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Electrophilic hexa(methoxycarbonyl)cycloheptatrienyl anion in the synthesis of electron-deficient 5-hydroxyisoquinolones

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General information

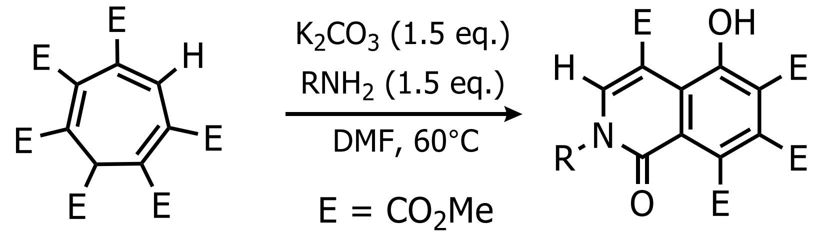
^{1}H NMR and ^{13}C NMR spectra were recorded on a «Bruker AVANCE II 300» spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$ with tetramethylsilane as an internal reference standard and DMSO-d_6. HRMS spectra were obtained with a Bruker microTOF II instrument (ESI, positive or negative ion modes, capillary voltage 4500 V). Melting points were determined on a melting point apparatus Stuart SMP10.

Quantum chemical calculations were carried out using ORCA 5.0.4 software package.[S1] A combination of CREST and CENSO level 2 software packages was used to find the most stable conformations of ground states.[S2,S3] Geometry optimization and frequency calculations were performed using the method r^{2}SCAN-3c.[S4] The optimized structures were verified by frequency computations as minima (zero imaginary frequencies) or transition structures (a single imaginary frequency).[S5] CPCM was used as the solvent model.[S6] Partial charges were calculated via the iboView software package using the EOS approach[S7] *via* revDSD-PBEP86(D4)/aug-cc-pVTZ//r^{2}SCAN-3c level of theory.[S8] Fukui function indices were obtained from Multiwfn 3.8[S9] software package *via* PBE0/def2-TZVP//r^{2}SCAN-3c/CPCM(DMSO) level of theory. Visualizations of the lowest unoccupied molecular orbital shapes was obtained *via* r^{2}SCAN-3c/CPCM(DMSO) level of theory. The energies of intermediates and transition states were obtained *via* revDSD-PBEP86(D4)/aug-cc-pVTZ/CPCM(DMF)//r^{2}SCAN-3c/CPCM(DMF) level of theory.

Hexamethyl cyclohepta-1,4,6-triene-1,2,3,4,5,6-hexacarboxylate **3** was obtained according to the literature procedure.[S10] All other reagents and solvents were commercially available and were used without additional purification.

Synthetic procedures

General procedure for **4a–c**



A flask equipped with a stir bar was charged with hexamethyl cyclohepta-1,4,6-triene-1,2,3,4,5,6-hexacarboxylate **3** (0.250 g, 0.56 mmol), DMF (1 ml), potassium carbonate (0.116 g, 0.84 mmol or 0.230 g, 1.68 mmol in case of the reaction with methylamine hydrochloride), amine (1.5 eq., 0.84 mmol), and the mixture was stirred in an oil bath at 60˚C for 8 hours. Then it was diluted with 5 ml of water, acidified with an excess of aqueous HCl until pH 1, and the product precipitated. The resulting mixture was stirred at room temperature for more 2 hours, and the product was filtered off and washed with water and diethyl ether and dried.

Tetramethyl 5-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-4,6,7,8-tetracarboxylate **4a**

The use of a 25% aqueous solution of methylamine gave 0.070 g (27%) of **4a**. The use of methylamine hydrochloride gave 0.114 g (43%) of **4a**, pale yellow powder, decomp. over 195°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.38 (s, 1H), 7.99 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H), 3.60 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.8, 168.4, 167.8, 165.6, 159.9, 154.6, 141.3, 129.6, 126.6, 126.2, 124.9, 120.2, 106.4, 53.7, 53.2, 53.1, 52.9, 38.0.
HRMS (ESI), *m/z*: $[M+H]^+$ calcd for $C_{18}H_{18}NO_{10}$: 408.0925; found: 408.0917.

Tetramethyl 5-hydroxy-2-isopropyl-1-oxo-1,2-dihydroisoquinoline-4,6,7,8-tetracarboxylate **4b**

Pale yellow powder, 0.182 g (65%), decomp. over 150°C.

^{1}H NMR (300 MHz, CDC13) δ: 12.33 (s, 1H), 7.97 (s, 1H), 5.24 (hept, *J* 6.8 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 6H), 3.88 (s, 3H), 1.41 (d, *J* 6.8 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.9, 168.5, 168.0, 165.8, 159.2, 154.8, 135.7, 129.8, 126.7, 125.6, 125.4, 119.3, 107.1, 53.6, 53.2, 53.0, 52.9, 47.8, 21.7.
HRMS (ESI), *m/z*: $[M+H]^+$ calcd for $C_{20}H_{22}NO_{10}$: 436.1238; found: 436.1244.

Tetramethyl 2-benzyl-5-hydroxy-1-oxo-1,2-dihydroisoquinoline-4,6,7,8-tetracarboxylate **4c**

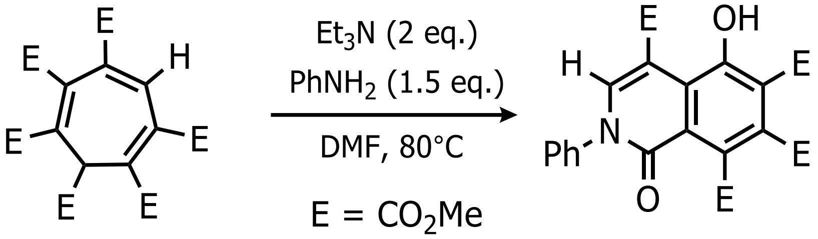
Pale yellow powder, 0.135 g (50%), decomp. over 150°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.31 (s, 1H), 7.86 (s, 1H), 7.42 – 7.24 (m, 5H), 5.17 (s, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 3.88 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.6, 168.4, 168.0, 165.8, 159.6, 155.1, 139.2, 134.9, 130.1, 129.2, 128.7, 128.4, 126.6, 125.9, 125.6, 119.1, 107.3, 53.5, 53.3, 53.1, 53.0, 52.4.

HRMS (ESI), *m/z* $[M+H]^+$ calcd for $C_{24}H_{22}NO_{10}$: 484.1238; found: 484.1227.

Synthesis of tetramethyl 5-hydroxy-1-oxo-2-phenyl-1,2-dihydroisoquinoline-4,6,7,8-tetracarboxylate **4d**



A flask equipped with a stir bar was charged with cycloheptatriene **3** (0.250 g, 0.56 mmol), DMF (1 ml), triethylamine (2 eq., 0.113 g, 1.12 mmol), aniline (1.5 eq., 0.84 mmol, 0.078 g), and the mixture was stirred in an oil bath at 80˚C for 72 hours. Then it was diluted with 5 ml of water, acidified with an excess of aqueous HCl until pH 1, and the product precipitated. The resulting mixture was stirred at room temperature for more 2 hours, and the product was filtered off, washed with water and diethyl ether, dried and then recrystallized from methanol to give a pale yellow powder, 0.063 g (16%), decomp. over 150°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.30 (s, 1H), 7.96 (s, 1H), 7.45 (m, 5H), 3.97 (s, 3H), 3.93 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H).

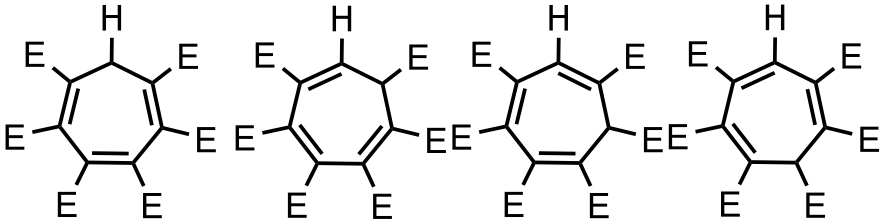
^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.5, 168.1, 168.1, 165.8, 159.3, 155.3, 139.7, 139.6, 130.5, 129.7, 129.3, 126.7, 126.0, 118.8, 107.5, 53.6, 53.3, 53.1, 53.0.

HRMS (ESI), *m/z*: $[M+H]^+$ calcd for $C_{23}H_{20}NO_{10}$: 470.1082; found: 470.1069.

Isomerization of cycloheptatriene 3

A mixture of isomeric cycloheptatrienes **3c** and **3d** in a 1.6:1 ratio is initially generated through a cascade reaction of dimethyl glutaconate with dimethyl bromomaleate and pyridine.[S10] The prevalence of isomer **3c** suggests its superior stability compared to other isomers (Figure S1). This observation was supported by quantum chemical calculations which provide a ~9:1 ratio of isomers **3c/3d** (Table S1). Intriguingly, it is isomer **3d** that readily crystallizes from a solution.[S10] Hence, we infer that the primary driving force for isomerization is solubility rather than thermodynamic stability.

The calculation of conformational ensembles of the four possible isomers was performed using the CENSO program package (level 2), at the r^{2}SCAN-3c level of theory.



3a **3b** **3c** **3d**

E = CO$_2$Me

Figure S1 Possible isomers of cycloheptatriene **3**.

Table S1 Isomeric composition of equilibrium mixture of cycloheptatriene **3**.

Isomer	NMR %	Calculated %
3a	38	11
3b	62	89
3c	<1	<1
3d	<1	<1

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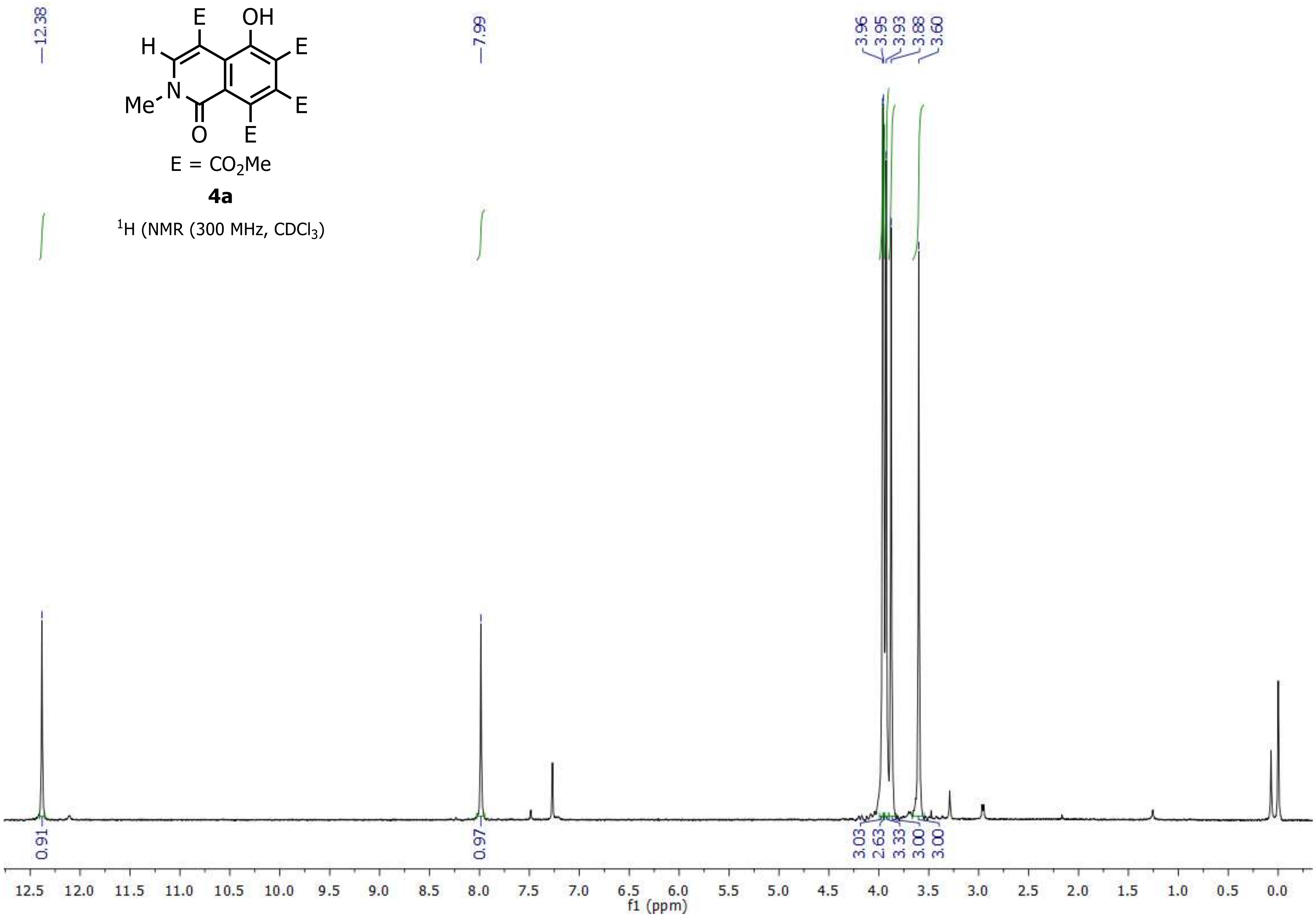
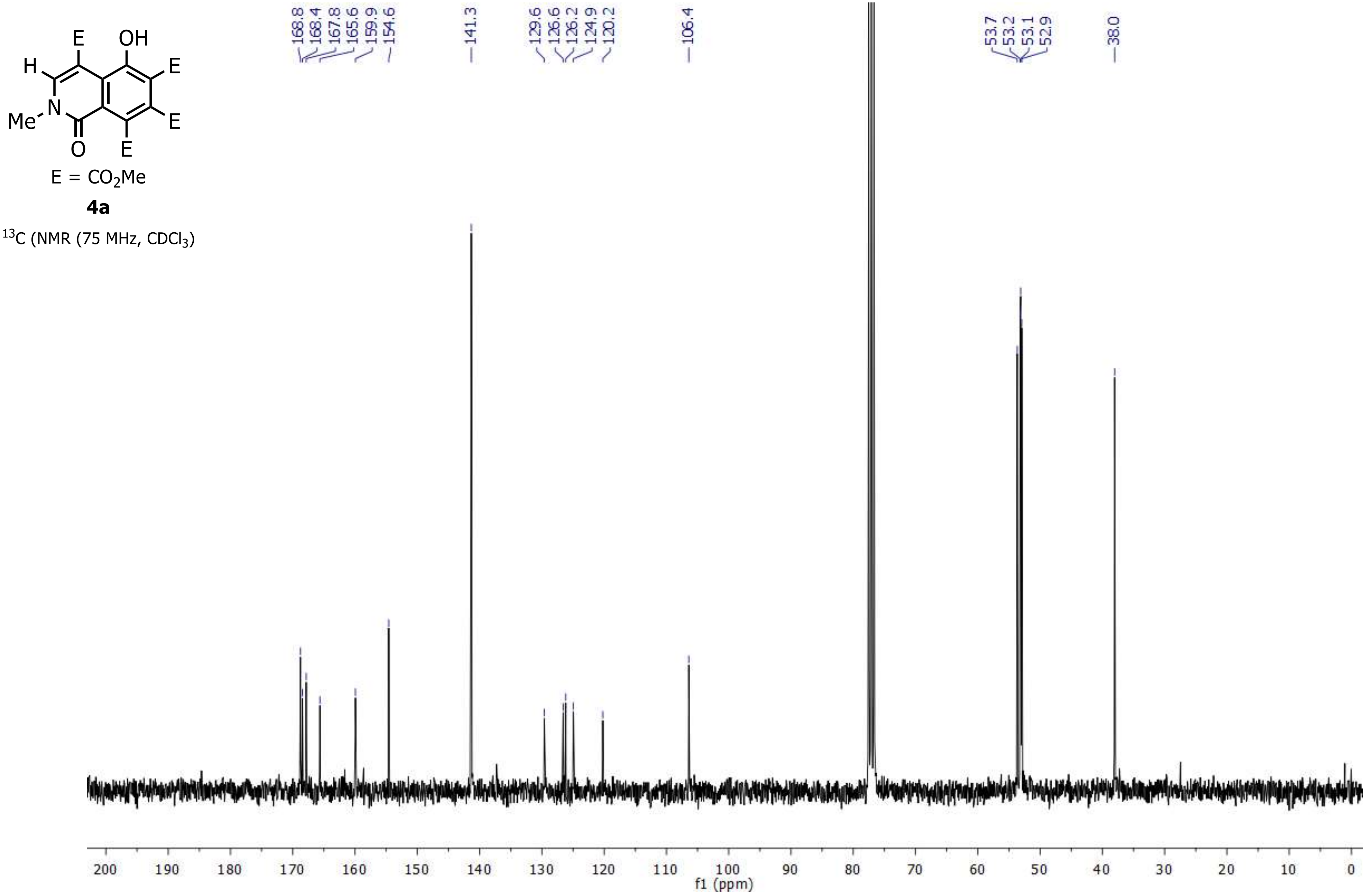
NMR spectra



E = CO_2Me

4a

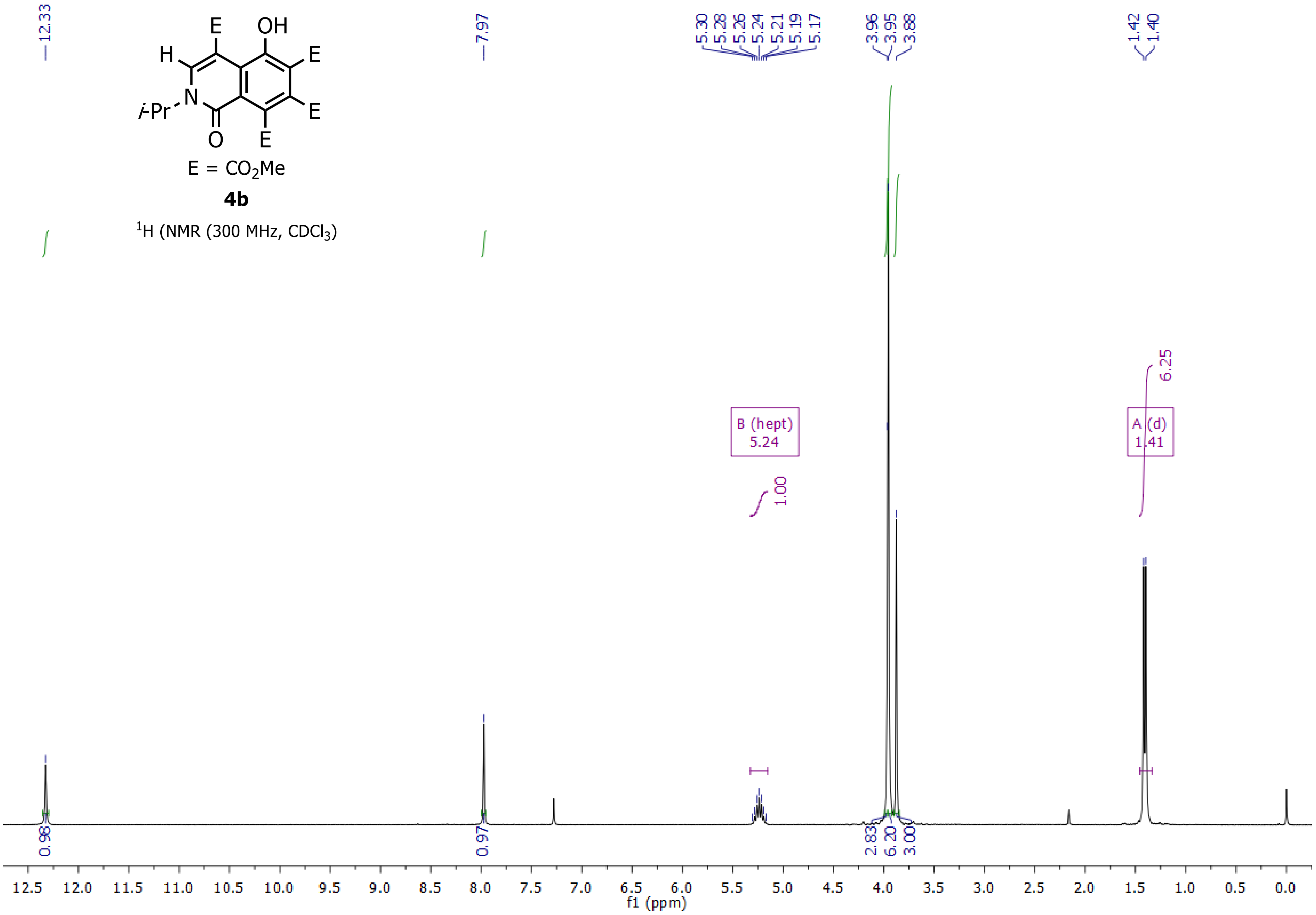
^{1}H (NMR (300 MHz, $CDCl_3$)



E = CO_2Me

4a

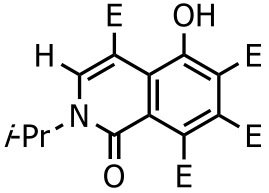
^{13}C (NMR (75 MHz, $CDCl_3$)



E = CO$_2$Me

4b

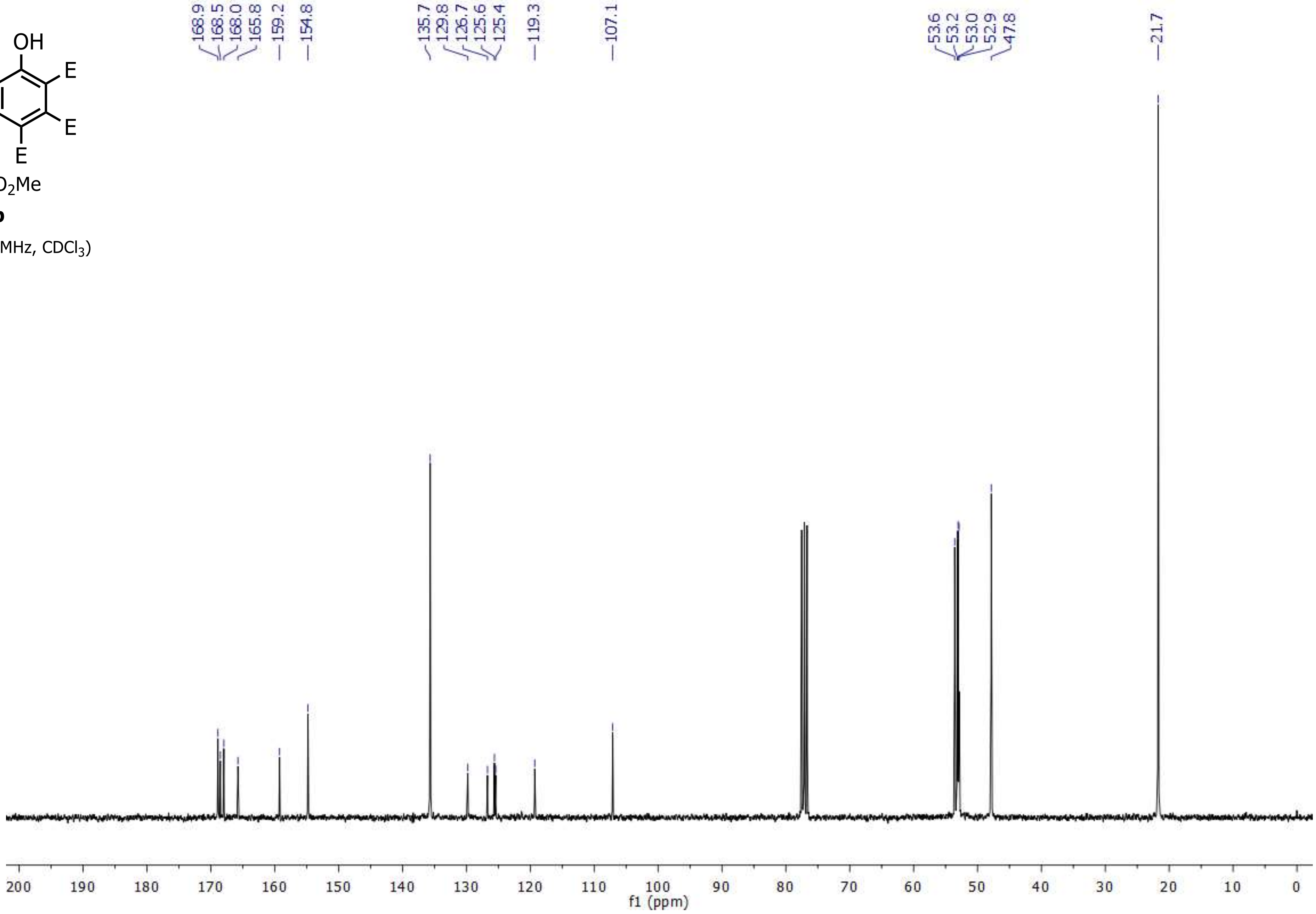
^{1}H (NMR (300 MHz, CDCl$_3$)

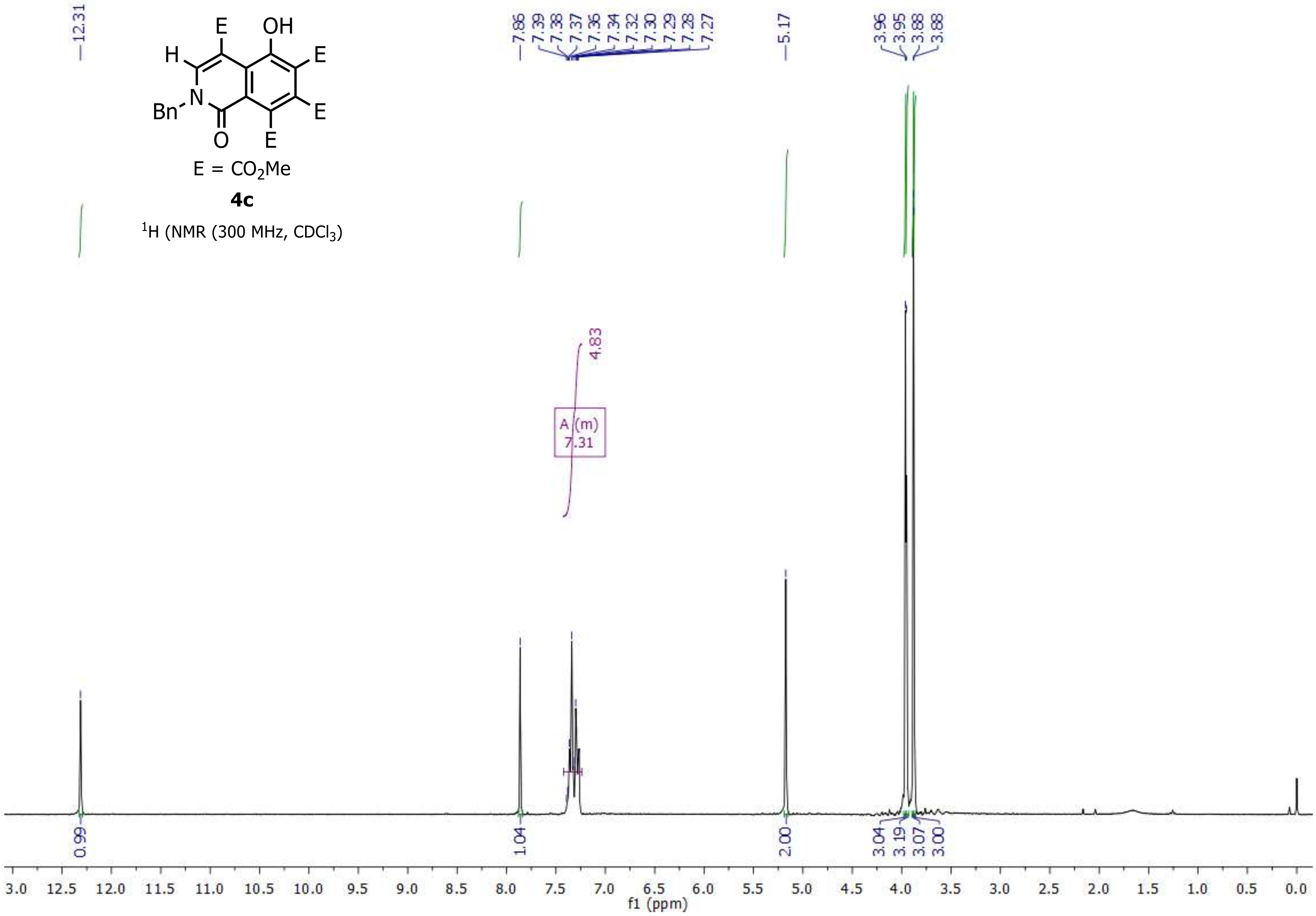


E = CO_2Me

4b

^{13}C (NMR (75 MHz, $CDCl_3$)

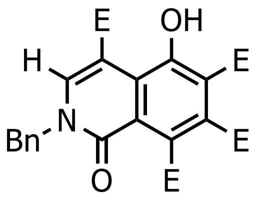




E = CO_2Me

4c

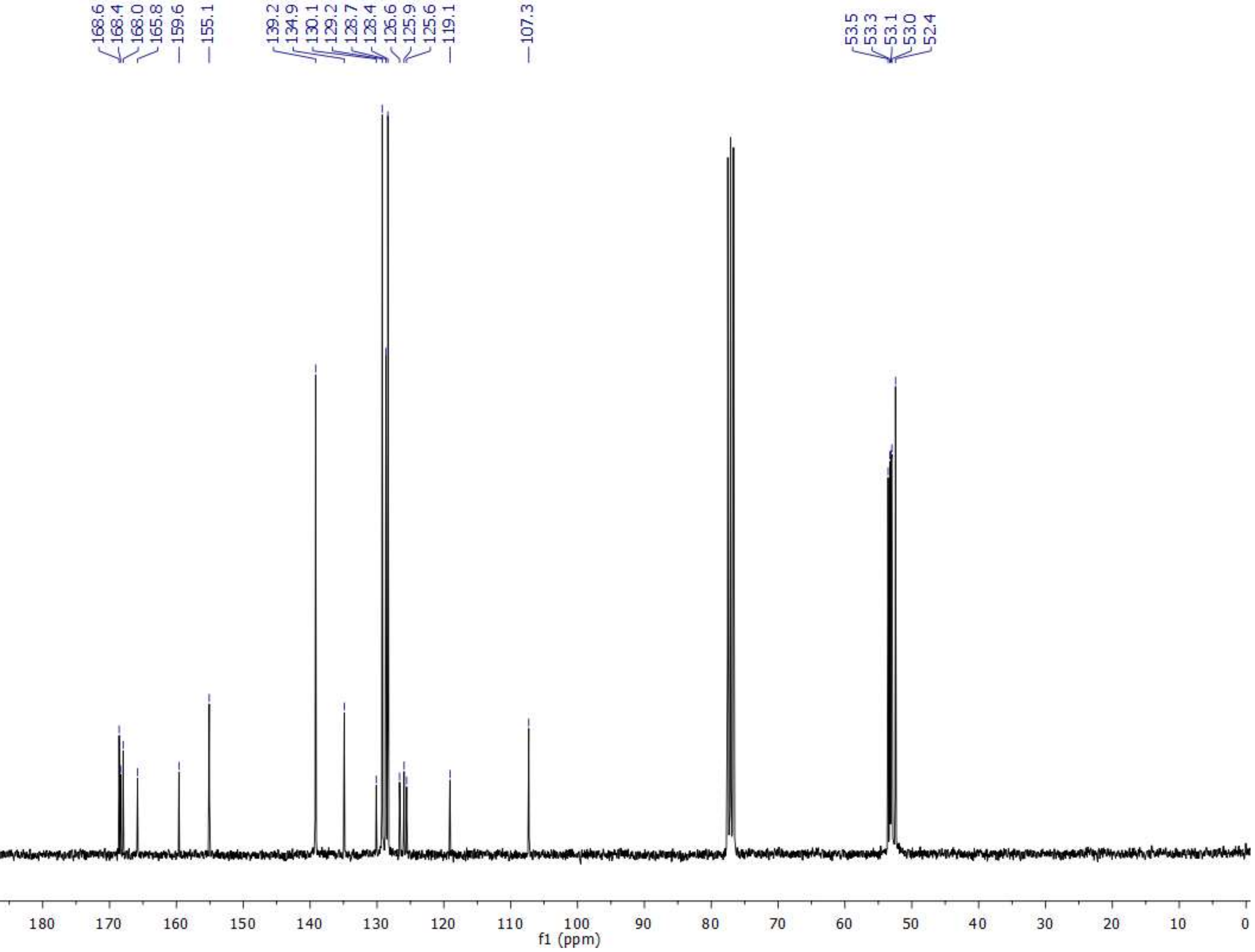
^{1}H (NMR (300 MHz, $CDCl_3$)

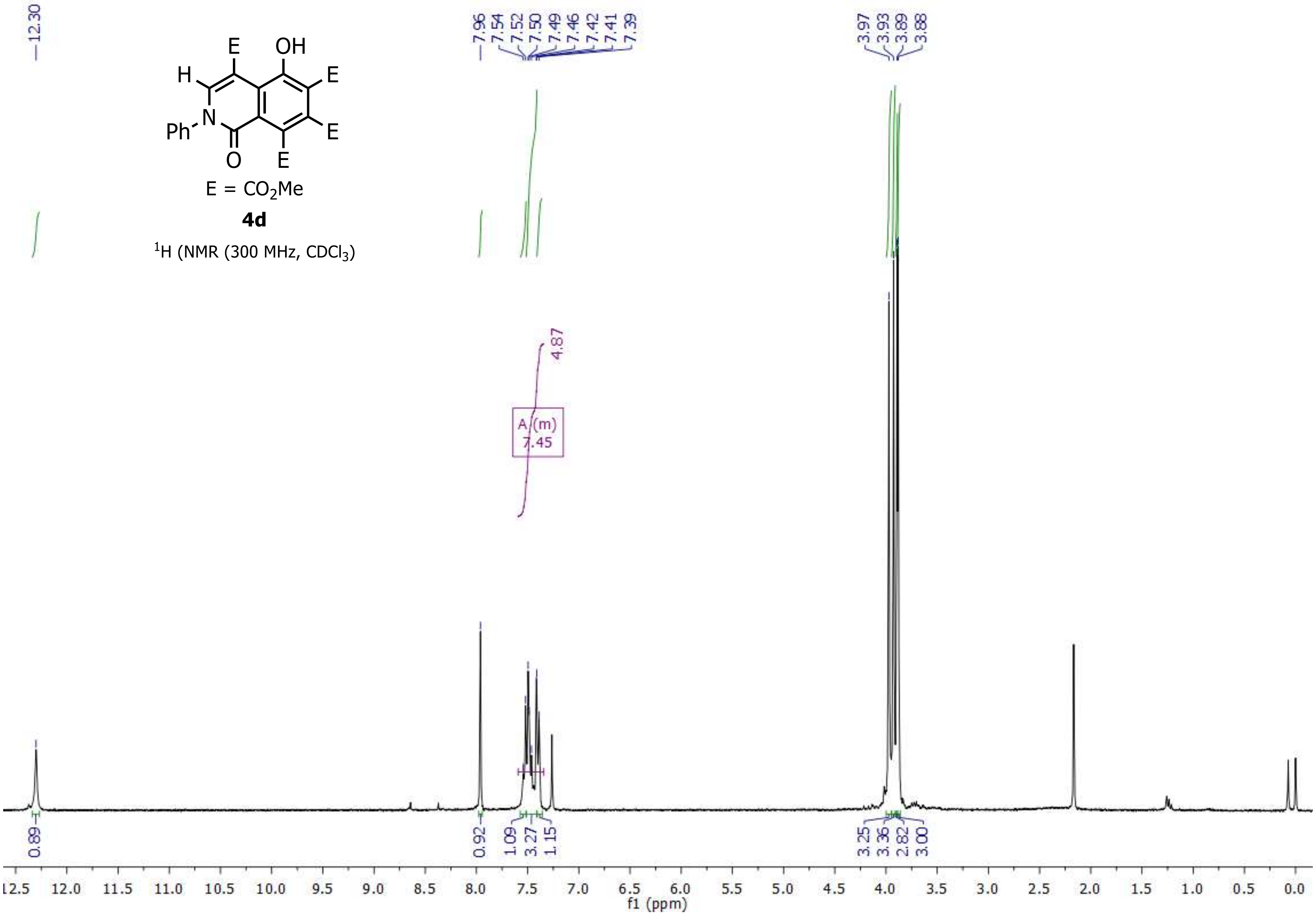


E = CO_2Me

4c

^{13}C (NMR (75 MHz, $CDCl_3$)

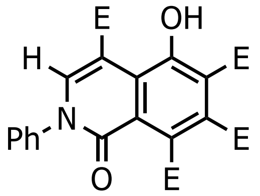




E = CO_2Me

4d

^1H (NMR (300 MHz, $CDCl_3$)



E = CO_2Me

4d

^{13}C (NMR (75 MHz, $CDCl_3$)