Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

A Concise Synthesis of Eupomatilones 4, 6, and 7 via Rhodium-Catalyzed Enantioselective Desymmetrization of Cyclic *meso*-Anhydrides with *in situ*-Generated Diorganozinc Reagents

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General Methods. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Tetrahydrofuran (THF) and dimethylformamide (DMF) were purged with argon and passed through two columns of neutral alumina. Column chromatography was performed using EM Science silica gel 60 (230-400 mesh.) Thin layer chromatography was performed using EM Science 0.25 mm silca gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate or bromocresol green dips followed by heating.

Anhydride **4** was prepared by cyclization of the corresponding commercially available diacid. Anhydrides **8**, **10**, and **14** are commercially available (Aldrich) and were utilized without further purification. Anhydride **12** is commercially available (Rieke) and was utilized without further purification. Aryl bromides **17**, **19**, **21**, and **23**, indole **29**, furan **25**, and vinyl ether **27** are commercially available (Aldrich) and were utilized without further purification. Aryl bromide **16** is commercially available (Alfa Aesar) and utilized without further purification. Aryl bromide **17** was prepared according to literature procedure.[1] Catalyst precursors $[Rh(COD)Cl]_2$, $[Rh(COD)_2]BF_4$, and $Pd(OAc)_2$ are commercially available (Strem) and utilized without further purification. $Zn(OTf)_2$ is commercially available (Aldrich) and utilized without further purification. Ligands **2**, **6**, and **7** are commercially available (Strem). Boronic acids **33**, **35** and **39** are commercially available (Lancaster and Alfa Aesar).

^1H and ^{13}C NMR spectra were obtained on a Varian 300 MHz or Varian 400 MHz spectrometer at ambient temperature. Infrared spectra were obtained on a Nicolet Avatar

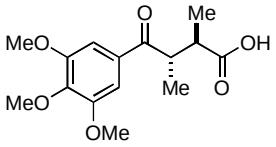
[1] T. Shirasaka, Y. Takuma, N. Imaki, *Synth. Commun.* **1990**, *20*, 1223.

320 FT-IR spectrometer. Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Mass spectra were obtained using a Fisions VC Autospec mass spectrometer. Analytic high performance liquid chromatography (HPLC) was performed on an Agilent 1100 series HPLC using Chiracel chiral columns. Optical rotations were measured on an Autopol III automatic polarimeter in a 1 dm cell.

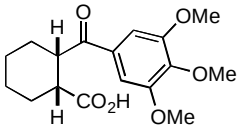
General procedure for the preparation of organozinc triflates will be illustrated with a specific example. An oven-dried round bottom flask was charged with 3,4,5-trimethoxy-1-bromobenzene (**16**) (124 mg, 0.5 mmol) and purged with Ar. **16** was subsequently dissolved in 1.5 mL THF and cooled to -78 °C in a dry ice/acetone bath. To this solution *n*BuLi (1.6 M in hexanes, 0.31 mL, 0.5 mmol) was slowly added and the mixture was allowed to stir for 30 min. Meanwhile, an oven-dried Schlenk flask was charged with $Zn(OTf)_2$ (182 mg, 0.5 mmol) in an inert atmosphere (N_2) glove box. Upon removal from the glove box, this solid was suspended in 1 mL THF. The aryl lithium formed in the initial step was then added via syringe to the suspension of $Zn(OTf)_2$ over blowing Ar. The mixture was stirred at ambient temperature for 2 h, at which time the THF was evaporated under reduced pressure. Addition of 1 mL DMF over blowing Ar to the resulting residue provided a solution (0.5 M) of the desired organozinc triflate.

General procedure for the enantioselective desymmetrization of succinic anhydrides will be illustrated with a specific example. An oven-dried round bottom flask was charged with $[Rh(COD)Cl]_2$ (6.0 mg, 0.012 mmol) and (-)-TADDOL-$PNMe_2$ (13.1 mg, 0.024 mmol) in an inert atmosphere (N_2) glove box. Upon removal from the glove box, the flask was purged with Ar and 1.0 mL DMF was added. The desired organozinc triflate (0.5 mmol), prepared according to the above procedure, was added to the catalyst solution. A solution of anhydride **4** (38 mg, 0.3 mmol) in 1 mL DMF was added via syringe and the reaction mixture was heated at 50 °C in an oil bath. After 20 h, the reaction mixture was diluted with 10 mL of Et_2O and quenched with 10 mL 1 M aq. HCl. The layers were separated and the aqueous layer extracted with Et_2O (2×10 mL). The combined organic layers were extracted with 1 M aq. Na_2CO_3 (2×5 mL), and the

combined aqueous layers were brought to pH ~ 1 with concentrated HCl. The acidified aqueous layer was then extracted with Et_2O (3 × 10 mL). The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield desired ketoacid **7**. For analysis of enantioselectivity, the corresponding methyl ester was generated by treatment of the ketoacid with $TMSCHN_2$ (2.0 M in Et_2O) in 3 mL of MeOH/PhH (1:1) at 23 °C for 5 min followed by quenching with AcOH.



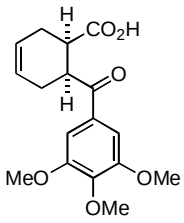
(2*R*,3*S*)-2,3-Dimethyl-4-oxo-4-(3,4,5-trimethoxy-phenyl)-butyric acid (7). According to the general procedure, 38 mg (0.3 mmol) of **4** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 50 °C. Standard work-up and purification by column chromatography (5:1 hex:EtOAc) provided the desired material as a white solid (75 mg, 0.25 mmol, 85%). The racemic compound has been previously characterized.[2] $[\alpha]_D^{23}$ = +23.4° (c = 0.7, $CHCl_3$). The corresponding methyl ester was utilized for ee determination. HPLC analysis (Chiralcel AD-H, 97:3 hex/*i*PrOH, 1.0 mL/min, 254 nm; tr (major) = 12.9 min, tr (minor) = 15.5 min) gave the isomeric composition of the product: 87% ee.



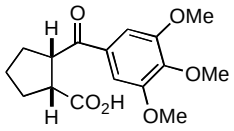
(1*R*,2*S*)-2-(3,4,5-Trimethoxy-benzoyl)-cyclohexanecarboxylic acid (9). According to the general procedure, 46 mg (0.3 mmol) of **8** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 50 °C. Standard work-up and purification by column chromatography (4:1 Hex:EtOAc) provided the desired material as viscous oil (69 mg, 0.22 mmol, 72%). R_f = 0.12 (1:1 Hex:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): 7.14 (s, 2H), 3.91 (s, 3H), 3.90 (s, 6H), 3.90-3.85 (m, 1H), 2.68 (ddd, 1H, *J* = 7.9, 4.4, 4.4 Hz), 2.29-2.20 (m, 1H), 2.17-2.09 (m, 1H), 1.94-2.06 (m, 1H), 1.75-1.86 (m, 2H), 1.44-1.53 (m, 1H), 1.27-1.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 179.4, 153.1, 142.3,

[2] E. A. Bercot, T. Rovis *J. Am. Chem. Soc.* **2005**, *127*, 247.

131.5, 105.8, 60.9, 56.2, 43.6, 42.7, 28.2, 25.2, 25.0, 22.3; IR (NaCl, $CDCl_3$) 2940, 1703, 1678, 1584, 1504, 1454, 1414, 1320, 1232, 1157 cm^{-1}. HRMS (FAB-) calcd for $C_{17}H_{21}O_6^-$, 321.1338. Found 321.1342. $[\alpha]_D^{23}$ = +17.3° (c = 0.3, $CHCl_3$). The product acid was converted to the corresponding methyl ester for ee determination. HPLC (Chiracel AD-H, 92:8 hex:*i*PrOH, 1.0 mL/min, 254 nm; tr (minor) = 16.1 min, tr (major) = 18.2 min) gave the isomeric composition of the product: 83 % ee.



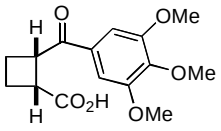
(1*R*,6*S*)- 6-(3,4,5-Trimethoxy-benzoyl)-cyclohex-3-enecarboxylic acid (11). According to the general procedure, 46 mg (0.3 mmol) of **10** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 50 °C. Standard work-up and purification by column chromatography (5:1 Hex/EtOAc) provided the desired material as a viscous oil which solidified upon standing (74 mg, 0.23 mmol, 77%). The racemic compound has been previously characterized.[3] $[\alpha]_D^{23}$ = +7.0° (c = 0.8, $CHCl_3$). The corresponding methyl ester was utilized for ee determination. HPLC analysis (Chiralcel AD-H, 92:8 hex/*i*PrOH, 1.0 mL/min, 254 nm; tr (major) = 17.7 min, tr (minor) = 22.8 min) gave the isomeric composition of the product: 82% ee.



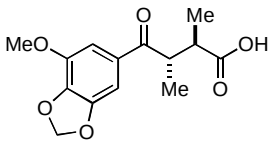
(1*R*,2*S*)-2-(3,4,5-Trimethoxy-benzoyl)-cyclopentanecarboxylic acid (13). According to the general procedure, 42 mg (0.3 mmol) of **12** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 25 °C (note change in temperature). Standard work-up and purification by column chromatography (6:1 Hex:EtOAc) provided the desired material as a white solid (57 mg, 0.18 mmol, 61%). R_f = 0.45 (1:1 Hex:EtOAc). ^1H NMR (300 MHz, $CDCl_3$): 7.18 (s, 2H), 4.10 (dt, 1H, *J* = 8.0, 4.0 Hz), 3.89 (s, 3H), 3.88 (s, 6H), 3.02 (dt, 1H, *J* = 8.0, 8.0 Hz), 2.24-1.57 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 199.6, 180.6, 152.9, 142.3, 131.1, 105.9, 60.8, 56.2, 48.4, 47.5, 28.5, 27.4, 23.8. IR (NaCl, neat) 2950, 1736, 1676, 1584, 1504, 1455, 1434, 1414, 1363, 1321, 1231, 1199 cm^{-1}. HRMS

[3] J. B. Johnson, R. T. Yu, P. Fink, E. A. Bercot, T. Rovis *Org. Lett.* **2006**, *8*, 4307.

(FAB+) calcd for $C_{16}H_{21}O_6^+$, 309.1333. Found 309.3682. $[\alpha]_D^{23}$ = +46.1° (c = 0.4, $CHCl_3$). The product acid was converted to the corresponding methyl ester for ee determination. HPLC (Chiracel ADH, 97:3 hex:*i*PrOH, 0.5 mL/min, 254 nm; tr (minor) = 35.8 min, tr (major) = 37.5 min) gave the isomeric composition of the product: 77 % ee.

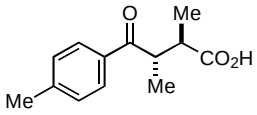


(1*R*,2*S*)-2-(3,4,5-Trimethoxy-benzoyl)-cyclobutanecarboxylic acid (15). According to the general procedure, 38 mg (0.3 mmol) of **14** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 25 °C (Note change in general procedure). Standard work-up and purification by column chromatography (6:1 Hex:EtOAc) provided the desired material as a white solid (50 mg, 0.17 mmol, 57%). R_f = 0.32 (1:1 Hex:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): 7.19 (s, 2H), 4.32-4.20 (m, 1H), 3.87 (s, 3H), 3.86 (s, 6H), 3.64-3.54 (m, 1H), 2.41-2.13 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 197.7, 180.1, 153.2, 142.7, 130.2, 105.8, 61.0, 56.3, 43.6, 39.2, 22.7, 22.0. IR (NaCl, neat) 2979, 2950, 1731, 1674, 1585, 1504, 1458, 1435, 1415, 1334, 1233, 1200, 1159 cm^{-1}. HRMS (FAB+) calcd for $C_{15}H_{19}O_6^+$, 295.1176. Found 294.5026. $[\alpha]_D^{23}$ = +10.3° (c = 0.4, $CHCl_3$). The product acid was converted to the corresponding methyl ester for ee determination. HPLC (Chiracel ODH, 97:3 hex:*i*PrOH, 0.5 mL/min, 254 nm; tr (major) = 28.5 min, tr (minor) = 30.6 min) gave the isomeric composition of the product: 76 % ee.

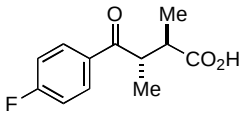


(2*R*,3*S*)-4-(7-Methoxy-benzo[1,3]dioxol-5-yl)-2,3-dimethyl-4-oxo-butyric acid (18). According to the general procedure, 38 mg (0.3 mmol) of **4** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 50 °C. Standard work-up and purification by column chromatography (5:1 Hex/EtOAc) provided the desired material as a viscous oil which solidified upon standing (73 mg, 0.26 mmol, 88%). The racemic compound has been previously characterized.[1] $[\alpha]_D^{23}$ = +32.8° (c = 0.6, $CHCl_3$). The corresponding methyl ester was utilized for ee determination. HPLC analysis (Chiralcel

OJ-H, 90:10 hex/*i*PrOH, 0.3 mL/min, 254 nm; tr (major) = 49.3 min, tr (minor) = 52.1 min) gave the isomeric composition of the product: 88% ee.

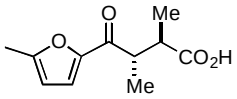


(2*R*,3*S*)-2,3-Dimethyl-4-oxo-4-*p*-tolyl-butyric acid (22). According to the general procedure, 38 mg (0.3 mmol) of **4** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 50 °C. Standard work-up and purification by column chromatography (5:1 Hex:EtOAc) provided the desired material as oily solid (49 mg, 0.22 mmol, 74%). R_f = 0.17 (1:1 Hex:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): 7.88 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 3.71 (dq, 1H, *J* = 8.5, 7.1 Hz), 2.97 (dq, 1H, *J* = 8.5, 7.1 Hz), 2.42 (s, 3H), 1.25 (d, 3H, *J* = 7.1 Hz), 1.19 (d, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): d 202.6, 181.0, 144.4, 133.7, 129.4, 128.6, 43.2, 42.4, 21.6, 16.6, 16.1; IR (NaCl, $CDCl_3$) 2987, 2954, 1729, 1677, 1607, 1454, 1161 cm^{-1}. HRMS (FAB+) calcd for $C_{13}H_{17}O_3^+$, 221.1178. Found 221.1187. $[\alpha]_D^{23}$ = +6.7° (c = 0.3, $CHCl_3$). The product acid was converted to the corresponding methyl ester for ee determination. HPLC (Chiracel OB-H, 98:2 hex:*i*PrOH, 0.5 mL/min, 254 nm; tr (minor) = 15.5 min, tr (major) = 17.6 min) gave the isomeric composition of the product: 87 % ee.

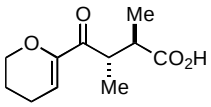


(2*R*,3*S*)-4-(4-Fluoro-phenyl)-2,3-dimethyl-4-oxo-butyric acid (24). According to the general procedure, 38 mg (0.3 mmol) of **4** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 50 °C. Standard work-up and purification by column chromatography (5:1 Hex:EtOAc) provided the desired material as an oily solid (52 mg, 0.23 mmol, 78%). R_f = 0.17 (1:1 Hex:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): 8.01 (dd, *J* = 8.9, 5.6 Hz, 2H), 7.16 (d, *J* = 8.9, 8.8 Hz, 2H), 3.70 (dq, 1H, *J* = 8.8, 7.1 Hz), 2.97 (dq, 1H, *J* = 8.8, 7.2 Hz), 1.25 (d, 3H, *J* = 7.1 Hz), 1.19 (d, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.1, 180.6, 165.9 (d, $J_{C\text{-}F}$ = 256.4 Hz), 132.7 (d, $J_{C\text{-}F}$ = 4.5 Hz), 131.1 (d, $J_{C\text{-}F}$ = 9.0 Hz), 115.9 (d, $J_{C\text{-}F}$ = 20.6 Hz), 43.2, 42.4, 16.6, 16.0; IR (NaCl, $CDCl_3$)

2983, 2954, 1730, 1681, 1598, 1156 cm^{-1}. HRMS (FAB+) calcd for $C_{12}H_{14}O_3F^+$, 225.0927. Found 225.0926. $[\alpha]_D^{23}$ = +21.9° (c = 0.3, $CHCl_3$). The product acid was converted to the corresponding methyl ester for ee determination. HPLC (Chiracel OB-H, 98:2 hex:*i*PrOH, 0.5 mL/min, 254 nm; tr (major) = 18.2 min, tr (minor) = 19.3 min) gave the isomeric composition of the product: 87 % ee.

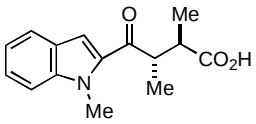


(2*R*,3*S*)-2,3-Dimethyl-4-(5-methyl-furan-2-yl)-4-oxo-butyric acid (26). According to the general procedure, 38 mg (0.3 mmol) of **4** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 50 °C. Standard work-up and purification by column chromatography (5:1 Hex:EtOAc) provided the desired material as a white solid (52 mg, 0.25 mmol, 82%). R_f = 0.17 (1:1 Hex:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): 7.21 (d, *J* = 3.5 Hz, 1H), 6.19 (d, *J* = 3.5 Hz, 1H), 3.41 (dq, 1H, *J* = 8.6, 7.1 Hz), 2.92 (dq, 1H, *J* = 8.6, 7.1 Hz), 2.41 (s, 3H), 1.25 (d, 3H, *J* = 6.9 Hz), 1.19 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 180.4, 159.0, 150.8, 120.7, 109.4, 43.8, 42.1, 16.5, 16.1, 14.2; IR (NaCl, $CDCl_3$) 2982, 2954, 1731, 1665, 1515, 1164 cm^{-1}. HRMS (FAB+) calcd for $C_{11}H_{15}O_4^+$, 211.0970. Found 211.0976. $[\alpha]_D^{23}$ = +16.0° (c = 0.8, $CHCl_3$). The product acid was converted to the corresponding methyl ester for ee determination. HPLC (Chiracel OB-H, 97:3 hex:*i*PrOH, 1.0 mL/min, 254 nm; tr (major) = 11.8 min, tr (major) = 15.3 min) gave the isomeric composition of the product: 85 % ee.

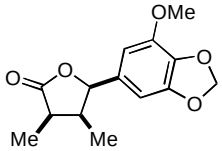


(2*R*,3*S*)-4-(5,6-Dihydro-4H-pyran-2-yl)-2,3-dimethyl-4-oxo-butyric acid (28). According to the general procedure, 38 mg (0.3 mmol) of **4** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 50 °C. Standard work-up and purification by column chromatography (4:1 Hex:EtOAc) provided the desired material as a colorless oil (62 mg, 0.23 mmol, 76%). R_f = 0.48 (1:1 Hex:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): 6.04 (dd, 1H, *J* = 4.5, 4.2 Hz), 4.07 (dd, 2H, *J* = 5.4, 5.7 Hz), 3.34 (dq, 1H, *J* = 8.7, 7.2 Hz), 2.83 (dq, 1H, *J* = 7.9, 7.2 Hz), 2.23 (dt, 2H, *J* = 6.3, 4.5 Hz), 1.90–1.81 (m, 2H), 1.14 (d, 3H, *J* = 6.9), 1.13

(d, 3H, J = 6.9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 180.6, 150.7, 111.2, 66.3, 42.5, 41.8, 21.4, 20.8, 15.8, 15.6. IR (NaCl, $CDCl_3$) 3019, 2938, 1708, 1626, 1463, 1288, 1217 cm^{-1}. HRMS (FAB+) calcd for $C_{11}H_{17}O_4$, 213.1127. Found 213.3729. $[\alpha]_D^{23}$ = +14.4° (c = 0.4, $CHCl_3$). The product acid was converted to the corresponding methyl ester for ee determination. HPLC (Chiracel OB-H, 97:3 hex:*i*PrOH, 0.5 mL/min, 254 nm; tr (major) = 9.9 min, tr (minor) = 10.9 min) gave the isomeric composition of the product: 80 % ee.

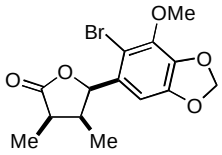


(2*R*,3*S*)-2,3-Dimethyl-4-(1-methyl-1H-indol-2-yl)-4-oxo-butyric acid (30). According to the general procedure, 38 mg (0.3 mmol) of **4** was treated with 0.5 mmol of the corresponding ArZnOTf, 6.0 mg (0.012 mmol) of $[Rh(COD)Cl]_2$ and 13.1 mg (0.024 mmol) of (-)-TADDOL-$PNMe_2$ in 3 mL DMF for 20 h at 50 °C. Standard work-up and purification by column chromatography (3:1 Hex:EtOAc) provided the desired material as crystalline solid (67 mg, 0.26 mmol, 84%). R_f = 0.14 (1:1 Hex:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): 7.67-7.71 (m, 1H), 7.35-7.39 (m, 3H), 7.12-7.18 (m, 1H), 4.06 (s, 3H), 3.63 (dq, 1H, J = 8.8, 7.2 Hz), 2.94 (dq, 1H, J = 8.4, 6.7 Hz), 1.29 (d, 3H, J = 7.1 Hz), 1.20 (d, 3H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 180.6, 140.7, 134.3, 126.5, 125.7, 123.1, 120.9, 112.3, 110.5, 45.3, 42.6, 32.3, 17.1, 16.2; IR (NaCl, $CDCl_3$) 2979, 2954, 1731, 1683, 1558, 1494, 1439, 1188 cm^{-1}. HRMS (FAB+) calcd for $C_{15}H_{18}NO_3^+$, 260.1287. Found 260.1285. $[\alpha]_D^{23}$ = +50.2° (c = 0.5, $CHCl_3$). The product acid was converted to the corresponding methyl ester for ee determination. HPLC (Chiracel OB-H, 90:10 hex:*i*PrOH, 1.0 mL/min, 210 nm; tr (minor) = 16.3 min, tr (major) = 22.3 min) gave the isomeric composition of the product: 86 % ee.

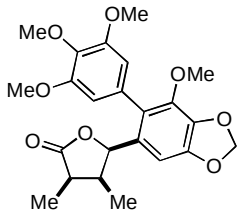


(3*R*, 4*S*, 5*R*)-5-(7-Methoxy-benzo[1,3]dioxol-5-yl)-3,4-dimethyl-dihydro-furan-2-one (31). A round bottom flask charged with 140 mg (0.50 mmol) of ketoacid **18** in 5 mL of THF was cooled to -78 °C and 1.2 mL of DIBAL (1.0 M in hexanes, 1.2 mmol) was added dropwise via syringe. The reaction was stirred for 3 h at -78 °C before the addition of 1 mL of 1 M aq. HCl and

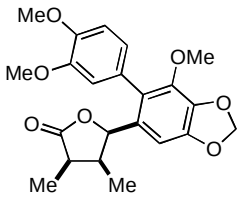
warming to room temperature. The reaction mixture was partitioned between EtOAc and 1 M aq. HCl (10 ml each) and transferred to a sepratory funnel where the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), the organic were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude hydroxy acid. The crude hydroxy acid was then taken up in 5 mL of 0.02 % CH_2Cl_2/TFA (v/v) and stirred at room temperature for 3 h. The reaction was concentrated and purified by column chromatography (3:1 Hex/EtOAc) to provide 108 mg (0.41 mmol, 82%) of the desired *syn*-lactone **31** as a colorless oil. dr = 97:3. Rf = 0.12 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 1H); 6.41 (s, 1H); 5.95 (s, 2H); 5.40 (d, 1H, *J* = 5.1 Hz); 3.87 (s, 3H); 2.96 (dq, 1H, *J* = 14.3, 7.0, 7.0 Hz); 2.72 (ddq, 1H, *J* = 14.3, 7.0, 7.0, 5.1 Hz); 1.19 (d, 3H, *J* = 7.3 Hz); 0.55 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 148.9; 143.5; 134.5; 130.6; 104.5; 101.5; 99.4; 82.0; 56.6; 41.0; 40.1; 10.1; 9.4; IR (NaCl, neat), 2976, 2941, 2881, 1774, 1635, 1514, 1452, 1433, 1173, 1095, 1051 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}O_5$, 264.0998. Found 264.0995. $[\alpha]_D^{23}$ = +37.6° (c = 0.7, $CHCl_3$).



(3*S*, 4*R*, 5*S*)-5-(6-bromo-7-methoxy-benzo[1,3]dioxol-5-yl)-3,4-dimethyl-dihydro-furan-2-one (32). A dry round bottom flask was charged with 174 mg (0.658 mmol) of **31** in 5 mL of $CHCl_3$. 128 mg (0.719 mmol) of NBS was added in one portion and the reaction stirred for 0.5 h at ambient temperature. Upon completion, 2 g of SiO_2 was added and the reaction concentrated. Column chromatography (9:1 Hex/EtOAc) yielded 184 mg (81 %) of the desired product as a colorless oil that solidified on standing. Rf = 0.25 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 5.99 (s, 2H), 5.62 (d, 1H, *J* = 5.1 Hz), 4.05 (s, 3H), 3.22-3.13 (m, 1H), 3.00 (dq, 1H, *J* = 7.3, 7.3 Hz), 1.20 (d, 3H, *J* = 7.3 Hz), 0.52 (d, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 148.9, 140.2, 136.7, 130.0, 105.1, 102.2, 101.1, 82.0, 60.1, 40.5, 37.3, 10.0, 9.7; IR (NaCl, neat), 2956, 2945, 1770, 1606, 1479, 1408, 1282, 1171, 1059, 1012, 980 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{15}O_5Br$, 344.0082. Found 344.0080. $[\alpha]_D^{23}$ = +46.1° (c = 0.4, $CHCl_3$).



eupomatilone-4 (34). A round bottom flask equipped with a reflux condenser was charged with 20 mg (0.058 mmol) of **32**, 25 mg (0.12 mmol) of 3,4,5-trimethoxyphenylboronic acid (**33**), and 25 mg (0.30 mmol) of $NaHCO_3$ in 1 mL of DME and 0.2 mL of H_2O. 3.8 mg (0.0032 mmol) of $Pd(PPh_3)_4$ in 1 mL of DME was added and argon was passed through the solution for 10 min before bring the reaction to reflux for 18 h. The reaction was quenched with 1M aq. HCl (10 mL) and the resulting aqueous layer was extracted with EtOAc (3×10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide a crude yellow oil that was purified by flash column chromatography (9:1 Hex/EtOAc) giving 24 mg (96 %) of eupomatilone-4 (**34**)[4] as a colorless oil. $[\alpha]_D^{23}$ = +23.6° (c = 0.4, $CHCl_3$). HPLC (Chiracel OD-H, 88:12 hex:*i*PrOH, 0.5 mL/min, 230 nm; tr (major) = 28.6 min, tr (minor) = 32.1 min) gave the isomeric composition of the product: 88 % ee.



eupomatilone-7 (36). A round bottom flask equipped with a reflux condenser was charged with 26 mg (0.076 mmol) of **32**, 29 mg (0.16 mmol) of 3,4-dimethoxyphenylboronic acid (**35**), and 32 mg (0.38 mmol) of $NaHCO_3$ in 1 mL of DME and 0.2 mL of H_2O. 5 mg (0.004 mmol) of $Pd(PPh_3)_4$ in 1 mL of DME was added and argon was passed through the solution for 10 min. before bring the reaction to reflux for 18 h. The reaction was quenched with 1M aq. HCl (10 mL) and the resulting aqueous layer was extracted with EtOAc (3×10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide a crude yellow oil that was purified by flash column chromatography (9:1 Hex/EtOAc) giving 27 mg (90 %) of eupomatilone-7 (**36**)[5] as a colorless oil. $[\alpha]_D^{23}$ = +24.3° (c = 0.6, $CHCl_3$). HPLC (Chiracel AD-H, 92:8 hex:*i*PrOH, 1.0 mL/min, 210 nm; tr (major) = 35.7 min, tr (minor) = 37.7 min) gave the isomeric composition of the product: 88 % ee.

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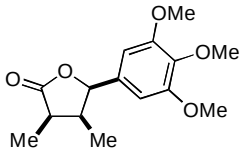
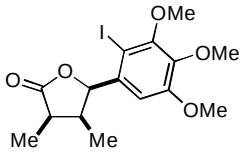
[4] (a) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1705-1714. (b) Coleman, R. S.; Gurrala, S. R. *Org. Lett.* **2004**, *6*, 4025-4028.

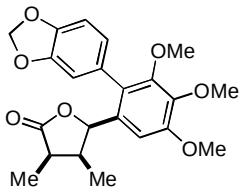


(3*R*, 4*S*, 5*R*)-3,4-dimethyl-5-(trimethoxy-phenyl)-dihydro-furan-2-one (37). A round bottom flask charged with 101 mg (0.341 mmol) of ketoacid **7** in 6 mL of THF/PhMe (5:1) was cooled to -78 °C and 0.15 mL of DIBAL (neat, 0.84 mmol) was added dropwise via syringe. The reaction was stirred for 2.5 h at -78 °C before the addition of 1 mL of 1 M aq. HCl and warming to room temperature. The reaction mixture was partitioned between EtOAc and 1 M aq. HCl (10 ml each) and transferred to a sepratory funnel where the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), the organic were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude hydroxy acid. The crude hydroxy acid was then taken up in 5 mL of 0.02 % CH_2Cl_2/TFA (v/v) and stirred at room temperature for 3 h. The reaction was concentrated and purified by column chromatography (3:1 Hex/EtOAc) to provide 90 mg (0.32 mmol, 94%) of the desired *syn*-lactone **37** as a colorless oil that solidified on standing. dr = > 98:2. mp ($CHCl_3$/Et_2O) = 87-89 °C. Rf = 0.19 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 2H), 5.44 (d, 1H, *J* = 4.7 Hz), 3.84 (s, 6H), 3.82 (s, 3H), 2.98 (dq, 1H, *J* = 14.2, 7.1, 7.1 Hz), 2.81-2.73 (m, 1H), 1.21 (d, 3H, *J* = 7.2 Hz), 0.57 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 153.3, 137.1, 131.7, 102.0, 82.1, 60.8, 56.2, 41.1, 40.1, 10.1, 9.5; IR (NaCl, $CHCl_3$), 2974, 2941, 2841, 1778, 1593, 1338, 1172 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{20}O_5$, 280.1311. Found 280.1303. $[\alpha]_D^{23}$ = +57.1° (c = 0.2, $CHCl_3$).



(3*R*, 4*S*, 5*R*)-5-(2-iodo-3,4,5-trimethoxy-phenyl)-3,4-dimethyl-dihydro-furan-2-one (38). A round bottom flask under argon was charged with 133 mg (0.474 mmol) of lactone **37** in 3 mL of $CHCl_3$ and 111 mg (0.503 mmol) of $Ag(OCOCF_3)_2$ were added in one portion. 141 mg (0.555 mmol) of I_2 in 3 mL of $CHCl_3$ was added dropwise via syringe over 0.5 h. The reaction was stirred an additional 10 min. before being filtered through a pad of celite that was washed thoroughly with $CHCl_3$ (20 mL). The filtrate was washed with sat. aq. $NaHSO_3$, dried over $MgSO_4$, filtered, and concentrated to yield a crude oil that was purified by flash column chromatography (9:1 Hex/EtOAc) to provide 172 mg (89 %) of **40** as a

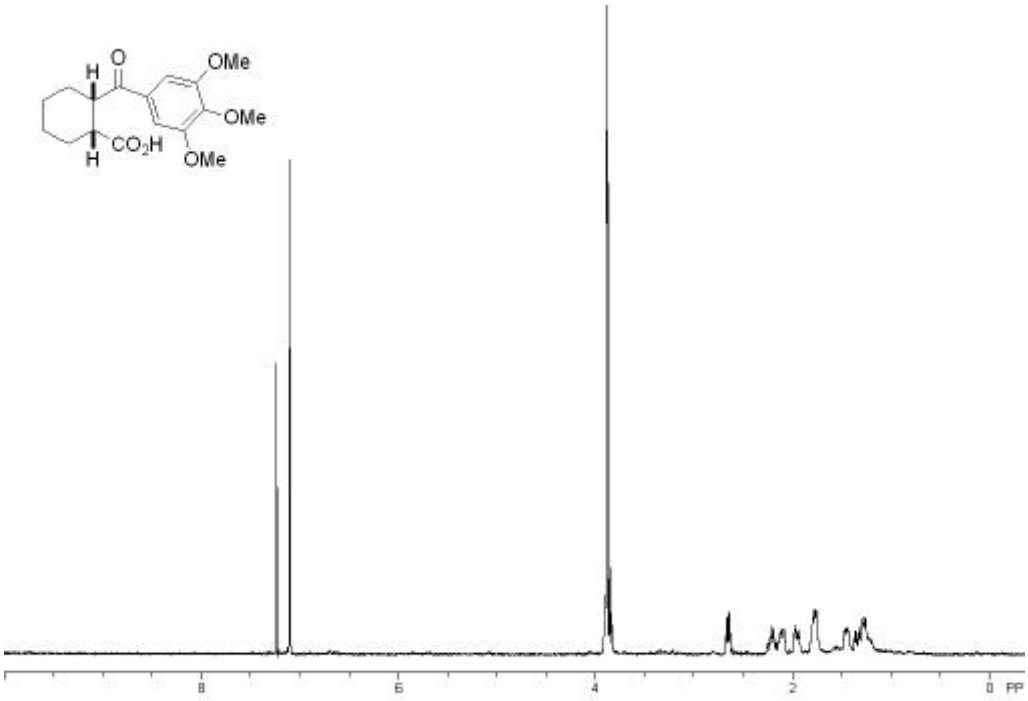
colorless oil that solidified upon standing. mp (Hex/EtOAc) = 91-93 °C. Rf = 0.52 (1:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 5.55 (d, 1H, *J* = 4.6 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.30 (ddq, 1H, *J* = 14.6, 7.3, 7.3, 5.0 Hz), 3.04 (dq, 1H, *J* = 14.4, 7.2, 7.2 Hz), 1.21 (d, 3H, *J* = 7.3 Hz), 0.50 (d, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 153.8, 152.8, 141.5, 133.8, 107.0, 85.5, 61.0, 60.9, 56.3, 40.6, 37.2, 10.1, 9.8; IR (NaCl, CCl_4), 2974, 2939, 1786, 1566, 1481, 1389, 1169, 1107 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{19}O_5I$, 406.0277. Found 406.0284. $[\alpha]_D^{23}$ = +36.1° (c = 0.5, $CHCl_3$).

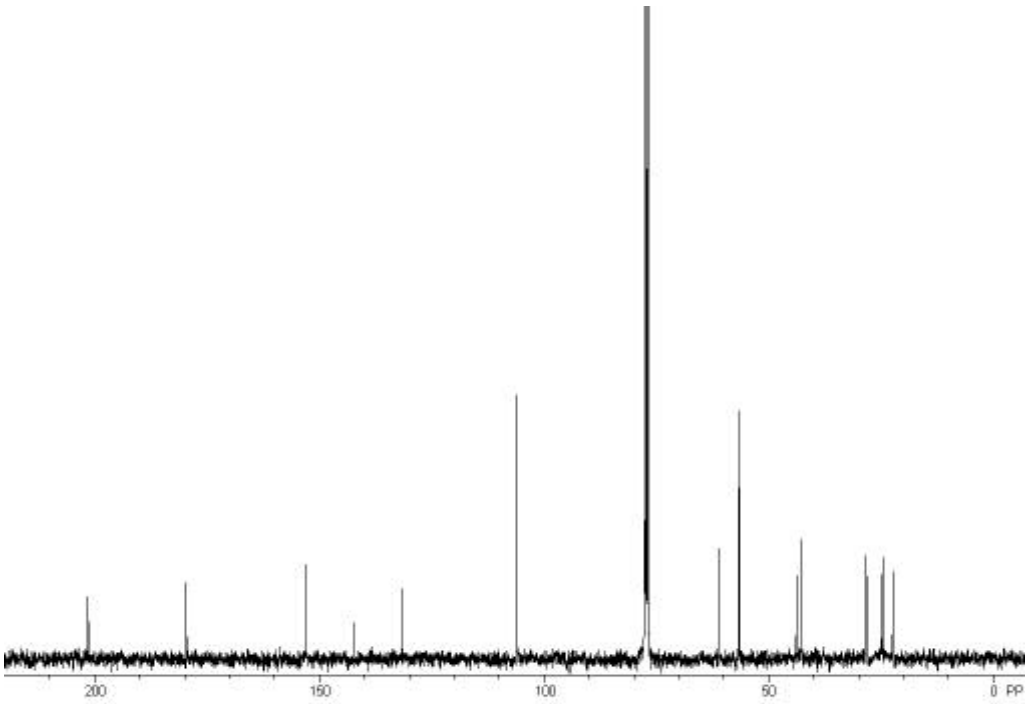


3-*epi*-eupomatilone-6 (40). A round bottom flask equipped with a reflux condenser was charged with 21 mg (0.052 mmol) of **38**, 13 mg (0.079 mmol) of boronic acid **39**, and 16 mg (0.19 mmol) of $NaHCO_3$ in 1 mL of DME and 0.2 mL of H_2O. 4 mg (0.003 mmol) of $Pd(PPh_3)_4$ in 1 mL of DME was added and argon was passed through the solution for 10 min. before bring the reaction to reflux for 18 h. The reaction was quenched with 1M aq. HCl (10 mL) and the resulting aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide a crude yellow oil that was purified by flash column chromatography (4:1 Hex/EtOAc) giving 18 mg (87 %) of 3-*epi*-eupomatilone-6 **(40)**[5] as yellow/brown foam. $[\alpha]_D^{23}$ = +22.7° (c = 0.8, $CHCl_3$). HPLC (Chiracel OD-H, 88:12 hex:*i*PrOH, 0.5 mL/min, 230 nm; tr (major) = 20.6 min, tr (minor) = 22.9 min) gave the isomeric composition of the product: 88 % ee.

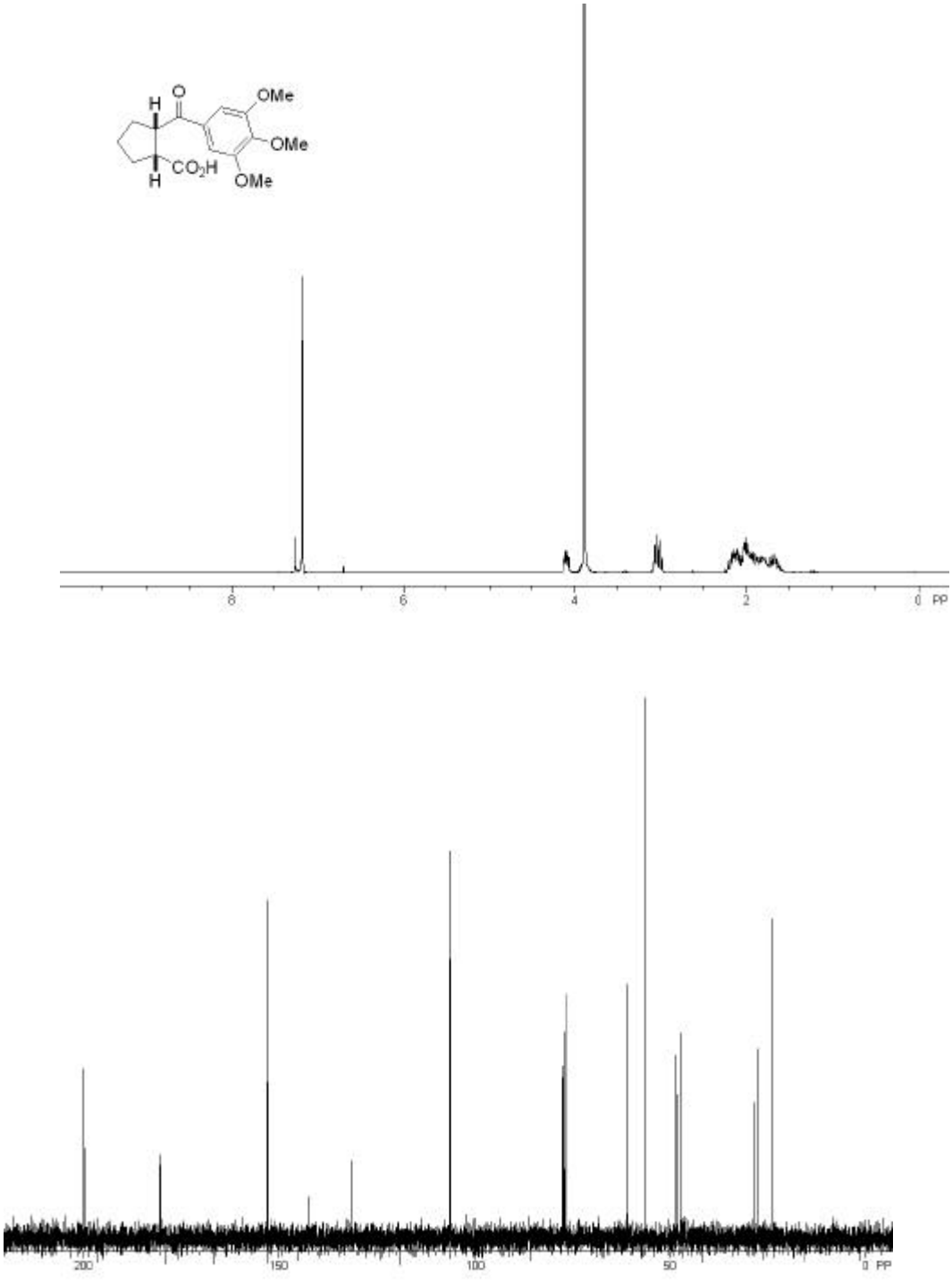
[5] Gurjar, M. K.; Cherian, J.; Ramana, C. V. *Org. Lett.* **2004**, *6*, 317-319.

^{1}H and ^{13}C NMR spectra for **9**:

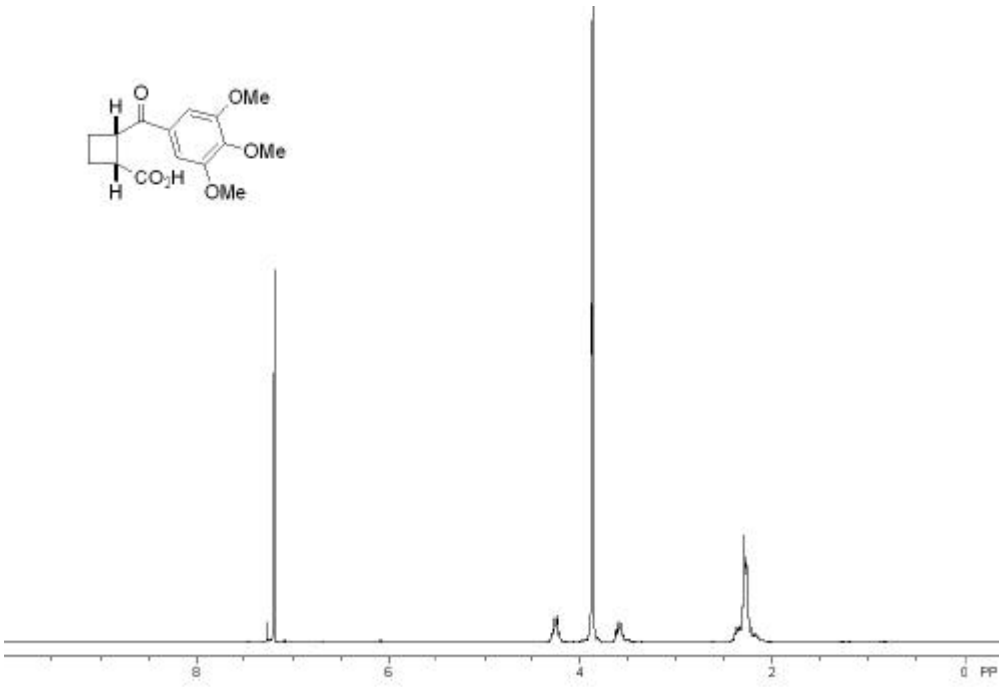


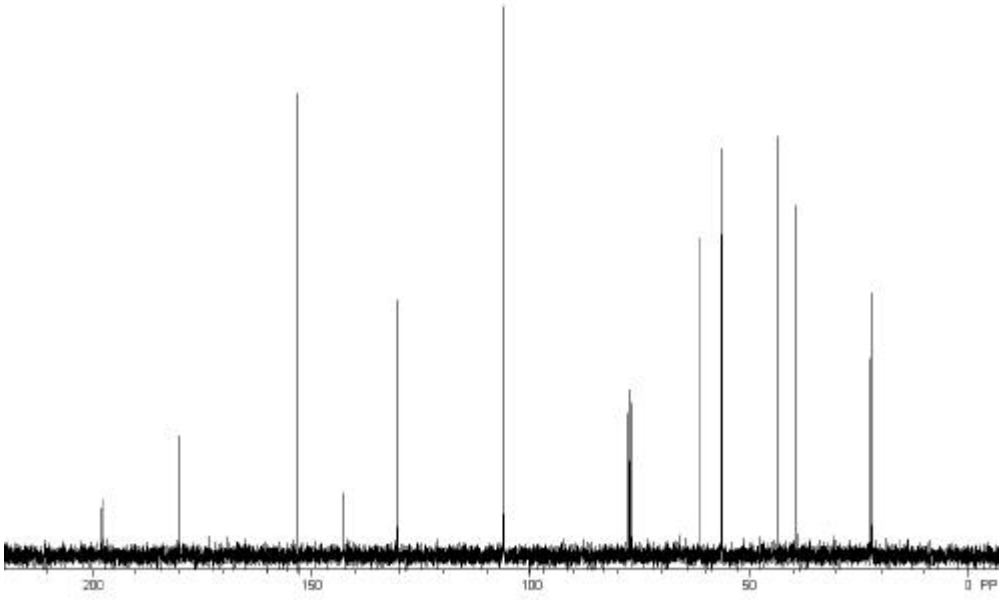


^{1}H and ^{13}C NMR spectra for **13**:

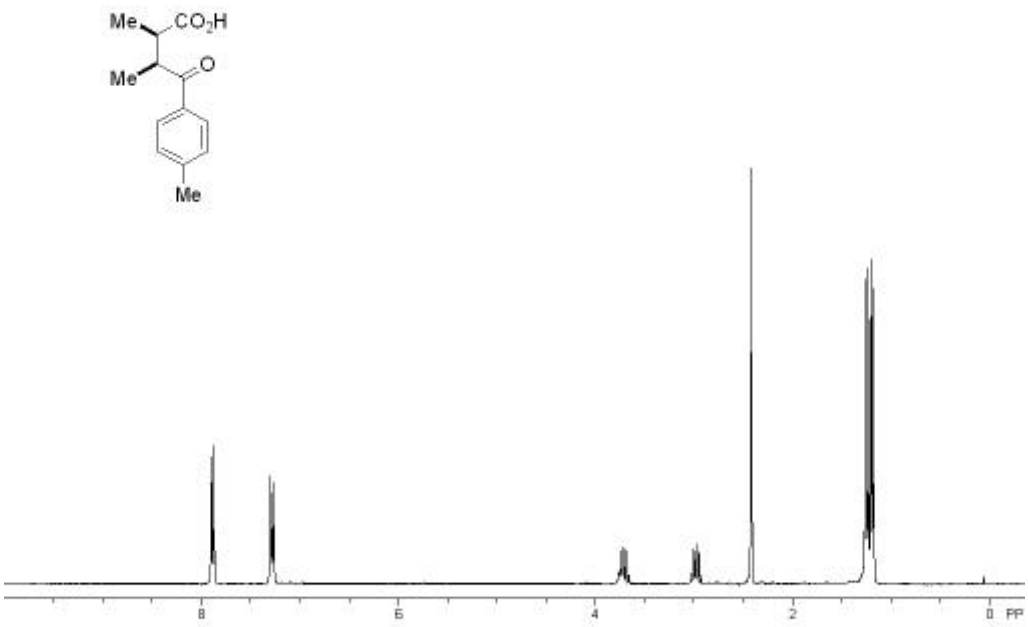


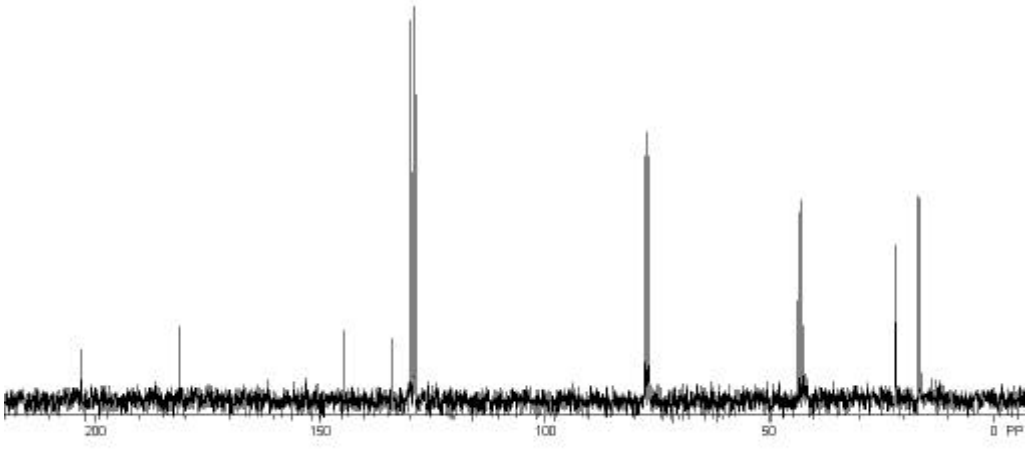
^{1}H and ^{13}C NMR spectra for **15**:



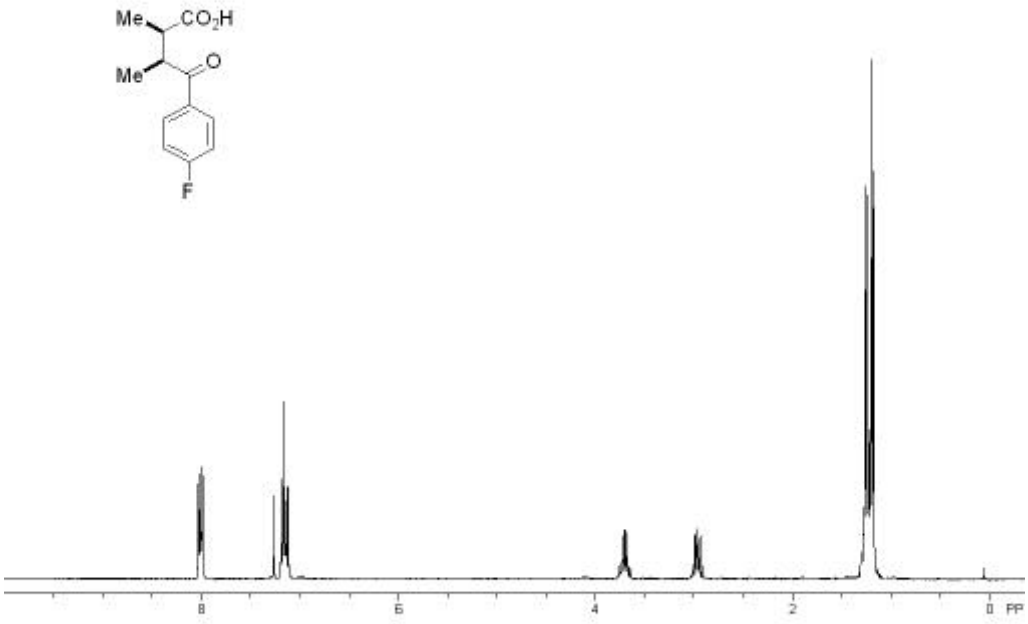


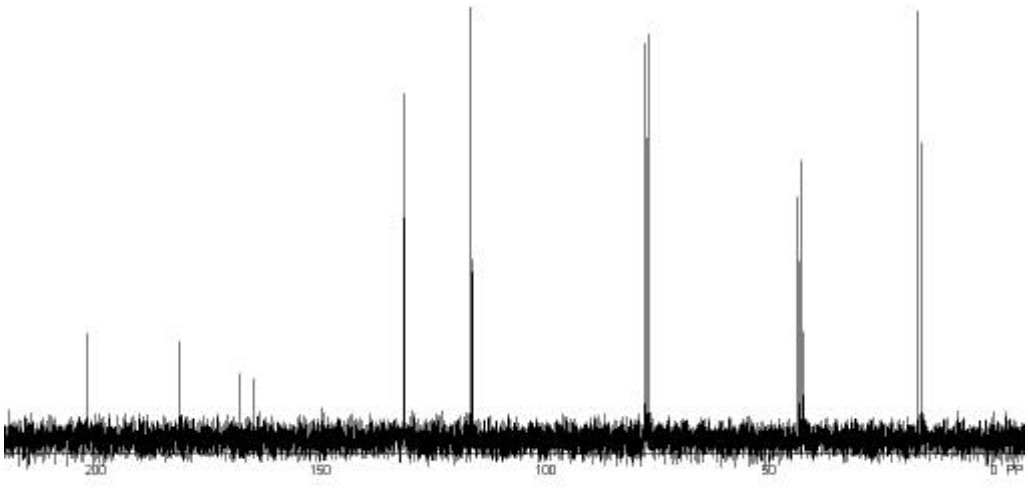
^{1}H and ^{13}C NMR spectra for **22**:



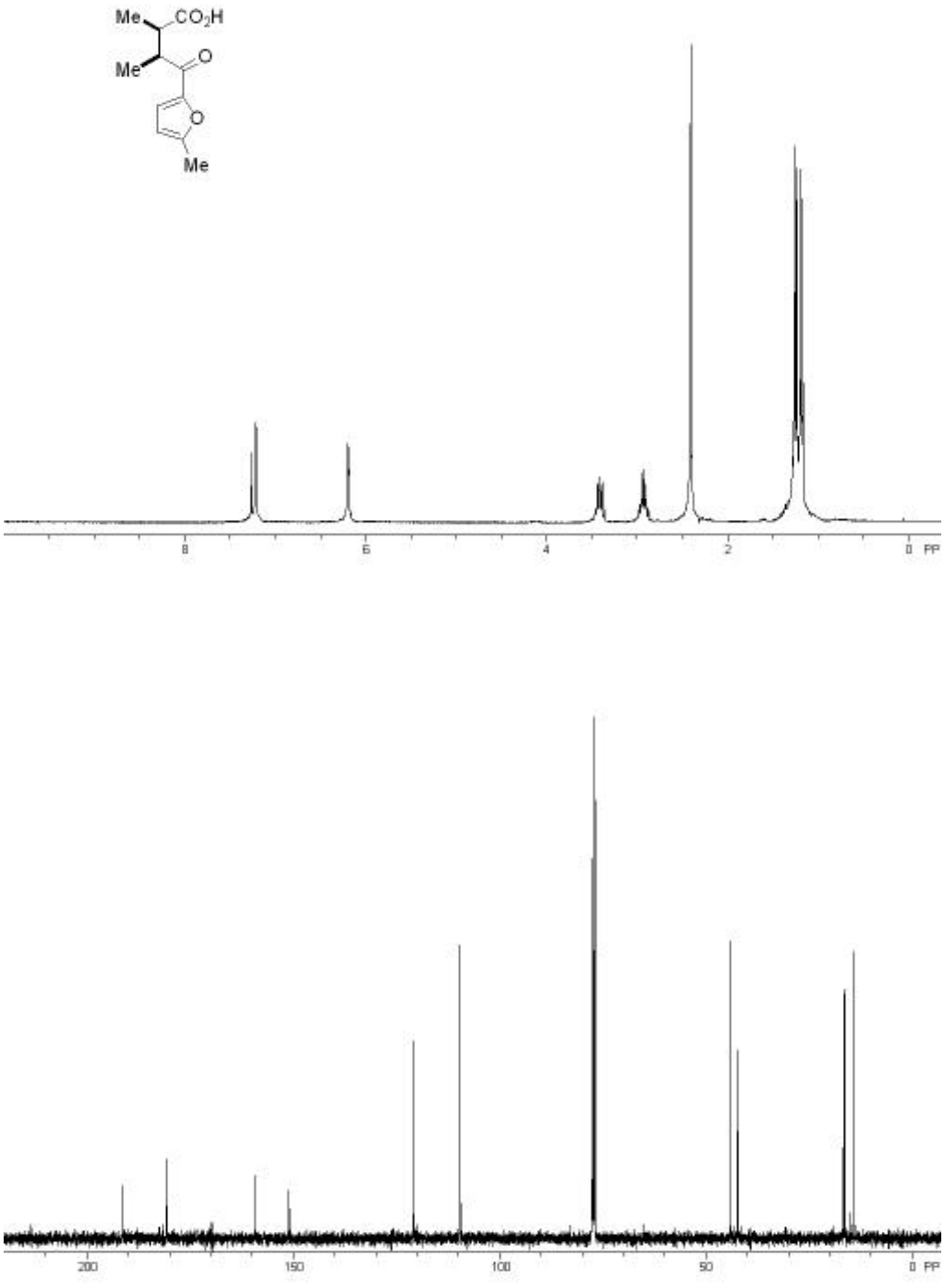


^{1}H and ^{13}C NMR spectra for **24**:

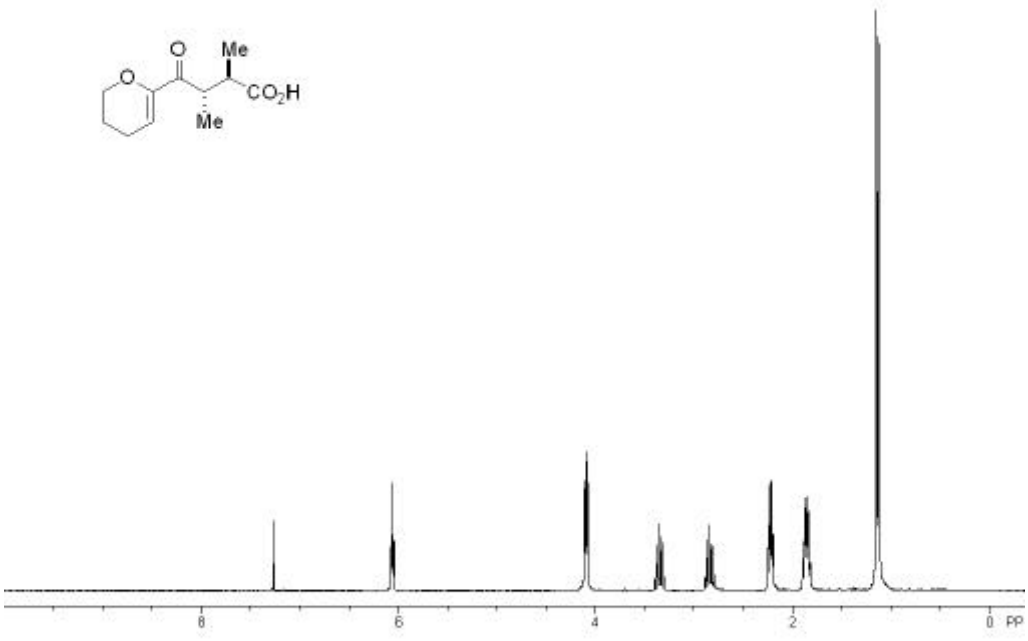


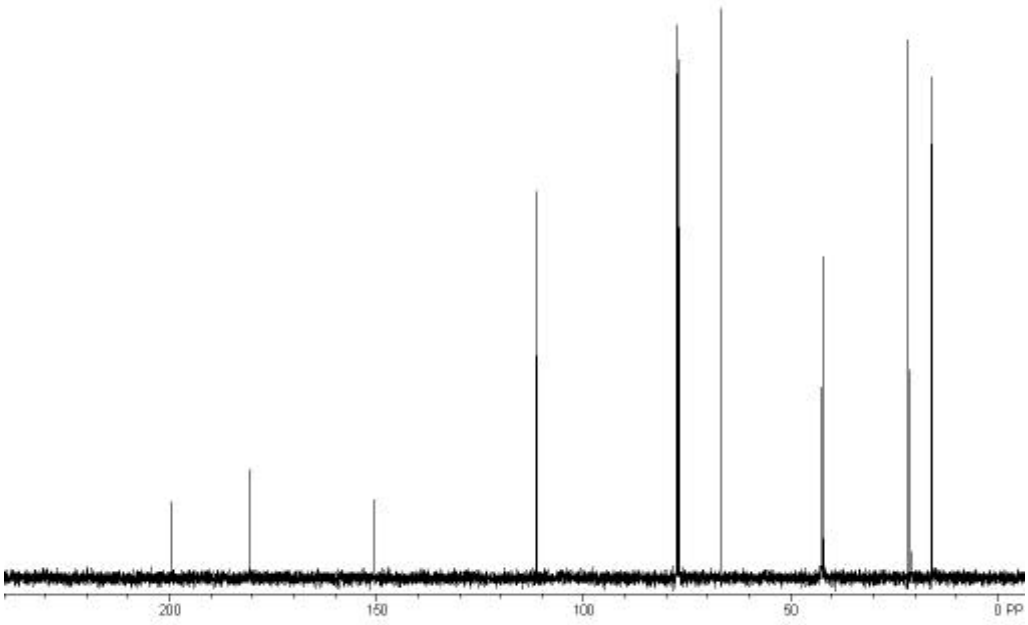


^{1}H and ^{13}C NMR spectra for **26**:

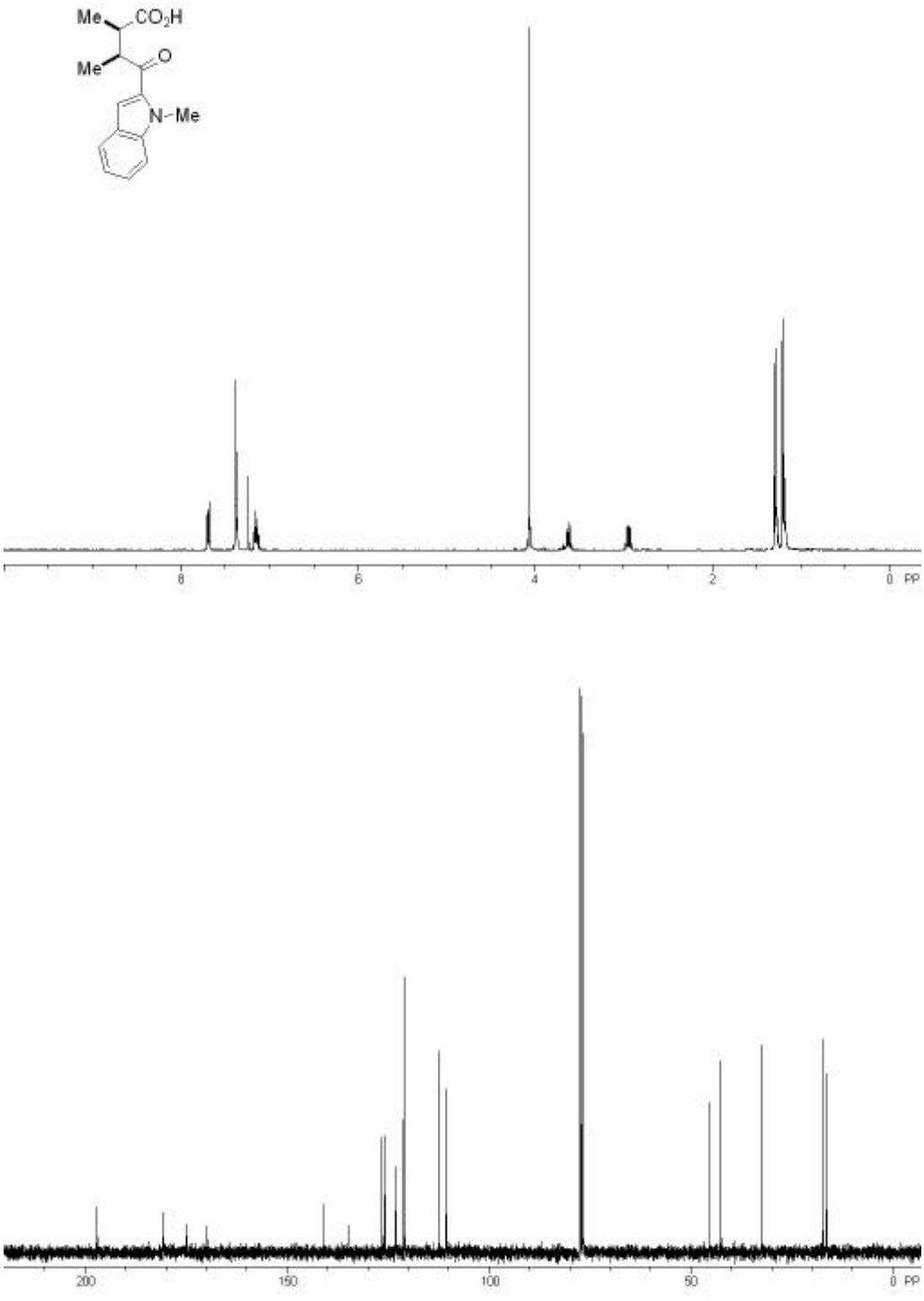


^{1}H and ^{13}C NMR spectra for **28**:

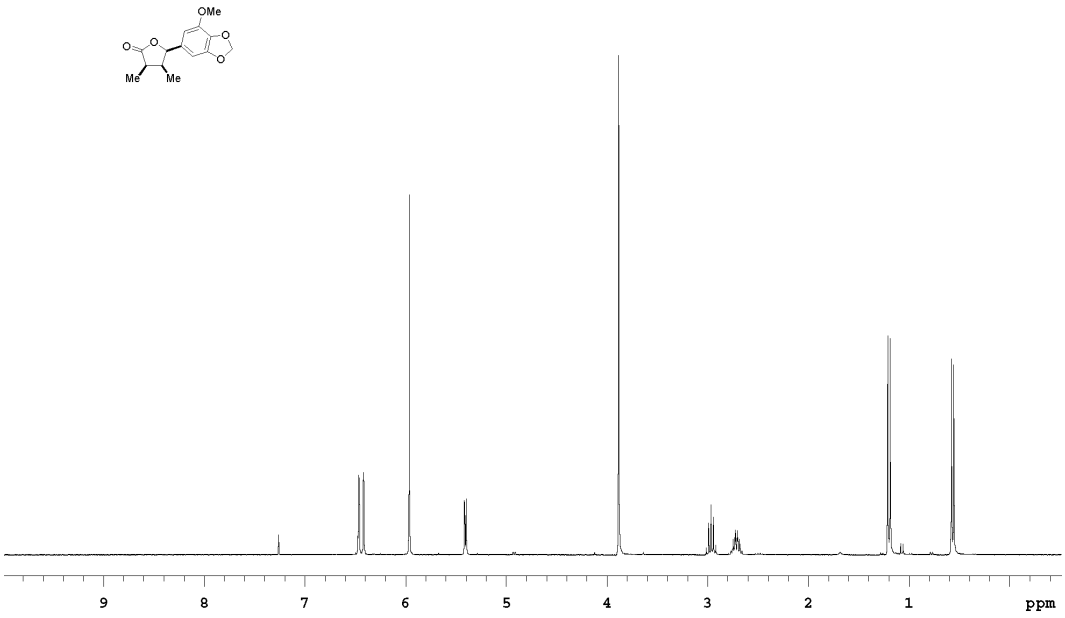


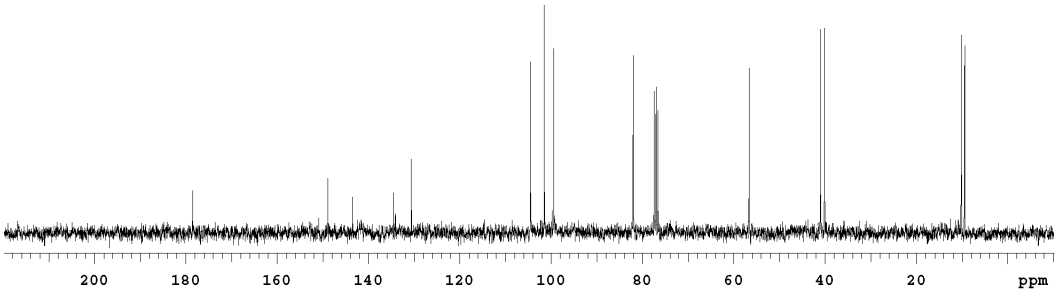


^{1}H and ^{13}C NMR spectra for **30**:

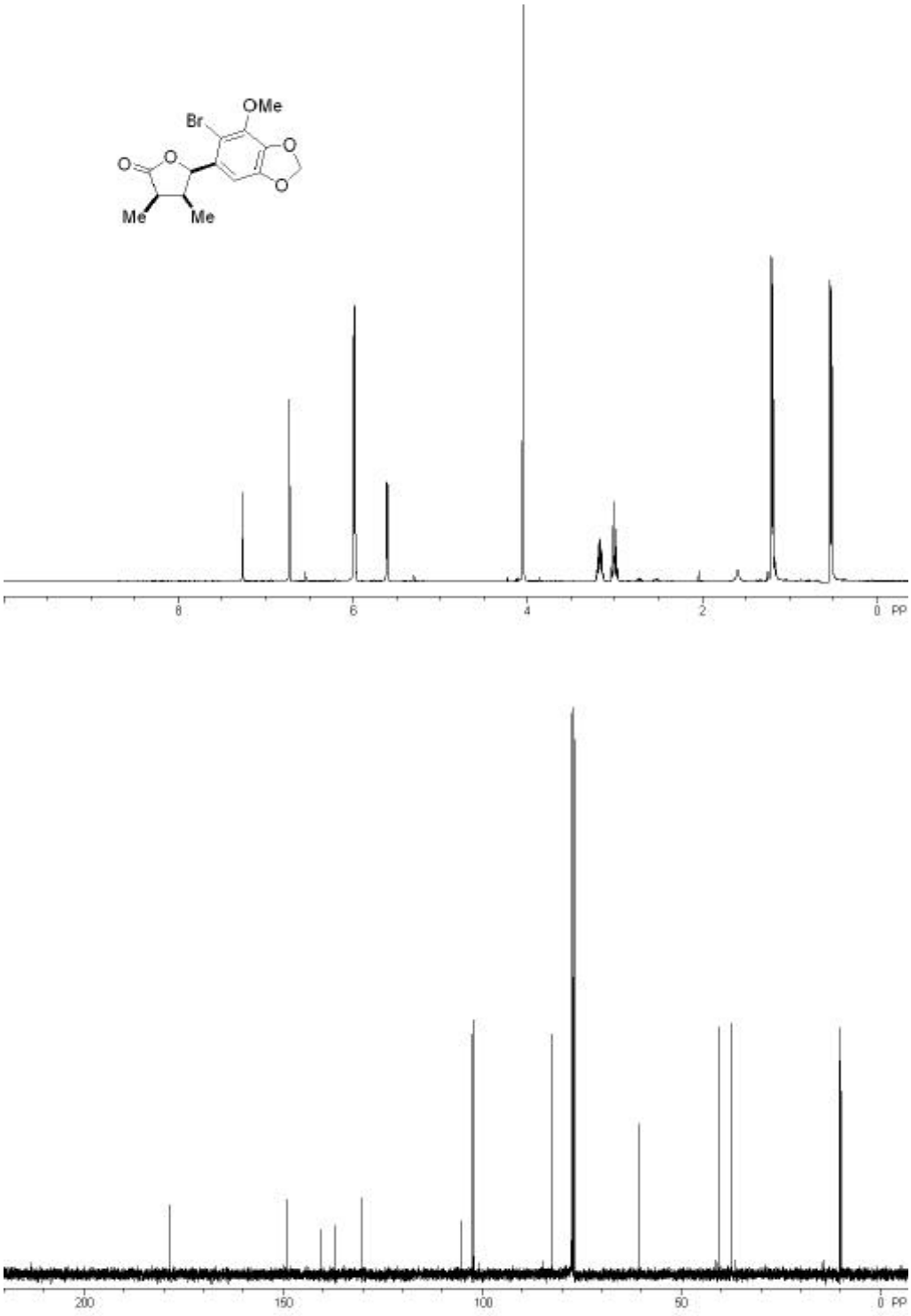


^{1}H and ^{13}C NMR spectra for **31**:

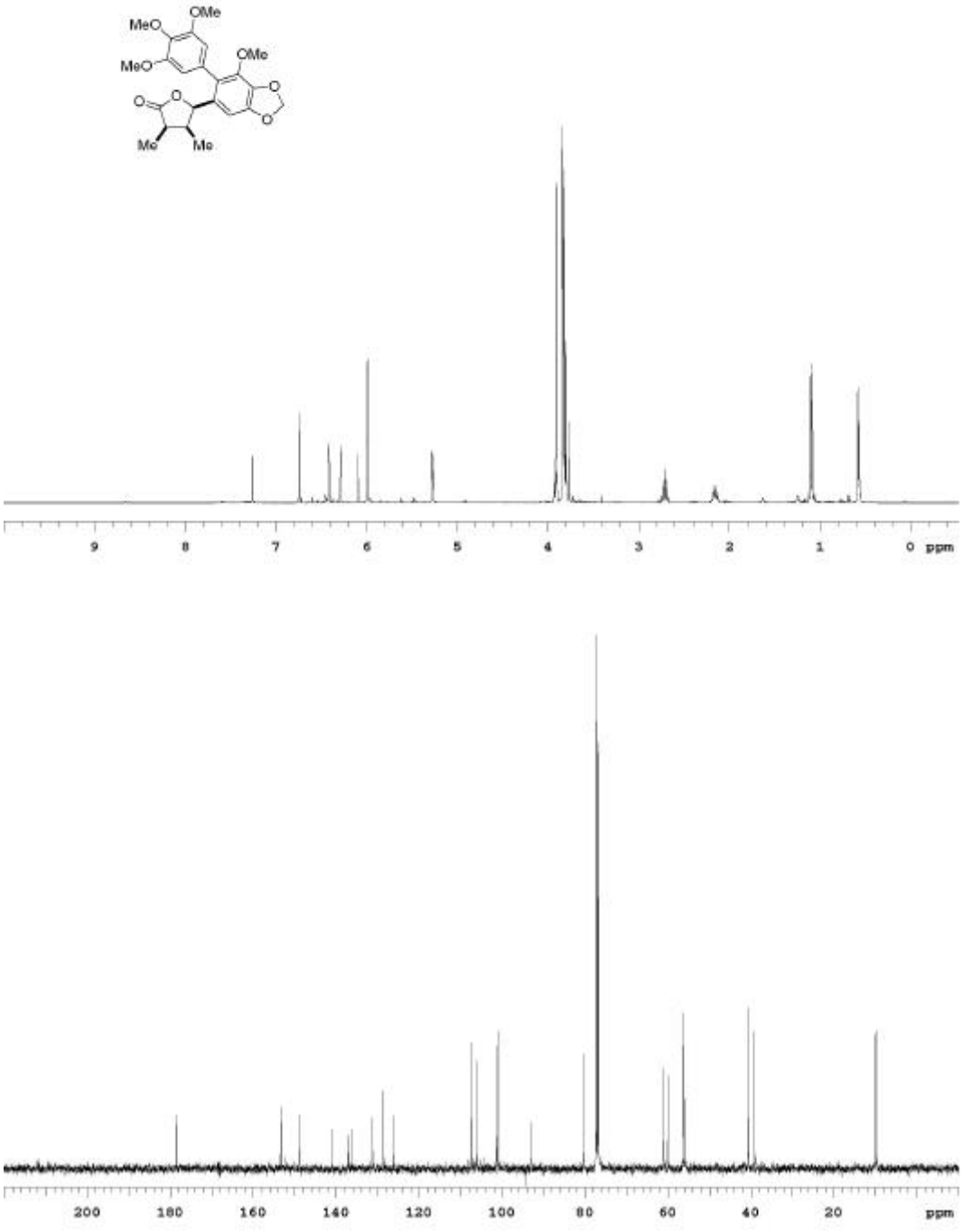




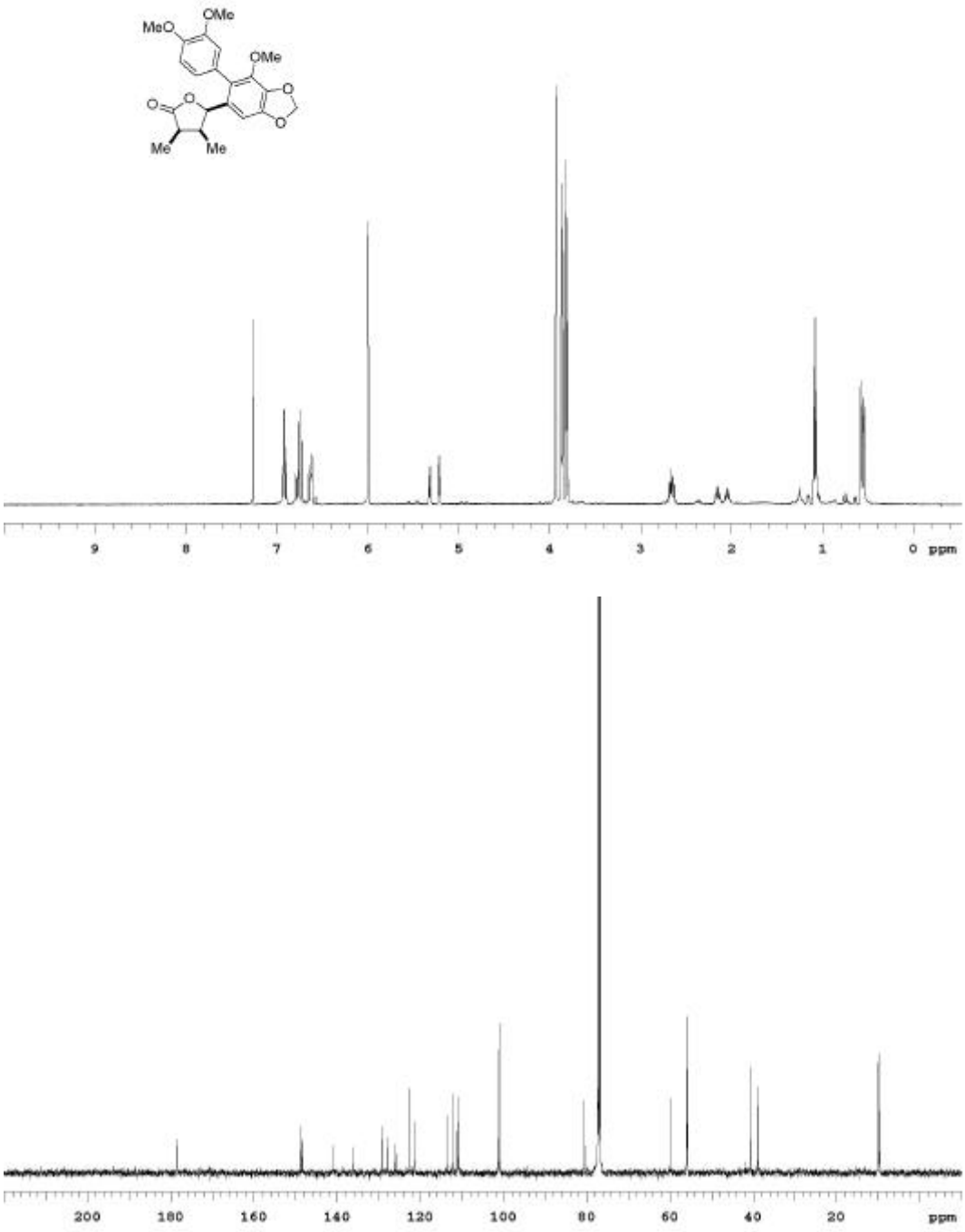
^{1}H and ^{13}C NMR spectra for **32**:



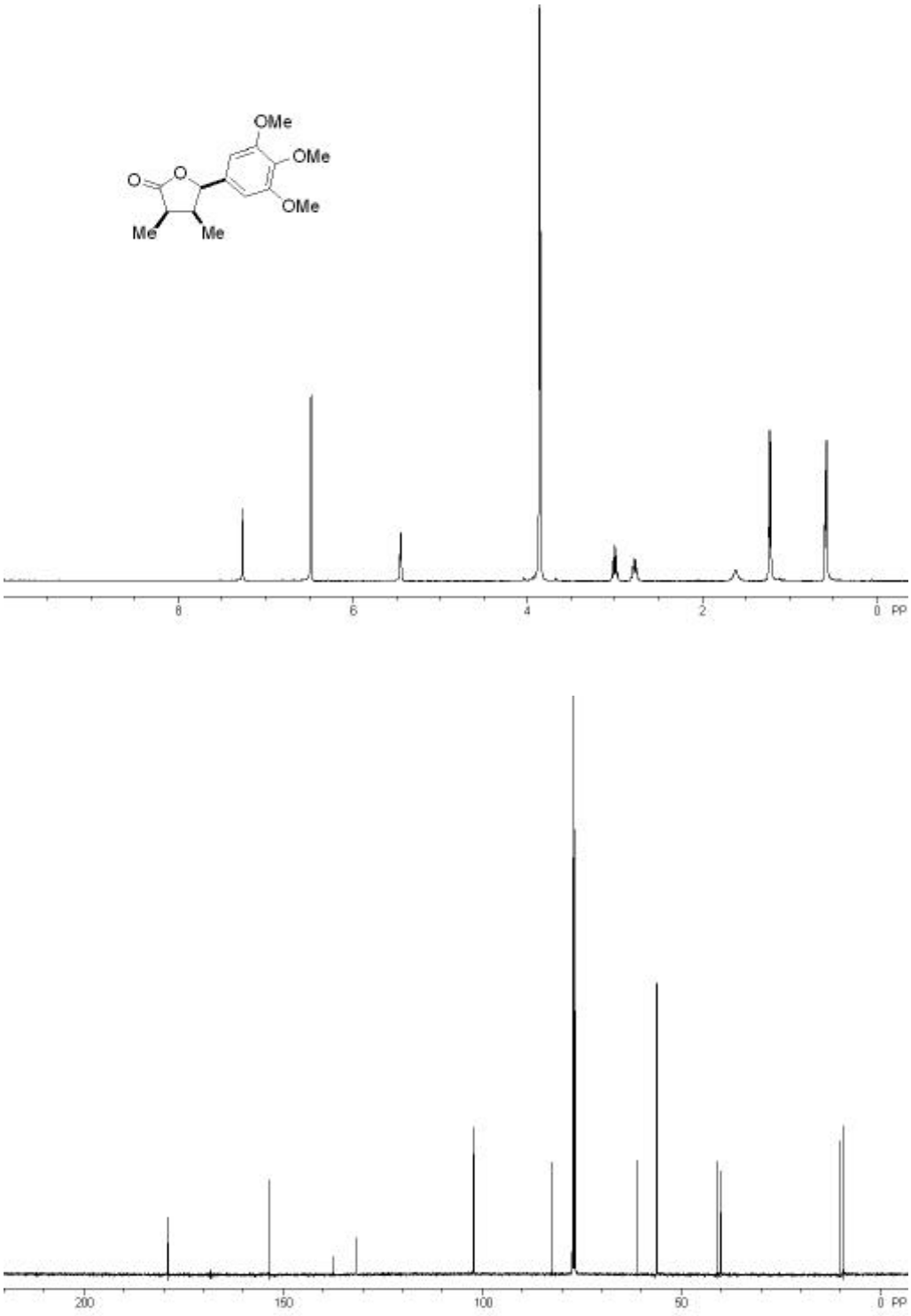
^{1}H and ^{13}C NMR spectra for **34**:



^{1}H and ^{13}C NMR spectra for **36**:



^{1}H and ^{13}C NMR spectra for **37**:



^{1}H and ^{13}C NMR spectra for **40**: