Electronic Supplementary Material (ESI) for Chemical Communications

Electronic Supplementary Information

Total Synthesis of (–)-Nakadomarin A

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Contents

1. General experimental

For reactions conducted under anhydrous conditions glassware was dried in an oven at 100 °C and carried out under a nitrogen or argon atmosphere. Catalyst **44** was handled using glovebox techniques under an argon atmosphere.

1.1. Solvents and reagents. Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl radical. CH_2Cl_2 and toluene were distilled from calcium hydride prior to use. Chlorobenzene was distilled from P_2O_5 under an atmosphere of argon. Triethylamine and pyridine were distilled from calcium hydride and stored over KOH. All work-up solvents and commercial reagents were used as supplied without further purification unless otherwise stated. Petroleum ether refers to the fractions boiling in the range 40-60 °C.

1.2. Chromatography. Flash column chromatography was performed on VWR Kieselgel 60 (40-63 μm) silica or Fluka neutral aluminium oxide (alumina) (0.05-0.15 mm) in the solvent system stated. All reactions were followed by thin-layer chromatography (TLC) where practical, using Merck Kieselgel 60 F_{254} (230-400 mesh) fluorescent treated silica plates which were visualised under UV light (250 nm) or by staining with aqueous basic potassium permanganate solutions as appropriate.

1.3. Spectroscopy. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer deposited as a thin film on a sodium chloride plate, with absorption maxima (ν_{max}) recorded in wavenumbers (cm^{-1}). Only selected maximum absorbances are reported. ^1H and ^{13}C-NMR spectra were acquired on either a Bruker DPX 400 (400 MHz ^1H, 100 MHz ^{13}C), Bruker AV400 (400 MHz ^1H, 100 MHz ^{13}C), Bruker AVII 500 (500 MHz ^1H, 125 MHz ^{13}C) or Bruker AVIII 700 (700MHz ^1H) and in the deuterated solvent stated. Chemical shift values (δ) are given in parts per million (ppm) reported relative to residual solvent peaks downfield from tetramethylsilane. Chemical shifts (δ) are given in parts per million (ppm). The multiplicity of each signal is designated using the following abbreviations; s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet. Quotation marks (" ") around a multiplicity is used to denote an observed coupling pattern, when this is clearly not the expected coupling pattern. DEPT 135 and two-dimensional (COSY, HSQC, HMBC) NMR spectroscopy were used where appropriate to assist the assignment of signals in the ^1H and ^{13}C-NMR spectra. Low resolution mass spectra were recorded on a Waters LCT premier XE mass spectrometer. High resolution mass spectra were recorded on a Bruker Microtof (ES) mass spectrometer. Optical rotations were recorded using a Perkin Elmer 241 optical activity polarimeter; specific rotations ($[\alpha]_D$) are reported in $10^{-1}deg.cm^{-2}.g^{-1}$; concentrations ($c$) are quoted in g/100 mL of solution; D refers to the D-line of sodium (589 nm); temperatures (T) are given in degrees Celsius (°C). Melting points were obtained using a Leica-Galen III apparatus and remain uncorrected. Compounds were named according to IUPAC nomenclature using ACD/I-Lab service.

1.4. Starting materials. The following compounds are commercially available: (5*R*)-5 (hydroxymethyl) pyrrolidin-2-one **24**, 1-bromobut-2-yne **31**, dimethyl (2-oxopropyl)phosphonate **30**, 2-oxopropane-1,3-diyl diacetate **33**, formaldehyde **(6)**, hex-5-enoyl chloride **41**, 1,4-diazabicyclo[2.2.2]octane **15**, tris(*t*-butoxy)(2,2-dimethylpropylidyne)tungsten(VI) **44** and 6-chlorohex-1-yne **38**. Catalyst **16** was synthesized from cinchonine according to literature procedures.[1a],[2].

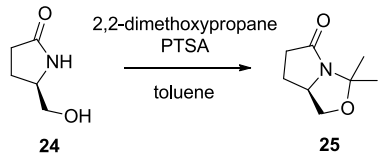
2. Practical experimental

2.1. Proof of principle studies in the stereoselective Michael addition

2.1.1. Synthesis and characterisation of pronucleophile 9

2.1.1.2 Synthesis and characterisation of 25

(7a*R*)-3,3-Dimethyltetrahydro-5*H*-pyrrolo[1,2-*c*][1,3]oxazol-5-one **25** [3]

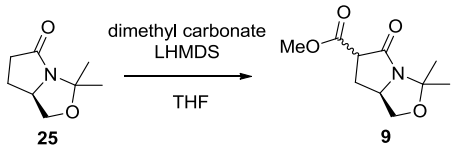


24 **25**

To a stirred suspension of (5*R*)-5-(hydroxymethyl)pyrrolidin-2-one **24** (20.7 g, 0.18 mol) in toluene (200 mL) was added PTSA (0.600 g, 3.15 mmol) and 2,2-dimethoxypropane (28 mL, 0.23 mol). The reaction was heated at reflux with the azeotropic removal of methanol for 2 h after which a second portion of 2,2-dimethoxypropane (28 mL, 0.23 mol) was added and the reaction continued at reflux with the azeotropic removal of methanol for 2 h. The reaction mixture was then cooled to rt and concentrated *in vacuo* before being purified by flash column chromatography (PE:Et_2O 1:1→Et_2O) to afford the title compound **25** as a crystalline colourless solid (20.8 g, 75%) which gave data in agreement with literature; [3] mp 36-37 °C, lit.[3] 38 °C; $[\alpha]_D^{20}$ = + 108.1 (*c* 1.0, $CHCl_3$); lit.[3] $[\alpha]_D^{20}$ = + 114.7 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.26 (tt, *J* = 9.0, 6.0 Hz, 1H, C*H*N), 4.08 (dd, *J* = 8.3, 5.7 Hz, 1H, C*H*H'O), 3.45 (dd, *J* = 9.1, 8.4 Hz, 1H, CH*H*'O), 2.80 (ddd, *J* = 16.6, 12.2, 8.5 Hz, 1H, C*H*H'C=O), 2.53 (ddd, *J* = 16.6, 9.2, 1.2 Hz, 1H, CH*H*'C=O), 2.17 (dddd, *J* = 12.5, 8.5, 6.4, 1.2 Hz, 1H, C*H*H'CHN), 1.81 - 1.71 (m, 1H, CH*H*'CHN), 1.67 (s, 3H, CH_3), 1.46 (s, 3H, CH_3).

2.1.1.3. Synthesis and characterisation of 9

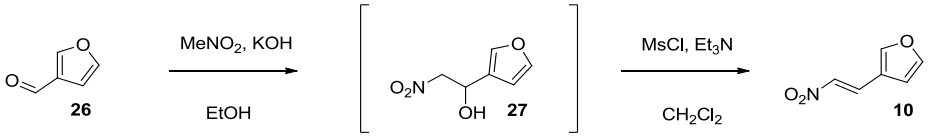
Methyl (6*R*,*S*,7aR)-3,3-dimethyl-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate **9**



A solution of (7a*R*)-3,3-dimethyltetrahydro-5*H*-pyrrolo[1,2-*c*]oxazol-5-one **25** (9.20 g, 59.3 mmol) and dimethyl carbonate (6.40 g, 71.0 mmol) in THF (214 mL) was added dropwise over 50 minutes to LHMDS (1 M solution in THF) (119 mL, 119 mmol) cooled to -78 °C. The mixture was stirred at -78 °C for 0.5 h before being slowly warmed to 0 °C over 3 h. Glacial acetic acid (17 mL, 296 mmol) was added dropwise at 0 °C, followed by addition of Et_2O (225 mL). The resulting mixture was stirred at room temperature for 10 minutes before being concentrated *in vacuo* to give an off white paste. Purification by flash column chromatography (PE:Et_2O 1:1→Et_2O) gave methyl (6*R*,*S*,7a*R*)-3,3-dimethyl-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate **9** as a colourless oil (2.3:1 mixture of diastereoisomers), which epimerised upon crystallisation with complete conversion to a single diastereoisomer as a colourless solid (9.3 g, 74%): mp 73-74 °C; $[\alpha]_D^{20}$ = - 157.3 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2986 (C-H), 2953 (C-H), 1741 (C=O), 1699 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.22 - 4.13 (m, 1H, C*H*N), 4.10 (dd, *J* = 8.1, 5.8 Hz, 1H, C*H*H'O), 3.83 (dd, *J* = 11.9, 8.1 Hz, 1H, C*H*C=O), 3.77 (s, 3H, OCH_3), 3.58 - 3.50 (m, 1H, CH*H*'O), 2.41 - 2.32 (m, 1H, C*H*H'CHN), 2.29 - 2.18 (m, 1H, CH*H*'CHN), 1.64 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 169.7 (*C*=O), 166.1 (*C*=O), 91.7 (N*C*$(CH_3)_2$O), 69.7 (*C*H_2O), 59.0 (*C*HN), 53.9 (*C*HC=O), 52.6 (O*C*H_3), 28.0 (*C*H_2CHN), 26.6 (*C*H_3), 23.7 (*C*H_3); *m/z* (ESI$^+$) 449 (95%, $[2M+Na]^+$), 236 (100%, $[M+Na]^+$), 214 (23%, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 236.0893, $C_{10}H_{15}NNaO_4$ requires 236.0893.

2.1.2. Synthesis of model electrophile 10

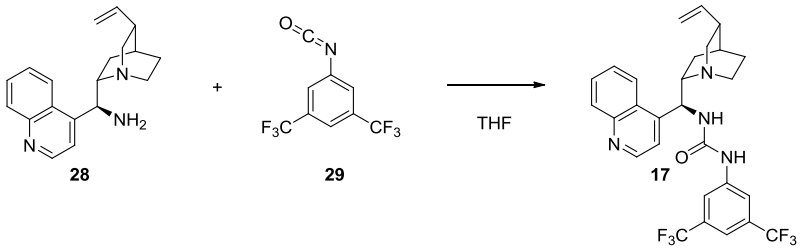
3-[(*E*)-2-Nitrovinyl]furan **10**



KOH (1.1 eq., 57.23 mmol, 28.62 mL of 2 M solution in absolute EtOH) was added dropwise to a solution of furan-3-carbaldehyde **26** (52.03 mmol, 5.000 g) and nitromethane (1.1 eq., 57.23 mmol, 3.493 g, 3.24 mL of 95% pure nitromethane) in EtOH (absolute, 73 mL) at 0 °C. The resulting solution was vigorously stirred at 0 °C. After 3 h the resulting suspension was poured portionwise onto a mixture of aqueous HCl (1 M, 132 mL) and ice (66 g) with vigorous stirring. The insoluble solid was filtered off, washed (water, 2 × 30 mL) and dried (Na_2SO_4) to yield nitro olefin **10** (4.441 g, 61%) as a yellow solid. The filtrate was extracted (Et_2O, 3 × 70 mL) and the organic phase washed (brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue containing Henry adduct 1-(3-furyl)-2-nitroethanol **27** (2.410 g, 15.34 mmol) was dissolved in CH_2Cl_2 (64 mL) and the solution was cooled to -15 °C. MsCl (1.0 eq., 15.34 mmol, 1.757 g, 1.192 mL) was added followed by dropwise addition of Et_3N (2 eq. 30.68 mmol, 3.105 g, 4.276 mL). The mixture was warmed to rt over 30 min and water (40 mL) was added. The separated water phase was further extracted (CH_2Cl_2, 2 × 30 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:Et_2O 90:10→65:35) yielding **10** (1.301 g, 61% for transformation **27** → **10**) as a yellow solid. The overall isolated amount of **10** was 3.721 g, which represents 79% overall yield from aldehyde **26** to the title compound **10**: mp 100-102 °C, lit.[4] mp 101-103 °C, lit.[5] mp 68-70 °C; ν_{max}(film)/cm^{-1} 1640 (C=C), 1492, 1360 (NO_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 13.5, 2.8 Hz, 1H, NO_2CH=C*H*), 7.84 (broad s, 1H, C*H*(2-furan)), 7.52 (broad s, 1H, C*H*(5-furan)), 7.40 (dd, *J* = 13.5, 3.0 Hz, 1H, NO_2C*H*=CH), 6.58 (broad s, 1H, C*H*(4-furan)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.3 (*C*H(furan)), 145.3 (*C*H(furan)), 136.6 (CH=*C*HNO_2), 129.6 (*C*H=$CHNO_2$), 118.1 (*C*(furan)), 107.2 (*C*H(furan)); HRMS m/z (FI^+) found $[M]^+$ 139.0271, $C_6H_5NO_3$ requires 139.0269,.

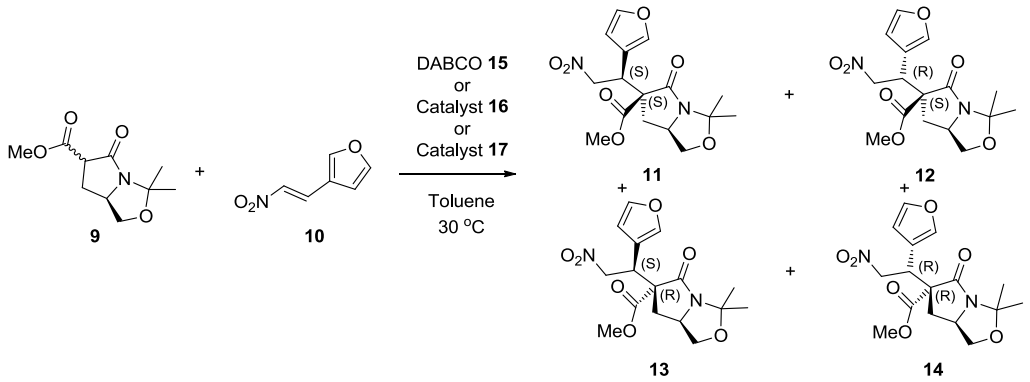
2.1.3. Synthesis of catalyst 17

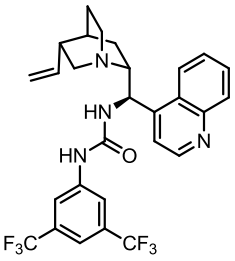
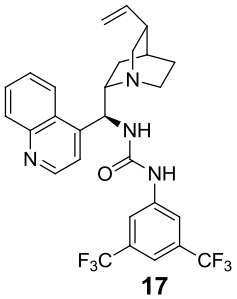
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-quinolin-4-yl((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methyl)urea **17**



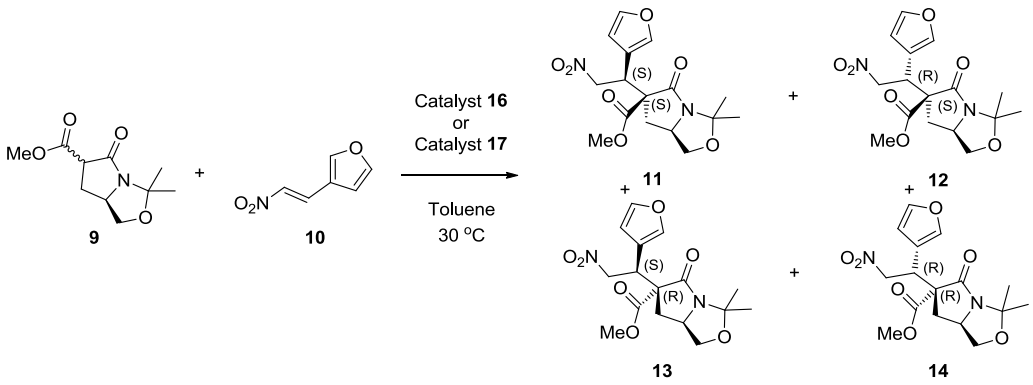
A solution of a 9-amino(9-deoxy) epicinchonidine **28** [1b] (2.69 mmol, 0.789 g) in anhydrous THF (3.2 mL) was added slowly to a solution of 3,5-bis(trifluoromethyl)phenyl isocyanate **29** (2.96 mmol, 0.755 g, 0.511 mL) in anhydrous THF (3 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred overnight. The resulting mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:MeOH:Et_3N 100:2:0→100:10:3) affording the title compound **17** as a pale yellow solid (1.37 g, 93%): mp 134–136 °C; $[\alpha]_D^{30}$ = - 6.0 (*c* 1.00, MeOH); ν_{max}(film)/cm^{-1} 1682; ^{1}H-NMR (500 MHz, CD_3OD) δ 8.85 (d, *J* = 4.6 Hz, 1H), 8.57 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 2H), 7.80 - 7.76 (m, 1H), 7.72 - 7.69 (m, 1H), 7.64 (d, *J* = 4.6 Hz, 1H), 7.42 (s, 1H), 5.80 (ddd, *J* = 8.0 Hz, *J* = 9.9 Hz, *J* = 16.6 Hz, 1H), 5.62 (broad s, 1H), 5.02 - 4.90 (m, 1H), 3.38 - 3.24 (m, 3H), 2.83 - 2.75 (m, 2H), 2.31 (broad s, 1H), 1.71 - 1.58 (m, 3H), 1.43 - 1.37 (m, 1H), 0.89 - 0.83 (m, 1H); ^{13}C-NMR (125 MHz, CD_3OD) δ 156.6, 151.0, 149.9, 149.1, 143.2, 142.6, 133.1 (q, $^2J_{CF}$ = 33.1 Hz, 2C), 131.0, 130.1, 128.8, 128.4, 125.1, 124.8 (q, $^1J_{CF}$ = 271.9 Hz, 2C), 120.8, 118.9 (2C), 115.6, 115.0, 61.2, 56.8, 52.4, 42.0, 40.7, 28.8, 28.6, 27.1; *m/z* (ESI^+) 549 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 549.2078, $C_{28}H_{27}ON_4F_6$ requires 549.2084.

2.1.4. Comparison of 'matched' and 'mismatched' substrate and catalyst control.



Catalyst	Reaction Conditions	Reaction Time	Yield	Diastereomeric Ratio 11:12:13:14
 15	Toluene, 30 °C	7 days	38%	4.3:1:0:0
 16	Toluene, 30 °C	2 days	80% (single diastereomer)	Crude 15:1:0:0 After Purification 1:0:0:0
 17	Toluene, 30 °C	5 days	61% (dr = 6:19:1:1)	Crude 4:12:1:1 After Purification 6:19:1:1

2.1.5. 'Matched' and 'mismatched' substrate and catalyst control studies



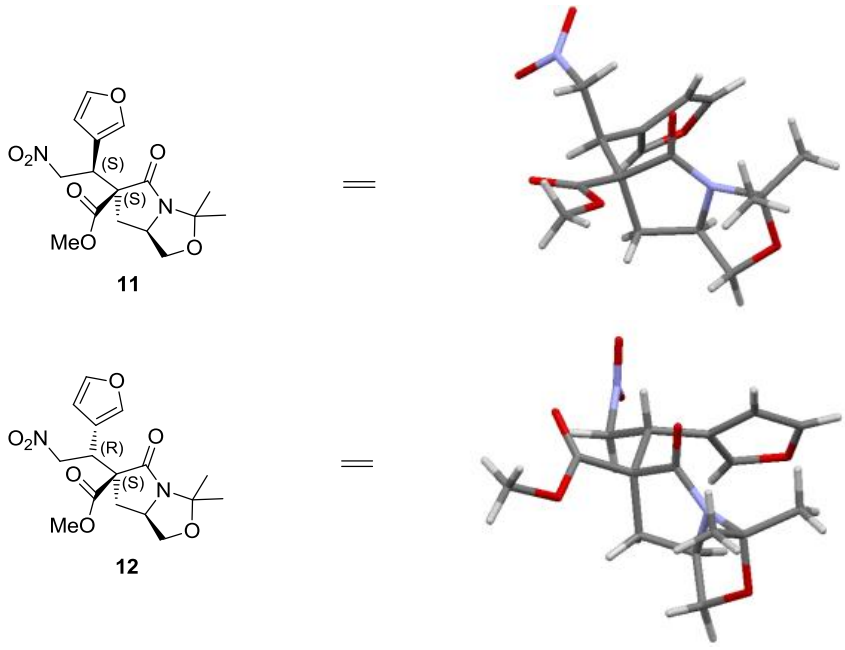
To a solution of 3-[(*E*)-2-nitrovinyl]furan **10** (65 mg, 0.47 mmol) and methyl (7a*R*)-3,3-dimethyl-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate **9** (200 mg, 0.94 mmol) in toluene (1.6 mL) was added catalyst **16** or catalyst **17** (26 mg, 0.047 mmol). The reaction was stirred at 30 °C until complete by tlc analysis (catalyst **16**, 2 days; catalyst **17**, 5 days) before being concentrated and the diastereomeric ratio established from the crude ^{1}H-NMR spectrum (catalyst **16**, 15:1:0:0 dr; catalyst **17**, 4:12:1:1 dr).

For the 'matched' case with catalyst **16**, the reaction mixture was purified by column chromatography (PE:EtOAc:CH_2Cl_2 5.5:4.5:0.8) to obtain the title compound as an off-colourless solid which was further purified by recrystallization from diethyl ether cooled to -20 °C to give methyl (6*S*,7a*R*)-6-[(1*S*)-1-(3-furyl)-2-nitroethyl]-3,3-dimethyl-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate **11** as a colourless crystalline solid (131 mg, 80%): mp 157 °C; $[\alpha]_D^{26}$ = + 2.1 (*c* 0.75, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2988 (C-H), 1721 (C=O), 1688 (C=O), 1547 (NO_2), 1381 (NO_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H, C*H*(2-furan)), 7.44 - 7.41 (m, 1H C*H*(5-furan)), 6.42 (s, 1H, C*H*(4-furan)), 5.03 - 4.88 (m, 2H, NO_2CH_2), 4.14 (dd, *J* = 10.6, 3.8 Hz, 1H, C*H*CH_2NO_2), 3.90 (dd, *J* = 7.8, 5.3 Hz, 1H, C*H*H'O), 3.82 (s, 3H, CH_3O), 3.40 (dd, *J* = 9.6, 7.8 Hz, 1H, CH*H*'O), 3.35 - 3.26 (m, 1H, C*H*N), 2.21 - 2.15 (m, 2H, CH_2CHN), 1.67 (s, 3H, CCH_3), 1.42 (s, 3H, CCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 171.6 (*C*=O), 167.2 (*C*=O), 144.0 (*C*(furan)), 142.0 (*C*(furan)), 119.2 (*C*(furan)), 109.4 (*C*(furan), 91.9 ($NC(CH_3)_2O$), 76.8 (NO_2CH_2), 69.9 (CH_2O), 63.5 (*C*(quat)), 58.6 (CH_2CHN), 53.4 (OCH_3), 38.6 (*C*H-furan), 33.3 (CH_2CHN), 26.2 (CCH_3), 23.3 (CCH_3); *m/z* (ESI$^+$) 375 (100%, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 375.1163, $C_{16}H_{20}N_2NaO_7$ requires 375.1163.

For the 'mismatched' case with catalyst **17**, the reaction mixture was purified by column chromatography (PE:EtOAc:CH_2Cl_2 5.5:4.5:0.8) to give **11**:**12**:**13**:**14** as a 6:19:1:1 mixture of

diastereoisomers as a colourless solid (100 mg, 61%). Further purification by repeated recrystallisation from diethyl ether cooled to -20 °C, gave a mixture of **11** and **12** (1:4 dr). Attempts to separate **11** and **12** completely by recrystallisation were unsuccessful. Recrystallisation from (Et_2O:MeOH:PE 10.0:0.2:1.0) gave large block crystals (the diastereomeric ratio of the combined crystals remained **11**:**12**, 1:4 dr). A large single crystal from this mixture was removed and the structure confirmed as **12** by single crystal X-ray analysis. ^{1}H-NMR analysis of this single crystal confirmed that a single diastereoisomer **12** was present: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H, C*H*(2-furan)), 7.39 (t, *J* = 1.5 Hz, 1H, C*H*(5-furan)), 6.38 (dd, *J* = 1.7, 0.9 Hz, 1H, C*H*(4-furan)), 5.11 (dd, *J* = 13.6, 3.7 Hz, 1H, NO_2CHH'), 5.00 (dd, *J* = 13.5, 10.4 Hz, 1H, NO_2CH*H*'), 4.15 (dd, *J* = 10.3, 3.7 Hz, 1H, C*H*CH_2NO_2), 4.07 (dd, *J* = 8.0, 5.5 Hz, 1H, C*H*H'O), 4.03-3.94 (m, 1H, C*H*N), 3.81 (s, 3H, CH_3O), 3.52 (dd, *J* = 9.2, 8.0 Hz, 1H, CH*H*'O), 2.49 (dd, *J* = 13.7, 7.9 Hz, 1H, C*H*H'CHN), 2.17 (dd, *J* = 13.6, 6.9 Hz, 1H, CH*H*'CHN), 1.63 (s, 3H, CCH_3), 1.40 (s, 3H, CCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 169.9 (*C*=O), 167.1 (*C*=O), 143.8 (*C*(furan)), 141.5 (*C*(furan)), 120.0 (*C*(furan)), 110.1 (*C*(furan), 92.1 (N*C*$(CH_3)_2$O), 76.6 (NO_2CH_2), 69.7 (CH_2O), 65.2 (*C*(quat)), 58.0 (CH_2CHN), 53.3 (OCH_3), 37.8 (*C*H-furan), 30.5 (CH_2CHN), 26.5 (CCH_3), 23.4 (CCH_3); *m/z* (ESI$^+$) 375 (100 %, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 375.1162, $C_{16}H_{20}N_2NaO_7$ requires 375.1163.

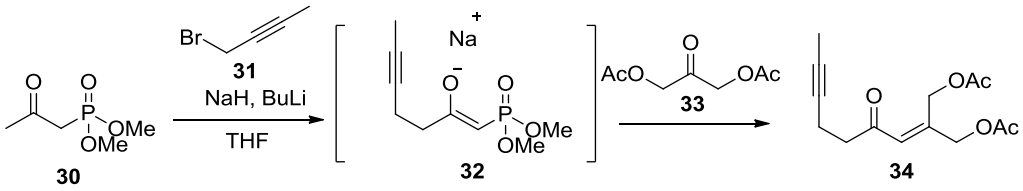
2.1.6. Single crystal x-ray structures of 11 and 12



2.2. Synthesis of electrophile 8

2.2.1. Synthesis and characterisation of 34

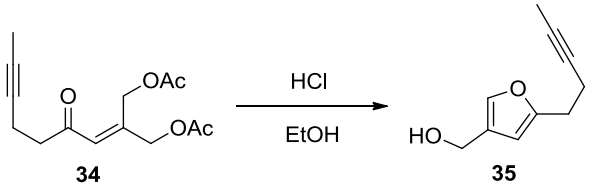
2-(Acetoxymethyl)-4-oxonon-2-en-7-yn-1-yl acetate **34**



To a suspension of NaH (60 % dispersion in mineral oil) (13.9 g, 347 mmol) in THF (640 mL) was added dimethyl (2-oxopropyl)phosphonate **30** (32.0 g, 193 mmol) dropwise at 0 °C. A white suspension was formed upon complete addition. The suspension was stirred for 0.5 h before BuLi (2.5 M in hexanes) (104 mL, 260 mmol) was added dropwise over 5 minutes and the resultant orange solution stirred for 20 minutes at 0 °C. 1-Bromobut-2-yne **31** (25.6 g, 193 mmol) was added dropwise, forming a white suspension, and the reaction mixture stirred for a further 10 minutes. 2-Oxopropane-1,3-diyl diacetate **33** (50.3 g, 289 mmol) was added in one portion at 0 °C and the reaction was allowed to warm to room temperature and stirred at room temperature for 2 h before being quenched with sat. aq. NH_4Cl solution (500 mL). After extraction with CH_2Cl_2 (2 x 500 mL) and drying ($MgSO_4$) the title compound **34** was obtained by column chromatography (3:1 → 5:1 diethyl ether : petroleum ether) as a pale yellow oil (19.5 g, 38%): ν_{max}(film)/cm^{-1} 2923 (C-H), 2860 (C-H), 1745 (C=O), 1697 (C=O), 1630 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (quin., *J* = 1.5 Hz, 1H, C(O)C*H*=C), 5.20 (s, 2H, CH_2OAc), 4.73 (s, 2H, CH_2OAc), 2.72 (t, *J* = 7.2 Hz, 2H, CH_2CO), 2.44-2.38 (m, 2H, C≡CCH_2), 2.13 (s, 3H, COCH_3), 2.07 (s, 3H, COCH_3), 1.75 (t, *J* = 2.5 Hz, 3H, C≡CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 198.5 (*C*=O), 170.5 (*C*=O), 170.2 (*C*=O), 147.6 (C=*C*), 124.2 (*C*=C), 77.5 (*C*≡C), 76.2 (C≡*C*), 63.6 (*C*H_2O), 62.1 (*C*H_2O), 43.3 (*C*H_2CO), 20.8 (C(O)*C*H_3), 20.7 (C(O)*C*H_3), 13.3 (C≡C*C*H_2), 3.5 (*C*H_3); *m/z* (ESI$^+$) 571 (52 %, [2M+K]$^+$), 555 (89, [2M+Na]$^+$), 305 (33, [M+K]$^+$), 289 (100, [M+Na]$^+$), 267 (28, [M+H]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 289.1042, $C_{14}H_{18}NaO_5$ requires 289.1046 (1.64 ppm).

2.2.2. Synthesis and characterisation of 35

5-(Pent-3-yn-1-yl)-3-furyl]methanol **35**

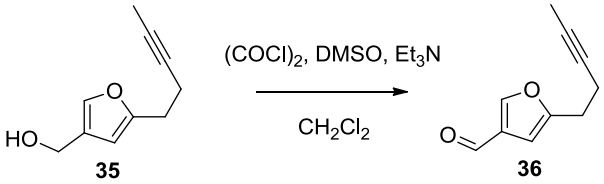


34 **35**

To a solution of 2-(acetoxymethyl)-4-oxonon-2-en-7-yn-1-yl acetate **34** (18.0 g, 67.6 mmol) in ethanol (1650 mL) at room temperature was added 1 M aq. HCl (67.6 mL, 67.6 mmol). The resulting pale yellow solution was heated to 65 °C for 15 h before being cooled to room temperature. The reaction was concentrated to ~800 mL and poured into water (600 mL) and neutralised with solid K_2CO_3. The solution was extracted with CH_2Cl_2 (3 x 500 mL), dried (Na_2SO_4) and concentrated to give a crude oil which was purified by column chromatography (3:1 petroleum ether : diethyl ether) to yield [5-(pent-3-yn-1-yl)-3-furyl]methanol **35** as an orange oil (7.8 g, 71%): ν_{max}(film)/cm^{-1} 3421 (O-H), 2920 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 1H, C*H*(5-furan)), 6.10 (s, 1H, C*H*(3-furan)), 4.45 (s, 2H, CH_2OH), 2.76 (t, *J* = 7.6 Hz, 2H, furan-CH_2), 2.46-2.39 (m, 2H, C≡CCH_2), 2.17 (s, 1H, O*H*), 1.75 (t, *J* = 2.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 155.6 (*C*(furan)), 138.3 (*C*(furan)), 125.8 (*C*(furan)), 105.7 (*C*(furan)), 78.0 (*C*≡C), 76.3 (C≡*C*), 56.7 (*C*H$_2$OH), 28.0 (furan-*C*H$_2$), 17.8 (C≡C*C*H$_2$), 3.5 (*C*H$_3$); *m/z* (ESI$^+$) 165 (3 %, [M+H]$^+$); HRMS *m/z* (TOF FI$^+$) found [M]$^+$ 164.0840, $C_{10}H_{12}O_2$ requires 164.0837.

2.2.3. Synthesis and characterisation of 36

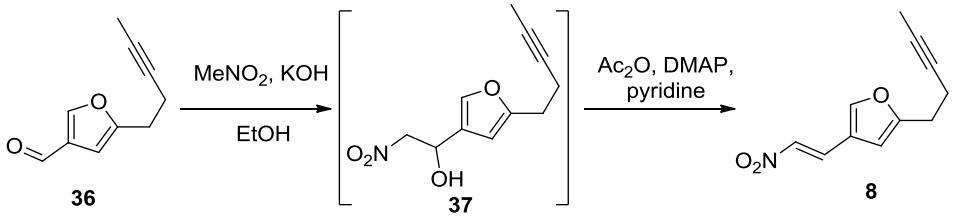
5-(Pent-3-yn-1-yl)-3-furaldehyde **36**



DMSO (7.53 mL, 106 mmol) was added dropwise over 5 minutes to a solution of oxalyl chloride (4.63 mL, 53 mmol) in CH_2Cl_2 (116 mL) cooled to -78 °C and the resulting solution stirred for 10 minutes at this temperature. A solution of [5-(pent-3-yn-1-yl)-3-furyl]methanol **35** (8.30 g, 51 mmol) in CH_2Cl_2 (84 mL) was added dropwise and the solution stirred for a further 15 minutes at -78 °C before triethylamine (35.20 mL, 252 mmol) was added and the solution warmed to room temperature over 0.5 h. The reaction mixture was partitioned with water (90 mL) and the aqueous phase was back extracted with CH_2Cl_2 (3 x 80 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give the crude aldehyde which was purified by column chromatography (5:1 → 2:1 petroleum ether : diethyl ether), yielding 5-(pent-3-yn-1-yl)-3-furaldehyde **36** as a yellow oil (7.36 g, 90%): ν_{max}(film)/cm^{-1} 3124 (C-H), 2920 (C-H), 1686 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H, C(O)*H*), 7.94 (s, 1H, C*H*(5-furan)), 6.46 (s, 1H, C*H*(3-furan)), 2.81 (t, *J* = 7.3 Hz, 2H, furan-CH_2), 2.48-2.42 (m, 2H, C≡CCH_2), 1.75 (t, *J* = 2.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 184.6 (C=O), 157.7 (*C*(furan)), 150.6 (*C*(furan)), 129.5 (*C*(furan)), 102.7 (*C*(furan)), 77.2 (*C*≡C), 76.8 (C≡*C*), 27.7 (furan-*C*H_2), 17.5 (C≡C*C*H_2), 3.4 (*C*H_3); *m/z* (ESI$^+$) 185 (37 %, $[M+Na]^+$); HRMS *m/z* (TOF FI$^+$) found $[M]^+$ 162.0685, $C_{10}H_{10}O_2$ requires 162.0681.

2.2.4. Synthesis and characterisation of 8

4-[(*E*)-2-Nitrovinyl]-2-(pent-3-yn-1-yl)furan **8**



To a solution of 5-(pent-3-yn-1-yl)-3-furaldehyde **36** (0.92 g, 5.67 mmol) and nitromethane (0.34 mL, 6.24 mmol) in EtOH (11 mL) cooled to 0 °C was added dropwise KOH (2 M solution in ethanol) (3.12 mL, 6.24 mmol). After 1 h the reaction mixture (yellow suspension) was poured into a vigorously stirred mixture of ice (10 g) and 2 M aq. HCl (5 mL). The resulting slurry was stirred for 10 minutes before being extracted with diethyl ether (3 x 30 mL), dried (Na_2SO_4) and concentrated to give a yellow solid containing a mixture of **37** and **8**. The crude material was purified by column chromatography (8:1 → 1:1 petroleum ether : diethyl ether) to give 4-[(*E*)-2-nitrovinyl]-2-(pent-3-yn-1-yl)furan **8** (0.58 g) as a fluffy yellow solid (R_f 0.65 3:1 petroleum ether : diethyl ether) and 2-nitro-1-[5-(pent-3-yn-1-yl)-3-furyl]ethanol **37** (0.52 g) as an orange oil (R_f 0.22 3:1 petroleum ether : diethyl ether): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H, *CH*(5-furan)), 6.10 (s, 1H, *CH*(3-furan)), 5.41-5.35 (m, 1H, C*H*OH), 4.63 (dd, *J* = 13.4, 9.1 Hz, 1H, C*H*'HNO$_2$), 4.53 (dd, *J* = 13.4, 3.2 Hz, 1H, CH'*H*NO$_2$), 2.78 (t, *J* = 7.9 Hz, 2H, furan-C*H*$_2$), 2.48-2.41 (m, 2H, C≡CC*H*$_2$), 1.77 (t, *J* = 2.6 Hz, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.5 (*C*(furan)), 138.4 (*C*(furan)), 123.9 (*C*(furan)), 103.8 (*C*(furan)), 80.2 (*C*NO$_2$), 77.7 (*C*≡C), 76.6 (C≡*C*), 64.4 (H*C*OH), 27.9 (furan-*C*H$_2$), 17.7 (C≡C*C*H$_2$), 3.5 (*C*H$_3$).

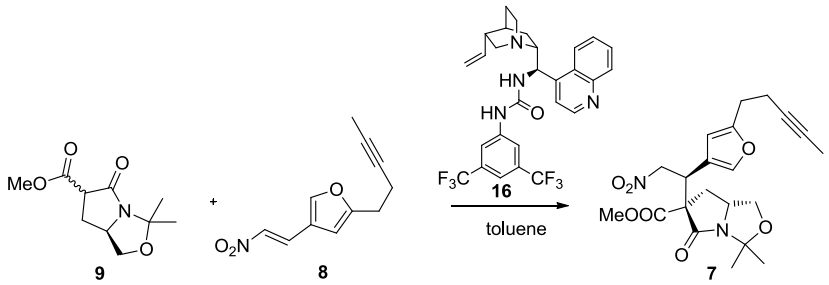
2-Nitro-1-[5-(pent-3-yn-1-yl)-3-furyl]ethanol **37** (0.52 g, 2.23 mmol) was dissolved in pyridine (20 mL) and the solution cooled to 0 °C. Acetic anhydride (0.33 mL, 3.49 mmol) and DMAP (0.05 g, 0.47 mmol) in pyridine (8 mL) were added and the resulting solution stirred for 30 minutes before being quenched with sat. aq. $NaHCO_3$ (50 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 40 mL) and the organic extracts washed with water (40 mL), brine (40 mL), dried (Na_2SO_4) and concentrated until 10 mL of pyridine remained. Attempts to concentrate the crude product fully lead to rapid decomposition. The crude product/pyridine mixture was purified by column chromatography (8:1 → 1:1 petroleum ether : diethyl ether) to give 4-[(*E*)-2-nitrovinyl]-2-(pent-3-yn-1-yl)furan **8** (0.37 g, 82%

overall yield from **36**) as a fluffy yellow solid: mp 91-93 °C; ν_{max}(film)/cm^{-1} 3106, 2923 (C-H), 1640 (C=C), 1490 (NO_2), 1355 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 13.4 Hz, 1H, NO_2C*H*), 7.72 (s, 1H, *CH*(5-furan)), 7.36 (d, *J* = 13.4 Hz, 1H, NO_2CH=C*H*), 6.26 (s, 1H, *CH*(3-furan)), 2.83 (t, *J* = 7.3 Hz, 2H, furan-CH_2), 2.52-2.45 (m, 2H, C≡CCH_2), 1.77 (t, *J* = 2.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 158.0 (*C*(furan)), 146.5 (*C*(furan)), 136.3 (NO_2CH=*C*H), 130.0 (NO_2*C*H=CH), 119.0 (*C*(furan)), 103.0 (*C*(furan)), 77.2 (*C*≡C), 76.9 (C≡*C*), 27.8 (furan-*C*H_2), 17.5 (C≡C*C*H_2), 3.5 (*C*H_3); *m/z* (ESI$^+$) 228 (100%, $[M+Na]^+$); HRMS *m/z* (TOF FI$^+$) found $[M]^+$ 205.0744, $C_{11}H_{11}NO_3$ requires 205.0739.

2.3. Route to (–)-nakadomarin A

2.3.1. Synthesis and characterisation of 7

Methyl (6*S*,7a*R*)-3,3-dimethyl-6-{(1*S*)-2-nitro-1-[5-(pent-3-yn-1-yl)-3-furyl]ethyl}-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate **7**

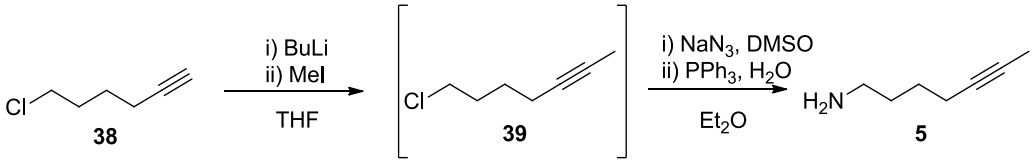


To a solution of 4-[(*E*)-2-nitrovinyl]-2-(pent-3-yn-1-yl)furan **8** (1.20 g, 5.85 mmol) and methyl (6*R*,*S*, 7aR)-3,3-dimethyl-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate **9** (2.49 g, 11.70 mmol) in toluene (19.5 mL) was added catalyst **16** (0.32 g, 0.58 mmol). The reaction was stirred at 30 °C for 52 h before being concentrated and purified by column chromatography (9:1 → 3:7 petroleum ether : diethyl ether). The title compound was obtained as a yellow crystalline solid (dr = 18:1) which was further purified by recrystallisation from diethyl ether cooled to -30 °C. Further purification of the mother liquors were also required in a similar manner to give methyl (6*S*,7a*R*)-3,3-dimethyl-6-{(1*S*)-2-nitro-1-[5-(pent-3-yn-1-yl)-3-furyl]ethyl}-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate **7** as a colourless crystalline solid (1.99 g, 81%, single diastereoisomer): mp 90-92 °C; $[\alpha]_D^{26}$ = + 10.8 (*c* 0.25, $CHCl_3$); ν_{max}(film)/cm^{-1} 2985 (C-H), 2921 (C-H), 1738 (C=O), 1696 (C=O), 1555 (NO_2), 1380 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H, C*H*(5-furan)), 6.09 (s, 1H, C*H*(3-furan)), 4.96 (dd, *J* = 13.3, 3.8 Hz, 1H, $NO_2CH'H$), 4.89 (dd, *J* = 13.3, 10.7 Hz, 1H, $NO_2CH'H$), 4.07 (dd, *J* = 10.7, 3.8 Hz, 1H, C*H*-furan), 3.91 - 3.88 (m, 1H, CHC*H*H'O), 3.82 (s, 3H, CH_3O), 3.44 - 3.37 (m, 2H, C*H*N, CHCH*H*'O), 2.74 (t, *J* = 7.2 Hz, 2H, furan-CH_2), 2.52 - 2.35 (m, 2H, C≡CCH_2), 2.22 - 2.15 (m, 2H, CH_2CHN), 1.74 (t, *J* = 2.5 Hz, 3H, alkyne-CH_3), 1.68 (s, 3H, CCH_3), 1.45 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.7 (*C*=O), 167.2 (*C*=O), 156.2 (*C*(furan)), 140.6 (*C*(furan)), 119.6 (*C*(furan)), 105.4 (*C*(furan)), 91.9 (N*C*(CH_3)$_2$O), 77.5 (*C*≡C), 76.8 (C≡*C*), 76.6 (NO_2CH_2), 70.0 (CH_2O), 63.5 (*C*(quat)), 58.7 (CH_2CHN), 53.4 (OCH_3), 38.8 (*C*H-furan), 33.4 (CH_2CHN), 27.9 (furan-CH_2), 26.2 (CCH_3), 23.3 (CCH_3), 17.6 (C≡CCH_2), 3.3 (alkyne-CH_3); *m/z* (ESI^+) 859 (100%,

$[2M+Na]^+$), 441 (34, $[M+Na]^+$), 419 (91, $[M+H]^+$]; HRMS *m/z* (ESI^+) found $[M+Na]^+$ 441.1638, $C_{21}H_{26}N_2NaO_7$ requires 441.1632.

2.3.2. Synthesis and characterisation of 5

Hept-5-yne amine **5**

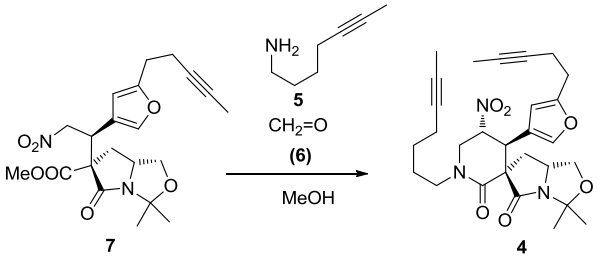


6-Chlorohex-1-yne **38** (7.28 mL, 7 g, 60 mmol) was dissolved in THF (90 mL) and cooled to 0 °C. Butyllithium (56.3 ml, 90 mmol, 1.6 M in hexanes) was added dropwise, and the solution stirred at 0 °C for 1 h before methyl iodide (5.98 mL, 13.6 g, 96 mmol) was added slowly and the solution warmed to room temperature over 30 minutes. The reaction was quenched with sat. aq. $NHCl_4$, (100 mL) extracted with diethyl ether (2 x 150 mL) and the organic phase dried (Na_2SO_4) and concentrated to give crude 7-chlorohept-2-yne **39**, which was used without further purification.

7-Chlorohept-2-yne **39** (7.00 g, 54 mmol) was dissolved in DMSO (50 mL) at ambient temperature. To this solution was added sodium azide (10.45 g, 161 mmol) portionwise and the reaction heated to 50 °C for 6 h after which it was cooled to ambient temperature and water (100 mL) and diethyl ether (50 mL) added. The organic phase was separated and the DMSO-water phase extracted further with diethyl ether (3 x 50 mL). The combined organics were then washed with water (40 mL) and brine (40 mL) before being dried ($MgSO_4$). The azide/ether solution was used without concentration or further purification. To this solution was added triphenylphosphine (22.60 g, 86 mmol) in small portions over 30 minutes. Water (3.87 mL, 215 mmol) was added and the reaction mixture was stirred at room temperature for 14 h. 1 M aq. HCl (70 ml) was added and the aqueous phase and the organic phase separated. The aqueous was washed with diethyl ether (2 x 50 mL) before being basified by the addition of 1 M aq. NaOH until pH 14 was reached. The aqueous phase was extracted with diethyl ether (3 x 60 mL) and the organic extracts dried (Na_2SO_4) and fractionally distilled to afford hept-5-yn-1-amine **5** as a colourless liquid (3.40 g, 51 %) with data in good agreement with literature[6],[7]: bp 90-92 ºC/30 mbar; lit[6]. bp 95-98 ºC/25 Torr); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.76 - 2.63 (m, 2H, CH_2NH$_2$), 2.21 - 2.07 (m, 2H, alkyne-CH_2), 1.83 - 1.73 (m, 3H, alkyne-CH_3), 1.60 - 1.45 (m, 4H, 2 x CH_2), 1.26 - 1.15 (m, 2H, NH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 79.5 (*C*≡C), 76.1 (C≡*C*), 42.3 (NH$_2$*C*H$_2$), 33.5 (*C*H$_2$), 26.8 (*C*H$_2$), 19.1 (*C*H$_2$), 3.9 (*C*H$_3$).

2.3.3. Synthesis and characterisation of 4

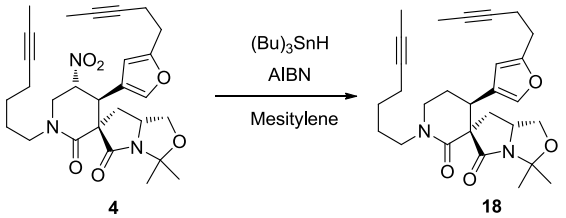
(3*R*,4*S*,5*R*,7a'*R*)-1-(Hept-5-yn-1-yl)-3',3'-dimethyl-5-nitro-4-[5-(pent-3-yn-1-yl)-3-furyl]dihydro-1'*H*,2*H*-spiro[piperidine-3,6'-pyrrolo[1,2-*c*][1,3]oxazole]-2,5'-dione **4**



A solution of methyl (6*S*,7a*R*)-3,3-dimethyl-6-{(1*S*)-2-nitro-1-[5-(pent-3-yn-1-yl)-3-furyl]ethyl}-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate **7** (0.60 g, 1.43 mmol), hept-5-yn-1-amine **5** (0.24 g, 2.15 mmol) and formaldehyde (**6**) (37 % solution in water) (0.161 mL, 2.15 mmol) in MeOH (30 mL) was refluxed for 8 h (a deep purple solution was formed after 5-10 minutes before slowly forming a dark brown solution). The solution was cooled to room temperature and concentrated before being purified by column chromatography (9:1 petroleum ether : diethyl ether → 100 % diethyl ether) to afford the title compound **4** as a brown oil (0.38 g, 52%): $[\alpha]_D^{26}$ = + 91.8 (*c* 0.34, $CHCl_3$); ν_{max}(film)/cm^{-1} 2920 (C-H), 1690 (C=O), 1650 (C=O), 1556 (NO_2), 1349 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 0.6 Hz, 1H, C*H*(5-furan)), 6.14 (d, *J* = 0.6 Hz, 1H, C*H*(3-furan)), 5.90 (ddd, *J* = 12.0, 9.4, 6.4 Hz, 1H, NO_2CH), 4.02 (dd, *J* = 12.0, 6.4 Hz, 1H, NC*H*H'), 3.90 (dd, *J* = 7.8, 5.2 Hz, 1H, CHC*H*H'O), 3.86 - 3.78 (m, 1H, NCH*H*'), 3.62 - 3.48 (m, 3H, NC*H*H', C*H*-furan, CHCH*H*'O), 3.47 - 3.35 (m, 2H, C*H*N, NCH*H*'), 3.02 (dd, *J* = 13.1, 7.2 Hz, 1H, C*H*H'CHN), 2.78 - 2.71 (m, 2H, furan-CH_2), 2.48 - 2.38 (m, 2H, C≡CCH_2), 2.23 - 2.12 (m, 2H, C≡CCH_2), 1.92 (dd, *J* = 13.2, 7.3 Hz, 1H, CH*H*'CHN), 1.78 (t, *J* = 2.5 Hz, 3H, alkyne-CH_3), 1.76 (t, *J* = 2.5 Hz, 3H, alkyne-CH_3), 1.74 - 1.65 (m, 2H, $NCH_2CH_2CH_2$), 1.59 (s, 3H, CCH_3), 1.55 - 1.45 (m, 2H, $NCH_2CH_2CH_2$), 1.36 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.2 (*C*=O), 167.2 (*C*=O), 156.2 (*C*(furan)), 140.1 (*C*(furan)), 118.7, (*C*(furan)), 105.3 (*C*(furan)), 91.5 (N*C*$(CH_3)_2$O), 81.3 (NO_2CH) 78.5 (*C*≡C), 77.4 (C≡*C*), 76.7 (*C*≡C), 76.1 (C≡*C*), 69.7 (*C*H_2O), 62.9 (*C*(quat)), 58.7 (CH_2CHN), 49.3 (*C*H_2N), 47.9 (*C*H_2N), 42.9 (*C*H-furan), 31.6 (*C*H_2CHN), 27.9 (furan-*C*H_2), 26.1 (C*C*H_3), 25.9 ($NCH_2CH_2CH_2$), 25.8 ($NCH_2CH_2CH_2$), 23.3 (C*C*H_3), 18.4 (C≡C*C*H_2), 17.6 (C≡C*C*H_2), 3.5 (alkyne-CH_3), 3.3 (alkyne-*C*H_3); *m/z* (ESI^+) 532 (100 %, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 532.2415, $C_{28}H_{35}N_3NaO_6$ requires 532.2418.

2.3.4. Synthesis and characterisation of 18

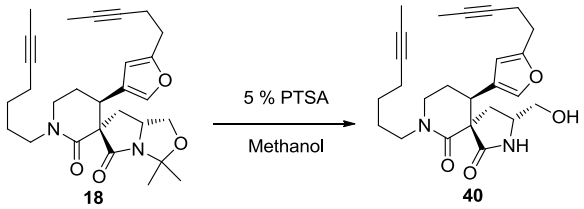
(3*R*,4*S*,7a'*R*)-1-(Hept-5-yn-1-yl)-3',3'-dimethyl-4-[5-(pent-3-yn-1-yl)-3-furyl]dihydro-1'*H*,2*H*-spiro[piperidine-3,6'-pyrrolo[1,2-*c*][1,3]oxazole]-2,5'-dione **18**



(3*R*,4*S*,5*R*,7a'*R*)-1-(Hept-5-yn-1-yl)-3',3'-dimethyl-5-nitro-4-[5-(pent-3-yn-1-yl)-3-furyl] dihydro-1'*H*,2*H*-spiro[piperidine-3,6'-pyrrolo[1,2-*c*][1,3]oxazole]-2,5'-dione **4** (4.84 g, 9.50 mmol) was dissolved in freshly distilled mesitylene (215 mL). To this was added AIBN (0.31 g, 1.90 mmol) and tributyltin hydride (12.77 mL, 47.48 mmol) and the mixture degassed by repeated cycles of vacuum/argon purge. The reaction was then heated rapidly to reflux in a pre-heated oil bath for 2.5 h before being cooled to room temperature. The reaction mixture was loaded directly onto silica and the mesitylene and excess tin compounds eluted with petroleum ether before ramping the solvent system (2:1 petroleum ether : diethyl ether → diethyl ether 100 %), to obtain the title compound **18** as a pale yellow oil (2.87 g, 65%): $[\alpha]_D^{24}$ = + 117.0 (*c* 1.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 2982 (C-H), 2936 (C-H), 1692 (C=O), 1634 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H, C*H*(5-furan)), 6.09 (s, 1H, C*H*(3-furan)), 3.85 (dd, *J* = 7.3, 5.1 Hz, 1H, C*H*H'O), 3.57 - 3.27 (m, 6H, 2 x CH_2N, CH_2C*H*N, CH*H*'O), 2.97 (dd, *J* = 12.8, 7.2 Hz, 1H, C*H*H'CHN), 2.94 - 2.85 (m, 2H, C*H*-furan, furan-CHC*H*H'), 2.76 - 2.70 (m, 2H, furan-CH_2), 2.45 - 2.36 (m, 2H, C≡CCH_2), 2.18 - 2.09 (m, 2H, C≡CCH_2), 1.83 (dd, *J* = 12.8, 6.9 Hz, 1H, CH*H*'CHN), 1.76 – 1.71 (m, 7H, 2 x alkyne-CH_3, furan-CHCH*H'*), 1.71 - 1.61 (m, 2H, NCH$_2$CH_2CH$_2$), 1.58 (s, 3H, CCH_3), 1.53 - 1.41 (m, 2H, NCH$_2$CH$_2$CH_2), 1.27 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.4 (*C*=O), 168.6 (*C*=O), 155.2 (*C*(furan)), 138.0 (*C*(furan)), 124.7, (*C*(furan)), 105.9 (*C*(furan)), 91.1 (NC(CH$_3$)$_2$O), 78.8 (*C*≡C), 77.7 (C≡*C*), 76.4 (*C*≡C), 75.7 (C≡*C*), 69.9 (*C*H$_2$O), 63.3 (*C*(quat)), 58.5 (CH$_2$*C*HN), 47.9 (*C*H$_2$N), 47.3 (*C*H$_2$N), 40.0 (*C*H-furan), 33.0 (*C*H$_2$CHN), 27.9 (furan-*C*H$_2$), 26.2 (C*C*H$_3$), 2 x 26.1 (NCH$_2$*C*H$_2$CH$_2$, NCH$_2$CH$_2$*C*H$_2$), 25.2 (furan-CH*C*H$_2$), 23.3 (C*C*H$_3$), 18.4 (C≡C*C*H$_2$), 17.7 (C≡C*C*H$_2$), 3.5 (alkyne-CH$_3$), 3.4 (alkyne-*C*H$_3$); *m/z* (ESI$^+$) 951 (100 %, [2M+Na]$^+$), 487 (99, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 487.2565, $C_{28}H_{36}N_2NaO_4$ requires 487.2567.

2.3.5. Synthesis and characterisation of 40

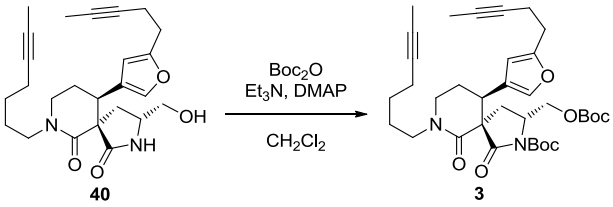
(3*R*,5*S*,10*S*)-7-(Hept-5-yn-1-yl)-3-(hydroxymethyl)-10-[5-(pent-3-yn-1-yl)-3-furyl]-2,7-diazaspiro[4.5]decane-1,6-dione **40**



PTSA (7.16 mg, 0.03 mmol) was added to a solution of (3*R*,4*S*,7a'*R*)-1-(hept-5-yn-1-yl)-3',3'-dimethyl-4-[5-(pent-3-yn-1-yl)-3-furyl]dihydro-1'*H*,2*H*-spiro[piperidine-3,6'-pyrrolo[1,2*c*][1,3]oxazole]-2,5'-dione **18** (0.35 g, 0.75 mmol) in methanol (34 mL) and the solution heated at reflux for 4 h. A further addition of PTSA (2 mg, 0.01 mmol) was required after this time. After heating at reflux for a further 1 h, the solution was cooled to room temperature, concentrated and purified by column chromatography (diethyl ether 100 % → 9:1 diethyl ether : methanol) to yield the title compound **40** as a colourless oil (0.25 g, 87%): $[\alpha]_D^{26}$ = + 112.2 (*c* 0.18, $CHCl_3$); ν_{max}(film)/cm^{-1} 3271 (O-H), 2919 (C-H), 2862 (C-H), 1692 (C=O), 1619 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H, C*H*(5-furan)), 6.71 (br. s., 1H, N*H*), 6.10 (s, 1H, C*H*(3-furan)), 4.52 (t, *J* = 5.4 Hz, 1H, O*H*), 3.56 - 3.51 (m, 2H, CH_2O), 3.51 - 3.35 (m, 3H, NCH_2, NC*H*H'), 3.32 - 3.18 (m, 2H, CH_2C*H*NH, NCH*H*'), 3.10 - 2.96 (m, 1H, furan-CHC*H*H'), 2.84 (dd, *J* = 13.3, 2.4 Hz, 1H, furan-C*H*), 2.73 (t, *J* = 7.5 Hz, 2H, furan-CH_2), 2.62 (dd, *J* = 13.5, 5.7 Hz, 1H, C*H*H'CHNH), 2.40 (td, *J* = 7.5, 2.5 Hz, 2H, C≡CCH_2), 2.18 - 2.10 (m, 2H, C≡CCH_2), 2.05 (dd, *J* = 13.5, 9.0 Hz, 1H, CH*H*'CHNH), 1.75 (s, 7H, alkyne-CH_3, furan-CHCH*H'*), 1.69 - 1.57 (m, 2H, $NCH_2CH_2CH_2$), 1.53 - 1.37 (m, 2H, $NCH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.8 (*C*=O), 170.6 (*C*=O), 155.3 (*C*(furan)), 138.3 (*C*(furan)), 124.3, (*C*(furan)), 106.1 (*C*(furan)), 78.7 (*C*≡C), 77.9 (C≡*C*), 76.2 (*C*≡C), 75.9 (C≡*C*), 65.7 (CH_2O), 55.9 (*C*(quat)), 53.2 (CH_2CHN), 48.1 (CH_2N), 47.6 (CH_2N), 40.5 (*C*H-furan), 34.0 (CH_2CHN), 28.0 (furan-CH_2), 26.1 ($NCH_2CH_2CH_2$), 26.0 ($NCH_2CH_2CH_2$), 25.3 (furan-CHCH_2) 18.5 (C≡CCH_2), 17.9 (C≡CCH_2), 3.5 (alkyne-CH_3), 3.4 (alkyne-CH_3); *m/z* (ESI$^+$) 871 (100%, $[2M+Na]^+$), 447 (78, $[M+Na]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 447.2256, $C_{25}H_{32}N_2NaO_4$ requires 447.2254.

2.3.6. Synthesis and characterisation of 3

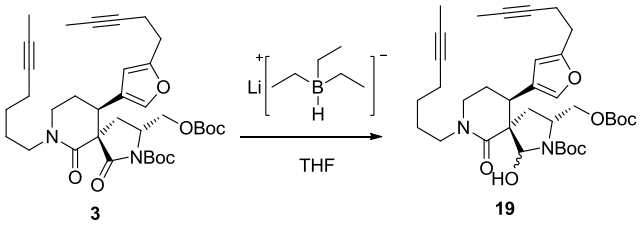
tert-Butyl (3*R*,5*R*,10*S*)-3-{[(*tert*-butoxycarbonyl)oxy]methyl}-7-(hept-5-yn-1-yl)-1,6-dioxo-10-[5-(pent-3-yn-1-yl)-3-furyl]-2,7-diazaspiro[4.5]decane-2-carboxylate **3**



To a solution of (3*R*,5*S*,10*S*)-7-(hept-5-yn-1-yl)-3-(hydroxymethyl)-10-[5-(pent-3-yn-1-yl)-3-furyl]-2,7-diazaspiro[4.5]decane-1,6-dione **40** (1.77 g, 4.17 mmol) in CH_2Cl_2 (85 mL) was added DMAP (0.05 g, 4.17 mmol) and triethylamine (2.90 mL, 20.87 mmol) before the portionwise addition of di-*tert*-butyl dicarbonate (4.54 g, 20.80 mmol). The solution was stirred for 15 h at room temperature. The dark yellow solution formed was concentrated and purified by column chromatography (9 : 1 → 1 : 4 petroleum ether : diethyl ether), to give the title compound **3** as a colourless oil (2.29 g, 88%): $[\alpha]_D^{26}$ = + 88.3 (*c* 0.41, $CHCl_3$); ν_{max}(film)/cm^{-1} 2973 (C-H), 2935 (C-H), 1778 (C=O), 1743 (C=O), 1639 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H, C*H*(5-furan)), 5.97 (s, 1H, C*H*(3-furan)), 4.42 (dd, *J* = 9.9, 4.3 Hz, 1H, C*H*H'O), 4.16 (dd, *J* = 9.8, 8.6 Hz, 1H, CH*H*'O), 3.82 (App. tt, *J* = 8.9, 4.6 Hz, 1H, CH_2C*H*N), 3.50 - 3.40 (m, 3H, NCH_2, NC*H*H'), 3.32 – 3.28 (m, 1H, NCH*H*'), 3.07 - 2.92 (m, 1H, furan-CHC*H*H'), 2.92 - 2.82 (m, 1H, furan-C*H*), 2.75 - 2.67 (m, 3H, C*H*H'CHN, furan-CH_2), 2.46 - 2.33 (m, 2H, C≡CCH_2), 2.17 - 2.13 (m, 2H, C≡CCH_2), 2.08 dd, *J* = 13.6, 9.3 Hz, 1H, CH*H*'CHN), 1.78 - 1.74 (m, 7H, 2 x alkyne-CH_3, furan-CHCH*H'*), 1.69 - 1.65 (m, 2H, NCH$_2$CH_2CH$_2$), 1.51 - 1.44 (m, 20H, 2 x (C(CH_3)$_3$, NCH$_2$CH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.8 (*C*=O), 167.7 (*C*=O), 155.7 (*C*(furan)), 153.0 (C=O), 149.3 (C=O), 138.5 (*C*(furan)), 123.9 (*C*(furan)), 105.5 (*C*(furan)), 83.3 (*C*(CH$_3$)$_3$), 82.1 (*C*(CH$_3$)$_3$) 78.8 (*C*≡C), 77.7 (C≡*C*), 76.3 (*C*≡C), 75.8 (C≡*C*), 68.1 (*C*H$_2$O), 57.0 (*C*(quat)), 53.4 (CH$_2$*C*HN), 47.9 (*C*H$_2$N), 47.3 (C*H*$_2$N), 41.6 (*C*H-furan), 31.3 (*C*H$_2$CHN), 28.1 (furan-*C*H$_2$), 27.9 (3 x C*C*H$_3$), 27.7 (3 x C*C*H$_3$), 26.1 (NCH$_2$*C*H$_2$CH$_2$), 26.1 (NCH$_2$CH$_2$*C*H$_2$), 25.1 (furan-CH*C*H$_2$) 18.5 (C≡C*C*H$_2$), 17.9 (C≡C*C*H$_2$), 3.5 (alkyne-CH$_3$), 3.4 (alkyne-*C*H$_3$); *m/z* (ESI$^+$) 647 (100%, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 647.3305, $C_{35}H_{48}N_2NaO_8$ requires 647.3303.

2.3.7. Synthesis and characterisation of 19

tert-Butyl (1*R*,*S*, 3*R*,5*S*,10*S*)-3-{[(*tert*-butoxycarbonyl)oxy]methyl}-7-(hept-5-yn-1-yl)-1-hydroxy-6-oxo-10-[5-(pent-3-yn-1-yl)-3-furyl]-2,7-diazaspiro[4.5]decane-2-carboxylate **19**

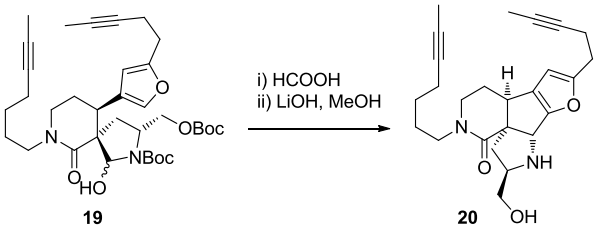


3 19

To a solution of *tert*-butyl (3*R*,5*R*,10*S*)-3-{[(*tert*-butoxycarbonyl)oxy]methyl}-7-(hept-5-yn-1-yl)-1,6-dioxo-10-[5-(pent-3-yn-1-yl)-3-furyl]-2,7-diazaspiro[4.5]decane-2-carboxylate **3** (0.34 g, 0.54 mmol) in THF (14 mL) was added dropwise lithium triethylborohydride (1.25 mL, 1.25 mmol, 1 M solution in THF) at -78 ºC and the solution stirred at this temperature for 2 h before being quenched with sat. aq. NH_4Cl solution (15 mL). The reaction was allowed to warm to room temperature over 1 h and then diluted with diethyl ether (15 mL). The aqueous layer was extracted and the organics dried (Na_2SO_4) and concentrated. The crude oil was purified by column chromatography (95 : 5 petroleum ether : diethyl ether → 1 : 1.5 petroleum ether : diethyl ether) to yield the title compound **19** as a colourless oil (0.27 g, 79%): The ^{1}H NMR spectrum of the title compound suffers from considerable broadening due to rotamers when run in $CDCl_3$ at 298 K. Attempts to improve this spectrum by collecting the data in toluene-d_8 at 363 K resulted in decomposition of the compound. The compound was therefore used in the next step without full characterisation: ^{1}H NMR (400 MHz, $CDCl_3$) (rotameric) δ 7.11 (br. s, 1H), 5.92 - 5.85 (m, 1H), 5.35 (br. s, 1H), 4.46 (br. s, 1H), 4.09 - 3.97 (m, 2H), 3.53 - 3.32 (m, 4H), 2.75 (t, *J* = 7.3 Hz, 3H), 2.42 (td, *J* = 2.6, 7.4 Hz, 3H), 2.23 - 2.12 (m, 3H), 1.82 - 1.75 (m, 6H), 1.75 - 1.61 (m, 3H), 1.48 (s, 13H), 1.44 - 1.32 (m, 8H); *m/z* (ESI$^+$) 649 (100%, $[M+Na]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 649.3454, $C_{35}H_{50}N_2NaO_8$ requires 649.3459 (0.8 ppm).

2.3.8. Synthesis and characterisation of 20

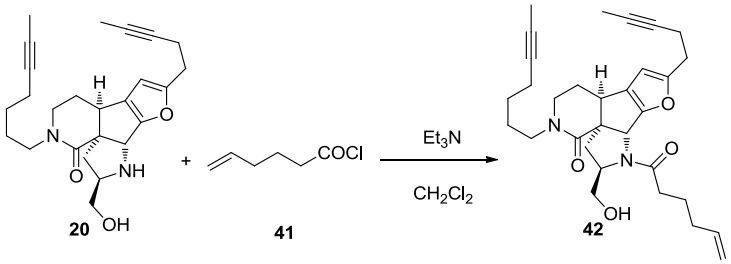
(2*R*,3a*S*,7a*S*,10b*R*)-5-(Hept-5-yn-1-yl)-2-(hydroxymethyl)-9-(pent-3-yn-1-yl)-1,2,3,5,6,7,7a,10b-octahydro-4*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridin-4-one **20**



tert-Butyl (1*R*,*S*, 3*R*,5*S*,10*S*)-3-{[(*tert*-butoxycarbonyl)oxy]methyl}-7-(hept-5-yn-1-yl)-1-hydroxy-6-oxo-10-[5-(pent-3-yn-1-yl)-3-furyl]-2,7-diazaspiro[4.5]decane-2-carboxylate **19** (1.00 g, 1.60 mmol) was dissolved in formic acid (15.80 mL) and the solution stirred at room temperature for 15 h before being concentrated to a crude oil. The crude oil was dissolved in methanol (37 mL) and $LiOH.H_2O$ (1.30 g, 31.91 mmol) added. The reaction was heated to 50 ºC for 5 h before being concentrated to approximately 20 % of the original volume. Water (30 mL) was added and the product extracted with 4:1 chloroform:IPA (5 x 55 mL). The organics were dried (Na_2SO_4) and concentrated to give a brown oil, which was purified by column chromatography (ethyl acetate 100% → 9 : 1 ethyl acetate : methanol) to give the tetracyclic product **20** as a pale yellow oil (0.56 g, 86%): $[\alpha]_D^{26}$ = - 78.1 (*c* 0.32, $CHCl_3$); ν_{max}(film)/cm^{-1} 3301 (O-H), 2920 (C-H), 2860 (C-H), 1615 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 1H, C*H*(4-furan)), 4.72 (s, 1H, furan-C*H*NH), 3.84 (dd, *J* = 11.3, 3.6 Hz, 1H, C*H*H'O), 3.74 (dd, *J* = 11.3, 3.9 Hz, 1H, CH*H*'O), 3.42 (td, *J* = 7.3, 1.5 Hz, 2H, CH_2N), 3.36 - 3.26 (m, 2H, CH_2N), 3.26 - 3.19 (m, 1H, CH_2C*H*NH), 3.14 - 3.05 (m, 1H, furan-C*H*), 2.80 (t, *J* = 7.6 Hz, 2H, furan-CH_2), 2.51 - 2.41 (m, 2H, C≡CCH_2), 2.36 (dd, *J* = 12.8, 8.7 Hz, 1H, C*H*H'CHNH), 2.22 - 2.09 (m, 3H, C≡CCH_2, furan-CHC*H*H'), 1.91 (dd, *J* = 12.8, 7.4 Hz, 1H, CH*H*'CHNH), 1.83-1.76 (m, 6H, alkyne-CH_3), 1.70 - 1.57 (m, 3H, NCH_2CH_2CH_2, furan-CHCH*H*'), 1.52 - 1.39 (m, 2H, NCH_2CH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.5 (*C*=O), 160.7 (*C*(furan)), 154.6 (*C*(furan)), 128.9, (*C*(furan)), 102.5 (*C*(furan)), 78.7 (*C*≡C), 78.0 (C≡*C*), 76.2 (*C*≡C), 75.8 (C≡*C*), 69.0 (furan-*C*HNH), 65.8 (*C*(quat)), 62.6 (*C*H_2O), 61.3 (CH_2*C*HN), 47.5 (*C*H_2N), 47.3 (CH_2N), 43.7 (*C*H-furan), 43.1 (*C*H_2CHN), 29.6 (furan-CH*C*H_2), 28.8 (furan-*C*H_2), 26.5 (NCH_2*C*H_2CH_2), 26.1 (NCH_2CH_2*C*H_2) 18.4 (C≡C*C*H_2), 17.8 (C≡C*C*H_2), 3.5 (alkyne-CH_3), 3.4 (alkyne-*C*H_3); *m/z* (ESI$^+$) 839 (95%, $[2M+Na]^+$), 817 (100, $[2M+H]^+$), 409 (96, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 431.2306, $C_{25}H_{32}N_2NaO_3$ requires 431.2305.

2.3.9. Synthesis and characterisation of 42

(2*R*,3a*S*,7a*S*,10b*R*)-5-(Hept-5-yn-1-yl)-1-(hex-5-enoyl)-2-(hydroxymethyl)-9-(pent-3-yn-1-yl)-1,2,3,5,6,7,7a,10b-octahydro-4*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta [1,2-*c*] pyridin-4-one **42**

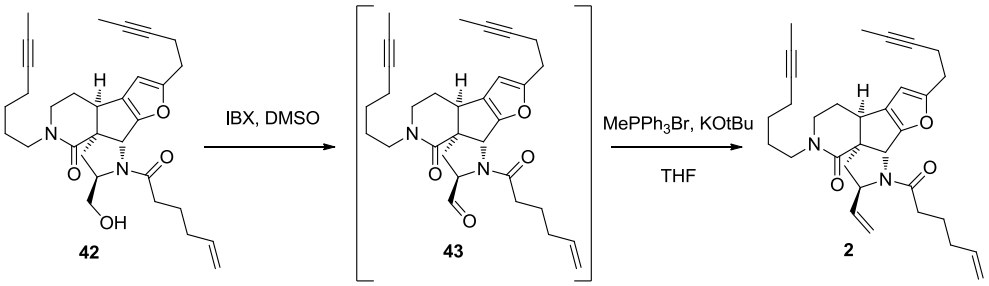


Tetracycle **20** (0.475 g, 1.16 mmol) and triethylamine (810 µL, 5.81 mmol) were dissolved in CH_2Cl_2 (24 mL) and the resulting solution was cooled to -20 °C. A solution of hex-5-enoyl chloride **41** (159 µL, 1.22 mmol) in CH_2Cl_2 (9 mL) pre-cooled to -20 °C was added and the reaction mixture warmed to room temperature over 0.5 h. After stirring at room temperature for 3 h the solution was concentrated under reduced pressure and purified by column chromatography (100% ethyl acetate) to give amide **42** as a colourless oil (0.520 g, 89%): $[\alpha]_D^{25}$ = - 0.82 (*c* 0.51, $CHCl_3$); ν_{max}(film)/cm^{-1} 3340 (O-H), 2920 (C-H), 2859 (C-H), 1634 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (s, 1H, C*H*(4-furan)), 5.90 - 5.75 (m, 1H, C*H*=CH_2), 5.26 (s, 1H, furan-C*H*N), 5.10 – 4.95 (m, 2H, CH=C*H*$_2$), 4.01 – 3.91 (m, 1H, CH_2C*H*N), 3.81 (dd, *J* = 12.5, 6.9 Hz, 1H, C*H*H'OH), 3.71-3.63 (m, 1H, CH*H*'OH), 3.43 (ddd, *J* = 13.7, 7.3, 7.0 Hz, 1H, C*H*H'N), 3.36 - 3.26 (m, 1H, CH*H*'N), 3.26 - 3.10 (m, 3H, furan-C*H*, C*H*$_2$N), 2.76 (t, *J* = 7.6 Hz, 2H, furan-C*H*$_2$), 2.72 - 2.64 (m, 1H, NC(O)C*H*H'), 2.60 - 2.50 (m, 1H, NC(O)CH*H*'), 2.45 - 2.37 (m, 2H, C≡CC*H*$_2$), 2.29 (dd, *J* = 12.9, 9.9 Hz, 1H, C*H*H'CHN), 2.18 - 2.08 (m, 5H, C≡CC*H*$_2$, H_2C=CHC*H*$_2$, furan-CHC*H*H'), 2.04 (dd, *J* = 12.9, 6.8 Hz, 1H, CH*H*'CHN), 1.85 - 1.77 (m, 3H, H_2C=CHCH_2C*H*$_2$, furan-CHCH*H*'), 1.77 - 1.72 (m, 6H, 2 x alkyne-C*H*$_3$), 1.59 (qd, *J* = 7.5, 7.3 Hz, 2H, NCH_2C*H*$_2$CH_2), 1.46 - 1.36 (m, 2H, NCH_2C*H*$_2$C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.0 (*C*=O), 171.5 (*C*=O), 161.1 (*C*(furan)), 153.2 (*C*(furan)), 138.1 (*C*H=CH_2), 129.8 (*C*(furan)), 115.1 (CH=*C*H$_2$), 102.7 (*C*(furan)), 78.5 (*C*≡C), 77.5 (C≡*C*), 76.5 (*C*≡C), 75.9 (C≡*C*), 66.6 (furan-*C*HN), 65.3 (*C*(quat)), 64.1 (*C*H_2O), 63.6 (CH_2*C*HN), 47.8 (*C*H_2N), 44.6 (*C*H_2N), 42.4 (*C*H-furan), 40.4 (*C*H_2CHN), 34.2 (NC(O)*C*H_2), 33.2 (H_2C=CH*C*H_2), 28.7 (furan-*C*H_2), 27.8 (furan-CH*C*H_2), 26.3 (NCH_2*C*H_2CH_2), 26.1 (NCH_2CH_2*C*H_2), 24.1 (H_2C=CHCH_2*C*H_2), 18.4 (C≡C*C*H_2), 17.7

(C≡C*C*H$_2$), 3.4 (2 x alkyne-*C*H$_3$); *m/z* (ESI$^+$) 527 (100%, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 527.2876, $C_{31}H_{40}N_2NaO_4$ requires 527.2880.

2.3.10. Synthesis and characterisation of 2

(2*R*,3a*S*,7a*S*,10b*R*)-5-(Hept-5-yn-1-yl)-1-(hex-5-enoyl)-9-(pent-3-yn-1-yl)-2-vinyl-1,2,3,5,6,7,7a,10b-octahydro-4*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*] pyridin-4-one **2**



2-Iodoxybenzoic acid (IBX) (0.512 g, 1.83 mmol) was added to a solution of **42** (0.205 g, 0.41 mmol) in DMSO (20 mL) and the resulting solution stirred at room temperature for 24 h. The solution was poured into sat. aq. $NaHCO_3$ solution (60 mL) and extracted with diethyl ether (4 x 60 mL). The combined organic extracts were washed with water (30 mL), dried (Na_2SO_4) and concentrated to give aldehyde **43** as a yellow oil (200 mg), which was used directly without further purification.

[Preparation of Ylide solution: KO^{t}Bu (0.217 g, 1.93 mmol) was added to $MePPh_3Br$ (0.870 g, 2.44 mmol) in toluene (13.5 mL). The resulting suspension was placed in a sonication bath until a homogenous bright yellow solution had formed (ca. 1 minute). This solution was stirred for 1.5 h at room temperature.]

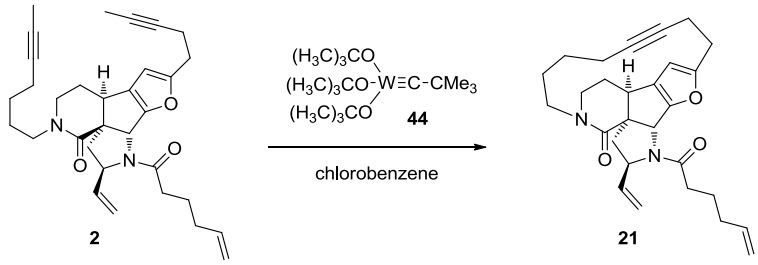
The crude aldehyde **43** was dissolved in THF (13.5 mL) and the solution added rapidly to the above freshly prepared ylide solution, at room temperature. After 15 min TLC analysis indicated complete consumption of starting material. Water (12 mL) was added and THF/toluene were removed under reduced pressure. Water (30 mL) and ethyl acetate (35 mL) were added to the residue. The layers were separated and the aqueous layer was further extracted with ethyl acetate (3 x 35 mL). The combined organic extracts were washed with brine (35 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (2 : 3 ethyl acetate : petroleum ether → 3 : 2 ethyl acetate : petroleum ether) to yield the title compound **2** as a yellow oil (0.150 g, 74% (2 steps)). The compound was rotameric resulting in complex ^{1}H and ^{13}C NMR spectra at 298 K. Data was collected at 373 K. At this temperature ^{1}H NMR and ^{13}C signals coalesced: $[\alpha]_D^{25}$ = - 0.56 (*c* 0.65, $CHCl_3$); ν_{max}(film)/cm^{-1} 2920 (C-H), 2859 (C-H), 1640 (C=O); ^{1}H NMR (500 MHz, 373 K, toluene-d_8) δ 6.48 (ddd, *J* = 17.0, 9.0, 8.7 Hz, 1H), 5.89 - 5.78 (m, 2H), 5.59 (br. s., 1H), 5.10

- 4.93 (m, 4H), 4.32 (br. s., 1H), 3.31 (ddd, *J* = 13.5, 7.1, 6.9 Hz, 1H), 3.23 (ddd, *J* = 13.5, 7.1, 6.9 Hz, 1H), 2.91 - 2.80 (m, 2H), 2.79 - 2.75 (m, 1H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.60-2.49 (m, 2H), 2.43 - 2.30 (m, 3H), 2.19 - 2.12 (m, 2H), 2.12 - 2.06 (m, 2H), 2.06 – 1.98 (m, 1H), 1.97 - 1.84 (m, 2H), 1.77 - 1.70 (m, 1H), 1.64 (t, *J* = 2.5 Hz, 3H), 1.61 (t, *J* = 2.5 Hz, 3H), 1.55-1.48 (m, 2H), 1.43 - 1.34 (m, 3H); ^{13}C NMR (125 MHz, 373 K, toluene-d_8) δ_C 172.0, 171.6, 161.3, 155.6[a], 142.0[b], 139.2, 128.4, 114.8, 113.8, 102.8, 79.2, 78.4, 76.6, 76.0, 66.6, 66.4[c], 62.5, 47.9, 2 x 45.3, 44.2, 34.9, 33.8, 2 x 29.5, 27.2, 27.0, 25.1, 18.9, 18.5, 2 x 3.2; ^{13}C NMR (rotameric) (125 MHz, 298 K, $CDCl_3$) δ_C 172.9, 172.8, 172.1, 171.6, 161.0, 160.8, 155.6, 154.0, 141.3, 139.7, 138.4, 129.2, 127.7, 114.9, 114.9, 114.8, 113.7, 102.7, 102.4, 78.7, 78.6, 78.0, 77.6, 76.5, 76.2, 75.9, 66.4, 65.4, 65.1, 62.3, 62.1, 61.7, 47.8, 47.7, 44.9, 44.8, 44.7, 43.9, 43.4, 42.7, 34.1, 34.1, 33.3, 33.2, 30.0, 29.7, 28.8, 28.8, 28.1, 26.6, 26.4, 26.2, 26.2, 24.2, 24.1, 18.5, 18.5, 17.9, 17.9, 3.5; *m/z* (ESI$^+$) 523 (100%, $[M+Na]^+$), 501 (15, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 523.2928, $C_{32}H_{40}N_2NaO_3$ requires 523.2931.

[a] Quaternary *C*(furan) signal not oberved in ^{13}C NMR spectrum , however it can be seen clearly in the rotameric ^{13}C NMR spectrum (298 K, $CDCl_3$) at 155.6 and 154.0 ppm.
[b] Signal not observed in ^{13}C NMR spectrum, however it can be seen clearly on the HSQC 2D NMR spectrum and in the rotameric ^{13}C NMR spectrum (298 K, $CDCl_3$).
[c] Quaternary *C*(quat) signal not oberved in ^{13}C NMR spectrum , however it can be seen clearly in the rotameric ^{13}C NMR spectrum (298 K, $CDCl_3$) 66.4 ppm.

2.3.11. Synthesis and characterisation of 21

(2*R*,3a*S*,7a*S*,10b*R*)-1-(Hex-5-enoyl)-2-vinyl-2,3,6,7,7a,10b-hexahydro-1*H*-9,5-oct[3]ynofuro[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridin-4-one **21**



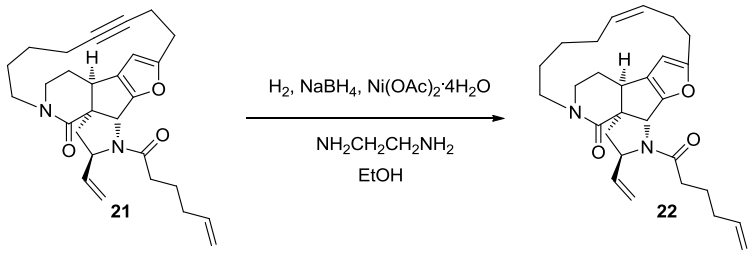
Tris(*t*-butoxy)(2,2-dimethylpropylidyne)tungsten(VI) **44** (10.2 mg, 0.022 mmol) was weighed into a Schlenk tube in a glovebox under an argon atmosphere. The flask was removed from the glovebox and maintained under argon. A solution of diyne **2** (36 mg, 0.072 mmol) in chlorobenzene (40 mL) was added to the catalyst and the reaction mixture heated to 80 ^{o}C under argon for 2 h. The reaction mixture was cooled to room temperature and opened to air. After stirring the reaction mixture for 0.5 h, the reaction mixture was concentrated under reduced pressure. (The rotary evaporator water bath was kept at room temperature when concentrating the reaction mixture. Decomposition of the product presumably by polymerisation occurred when the reaction mixture was concentrated using a warm (40 ^{o}C) water bath and without first exposing the reaction mixture to air). The crude residue was purified by column chromatography (7 : 3 diethyl ether : petroleum ether → 1 : 1 diethyl ether : ethyl acetate) to yield the title compound **21** as a colourless oil (22 mg, 69%). The compound was rotameric resulting in complex ^{1}H and ^{13}C NMR spectra at 298 K. Data was collected at 363 K: $[\alpha]_D^{25}$ = -48.1 (*c* 0.50, $CHCl_3$); ν_{max}(film)/cm^{-1} 2928 (C-H), 1632 (C=O); ^{1}H NMR (500 MHz, 363 K, toluene-d_8) δ 5.93 (br. s., 1H), 5.78 - 5.66 (m, 1H), 5.65 (s, 1H), 5.19 (br. s, 1H), 5.14 - 5.00 (m, 1H), 5.00 - 4.83 (m, 3H), 4.55 (br. s., 1H), 4.46 (ddd, *J* = 13.6, 10.6, 3.0 Hz, 1H), 3.09 (td, *J* = 12.1, 3.5 Hz, 1H), 3.02 (br. s., 1H), 2.61 - 2.50 (m, 2H), 2.47 (dd, *J* = 12.0, 4.7 Hz, 1H), 2.44 - 2.30 (m, 3H), 2.29 - 2.14 (m, 1H), 2.07 - 1.97 (m, 4H), 1.97 – 1.89 (m, 1H), 1.82 (dd, *J* = 12.8, 6.8 Hz, 1H), 1.78 - 1.62 (m, 3H), 1.62 - 1.49 (m, 2H), 1.31 - 1.11 (m, 2H), 1.09 - 0.99 (m, 1H), 0.90 - 0.79 (m, 1H); ^{13}C NMR (rotameric) (125 MHz, 298 K, toluene-d_8) δ 171.9, 171.5, 171.2, 171.0, 160.5, 158.5, 157.0, 141.8, 141.0, 139.4, 130.8, 115.1, 114.9, 113.8, 103.7, 102.6, 83.0, 82.8, 79.0, 78.7, 70.8, 69.3, 67.6, 63.7, 63.6, 47.5, 47.4, 44.5, 41.0, 40.4, 39.8, 38.9, 35.1, 34.1, 28.5, 28.1, 28.0, 27.9, 25.3, 24.9,

23.4, 22.8, 19.1; *m/z* (ESI^+) 915 (97%, $[2M+Na]^+$), 469 (100, $[M+Na]^+$), 447 (38, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 469.2463, $C_{28}H_{34}N_2NaO_3$ requires 469.2462.

A ^{13}C NMR spectrum was obtained at 363 K, at which temperature the signals coalesced, however not all signals were observed hence the rotameric ^{13}C NMR spectrum collected at 298 K is reported. A copy of the ^{13}C NMR spectrum at 363 K is included in the spectra section for information.

2.3.12. Synthesis and characterisation of 22

(2*R*,3a*S*,7a*S*,10b*R*,13*Z*)-1-(Hex-5-enoyl)-2-vinyl-2,3,6,7,7a,10b-hexahydro-1*H*-9,5-oct[3]enofuro[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridin-4-one **22**

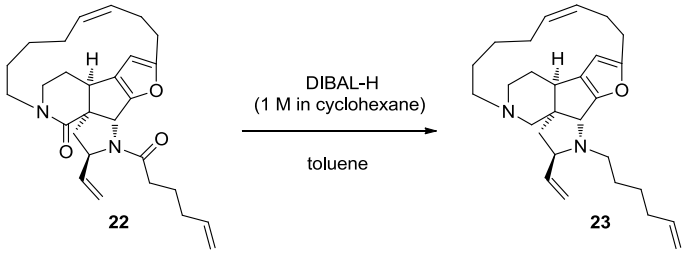


Under an atmosphere of H_2 (~1 atm.), sodium borohydride (3.4 mg, 0.090 mmol, 0.7 mL of a stock solution in ethanol (23.5 mg in 5 mL of ethanol)) was added to a suspension of $Ni(OAc)_2{\cdot}4H_2O$ (11.1 mg, 0.045 mmol) in ethanol (1.2 mL) at room temperature. Ethylene diamine (67.4 mg, 75 μL, 11.215 mmol) was added immediately in one portion to the black suspension which was then stirred for 0.5 h. Pentacycle **21** (20.0 mg, 0.045 mmol) in ethanol (1.2 mL) was added to the black suspension. The desired product **22** and starting material **21** co-elute by TLC analysis therefore the reaction was closely monitored by mass spectrometry until all starting material had been consumed (typically 0.75 h – 1.25 h). The reaction mixture was filtered through a celite plug washing with ethyl acetate. The solvent was removed under reduced pressure and the crude residue was re-dissolved in ethyl acetate and passed through a second celite plug to remove any remaining inorganic salts. The solvent was removed under reduced pressure and the crude residue purified by column chromatography (100% diethyl ether → 100% ethyl acetate) to give the title compound **22** as a colourless oil (17.5 mg, 87%). The compound was rotameric resulting in complex ^1H and ^{13}C NMR spectra at 298 K. Data was collected at 373 K: $[\alpha]_D^{25}$ = -93.3 (*c* 0.43, $CHCl_3$); ν_{max}(film)/cm^{-1} 2931 (C-H), 2862 (C-H), 1633 (C=O); ^1H NMR (500 MHz, 373 K, toluene-d_8) δ 6.07 - 5.84 (m, 1H), 5.80 - 5.67 (m, 1H), 5.55 (s, 1H), 5.45 - 5.34 (m, 1H), 5.23 - 5.15 (m, 1H), 5.15 - 5.04 (m, 2H), 5.01 – 4.87 (m, 3H), 4.63 - 4.50 (m, 2H), 3.00 (br. s, 1H), 2.91 (td, *J* = 12.3, 3.8 Hz, 1H), 2.69 - 2.61 (m, 1H), 2.53 (dd, *J* = 12.9, 9.8 Hz, 1H), 2.47 - 2.42 (m, 1H), 2.38 - 2.18 (m, 3H), 2.18 - 2.14 (m, 2H), 2.04 (q, *J* = 6.7 Hz, 2H), 2.01 – 1.90 (m, 1H), 1.87 - 1.63 (m, 5H), 1.57 - 1.44 (m, 2H), 1.32 - 1.18 (m, 1H), 1.10 - 1.00 (m, 1H), 0.98 - 0.85 (m, 1H), 0.19 - 0.06 (m, 1H); ^{13}C NMR (rotameric) (125 MHz, toluene-d_8) δ 171.8, 171.4, 171.3, 170.9, 160.5, 160.1, 159.2, 157.5, 141.8, 140.9, 139.4, 131.2, 130.8, 130.4, 128.6, 115.1, 114.9, 113.9, 104.0, 103.2, 71.4, 69.3, 68.1, 67.6, 63.7, 63.6, 47.1, 46.9, 43.5, 40.6, 40.1, 39.6, 38.5, 35.1, 34.1, 29.3, 29.2, 27.2, 26.3, 25.3, 24.9, 22.9, 22.3; *m/z* (ESI^+) 919 (100%, $[2M+Na]^+$), 471 (97,

$[M+Na]^+$), 449 (27, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 471.2615, $C_{28}H_{36}N_2NaO_3$ requires 471.2618.

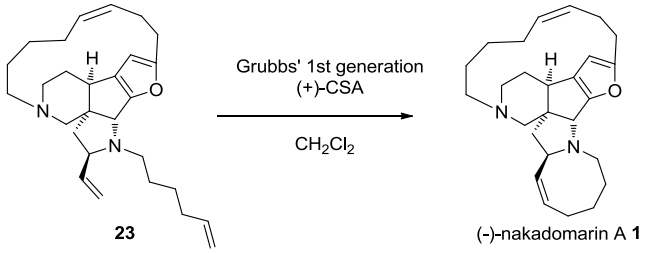
2.3.13. Synthesis and characterisation of 23

(2*R*,3a*R*,7a*R*,10b*R*,13*Z*)-1-(Hex-5-en-1-yl)-2-vinyl-2,3,6,7,7a,10b-hexahydro-1*H*-9,5-oct[3]enofuro[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridine **23**



DIBAL-H (189 μL, 0.189 mmol, 1 M solution in cyclohexane) was added to a solution of triene **22** (17.0 mg, 0.038 mmol) in toluene (1.8 mL) at 0 ^{o}C. The reaction mixture was stirred for 4 h at 0 ^{o}C followed by addition of a second portion of DIBAL-H (189 μL, 0.189 mmol, 1 M solution in cyclohexane). The reaction mixture was warmed to room temperature and stirred for a further 2 h followed by addition of methanol (0.3 mL). After a further 0.5 h, $Na_2SO_4 \cdot 10H_2O$ (50 mg) and diethyl ether (3.5 mL) were added and the reaction mixture stirred for 5 h before being filtered through celite, washing with diethyl ether, and concentrated under reduced pressure. The crude residue was purified by column chromatography using neutral alumina (3:7 diethyl ether : petroleum ether – 1:1 diethyl ether : petroleum ether) to give diamine **23** as a colourless oil (9.4 mg, 59%): $[\alpha]_D^{25} = -17.1$ (*c* 0.37, $CHCl_3$); ν_{max}(film)/cm^{-1} 2924 (C-H), 2854 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 - 5.84 (m, 1H), 5.78 (s, 1H), 5.70 - 5.60 (m, 1H), 5.53 - 5.45 (m, 1H), 5.32 - 5.22 (m, 1H), 5.16 - 5.01 (m, 3H), 4.98 - 4.93 (m, 1H), 4.16 (s, 1H), 3.16 - 3.08 (m, 1H), 3.01 (d, *J* = 12.0 Hz, 1H), 2.78 (br. s., 1H), 2.76 - 2.70 (m, 1H), 2.65 - 2.54 (m, 3H), 2.54 - 2.46 (m, 1H), 2.41 (dt, *J* = 12.0, 3.3 Hz, 1H), 2.34 - 2.22 (m, 3H), 2.18 (s, 1H), 2.15 - 2.09 (m, 3H), 2.01 – 1.86 (m, 3H), 1.78 (ddd, *J* = 14.0, 7.0, 2.7 Hz, 1H), 1.69 (dd, *J* = 12.0, 4.4 Hz, 1H), 1.66 - 1.61 (m, 1H), 1.59 - 1.54 (m, 1H), 1.48 - 1.39 (m, 3H), 1.33 - 1.28 (m, 1H), 1.09 - 0.97 (m, 2H), 0.86 - 0.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.5, 156.1, 140.7, 139.3, 133.5, 131.6, 127.9, 116.6, 114.1, 103.2, 70.9, 66.6, 62.4, 59.5, 58.2, 49.7, 45.0, 42.5, 41.3, 33.7, 29.7, 28.7, 28.1, 27.5, 27.1, 26.3, 26.2, 22.1; *m/z* (ESI$^+$) 421 (100%, $[M+H]^+$); HRMS *m/z* (ESI$^+$) found $[M+H]^+$ 421.3212, $C_{28}H_{41}N_2O$ requires 421.3213.

2.3.14. Synthesis and characterisation of (–)-nakadomarin A 1

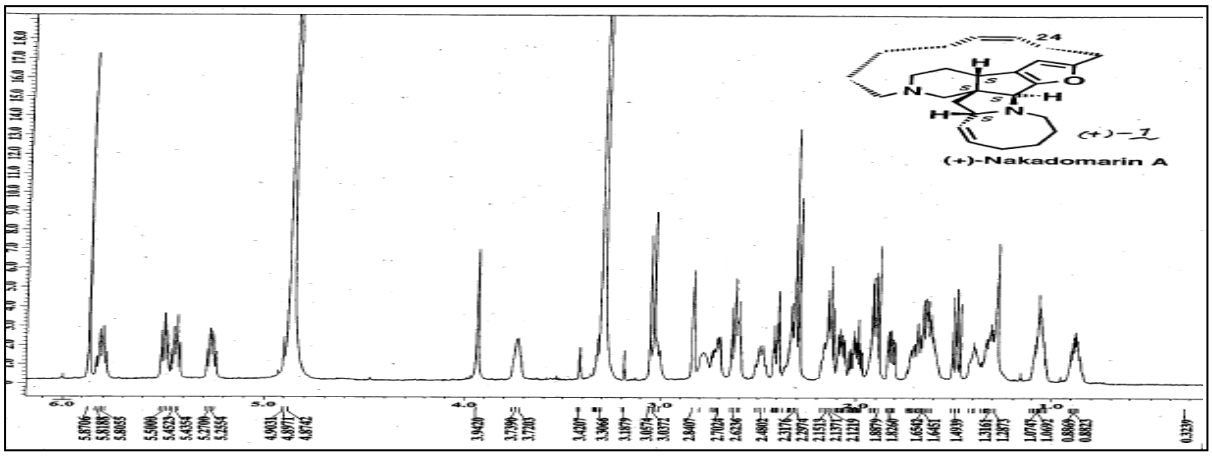


Diamine **23** (10.0 mg, 0.024 mmol) and (+)-CSA (16.6 mg, 0.072 mmol) were dissolved in CH_2Cl_2 (4 mL) and stirred for 10 minutes at room temperature. The reaction mixture was diluted with CH_2Cl_2 (83 mL) and a solution of Grubbs' 1st generation catalyst (5.9 mg, 0.007 mmol) in CH_2Cl_2 (1 mL) added. The solution was heated at reflux for 5 h before addition of a further portion of Grubbs' 1st generation catalyst (2.0 mg, 0.002 mmol) in CH_2Cl_2 (0.5 mL). After a further 3 h the reaction mixture was concentrated to ~10 mL and extracted with 1 M aq. HCl (4 x 10 mL). The aqueous extracts were combined, cooled to 0 °C and the pH adjusted to 14 by addition of sat. aq. NaOH solution. The product was extracted with diethyl ether (2 x 10 mL) and CH_2Cl_2 (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography using neutral alumina (3 : 7 diethyl ether : petroleum ether → 1 : 1 diethyl ether : petroleum ether) to give (–)-nakadomarin A **1** as a colourless oil (6.5 mg, 70 %): $[\alpha]_D^{25}$ = -67.0 (*c* 0.50, MeOH), lit.[8] $[\alpha]_D^{25}$ -65.6 (*c* 0.66, MeOH), lit.[9] $[\alpha]_D^{23}$ -73.0 (*c* 0.08, MeOH), lit.[10] (ent)-(+)-nakadomarin A $[\alpha]_D^{25}$ +70.4 (*c* 0.94, MeOH), lit.[10] (ent)-(+)-nakadomarin A, $[\alpha]_D^{25}$ +79.2 (*c* 0.12, MeOH), lit.[11] (ent)-(+)-nakadomarin A $[\alpha]_D^{25}$ +60.7 (*c* 0.27, MeOH); ^{1}H NMR (700 MHz, CD_3OD) δ 5.88 (s, 1H), 5.82 (dd, *J* = 9.5, 8.5 Hz, 1 H), 5.51 (dd, *J* = 9.5, 8.5 Hz, 1H), 5.49 - 5.43 (m, 1H), 5.31 - 5.24 (m, 1H), 3.95 (s, 1H), 3.78 - 3.72 (m, 1H), 3.06 (d, *J* = 11.9 Hz, 1H), 3.10 - 3.01 (m, 1H), 2.87 - 2.84 (m, 1H), 2.84 - 2.76 (m, 1H), 2.76 - 2.70 (m, 1H), 2.67 - 2.60 (m, 2H), 2.54 - 2.47 (m, 1H), 2.42 (dt, *J* = 11.8, 3.6 Hz, 1H), 2.32 (d, *J* = 11.9 Hz, 1H), 2.37 - 2.30 (m, 2H), 2.21 - 2.13 (m, 2H), 2.12 - 2.07 (m, 1H), 2.05-1.99 (m, 1H), 1.97 - 1.88 (m, 1H), 1.92 (dd, *J* = 12.3, 4.8 Hz, 1H), 1.84 (ddd, *J* = 14.0, 7.1, 2.7 Hz, 1H), 1.75 - 1.59 (m, 4H), 1.50 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.44 - 1.38 (m, 1H), 1.38 - 1.31 (m, 1H), 1.12 - 1.03 (m, 2H), 0.94 - 0.85 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ_C 162.5, 156.7, 135.3, 134.6, 132.4, 131.8, 129.4, 104.9, 74.8, 63.8, 60.8, 59.4, 58.3, 51.1, 46.2, 43.6, 43.3, 29.6, 2 x 29.4, 29.0, 27.3, 27.3, 2 x 26.1, 23.1; *m/z* (ESI^+) 393 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 393.2901, $C_{26}H_{37}N_2O$ requires 393.2900.

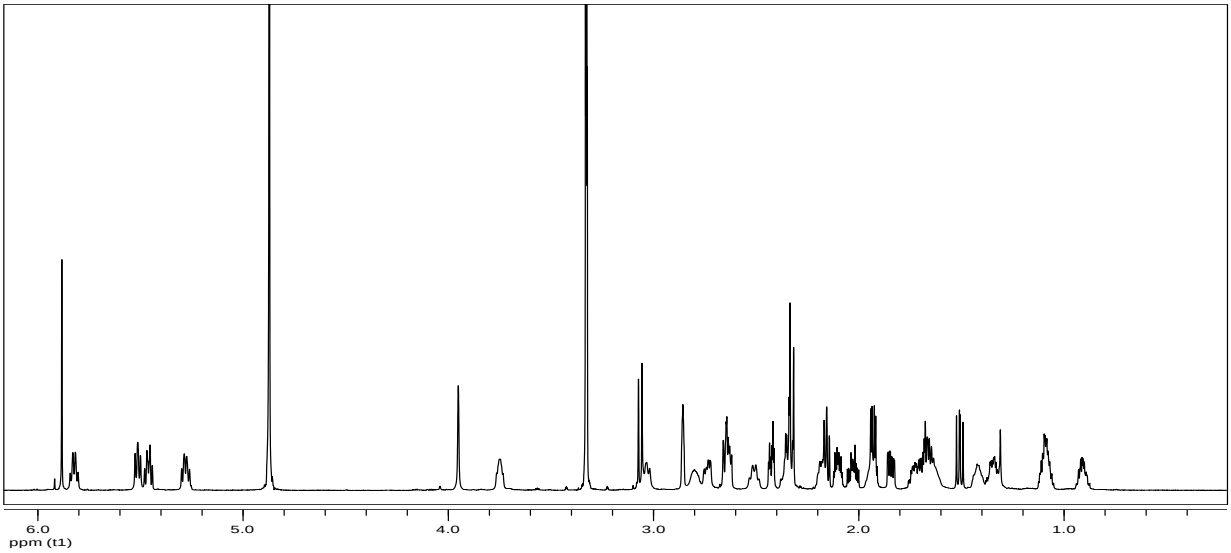
3. Confirmation of structure of nakadomarin A 1

3.1. Comparison of Nishida and Dixon ^{1}H-NMR spectra of (–)-nakadomarin A 1

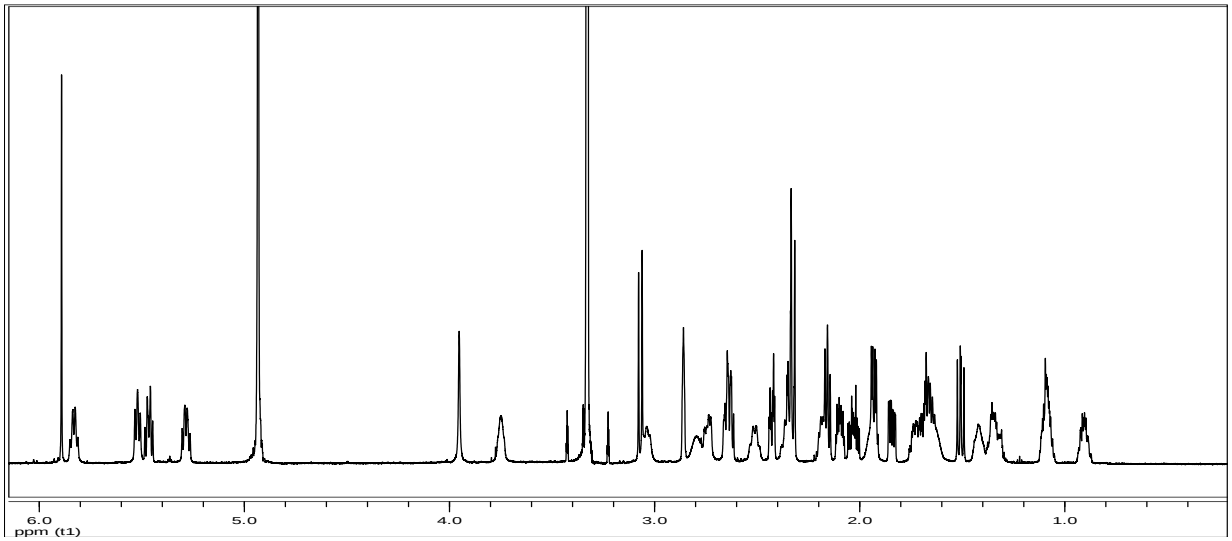
Nishida ^{1}H-NMR (600 MHz, CD_3OD) spectrum of (+)-nakadomarin A **1** (*J. Am. Chem. Soc.* **2003**, *125*, 7484)[10]



Dixon ^{1}H-NMR (700 MHz, CD_3OD) spectrum of (–)-nakadomarin A **1**

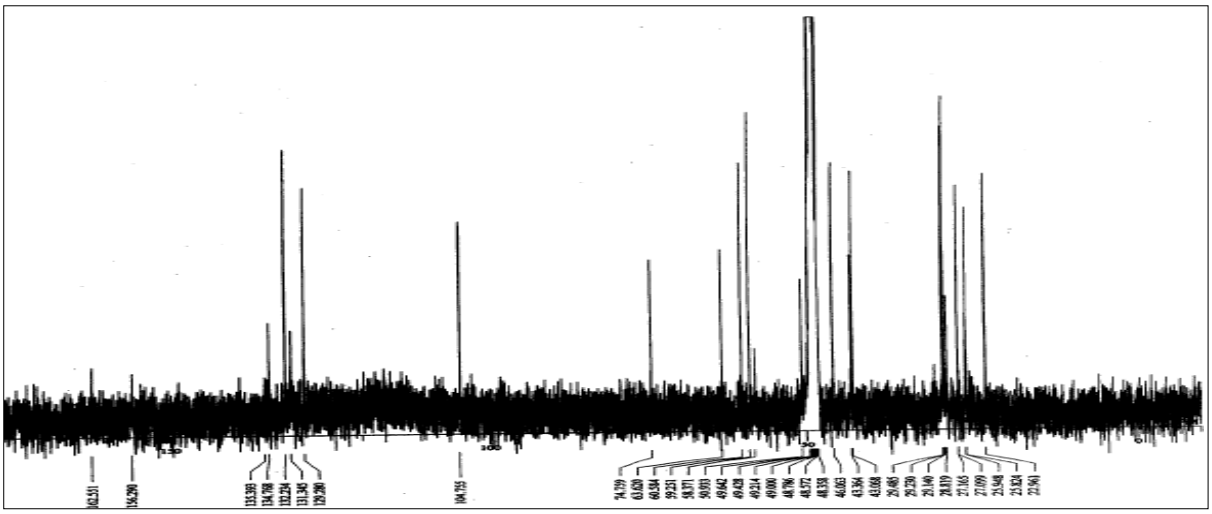


Dixon ^{1}H-NMR (700 MHz, CD_3OD) spectrum of (-)-nakadomarin A **1** (*J. Am. Chem. Soc.* **2009**, *131*, 16632)[8]

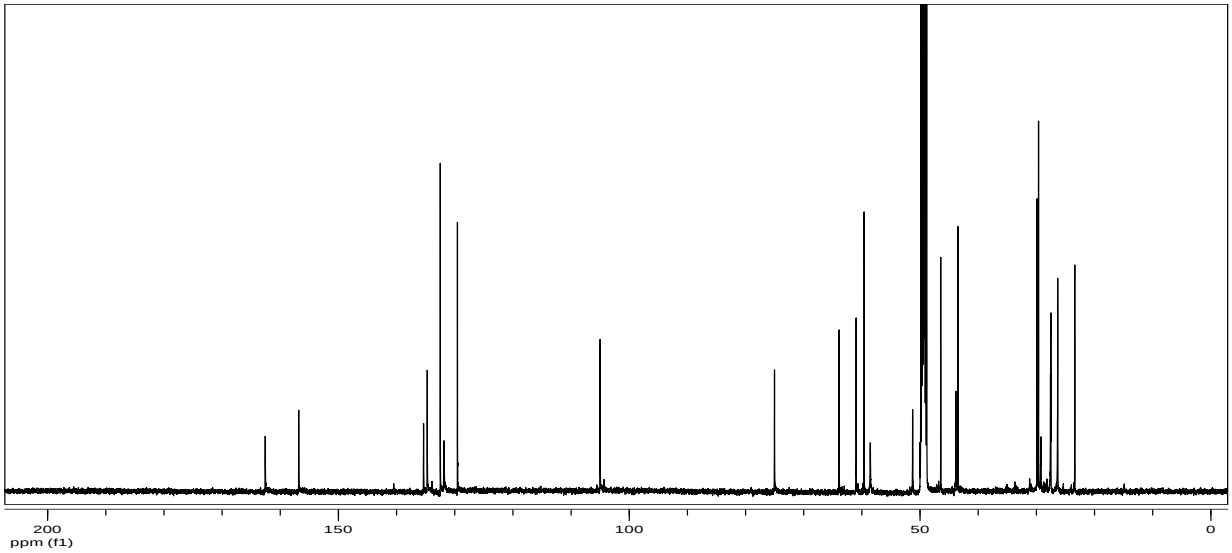


3.2. Comparison of Nishida and Dixon ^{13}C-NMR spectra of (–)-nakadomarin A 1

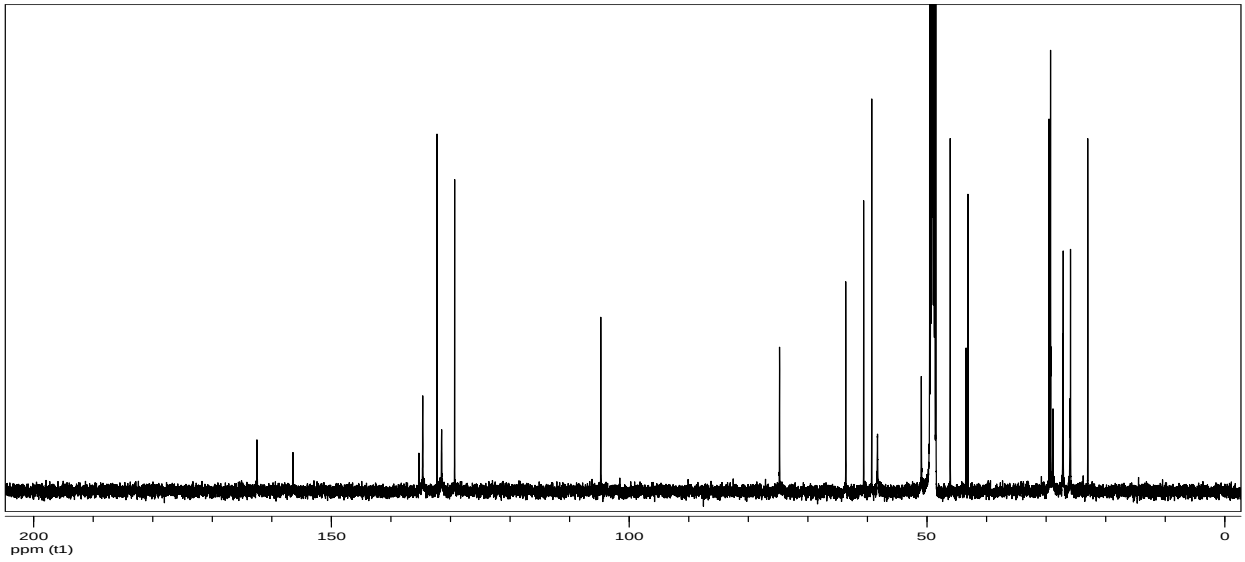
Nishida ^{13}C NMR (100 MHz) spectrum of (–)-nakadomarin A **1** (*Angew. Chem. Int. Ed.* **2004**, *116*, 2020)[9]



Dixon ^{13}C-NMR (125 MHz, CD_3OD) spectrum of (–)-nakadomarin A **1**



Dixon ^{13}C-NMR (125 MHz, CD_3OD) spectrum of (–)-nakadomarin A **1** (*J. Am. Chem. Soc.* **2009**, *131*, 16632)[8]



4. References:

1. (a) M. Amere, M.-C. Lasne and J. Rouden, *Org. Lett.*, 2007, **9**, 2621–2624; (b) C. G. Oliva, A. M. S. Silva, D. I. S. P. Resende, F. A. A. Paz, J. A. S. Cavaleiro, *Eur. J. Org. Chem.* 2010, **18**, 3449.
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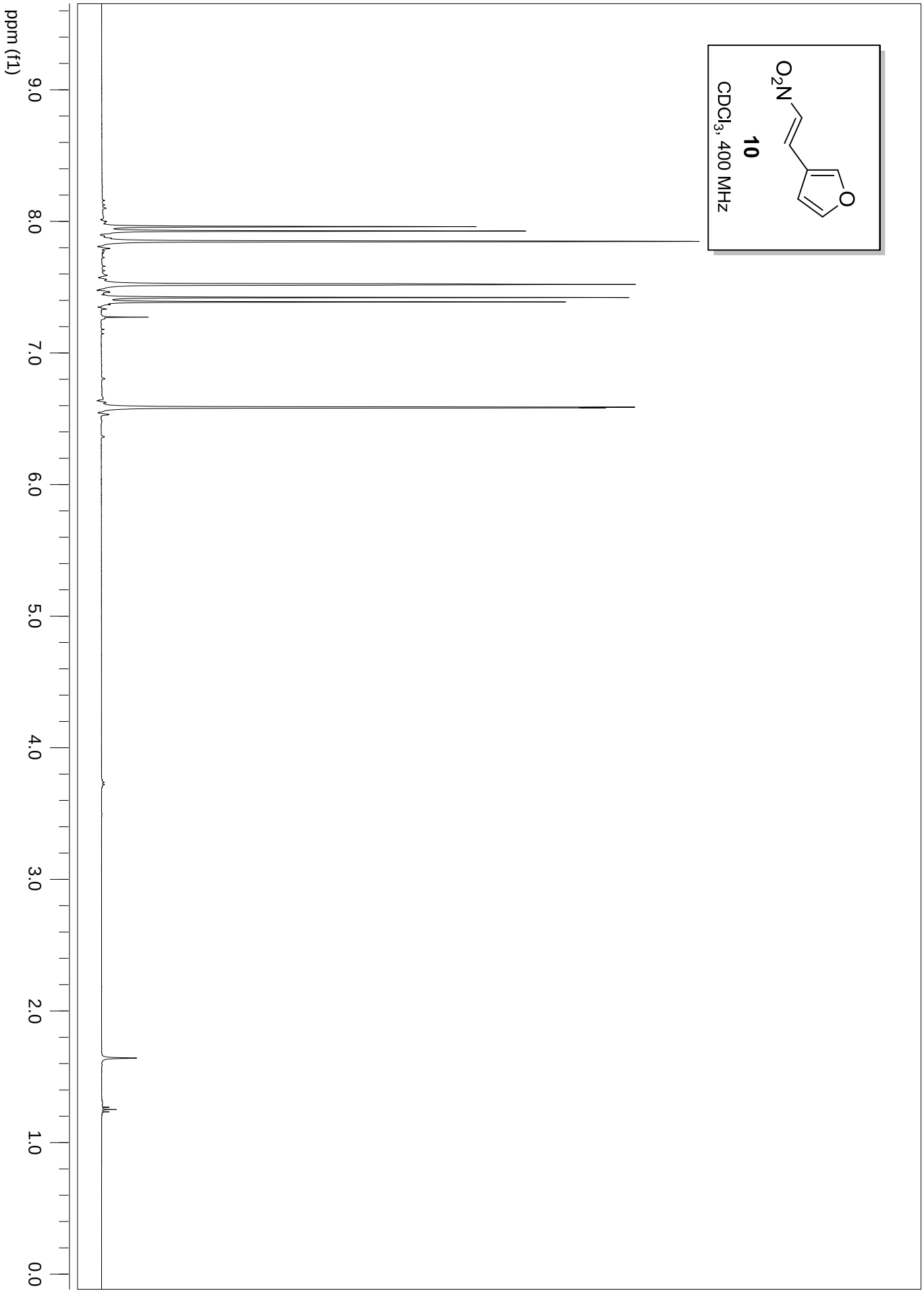
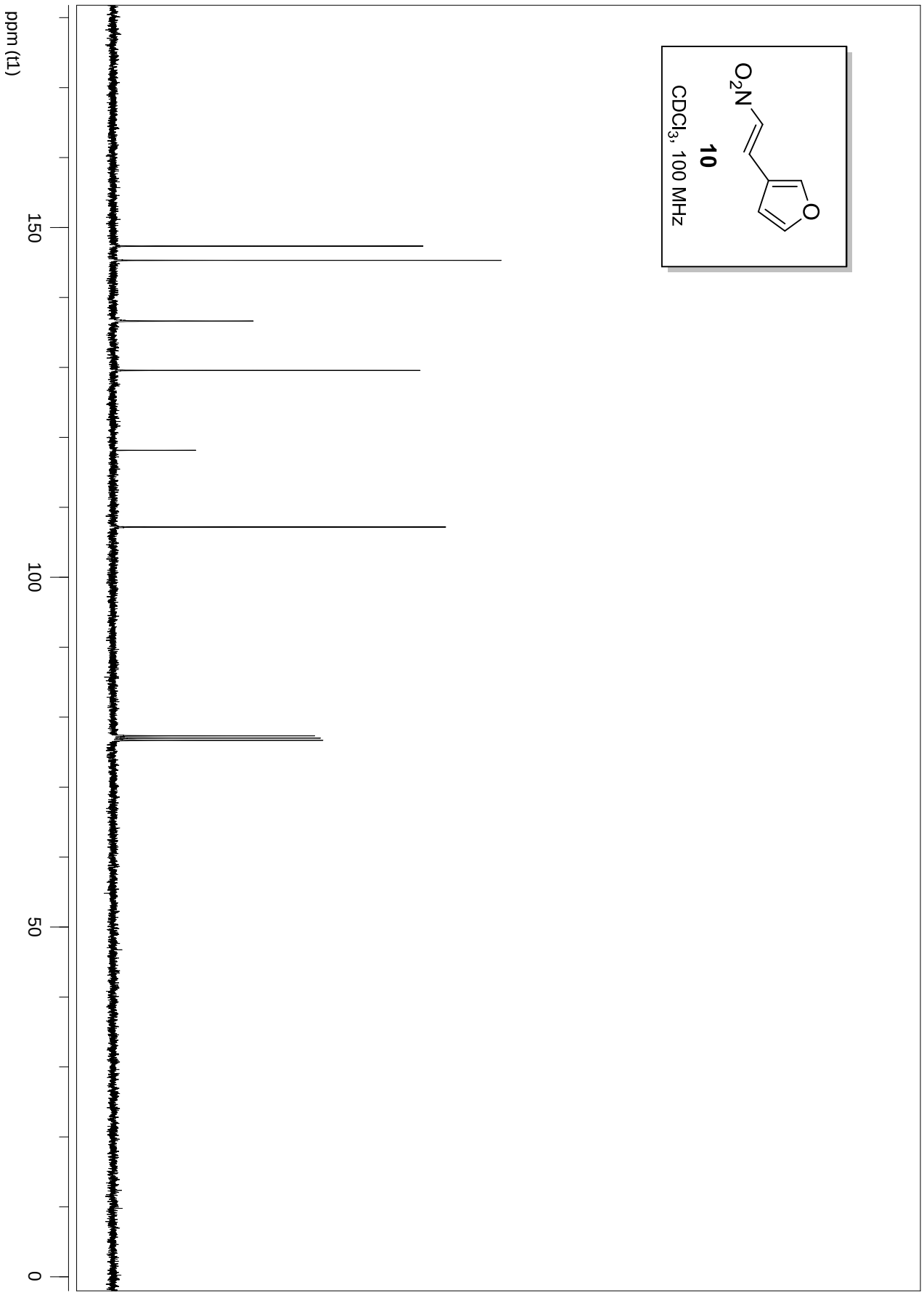
12. Data were collected at low temperature [J. Cosier and A. M. Glazer, *J. Appl. Cryst.*, 1986, **19**, 105-107.] using an Enraf-Nonius KCCD diffractometer [Z. Otwinowski, W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode Methods Enzymol*; C. W. Carter and R. M.Sweet, Eds.; Academic Press, 1997; p 276]. The crystal structure of **11** and **12** were solved using SIR92 [Altomare et al. *J. Appl. Cryst.*, 1994, **27**, 435] and refined using the CRYSTALS software suite [Betteridge et al. *J. Appl. Cryst.*, 2003, **36**, 1487], H atoms were treated in the usual manner [R. I. Cooper, A. L. Thompson and D. J. Watkin, *J. Appl. Cryst.*, 2010, **43**, 1100–1107] as per the supporting information (CIF file).

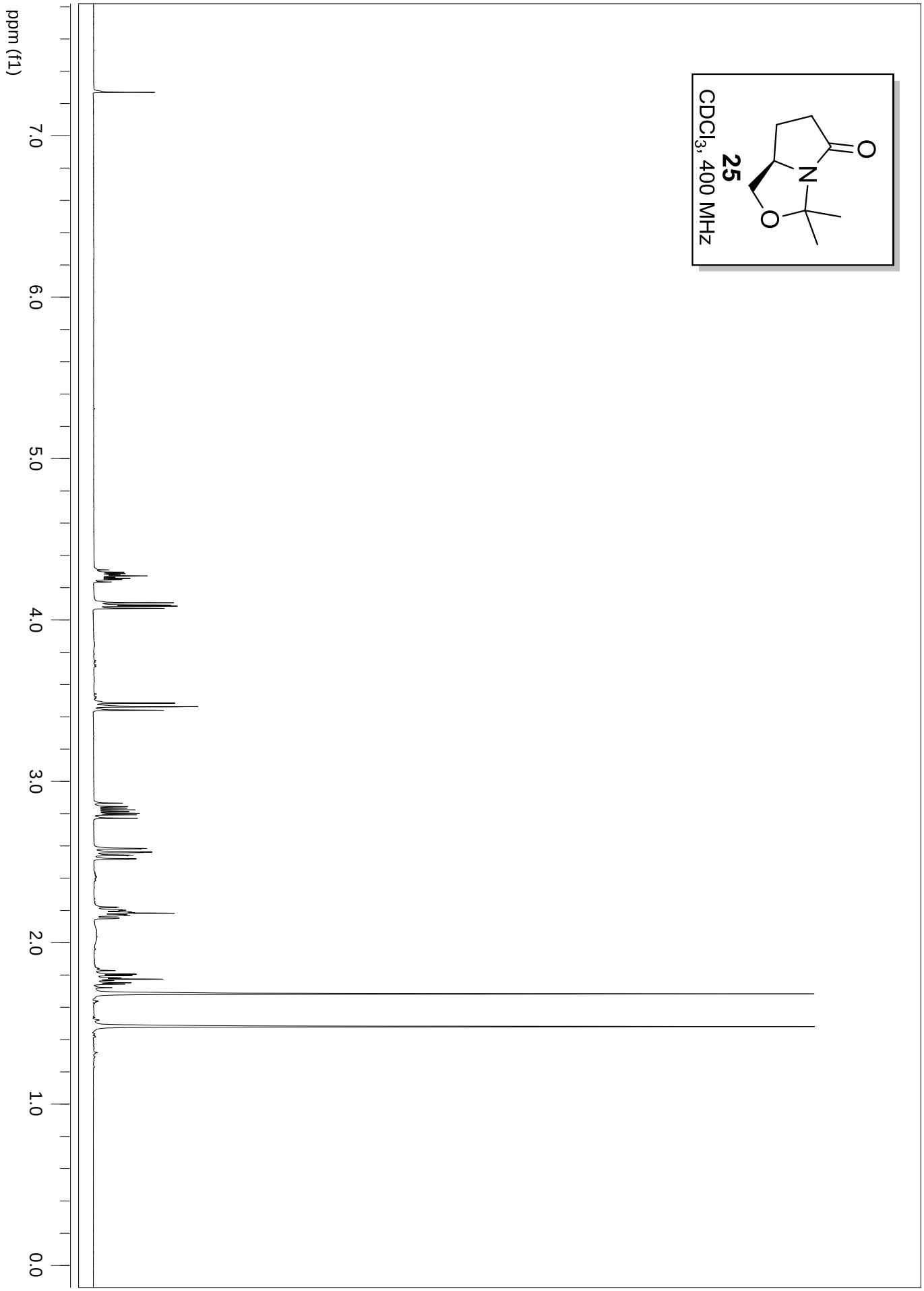
5. ^{1}H and ^{13}C NMR spectra

5.1. ^{1}H- and ^{13}C-NMR spectra of **10**

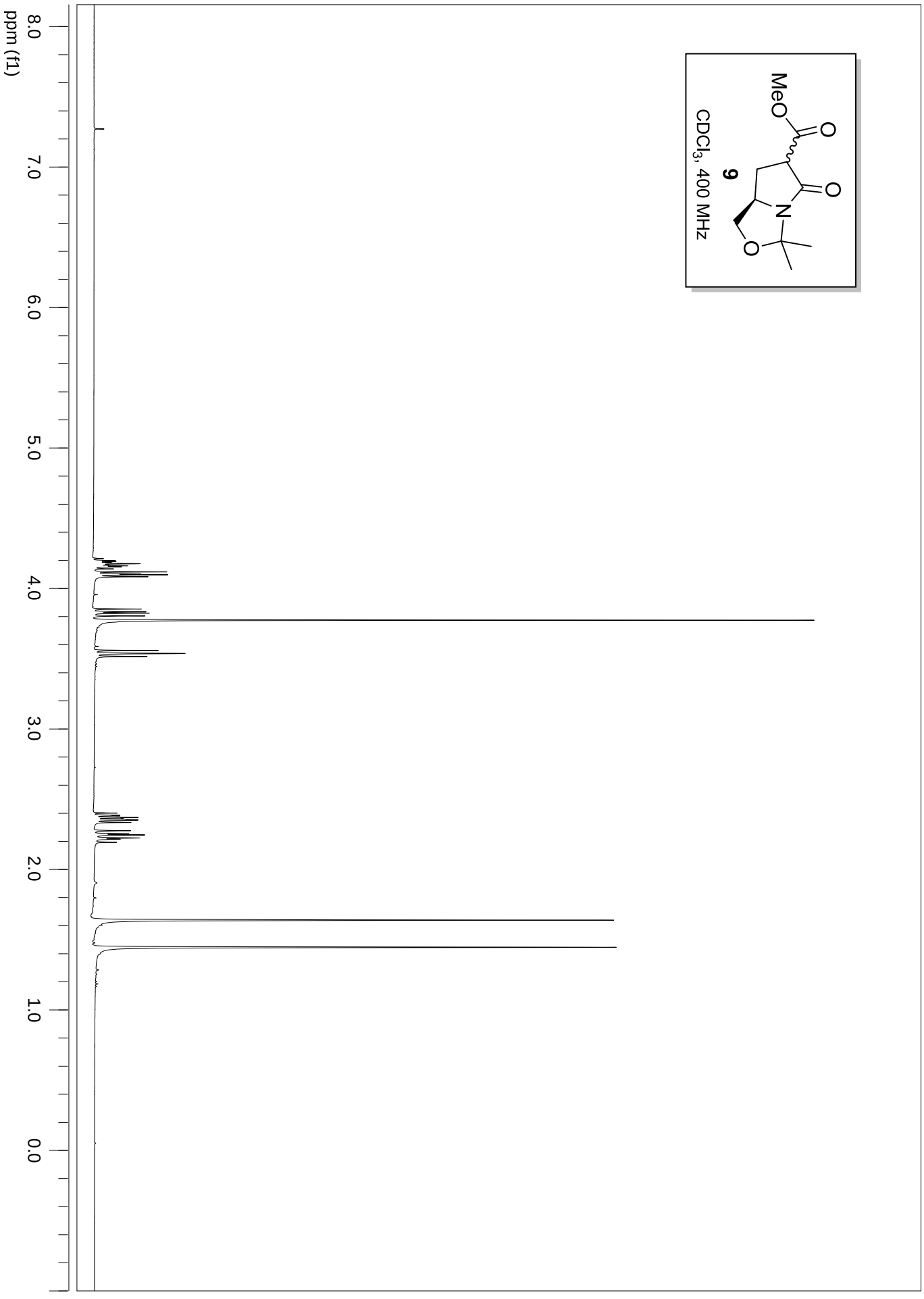


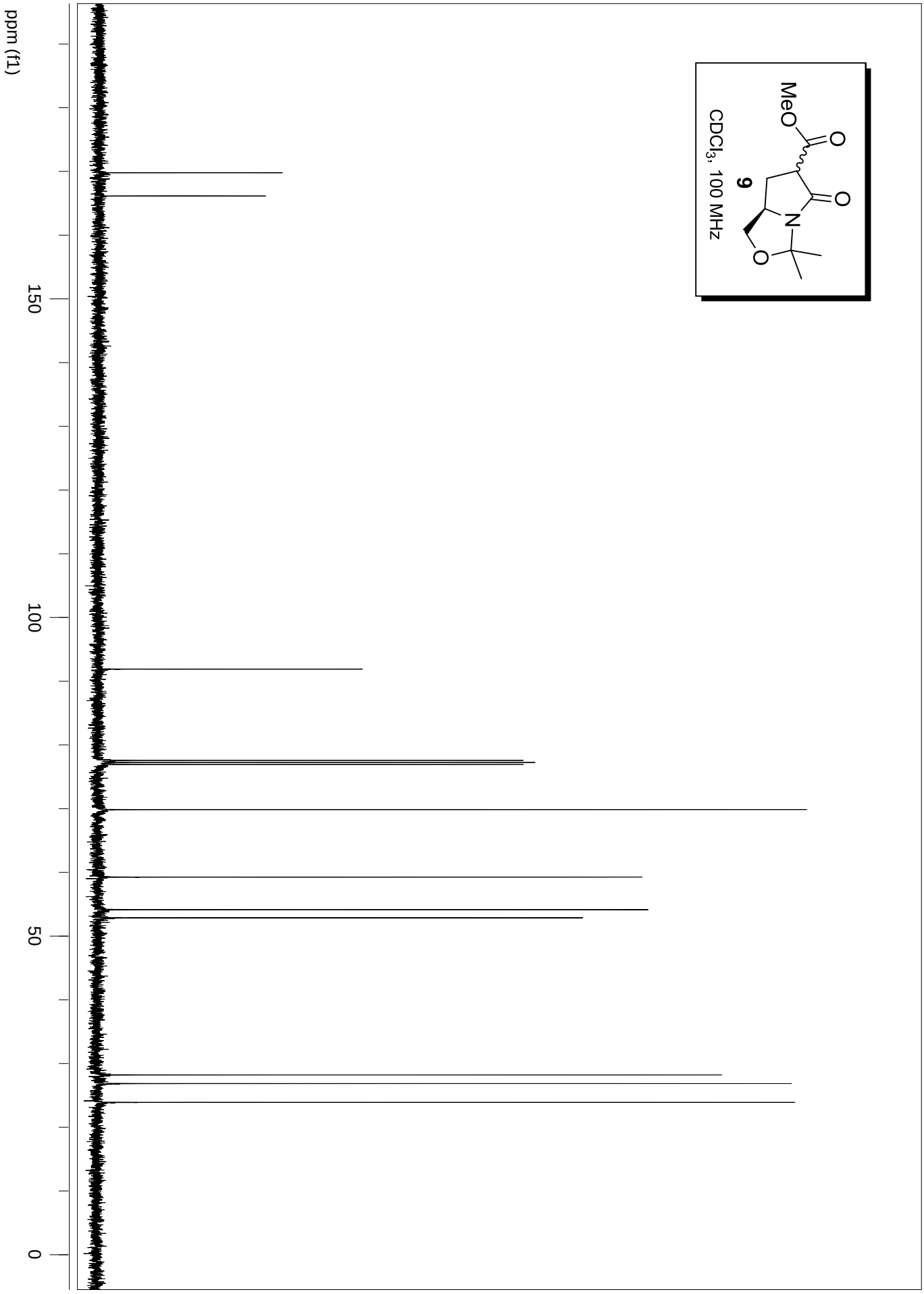


5.2. ^{1}H-NMR spectrum of **25**

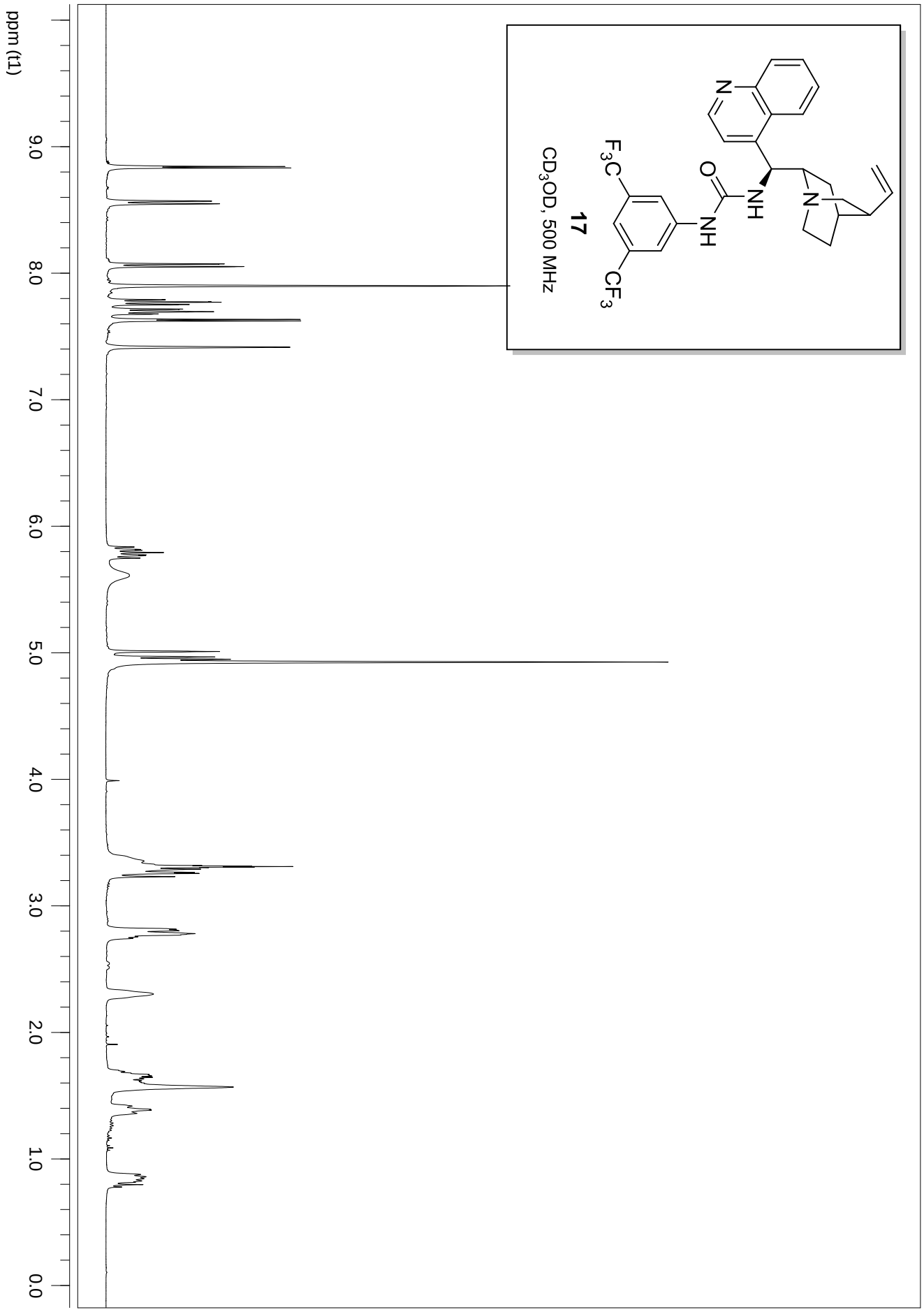


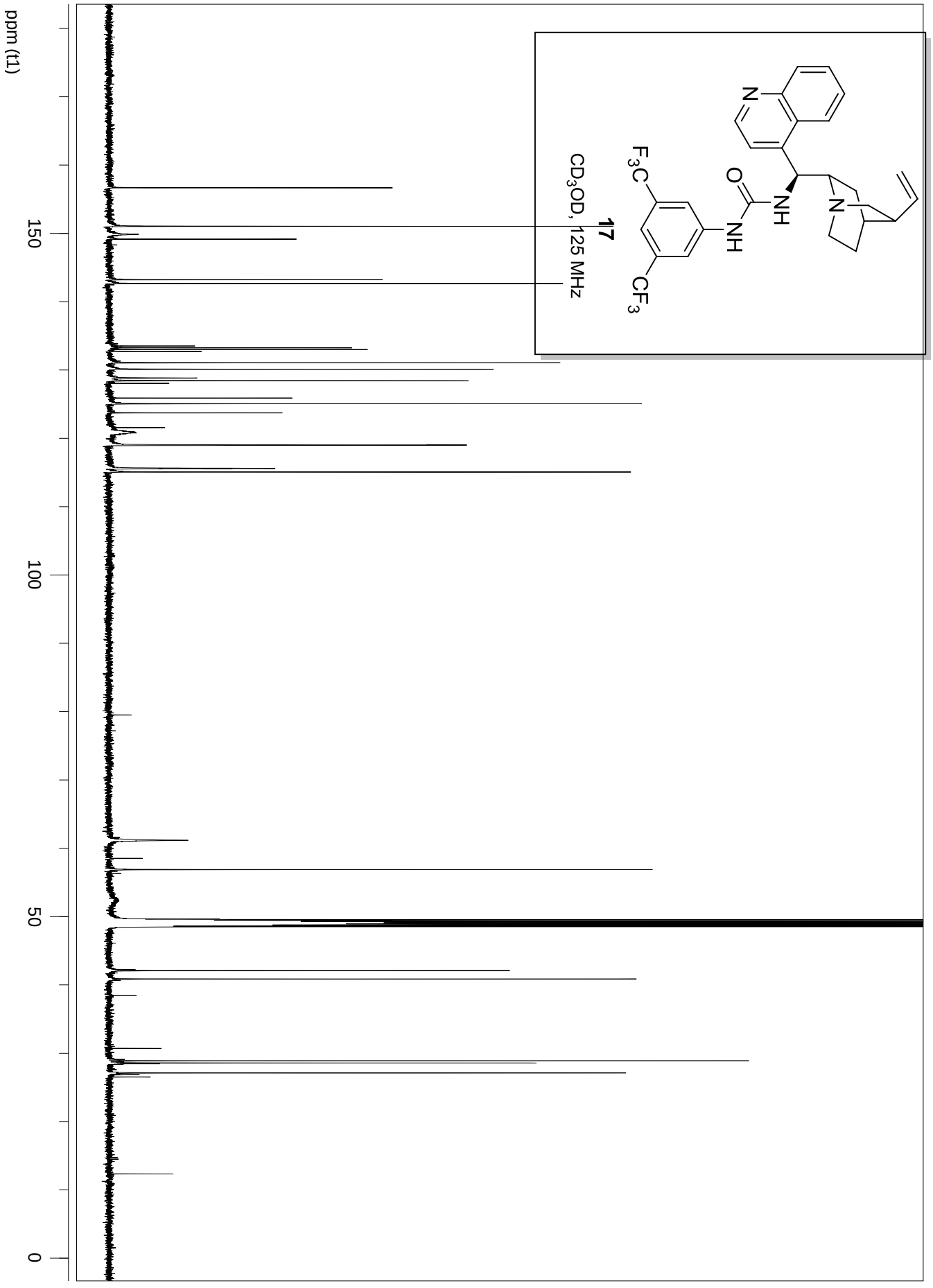
5.3. ^{1}H- and ^{13}C-NMR spectra of **9**



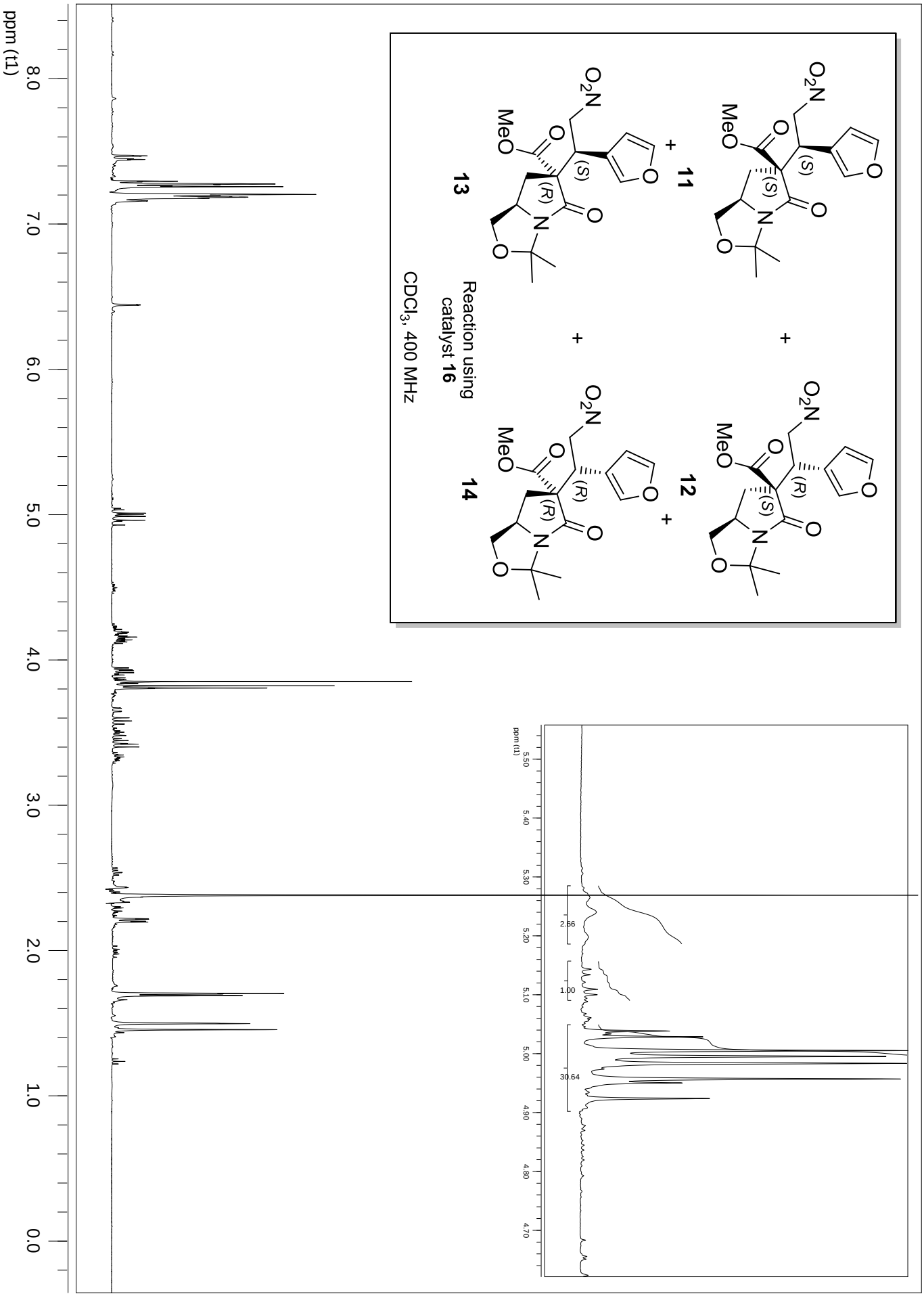

ppm (f1)
150
100
50
0
MeO
O
O
9
N
O
CDCl3, 100 MHz

5.4. ^{1}H- and ^{13}C-NMR spectra of **17**

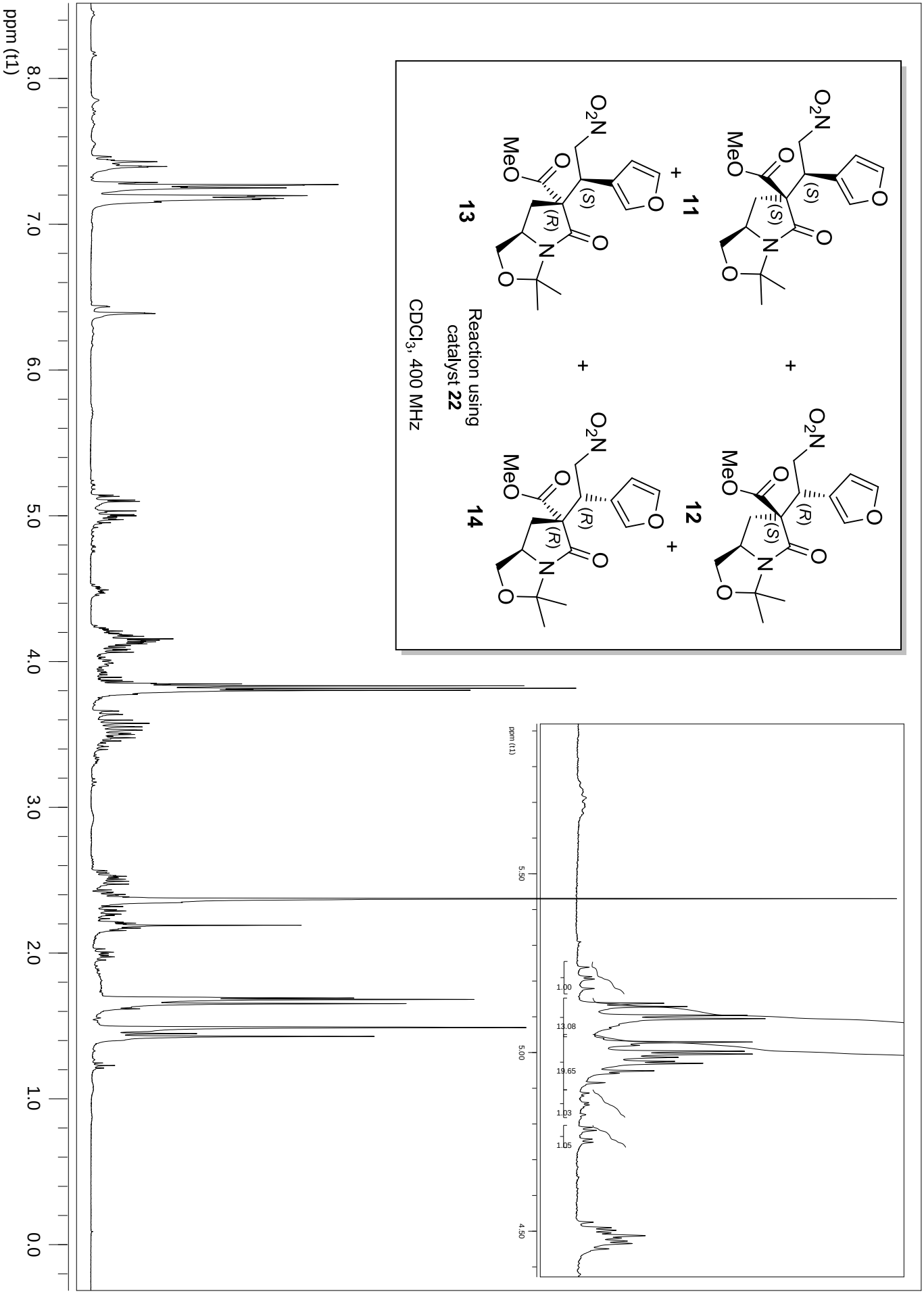



ppm (t1)
150
100
50
0
17
CD3OD, 125 MHz
F3C
CF3
NH
NH
O
N
N

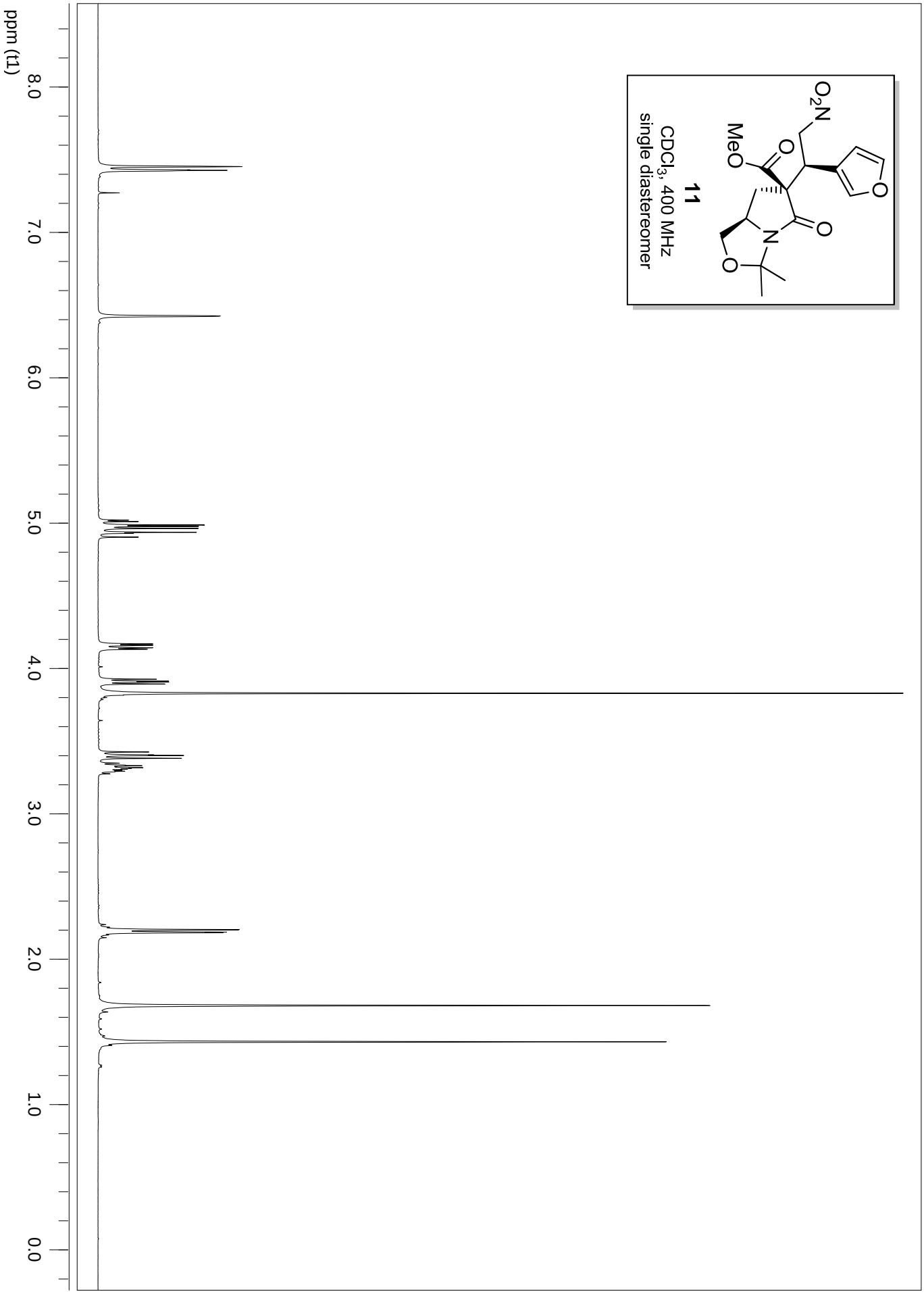
5.5. ^{1}H-NMR spectrum of Michael adduct (crude) using catalyst **16**

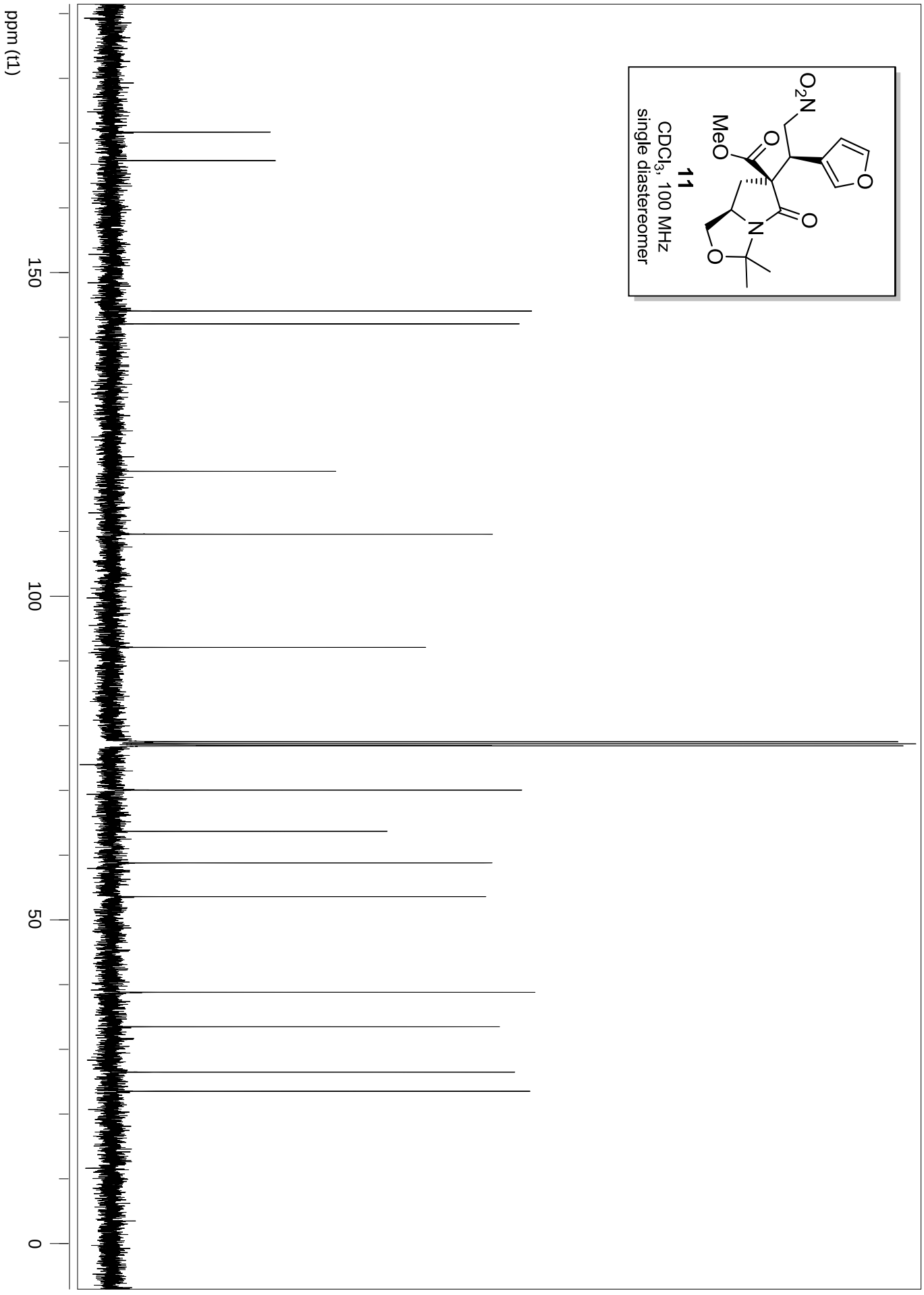


5.6. ^{1}H-NMR spectrum of Michael adduct (crude) using catalyst **17**

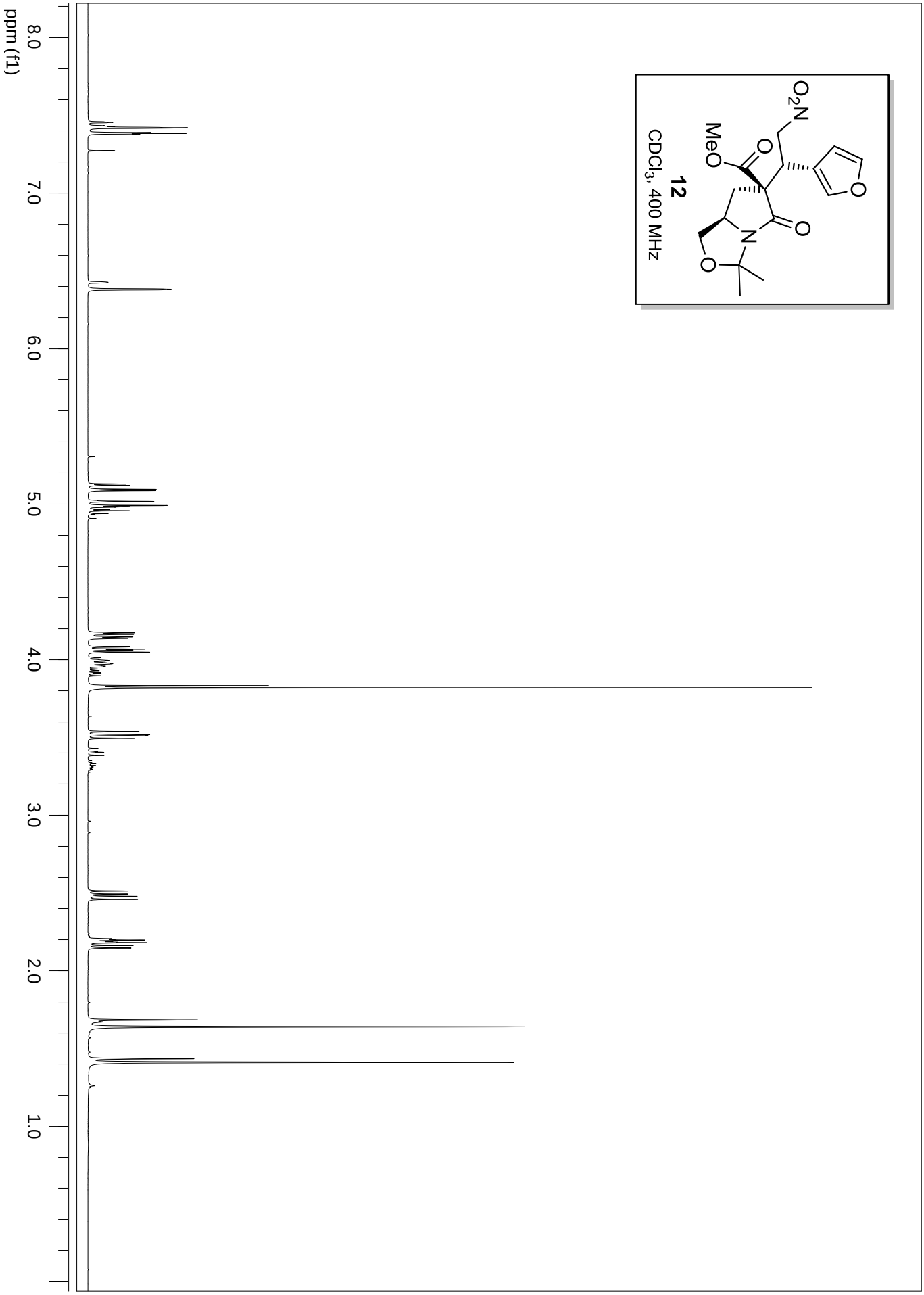


5.7. ^{1}H- and ^{13}C-NMR spectra of **11** (single diastereomer)

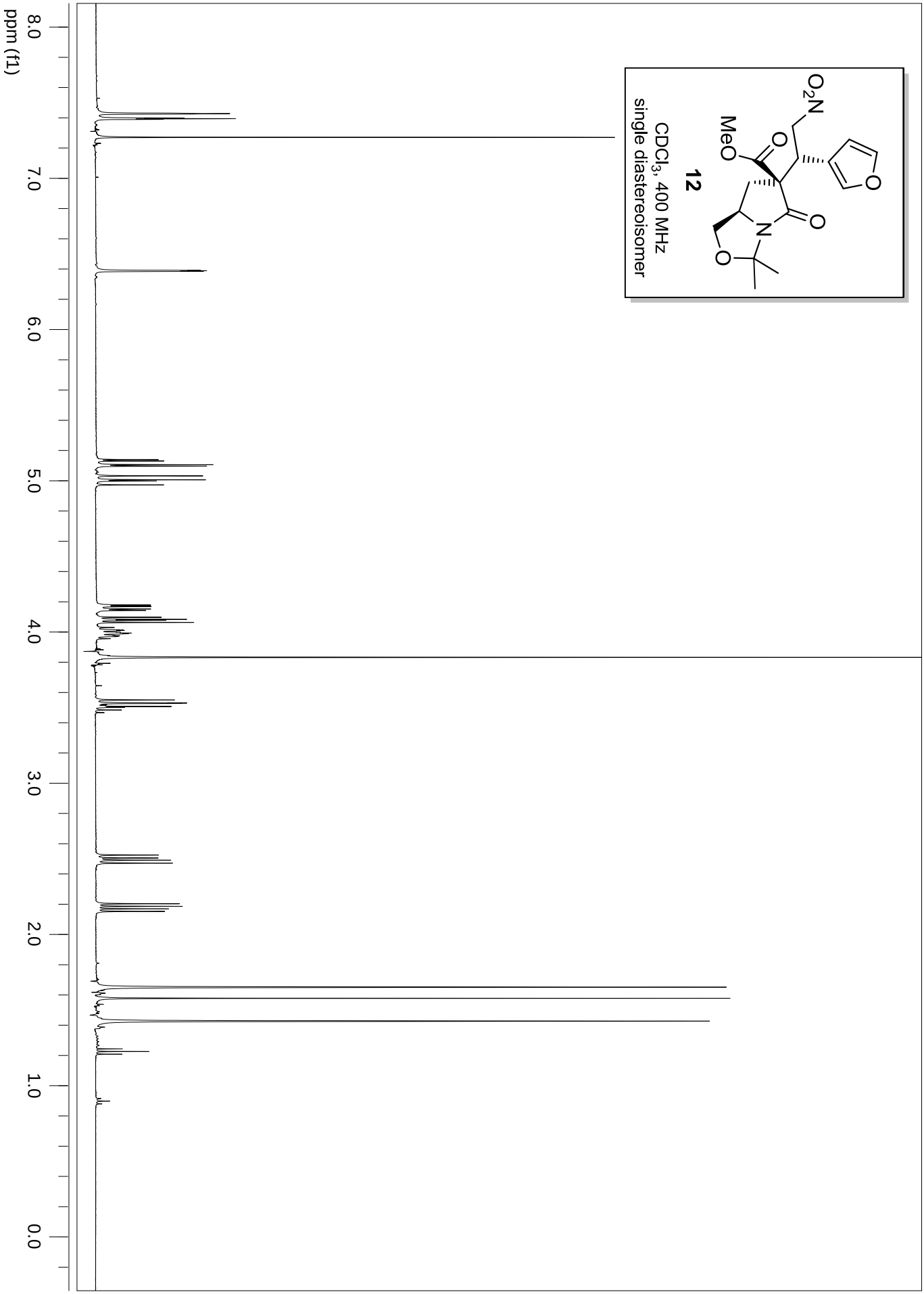


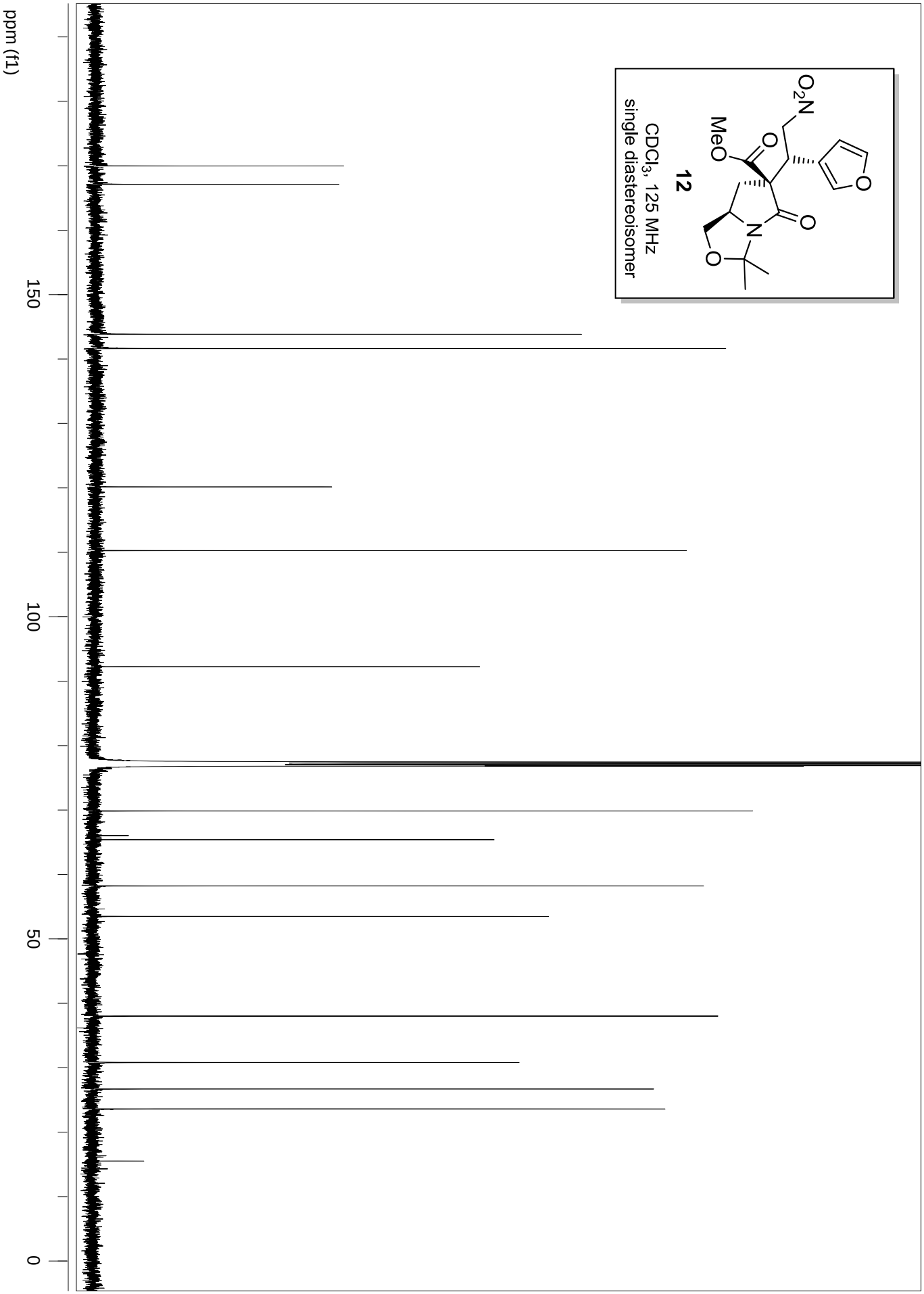


5.8. ^{1}H-NMR spectrum of **12** (mixture of diastereoisomers (1:4 dr **11**:**12**))

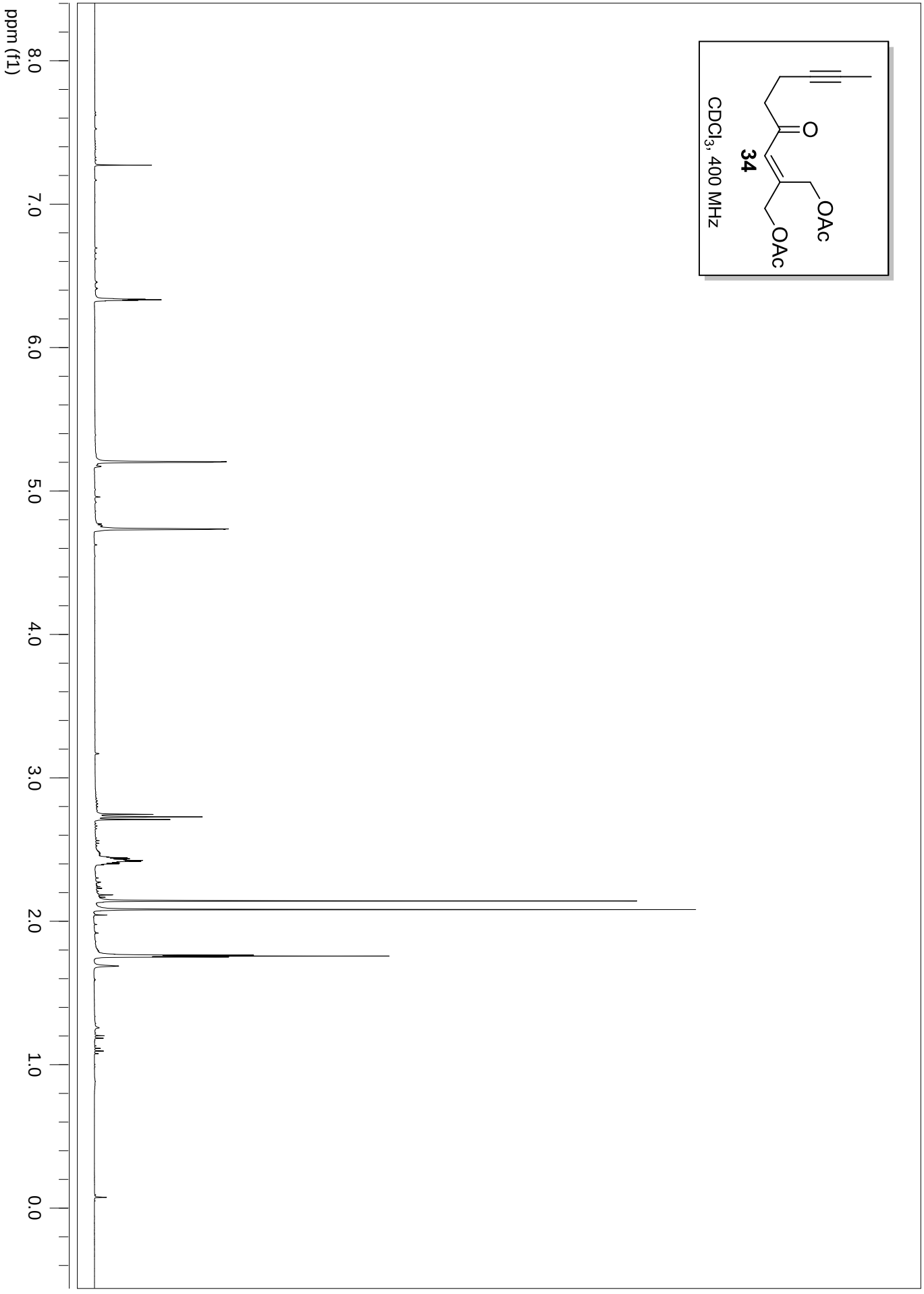


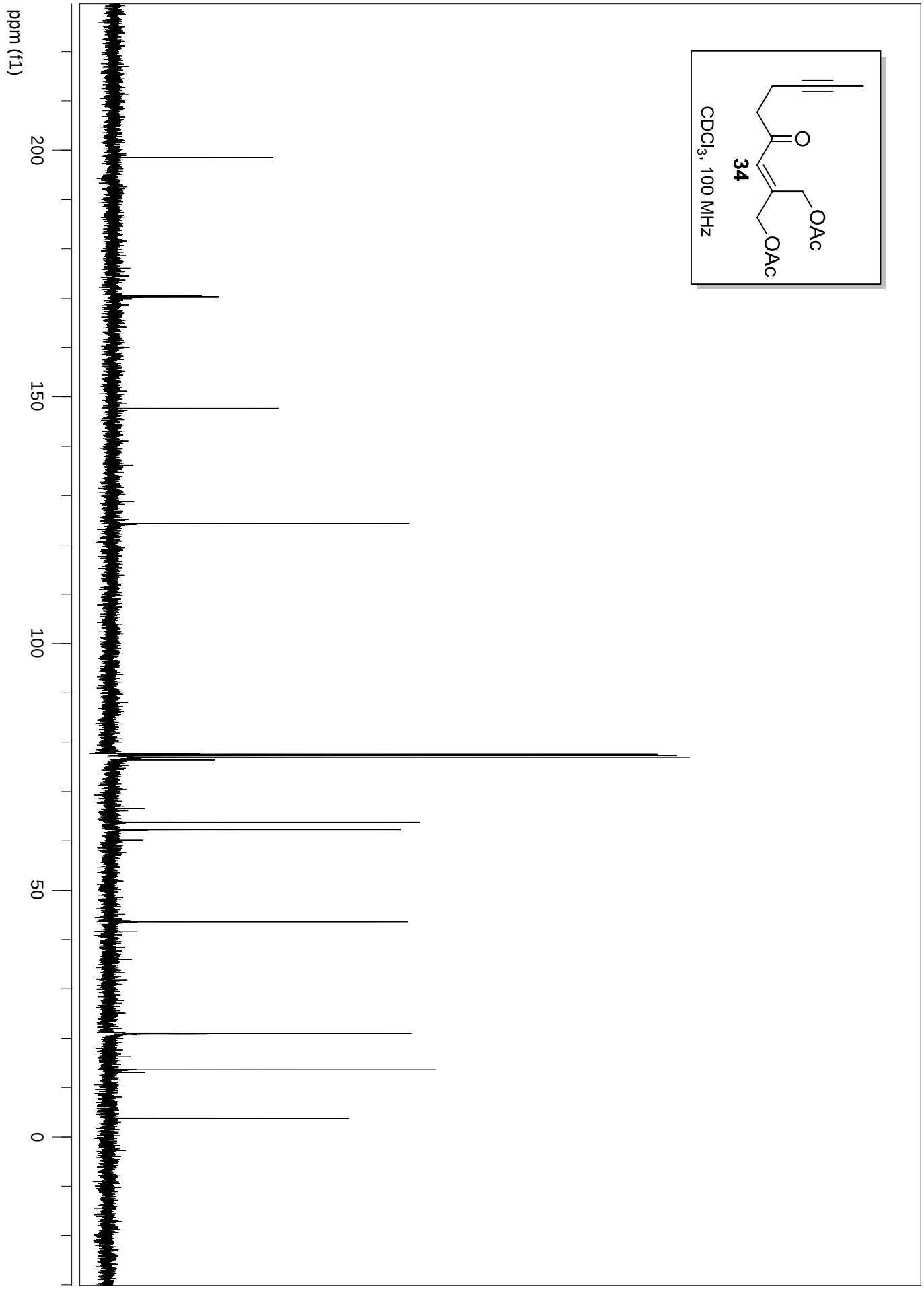
5.9. ^{1}H- and ^{13}C-NMR spectra of **12** (single diastereoisomer - single crystal x-ray analysis)



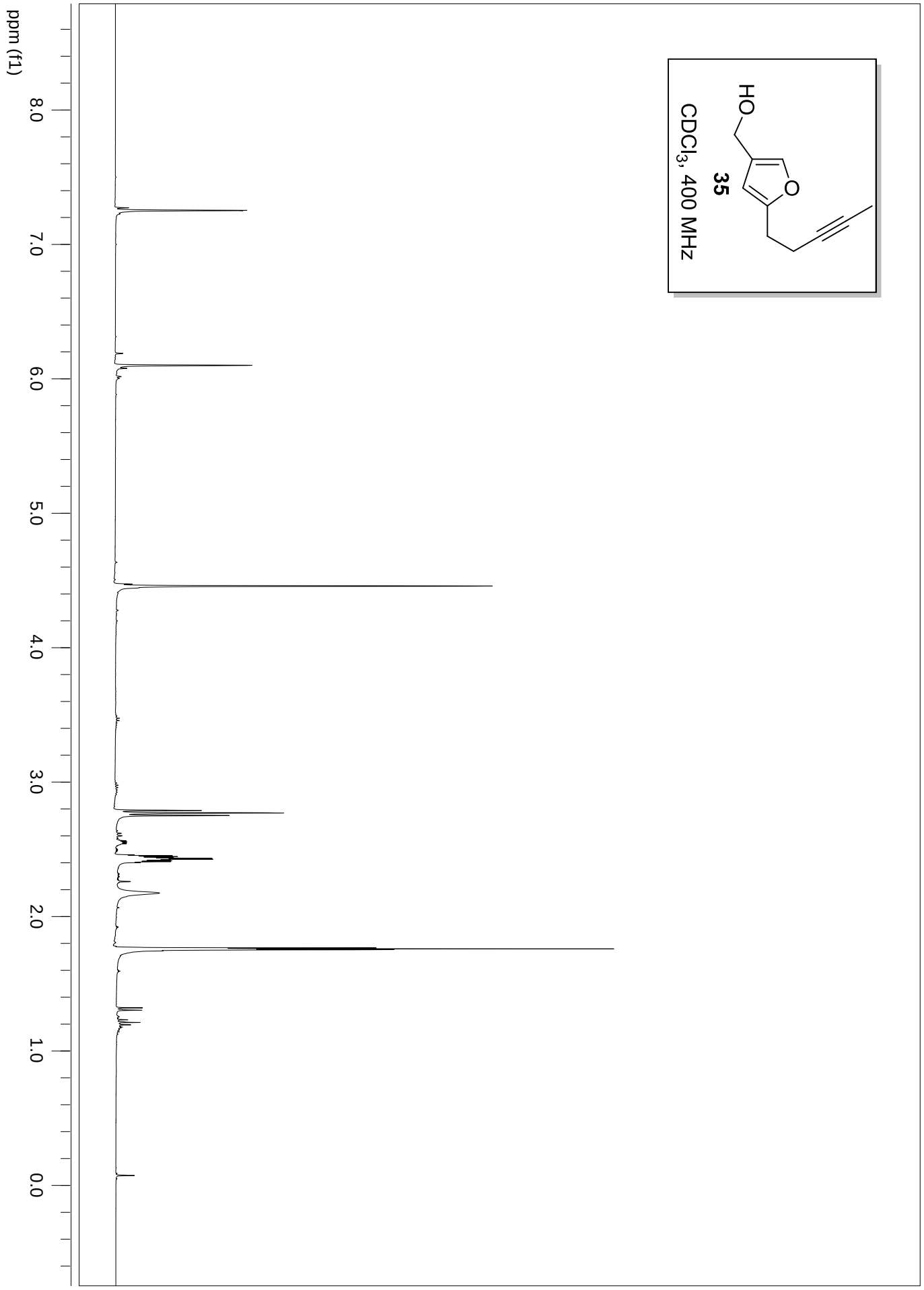


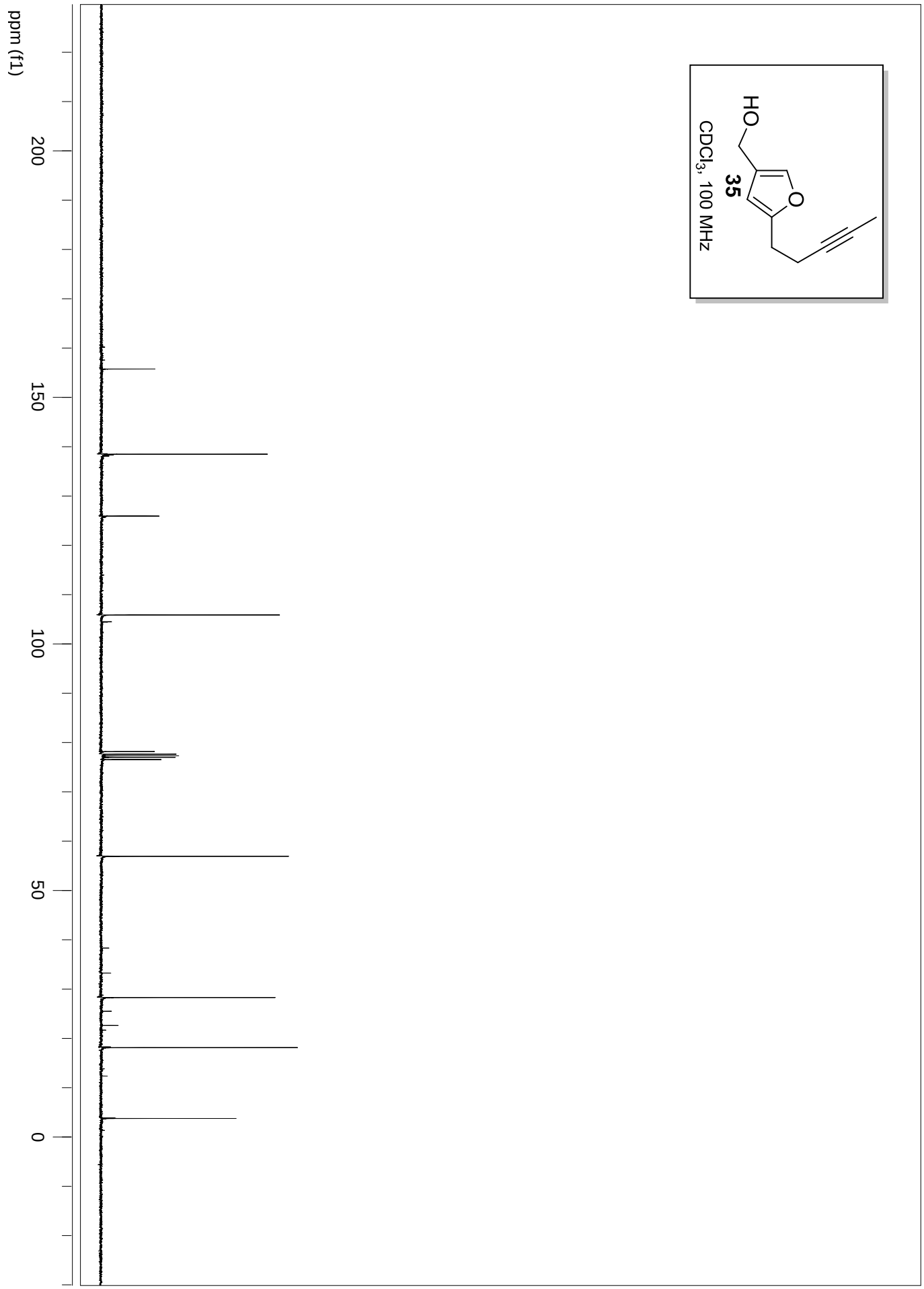
5.10. ^{1}H- and ^{13}C-NMR spectra of **34**



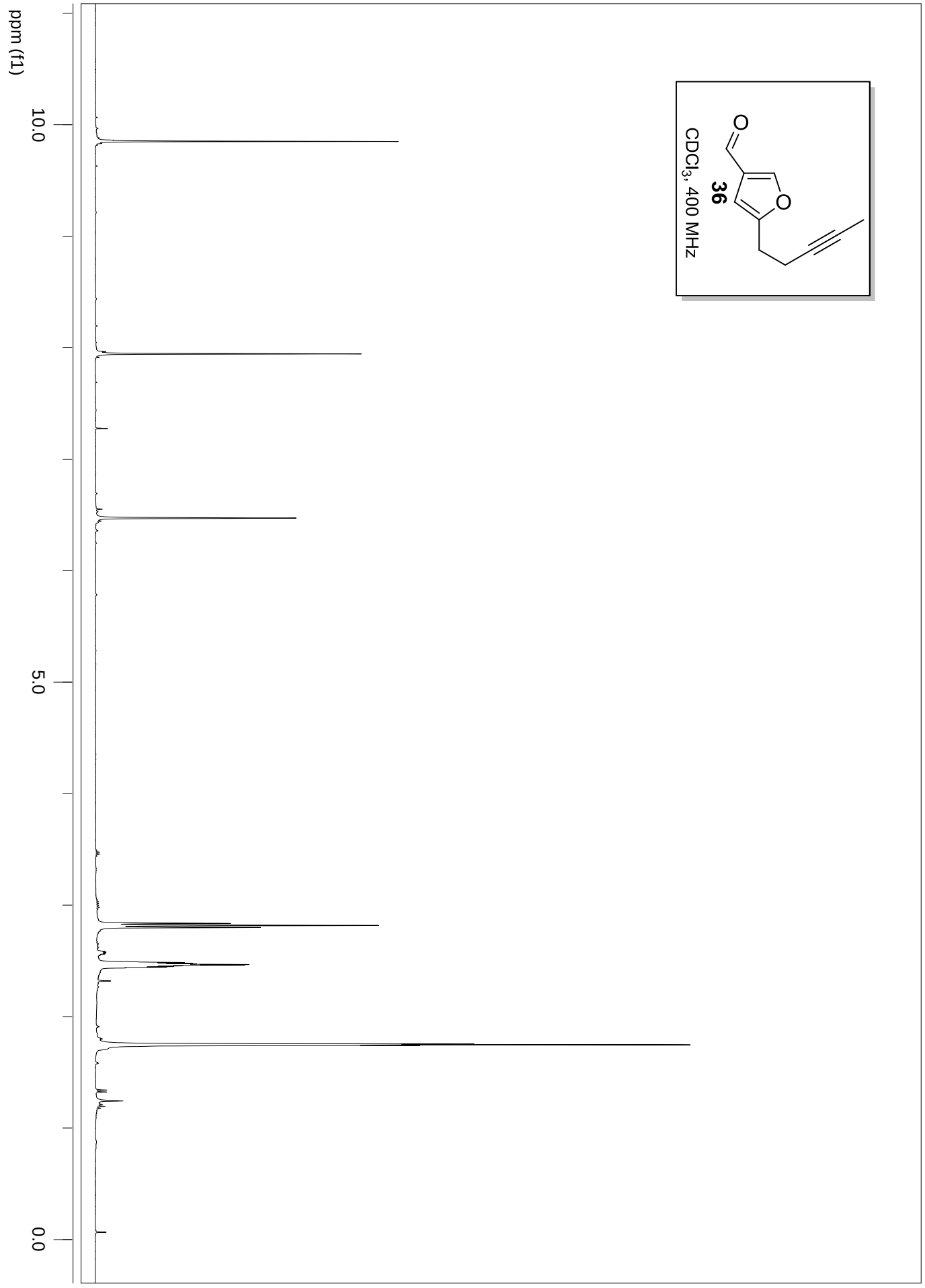


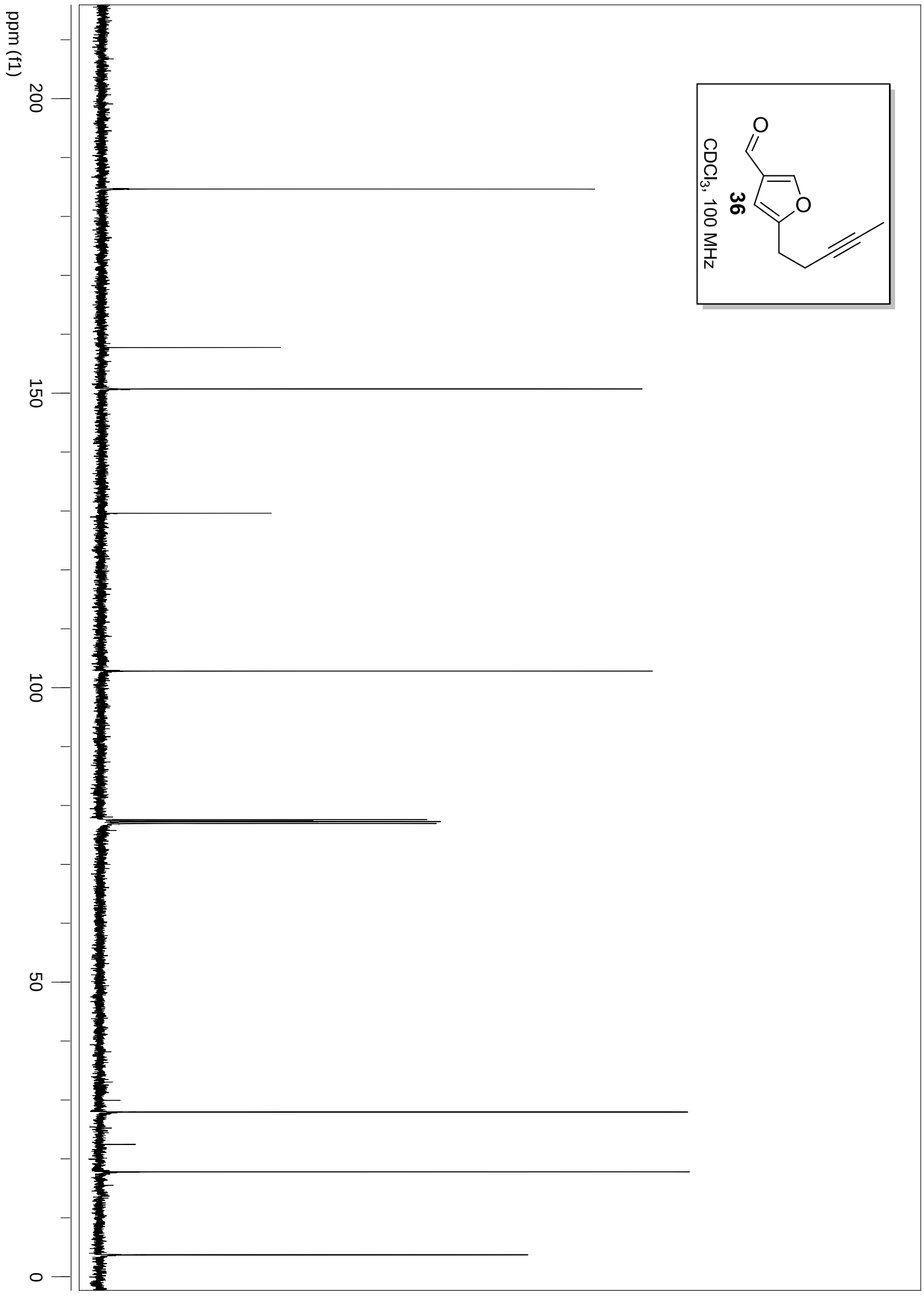
5.11. ^{1}H- and ^{13}C- NMR spectra of **35**



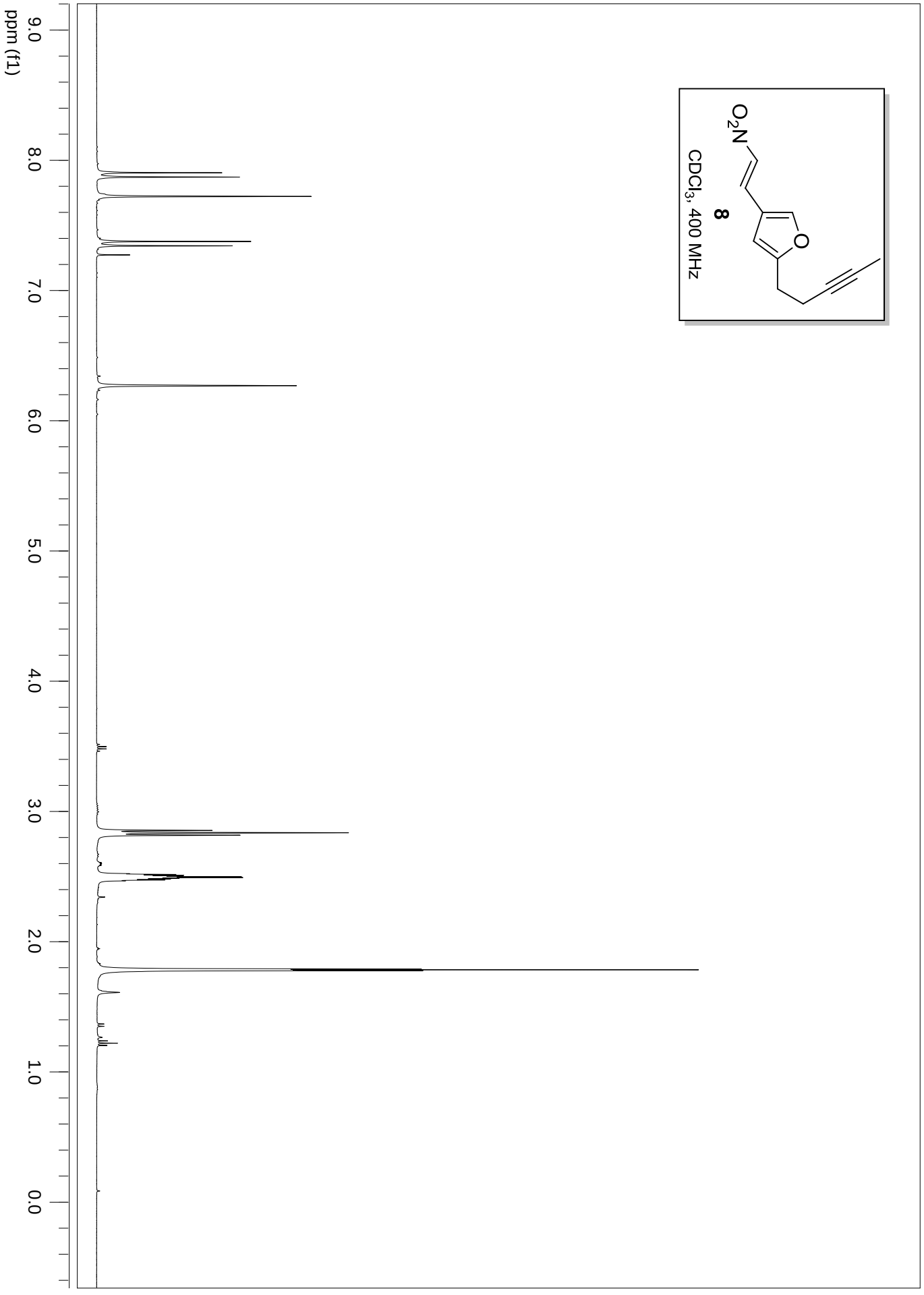

ppm (f1)
200
150
100
50
0
HO
O
35
CDCl3, 100 MHz

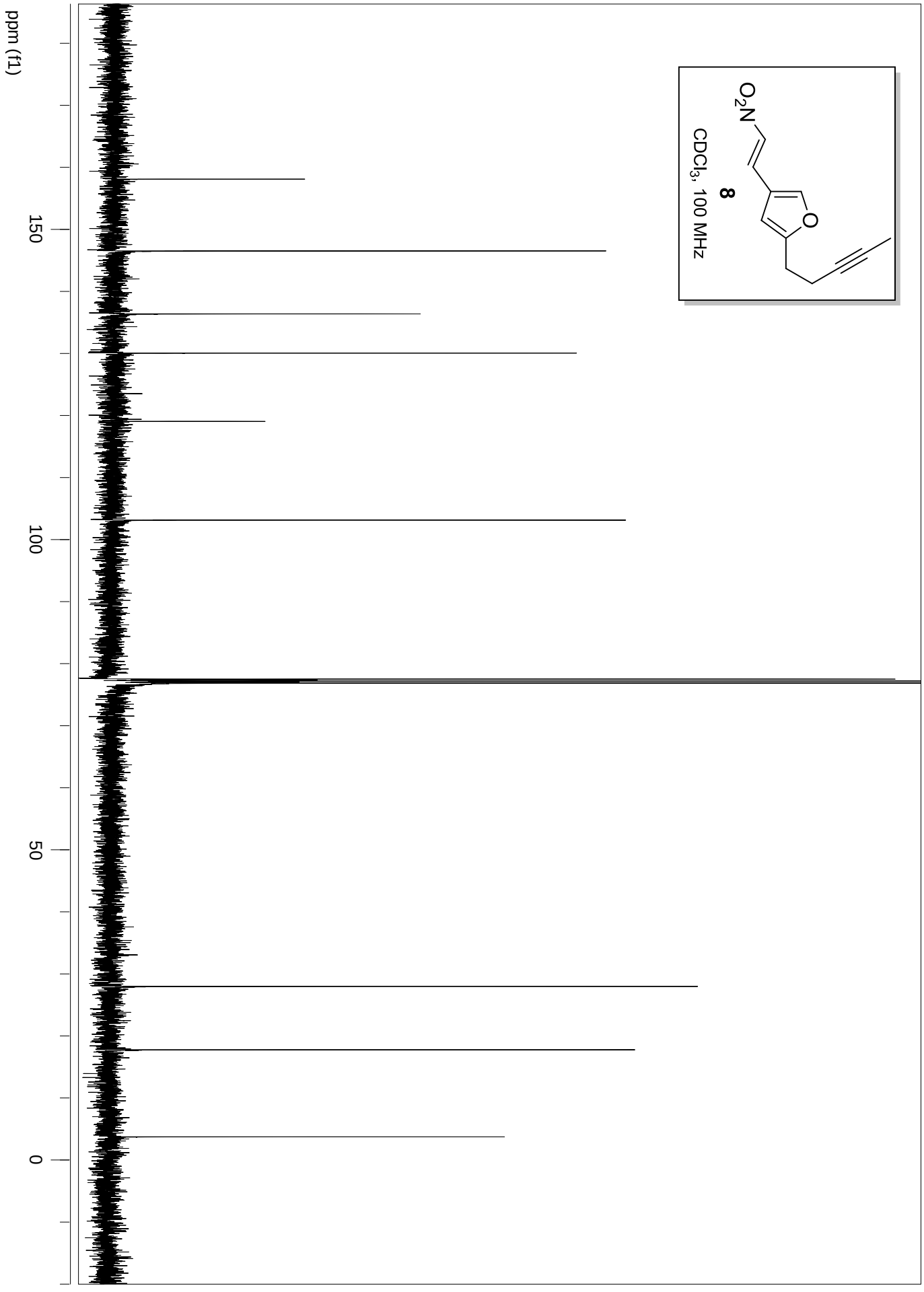
5.12. ^{1}H- and ^{13}C- NMR spectra of **36**



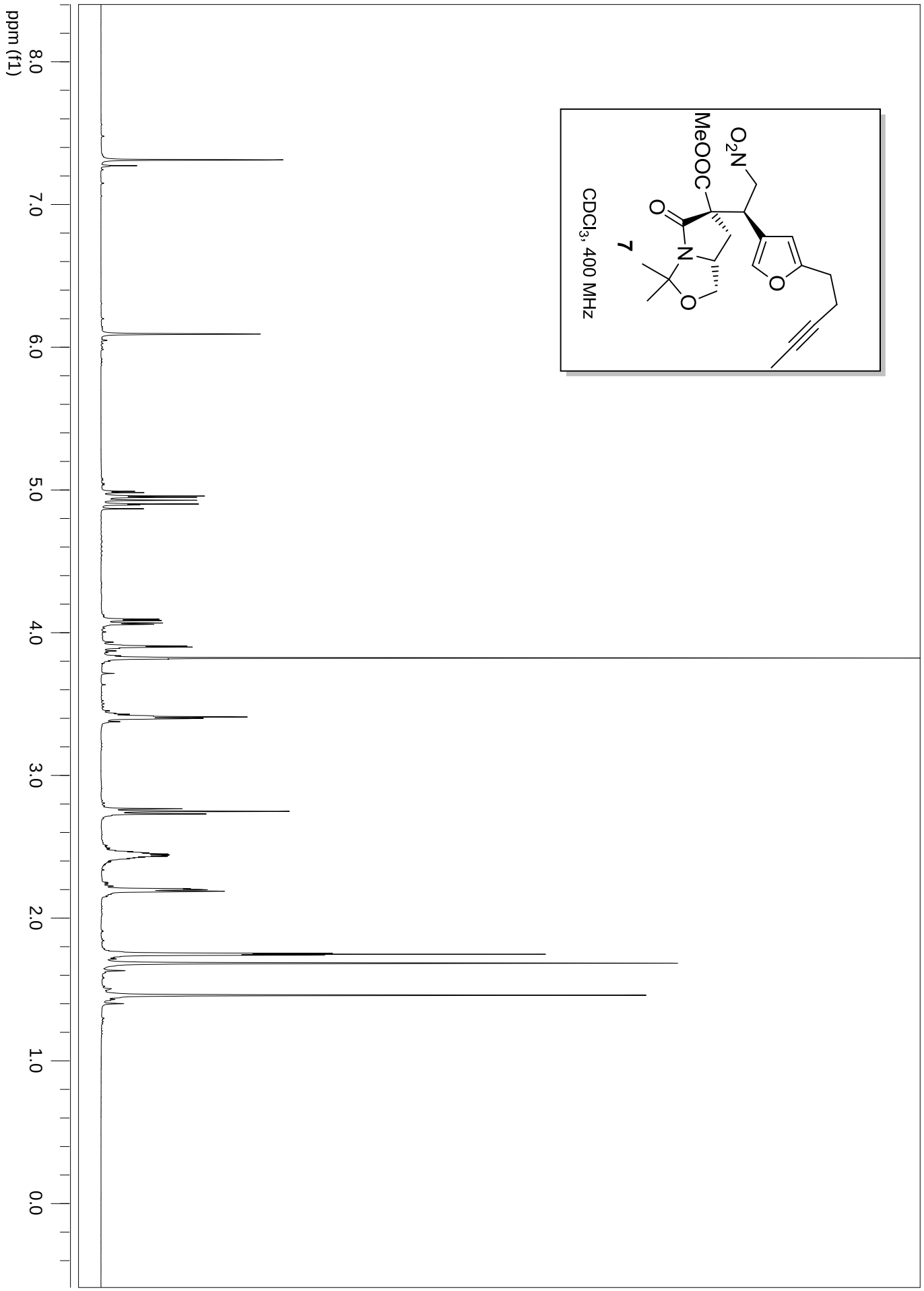

ppm (f1)
200
150
100
50
0
O
O
36
CDCl3, 100 MHz

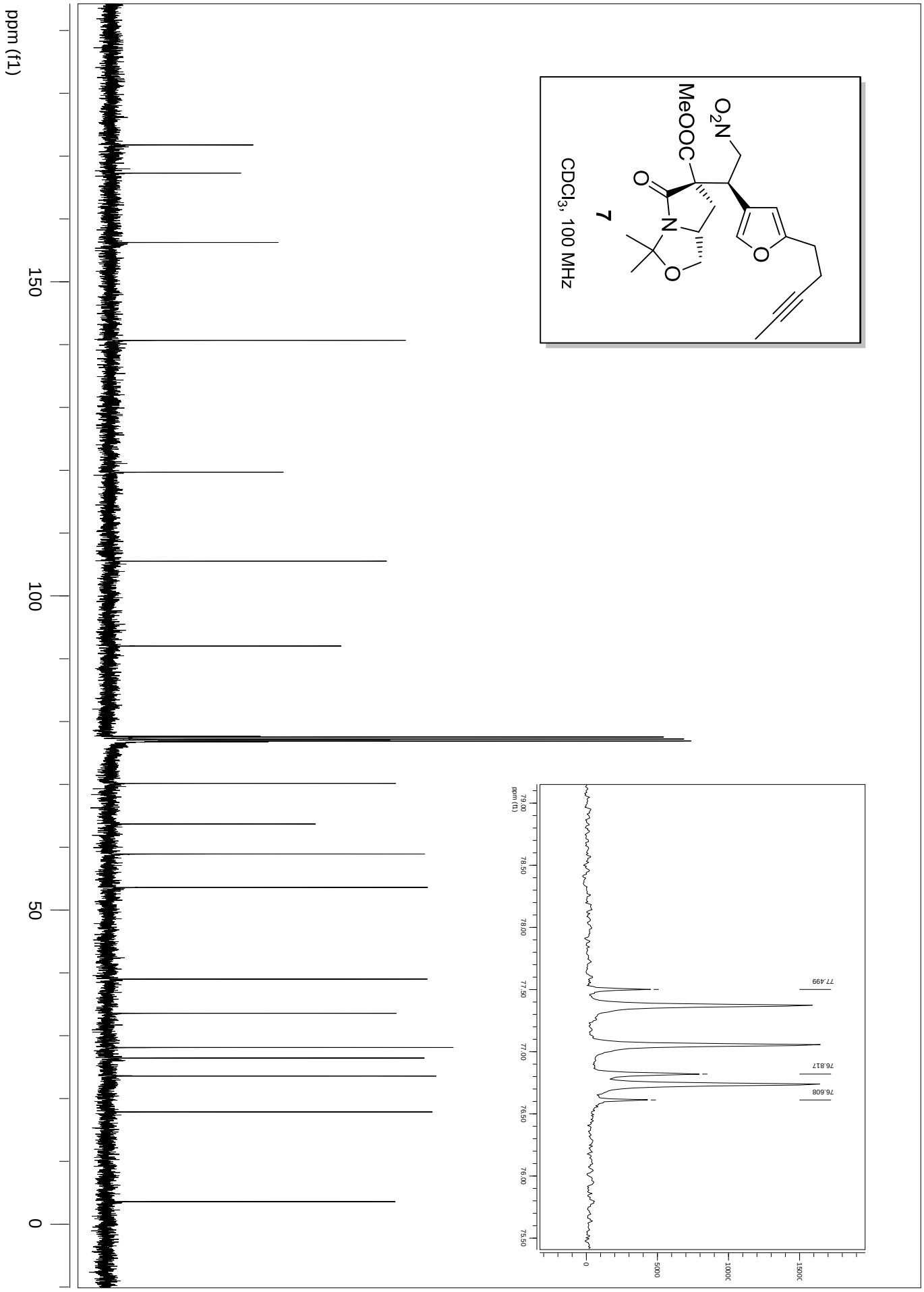
5.13. ^{1}H- and ^{13}C- NMR spectra of **8**



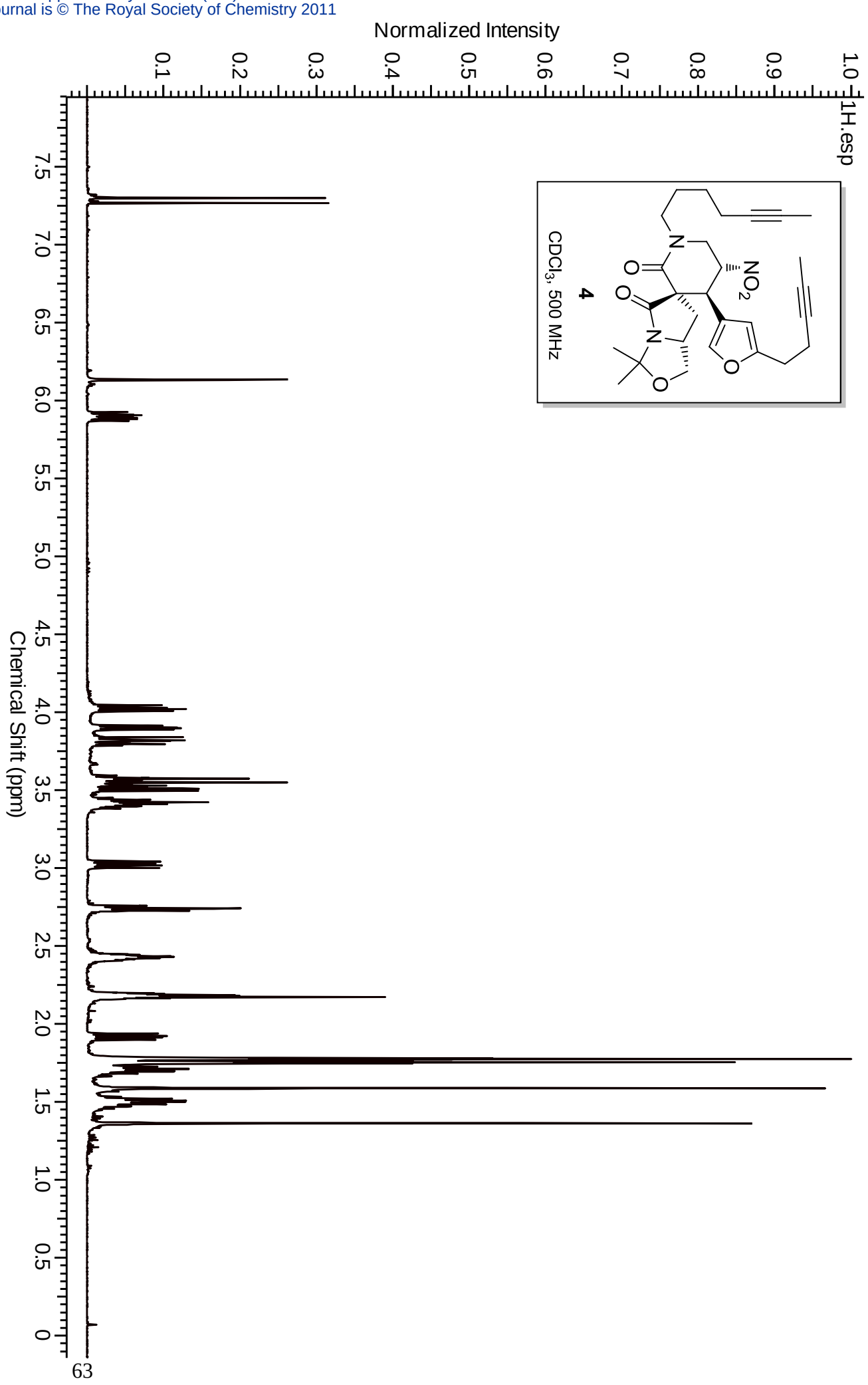

ppm (f1)
150
100
50
0
O2N
O
8
CDCl3, 100 MHz

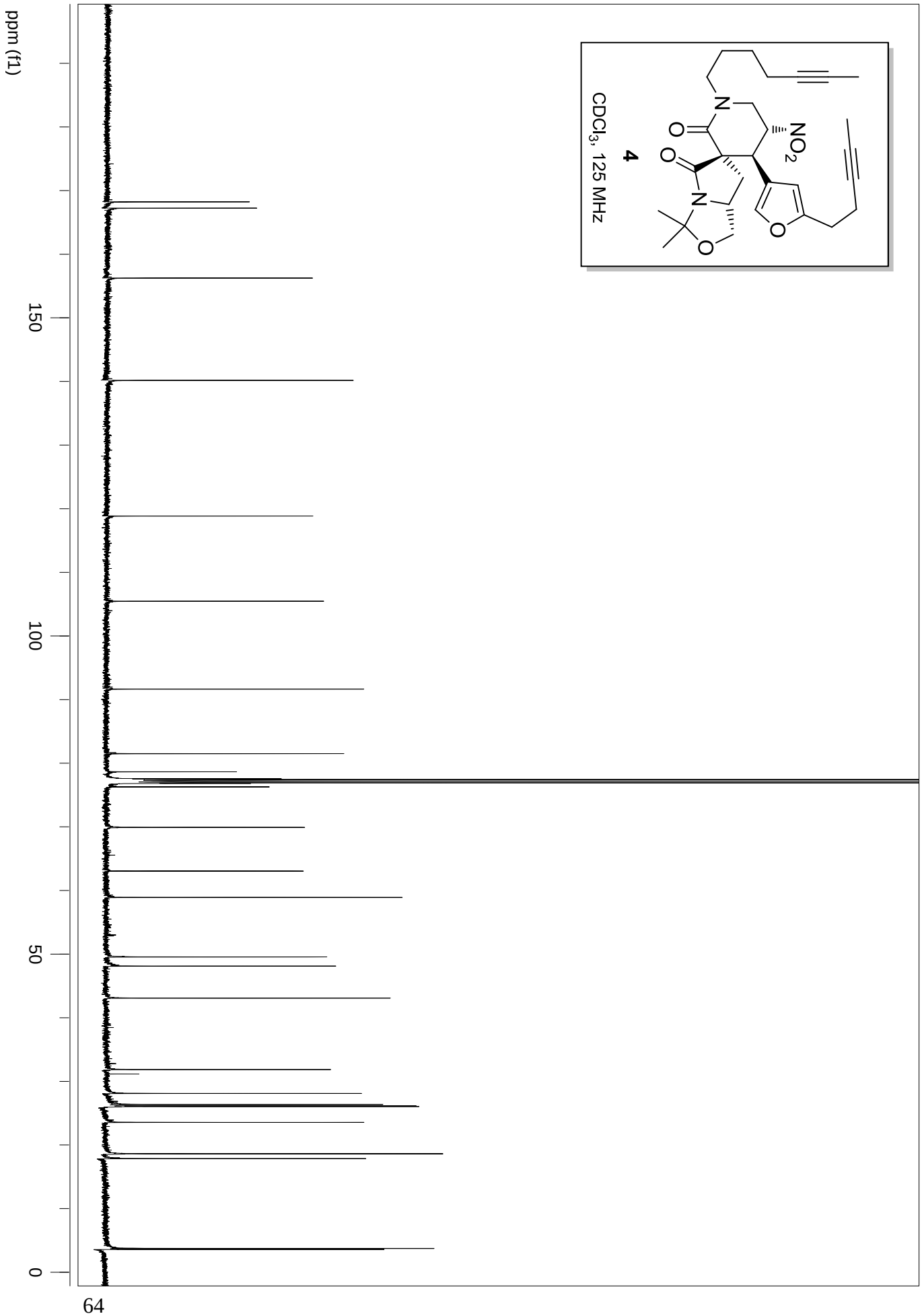
5.14. ^{1}H- and ^{13}C-NMR spectra of **7**



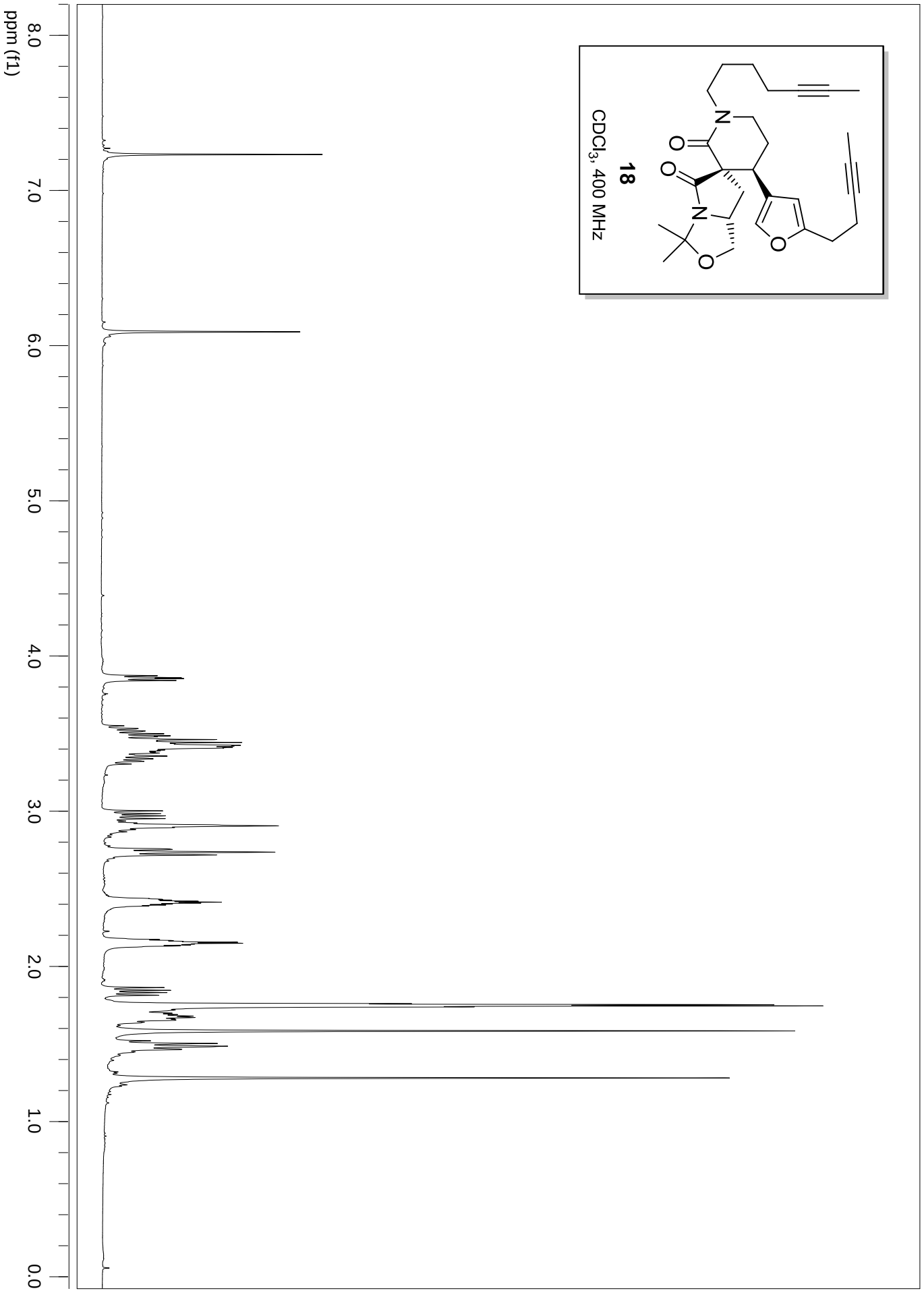

ppm (f1)
150
100
50
0
7
CDCl3, 100 MHz
O2N
MeOOC
O
N
O
O
79.00
78.50
78.00
77.50
77.00
76.50
76.00
75.50
77.499
76.817
76.608
0
5000
10000
15000

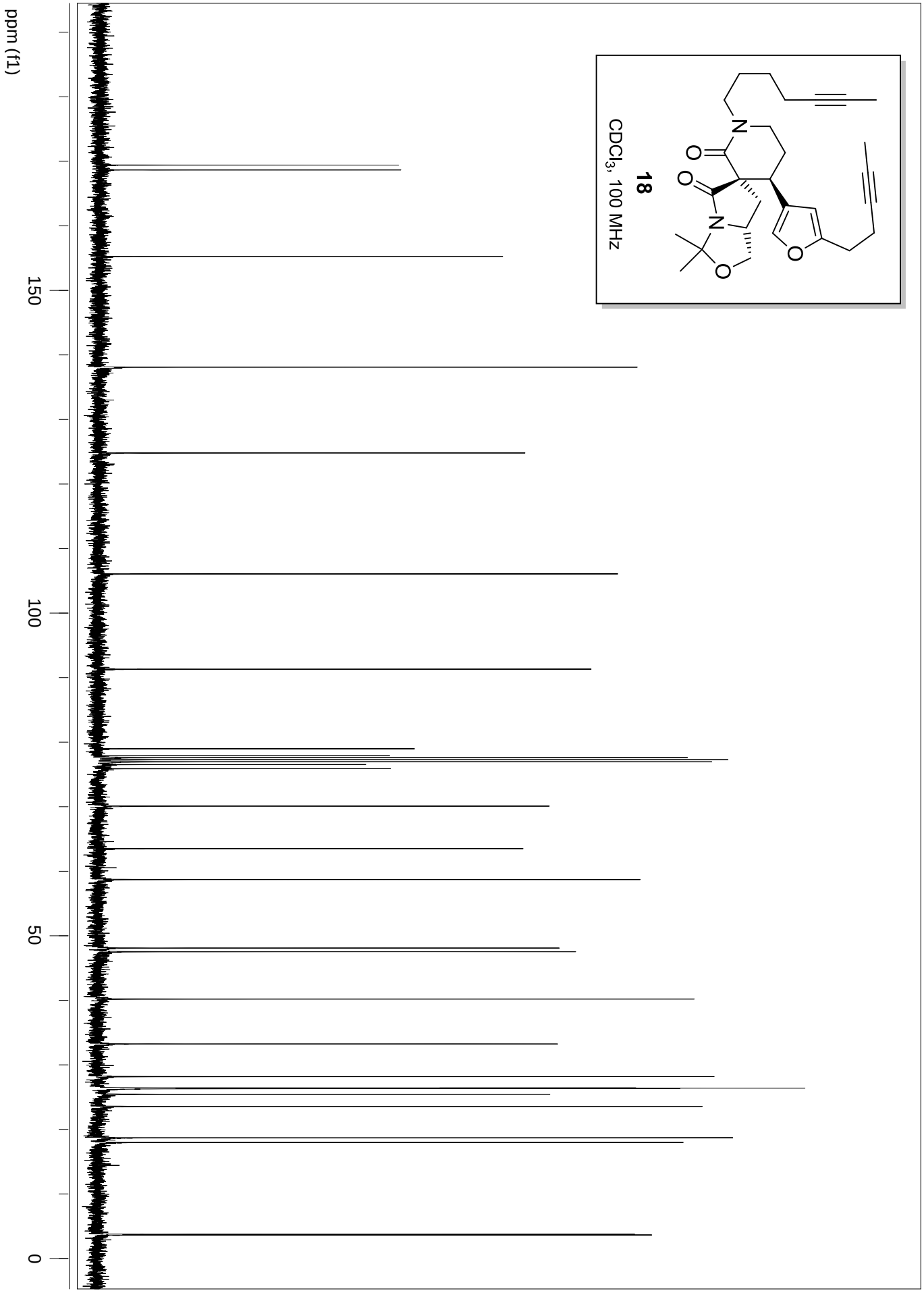
5.15. ^{1}H- and ^{13}C-NMR spectra of **4**



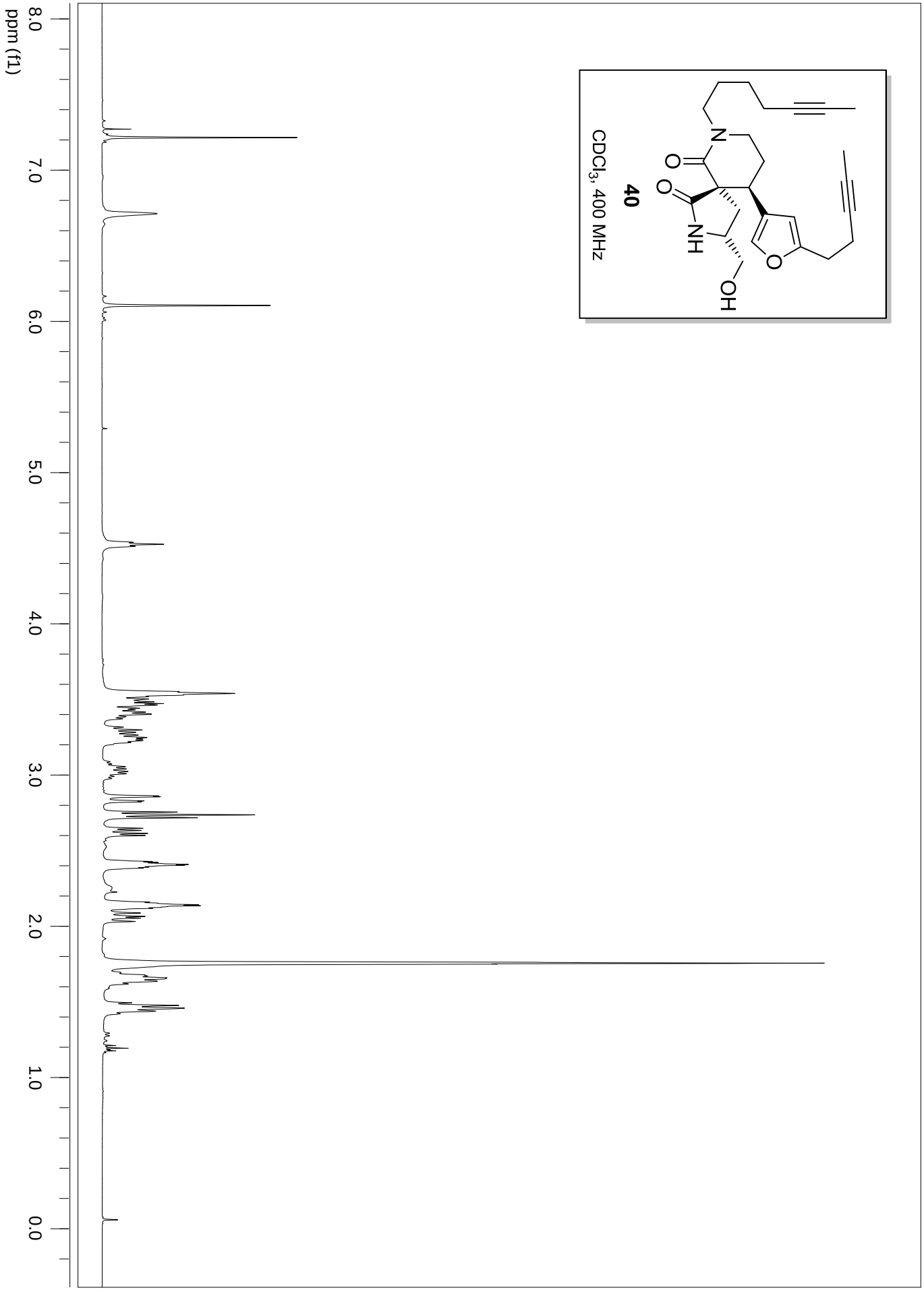


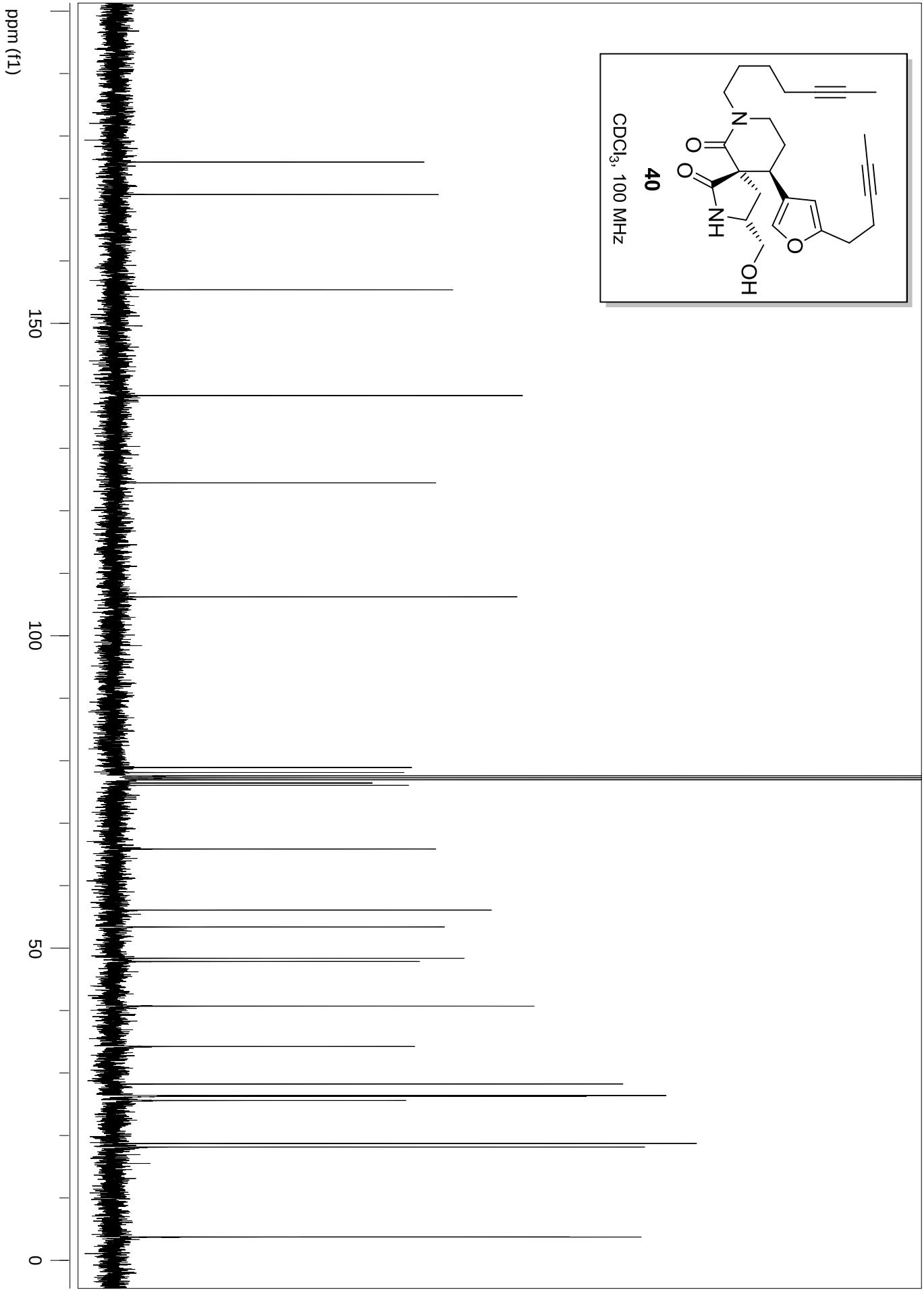
5.16. ^{1}H- and ^{13}C-NMR spectra of **18**



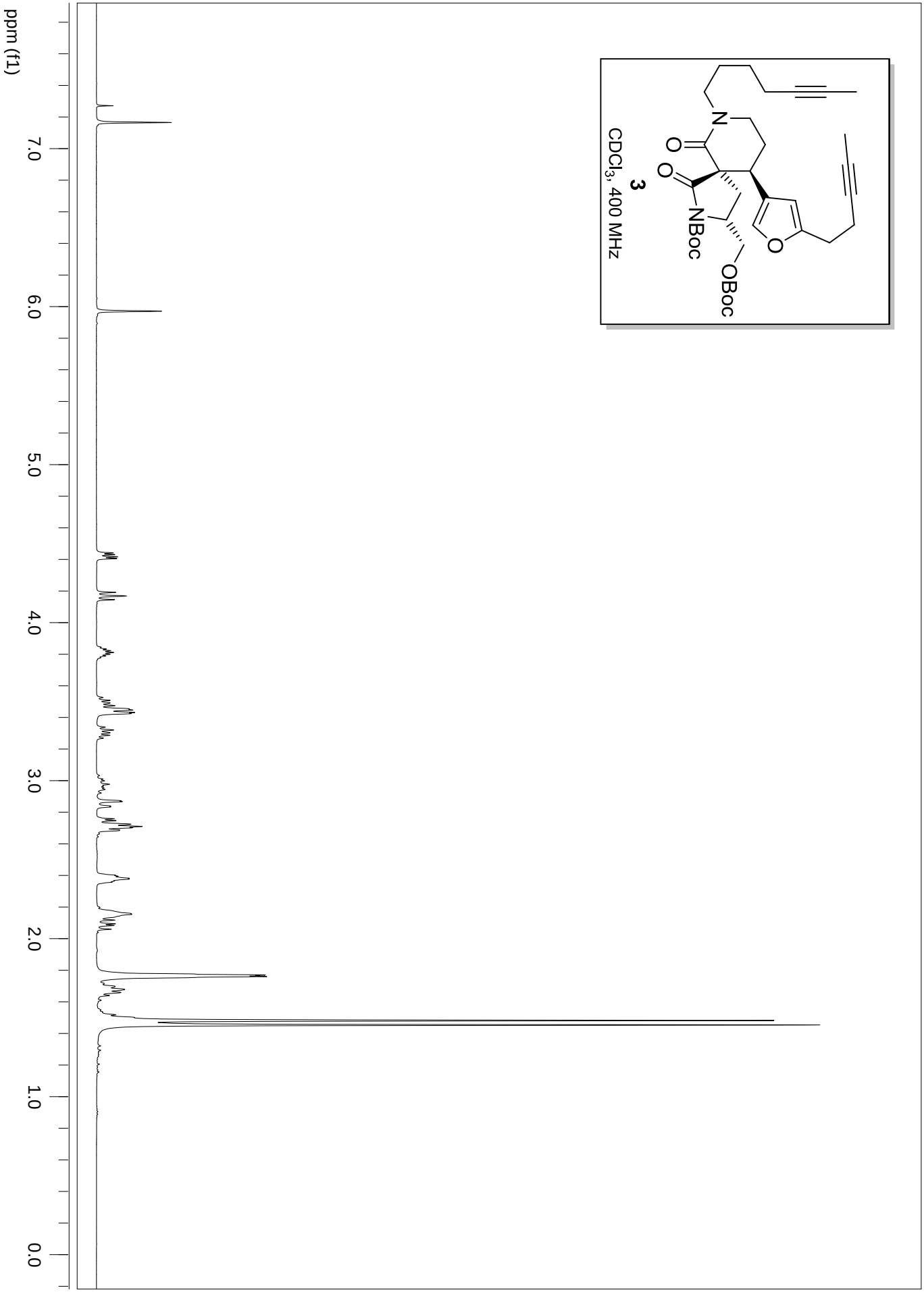

ppm (f1)
150
100
50
0
18
$CDCl_3$, 100 MHz
N
O
O
N
O
O
N
O

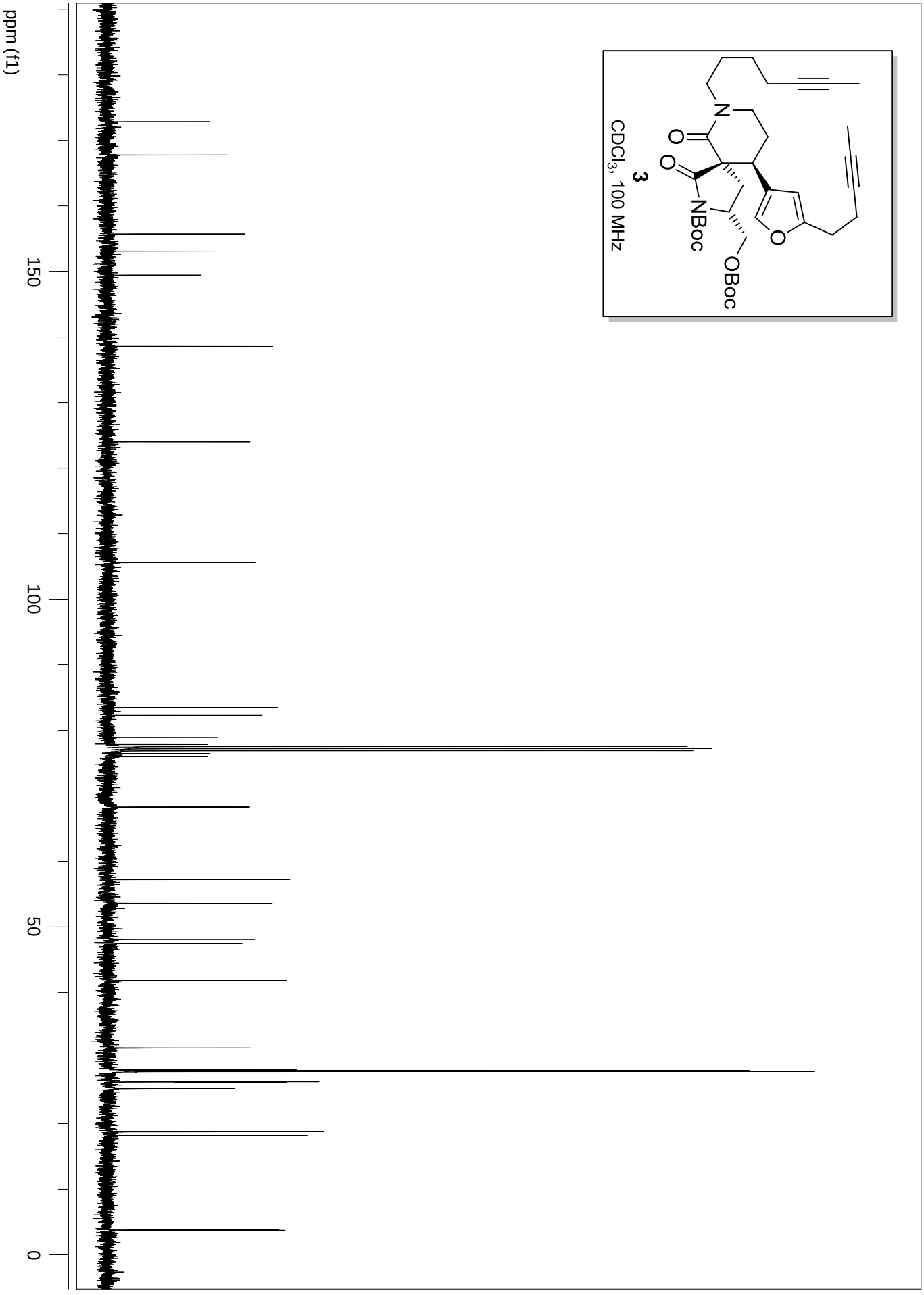
5.17. ^{1}H- and ^{13}C-NMR spectra of **40**



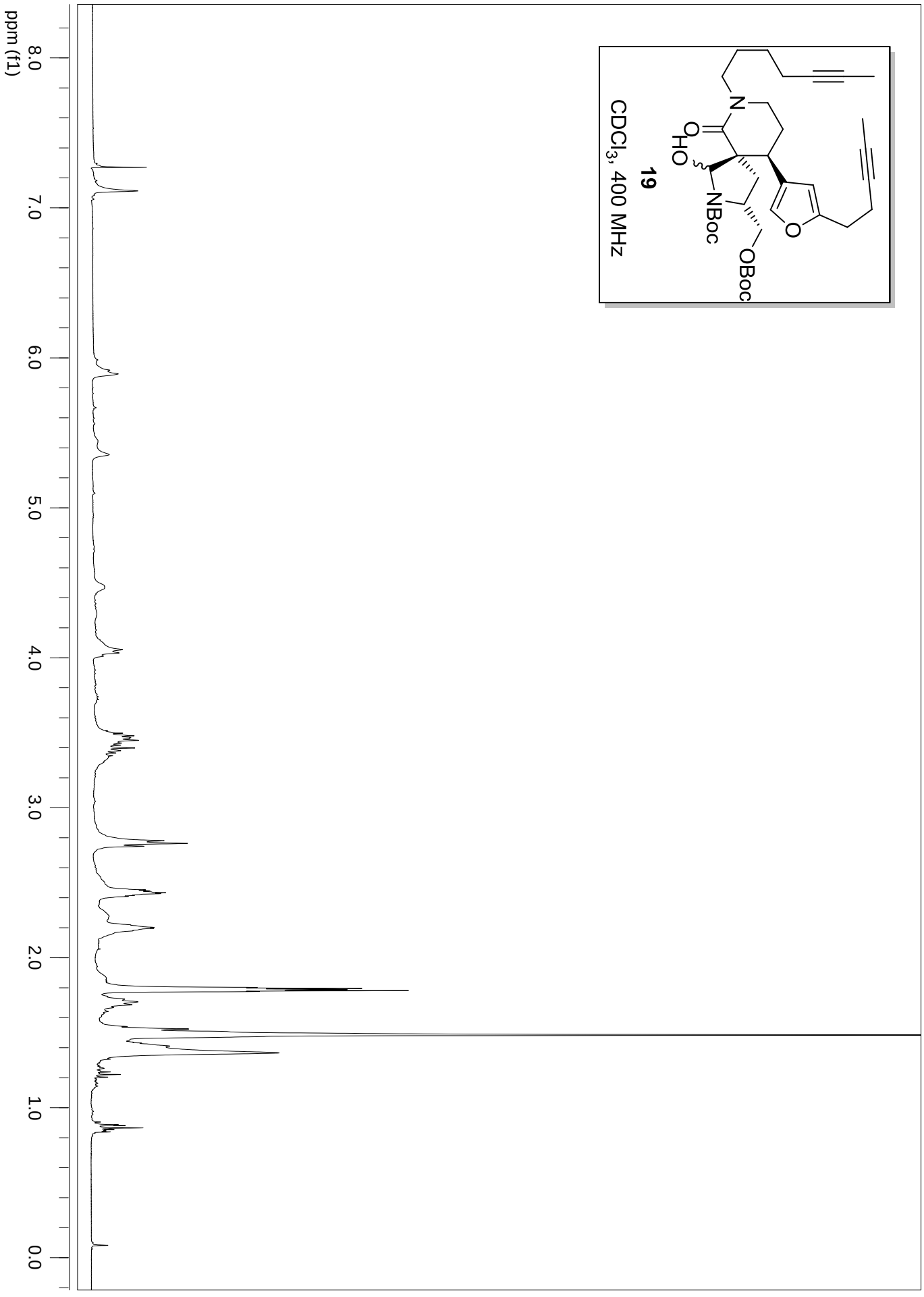


5.18. ^{1}H- and ^{13}C-NMR spectra of **3**

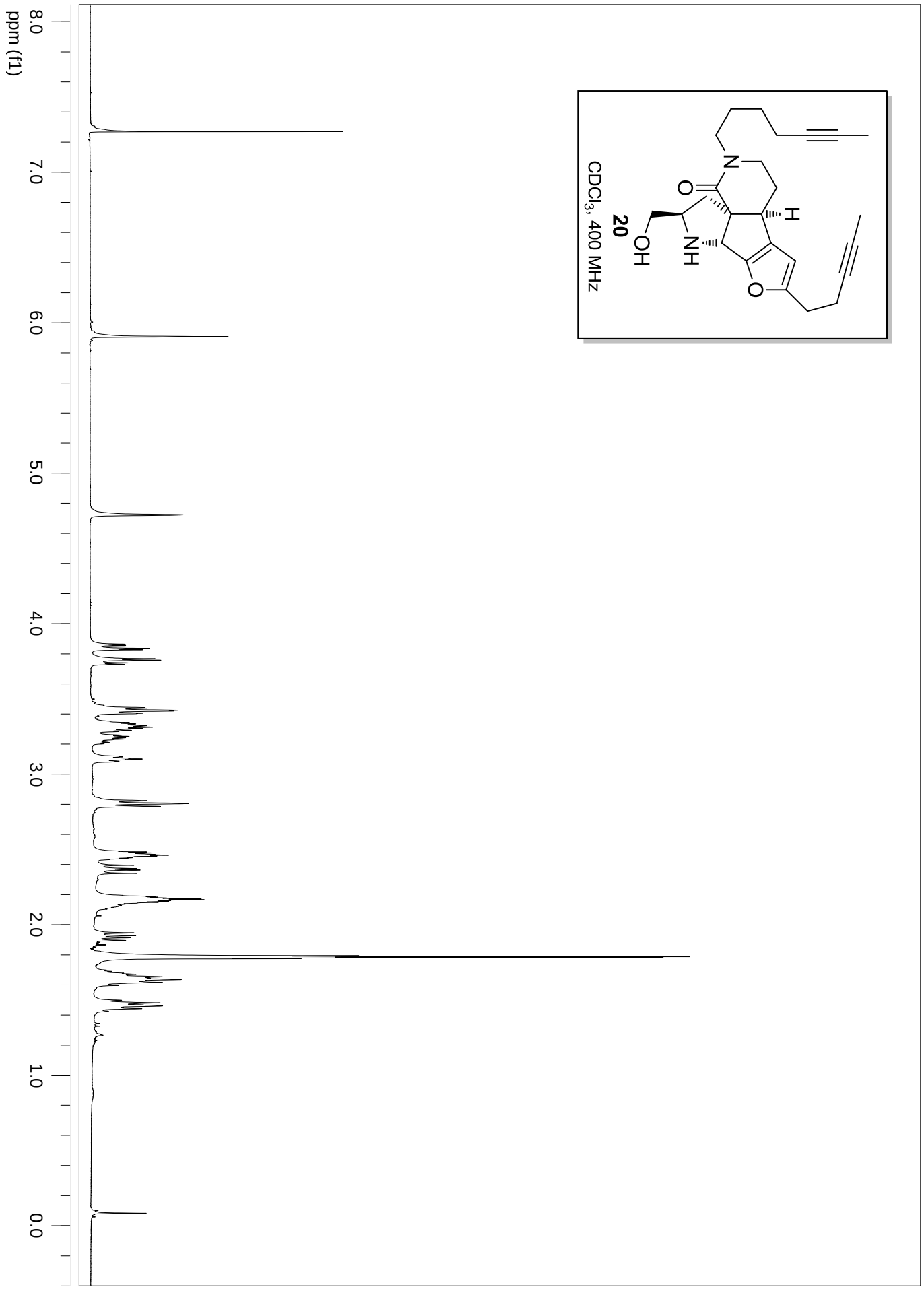


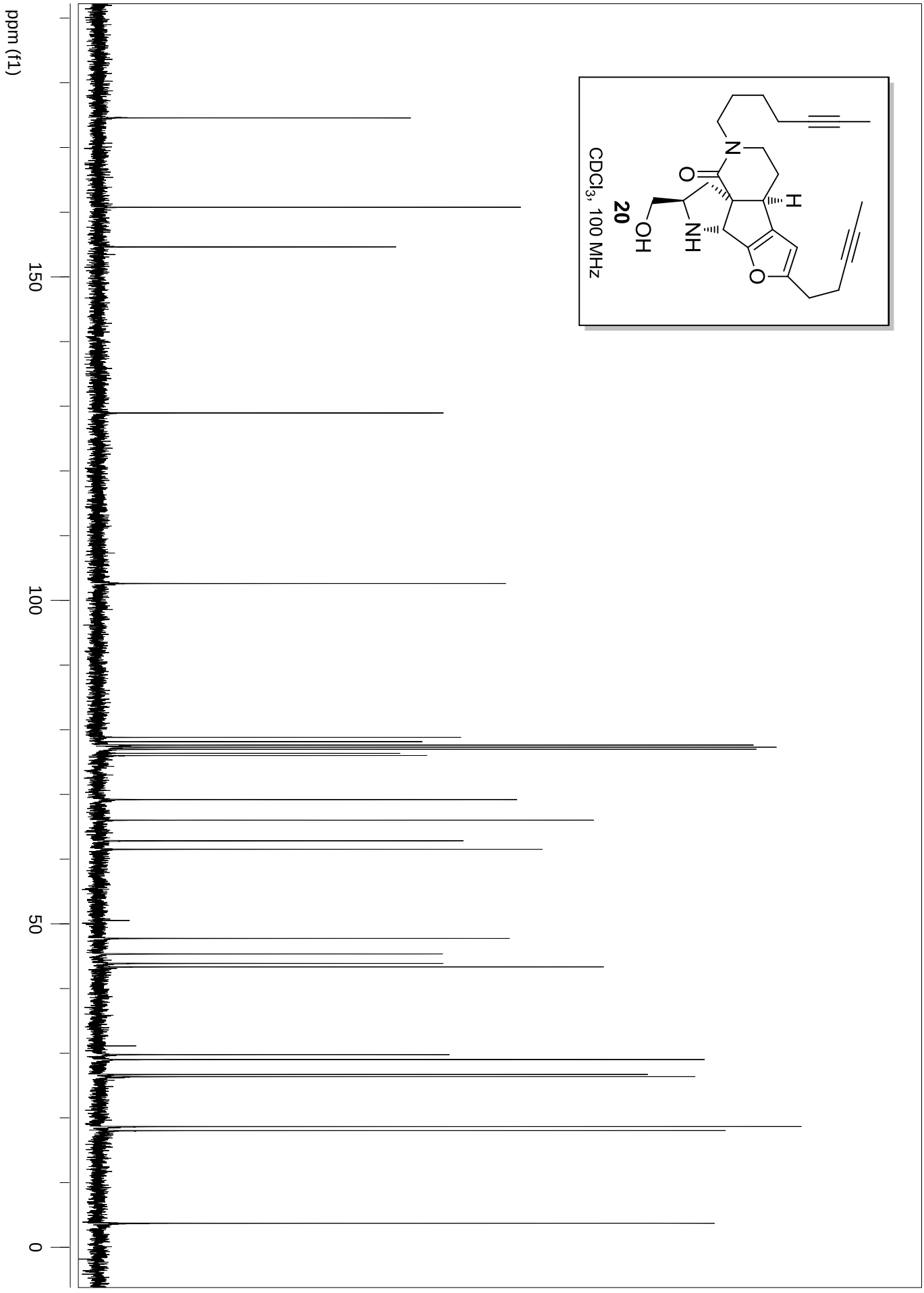

ppm (f1)
150
100
50
0
3
CDCl3, 100 MHz
N
O
O
NBoc
OBoc
O

5.19. ^{1}H-NMR spectrum of **19**

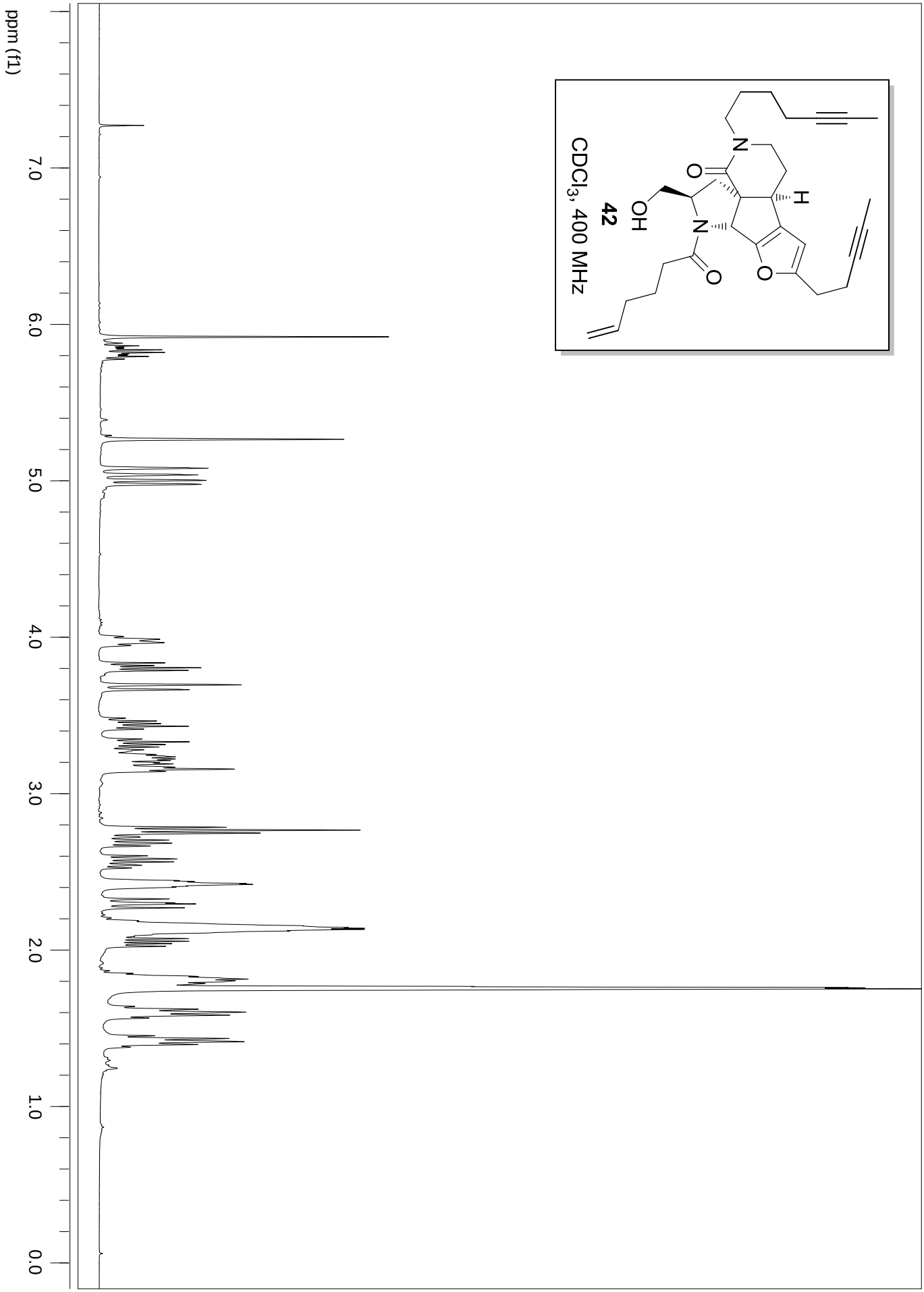


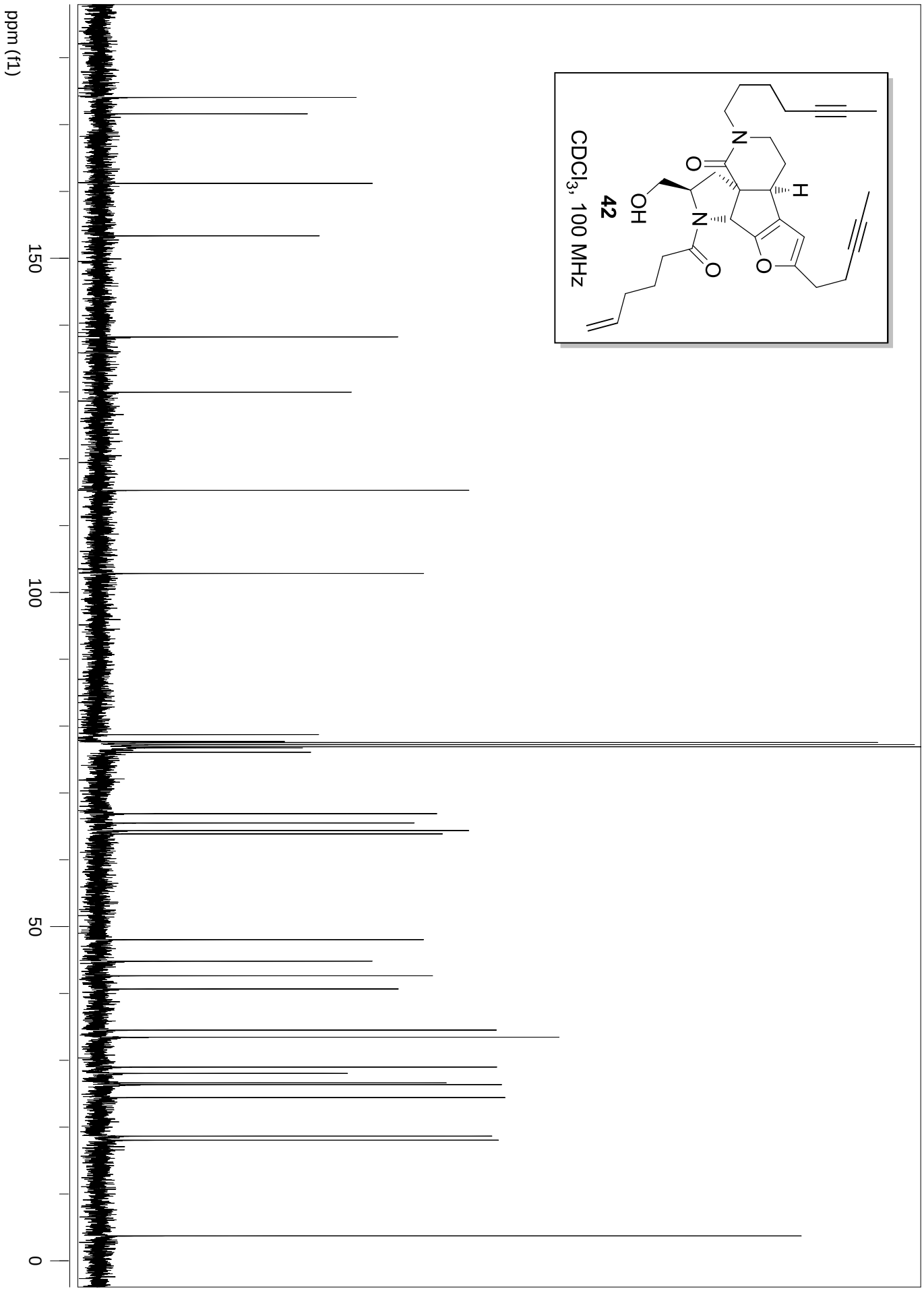
5.20. ^{1}H- and ^{13}C-NMR spectra of **20**



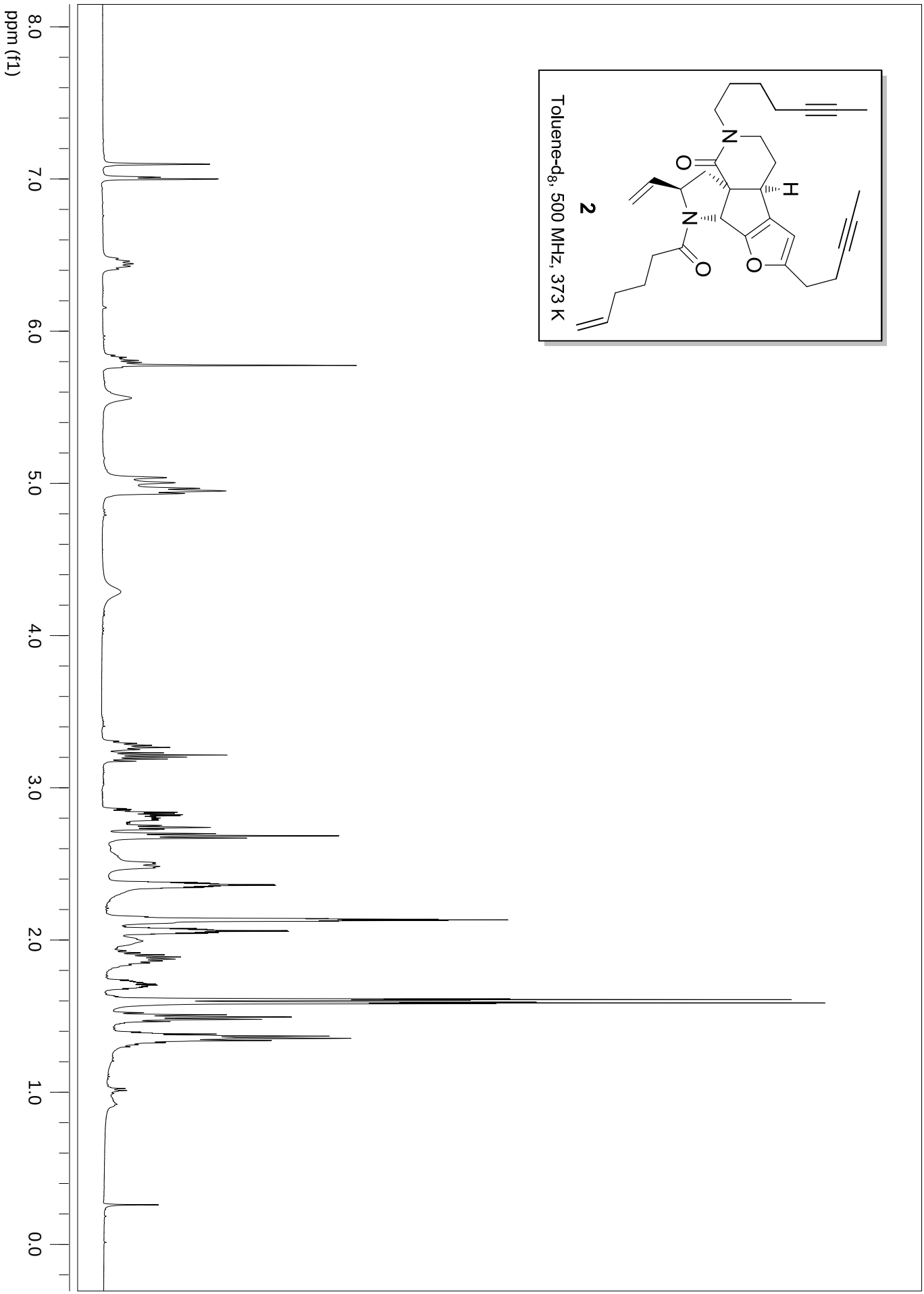


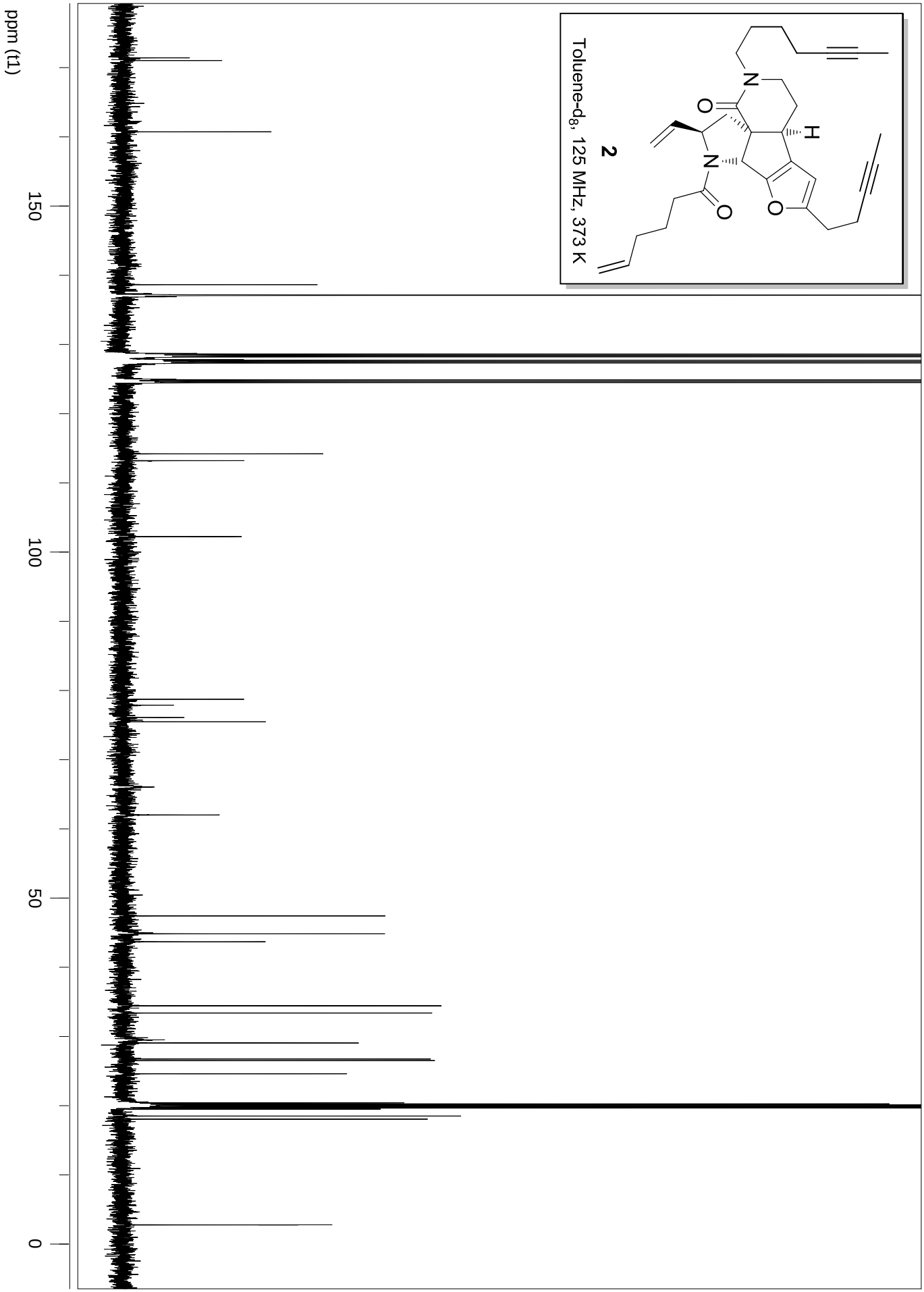
5.21. ^{1}H- and ^{13}C-NMR spectra of **42**

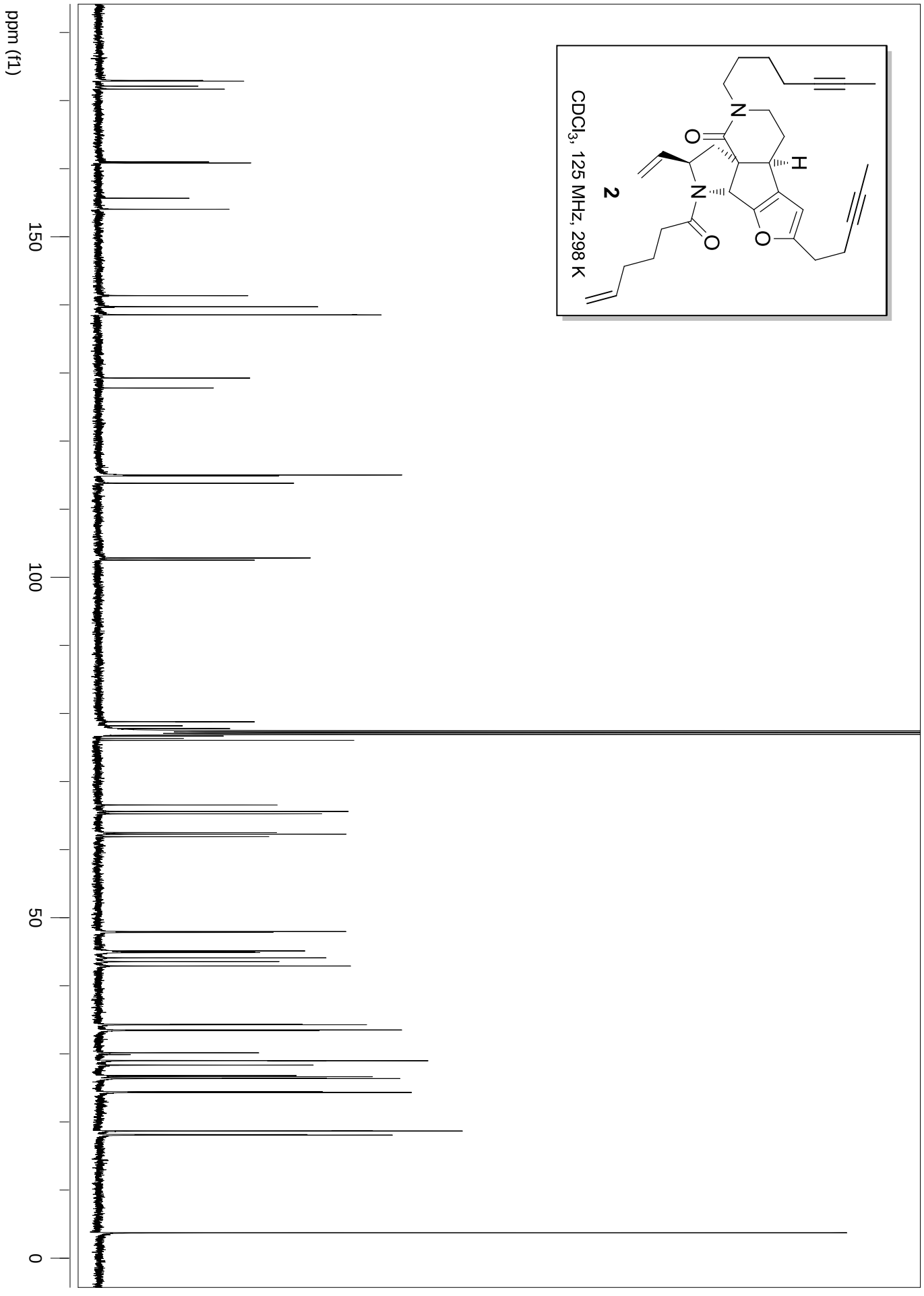




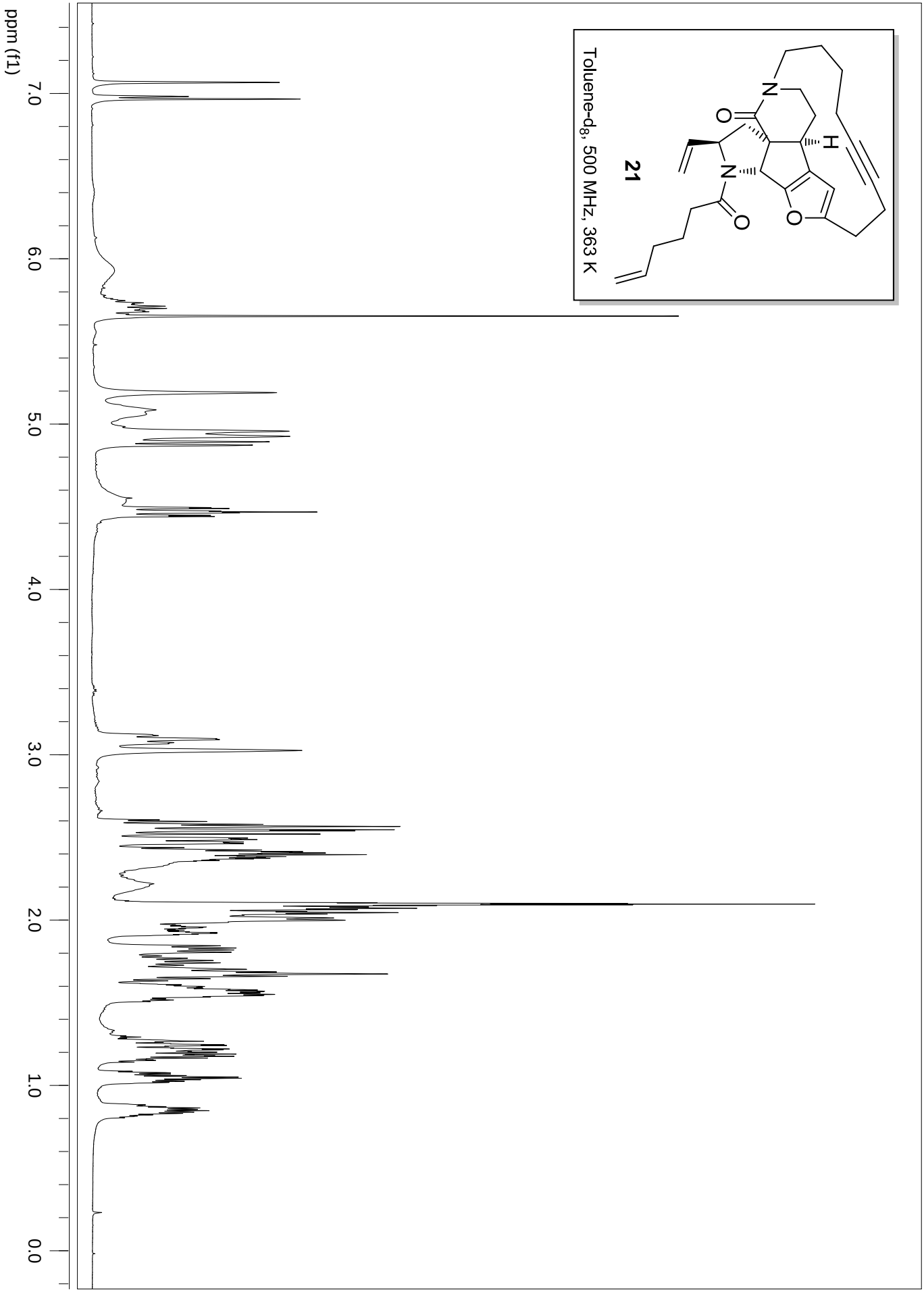
5.22. ^{1}H- and ^{13}C-NMR spectra of **2**

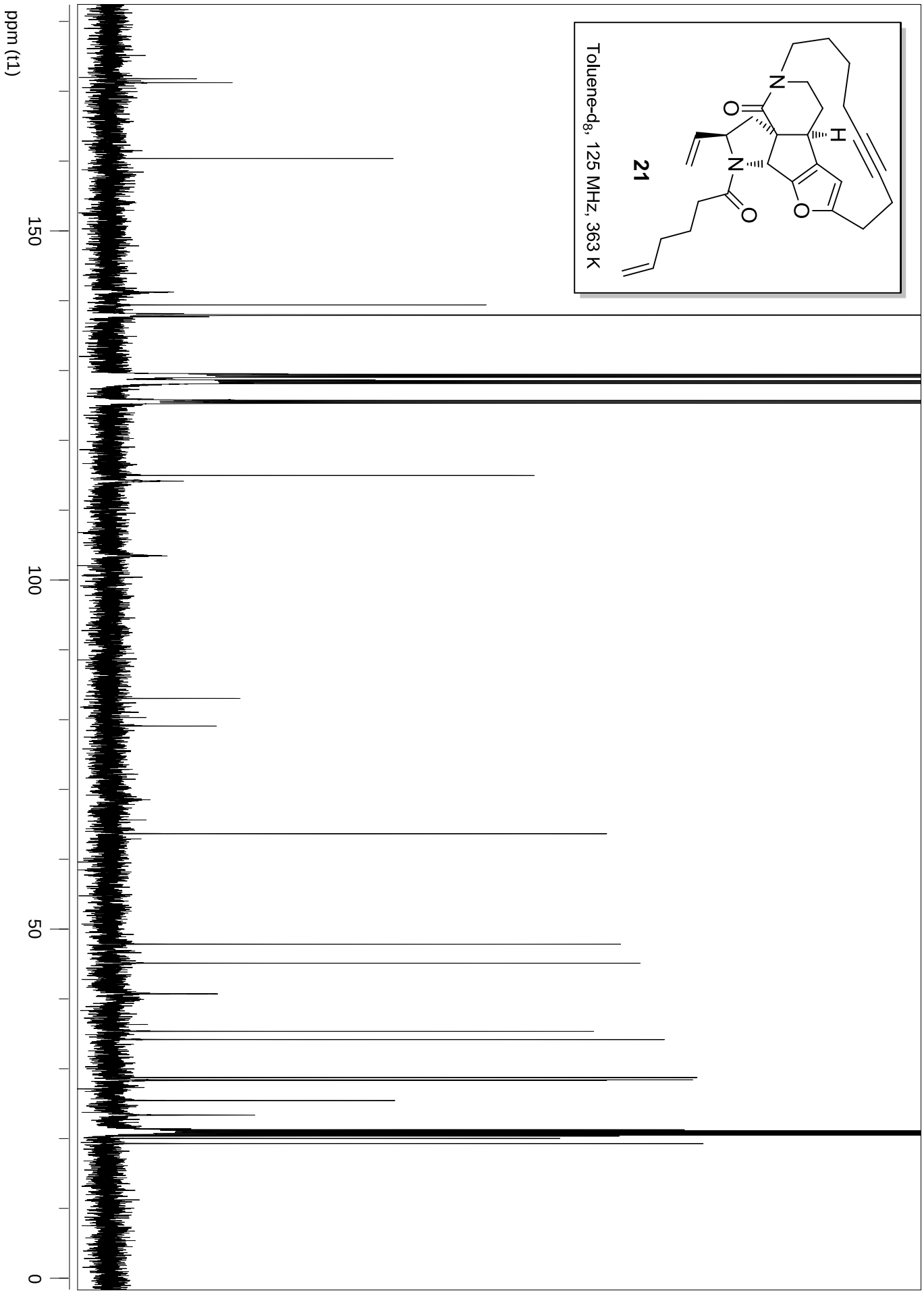


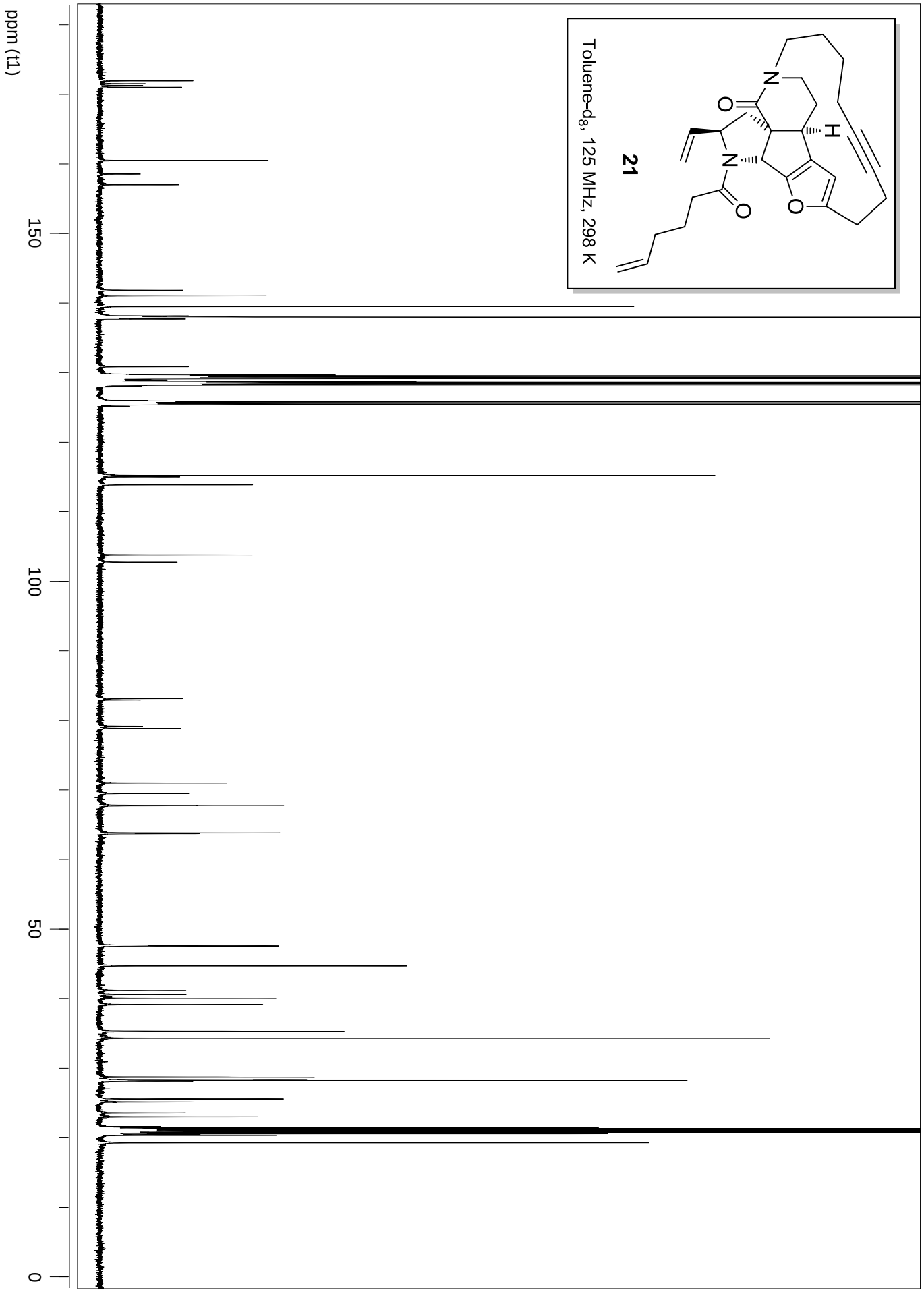

ppm (t1)
150
100
50
0
Toluene-d8, 125 MHz, 373 K
2
N
O
N
O
H
O



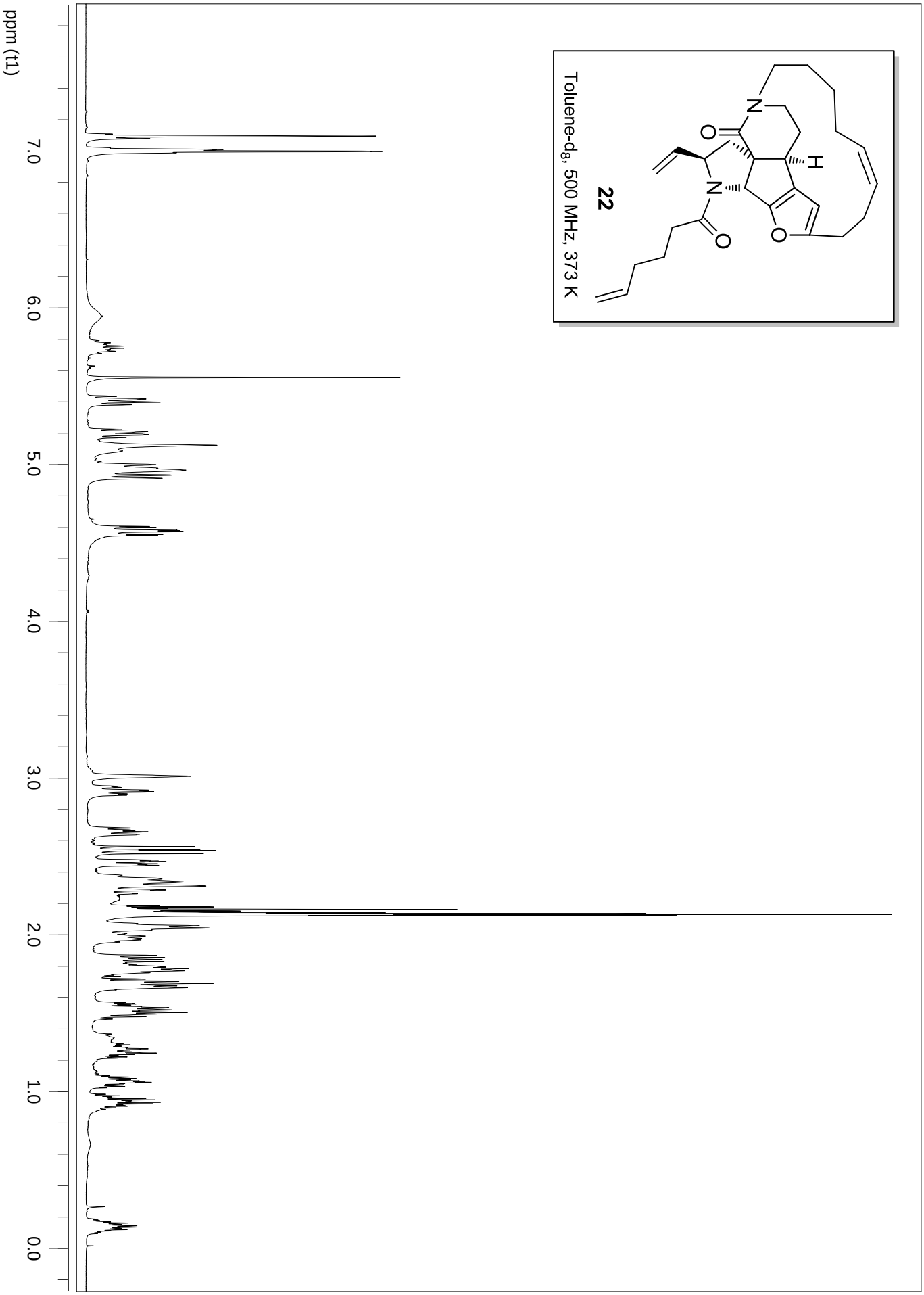
5.23. ^{1}H- and ^{13}C-NMR spectra of **21**

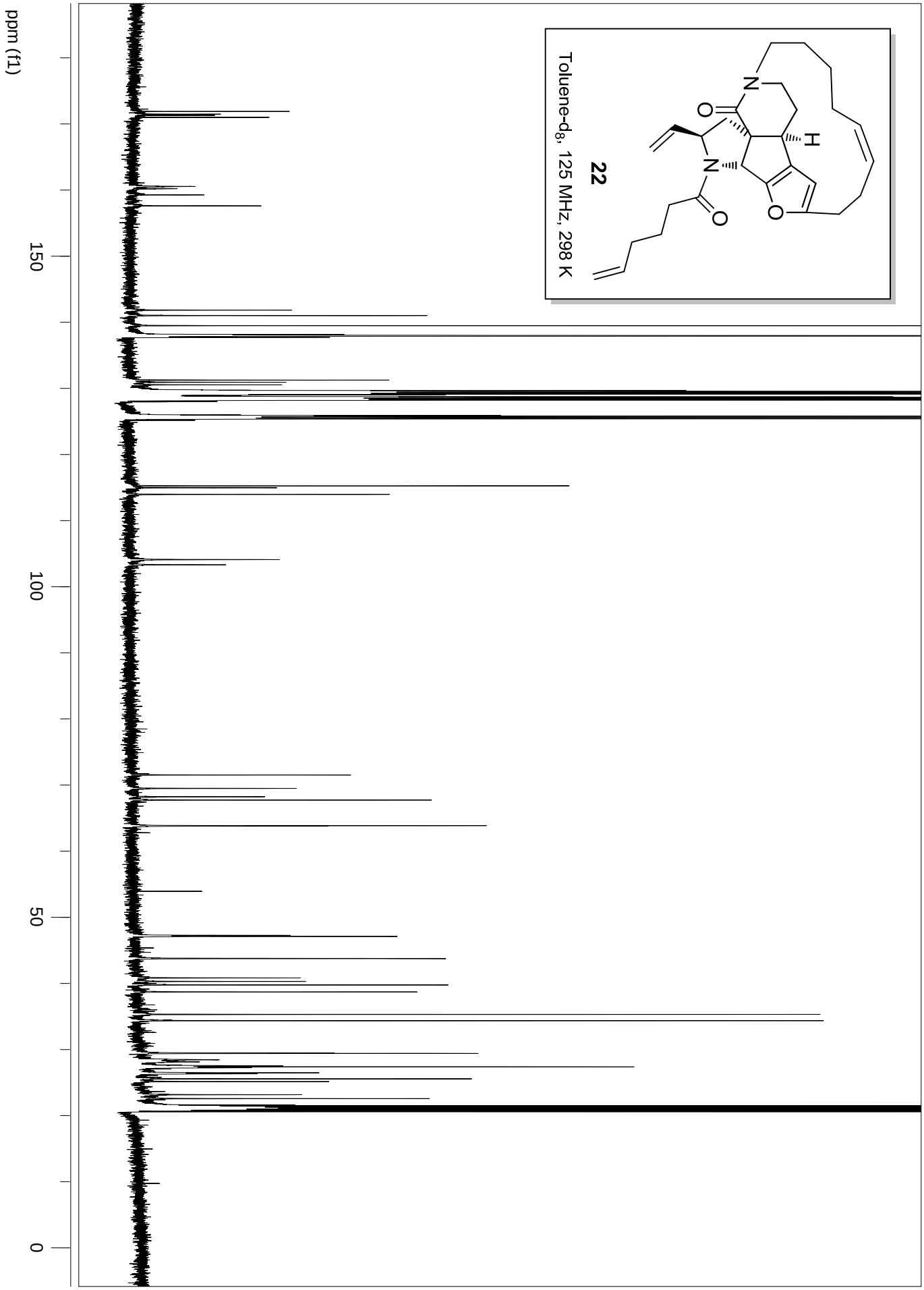




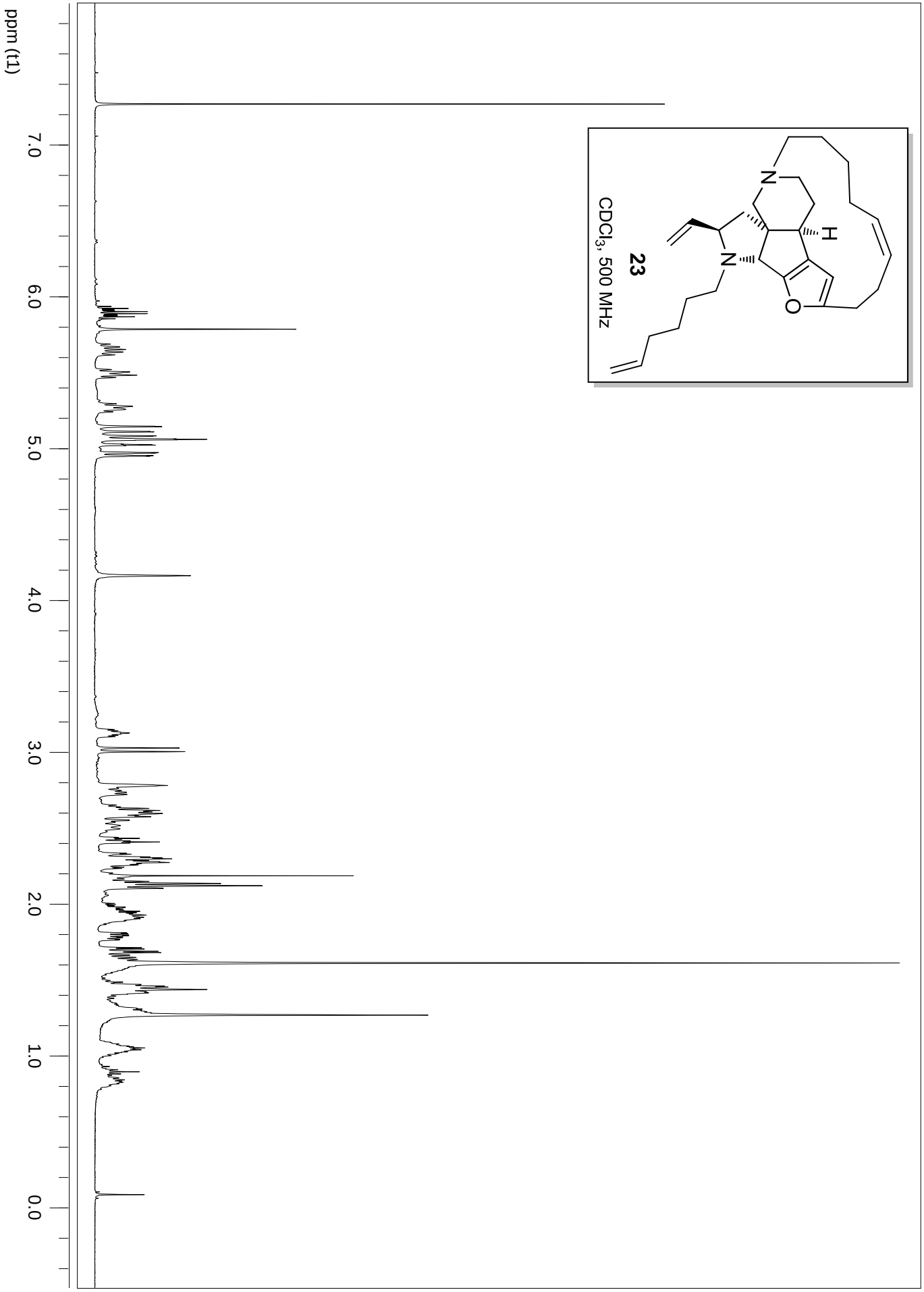


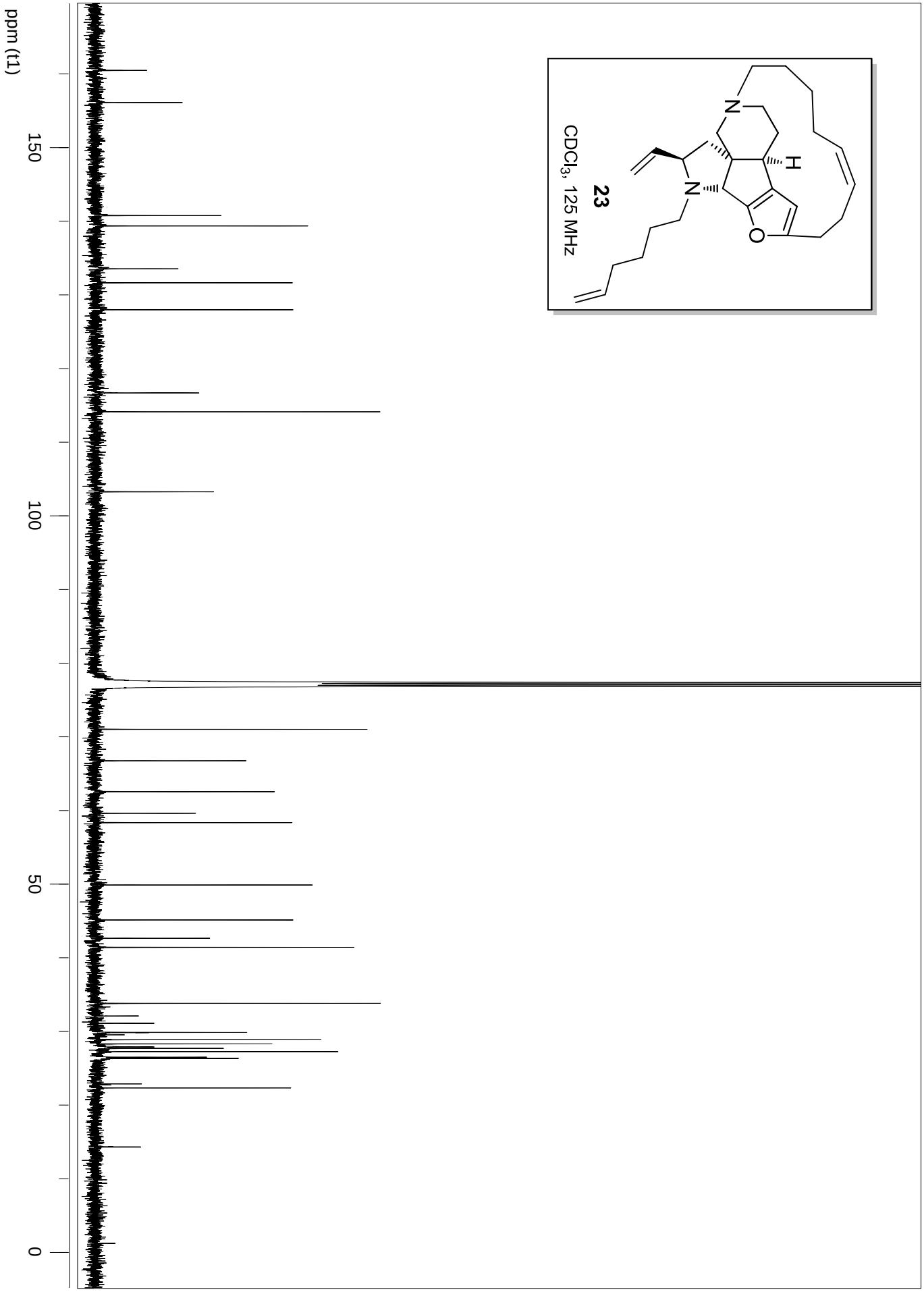
5.24. ^{1}H- and ^{13}C-NMR spectra of **22**

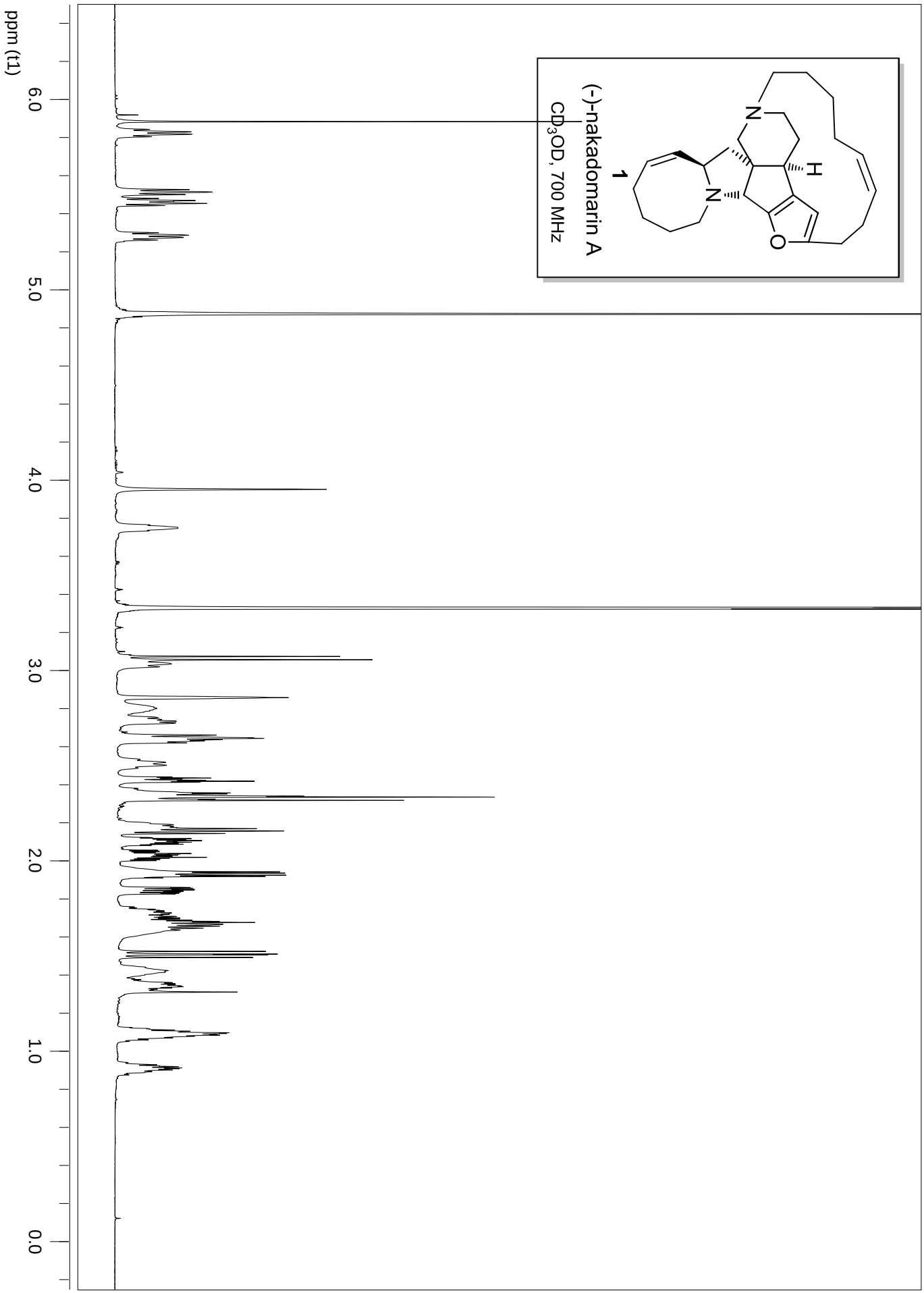



ppm (f1)
150
100
50
0
22
Toluene-d8, 125 MHz, 298 K
N
O
N
O
O
H

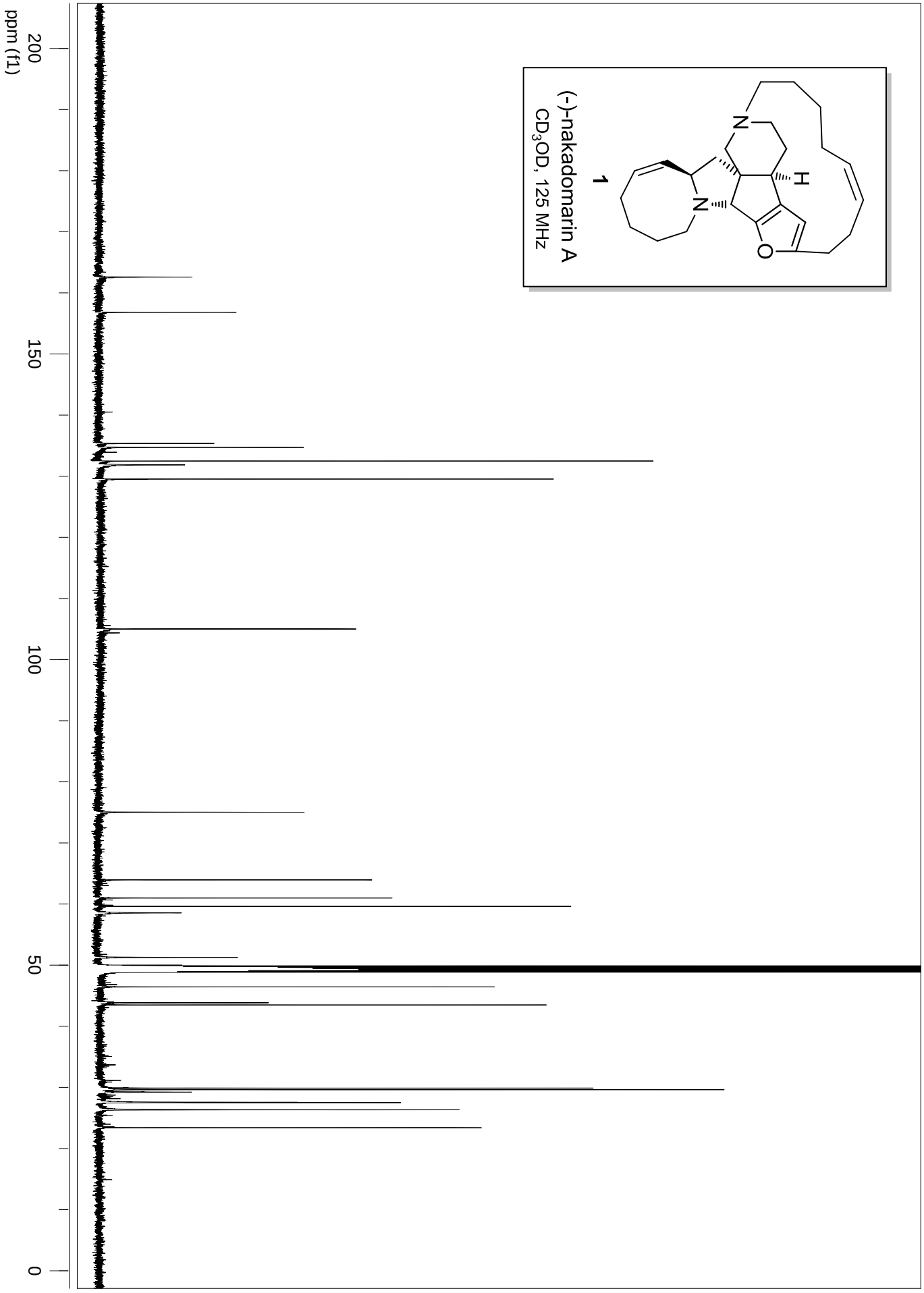
5.25. ^{1}H- and ^{13}C-NMR spectra of **23**





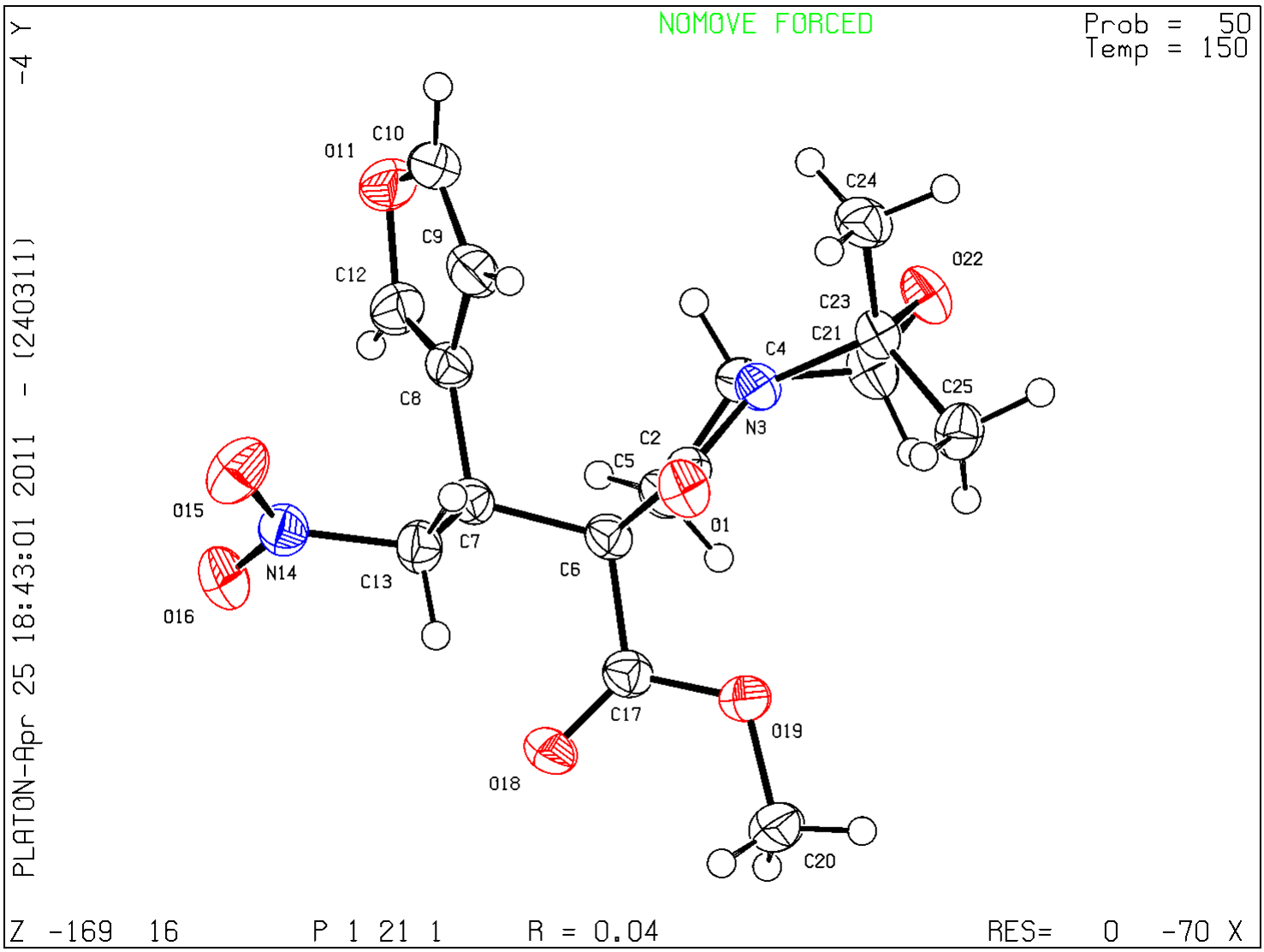


5.26. ^{1}H- and ^{13}C-NMR spectra of (-)-nakadomarin A **1**

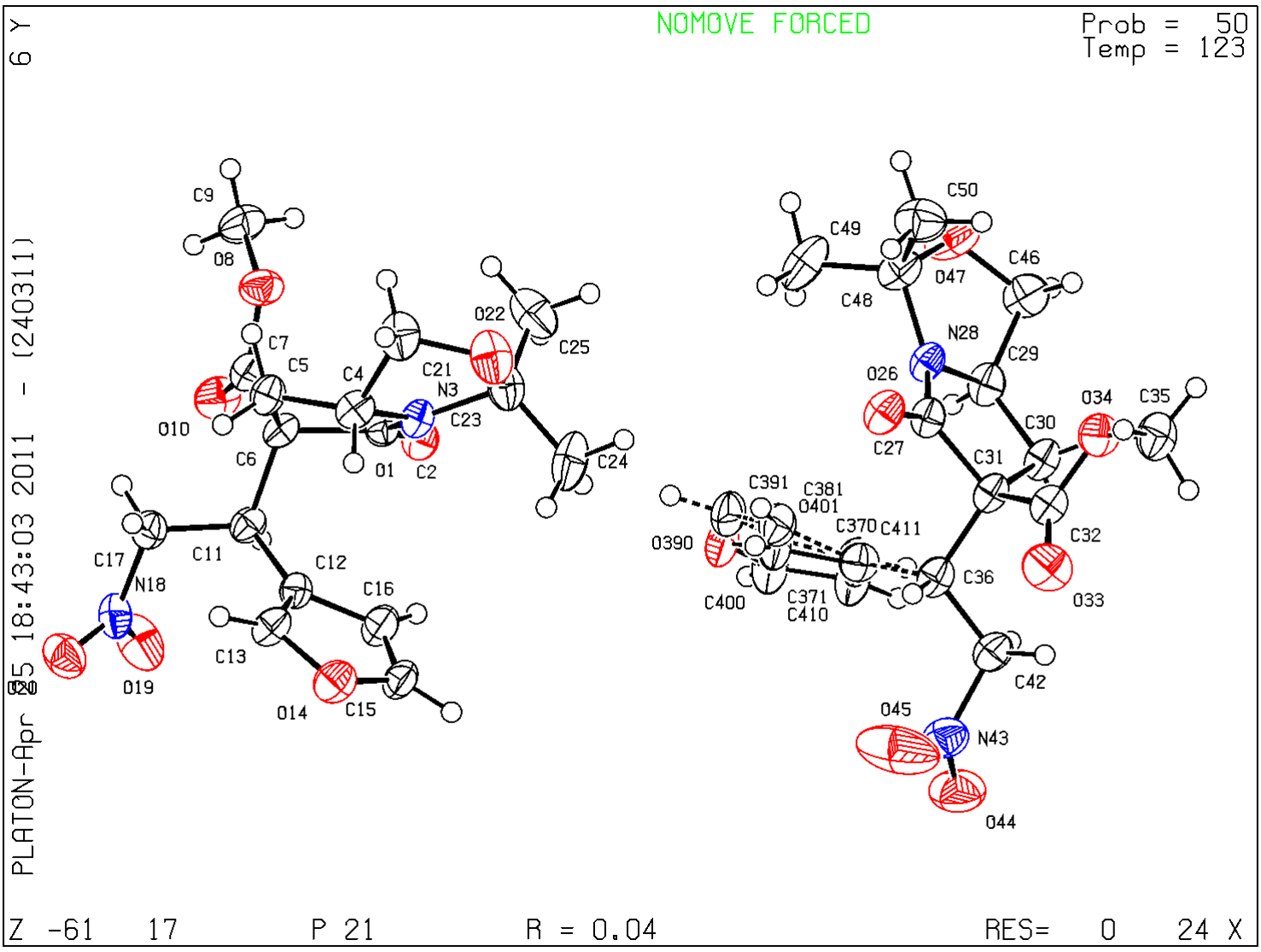


6. X-ray Crystallography [12]

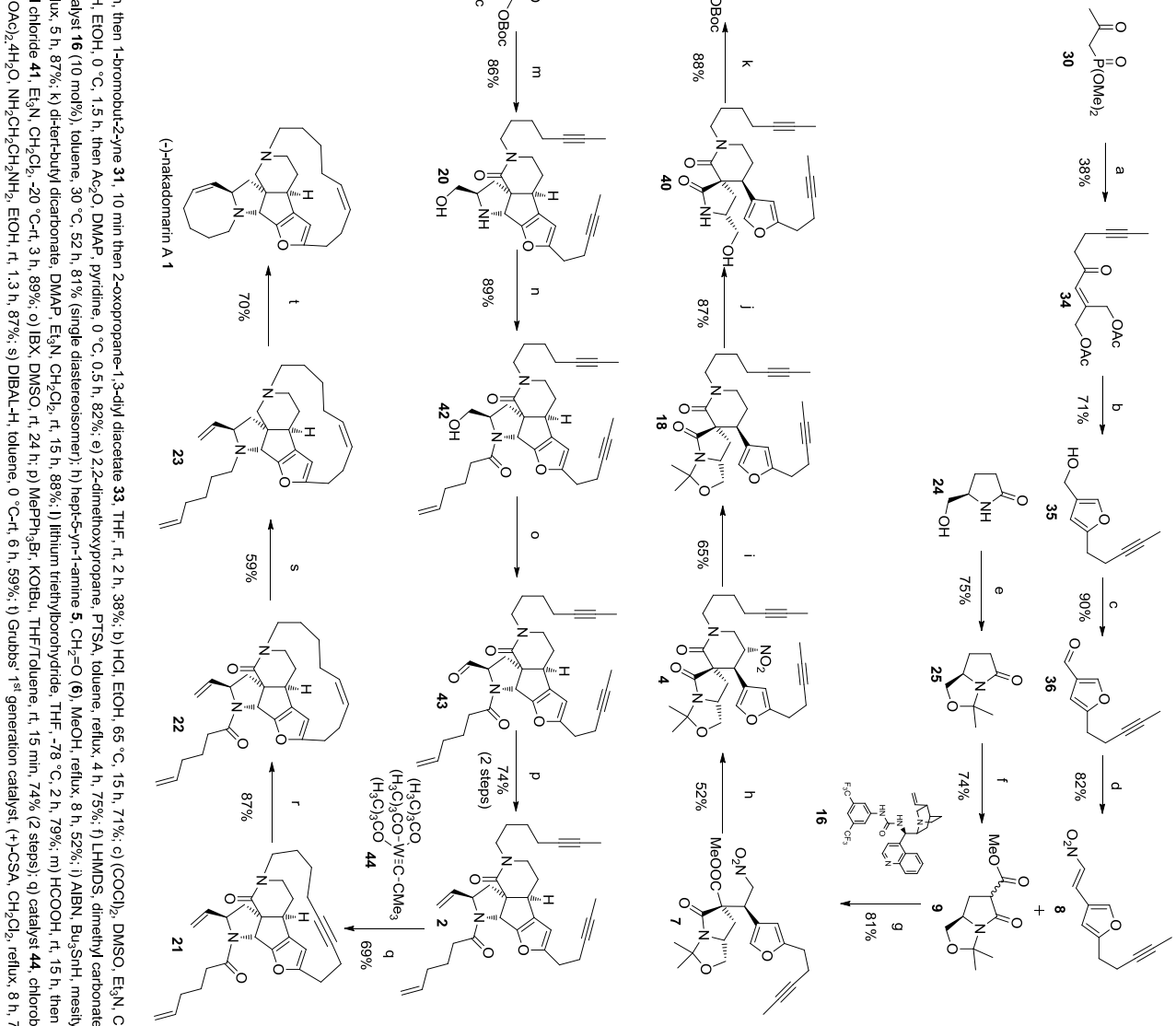
6.1. Thermal ellipsoid plot of 11



6.2. Thermal ellipsoid plot of 12



7. Complete synthetic route to (-)-nakadomarin A.



a) NaH, BuLi, THF, 0 °C, 1 h, then 1-bromobut-2-yne **31**, 10 min then 2-oxopropane-1,3-diyl diacetate **33**, THF, rt, 2 h, 38%; b) HCl, EtOH, 65 °C, 15 h, 71%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt, 0.5 h, 90%; d) $MeNO_2$, KOH, EtOH, 0 °C, 1.5 h, then Ac_2O, DMAP, pyridine, 0 °C, 0.5 h, 82%; e) 2,2-dimethoxypropane, PTSA, toluene, reflux, 4 h, 75%; f) LHMDS, dimethyl carbonate, THF, -78 °C to 0 °C, 3 h, 74 %; g) organocatalyst **16** (10 mol%), toluene, 30 °C, 52 h, 81% (single diastereoisomer); h) hept-5-yn-1-amine **5**, CH_2=O (**6**), MeOH, reflux, 8 h, 52%; i) AIBN, Bu_3SnH, mesitylene, 165 °C, 2.5 h, 65%; j) PTSA, MeOH, reflux, 5 h, 87%; k) di-tert-butyl dicarbonate, DMAP, Et_3N, CH_2Cl_2, rt, 15 h, 88%; l) lithium triethylborohydride, THF, -78 °C, 2 h, 79%; m) HCOOH, rt, 15 h, then LiOH, MeOH, 50 °C, 5 h, 86%; n) hex-5-enoyl chloride **41**, Et_3N, CH_2Cl_2, -20 °C-rt, 3 h, 89%; o) IBX, DMSO, rt, 24 h; p) $MePPh_3Br$, KOtBu, THF/Toluene, rt, 15 min, 74% (2 steps); q) catalyst **44**, chlorobenzene, 80 °C, 2 h, 69%; r) H_2, $NaBH_4$, Ni(II)$(OAc)_2.4H_2O$, $NH_2CH_2CH_2NH_2$, EtOH, rt, 1.3 h, 87%; s) DIBAL-H, toluene, 0 °C-rt, 6 h, 59%; t) Grubbs' 1st generation catalyst, (+)-CSA, CH_2Cl_2, reflux, 8 h, 70%.