Cross-Couplings Between Benzyl and Aryl Halides "On Water." Synthesis of Diarymethanes

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Supporting Information

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Instrumentation and Chemicals

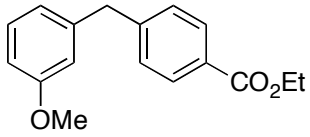
General. Reactions were performed in a 10 mL round bottom flask under an argon atmosphere containing a Teflon coated stir bar and septum. All commercially available reagents were used without further purification. Water was degassed with argon. Zinc powder 99.9% (-325 mesh) and zinc dust 97.5% (-325 mesh) were purchased from Strem Chemicals (catalog #93-3060 and #93-3056) and was stored in the glove box. $PdCl_2(Amphos)_2$ (CAS #887919-35-9) was obtained from Johnson Matthey (Pd-132, catalog #C4138). Column chromatography was preformed 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 ^{13}C 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 ($CDCl_3$, 7.26 ppm), multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), and integration. ^{13}C Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$, 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 $PdCl_2(Amphos)_2$ (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.

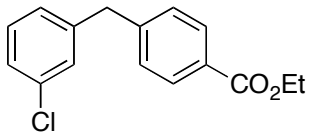
From zinc *powder* (390 mg, 6 mmol), 3-methoxybenzyl chloride (624 mg, 4 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (514 mg) was obtained in 95% yield.

^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).

^{13}C 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 ($C_{17}H_{18}O_3$) 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.

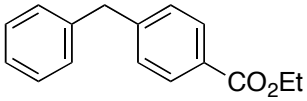
From zinc powder (390 mg, 6 mmol), 3-chlorobenzyl chloride (640 mg, 4 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (526 mg) was obtained in 96% yield.

^{1}H 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 ($C_{16}H_{15}ClO$) calcd. 274.0760, found 206.0762.

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



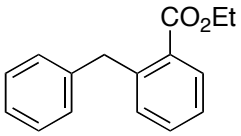
From zinc dust (390 mg, 6 mmol), benzyl bromide (845 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (450 mg) was obtained in 94% yield.

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 ($C_{16}H_{16}O_2$) 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]

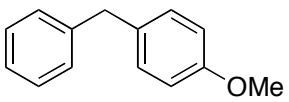


From zinc dust (390 mg, 6 mmol), benzyl chloride (630 mg, 5 mmol) and ethyl 2-bromobenzoate (458 mg, 2 mmol), the product (441 mg) was obtained in 92% yield.

HRMS ($C_{16}H_{16}O_2$) 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]

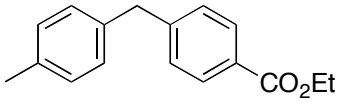


From zinc dust (390 mg, 6 mmol), benzyl chloride (504 mg, 4 mmol) and 4-bromoanisole (372 mg, 2 mmol), the product (388 mg) was obtained in 92% yield.

HRMS ($C_{14}H_{14}O$) 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)



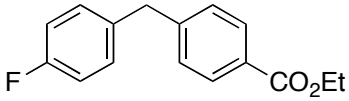
From zinc dust (390 mg, 6 mmol), 4-methylbenzyl bromide (915 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (355 mg) was obtained in 70% yield.

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.

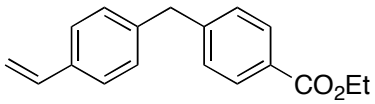
From zinc powder (390 mg, 6 mmol), 4-fluorobenzyl chloride (720 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (495 mg) was obtained in 96% yield.

^{1}H 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, *2*H), 6.99-6.95 (m, *2*H), 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)



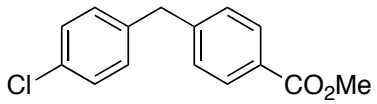
From zinc dust (390 mg, 6 mmol), 4-vinylbenzyl chloride (760 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (393 mg) was obtained in 74% yield.

^{1}H 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)



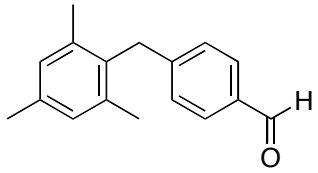
From zinc powder (390 mg, 6 mmol), methyl 4-(chloromethyl)benzoate (990 mg, 5 mmol) and 1-bromo-4-chlorobenzene (382 mg, 2 mmol), the product (433 mg) was obtained in 79% yield.

^{1}H 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 ($C_{16}H_{15}ClO_2$) calcd. 274.0760, found 274.0762.

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



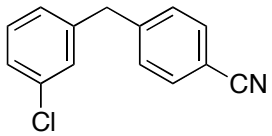
From zinc dust (390 mg, 6 mmol), 2,4,6-trimethylbenzylchloride (840 mg, 5 mmol) and 4-bromobenzaldehyde (366 mg, 2 mmol), the product (371 mg) was obtained in 78% yield.

^{1}H 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 ($C_{17}H_{18}O$) calcd. 238.1357, found 238.1360.

4-(3-chlorobenzyl)benzonitrile (11)



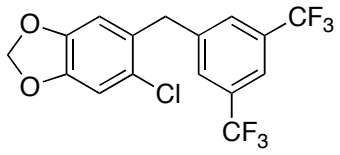
From zinc powder (390 mg, 6 mmol), 3-chlorobenzylchloride (795 mg, 5 mmol) and 4-bromobenzonitrile (364 mg, 2 mmol), the product (363 mg) was obtained in 80% yield.

^{1}H 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 ($C_{14}H_{10}ClN$) calcd 227.0501, found 227.0508.

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



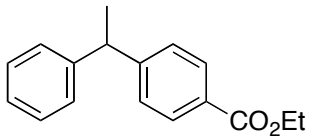
From zinc dust (390 mg, 6 mmol), 6-chloropiperonyl chloride (1020 mg, 5 mmol) and 1-bromo-3,5-bis(trifluoromethyl)benzene (586 mg, 2 mmol), the product (535 mg) was obtained in 70% yield.

^{1}H 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 ($C_{16}H_9ClF_6O_2$) calcd. 382.0195, found 382.0179.

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

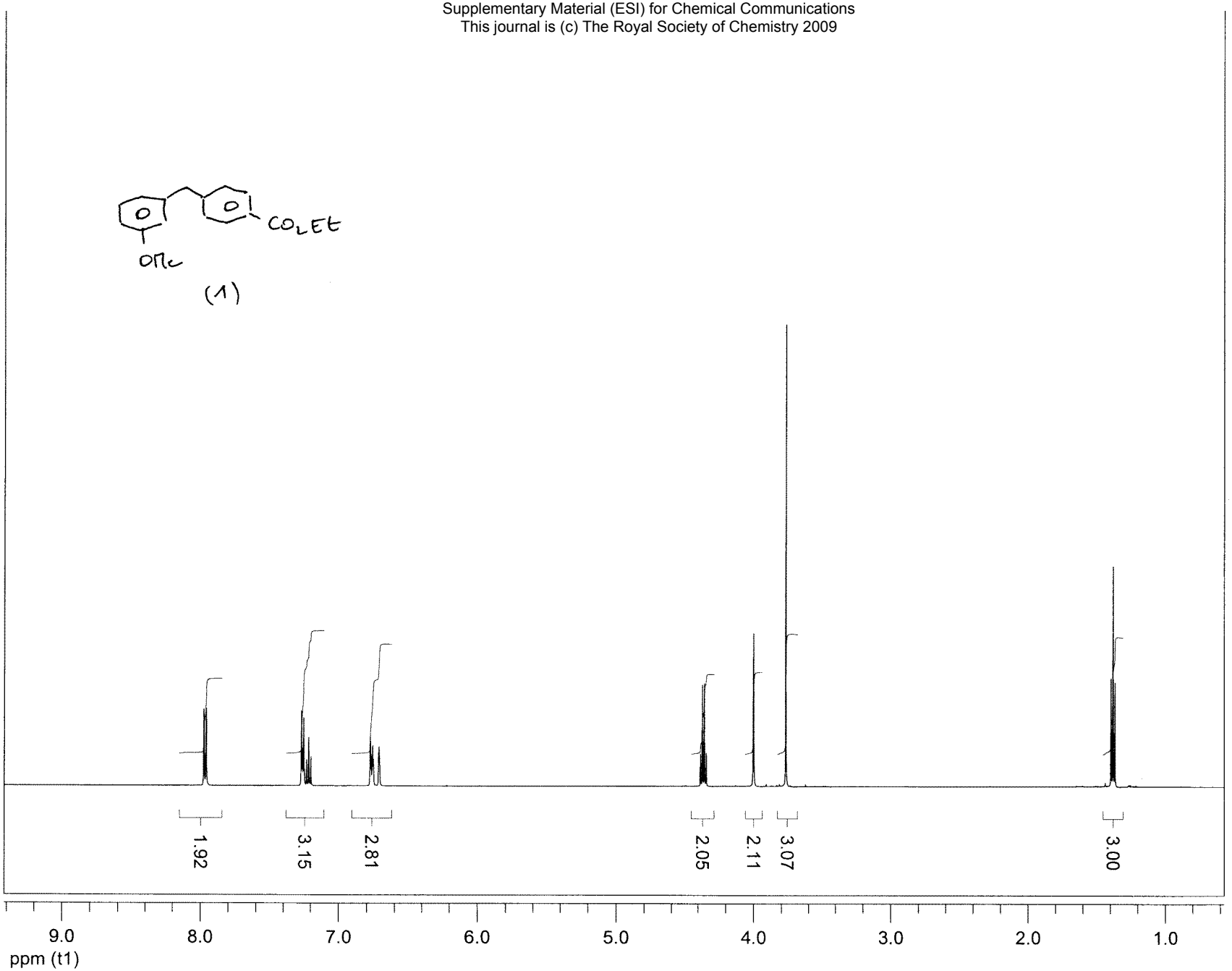


From zinc dust (390 mg, 6 mmol), TMEDA (116 mg, 1 mmol), (1-chloroethyl)benzene (700 mg, 5 mmol) and ethyl 4-bromobenzoate (458 mg, 2 mmol), the product (497 mg) was obtained in 98% yield.

HRMS ($C_{17}H_{18}O_2$) 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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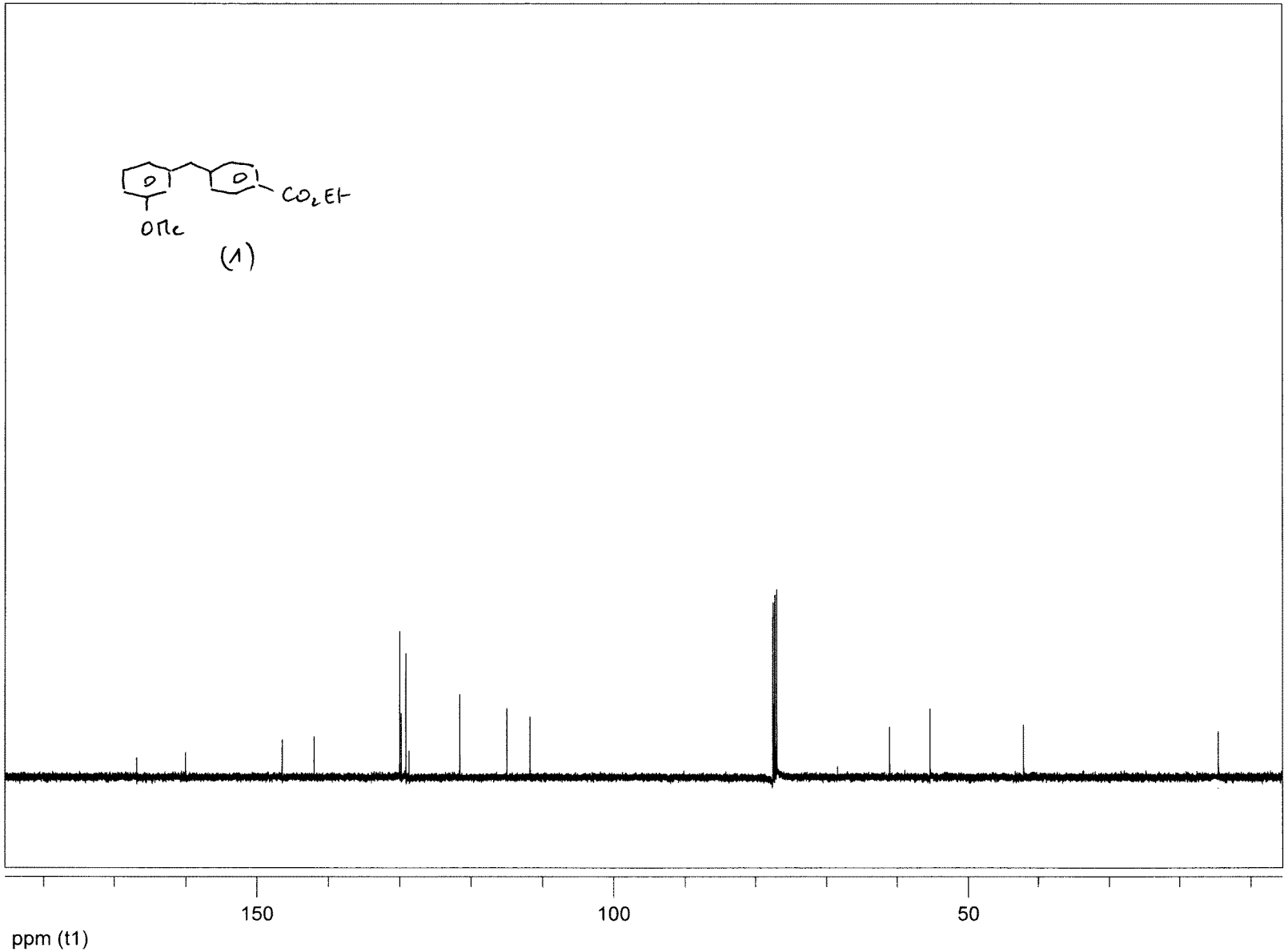
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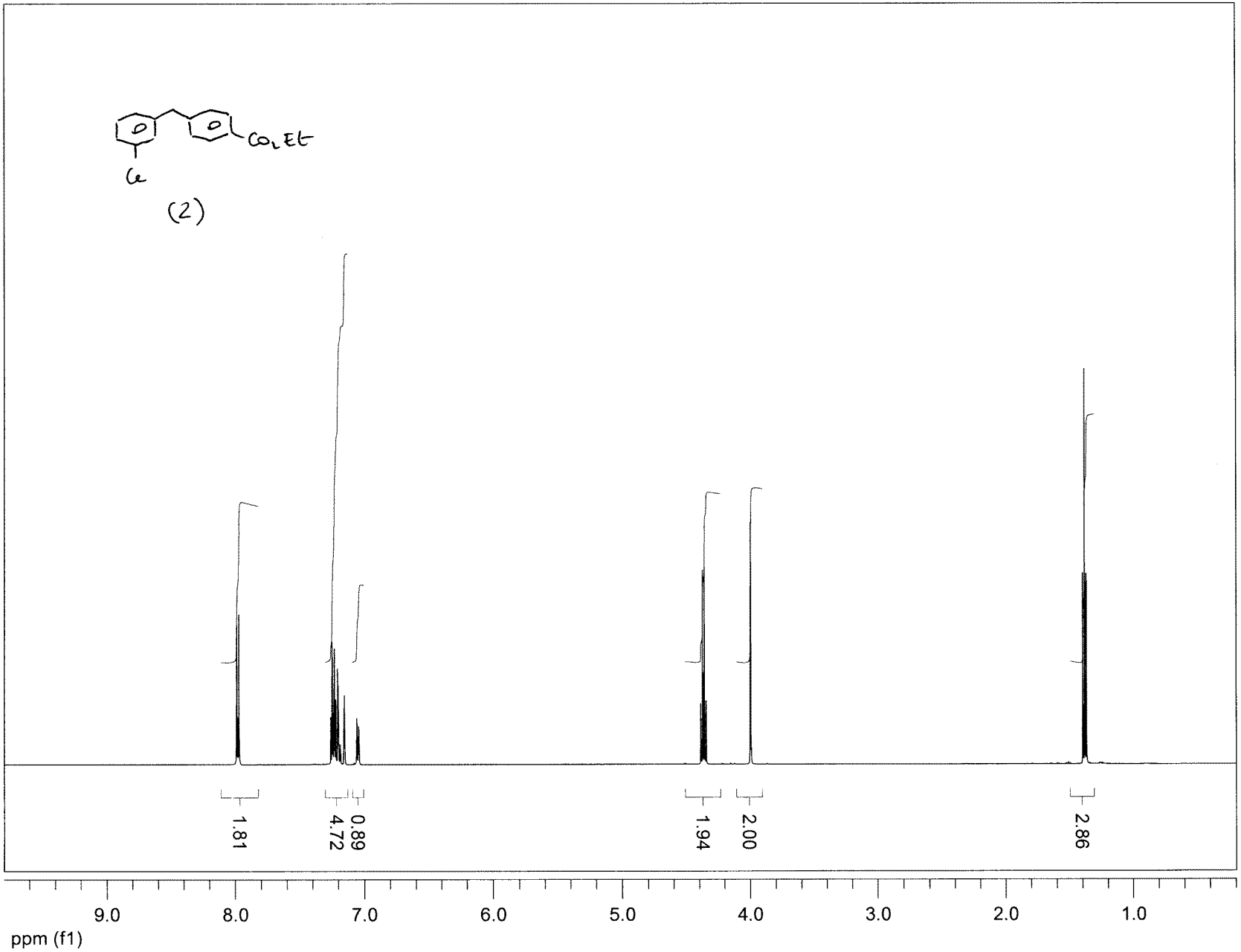
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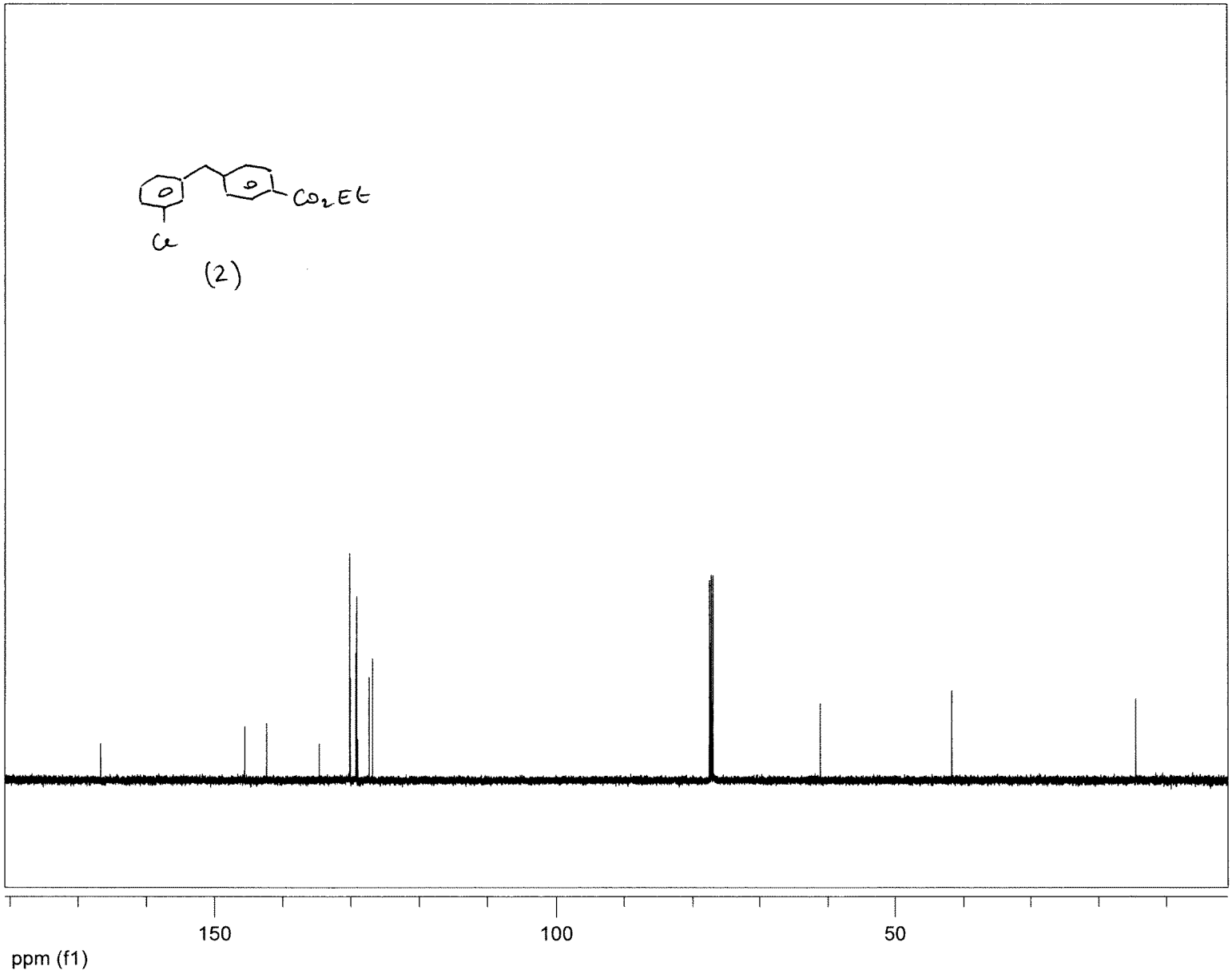
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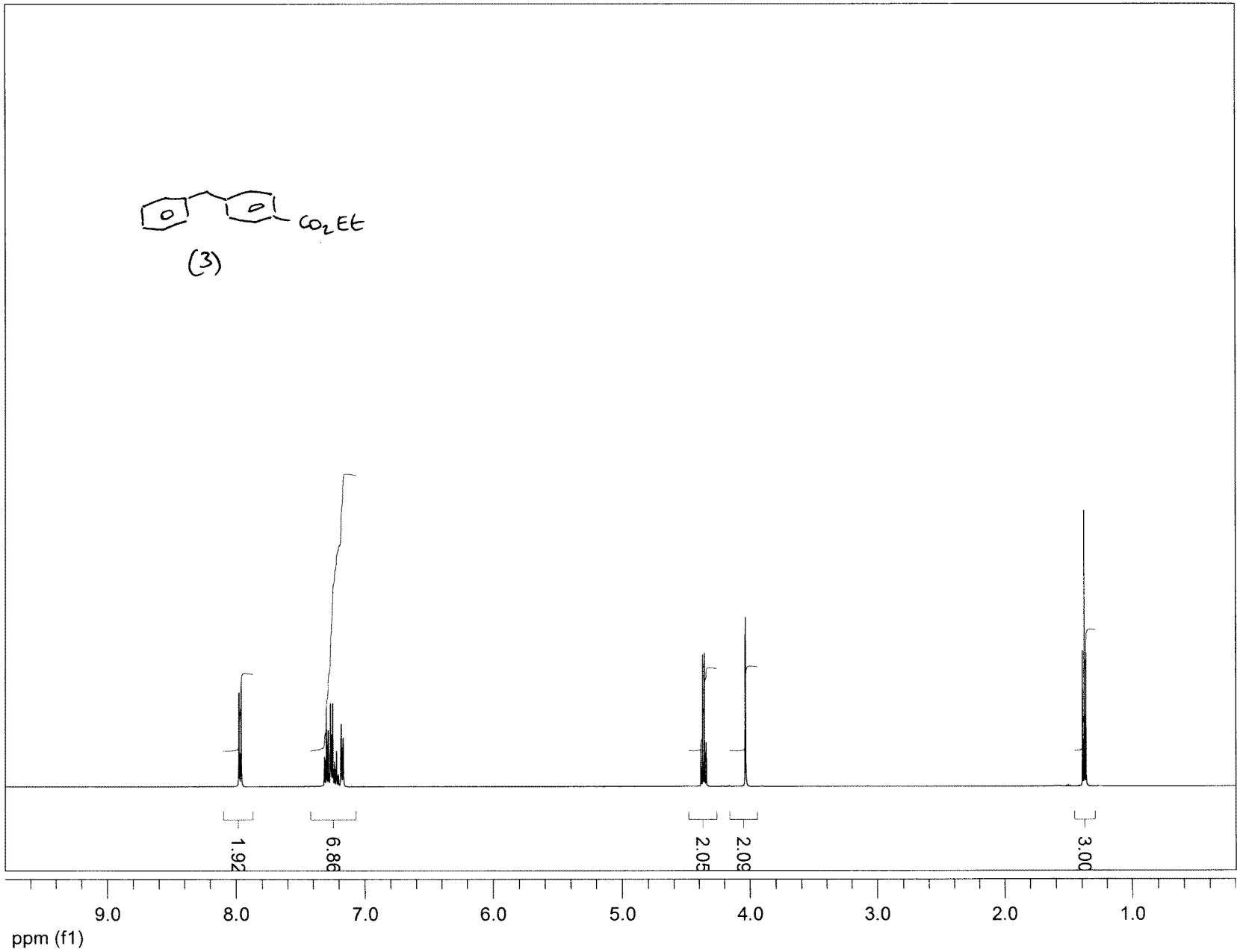
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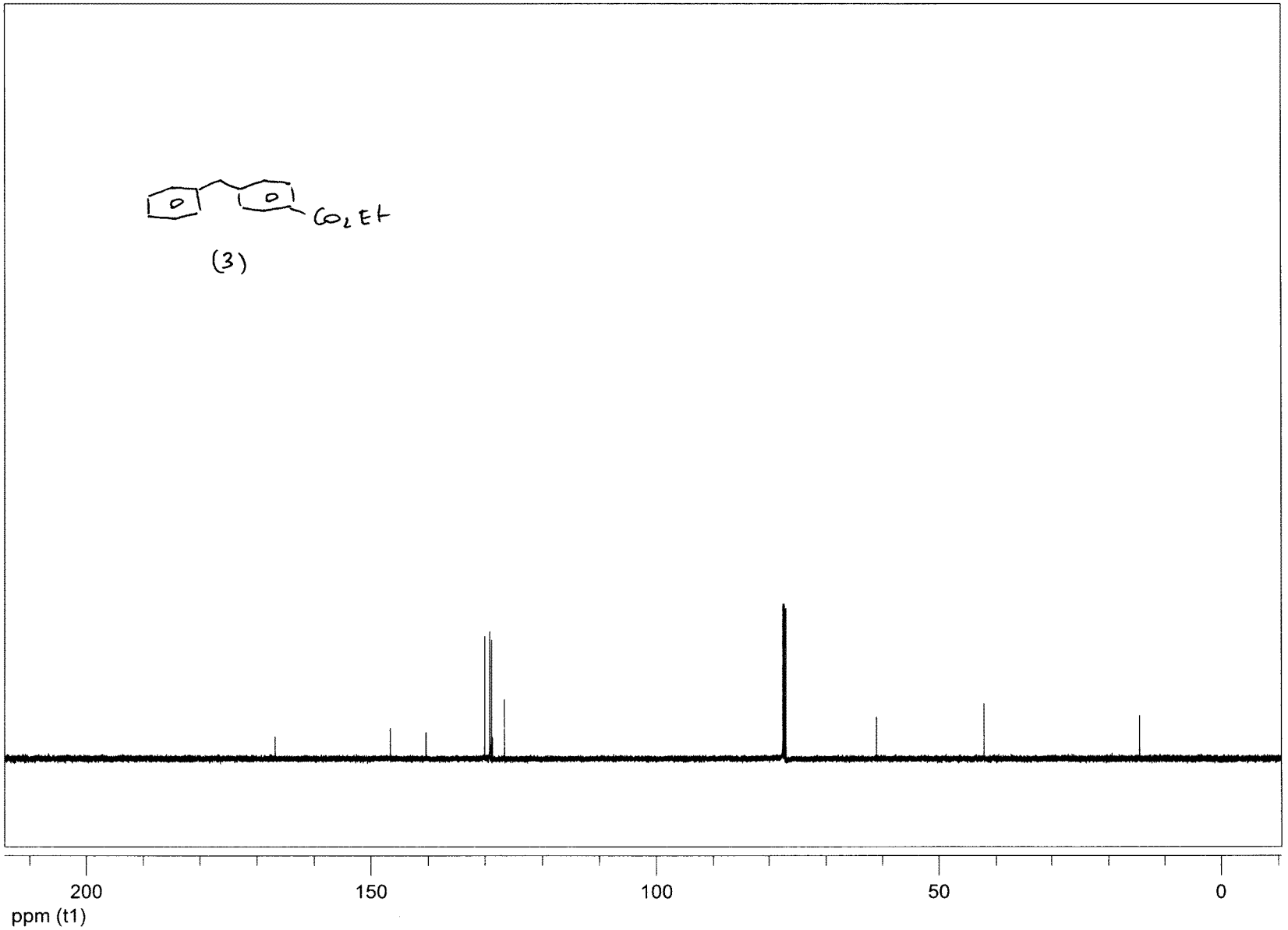
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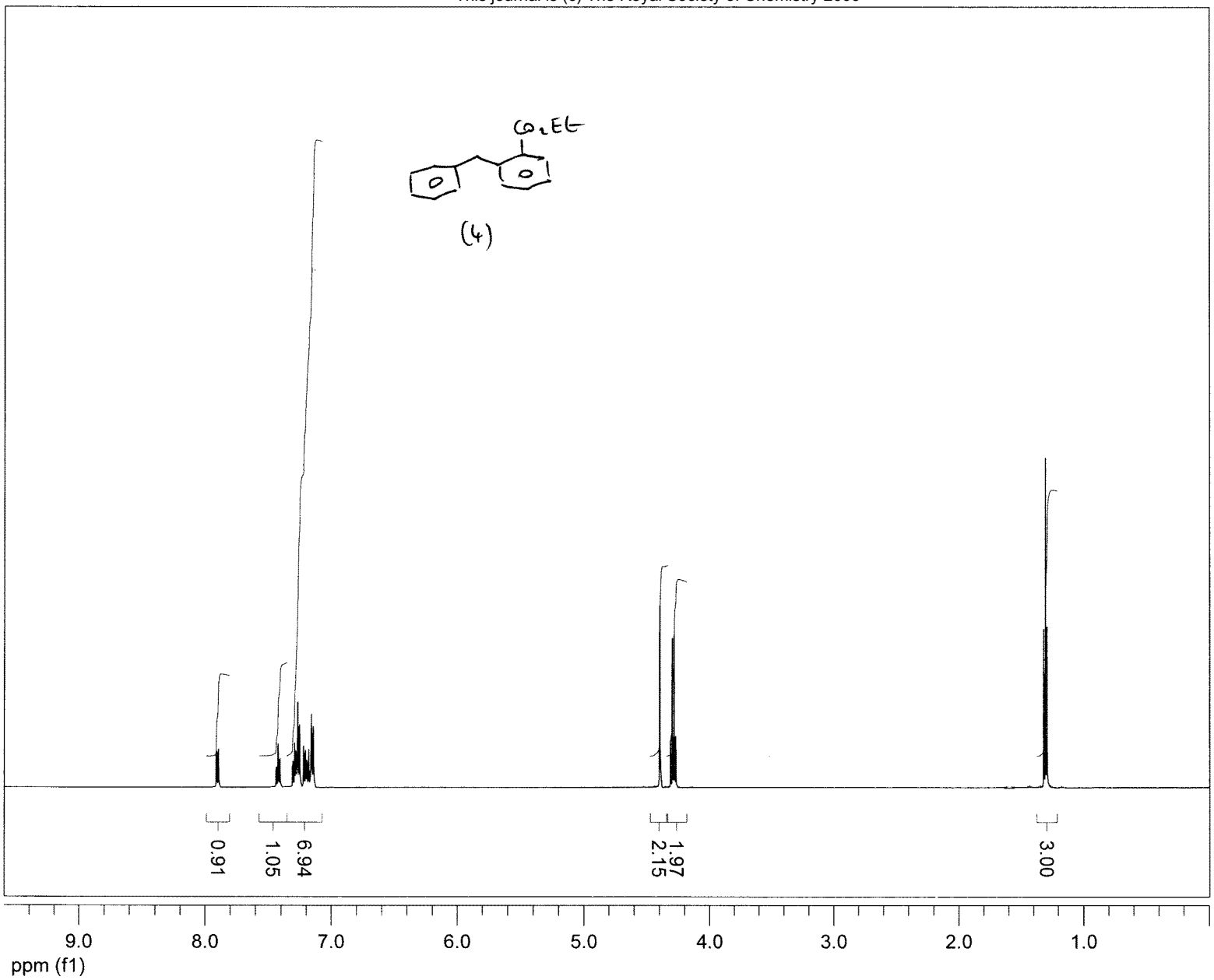
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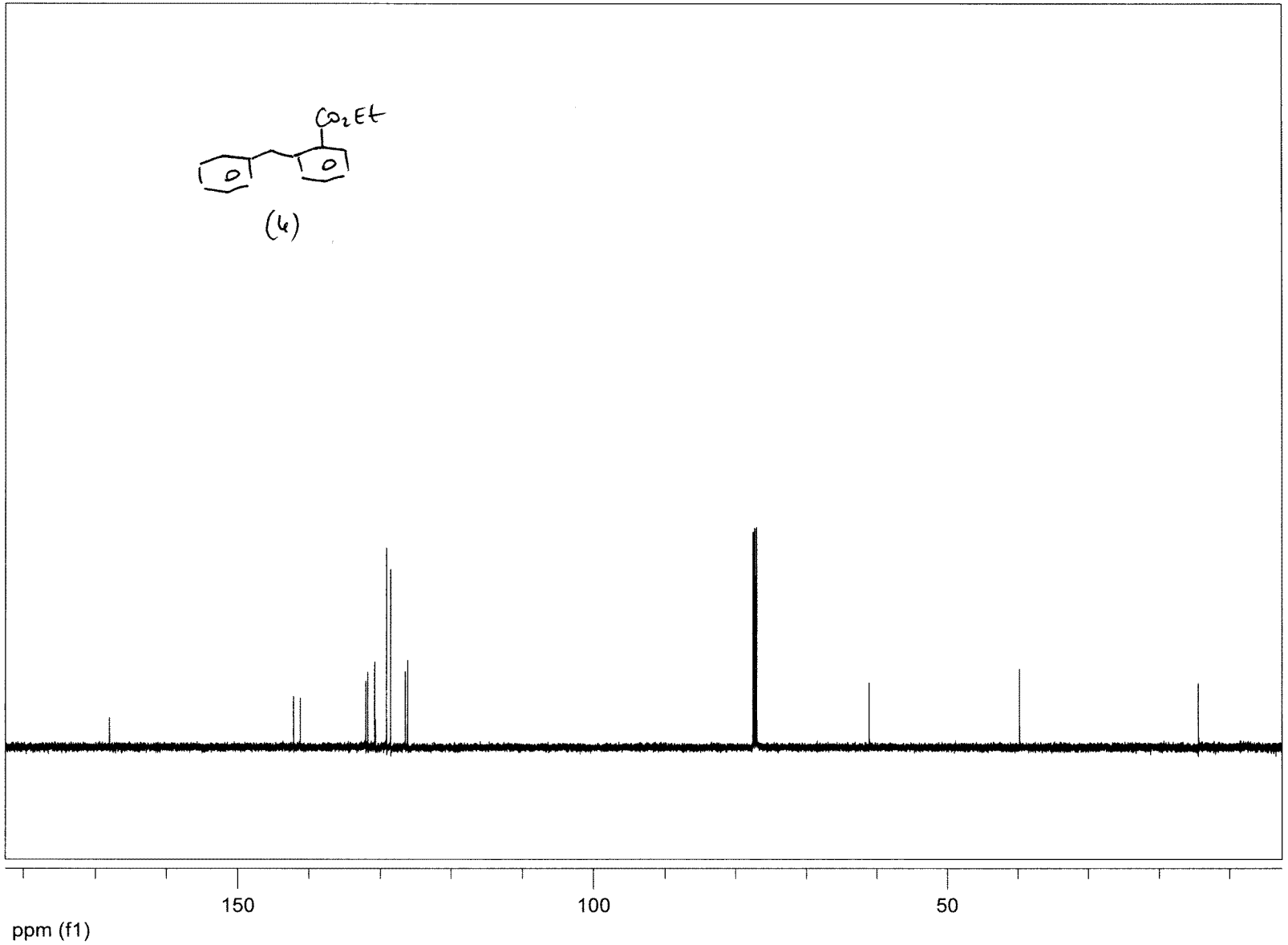
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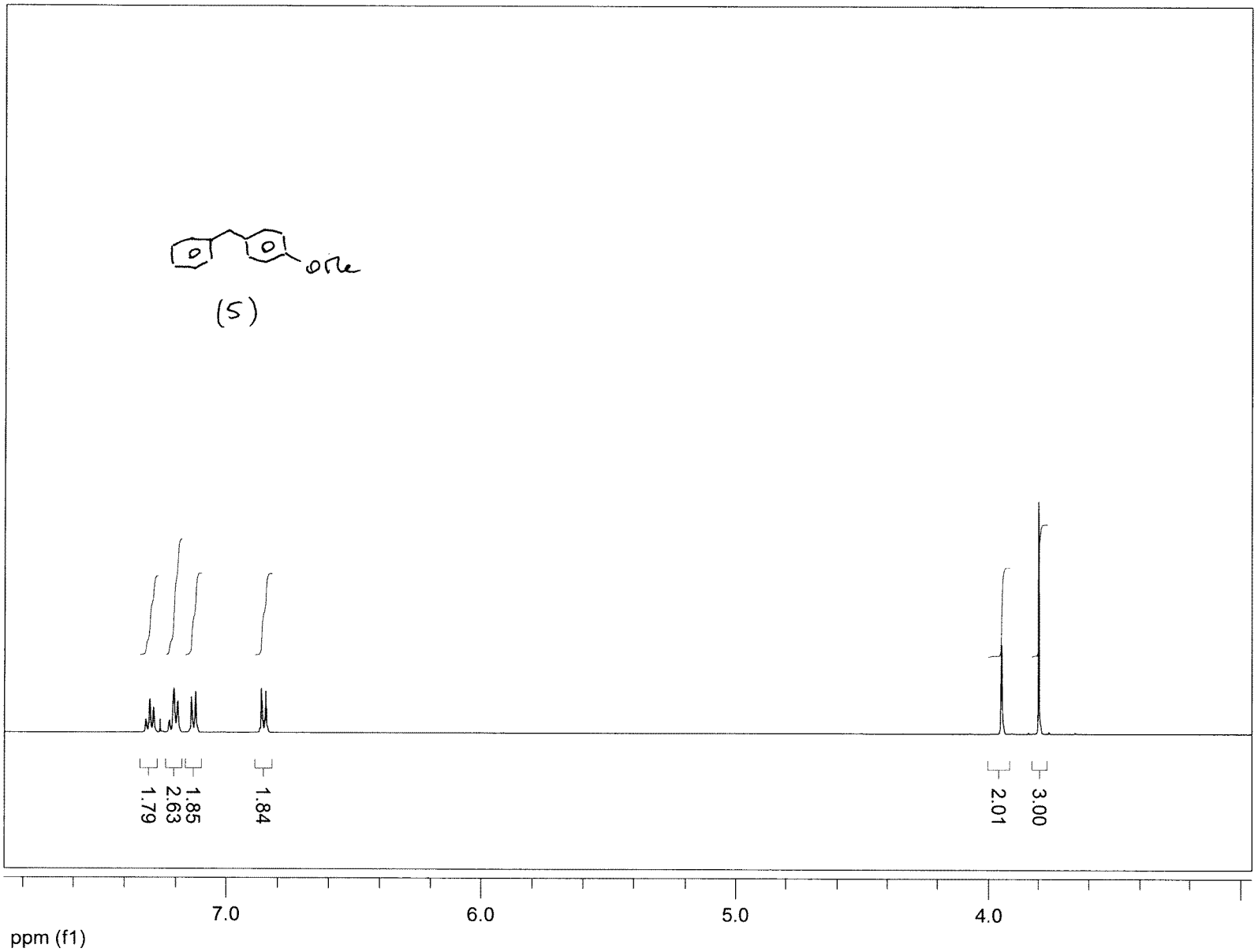
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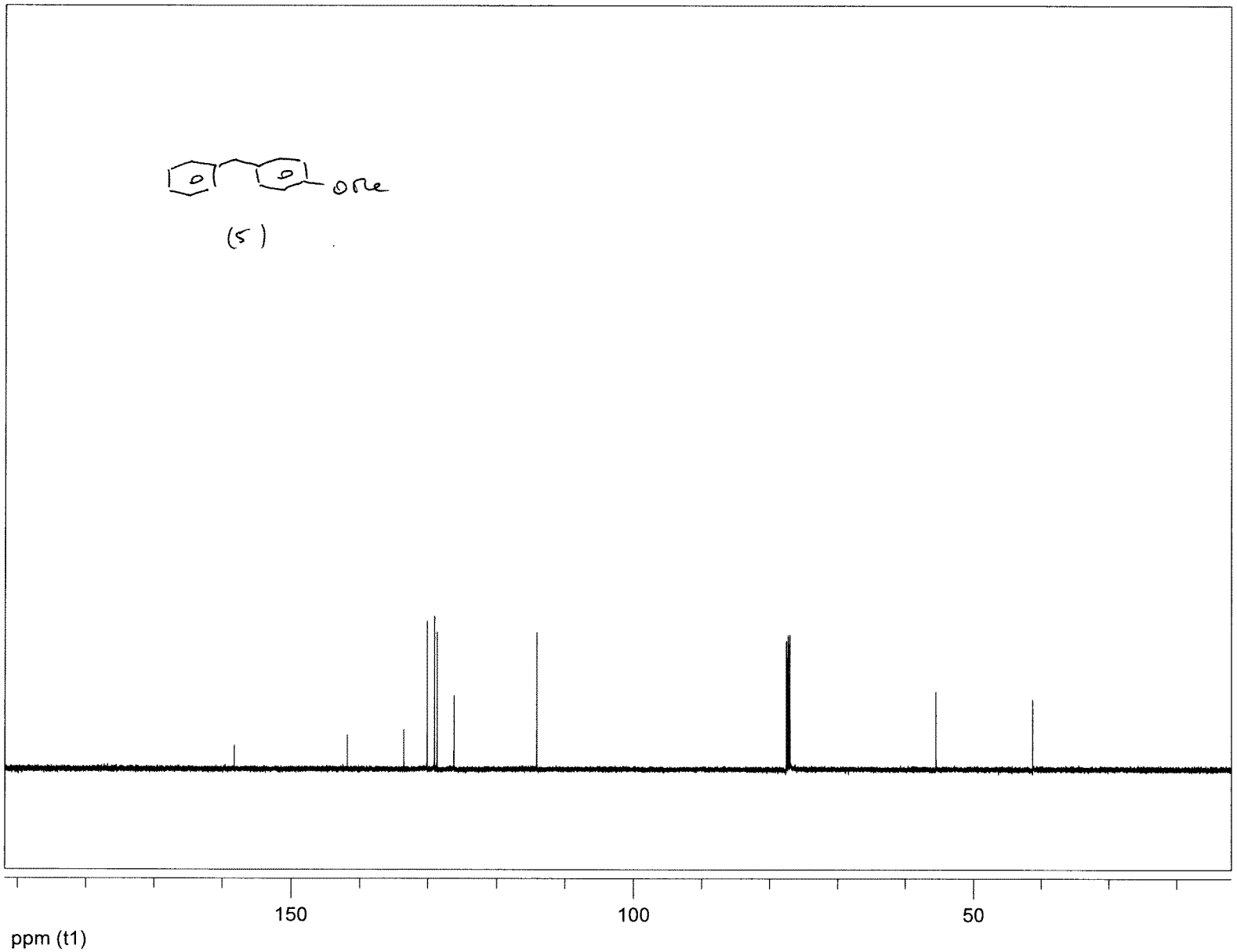
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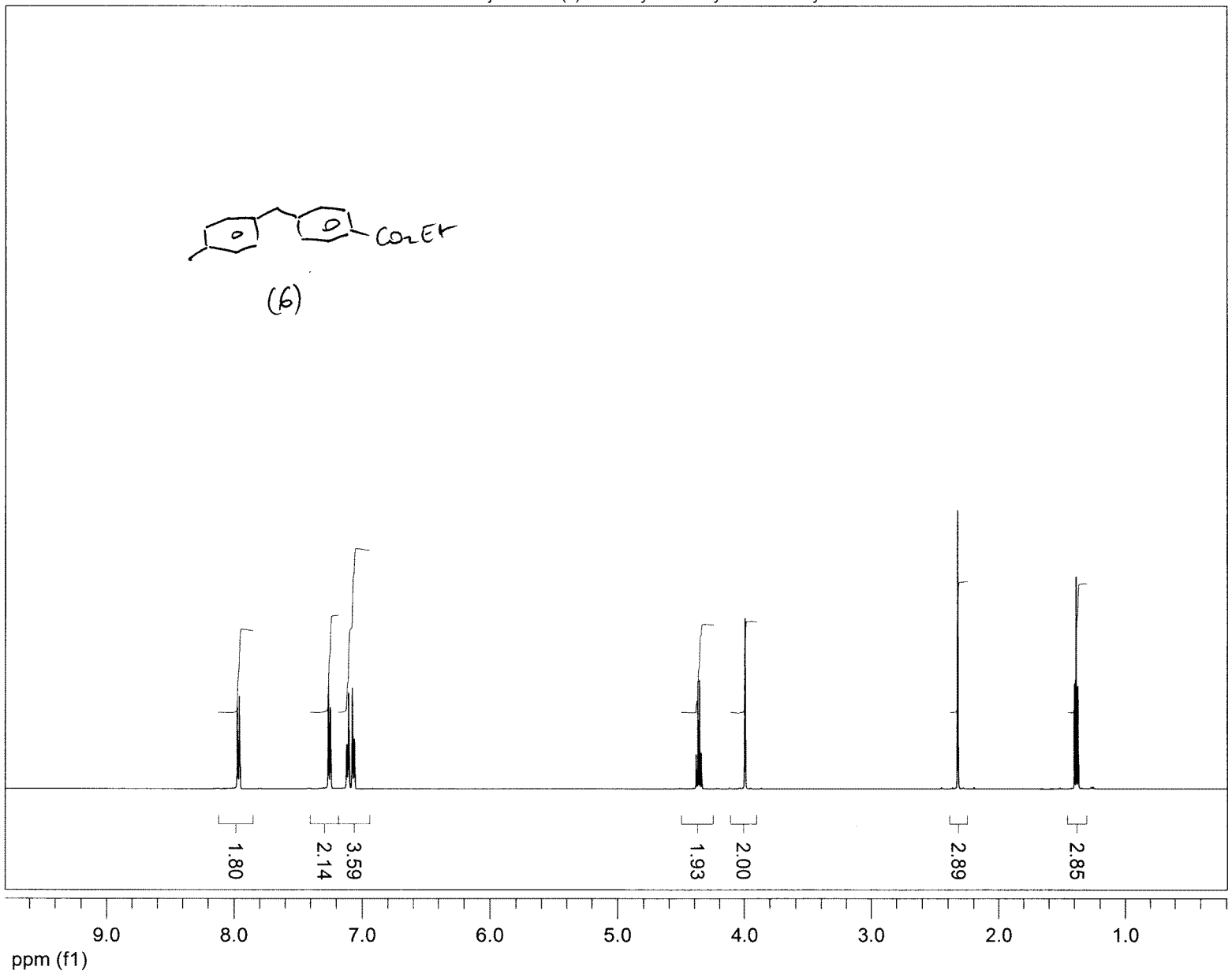
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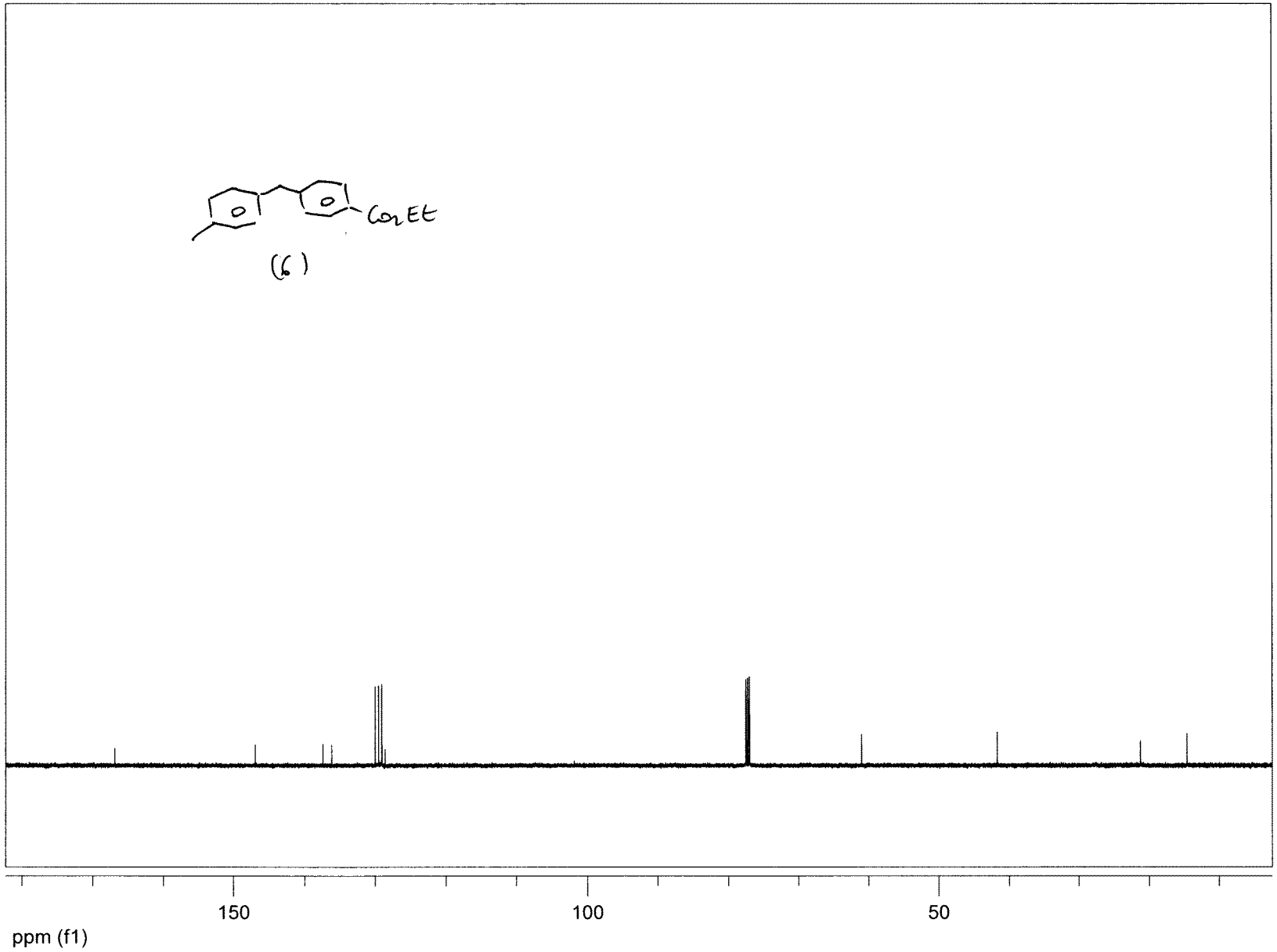
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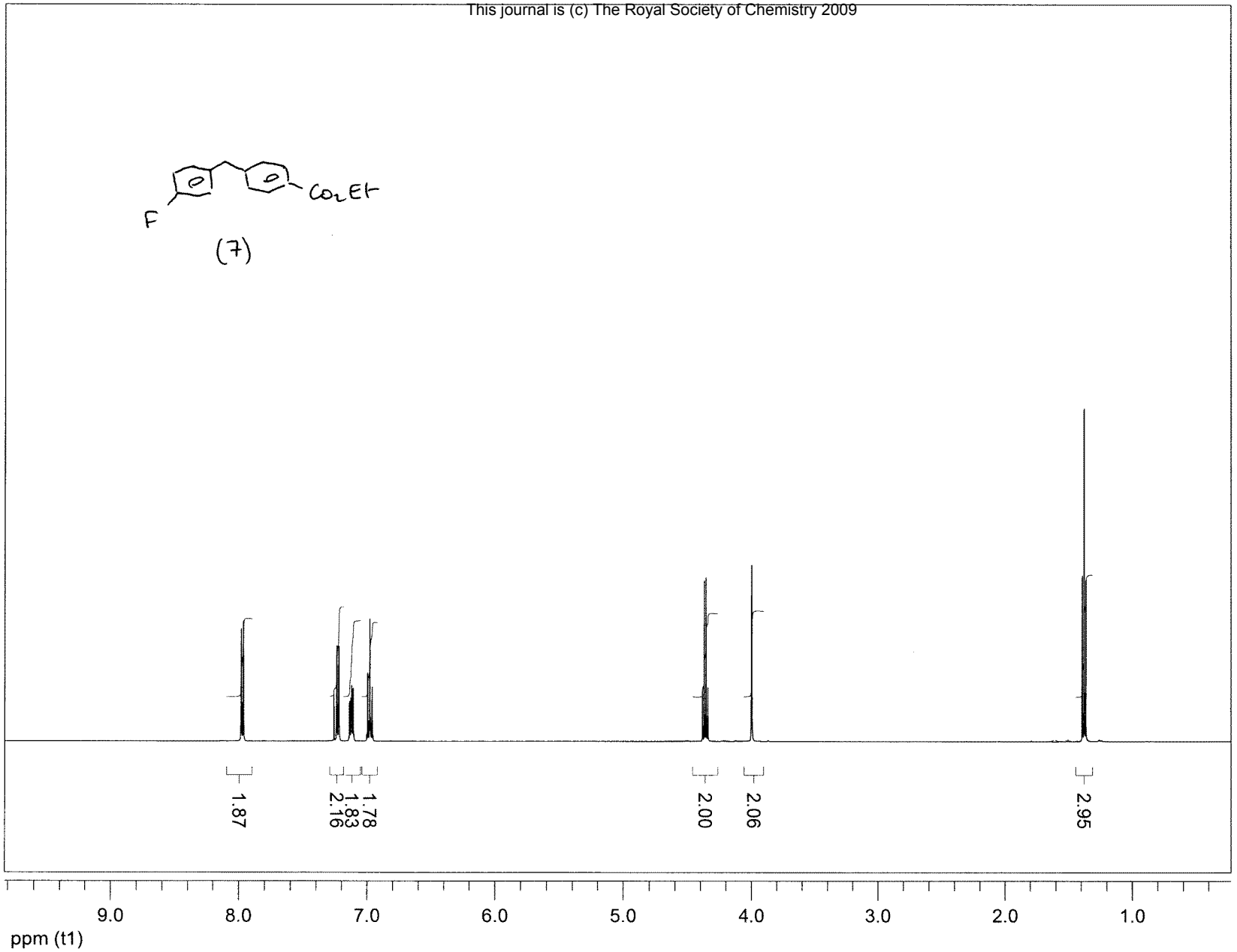
(6)
150
100
50
ppm (f1)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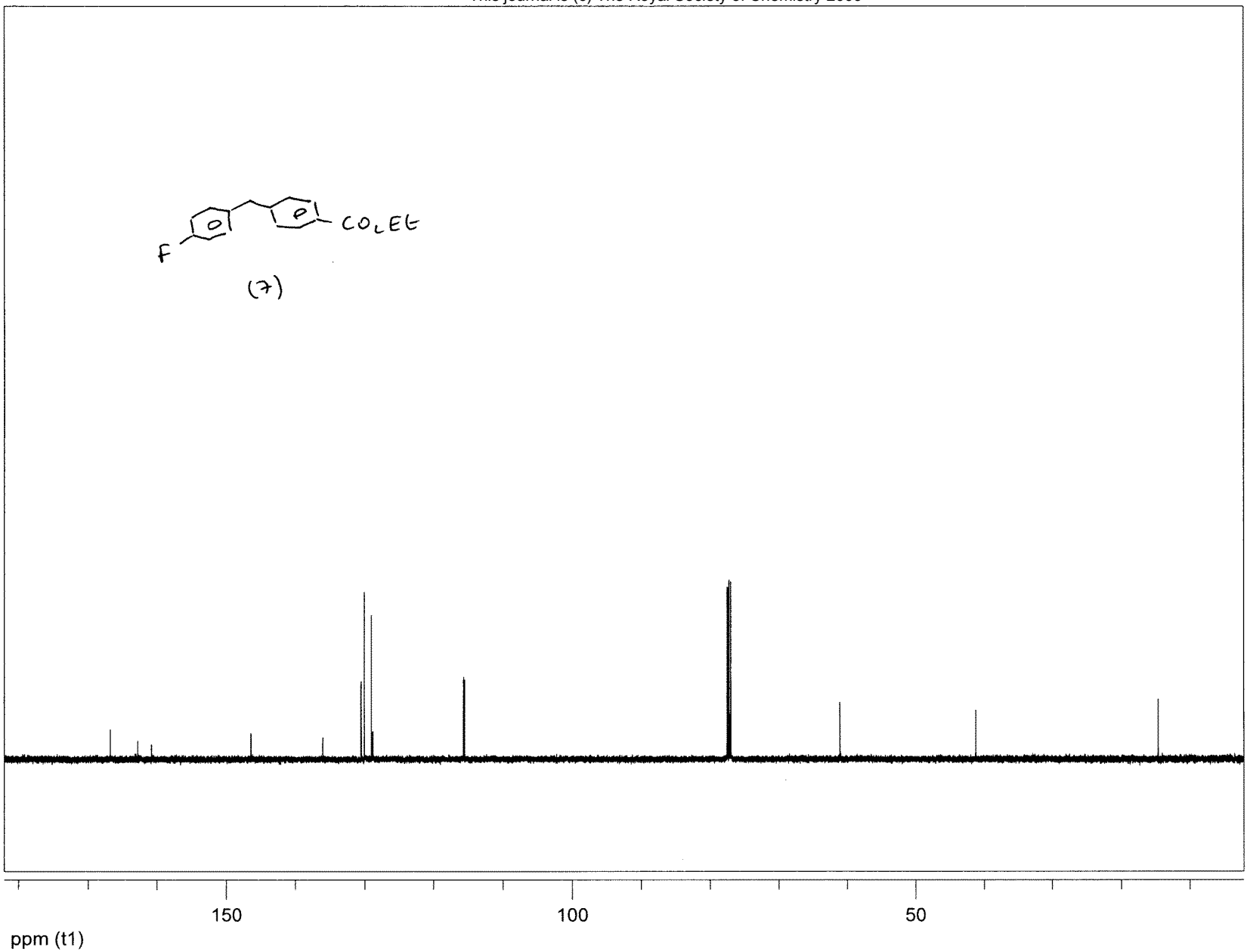
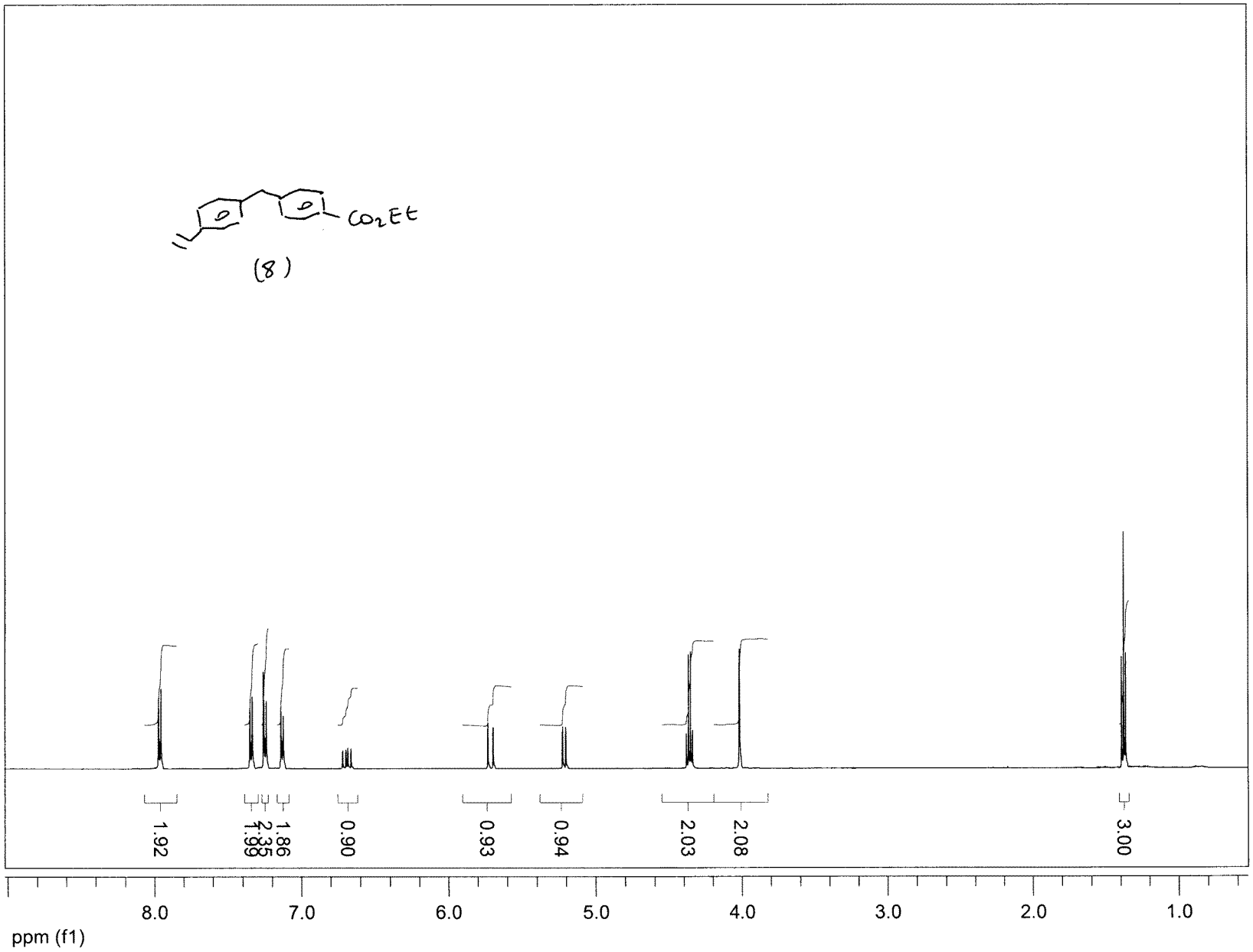
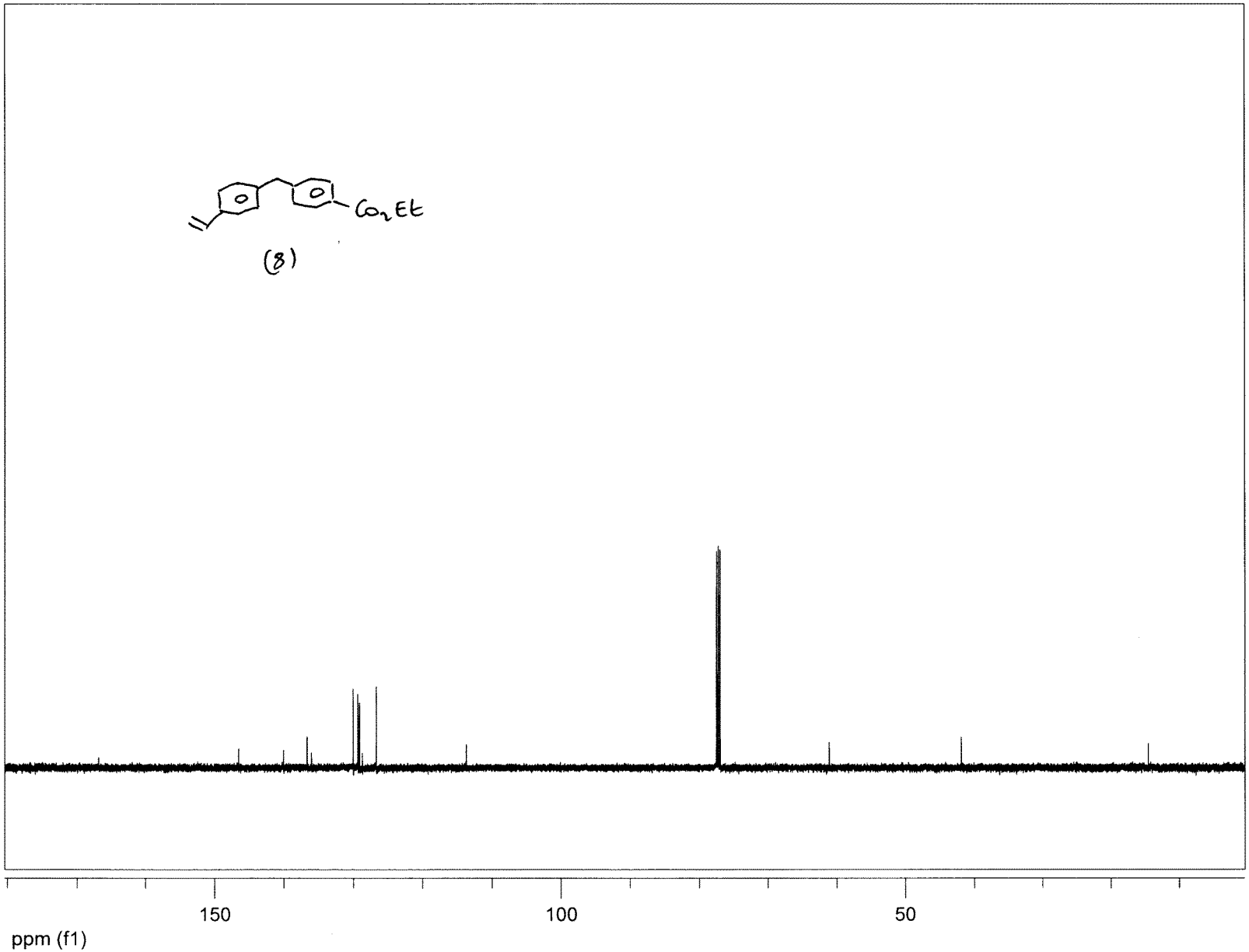
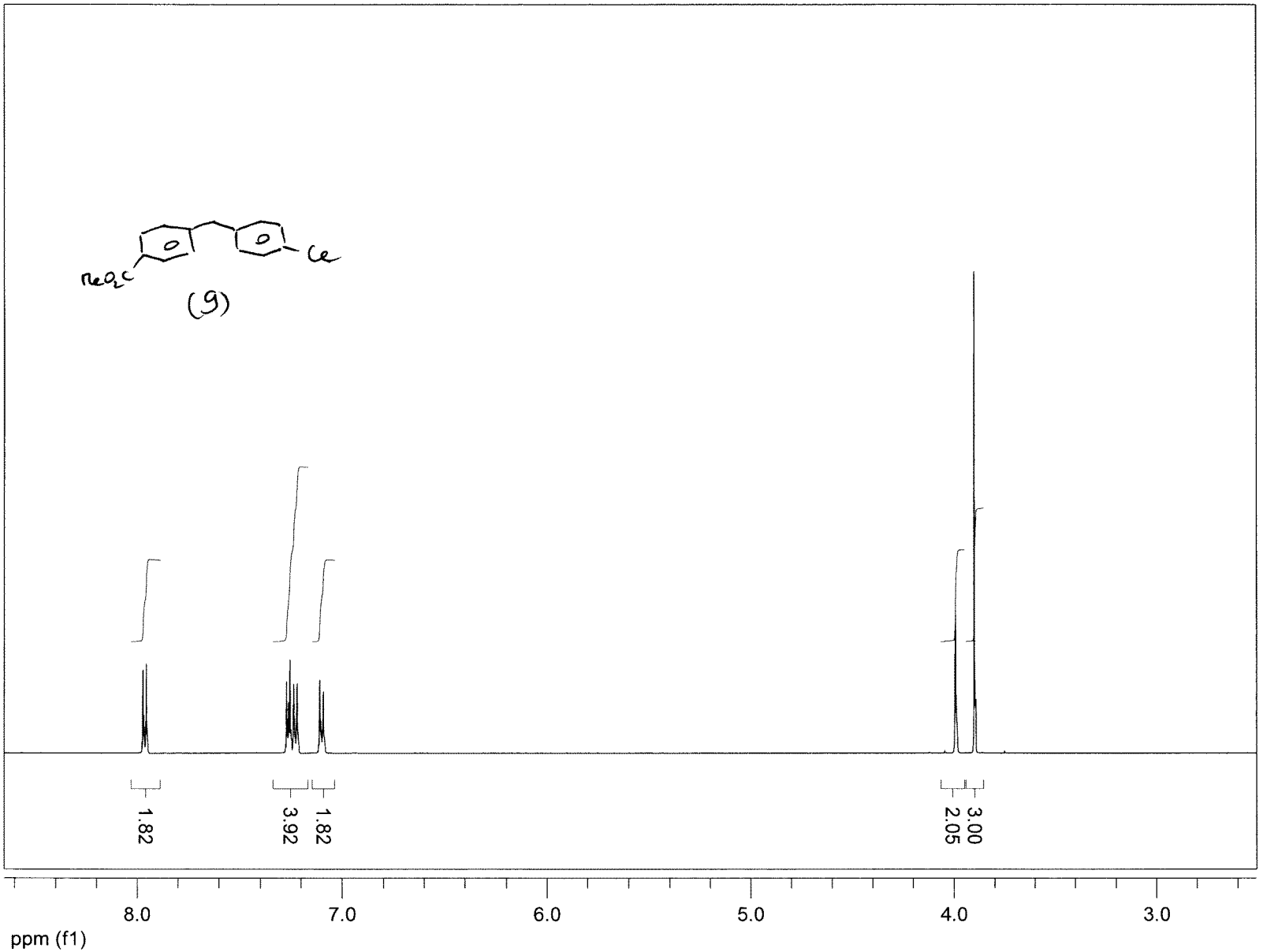
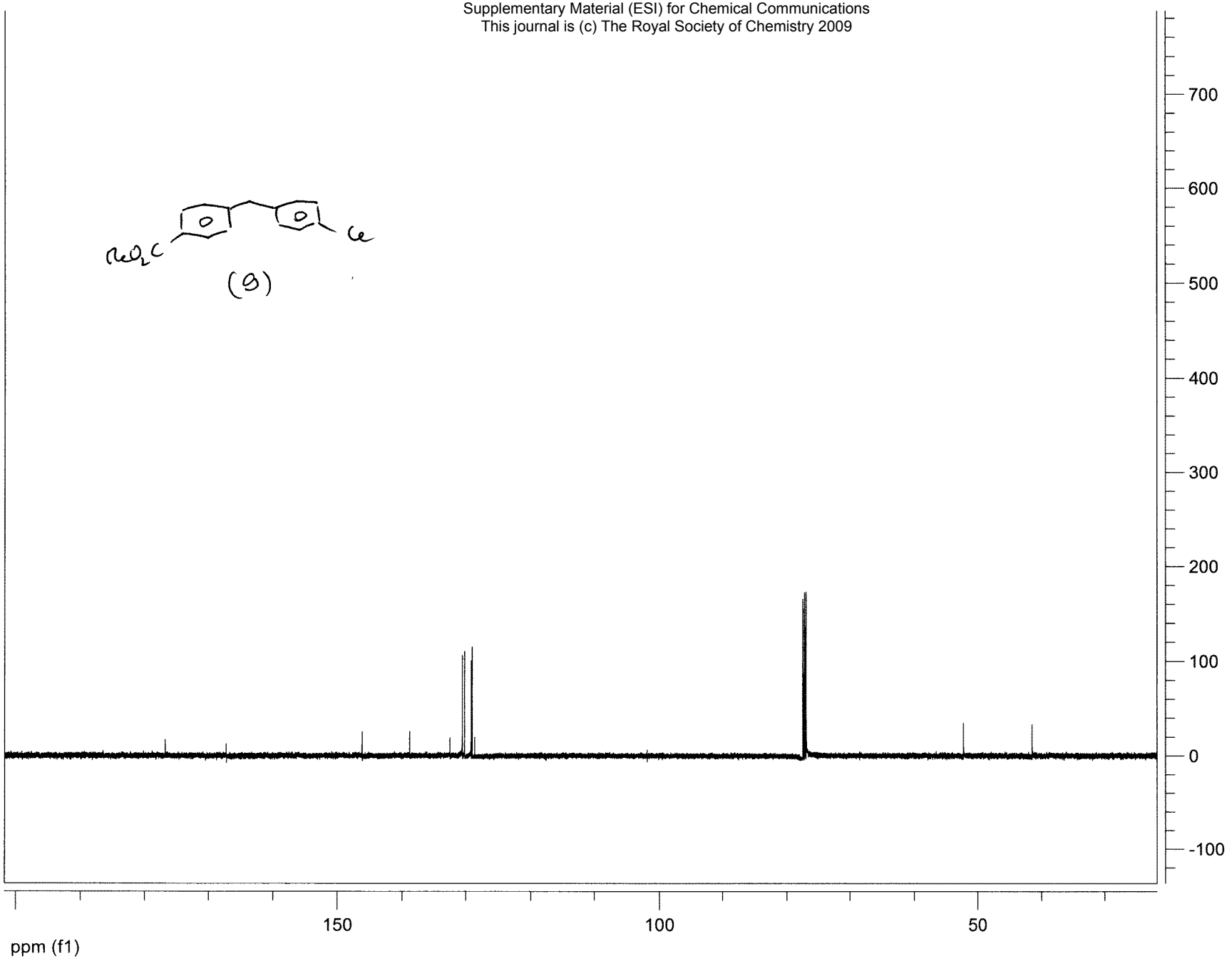
4.0
3.0
2.0
1.0
ppm (t1)

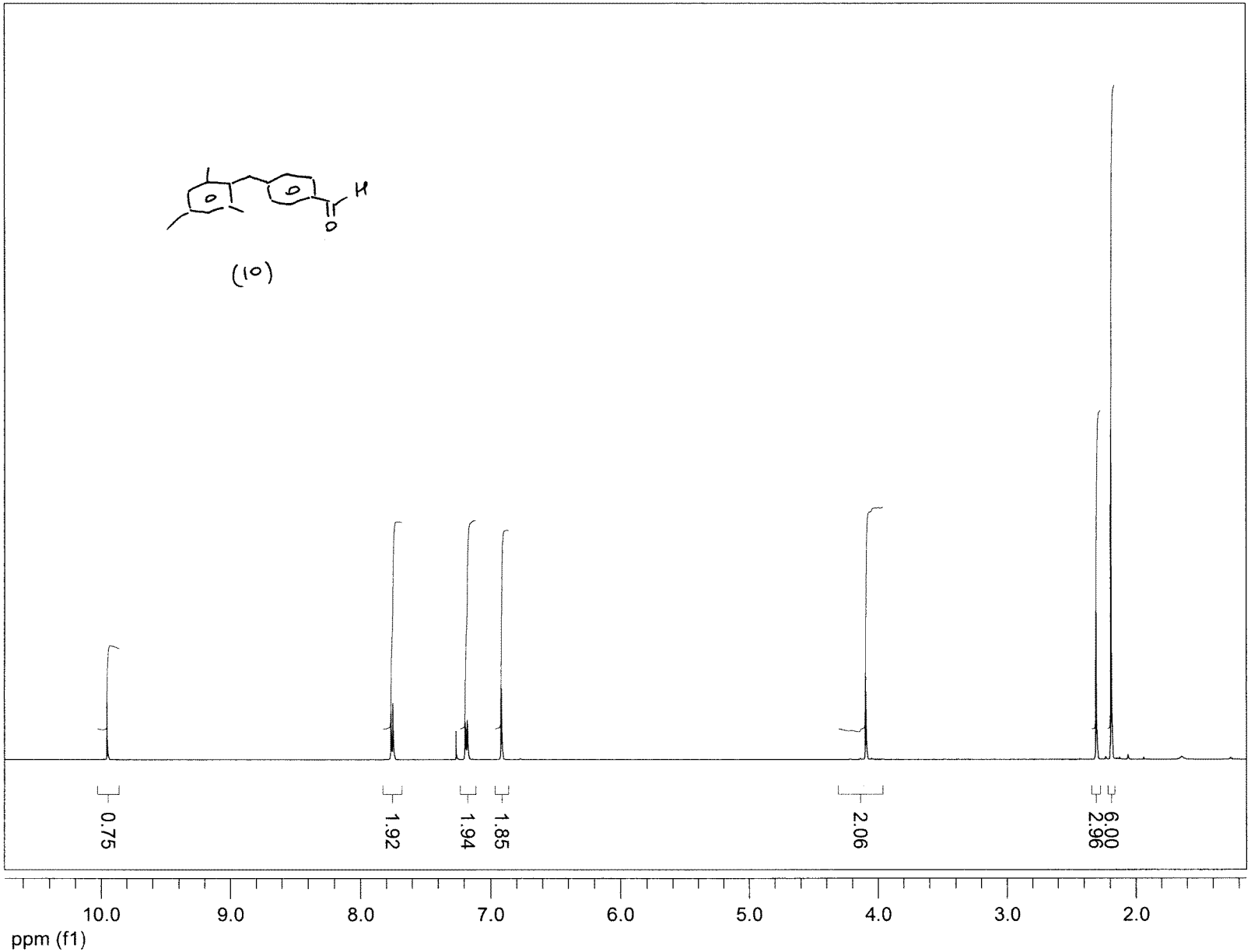

F
CO2Et
(7)
150
100
50
ppm (t1)

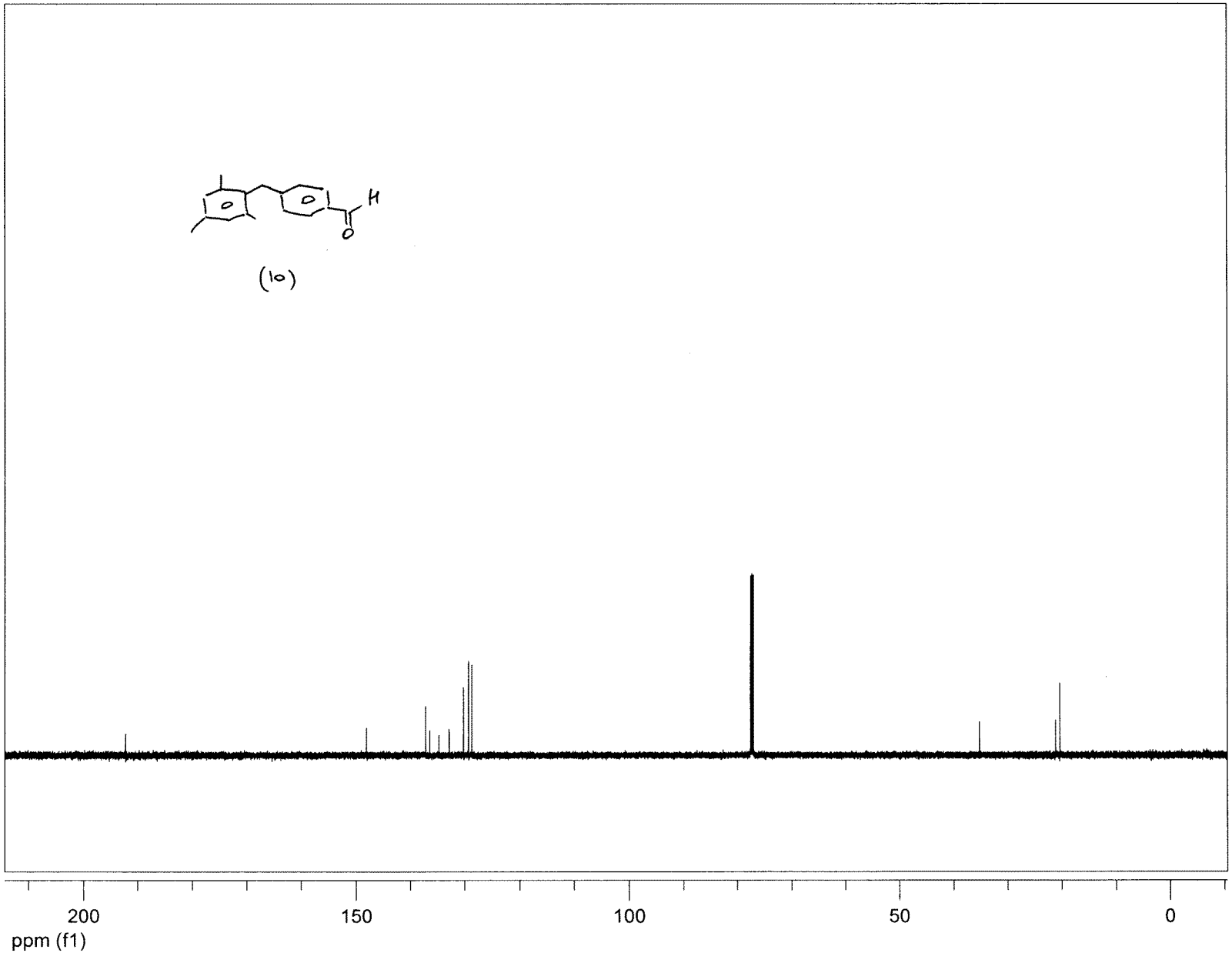

CO2Et
(8)
1.92
1.99
2.35
1.86
0.90
0.93
0.94
2.03
2.08
3.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

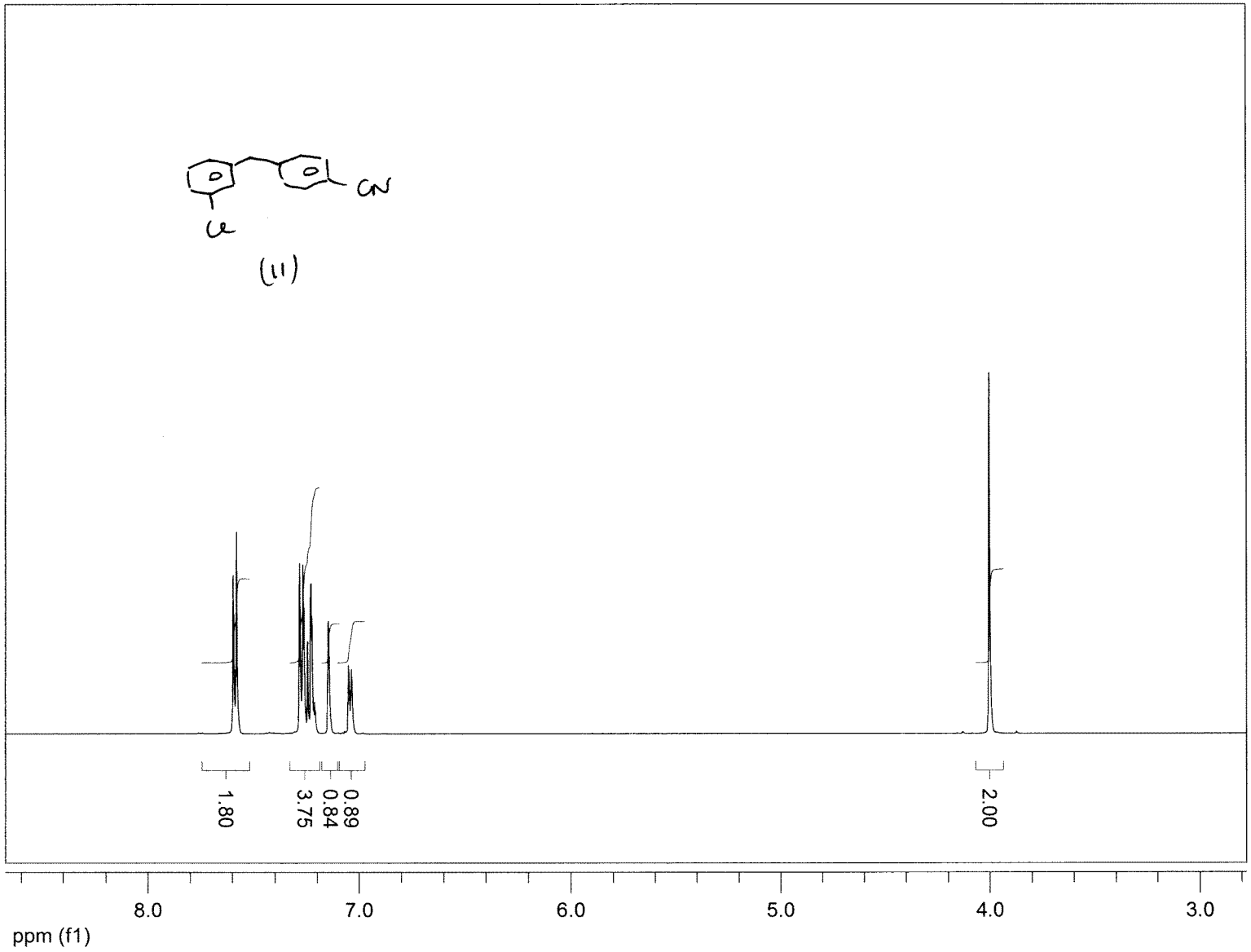

CO2Et
(8)
150
100
50
ppm (f1)


(9)
1.82
3.92
1.82
2.05
3.00
8.0
7.0
6.0
5.0
4.0
3.0
ppm (f1)

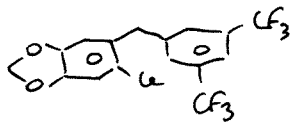

MeO2C
Me
(8)
700
600
500
400
300
200
100
0
-100
150
100
50
ppm (f1)


H
O
(10)
0.75
1.92
1.94
1.85
2.06
2.96
6.00
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (f1)

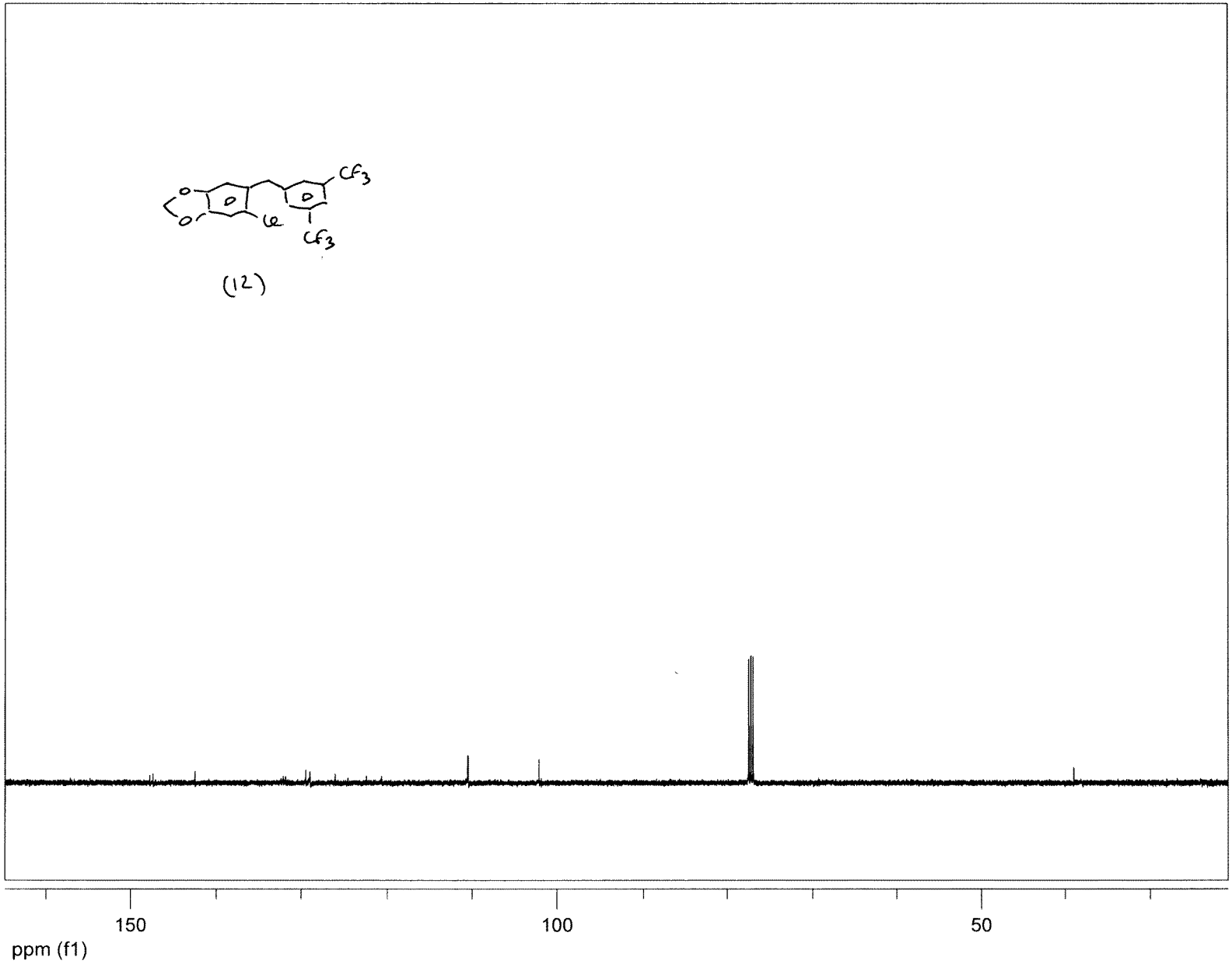

H
O
(10)
200
150
100
50
0
ppm (f1)

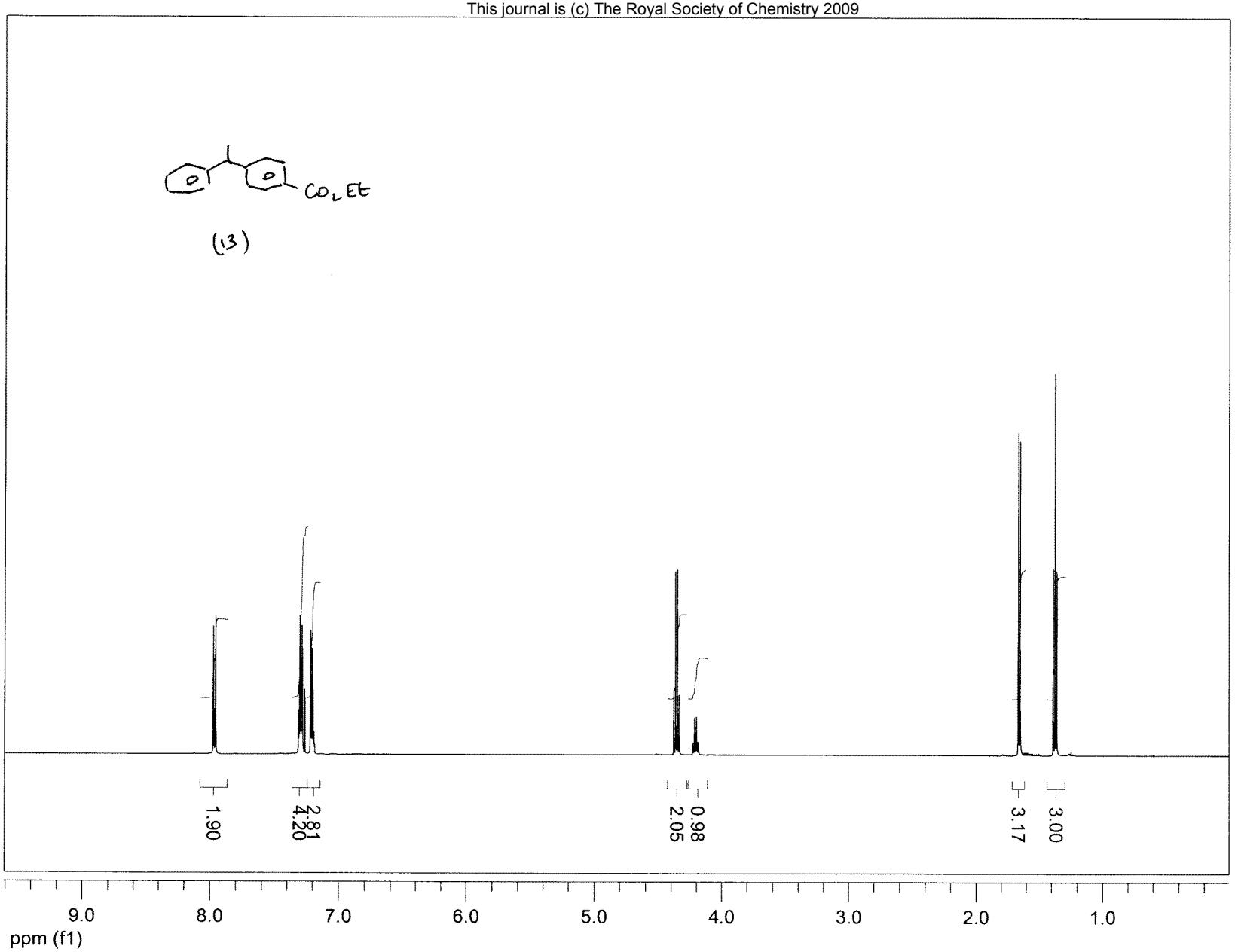

CN
Cl
(11)
1.80
3.75
0.84
0.89
2.00
8.0
7.0
6.0
5.0
4.0
3.0
ppm (f1)

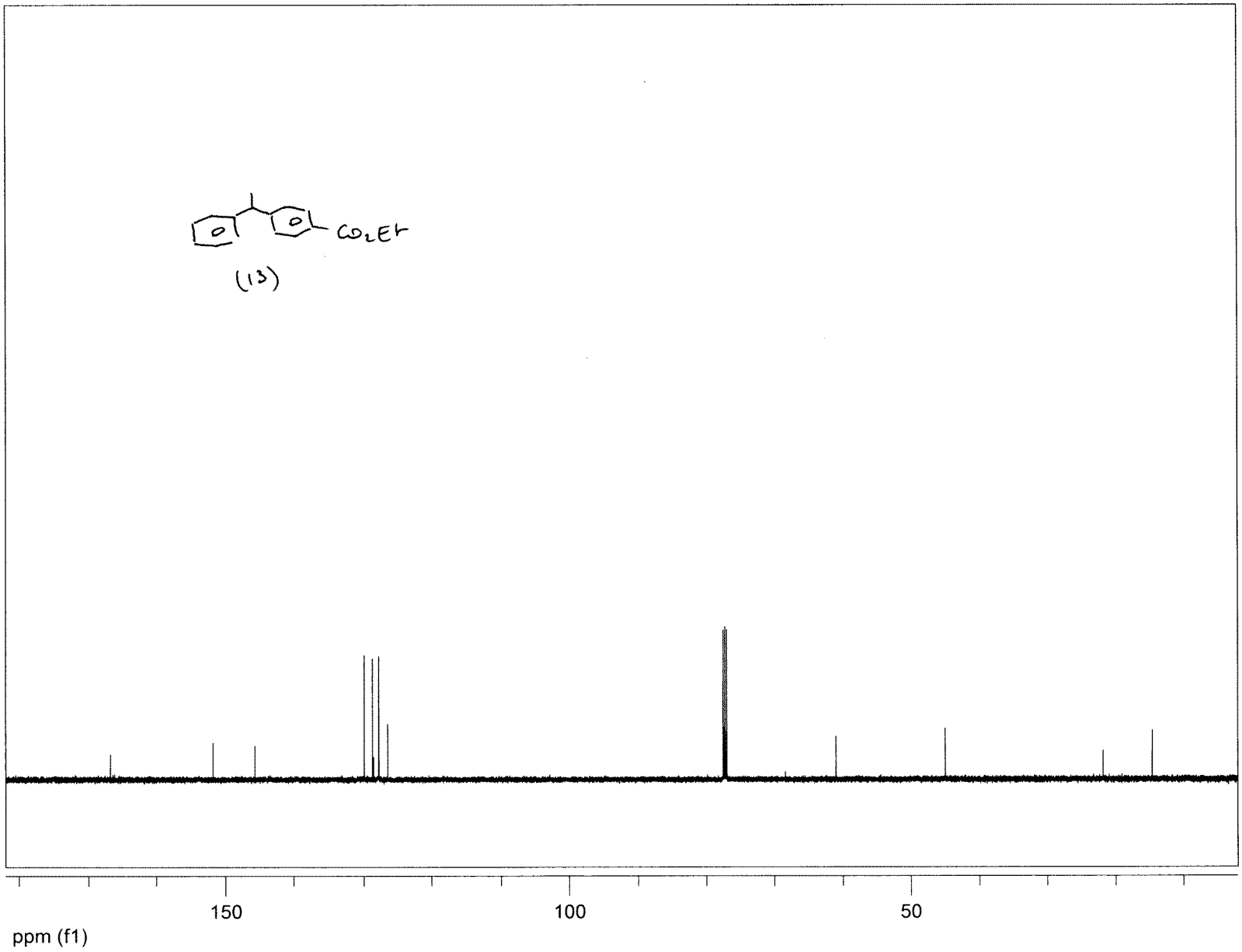
(11)



(12)


CF3
CF3
(12)
150
100
50
ppm (f1)


CO2Et
(13)
1.90
4.20
2.81
2.05
0.98
3.17
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


CO2Et
(13)
150
100
50
ppm (f1)