Enantioselective Total Synthesis of Nigelladine A via Late-Stage C–H Oxidation Enabled by an Engineered P450 Enzyme

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Materials and Methods

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).[1] Commercially obtained reagents were used as received with the exception of anhydrous cerium trichloride ($CeCl_3$), [2] dipalladium tris(dibenzylideneacetone) ($Pd_2(dba)_3$), palladium (II) chloride ($PdCl_2$), anhydrous copper (I) chloride (CuCl), bis(pinacolato)diboron (B_2Pin_2), anhydrous lithium chloride (LiCl), and anhydrous potassium acetate (KOAc), which were stored in a nitrogen-filled glovebox. Triethylamine (Et_3N) and Diisopropylethylamine (*i*-Pr_2NH) were distilled over potassium hydride prior to use, while allyl chloroformate was freshly distilled prior to use. N-bromosuccinimide was recrystallized prior to use.[3] (*S*)-$(CF_3)_3$-*t*-BuPHOX,[4] (*R*)-$(CF_3)_3$-*t*-BuPHOX,[4] and Dess–Martin periodinane[5] were prepared by known methods. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Reaction progress was monitored by thin-layer chromatography (TLC), which was performed using E. Merck silica gel 60 F254 precoated glass plated (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, p-anisaldehyde, or iodine staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40-63 nm) was used for column chromatography. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively), Varian Mercury 300 spectrometer (300 MHz and 75 MHz, respectively), Varian 600 MHz Spectrometer (600 MHz), and a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and δ 77.16, respectively) and CH_3OH (δ 3.31 and δ 39.00 respectively). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sept = septet, m = multiplet, and br s = broad singlet. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100-mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing CHIRALCEL OB-H and CHIRALPAK IC columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254, 230, and 210 nm. High resolution mass spectra were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) ionization mode or a Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed (ESI/APCI) ionization mode.

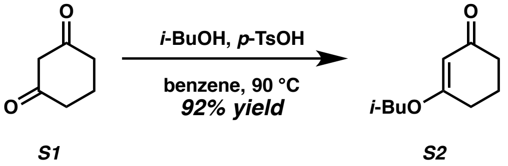
Protocols for protein expression and lysis

The genes for wild-type P450$_{BM3}$ and the variants were previously cloned into the pCWori vector, which was used to transform *Escherichia coli* DH5α.[6] In addition to the mutations listed in Table 2, all variants had the following mutations: V78A F87V P142S T175I A184V S226R H236Q E252G A290V L353V I366V E442K.

For protein expression, a culture (typically 5 mL) of lysogeny broth with 100 µg/mL of ampicillin (LB$_{amp}$) was inoculated with a glycerol stock of *E. coli* DH5α containing the desired plasmid. This culture was shaken at 37 °C and 230 rpm. After 12 hours, the culture was used to inoculate an expression culture (1:100 v/v) of Terrific Broth containing 100 µg/mL of ampicillin (TB$_{amp}$) plus 0.1% by volume of trace metal mix (aqueous solution of 50 mM $FeCl_3$, 20 mM $CaCl_2$, 10 mM $MnSO_4$, 10 mM $ZnSO_4$, 2 mM $CoSO_4$, 2 mM $CuCl_2$, 2 mM $NiCl_2$, 2 mM Na_2MoO_4, 2 mM H_3BO_3). The expression culture was shaken at 37 °C and 230 rpm. After ~3 hours, the OD$_{600}$ was 0.6–0.8, whereupon the culture was chilled in ice for 30 minutes, then induced with the addition of aminolevulinic acid (1 mM final concentration) and isopropyl β-D-thiogalactopyranoside (0.5 mM final concentration). The culture was then shaken at 230 rpm and 20 °C. After 16–20 hours, the culture was subjected to centrifugation at 5,000×*g* and 4 °C for 10 minutes. The supernatant was discarded, then the cell pellet was stored at –30 °C until further use.

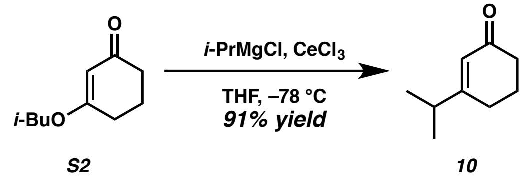
For lysis, the cell pellet was thawed, then suspended in 4 mL/mg of potassium phosphate buffer (100 mM, pH 8) that contained 1 mg/mL of hen egg white lysozyme and 0.1 mg/mL of bovine pancreas DNase I. The suspension was shaken at 37 °C and 230 rpm (19 mm radius). After 1 hour, the culture was cooled on ice, then subjected to centrifugation at 15,000×*g* and 4 °C for 10 min. The supernatant was used directly in the biocatalytic transformation. To determine protein concentration, 900 µL of fivefold-diluted lysate was treated with a spatula tip of dithionite, then exposed to an atmosphere of carbon monoxide (CO) for 30 minutes. The absorbance of the CO-bound lysate at 450 nm minus the absorbance at 490 nm was converted to protein concentration using the extinction coefficient $\varepsilon = 91\ mM^{-1}cm^{-1}$.

Experimental Procedures and Characterization Data



3-isobutoxycyclohex-2-en-1-one S2.[7]

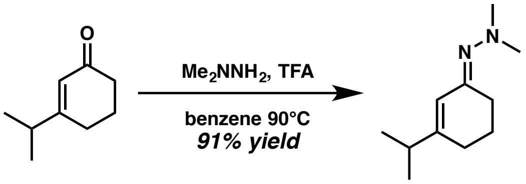
1,3-cyclohexadione (**S1**, 22.4 g, 200 mmol, 1.0 equiv), *iso*-butyl alcohol (55 mL, 600 mmol, 3 equiv), and *para*-toluenesulfonic acid (*p*-TsOH, 190 mg, 1.0 mmol, 0.005 equiv) were added to a flask and diluted in benzene (123 mL, 1.6 M). The flask was then fitted with a Dean–Stark trap filled with additional benzene. The reaction flask was heated to reflux with stirring for 8 h, at which time the starting material had been completely consumed (determined by TLC analysis, 8:1 hexanes:EtOAc). The reaction mixture was cooled to ambient temperature (ca. 23 °C) and Et_3N (0.7 mL, 5 mmol, 0.025 equiv) was added. The crude reaction mixture was then concentrated in vacuo and distilled by short path distillation (Pressure 1.0 torr, neck temperature 118 °C, bath temperature 150 °C) to provide vinylogous ester **S2** (32.6 g, 97% yield) as a clear colorless oil; R_f= 0.5 (8:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.59 (d, *J* = 6.5 Hz, 2H), 2.41 (t, *J* = 6.3 Hz, 2H), 2.34 (dd, *J* = 7.2, 6.0 Hz, 2H), 2.10–1.91 (m, 3H), 0.97 (dd, *J* = 6.7, 0.7 Hz, 6H). All other characterization matches literature values.[8]



3-isopropylcyclohex-2-en-1-one 10.

In a nitrogen-filled glovebox, $CeCl_3$ (49g, 200 mmol, 1.5 equiv) was added to a round bottom flask with a magnetic stir bar. The flask was sealed with a rubber septum and removed from the glovebox. The flask was heated at 140 °C under vacuum (ca. 1 Torr) with stirring for 8 h. $CeCl_3$ was allowed to cool to ambient temperature (23 °C) and the flask was refilled with Ar. The $CeCl_3$ was then cooled to 0 °C (H_2O:ice bath) and diluted with THF (444 mL, 0.3 M) with vigorous stirred for 3 h. The reaction flask was then cooled to –78 °C (dry ice:acetone bath) where upon ester **S2** (22.4 g, 133 mmol, 1 equiv) was added. After 1h at –78 °C, *i*-PrMgCl (2.0 M in THF, 100 mL, 1.5 equiv) was added dropwise via cannula and allowed to stir for 1h, at which time the starting material had been completely consumed (determined by TLC, 8:1 hexanes:Et_2O). The reaction was then quenched with 1 M HCl (300 mL) and allowed to warm to ambient temperature. The product was extracted from the biphasic mixture with Et_2O (3 × 200 mL), and then the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product can be purified by either flash chromatography (SiO_2, 4:1 hexanes:Et_2O) or by Kugelrohr distillation (pressure 1.0 Torr, 115 °C) to provide enone **10** (16.8 g, 91% yield) as a pale yellow oil, which solidifies to a white solid upon cooling to –20 °C; R_f = 0.29 (4:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, C_6D_6) δ 5.95 (q, *J* = 1.4

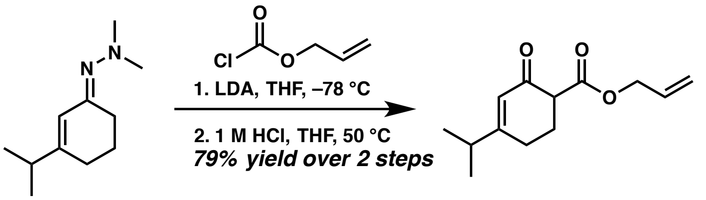
Hz, 1H), 2.17–2.10 (m, 2H), 1.88 (pd, J = 6.8, 1.0 Hz, 1H), 1.66–1.60 (m, 2H), 1.47–1.38 (m, 2H), 0.74 (d, J = 6.9 Hz, 6H). All other characterization matches literature values.[9]



10 *11*
1.7:1 *E:Z*

2-(3-isopropylcyclohex-2-en-1-ylidene)-1,1-dimethylhydrazine 11.

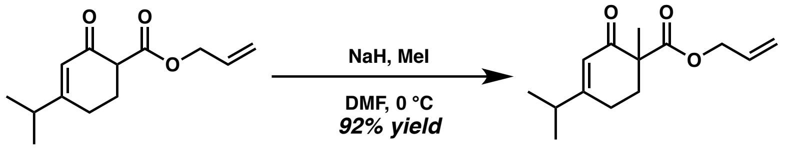
Hydrazone condensation was adapted from the literature.[10] Enone **10** (8.2g, 59.0 mmol, 1 equiv), *N,N*-dimethylhydrazine (9 mL, 118 mmol, 2 equiv), TFA (0.1 mL), and benzene (120 mL, 0.4 M) were added to a roundbottom flask. The flask was fitted with a Dean-Stark trap filled with additional benzene. The reaction flask was heated to reflux with stirring for 8 h, at which time the starting material had been completely consumed (determined by TLC analysis, 1:1 hexanes:EtOAc). The crude reaction mixture was then cooled to ambient temperature and concentrated in vacuo. The crude product can be purified by either flash chromatography (SiO_2, 1:1 hexanes:EtOAc) or short path distillation (pressure 1 Torr, neck temperature 130 °C, bath temperature 160 °C) to generate hydrazone **11** (9.7 g, 91% yield, 1.7:1 E:Z ratio) as a yellow oil; R_f = 0.5 (E); 0.26 (Z) (1:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) (E) δ 6.00 (q, J = 1.4 Hz, 1H), 2.59 (dd, J = 7.5, 5.8 Hz, 2H), 2.52 (s, 6H), 2.33 (sept, J = 6.9 Hz, 1H), 2.20–2.16 (m, 2H), 1.79 (dtd, J = 7.5, 6.4, 5.6 Hz, 2H), 1.08 (d, J = 6.9 Hz, 6H), (Z) δ 6.54 (q, J = 1.5 Hz, 1H), 2.49 (s, 6H), 2.43–2.33 (m, 3H), 2.21–2.17 (m, 2H), 1.85–1.78 (m, 2H), 1.08 (d, J = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) (E) δ 164.9, 157.3, 121.1, 47.4, 35.6, 27.7, 26.2, 22.5, 21.0, (Z) δ 162.5, 160.2, 113.6, 47.9, 36.0, 31.9, 27.7, 22.9, 21.1; IR thin film, NaCl) 2960, 2857, 2816, 2771, 1634, 1589, 1466, 1436, 1383, 1362, 1327, 1304, 1267, 1251, 1222, 1200, 1154, 1142, 1089, 1022, 980, 969, 890, 790 cm^{-1}; HRMS (ES/APCI) m/z cal'd $C_{11}H_{21}N_2$ $[M+H]^+$: 181.1699, found: 181.1705.



11 *S3*

Allyl 4-isopropyl-2-oxocyclohex-3-ene-1-carboxylate S3.

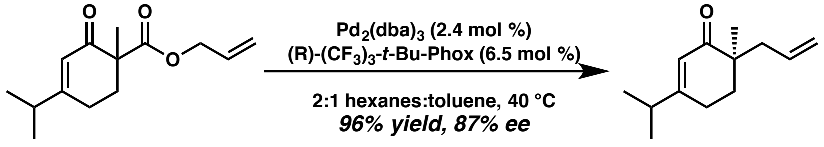
A flame-dried round bottom flask was charged with Diisopropylamine (*i*-Pr_2NH, 9.58 mL, 68.4 mmol, 1.5 equiv) in THF (61 mL, 1.1 M) and cooled to 0 °C. A solution of *n*-BuLi in hexanes (2.3 M, 29.7 mL, 68.4 mmol, 1.5 equiv) was added dropwise and the resulting solution was allowed to stir for 0.5 h at 0 °C. Hydrazone **11** (8.22 g, 45.6 mmol, 1 equiv) was added dropwise to the LDA solution, which was then stirred for 1 h at 0 °C. The reaction mixture was cannulated to a separate flame dried flask containing allyl chloroformate (7.3 mL, 68.4 mL, 1.5 equiv) in THF (320 mL, 0.2 M) at –78 °C. The solution was stirred for 1 h, at which time the starting material had been completely consumed (determined by TLC analysis, 4:1 hexanes:EtOAc). The solution was quenched at –78 °C with aqueous NH_4Cl (200 mL) and allowed to warm to ambient temperature. The product was extracted from the biphasic solution with Et_2O (3 × 150 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude compound was diluted with THF (230 mL, 0.2 M) and 1 M HCl (91.2 mL, 91.2 mmol, 2.0 equiv) and heated to 50 °C for 12 h, at which time the starting material had been completely consumed (determined by TLC analysis, 4:1 pentane:Et_2O). The product was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 9:1 hexanes:EtOAc) to yield β-Ketoester **S3** (7.96 g, 79% yield) as a pale yellow oil; $R_f = 0.2$ (4:1 pentane:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98–5.85 (m, 2H), 5.32 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.22 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.71–4.58 (m, 2H), 3.42–3.32 (m, 1H), 2.50–2.29 (m, 4H), 2.24–2.17 (m, 1H), 1.09 (dd, *J* = 6.8, 0.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.3, 172.2, 170.1, 131.9, 123.0, 118.5, 65.8, 53.2, 35.8, 26.3, 26.0, 20.8, 20.6; IR thin film, NaCl) 2965, 2940, 2875, 1741, 1650, 1624, 1457, 1425, 1375, 1364, 1307, 1275, 1216, 1166, 1151, 1050, 1027, 989, 884, 767 cm^{-1}; HRMS (ES/APCI) m/z calc'd $C_{13}H_{19}O_3$ $[M+H]^+$: 223.1329, found: 223.1329.



S3 ***9***

Allyl 4-isopropyl-1-methyl-2-oxocyclohex-3-ene-1-carboxylate 9.

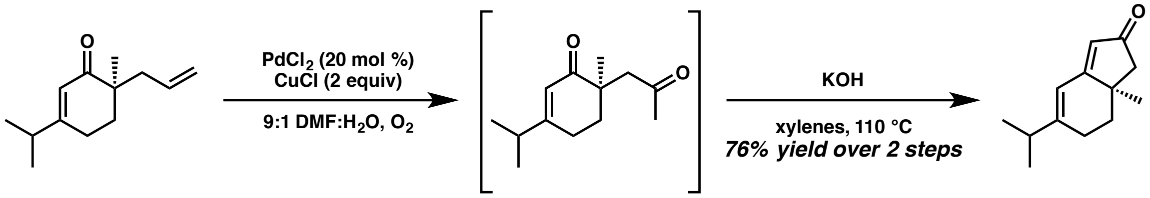
NaH (60% dispersion, 3.3 g, 81.9 mmol, 1.4 equiv) was added to DMF (31.5 mL, 2.6 M) at 0 °C. The solution was then charged with β-Ketoester **S3** (13 g, 58.4 mmol, 1.0 equiv) in a solution of DMF (25 mL, 2.3 M) and allowed to stir for 1 h at 0 °C. MeI (12.7 mL, 204.4 mmol, 3.5 equiv) was added, followed by additional DMF (20 mL). The reaction was allowed to stir for 1.5 h, at which time the starting material had been completely consumed (determined by TLC analysis, 9:1 hexanes:EtOAc). The reaction was then quenched with water and the product was extracted with Et_2O (40 mL × 3). The combined organic layers were washed with brine (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 9:1 hexanes:EtOAc) to generate β-Ketoester **9** (12.7 g, 92% yield) as a pale yellow oil; $R_f = 0.30$ (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (dt, *J* = 2.1, 1.1 Hz, 1H), 5.86 (ddt, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.28 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.64 (ddt, *J* = 13.4, 5.6, 1.5 Hz, 1H), 4.56 (ddt, *J* = 13.4, 5.5, 1.5 Hz, 1H), 2.53–2.37 (m, 3H), 2.33–2.26 (m, 1H), 1.87 (ddd, *J* = 13.0, 8.4, 5.0 Hz, 1H), 1.39 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.4, 172.7, 170.7, 131.9, 122.8, 118.3, 65.7, 52.9, 35.7, 33.6, 25.3, 20.9, 20.7, 20.5; IR thin film, NaCl) 2965, 2935, 2875, 1731, 16678, 1626, 1456, 1425, 1375, 1302, 1248, 1217, 1170, 1105, 987, 26, 882, 771, 749 cm^{-1}; HRMS (ES/APCI) m/z calc'd $C_{14}H_{21}O_3$ $[M+H]^+$: 237.1485, found: 237.1482.



9 **8**

(*R*)-6-allyl-3-isopropyl-6-methylcyclohex-2-en-1-one 8.

In a nitrogen filled glovebox, $Pd_2(dba)_3$ (725 mg, 0.79 mmol, 0.024 equiv) and (*R*)-$(CF_3)_3$-*t*-Bu-PHOX (1.3 g, 2.2 mmol, 0.065 equiv) were added to a flask. The flask was sealed and removed from the glovebox. The catalyst and ligand were then diluted with a 2:1 hexanes:toluene (1 L, 0.033M) and allowed to stir for 40 minutes at 40 °C. β-Ketoester **9** (8.0 g, 33.9 mmol, 1.0 equiv) was then added in one portion. After 62 h, the consumption of starting material was complete (as determined by TLC analysis, 9:1 hexanes:EtOAc). The crude solution was directly purified by column chromatography (SiO_2, 100% hexanes then 12:1 hexanes:Et_2O) to furnish enone **8** (6.25 g, 96% yield, 87% ee) as a pale yellow oil; R_f = 0.46 (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (q, *J* = 1.4 Hz, 1H), 5.73 (ddt, *J* = 16.8, 10.3, 7.4 Hz, 1H), 5.09–5.01 (m, 2H), 2.43–2.35 (m, 1H), 2.35–2.29 (m, 3H), 2.16 (ddt, *J* = 13.7, 7.7, 1.2 Hz, 1H), 1.90 (ddd, *J* = 13.6, 6.9, 5.6 Hz, 1H), 1.71 (ddd, *J* = 13.6, 6.6, 5.4 Hz, 1H), 1.09 (d, *J* = 6.8 Hz, 6H), 1.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.3, 169.8, 134.4, 122.4, 118.0, 43.7, 41.3, 35.6, 33.4, 24.8, 21.9, 20.9, 20.9; IR thin film, NaCl) 2964, 2929, 2873, 1663, 1627, 461, 1428, 1373, 1323, 1274, 1213, 1126, 1107, 999, 912, 881, 613 cm^{-1}; HRMS (ES/APCI) m/z calc'd $C_{13}H_{21}O$ $[M+H]^+$: 193.1587, found: 193.1582; (R): $[\alpha]_D^{25}$ +3.15° (*c* 1.215, $CDCl_3$, 87% ee); (S): $[\alpha]_D^{25}$ –1.34° (*c* 0.675, $CDCl_3$, 87% ee); SFC (OB-H (4 x 25 cm), 1% *i*-PrOH) (*R*) retention time: 1.93 min, (*S*) retention time: 2.30 min.



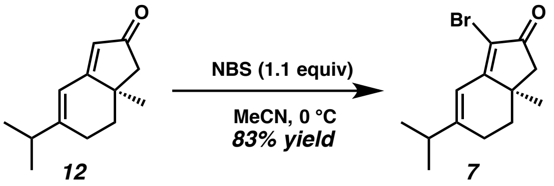
8 **S4** **12**

(*R*)-5-isopropyl-7a-methyl-1,6,7,7a-tetrahydro-2*H*-inden-2-one 12.

A flask containing enone **8** (1.0 g, 5.2 mmol, 1.0 equiv) in 9:1 DMF:H_2O (52 mL, 0.1 M) was charged with $PdCl_2$ (0.18 g, 1 mmol, 0.2 equiv) and $CuCl_2$ (1.0 g, 10.4 mmol, 2.0 equiv). The reaction was evacuated/backfilled (vacuum/O_2) and allowed to stir for 14 h, at which time the consumption of starting material was complete (as determined by TLC analysis, 8:2 hexanes:EtOAc). The reaction was then diluted with H_2O and brine and the product was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (3 × 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 9:1 hexanes:EtOAc to 8:2 hexanes:EtOAc) to generate ketone **S4** (1.02 g, 7:1 ketone:aldehyde) as a pale yellow oil which was carried on to the next reaction without further purification.

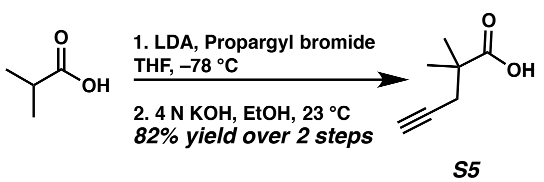
Enone **S4** (1.0 g, 4.8 mmol, 1.0 equiv) was dissolved in xylenes (53 mL) in a flask fitted with a Dean–Stark trap and a reflux condenser. Freshly powdered KOH (300 mg, 5.3

mmol, 1.1 equiv) was added in one portion. The reaction was allowed to stir for 14 h at 110 °C, at which time the consumption of starting material was complete (as determined by TLC analysis, 4:1 hexanes:EtOAc). The crude solution was directly purified by flash chromatography (SiO_2, 100% hexanes then 9:1 hexanes:EtOAc) to furnish enone **12** (674 mg, 76% yield over 2 steps) as a yellow oil; R_f = 0.24 (4:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.4 Hz, 1H), 5.69 (s, 1H), 2.46–2.28 (m, 4H), 2.20 (d, *J* = 17.4 Hz, 1H), 1.92 (ddd, *J* = 12.9, 5.3, 1.7 Hz, 1H), 1.71–1.62 (m, 1H), 1.15 (s, 3H), 1.11 (dd, *J* = 6.9, 0.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 179.2, 159.3, 122.7, 116.4, 51.7, 40.4, 35.9, 34.2, 25.8, 25.6, 21.5, 21.1; IR thin film, NaCl) 2962, 2927, 2872, 1698, 1622, 1581, 1464, 1414, 1375, 1329, 1288, 1266, 1247, 1179, 1143, 898 882 cm^{-1}; HRMS (ES/APCI) m/z calc'd $C_{13}H_{19}O$ [M+H]$^+$: 191.1430, found: 191.1440; (R): $[\alpha]_D^{25}$ –435.36° (*c* 0.93, $CDCl_3$, 87% ee); (S): $[\alpha]_D^{25}$ +302.67° (*c* 0.59, $CDCl_3$, 87% ee).



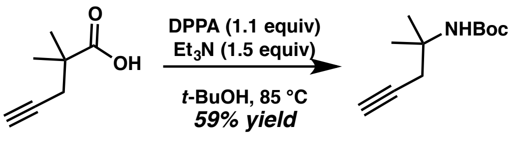
(*R*)-3-bromo-5-isopropyl-7a-methyl-1,6,7,7a-tetrahydro-2*H*-inden-2-one 7.

A flask covered in aluminum foil with enone **12** (100 mg, 0.53 mmol, 1.0 equiv) diluted with MeCN (16 mL, 0.03 M) and cooled to 0 °C. NBS (104 mg, 0.58 mmol, 1.1 equiv) dissolved in MeCN (1.6 mL, 0.3 M) was added dropwise to the reaction over 4 h via syringe pump. After complete addition of NBS, the reaction was allowed to stir for 1 h at 0 °C, at which time complete consumption of starting material was observed (determined by TLC analysis, 4:1hexanes:EtOAc). The reaction was concentrated in vacuo and purified directly by flash chromatography (9:1 hexanes:EtOAc) to yield vinyl bromide **7** (118 mg, 83% yield) as a yellow oil; R_f = 0.36 (4:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (dq, *J* = 2.5, 0.9 Hz, 1H), 2.53–2.23 (m, 5H), 1.92 (ddd, *J* = 13.1, 5.1, 2.0 Hz, 1H), 1.64 (ddd, *J* = 13.0, 11.1, 6.1 Hz, 1H), 1.17 (s, 3H), 1.15 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 173.6, 162.2, 115.4, 114.8, 49.6, 40.7, 36.2, 34.2, 26.2, 25.7, 21.5, 21.1; IR thin film, NaCl) 2963, 2928, 2872, 1712, 1614, 1579, 1458, 1421, 1374, 1314, 1259, 1245, 1211, 1175, 955, 881 cm^{-1}; HRMS (ES/APCI) m/z calc'd $C_{13}H_{18}OBr$ [M+H]$^+$: 269.0536, found: 269.0547; (R): $[\alpha]_D^{25}$ –311.57° (*c* 0.875, $CDCl_3$, 87% ee); (S): $[\alpha]_D^{25}$ +329.26° (*c* 1.245, $CDCl_3$, 87% ee).



2,2-dimethylpent-4-ynoic acid S5.

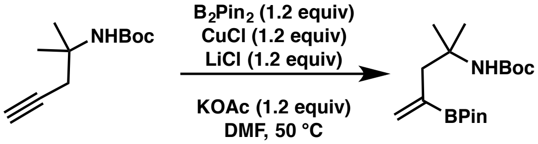
Acid **S5** was formed using known literature procedures[11] as a pale orange amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.52 (bs, 1H), 2.47 (d, *J* = 2.7 Hz, 2H), 2.04 (t, *J* = 2.7 Hz, 1H), 1.32 (s, 6H). All other characterization data match known literature values.[11]



S5 ***S6***

***tert*-butyl (2-methylpent-4-yn-2-yl)carbamate S6.**

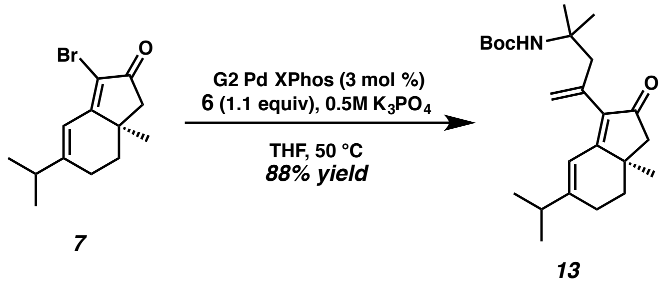
A flask containing alkyne **S5** (3.5 g, 28 mmol, 1.0 equiv) in anhydrous *t*-BuOH (100 mL, 0.28 M) was charged with Et_3N (5.9 mL, 42 mmol, 1.5 equiv) and diphenyl phosphoryl azide (DPPA, 6.7 mL, 30.8 mmol, 1.1 equiv). The reaction was heated to reflux and allowed to stir for 24 h. The reaction was then concentrated in vacuo, dissolved in EtOAc (100 mL), and washed sequentially with 5% citric acid and saturated $NaHCO_3$. The organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 5% EtOAc in hexanes) to generate alkyne **S6** (3.3 g, 59% yield) as a white amorphous solid; R_f = 0.35 (12:1 hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (bs, 1H), 2.59 (d, *J* = 2.7 Hz, 2H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.43 (s, 9H), 1.35 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 81.3, 79.2, 70.5, 51.9, 30.6, 28.6, 26.9; IR thin film, NaCl) 3361, 3310, 2977, 2932, 1718, 1501, 1457, 1390, 1367, 1290, 1247, 1170, 1079, 865 cm^{-1}; HRMS (FAB+) m/z calc'd $C_{11}H_{20}NO_2$ $[M+H]^+$: 198.1494, found: 198.1482.



S6 ***6***

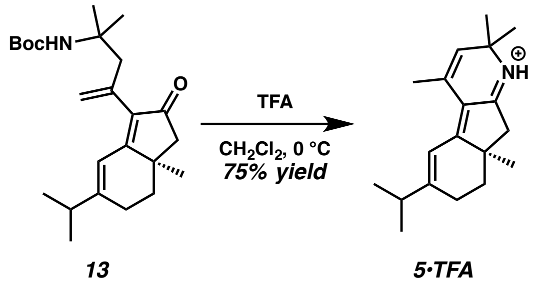
***tert*-butyl (2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-en-2-yl)carbamate 6.**

Hydroboration of **6** was adapted from a known procedure.[12] In a nitrogen-filled glovebox, CuCl (420 mg, 4.3 mmol, 1.2 equiv) and LiCl (175 mg, 4.3 mmol, 1.2 equiv) were distributed evenly between seven 1-dram vials (60 mg and 25 mg per vial respectively). DMF (0.85 mL, 0.6 M) was added to each vial and the resulting suspensions were stirred vigorously for 1 h. Each vial was then charged sequentially with KOAc (60 mg, 0.61 mmol, 1.2 equiv), B_2Pin_2 (154 mg, 0.61 mmol, 1.2 equiv), and alkyne **S6** (100 mg, 0.51 mmol, 1.0 equiv) dissolved in DMF (0.2 mL). The reactions were heated to 50 °C and stirred for 24 h. The vials were combined and diluted with saturated aqueous solution of NH_4Cl (40 mL) and EtOAc (50 mL). The product was extracted from the biphasic solution with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude solution was purified by flash chromatography (SiO_2, 5% Et_2O in hexanes) to generate vinyl boronic ester **6** (610 mg, 53% yield) as a white amorphous solid; R_f = 0.33 (12:1 hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.98 (d, *J* = 3.6 Hz, 1H), 5.65 (d, *J* = 3.6 Hz, 1H), 5.40 (bs, 1H), 2.33 (d, *J* = 1.0 Hz, 2H), 1.41 (s, 9H), 1.28 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 84.1, 78.3, 52.8, 51.0, 47.7, 29.9, 28.7, 26.7, 24.8; IR thin film, NaCl) 3396, 2976, 2930, 1719, 1517, 1447, 1365, 1305, 1269, 1252, 1165, 1142, 1064, 960, 951, 861, 733 cm^{-1}; HRMS (ES/APCI) m/z calc'd $C_{17}H_{33}{}^{11}BO_4N$ $[M+H]^+$: 326.2497, found: 326.2507.



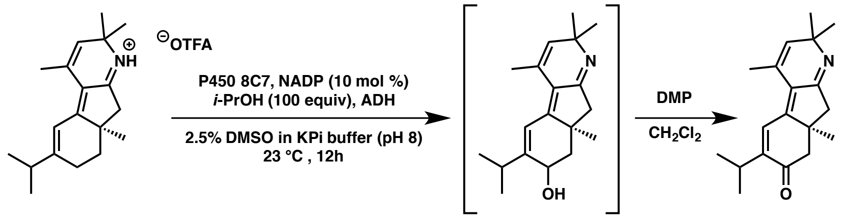
***tert*-butyl (*R*)-(4-(5-isopropyl-7a-methyl-2-oxo-2,6,7,7a-tetrahydro-1*H*-inden-3-yl)-2-methylpent-4-en-2-yl)carbamate 13.**

A flask was charged with vinyl bromide **7** (300 mg, 1.11 mmol, 1.0 equiv), vinyl boronic acid **6** (387 mg, 1.22 mmol, 1.1 equiv), 0.5 M K_3PO_4 in degassed H_2O (4.4 mL, 0.25 M), and THF (2.2 mL, 0.5 M). Buchwald's 2nd generation precatalyst XPhos (26 mg, 0.03 mmol, 0.03 equiv) was added to the reaction with an overpressure of Ar. The reaction was allowed to stir for 16 h at 60 °C, at which time complete consumption of starting material was observed (determined by TLC analysis, 9:1 hexanes:EtOAc). The product was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2 9:1 hexanes:EtOAc) to furnish enone **13** (377 mg, 88% yield) as a white crystalline solid; R_f = 0.17 (9:1 hexanes:EtOAc); mp: 97.7 – 98.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.49 (d, *J* = 2.5 Hz, 1H), 5.24 (d, *J* = 2.3 Hz, 1H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.49 (s, 1H), 2.79 (d, *J* = 13.6 Hz, 1H), 2.66 (d, *J* = 13.5 Hz, 1H), 2.49–2.24 (m, 4H), 2.20 (d, *J* = 17.4 Hz, 1H), 1.93 (ddd, *J* = 12.9, 5.4, 1.6 Hz, 1H), 1.62 (dt, *J* = 12.5, 6.2 Hz, 1H), 1.41 (s, 9H), 1.22 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 1.13 (d, *J* = 0.9 Hz, 3H), 1.11 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2, 171.3, 159.1, 137.9, 135.2, 121.0, 115.5, 78.5, 52.7, 51.4, 45.7, 38.4, 36.0, 34.1, 28.5, 27.5, 25.5, 25.1, 21.6, 21.0; IR thin film, NaCl) cm^{-1}; HRMS (ES/APCI) m/z calc'd $C_{24}H_{38}NO_3$ $[M+H]^+$: 388.2846, found: 388.2864; (R): $[\alpha]_D^{25}$ –256.26° (*c* 0.45, $CDCl_3$, 87% ee); (S): $[\alpha]_D^{25}$ +265.13° (*c* 0.27, $CDCl_3$, 87% ee); SFC (IC, 30% IPA) (R) retention time: 6.385, (S) retention time: 5.691. The ee of **13** can be increased to 99% through preparative HPLC (IC, 20 x 250 μm, 30% IPA in hexanes, (R) retention time: 18.2 min, (S) retention time: 16.6 min); (R): $[\alpha]_D^{25}$ –297.74° (*c* 0.51, $CHCl_3$, 99% ee); (S): $[\alpha]_D^{25}$ +294.25° (*c* 0.44, $CHCl_3$, 99% ee).



(*R*)-6-isopropyl-2,2,4,8a-tetramethyl-7,8,8a,9-tetrahydro-2*H*-indeno[2,1-*b*]pyridine 5.

TFA (0.34 mL, 0.4 M) was added to enone **13** (53 mg, 0.14 mmol) in CH_2Cl_2 (1.4 mL, 0.1 M) at 0 °C. The reaction was allowed to warm to ambient temperature and stirred for an additional 1 h, at which time complete consumption of starting material was observed (determined by TLC analysis (4:1 hexanes:EtOAc). The reaction was quenched with saturated aqueous NaHCO$_3$ until the solution was neutralized and allowed to stir for 1 h, at which time complete cyclization occured (determined through LC-MS analysis, m/z = 270.1 $[M+H]^+$). The product was extracted from the biphasic mixture with CH$_2$Cl$_2$ (3 × 30 mL), dried over Na$_2$SO$_4$ and filtered. SiO$_2$ was added and the suspension was stirred for 1 h. The solution was concentrated and purified by flash chromatography (SiO$_2$, 0–10% methanol in EtOAc) to generate imine **5**•TFA as a tan amorphous solid. **5**•TFA can be deprotonated by washing a 10% aqueous solution of potassium carbonate to afford **5** (28 mg, 75% yield) as a viscous yellow oil; R_f = 0.25 (8% methanol in EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.56 (d, *J* = 2.4 Hz, 1H), 5.56 (d, *J* = 1.5 Hz, 1H), 2.51 – 2.27 (m, 4H), 2.24 – 2.15 (m, 1H), 2.02 (d, *J* = 1.5 Hz, 3H), 1.88 (ddd, *J* = 12.7, 5.6, 1.7 Hz, 1H), 1.59 (td, *J* = 12.3, 5.8 Hz, 1H), 1.24 (d, *J* = 4.1 Hz, 6H), 1.08 (d, *J* = 6.8 Hz, 6H), 1.06 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.1, 152.2, 150.5, 135.6, 125.0, 119.3, 115.1, 58.4, 45.9, 39.3, 34.9, 33.6, 30.3, 30.1, 27.4, 24.1, 24.0, 20.6, 20.2, 20.1; IR thin film, NaCl) 2962, 2922, 2177, 1660, 1615, 1456, 1407, 1374, 1286, 1261, 1154, 1048, 873, 842, 811, 732 cm^{-1}; HRMS (ES/APCI) m/z calc'd $C_{19}H_{28}N$ $[M+H]^+$: 270.2216, found: 270.2228; (R): $[\alpha]_D^{25}$ –223.18 (*c* 0.3, CHCl3, 87% ee); (S): $[\alpha]_D^{25}$ +250.16° (*c* 0.28, CDCl$_3$, 87% ee); (R): $[\alpha]_D^{25}$ –340.60° (*c* 0.6, CHCl$_3$, 99% ee); (S): $[\alpha]_D^{25}$ +391.68° (*c* 1.39, CHCl$_3$, 99% ee).



5·TFA *S7* *1*

21% yield over 2 steps
43% yield based on recovered 5

Nigelladine A 1.

Lysate containing the enzyme "8C7" was prepared from a 500-mL TB$_{amp}$ expression culture as described above. The concentration of 8C7 was determined to be 8.5 μM.

A 1-L Erlenmeyer flask was charged with **5**•trifluoroacetate (160 mg, 417 μmol), followed by NADP disodium salt (33 mg, 41.7 μmol). The solids were dissolved in 10 mL of DMSO and 400 mL of potassium phosphate buffer (100 mM, pH 8). Next, isopropanol (3.2 mL) and lysate (21 mL) were added. Finally, alcohol dehydrogenase (recombinant from *E. coli*, 49641 Sigma) was added. The reaction was shaken at ambient temperature and 100 rpm (19 mm radius). After 12 hours, the reaction volume was reduced *in vacuo* to ~100 mL, then the products were extracted with ethyl acetate (250 mL plus 2×100 mL). An emulsion formed on the third extraction, so the mixture was subjected to centrifugation (5,000×*g*, 20 °C, 2 minutes) in order to separate the layers. The combined organic extracts were dried over sodium sulfate, filtered, then concentrated *in vacuo*. The crude reaction was subjected to column chromatography (SiO$_2$, 0–15% methanol in ethyl acetate) yielding free imine **5** (57 mg, 0.21 mmol, 51% recovery) and an inseparable mixture of diastereomers and constitutional isomers, which were carried on to the next reaction without further purification. Crude alcohol **S7** (55.4 mg, 0.19 mmol, 1.0 equiv) was dissolved in wet CH_2Cl_2 (4 mL, 0.05M). DMP (98.7 mg, 0.23 mmol, 1.2 equiv) was added in one portion and allowed to stir at ambient temperature. After 3 hours, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the product was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and washed with a saturated aqueous solution of K_2CO_3 dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 0–16% methanol in ethyl acetate) to generate nigelladine A (**1**) (25 mg, 21% yield) as an orange oil; R_f = 0.54 (8% methanol in ethyl acetate); ^1H NMR (400 MHz, C_6D_6) δ 7.22 (d, *J* = 1.0 Hz, 1H), 5.63 (q, *J* = 1.4 Hz, 1H), 3.16 (pd, *J* = 6.8, 1.1 Hz, 1H), 2.47 (d, *J* = 15.4 Hz, 1H), 2.42 (d, *J* = 16.9 Hz, 1H), 2.27 (d, *J* = 16.9 Hz, 1H), 2.09 (dd, *J* = 15.4, 0.9 Hz, 1H), 1.77 (d, *J* = 1.4 Hz, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 196.1, 170.2, 147.2, 147.0, 141.9, 130.6, 126.0, 125.1, 61.2, 51.7, 46.5, 43.6, 31.1, 30.8, 27.5, 26.8, 22.1, 21.7, 21.0; IR thin film, NaCl) 2962, 2926, 2872, 1670, 1618, 1458, 1375, 1303, 1230, 1147, 1045, 920, 840 cm^{-1}; HRMS (ES/APCI) m/z calc'd $C_{19}H_{26}NO$ $[M+H]^+$: 284.2009, found: 284.2021; (*R*): $[\alpha]_D^{25}$ –200.3 (*c* 0.10, MeOH).

Initial Enzymatic Screens and Enantiomer Screen

Initial screen of enzymes:

Lysates containing the desired enzymes were prepared from 5-mL expression cultures according to the procedure described above.

A 2-mL vial was charged with 5•trifluoroacetate as a solution in DMSO (5 µL, 280 mM). Potassium phosphate buffer (100 mM, pH 8, 35 µL) was added, followed by lysate (80 µL). The reactions were initiated by the addition of NADPH (80 µL, 50 mM aqueous solution) and shaken at ambient temperature and 450 rpm (Labnet Orbit P4 shaker). After 1 hour, the reactions were diluted with 1:1 CH3CN/H2O (800 µL), and subjected to centrifugation at 20,000×g and 4 °C (10 minutes). The supernatant was analyzed by LCMS (ESI, positive mode) with a C-18 column (1.8 µm, 2.1 × 50 mm). The compounds were eluted with water (0.1% acetic acid by volume) and acetonitrile at a gradient of 5% to 95% acetonitrile over 4 minutes. Selectivity was approximated by extracting m/z = 286 from the total ion count, and comparing the integration of the desired product (1.6 min) to the isopropyl oxidation product (1.3 min) and an additional product (1.8 min).

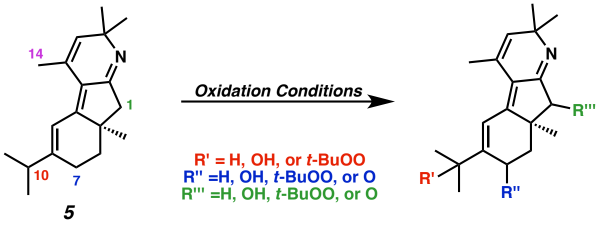
Comparison of enantiomers:

Lysates containing the desired enzymes were prepared from 5-mL expression cultures according to the procedure described above. Reactions were conducted in duplicate.

A 2-mL vial was charged with 5•trifluoroacetate as a solution in DMSO (10 µL, 200 mM). Potassium phosphate buffer (100 mM, pH 8, 290 µL) was added, followed by lysate (20 µL). Finally, the reactions were initiated by the addition of NADPH (80 µL, 50 mM aqueous solution) and shaken at ambient temperature and 500 rpm (Labnet Orbit P4 shaker). After 15 minutes, the reactions were diluted fivefold with 1:1 CH3CN/H2O, and subjected to centrifugation at 20,000×g and 4 °C (10 minutes). The supernatant was analyzed by LCMS using the method described above. Selectivity was approximated by extracting m/z from 269.5 to 286.5, so as to include residual starting material and all mono-oxygenation products. The desired product peak partially overlapped with a trace oxidation byproduct formed during preparation of the starting material, therefore the % integration of the peak at 1.4 minutes was subtracted by the % integration of the corresponding peak in the unreacted starting material. This gave % integrations of the desired product of 2.763% and 3.144% for the *S* enantiomer, and 3.828% and 4.069% for the *R* enantiomer. The *k*rel was approximated as the ratio of the average % integration for each enantiomer.

Chemical Oxidations Tables

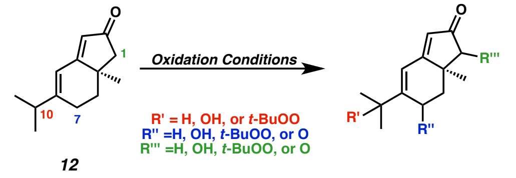
Oxidations of Imine 5 (Table S1)[13,14]



			HPLC Yield of Oxygenation Products (%)[a,b,c]												
Entry	Conditions	SM	C1	C7		C10		Polyoxygenation							
	M/z=	(270)	(284)	(286)	(284)	(286)	(358)	(302)	(300)	(298)	(314)	(374)	(316)	(390)
1	SeO_2, DCM, 40 °C	21	79 (57)[d]	–	–	–	–	–	–	–	–	–	–	–
2	SeO_2 (anhydrous), dioxane, 80 °C	–	–	–	–	–	–	–	–	60 (24)	12	–	5	–
3	Pd/C (10 wt%), TPHP, 0 °C	3	–	–	3	–	44	–	–	4	–	35	–	7
4	Cr(V) (5 equiv), MnO_2, $CF_3C_6H_5$, 15-crown-5, 80 °C	–	–	–	5	–	–	6	–	55	10	–	19	–
5	Cr(V) (1 equiv), MnO_2, $CF_3C_6H_5$, 15-crown-5, 80 °C	55	3	–	35[e]	–	–	2	1	3	–	–	–	–
6	$Rh_2(esp)_2$, T-HYDRO, 23 °C	2	8	–	21 (10)	–	–	4	–	–	–	–	4	–
7	CrO_3, 3,5-dimethylpyrazole,[f] DCE, 80 °C	–	–	–	–	–	–	–	–	–	–	–	–	–
8	8C7 P450 oxidation	47	–	32	–	11	–	–	1	–	–	–	–	–

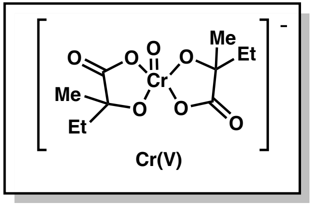
[a] Approximated by separating the products on UHPLC-MS and comparing ion count of the various oxidation products. [b] Remaining percent balance remaining were unidentified side products. [c] Numbers given in parentheses indicate isolated yields of the oxidized product. [d] Protection of **5** to as an N-acyl enamide results in oxidation at C-14. [e] Observed C–7 olefin isomerization yielding ketone oxidized **S14**.[f] No reaction observed.

Oxidations of Enone 12 (Table S2)[13]

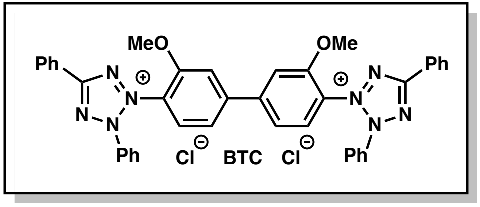


Entry	Conditions	SM	C1	C7		C10		Polyoxygenation				
								HPLC Yield of Oxygenation Products (%)[a,b,c]				
	M/z=	(191)	(205)	(205)	(207)	(279)	(207)	(223)	(295)	(367)	(221)	(238)
1	SeO_2, DCM, 40 °C	5	26 (22)	–	–	–	–	–	–	–	15	–
2	Pd/C (10 wt%), TPHP, 0 °C[d]	46	–	2	–	40 (23)	2	3	1	–	–	–
3	$Rh_2(esp)_2$, T-HYDRO, 23 °C	–	–	10	5	14	2	9	9	15	10	–
4	Cr(V) (5 equiv), MnO_2, $CF_3C_6H_5$, 15-crown-5, 80 °C	58	2	7	–	–	15	–	–	–	4	–
5	Cr(V) (1 equiv), MnO_2, $CF_3C_6H_5$, 15-crown-5, 80 °C	84	–	4	–	–	5	–	–	–	–	1
6	PIFA, TBHP, Cs_2CO_3, O_2, 4 Å mol sieves, EtOAc, –78 to – 15 °C	76	–	–	–	24[e]	–	–	–	–	–	–
7	Cl_4-NHPI, $LiClO_4$, acetone TBHP, pyridine, e^-	68	–	–	–	5	–	4	–	–	–	–
8	PCC, NaOAc benzene, celite, 80 °C	79	9	4	–	–	–	–	–	–	–	–
9	CrO_3, 3,5-dimethylpyrazole,[f] DCE, 80 °C	–	–	–	–	–	–	–	–	–	–	–
10	$Pd(OAc)_2$, L2, AcOH,[f] dioxane, air	–	–	–	–	–	–	–	–	–	–	–
11	$Pd(OAc)_2$, oxone,[g] AcOH, 95 °C	–	–	–	–	–	–	–	–	–	–	–
12	BTC, KOH, EtOH, 80 °C[g]	–	–	–	–	–	–	–	–	–	–	–
13	$Pd(OH)_2$/C (10 wt%),[f] trityl peroxide,0 °C CH_2Cl_2	–	–	–	–	–	–	–	–	–	–	–

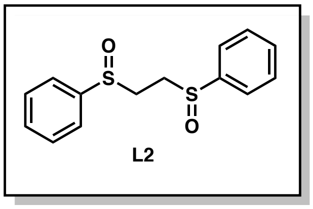
[a] Approximated by separating the products on UHPLC-MS and comparing ion count of the various oxidation products. [b] Remaining percent balance remaining were unidentified side products. [c] Numbers given in parentheses indicate isolated yields of the oxidized product. [d] Shortened reaction time used to observe inherent regioselectivity without over oxidation. [e] Site-selectivity determined by analogy from Table S1 entry 3. [f] No reaction observed. [g] Decomposition observed.



Cr(V)



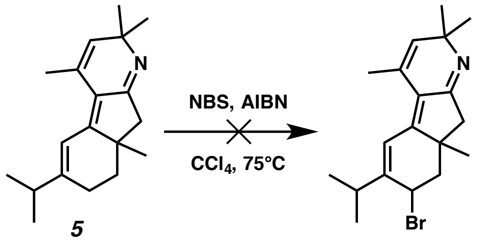
BTC



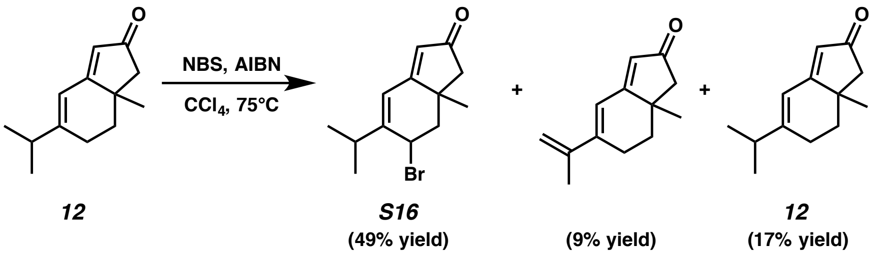
L2

Additional Oxidations Attempted

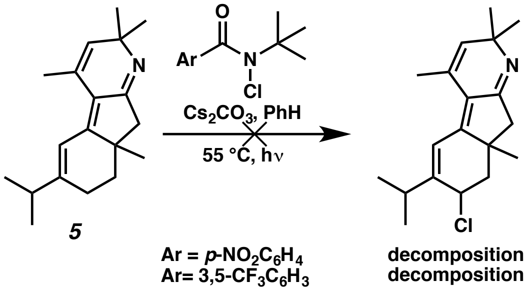
Radical Bromination of Imine 5.[13m]



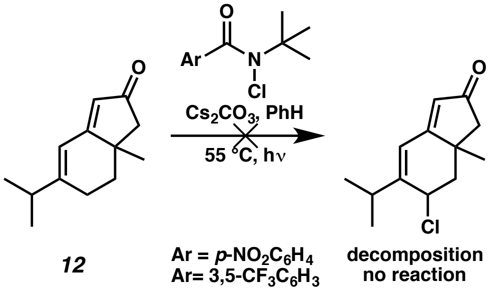
Radical Bromination of Enone 12.[13m]



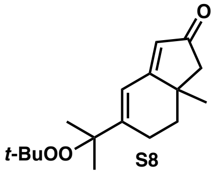
Radical Chlorination of Imine 5.[13n]



Radical Chlorination of Enone 12.[13n]

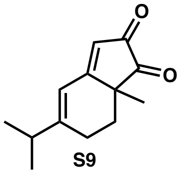


Partial Characterization of Oxidation Products


S8

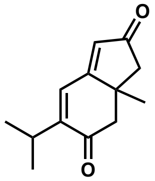
5-(2-(*tert*-butylperoxy)propan-2-yl)-7a-methyl-1,6,7,7a-tetrahydro-2*H*-inden-2-one (S8).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, J = 2.5 Hz, 1H), 5.74 (s, 1H), 2.53 (ddd, J = 19.5, 6.1, 1.8 Hz, 1H), 2.44 (dddd, J = 19.5, 11.5, 5.2, 2.6 Hz, 1H), 2.34 (d, J = 17.5 Hz, 1H), 2.21 (d, J = 17.4 Hz, 1H), 1.94 (ddd, J = 12.9, 5.2, 1.9 Hz, 1H), 1.63 (dt, J = 11.8, 6.3 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 1.21 (d, J = 0.5 Hz, 9H), 1.16 (s, 3H).


S9

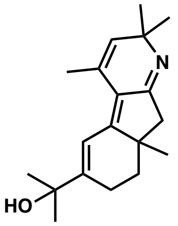
5-isopropyl-7a-methyl-7,7a-dihydro-1*H*-indene-1,2(6*H*)-dione (S9).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1H), 6.46 (d, J = 2.3 Hz, 1H), 2.57–2.41 (m, 3H), 2.05 (ddd, J = 13.2, 5.0, 1.9 Hz, 1H), 1.63 (ddd, J = 13.3, 11.2, 6.3 Hz, 1H), 1.25 (s, 3H), 1.16 (d, J = 2.0 Hz, 3H), 1.15 (d, J = 2.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 188.2, 174.9, 165.2, 126.9, 117.2, 44.1, 36.4, 26.7, 25.8, 21.4, 21.0.


S10

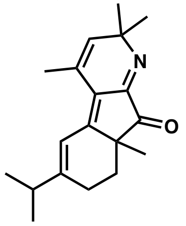
5-isopropyl-7a-methyl-7,7a-dihydro-1*H*-indene-2,6-dione (S10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.12 (s, 1H), 3.04 (septd, J = 6.8, 1.2 Hz, 1H), 2.82 (dd, J = 15.4, 0.8 Hz, 1H), 2.62 (dq, J = 15.4, 1.0 Hz, 1H), 2.46 (s, 2H), 1.31 (s, 4H), 1.15 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4, 196.8, 174.5, 152.2, 129.9, 128.4, 51.7, 51.6, 44.6, 27.9, 27.2, 21.8, 21.6.


S11

2-(2,2,4,8a-tetramethyl-7,8,8a,9-tetrahydro-2*H*-indeno[2,1-*b*]pyridin-6-yl)propan-2-ol (S11).

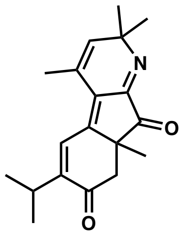
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.12 (s, 1H, CH), 5.50 (s, 1H, CH), 3.33 (d, *J* = 19.5 Hz, 1H, CH$_2$), 2.84 (d, *J* = 19.5 Hz, 1H, CH$_2$), 2.51–2.43 (m, 2H, CH$_2$), 2.12 (s, 3H, CH$_3$), 2.09–2.04 (m, 1H, CH$_2$), 1.65 (t, *J* = 7.0 Hz, 1H, CH$_2$), 1.60 (s, 6H, CH$_3$), 1.44 (s, 6H, CH$_3$), 1.15 (s, 3H, CH$_3$).



S12

6-isopropyl-2,2,4,8a-tetramethyl-2,7,8,8a-tetrahydro-9*H*-indeno[2,1-*b*]pyridin-9-one (S12).

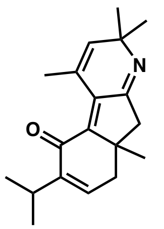
^{1}H NMR (400 MHz, CDCl$_3$) δ 6.67–6.56 (m, 1H), 5.62 (q, *J* = 1.5 Hz, 1H), 2.50–2.26 (m, 3H), 2.12–2.02 (m, 4H), 1.55–1.51 (m, 1H), 1.36 (s, 3H), 1.36 (s, 3H), 1.16 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 207.4, 161.7, 155.9, 145.4, 137.2, 126.2, 123.4, 115.7, 61.7, 46.7, 36.2, 31.1, 27.4, 24.5, 21.7, 21.2, 21.2, 21.0.



S13

6-isopropyl-2,2,4,8a-tetramethyl-8,8a-dihydro-2*H*-indeno[2,1-*b*]pyridine-7,9-dione (S13).

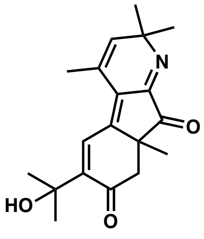
^{1}H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.51 (d, *J* = 1.1 Hz, 1H), 5.96 (d, *J* = 1.4 Hz, 1H), 2.74 (d, *J* = 15.9 Hz, 1H), 2.54 (dd, *J* = 15.9, 0.8 Hz, 1H), 2.15 (d, *J* = 1.5 Hz, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.27 (d, *J* = 0.9 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H); HRMS (ES/APCI) m/z calc'd $C_{19}H_{24}NO_2$ $[M+H]^+$: 298.1802, found: 298.1811



S14

6-isopropyl-2,2,4,8a-tetramethyl-2,8,8a,9-tetrahydro-5*H*-indeno[2,1-*b*]pyridin-5-one (S14).

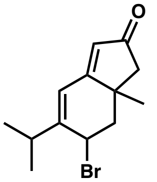
^{1}H NMR (400 MHz, CD$_3$OD) δ 6.73 (dd, *J* = 2.3, 1.2 Hz, 1H), 5.70 (q, *J* = 1.5 Hz, 1H), 2.56–2.34 (m, 3H), 2.10 (d, *J* = 1.5 Hz, 3H), 2.01 (ddd, *J* = 13.0, 5.6, 1.6 Hz, 1H), 1.53 (ddd, *J* = 13.0, 11.8, 6.0 Hz, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.15 (s, 6H), 1.13 (s, 3H).



S15

6-(2-hydroxypropan-2-yl)-2,2,4,8a-tetramethyl-8,8a-dihydro-2*H*-indeno[2,1-*b*]pyridine-7,9-dione (S15).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 (s, 1H), 6.03 (d, *J* = 1.4 Hz, 1H), 2.85 (d, *J* = 16.0 Hz, 1H), 2.62 (dd, *J* = 16.1, 0.8 Hz, 1H), 2.16 (d, *J* = 1.4 Hz, 3H), 1.51 (s, 6H), 1.43 (s, 3H), 1.43 (s, 3H), 1.34 (d, *J* = 0.7 Hz, 3H); HRMS (ES/APCI) m/z calc'd $C_{19}H_{24}NO_3$ [M+H]$^+$: 314.1751, found: 314.1759.



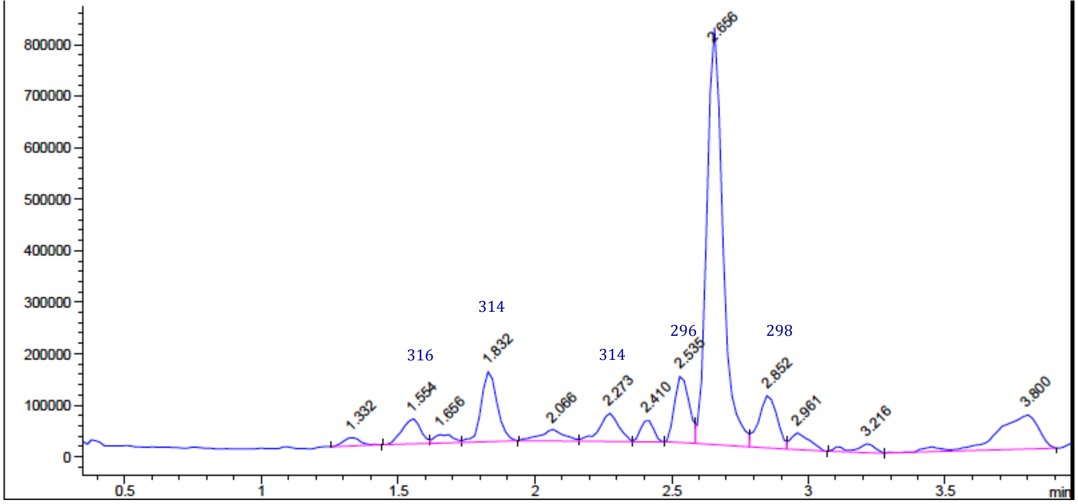
(S16)

6-bromo-5-isopropyl-7a-methyl-1,6,7,7a-tetrahydro-2*H*-inden-2-one (S16).[15]

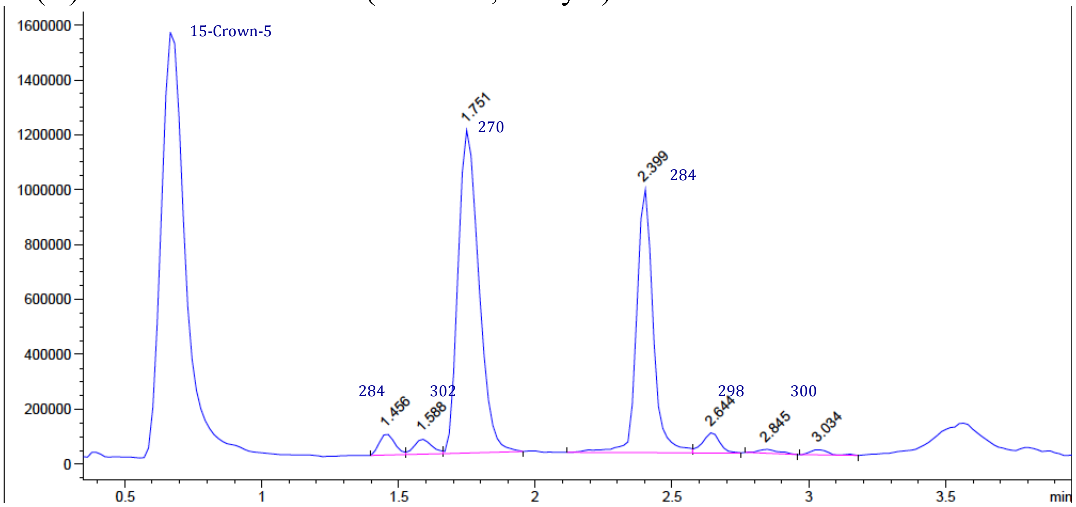
^{1}H NMR (400 MHz, CDCl$_3$) δ 6.51 (dt, *J* = 1.7, 0.9 Hz, 1H), 5.84 (s, 1H), 5.04 (dddd, *J* = 10.5, 5.3, 1.8, 1.0 Hz, 1H), 2.99 (p, *J* = 6.8 Hz, 1H), 2.67 (ddd, *J* = 13.0, 5.9, 0.6 Hz, 1H), 2.37–2.27 (m, 3H), 1.22 (d, *J* = 6.7 Hz, 3H), 1.16 (s, 3H), 1.12 (d, *J* = 6.9 Hz, 3H); ^{13}C (101 MHz, CDCl$_3$) δ 207.1, 176.0, 155.9, 124.5, 118.2, 51.1, 49.2, 46.7, 43.3, 33.2, 25.5, 22.6, 20.8; HRMS (ES/APCI) m/z calc'd $C_{13}H_{18}OBr$ [M+H]$^+$: 269.0536, found: 269.0522.

Example of UHPLC-MS Traces Used for Analysis

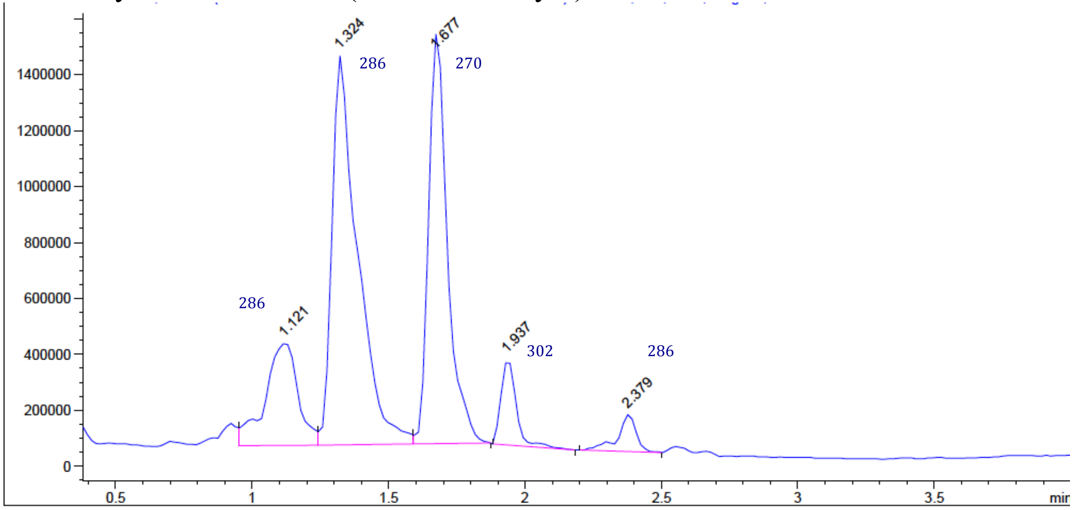
SeO_2 Oxidation of Imine **5** (Table S1, Entry 2)



Cr(V) Oxidation of Imine **5** (Table S1, Entry 5)



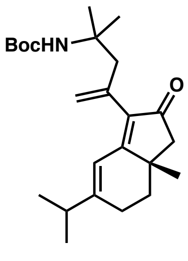
8C7 Enzymatic Oxidation (Table S1 Entry 8)



Comparison of Synthetic and Natural Nigelladine A (Table S3)[16]

Synthetic mono-deuterated, HCl salt of Nigelladine A (**1**)	Isolated Nigelladine A[17]
^{1}H NMR (400 MHz, methanol-d_4)	*^{1}H NMR (600 MHz, methanol-d_4)*
7.64 (br, 1H)	7.64 (br, 1H)
5.97 (q, *J* = 1.5 Hz, 1H)	5.97 (q, *J* = 1.2 Hz, 1H)
3.05 (pd, *J* = 6.8, 1.1 Hz, 1H)	3.05 (pd, *J* = 6.9, 0.8 Hz, 1H)
2.99 (s, 1H)	3.01 (s, 1H)
2.84 (s, 2H)	2.84 (s, 2H)
2.25 (d, *J* = 1.5 Hz, 3H)	2.25 (d, *J* = 1.2 Hz, 3H)
1.55 (s, 3H)	1.55 (s, 3H)
1.53 (s, 3H)	1.54 (s, 3H)
1.17 (d, *J* = 6.8 Hz, 3H)	1.17 (d, *J* = 6.9 Hz, 3H)
1.14 (d, *J* = 6.9 Hz, 3H)	1.14 (d, *J* = 7.2 Hz, 3H)
^{13}C NMR (101 MHz, Methanol-d_4)	*^{13}C NMR (150 MHz, Methanol-d_4)*
197.5	197.6
184.3	184.3
165.8	165.8
154.6	154.7
136.2	136.4
130.1	130.1
126.6	126.7
125.9	126.0
61.3	61.5
51.4	51.6
49.7	49.6
44.0	44.2
29.3	29.5
29.0	29.2
29.0	29.1
27.7	27.8
22.0	22.1
21.5	21.6
20.5	20.6
Optical Rotation	*Optical Rotation*
$[\alpha]_D^{26}$ = –200.3 (*c* 0.10, MeOH)	$[\alpha]_D^{20}$ = –53 (*c* 0.10, MeOH)

X-Ray Coordinate Data for Ent-12 (CCDC 1546461)



Ent-(12)

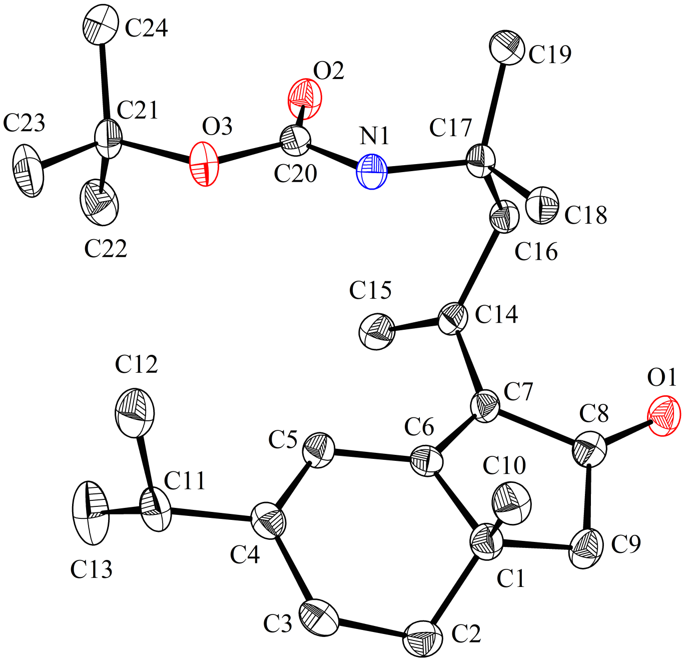


Table S4. Coordinate Data for Ent-12

Empirical formula	C24 H37 N O3	
Formula weight	387.54	
Temperature	100 K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 9.6892(11) Å	a= 89.402(8)°
	b = 10.0478(9) Å	b= 77.360(8)°
	c = 11.9882(11) Å	g = 89.745(8)°
Volume	1138.76(19) Å^3	
Z	2	
Density (calculated)	1.130 Mg/m^3	
Absorption coefficient	0.574 mm^{-1}	
F(000)	424	
Crystal size	0.31 x 0.15 x 0.15 mm^3	
Theta range for data collection	3.779 to 79.188°.	
Index ranges	-12<=h<=12, -12<=k<=12, -15<=l<=15	
Reflections collected	44144	

Independent reflections	9136 [R(int) = 0.0587]
Completeness to theta = 67.000°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9470 and 0.8656
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9136 / 3 / 521
Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0497, wR2 = 0.1066
R indices (all data)	R1 = 0.0568, wR2 = 0.1114
Absolute structure parameter	0.08(8)
Extinction coefficient	n/a
Largest diff. peak and hole	0.318 and -0.238 e.Å^{-3}

Table S5. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for Ent-12. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6427(3)	5529(2)	4290(2)	25(1)
O(2)	1594(2)	3334(2)	8236(2)	24(1)
O(3)	2950(3)	2423(2)	9381(2)	24(1)
N(1)	3663(3)	4279(3)	8426(2)	19(1)
C(1)	8553(4)	3624(3)	5846(3)	22(1)
C(2)	9499(4)	2396(4)	5692(3)	27(1)
C(3)	9318(4)	1614(3)	6823(3)	26(1)
C(4)	7794(4)	1450(3)	7447(3)	23(1)
C(5)	6748(4)	2160(3)	7164(3)	21(1)
C(6)	7031(4)	3176(3)	6278(3)	19(1)
C(7)	6109(3)	3839(3)	5775(3)	19(1)
C(8)	6912(4)	4726(3)	4874(3)	21(1)
C(9)	8471(4)	4390(3)	4741(3)	25(1)
C(10)	8980(4)	4589(4)	6705(3)	28(1)
C(11)	7516(4)	404(3)	8396(3)	28(1)
C(12)	6811(5)	994(4)	9543(3)	40(1)
C(13)	6667(5)	-743(4)	8076(4)	45(1)
C(14)	4548(3)	3702(3)	6030(2)	18(1)
C(15)	3982(4)	2511(3)	5934(3)	24(1)

C(16)	3632(3)	4898(3)	6411(3)	18(1)
C(17)	3666(3)	5403(3)	7625(3)	19(1)
C(18)	5001(4)	6206(3)	7619(3)	22(1)
C(19)	2376(4)	6285(3)	8055(3)	24(1)
C(20)	2632(3)	3355(3)	8639(3)	19(1)
C(21)	1988(4)	1295(3)	9736(3)	26(1)
C(22)	1986(4)	410(3)	8715(3)	31(1)
C(23)	2671(5)	576(4)	10590(3)	37(1)
C(24)	514(5)	1766(4)	10308(4)	47(1)
O(1B)	6314(3)	4207(2)	-587(2)	25(1)
O(2B)	1567(2)	6339(2)	3346(2)	23(1)
O(3B)	3051(2)	7332(2)	4333(2)	21(1)
N(1B)	3720(3)	5462(3)	3414(2)	20(1)
C(1B)	8278(3)	6485(3)	780(3)	21(1)
C(2B)	8972(4)	6488(4)	1797(3)	27(1)
C(3B)	8775(4)	7833(4)	2410(3)	30(1)
C(4B)	7286(4)	8363(3)	2592(3)	23(1)
C(5B)	6354(4)	7851(3)	2047(3)	21(1)
C(6B)	6729(3)	6804(3)	1209(3)	19(1)
C(7B)	5858(3)	6011(3)	769(3)	19(1)
C(8B)	6728(4)	5017(3)	34(3)	22(1)
C(9B)	8233(4)	5137(4)	190(3)	27(1)
C(10B)	8957(4)	7542(4)	-132(3)	29(1)
C(11B)	6859(4)	9458(3)	3462(3)	26(1)
C(12B)	7716(4)	10730(4)	3123(4)	38(1)
C(13B)	6903(5)	8998(5)	4671(3)	39(1)
C(14B)	4297(3)	6029(3)	1009(3)	19(1)
C(15B)	3619(4)	7141(3)	826(3)	24(1)
C(16B)	3495(3)	4785(3)	1467(3)	21(1)
C(17B)	3681(4)	4317(3)	2662(3)	21(1)
C(18B)	5065(4)	3555(3)	2590(3)	24(1)
C(19B)	2448(4)	3397(3)	3194(3)	27(1)
C(20B)	2677(3)	6368(3)	3662(3)	19(1)
C(21B)	2079(4)	8434(3)	4721(3)	22(1)
C(22B)	2867(4)	9229(3)	5458(3)	28(1)
C(23B)	1886(4)	9273(4)	3704(3)	33(1)

C(24B)	690(4)	7918(4)	5439(3)	29(1)

Table S6. Bond lengths [Å] and angles [°] for Ent-12.

O(1)-C(8)	1.221(4)
O(2)-C(20)	1.208(4)
O(3)-C(20)	1.365(4)
O(3)-C(21)	1.470(4)
N(1)-H(1)	0.8800
N(1)-C(17)	1.475(4)
N(1)-C(20)	1.348(4)
C(1)-C(2)	1.522(5)
C(1)-C(6)	1.520(5)
C(1)-C(9)	1.542(4)
C(1)-C(10)	1.543(5)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(2)-C(3)	1.537(5)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(3)-C(4)	1.510(5)
C(4)-C(5)	1.337(5)
C(4)-C(11)	1.522(4)
C(5)-H(5)	0.9500
C(5)-C(6)	1.450(4)
C(6)-C(7)	1.351(4)
C(7)-C(8)	1.478(4)
C(7)-C(14)	1.484(4)
C(8)-C(9)	1.520(5)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-H(11)	1.0000
C(11)-C(12)	1.520(6)

C(11)-C(13)	1.520(5)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-C(15)	1.335(4)
C(14)-C(16)	1.505(4)
C(15)-H(15A)	0.9500
C(15)-H(15B)	0.9500
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(16)-C(17)	1.554(4)
C(17)-C(18)	1.526(4)
C(17)-C(19)	1.526(5)
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(21)-C(22)	1.520(5)
C(21)-C(23)	1.512(5)
C(21)-C(24)	1.519(6)
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
O(1B)-C(8B)	1.234(4)
O(2B)-C(20B)	1.217(4)

O(3B)-C(20B)	1.365(4)
O(3B)-C(21B)	1.463(4)
N(1B)-H(1B)	0.8800
N(1B)-C(17B)	1.474(4)
N(1B)-C(20B)	1.343(4)
C(1B)-C(2B)	1.516(5)
C(1B)-C(6B)	1.510(5)
C(1B)-C(9B)	1.539(5)
C(1B)-C(10B)	1.557(4)
C(2B)-H(2BA)	0.9900
C(2B)-H(2BB)	0.9900
C(2B)-C(3B)	1.536(5)
C(3B)-H(3BA)	0.9900
C(3B)-H(3BB)	0.9900
C(3B)-C(4B)	1.507(5)
C(4B)-C(5B)	1.333(5)
C(4B)-C(11B)	1.516(5)
C(5B)-H(5B)	0.9500
C(5B)-C(6B)	1.451(4)
C(6B)-C(7B)	1.355(4)
C(7B)-C(8B)	1.473(5)
C(7B)-C(14B)	1.477(4)
C(8B)-C(9B)	1.515(5)
C(9B)-H(9BA)	0.9900
C(9B)-H(9BB)	0.9900
C(10B)-H(10D)	0.9800
C(10B)-H(10E)	0.9800
C(10B)-H(10F)	0.9800
C(11B)-H(11B)	1.0000
C(11B)-C(12B)	1.529(5)
C(11B)-C(13B)	1.526(5)
C(12B)-H(12D)	0.9800
C(12B)-H(12E)	0.9800
C(12B)-H(12F)	0.9800
C(13B)-H(13D)	0.9800
C(13B)-H(13E)	0.9800

C(13B)-H(13F)	0.9800
C(14B)-C(15B)	1.334(5)
C(14B)-C(16B)	1.509(4)
C(15B)-H(15C)	0.9500
C(15B)-H(15D)	0.9500
C(16B)-H(16C)	0.9900
C(16B)-H(16D)	0.9900
C(16B)-C(17B)	1.551(4)
C(17B)-C(18B)	1.528(5)
C(17B)-C(19B)	1.534(4)
C(18B)-H(18D)	0.9800
C(18B)-H(18E)	0.9800
C(18B)-H(18F)	0.9800
C(19B)-H(19D)	0.9800
C(19B)-H(19E)	0.9800
C(19B)-H(19F)	0.9800
C(21B)-C(22B)	1.523(4)
C(21B)-C(23B)	1.520(5)
C(21B)-C(24B)	1.520(5)
C(22B)-H(22D)	0.9800
C(22B)-H(22E)	0.9800
C(22B)-H(22F)	0.9800
C(23B)-H(23D)	0.9800
C(23B)-H(23E)	0.9800
C(23B)-H(23F)	0.9800
C(24B)-H(24D)	0.9800
C(24B)-H(24E)	0.9800
C(24B)-H(24F)	0.9800

C(20)-O(3)-C(21)	119.5(3)
C(17)-N(1)-H(1)	118.6
C(20)-N(1)-H(1)	118.6
C(20)-N(1)-C(17)	122.9(3)
C(2)-C(1)-C(9)	115.8(3)
C(2)-C(1)-C(10)	110.7(3)
C(6)-C(1)-C(2)	108.4(3)

C(6)-C(1)-C(9)	102.1(3)
C(6)-C(1)-C(10)	110.1(3)
C(9)-C(1)-C(10)	109.4(3)
C(1)-C(2)-H(2A)	109.6
C(1)-C(2)-H(2B)	109.6
C(1)-C(2)-C(3)	110.5(3)
H(2A)-C(2)-H(2B)	108.1
C(3)-C(2)-H(2A)	109.6
C(3)-C(2)-H(2B)	109.6
C(2)-C(3)-H(3A)	108.8
C(2)-C(3)-H(3B)	108.8
H(3A)-C(3)-H(3B)	107.7
C(4)-C(3)-C(2)	113.7(3)
C(4)-C(3)-H(3A)	108.8
C(4)-C(3)-H(3B)	108.8
C(3)-C(4)-C(11)	116.0(3)
C(5)-C(4)-C(3)	122.1(3)
C(5)-C(4)-C(11)	121.9(3)
C(4)-C(5)-H(5)	119.3
C(4)-C(5)-C(6)	121.4(3)
C(6)-C(5)-H(5)	119.3
C(5)-C(6)-C(1)	118.0(3)
C(7)-C(6)-C(1)	113.0(3)
C(7)-C(6)-C(5)	128.9(3)
C(6)-C(7)-C(8)	108.8(3)
C(6)-C(7)-C(14)	127.2(3)
C(8)-C(7)-C(14)	123.9(3)
O(1)-C(8)-C(7)	127.0(3)
O(1)-C(8)-C(9)	125.5(3)
C(7)-C(8)-C(9)	107.3(3)
C(1)-C(9)-H(9A)	110.8
C(1)-C(9)-H(9B)	110.8
C(8)-C(9)-C(1)	104.7(3)
C(8)-C(9)-H(9A)	110.8
C(8)-C(9)-H(9B)	110.8
H(9A)-C(9)-H(9B)	108.9

C(1)-C(10)-H(10A)	109.5
C(1)-C(10)-H(10B)	109.5
C(1)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(4)-C(11)-H(11)	107.4
C(12)-C(11)-C(4)	112.1(3)
C(12)-C(11)-H(11)	107.4
C(13)-C(11)-C(4)	110.5(3)
C(13)-C(11)-H(11)	107.4
C(13)-C(11)-C(12)	111.8(4)
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(11)-C(13)-H(13A)	109.5
C(11)-C(13)-H(13B)	109.5
C(11)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(7)-C(14)-C(16)	119.6(3)
C(15)-C(14)-C(7)	119.2(3)
C(15)-C(14)-C(16)	121.2(3)
C(14)-C(15)-H(15A)	120.0
C(14)-C(15)-H(15B)	120.0
H(15A)-C(15)-H(15B)	120.0
C(14)-C(16)-H(16A)	108.5
C(14)-C(16)-H(16B)	108.5
C(14)-C(16)-C(17)	114.9(3)
H(16A)-C(16)-H(16B)	107.5
C(17)-C(16)-H(16A)	108.5
C(17)-C(16)-H(16B)	108.5

N(1)-C(17)-C(16)	110.9(2)
N(1)-C(17)-C(18)	106.7(2)
N(1)-C(17)-C(19)	109.6(3)
C(18)-C(17)-C(16)	111.5(3)
C(18)-C(17)-C(19)	108.8(3)
C(19)-C(17)-C(16)	109.1(3)
C(17)-C(18)-H(18A)	109.5
C(17)-C(18)-H(18B)	109.5
C(17)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(17)-C(19)-H(19A)	109.5
C(17)-C(19)-H(19B)	109.5
C(17)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
O(2)-C(20)-O(3)	124.8(3)
O(2)-C(20)-N(1)	126.1(3)
N(1)-C(20)-O(3)	109.1(3)
O(3)-C(21)-C(22)	109.7(3)
O(3)-C(21)-C(23)	102.3(3)
O(3)-C(21)-C(24)	111.4(3)
C(23)-C(21)-C(22)	110.2(3)
C(23)-C(21)-C(24)	110.4(3)
C(24)-C(21)-C(22)	112.4(4)
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(21)-C(23)-H(23A)	109.5
C(21)-C(23)-H(23B)	109.5
C(21)-C(23)-H(23C)	109.5

H(23A)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(21)-C(24)-H(24A)	109.5
C(21)-C(24)-H(24B)	109.5
C(21)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(20B)-O(3B)-C(21B)	119.7(2)
C(17B)-N(1B)-H(1B)	118.3
C(20B)-N(1B)-H(1B)	118.3
C(20B)-N(1B)-C(17B)	123.3(3)
C(2B)-C(1B)-C(9B)	116.2(3)
C(2B)-C(1B)-C(10B)	111.3(3)
C(6B)-C(1B)-C(2B)	107.8(3)
C(6B)-C(1B)-C(9B)	102.6(3)
C(6B)-C(1B)-C(10B)	109.4(3)
C(9B)-C(1B)-C(10B)	109.1(3)
C(1B)-C(2B)-H(2BA)	109.3
C(1B)-C(2B)-H(2BB)	109.3
C(1B)-C(2B)-C(3B)	111.4(3)
H(2BA)-C(2B)-H(2BB)	108.0
C(3B)-C(2B)-H(2BA)	109.3
C(3B)-C(2B)-H(2BB)	109.3
C(2B)-C(3B)-H(3BA)	108.9
C(2B)-C(3B)-H(3BB)	108.9
H(3BA)-C(3B)-H(3BB)	107.7
C(4B)-C(3B)-C(2B)	113.2(3)
C(4B)-C(3B)-H(3BA)	108.9
C(4B)-C(3B)-H(3BB)	108.9
C(3B)-C(4B)-C(11B)	117.7(3)
C(5B)-C(4B)-C(3B)	121.4(3)
C(5B)-C(4B)-C(11B)	120.9(3)
C(4B)-C(5B)-H(5B)	118.9
C(4B)-C(5B)-C(6B)	122.2(3)

C(6B)-C(5B)-H(5B)	118.9
C(5B)-C(6B)-C(1B)	118.1(3)
C(7B)-C(6B)-C(1B)	113.5(3)
C(7B)-C(6B)-C(5B)	128.4(3)
C(6B)-C(7B)-C(8B)	108.4(3)
C(6B)-C(7B)-C(14B)	128.1(3)
C(8B)-C(7B)-C(14B)	123.4(3)
O(1B)-C(8B)-C(7B)	126.6(3)
O(1B)-C(8B)-C(9B)	125.4(3)
C(7B)-C(8B)-C(9B)	107.9(3)
C(1B)-C(9B)-H(9BA)	110.8
C(1B)-C(9B)-H(9BB)	110.8
C(8B)-C(9B)-C(1B)	104.9(3)
C(8B)-C(9B)-H(9BA)	110.8
C(8B)-C(9B)-H(9BB)	110.8
H(9BA)-C(9B)-H(9BB)	108.8
C(1B)-C(10B)-H(10D)	109.5
C(1B)-C(10B)-H(10E)	109.5
C(1B)-C(10B)-H(10F)	109.5
H(10D)-C(10B)-H(10E)	109.5
H(10D)-C(10B)-H(10F)	109.5
H(10E)-C(10B)-H(10F)	109.5
C(4B)-C(11B)-H(11B)	106.7
C(4B)-C(11B)-C(12B)	112.2(3)
C(4B)-C(11B)-C(13B)	112.2(3)
C(12B)-C(11B)-H(11B)	106.7
C(13B)-C(11B)-H(11B)	106.7
C(13B)-C(11B)-C(12B)	111.8(3)
C(11B)-C(12B)-H(12D)	109.5
C(11B)-C(12B)-H(12E)	109.5
C(11B)-C(12B)-H(12F)	109.5
H(12D)-C(12B)-H(12E)	109.5
H(12D)-C(12B)-H(12F)	109.5
H(12E)-C(12B)-H(12F)	109.5
C(11B)-C(13B)-H(13D)	109.5
C(11B)-C(13B)-H(13E)	109.5

C(11B)-C(13B)-H(13F)	109.5
H(13D)-C(13B)-H(13E)	109.5
H(13D)-C(13B)-H(13F)	109.5
H(13E)-C(13B)-H(13F)	109.5
C(7B)-C(14B)-C(16B)	119.1(3)
C(15B)-C(14B)-C(7B)	119.8(3)
C(15B)-C(14B)-C(16B)	121.1(3)
C(14B)-C(15B)-H(15C)	120.0
C(14B)-C(15B)-H(15D)	120.0
H(15C)-C(15B)-H(15D)	120.0
C(14B)-C(16B)-H(16C)	108.5
C(14B)-C(16B)-H(16D)	108.5
C(14B)-C(16B)-C(17B)	115.1(2)
H(16C)-C(16B)-H(16D)	107.5
C(17B)-C(16B)-H(16C)	108.5
C(17B)-C(16B)-H(16D)	108.5
N(1B)-C(17B)-C(16B)	111.0(3)
N(1B)-C(17B)-C(18B)	106.7(3)
N(1B)-C(17B)-C(19B)	110.0(3)
C(18B)-C(17B)-C(16B)	111.8(3)
C(18B)-C(17B)-C(19B)	108.5(3)
C(19B)-C(17B)-C(16B)	108.8(3)
C(17B)-C(18B)-H(18D)	109.5
C(17B)-C(18B)-H(18E)	109.5
C(17B)-C(18B)-H(18F)	109.5
H(18D)-C(18B)-H(18E)	109.5
H(18D)-C(18B)-H(18F)	109.5
H(18E)-C(18B)-H(18F)	109.5
C(17B)-C(19B)-H(19D)	109.5
C(17B)-C(19B)-H(19E)	109.5
C(17B)-C(19B)-H(19F)	109.5
H(19D)-C(19B)-H(19E)	109.5
H(19D)-C(19B)-H(19F)	109.5
H(19E)-C(19B)-H(19F)	109.5
O(2B)-C(20B)-O(3B)	124.9(3)
O(2B)-C(20B)-N(1B)	125.7(3)

N(1B)-C(20B)-O(3B)	109.4(3)
O(3B)-C(21B)-C(22B)	102.6(3)
O(3B)-C(21B)-C(23B)	110.0(3)
O(3B)-C(21B)-C(24B)	110.6(3)
C(23B)-C(21B)-C(22B)	109.9(3)
C(24B)-C(21B)-C(22B)	110.3(3)
C(24B)-C(21B)-C(23B)	113.0(3)
C(21B)-C(22B)-H(22D)	109.5
C(21B)-C(22B)-H(22E)	109.5
C(21B)-C(22B)-H(22F)	109.5
H(22D)-C(22B)-H(22E)	109.5
H(22D)-C(22B)-H(22F)	109.5
H(22E)-C(22B)-H(22F)	109.5
C(21B)-C(23B)-H(23D)	109.5
C(21B)-C(23B)-H(23E)	109.5
C(21B)-C(23B)-H(23F)	109.5
H(23D)-C(23B)-H(23E)	109.5
H(23D)-C(23B)-H(23F)	109.5
H(23E)-C(23B)-H(23F)	109.5
C(21B)-C(24B)-H(24D)	109.5
C(21B)-C(24B)-H(24E)	109.5
C(21B)-C(24B)-H(24F)	109.5
H(24D)-C(24B)-H(24E)	109.5
H(24D)-C(24B)-H(24F)	109.5
H(24E)-C(24B)-H(24F)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S7. Anisotropic displacement parameters ($Å^2$x 10^3) for Ent-12. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	24(1)	28(1)	23(1)	8(1)	-7(1)	-1(1)
O(2)	21(1)	26(1)	26(1)	6(1)	-8(1)	-4(1)
O(3)	32(1)	18(1)	23(1)	6(1)	-12(1)	-4(1)

N(1)	21(1)	19(1)	17(1)	2(1)	-6(1)	-1(1)
C(1)	22(2)	22(2)	24(2)	3(1)	-6(1)	-1(1)
C(2)	23(2)	29(2)	27(2)	0(1)	-4(1)	2(2)
C(3)	26(2)	25(2)	31(2)	-1(1)	-10(2)	5(1)
C(4)	27(2)	20(2)	23(2)	-1(1)	-7(1)	1(1)
C(5)	23(2)	21(2)	19(2)	2(1)	-4(1)	-1(1)
C(6)	22(2)	16(1)	17(1)	-3(1)	-2(1)	1(1)
C(7)	24(2)	14(1)	17(1)	0(1)	-1(1)	-1(1)
C(8)	23(2)	21(2)	20(2)	-1(1)	-5(1)	-3(1)
C(9)	20(2)	28(2)	27(2)	6(1)	-6(1)	-5(1)
C(10)	28(2)	27(2)	32(2)	1(2)	-10(2)	-3(2)
C(11)	34(2)	21(2)	31(2)	8(1)	-11(2)	0(2)
C(12)	50(3)	38(2)	30(2)	11(2)	-7(2)	4(2)
C(13)	55(3)	31(2)	54(3)	16(2)	-27(2)	-14(2)
C(14)	20(2)	20(1)	14(1)	2(1)	-2(1)	-1(1)
C(15)	23(2)	24(2)	25(2)	0(1)	-4(1)	-2(1)
C(16)	18(2)	18(1)	19(1)	3(1)	-4(1)	0(1)
C(17)	21(2)	17(1)	18(1)	2(1)	-4(1)	0(1)
C(18)	26(2)	20(2)	20(2)	0(1)	-5(1)	-2(1)
C(19)	26(2)	22(2)	24(2)	0(1)	-3(1)	4(1)
C(20)	21(2)	17(1)	17(1)	0(1)	-2(1)	2(1)
C(21)	33(2)	17(2)	26(2)	6(1)	-1(2)	-2(1)
C(22)	33(2)	21(2)	42(2)	0(2)	-13(2)	-5(2)
C(23)	57(3)	20(2)	34(2)	9(2)	-12(2)	-1(2)
C(24)	43(3)	35(2)	50(3)	18(2)	16(2)	8(2)
O(1B)	27(1)	24(1)	24(1)	-6(1)	-6(1)	4(1)
O(2B)	20(1)	27(1)	24(1)	-6(1)	-7(1)	2(1)
O(3B)	22(1)	20(1)	23(1)	-6(1)	-8(1)	4(1)
N(1B)	21(1)	21(1)	19(1)	-5(1)	-5(1)	2(1)
C(1B)	19(2)	23(2)	19(2)	1(1)	-1(1)	0(1)
C(2B)	22(2)	31(2)	28(2)	0(1)	-7(1)	2(2)
C(3B)	26(2)	36(2)	32(2)	-6(2)	-12(2)	0(2)
C(4B)	25(2)	22(2)	22(2)	1(1)	-5(1)	-1(1)
C(5B)	21(2)	20(2)	20(2)	1(1)	-1(1)	-1(1)
C(6B)	21(2)	19(2)	16(1)	3(1)	-2(1)	-2(1)
C(7B)	23(2)	19(1)	16(1)	2(1)	-3(1)	1(1)

C(8B)	26(2)	19(2)	19(2)	2(1)	-4(1)	2(1)
C(9B)	24(2)	27(2)	31(2)	-7(1)	-6(1)	6(2)
C(10B)	26(2)	28(2)	31(2)	6(2)	2(2)	2(2)
C(11B)	27(2)	25(2)	27(2)	-5(1)	-8(1)	-1(2)
C(12B)	34(2)	33(2)	45(2)	-10(2)	-3(2)	-2(2)
C(13B)	45(3)	45(2)	30(2)	-7(2)	-10(2)	11(2)
C(14B)	21(2)	20(2)	15(1)	-3(1)	-4(1)	-1(1)
C(15B)	25(2)	23(2)	25(2)	2(1)	-6(1)	0(1)
C(16B)	20(2)	23(2)	19(2)	-5(1)	-3(1)	-1(1)
C(17B)	24(2)	20(2)	18(2)	-4(1)	-3(1)	0(1)
C(18B)	31(2)	19(2)	21(2)	1(1)	-4(1)	4(1)
C(19B)	29(2)	23(2)	25(2)	1(1)	1(1)	-5(2)
C(20B)	20(2)	20(2)	16(1)	-2(1)	-2(1)	0(1)
C(21B)	25(2)	16(1)	26(2)	-2(1)	-5(1)	-1(1)
C(22B)	27(2)	22(2)	32(2)	-9(1)	-2(2)	-4(1)
C(23B)	34(2)	23(2)	43(2)	6(2)	-13(2)	2(2)
C(24B)	26(2)	28(2)	31(2)	-9(2)	0(2)	-4(2)

Table S8. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Ent-12.

	x	y	z	U(eq)
H(1)	4366	4207	8780	22
H(2A)	10499	2670	5430	32
H(2B)	9253	1819	5100	32
H(3A)	9749	721	6664	32
H(3B)	9838	2079	7328	32
H(5)	5799	1993	7553	25
H(9A)	9048	5210	4663	30
H(9B)	8810	3830	4061	30
H(10A)	8415	5405	6742	43
H(10B)	9985	4809	6455	43
H(10C)	8810	4167	7463	43
H(11)	8453	39	8472	34

H(12A)	7392	1723	9724	60
H(12B)	6712	304	10138	60
H(12C)	5873	1337	9504	60
H(13A)	5734	-419	8004	67
H(13B)	6551	-1434	8672	67
H(13C)	7167	-1115	7346	67
H(15A)	4578	1765	5703	29
H(15B)	2983	2410	6095	29
H(16A)	2643	4676	6392	22
H(16B)	3935	5632	5855	22
H(18A)	4964	6554	8386	33
H(18B)	5063	6949	7074	33
H(18C)	5833	5631	7394	33
H(19A)	1512	5767	8092	36
H(19B)	2392	7042	7531	36
H(19C)	2396	6611	8819	36
H(22A)	1610	910	8140	47
H(22B)	1391	-370	8965	47
H(22C)	2954	120	8383	47
H(23A)	3615	266	10207	55
H(23B)	2089	-189	10912	55
H(23C)	2753	1185	11206	55
H(24A)	576	2379	10925	71
H(24B)	-67	998	10624	71
H(24C)	83	2225	9743	71
H(1B)	4464	5557	3715	24
H(2BA)	9994	6299	1534	32
H(2BB)	8554	5774	2340	32
H(3BA)	9033	7732	3161	36
H(3BB)	9429	8489	1953	36
H(5B)	5412	8182	2213	25
H(9BA)	8914	5122	-557	33
H(9BB)	8462	4400	674	33
H(10D)	8543	7468	-805	44
H(10E)	9979	7390	-355	44
H(10F)	8774	8435	190	44

H(11B)	5851	9685	3469	31
H(12D)	8713	10555	3115	57
H(12E)	7359	11429	3676	57
H(12F)	7623	11020	2359	57
H(13D)	6310	8206	4871	59
H(13E)	6548	9711	5211	59
H(13F)	7880	8782	4707	59
H(15C)	4140	7918	543	29
H(15D)	2615	7157	980	29
H(16C)	3803	4057	918	25
H(16D)	2476	4943	1507	25
H(18D)	5865	4149	2300	36
H(18E)	5101	2802	2071	36
H(18F)	5116	3225	3352	36
H(19D)	2575	3069	3938	40
H(19E)	2426	2642	2688	40
H(19F)	1556	3892	3296	40
H(22D)	3045	8663	6083	41
H(22E)	2293	9998	5777	41
H(22F)	3769	9539	4990	41
H(23D)	2813	9553	3259	49
H(23E)	1315	10060	3976	49
H(23F)	1405	8746	3220	49
H(24D)	188	7418	4952	44
H(24E)	105	8670	5780	44
H(24F)	881	7332	6046	44

Table S9. Torsion angles [°] for Ent-12.

O(1)-C(8)-C(9)-C(1)	165.9(3)
C(1)-C(2)-C(3)-C(4)	44.6(4)
C(1)-C(6)-C(7)-C(8)	4.9(4)
C(1)-C(6)-C(7)-C(14)	-176.8(3)
C(2)-C(1)-C(6)-C(5)	43.1(4)
C(2)-C(1)-C(6)-C(7)	-138.5(3)
C(2)-C(1)-C(9)-C(8)	137.0(3)

C(2)-C(3)-C(4)-C(5)	-13.6(5)
C(2)-C(3)-C(4)-C(11)	164.9(3)
C(3)-C(4)-C(5)-C(6)	-3.1(5)
C(3)-C(4)-C(11)-C(12)	121.6(4)
C(3)-C(4)-C(11)-C(13)	-113.0(4)
C(4)-C(5)-C(6)-C(1)	-12.6(5)
C(4)-C(5)-C(6)-C(7)	169.3(3)
C(5)-C(4)-C(11)-C(12)	-59.8(5)
C(5)-C(4)-C(11)-C(13)	65.6(5)
C(5)-C(6)-C(7)-C(8)	-176.9(3)
C(5)-C(6)-C(7)-C(14)	1.4(5)
C(6)-C(1)-C(2)-C(3)	-57.7(4)
C(6)-C(1)-C(9)-C(8)	19.6(3)
C(6)-C(7)-C(8)-O(1)	-175.4(3)
C(6)-C(7)-C(8)-C(9)	8.6(3)
C(6)-C(7)-C(14)-C(15)	-58.0(5)
C(6)-C(7)-C(14)-C(16)	121.0(3)
C(7)-C(8)-C(9)-C(1)	-18.0(3)
C(7)-C(14)-C(16)-C(17)	-69.5(3)
C(8)-C(7)-C(14)-C(15)	120.0(3)
C(8)-C(7)-C(14)-C(16)	-60.9(4)
C(9)-C(1)-C(2)-C(3)	-171.6(3)
C(9)-C(1)-C(6)-C(5)	165.8(3)
C(9)-C(1)-C(6)-C(7)	-15.8(4)
C(10)-C(1)-C(2)-C(3)	63.1(4)
C(10)-C(1)-C(6)-C(5)	-78.1(4)
C(10)-C(1)-C(6)-C(7)	100.3(3)
C(10)-C(1)-C(9)-C(8)	-97.0(3)
C(11)-C(4)-C(5)-C(6)	178.4(3)
C(14)-C(7)-C(8)-O(1)	6.2(5)
C(14)-C(7)-C(8)-C(9)	-169.8(3)
C(14)-C(16)-C(17)-N(1)	-40.6(4)
C(14)-C(16)-C(17)-C(18)	78.2(3)
C(14)-C(16)-C(17)-C(19)	-161.5(3)
C(15)-C(14)-C(16)-C(17)	109.5(3)
C(17)-N(1)-C(20)-O(2)	-1.4(5)

C(17)-N(1)-C(20)-O(3)	177.9(3)
C(20)-O(3)-C(21)-C(22)	66.4(4)
C(20)-O(3)-C(21)-C(23)	-176.6(3)
C(20)-O(3)-C(21)-C(24)	-58.7(4)
C(20)-N(1)-C(17)-C(16)	-58.1(4)
C(20)-N(1)-C(17)-C(18)	-179.7(3)
C(20)-N(1)-C(17)-C(19)	62.6(4)
C(21)-O(3)-C(20)-O(2)	0.1(5)
C(21)-O(3)-C(20)-N(1)	-179.2(3)
O(1B)-C(8B)-C(9B)-C(1B)	165.9(3)
C(1B)-C(2B)-C(3B)-C(4B)	45.3(4)
C(1B)-C(6B)-C(7B)-C(8B)	2.9(4)
C(1B)-C(6B)-C(7B)-C(14B)	179.1(3)
C(2B)-C(1B)-C(6B)-C(5B)	42.3(4)
C(2B)-C(1B)-C(6B)-C(7B)	-135.5(3)
C(2B)-C(1B)-C(9B)-C(8B)	133.4(3)
C(2B)-C(3B)-C(4B)-C(5B)	-13.9(5)
C(2B)-C(3B)-C(4B)-C(11B)	163.2(3)
C(3B)-C(4B)-C(5B)-C(6B)	-3.1(5)
C(3B)-C(4B)-C(11B)-C(12B)	63.3(4)
C(3B)-C(4B)-C(11B)-C(13B)	-63.5(4)
C(4B)-C(5B)-C(6B)-C(1B)	-12.2(5)
C(4B)-C(5B)-C(6B)-C(7B)	165.2(3)
C(5B)-C(4B)-C(11B)-C(12B)	-119.5(4)
C(5B)-C(4B)-C(11B)-C(13B)	113.7(4)
C(5B)-C(6B)-C(7B)-C(8B)	-174.6(3)
C(5B)-C(6B)-C(7B)-C(14B)	1.6(5)
C(6B)-C(1B)-C(2B)-C(3B)	-57.8(4)
C(6B)-C(1B)-C(9B)-C(8B)	16.0(3)
C(6B)-C(7B)-C(8B)-O(1B)	-173.1(3)
C(6B)-C(7B)-C(8B)-C(9B)	8.2(3)
C(6B)-C(7B)-C(14B)-C(15B)	57.4(5)
C(6B)-C(7B)-C(14B)-C(16B)	-122.1(3)
C(7B)-C(8B)-C(9B)-C(1B)	-15.4(3)
C(7B)-C(14B)-C(16B)-C(17B)	63.7(4)
C(8B)-C(7B)-C(14B)-C(15B)	-126.9(3)

C(8B)-C(7B)-C(14B)-C(16B)	53.6(4)
C(9B)-C(1B)-C(2B)-C(3B)	-172.3(3)
C(9B)-C(1B)-C(6B)-C(5B)	165.5(3)
C(9B)-C(1B)-C(6B)-C(7B)	-12.3(4)
C(10B)-C(1B)-C(2B)-C(3B)	62.1(4)
C(10B)-C(1B)-C(6B)-C(5B)	-78.8(4)
C(10B)-C(1B)-C(6B)-C(7B)	103.4(3)
C(10B)-C(1B)-C(9B)-C(8B)	-99.9(3)
C(11B)-C(4B)-C(5B)-C(6B)	179.9(3)
C(14B)-C(7B)-C(8B)-O(1B)	10.4(5)
C(14B)-C(7B)-C(8B)-C(9B)	-168.3(3)
C(14B)-C(16B)-C(17B)-N(1B)	38.7(4)
C(14B)-C(16B)-C(17B)-C(18B)	-80.3(3)
C(14B)-C(16B)-C(17B)-C(19B)	159.9(3)
C(15B)-C(14B)-C(16B)-C(17B)	-115.8(3)
C(17B)-N(1B)-C(20B)-O(2B)	3.0(5)
C(17B)-N(1B)-C(20B)-O(3B)	-177.3(3)
C(20B)-O(3B)-C(21B)-C(22B)	178.2(3)
C(20B)-O(3B)-C(21B)-C(23B)	-64.9(3)
C(20B)-O(3B)-C(21B)-C(24B)	60.5(4)
C(20B)-N(1B)-C(17B)-C(16B)	57.1(4)
C(20B)-N(1B)-C(17B)-C(18B)	179.1(3)
C(20B)-N(1B)-C(17B)-C(19B)	-63.4(4)
C(21B)-O(3B)-C(20B)-O(2B)	-0.1(4)
C(21B)-O(3B)-C(20B)-N(1B)	-179.8(2)

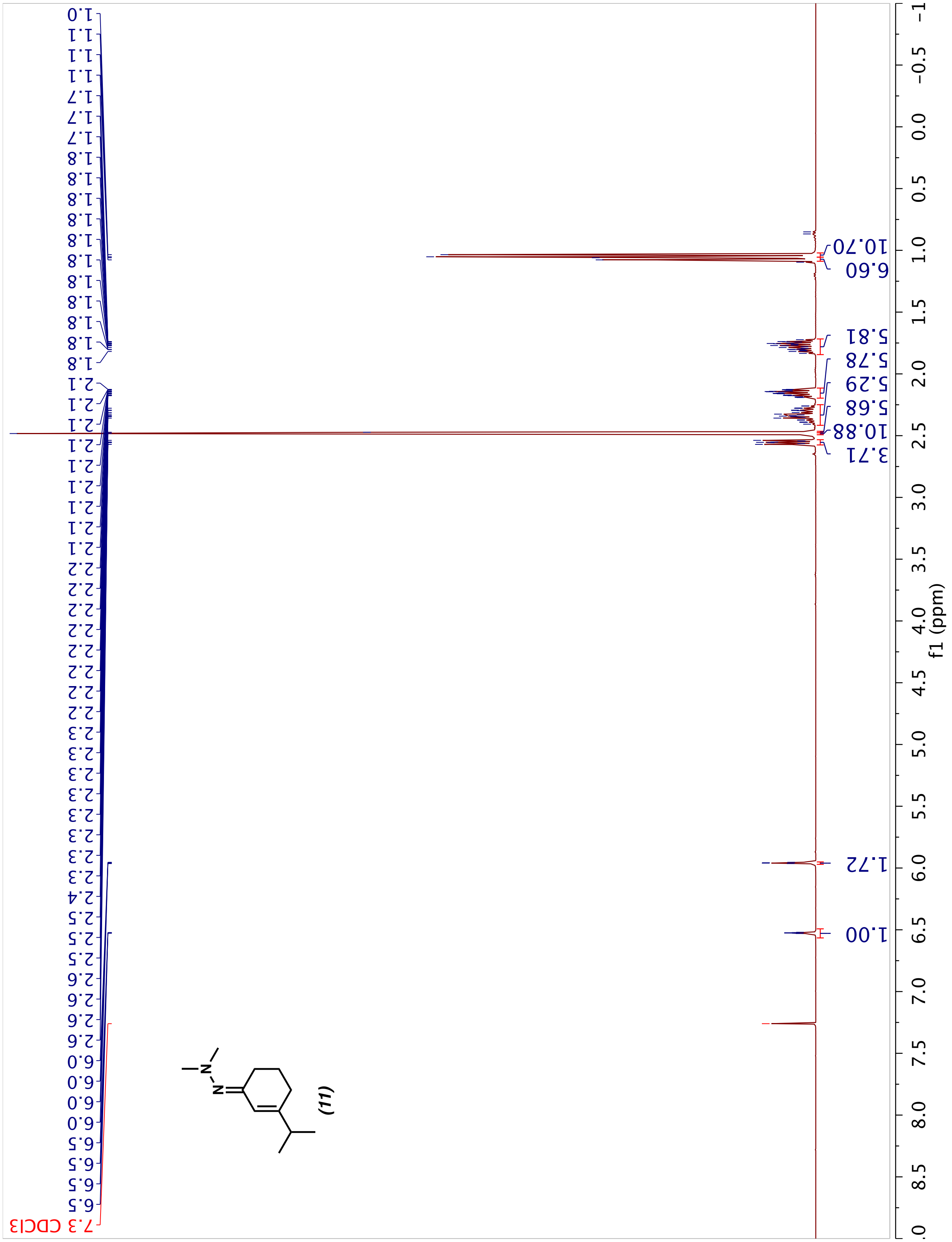
Symmetry transformations used to generate equivalent atoms:

Table S10. Hydrogen bonds for Ent-12 [Å and °].

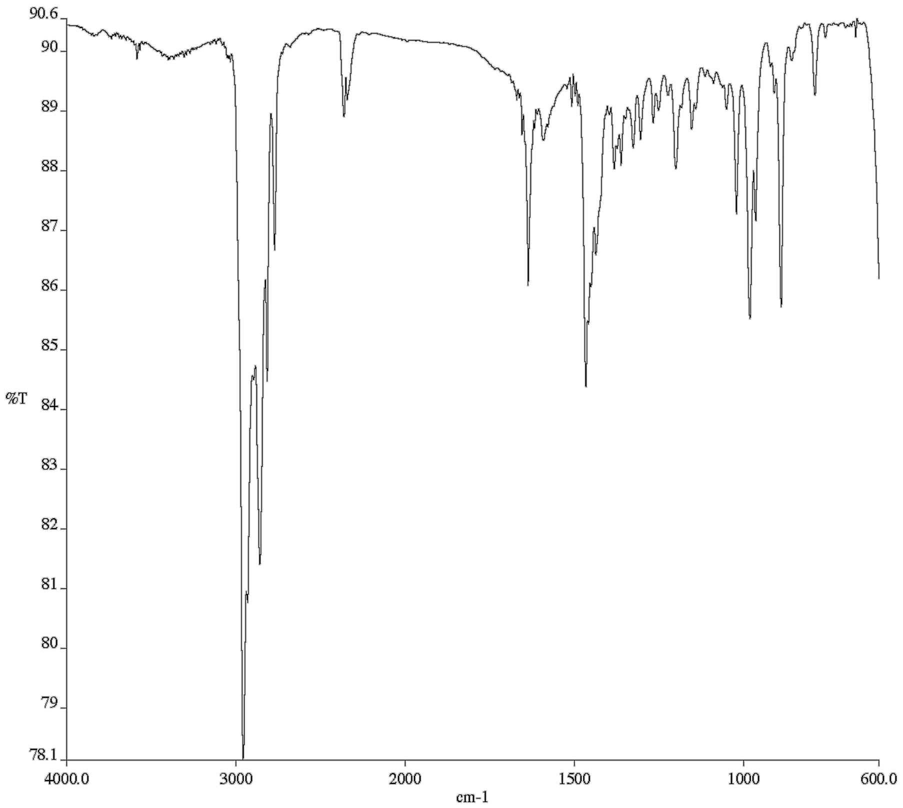
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(1B)#1	0.88	2.18	3.054(4)	170.5
N(1B)-H(1B)...O(1)	0.88	2.16	3.032(4)	171.0

Symmetry transformations used to generate equivalent atoms:

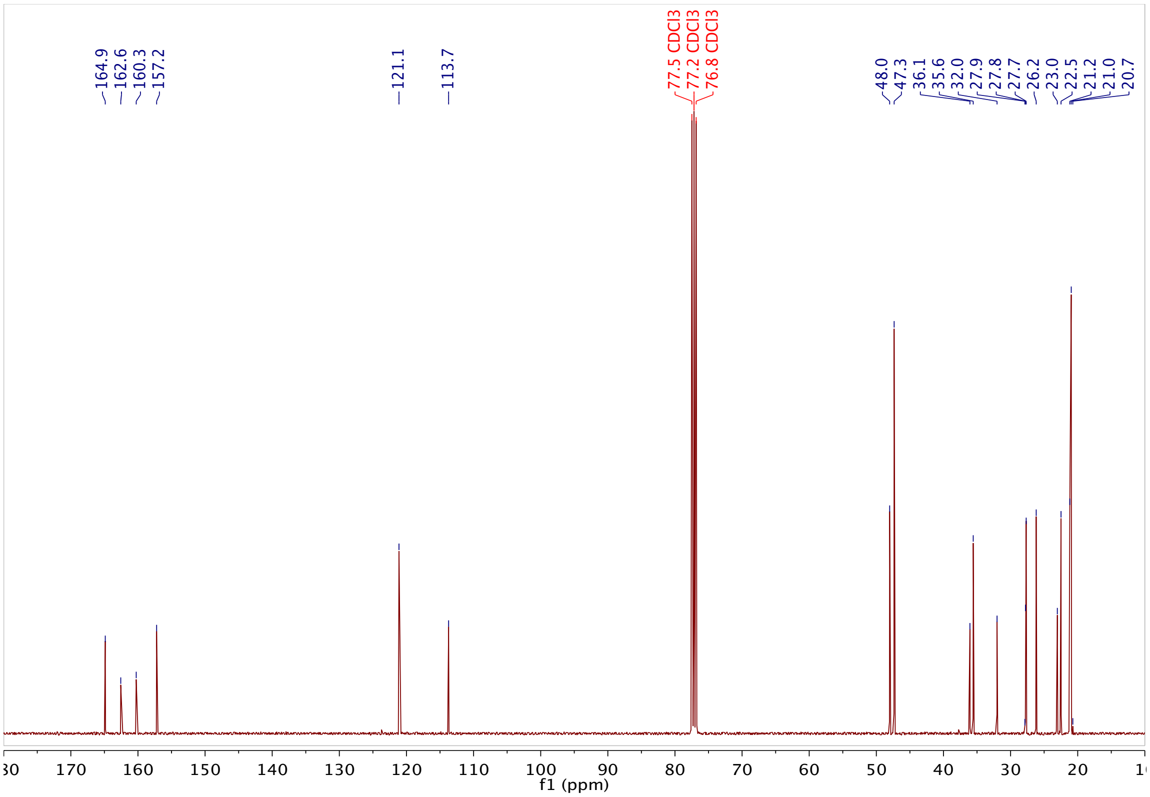
#1 x,y,z+1



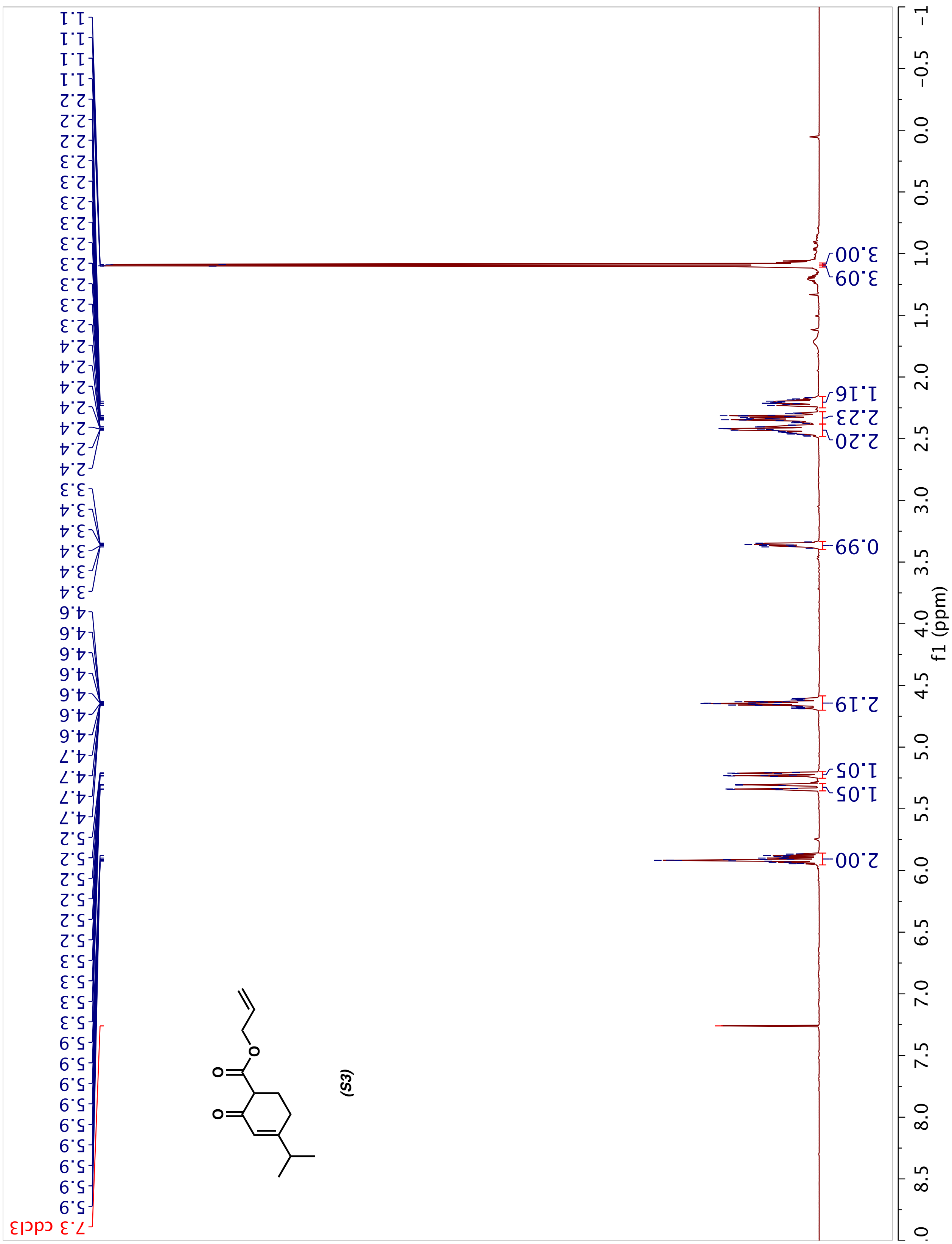
^{1}H NMR (400 MHz, CDCl$_3$) of compound **11**.



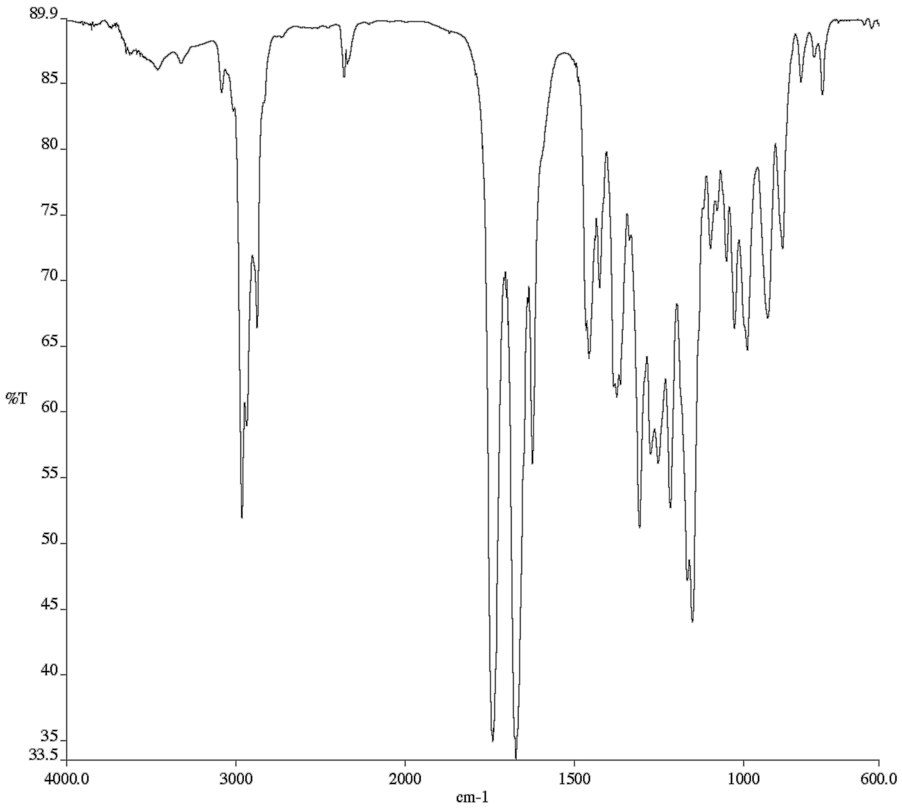
Infrared spectrum (Thin Film, NaCl) of compound



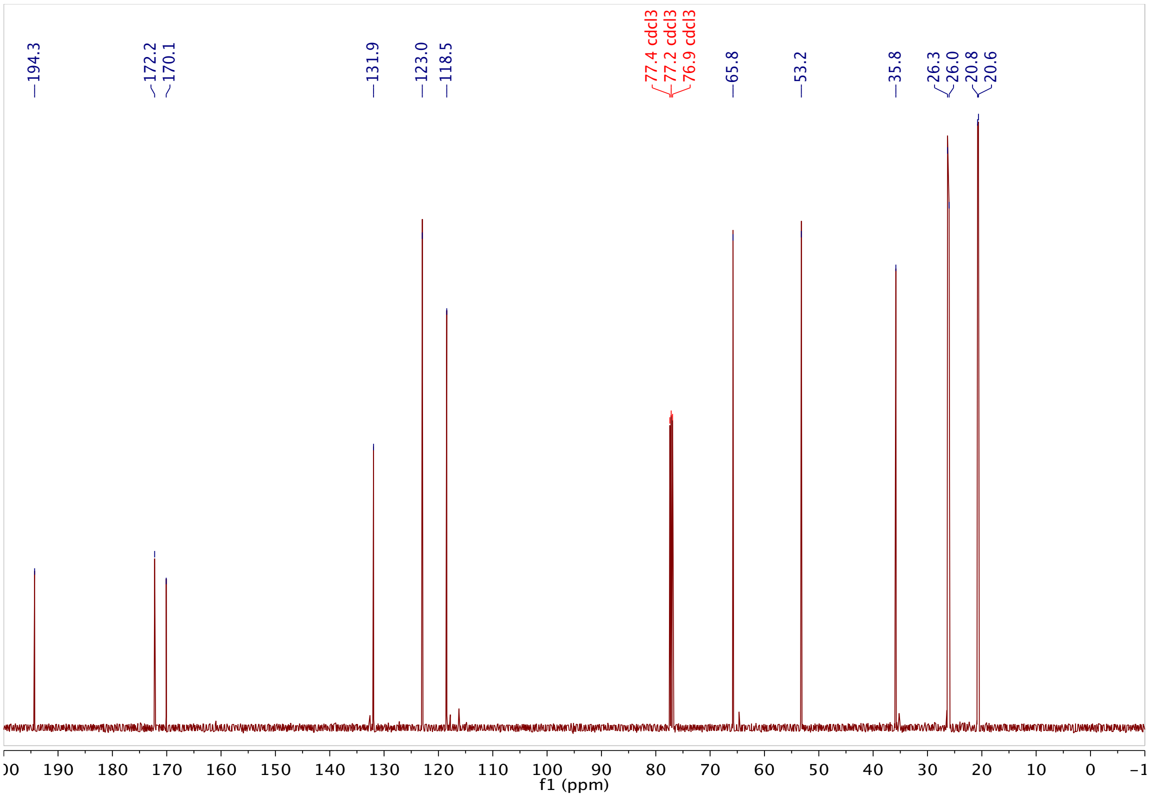
^{13}C NMR (101 MHz, $CDCl_3$) of compound **11.**



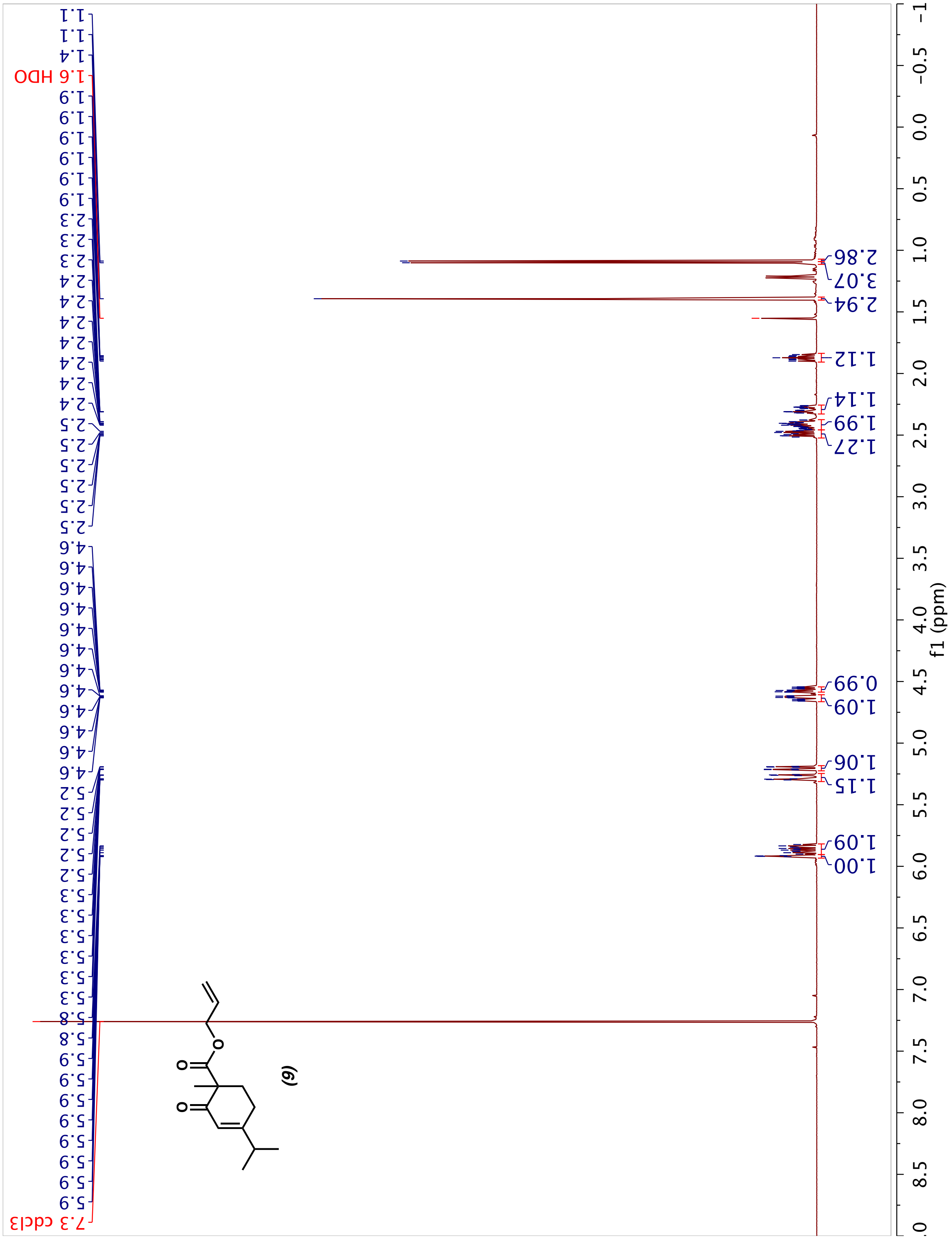
^{1}H NMR (400 MHz, CDCl$_3$) of compound **S3**.



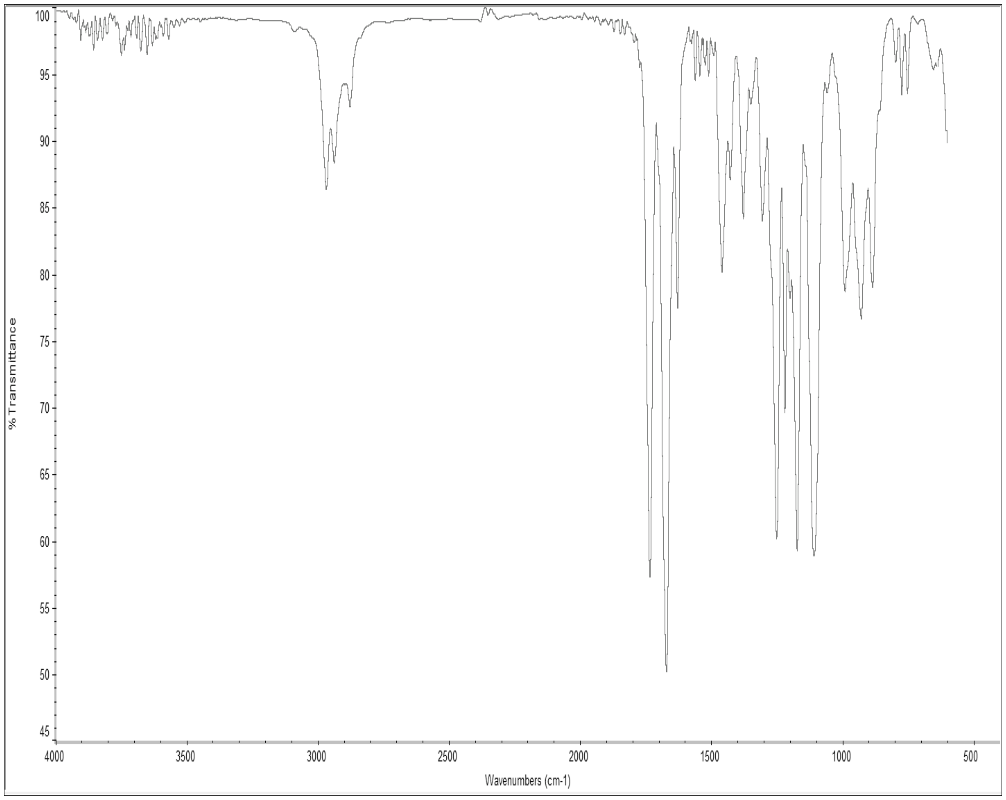
Infrared spectrum (Thin Film, NaCl) of compound



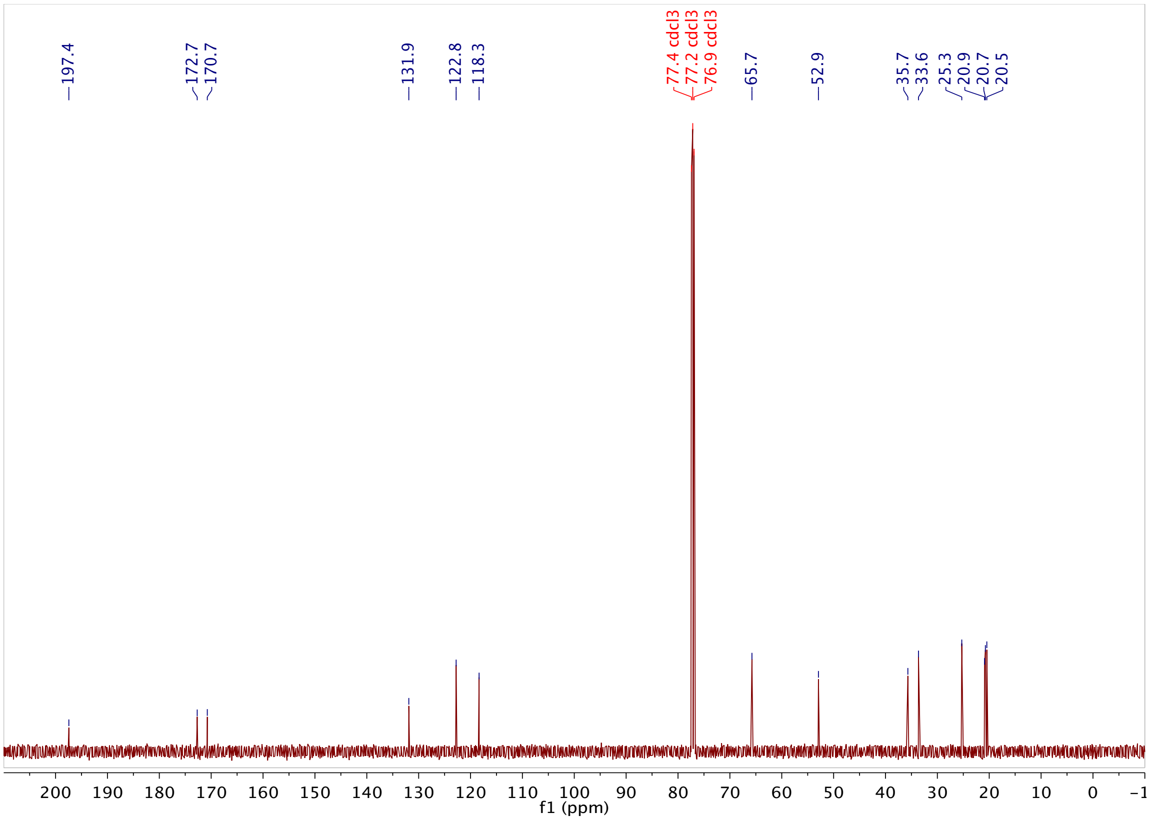
^{13}C NMR (101 MHz, CDCl$_3$) of compound **S3**.



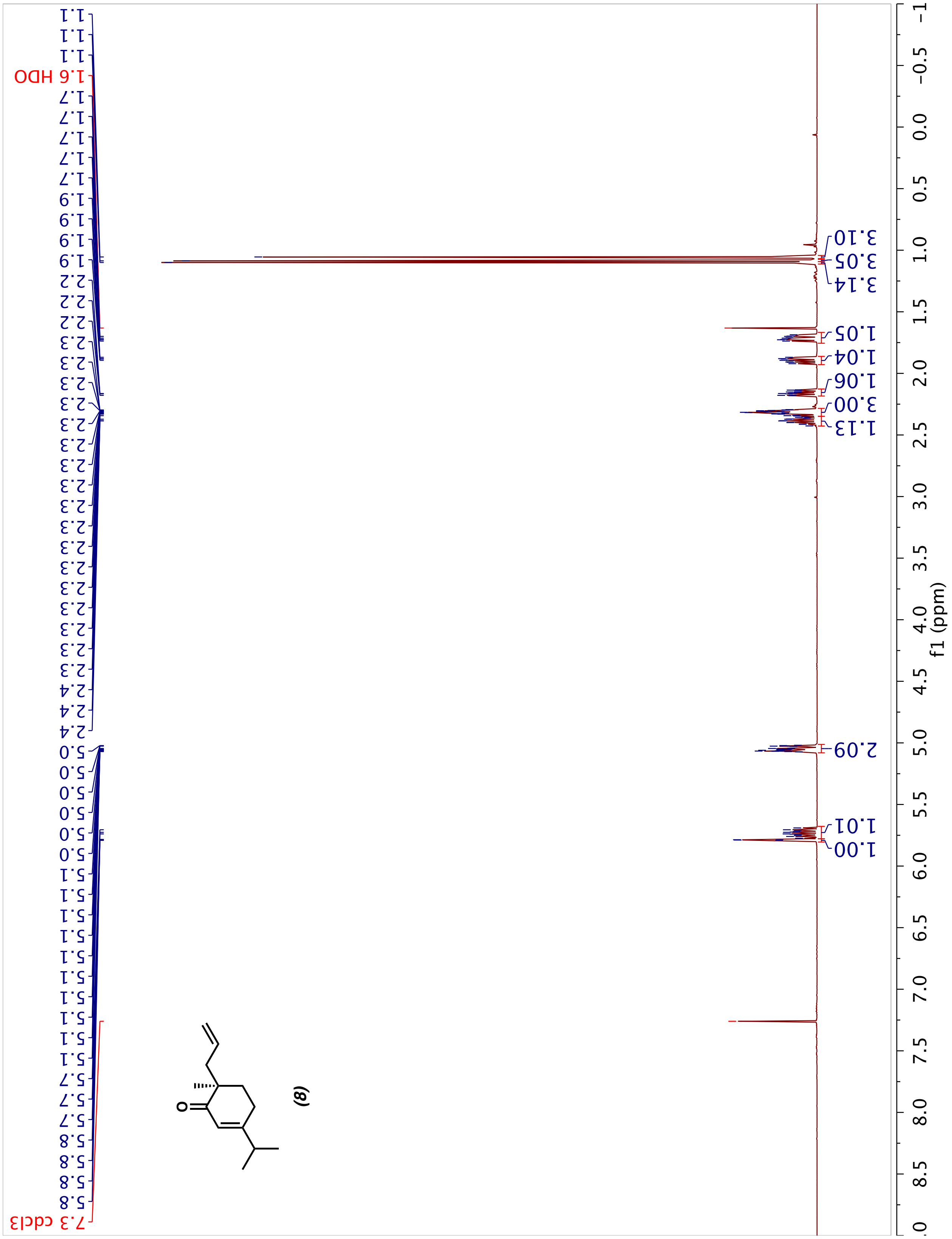
^{1}H NMR (400 MHz, $CDCl_3$) of compound **9**.



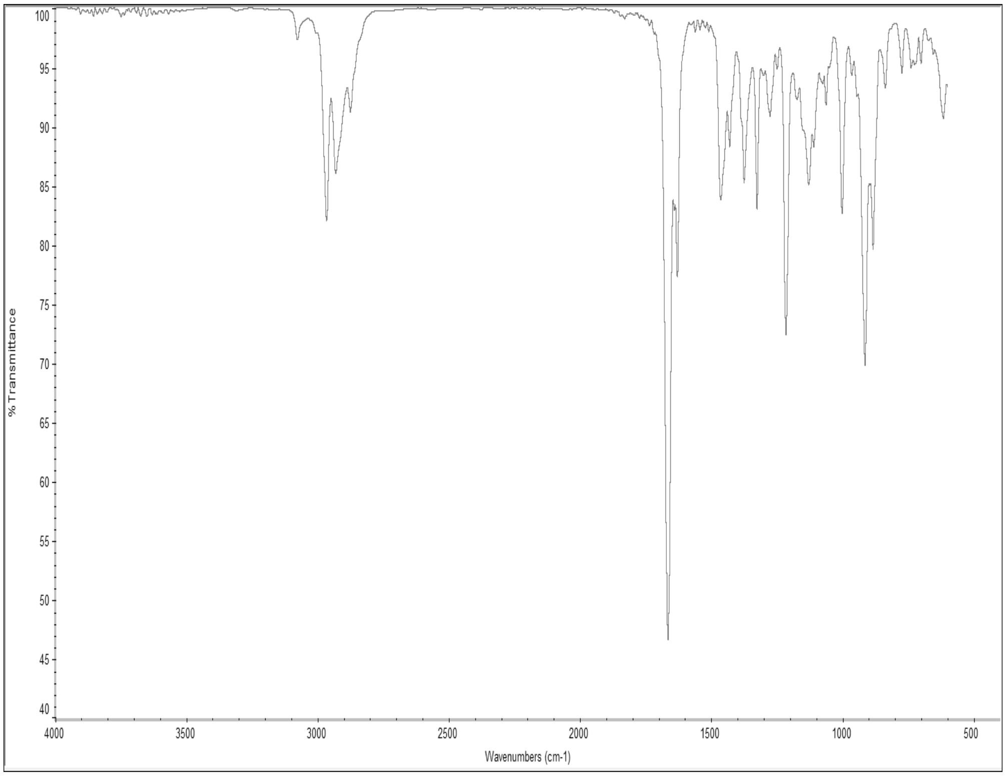
Infrared spectrum (Thin Film, NaCl) of compound



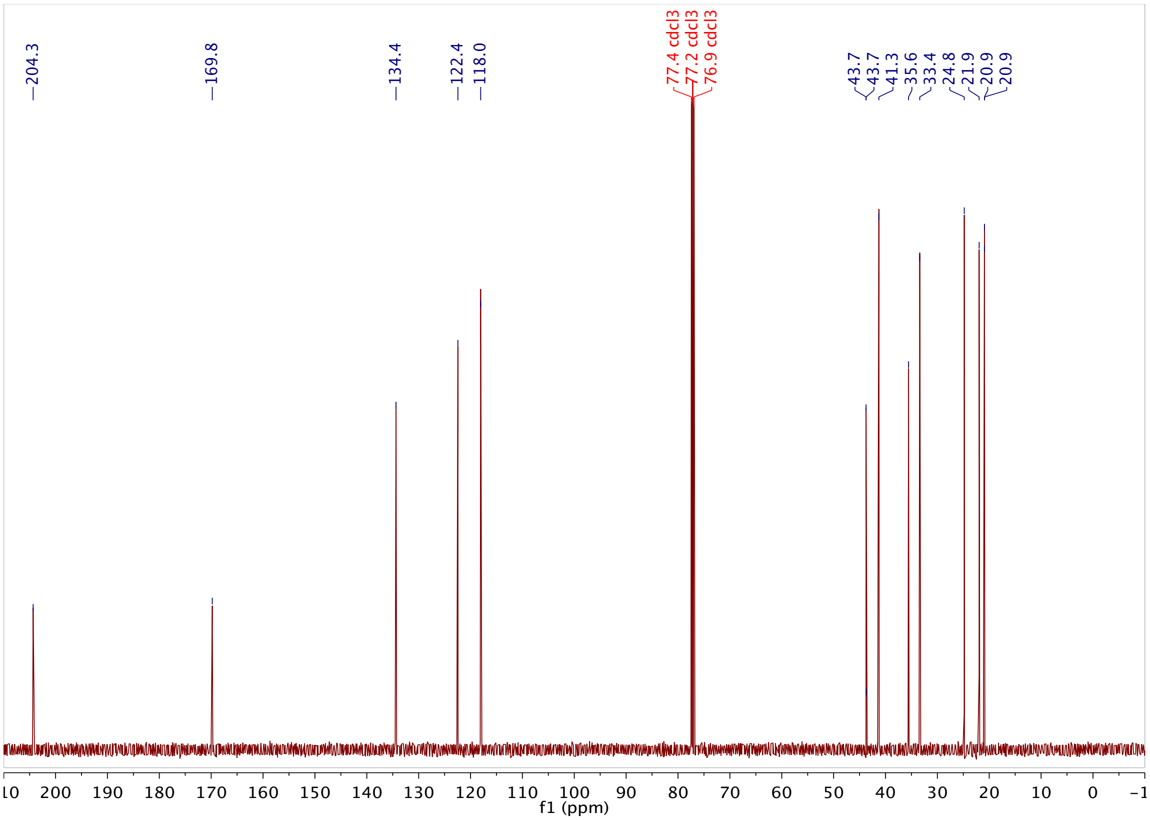
^{13}C NMR (101 MHz, $CDCl_3$) of compound **9**.



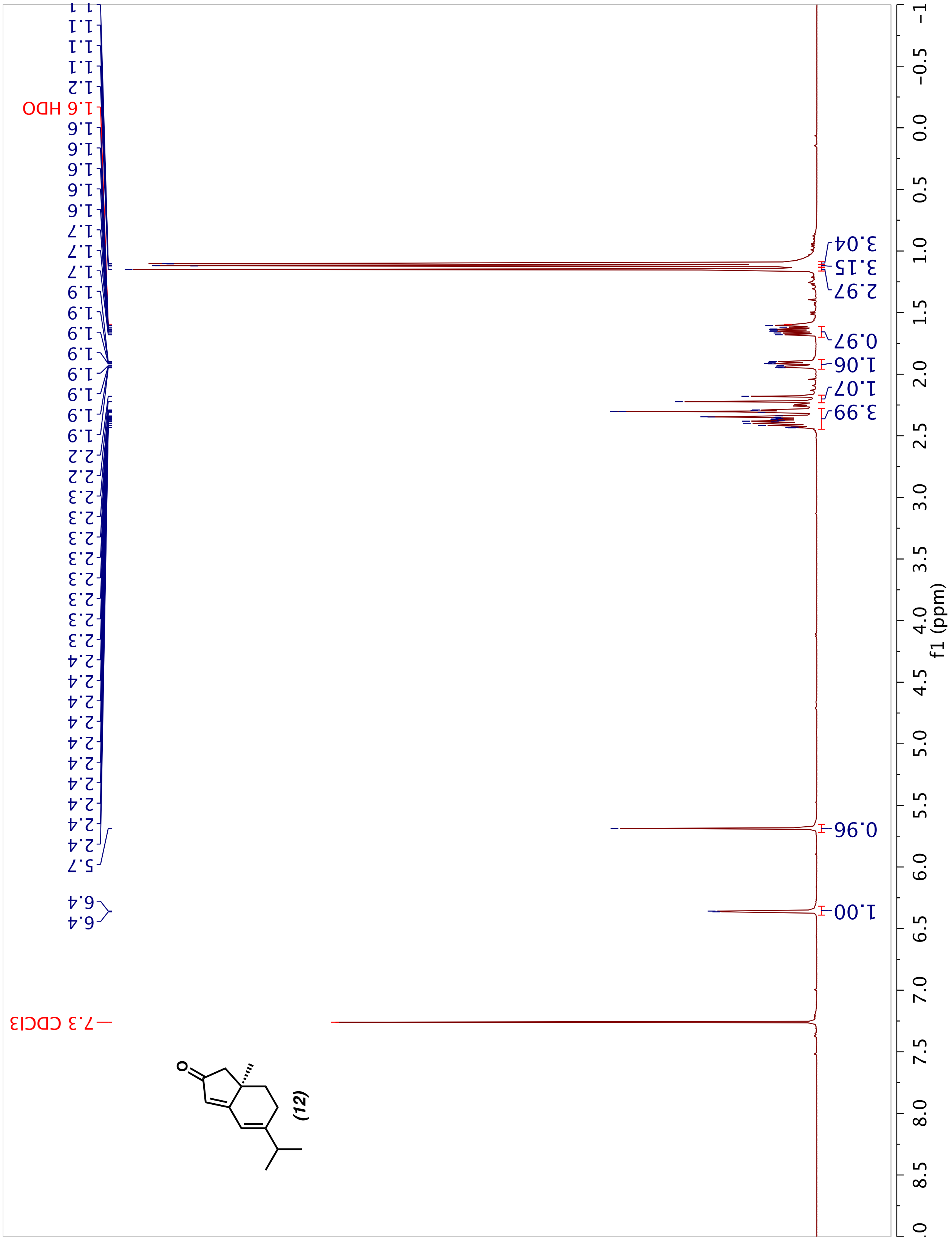
^{1}H NMR (400 MHz, CDCl$_3$) of compound **8**.



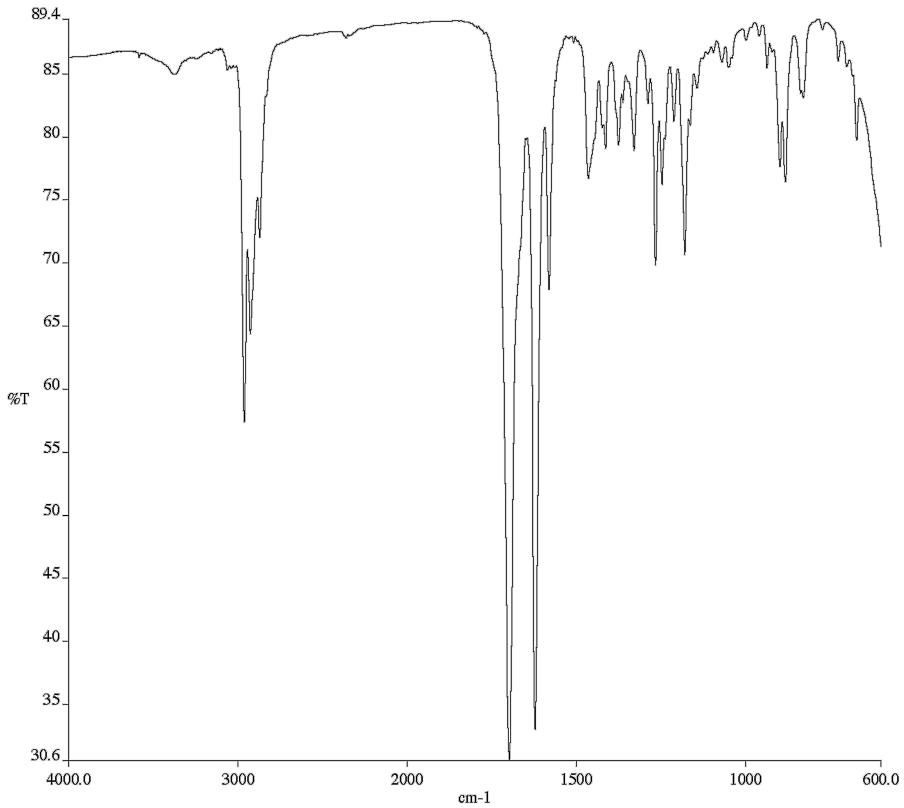
Infrared spectrum (Thin Film, NaCl) of compound



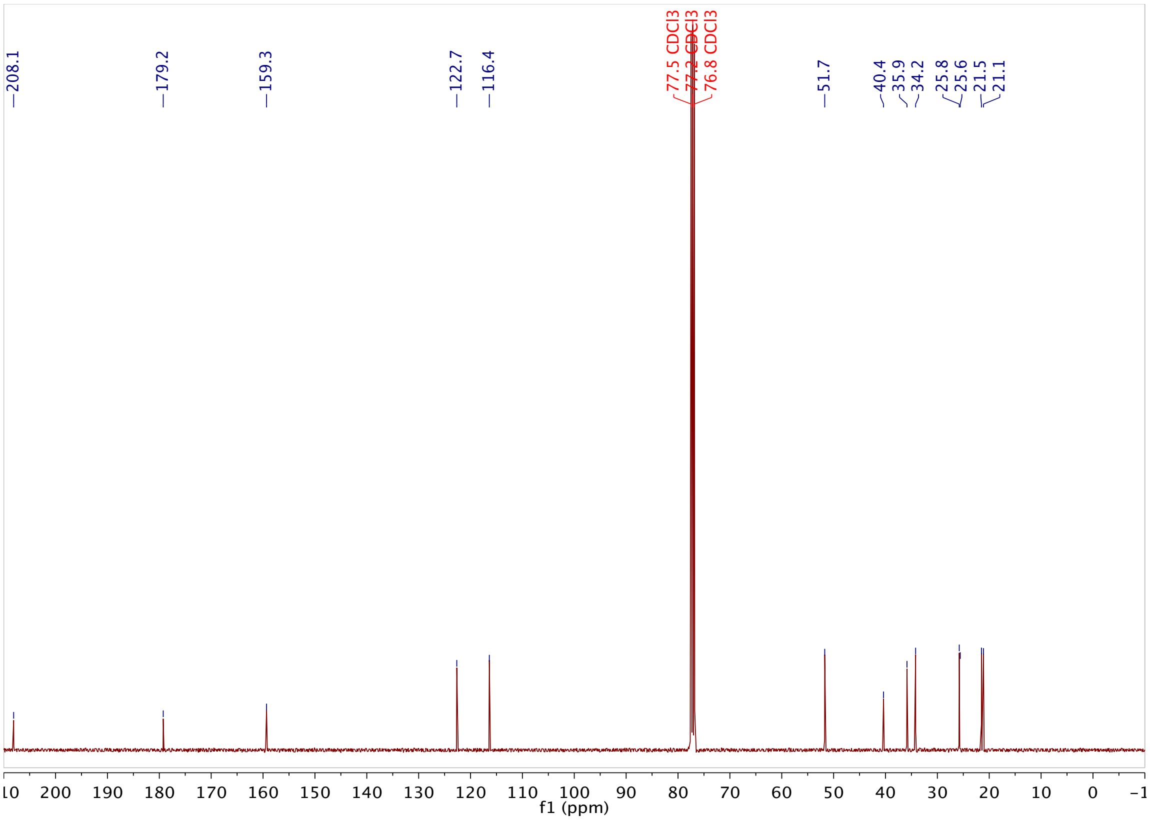
^{13}C NMR (101 MHz, CDCl$_3$) of compound **8**.



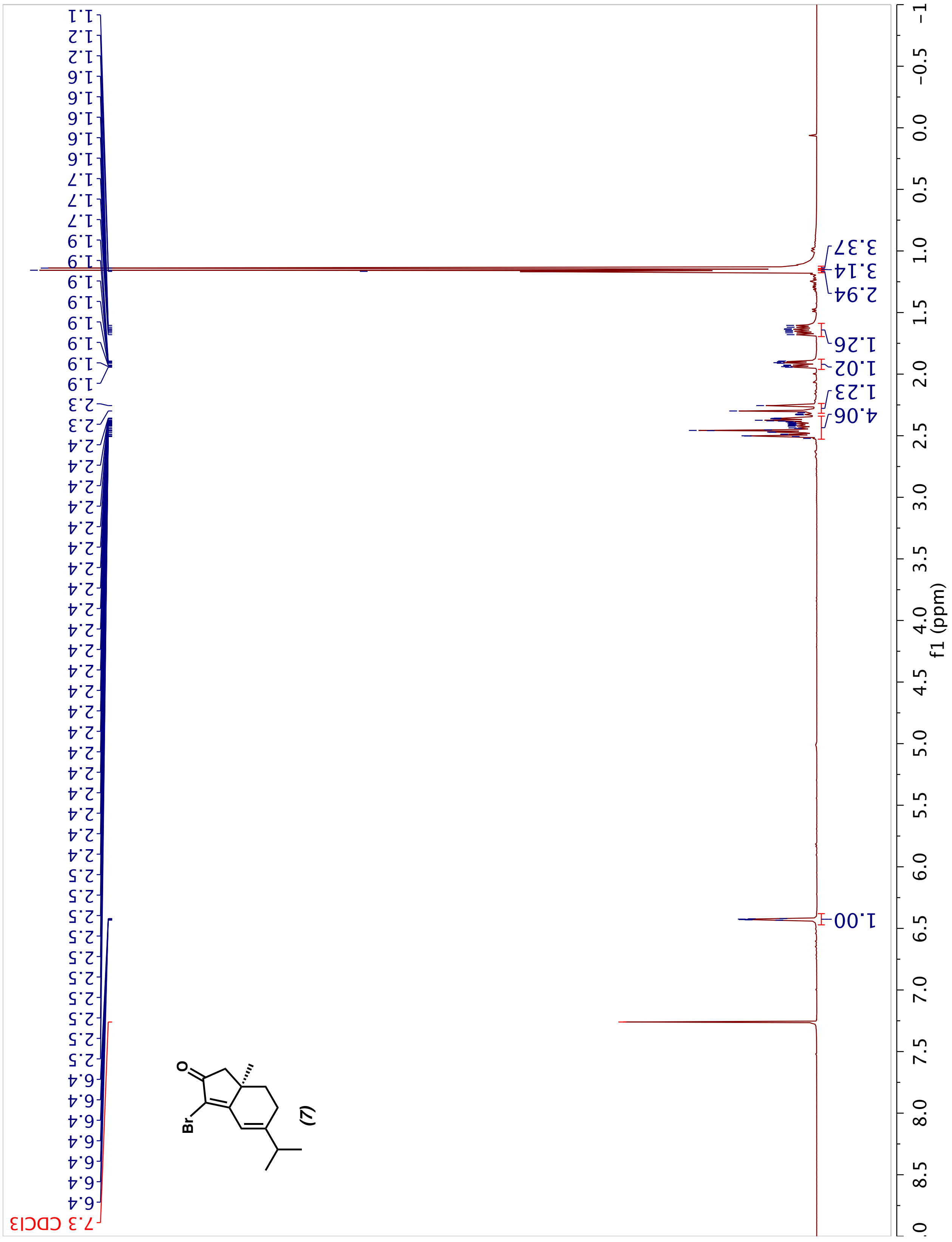
^{1}H NMR (400 MHz, CDCl$_3$) of compound **12**.



Infrared spectrum (Thin Film, NaCl) of compound

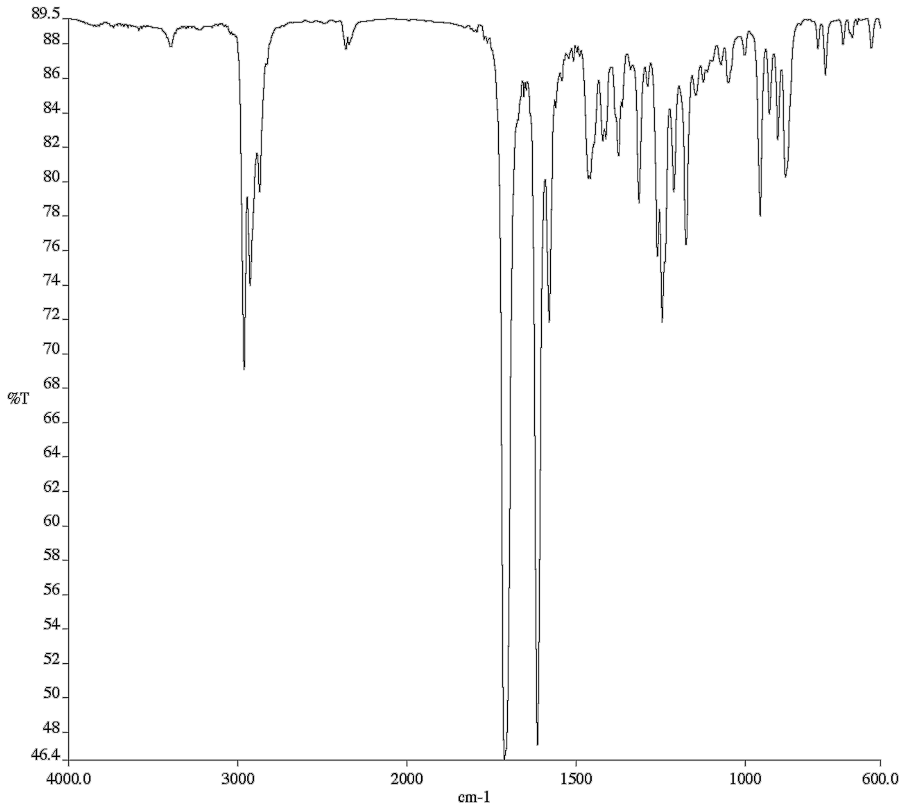


^{13}C NMR (101 MHz, CDCl$_3$) of compound **12**.

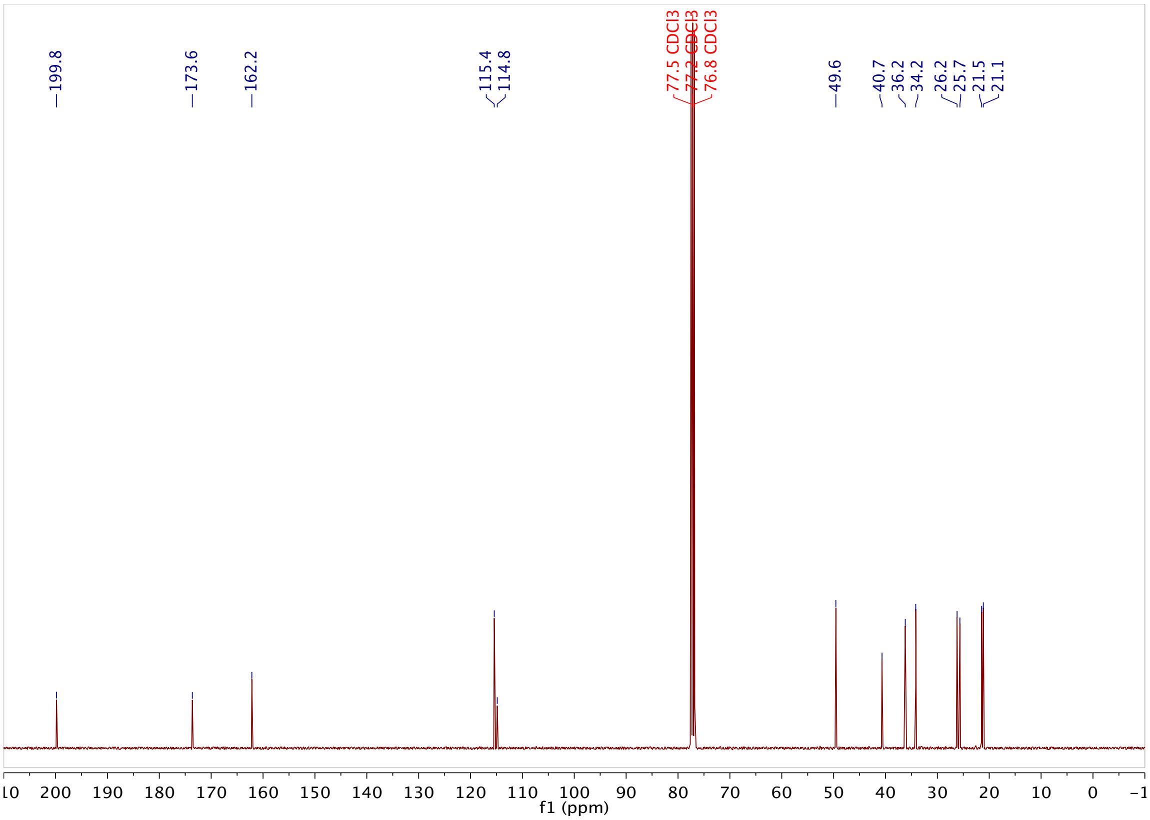


(7)

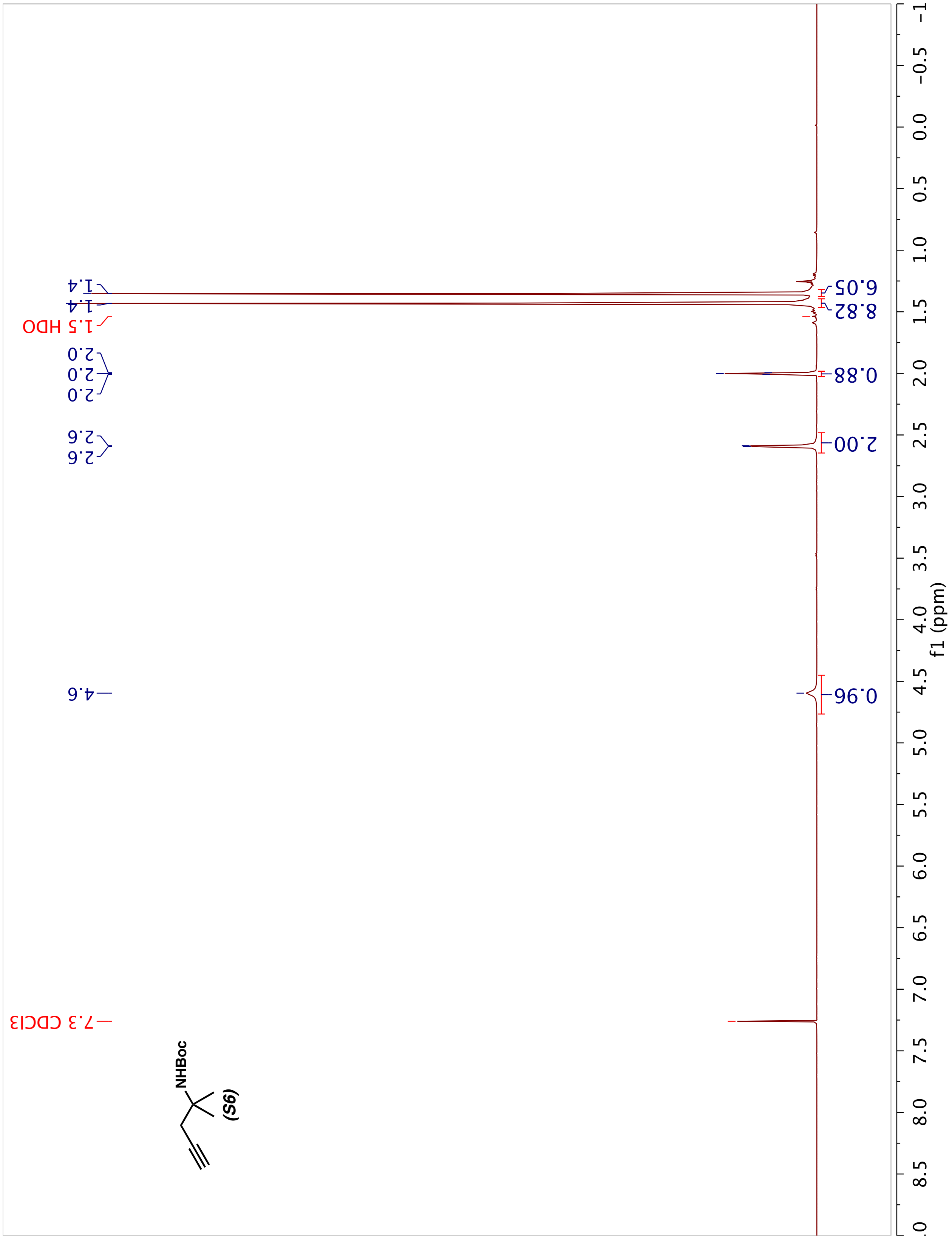
^{1}H NMR (400 MHz, CDCl$_3$) of compound **7**.



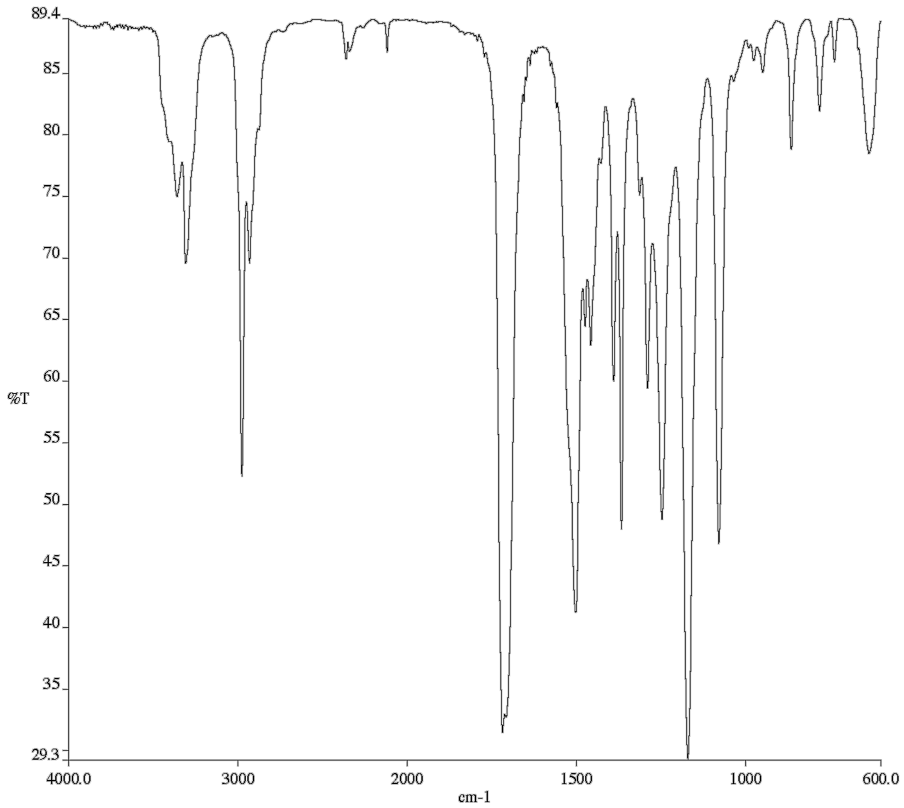
Infrared spectrum (Thin Film, NaCl) of compound



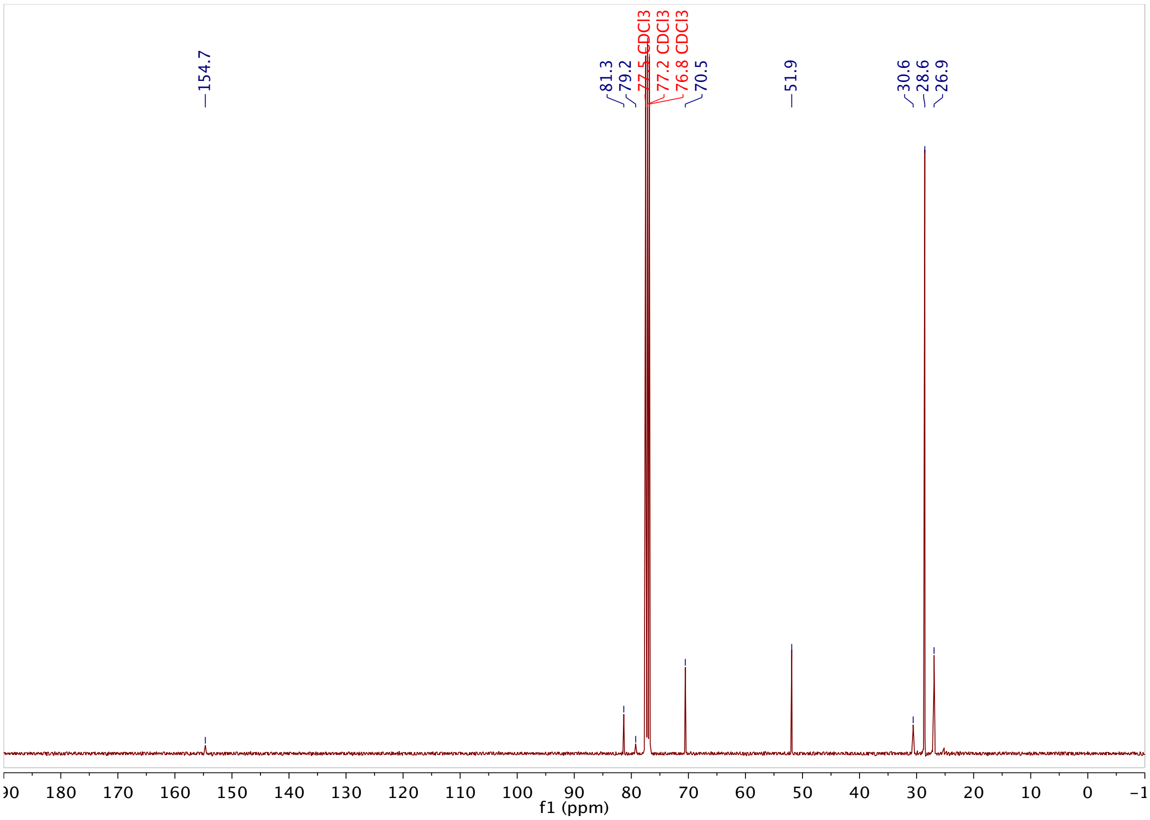
^{13}C NMR (101 MHz, $CDCl_3$) of compound **7**.



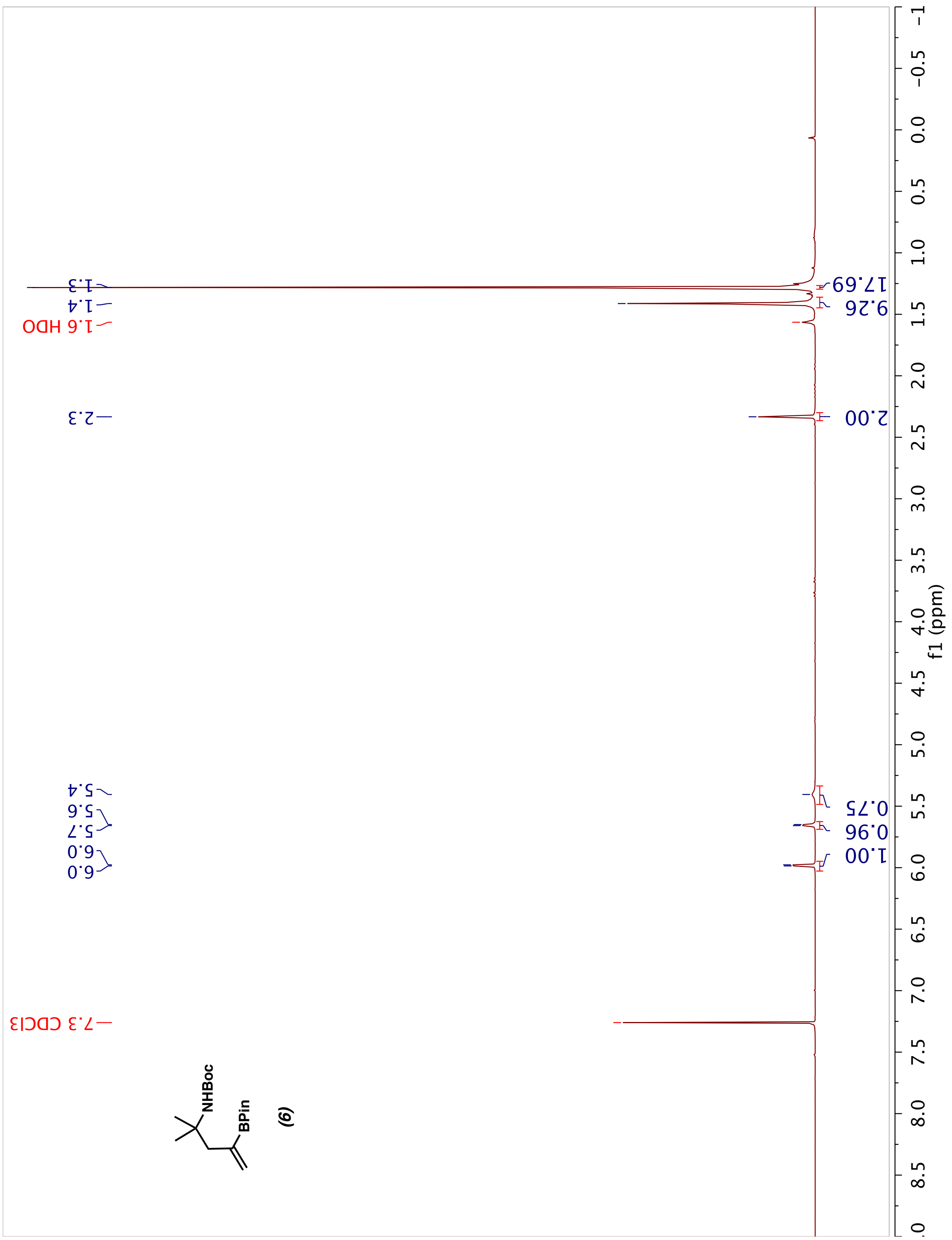
^{1}H NMR (400 MHz, CDCl$_3$) of compound **S6.**



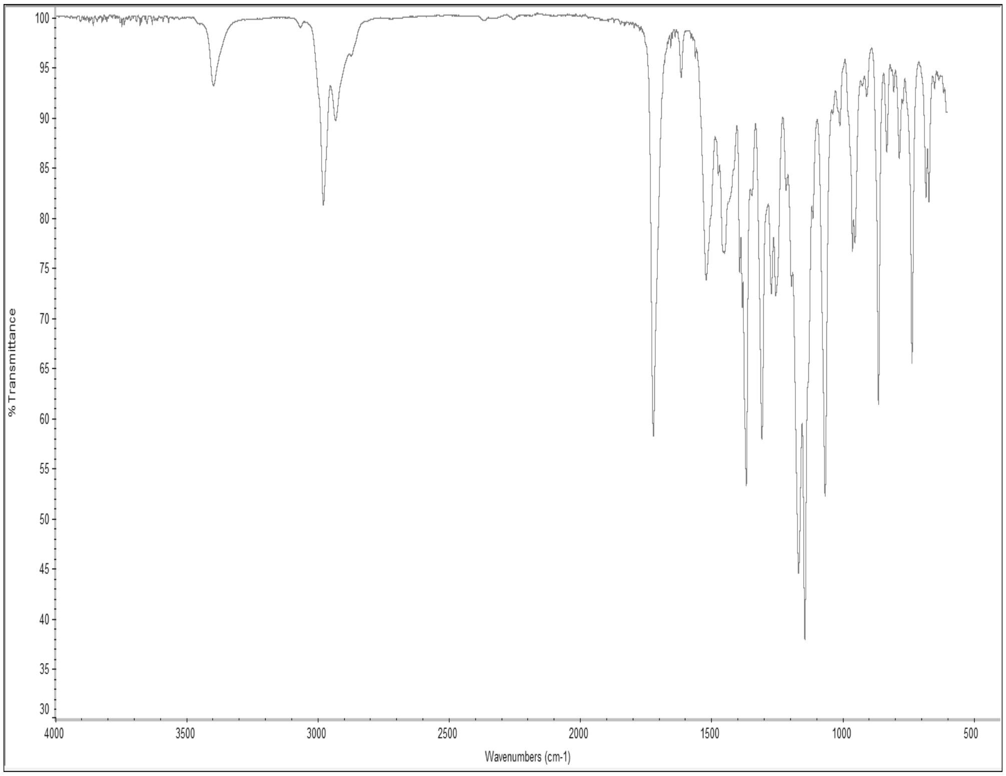
Infrared spectrum (Thin Film, NaCl) of compound



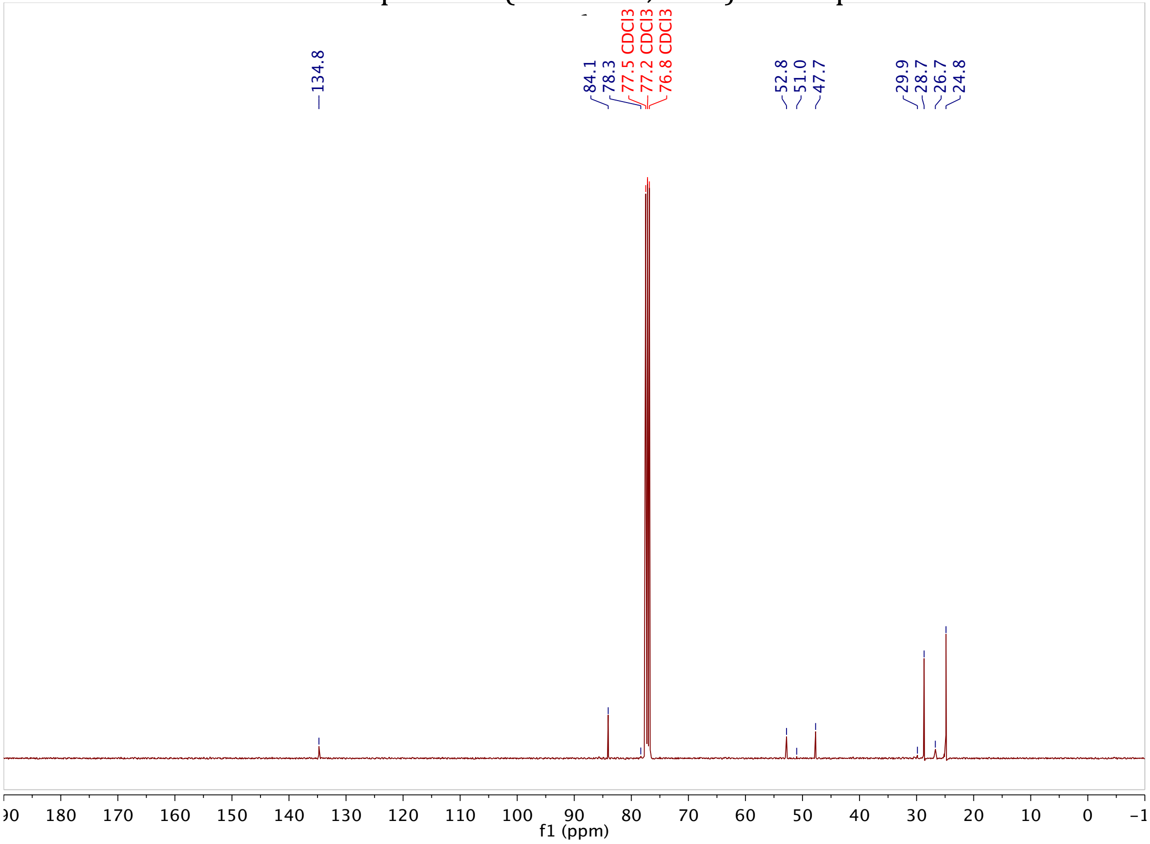
^{13}C NMR (101 MHz, $CDCl_3$) of compound **S6.**



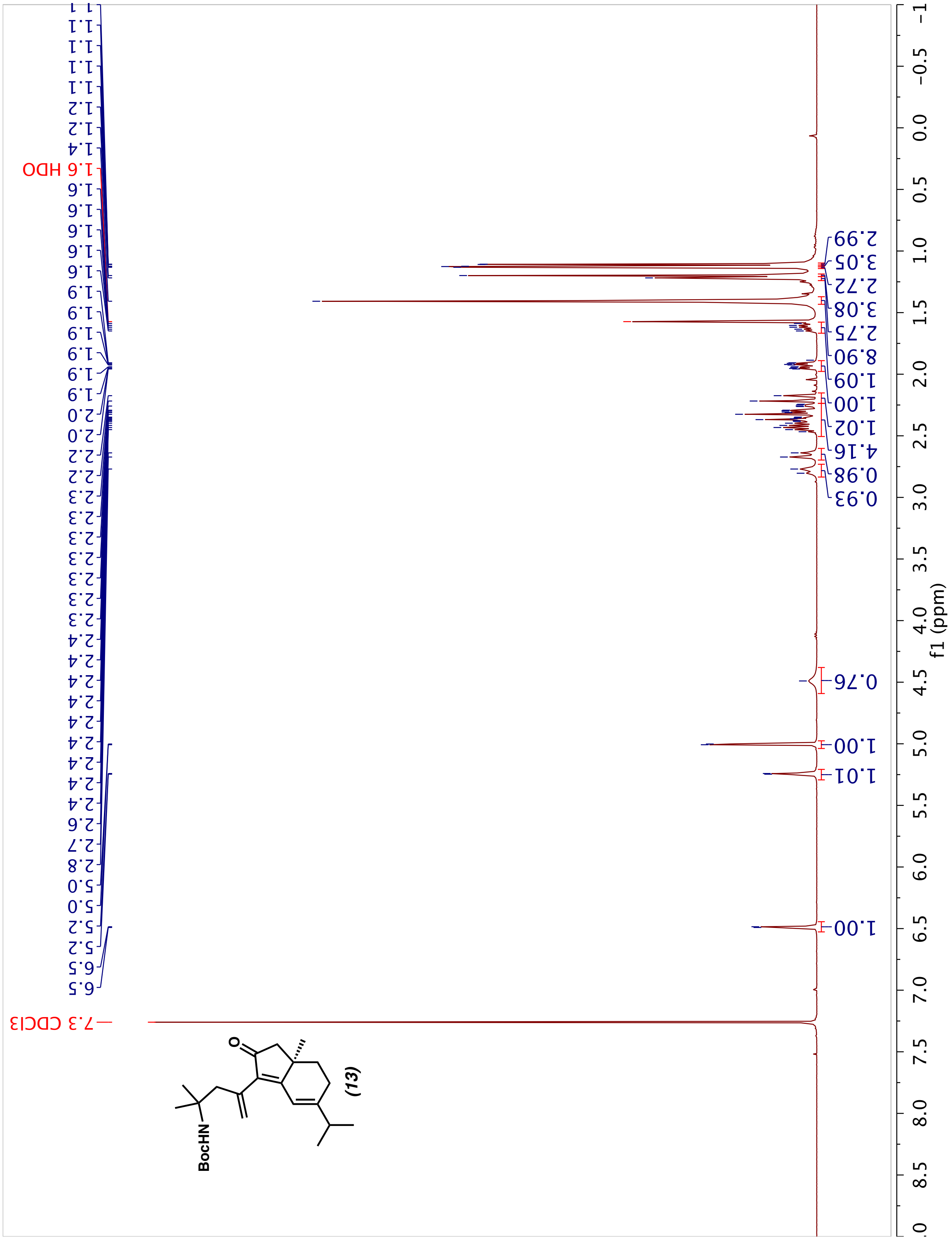
^{1}H NMR (400 MHz, CDCl$_3$) of compound **6.**



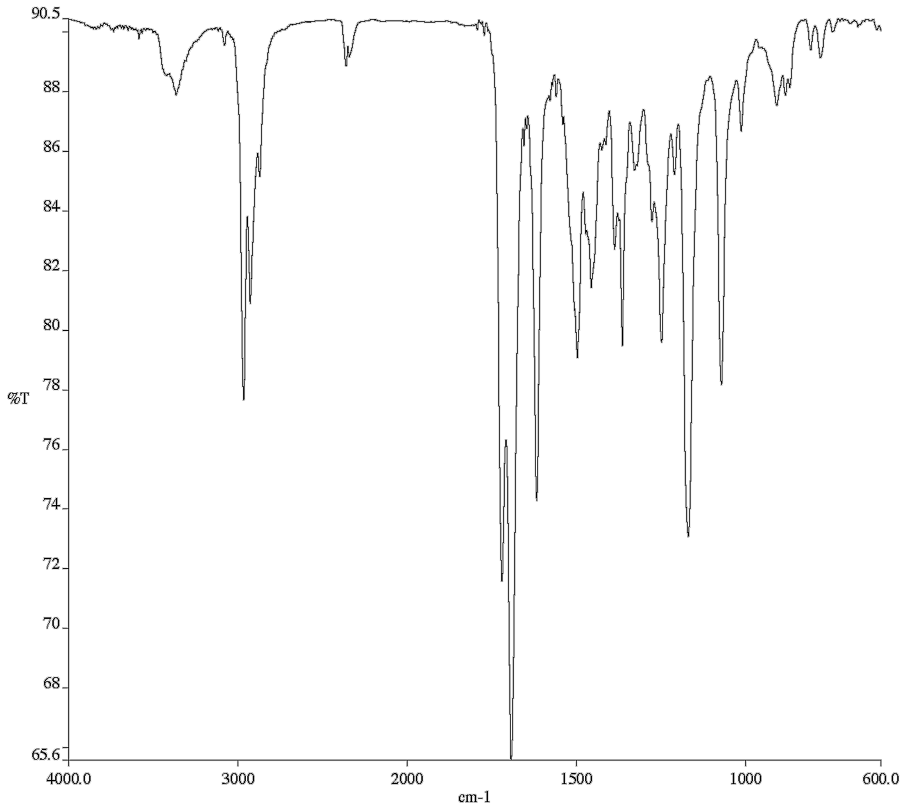
Infrared spectrum (Thin Film, NaCl) of compound



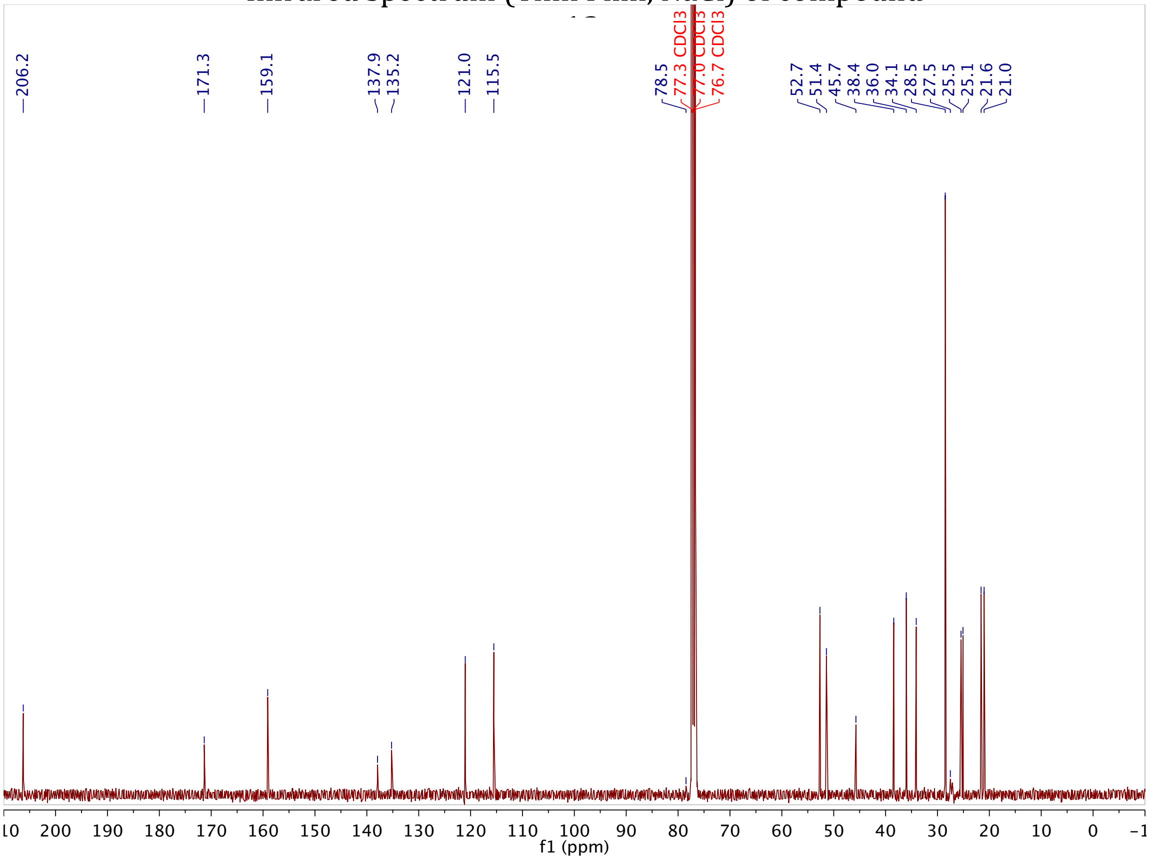
^{13}C NMR (101 MHz, CDCl$_3$) of compound **6.**



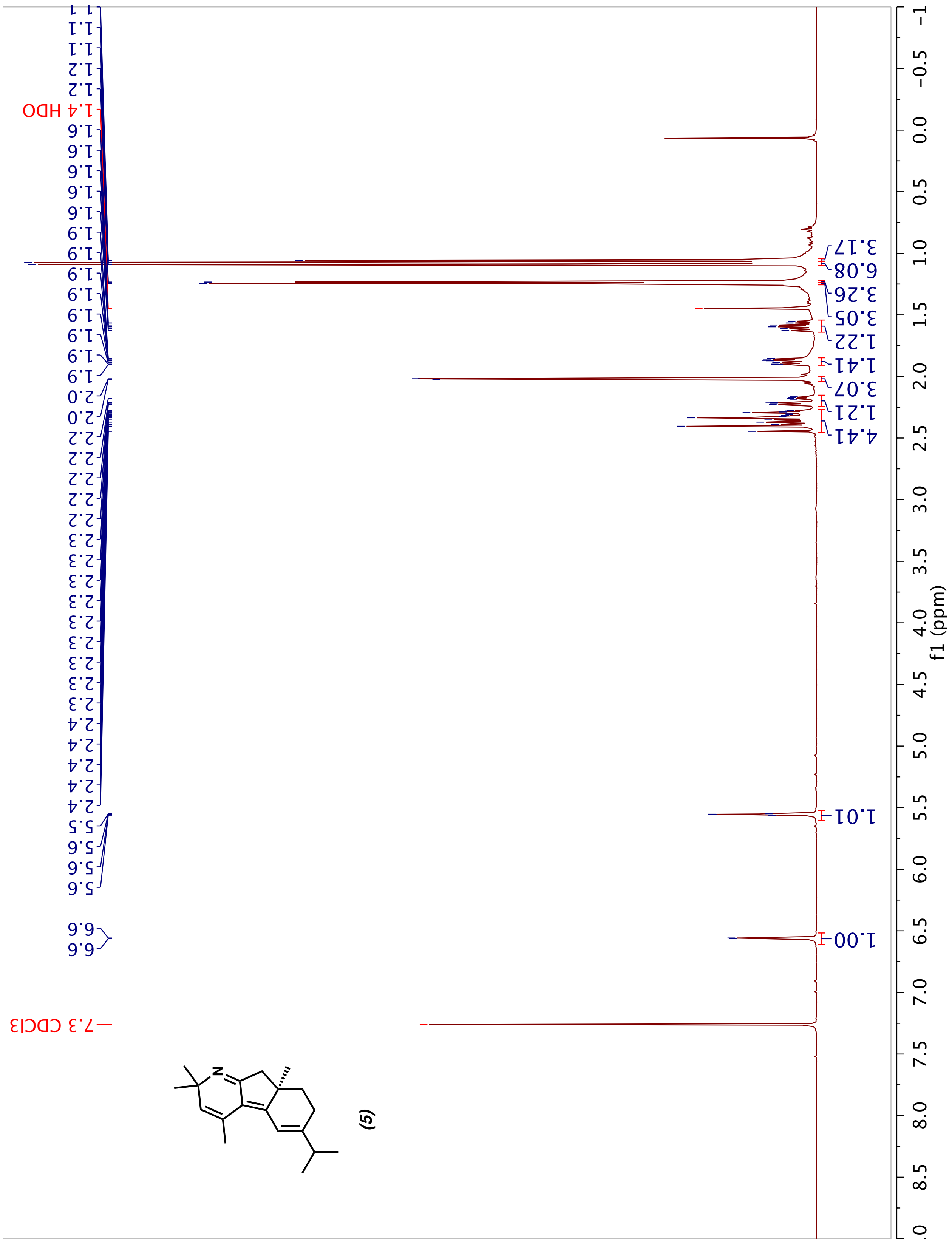
^{1}H NMR (400 MHz, CDCl$_3$) of compound **13**.



Infrared spectrum (Thin Film, NaCl) of compound

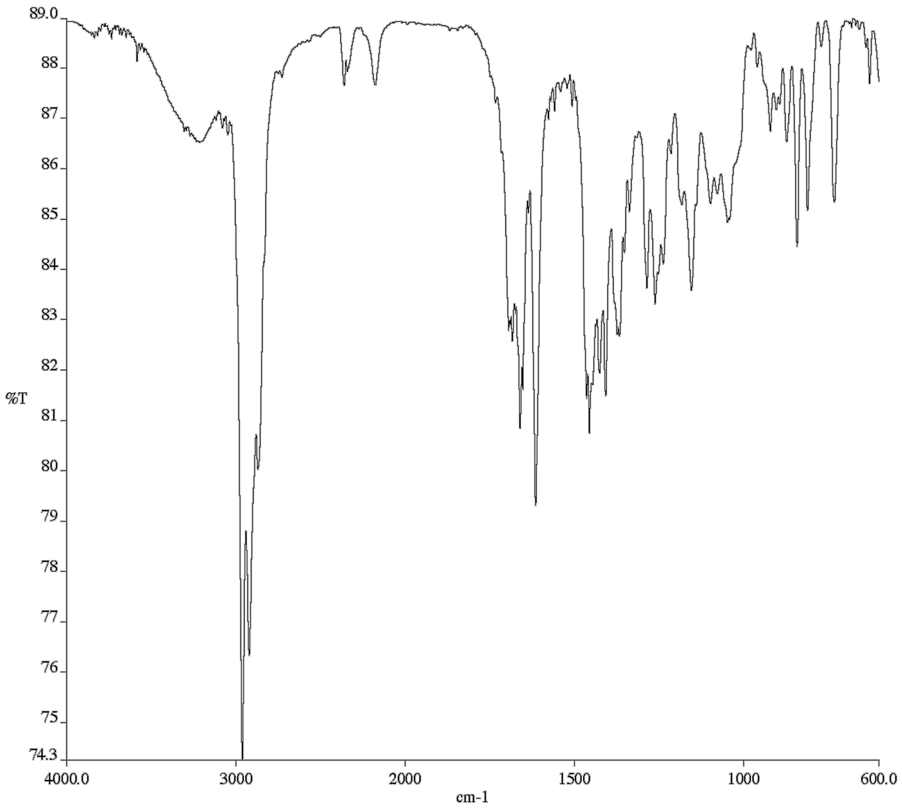


^{13}C NMR (101 MHz, CDCl$_3$) of compound **13.**

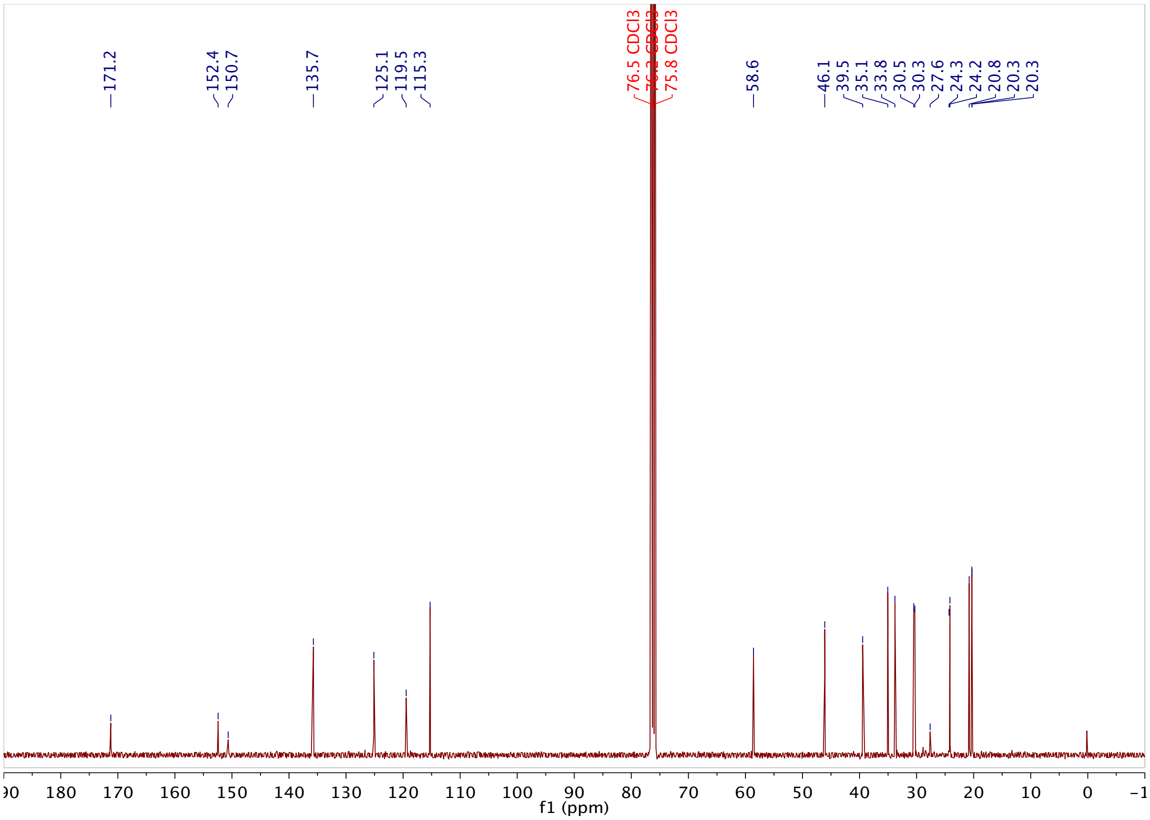


(5)

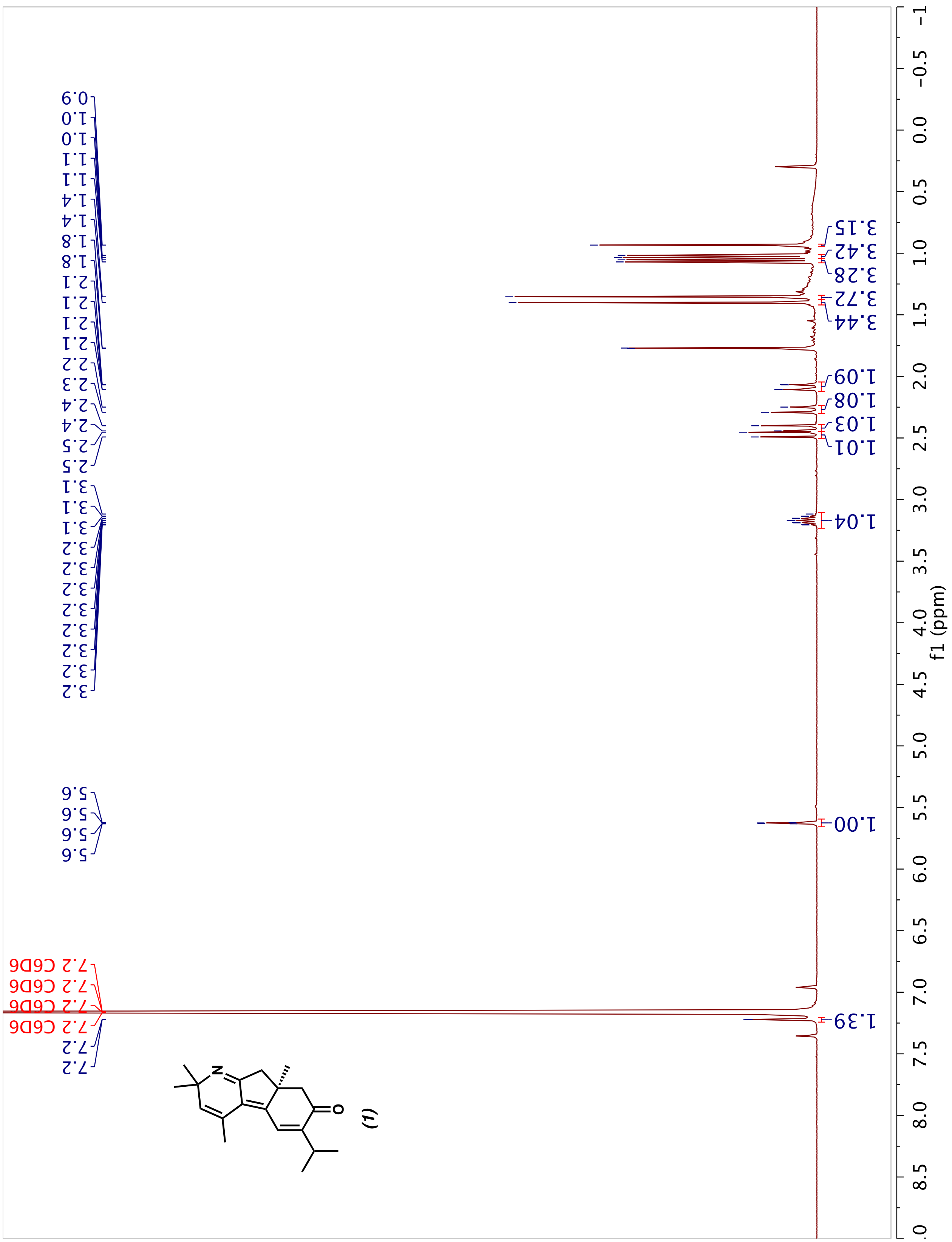
^{1}H NMR (400 MHz, CDCl$_3$) of compound **5.**



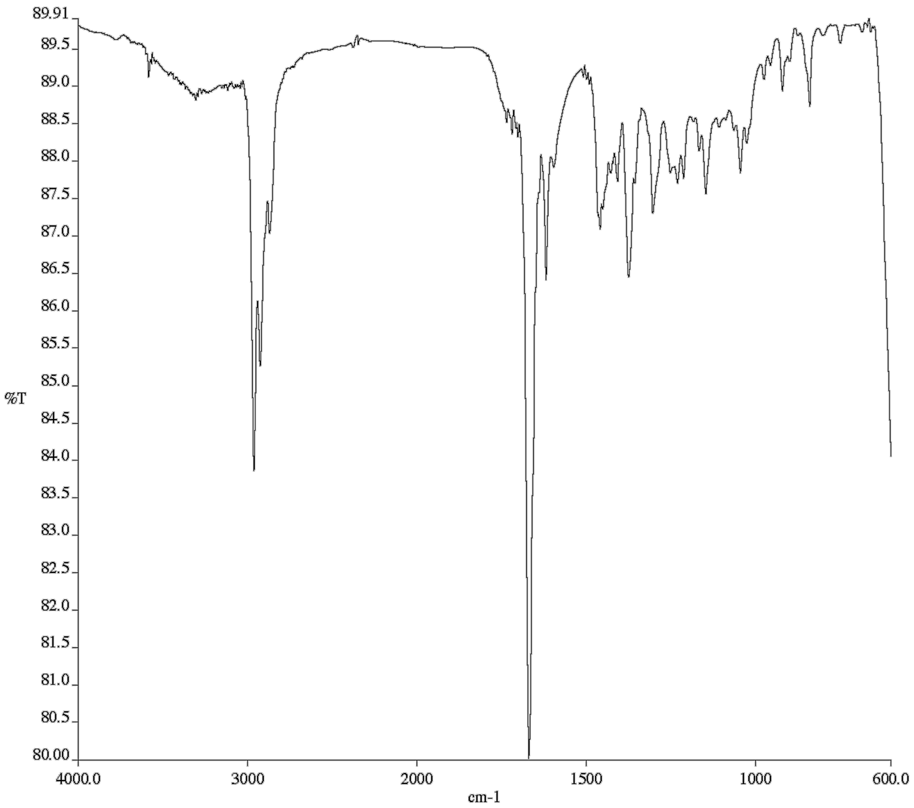
Infrared spectrum (Thin Film, NaCl) of compound



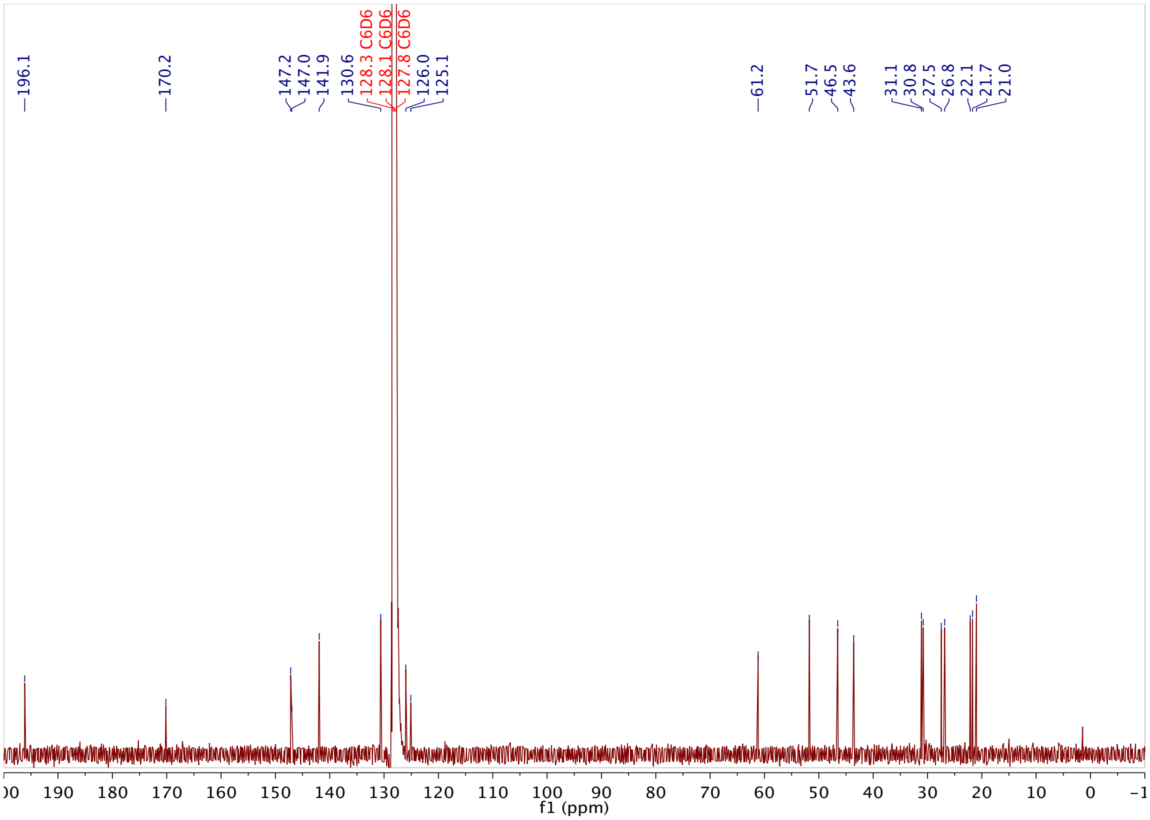
^{13}C NMR (101 MHz, $CDCl_3$) of compound **5**.



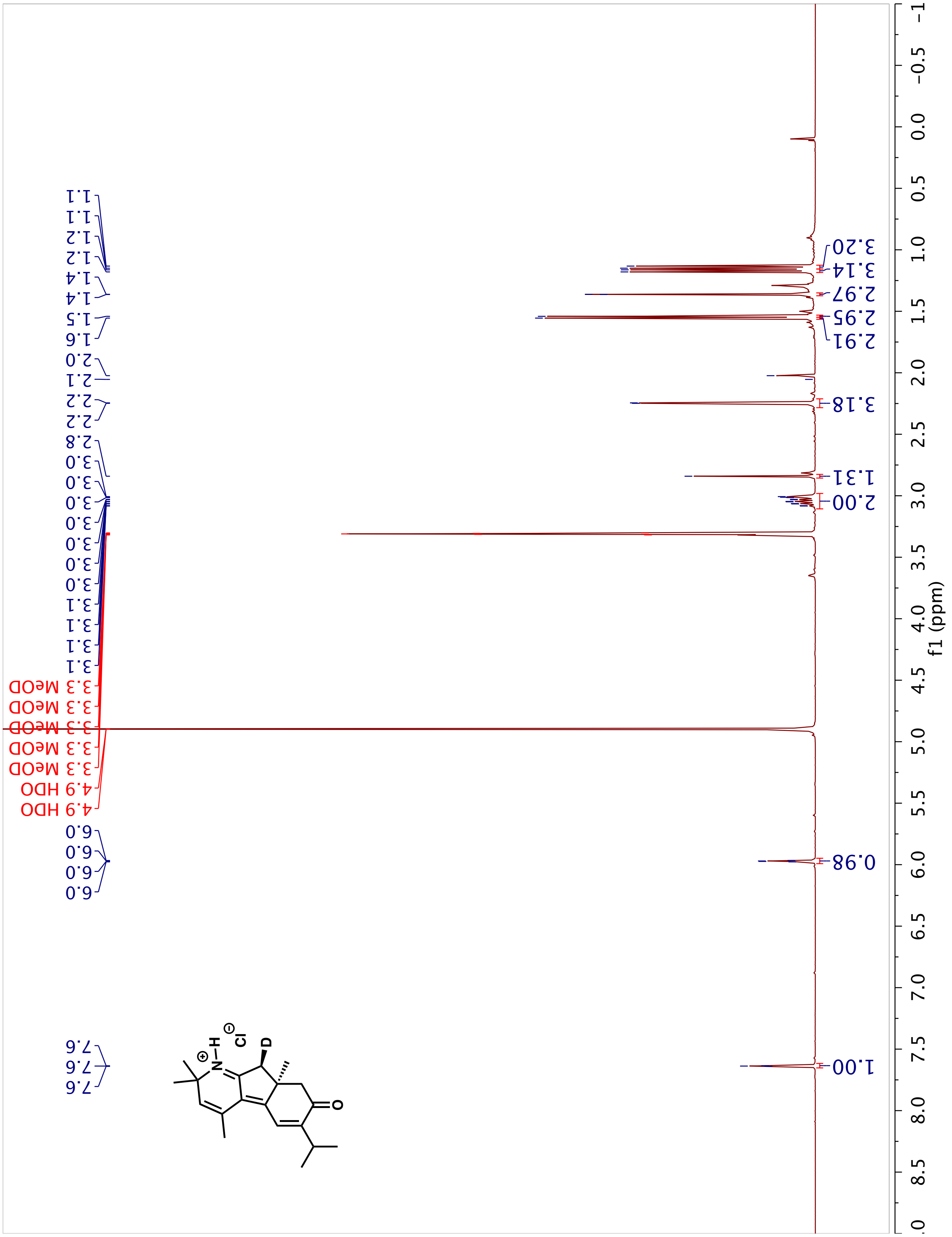
^{1}H NMR (400 MHz, C_6D_6) of compound **1**.



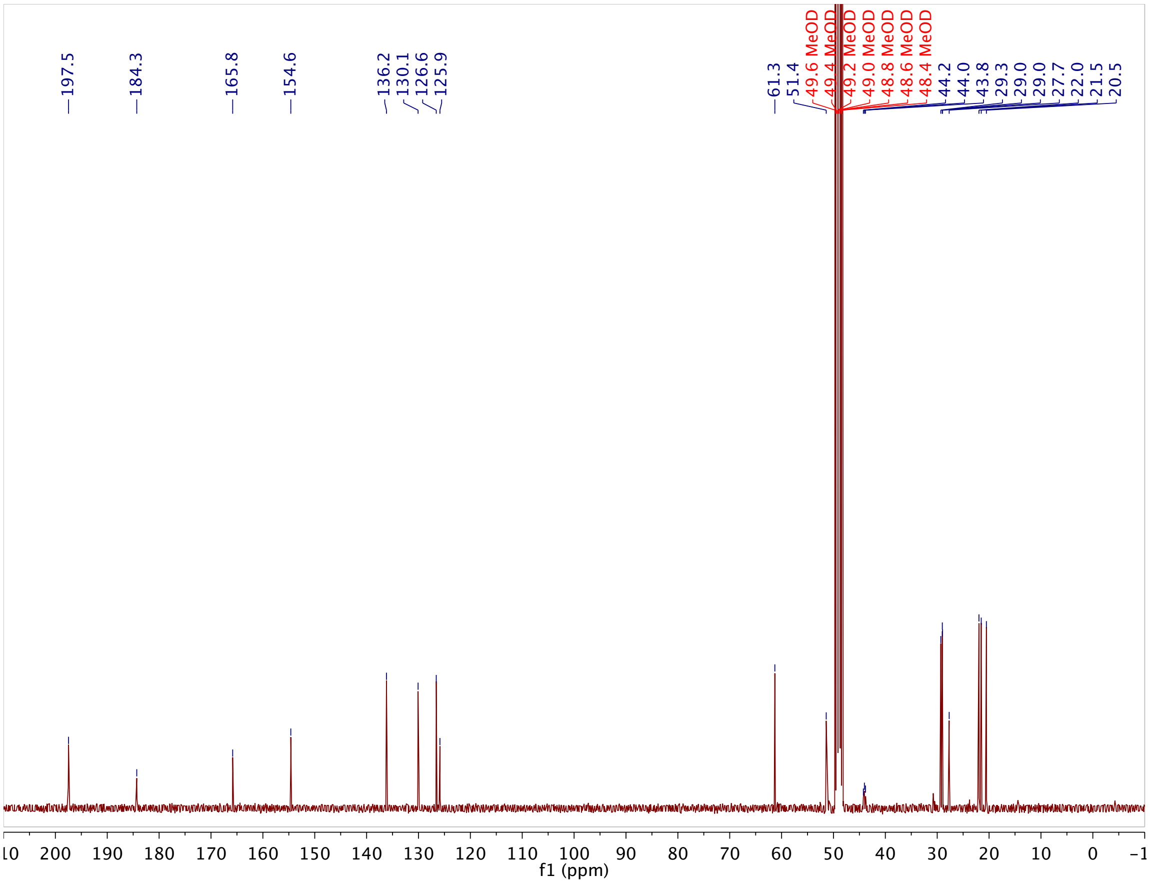
Infrared spectrum (Thin Film, NaCl) of compound



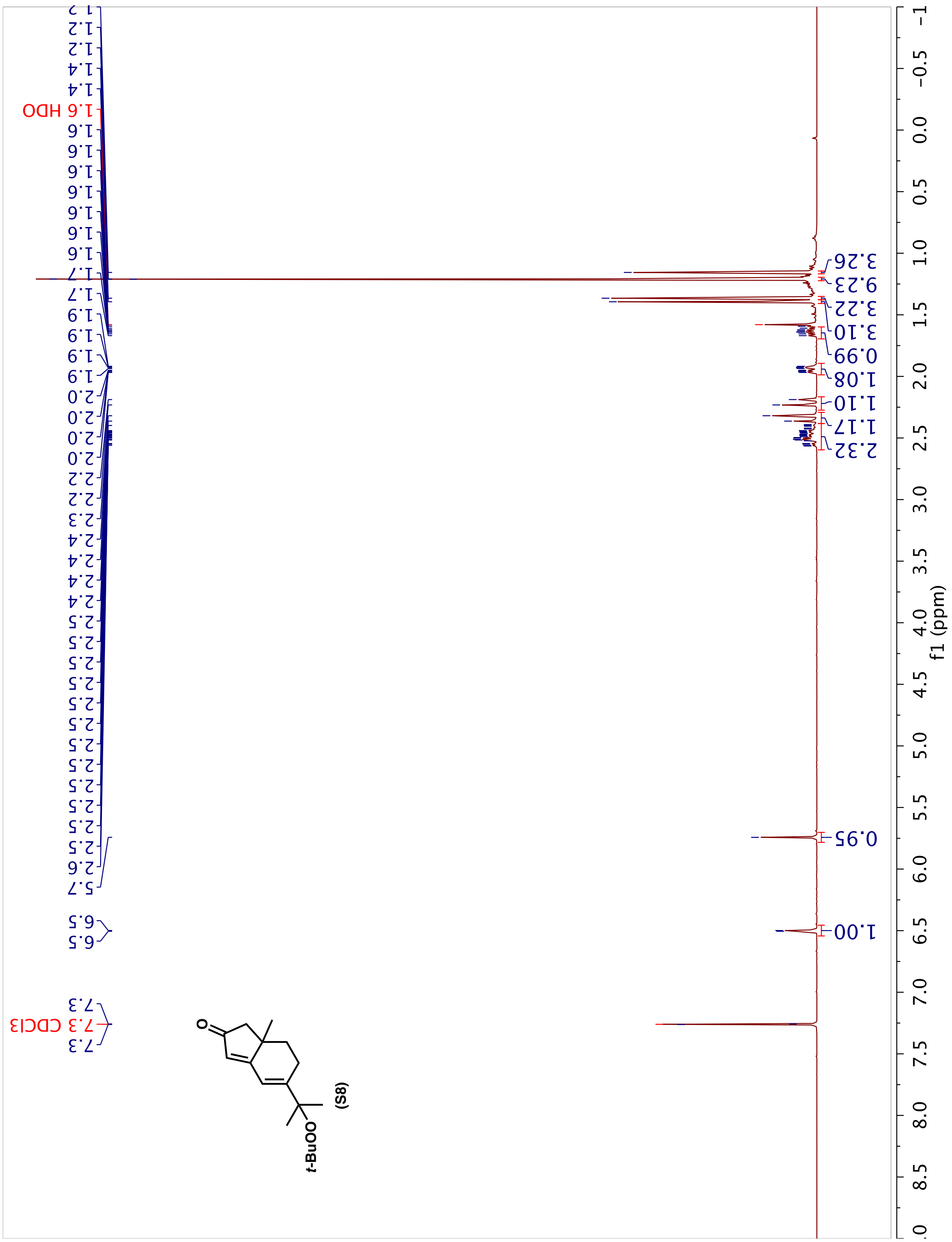
^{13}C NMR (101 MHz, C_6D_6) of compound **1**.



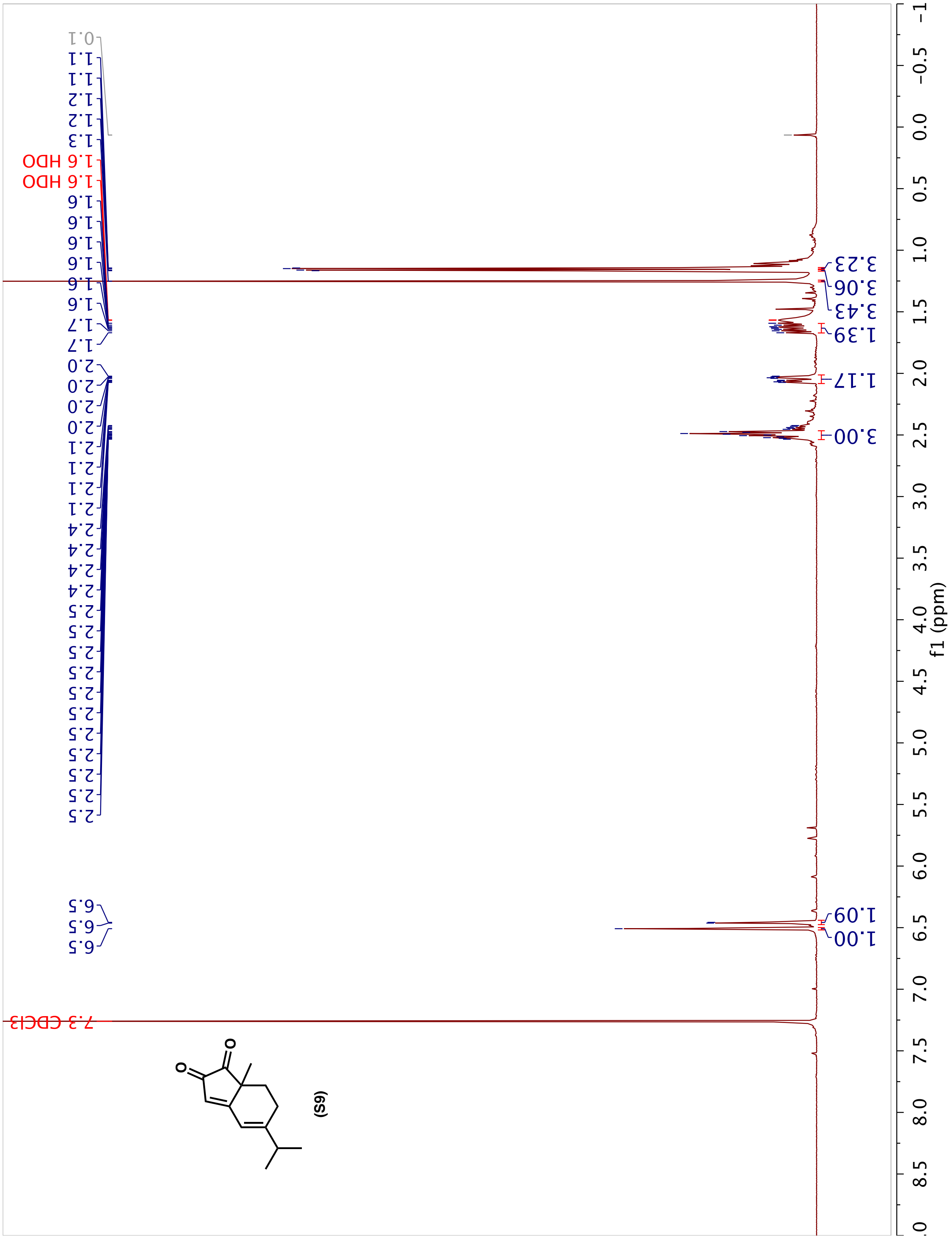
^{1}H NMR (400 MHz, CD$_3$OD) of nigelladine A.



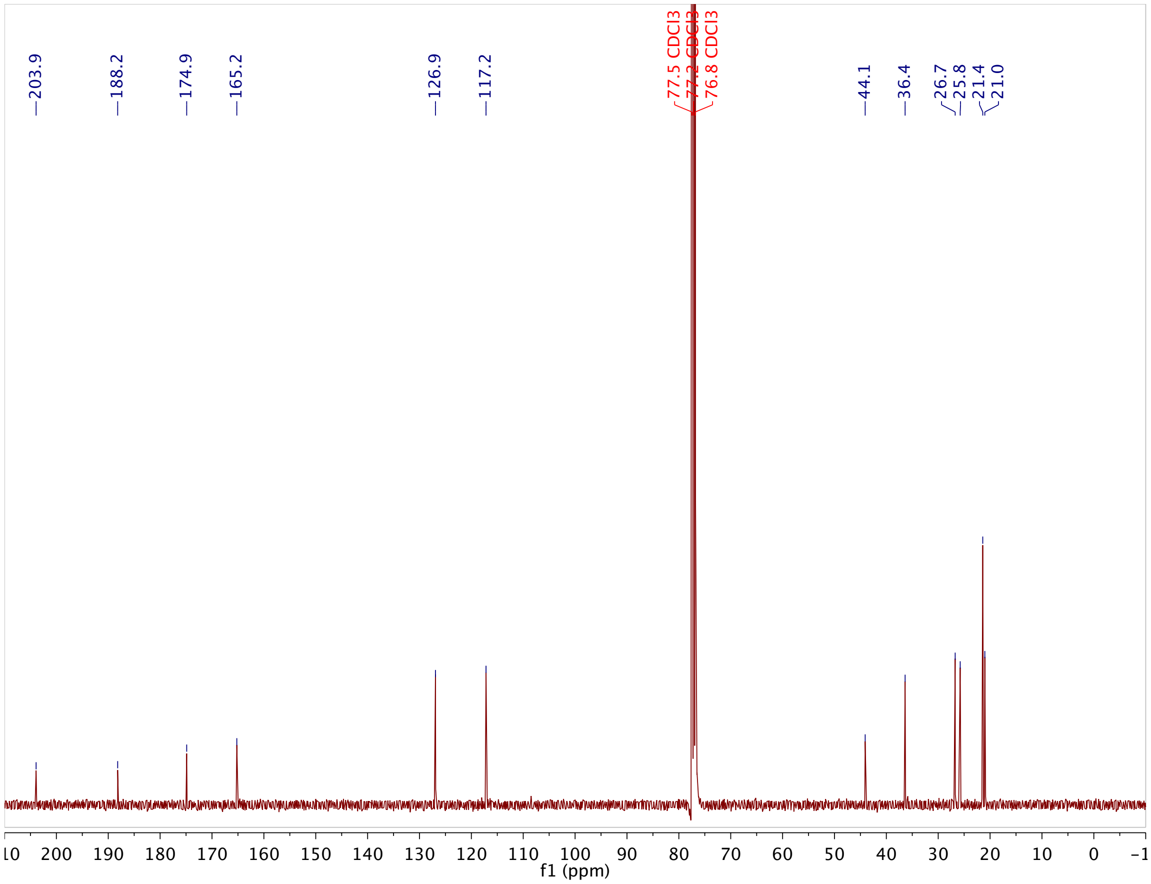
^{13}C NMR (101 MHz, CD_3OD) of nigelladine A.



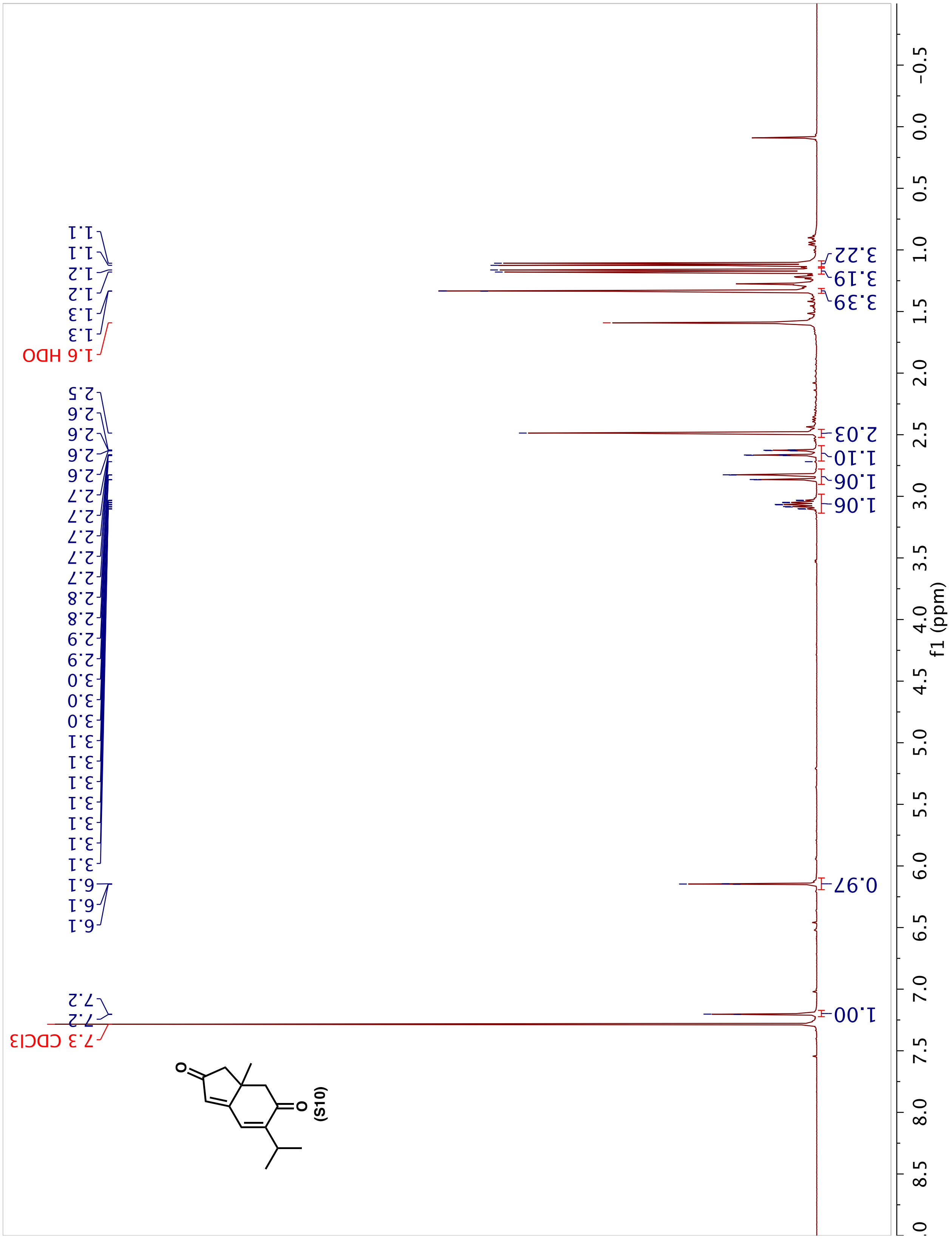
^{1}H NMR (400 MHz, CDCl$_3$) of **S8.**



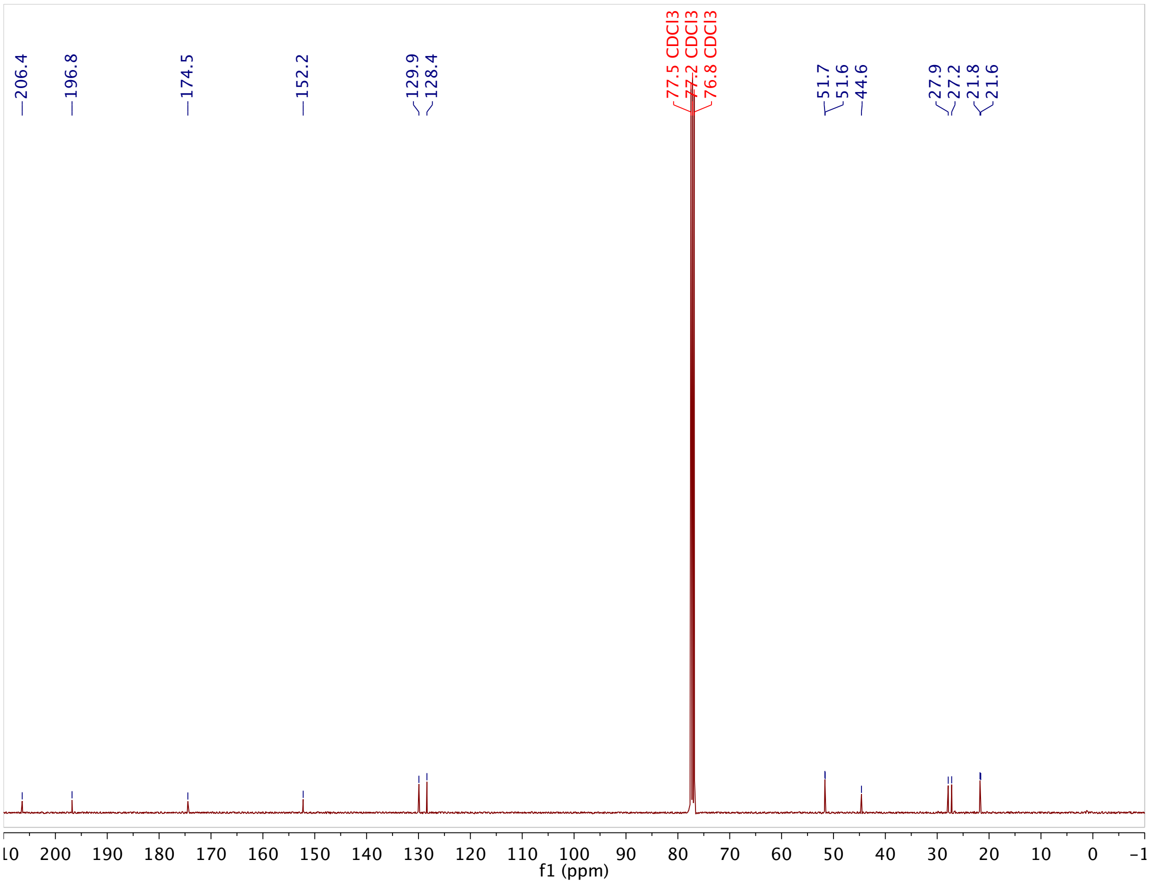
^{1}H NMR (400 MHz, $CDCl_3$) of **S9**.



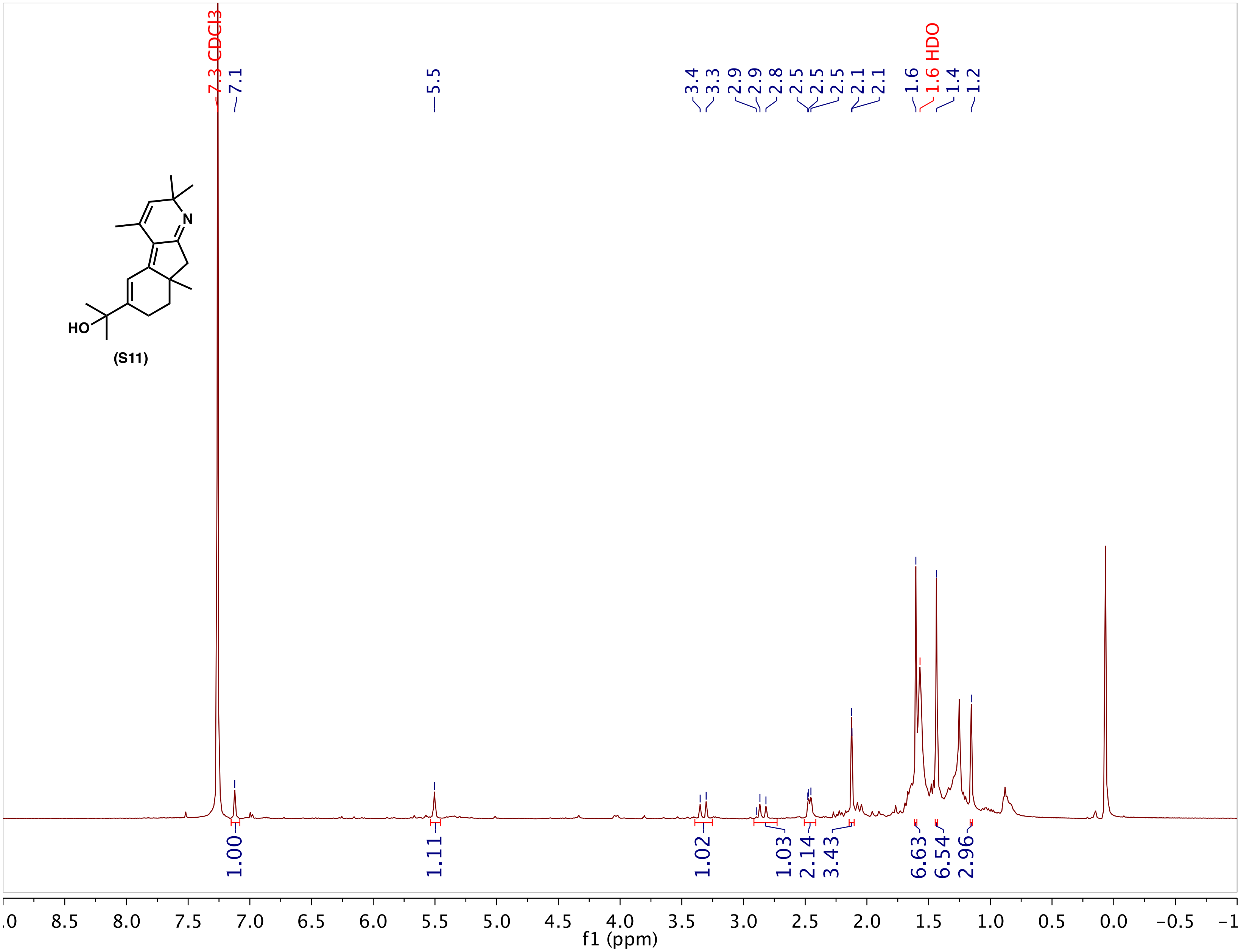
^{13}C NMR (101 MHz, $CDCl_3$) of **S9**.



^{1}H NMR (400 MHz, CDCl$_3$) of **S10**.

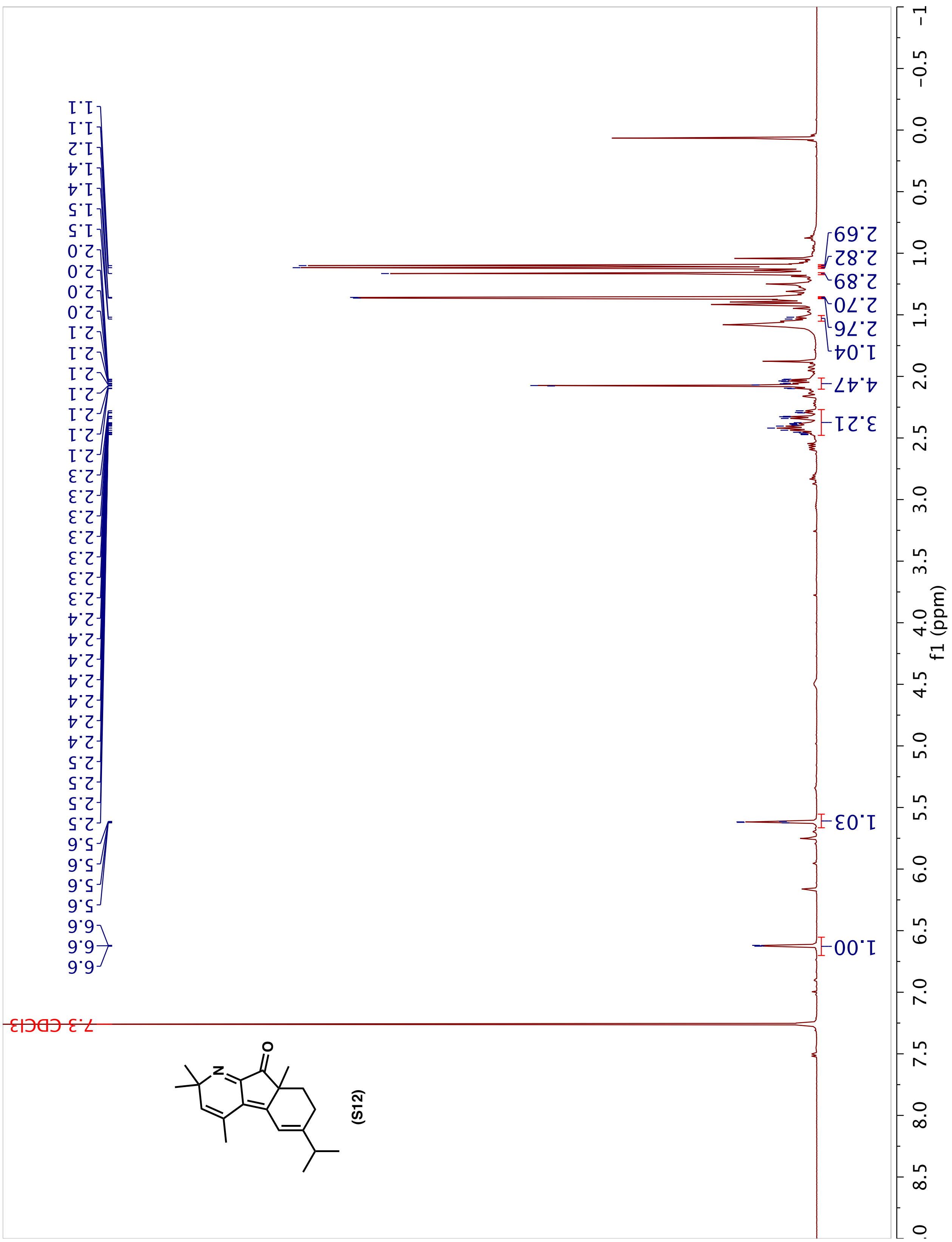


^{13}C NMR (101 MHz, CDCl$_3$) of **S10**.

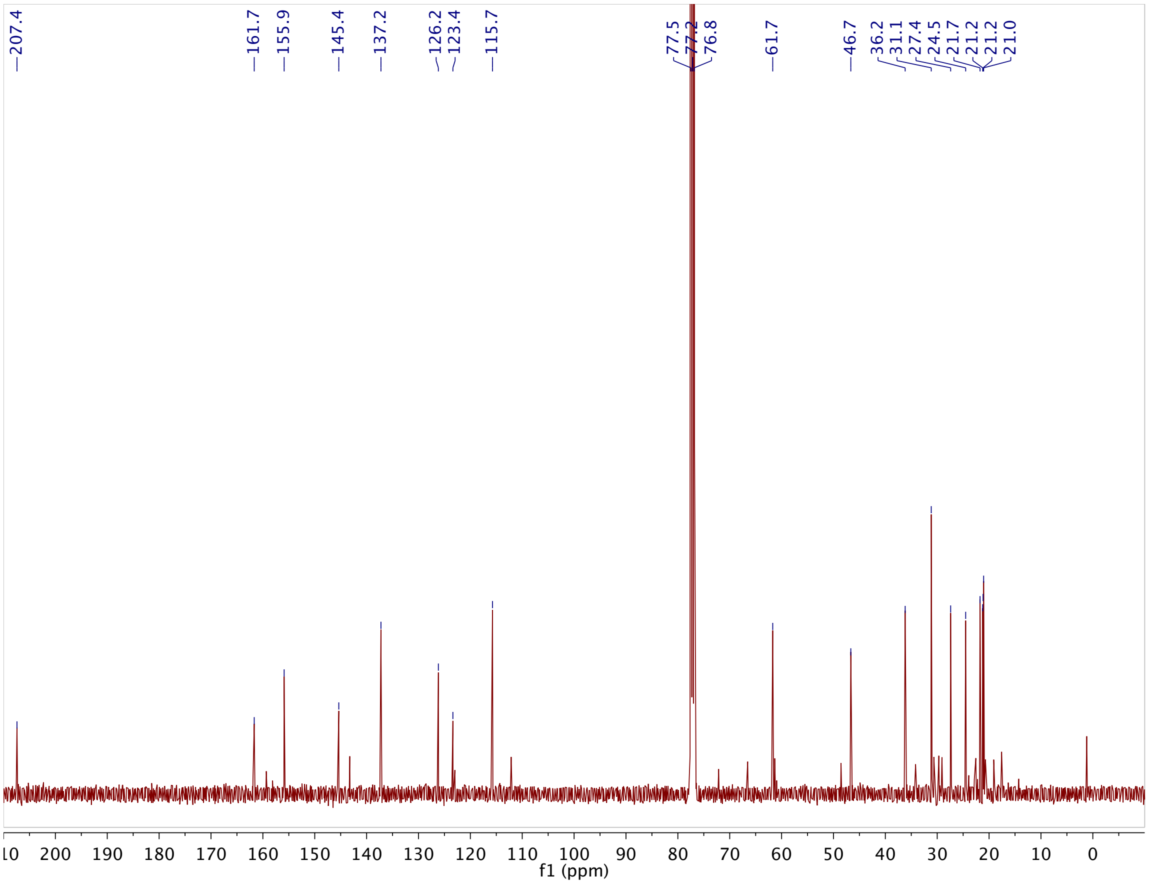


(S11)

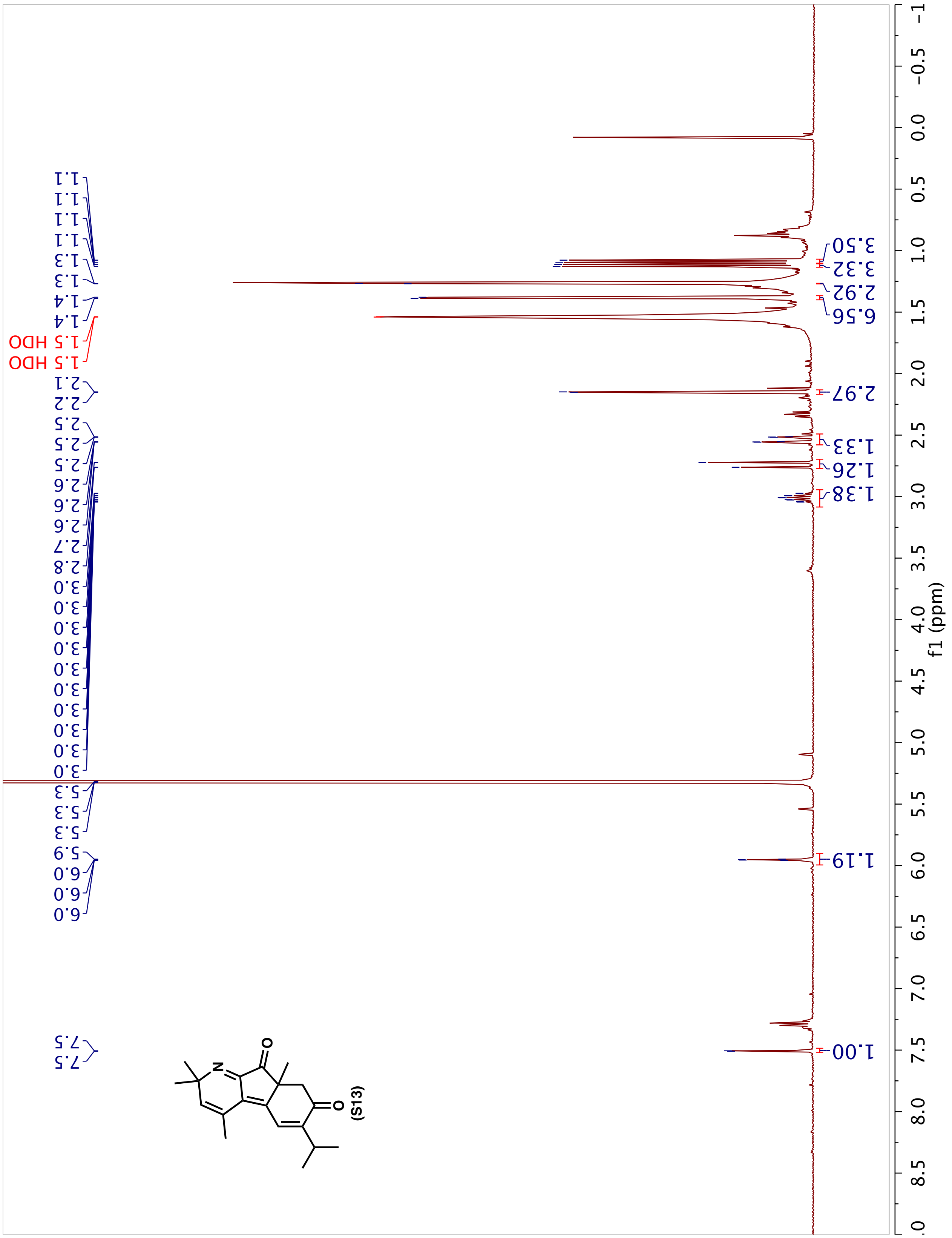
^{1}H NMR (400 MHz, CDCl$_3$) of **S11**.



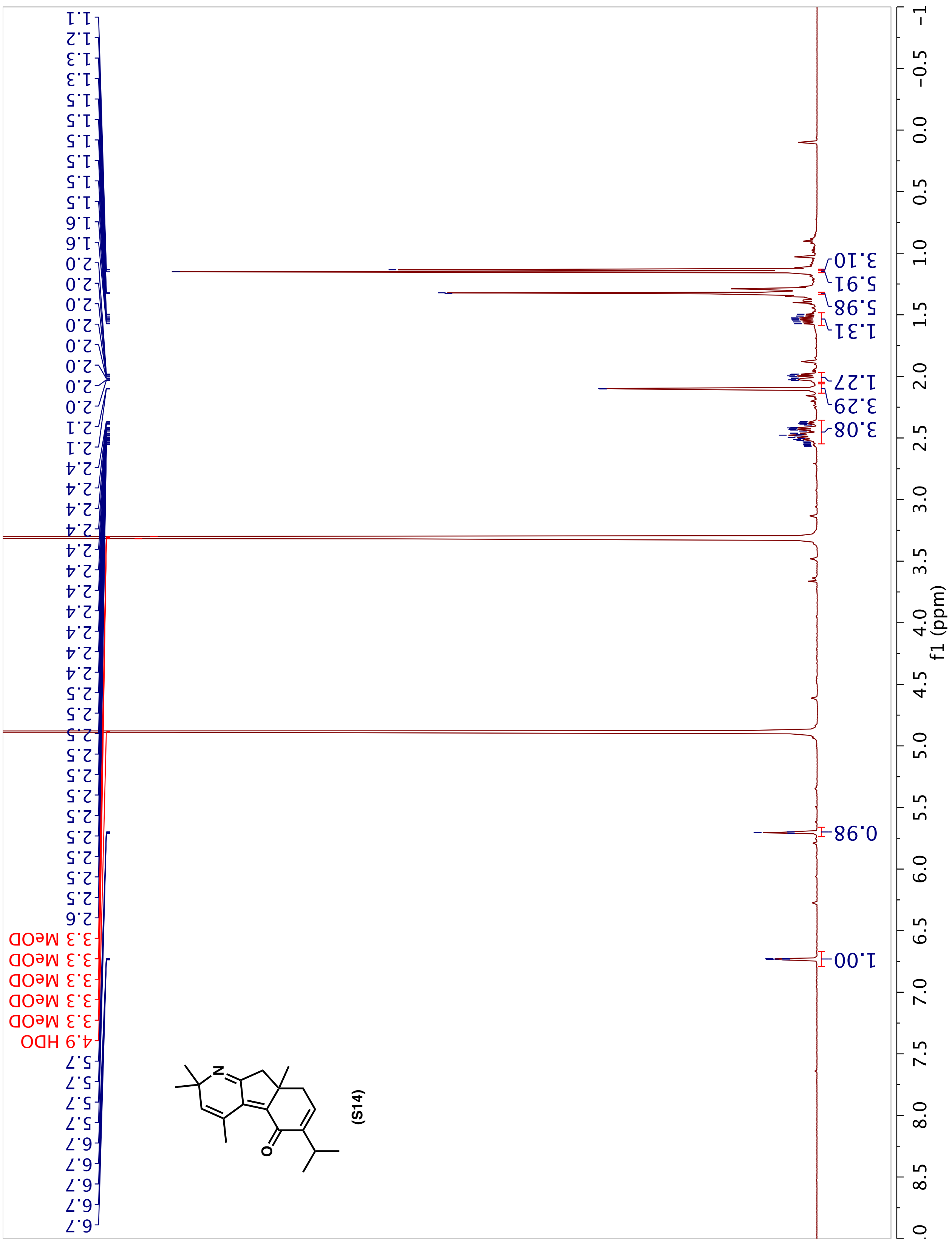
^{1}H NMR (400 MHz, $CDCl_3$) of **S12**.



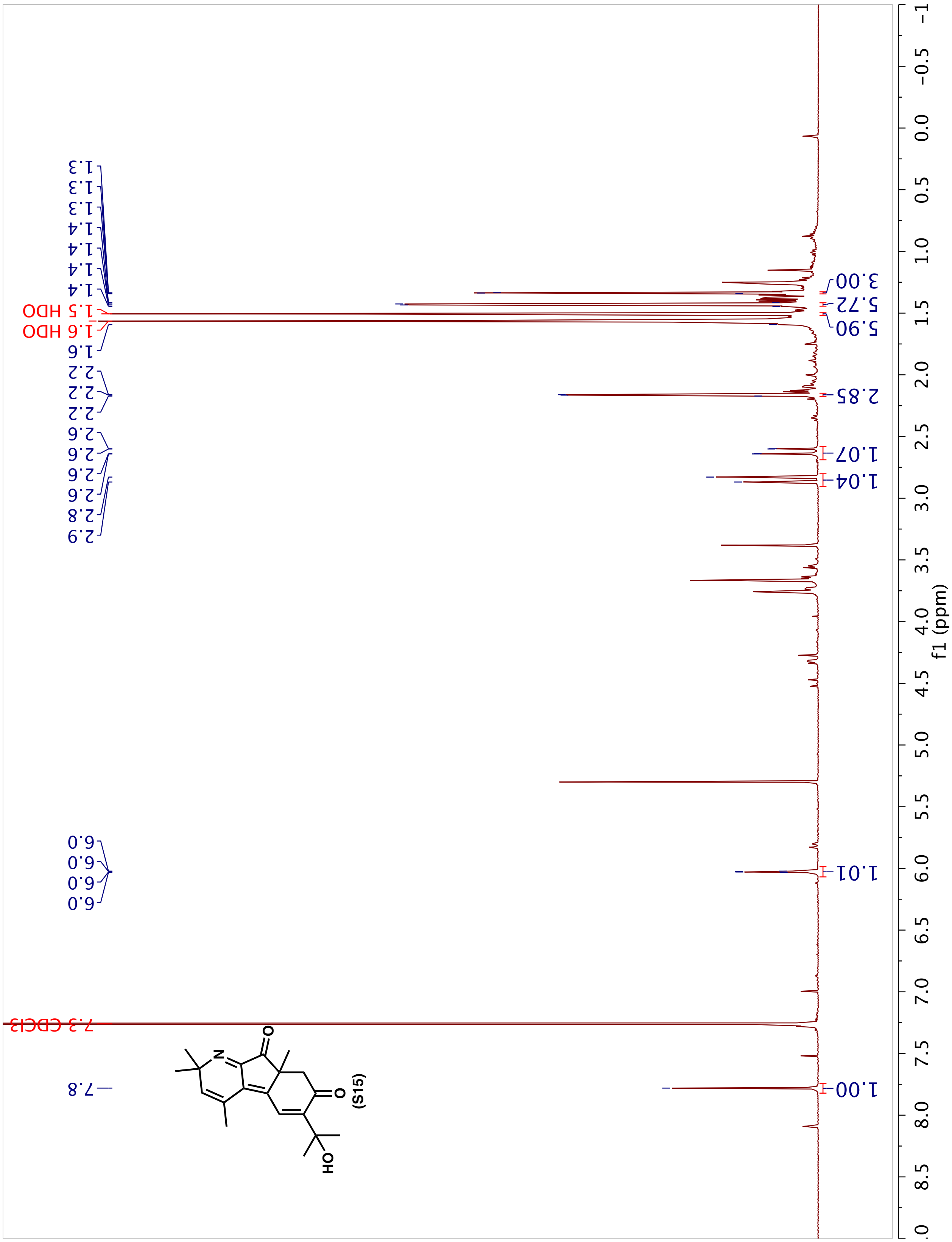
^{13}C NMR (101 MHz, CDCl$_3$) of **S12**.



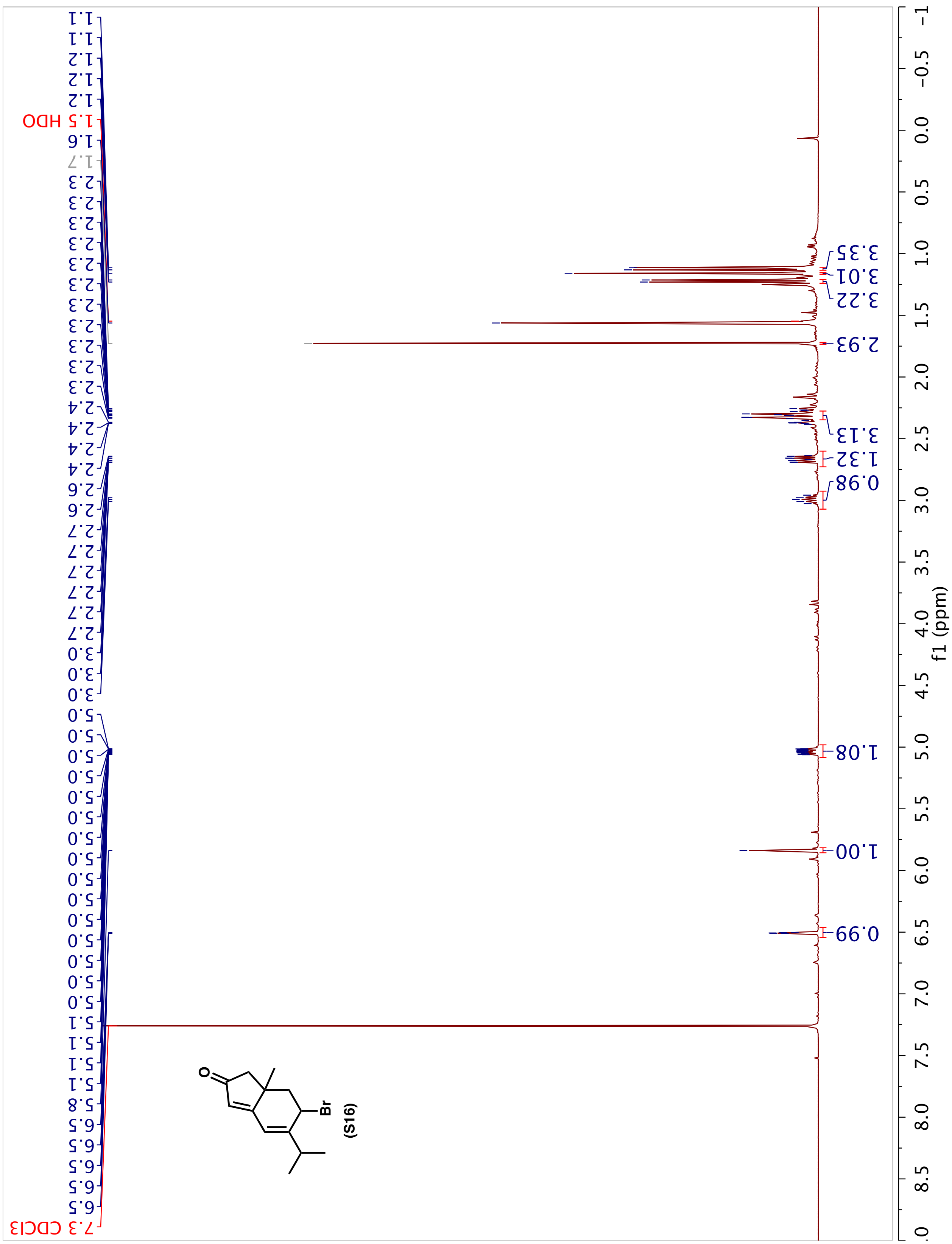
^{1}H NMR (400 MHz, CD_2Cl_2) of **S13**.



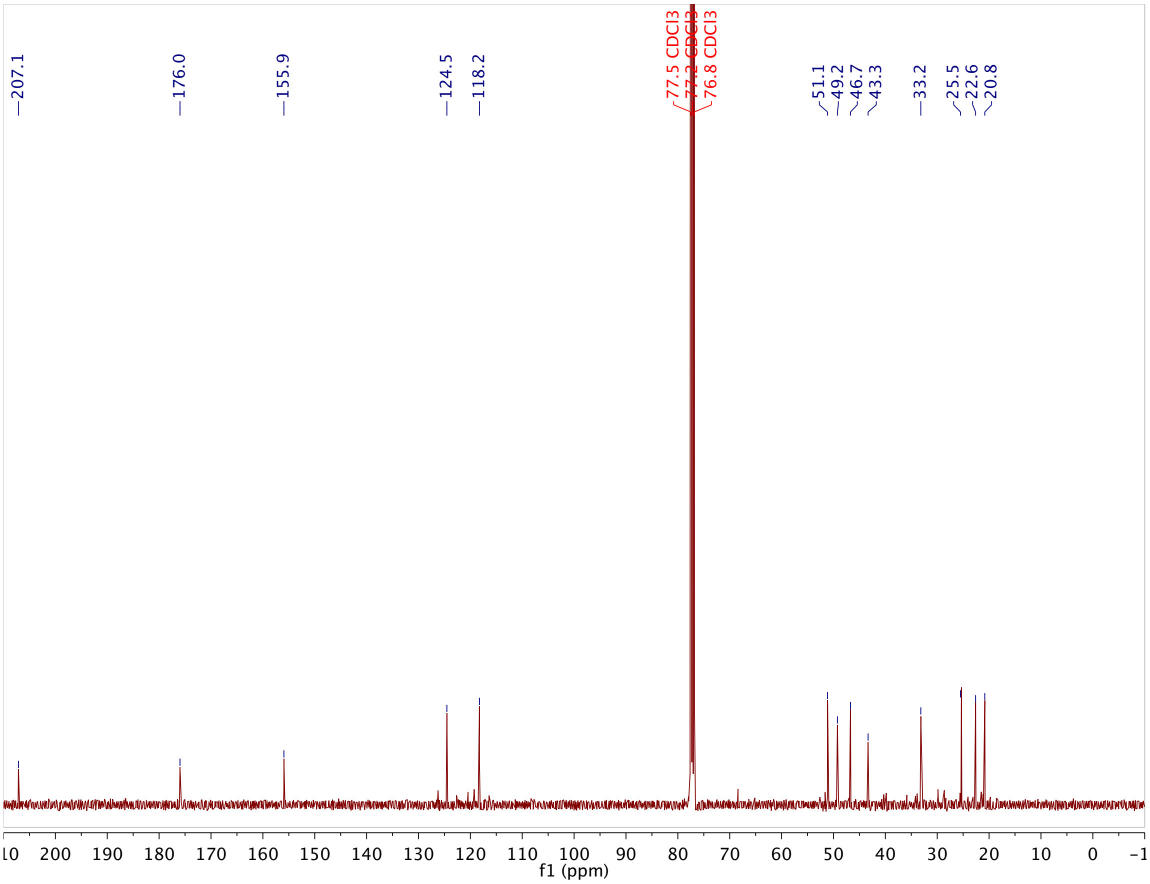
^{1}H NMR (400 MHz, CD$_3$OD) of **S14**.



^{1}H NMR (400 MHz, CDCl$_3$) of **S15**.



^{1}H NMR (400 MHz, CDCl$_3$) of **S16**.



^{13}C NMR (101 MHz, CDCl$_3$) of **S16.**

Notes and References

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[1] Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

[2] Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787–6790.

[3] Dauben, H. J.; McCoy, L. L. *J. Am. Chem. Soc.* **1959**, *81*, 4863–4873.

[4] McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554.

[5] Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899–2899.

[6] Lewis, J. C.; Mantovani, S. M.; Fu, Y.; Snow, C. D.; Komor, R. S.; Wong, C.-H.; Arnold, F. H. *ChemBioChem* **2010**, *11*, 2502–2505.

[7] Liu, Y.; Liniger, M.; McFadden, R. M.; Roizen, J. L.; Malette, J.; Reeves, C. M.; Behenna, D. C.; Seto, M.; Kim, J.; Mohr, J. T. *Beilstein J. Org. Chem.* **2014**, *10*, 2501–2512.

[8] Gulias, M.; Rodriguez, J. R.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2003**, *5*, 1975–1977.

[9] Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 12268–13369.

[10] Mino, T.; Masuda, S.; Nishio, M; Yamashita, M. *J. Org. Chem.* **1997**, *62*, 2633–2635.

[11] Doering, W. V. E.; Yamashita, Y. *J. Am. Chem. Soc.* **1983**, *105*, 5368–5372.

[12] Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, 47–53.

[13] a) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057–2059. b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, C. M. *J. Am. Chem. Soc.* **2005**, *127*, 6970–6971. c) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727–2730. d) Xing, X.; O'Connor, N. R.; Stoltz, B. M. *Angew. Chem., Int. Ed. Engl.* **2015**, *54*, 11186–11190. e) Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644–647. f) Schmuff, N. R.; Trost, B. M. *J. Org. Chem.* **1983**, *48*, 1404–1412. g) Zhao, Y.; Yeung, Y.-Y. *Org. Lett.* **2010**, *12*, 2128–2131. h) Wang, Y.; Kuang, Y.; Wang, Y. *Chem. Commun.* **2015**, *51*, 5852–5855. i) Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4909–4912. j) Young, W. B.; Masters, J. J.; Danishefsky, S. *J. Am. Chem. Soc.* **1995**, *117*, 5228–5234. k) Jasiczak, J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2687–2692. l) Horn, E. J.; Rosen, B. R.; Chen, Y.; Tang, J.; Chen, K.; Eastgate, M. D.; Baran, P. S. *Nature* **2016**, *533*, 77–81. m) Allen, J. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 351–352. n) Quinn, R. K.; Könst, Z. A.; Michalak, S. E.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Vanderwal, C. D.; Alexanian, E. *J. Am. Chem. Soc.* **2016**, *138*, 696–702.

[14] Entries 1–3, and 8 were also attempted with **5•TFA**. The TFA salt showed no significant difference in selectivity.

[15] Co-isolated with AIBN

[16] Nigelladine A **1** was repurified by preparative HPLC prior to optical rotation and therefore we believe that nigelladine A is either possibly isolated as a scalemic mixture or the isolation chemists isolated a mixture of protonated and free imine.

[17] Chen, Q. B.; Xin, X. L.; Yang, Y.; Lee, S. S.; Aisa, H. A. *J. Nat. Prod.* **2014**, *77*, 807–812.