

Cross-Couplings Between Benzyl and Aryl Halides “On Water.”

Synthesis of Diarymethanes

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Instrumentation and Chemicals

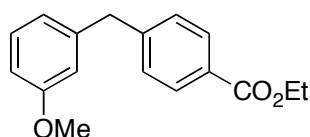
General. Reactions were performed in a 10 mL round bottom flask under an argon atmosphere containing a Teflon coated stir bar and septum. All commercially available reagents were used without further purification. Water was degassed with argon. Zinc powder 99.9% (-325 mesh) and zinc dust 97.5% (-325 mesh) were purchased from Strem Chemicals (catalog #93-3060 and #93-3056) and was stored in the glove box. PdCl₂(Amphos)₂ (CAS #887919-35-9) was obtained from Johnson Matthey (Pd-132, catalog #C4138). Column chromatography was performed using Silicycle Silia-P 60 Å flash silica gel. GC analyses were recorded on a Hewlett-Packard HP 6890 chromatograph equipped with a capillary column HP-1 (30 m × 0.25 mm × 0.25 μm). ¹H and ¹³C NMR spectra were measured on a Varian Inova-400 (400 and 100 MHz, respectively) spectrometer at ambient temperature. Proton NMR data were recorded as follows: chemical shift in ppm referenced from residual solvent peak (CDCl₃, 7.26 ppm), multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), and integration. ¹³C Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (CDCl₃, 77.00 ppm). Mass spectral data were acquired on either a VF Autospec or an analytical VG-70-250 HF instrument.

Experimental Procedures and Characterization Data

General procedure for cross-coupling reactions of benzyl halides with aryl bromides.

In a 10 mL round-bottom flask under argon containing zinc (390 mg, 6 mmol) and PdCl₂(Amphos)₂ (7 mg, 0.01 mmol) was added degassed water (5 mL). *N,N,N',N'*-Tetramethylethylenediamine (TMEDA, 58 mg, 0.5 mmol) was added at rt followed by the addition of the benzylic halide (4-5 mmol) and the aryl bromide (2 mmol). The flask was stirred vigorously at rt for 8 h. The reaction mixture was then filtered through a pad of silica (10 g) and washed with diethyl ether (70 mL) into a 100 mL flask containing 2 g of silica. Solvents were removed under vacuum. The resulting dry, crude silica was introduced on top of a silica gel chromatographic column to purify the product.

Ethyl 4-(3-methoxybenzyl)benzoate (1)



From zinc *dust* (390 mg, 6 mmol), 3-methoxybenzyl chloride (624 mg, 4 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (518 mg) was obtained in 96% yield.

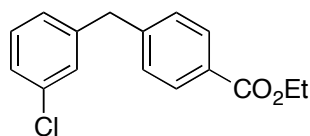
From zinc *powder* (390 mg, 6 mmol), 3-methoxybenzyl chloride (624 mg, 4 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (514 mg) was obtained in 95% yield.

¹H NMR (400 MHz): δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.71 (s, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.00 (s, 2H), 3.76 (s, 1H), 1.38 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (100 MHz): δ 166.1, 160.0, 146.4, 141.9, 130.0, 129.7, 129.1, 128.7, 121.5, 115.0, 111.7, 61.0, 55.3, 42.1, 14.5.

HRMS (C₁₇H₁₈O₃) calcd 270.1255, found 270.1265.

Ethyl 4-(3-chlorobenzyl)benzoate (2)



From zinc dust (390 mg, 6 mmol), 3-chlorobenzyl chloride (640 mg, 4 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (504 mg) was obtained in 92% yield.

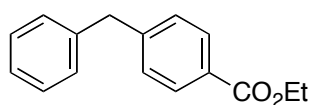
From zinc powder (390 mg, 6 mmol), 3-chlorobenzyl chloride (640 mg, 4 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (526 mg) was obtained in 96% yield.

^1H NMR (400 MHz): δ 7.97 (d, J = 8.3 Hz, 2H), 7.26-7.15 (m, 5H), 7.05 (d, J = 7 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.00 (s, 2H), 3.76 (s, 1H), 1.38 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz): δ 166.7, 145.5, 142.4, 134.6, 130.1, 130.0, 129.2, 129.1, 128.9, 127.3, 126.8, 61.0, 41.7, 14.5.

HRMS ($\text{C}_{16}\text{H}_{15}\text{ClO}$) calcd. 274.0760, found 206.0762.

Ethyl 4-benzylbenzoate (3) [CAS: 18908-74-2]



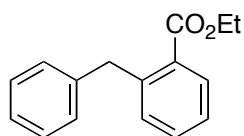
From zinc dust (390 mg, 6 mmol), benzyl bromide (845 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (450 mg) was obtained in 94% yield.

From zinc dust (390 mg, 6 mmol), benzyl chloride (504 mg, 4 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (460 mg) was obtained in 96% yield.

HRMS ($\text{C}_{16}\text{H}_{16}\text{O}_2$) calcd. 240.1105, found 240.1159.

The corresponding spectroscopic data matched those reported in the literature for ethyl 4-benzylbenzoate.¹

Ethyl 2-benzylbenzoate (4) [CAS: 1585-99-5]

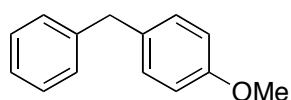


From zinc dust (390 mg, 6 mmol), benzyl chloride (630 mg, 5 mmol) and ethyl 2-bromobenzoate (458 mg, 2 mmol), the product (441 mg) was obtained in 92% yield.

HRMS ($\text{C}_{16}\text{H}_{16}\text{O}_2$) calcd. 240.1150, found 240.1159.

The corresponding spectroscopic data matched those reported in the literature for ethyl 2-benzylbenzoate.¹

4-Methoxydiphenylmethane (5) [CAS: 834-14-0]

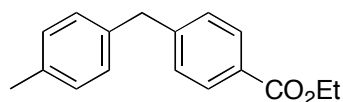


From zinc dust (390 mg, 6 mmol), benzyl chloride (504 mg, 4 mmol) and 4-bromoanisole (372 mg, 2 mmol), the product (388 mg) was obtained in 92% yield.

HRMS ($\text{C}_{14}\text{H}_{14}\text{O}$) calcd. 198.1044, found 198.1048.

The corresponding spectroscopic data matched those reported in the literature for 4-methoxydiphenylmethane.¹

Ethyl 4-(4-methylbenzyl)benzoate (6)



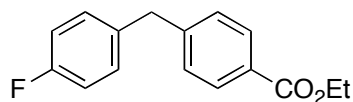
From zinc dust (390 mg, 6 mmol), 4-methylbenzyl bromide (915 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (355 mg) was obtained in 70% yield.

From zinc dust (390 mg, 6 mmol), 4-methylbenzyl chloride (700 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (482 mg) was obtained in 95% yield.

HRMS ($C_{17}H_{18}O_2$) calcd. 254.1306, found 254.1303.

The corresponding spectroscopic data matched those reported in the literature for ethyl 4-(4-methylbenzyl)benzoate.²

Ethyl 4-(4-fluorobenzyl)benzoate (7)



From zinc powder (390 mg, 6 mmol), 4-fluorobenzyl bromide (935 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (294 mg) was obtained in 57% yield.

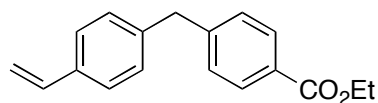
From zinc powder (390 mg, 6 mmol), 4-fluorobenzyl chloride (720 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (495 mg) was obtained in 96% yield.

1H NMR (400 MHz): δ 7.97 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.13-7.10 (m, 2H), 6.99-6.95 (m, 2H), 4.37 (q, J = 7.2 Hz, 2H), 4.00 (s, 2H), 1.38 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz): δ 166.7, 162.7, 160.7, 146.3, 136.0, 130.5, 130.0, 129.0, 128.8, 115.5, 61.0, 41.2, 14.5.

HRMS ($C_{16}H_{15}FO_2$) calcd. 258.1056, found 258.1053.

Ethyl 4-(4-vinylbenzyl)benzoate (8)



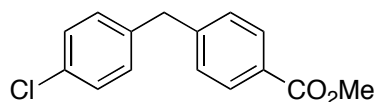
From zinc dust (390 mg, 6 mmol), 4-vinylbenzyl chloride (760 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (393 mg) was obtained in 74% yield.

1H NMR (400 MHz): δ 7.97 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 6.66 (dd, J = 17.5 Hz, J = 10.9 Hz, 1H), 5.69 (d, J = 17.5 Hz, 1H), 5.20 (d, J = 10.9 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.00 (s, 2H), 1.38 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz): δ 166.8, 146.4, 140.0, 136.6, 136.0, 130.0, 129.3, 129.0, 126.6, 113.7, 61.0, 41.8, 14.5.

HRMS ($C_{18}H_{18}O_2$) calcd. 266.1306, found 266.1306.

Methyl 4-(4-chlorobenzyl)benzoate (9)



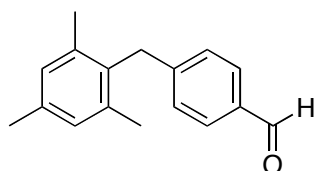
From zinc powder (390 mg, 6 mmol), methyl 4-(chloromethyl)benzoate (990 mg, 5 mmol) and 1-bromo-4-chlorobenzene (382 mg, 2 mmol), the product (433 mg) was obtained in 79% yield.

^1H NMR (400 MHz): δ 7.97 (d, J = 8.2 Hz, 2H), 7.27-7.25 (m, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 4.00 (s, 2H), 3.90 (s, 3H).

^{13}C NMR (100 MHz): δ 167.7, 146.1, 138.8, 132.4, 130.5, 130.1, 129.1, 128.9, 128.5, 52.2, 41.4.

HRMS ($\text{C}_{16}\text{H}_{15}\text{ClO}_2$) calcd. 274.0760, found 274.0762.

4-(2,4,6-trimethylbenzyl)benzaldehyde (10)



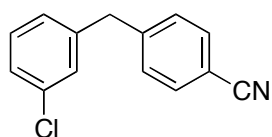
From zinc dust (390 mg, 6 mmol), 2,4,6-trimethylbenzylchloride (840 mg, 5 mmol) and 4-bromobenzaldehyde (366 mg, 2 mmol), the product (371 mg) was obtained in 78% yield.

^1H NMR (400 MHz): δ 9.95 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 6.91 (s, 2H), 4.09 (s, 2H), 2.31 (s, 3H), 2.19 (s, H).

^{13}C NMR (100 MHz): δ 192.1, 148.0, 137.1, 136.4, 134.7, 132.8, 130.2, 129.3, 128.7, 35.2, 21.1, 20.3.

HRMS ($\text{C}_{17}\text{H}_{18}\text{O}$) calcd. 238.1357, found 238.1360.

4-(3-chlorobenzyl)benzonitrile (11)



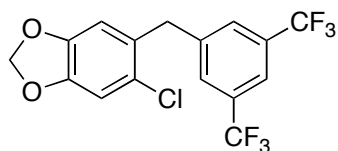
From zinc powder (390 mg, 6 mmol), 3-chlorobenzylchloride (795 mg, 5 mmol) and 4-bromobenzonitrile (364 mg, 2 mmol), the product (363 mg) was obtained in 80% yield.

^1H NMR (400 MHz): δ 7.57 (d, J = 8.3 Hz, 2H), 7.28-7.22 (m, 4H), 7.14 (s, 1H), 7.05 (d, J = 7.0 Hz, 1H), 4.00 (s, 2H).

^{13}C NMR (100 MHz): δ 145.9, 141.5, 134.7, 132.6, 130.2, 129.8, 129.2, 127.3, 127.1, 119.0, 110.6, 41.7.

HRMS ($\text{C}_{14}\text{H}_{10}\text{ClN}$) calcd 227.0501, found 227.0508.

1,3-bis(trifluoromethane)-5-(6-chloropiperonyl)benzene (12)



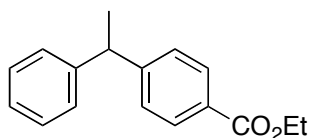
From zinc dust (390 mg, 6 mmol), 6-chloropiperonyl chloride (1020 mg, 5 mmol) and 1-bromo-3,5-bis(trifluoromethyl)benzene (586 mg, 2 mmol), the product (535 mg) was obtained in 70% yield.

^1H NMR (400 MHz): δ 7.73 (s, 1H), 7.60 (s, 2H), 6.87 (s, 1H), 6.63 (s, 1H), 5.99 (s, 2H), 4.11 (s, 2H).

^{13}C NMR (100 MHz): δ 147.6, 147.2, 142.4, 132.0, 131.7, 129.4, 128.9, 126.0, 122.4, 120.6, 110.4, 102.1, 38.9.

HRMS ($\text{C}_{16}\text{H}_9\text{ClF}_6\text{O}_2$) calcd. 382.0195, found 382.0179.

Ethyl 4-(1-phenylethyl)benzoate (13)



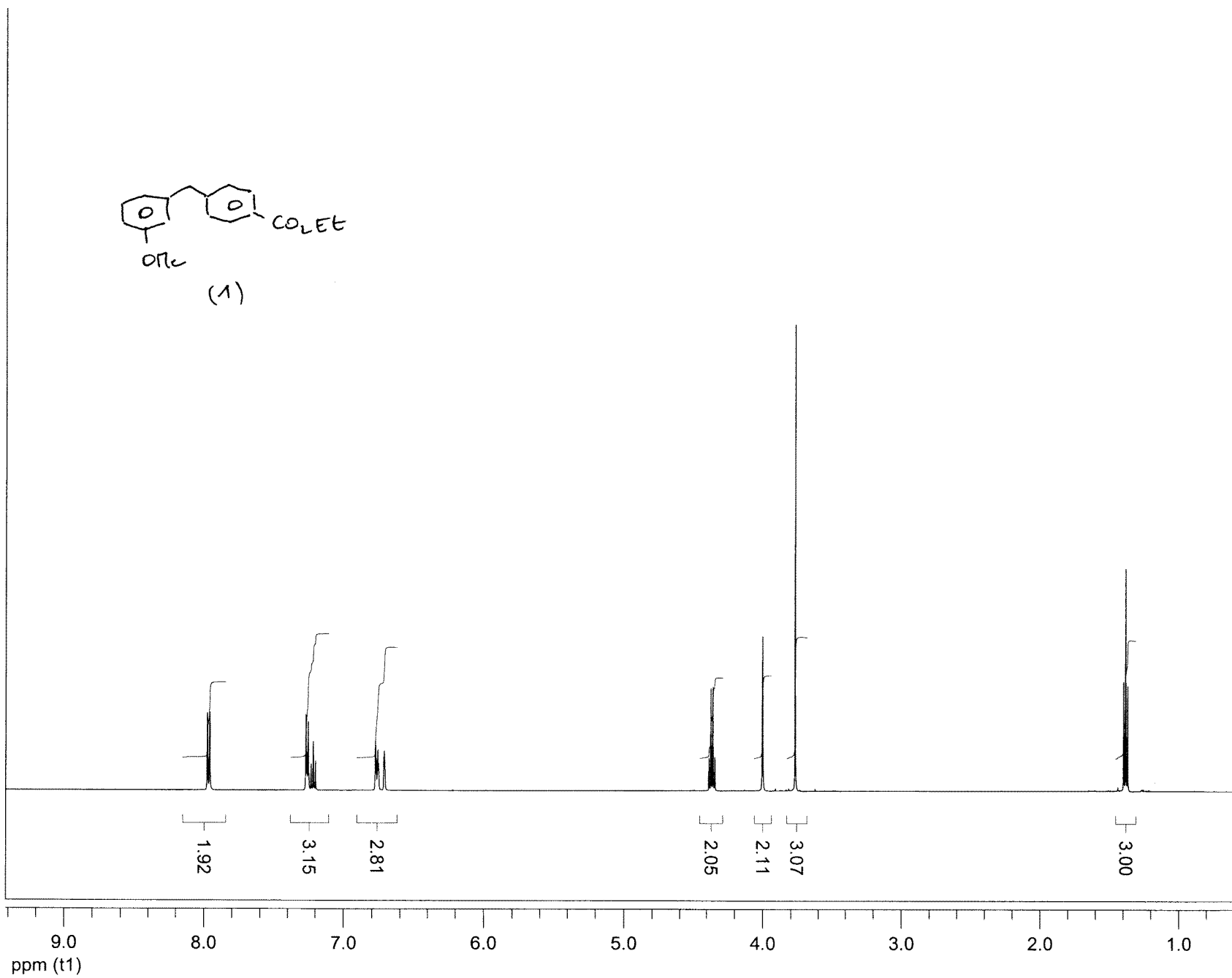
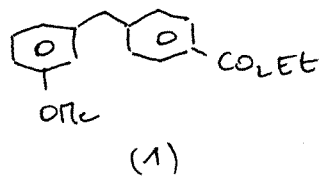
From zinc dust (390 mg, 6 mmol), TMEDA (116 mg, 1 mmol), (1-chloroethyl)benzene (700 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (497 mg) was obtained in 98% yield.

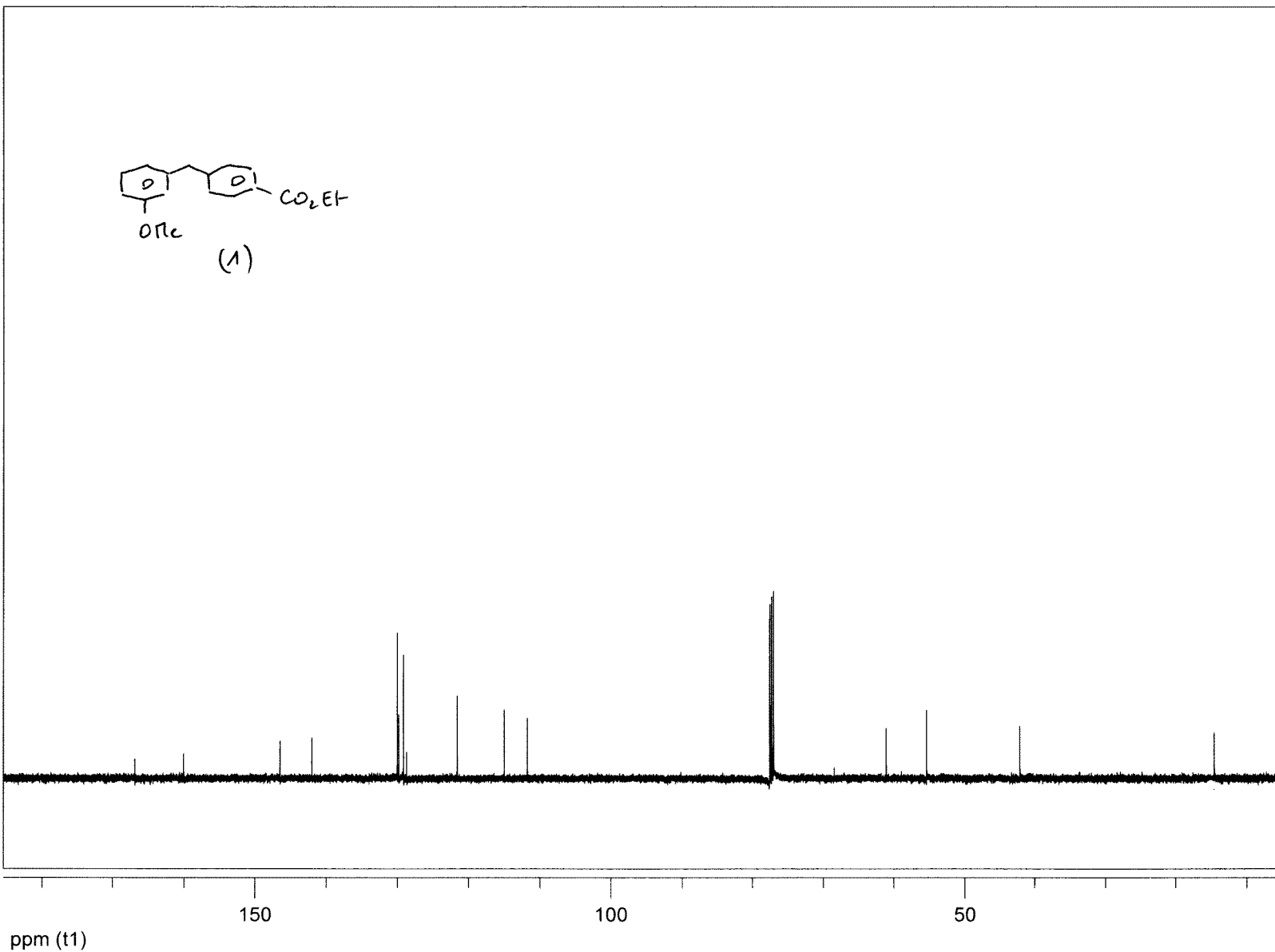
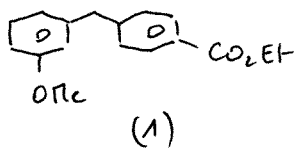
HRMS ($\text{C}_{17}\text{H}_{18}\text{O}_2$) calcd. 254.1306, found 254.1307.

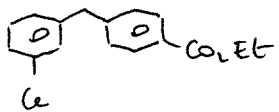
The corresponding spectroscopic data matched those reported in the literature ethyl 4-(1-phenylethyl)benzoate.¹

(1) M. Amatore, C. Gosmini, *Chem. Comm.* **2009**, 5019.

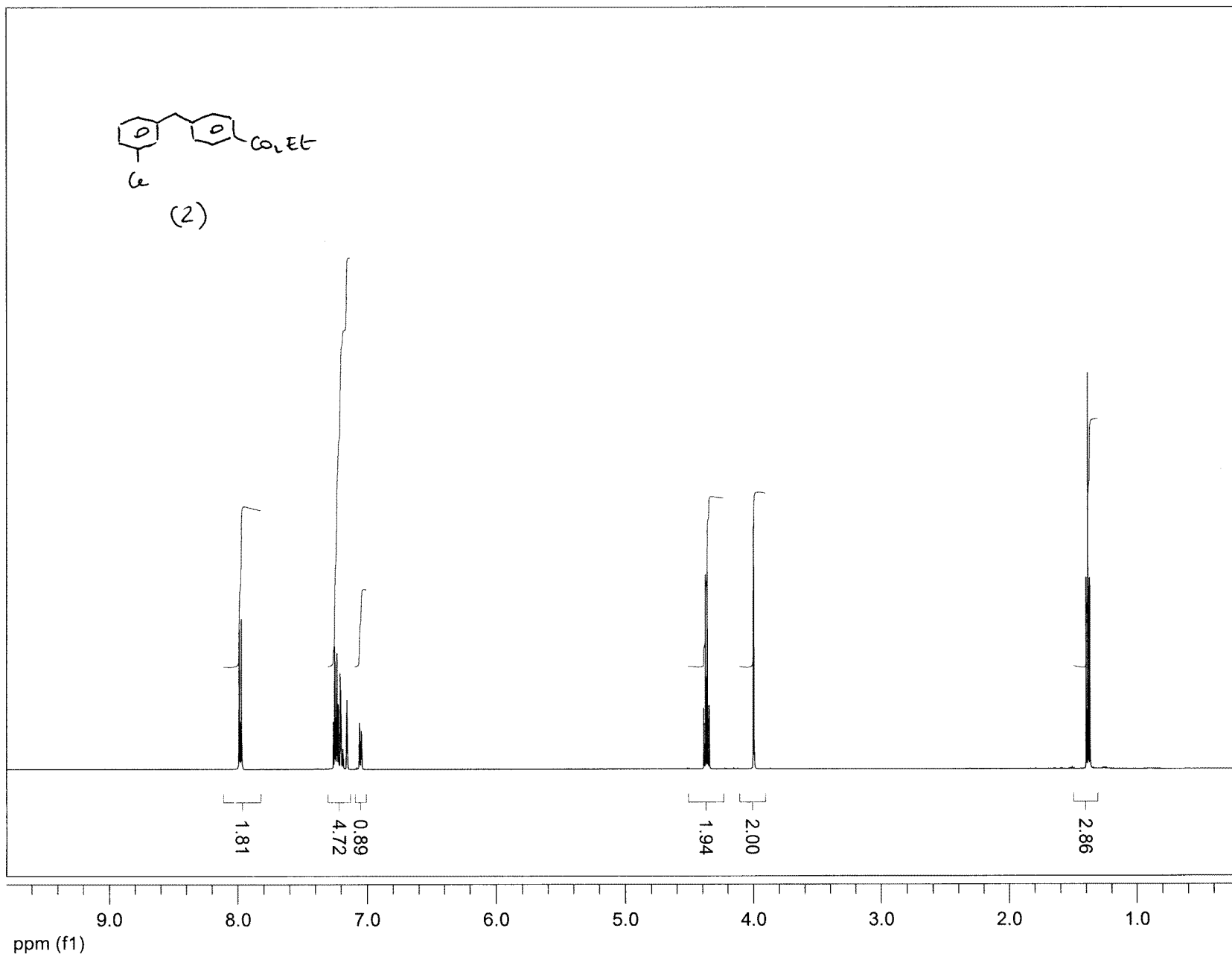
(2) C. C. Kofink, P. Knochel, *Org. Lett.* **2006**, *8*, 4121.

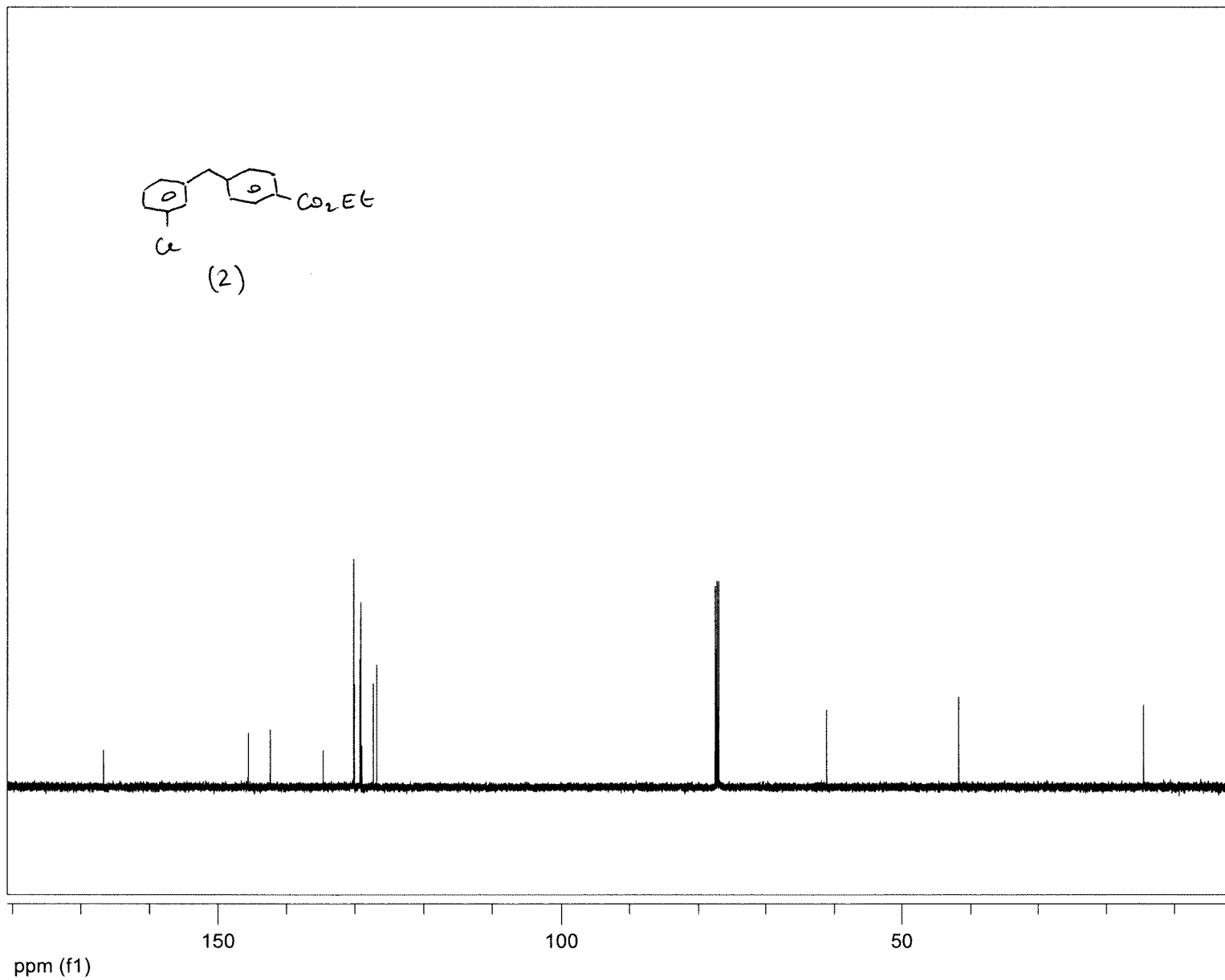
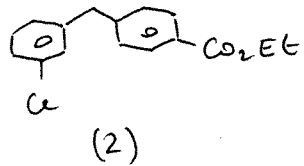


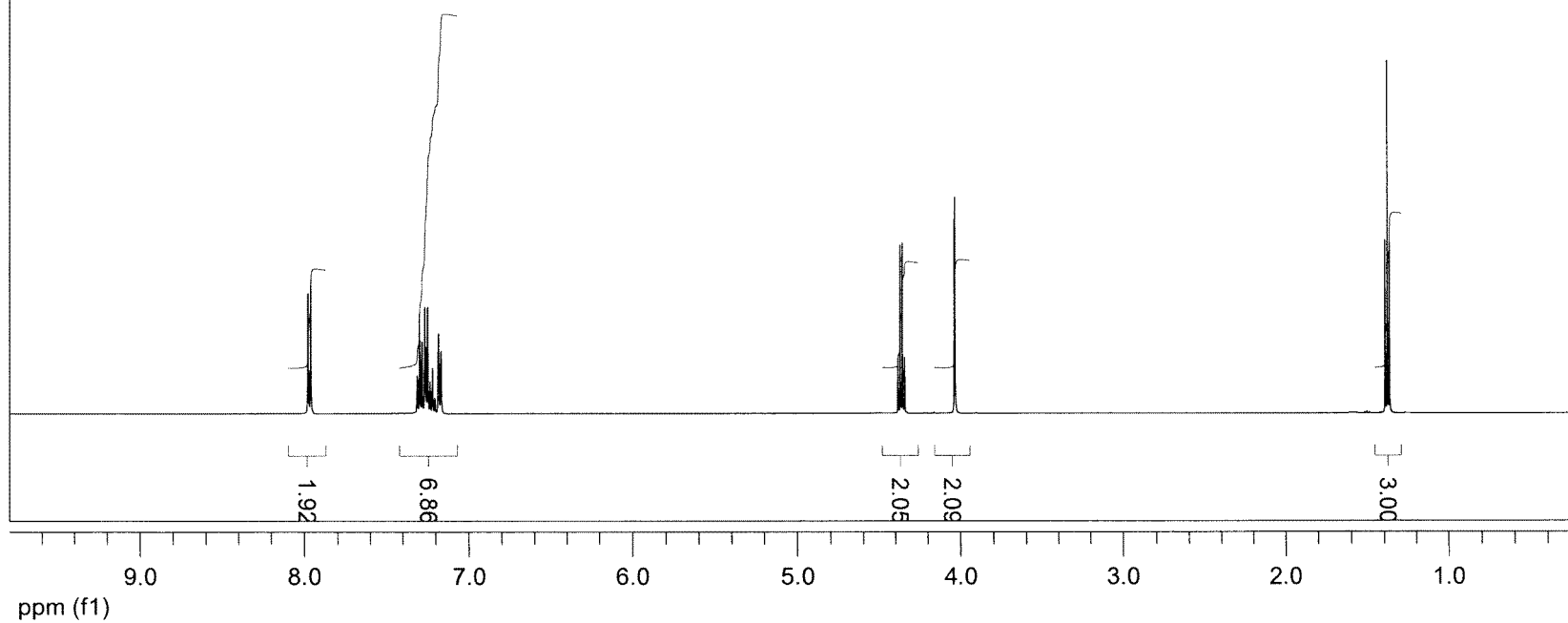
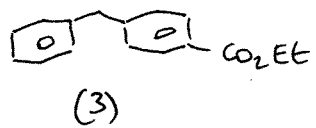




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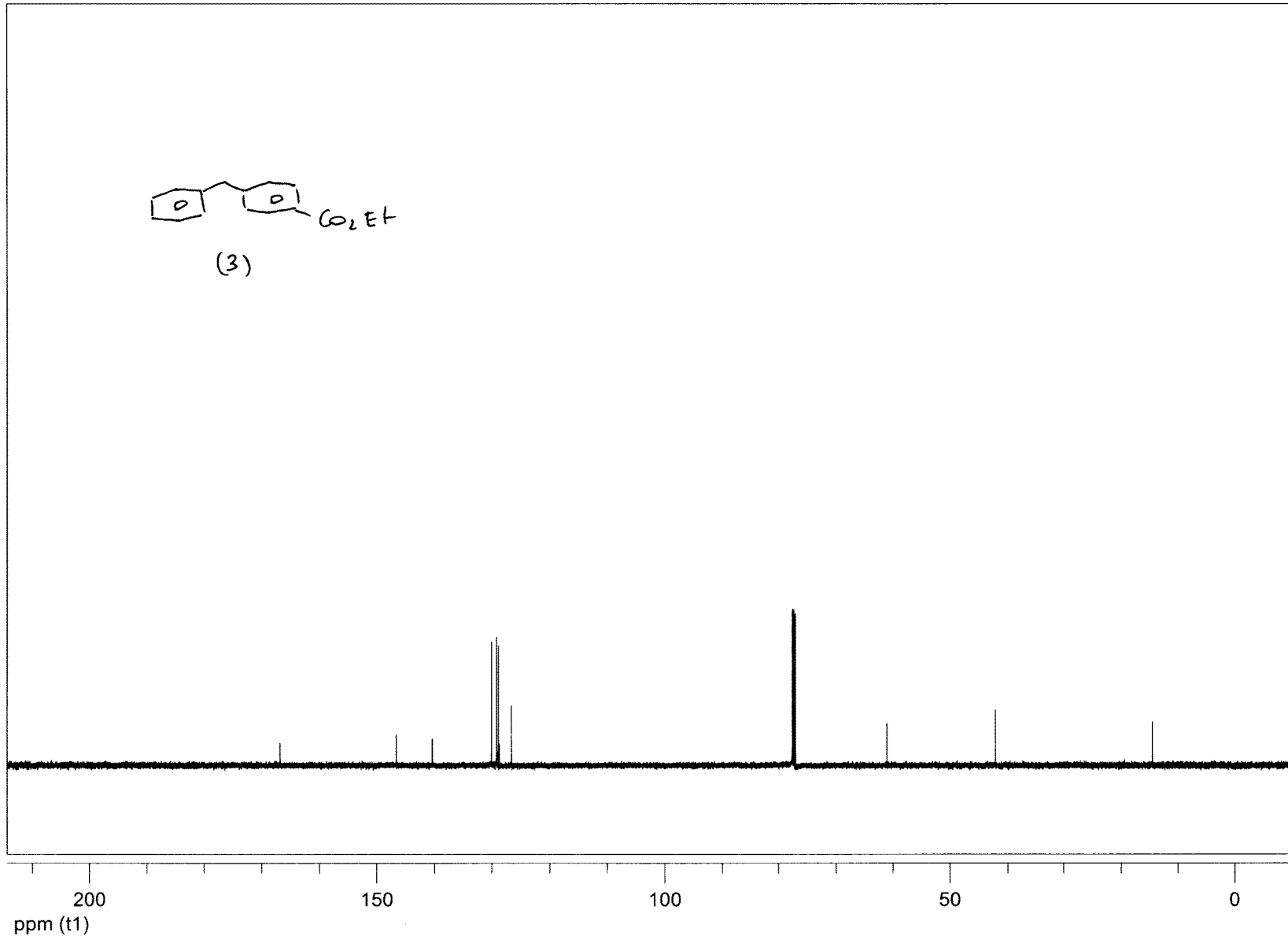


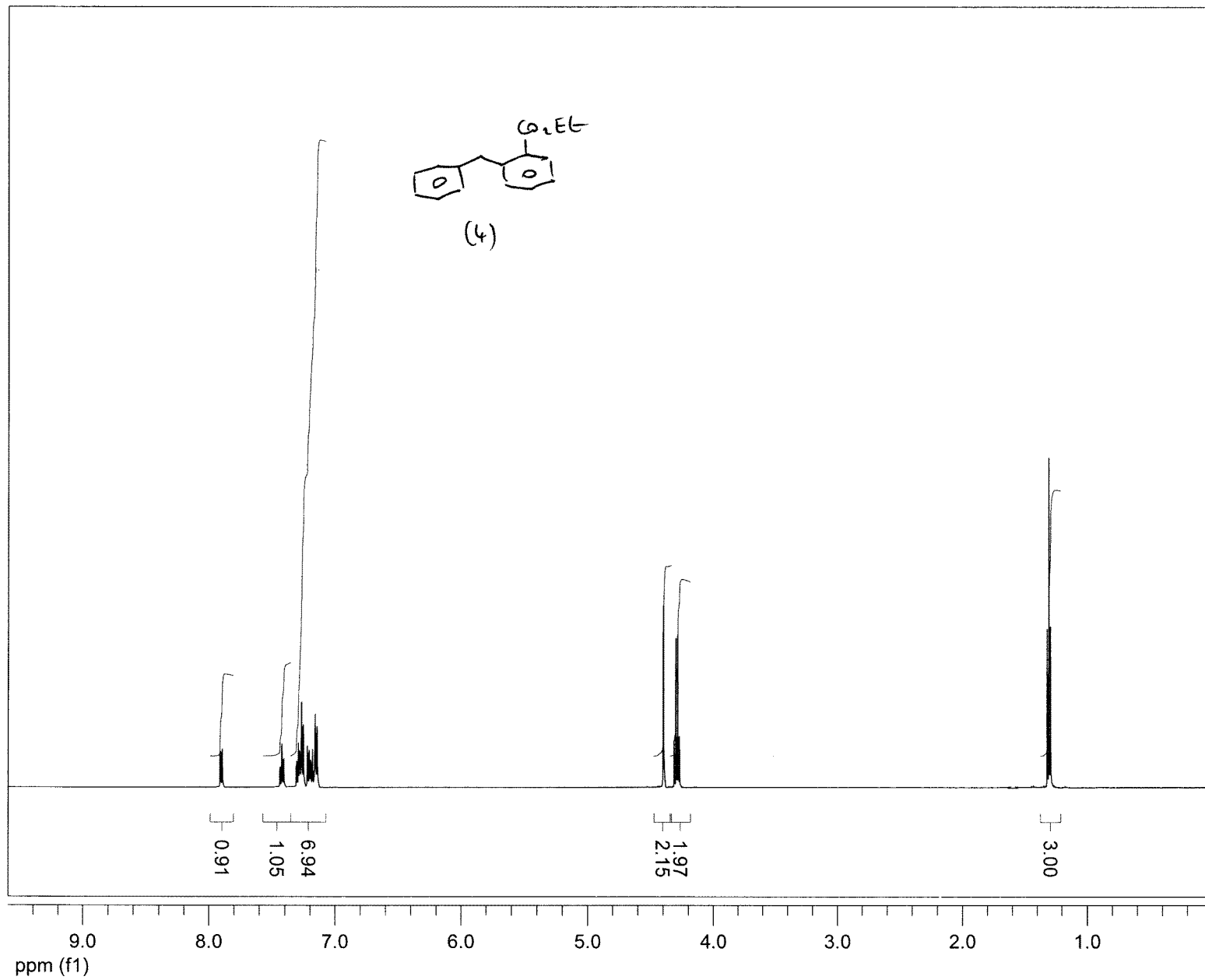


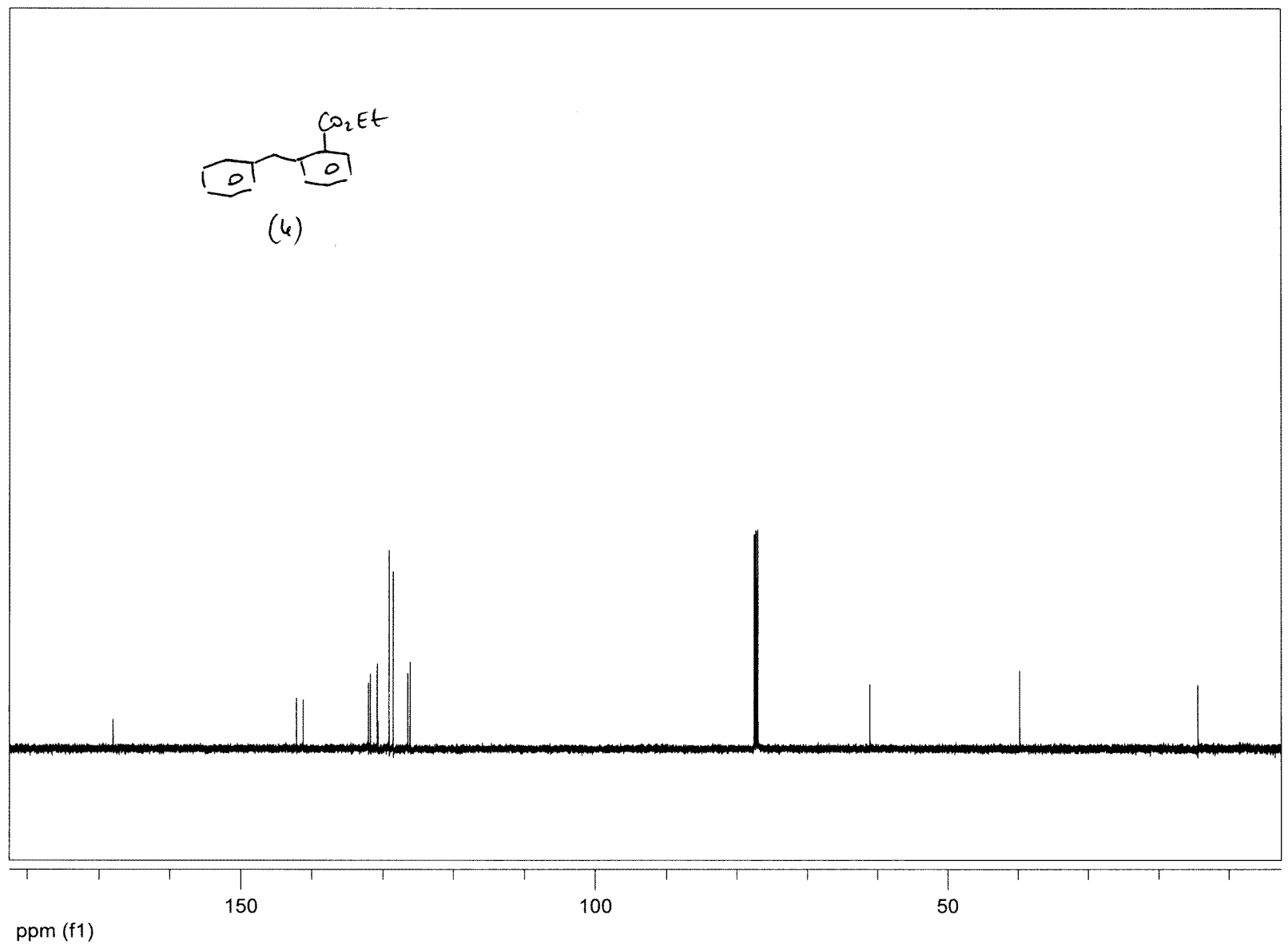
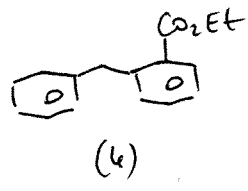


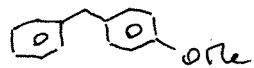


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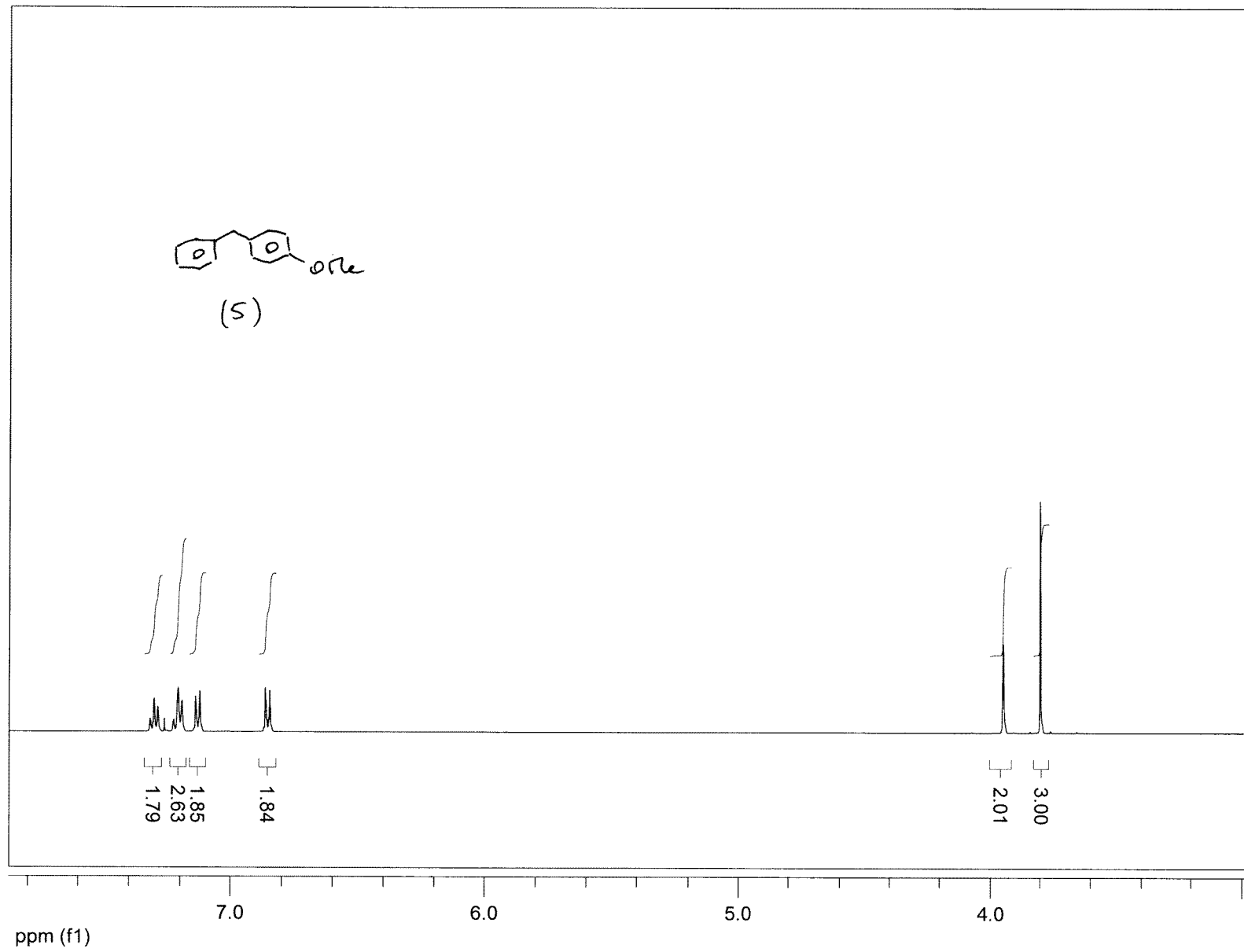






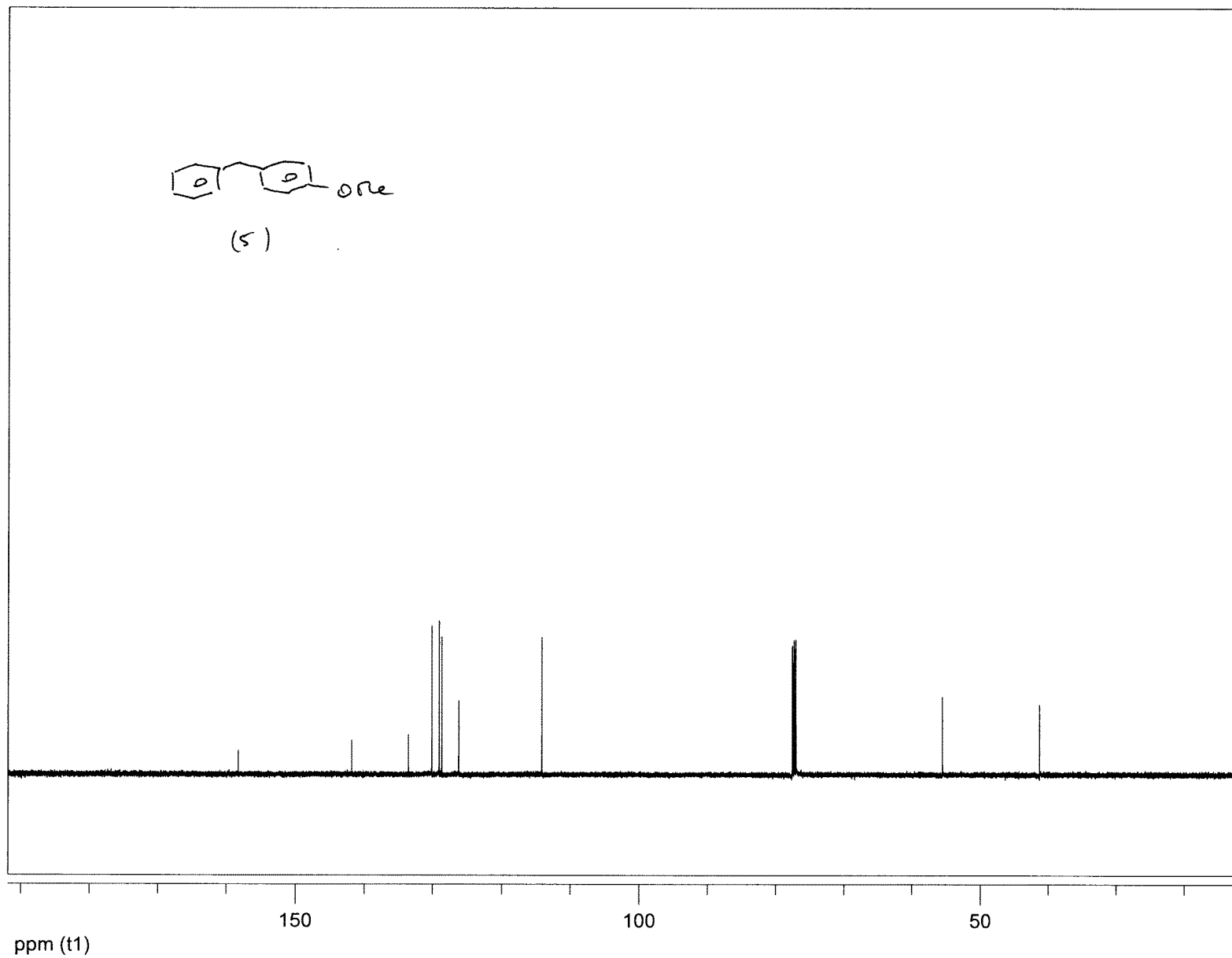


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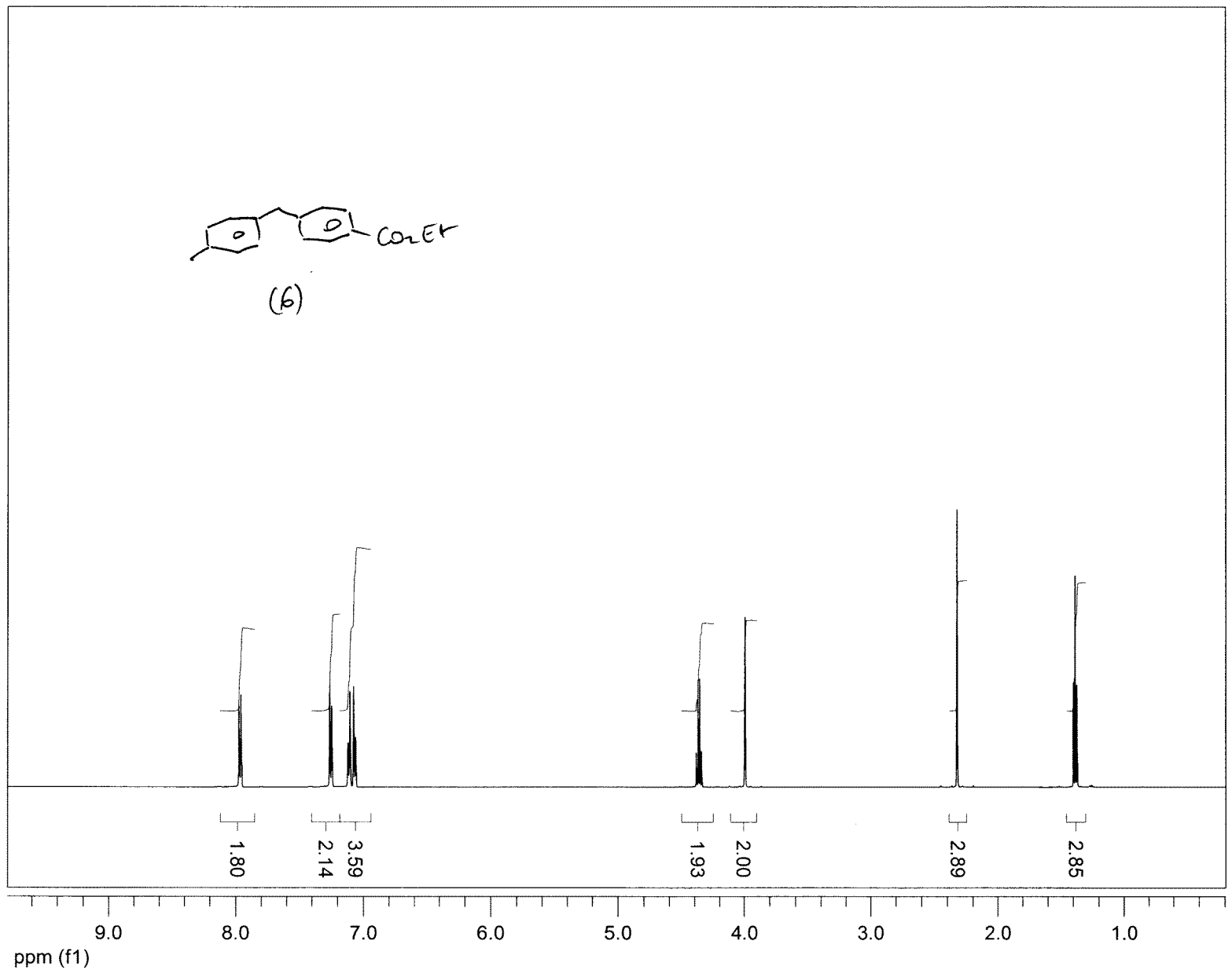


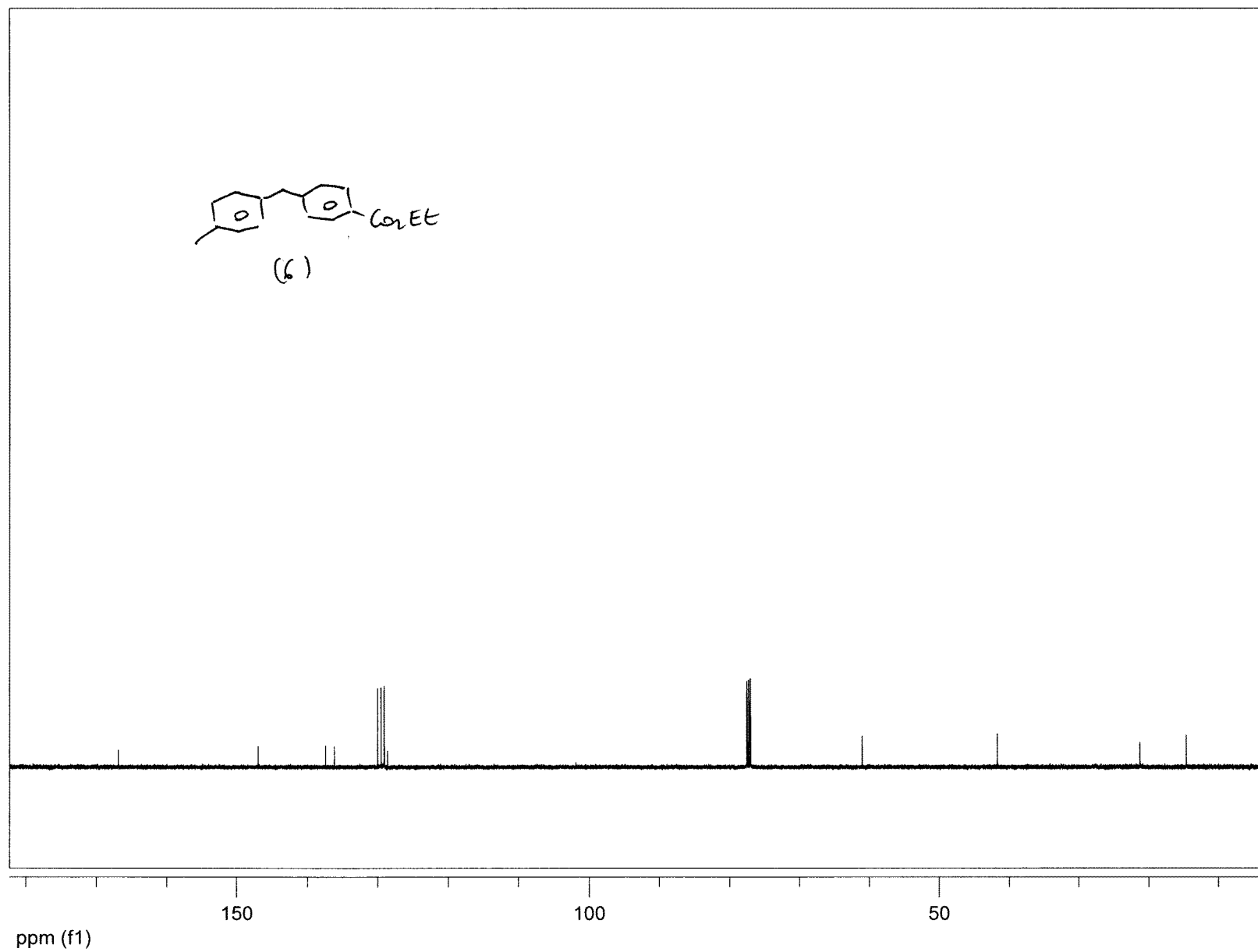
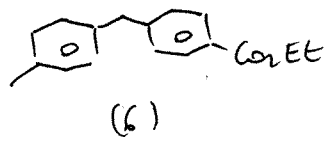
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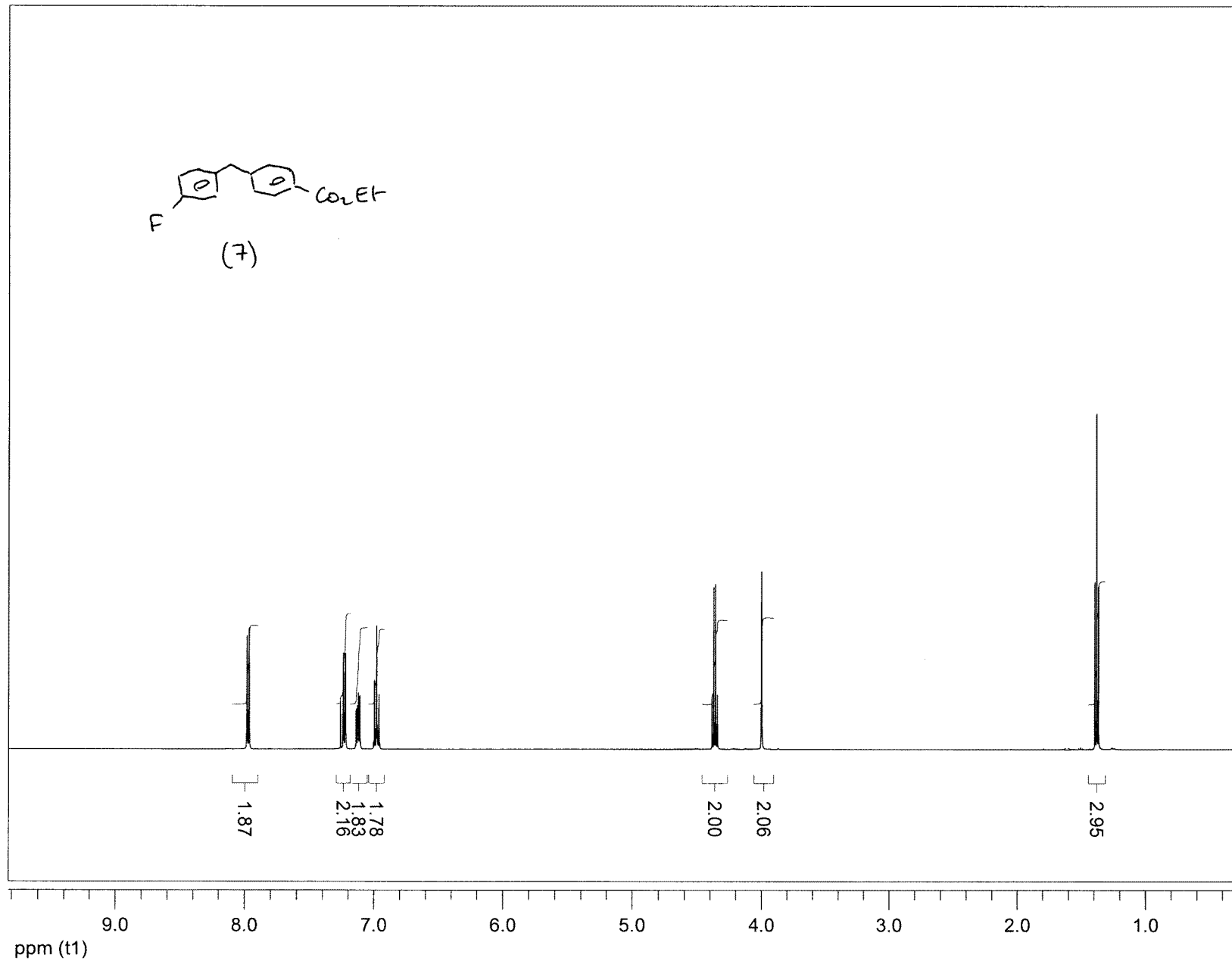
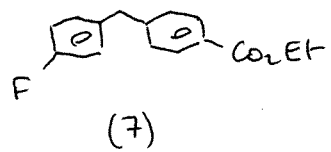


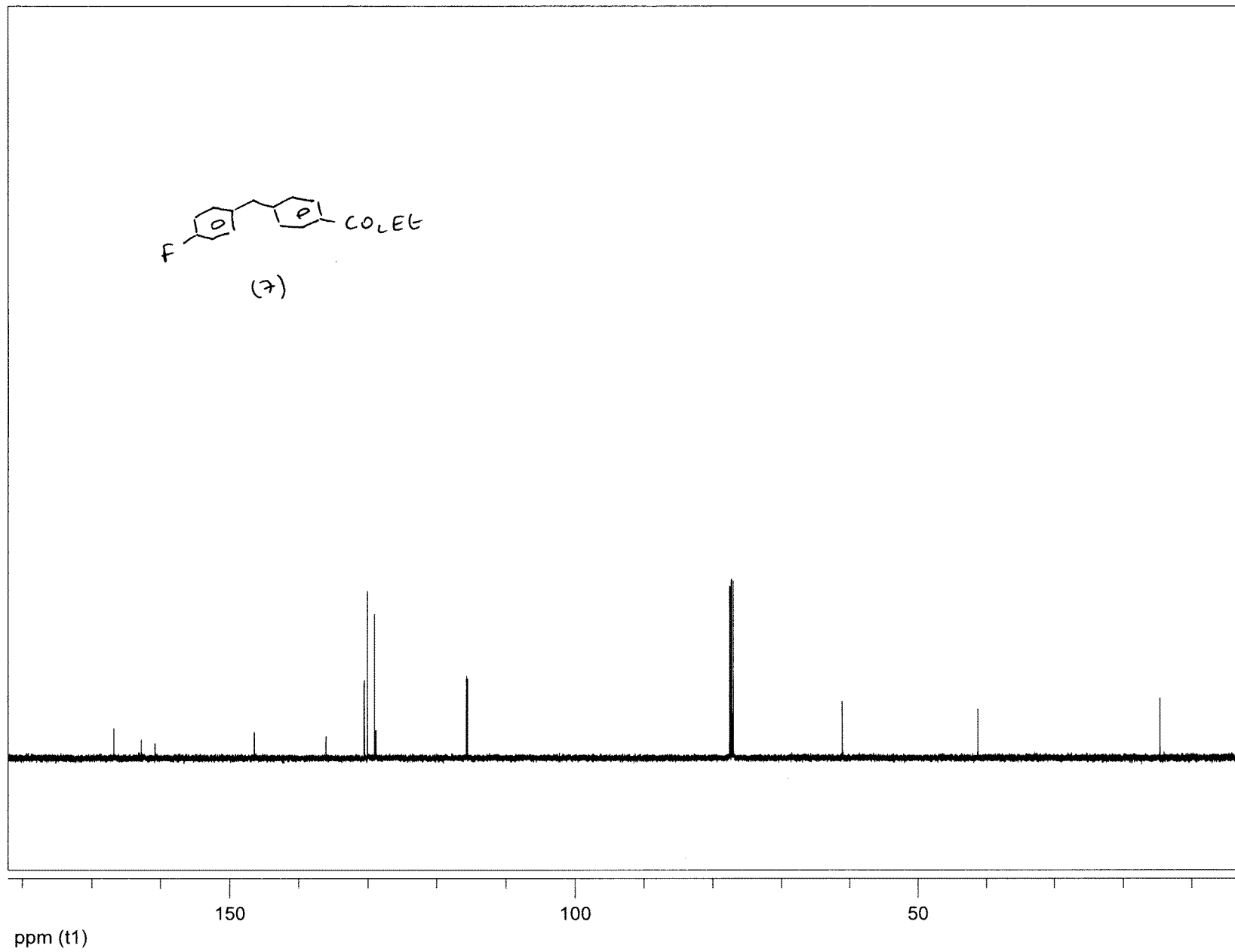
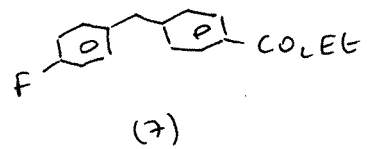


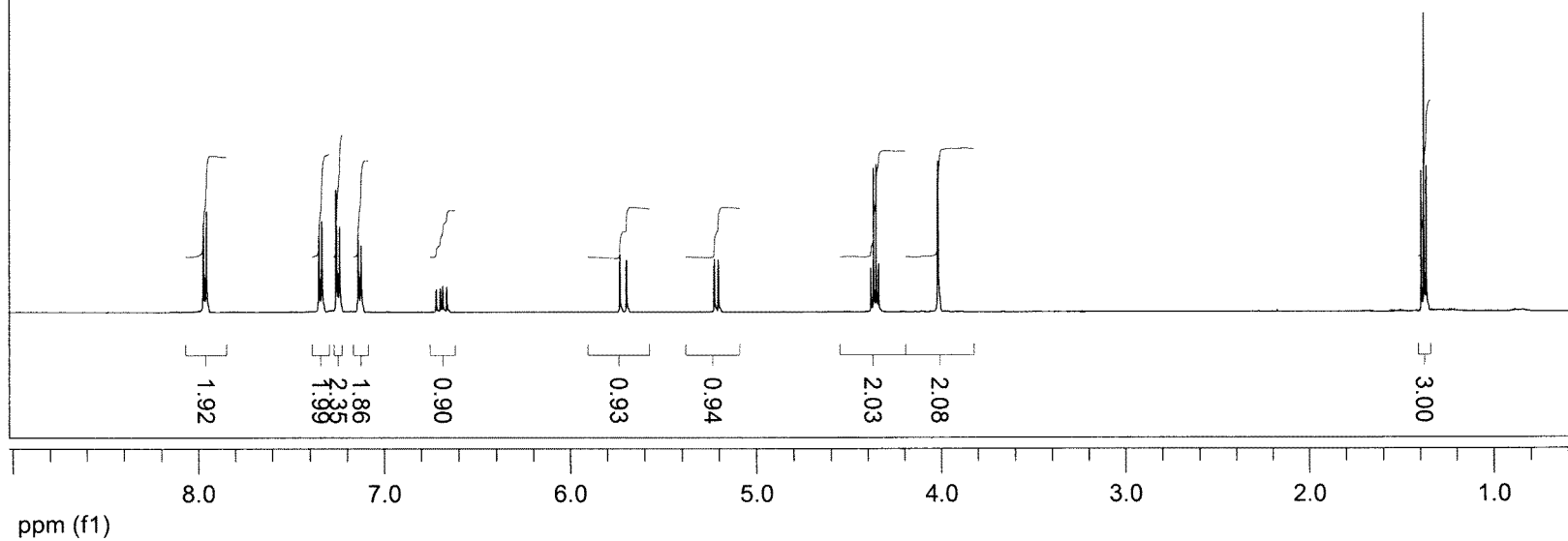
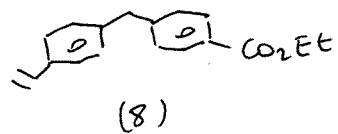
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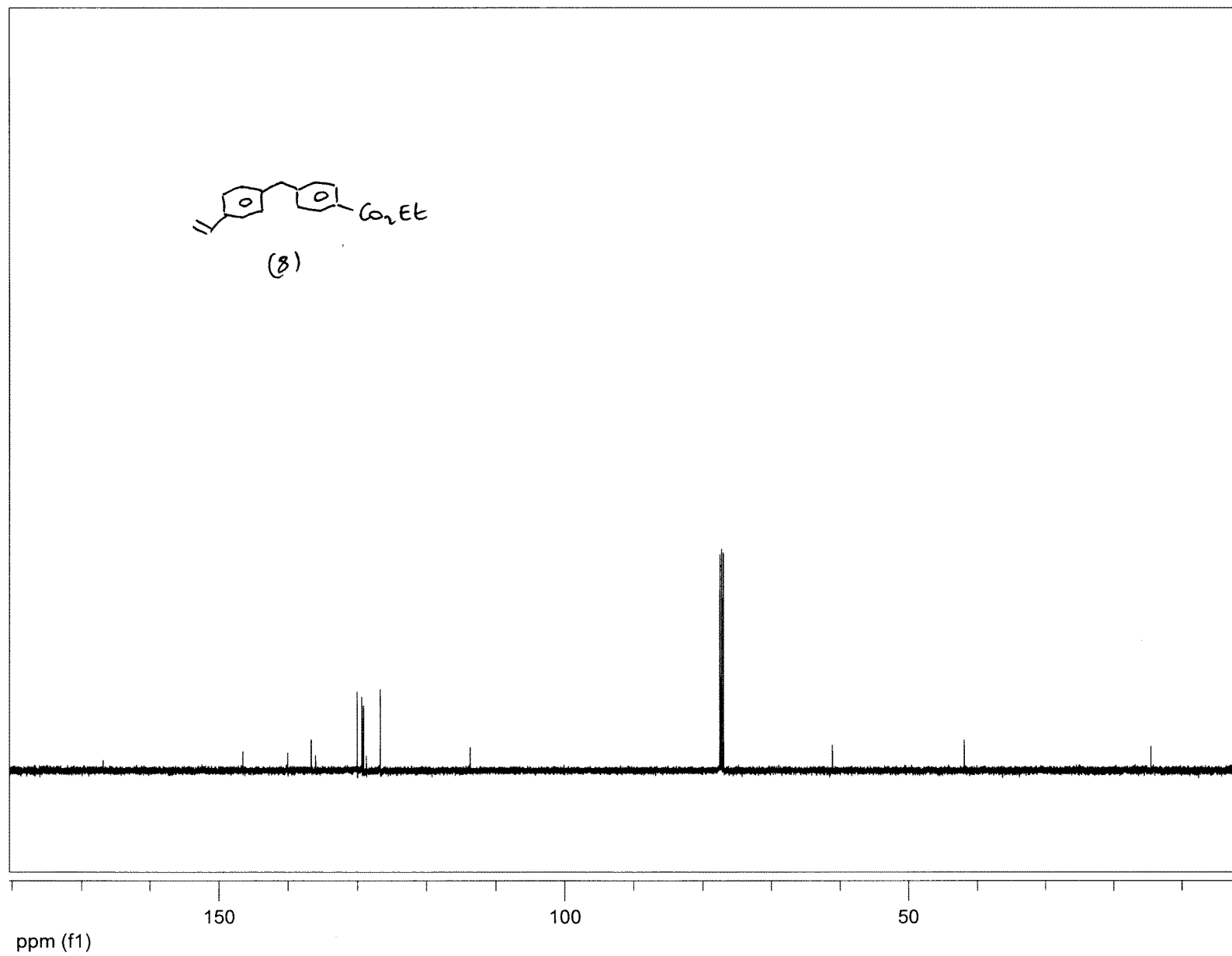
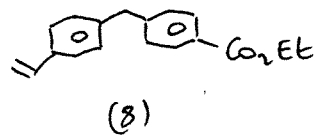


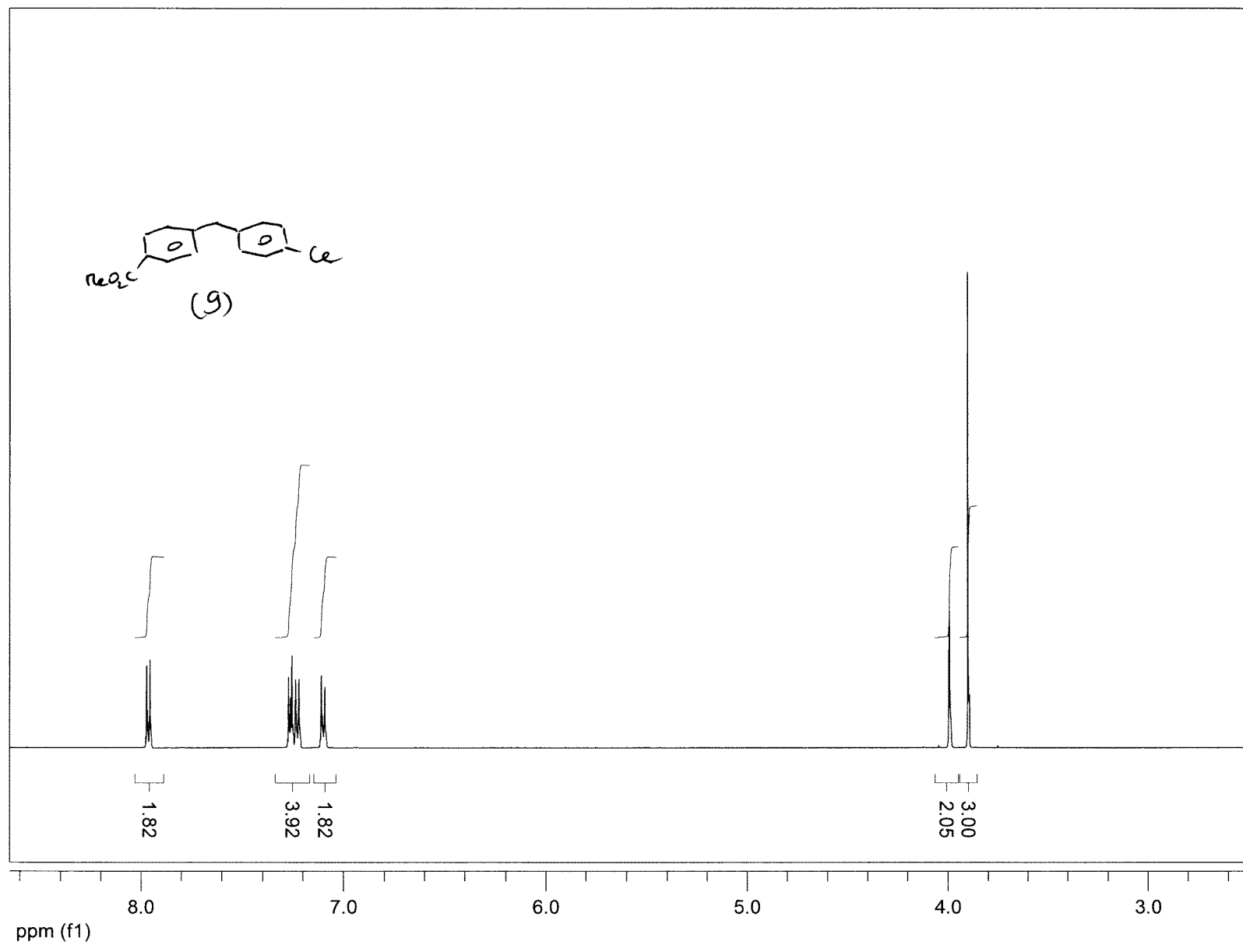


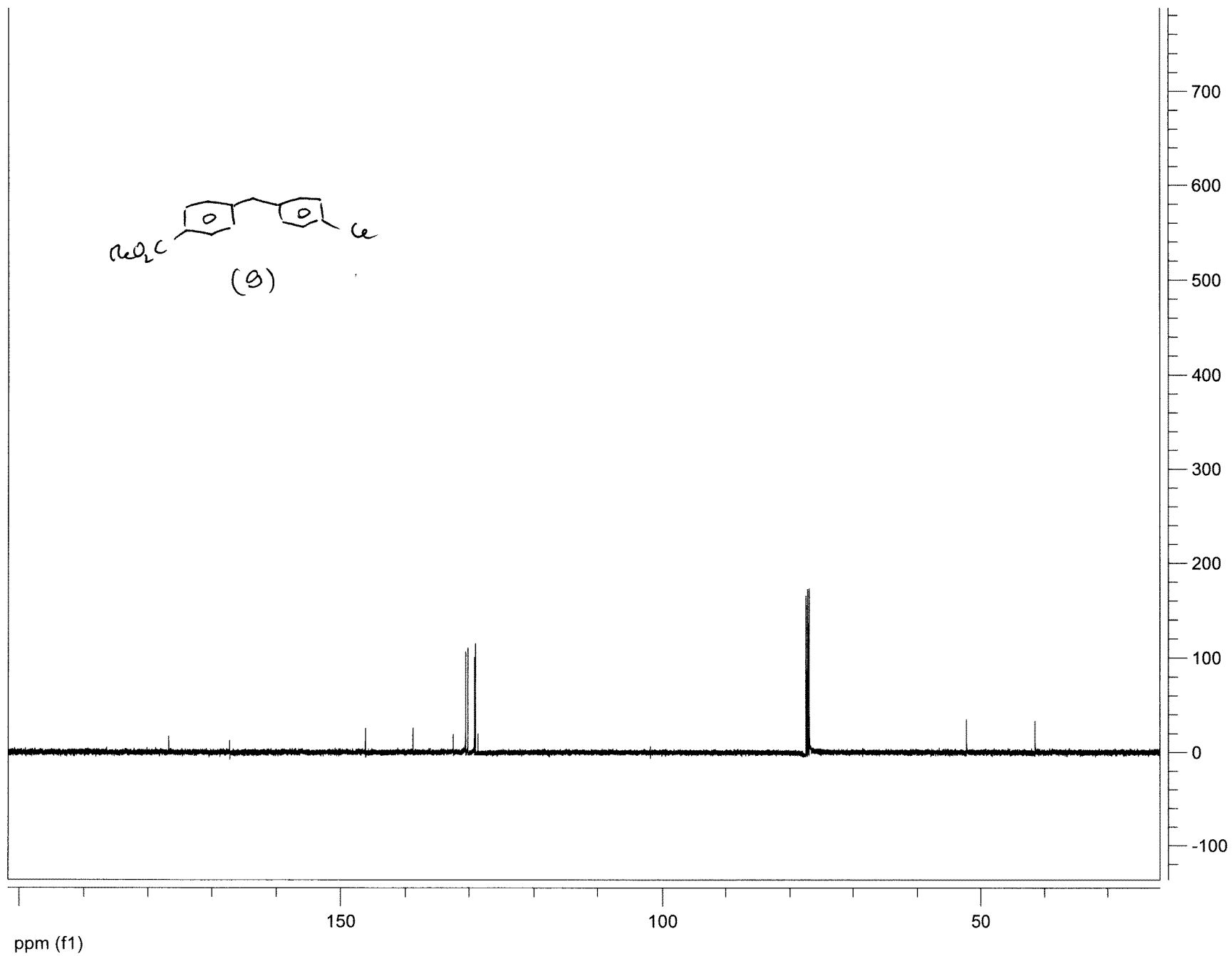


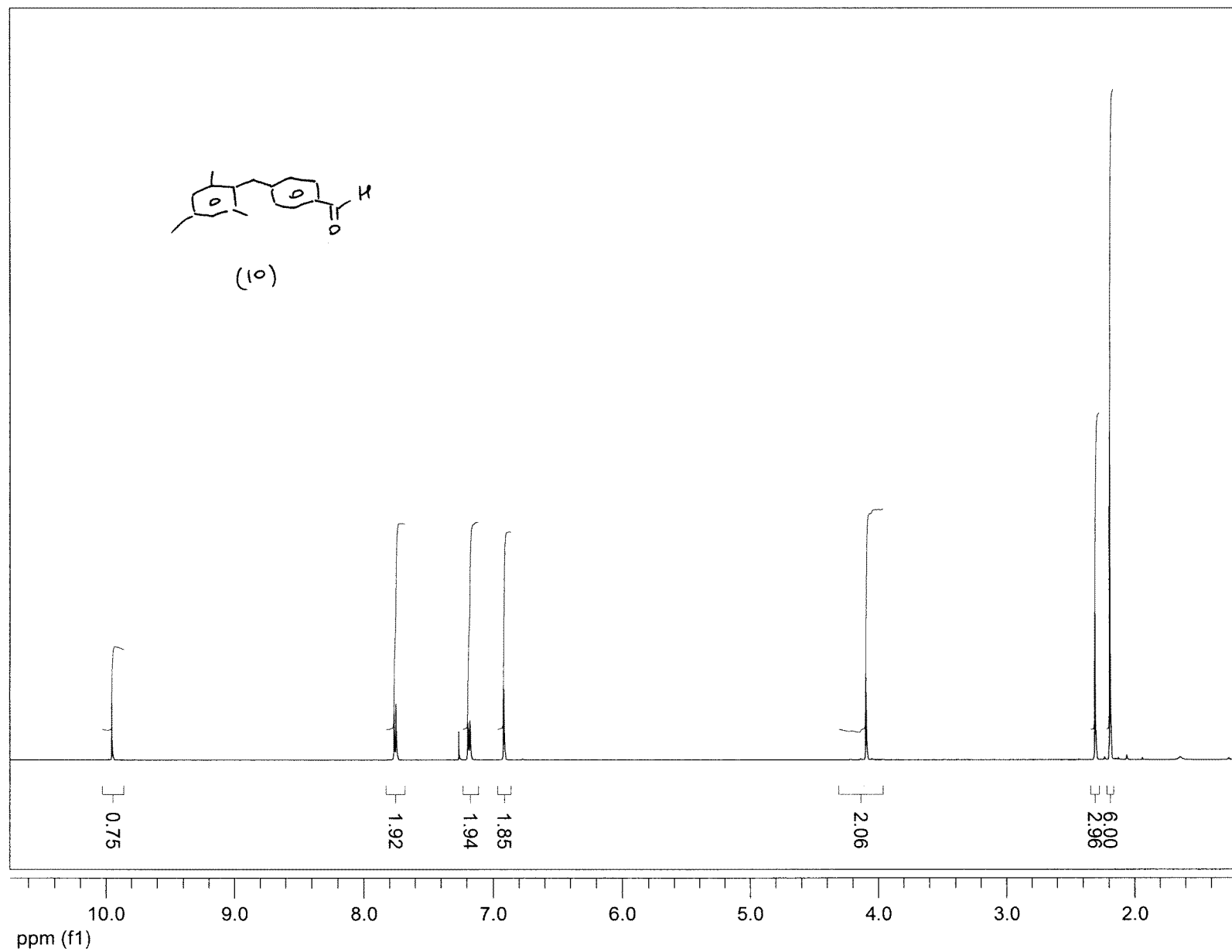


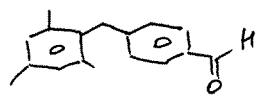




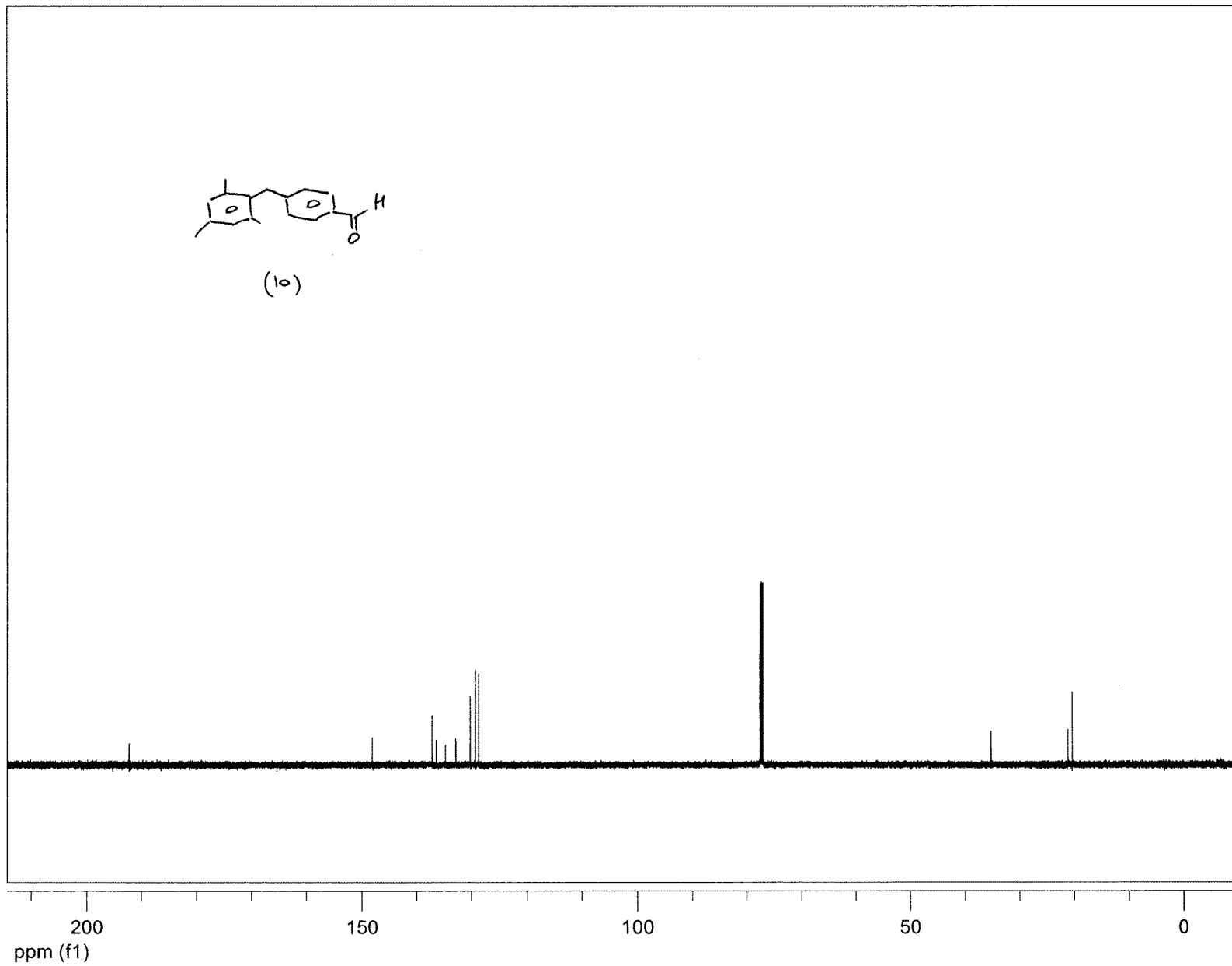


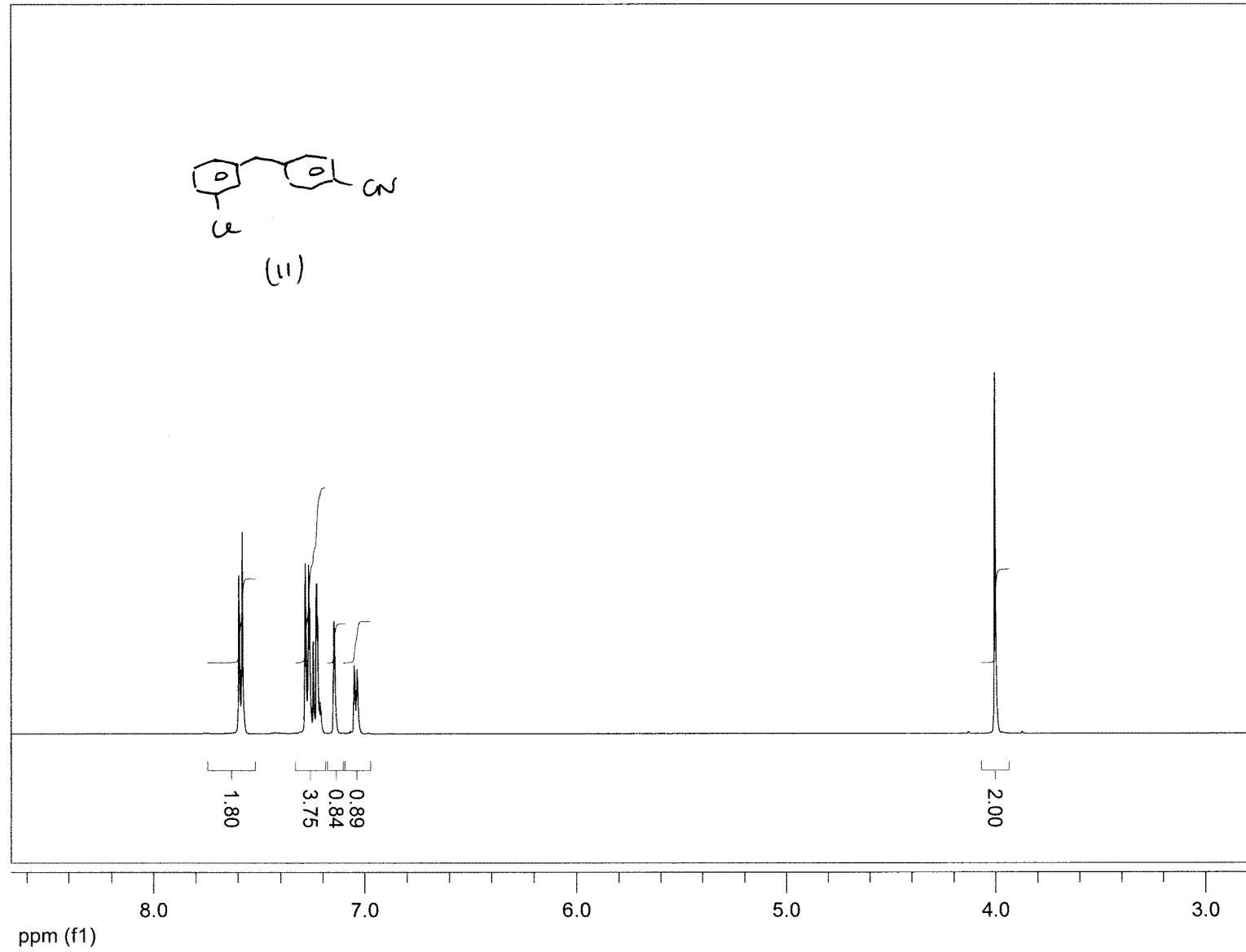
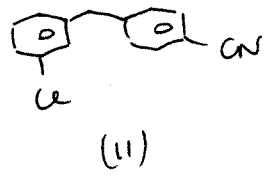


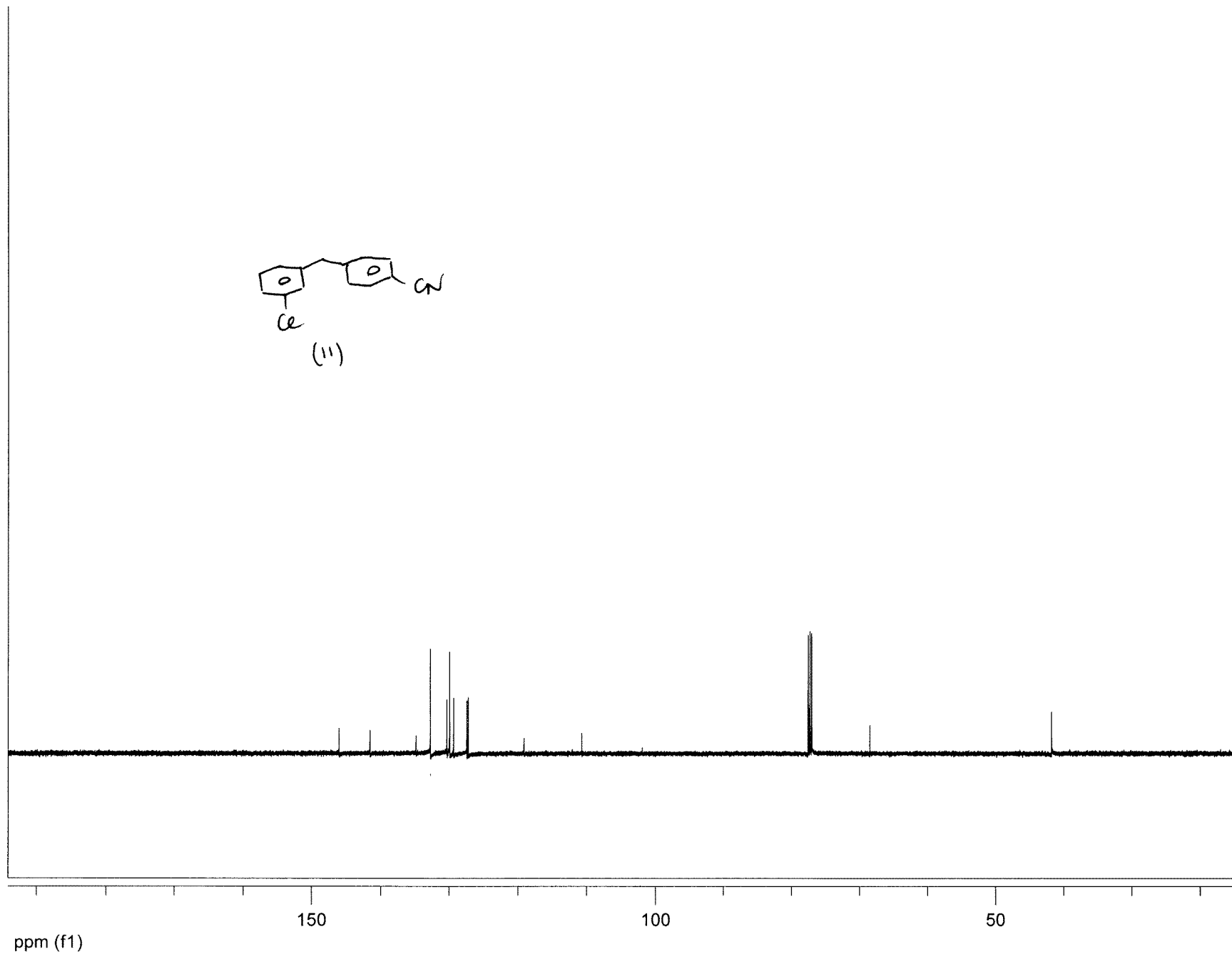
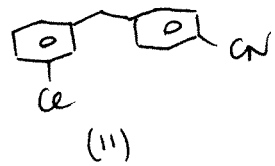


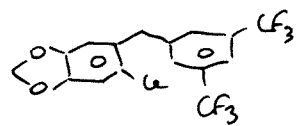


(10)

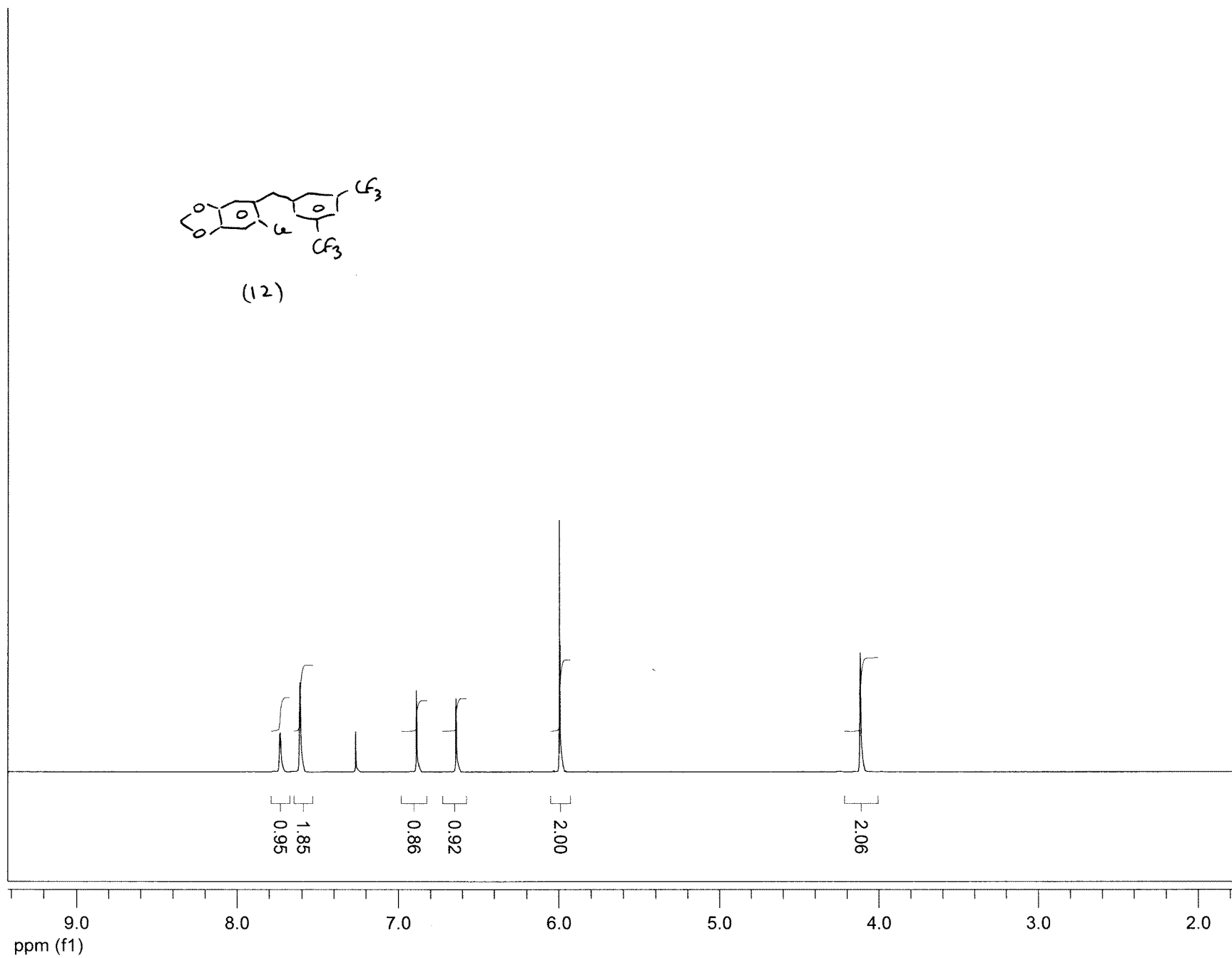


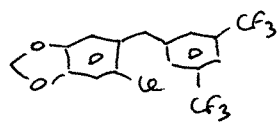




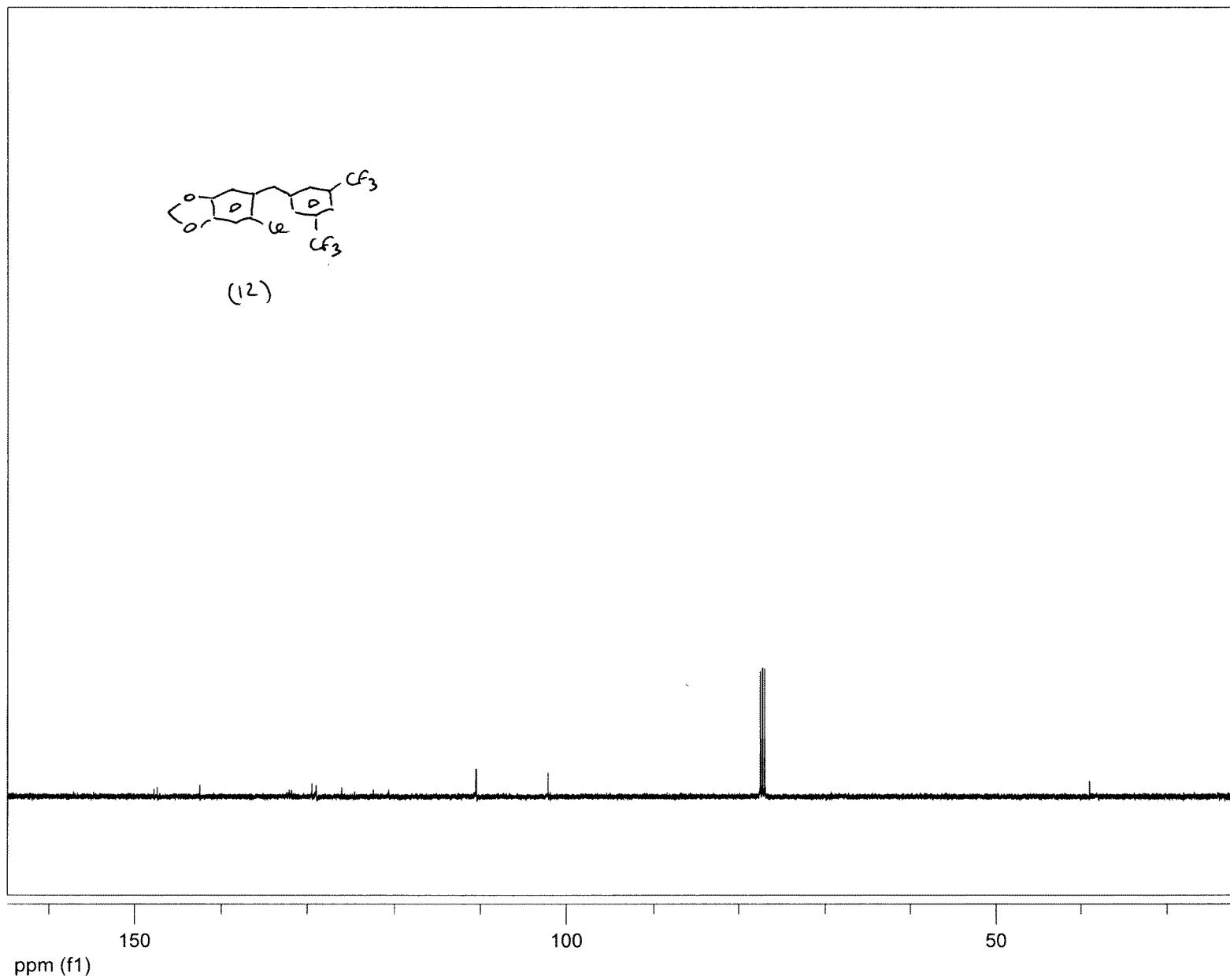


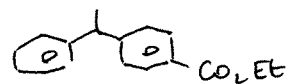
(12)





(12)





(13)

