Advanced Synthesis & Catalysis

Supporting Information

An Efficient Protocol for the Palladium-catalyzed Asymmetric Decarboxylative Allylic Alkylation Using Low Palladium Concentrations and a Palladium(II) Precatalyst

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Materials and Methods. 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 unless otherwise noted. Sure/Seal™ bottles of *t*-AmylOH, EtOH and acetone were purchased from Aldrich and stored in a glove box. EtOAc was distilled over K_2CO_3 under an atmosphere of nitrogen, sparged with nitrogen for 30 min and stored in a glove box. $Pd(OAc)_2$ was purchased from Aldrich and stored in a glove box. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was purchased from Strem and stored in a glove box. Tetrabutylammonium difluorotriphenylsilicate (TBAT) was purchased from Sigma-Aldrich, triturated twice with EtOAc under a cone of argon, dried for 24 h in vacuo (0.30 torr) and stored in a glove box. (*S*)-*t*-BuPHOX[1] and (*S*)-$(CF_3)_3$-*t*-BuPHOX[2] were prepared by known methods and stored in a glove box. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, $KMnO_4$, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OJ-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 220 or 254 nm. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralcel (OD-H or OJ-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 210 or 254 nm. Analytical achiral GC was performed with an Agilent 6890 Series GC utilizing an HP-5 column (30 m x 0.25 mm). GC yields are reported relative to an internal standard of tridecane and fitted to a calibration curve. Analytical chiral GC performed with an Agilent 6850 Series GC utilizing a G-TA column (22 m x 0.25 mm). Optical rotations were measured with a Jasco P-2000 polarimeter at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian MR 400 (at 400 MHz and 101 MHz, respectively), and are reported relative to residual protio solvent ($CDCl_3$ = 7.26 and 77.0 ppm, respectively). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). IR

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[1] M. R. Krout, J. T. Mohr, B. M. Stoltz, *Org. Synth.*, **2009**, *86*, 181–193.

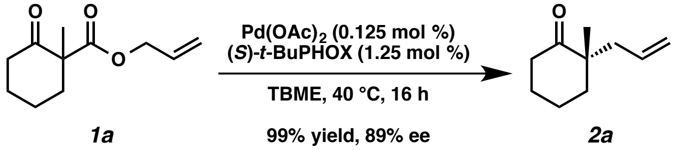
[2] N. T. McDougal, J. Streuff, H. Mukherjee, S. C. Virgil, B. M. Stoltz, *Tetrahedron Lett.*, **2010**, *51*, 5550–5554.

spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in electron ionization (EI+) mode.

Low Pd-Loading Allylic Alkylation Reactions

General Method

In a nitrogen-filled glove box, $Pd(OAc)_2$ (1.1 mg, 4.9 µmol) was weighed into a 20 mL scintillation vial and dissolved in TBME (20 mL). In a separate 1-dram vial, (*S*)-*t*-BuPHOX (1.9 mg, 4.9 µmol) was dissolved in TBME (1 mL). To a 2-dram vial equipped with a magnetic stirbar, 1.02 mL of the $Pd(OAc)_2$ solution was added (56 µg, 0.25 µmol, 0.125 mol %) followed by 0.51 mL of the (*S*)-*t*-BuPHOX solution (0.97 mg, 2.5 µmol, 1.25 mol %). This mixture was stirred at ambient temperature (28 °C) in the glove box for 30–40 min. Substrate (0.20 mmol, 1.0 equiv) was taken up in TBME (0.5 mL) and added to the stirring catalyst solution. For reactions analyzed by GC, tridecane (24 µL, 0.1 mmol, 0.5 equiv) was added. The reaction was sealed with a Teflon-lined cap, removed from the glove box and stirred at the indicated temperature for the indicated period of time. At this point, the reaction was analyzed by GC, or passed through a silica plug, concentrated in vacuo, and purified by column chromatography.



(*S*)-2-allyl-2-methylcyclohexan-1-one (2a). RF = Synthesized according to the general method from cyclohexanone **1a**.[3] The reaction was passed through a plug of SiO_2 and analyzed by GC (99% yield). The product could be isolated by column chromatography (SiO_2, 5% Et_2O in pentane) as a colorless oil and matched previously reported characterization data:[3] ^1H NMR (300 MHz, $CDCl_3$) δ 5.75-5.61 (m, 1H), 5.05 (s, 1H), 5.01 (m, 1H), 2.40-2.31 (m, 3H), 2.21 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.78 (m, 5H), 1.56 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 133.7, 117.9, 48.4, 41.9, 38.8, 38.5, 27.4,

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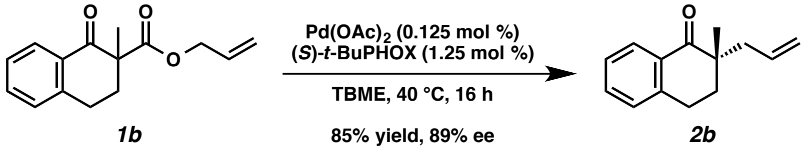
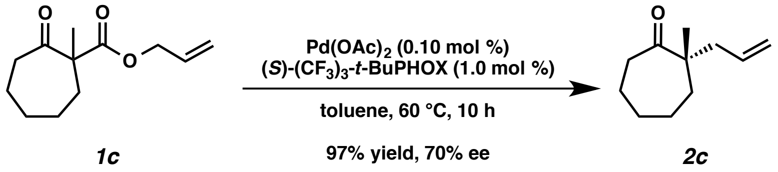
[3] D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.*, **2004**, *126*, 15044–15045.

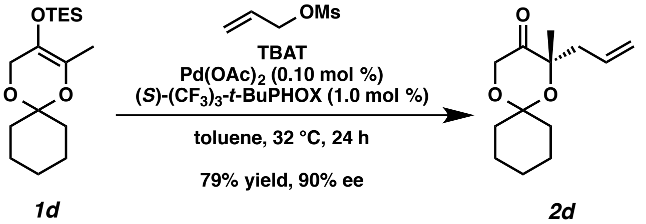
22.6, 21.0; IR (Neat Film NaCl) 2934, 2865, 1707, 1451, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1204; $[\alpha]_D^{28}$ –22.90° (*c* 2.09, hexane, 89 % ee).



(*S*)-2-allyl-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (2b). Synthesized according to the general method from tetralone **1b**.[3] Product was isolated by column chromatography (SiO_2, 5–10% Et_2O in hexanes) as a pale yellow oil (85% yield) and matched previously reported characterization data:[3] ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.45 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.29 (app. t, *J* = 7.2 Hz, 1H), 7.21 (app. d, *J* = 7.5 Hz, 1H), 5.85-5.71 (m, 1H), 5.10 (s, 1H), 5.05 (s, 1H), 2.97 (t, *J* = 6.3 Hz, 2H), 2.46 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.27 (ddt, *J* = 14.0, 7.5, 1.2 Hz, 1H), 2.07 (ddd, *J* = 13.4, 7.2, 6.0 Hz 1H), 1.89 (ddd, *J* = 14.0, 6.9, 5.7 1H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 143.2, 133.9, 133.0, 131.5, 128.6, 127.9, 126.5, 118.1, 44.5, 41.0, 33.2, 25.3, 21.8; IR (Neat Film NaCl) 3073, 2930, 1682, 1455, 1220, 916, 742 cm^{-1}; HRMS *m/z* calc'd for $C_{14}H_{16}O$ $[M]^+$: 200.1201, found 200.1194; $[\alpha]_D^{27}$ –18.59° (*c* 2.08, hexane, 88 % ee).



(*S*)-2-allyl-2-methylcycloheptan-1-one (2c). Synthesized according to the general method from cycloheptanone **1c**[3] using 1.0 mol % (*S*)-*t*-BuPHOX and 0.10 mol % $Pd(OAc)_2$ in toluene at 60 °C for 10 h. Product was isolated by column chromatography (SiO_2, 3% Et_2O in pentane) as a colorless oil (97% yield) and matched previously reported characterization data:[3] ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (ddt, *J* = 16.8, 10.2, 7.5, 1H), 5.02 (m, 2H), 2.59 (app. td, *J* = 11.1, 2.7 Hz, 1H), 2.42 (app. t, *J* = 9.0 Hz, 1H), 2.24 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.16 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.78-1.30 (m, 8H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.4, 133.8, 117.9, 50.8, 43.6, 40.6, 36.6, 30.6, 26.4, 24.4, 22.3; IR (Neat Film NaCl) 2930, 1702, 1458 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{18}O$ [M]$^+$: 166.1358, found 166.1360; $[\alpha]_D^{28}$ –34.70° (*c* 1.52, hexane, 87 % ee).



(*S*)-2-allyl-2-methyl-1,5-dioxaspiro[5.5]undecan-3-one (2d). A 20 mL vial was soaked in a 20:1 isopropanol:toluene bath saturated with potassium hydroxide for 12 h, rinsed with deionized water, acetone, and dried in a 120 °C oven overnight. The hot vial was the cycled into a nitrogen-filled glovebox and allowed to cool to ambient temperature. The vial was then charged $Bu_4NPh_3SiF_2$ (TBAT, 184 mg, 0.34 mmol, 1.00 equiv) and toluene (12.0 mL, 0.033 M) with stirring, followed by $Pd(OAc)_2$ (0.10 mg, 0.0004 mmol, 1.0 mg/mL in toluene, 0.00125 equiv) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (2.37 mg, 0.004 mmol, 10 mg/mL in toluene, 0.0125 equiv). The reaction vessel was immediately introduced to a heat block at 32 °C and allowed to stir for 20 minutes. To the resulting tan solution was added allylmesylate[4] (57 mg, 0.42 mmol, 1.20 equiv) quickly dropwise. After 3 minutes, silyl enol ether **1d**[5] (100 mg, 0.34 mmol, 1.00 equiv) was added quickly dropwise. Upon complete consumption of the enol ether (as determined by TLC analysis, 24 h), the resultant tan solution was removed from the heat block, allowed to cool to ambient temperature, and removed from the glove box. The reaction mixture was filtered through a pad of SiO_2 using hexanes eluent to remove toluene, followed by Et_2O eluent to isolate the volatile reaction products. The filtrate was concentrated in vacuo to a brown oil which was subsequently purified by flash chromatography (SiO_2, 4% Et_2O in hexanes) to afford volatile allyl ketal **2d** (60 mg, 79% yield) as a clear, colorless oil: R_f = 0.35 (19:1 hexanes:Et_2O); ^1H NMR (400 MHz, $CDCl_3$), 5.85 (ddt, *J* = 17.4, 10.3, 7.2 Hz, 1H), 5.14–5.03 (m, 2H), 4.20 (d, *J* = 1.0 Hz, 2H), 2.51 (ddt, *J* = 14.0, 7.2, 1.2 Hz, 1H), 2.41 (ddt, *J* = 14.0, 7.2, 1.2 Hz, 1H), 1.87–1.42 (m, 10H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$), 211.4, 132.7, 118.8, 100.0, 82.0, 66.6, 44.0, 35.8, 35.5, 25.4, 24.7, 23.1,

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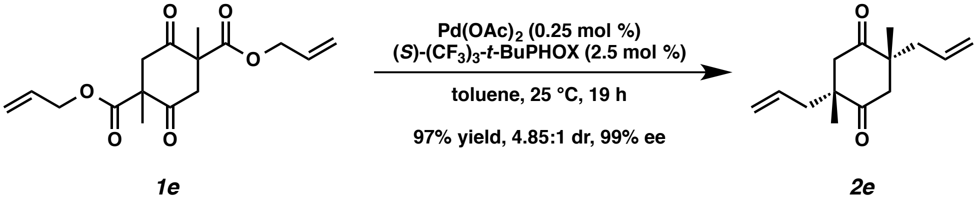
[4] a) I. N. Mykola, H. Wolfgang, S. Martin, B. Andreas, S. Jens, K. Karsten, M. Thorsten, B. Peter, F. Walter, Production of Compounds Comprising CF30 groups. U.S. Patent # 2011082312 A1, April 7, 2011; b) S. Dykstra, H. S. Mosher, *J. Am. Chem. Soc.* **1957**, *79*, 3474–3475.

[5] R. A. Craig, II, J. L. Roizen, R. C. Smith, A. C. Jones, B. M. Stoltz, *Org. Lett.*, **2012**, *14*, 5716–5719.

23.1; IR (Neat Film, NaCl) 2938, 2860, 1742, 1446, 1365, 1259, 1159, 1112, 1056, 1000, 943, 916, 826 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{13}H_{20}O_3$ $[M•]^+$: 224.1412, found 224.1409; $[\alpha]_D^{25.0}$–45.9° (*c* 1.10, $CHCl_3$, 90% ee).



(2*R*,5*R*)-2,5-diallyl-2,5-dimethylcyclohexane-1,4-dione (2e). Synthesized according to the general method from diketone **1e**[6] using 2.5 mol % (*S*)-$(CF_3)_3$-*t*-BuPHOX and 0.25 mol % $Pd(OAc)_2$ in toluene at 25 °C for 19 h. Product was isolated by column chromatography (SiO_2, 3% EtOAc in hexanes) as a colorless oil (97% yield) and matched previously reported characterization data:[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (dddd, *J* = 18.3, 10.2, 6.9, 6.9 Hz, 2H), 5.17–5.09 (comp. m, 3H), 5.07–5.04 (m, 1H), 2.82 (d, *J* = 14.7 Hz, 2H), 2.38 (d, *J* = 15 Hz, 2H), 2.34 (app ddt, *J* = 13.2, 6.9, 1.0 Hz, 2H), 2.09 (app ddt, *J* = 13.5, 7.8, 0.9 Hz, 2H), 1.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.8, 132.4, 120.0, 49.4, 48.4, 43.8, 24.3; IR (Neat film, NaCl) 3078, 2978, 1712, 1640, 1458, 1378, 1252, 1129, 1101, 998, 921 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{20}O_2$ $[M]^+$: 220.1463, found 220.1466; $[\alpha]^{25}_D$ –163.1 (*c* 0.52, CH_2Cl_2). Chiral GC assay (GTA column): 100 °C isothermal method over 90 min. Retention times: 67.7 min (Major enantiomer, *C*$_2$ diastereomer, 81.7%), 74.1 min (Minor enantiomer, *C*$_2$ diastereomer, 0.6%), 77.4 min (*meso* diastereomer, 17.6%). Achiral GC assay (DB-Wax column): 100 °C isotherm over 2.0 min, ramp 5 °C/min to 190 °C, then 190 °C isotherm for 10.0 min. Retention times: 18.5 min (*C*$_2$ diastereomer, 81.0%), 18.7 min (*meso* diastereomer, 19.0%).

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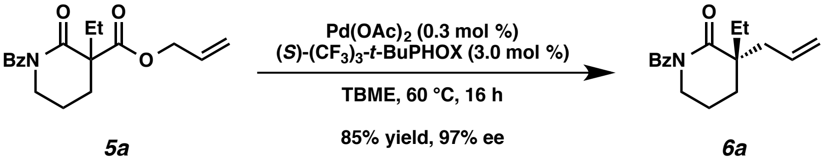
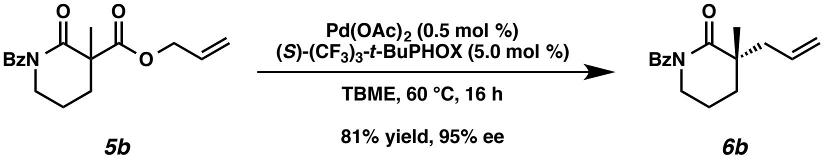
[6] J. A. Enquist, B. M. Stoltz, *Nature*, **2008**, *453*, 1228–1231.



(*S*)-3-allyl-1-benzoyl-3-ethylpiperidin-2-one (6a). Synthesized according to the general method from lactam **5a**[7] using 3.0 mol % (*S*)-$(CF_3)_3$-*t*-BuPHOX and 0.30 mol % $Pd(OAc)_2$. Product was isolated by column chromatography (SiO_2, 15–20% Et_2O in hexanes) as a colorless oil (85% yield) and matched previously reported characterization data:[7] R_f = 0.39 (20% Et_2O in hexanes); ^{1}H NMR (500 MHz, CDCl3) δ 7.53–7.49 (m, 2H), 7.48–7.43 (m, 1H), 7.41–7.34 (m, 2H), 5.74 (dddd, *J* = 16.7, 10.4, 7.6, 7.0 Hz, 1H), 5.19–5.02 (m, 2H), 3.84–3.70 (m, 2H), 2.51 (ddt, *J* = 13.8, 7.0, 1.3 Hz, 1H), 2.28 (ddt, *J* = 13.8, 7.6, 1.2 Hz, 1H), 2.06–1.91 (m, 2H), 1.91–1.74 (m, 3H), 1.74–1.63 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 178.0, 175.6, 136.7, 133.6, 131.2, 128.1, 127.4, 118.6, 47.4, 46.9, 41.3, 30.3 (2C), 19.6, 8.3; IR (Neat Film NaCl) 3072, 2970, 2941, 2880, 1678, 1448, 1384, 1283, 1147, 916, 725, 694 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found 272.1649; $[\alpha]_D^{25}$ –28.6° (c 1.15, $CHCl_3$, 99% ee).



(*S*)-3-allyl-1-benzoyl-3-methylpiperidin-2-one (6b). Synthesized according to the general method from lactam **5b**[7] using 5.0 mol % (*S*)-$(CF_3)_3$-*t*-BuPHOX and 0.50 mol % $Pd(OAc)_2$. Product was isolated by column chromatography (SiO_2, 5–10% Et_2O in hexanes) as a colorless oil (81% yield) and matched previously reported characterization data:[7] R_f = 0.55 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, CDCl3) δ 7.54–7.50 (m, 2H), 7.49–7.43 (m, 1H), 7.40–7.35 (m, 2H), 5.75 (dddd, *J* = 17.1, 10.2, 7.7, 7.0 Hz, 1H), 5.19–5.03 (m, 2H), 3.92–3.78 (m, 1H), 3.72 (ddt, *J* = 12.6, 6.4, 6.0, 1.2 Hz, 1H), 2.55 (ddt, *J* = 13.7, 7.0, 1.2 Hz, 1H), 2.29 (ddt, *J* = 13.7, 7.7, 1.1 Hz, 1H), 2.07–1.87 (m, 3H), 1.75–1.60 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 179.0, 175.3, 136.5, 133.3, 131.3, 128.1, 127.4,

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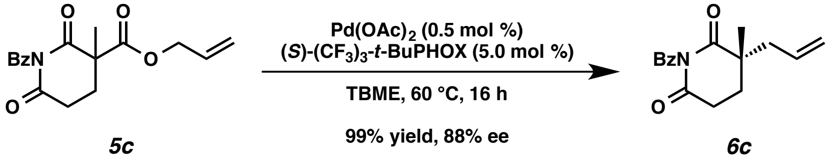
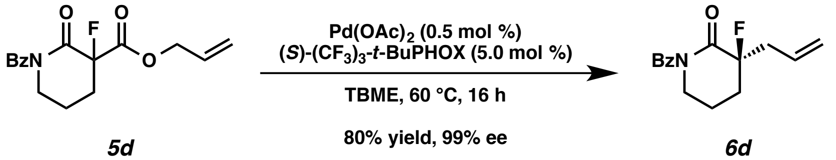
[7] D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nature Chem.*, **2012**, *4*, 130–133.

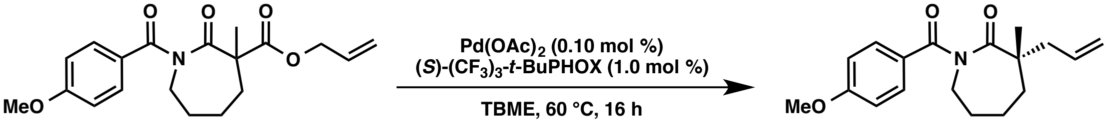
118.9, 47.1, 44.0, 43.3, 33.3, 25.1, 19.5; IR (Neat Film NaCl) 3074, 2939, 2870, 1683, 1478, 1449, 1386, 1282, 1151, 919, 726, 695 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1489, found 258.1491; $[\alpha]_D^{25}$ –91.2° (c 1.07, $CHCl_3$, 99% ee).



(*S*)-3-allyl-1-benzoyl-3-methylpiperidine-2,6-dione (6c). Synthesized according to the general method from imide **5c**[7] using 1.25 mol % (*S*)-$(CF_3)_3$-*t*-BuPHOX and 0.125 mol % $Pd(OAc)_2$. Product was isolated by column chromatography (SiO_2, 10–20% EtOAc in hexanes) as a colorless oil (99% yield) and matched previously reported characterization data:[7] R_f = 0.21 (25% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.29 Hz, 2H), 7.63 (t, *J* = 7.45 Hz, 1H), 7.48 (dd, *J* = 8.29, 7.45 Hz, 2H), 5.77 (dddd, *J* = 17.4, 10.2, 7.4, 7.0 Hz, 1H), 5.22–5.16 (m, 2H), 2.87–2.77 (m, 2H), 2.59 (ddt, *J* = 13.8, 7.0, 1.0 Hz, 1H), 2.40 (ddt, *J* = 13.8, 7.4, 1.0 Hz, 1H), 2.12 (ddd, *J* = 14.2, 7.73, 6.81 Hz, 1H), 1.85 (ddd, *J* = 14.2, 6.5, 6.1 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 171.6, 170.9, 134.8, 132.0, 131.9, 130.0, 129.1, 120.0, 41.9, 41.7, 29.2, 28.2, 22.8; IR (Neat Film NaCl) 3077, 2975, 2935, 1750, 1713, 1683, 1450, 1340, 1239, 1198, 981, 776 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{16}H_{18}NO_3[M+H]^+$: 272.1281, found 272.1281; $[\alpha]_D^{25}$ –31.3° (c 1.00, $CHCl_3$, 94% ee).



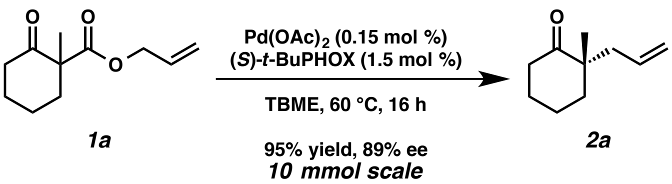
(*R*)-3-allyl-1-benzoyl-3-fluoropiperidin-2-one (6d). Synthesized according to the general method from lactam **5d**[7] using 1.25 mol % (*S*)-$(CF_3)_3$-*t*-BuPHOX and 0.125 mol % $Pd(OAc)_2$. Product was isolated by column chromatography (SiO_2, 10–20% EtOAc in hexanes) as a colorless oil (80% yield) and matched previously reported characterization data:[7] R_f = 0.35 (35% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.62–7.57 (m, 2H), 7.53–7.47 (m, 1H), 7.44–7.37 (m, 2H), 5.87–5.70 (m, 1H), 5.28–5.15 (m, 2H), 3.91 (dddd, *J* = 12.8, 6.0, 4.7, 1.4 Hz, 1H), 3.74 (dddd, *J* = 13.6, 9.2, 4.5, 2.4 Hz, 1H), 2.86–2.60 (m, 2H), 2.33–2.14 (m, 2H), 2.13–1.89 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 170.8 (d, $J_{C\text{-}F}$ = 23.5 Hz), 135.0, 132.0, 130.6 (d, $J_{C\text{-}F}$ = 6.5 Hz), 128.3, 128.0, 120.4, 93.9 (d, $J_{C\text{-}F}$ = 179.3 Hz), 46.4, 40.0 (d, $J_{C\text{-}F}$ = 23.6 Hz), 32.1 (d, $J_{C\text{-}F}$ = 22.5 Hz), 19.1 (d, $J_{C\text{-}F}$ = 4.6 Hz); IR (Neat Film NaCl) 3078, 2956, 1715, 1687, 1478, 1449, 1435, 1390, 1288, 1273, 1175, 1152, 1000, 930, 725, 694, 662 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{16}NO_2F$ [M+H]$^+$: 262.1238, found 262.1244; $[\alpha]_D^{25}$ –120.6° (c 1.09, $CHCl_3$, 99% ee).



5e *6e*

(*S*)-3-allyl-1-(4-methoxybenzoyl)-3-methylazepan-2-one (6e). Synthesized according to the general method from lactam **5e**[7] using 1.25 mol % (*S*)-$(CF_3)_3$-*t*-BuPHOX and 0.125 mol % $Pd(OAc)_2$. Product was isolated by column chromatography (SiO_2, 10–20% EtOAc in hexanes) as a colorless oil (95% yield) and matched previously reported characterization data:[7] R_f = 0.48 (25% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.56–7.48 (m, 2H), 6.91–6.82 (m, 2H), 5.86–5.66 (m, 1H), 5.18–5.02 (m, 2H), 4.03 (ddd, *J* = 15.0, 8.0, 2.4 Hz, 1H), 3.88 (ddd, *J* = 15.1, 8.5, 2.1 Hz, 1H), 3.83 (s, 3H), 2.50 (ddt, *J* = 13.6, 7.0, 1.2 Hz, 1H), 2.35 (ddt, *J* = 13.7, 7.6, 1.1 Hz, 1H), 1.92–1.77 (m, 4H), 1.77–1.62 (m, 2H), 1.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.3, 174.7, 162.2, 133.9, 130.0, 128.9, 118.6, 113.5, 55.4, 47.7, 44.7, 43.0, 35.1, 28.2, 25.0, 23.4; IR (Neat Film NaCl) 3074, 2932, 1673, 1605, 1511, 1279, 1255, 1168, 1112, 1025, 837 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{24}NO_3$ [M+H]$^+$: 302.1751, found 302.1744; $[\alpha]_D^{25}$ –34.7° (c 0.75, $CHCl_3$, 93% ee).

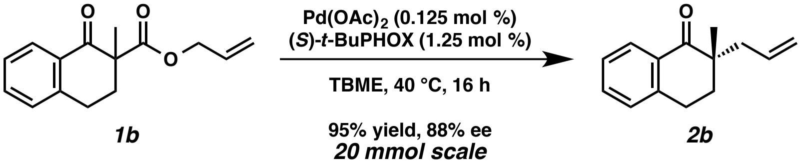
Scale Up Procedures



1a *2a*

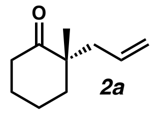
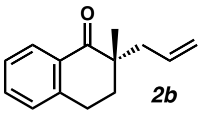
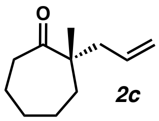
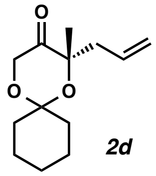
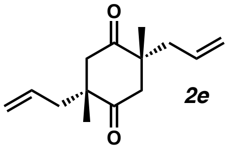
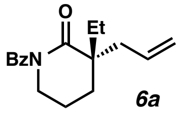
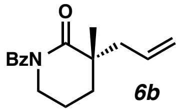
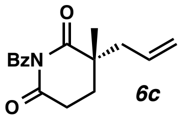
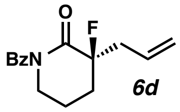
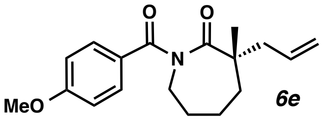
(*S*)-2-allyl-2-methyl-cyclohexanone (2a). An oven-dried 250 mL round-bottom flask equipped with a magnetic stir bar was fitted with a rubber septum and cooled to room temperature under an atmosphere of argon. To the flask were added $Pd(OAc)_2$ (3.37 mg, 15 μmol, 0.150 mol %) and (*S*)-*t*-

BuPHOX (58 mg, 150 µmol, 1.50 mol %). The flask was evacuated and backfilled with argon three times. TBME (90 mL) was added to the flask and the mixture was stirred for 30 min in a 40 °C oil bath. Substrate **1a** (1.96 g, 10.0 mmol, 1.0 equiv) was taken up in TBME (10 mL) and added to the stirring catalyst solution. The reaction was stirred for 16 h at 60 °C, the reaction mixture was passed through a pad of silica gel (2 cm diameter x 3 cm height) and rinsed with diethyl ether (50 mL). The filtrate was concentrated in vacuo and the remaining oil was distilled through a short path apparatus (bp. 91–93 °C/16 mmHg) into a receiving flask immersed in an ice water bath to yield product **2a** as a pale yellow oil (1.45 g, 9.50 mmol, 95% yield). The product was determined to be in 89% ee by chiral GC and matched previously reported characterization data (*vide supra*).[3]

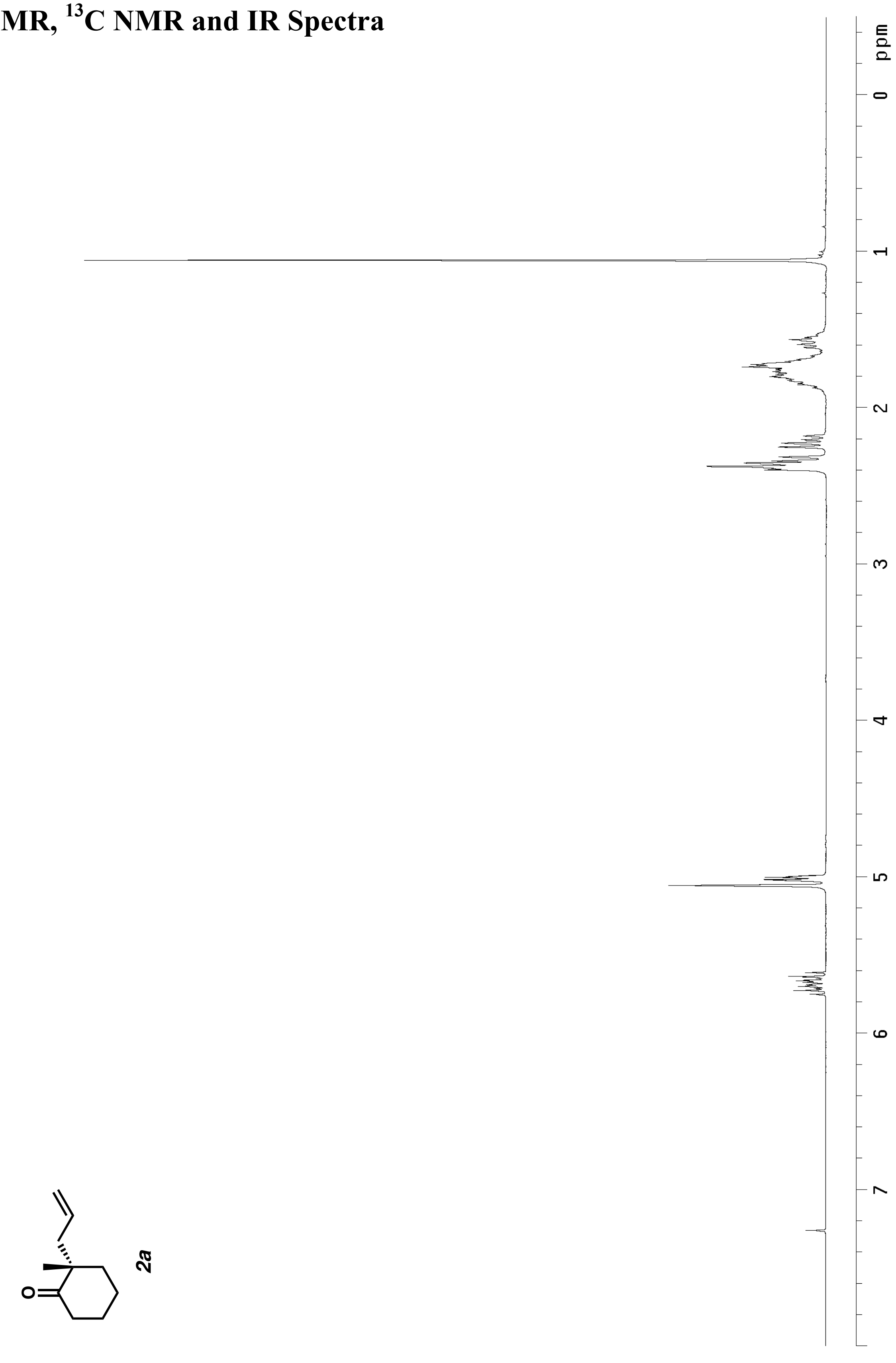


(*S*)-2-allyl-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (2b). An oven-dried 500 mL round-bottom flask equipped with a magnetic stir bar was fitted with a rubber septum and cooled to room temperature under an atmosphere of argon. To the flask were added $Pd(OAc)_2$ (5.6 mg, 25 µmol, 0.125 mol %) and (*S*)-*t*-BuPHOX (97 mg, 250 µmol, 1.25 mol %). The flask was evacuated and backfilled with argon three times. TBME (190 mL) was added to the flask and the mixture was stirred for 30 min in a 40 °C oil bath. Substrate **1b** (4.89 g, 20.0 mmol, 1.0 equiv) was taken up in TBME (10 mL) and added to the stirring catalyst solution. The reaction was stirred for 16 h, concentrated in vacuo and purified by column chromatography (SiO_2, 5–10–20% Et_2O/hexanes) to yield product **2b** as a pale yellow oil (3.81 g, 19.0 mmol, 95% yield). The product was determined to be in 88% ee by chiral SFC and matched previously reported characterization data (*vide supra*).[3]

Methods for the Determination of Enantiomeric Excess

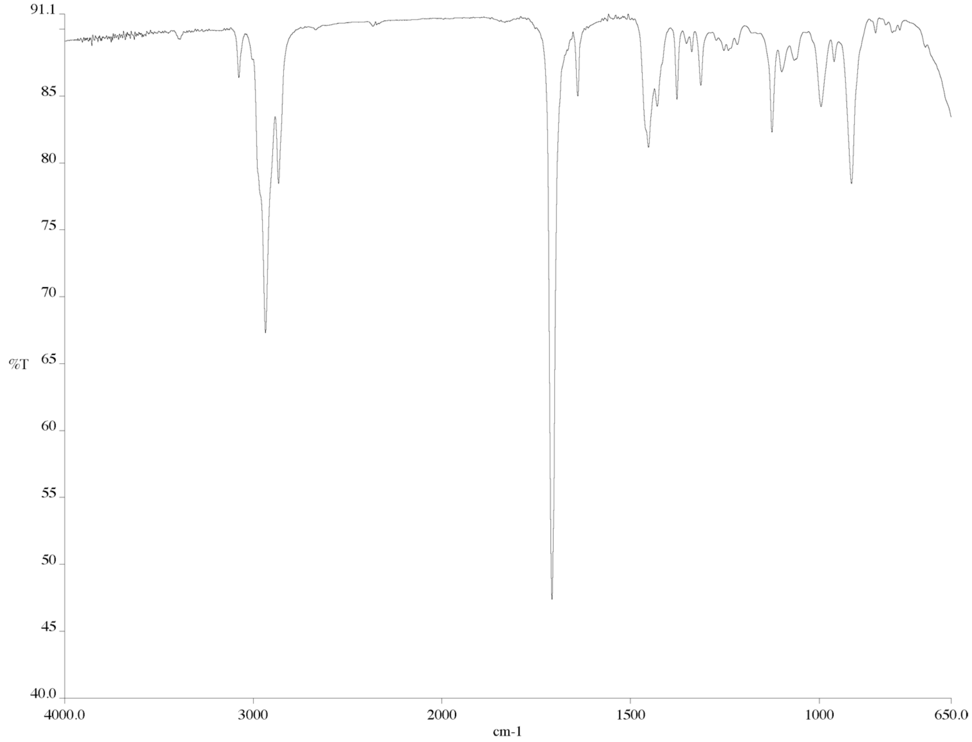
entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 **2a**	GC G-TA 100 °C isotherm	15.09	16.31	89
2	 **2b**	SFC Chiralcel OD-H 0.5% *i*-PrOH in CO_2 isocratic 3.0 mL/min 254 nm	6.40	6.89	89
3	 **2c**	GC G-TA 100 °C isotherm	15.07	16.35	70
4	 **2d**	GC chiral Supelco Beta-Dex-120 followed by chiral Supelco Beta-Dex 110 100–140 °C gradient over 120 min	110.80	111.54	90
5	 **2e**	GC G-TA 100 °C isotherm	67.01	70.18	99
6	 **6a**	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic 5.0 mL/min 254 nm	3.85	2.49	97
7	 **6b**	HPLC Chiralcel OJ-H 5% *i*-PrOH in hexanes isocratic 1.0 mL/min 254 nm	32.97	31.16	95
8	 **6c**	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic 3.0 mL/min 254 nm	5.89	5.20	88
9	 **6d**	SFC Chiralcel OJ-H 5% MeOH in CO_2 isocratic 3.0 mL/min 254 nm	3.83	4.28	99
10	 **6e**	SFC Chiralcel OJ-H 5% *i*-PrOH in CO_2 isocratic 3.0 mL/min 254 nm	6.13	5.51	90

^{1}H NMR, ^{13}C NMR and IR Spectra

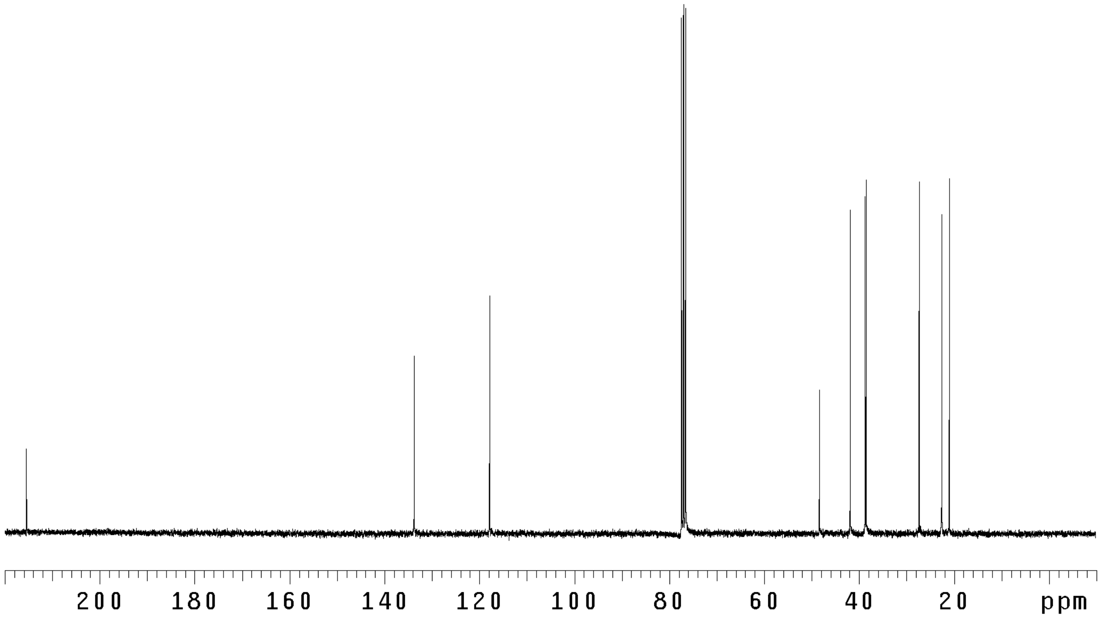


2a

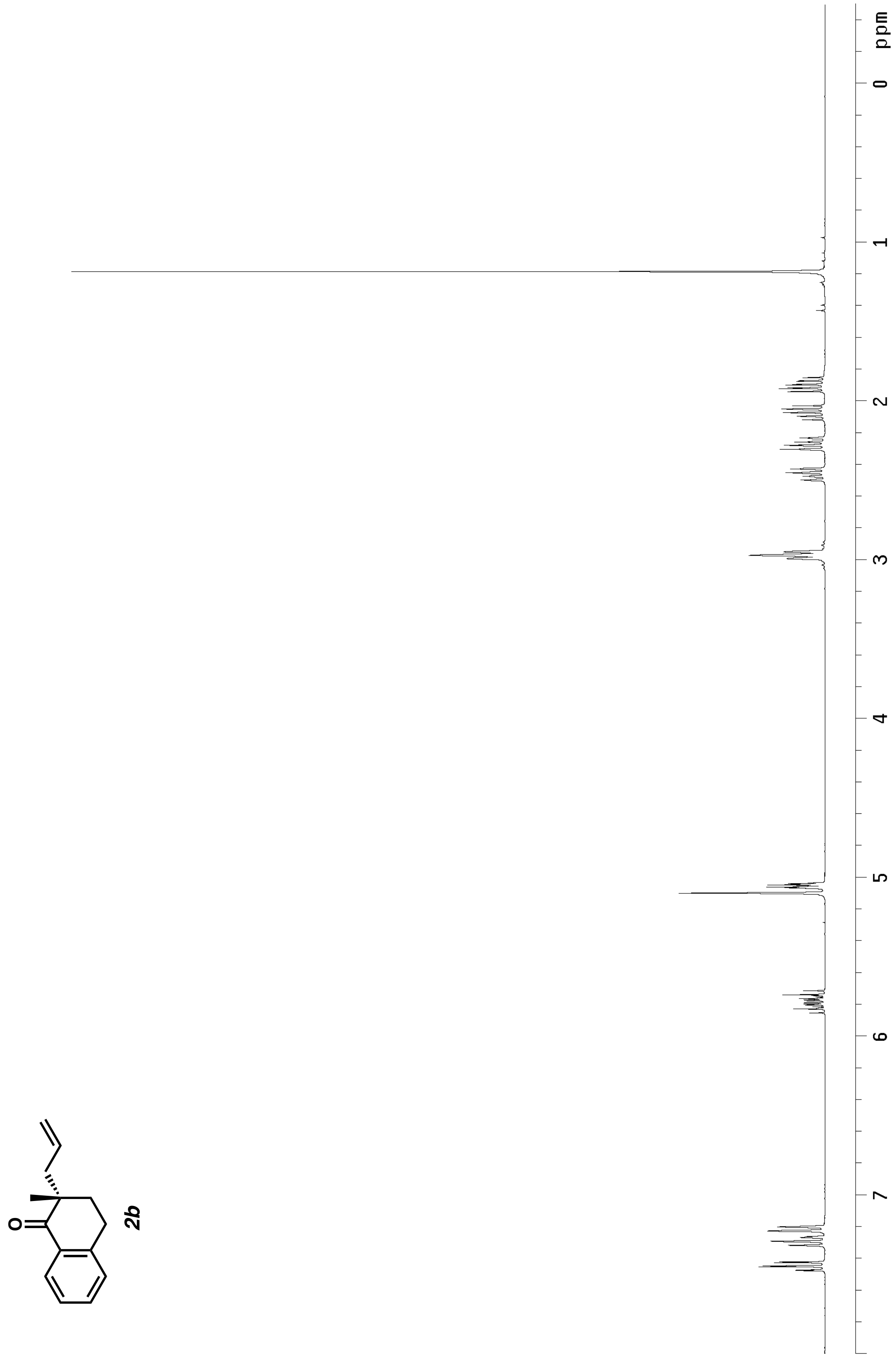
^{1}H NMR of compound **2a** (300 MHz, CDCl$_3$)



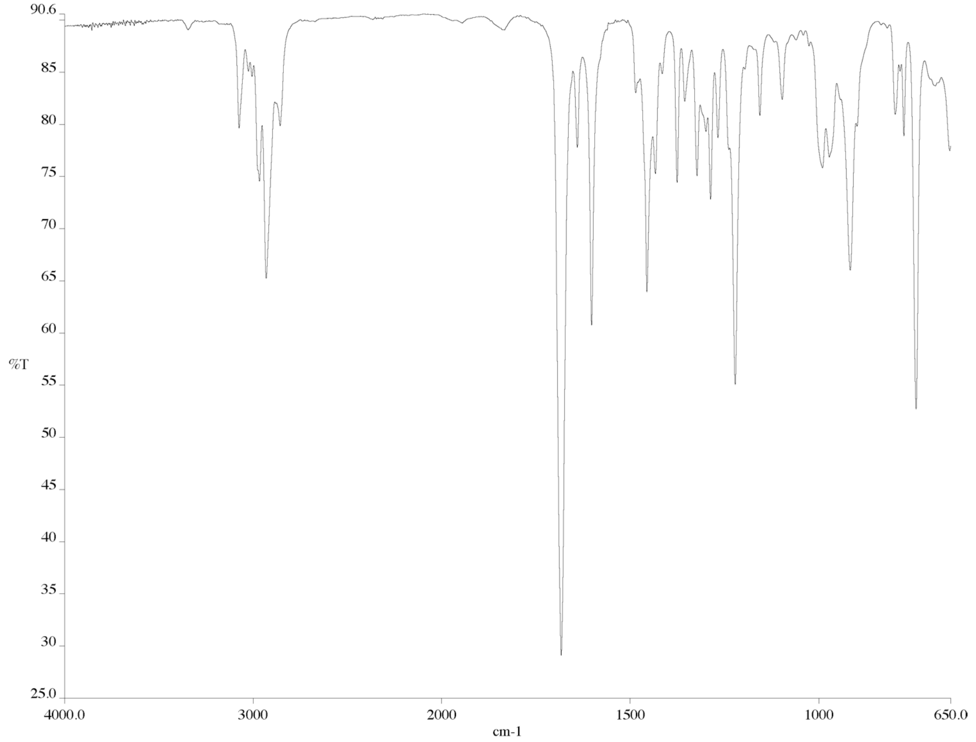
IR of compound **2a** (NaCl/film)



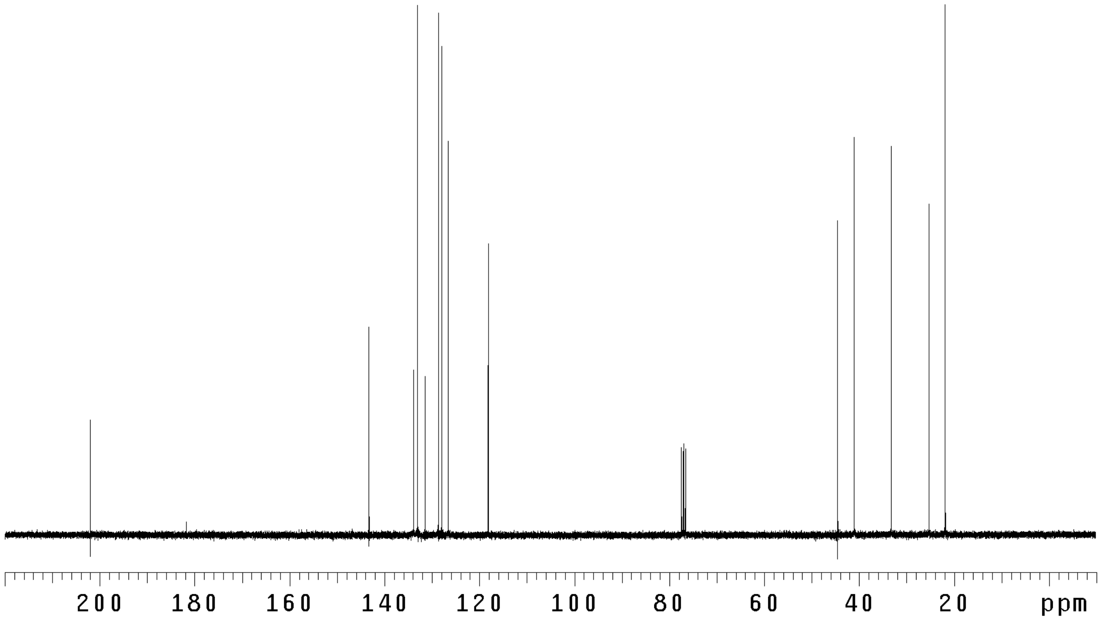
^{13}C NMR of compound **2a** (75 MHz, CDCl$_3$)



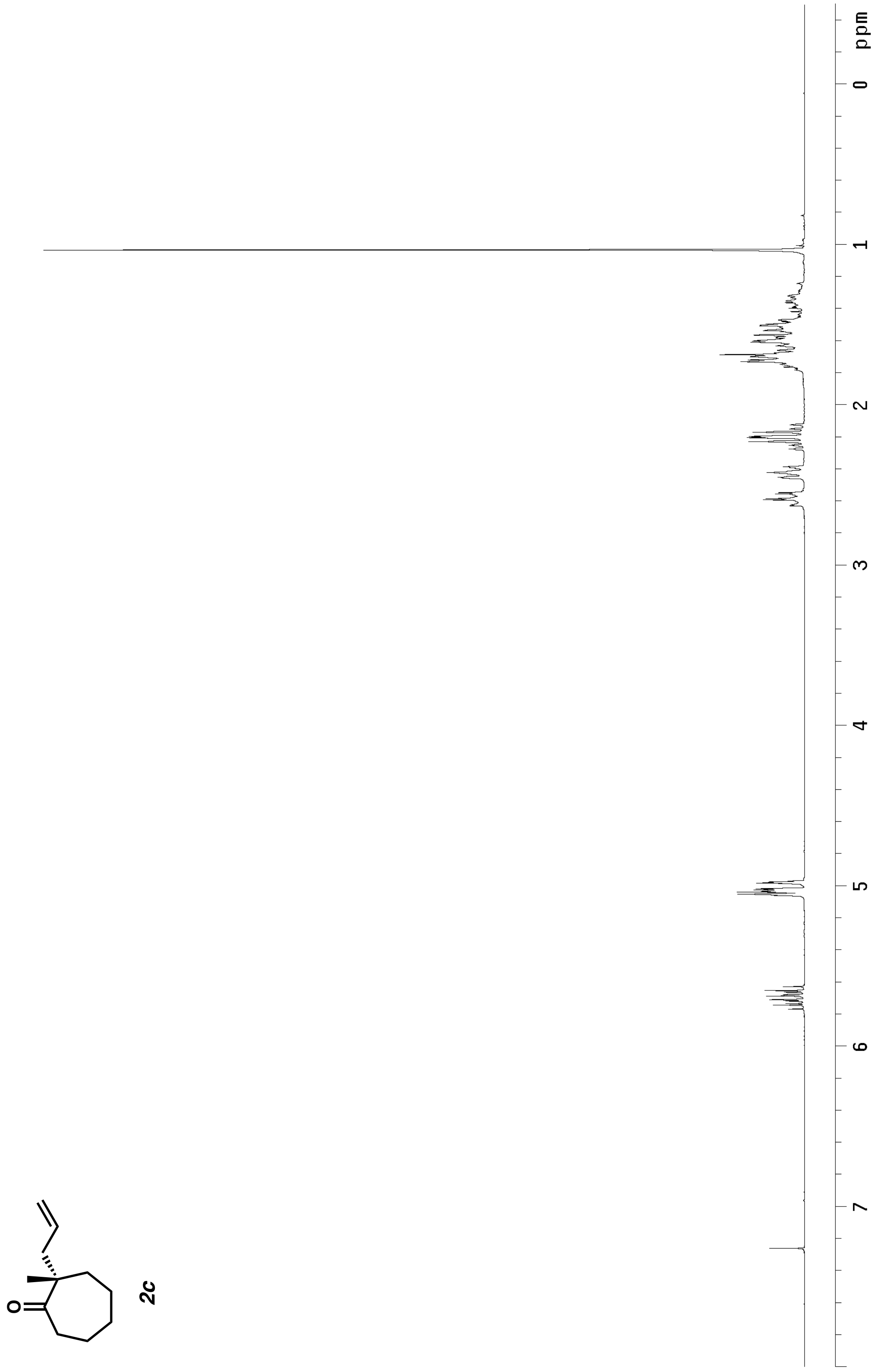
^{1}H NMR of compound **2b** (300 MHz, CDCl$_3$)



IR of compound **2b** (NaCl/film)

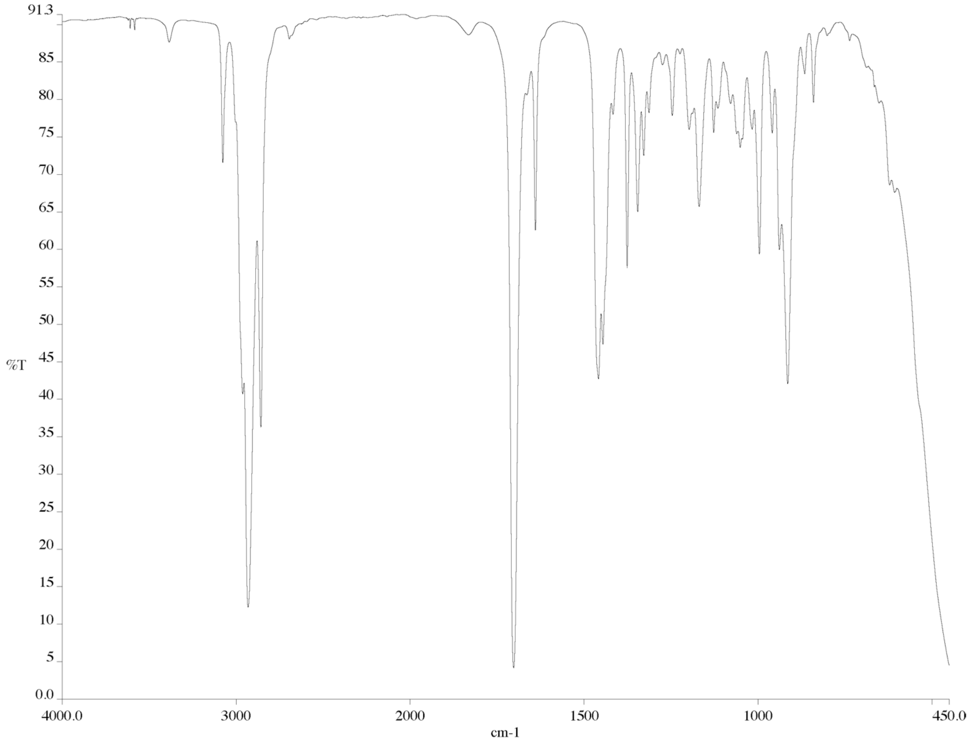


^{13}C NMR of compound **2b** (75 MHz, $CDCl_3$)

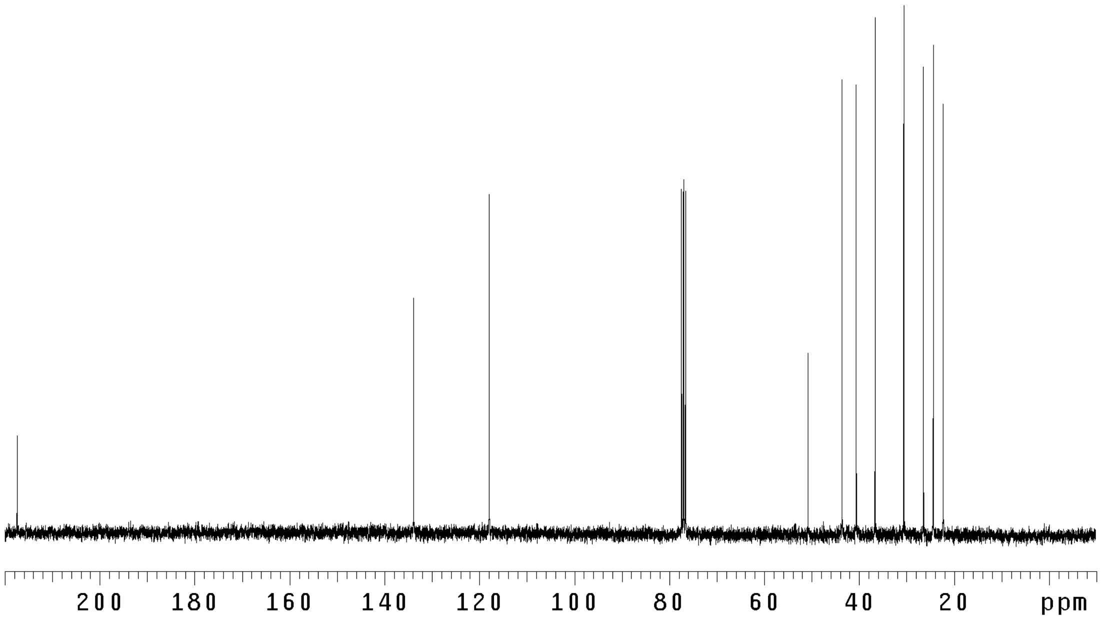


2c

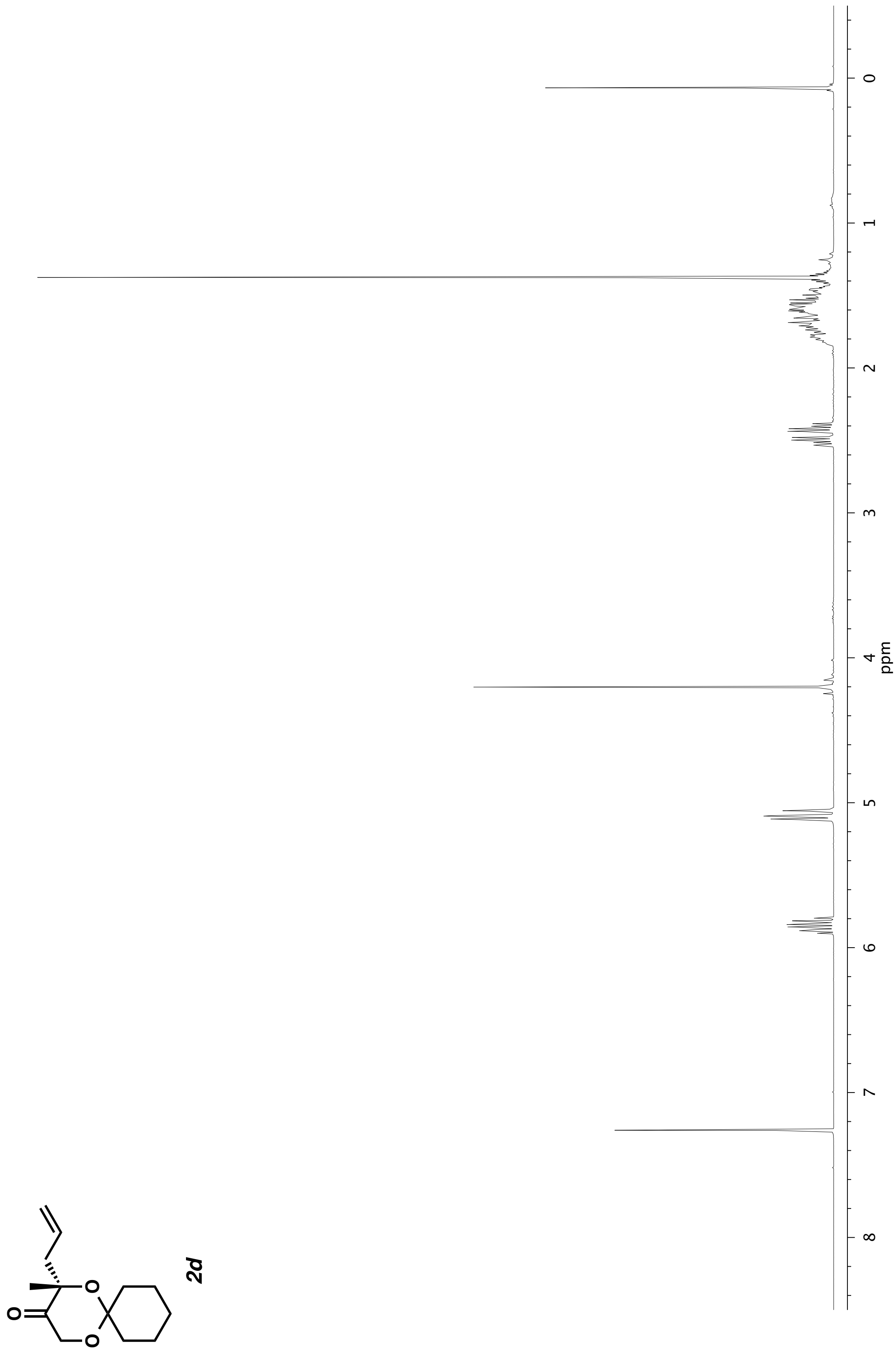
^{1}H NMR of compound **2c** (300 MHz, $CDCl_3$)



IR of compound **2c** (NaCl/film)

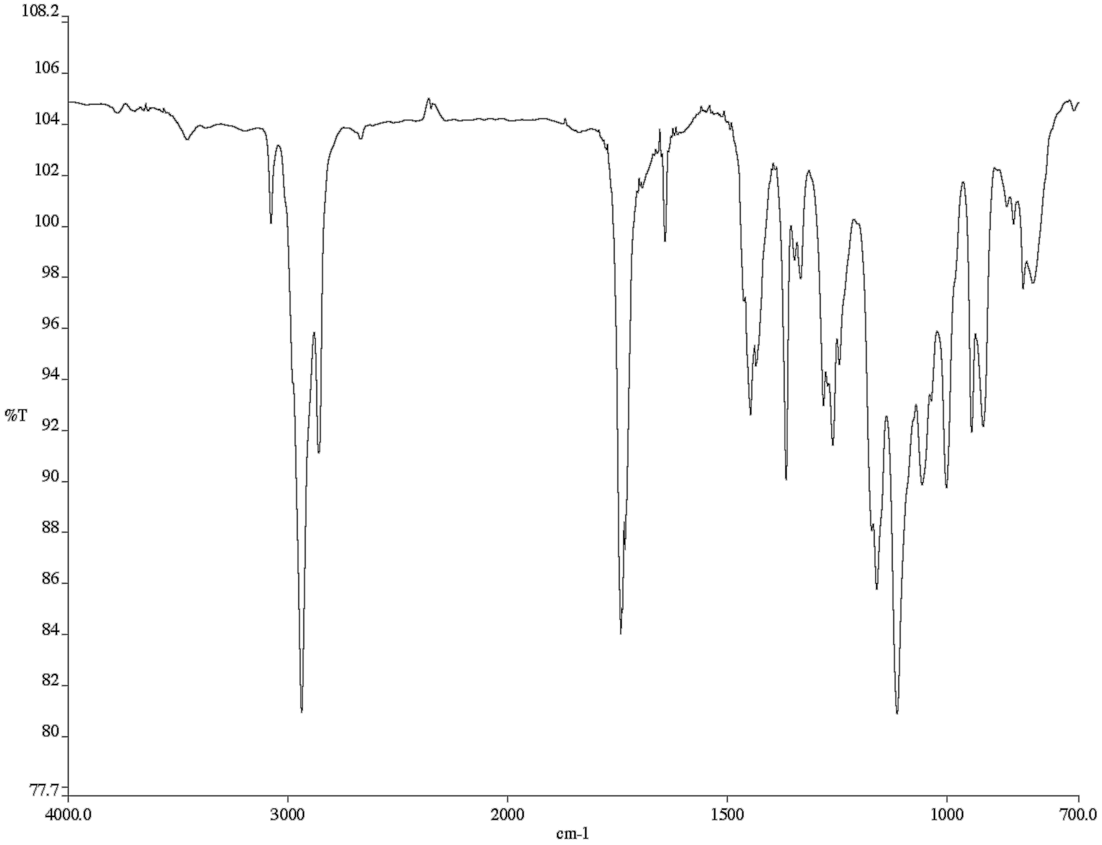


^{13}C NMR of compound **2c** (75 MHz, $CDCl_3$)

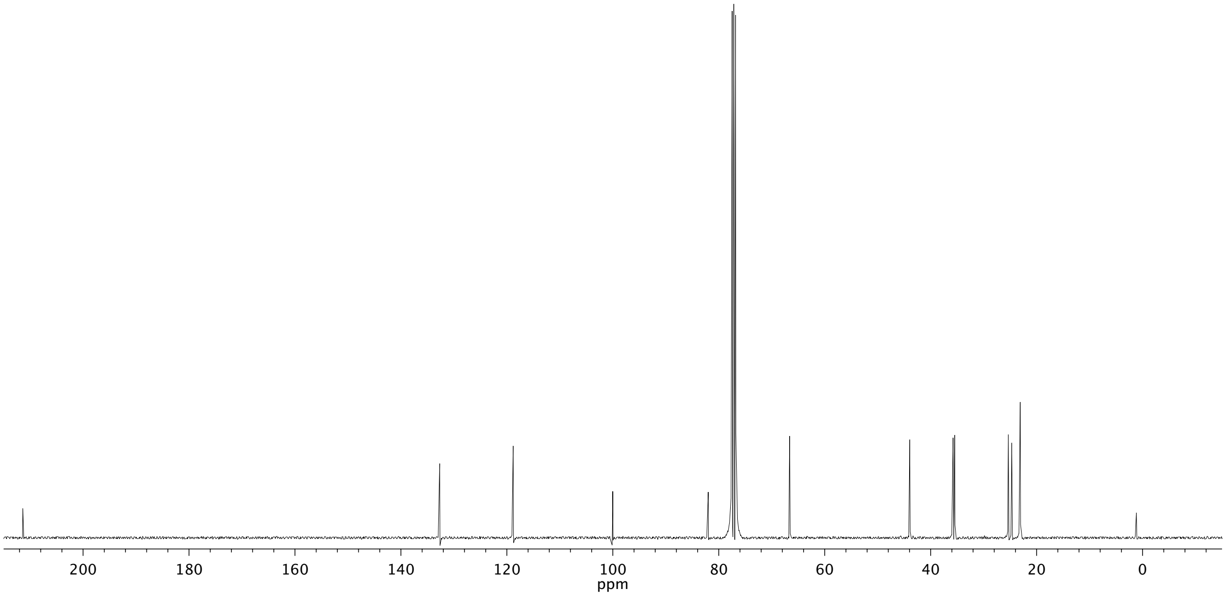


2d

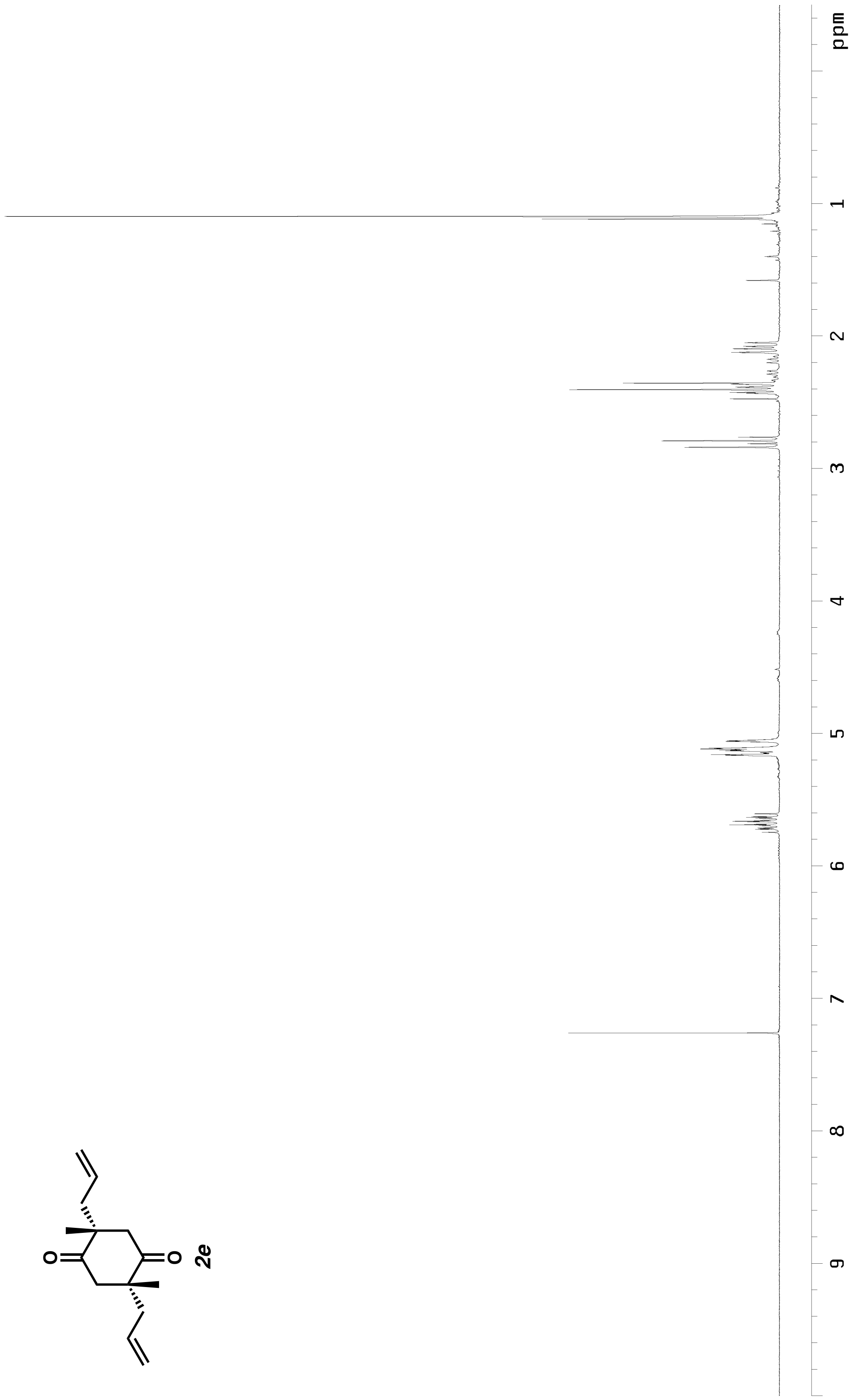
^{1}H NMR (400 MHz, CDCl$_3$) of compound **2d**.



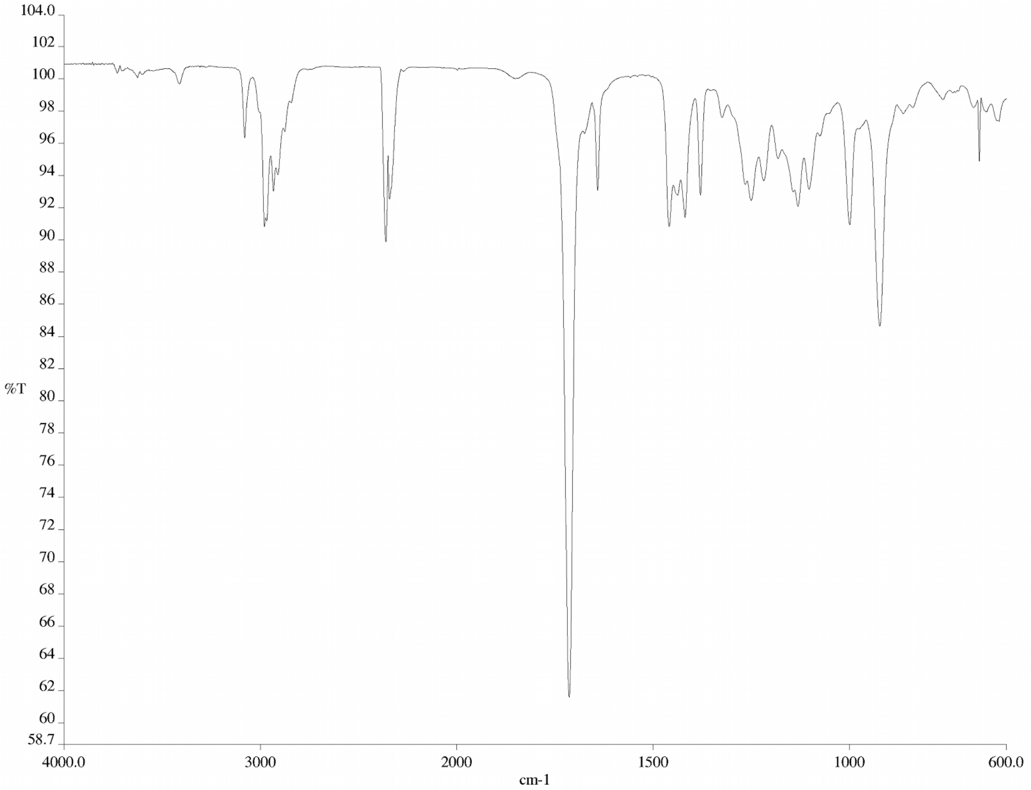
Infrared spectrum (Thin Film, NaCl) of compound **2d**.



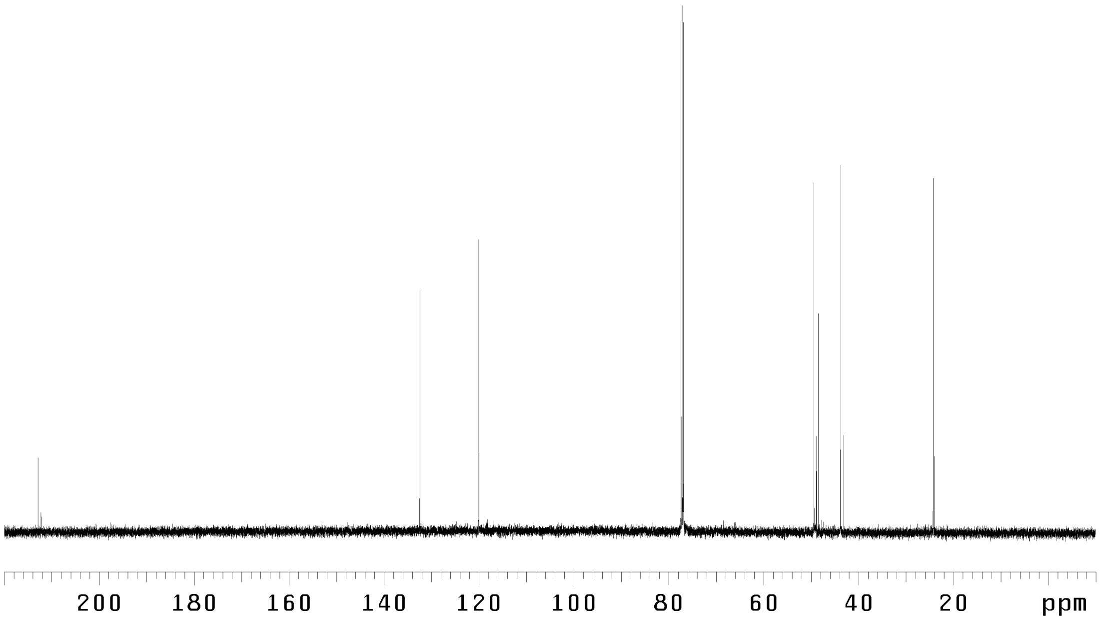
^{13}C NMR (101 MHz, CDCl$_3$) of compound **2d**.



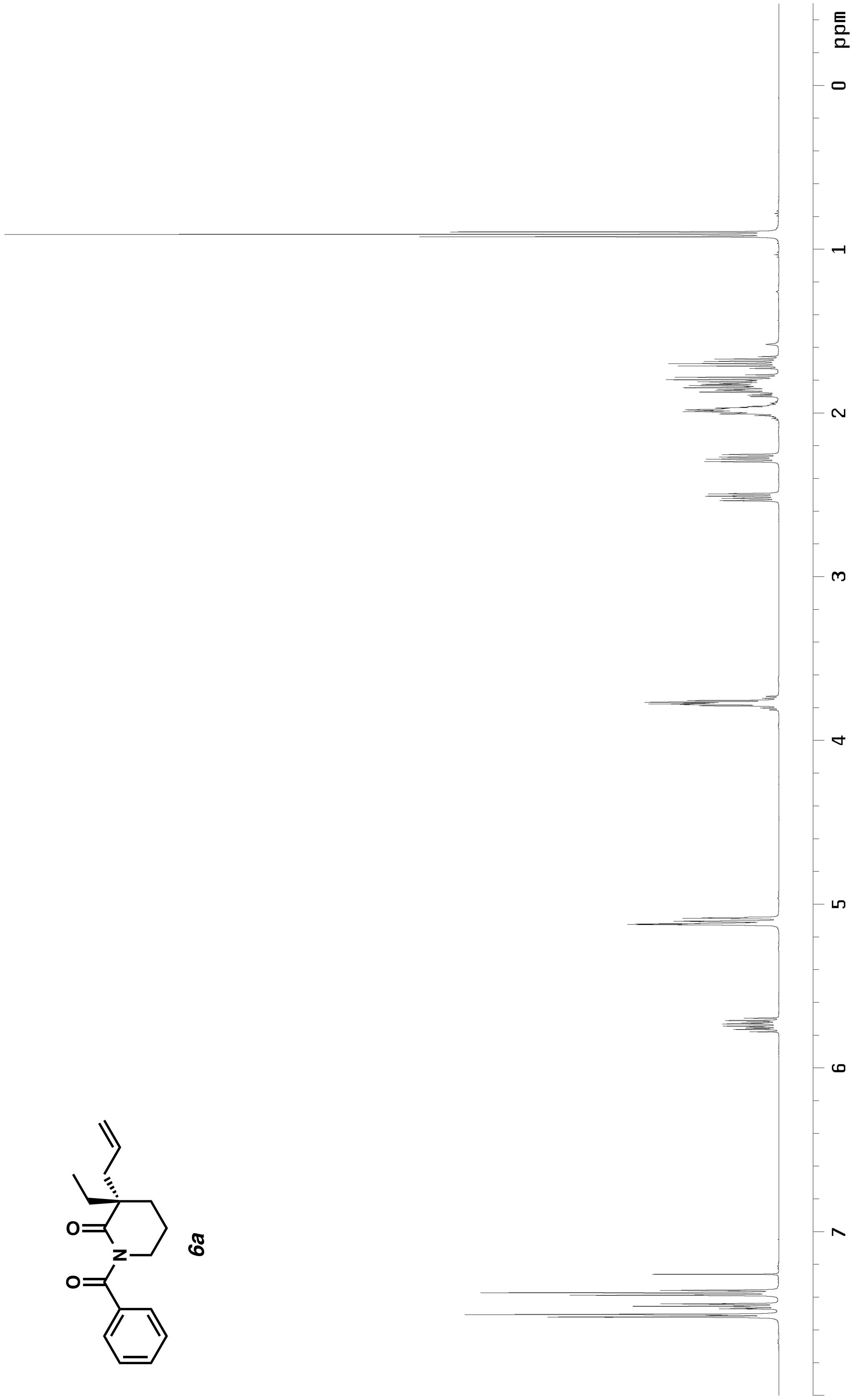
^{1}H NMR (300 MHz, $CDCl_3$) of diketone **2e**.



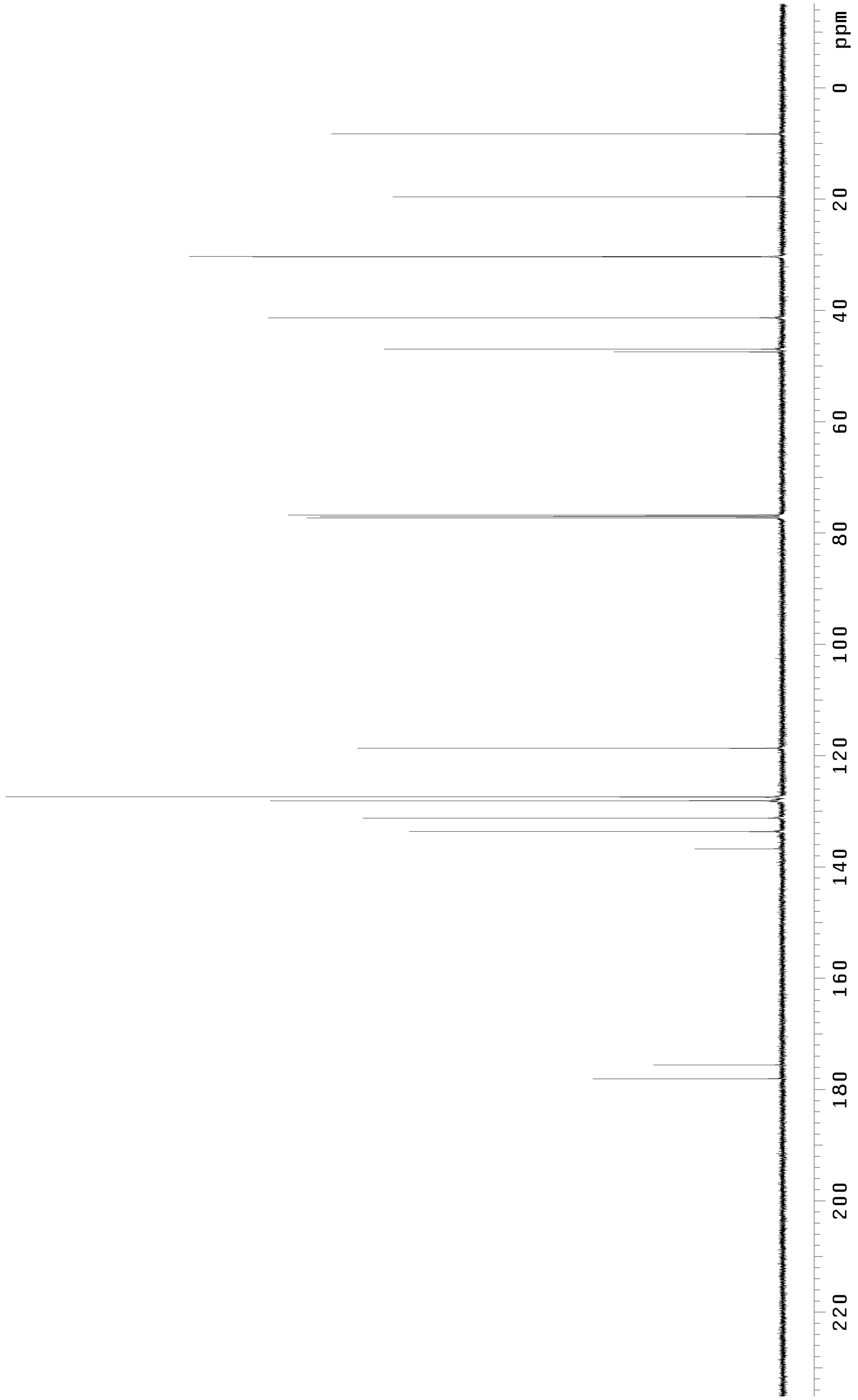
Infrared spectrum (thin film/NaCl) of diketone **2e**.



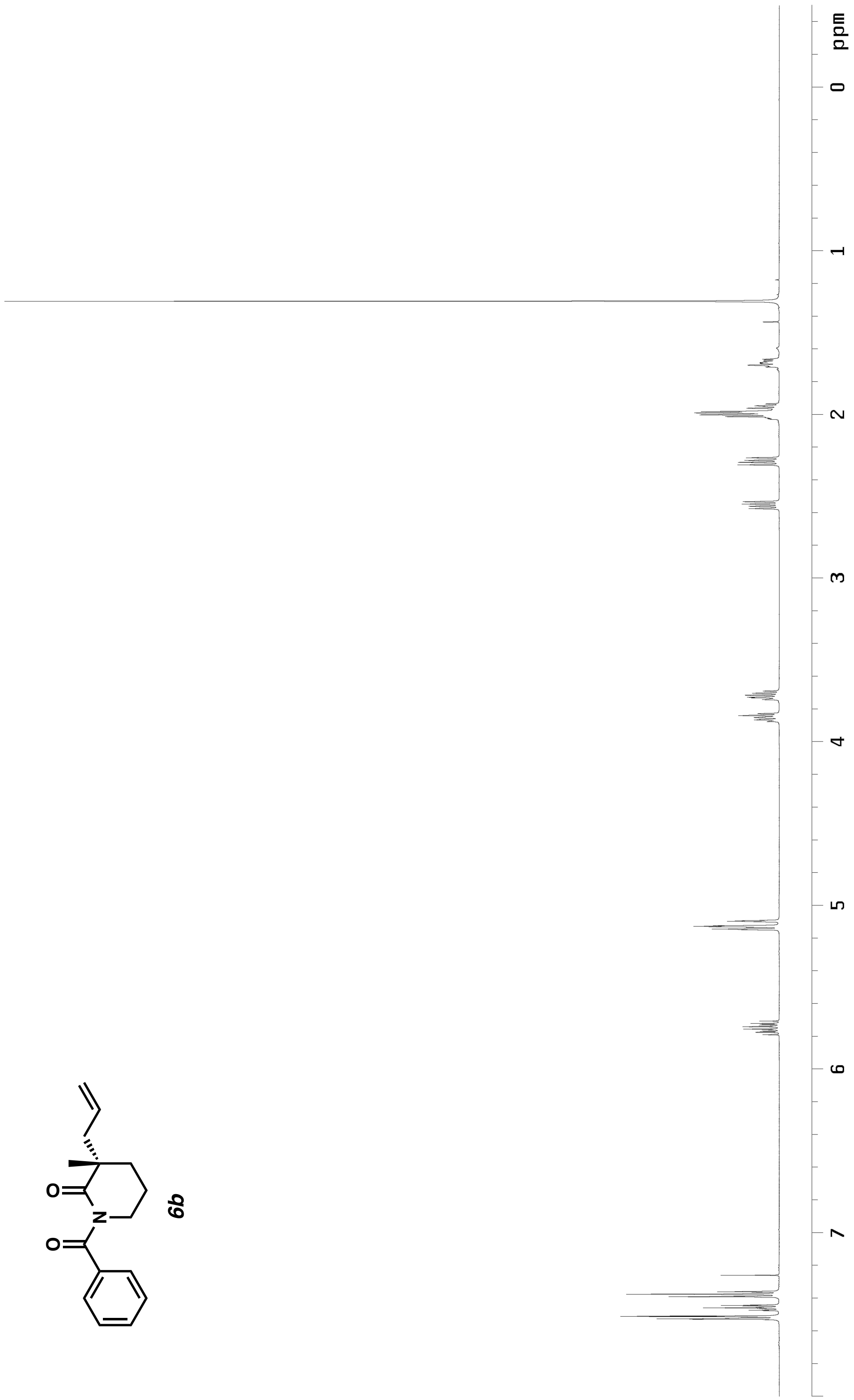
^{13}C NMR (126 MHz, CDCl$_3$) of diketone **2e**.



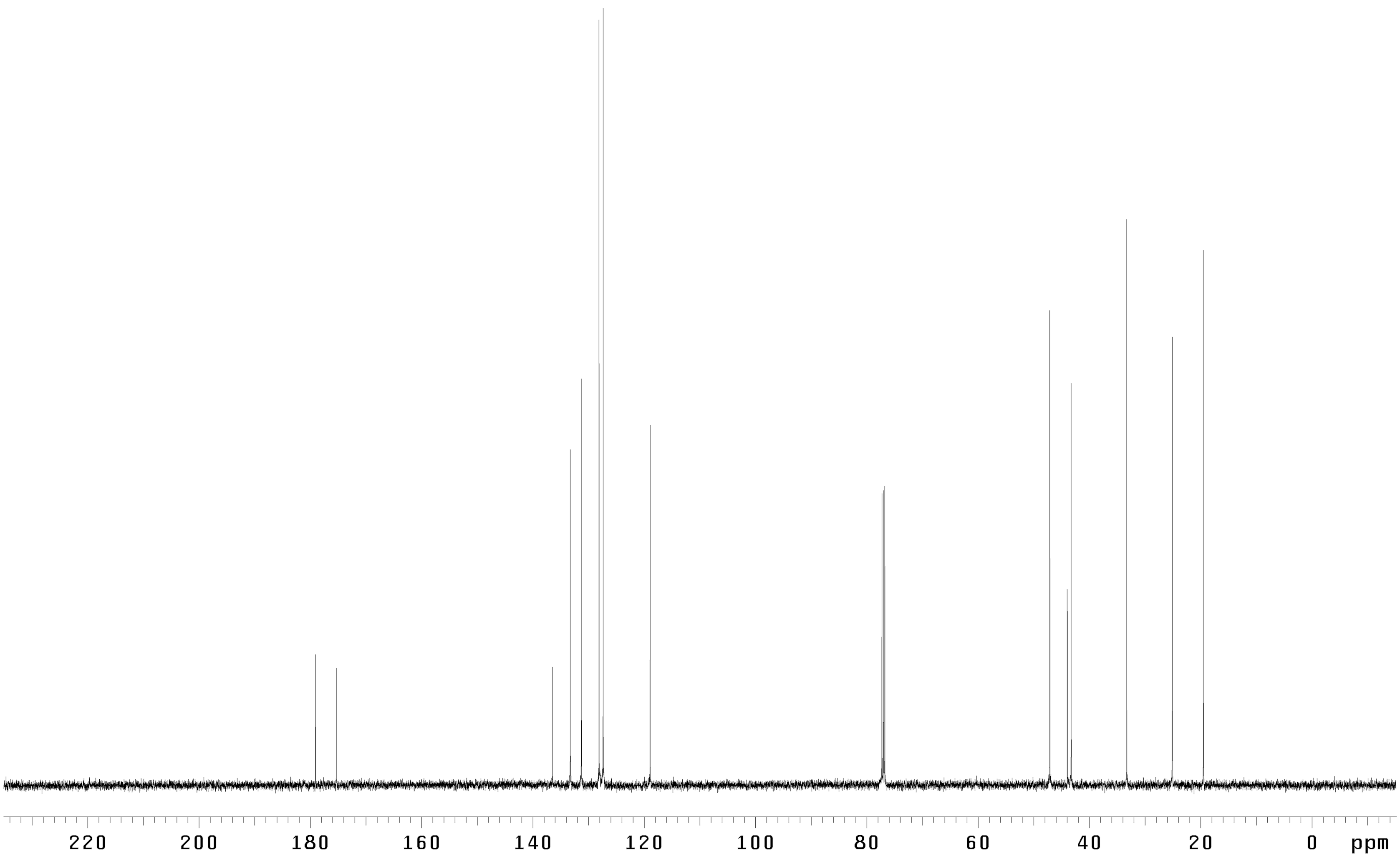
^{1}H NMR (500 MHz, $CDCl_3$) of diketone **6a**.



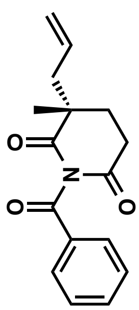
^{13}C NMR (126 MHz, CDCl$_3$) of diketone **6a**.



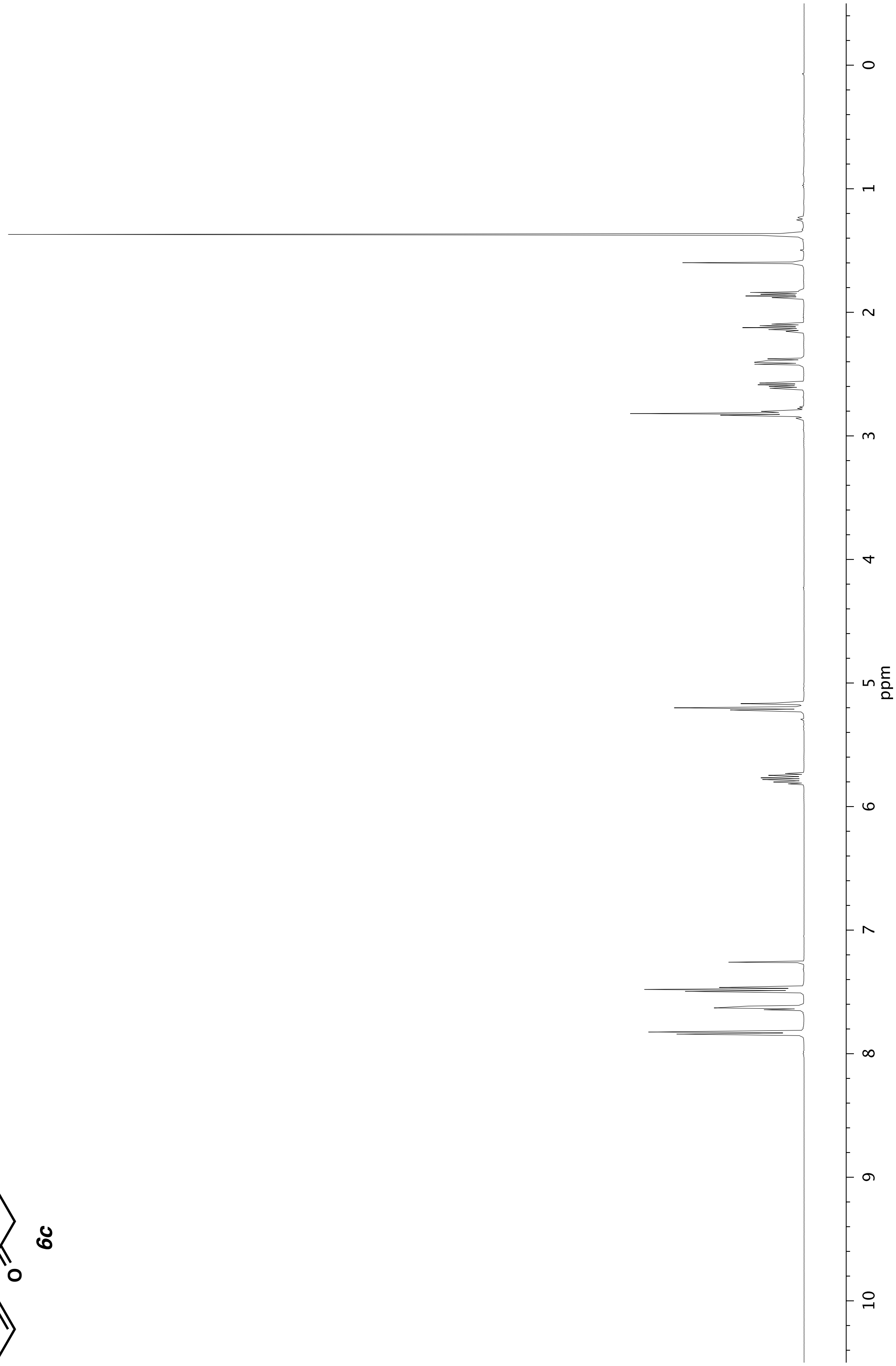
^{1}H NMR (500 MHz, CDCl$_3$) of diketone **6b**.



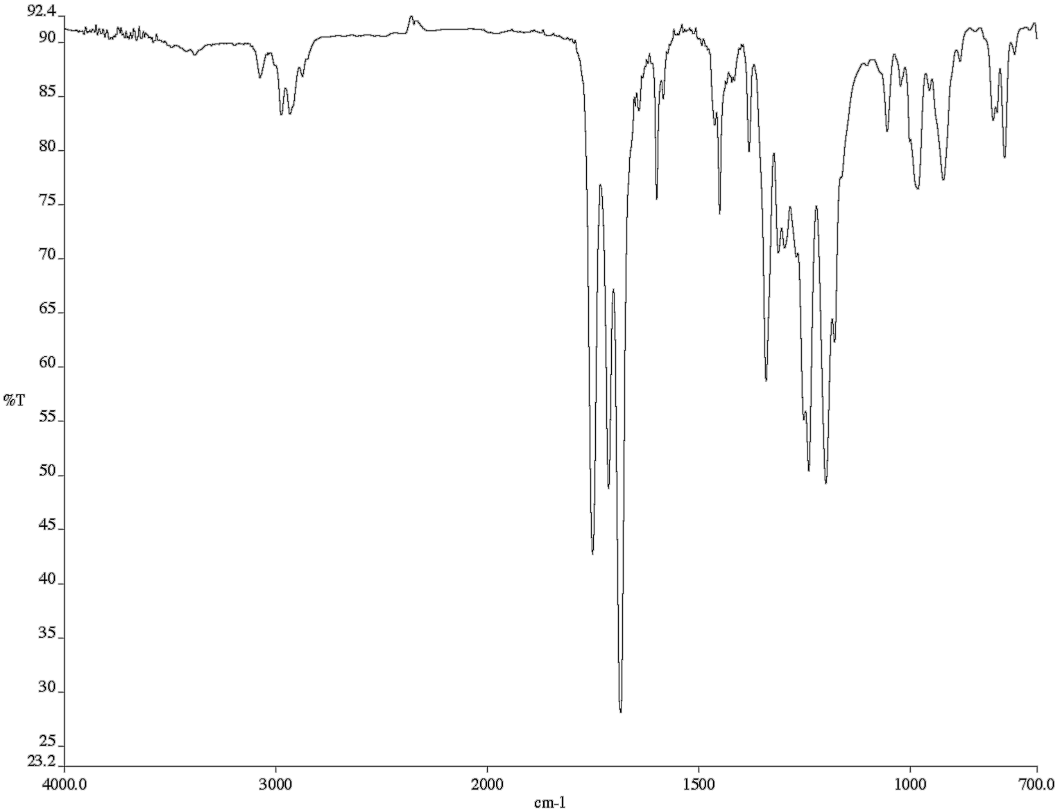
^{13}C NMR (126 MHz, $CDCl_3$) of diketone **6b**.



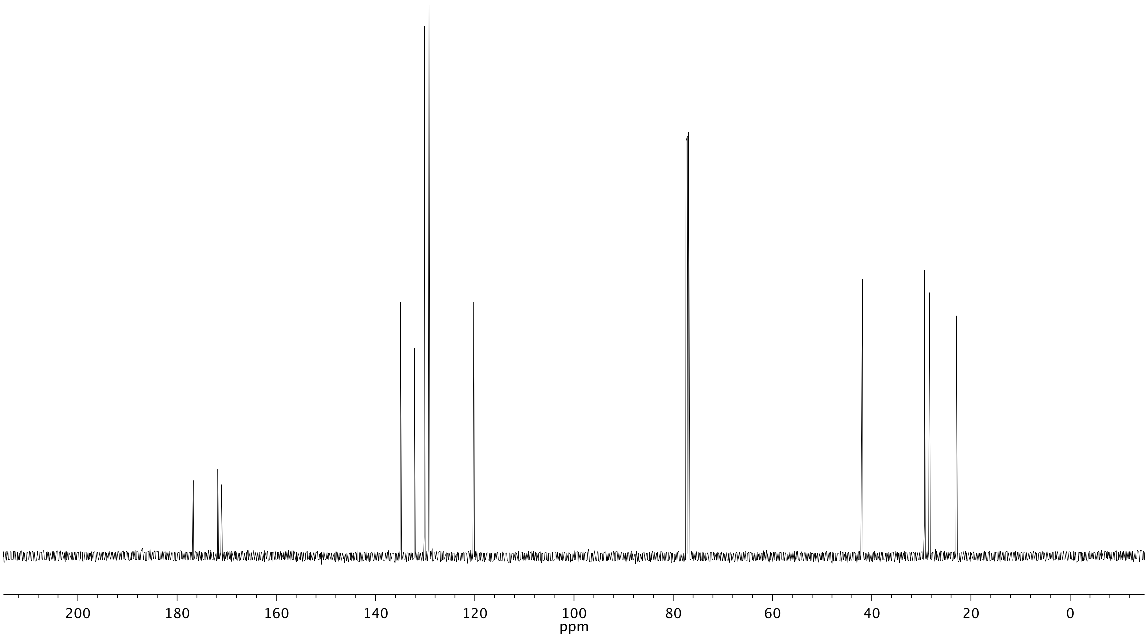
6c



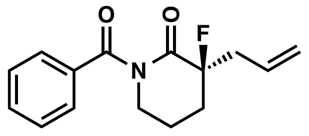
^{1}H NMR (500 MHz, CDCl$_3$) of compound **6c**.



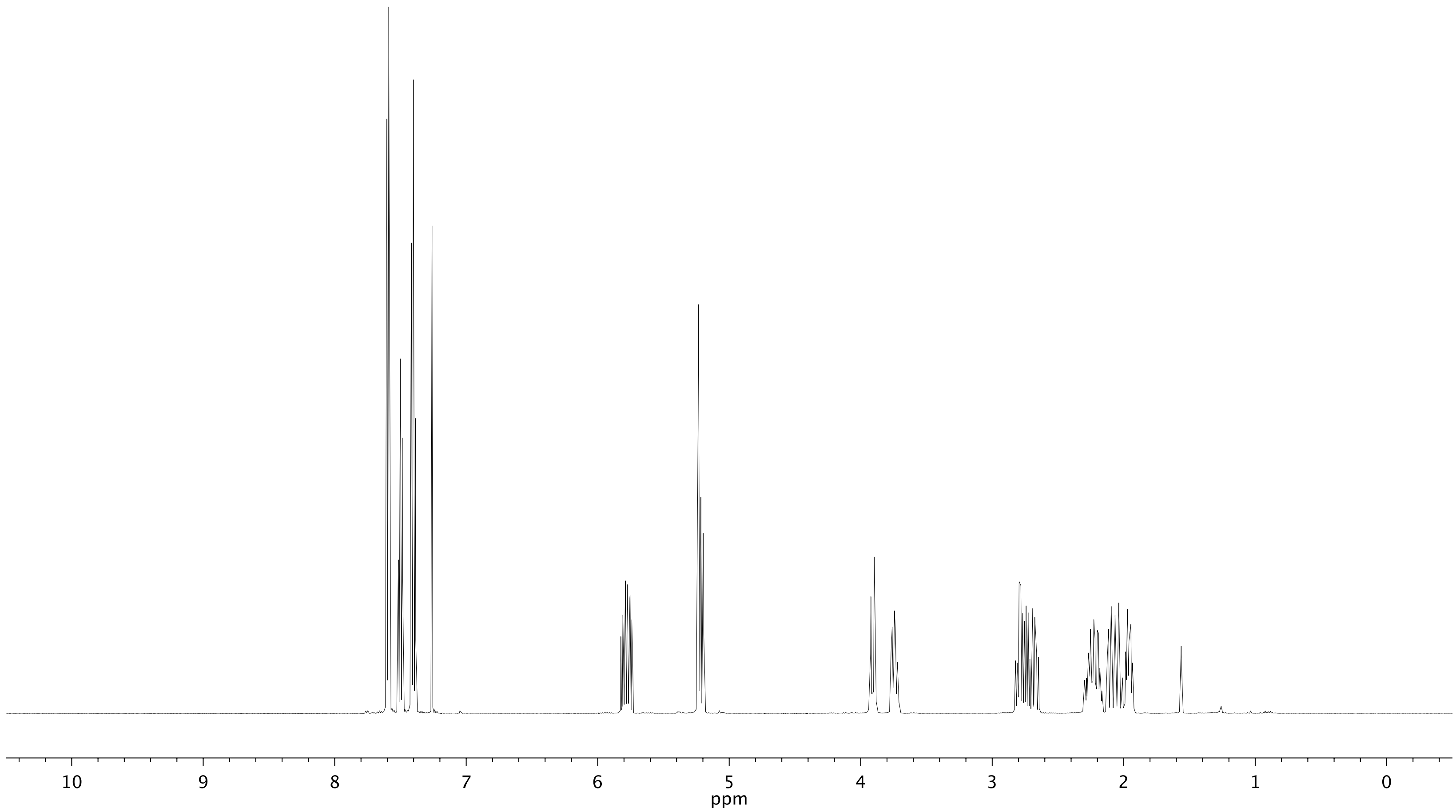
Infrared spectrum (Thin Film, NaCl) of compound **6c**.



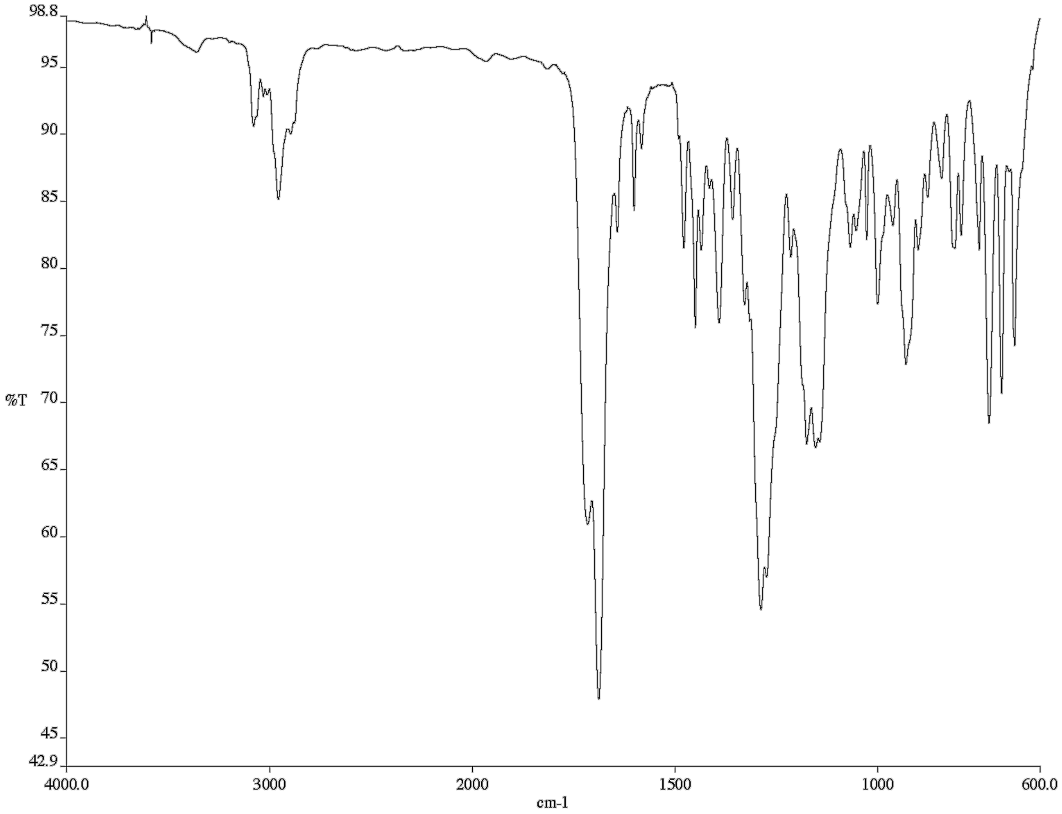
^{13}C NMR (126 MHz, CDCl$_3$) of compound **6c**.



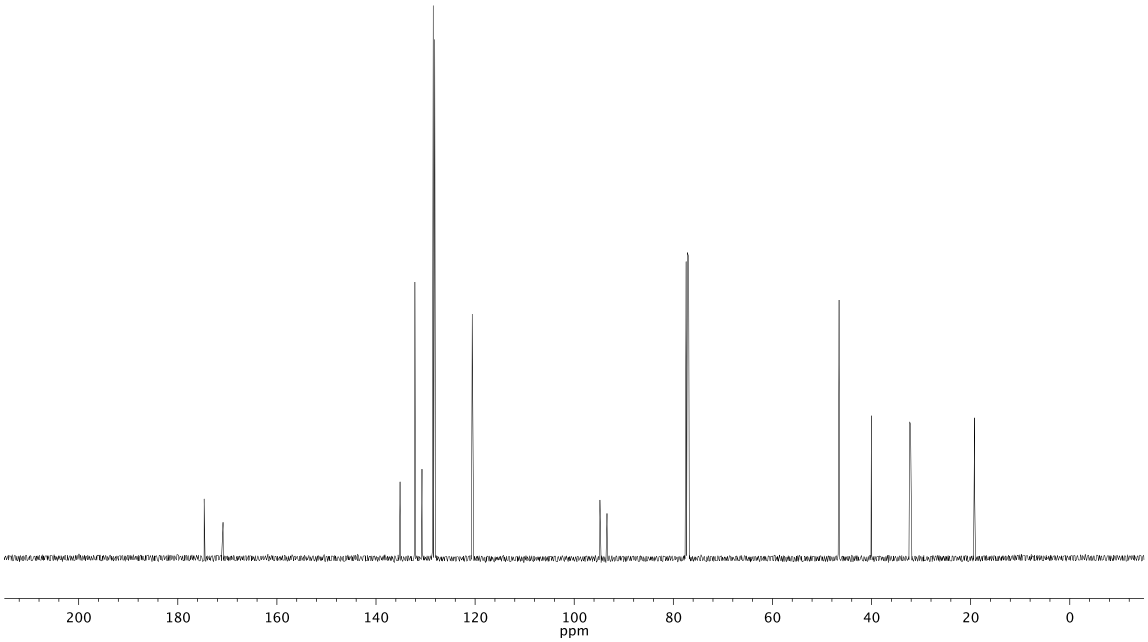
6d



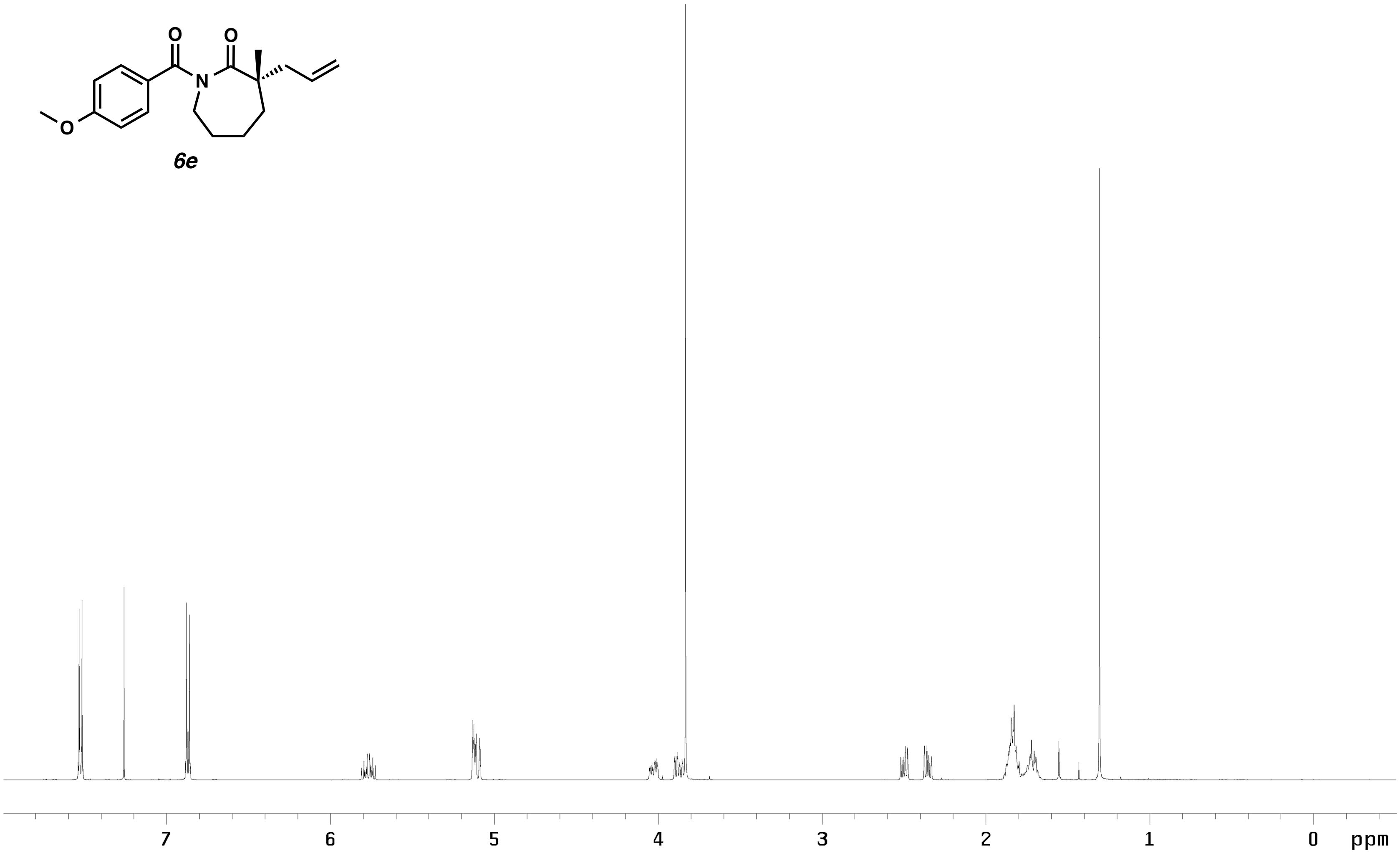
^{1}H NMR (500 MHz, CDCl$_3$) of compound **6d**.



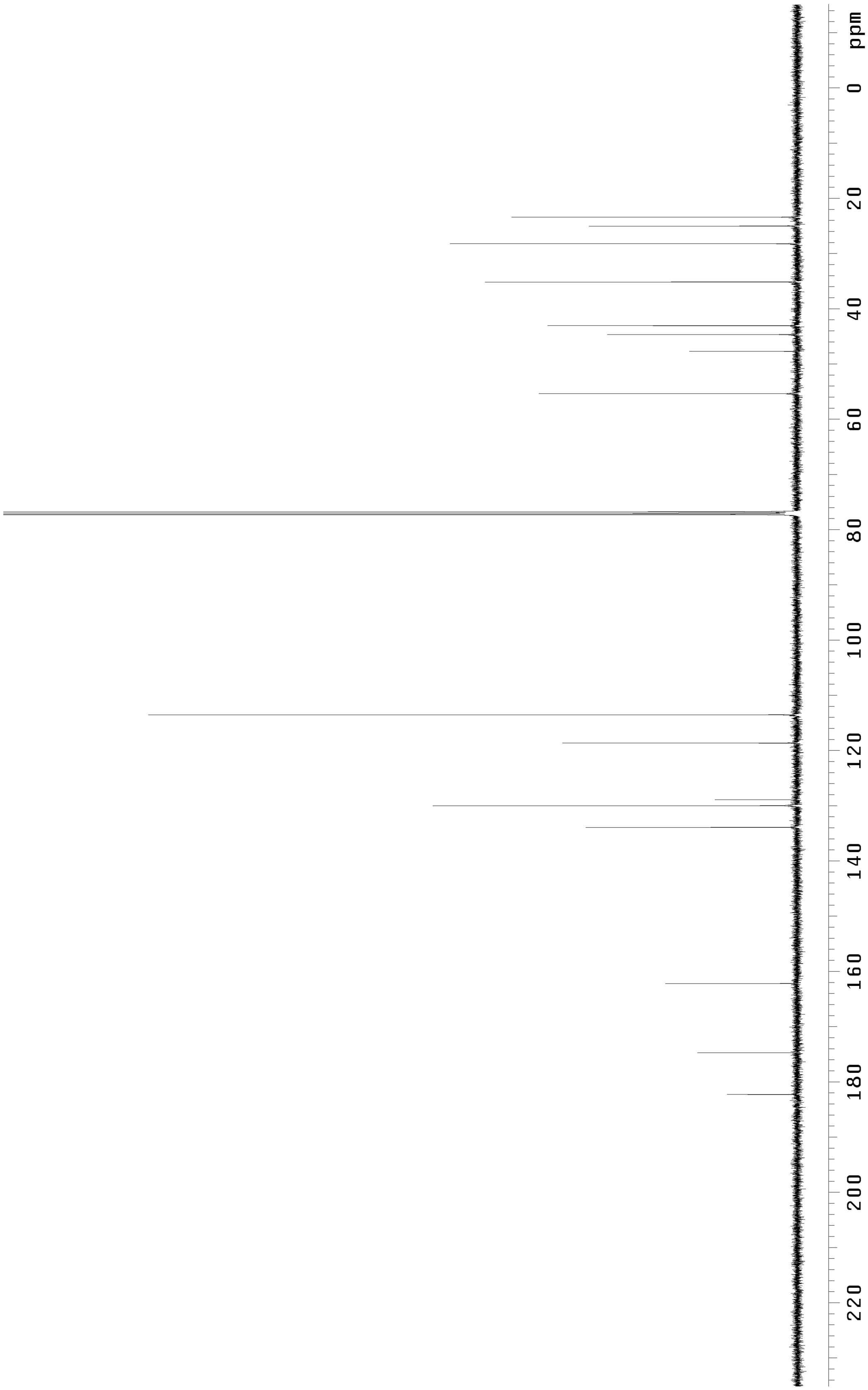
Infrared spectrum (Thin Film, NaCl) of compound **6d**.



^{13}C NMR (126 MHz, CDCl$_3$) of compound **6d**.



^{1}H NMR (500 MHz, CDCl$_3$) of diketone **6e**.



^{13}C NMR (126 MHz, CDCl$_3$) of diketone **6e**.