Supporting Information

Cu(I)-catalyzed annulation for the synthesis of substituted naphthalenes using *o*-bromobenzaldehydes and *β*-ketoesters as substrates

Chandi C. Malakar, Kavitha Sudheendran, Hans-Georg Imrich, Sabine Mika and Uwe Beifuss*

Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstr. 30, 70599 Stuttgart (Deutschland)

Fax: (+49) 711-459-22951, E-mail: ubeifuss@uni-hohenheim.de

Graphical Abstract

Table of Contents

1. General remarks

All starting materials were purchased from commercial suppliers (Sigma-Aldrich Chemical Co., Acros Organics, Alfa-Aesar). The *o*-bromobenzaldehydes were used without further purification. All *β*-ketoesters were freshly distilled over $MgSO_4$ prior to use. All reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. Solvents used in extraction and purification were distilled prior to use. TLC was performed on Alugram SIL G/UV_{254} (Macherey and Nagel). Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in an ethanolic vanillin solution followed by heating. Products were purified by flash chromatography on silica gel 60 M, 230 - 400 mesh (Macherey & Nagel). Melting points were determined on a Büchi melting point apparatus B-545 with open capillary tubes and are not corrected. IR spectra were measured on a Perkin-Elmer Spectrum One (FT-IR-spectrometer). UV/VIS spectra were recorded with a Varian Cary 50. ^{1}H (^{13}C) NMR spectra were recorded at 300 (75) MHz on a Varian ^{Unity}Inova spectrometer using $CDCl_3$ as solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at $\delta_{H/C}$ 7.26 /77.00 ($CDCl_3$) relative to TMS as internal standards. HSQC-, HMBC- and COSY-spectra were recorded on a Varian ^{Unity}Inova at 300 MHz. Coupling constants *J* [Hz] were directly taken from the spectra and are not averaged.

2. General procedures for the Cu(I)-catalyzed synthesis of naphthalenes 3a-i

a) General procedure using *o*-bromobenzaldehydes as substrates

An oven dried 10 mL vial was charged successively with 9.5 mg (0.05 mmol) CuI (99.999%), 18.6 mg (0.15 mmol) 2-picolinic acid (99%) (**4**), 652 mg (2.0 mmol) Cs_2CO_3 (99.9%), 0.5 mmol of an *o*-bromobenzaldehyde **1** and 160 mg molecular sieves (4Å). The vial was sealed, evacuated and backfilled with argon (six times). Then, 1.5 mmol freshly distilled *β*-ketoester **2** and 3 mL of freshly distilled DMF were added using a syringe. The reaction mixture was heated in an oil bath at 60 °C for 40 h and the reaction was monitored by TLC (PE/EtOAc = 5:1). After cooling to room temperature the reaction mixture was partitioned between 50 mL ethyl acetate and 20 mL brine. The aqueous phase was extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The residue thus obtained was purified by flash column chromatography over silica gel (PE/EtOAc = 20:1).

b) Synthesis of 3a using *o*-Iodobenzaldehyde (1b) as substrate

An oven dried 10 mL vial was charged successively with 9.5 mg (0.05 mmol) CuI (99.999%), 18.6 mg (0.15 mmol) 2-picolinic acid (99%) (**4**), 652 mg (2.0 mmol) Cs_2CO_3 (99.9%), 116.0 mg (0.5 mmol) of *o*-iodobenzaldehyde (**1b**) and 160 mg molecular sieves (4Å). The vial was sealed, evacuated and backfilled with argon (six times). Then, 195.0 mg (1.5 mmol) freshly distilled ethyl acetoacetate (**2a**) and 3 mL of freshly distilled DMF were added using a syringe. The reaction mixture was heated in an oil bath at 60 °C for specified time and the reaction was monitored by TLC (PE/EtOAc = 5:1). After cooling to room temperature the reaction mixture was partitioned between 50 mL ethyl acetate and 20 mL brine. The aqueous phase was extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The residue thus obtained was purified by flash column chromatography over silica gel (PE/EtOAc = 20:1).

Table 1 Reactions between **1b** and **2a**.

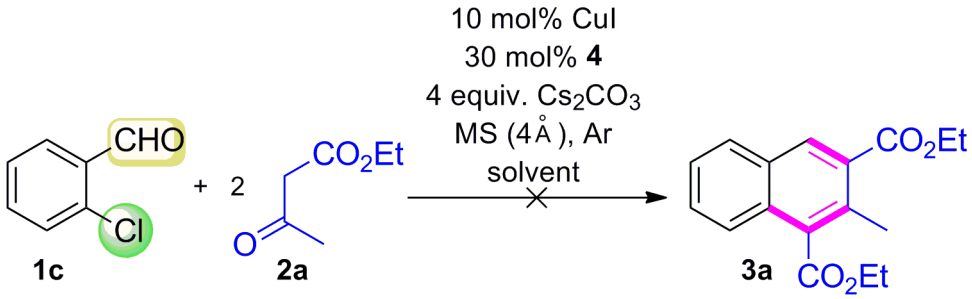
entry	T (°C)	*t* (h)	Solvent	**3a** yield (%)
1	60	40	DMF	73
2	60	20	DMF	63

c) **Attempted synthesis of 3a using *o*-chlorobenzaldehyde (1c) as substrate**

An oven dried 10 mL vial was charged successively with 9.5 mg (0.05 mmol) CuI (99.999%), 18.6 mg (0.15 mmol) 2-picolinic acid (99%) (**4**), 652 mg (2.0 mmol) Cs_2CO_3 (99.9%), 70.0 mg (0.5 mmol) of *o*-chlorobenzaldehyde (**1c**) and 160 mg molecular sieves (4Å). The vial was sealed, evacuated and backfilled with argon (six times). Then, 195.0 mg (1.5 mmol) freshly

distilled ethyl acetoacetate **2a** and 3 mL of freshly distilled DMF or NMP were added using a syringe. The reaction mixture was heated in an oil bath and the reaction was monitored by TLC (PE/EtOAc = 5:1).

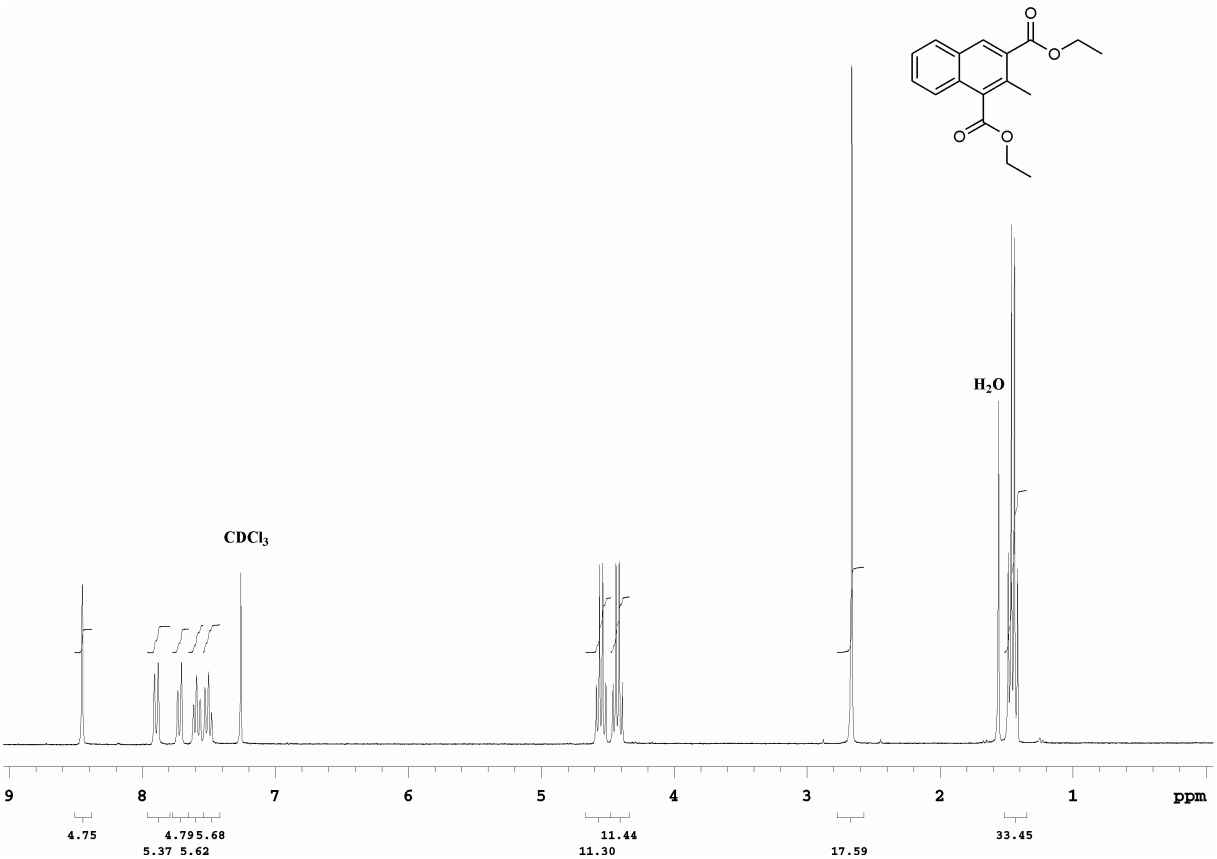
Table 2 Attempted synthesis of **3a** using **1c** and **2a**.



entry	T (°C)	*t* (h)	Solvent	**3a** yield (%)
1	60	40	DMF	--
2	40	40	DMF	--
3	60	16	DMF	--
4	100	16	DMF	--
5	100	24	NMP	--

3. NMR spectra for naphthalenes 3a-i

Diethyl-2-methylnaphthalene-1,3-dicarboxylate (3a)[1]



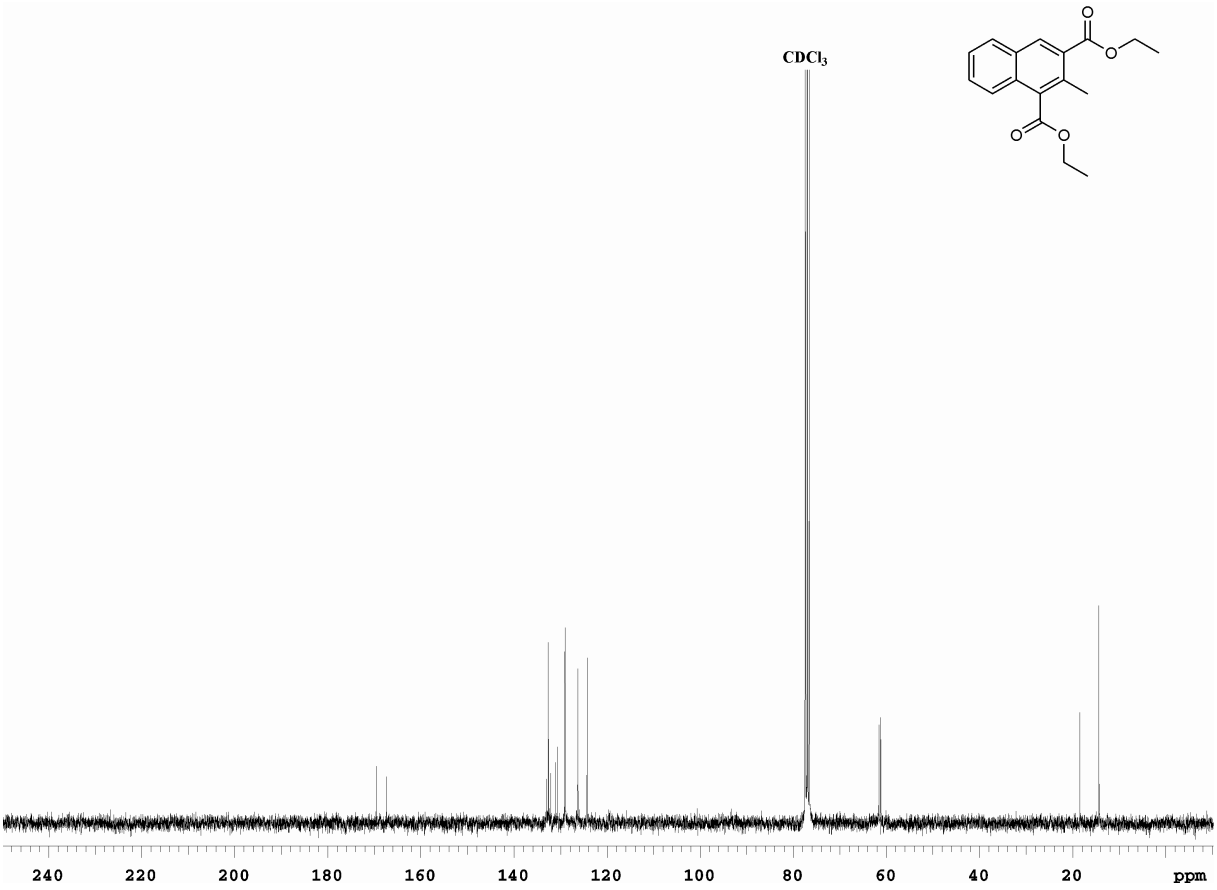


Figure 1. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **3a** in $CDCl_3$.

Dimethyl-2-methylnaphthalene-1,3-dicarboxylate (3b)[1]

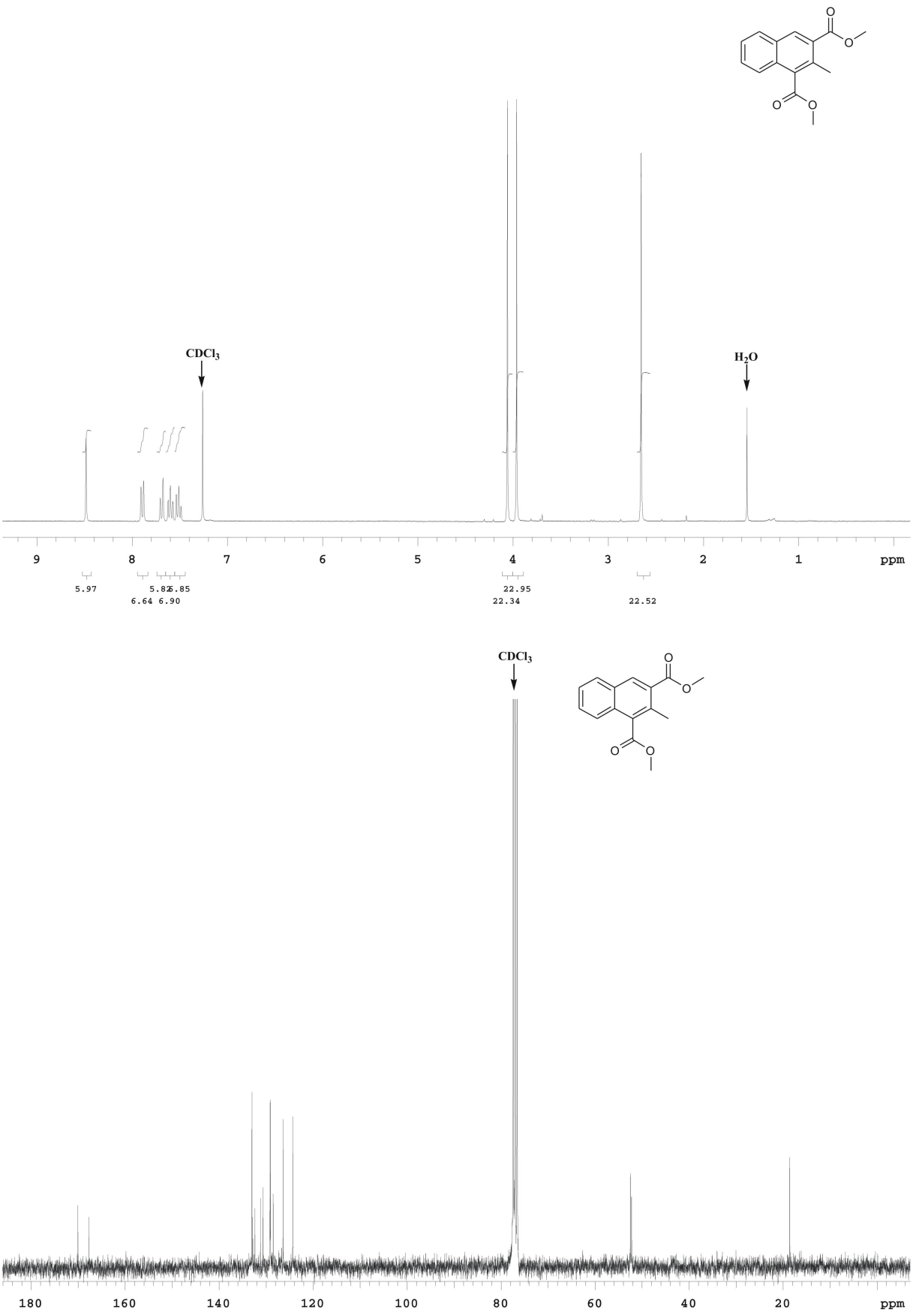
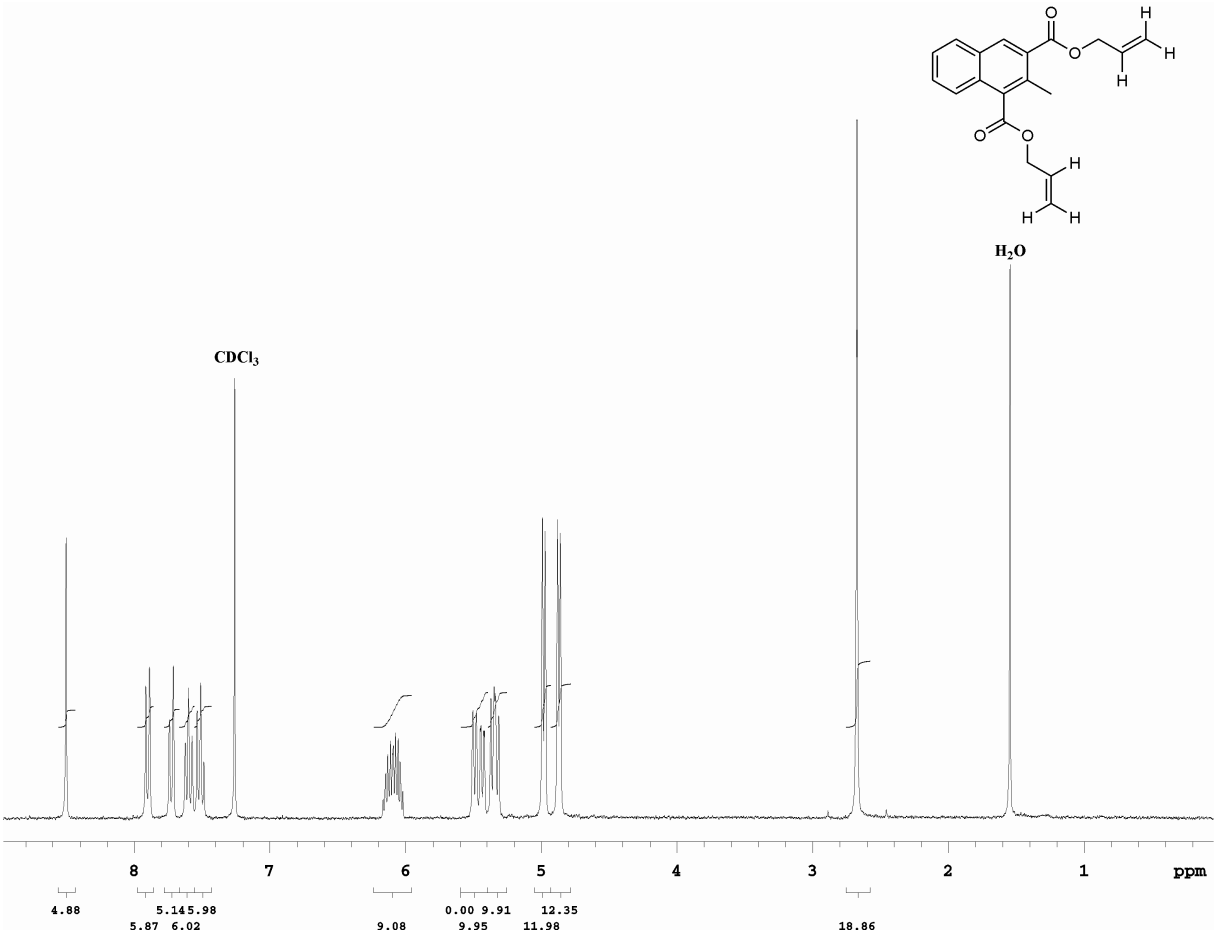


Figure 2. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **3b** in $CDCl_3$.

Diallyl-2-methylnaphthalene-1,3-dicarboxylate (3c)[1]



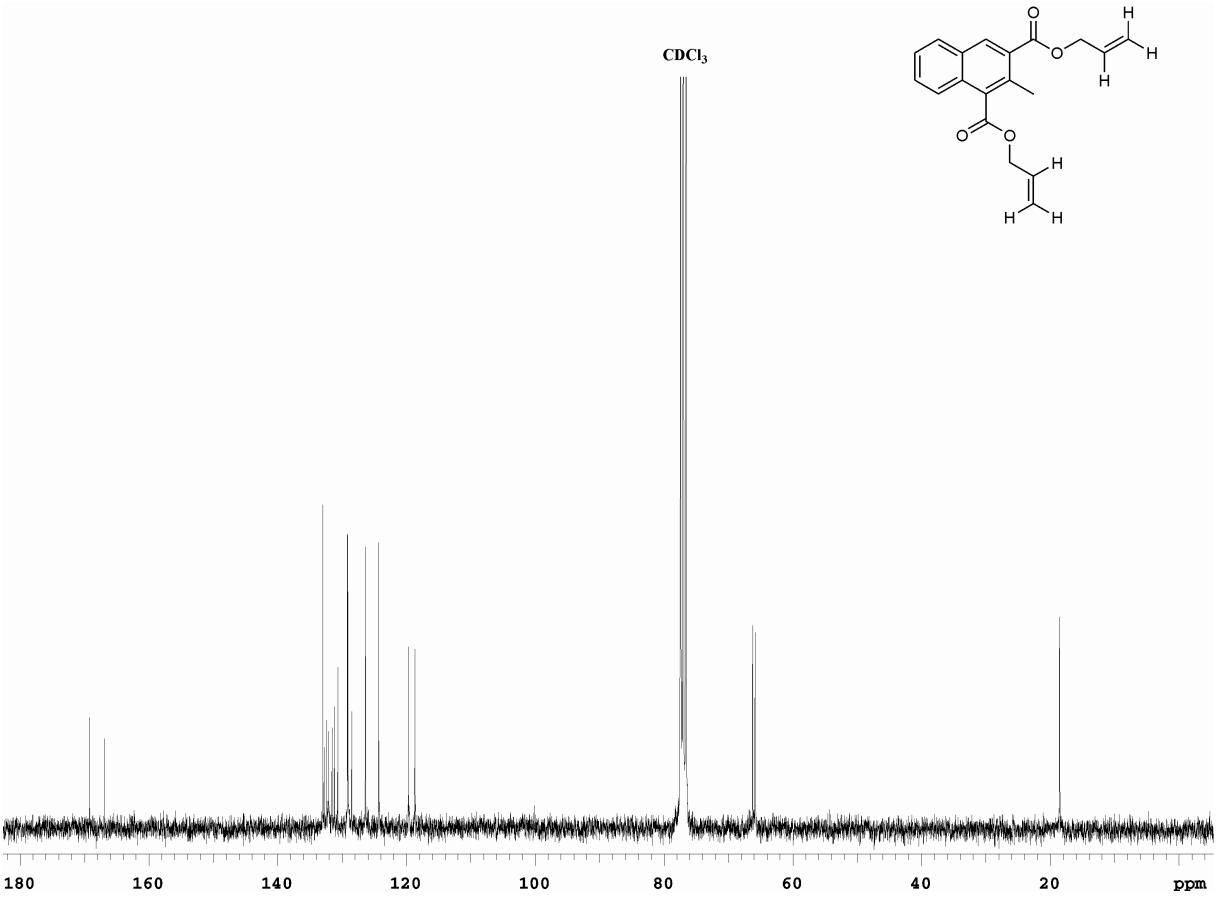


Figure 3. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **3c** in $CDCl_3$.

Dibenzyl-2-methylnaphthalene-1,3-dicarboxylate (3d)[1]

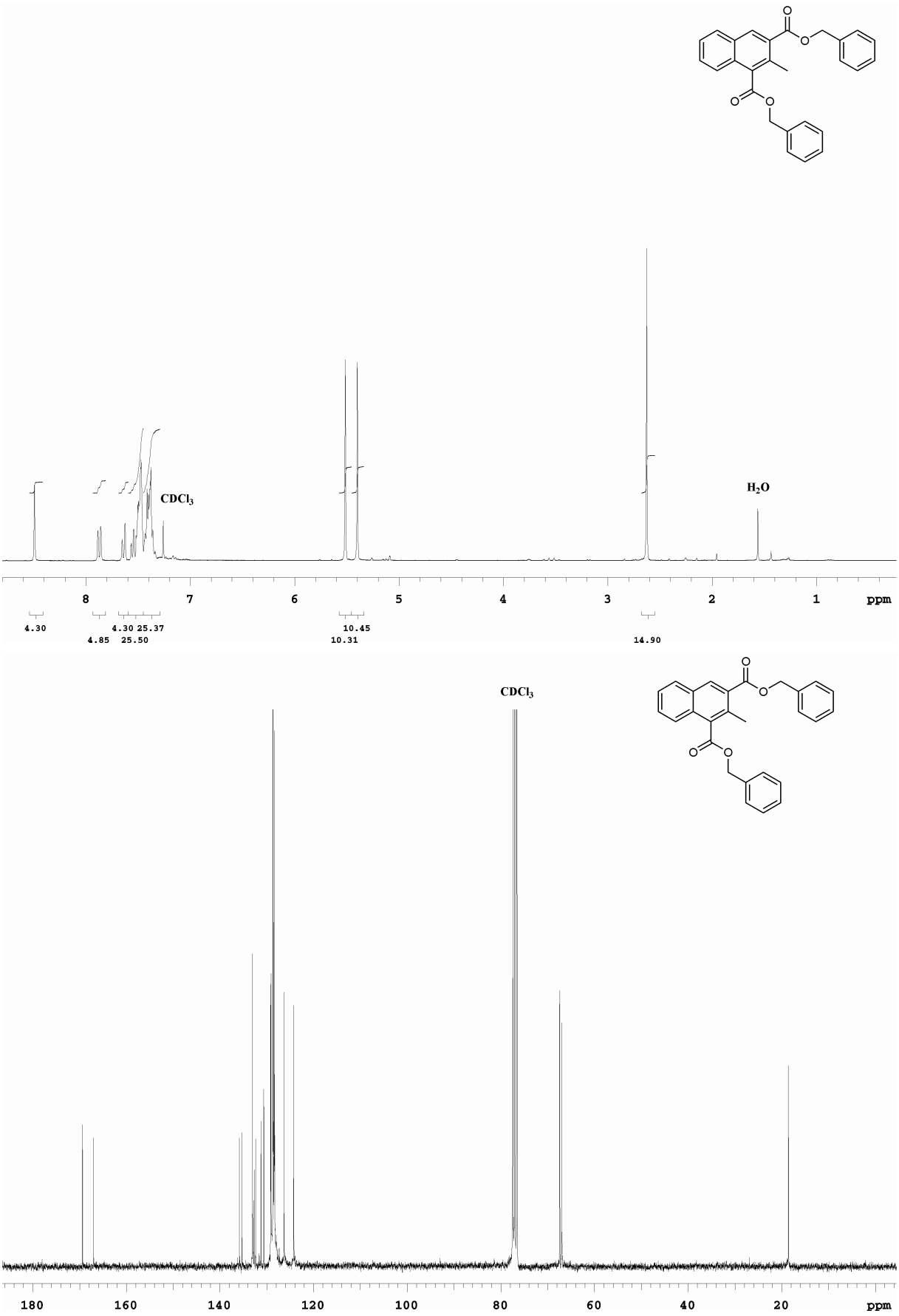
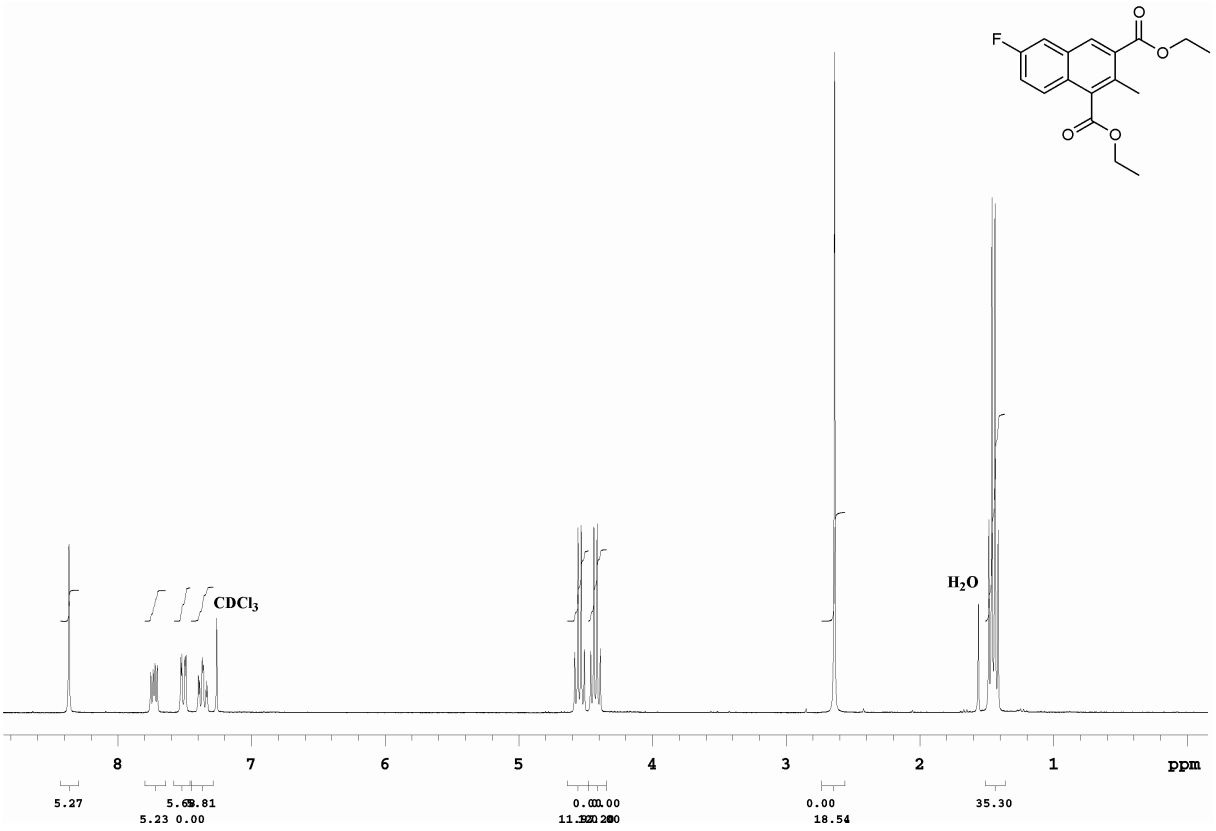


Figure 4. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **3d** in $CDCl_3$.

Diethyl-6-fluoro-2-methylnaphthalene-1,3-dicarboxylate (3e)[1]



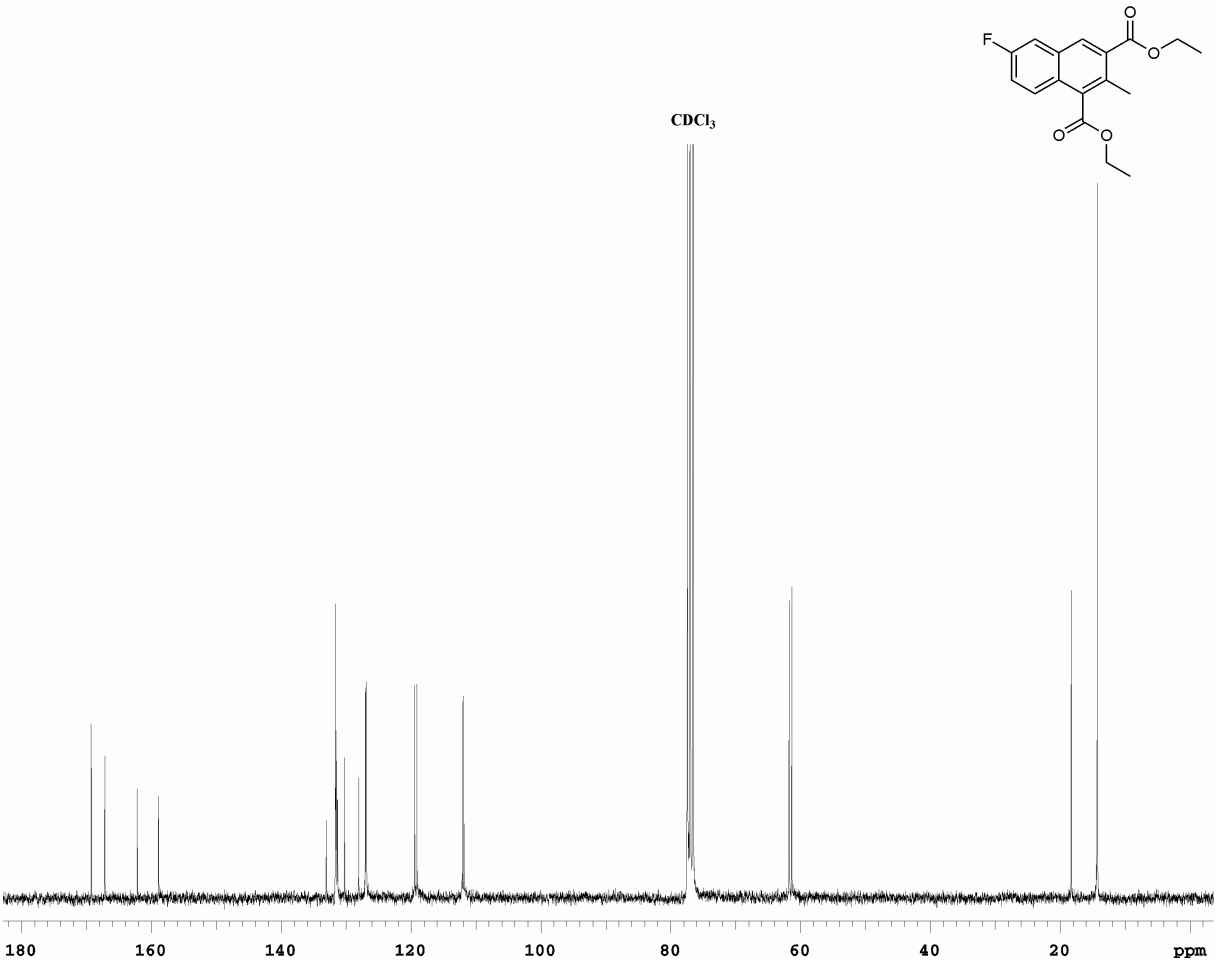


Figure 5. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **3e** in $CDCl_3$

Diethyl-7-methyl-2-methylnaphthalene-1,3-dicarboxylate (3f)

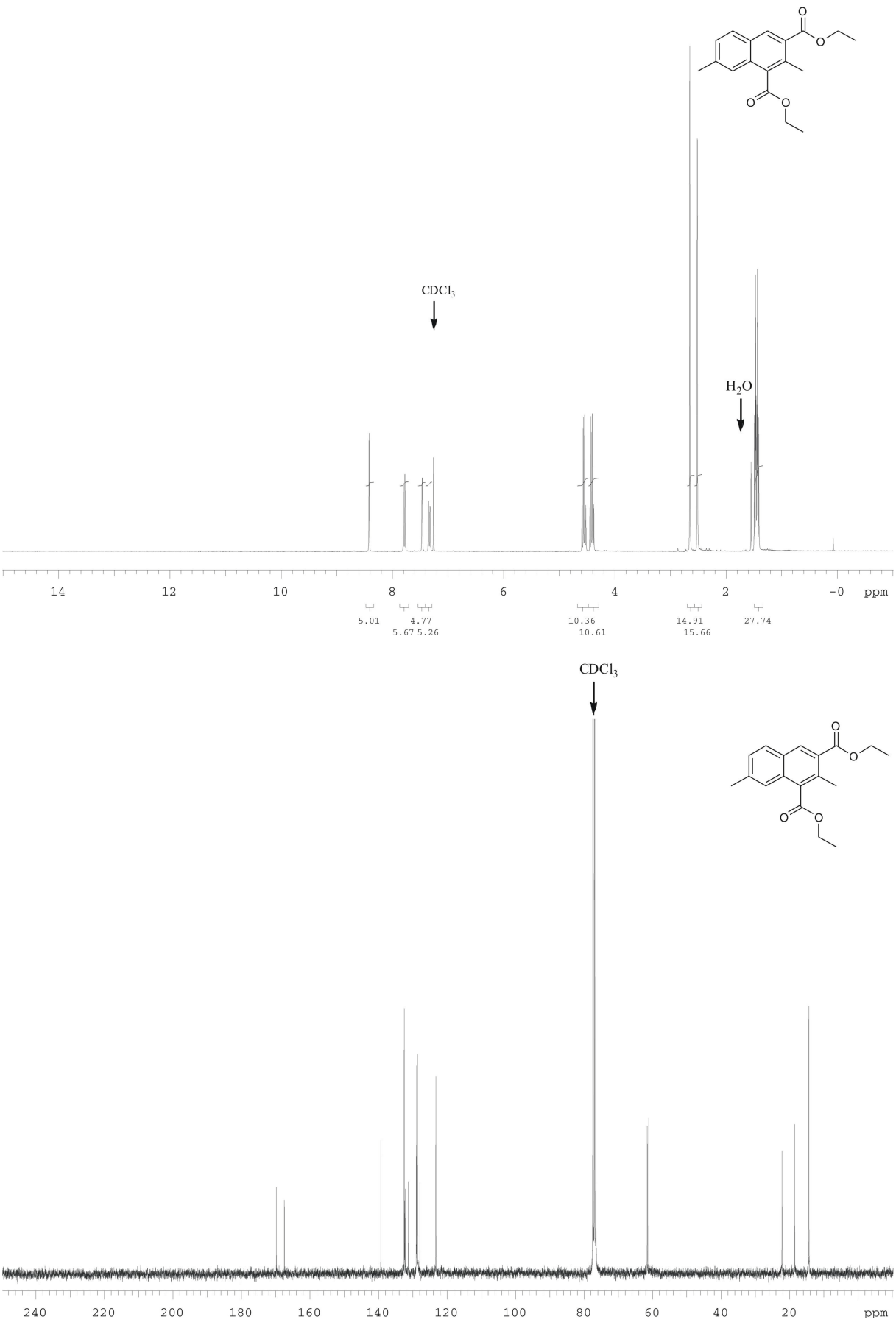
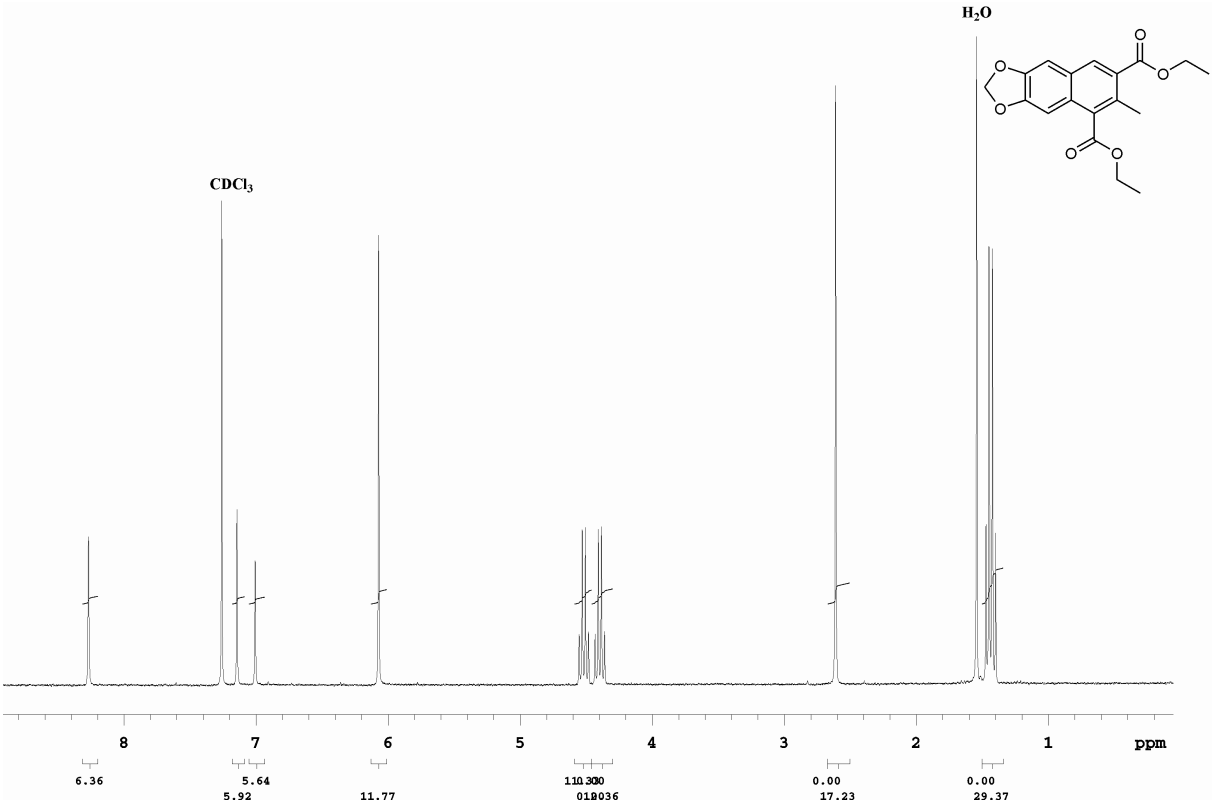


Figure 6. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **3f** in $CDCl_3$

Diethyl-2-methyl-6,7-methylenedioxy-naphthalene-1,3-dicarboxylate (3g)[1]



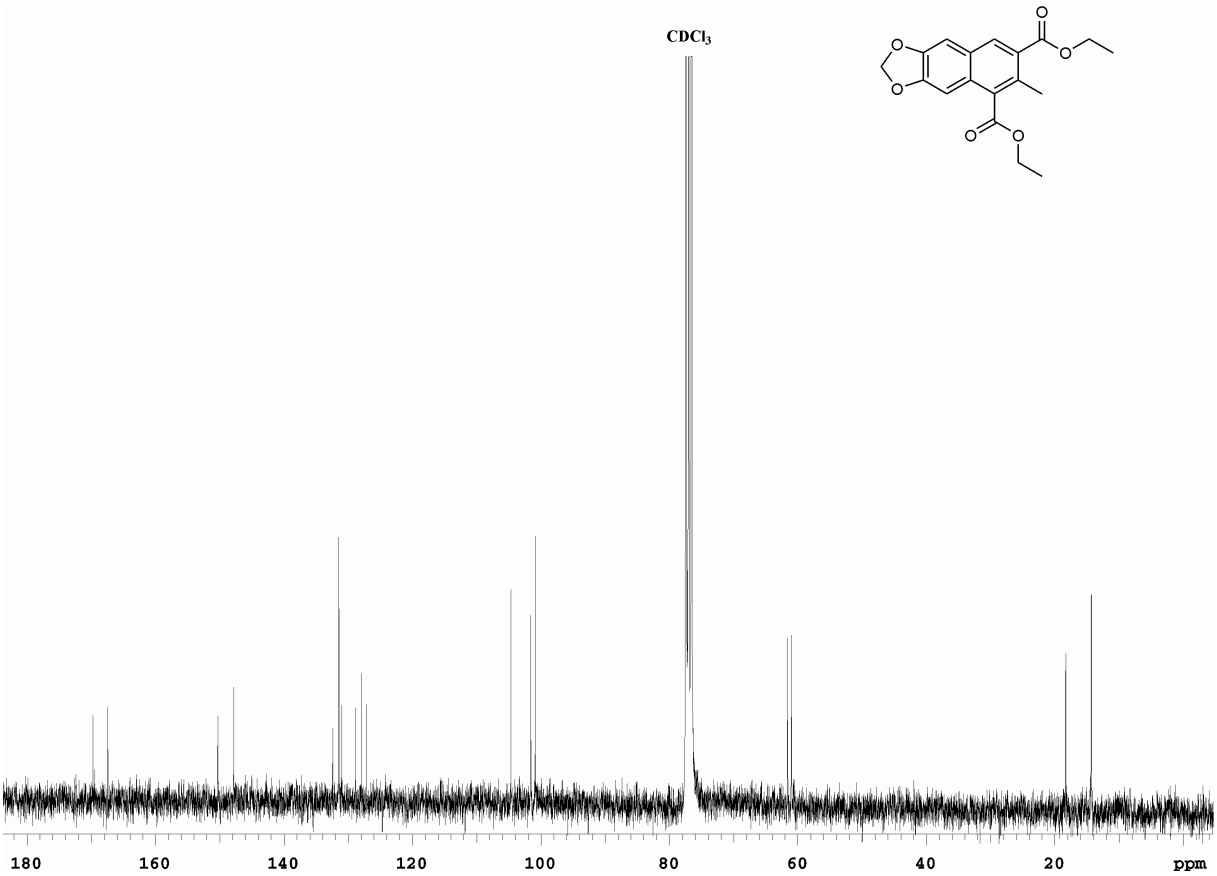


Figure 7. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **3g** in $CDCl_3$.

Diethyl-2-ethyl-6,7-methylenedioxy-naphthalene-1,3-dicarboxylate (3h)[1]

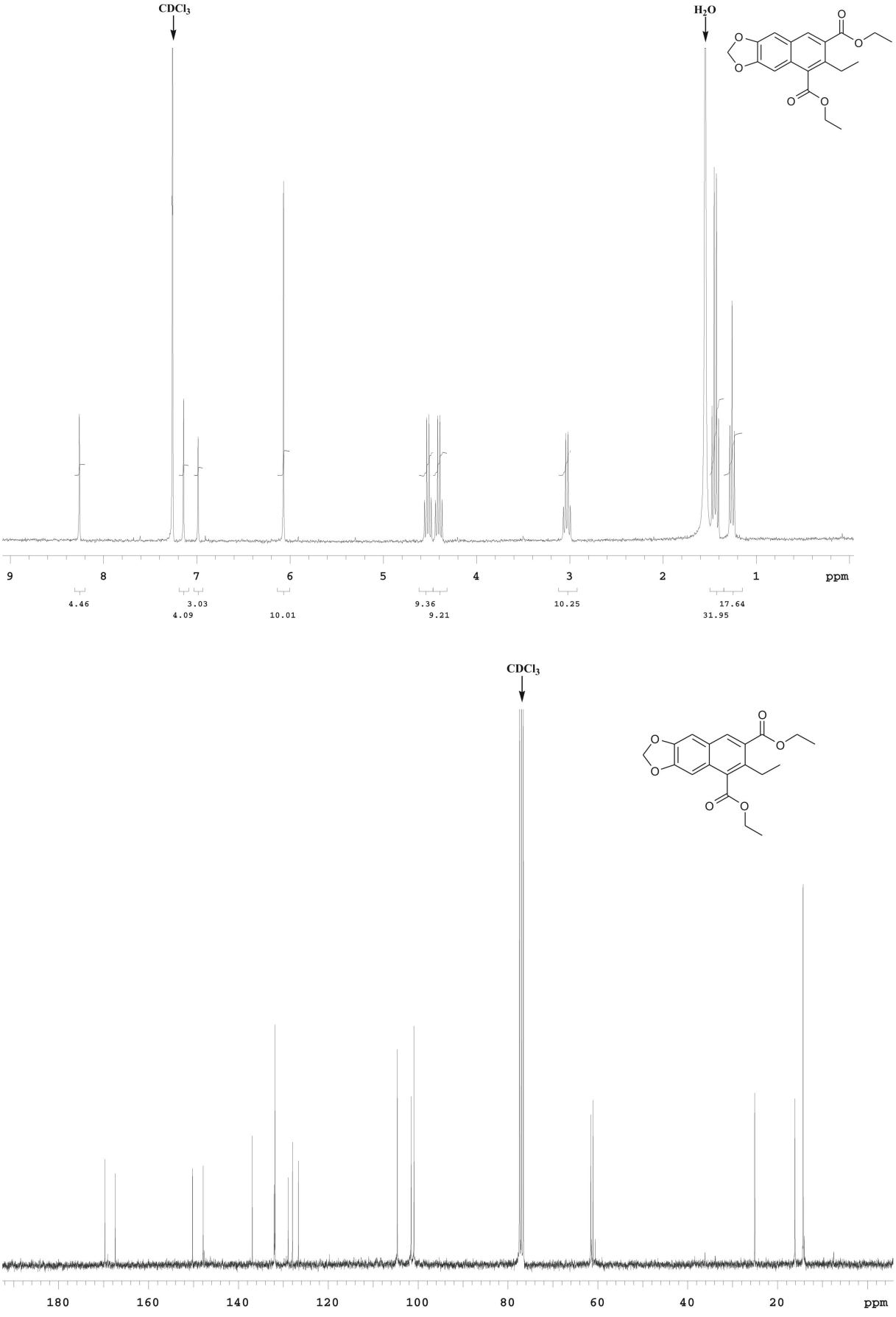
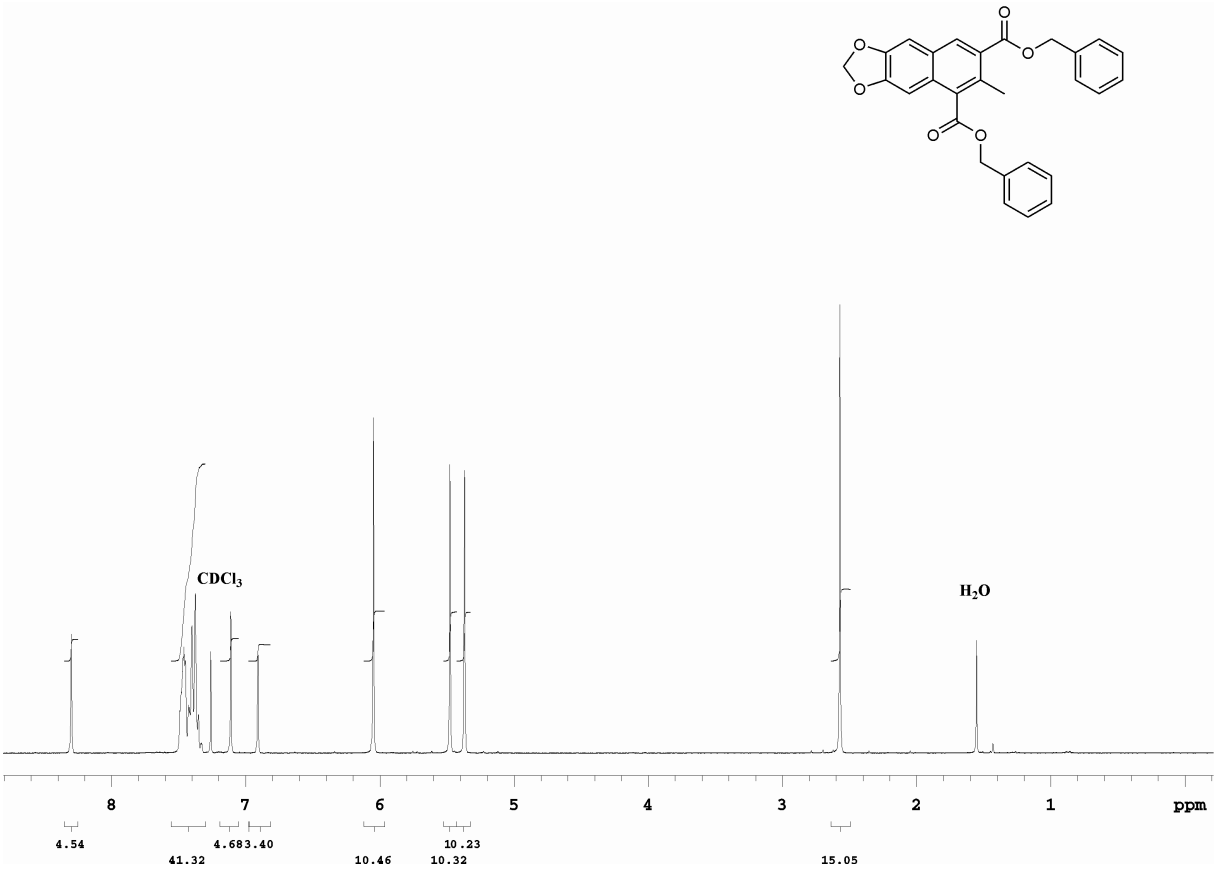


Figure 8. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **3h** in $CDCl_3$.

Dibenzyl-2-methyl-6,7-methylenedioxy-naphthalene-1,3-dicarboxylate (3i)[1]



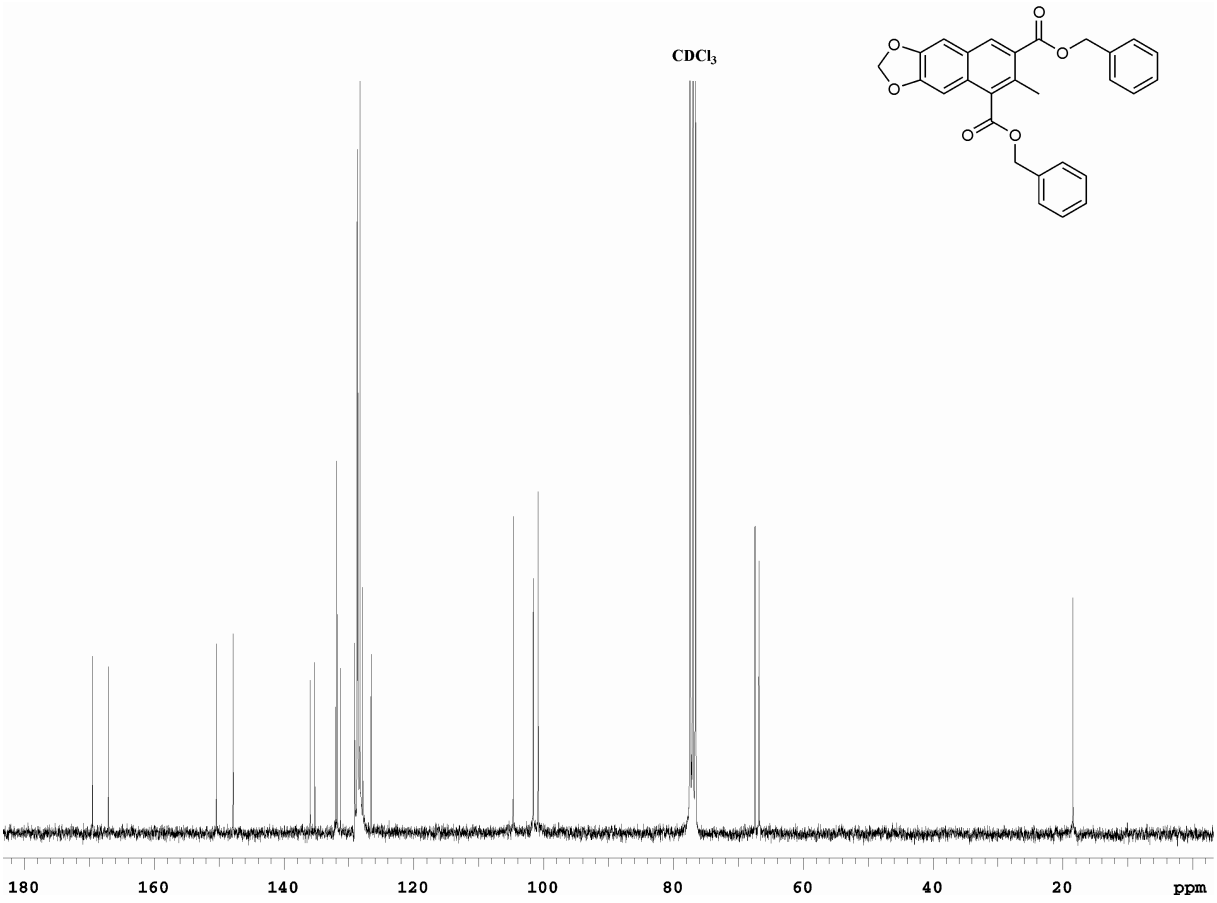


Figure 9. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **3i** in $CDCl_3$.

4. Reference

(1) C. C. Malakar, D. Schmidt, J. Conrad, U. Beifuss *Org. Lett.* **2011**, *13*, 1972-1975