Catalytic Friedel-Crafts Alkylation of Electron Rich Aromatic Derivatives with α-Aryl Diazoacetates Mediated by Brønsted Acids

Rafael D. C. Gallo, Patricia B. Momo, David P. Day and Antonio C. B. Burtoloso*

São Carlos Institute of Chemistry, University of São Paulo, 13560-970, São Carlos, SP, Brazil

SUPPORTING INFORMATION

Table of Contents

General Information

All commercially available reagents were used without further purification unless otherwise noted. All solvents used for reactions and chromatography were dried and purified by standard methods. All reactions were performed at the specified temperatures described in general procedures section. When necessary, a silicone oil bath with a heating probe was used to obtain the desired temperature. TLC analyses were performed using silica gel 60F 254 precoated plates, with detection by UV-absorption (254 nm) and by spraying with *p*-anisaldehyde, potassium permanganate and phosphomolybdic acid solutions followed by charring at ~150 °C for visualization. Flash column chromatography was performed using silica gel 200-400 Mesh. All NMR analyses were recorded using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are reported in ppm downfield from TMS with reference to internal solvent. Infrared spectra were obtained using FT-IR (Bruker, model ALPHA) at 4.0 cm^{-1} resolution and are reported in wavenumbers. The samples were dispersed in a ZnSe crystal (ATR mode), using DCM as solvent or when dealing with DCM insoluble samples, the solid was directly pressed in the crystal. Melting points were determined using a digital melting point apparatus (Fisatom, model 430D). High-resolution mass spectra (HRMS) were recorded using electron spray ionization in positive mode (ESI) in a Waters, model Xevo G2 or in a ThermoFischer, model Orbitrap LTQ Velos.

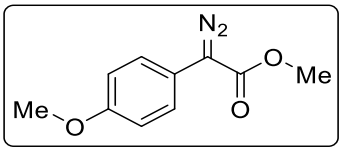
Experimental Procedures and Characterization Data

General Procedures

Preparation of diazo compounds

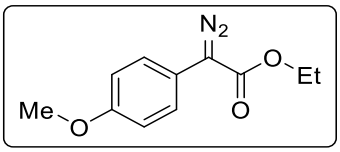
To a mixture of ester (0.5-20.0 mmol) and *p*-ABSA (1.2-1.5 equiv.) in anhydrous CH_3CN (2-60 mL) at 0 °C, DBU (1.4-1.5 equiv.) was added. The reaction mixture was stirred at room temperature overnight. Upon complete consumption of the starting materials, the reaction mixture was diluted with distilled water (2-20 mL), followed by extraction with diethyl ether (3 × 5-10 mL). After washing with 10% NH_4Cl solution (3 × 5-10 mL) and brine (3 × 5-10 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was purified by flash chromatography to afford the diazoesters.

Methyl 2-diazo-2-(4-methoxyphenyl)acetate **4**[1]



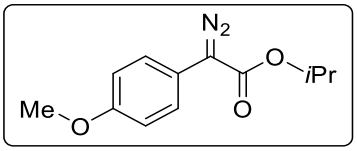
Following the general procedure for the preparation of diazo compounds, reaction of methyl 2-(4-methoxyphenyl)acetate (20.0 mmol), *p*-ABSA (24.0 mmol) and DBU (28.0 mmol) afforded the title compound **4** as an orange solid (2.39 g, 58%) m.p. 45-50 °C. R_f = 0.32 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H).

Ethyl 2-diazo-2-(4-methoxyphenyl)acetate **S1**[2]



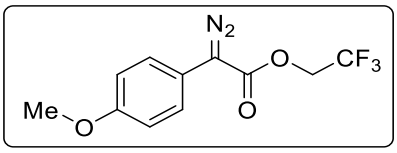
Following the general procedure for the preparation of diazo compounds, reaction of ethyl 2-(4-methoxyphenyl)acetate (4.10 mmol), *p*-ABSA (4.92 mmol) and DBU (6.15 mmol) afforded the title compound **S1** as an red solid (755 mg, 84%) m.p. 49-51 °C. R_f = 0.42 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

Isopropyl 2-diazo-2-(4-methoxyphenyl)acetate **S2**[3]



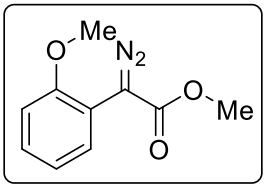
Following the general procedure for the preparation of diazo compounds, reaction of isopropyl 2-(4-methoxyphenyl)acetate (4.80 mmol), *p*-ABSA (5.76 mmol) and DBU (7.20 mmol) afforded the title compound **S2** as an orange solid (822 mg, 73%) m.p. 48-50 °C. R_f = 0.32 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 5.20 (hept, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 1.33 (d, *J* = 6.3 Hz, 6H).

2,2,2-Trifluoroethyl 2-diazo-2-(4-methoxyphenyl)acetate **S3**[4]



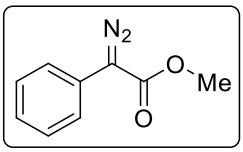
Following the general procedure for the preparation of diazo compounds, reaction of 2,2,2-trifluoroethyl 2-(4-methoxyphenyl)acetate (1.00 mmol), *p*-ABSA (1.20 mmol) and DBU (1.50 mmol) afforded the title compound **S3** as an orange oil (199 mg, 73%). R_f = 0.35 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 4.64 (q, *J* = 8.4 Hz, 2H), 3.82 (s, 3H).

Methyl 2-diazo-2-(2-methoxyphenyl)acetate **S4**[5]



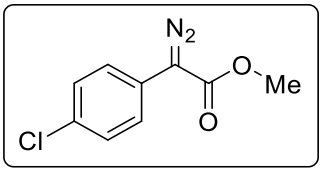
Following the general procedure for the preparation of diazo compounds, reaction of methyl 2-(2-methoxyphenyl)acetate (4.80 mmol), *p*-ABSA (7.33 mmol) and DBU (7.20 mmol) afforded the title compound **S4** as an orange solid (1.05 g, 95%). m.p. 39-40 °C. R_f = 0.35 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.26 (ddd, *J* = 8.3, 7.1, 1.7 Hz, 1H), 7.02 (td, *J* = 7.7, 1.2 Hz, 1H), 6.90 (dd, *J* = 8.3, 1.0 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H).

Methyl 2-diazo-2-phenylacetate **S5**[6]



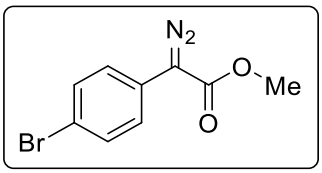
Following the general procedure for the preparation of diazo compounds, reaction of methyl 2-phenylacetate (6.70 mmol), *p*-ABSA (8.00 mmol) and DBU (10.0 mmol) afforded the title compound **S5** as red oil (540 mg, 46%). R_f = 0.47 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.49 – 7.47 (m, 2H), 7.39 – 7.36 (m, 2H), 7.19 – 7.18 (m, 1H), 3.86 (s, 3H).

Methyl 2-(4-chlorophenyl)-2-diazoacetate **S6**[1]



Following the general procedure for the preparation of diazo compounds, reaction of methyl 2-(4-chlorophenyl)-2-diazoacetate (5.2 mmol), *p*-ABSA (6.2 mmol) and DBU (7.8 mmol) afforded the title compound **S6** as an orange solid (924 mg, 85%). m.p. 77-78 °C. R_f = 0.40 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H).

Methyl 2-(4-bromophenyl)-2-diazoacetate **S7**[1]



Following the general procedure for the preparation of diazo compounds, reaction of methyl 2-(4-bromophenyl) acetate (1.32 mmol), *p*-ABSA (1.58 mmol) and DBU (1.98 mmol) afforded the title compound **S7** as an orange solid (142 mg, 43%). m.p. 39-40 °C. R_f = 0.48 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H).

Preparation of sulfuric acid adsorbed on silica gel (H_2SO_4–SiO_2)

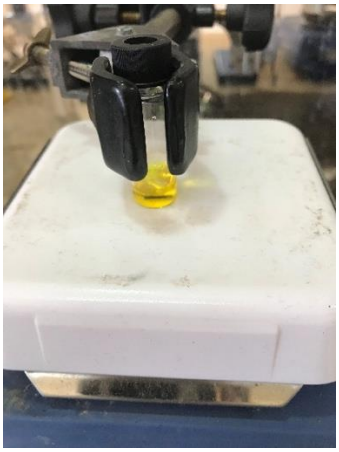
The preparation of H_2SO_4–SiO_2 was carried out following some modifications of the originally reported procedure.[7] To a suspension of silica gel (10 g, 230–400 mesh) in EtOAc (20 mL) was added H_2SO_4 (0.5 g, 5.2 mmol, 0.27 mL of a 98% aq. solution of H_2SO_4) and the mixture was stirred magnetically for 30 min at rt. Remaining EtOAc was removed under reduced pressure (rotary evaporator) and the residue was heated at 100 °C for 4 h under vacuum to afford H_2SO_4–SiO_2 (0.5 mmol H_2SO_4 in 1g of silica).

General procedure for Friedel-Crafts synthesis

To a 4 mL vial equipped with a magnetic stir-bar was added 0.1 mmol of diazoester (1 equiv), aryl species (1.5 equiv) and dissolved in DCE (0.3 mL) at 25 °C. After 1 min of pre-stirring, H_2SO_4-SiO_2 (5 mol%) was added in one portion. After 5 minutes, the reaction was judged to be complete (TLC), the solid filtered off, and washed with ethyl acetate (2 x 10 mL) and organic solvents were removed under reduced pressure. The resulting residue was purified by flash column chromatography using silica gel (230-400 mesh) and a hexane: ethyl acetate (9:1) mobile phase, affording the desired products.

*N.B. A noticeable colour change was observed in all Friedel-Crafts reactions conducted, with the bright orange / yellow colour of the reaction mixture disappearing with time. Upon reaction completion, all colour in the mixture had gone (see below).

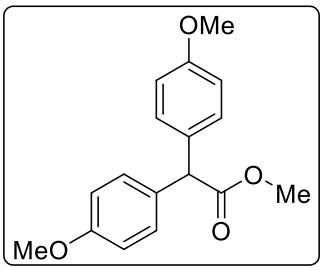
Before H_2SO_4-SiO_2 Addition



During Reaction N_2 evolution

Completion

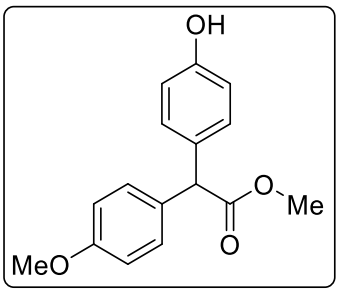
(±)-Methyl 2,2-bis(4-methoxyphenyl)acetate **5**



Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and anisole (0.15 mmol, 16.3 µL) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **5** as colorless oil (23.7 mg, 83%). For the specific case of anisole as substrate, different yields were obtained later when other batches of the catalyst were employed (35-83%). R_f = 0.25 (10% EtOAc:Hexane; pink color in CAM stain). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.22 – 7.20 (m, 4H), 6.86 – 6.83 (m, 4H), 4.93 (s, 1H), 3.77 (s, 6H), 3.72 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.6, 158.8, 131.2, 129.6, 114.0, 55.4, 55.3, 52.3. **IR** ν_{max} (cm^{-1}): 3000, 2952, 2918, 2848, 2837, 1734, 1609, 1583, 1509, 1462, 1437, 1302, 1289, 1246, 1176, 1152, 1032, 818, 757. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{18}O_4Na$ 309.1103, found 309.1095.

1 mmol scale reaction: To a 10 mL round bottom flask equipped with a magnetic stir-bar was added diazoester **4** (1.31 mmol, 269.8 mg), anisole (2.0 mmol, 217 µL) and dissolved in DCE (4 mL) at 25 °C. After 1 min of pre-stirring, H_2SO_4-SiO_2 (5 mol%, 130 mg) was added in one portion. After 10 minutes, the reaction was judged to be complete (TLC), the solid filtered off, and washed with ethyl acetate (2 x 25 mL) and organic solvents were removed under reduced pressure. The resulting residue was purified by flash column chromatography using silica gel (230-400 mesh) and a hexane: ethyl acetate (9:1) mobile phase, affording compound **5** as a colorless oil (start to solidify after some hours in the refrigerator) (149 mg, 40%).

(±)-Methyl 2-(4-hydroxyphenyl)-2-(4-methoxyphenyl)acetate **6**

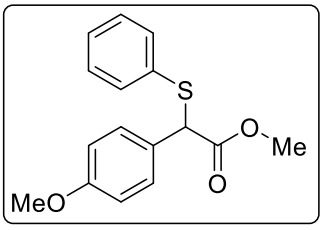


Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and phenol (0.15 mmol, 14.1 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **6** as white solid (22.6 mg, 83%). m.p. 108-109 °C (lit. 112.6 °C)[11] R_f = 0.10 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 5.67 (s, 1H), 4.92 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.7, 158.7, 154.8, 131.0, 130.9, 129.7, 129.5, 115.4, 114.0, 55.3, 55.2, 52.3. **IR** ν_{max} (cm^{-1}): 3403, 3003, 2952, 2931, 2838, 1733, 1714, 1610, 1509, 1438, 1342, 1247, 1174, 1112, 1032, 1005, 830, 759. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}O_4Na$ 295.0946, found 295.0933.

1 mmol scale reaction: To a 10 mL round bottom flask equipped with a magnetic stir-bar was added diazoester **4** (1.02 mmol, 210.8 mg), phenol (1.53 mmol, 144 mg) and dissolved in DCE (3.1 mL) at 25 °C. After 1 min of pre-stirring, H_2SO_4-SiO_2 (5 mol%, 102 mg) was added in

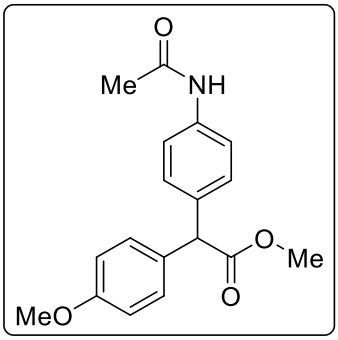
one portion. After 10 minutes, the reaction was judged to be complete (TLC), the solid filtered off, and washed with ethyl acetate (2 x 25 mL) and organic solvents were removed under reduced pressure. The resulting residue was purified by flash column chromatography using silica gel (230-400 mesh) and a hexane: ethyl acetate (7:3) mobile phase, affording compound **6** as a colorless oil (177.3 mg, 64%).

(±)-Methyl 2-(4-methoxyphenyl)-2-(phenylthio)acetate **7**[8]



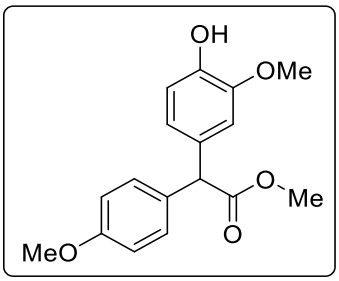
Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and thiophenol (0.15 mmol, 15.3 µL) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **7** as colorless oil (26.5 mg, 92%). R_f = 0.15 (5% EtOAc:Hexane). The spectroscopy data were in good agreement with the literature.[8] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.34 (m, 4H), 7.25-7.24 (m, 3H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.87 (s, 1H), 3.77 (s, 3H), 3.65 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.2, 159.7, 134.0, 132.7, 129.8, 129.1, 128.1, 127.6, 114.2, 55.8, 55.4, 52.8. **IR** ν_{max} (cm^{-1}): 3003, 2951, 2838, 1737, 1607, 1509, 1443, 1251, 1154, 1027.

(±)-Methyl 2-(4-acetamidophenyl)-2-(4-methoxyphenyl)acetate **11**



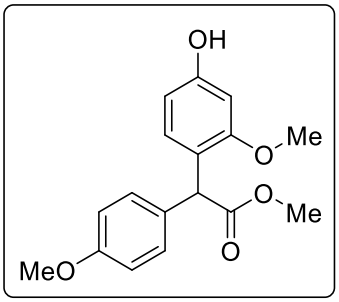
Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and *N*-phenylacetamide (0.15 mmol, 20.3 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **11** as colorless oil (12.8 mg, 41%). R_f = 0.15 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.5 Hz, 3H), 7.21 (dd, *J* = 11.1, 8.6 Hz, 4H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.94 (s, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 2.13 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.4, 168.4, 158.9, 137.1, 134.9, 130.8, 129.7, 129.1, 120.1, 114.1, 55.7, 55.3, 52.4, 24.6. **IR** ν_{max} (cm^{-1}): 3304, 3191,40 3122, 3002, 2952, 2928, 2838, 2349, 1734, 1666, 1603, 1510, 1461, 1436, 1410, 1370, 1317, 1250, 1199, 1153, 1032, 1005, 966, 915, 811, 758, 658. **HRMS** (ESI-TOF) m/z: $[M+K]^+$ Calcd for $C_{18}H_{19}NO_4K$ 352.0951, found 352.0905.

(±)-Methyl 2-(4-hydroxy-3-methoxyphenyl)-2-(4-methoxyphenyl)acetate **12**



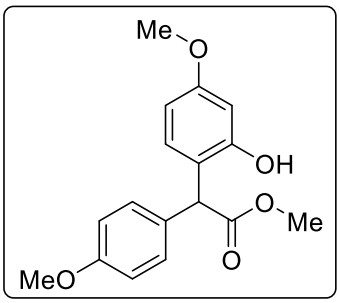
Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 2-methoxyphenol (0.15 mmol, 18.6 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **12** as colorless oil (25.4 mg, 84%). R_f = 0.25 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.22 – 7.20 (m, 2H), 6.87 – 6.84 (m, 3H), 6.82 – 6.78 (m, 2H), 5.57 (s, 1H), 4.91 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.4, 158.7, 146.5, 144.8, 131.0, 130.7, 129.4, 121.4, 114.2, 113.9, 111.0, 55.8, 55.7, 55.3, 52.3. **IR** ν_{max} (cm^{-1}): 3400, 3002, 2952, 2838, 1735, 1712, 1612, 1510, 1465, 1336, 1296, 1247, 1176, 1113, 1034, 1008, 957, 833, 802, 762, 635, 608. **HRMS** (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{17}H_{18}O_5$ 302.1154, found 302.1142.

(±)-Methyl 2-(4-hydroxy-2-methoxyphenyl)-2-(4-methoxyphenyl)acetate **13**



Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 3-methoxyphenol (0.15 mmol, 18.6 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **13** as colorless oil (14.5 mg, 48%). R_f = 0.1 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.24 – 7.18 (m, 2H), 6.89 – 6.85 (m, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.39 – 6.38 (m, 1H), 6.29 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.15 (s, 1H), 5.10 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.3, 160.8, 158.9, 156.0, 131.8, 129.2, 129.0, 128.9, 116.4, 114.2, 106.7, 103.6, 55.45, 55.41, 53.5, 53.1. **IR** ν_{max} (cm^{-1}): 3400, 3001, 2952, 2837, 1735, 1712, 1612, 1509, 1465, 1336, 1295, 1247, 1175, 1112, 1033, 1008, 957, 832, 801, 762, 635, 607. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{18}NaO_5$ 325.1052, found 325.1038.

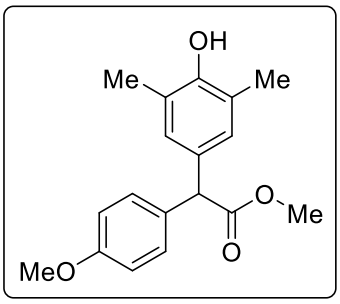
(±)-Methyl 2-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)acetate **14**



Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 3-methoxyphenol (0.15 mmol, 18.6 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg)

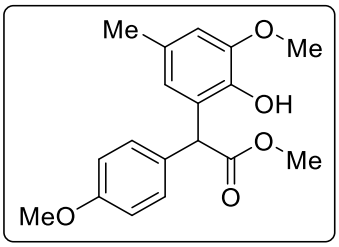
afforded the title compound **14** as colorless oil (7.0 mg, 23%). R_f = 0.2 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.14 (dd, *J* = 8.9, 0.6 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 2.6 Hz, 1H), 6.45 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.00 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.3, 160.8, 158.9, 156.0, 131.8, 129.2, 128.9, 116.4, 114.2, 106.7, 103.6, 55.5, 55.4, 53.5, 53.1. **IR** ν_{max} (cm^{-1}): 3390, 3001, 2953, 2911, 2837, 1736, 1711, 1613, 1511, 1462, 1440, 1331, 1290, 1249, 1203, 1176, 1164, 1109, 1091, 1034, 959, 829, 798, 767. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{18}NaO_5$ 325.1052, found 325.1034.

(±)-Methyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **15**



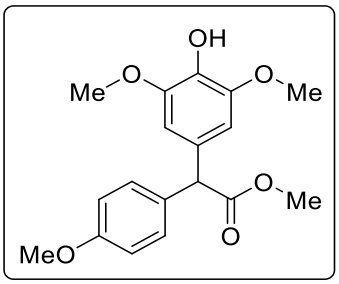
Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 2,6-dimethylphenol (0.15 mmol, 18.3 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound 1**5** as colorless oil (26.4 mg, 88%). R_f = 0.10 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 8.9, 0.6 Hz, 2H), 6.90 (d, *J* = 0.6 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.86 (s, 1H), 4.62 (s, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 2.21 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.8, 158.8, 151.6, 131.4, 130.6, 129.7, 128.7, 123.3, 114.1, 55.6, 55.4, 52.4, 16.1. **IR** ν_{max} (cm^{-1}): 3487, 2923, 2859, 1727, 1605, 1505, 1458, 1260, 1149, 1078, 1025, 800, 744. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}NaO_4$ 323.1259, found 323.1244.

(±)-Methyl 2-(4-hydroxy-3-methoxy-5-methylphenyl)-2-(4-methoxyphenyl)acetate **16**



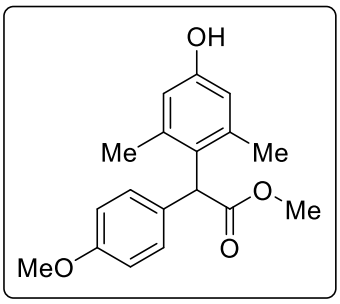
Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 2-methoxy-4-methylphenol (0.15 mmol, 20.7 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **16** as colorless oil (25.3 mg, 80%). R_f = 0.20 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.81 (s, 1H), 6.66 (s, 1H), 5.45 (s, 1H), 5.05 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.72 (s, 3H), 2.20 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.4, 158.6, 145.3, 143.5, 130.1, 129.9, 129.8, 127.7, 114.5, 113.9, 113.0, 55.9, 55.2, 52.5, 52.2, 19.3. **IR** ν_{max} (cm^{-1}): 3390, 3001, 2953, 2911, 2837, 1736, 1711, 1613, 1511, 1462, 1440, 1331, 1290, 1249, 1203, 1176, 1164, 1109, 1091, 1034, 959, 829, 798, 767. **HRMS** (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{20}NaO_5$ 339.1208, found 339.1206.

(±)-Methyl 2-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acetate **17**



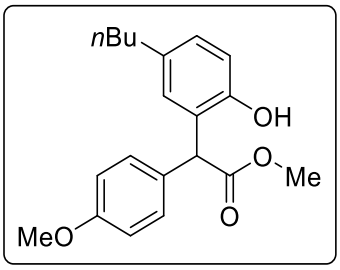
Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 2,6-dimethoxyphenol (0.15 mmol, 23.1 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **17** as colorless oil (27.9 mg, 84%). R_f = 0.15 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.54 (s, 2H), 5.46 (s, 1H), 4.89 (s, 1H), 3.85 (s, 6H), 3.79 (s, 3H), 3.74 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.5, 158.9, 147.1, 134.1, 130.9, 129.9, 129.5, 114.1, 105.5, 56.5, 56.1, 55.4, 52.4. **IR** ν_{max} (cm^{-1}): 3443, 3000, 2952, 2938, 2839, 1732, 1611, 1510, 1460, 1429, 1364, 1325, 1304, 1247, 1215, 1179, 1158, 1112, 1032, 835, 748. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}NaO_6$ 355.1158, found 355.1151.

(±)-Methyl 2-(4-hydroxy-2,6-dimethylphenyl)-2-(4-methoxyphenyl)acetate **18**



Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 3,5-dimethylphenol (0.15 mmol, 18.3 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **18** as colorless oil (20.1 mg, 67%). R_f = 0.12 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.04 – 6.99 (m, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.55 (s, 2H), 5.26 (s, 1H), 5.15 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.14 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.4, 158.4, 154.4, 139.3, 129.9, 128.8, 128.1, 115.9, 113.7, 55.4, 52.5, 49.8, 21.1. **IR** ν_{max} (cm^{-1}): 3493, 3061, 3028, 2951, 2921, 2851, 1726, 1602, 1489, 1434, 1302, 1286, 1273, 1195, 1150, 1025, 1006, 731, 699, 666. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}NaO_4$ 323.1259, found 323.1244.

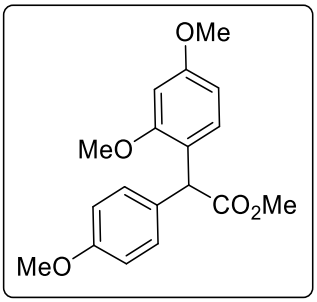
(±)-Methyl 2-(5-butyl-2-hydroxyphenyl)-2-(4-methoxyphenyl)acetate **19**



Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 4-butylphenol (0.15 mmol, 22.5 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **19** as colorless oil (24.6 mg, 75%). R_f = 0.10 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.4 Hz, 2H), 7.01 (dd, *J* = 8.1,

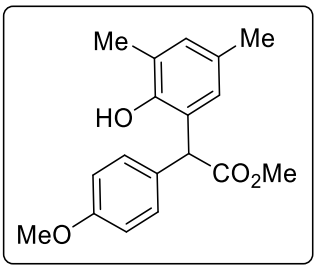
2.2 Hz, 2H), 6.91 (d, *J* = 2.1 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.05 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.49 (d, *J* = 7.5 Hz, 1H), 2.47 (d, *J* = 7.5 Hz, 1H), 1.58 (td, *J* = 15.1, 7.4 Hz, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.8, 158.9, 152.6, 135.1, 130.9, 129.3, 129.21, 129.16, 123.8, 117.7, 114.2, 55.4, 53.8, 53.0, 37.3, 29.8, 24.8, 13.9. **IR** ν_{max} (cm^{-1}): 3399, 2955, 2926, 2870, 2852, 1803, 1736, 1716, 1610, 1510, 1462, 1435, 1249, 1203, 1178, 1033, 822. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{24}O_4Na$ = 351.1567, found 351.1543.

(±)-Methyl 2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)acetate **20**



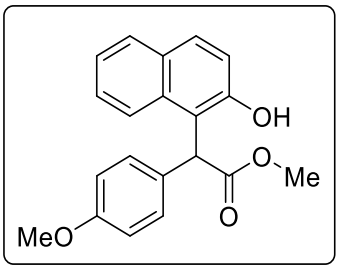
Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 1,3-dimethoxybenzene (0.15 mmol, 20.7 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **20** as colorless oil (26.5 mg, 84%). R_f = 0.30 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.93 (dd, *J* = 8.4, 0.4 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.40 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.16 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.70 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.0, 160.1, 158.8, 157.8, 130.2, 130.1, 129.6, 120.7, 114.0, 104.1, 98.7, 55.6, 55.4, 55.3, 52.2, 49.6. **IR** ν_{max} (cm^{-1}): 3000, 2950, 2836, 1736, 1611, 1586, 1509, 1462, 1438, 1333, 1296, 1249, 1208, 1177, 1157, 1117, 1033, 936, 925, 831, 798, 762, 635. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}O_5Na$ 339.1208, found 339.1191.

(±)-Methyl 2-(2-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **21**



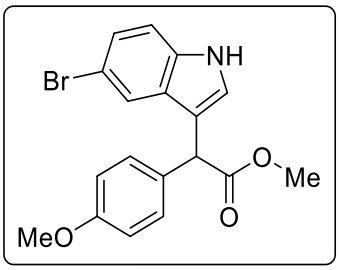
Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 2,4-dimethylphenol (0.15 mmol, 18.3 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **21** as colorless oil (24.6 mg, 82%). R_f = 0.25 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.19 – 7.14 (m, 2H), 6.93 – 6.88 (m, 2H), 6.87 – 6.82 (m, 2H), 6.76 (d, *J* = 1.6 Hz, 1H) 5.03 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.8, 158.8, 150.6, 131.3, 129.3, 129.01, 129.00, 128.9, 125.9, 123.4, 114.0, 55.2, 53.8, 52.8, 20.4, 16.1. **IR** ν_{max} (cm^{-1}): 3468, 3002, 2952, 2922, 2838, 1810, 1790, 1736, 1710, 1609, 1510, 1482, 1462, 1439, 1302, 1249, 1218, 1177, 1163, 1094, 1031, 899, 833, 757, 728. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}NaO_4$ 323.1259, found 323.1246.

(±)-Methyl 2-(2-hydroxynaphthalen-1-yl)-2-(4-methoxyphenyl)acetate **22**



Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and naphthalen-2-ol (0.15 mmol, 21.6 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **22** as colorless oil (19.3 mg, 60%). R_f = 0.15 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.09 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.81 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.50 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.36 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.12 (dd, *J* = 8.9, 0.7 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 5.95 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.8, 158.9, 154.0, 133.3, 130.4, 129.6, 129.1, 128.8, 128.4, 127.3, 123.4, 121.8, 120.5, 114.9, 114.1, 55.3, 53.3, 47.7. **IR** ν_{max} (cm^{-1}): 3445, 3001, 2952, 2839, 1732, 1609, 1587, 1509, 1462, 1444, 1282, 1246, 1195, 1175, 1156, 1088, 1028, 1005, 883, 829, 761, 733, 701. **HRMS** (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{19}O_4$ 323.1283, found 323.1262.

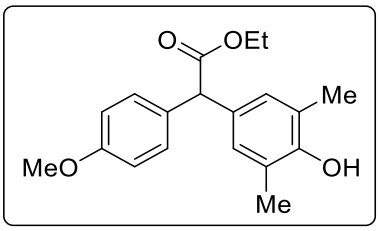
(±)-Methyl 2-(5-bromo-1H-indol-3-yl)-2-(4-methoxyphenyl)acetate **23**



Following the general procedure for Friedel-Crafts, reaction of diazoester **4** (0.10 mmol, 20.6 mg) and 5-bromo-1*H*-indole (0.15mmol, 29.1 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **23** as colorless oil (28.7 mg, 77%). R_f = 0.25 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.23 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 7.13 (d, *J* = 2.2 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.13 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.5, 159.0, 135.0, 130.3, 129.4, 128.4, 125.3, 124.5, 121.6, 114.2, 113.8, 113.1, 112.8, 55.4, 52.5, 47.9. **IR** ν_{max} (cm^{-1}): 3415, 3371, 3003, 2944, 2921, 2845, 1725, 1610, 1509, 1452, 1315, 1247, 1165, 1101, 1030, 877, 800, 757, 660. **HRMS** (ESI-TOF) m/z: $[M-H]^-$ Calcd for $C_{18}H_{15}NO_3Br$ 372.0241, found 372.0226.

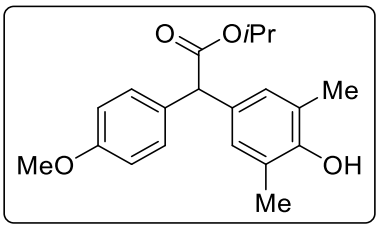
<u>1 mmol scale reaction:</u> To a 25 mL round bottom flask equipped with a magnetic stir-bar was added diazoester **4** (1 mmol, 206 mg), 5-bromoindole (1.5 mmol, 290 mg) and dissolved in DCE (3 mL) at 25 °C. After 1 min of pre-stirring, H_2SO_4-SiO_2 (5 mol%, 100 mg) was added in one portion. After 10 minutes, the reaction was judged to be complete (TLC), the solid filtered off, and washed with ethyl acetate (2 x 25 mL) and organic solvents were removed under reduced pressure. The resulting residue was purified by flash column chromatography using silica gel (230-400 mesh) and a hexane: ethyl acetate (9:1) mobile phase, affording compound **23** as a colorless oil (227 mg, 61%).

(±)-Ethyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **25**



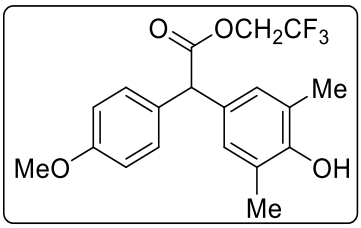
Following the general procedure for Friedel-Crafts, reaction of diazoester **S1** (0.10 mmol, 22.0 mg) and 2,6-dimethylphenol (0.15 mmol, 18.3 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound 2**5** as colorless oil (27.6 mg, 88%). R_f = 0.23 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.90 (s, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.83 (s, 1H), 4.63 (s, 1H), 4.22 – 4.15 (m, 2H), 3.78 (s, 3H), 2.20 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.2, 158.6, 151.4, 131.4, 130.6, 129.5, 128.6, 123.1, 113.9, 61.0, 55.5, 55.2, 16.0, 14.2. **IR** ν_{max} (cm^{-1}): 3485, 2965, 2920, 2844, 1721, 1607, 1500, 1480, 1453, 1375, 1294, 1247, 1151, 1098, 1023, 875, 800, 746, 693, 646. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{22}NaO_4$ 337.1416, found 337.1391.

(±)-Isopropyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **26**



Following the general procedure for Friedel-Crafts, reaction of diazoester **S2** (0.10 mmol, 21.8 mg) and 2,6-dimethylphenol (0.15 mmol, 18.3 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **26** as colorless oil (28.2 mg, 86%). R_f = 0.18 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.90 (s, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.06 (hept, *J* = 6.3 Hz, 1H), 4.79 (s, 1H), 4.59 (s, 1H), 3.79 (s, 3H), 2.20 (s, 6H), 1.22 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.8, 158.7, 151.4, 131.7, 130.9, 129.6, 128.7, 123.1, 114.0, 68.5, 55.8, 55.4, 21.8, 16.1. **IR** ν_{max} (cm^{-1}): 3485, 2977, 2928, 2845, 1718, 1608, 1502, 1480, 1455, 1371, 1294, 1246, 1177, 1104, 1030, 977, 946, 903, 830, 793, 733, 644. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{24}NaO_4$ 351.1572, found 351.1544.

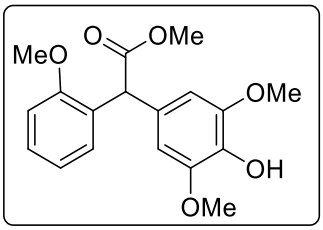
(±)-2,2,2-Trifluoroethyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **27**



Following the general procedure for Friedel-Crafts, reaction of diazoester **S3** (0.10 mmol, 27.4 mg) and 2,6-dimethylphenol (0.15 mmol, 18.3 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **27** as colorless oil (26.9 mg, 73%). R_f = 0.30 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 0.5 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.94 (s, 1H), 4.62 (s, 1H), 4.55 – 4.47 (m, 2H), 3.78 (s, 3H), 2.20 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.8, 159.0, 151.8, 130.4, 129.62, 129.60, 128.6, 123.4, 123.0 (q, *J* = 277 Hz), 114.9, 60.7 (q, *J* = 36.6 Hz), 55.4, 55.0, 16.0. **IR** ν_{max} (cm^{-1}):

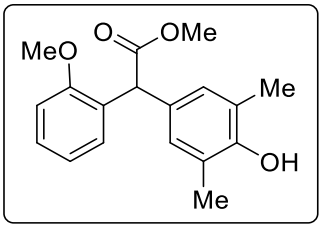
3521, 3005, 2957, 2924, 2852, 2840, 1752, 1609, 1511, 1489, 1462, 1442, 1407, 1276, 1250, 1166, 1135, 1032, 979, 884, 835, 803, 795, 764, 730, 662, 645. **HRMS** (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{20}F_3O_4$ 369.1308, found 369.1333.

(±)-Methyl 2-(4-hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxyphenyl)acetate **28**



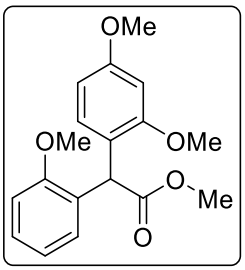
Following the general procedure for Friedel-Crafts, reaction of diazoester **S4** (0.10 mmol, 20.6 mg) and 2,6-dimethoxyphenol (0.15 mmol, 23.1 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **28** as colorless oil (21.9 mg, 66%). R_f = 0.12 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.28-7.23 (m, 1H), 7.00 (ddd, *J* = 7.8, 1.8, 0.7 Hz, 1H), 6.89 (ddd, *J* = 6.6, 3.5, 2.4 Hz, 2H), 6.56 (s, 2H), 5.47 (s, 1H), 5.16 (s, 1H), 3.85 (s, 6H), 3.84 (s, 3H), 3.73 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.7, 156.9, 147.2, 134.2, 129.1, 128.6, 128.4, 128.1, 120.7, 110.5, 106.0, 56.4, 55.7, 52.4, 51.2. **IR** ν_{max} (cm^{-1}): 3443, 3000, 2952, 2938, 2839, 1732, 1612, 1510, 1460, 1247, 1112, 835, 748. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}NaO_6$ = 355.1158, found 355.1161.

(±)-Methyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(2-methoxyphenyl)acetate **29**



Following the general procedure for Friedel-Crafts, reaction of diazoester **S4** (0.10 mmol, 20.6 mg) and 2,6-dimethylphenol (0.15 mmol, 18.3 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **29** as colorless oil (18.3 mg, 61%). R_f = 0.20 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.25-7.21 (m, 1H), 7.02 (ddd, *J* = 8.0, 1.8, 0.7 Hz, 1H), 6.92 (d, *J* = 0.5 Hz, 2H), 6.90-6.86 (m, 2H), 5.16 (s, 1H), 4.70 (s, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 2.20 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.1, 156.9, 151.6, 129.30, 129.28, 129.0, 128.4, 128.3, 123.4, 120.6, 110.5, 55.7, 52.3, 50.3, 16.1. **IR** ν_{max} (cm^{-1}): 3485, 3004, 2952, 2923, 2842, 1735, 1600, 1493, 1462, 1437, 1332, 1286, 1245, 1189, 1166, 1115, 1073, 1048, 1024, 979, 941, 911, 868, 802, 788, 755. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}NaO_4$ 323.1259, found 323.1240.

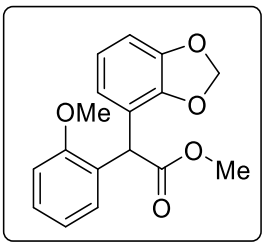
(±)-Methyl 2-(2,4-dimethoxyphenyl)-2-(2-methoxyphenyl)acetate **30**



Following the general procedure for Friedel-Crafts, reaction of diazoester S**4** (0.10 mmol, 20.6 mg) and 1,3-dimethoxybenzene (0.15 mmol, 20.7mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0

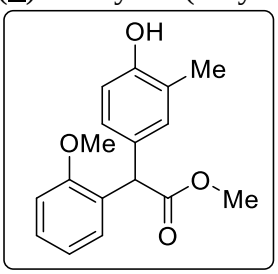
mg) afforded the title compound **30** as colorless oil (22.1 mg, 70%). R_f = 0.30 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.27 – 7.23 (m, 1H), 7.02 (ddd, *J* = 7.7, 1.7, 0.5 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.89 (ddd, *J* = 6.2, 5.7, 1.0 Hz, 2H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.54 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.2, 160.2, 158.2, 157.3, 129.9, 129.3, 128.4, 127.2, 120.6, 119.2, 110.7, 104.2, 98.8, 55.7 (2C), 55.4, 52.2, 44.2. **IR** ν_{max} (cm^{-1}): 3000, 2949, 2837, 1734, 1611, 1586, 1504, 1492, 1460, 436, 1334, 1292, 1242, 1206, 1171, 1153, 1106, 1010, 936, 925, 833, 785, 754, 638. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}NaO_5$ 339.1208, found 339.1198.

(±)-Methyl 2-(benzo[d][1,3]dioxol-4-yl)-2-(2-methoxyphenyl)acetate **31**



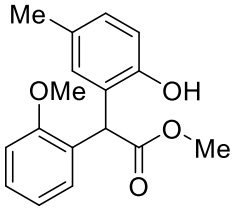
Following the general procedure for Friedel-Crafts, reaction of diazoester S**4** (0.10 mmol, 20.6 mg) and benzo[*d*][1,3]dioxole (0.15 mmol, 18.3 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **31** as colorless oil (17.4 mg, 58%). R_f = 0.35 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.25 – 7.23 (m, 1H), 7.08 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.89 (ddd, *J* = 15.3, 7.7, 0.9 Hz, 2H), 6.83 – 6.82 (m, 1H), 6.77 (d, *J* = 1.1 Hz, 2H), 5.94 (s, 2H), 5.21 (s, 1H), 3.82 (s, 3H), 3.72 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.1, 157.0, 153.3, 131.8, 129.6, 129.2, 128.5, 128.3, 127.8, 124.1, 120.7, 115.2, 110.6, 55.7, 52.3, 50.3, 16.0. **IR** ν_{max} (cm^{-1}): 2952, 2923, 2841, 1736, 1599, 1489, 1461, 1440, 1290, 1232, 1194, 1157, 1035, 930, 810, 755, 654. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{16}NaO_5$ 323.0895, found 323.0889.

(±)-Methyl -2-(4-hydroxy-3-methylphenyl)-2-(2-methoxyphenyl)acetate **32**



Following the general procedure for Friedel-Crafts, reaction of diazoester **S4** (0.10 mmol, 20.6 mg) and *o*-cresol (0.15 mmol, 16.2 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **32** as colorless oil (21.2 mg, 74%). R_f = 0.25 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.23 (td, *J* = 7.9, 1.7 Hz, 1H), 7.05 (d, *J* = 2.1 Hz, 1H), 7.03 – 7.01 (m, 1H), 6.99 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.88 (dd, *J* = 11.8, 4.4 Hz, 2H), 6.70 (d, *J* = 8.2 Hz, 1H), 5.19 (s, 1H), 4.95 (s, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 2.21 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.0, 156.9, 153.2, 131.7, 129.6, 129.2, 128.4, 128.2, 127.8, 124.1, 120.6, 115.1, 110.5, 55.6, 52.3, 50.3, 15.9. **IR** ν_{max} (cm^{-1}): 3420, 3004, 2952, 2925, 2839,1717, 1600, 1588, 1507, 1490, 1461, 1436, 1326, 1265, 1241, 1195, 1172, 1161, 1118, 1106, 1027, 908, 814, 728, 635. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}NaO_4$ 308.1103, found 308.1090.

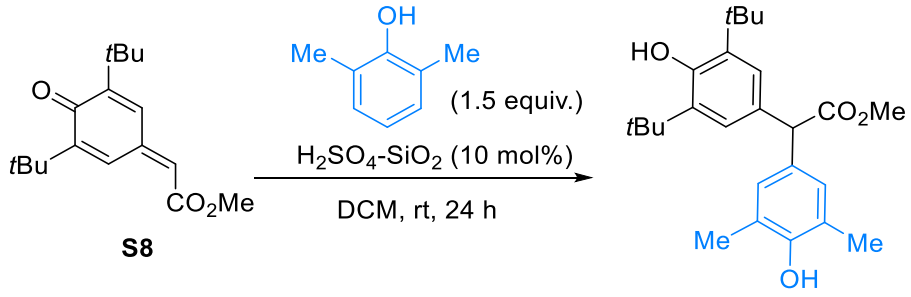
(±)-Methyl 2-(2-hydroxy-5-methylphenyl)-2-(2-methoxyphenyl)acetate **33**



Following the general procedure for Friedel-Crafts, reaction of diazoester **S4** (0.10 mmol, 20.6 mg) and *p*-cresol (0.15 mmol, 16.2 mg) catalyzed by H_2SO_4-SiO_2 (5 mol%, 10.0 mg) afforded the title compound **33** as colorless oil (20.9 mg, 73%). R_f = 0.25 (10% EtOAc:Hexane). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.29-7.25 (m, 1H), 7.04-7.02 (m, 2H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.92-6.89 (m, 3H), 6.84 (d, *J* = 8.2 Hz, 1H), 5.19 (s, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 2.26 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.7, 156.7, 153.0, 131.7, 130.2, 130.1, 129.2, 128.9, 125.2, 121.9, 121.0, 117.7, 110.7, 55.8, 52.9, 49.2, 20.7. **IR** ν_{max} (cm^{-1}): 3413, 2951, 2923, 2839, 1713, 1611, 1509, 1491, 1460, 1435, 1325, 1264, 1243, 1200, 1175, 1161, 1102, 1026, 815, 753. **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{18}NaO_4$ 309.1103, found 309.1095.

Control experiments details

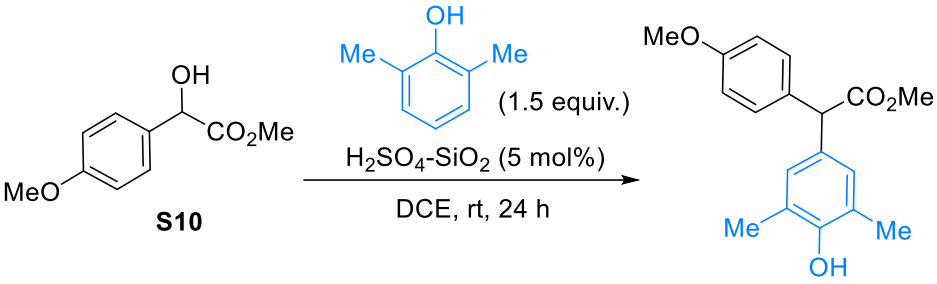
Synthesis of Methyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-(4-hydroxy-3,5-dimethylphenyl)acetate **S9**



S9 72% yield

To a round bottom flask was added methyl 2-(3,5-di-tert-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)acetate **S8**[9] (20 mg, 0.07 mmol) and dissolved in dichloromethane (0.3 mL) under argon. To the stirring solution was added 2,6-dimethylphenol (13 mg, 0.11 mmol), followed by H_2SO_4-SiO_2 (10 mol%, 14.0 mg). The reaction was left to stir for 24 h. Upon completion (as detected by consumption of the starting materials by TLC), the reaction was filtered to remove the catalyst, and remaining organic solvents removed under reduced pressure. The residue was purified by silica gel chromatography using hexane-acetone (8-1). methyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-(4-hydroxy-3,5-dimethylphenyl)acetate (20 mg, 72%) was isolated as a pale yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.12 (2H, s), 6.95 (2H, s), 5.13 (1H, s), 4.79 (1H, s), 4.55 (1H, s), 3.71 (3H, s), 2.21 (6H, s), 1.41 (18H, s). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 174.1, 153.0, 151.4, 135.8, 130.9, 129.6, 128.8, 125.3, 123.1, 56.3, 52.3, 34.5, 30.4, 16.2. **IR** ν_{max} (cm^{-1}): 3637, 3494, 2954, 2917, 2873, 1724, 1605, 1489, 1434, 1320, 1235, 1195, 1152, 1024, 732. **HRMS** (ESI-TOF) m/z: $[M-H]^-$ Calcd for $C_{25}H_{33}O_4$ 397.2379, found 397.2364.

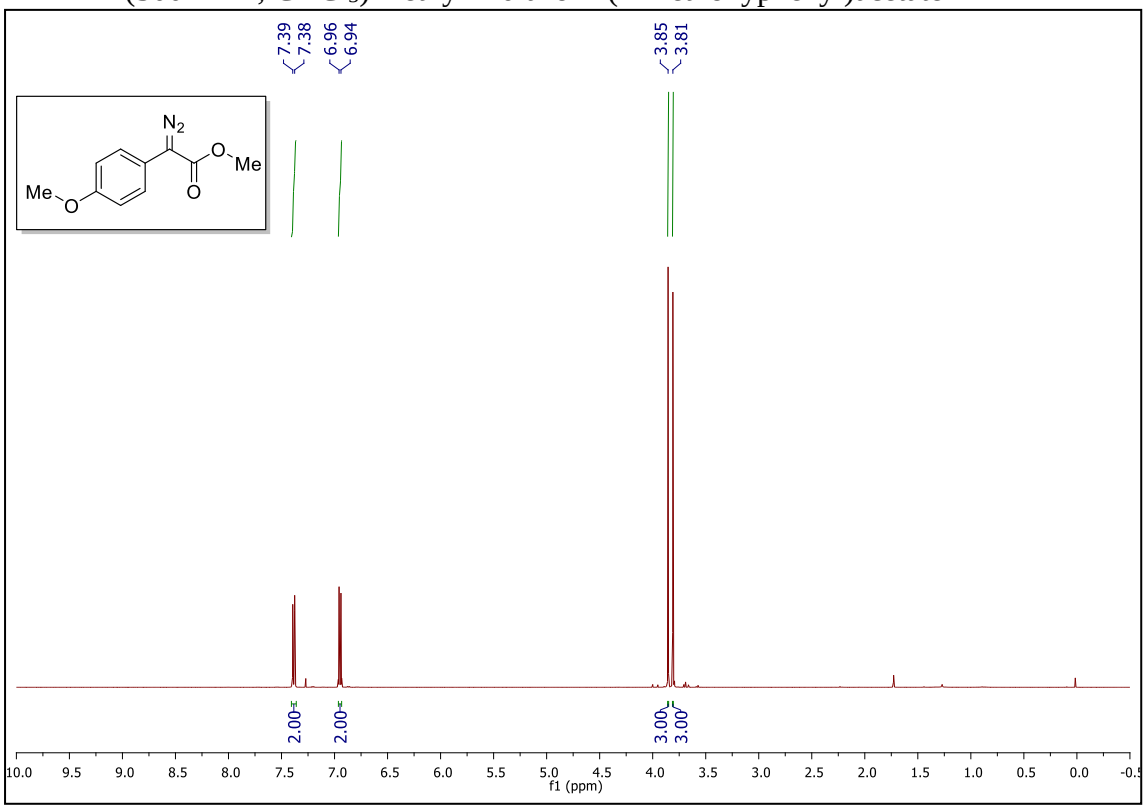
Attempted synthesis of Methyl (+)-2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **15** from methyl 2-hydroxy-2-(4-methoxyphenyl)acetate **S10**



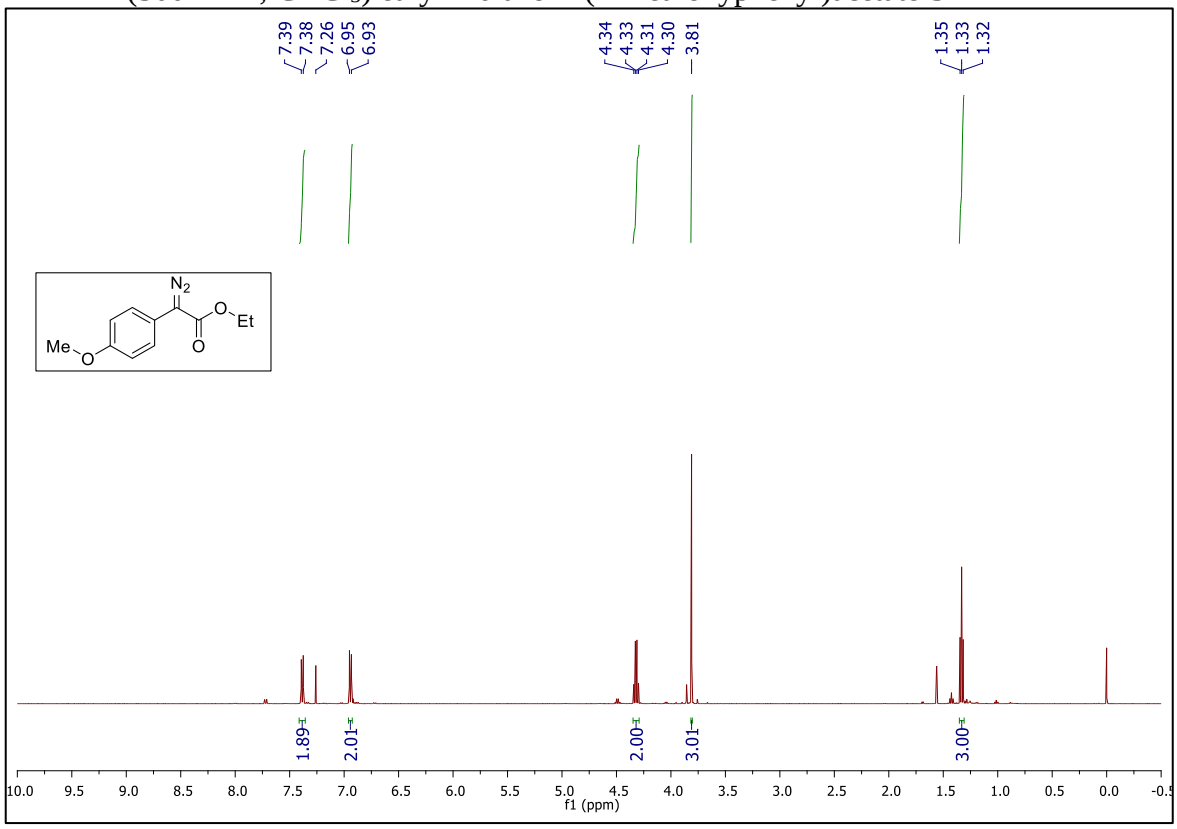
15 0% yield

To a round bottom flask was added methyl 2-hydroxy-2-(4-methoxyphenyl)acetate **S10**[10] (20 mg, 0.1 mmol) and dissolved in dichloromethane (0.3 mL) under argon. To the stirring solution was added 2,6-dimethylphenol (18 mg, 0.15 mmol), followed by H_2SO_4-SiO_2 (5 mol%, 10 mg). The reaction was left to stir for 24 h. During this time, TLC analysis confirmed no desired product **15** was formed, with both starting materials remaining in the reaction mixture.

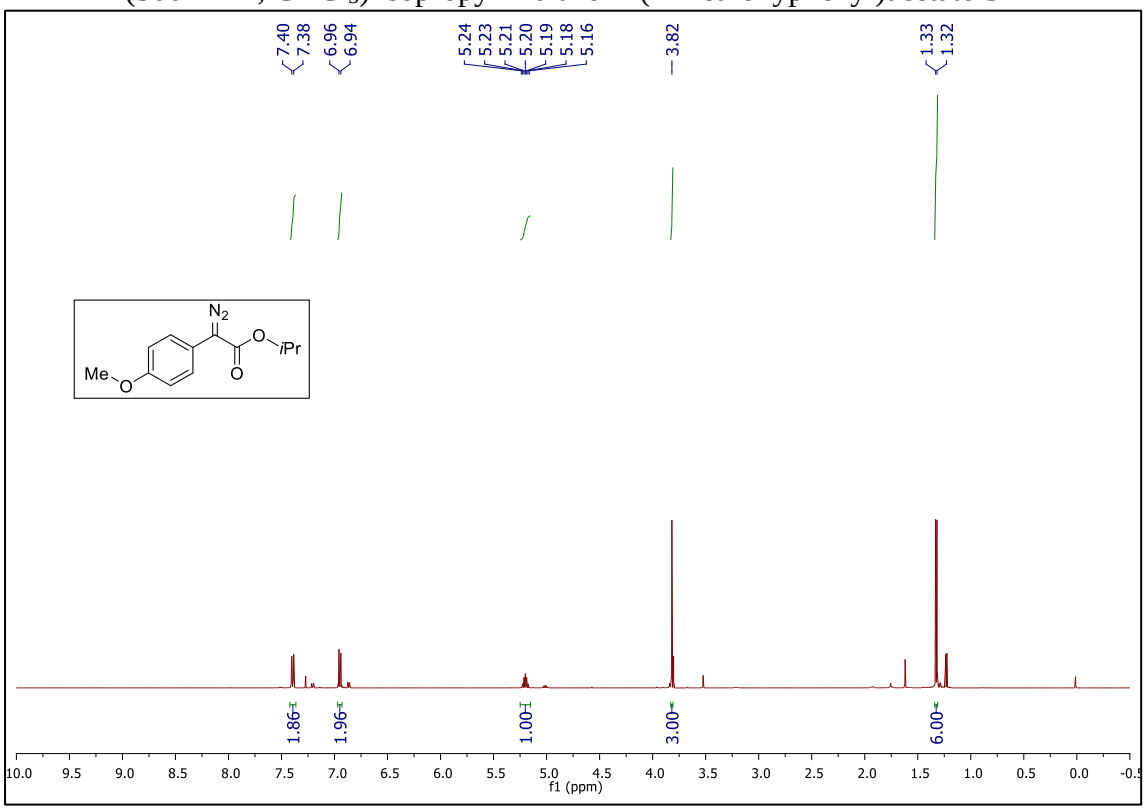
^{1}H NMR (500 MHz, $CDCl_3$) methyl 2-diazo-2-(4-methoxyphenyl)acetate **4**



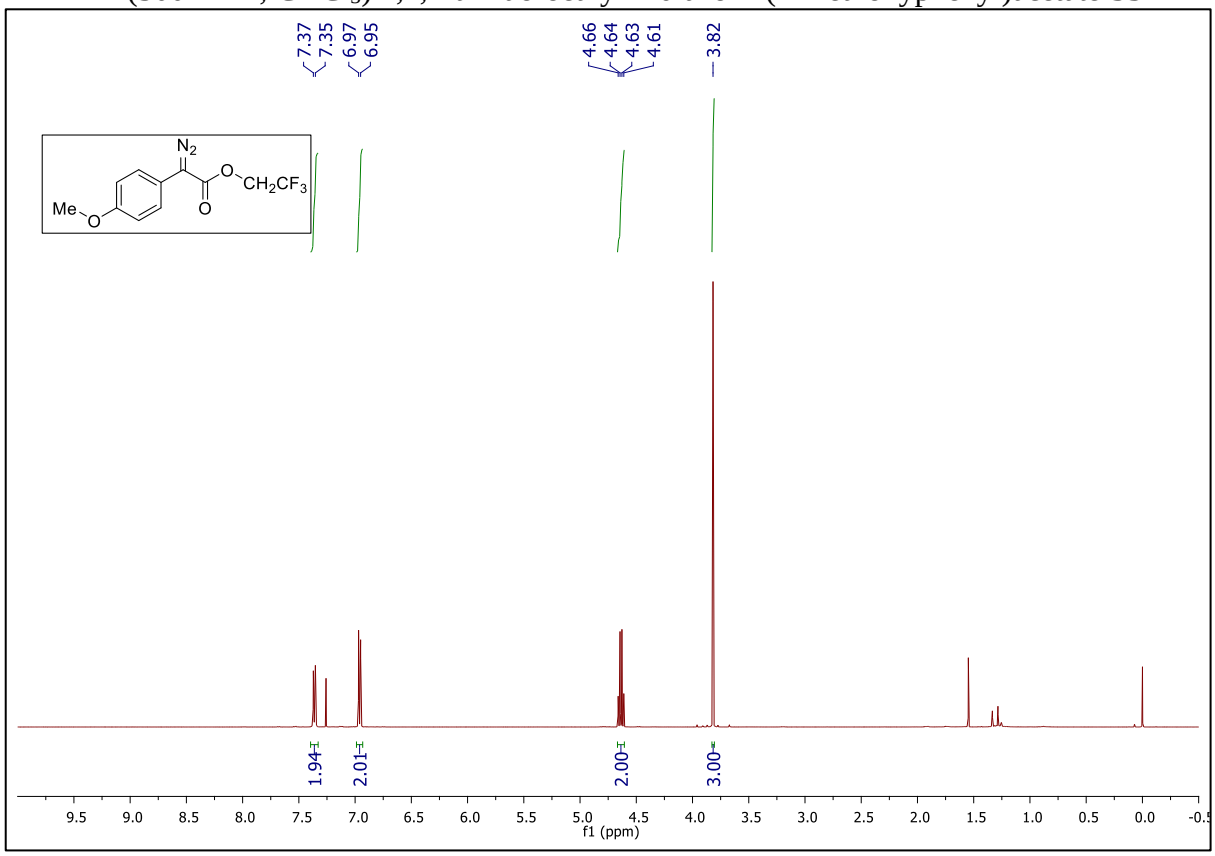
^{1}H NMR (500 MHz, $CDCl_3$) ethyl 2-diazo-2-(4-methoxyphenyl)acetate **S1**



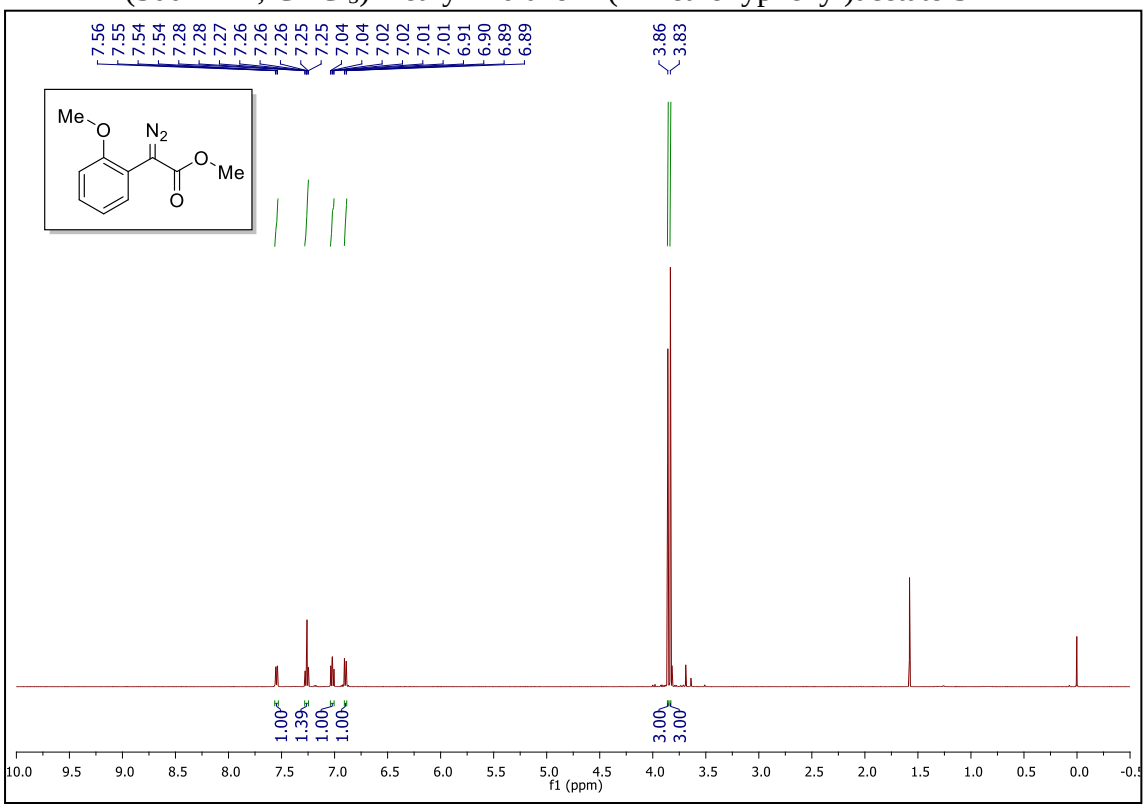
^{1}H NMR (500 MHz, $CDCl_3$) isopropyl 2-diazo-2-(4-methoxyphenyl)acetate **S2**



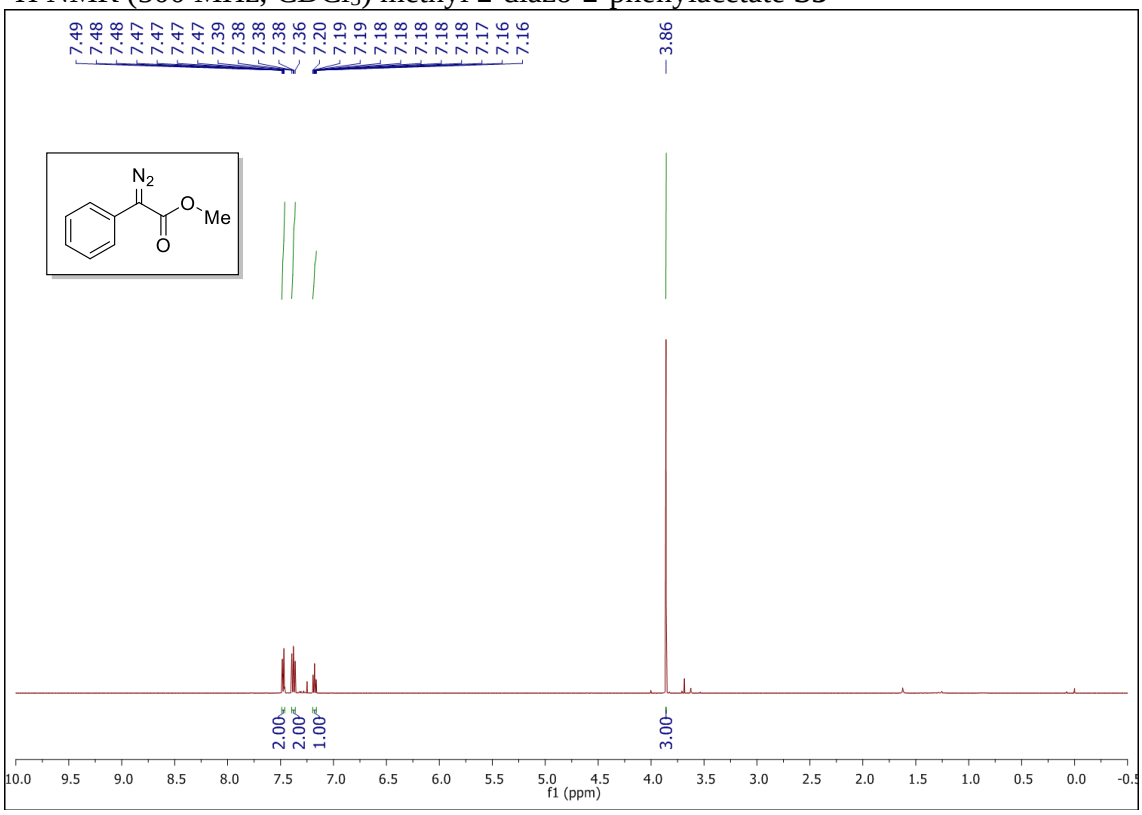
^{1}H NMR (500 MHz, $CDCl_3$) 2,2,2-trifluoroethyl 2-diazo-2-(4-methoxyphenyl)acetate **S3**



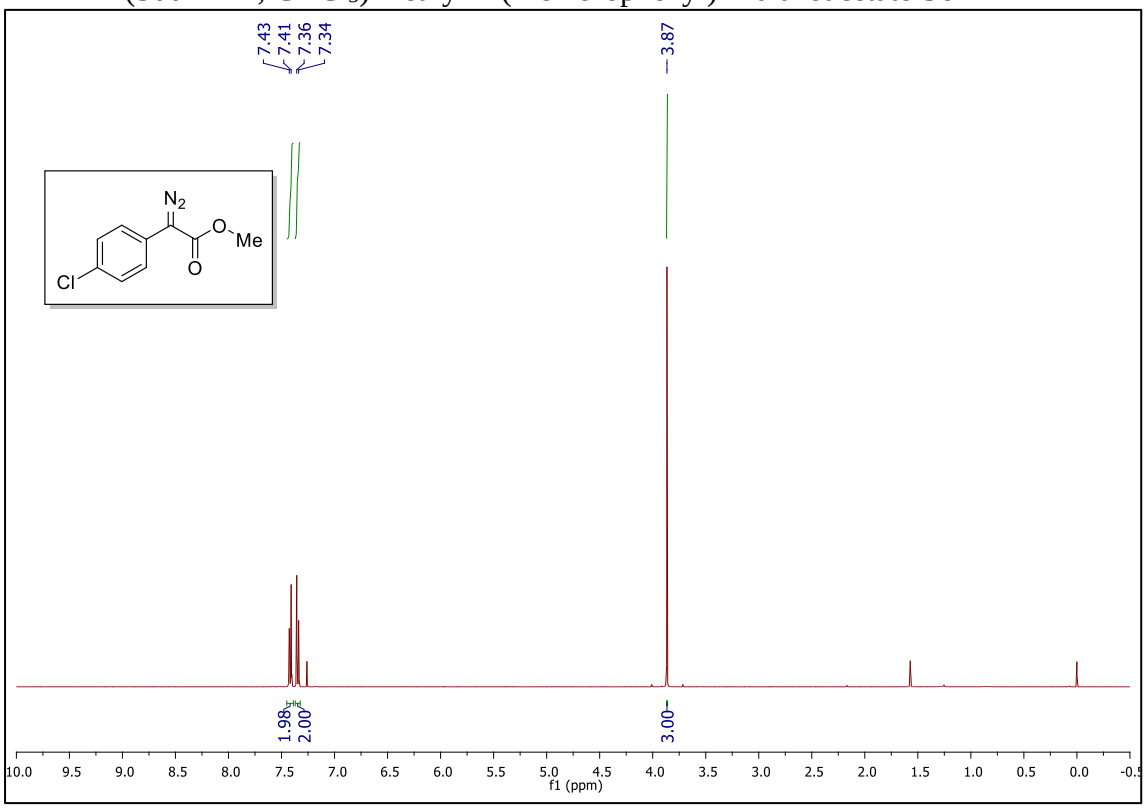
^{1}H NMR (500 MHz, $CDCl_3$) methyl 2-diazo-2-(2-methoxyphenyl)acetate **S4**



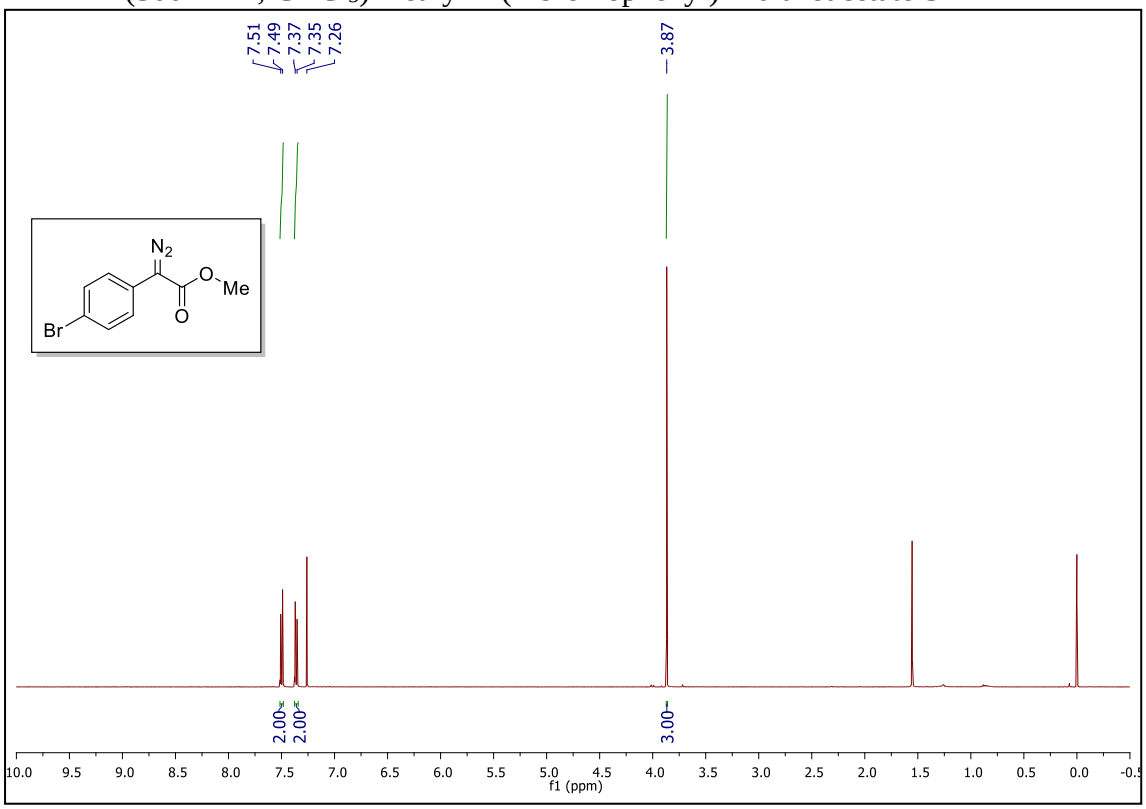
^{1}H NMR (500 MHz, $CDCl_3$) methyl 2-diazo-2-phenylacetate **S5**



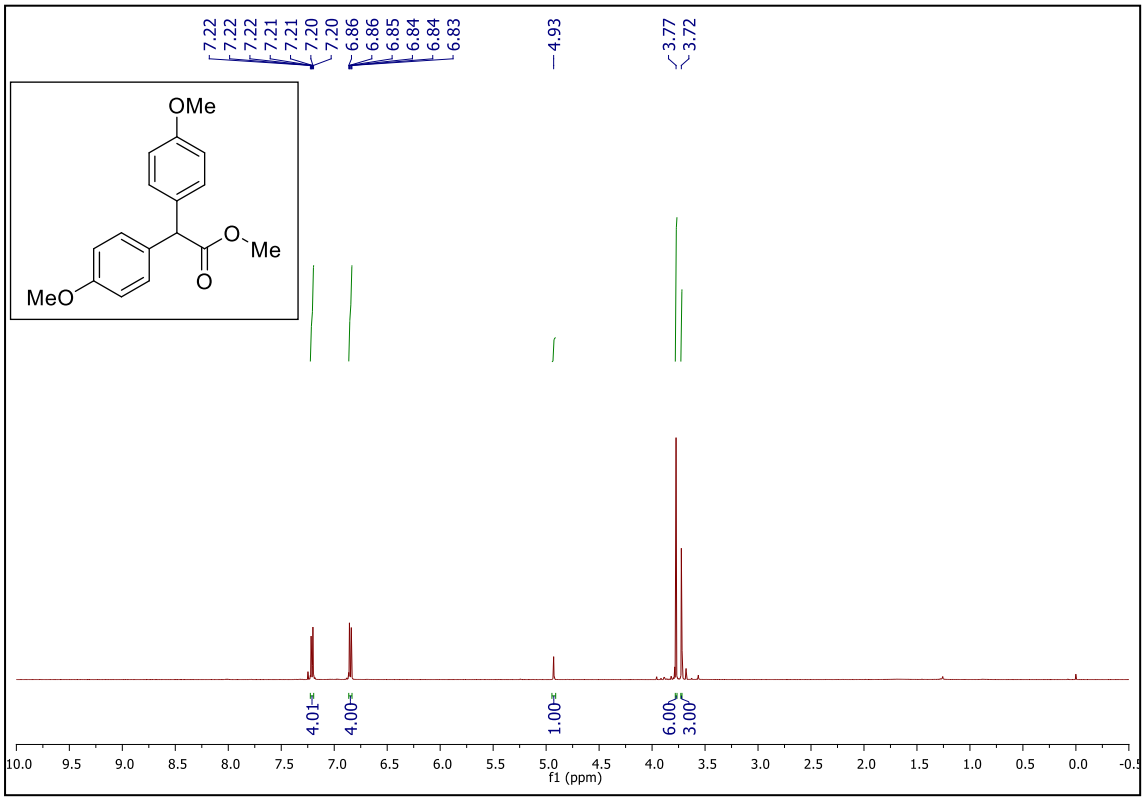
^{1}H NMR (500 MHz, $CDCl_3$) methyl 2-(4-chlorophenyl)-2-diazoacetate **S6**



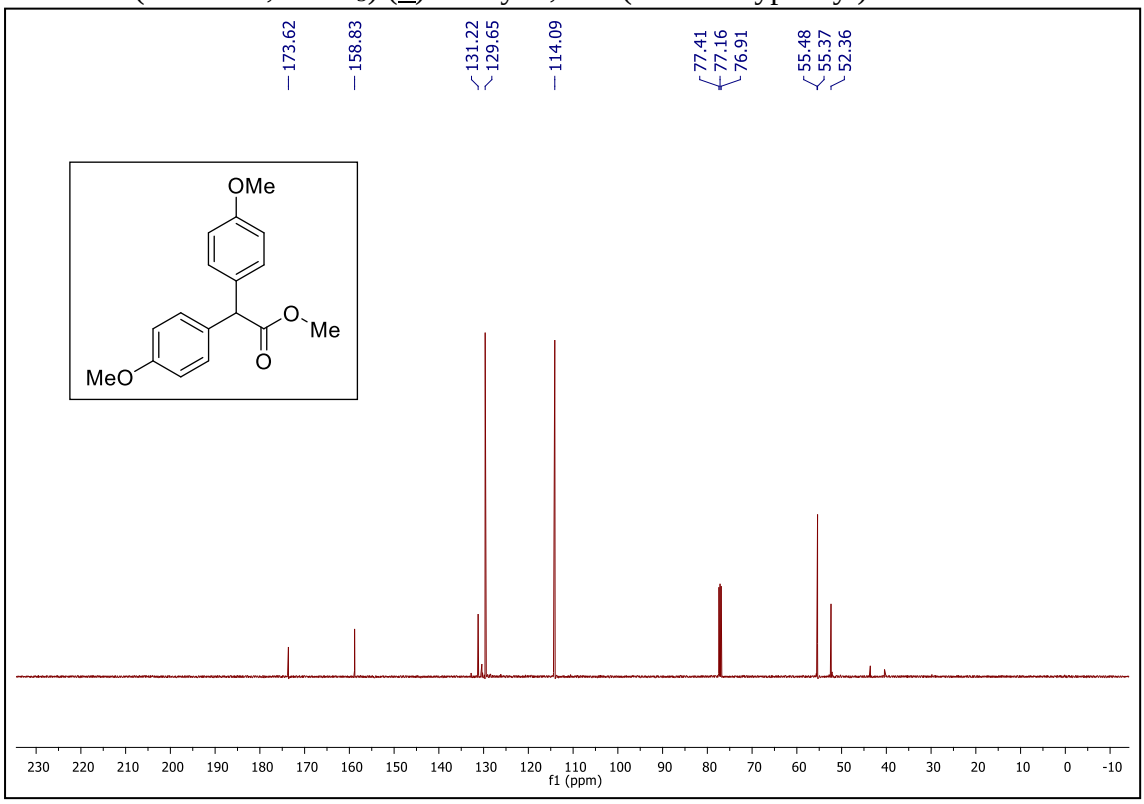
^{1}H NMR (500 MHz, $CDCl_3$) methyl 2-(4-bromophenyl)-2-diazoacetate **S7**



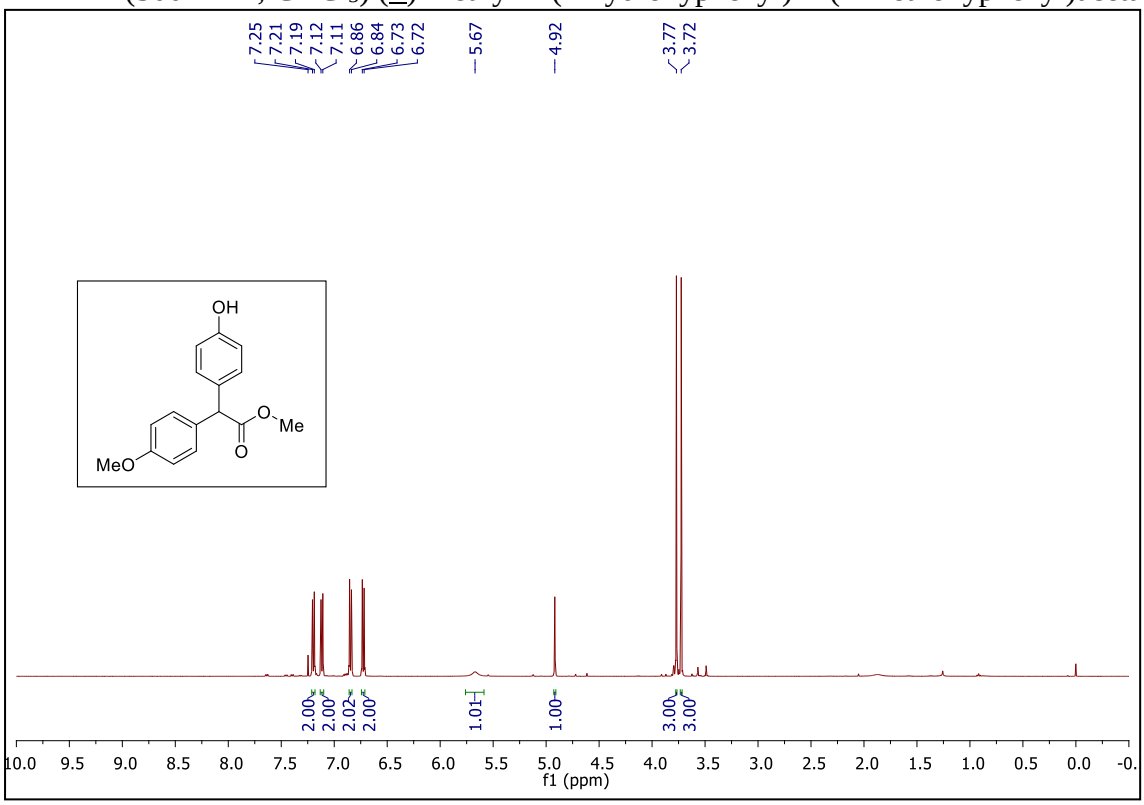
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2,2-bis(4-methoxyphenyl)acetate **5**



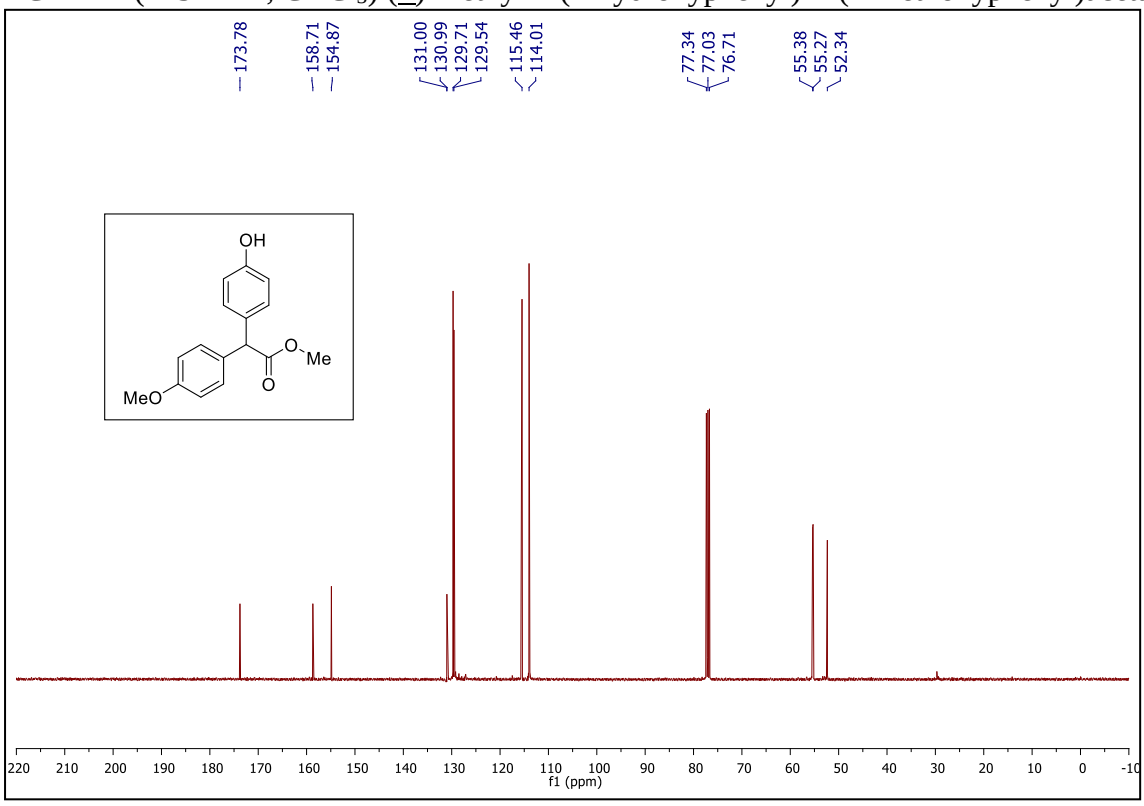
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2,2-bis(4-methoxyphenyl)acetate **5**



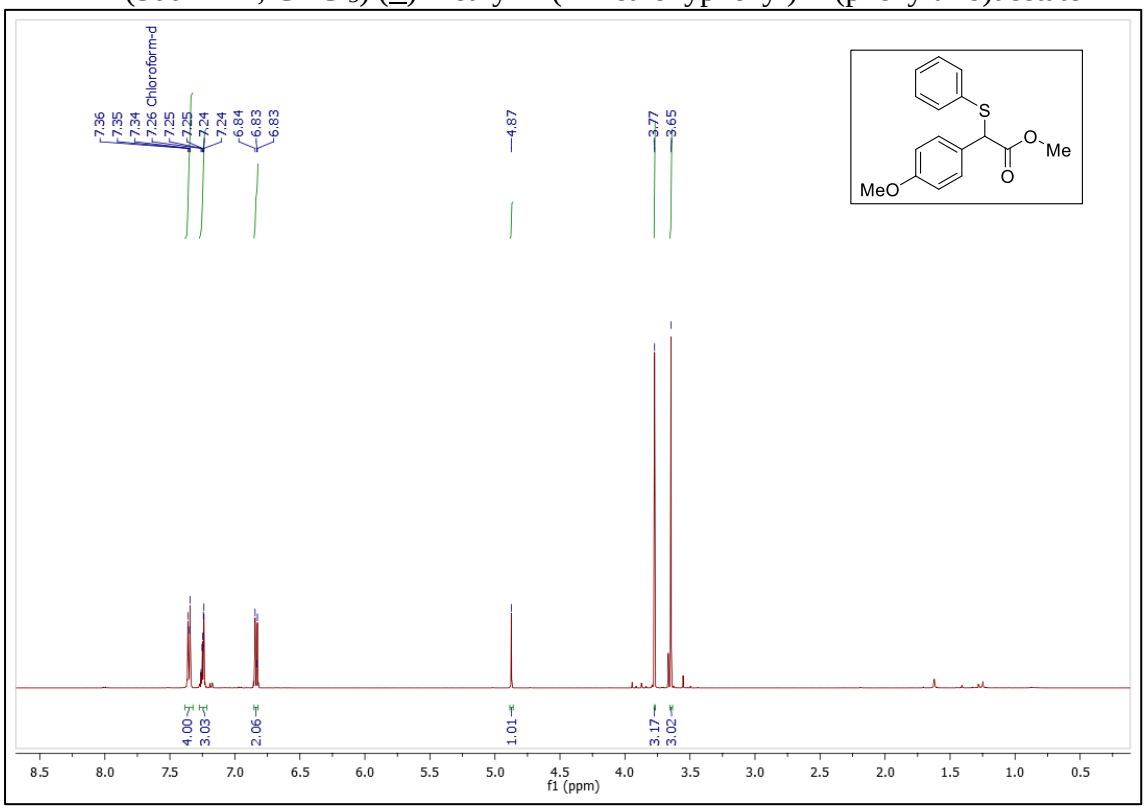
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxyphenyl)-2-(4-methoxyphenyl)acetate **6**



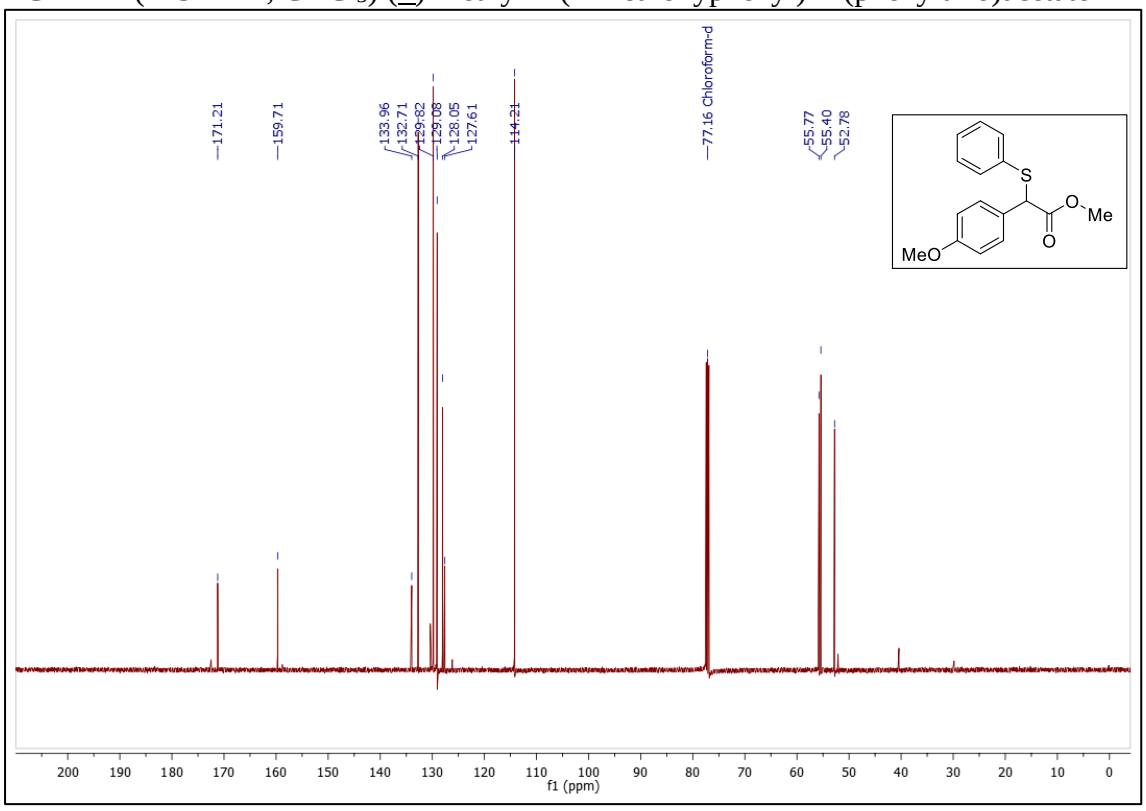
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxyphenyl)-2-(4-methoxyphenyl)acetate **6**



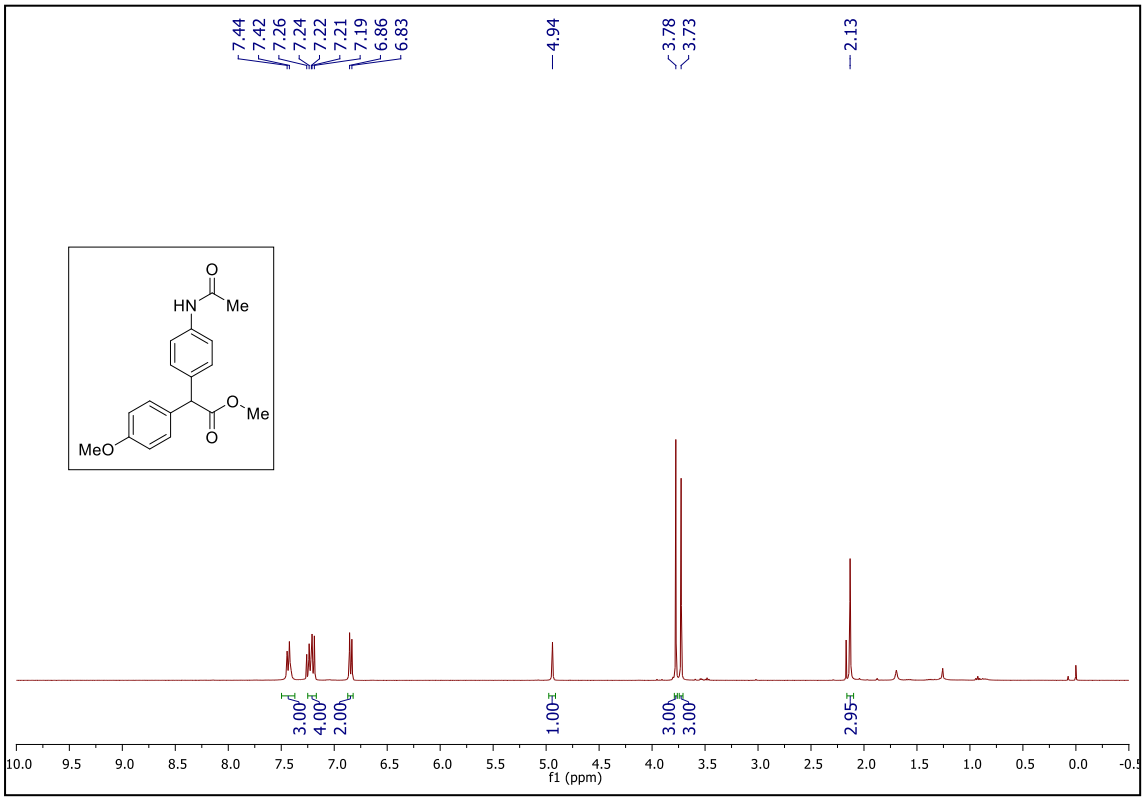
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-methoxyphenyl)-2-(phenylthio)acetate **7**



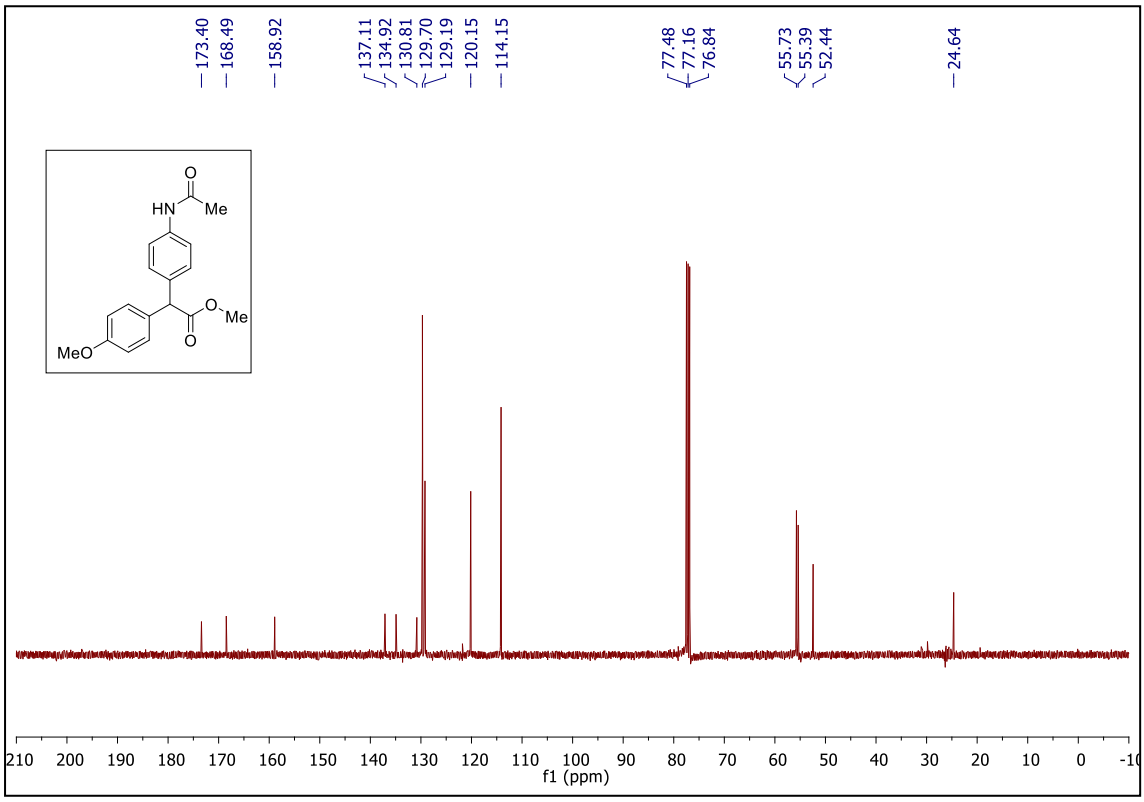
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-methoxyphenyl)-2-(phenylthio)acetate **7**



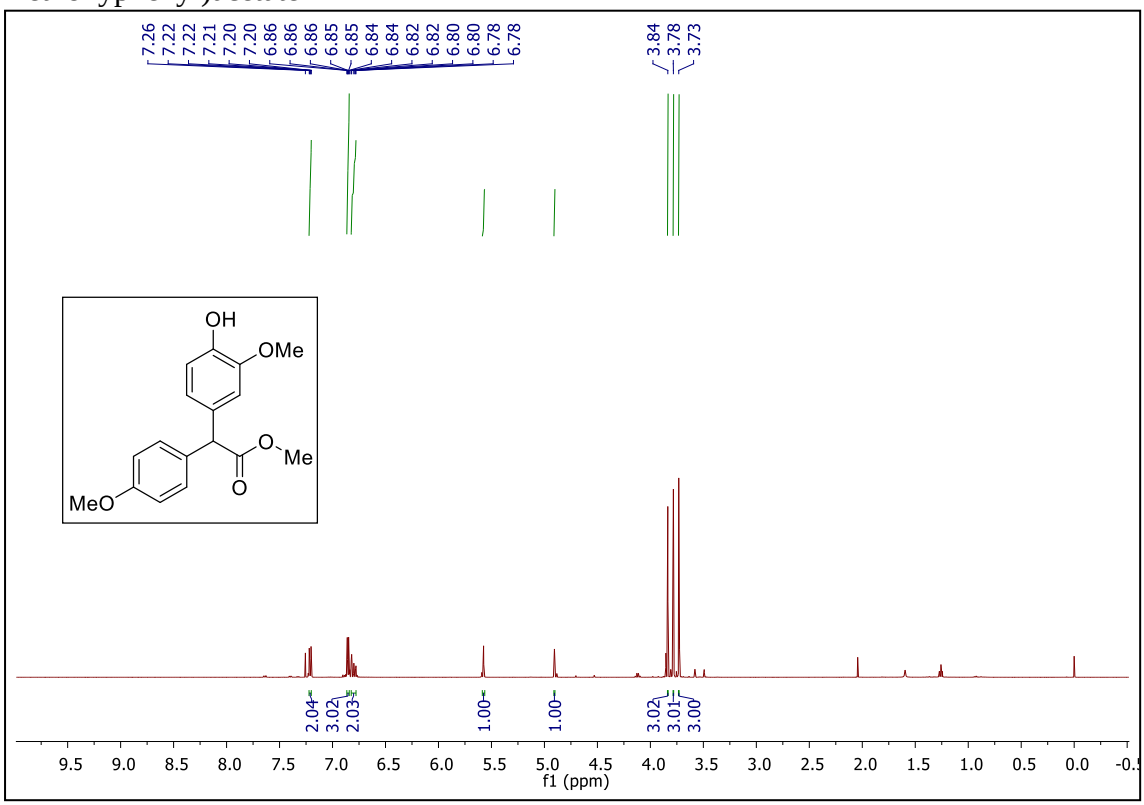
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-acetamidophenyl)-2-(4-methoxyphenyl)acetate **11**



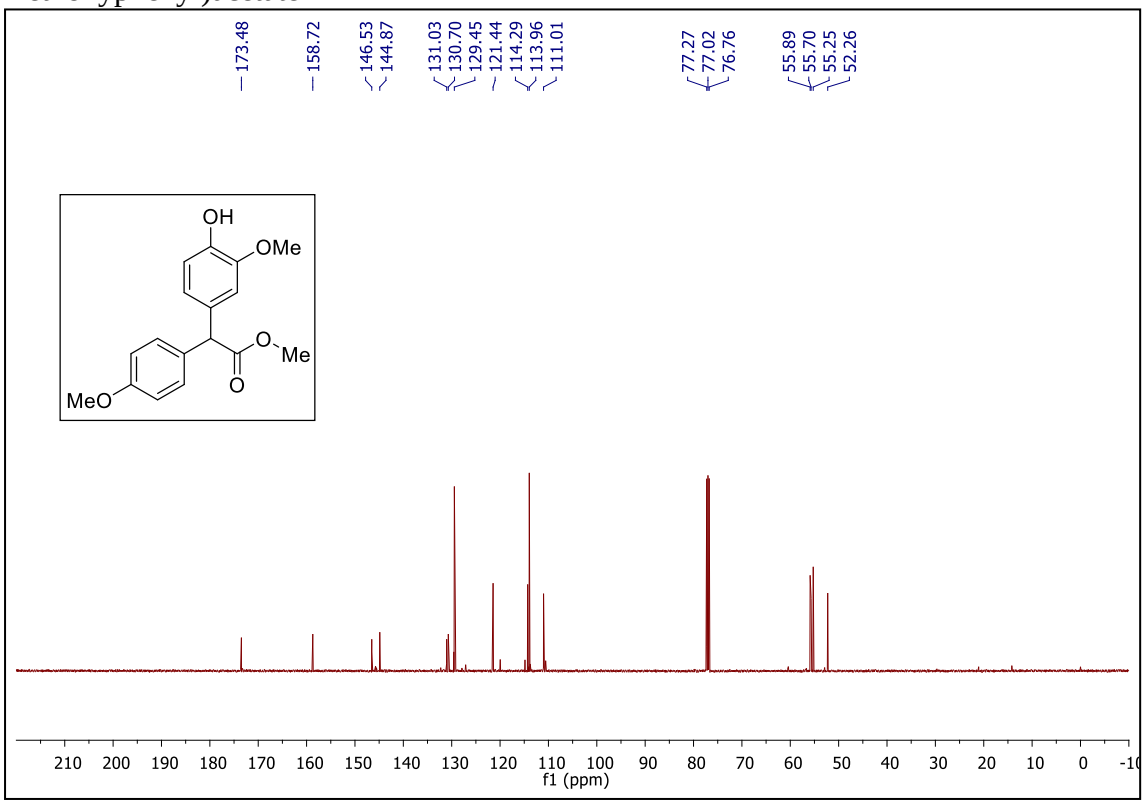
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-acetamidophenyl)-2-(4-methoxyphenyl)acetate **11**



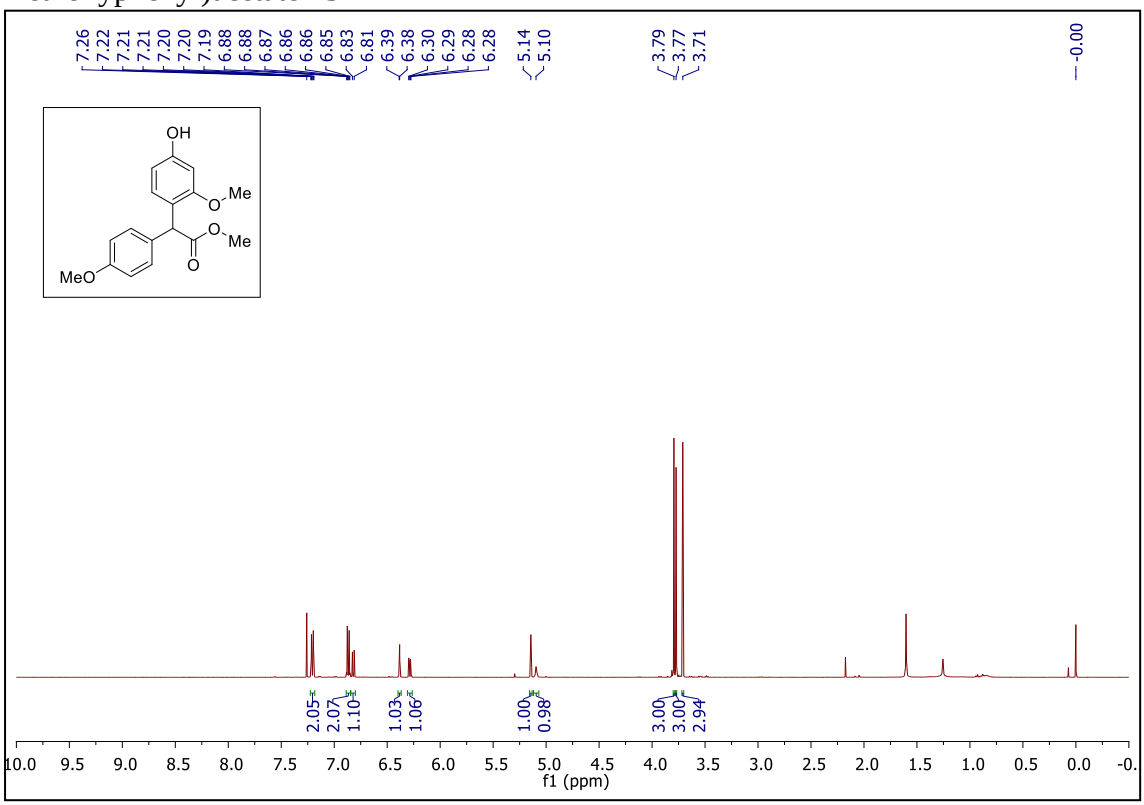
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3-methoxyphenyl)-2-(4-methoxyphenyl)acetate **12**



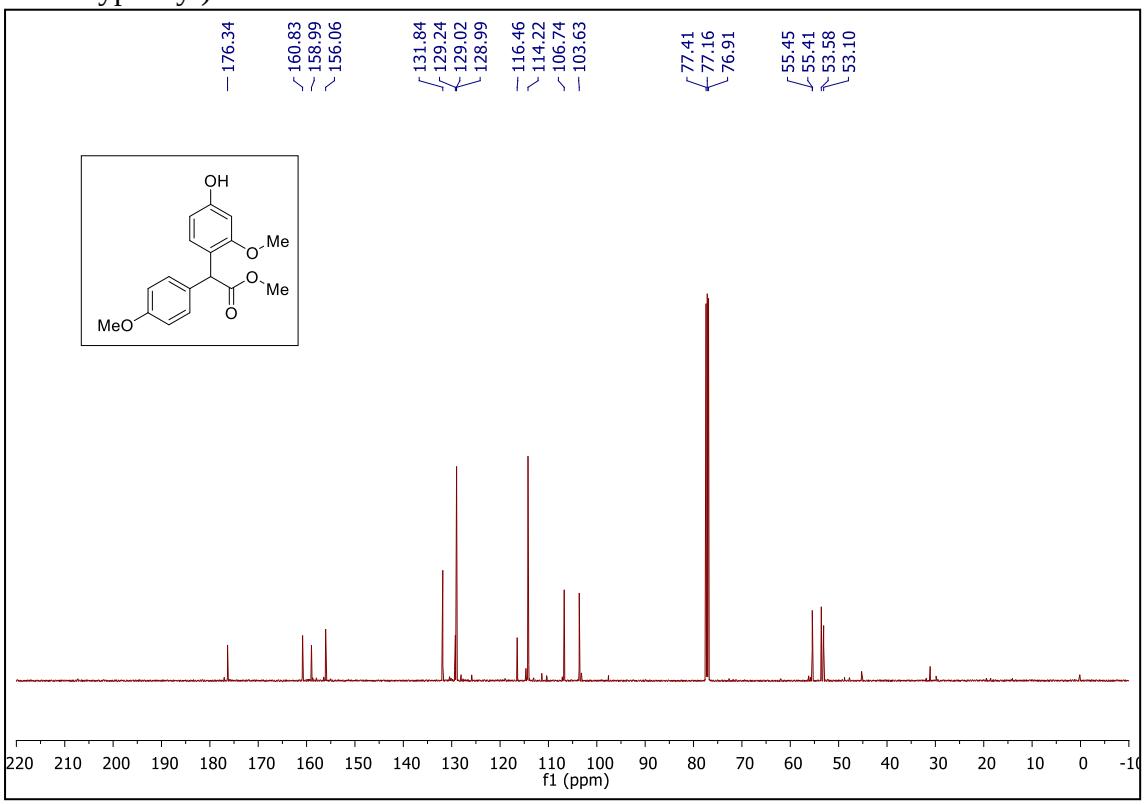
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3-methoxyphenyl)-2-(4-methoxyphenyl)acetate **12**



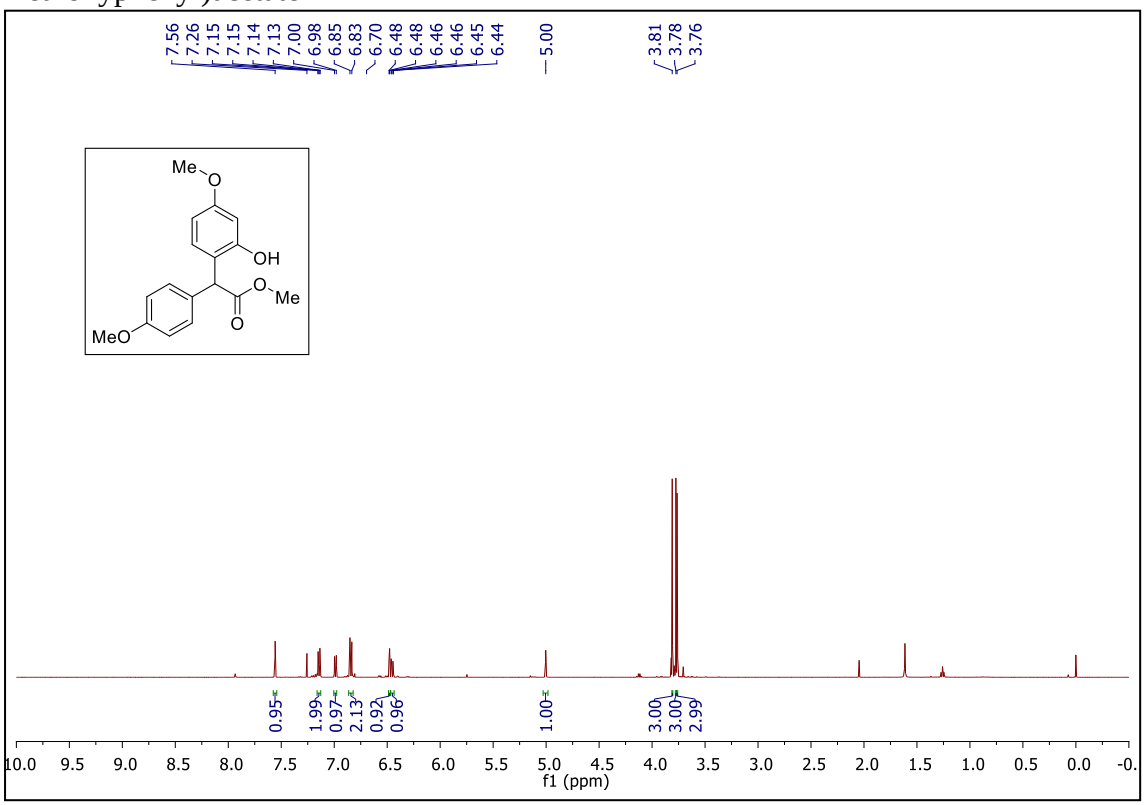
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-2-methoxyphenyl)-2-(4-methoxyphenyl)acetate **13**



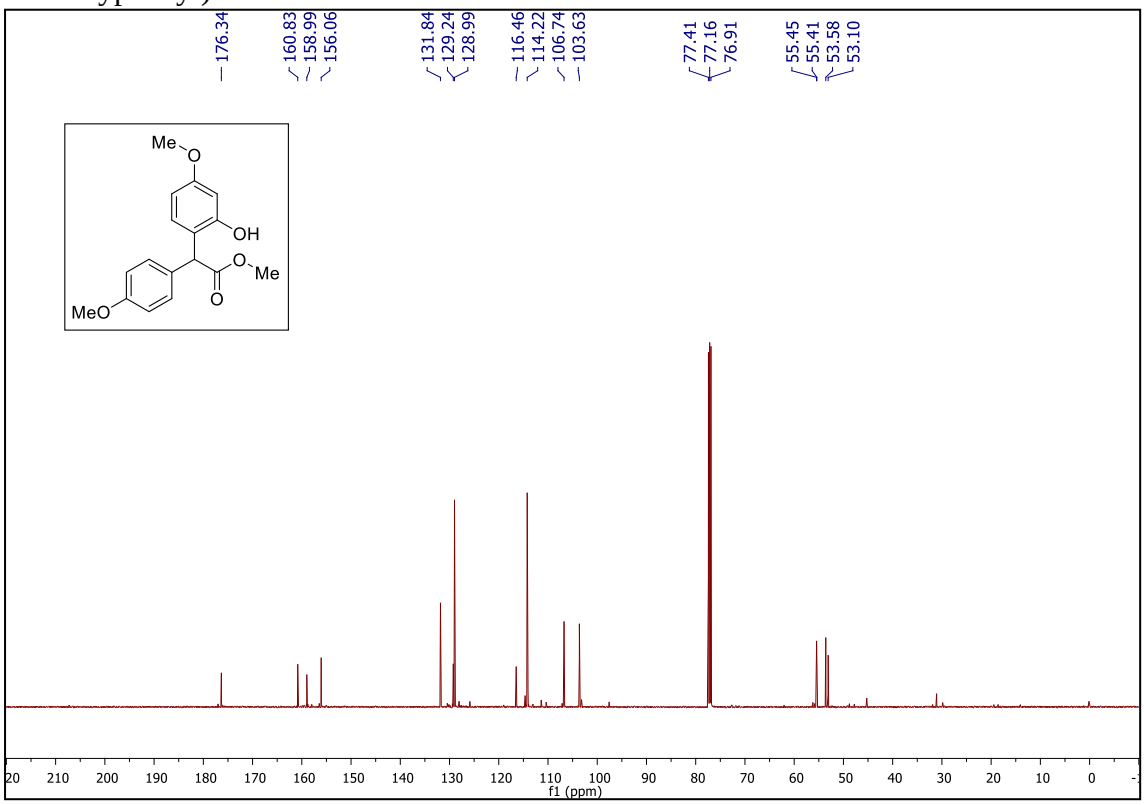
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-2-methoxyphenyl)-2-(4-methoxyphenyl)acetate **13**



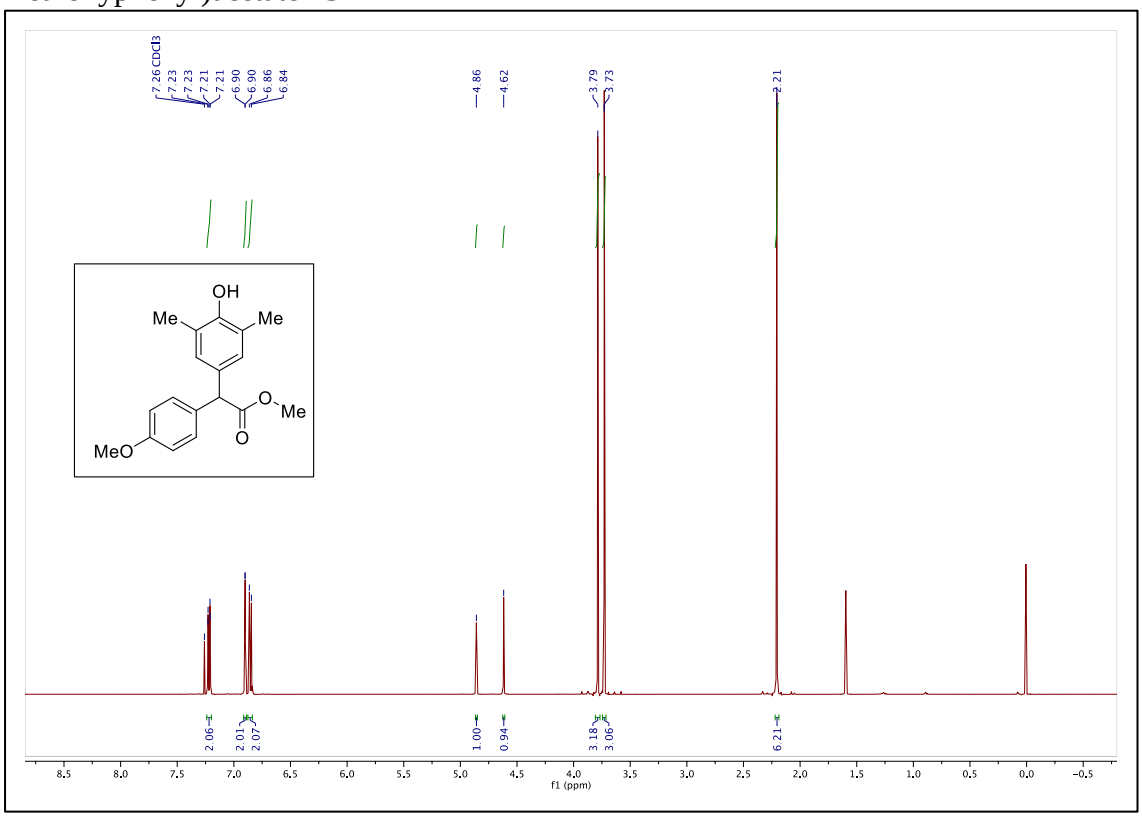
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)acetate **14**



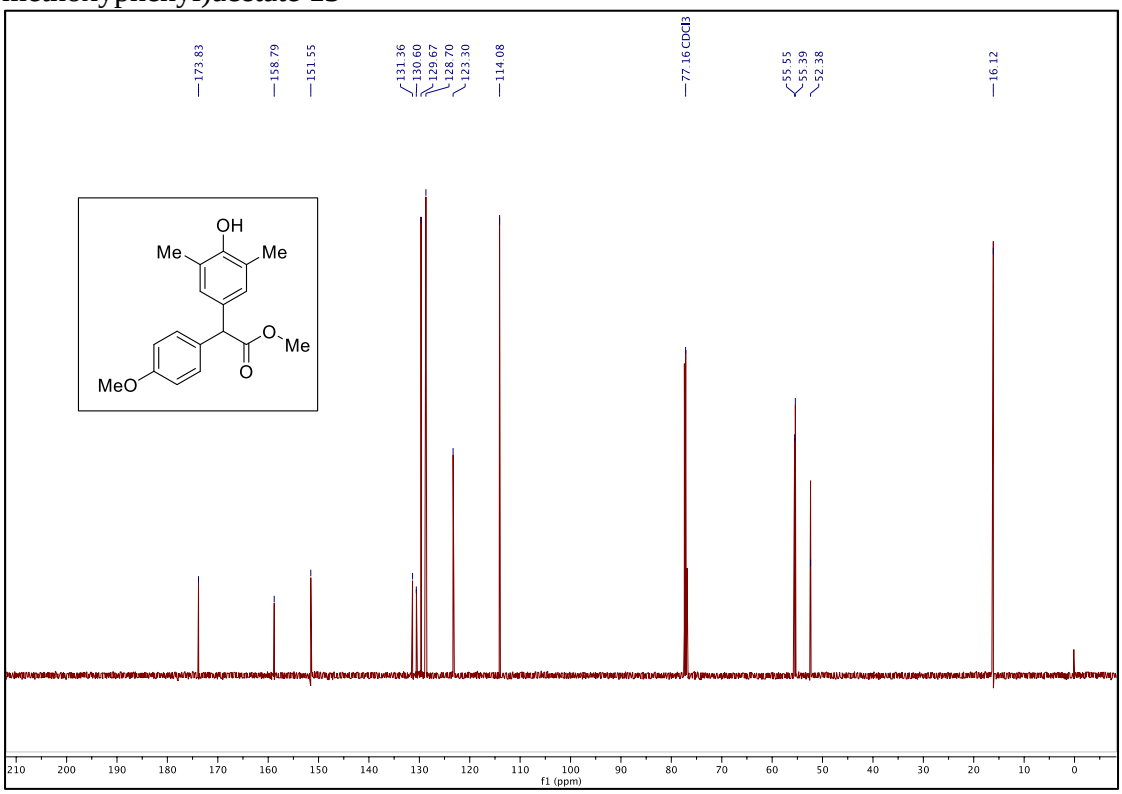
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)acetate **14**



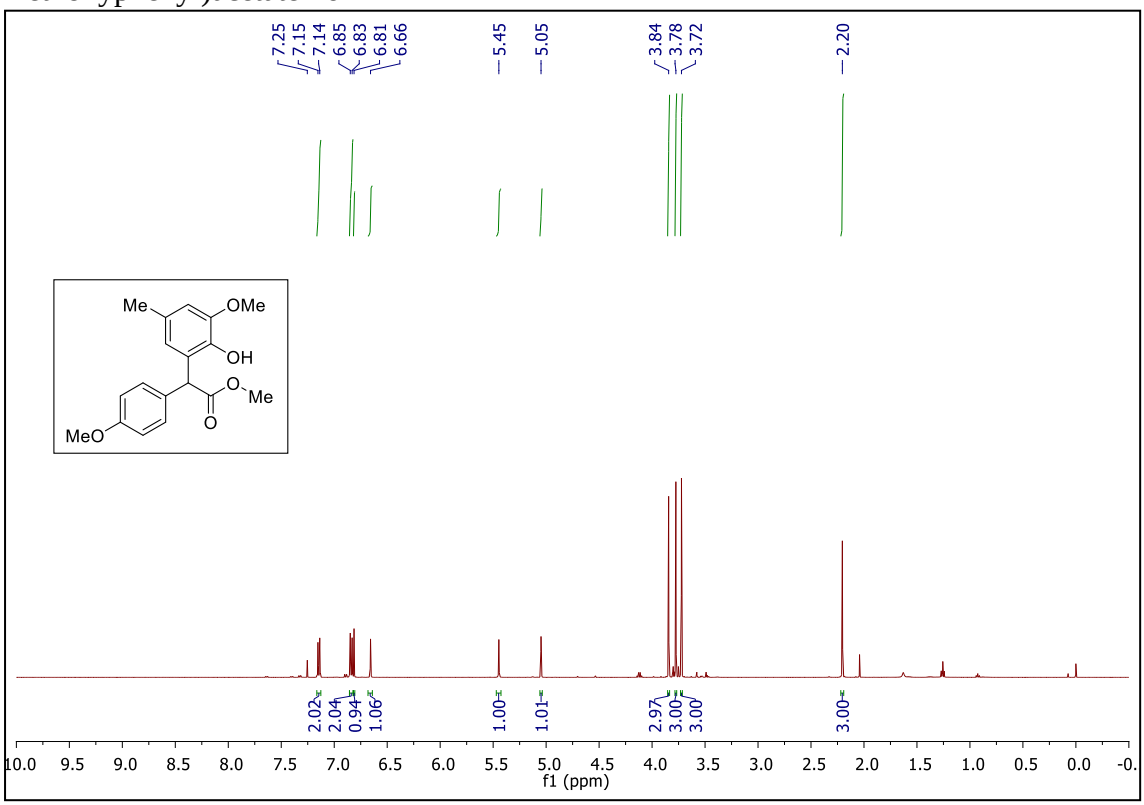
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **15**



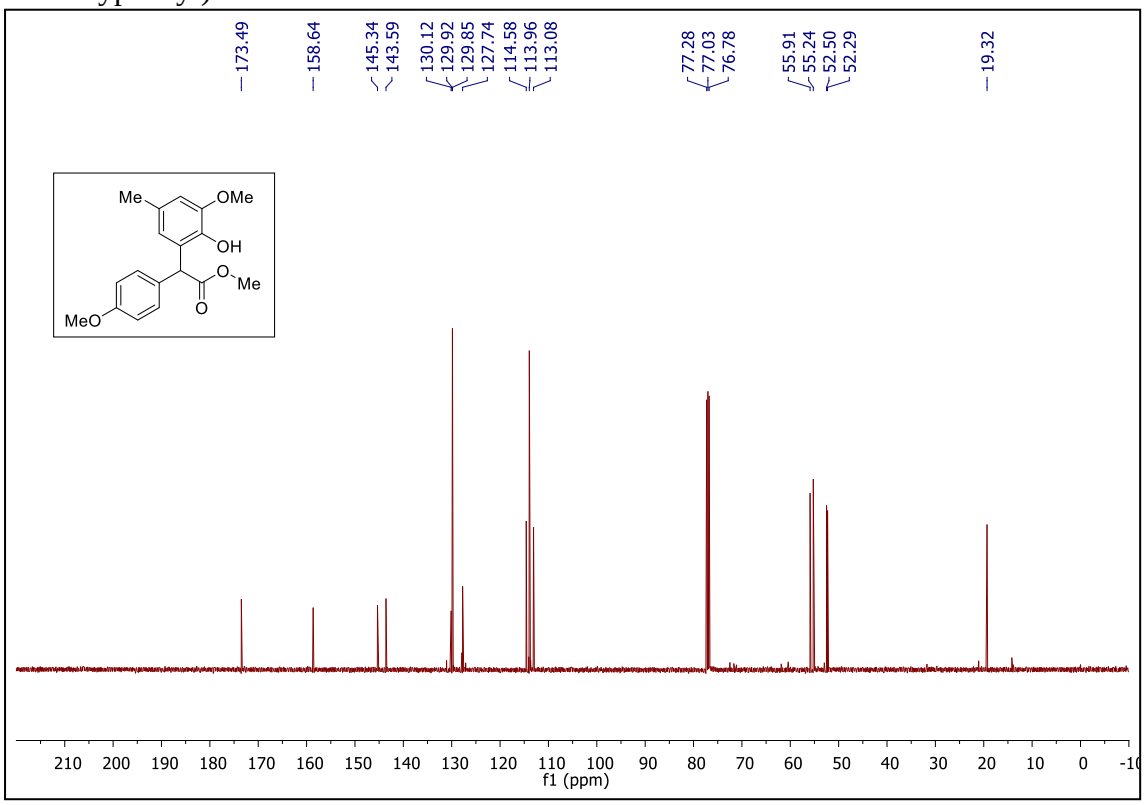
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **15**



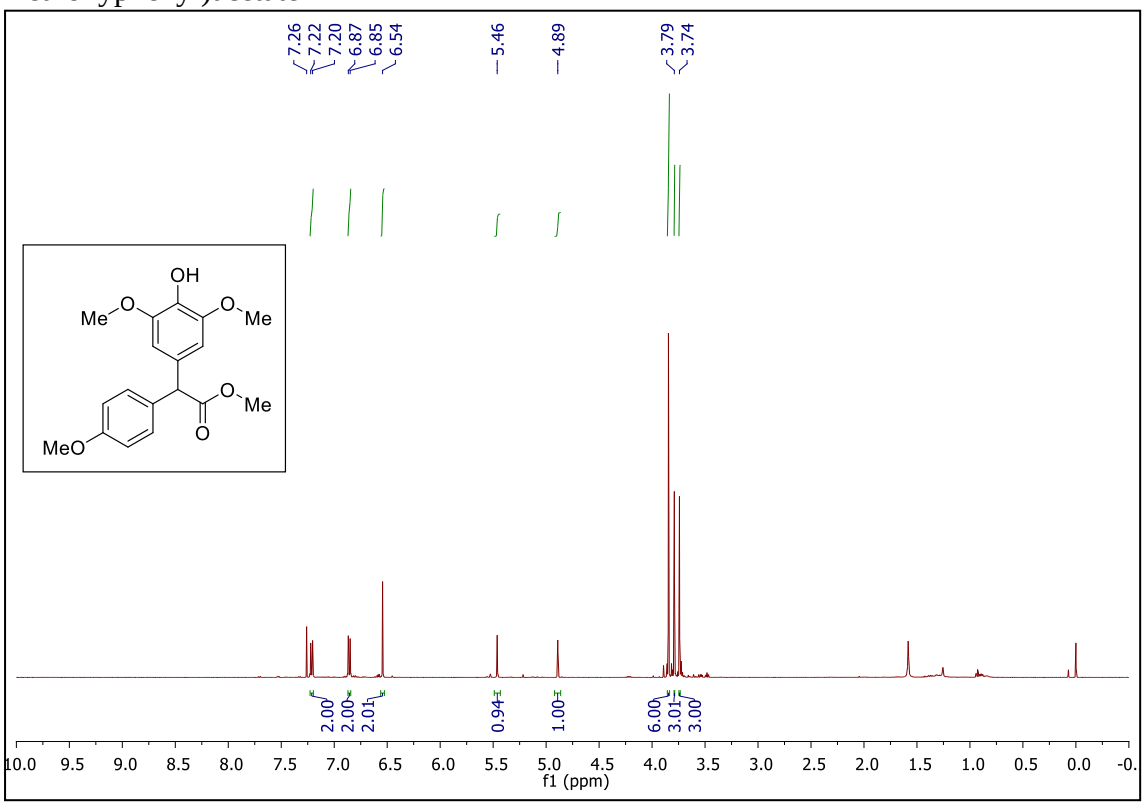
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3-methoxy-5-methylphenyl)-2-(4-methoxyphenyl)acetate **16**



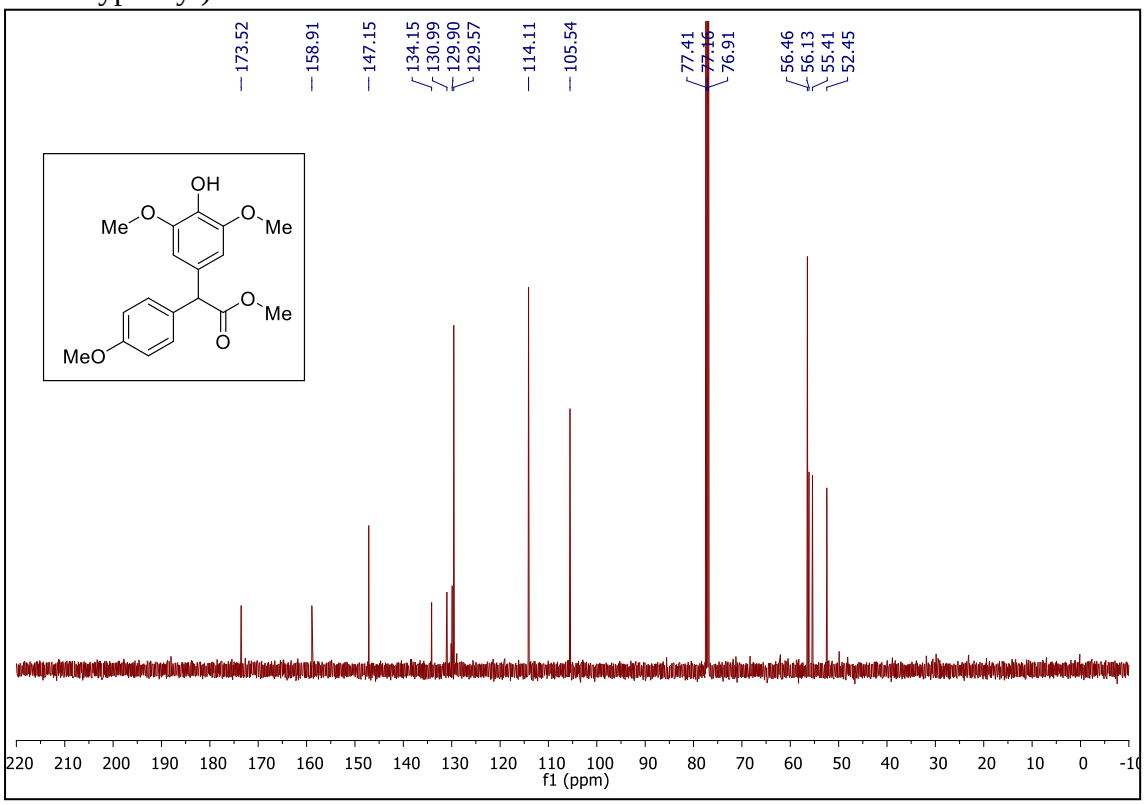
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3-methoxy-5-methylphenyl)-2-(4-methoxyphenyl)acetate **16**



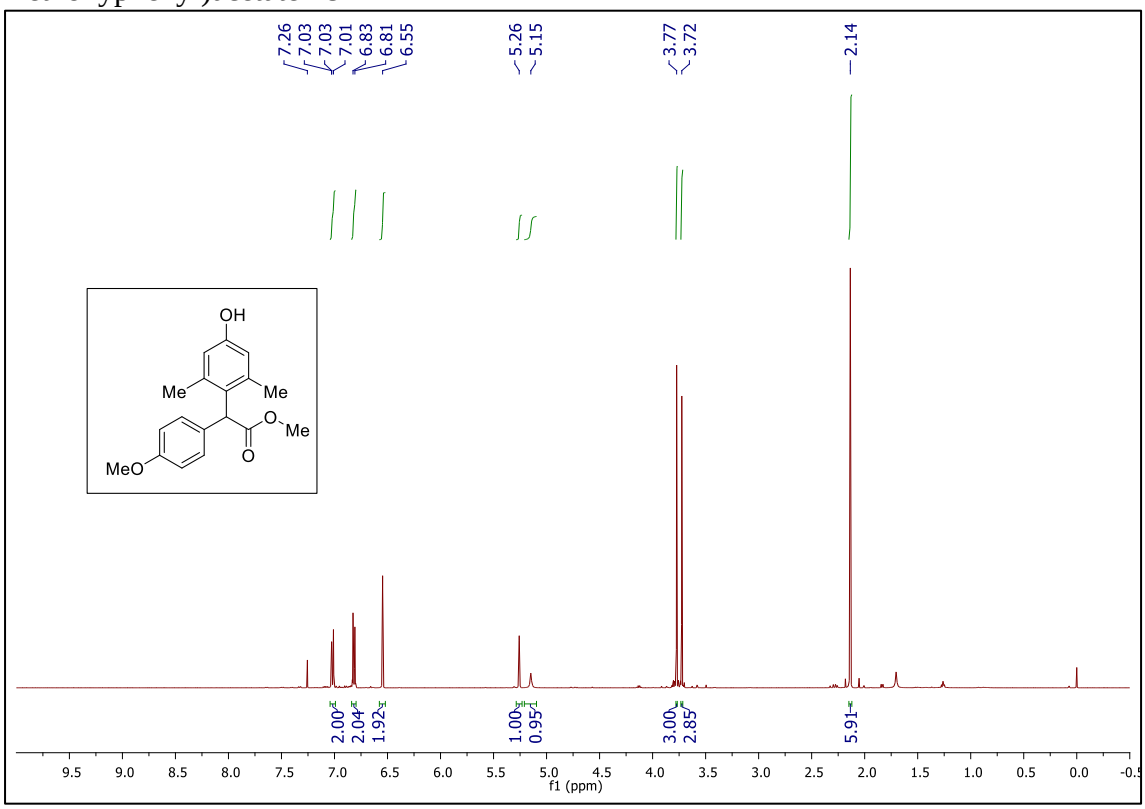
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acetate **17**



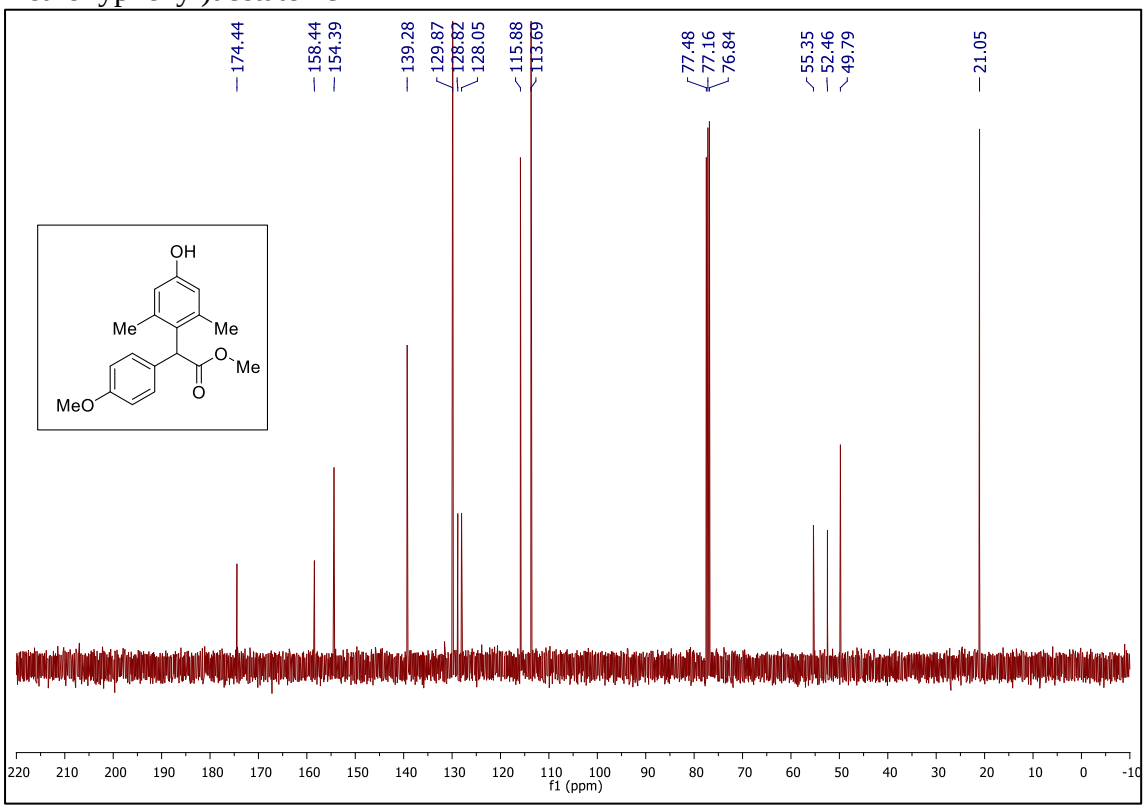
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acetate **17**



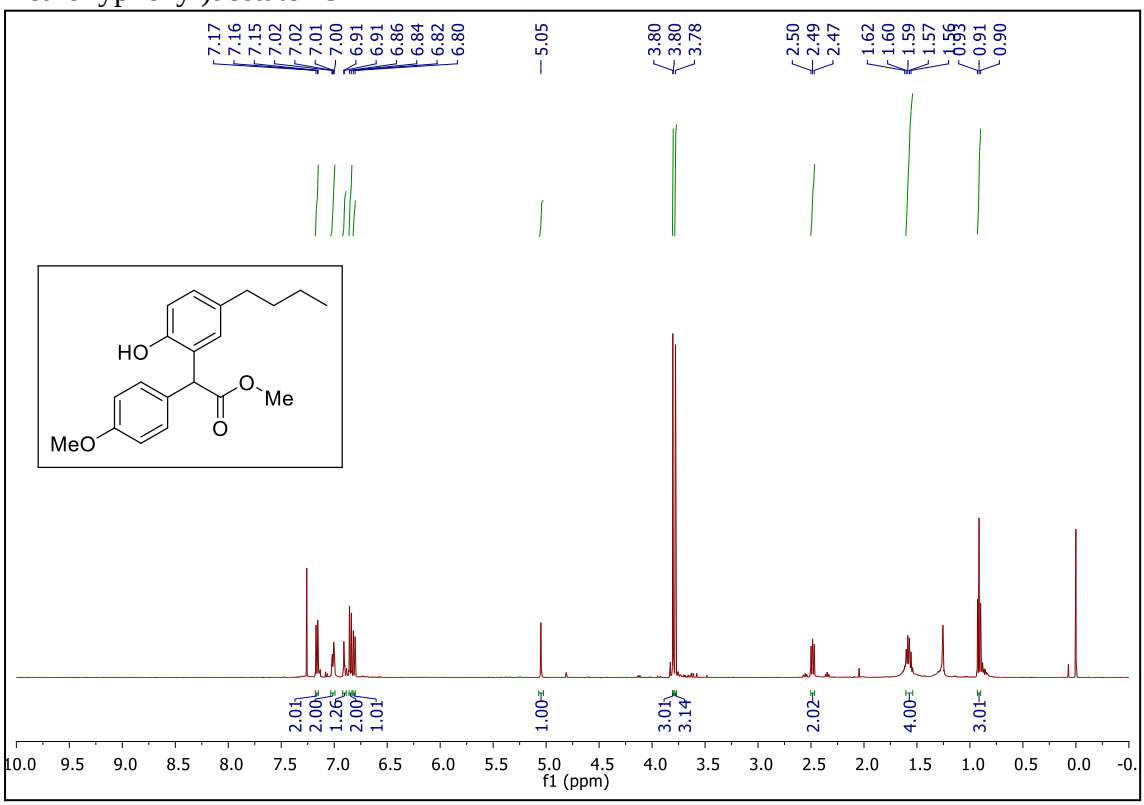
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-2,6-dimethylphenyl)-2-(4-methoxyphenyl)acetate **18**



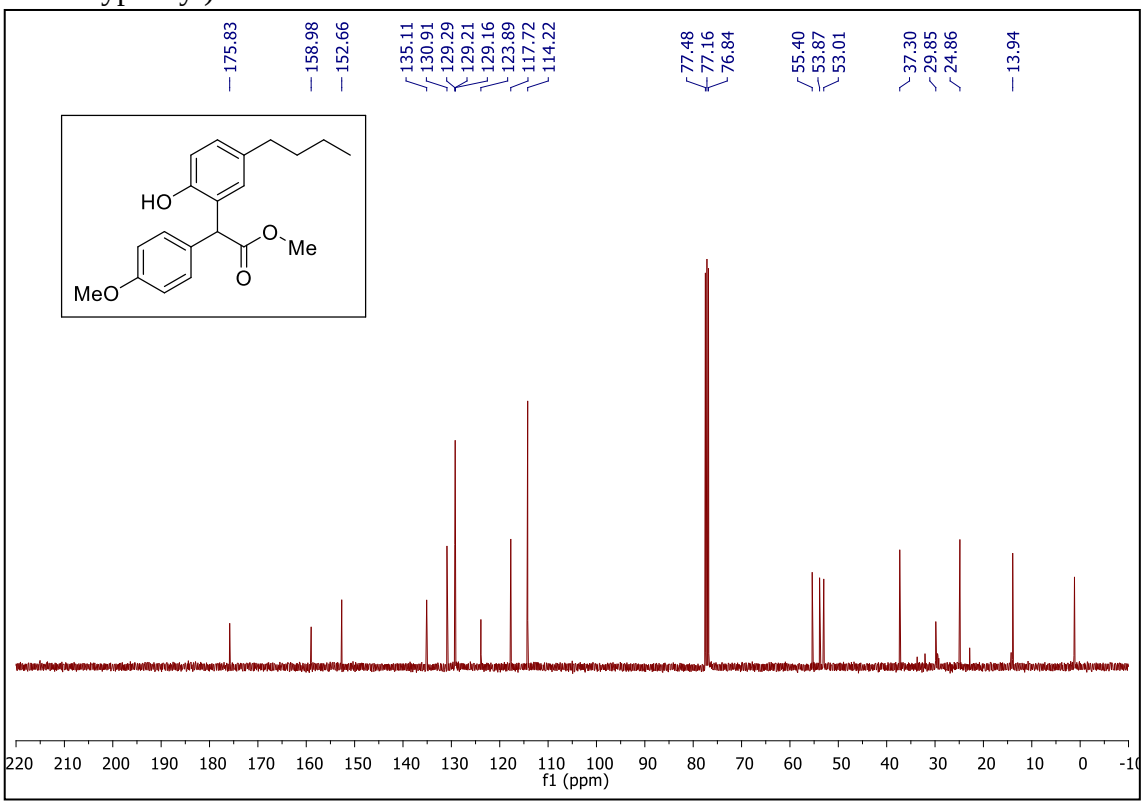
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-2,6-dimethylphenyl)-2-(4-methoxyphenyl)acetate **18**



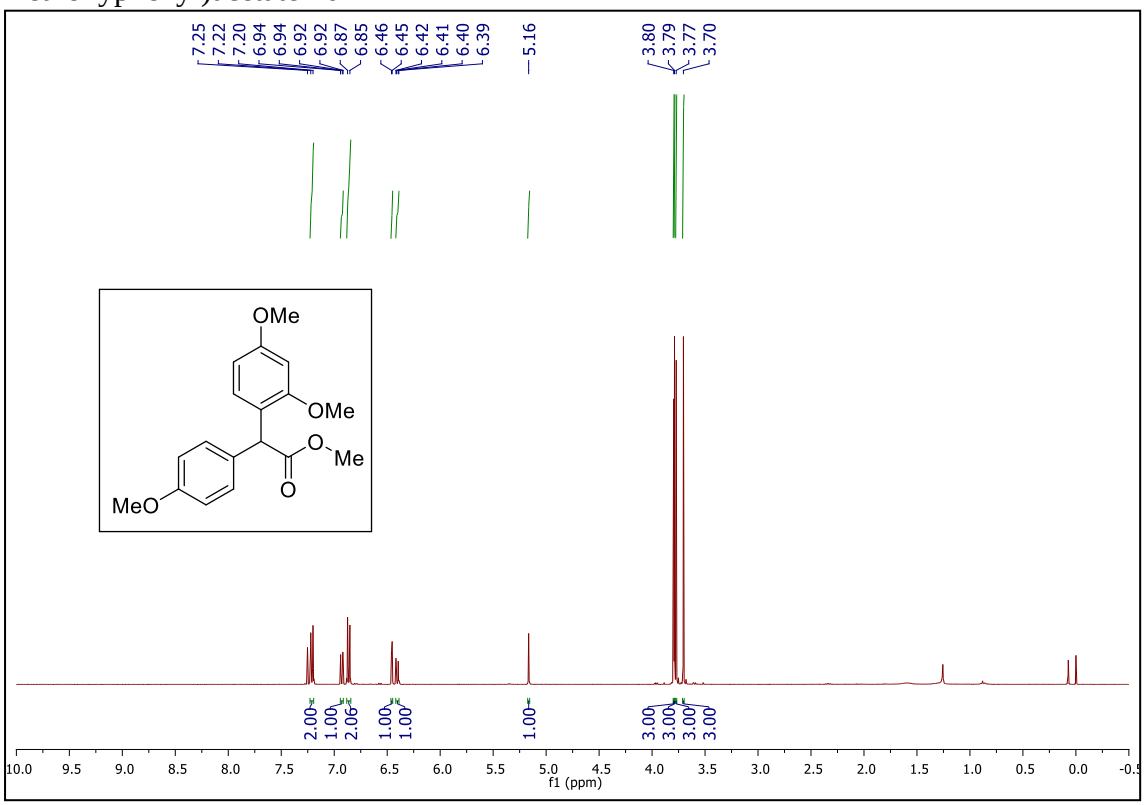
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(5-butyl-2-hydroxyphenyl)-2-(4-methoxyphenyl)acetate **19**



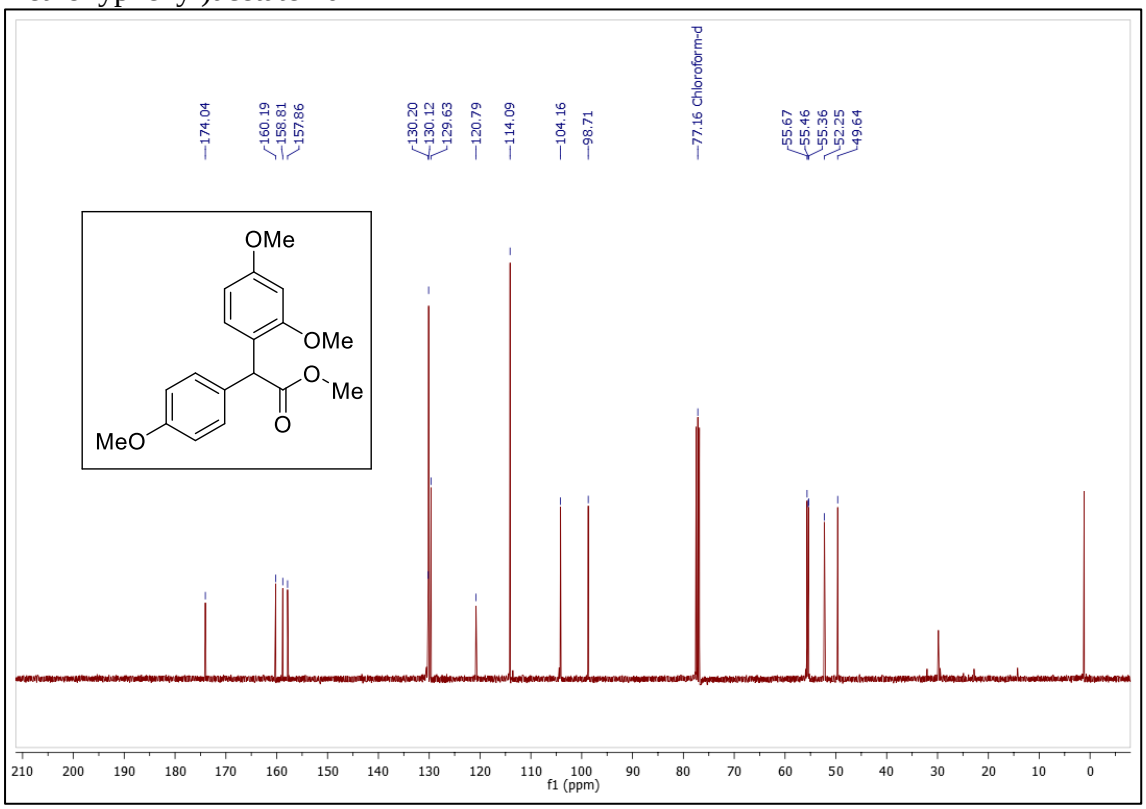
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(5-butyl-2-hydroxyphenyl)-2-(4-methoxyphenyl)acetate **19**



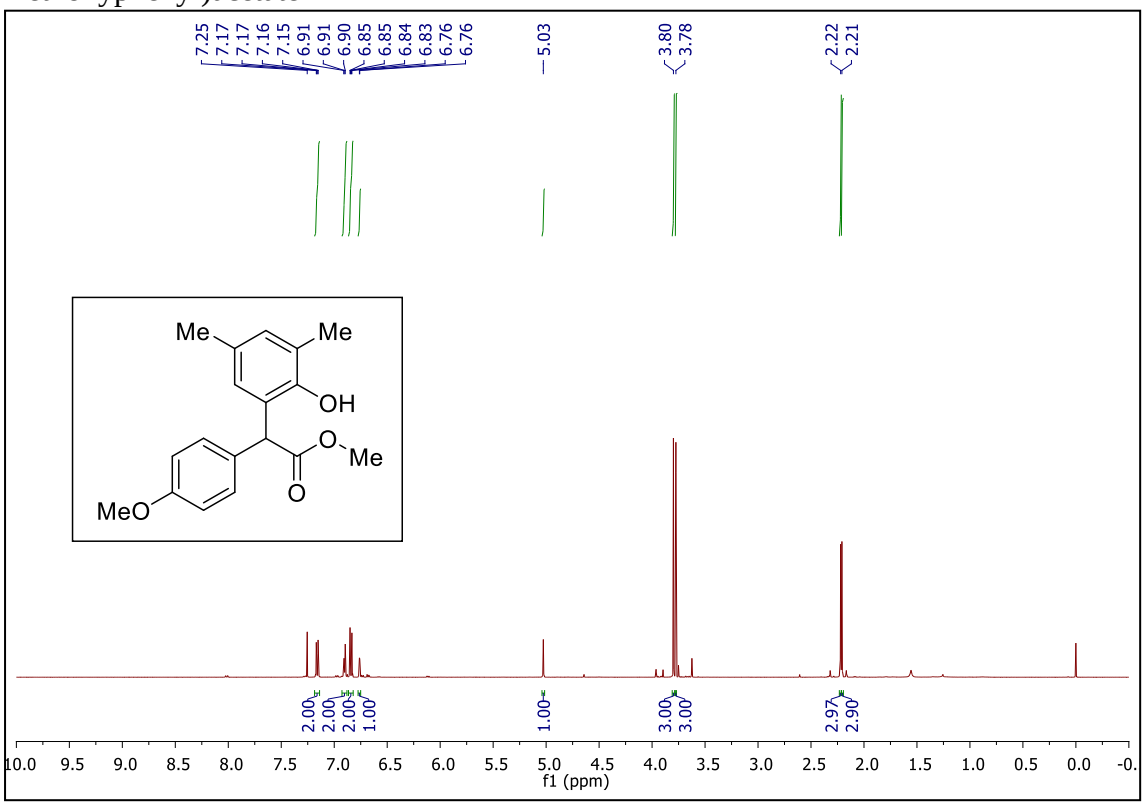
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)acetate **20**



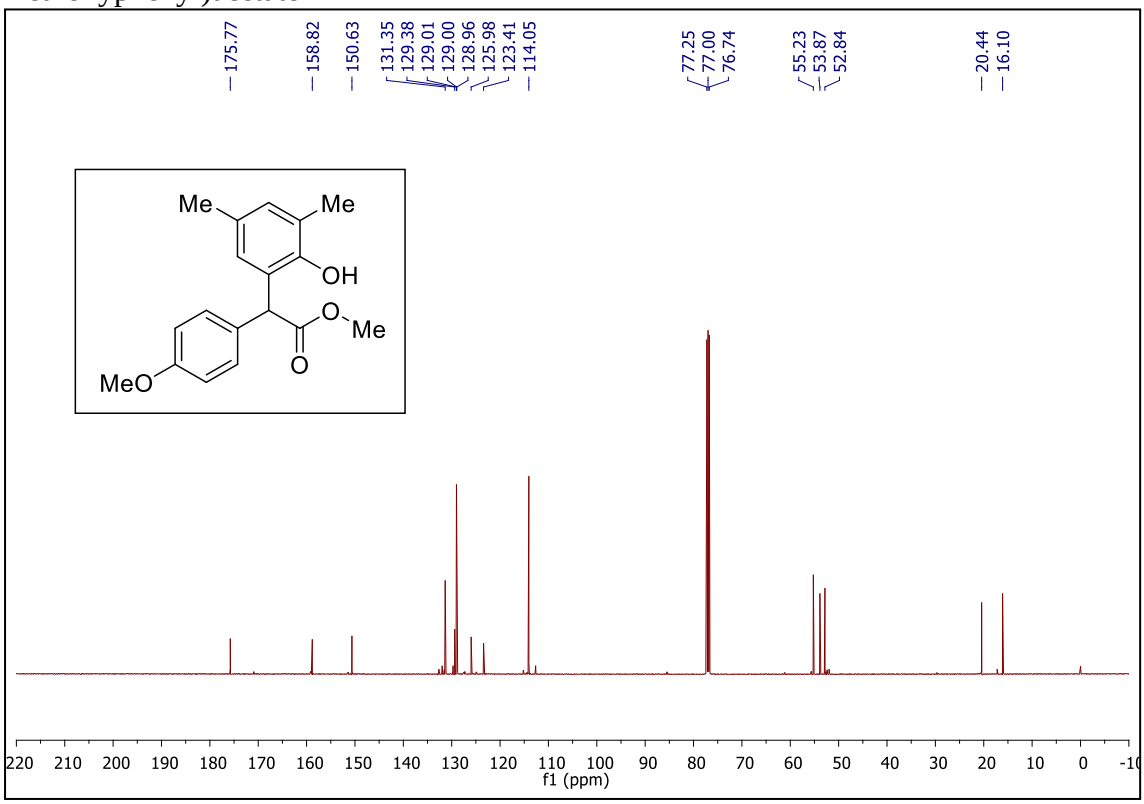
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)acetate **20**



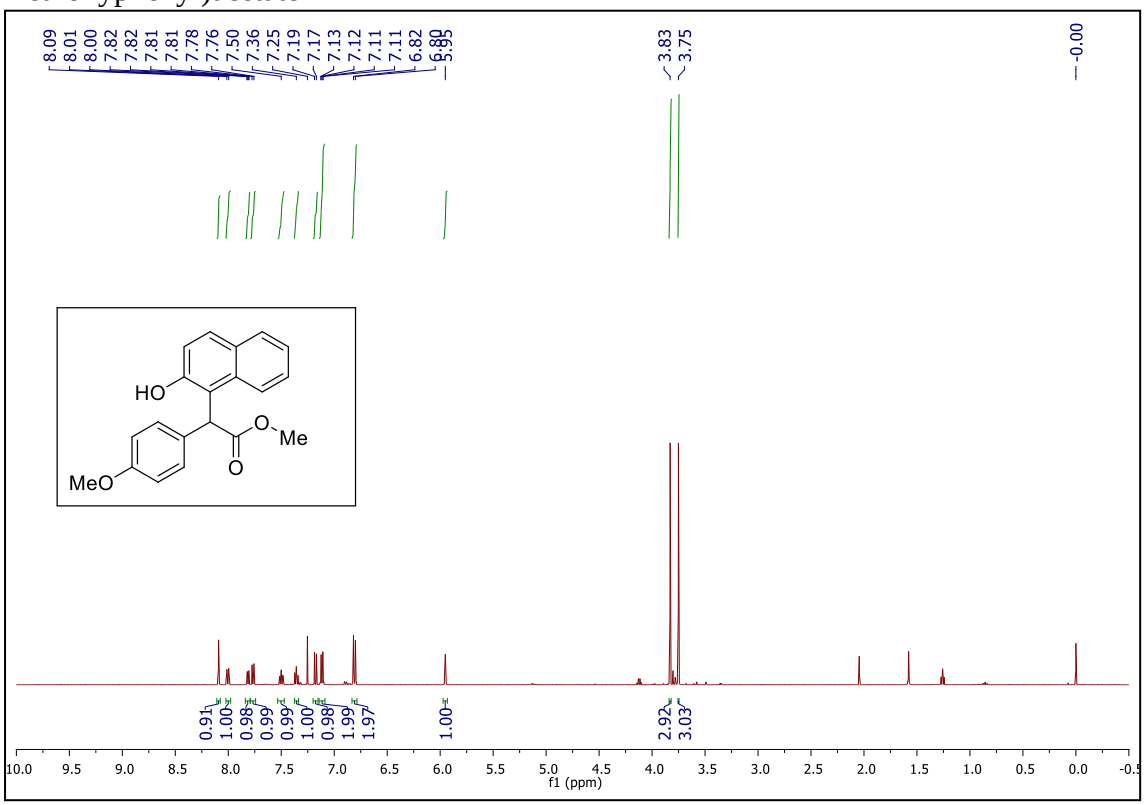
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(2-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **21**



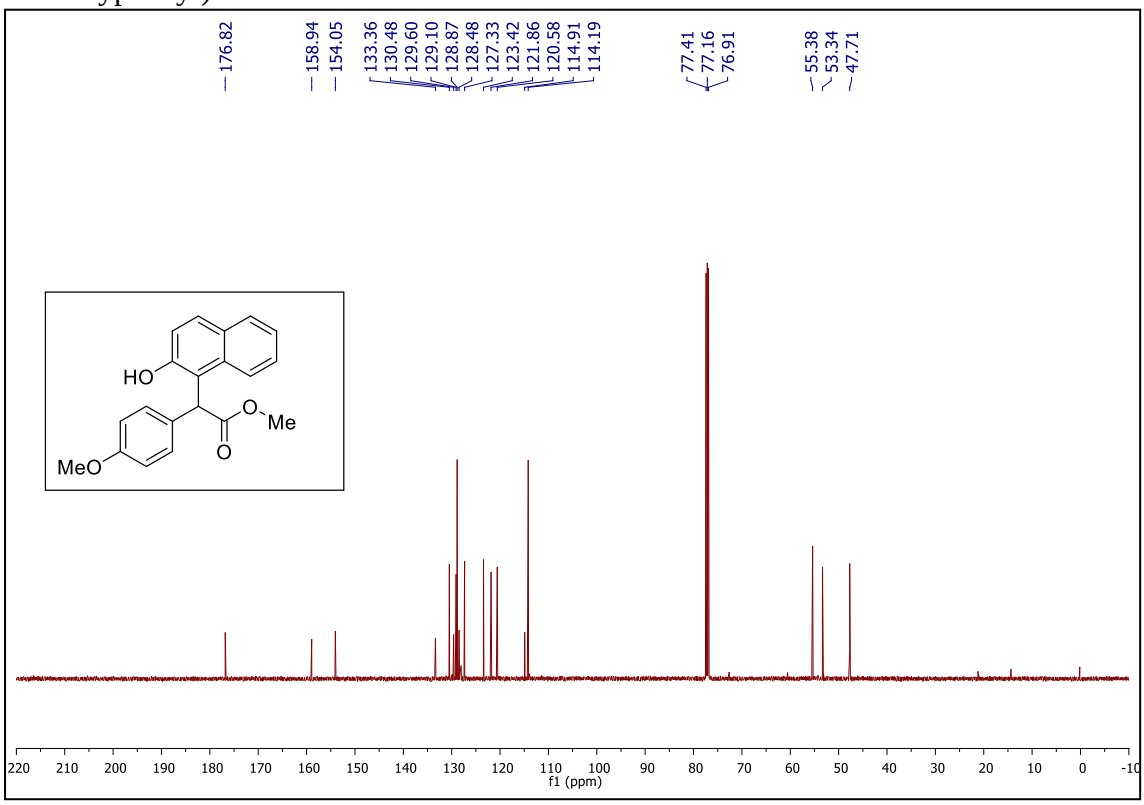
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(2-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **21**



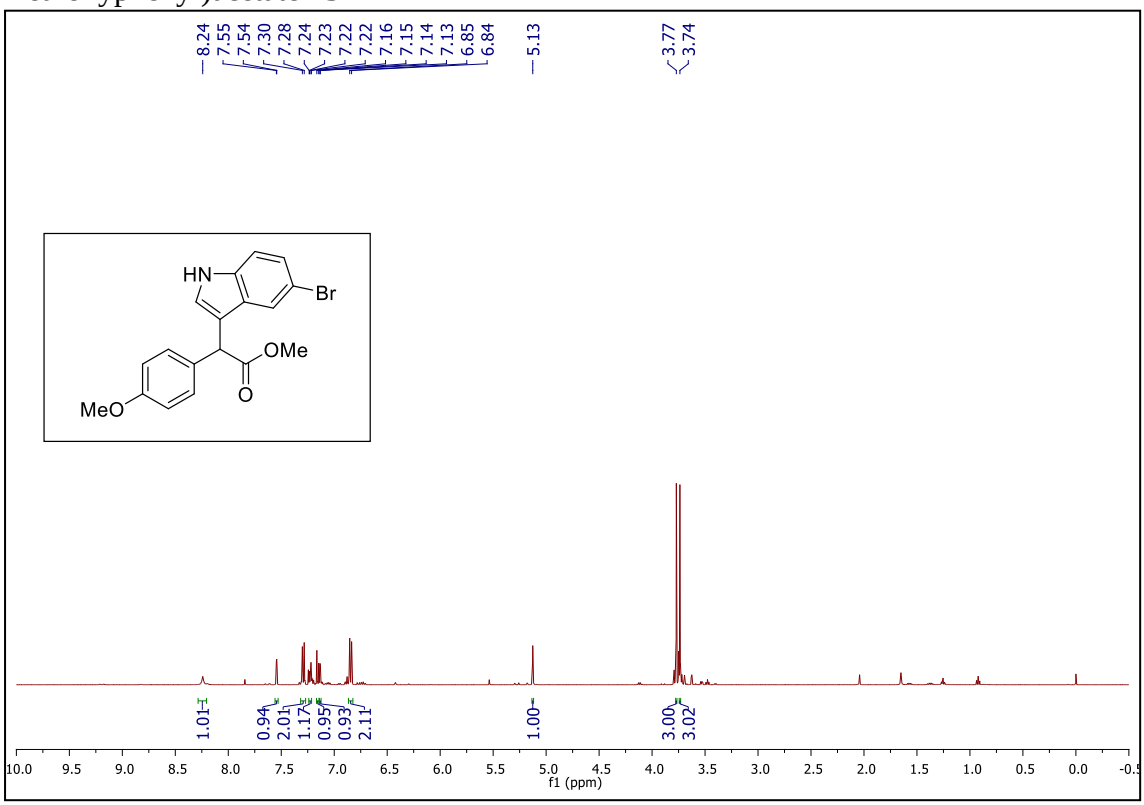
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(2-hydroxynaphthalen-1-yl)-2-(4-methoxyphenyl)acetate **22**



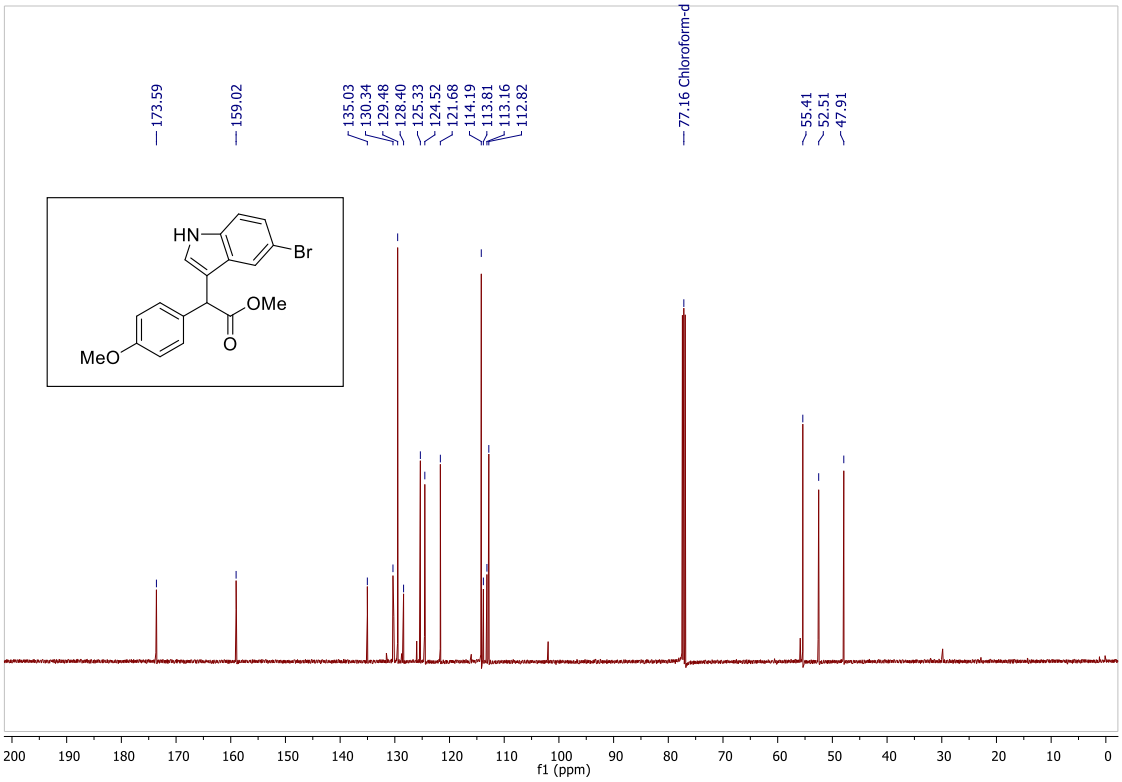
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(2-hydroxynaphthalen-1-yl)-2-(4-methoxyphenyl)acetate **22**



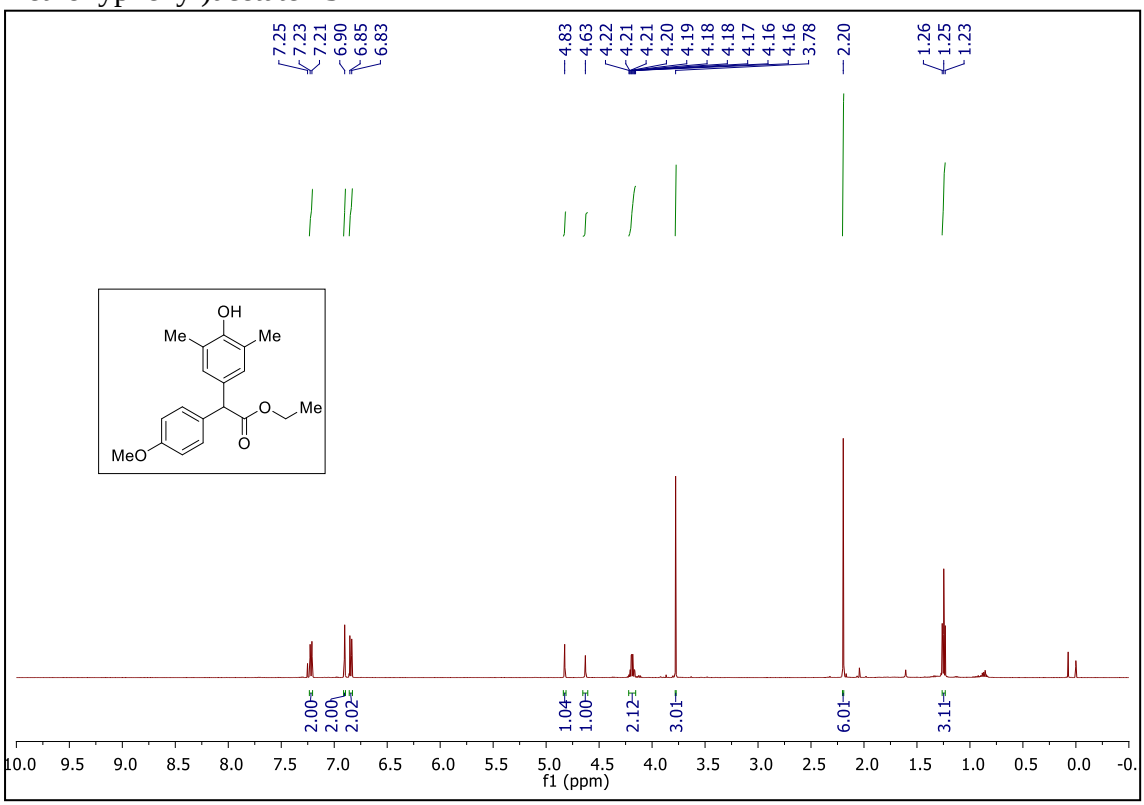
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(5-bromo-1H-indol-3-yl)-2-(4-methoxyphenyl)acetate **23**



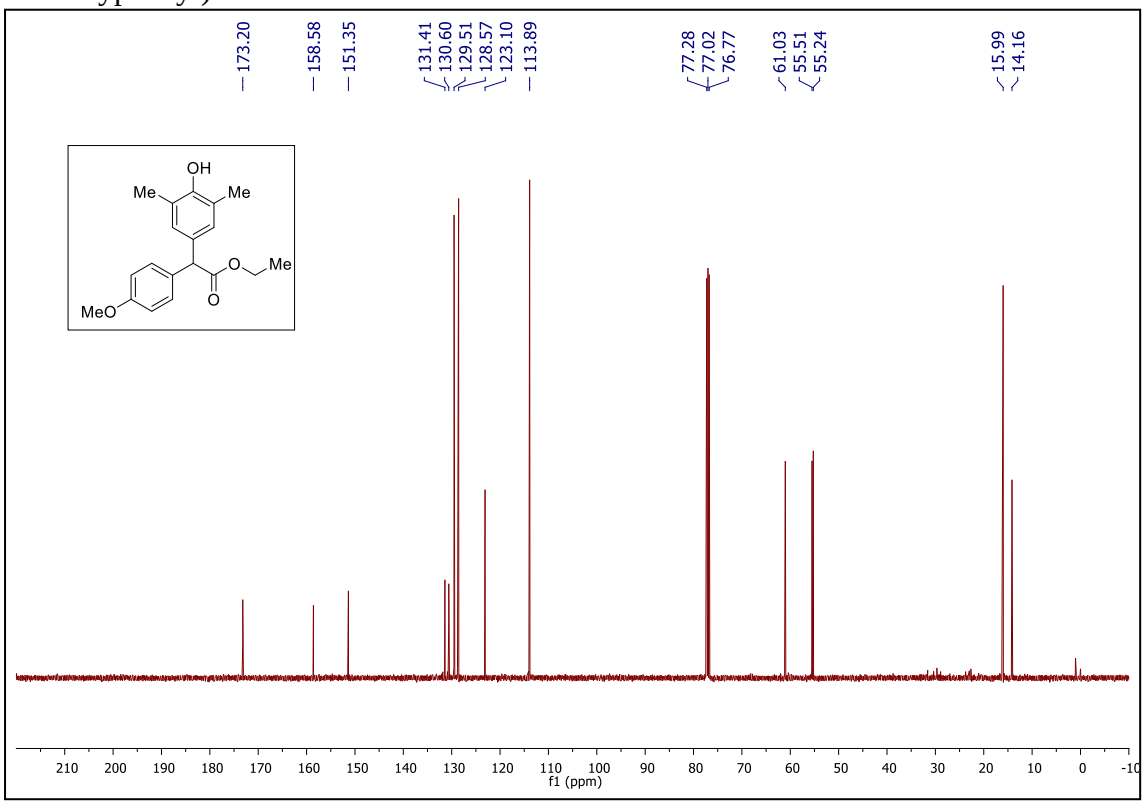
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(5-bromo-1H-indol-3-yl)-2-(4-methoxyphenyl)acetate **23**



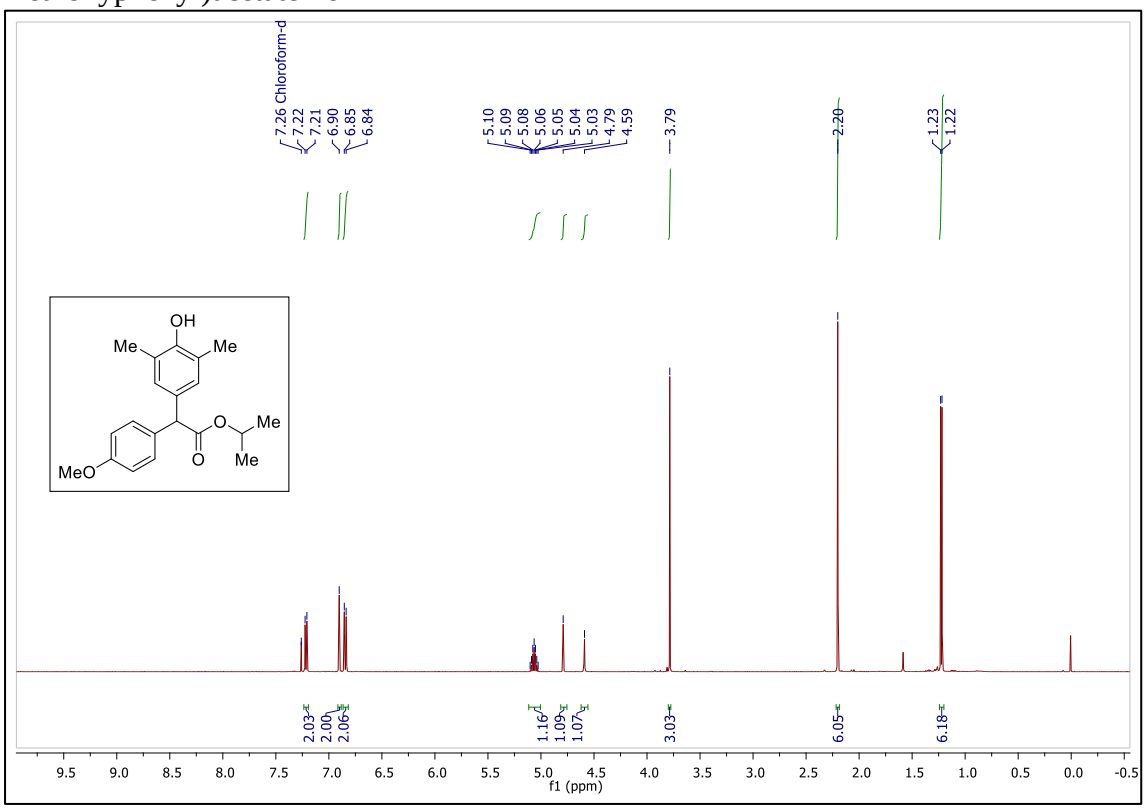
^{1}H NMR (500 MHz, $CDCl_3$) (±)-ethyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **25**



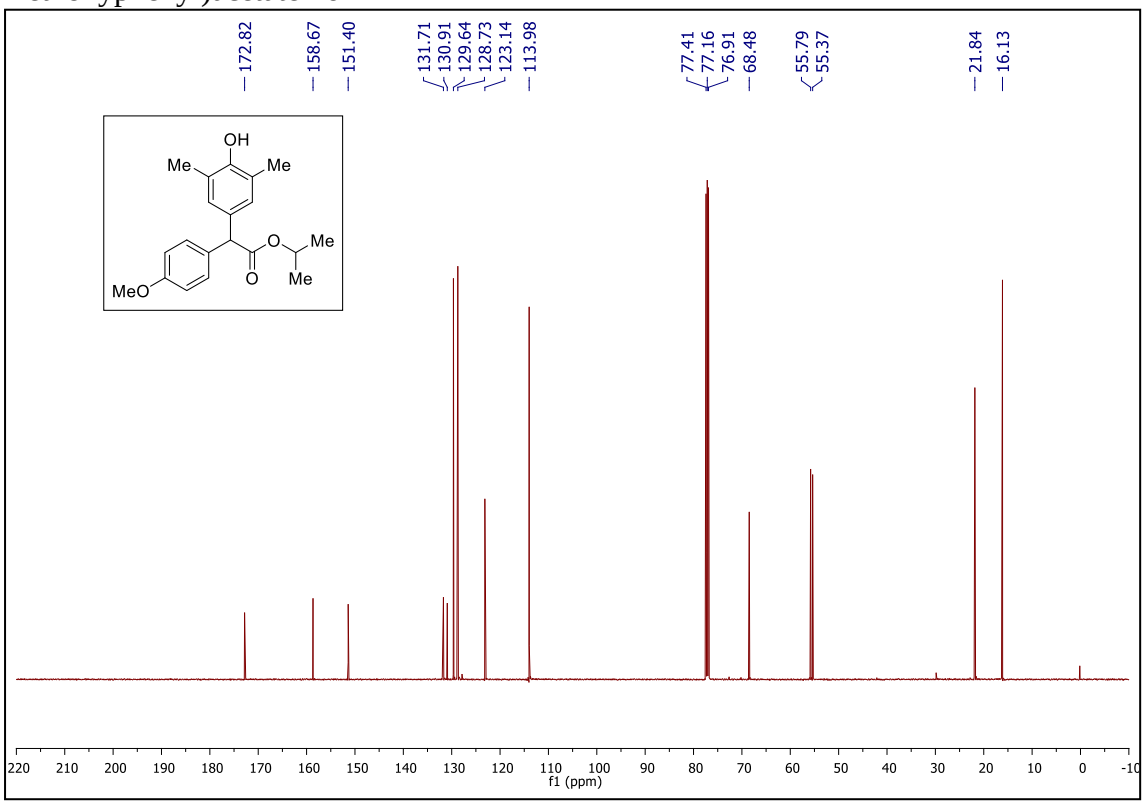
^{13}C NMR (125 MHz, $CDCl_3$) (±)-ethyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **25**



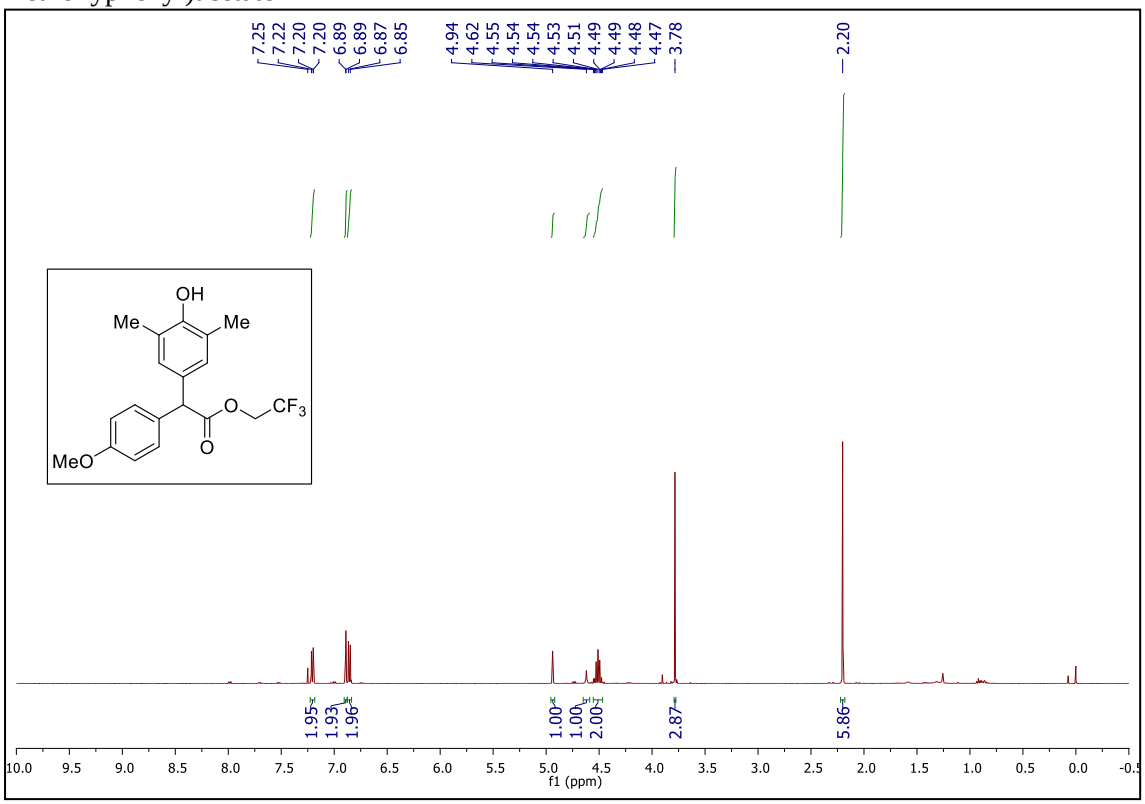
^{1}H NMR (500 MHz, $CDCl_3$) (±)-isopropyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **26**



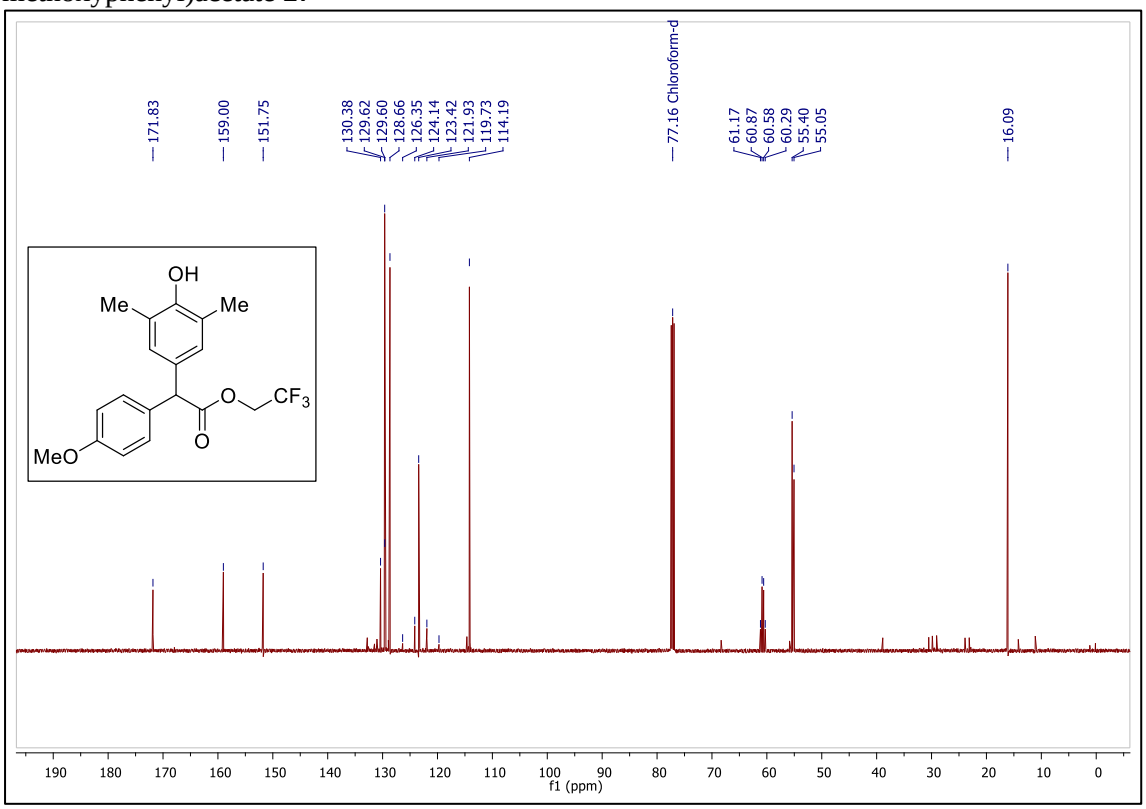
^{13}C NMR (125 MHz, $CDCl_3$) (±)-isopropyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **26**



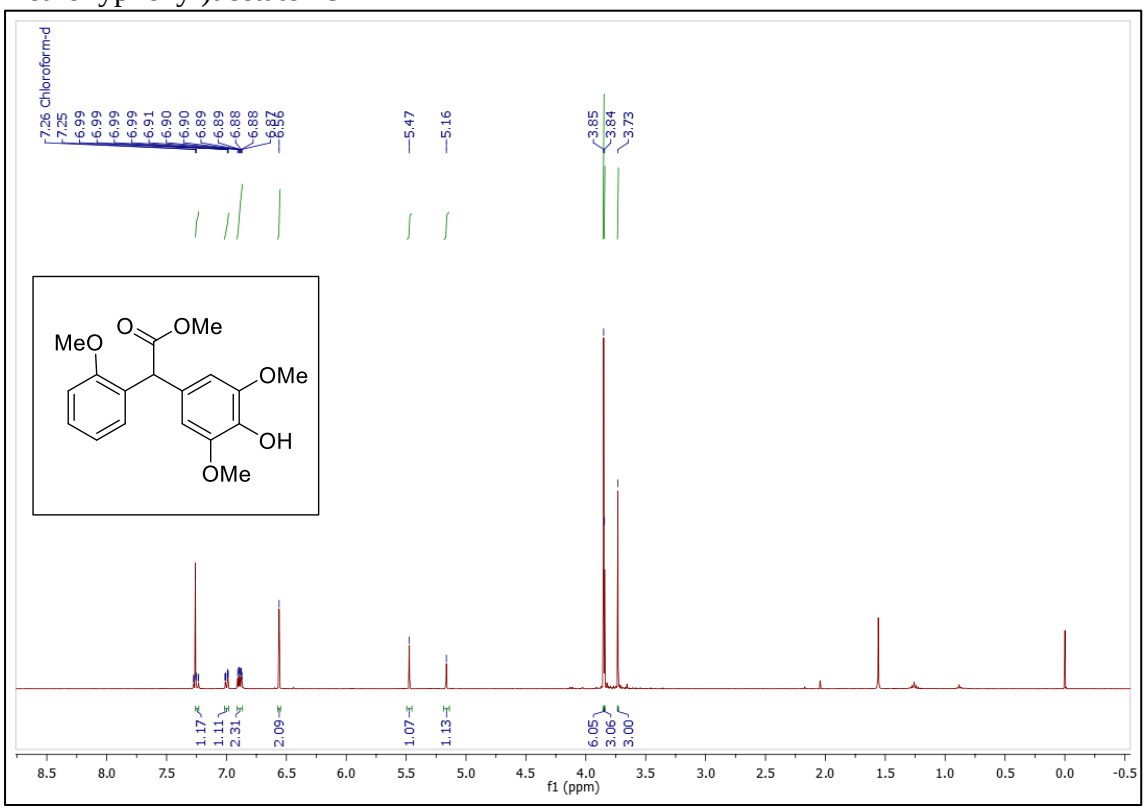
^{1}H NMR (500 MHz, $CDCl_3$) (±)-2,2,2-trifluoroethyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **27**



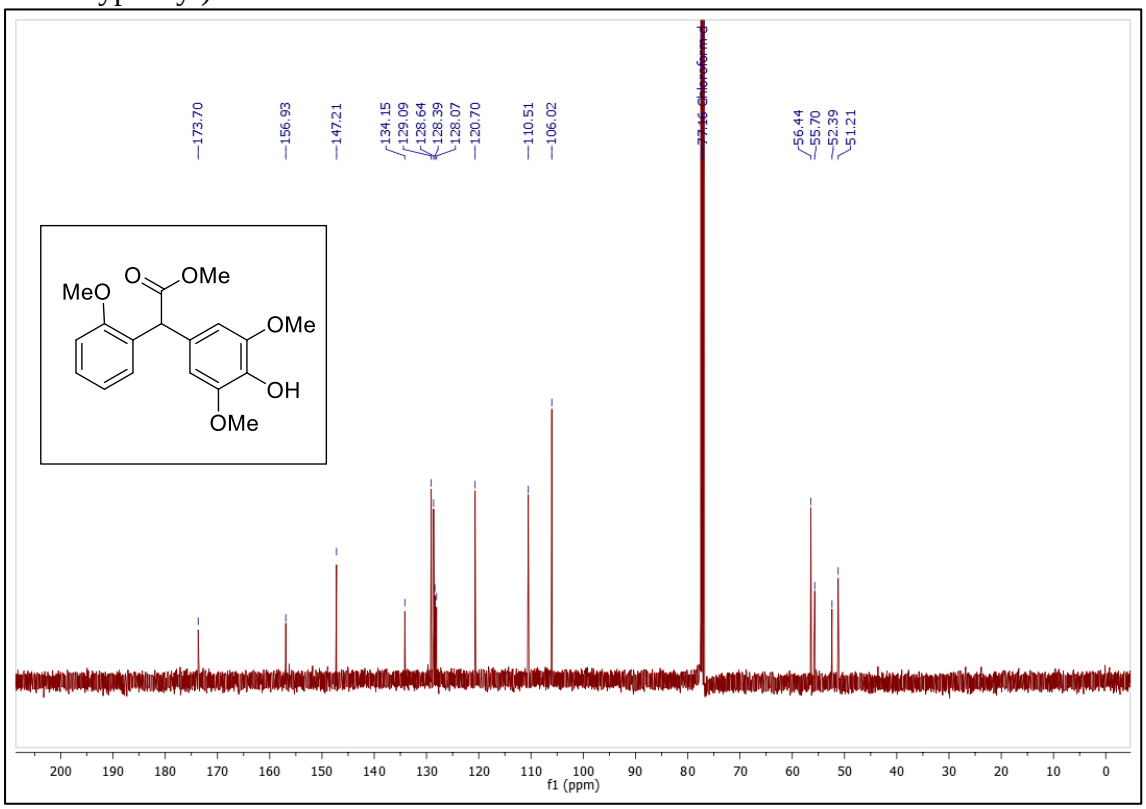
^{13}C NMR (125 MHz, $CDCl_3$) (±)-2,2,2-trifluoroethyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(4-methoxyphenyl)acetate **27**



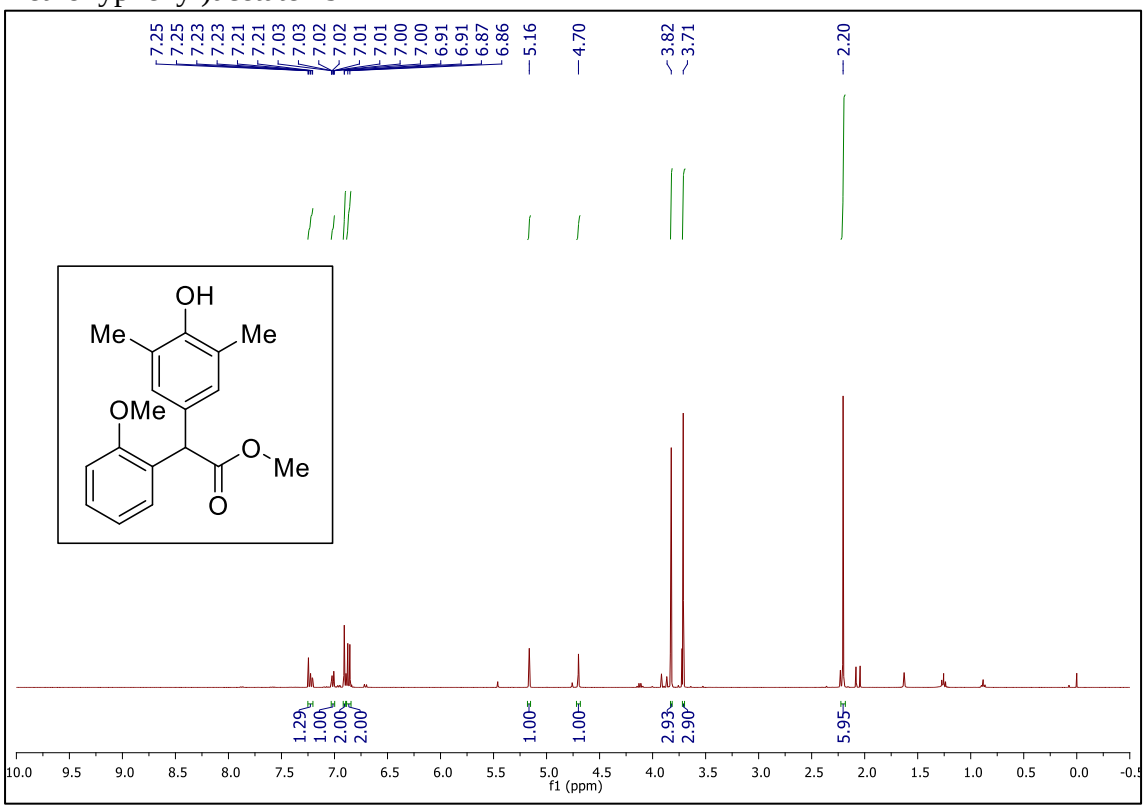
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxyphenyl)acetate **28**



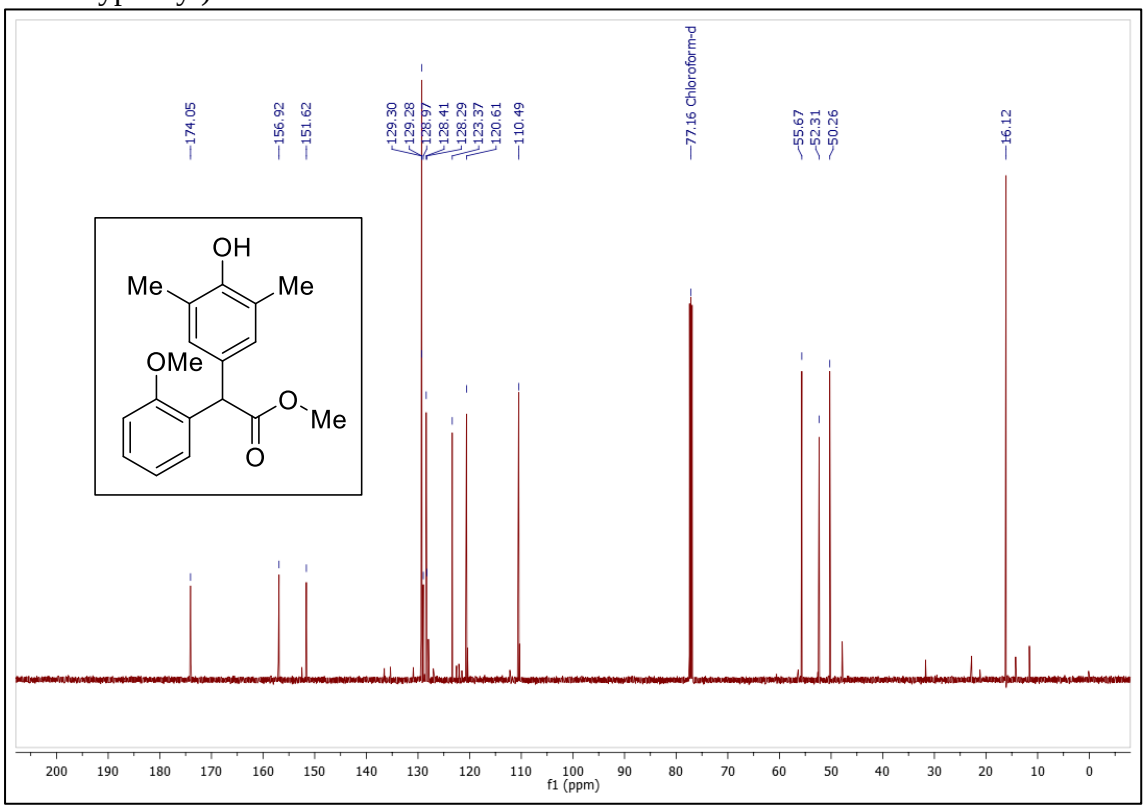
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxyphenyl)acetate **28**



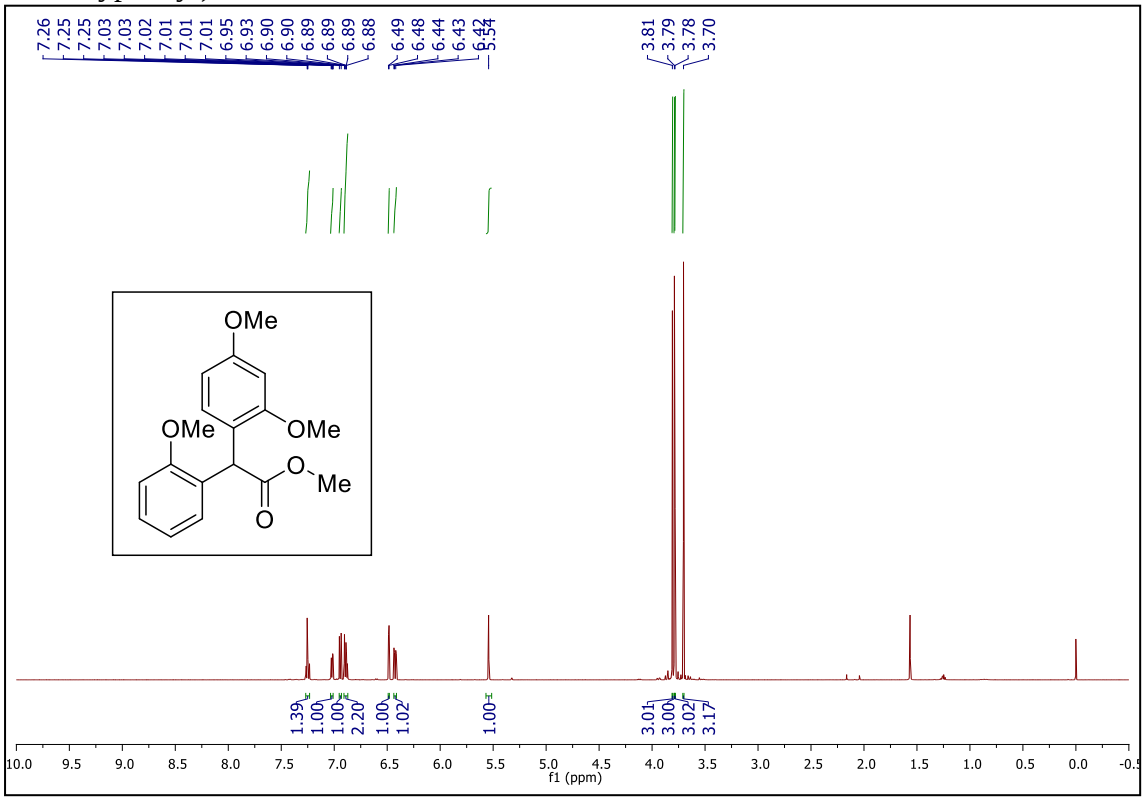
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(2-methoxyphenyl)acetate **29**



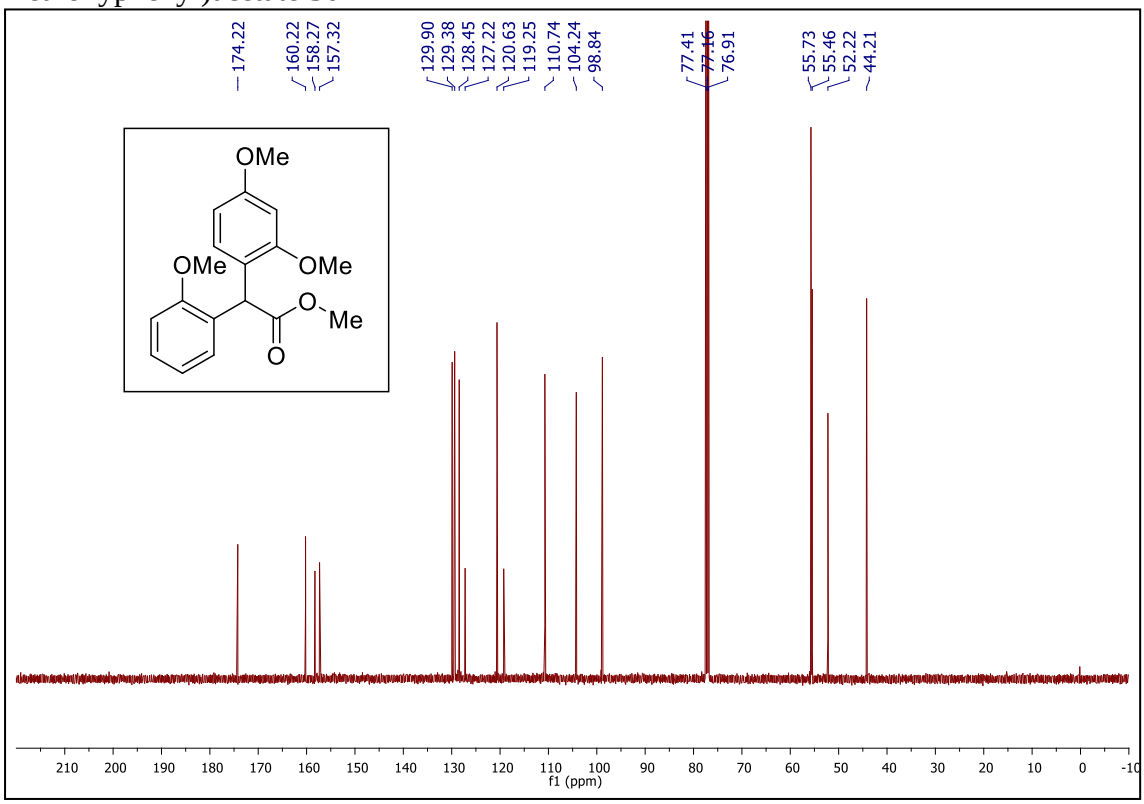
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3,5-dimethylphenyl)-2-(2-methoxyphenyl)acetate **29**



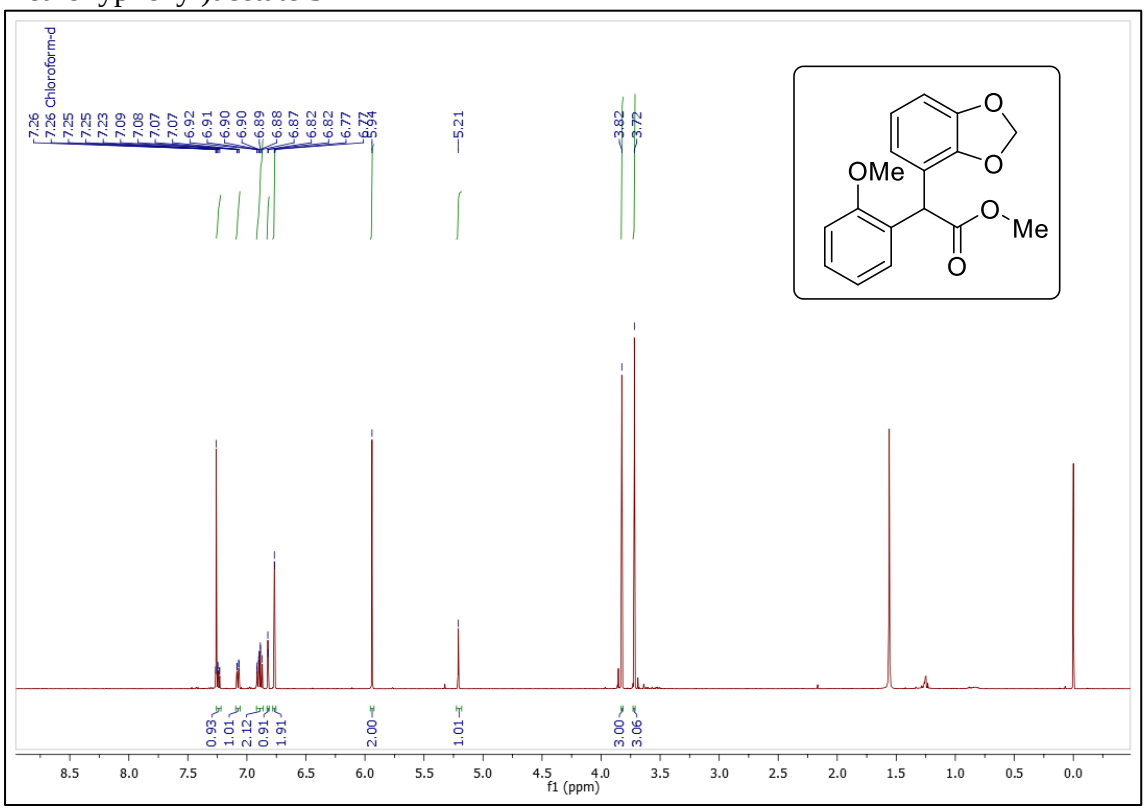
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(2,4-dimethoxyphenyl)-2-(2-methoxyphenyl)acetate **30**



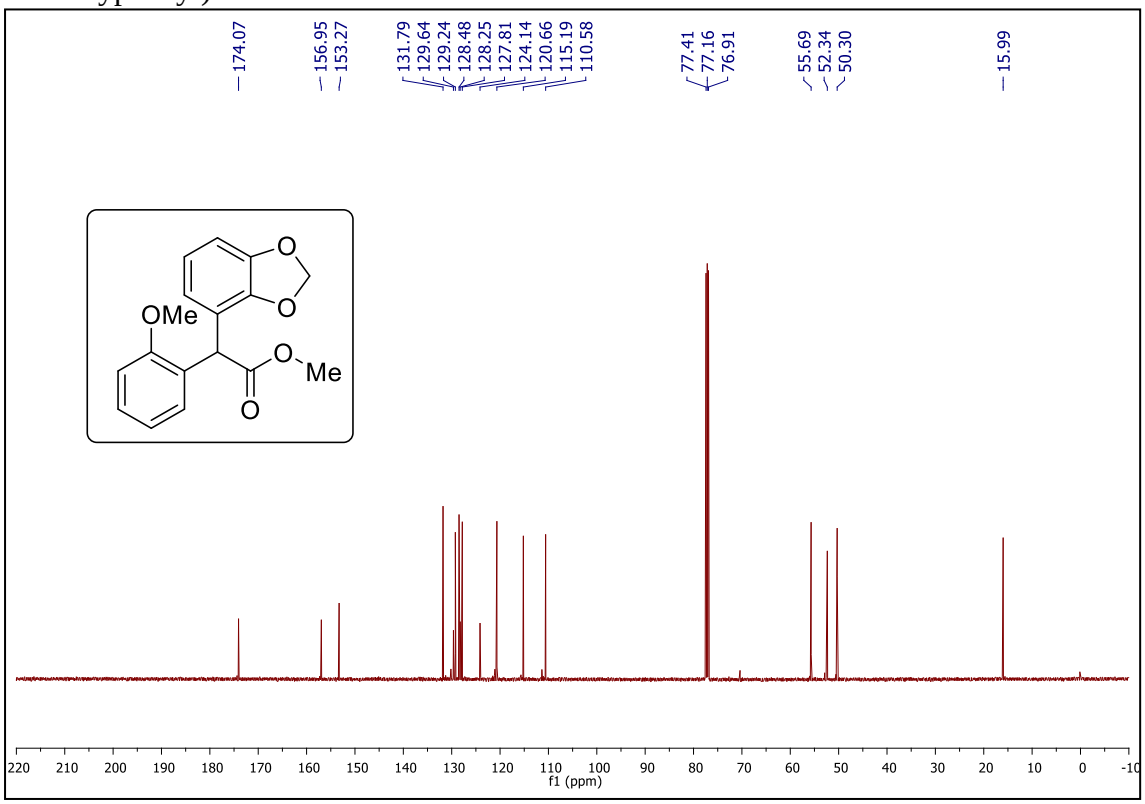
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(2,4-dimethoxyphenyl)-2-(2-methoxyphenyl)acetate **30**



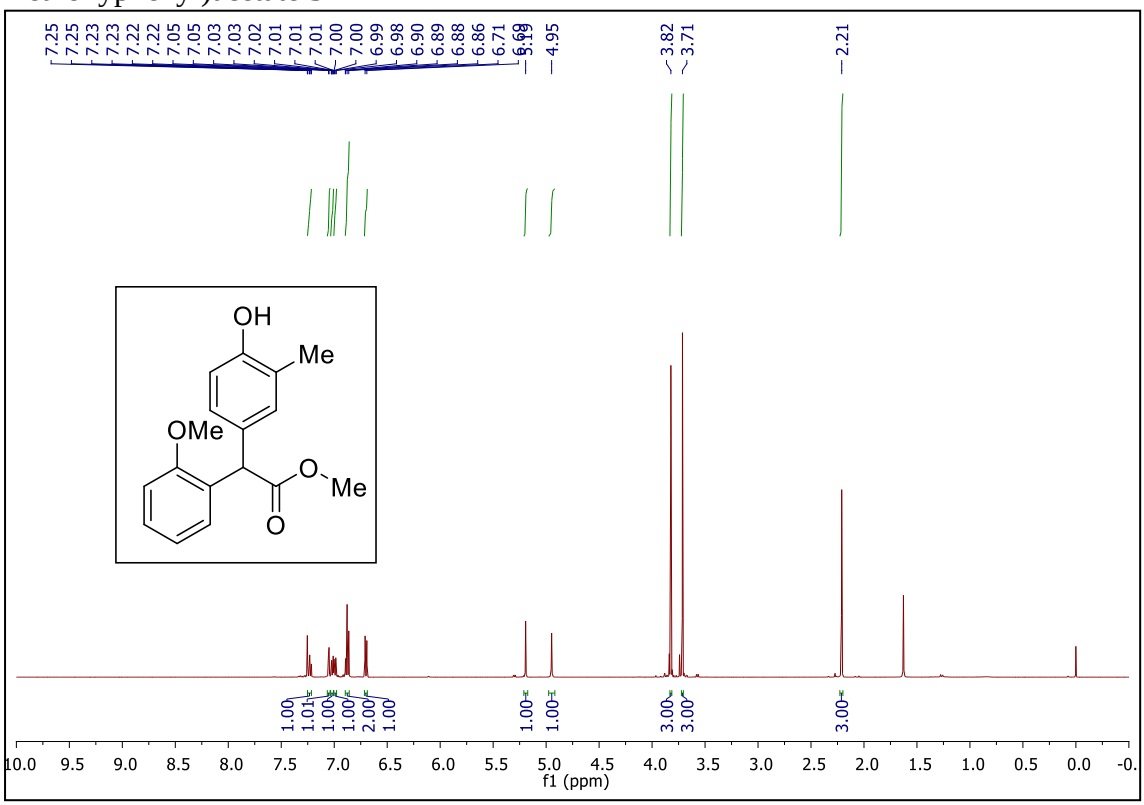
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(benzo[d][1,3]dioxol-4-yl)-2-(2-methoxyphenyl)acetate **31**



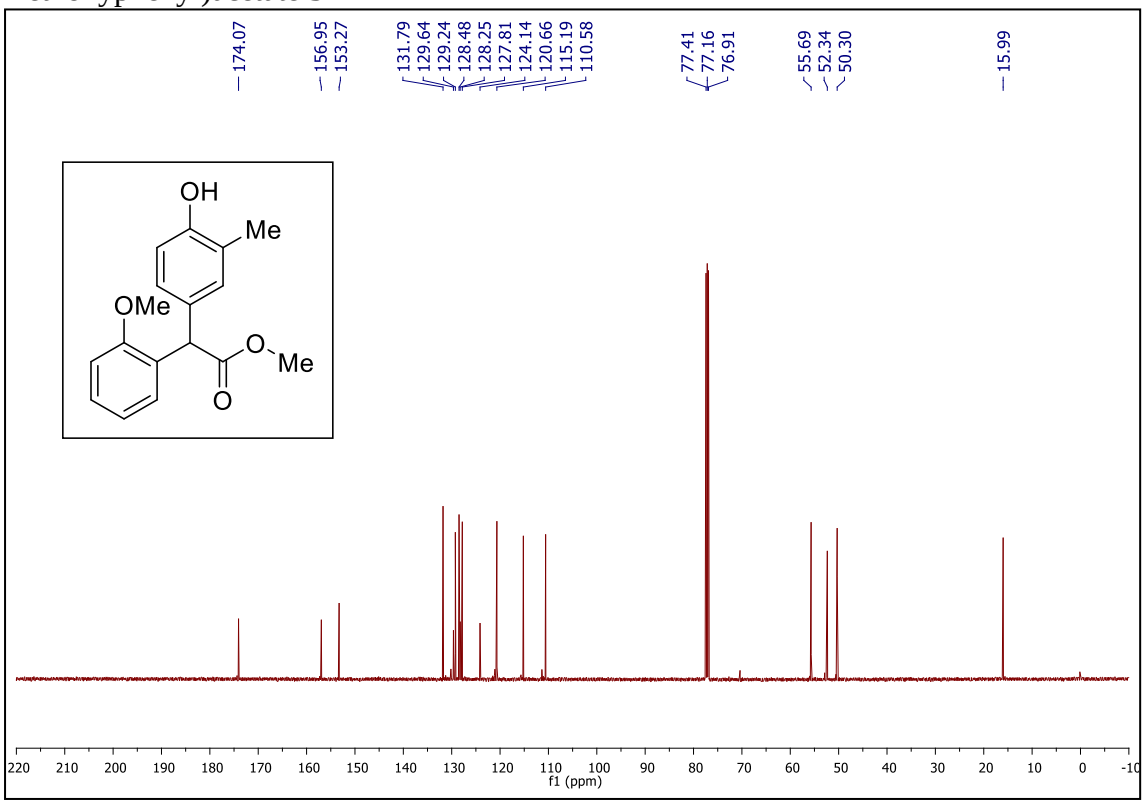
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(benzo[d][1,3]dioxol-4-yl)-2-(2-methoxyphenyl)acetate **31**



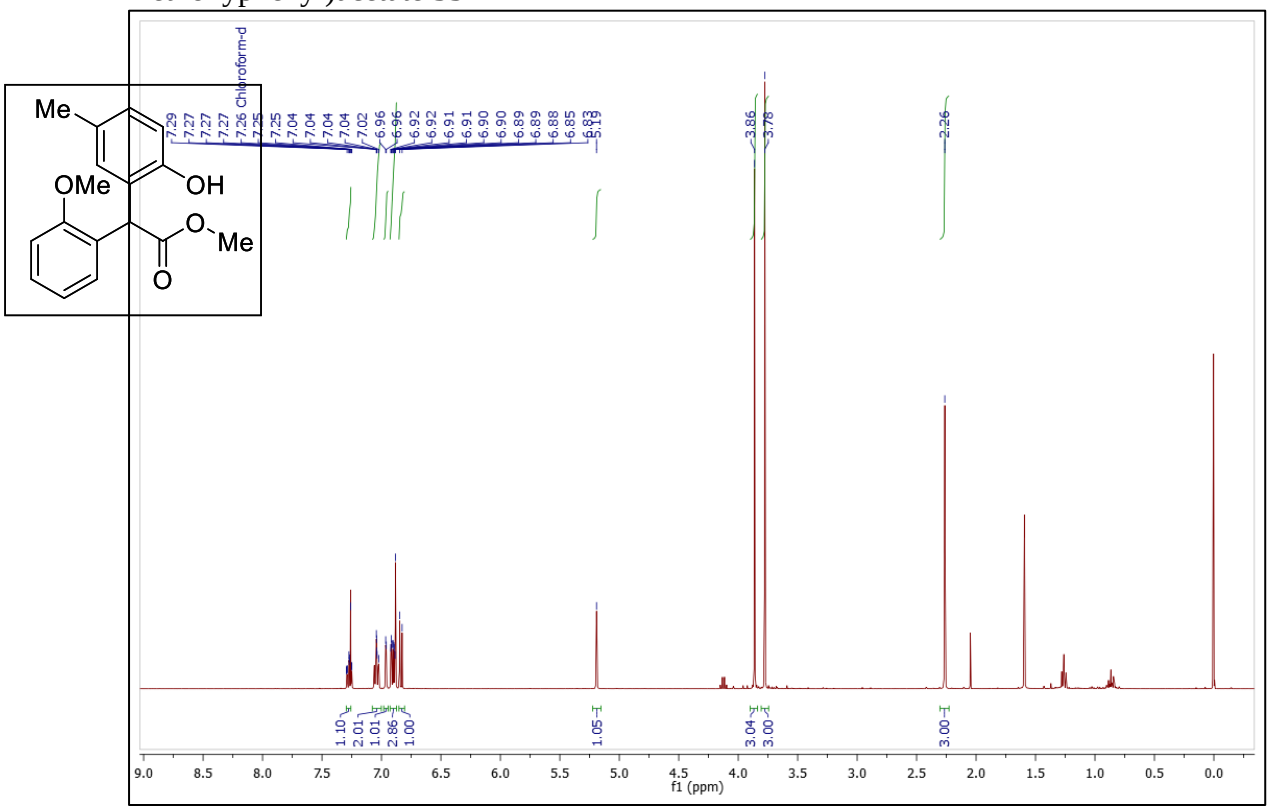
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3-methylphenyl)-2-(2-methoxyphenyl)acetate **32**



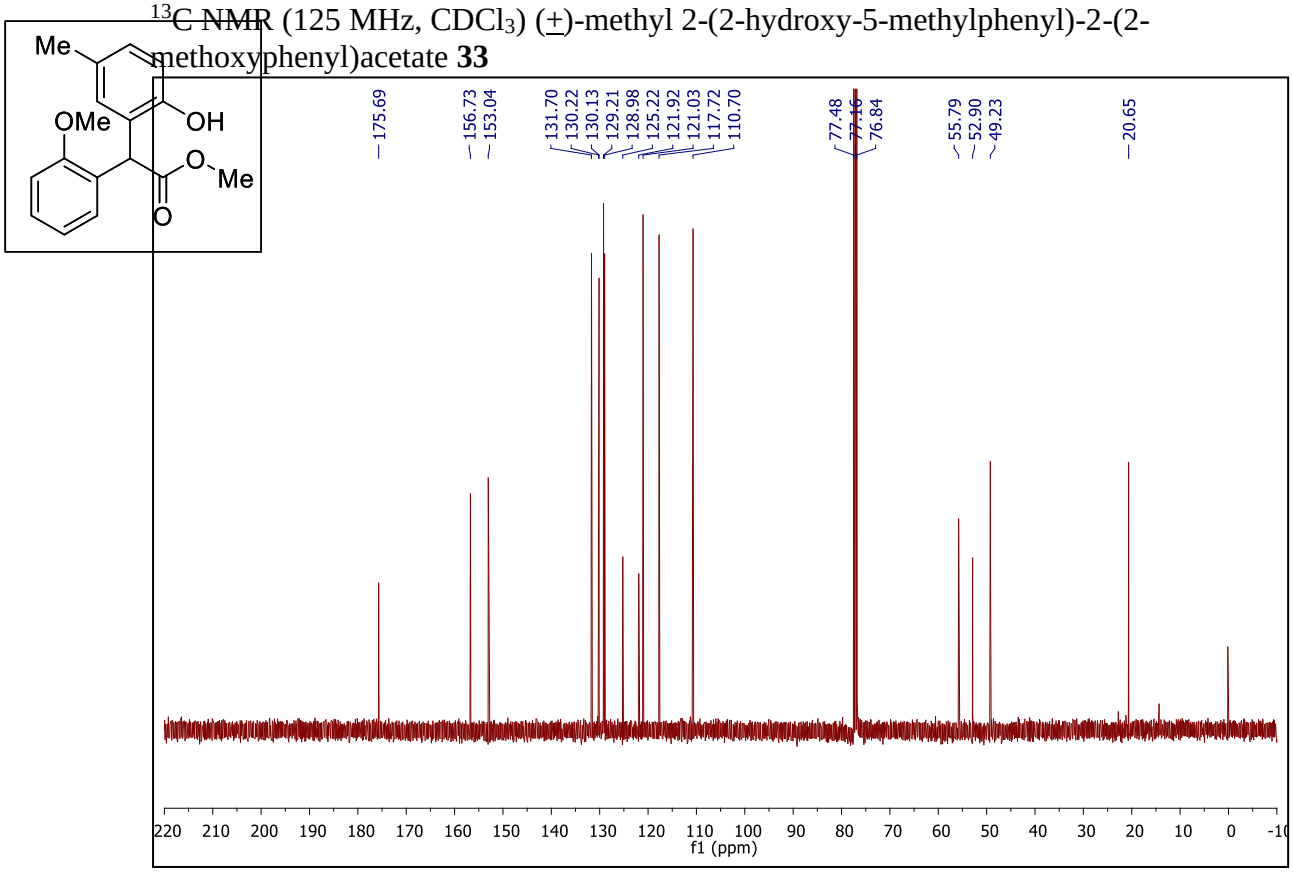
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(4-hydroxy-3-methylphenyl)-2-(2-methoxyphenyl)acetate **32**



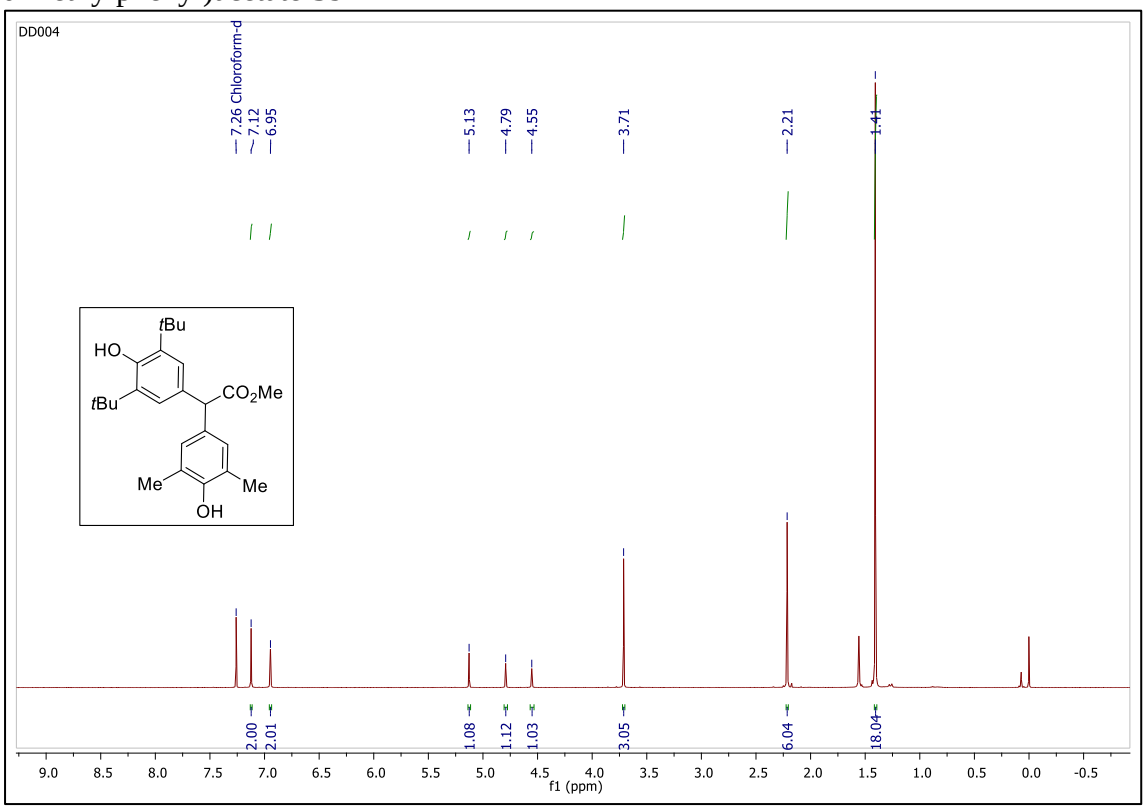
^{1}H NMR (500 MHz, $CDCl_3$) (±)-methyl 2-(2-hydroxy-5-methylphenyl)-2-(2-methoxyphenyl)acetate **33**



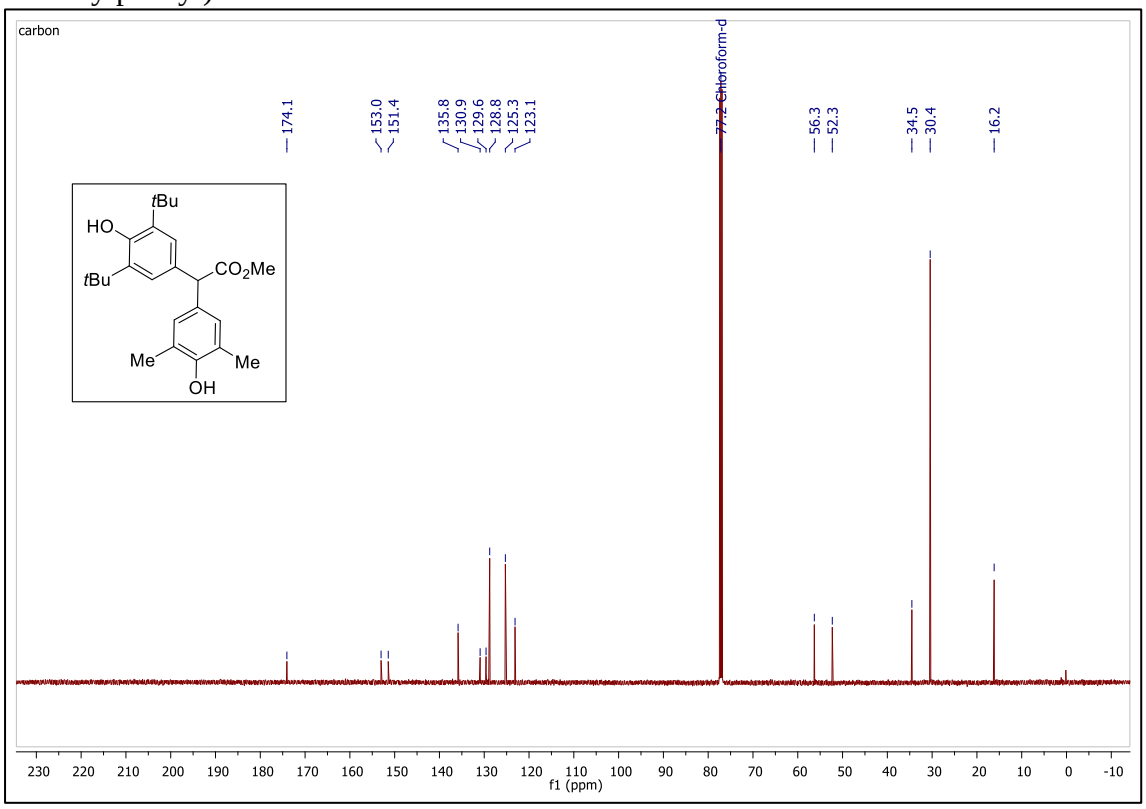
^{13}C NMR (125 MHz, $CDCl_3$) (±)-methyl 2-(2-hydroxy-5-methylphenyl)-2-(2-methoxyphenyl)acetate **33**



^{1}H NMR (500 MHz, $CDCl_3$) (±)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-(4-hydroxy-3,5-dimethylphenyl)acetate **S9**



^{13}C NMR (125 MHz, $CDCl_3$) (±)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-(4-hydroxy-3,5-dimethylphenyl)acetate **S9**



References

1. Song, Z.; Wu, Y.; Xin, T.; Jin, C.; Wen, X.; Sun, H.; Xu, Q.-L. (*Chem. Commun.* **2016**, *52*, 6079-6082).

2. Thurow, S.; Fernandes, A. A. G.; Quevedo-Acosta, Y.; de Oliveira, M. F.; de Oliveira, M. G.; Jurberg, I. D. (*Org. Lett.* **2019**, *21*, 6909-6913).

3. Hu, M.; Ni, C.; Hu, J. (*J. Am. Chem. Soc.* **2012**, *134*, 15257-15260).

4. Liao, K.; Pickel, T. C.; Boyarskikh, V.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L. (*Nature* **2017**, *551*, 609-613).

5. Tsoi, Y.-T.; Zhou, Z.; Yu, W.-Y. (*Org. Lett.* **2011**, *13*, 5370-5373).

6. Muthusamy, S.; Sivaguru, M. (*Org. Lett.* **2014**, *16*, 4248-4251).

7. Rasheed, Sk.; Rao, D. N.; Reddy, A. S.; Shankar, R.; Das, P. (*RSC Adv*. **2015**, *5*, 10567-10574).

8. Bernadim, B.; Couch, E. D.; Hardman-Baldwin, A. M.; Burtoloso, A. C. B.; Mattson, A. E. (*Synthesis* **2016**, *48*, 677-686).

9. Sexton, K. E.; Lee, H. T.; Massa, M.; Padia, J.; Patt, W. C.; Liao, P.; Pontrello, J. K.; Roth, B. D.; Spahr, M. A.; Ramharack, R. (*Bioorg. Med. Chem*. **2003**, *11*, 4827-4845).

10. Gallo, R. D. C.; Burtoloso, A. C. B. (*Green. Chem.*, **2018**, *20*, 4547-4556).

11. Schultz, O. E.; Schnekenburger, J. (*Arch. Pharm.*, **1958**, *291*, 356-361).