Supporting Information

Catalytic asymmetric synthesis of cyclic amino acids and alkaloid derivatives: Application to (+)-dihydropinidine and Selfotel synthesis

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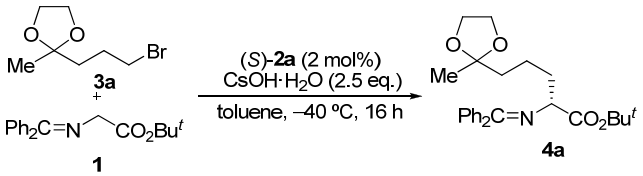
General Information: Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane (in the case of $CDCl_3$) as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quintet, m = multiplet, br = broad, and app = apparent), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JNM-FX400 (100MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using a Daicel CHIRALPAK AD-H, AS-H and CHIRALCEL OD-H 4.6 mm × 25 cm column. The high-resolution mass spectra (HRMS) were performed on Applied Biosystems Mariner 8295 API-TOF and Bruker microTOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230-400 mesh). Glycine *t*-butyl ester-benzophenoneimine Shiff base **1**,[1] alanine *t*-butyl ester-*p*-chlorobenzaldimine Shiff base **6**,[2] chiral phase transfer catalysts (*S*)-**2a**, (*S*)-**2b** and (*S*)-**2c** were prepared according to literature procedure.[3] Alkyl halides **3**,[4-6] **8**[4] and **13**[7] were prepared according to literature procedure. Cyclic amino esters **5a**,[8] **12b**[9] and **12c**[9] are known compounds. Selfotel (CGS-19755) was prepared by a similar method described in literature.[10] Other simple chemicals were purchased and used as such.

General Procedure for Asymmetric Alkylation under Phase-Transfer Conditions



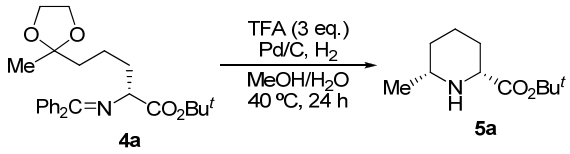
To a mixture of **1** (30 mg, 0.10 mmol), **3a** (209 mg, 1.0 mmol) and (*S*)-**2a** (1.5 mg, 0.002 mmol) in toluene (1 mL) was added CsOH (42 mg, 0.25 mmol) at –40 ˚C, and the reaction mixture was vigorously stirred for 16 h. After the consumption of the starting material, the mixture was diluted with H_2O, extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and purified by chromatography on silica gel (hexane/ethyl acetate = 5/1 as eluent) to afford **4a** (36 mg, 0.085 mmol, 85% yield) as an oil. The

enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 6.3 min (major) and 10.0 min (minor)). $[\alpha]_D^{25}$ = 81.1 (*c* 1.0, $CHCl_3$; 99% ee); ^{1}H NMR δ 1.27 (3H, s), 1.30-1.40 (2H, m), 1.44 (9H, s), 1.55-1.60 (2H, m), 1.87-1.93 (2H, m), 3.84-3.93 (5H, m), 7.17-7.19 (2H, m), 7.29-7.45 (6H, m), 7.63-7.66 (2H, m); ^{13}C NMR δ 20.6, 23.8, 28.1, 33.8, 38.9, 64.6, 66.0, 80.8, 110.0, 127.88, 127.94, 128.4, 128.5, 128.8, 130.1, 136.7, 139.7, 169.9, 171.5; IR (neat) 1069, 1148, 1368, 1447, 1622, 1732, 2951 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{26}H_{34}NO_4$: 424.2482 ($[M + H]^+$), Found: 424.2491 ($[M + H]^+$).

(*R*)-*tert*-Butyl 2-(Diphenylmethyleneamino)-6-(2-methyl-1,3-dioxolan-2-yl)hexanoate 4b

Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 12.0 min (major) and 15.7 min (minor). $[\alpha]_D^{20}$ = 83.6 (*c* 0.5, $CHCl_3$; 98% ee); ^{1}H NMR δ 1.20-1.37 (7H, m), 1.44 (9H, s), 1.57-1.61 (2H, m), 1.88 (2H, q, *J* = 7.6 Hz), 3.85-3.94 (5H, m), 7.15-7.18 (2H, m), 7.30-7.56 (6H, m), 7.63-7.65 (2H, m); ^{13}C NMR δ 23.7, 23.9, 26.3, 28.1, 33.6, 34.7, 39.1, 64.6, 66.0, 80.8, 110.0, 127.9, 128.0, 128.37, 128.42, 128.8, 130.1, 135.3, 136.8, 169.8, 171.6; IR (neat) 1152, 1368, 1622, 1732, 2359, 2978 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{27}H_{36}NO_4$: 438.2639 ($[M + H]^+$), Found: 438.2646 ($[M + H]^+$).

General Procedure for Diastereoselective Reductive Amination



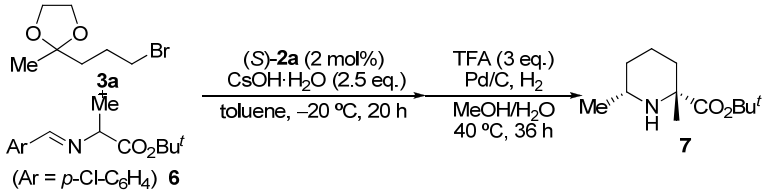
4a **5a**

To a mixture of **4a** (67 mg, 0.16 mmol), MeOH (3 mL) and H_2O (1.5 mL) was added TFA (36 μL, 0.48 mmol). After stirring for 1 h, to the mixture was added 10% Pd/C (34 mg) and the mixture was stirred at 40 ˚C for 24 h under hydrogen atmosphere. After filtration through celite, the filtrate was basified with aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and purified by chromatography on silica gel (dichloromethane/methanol = 50/1 as eluent) to afford **5a** (28 mg, 0.14 mmol 88% yield) as an oil. $[\alpha]_D^{21}$ = 7.1 (*c* 0.7, $CHCl_3$; 99% ee); ^{1}H NMR δ 0.98-1.08 (1H, m), 1.12 (3H, d, *J* = 6.4 Hz), 1.25-1.44 (2H, m), 1.46 (9H, s), 1.57-1.62 (1H, m), 1.77 (1H, br), 1.83-1.89 (1H, m), 1.94-1.99 (1H, m), 2.64 (1H, dqd, *J* = 11.0, 6.4, 2.7 Hz), 3.22 (1H, dd, *J* = 11.5, 2.7 Hz); ^{13}C NMR δ 22.8, 24.6, 28.0, 29.0, 33.8, 51.8, 59.8, 80.8, 172.6; IR (neat) 1153, 1368, 1730, 2357, 2930 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{11}H_{22}NO_2$: 200.1645 ($[M + H]^+$), Found: 200.1644 ($[M + H]^+$).

(2*R*,7*R*)-*tert*-Butyl 7-Methylazepane-2-carboxylate 5b

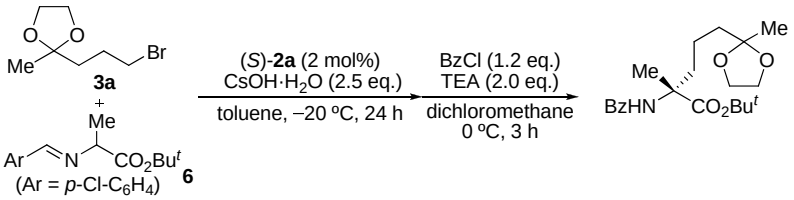
$[\alpha]_D^{22}$ = 15.0 (*c* 0.5, $CHCl_3$; 98% ee); ^{1}H NMR δ 1.12 (3H, d, *J* = 6.6 Hz), 1.26-1.34 (1H, m), 1.40-1.44 (1H, m), 1.46 (9H, s), 1.61-1.76 (5H, m), 1.88 (1H, br), 1.98-2.07 (1H, m), 2.71-2.79 (1H, m), 3.39 (1H, dd, *J* = 9.8, 5.1 Hz); ^{13}C NMR δ 23.9, 25.0, 25.3, 28.0, 33.6, 39.6, 54.5, 61.0, 80.9, 174.1; IR (neat) 1157, 1368, 1726, 2359, 2926 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{12}H_{24}NO_2$: 214.1802 ($[M + H]^+$), Found: 214.1799 ($[M + H]^+$).

Synthesis of (2*R*,6*R*)-*tert*-Butyl 2,6-Dimethylpiperidine-2-carboxylate 7



To a mixture of **8** (161 mg, 0.60 mmol), **3a** (254 mg, 6.0 mmol) and (*S*)-**2a** (9 mg, 0.012 mmol) in toluene (6 mL) was added CsOH (280 mg, 1.5 mmol) at –20 ˚C, and the reaction mixture was vigorously stirred for 20 h. After the consumption of the starting material, the mixture was concentrated under reduced pressure, and to the residue were added EtOH (3mL), H_2O (3mL), and TFA (245 μL, 3.3 mmol). After stirring for 1 h, to the mixture was added 10% Pd/C (80 mg) and the mixture was stirred at 40 ˚C for 36 h under hydrogen atmosphere. After filtration through celite, the result solution was basified with aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and purified by chromatography on silica gel (dichloromethane/methanol = 30/1 as eluent) to afford **7** (79 mg, 0.37 mmol, 61% yield) as an oil. $[\alpha]_D^{21}$ = 18.3 (*c* 1.0, $CHCl_3$; 96% ee); ^{1}H NMR δ 0.91-1.02 (1H, m), 1.07 (3H, d, *J* = 6.4 Hz), 1.35 (3H,
s), 1.46 (9H, s), 1.49-1.73 (6H, m), 2.86-2.91 (1H, m); ^{13}C NMR δ 20.1, 20.6, 22.9, 27.8, 32.8, 34.0, 45.5, 58.1, 80.4, 175.7; IR (neat) 1145, 1284, 1368, 1454, 1724, 2932 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{12}H_{24}NO_2$: 214.1802 ($[M + H]^+$), Found: 214.1794 ($[M + H]^+$).

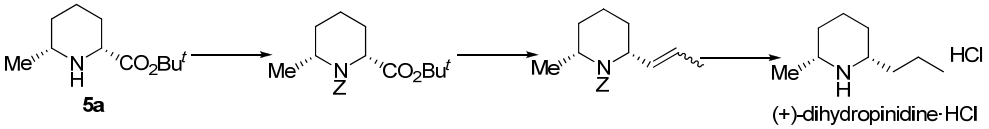
Determination of the Enantiomeric Excess of (*R*)-*tert*-Butyl 2-Amino-2-methyl-5-(2-methyl-1,3-dioxolan-2-yl)pentanoate



To a mixture of **6** (54 mg, 0.20 mmol), **3a** (418 mg, 2.0 mmol) and (*S*)-**2a** (3 mg, 0.004 mmol) in toluene (2 mL) was added CsOH (93 mg, 0.50 mmol) at –20 ˚C, and the reaction mixture was vigorously stirred for 24 h. After the consumption of the starting material, the mixture was concentrated under reduced pressure, and to the residue were added MeOH (1mL), H_2O (1mL), and TFA (53 μL, 0.7 mmol). After stirring for 0.5 h, the solution was basified with aqueous $NaHCO_3$, extracted with dichloromethane, dried over Na_2SO_4 and concentrated. To a solution of the residue and triethylamine (56 μL, 0.40 mmol) in dichloromethane (2 mL) was added benzoyl chloride (34 μL, 0.24 mmol) at 0 ˚C. After stirring for 3 h at 0 ˚C, the mixture was quenched with H_2O and extracted with dichloromethane. The organic layer was drid over Na_2SO_4 and purified by chromatography on silica gel (hexane/ethylacetate = 5/1 as eluent) to afford *N*-benzoylated

derivative of the title compound (41 mg, 0.11 mmol, 51% yield) as an oil. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 19.2 min (major) and 30.2 min (minor)). $[\alpha]_D^{19}$ = –12.6 (*c* 0.9, $CHCl_3$; 96% ee); ^{1}H NMR δ1.26 (3H, s), 1.38-1.48 (2H, m), 1.51 (9H, s), 1.55-1.69 (2H, m), 1.71 (3H, s), 1.78-1.86 (1H, m), 2.52-2.60 (1H, m), 3.83-3.92 (4H, m), 7.41-7.51 (3H, m), 7.78-7.81 (2H, m); ^{13}C NMR δ19.1, 23.4, 23.7, 27.9, 36.0, 38.8, 61.2, 64.5, 64.6, 82.3, 109.8, 126.8, 128.5, 131.3, 135.2, 166.0, 174.2; IR (neat) 1152, 1663, 1728, 2980, 3408 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{32}NO_5$: 378.2275 ($[M + H]^+$), Found: 378.2271 ($[M + H]^+$).

Asymmetric Synthesis of (+)-Dihydropinidine Hydrochloride



To a solution of **5a** (123 mg, 0.64 mmol) in dioxane (2 mL) and H_2O (2 mL) were added $NaHCO_3$ (59 mg, 0.70 mmol) and Benzyl Chloroformate (101 μL, 0.70 mmol) at 0 ˚C. The resulting solution was stitted at room temperature overnight. The reaction mixture was evaporated to remove dioxane, extracted with dichloromethane and washed with 1 N HCl and H_2O. The organic layer was dried over Na_2SO_4 and purified by chromatography on silica gel (hexane/ethyl acetate = 5/1 as eluent) to afford the (2*R*,6*R*)-1-benzyl 2-*tert*-butyl 6-methylpiperidine-1,2-dicarboxylate (193 mg, 91% yield). The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 22.1 min (minor) and 24.0 min (major)). $[\alpha]_D^{27}$ = 36.2 (*c* 1.0, $CHCl_3$, 99% ee); ^{1}H NMR δ1.18 (3H, d, *J* = 7.1 Hz), 1.41 (9H, s), 1.47-1.71 (5H, m), 2.28 (1H, d, *J* = 6.6 Hz), 4.38-4.44 (1H, m), 4.73 (1H, br), 5.16 (2H, s), 7.26-7.36 (5H, m); ^{13}C NMR δ15.5, 18.7, 25.8, 27.8, 30.0, 46.7, 53.3, 67.0, 81.2, 127.78, 127.81, 128.4, 136.8, 156.1, 171.6; IR (neat) 1074, 1153, 1406, 1740, 2357 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{19}H_{27}NNaO_4$: 356.1832 ($[M + Na]^+$), Found: 356.1827 ($[M + Na]^+$).

To a solution of (2*R*,6*R*)-1-benzyl 2-*tert*-butyl 6-methylpiperidine-1,2-dicarboxylate (181mg, 0.54 mmol) in toluene (9 mL) was added DIBAL-H (0.43 mL, 1.5 M in toluene) in a dropwise fashion at –78 °C. After being stirred at the same temperature for 2 h, ethyl acetate (1 mL) was added dropwise. After stirring for 30 min, a few drops of H_2O were then added. The resulting mixture was then warmed to room temperature and stirred vigorously for 1 h. The mixture was filtered through celite with dichloromethane as eluent. The filtrate was concentrated to afford crude aldehyde, which was used for the next reaction without further purification.

To a flask charged with $Ph_3PCH_2CH_3Br$ (301 mg, 0.81 mmol) in THF (8 mL) was added *n*-BuLi (0.50 mL, 1.6 M in hexane) at –78 °C. After being stirred for 1 h at room temperature, the crude aldehyde obtained above in THF (1 mL) was added at –78 °C. The resuling mixture was stirred overnight at room temperature. The reaction mixture was quenched with 1 N HCl, extracted with dichloromethane, dried over Na_2SO_4 and purified by chromatography on silica gel (hexane/ethyl acetate = 20/1 as eluent) to afford E·Z mixture of (2*R*,6*R*)-benzyl 2-methyl-6-(prop-1-enyl)piperidine-1-carboxylate (81 mg, 55% yield, E (98% ee)/Z (95%

ee) = 1/5). The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 40/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 15.5 min (Z: minor), 16.3 min (Z: major), 18.0 min (E: major), 19.5 min (E: minor)). ^{1}H NMR δ 1.17 (0.50H, d, J = 7.1 Hz), 1.24 (2.50H, d, J = 7.1 Hz), 1.45-1.50 (1H, m), 1.55-1.76 (8H, m), 4.40-4.44 (1H, m), 4.73 (0.17H, br), 5.03-5.07 (1H, m), 5.13 (1.67H, s), 5.14 (0.33H, d, J = 4.6 Hz), 5.44-5.48 (0.83H, m), 5.55-5.57 (0.17H, m), 5.72 (0.83H, ddq, J = 11.2, 9.5, 1.7 Hz), 7.28-7.36 (5H, m); ^{13}C NMR δ (E isomer / Z isomer) 14.3/14.5, 17.8/12.7, 20.5/20.9, 28.8/30.0, 30.2/30.4, 46.4/46.3, 51.4/47.6, 66.8/66.9, 125.9/125.2, 127.71/127.75, 127.73/127.8, 128.4/128.3, 132.5/131.7, 137.2/137.1, 155.8/155.7; IR (neat) 1072, 1307, 1692, 2340, 2936 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{17}H_{24}NO_2$: 274.1802 ([M + H]$^+$), Found: 274.1800 ([M + H]$^+$).

To a solution of (2*R*,6*R*)-benzyl 2-methyl-6-(prop-1-enyl)piperidine-1-carboxylate (45mg, 0.17 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The mixture was stirred under hydrogen atmosphere for 24 h at room temperature. The resulting mixture was filtered through celite with MeOH as eluent. To the filtrate was added HCl (3 mL, 1 M in MeOH) and the whole mixture was concentrated. The residue was recrystalized from ethyl acetate to yield (+)-dihydropinidine hydrochloride (20 mg, 67% yield): $[\alpha]_D^{26}$ = 12.0 (*c* 0.2, EtOH); ^{1}H NMR (CD_3OD) δ 0.97 (3H, t, J = 4.0 Hz), 1.32-1.66 (10H, m), 1.87-1.93 (2H, m), 2.00 (1H, d, J = 12.0 Hz), 3.06 (1H, br), 3.18 (1H, br); ^{13}C NMR δ 14.2, 19.5, 19.6, 23.5, 29.1, 31.7, 37.0, 55.0, 58.7; IR (neat) 1129, 1372, 1461, 2958 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_9H_{20}N$: 142.1590 ([M + H]$^+$), Found: 142.1596 ([M + H]$^+$).

Synthesis of 6-(2-Bromoethyl)-1,4-dioxaspiro[4.4]nonane 8b

The title compound was prepared by a similar method described in literature.[4]
^{1}H NMR δ 1.31-1.36 (1H, m), 1.63-1.84 (5H, m), 1.91-1.95 (1H, m), 2.05-2.12 (2H, m), 3.35-3.40 (1H, m), 3.42-3.52 (1H, m), 3.87-3.95 (4H, m); ^{13}C NMR δ 20.6, 28.9, 32.6, 32.8, 35.5, 44.6, 64.4, 64.5, 117.8; IR (neat) 1026, 1139, 1206, 1260, 1315, 1738, 2876, 2957 cm^{-1}.

Synthesis of 6-(2-Bromoethyl)-1,4-dioxaspiro[4.5]decane 8c

The title compound was prepared by a similar method described in literature.[4]
^{1}H NMR δ 1.25-1.39 (3H, m), 1.43-1.49 (1H, m), 1.59-1.72 (3H, m), 1.76-1.81 (3H, m), 2.15-2.28 (1H, m), 3.38-3.45 (1H, m), 3.49-3.55 (1H, m), 3.91-3.99 (4H, m); ^{13}C NMR δ 23.6, 24.5, 29.1, 32.3, 32.9, 34.5, 43.2, 64.5, 64.7, 110.4; IR (neat) 1117, 1221, 1524, 1713, 2978, 3335 cm^{-1}.

Diastereo-mixture of (2*R*)-*tert*-Butyl 2-(Diphenylmethyleneamino)-5-(2-methyl-1,3-dioxolan-2-yl) hexanoate 9a

(2*R*,5*R*)/(2*R*,5*S*) = 1/1. ^{1}H NMR δ 0.91 (1.5H, d, J = 6.8 Hz), 0.93 (1.5H, d, J = 7.1 Hz), 0.99-1.11 (1H, m), 1.19 (3H, s), 1.44 (4.5H, s), 1.45 (4.5H, s), 1.51-1.65 (2H, m), 1.69-1.88 (1H, m), 1.97-2.10 (1H, m), 3.79-3.93 (5H, m), 7.16-7.19 (2H, m), 7.3-7.46 (6H, m), 7.63-7.65 (2H, m); ^{13}C NMR δ 14.5, 14.6, 20.2, 20.3, 28.06, 28.12, 31.4, 31.8, 32.0, 32.1, 41.3, 41.4, 47.5, 47.6, 48.8, 48.9, 64.49, 65.54, 66.3, 66.6, 80.76, 80.81, 112.29, 112.34, 127.89, 127.90, 127.94, 128.35, 128.37, 128.43, 128.77, 128.82, 129.9, 130.1, 136.78, 136.82, 139.80, 139.83, 169.7, 169.9, 171.5, 171.6; IR (neat) 1150, 1368, 1732, 2976 cm^{-1}; HRMS

(ESI-TOF) Calcd. for $C_{27}H_{36}NO_4$: 438.2639 ($[M + H]^+$), Found: 438.2622 ($[M + H]^+$).

Diastereo-mixture of (2*R*,6*R*)-*tert*-Butyl 5,6-Dimethylpiperidine-2-carboxylate 12a

(2*R*,5*R*,6*R*)/(2*R*,5*S*,6*R*) = 2.5/1. ^{1}H NMR (toluene-d8, 80 ˚C) δ 0.85 (0.86H, d, *J* = 6.1 Hz), 0.89 (2.14H, d, *J* = 7.1 Hz), 1.03 (2.14H, d, *J* = 6.6 Hz), 1.11 (0.86H, d, *J* = 6.4 Hz), 1.46 (9H, s), 1.47-1.71 (5.42H, m), 1.78-1.81 (0.29H, m), 1.95-2.00 (0.29H, m), 2.24 (0.29H, dq, *J* = 8.8, 6.4 Hz), 2.85 (0.71H, dq, *J* = 6.6, 2.9 Hz), 3.21-3.26 (1H, m); ^{13}C NMR δ (2*R*,5*R*,6*R*/2*R*,5*S*,6*R*) 10.9/18.4, 20.0/20.3, 23.6/29.9, 28.01/28.00, 31.5/32.0, 33.8/37.7, 57.9/53.6, 60.2/59.7, 80.7/80.6, 172.9/172.6; IR (neat) 1155, 1233, 1368, 1730, 2930 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{12}H_{24}NO_2$: 214.1802 ($[M + H]^+$), Found: 214.1807 ($[M + H]^+$).

Determination of the Enantiomeric Excess of 12a

The enantiomeric excess of 12a was determined by HPLC analysis after conversion to the corresponding benzamide. (2*R*,5*R*,6*R*)/(2*R*,5*S*,6*R*) = 2.5 (99% ee)/1(99% ee). Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: (2*R*,5*S*,6*R*: 9.8 min (minor), 10.9 min (major)), (2*R*,5*R*,6*R*: 12.1 min (major), 20.7 min (minor)). ^{1}H NMR (toluene-d8, 80 ˚C) δ 0.38 (2.14H, d, *J* = 6.6 Hz), 0.61 (0.86H, d, *J* = 7.1 Hz), 0.77-0.79 (0.29H, m), 0.81 (2.14H, d, *J* = 7.1 Hz), 0.93 (0.71H, m), 0.95 (0.86H, d, *J* = 7.6 Hz), 1.09-1.49 (11H, m), 1.55-1.64 (0.29H, m), 1.74-1.80 (0.29H, m), 1.85-1.88 (0.71H, m), 1.96 (0.71H, d, *J* = 13.2 Hz), 3.76-4.69 (2H, m), 6.82-6.90 (3H, m), 7.13-7.19 (2H, m); ^{13}C NMR δ (2*R*,5*R*,6*R*/2*R*,5*S*,6*R*) 15.6/23.1, 21.5/21.4, 27.3/26.1, 30.9/29.3, 36.17/36.15, 37.8/37.7, 56.1/55.1, 56.9/55.4, 84.0/83.8, 130.0/129.9, 131.2/131.9, 140.4/140.7, 141.4/141.5, 174.1/174.4, 174.8/175.5; IR (neat) 1155, 1412, 1641, 1726, 2361, 2976 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{19}H_{28}NO_3$: 318.2064 ($[M + H]^+$), Found: 318.2048 ($[M + H]^+$).

Diastereo-mixture of (2*R*)-*tert*-Butyl 2-(Diphenylmethyleneamino)-4-(1,4-dioxaspiro[4.4]nonan-6-yl) butanoate 9b

$[\alpha]_D^{24}$ = 91.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.21-1.42 (3H, m), 1.44 (9H, s), 1.57-1.74 (4H, m), 1.81-1.94 (4H, m), 3.81-3.91 (5H, m), 7.17-7.19 (2H, m), 7.29-7.44 (6H, m), 7.63-7.65 (2H, m); ^{13}C NMR δ20.6, 25.4, 28.1, 29.4, 31.6, 32.5, 35.8, 46.0, 64.4, 64.6, 66.3, 80.7, 118.2, 127.9, 128.3, 128.4, 128.8, 130.1, 136.8, 139.8, 169.8, 171.6; IR (neat) 1030, 1148, 1732, 2953 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{28}H_{36}NO_4$: 450.2639 ($[M + H]^+$), Found: 450.2619 ($[M + H]^+$).

Determination of the Enantiomeric Excess of 12b

The enantiomeric excess of 12b was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 16.4 min (major) and 22.3 min (minor). $[\alpha]_D^{20}$ = 41.6 (*c* 0.7, $CHCl_3$; 99% ee); ^{1}H NMR (toluene-d8, 80 ˚C) δ 0.92-1.06 (4H, m), 1.12 (9H, s), 1.27 (3H, br), 1.51-1.57 (1H, m), 1.65-1.73 (2H, m), 1.84-1.88 (1H, m), 4.04 (1H, br), 4.68 (1H, br), 6.86-6.89 (3H, m), 7.13-7.15 (2H, m); ^{13}C NMR δ24.4, 27.7, 28.1, 30.9, 31.8, 33.1, 39.6, 57.2, 60.2, 83.8, 129.9, 131.2, 140.4, 141.6, 174.4, 174.6; IR (neat) 1153, 1368, 1414, 1603, 1726, 2972 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{20}H_{28}NO_3$: 330.2064 ($[M + H]^+$), Found: 330.2069 ([M +

$H]^+$).

Diastereo-mixture of (2*R*)-*tert*-Butyl 2-(Diphenylmethyleneamino)-4-(1,4-dioxaspiro[4.5]decan-6-yl) butanoate 9c

(2*R*,4*R*)/(2*R*,4*S*) = 1/1. $[\alpha]_D^{22}$ = 87.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.18-1.34 (4H, m), 1.41-1.44 (2H, m), 1.44 (4.5H, s), 1.45 (4.5H, s), 1.47-1.50 (1H, m), 1.59-1.62 (2H, m), 1.65-1.81 (3H, m), 1.97-2.00 (1H, m), 3.81-3.93 (5H, m), 7.16-7.20 (2H, m), 7.29-7.44 (6H, m), 7.63-7.66 (2H, m); ^{13}C NMR δ 21.8, 23.8, 23.9, 24.49, 24.52, 24.6, 24.7, 28.1, 29.0, 29.2, 31.8, 31.9, 34.8, 34.9, 44.39, 44.43, 64.61, 64.64, 64.7, 64.8, 66.3, 66.7, 80.7, 82.0, 110.80, 110.83, 127.89, 127.91, 127.93, 128.0, 128.26, 128.28, 128.36, 128.42, 128.75, 128.77, 130.01, 130.03, 136.8, 136.9, 139.8, 139.9, 169.5, 169.8, 171.6, 171.7; IR (neat) 1150, 1368, 1732, 2932 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{29}H_{38}NO_4$: 464.2795 ($[M + H]^+$), Found: 464.2785 ($[M + H]^+$).

Determination of the Enantiomeric Excess of 12c

The enantiomeric excess of 12c was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 13.6 min (major) and 16.5 min (minor). $[\alpha]_D^{19}$ = 67.1 (*c* 1.0, $CHCl_3$; 99% ee); ^{1}H NMR (toluene-d8, 80 ˚C) δ 1.23-1.33 (4H, m), 1.51 (9H, s), 1.54-1.67 (2H, m), 1.73-1.88 (3H, m), 2.01-2.12 (2H, m), 2.27-2.28 (1H, m), 2.46 (1H, d, *J* = 12.4 Hz), 4.45 (1H, br), 5.05 (1H, br), 7.15-7.17 (1H, m), 7.23-7.30 (3H, m), 7.57-7.59 (1H, m); ^{13}C NMR δ 24.7, 29.3, 30.1, 30.9, 34.9, 35.8, 38.0, 39.3, 55.9, 58.0, 83.9, 129.9, 131.2, 140.4, 141.4, 174.1, 174.2; IR (neat) 1153, 1325, 1368, 1411, 1638, 1724, 2930 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{29}NNaO_3$: 366.2040 ($[M + H]^+$), Found: 366.2033 ($[M + H]^+$).

(*R*,*Z*)-*tert*-Butyl 2-(Diphenylmethyleneamino)-6,6-dimethoxy-4-methylhex-4-enoate 14a

Daicel Chiralpak OD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 17.2 min (minor) and 23.4 min (major). $[\alpha]_D^{19}$ = 82.2 (*c* 0.9, $CHCl_3$; 92% ee); ^{1}H NMR δ 1.45 (9H, s), 1.52 (3H, d, *J* = 1.2 Hz), 2.56-2.68 (2H, m), 3.15 (3H, s), 3.26 (3H, s), 4.07 (1H, dd, *J* = 8.3, 5.1 Hz), 4.95 (1H, d, *J* = 6.4 Hz), 5.30 (1H, dd, *J* = 6.4, 0.8 Hz), 7.14-7.18 (2H, m), 7.28-7.46 (6H, m), 7.62-7.65 (2H, m); ^{13}C NMR δ 17.1, 28.0, 43.4, 51.5, 52.6, 64.7, 81.2, 100.1, 124.9, 127.91, 127.94, 128.3, 128.5, 128.8, 130.1, 136.4, 138.1, 139.6, 170.0, 171.0; IR (neat) 1053, 1150, 1734, 2367 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{26}H_{34}NO_4$: 424.2482 ($[M + H]^+$), Found: 424.2465 ($[M + H]^+$).

(2*R*,4*S*)-*tert*-Butyl 4-Methylpiperidine-2-carboxylate 15a

Daicel Chiralpak AD-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, λ = 220 nm, retention time: 19.2 min (major) and 42.7 min (minor). $[\alpha]_D^{21}$ = 8.8 (*c* 0.4, $CHCl_3$; 92% ee); ^{1}H NMR δ 0.94 (3H, d, *J* = 6.4 Hz), 0.95-1.05 (2H, m), 1.46 (9H, s), 1.48-1.63 (2H, m), 1.93-1.99 (1H, m), 2.60 (1H, td, *J* = 12.5, 2.7 Hz), 3.11-3.16 (1H, m), 3.18 (1H, dd, *J* = 11.7, 2.7 Hz); ^{13}C NMR δ 22.4, 28.0, 31.3, 34.7, 38.1, 45.8, 59.6, 80.8, 172.6; IR (neat) 1161, 1269, 1368, 1732, 2924, 2949 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{11}H_{22}NO_2$: 200.1645 ($[M + H]^+$), Found: 200.1641 ($[M + H]^+$).

Synthesis of (*Z*)-2-(3-(Benzyloxy)-2-(bromomethyl)prop-1-enyl)-1,3-dioxolane 13b

2-(3-Bromo-2-(bromomethyl)prop-1-enyl)-1,3-dioxolane was prepared by a similar method described in literature.[11, 12] ^{1}H NMR δ 3.89-3.97 (2H, m), 3.99- 4.07 (2H, m), 4.13 (2H, s), 4.27 (2H, d, *J* = 1.6 Hz), 5.55 (1H, dd, *J* = 6.0, 1.6 Hz), 5.77 (1H, dd, *J* = 6.0, 0.8 Hz); ^{13}C NMR δ 26.4, 34.3, 65.1, 98.9, 130.4, 138.7; IR (neat) 939, 1051, 1117, 1207, 1396, 2887 cm^{-1}.

The title compound was prepared by a similar method described in literature[13] starting from 2-(3-bromo-2-(bromomethyl)prop-1-enyl)-1,3-dioxolane. ^{1}H NMR δ 3.82-3.93 (2H, m), 3.95-4.05 (2H, m), 4.08 (2H, s), 4.28 (2H, s), 4.52 (2H, s), 5.50 (1H, d, *J* = 6.8 Hz), 5.78 (1H, d, *J* = 6.8 Hz), 7.27-7.36 (5H, m); ^{13}C NMR δ 34.1, 64.9, 65.0, 72.5, 98.8, 127.7, 127.8, 128.4, 129.6, 137.8, 139.9; IR (neat) 1055, 1246, 1396, 1703, 2884 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{14}H_{17}BrNaO_3$: 335.0253 ([M + Na]$^+$), Found: 335.0247 ([M + Na]$^+$)

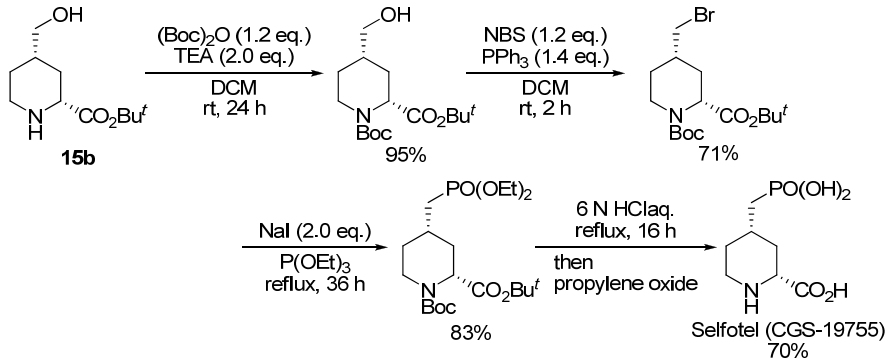
(*R,E*)-*tert*-Butyl 4-(Benzyloxymethyl)-5-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)pent-4-enoate 14b

Daicel Chiralpak AD-H, Hexane/EtOH = 50/1, flow late 0.5 mL/min, λ = 254nm, retention time: 19.6 min (minor) and 20.5 min (major). $[\alpha]_D^{21}$ = 62.6 (*c* 0.4, $CHCl_3$; 97% ee); ^{1}H NMR δ 1.44 (9H, s), 2.67 (1H, dd, *J* = 14.0, 8.8), 2.87 (1H, dd, *J* = 14.0, 4.4 Hz), 3.75-3.83 (4H, m), 3.90-3.92 (1H, m), 3.99 (1H, d, *J* = 12.4), 4.13 (1H, dd, *J* = 8.8, 4.4 Hz), 4.29 (2H, dd, *J* = 31.2, 11.6 Hz), 5.48 (2H, s), 7.16-7.19 (2H, m), 7.22-7.38 (11H, m), 7.60-7.64 (2H, m); ^{13}C NMR δ 28.0, 38.3, 64.7, 64.8, 64.9, 67.1, 71.8, 81.1, 99.2, 127.45, 127.48, 127.6, 127.9, 128.1, 128.3, 128.5, 128.6, 128.9, 130.0, 136.5, 138.2, 139.8, 139.9, 170.3, 170.8; IR (neat) 959, 1069, 1148, 1730, 2884 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{33}H_{38}NO_5$: 528.2745 ([M + H]$^+$), Found: 528.2752 ([M + H]$^+$).

(2*R*,4*S*)-*tert*-Butyl 4-(Hydroxymethyl)piperidine-2-carboxylate 15b

$[\alpha]_D^{26}$ = 3.1 (c 1.4, $CHCl_3$); ^{1}H NMR δ 1.08-1.21 (2H, m), 1.25 (1H, br), 1.46 (9H s), 1.62-1.72 (2H, m), 2.08 (1H, d, *J* = 14.4), 2.32 (1H, br), 2.67 (1H, td, *J* = 12.4, 2.8), 3.23-3.27 (2H, m), 3.48-3.55 (2H, m); ^{13}C NMR δ 28.0, 28.8, 32.4, 38.9, 45.3, 59.0, 67.8, 81.3, 172.1; IR (neat) 1045, 1732, 1254, 1732, 2930 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{11}H_{22}NO_3$: 216.1594 ([M + H]$^+$), Found: 216.1586 ([M + H]$^+$).

Synthesis of Selfotel (CGS-19755)



Title compound was prepared by a similar method described in literature[10] starting from **15b** in 39%

overall yield. Spectrum data of obtained compound corresponded with literature.[10]

(2*R*,4*S*)-Di-*tert*-butyl 4-(Hydroxymethyl)piperidine-1,2-dicarboxylate

95% yield. $[\alpha]_D^{26}$ = 39.4 (c 1.5, $CHCl_3$); ^{1}H NMR δ 1.45 (9H, s), 1.47 (9H, s), 1.70-1.80 (1H, m), 1.91-1.97 (2H, m), 2.03-2.08 (1H, m), 2.26 (1H, br), 3.08 (1H, br), 3.46 (1H, dd, *J* = 11.2, 7.6 Hz), 3.54 (1H, dd, *J* = 11.2, 6.8 Hz), 3.76 (1H, br), 4.41 (1H, br); ^{13}C NMR δ 25.2, 26.7, 27.8, 28.0, 28.3, 53.78, 53.81, 63.6, 79.8, 81.5, 155.5, 172.4; IR (neat) 1152, 1366, 1697, 1734, 2976, 3435 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{16}H_{29}NNaO_5$: 338.1938 ($[M + Na]^+$), Found: 338.1923 ($[M + Na]^+$).

(2*R*,4*S*)-*tert*-Butyl 4-(Bromomethyl)piperidine-2-carboxylate

71% yield. $[\alpha]_D^{23}$ = 7.8 (c 0.9, $CHCl_3$); ^{1}H NMR δ 1.45 (9H, s), 1.48 (9H, s), 1.66-1.68 (1H, m), 1.79-1.86 (1H, m), 2.03-2.10 (3H, m), 3.17 (1H, br), 3.33-3.41 (2H, m), 3.75 (1H, m), 4.35-4.38 (1H, m); ^{13}C NMR δ 27.5, 27.9, 28.0, 28.3, 29.3, 33.9, 36.0, 53.7, 80.0, 81.5, 155.5, 171.8; IR (neat) 1150, 1366, 1697, 1732, 2976 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{16}H_{28}BrNNaO_4$: 400.1094 ($[M + Na]^+$), Found: 400.1088 ($[M + Na]^+$).

(2*R*,4*S*)-Di-*tert*-butyl 4-((Diethoxyphosphoryl)methyl)piperidine-1,2-dicarboxylate

83% yield. $[\alpha]_D^{25}$ = 27.0 (c 0.4, $CHCl_3$); ^{1}H NMR δ 1.30 (6H, m), 1.44 (9H, s), 1.46 (9H, s), 1.63- 1.84 (4H, m), 1.95-2.08 (2H, m), 2.16-2.24 (1H, m), 3.21 (1H, br), 3.72 (1H, br), 4.04-4.12 (4H, m), 4.35 (1H, dd, *J* = 6.8, 5.2 Hz); ^{13}C NMR δ 14.1, 16.4 (d, *J* = 2.7 Hz), 16.5 (d, *J* = 2.7 Hz), 27.9, 28.27, 28.31, 29.1 (d, *J* = 5.8 Hz), 29.7, 32.1 (d, *J* = 13.2 Hz), 53.8, 61.4 (d, *J* = 6.6 Hz), 61.5 (d, *J* = 6.6 Hz), 79.9, 81.4, 155.7, 172.0; IR (neat) 1030, 1163, 1248, 1699, 2359, 2926, 2978 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{20}H_{38}NNaO_7P$: 458.2278 ($[M + Na]^+$), Found: 458.2285 ($[M + Na]^+$).

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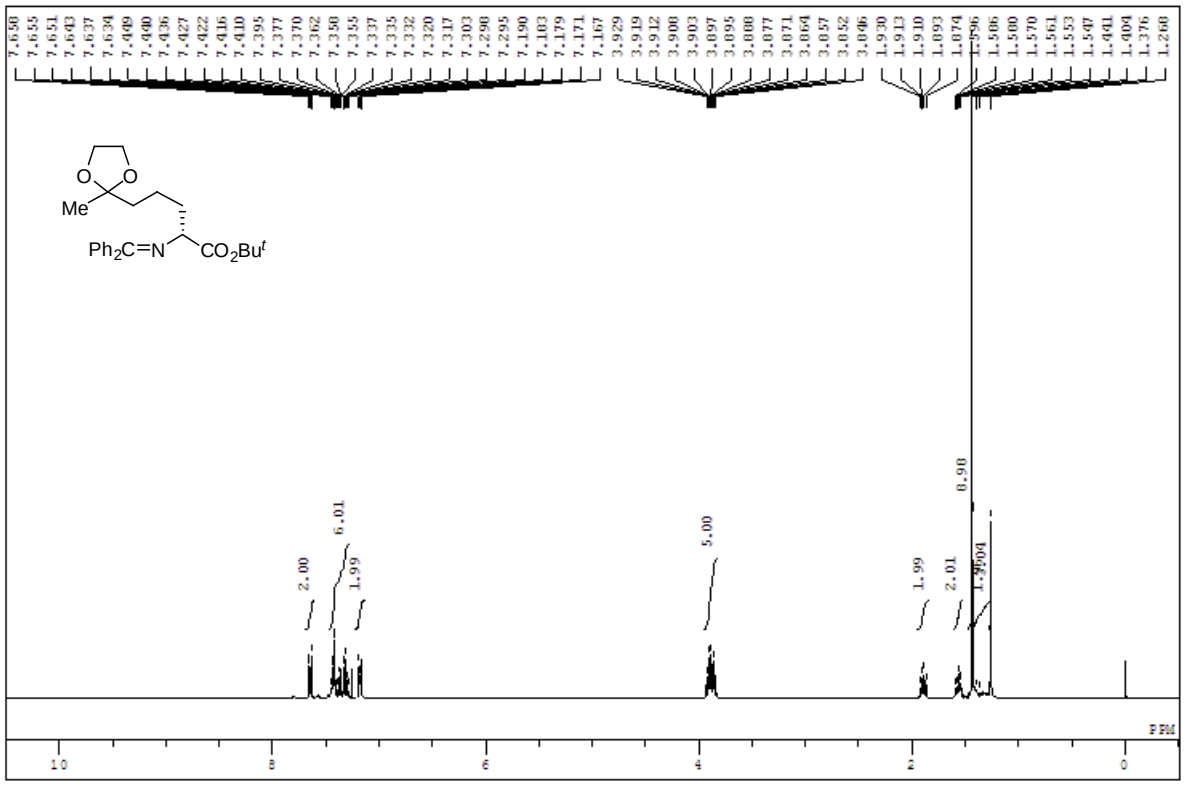
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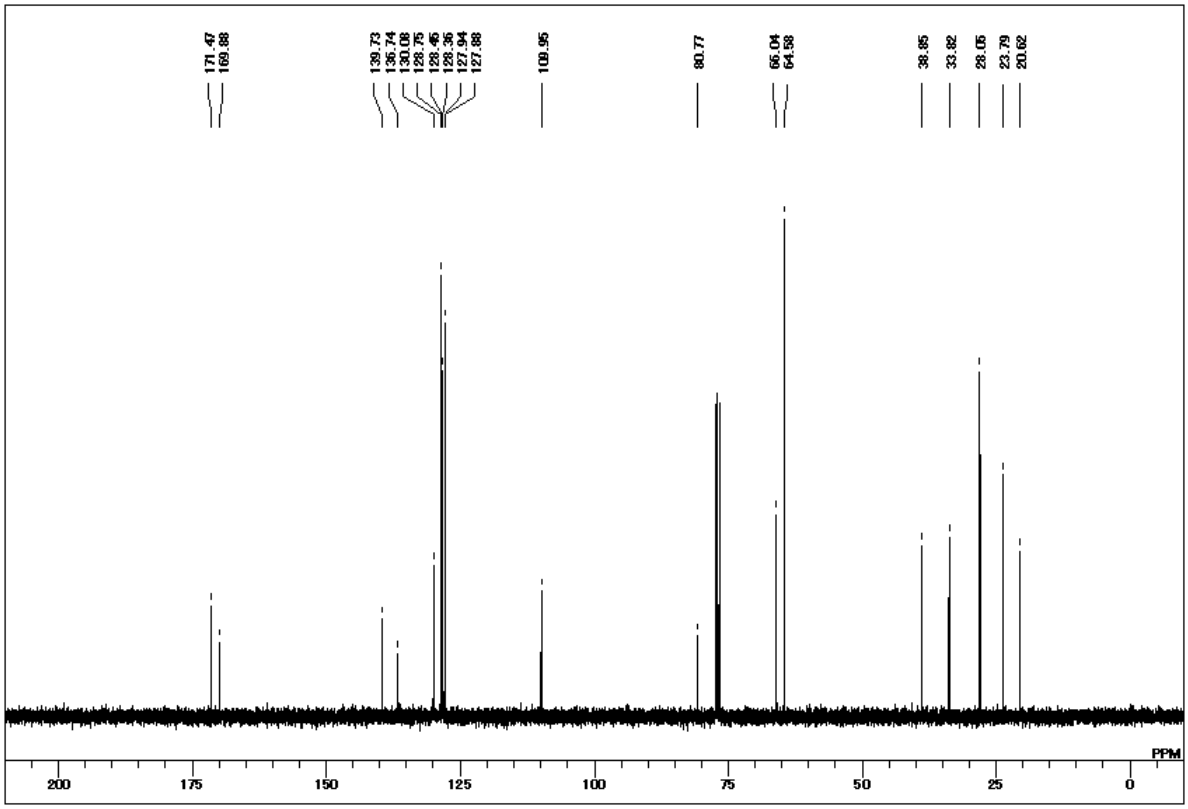
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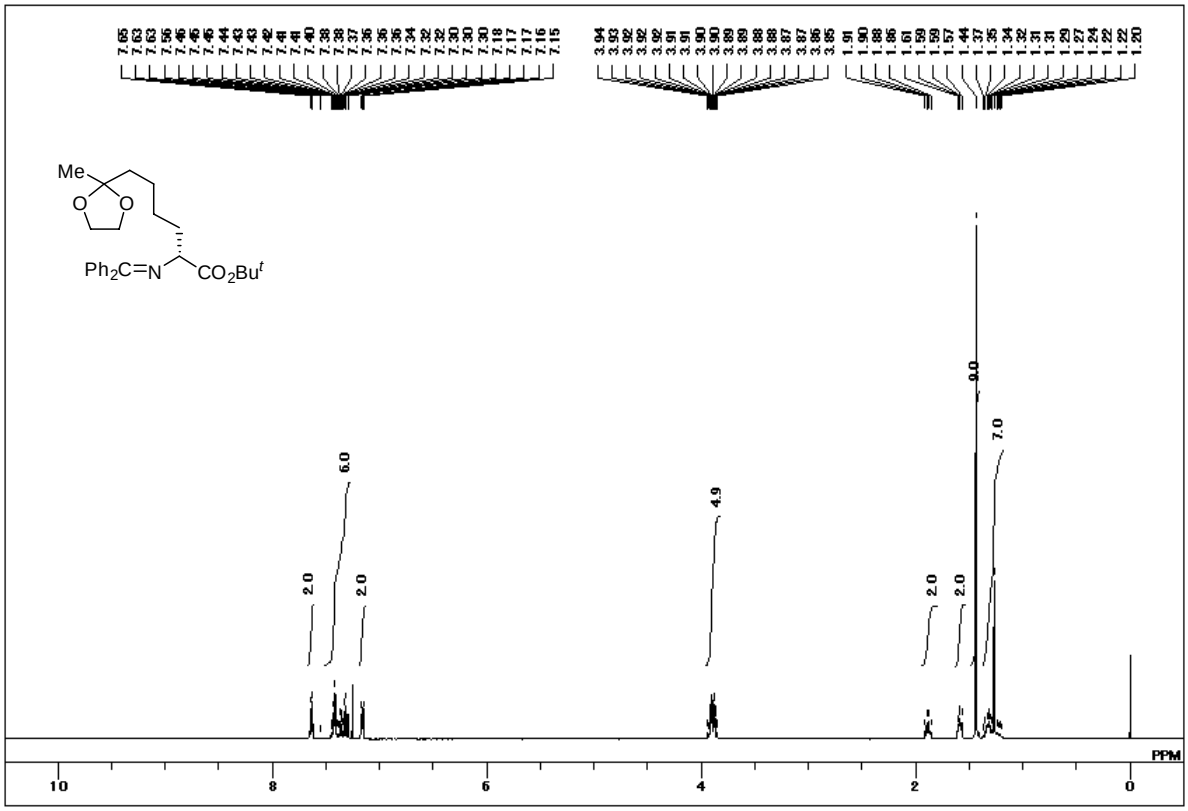
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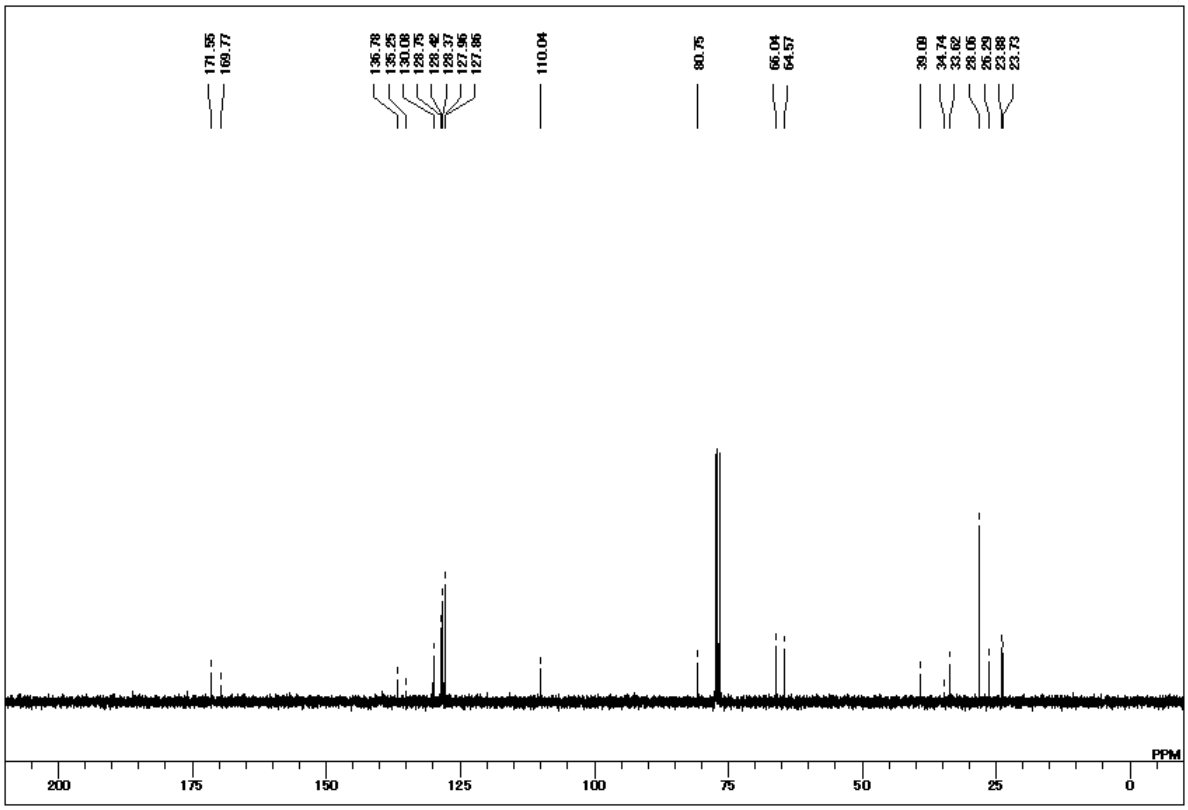
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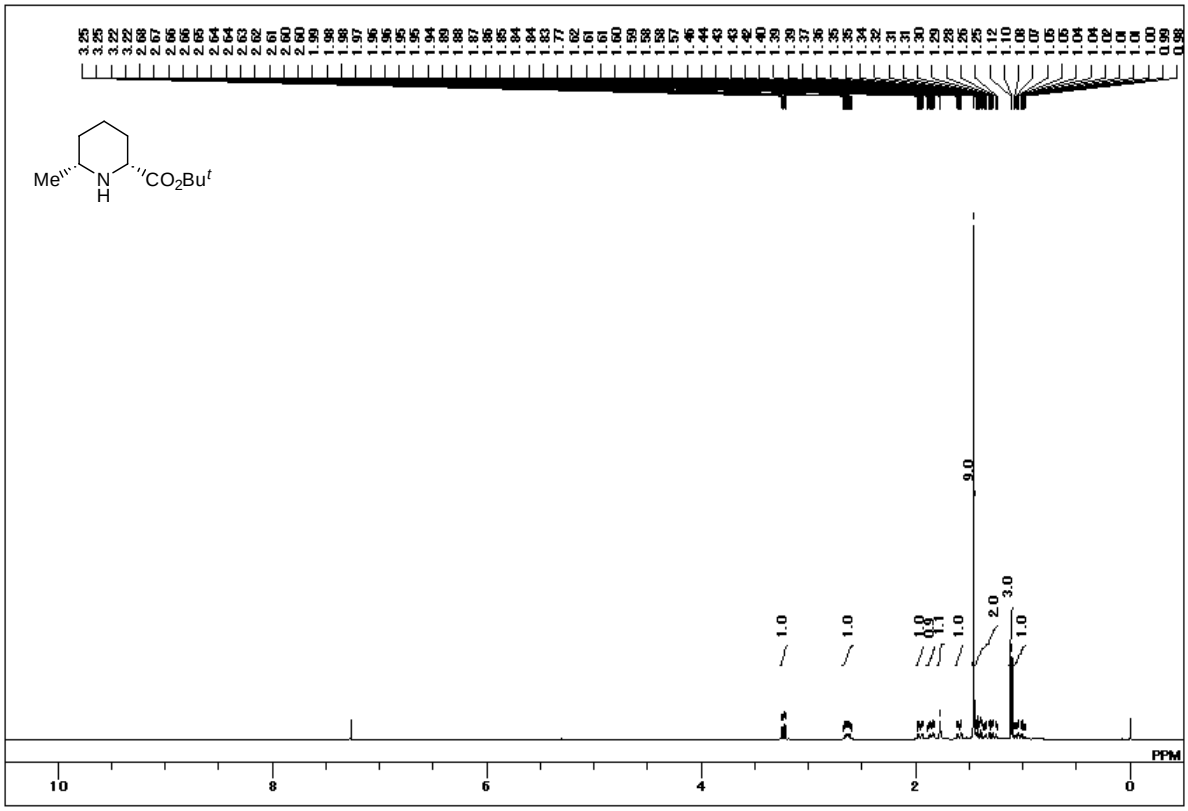
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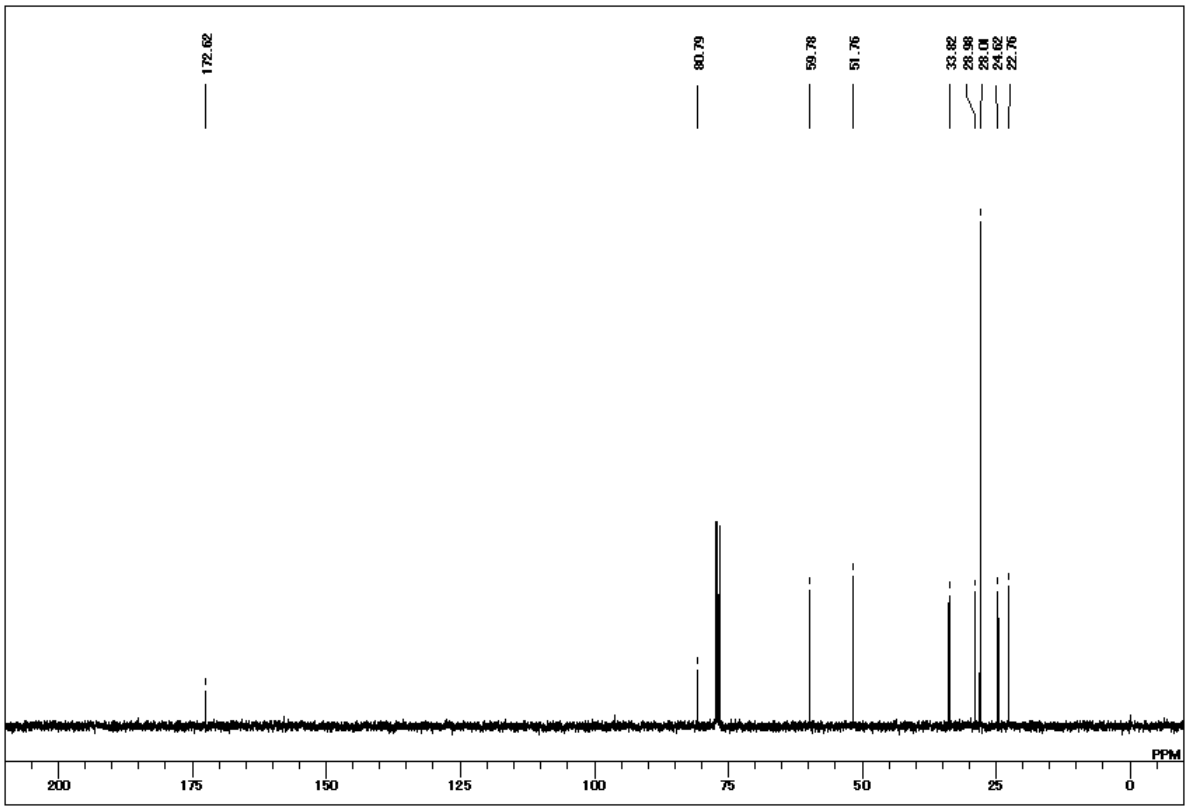
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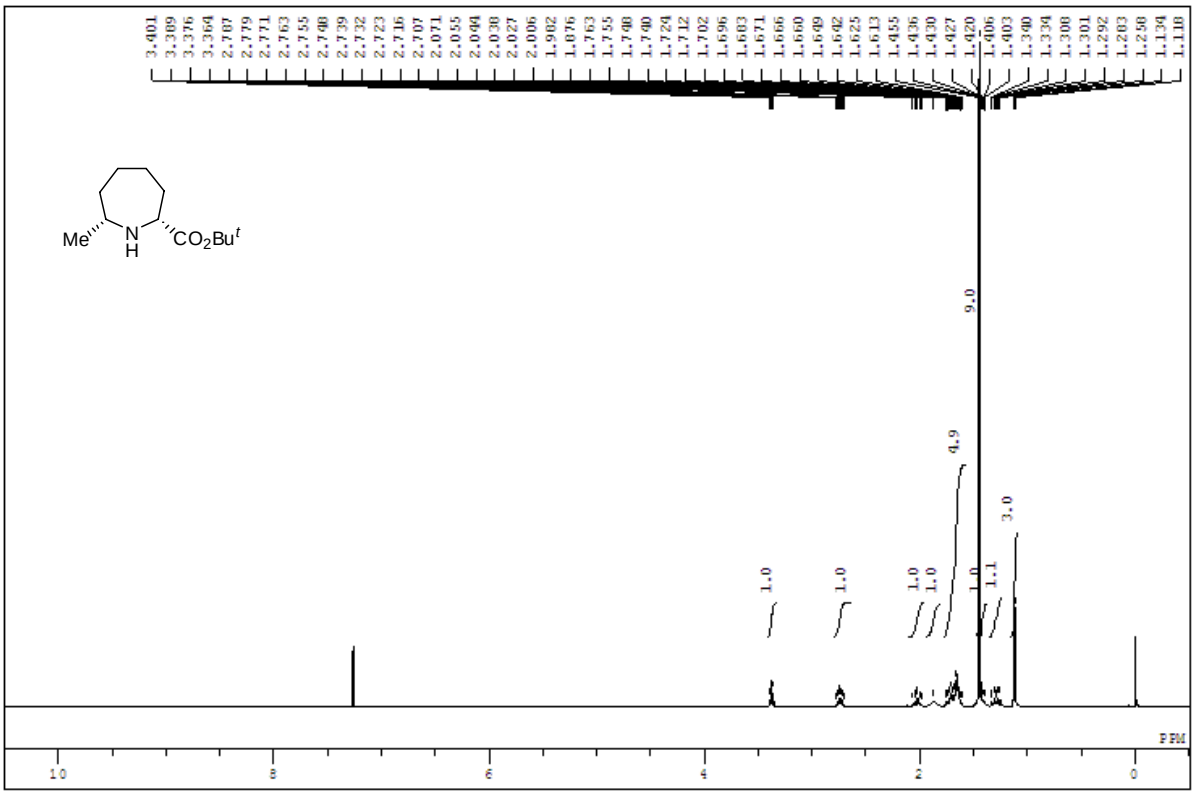
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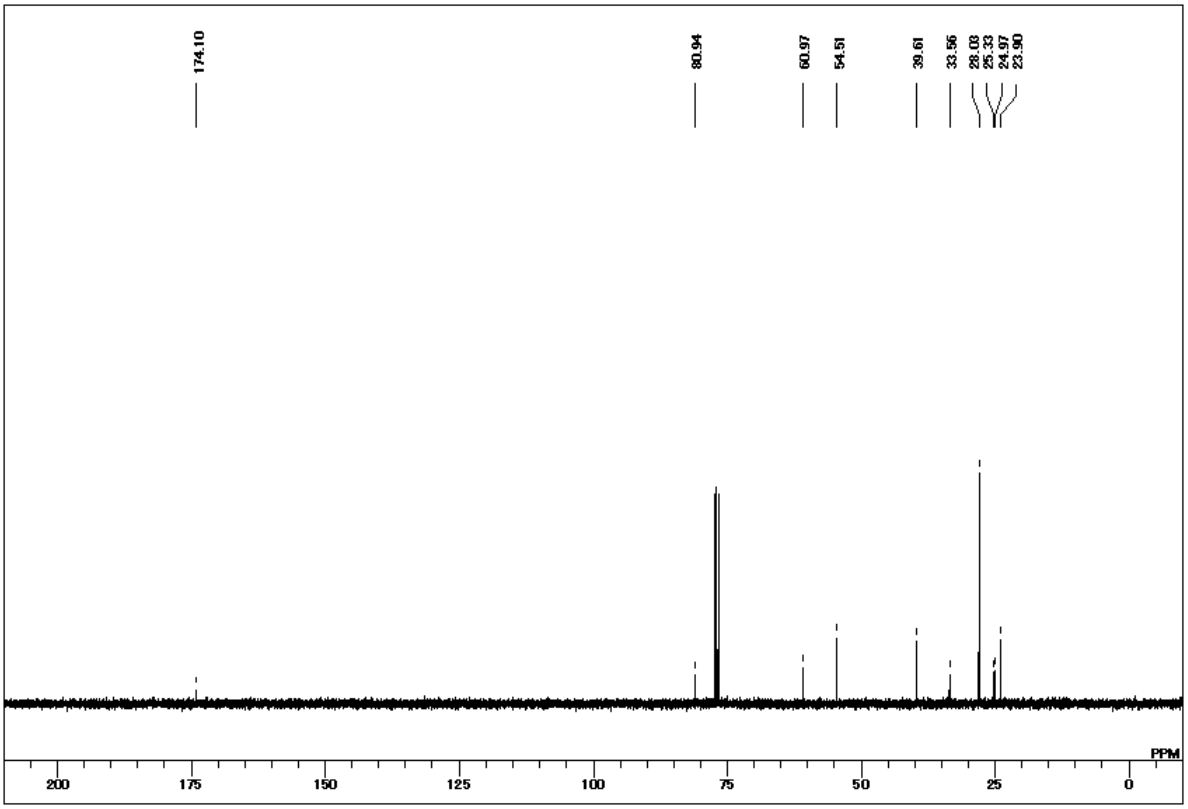
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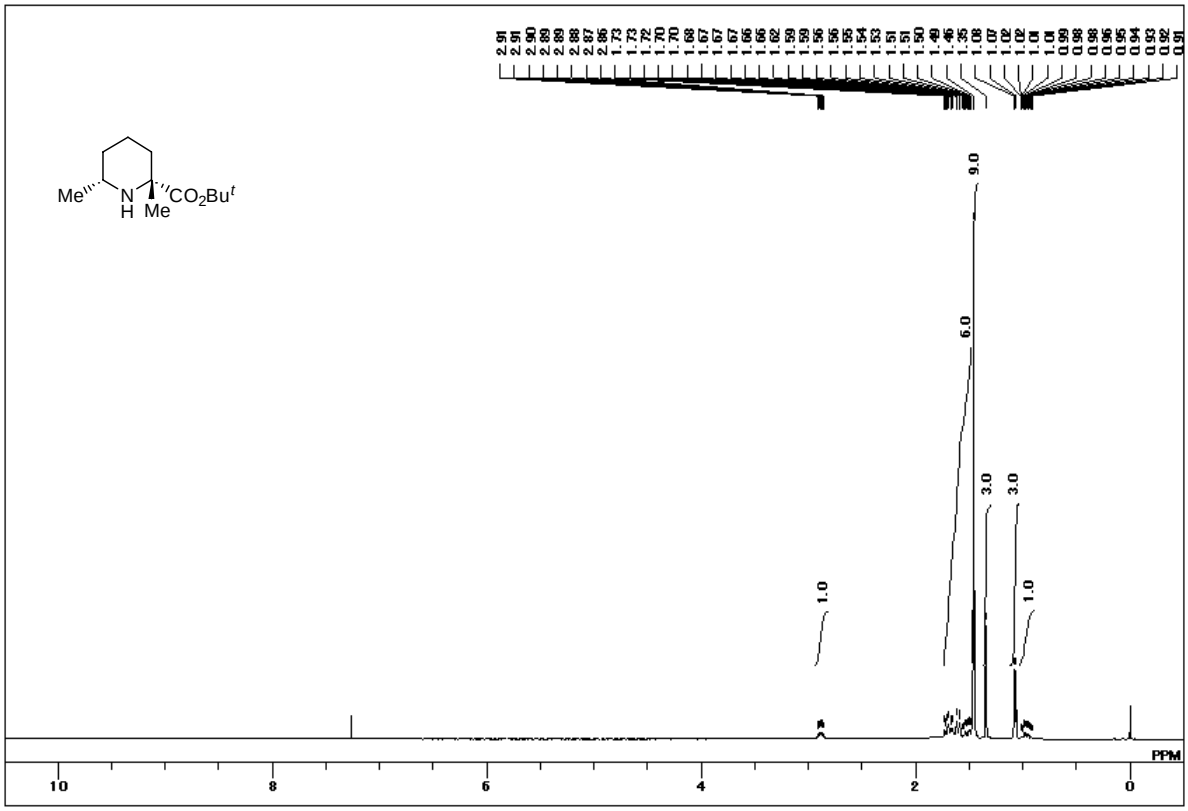
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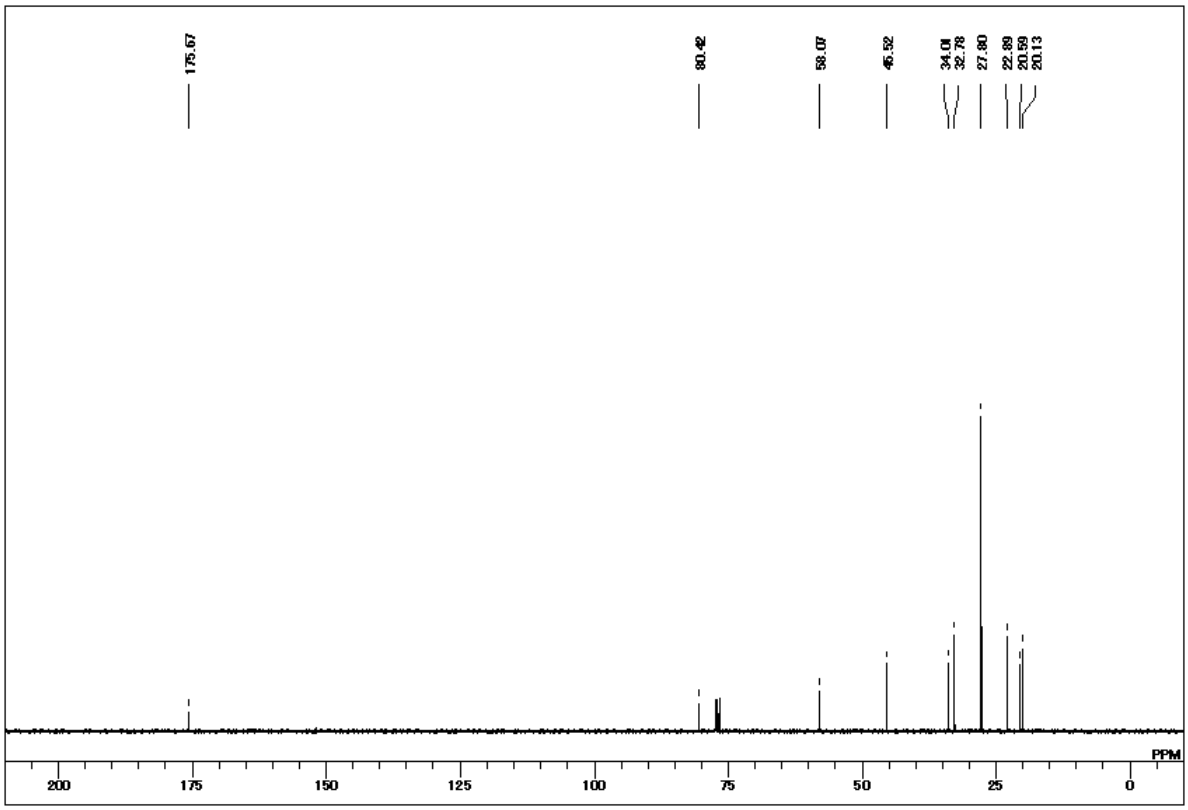
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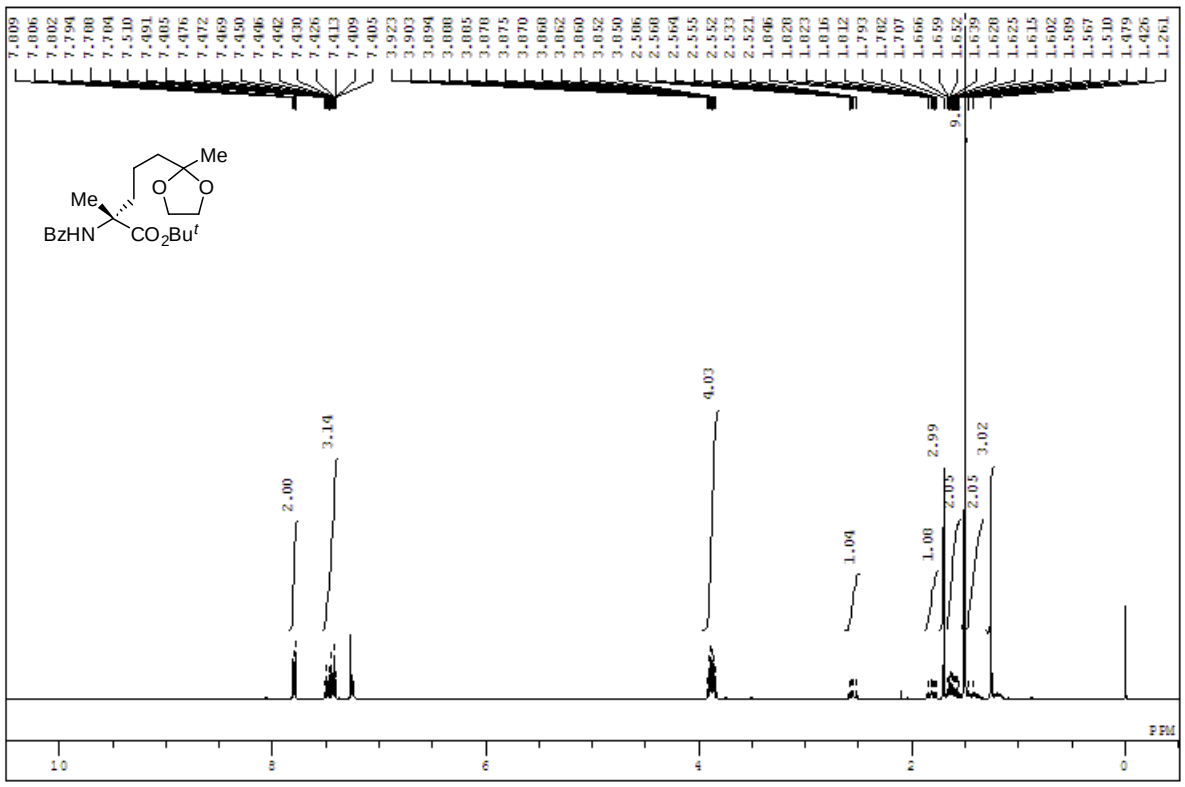
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O
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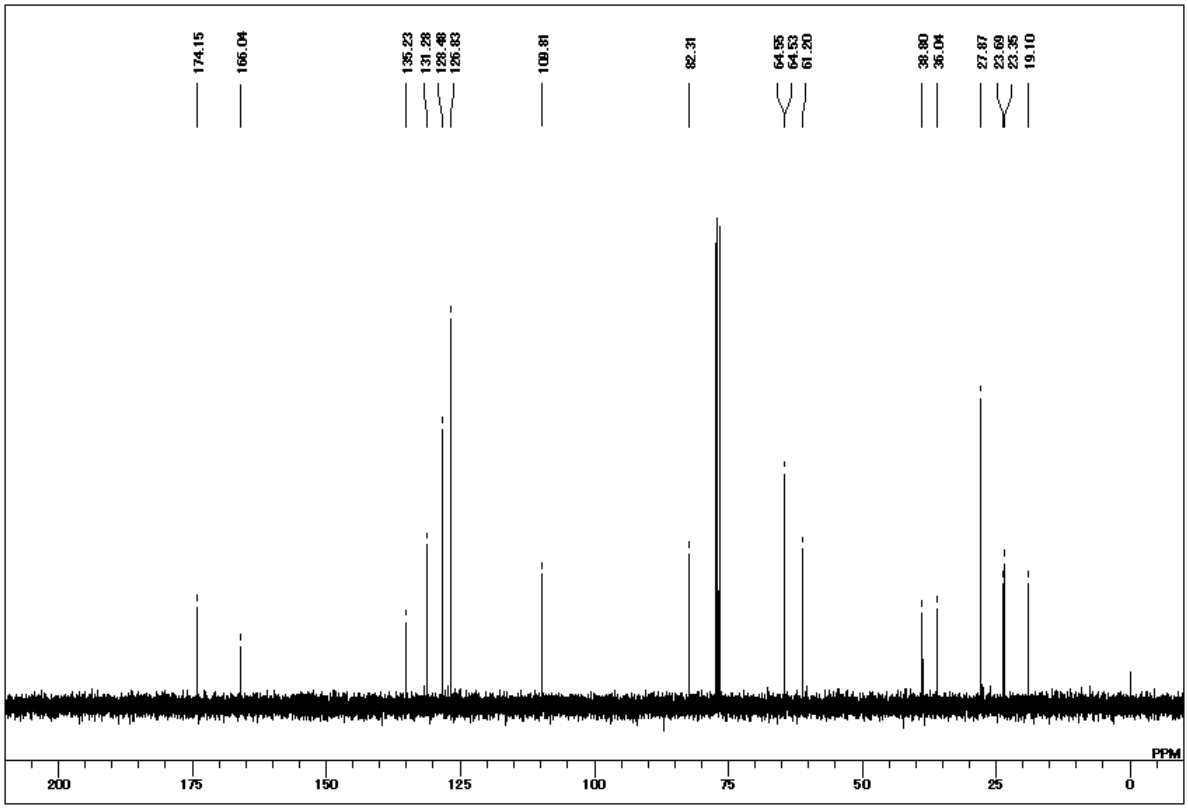
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109.81
82.31
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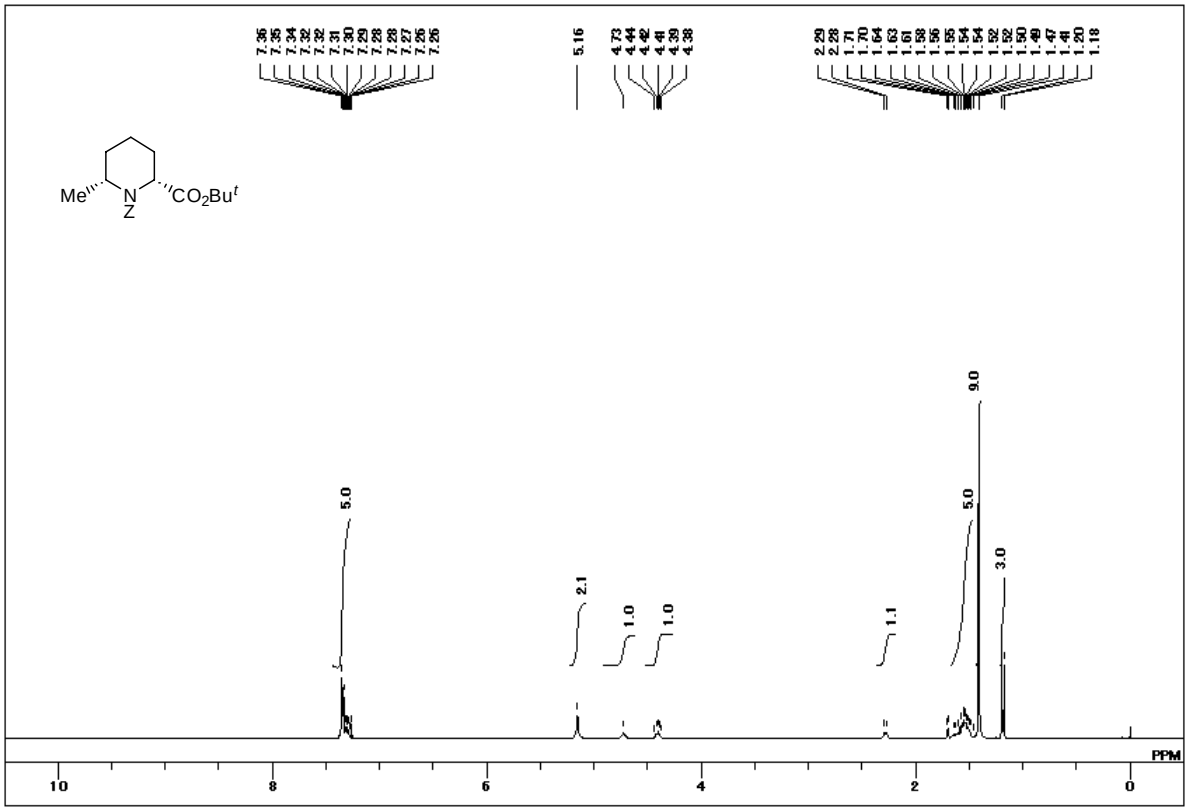
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4.44
4.42
4.41
4.39
4.38
2.29
2.28
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1.70
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1.63
1.61
1.58
1.56
1.55
1.54
1.54
1.52
1.52
1.50
1.49
1.47
1.41
1.20
1.18
Me
N
Z
CO2But
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1.0
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5.0
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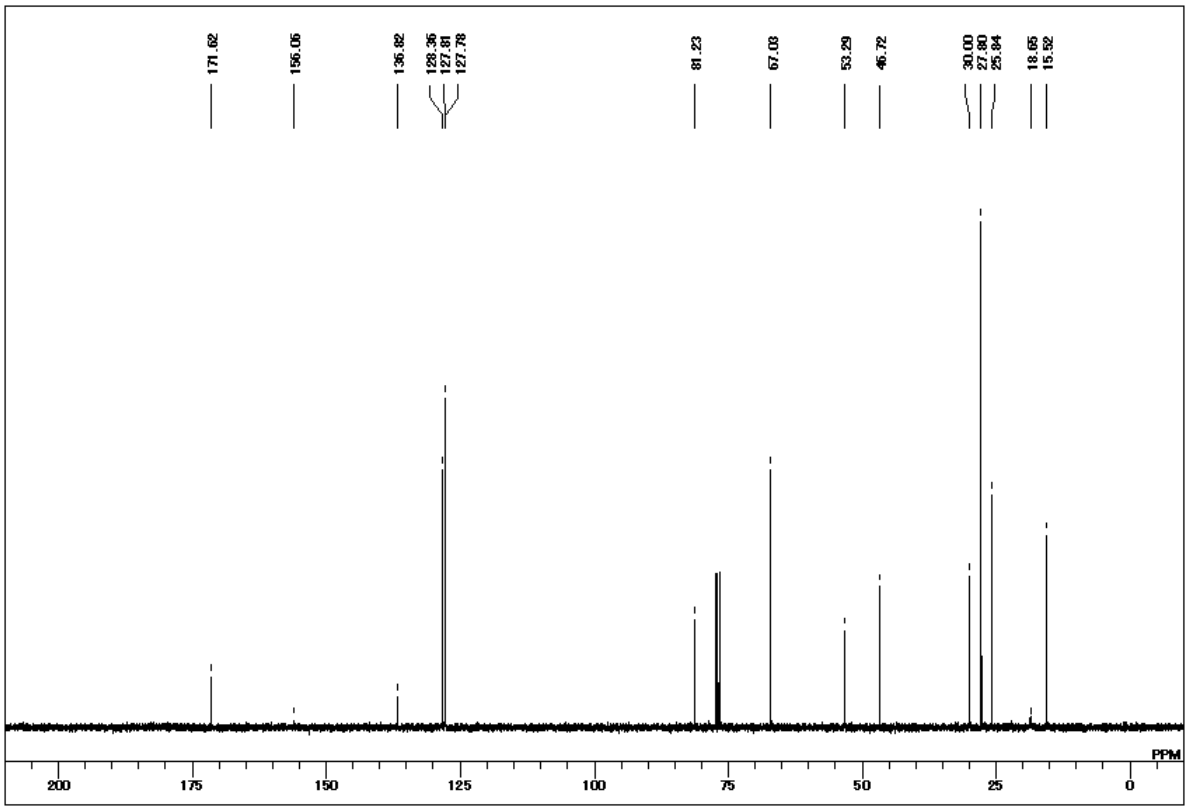
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127.78
81.23
67.03
53.29
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15.52
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50
25
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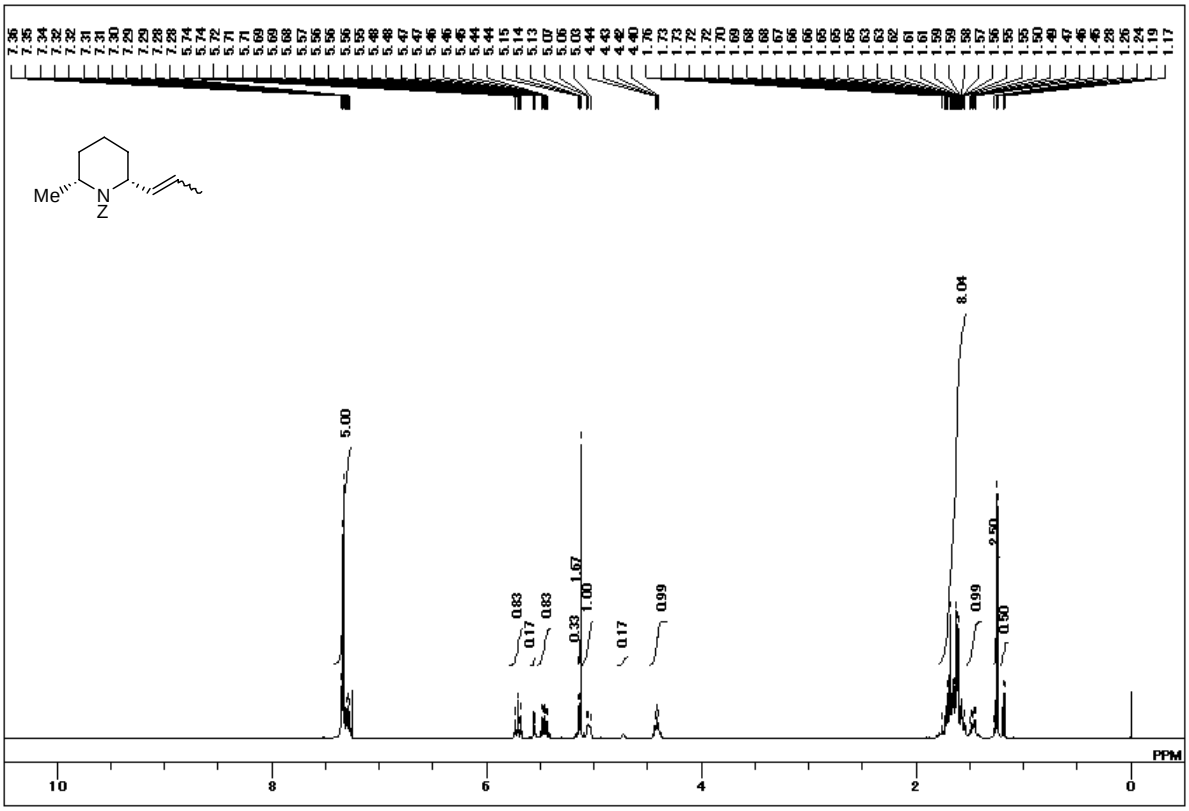
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0.99
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0.99
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6
4
2
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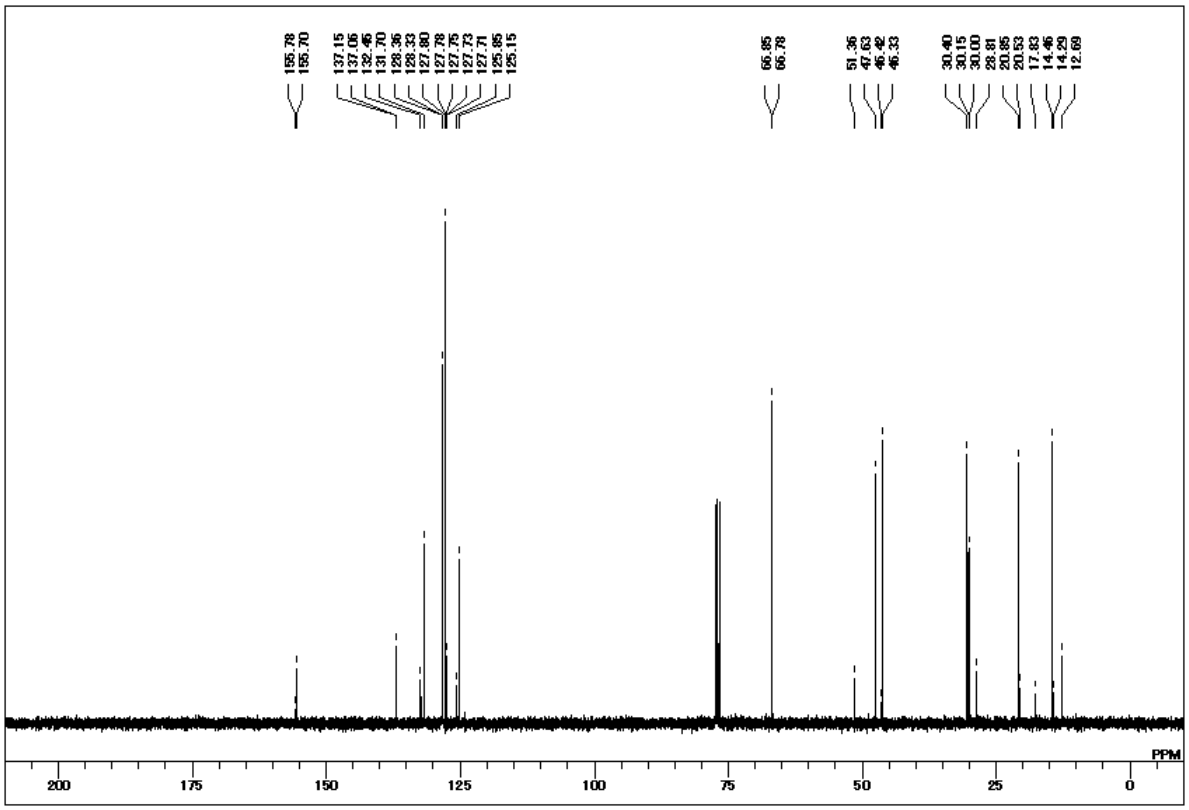
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131.70
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128.33
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127.78
127.76
127.73
127.71
125.85
125.15
66.85
66.78
51.36
47.63
46.42
46.33
30.40
30.15
30.00
28.81
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20.53
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14.29
12.69
PPM
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175
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125
100
75
50
25
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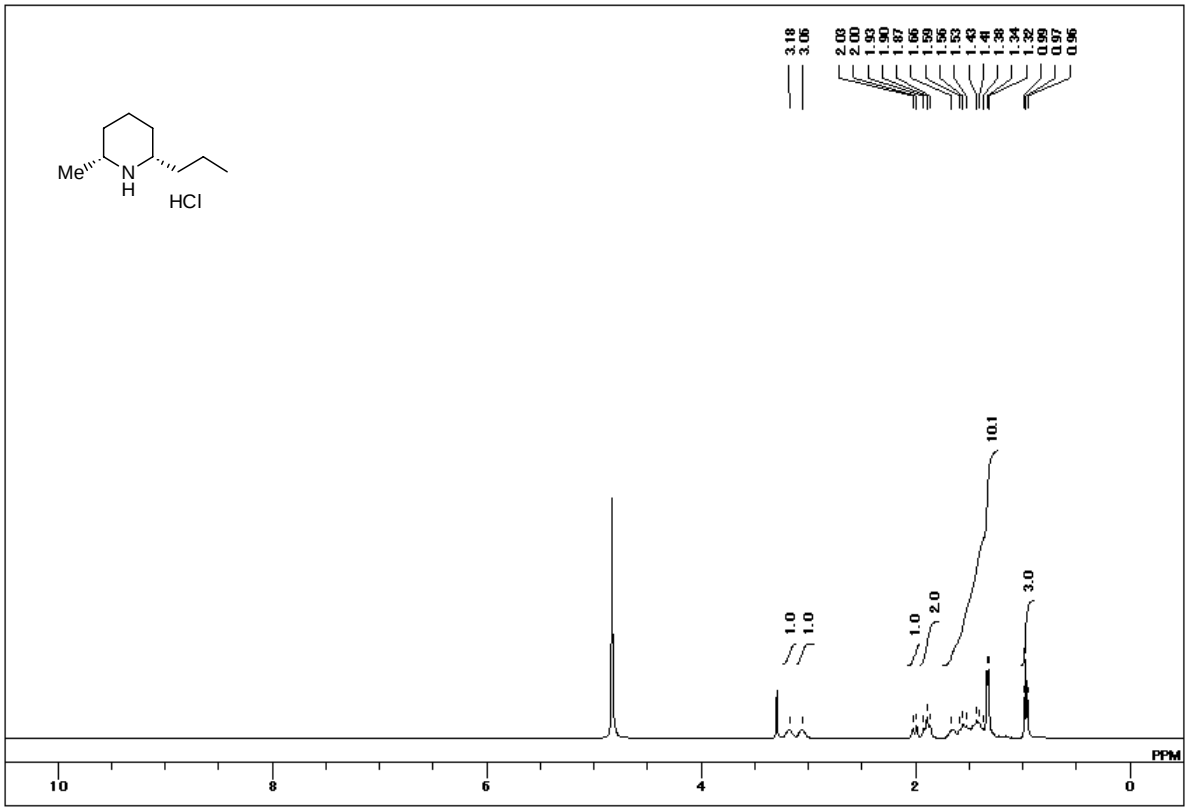
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1.87
1.66
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1.56
1.53
1.43
1.41
1.38
1.34
1.32
0.99
0.97
0.96
Me
N
H
HCl
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1.0
1.0
2.0
10.1
3.0
PPM
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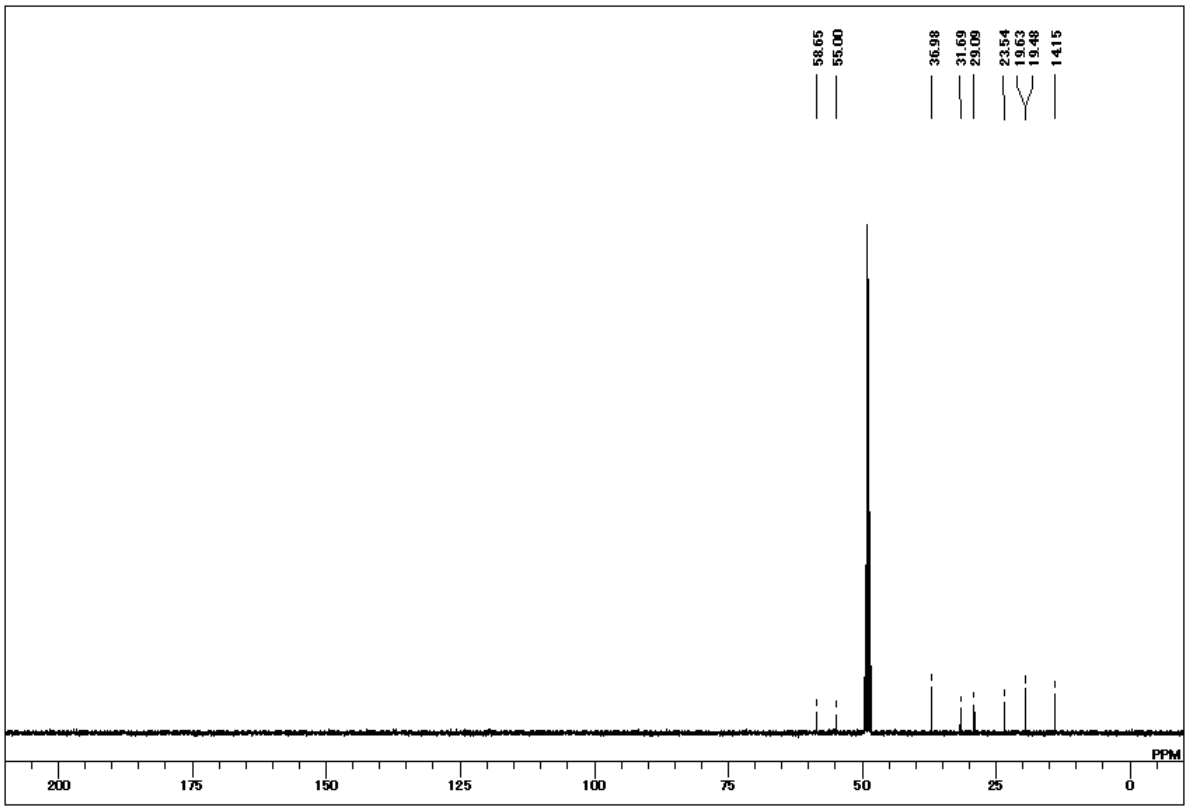
6
4
2
0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14.15
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75
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25
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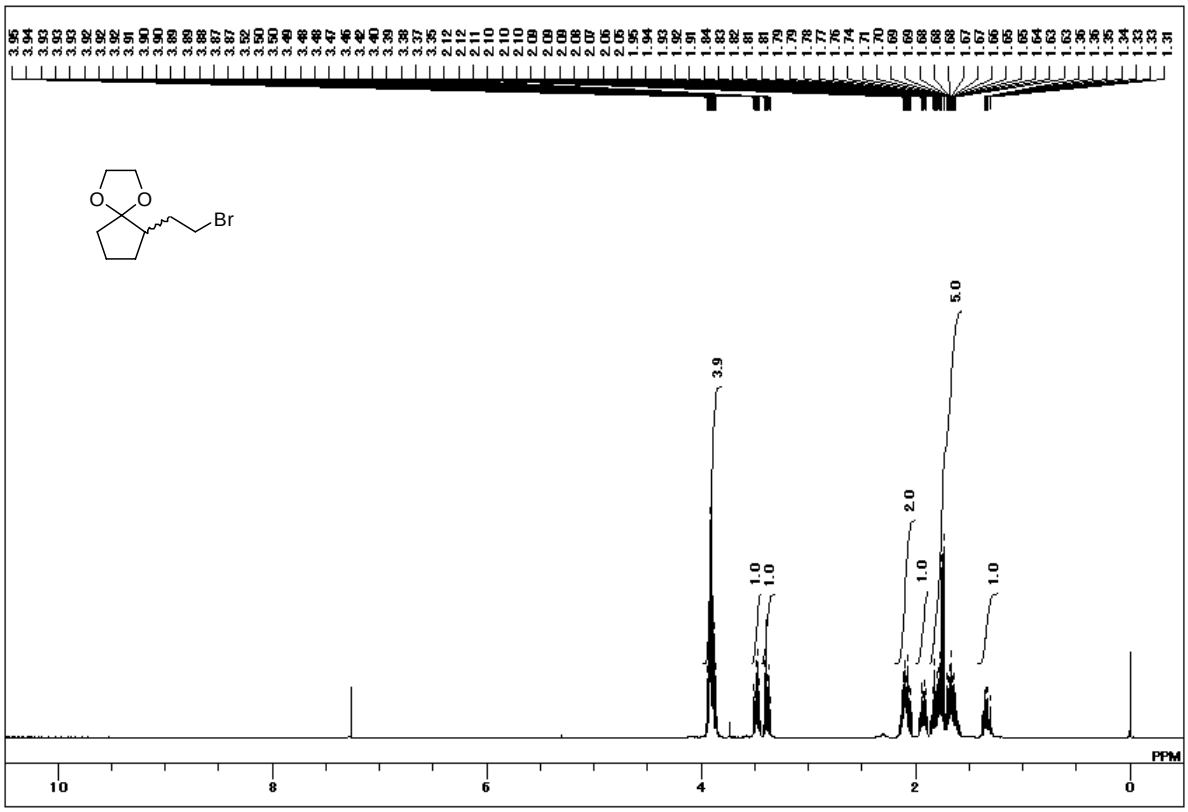
O
O
Br
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5.0
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PPM
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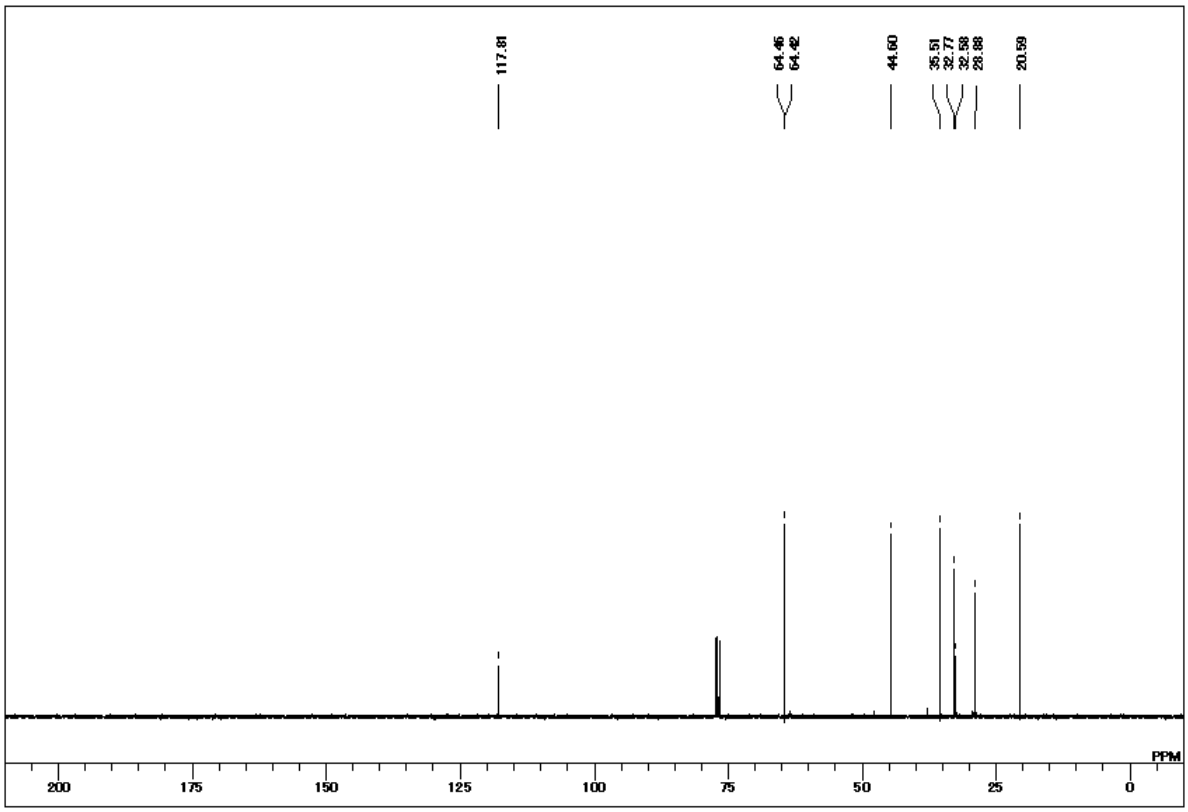
6
4
2
0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32.58
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20.59
PPM
200
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150
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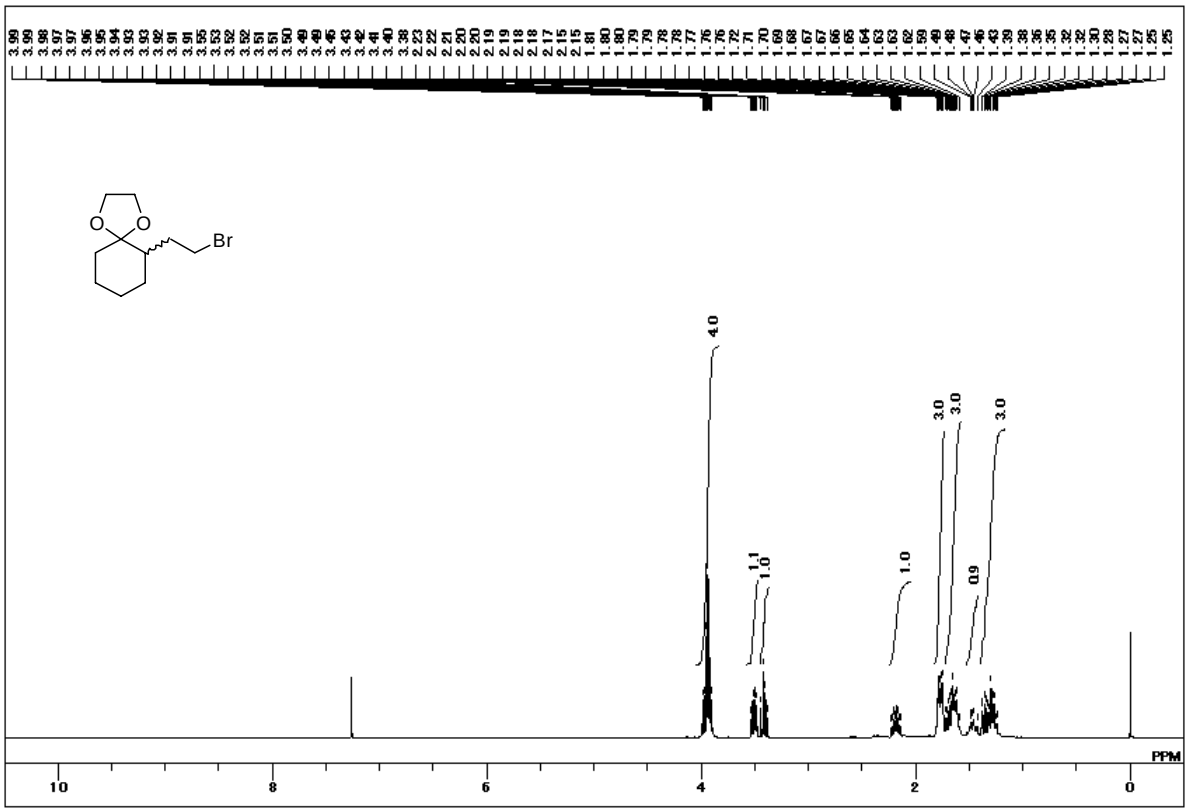
100
75
50
25
0


O
O
Br
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1.1
1.0
1.0
0.9
3.0
3.0
3.0
PPM
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6
4
2
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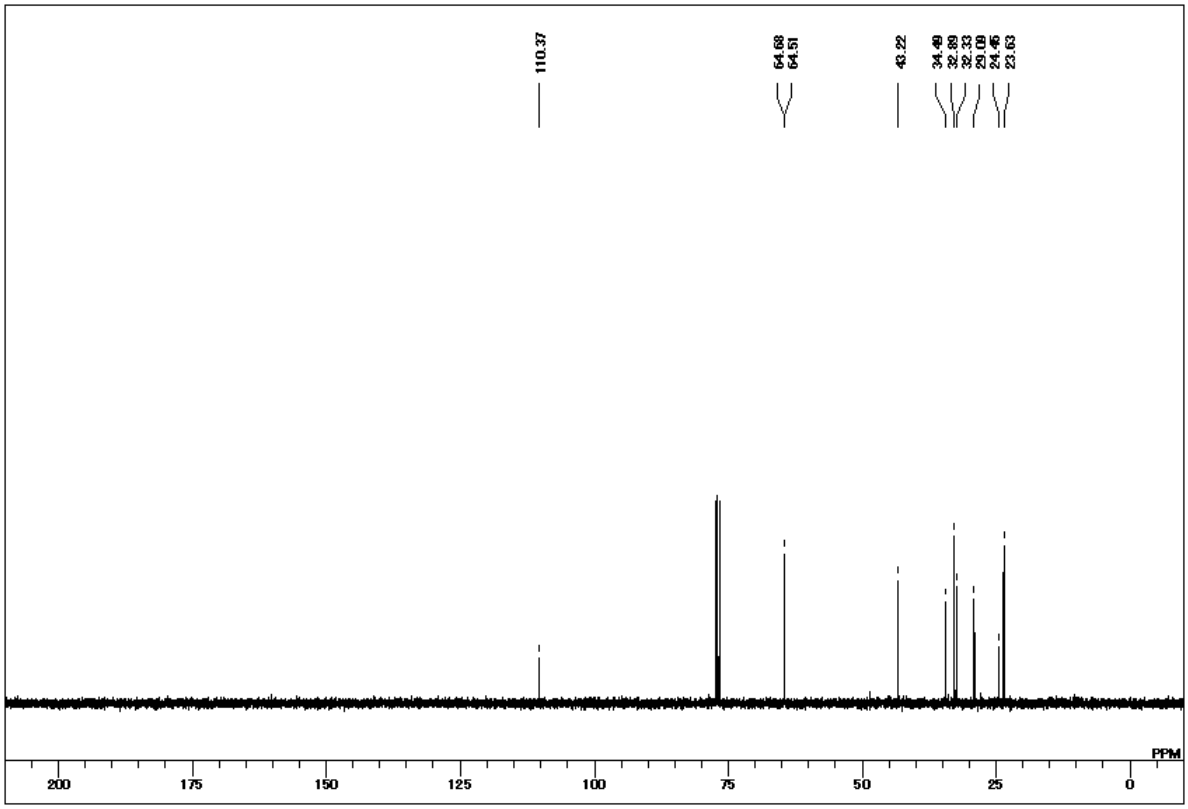
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43.22
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32.89
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29.09
24.46
23.63
PPM
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25
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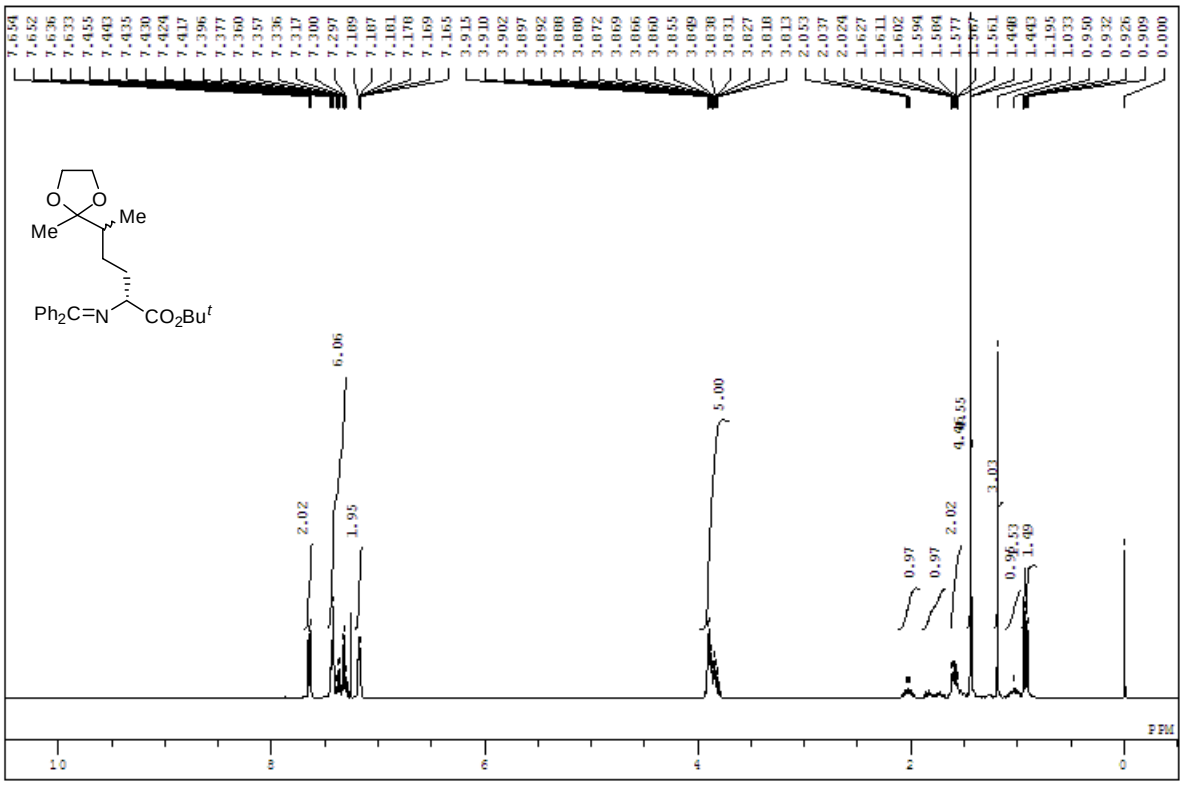
Me
Me
Ph2C=N
CO2Bu^t
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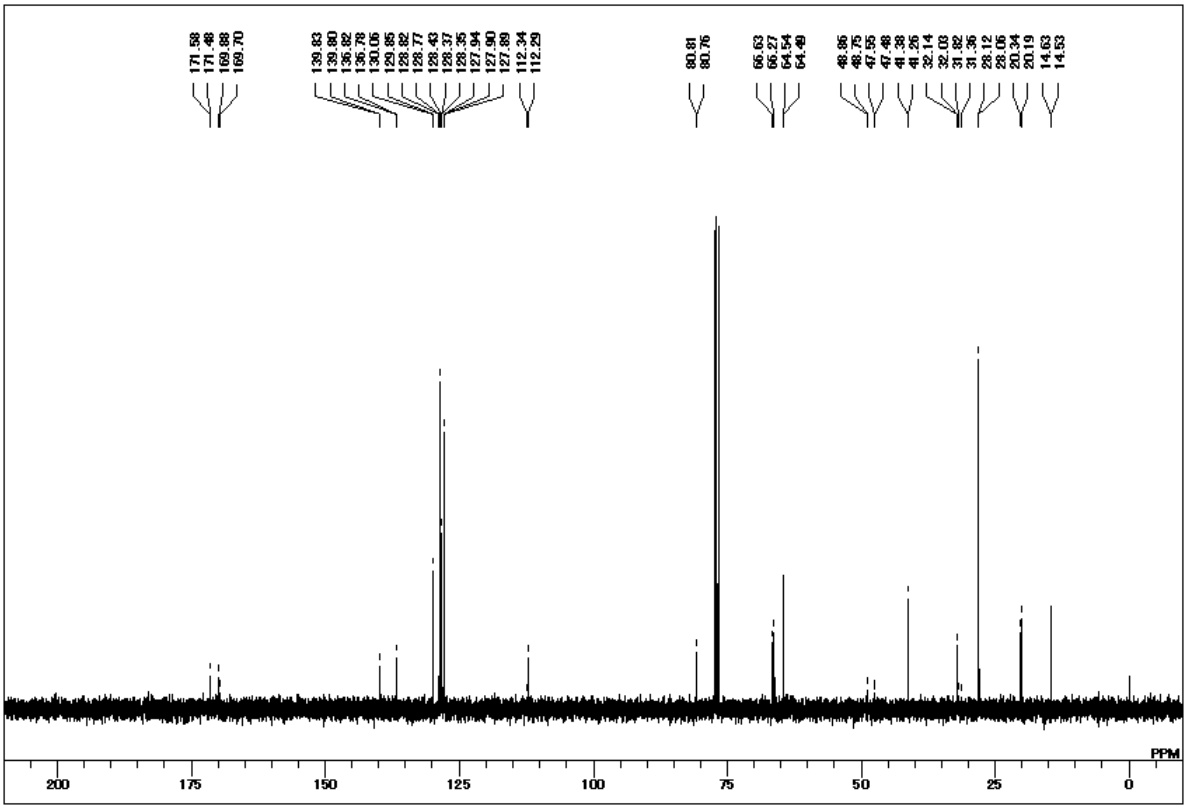
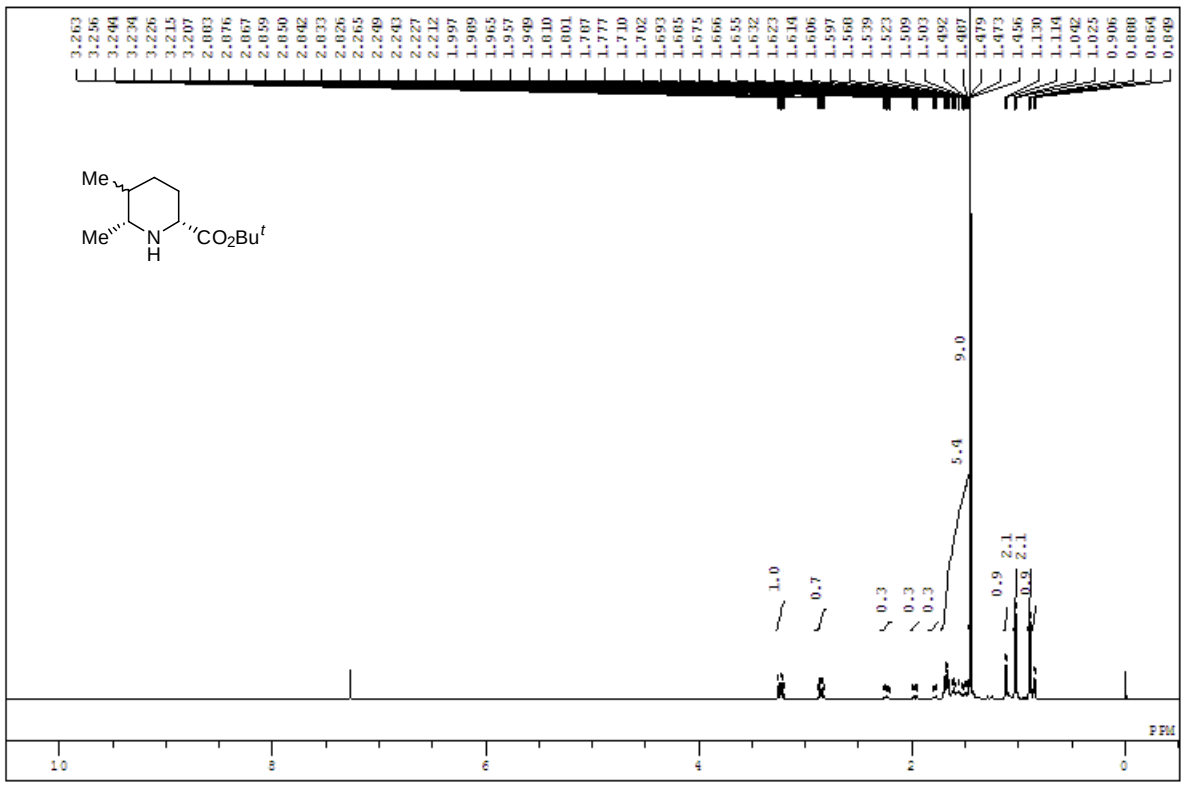
1.95
0.97
0.97
2.02
3.03
0.96
1.49
PPM


PPM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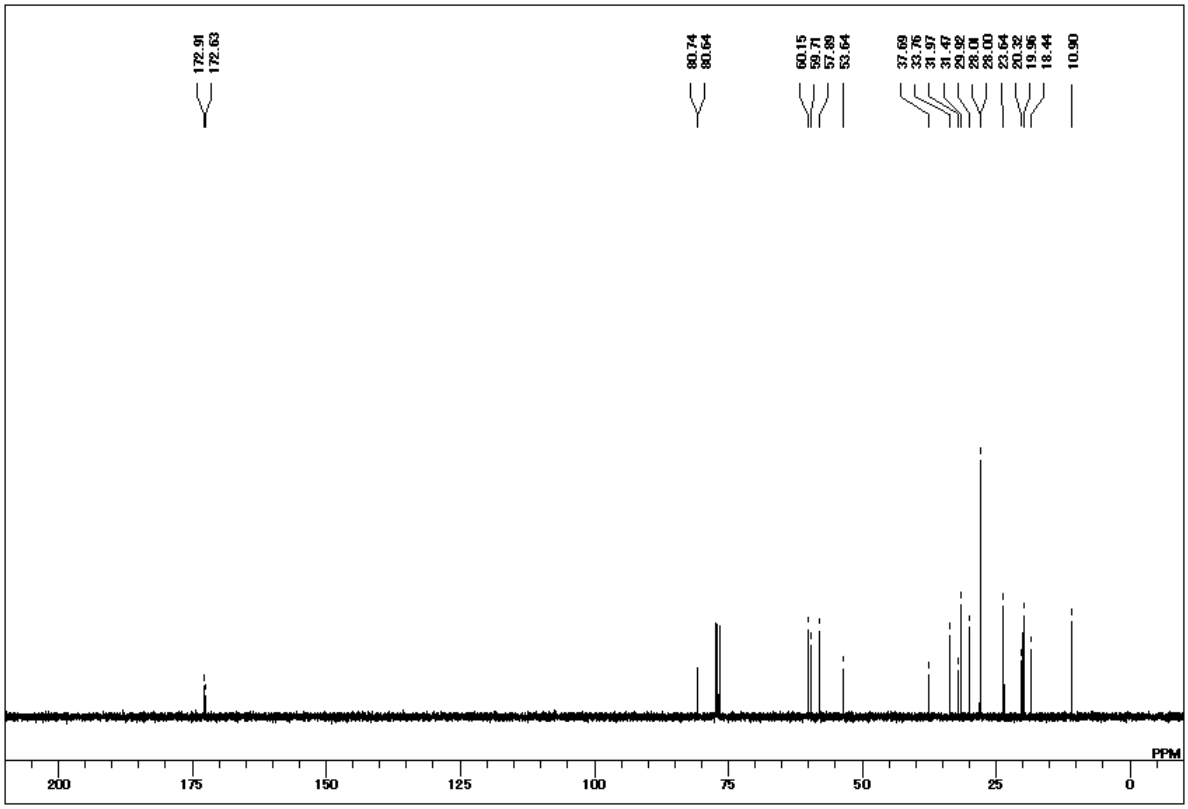
Me
N
H
CO2But
PPM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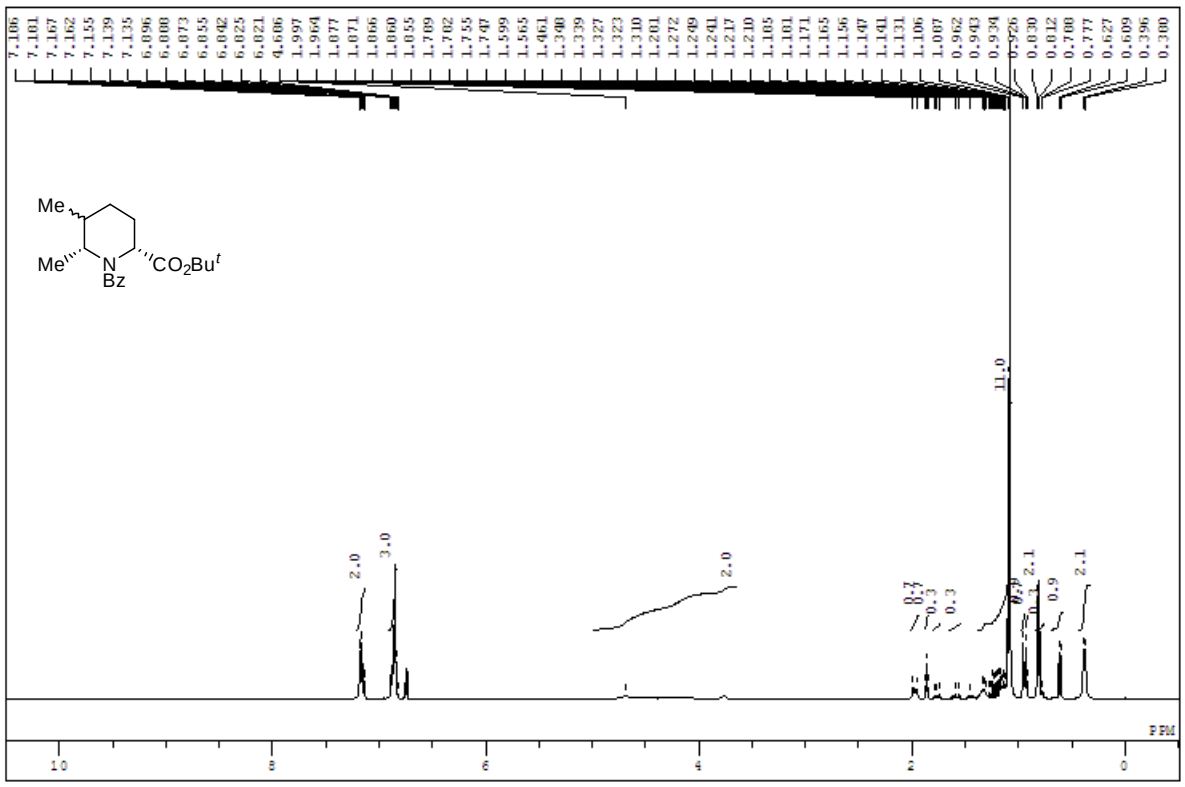
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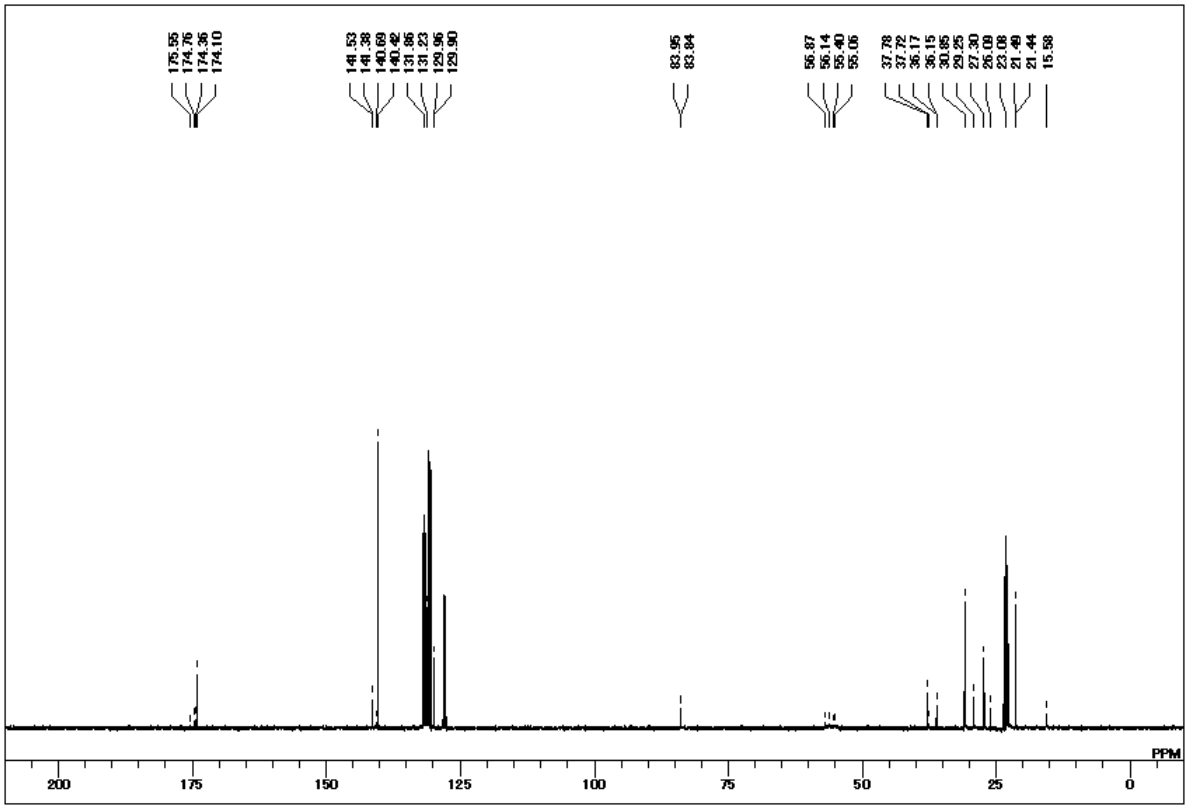
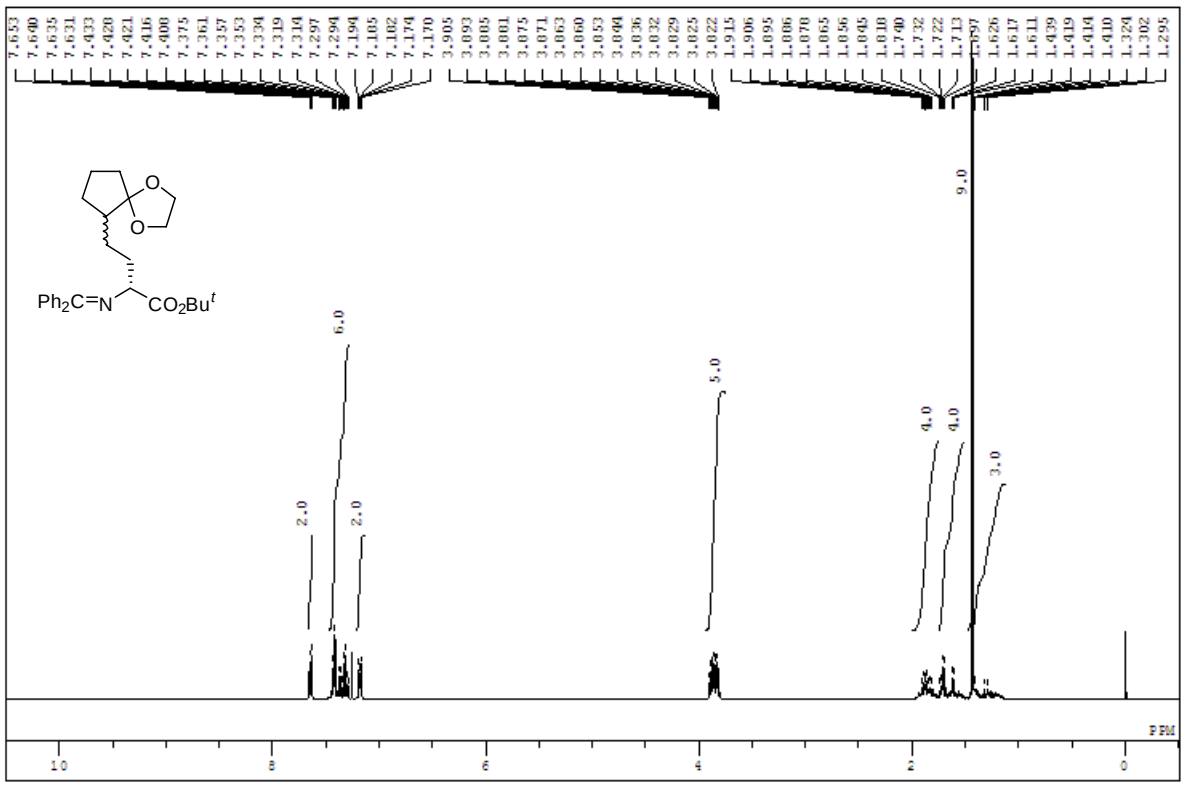
Bz
CO2But
PPM


PPM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7.353
7.334
7.319
7.314
7.297
7.294
7.194
7.185
7.182
7.174
7.170
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3.893
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3.863
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3.836
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3.829
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3.822
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1.906
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1.722
1.713
1.697
1.626
1.617
1.611
1.439
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1.414
1.410
1.324
1.302
1.295
O
O
Ph2C=N
CO2Bu^t
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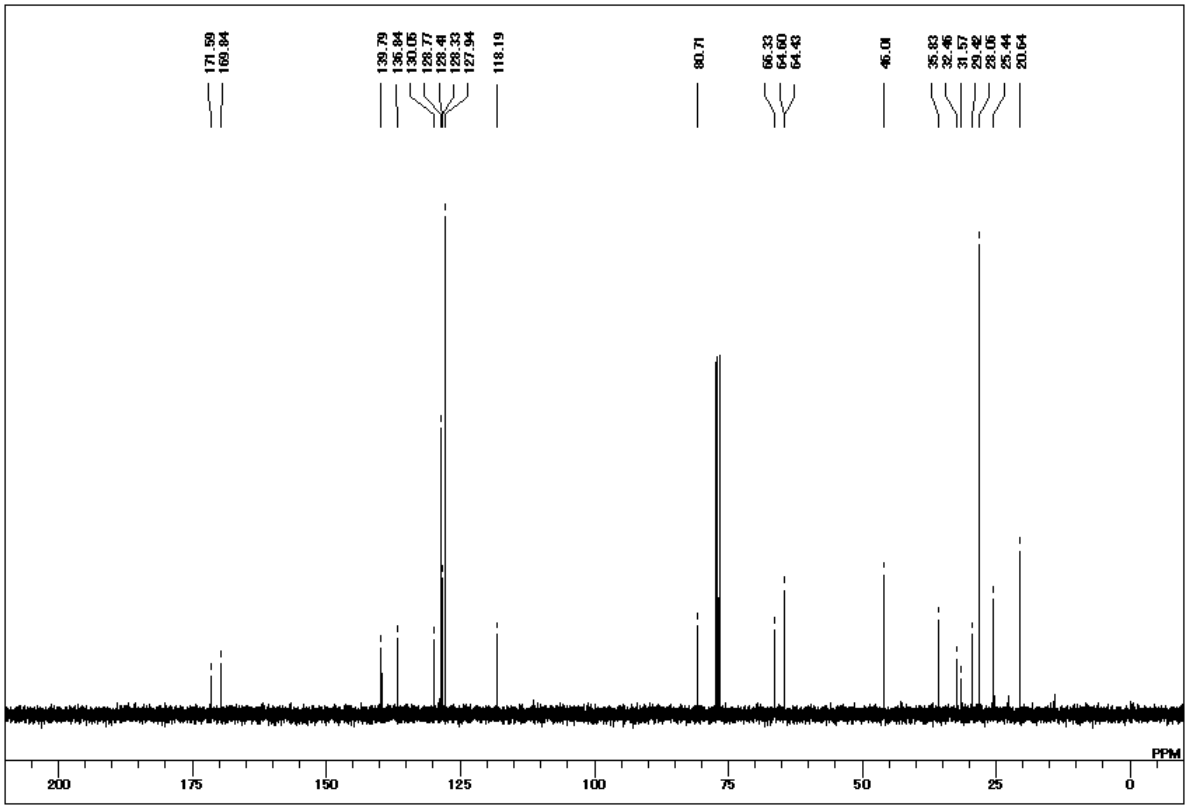
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64.60
64.43
46.01
35.83
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20.64
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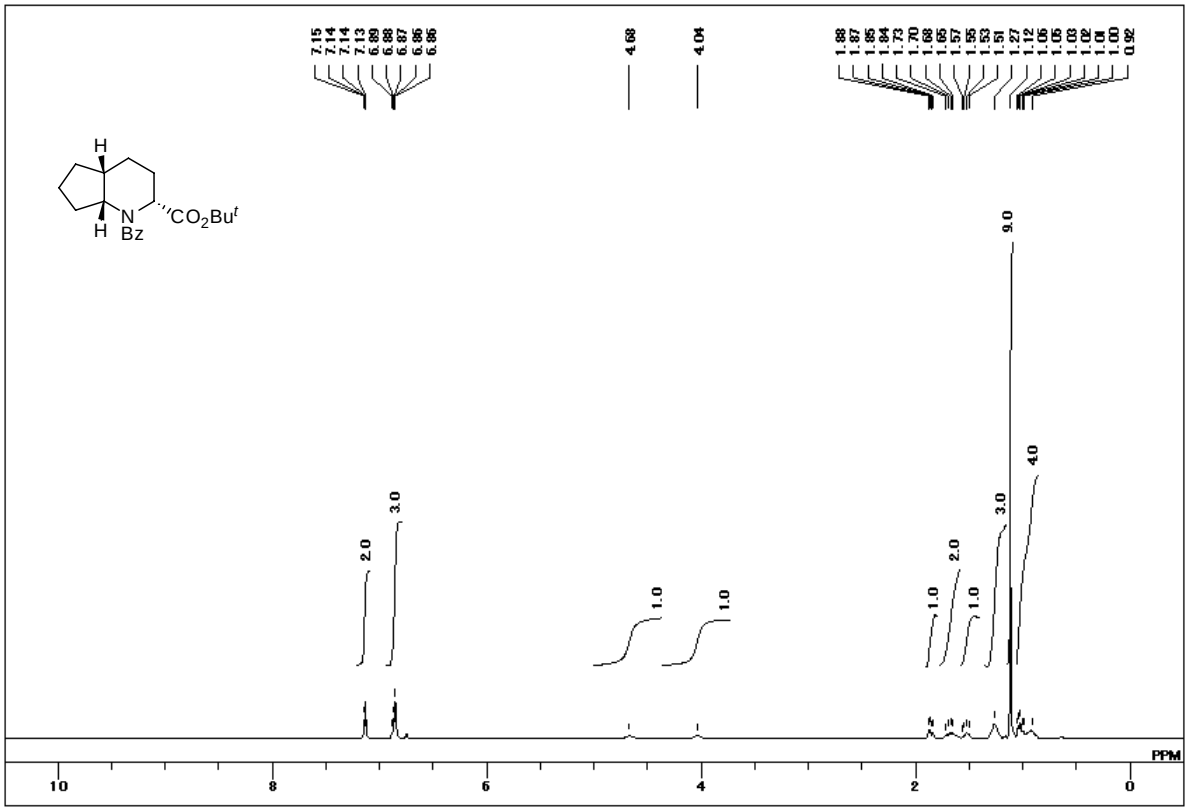
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6.87
6.86
6.86
4.68
4.04
1.88
1.87
1.85
1.84
1.73
1.70
1.68
1.65
1.57
1.55
1.53
1.51
1.27
1.12
1.05
1.03
1.02
1.01
1.00
0.92
H
N
H
Bz
CO2But
9.0
4.0
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2.0
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1.0
1.0
1.0
PPM
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6
4
2
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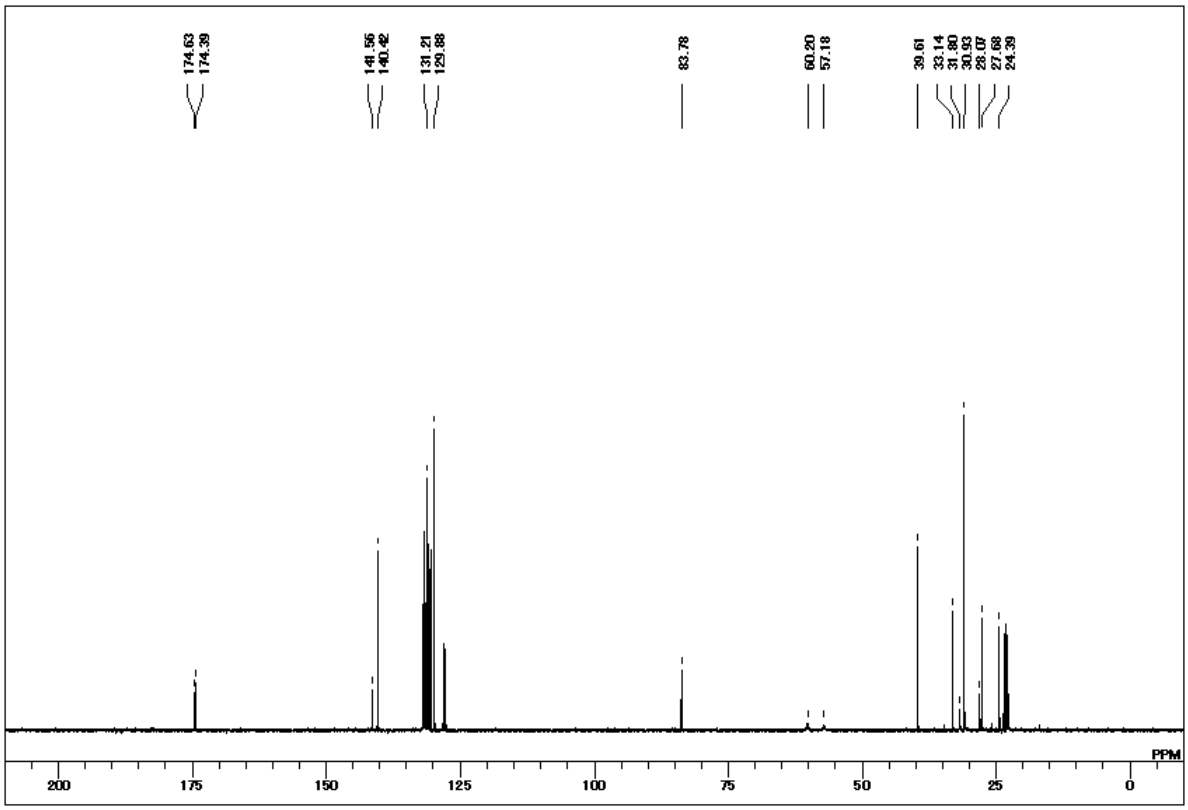
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60.20
57.18
39.61
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28.07
27.68
24.39
PPM
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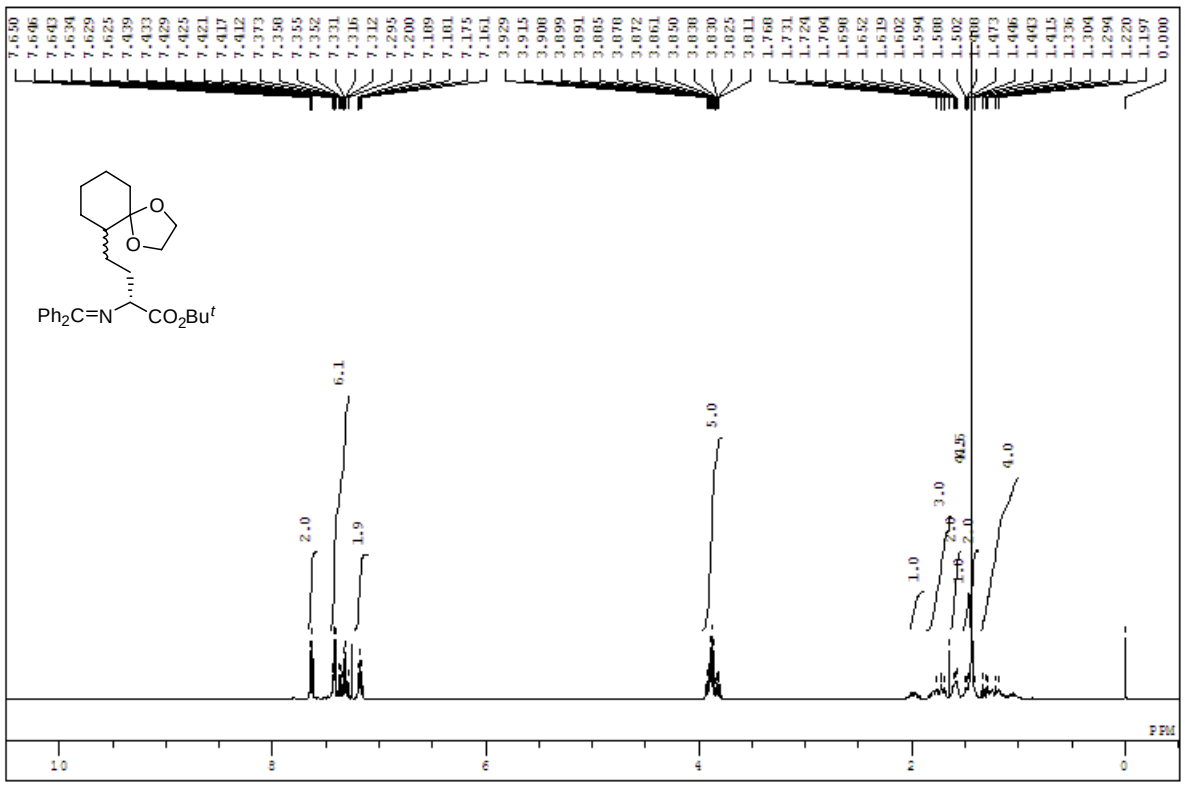
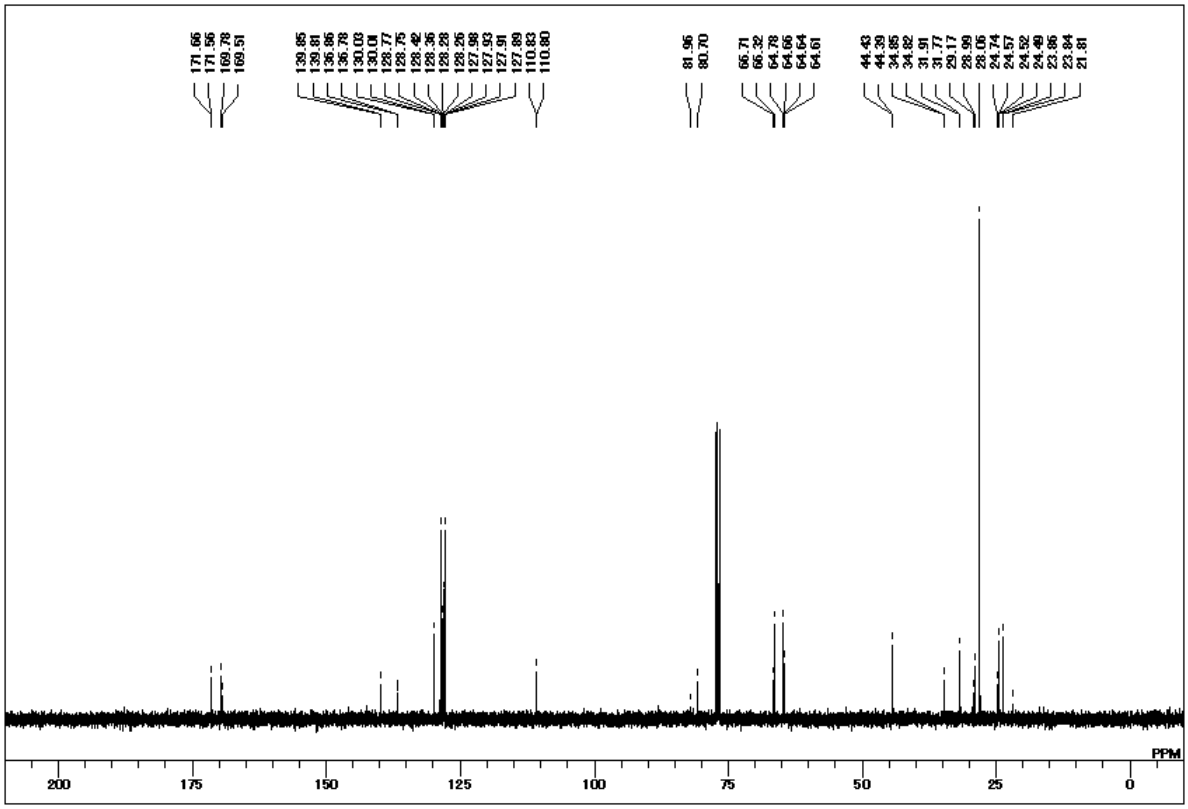
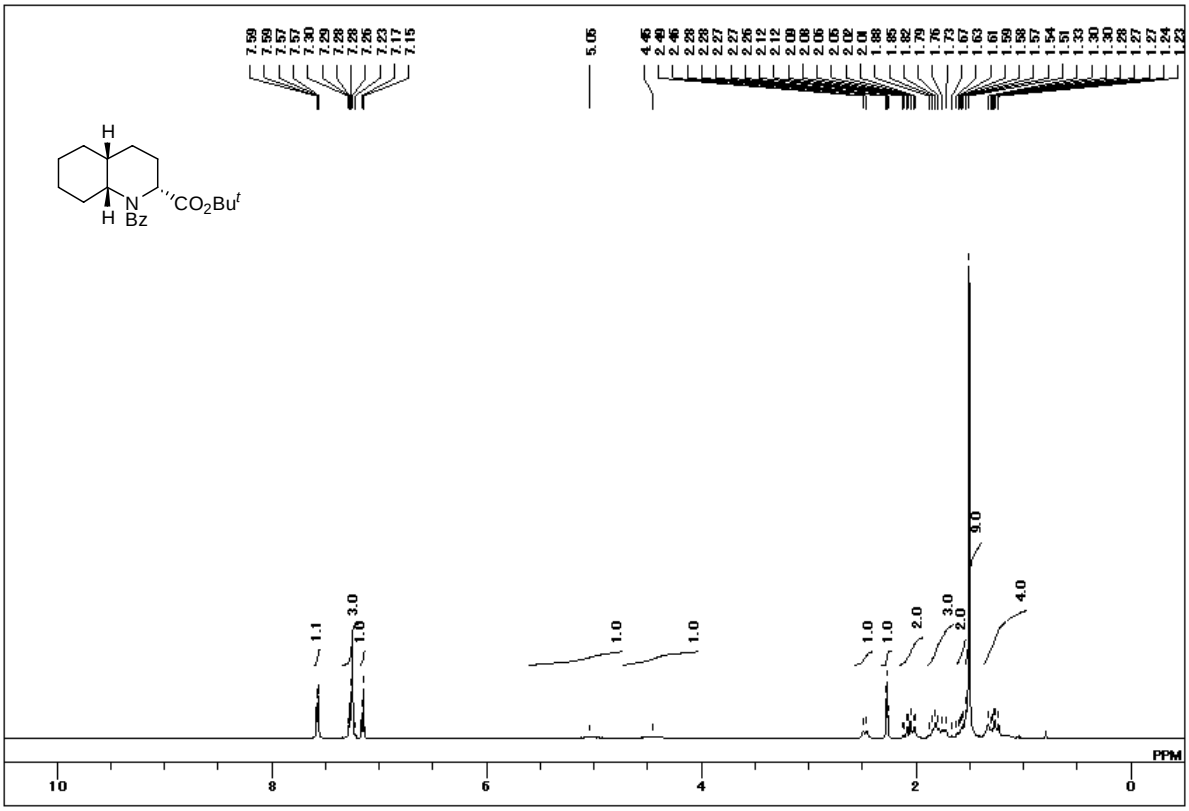
175
150
125
100
75
50
25
0


Ph2C=N
CO2Bu^t
PPM


PPM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7.23
7.17
7.15
5.05
4.45
2.49
2.46
2.28
2.28
2.27
2.27
2.26
2.12
2.12
2.09
2.08
2.06
2.05
2.02
2.01
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1.27
1.27
1.24
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H
Bz
CO2But
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1.0
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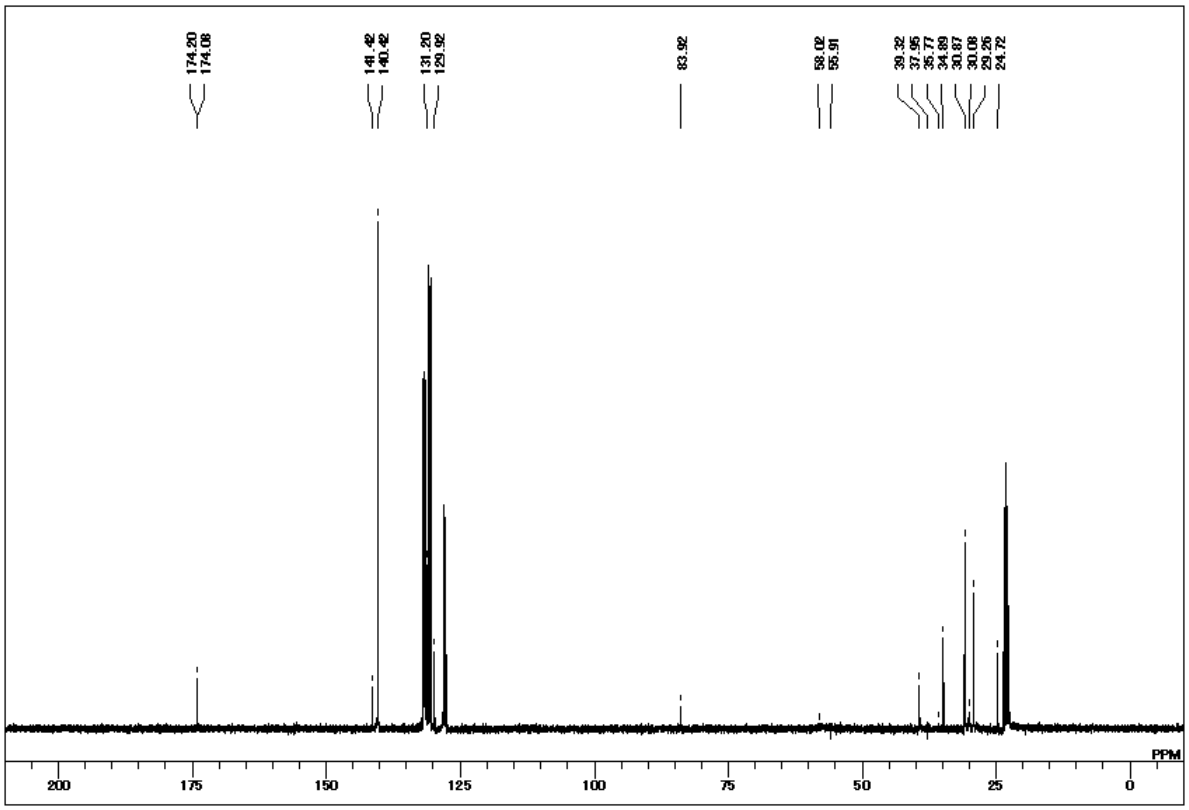
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83.92
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39.32
37.95
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34.89
30.87
30.08
29.26
24.72
PPM
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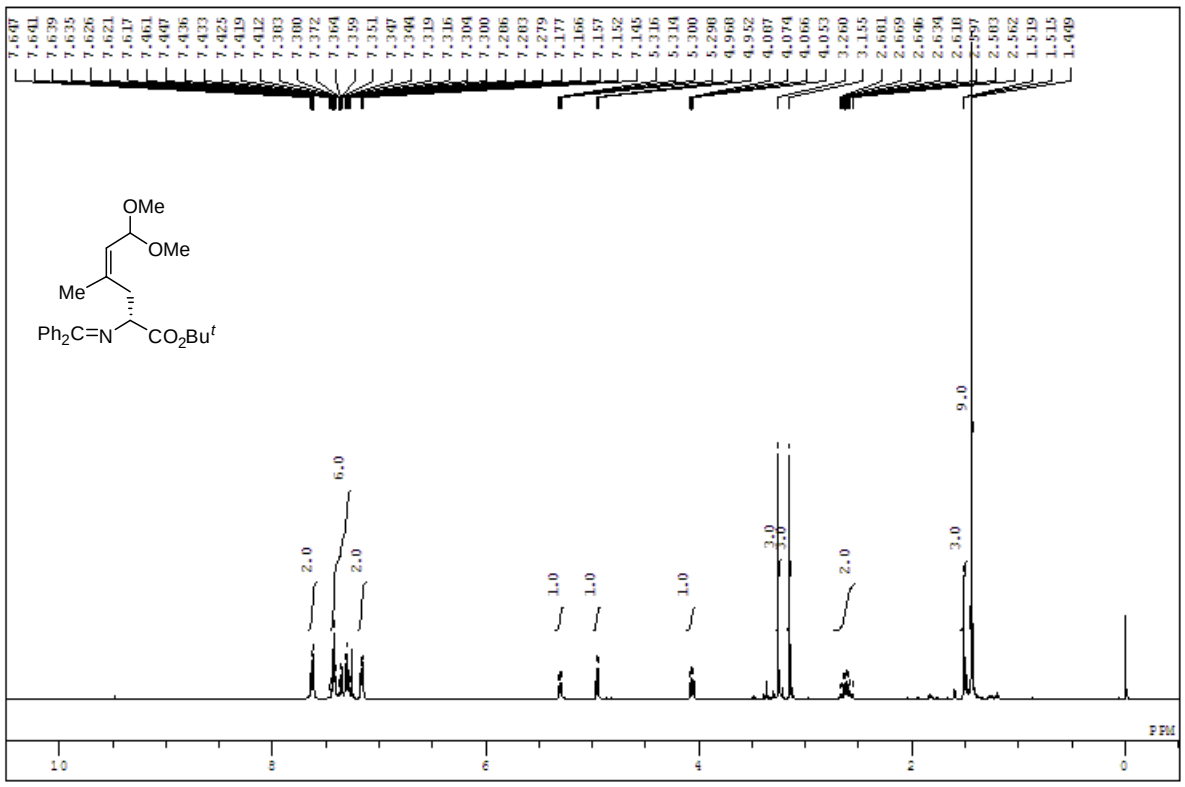
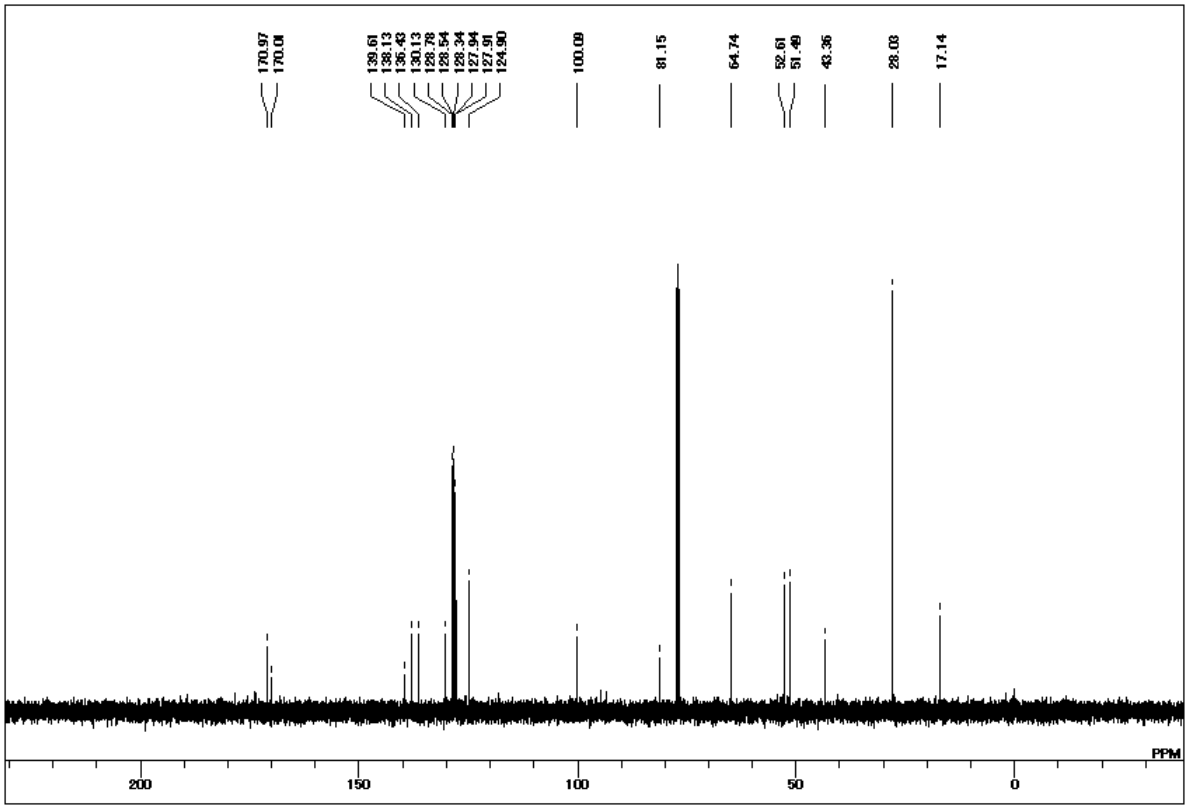
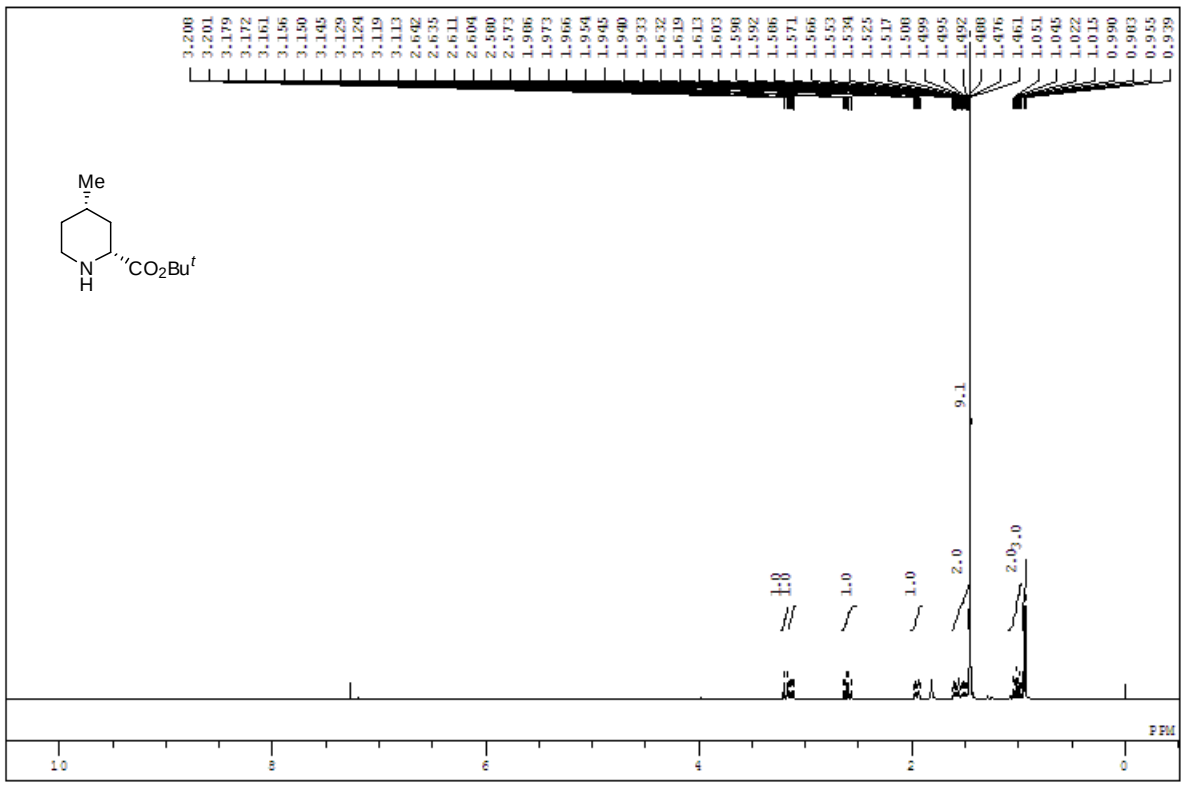
175
150
125
100
75
50
25
0


OMe
OMe
Me
Ph2C=N
CO2But
PPM


PPM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H
CO2But
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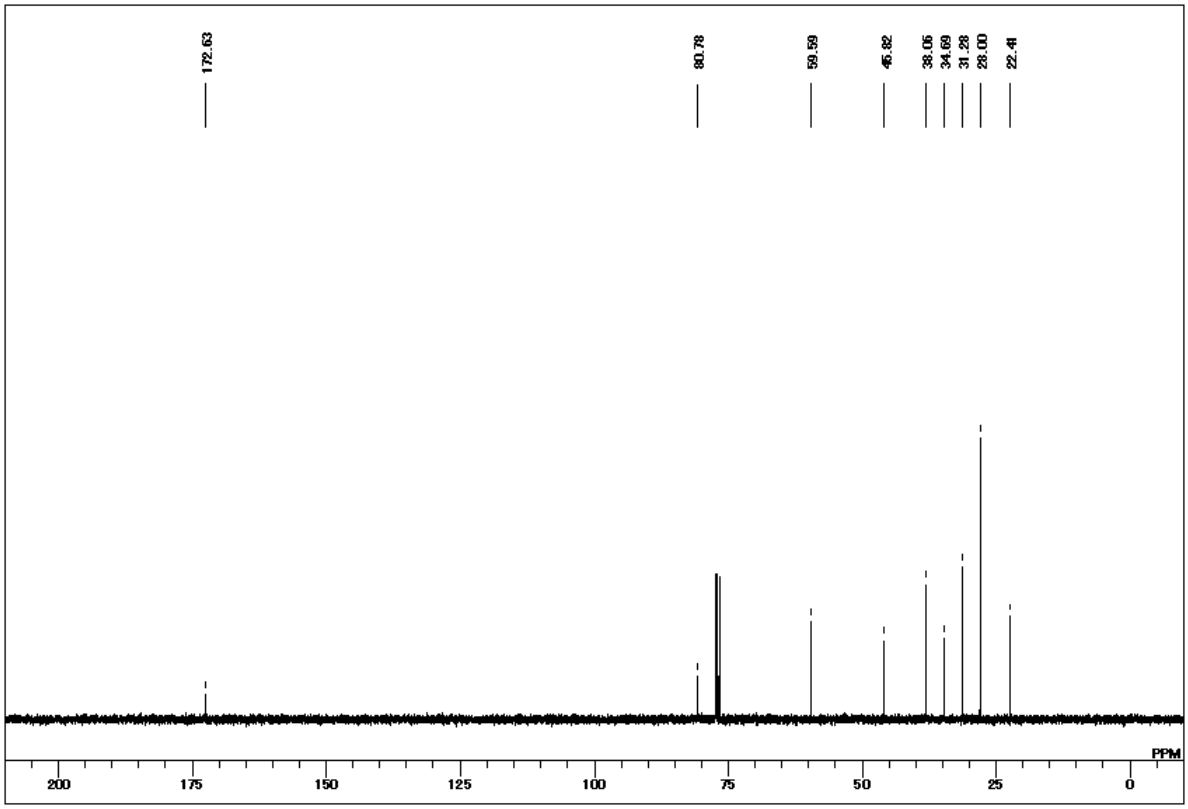
PPM


172.63
80.78
59.59
45.82
38.06
34.69
31.28
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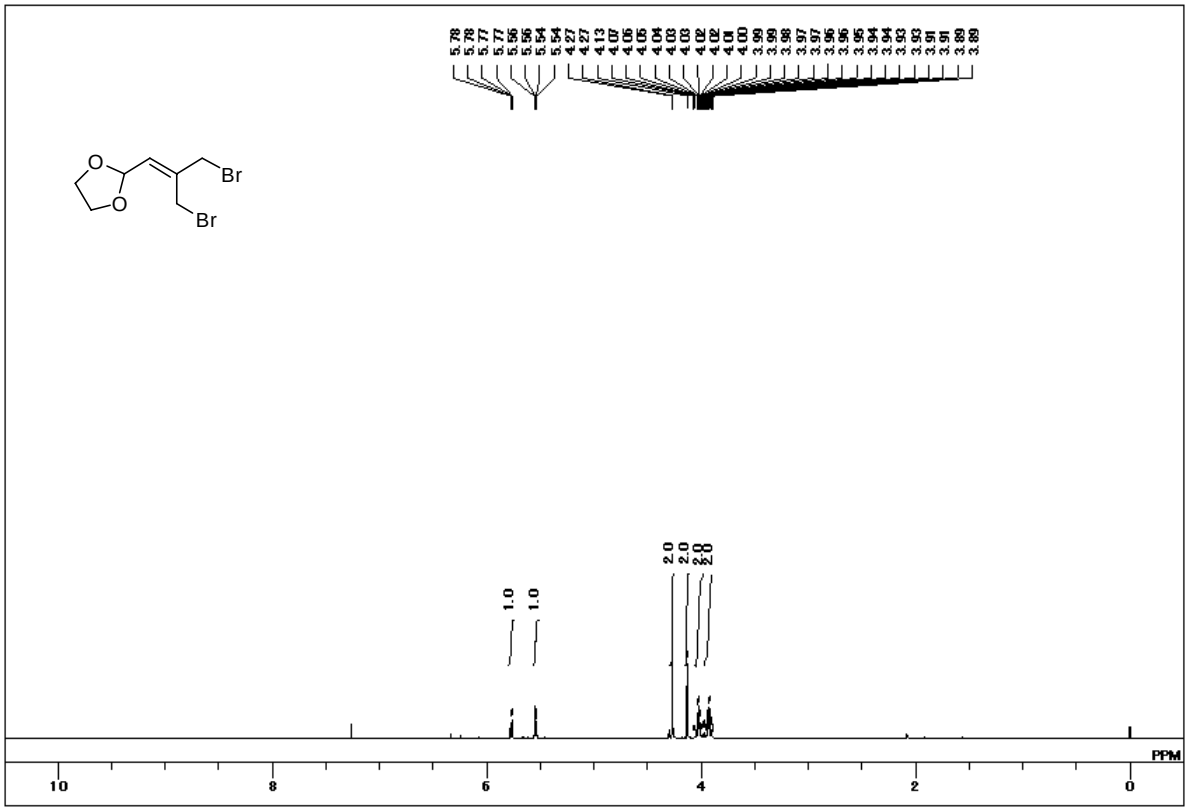
22.41
PPM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5.77
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5.54
4.27
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4.07
4.06
4.06
4.04
4.03
4.03
4.02
4.02
4.01
4.00
3.99
3.99
3.98
3.97
3.97
3.96
3.95
3.94
3.94
3.93
3.91
3.91
3.89
3.89
O
O
Br
Br
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1.0
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2.0
PPM
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8
6
4
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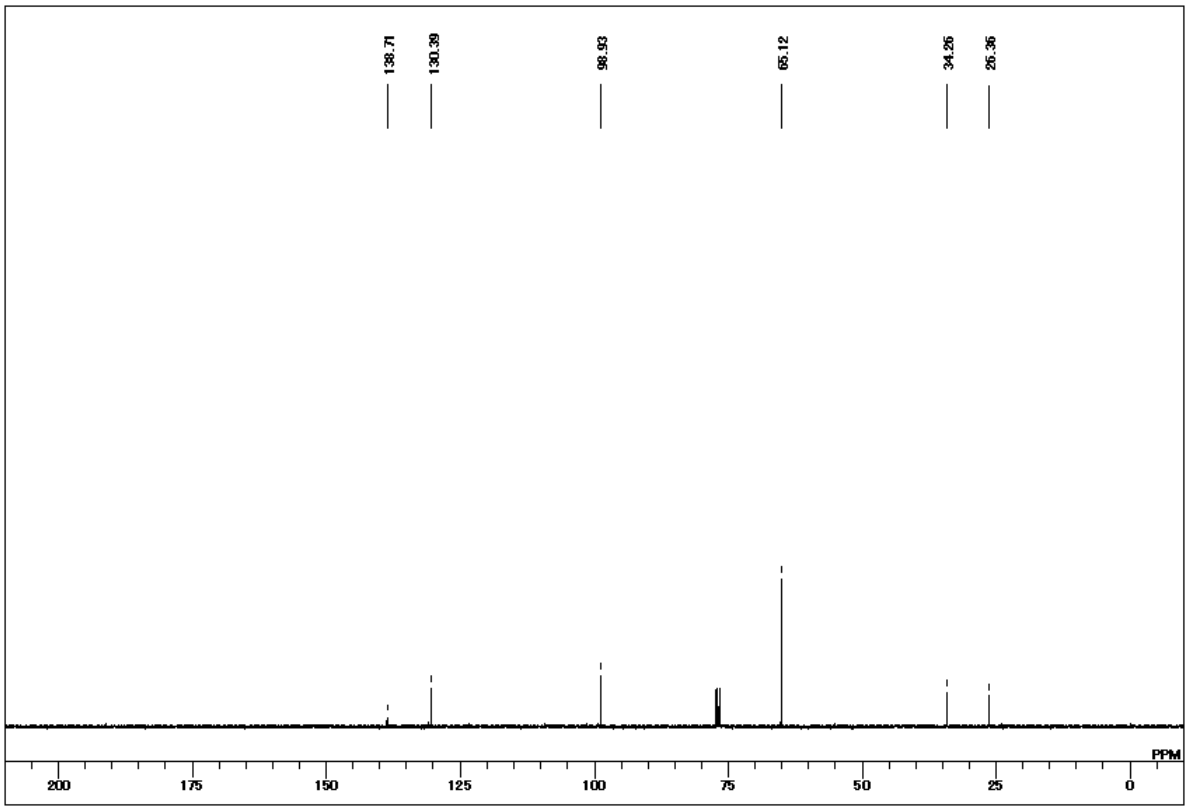
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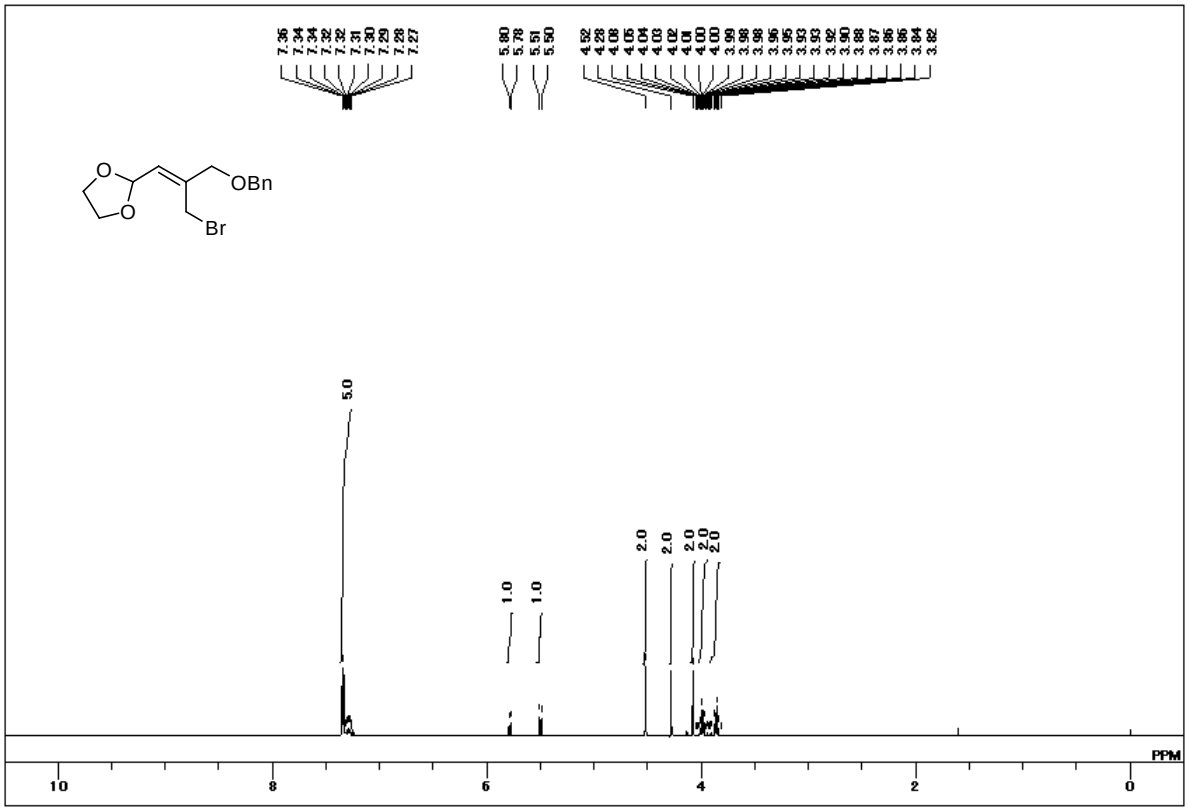
130.39
98.93
65.12
34.26
26.36
PPM
200
175
150
125
100
75
50
25
0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7.31
7.30
7.29
7.28
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5.80
5.78
5.51
5.50
4.52
4.28
4.08
4.05
4.04
4.03
4.02
4.01
4.00
4.00
3.99
3.98
3.98
3.96
3.95
3.93
3.92
3.90
3.88
3.87
3.86
3.85
3.84
3.82
O
O
OBn
Br
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1.0
2.0
2.0
2.0
2.0
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8
6
4
2
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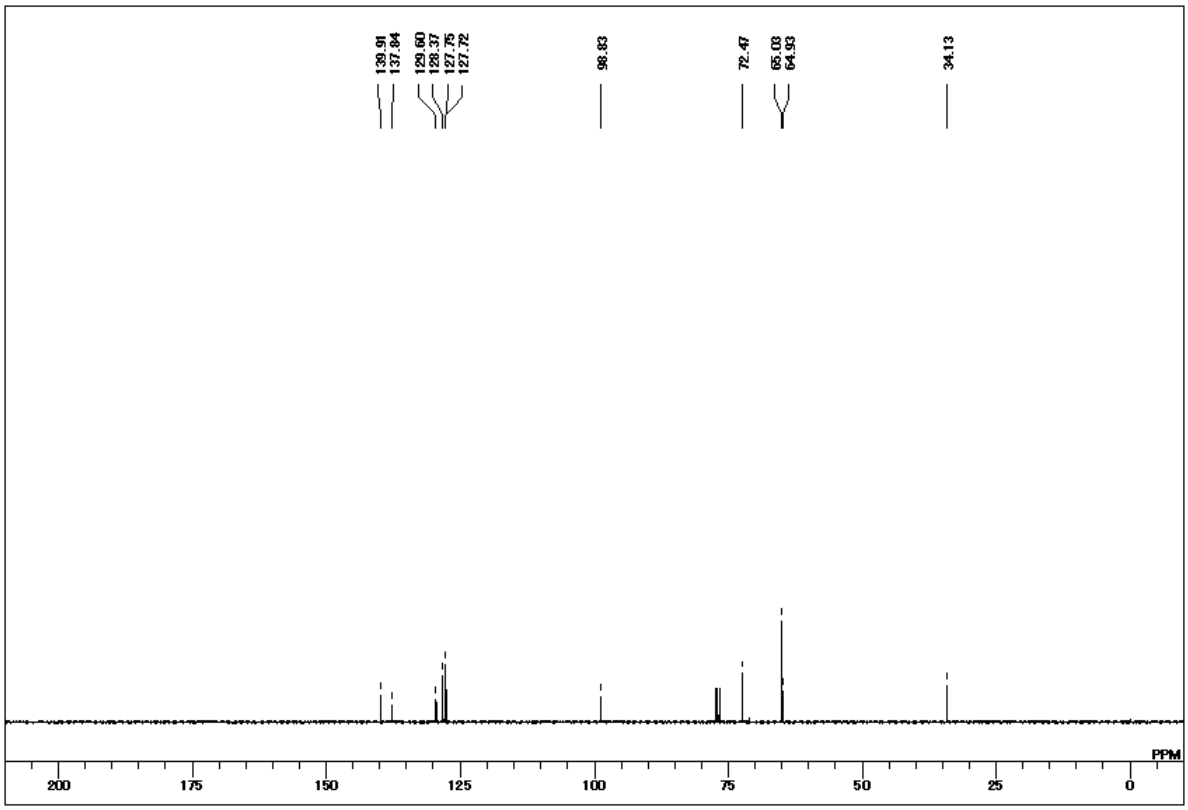
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128.37
127.75
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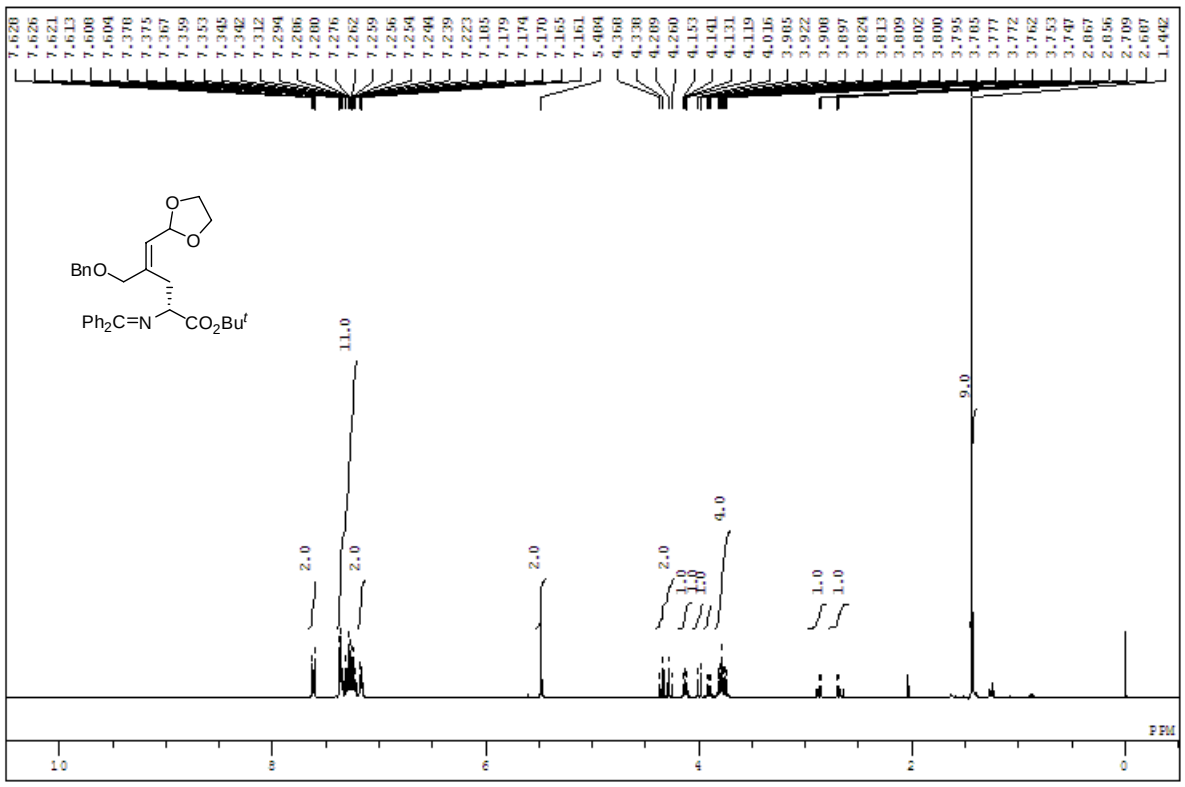
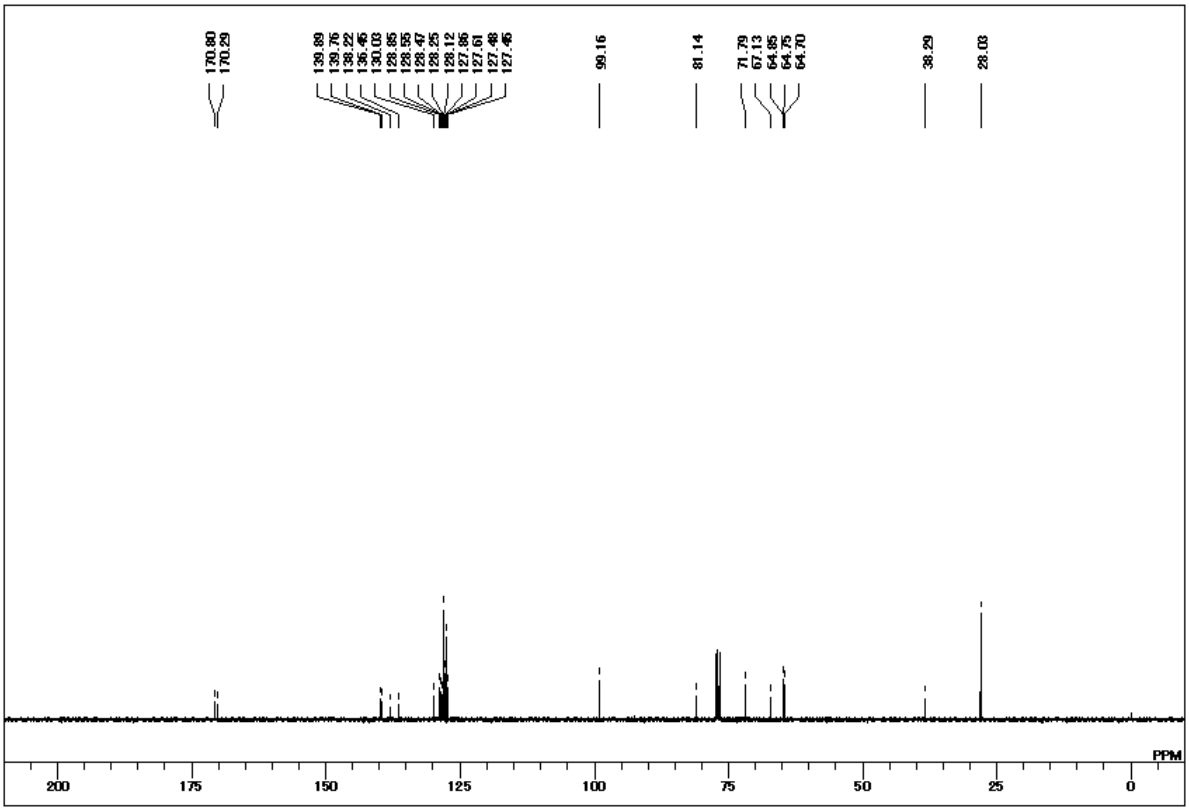
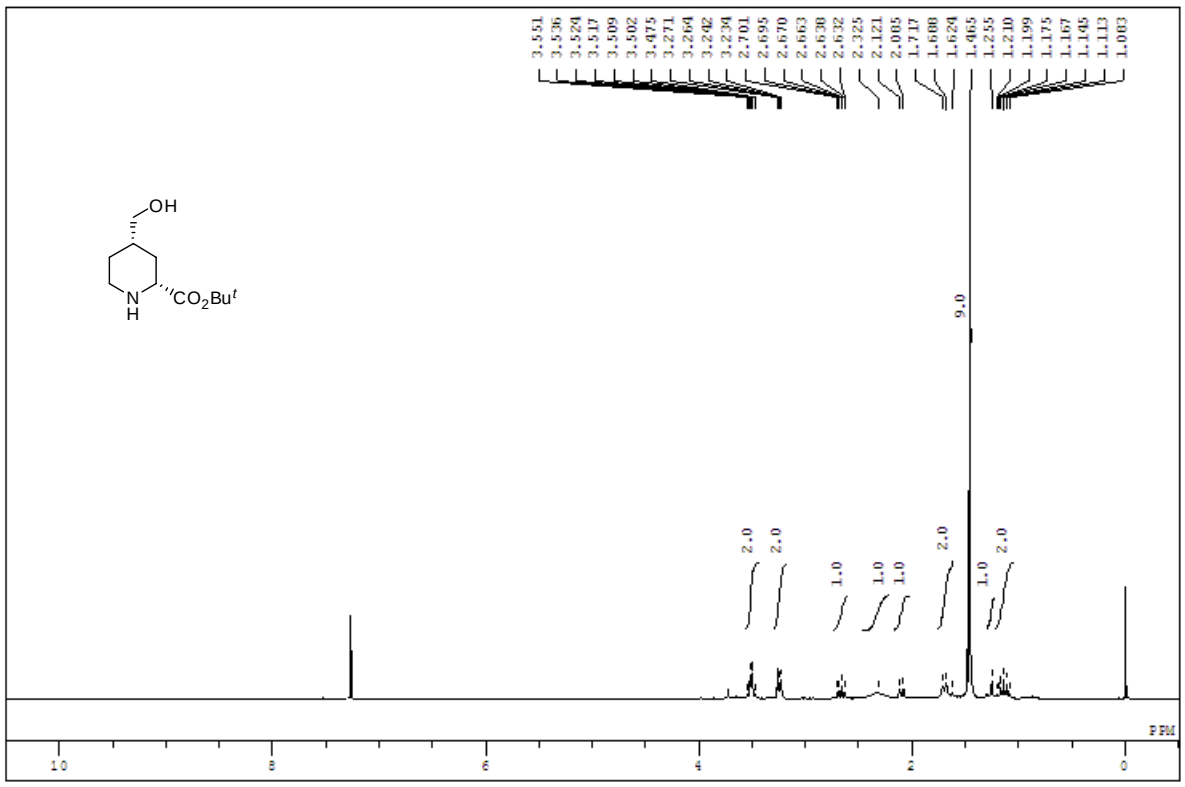
72.47
65.03
64.93
34.13
PPM
200
175
150
125
100
75
50
25
0


BnO
Ph2C=N
CO2Bu^t
PPM


PPM


OH
N
H
CO2But
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3.524
3.517
3.509
3.502
3.475
3.271
3.264
3.242
3.234
2.701
2.695
2.670
2.663
2.638
2.632
2.325
2.121
2.085
1.717
1.688
1.624
1.465
1.255
1.210
1.199
1.175
1.167
1.145
1.113
1.083
9.0
2.0
2.0
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1.0
1.0
2.0
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2.0
PPM
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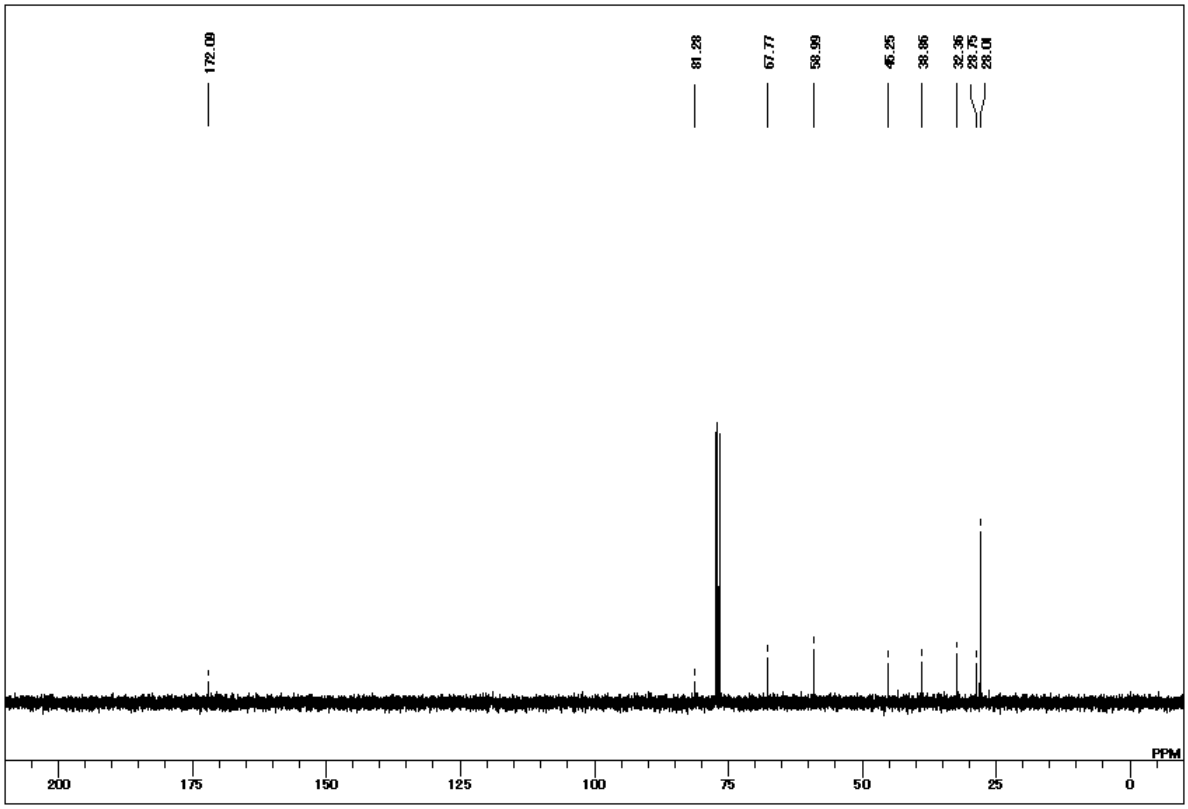
6
4
2
0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81.28
67.77
58.99
46.25
38.86
32.36
28.75
28.04
PPM
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175
150
125
100
75
50
25
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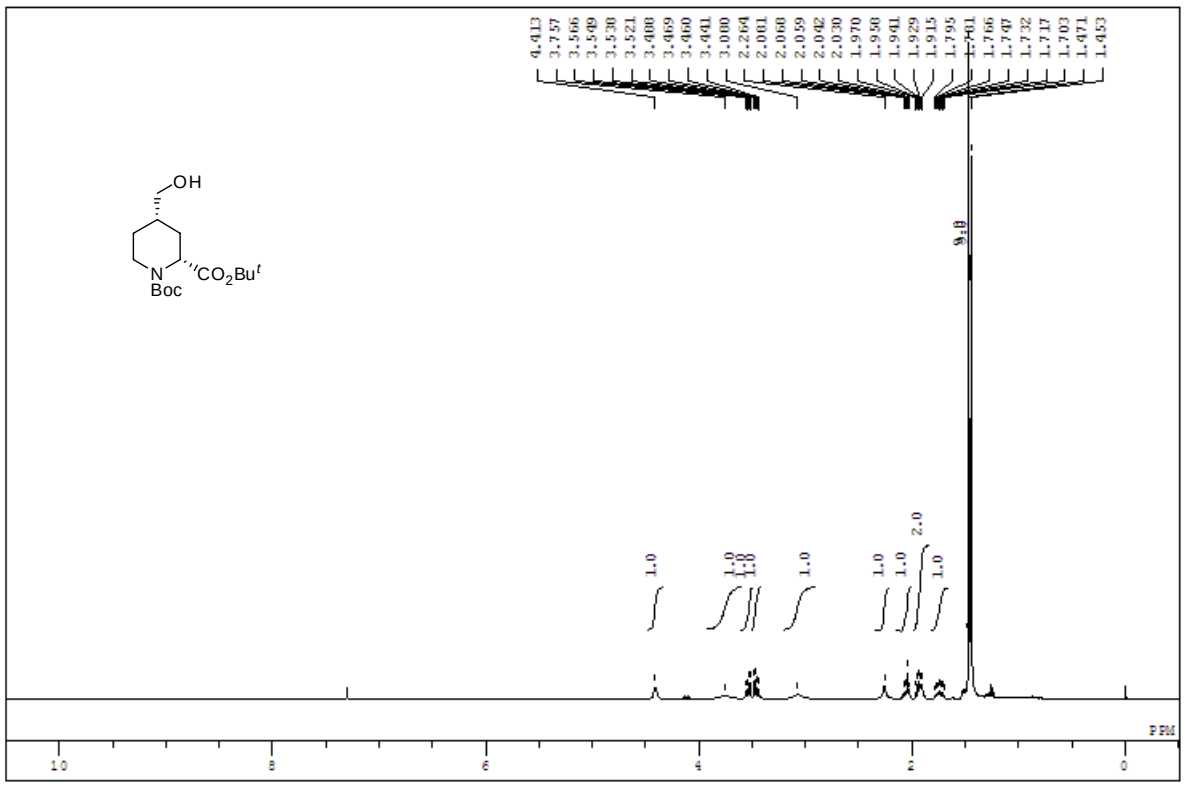
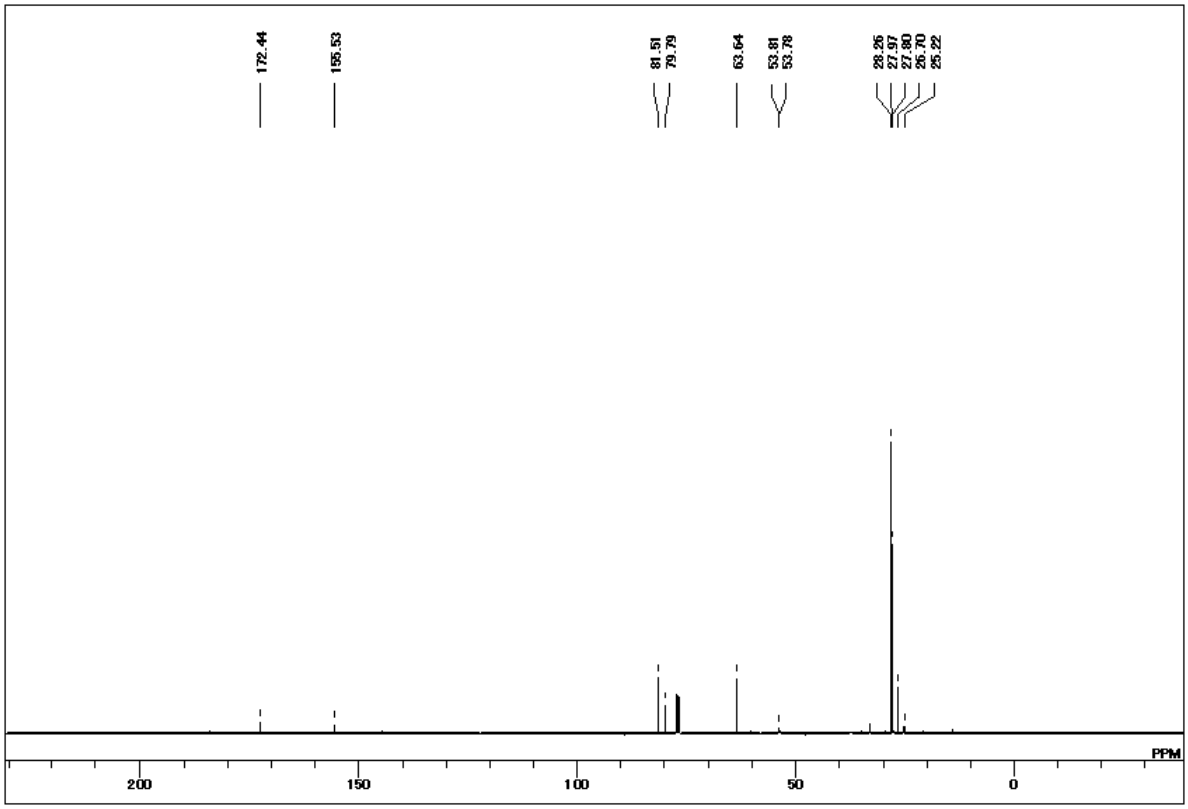

OH
N
Boc
CO2But
PPM
10
8
6
4
2
0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79.79
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53.81
53.78
28.26
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27.80
26.70
25.22
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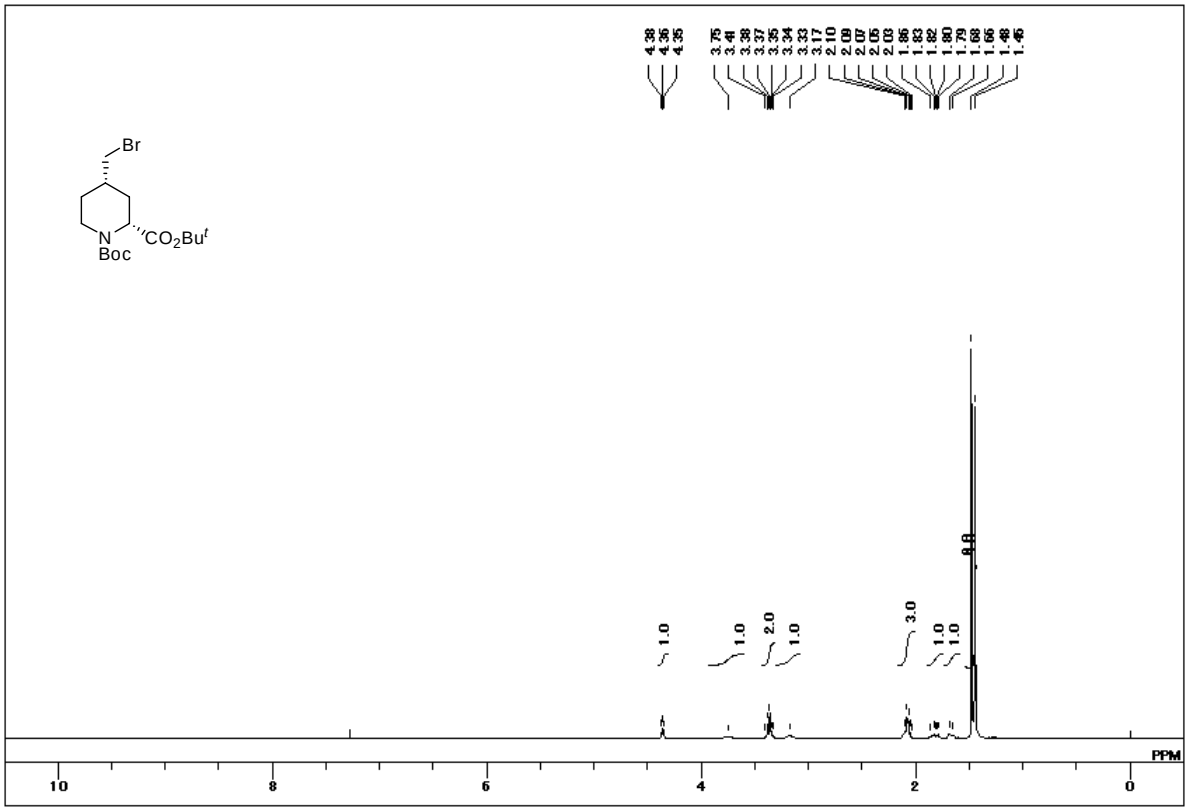
150
100
50
0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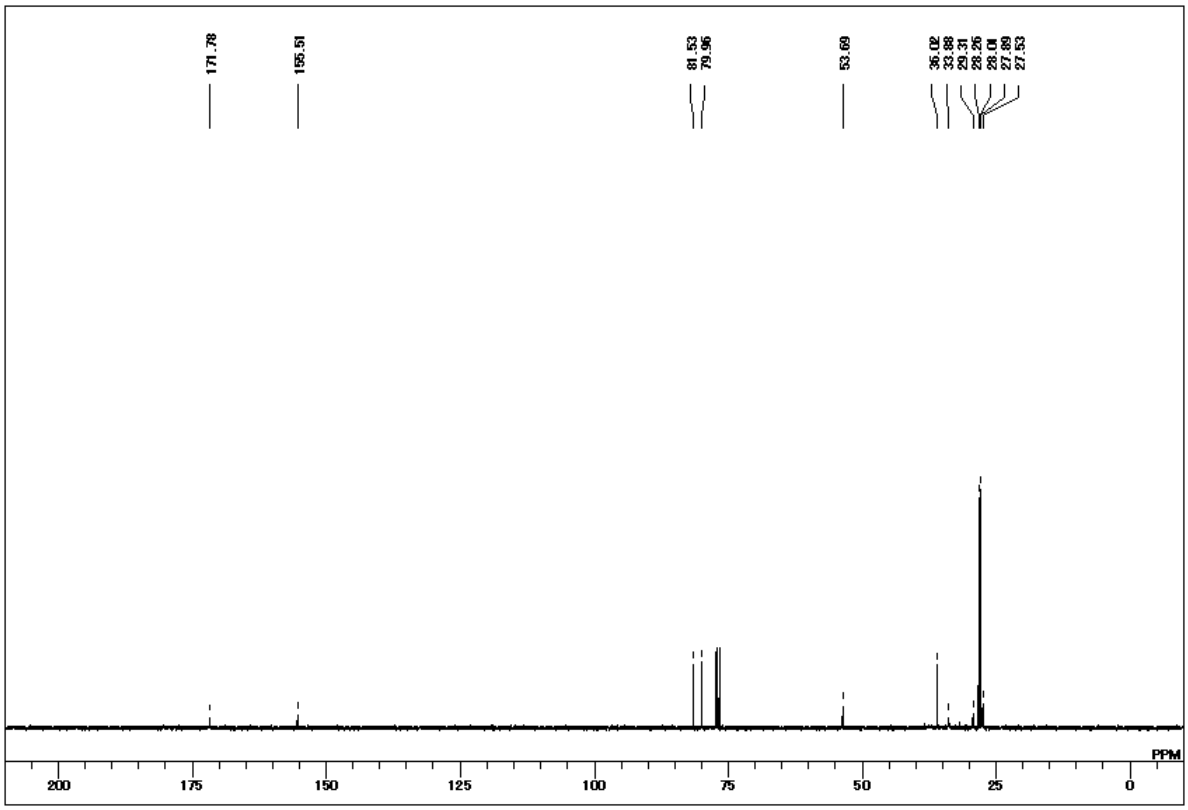
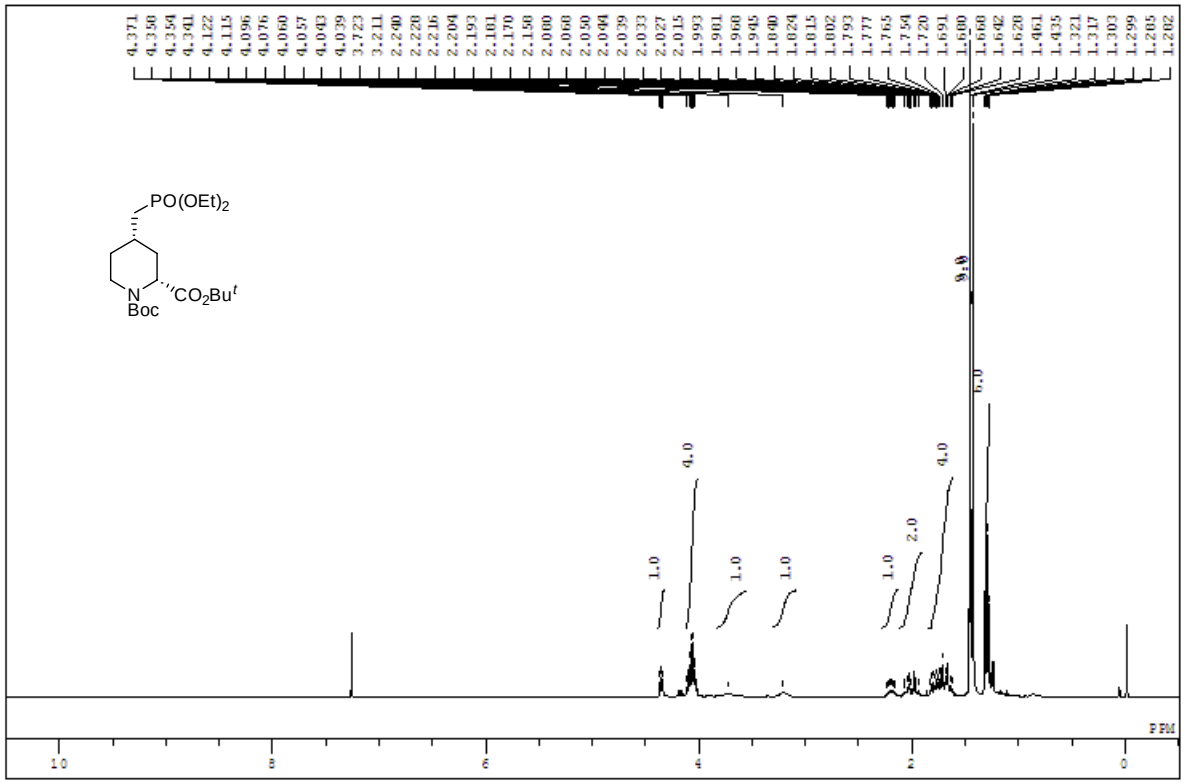
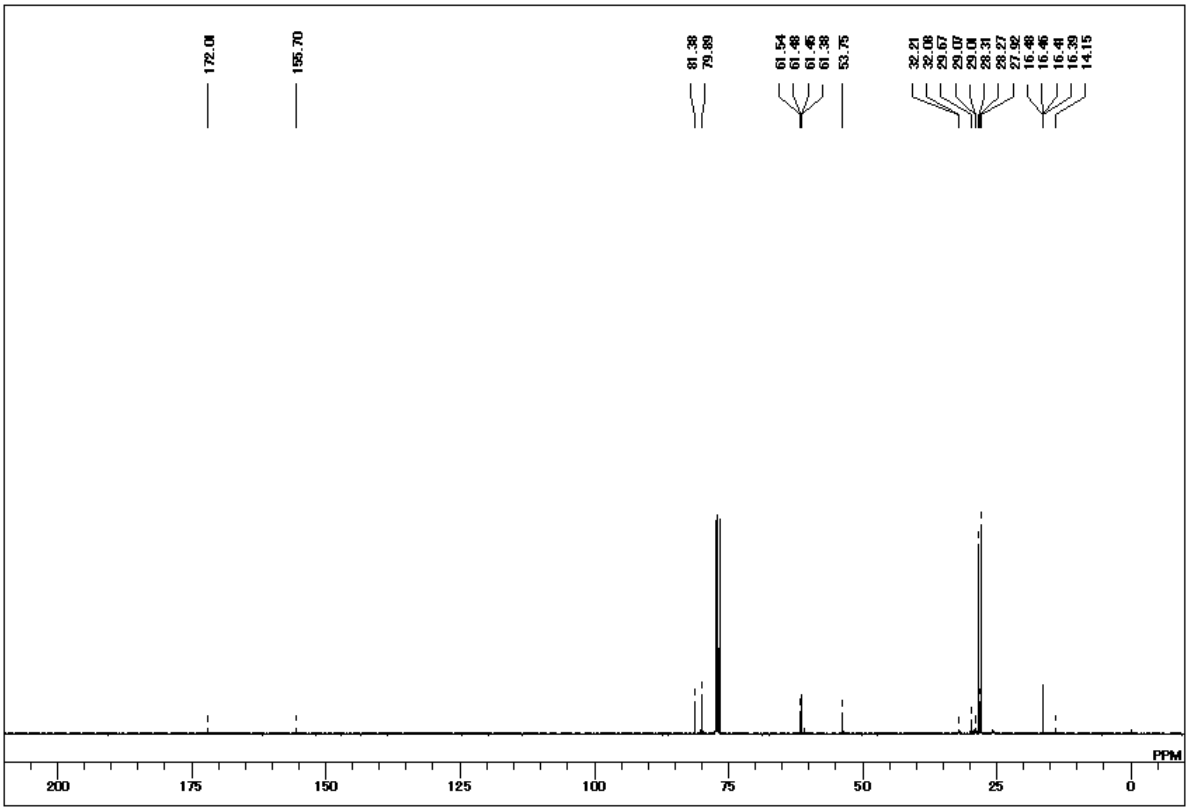
4.36
4.35
3.75
3.41
3.38
3.37
3.35
3.34
3.33
3.17
2.10
2.09
2.05
2.03
1.86
1.83
1.82
1.80
1.79
1.68
1.66
1.48
1.46
Br
N
Boc
CO2But
1.0
1.0
2.0
1.0
3.0
1.0
1.0
9.0
PPM
10
8
6
4
2
0


171.78
155.51
81.53
79.96
53.69
36.02
33.88
29.31
28.26
28.04
27.89
27.53
PPM
200
175
150
125
100
75
50
25
0


PO(OEt)2
N
Boc
CO2But
PPM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79.89
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61.45
61.38
53.75
32.21
32.06
29.67
29.07
29.06
28.31
28.27
27.92
16.48
16.46
16.44
16.39
14.15
PPM