Decarbonylative Cross-Coupling of Cyclic Anhydrides- Introducing Stereochemistry at an sp^3 Carbon in the Cross-Coupling Event

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Supporting Information

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring, Tetrahydrofuran was degassed with argon and passed through two columns of neutral alumina. Dioxane was distilled over calcium hydride, followed by distillation over sodium under an atmosphere of argon. Kügelrohr distillation was performed on a Büchi-GKR-51. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Visualization was accomplished with ceric ammonium molybdate or bromocresol green.

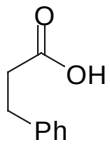
Anhydrides **1, 13, 17, 19, 23,** and **25** were all purchased from Aldrich Chemical Co. and used without further purification. Anhydrides **27** and **31** were prepared by literature methods.[1] Anhydrides **4, 15,** and **21** were prepared by hydrogenation of **27, 17** and **19** respectively (H_2, 10% Pd/C, EtOAc). $Ni(COD)_2$ was purchased from Strem Chemical, Inc. and used without further purification. Ph_2Zn was either purchased from Strem Chemicals or prepared according to literature procedure.[2]

Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [tetramethylsilane (TMS) or deuterated chloroform ($CDCl_3$)]. Multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = muliplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 300 or 400 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec.

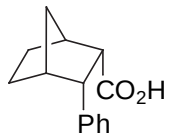
General procedure for the decarbonylative cross-coupling of cyclic anhydrides: A flame-dried round bottom flask equipped with a reflux condenser and magnetic stir bar was charged with $Ni(COD)_2$ (1.5-2 equiv), bis(diphenylphosphino)butane (dppb) (0.5 equiv) and 2,9-dimethyl-1,10-phenanthroline (neocuproine) or tetramethylethylenediamine (TMEDA) (1.0 –1.5 equiv) in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 1.0 ml THF was added via syringe and the solution was stirred at ambient temperature for 15 minutes. A solution of the anhydride

[1] (a) Corey, E.J.; Peterson, R.T. *Tetrahedron Lett*. **1985**, *26*, 5025-5028; (b) Paquette, L. A.; Boulet, S.L. *Synthesis.* **2002**, *No.7*, 888-894.
[2] Markies, P. R.; Schat, G.; Akkerman, O. S.; Bickelhaupt, F.; Smeets, W. J. J.; Spek, A. L. *Organometallics* **1990**, *9*, 2243-2247.

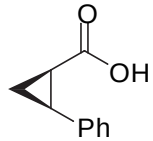
(1 equiv) in THF was then added via cannula and the solution was stirred for the time and temperature indicated. 4-fluorostyrene (1 equiv) was added via syringe followed by a solution of diphenylzinc (2 equiv in 2 mL THF) *via* cannula. The reaction mixture was then stirred for the time and temperature indicated. Reaction mixture was diluted with 10 ml of ethyl acetate and quenched with 20 ml 10% HCl (v/v). The layers were separated and the aqueous layer extracted with ethyl acetate (2 X 50 ml). The combined organic layers were combined and extracted with 20% NaOH (m/v) (2 X 20 ml) and the basic layers were then combined and brought to pH = 1-2 with 10% HCl (v/v). The acidified aqueous layer was extracted with EtOAc (3 X 50 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of products was accomplished by heating the crude mixture under vacuum to 120 ºC for 2h to remove reduction by-products; unless otherwise indicated, the desired product was obtained analytically pure after this process.



3-phenyl-propionic acid (2). According to the general procedure, 38 mg (0.14 mmol) of $Ni(COD)_2$, 30 mg of neocuproine (0.14 mmol) in 2 ml of THF was stirred for 15 minutes. 16 mg (0.14 mmol) of anhydride **1** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 4-fluorostyrene (1 equiv.) and diphenylzinc (2 equiv. in 2 ml of THF) were added via cannula and the reaction was stirred for 5 hours at 66 °C. Kügelrohr distillation, after the workup procedure, yielded pure acid **2** (78%) as a white solid: Registry number: 501-52-0.

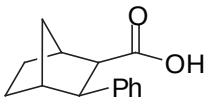


***endo*-3-phenyl-bicyclo[2.2.1]heptane-2-carboxylic acid (5).** According to the general procedure, 60 mg (0.21 mmol) of $Ni(COD)_2$, 30 mg of neocuproine (0.14 mmol), and 30 mg of dppb (0.07 mmol) in 2 ml of THF was stirred for 15 minutes. 23 mg (0.14 mmol) of anhydride **4** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 4-fluorostyrene (1 equiv) and diphenylzinc (2 equiv. in 2 ml of THF) were added via cannula and the reaction was stirred for 5 hours at 66 °C. Heating under vacuum yielded pure acid **5** (77%) as a white solid: mp 115-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.61 (m, 5H), 2.01 (m, 1H), 2.42 (s, 1H), 2.59 (s, 1H), 3.19 (ddd, 1H, *J* = 1.7, 4.1, 12.4 Hz), 3.51 (ddm, 1H, *J* = 3.6, 12.3 Hz), 7.12- 7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 23.7, 40.4, 40.5, 42.9, 47.6, 47.9, 125.8, 127.7, 128.3, 140.1, 177.5; IR (NaCl, CH_2Cl_2) 3165, 2960, 1701, 1593 cm^{-1}; HRMS $[C_{14}H_{16}O_2]^+$ calcd 216.1150. Found 216.1147 (EI+).

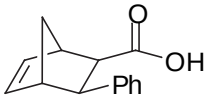


2-phenyl-cyclopropanecarboxylic acid (14). According to the general procedure, 60 mg (0.21 mmol) of $Ni(COD)_2$, 30 mg of neocuproine (0.14 mmol), and 30 mg of dppb (0.07 mmol) in 2 ml of THF was stirred for 15 minutes. 17 mg (0.14 mmol) of anhydride **13** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 4-fluorostyrene (1 equiv.) and diphenylzinc (2 equiv. in 2 ml of THF) were added via cannula and the reaction was stirred for 5 hours at 66 °C. Heating under vacuum yielded pure acid **14** (60%) as a white solid: mp 98-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (ddd, 1H, *J* = 5.1, 7.6, 9.0 Hz), 1.67 (ddd, 1H, *J* = 5.4, 5.4, 7.8 Hz), 2.05 (ddd, 1H, *J* = 9.1, 7.6, 5.5 Hz), 2.63 (ddd, 1H, *J*

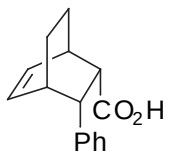
= 7.7, 7.7, 9.1 Hz), 7.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 21.3, 26.5, 126.8, 128.0, 129.2, 135.8, 176.5; IR (NaCl, CH_2Cl_2) 3027, 2919, 1695, 1449 cm^{-1}; HRMS $[C_{10}H_{10}O_2]^+$ calcd 162.0680. Found 162.0677 (EI+).



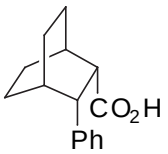
***exo*-3-phenyl-bicyclo[2.2.1]heptane-2-carboxylic acid (16).** According to the general procedure, 60 mg (0.21 mmol) of $Ni(COD)_2$, 30 mg of neocuproine (0.14 mmol), and 30 mg of dppb (0.07mmol) in 2 ml of THF was stirred for 15 minutes. 23 mg (0.14 mmol) of anhydride **15** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 4-fluorostyrene (1 equiv.) and diphenylzinc (2 equiv. in 2 ml of THF) were added via cannula and the reaction was stirred for 5 hours at 66 °C. Heating under vacuum yielded pure acid **16** (78%) as a white solid: mp 114-118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (m, 2H), 1.41 (m, 2H), 1.64 (m, 2H), 2.29 (dm, 1H, *J* = 10.0 Hz), 2.50 (s, 1H), 2.83 (d, 1H, *J* = 10.2 Hz), 3.15 (dm, 1H, *J* = 10.2 Hz) 7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 30.6, 37.1, 40.0, 41.2, 52.0, 54.2, 126.1, 127.9, 128.1, 141.6, 177.3; IR (NaCl, CH_2Cl_2) 3150, 2970, 1701, 1424 cm^{-1}; HRMS $[C_{14}H_{16}O_2]^+$ calcd 216.1150. Found 216.1146 (EI+).



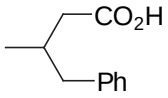
***exo*-3-phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (18).** According to the general procedure, 60 mg (0.21 mmol) of $Ni(COD)_2$, 30 mg of neocuproine (0.14 mmol), and 30 mg of dppb (0.07 mmol) in 2 ml of THF was stirred for 15 minutes. 23 mg (0.14 mmol) of anhydride **17** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 4-fluorostyrene (1 equiv.) and diphenylzinc (2 equiv. in 2 ml of THF) were added via cannula and the reaction was stirred for 5 hours at 66 °C. Heating under vacuum yielded pure acid **18** (56%) as a white solid: mp 147-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (dm, 1H, *J* = 9.0 Hz), 2.32 (dm, 1H, *J* = 8.8 Hz), 2.70 (dd, 1H, *J* = 2.0, 9.3 Hz), 3.02 (s, 2H), 3.10 (dm, 1H, *J* = 10.0 Hz), 6.20 (m, 1H), 6.38 (m, 1H), 7.16 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.6, 45.9, 46.4, 48.4, 48.6, 126.3, 128.0, 128.4, 137.4, 140.4, 140.6, 177.8; IR (NaCl, CH_2Cl_2) 3053, 2981, 1701, 1419 cm^{-1}; HRMS $[C_{14}H_{14}O_2]^+$ calcd 214.0993. Found 214.0989 (EI+).



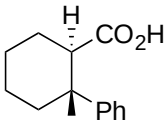
***endo*-3-phenyl-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid (20).** According to the general procedure, 60 mg (0.21 mmol) of $Ni(COD)_2$, 30 mg of neocuproine (0.14 mmol), and 30 mg of dppb (0.07 mmol) in 2 ml of dioxane was stirred for 15 minutes. 25 mg (0.14 mmol) of anhydride **19** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 4-fluorostyrene (1 equiv) and diphenylzinc (2 equiv. in 2 ml of dioxane) were added via cannula and the reaction was stirred for 5 hours at 66 °C. Heating under vacuum yielded pure acid **20** (51%) as a white solid: mp 96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25-1.41 (m, 2H), 1.59-1.75 (m, 2H), 2.70 (m, 1H), 2.88 (m, 1H), 3.21 (dm, 1H, *J* = 11.7 Hz), 3.41 (dm, 1H, *J* = 11.3 Hz), 6.38 (m, 1H), 6.53 (m, 1H), 7.15 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.3, 32.2, 36.7, 49.6, 51.8, 126.3, 127.9, 128.4, 132.4, 134.3, 143.0, 176.3; IR (NaCl, CH_2Cl_2) 3068, 2934, 1701 cm^{-1}; HRMS $[C_{15}H_{16}O_2]^+$ calcd 228.1150. Found 228.1144 (EI+).



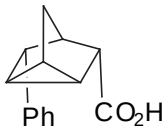
***endo*-3-phenyl-bicyclo[2.2.2]octane-2-carboxylic acid (22).** According to the general procedure, 60 mg (0.21 mmol) of $Ni(COD)_2$, 30 mg of neocuproine (0.14 mmol), and 30 mg of dppb (0.07 mmol) in 2 ml of dioxane was stirred for 15 minutes. 25 mg (0.14 mmol) of anhydride **21** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 4-fluorostyrene (1 equiv) and diphenylzinc (2 equiv in 2 ml of dioxane) were added via cannula and the reaction was stirred for 5 hours at 66 °C. Heating under vacuum yielded pure acid **22** (50%) as an oil: Rf = 0.27 (2% MeOH/ 98% CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-2.05 (m, 10H), 3.19 (ddd, 1H, *J* = 1.8, 1.8, 11.9 Hz), 3.3 (dm, 1H, *J* = 11.9 Hz), 7.23-7.26 (m, 5H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.7, 26.5, 26.6, 27.3, 29.8, 44.5, 46.0, 125.8, 127.8, 128.1, 142.8, 176.3; IR (NaCl, CH_2Cl_2) 3068, 2868, 1701 cm^{-1}; HRMS $[C_{15}H_{16}O_2]^+$ calcd. 230.1306. Found 230.1309 (EI+).



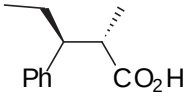
3-methyl-4-phenyl-butyric acid (24). According to the general procedure, 80 mg (0.28 mmol) of $Ni(COD)_2$, 30 µl of TMEDA (0.21 mmol), and 30 mg of dppb (0.07 mmol) in 2 ml of THF was stirred for 15 minutes. 23 mg (0.14 mmol) of anhydride **23** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 4-fluorostyrene (1 equiv) and diphenylzinc (2 equiv in 2 ml of THF) was added via cannula and the reaction was stirred for 5 hours at 66 °C. Kügelrohr distillation yielded pure acid **24** (85%) as a white solid: Registry number: 7315-68-6.



***trans*-2-phenyl-cyclohexanecarboxylic acid (26).** According to the general procedure, 60 mg (0.21 mmol) of $Ni(COD)_2$, 30 mg of neocuproine (0.14 mmol) , and 30 mg of dppb (0.07 mmol) in 2 ml of THF was stirred for 15 minutes. 22 mg (0.14 mmol) of anhydride **27** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 45 °C. 4-fluorostyrene (1 equiv) and diphenylzinc (2 equiv in 2 ml of THF) were added via cannula and the reaction was stirred for 5 hours at 66 °C. Heating under vacuum yielded 22 mg (77%) acid **28** as a white solid: Registry number: 24905-75-7.



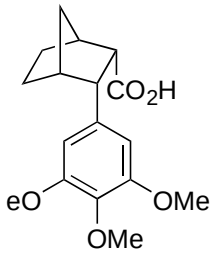
7-phenyl-tricyclo[2.2.1.0]heptane-3-carboxylic acid (28). According to the general procedure, 60 mg (0.21 mmol) of $Ni(COD)_2$, 30 mg of neocuproine (0.14 mmol) , and 30 mg of dppb (0.07 mmol) in 2 ml of THF was stirred for 15 minutes. 23 mg (0.14 mmol) of anhydride **27** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. Diphenylzinc (2 equiv in 2 ml of THF) was added via cannula and the reaction was stirred for 5 hours at 66 °C. Heating under vacuum yielded pure acid **28** (56%) as a white solid: mp 113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54-1.67 (m, 5H), 2.33 (m, 1H), 2.55 (s, 1H), 3.01 (s, 1H), 7.10-7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 11.9, 13.1, 35.6, 38.4, 48.5, 49.2, 126.2, 127.5, 128.8, 139.8, 176.7; IR (NaCl, CH_2Cl_2) 3063, 2950, 1696, 1501 cm^{-1}; HRMS $[C_{14}H_{14}O_2]^+$ calcd 215.1072. Found 215.1063 (EI+).



2-methyl-3-phenyl-pentanoic acid (32). According to the general procedure, 80 mg (0.28 mmol) of $Ni(COD)_2$, 30 µl of TMEDA (0.21 mmol) , and 30 mg of dppb (0.07 mmol) in 2 ml of THF was stirred for

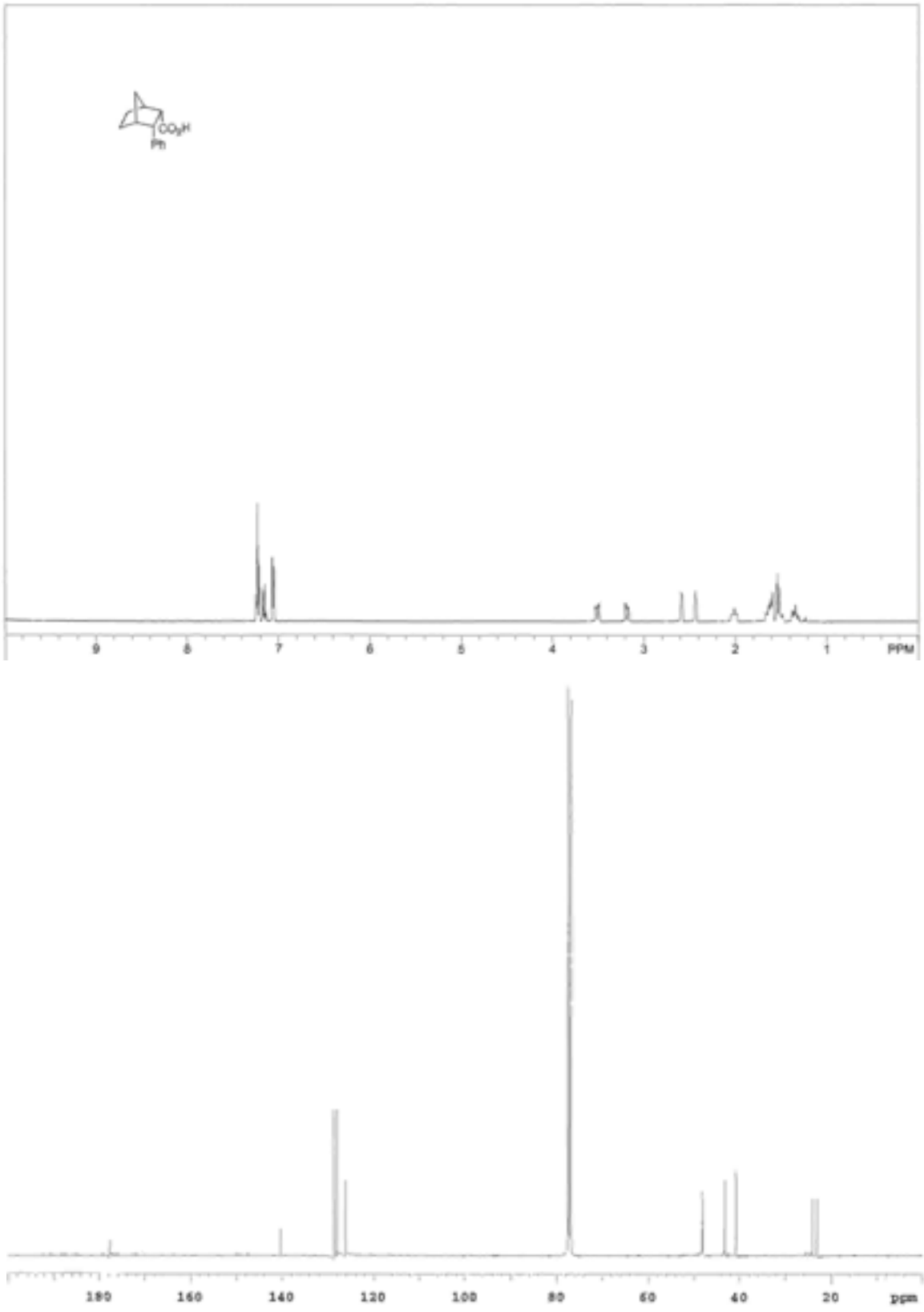
15 minutes. 23 mg (0.14 mmol) of anhydride **31** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 4-fluorostyrene (1 equiv.) and diphenylzinc (2 equiv. in 2 ml of THF) were added via cannula and the reaction was stirred for 5 hours at 66 °C. Column chromatography (98:2 CH_2Cl_2/MeOH) yielded pure acid **32** (74%) as a white solid: mp 79-83°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (t, 3H, *J* = 7.4 Hz), 1.19 (d, 3H, *J* = 6.5 Hz), 1.62 (m, 1H), 1.80 (m, 1H), 2.79 (ddd, 1H, *J* = 3.6, 8.3, 8.3 Hz), 2.72 (dq, 1H, *J* = 6.6, 7.6 Hz), 7.08-7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 14.4, 24.2, 45.3, 49.9, 126.5, 128.2, 128.3, 142.3, 179.9; IR (NaCl, CH_2Cl_2) 3160, 3048, 2976, 1701, 1419 cm^{-1}; HRMS $[C_{12}H_{16}O_2]^+$ calcd 192.1150. Found 192.1156 (EI+).

Proof of relative stereochemistry for 32: X-ray analysis of **32** revealed the illustrated product.



***endo*-3-(3,4,5-trimethoxyphenyl)-bicyclo[2.2.1]heptane-2-carboxylic acid. Preparation of bis-(3,4,5-trimethoxyphenyl) zinc:** A flame-dried 10ml heart shaped flask equipped with a magnetic stir bar under argon was charged with 148 mg (0.60 mmol) of 3,4,5-trimethoxybromobenzene in 2 ml of THF. The resulting solution was cooled to –78ºC and 0.4 ml (0.64 mmol) of *n*-butyllithium (1.6 M in hexanes) were added via syringe. After 0.5 h, 0.63 ml (0.32 mmol) of $ZnCl_2$ (0.5 M in THF) were added and the reaction was allowed to warm to room temperature over 0.5 h prior to use. According to the general procedure, 62 mg (0.23 mmol) of $Ni(COD)_2$, 32 mg of neocuproine (0.15 mmol) , and 31 mg of dppb (0.08 mmol) in 2 ml of THF was stirred for 15 minutes at room temperature. 25 mg (0.15 mmol) of anhydride **4** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 18 μl (0.15 mmol) of 4-fluorostyrene and bis-(3,4,5-trimethoxyphenyl) zinc (see above) were added via cannula and the reaction was stirred for 5 hours at 66 °C. After standard work-up, column chromatography (99:1 CH_2Cl_2/MeOH) yielded 28 mg (52%) the desired acid as a white solid: mp 190-194°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33-1.72 (m, 5H), 2.05-2.12 (m, 1H), 2.44 (s, 1H), 2.59 (s, 1H), 3.18 (dd, 1H, *J* = 2.2, 12.3 Hz), 3.50 (dd, 1H, *J* = 3.0, 12.0 Hz), 3.79 (s, 6H), 3.81 (s, 3H), 6.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 23.6, 40.5, 40.6, 43.3, 48.2, 48.3, 55.9, 60.8, 105.5, 135.7, 152.4, 179.2; IR (NaCl, $CHCl_3$) 2956, 2875, 1687, 1591, 1512, 1427, 1252, 1124 cm^{-1}

Spectral Data for **5**:



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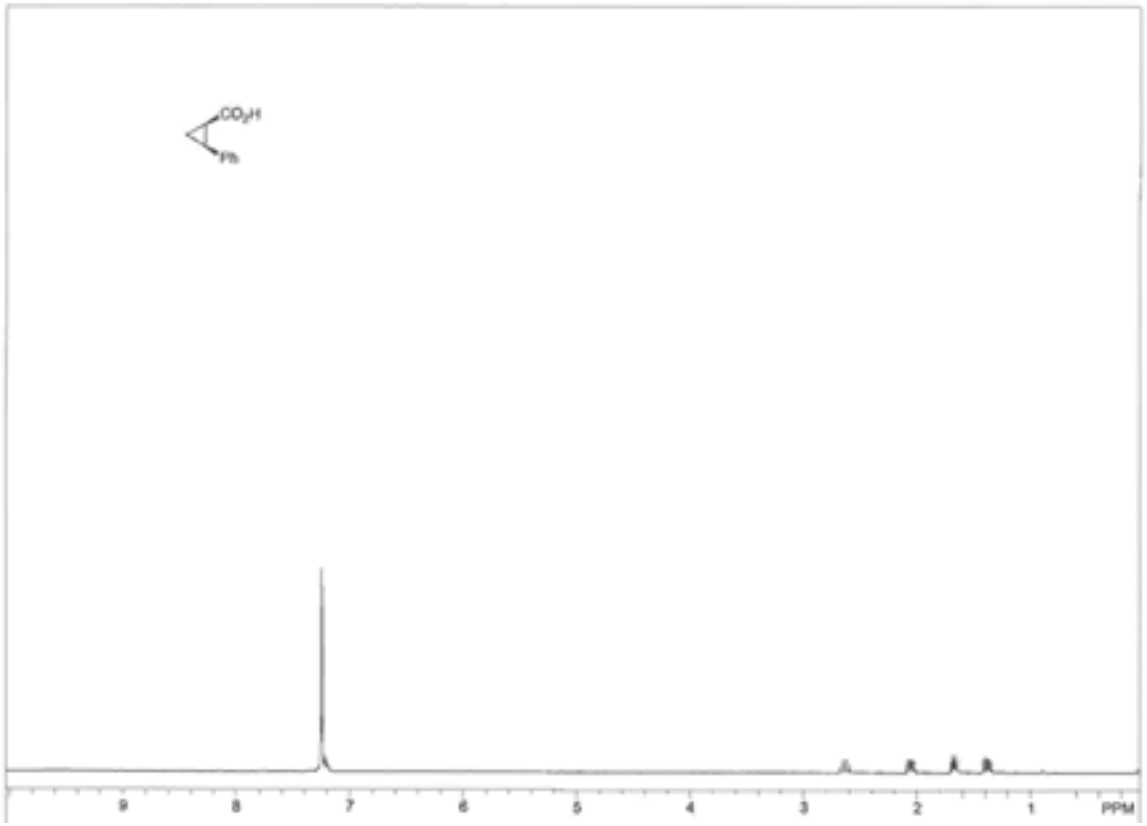
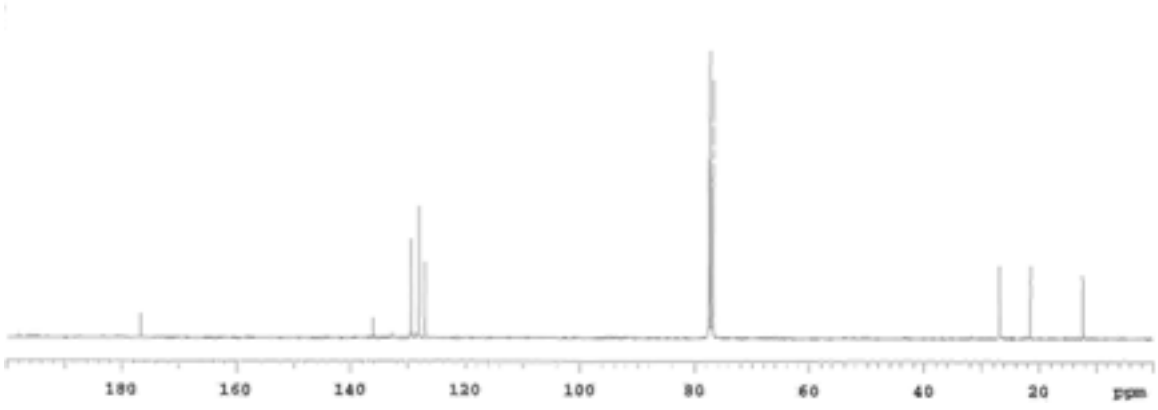
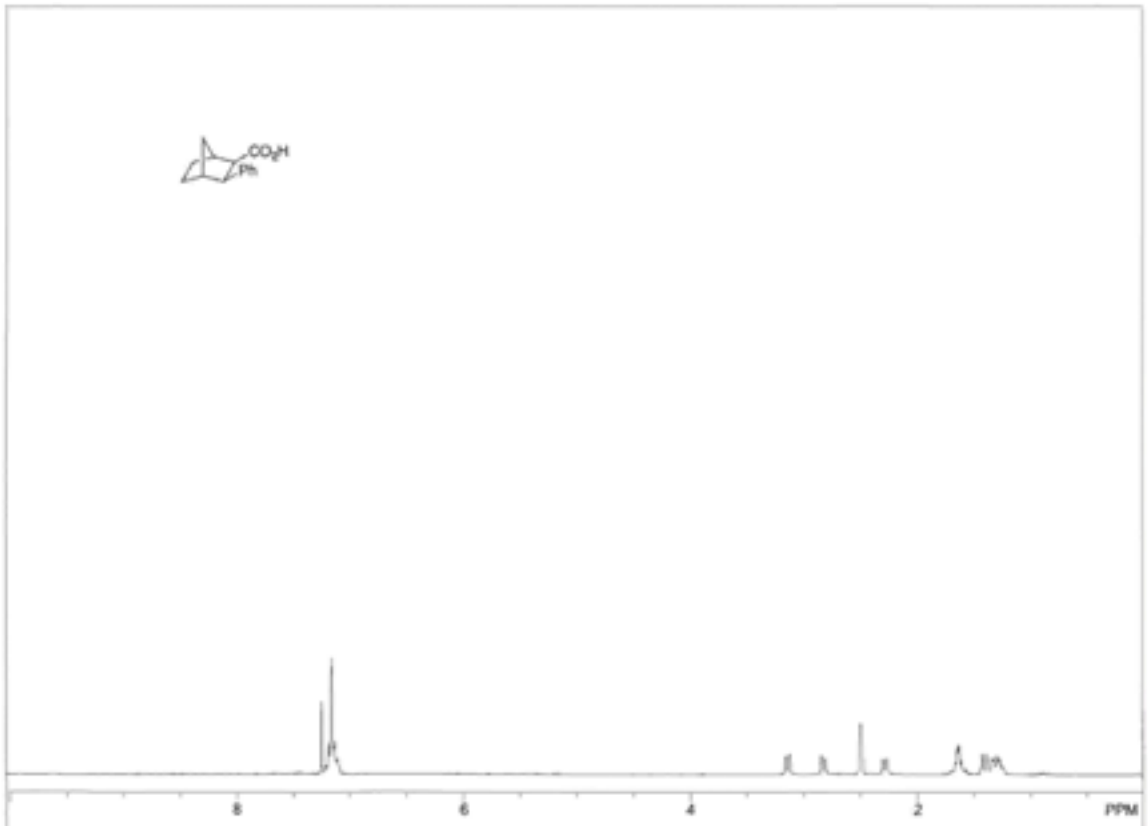
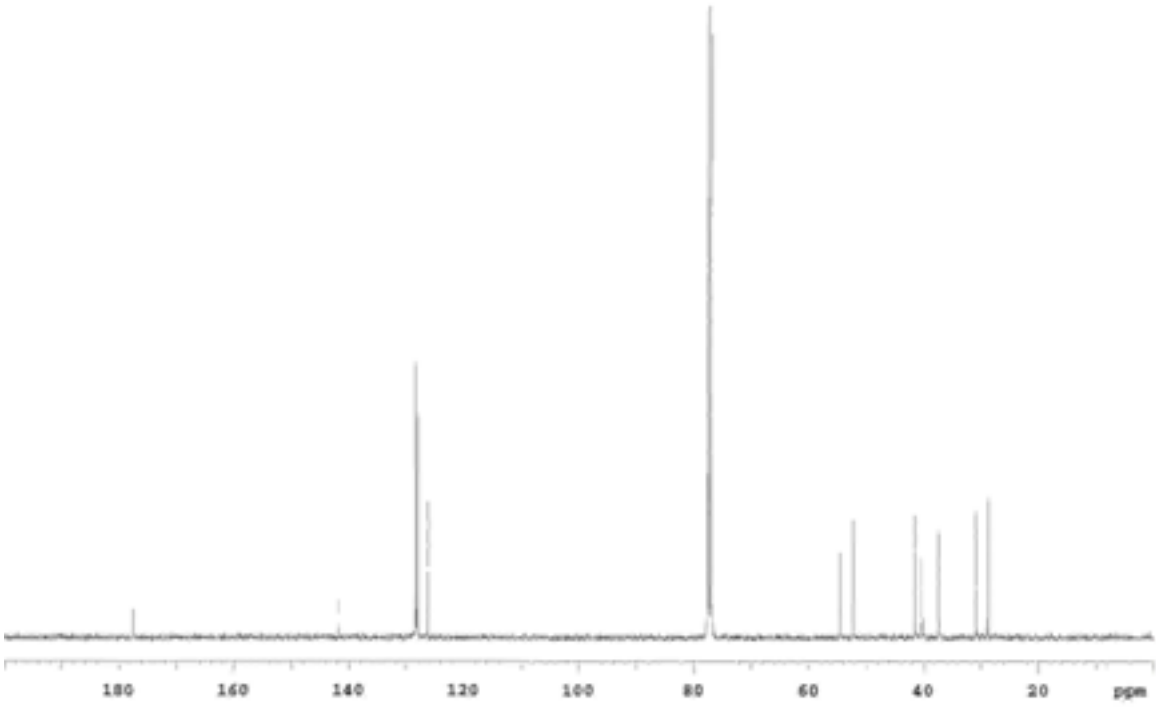


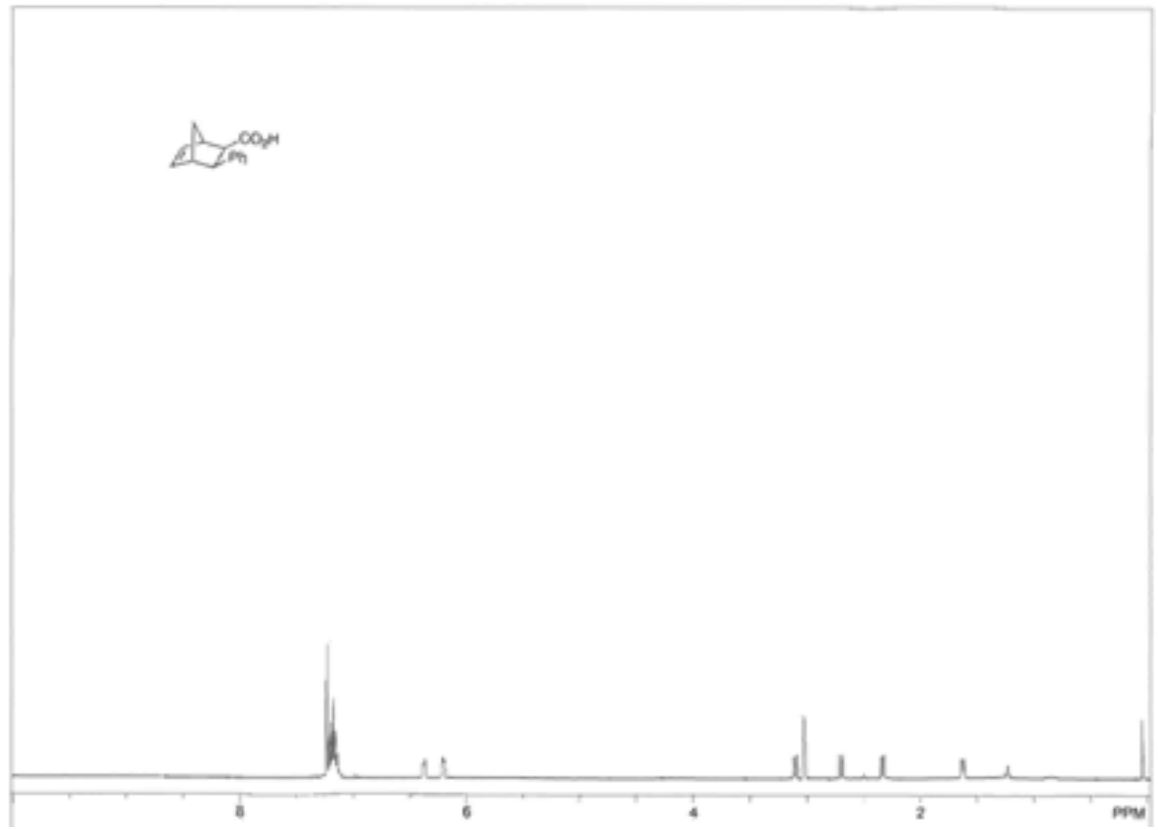


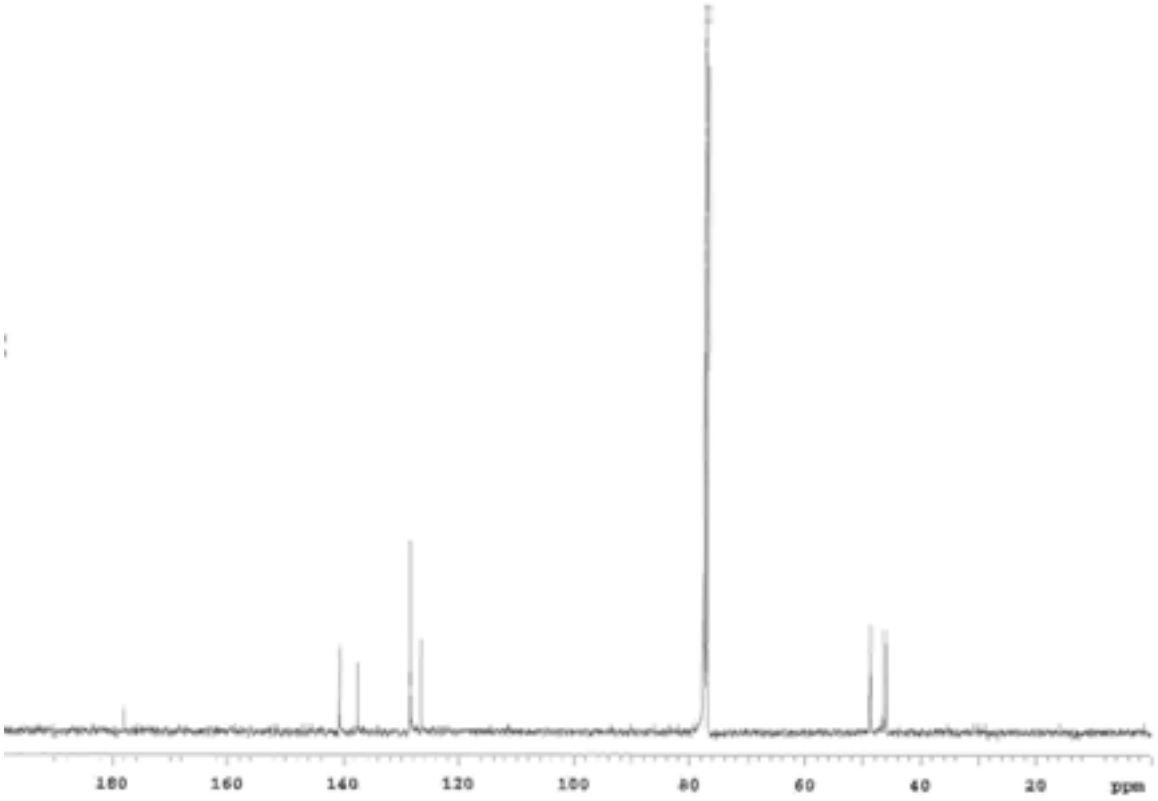
Spectral Data for **16**:



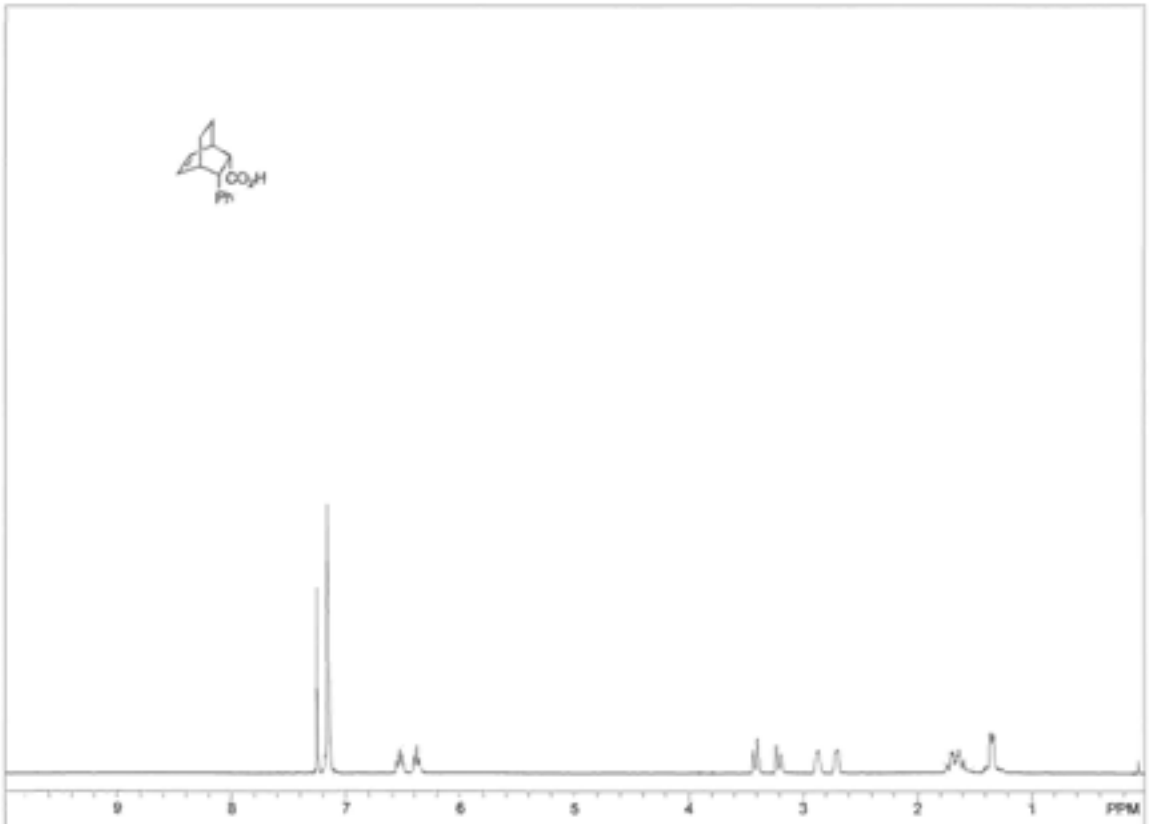


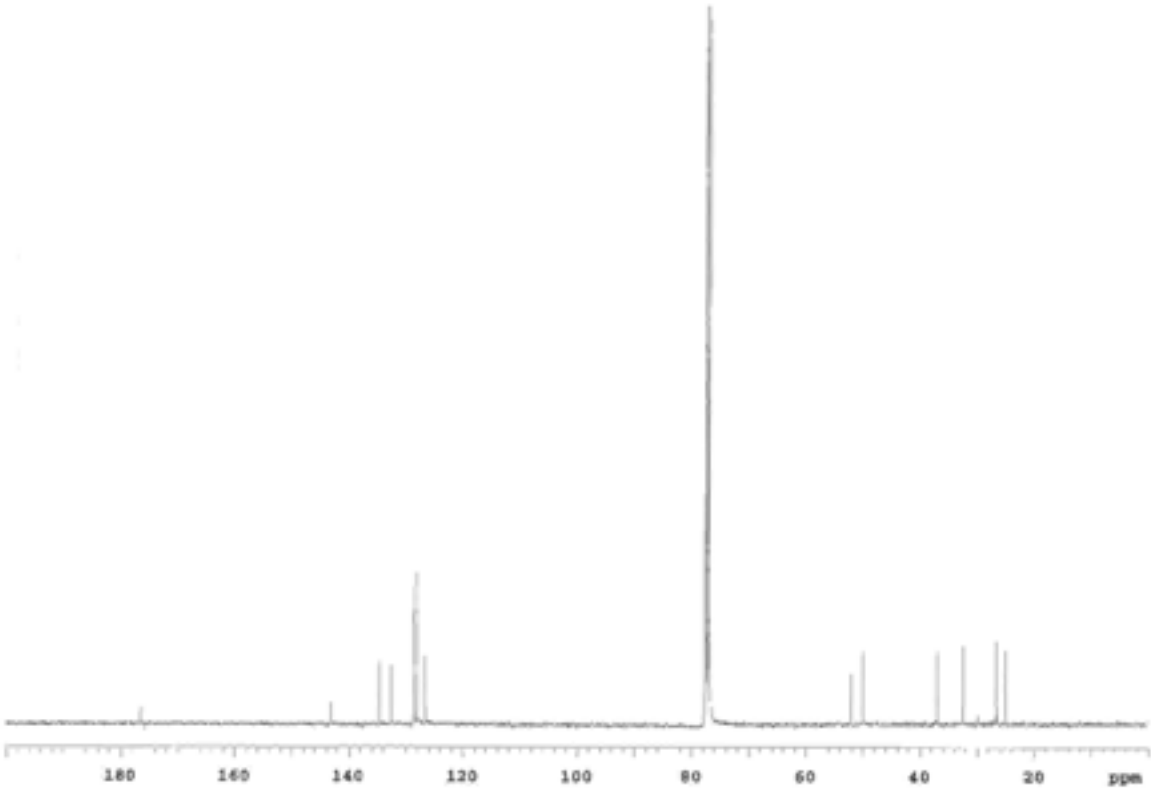
Spectral Data for **18**:



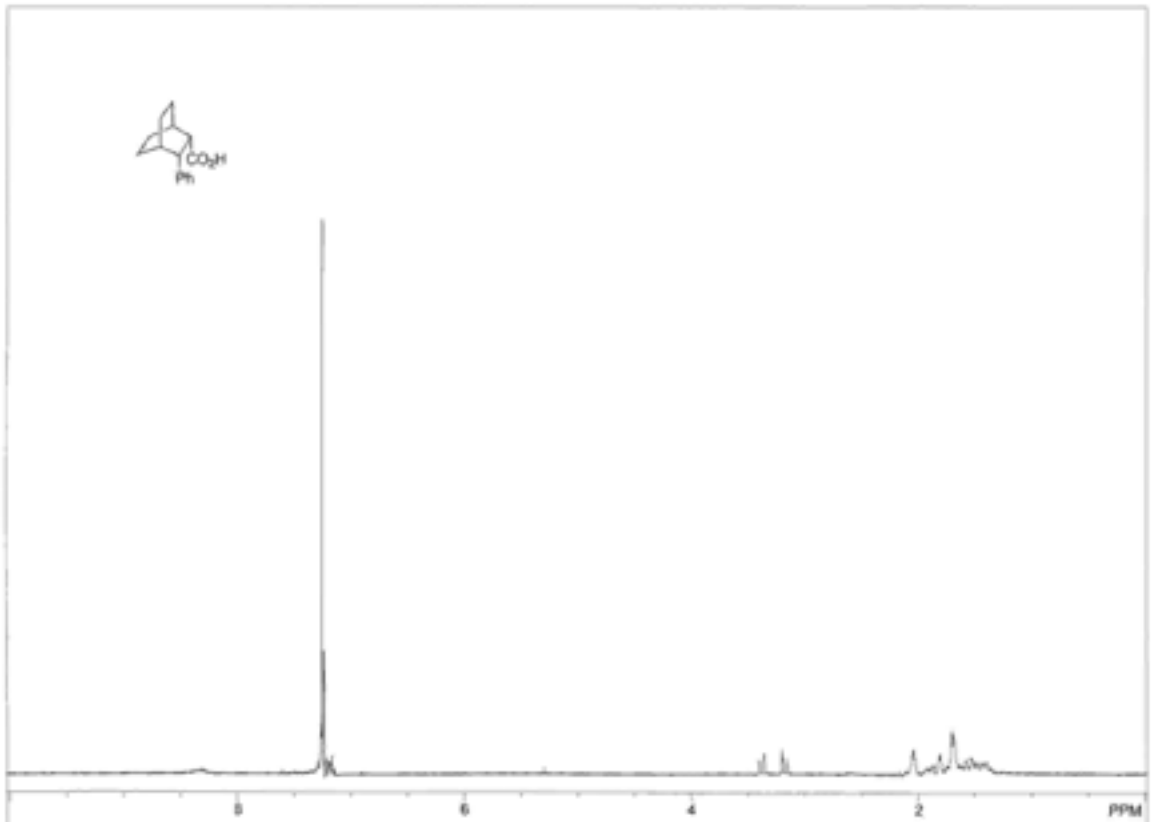


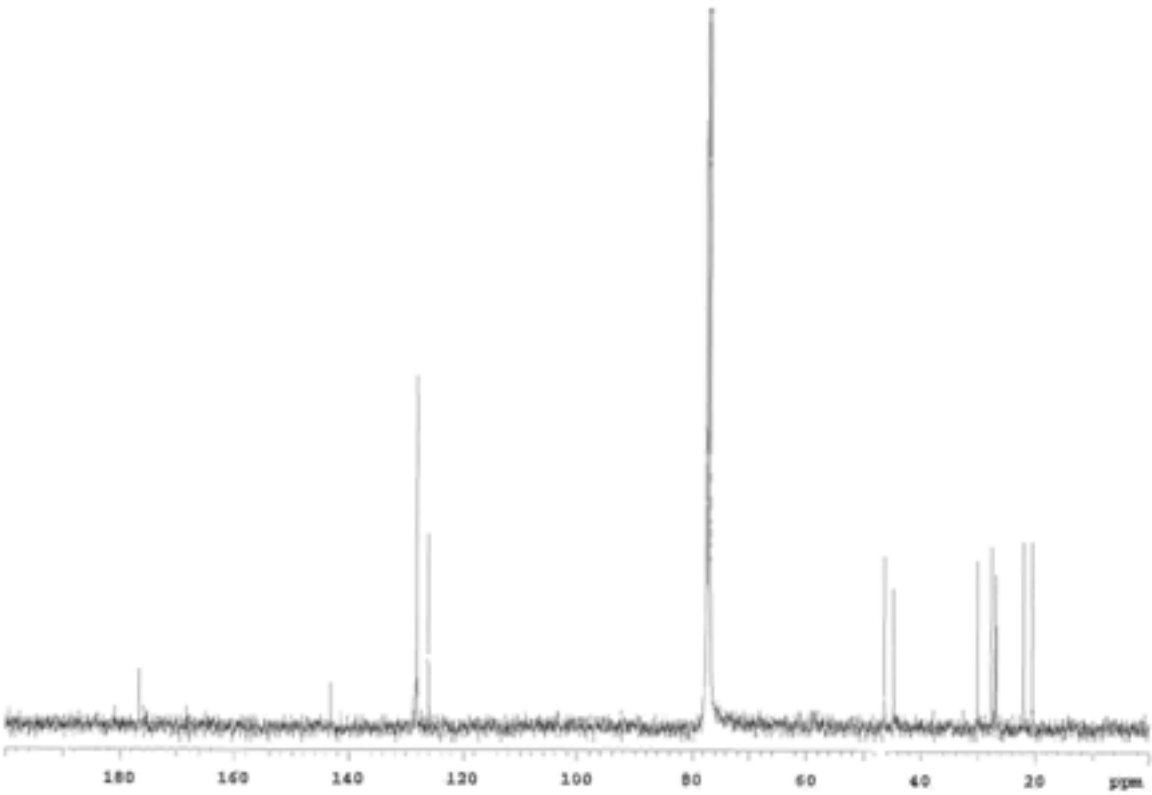
Spectral Data for **20**:



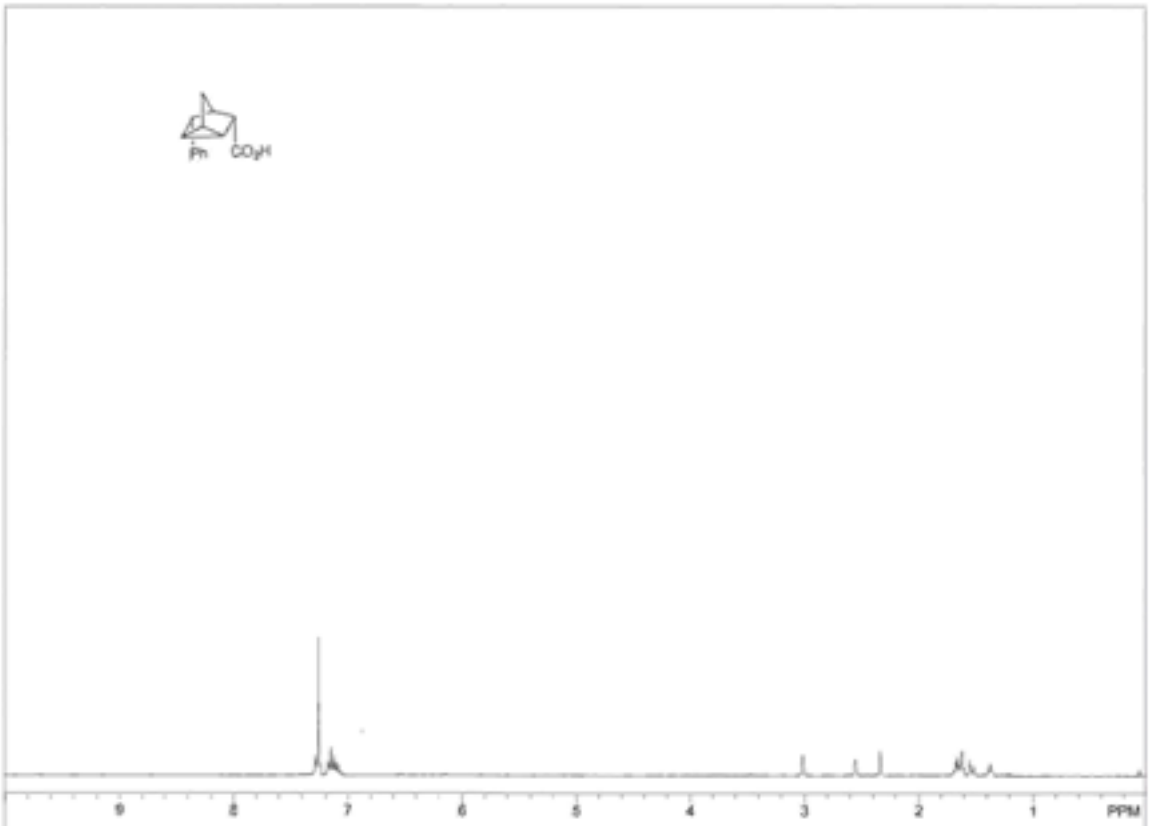


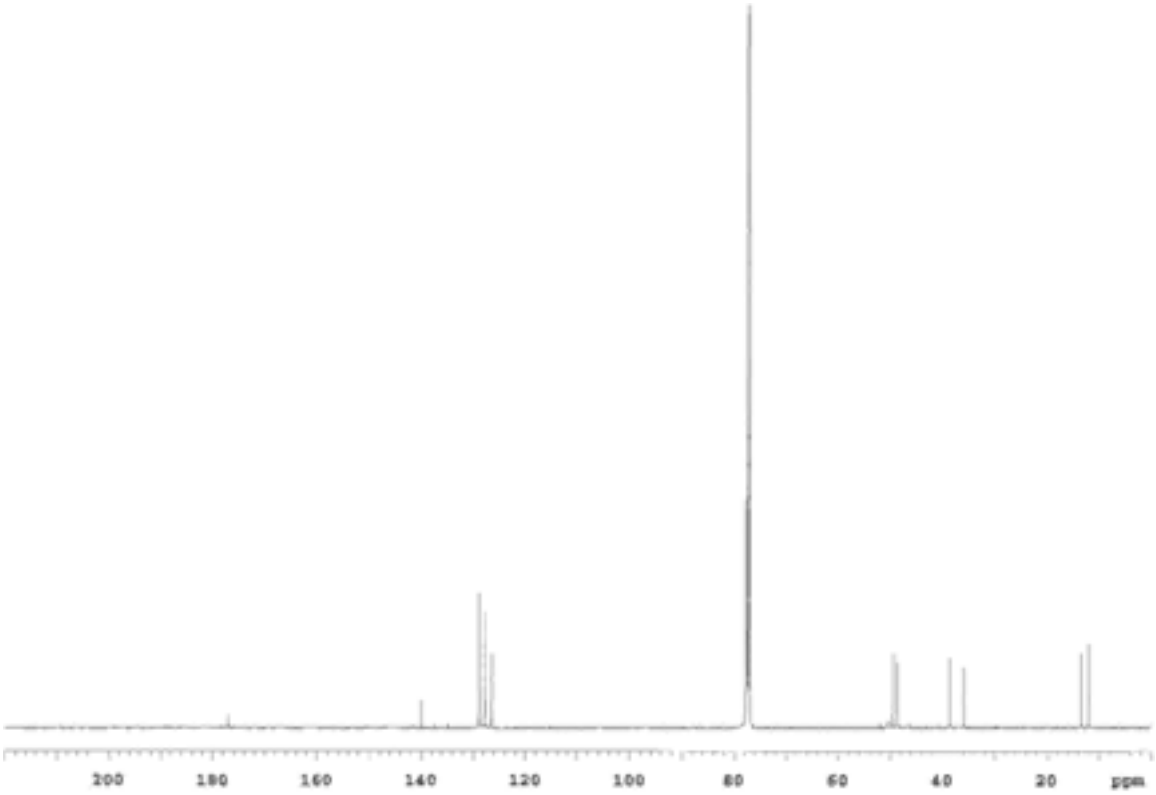
Spectral Data for **22**:





Spectral Data for **28**:





Spectral Data for **32**: