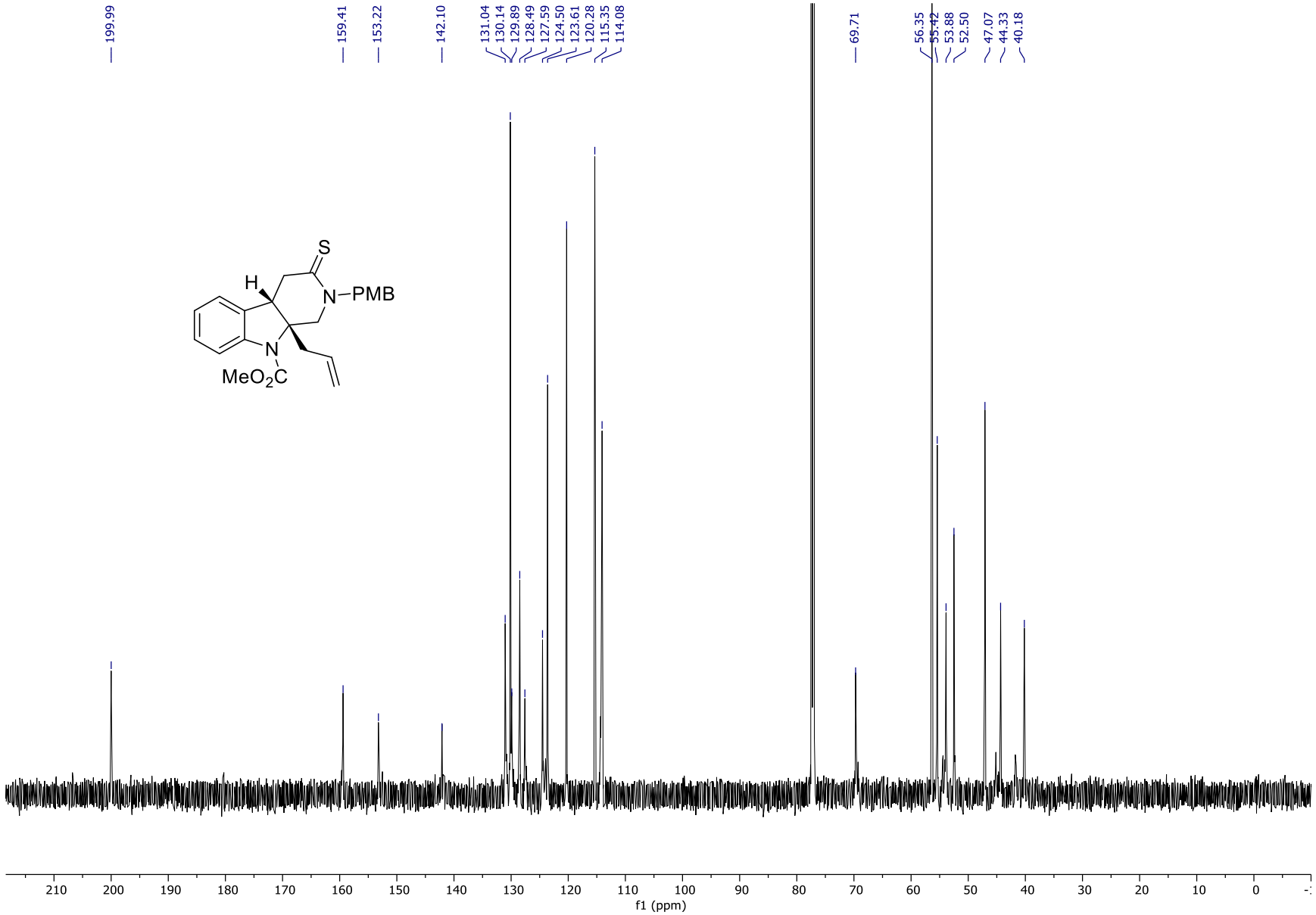
2.00
2.00
1.00
1.95
2.06
2.06
1.06
1.09
3.08
5.12
2.11
1.14
1.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)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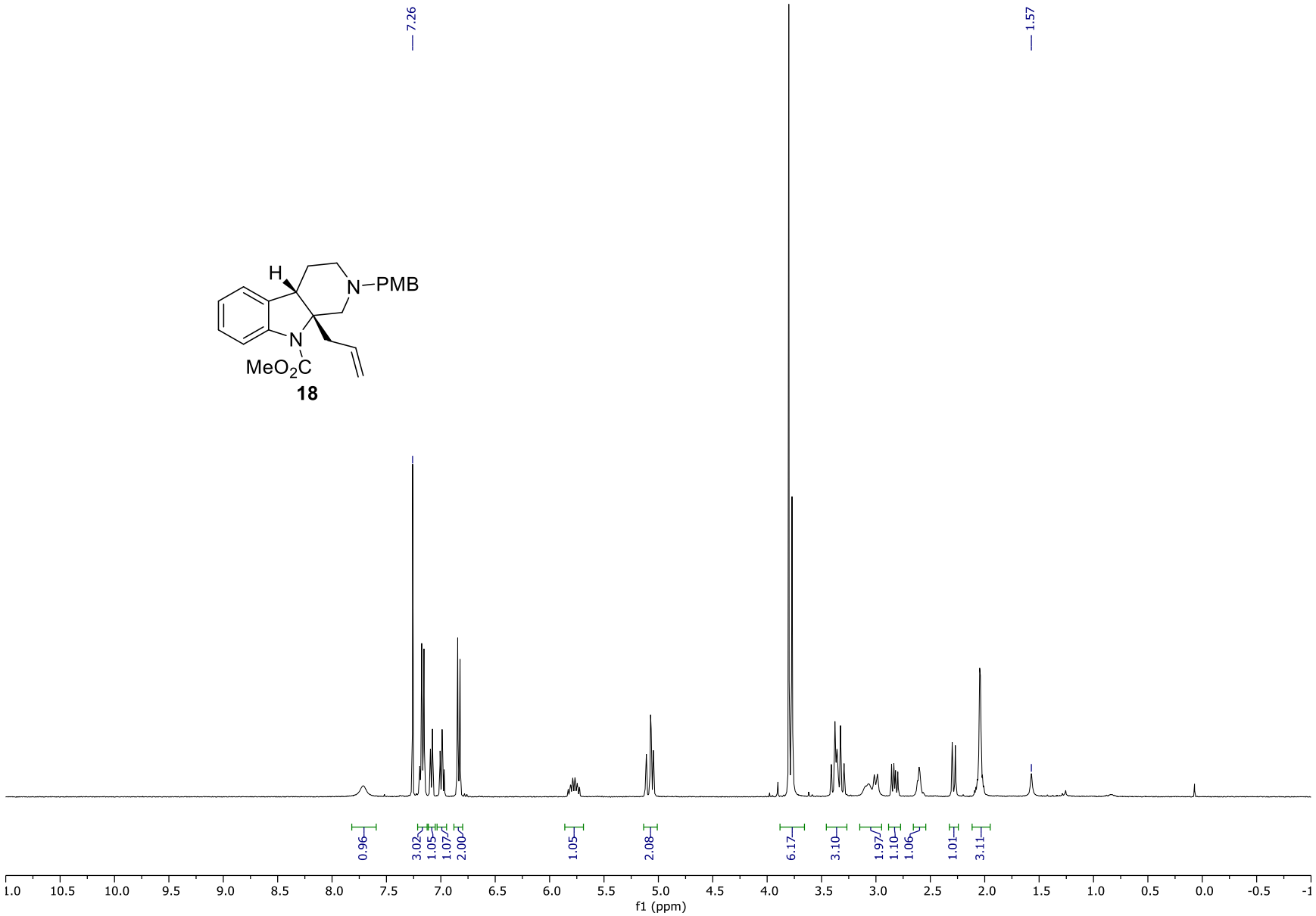
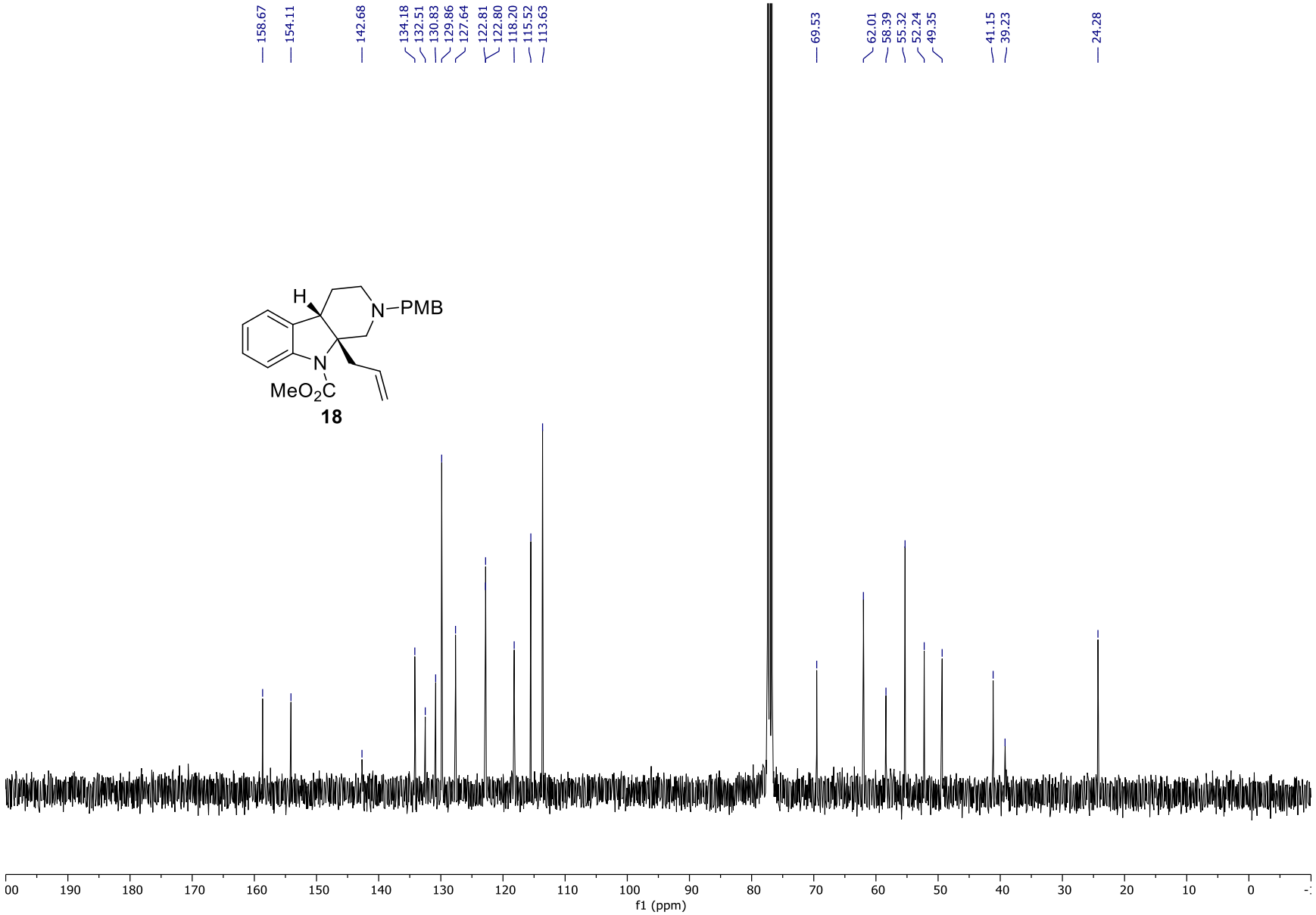
124.50
123.61
120.28
115.35
114.08
69.71
56.35
55.42
53.88
52.50
47.07
44.33
40.18
S
H
N–PMB
N
MeO2C
f1 (ppm)


7.26
1.57
H
N–PMB
N
MeO2C
18
0.96
3.02
1.05
1.07
2.00
1.05
2.08
6.17
3.10
1.97
1.10
1.06
1.01
3.11
f1 (ppm)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129.86
127.64
122.81
122.80
118.20
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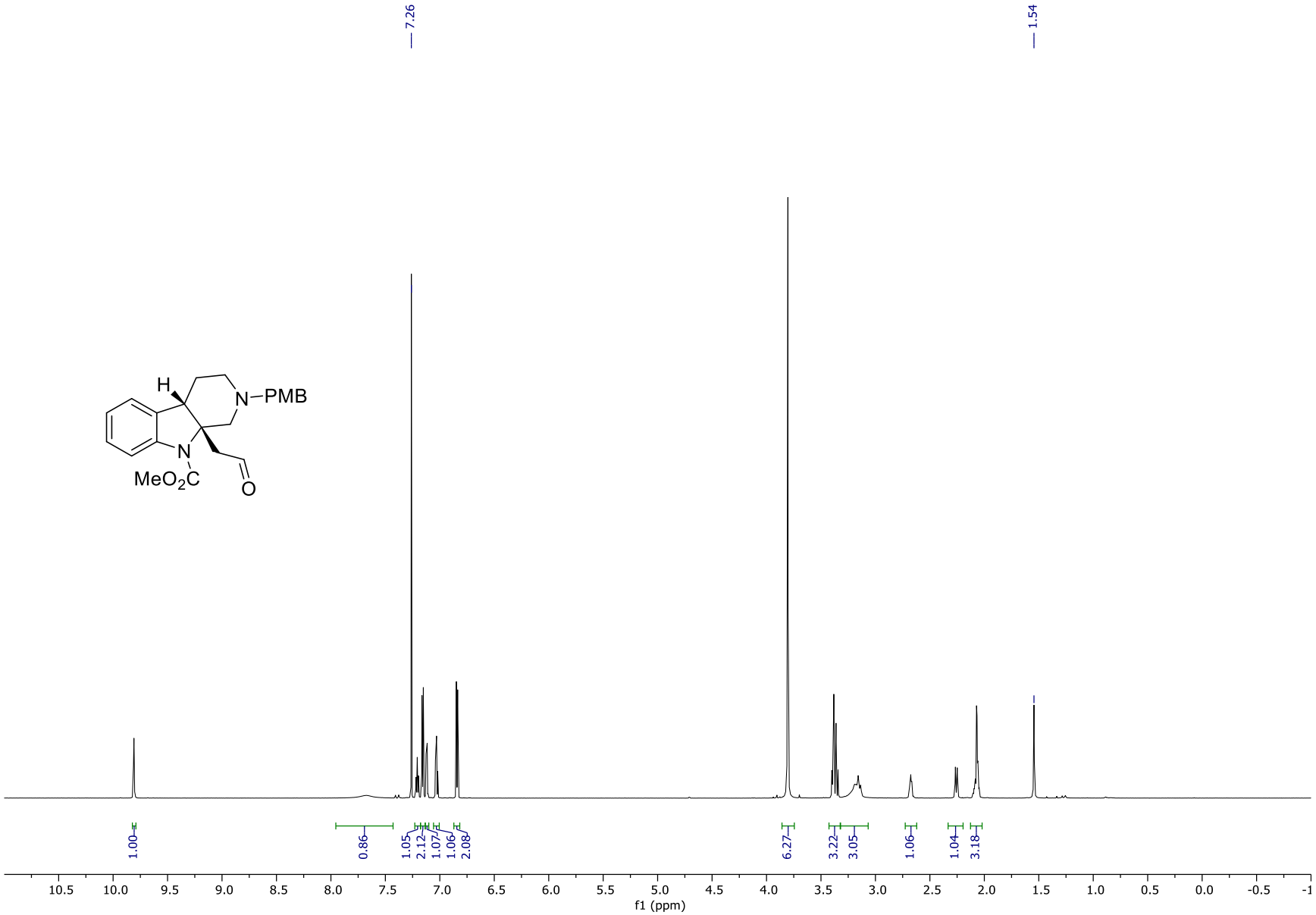
113.63
69.53
62.01
58.39
55.32
52.24
49.35
41.15
39.23
24.28
H
N–PMB
N
MeO2C
18
f1 (ppm)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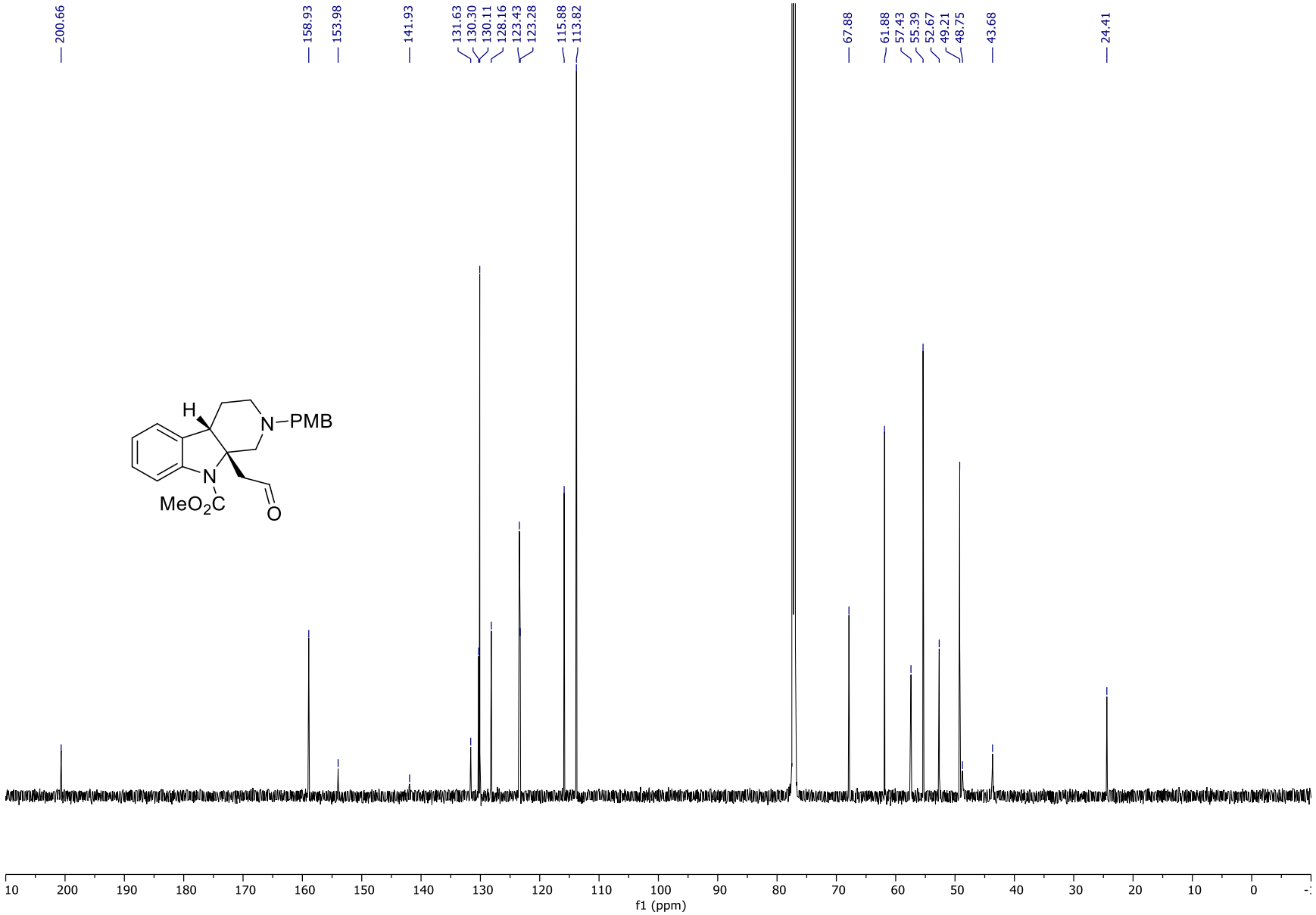
1.54
H
N–PMB
N
MeO2C
O
1.00
0.86
1.05
2.12
1.07
1.06
2.08
6.27
3.22
3.05
1.06
1.04
3.18
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)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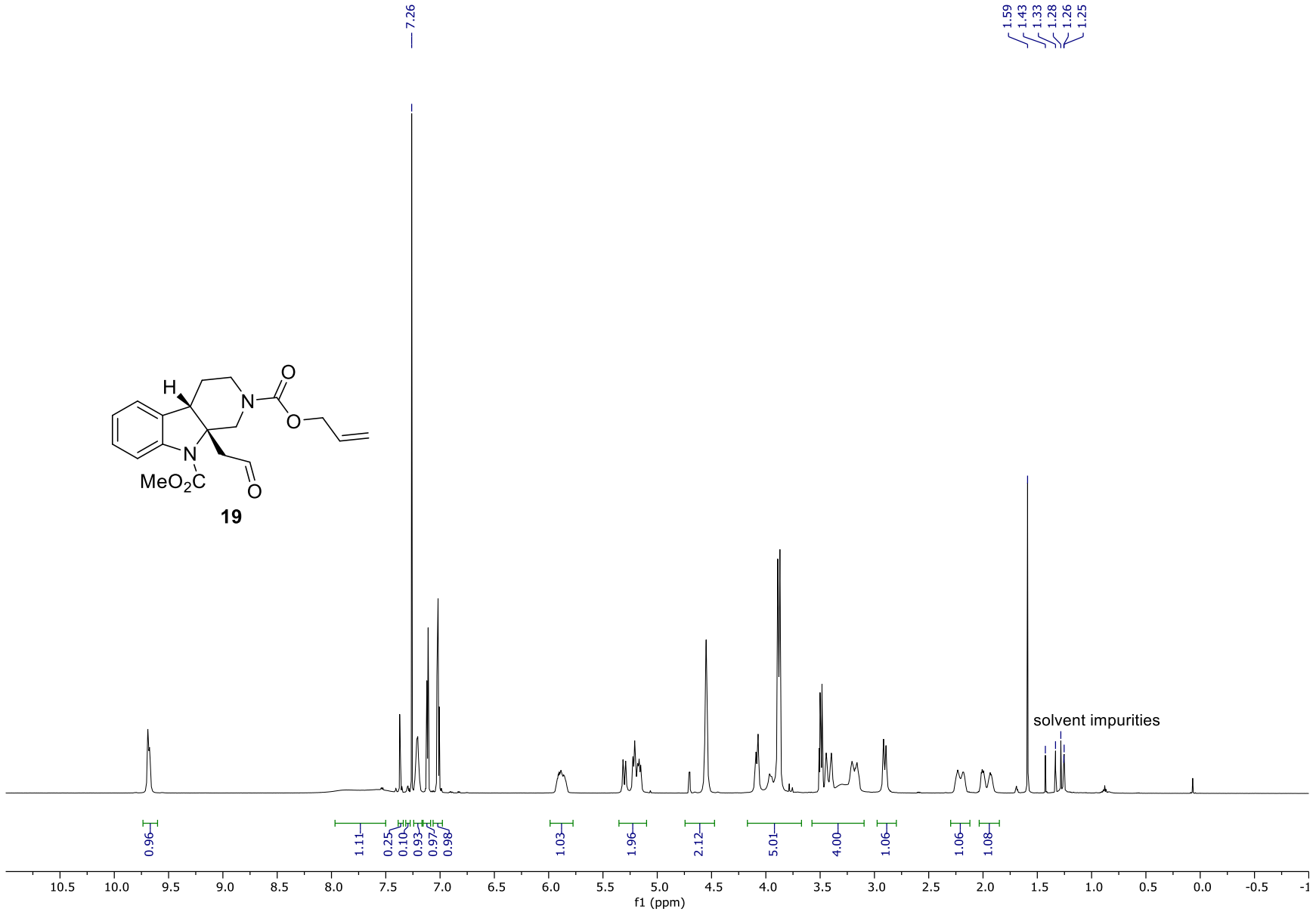
131.63
130.30
130.11
128.16
123.43
123.28
115.88
113.82
67.88
61.88
57.43
55.39
52.67
49.21
48.75
43.68
24.41
H
N–PMB
N
MeO2C
O
f1 (ppm)


7.26
1.59
1.43
1.33
1.28
1.26
1.25
H
N
O
O
N
MeO2C
O
19
solvent impurities
0.96
1.11
0.25
0.10
0.93
0.97
0.98
1.03
1.96
2.12
5.01
4.00
1.06
1.06
1.08
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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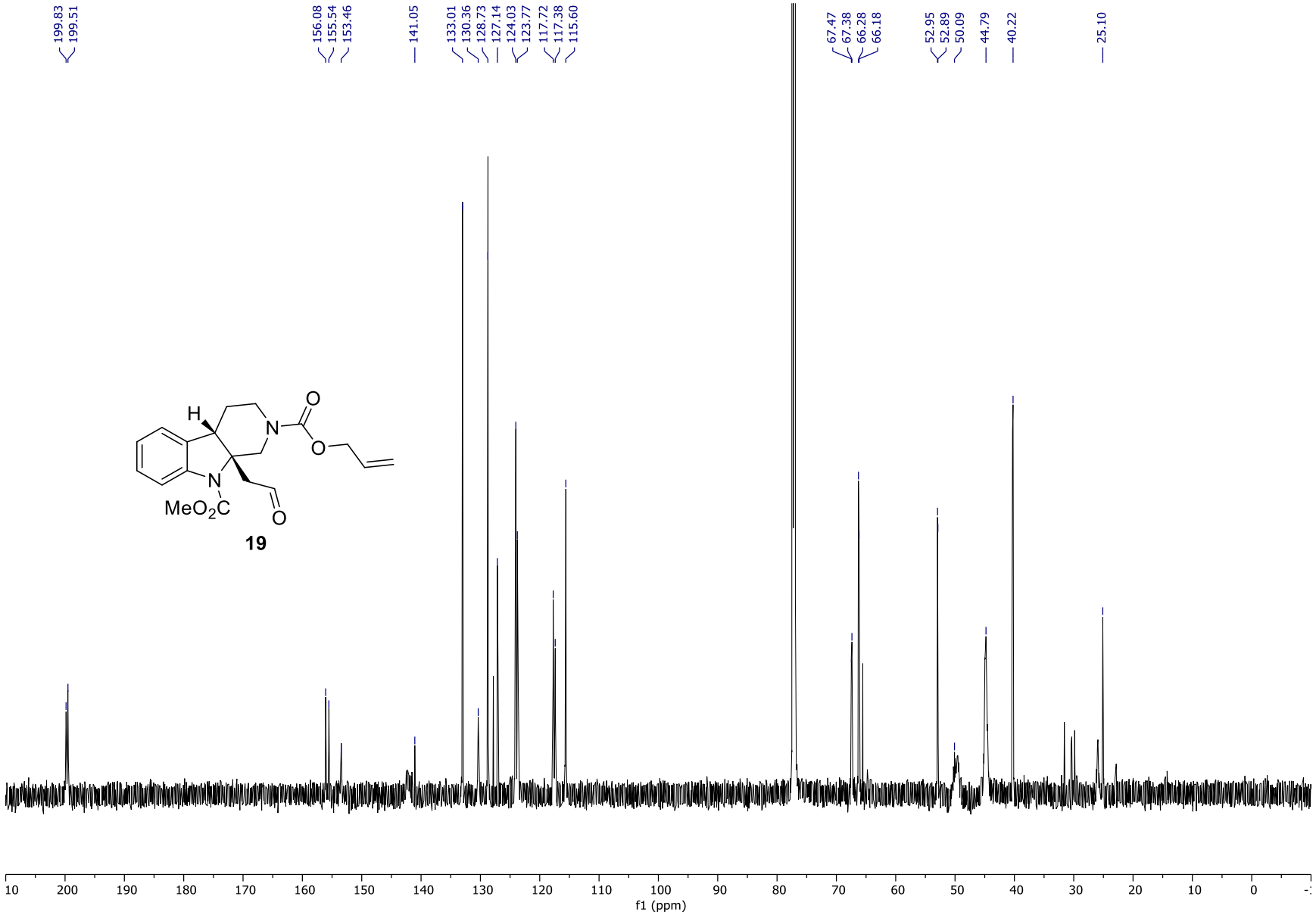
-1
f1 (ppm)


199.83
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153.46
141.05
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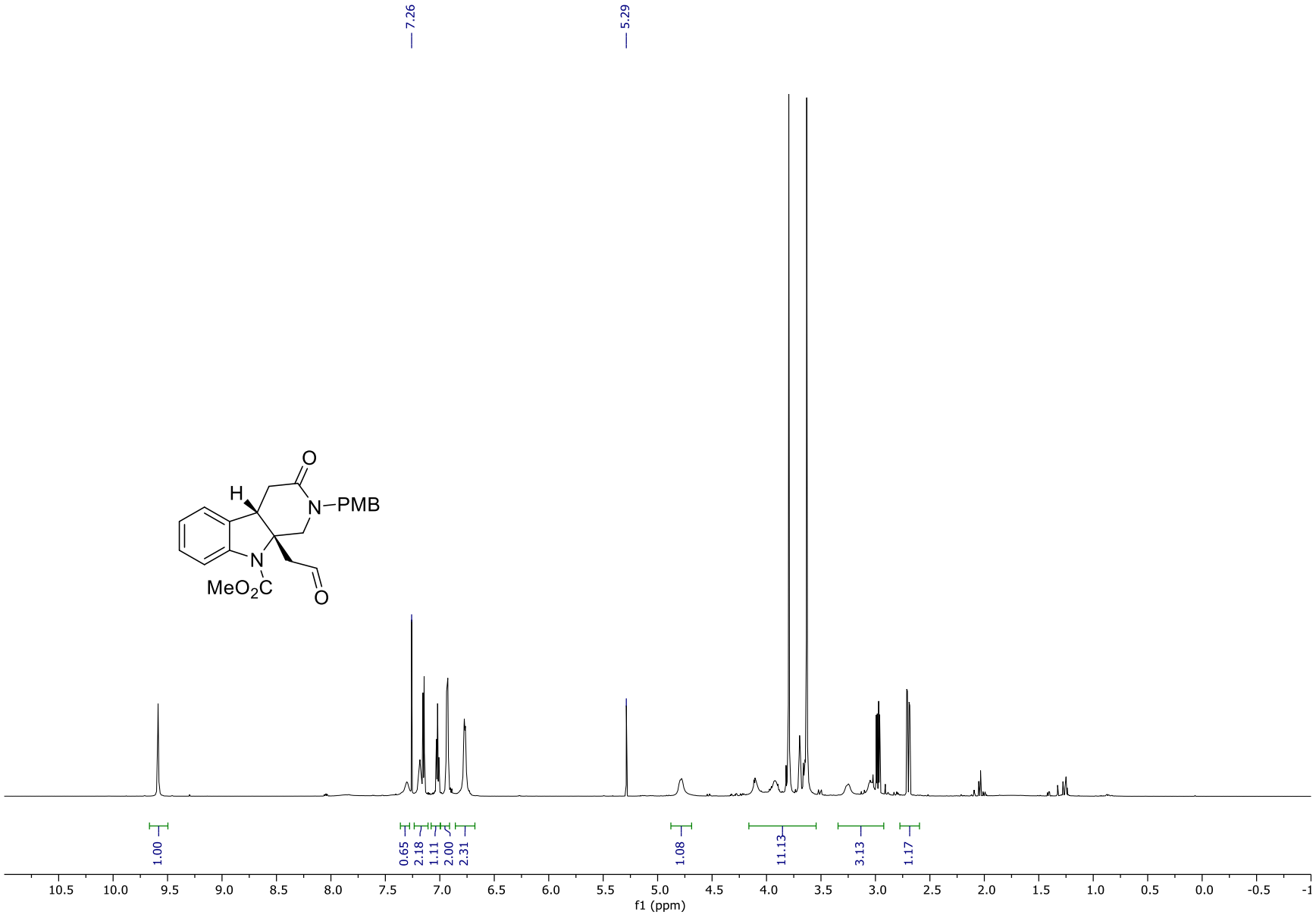
127.14
124.03
123.77
117.72
117.38
115.60
67.47
67.38
66.28
66.18
52.95
52.89
50.09
44.79
40.22
25.10
H
N
O
O
N
MeO2C
O
19
f1 (ppm)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5.29
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H
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N
MeO2C
O
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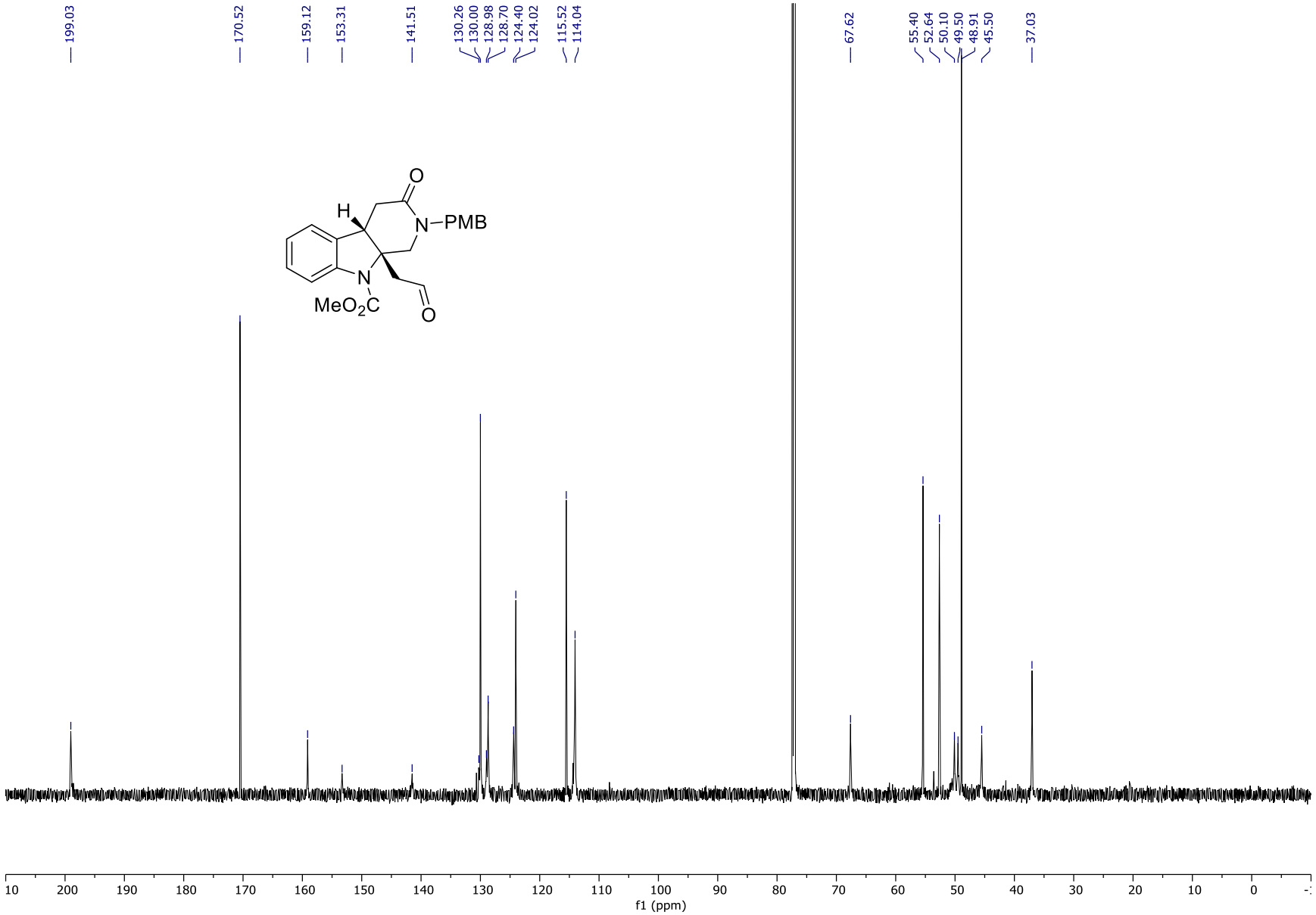
0.65
2.18
1.11
2.00
2.31
1.08
11.13
3.13
1.17
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)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130.26
130.00
128.98
128.70
124.40
124.02
115.52
114.04
67.62
55.40
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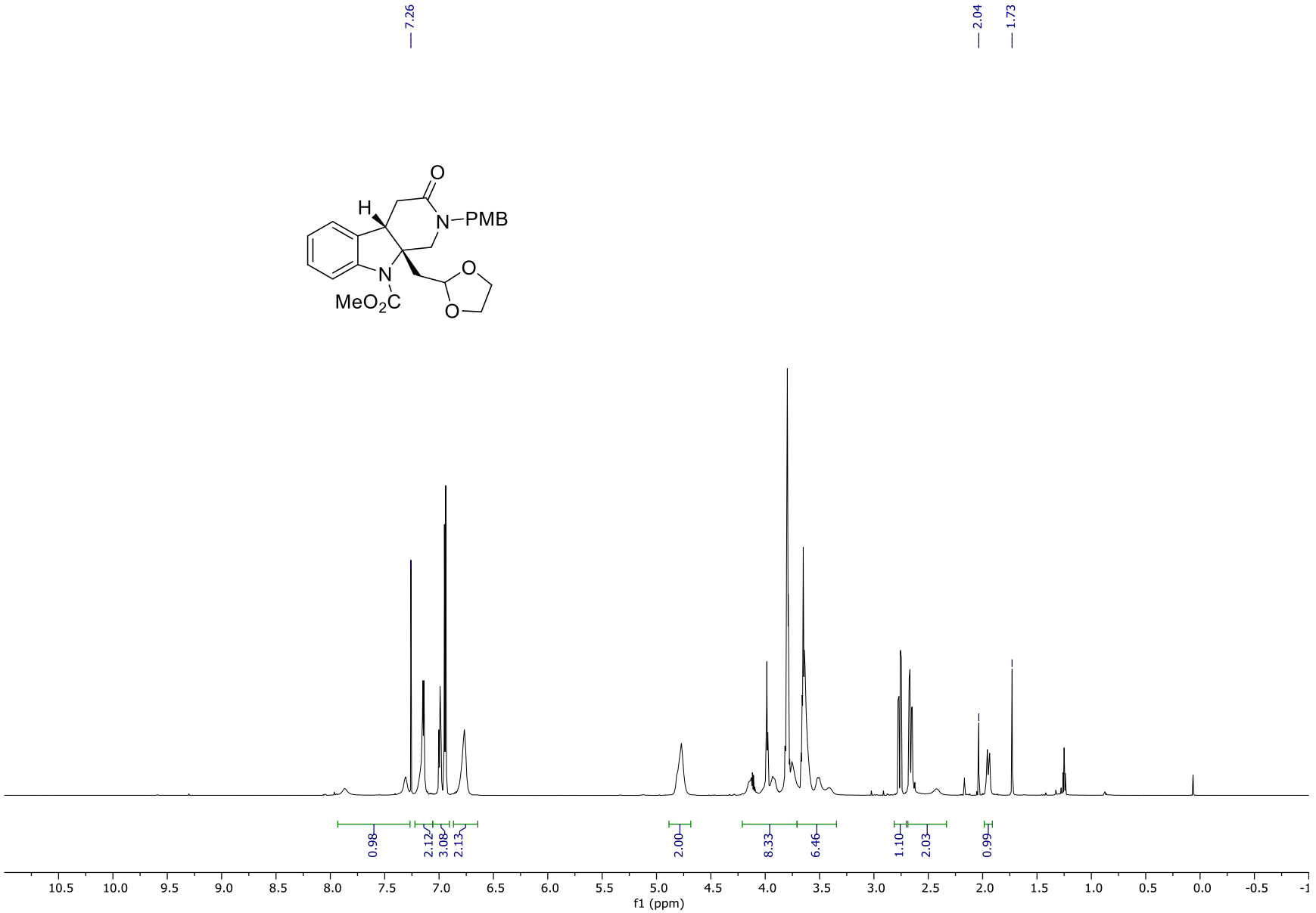
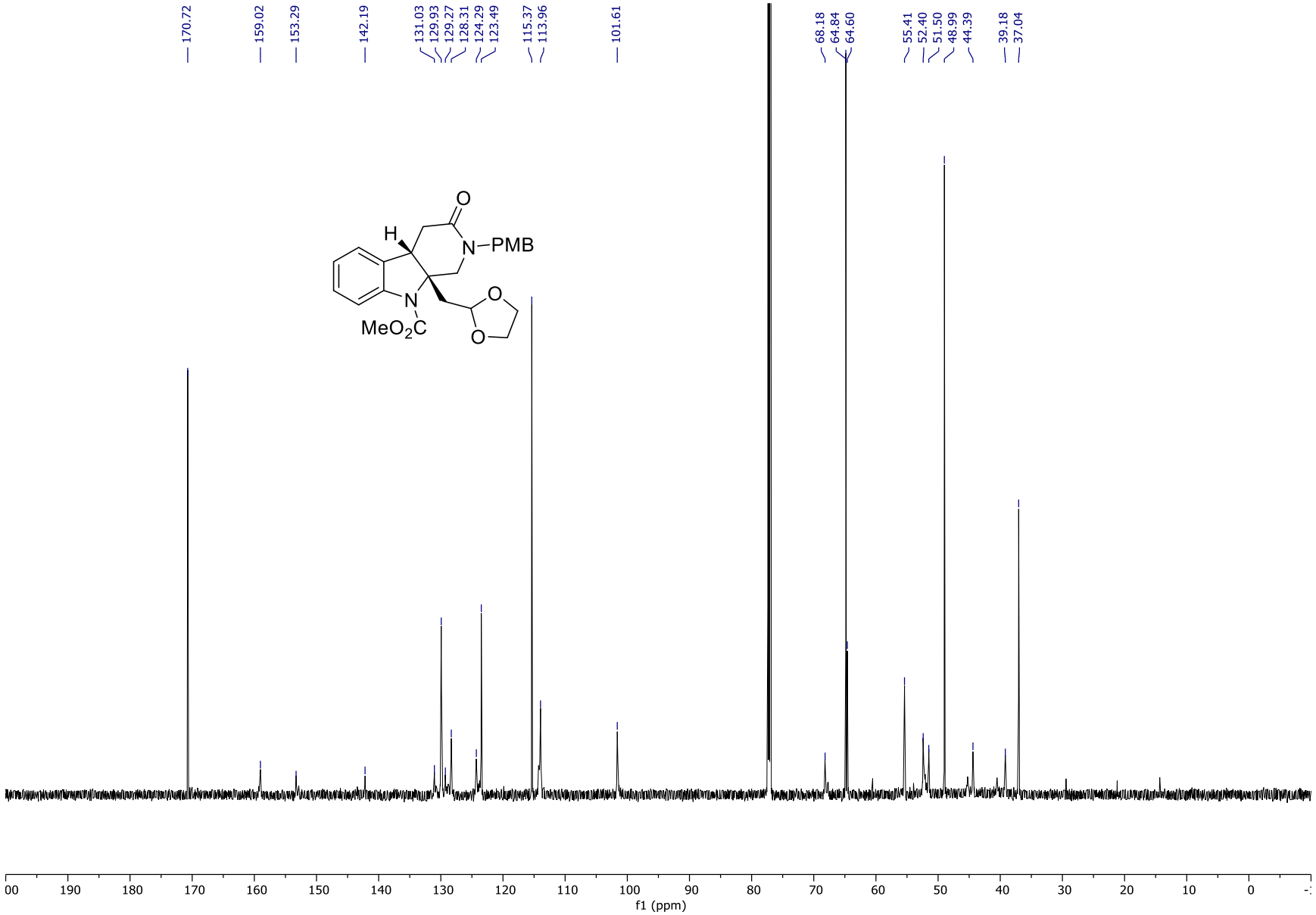
37.03
O
H
N–PMB
N
MeO2C
O
f1 (ppm)


7.26
2.04
1.73
O
H
N–PMB
N
O
MeO2C
O
0.98
2.12
3.08
2.13
2.00
8.33
6.46
1.10
2.03
0.99
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


170.72
159.02
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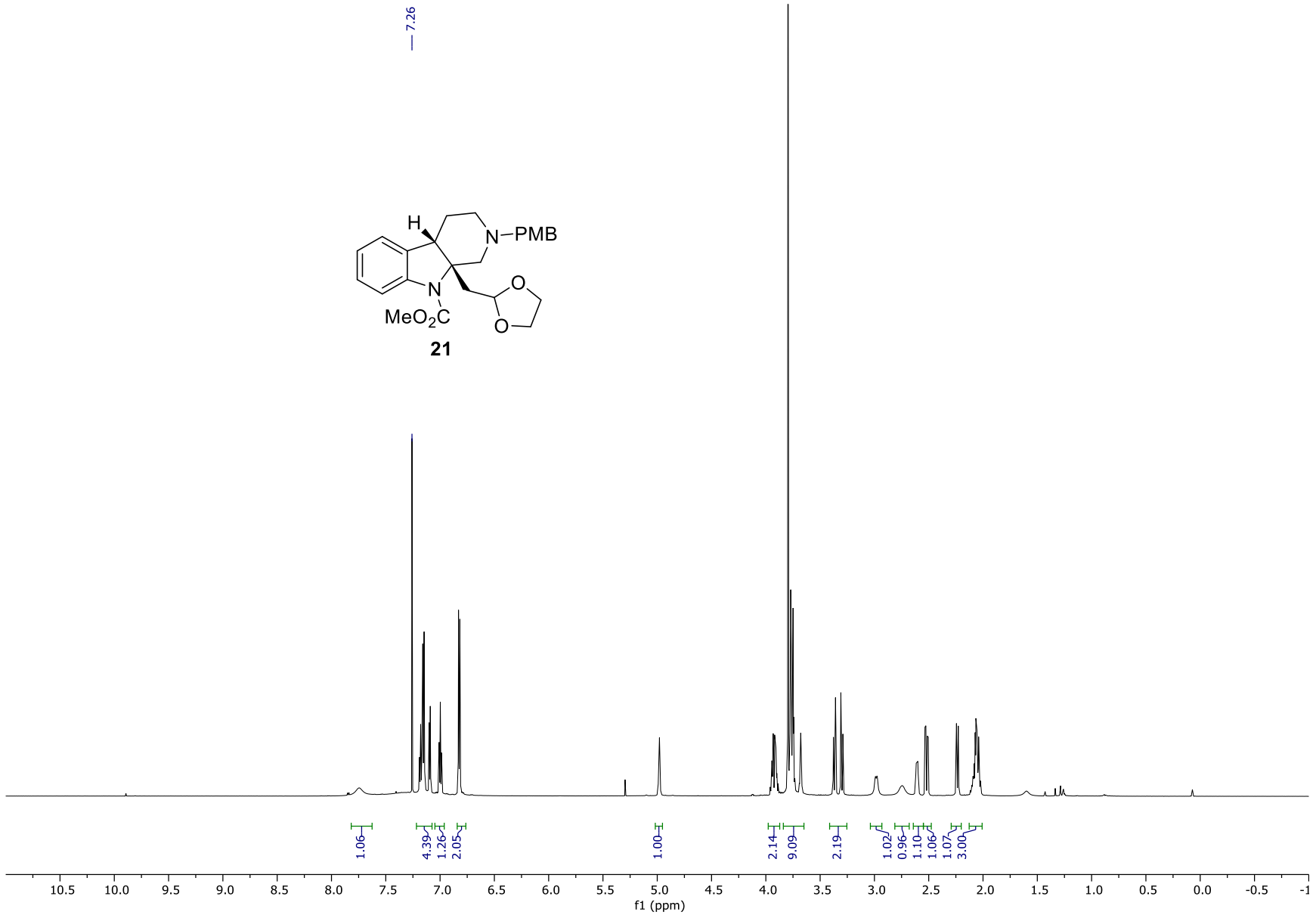
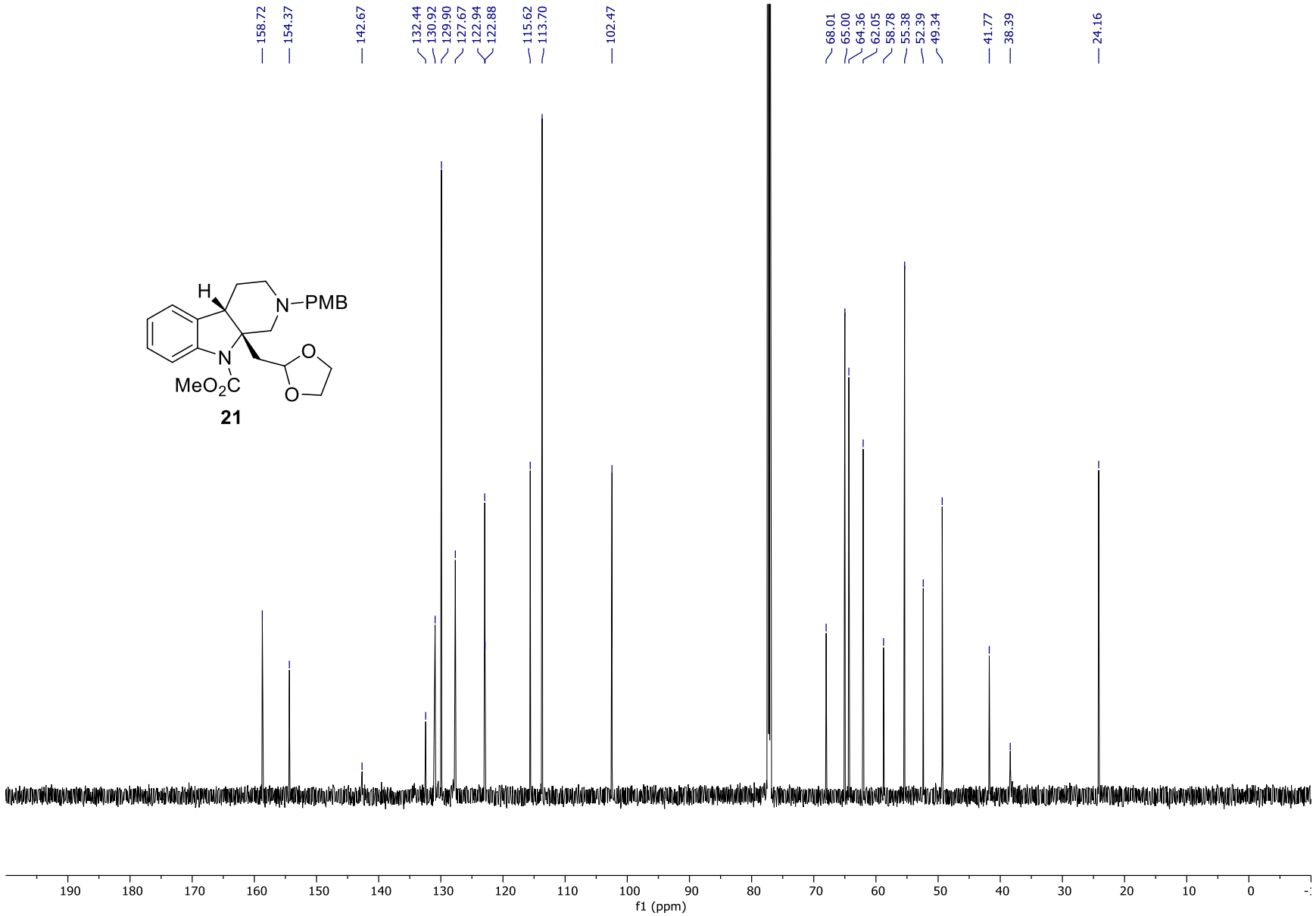
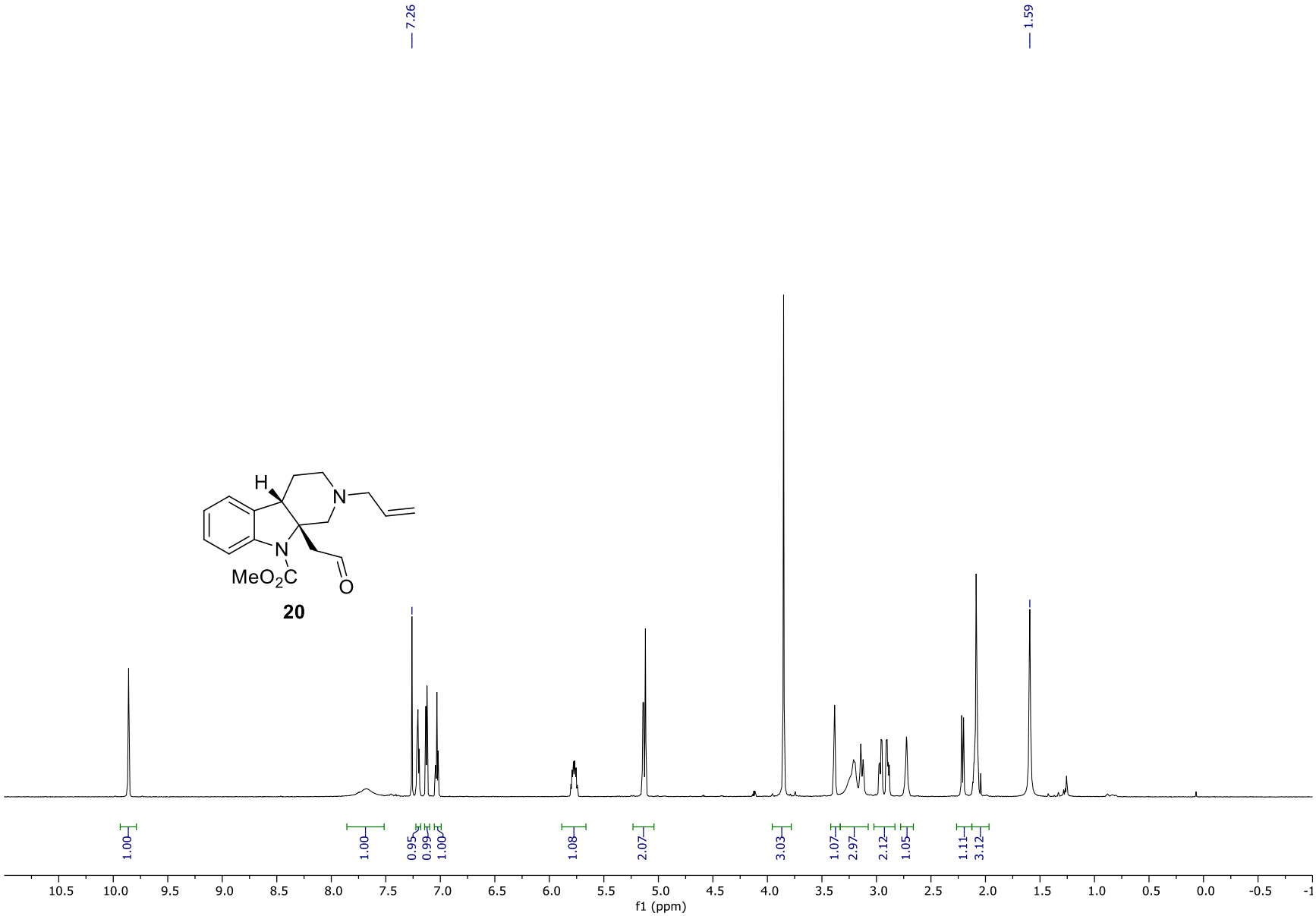
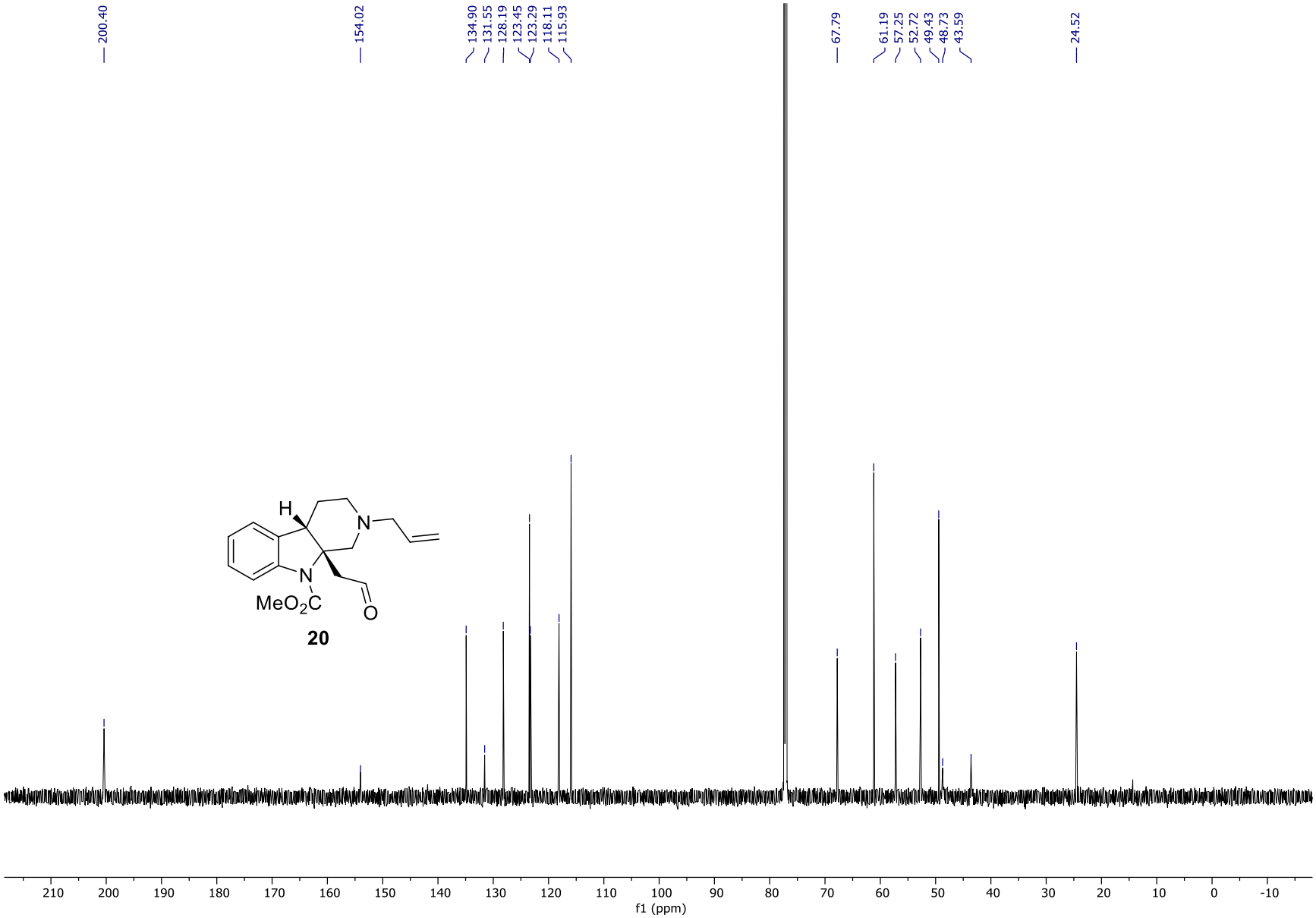
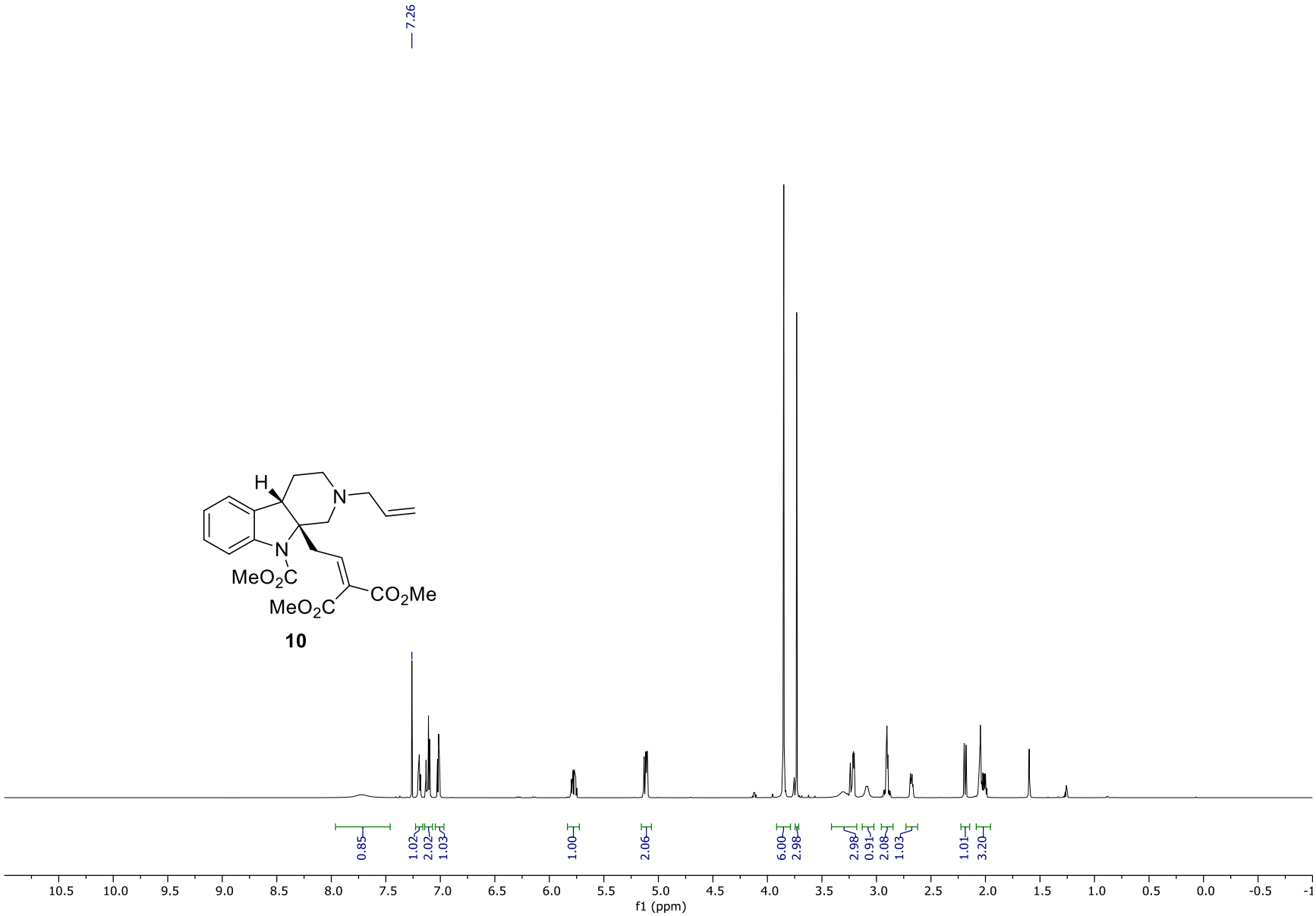
142.19
131.03
129.93
129.27
128.31
124.29
123.49
115.37
113.96
101.61
68.18
64.84
64.60
55.41
52.40
51.50
48.99
44.39
39.18
37.04
O
H
N–PMB
N
MeO2C
O
O
f1 (ppm)

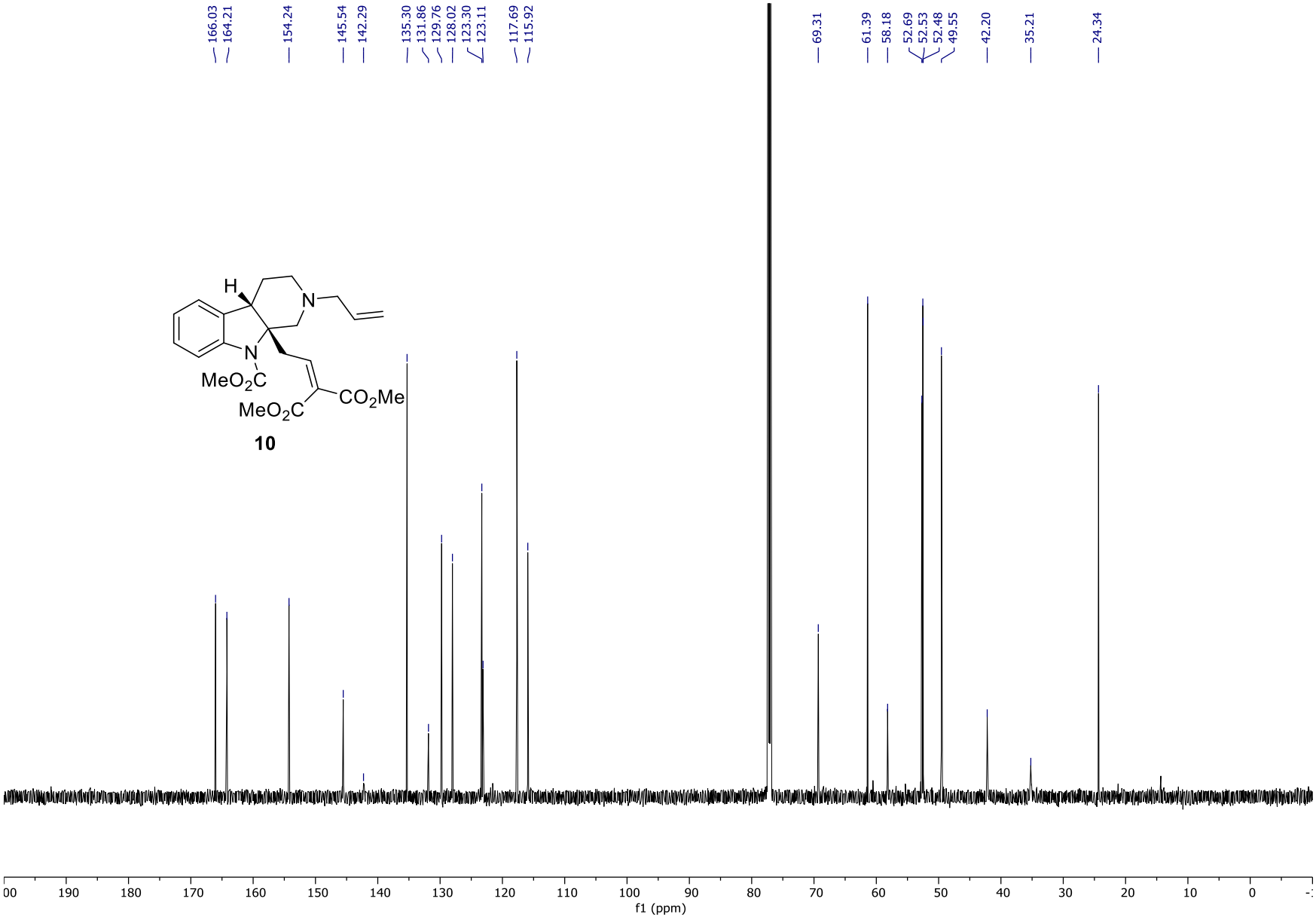

7.26
H
N–PMB
N
MeO2C
O
O
21
1.06
4.39
1.26
2.05
1.00
2.14
9.09
2.19
1.02
0.96
1.10
1.06
1.07
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

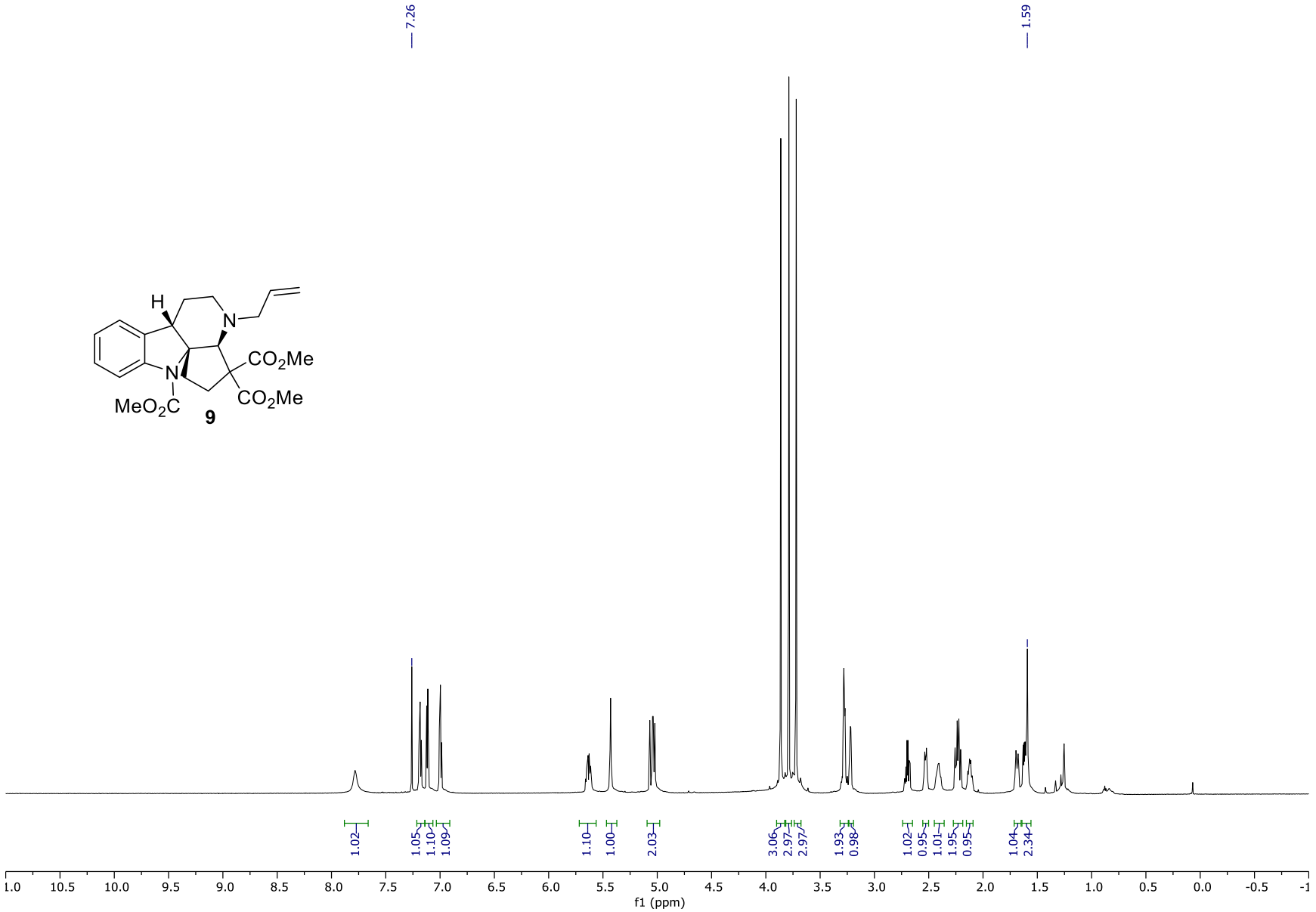

158.72
154.37
142.67
132.44
130.92
129.90
127.67
122.94
122.88
115.62
113.70
102.47
68.01
65.00
64.36
62.05
58.78
55.38
52.39
49.34
41.77
38.39
24.16
H
N–PMB
N
MeO2C
O
O
21
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

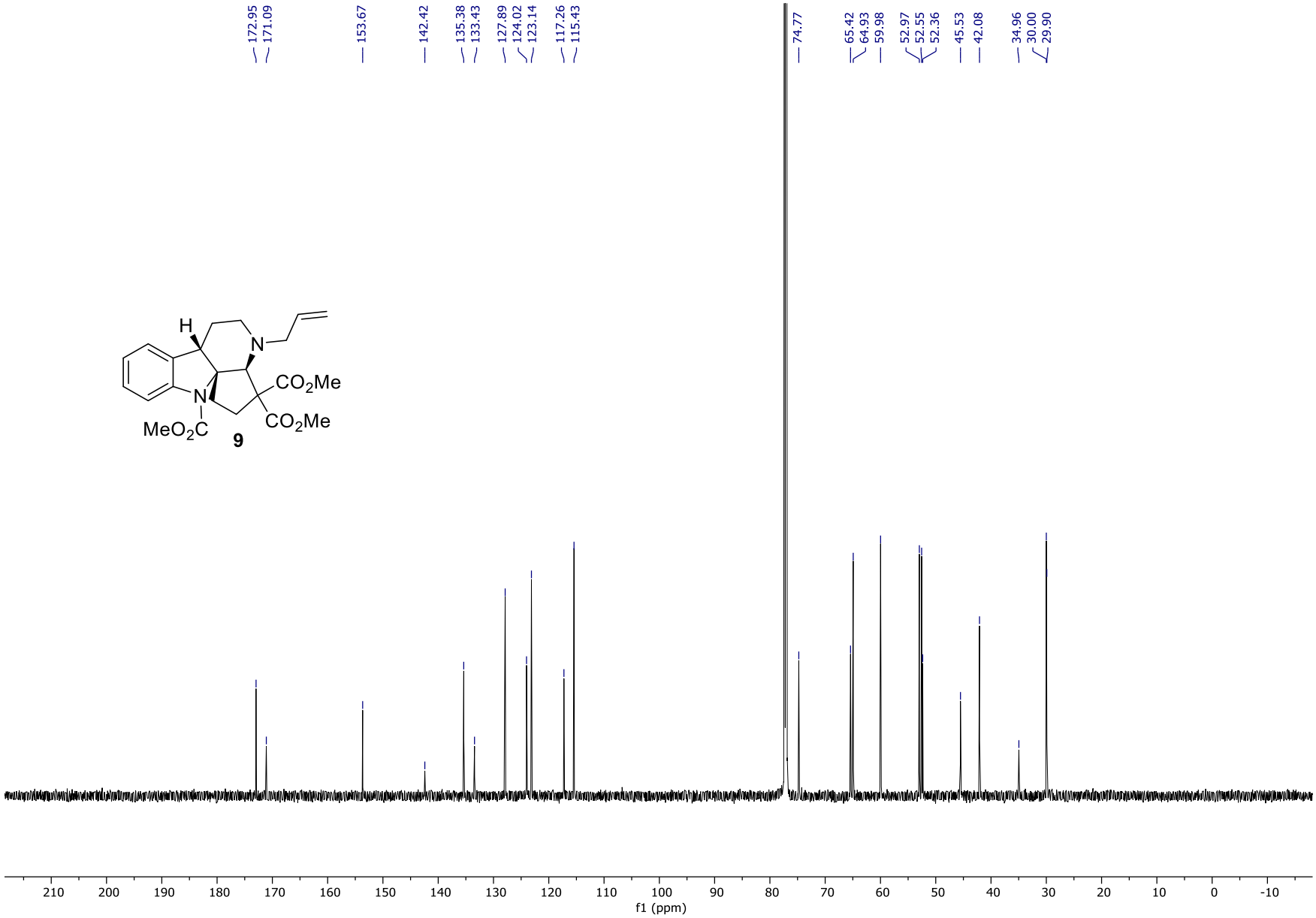

7.26
1.59
H
N
N
MeO2C
O
20
1.00
1.00
0.95
0.99
1.00
1.08
2.07
3.03
1.07
2.97
2.12
1.05
1.11
3.12
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

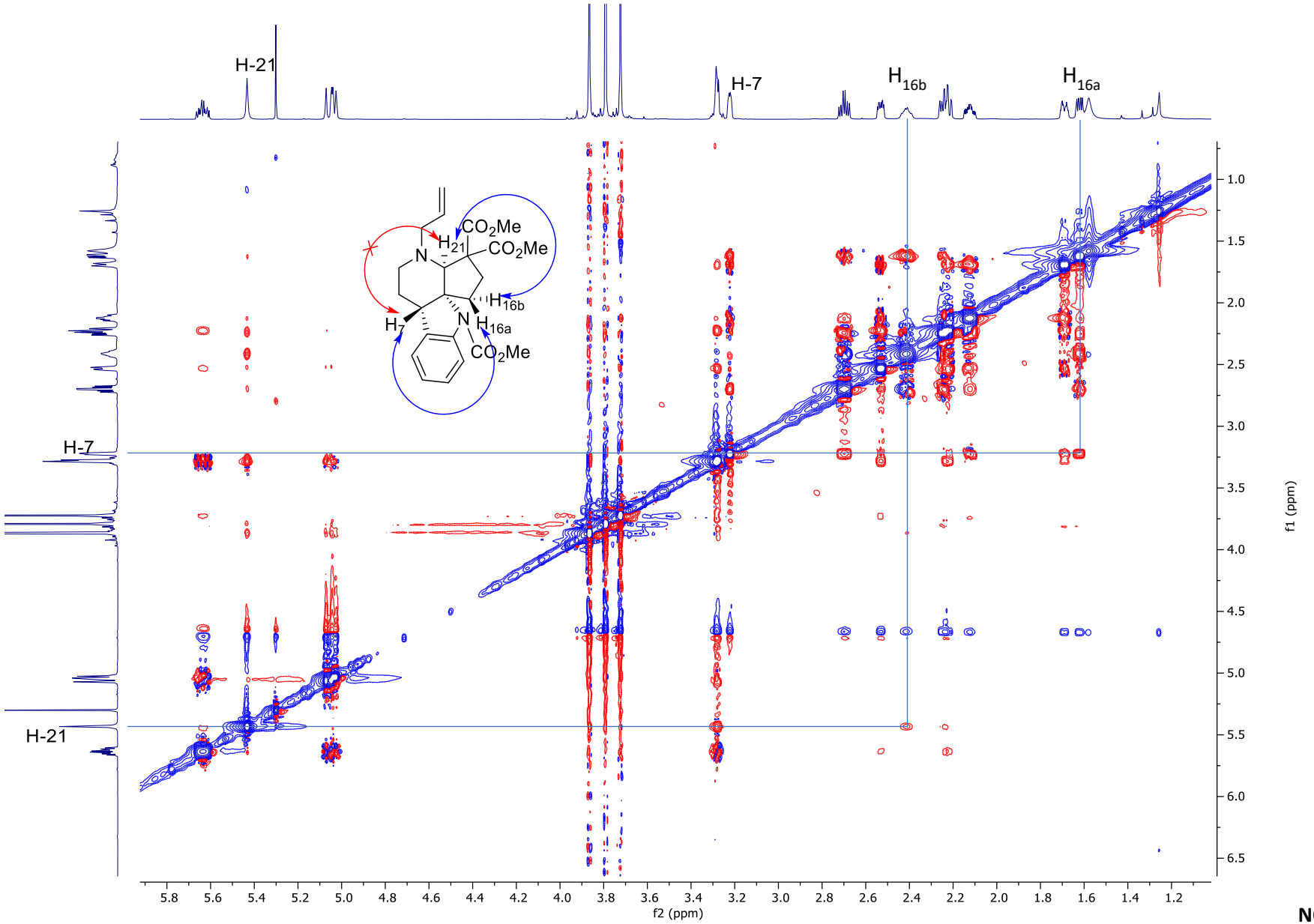

200.40
154.02
134.90
131.55
128.19
123.45
123.29
118.11
115.93
67.79
61.19
57.25
52.72
49.43
48.73
43.59
24.52
H
N
N
MeO2C
O
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.26
H
N
N
MeO2C
MeO2C
CO2Me
10
0.85
1.02
2.02
1.03
1.00
2.06
6.00
2.98
2.98
0.91
2.08
1.03
1.01
3.20
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

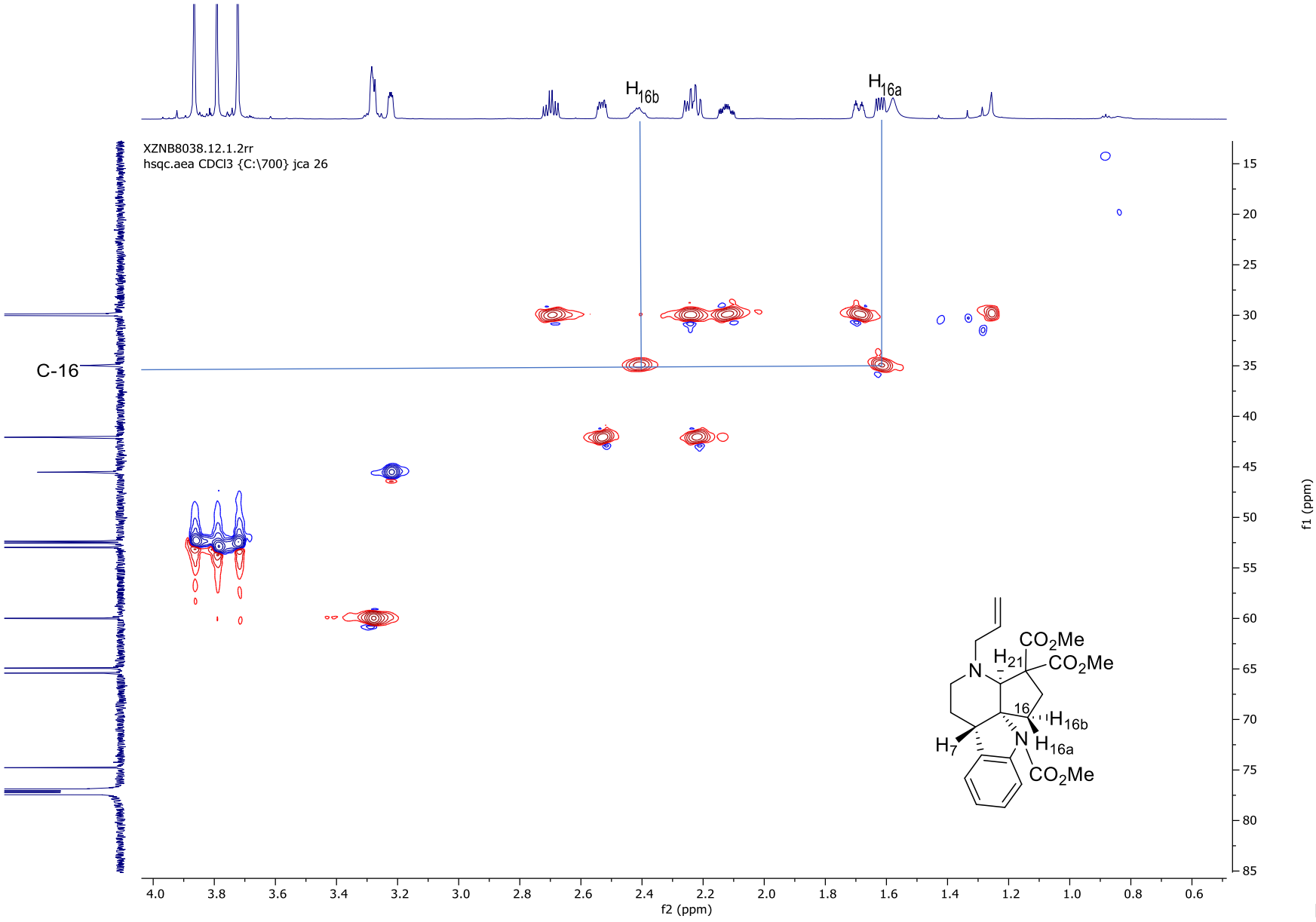

166.03
164.21
154.24
145.54
142.29
135.30
131.86
129.76
128.02
123.30
123.11
117.69
115.92
69.31
61.39
58.18
52.69
52.53
52.48
49.55
42.20
35.21
24.34
H
N
N
MeO2C
CO2Me
MeO2C
10
f1 (ppm)


7.26
1.59
H
N
N
CO2Me
CO2Me
MeO2C
9
1.02
1.05
1.10
1.09
1.10
1.00
2.03
3.06
2.97
2.97
1.93
0.98
1.02
0.95
1.01
1.95
0.95
1.04
2.34
f1 (ppm)

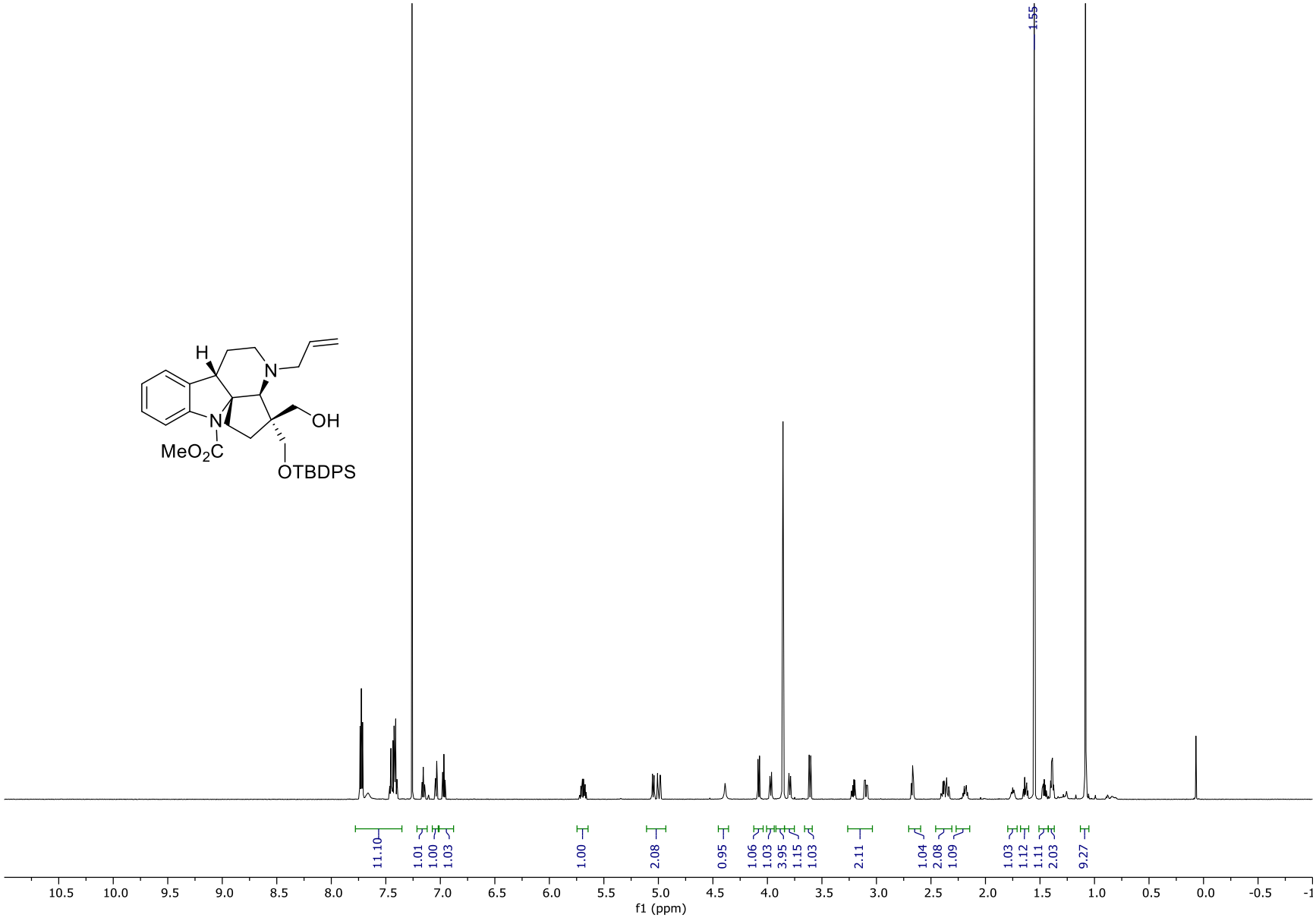

172.95
171.09
153.67
142.42
135.38
133.43
127.89
124.02
123.14
117.26
115.43
74.77
65.42
64.93
59.98
52.97
52.55
52.36
45.53
42.08
34.96
30.00
29.90
H
N
N
CO2Me
CO2Me
MeO2C
9
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

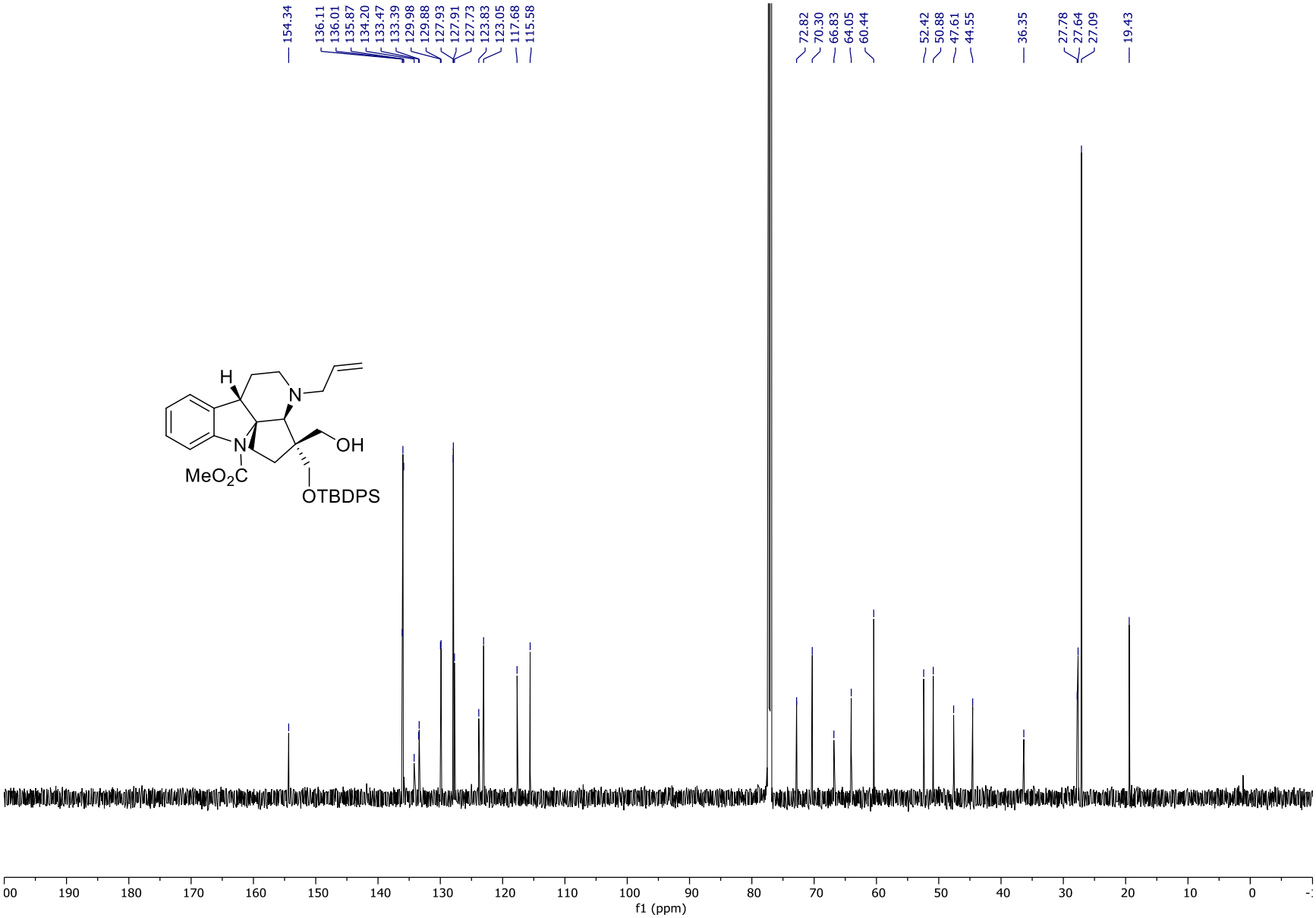

H-21
H-7
H16b
H16a
H-7
H-21
CO2Me
CO2Me
H21
N
H16b
H7
N
H16a
CO2Me
f2 (ppm)
f1 (ppm)

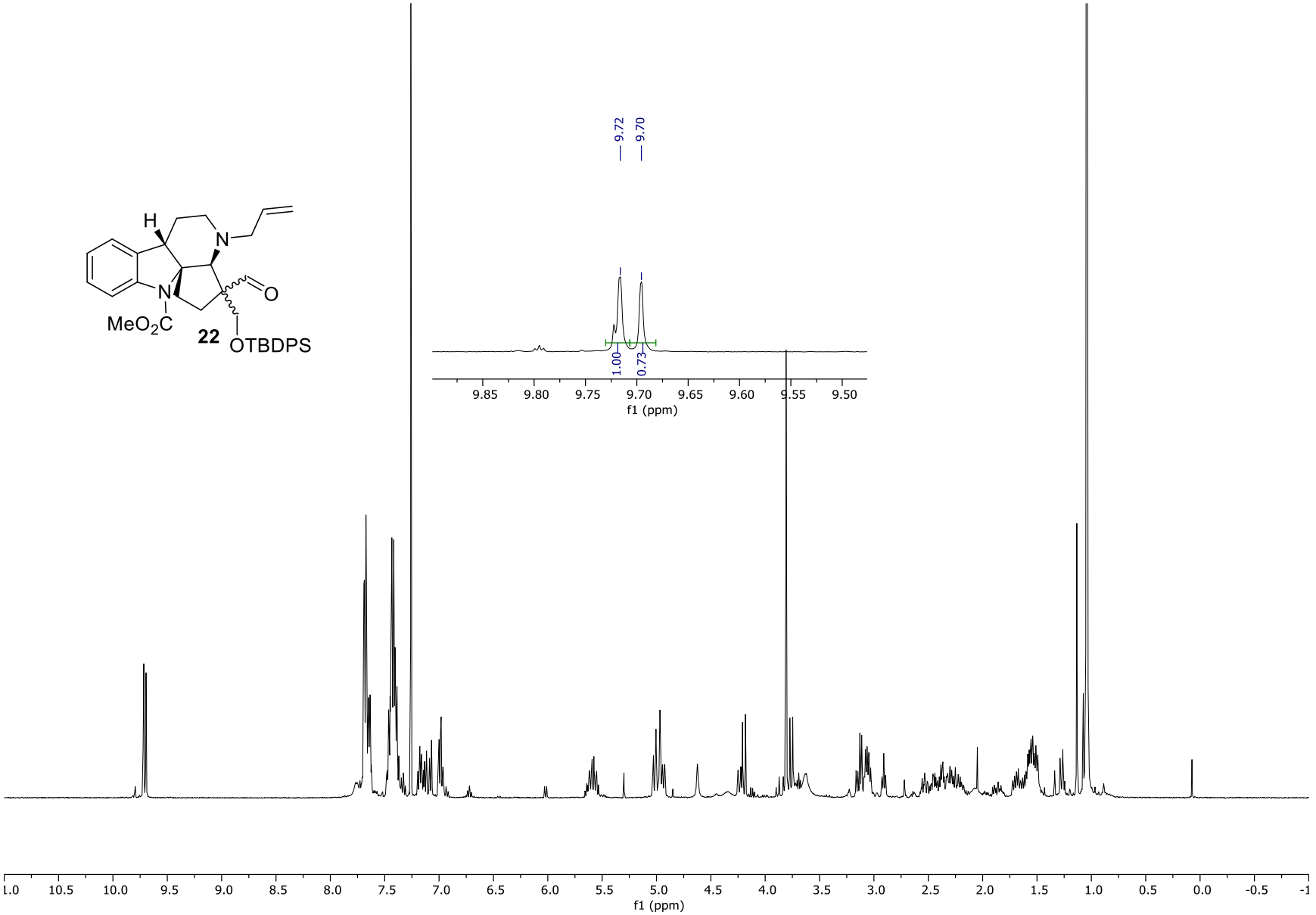
NOESY

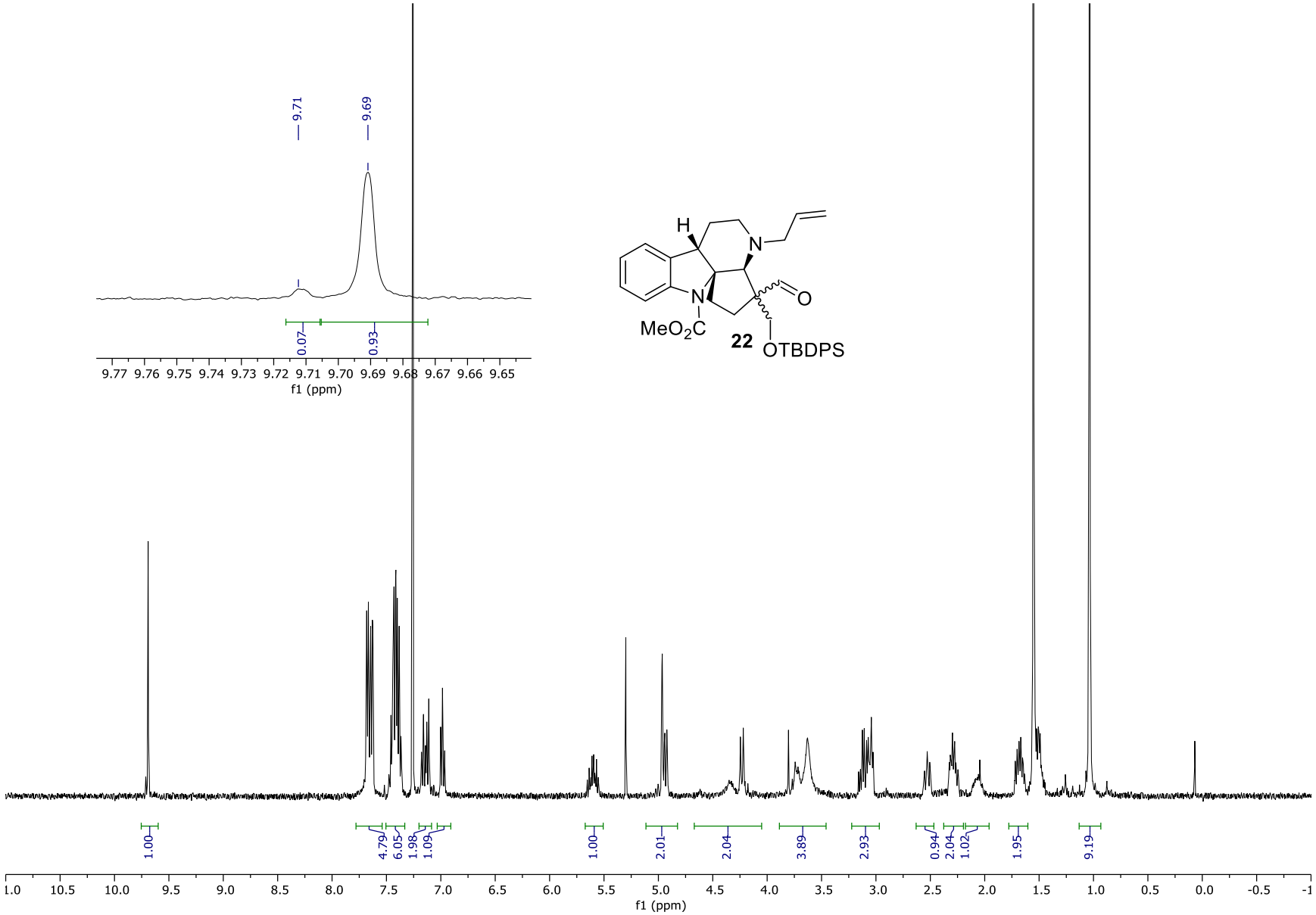

H16b
H16a
XZNB8038.12.1.2rr
hsqc.aea CDCl3 {C:\700} jca 26
C-16
f2 (ppm)
f1 (ppm)
CO2Me
H21
CO2Me
N
16
H16b
H7
N
H16a
CO2Me

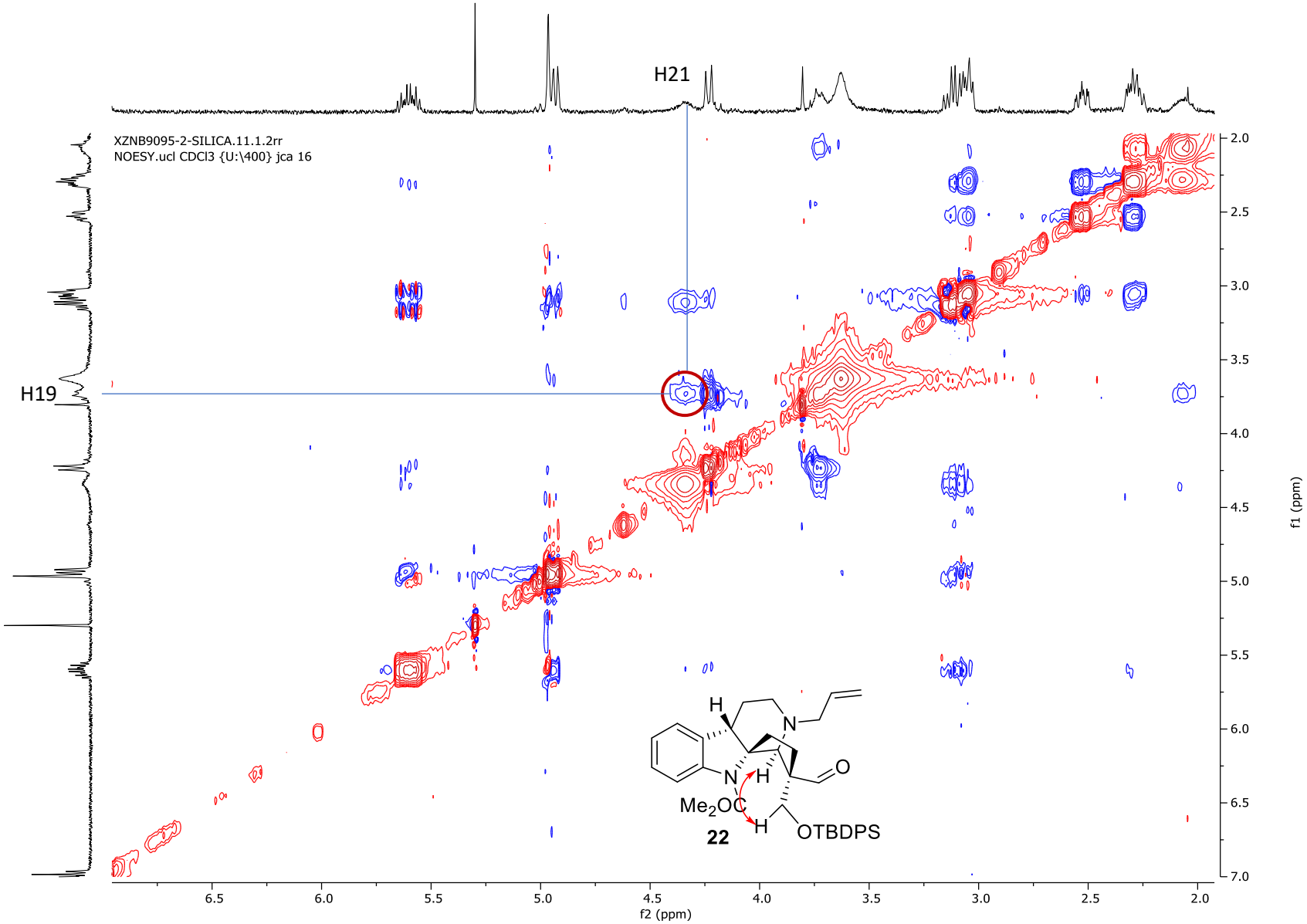
HSQC

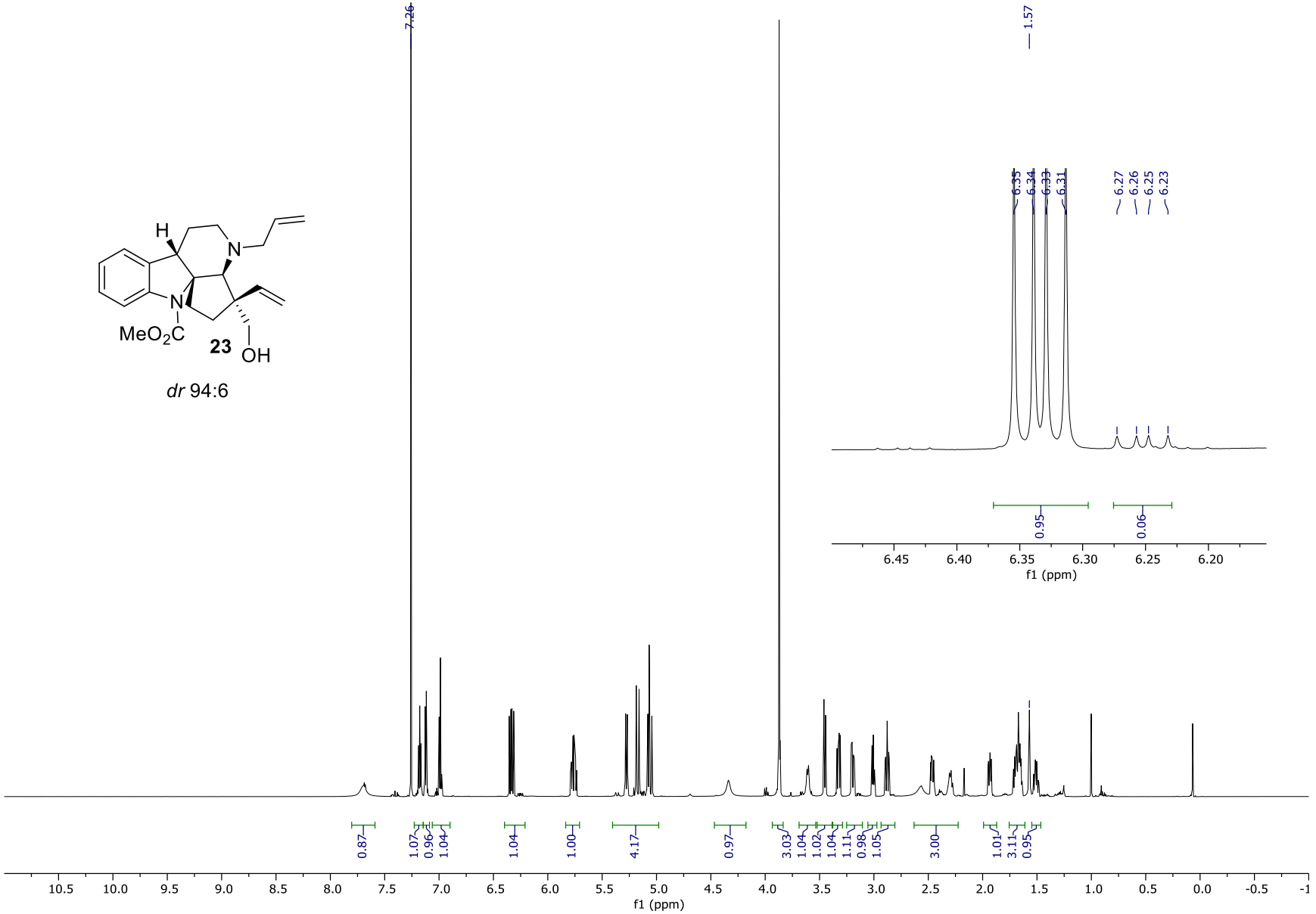

H
N
N
OH
MeO2C
OTBDPS
1.55
11.10
1.01
1.00
1.03
1.00
2.08
0.95
1.06
1.03
3.95
1.15
1.03
2.11
1.04
2.08
1.09
1.03
1.12
1.11
2.03
9.27
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

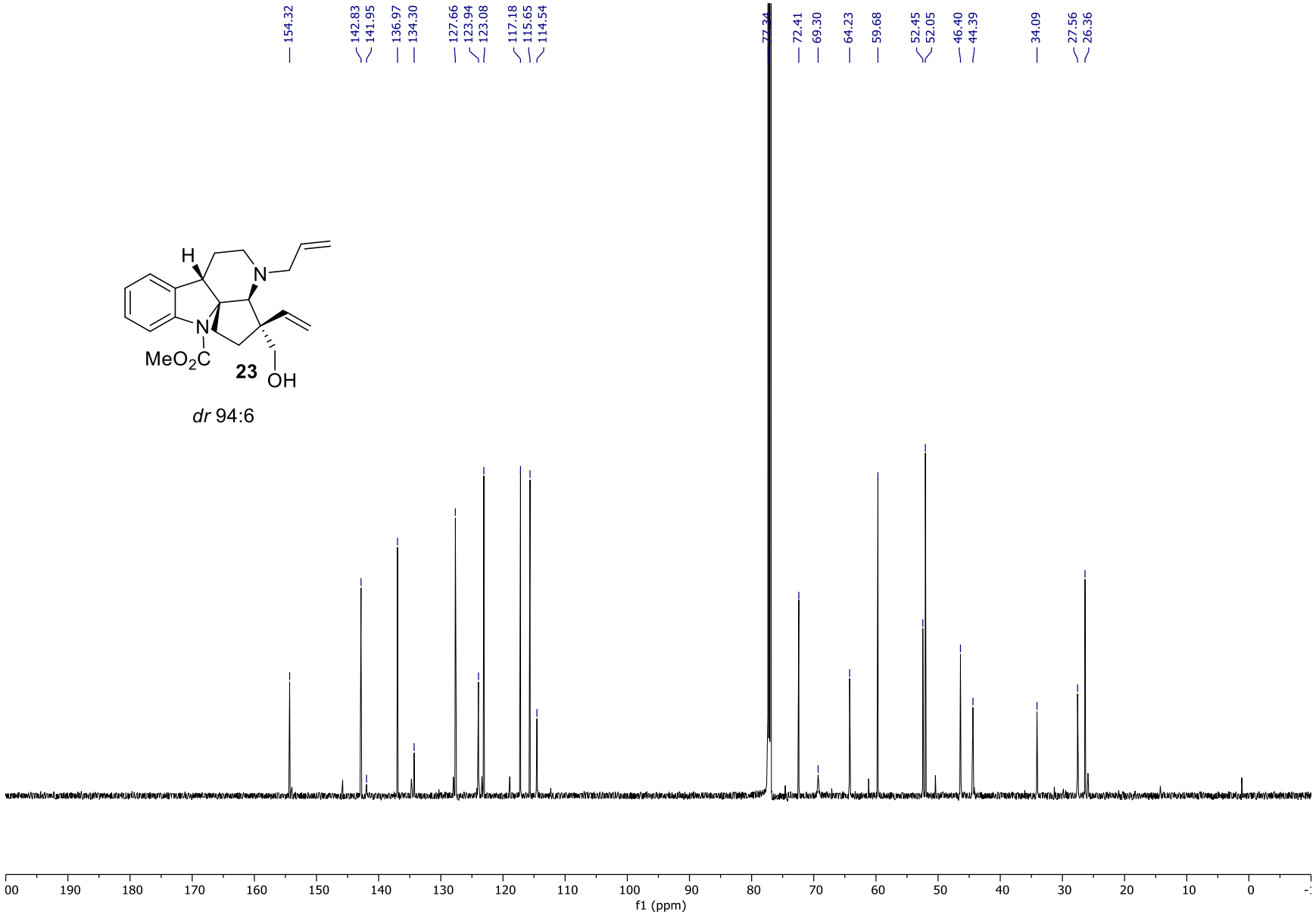

154.34
136.11
136.01
135.87
134.20
133.47
133.39
129.98
129.88
127.93
127.91
127.73
123.83
123.05
117.68
115.58
72.82
70.30
66.83
64.05
60.44
52.42
50.88
47.61
44.55
36.35
27.78
27.64
27.09
19.43
H
N
N
OH
MeO2C
OTBDPS
f1 (ppm)

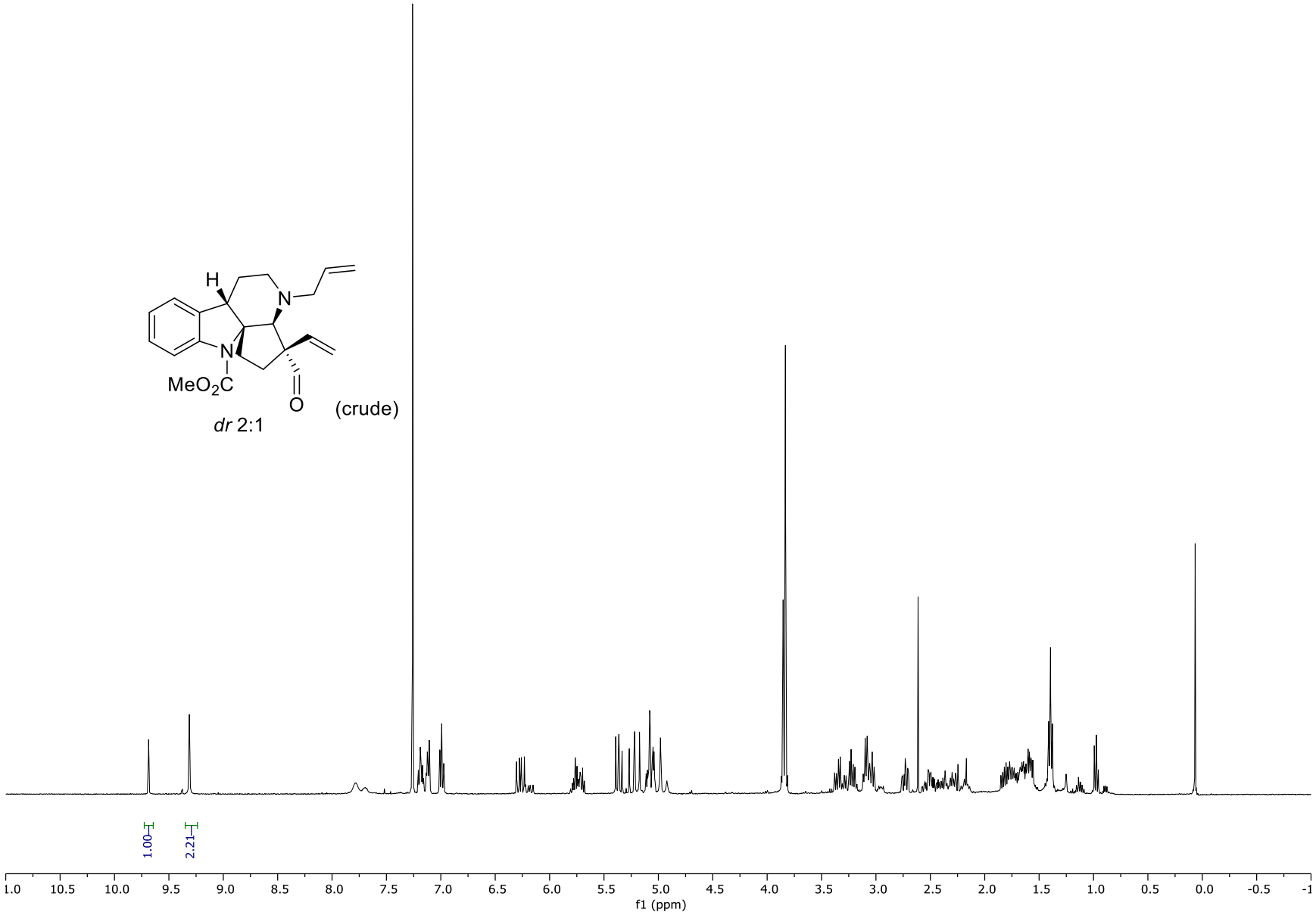

H
N
N
O
MeO2C
22
OTBDPS
9.72
9.70
1.00
0.73
9.85 9.80 9.75 9.70 9.65 9.60 9.55 9.50
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

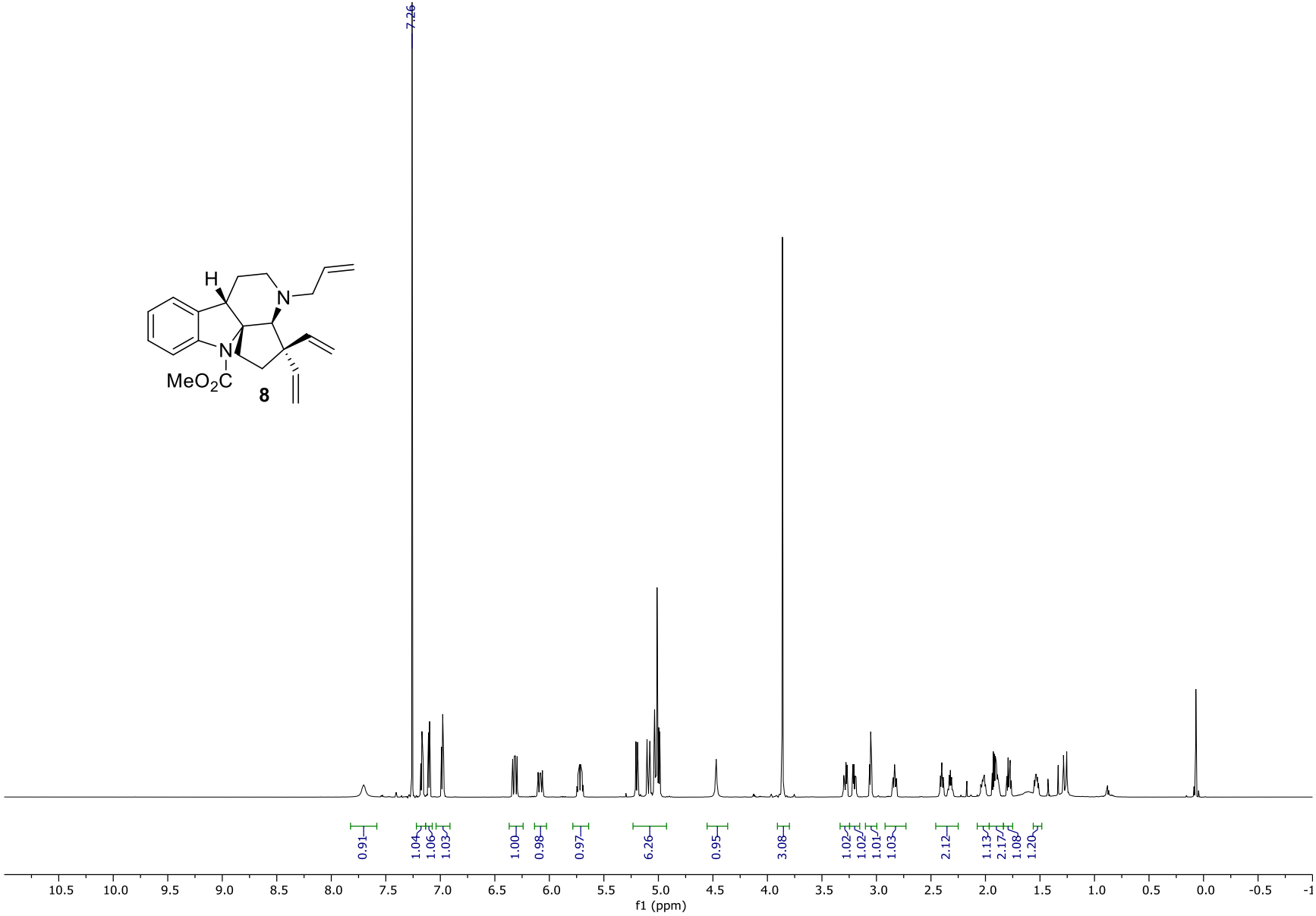

9.71
9.69
0.07
0.93
9.77 9.76 9.75 9.74 9.73 9.72 9.71 9.70 9.69 9.68 9.67 9.66 9.65
f1 (ppm)
H
N
N
O
MeO2C
22
OTBDPS
1.00
4.79
6.05
1.98
1.09
1.00
2.01
2.04
3.89
2.93
0.94
2.04
1.02
1.95
9.19
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

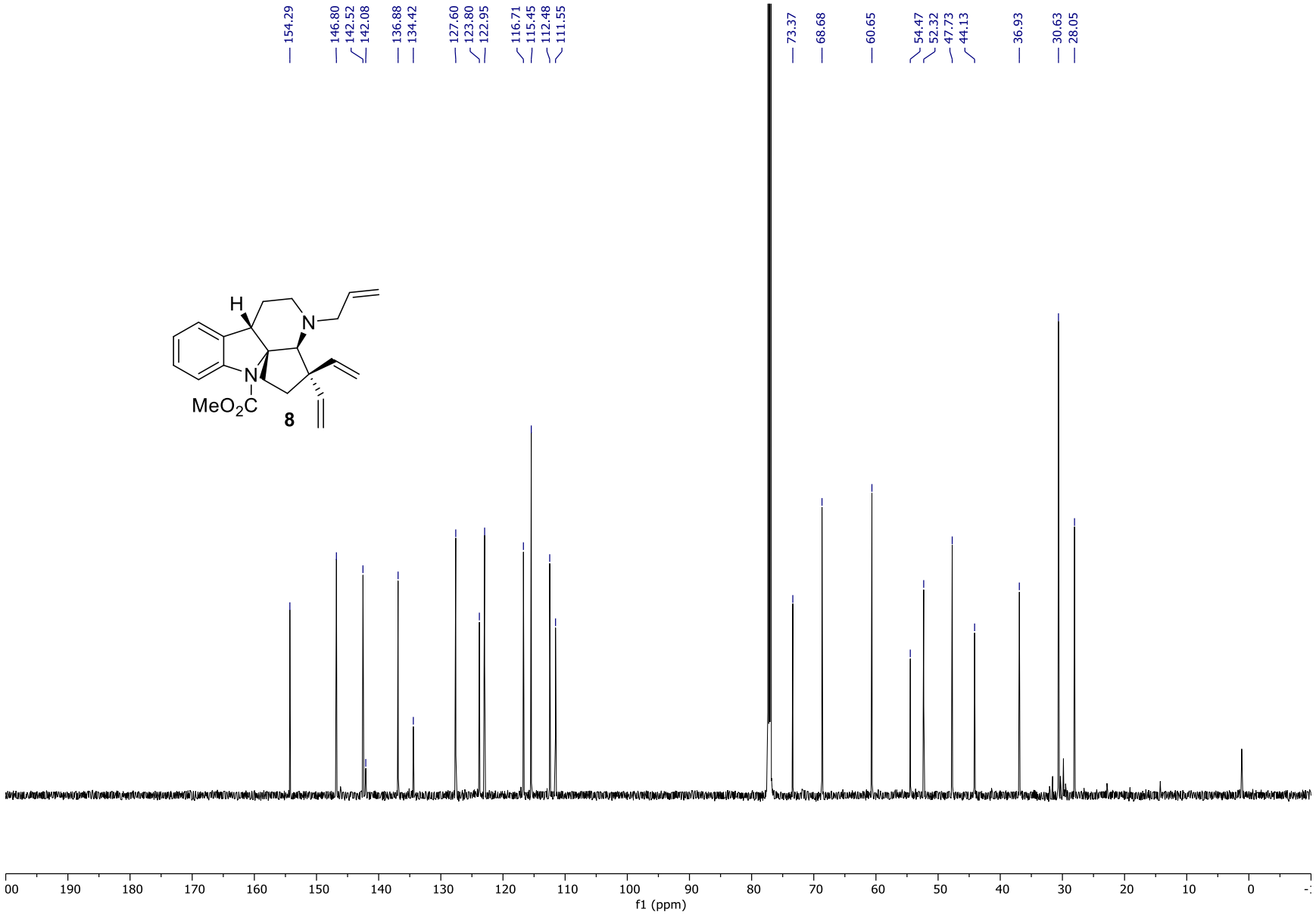

H21
H19
XZNB9095-2-SILICA.11.1.2rr
NOESY.ucl CDCl3 {U:\400} jca 16
H
N
O
N
H
Me2OC
H
OTBDPS
22
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
f1 (ppm)

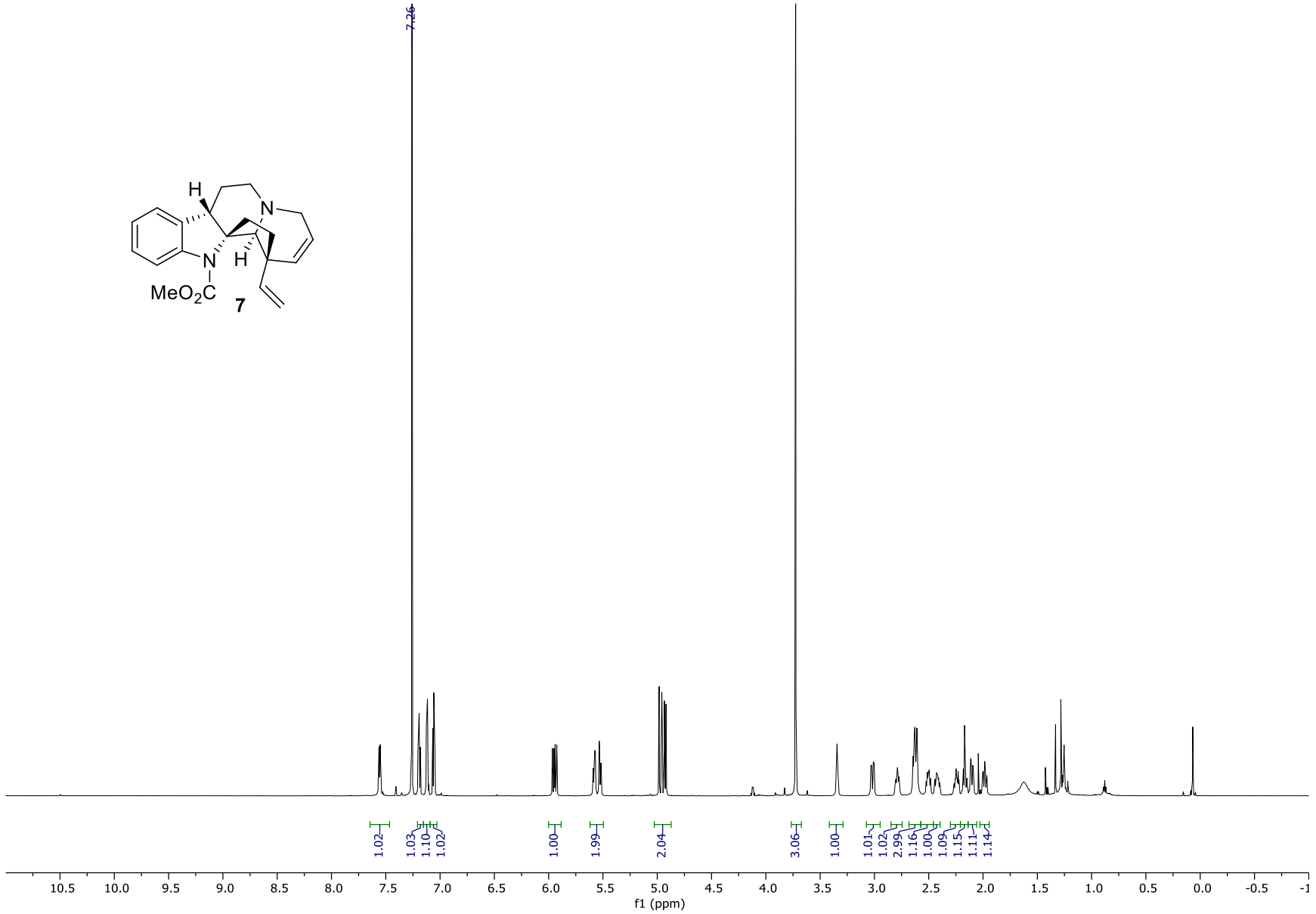

H
N
N
MeO2C
23
OH
dr 94:6
7.26
1.57
6.35
6.34
6.33
6.31
6.27
6.26
6.25
6.23
0.95
0.06
6.45
6.40
6.35
6.30
6.25
6.20
f1 (ppm)
0.87
1.07
0.96
1.04
1.04
1.00
4.17
0.97
3.03
1.04
1.02
1.04
1.11
0.98
1.05
3.00
1.01
3.11
0.95
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

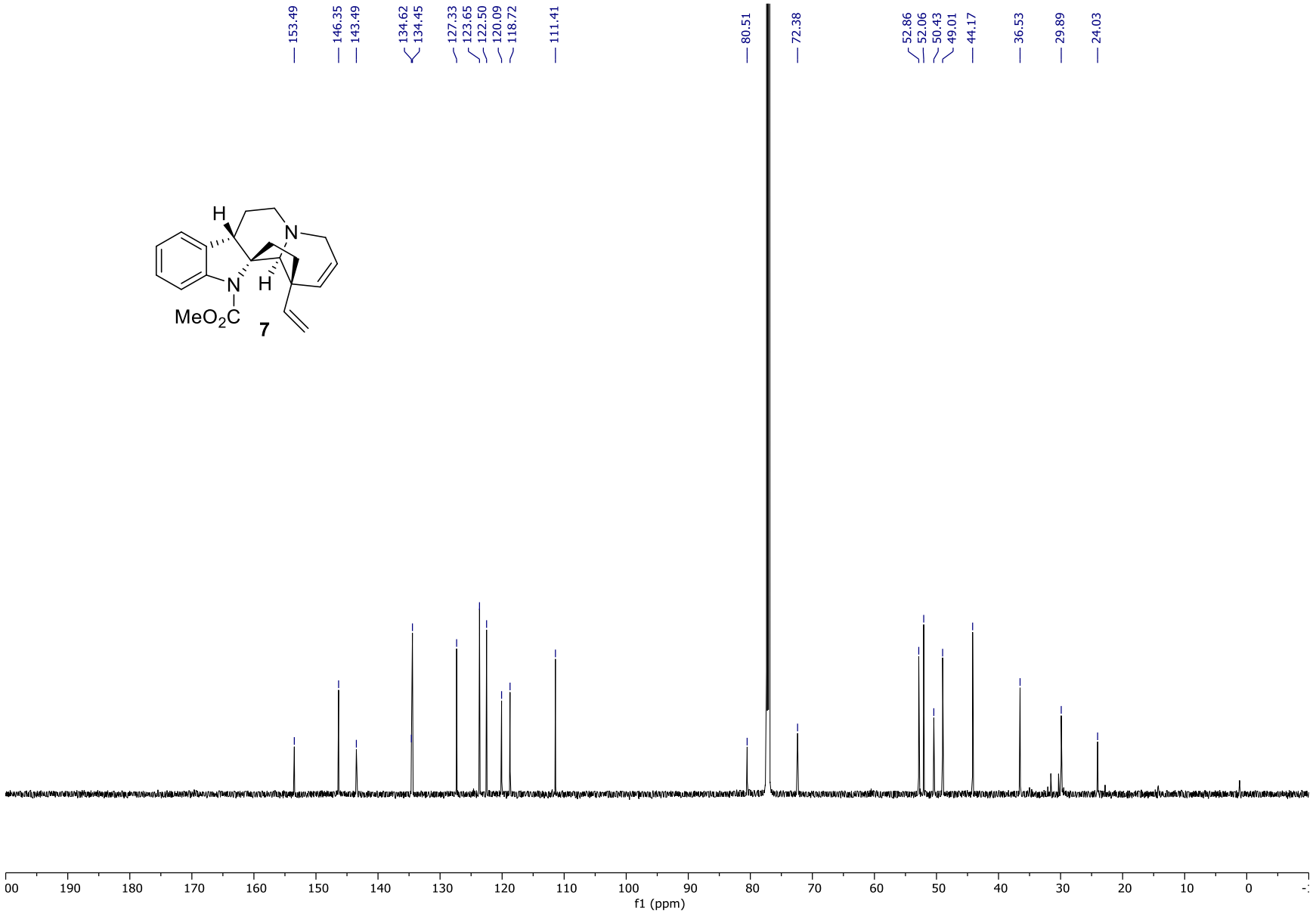

154.32
142.83
141.95
136.97
134.30
127.66
123.94
123.08
117.18
115.65
114.54
77.34
72.41
69.30
64.23
59.68
52.45
52.05
46.40
44.39
34.09
27.56
26.36
H
N
N
MeO2C
23
OH
dr 94:6
f1 (ppm)

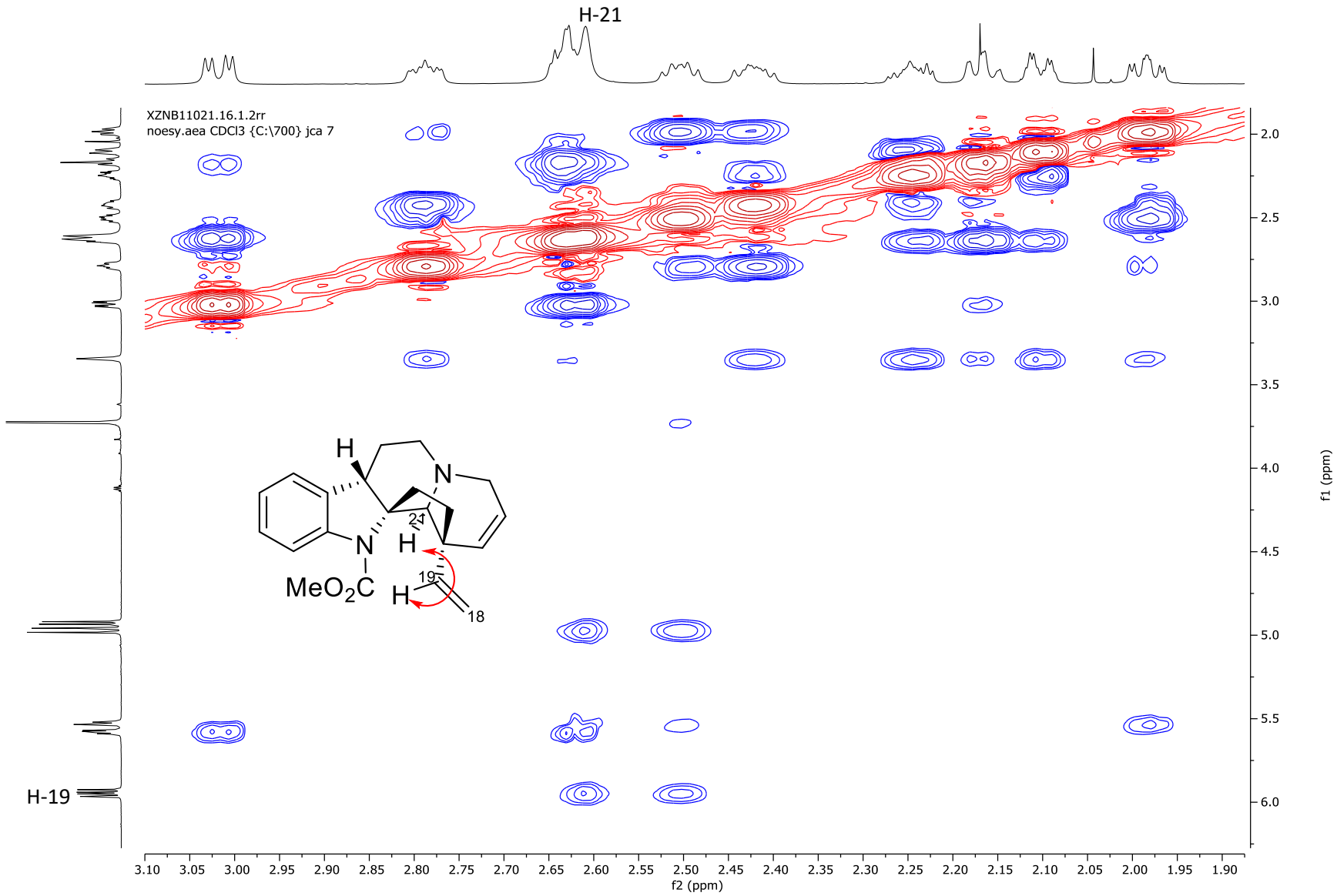

H
N
N
MeO2C
O
dr 2:1
(crude)
1.00
2.21
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

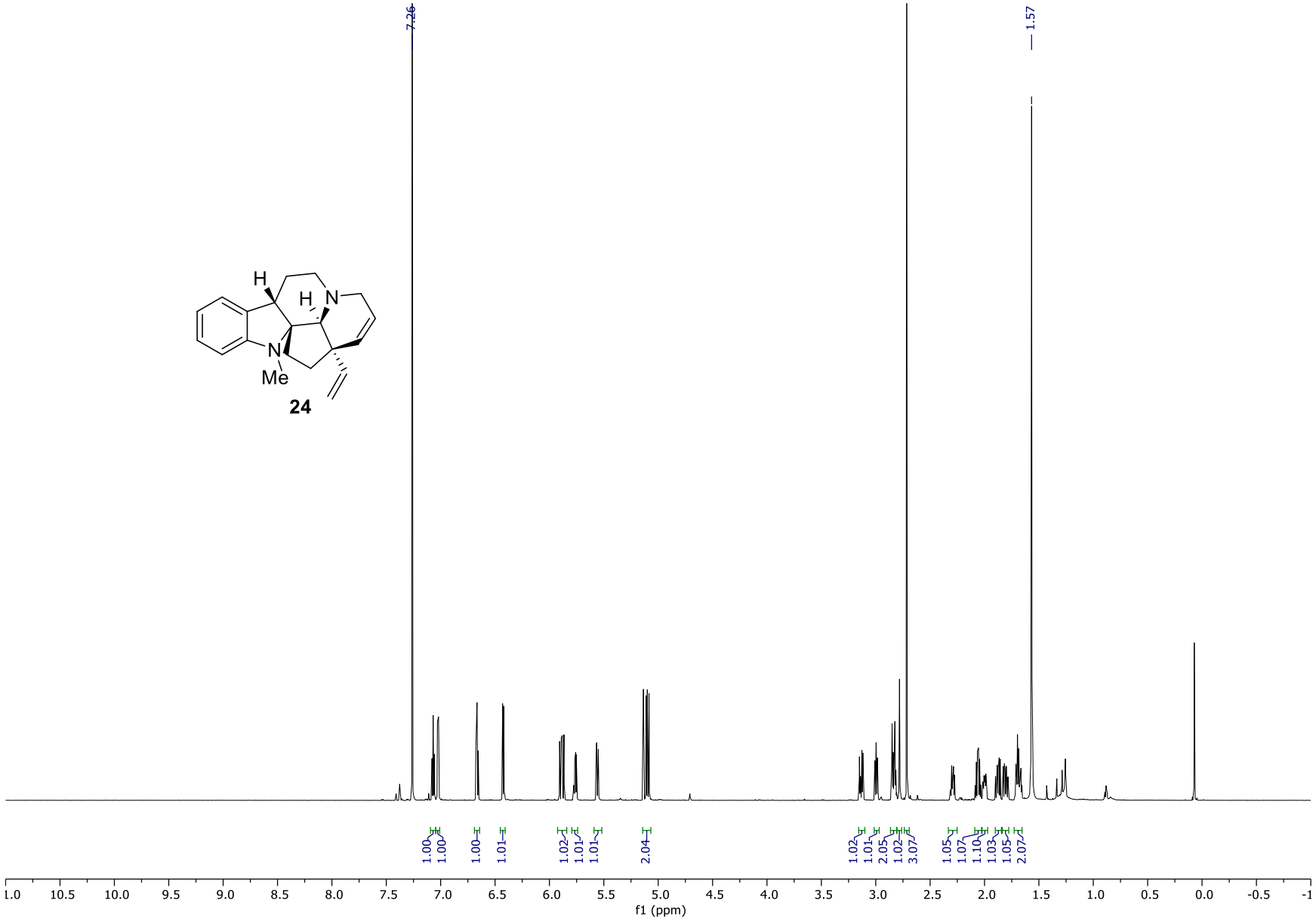

7.26
H
N
N
MeO2C
8
0.91
1.04
1.06
1.03
1.00
0.98
0.97
6.26
0.95
3.08
1.02
1.02
1.01
1.03
2.12
1.13
2.17
1.08
1.20
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

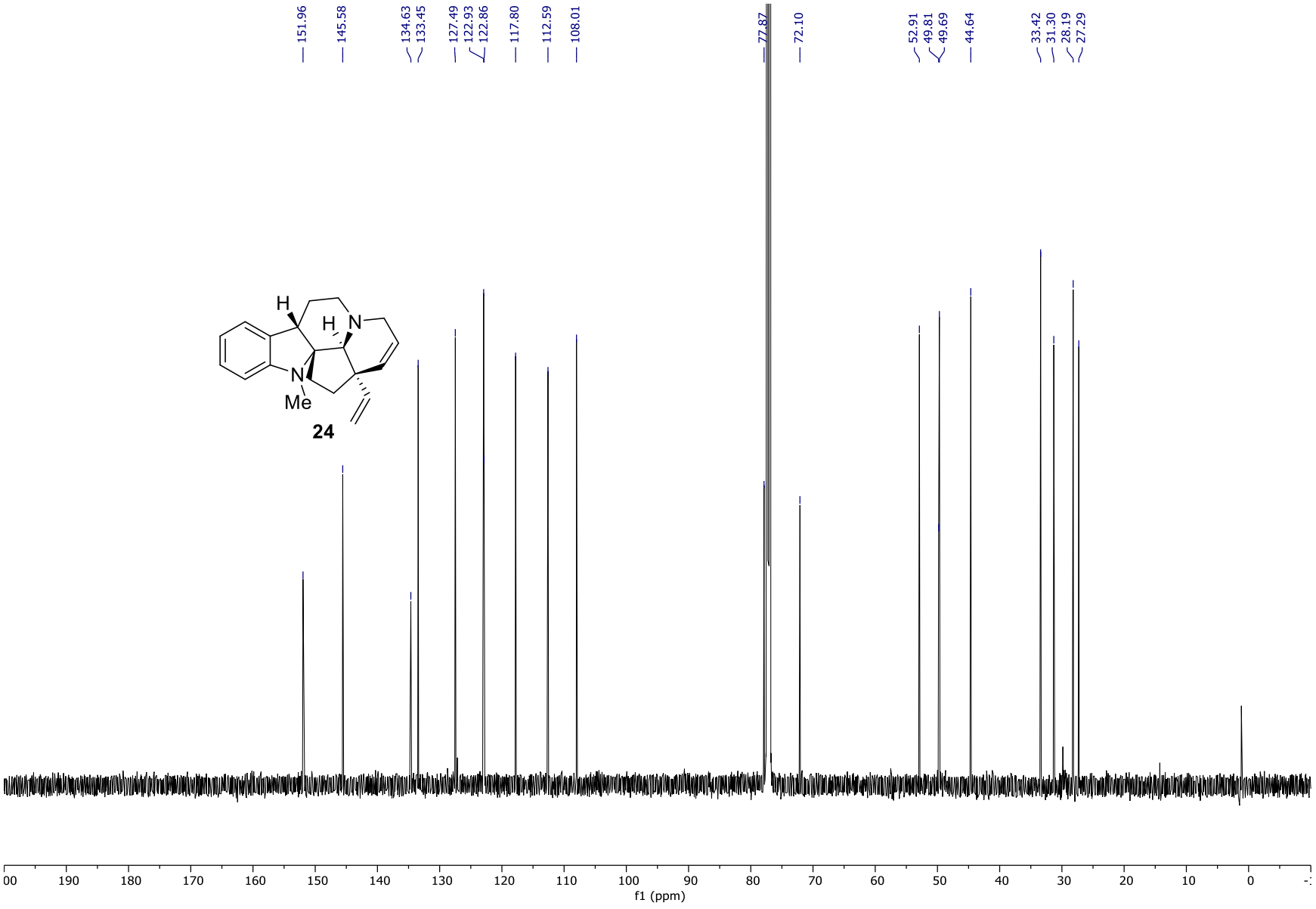

154.29
146.80
142.52
142.08
136.88
134.42
127.60
123.80
122.95
116.71
115.45
112.48
111.55
73.37
68.68
60.65
54.47
52.32
47.73
44.13
36.93
30.63
28.05
H
N
N
MeO2C
8
f1 (ppm)

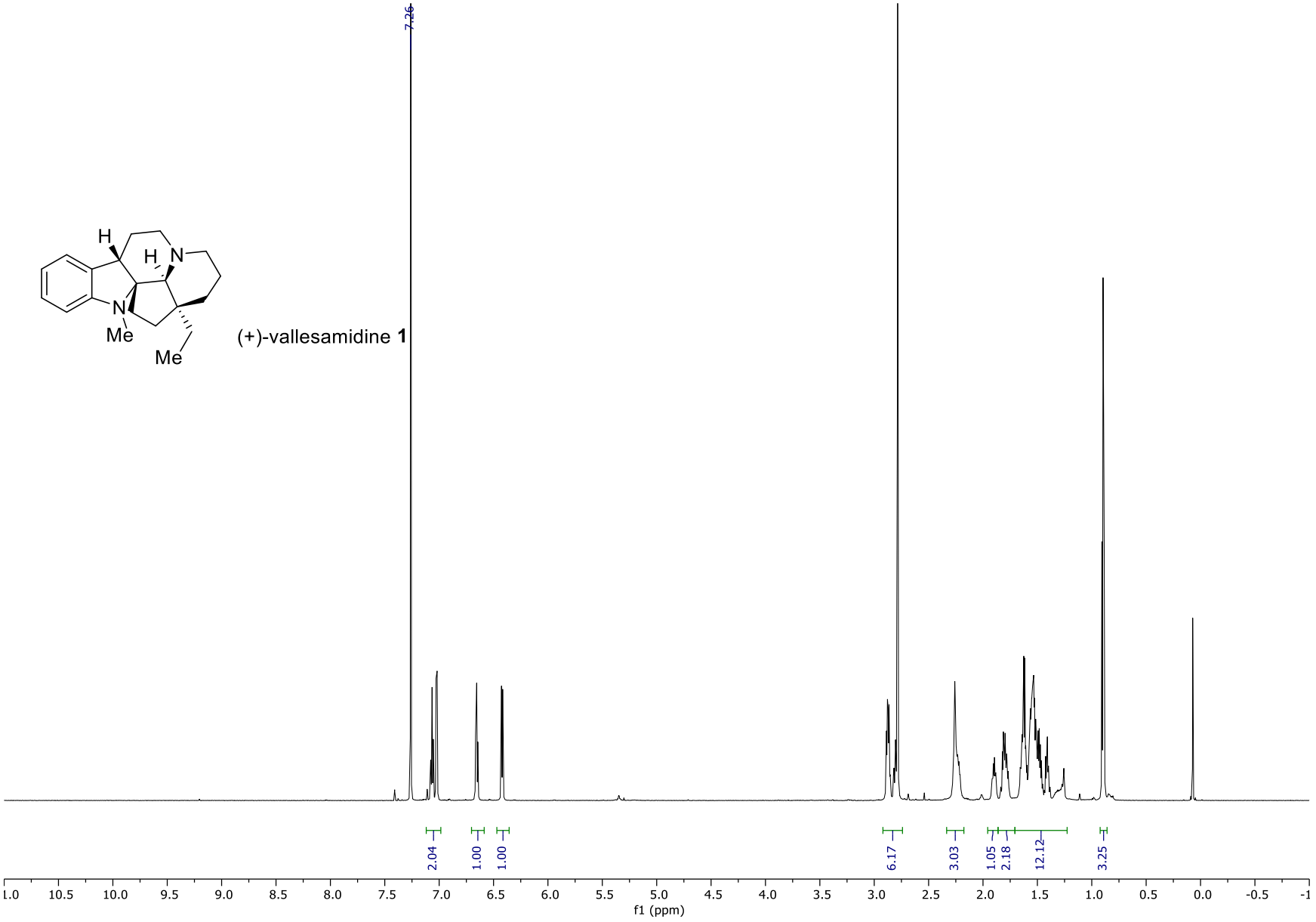

H
N
N
H
MeO2C
7
7.26
1.02
1.03
1.10
1.02
1.00
1.99
2.04
3.06
1.00
1.01
1.02
2.99
1.16
1.00
1.09
1.15
1.11
1.14
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

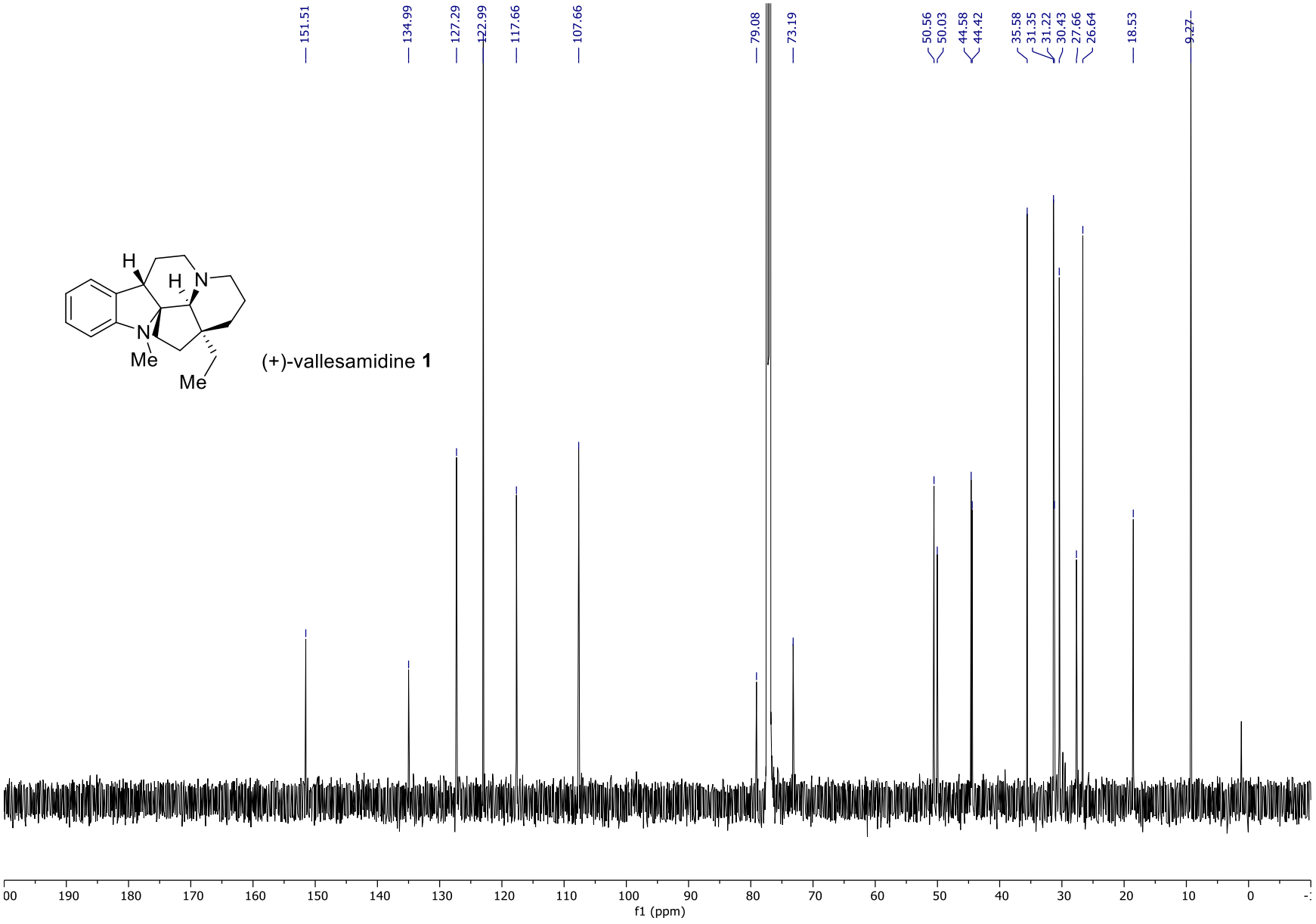

153.49
146.35
143.49
134.62
134.45
127.33
123.65
122.50
120.09
118.72
111.41
80.51
72.38
52.86
52.06
50.43
49.01
44.17
36.53
29.89
24.03
H
N
N
H
MeO2C
7
f1 (ppm)

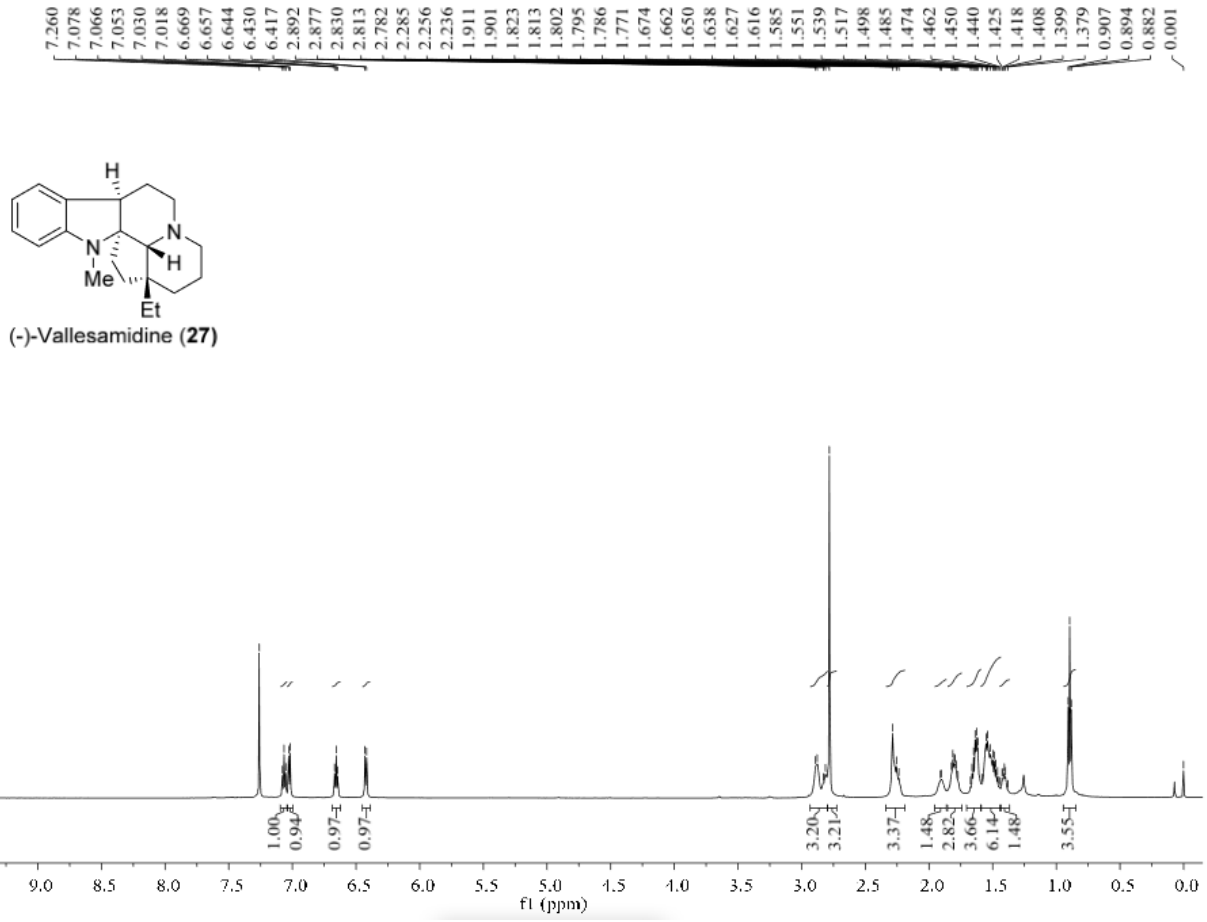

H-21
XZNB11021.16.1.2rr
noesy.aea CDCl3 {C:\700} jca 7
H-19
MeO2C
21
19
18
f2 (ppm)
f1 (ppm)


7.26
1.57
H
H
N
N
Me
24
1.00
1.00
1.00
1.01
1.02
1.01
1.01
2.04
1.02
1.01
2.05
1.02
3.07
1.05
1.07
1.10
1.03
1.05
2.07
f1 (ppm)

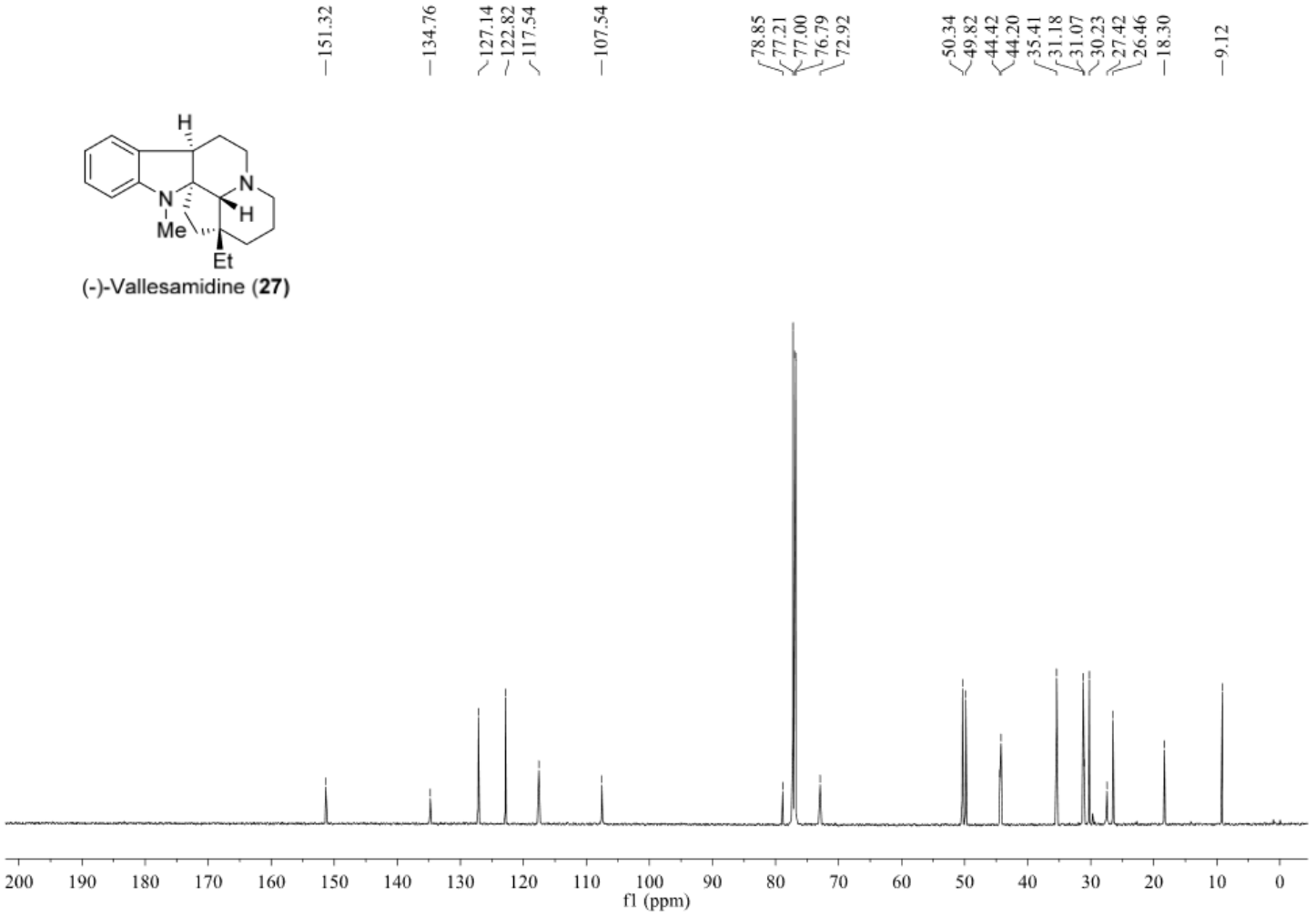

151.96
145.58
134.63
133.45
127.49
122.93
122.86
117.80
112.59
108.01
77.87
72.10
52.91
49.81
49.69
44.64
33.42
31.30
28.19
27.29
H
H
N
N
Me
24
f1 (ppm)


H
H
N
N
Me
Me
(+)-vallesamidine 1
7.26
2.04
1.00
1.00
6.17
3.03
1.05
2.18
12.12
3.25
f1 (ppm)

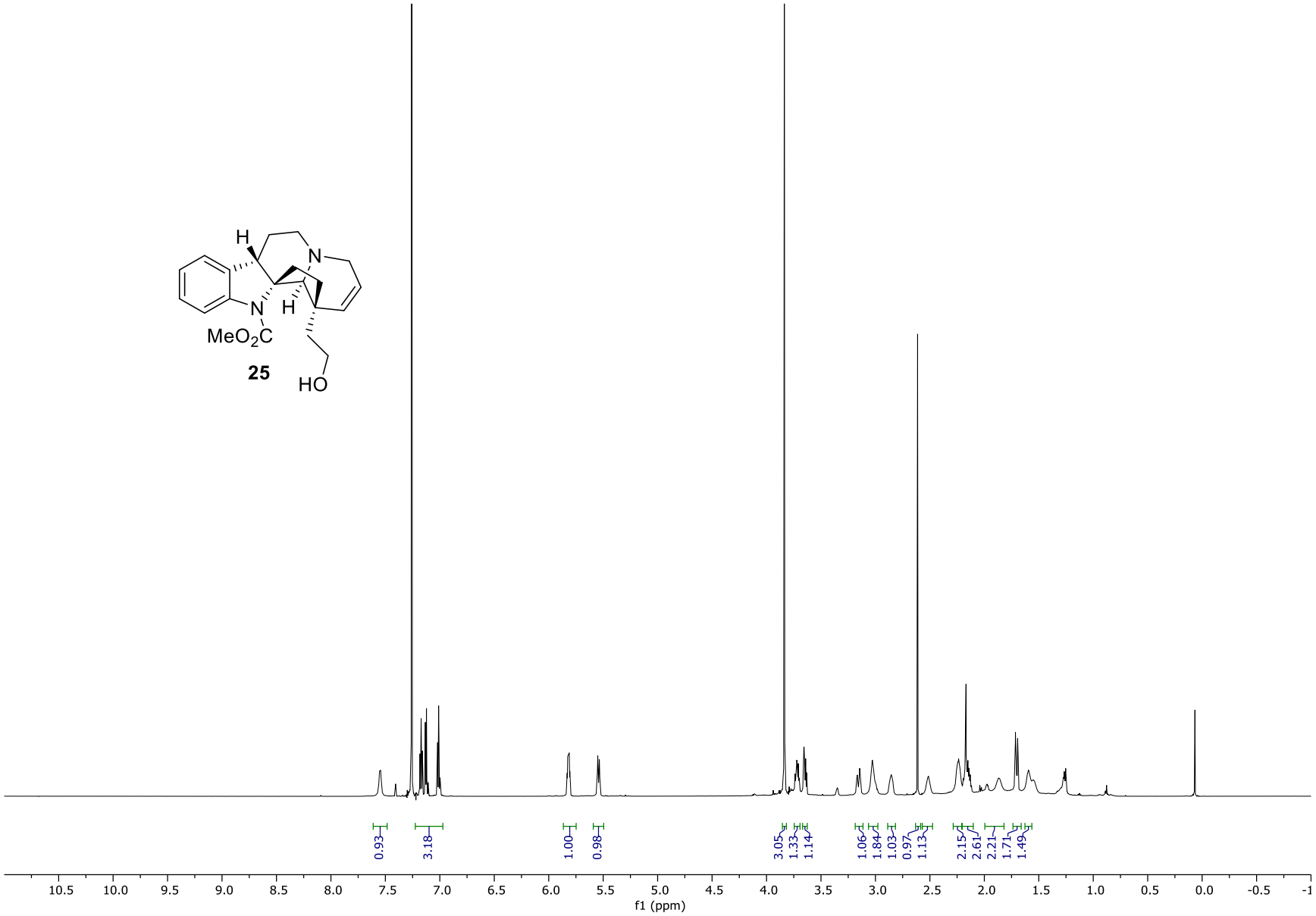

151.51
134.99
127.29
122.99
117.66
107.66
79.08
73.19
50.56
50.03
44.58
44.42
35.58
31.35
31.22
30.43
27.66
26.64
18.53
9.27
H
H
N
N
Me
Me
(+)-vallesamidine 1
f1 (ppm)

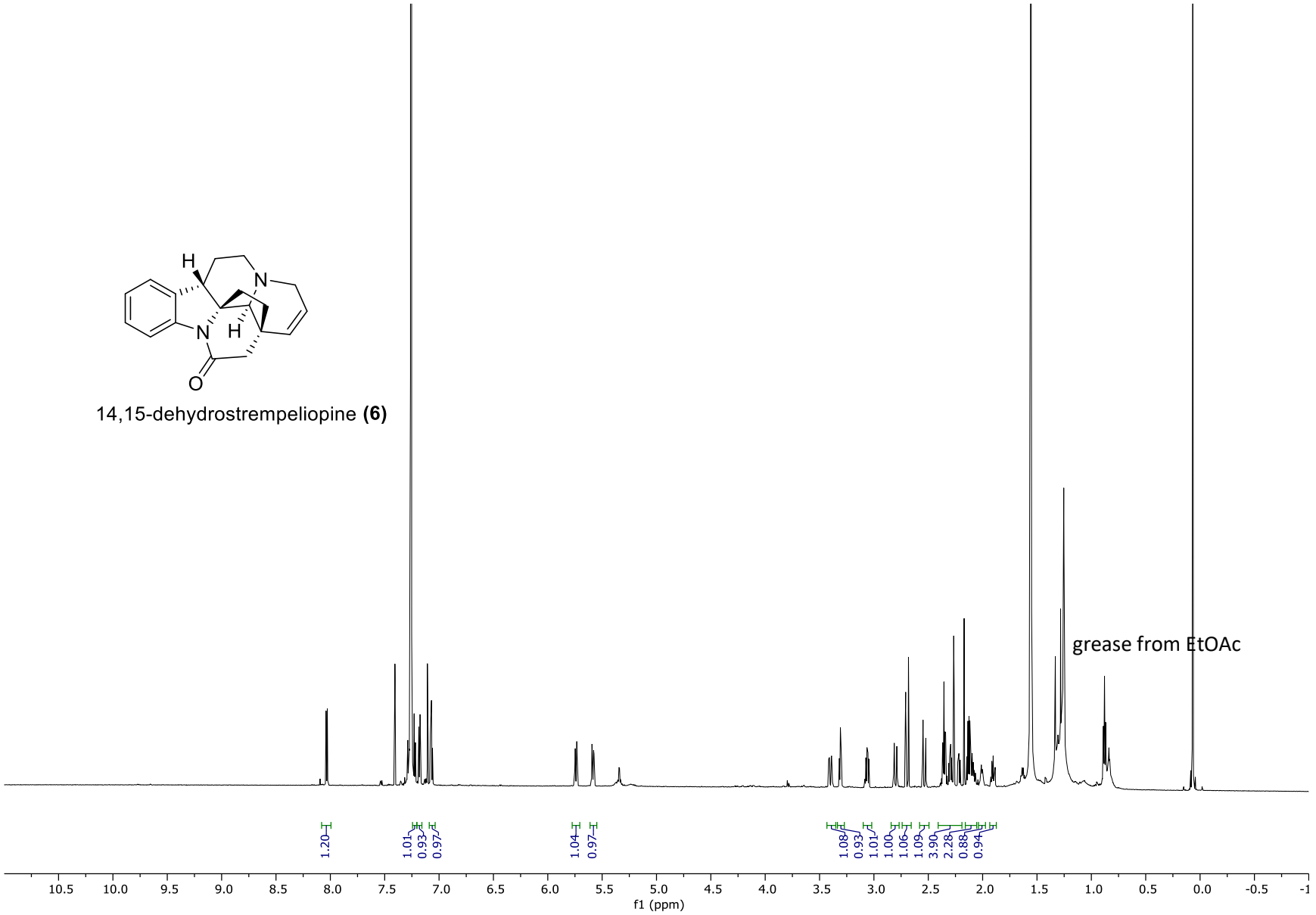


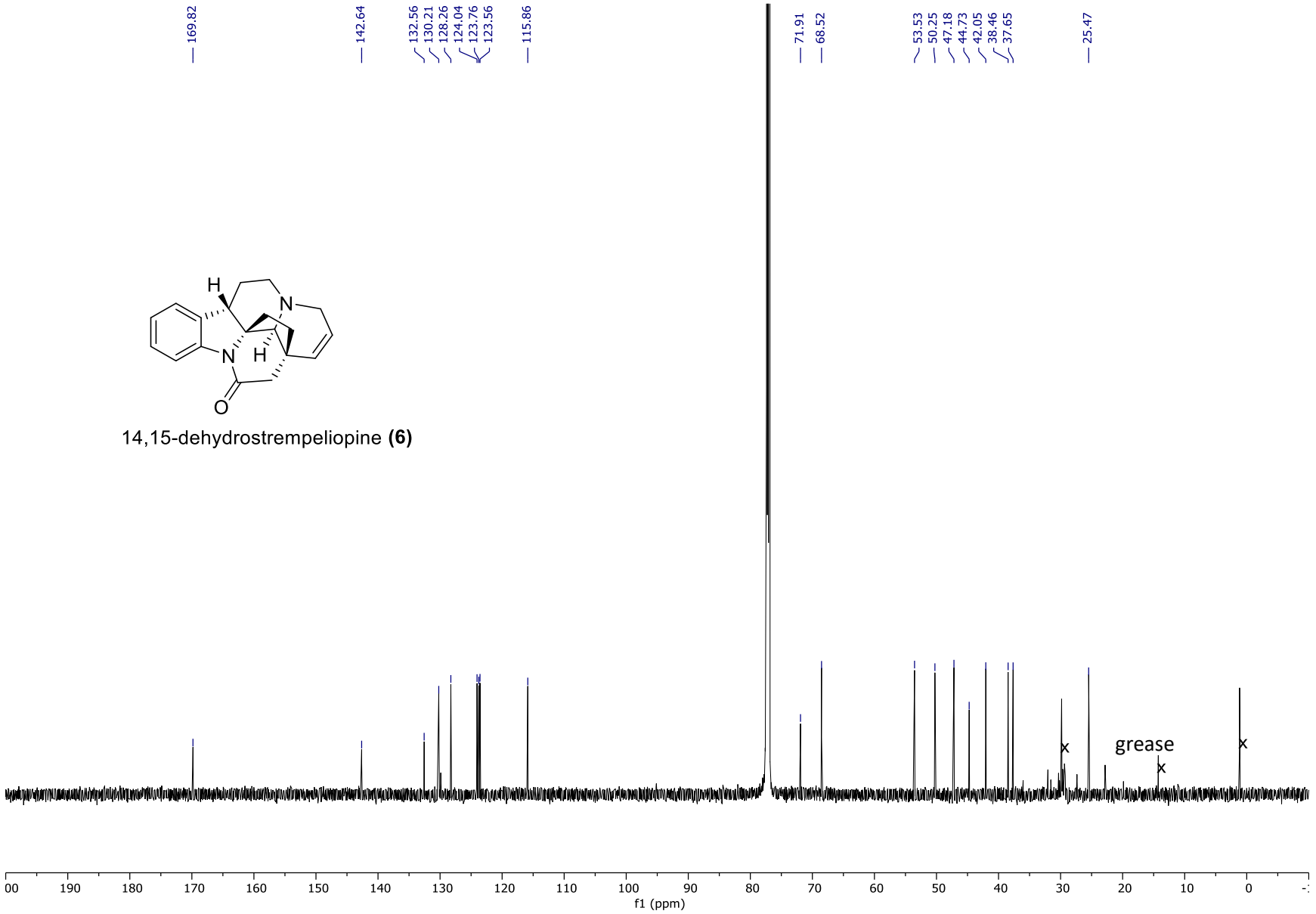
Literature spectra of vallesamidine (**1**)[4]



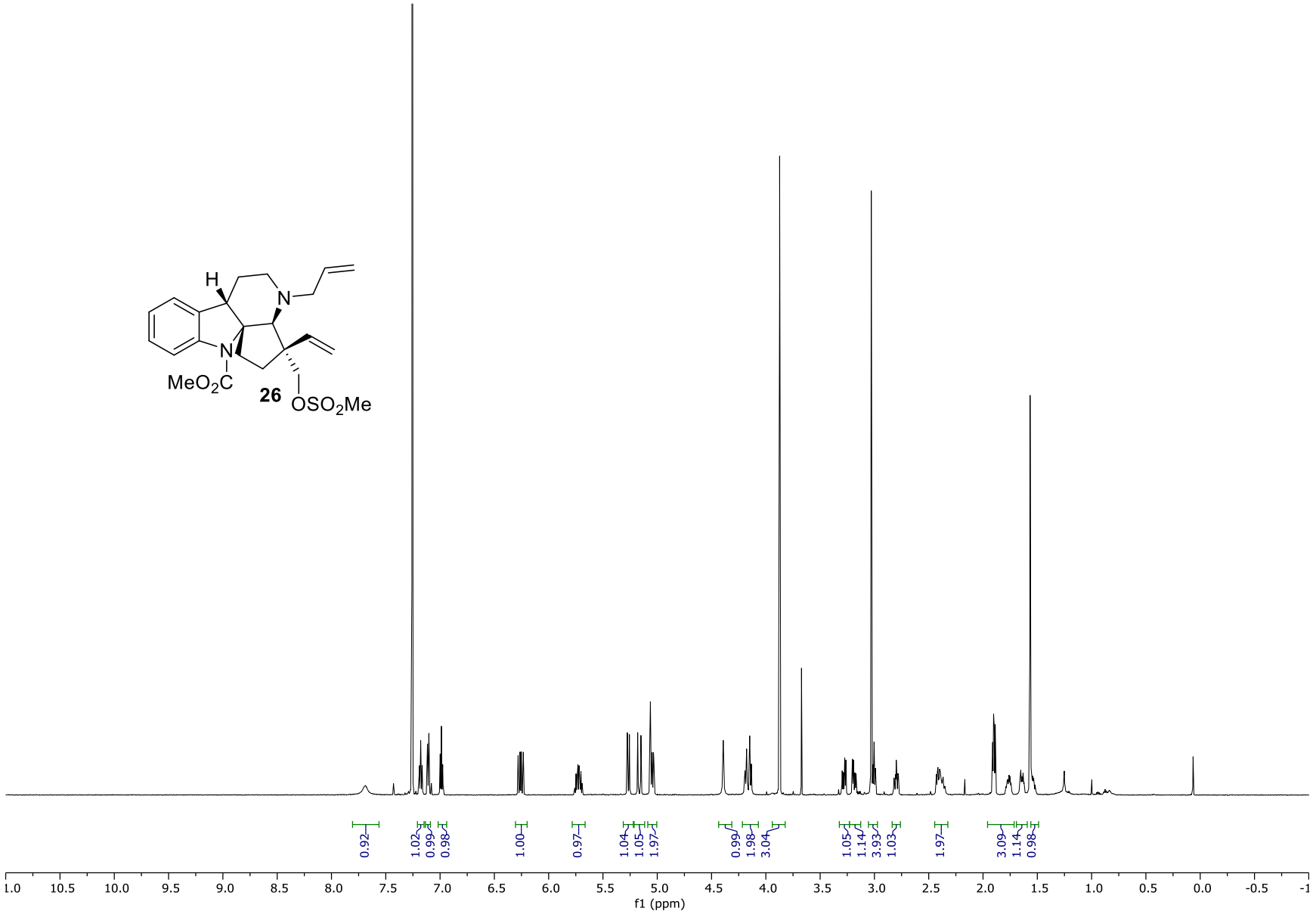
Literature spectra of vallesamidine (**1**)[4]

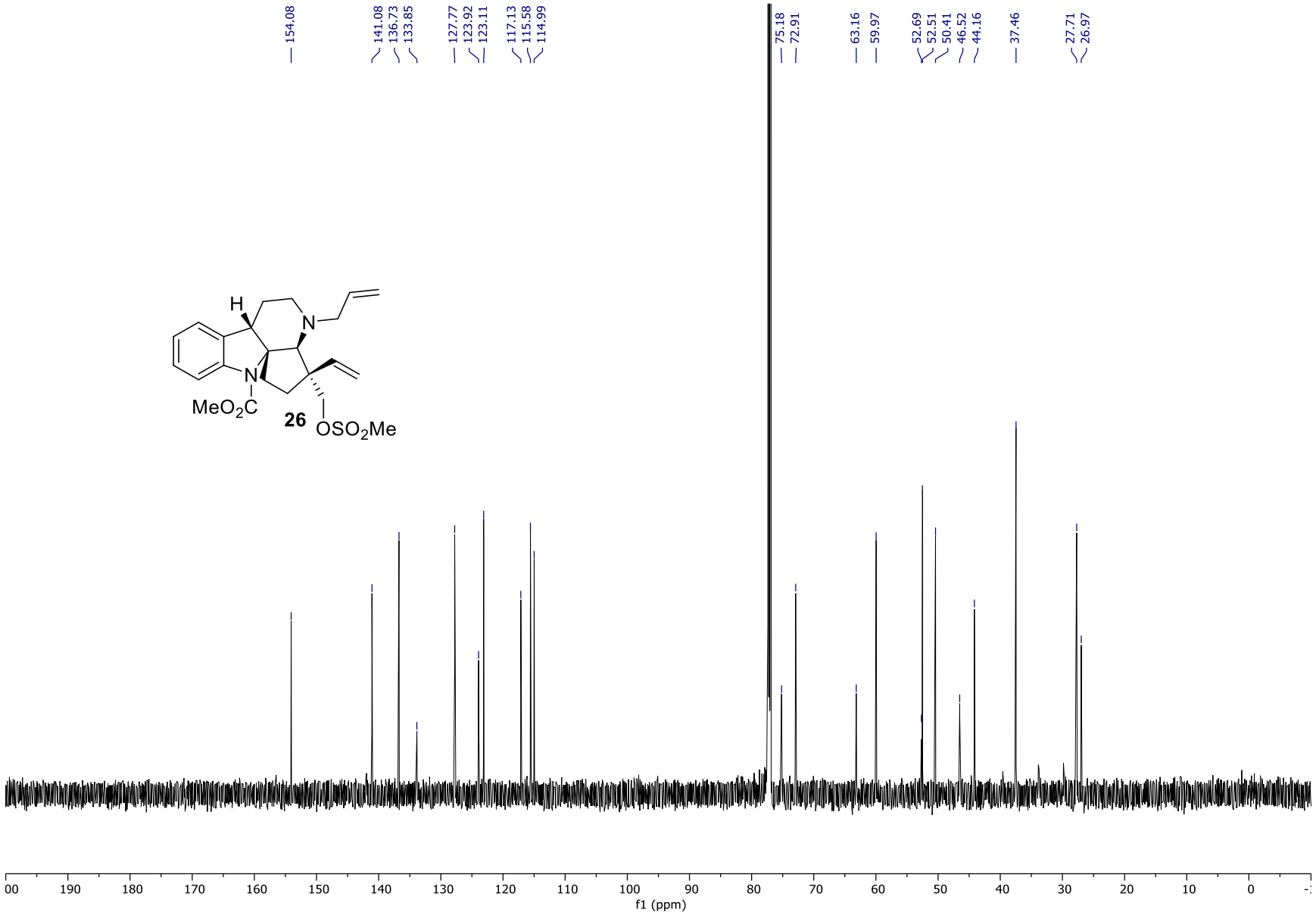

H
N
N
H
MeO2C
25
HO
0.93
3.18
1.00
0.98
3.05
1.33
1.14
1.06
1.84
1.03
0.97
1.13
2.15
2.61
2.21
1.71
1.49
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

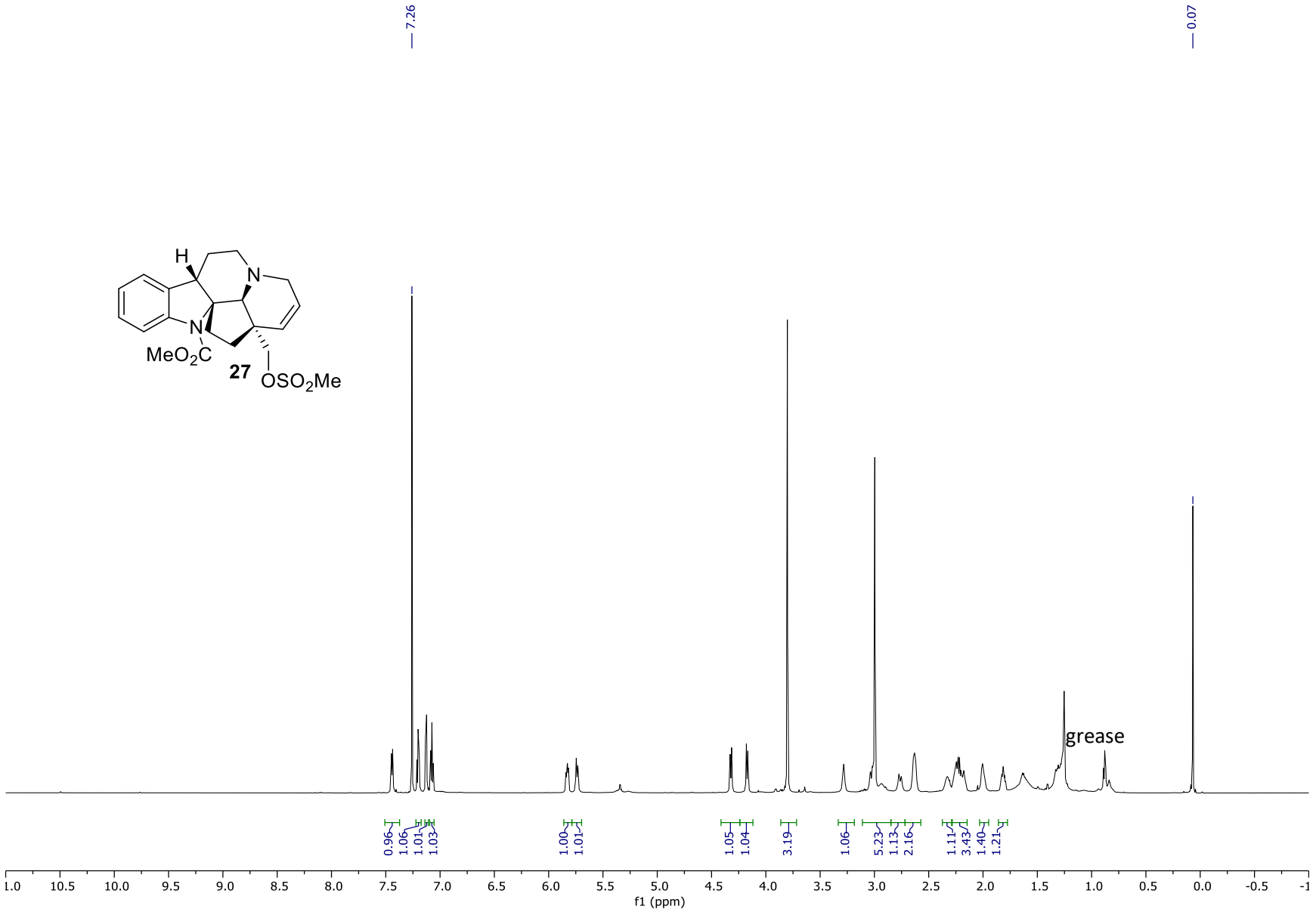

H
N
N
H
O
14,15-dehydrostrempeliopine (6)
grease from EtOAc
1.20
1.01
0.93
0.97
1.04
0.97
1.08
0.93
1.01
1.00
1.06
1.09
3.90
2.28
0.88
0.94
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

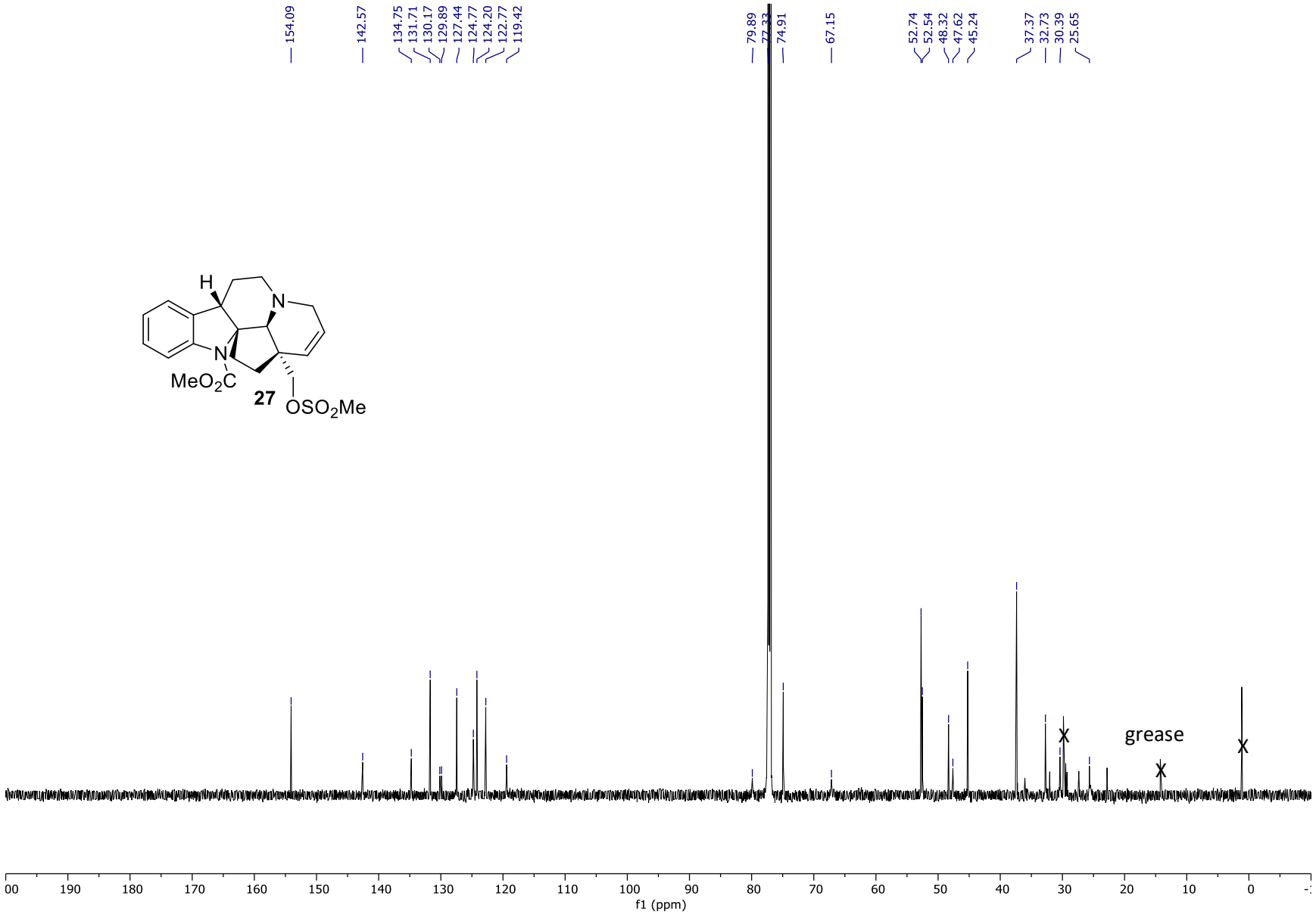


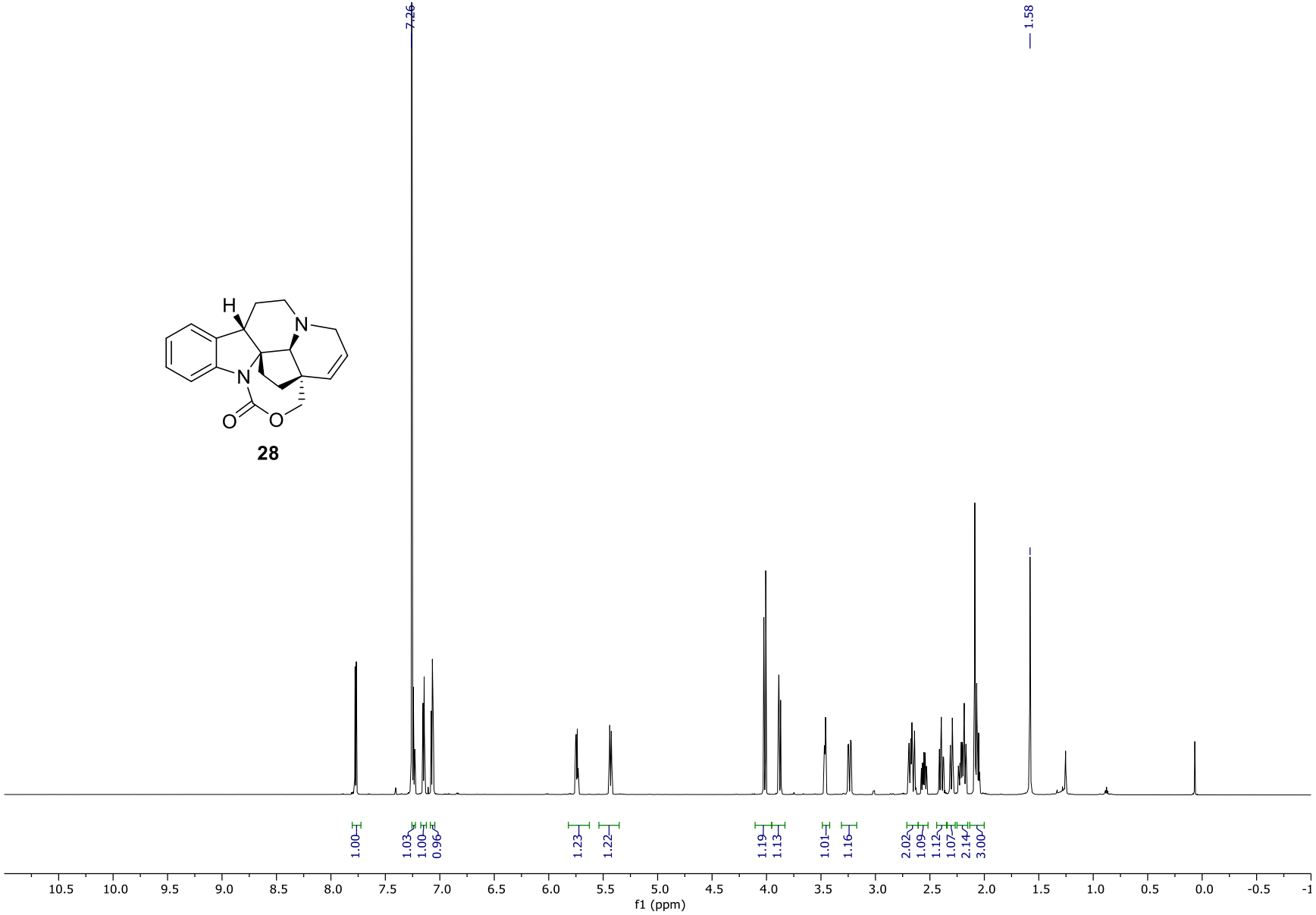
14,15-dehydrostrempeliopine **(6)**

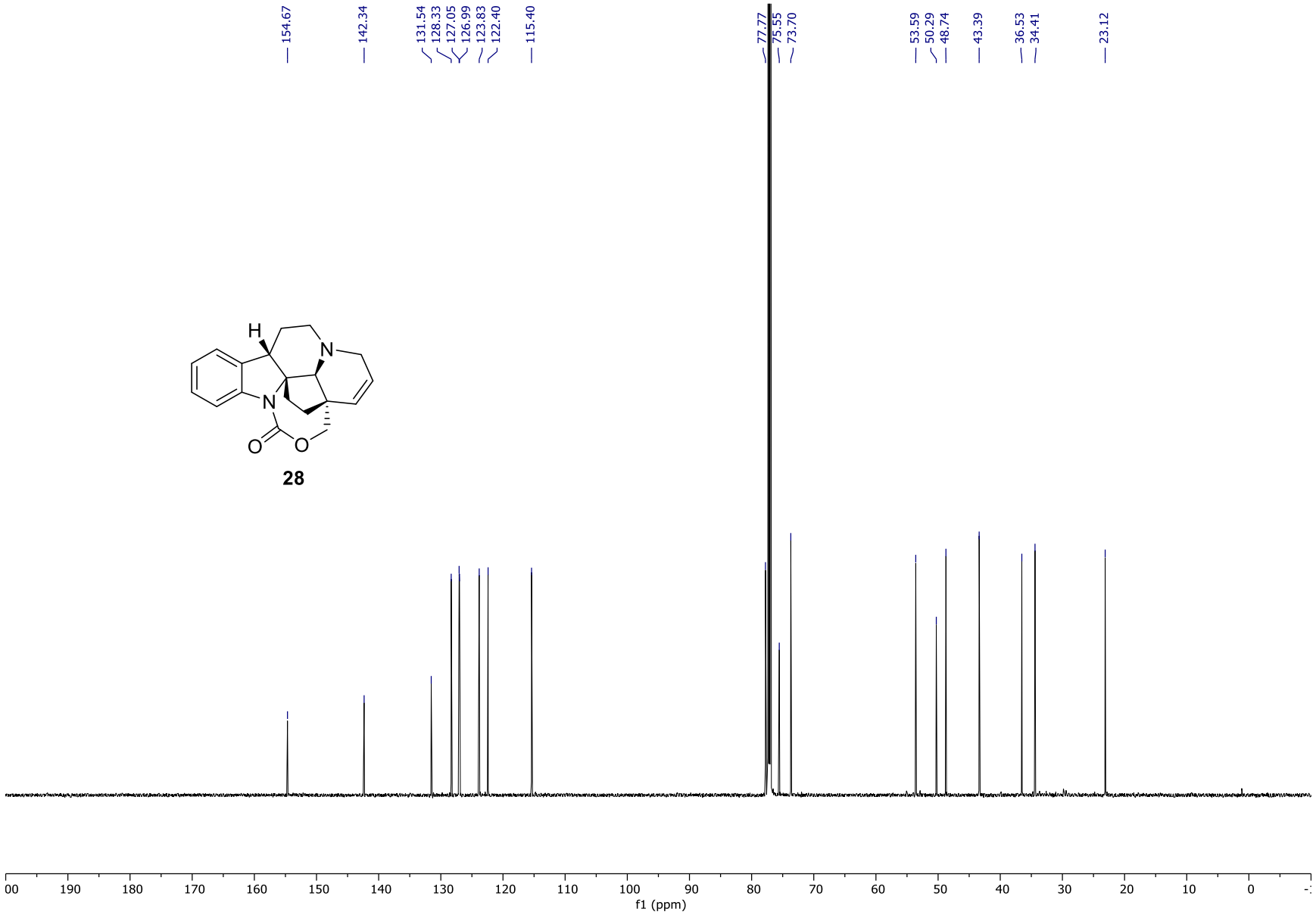

H
N
N
MeO2C
26
OSO2Me
0.92
1.02
0.99
0.98
1.00
0.97
1.04
1.05
1.97
0.99
1.98
3.04
1.05
1.14
3.93
1.03
1.97
3.09
1.14
0.98
f1 (ppm)


154.08
141.08
136.73
133.85
127.77
123.92
123.11
117.13
115.58
114.99
75.18
72.91
63.16
59.97
52.69
52.51
50.41
46.52
44.16
37.46
27.71
26.97
H
N
N
MeO2C
OSO2Me
26
f1 (ppm)

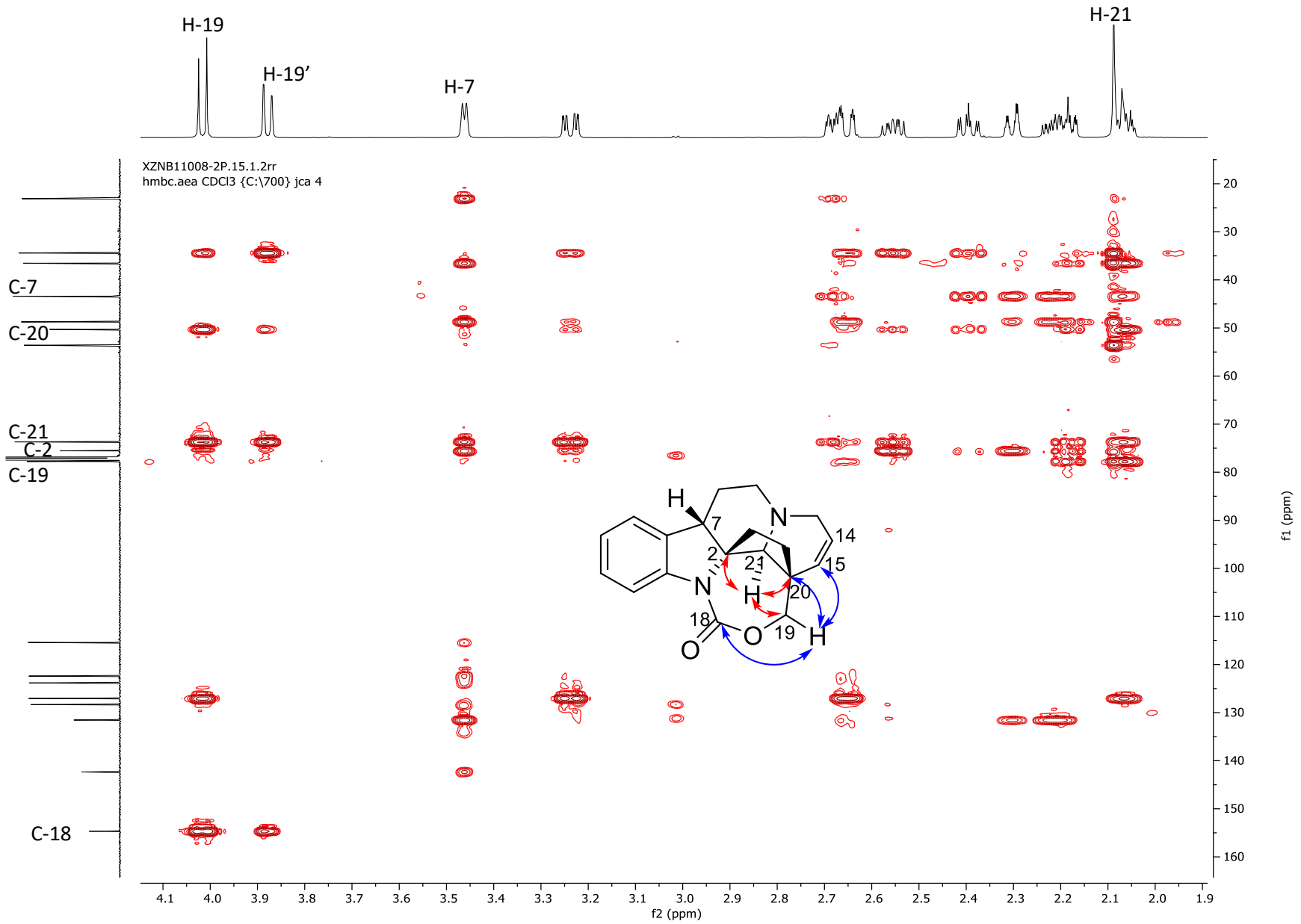

7.26
0.07
H
N
N
MeO2C
27
OSO2Me
grease
0.96
1.06
1.01
1.03
1.00
1.01
1.05
1.04
3.19
1.06
5.23
1.13
2.16
1.11
3.43
1.40
1.21
f1 (ppm)

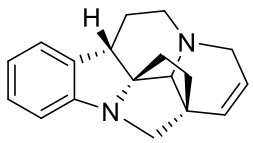

154.09
142.57
134.75
131.71
130.17
129.89
127.44
124.77
124.20
122.77
119.42
79.89
77.33
74.91
67.15
52.74
52.54
48.32
47.62
45.24
37.37
32.73
30.39
25.65
H
N
N
MeO2C
27
OSO2Me
grease
f1 (ppm)


7.26
1.58
H
N
N
O
O
28
1.00
1.03
1.00
0.96
1.23
1.22
1.19
1.13
1.01
1.16
2.02
1.09
1.12
1.07
2.14
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


154.67
142.34
131.54
128.33
127.05
126.99
123.83
122.40
115.40
77.77
75.55
73.70
53.59
50.29
48.74
43.39
36.53
34.41
23.12
H
N
N
O
O
f1 (ppm)

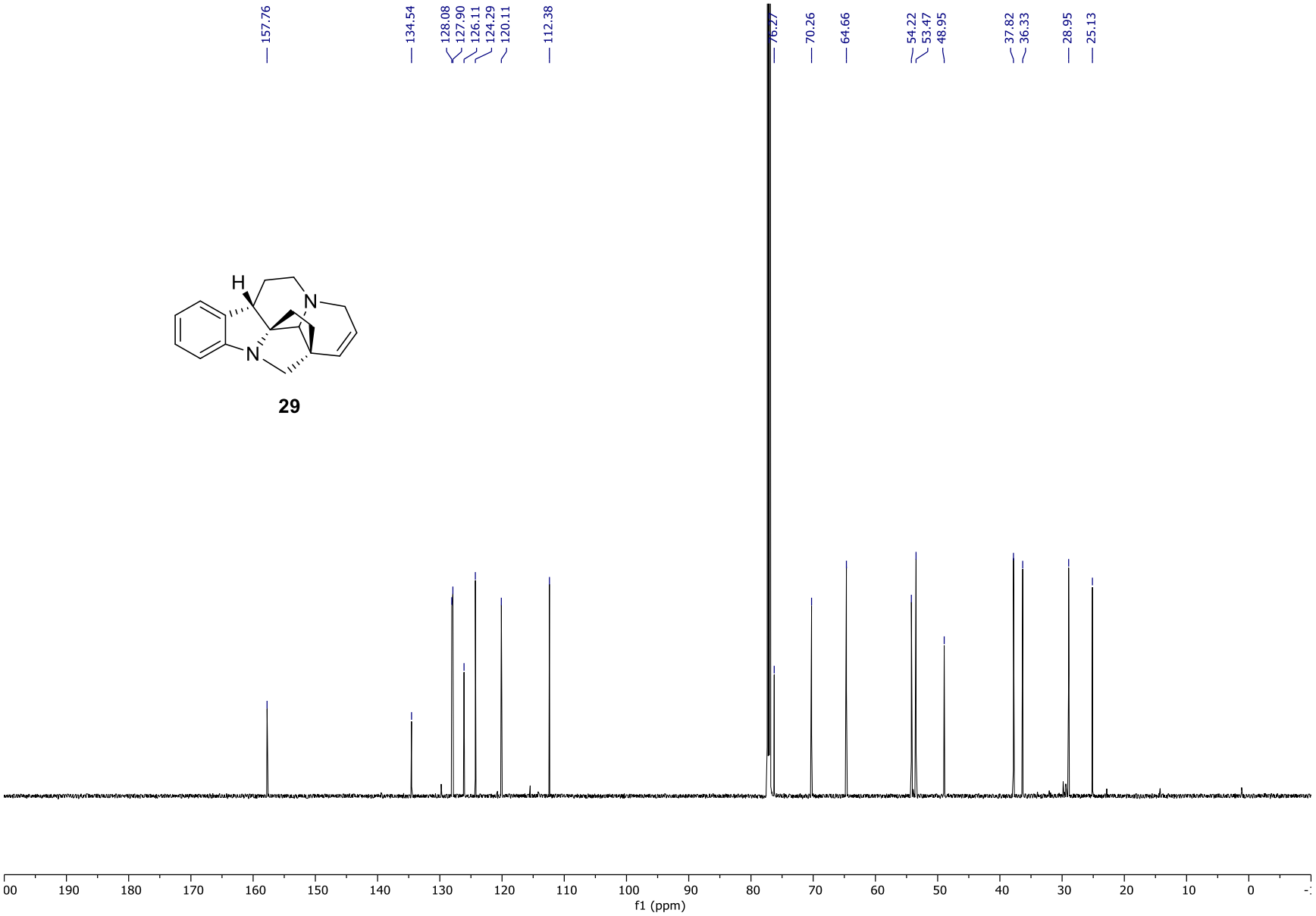
28


H-19
H-19'
H-7
H-21
XZNB11008-2P.15.1.2rr
hmbc.aea CDCl3 {C:\700} jca 4
C-7
C-20
C-21
C-2
C-19
C-18
H
7
N
14
2
21
15
N
H
20
18
O
O
19
H
f2 (ppm)
f1 (ppm)

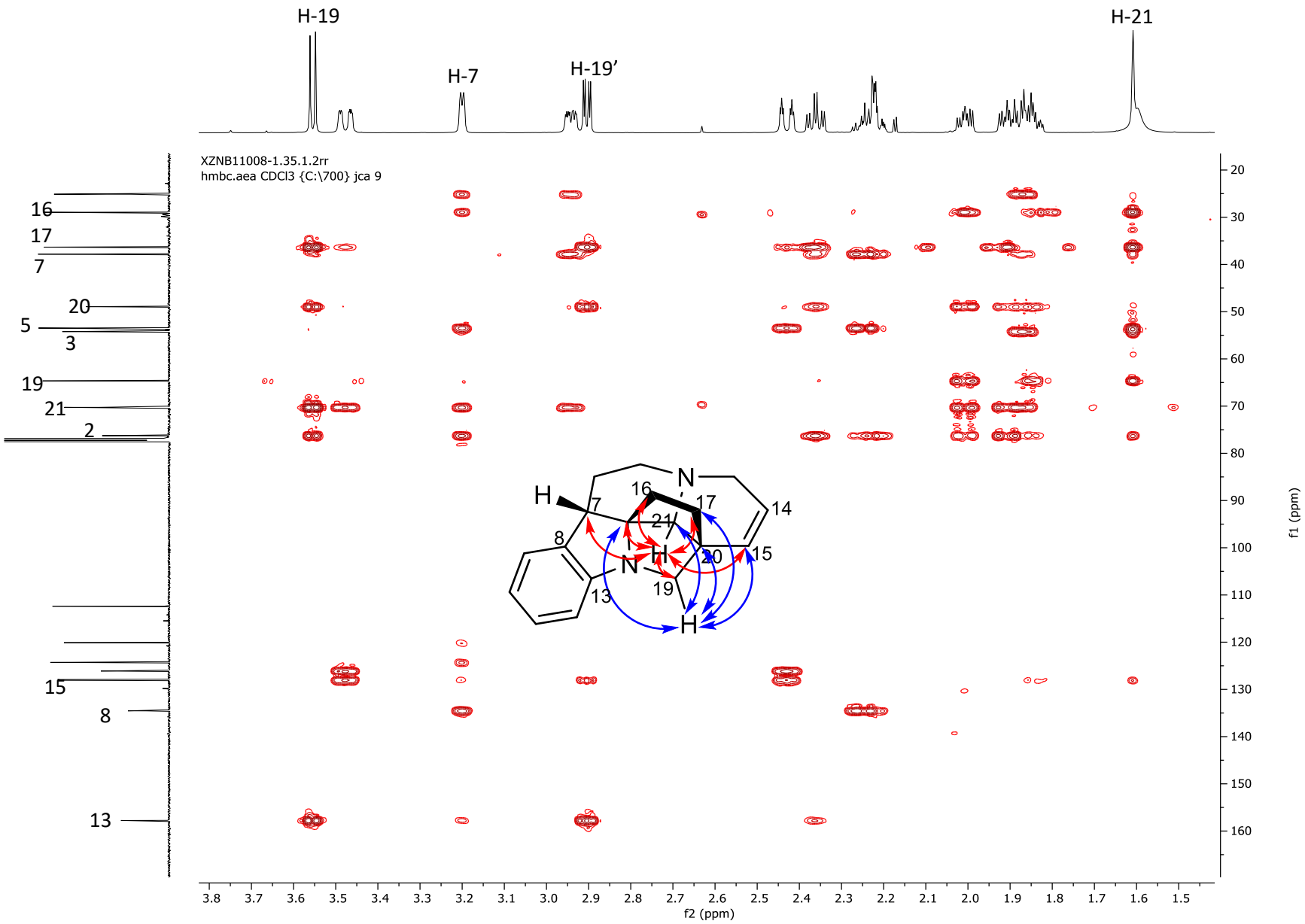

H
N
N

29

2.03
1.06
1.00
1.00
1.01
1.06
1.04
1.02
2.08
1.05
1.04
2.23
1.15
3.18
1.36
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


157.76
134.54
128.08
127.90
126.11
124.29
120.11
112.38
76.27
70.26
64.66
54.22
53.47
48.95
37.82
36.33
28.95
25.13
H
N
N
f1 (ppm)

29


H-19
H-7
H-19'
H-21
XZNB11008-1.35.1.2rr
hmbc.aea CDCl3 {C:\700} jca 9
16
17
7
20
5
3
19
21
2
15
8
13
f2 (ppm)
f1 (ppm)

References:

[1] C.-F. Chang, C.-Y. Huang, Y.-C. Huang, K.-Y. Lin, Y.-J. Lee, C.-Y. Wang, *Syn. Commun.* **2010**, *40*, 3452-3466.

[2] D. A. Evans, D. Seidel, *J. Am. Chem. Soc.* **2005,** *127*, 9958-9959. The catalyst was synthesised in lab following the protocol therein.

[3] H. Zhang, Q. Cai, D. Ma, *J. Org. Chem.* **2005**, *70*, 5164–5173.

[4] X. Wang, D. Xia, W. Qin, R. Zhou, X. Zhou, Q. Zhou, W. Liu, X. Dai, H. Wang, S. Wang, L. Tan, D. Zhang, H, Song, X. Liu, Y. Qin, *Chem* **2017**, *2*, 803–816.

[5] H. Tanino, K. Fukuishi, M. Ushiyama, K. Okada, *Tetrahedron* **2004**, *60*, 3273–3282.