

Simple and efficient process for the large scale preparation of Agomelatine: an antidepressant drug

Satish Kumar Vujjini,[‡] Sunitha Vyala,[‡] Krishna Rao Badarla,[‡] Sreenatha Charyulu Kandala,[‡]
Rakeshwar Bandichhor,[‡] Mukkanti Kagga[§] and Praveen Cherukupalli[‡]

[‡]*API-Research and Development, Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd., Bachupally, Qutubullapur, R R Dist-500090, Telangana, India.*

[§]*Department of Chemistry, Institute of Science and Technology, J.N.T University, Kukatpally, Hyderabad, India*

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E-mail: praveen_cherukupally@yahoo.in

Supporting Information

Table of Contents

	Pages	
1	General Experimental	S-1
2	Experimentation section	S-2 to S-4
3	Appendix – Copies of ¹ H and ¹³ C NMR data	S-4 to S-17

1. General Experimental

Solvents and reagents were obtained from commercial sources and used without further purification. ¹H NMR spectra were recorded in CDCl₃ or DMSO-*d*₆ at room temperature on Varian mercury plus at 400 MHz using TMS as an internal standard. ¹³C NMR spectra were obtained from a Varian mercury plus 400 MHz spectrometer in DMSO-*d*₆ at room temperature. IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT IR spectrometer. The mass spectrum (70 eV) was recorded on an HP 5989 A LC-MS spectrometer. TLC analyses were performed on Merck silica gel 60 F254 plate.

2. Experimentation section

2-acetoxynaphthalene (3): To a stirred mixture of 2-naphthol (100 g, 0.69 mol), acetone (600 mL) and K_2CO_3 (100 g, 0.72 mol), acetic anhydride (100 mL, 0.92 mol) was added at 35 °C. The resulted reaction mixture was heated to 55 °C. After 90 min stirring at 55 °C, reaction mixture was diluted with water (500 mL) and the solvent was distilled under reducing pressure then water (1000 mL) was added. The reaction mixture was cooled to 25 °C and continued stirring for 2 h. The solid was filtered and recrystallized in acetone (100 mL) and water (1500 mL) to afford 2-acetoxynaphthalene **3** with 92% (120 g) yield.

ESI-MS: $m/z = 187.2$ [M+H, 100%]; calcd. for $C_{12}H_{10}O_2$: 186.2; 1H NMR (400 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H), 7.22 (dd, $J = 2.2, 8.7$ Hz, 1H, Ar-H), 7.43-7.50 (m, 2H, Ar-H), 7.55 (d, $J = 2.2$ Hz, 1H, Ar-H), 7.80 (dd, $J = 6.0, 7.9$ Hz, 1H, Ar-H), 7.82-7.86 (m, 2H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 21.2, 76.7, 77.0, 77.4, 118.5, 121.2, 125.7, 126.6, 127.7, 127.8, 129.4, 131.5, 133.8, 148.4, 169.7$; IR ν_{max} cm^{-1} 3487, 3058, 1759, 1511, 1372, 1213, 1152, 1015.

1-chloroacetyl-7-acetoxynaphthalene (4): To the solution of dichloromethane (4 L) at 0 °C, aluminium chloride (1.61 kg, 12.1 mol) was added and then chloroacetyl chloride (0.66 mL, 4.03 mol) was added slowly. The reaction mixture was further cooled to -5 °C and a solution of 2-acetoxynaphthalene (0.5 kg, 2.69 mol) in dichloromethane (1.5 L) was added slowly at -5 °C, after 4h stirring the mixture was quenched slowly by adding the reaction mixture into chilled 2N HCl (5 L) solution. The organic layer was separated and washed with 1% Na_2CO_3 (5 L) solution. The organic layer was distilled under reduced pressure and co-distilled with MeOH (1 L), then MeOH (5 L) was added and heated to reflux. The reaction mixture was cooled to 25 °C and stirred for 2h. The intermediate **4** was isolated by filtration and dried under vacuum at 50 °C to obtain 0.38 kg (55 %).

Anal. Calcd for $C_{14}H_{11}ClO_3$: C, 64.01; H, 4.22; Cl 13.50; O, 18.27. Found: C, 64.03; H, 4.19; Cl 13.51; O, 18.27; ESI-MS: $m/z = 263.4$ (M+H); calcd. for $C_{14}H_{11}ClO_3$: 262.69; 1H NMR (400 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H, CH_3CO), 4.78 (s, 2H, $COCH_2Cl$), 7.35 (dd, $J = 2.28, 8.84$ Hz, 1H, Ar-H), 7.51 (t, $J = 7.32$ Hz, 1H, Ar-H), 7.92 (d, $J = 8.84$ Hz, 1H, Ar-H), 7.95 (dd, $J = 1.12, 7.28$ Hz, 1H, Ar-H), 8.07 (d, $J = 8.28$ Hz, 1H, Ar-H), 8.50 (d, $J = 2.28$ Hz, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 21.1, 47.8, 76.7, 77.0, 77.2, 77.3, 117.3, 12.5, 124.1, 129.5, 130.0, 131.1, 131.5, 132.1, 134.0, 150.8, 169.6, 193.7$; IR ν_{max} cm^{-1} 2954, 1746, 1682, 1578, 1212, 1162, 1014.

1-(2-chloroethyl)-7-hydroxynaphthalene (6): To a solution of 1-chloroacetyl-7-acetoxynaphthalene **4** (0.35 kg, 1.34 mol) and dichloromethane (2.45 L), triethylsilane (715 mL, 4.68 mol) was added and the mixture was cooled to 0 °C, $TiCl_4$ (367 mL, 3.34 mol) was added slowly at 0 °C and the mixture was stirred at same temperature for 90 min. After completion of the reaction as indicated by TLC, the reaction mixture was quenched by adding 1N HCl (3.5 L) below 25 °C and continued stirring for 2h. The organic layer was separated and methanol (1.05 L) and K_2CO_3 (0.19 kg, 1.33 mol) were added and the resulting mixture was stirred for 3 h at 35 °C. After completion of the reaction as indicated by TLC, pH of the reaction mixture adjusted to

3.0 with 1N HCl (2.0 L). Organic layer was separated and distilled under reduced pressure to obtain as oily residue. n-hexane (1.75 L) was added to the reaction mixture and cooled the mixture to 0 °C. After 2h stirring at 0 °C, the solid was filtered and dried at 35 °C under vacuum to afford intermediate **6** in 80% (0.22 kg) yield.

Anal. Calcd for C₁₂H₁₂ClO: C, 69.74; H, 5.37; Cl 17.15; O, 7.74. Found: C, 69.71; H, 5.35; Cl 17.14; O, 7.74.; ESI-MS: m/z = 208 (M+H); calcd. for C₁₂H₁₂ClO: 206.67; ¹H NMR (400 MHz, CDCl₃): δ = 3.38 (t, *J* = 3.6 Hz, 2H, CH₂CH₂Cl), 3.75 (t, *J* = 7.48 Hz, 2H, CH₂CH₂Cl), 5.68 (s, 1H, OH), 7.10 (dd, *J* = 2.44, 8.80 Hz, 1H, Ar-H), 7.22-7.32 (m, 3H, Ar-H), 7.68 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.76 (d, *J* = 8.80 Hz, 1H, Ar-H); ¹³C NMR (400 MHz, CDCl₃): δ = 36.6, 44.0, 76.8, 77.1, 77.4, 105.6, 117.6, 123.3, 127.6, 127.8, 129.3, 131.0, 132.4, 133.0, 153.8; IR ν_{max} cm⁻¹ 3309, 3044, 1729, 1626, 1600, 1518, 1209, 1070.

7-methoxy-1-vinylnaphthalene (13): To a stirred mixture of 1-(2-chloroethyl)-7-methoxynaphthalene (5 g, 0.022 mol) and methanol (25 mL) added sodium methoxide (1.22 g 0.022 mol). The reaction mixture was heated to 55 °C and stirred for 1h, then solvent was removed under reduced pressure to obtain oily residue. The oily residue was diluted with ethyl acetate (25 mL) and washed with 2N HCl (25 mL). Then organic layer was concentrated under reduced pressure to obtain white solid¹ (3.8g, 90 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 3.91 (s, 3H, OCH₃), 5.49 (dd, *J* = 1.60, 10.92 Hz, 1H, CH=CH_aH_b), 5.87 (dd, *J* = 1.60, 17.24 Hz, 1H, CH=CH_aH_b), 7.21 (dd, *J* = 2.48, 8.92 Hz, 1H, Ar-H), 7.37 (t, *J* = 7.84 Hz, 1 H, Ar-H), 7.45 (d, *J* = 2.44 Hz, 1H, Ar-H), 7.59 (q, *J* = 10.96 Hz, 1H, Ar-H), 7.67 (d, *J* = 7.12 Hz, 1H, Ar-H), 7.81 (d, *J* = 8.12 Hz, 1H, Ar-H), 7.86 (d, *J* = 8.96 Hz, 1H, Ar-H); ¹³C NMR (400 MHz, DMSO-*d*₆) δ = 39.3, 39.6, 39.8, 40.0, 40.2, 40.4, 40.6, 55.7, 102.6, 117.2, 118.8, 123.8, 124.2, 128.3, 129.2, 130.5, 132.2, 134.0, 134.6, 158.0; IR ν_{max} cm⁻¹ 3082, 3004, 1680, 1623, 1257, 1215, 1029.

2-(7-methoxy-1-naphthyl)ethyl formate (14): Filtrate of **10** was concentrated under reduced pressure then eluted through silica packed column with n-hexane. The required fraction was concentrated to obtain colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 3.35 (s, 3H, OCH₃), 4.43 (t, *J* = 6.3 Hz, 2H, CH₂CHO), 7.20 (dd, *J* = 2.44, 8.92 Hz, 1H, Ar-H), 7.27-7.31 (m, 1 H, Ar-H), 7.39 (d, *J* = 6.3 Hz, 1H, Ar-H), 7.44 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.75 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.86 (d, *J* = 8.9 Hz, 1H, Ar-H), 8.24 (s, 1H, CHO); ¹³C NMR (400 MHz, DMSO-*d*₆) δ = 32.1, 39.4, 39.6, 40.0, 40.2, 40.1, 40.6, 55.7, 63.8, 102.8, 118.5, 123.6, 127.4, 128.0, 129.3, 130.7, 132.7, 133.3, 158.0, 152.7; IR ν_{max} cm⁻¹ 3423, 2958, 1721, 1627, 1512, 1479, 1257, 1213, 1167, 1032. ESI-MS: m/z = 245.29 [M+H, 100%]; calcd. for C₁₅H₁₆O₃: 244.29

2-(7-methoxy-1-naphthyl)ethanol (15): To a stirred mixture of **14** (1 g, 0.004 mol) and methanol (5 mL) potassium carbonate (0.59 g, 0.004 mol) was added, and continued the stirring

for 1h at 25 °C. Then reaction mixture was concentrated under reduced pressure and diluted with water (5 mL). Then extracted with ethyl acetate (2 x 5 mL), the combined organic extracts were concentrated under reduced pressure to obtain crude residue. n-Hexane (5 mL) was added to the crude and stirred for 30 min. Product was isolated by filtration to afford **15**² (98.0%) in 0.92 g. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 3.18 (t, *J* = 7.2 MHz, 2H, CH₂CH₂OH), 3.73 (q, *J* = 5.7 MHz, 2H, CH₂CH₂OH), 4.77 (t, *J* = 5.4 MHz, 1H, OH), 7.17 (dd, *J* = 2.5, 8.9 MHz, 1H, Ar-H), 7.20-7.28 (m, 1H, Ar-H), 7.33-7.37 (m, 2H, Ar-H), 7.71 (d, *J* = 8.0 Hz, 1H, Ar-H) 7.83 (d, *J* = 8.9 Hz, 1H, Ar-H); ¹³C NMR (400 MHz, DMSO-*d*₆) δ = 36.6, 39.1, 39.3, 39.5, 39.7, 39.9, 40.2, 40.4, 55.6, 61.8, 103.0, 118.2, 123.6, 126.7, 127.7, 129.2, 130.6, 133.4, 134.5, 157.7; IR ν_{max} cm⁻¹ 3271, 2879, 2830, 1667, 1626, 1508, 1473, 1249, 1213, 1042, 1017.

N-[2-(7-hydroxy-naphthyl)ethyl]acetamide (16): To a stirred mixture of **10** (2 g) and methanol (10 mL), HCl (10 mL) was added and stirred at 75 °C for 12 h, then the mixture was concentrated to obtain suspension. The suspension was dissolved in water (24 mL) and ethyl acetate (10 mL). K₂CO₃ solution (10 g of K₂CO₃ in 20 mL water), acetic anhydride (0.9 mL) were charged to the reaction mixture stirred for 30 min at 30 °C. Organic layer was separated, then concentrated to obtain crude residue. The crude was crystallized in toluene (3 mL) to afford 1.6 g (85 %) of **16**. Anal. Calcd for C₁₄H₁₅NO₂: C, 73.34; H, 6.59; N 6.11; O, 13.96. Found: C, 73.37; H, 6.55; N 6.10; O, 13.92. ¹H NMR (400 MHz, DMSO-*d*₆) 1.82 (s, 3H, NHCOCH₃) 3.05 (t, 2H, CH₂CH₂), 3.34 (t, 2H, CH₂CH₂NHAc), 7.08 (dd, *J* = 2.28, 8.8 Hz, 1H, Ar-H), 7.19 (t, *J* = 8.0 Hz, 1 H, Ar-H), 7.24 (d, *J* = 6.0, 1H, Ar-H), 7.32 (d, *J* = 2.16 Hz, 1H, Ar-H), 7.64 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.75 (d, *J* = 8.88 Hz, 1H, Ar-H), 8.13 (t, *J* = 5.40 Hz, 1H, NHAc), 10.0 (br s, 1H, COH); ¹³C NMR (400 MHz, DMSO-*d*₆) δ = 22.9, 32.8, 38.8, 39.0, 39.2, 39.4, 39.6, 39.8, 40.1, 105.6, 118.5, 122.9, 127.1, 128.5, 130.7, 133.5, 133.7, 155.7, 170.7; IR ν_{max} cm⁻¹ 3348, 3102, 1639, 1598, 1574, 1465, 1251, 1215, 1033.

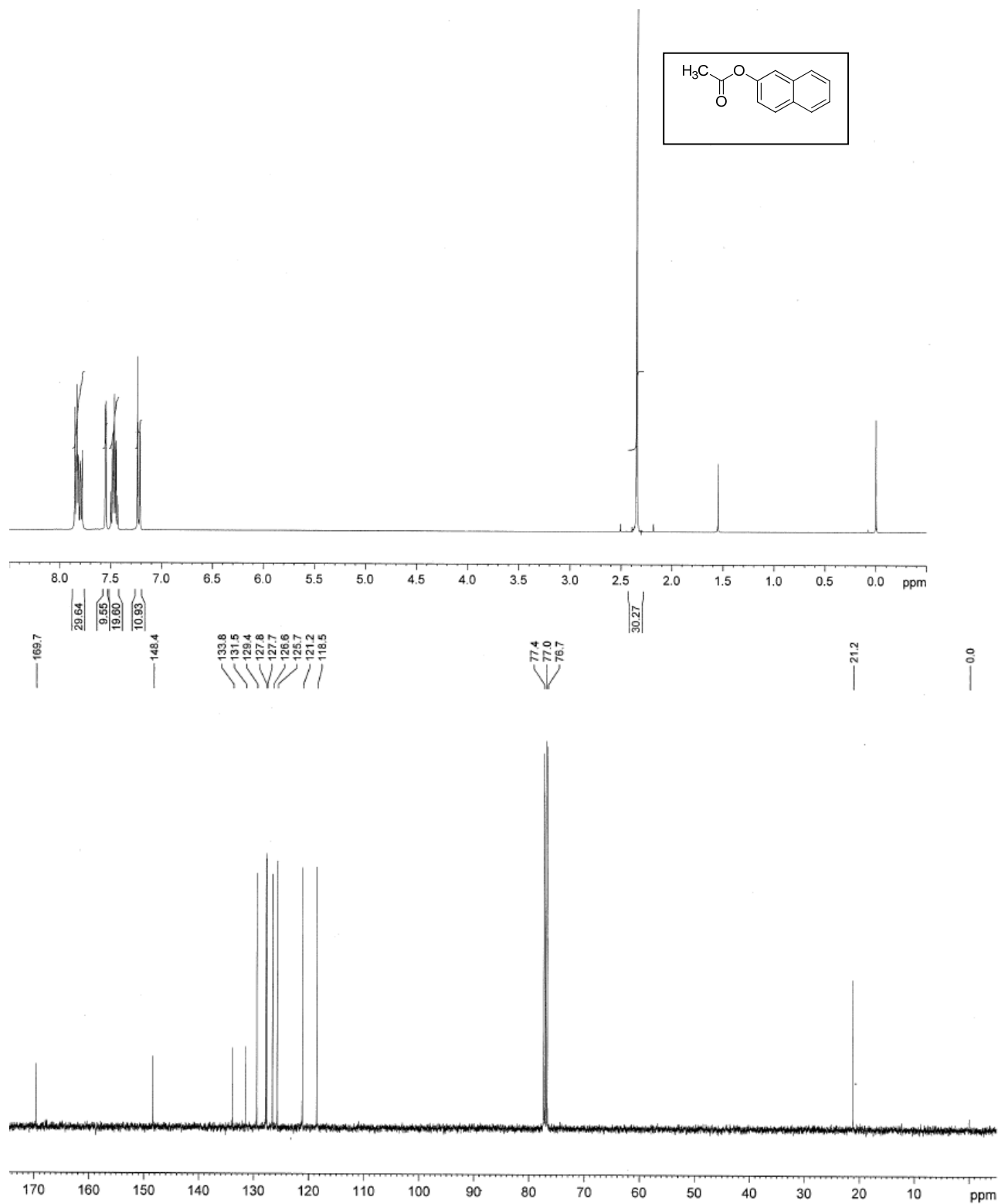
Sodiumdiformylamide (12): To a stirred mixture of sodium methoxide (0.2 kg, 3.7 mol) and DMF (1.0 L), formamide (0.35 L, 7.8 mol) was added below 50 °C. The mixture was heated to 100 °C and collected the by-product methanol as distillate. Then solvent (~0.3 L) was distilled out from the reaction mixture under reduced pressure, and then reaction mixture was cooled to 30 °C. The solid was filtered and washed with DMF (0.2 L), and dried at 75 °C under vacuum to obtain **12** (0.3 kg, 85%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.96 (s, 2H, COCH); ¹³C NMR (400 MHz, DMSO-*d*₆): δ 180.6

REFERENCES

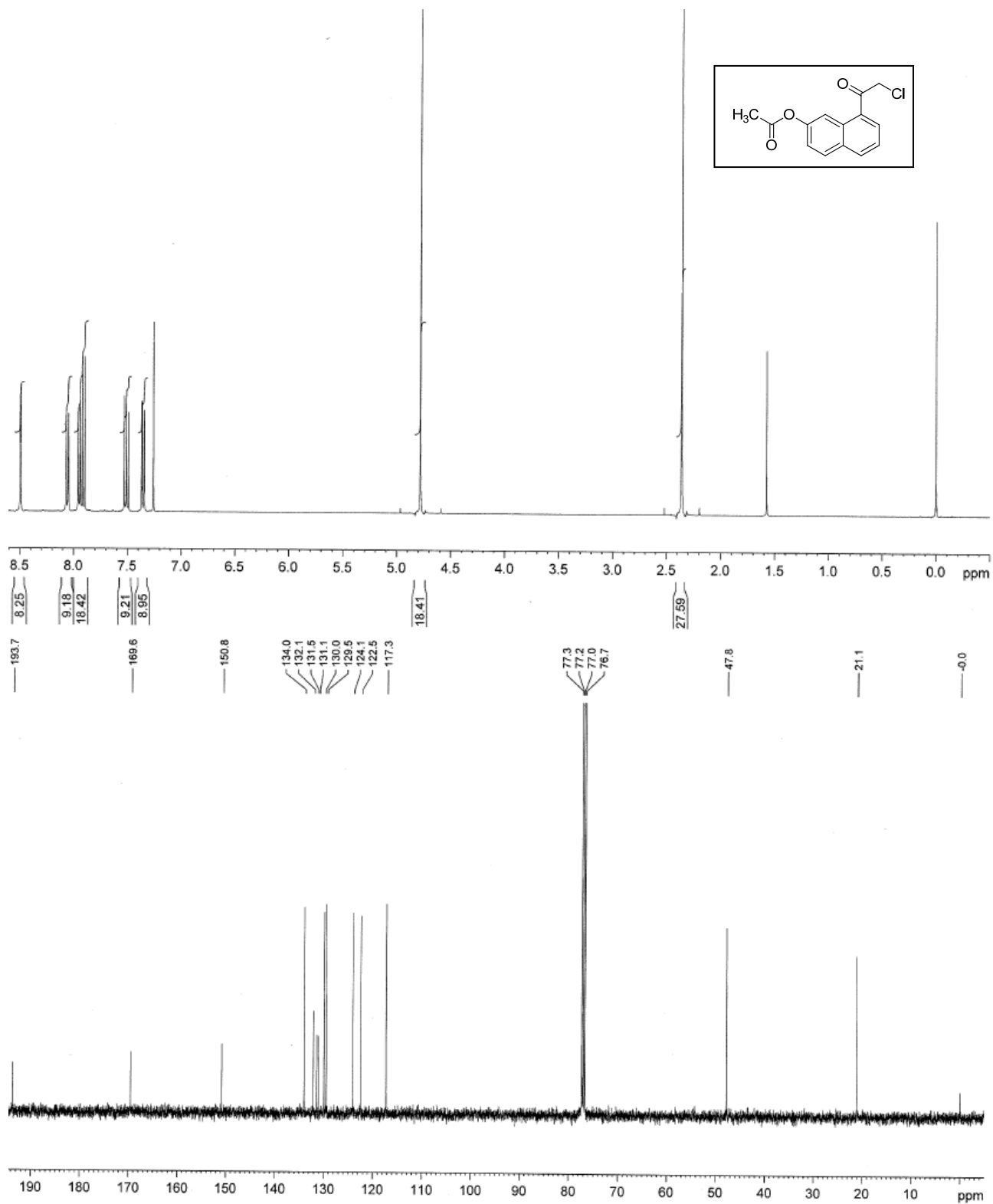
- 1) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1985**, *52*, 422-424.
- 2) Silverman, R.; Daub, G. H.; David, L.; Jagt, D. L. V. *J. Org. Chem.* **1985**, *50*, 5550-5556.
- 3) Volante, R. P. *J. Org. Chem.* **2004**, *69*, 8723-8730.

3. Appendix – Copies of ^1H and ^{13}C NMR data

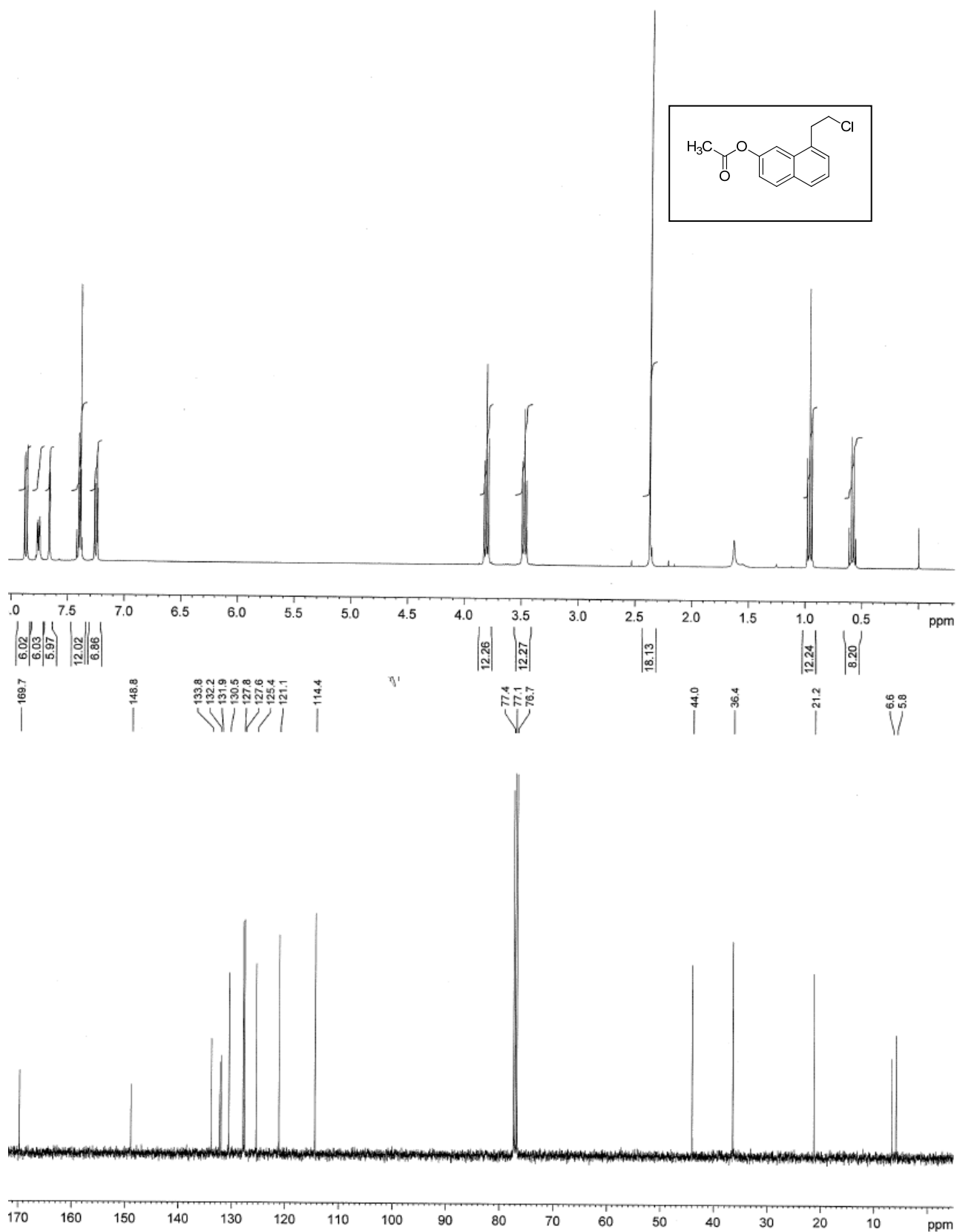
^1H NMR and ^{13}C NMR of 7-acetoxynaphthalene (**3**)



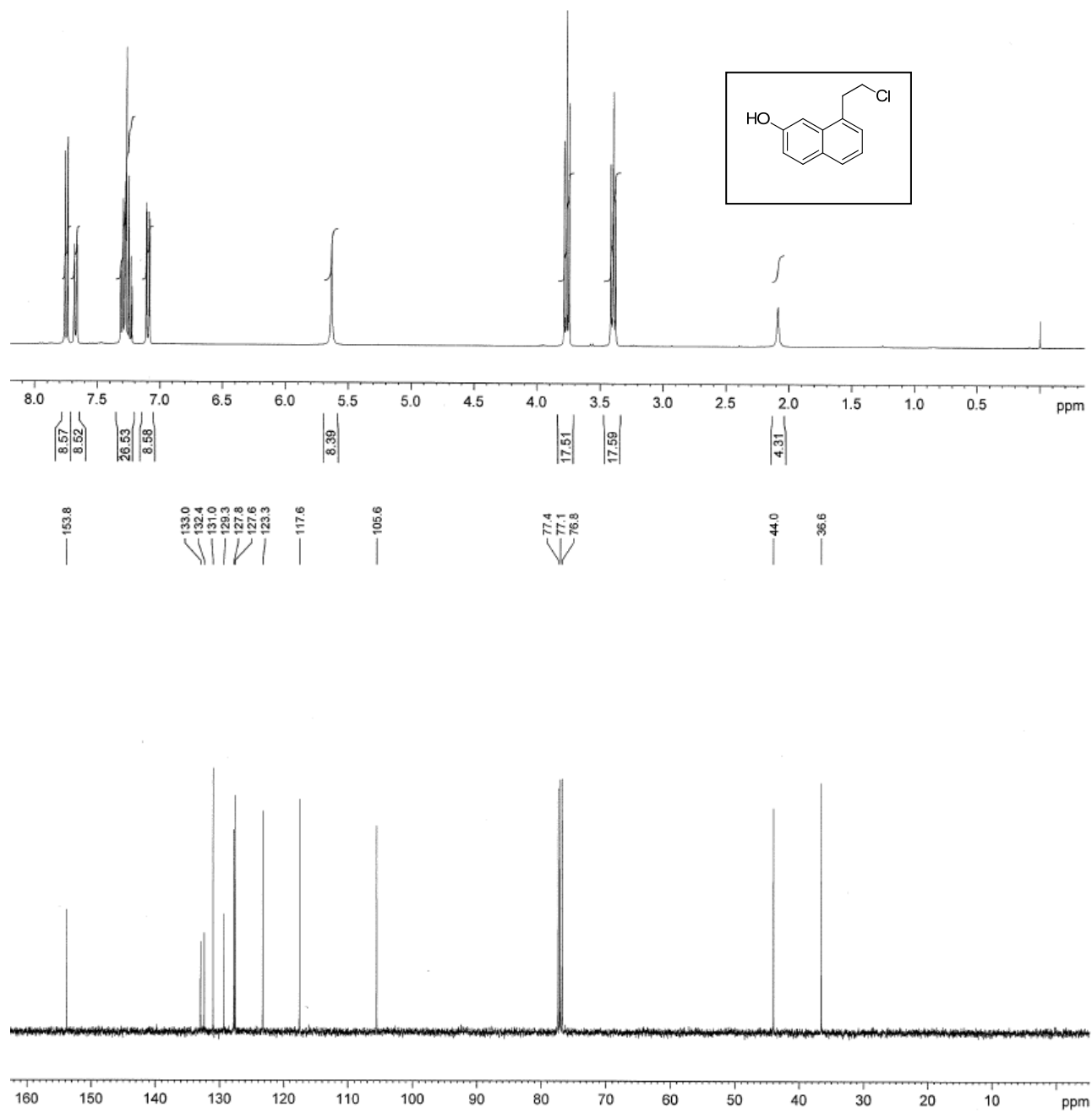
^1H NMR and ^{13}C NMR of 1-chloroacetyl-7-acetoxynaphthalene (**4**)



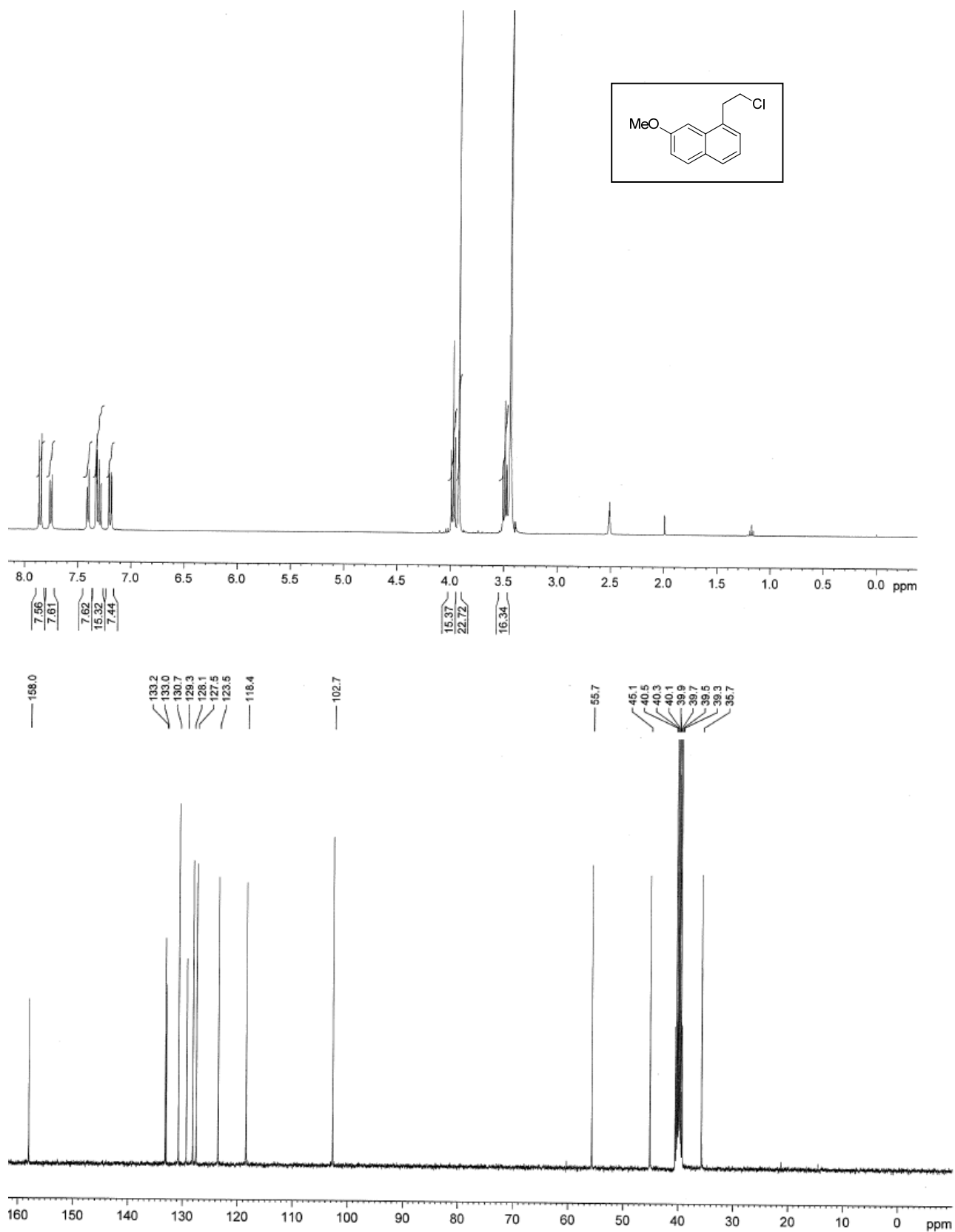
^1H NMR and ^{13}C NMR of 8-(2-chloroethyl)naphthalen-2-yl acetate (**5**)



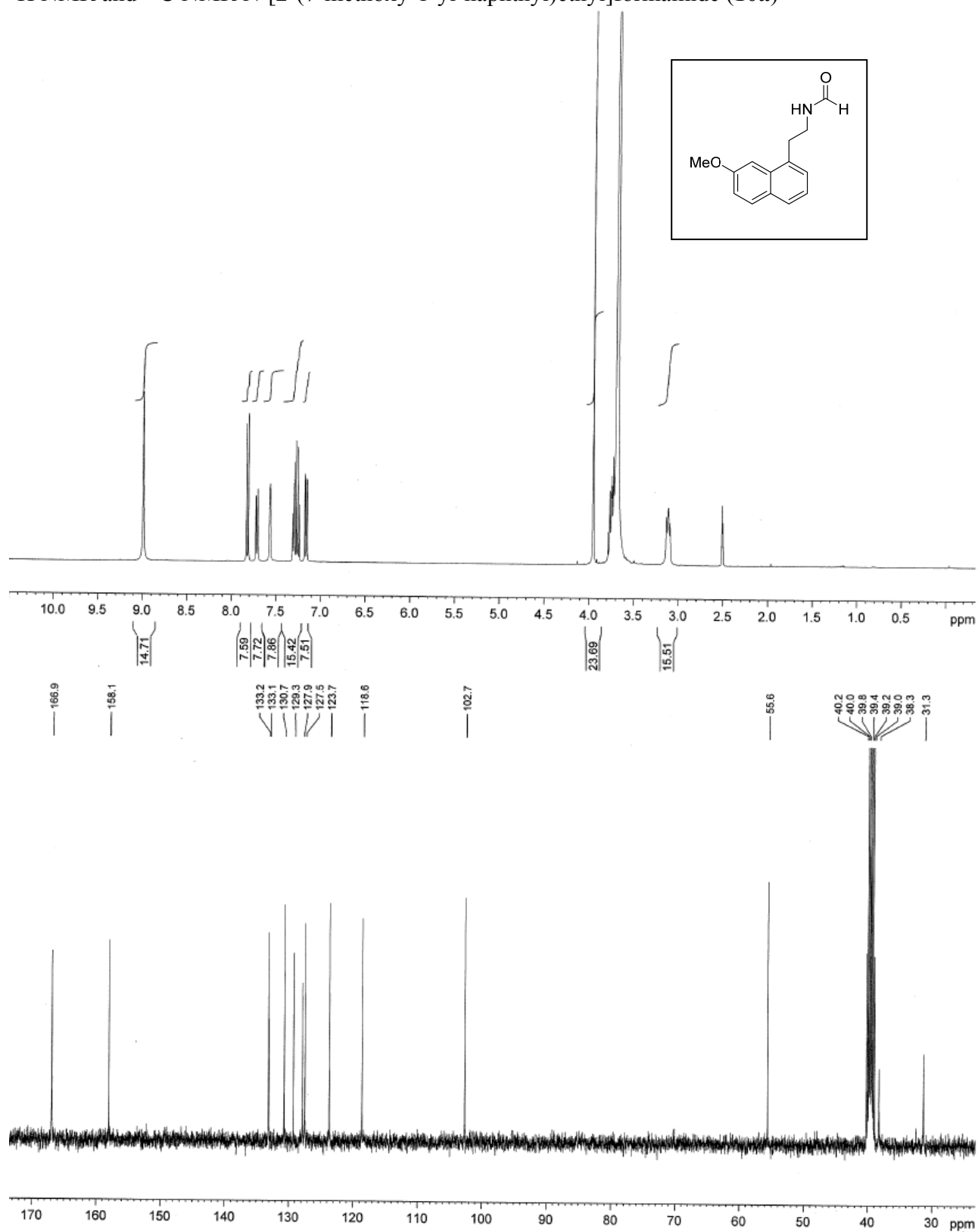
^1H NMR and ^{13}C NMR of 1-(2-chloroethyl)-7-hydroxynaphthalene (**6**)



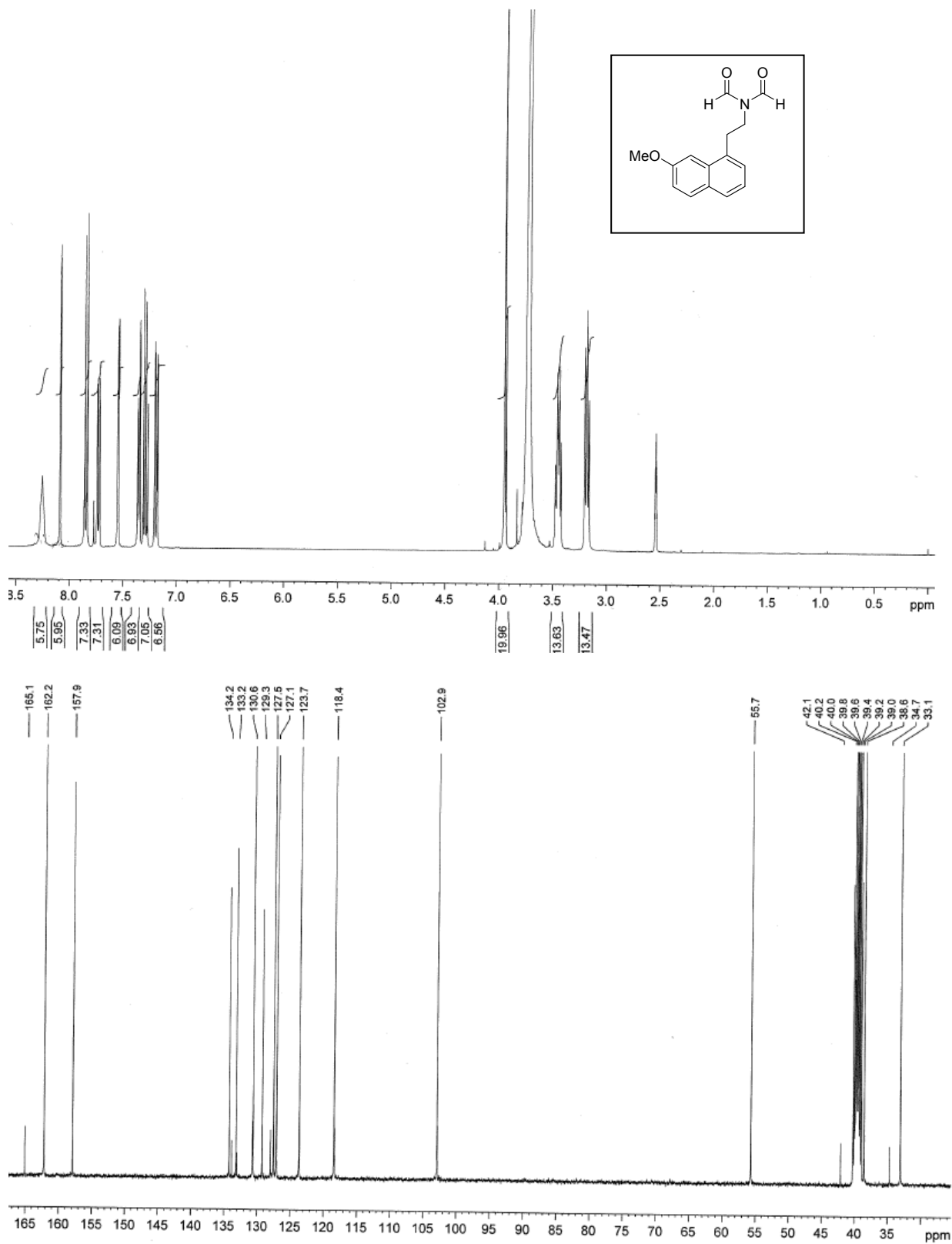
^1H NMR and ^{13}C NMR of 1-(2-chloroethyl)-7-methoxynaphthalene (**9**)



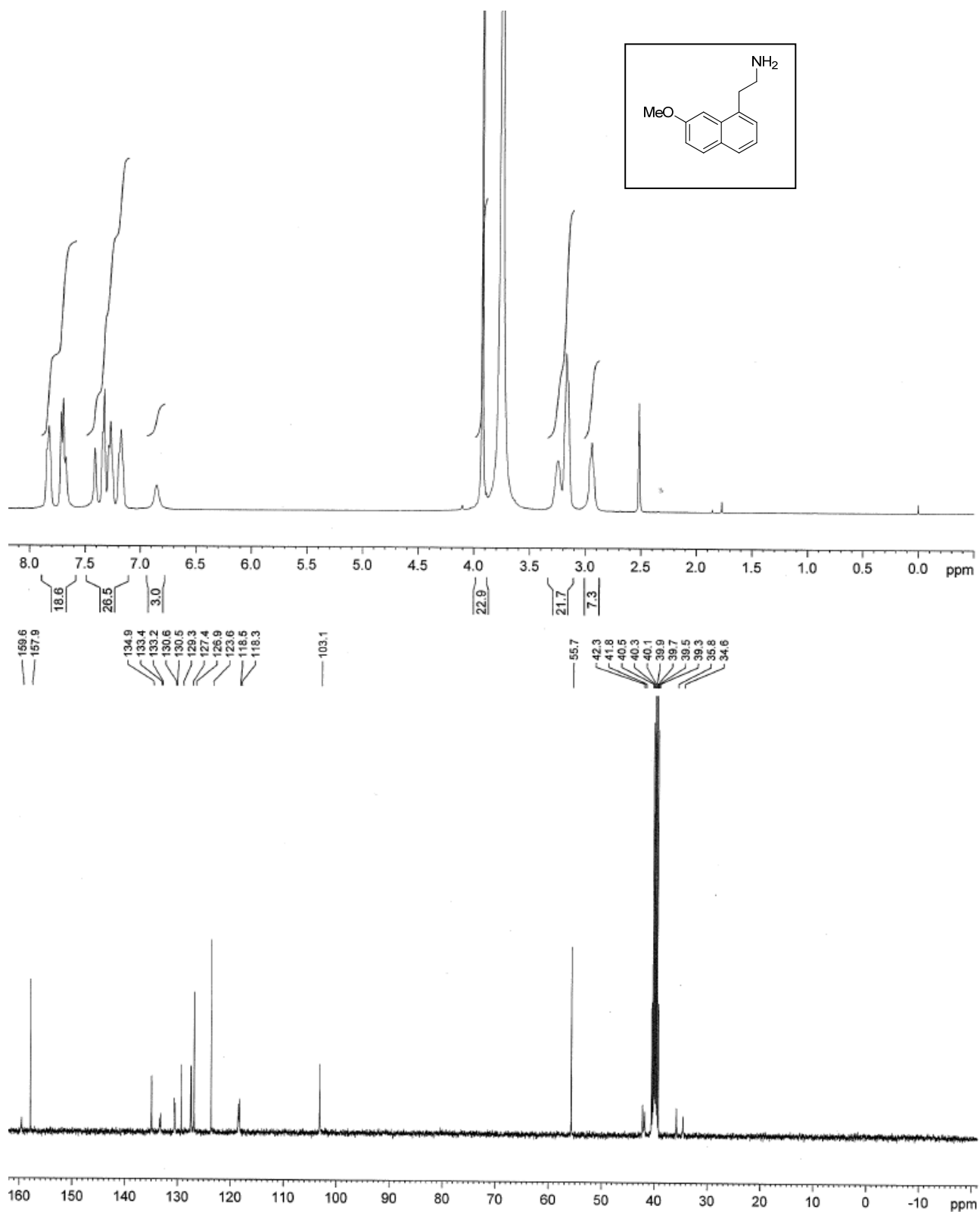
^1H NMR and ^{13}C NMR N-[2-(7-methoxy-1-yl-naphthyl)ethyl]formamide (**10a**)



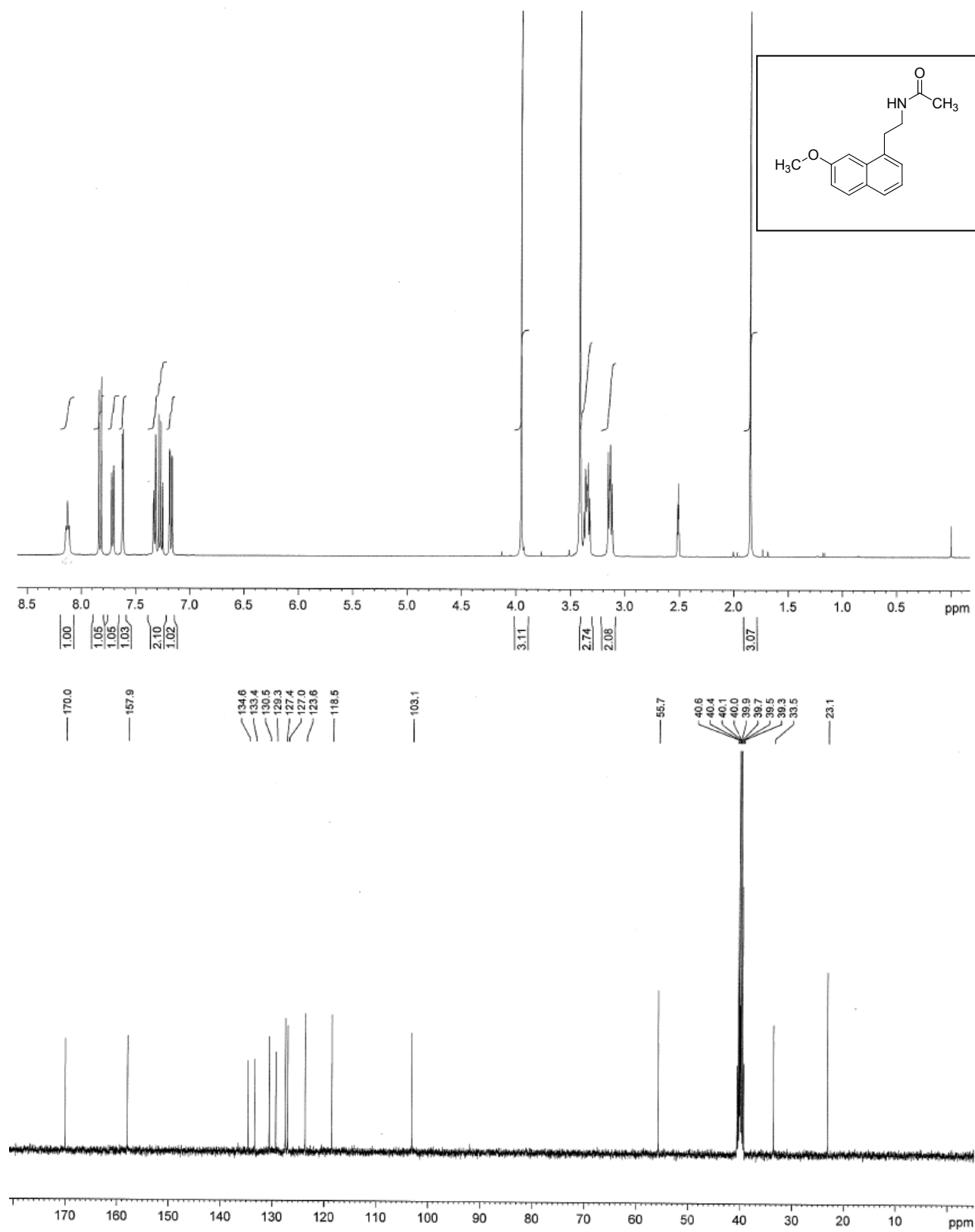
^1H NMR and ^{13}C NMR of 1-(N,N-diformylaminoethyl)-7-methoxynaphthalene (**10b**)



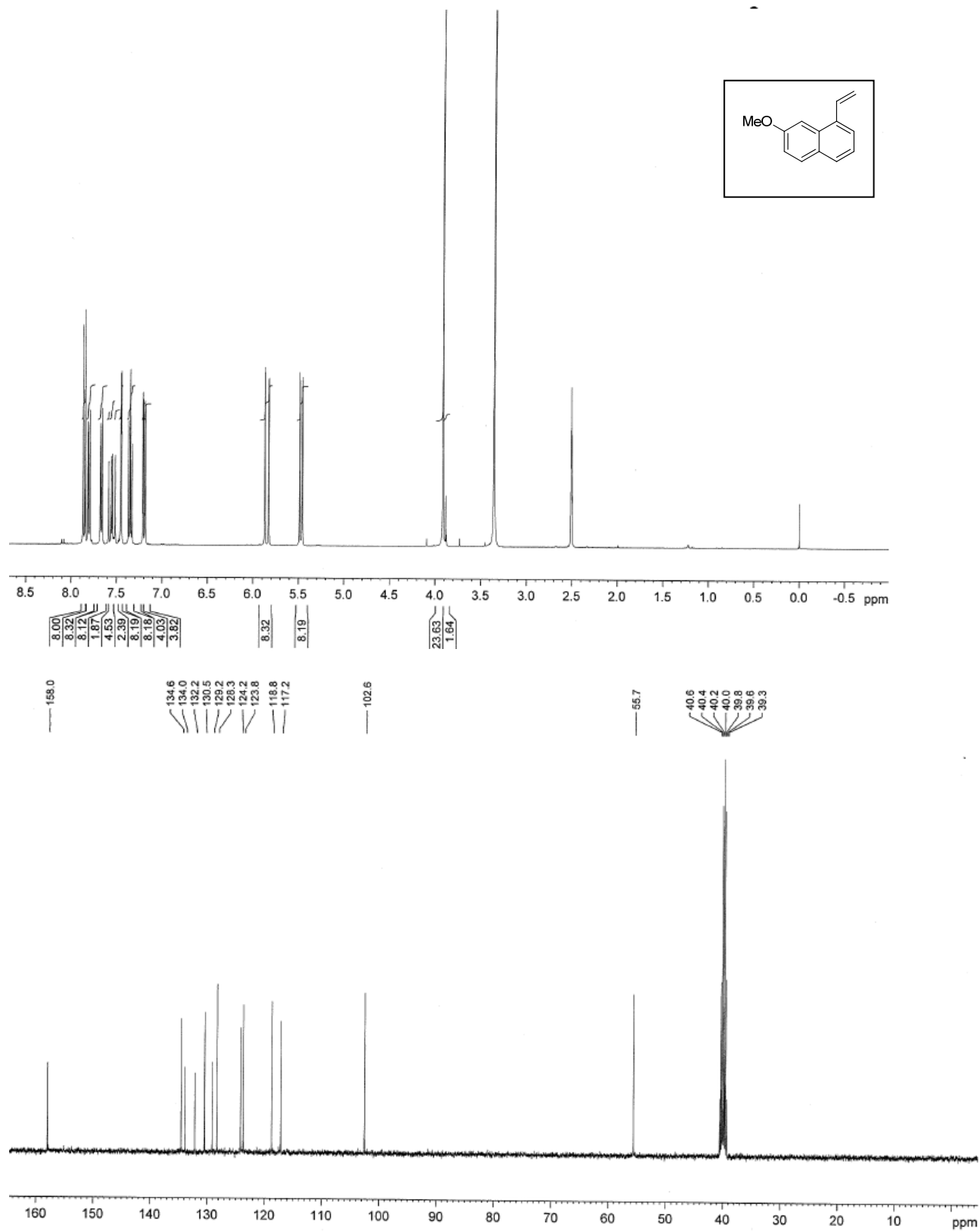
^1H NMR and ^{13}C NMR of 2-(6-methoxy-1-naphthyl)ethanamine (**11** free base)



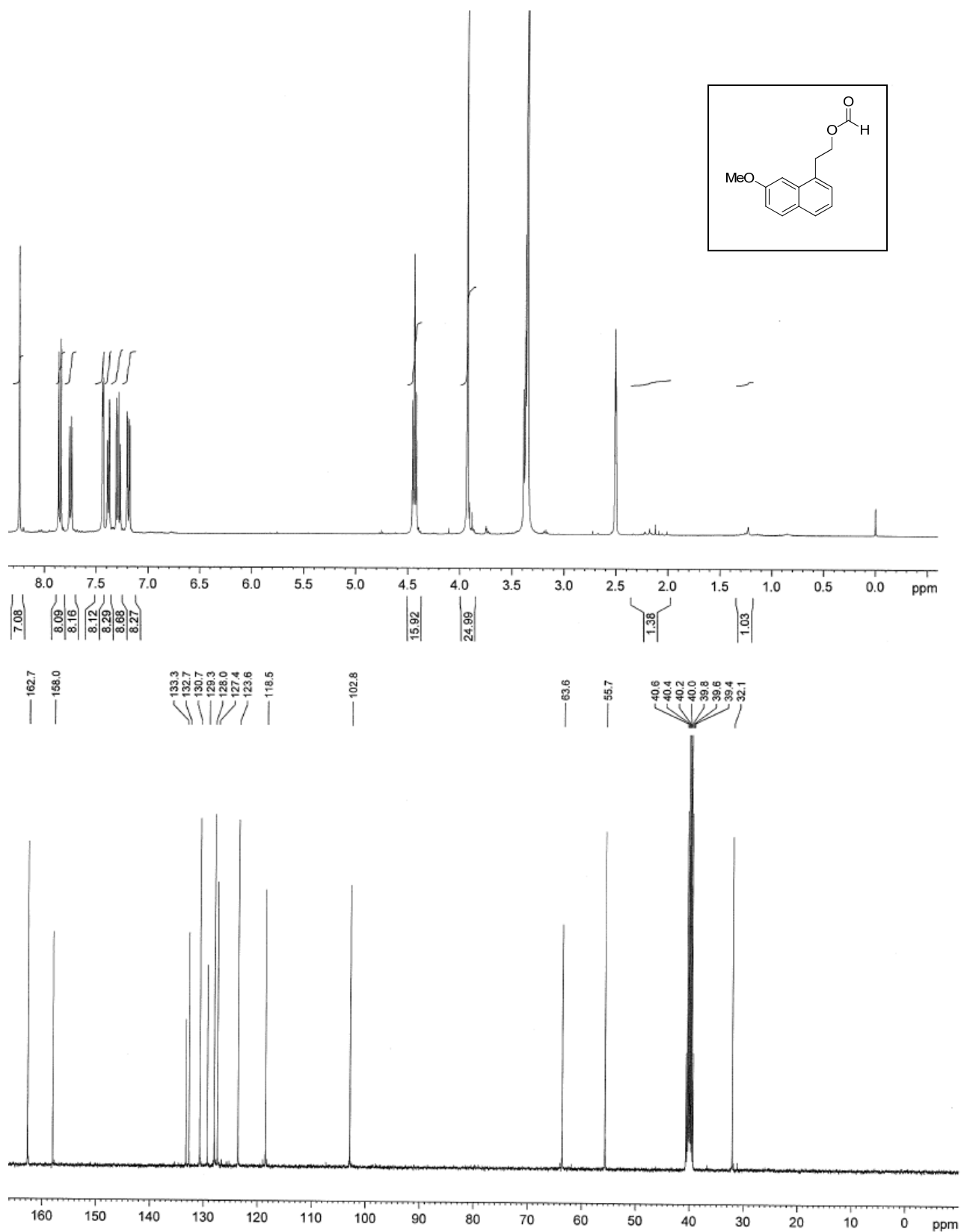
^1H NMR and ^{13}C NMR of N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide (**1**)



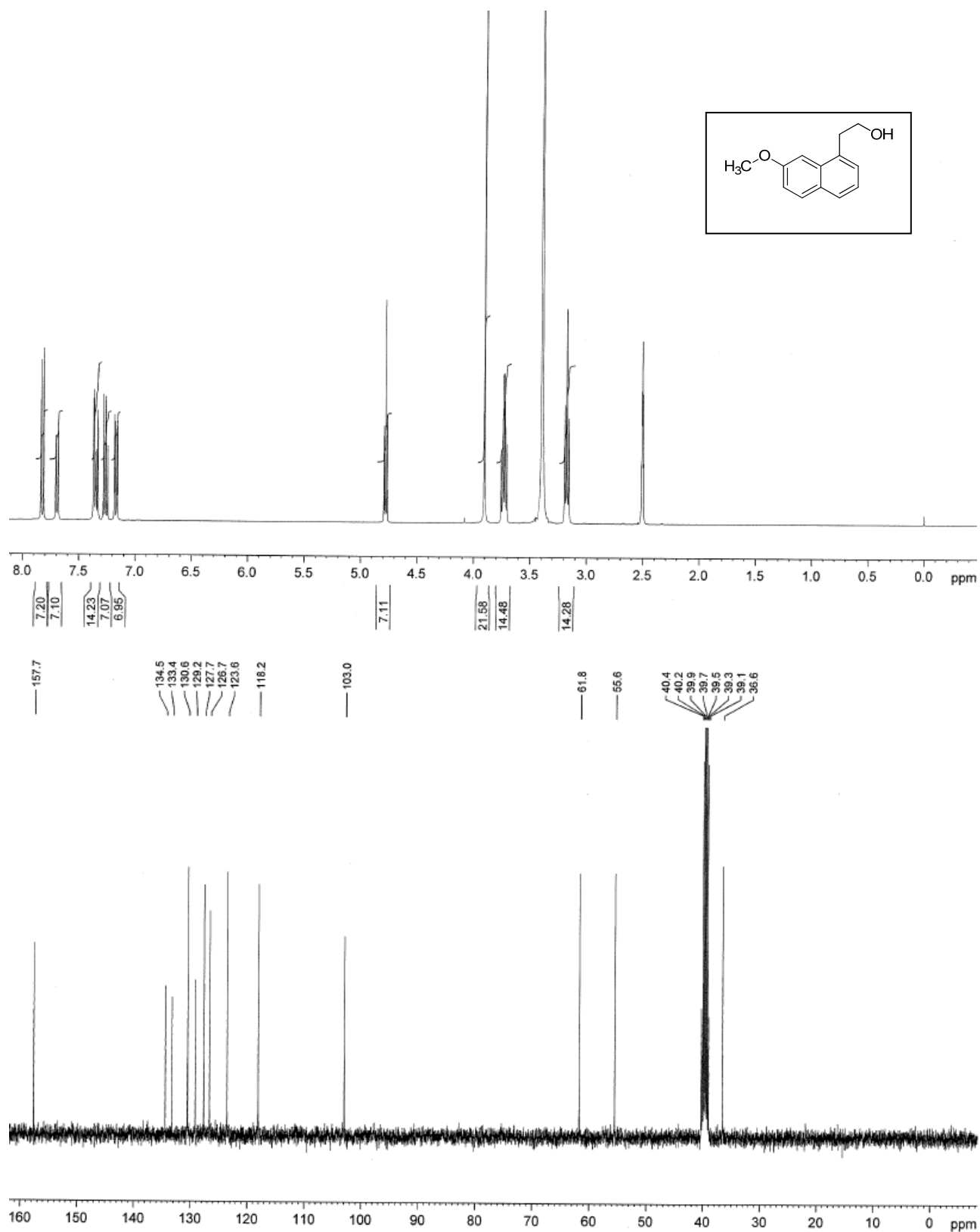
^1H NMR and ^{13}C NMR of 7-methoxy-1-vinylnaphthalene (**13**)



^1H NMR and ^{13}C NMR of 2-(7-methoxy-1-naphthyl)ethyl formate (**14**)



^1H NMR and ^{13}C NMR of 2-(7-methoxy-1-naphthyl)ethanol (**15**)



^1H NMR and ^{13}C NMR of N-[2-(7-hydroxy-naphthyl)ethyl]acetamide (**16**)

