Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Catalytic asymmetric synthesis of cyclic amino acid derivatives

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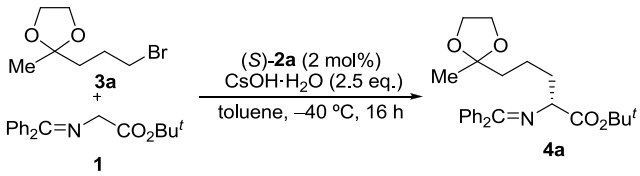
General Information: Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane (in the case of $CDCl_3$) as an internal standard. Data were reported 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 **5b**,[8] **5d**,[9] **5a**,[10] **10e**[11] and **10f**[11] are known compounds. Other simple chemicals were purchased and used as such.

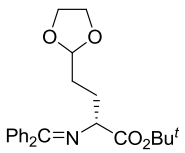
General procedure for asymmetric alkylation under phase-transfer conditions



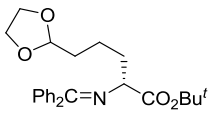
To a mixture of **1** (30 mg, 0.10 mmol), **3a** (209 mg, 1.0 mmol) and (*S*)-**2a** (1.5 mg, 0.002 mmol) in toluene (1 mL) was added CsOH (42 mg, 0.25 mmol) at –40 ˚C, and the reaction mixture was vigorously stirred for 16 h. After the consumption of the starting material, the mixture was diluted with 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 7.66-7.63 (2H, m), 7.45-7.29 (6H, m), 7.19-7.17 (2H, m), 3.93-3.84 (5H, m),

1.93-1.87 (2H, m), 1.60-1.55 (2H, m), 1.44 (9H, s), 1.40-1.30 (2H, m), 1.27 (3H, s); ^{13}C NMR δ 171.5, 169.9, 139.7, 136.7, 130.1, 128.8, 128.5, 128.4, 127.94, 127.88, 111.0, 80.8, 66.0, 64.6, 38.9, 33.8, 28.1, 23.8, 20.6; IR (neat) 2951, 1732, 1622, 1447, 1368, 1148, 1069 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{26}H_{34}NO_4$: 424.2482 ([M + H]$^+$), Found: 424.2491 ([M + H]$^+$).

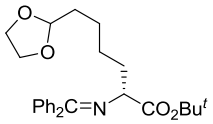
(*R*)-*tert*-Butyl 4-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)butanoate (4b): Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 9.7 min (major) and 12.9 min (minor); $[\alpha]_D^{21}$ = 74.3 (*c* 1.0, $CHCl_3$, 90% ee); ^{1}H NMR δ 7.66-7.63 (2H, m), 7.46-7.28 (6H, m), 7.19-7.17 (2H, m), 4.82 (1H, t, *J* = 4.8 Hz), 3.97-3.87 (3H, m), 3.84-3.75 (2H, m), 2.07-1.98 (2H, m), 1.76-1.67 (1H, m), 1.63-1.55 (1H, m), 1.44 (9H, s); ^{13}C NMR δ 171.1, 170.1, 139.6, 136.6, 130.1, 128.7, 128.4, 128.3, 127.9, 127.8, 104.2, 80.8, 65.5, 64.8, 64.7, 30.4, 28.02, 27.98; IR (neat) 2976, 2355, 1732, 1368, 1146 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{24}H_{30}NO_4$: 396.2169 ([M + H]$^+$), Found: 396.2181 ([M + H]$^+$).



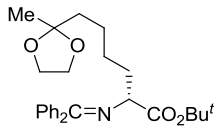
(*R*)-*tert*-Butyl 5-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)pentanoate (4d): Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 7.7 min (major) and 9.9 min (minor); $[\alpha]_D^{23}$ = 20.1 (*c* 1.0, $CHCl_3$, 99% ee); ^{1}H NMR δ 7.66-7.63 (2H, m), 7.46-7.29 (6H, m), 7.20-7.15 (2H, m), 4.81 (1H, t, *J* = 4.8 Hz), 3.96-3.88 (3H, m), 3.85-3.77 (2H, m), 1.97-1.91 (2H, m), 1.63-1.58 (2H, m), 1.44 (9H, s), 1.42-1.26 (2H, m); ^{13}C NMR δ 171.4, 170.0, 139.7, 136.7, 130.1, 128.7, 128.43, 128.36, 127.9, 127.8, 104.4, 80.8, 65.9, 64.8, 33.7, 33.5, 28.0, 20.6; IR (neat) 2949, 1732, 1622, 1368, 1146 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{25}H_{32}NO_4$: 410.2326 ([M + H]$^+$), Found: 410.2334 ([M + H]$^+$).



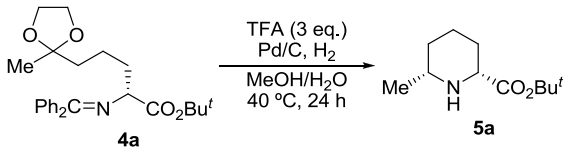
(*R*)-*tert*-Butyl 6-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)hexanoate (4e): Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 8.1 min (major) and 10.8 min (minor); $[\alpha]_D^{28}$ = 7.4 (*c* 1.0, $CHCl_3$, 99% ee); ^{1}H NMR δ 7.66-7.63 (2H, m), 7.46-7.29 (6H, m), 7.18-7.16 (2H, m), 4.80 (1H, t, *J* = 4.8 Hz), 3.97-3.88 (3H, m), 3.85-3.77 (2H, m), 1.92-1.87 (2H, m), 1.65-1.60 (2H, m), 1.44 (9H, s), 1.41-1.20 (4H, m); ^{13}C NMR δ 171.4, 169.8, 139.7, 136.7, 130.0, 128.7, 128.4, 128.3, 127.9, 127.8, 104.4, 80.7, 65.9, 64.7, 33.7, 33.5, 28.0, 25.9, 23.8; IR (neat) 2976, 1732, 1622, 1144, 1030 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{26}H_{34}NO_4$: 424.2482 ([M + H]$^+$), Found: 424.2488 ([M + H]$^+$).



(*R*)-*tert*-Butyl 2-(diphenylmethyleneamino)-6-(2-methyl-1,3-dioxolan-2-yl)hexanoate (4f): 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 7.65-7.63 (2H, m), 7.56-7.30 (6H, m), 7.18-7.15 (2H, m), 3.94-3.85 (5H, m), 1.88 (2H, q, *J* = 7.6 Hz), 1.61-1.57 (2H, m), 1.44 (9H, s), 1.37-1.20 (7H, m); ^{13}C NMR δ 171.6, 169.8, 136.8, 135.3, 130.1, 128.8, 128.42, 128.37, 128.0, 127.9, 110.0, 80.8, 66.0, 64.6, 39.1, 34.7, 33.6, 28.1, 26.3, 23.9, 23.7; IR (neat) 2978, 2359, 1732, 1622, 1368, 1152 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{27}H_{36}NO_4$: 438.2639 ([M + H]$^+$), Found: 438.2646 ([M + H]$^+$).

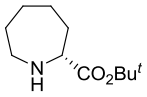


General procedure for diastereoselective reductive amination

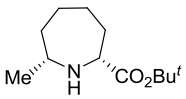


To a mixture of **4a** (67 mg, 0.16 mmol), EtOH (3 mL) and H_2O (1.5 mL) was added TFA (36 μL, 0.48 mmol). After stirring for 1 h, to the mixture was added 10% Pd/C (34 mg) and the mixture was stirred at 40 ˚C for 24 h under hydrogen atmosphere. After filtration through celite, the filtrate was basified 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 3.22 (1H, dd, *J* = 11.5, 2.7 Hz), 2.64 (1H, dqd, *J* = 11.0, 6.4, 2.7 Hz), 1.99-1.94 (1H, m), 1.89-1.83 (1H, m), 1.77 (1H, br), 1.62-1.57 (1H, m), 1.46 (9H, s), 1.44-1.25 (2H, m), 1.12 (3H, d, *J* = 6.4 Hz), 1.08-0.98 (1H, m); ^{13}C NMR δ 172.6, 80.8, 59.8, 51.8, 33.8, 29.0, 28.0, 24.6, 22.8; IR (neat) 2357, 2930, 2357, 1730, 1368, 1153 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{11}H_{22}NO_2$: 200.1645 ($[M + H]^+$), Found: 200.1644 ($[M + H]^+$).

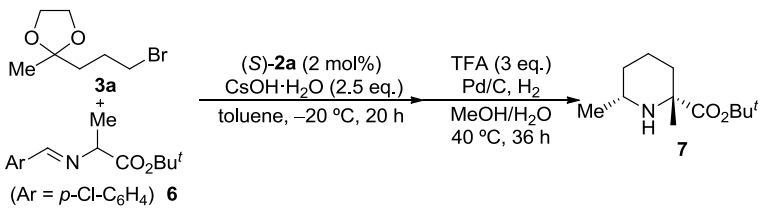
(*R*)-*tert*-Butyl azepane-2-carboxylate (5e): $[\alpha]_D^{23}$ = –6.3 (*c* 1.2, $CHCl_3$, 99% ee); ^{1}H NMR δ 3.42 (1H, dd, *J* = 8.8, 5.2 Hz), 3.10-3.04 (1H, m), 2.75-2.68 (1H, m), 2.57 (1H, br), 2.09-2.02 (1H, m), 1.76-1.54 (7H, m), 1.46 (9H, s); ^{13}C NMR δ 172.0, 82.1, 59.9, 45.8, 31.3, 29.5, 28.0, 27.4, 25.0; IR (neat) 2928, 1728, 1368, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{11}H_{22}NO_2$: 200.1645 ($[M + H]^+$), Found: 200.1648 ($[M + H]^+$).



(2*R*,7*R*)-*tert*-Butyl 7-methylazepane-2-carboxylate (5f): $[\alpha]_D^{22}$ = 15.0 (*c* 0.5, $CHCl_3$; 98% ee); ^{1}H NMR δ 3.39 (1H, dd, *J* = 9.8, 5.1 Hz), 2.79-2.71 (1H, m), 2.07-1.98 (1H, m), 1.88 (1H, br), 1.61-1.76 (5H, m), 1.46 (9H, s), 1.44-1.40 (1H, m), 1.34-1.26 (1H, m), 1.12 (3H, d, *J* = 6.6 Hz); ^{13}C NMR δ 174.1, 80.9, 61.0, 54.5, 39.6, 33.6, 28.0, 25.3, 25.0, 23.9; IR (neat) 2926, 2359, 1726, 1368, 1157 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{12}H_{24}NO_2$: 214.1802 ($[M + H]^+$), Found: 214.1799 ($[M + H]^+$).



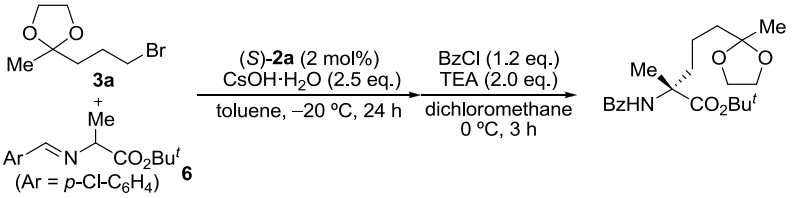
(2*R*,6*R*)-*tert*-Butyl 2,6-dimethylpiperidine-2-carboxylate (7)



To a mixture of **6** (161 mg, 0.60 mmol), **3a** (1.25 g, 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

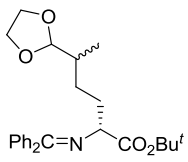
the mixture was added 10% Pd/C (80 mg) and the mixture was stirred at 40 ˚C for 36 h under hydrogen atmosphere. After filtration through celite, the result solution was basified with aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and purified by chromatography 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 2.91-2.86 (1H, m), 1.73-1.49 (6H, m), 1.46 (9H, s), 1.35 (3H, s), 1.07 (3H, d, *J* = 6.4 Hz), 1.02-0.91 (1H, m); ^{13}C NMR δ 175.7, 80.4, 58.1, 45.5, 34.0, 32.8, 27.8, 22.9, 20.6, 20.1; IR (neat) 2932, 1724, 1454, 1368, 1284, 1145 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

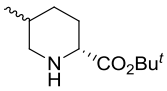


To a mixture of **6** (54 mg, 0.20 mmol), **3a** (418 mg, 2.0 mmol) and (*S*)-**2a** (3 mg, 0.004 mmol) in toluene (2 mL) was added CsOH (93 mg, 0.50 mmol) at –20 ˚C, and the reaction mixture was vigorously stirred for 24 h. After the consumption of the starting material, the mixture was concentrated 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. $[\alpha]_D^{19}$ = –12.6 (*c* 0.9, $CHCl_3$; 96% ee); ^{1}H NMR δ 7.81-7.78 (2H, m), 7.51-7.41 (3H, m), 3.92-3.83 (4H, m), 2.60-2.52 (1H, m), 1.86-1.78 (1H, m), 1.71 (3H, s), 1.69-1.55 (2H, m), 1.51 (9H, s), 1.48-1.38 (2H, m), 1.26 (3H, s); ^{13}C NMR δ 174.2, 166.0, 135.2, 131.3, 128.5, 126.8, 109.8, 82.3, 64.6, 64.5, 61.2, 38.8, 36.0, 27.9, 23.7, 23.4, 19.1; IR (neat) 3408, 2980, 1728, 1663, 1152 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{32}NO_5$: 378.2275 ($[M + H]^+$), Found: 378.2271 ($[M + H]^+$).

(*R*)-*tert*-Butyl 5-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)hexanoate (9b): $[\alpha]_D^{23}$ = 82.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 7.66-7.63 (2H, m), 7.46-7.30 (6H, m), 7.19-7.16 (2H, m), 4.65 (1H, d, *J* = 5.0 Hz), 3.95-3.87 (3H, m), 3.86-3.78 (2H, m), 2.04-1.85 (2H, m), 1.60-1.67 (2H, m), 1.44 (9H, s), 1.22-1.13 (1H, m), 0.91 (3H, d, *J* = 6.8 Hz),; ^{13}C NMR δ 171.5, 170.0, 139.7, 136.8, 130.1, 128.8, 128.42, 128.35, 127.94, 127.87, 107.5, 80.8, 66.2, 64.97, 64.95, 36.8, 31.3, 28.0, 27.9, 13.7; IR (neat) 2974, 1732, 1622, 1447, 1368, 1150 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{26}H_{34}NO_4$: 424.2482 ($[M + H]^+$), Found: 424.2469 ($[M + H]^+$).

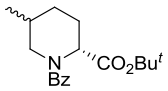


Diastereo-mixture of (*R*)-*tert*-butyl 5-methylpiperidine-2-carboxylate (10b): (2*R*,5*R*)/(2*R*,5*S*) = 1.2/1. ^{1}H



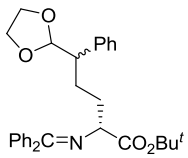
NMR δ 3.45-3.42 (0.55H, m), 3.11 (0.45H, dd, *J* = 11.6, 2.8 Hz), 3.08-3.04 (0.45H, m), 2.80 (0.55H, dd, *J* = 11.6, 3.6 Hz), 2.52 (0.55H, dd, *J* = 11.6, 9.2 Hz), 2.30 (1H, br), 2.22 (0.45H, app t), 2.04-1.96 (1H, m), 1.86-1.62 (3H, m), 1.48 (4.95H, s), 1.46 (4.05H, s), 1.15-1.01 (1H, m), 0.88 (1.65H, d, *J* = 6.4 Hz), 0.82 (1.35H, d, *J* = 6.8 Hz); ^{13}C NMR δ 173.2, 172.6, 80.7, 63.4, 59.2, 56.5, 53.5, 50.3, 33.2, 31.5, 30.1, 30.0, 29.7, 28.0, 27.9, 26.0, 19.2, 18.8; IR (neat) 2930, 1728, 1456, 1368, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{11}H_{22}NO_2$: 200.1645 ([M + H]$^+$), Found: 200.1654 ([M + H]$^+$).

Determination of the enantiomeric excess of (*R*)-*tert*-butyl 5-methylpiperidine-2-carboxylate (10b):



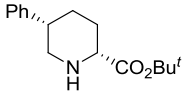
The enantiomeric excess of **10b** was determined by HPLC analysis after conversion to the corresponding benzamide. (2*R*,5*R*)/(2*R*,5*S*) = 1.2 (98% ee)/1(96% ee). Daicel Chiralpak OD-H, hexane/2-propanol = 200/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: (2*R*,5*R*: 56.2 min (major) and 102.7 min (minor)), (2*R*,5*S*: 62.5 min (major) and 78.9 min (minor)); ^{1}H NMR (toluene-d_8, 80 ˚C) δ 7.48-7.46 (2H, m), 7.15-7.05 (3H, m), 5.07 (0.45H, br), 3.60 (0.55H, br), 3.35 (0.45H, d, *J* = 13.2 Hz), 2.85 (0.55H, br), 2.22-2.17 (1.55H, m), 2.01-1.98 (0.45H, m), 1.83-1.80 (0.55H, m), 1.69-1.48 (2.45H, m), 1.43 (4.05H, s), 1.41 (4.95H, s), 1.24-1.21 (0.45H, m), 1.14-1.04 (0.55H, m), 0.87 (1.35H, d, *J* = 6.8 Hz), 0.65 (1.65H, br); ^{13}C NMR δ 174.6, 173.6, 173.2, 173.1, 140.40, 140.35, 132.3, 132.1, 131.3, 130.4, 130.3, 130.0, 84.2, 83.8, 61.2, 55.4, 55.2, 49.7, 34.5, 33.7, 33.2, 30.8, 30.3, 29.9, 24.4, 22.2, 21.8, 19.2; IR (neat) 2930, 1728, 1638, 1420, 1225, 1142 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{18}H_{26}NO_3$: 304.1907 ([M + H]$^+$), Found: 304.1915 ([M + H]$^+$).

(*R*)-*tert*-Butyl 5-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)-5-phenylpentanoate (9c): $[\alpha]_D^{24}$ = 41.5



(*c* 1.3, $CHCl_3$); ^{1}H NMR δ 7.64-7.61 (2H, m), 7.43-7.10 (13H, m), 4.96 (0.5H, d, *J* = 4.8 Hz), 4.94 (0.5H, d, *J* = 4.4 Hz), 3.88-3.87 (1H, m), 3.80-3.74 (4H, m), 2.80-2.76 (1H, m), 1.89-1.70 (4H, m), 1.41 (4.5H, s), 1.39 (4.5H, s); ^{13}C NMR δ 171.4, 171.2, 169.8, 169.7, 140.0, 139.9, 139.74, 139.69, 136.69, 136.65, 130.08, 130.06, 128.9, 128.78, 128.75, 128.44, 128.41, 128.38, 128.36, 128.3, 128.20, 128.17, 128.0, 127.93, 127.87, 127.85, 126.7, 126.6, 111.6, 106.8, 80.8, 80.7, 66.2, 65.9, 65.10, 65.07, 65.0, 49.9, 49.7, 33.9, 31.5, 28.02, 28.01, 26.3, 26.2, 20.9; IR (neat) 2976, 1732, 1368, 1146 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{31}H_{36}NO_4$: 486.2639 ([M + H]$^+$), Found: 486.1632 ([M + H]$^+$).

(2*R*,5*S*)-*tert*-Butyl 5-phenylpiperidine-2-carboxylate ((2*R*,5*S*)-10c): Daicel Chiralpak AD-H,



hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 25.1 min (major) and 28.9 min (minor); $[\alpha]_D^{25}$ = 1.0 (*c* 0.4, $CHCl_3$, 92% ee); ^{1}H NMR δ 7.31-7.27 (2H, m), 7.21-7.18 (3H, m), 3.58 (1H, dd, *J* = 5.2, 3.2 Hz), 3.01-2.92 (2H, m), 2.80-2.73 (1H, m), 2.28-2.23 (1H, m), 1.93-1.81 (3H, m), 1.52 (9H, m), 1.48-1.41 (1H, m); ^{13}C NMR δ 173.4, 144.6, 128.4, 127.2, 126.3, 81.0, 55.9, 49.6, 42.5, 28.8, 28.2, 26.8; IR (neat) 2932, 1724, 1368, 1150 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{16}H_{24}NO_2$: 262.1802 ([M + H]$^+$), Found: 262.1794 ([M + H]$^+$).

(2*R*,5*R*)-*tert*-Butyl 5-phenylpiperidine-2-carboxylate ((2*R*,5*R*)-10c): Daicel Chiralpak AS-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 18.2 min (major) and 20.2 min (minor); $[\alpha]_D^{22}$ = –6.3 (*c* 0.8, $CHCl_3$, 89% ee); ^{1}H NMR δ 7.32-7.28 (2H, m), 7.22-7.19 (3H, m), 3.30-3.25 (2H, m), 2.74-2.63 (2H, m), 2.17-2.06 (3H, m), 1.75-1.54 (2H, m), 1.48 (9H, s); ^{13}C NMR δ 172.4, 144.1, 128.4, 127.0, 126.4, 81.0, 59.2, 53.0, 43.4, 31.6, 29.9, 28.0; IR (neat) 2932, 1730, 1368, 1153 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{16}H_{24}NO_2$: 262.1802 ([M + H]$^+$), Found: 262.1799 ([M + H]$^+$).

Diastereo-mixture of (2*R*)-*tert*-butyl 2-(diphenylmethyleneamino)-5-(2-methyl-1,3-dioxolan-2-yl) hexanoate (9d): (2*R*,5*R*)/(2*R*,5*S*) = 1/1. ^{1}H NMR δ 7.16-7.19 (2H, m) 7.65-7.63 (2H, m), 7.46-7.30 (6H, m), 3.93-3.79 (5H, m), 2.10-1.97 (1H, m), 1.88-1.69 (1H, m), 1.65-1.51 (2H, m), 1.45 (4.5H, s), 1.44 (4.5H, s), 1.19 (3H, s), 1.11-0.99 (1H, m), 0.93 (1.5H, d, *J* = 7.1 Hz), 0.91 (1.5H, d, *J* = 6.8 Hz); ^{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, 171.5, 169.9, 169.7, 139.83, 139.80, 136.82, 136.78, 130.1, 129.9, 128.82, 128.77, 128.43, 128.37, 128.35, 127.94, 127.90, 127.89, 112.34, 112.29, 80.81, 80.76, 66.6, 66.3, 65.54, 64.49, 48.9, 48.8, 47.6, 47.5, 41.4, 41.3, 32.1, 32.0, 31.8, 31.4, 28.12, 28.06, 20.3, 20.2, 14.6, 14.5; IR (neat) 2976, 1732, 1368, 1150 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 (10d): (2*R*,5*R*,6*R*)/(2*R*,5*S*,6*R*) = 2.5/1. ^{1}H NMR (toluene-d_8, 80 ˚C) δ 3.26-3.21 (1H, m), 2.85 (0.71H, dq, *J* = 2.9, 6.6 Hz), 2.24 (0.29H, dq, *J* = 8.8, 6.4 Hz), 2.00-1.95 (0.29H, m), 1.81-1.78 (0.29H, m), 1.71-1.47 (5.42H, m), 1.46 (9H, s), 1.11 (0.86H, d, *J* = 6.4 Hz), 1.03 (2.14H, d, *J* = 6.6 Hz), 0.89 (2.14H, d, *J* = 7.1 Hz), 0.85 (0.86H, d, *J* = 6.1 Hz); ^{13}C NMR δ (2*R*,5*R*,6*R*/2*R*,5*S*,6*R*) 172.9/172.6, 80.7/80.6, 60.2/59.7, 57.9/53.6, 33.8/37.7, 31.5/32.0, 28.01/28.00, 23.6/29.9, 20.0/20.3, 10.9/18.4; IR (neat) 1730, 1368, 1233, 1155 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 10d

The enantiomeric excess of **10d** 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-d_8, 80 ˚C) δ 7.19-7.13 (2H, m), 6.90-6.82 (3H, m), 4.69-3.76 (2H, m), 1.96 (0.71H, d, *J* = 13.2 Hz), 1.88-1.85 (0.71H, m), 1.80-1.74 (0.29H, m), 0.81 (2.14H, d, *J* = 7.1 Hz), 1.64-1.55 (0.29H, m), 1.49-1.09 (11H, m), 0.95 (0.86H, d, *J* = 7.6 Hz), 0.93 (0.71H, m), 0.79-0.77 (0.29H, m), 0.61 (0.86H, d, *J* =

7.1 Hz), 0.38 (2.14H, d, *J* = 6.6 Hz); ^{13}C NMR δ (2*R*,5*R*,6*R*/2*R*,5*S*,6*R*) 174.8/175.5, 174.1/174.4, 141.4/141.5, 140.4/140.7, 131.2/131.9, 130.0/129.9, 84.0/83.8, 56.9/55.4, 56.1/55.1, 37.8/37.7, 36.17/36.15, 30.9/29.3, 27.3/26.1, 21.5/21.4, 15.6/23.1; IR (neat) 2976, 2361, 1726, 1641, 1412, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{19}H_{28}NO_3$: 318.2064 ([M + H]$^+$), Found: 318.2048 ([M + H]$^+$).

6-(2-Bromoethyl)-1,4-dioxaspiro[4.4]nonane (8e): The title compound was prepared by a similar method described in literature.[4] ^{1}H NMR δ 3.95-3.87 (4H, m), 3.52-3.42 (1H, m), 3.40-3.35 (1H, m), 2.12-2.05 (2H, m), 1.95-1.91 (1H, m), 1.84-1.63 (5H, m), 1.36-1.31 (1H, m); ^{13}C NMR δ 117.8, 64.5, 64.4, 44.6, 35.5, 32.8, 32.6, 28.9, 20.6; IR (neat) 2876, 2957, 2876, 1738, 1315, 1260, 1206, 1139, 1026 cm^{-1}.

Diastereo-mixture of (2*R*)-*tert*-butyl 2-(diphenylmethyleneamino)-4-(1,4-dioxaspiro[4.4]nonan-6-yl) butanoate (9e): $[\alpha]_D^{24}$ = 91.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.65-7.63 (2H, m), 7.44-7.29 (6H, m), 7.19-7.17 (2H, m), 3.91-3.81 (5H, m), 1.94-1.81 (4H, m), 1.74-1.57 (4H, m), 1.44 (9H, s), 1.42-1.21 (3H, m); ^{13}C NMR δ 171.6, 169.8, 139.8, 136.8, 130.1, 128.8, 128.4, 128.3, 127.9, 118.2, 80.7, 66.3, 64.6, 64.4, 46.0, 35.8, 32.5, 31.6, 29.4, 28.1, 25.4, 20.6; IR (neat) 2953, 1732, 1148, 1030 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 10e

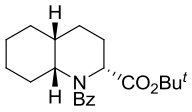
The enantiomeric excess of **10e** was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 16.4 min (major) and 22.3 min (minor). $[\alpha]_D^{20}$ = 41.6 (*c* 0.7, $CHCl_3$; 99% ee); ^{1}H NMR (toluene-d_8, 80 ˚C) δ 7.15-7.13 (2H, m), 6.89-6.86 (3H, m), 4.68 (1H, br), 4.04 (1H, br), 1.88-1.84 (1H, m), 1.73-1.65 (2H, m), 1.57-1.51 (1H, m), 1.27 (3H, br), 1.12 (9H, s), 1.06-0.92 (4H, m); ^{13}C NMR δ 174.6, 174.4, 141.6, 140.4, 131.2, 129.9, 83.8, 60.2, 57.2, 39.6, 33.1, 31.8, 30.9, 28.1, 27.7, 24.4; IR (neat) 1726, 2972, 1726, 1603, 1414, 1368, 1153 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{20}H_{28}NO_3$: 330.2064 ([M + H]$^+$), Found: 330.2069 ([M + H]$^+$).

6-(2-Bromoethyl)-1,4-dioxaspiro[4.5]decane (8f): The title compound was prepared by a similar method described in literature.[4] ^{1}H NMR δ 3.99-3.91 (4H, m), 3.55-3.49 (1H, m), 3.45-3.38 (1H, m), 2.28-2.15 (1H, m), 1.81-1.76 (3H, m), 1.72-1.59 (3H, m), 1.49-1.43 (1H, m), 1.39-1.25 (3H, m); ^{13}C NMR δ 110.4, 64.7, 64.5, 43.2, 34.5, 32.9, 32.3, 29.1, 24.5, 23.6; IR (neat) 2978, 3335, 2978, 1713, 1524, 1221, 1117 cm^{-1}.

Diastereo-mixture of (2*R*)-*tert*-butyl 2-(diphenylmethyleneamino)-4-(1,4-dioxaspiro[4.5]decan-6-yl) butanoate (9f): (2*R*,4*R*)/(2*R*,4*S*) = 1/1. $[\alpha]_D^{22}$ = 87.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.66-7.63 (2H, m), 7.44-7.29 (6H, m), 7.20-7.16 (2H, m), 3.93-3.81 (5H, m), 2.00-1.97 (1H, m), 1.81-1.65 (3H, m), 1.62-1.59 (2H, m), 1.50-1.47 (1H, m), 1.45 (4.5H, s), 1.44 (4.5H, s), 1.44-1.41

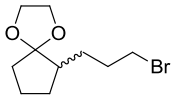
(2H, m), 1.34-1.18 (4H, m),; ^{13}C NMR δ 171.7, 171.6. 169.8. 169.5. 139.9. 139.8. 136.9. 136.8. 130.03. 130.01. 128.77. 128.75. 128.42. 128.36. 128.28. 128.26. 128.0. 127.93. 127.91. 127.98. 110.83. 110.80. 82.0. 80.7. 66.7. 66.3. 64.8. 64.7. 64.64. 64.61. 44.43. 44.39. 34.9. 34.8. 31.9. 31.8. 29.2. 29.0. 28.1. 24.7. 24.6. 24.52. 24.49. 23.9. 23.8. 21.8; IR (neat) 2932. 1732. 1368. 1150 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 10f

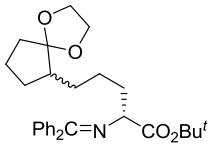


The enantiomeric excess of **10f** was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 13.6 min (major) and 16.5 min (minor). $[\alpha]_D^{19}$ = 67.1 (*c* 1.0, $CHCl_3$; 99% ee); ^{1}H NMR (toluene-d_8, 80 ˚C) δ 7.59-7.57 (1H, m), 7.30-7.23 (3H, m), 7.17-7.15 (1H, m), 5.05 (1H, br), 4.45 (1H, br), 2.46 (1H, d, *J* = 12.4 Hz), 2.28-2.27 (1H, m), 2.12-2.01 (2H, m), 1.88-1.73 (3H, m), 1.67-1.54 (2H, m), 1.51 (9H, s), 1.33-1.23 (4H, m); ^{13}C NMR δ 174.2, 174.1, 141.4, 140.4, 131.2, 129.9, 83.9, 58.0, 55.9, 39.3, 38.0, 35.8, 34.9, 30.9, 30.1, 29.3, 24.7; IR (neat) 2930, 1724, 1638, 1411, 1368, 1325, 1153 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{29}NNaO_3$: 366.2040 ([M + H]$^+$), Found: 366.2033 ([M + H]$^+$).

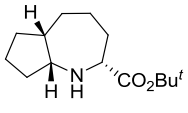
6-(3-Bromopropyl)-1,4-dioxaspiro[4.4]nonane (8g): The title compound was prepared by a similar method described in literature.[1] ^{1}H NMR δ 3.94-3.86 (4H, m), 3.45-3.36 (2H, m), 1.95-1.82 (4H, m), 1.80-1.54 (5H, m), 1.40-1.30 (2H, m); ^{13}C NMR δ 118.0, 64.5, 64.4, 45.4, 35.7, 34.1, 31.6, 29.5, 27.7, 20.6; IR (neat) 2876, 2953, 2876, 1450, 1209, 1142, 1110, 1028 cm^{-1}.

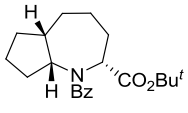


(*R*)-*tert*-Butyl 2-(diphenylmethyleneamino)-5-(1,4-dioxaspiro[4.4]nonan-6-yl)pentanoate (9g): $[\alpha]_D^{23}$ = 70.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 7.65-7.63 (2H, m), 7.46-7.29 (6H, m), 7.18-7.16 (2H, m), 3.92-3.79 (5H, m), 1.94-1.80 (4H, m), 1.74-1.58 (4H, m), 1.44 (9H, s), 1.42-1.40 (1H, m), 1.30-1.15 (4H, m); ^{13}C NMR δ 171.57, 171.56, 169.68, 169.66, 139.73, 139.71, 136.78, 136.75, 130.1, 130.0, 128.7, 128.37, 128.35, 128.32, 127.90, 127.85, 127.83, 127.82, 118.17, 118.15, 80.8, 66.1, 66.0, 64.52, 64.47, 64.4, 46.04, 45.96, 35.7, 34.0, 33.9, 29.4, 29.3, 28.7, 28.5, 28.0, 24.71, 24.67, 20.6; IR (neat) 2947, 1732, 1622, 1368, 1287, 1150 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{29}H_{38}NO_4$: 464.2795 ([M + H]$^+$), Found: 464.2796 ([M + H]$^+$).



(2*R*,5*aR*,8*aR*)-*tert*-Butyl decahydrocyclopenta[b]azepine-2-carboxylate (10g): $[\alpha]_D^{23}$ = –6.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 3.59 (1H, app t), 2.75-2.70 (1H, m), 2.44-2.42 (1H, m), 2.04-1.51 (11H, m), 1.45 (9H, s), 1.26-1.15 (1H, m), 1.12-1.02 (1H, m); ^{13}C NMR δ 174.3, 80.9, 63.2, 60.5, 50.2, 34.3, 33.2, 32.6, 32.4, 28.0, 23.7, 21.6; IR (neat) 2930, 1724, 1368, 1225, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{14}H_{26}NO_2$: 240.1952 ([M + H]$^+$), Found: 240.1958 ([M + H]$^+$).

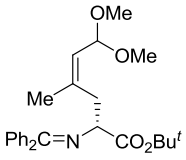




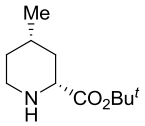
Determination of the enantiomeric excess of (2*R*,5*aR*,8*aR*)-*tert*-butyl decahydrocyclopenta[b]azepine-2-carboxylate (10g): The enantiomeric excess of **10g**

was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak OD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 13.8 min (minor) and 16.8 min (major); $[\alpha]_D^{23}$ = –5.6 (*c* 1.1, $CHCl_3$, 90% ee); ^{1}H NMR (toluene-d_8, 80 ˚C) δ 7.51-7.48 (2H, m), 7.19-7.12 (2H, m), 7.08-7.06 (1H, m), 5.04 (1H, br), 4.06-3.99 (1H, m), 2.79 (1H, br), 2.30-1.92 (3H, m), 1.85-1.81 (1H, m), 1.76-1.42 (6H, m), 1.42 (9H, s), 1.29-1.09 (2H, m); ^{13}C NMR δ 175.0, 174.1, 142.1, 140.4, 132.1, 130.0, 84.0, 69.2, 64.1, 46.3, 36.6, 35.5, 35.3, 35.2, 31.0, 27.5, 24.4, ; IR (neat) 2930, 1728, 1639, 1404, 1327, 1155 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{30}NO_3$: 344.2220 ($[M + H]^+$), Found: 344.2211 ($[M + H]^+$).

(*R*,*Z*)-*tert*-Butyl 2-(diphenylmethyleneamino)-6,6-dimethoxy-4-methylhex-4-enoate (14): 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 7.65-7.62 (2H, m), 7.46-7.28 (6H, m), 7.18-7.14 (2H, m), 5.30 (1H, dd, *J* = 6.4, 0.8 Hz), 4.95 (1H, d, *J* = 6.4 Hz), 4.07 (1H, dd, *J* = 8.3, 5.1 Hz), 3.26 (3H, s), 3.15 (3H, s), 2.68-2.56 (2H, m), 1.52 (3H, d, *J* = 1.2 Hz), 1.45 (9H, s); ^{13}C NMR δ 171.0, 170.0, 139.6, 138.1, 136.4, 130.1, 128.8, 128.5, 128.3, 127.94, 127.91, 124.9, 100.1, 81.2, 64.7, 52.6, 51.5, 43.4, 28.0, 17.1; IR (neat) 2367, 1734, 1150, 1053 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 (15): $[\alpha]_D^{21}$ = 8.8 (*c* 0.4, $CHCl_3$; 92% ee); ^{1}H NMR δ 3.18 (1H, dd, *J* = 11.7, 2.7 Hz), 3.16-3.11 (1H, m), 2.60 (1H, td, *J* = 12.5, 2.7 Hz), 1.99-1.93 (1H, m), 1.63-1.48 (2H, m), 1.46 (9H, s), 1.05-0.95 (2H, m), 0.94 (3H, d, *J* = 6.4 Hz); ^{13}C NMR δ 172.6, 80.8, 59.6, 45.8, 38.1, 34.7, 31.3, 28.0, 22.4; IR (neat) 2949, 2924, 1732, 1368, 1269, 1161 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{11}H_{22}NO_2$: 200.1645 ($[M + H]^+$), Found: 200.1641 ($[M + H]^+$).



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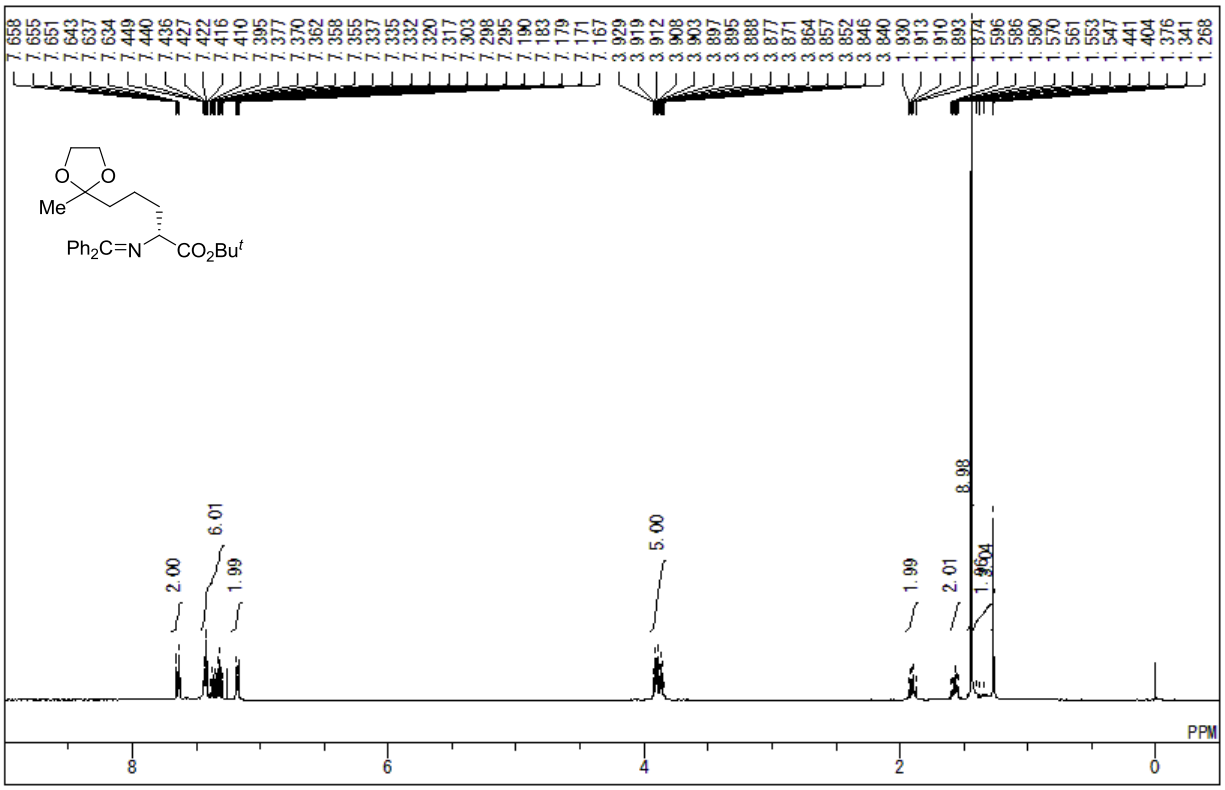

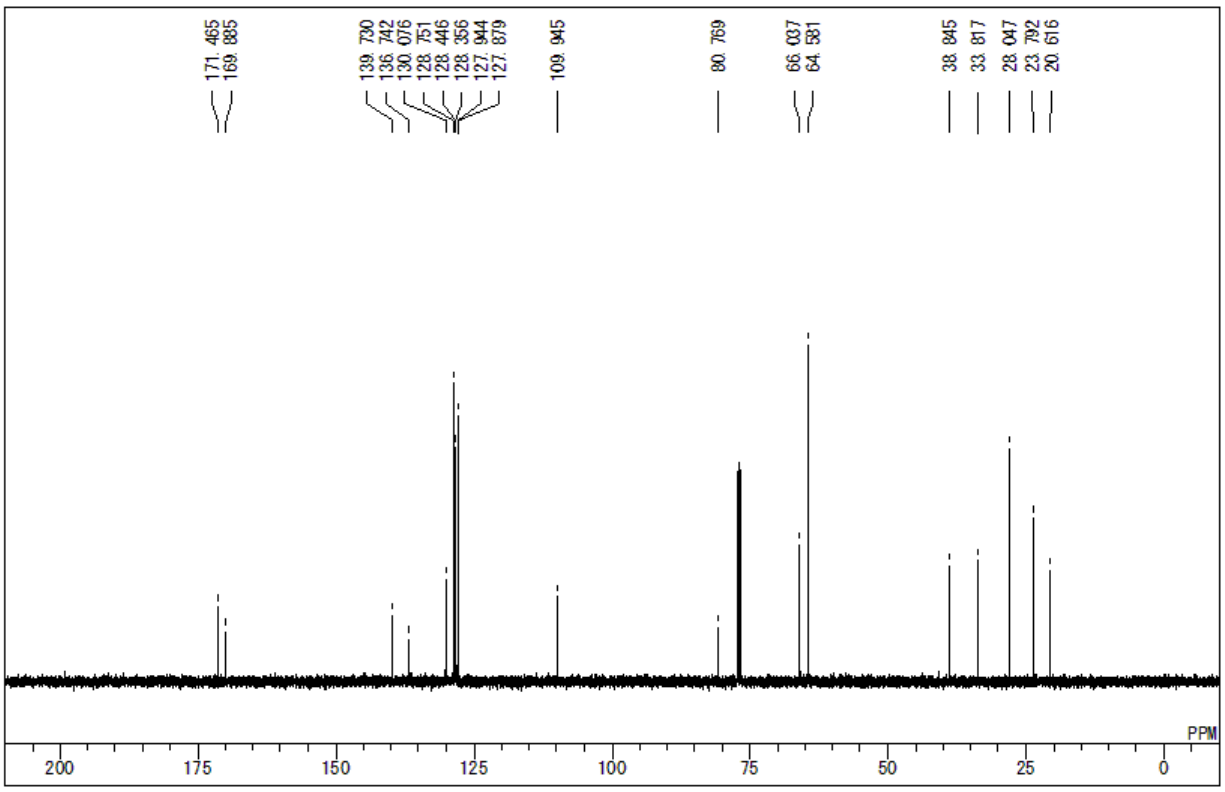

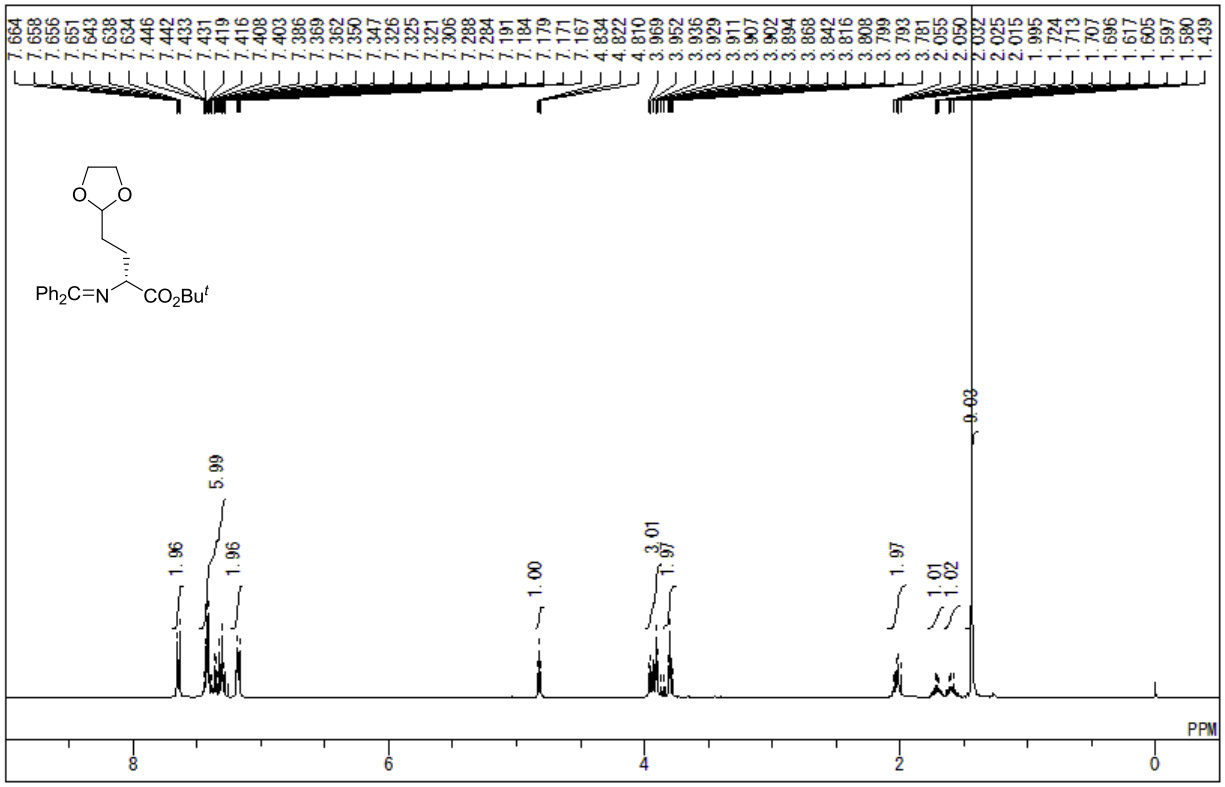

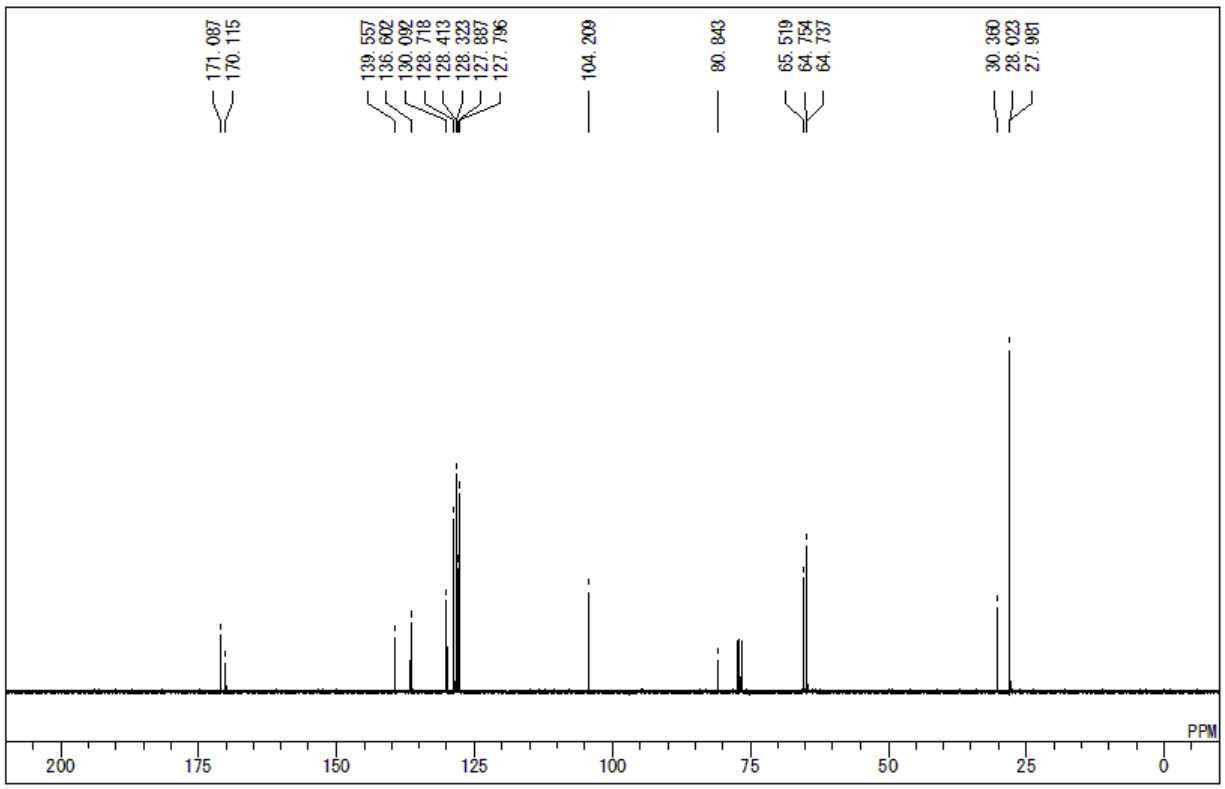

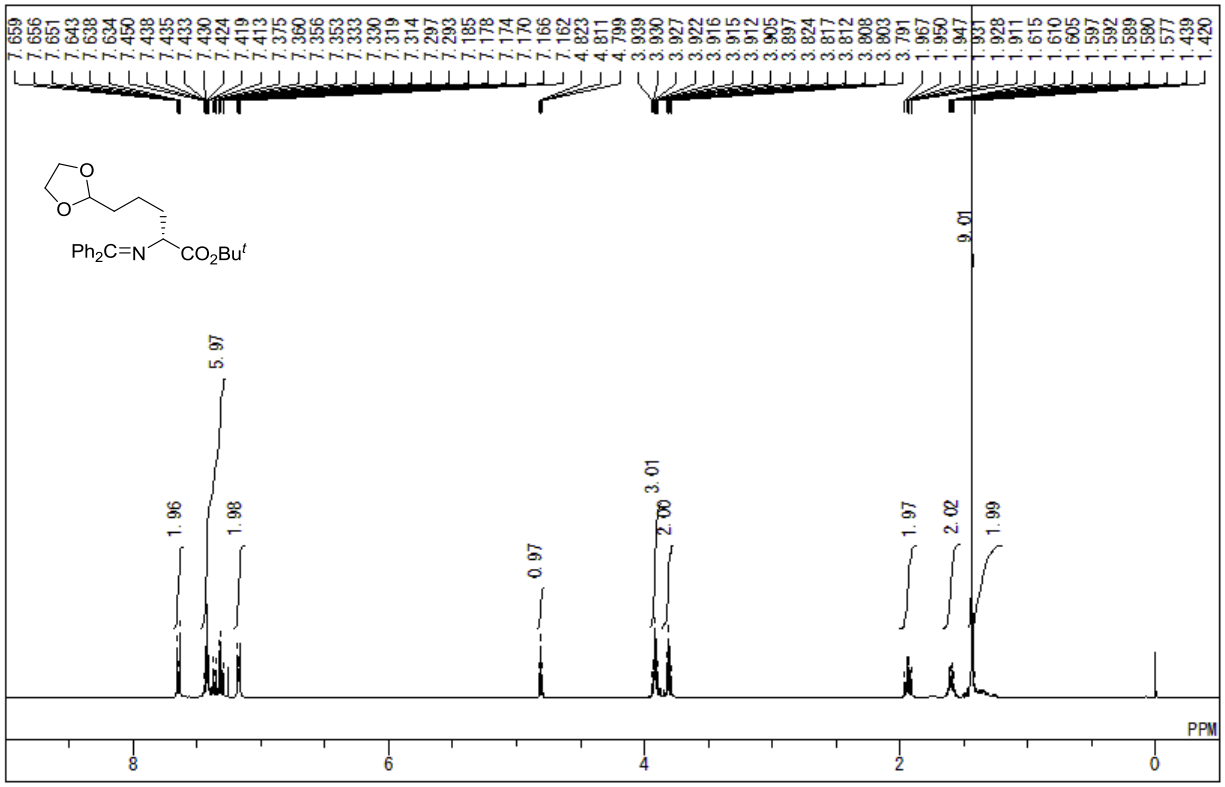

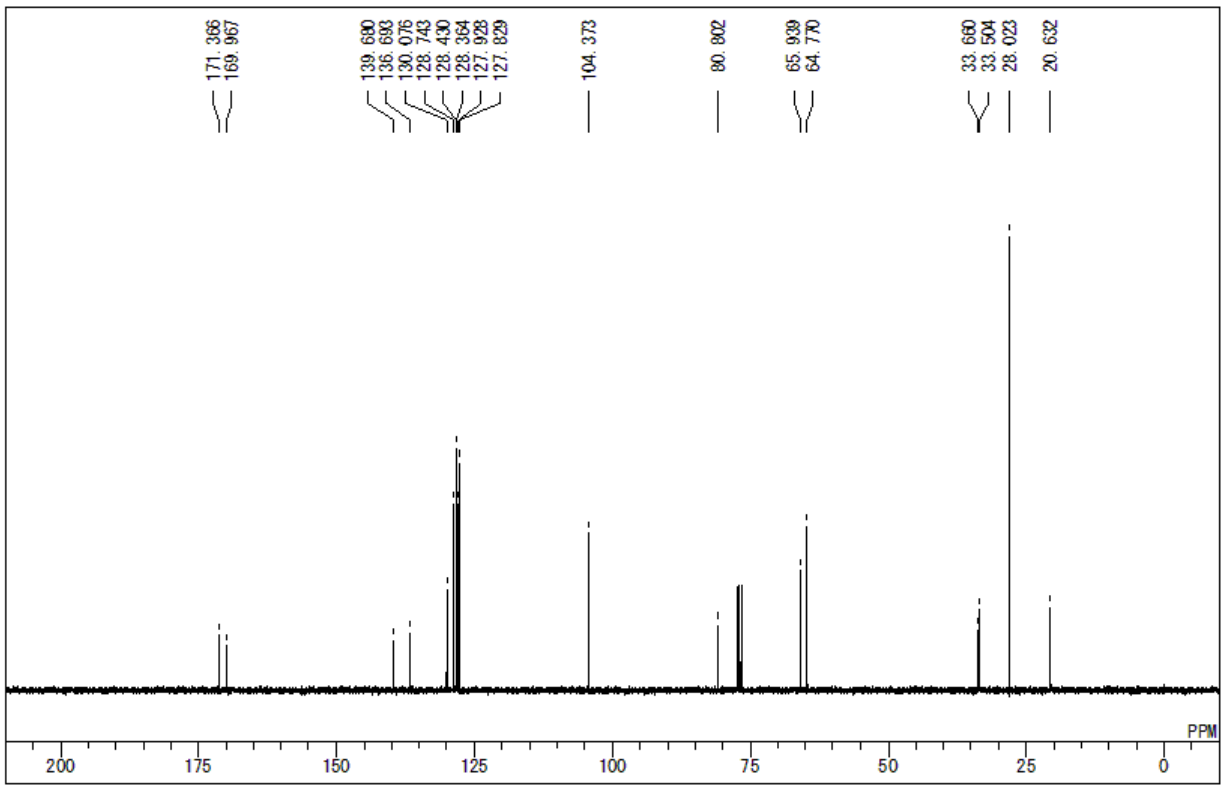

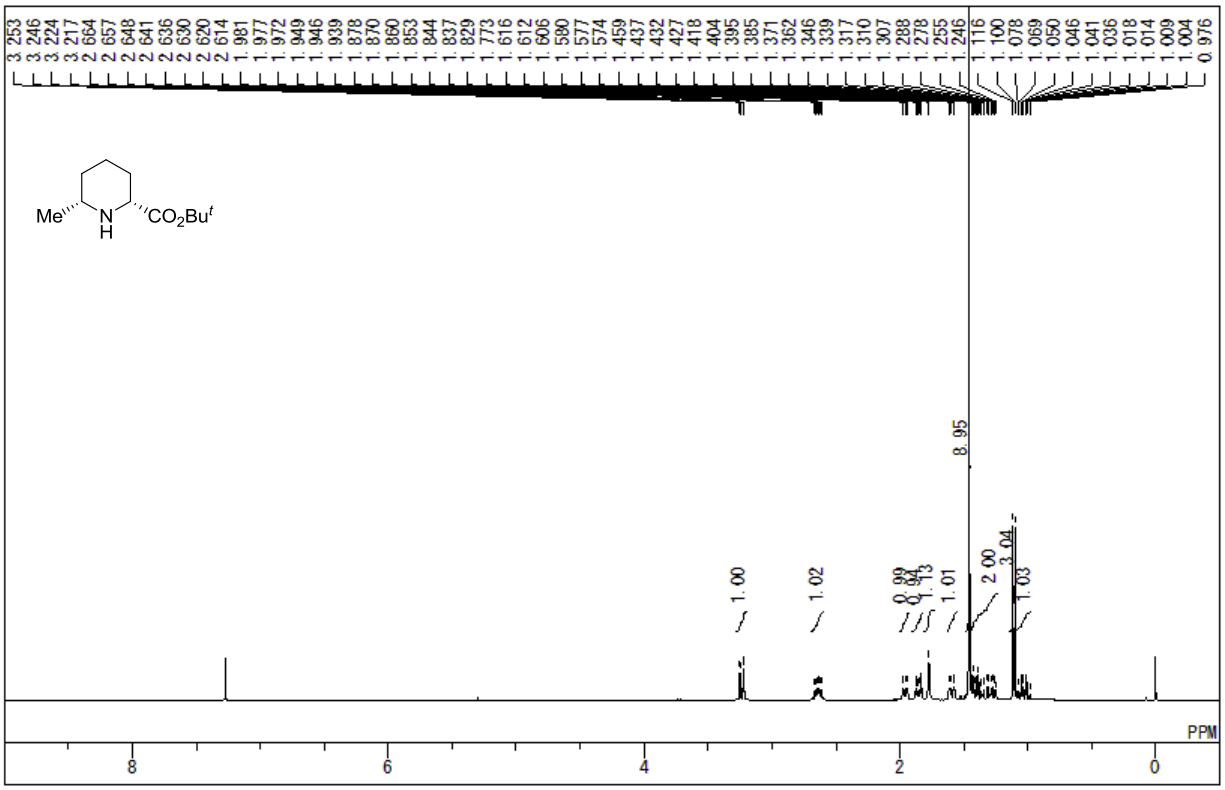
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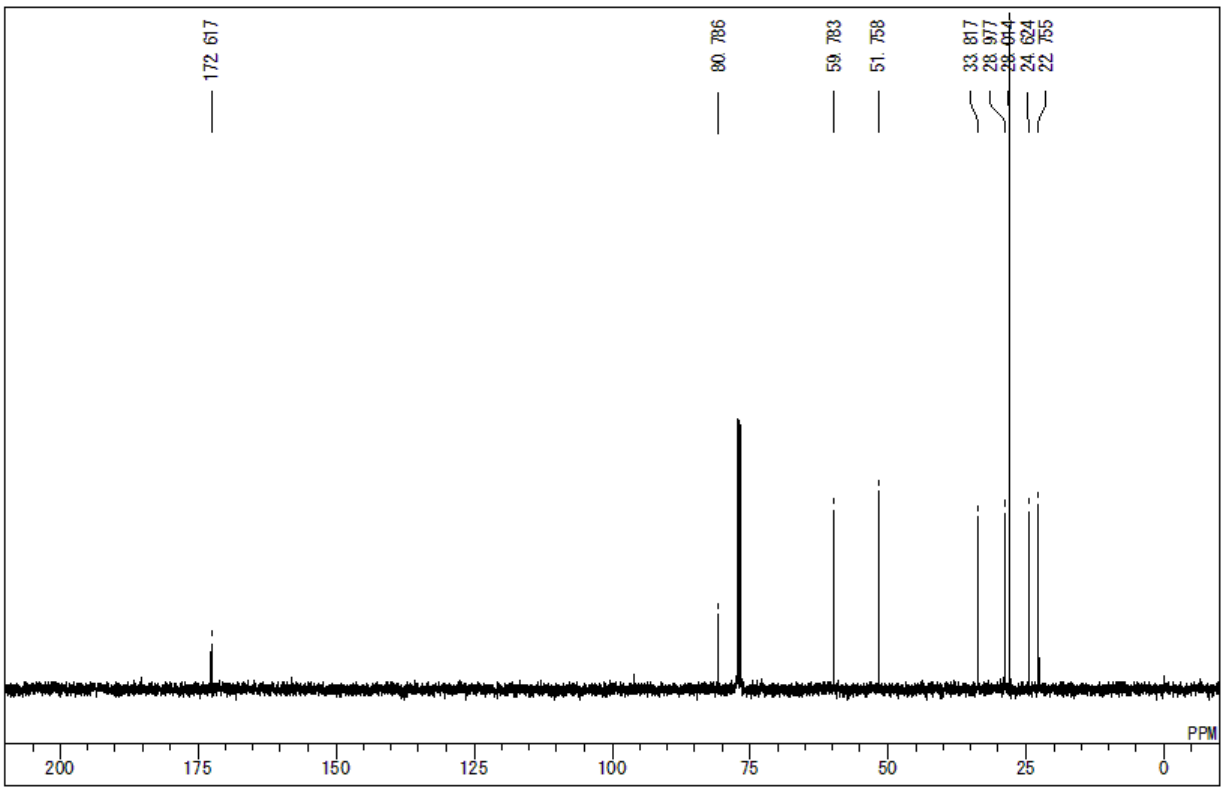
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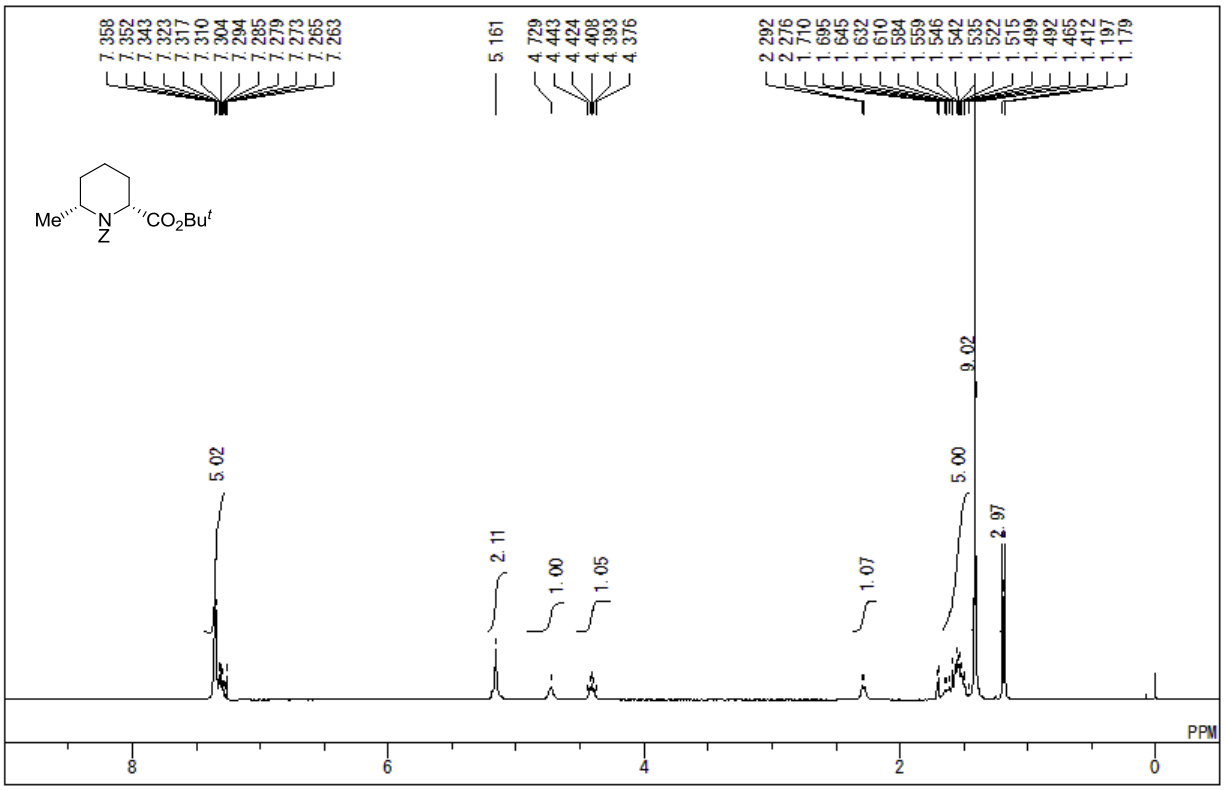

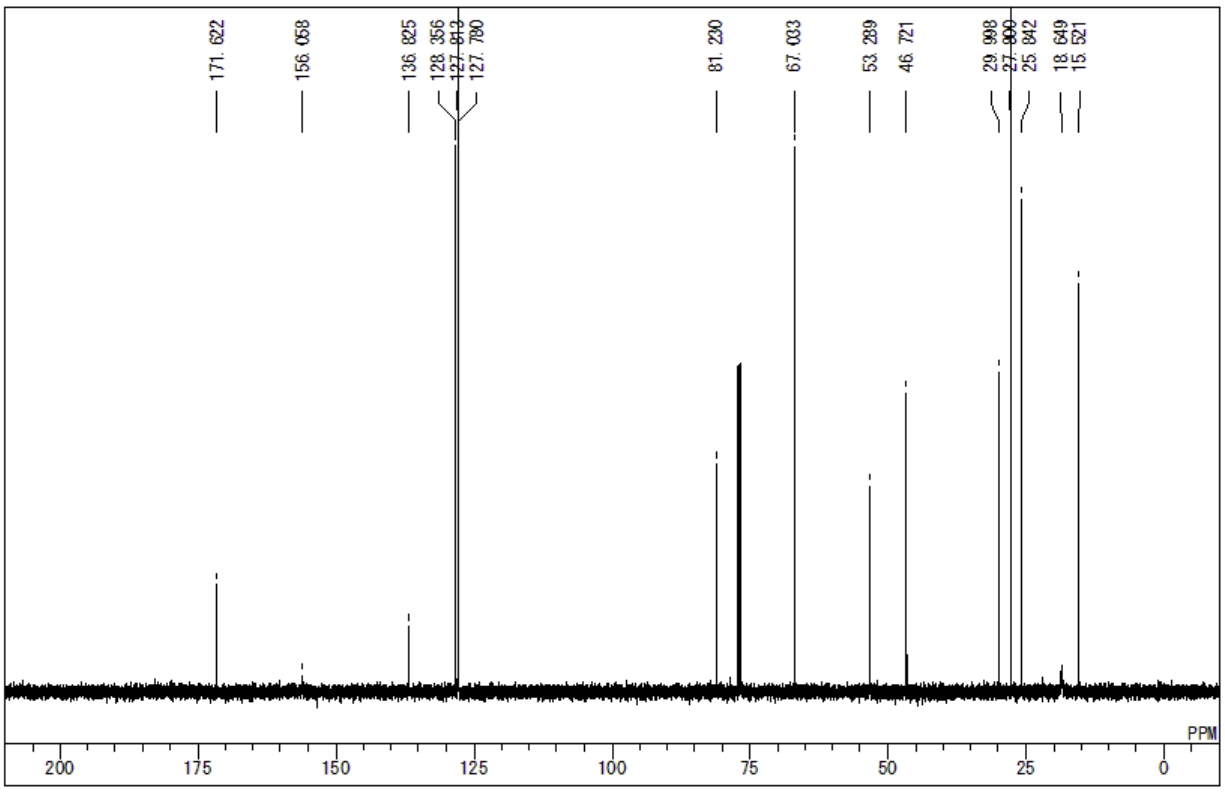

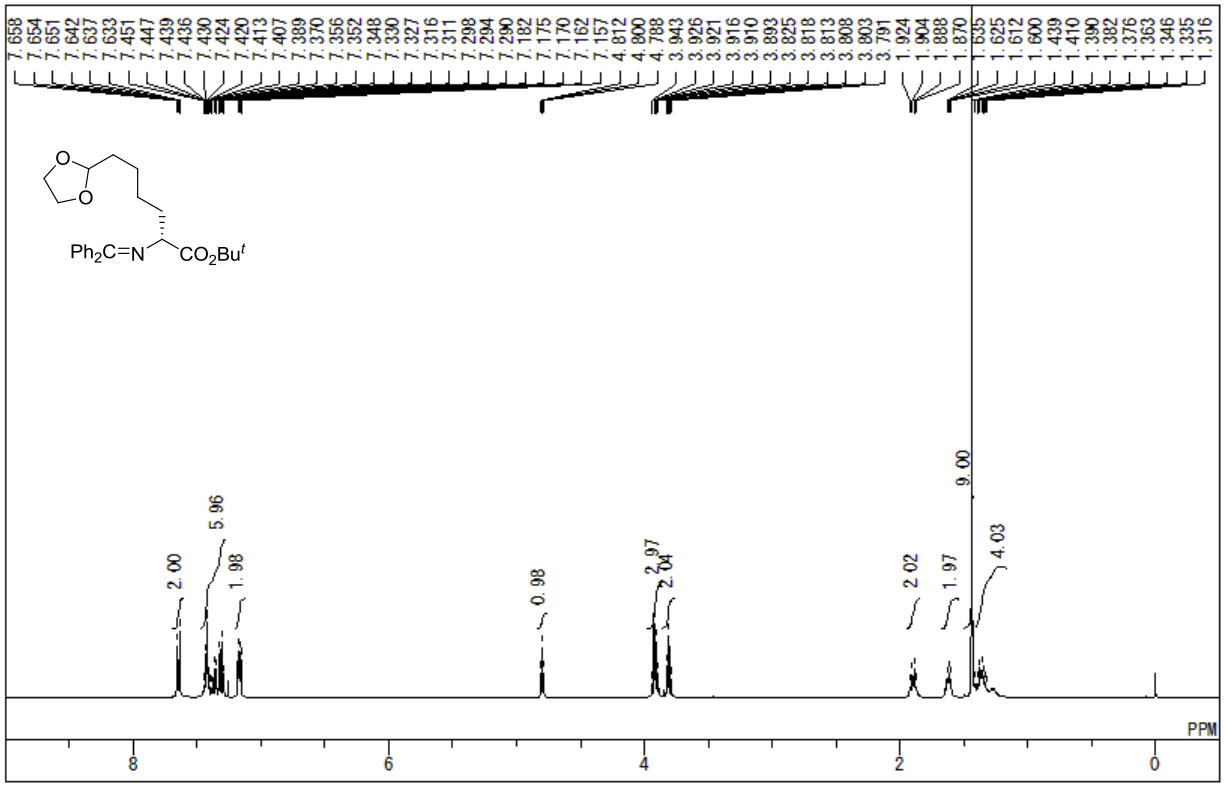

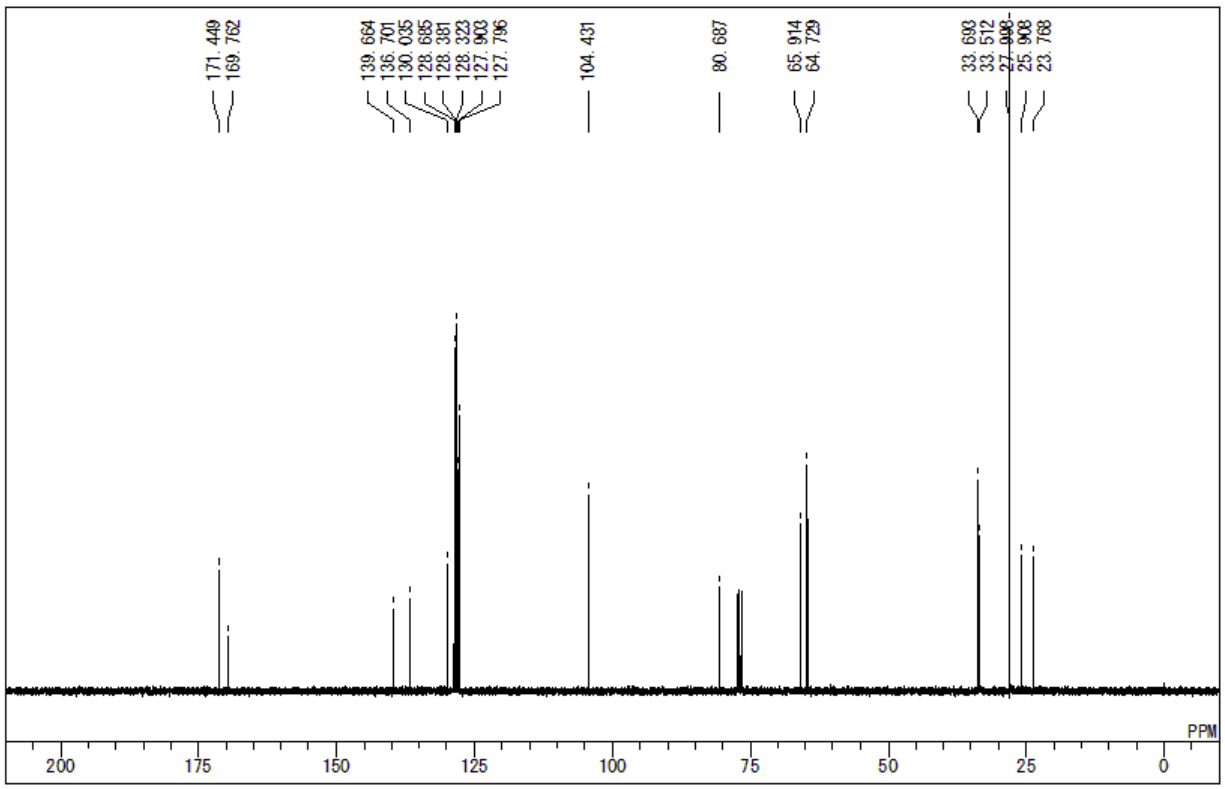

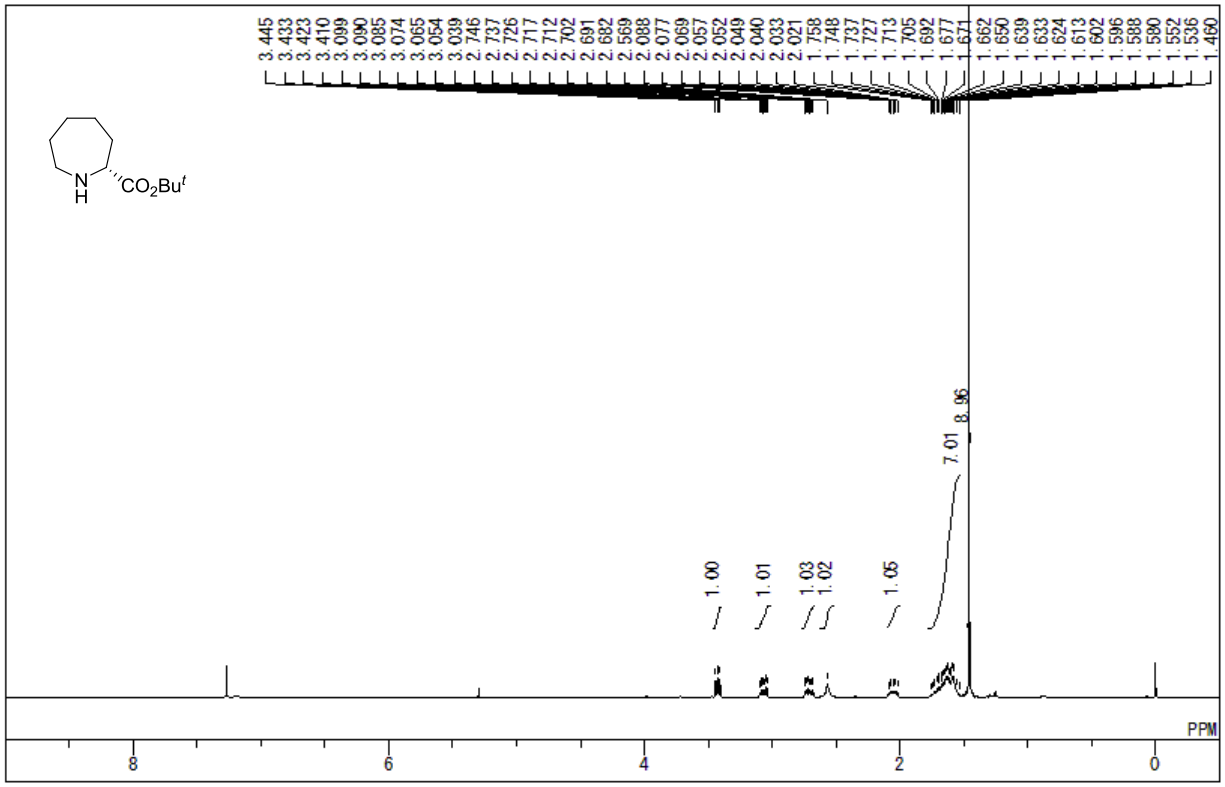

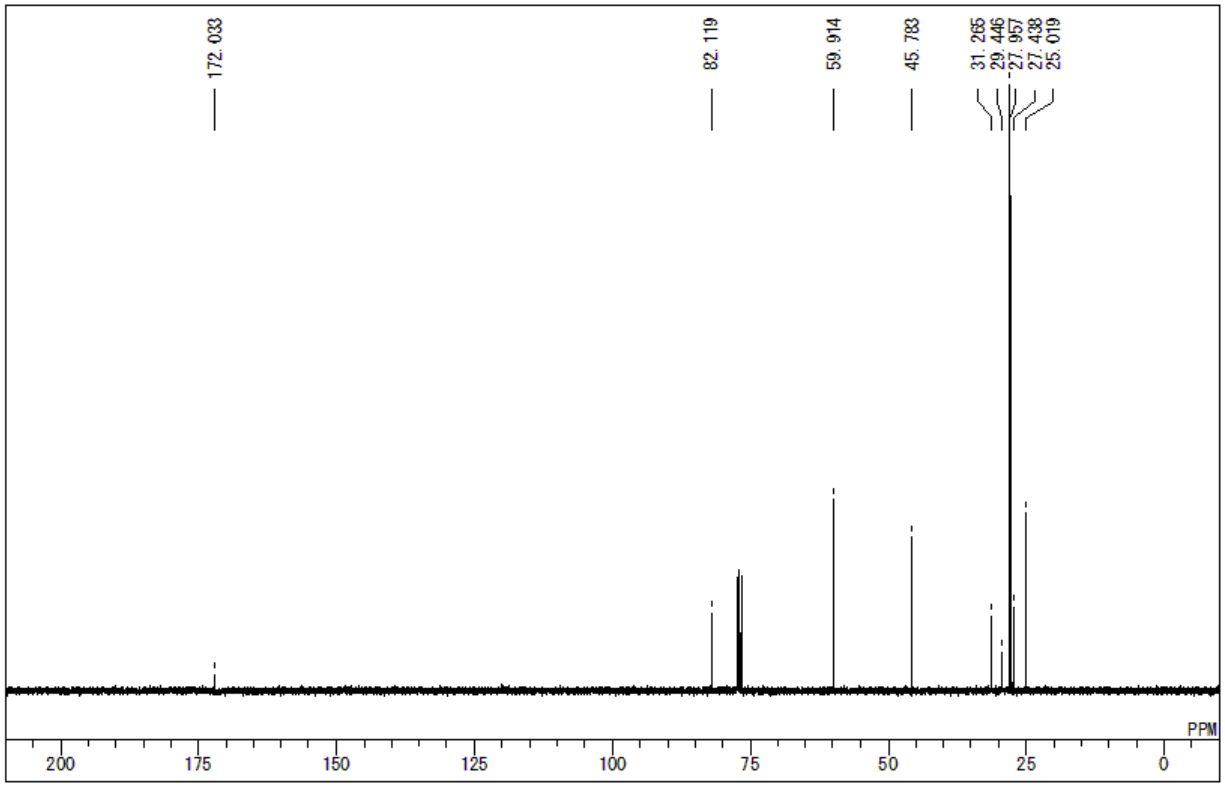

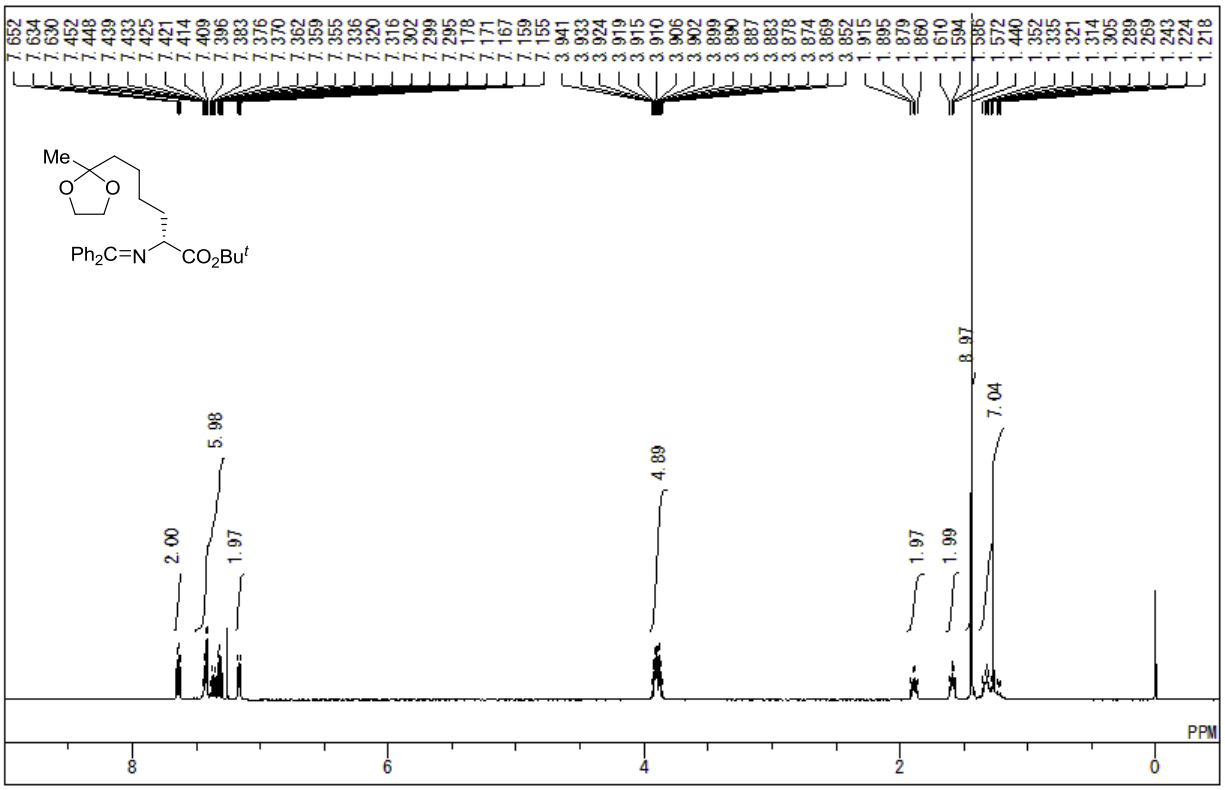

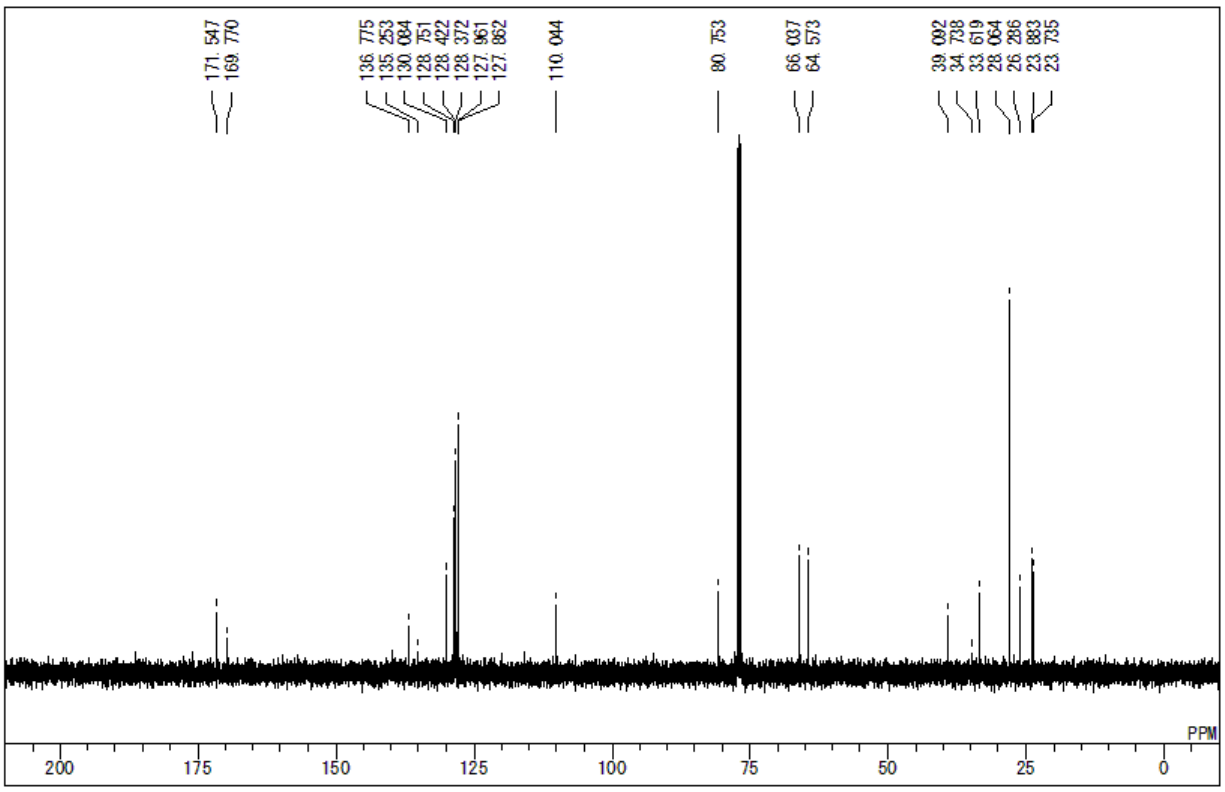

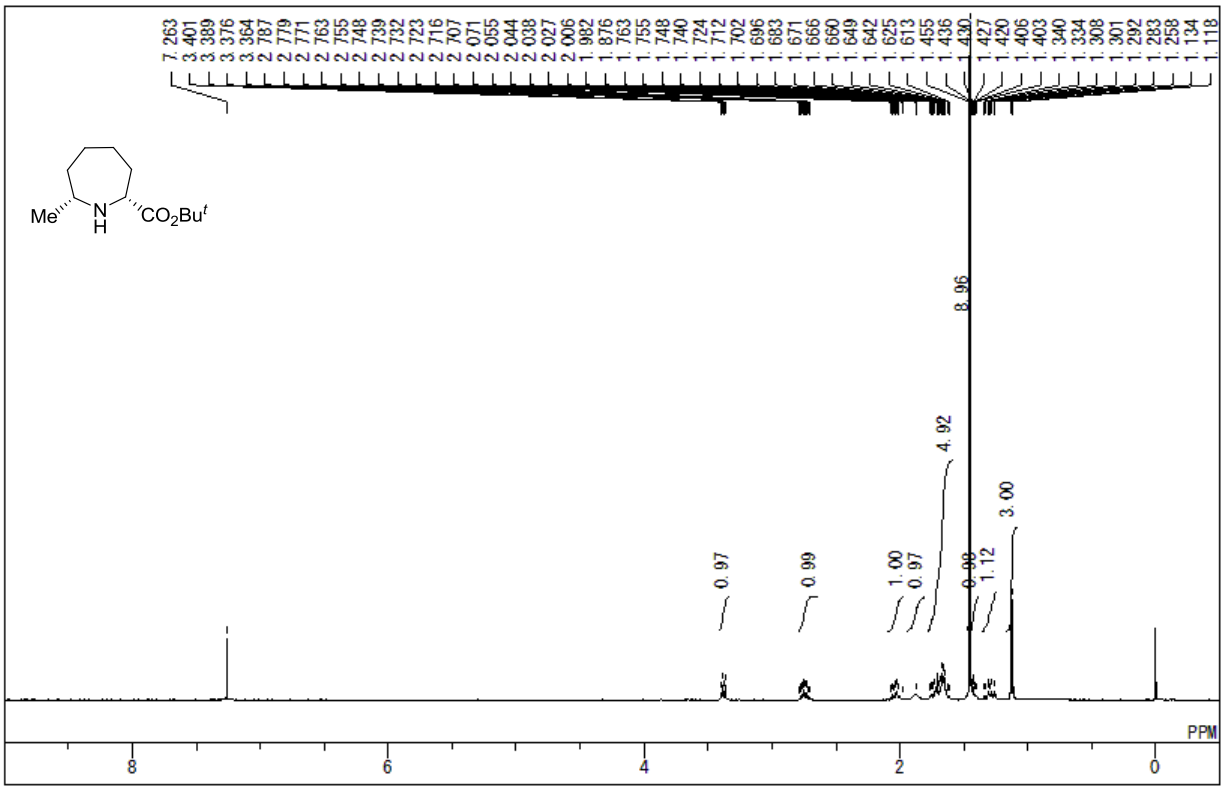
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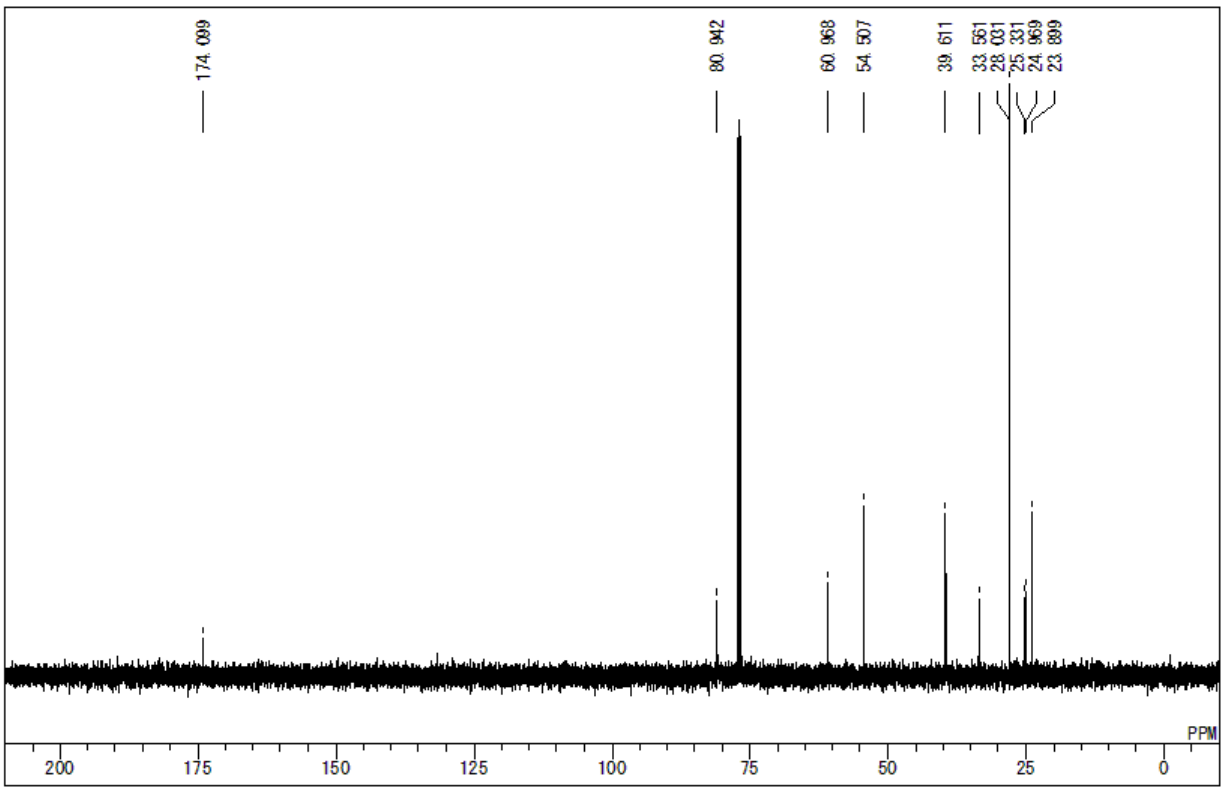
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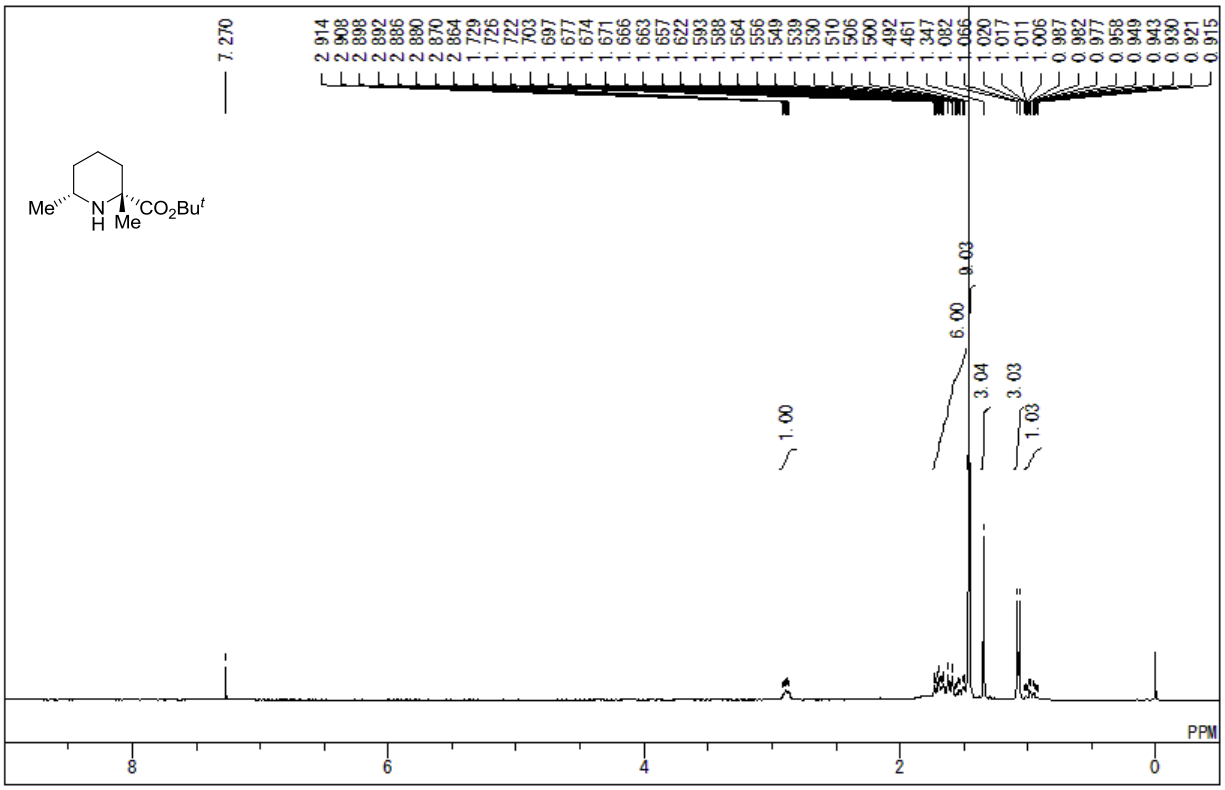
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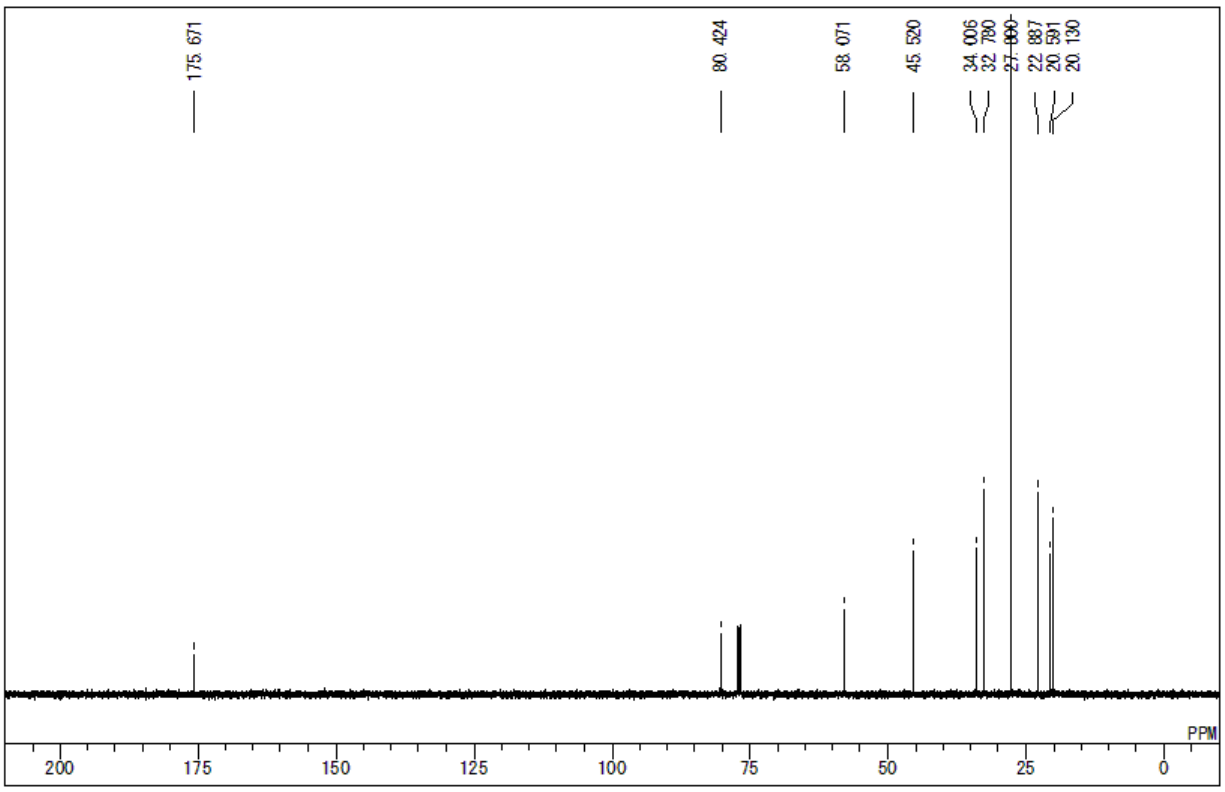
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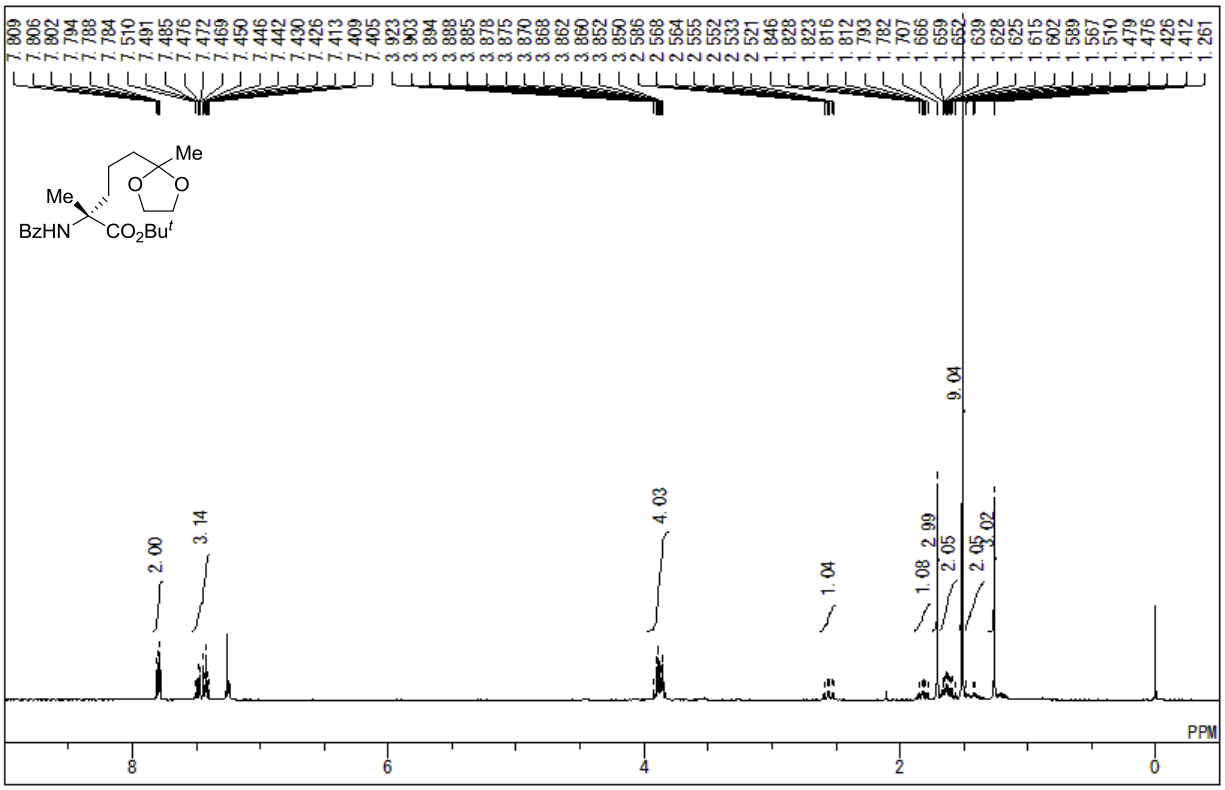

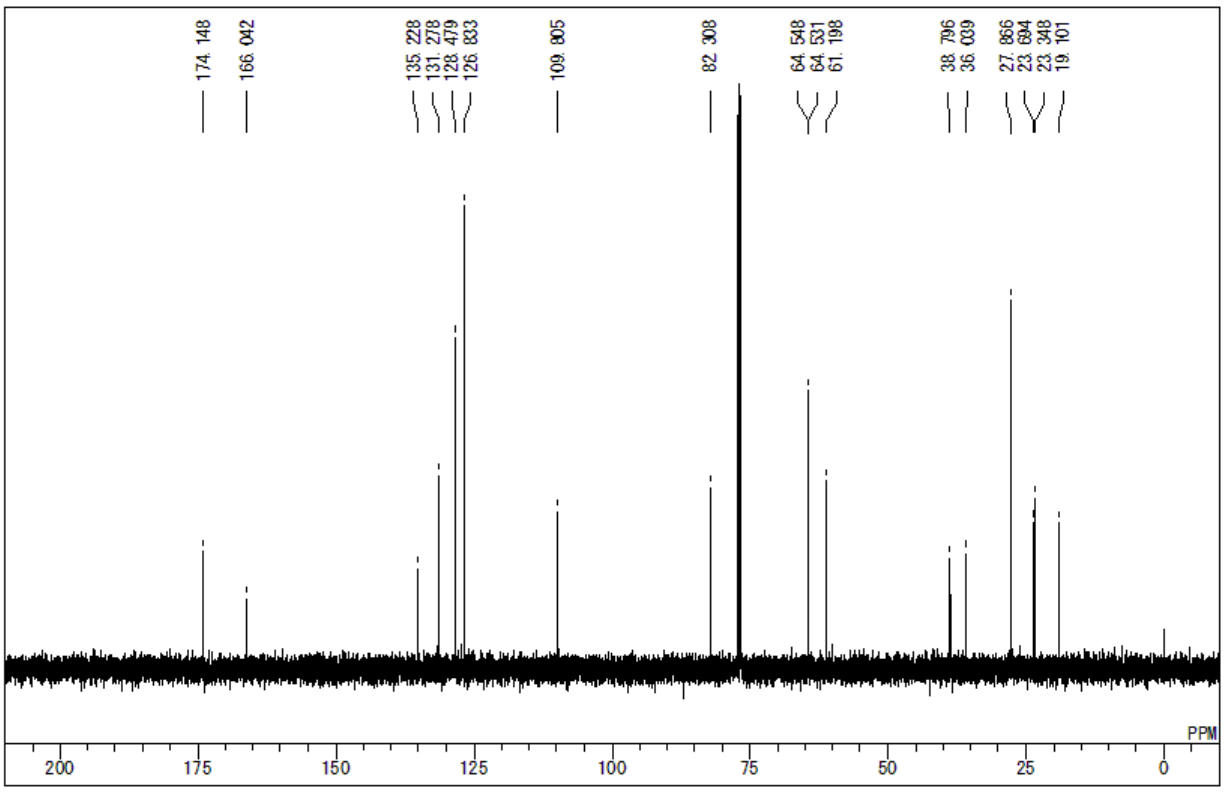

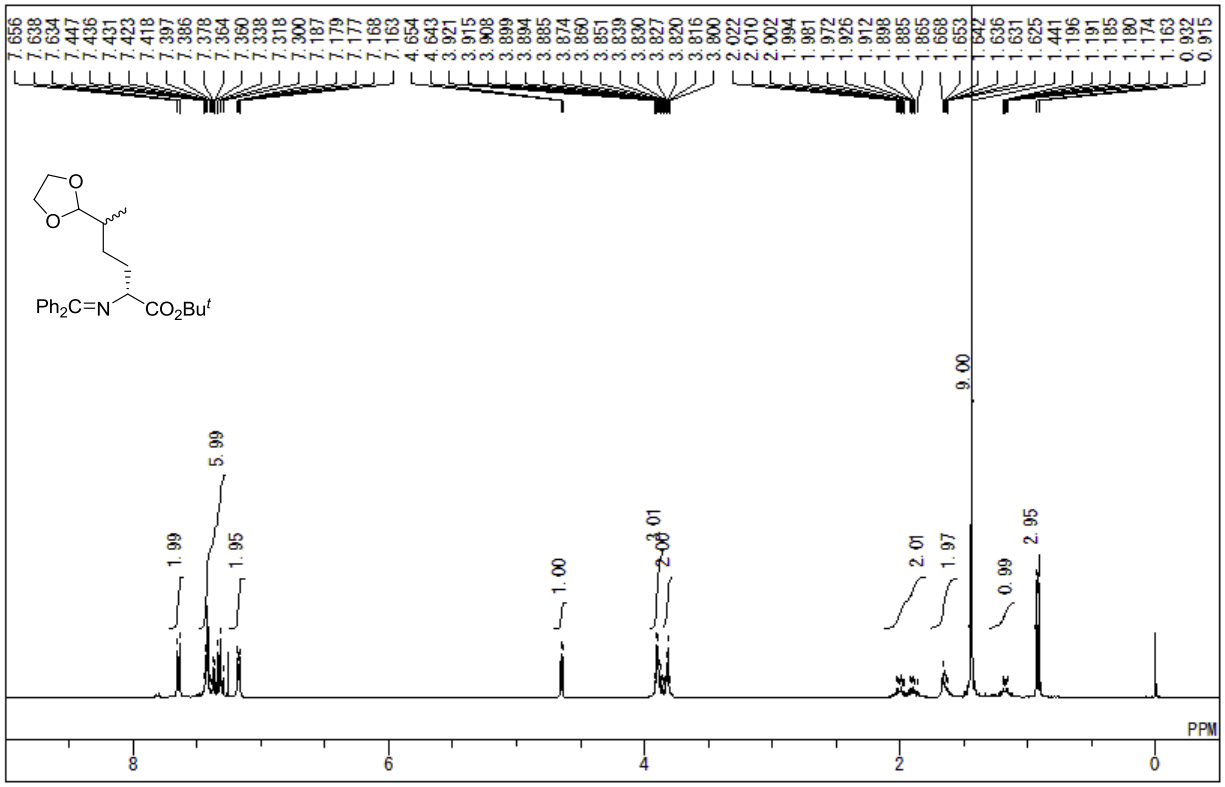
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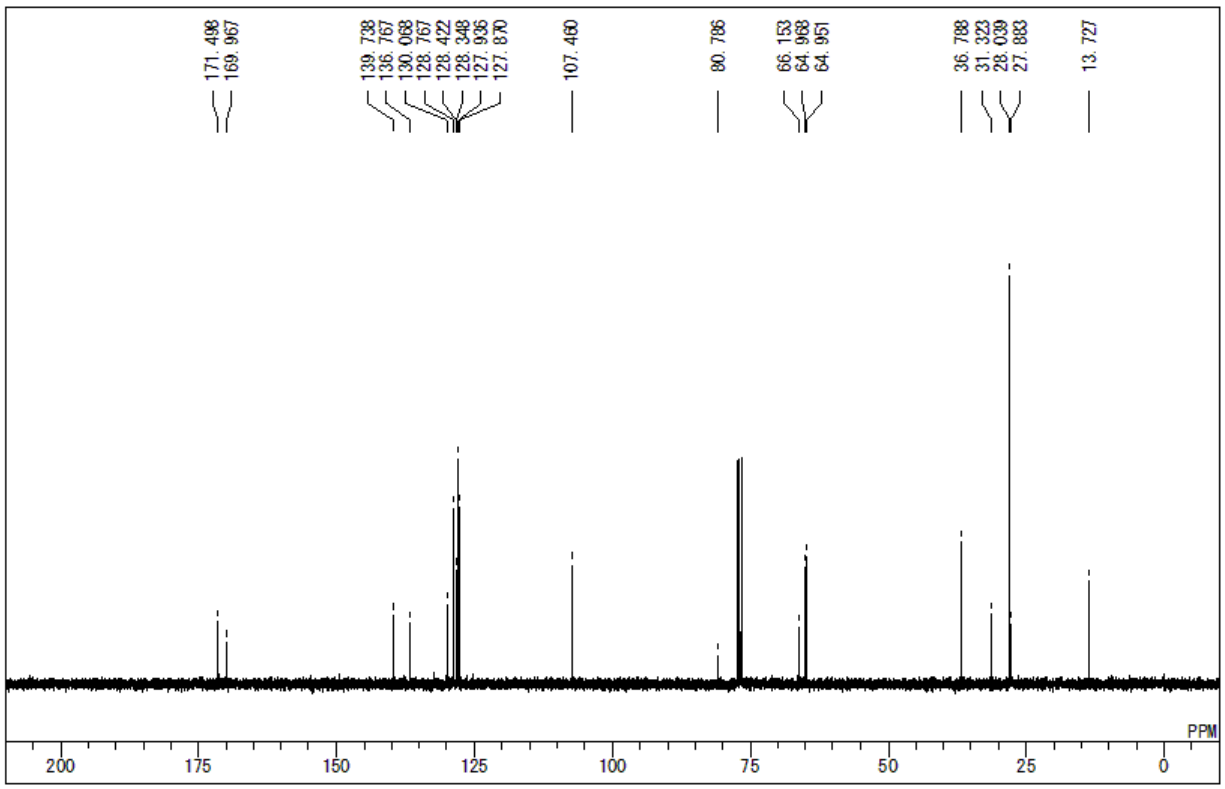
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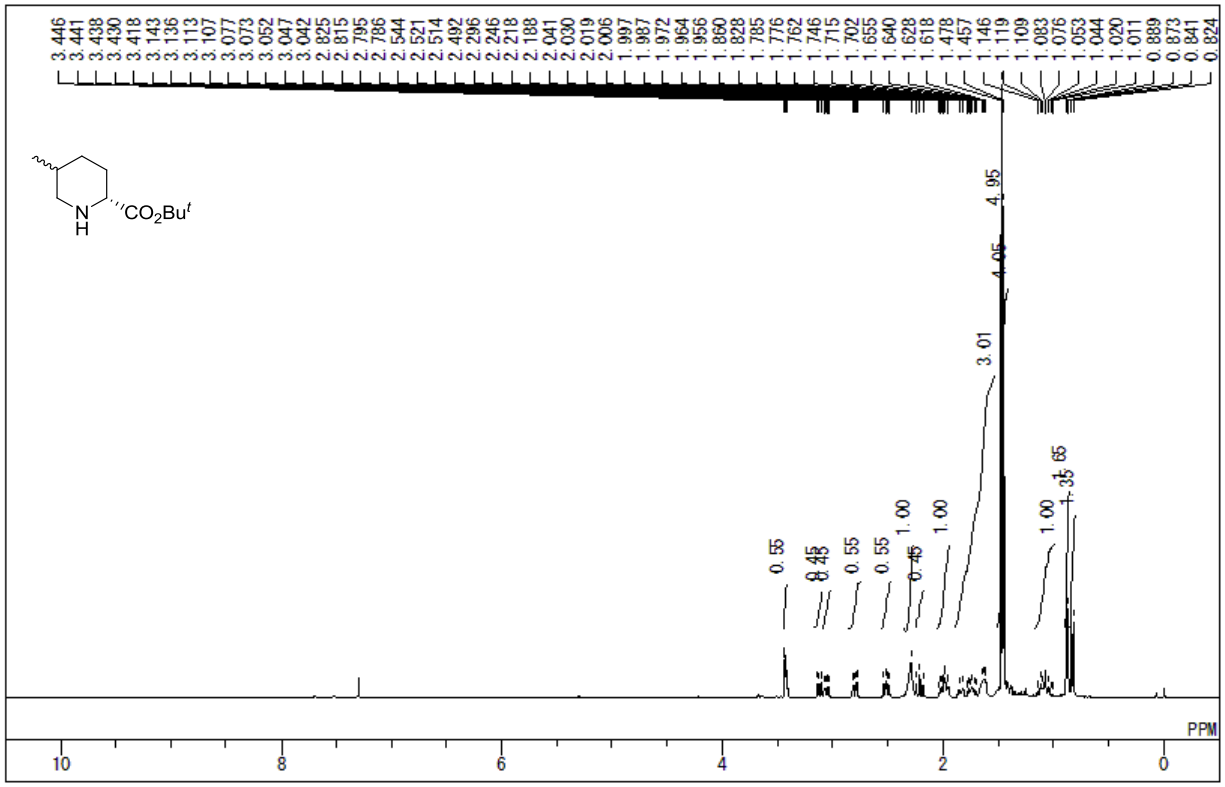

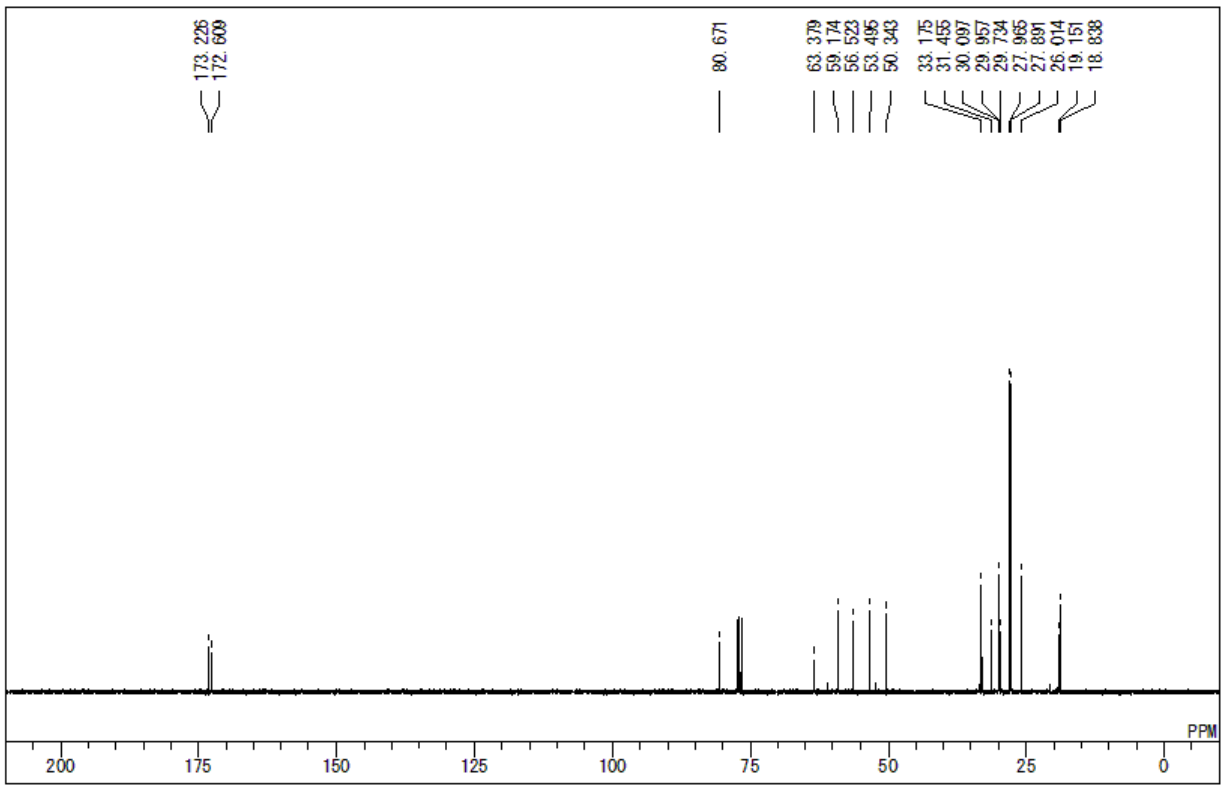

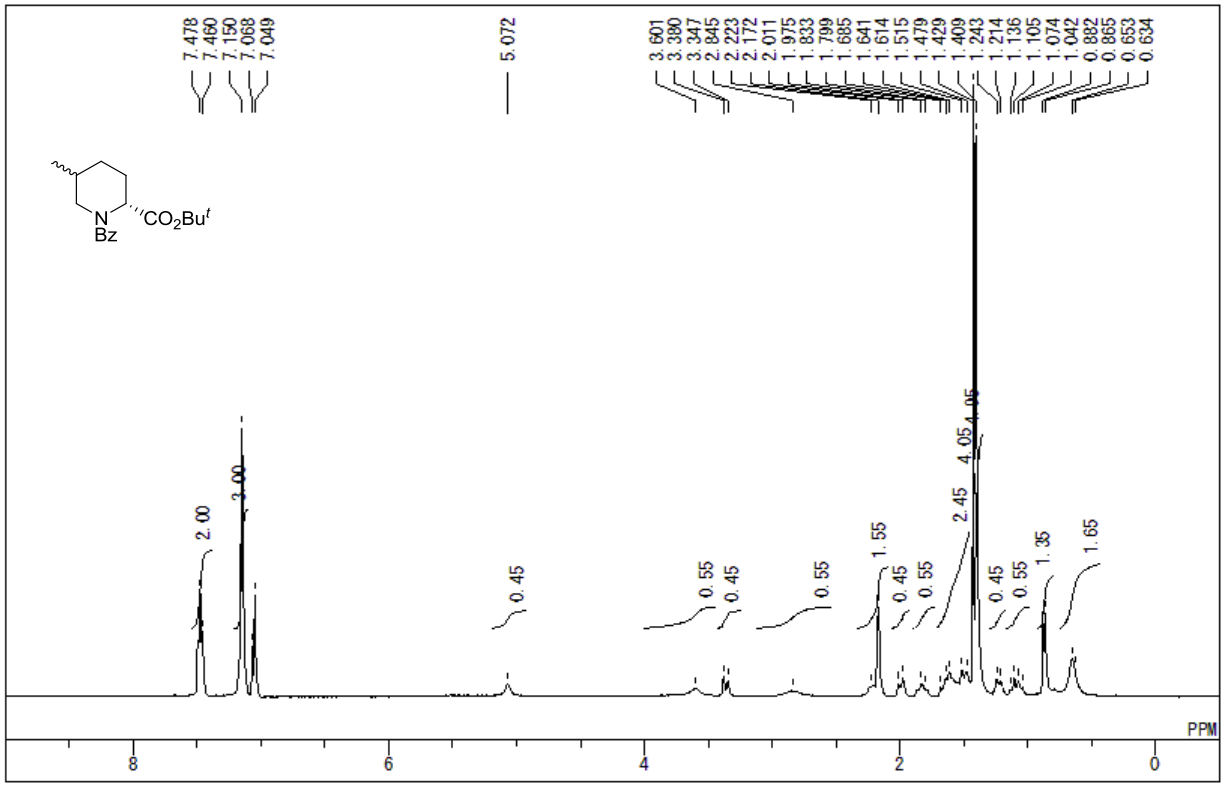
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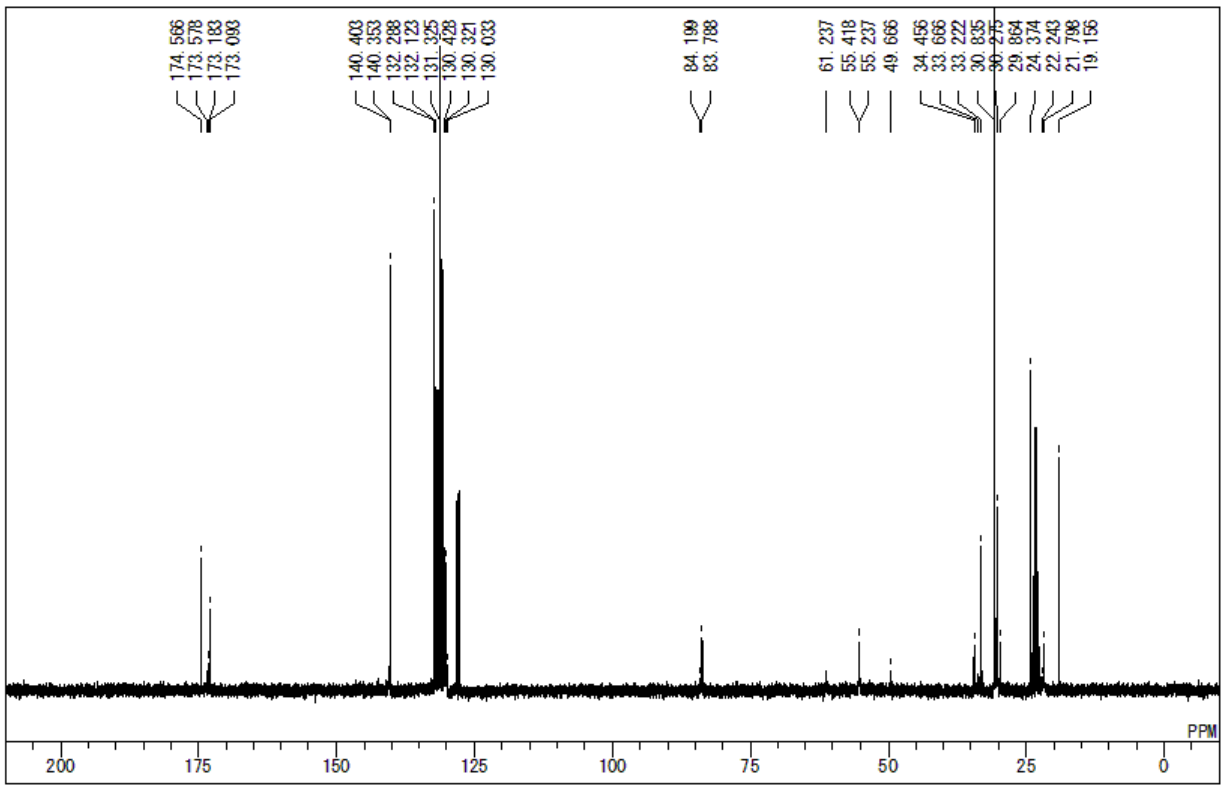
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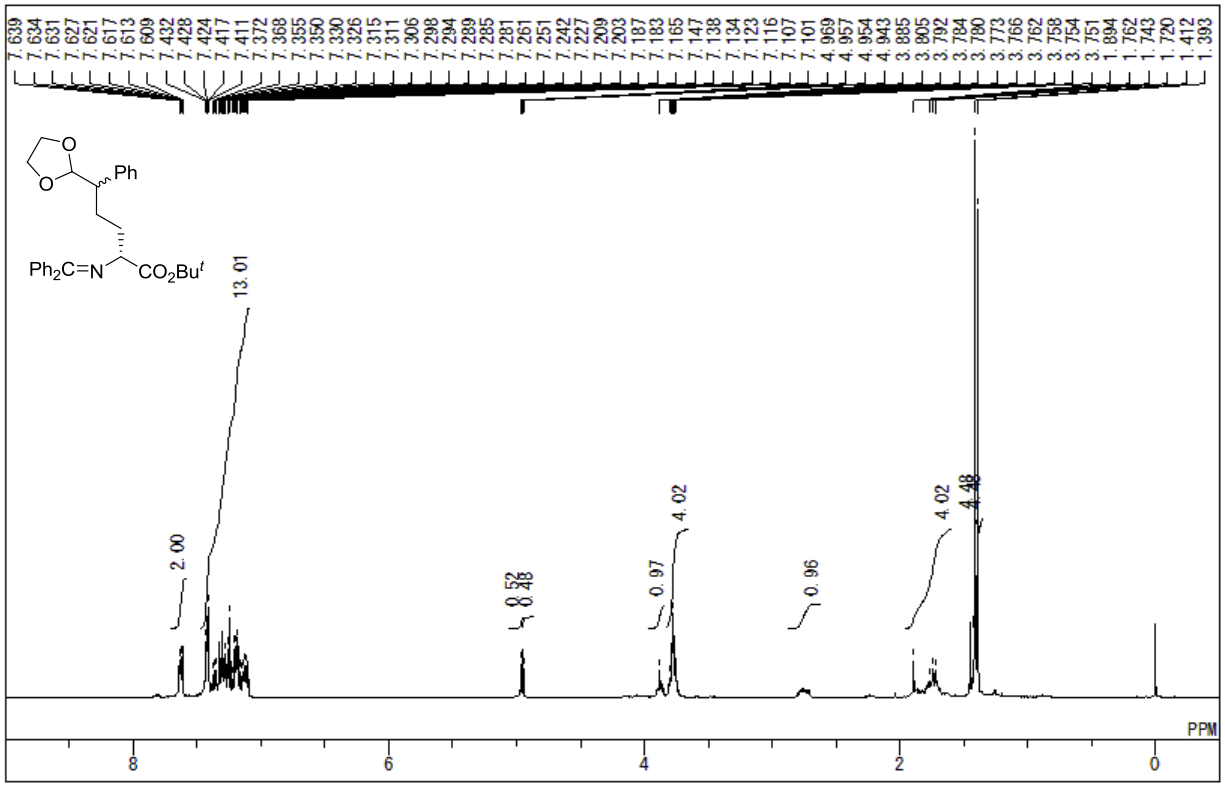

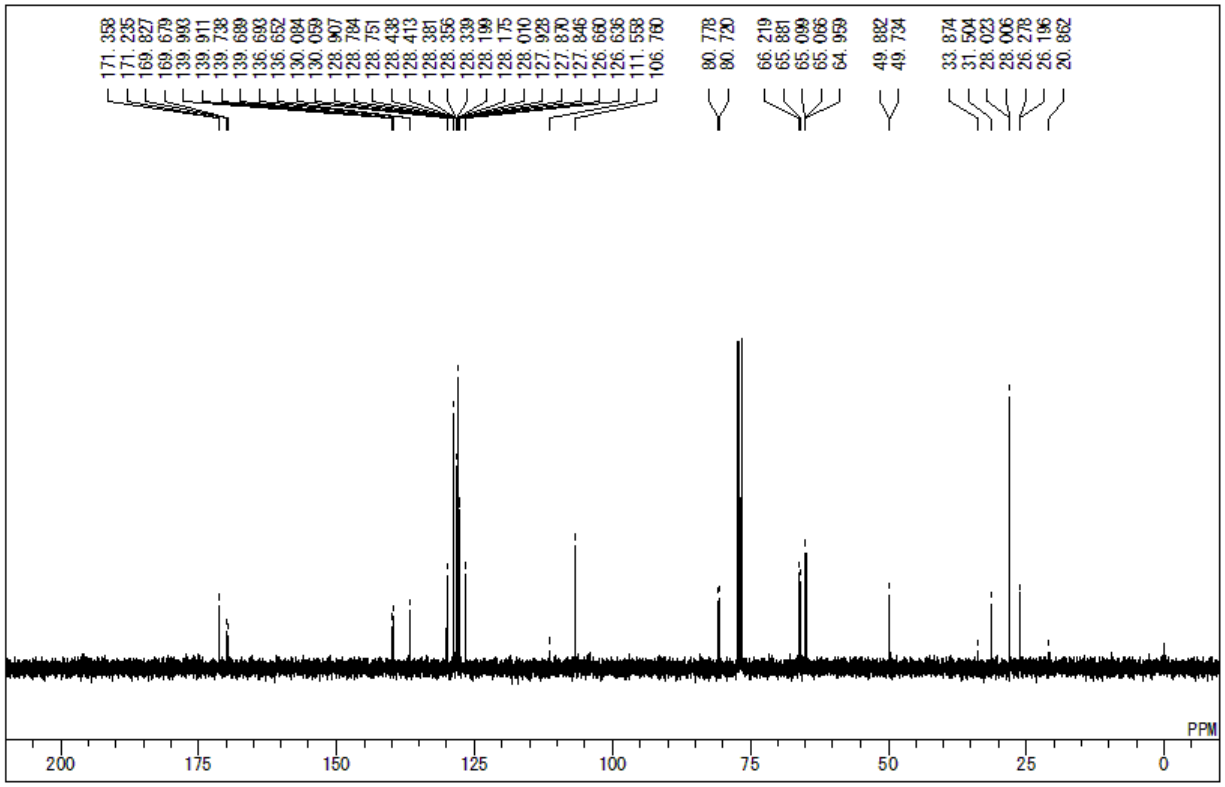

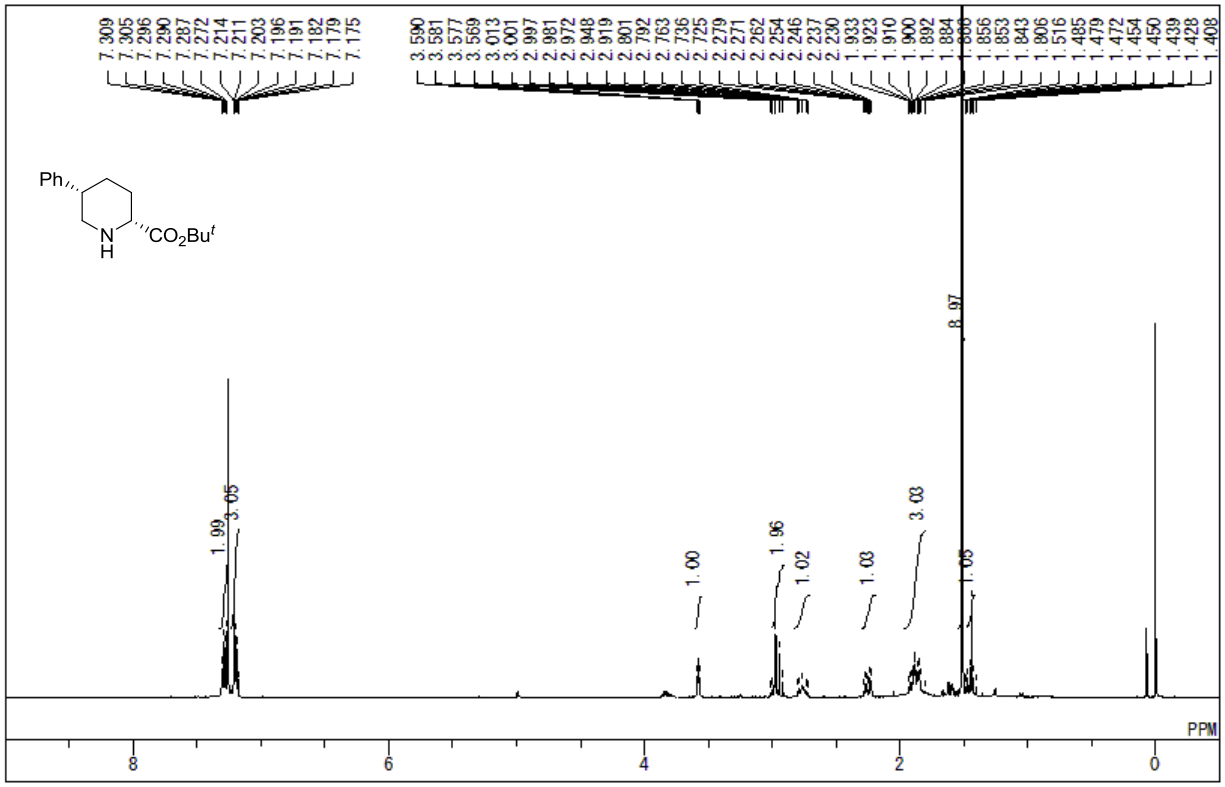

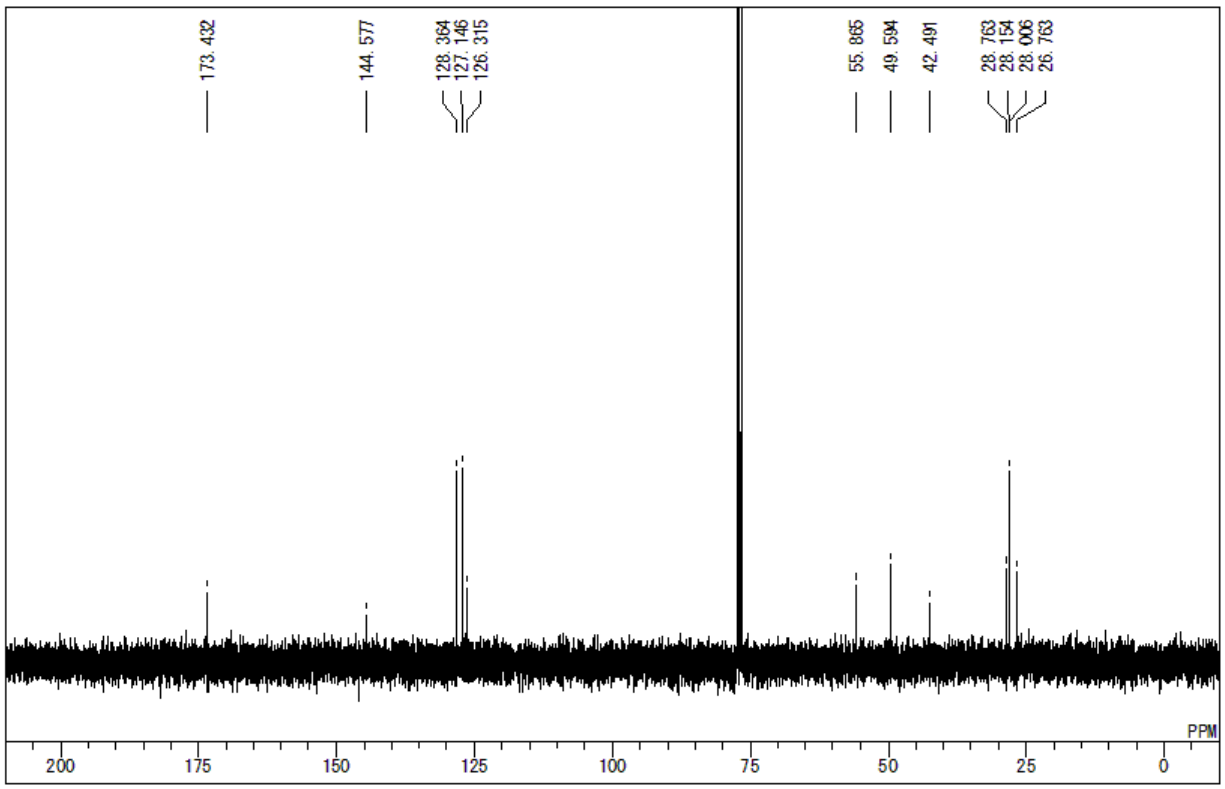

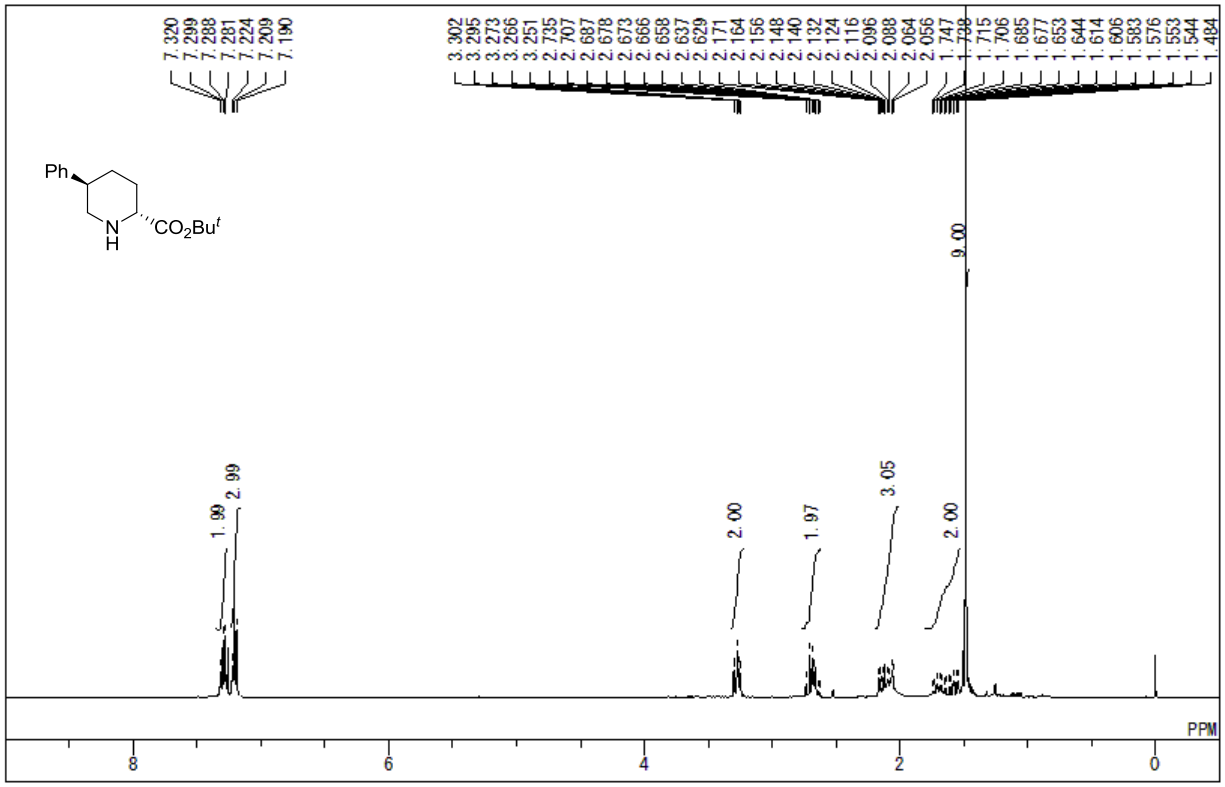
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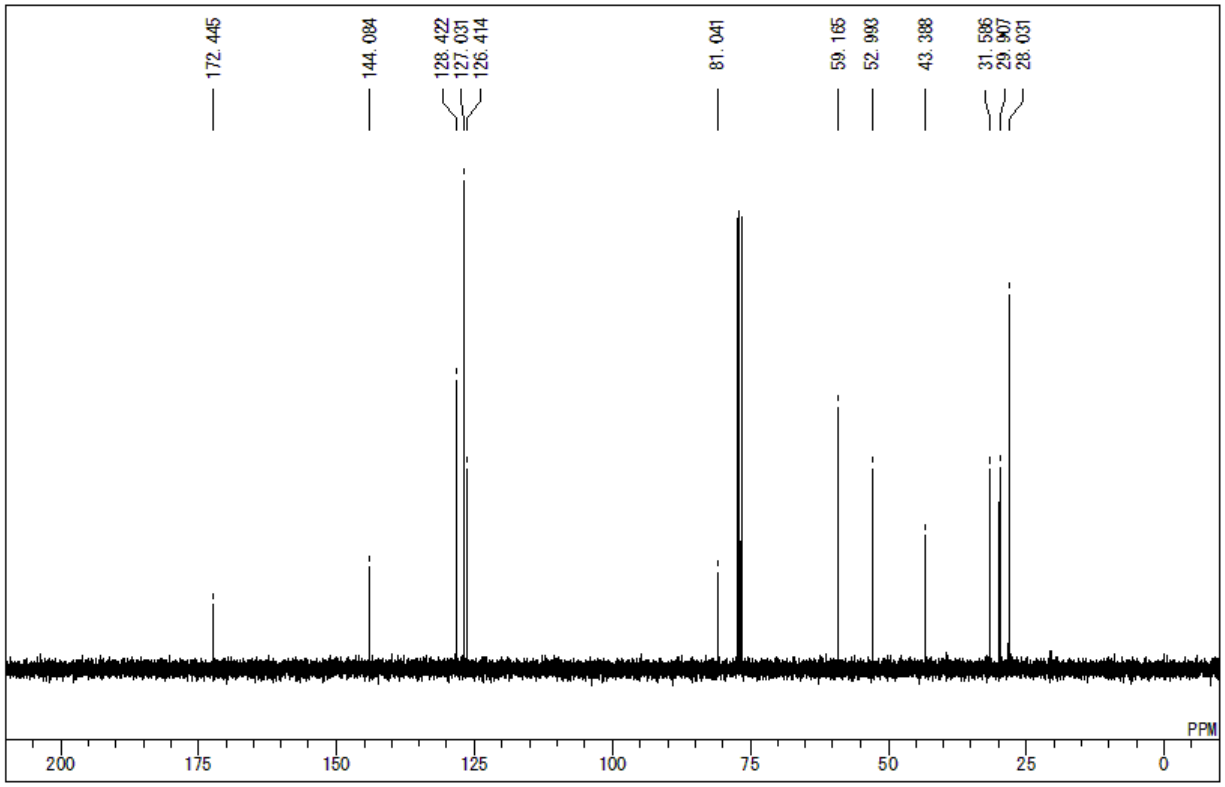
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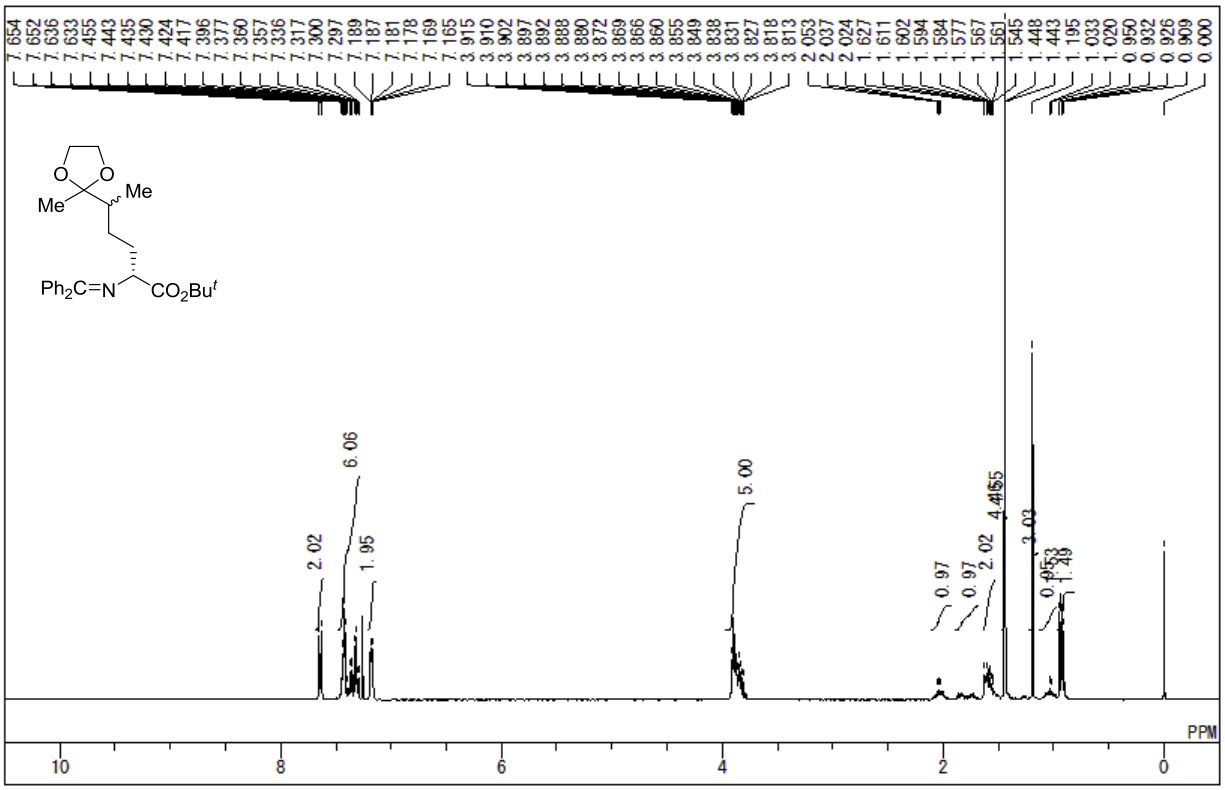

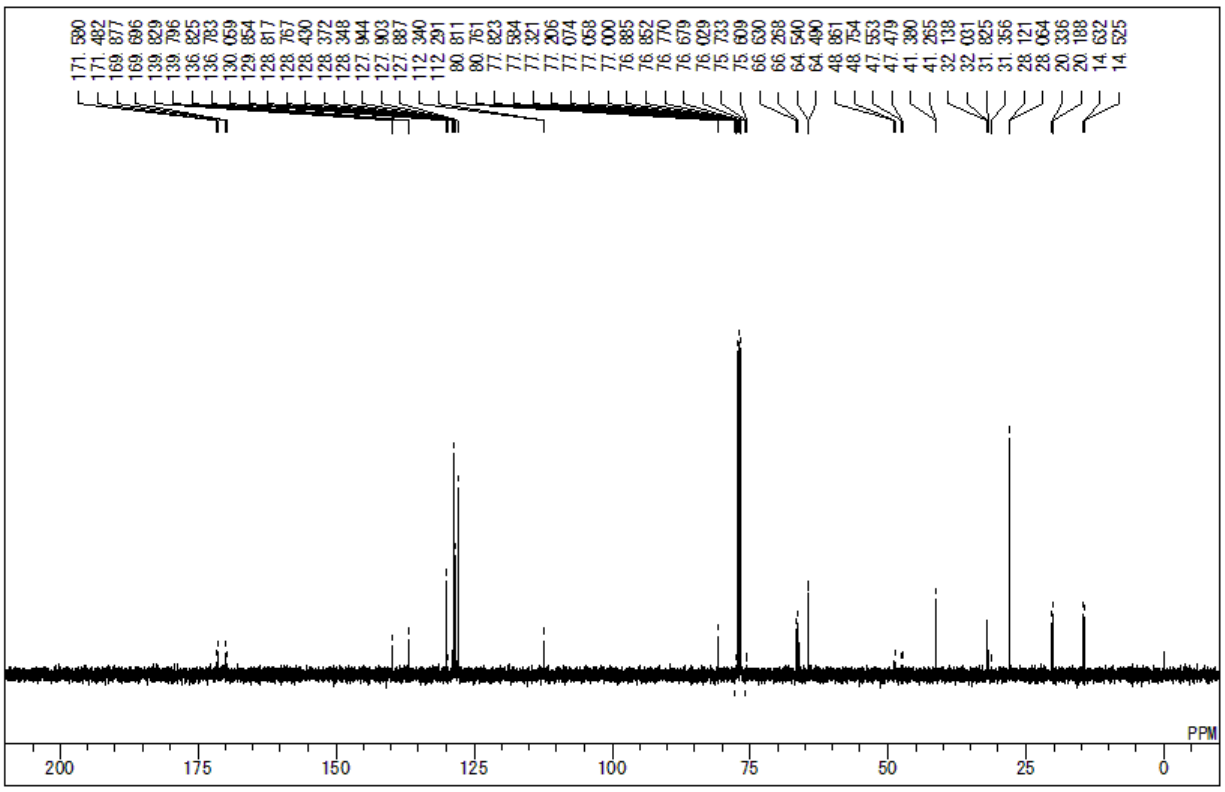

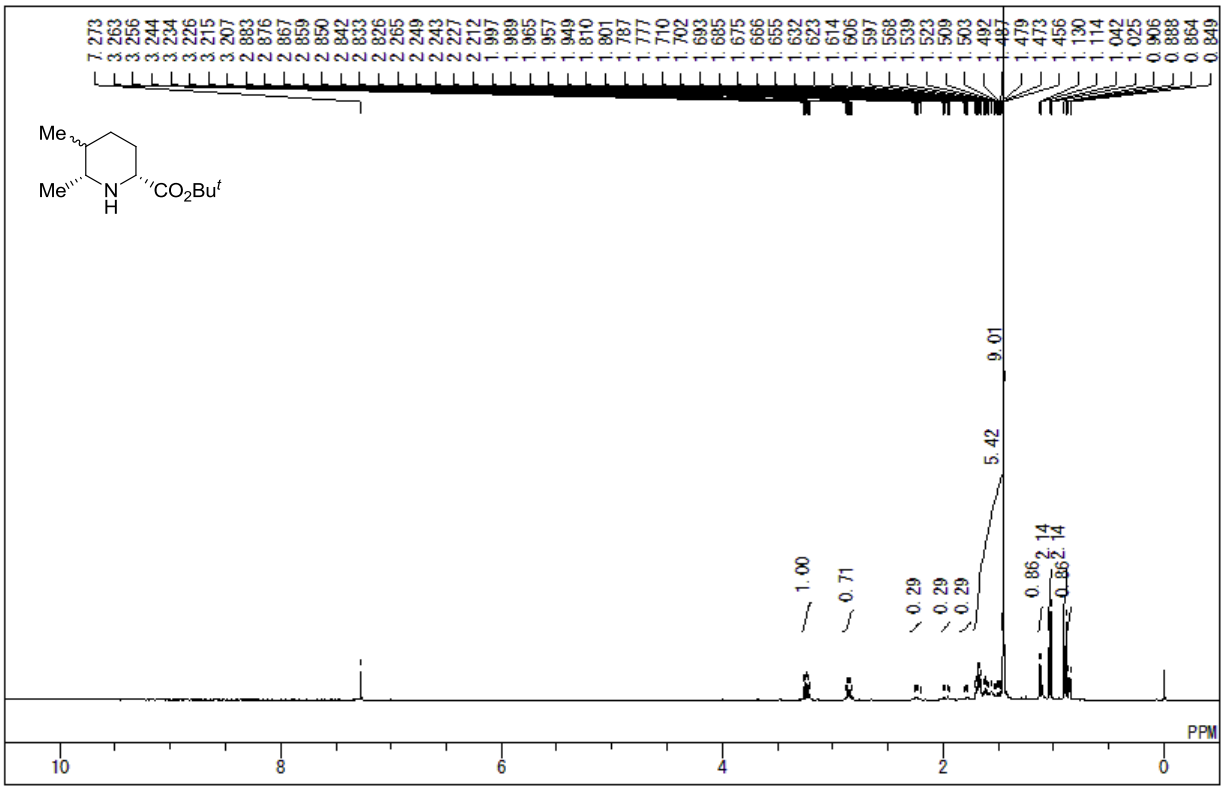

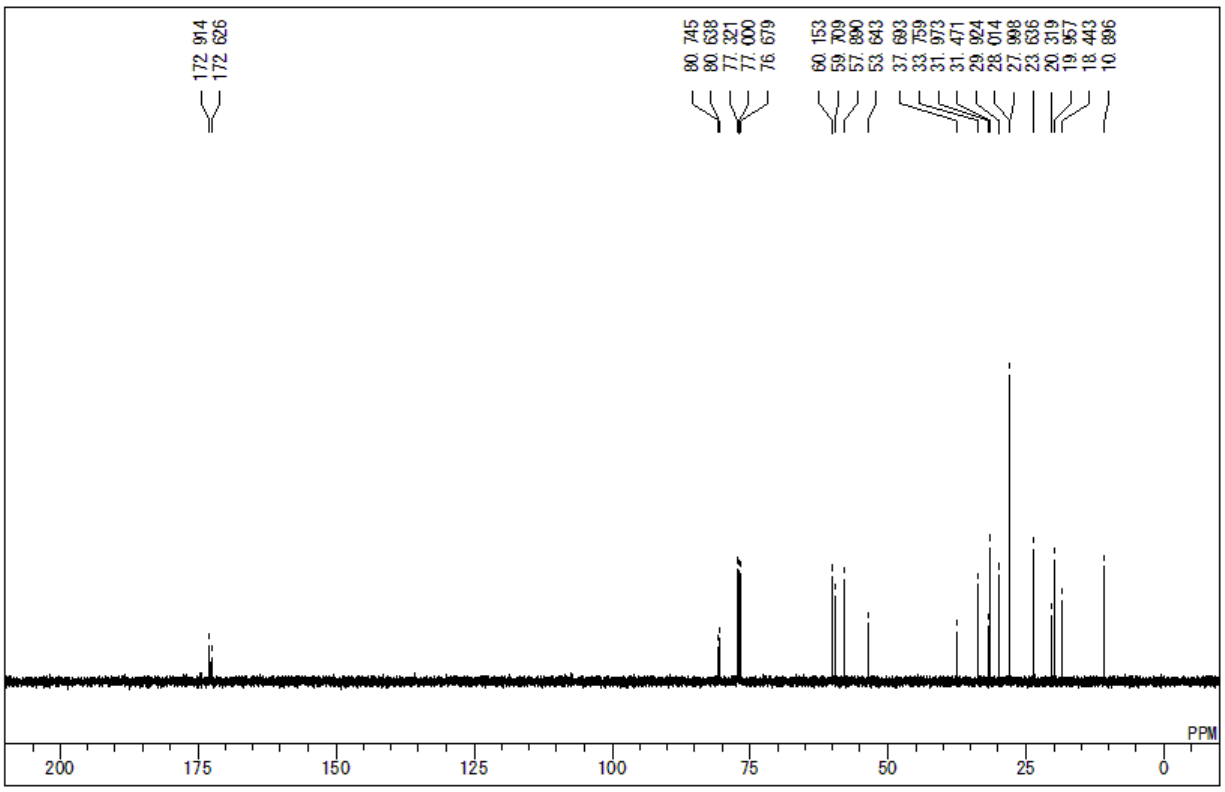

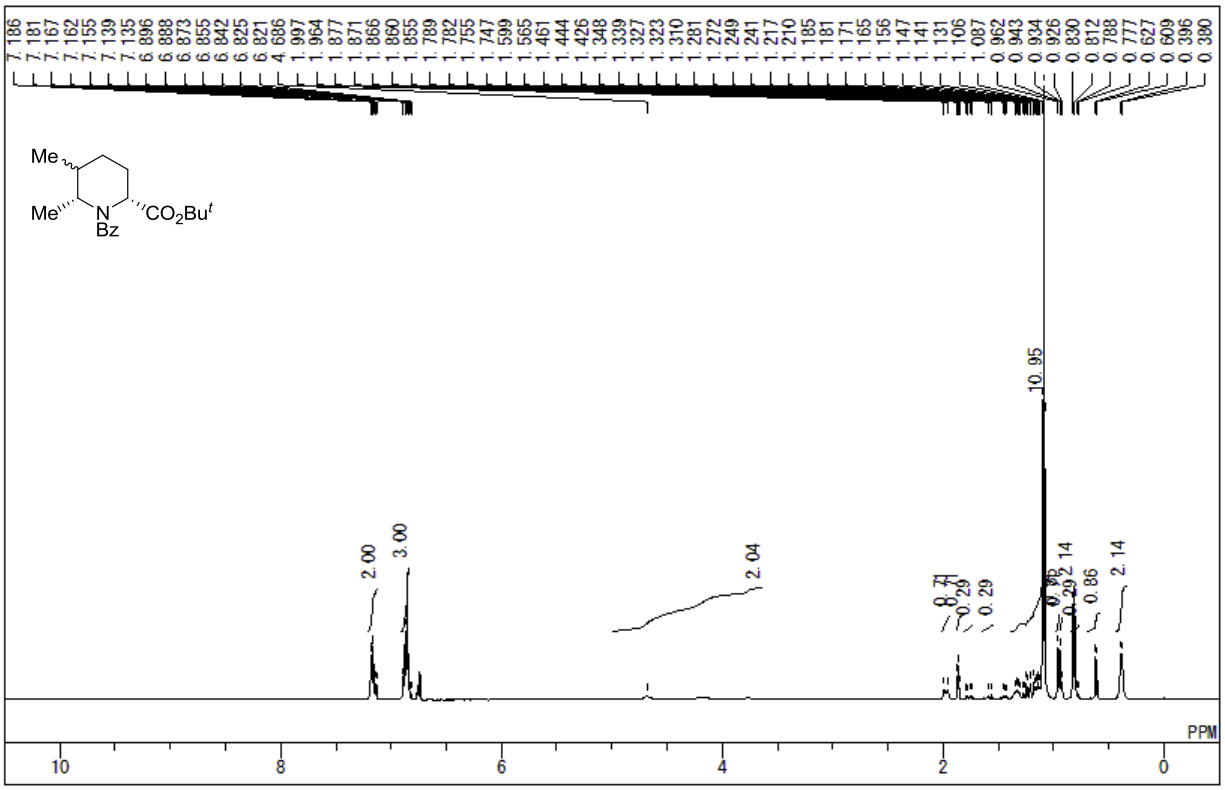

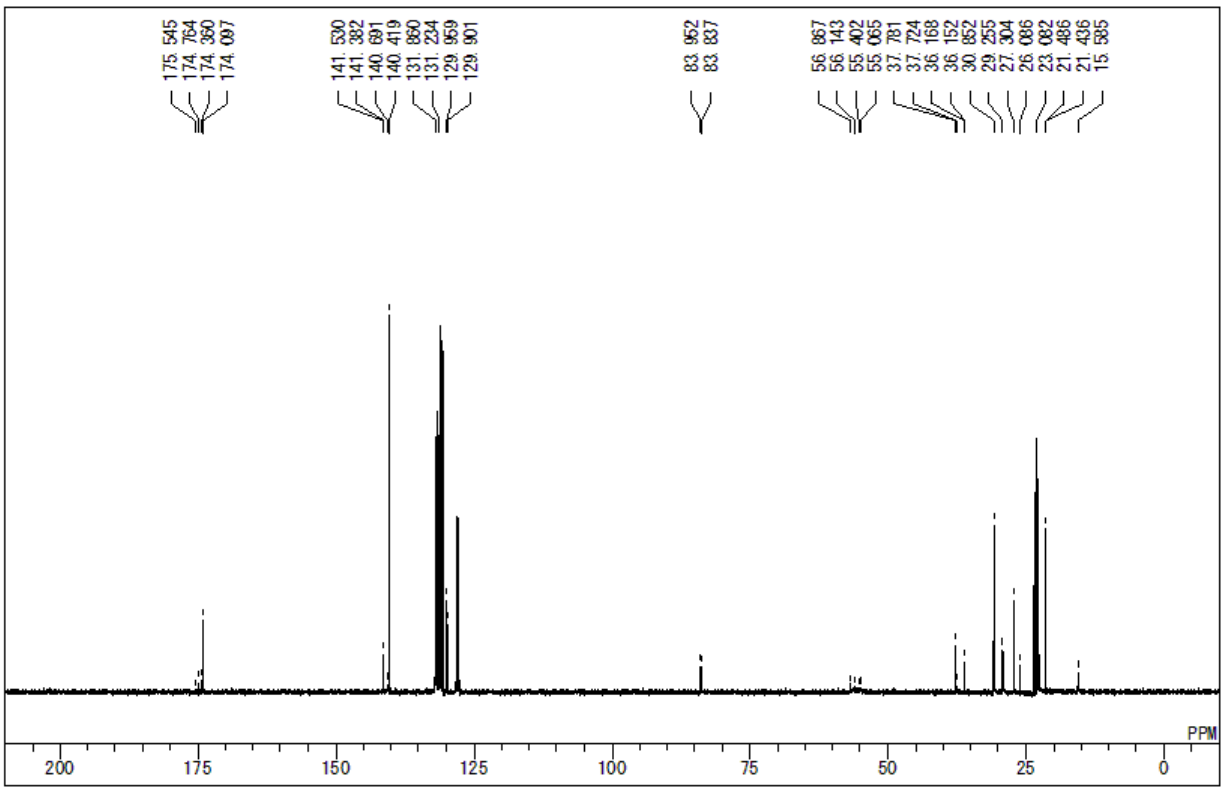

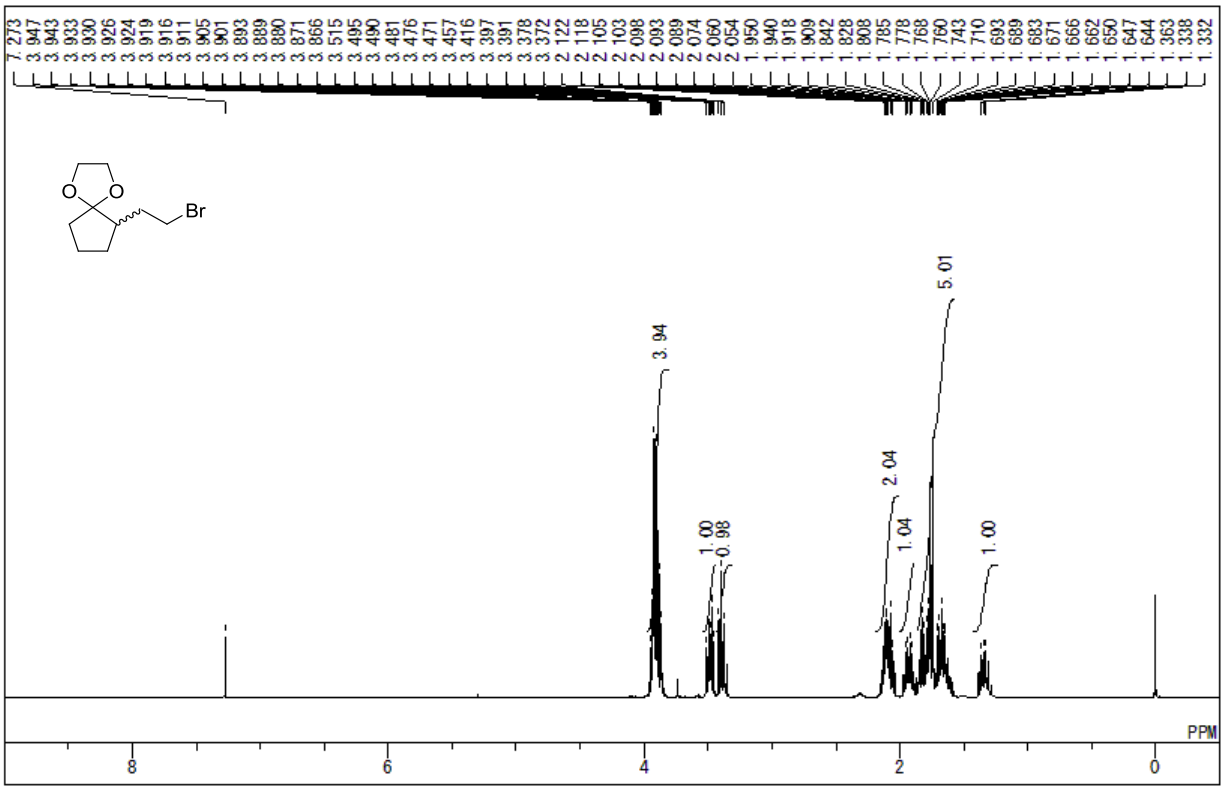
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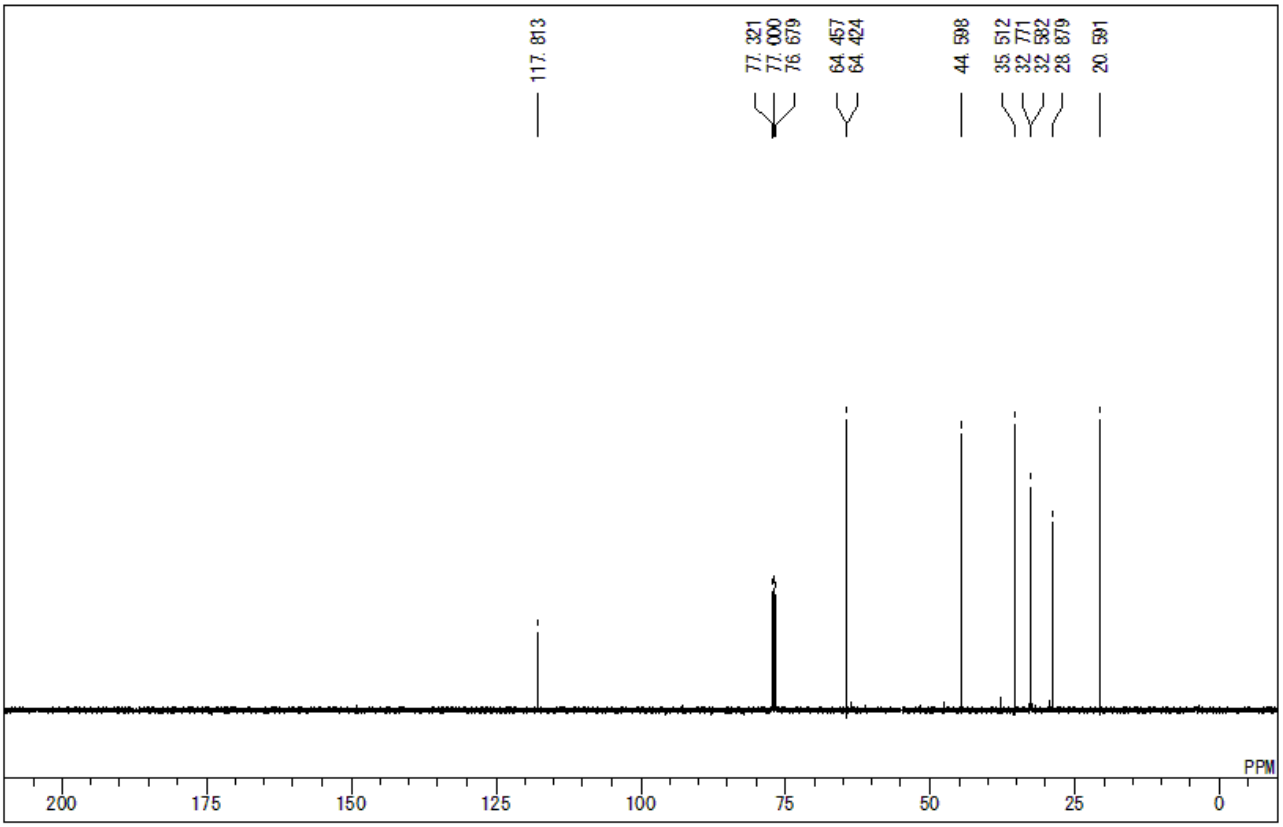
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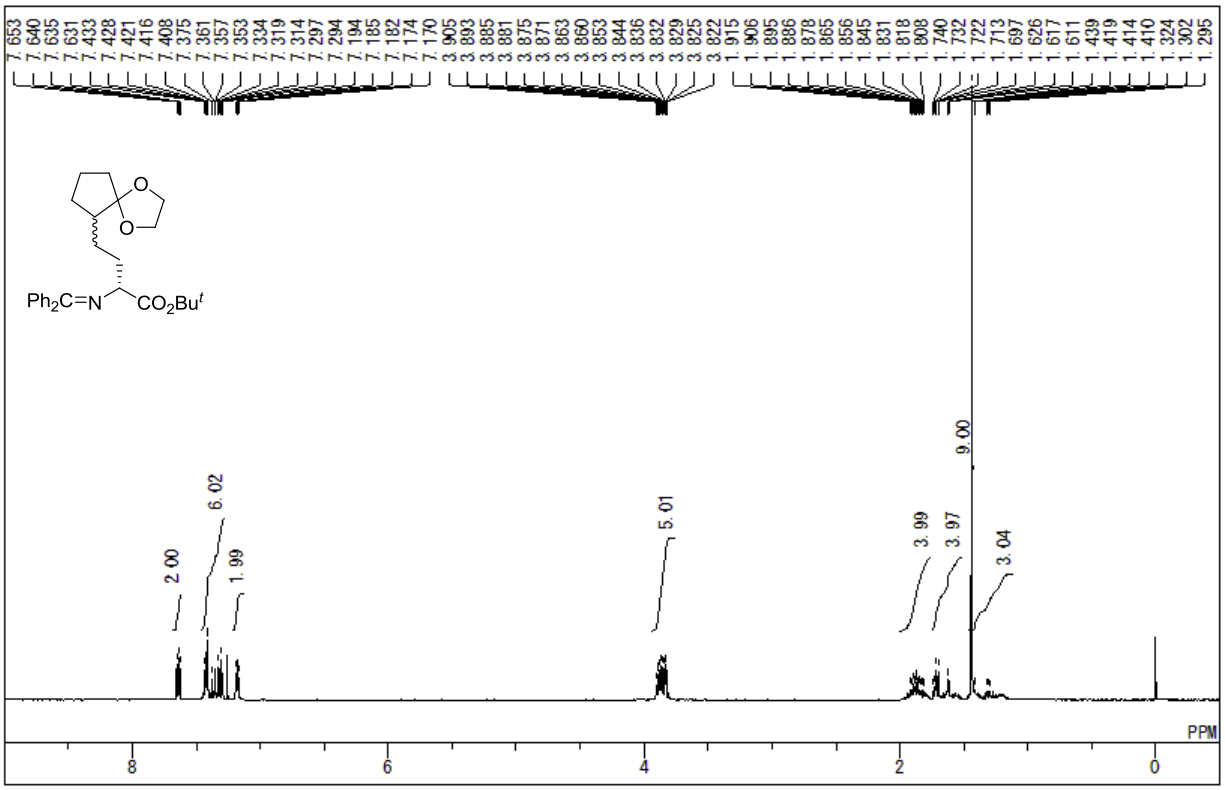

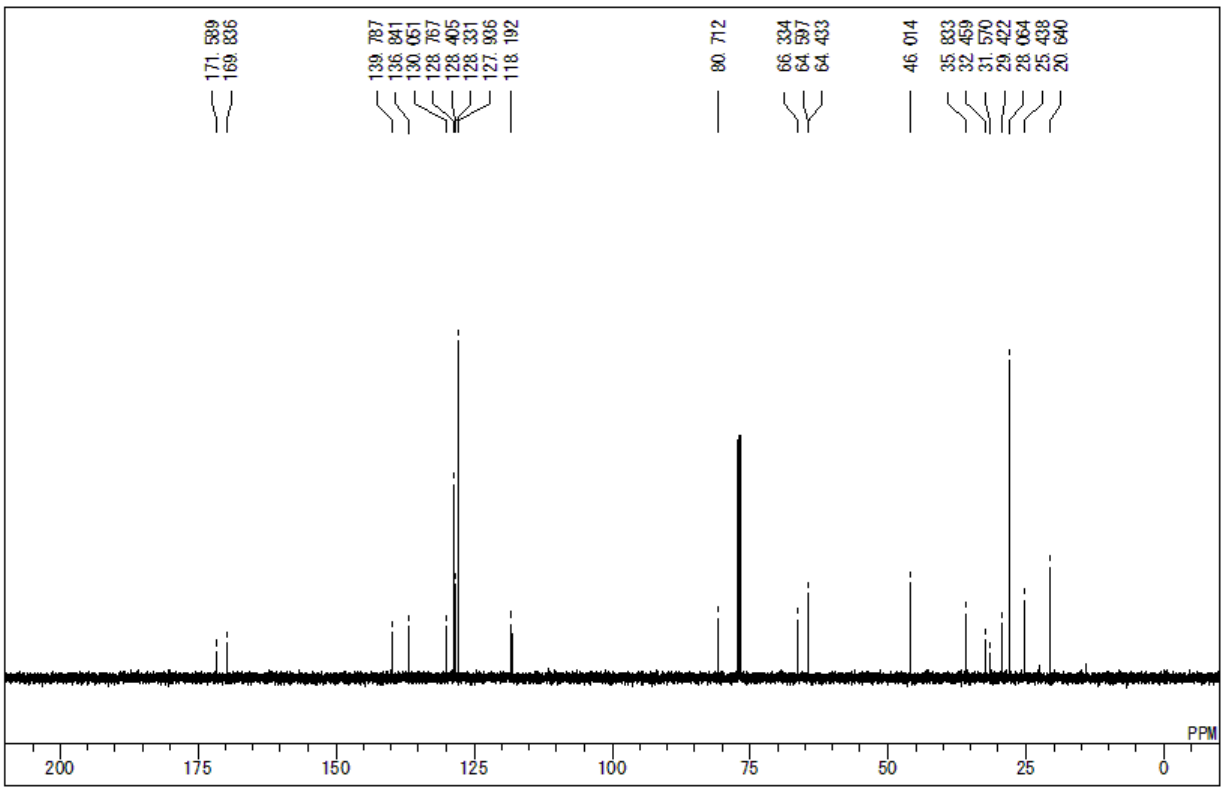

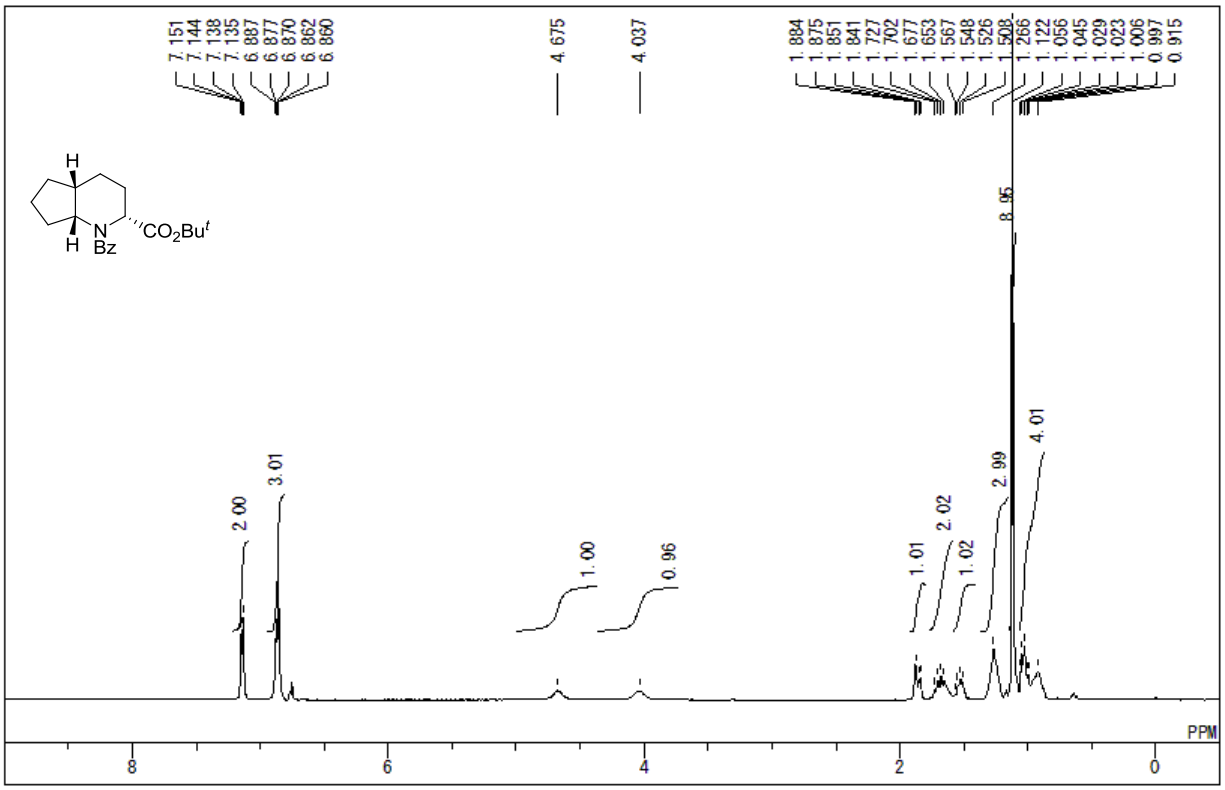

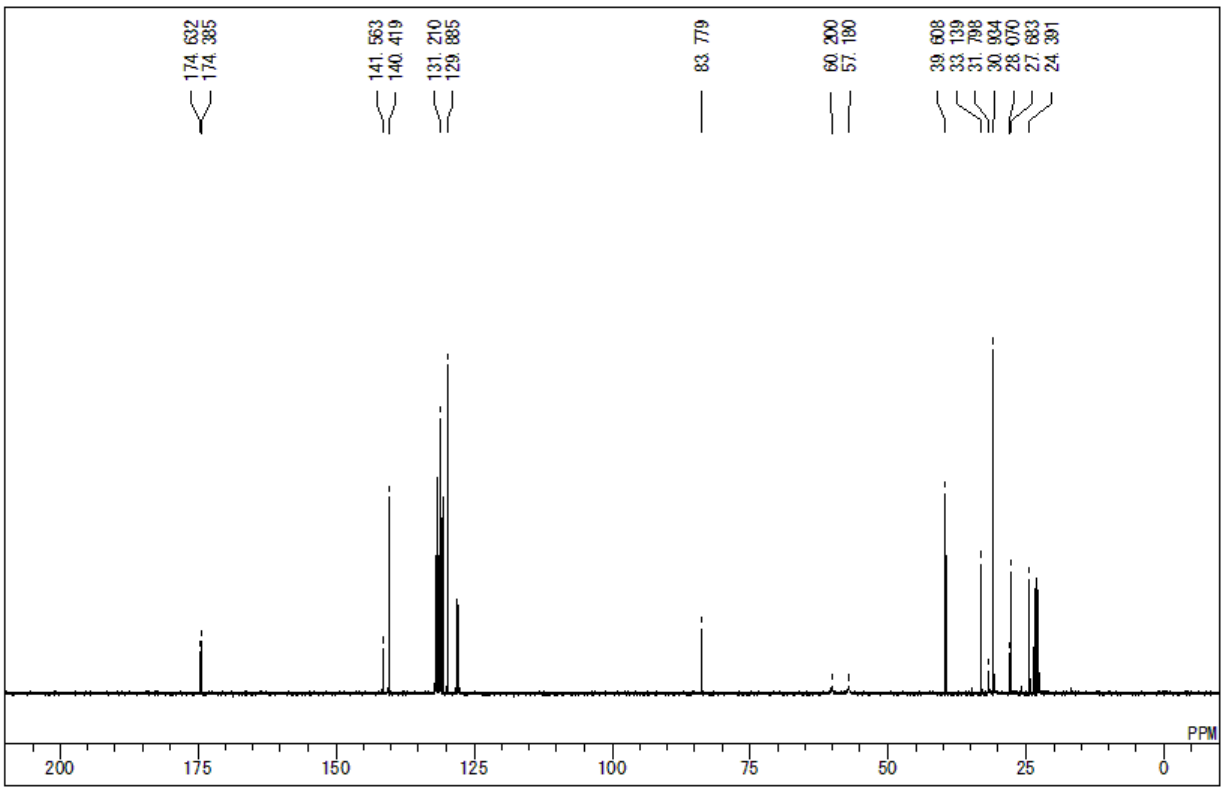

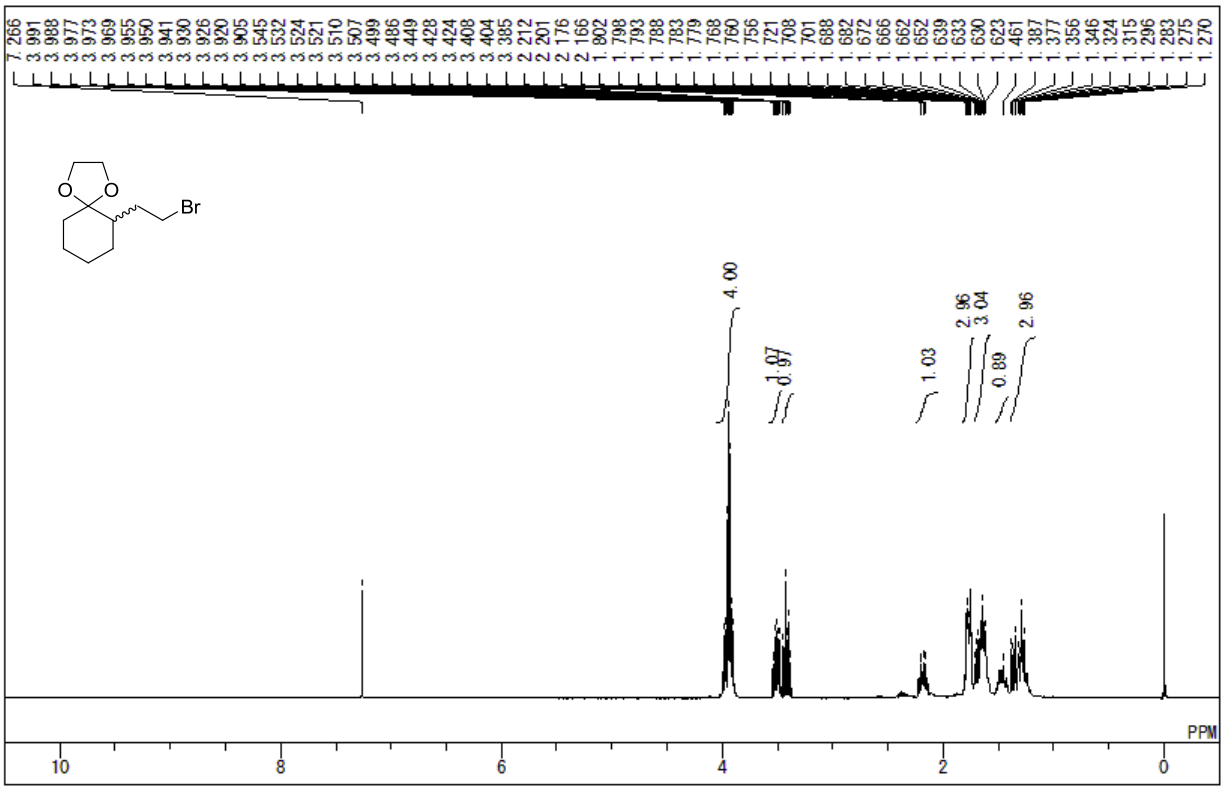

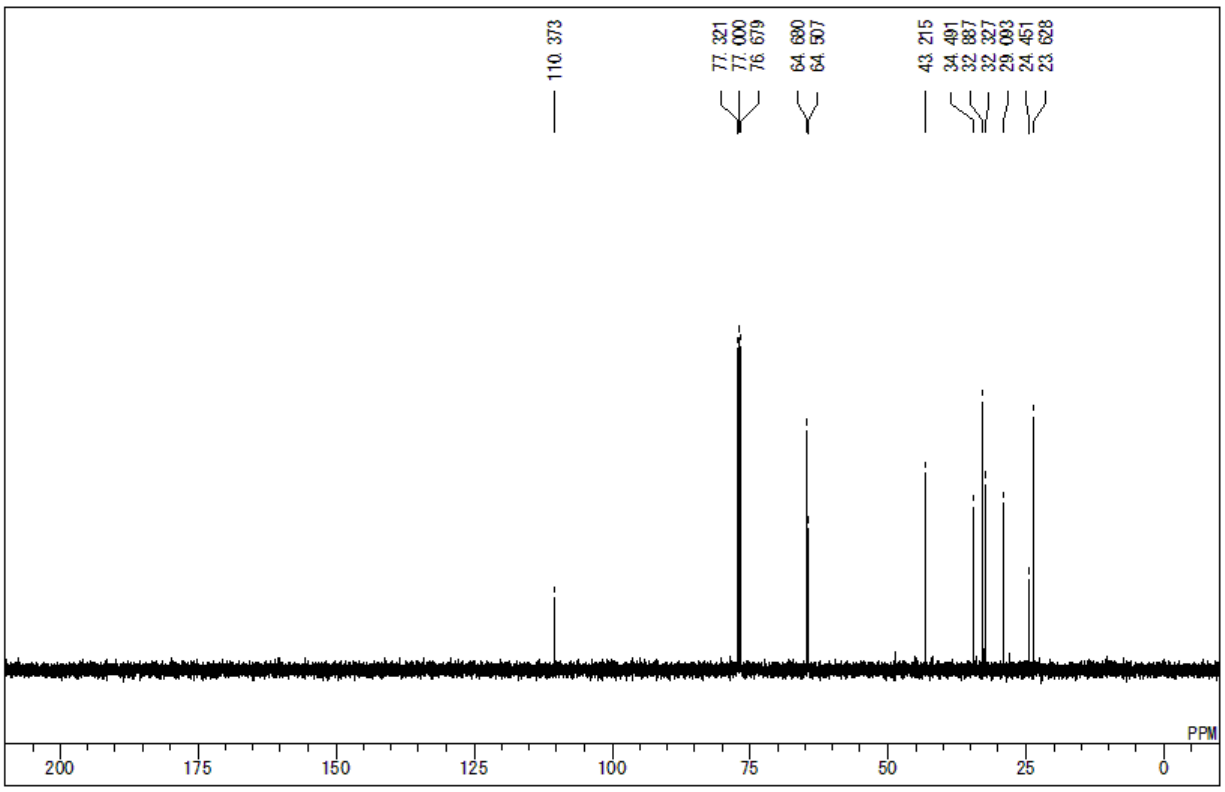

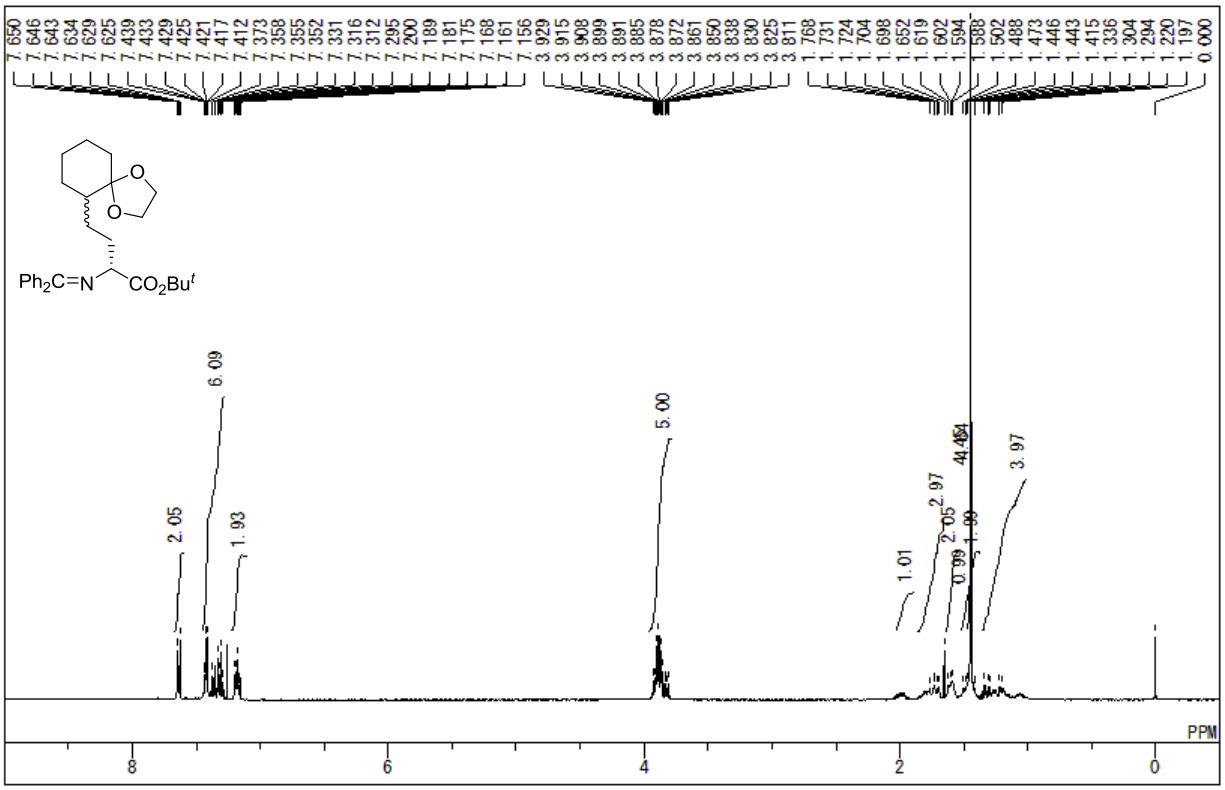

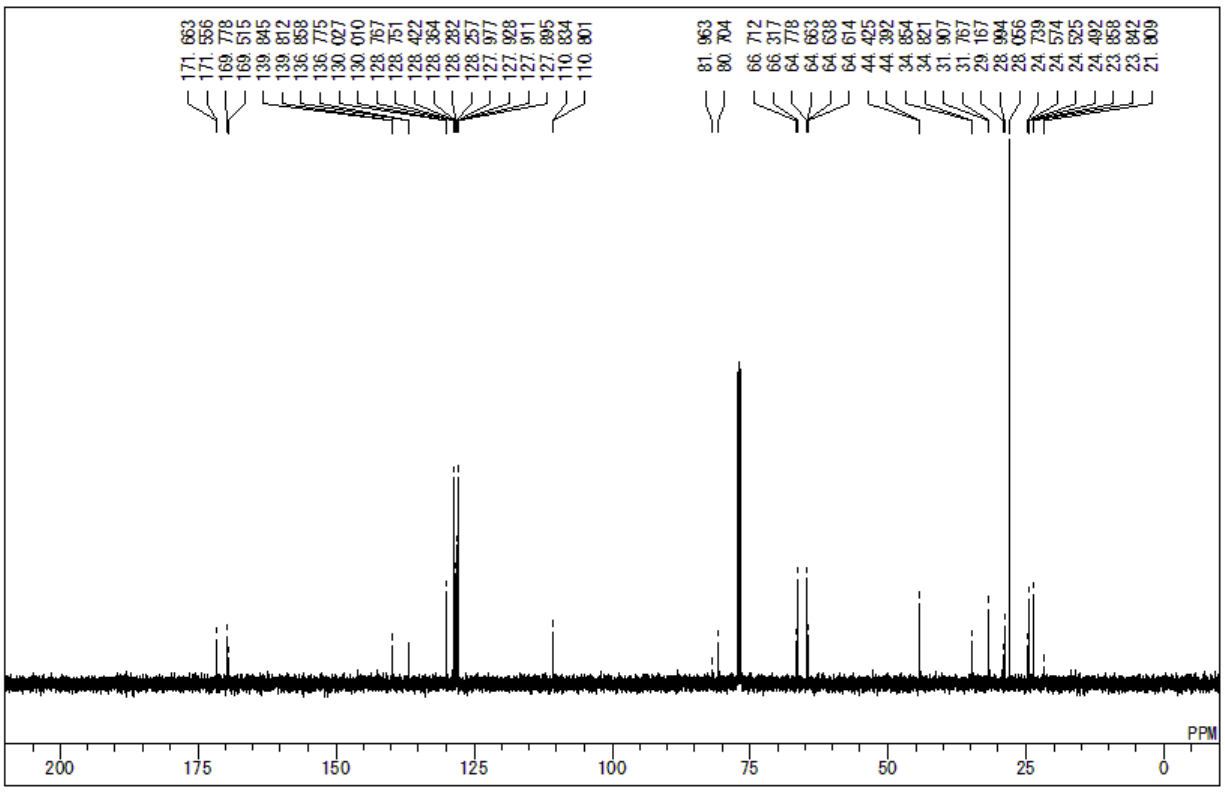

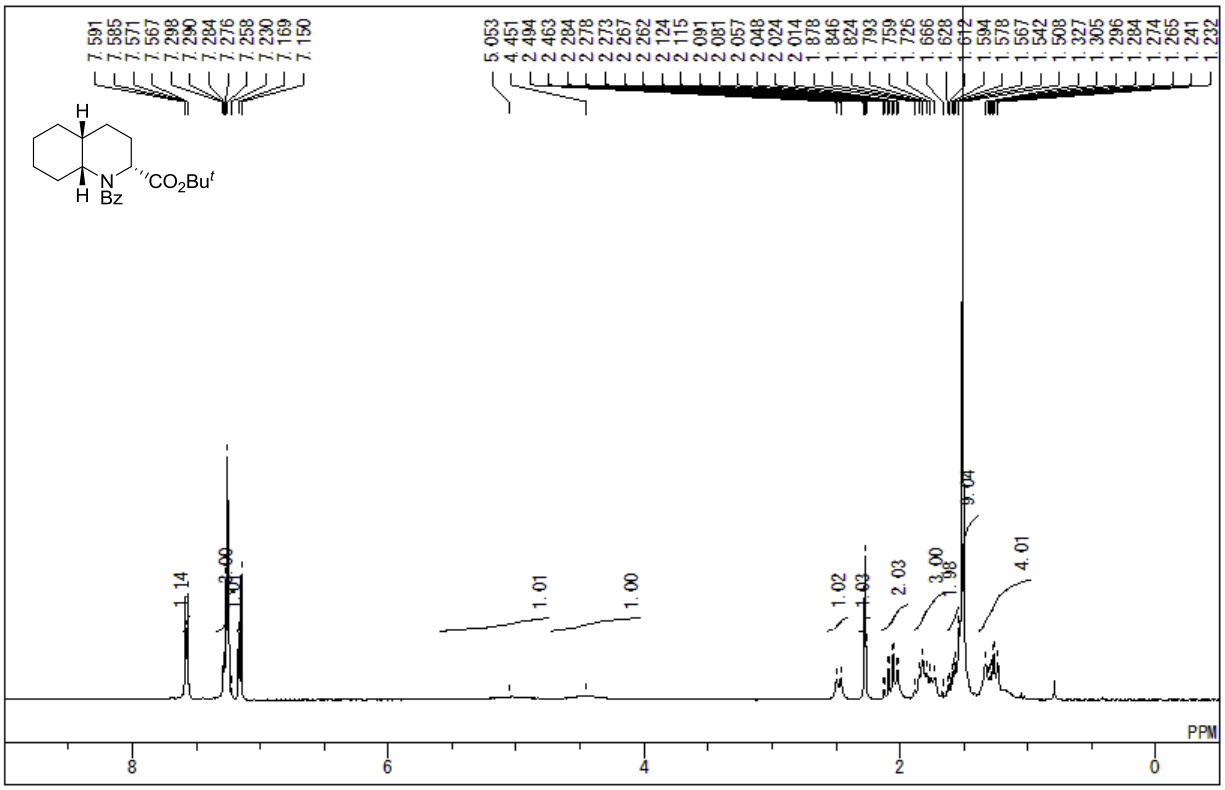
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H Bz
CO2But
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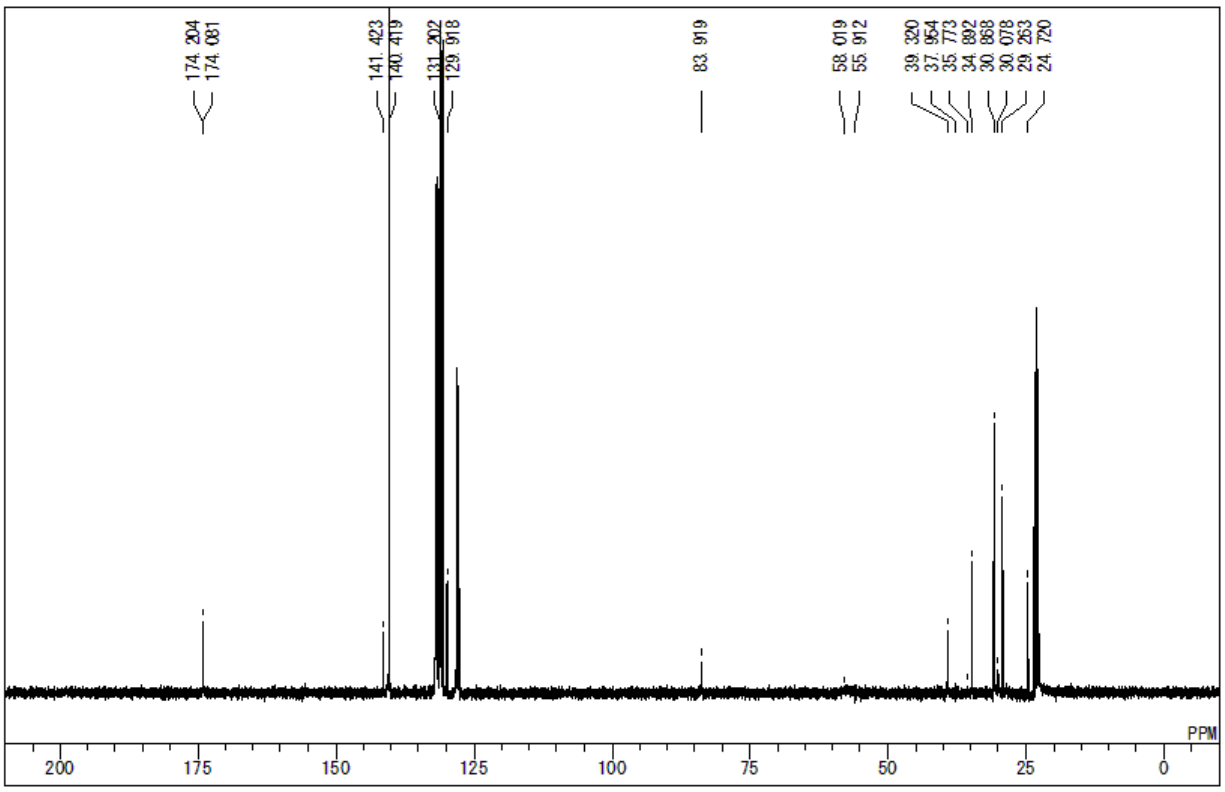
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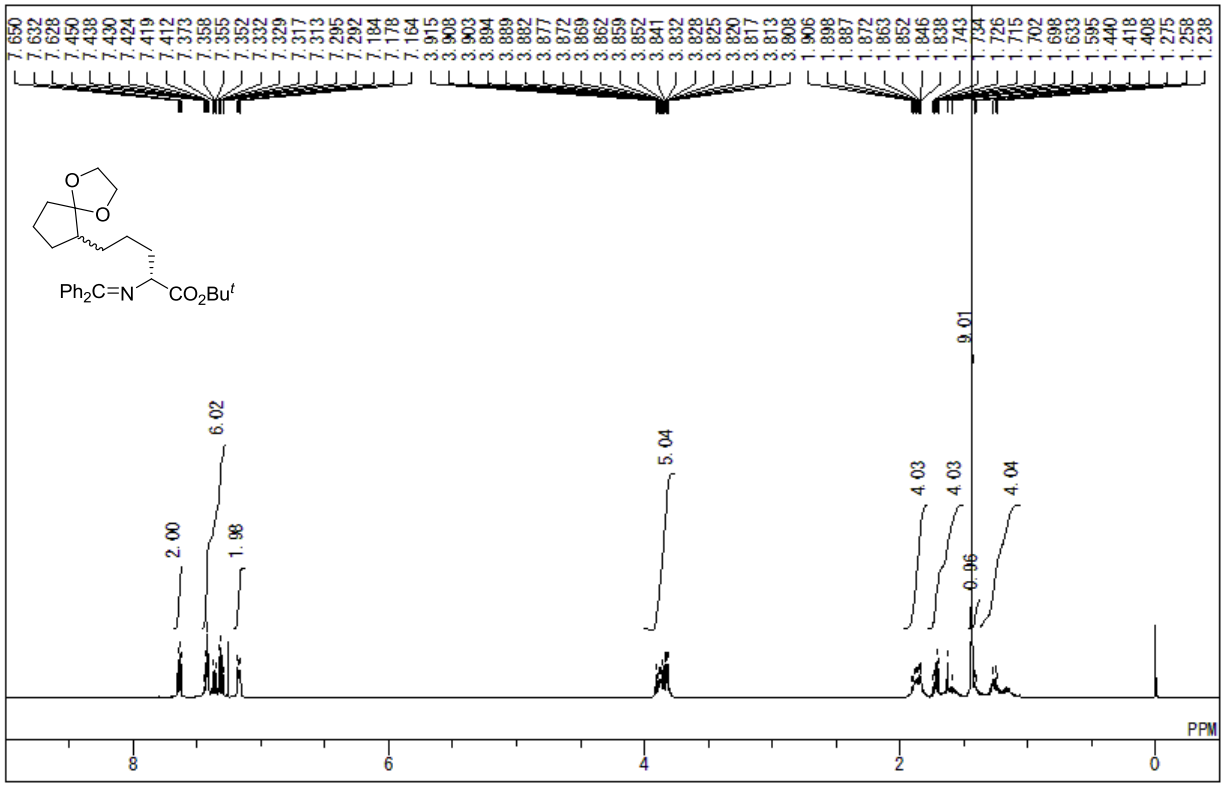

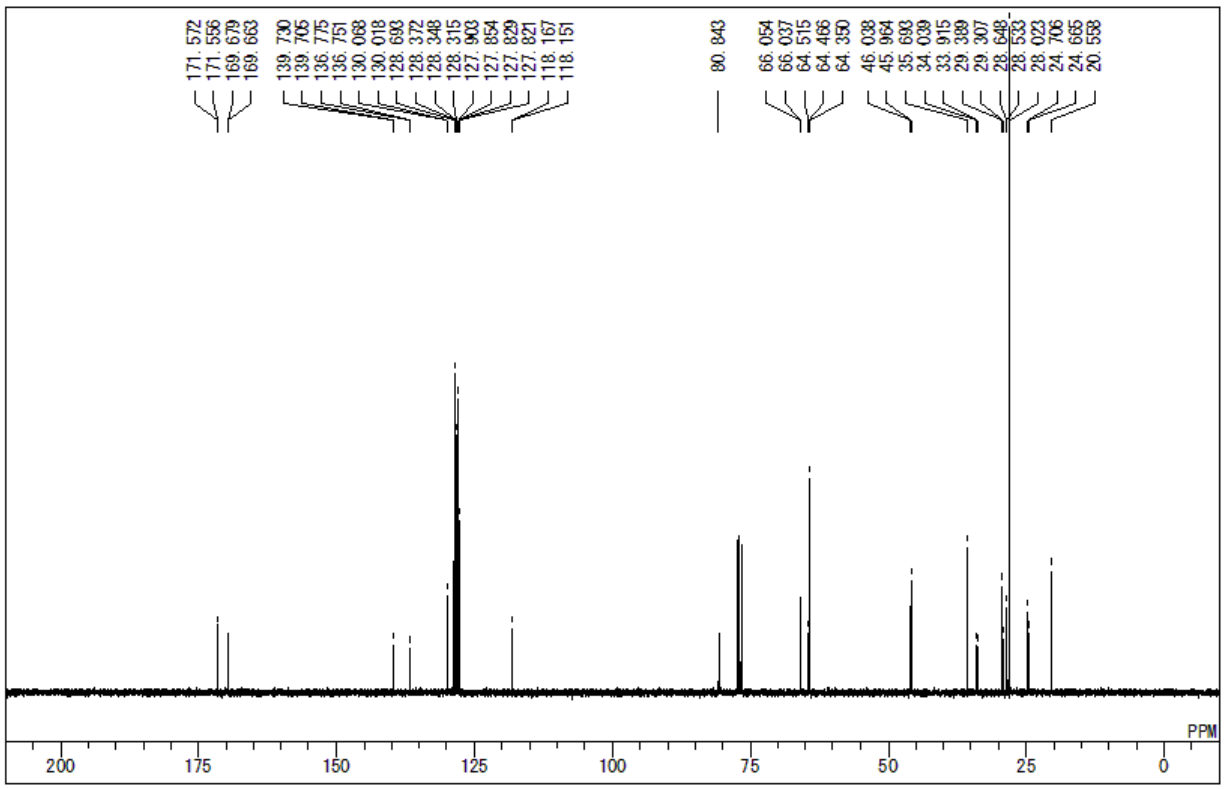

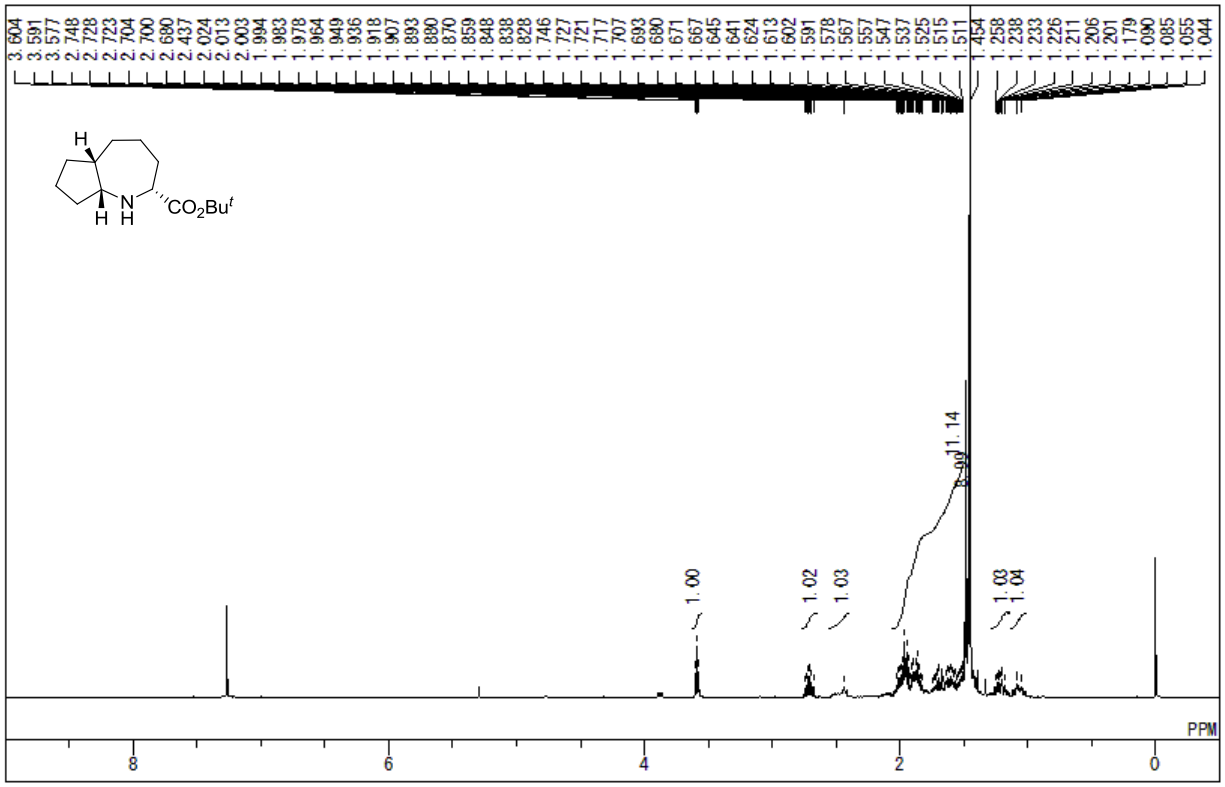
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H
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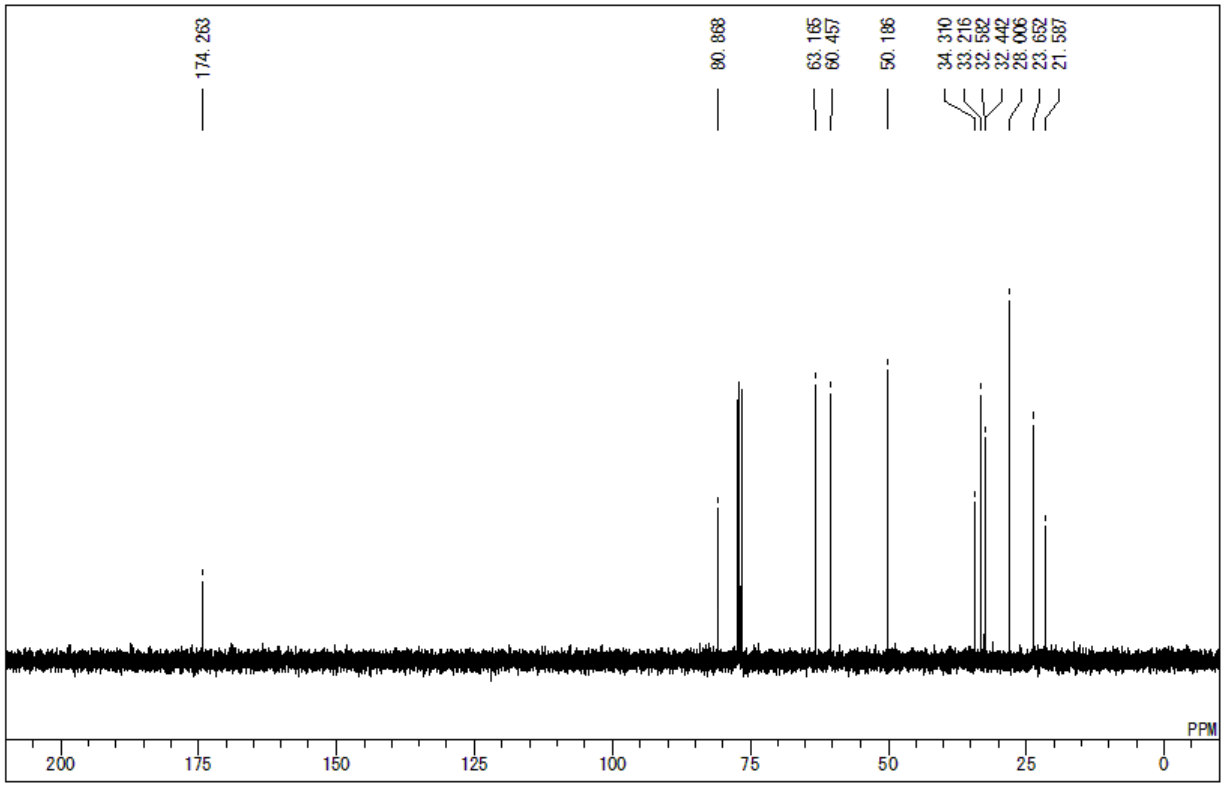
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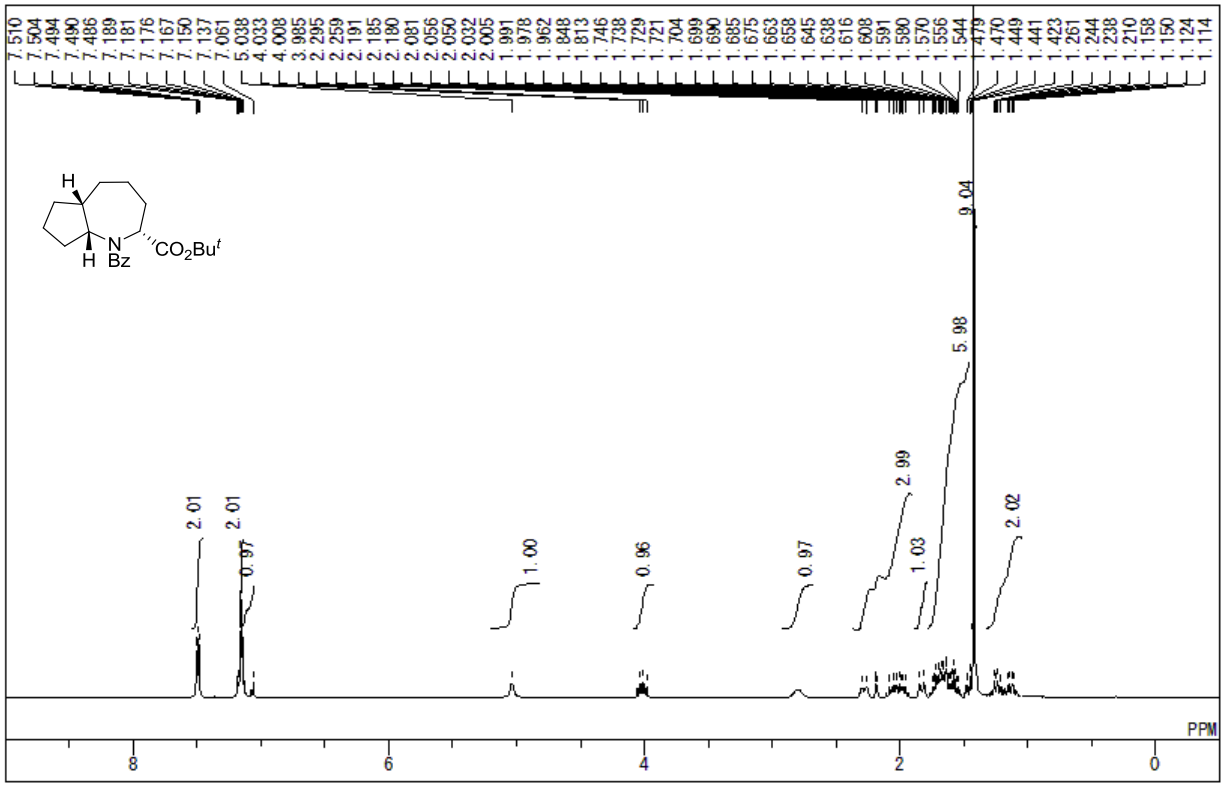
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N
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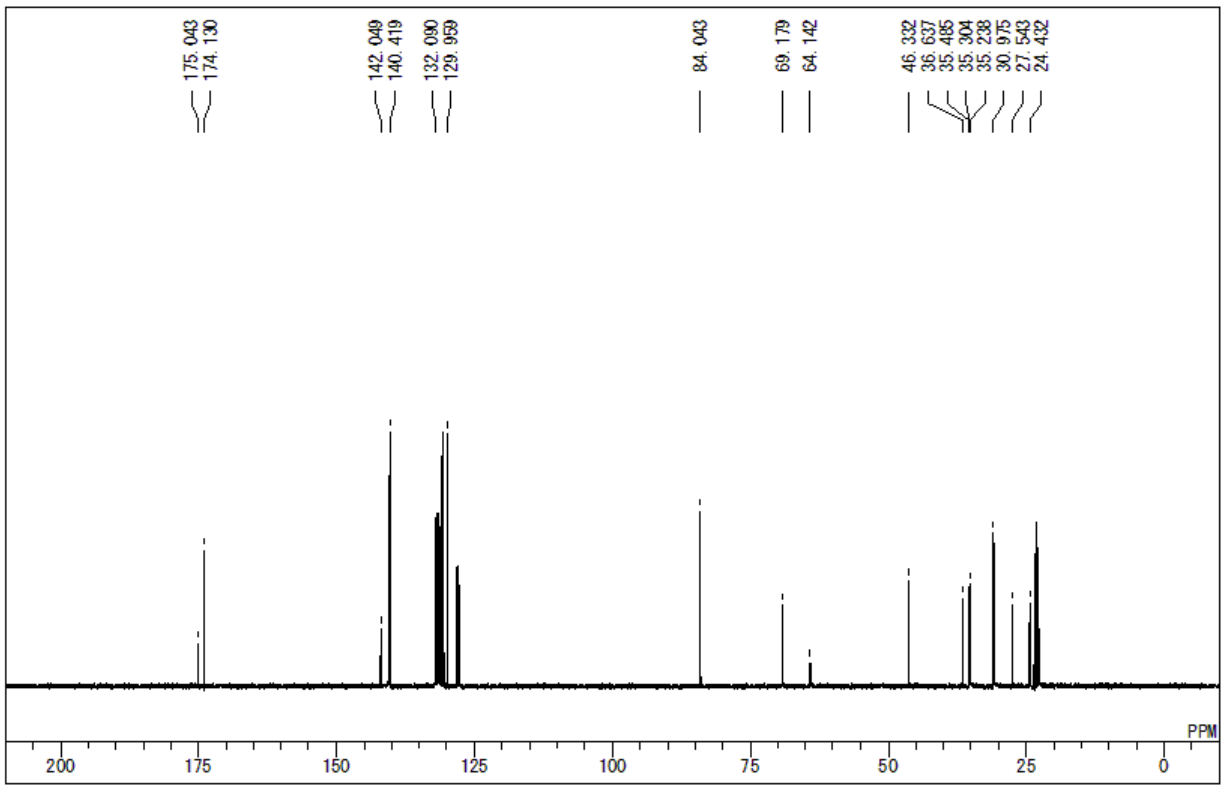
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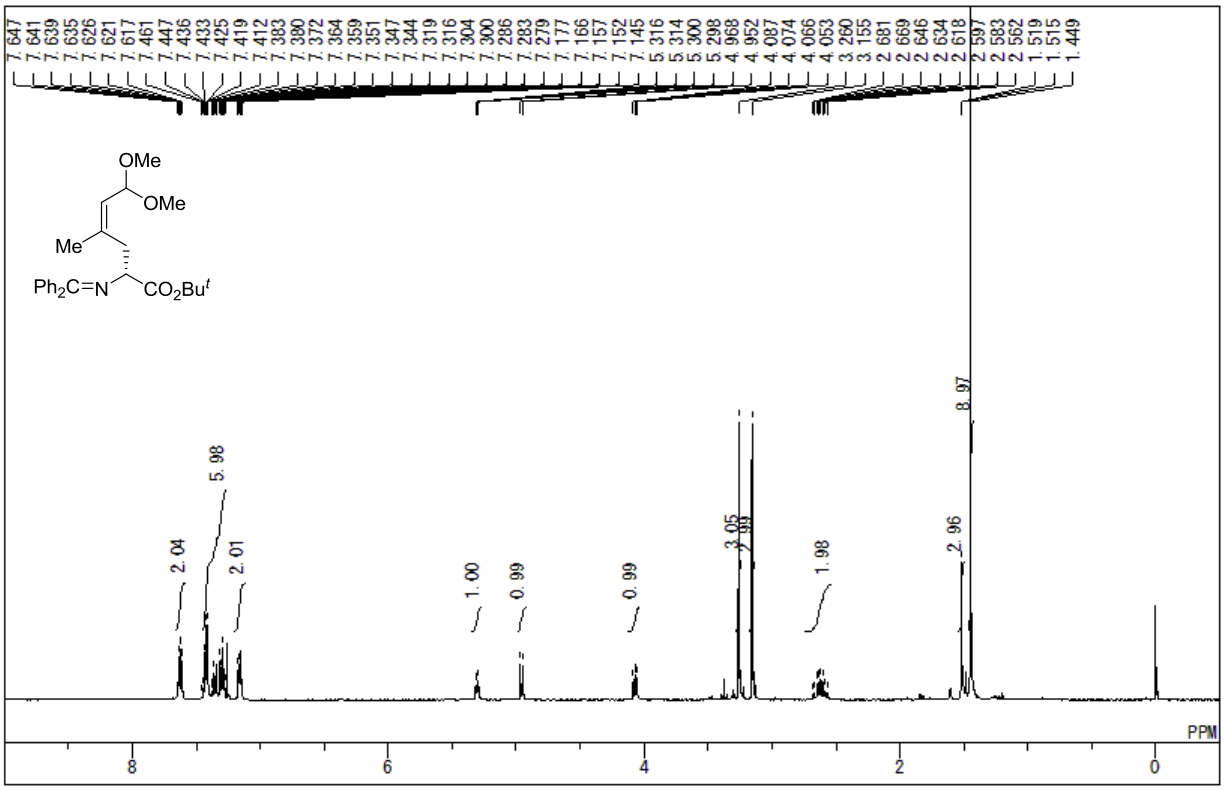
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OMe
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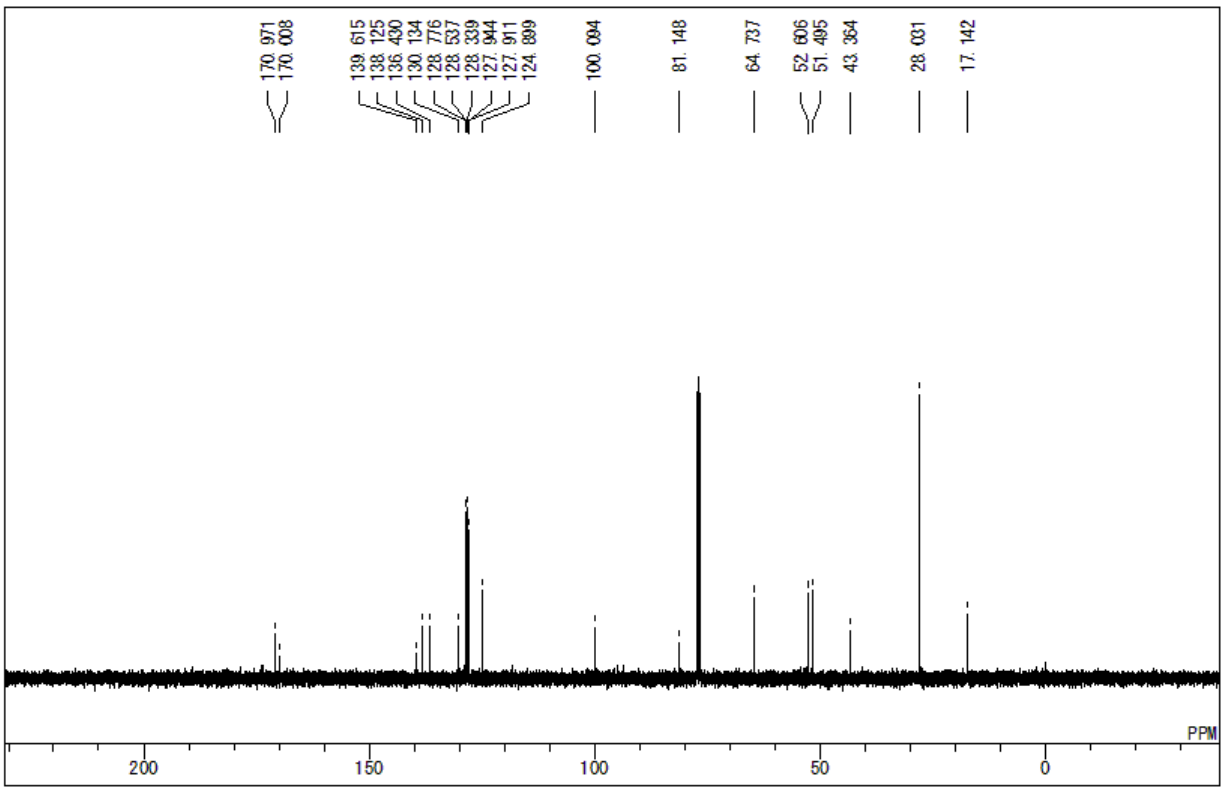
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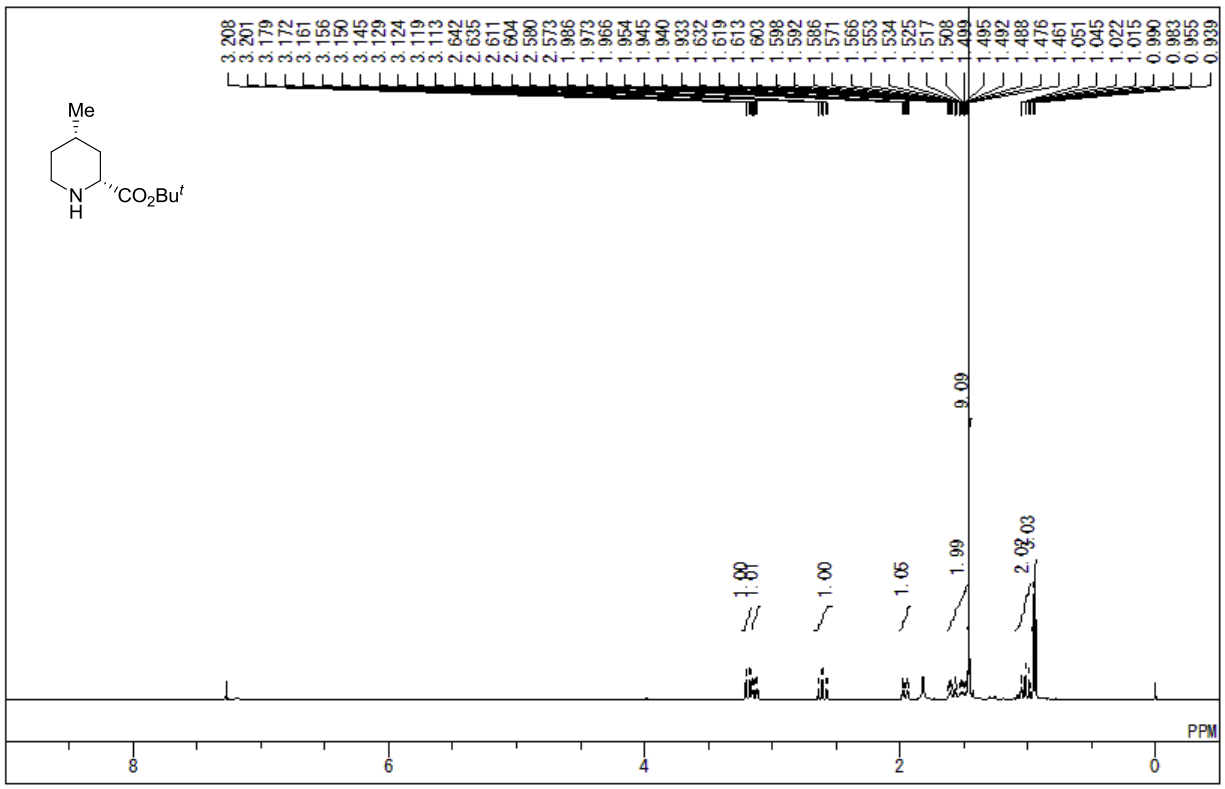
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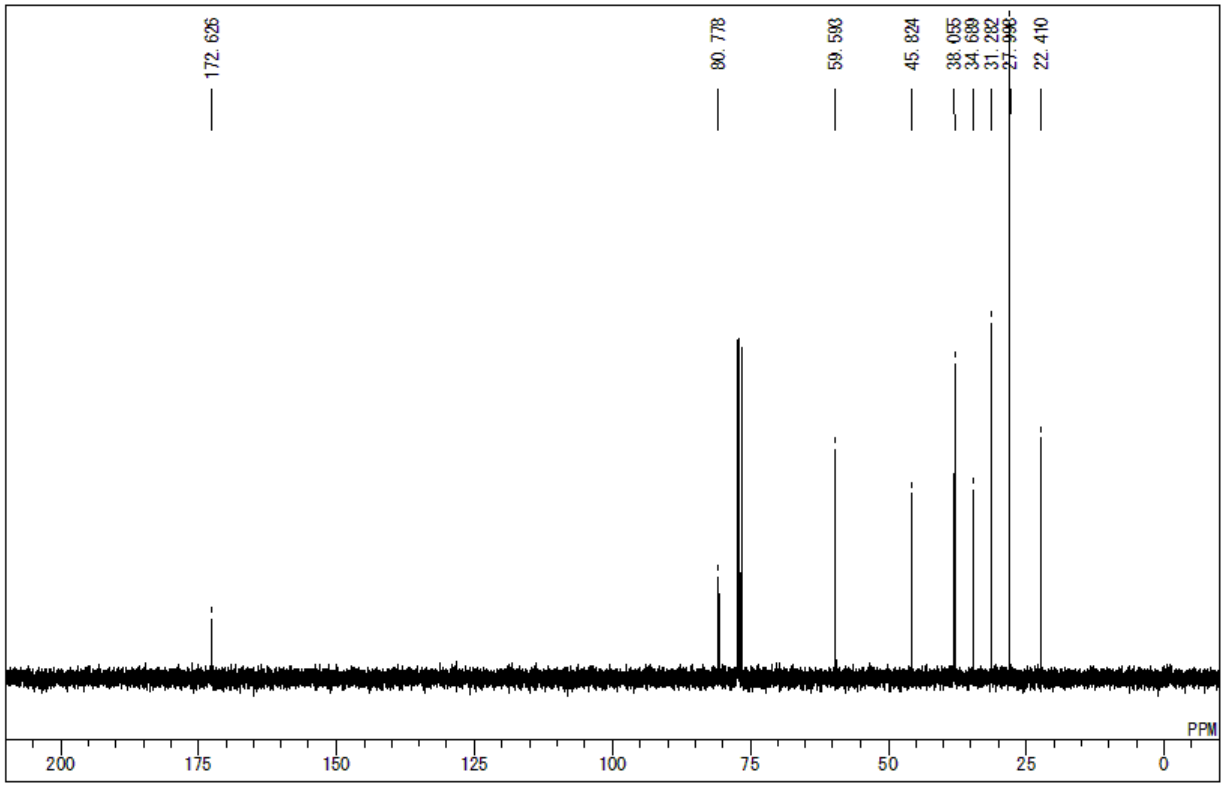
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