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Supporting Information

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Thermally Induced and Silver Salt-Catalyzed [2+2] Cycloadditions of Imines to (Alkoxymethylene)cyclopropanes

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Contents

General information. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM AL 400 (400 MHz) spectrometers. IR spectra were recorded on a JASCO FT/IR-460 *Plus* spectrometer. High-resolution mass spectra were obtained on a HITACHI M-2500s spectrometer. X-ray crystallographic data was obtained with a Rigaku / MSC Saturn. Cu-CCD device. Column chromatography was carried out employing Silica-gel BW-300 (Fuji Silysia Chemical Ltd.) and Silica-gel 60N (spherical, neutral, KANTO Chemical Co.). Analytical thin-layer chromatography (TLC) was performed on 0.2 mm precoated plates with Kieselgel 60 F_{254} (Merck).

General procedure for the [2+2] cycloaddition of imines 2 to alkoxymethylenecyclopropanes 1.

Thermal condition: To a solution of the respective imine **2** (0.2 mmol) in acetonitrile (0.1 mL) was added **1** (0.3 mmol) under argon atmosphere in a Wheaton microreactor. After stirring the mixture at 80 °C for 4–61 h, the product **3** was purified by column chromatography on silica gel (Fuji Silysia) eluting with hexane/EtOAc/Et_3N (20/1/2).

Catalytic condition: To a mixture of Ag(fod) (6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octane-dionato silver) (12.1 mg, 0.030 mmol) and the respective imine **2** (0.3 mmol) in ethyl acetate (0.3 mL) was added **1** (0.3 mmol) under argon atmosphere in a Wheaton microreactor. After stirring for 37–42 h, the reaction mixture was filtered through a short silica gel (Fuji Silysia) column eluting with EtOAc/Et_3N (10/1). Purification of the crude product by chromatography on silica gel (Fuji Silysia) eluting with hexane/EtOAc/Et_3N (20/1/2) afforded **3**.

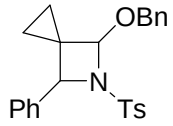
Preparation of the b**-amino aldehyde 8.** A solution of 372 mg (0.83 mmol) *N*-nosylazetidine **3ag** in a mixture of acetone (4 mL) and water (1 mL) was stirred with Amberlyst-15 H^+ (240 mg) at room temperature under argon atmosphere overnight. After filtration and concentration in vacuo, the residue was dissolved in ethyl acetate (20 mL), the organic layer was dried over $MgSO_4$ and concentrated in vacuo. Recrystallization of the crude solid from ethanol afforded 255 mg (86 %) of **8**.

Preparation of the b**-amino carboxylic acid 9.** To a solution of 92 mg (0.26 mmol) of the aldehyde **8** in acetone (3 mL) cooled at –20 °C, was added a solution of Jones reagent (102 mg of CrO_3 in 0.6 mL of concd H_2SO_4, 3.6 mL of water) in two portions. The reaction mixture was stirred at room temperature for 3 days and sat. NH_4Cl solution (5 mL) and isopropyl alcohol (5 mL) were added. After the solvent had been evaporated in vacuo, the crude mixture was extracted with ethyl acetate and dried over Na_2SO_4. Purification of the crude product by chromatography on silica gel (KANTO) eluting with chloroform/acetone/methanol (25/5/1) afforded 87 mg (90 %) of **9**.

Preparation of the b**-amino acid 10.** To a solution of 15 mg (0.040 mmol) of the carboxylic acid **9** and Amberlyst A-21 (10 equiv.) in acetonitrile (3mL) was added ethyl thioglycolate (5 equiv.), and

the mixture was stirred at room temperature for 3 days. The resulting solution was filtered and the resin eluted with MeCN. Then, the resin was eluted with AcOH/MeCN (1/1) and the resulting filtrate was evaporated in vacuo to afford 7.6 mg (100 %) of the pure β-amino acid **10**.

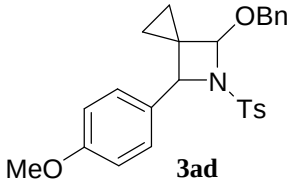
4-Benzyloxy-6-phenyl-5-(toluene-4-sulfonyl)-5-azaspiro[2.3]hexane (3ac).



3ac

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05−0.08 (m, 1 H), 0.55−0.60 (m, 2 H), 0.78−0.82 (m, 1 H), 2.39 (s, 3 H), 4.84 (dd, *J* = 84, 12.4 Hz, 2 H), 4.85 (s, 1 H), 5.50 (s, 1 H), 7.20−7.37 (m, 12 H), 7.65 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.44, 8.32, 21.58, 29.67, 65.38, 70.58, 92.26, 127.44, 127.60, 127.66, 127.72, 127.93, 128.17, 128.32, 129.38, 135.23, 137.30, 137.70, 143.64. IR (neat) 3062−2953, 2902, 1596, 1338, 1250, 1115 cm^{-1}. Anal Calcd for $C_{25}H_{25}NO_3S$ (419.54): C, 71.57; H, 6.01; N, 3.34; S, 7.64. Found: C, 71.40; H, 6.14; N, 3.34; S, 7.56. HRMS(EI) Calcd for $C_{25}H_{25}NO_3S$: m/z 419.1555. Found: m/z 419.1550.

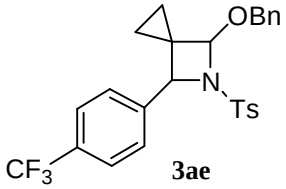
4-Benzyloxy-6-(4-methoxy-phenyl)-5-(toluene-4-sulfonyl)-5-azaspiro[2.3]hexane (3ad).



3ad

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09−0.11 (m, 1 H), 0.52−0.59 (m, 2 H), 0.80−0.84 (m, 1 H), 2.39 (s, 3 H), 3.78 (s, 3 H), 4.79 (s, 1 H), 4.82 (dd, *J* = 86, 12 Hz, 2 H), 5.46 (s, 1 H), 6.79 (d, *J* = 8.4 Hz, 2 H), 7.19−7.22 (m, 4 H), 7.29−7.38 (m, 5 H), 7.64 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.47, 8.25, 21.60, 29.75, 55.26, 65.17, 70.60, 92.17, 113.60, 127.60, 127.67, 128.32, 128.96, 129.38, 129.57, 135.31, 137.72, 143.57, 159.34. IR (neat) 3006−2939, 2902, 1616, 1334, 1249, 1154 cm^{-1}. Anal Calcd for $C_{26}H_{27}NO_4S$ (449.57): C, 69.46; H, 6.05; N, 3.12 S, 7.13. Found: C, 69.24; H, 6.15; N, 3.05; S, 7.20. HRMS(ESI) Calcd for [M+Na] ($C_{26}H_{27}NNaO_4S$): m/z 472.1558. Found: m/z 472.1553.

4-Benzyloxy-5-(toluene-4-sulfonyl)-6-(4-trifluoromethyl-phenyl)-5-azaspiro[2.3]hexane (3ae).



3ae

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00−0.04 (m, 1 H), 0.56−0.64 (m, 2 H), 0.80−0.88 (m, 1 H), 2.39 (s, 3 H), 4.84 (dd, *J* = 91, 12 Hz, 2 H), 4.87 (s, 1 H), 5.50 (s, 1 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.30−7.37 (m, 7 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.36, 8.38, 11.69, 21.54, 29.74, 46.30, 64.59, 70.86, 92.26, 125.21, 127.61, 127.71, 127.75, 127.78, 128.38, 129.50, 134.76, 137.44, 141.36, 144.04. IR (neat) 3031−2950, 2907, 1619, 1324, 1255, 1113 cm^{-1}. Anal Calcd for $C_{26}H_{24}F_3NO_3S$ (487.53): C, 64.05; H, 4.96; F, 11.69; N, 2.87 S, 6.58. Found: C, 63.79; H, 5.22; F, 11.97; N, 2.77; S, 6.34. HRMS(ESI) Calcd for [M+Na] ($C_{26}H_{27}F_3NNaO_3S$): m/z 510.1327. Found: m/z 510.1321

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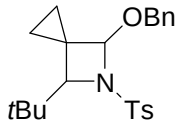
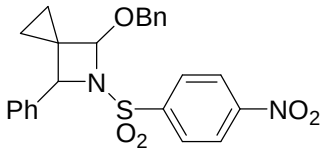
4-Benzyloxy-6-tert-butyl-5-(toluene-4-sulfonyl)-5-azaspiro[2.3]hexane (3af).



3af

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.29 (t, *J* = 8.4 Hz, 2 H), 0.90 (s, 9 H), 0.74−0.95 (m, 2 H), 2.44 (s, 3 H), 3.65 (s, 1 H), 4.75 (dd, *J* = 135, 12 Hz, 2 H), 5.09 (s, 1 H), 7.28−7.34 (m, 7 H), 7.76 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.15, 9.93, 21.63, 24.04, 26.20, 34.53, 69.92, 74.29, 77.20, 94.15, 121.47, 127.57, 127.84, 128.25, 129.40, 135.40, 143.52. IR (neat) 3088−2955, 2905, 1597, 1344, 1255, 1088 cm^{-1}. Anal Calcd for $C_{23}H_{29}NO_3S$ (399.55): C, 69.14; H, 7.32; N, 3.51 S, 8.03. Found: C, 69.13; H, 7.40; N, 3.38; S, 8.29. HRMS(ESI) Calcd for [M+Na] ($C_{23}H_{29}NNaO_3S$): m/z 422.1766. Found: m/z 422.1760.

4-Benzyloxy-5-(4-nitro-benzenesulfonyl)-6-phenyl-5-azaspiro[2.3]hexane (3ag).

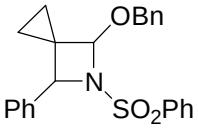


3ag

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07−0.16 (m, 1 H), 0.64−0.68 (m, 2 H), 0.86−0.91 (m, 1 H), 4.83 (dd, *J* = 70, 12 Hz, 2 H), 5.03 (s, 1 H), 5.71 (s, 1 H), 7.22−7.24 (m, 5 H), 7.29−7.37 (m, 5 H), 7.78 (d, *J* = 8.8 Hz, 2 H), 8.14 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.57, 8.55, 29.87, 65.59,

71.39, 92.93, 123.81, 127.45, 127.81, 127.90, 128.33, 128.42, 128.44, 128.50, 136.44, 137.30, 145.22, 149.82. IR (neat) 3092−2957, 2907, 1604, 1531, 1352, 1249, 1169 cm^{-1}. HRMS(ESI) Calcd for [M+Na] ($C_{24}H_{22}N_2NaO_5S$): m/z 473.1147. Found: m/z 473.1142.

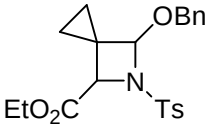
5-Benzenesulfonyl-4-benzyloxy-6-phenyl-5-azaspiro[2.3]hexane (3ah)



3ah

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04−0.09 (m, 1 H), 0.54−0.61 (m, 2 H), 0.78−0.84 (m, 1 H), 4.84 (dd, *J* = 85, 12 Hz, 2 H), 4.89 (s, 1 H), 5.54 (s, 1 H), 7.20−7.25 (m, 5 H), 7.29−7.36 (m, 5 H), 7.37−7.41 (m, 2 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.76 (d, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.44, 8.32, 29.68, 65.43, 70.67, 92.32, 127.42, 127.56, 127.66, 127.97, 128.11, 128.15, 128.30, 128.72, 132.77, 137.11, 137.57, 138.30. IR (neat) 3062−2951, 2902, 1603, 1338, 1250, 1164 cm^{-1}. Anal Calcd for $C_{24}H_{23}NO_3S$ (405.51): C, 71.09; H, 5.72; N, 3.45 S, 7.91. Found: C, 71.01; H, 5.55; N, 3.31; S, 7.70. HRMS(EI) Calcd for $C_{24}H_{23}NO_3S$: m/z 405.1399. Found: m/z 405.1393.

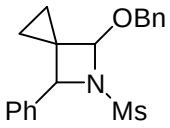
6-Benzyloxy-5-(toluene-4-sulfonyl)-5-azaspiro[2.3]hexane-4-carboxylic acid ethyl ester (3ai).



3ai

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64−0.74 (m, 2 H), 0.76−0.81 (m, 1 H), 0.85−0.90 (m, 1 H), 1.18 (t, *J* = 7.2 Hz, 3 H), 2.42 (s, 3 H), 4.14 (dq, *J* = 10.8, 7.2 Hz, 2 H), 4.60 (s, 1 H), 4.66 (dd, *J* = 42, 12 Hz, 2 H), 5.58 (s, 1 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 7.26−7.30 (m, 5 H), 7.88 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.47, 8.51, 14.26, 21.64, 24.95, 60.33, 61.26, 69.20, 92.13, 127.56, 127.63, 127.75, 128.24, 129.43, 136.08, 137.31, 143.85, 168.17. IR (neat) 3088−2936, 1758, 1336, 1291, 1172 cm^{-1}. HRMS(ESI) Calcd for [M+Na] ($C_{22}H_{25}NNaO_5S$): m/z 438.1351. Found: m/z 438.1346.

4-Benzyloxy-5-methanesulfonyl-6-phenyl-5-azaspiro[2.3]hexane (3aj).

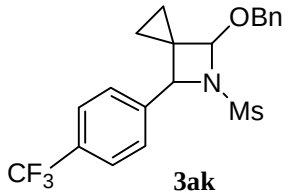


3aj

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07−0.12 (m, 1 H), 0.64−0.68 (m, 2 H), 0.85−0.90 (m, 1 H), 2.72 (s, 3 H), 4.84 (dd, *J* = 86, 12 Hz, 2 H), 5.04 (s, 1 H), 5.69 (s, 1 H), 7.27−7.42 (m, 10 H). ^{13}C NMR (100

MHz, $CDCl_3$) δ 4.47, 8.27, 29.69, 41.40, 64.73, 71.17, 91.31, 127.45, 127.64, 127.68, 128.31, 128.37, 128.52, 137.34, 137.71. IR (neat) 3066−2960, 2920, 1607, 1312, 1253, 1145 cm^{-1}. Anal Calcd for $C_{19}H_{21}NO_3S$ (343.44): C, 66.45; H, 6.16; N, 4.08; S, 9.34. Found: C, 66.33; H, 6.23; N, 3.90; S, 9.50. HRMS(ESI) Calcd for $C_{19}H_{21}NNaO_3S$: m/z 366.1140. Found: m/z 366.1134

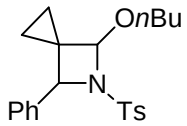
4-Benzyloxy-5-methanesulfonyl-6-(4-trifluoromethylphenyl)-5-azaspiro[2.3]hexane (3ak).



3ak

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01−0.07 (m, 1 H), 0.67−0.73 (m, 2 H), 0.85−0.91 (m, 1 H), 2.75 (s, 3 H), 4.82 (dd, *J* = 82, 12 Hz, 2 H), 5.09 (s, 1 H), 5.69 (s, 1 H), 7.28−7.39 (m, 5 H), 7.52 (d, *J* = 8 Hz, 2 H), 7.63 (d, *J* = 8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.54, 8.51, 29.72, 41.49, 64.07, 71.42, 91.75, 125.61, 125.66, 127.54, 127.88, 127.95, 128.44, 137.52, 141.59. IR (neat) 3087−3010, 2928, 1618, 1319, 1266, 1119 cm^{-1}. HRMS(ESI) Calcd for [M+Na] ($C_{20}H_{20}F_3NNaO_3S$): m/z 434.1014. Found: m/z 434.1008.

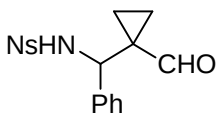
4-Butoxy-6-phenyl-5-(toluene-4-sulfonyl)-5-azaspiro[2.3]hexane (3bc)



3bc

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02−0.04 (m, 1 H), 0.56−0.59 (m, 1 H), 0.60−0.68 (m, 1 H), 0.71−0.74 (m, 1 H), 0.90 (t, *J* = 7.2 Hz, 3 H), 1.34 (sext, *J* = 7.2 Hz, 2 H), 1.53 (ddt, *J* = 6.4, 6.4, 7.2 Hz, 2 H), 2.38 (s, 3 H), 3.55 (dt, *J* = 9.6, 6.4 Hz, 1 H), 3.87 (dt, *J* = 9.6, 6.4 Hz, 1 H), 4.84 (s, 1 H), 5.38 (s, 1 H), 7.20−7.25 (m, 7 H), 7.65 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.20, 8.36, 13.83, 19.19, 21.50, 29.60, 31.69, 65.14, 68.87, 93.02, 127.33, 127.60, 127.78, 128.06, 129.28, 135.32, 137.42, 143.48. IR (neat) 3034−2934, 2870, 1595, 1342, 1261, 1163 cm^{-1}. HRMS(ESI) Calcd for [M+Na] ($C_{22}H_{27}NNaO_3S$): m/z 408.1609. Found: m/z 408.1604.

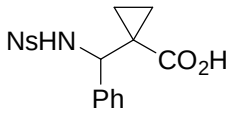
***N*-[(1-Formylcyclopropyl)phenyl-methyl]-4-nitrobenzenesulfonamide (8).**



8

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23−1.37 (m, 4 H), 4.13 (d, *J* = 8.8 Hz, 1 H), 6.40 (d, *J* = 8.8 Hz, 1 H), 7.06−7.17 (m, 5 H), 7.76 (d, *J* = 9.2 Hz, 2 H), 8.10 (d, *J* = 9.2 Hz, 2 H), 8.48 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.84, 14.42, 37.15, 61.35, 123.76, 127.22, 127.95, 128.03, 128.43, 137.47, 146.49, 149.53, 200.07. IR (neat) 3174−2921, 2852, 1688, 1523, 1338, 1158 cm^{-1}. HRMS(ESI) Calcd for [M+Na] ($C_{17}H_{16}N_2NaO_5S$): m/z 383.0678. Found: m/z 383.0672.

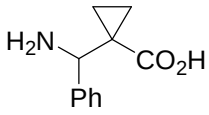
1-[(4-Nitro-benzenesulfonylamino)phenylmethyl]cyclopropanecarboxylic acid (9).



9

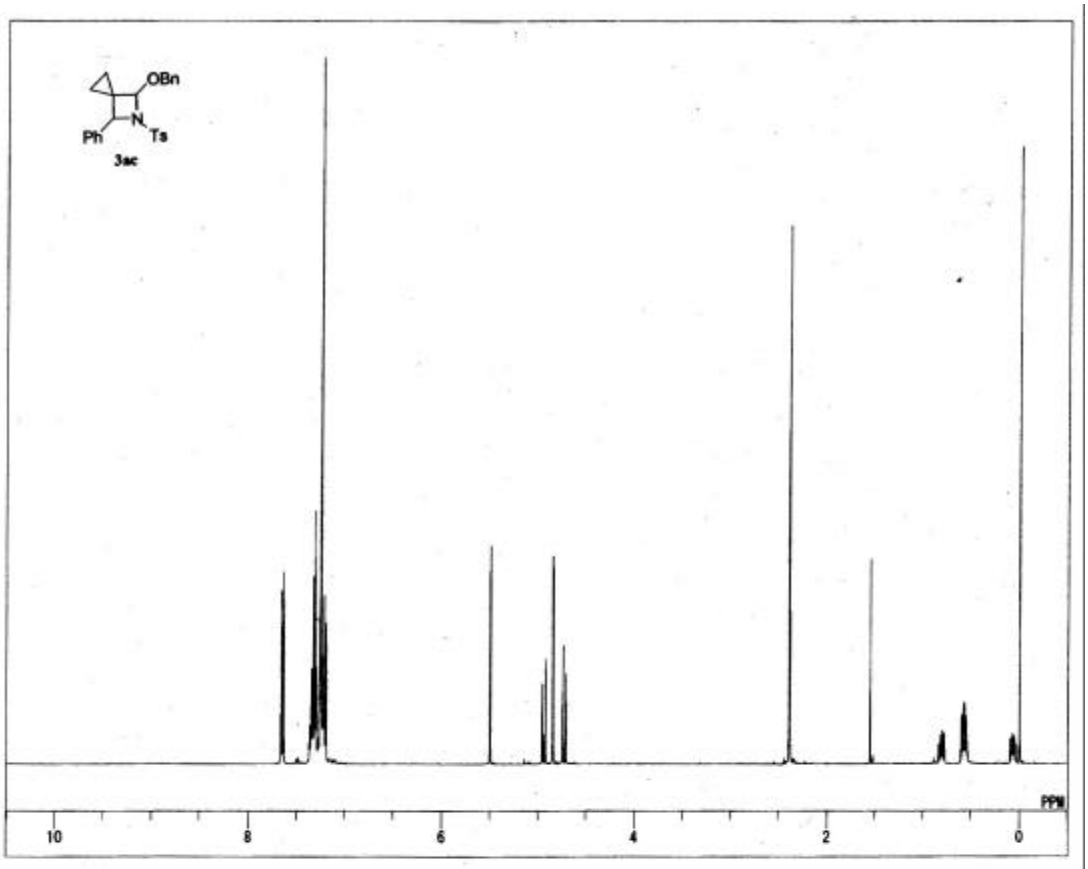
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16−1.26 (m, 4 H), 1.41−1.44 (m, 1 H), 1.58−1.61 (m, 1 H), 4.02 (d, *J* = 10 Hz, 1 H), 6.81 (d, *J* = 10 Hz, 1 H), 7.12−7.18 (m, 5 H), 7.78 (d, *J* = 9.2 Hz, 2 H), 8.09 (d, *J* = 9.2 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.84, 14.42, 37.15, 61.35, 123.76, 127.22, 127.95, 128.03, 128.43, 137.47, 146.49, 149.53, 200.07. IR (neat) 3097−3033, 2870, 1679, 1531, 1347, 1117 cm^{-1}. HRMS(ESI) Calcd for [M+Na] ($C_{17}H_{16}N_2NaO_6S$): m/z 399.0627. Found: m/z 399.0621.

1-(Aminophenylmethyl)cyclopropanecarboxylic acid (10).



10

^{1}H NMR (400 MHz, D_2O) δ 0.69−0.79 (m, 2 H), 0.98−1.03 (m, 1 H), 1.13−1.20 (m, 1 H), 4.12 (s, 1 H), 7.27−7.39 (m, 5 H). ^{13}C NMR (100 M Hz, D_2O, 1,4-dioxane was used as an internal standard) δ 11.16, 14.65, 26.14, 48.83, 58.76, 127.05, 128.69, 135.23, 180.13. IR (neat) 3006−2921, 1667, 1556, 1392, 1115 cm^{-1}. HRMS(ESI) Calcd for [M+Na] ($C_{11}H_{13}NNaO_2$): m/z 214.0844. Found: m/z 214.0838.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N
Ts
3ac
PPM
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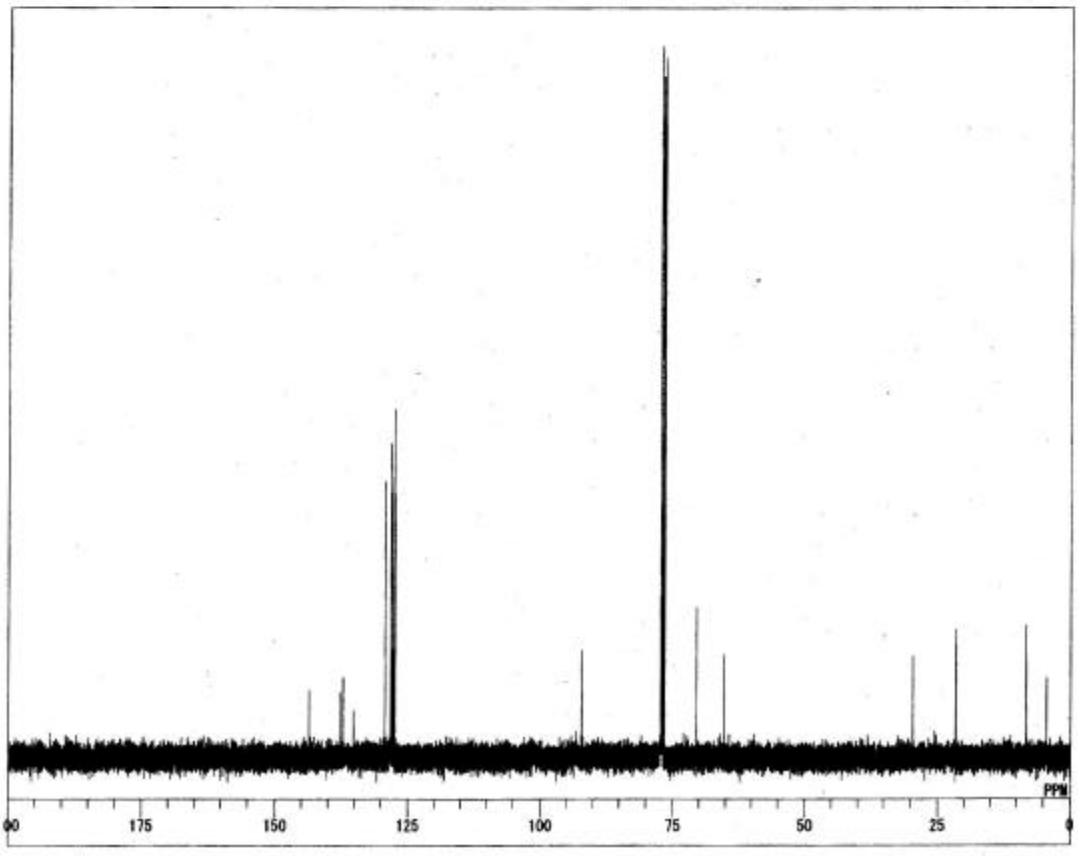
8
6
4
2
0


PPM
175
150
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100
75
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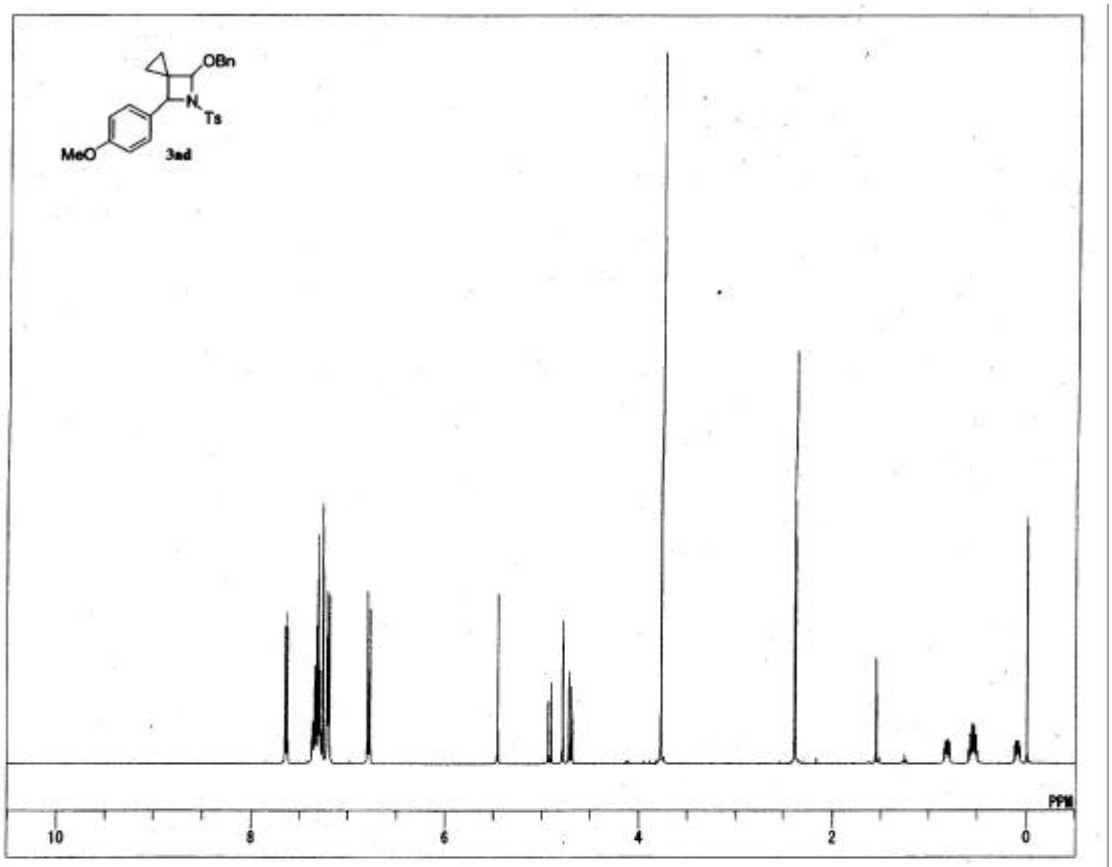
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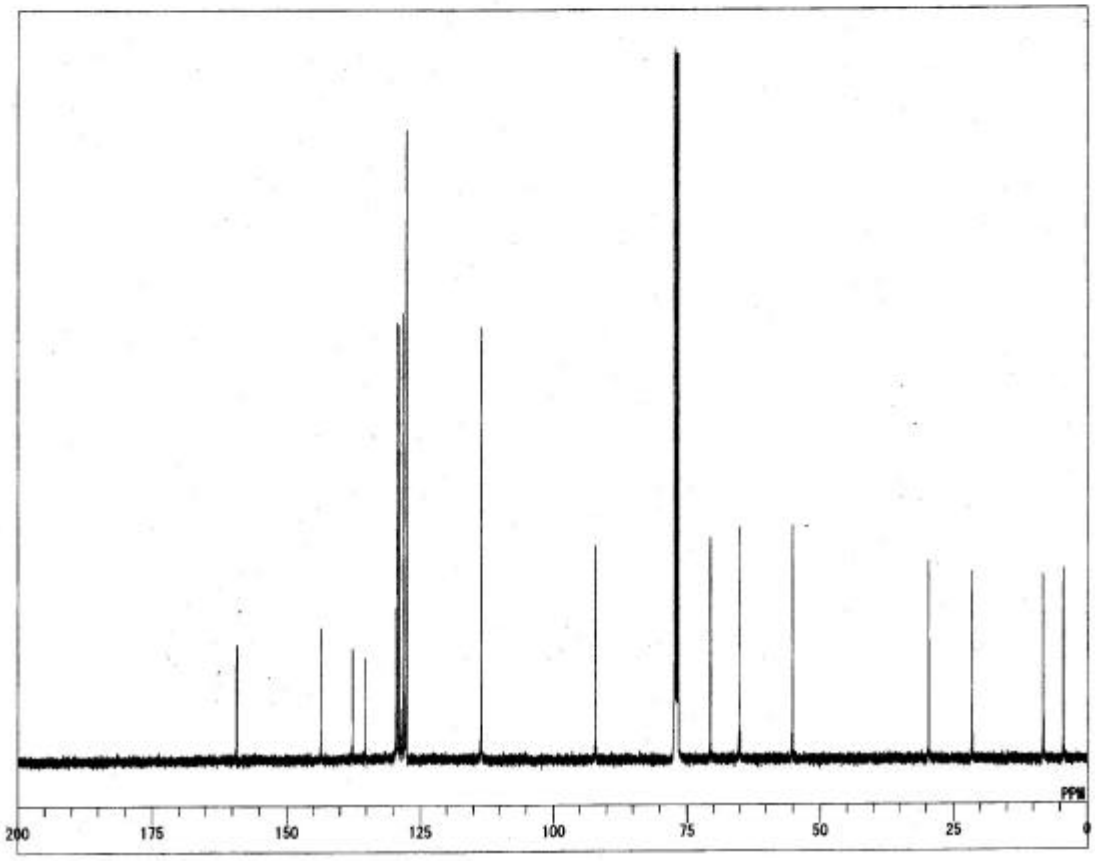
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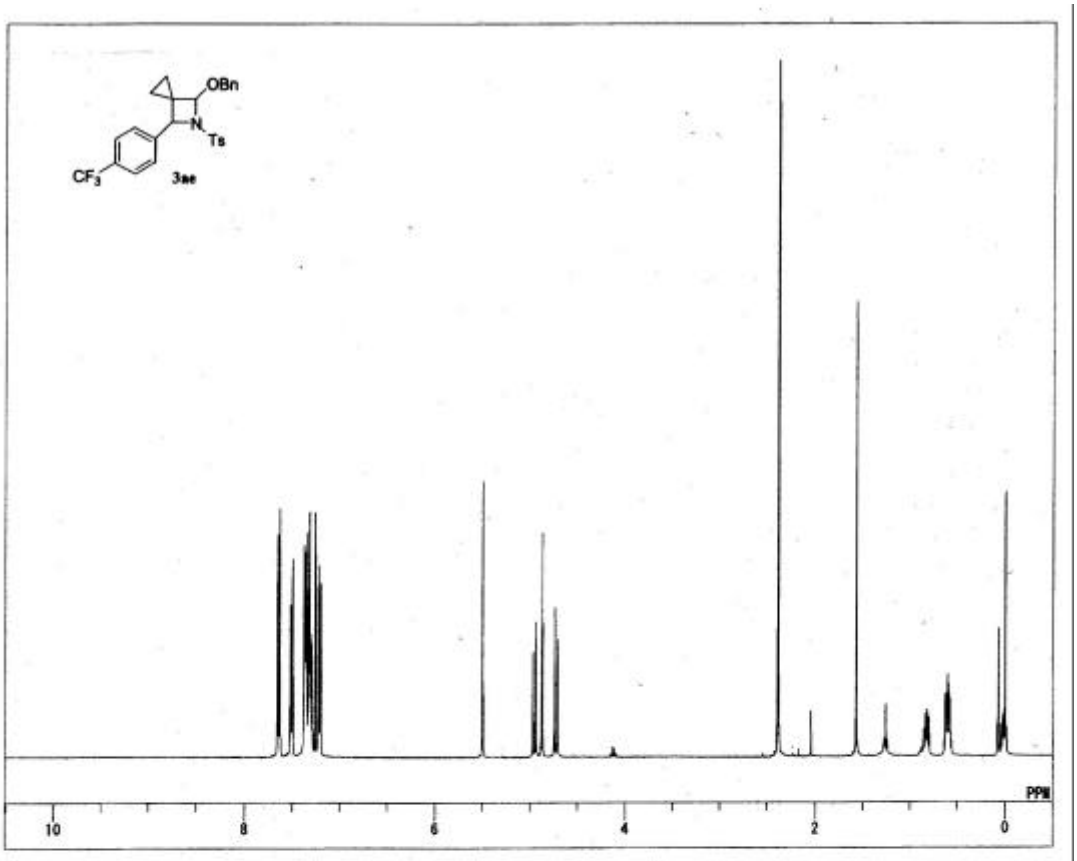
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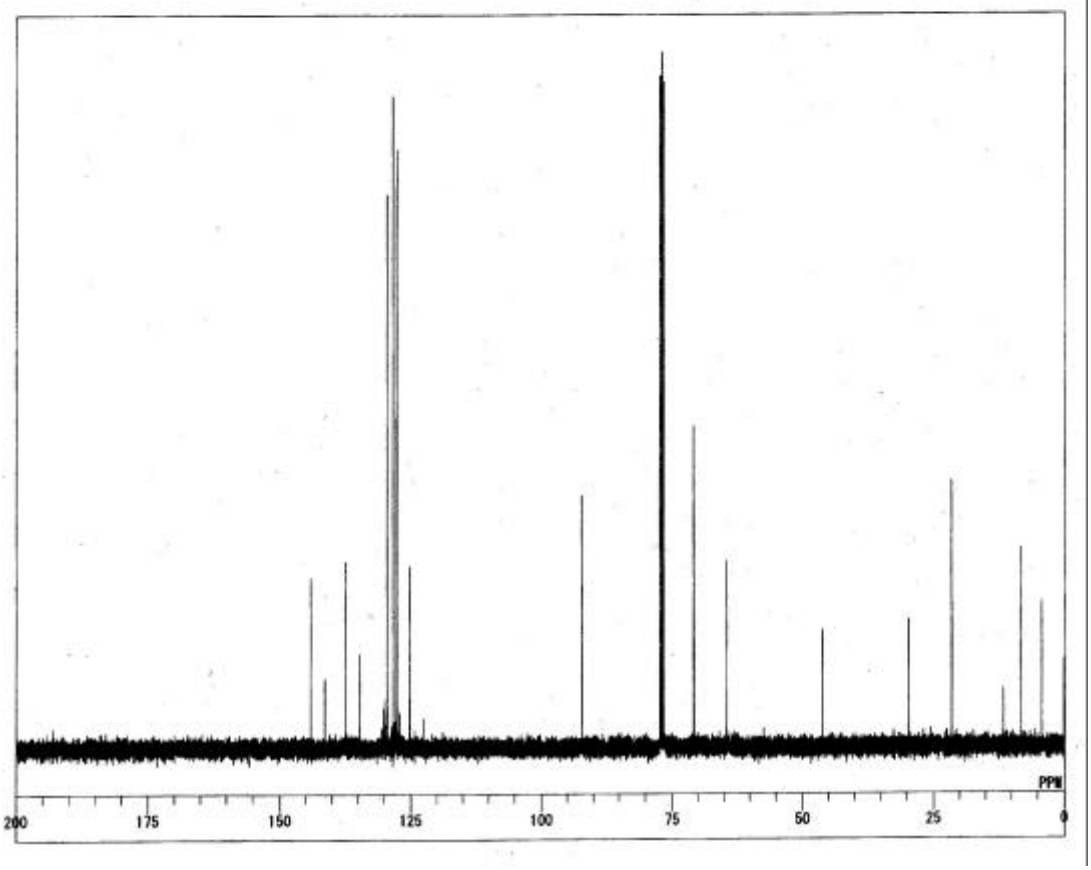
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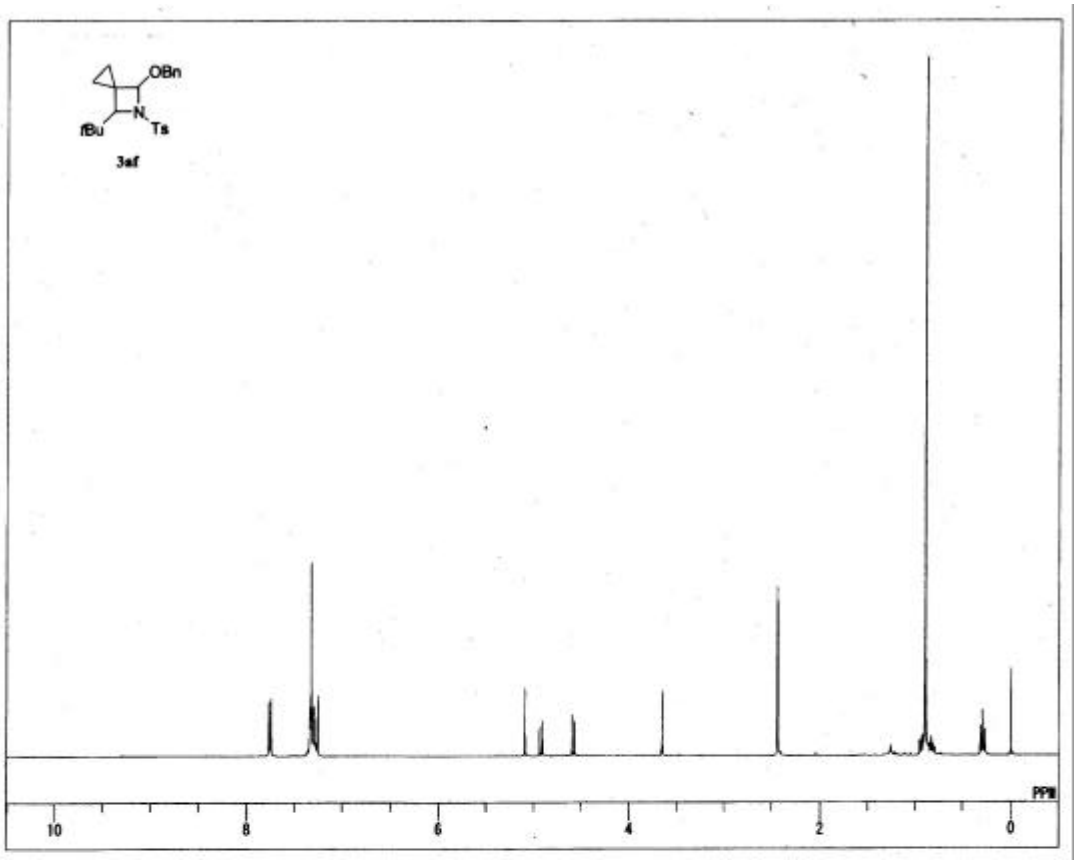
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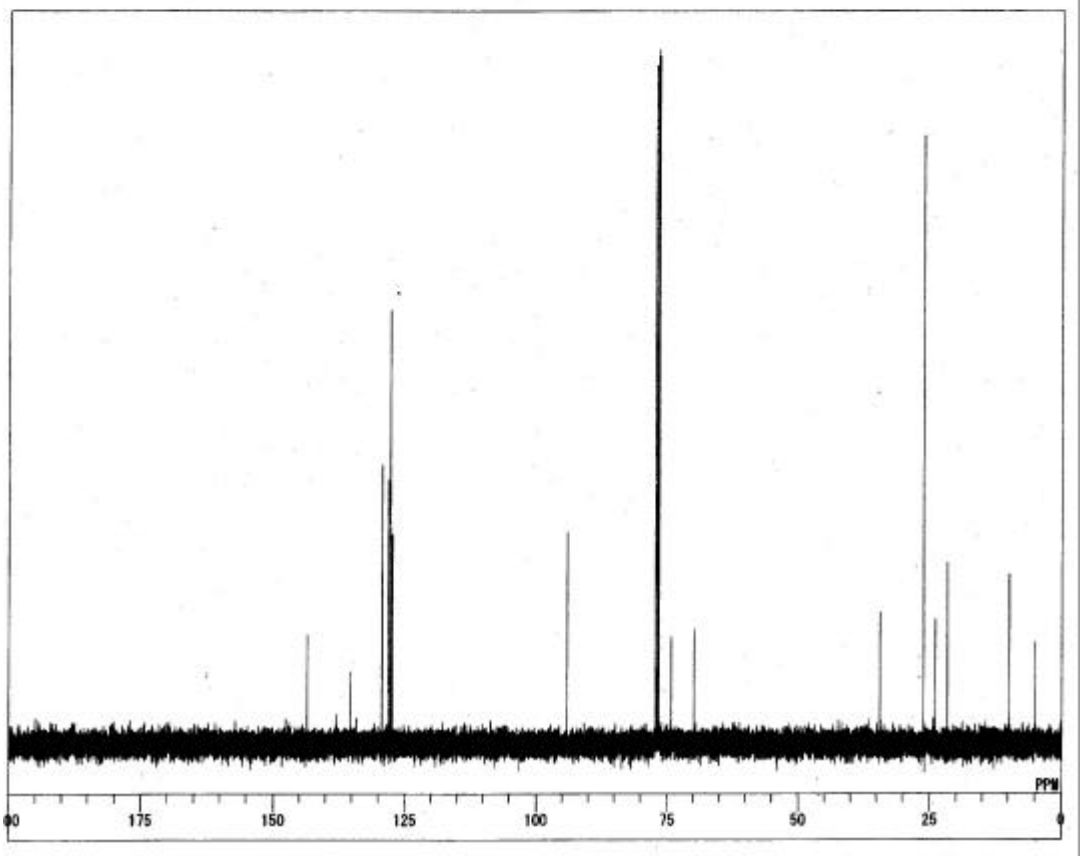
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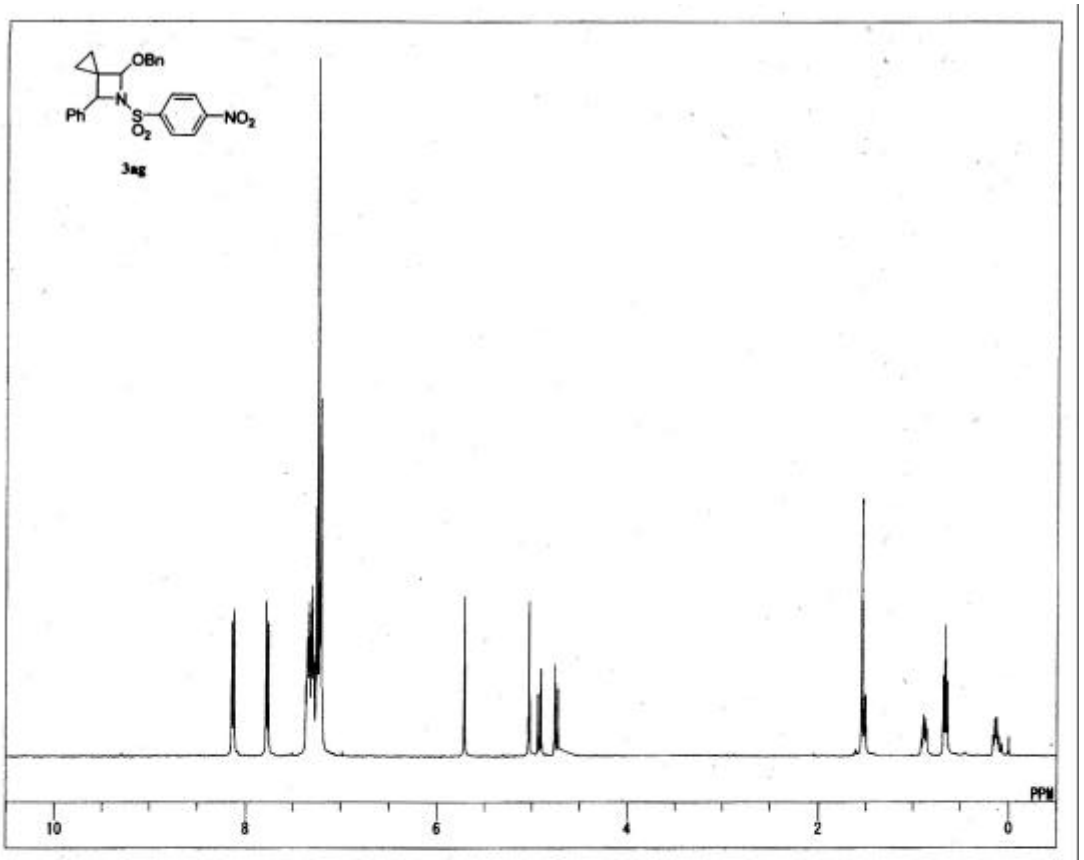
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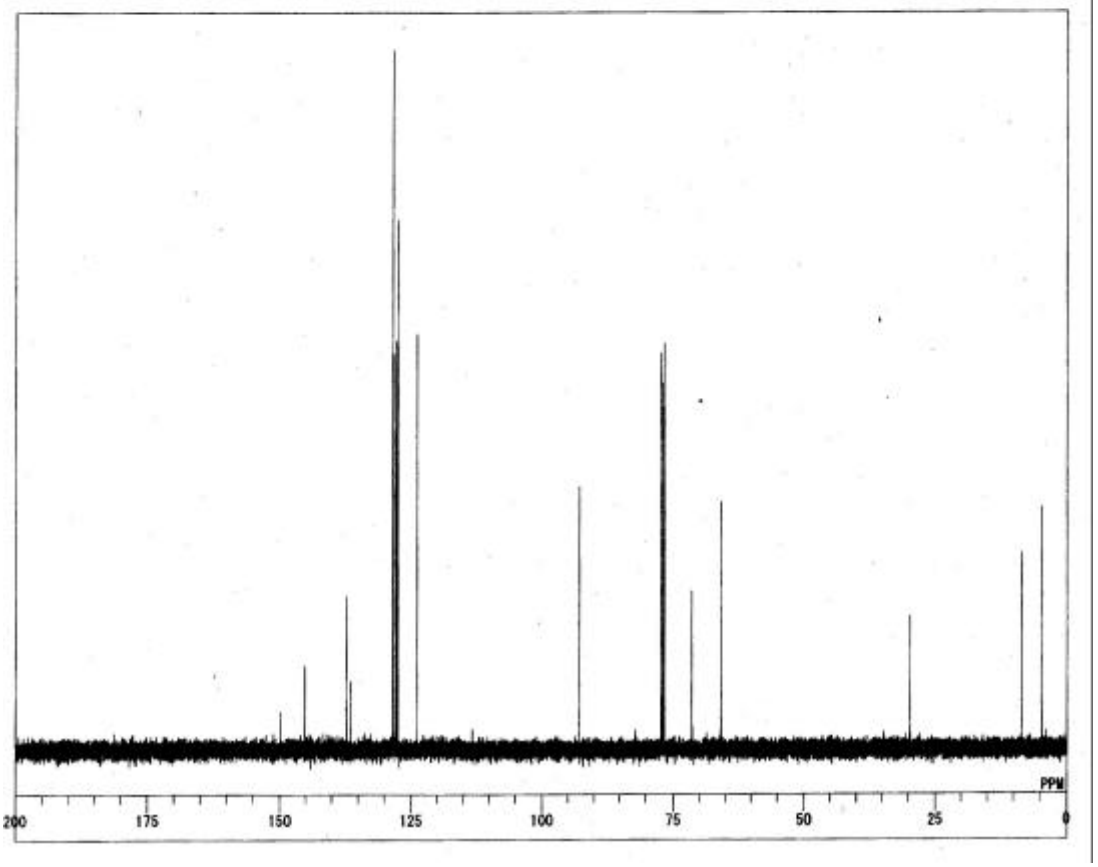
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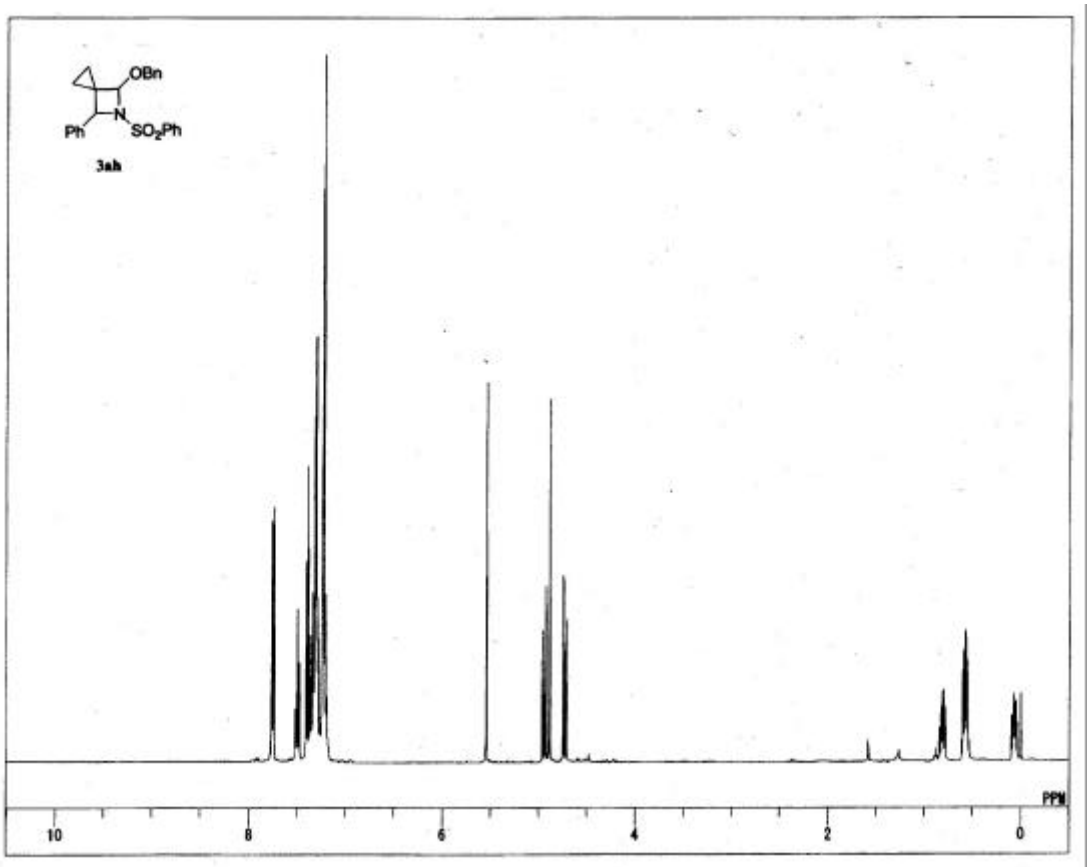
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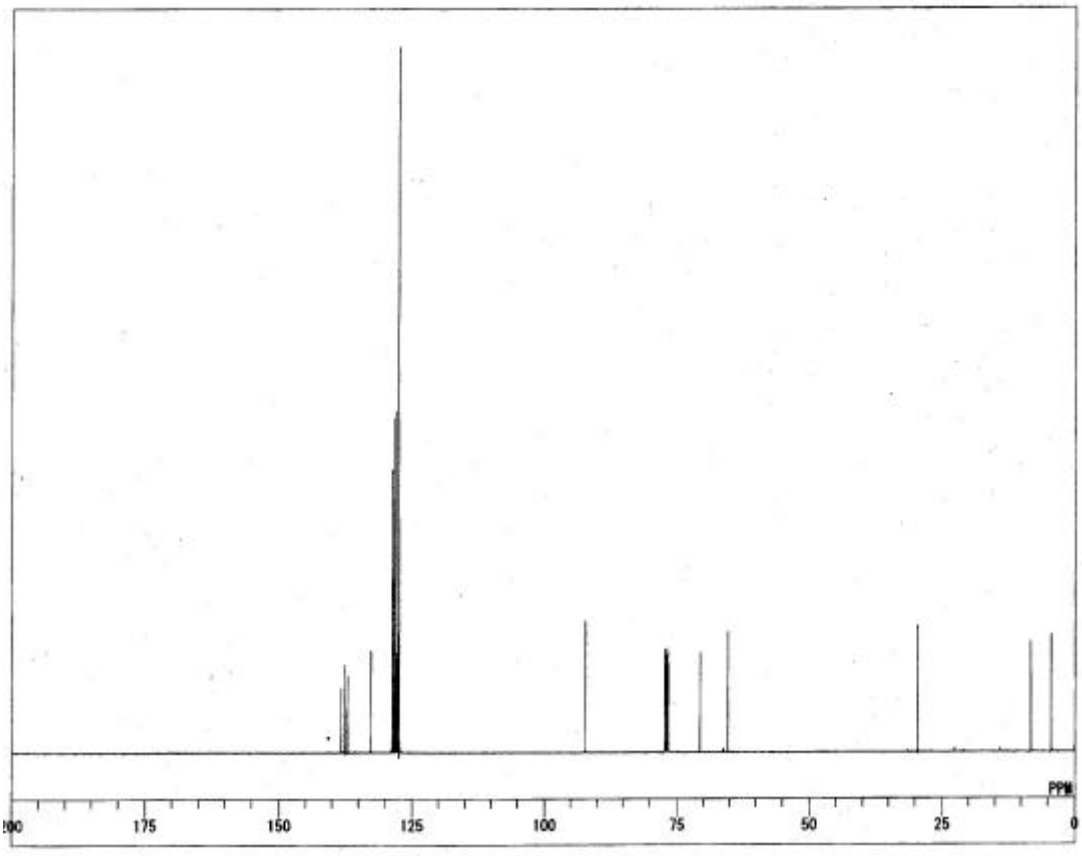
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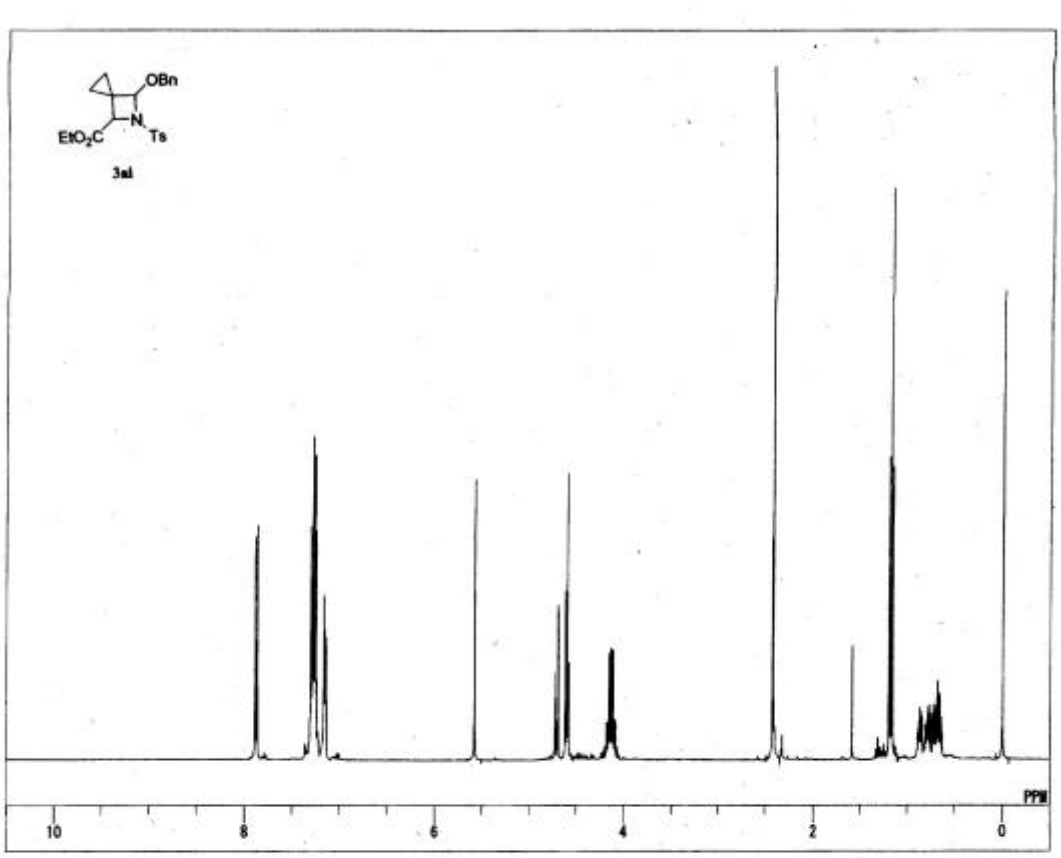
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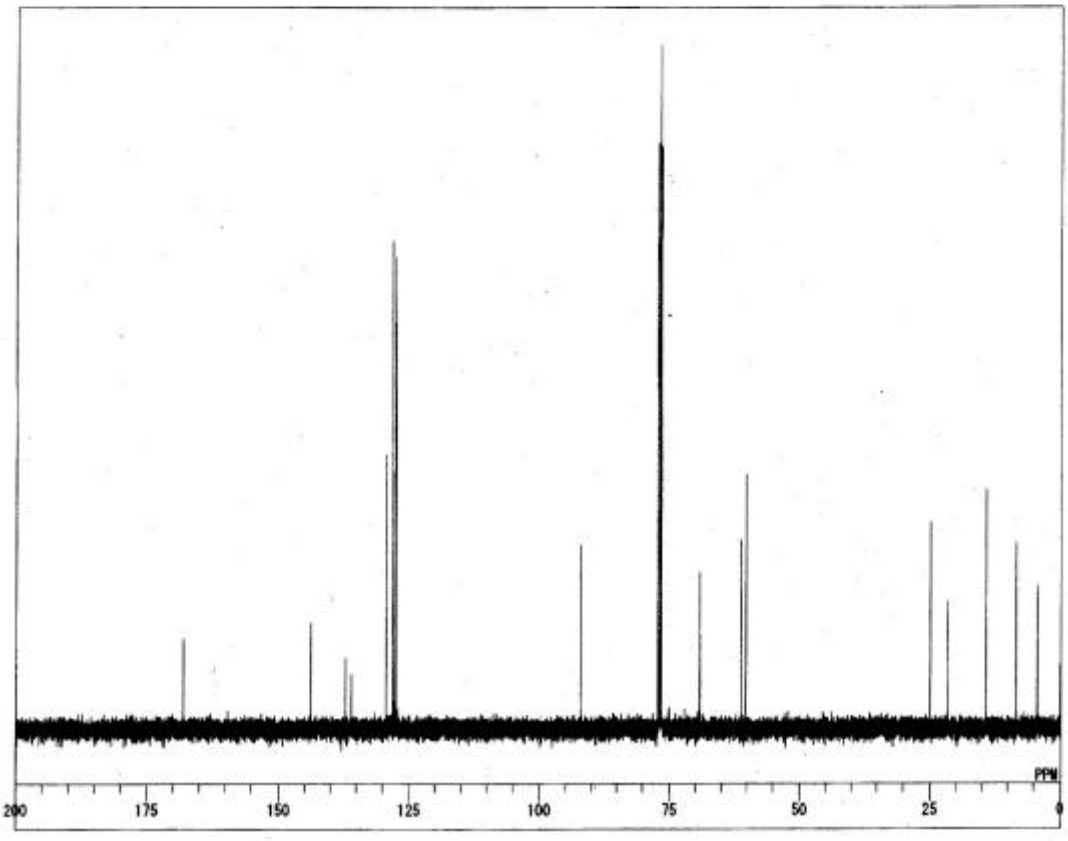
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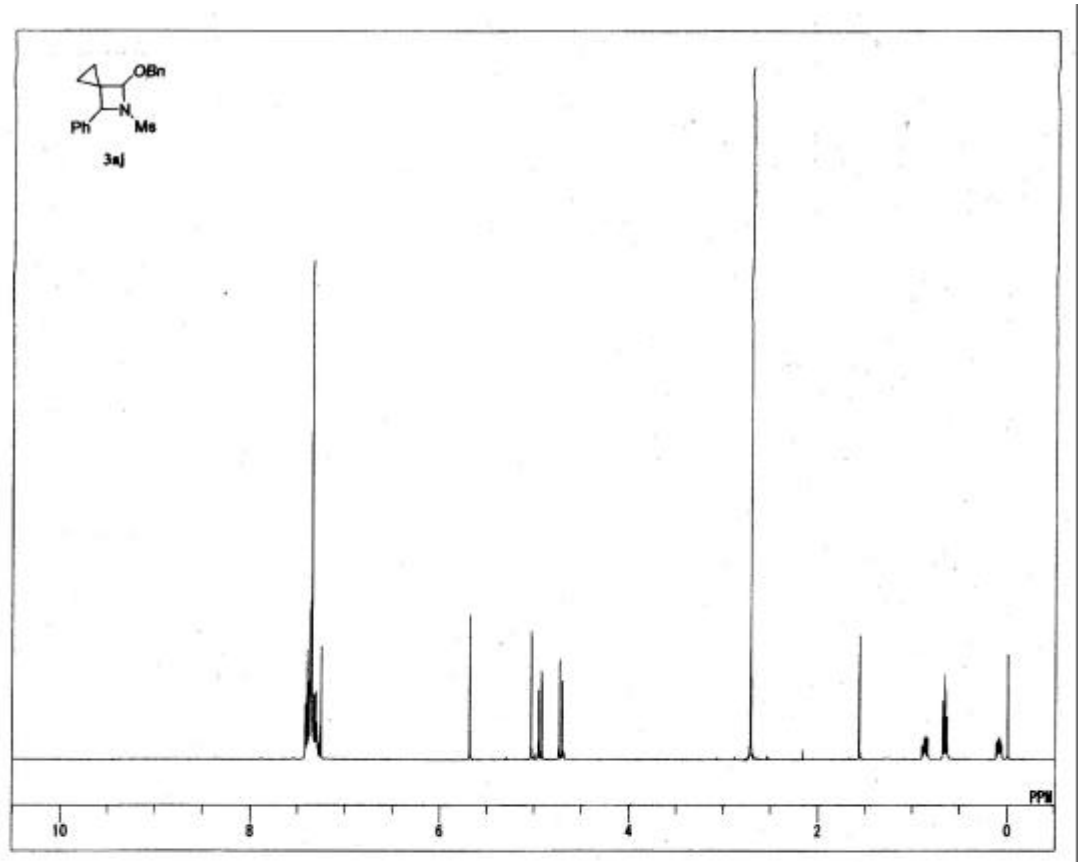
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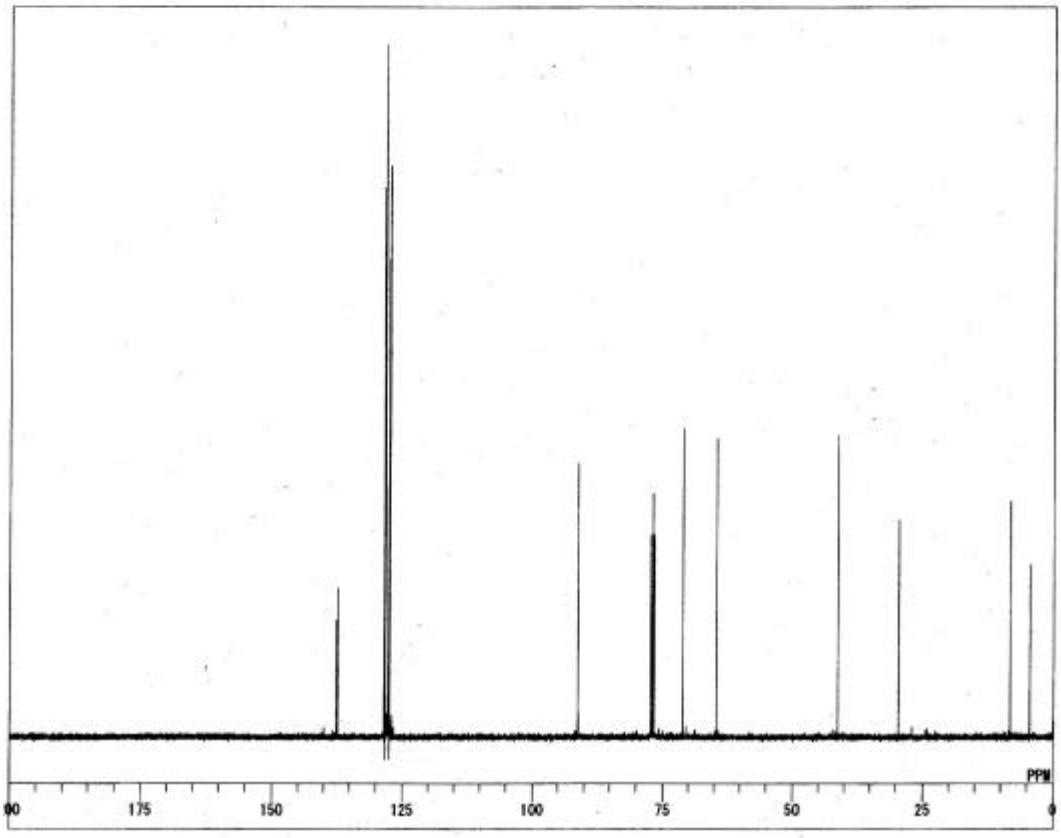
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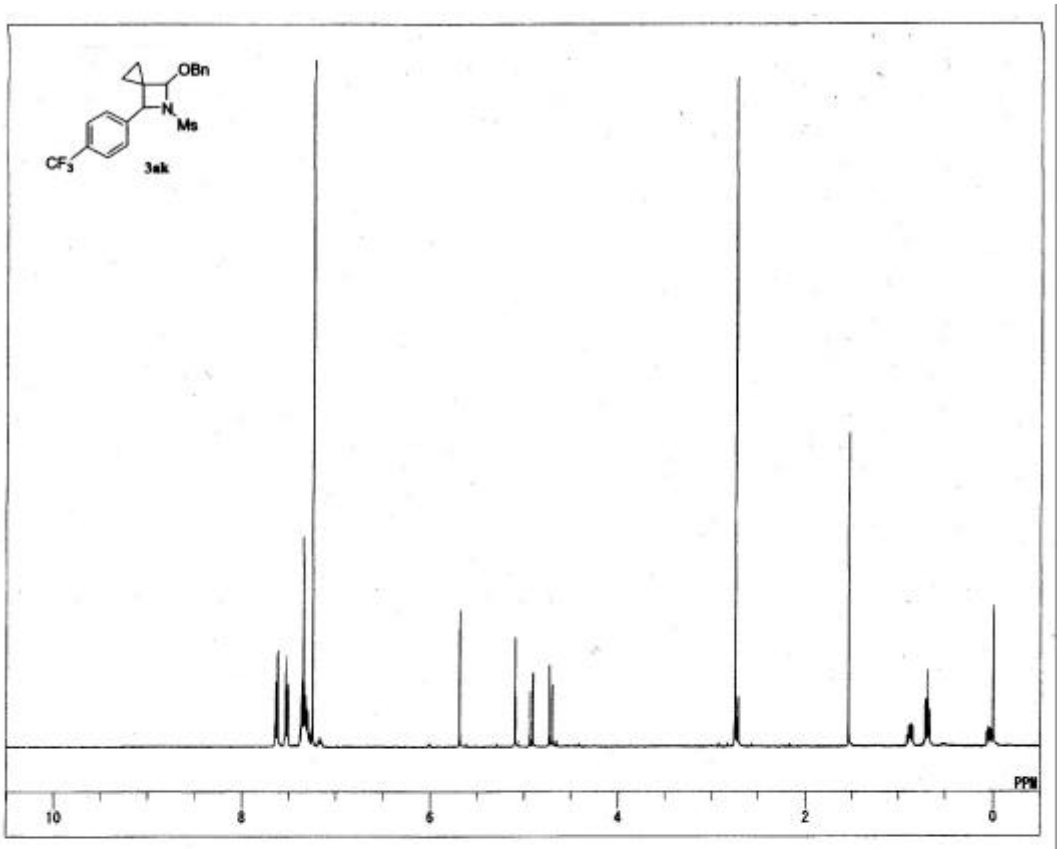
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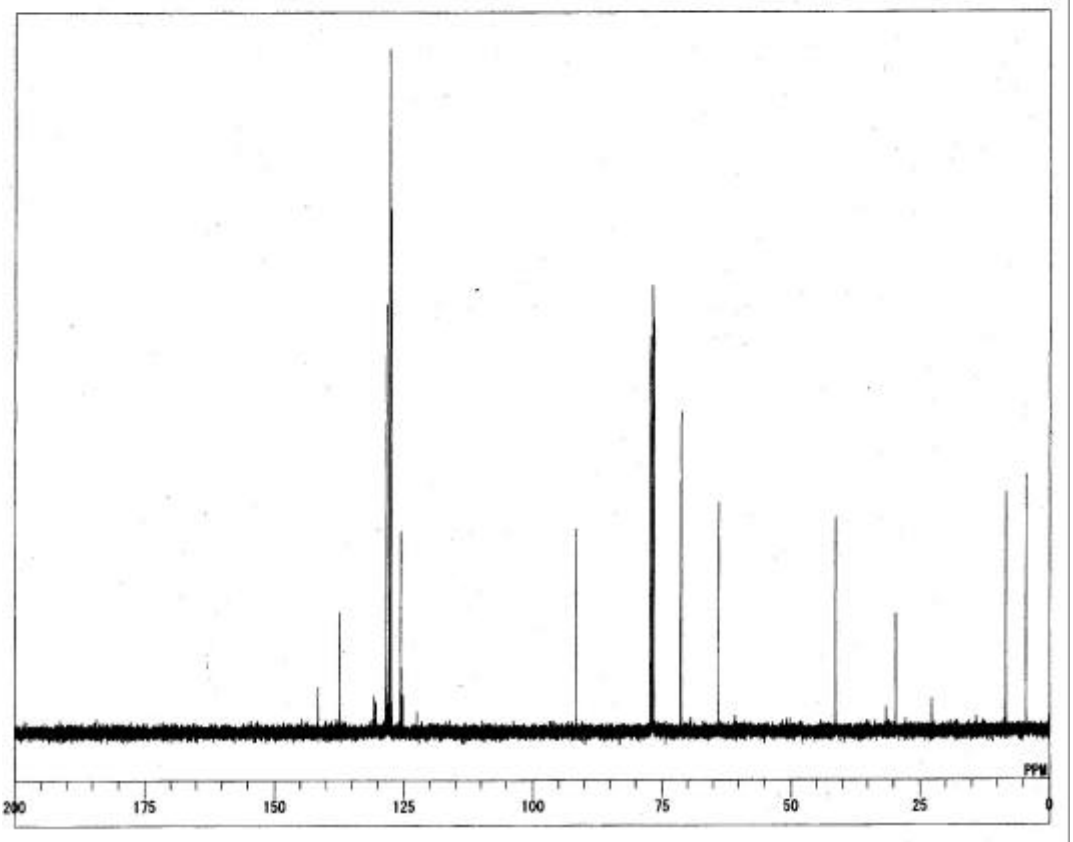
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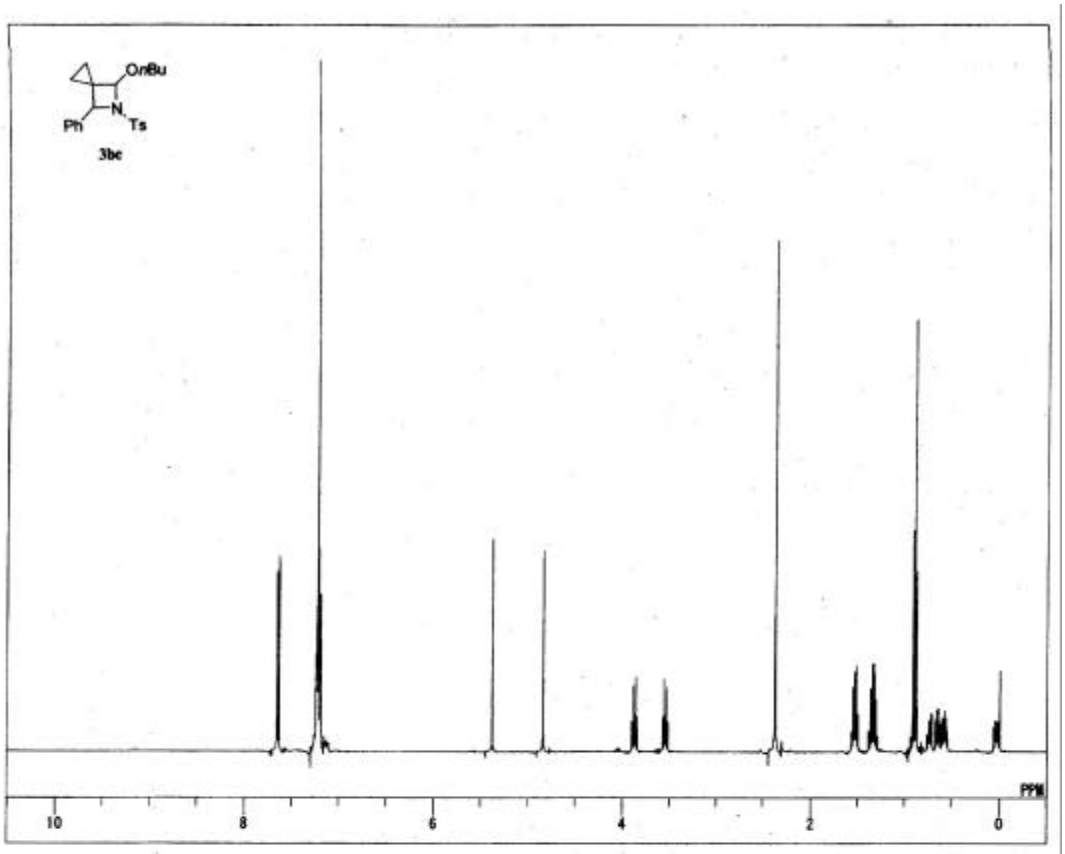
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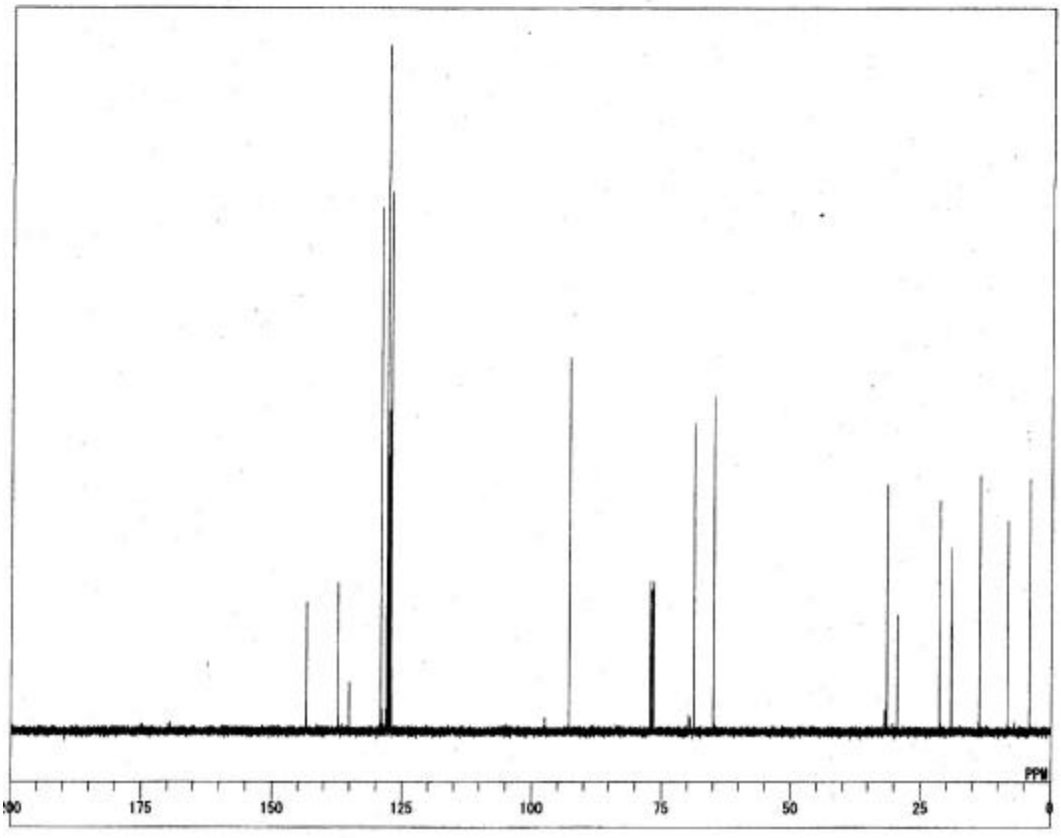
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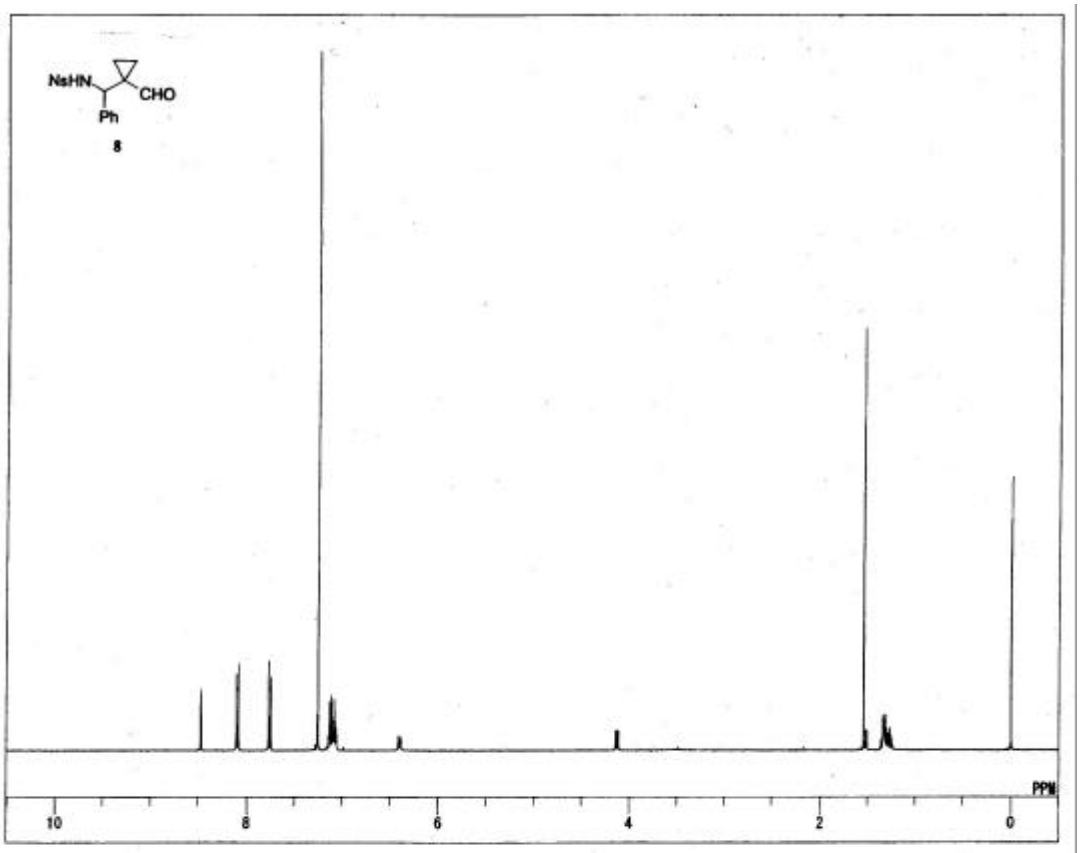
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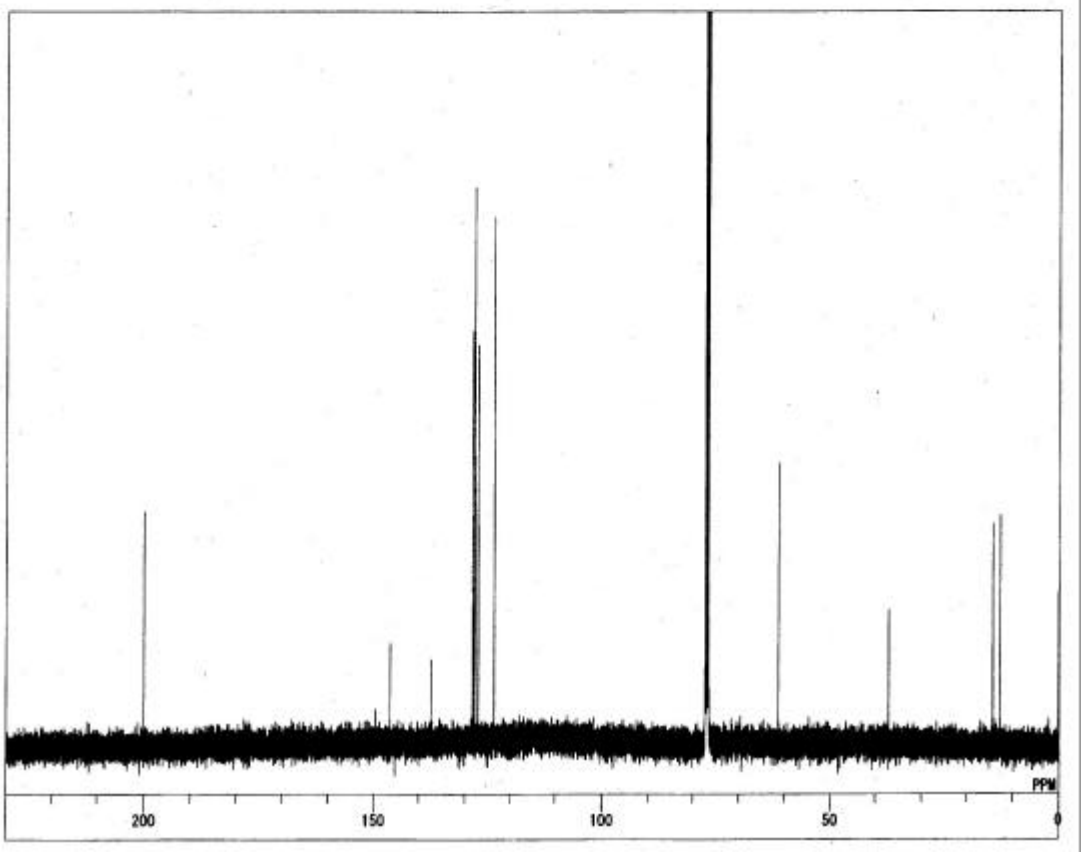
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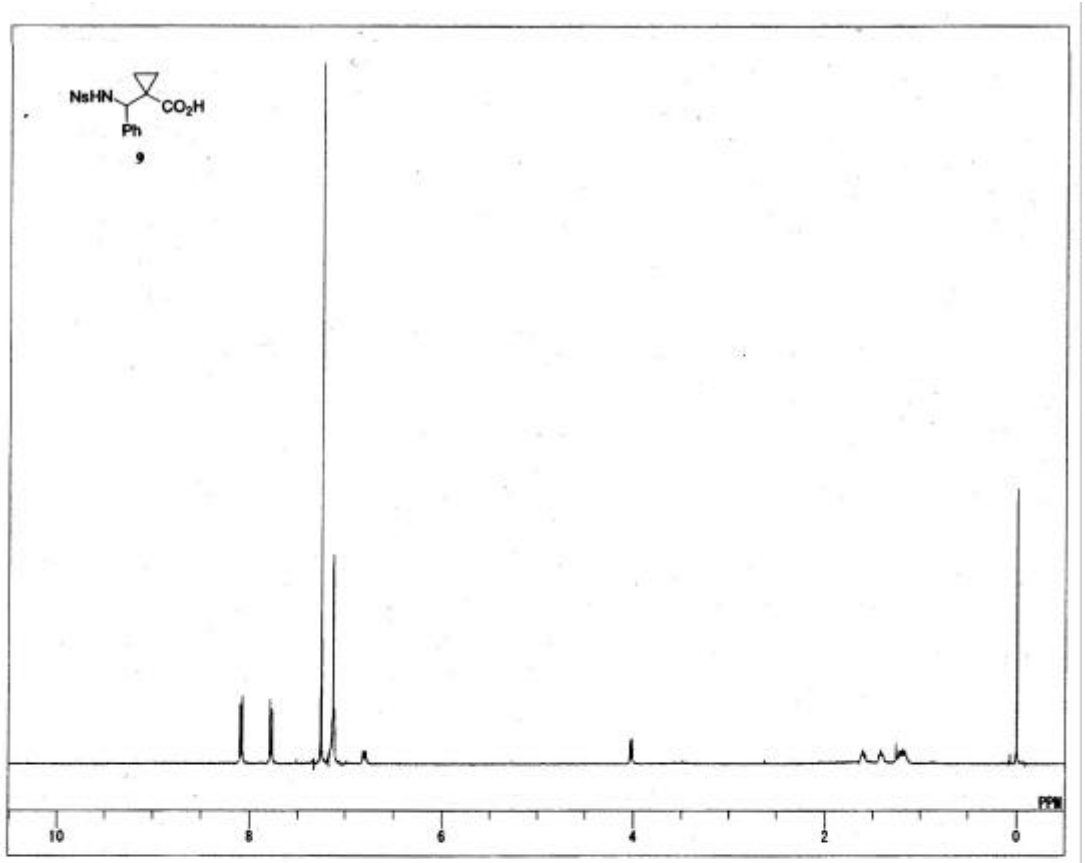
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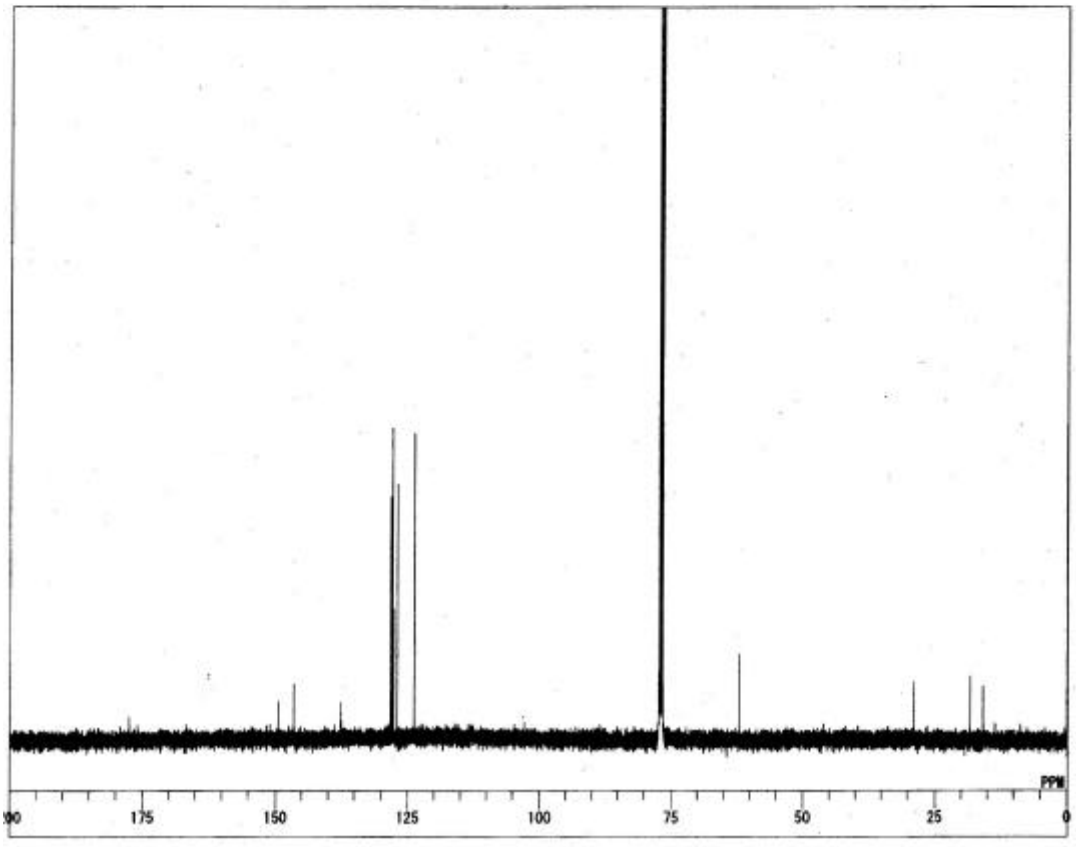
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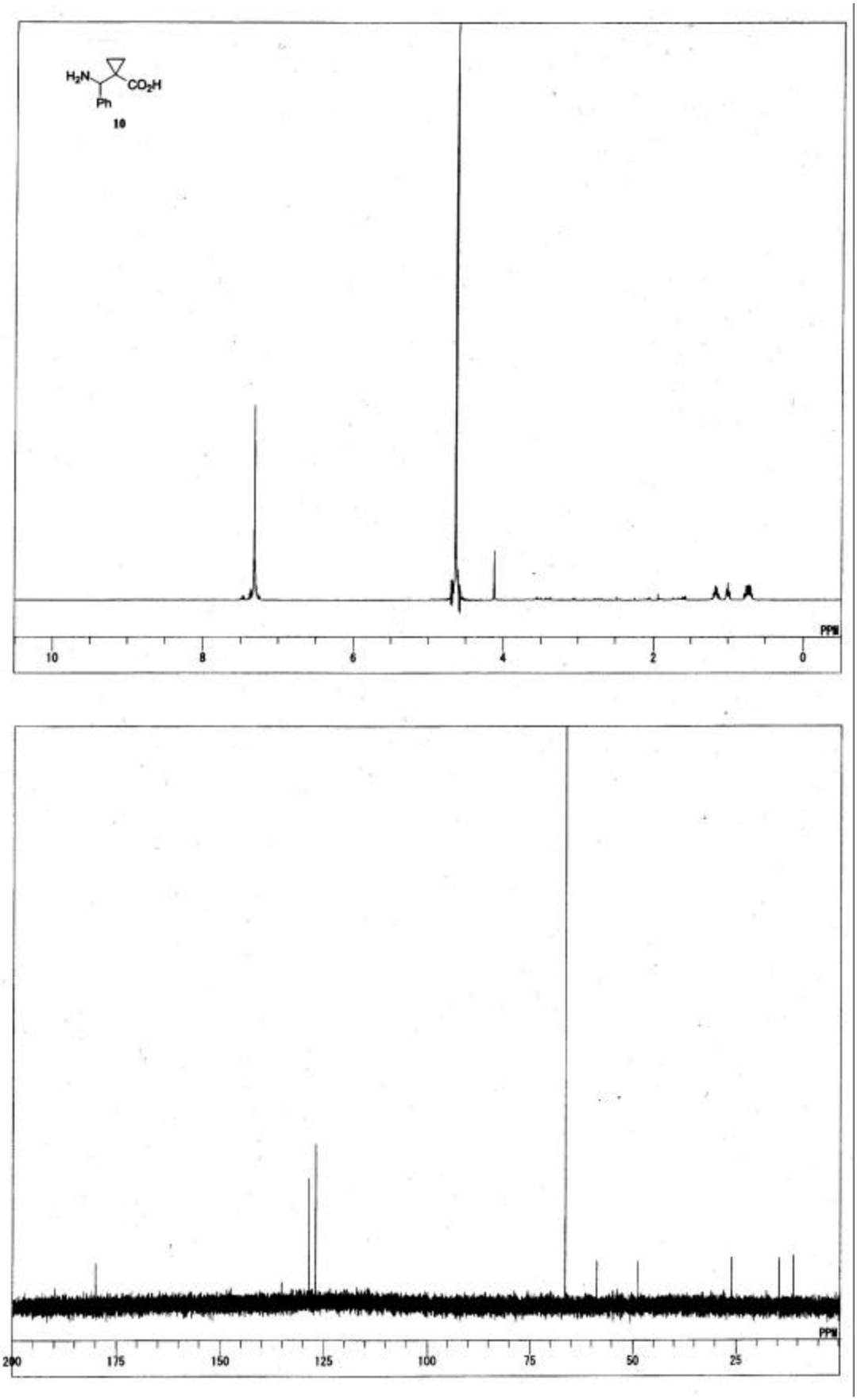
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