Aryne Acyl-Alkylation in the General and Convergent Synthesis of Benzannulated Macrolactone Natural Products: An Enantioselective Synthesis of (–)-Curvularin

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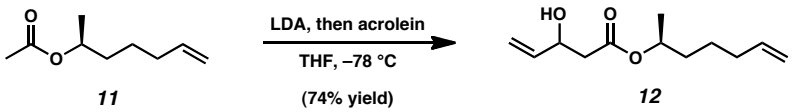
Materials and Methods. Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). (*S*)-hept-6-en-2-yl acetate (**11**) was prepared according to literature procedure.[1] Commercially obtained reagents were used as received with the exception of acrolein, which was distilled over hydroquinone under an argon atmosphere prior to use. Syringe-pump additions were performed using a kdScientific single syringe pump. 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, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode. Optical rotations were measured on a Jasco P-1010 polarimeter using a 50 mm path-length cell.

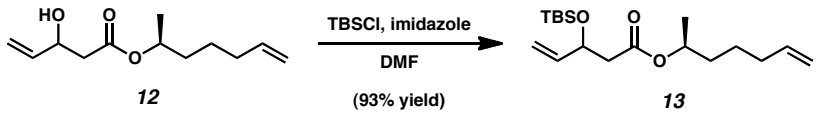
Experimental Procedures



11 *12*

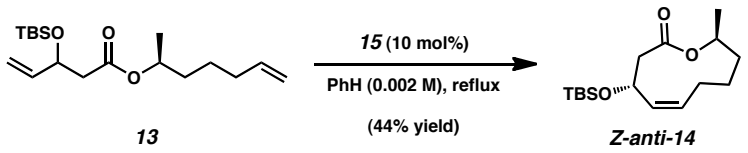
β-Hydroxyester 12. To a solution of diisopropyl amine (987 μL, 7.04 mmol) in THF (28 mL) at –78 °C was added *n*-butyllithium (2.5 M solution in hexanes, 2.82 mL) dropwise. After 30 minutes, **11** (1.00 g, 6.40 mmol) was added at –78 °C as a solution in THF (2 mL). After 20 minutes, acrolein (856 μL, 12.8 mmol) was added as a solution in THF (2.5 mL) and the reaction was maintained for 20 minutes at –78 °C. The reaction solution was quenched with 10 mL saturated amminium chloride solution and warmed to ambient temperature. The reaction was diluted with brine (20 mL) and subsequently extracted with diethyl ether (2 x 50 mL). The combined organic extracts were dried over magnesium sulfate, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield **12** (1.04 g, 76% yield) as a 1:1 mixture of diastereomers: R_f = 0.42 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.85–5.72 (m, 1H), 5.33 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.17 (dt, *J* = 10.5, 1.4 Hz, 1H), 5.06–4.92 (m, 3H), 4.54 (d, *J* = 4.0 Hz, 1H), 3.00 (dd, *J* = 10.3, 4.6 Hz, 1H), 2.58 (dd, *J* = 16.2, 4.0 Hz, 1H), 2.55–2.46 (m, 1H), 2.07 (q, *J* = 6.9 Hz, 2H), 1.68–1.57 (m, 1H), 1.57–1.32 (m, 4H), 1.24 (d, *J* = 1.4 Hz, 1.5H), 1.23 (d, *J* = 1.4 Hz, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.16, 172.14, 139.02, 138.54, 115.60, 115.59, 115.07, 71.79, 71.76, 69.23, 69.16, 41.57, 41.56, 35.50, 35.49, 33.65, 33.64, 24.86, 24.84, 20.20; IR (NaCl/film) 3448, 2978, 2936, 1730, 1422, 1378, 1272, 1178, 1125, 1039 cm^{-1};

HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{21}O_3$ $[M+H]^+$: 213.1485, found 213.1478; $[\alpha]^{22}_D$ +7.51° (*c* 0.96, CH_2Cl_2).



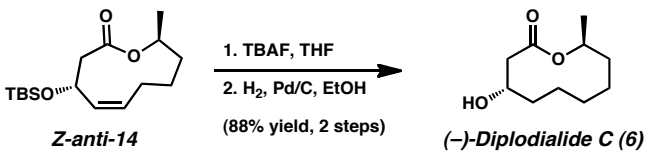
Silyl Ether 13. To a solution of β-hydroxyester **12** (1.01 g, 4.76 mmol) in DMF (10 mL) was added imidazole (485 mg, 7.14 mmol) and *tert*-butyl(chloro)dimethyl silane (TBSCl, 860 mg, 5.71 mmol). The reaction was maintained at room temperature until β-hydroxyester **12** was fully consumed by TLC analysis. Upon completion, the reaction was diluted with ethyl ether (50 mL) and washed with water (25 mL) and brine (25 mL). The organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (25:1 hexanes:ethyl acetate eluent) to yield silyl ether **13** (1.43 g, 93% yield) as a 1:1 mixture of diastereomers: R_f = 0.43 (10:1 petroleum ether:ethyl ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90–5.71 (m, 2H), 5.22 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 5.03–4.97 (m, 1H), 4.95 (ddd, *J* = 10.2, 2.0, 1.0 Hz, 1H), 4.93–4.84 (m, 1H), 4.57 (dd, *J* = 13.3, 6.1 Hz, 1H), 2.52 (ddd, *J* = 14.7, 7.6, 1.9 Hz, 1H), 2.41 (ddd, *J* = 14.8, 5.6, 0.6 Hz, 1H), 2.05 (q, *J* = 6.7 Hz, 2H), 1.67–1.31 (m, 5H), 1.21 (d, *J* = 3.0 Hz, 1.5H), 1.20 (d, *J* = 3.0 Hz, 1.5H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.73, 175.69, 145.34, 145.31, 143.44, 143.43, 119.76, 119.74, 119.64, 119.61, 76.04, 75.96, 75.87, 75.81, 48.90, 40.34, 38.53, 38.49, 30.81, 30.80, 29.67, 29.64, 25.01, 24.94, 23.13, 0.63, 0.03, 0.00; IR (NaCl/film) 2931, 1734, 1463, 1374, 1253, 1180, 1126, 1086, 956, 924, 836, 778 cm^{-1}; HRMS (MM: ESI-APCI)

m/*z* calc'd for $C_{18}H_{35}O_3Si$ $[M+H]^+$: 327.2350, found 327.2345; $[\alpha]^{25}_D$ +2.77° (*c* 0.55, $CHCl_3$).



β-Silyloxy lactone *Z-anti*-14. A solution of silyl ether **13** (25 mg, 0.0766 mmol) in benzene (40 mL) in a 3-neck flask equipped with a condenser was heated to reflux under a nitrogen atmosphere. Meanwhile, a solution of Grubbs 2nd generation catalyst (**15**, 6.5 mg, 0.00766 mmol) in benzene (10 mL) was prepared in a conical flask. A syringe filled with argon gas was loaded into a syringe pump and connected to the flask containing catalyst **15**. A cannula was inserted into the catalyst solution and connected to the refluxing substrate flask. With the aid of the syringe pump, the catalyst solution was added by cannula to the refluxing substrate solution over a period of 10 hours. Following the addition, the reaction was further maintained at reflux for 10 hours. Upon completion, the reaction was cooled to room temperature, quenched with ethyl vinyl ether (500 μL), concentrated under vacuum, and purified by flash chromatography (50:1 petroleum ether:ethyl ether eluent) to yield ***Z-anti*-14** (10 mg, 44% yield): R_f = 0.32 (10:1 petroleum ether:ethyl ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (ddd, *J* = 11.1, 9.0, 2.0 Hz, 1H), 5.35–5.25 (m, 1H), 5.15–5.03 (m, 1H), 5.00–4.88 (m, 1H), 2.79 (dd, *J* = 14.3, 5.8 Hz, 1H), 2.59 (m, 1H), 2.31 (dd, *J* = 14.2, 10.8 Hz, 1H), 2.13–1.96 (m, 2H), 1.90 (m, 2H), 1.50–1.30 (m, 3H), 1.26 (d, *J* = 6.7 Hz, 4H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.51, 137.66, 135.14, 75.67, 70.21, 48.94, 34.27, 31.59, 30.69, 27.08, 23.04, 22.04, 0.38, 0.00; IR (NaCl/film) 2944, 1736, 1444, 1248, 1067

cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{30}O_3Si$ $[M+H]^+$: 299.2037, found 299.2037; $[\alpha]^{25}_D$ –12.1° (*c* 0.56, $CHCl_3$).

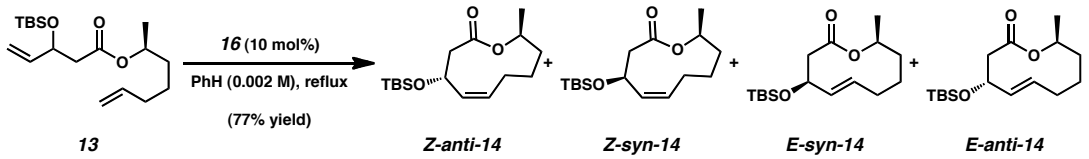


Z-anti-14 *(–)-Diplodialide C (6)*

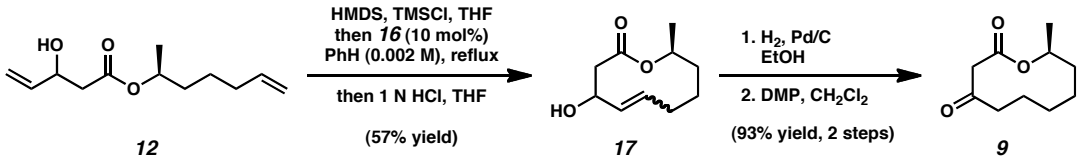
(–)-Diplodialide C (6). Tetra-*n*-butylammonium fluoride solution (1 M in THF, 131 μL, 0.131 mmol) was added to a solution of ***Z-anti*-14** (32.6 mg, 0.109 mmol) in THF (1.0 mL). The solution was maintained at room temperature until the starting material was consumed by TCL analysis. Upon completion, the reaction was diluted with ethyl ether (25 mL) and washed with water (3 x 10 mL) and brine (10 mL). The organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (3:1 hexanes:ethyl acetate eluent).

The purified residue (19.1 mg, 0.104 mmol) was taken up in anhydrous ethanol (1.0 mL). To this solution was added 10 wt. % Pd/C (11 mg, 0.0104 mmol) and a hydrogen balloon. The reaction was maintained at room temperature with vigorous stirring until the starting material had been consumed by TLC analysis. Upon completion, the reaction was filtered through a silica plug, concentrated under vacuum, and purified by flash chromatography (3:1 hexanes:ethyl acetate eluent) to yield (–)-diplodialide C (**6**, 17.1 mg, 88% yield, 2 steps): R_f = 0.17 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11–4.92 (m, 1H), 4.45–4.30 (m, 1H), 2.84 (dd, *J* = 15.4, 3.8 Hz, 1H), 2.36 (dd, *J* = 15.5, 10.0 Hz, 1H), 2.05–1.87 (m, 1H), 1.83–1.34 (m, 8H), 1.25 (comp m, 4H), 1.17–0.99 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.64, 73.15, 66.42, 43.54, 36.95, 31.56, 25.46, 23.43, 22.86, 19.37; IR (NaCl/film) 3400, 2935, 1726, 1705,

1452, 1356, 1251, 1145, 1032, 963, 867 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{19}O_3$ $[M+H]^+$: 187.1329, found 187.1323; $[\alpha]^{26}_D$ +34.6° (*c* 0.50, $CHCl_3$).



β-Silyloxy lactone 14. A solution of silyl ether **13** (300 mg, 0.918 mmol) in benzene (450 mL) in a 3-neck flask equipped with a condenser was heated to reflux under a nitrogen atmosphere. Meanwhile, a solution of Grubbs–Hoveyda third generation catalyst (**16**, 52.5 mg, 0.0918 mmol) in benzene (10 mL) was prepared in a conical flask. The catalyst solution was added to the refluxing substrate solution over a period of 10 hours by syringe pump using the method described for preparation of silyl ether ***Z-anti-14***. Following the addition, the reaction was further maintained at reflux for 10 hours. Upon completion, the reaction was cooled to room temperature, quenched with ethyl vinyl ether (1 mL), concentrated under vacuum, and purified by flash chromatography (25:1 petroleum ether:ethyl ether eluent) to yield **14** (210.8 mg, 77% yield) as a complex mixture of diastereomers and olefin isomers: R_f = 0.32 (10:1 petroleum ether:ethyl ether); For ^1H and ^{13}C NMR data, see Figures 5.1 and 5.3; IR (NaCl/film) 3429, 2953, 2929, 2857, 1739, 1655, 1472, 1360, 1278, 1245, 1077, 966, 861, 837, 777, 735 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{30}O_3Si$ $[M+H]^+$: 299.2037, found 299.2032; $[\alpha]^{23}_D$ –13.5° (*c* 0.69, $CHCl_3$).

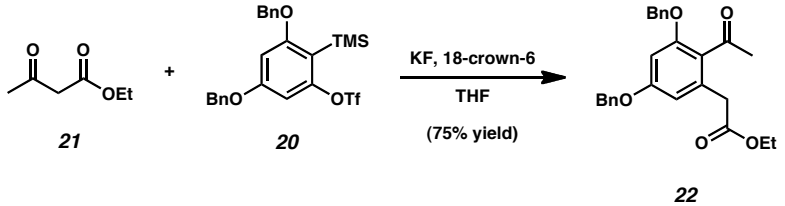


β-Ketolactone 9. β-Hydroxyketone **12** (50 mg, 0.236 mmol) was combined with hexamethyldisilazane (HMDS, 49.2 μL, 0.236 mmol) and chlorotrimethyl silane (TMSCl, 10 μL, 0.079 mmol) in THF (2.5 mL) and heated to 70 °C for a period of 5 h. After this period, the reaction was filtered and concentrated under vacuum. The residue was then taken up in benzene (110 mL) in a flame-dried 3-neck flask equipped with a condenser and heated to reflux under a nitrogen atmosphere. Meanwhile, a solution of Grubbs–Hoveyda 3rd generation catalyst (**16**, 13.4 mg, 0.0236 mmol) in benzene (10 mL) was prepared in a conical flask. The catalyst solution was added to the refluxing substrate solution over a period of 10 hours by syringe pump using the method described for the preparation of ***Z-anti*-14**. Following the addition, the reaction was further maintained at reflux for 10 hours. Upon completion, the reaction was cooled to room temperature, quenched with ethyl vinyl ether (500 μL), and concentrated under vacuum. The resulting residue was taken up in THF (2 mL) and 1 N hydrochloric acid solution (2 mL) and maintained at room temperature for 2 h. Following this period, the reaction was diluted with Et_2O (25 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (3:1 hexanes:ethyl acetate eluent) to yield β-hydroxylactone **17** (25 mg, 57% yield) as a mixture of diastereomers and olefin isomers.

β-Hydroxylactone **17** (29.8 mg, 0.162 mmol) was taken up in anhydrous ethanol (2 mL). To this solution was added 10 wt.% Pd/C (17.2 mg, 0.0162 mmol). A hydrogen balloon was added and the reaction was maintained with vigorous stirring until β-hydroxylactone **17** was consumed by TLC analysis. Upon completion, the reaction was

filtered through silica and the filtrate was concentrated under vacuum. The crude residue was used without further purification.

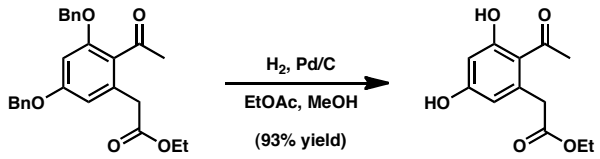
The crude residue was taken up in CH_2Cl_2 (2 mL). To this solution was added Dess–Martin periodinane (DMP, 103 mg, 0.243 mmol) and the reaction was maintained with stirring until all starting material had been consumed by TLC analysis. Following this period, the reaction was quenched by addition of a 1:1 v/v mixture of saturated sodium bicarbonate and saturated sodium thiosulfate solutions (1 mL total volume) and stirred for a period of 30 minutes. The biphasic solution was then diluted with CH_2Cl_2 (25 mL) and washed with water (10 mL) and brine (10 mL). The organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield β-ketolactone **9** (27 mg, 93% yield): $R_f = 0.38$ (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22–4.95 (m, 1H), 3.41 (d, J = 15.1 Hz, 1H), 3.36 (d, J = 15.1 Hz, 1H), 2.74 (ddd, J = 14.3, 10.1, 4.4 Hz, 1H), 2.28 (ddd, J = 14.2, 6.8, 5.0 Hz, 1H), 2.02–1.90 (m, 1H), 1.83 (dddd, J = 14.4, 8.6, 3.4, 2.1 Hz, 1H), 1.74–1.63 (m, 1H), 1.62–1.52 (m, 1H), 1.50–1.38 (m, 2H), 1.35–1.28 (m, 1H), 1.27 (d, J = 6.4 Hz, 3H), 1.22–1.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.90, 167.39, 74.77, 51.96, 39.54, 33.76, 26.78, 23.62, 22.39, 20.52; IR (NaCl/film) 2935, 1742, 1711, 1265, 1175, 1126, 1071, 961 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{10}H_{17}O_3$ $[M+H]^+$: 185.1172, found 185.1173; $[\alpha]^{25}_D$ +130.6° (*c* 1.53, MeOH).



21 *20* *22*

Di-*O,O'*-benzyl curvulin (22). Silyl aryl triflate **20** (65 mg, 0.127 mmol) and ethyl acetoacetate (**21**, 10.8 μL, 0.0849 mmol) were combined in THF (1 mL). 18-Crown-6

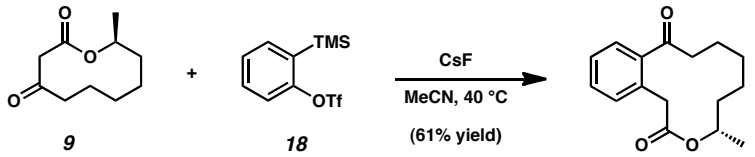
(67.3 mg, 0.255 mmol) and KF (14.8 mg, 0.255 mmol) were added sequentially. The suspension was maintained with vigorous stirring at room temperature for a period of 18 hours. Following this time, the reaction was diluted with ethyl ether (10 mL) and washed with water (2 x 5 mL) and brine (10 mL). The organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield di-*O,O'*-benzyl curvulin (**22**, 26.7 mg, 75% yield): R_f = 0.3 (hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.31 (m, 10H), 6.56 (d, *J* = 2.2 Hz, 1H), 6.49 (d, *J* = 2.2 Hz, 1H), 5.07 (s, 2H), 5.06 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 2H), 2.52 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.87, 171.28, 160.58, 158.32, 136.29, 136.08, 135.01, 128.67, 128.66, 128.21, 128.18, 127.56, 127.43, 124.43, 109.39, 99.43, 70.72, 70.19, 60.88, 39.17, 32.45, 14.20; IR (NaCl/film) 2980, 1731, 1680, 1601, 1453, 1434, 1369, 1317, 1262, 1161, 1085, 1027, 834, 738, 697 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{26}H_{27}O_5$ $[M+H]^+$: 419.1853, found 419.1838.



22 ***Curvulin (23)***

Curvulin (23).[2] Di-*O,O'*-benzyl curvulin (**22**, 12.6 mg, 0.030 mmol) was dissolved in a 1:1 v/v mixture of ethyl acetate (1 mL) and methanol (1 mL). To this solution was added 10 wt. % Pd/C (3.2 mg, 0.0030 mmol) and a hydrogen balloon. The reaction was maintained with vigorous stirring at room temperature until the starting material had been consumed by TLC analysis. Upon completion, the reaction was filtered, concentrated

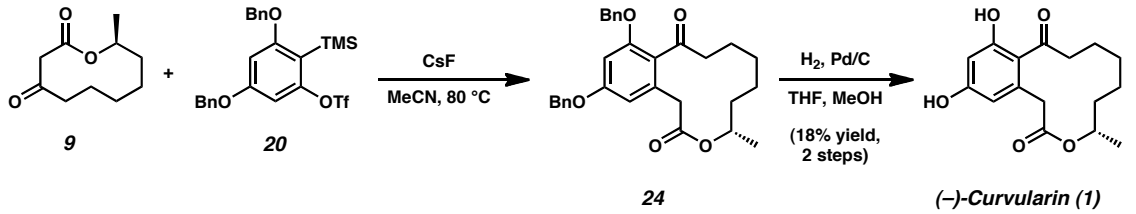
under vacuum, and purified by flash chromatography (2:1 hexanes:ethyl acetate eluent) to yield curvulin (**23**, 6.6 mg, 93% yield): R_f = 0.28 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, acetone-d_6) δ 6.37 (d, J = 2.4 Hz, 1H), 6.34 (d, J = 2.4 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.80 (s, 2H), 2.53 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 202.57, 170.69, 160.97, 160.64, 137.09, 118.57, 111.46, 101.84, 60.19, 39.80, 31.28, 13.61; IR (NaCl/film) 3412, 1706, 1636, 1264, 1166, 1024 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{12}H_{15}O_5$ $[M+H]^+$: 239.0914, found 239.0917.



9 ***18*** ***19***

Lactone 19. β-Ketolactone **9** (10 mg, 0.0543 mmol) and CsF (24.7 mg, 0.163 mmol) were combined in MeCN (0.5 mL) and heated in a sealed vial to 40 °C. Silyl aryl triflate **18** (19 μL, 0.0651 mmol) was added to the β-ketolactone suspension over a period of 1.5 hours. The suspension was maintained at 40 °C with stirring after the addition of aryne precursor **18** until β-ketolactone **9** has been consumed by TLC analysis. Upon completion, the reaction was cooled to room temperature, concentrated under vacuum, and purified by flash chromatography to yield lactone **19** (8.6 mg, 61% yield) as a mixture of ester and enol tautomers in a 1.0:0.06 ratio (as determined by ^{1}H NMR): R_f = 0.26 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, J = 5.6, 3.6 Hz, 0.06H), 7.68 (dd, J = 7.7, 1.3 Hz, 1H), 7.44 (td, J = 7.5, 1.4 Hz, 1H), 7.41–7.34 (m, 1H), 7.34–7.31 (m, 0.21H), 7.31–7.28 (m, 1H), 6.94–6.90 (m, 0.07H), 6.05 (s, 0.06H), 5.13–5.02 (m, 0.06H), 5.02–4.88 (m, 1H), 4.25 (d, J = 16.0 Hz, 1H), 3.87 (d, J = 16.0 Hz,

1H), 3.42 (ddd, *J* = 14.3, 9.1, 2.5 Hz, 0.06H), 3.11 (ddd, *J* = 14.4, 8.1, 3.7 Hz, 1H), 2.73 (ddd, *J* = 14.4, 8.5, 3.8 Hz, 1H), 2.56 (ddd, *J* = 14.3, 9.7, 2.7 Hz, 0.07H), 1.90 (d, *J* = 6.7 Hz, 0.08H), 1.82–1.68 (m, 2H), 1.57–1.25 (m, 6H), 1.13 (d, *J* = 6.4 Hz, 0.30H), 1.11 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.71, 170.42, 138.15, 134.23, 132.61, 131.40, 130.40, 129.80, 128.75, 128.40, 127.27, 127.11, 126.55, 71.99, 54.06, 40.66, 40.57, 40.27, 31.39, 31.13, 26.13, 25.95, 23.02, 22.44, 22.22, 20.02, 19.77; IR (NaCl/ film) 2929, 1724, 1447, 1244, 756 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{21}O_5$ $[M+H]^+$: 261.1485, found 261.1489; $[\alpha]^{26}_D$ +10.2° (*c* 0.87, $CHCl_3$).



9 *20* *24* ***(–)-Curvularin (1)***

(–)-Curvularin (1). β-Ketolactone **9** (15 mg, 0.0814 mmol) and CsF (37.1 mg, 0.244 mmol) were combined in MeCN (800 μL) and heated in a sealed vial to 40 °C. Silyl aryl triflate **20** (62.3 mg, 0.122 mmol) was added to the β-ketolactone suspension as a 500 μL MeCN solution over a period of 1.5 hours. The suspension was maintained at 40 °C with stirring following the addition of aryne precursor **20** until β-ketolactone **9** has been consumed by TLC analysis. The reaction was cooled to room temperature and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield lactone **24** (11.3 mg, 30% yield), which was immediately carried on to the next step.

Lactone **24** (11.3 mg, 0.0239 mmol) was taken up in a 1:1 v/v mixture of THF and MeOH (2 mL each). To this solution was added 10 wt. % Pd/C (14 mg, 0.0131 mmol) and a hydrogen balloon. The reaction was maintained at room temperature with

vigorous stirring until lactone **24** had been consumed by TLC analysis. The suspension was filtered and the filtrate concentrated under vacuum. The resulting crude residue was purified by flash chromatography (7:3 hexanes:ethyl acetate eluent) to yield (–)-curvularin (**1**, 4.0 mg, 60% yield): R_f = 0.24 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, acetone-d_6) δ 6.39 (d, J = 2.3 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 4.91 (m, 1H), 3.78 (d, J = 15.7 Hz, 1H), 3.70 (d, J = 15.7 Hz, 1H), 3.11 (ddd, J = 15.5, 8.5, 3.0 Hz, 1H), 2.77 (ddd, J = 15.5, 9.7, 3.0 Hz, 2H), 1.81–1.68 (m, 1H), 1.66–1.18 (m, 7H), 1.12 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 205.77, 170.10, 159.24, 157.34, 136.04, 120.46, 111.32, 101.64, 71.66, 43.07, 38.80, 32.00, 26.63, 23.68, 22.59, 19.68; IR (NaCl/film) 3428, 1644, 1461, 1266, 1162, 845 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{16}H_{21}O_5$ $[M+H]^+$: 293.1384, found 293.1385; $[\alpha]^{27}_D$ –31.2° (*c* 0.12, EtOH).

References

(1) Lin, W.; Zercher, C. K. *J. Org. Chem.* **2007**, *72*, 4390–4395.
(2) Bracher, F.; Krauss, J. *Nat. Prod. Lett.* **1998**, *12*, 31–34.

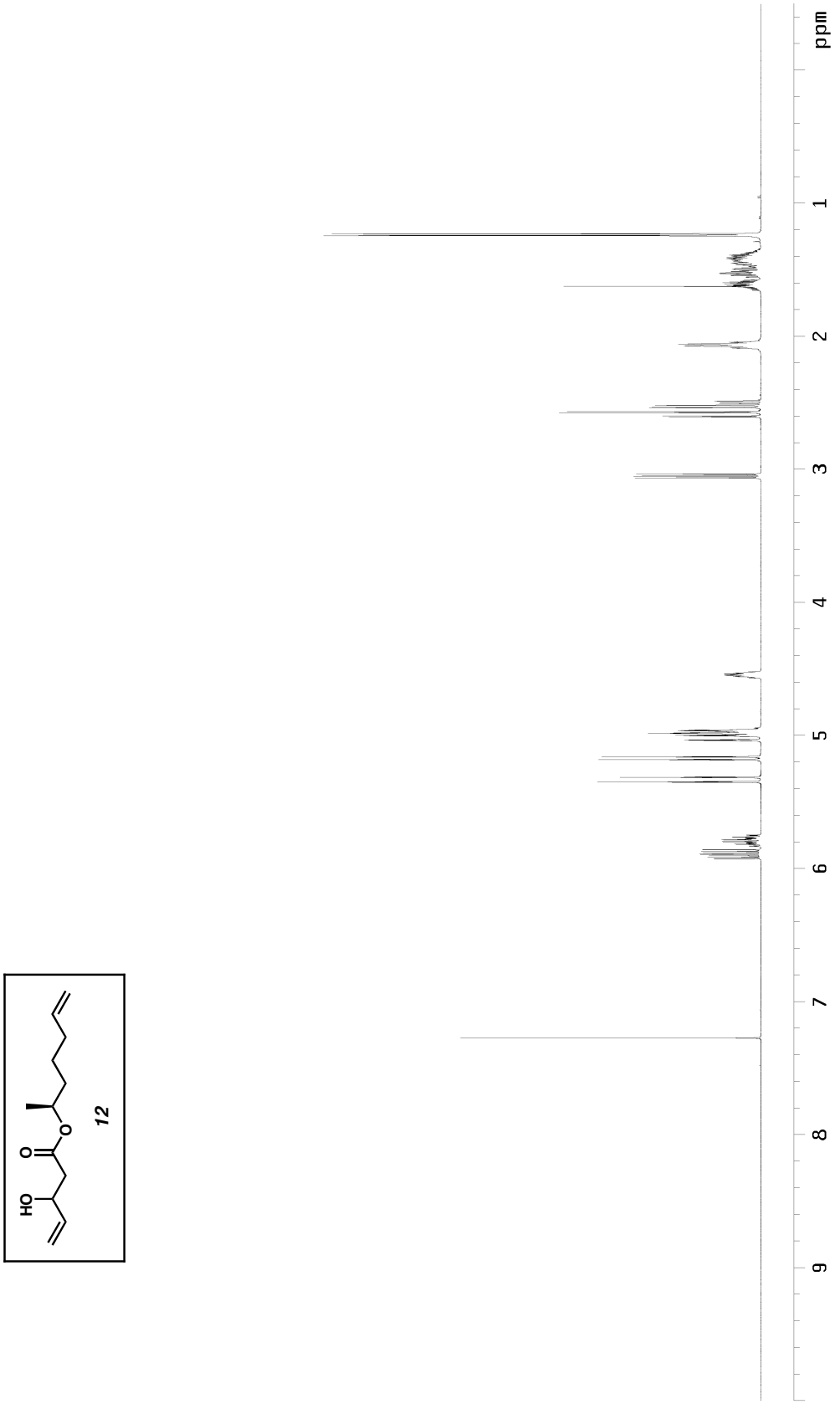


Figure 1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of β-hydroxyester **12**.

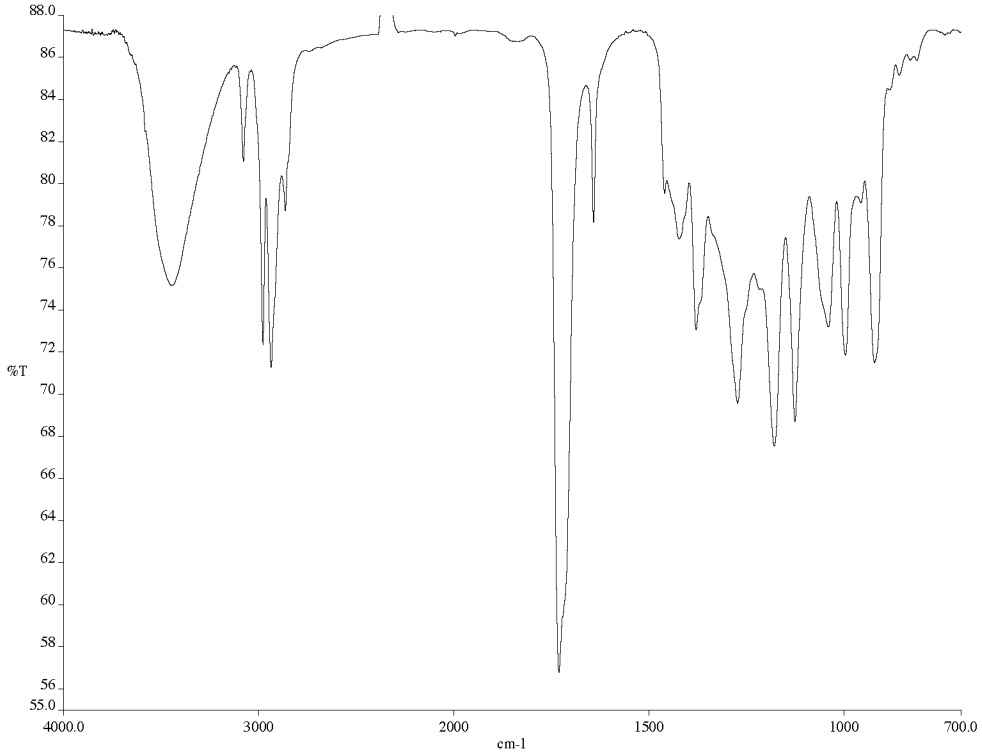


Figure 1.2. Infrared spectrum (thin film/NaCl) of β-hydroxyester **12**.

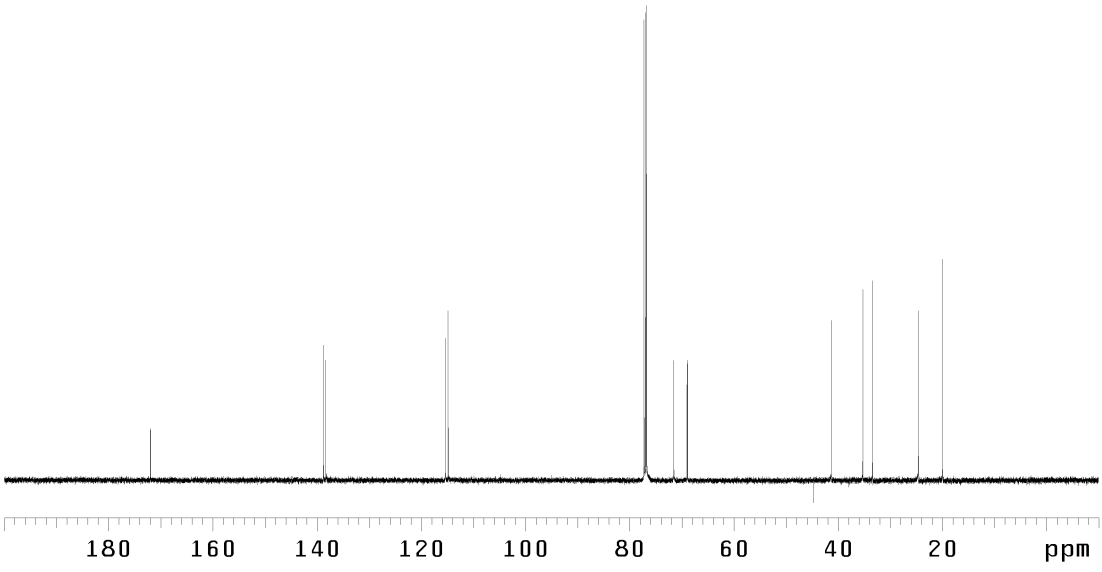


Figure 1.3. ^{13}C NMR (125 MHz, $CDCl_3$) of β-hydroxyester **12**.

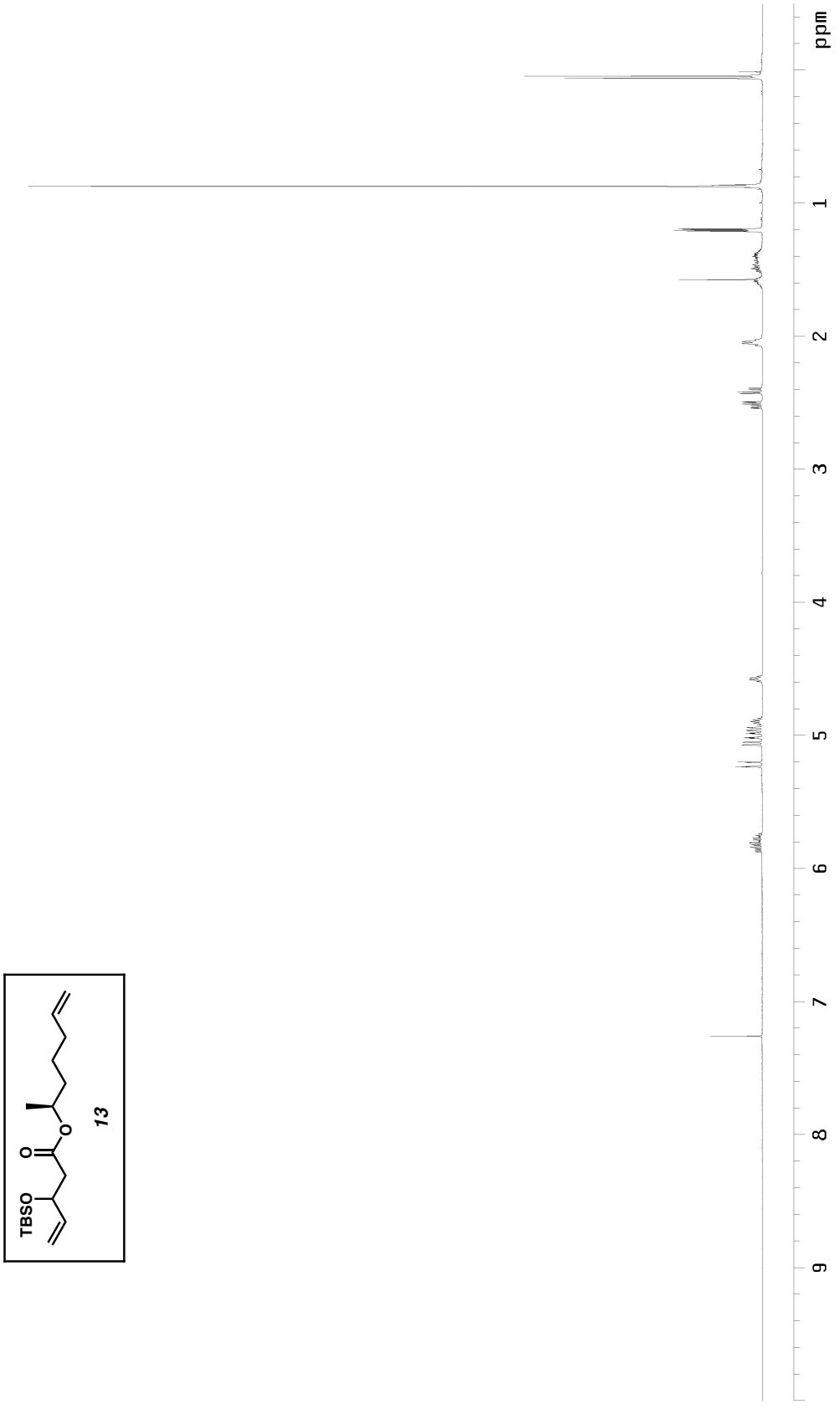


Figure 2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of silyl ether **13**.

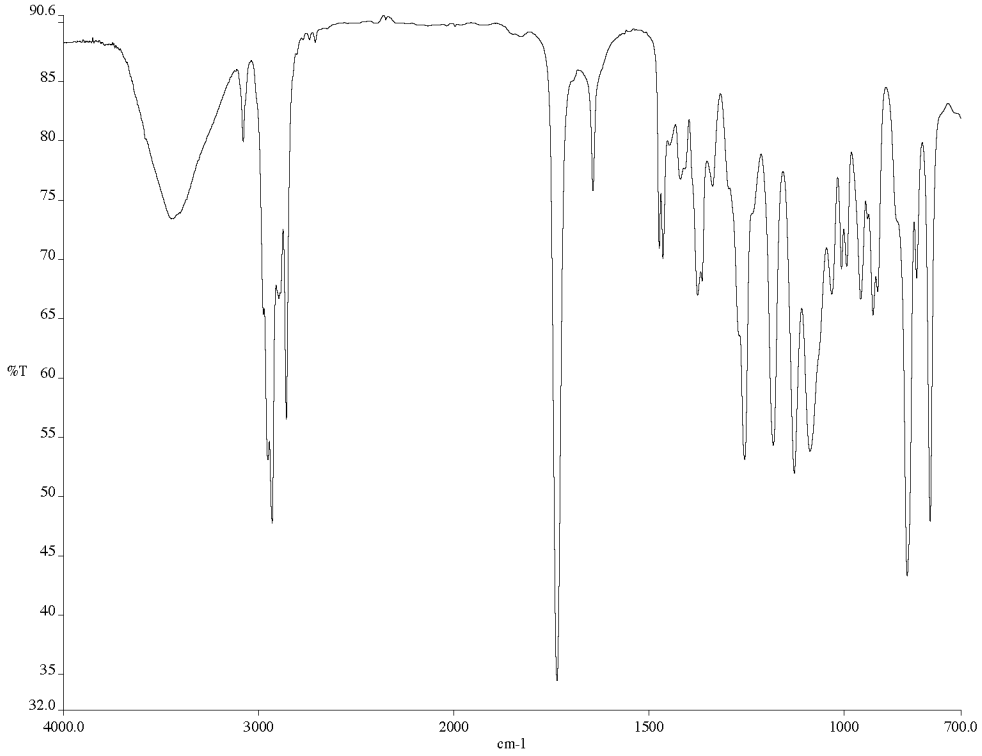


Figure 2.2. Infrared spectrum (thin film/NaCl) of silyl ether **13**.

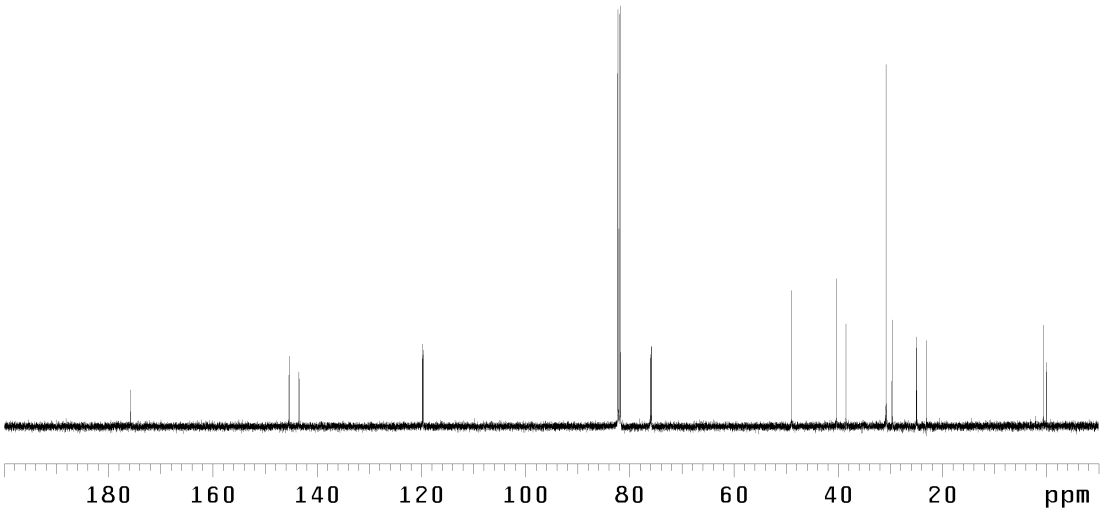


Figure 2.3. ^{13}C NMR (125 MHz, $CDCl_3$) of silyl ether **13**.

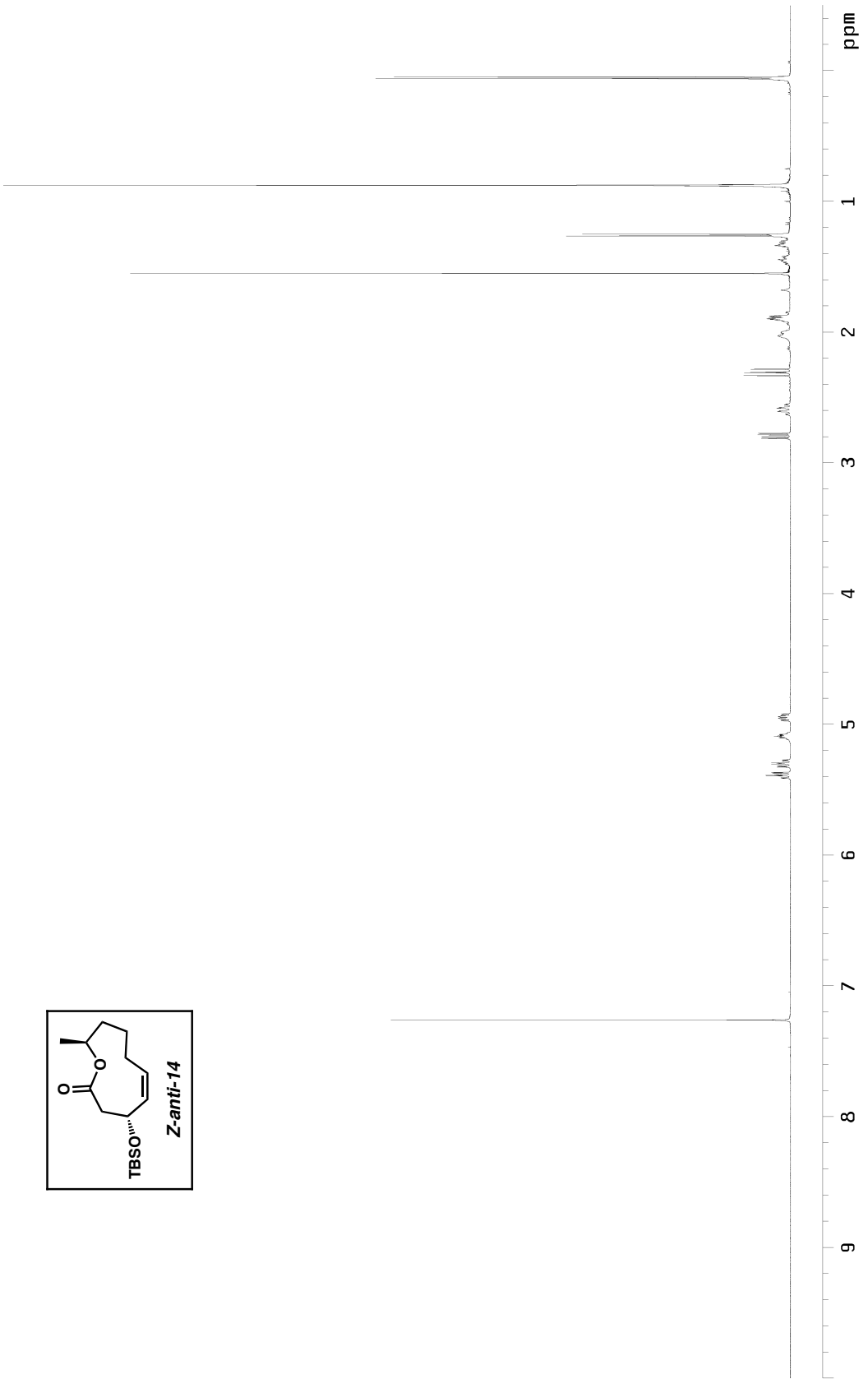


Figure 3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of ester ***Z-anti*-14**.

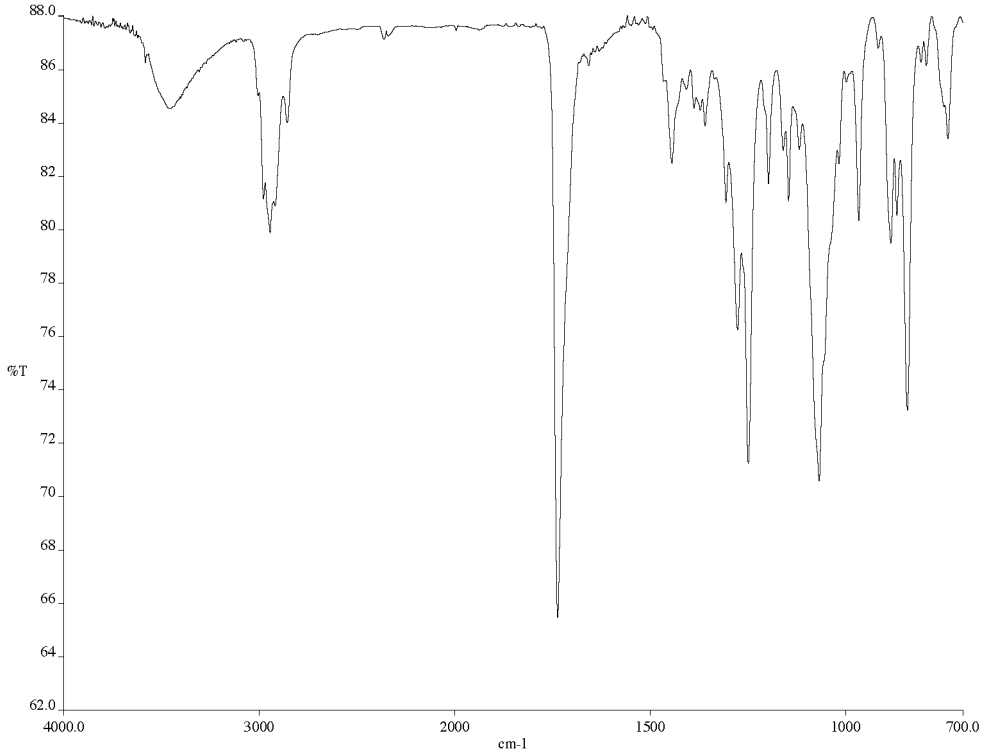


Figure 3.2. Infrared spectrum (thin film/NaCl) of ester ***Z-anti*-14**.

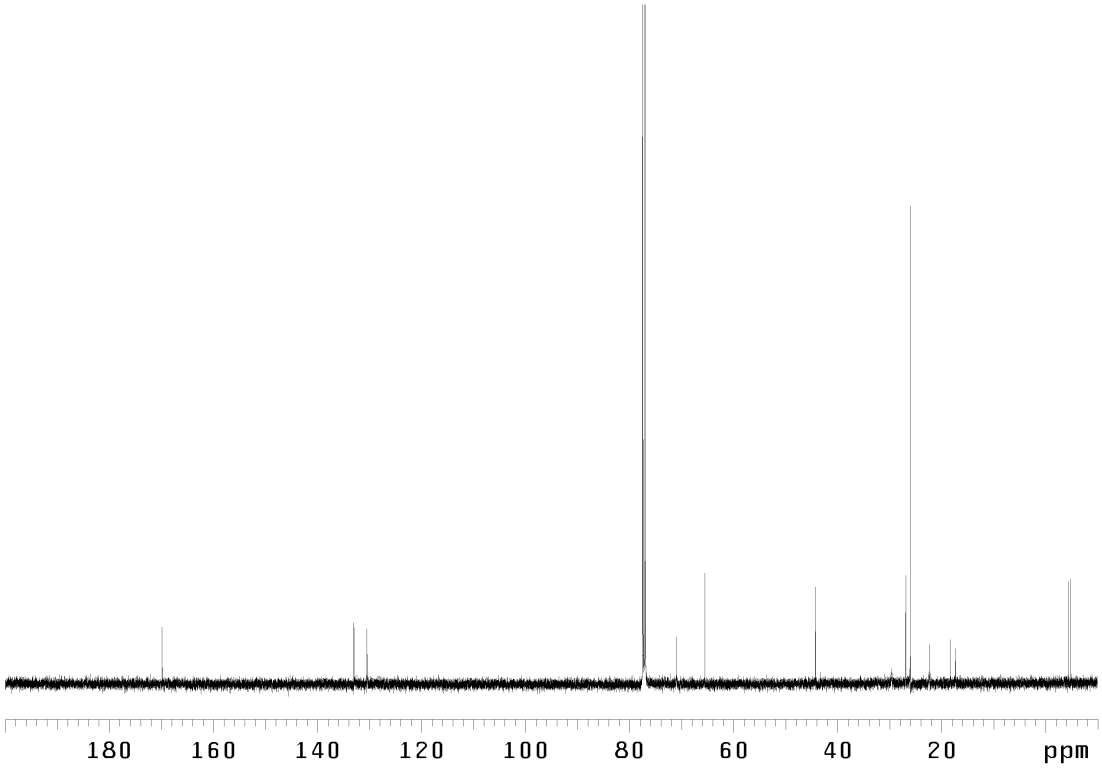


Figure 3.3. ^{13}C NMR (125 MHz, $CDCl_3$) of ester ***Z-anti*-14**.

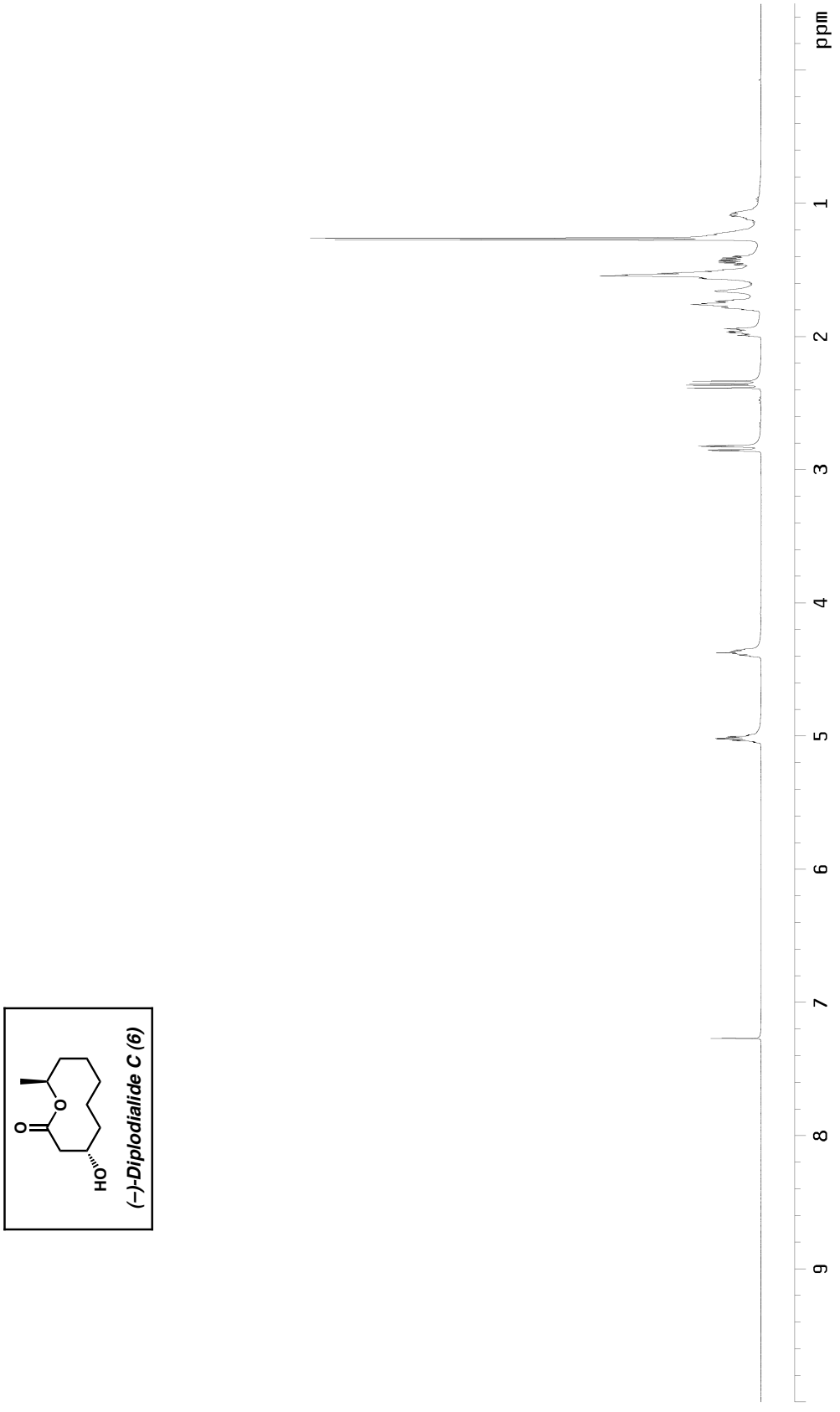


Figure 4.1 ^{1}H NMR (500 MHz, $CDCl_3$) of (–)-diplodialide C (**6**).

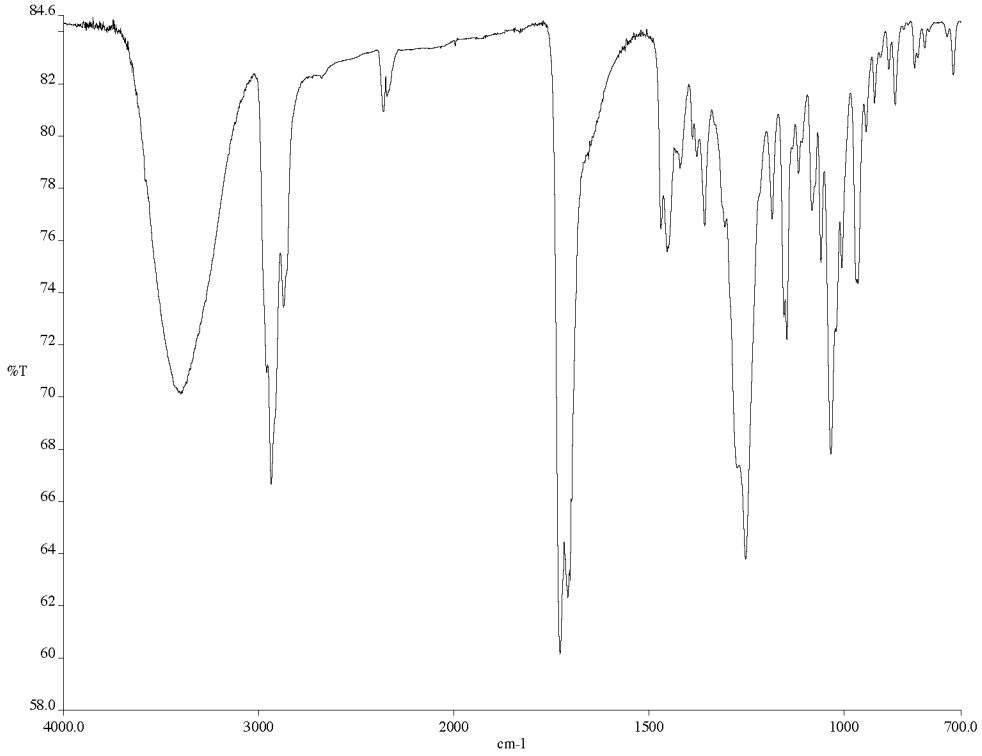


Figure 4.2. Infrared spectrum (thin film/NaCl) of (–)-diplodialide C (**6**).

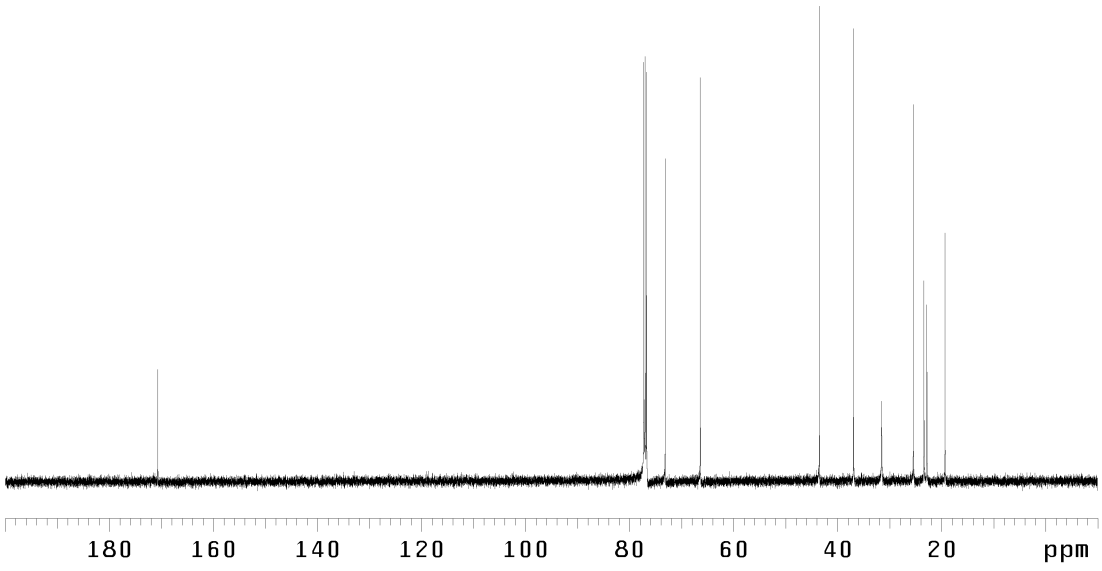


Figure 4.3. ^{13}C NMR (125 MHz, $CDCl_3$) of (–)-diplodialde C (**6**).

Figure 5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of ester **14**.

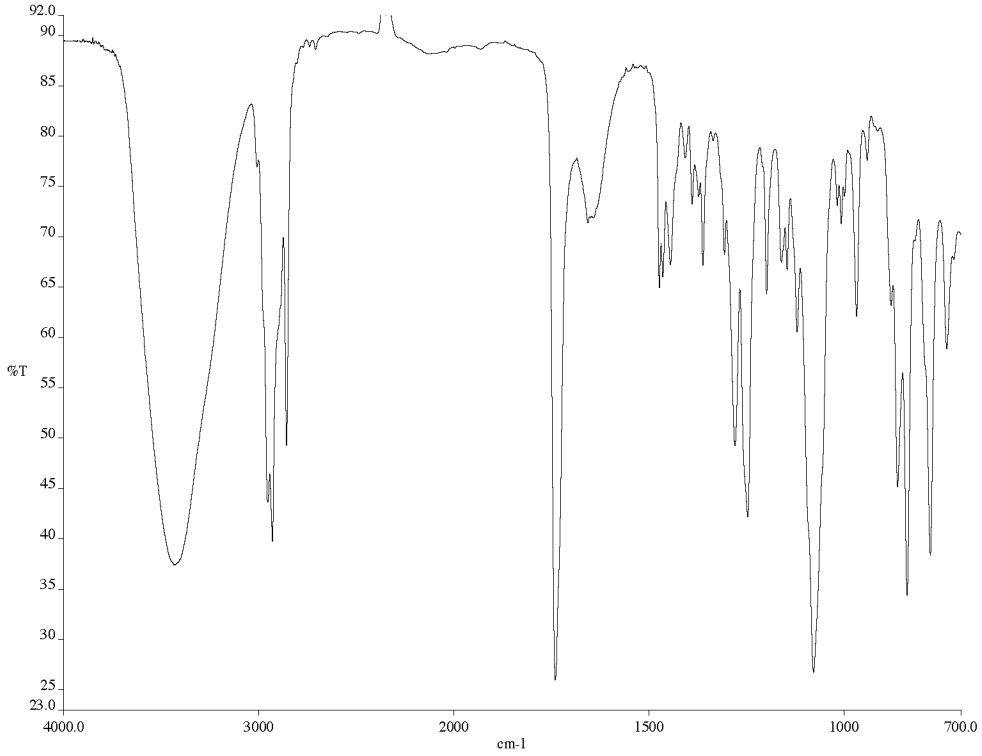


Figure 5.2. Infrared spectrum (thin film/NaCl) of ester **14**.

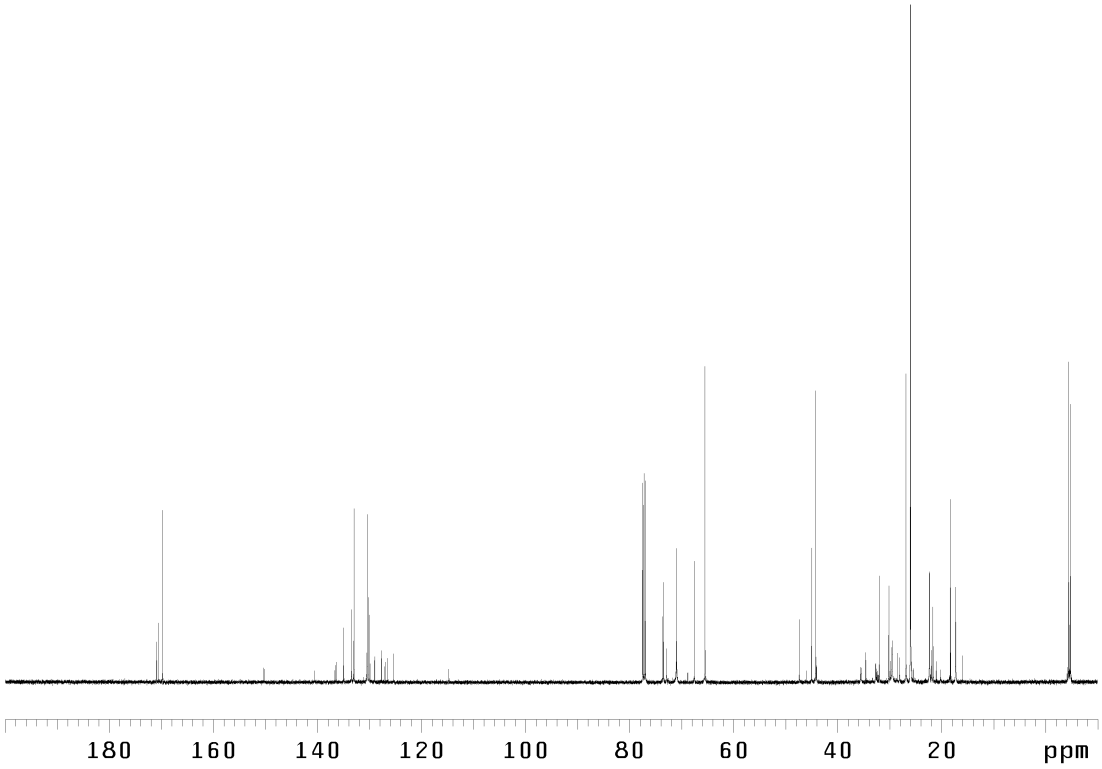


Figure 5.3. ^{13}C NMR (125 MHz, $CDCl_3$) of ester **14**.

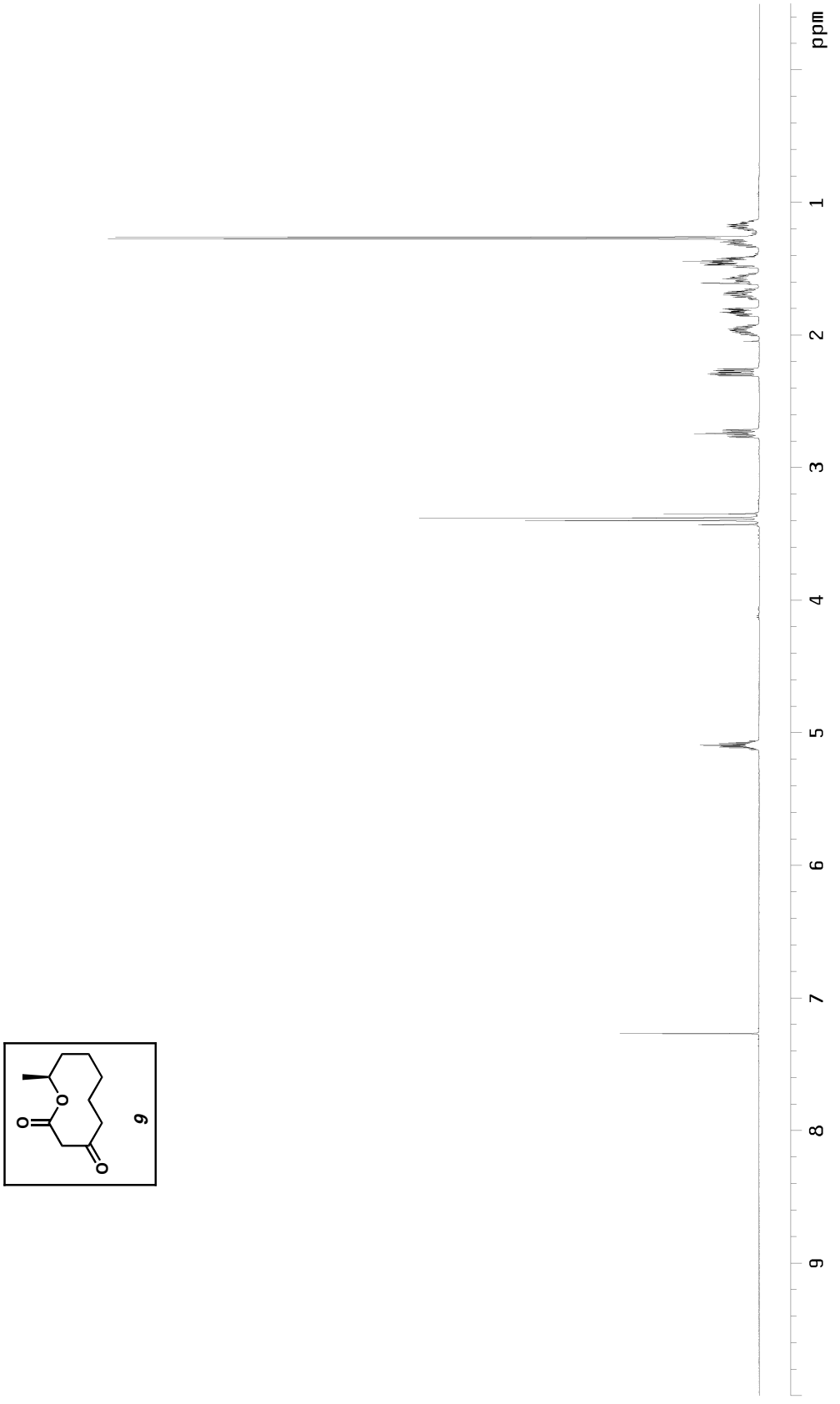


Figure 6.1 ^{1}H NMR (500 MHz, $CDCl_3$) of β-ketolactone **9**.

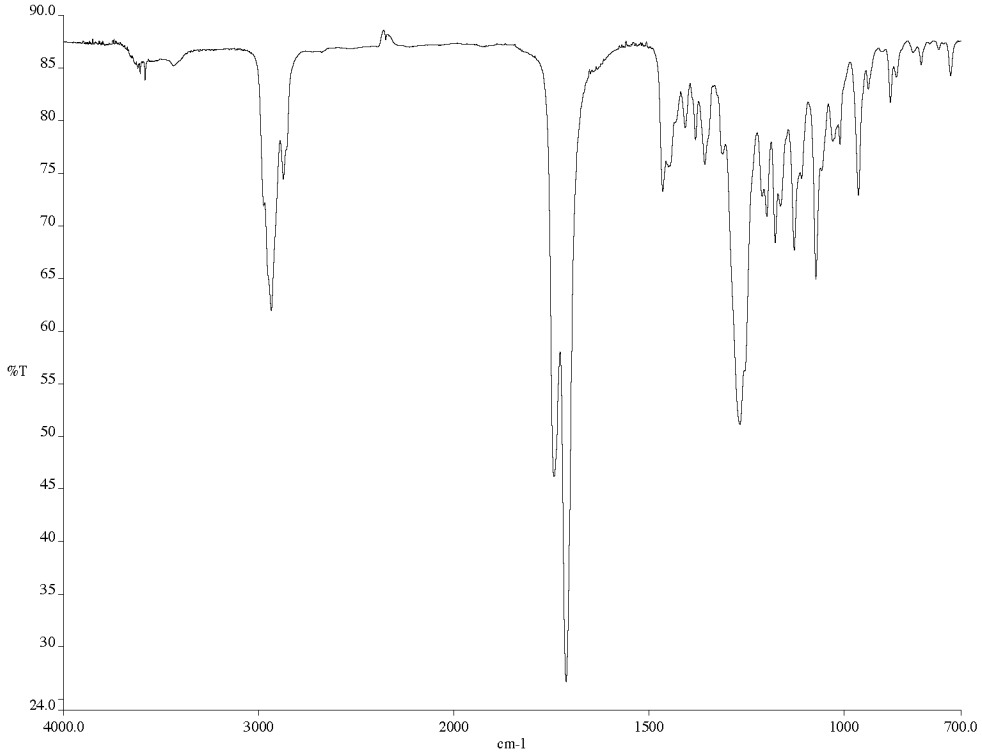


Figure 6.2. Infrared spectrum (thin film/NaCl) of β-ketolactone **9**.

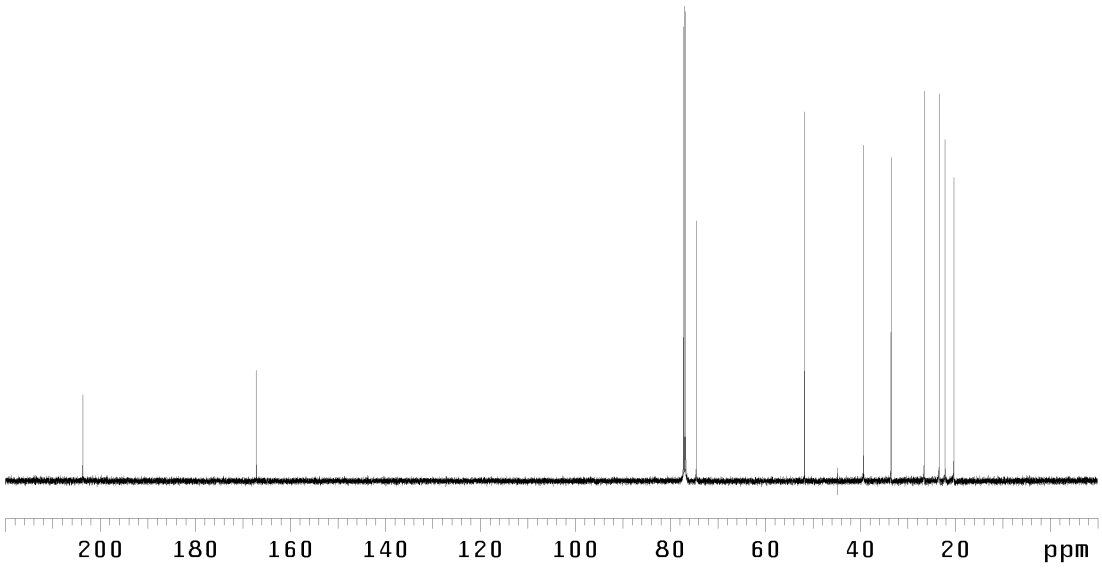


Figure 6.3. ^{13}C NMR (125 MHz, $CDCl_3$) of β-ketolactone **9**.

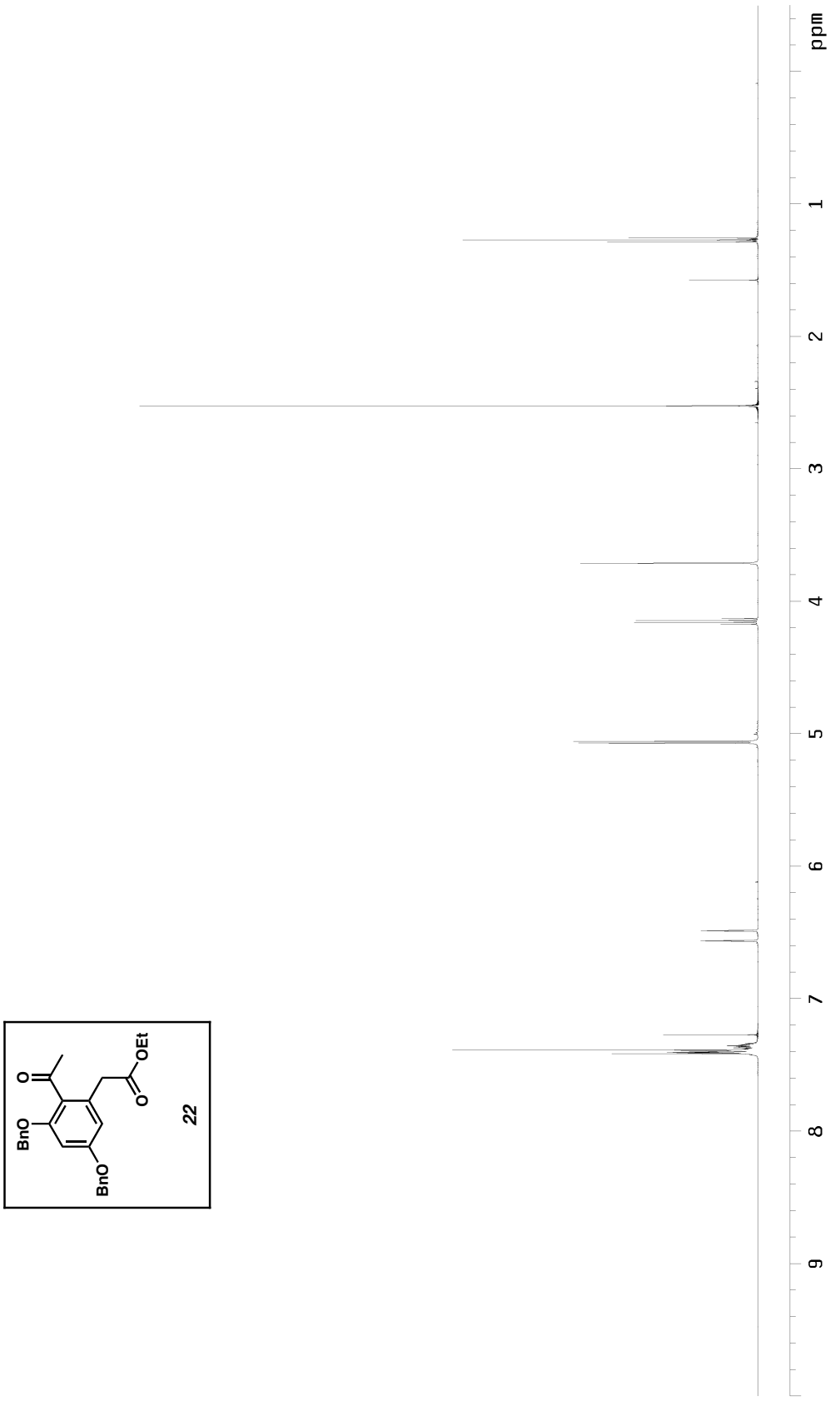


Figure 7.1 ^{1}H NMR (500 MHz, $CDCl_3$) of arene **22**.

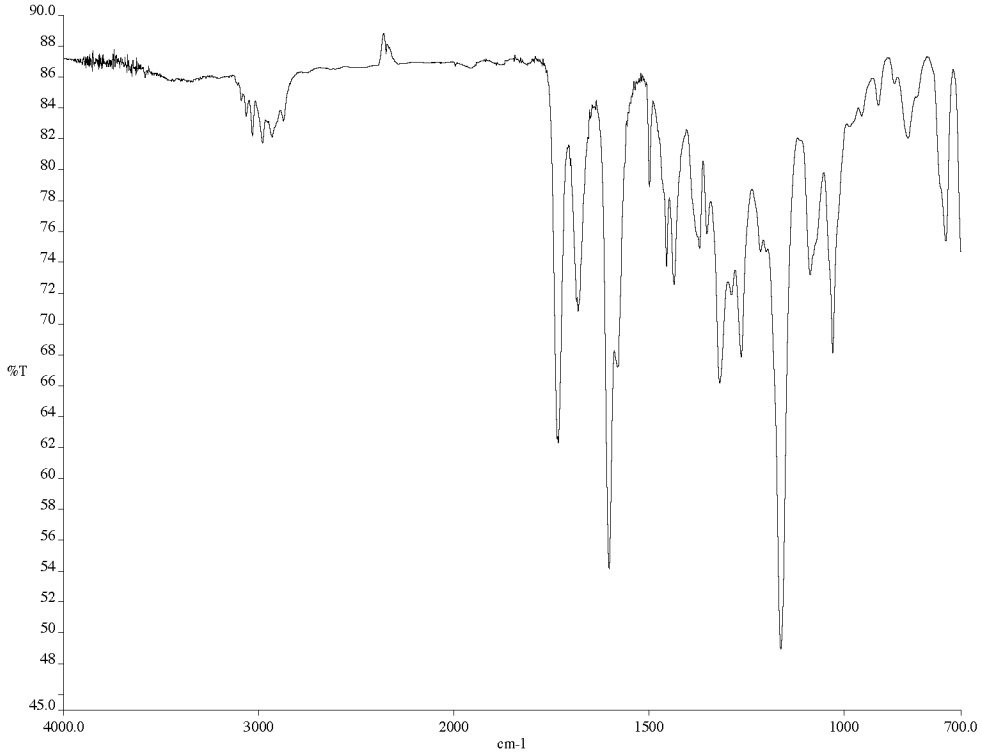


Figure 7.2. Infrared spectrum (thin film/NaCl) of arene **22**.

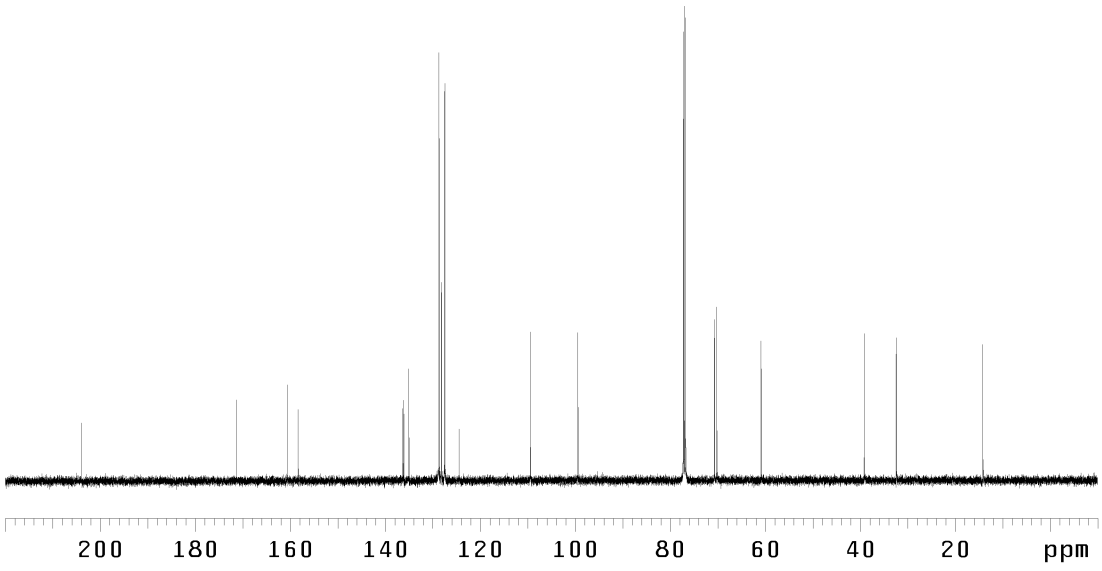


Figure 7.3. ^{13}C NMR (125 MHz, $CDCl_3$) of arene **22**.

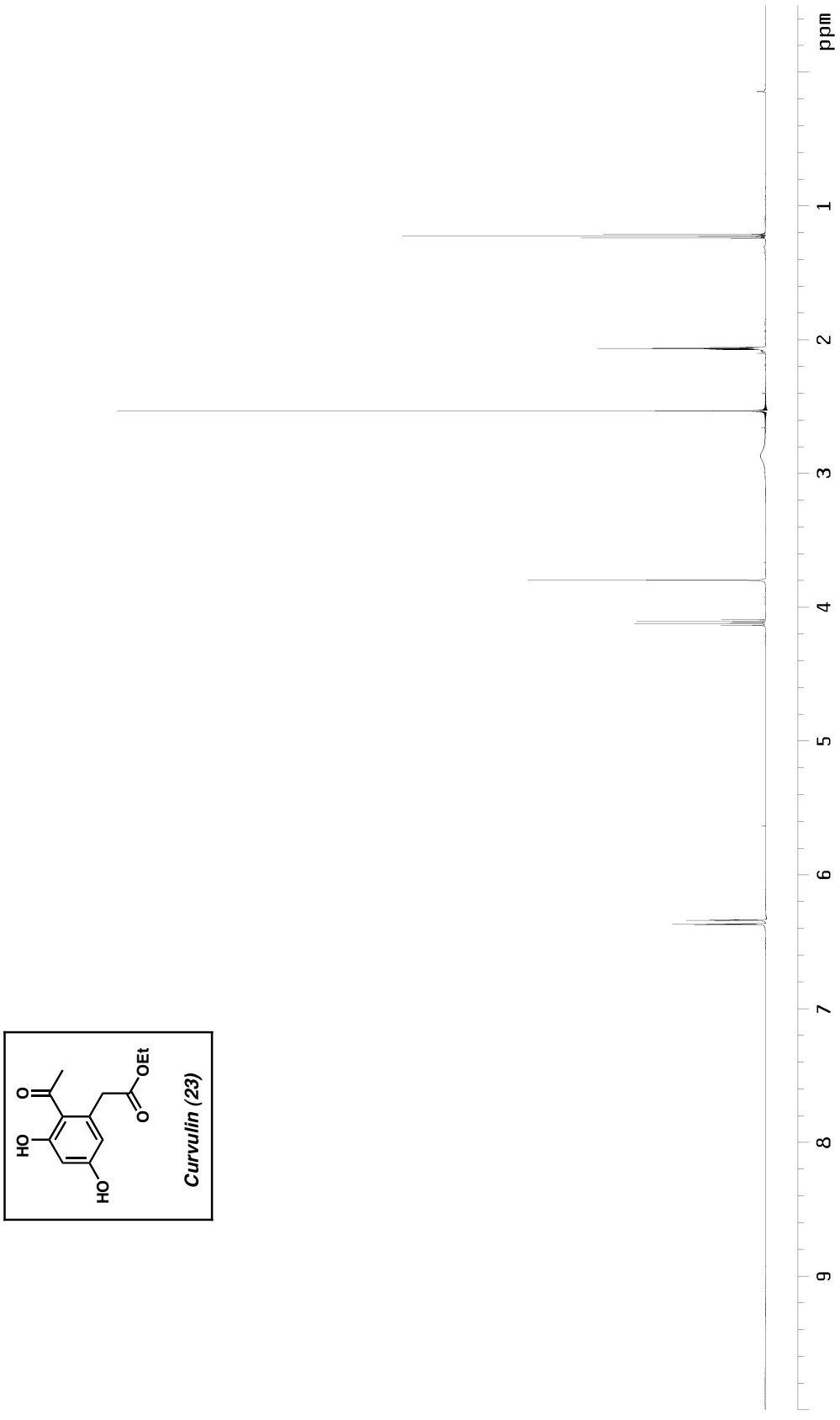


Figure 8.1 ^{1}H NMR (500 MHz, acetone-d_6) of curvulin (**23**).

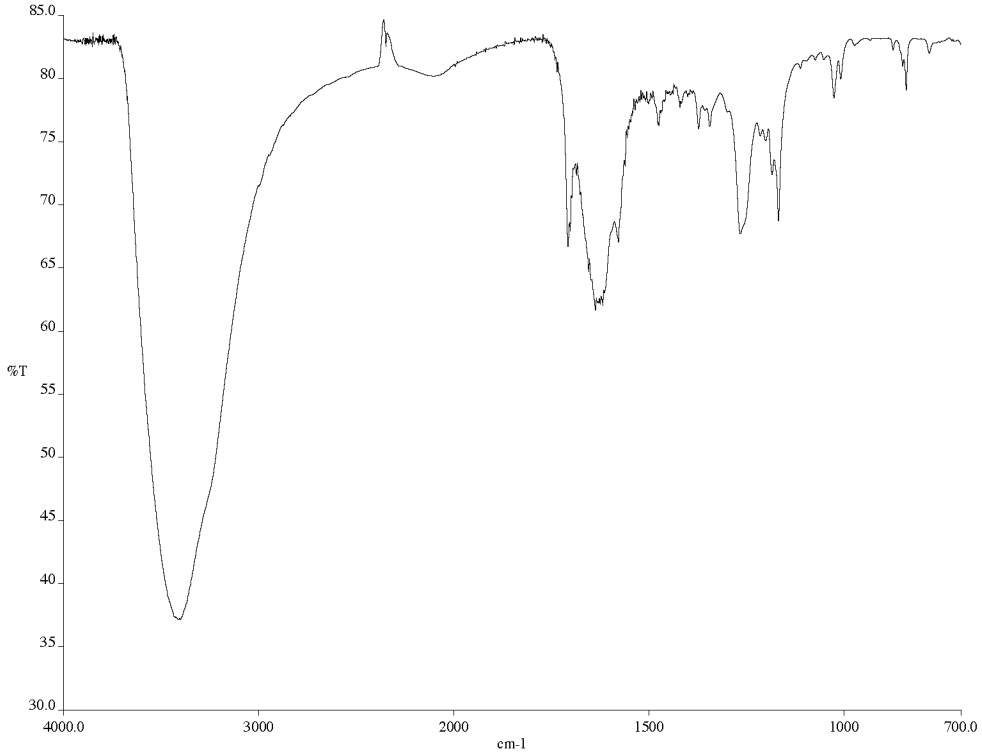


Figure 8.2. Infrared spectrum (thin film/NaCl) of curvulin (**23**).

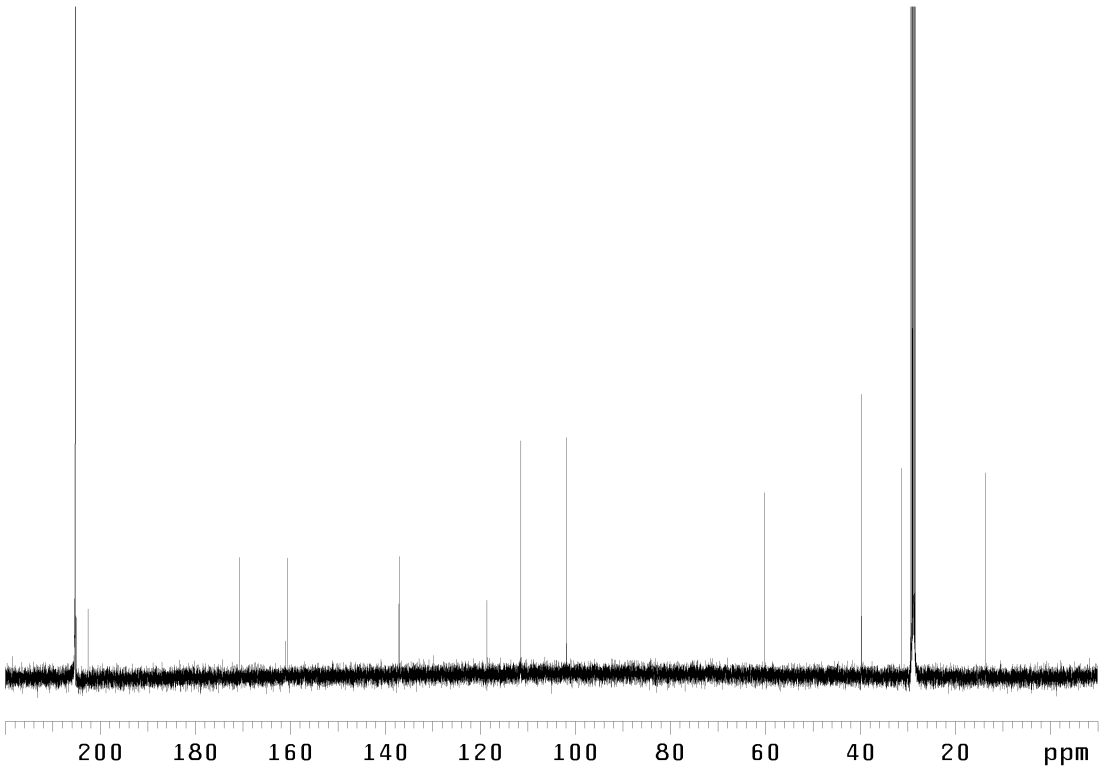


Figure 8.3. ^{13}C NMR (125 MHz, acetone-d_6) of curvulin (**23**).

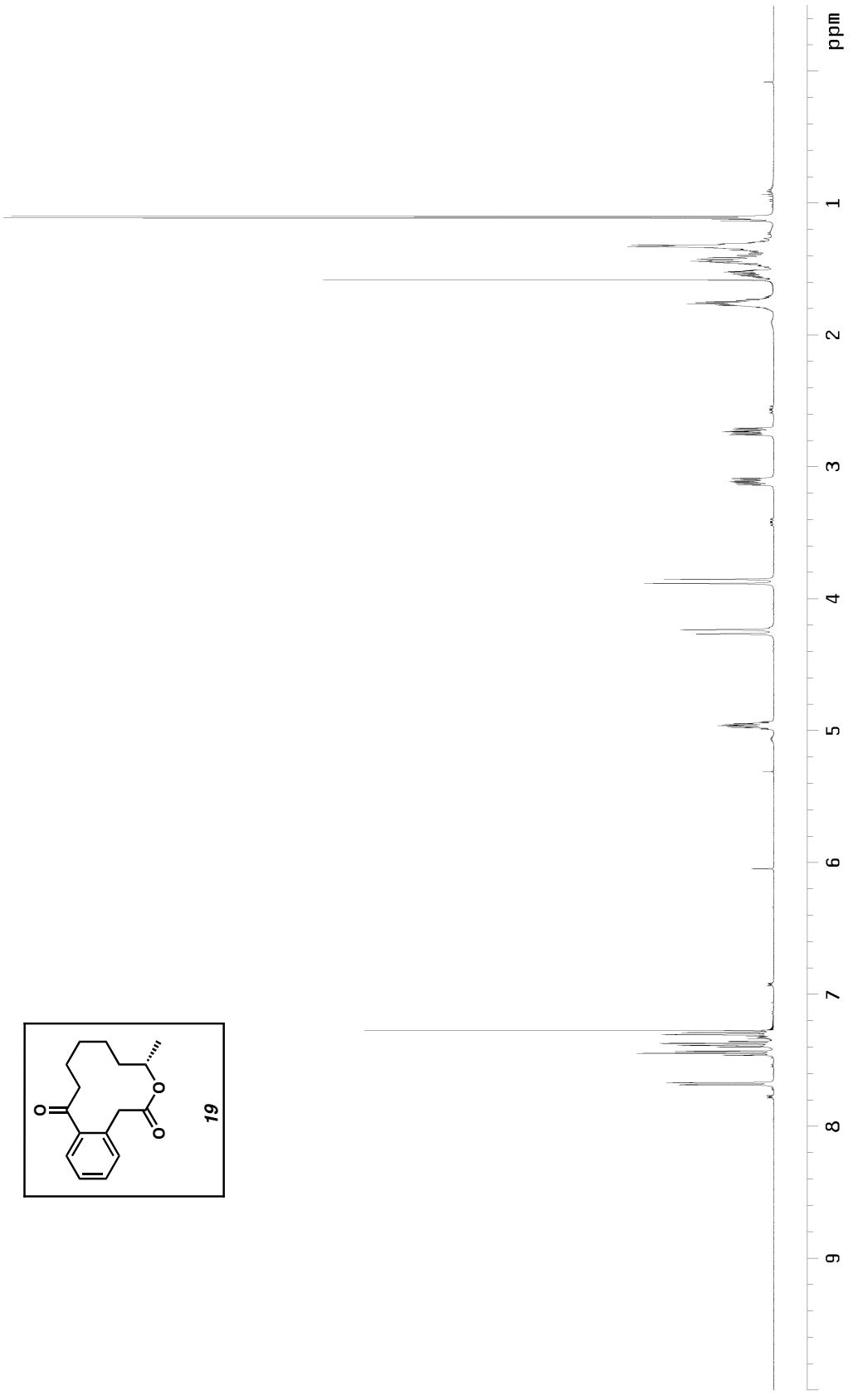


Figure 9.1 ^{1}H NMR (500 MHz, $CDCl_3$) of macrolactone **19**.

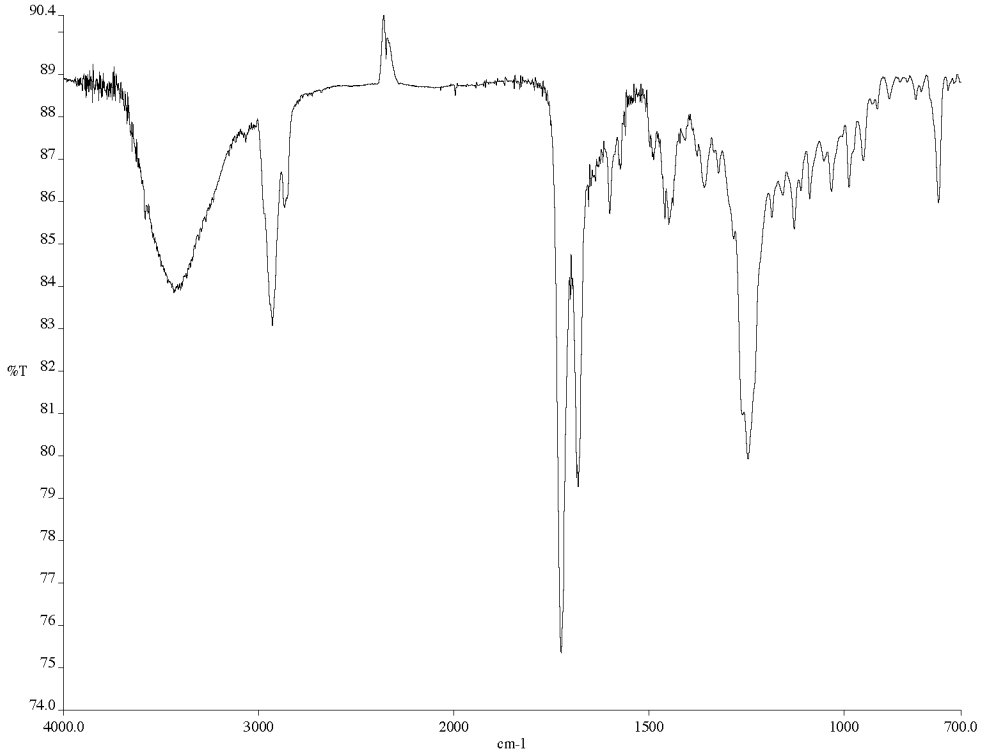


Figure 9.2. Infrared spectrum (thin film/NaCl) of macrolactone **19**.

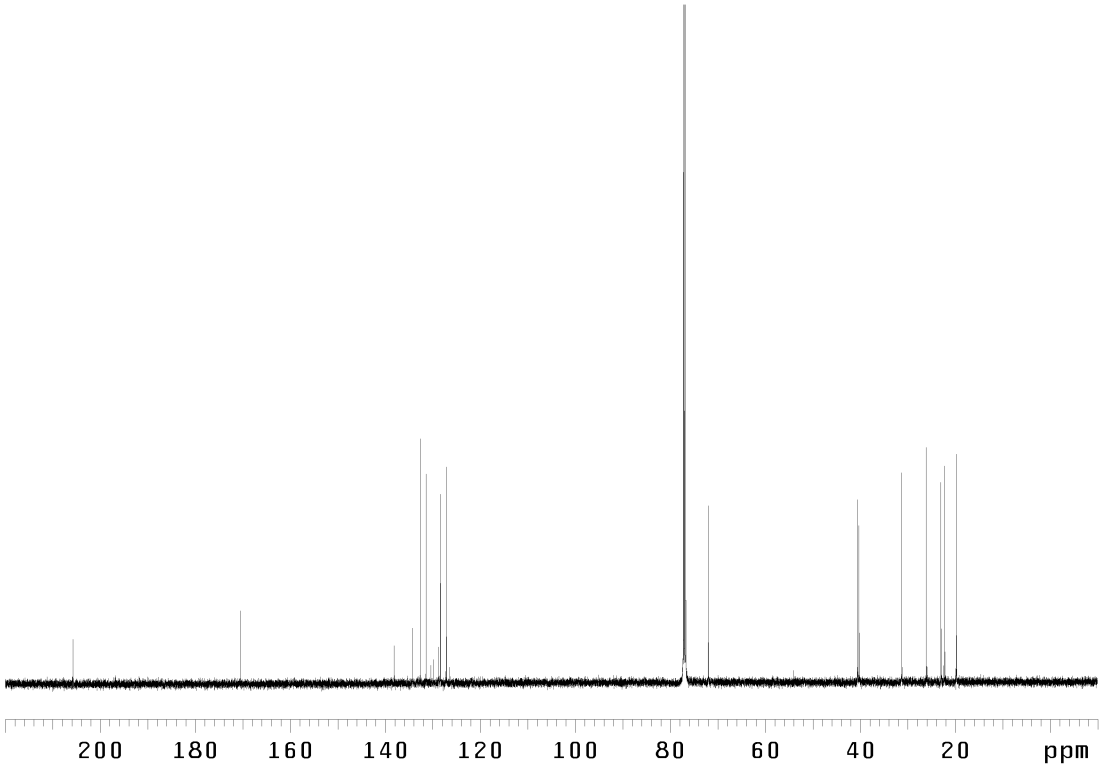


Figure 9.3. ^{13}C NMR (125 MHz, $CDCl_3$) of macrolactone **19**.

Figure 10.1 ^{1}H NMR (500 MHz, acetone-d_6) of (–)-curvularin (**1**).

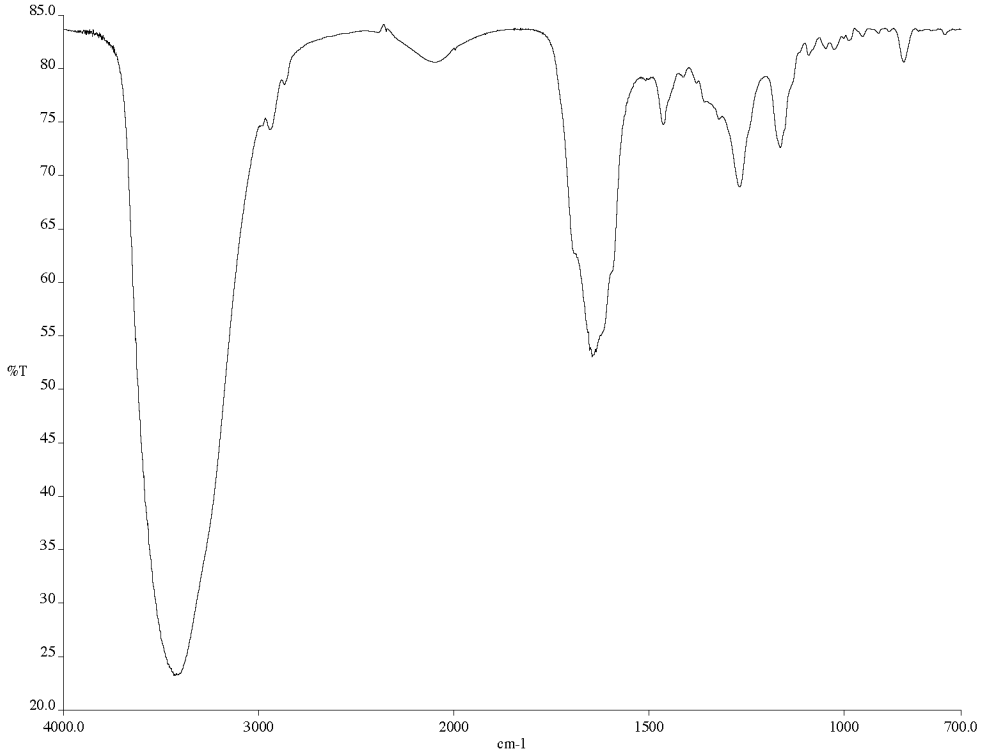


Figure 10.2. Infrared spectrum (thin film/NaCl) of (–)-curvularin (**1**).

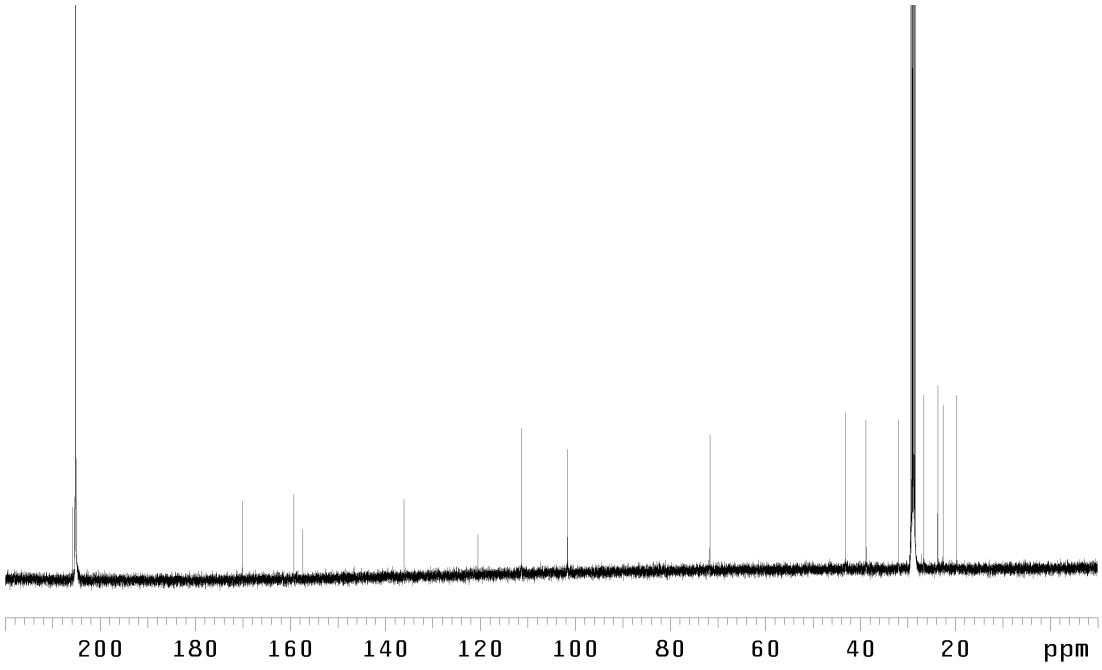


Figure 10.3. ^{13}C NMR (125 MHz, acetone-d_6) of (–)-curvularin (**1**).