Supporting Information for

Some Unusual Transformations of a Highly Reactive α-Bromocaranone

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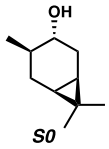
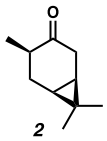
General considerations

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[1] (+)-3-Carene was purchased from TCI and used as received, *N*-bromosuccinimide (NBS) was recrystallized from boiling water prior to use, trimethylsilyl chloride (TMSCl) was distilled under argon prior to use, all other reagents and solvents were purchased from various commercial suppliers and used as received. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching or *p*-anisaldehyde staining. Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 μm) or Sigma-Aldrich aluminum oxide (activated, neutral, Brockmann Activity I) were used for flash chromatography. Preparatory HPLC was performed on an Agilent 1200 preparatory HPLC system using a 9.4 x 250 mm Eclipse XDB-C18 column. A water/MeCN gradient was used as the mobile phase and the compounds were detected at 230.8 nm and 254.4 nm. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. ^{1}H NMR spectra were recorded on Varian Inova 500 MHz, Varian 400 MHz, and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz), a Varian 400 MHz spectrometer (100 MHz), and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^{1}H 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, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm) Some reported spectra include minor solvent impurities of water (δ 1.56ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), acetone (δ 2.17 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and 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. High-resolution mass spectrometry was performed by the Multi User Mass Spectrometry Laboratory at the California Institute of Technology using a JMS-T200 GC AccuTOF GC-Alpha mass spectrometer.

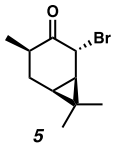
Synthetic Procedures and Characterization of Compounds



(1R,3R,4R,6S)-4,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (S0). The procedure was adapted from the literature:[2] To a dried 500 mL round bottom flask was added $NaBH_4$ (6.94 g, 183 mmol, 1.0 equiv), THF (60 mL), and (+)-3-carene (25 g, 180 mmol, 1.0 equiv). The reaction flask was cooled to 0 °C in an ice bath, and BF_3•OEt_2 (26 g, 160 mmol, 1.0 equiv) was added dropwise over 30 min. The reaction was stirred at this temperature for 4 h, after which the reaction was cooled to –10 °C and aq. NaOH (3M, 60 mL) was added dropwise over 40 min. H_2O_2 (30 wt %, 100 mL) was then added dropwise over 1 h, and the reaction allowed to warm to 20 °C. The solution was concentrated under reduced pressure to remove THF, and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, and filtered. Concentration under reduced pressure afforded an oil that was distilled under vacuum (0.5 mmHg, 150 °C) to afford **S0** (22 g, 78%) as a colorless oil that solidified upon cooling. ^{1}H NMR (chloroform-*d*, 400 MHz): δ = 3.07 (ddd, *J* = 10.3, 9.3, 6.6 Hz, 1H), 2.10 (ddd, *J* = 14.1, 6.6, 0.9 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.61 – 1.51 (m, 1H), 1.29 – 1.17 (m, 1H), 0.97 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 3H), 0.86 – 0.77 (m, 1H), 0.75 – 0.67 (m, 2H). Spectral data are in agreement with previously reported values.[3]

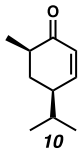


(1R,4R,6S)-4,7,7-trimethylbicyclo[4.1.0]heptan-3-one (2). A procedure from the literature[4] was modified as follows: To a 1 L round bottom flask was added alcohol **S0** (20 g, 130 mmol, 1.0 equiv) and Et_2O (280 mL). The solution was cooled in an ice bath, and Brown–Garg (BG) reagent[5,6] (70 mL) was added dropwise over 20 min with vigorous stirring, maintaining the reaction temperature below 20 °C. The ice bath was then removed, and the solution stirred for 1 h. Additional BG reagent (70 mL) was added slowly, and the reaction was left to stir for 18 h. The organic layer was then separated, and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residual oil was distilled under vacuum (0.5 mmHg, 130 °C) to yield **2** (12.8 g, 65%) as fragrant, yellow oil. ^{1}H NMR (chloroform-*d*, 400 MHz): δ = 2.52 (ddd, *J* = 18.0, 8.4, 0.9 Hz, 1H), 2.41 – 2.32 (m, 1H), 2.32 – 2.25 (m, 2H), 1.31 – 1.19 (m, 1H), 1.07 (m, 1H), 1.04 (s, 3H), 1.02 – 0.97 (m, 1H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.84 (s, 3H). Spectral data are in agreement with previously reported values.[4]



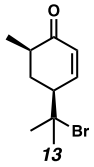
5

(1R,2R,4R,6S)-2-bromo-4,7,7-trimethylbicyclo[4.1.0]heptan-3-one (5). To a flame-dried 250 mL Schlenk flask was added THF (29 mL) and diisopropylamine (1.59 g, 15.8 mmol, 1.2 equiv). The solution was cooled to –78 °C and *n*-butyllithium (2.5 M in hexanes, 5.5 mL, 13.8 mmol, 1.05 equiv) was added dropwise over 8 min. After stirring for 30 min, a solution of ketone **2** (2 g, 13.1 mmol, 1.0 equiv) in THF (2 mL) was added dropwise over 5 min and the reaction mixture allowed to stir at –78 °C for 1.5 h. TMSCl (2.14 g, 19.7 mmol, 1.5 equiv) was added and the reaction was allowed to warm to 0 °C in an ice bath, and further stirred at 0 °C for 1 h. The reaction flask was then wrapped in Al foil to exclude light and NBS (3.5 g, 19.7 mmol, 1.5 equiv) was added in a single portion. After stirring for a further 30 min in the dark, the reaction was quenched* with saturated aq. $NaHCO_3$ (50 mL) and extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with water (2 x 40 mL) and brine (40 mL), dried over Na_2SO_4, and filtered. The solution was concentrated under reduced pressure to yield 2.1 g of residue. A small amount of this residue (255 mg) was purified *via* flash chromatography on neutral alumina (hexanes) to yield **5** (173 mg, extrapolated to 48% overall yield) as an unstable straw-colored oil which crystallized when pure. **5** was used immediately or stored as a frozen solution in benzene. ^{1}H NMR (chloroform-*d*, 400 MHz): δ = 4.37 (d, *J* = 1.2 Hz, 1H), 3.22 (ddq, *J* = 13.0, 7.7, 6.5 Hz, 1H), 2.45 (ddd, *J* = 14.7, 9.7, 7.6 Hz, 1H), 1.52 (dd, *J* = 8.6, 1.3 Hz, 1H), 1.40 (ddd, *J* = 14.8, 13.0, 4.3 Hz, 1H), 1.18 (td, *J* = 8.9, 4.2 Hz, 1H), 1.07 (s, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.84 (s, 3H); ^{13}C{^{1}H} NMR (chloroform-d, 100 MHz): δ = 209.7, 48.2, 36.2, 33.7, 30.7, 28.2, 22.2, 20.5, 14.7, 14.1; IR (Neat Film, NaCl) 2933, 1719, 1455, 1378, 1162, 848, 776, 622 cm^{-1}; HRMS (FI+): *m/z* calc'd for $C_{10}H_{15}OBr$ [M]$^+$: 230.0301 found, 230.0308; $[\alpha]_D^{22.16}$ –278.99 (c 1.0, $CHCl_3$). *Due to the light-sensitivity of the product, it is recommended to perform the work-up in the dark.



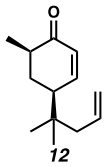
10

(4R,6R)-4-isopropyl-6-methylcyclohex-2-en-1-one (10). AIBN (20 mg, 0.121 mmol, 0.2 equiv) was loaded into a 20 mL vial with septum cap. A solution of bromide **5** (140 mg, 0.606 mmol, 1.0 equiv) and Bu_3SnH (353 mg, 1.21 mmol, 2.0 equiv) in anhydrous benzene (6 mL) was added. The reaction mixture was stirred at 86 °C for 1 h, after which the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica (0–10% EtOAc in hexanes) to afford **10** (82 mg, 89%) as a colorless oil. The resulting product is pure enough for most purposes, but a sample of higher purity for analysis was obtained by distillation. ^{1}H NMR (chloroform-*d*, 400 MHz): δ = 6.82 (dt, *J* = 10.2, 2.2 Hz, 1H), 6.01 (dd, *J* = 10.2, 3.0 Hz, 1H), 2.39 (m, 2H), 1.96 (dtd, *J* = 13.0, 4.5, 2.0 Hz, 1H), 1.80 (pd, *J* = 6.9, 4.8 Hz, 1H), 1.54 – 1.49 (ddd, *J* = 13.9, 13.0, 11.4 Hz, 1H), 1.15 (d, *J* = 6.6, 3H), 0.96 (d, *J* = 7.1, 3H), 0.94 (d, *J* = 6.9, 3H); ^{13}C{^{1}H} NMR (chloroform-d, 100 MHz): δ = 202.7, 153.5, 129.7, 43.5, 41.7, 34.2, 31.8, 19.6, 19.3, 15.2; IR (Neat Film, NaCl) 2959, 2872, 1684, 1458, 1386, 1219, 803 cm^{-1}; HRMS (FI+): *m/z* calc'd for $C_{10}H_{16}O$ [M]$^+$: 152.1196 found, 152.1198; $[\alpha]_D^{22.31}$ –35.30 (c 1.0, $CHCl_3$).



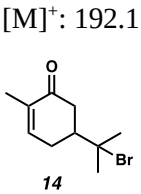
13

(4S,6R)-4-(2-bromopropan-2-yl)-6-methylcyclohex-2-en-1-one (13). To a 4 mL vial was added bromide **5** (36 mg, 0.156 mmol, 1.0 equiv) in anhydrous benzene (1.5 mL). To this solution was added allyltributyltin (21 mg, 0.062 mmol, 0.4 equiv) and AIBN (5 mg, 0.03 mmol, 0.2 equiv). The vial was sealed, and the reaction mixture stirred at 86 °C for 4 h. The reaction was then allowed to cool to 20 °C and concentrated under reduced pressure. The residue was purified *via* flash chromatography on silica (5–10% EtOAc in hexanes) to afford **13** (26 mg, 72%) as a colorless oil. ^{1}H NMR (chloroform-*d*, 400 MHz): δ = 7.09 (dt, *J* = 10.3, 2.1 Hz, 1H), 6.09 (dd, *J* = 10.3, 2.8 Hz, 1H), 2.85 (dddd, *J* = 11.4, 4.6, 2.9, 2.0 Hz, 1H), 2.41 (dqd, *J* = 13.4, 6.7, 4.5 Hz, 1H), 2.24 (dtd, *J* = 12.7, 4.4, 2.2 Hz, 1H), 1.89 (s, 3H), 1.74 (s, 3H), 1.67 – 1.58 (m, 1H), 1.17 (d, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (chloroform-d, 100 MHz): δ = 201.3, 150.1, 130.2, 68.3, 50.5, 41.0, 34.2, 32.9, 30.9, 15.1; IR (Neat Film, NaCl) 2967, 1682, 1455, 1372, 1213, 1125, 803, 644, 601 cm^{-1}; HRMS (FI+): *m/z* calc'd for $C_{10}H_{15}OBr$ [M]$^{+}$: 230.0301, found 230.0300; $[\alpha]_D^{22.13}$ –62.67 (c 1.0, $CHCl_3$).



12

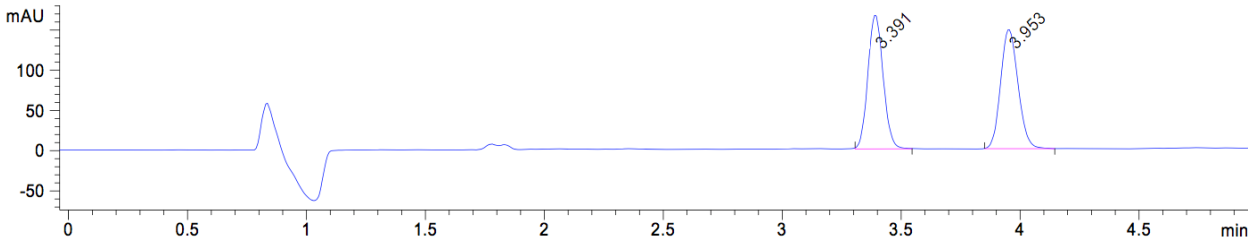
(4S,6R)-6-methyl-4-(2-methylpent-4-en-2-yl)cyclohex-2-en-1-one (12). To a 20 mL vial was added bromide **13** (45 mg, 0.195 mmol, 1.0 equiv) in anhydrous benzene (4 mL). To this was added allyltributyltin (390 mg, 1.17 mmol, 6.0 equiv) and AIBN (6.4 mg, 0.039 mmol, 0.2 equiv). The vial was sealed, and the reaction mixture stirred at 86 °C for 48 h. The solution was concentrated under reduced pressure and the residue purified *via* flash chromatography on silica (5% EtOAc in hexanes) to afford **12** (24 mg, 63%) as a colorless oil. The compound is pure enough for most purposes, but a sample of higher purity for analysis was obtained by preparatory HPLC (60–80% MeCN in H_2O over 5 min at 12 mL/min). ^{1}H NMR (chloroform-*d*, 400 MHz): δ = 6.96 (dt, *J* = 10.3, 2.1 Hz, 1H), 6.03 (dd, *J* = 10.3, 3.0 Hz, 1H), 5.83 (ddt, *J* = 16.8, 10.2, 7.4 Hz, 1H), 5.13 – 5.02 (m, 2H), 2.36 (m, 2H), 2.11 – 2.06 (m, 2H), 2.03 (ddq, *J* = 11.0, 4.4, 2.2 Hz, 1H), 1.55 – 1.46 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 0.95 (s, 3H), 0.92 (s, 3H); ^{13}C{^{1}H} NMR (chloroform-d, 100 MHz): δ = 202.4, 151.7, 134.7, 130.0, 118.0, 45.7, 44.5, 41.8, 35.7, 33.1, 24.9, 24.6, 15.3; IR (Neat Film, NaCl) 2961, 1683, 1385, 1222, 914, 802 cm^{-1}; HRMS (FI+): *m/z* calc'd for $C_{13}H_{20}O$ [M]$^{+}$: 192.1509, found 192.1509; $[\alpha]_D^{22.49}$ –25.44 (c 0.25, $CHCl_3$).



14

(S)-5-(2-bromopropan-2-yl)-2-methylcyclohex-2-en-1-one (14). To a 4 mL vial was added bromide **5** (86 mg, 0.372 mmol, 1.0 equiv) in anhydrous benzene (1.6 mL). The vial was sealed, and the reaction mixture stirred at 86 °C for 25 min. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography on neutral alumina (5% EtOAc in hexanes) to afford **14** (63 mg, 73%) as a colorless oil. ^{1}H NMR (chloroform-*d*, 400 MHz): δ = 6.75 (ddq, *J* = 5.4, 2.8, 1.4 Hz, 1H), 2.74 (ddd, *J* = 16.0, 3.7, 1.8 Hz, 1H), 2.59 (dddt, *J* = 18.2, 6.2, 4.6, 1.5 Hz, 1H), 2.41 (m, 2H), 2.05 (dddd, *J* = 13.5, 11.1, 4.6, 3.7 Hz, 1H), 1.79 (m, 3H), 1.79 (s, 3H), 1.77 (s, 3H); ^{13}C{^{1}H} NMR (chloroform-d, 100 MHz): δ =

199.2, 144.3, 135.4, 70.1, 48.3, 41.2, 32.5, 32.2, 29.2, 15.7; IR (Neat Film, NaCl) 2972, 1674, 1451, 1370, 1254, 1103, 1062, 904, 690 cm^{-1}; HRMS (FI+): *m/z* calc'd for $C_{10}H_{15}OBr$ $[M]^+$: 230.0301, found 230.0302. **14** was determined to be racemic by chiral SFC analysis (AD-H, EtOH/CO_2 = 5/95, flow rate = 3.5 mL/min, λ = 210 nm) t_R = 3.39, 3.95.



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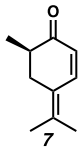
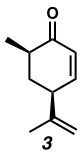
2	3.953	BB	0.0839	753.20081	146.78207	50.3420
Totals :				1496.16888	312.37704	

Procedure for the Ag^I–mediated fragmentation of bromide 5.

To a solution of the indicated silver salt (0.182 mmol, 2.1 equiv) in THF (0.6 mL) was added a solution of bromoketone **5** (20 mg, 0.0865 mmol, 1.0 equiv) in THF (0.3 mL, 0.1 M total concentration) dropwise over 1 min with stirring at 20 °C. In all cases, a thick precipitate immediately formed. Stirring was continued for an additional 20 min, after which the reaction mixture was quenched with saturated aq. $NaHCO_3$ (1 mL) and filtered through a plug of celite with EtOAc. The layers were separated and the organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure to provide a crude product that was purified by silica gel flash chromatography (5% EtOAc in hexanes).

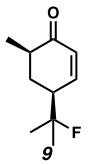


(R)-6-methyl-4-(propan-2-ylidene)cyclohex-2-en-1-one (7). 8.7 mg (67%) yield with $AgClO_4$; 7.1 mg (55%) yield with AgOTf; ^1H NMR (chloroform-d, 400 MHz): δ = 7.42 (dd, *J* = 10.1, 0.9 Hz, 1H), 5.80 (d, *J* = 10.0 Hz, 1H), 2.84 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.48 (dqd, *J* = 10.9, 6.8, 5.4 Hz, 1H), 2.39 – 2.27 (m, 1H), 1.93 (dd, *J* = 1.6, 0.8 Hz, 3H), 1.90 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (chloroform-d, 100 MHz): δ = 203.0, 143.1, 139.4, 126.7, 124.0, 40.9, 34.1, 21.9, 20.8, 15.9; IR (Neat Film, NaCl) 2927, 1672, 1623, 1453, 1216, 812 cm^{-1}; HRMS (FI+): *m/z* calc'd for $C_{10}H_{14}O$ $[M]^+$: 150.1039, found 150.1039; $[\alpha]_D^{21.95}$ +137.36 (c 0.5, $CHCl_3$).



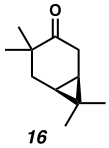
(4S,6R)-6-methyl-4-(prop-1-en-2-yl)cyclohex-2-en-1-one (3). Isopropenyl enone **3** was observed in trace quantities in the Ag^I-mediated fragmentation of bromide **5**. 0.7 mg (5% yield) with $AgBF_4$. A sample suitable for characterization, albeit containing a minor impurity, could be obtained by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc in hexanes) on a 100 mg scale. ^1H NMR

(chloroform-d, 400 MHz): δ = 6.81 (dt, *J* = 10.1, 2.0 Hz, 1H), 6.03 (dd, *J* = 10.1, 3.0 Hz, 1H), 4.86 (p, *J* = 1.5 Hz, 1H), 4.81 (dq, *J* = 1.6, 0.8 Hz, 1H), 3.21 – 3.12 (m, 1H), 2.42 (dqd, *J* = 13.5, 6.7, 4.5 Hz, 1H), 2.13 (dtd, *J* = 13.0, 4.5, 2.0 Hz, 1H), 1.77 (dd, *J* = 1.4, 0.9 Hz, 3H), 1.72 – 1.61 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (chloroform-d, 100 MHz): δ = 202.0, 152.5, 146.9, 129.6, 112.0, 45.2, 41.8, 37.7, 20.8, 15.1; IR (Neat Film, NaCl) 2964, 2934, 2862, 1683, 1649, 1454, 1376, 1215, 1188, 1118, 895, 804 cm^{-1}; HRMS (FI+): *m/z* calc'd for $C_{10}H_{14}O$ $[M]^+$: 150.1039, found 150.1030; $[\alpha]_D^{21.23}$ –92.59 (c 0.33, $CHCl_3$).



9

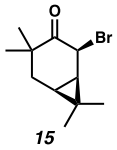
(4S,6R)-4-(2-fluoropropan-2-yl)-6-methylcyclohex-2-en-1-one (9). 6.6 mg of a 3.4:1 (*w/w*) mixture of fluoride **9** and dienone **7** was isolated, corresponding to a 35% yield of fluoride **9**. While this mixture was inseparable by silica gel flash chromatography, an analytical sample of **9** was isolated by reverse-phase preparative HPLC (50–70% MeCN in H_2O over 3.5 min at 10 mL/min); ^{1}H NMR (chloroform-d, 400 MHz): δ = 6.96 (dt, *J* = 10.3, 2.0 Hz, 1H), 6.09 (dd, *J* = 10.3, 3.0 Hz, 1H), 2.88 – 2.75 (m, 1H), 2.41 (dqd, *J* = 13.5, 6.7, 4.6 Hz, 1H), 2.08 (dtdd, *J* = 12.8, 4.5, 2.1, 0.9 Hz, 1H), 1.53 – 1.45 (m, 1H), 1.42 (d, *J* = 22.0 Hz, 3H), 1.32 (d, *J* = 22.0 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (chloroform-d, 100 MHz): δ = 201.6, 148.9, 148.8, 130.5, 97.3, 95.6, 47.4, 47.2, 41.3, 33.4, 33.4, 25.6, 25.4, 23.7, 23.4, 15.1; IR (Neat Film, NaCl) 2930, 1682, 1453, 1376, 1219, 878, 812, 522 cm^{-1}; HRMS (FI+): *m/z* calc'd for $C_{10}H_{15}FO$ $[M]^+$: 170.1101, found 170.1099; $[\alpha]_D^{21.82}$ –37.10 (c 0.167, $CHCl_3$).



16

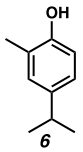
(1R,6S)-4,4,7,7-tetramethylbicyclo[4.1.0]heptan-3-one (16). To a rapidly stirred suspension of NaH (60% dispersion in mineral oil, 289 mg, 7.23 mmol, 1.1 equiv) in THF (5.6 mL, 1 M final substrate concentration) in a 50 mL 2-neck flask equipped with a reflux condenser was added ketone **2** (1.00 g, 6.57 mmol, 1.0 equiv) through the top of the condenser. Additional THF (1 mL) was used to rinse the ketone into the reaction mixture. The suspension was then heated to reflux in an oil bath and stirred for 1.5 h. Then, HMDS (0.21 mL, 0.986 mmol, 0.15 equiv) was added through the top of the condenser and the reaction mixture was stirred under reflux for an additional 25 min. The flask was then cooled to 0 °C in an ice bath, and the reflux condenser was replaced with a septum. MeI (0.45 mL, 7.23 mmol, 1.1 equiv) was added dropwise, after which the ice bath was removed. After stirring at 20 °C for 17 h, the reaction mixture was quenched with H_2O (20 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (4x10 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and purified *via* silica gel flash chromatography (10% Et_2O in hexanes). The resulting oil was purified again by automated silica gel flash chromatography (Teledyne ISCO, 0→10% EtOAc in hexanes) to provide dimethyl ketone **16** (361 mg, 29% yield desired isomer) as a fragrant, colorless oil containing 11% of an inseparable isomeric impurity; ^{1}H NMR (chloroform-*d*, 400 MHz): δ = 2.65 – 2.52 (m, 1H), 2.19 – 2.07 (m, 1H), 1.94 (ddt, *J* = 14.9, 9.3, 1.4 Hz, 1H), 1.39 (ddt, *J* = 14.9, 6.2, 0.9 Hz, 1H), 1.22 (s, 3H), 1.11 – 1.06 (m, 1H), 1.04 (s, 3H), 0.94 (s, 3H), 0.90 – 0.80 (m, 4H); $^{13}C\{^{1}H\}$ NMR (chloroform-d, 100 MHz): δ =

218.9, 42.4, 35.1, 34.6, 28.0, 24.8, 24.3, 22.4, 19.5, 18.2, 14.9; IR (Neat Film, NaCl) 2930, 2867, 1709, 1460, 1412, 1379, 1111, 1051, 986, 808 cm^{-1}; *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1352, found 166.1358; $[\alpha]_D^{21.48}$ –68.91 (c 1.0, $CHCl_3$).



15

(1R,2S,6S)-2-bromo-4,4,7,7-tetramethylbicyclo[4.1.0]heptan-3-one (15). To a solution of diisopropylamine (0.10 mL, 0.722 mmol, 1.2 equiv) in THF (1.3 mL, 0.45 M substrate concentration) was added *n*-butyllithium (2.5 M in hexanes, 0.25 mL, 0.632 mmol, 1.05 equiv) dropwise at –78 °C. The solution was allowed to warm to 0 °C and immediately cooled back to –78 °C, whereafter ketone **16** (100 mg, 0.602 mmol, 1.0 equiv) was added dropwise and the solution stirred at –78 °C for 1 h. TMSCl (0.11 mL, 0.903 mmol, 1.5 equiv) was added and the reaction was allowed to warm to 0 °C in an ice bath and stirred for an additional 45 min. The reaction was then protected from light and NBS (161 mg, 0.903 mmol, 1.5 equiv) was added in one portion. After stirring for a further 30 min in the dark, the reaction was quenched with saturated aq. $NaHCO_3$ (1 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (1 mL). The combined organic layers were washed with water (1 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified *via* silica gel flash chromatography to afford α-bromoketone **15** (126 mg, 89% yield desired isomer) as a white crystalline solid containing 8% of an inseparable isomeric impurity; ^{1}H NMR (chloroform-*d*, 400 MHz): δ = 4.23 (dd, *J* = 6.0, 0.8 Hz, 1H), 1.91 (ddd, *J* = 15.1, 8.3, 0.9 Hz, 1H), 1.44 (ddd, *J* = 15.0, 8.4, 0.8 Hz, 1H), 1.40 – 1.35 (m, 4H), 1.13 (s, 3H), 1.11 – 1.05 (m, 4H), 1.03 (s, 3H); ^{13}C{^{1}H} NMR (chloroform-d, 100 MHz): δ = 209.2, 49.2, 44.4, 33.7, 30.4, 27.7, 26.6, 26.0, 21.8, 21.5, 14.2; IR (Neat Film, NaCl) 2954, 2869, 1721, 1462, 1376, 1244, 1054, 911, 742 cm^{-1}; *m/z* calc'd for $C_{11}H_{17}OBr$ $[M]^+$: 244.0457, found 244.0459; $[\alpha]_D^{21.55}$ –148.50 (c 1.0, $CHCl_3$).



6

4-isopropyl-2-methylphenol (6). **5** (39 mg, 0.17 mmol) was left in a sealed 4 mL vial under ambient conditions for 24 h. During this time, the oil was found to spontaneously decompose with notable exotherm* and change in consistency. The blackened tar was purified *via* flash chromatography on silica (5% EtOAc in hexanes) to afford **6** (8 mg, 32%) as a colorless oil. ^{1}H NMR (chloroform-*d*, 400 MHz): δ = 6.99 (d, *J* = 2.3 Hz, 1H), 6.94 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 4.62 (s, 1H), 2.83 (hept, *J* = 7.0 Hz, 1H), 2.26 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 6H). Spectral data are in agreement with previously reported values.[7] *On large scales (>200 mg) the exotherm and release of HBr can lead to dangerous pressure build up, this can be avoided by leaving the vial open to atmosphere.

DFT Calculations

All quantum mechanical calculations were carried out with the ORCA program.[8,9] DFT geometry optimizations and harmonic frequency calculations were carried out in the gas phase with the M06-2X functional[10] and def2-TZVP basis set[11] on all atoms. Thermodynamic corrections from harmonic frequency calculations employ the quasi-ridged rotor harmonic oscillator approach to correct for the breakdown of the harmonic oscillator approximation at low vibrational frequencies.[12] Stationary points are characterized by the correct number of imaginary vibrational modes (zero for minima and one for saddle points). Intrinsic reaction coordinate (IRC) analysis[13] confirms the nature of transition states. Cartesian coordinates of all optimized structures are included as ".xyz" files and are available online in a zip file format. Electronic energies are further refined with single point calculations at the M06-2X/def2-TZVPP level of theory employing the SMD implicit solvation model for benzene.[14] Final Gibbs free energies were obtained by applying thermodynamic corrections obtained at the optimization level of theory to these refined solvated electronic energies. All computed QM numbers are included as a ".xlsx" file and is available online.

The resolution of identity (RI) and Chain-of-Spheres (COS) approximations are employed for efficient evaluation of Coulomb and exchange integrals, respectively.[15] The def2/J auxiliary basis[16] and very fine grid settings are employed in all calculations (keyword: DefGrid3). Calculations on open-shell systems employ unrestricted Kohn–Sham orbitals (UKS). Spin contamination is generally minor.

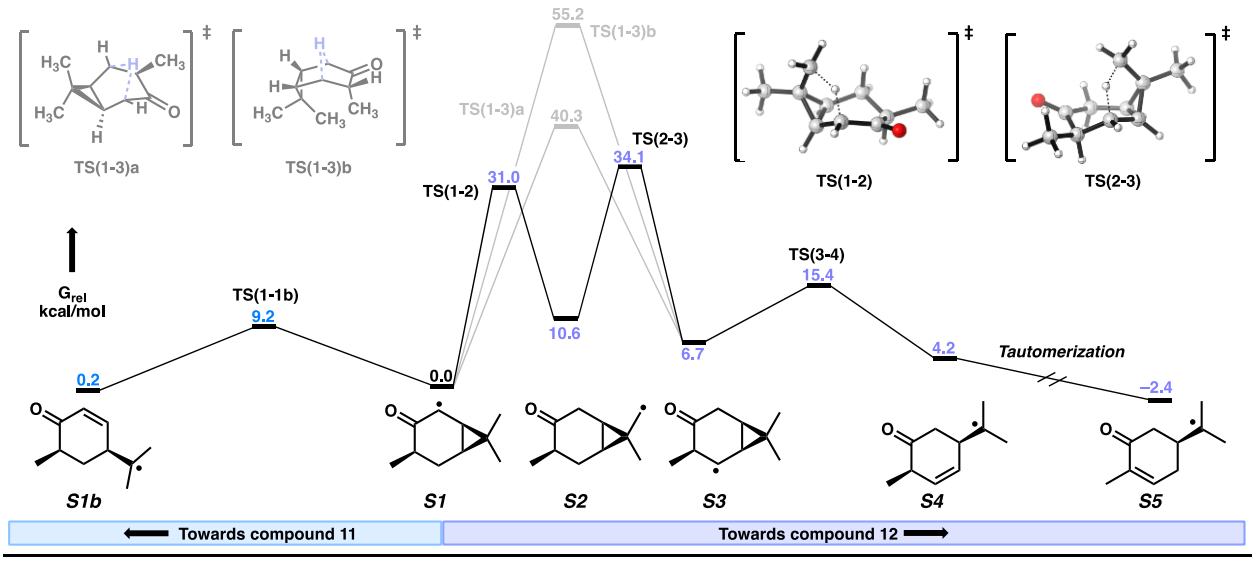


Figure S1. Minimum free energy pathway from **S1** towards **S1b** and **S3**. Relative free energies (in blue) provided in kcal/mol obtained at the M06-2X/def2-TZVPP/SMD(Benzene)//M06-2X/def2-TZVP level of theory. Note that **S1** and **S1b** exist in a rapid equilibrium. Direct 1,4-HAT over (**TS(1-3)a**) or under (**TS(1-3)b**) the ring, as well as indirect HAT through primary radical **S2**, involve barriers that are kinetically inaccessible at the temperatures at which these reactions were performed.

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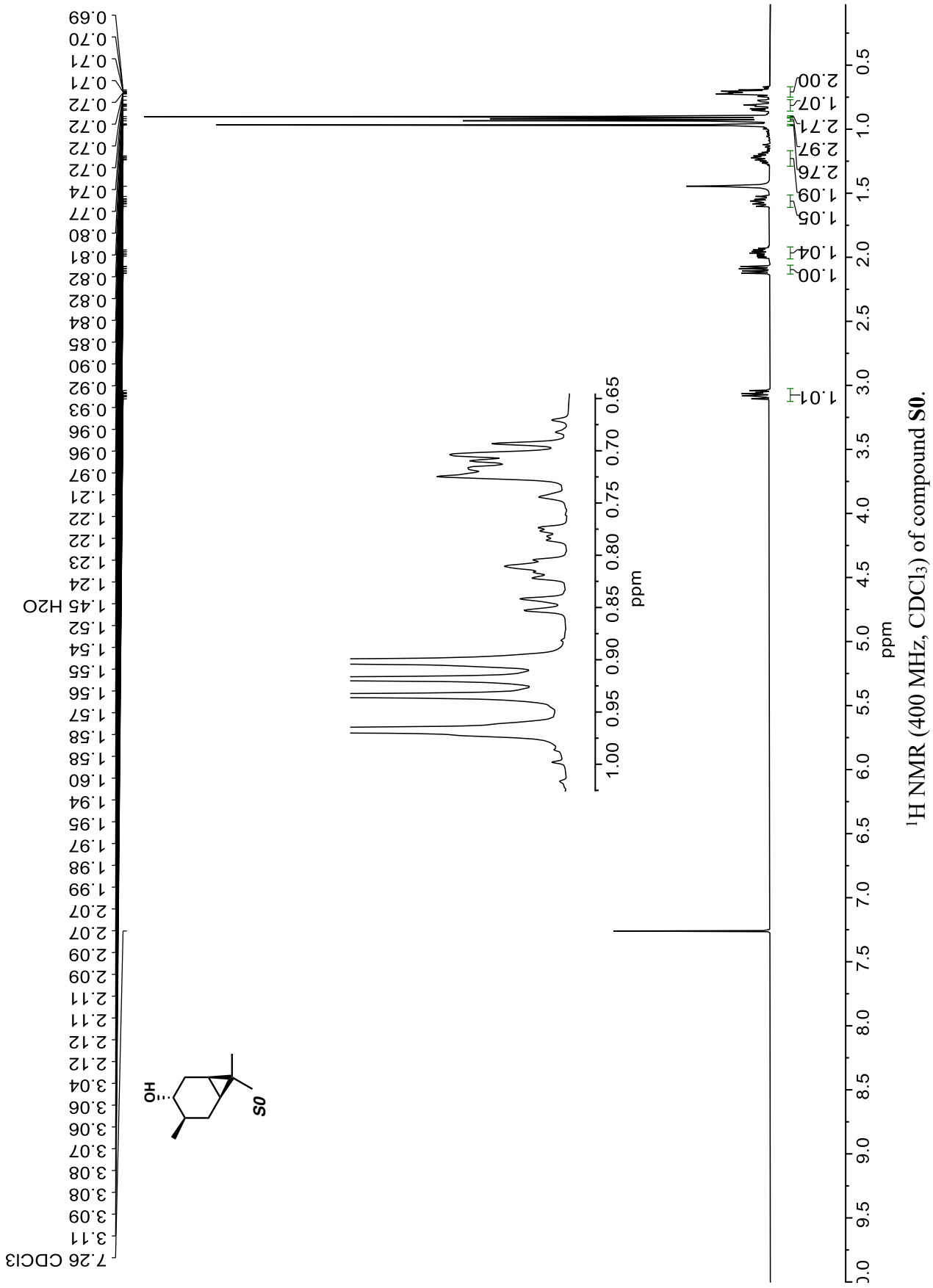
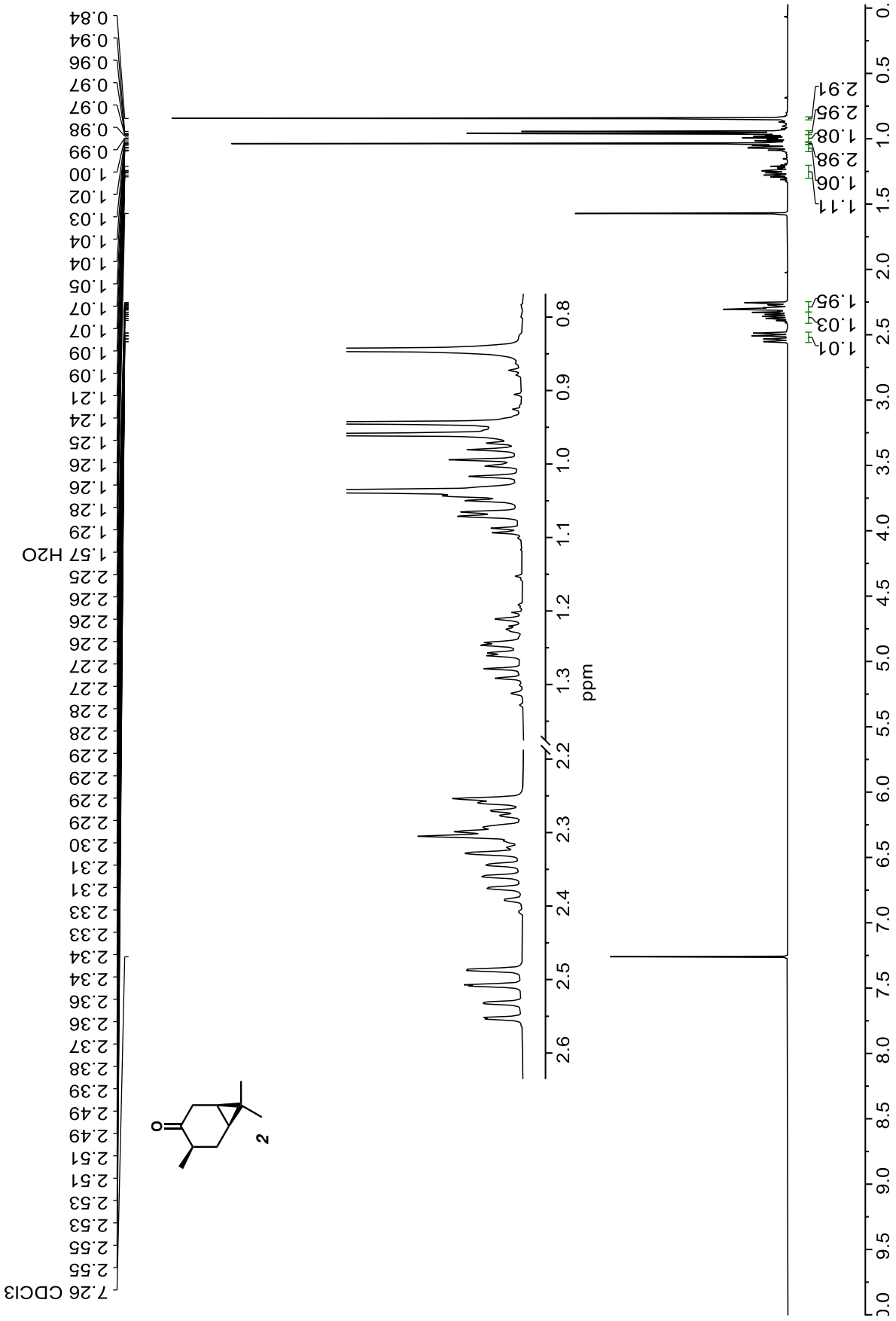
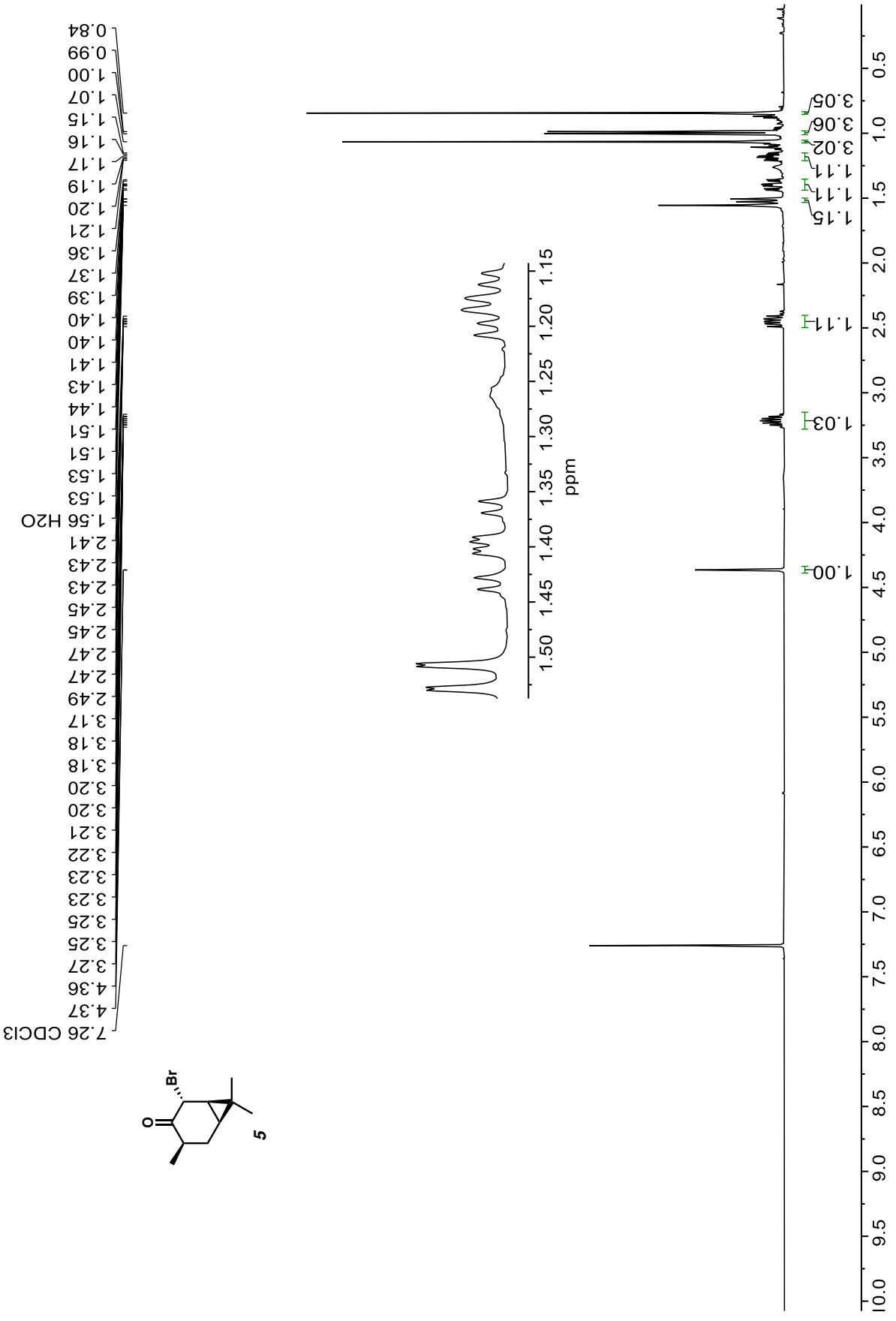


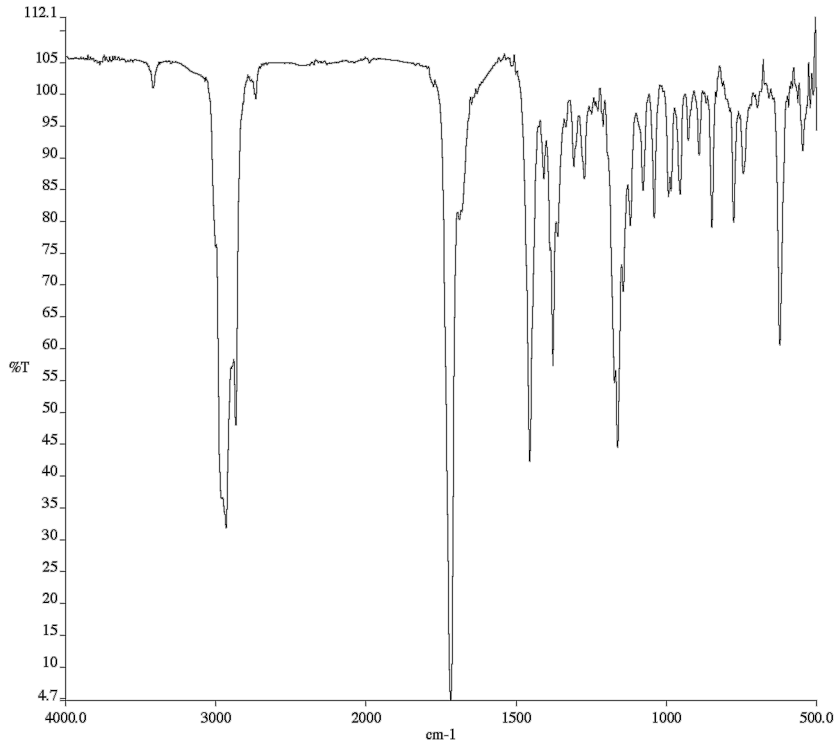
^{1}H NMR (400 MHz, $CDCl_3$) of compound **S0**.



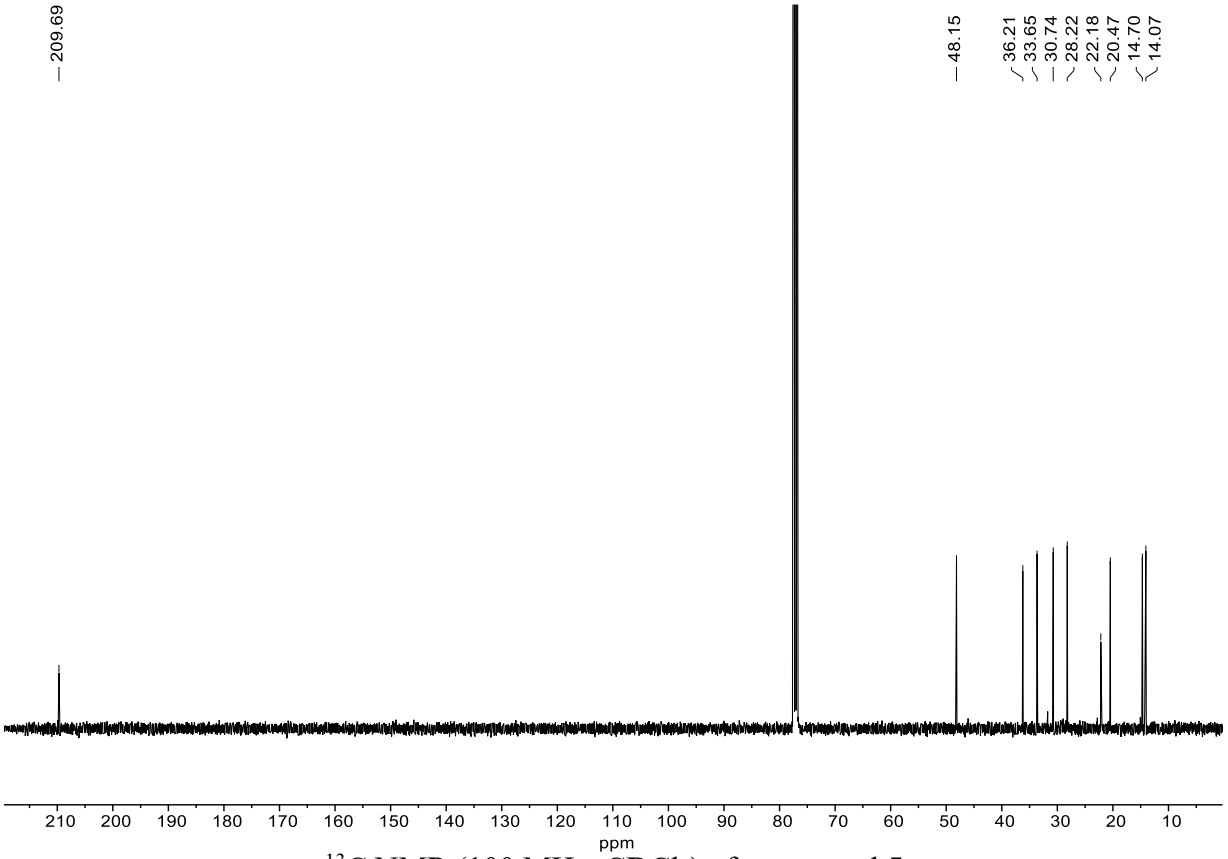
^{1}H NMR (400 MHz, $CDCl_3$) of compound **2**.



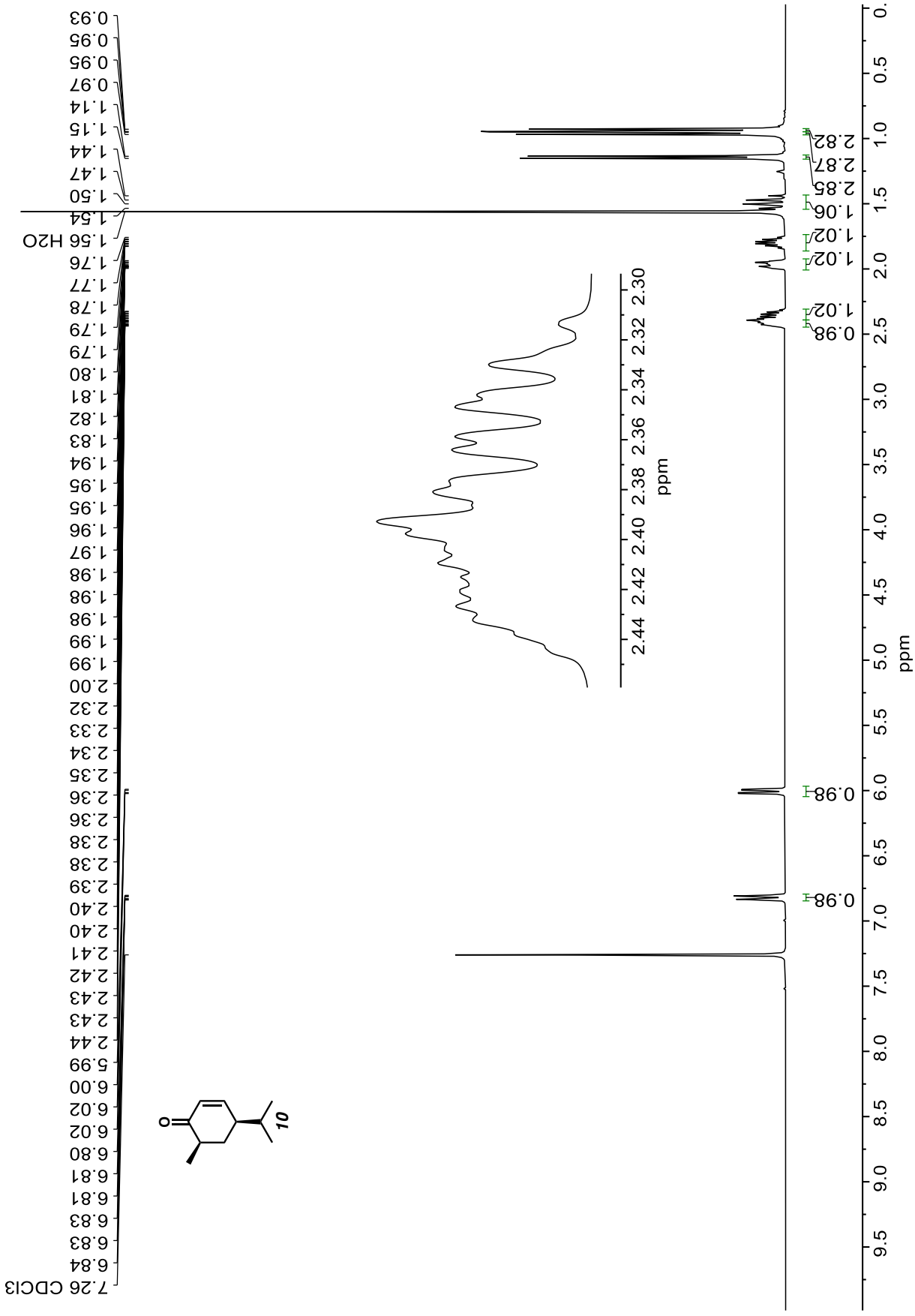
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5**.



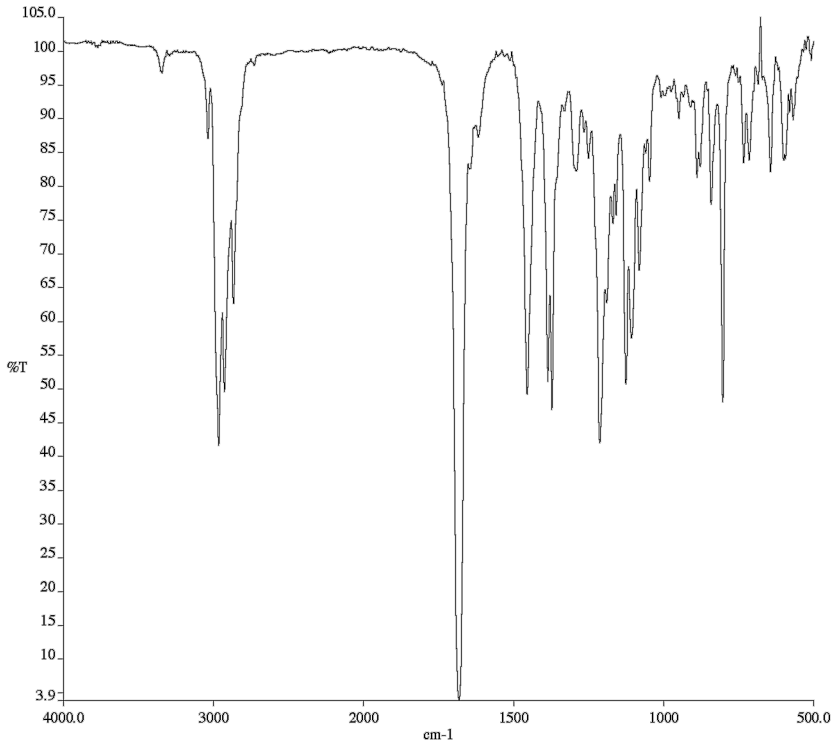
Infrared spectrum (Thin Film, NaCl) of compound **5**.



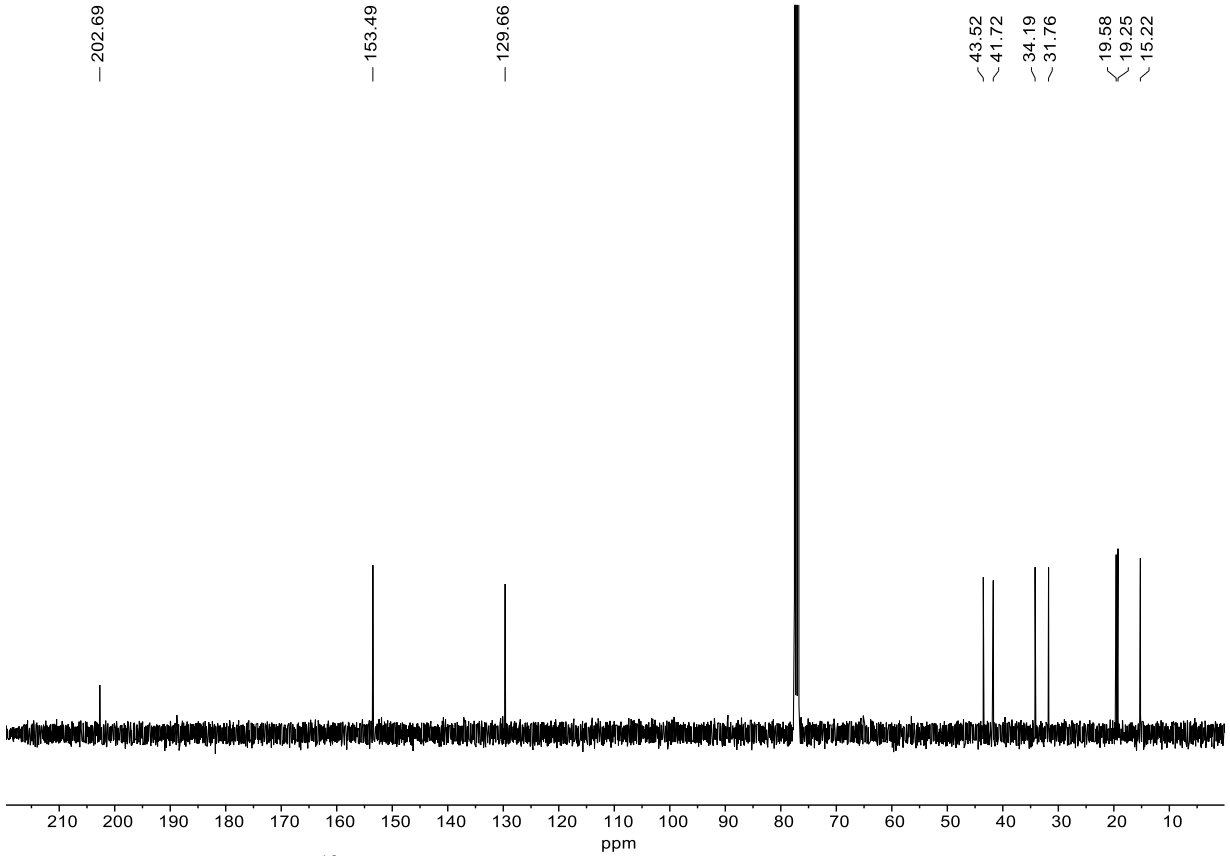
^{13}C NMR (100 MHz, $CDCl_3$) of compound **5**.



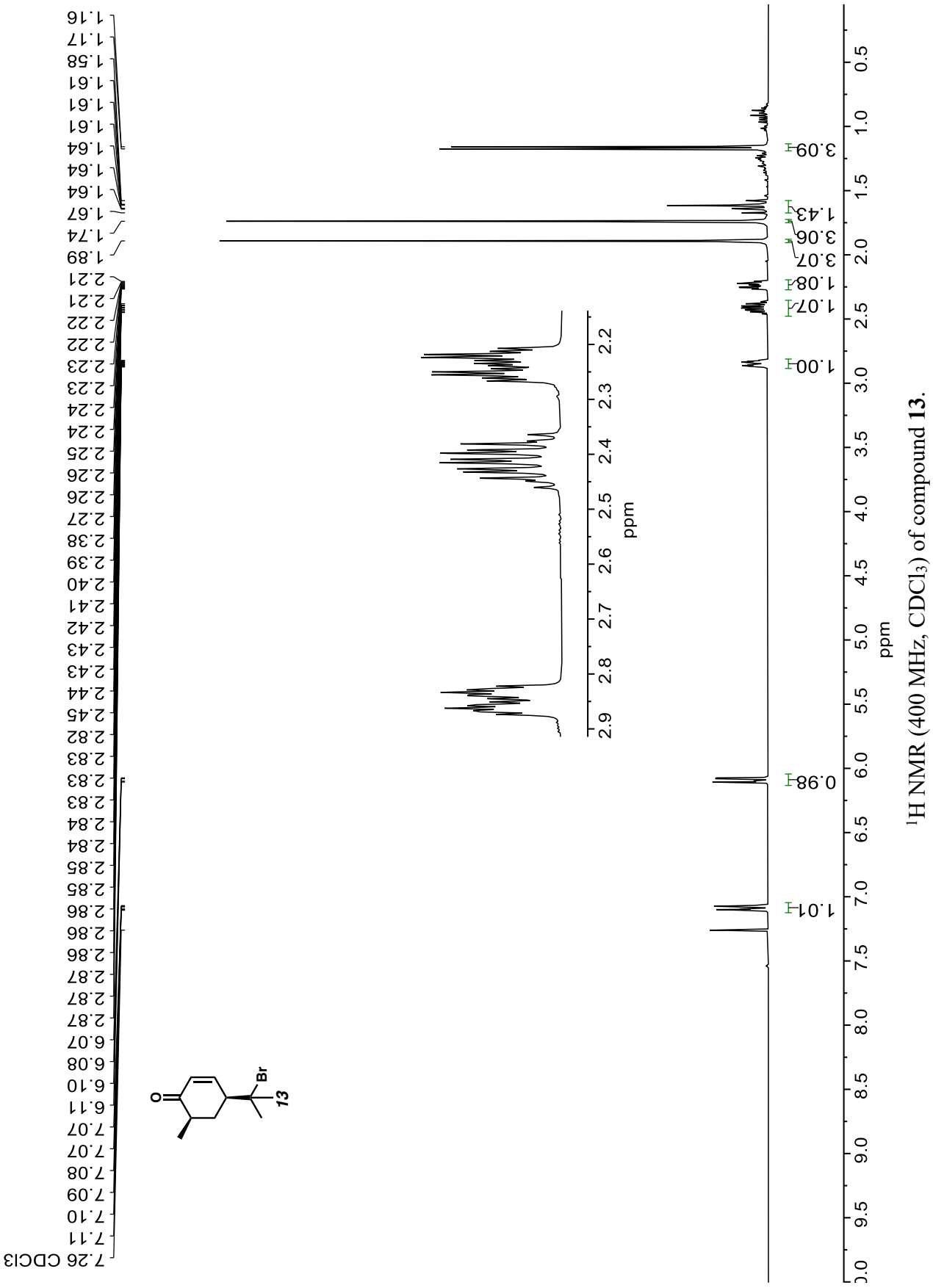
^{1}H NMR (400 MHz, $CDCl_3$) of compound **10**.



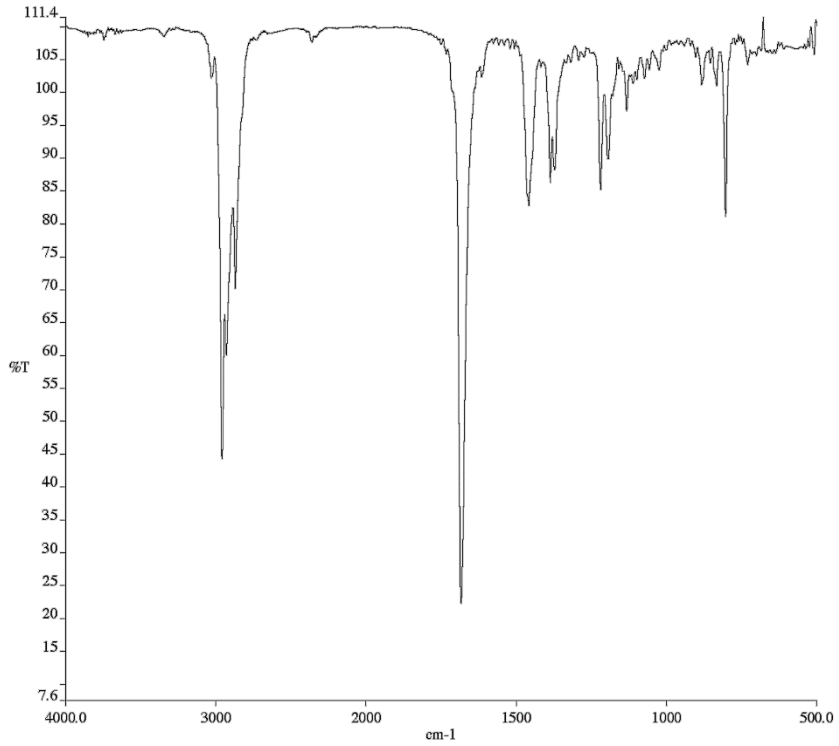
Infrared spectrum (Thin Film, NaCl) of compound **10**.



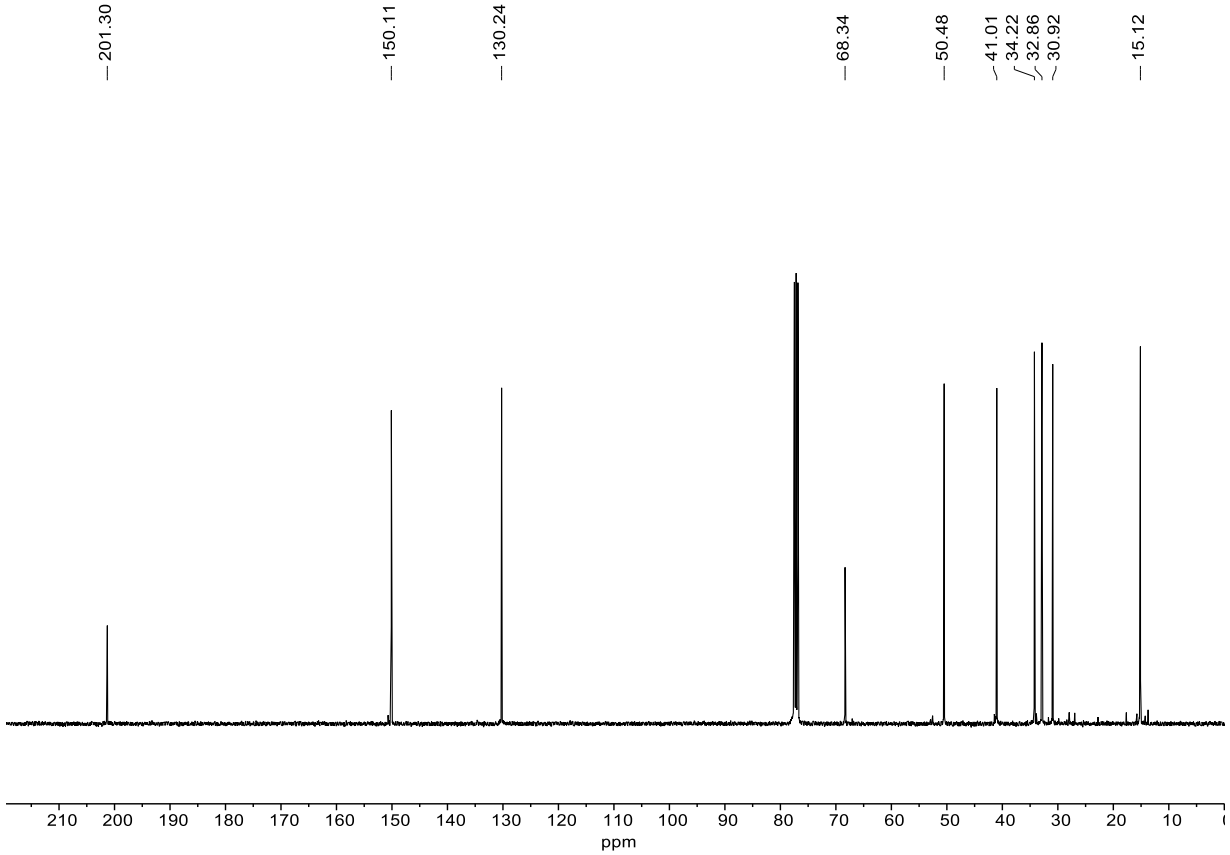
^{13}C NMR (100 MHz, $CDCl_3$) of compound **10**.



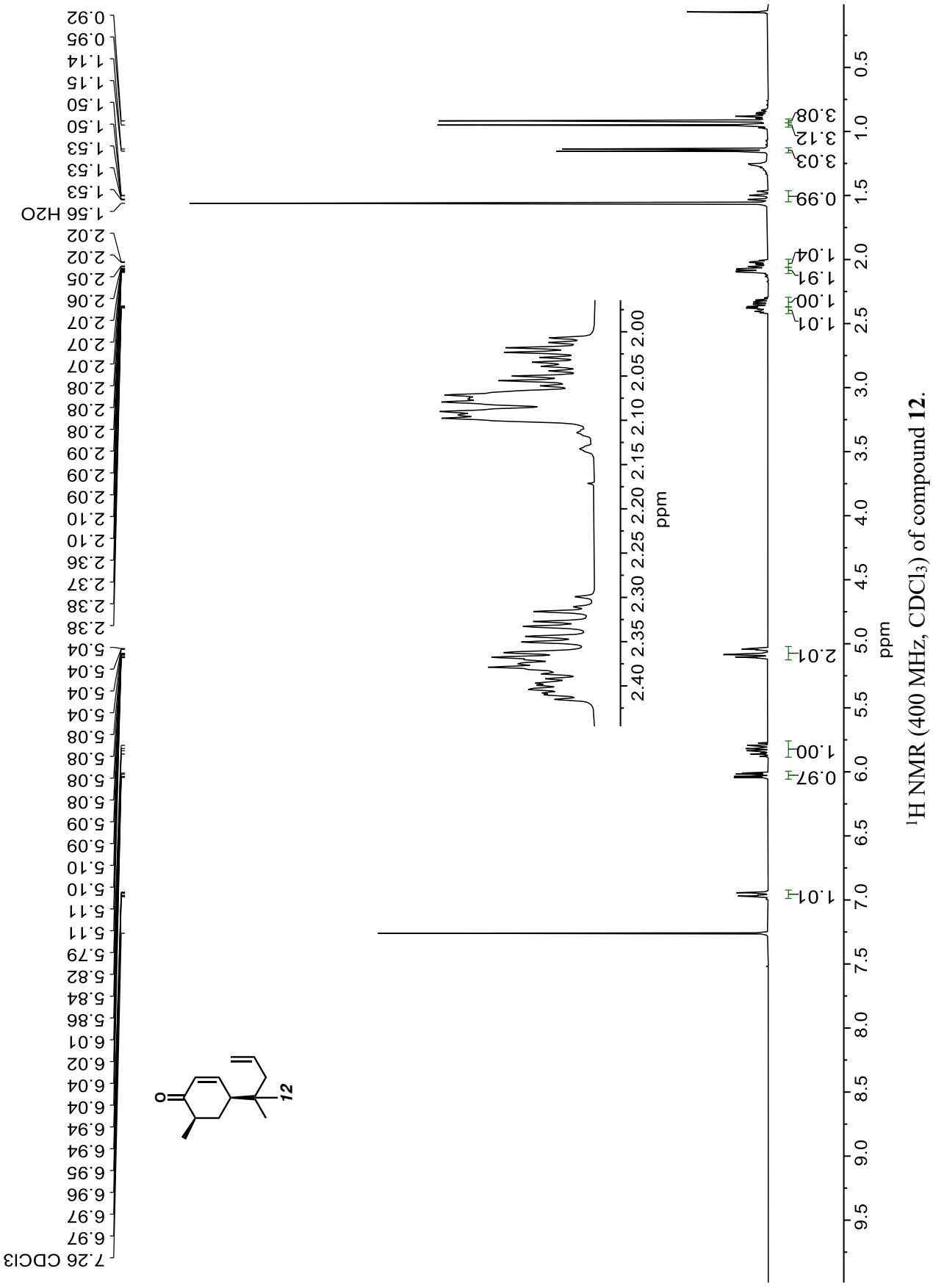
^{1}H NMR (400 MHz, $CDCl_3$) of compound **13**.



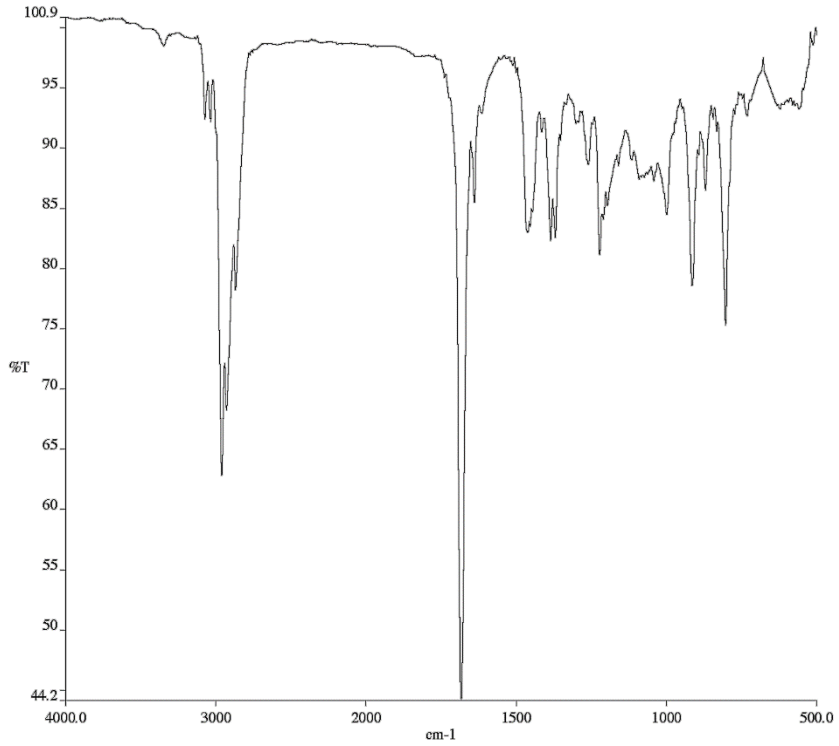
Infrared spectrum (Thin Film, NaCl) of compound **13**.



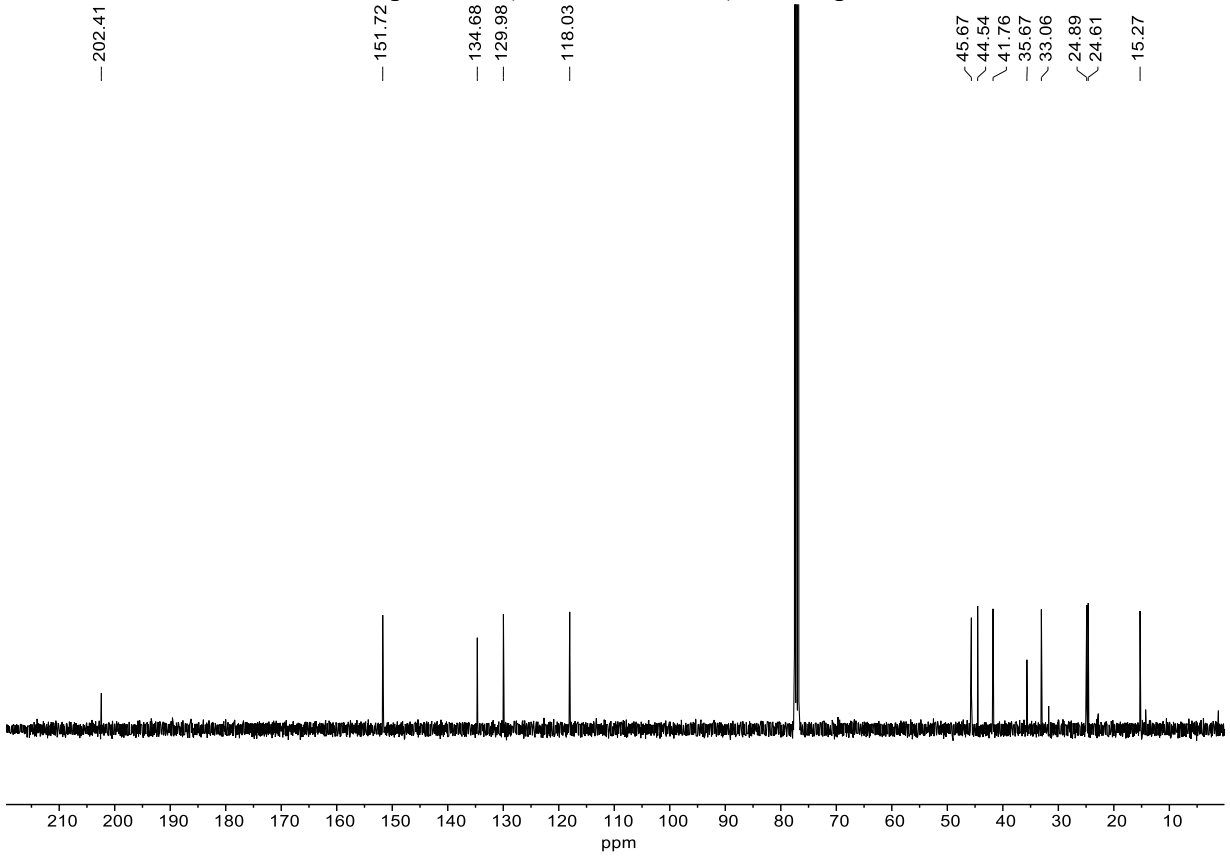
^{13}C NMR (100 MHz, $CDCl_3$) of compound **13**.



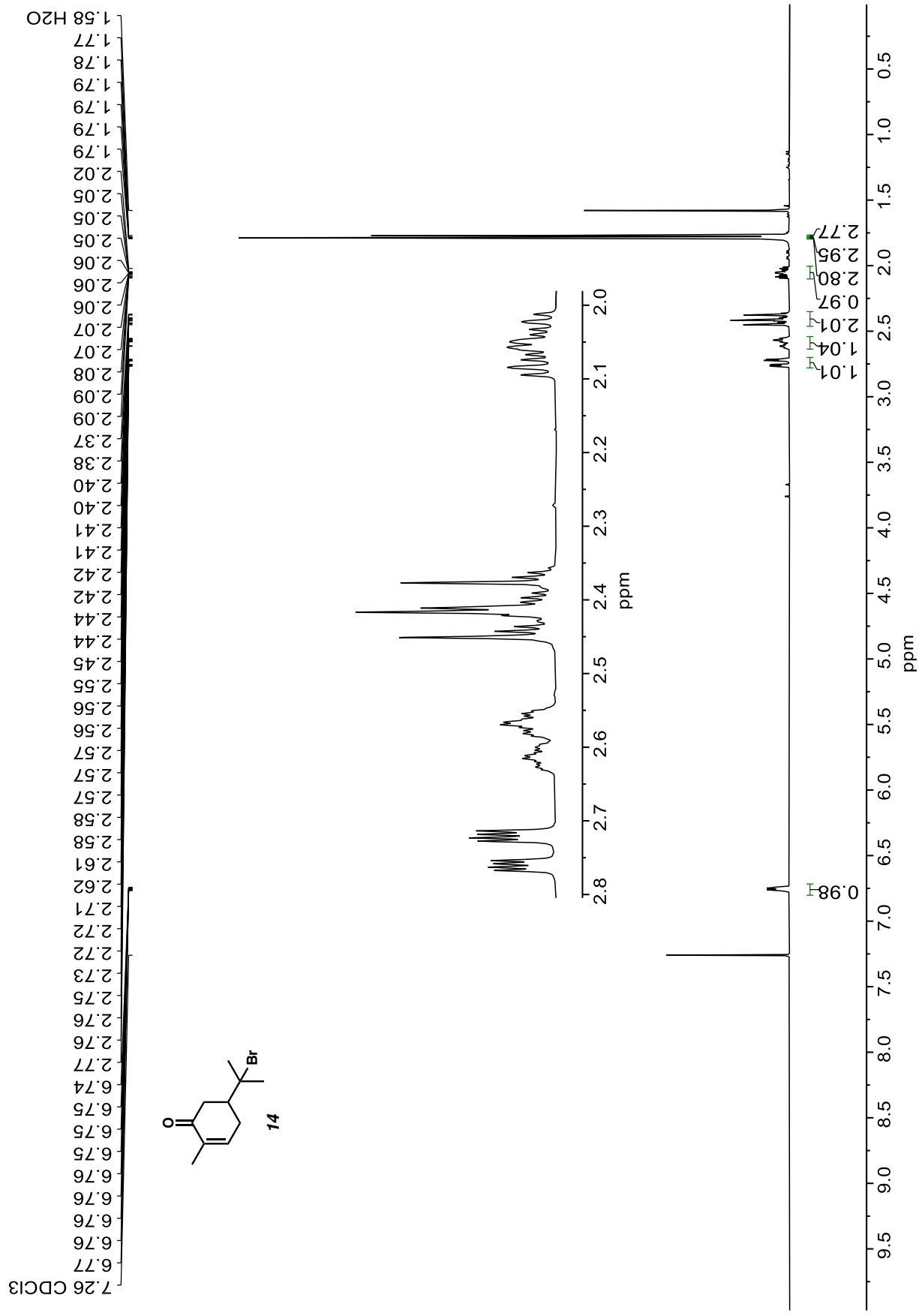
^{1}H NMR (400 MHz, $CDCl_3$) of compound **12**.



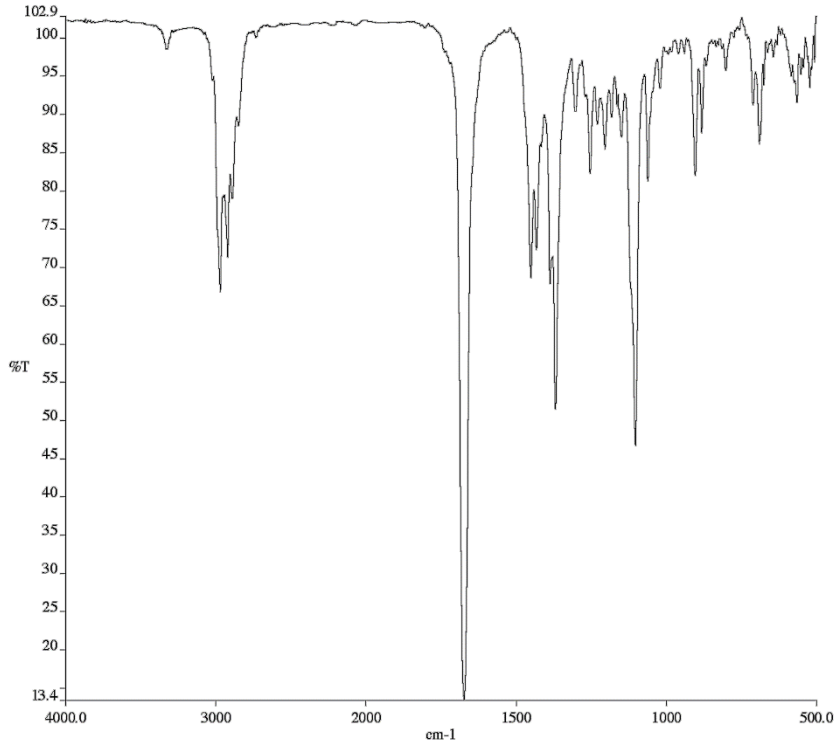
Infrared spectrum (Thin Film, NaCl) of compound **12**.



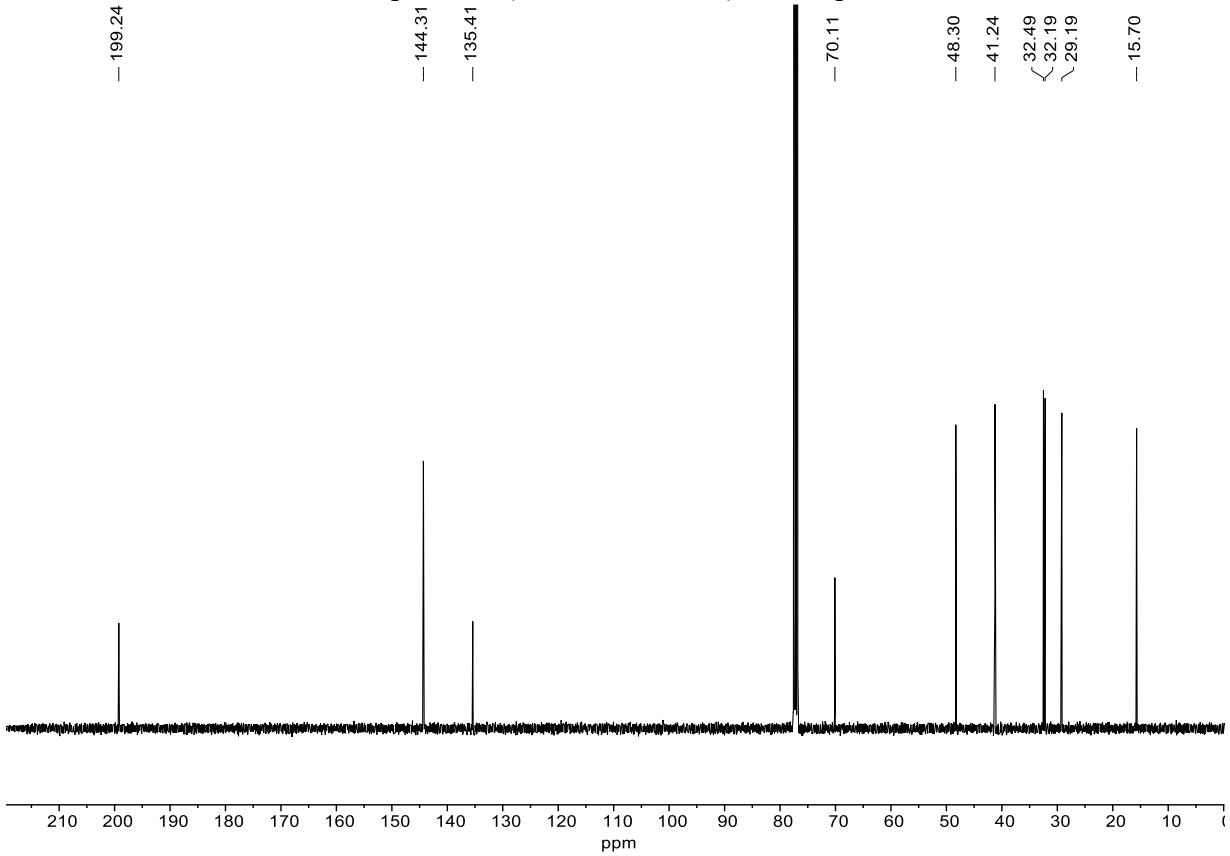
^{13}C NMR (100 MHz, $CDCl_3$) of compound **12**.



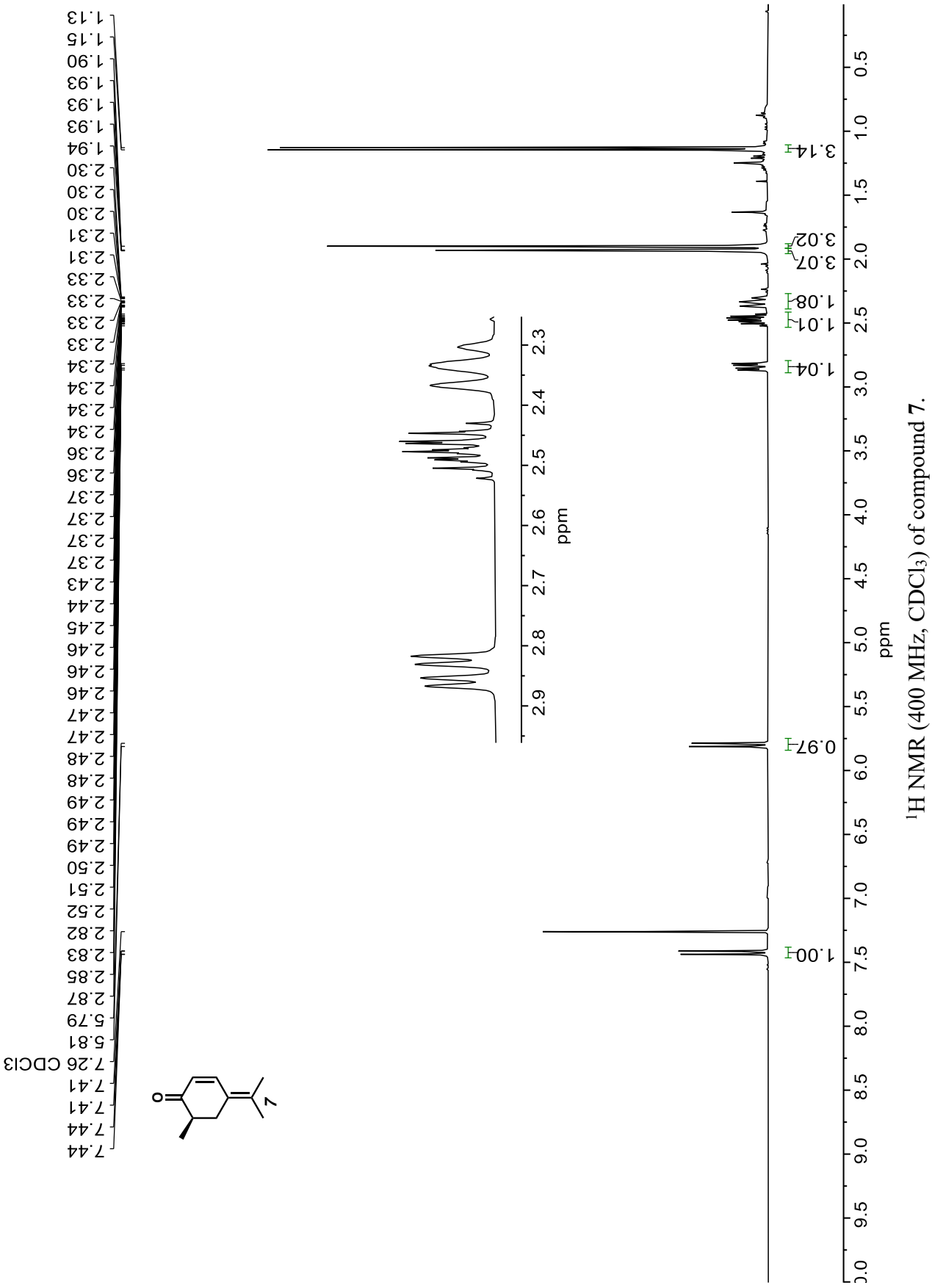
^{1}H NMR (400 MHz, $CDCl_3$) of compound **14**.



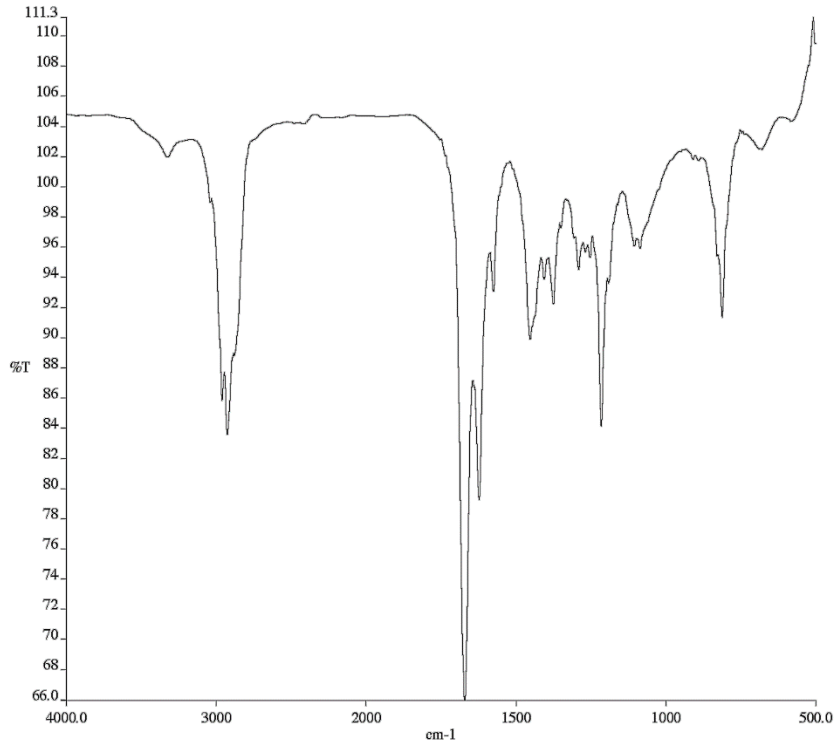
Infrared spectrum (Thin Film, NaCl) of compound **14**.



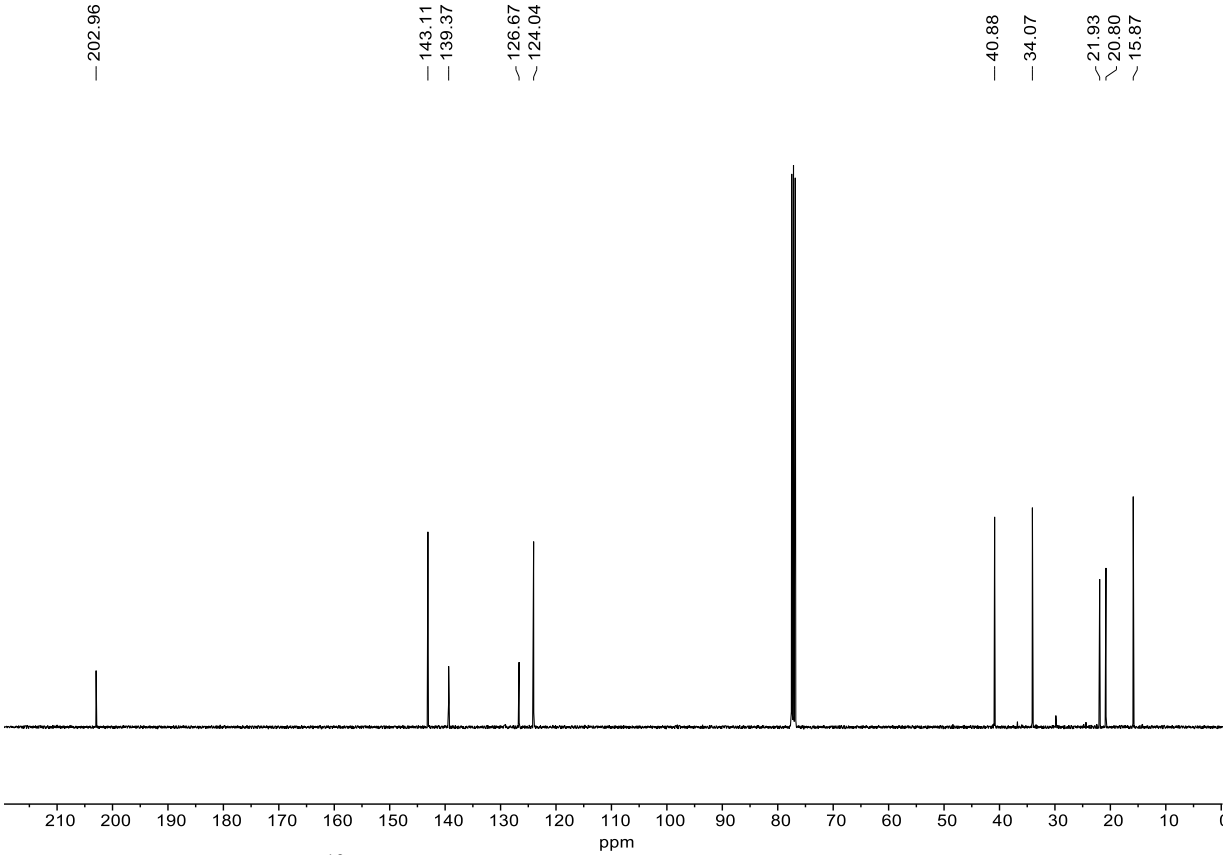
^{13}C NMR (100 MHz, $CDCl_3$) of compound **14**



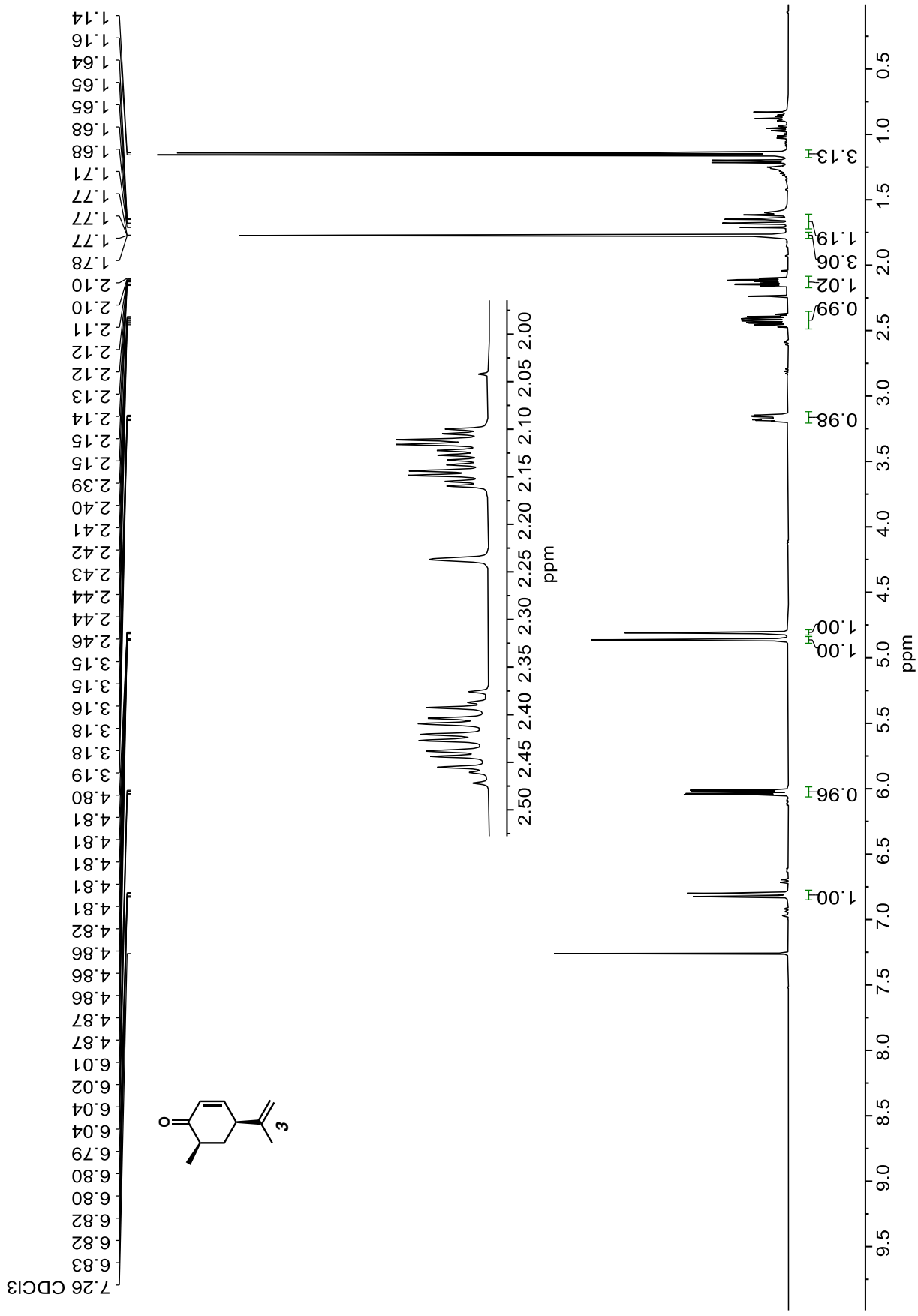
^{1}H NMR (400 MHz, $CDCl_3$) of compound **7**.



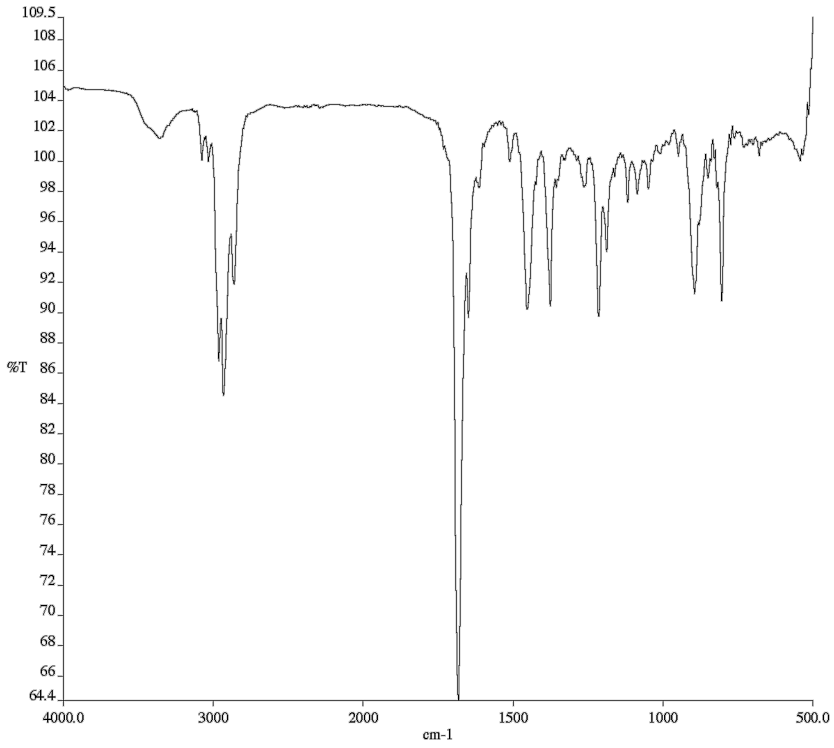
Infrared spectrum (Thin Film, NaCl) of compound **7**.



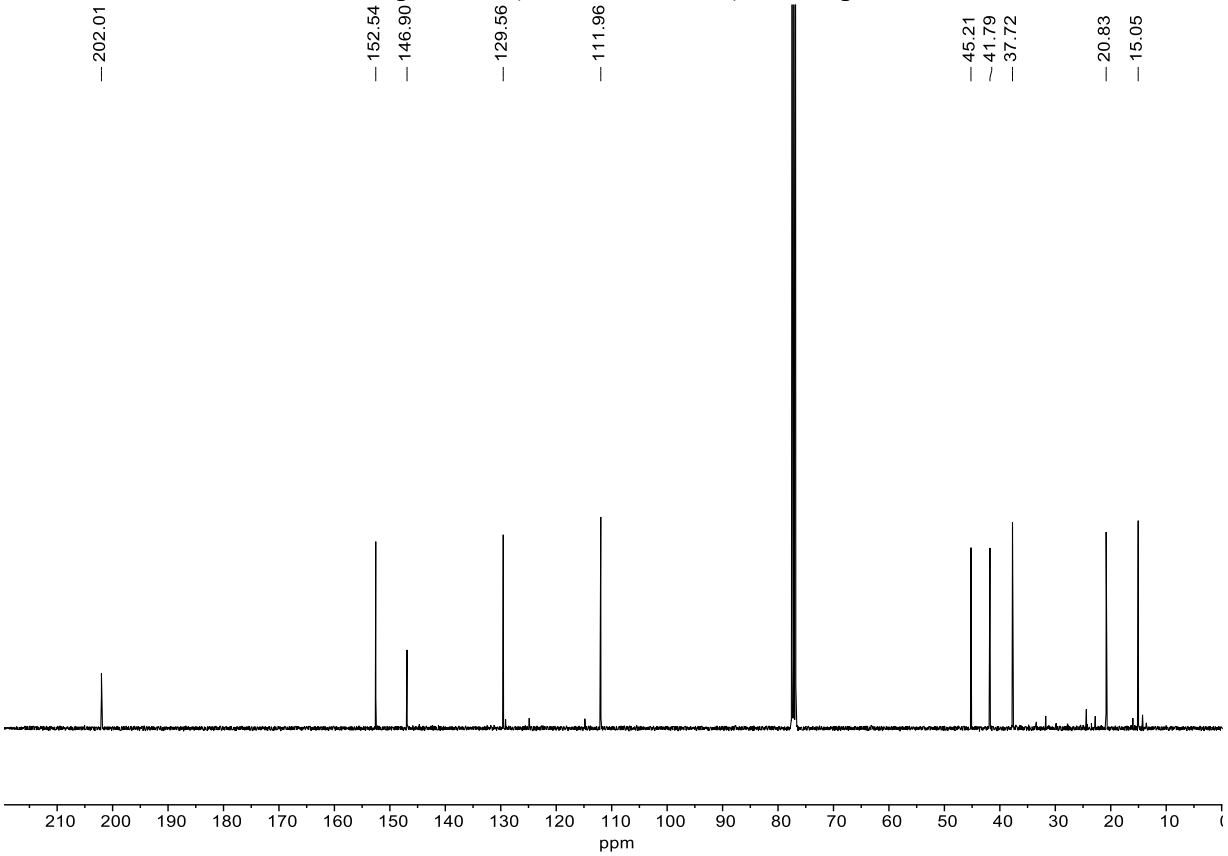
^{13}C NMR (100 MHz, $CDCl_3$) of compound **7**.



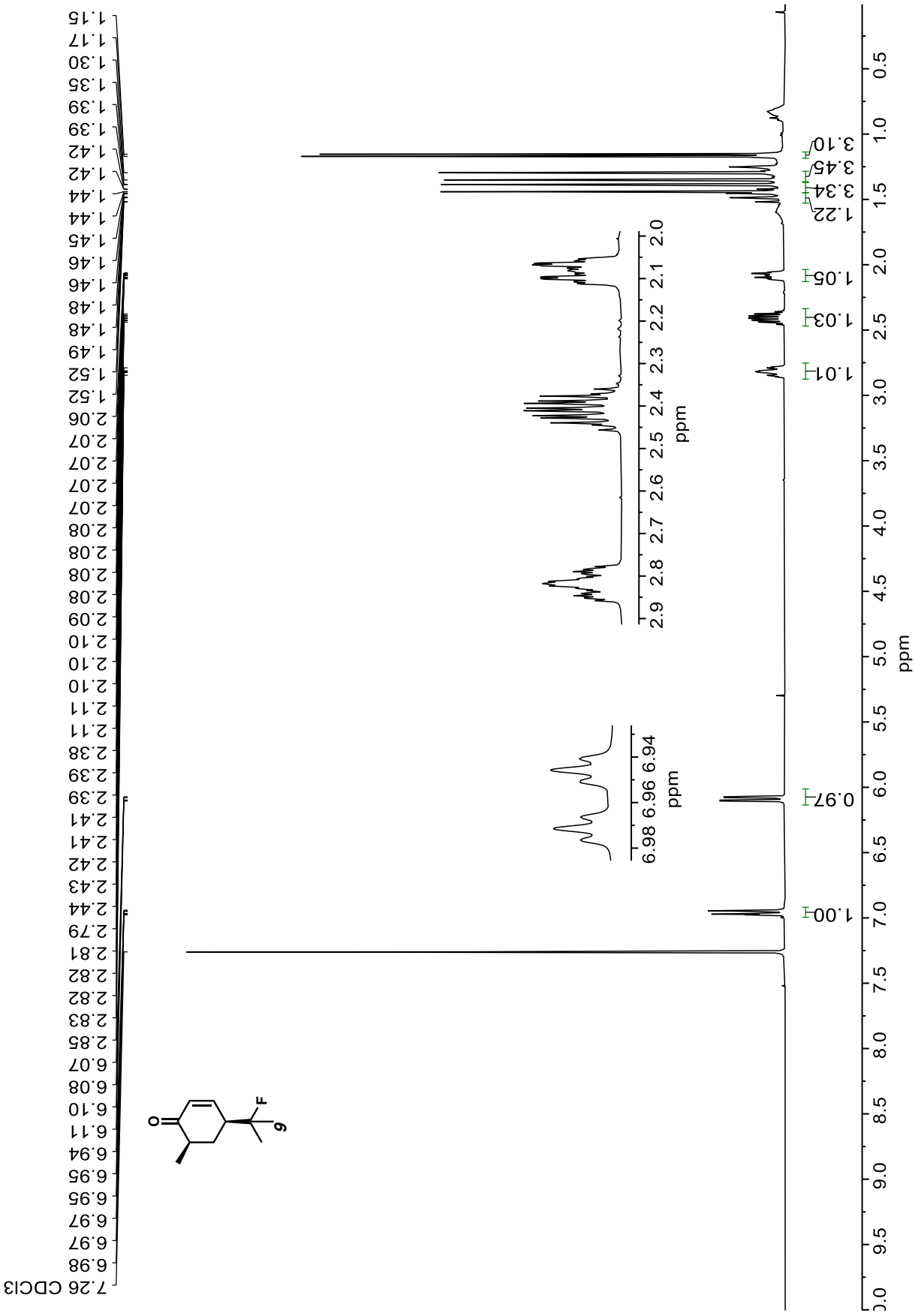
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3**.



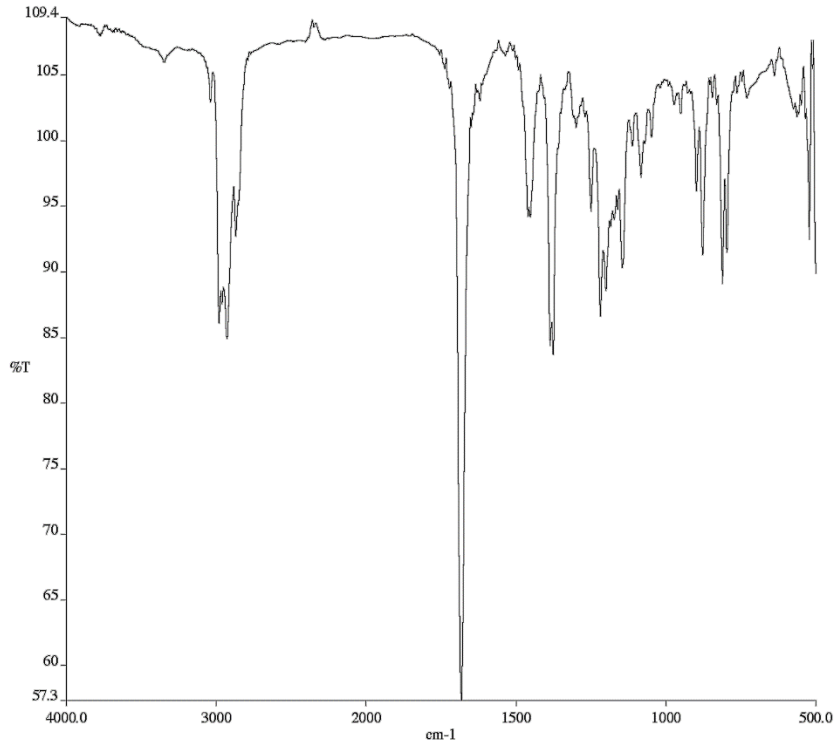
Infrared spectrum (Thin Film, NaCl) of compound **3**.



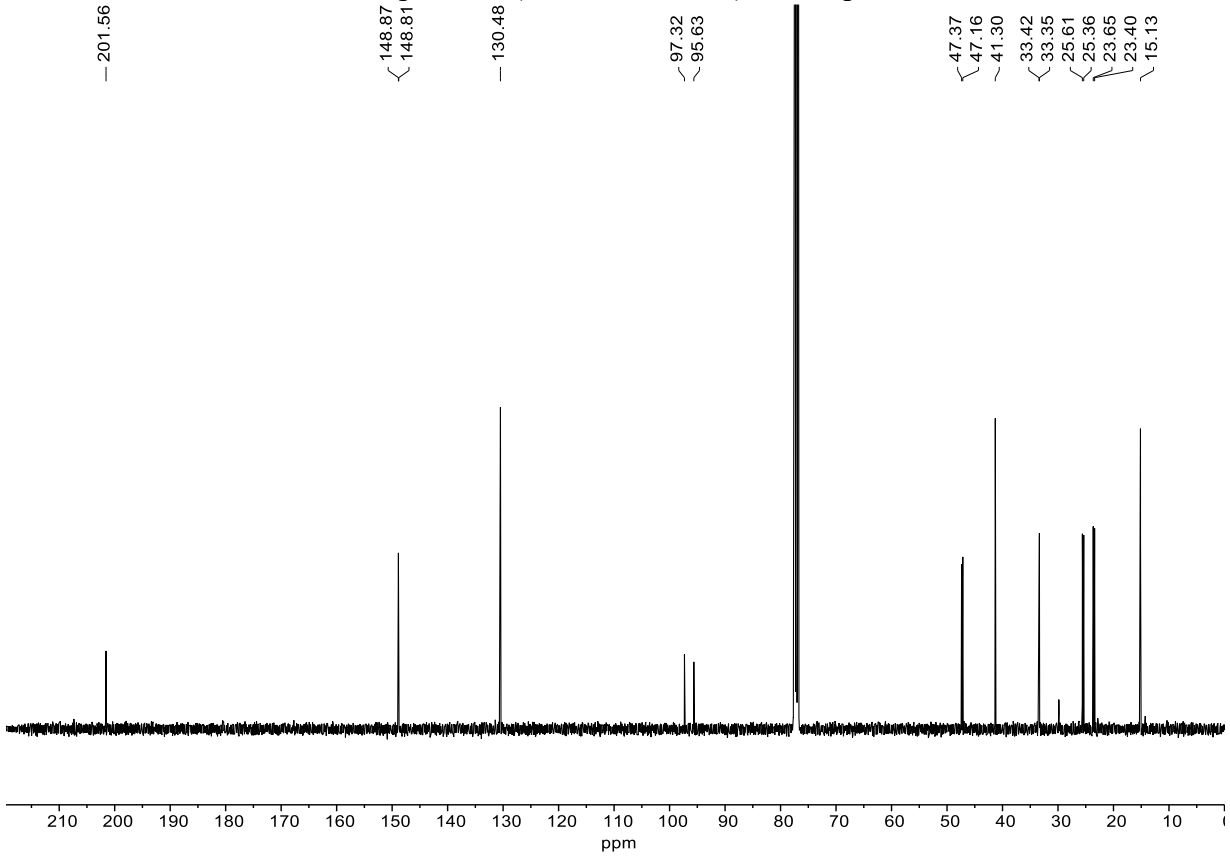
^{13}C NMR (100 MHz, $CDCl_3$) of compound **3**.



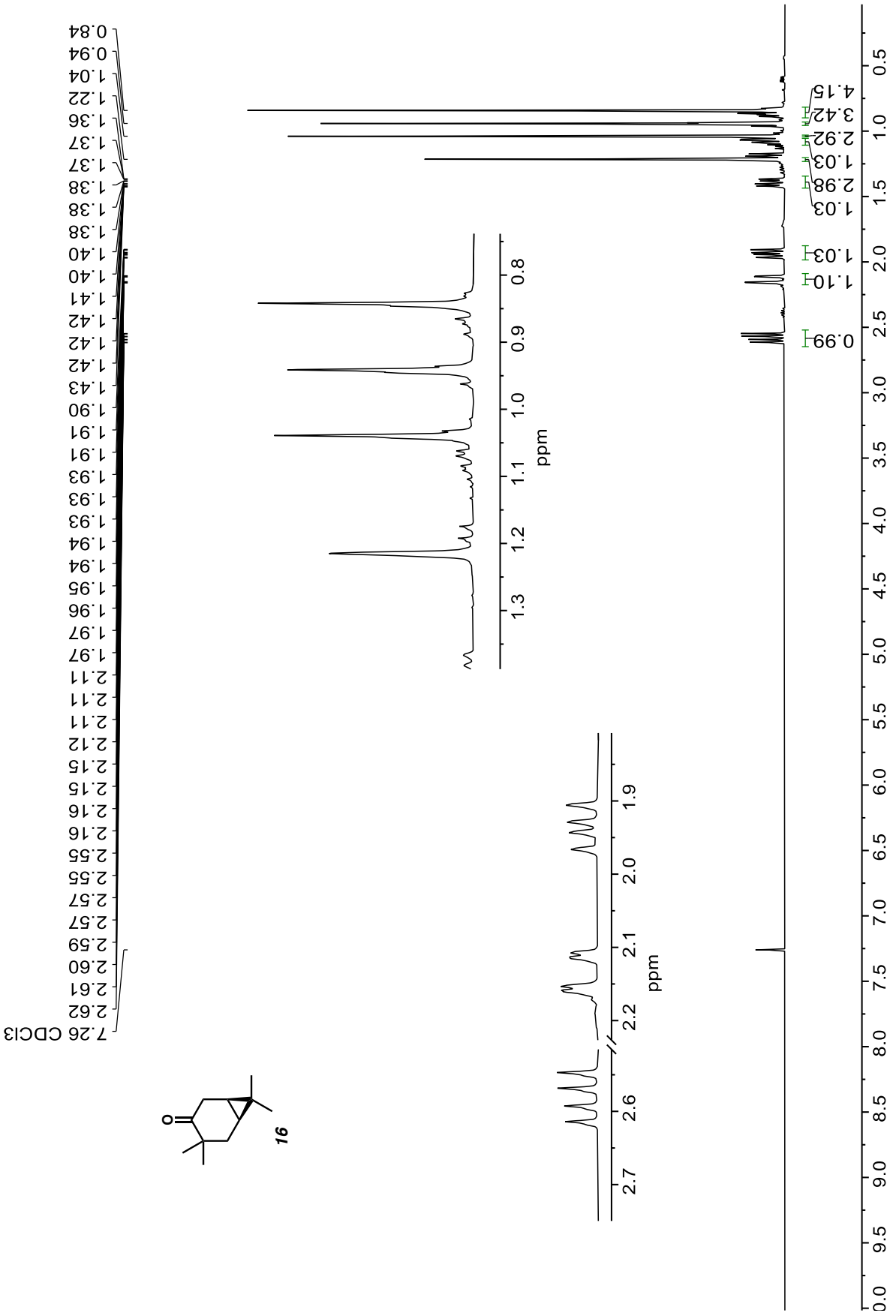
^{1}H NMR (400 MHz, $CDCl_3$) of compound **9**.



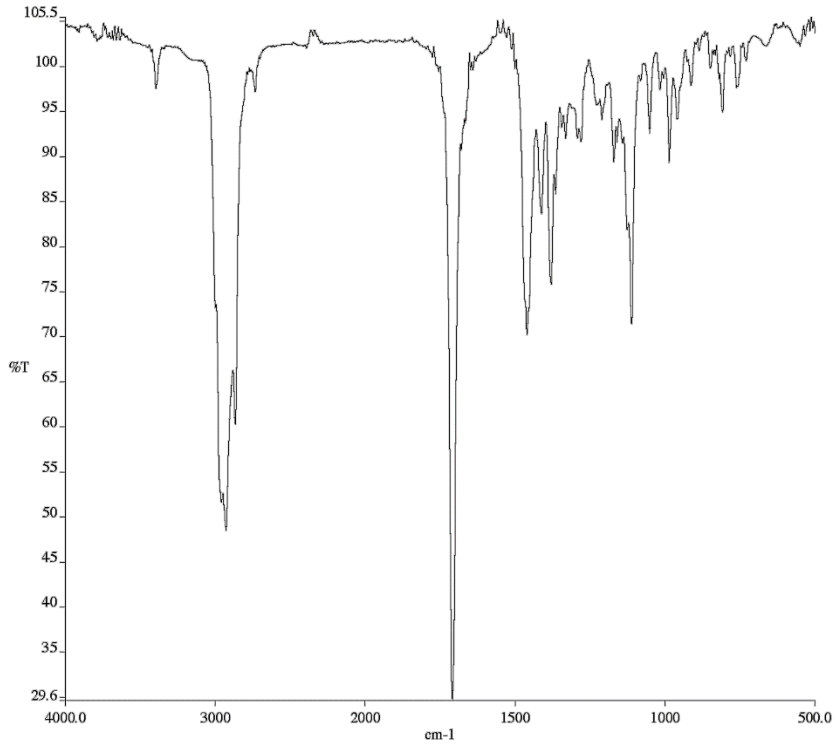
Infrared spectrum (Thin Film, NaCl) of compound **9**.



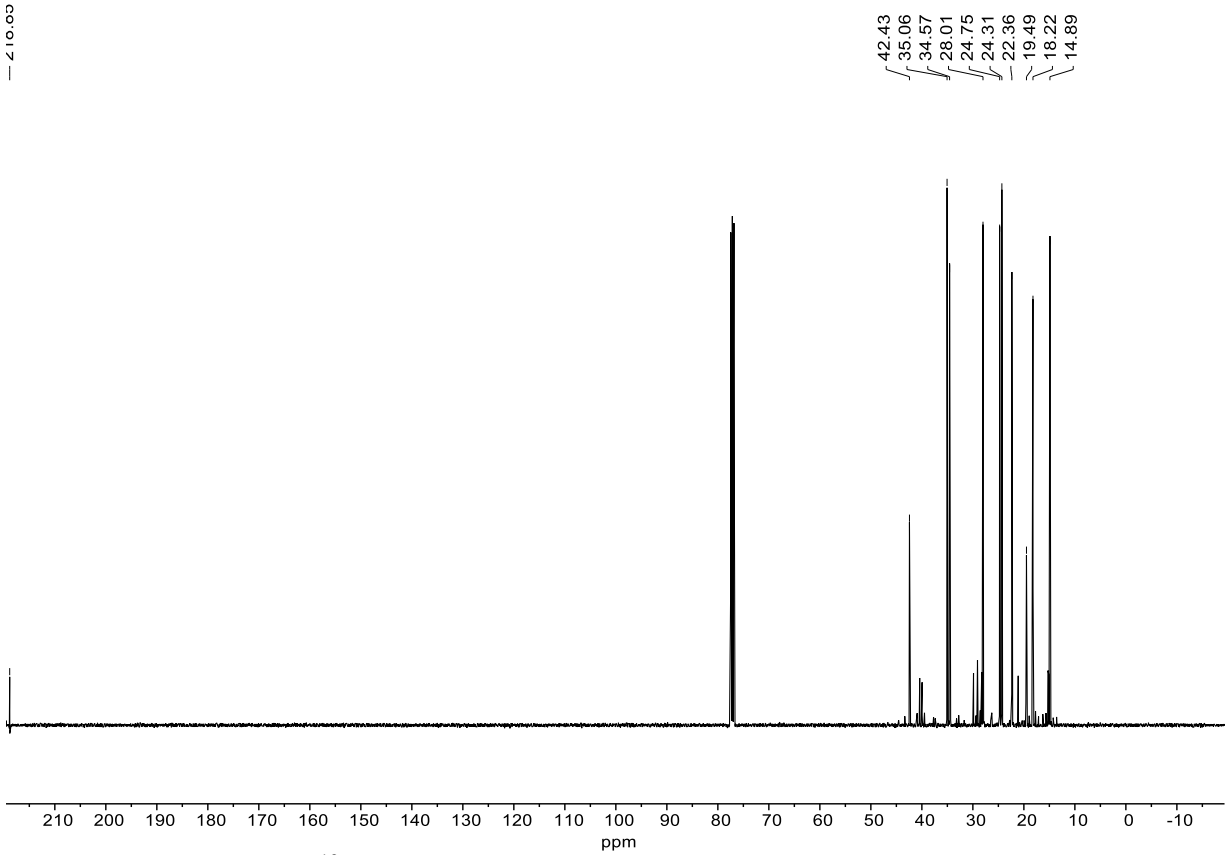
^{13}C NMR (100 MHz, $CDCl_3$) of compound **9**.



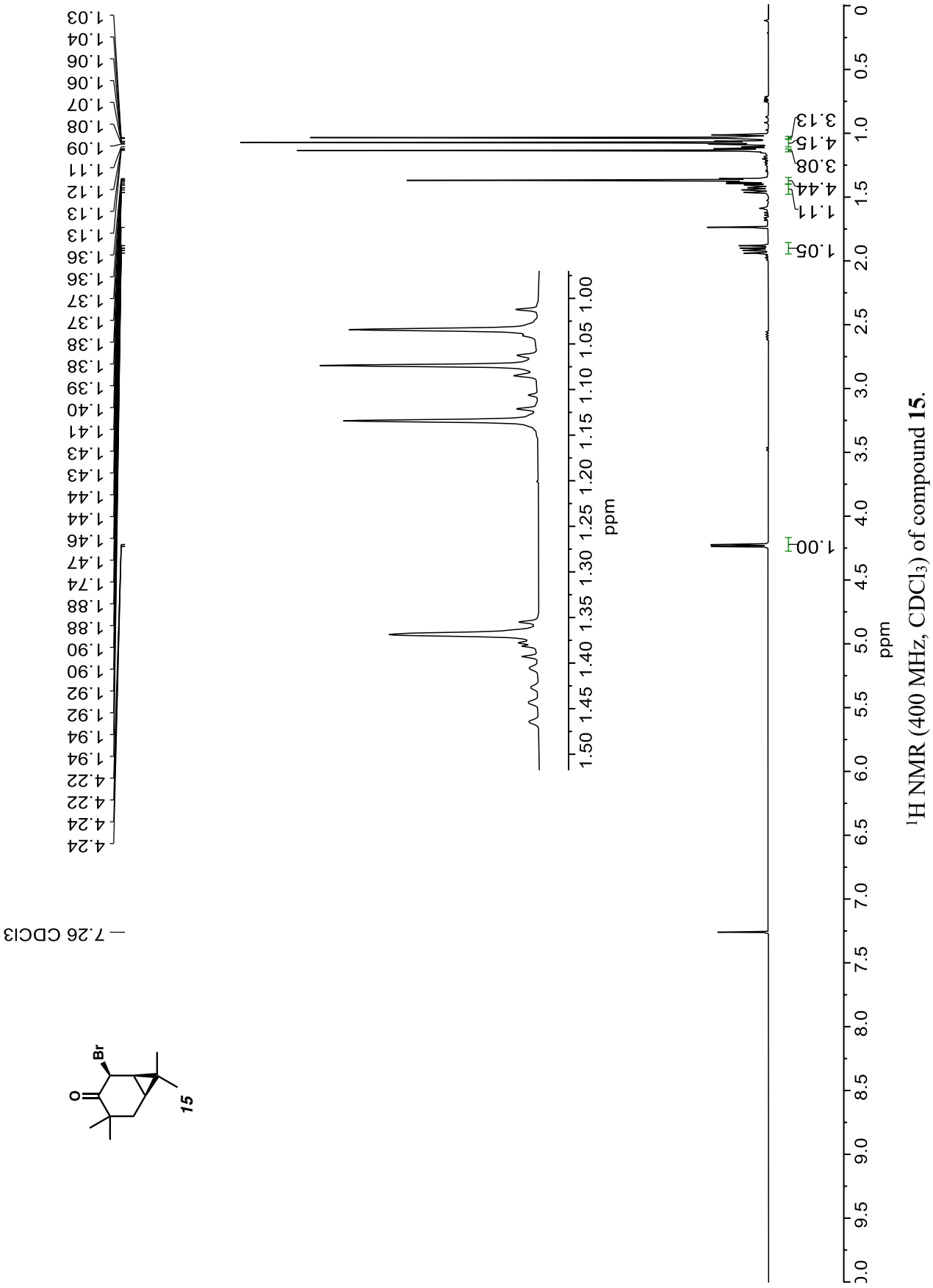
^{1}H NMR (400 MHz, $CDCl_3$) of compound **16**.



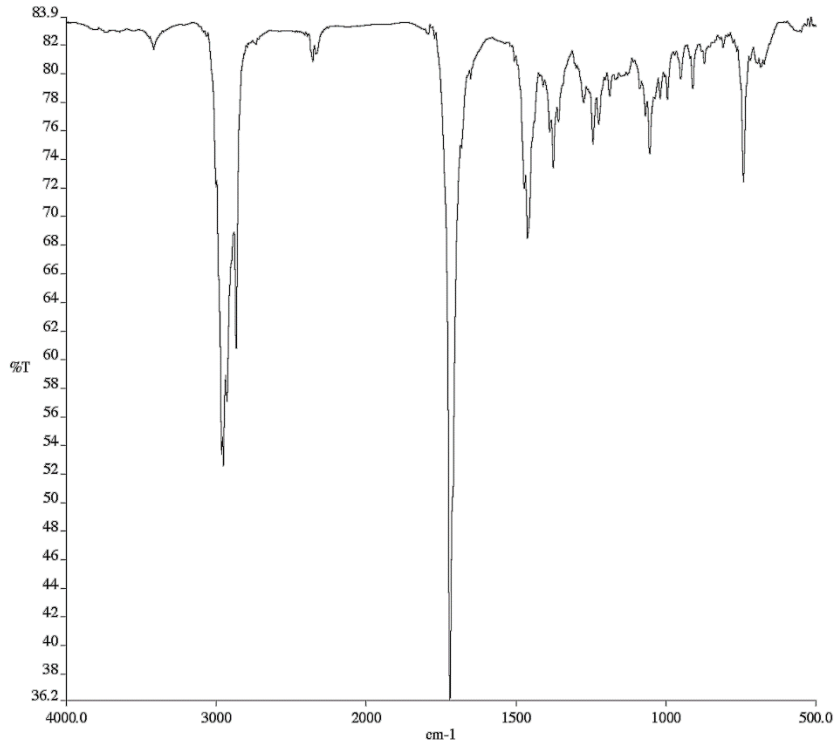
Infrared spectrum (Thin Film, NaCl) of compound **16**.



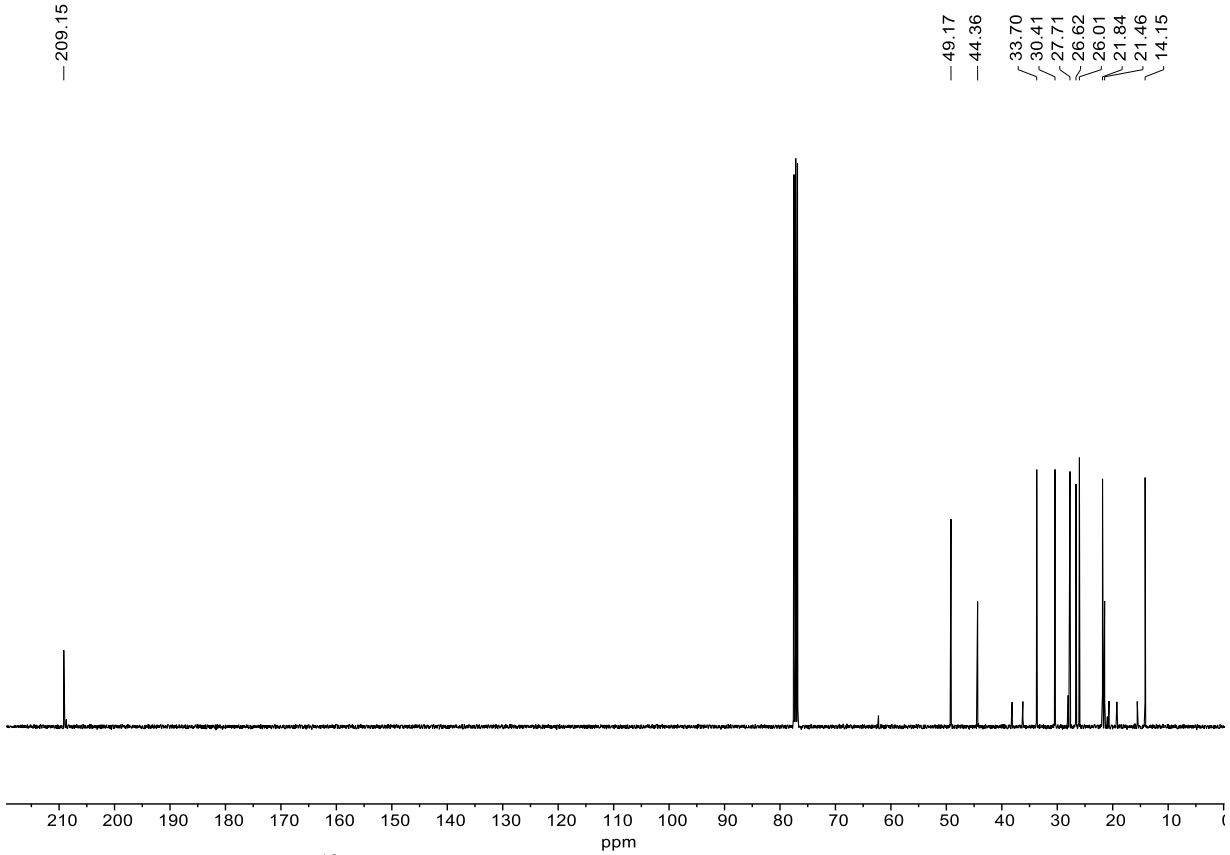
^{13}C NMR (100 MHz, $CDCl_3$) of compound **16**.



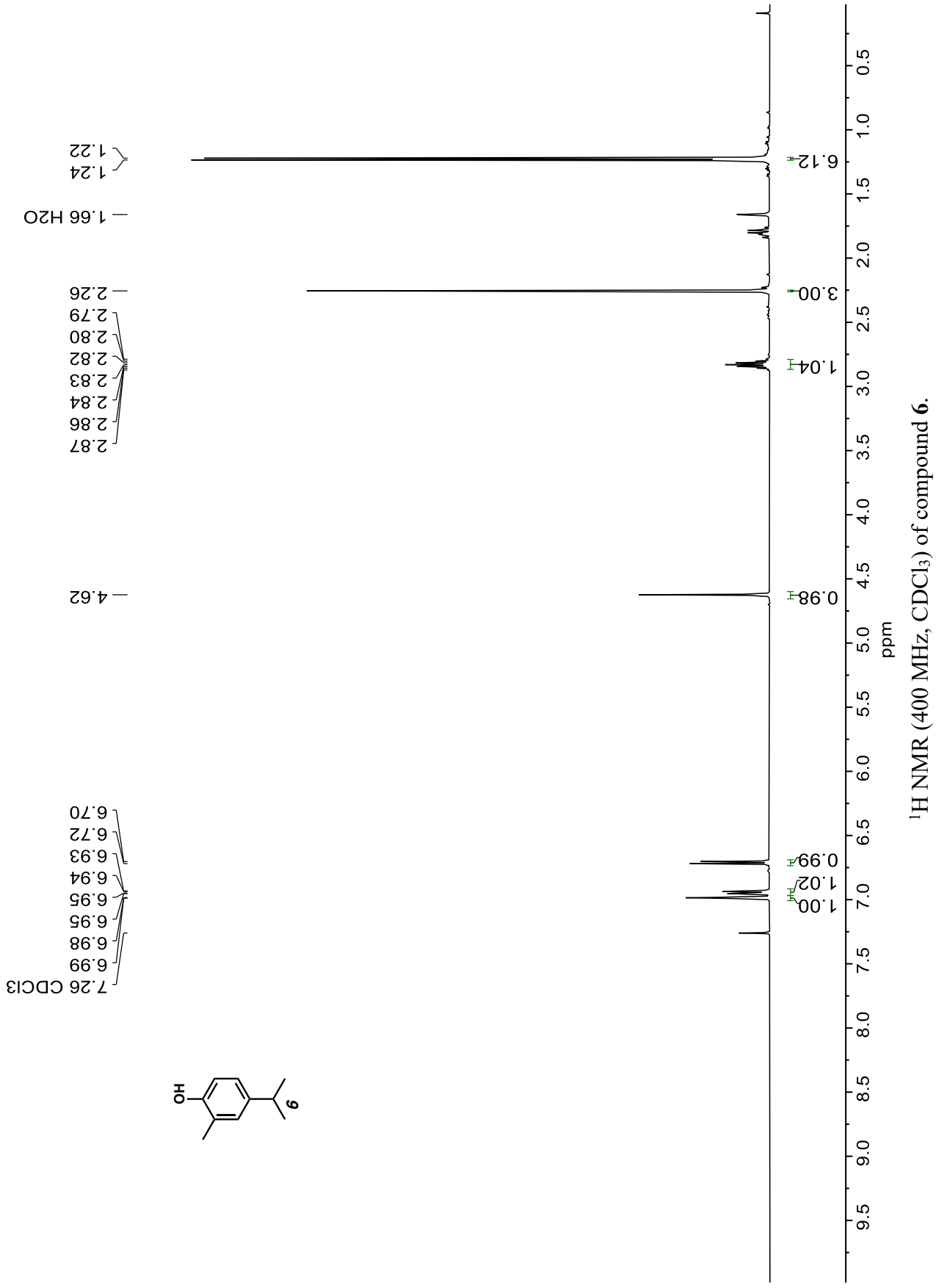
^{1}H NMR (400 MHz, $CDCl_3$) of compound **15**.



Infrared spectrum (Thin Film, NaCl) of compound **15**.



^{13}C NMR (100 MHz, $CDCl_3$) of compound **15**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **6**.