

The reaction of azides and enolisable aldehydes under the catalysis of Cinchona based quaternary ammonium salts and organic bases.

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Supporting information

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1. General experimental

NMR experiments were performed on a Bruker Avance 400 and samples were obtained in CDCl₃ (referenced to 7.26 ppm for ¹H and 77.0 for ¹³C). Coupling constants are in Hz. Multiplicities are reported as follows: s, singlet, d, doublet, dd, doublets of doublets, t, triplet, q, quartet, m, multiplet, br, broad. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD, Chiralpak AS, Chiralcel OD), using a UV detector operating at 254 nm. All reagents and solvents were used as purchased from Aldrich. Reactions were checked for completion by TLC (from EMD/Merk KGaA, silica gel 60 F254) or by NMR (as for the case of the triazoline synthesis, where the product decomposes over silica). Retention factors are reported to ± 0.05. High resolution mass spectra were obtained analysing 0.5 mM solutions of pure products with a Waters Quattro *micro*TM LC-MS/MS System situated at CSCB Mass Spectrometry Facility. Photochemical reactions were carried out in a chamber reactor Rayonet RPR-100 (fluorescent tubes at 254, 300 and 350 nm). Infrared spectra (IR) were recorded as KBr disc using a Bruker Tensor27 FT-IR instrument. Absorption maximum (vmax) was reported in wave numbers (cm⁻¹) and only selected peaks are reported. Quantitative NMR (qNMR) analysis was employed to determine the purity of purchased starting materials or while the isolation of a sensitive compound wasn't possible through standard chromatography procedures. Duroquinone TraceCERT® (99.31% certified purity grade, δ 2.01 ppm) was adopted as our internal standard. 10.0 mg of duroquinone were dissolved into a solution of the sample in deuterated chloroform (20.0 mg/ml). The solution was sonicated for 5 min and analysed by H-NMR using an inverse-gated ¹³C-decoupled sequence. The absolute purity of a given product was calculated as follows:

$$P_{sample} = \frac{I_{sample}}{I_{ref}} \times \frac{N_{ref}}{N_{sample}} \times \frac{M_{sample}}{M_{ref}} \times \frac{m_{ref}}{m_{sample}} \times P_{ref}$$

I = sum of the integrals of the measured hydrogens;

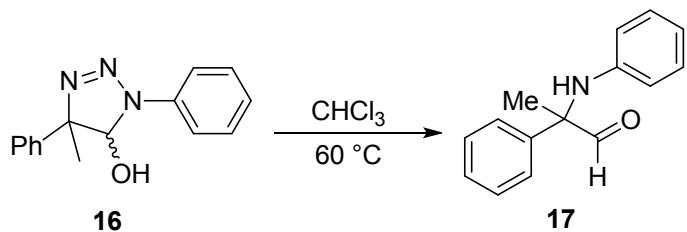
N = number of hydrogen of the molecule;

M = molecular weight of the molecule;

m = weighted mass;

P = purity (mass%).

2. Synthesis of (*N*,2)-Diphenyl-2-aminopropionadehyde **17**



Dry crude hydroxytriazoline **16** (1 mmol) was dissolved in chloroform (10 ml). The solution was stirred for 3 h at $60\text{ }^\circ\text{C}$. The mixture was evaporated and purification by flash column chromatography (Et_2O / petroleum ether 1:10) yielded **16** as a white solid (75% yield).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.31 (s, 1H), 7.50 (d, $J = 7.3$ Hz, 2H), 7.42 (t, $J = 7.5$ Hz, 2H), 7.36 – 7.33 (m, 1H), 7.09 – 7.05 (m, 2H), 6.68 (t, $J = 7.3$ Hz, 1H), 6.45 (d, $J = 7.7$ Hz, 2H), 5.20 (s, 1H), 1.85 (s, 3H).

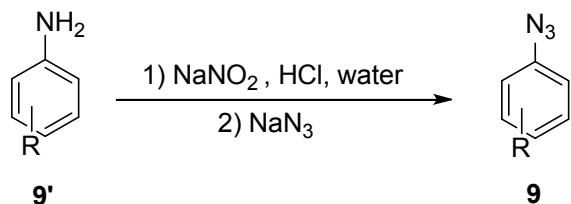
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 196.7, 144.3, 137.7, 129.3, 129.0, 128.2, 127.3, 117.7, 115.1, 66.3, 19.6.

IR (KBr, cm^{-1}) 1717, 1595, 751.

HR-MS (ES+) calculated for $\text{C}_{15}\text{H}_{16}\text{NO}$ ($[\text{M}+\text{CH}_3]^+$): 226.1232; found: 226.1221.

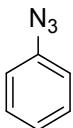
Chiral HPLC (Chiralpak AD, 2:98 iPrOH/hexane, 0.5 ml/min) Retention time= 15.94 min, 17.16 min.

3. General procedure for the preparation of azides 9a-l



To a stirring solution of HCl in water (89 mmol, 20ml, 4.5 M), aniline **9'** (15.9 mmol) was added dropwise. After 10 min the mixture was cooled down to 0 °C and added with an aqueous solution of NaNO₂ (15.9 mmol, 3 M) over 5 min. After 40 min the pH was carefully adjusted to 7 with saturated NaHCO₃ and an aqueous solution of NaN₃ (15.6 mmol, 3 M) was slowly added. The ice bath was removed after 5 min and the mixture was left stirring for additional 30 minutes. The crude was extracted with Et₂O (1x80 ml, 2x40 ml). The reunited organic phase was dried over sodium sulfate and evaporated under vacuum (bath temperature < 20°C). Column chromatography (hexane) yielded pure azides **9a-e,g-l**.

Azidobenzene **9a**



Pale yellow liquid, 78% yield.

¹H NMR (400 MHz, CDCl₃): δ 7.36 – 7.34 (m, 2H), 7.17 – 7.13 (m, 1H), 7.05 – 7.03 (d, *J* =

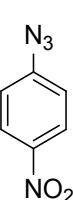
8Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 140.0, 129.8, 124.9, 119.0.

IR (KBr) (cm⁻¹) 2127, 2095, 1594, 1493, 1455, 1175, 1130, 688, 670.

HRMS (ES+) calculated for C₆H₅N₃ ([M+Na]⁺): 119.0478; found: 119.0480.

4-Nitro-azidobenzene **9b**



Orange oil, 30% yield.

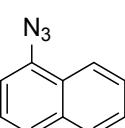
¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J* = 9.0 Hz, 2H), 7.14 (d, *J* = 9.0 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 146.9, 144.6, 125.6, 119.4.

IR (KBr, cm⁻¹) 3111.77, 2121.20, 1589.32, 1511.28, 1487.23, 1338.33, 1285.15.

ES-MS (*m/z*): 164.1 (M⁺).

1-Azidonaphthalene **9c**



White solid, 63% yield.

¹H NMR (400 MHz, CDCl₃) δ 8.19 – 8.10 (m, 1H), 7.89 – 7.81 (m, 1H), 7.66 (d, *J* = 8.2

Hz, 1H), 7.59 – 7.43 (m, 3H), 7.27 (d, *J* = 7.3 Hz, 1H).

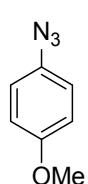
¹³C NMR (101 MHz, CDCl₃) δ 136.5, 134.4, 127.7, 126.9, 126.4, 126.2, 125.7, 124.7,

122.6, 113.9.

IR (KBr, cm⁻¹): 2112.

ES-MS (*m/z*): 169.0 (M⁺).

4-Azidoanisole **9d**



Yellow oil, 66% yield.

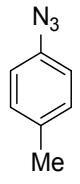
¹H NMR (400 MHz, CDCl₃) δ 6.96 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 157.0, 132.3, 120.0, 115.1, 55.6.

IR (NaCl, cm⁻¹) 2131, 2016.

EI-MS (*m/z*): 149.0 (M⁺).

4-Azidotoluene **9e**



Pale yellow oil, 88% yield.

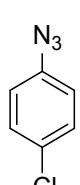
¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 2.35 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 137.2, 134.3, 130.4, 118.9, 20.8.

IR (KBr, cm⁻¹) 2130, 2106.

ES-MS (*m/z*): 133.1 (M⁺).

4-Chloro-azidobenzene **9g**



Orange oil, 44%

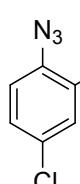
¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 138.7, 130.2, 129.8, 120.3.

IR (KBr, cm⁻¹): 2135, 1488, 1303.

HRMS (EI+) calculated for C₆H₄N₃Cl ([M]⁺): 153.0094; found: 153.0089.

2,4-Dichloro-azidobenzene **9h**



Pale yellow solid, 68% yield.

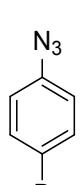
¹H NMR (400 MHz, CDCl₃) δ 7.39 (d, *J* = 2.3 Hz, 1H), 7.27 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 136.0, 130.5, 130.4, 128.1, 125.7, 120.4.

IR (KBr, cm⁻¹): 2118, 1476, 1305.

HRMS (EI+) calculated for C₆H₃N₃Cl₂ ([M]⁺): 186.9704; found: 186.9706.

4-Bromo-azidobenzene **9i**



Orange solid, 53%

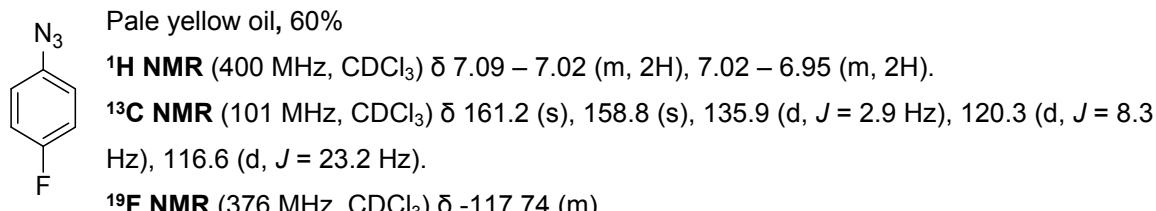
¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 139.3, 132.8, 120.7, 117.8.

IR (KBr, cm⁻¹): 2125, 1476, 1066.

HRMS (EI+) calculated for C₆H₄N₃Br ([M]⁺): 196.9589; found: 196.9598.

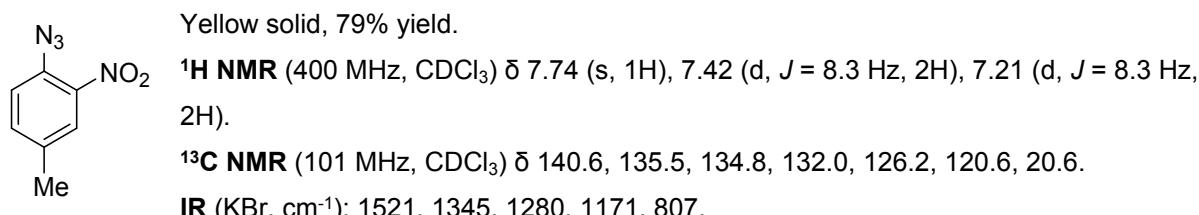
4-Fluoro-azidobenzene **9j**



IR (KBr, cm⁻¹): 2118, 1504, 1303, 1226, 823.

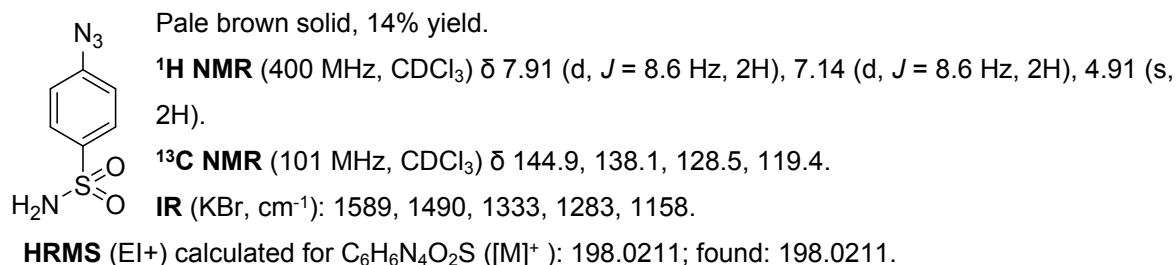
HRMS (EI+) calculated for C₆H₄N₃F ([M]⁺): 137.0389; found: 137.0384.

4-Methyl-2-nitro-azidobenzene **9k**

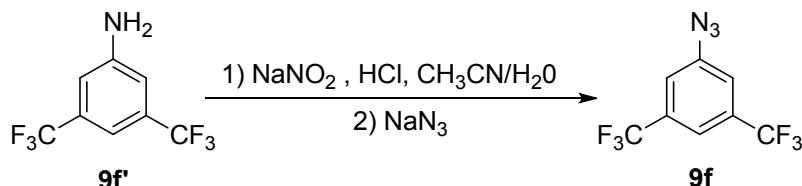


Not stable under ESMS conditions.

4-Azido-benzenesulfonamide **9l**



4. Preparation of azide **9f**



37% HCl (40 mmol, 3.3 ml) was added to a stirring solution of 3,5-di-(trifluoromethyl)-azidobenzene (1.04 g, 4.54 mmol) in acetonitrile / water 1 : 8. After 10 min, NaNO₂ (630 mg, 9.1 mmol) was slowly added and the solution was stirred for 1 h. The pH was then neutralised with NaHCO₃ sat., and the mixture was cooled down to 0 °C with an ice bath. A water solution of NaN₃ (9.1 mmol, 10 ml) was added dropwise and the solution was stirred for 1 h. The crude was extracted with Et₂O (1x80 ml, 2x40 ml). The reunited organic phase was dried over sodium sulfate and evaporated under vacuum (bath temp < 20 °C). Column chromatography (hexane) yielded the pure azide **9f** as a pale yellow oil (613 mg, 53% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.64 (s, 1H), 7.44 (s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 142.4 (s), 133.4 (q, *J* = 34.0 Hz), 122.7 (q, *J* = 273.0 Hz), 119.2 (m), 118.5 (m).

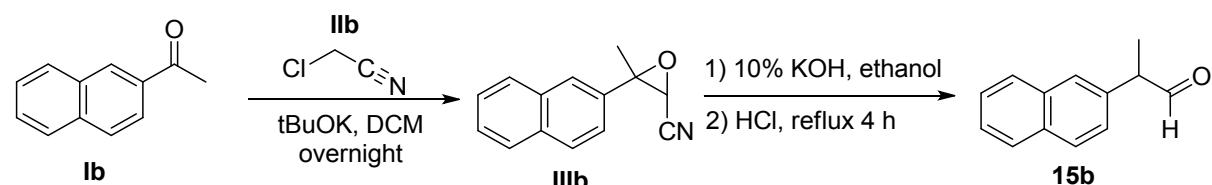
¹⁹F NMR (376 MHz, C₆D₆): δ -63.2.

IR (KBr, cm⁻¹): 2117, 1463, 1372, 1282, 1183, 1132.

HRMS (ES+) calculated for C₈H₃F₆N₃ ([M]⁺): 255.0226; found: 255.0219.

5. Synthesis of branched aldehydes

2-(β-Naphtyl)-propionaldehyde **15b**



Potassium tert-butoxide (4.7 g, 42 mmol) was slowly added to a solution of methyl-β-naphtyl ketone **Ib** (6.0 g, 35.2 mmol) and chloroacetonitrile **IIb** (2.2 ml, 2.38 g, 35.2 mmol) in 30 ml of dichloromethane at 5 °C. The solution was stirred overnight letting the temperature slowly rise to 20 °C. The crude mixture was added with 150 ml of ice-cold water and extracted with Et₂O (3 x 80 ml). The reunited organic phase was washed with water (50 ml) and brine (50 ml), dried over sodium sulfate and evaporated under vacuum to yield a brown oil. Crude epoxynitrile **IIIb** was dissolved in ethanol (45 ml), added with a 10% aqueous KOH (34 ml) and refluxed overnight. The residue was evaporated under vacuum, diluted with water (50 ml) and with Et₂O (4 x 50 ml). The aqueous solution was acidified to pH=1 with 37% HCl and refluxed for 4 hours. The crude mixture then was extracted with Et₂O (4 x 50 ml) and the organic layer was washed with saturated NaHCO₃ solution, water and brine. After drying over sodium sulfate, the crude was evaporated under vacuum and purified by flash chromatography (Et₂O / Petroleum ether 1:20) obtaining pure 2-(β-naphtyl)-propionaldehyde **15b** as a pale yellow solid (904 mg, 14 % yield over two steps).

¹H NMR (400 MHz, CDCl₃) δ 9.77 (s, 1H), 7.95 – 7.77 (m, 3H), 7.69 (s, 1H), 7.57 – 7.42 (m, 2H), 7.34 – 7.42 (m, 1H), 3.82 (q, *J* = 7.0, 1H), 1.55 (d, *J* = 7.0 Hz, 3H).

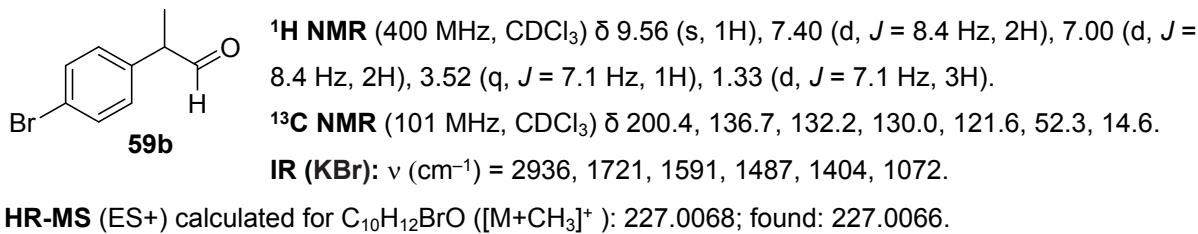
¹³C NMR (101 MHz, CDCl₃) δ 201.1, 135.1, 133.6, 132.7, 128.9, 127.7, 127.2, 126.5, 126.2, 126.1, 53.1, 14.7.

IR (KBr): ν (cm⁻¹) = 2923, 2853, 1712, 1504, 1453, 1387, 1273.

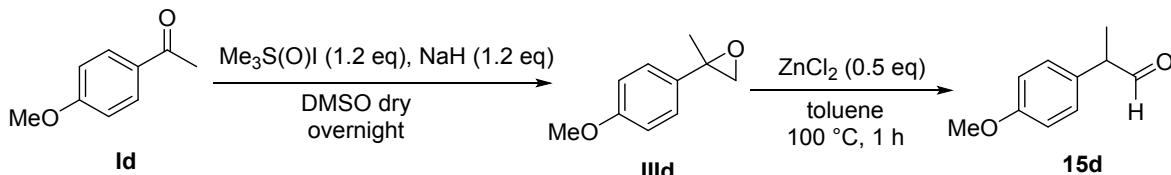
HR-MS (ES+) calculated for C₁₃H₁₂O ([M+CH₃]⁺): 199.1121; found: 199.1117.

4-Bromo-phenylpropionaldehyde **15c**

Yellow solid, 5.77 g, 36 % yield over two steps.



2-(4-methoxyphenyl)-propionaldehyde **15d**



To a stirring solution of NaH (60% in mineral oil, 0.27 g, 6.75 mmol) in dry DMSO (6 ml), Me₃S(O)I (1.50 g, 6.75 mmol) was added at room temperature. The reaction mixture was left stirring for 1 h at room temperature. A solution of 4-methoxyacetophenone **Id** (928 mg, 5.62 mmol) in dry DMSO (3 ml) was added dropwise and the reaction mixture was left stirring for 24 h. The reaction mixture was diluted with H₂O (10 ml), followed by extractions with EtOAc (3 x 10 ml). The combined organic phases were dried over sodium sulfate and the solvent was evaporated under vacuum. The crude epoxide **IIIId** was then dissolved in toluene (28 ml) and added with zinc chloride (804 mg, 5.9 mmol). The mixture was refluxed at 110 °C for 1 h. Evaporation of the solvent yielded pure 4-methoxy-phenyl-propionaldehyde **15d** as a yellow oil (643 mg, 64% yield).

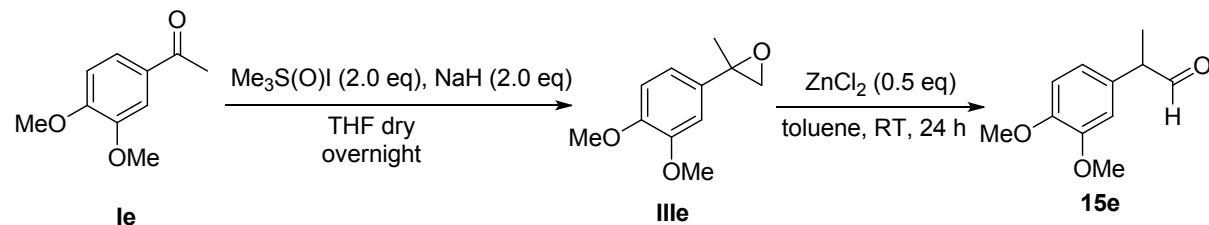
¹H NMR (400 MHz, CDCl₃) δ 9.65 (s, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.58 (q, *J* = 7.1, 1H), 1.41 (d, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 201.2, 159.0, 129.6, 129.4, 114.5, 55.3, 52.2, 14.7.

IR (KBr): ν (cm⁻¹) = 2933, 1717, 1610, 1585, 1244, 1178.

HR-MS (ES+) calculated for C₁₀H₁₃O₂ ([M+H]⁺): 165.0914; found: 165.0910.

2-(3,4-Di-methoxyphenyl)-propionaldehyde **15e**



To a stirring dispersion of NaH (60% in mineral oil, 3.2 g, 80.4 mmol) in dry THF (40 ml) at room temperature, $\text{Me}_3\text{S}(\text{O})\text{I}$ (17.7 g, 80.4 mmol) was added portion wise under nitrogen flow. The mixture was refluxed at 70 °C for 1 h, added with a solution of 3,4-di-methoxyacetophenone **Ie** (7.24 g, 40.2 mmol dissolved in 40 ml of THF) and reacted at room temperature for 20 h. The reaction mixture was diluted with H_2O , and extracted with Et_2O . The combined organic layers were dried over sodium sulfate and the solvent was evaporated under vacuum. The crude epoxide **IIIe** was dissolved in toluene (100 ml) and added with zinc (II) chloride (523 mg, 8 mmol). The mixture was reacted at room temperature for 18 h yielding crude 3,4-di-methoxyphenylpropionaldehyde **15e**. To the crude mixture were added sodium bisulfite (6.2 g, 60 mmol), ethyl acetate (50 ml), ethanol (30 ml) and water (10 ml). The heterogeneous mixture was stirred at 40 °C for 2 h then allowed to cool down to room temperature, filtered, washed with cold ethanol (10 ml) and dried to give the bisulfite adduct as white crystals. The regeneration of the aldehyde was performed adding 20 ml of saturated sodium bicarbonate and 20 ml of dichloromethane to the bisulfite adduct. The mixture was left stirring vigorously for 1 h at room temperature then it was extracted three times with dichloromethane, dried over sodium sulfate and evaporated under vacuum to yield 4.21 g of aldehyde **15e** as a yellow oil (4.76 g, 61% yield).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.65 (s, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.77 (dd, J = 8.2, 2.1 Hz, 1H), 6.68 (d, J = 2.1 Hz, 1H), 3.88 (s, 6H), 3.58 (q, J = 7.1 Hz, 1H), 1.43 (d, J = 7.1 Hz, 3H).

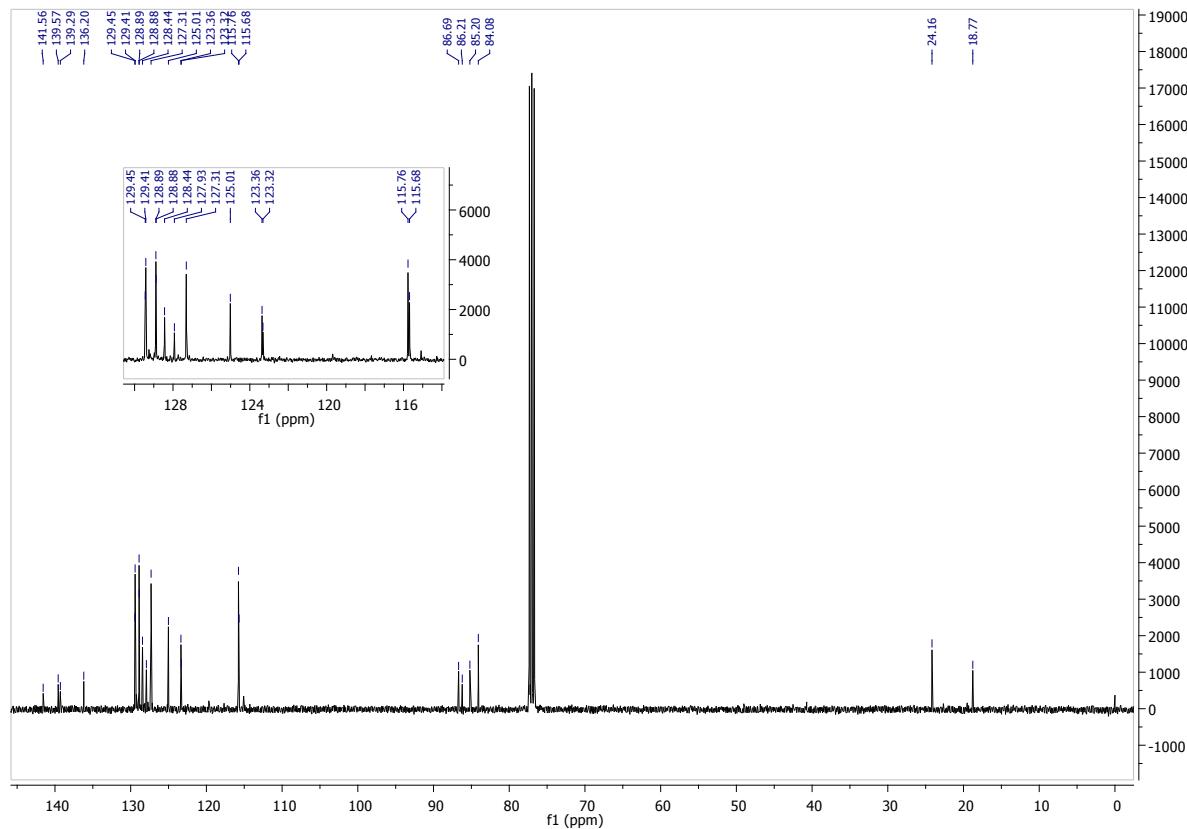
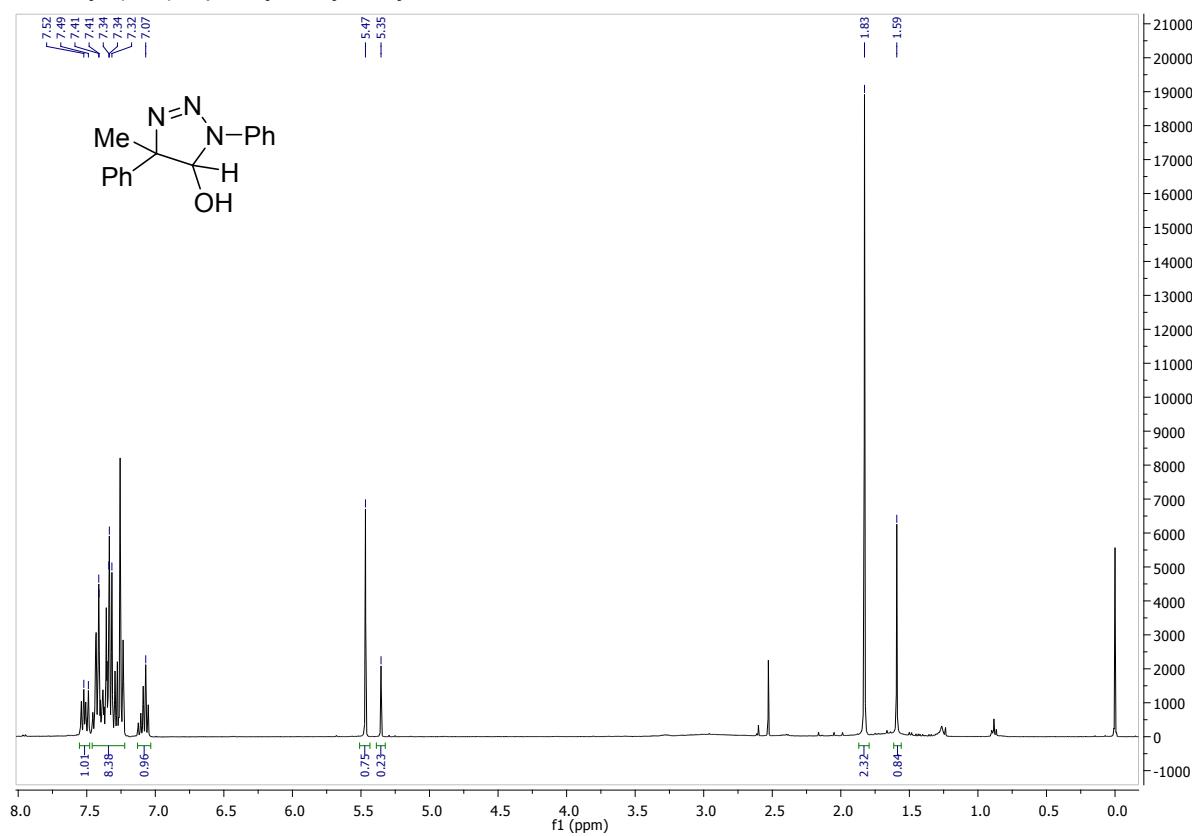
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 201.0, 149.5, 148.5, 130.0, 120.5, 111.7, 111.3, 55.9 (2C), 52.6, 14.6.

IR (KBr, cm^{-1}): 1721, 1520, 1267.

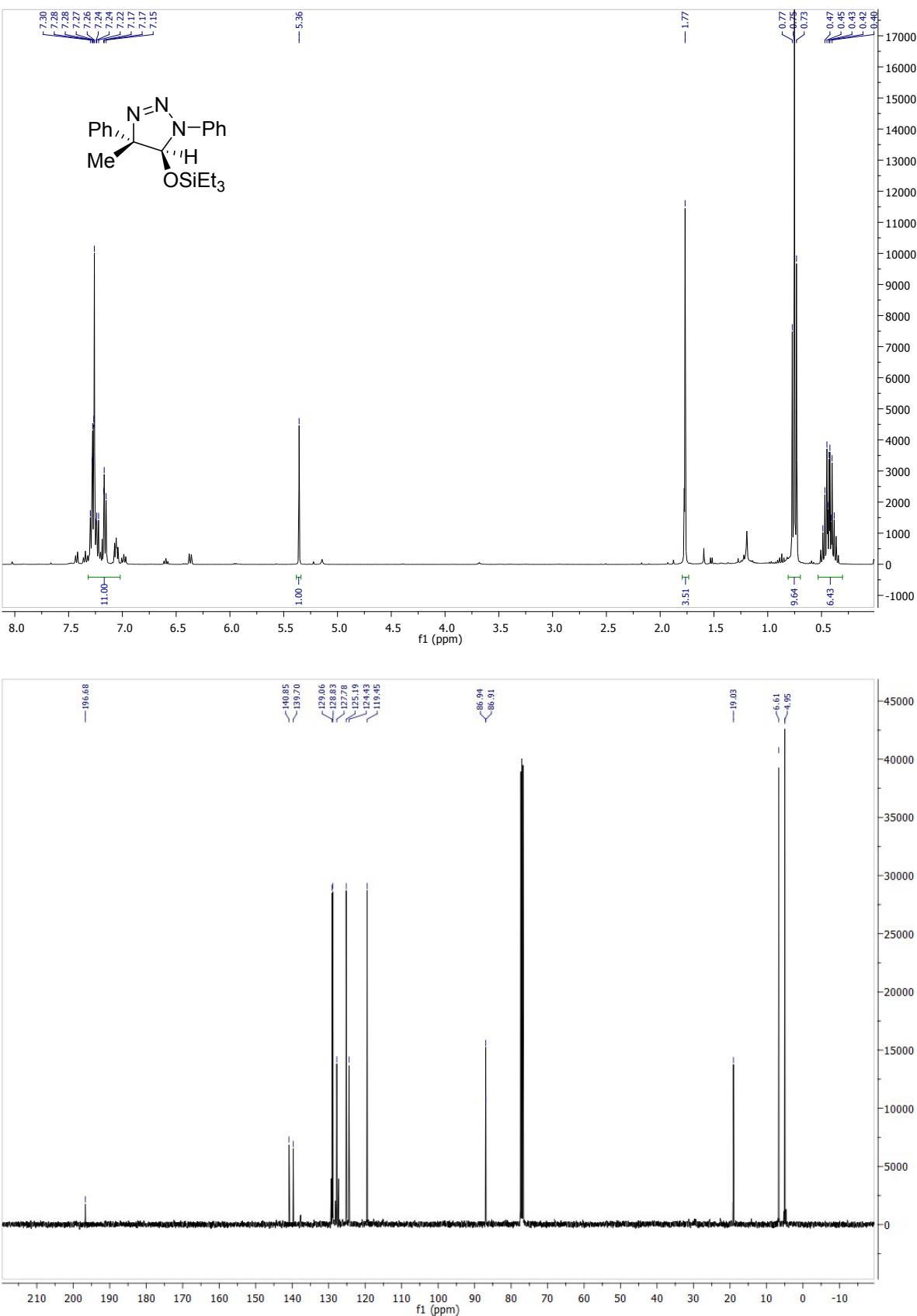
HRMS (ES+) calculated for $\text{C}_{11}\text{H}_{14}\text{O}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$): 217.0841; found: 217.0838.

6. NMR Spectra

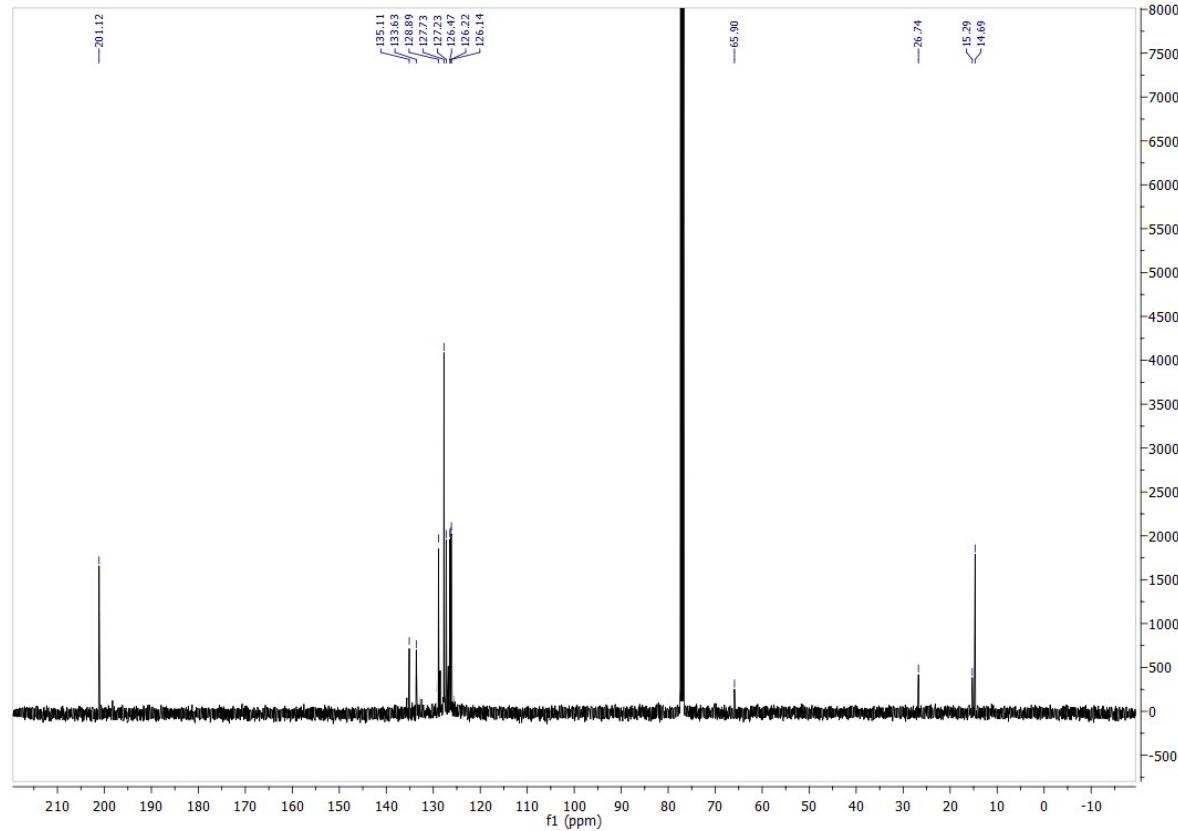
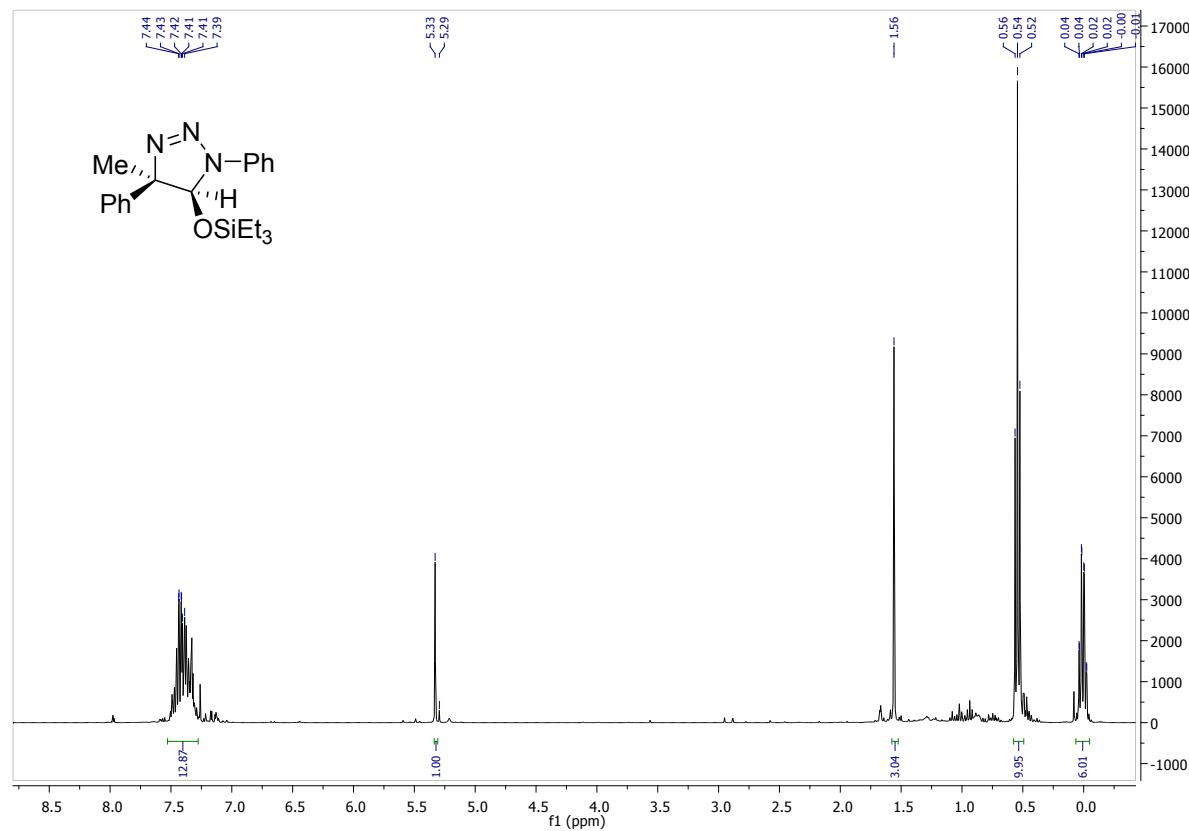
4-Methyl-(*N*,4)-diphenyl-5-hydroxytriazoline **16**



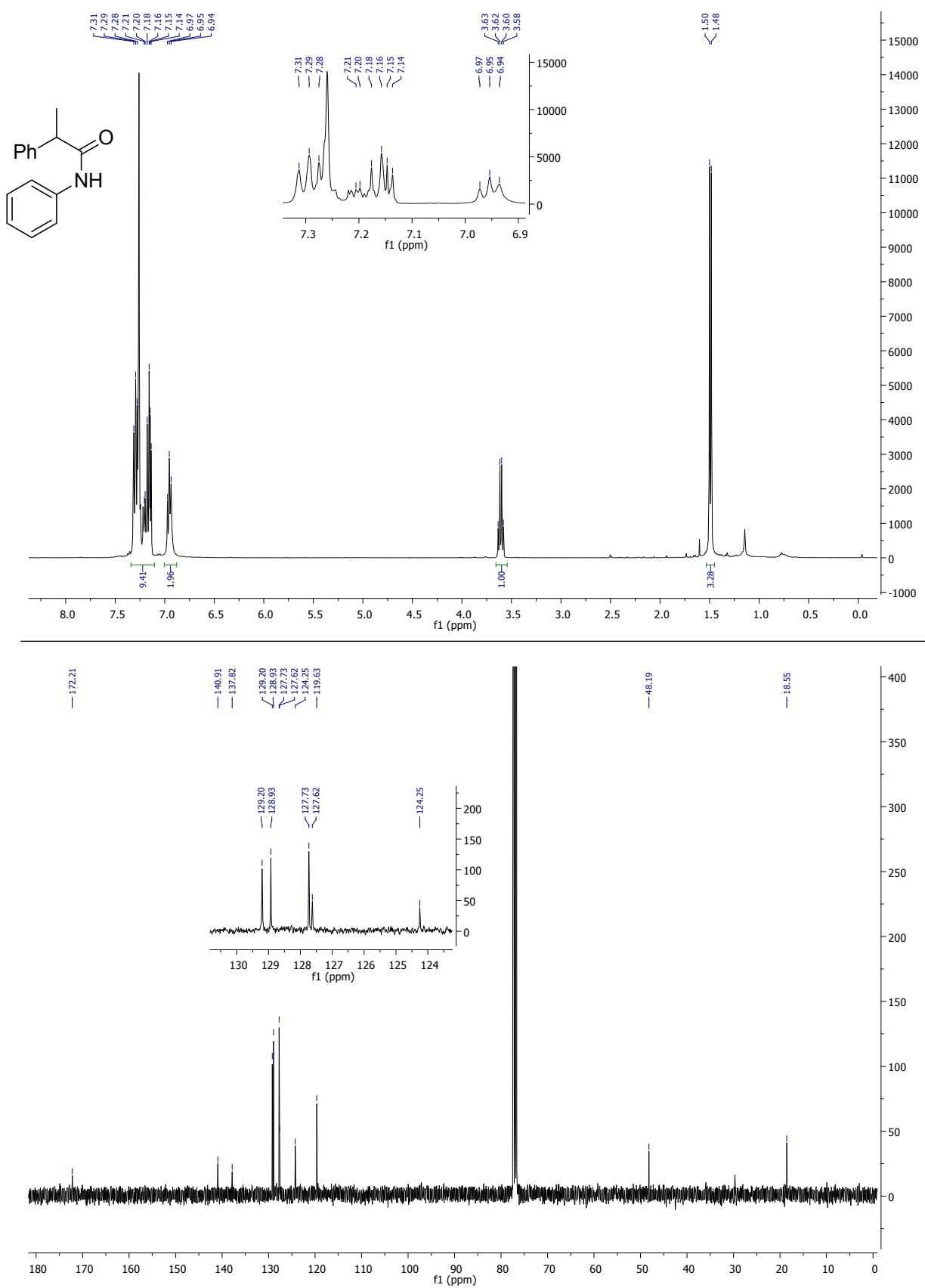
anti-4-Methyl-(N,4)-diphenyl-5-triethylsilyloxytriazoline **20a**



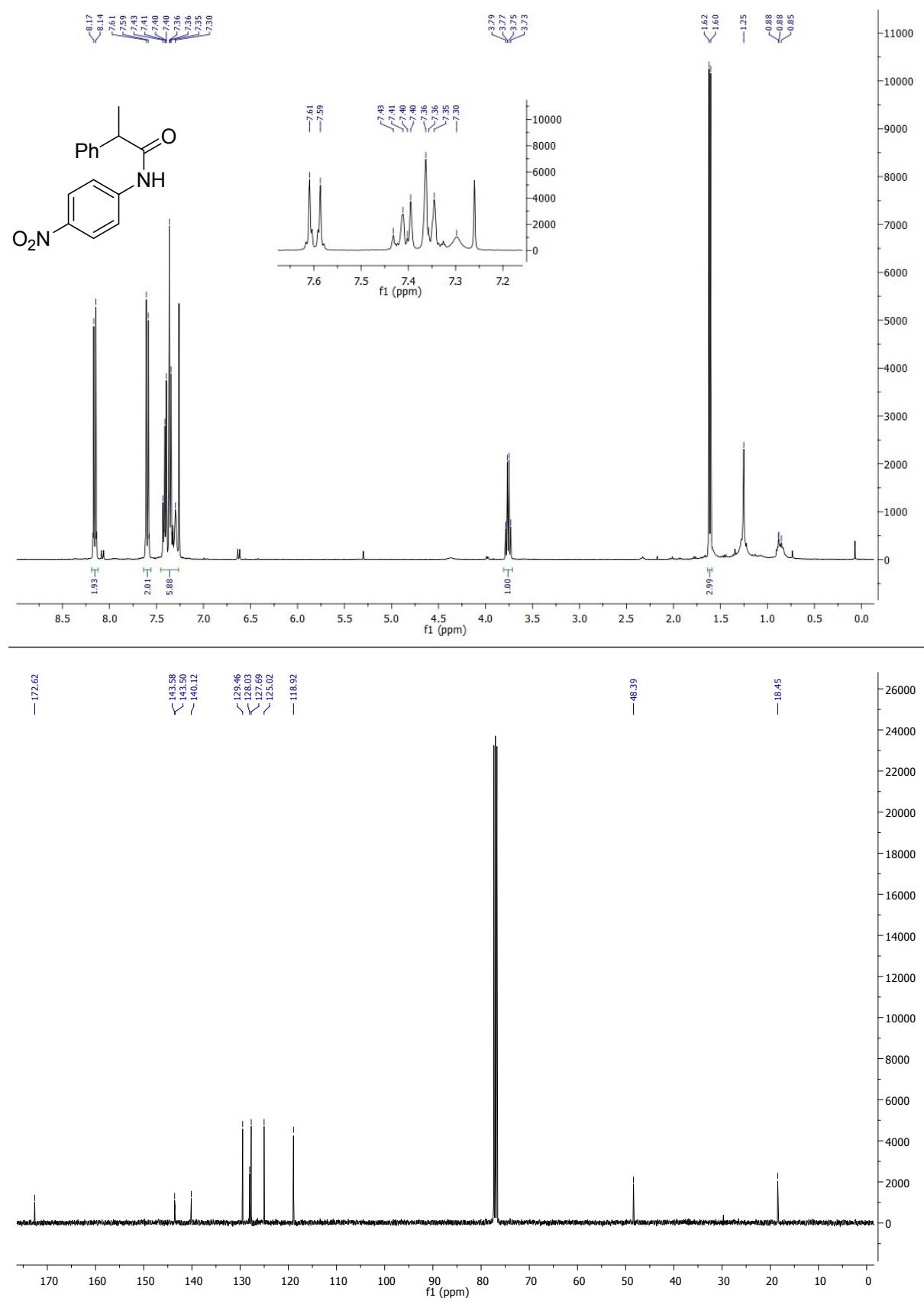
syn-4-Methyl-(*N*,4)-diphenyl-5-triethylsilyloxytriazoline **20b**



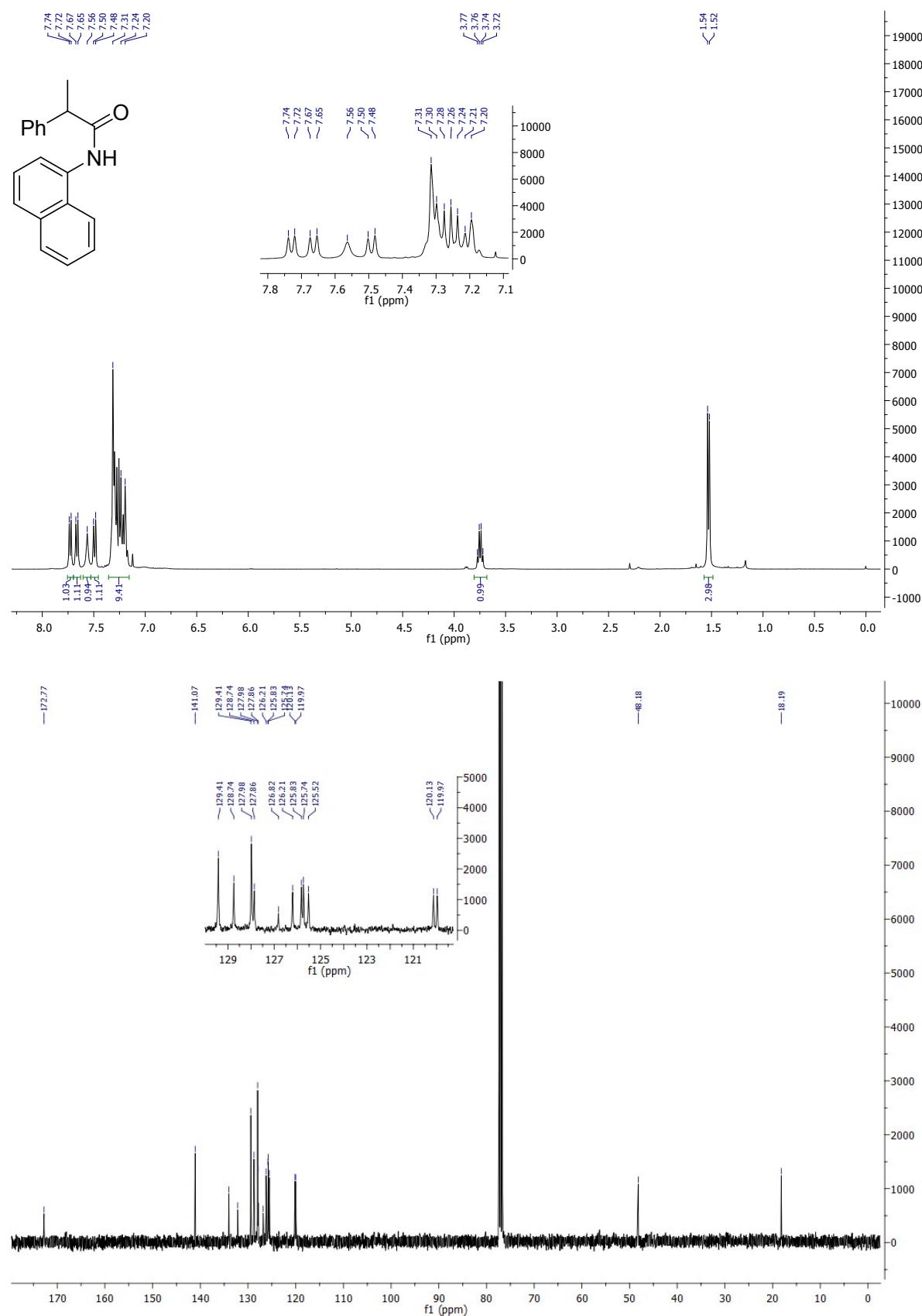
2,N-Diphenylpropionamide 18a



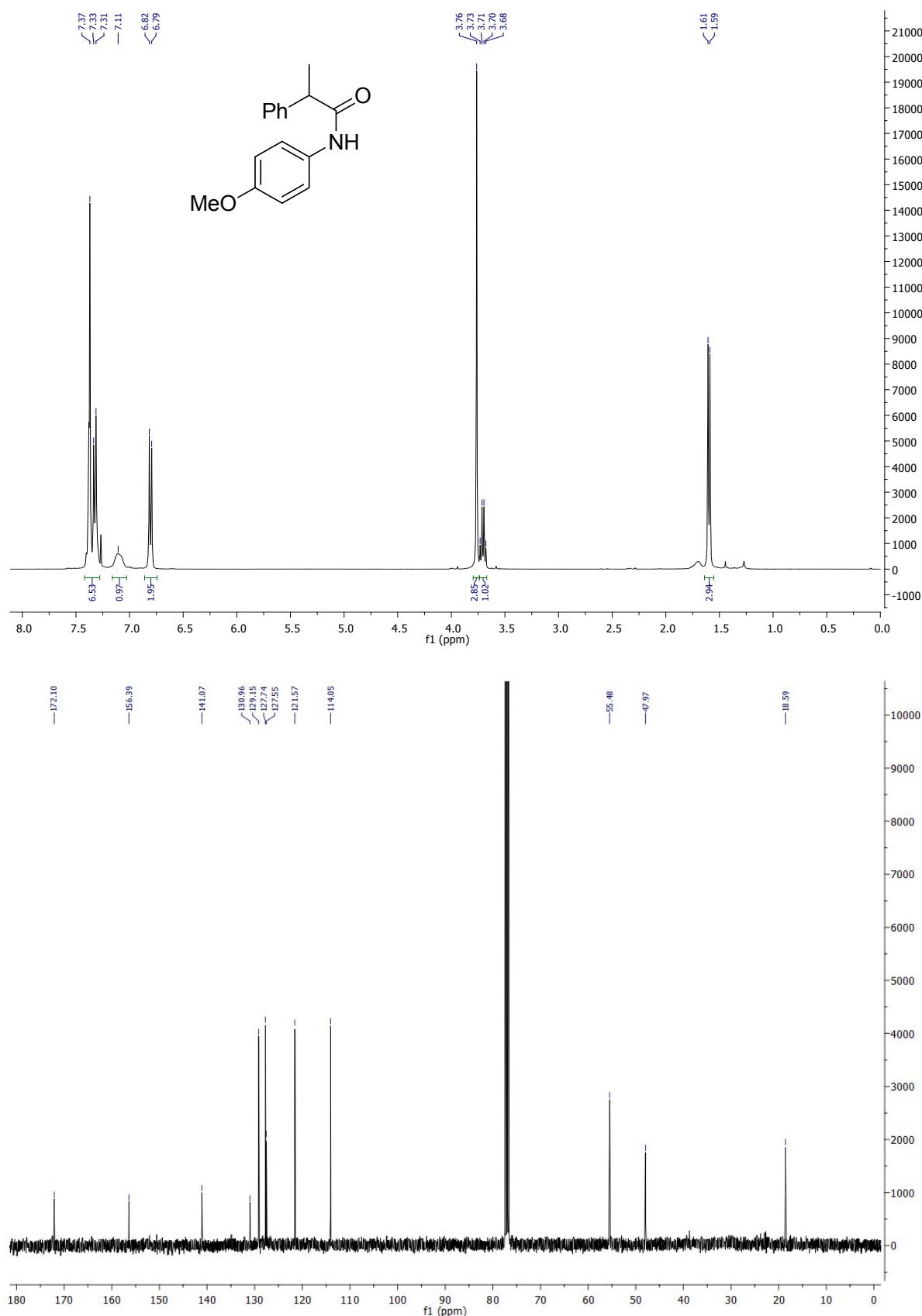
N-(4-Nitrophenyl)-2-phenylpropionamide 18b



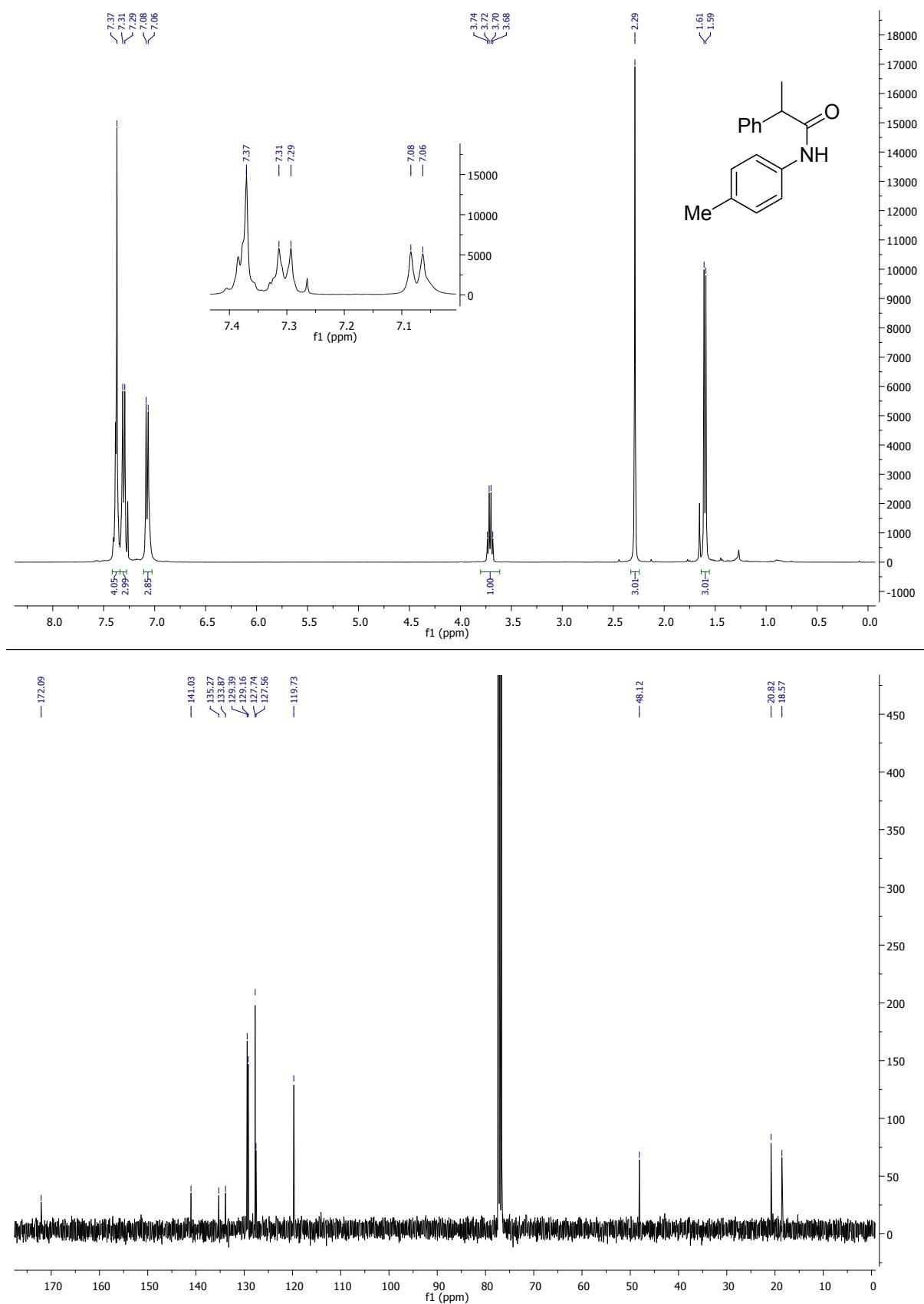
N-(2-Naphthyl)-2-phenylpropionamide 18c



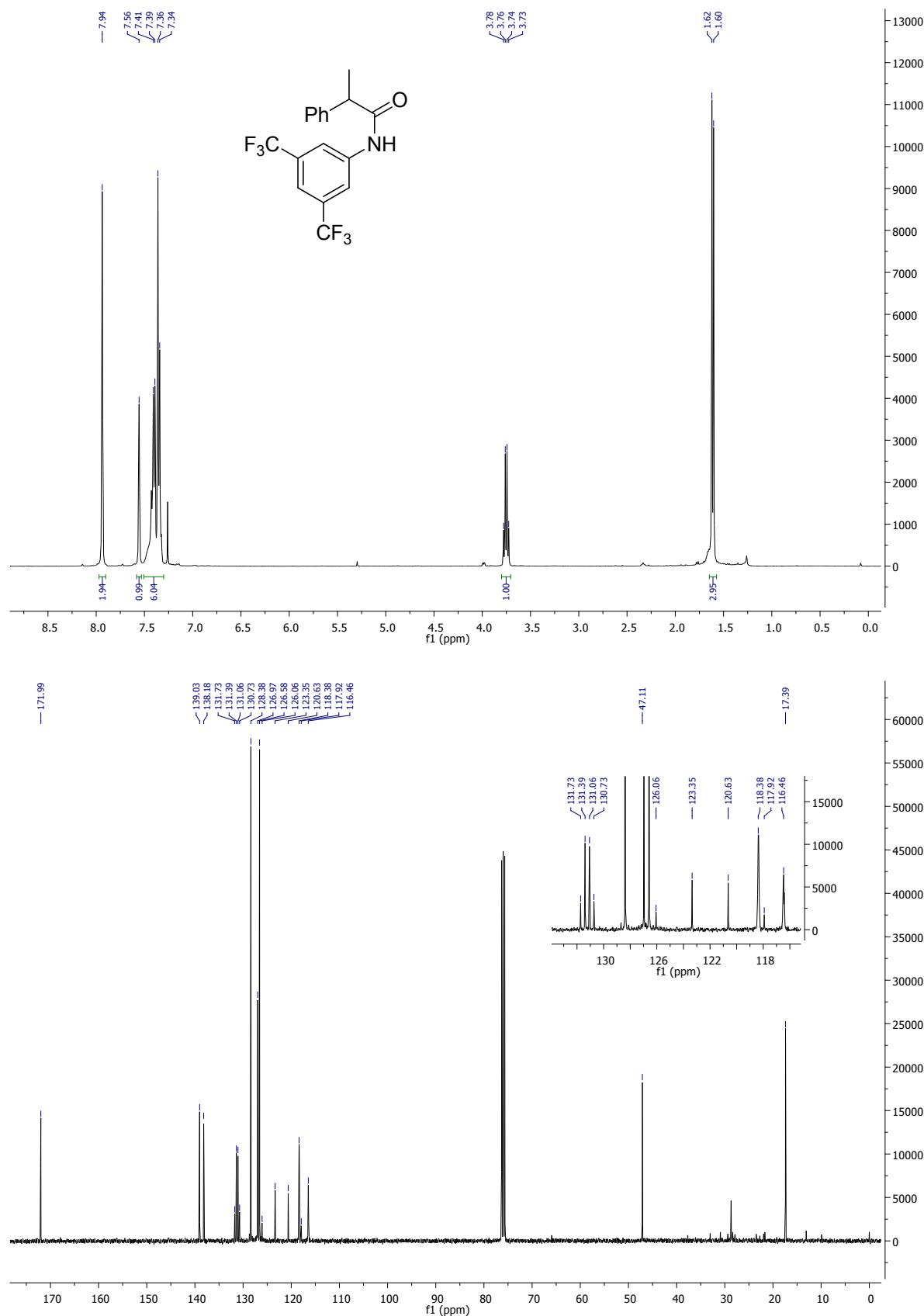
N-(4-methoxyphenyl)-2-phenylpropionamide **18d**

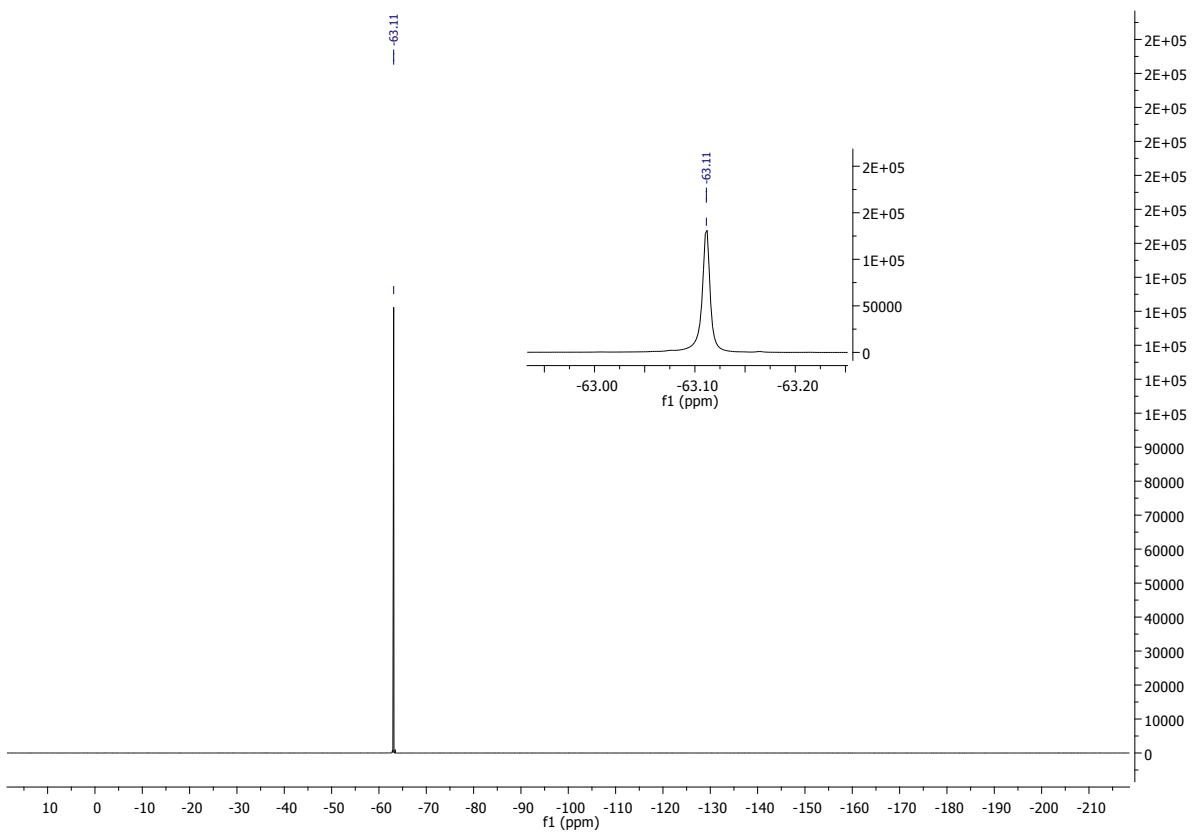


N-(4-Methylphenyl)-2-phenylpropionamide 18e

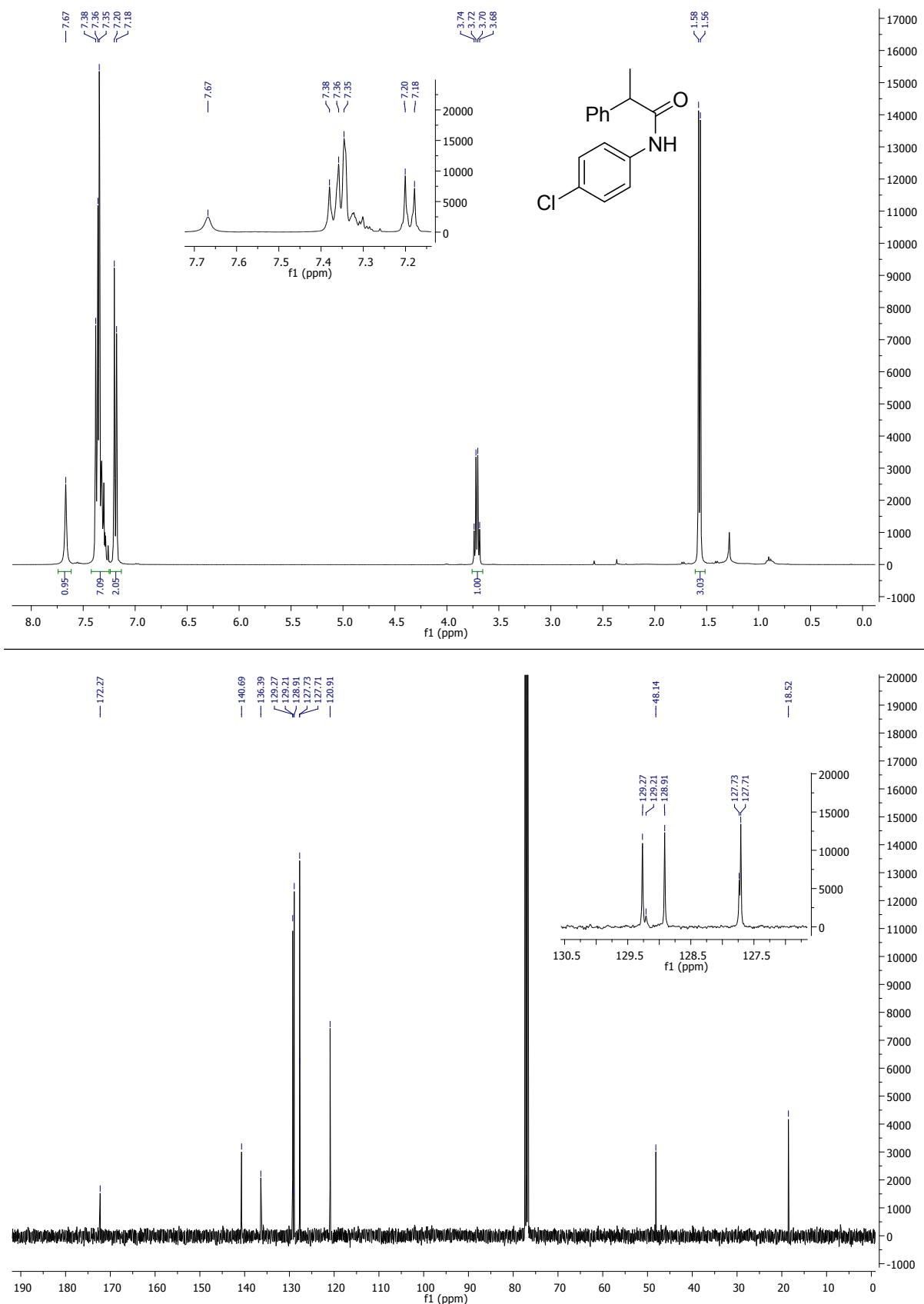


N-(3,5-Di-(trifluoromethyl)-phenyl)-2-phenylpropionamide 18f

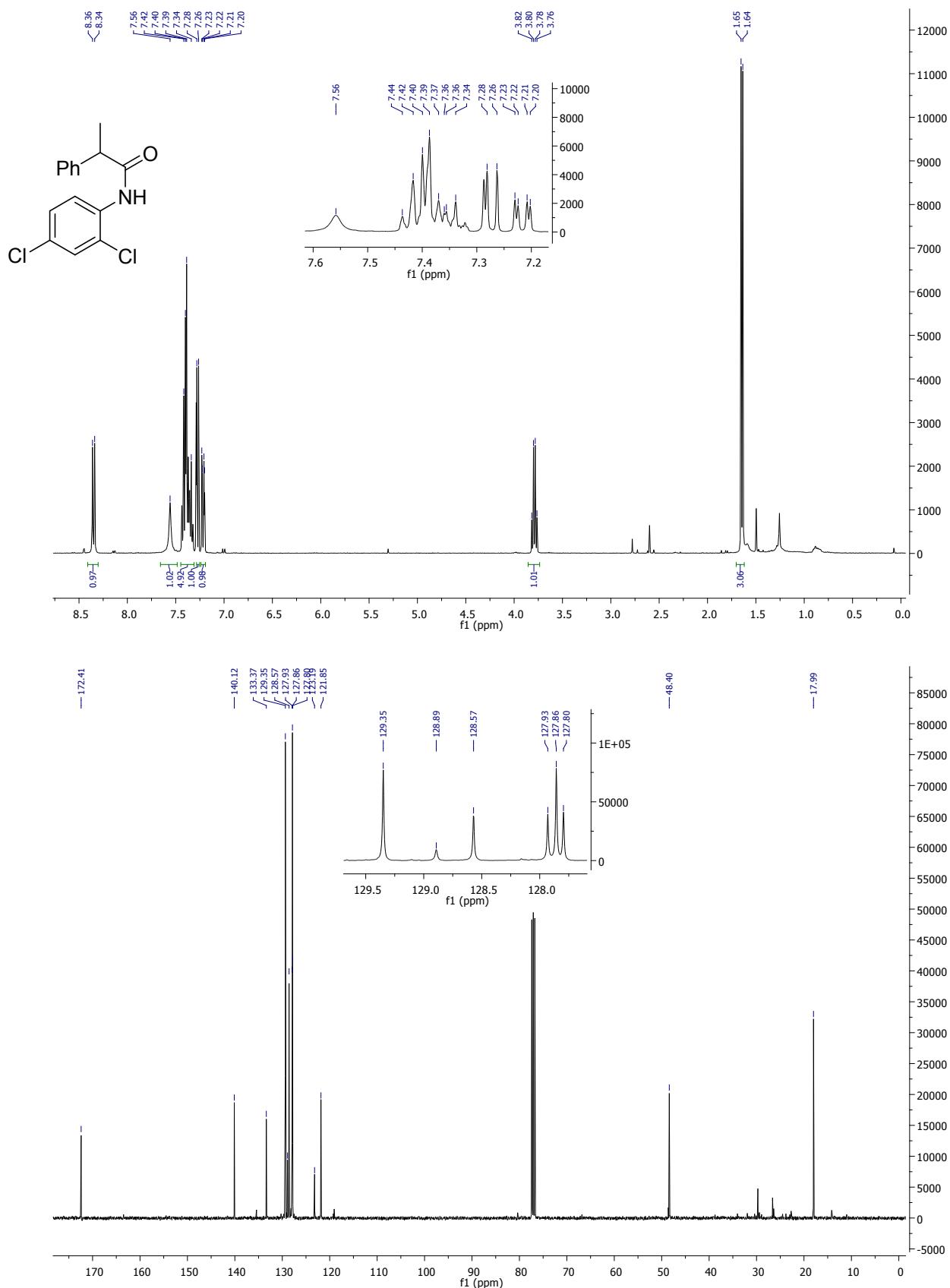




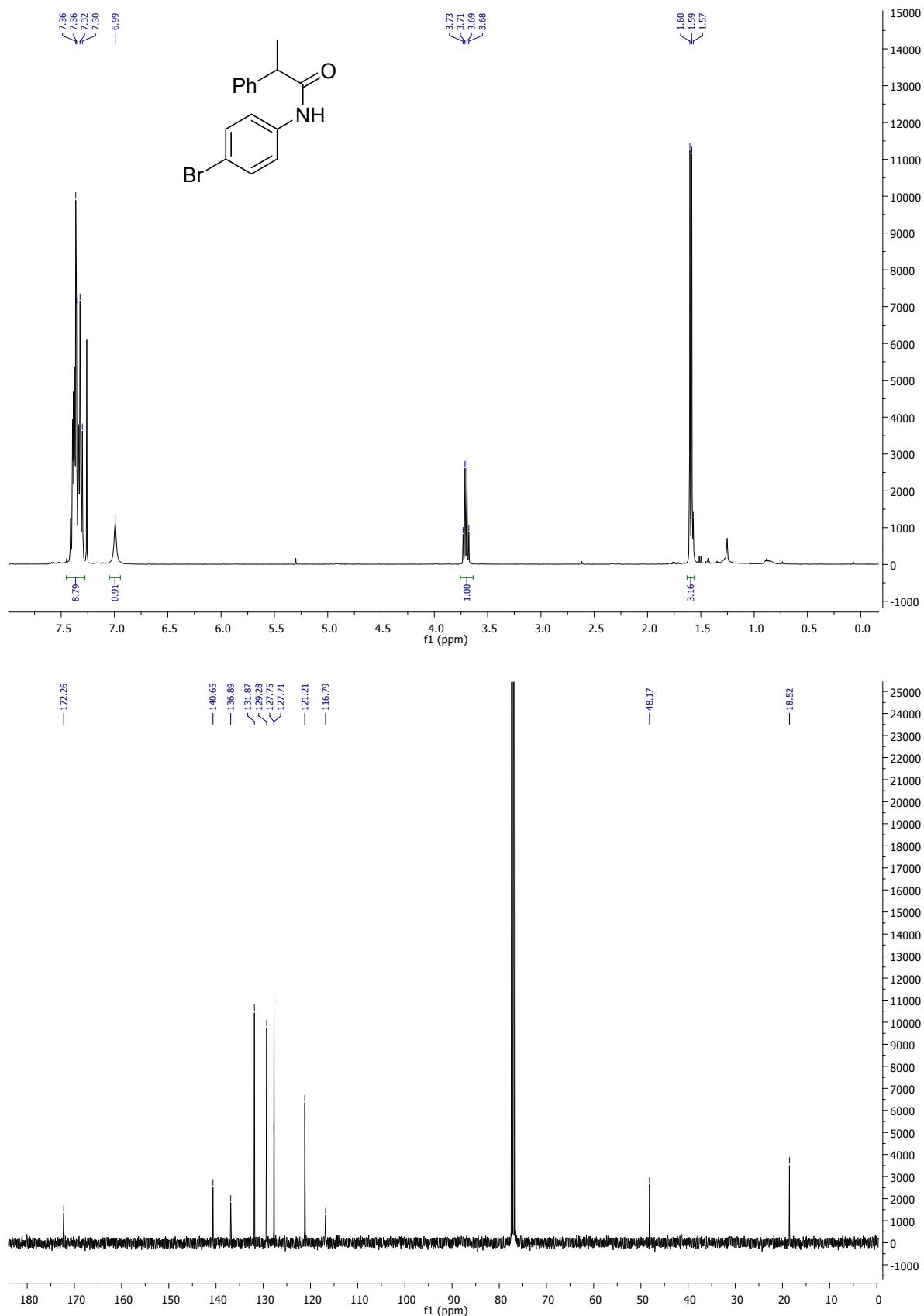
N-(4-Chlorophenyl)-2-phenylpropionamide 18g



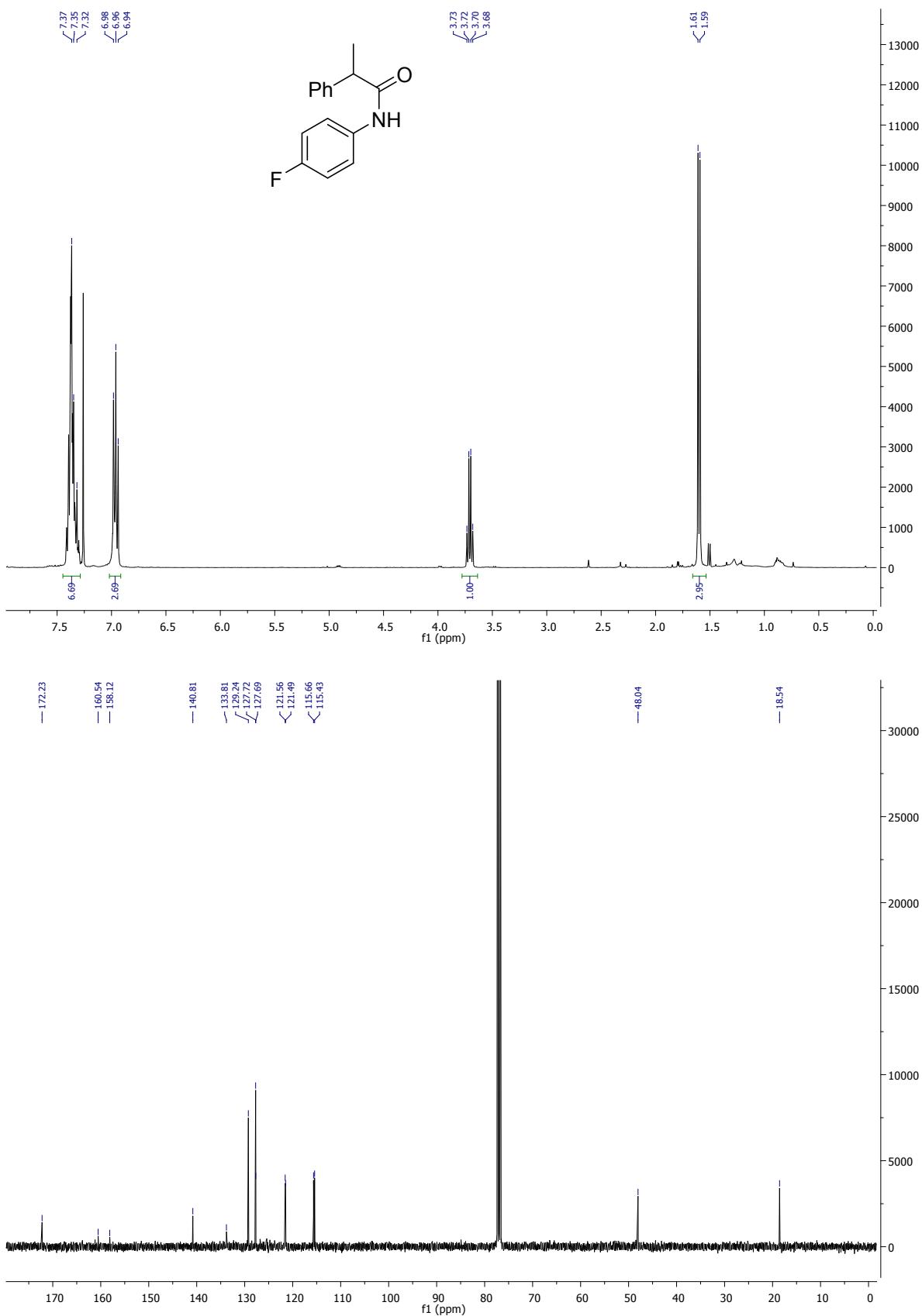
N-(2,4-Dichlorophenyl)-2-phenylpropionamide **18h**

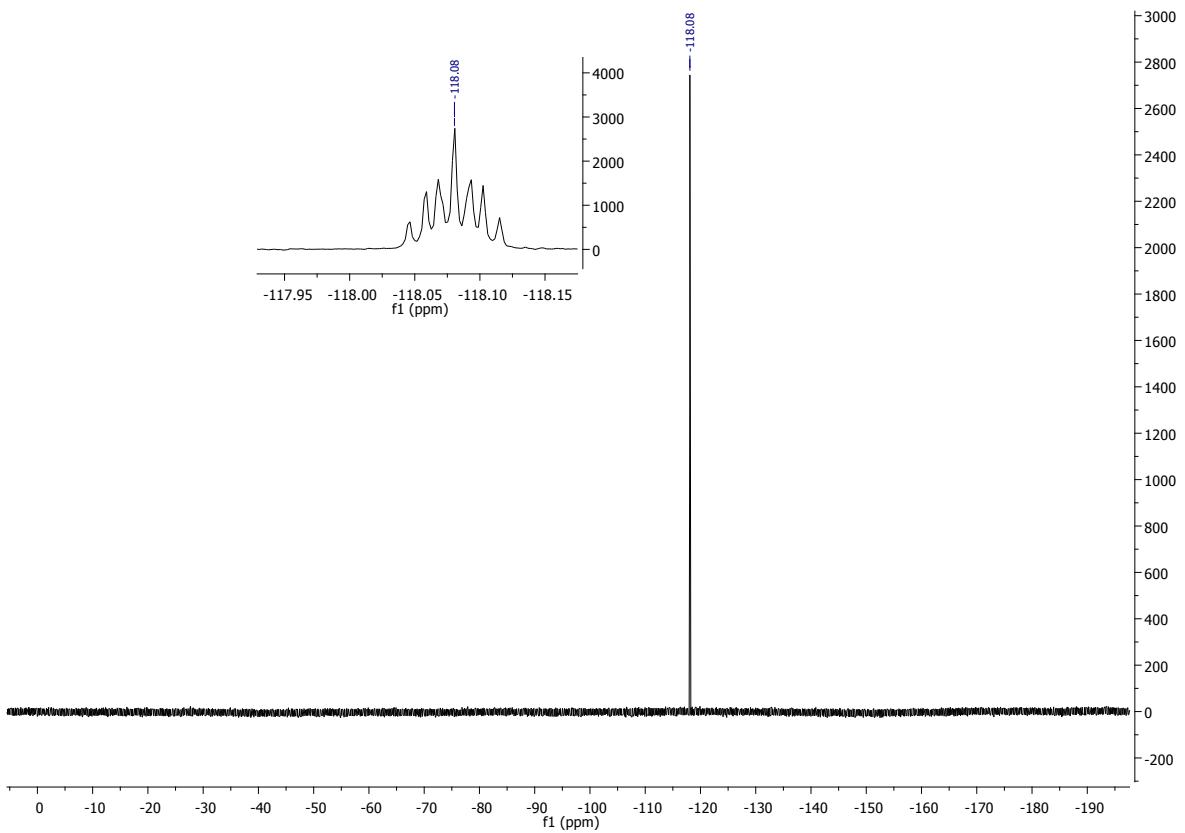


N-(4-Bromophenyl)-2-phenylpropionamide **18i**

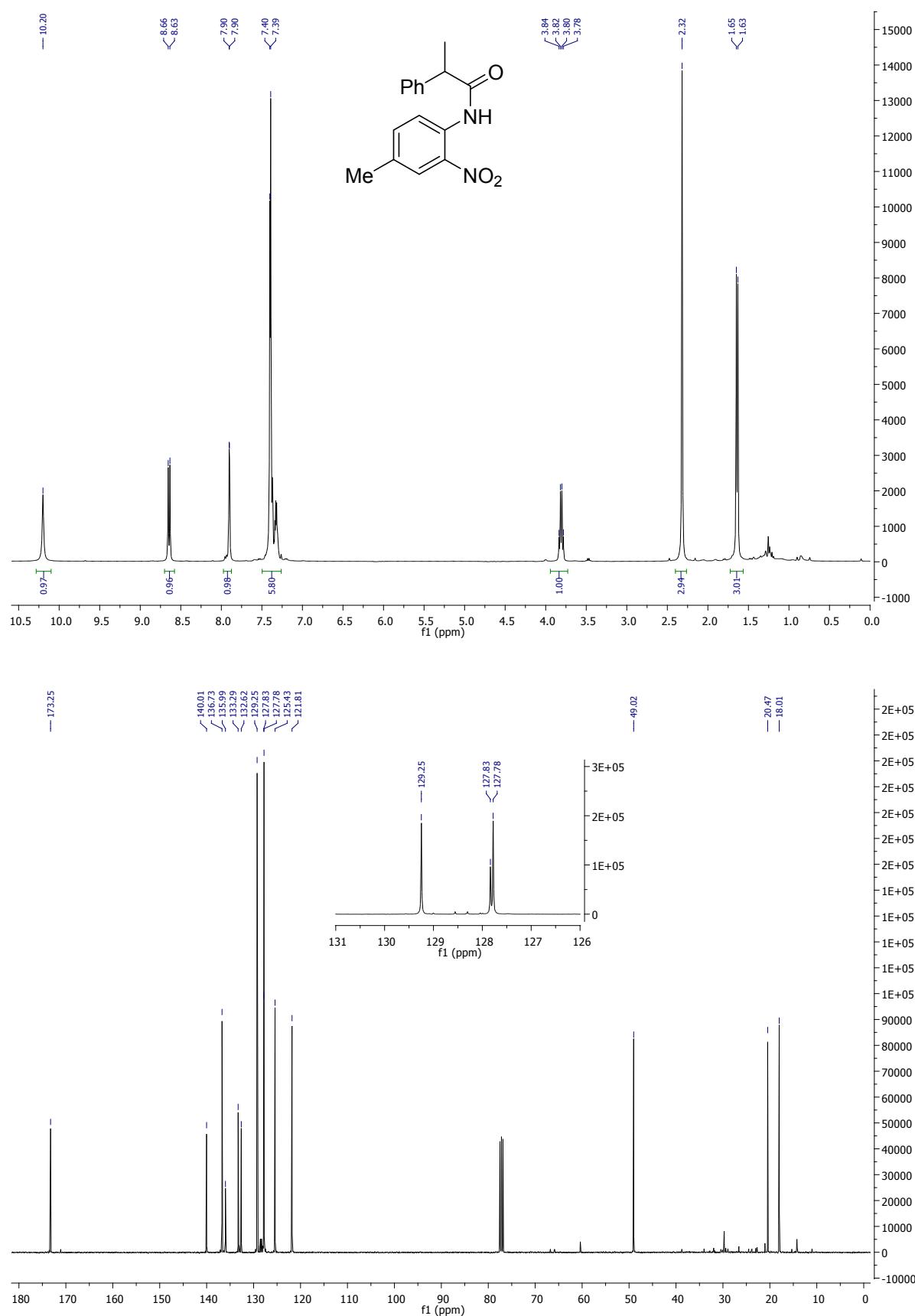


N*-(4-Fluorophenyl)-2-phenylpropionamide **18j*

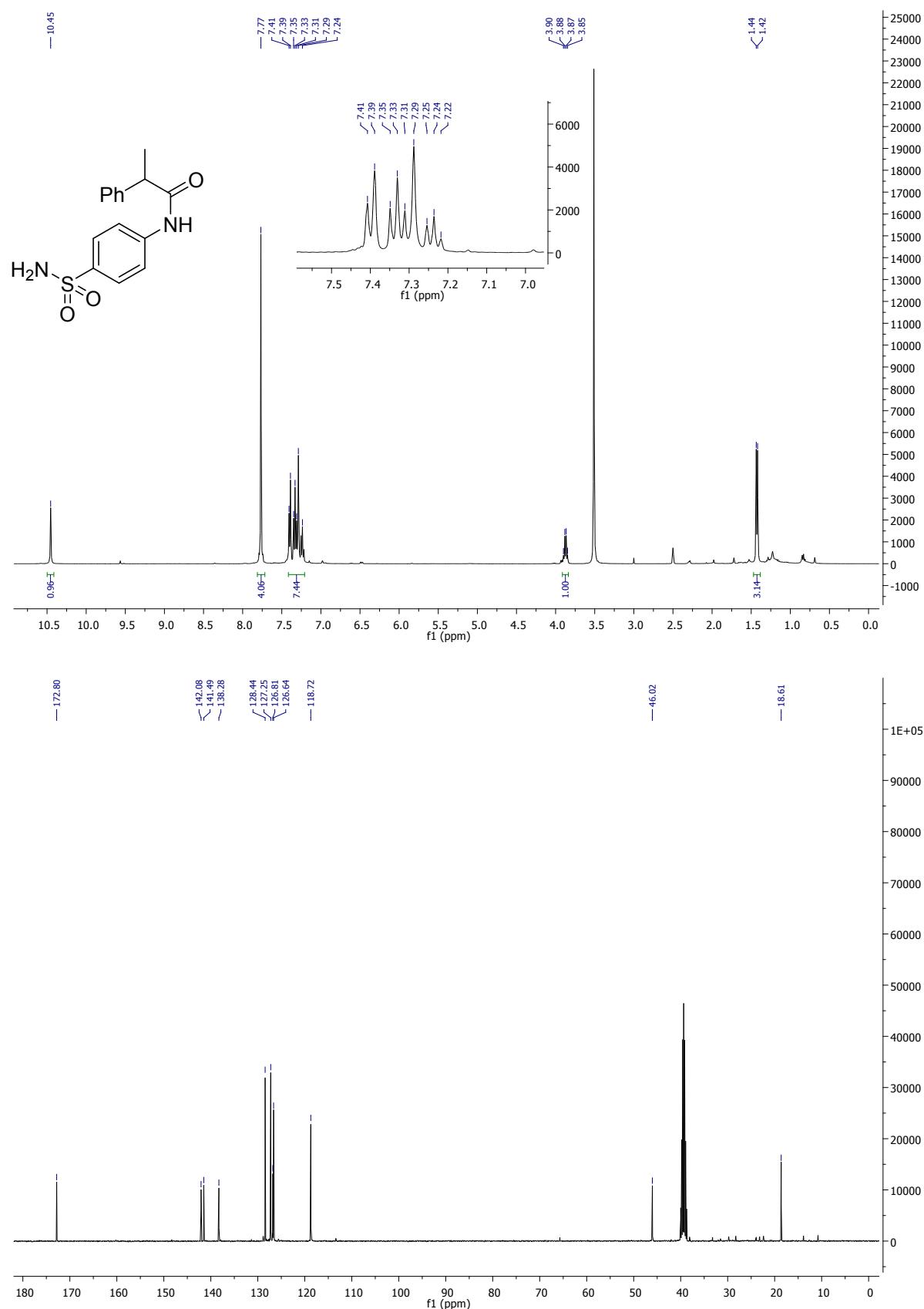




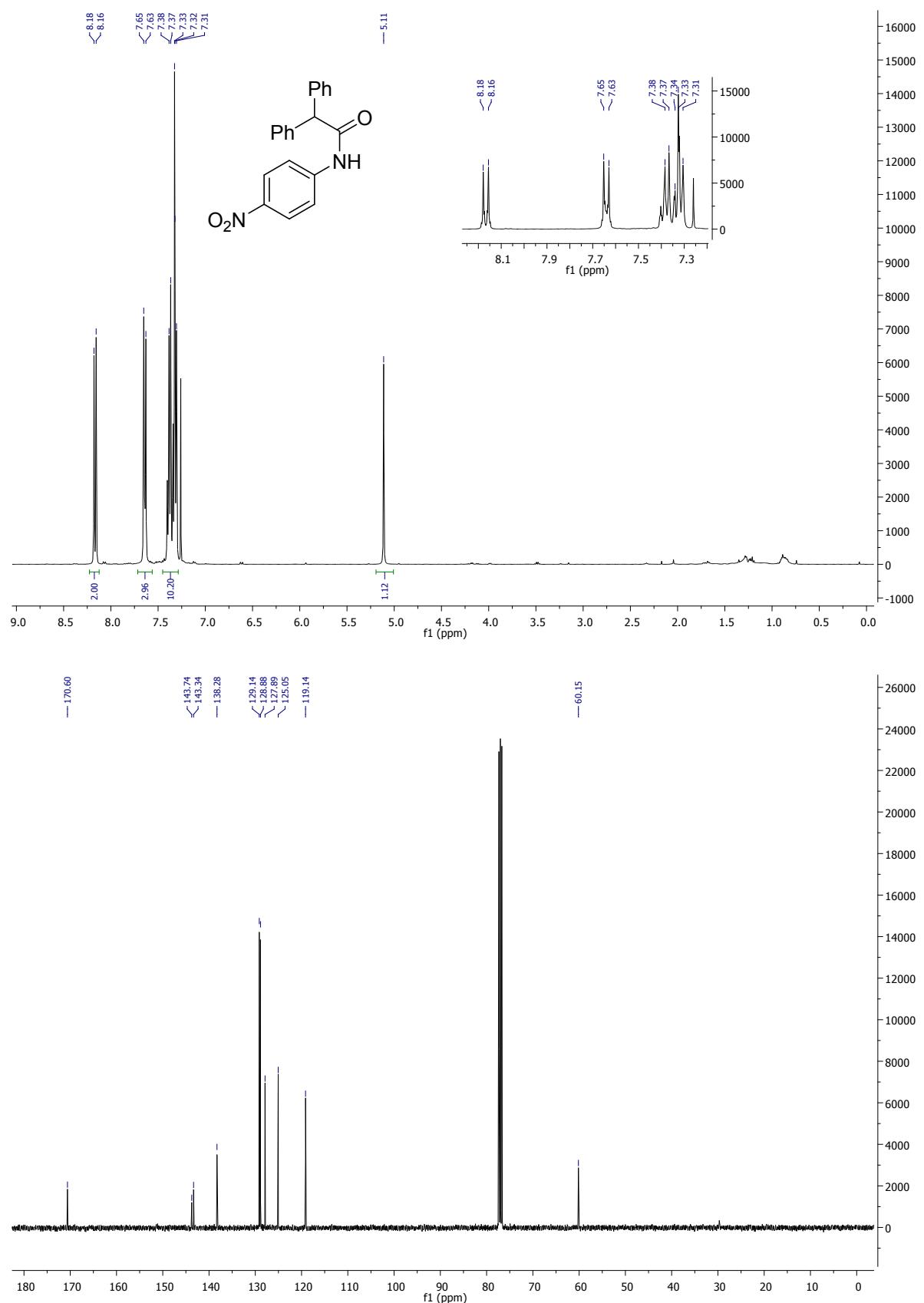
N-(4-Methyl-2-nitrophenyl)-2-phenylpropionamide **18k**



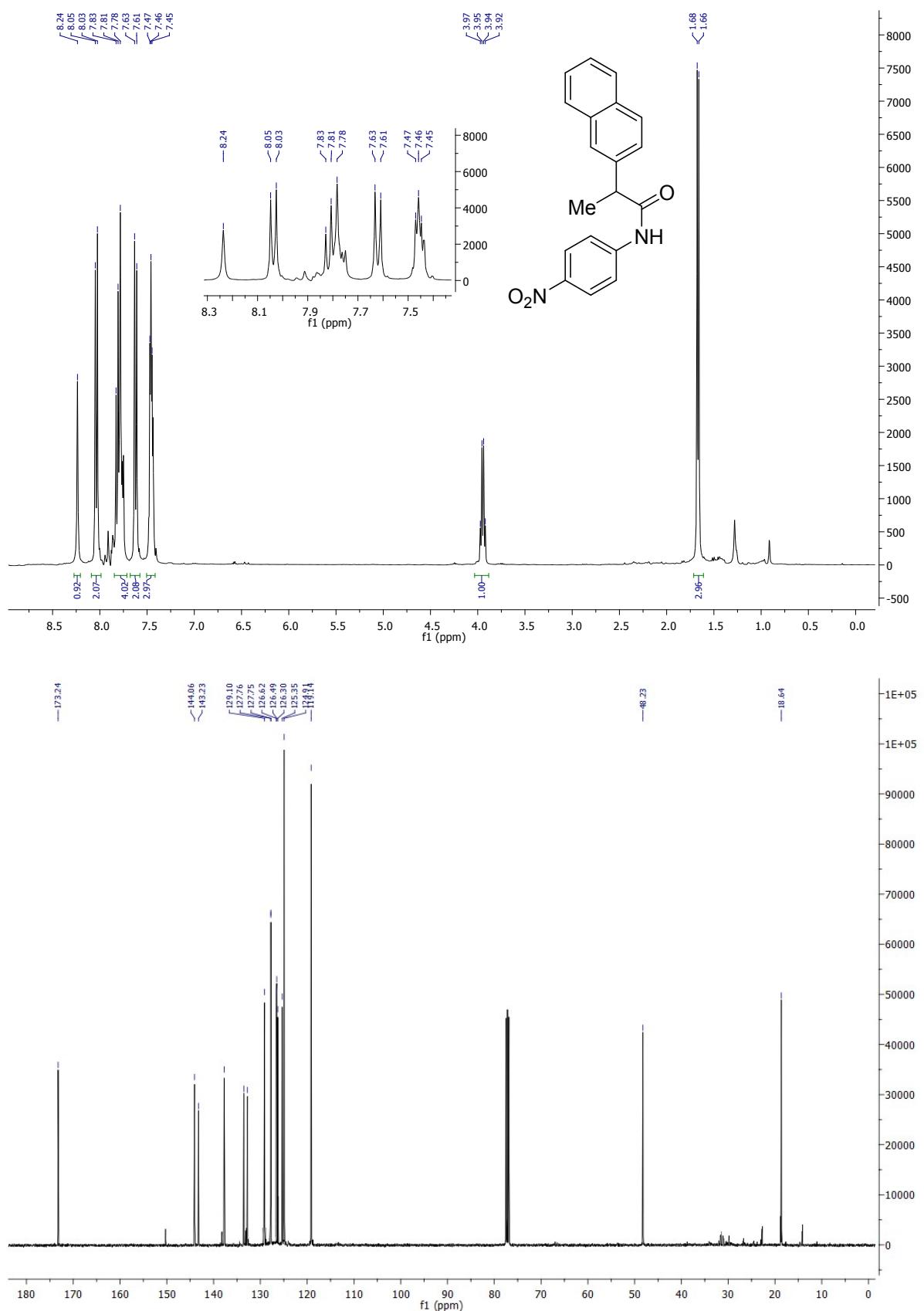
N-(4-Sulfamoylphenyl)-2-phenylpropionamide **18I** (solvent DMSO-d₆)



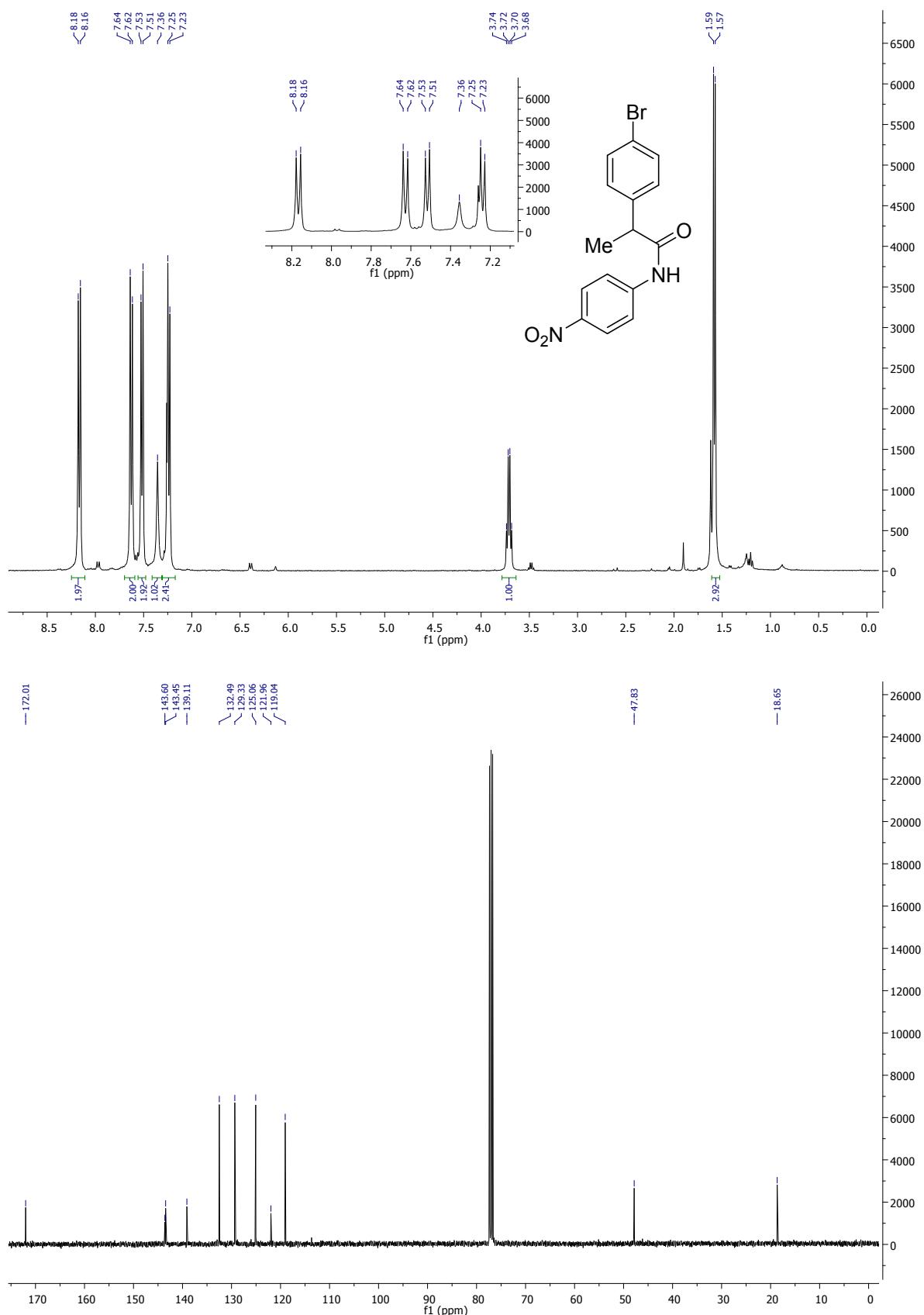
N-(4-Nitrophenyl)-2,2-di-phenylpropionamide **18m**



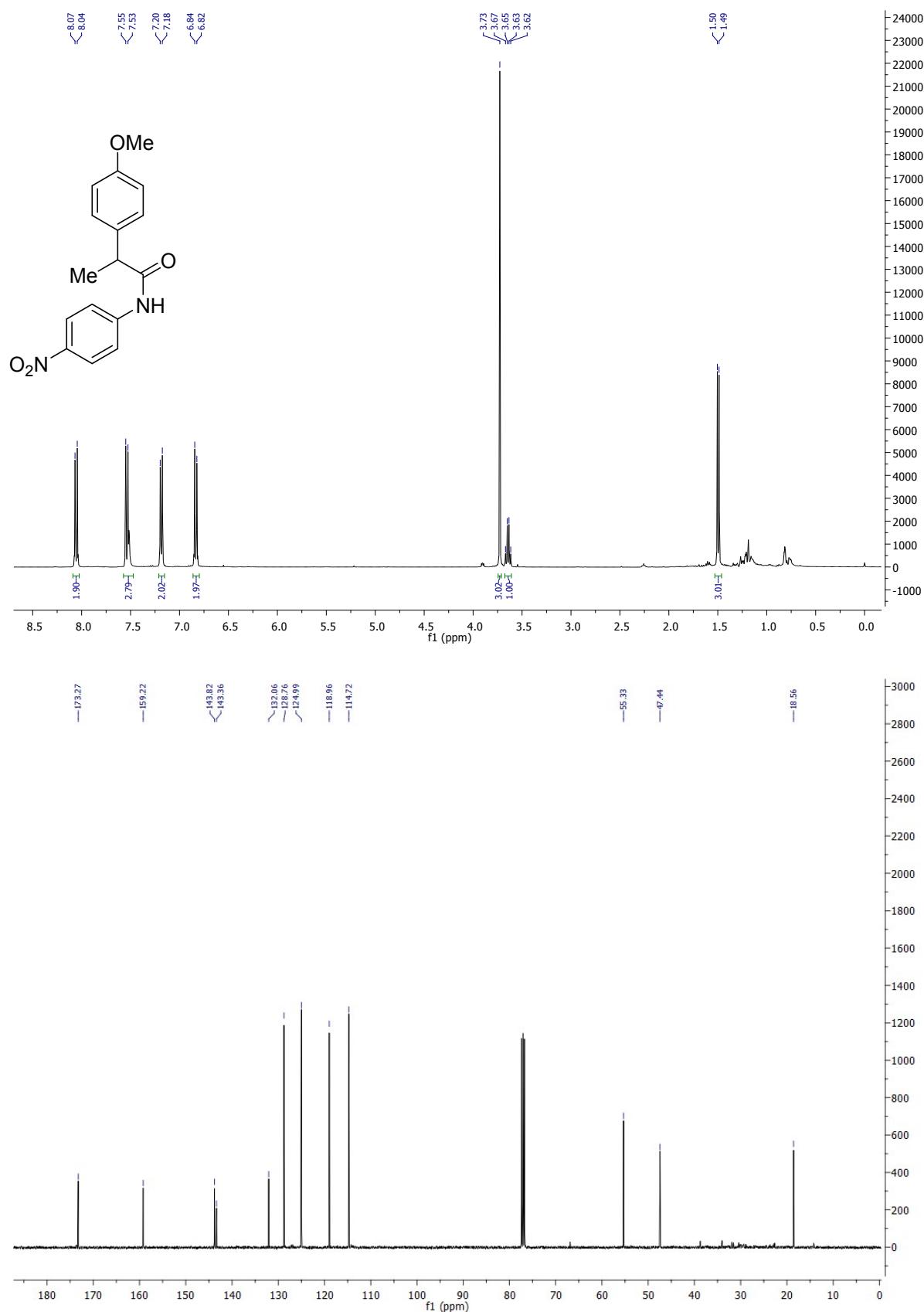
***N*-(4-Nitrophenyl)-2-(2-naphtyl)-propionamide 18n**



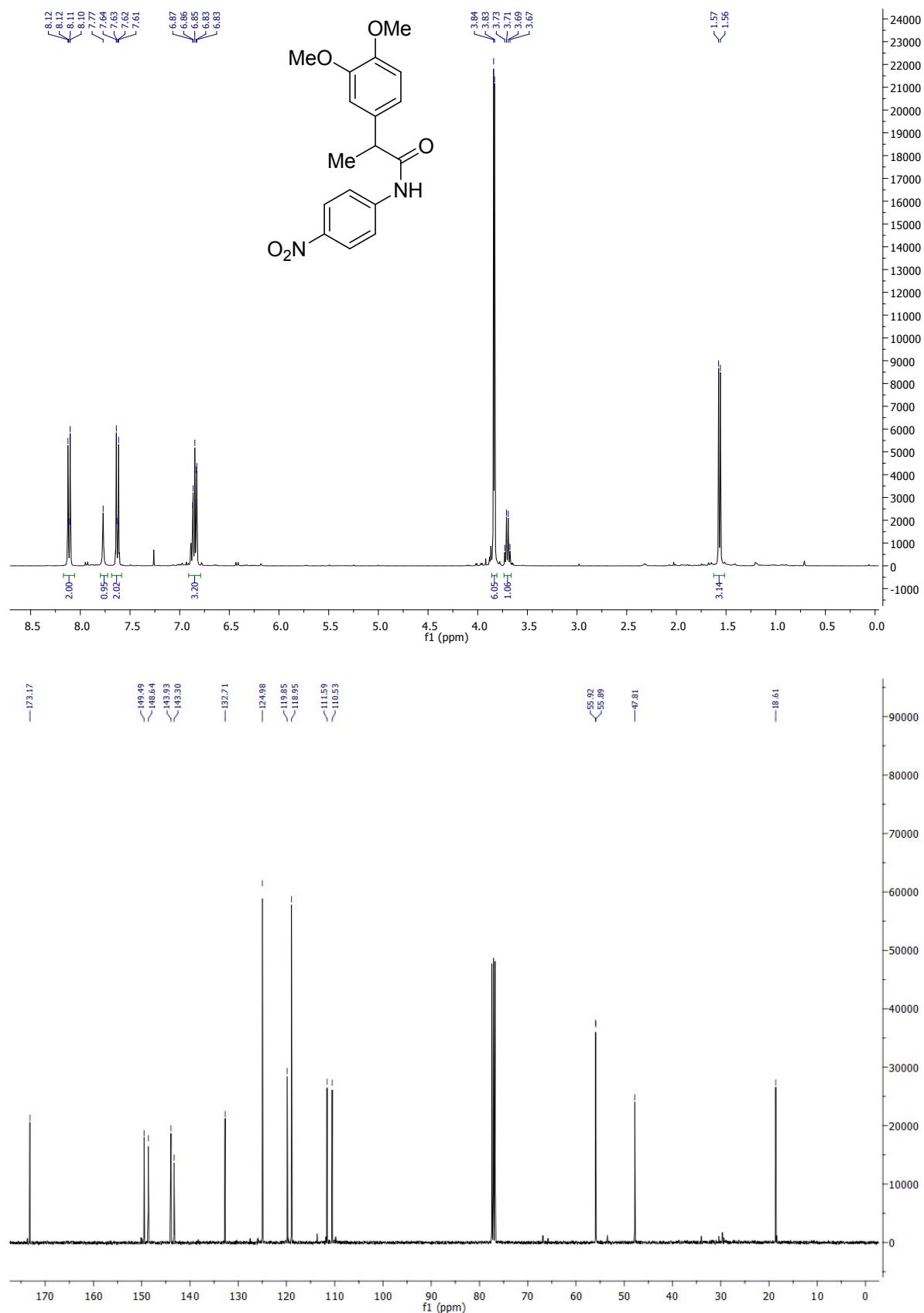
N-(4-Nitrophenyl)-2-(4-bromophenyl)-propionamide 18o



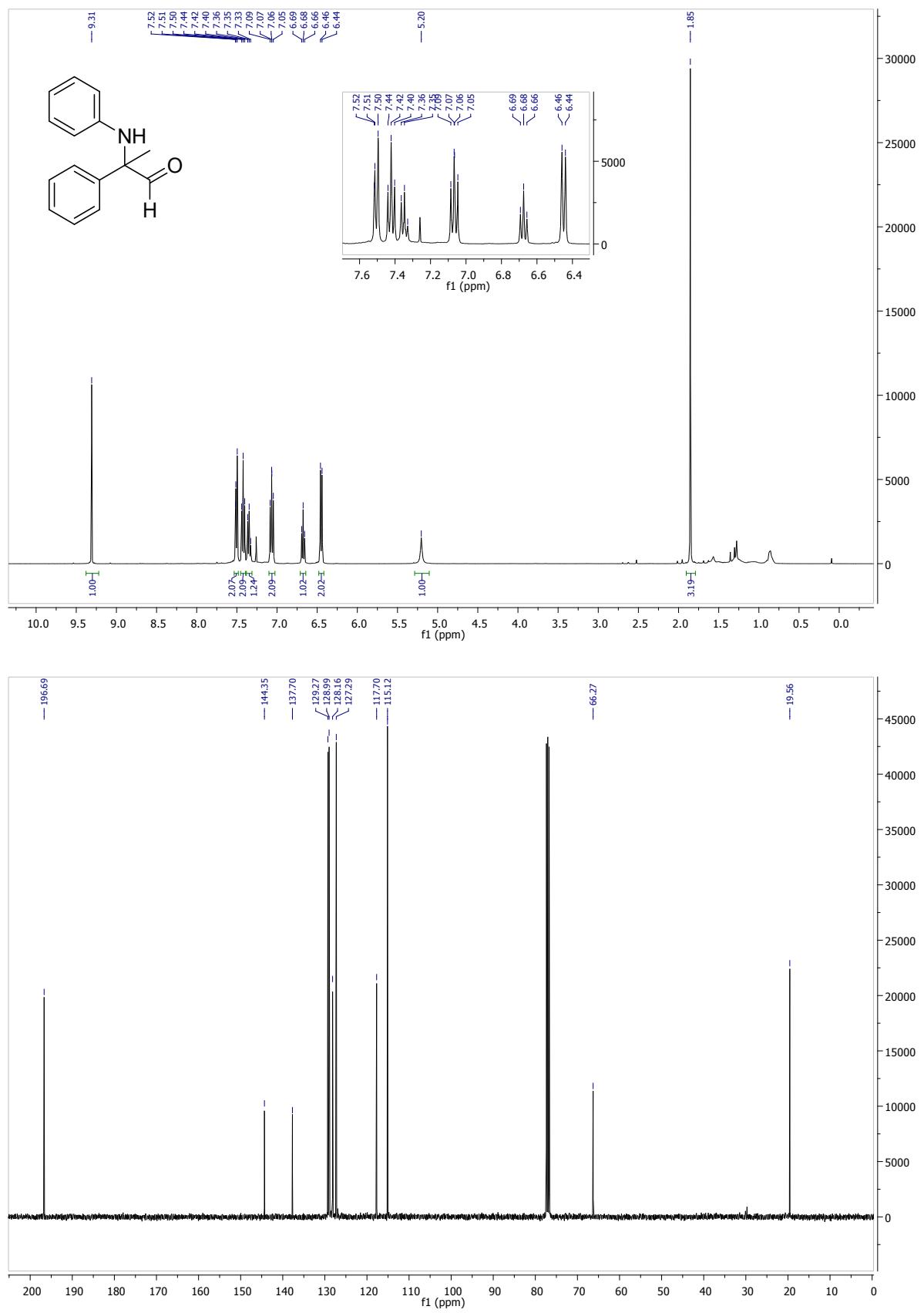
N-(4-Nitrophenyl)-2-(4-methoxyphenyl)-propionamide 18p



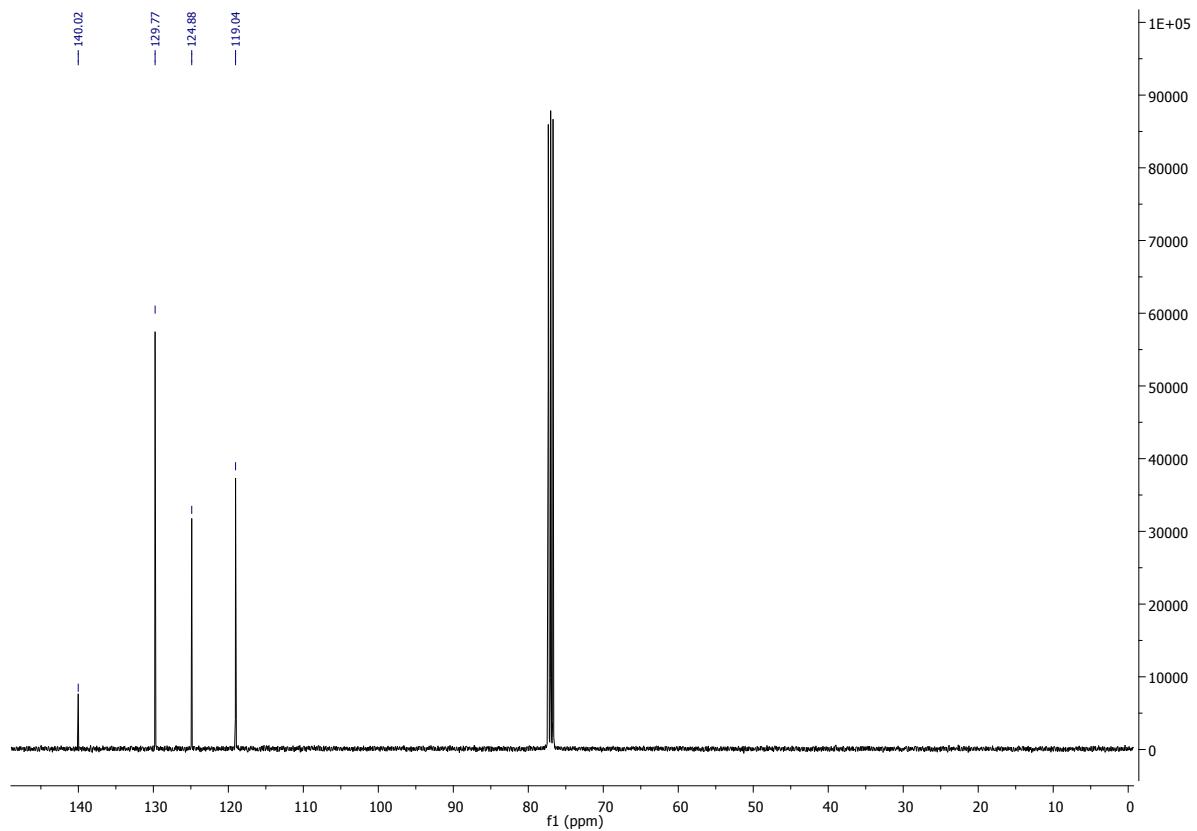
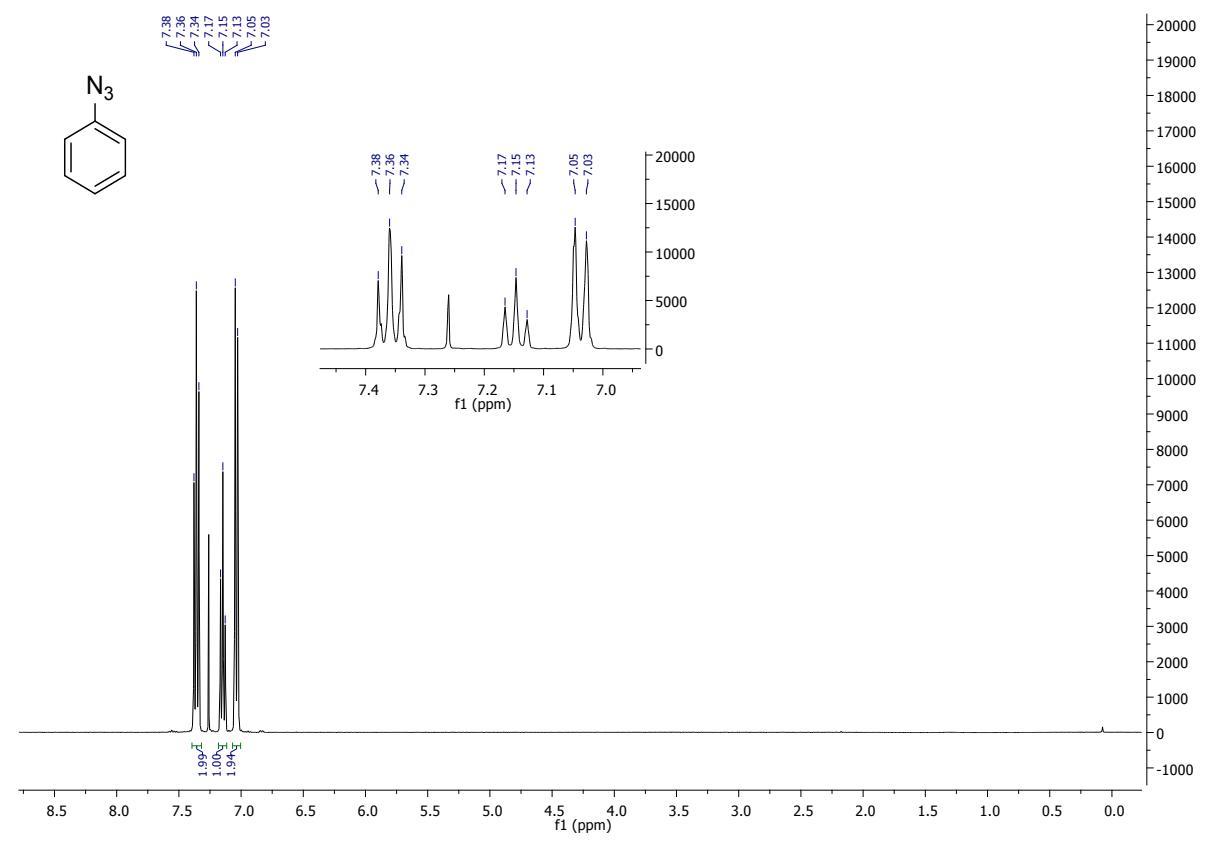
N-(4-Nitrophenyl)-2-(2,4-dimethoxyphenyl)-propionamide 18q



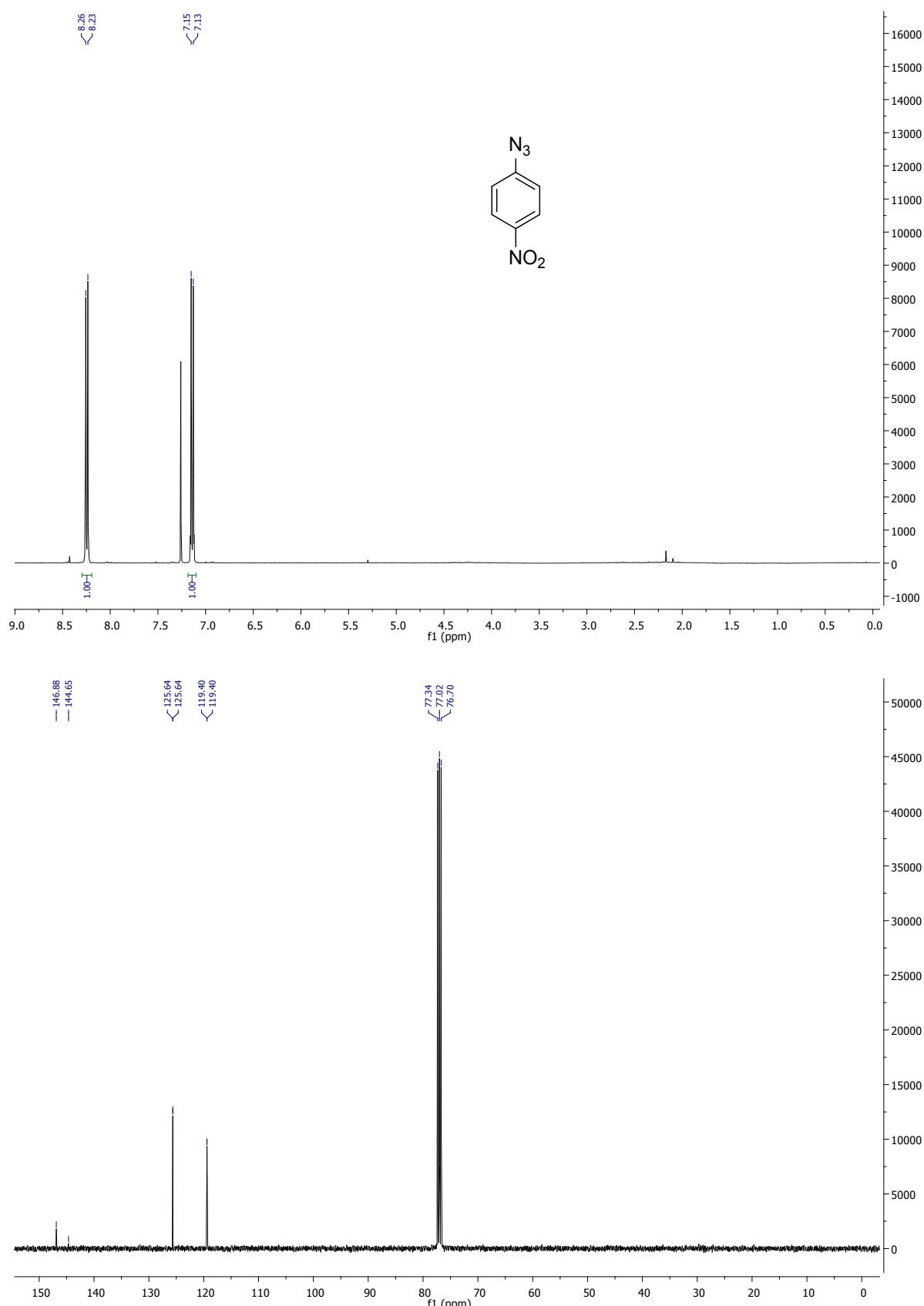
(N,2)-Diphenyl-2-aminopropionadehyde **17**



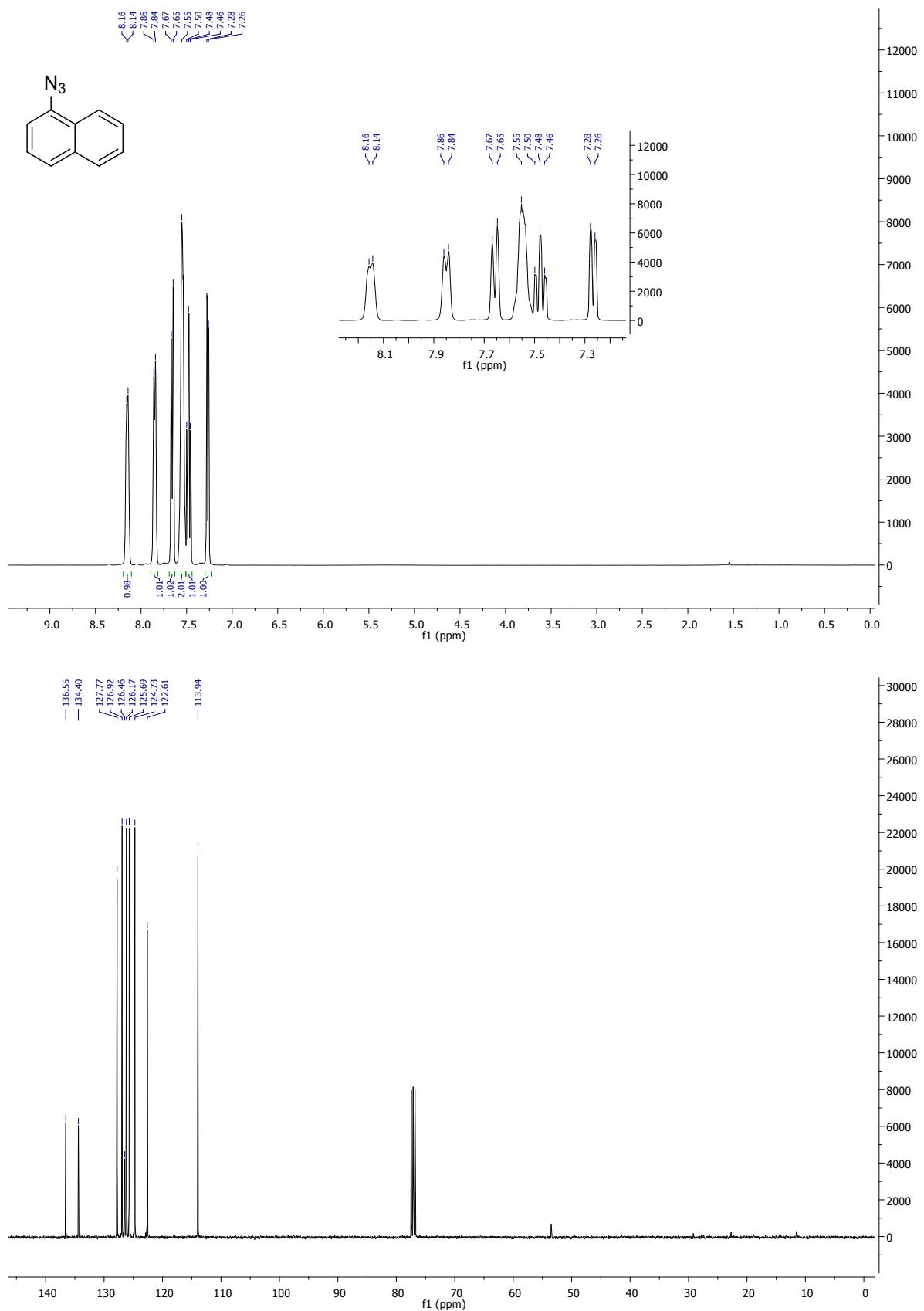
Azidobenzene **9a**



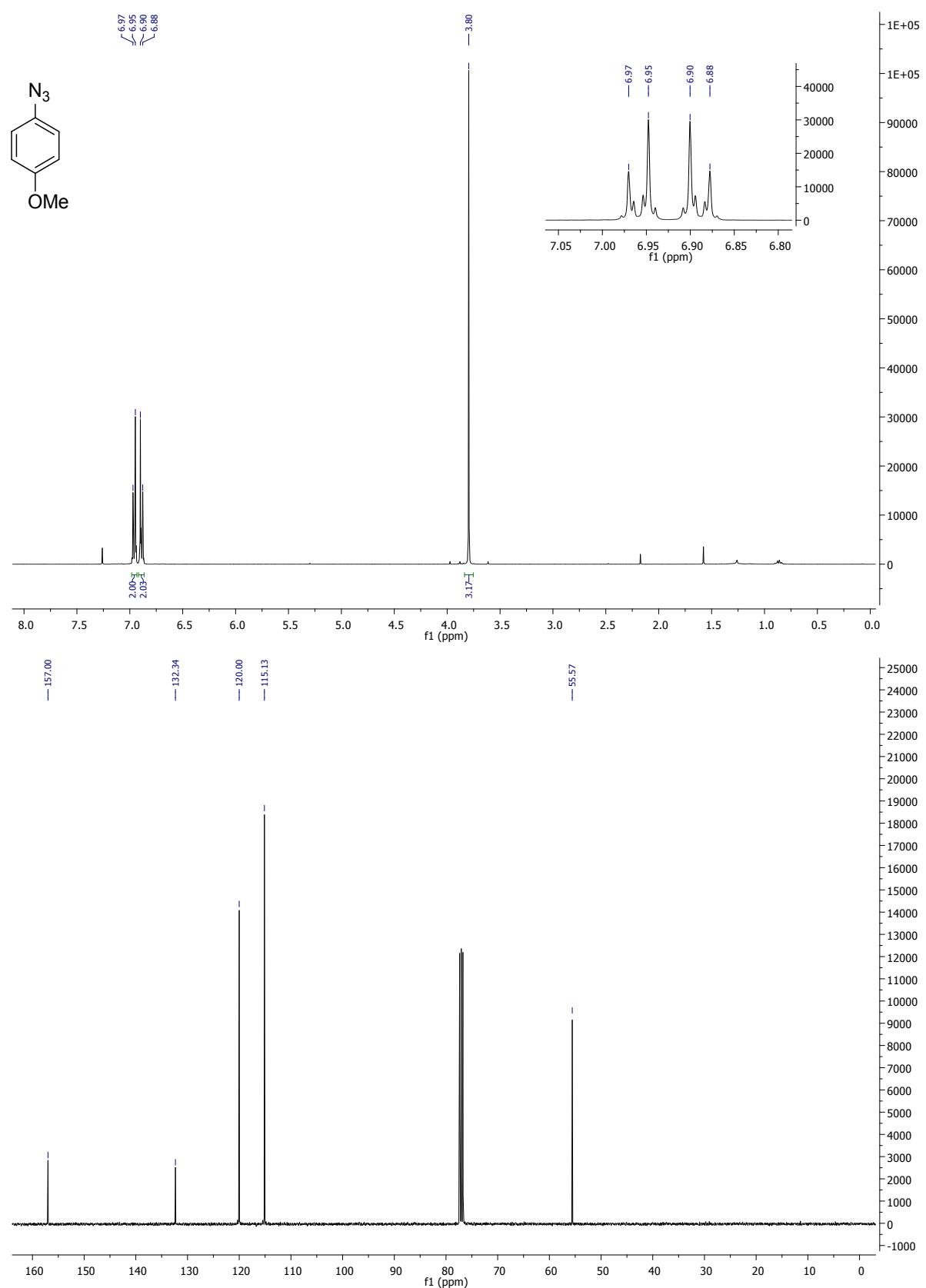
4-Nitro-azidobenzene **9b**



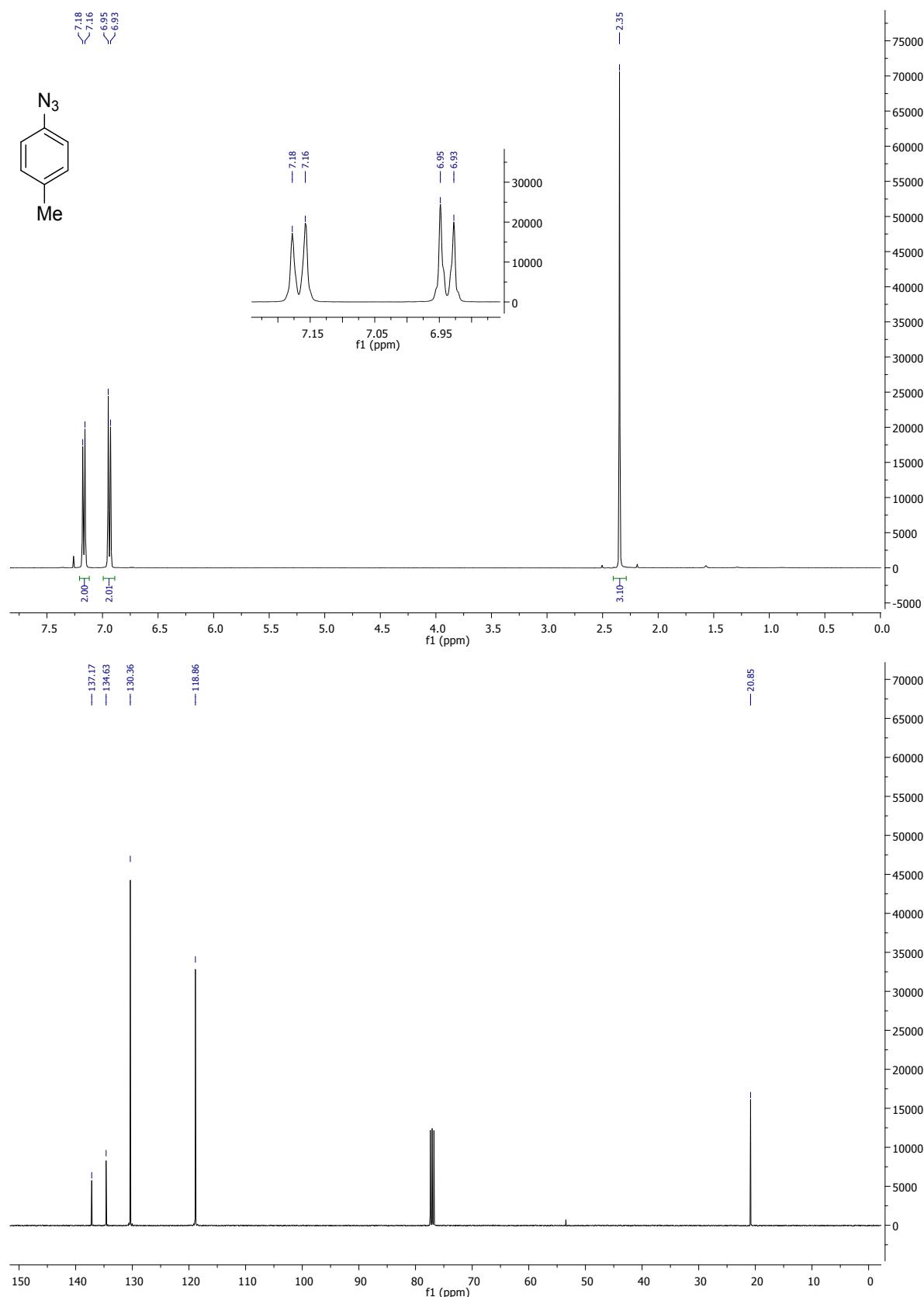
1-Azidonaphthalene **9c**



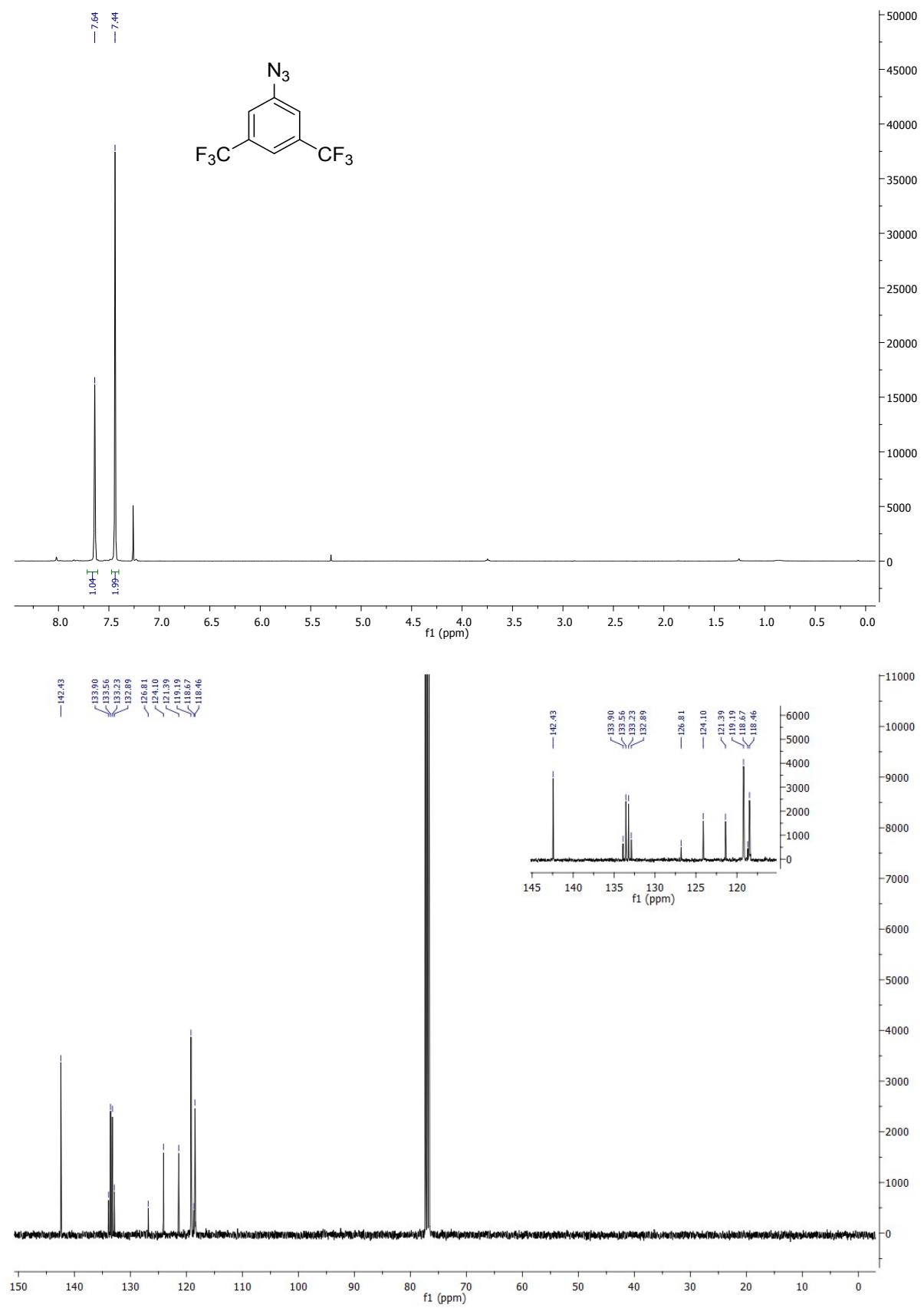
4-Azidoanisole **9d**



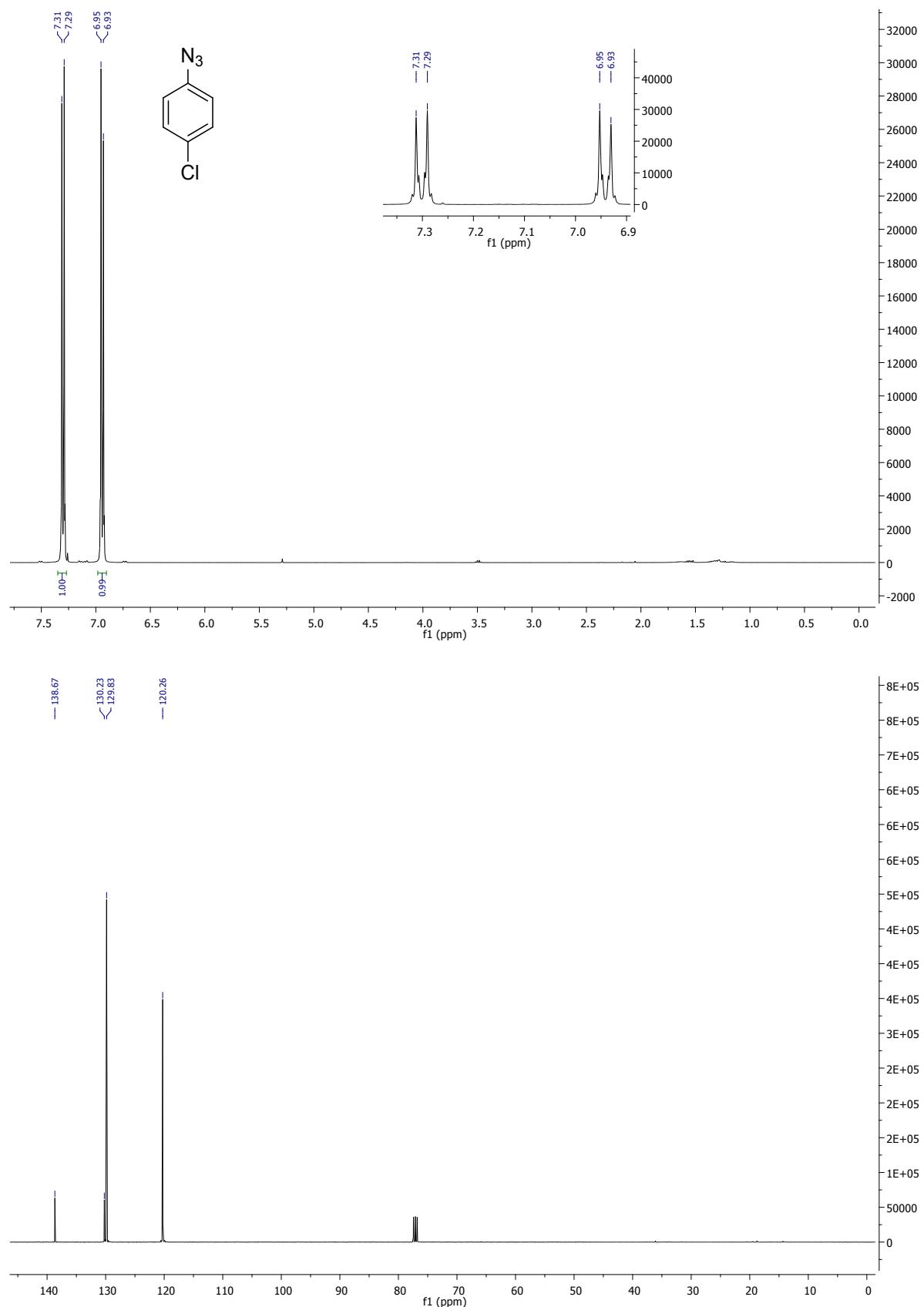
4-Azidotoluene **9e**



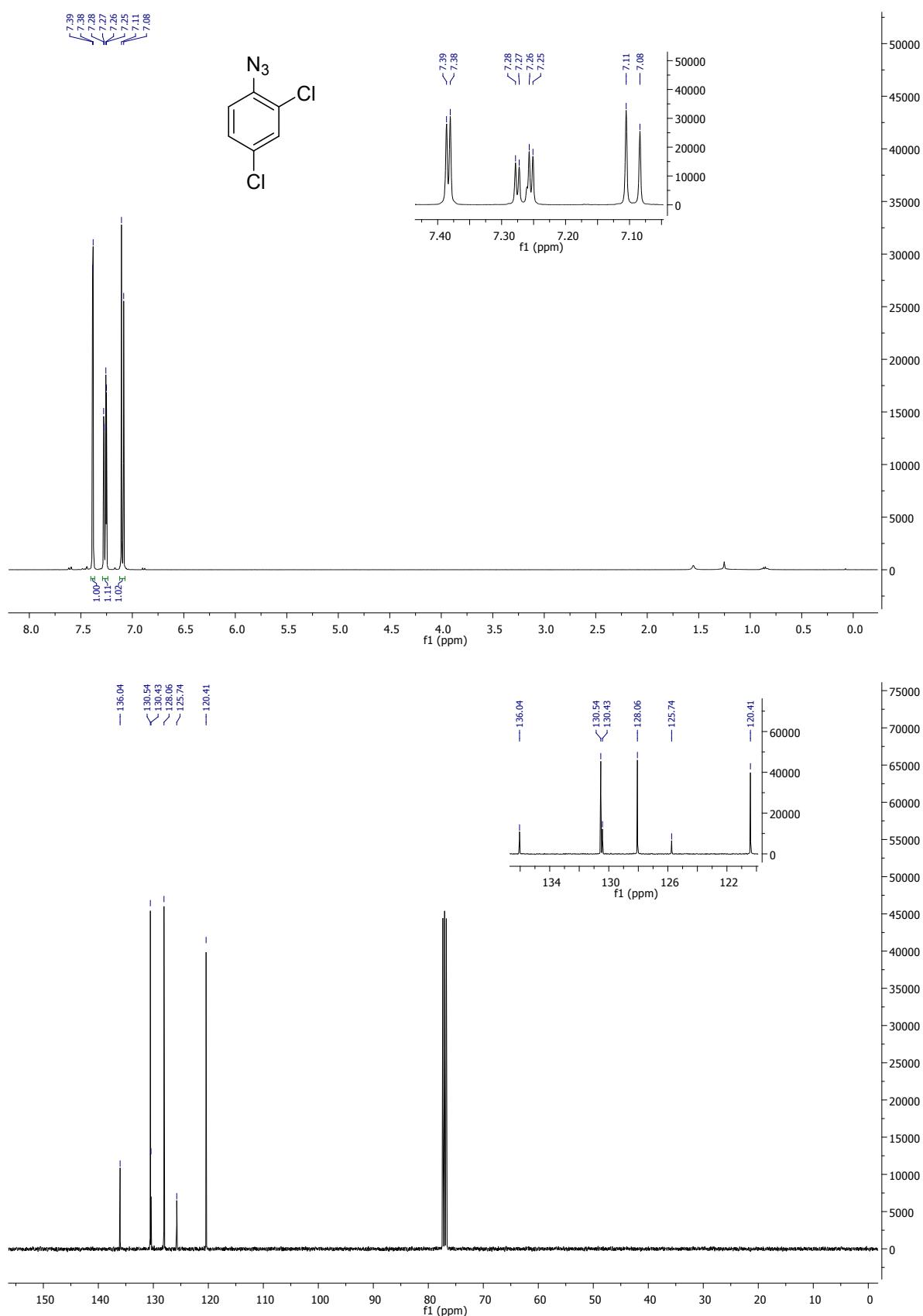
3,5-Di-(trifluoromethyl)-azidobenzene **9f**



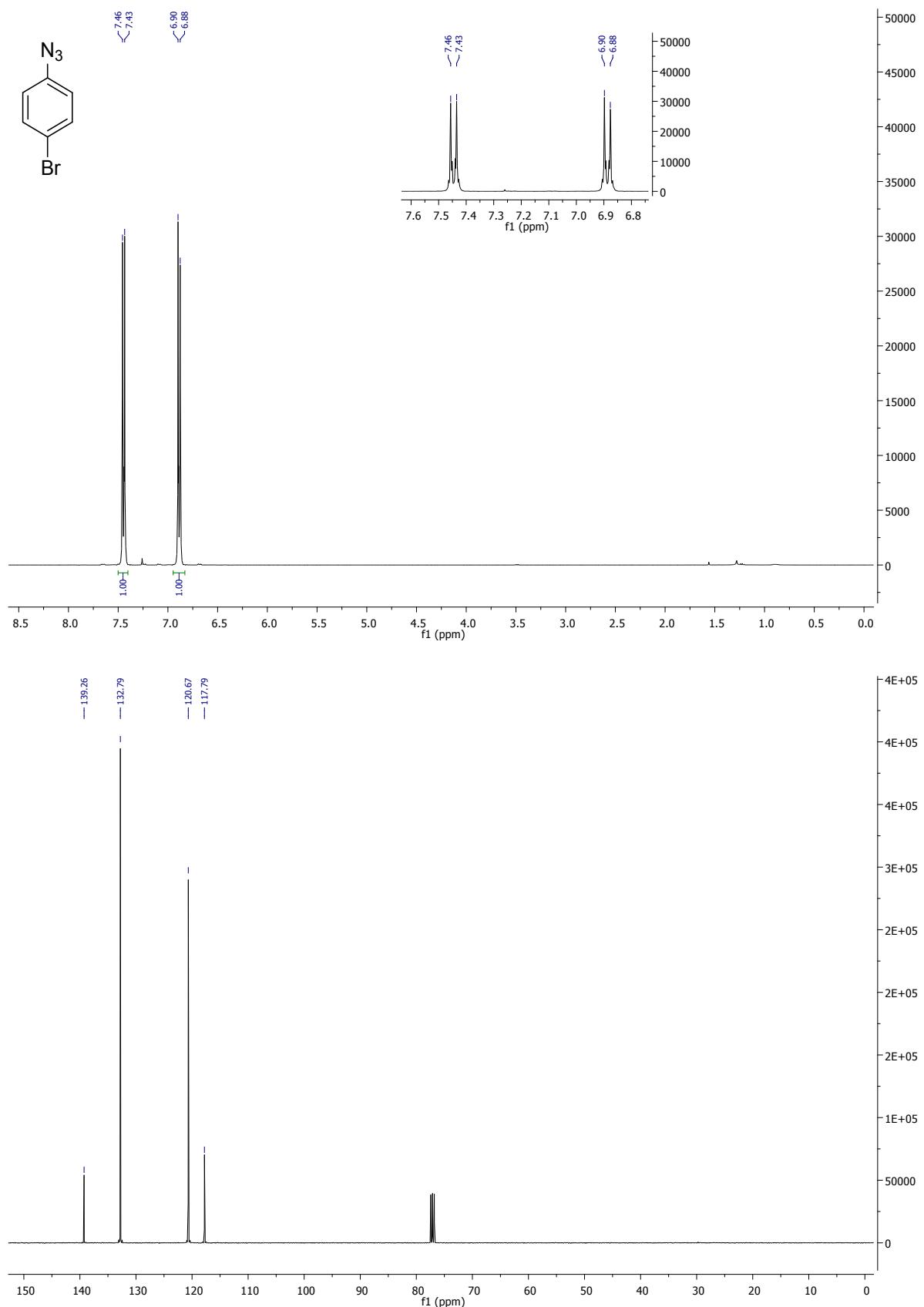
4-Chloro-azidobenzene **9g**



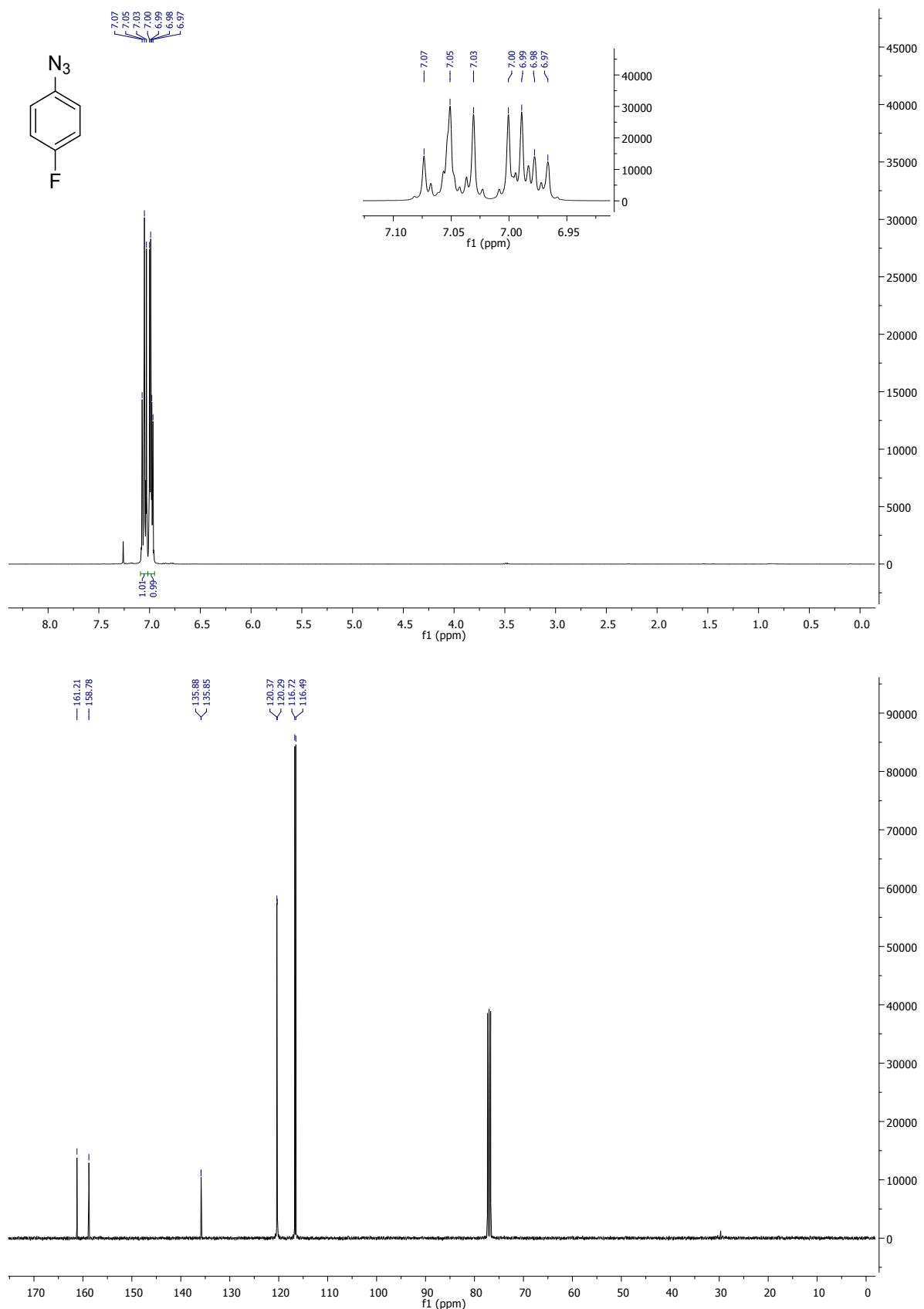
2,4-Dichloro-azidobenzene **9h**

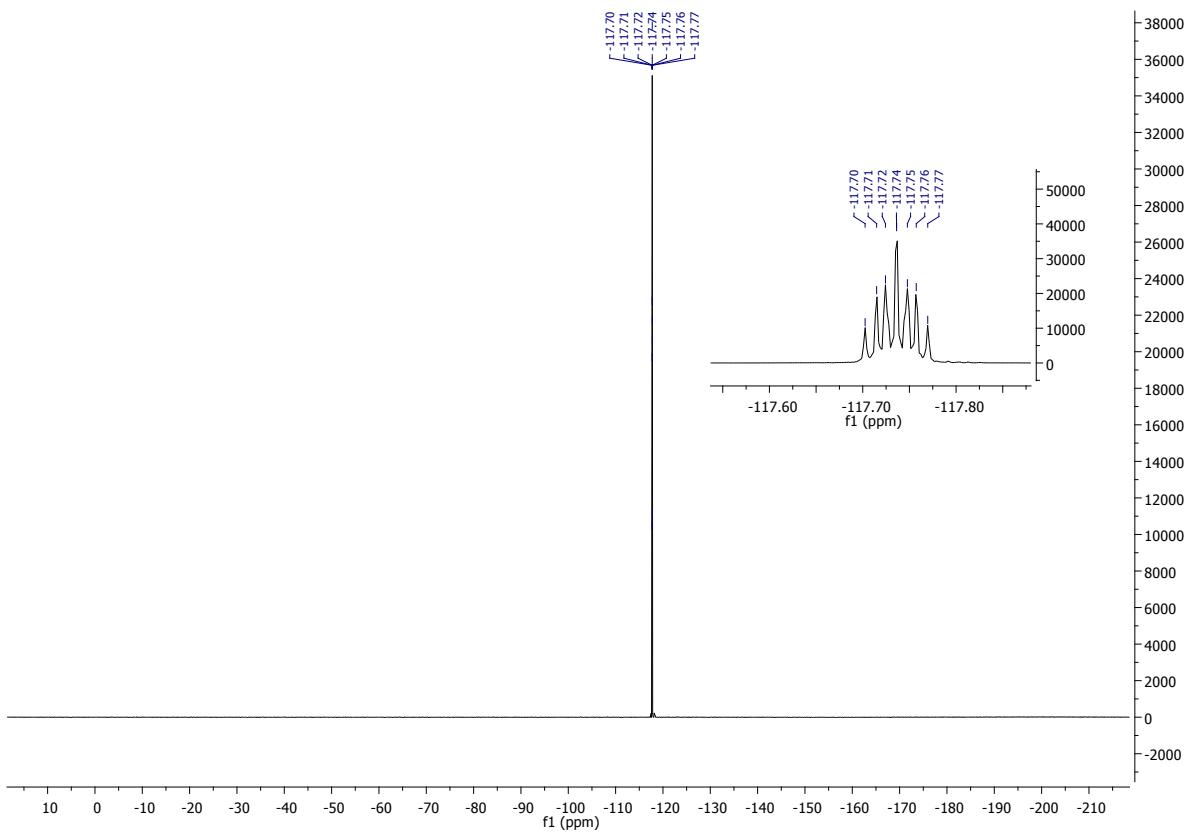


4-Bromo-azidobenzene **9i**

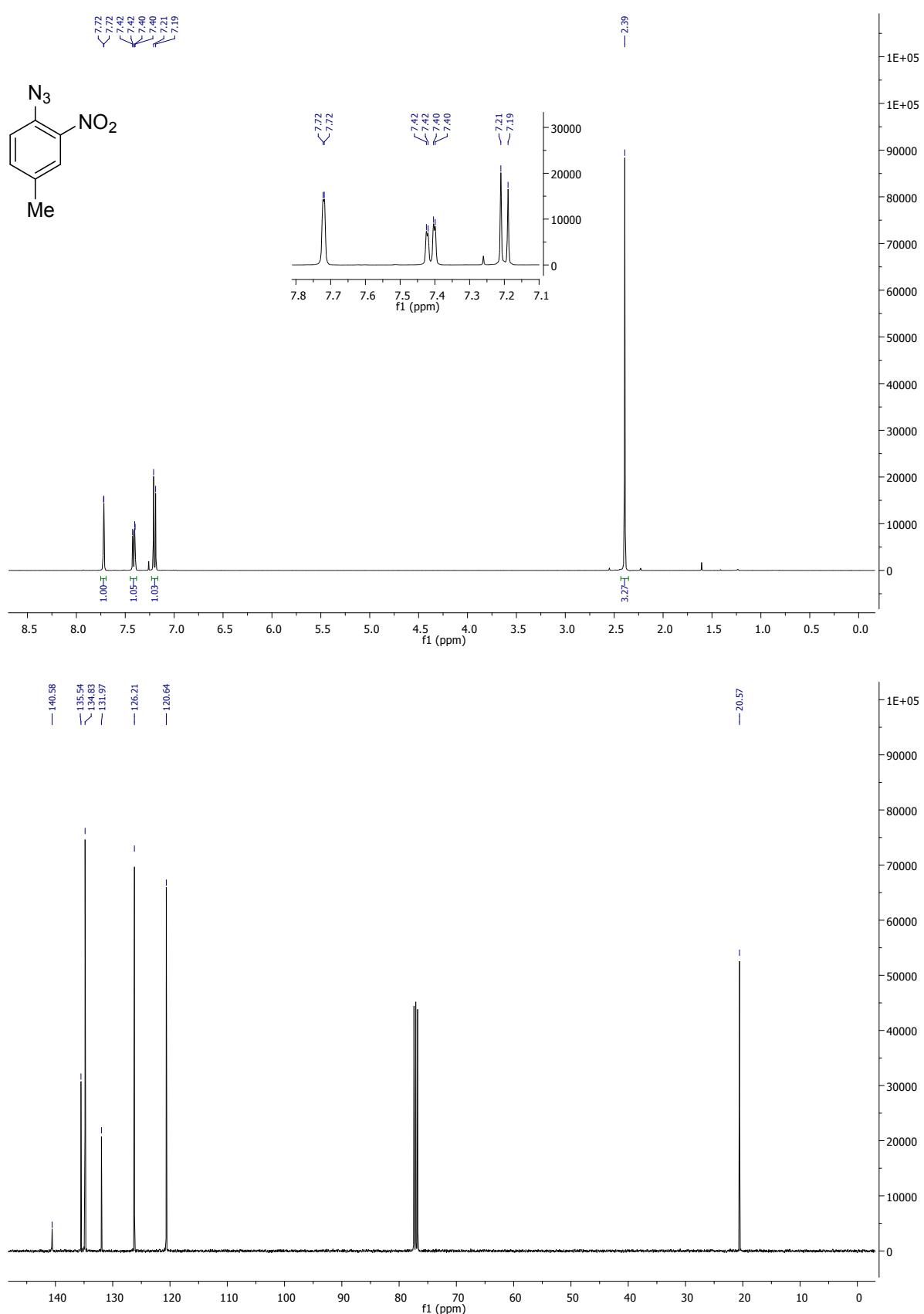


4-Fluoro-azidobenzene **9j**

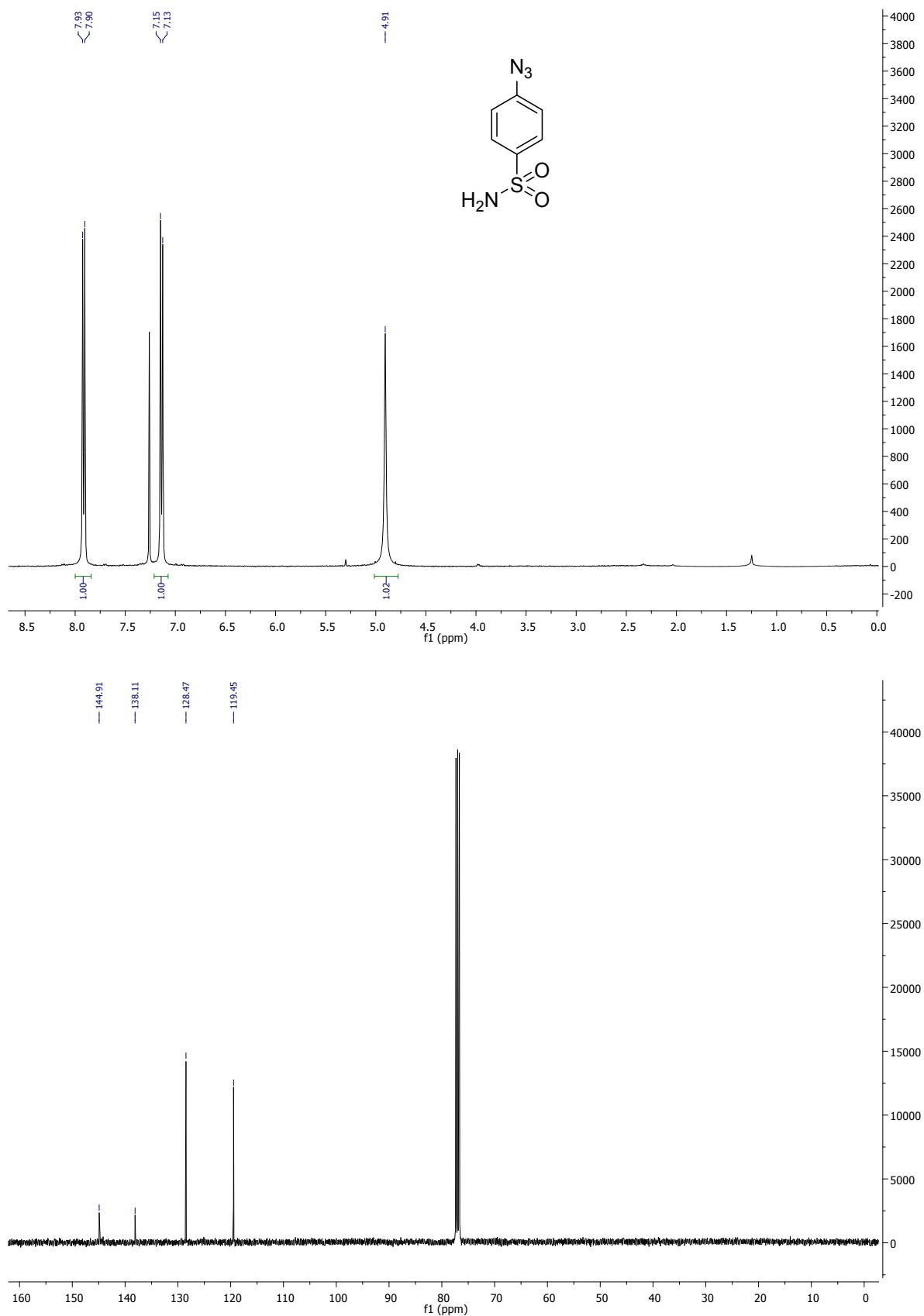




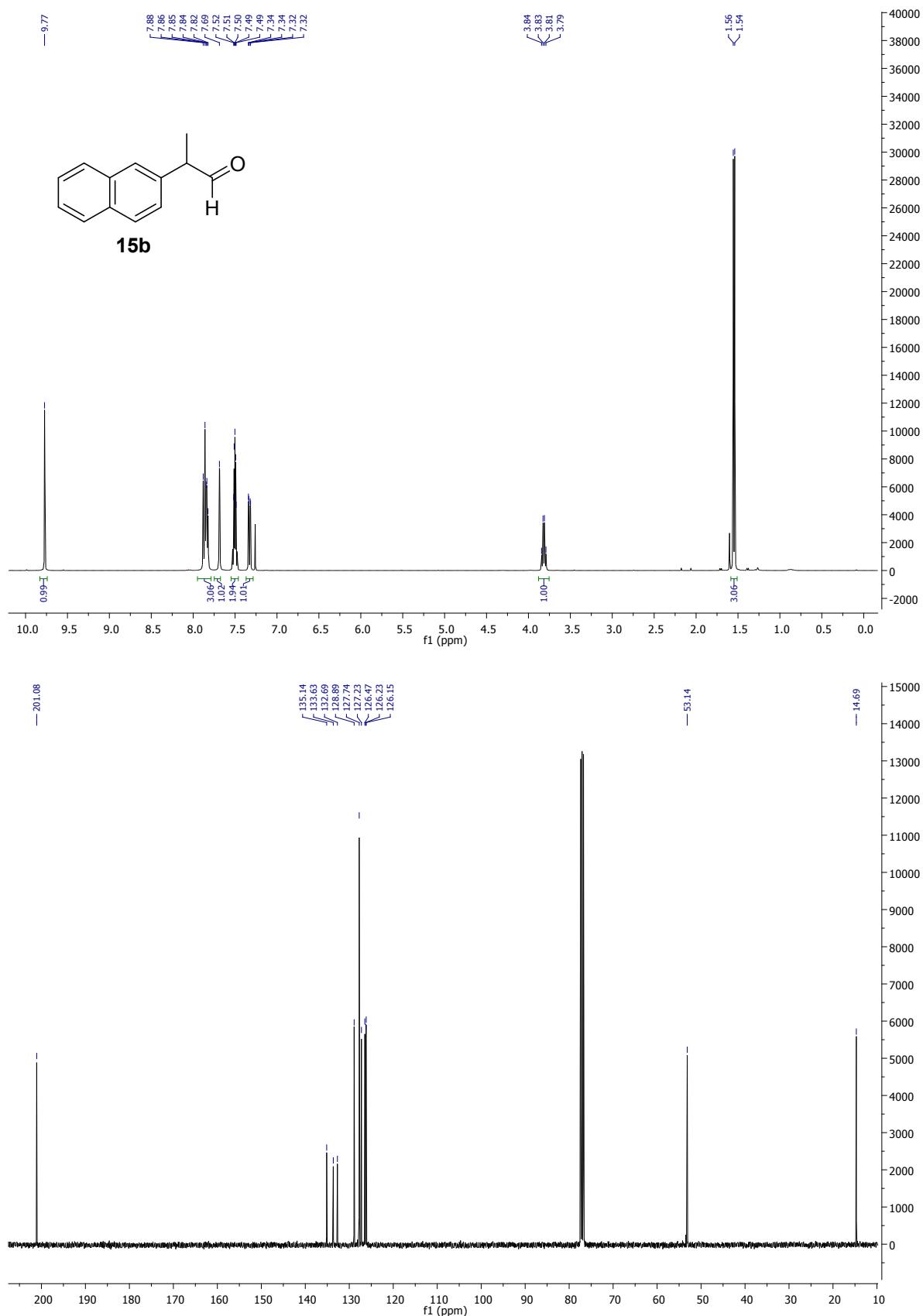
4-methyl-2-nitro-azidobenzene **9k**



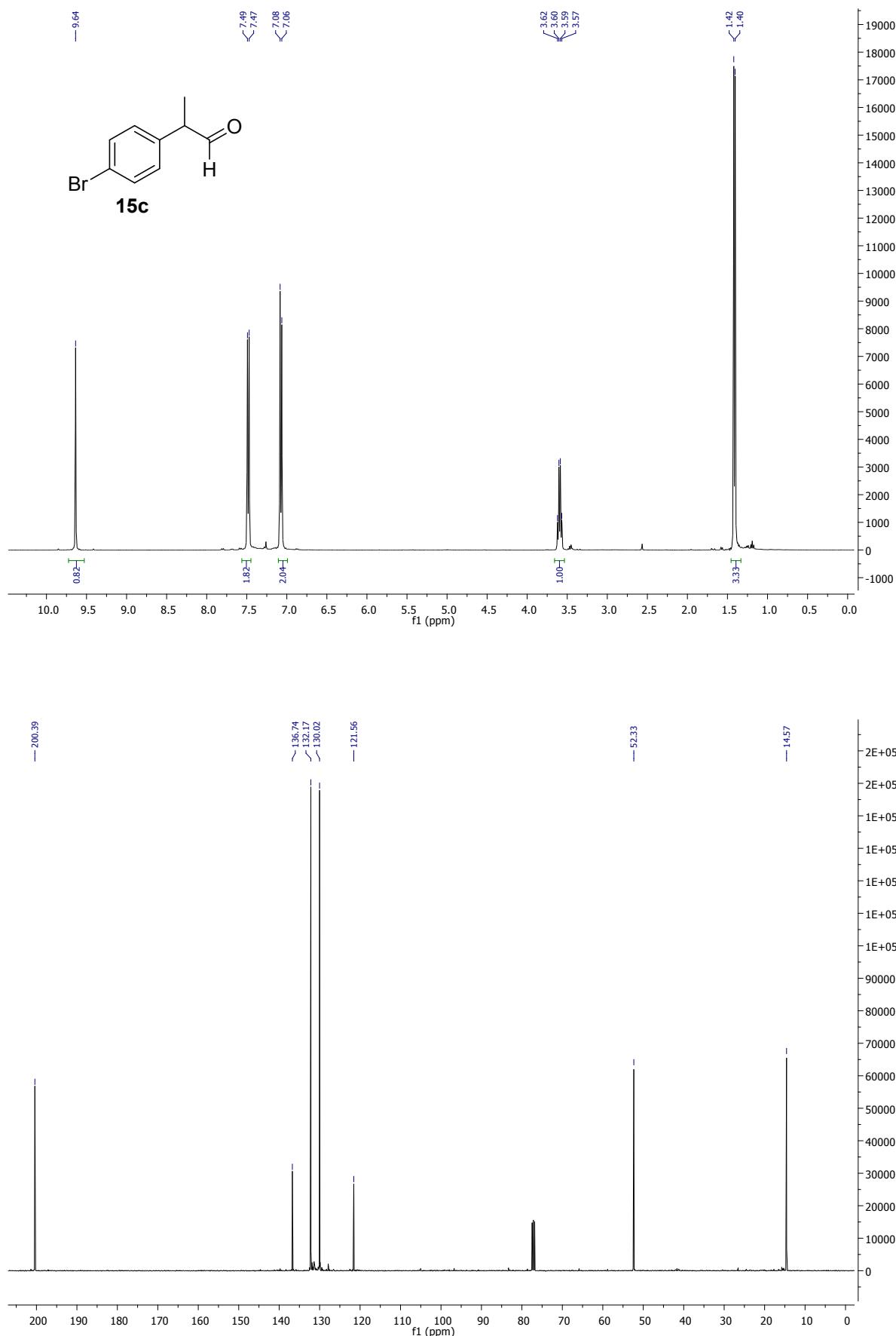
4-Azido-benzenesulfonamide **9I**



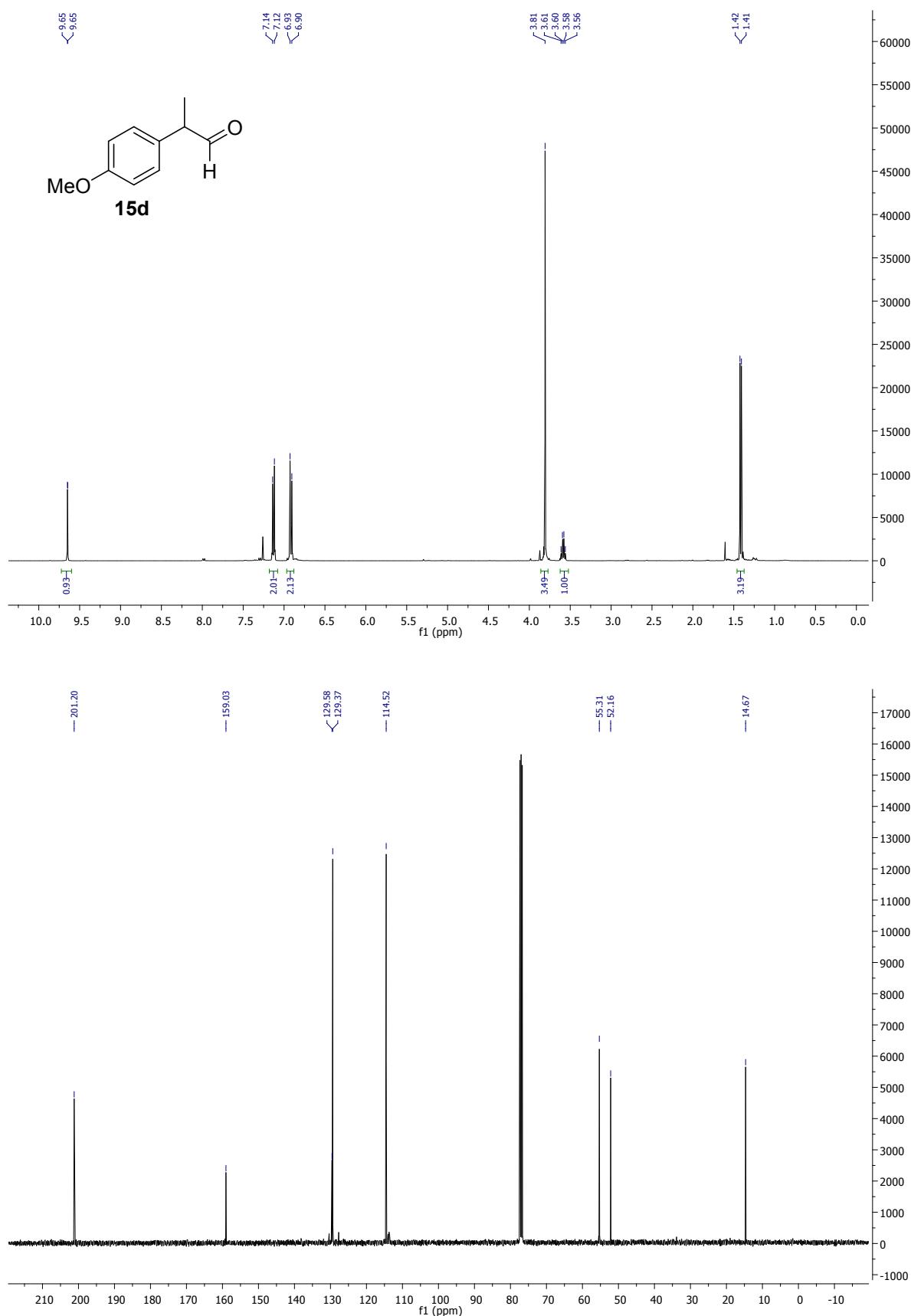
2-(β -Naphtyl)-propionaldehyde **15b**



2-(4-Bromophenyl)-propionaldehyde **15c**



2-(4-Methoxyphenyl)-propionaldehyde **15d**



2-(3,4-di-methoxyphenyl)-propionaldehyde **15e**

