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SUPPORTING INFORMATION

Intramolecular Palladium(II)/(IV) Catalysed C(sp^3)–H Arylation of Tertiary Aldehydes using a Transient Imine Directing Group

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General Experimental Considerations

All nonaqueous reactions were run under an inert atmosphere (argon, balloon) with flame-dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (THF, Et_2O, CH_2Cl_2). Hexafluoroisopropanol, $Pd(OAc)_2$ and AgTFA were purchased from Fluorochem and used as provided. Acetic acid, AgOAc and other Pd catalysts were purchased from Sigma Aldrich and used as provided. Commercial aldehydes were distilled prior to use. All other commercial reagents were used as supplied or purified by standard techniques where necessary. All extractions were conducted three times in equivolume solvent unless stated otherwise.

Reactions in sealed tubes were run using Biotage microwave vials (2–5 mL) and aluminium caps with molded butyl (when using HFIP:AcOH) or butyl/PTFE (when using benzene) septa.

Flash column chromatography was performed using 230-400 mesh silica with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualisation of the developed chromatogram was performed by UV absorbance (254 nm), phosphomolybdic acid or *p*-anisaldehyde stains.

Infrared spectra (ν_{max}, FTIR ATR) were recorded in reciprocal centimeters (cm^{-1}).

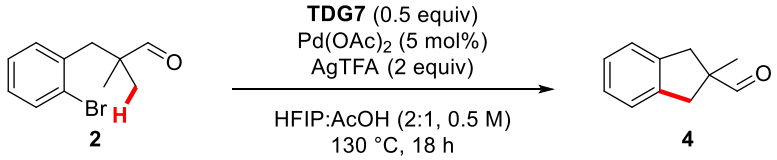
Nuclear magnetic resonance spectra were recorded on 400 MHz spectrometers. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform δ = 7.27 ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet and b = broad), coupling constant in Hz, integration, assignment]. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ = 77.00 ppm). ^{19}F NMR spectra were recorded with complete proton decoupling. *J* values are reported in Hz. Assignments of $^1H/^{13}C$ spectra were made by the analysis of δ/*J* values, and COSY, HSQC, and HMBC experiments as appropriate. ^{19}F NMR spectra were recorded with or without complete proton decoupling. Decoupling is indicated as ($^{19}F\{^1H\}$) and where relevant this is stated in each assignment and spectrum. ^{19}F spectra are indirectly referenced to $CFCl_3$, automatically via direct measurement of the absolute frequency of the deuterium lock signal by the spectrometer hardware. For clarity NMR spectra are displayed as follows unless this would obscure signals: ^1H NMR spectra are displayed between 10.5 ppm and –0.5 ppm; ^{13}C NMR spectra are displayed between 230 ppm and 0 ppm.

Melting points are uncorrected.

The high resolution mass spectrometry (HRMS) analyses were performed using electrospray ion source (ESI) or pneumatically assisted atmospheric pressure chemical ionization (APCI) using an atmospheric solids analysis probe (ASAP). ESI was performed using a Waters LCT Premier equipped with an ESI source operated in positive ion mode. The software used was MassLynx 4.1, this software does not account for the electron and all the calibrations/references are calculated accordingly, i.e. $[M+H]^+$ is detected and the mass is calibrated to output [M+H]. APCI was performed using an Orbitrap XL or Xevo G2S using an ASAP to insert samples into the APCI source. The sample was introduced at ambient temperature and the temperature increased until the sample vaporised.

All raw and processed data for this manuscript can be found at the Imperial College London Research Data Repository (**doi**: 10.14469/hpc/5614).

Optimisation and control reactions of intramolecular C(sp^3)–H arylation



Entry	description	RSM (%)[a]	yield 4 (%)[a]
1	No Pd	98	0
2	No AgTFA	88	6
3	AgOAc instead of AgTFA	37	10
4	AgF instead of AgTFA	42	24
5	Ag_2O instead of AgTFA	49	13
6	AgOAc + 2 equiv TFA	33	28
7	AgOAc + 2 equiv KTFA	40	15
8	KTFA instead of AgTFA	81	6
9	Reaction conducted under air	21	40
10	120 °C	22	42
11	110 °C	30	37
12	2.5 mol% $Pd(OAc)_2$	35	42
13	2.5 mol% $Pd(OAc)_2$, 0.3 M	38	45
14	2.5 mol% $Pd(OAc)_2$, 0.15 M	32	47
15	5-(trifluoromethyl)pyridin-2-ol additive (0.5 equiv)	43	31
16	dibenzyl hydrogen phosphate additive (0.5 equiv)	46	41
17	Solvent = HFIP:TFA (9:1)	40	15
18	Solvent = HFIP + 1 equiv 12 M HCl_{aq}	77	7
19	Solvent = Benzene + 5 equiv $C_6F_5CO_2H$	76	11

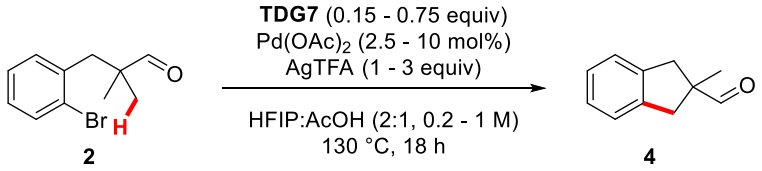
Table S1: C(sp^3)–H annulation optimisation and controls, 0.2 mmol scale **2**. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Control reactions were conducted to investigate the importance of the reaction components. In the absence of palladium, no reaction occured. As the effect of TFA in our previous work was so substantial,[1] use of alternative souces of Ag and TFA were investigated (Entries 2–8). Unlike what was observed for the *inter*molecular variant of the the reaction, the presence of TFA was not critical, but did lead to much improved yields. Use of AgOAc in lieu of AgTFA resulted in low yields of the desired cyclised product. The reaction could be run under aerobic conditions with only a slight drop in yield (Entry 9). Lowering the temperature to 120 or 110 °C led to sequentially lower yields (Entries 10, 11). Low loadings (2.5 mol%) of catalyst could be used with maintained yields, particularly at lower solvent concentrations. Additives known to assist in C(sp^3)–H activation did not enhance the yield (Entries 15, 16). Alternative solvent/acid combinations as used in the literature were also less effective (Entries 17–19).

DOE experiments

A DOE study was conducted to identify interactions between the different continuous reaction parameters following selection the of the discrete variables, and to potentially achieve greater yields of indane product **4**. The software used for this investigation was JMP Pro 14. The custom design was a response surface methodology with one centre point and 3 replica runs for a default number of runs (21). This design investigated the extremes and midpoints of all factors.

The continuous factors investigated were: TDG loading, catalyst loading, AgTFA loading and concentration. The ranges chosen for all factors selected are given in Table S2. Yield was selected as the only response (min = 0, max = 100).



Factor	Role	Min	Max
TDG loading	Continuous	0.15	0.75
Cat loading	Continuous	2.5	10
AgTFA loading	Continuous	1	3
Concentration	Continuous	0.2	1

Table S2: Factors in select ranges investigated for the DOE study.

General procedure for DOE study: Indane precursor **4** (24 mg, 0.10 mmol), 2-methoxyethan-1-amine **TDG7** (0.15–0.75 equiv), palladium acetate (2.5–7.5 mol%), silver trifluoroacetate (1–3 equiv) and HFIP:AcOH (2:1, 0.2–1.0 M) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 130 °C for 18 h. The reaction was allowed to cool to room temperature, diluted with CH_2Cl_2, filtered through a short plug of silica (eluting with CH_2Cl_2) and concentrated under reduced pressure. 10–20 mg of accurately weighed 1,3,5-trimethoxybenzene was added, the residue was fully dissolved in $CDCl_3$ and the yield of the cyclised indane product **4** was calculated by ^{1}H NMR by comparison to the internal standard. NOTE: Due to the low volumes, all liquids of known density, including solvents, were added using a Gilson micropipette.

These experiments were conducted in a randomised order to minimise systematic error. Three repeats were also included (Entries 1 and 14, 3 and 13 and 5 and 17). The factors and responses have been colour coded to represent the values (Table S3).

Run order	TDG loading	Cat loading	AgTFA loading	Conc	Yield (%)[a]
1 (14)	0.45	6.25	2	0.2	**46**
2	0.15	2.5	1	1	**9**
3 (13)	0.15	6.25	2	0.6	**26**
4	0.75	10	1	0.6	**31**
5 (17)	0.45	2.5	2	0.6	**47**
6	0.15	2.5	3	1	**4**
7	0.15	10	1	0.2	**42**
8	0.45	6.25	2	0.6	**34**
9	0.75	2.5	1	0.2	**35**
10	0.15	2.5	2	0.2	**45**
11	0.45	10	3	0.6	**32**
12	0.75	6.25	3	1	**28**
13	0.15	6.25	2	0.6	**30**
14	0.45	6.25	2	0.2	**46**
15	0.15	10	2	1	**36**
16	0.15	10	3	0.2	**31**
17	0.45	2.5	2	0.6	**33**
18	0.75	10	2	0.2	**47**
19	0.45	6.25	1	1	**13**
20	0.75	2.5	3	0.2	**49**
21	0.75	2.5	2	1	**14**

Factor value
Low
medium
High
Yield
>45%
15-44%
<15%

Table S3: Experimental results from DOE study. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

With this data, the model was fitted with the following properties: personality = standard least squares, emphasis = effect screening. The predicted *vs* actual yields for the model had a positive correlation with an R^2 value of 0.94, suggesting a good model validity (Figure S1). A single outlier was identified (Table S3, Entry 18).

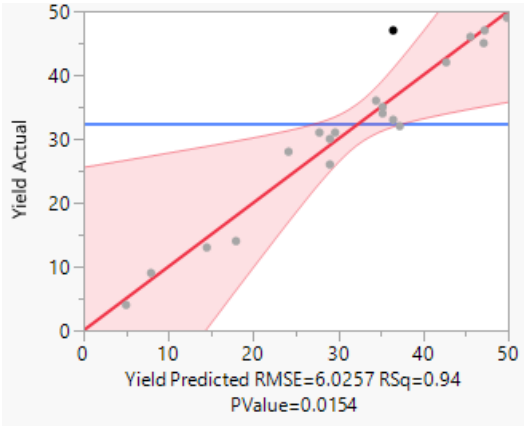


Figure S1: Predicted *vs* actual yield showing good model validity and a single outlier

The influence of various factors on the product yield are summarised in Figure S2.

Source	LogWorth	PValue
Concentration(0.2,1)	2.908	0.00124
Cat loading*Concentration	1.476	0.03345
AgTFA loading*AgTFA loading	1.395	0.04029
TDG loading*AgTFA loading	1.362	0.04346
Cat loading(2.5,10)	1.279	0.05256
Cat loading*Cat loading	0.854	0.14010
TDG loading*TDG loading	0.590	0.25680
TDG loading(0.15,0.75)	0.544	0.28592
AgTFA loading(1,3)	0.310	0.48998
Cat loading*AgTFA loading	0.272	0.53468
AgTFA loading*Concentration	0.268	0.53966
TDG loading*Cat loading	0.048	0.89509
TDG loading*Concentration	0.025	0.94339
Concentration*Concentration	0.014	0.96833

Figure S2: Effect summary, larger LogWorth denotes a larger impact on product yield

The largest impact on product yield was due to the concentration, followed by the Ag loading, where the squared value means there is a maxima or minima in yield in the range tested. There is also a strong influence on yield related to the interactions between the catalyst loading and concentration, as well as between the TDG and AgTFA loading. This will be discussed in more detail below. The catalyst loading is also important; however it was observed in Table S3 that good yields can be achieved at either high *or* low loadings or catalyst.

NOTE: Due to the smaller scale used in the DOE study (0.1 mmol *vs* 0.2 mmol for optimisation) high solvent concentrations are more likely to impact stirring and mass transport, leading to reduced yields.

The influence the four factors investigated had on each other were qualitatively observed using interaction profiles (Figure S3).

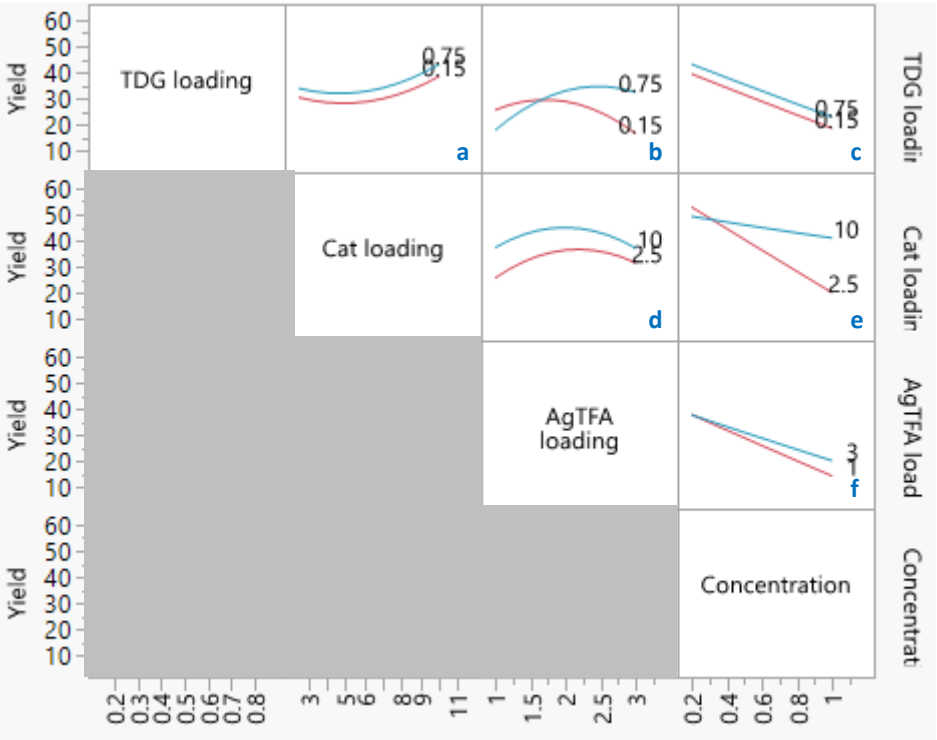


Figure S3: Interaction profiles, inverse relationships have been greyed out for clarity.

In Figure S3, each vertical column represents the factors given in the diagonal boxes (i.e. left to right: TDG loading, Cat loading, AgTFA loading, concentration). Each horizontal row represents the factor listed in the right-hand side (i.e. top to bottom: TDG loading, Cat loading, AgTFA loading, concentration). Where these cross in the table represents the interactions at the high and low limits of the loading or concentration values. For example, box a describes the effect of different catalyst loadings on product yield at both high (blue) and low (red) loadings of the TDG.

Box a: At either high or low TDG loadings, the highest yields are at either high or low catalyst loadings, meaning that the TDG loading and catalyst loading do not significantly interact (the same trend is observed at either 0.15 or 0.75 equiv TDG).

Box b: At high loadings of the TDG (blue), the yield increases in the presence of more AgTFA. At low loadings of the TDG (red) however, addition of more AgTFA is detrimental. Silver(I) salts can lead to the α-oxidation of amines,[2] which can deactivate the amine TDG. This can be used to rationalise the observed trend. When there is an abundance of TDG present at 0.75 equivalents, oxidation by silver is less impactful, at low TDG loadings however, oxidation of the amine by silver leads to a shortfall in amine to form the transient imine directing group, leading to lower product yields.

Box c: At either a high or low TDG loading, an increased concentration has the same (negative) trend in yield, so that these factors do not interact.

Box d: The curvature of the two catalyst loading profiles at different loadings of AgTFA are similar, showing that there isn't a large interaction between these factors. At any AgTFA loading more catalyst is better (blue), and for either catalyst concentration a medium value of silver is best.

Box e: There is a negative correlation between concentration and yield, but the effect is much more pronounced at lower catalyst loadings (red). At high concentrations, competing reactions are more prevalent; also seen by the reduced mass recovery. This is more significant an issue when less catalyst is present in the reaction.

Box f: There is almost no relationship between AgTFA loading and concentration.

The prediction profiler was used to access the desirability profiles for each of the factors (Figure S4). A yield of 100% of the cyclised product would be a desirability of 1.

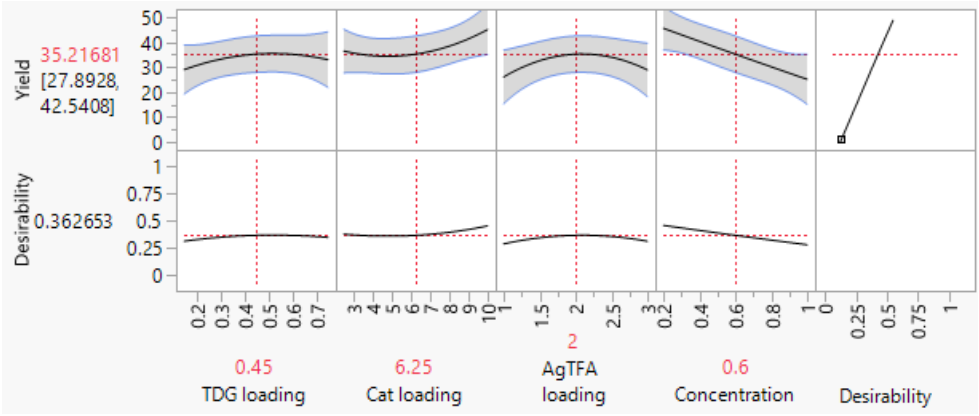


Figure S4: Prediction profiler shows optimal conditions for each factor

The software suggests that a medium value of TDG loading is best, and a slight preference for higher catalyst loadings, although low loadings are also better than the medium values. There is a clear preference for a medium value (2) of AgTFA loading. Low concentrations are optimal at this scale. A lower concentration is generally advantageous for an intramolecular reaction, suggesting it is not the coming together of the of the amine and aldehyde which is affecting the yield of the reaction, but rather one of the intramolecular steps (i.e. C–H activation, oxidative addition, reductive elimination or imine hydrolysis).

Reaction profile and positive order in catalyst

Discrete reactions were taken at different timepoints to consider the rate of the C(sp^3)–H arylation (Figure S5).

General procedure for kinetic studies: Indane precursor **4** (24 mg, 0.10 mmol), 2-methoxyethan-1-amine **TDG7** (4.3 µL, 0.05 mmol), palladium acetate (1.1 mg, 0.005 mmol), silver trifluoroacetate (44 mg, 0.2 mmol), HFIP (133 µL) and AcOH (67 µL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 130 °C for 18 h. The reaction was allowed to cool to room temperature, diluted with CH_2Cl_2, filtered through a short plug of silica (eluting with CH_2Cl_2) and concentrated under reduced pressure. 10–20 mg of accurately weighed 1,3,5-trimethoxybenzene was added, the residue was fully dissolved in $CDCl_3$ and the yield of the cyclised indane product **4** was calculated by ^{1}H NMR by comparison to the internal standard. NOTE: Due to the low volumes, all liquids of known density, including solvents, were added using a Gilson micropipette.

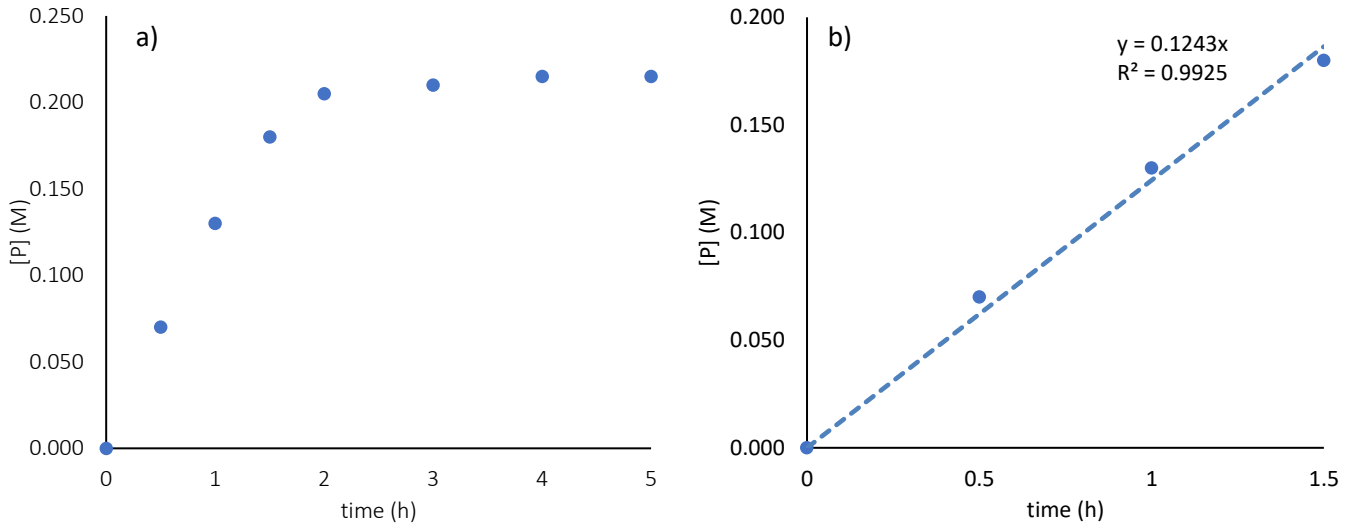


Figure S5: Reaction profile under standard conditions a) full profile, b) Linear, zero order section of profile with fitted trendline

The reaction progresses rapidly, reaching almost the maximum yield at 2 h before plateauing. Prior to the plateau, the reaction appears to be zero order, and this section provides an excellent R^2 value on fitting a linear trendline with a 0 M intercept. The gradient gives a reaction rate for the intramolecular arylation of 0.124 mmol.h^{-1}.

Some time points were also conducted using 2.5 mol% of catalyst (Figure S6), which showed a slower reaction, suggesting there is a positive order in the Pd catalyst. As the rate is approximately half for half the amount of Pd, this suggests a first order in the Pd catalyst.

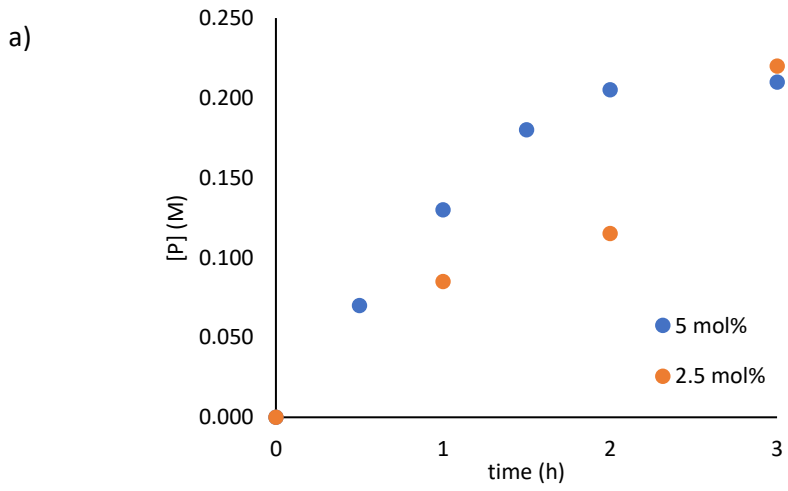


Figure S6: Slower reaction progress when using only 2.5 mol% of $Pd(OAc)_2$.

Same excess experiments product inhibition study

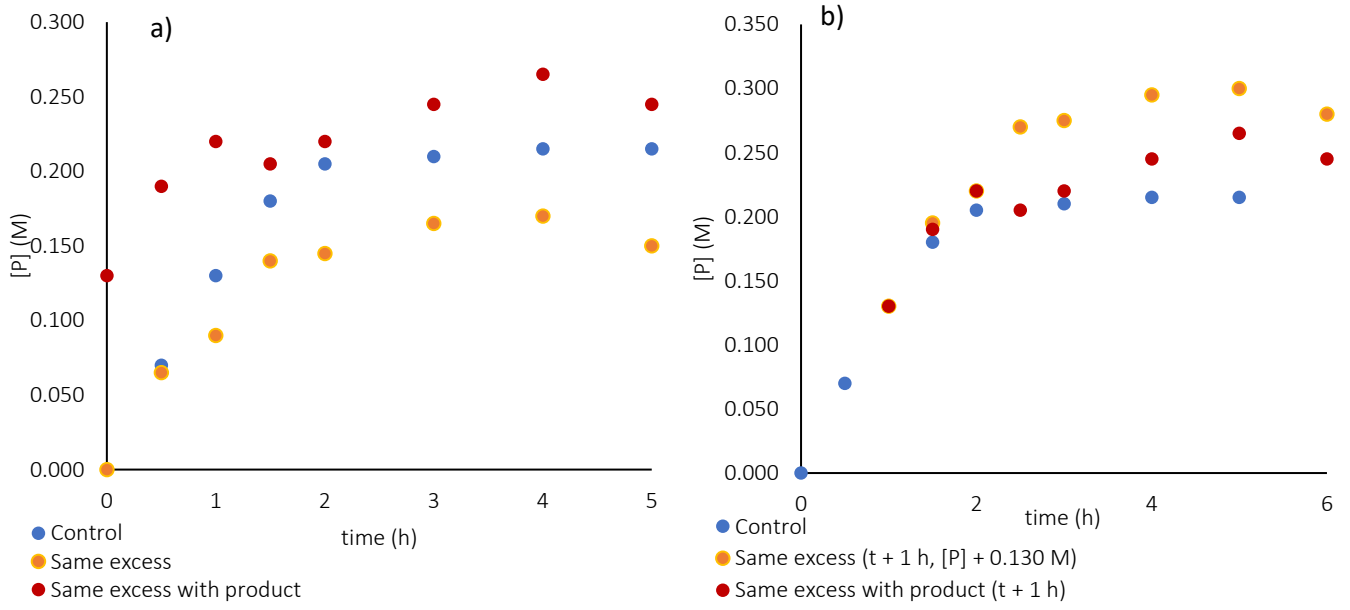
To probe proposed product inhibition, a same excess study was conducted. Same excess experiments were pioneered by Blackmond for RPKA,[4] but have since been used by Blackmond and Yu with use for visual comparison of concentration profiles.[5] This reaction is intramolecular, and so the only change is between the control reaction and the same excess is a lower initial concentration of aldehyde **2** was used, chosen to be the concentration of starting material at the 1 h timepoint where 26% is converted to the product. To consider product inhibition, the same excess experiment was also conducted with the addition of the product **4** for each discrete experiment at the concentration expected at the 1 h time point (26%; 4.2 mg, 0.026 mmol, 0.130 M). The starting concentrations are given in Table S4, and the product concentrations observed for each time point in Table S5.

Experiment	Concentration SM (M)	Concentration P added (M)
Control	0.50	0
Same Excess t = 1 h	**0.37**	0
Same Excess t = 1 h + product **4**	**0.37**	**0.13**

Table S4: Starting concentrations (M) for same excess experiments.

		[P] (M)			
Time (h) *or*	Adjusted time (h)	Control	Same excess t = 1 h →	Same excess t = 1 h [P] adjusted	same excess t = 1 h + product 4
0	**1**	0.000	0.000	0.130	0.130
0.5	**1.5**	0.070	0.065	0.195	0.190
1	**2**	0.130	0.090	0.220	0.220
1.5	**2.5**	0.180	0.140	0.270	0.205
2	**3**	0.205	0.145	0.275	0.220
3	**4**	0.210	0.165	0.295	0.245
4	**5**	0.215	0.170	0.300	0.265
5	**6**	0.215	0.150	0.280	0.245

Table S5: Raw data for same excess experiments, for [P] adjustment, a value of 0.130 M of product **4** was added to each observed value. Where product was added, 0.130 M of product **4** was added to each reaction with all other reagents (for each point), which is included in this value.

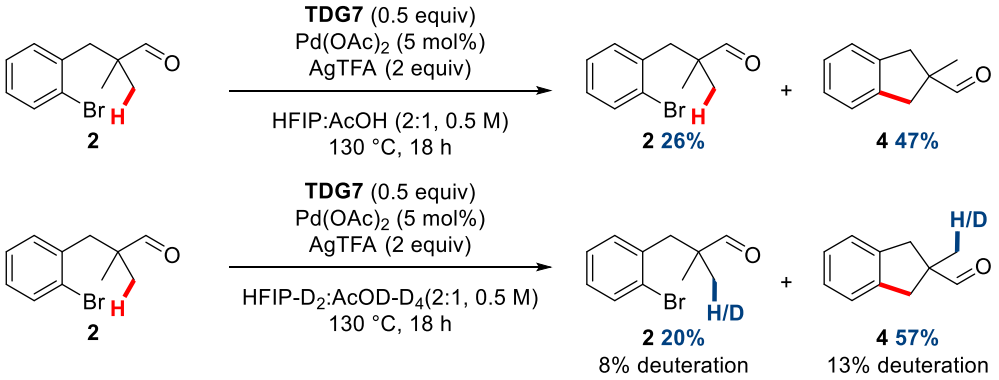


Figue S7: a) Raw data collected for same excess experiments b) Adjusted plot for same excess experiments

In the adjusted plot (Figure S7b), the same excess curve (yellow) reaches higher product yields than the control curve (blue) showing that there is either product inhibition or catalyst deactivation occuring in the control reaction. Addition of the product for each time point in the same excess experiment (red) resulted in a curve matching more closely to the control curve, suggesting there is some product inhibition, though deactivation through other mechanisms is also likely.

Reaction in deuterated solvents

To probe the reversibility of the C–H activation step, the reaction was conducted in deuterated solvent, and compared to the relevant result in protic solvents (Scheme S1, Figure S6).



Scheme S1: Reaction in proteo and deuterated solvents, 0.2 mmol of **2**. Yields determined by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard

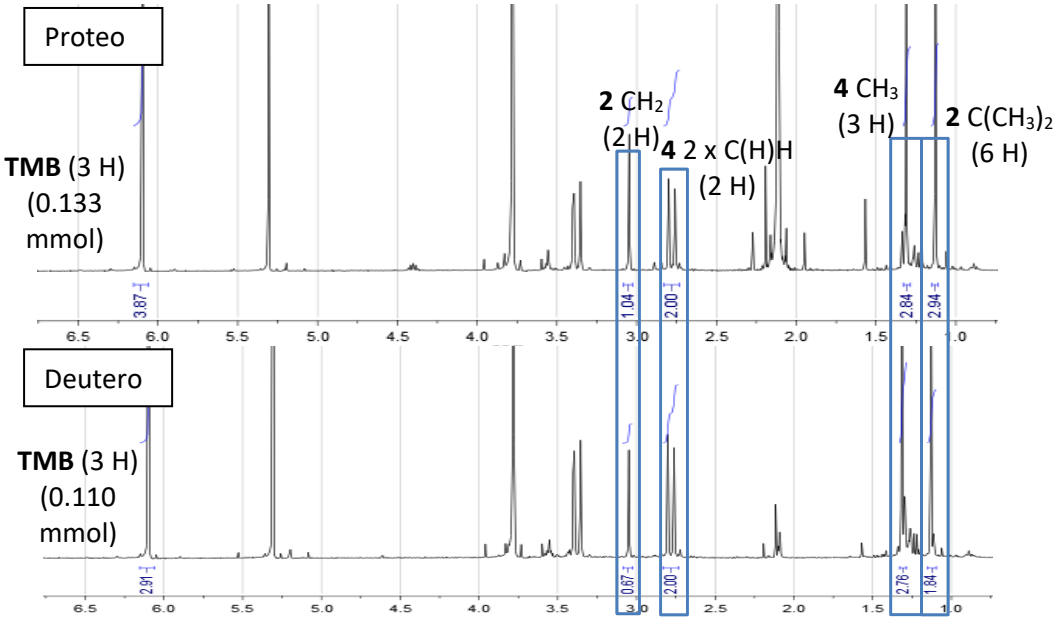


Figure S6: Reaction in proteo and deuterated solvents, comparative crude ^{1}H NMR spectra

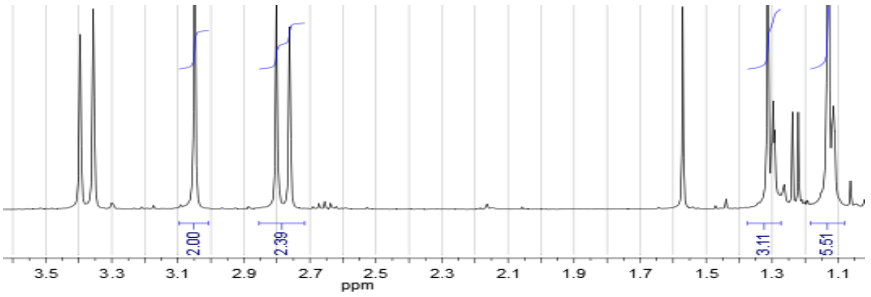
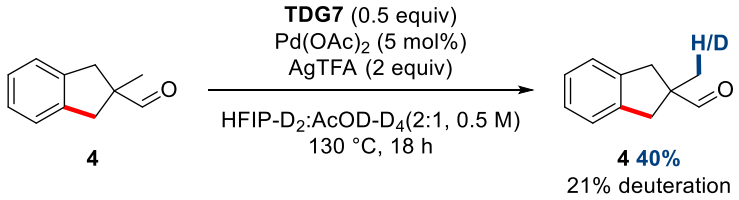


Figure S7: Isolated mixture of RSM and product in deteration study, to calculate deuteration levels

There is some deuteration to the methyl groups of both the RSM and product when running the reaction in deuterated solvents. This is determined by both the lower intergrals in the isolated mixture (Figure S7), as well as the presence of the new triplet slightly upfield to the gem-dimetyl and methyl signals showing a monodeuterated species. This suggests that the reverse C–H activation step is possible, but somewhat slower than the oxidative addition of the intramolecular aryl bromide, however where no oxidative addition could occur in the case of the product; the C–H activation is slightly more reversible and so the product has higher levels of deuteration. The presence of this reversible C–H activation of the product may elude to the mechanism of product inhibition in the reaction.

NOTE: The yield of the reaction in the deuterated solvents was higher, which may be related to the presence of deuterium atoms but also the dryness and grade of the solvents.

Subjecting indane **4** (10 mg, 0.062 mmol) to the reaction conditions in deuterated solvents led to 21% deuterium incorporation into the methyl group (Scheme S2). No deuterium incorporation was obseved on the methylene groups. Mass recovery was moderate, with 7% conversion to the carboxllic acid as well as formation of other unknown products.

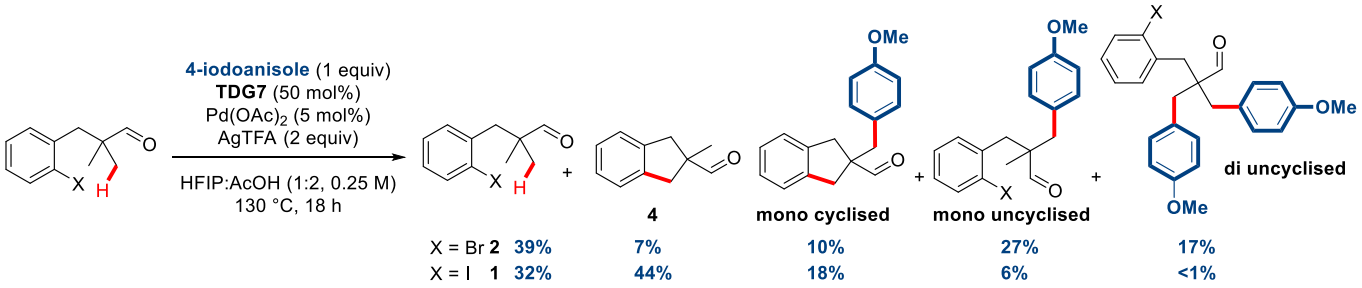


4 **4 40%**
21% deuteration

Scheme S2: Resubjecting indane product **4** to the reaction conditions in deuterated solvents. Yields determined by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard

Comparison of inter- and intramolecular C–H arylation

We have previously shown that 4-iodoanisole is a suitable coupling partner for intermolecular arlation of tertiary aldehydes using amine **TDG7** as a transient directing group.[6] We therefore added 4-iodoanisole as an external aryl iodide to compare the inter- and intramolecular arylation using either the bromide or iodide as the internal aryl halide, under the intramolecular arylation conditions but using a lower solvent concentration to promote the intramolecular arylation (Scheme S3).



Scheme S3: Comparason of inter- and intramolecular arylation of tertiary aldehydes

When using the internal aryl bromide as the substrate (**2**) the intermolecular arylation with iodoanisole was favoured. Use of iodo substrate (**1**) however, led to a more efficient cyclisation, with only low yields of the mono- and diarylated uncyclised products. These results suggest a sluggish oxidative addition of aryl bromides, even when in an intramoecular fashion, however the intramolecular arylation when using the aryl iodide is faster than the intermolecular reaction. NOTE: intermolecular arylation of tertiary aldehydes using aryl bromides was not possible, as shown in our previous work.[6] Cyclisation must happen prior to intermolecular arylation, as hinderance at the secondary alkyl group supresses cyclisation.

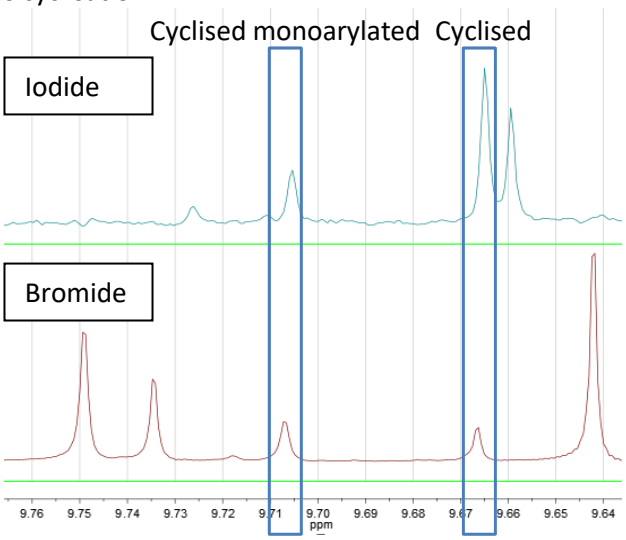


Figure S7: Aldehyde signals in inter- and intramolecular arylation competition experiments, comparative crude ^{1}H NMR spectra

Samples of the products were isolated for characterisation data to enable determination of conversions using aldehyde signals.

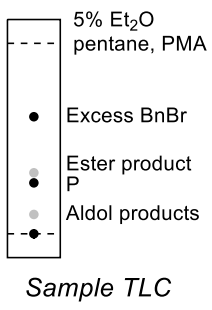
Mono cyclised: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1 H, CHO), 7.26–7.07 (m, 4 H, Ar-H), 7.07–7.00 (m, 2 H, Ar-H), 6.85–6.81 (m, 2 H, Ar-H), 3.05 (d, *J* = 13.8 Hz, 2 H, 2 × C(H)*H*), 2.76 (d, *J* = 13.8 Hz, 2 H, 2 × C(*H*)H).

Mono uncyclised bromide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1 H, CHO), 7.55 (dd, *J* = 8.0, 1.2 Hz, 1 H, Ar-H), 7.25–7.05 (m, 2 H, Ar-H), 7.05–7.01 (m, 2 H, Ar-H), 6.85–6.79 (m, 2 H, Ar-H), 3.79 (s, *J* = 5.2 Hz, 3 H, OCH_3), 3.23 (dd, *J* = 18.6, 15.0 Hz, 2 H, CH_2), 3.09–2.95 (m, 2 H, CH_2), 1.02 (s, 3 H, CH_3).

Di uncyclised bromide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1 H, CHO), 7.55 (t, *J* = 7.4 Hz, 1 H, Ar-H), 7.23 (d, *J* = 4.1 Hz, 2 H, Ar-C), 7.12–7.06 (m, 1 H, Ar-C), 7.04 (d, *J* = 8.7 Hz, 4 H, Ar-C), 6.81 (d, *J* = 8.7 Hz, 4 H, Ar-C), 3.79 (s, 6 H, 2 × OCH_3), 3.08 (s, 2 H, CH_2), 2.94 (dd, *J* = 34.7, 14.2 Hz, 4 H, 2 × CH_2).

Experimental procedures and characterisation data

Preparation of Intramolecular C–H arylation substrates (1-3, 5-17)

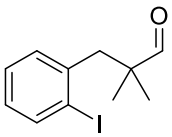


Sample TLC

General Procedure A: Methodology from Werz et. al.[7] Benzyl bromide (1.1 equiv) and aldehyde (1.0 equiv) were dissolved in the minimum amount of benzene and the resulting solution was added dropwise to a stirred suspension of ground sodium hydroxide pellets (1.0 equiv) and tetrabutylammonium iodide (1 mol%) in benzene (7.7 M) at 60 °C under Ar. The vial was crimped and the reaction stirred at 60 °C for 20 h. The reaction mixture was diluted with water and the crude product extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography (1–5% Et_2O/pentane) afforded the title aldehydes.

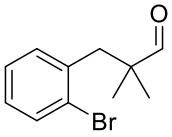
NOTE: Purity of the aldehyde is key in this reaction, if any acid is present, this then attacks the bromide forming an ester which is very close in R_f to the desired aldehyde product, visible in the ^{1}H NMR by a singlet 5.1–5.4 ppm. Isobutraldehyde should be distilled for immediate use.

3-(2-Iodophenyl)-2,2-dimethylpropanal (1)



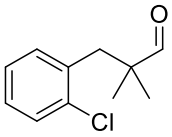
General procedure A was followed using 1-(Bromomethyl)-2-iodobenzene (1.63 g, 5.5 mmol) and isobutyraldehyde (456 µL, 5.0 mmol) to afford aldehyde **1** as a colorless oil (868 mg, 55%). R_f 0.25 (5% Et_2O/pentane). IR (film)/cm^{-1} 2969, 2929, 1723 (C=O), 1463, 1433, 1364, 1008. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H, CHO), 7.85 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar-H), 7.26 (td, *J* = 7.6, 1.3 Hz, 1 H, Ar-H), 7.15 (dd, *J* = 7.6, 1.7 Hz, 1 H, Ar-H), 6.93–6.88 (m, 1 H, Ar-H), 3.07 (s, 2 H, CH_2), 1.15 (s, 6 H, C(CH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (CHO), 140.4 (Ar-C_q), 140.0 (Ar-C), 130.7 (Ar-C), 128.4 (Ar-C), 128.1 (Ar-C), 102.7 (Ar-C_q) 48.0 (*C*(CH_3)$_2$), 46.2 (CH_2), 21.6 (C(*C*H_3)$_2$). Spectroscopic data for this compound is consistent with that shown in the literature.[7]

3-(2-Bromophenyl)-2,2-dimethylpropanal (2)



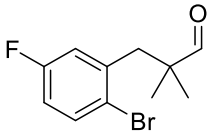
General procedure A was followed using 1-(bromomethyl)-2-bromobenzene (2.75 g, 11 mmol) and isobutyraldehyde (913 µL, 10 mmol) to afford aldehyde **2** as a colorless oil (1.26 g, 47%). R_f 0.31 (5% Et_2O/pentane). IR (film)/cm^{-1} 2968, 2930, 2698, 1722 (C=O), 1467, 1438, 1027. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1 H, CHO), 7.56 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar-H), 7.23 (td, *J* = 7.5, 1.3 Hz, 1 H, Ar-H), 7.16 (dd, *J* = 7.7, 1.8 Hz, 1 H, Ar-H), 7.11–7.07 (m, 1 H, Ar-H), 3.05 (s, 2 H, CH_2), 1.13 (s, 6 H, C(CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (CHO), 136.9 (Ar-C_q), 133.2 (Ar-C), 132.0 (Ar-C), 128.3 (Ar-C), 127.2 (Ar-C), 125.7 (Ar-C_q), 47.7 (*C*(CH_3)$_2$), 41.7 (CH_2), 21.5 (C(*C*H_3)$_2$). Spectroscopic data for this compound is consistent with that shown in the literature.[8]

3-(2-Chlorophenyl)-2,2-dimethylpropanal (3)



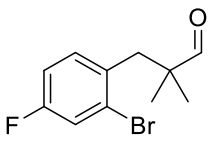
General procedure A was followed using 1-(chloromethyl)-2-bromobenzene (1.23 mL, 11 mmol) and isobutyraldehyde (913 µL, 10 mmol) to afford aldehyde **3** as a colorless oil (767 mg, 39%). R_f 0.31 (5% Et_2O/pentane). IR (film)/cm^{-1} 2967, 2702, 1722 (C=O), 1468, 1438, 1039. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.37–7.35 (m, 1 H, Ar-H), 7.21–7.14 (m, 3 H, Ar-H), 3.01 (s, 2 H, CH_2), 1.11 (s, 6 H, C(CH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.4 (CHO), 135.0 (Ar-C_q), 134.8 (Ar-C_q), 132.2 (Ar-C), 129.8 (Ar-C), 128.1 (Ar-C), 126.5 (Ar-C), 47.7 (*C*(CH_3)$_2$), 39.3 (CH_2), 21.4 (C(*C*H_3)$_2$). Spectroscopic data for this compound is consistent with that shown in the literature.[9]

3-(2-Bromo-5-fluorophenyl)-2,2-dimethylpropanal (5)



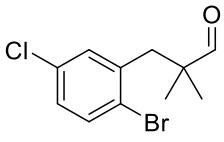
General procedure A was followed using 2-bromo-1-(bromomethyl)-5-fluorobenzene (884 mg, 3.30 mmol) and isobutyraldehyde (234 µL, 3.00 mmol) to afford aldehyde **5** as a colorless oil (394 mg, 51%). R_f 0.29 (5% Et_2O/pentane). IR (film)/cm^{-1} 2967, 2929, 2709, 1722 (C=O), 1580, 1468, 1230, 1155, 1028. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1 H, CHO), 7.51 (dd, *J* = 8.8, 5.5 Hz, 1 H, Ar-H), 6.92 (dd, *J* = 9.4, 3.0 Hz, 1 H, Ar-H), 6.86–6.81 (m, 1 H, Ar-H), 3.02 (s, 2 H, CH_2), 1.14 (s, 6 H, C(CH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8 (CHO), 161.5 (d, $^1J_{C\text{-}F}$ = 246.5 Hz, Ar-C_qF), 139.1 (d, $^3J_{C\text{-}F}$ = 7.5 Hz, ^{F}Ar-C_q), 134.2 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, ^{F}Ar-C), 119.8 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, ^{F}Ar-C_qBr), 118.8 (d, $^2J_{C\text{-}F}$ = 22.6 Hz, ^{F}Ar-C), 115.6 (d, $^4J_{C\text{-}F}$ = 22.3 Hz, ^{F}Ar-C), 47.7 (*C*(CH_3)$_2$), 41.6 (CH_2), 21.6 (C(*C*H_3)$_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.8. HRMS (EI$^+$) m/z Calcd. for $C_{11}H_{12}O^{79}BrF$ [M]$^+$: 258.0056; Found: 258.0065.

3-(2-Bromo-4-fluorophenyl)-2,2-dimethylpropanal (6)



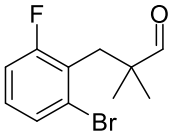
General procedure A was followed using 2-bromo-1-(bromomethyl)-4-fluorobenzene (884 mg, 3.30 mmol) and isobutyraldehyde (234 µL, 3.00 mmol) to afford aldehyde **6** as a colorless oil (114 mg, 15%). R_f 0.20 (5% Et_2O/pentane). IR (film)/cm^{-1} 2967, 2929, 2702, 1722 (C=O), 1599, 1487, 1230, 1032. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.31 (dd, *J* = 8.3, 2.7 Hz, 1 H, Ar-H), 7.14 (dd, *J* = 8.6, 6.0 Hz, 1 H, Ar-H), 6.99–6.94 (m, 1 H, Ar-H), 3.01 (s, 2 H, CH_2), 1.12 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.1 (CHO), 161.0 (d, $^1J_{C\text{-}F}$ = 249.6 Hz, Ar-C_qF), 132.8 (d, $^4J_{C\text{-}F}$ = 3.4 Hz, ^{F}Ar-C_qBr), 132.7 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, ^{F}Ar-C), 125.5 (^{F}Ar-C_q), 120.2 (d, $^2J_{C\text{-}F}$ = 24.1 Hz, ^{F}Ar-C), 114.4 (d, $^2J_{C\text{-}F}$ = 20.8 Hz, ^{F}Ar-C), 47.7 (*C*$(CH_3)_2$), 40.8 (CH_2), 21.5 (C(*C*$H_3)_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.9. HRMS (EI$^+$) m/z Calcd. for $C_{11}H_{12}O^{79}BrF$ $[M]^+$: 258.0056; Found: 258.0068

3-(2-Bromo-5-chlorophenyl)-2,2-dimethylpropanal (7)



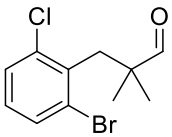
General procedure A was followed using 1-bromo-2-(bromomethyl)-4-chlorobenzene (938 mg, 3.30 mmol) and isobutyraldehyde (234 µL, 3.00 mmol) to afford aldehyde **7** as a colorless oil (341 mg, 41%). R_f 0.36 (5% Et_2O/pentane). IR (film)/cm^{-1} 2967, 2929, 2706, 1722 (C=O), 1461, 1390, 1095, 1028. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1 H, CHO), 7.48 (d, *J* = 8.5 Hz, 1 H, Ar-H), 7.17 (d, *J* = 2.5 Hz, 1 H, Ar-H), 7.08 (dd, *J* = 8.5, 2.5 Hz, 1 H, Ar-H), 3.01 (s, 2 H, CH_2), 1.13 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8 (CHO), 138.8 (Ar-C_q), 134.1 (Ar-C), 133.1 (Ar-C_q), 131.8 (Ar-C), 128.4 (Ar-C), 123.5 (Ar-C_q), 47.7 (*C*$(CH_3)_2$), 41.4 (CH_2), 21.5 (C(*C*$H_3)_2$). HRMS (pAPCI) m/z Calcd. for $C_{11}H_{11}O^{79}Br^{35}Cl$ $[M\text{-}H]^+$: 272.9676; Found: 272.9672.

3-(2-Bromo-6-fluorophenyl)-2,2-dimethylpropanal (8)



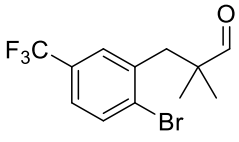
General procedure A was followed using 1-bromo-2-(bromomethyl)-3-fluorobenzene (460 µL, 3.30 mmol) and isobutyraldehyde (234 µL, 3.00 mmol) to afford aldehyde **8** as a colorless oil (449 mg, 58%). R_f 0.31 (5% Et_2O/pentane). IR (film)/cm^{-1} 2970, 2933, 2810, 2706, 1725 (C=O), 1602, 1572, 1446, 1241, 1177. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, $J_{C\text{–}F}$ = 3.2 Hz, 1 H, CHO), 7.38 (dt, *J* = 8.1, 1.1 Hz, 1 H, Ar-H), 7.10 (td, *J* = 8.1, 6.0 Hz, 1 H, Ar-H), 7.01 (ddd, *J* = 9.5, 8.1, 1.1 Hz, 1 H, Ar-H), 3.08 (d, $J_{C\text{–}F}$ = 2.9 Hz, 2 H, CH_2), 1.14 (d, $J_{C\text{–}F}$ = 1.2 Hz, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (CHO), 161.4 (d, $^1J_{C\text{-}F}$ = 248.8 Hz, Ar-C_qF), 129.0 (d, $^3J_{C\text{-}F}$ = 9.5 Hz, ^{F}Ar-C), 128.9 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, ^{F}Ar-C), 126.5 (d, $^3J_{C\text{-}F}$ = 5.2 Hz, ^{F}Ar-C_q), 125.4 (d, $^2J_{C\text{-}F}$ = 18.9 Hz, ^{F}Ar-C_q), 114.7 (d, $^2J_{C\text{-}F}$ = 23.9 Hz, ^{F}Ar-C), 47.7 (*C*$(CH_3)_2$), 35.8 (CH_2), 21.5 (C(*C*$H_3)_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ -106.4. HRMS (pAPCI) m/z Calcd. for $C_{11}H_{13}O^{79}BrF$ $[M+H]^+$: 259.0128; Found: 259.0127.

3-(2-Bromo-6-chlorophenyl)-2,2-dimethylpropanal (9)



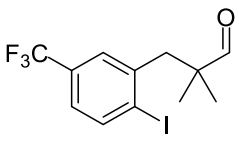
General procedure A was followed using 1-bromo-2-(bromomethyl)-3-chlorobenzene (938 mg, 3.30 mmol) and isobutyraldehyde (234 µL, 3.00 mmol) to afford aldehyde **9** as a colorless oil (289 mg, 35% (90% purity)). R_f 0.31 (5% Et_2O/pentane). IR (film)/cm^{-1} 2967, 2810, 2706, 1722 (C=O), 1554, 1431, 1196, 1118, 1062. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1 H, CHO), 7.50 (dd, *J* = 8.0, 1.2 Hz, 1 H, Ar-H), 7.35 (dd, *J* = 8.0, 1.2 Hz, 1 H, Ar-H), 7.04 (t, *J* = 8.0 Hz, 1 H, Ar-H), 3.29 (s, 2 H, CH_2), 1.18 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (CHO), 136.0 (Ar-C_q), 135.7 (Ar-C_q), 132.0 (Ar-C), 129.2 (Ar-C), 128.8 (Ar-C), 127.0 (Ar-C_q), 47.7 (*C*$(CH_3)_2$), 40.0 (CH_2), 22.1 (C(*C*$H_3)_2$). HRMS (pAPCI) m/z Calcd. for $C_{11}H_{13}O^{79}Br^{35}Cl$ $[M+H]^+$: 274.9833; Found: 274.9837.

3-(2-Bromo-5-(trifluoromethyl)phenyl)-2,2-dimethylpropanal (10)



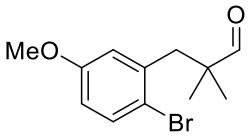
General procedure A was followed using 1-bromo-2-(bromomethyl)-4-(trifluoromethyl)benzene (557 µL, 3.30 mmol) and isobutyraldehyde (234 µL, 3.00 mmol) to afford aldehyde **10** as a colorless oil (293 mg, 32%). R_f 0.34 (5% Et_2O/pentane). IR (film)/cm^{-1} 2970, 1722 (C=O), 1468, 1330, 1170, 1121, 1080, 1028. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.69 (d, *J* = 8.3 Hz, 1 H, Ar-H), 7.43 (d, *J* = 1.8 Hz, 1 H, Ar-H), 7.35 (dd, *J* = 8.3, 1.8 Hz, 1 H, Ar-H), 3.10 (s, 2 H, CH_2), 1.14 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5 (CHO), 138.2 (Ar-C_q), 133.8 (Ar-C), 129.7 (q, $^2J_{C\text{-}F}$ = 33.2 Hz, Ar-C_q), 128.7 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, Ar-C), 124.9 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, Ar-C), 123.6 (q, $^1J_{C\text{-}F}$ = 271.8 Hz, CF_3), 47.7 (*C*$(CH_3)_2$), 41.4 (CH_2), 21.5 (C(*C*$H_3)_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.8. HRMS (pAPCI) m/z Calcd. for $C_{12}H_{11}O^{79}BrF_3$ $[M\text{-}H]^-$: 306.9940; Found: 306.9942.

3-(2-Iodo-5-(trifluoromethyl)phenyl)-2,2-dimethylpropanal (11)



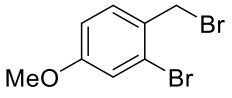
General procedure A was followed using 2-(bromomethyl)-1-iodo-4-(trifluoromethyl)benzene (1.01 g, 2.76 mmol) and isobutyraldehyde (230 µL, 2.51 mmol) to afford aldehyde **11** as a colorless oil (130 mg, 13%). R_f 0.33 (5% Et_2O/pentane). IR (film)/cm^{-1} 2970, 2709, 1729 (C=O), 1468, 1401, 1334, 1170, 1129, 1084, 1013. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1 H, CHO), 7.99 (d, *J* = 8.3 Hz, 1 H, Ar-H), 7.40 (d, *J* = 2.0 Hz, 1 H, Ar-H), 7.16 (dd, *J* = 8.3, 2.0 Hz, 1 H, Ar-H), 3.13 (s, 2 H, CH_2), 1.16 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5 (CHO), 141.7 (Ar-C_q), 140.6 (Ar-C), 130.7 (q, $^2J_{C\text{-}F}$ = 32.9 Hz, Ar-C_q), 127.1 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, Ar-C), 124.8 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, Ar-C), 123.7 (q, $^1J_{C\text{-}F}$ = 272.4 Hz, CF_3), 106.8 (Ar-C_q), 47.9 ($C(CH_3)_2$), 45.8 (CH_2), 21.7 ($C(CH_3)_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.0. HRMS (EI^+) m/z Calcd. for $C_{12}H_{12}OF_3I$ $[M]^+$: 355.9885; Found: 355.9892.

3-(2-Bromo-5-methoxyphenyl)-2,2-dimethylpropanal (12)



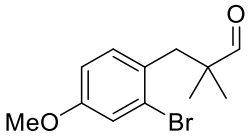
General procedure A was followed using 1-bromo-2-(bromomethyl)-4-methoxybenzene (924 mg, 3.30 mmol) and isobutyraldehyde (234 µL, 3.00 mmol) to afford aldehyde **12** as a colorless oil (175 mg, 22%). R_f 0.30 (10% Et_2O/pentane). IR (film)/cm^{-1} 2963, 2706, 1722 (C=O), 1595, 1572, 1464, 1282, 1237, 1162, 1054, 1013. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1 H, CHO), 7.43 (d, *J* = 8.7 Hz, 1 H, Ar-H), 6.71 (d, *J* = 3.0 Hz, 1 H, Ar-H), 6.66 (dd, *J* = 8.7, 3.0 Hz, 1 H, Ar-H), 3.77 (s, 3 H, OCH_3), 3.00 (s, 2 H, CH_2), 1.13 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (CHO), 158.5 (Ar-C_q), 137.9 (Ar-C_q), 133.6 (Ar-C), 117.6 (Ar-C), 116.2 (Ar-C_q), 114.0 (Ar-C), 55.4 (OCH_3), 47.7 ($C(CH_3)_2$), 41.9 (CH_2), 21.6 ($C(CH_3)_2$). HRMS (pAPCI) m/z Calcd. for $C_{12}H_{16}O_2{}^{79}Br$ $[M+H]^+$: 271.0328; Found: 271.0329.

2-Bromo-1-(bromomethyl)-4-methoxybenzene (13-Br)



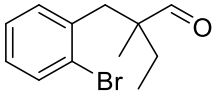
NBS (783 mg, 4.40 mmol) followed by benzoyl peroxide (12 mg, 0.048 mmol, wetted with 25% water) was added to a stirred solution of 2-bromo-4-methoxy-1-methylbenzene (585 µL, 4.00 mmol) in CCl_4 (5.0 mL) and the reaction was refluxed for 4 h. The reaction was allowed to cool to room temperature and diluted with CH_2Cl_2, washed with 1 M aqueous HCl then saturated aqueous sodium bicarbonate solution, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography afforded benzyl bromide **13-Br** as a white solid (839 mg, 75%). R_f 0.26 (2.5% Et_2O/pentane). m.p. = 59–60 °C (Lit = 59–60 °C).[10] IR (film)/cm^{-1} 2963, 2836, 1599, 1565, 1490, 1438, 1312, 1241, 1028. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.5 Hz, 1 H, Ar-H), 7.13 (d, *J* = 2.6 Hz, 1 H, Ar-H), 6.85 (dd, *J* = 8.5, 2.6 Hz, 1 H, Ar-H), 4.61 (s, 2 H, CH_2), 3.81 (s, 3 H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2 (Ar-C_q), 131.9 (Ar-C), 129.1 (Ar-C_q), 125.1 (Ar-C_q), 118.5 (Ar-C), 114.0 (Ar-C), 55.6 (OCH_3), 33.7 (CH_2). Spectroscopic data for this compound is consistent with that shown in the literature.[10]

3-(2-Bromo-4-methoxyphenyl)-2,2-dimethylpropanal (13)



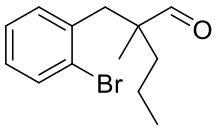
General procedure A was followed using 2-bromo-1-(bromomethyl)-4-methoxybenzene (**13-Br**) (616 mg, 2.20 mmol) and isobutyraldehyde (183 µL, 2.00 mmol) to afford aldehyde **13** as a colorless oil (310 mg, 57%). R_f 0.16 (5% Et_2O/pentane). IR (film)/cm^{-1} 2963, 2702, 1722 (C=O), 1602, 1565, 1490, 1464, 1285, 1237, 1028. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1 H, CHO), 7.10 (d, *J* = 2.6 Hz, 1 H, Ar-H), 7.06 (d, *J* = 8.5 Hz, 1 H, Ar-H), 6.79 (dd, *J* = 8.5, 2.6 Hz, 1 H, Ar-H), 3.78 (s, 3 H, OCH_3), 2.97 (s, 2 H, CH_2), 1.11 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.6 (CHO), 158.7 (Ar-C_q), 132.3 (Ar-C), 128.7 (Ar-C_q), 125.8 (Ar-C_q), 118.0 (Ar-C), 113.5 (Ar-C), 55.5 (OCH_3), 47.8 ($C(CH_3)_2$), 41.0 (CH_2), 21.5 ($C(CH_3)_2$). HRMS (pAPCI) m/z Calcd. for $C_{12}H_{14}O_2{}^{79}Br$ $[M-H]^+$: 269.0172; Found: 269.0172.

2-(2-Bromobenzyl)-2-methylbutanal (14)



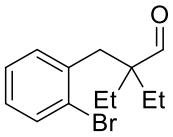
General procedure A was followed using 1-(bromomethyl)-2-bromobenzene (1.73 g, 5.50 mmol) and 2-methylbutanal (534 µL, 5.00 mmol) to afford aldehyde **14** as a colorless oil (607 mg, 48%). R_f 0.31 (5% Et_2O/pentane). IR (film)/cm^{-1} 2967, 2691, 1722 (C=O), 1461, 1021. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.54 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar-H), 7.22 (td, *J* = 7.7, 1.3 Hz, 1 H, Ar-H), 7.14 (dd, *J* = 7.7, 1.8 Hz, 1 H, Ar-H), 7.10–7.05 (m, 1 H, Ar-H), 3.12 (d, *J* = 14.0 Hz, 1 H, ArC(H)*H*), 2.99 (d, *J* = 14.0 Hz, 1 H ArC(*H*)H), 1.82–1.71 (m, 1 H, C(H)*H*), 1.62–1.53 (m, 1 H, C(*H*)H), 1.04 (s, 3 H, CH_3), 0.90 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.9 (CHO), 136.9 (Ar-C_q), 133.1 (Ar-C), 131.9 (Ar-C), 128.2 (Ar-C), 127.2 (Ar-C), 125.8 (Ar-C), 51.3 ($C(CH_3)$), 40.5 (CH_2), 28.9 (CH_2), 17.1 (CH_2), 8.5 (CH_3). HRMS (ESI) m/z Calcd. for $C_{12}H_{16}O^{79}Br$ $[M+H]^+$: 255.0385; Found: 255.0391.

2-(2-Bromobenzyl)-2-methylpentanal (15)



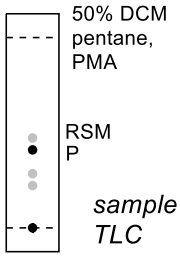
General procedure A was followed using 1-(bromomethyl)-2-bromobenzene (1.73 g, 5.50 mmol) and 2-methylpentanal (620 µL, 5.00 mmol) to afford aldehyde **15** as a colorless oil (456 mg, 34%). R_f 0.41 (5% Et_2O/pentane). IR (film)/cm^{-1} 2959, 2932, 2872, 2700, 1723 (C=O), 1467, 1438, 1022. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.55 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar-H), 7.22 (td, *J* = 7.7, 1.3 Hz, 1 H, Ar-H), 7.13 (dd, *J* = 7.7, 1.8 Hz, 1 H, Ar-H), 7.10–7.05 (m, 1 H, Ar-H), 3.13 (d, *J* = 14.0 Hz, 1 H, ArC(H)*H*), 2.99 (d, *J* = 14.0 Hz, 1 H, ArC(*H*)H), 1.68 (ddd, *J* = 13.8, 12.3, 4.7 Hz, 1 H, C(H)*H*), 1.50 (ddd, *J* = 13.8, 12.3, 4.7 Hz, 1 H, C(*H*)H), 1.41–1.30 (m, 1 H, C(H)*H*), 1.30–1.17 (m, 1 H, C(*H*)H), 1.05 (s, 3 H, CH_3), 0.94 (t, *J* = 7.2 Hz, 3 H, CH_2*CH_3*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.8 (CHO), 137.0 (Ar-C_q), 133.2 (Ar-C), 132.0 (Ar-C), 128.2 (Ar-C), 127.2 (Ar-C), 125.8 (Ar-C_q), 51.2 (*C*(CH_3)), 40.8 (CH_2), 38.7 (CH_2), 17.6 (CH_2), 17.5 (CH_2), 14.7 (CH_3). HRMS (ESI) m/z Calcd. for $C_{13}H_{18}O^{79}Br$ $[M+H]^+$: 269.0541; Found: 269.0537.

2-(2-Bromobenzyl)-2-ethylbutanal (16)



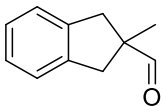
General procedure A was followed using 1-(bromomethyl)-2-bromobenzene (820 mg 3.30 mmol) and 2-ethylbutanal (369 µL, 3.00 mmol) to afford aldehyde **17** as a colorless oil (156 mg, 19%). R_f 0.36 (5% Et_2O/pentane). IR (film)/cm^{-1} 2967, 2881, 2968, 1722 (C=O), 1438, 1382, 1021. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1 H, CHO), 7.54 (dd, *J* = 8.0, 1.2 Hz, 1 H, Ar-H), 7.22 (td, *J* = 7.5, 1.2 Hz, 1 H, Ar-H), 7.16 (dd, *J* = 7.5, 1.8 Hz, 1 H, Ar-H), 7.08 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1 H, Ar-H), 3.05 (s, 2 H, CH_2), 1.74 – 1.54 (m, 4 H, 2 × CH_2), 0.88 (t, *J* = 7.5 Hz, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4 (CHO), 136.7 (Ar-C_q), 133.2 (Ar-C), 131.8 (Ar-C), 128.2 (Ar-C), 127.2 (Ar-C), 125.8 (Ar-C_q), 53.8 (*C*(CH_3)$_2$), 38.8 (CH_2), 23.5 (2 × CH_2), 7.9 (2 × CH_3). HRMS (pAPCI) m/z Calcd. for $C_{13}H_{18}O^{79}Br$ $[M+H]^+$: 269.0536; Found: 269.0531.

Intramolcular C(sp³)–H arylation of aldehydes with a transient directing group (4, 18-25)



General procedure B: Indane precursor (0.40 mmol), 2-methoxyethan-1-amine **TDG7** (17.4 µL, 0.20 mmol), palladium acetate (4.5 mg, 5 mol%), silver trifluoroacetate (176 mg, 0.80 mmol), HFIP (0.53 mL) and acetic acid (0.27 mL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 130 °C for 18 h. The reaction was allowed to cool to room temperature, diluted with CH_2Cl_2, filtered through a short plug of silica (eluting with CH_2Cl_2) and concentrated under reduced pressure. Purification by flash chromatography (silica, 10-30% CH_2Cl_2/pentane) afforded the cyclised indane aldehydes**.**

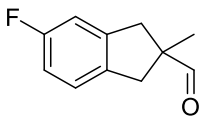
2-Methyl-2,3-dihydro-1H-indene-2-carbaldehyde (4)



General procedure B was followed using 3-(2-bromophenyl)-2,2-dimethylpropanal **2** (97 mg, 0.40 mmol) to afford cyclised aldehyde **4** as a colourless oil (27 mg, 42%). R_f 0.45 (50% CH_2Cl_2/pentane). IR (film)/cm^{-1} 3025, 2970, 1724 (s, C=O), 1457, 1433, 1370, 1231, 1217, 1023. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1 H, CHO), 7.25–7.15 (m, 4 H, Ar-H), 3.38 (d, *J* = 15.8 Hz, 2 H, 2 × C(*H*)H), 2.78 (d, *J* = 15.8 Hz, 2 H, 2 × C(H)*H*), 1.31 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (CHO), 140.9 (2 × Ar-C_q), 126.8 (2 × Ar-C), 124.7 (2 × Ar-C), 54.3 (C_q(CH_3)), 40.9 (2 × CH_2), 20.9 (CH_3). Spectroscopic data for this compound is consistent with that shown in the literature.[11]

The reaction was also conducted with 482 mg, 2.00 mmol of **2** to form indane **4** in 110 mg, 34% yield and using 965 mg, 4.00 mmol of **2** to form indane **4** in 216 mg, 33%, data collected was equivalent. 3-(2-Iodophenyl)-2,2-dimethylpropanal (**1**) (115 mg, 0.40 mmol) was also used as the starting material to form indane **4** in 13 mg, 20% yield, data collected was equivalent**.**

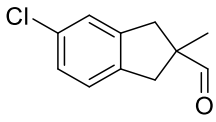
5-Fluoro-2-methyl-2,3-dihydro-1H-indene-2-carbaldehyde (18)



General procedure B was followed using 3-(2-bromo-5-fluorophenyl)-2,2-dimethylpropanal **5** (97 mg, 0.40 mmol) to afford cyclised aldehyde **18** as a pale yellow oil (29 mg, 41%). R_f 0.60 (50% CH_2Cl_2/pentane). IR (film)/cm^{-1} 2967, 2929, 2706, 1722 (C=O), 1599, 1487, 1435, 1248, 1125. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H, CHO), 7.13 (dd, *J* = 8.1, 5.2 Hz, 1 H, Ar-H), 6.92–6.83 (m, 2 H, Ar-H), 3.38–3.29 (m, 2 H, 2 × C(H)*H*), 2.78–2.71 (m, 2 H, 2 × C(*H*)H), 1.32 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4 (CHO), 162.3 (d, $^1J_{C\text{-}F}$ = 243.5 Hz, Ar-C_qF), 143.1 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, ^{F}Ar-C_q), 136.2 (d, $^4J_{C\text{-}F}$ = 2.7 Hz, ^{F}Ar-C_q), 125.6 (d, $^3J_{C\text{-}F}$ = 8.9 Hz, ^{F}Ar-C), 113.8 (d, $^2J_{C\text{-}F}$ = 22.4 Hz, ^{F}Ar-C), 111.8 (d, $^2J_{C\text{-}F}$ = 22.2 Hz, ^{F}Ar-C), 54.9 (*C*(CHO), 40.7 (CH_2), 40.0 (CH_2), 20.9 (CH_3). ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.7. HRMS (pAPCI) m/z Calcd. for $C_{11}H_{12}OF$ $[M+H]^+$: 179.0867; Found: 179.0862.

3-(2-Bromo-4-fluorophenyl)-2,2-dimethylpropanal (**6**) (97 mg, 0.40 mmol) was also used as the starting material to form indane **18** in 30 mg, 42% yield, data collected was equivalent.

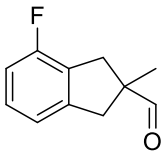
5-Chloro-2-methyl-2,3-dihydro-1H-indene-2-carbaldehyde (19)



General procedure B was followed using 3-(2-bromo-5-chlorophenyl)-2,2-dimethylpropanal **7** (110 mg, 0.40 mmol) to afford cyclised aldehyde **19** as a colourless oil (36 mg, 46%). R_f 0.49 (50% CH_2Cl_2/pentane). IR (film)/cm^{-1} 2963, 2706, 1722 (C=O), 1476, 1431, 1166. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1 H, CHO), 7.19 (s, 1 H, Ar-H), 7.16–7.10 (m, 2 H, Ar-H), 3.37–3.30 (m, 2 H, 2 × C(H)*H*), 2.77–2.71 (m, 2 H, 2 × C(*H*)H), 1.31 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3 (CHO), 142.9 (Ar-C_q), 139.4 (Ar-C_q), 132.5 (Ar-C_q), 127.0 (Ar-C), 125.7 (Ar-C), 124.9 (Ar-C), 54.7 (*C*(CHO), 40.6 (CH_2), 40.2 (CH_2), 20.9 (CH_3). HRMS (pAPCI) m/z Calcd. for $C_{11}H_{12}O^{35}Cl$ $[M+H]^+$: 195.0571; Found: 195.0576.

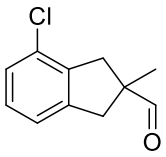
The reaction was also conducted using 276 mg, 2.00 mmol of **7** to form indane **19** in 181 mg, 47% yield, data collected was equivalent.

4-Fluoro-2-methyl-2,3-dihydro-1H-indene-2-carbaldehyde (20)



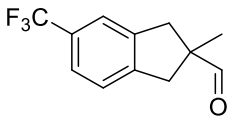
General procedure B was followed using 3-(2-bromo-6-fluorophenyl)-2,2-dimethylpropanal **8** (110 mg, 0.40 mmol) to afford cyclised aldehyde **20** as a yellow oil (27 mg, 38%) as a mixture with starting material **8** (17 mg, 16%). R_f 0.43 (50% CH_2Cl_2/pentane). IR (film)/cm^{-1} 2967, 2929, 2706, 1725 (C=O), 1587, 1472, 1244. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1 H, CHO), 7.18–7.13 (m, 1 H, Ar-H), 7.04–6.98 (m, 1 H, Ar-H), 6.87 (t, *J* = 8.5 Hz, 1 H, Ar-H), 3.42–3.38 (m, 2 H, 2 × C(H)*H*), 2.84–2.78 (m, 2 H, 2 × C(*H*)H), 1.34 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1 (CHO), 159.4 (d, $^1J_{C\text{-}F}$ = 247.4 Hz, Ar-C_qF), 144.5 (Ar-C_q), 128.8 (d, $^3J_{C\text{-}F}$ = 7.4 Hz, ^{F}Ar-C), 127.0 (d, $^2J_{C\text{-}F}$ = 17.9 Hz, ^{F}Ar-C_q), 120.3 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, ^{F}Ar-C), 113.4 (d, $^2J_{C\text{-}F}$ = 20.2 Hz, ^{F}Ar-C), 54.5 (*C*(CHO)), 40.9 (CH_2), 36.7 (CH_2), 21.0 (CH_3). ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.8. HRMS (EI$^+$) m/z Calcd. for $C_{11}H_{11}OF$ [M]$^+$: 178.0794; Found: 178.0801.

4-Chloro-2-methyl-2,3-dihydro-1H-indene-2-carbaldehyde (21)



General procedure B was followed using 3-(2-bromo-6-chlorophenyl)-2,2-dimethylpropanal **9** (110 mg, 0.40 mmol) to afford cyclised aldehyde **21** as a yellow oil (41 mg, 53%) as a mixture with starting material **9** (11 mg, 10%). R_f 0.76 (50% CH_2Cl_2/pentane). IR (film)/cm^{-1} 2967, 2929, 2706, 1722 (C=O), 1572, 1453, 1118. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1 H, CHO), 7.18–7.09 (m, 3 H, Ar-H), 3.47–3.40 (m, 2 H, 2 × C(H)*H*), 2.86–2.81 (m, 2 H, 2 × C(*H*)H), 1.34 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1 (CHO), 143.0 (Ar-C_q), 139.2 (Ar-C_q), 132.0 (Ar-C_q), 128.5 (Ar-C), 126.9 (Ar-C), 123.0 (Ar-C), 53.5 (*C*(CHO)), 41.3 (CH_2), 40.1 (CH_2), 21.2 (CH_3). HRMS (EI$^+$) m/z Calcd. for $C_{11}H_{11}O^{35}Cl$ [M]$^+$: 194.0498; Found: 194.0505.

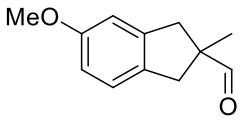
2-Methyl-5-(trifluoromethyl)-2,3-dihydro-1H-indene-2-carbaldehyde (22)



General procedure B was followed using 3-(2-bromo-5-(trifluoromethyl)phenyl)-2,2-dimethylpropanal **10** (124 mg, 0.40 mmol) to afford cyclised aldehyde **22** as a pale yellow oil (38 mg, 42%). R_f 0.50 (50% CH_2Cl_2/pentane). IR (film)/cm^{-1} 2967, 2709, 1725 (C=O), 1435, 1319, 1285, 1155, 1114. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1 H, CHO), 7.46–7.43 (m, 2 H, Ar-H), 7.31 (d, *J* = 7.9 Hz, 1 H, Ar-H), 3.42 (d, *J* = 16.3 Hz, 2 H, 2 × C(H)*H*), 2.85–2.80 (m, 2 H, 2 × C(*H*)H), 1.34 (d, *J* = 2.2 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0 (CHO), 145.1 (Ar-C_q), 141.7 (Ar-C_q), 129.4 (q, $^2J_{C\text{–}F}$ = 32.0 Hz, Ar-C_q), 125.0 (Ar-C), 124.3 (q, $^1J_{C\text{–}F}$ = 272.1 Hz, CF_3), 124.1 (q, $^3J_{C\text{–}F}$ = 3.8 Hz, Ar-C), 121.6 (q, $^3J_{C\text{–}F}$ = 3.6 Hz, Ar-C), 54.5 (*C*(CHO), 40.6 (CH_2), 40.5 (CH_2), 20.9 (CH_3). HRMS (EI$^+$) m/z Calcd. for $C_{12}H_{11}F_3O$ [M]$^+$: 228.0762; Found: 228.0770.

3-(2-Iodo-5-(trifluoromethyl)phenyl)-2,2-dimethylpropanal (**11**) (71 mg, 0.2 mmol) was also used as a starting material to form indane **22** in 13 mg, 28% yield, data collected was equivalent.

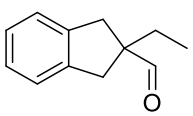
5-Methoxy-2-methyl-2,3-dihydro-1H-indene-2-carbaldehyde (23)



General procedure B was followed using 3-(2-bromo-4-methoxyphenyl)-2,2-dimethylpropanal **13** (108 mg, 0.40 mmol) to afford cyclised aldehyde **23** as a pale yellow oil (20 mg, 26%). R_f 0.45 (50% CH_2Cl_2/pentane). IR (film)/cm^{-1} 2959, 2929, 1836, 2706. 2725 (C=O), 1610, 1490, 1461, 1252, 1032. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H, CHO), 7.10 (d, *J* = 8.2 Hz, 1 H, Ar-H), 6.77–6.72 (m, 2 H, Ar-H), 3.79 (s, 3 H, OCH_3), 3.32 (dd, *J* = 23.1, 16.0 Hz, 2 H, 2 × C(H)*H*), 2.73 (dd, *J* = 15.9, 10.0 Hz, 2 H, 2 × C(*H*)H), 1.31 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (CHO), 159.1 (Ar-C_q), 142.5 (Ar-C_q), 132.8 (Ar-C_q), 125.2 (Ar-C), 112.8 (Ar-C), 110.1 (Ar-C), 55.4 (OCH_3), 54.7 (*C*(CHO)), 41.0 (CH_2), 40.1 (CH_2), 20.9 (CH_3). HRMS (pAPCI) m/z Calcd. for $C_{12}H_{15}O_2$ [M+H]$^+$: 191.1067; Found: 191.1072.

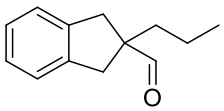
3-(2-Bromo-5-methoxyphenyl)-2,2-dimethylpropanal **12** (108 mg, 0.4 mmol) was also used as a starting material to form indane **23** in 4 mg, 5% yield, data collected was equivalent.

2-Ethyl-2,3-dihydro-1H-indene-2-carbaldehyde (24)



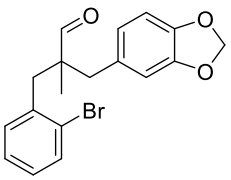
General procedure B was followed using 2-(2-bromobenzyl)-2-methylbutanal **14** (102 mg, 0.40 mmol) to afford cyclised aldehyde **24** as a colourless oil (18 mg, 26%). R_f 0.52 (50% CH_2Cl_2/pentane). IR (film)/cm^{-1} 2967, 2922, 2694, 1722 (C=O), 1483, 1461. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1 H, CHO), 7.21–7.14 (m, 4 H, Ar-H), 3.34 (d, *J* = 16.0 Hz, 2 H, 2 × C(H)*H*), 2.86 (d, *J* = 16.0 Hz, 2 H, 2 × C(*H*)H), 1.83 (q, *J* = 7.5 Hz, 2 H, CH_2), 0.91 (t, *J* = 7.5 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.2 (CHO), 140.9 (2 × Ar-C_q), 126.7 (2 × Ar-C), 124.5 (2 × Ar-C), 58.6 (*C*(CHO), 38.4 (2 × CH_2), 28.1 (CH_2), 9.5 (CH_3). HRMS (pAPCI) m/z Calcd. for $C_{12}H_{15}O$ [M+H]$^+$: 175.1117; Found: 175.1116.

2-Propyl-2,3-dihydro-1H-indene-2-carbaldehyde (25)

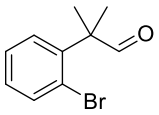


General procedure B was followed using 2-(2-bromobenzyl)-2-methylpentanal **15** (108 mg, 0.40 mmol) to afford cyclised aldehyde **25** as a colourless oil (17 mg, 23%). R_f 0.54 (50% CH_2Cl_2/pentane). IR (film)/cm^{-1} 2959, 2698, 1722 (C=O), 1461. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1 H, CHO), 7.20–7.14 (m, 4 H, Ar-H), 3.34 (d, *J* = 16.0 Hz, 2 H, 2 × C(H)*H*), 2.86 (d, *J* = 16.0 Hz, 2 H, 2 × C(*H*)H), 1.78–1.74 (m, 2 H, CH_2), 1.34–1.24 (m, 2 H, CH_2), 0.93 (t, *J* = 7.3 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.1 (CHO), 141.0 (2 × Ar-C_q), 126.7 (2 × Ar-C), 124.5 (2 × Ar-C_q), 58.3 (*C*(CHO), 38.8 (2 × CH_2), 37.9 (CH_2), 18.6 (CH_2), 14.6 (CH_3). HRMS (ESI) m/z Calcd. for $C_{13}H_{17}O$ $[M+H]^+$: 189.1279; Found: 189.1279.

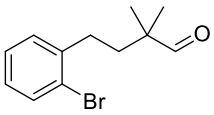
Unsuccessful substrates



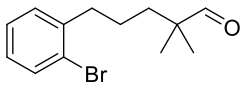
Cyclisation observed, but only in trace amounts



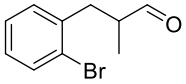
Cyclisation observed, but only in trace amounts



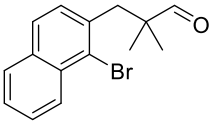
Cyclisation observed, but only in trace amounts



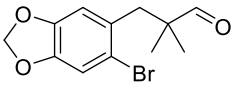
No cyclisation to form the 7-membered ring



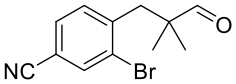
No cyclisation observed, but oxidation to α,β-unsaturated aldehyde prevalent



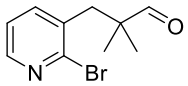
Cyclisation observed, but only in trace amounts



Cyclisation observed, but only in trace amounts



Complex mix of products from nitrile hydrolysis

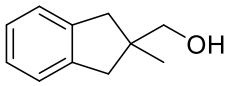


Cyclisation observed, but only in trace mounts

Formation of the 4- or 6-membered rings using this approach led to low conversions (<10%) with mostly starting material remaining. No coversion was observed for 7-membered ring formation. Steric hinderance at the position *ortho* to oxidative addition and high electron density of the aromatic significantly hindered cyclisation (conversions <10%). Nitrile groups are not stable under these reaciton conditions. Coordination from a pyridine nitrogen caused catalyst deactivation and low conversion for the cyclisation. Secondary aldehydes are not tolerated under these conditions, with preferential oxidation to the conjugated alkene occuring.

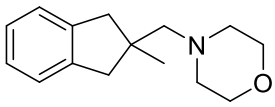
Derivatisations of cyclised products (27-30)

(2-Methyl-2,3-dihydro-1H-inden-2-yl)methanol (27)



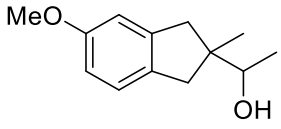
$NaBH_4$ (9 mg, 0.24 mmol) was added to a stirred solution of 2-methyl-2,3-dihydro-1H-indene-2-carbaldehyde (**4**) (32 mg, 0.20 mmol) in MeOH (0.4 mL) at 0 °C and the reaction was allowed to warm to room temperature and stirred for 2 h. Water was added and the product extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography (SiO_2, 20–30% Et_2O/pentane) afforded alcohol **27** as white solid (30 mg, 92%). R_f 0.21 (30% Et_2O/pentane). mp = 50–52 °C. IR (film)/cm^{-1} 3350 (br, OH), 2914, 2870, 1461, 1032. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.13 (m, 4 H, Ar-H), 3.55 (s, 2 H, OCH_2), 2.93 (d, *J* = 15.7 Hz, 2 H, 2 × C(H)*H*), 2.68 (d, *J* = 15.7 Hz, 2 H, 2 × C(*H*)H), 1.47 (bs, 1 H, OH), 1.20 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5 (2 × Ar-C_q), 126.2 (2 × Ar-C), 124.8 (2 × Ar-C), 70.6 (OCH_2), 44.9 (*C*(CH_3)), 42.7 (2 × CH_2), 24.0 (CH_3). Spectroscopic data for this compound is consistent with that shown in the literature.[11]

4-((2-Methyl-2,3-dihydro-1H-inden-2-yl)methyl)morpholine (28)



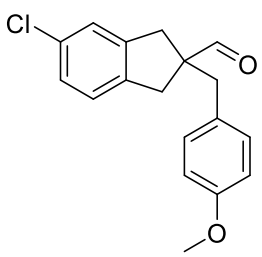
2-Methyl-2,3-dihydro-1H-indene-2-carbaldehyde (**4**) (32 mg, 0.20 mmol) and morpholine (21 µL, 0.24 mmol) were stirred in CH_2Cl_2 (0.67 mL) at room temperature for 2.5 h. $NaBH(OAc)_3$ (51 mg, 0.24 mmol) was added and the reaction was stirred for overnight. 1 M aqueous NaOH was added and the product extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and solvent removed under reduced pressure. The crude reaction mixture was dissolved in Et_2O and the protonated amine extracted with 1 M aqueous HCl. The aqueous phase was basified with ground sodium hydroxide pellets and free amine extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford amine **28** as a pale yellow oil (20 mg, 43%). R_f 0.12 (10% Et_2O/pentane). IR (film)/cm^{-1} 2952, 2847, 2803, 1457, 1118, 1013. ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.12 (m, 4 H, Ar-H), 3.71–3.68 (m, 4 H, 2 × OCH_2), 2.88 (d, *J* = 15.4 Hz, 2 H, 2 × C(H)*H*), 2.62 (d, *J* = 15.4 Hz, 2 H, 2 × C(H)*H*), 2.54–2.52 (m, 4 H, 2 × NCH_2), 2.35 (s, 2 H, NCH_2), 1.14 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (2 × Ar-C_q), 126.1 (2 × Ar-C), 124.7 (2 × Ar-C), 68.0 (NCH_2), 67.3 (2 × OCH_2), 55.8 (2 × NCH_2), 45.2 (*C*(CH_3)), 44.8 (2 × CH_2), 25.4 (CH_3). HRMS (ES^+) m/z Calcd. for $C_{15}H_{22}NO$ [M+H]: 232.1701; Found: 232.1707.

1-(5-Methoxy-2-methyl-2,3-dihydro-1H-inden-2-yl)ethan-1-ol (29)



Methylmagnesium chloride (67 µL, 0.20 mmol, 3 M solution in THF) was added dropwise to a stirred solution of 5-methoxy-2-methyl-2,3-dihydro-1H-indene-2-carbaldehyde (**23**) (17.5 mg, 0.10 mmol) in Et_2O (0.33 mL) at 0 °C and the reaction was stirred at 0 °C for 1 h then allowed to warm to room temperature and stirred for 30 minutes. Saturated aqueous ammonium chloride solution was added and the product extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography (SiO_2, 30% Et_2O/pentane) afforded alcohol **29** as a pale yellow oil (10 mg, 48%). The primary alcohol was isolated as a side product with the addition of methyl or vinyl Grignard's. R_f 0.18 (30% Et_2O/pentane). IR (film)/cm^{-1} 3436 (br, OH), 2967, 2933, 2836, 1610, 1490, 1464, 1248, 1088, 1036. ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.1, 4.9 Hz, 1 H, Ar-H), 6.75–6.69 (m, 2 H, Ar-H), 3.84–3.79 (m, 1 H, C*H*OH), 3.79 (s, 3 H, OCH_3), 3.04–2.87 (m, 2 H, 2 × C(H)*H*), 2.67–2.58 (m, 1 H, C(H)*H*), 2.53–2.46 (m, 1 H, C(H)*H*), 1.43 (bs, 1 H, OH), 1.21 (d, *J* = 6.4 Hz, 3 H, CH*C*H_3), 1.06 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.67 and 158.65 (Ar-C_q, diastereomers), 144.1 and 144.0 (Ar-C_q, diastereomers), 134.6 and 134.5 (Ar-C_q, diastereomers), 125.3 and 125.2 (Ar-C, diastereomers), 112.1 and 112.0 (Ar-C, diastereomers), 110.31 and 110.26 (Ar-C_f, diastereomers), 74.6 and 74.5 (CHOH, diastereomers), 55.4 (OCH), 48.5 (*C*(CH_3), 43.7 and 43.4 (CH_2, diastereomers), 42.5 and 42.4 (CH_2, diastereomers), 21.5 and 21.4 (CH_3, diastereomers), 19.0 (CH_3). HRMS (pAPCI) m/z Calcd. for $C_{13}H_{17}O$ $[M\text{-}OH]^+$: 189.1274; Found: 189.1268.

5-Chloro-2-(4-methoxybenzyl)-2,3-dihydro-1H-indene-2-carbaldehyde (30)



Procedure from our previous study on tertiary aldehyde arylation.[1] 5-Chloro-2-methyl-2,3-dihydro-1H-indene-2-carbaldehyde (**19**) (78 mg, 0.40 mmol), *N*-(2-aminoethyl)-4-methylbenzenesulfonamide (**TDG1**) (43 mg, 0.20 mmol), 4-iodoanisole (225 mg, 0.96 mmol), palladium pivalate (6.2 mg, 5 mol%), silver trifluoroacetate (176 mg, 0.80 mmol), DMSO (28.4 µL, 0.40 mmol), acetic acid (0.4 mL) and HFIP (0.4 mL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 130 °C for 3 h. The reaction was allowed to cool to room temperature, dissolved in CH_2Cl_2, filtered through a short plug of silica, washed with CH_2Cl_2 and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 2.5% Et_2O/pentane) afforded aldehyde **30** as a pale yellow oil (48 mg, 40%, ≈ 85% purity). R_f 0.13 (10% Et_2O/pentane). IR (film)/cm^{-1} 2907, 2836, 1722 (C=O), 1610, 1509, 1472, 1244, 1177, 1032. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1 H, CHO), 7.16 (s, 1 H, Ar-H), 7.14–7.08 (m, 2 H, Ar-H), 7.06–7.01 (m, 2 H, Ar-H), 6.84–6.81 (m, 2 H, Ar-H), 3.79 (s, 3 H, OCH_3), 3.25–3.19 (m, 2 H, 2 × C(H)*H*), 3.02 (s, 2 H, CH_2), 2.96–2.90 (m, 2 H, 2 × C(*H*)H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8 (CHO), 158.5 (Ar-C_q), 142.7 (Ar-C_q), 139.1 (Ar-C_q), 130.9 (2 × Ar-C), 128.8 (Ar-C_q), 127.0 (Ar-C), 125.7 (Ar-C), 124.8 (Ar-C), 122.3 (Ar-C_q), 113.9 (2 × Ar-C), 60.0 (*C*(CH_3)), 55.2 (OCH_3), 39.8 (CH_2), 38.3 (CH_2), 38.0 (CH_2). HRMS (pAPCI) m/z Calcd. for $C_{18}H_{18}O_2{}^{35}Cl$ $[M+H]^+$: 301.0990; Found: 301.0989.

References

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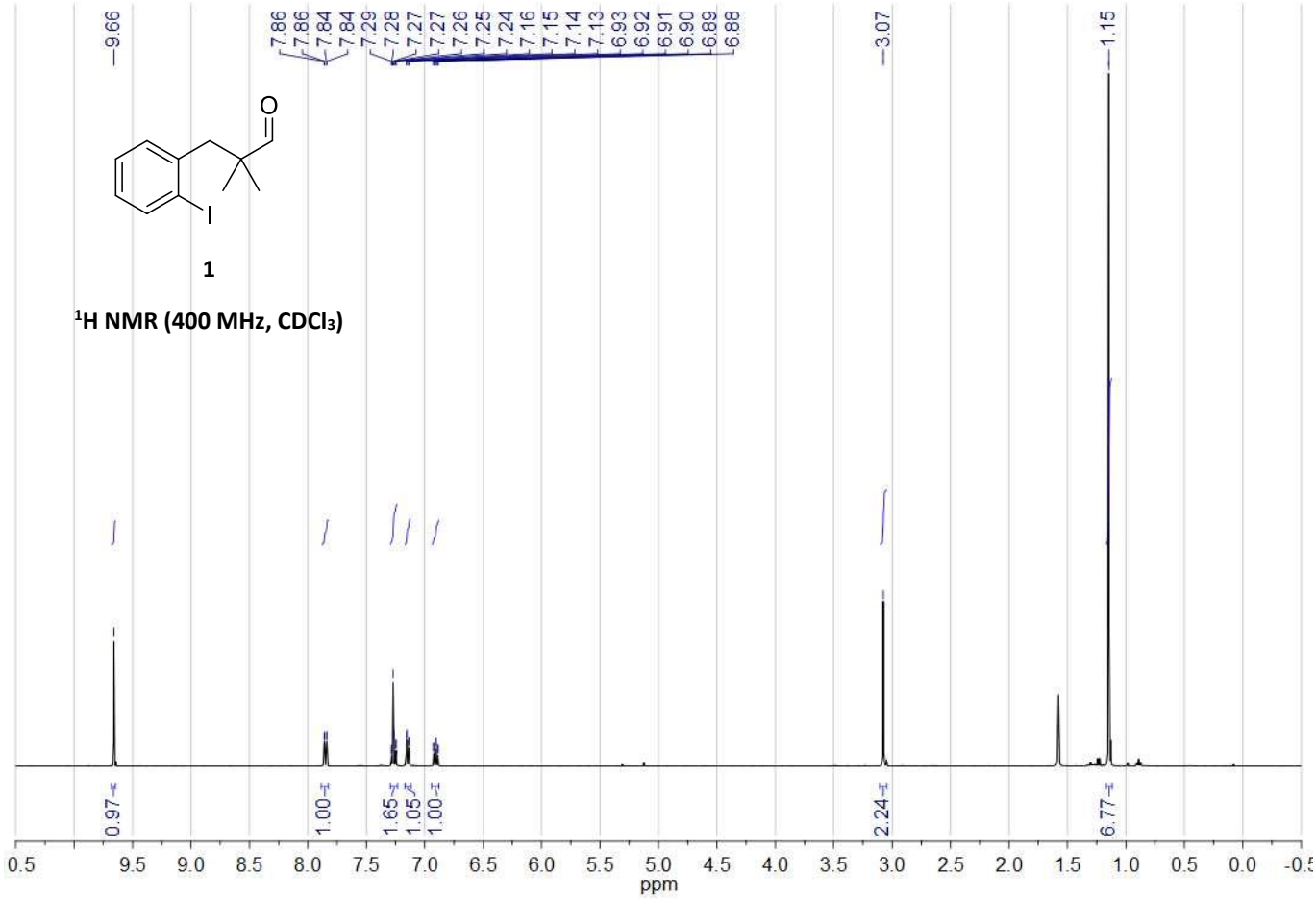
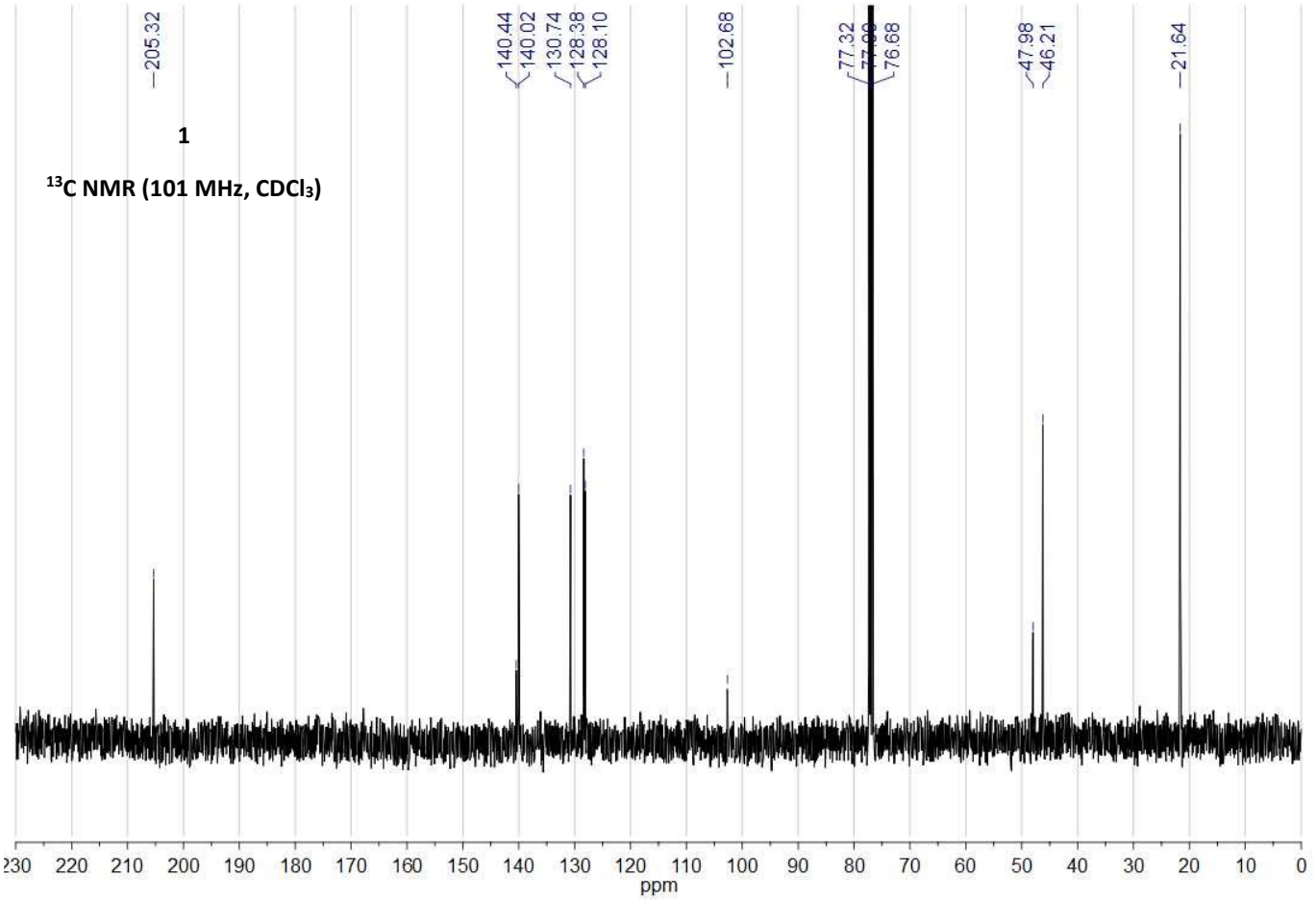
^{1}H and ^{13}C NMR spectra of selected compounds



1

^{1}H NMR (400 MHz, $CDCl_3$)



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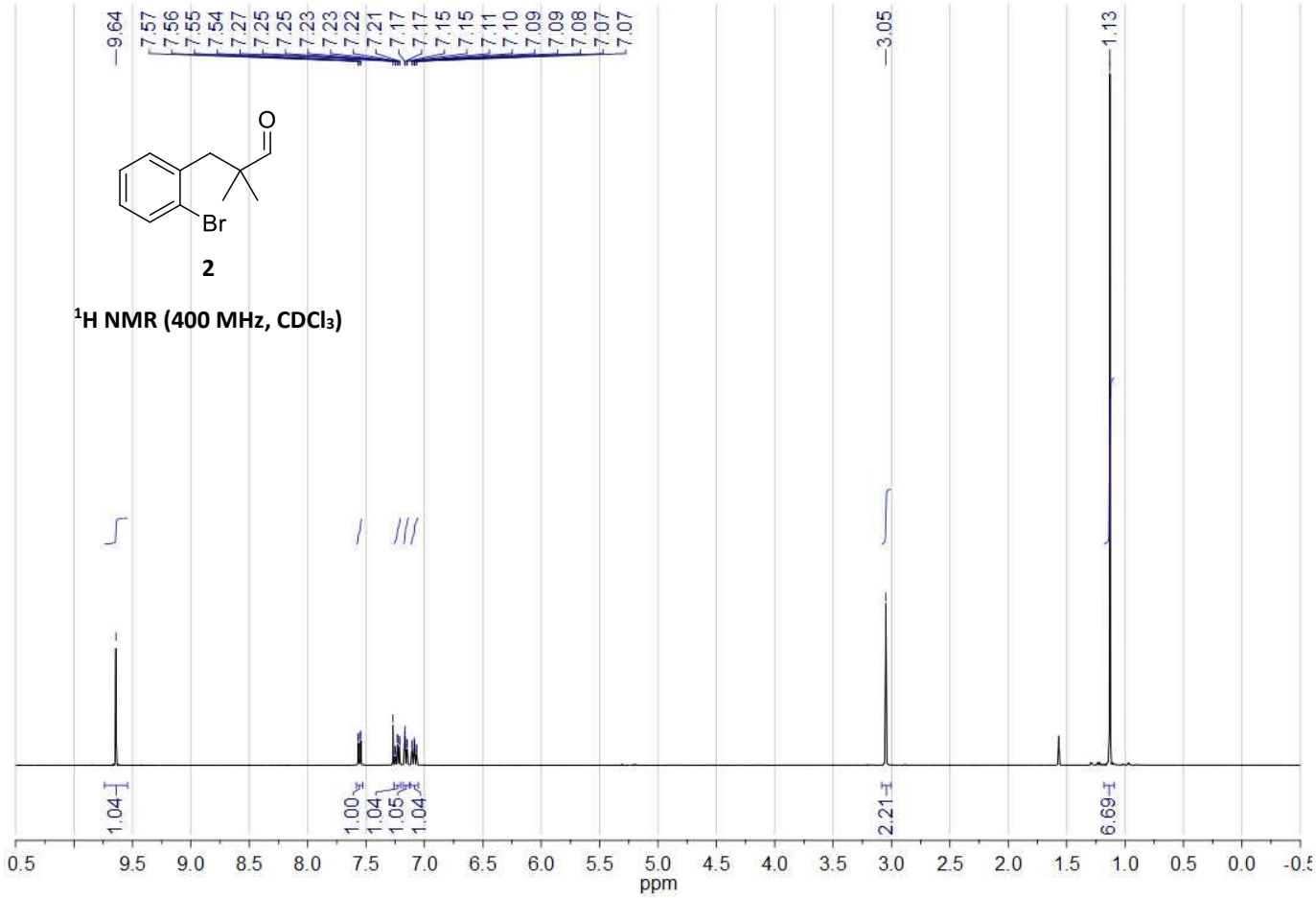
^{13}C NMR (101 MHz, $CDCl_3$)



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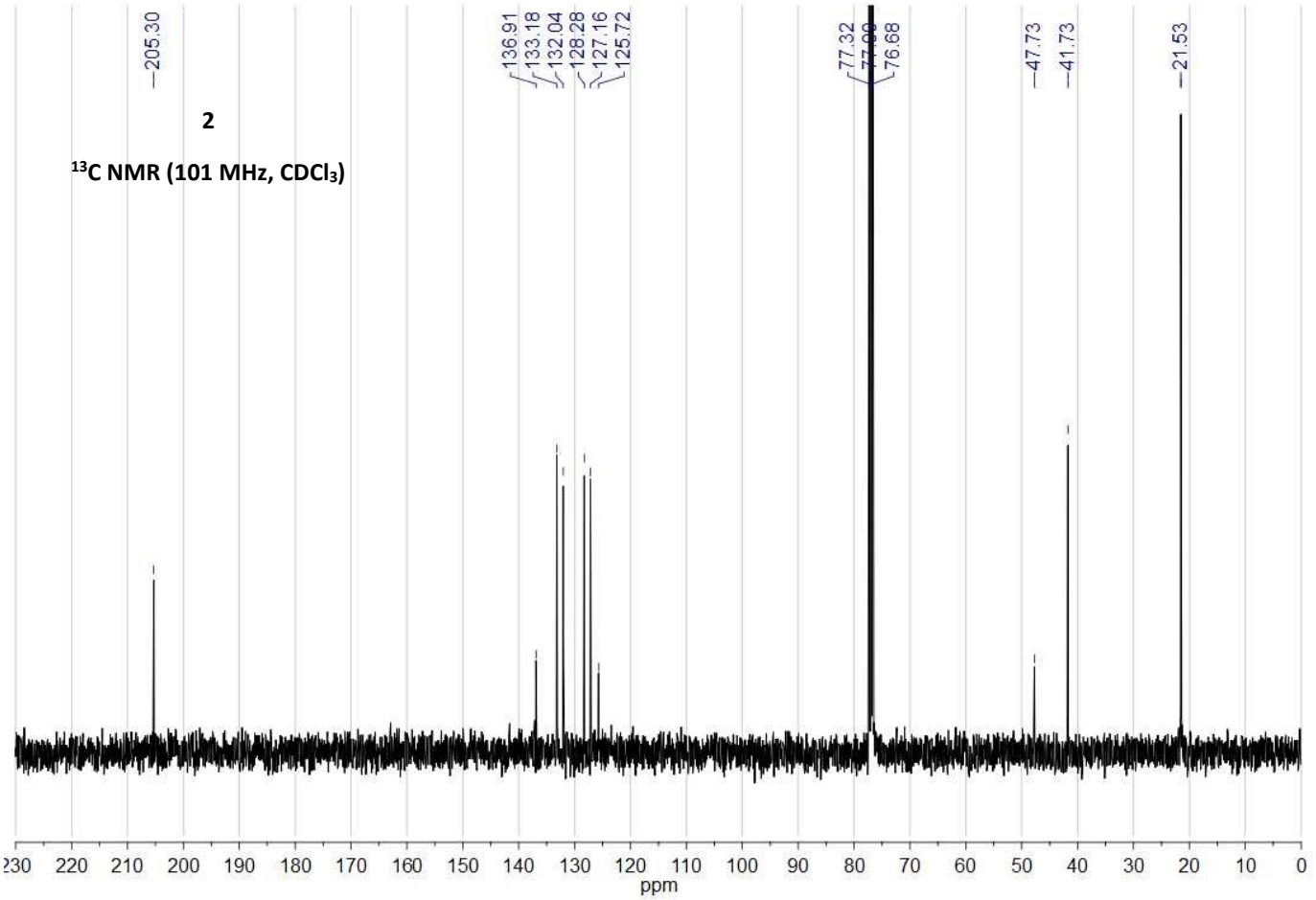
^{1}H NMR (400 MHz, $CDCl_3$)



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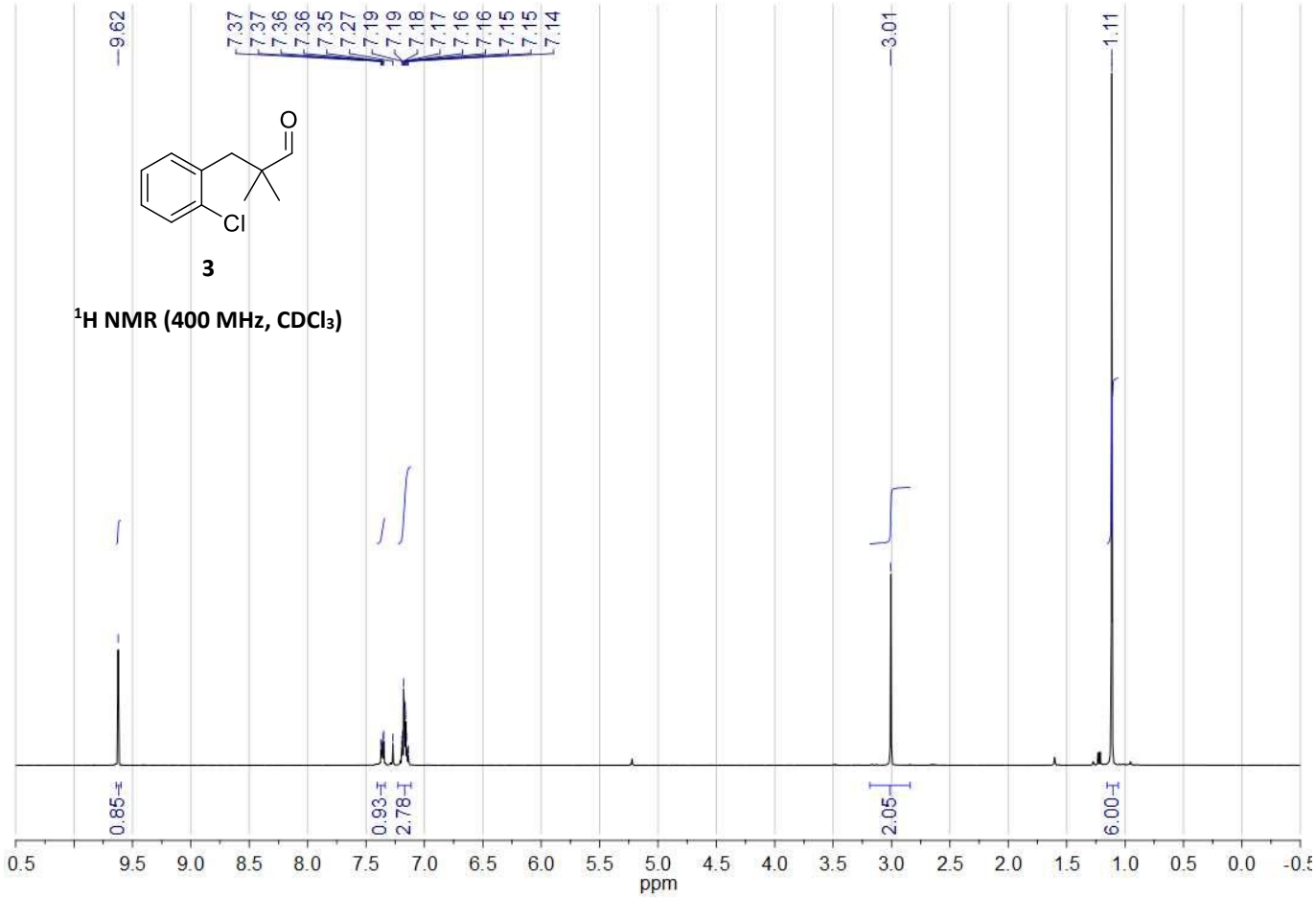
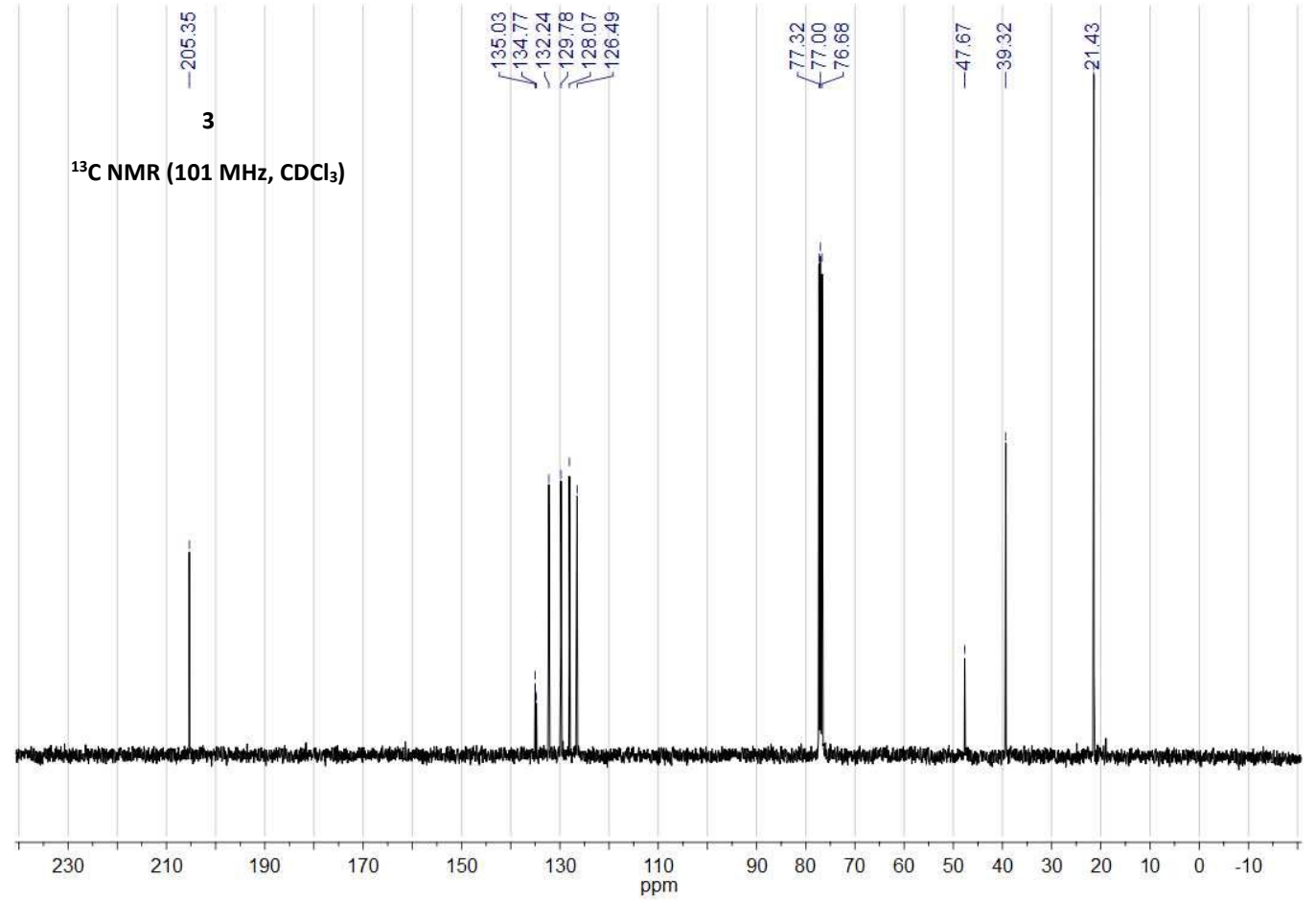


3

^{1}H NMR (400 MHz, $CDCl_3$)



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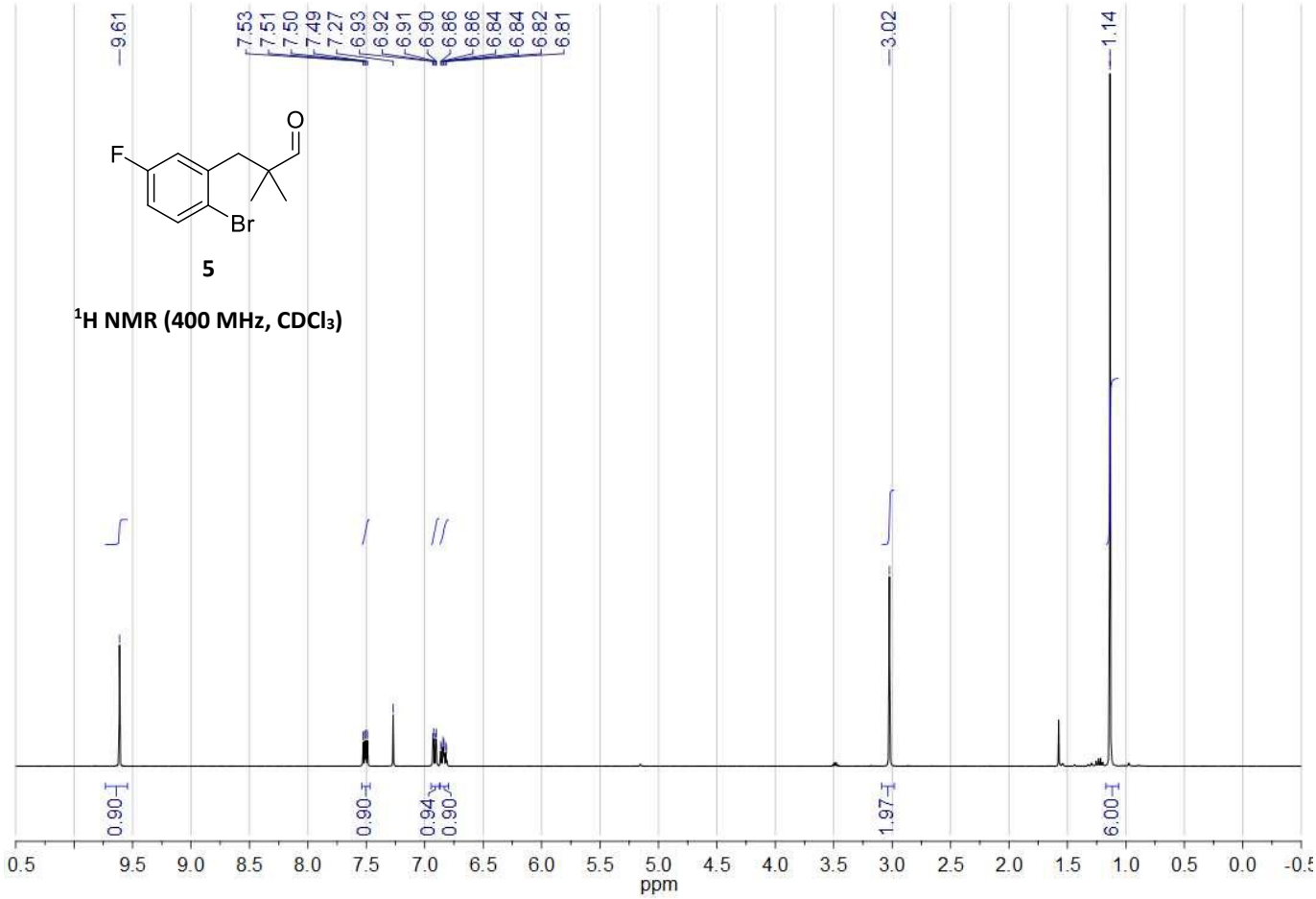
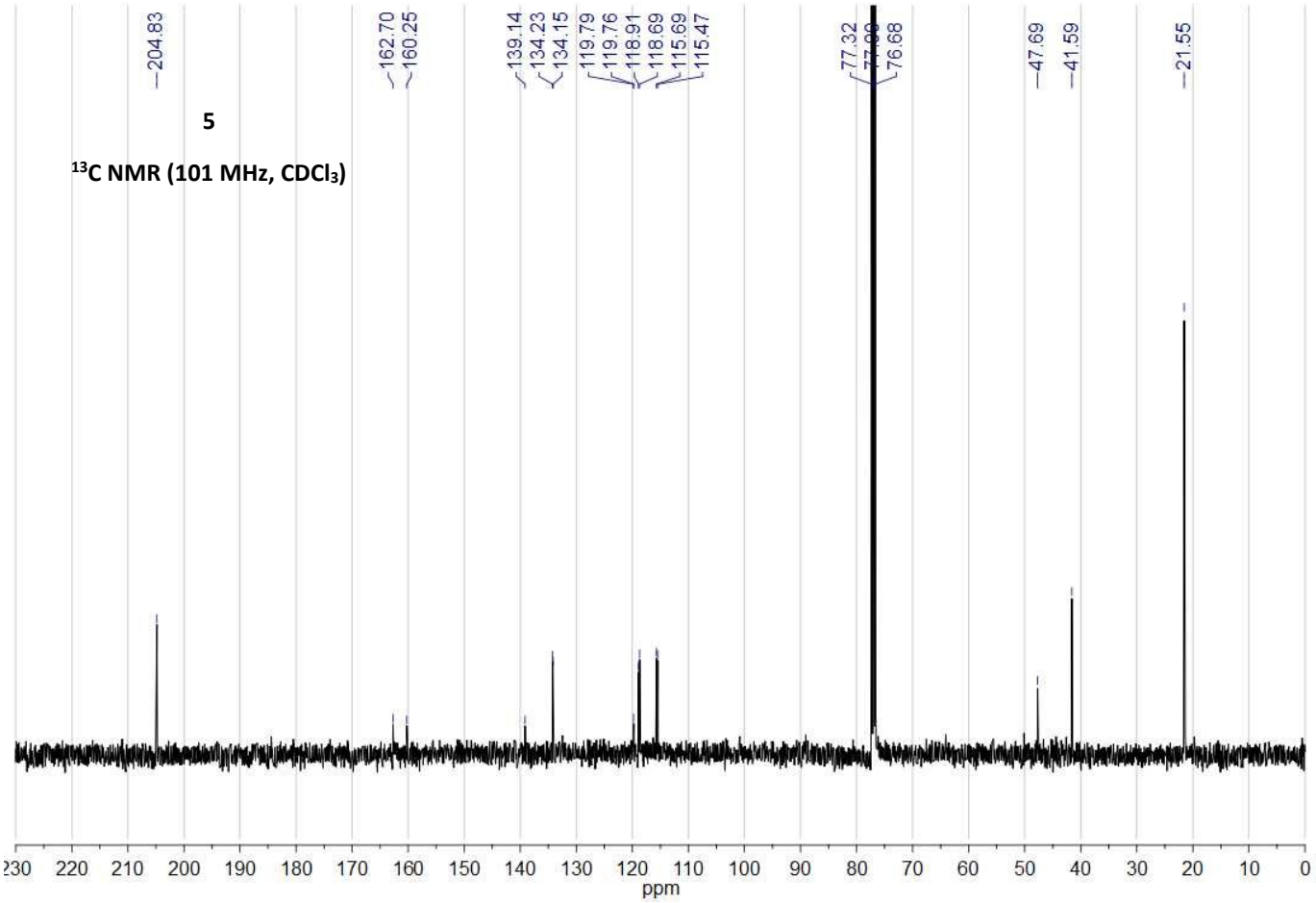
^{13}C NMR (101 MHz, $CDCl_3$)



5

^{1}H NMR (400 MHz, $CDCl_3$)



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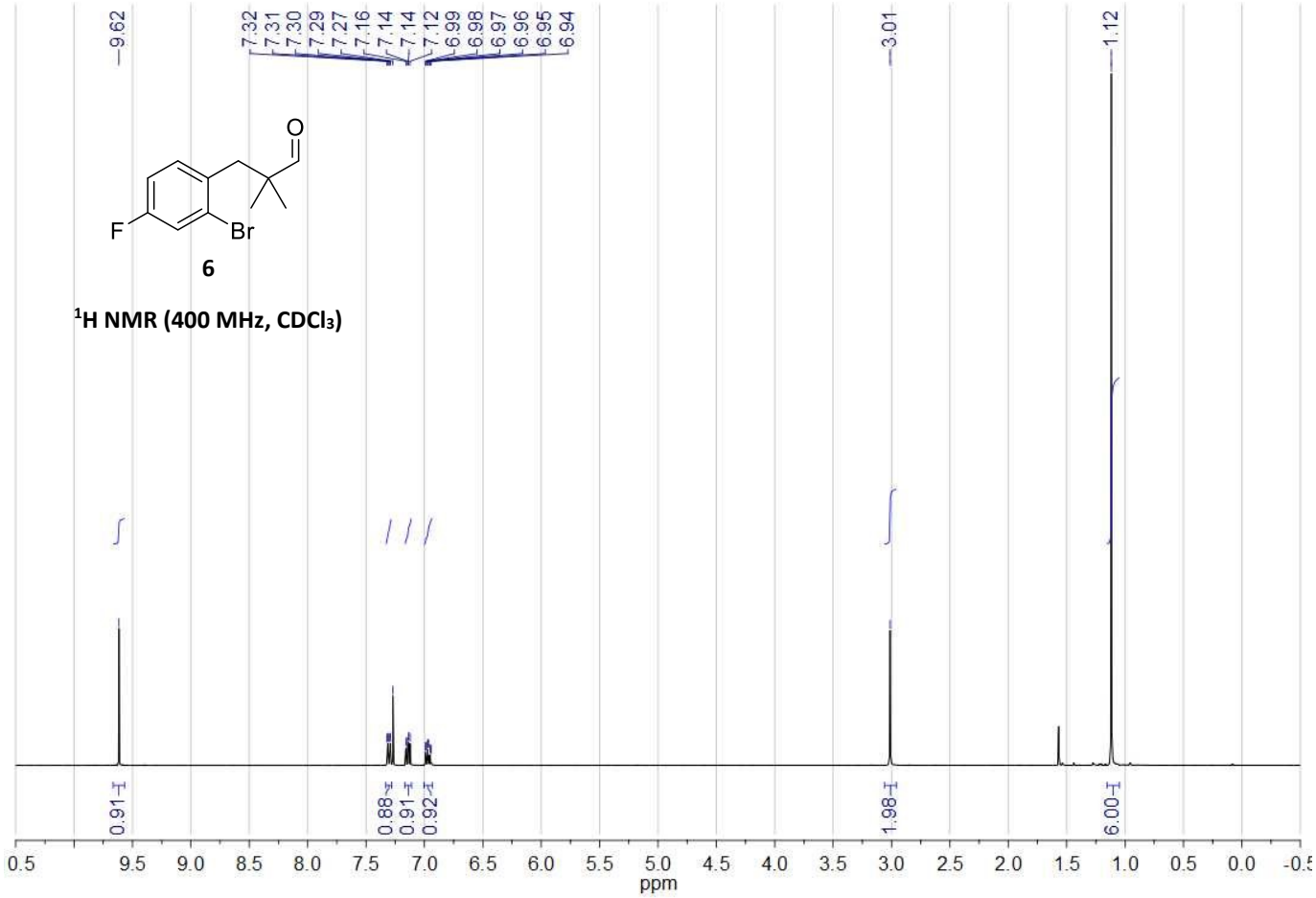
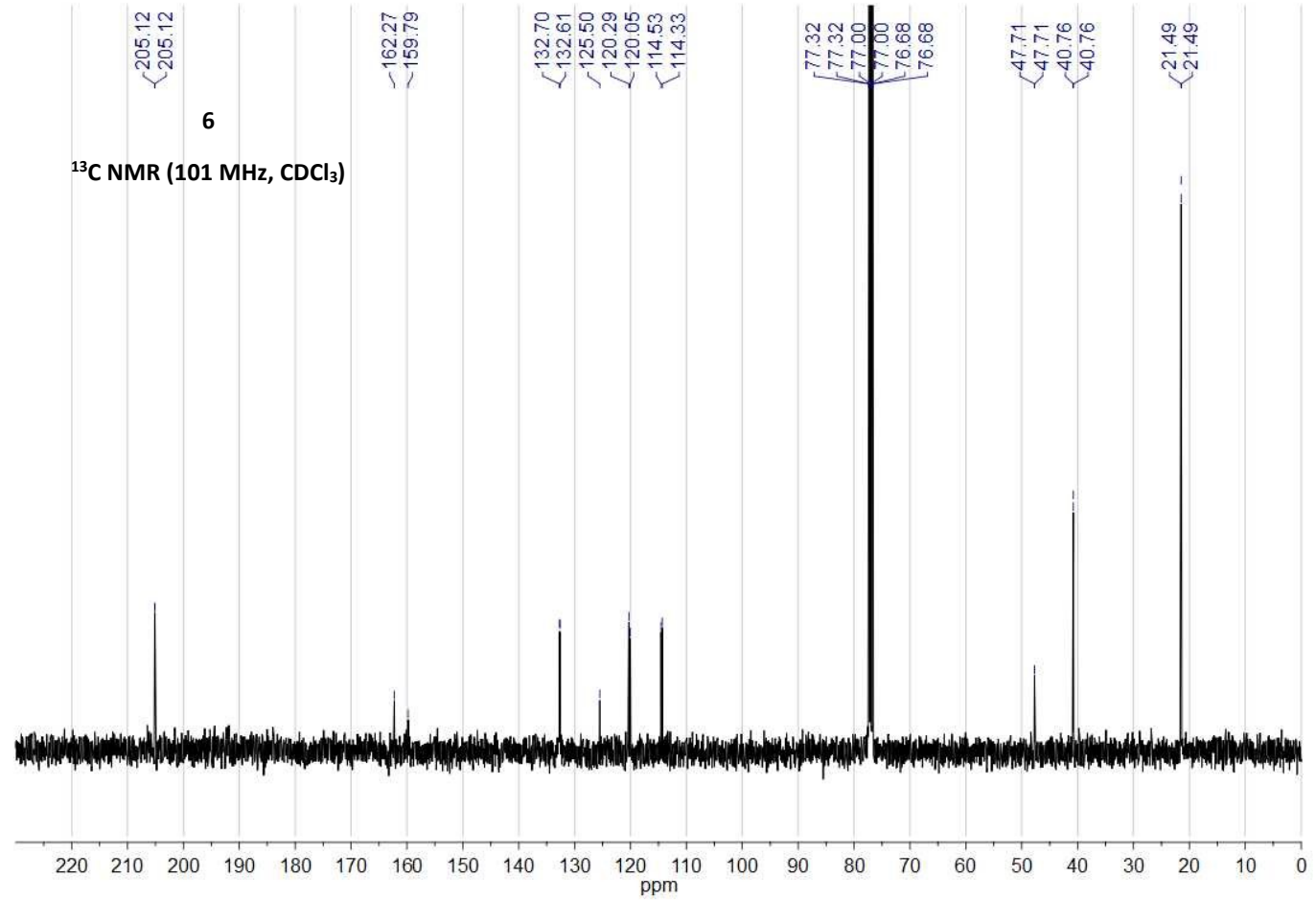
^{13}C NMR (101 MHz, $CDCl_3$)



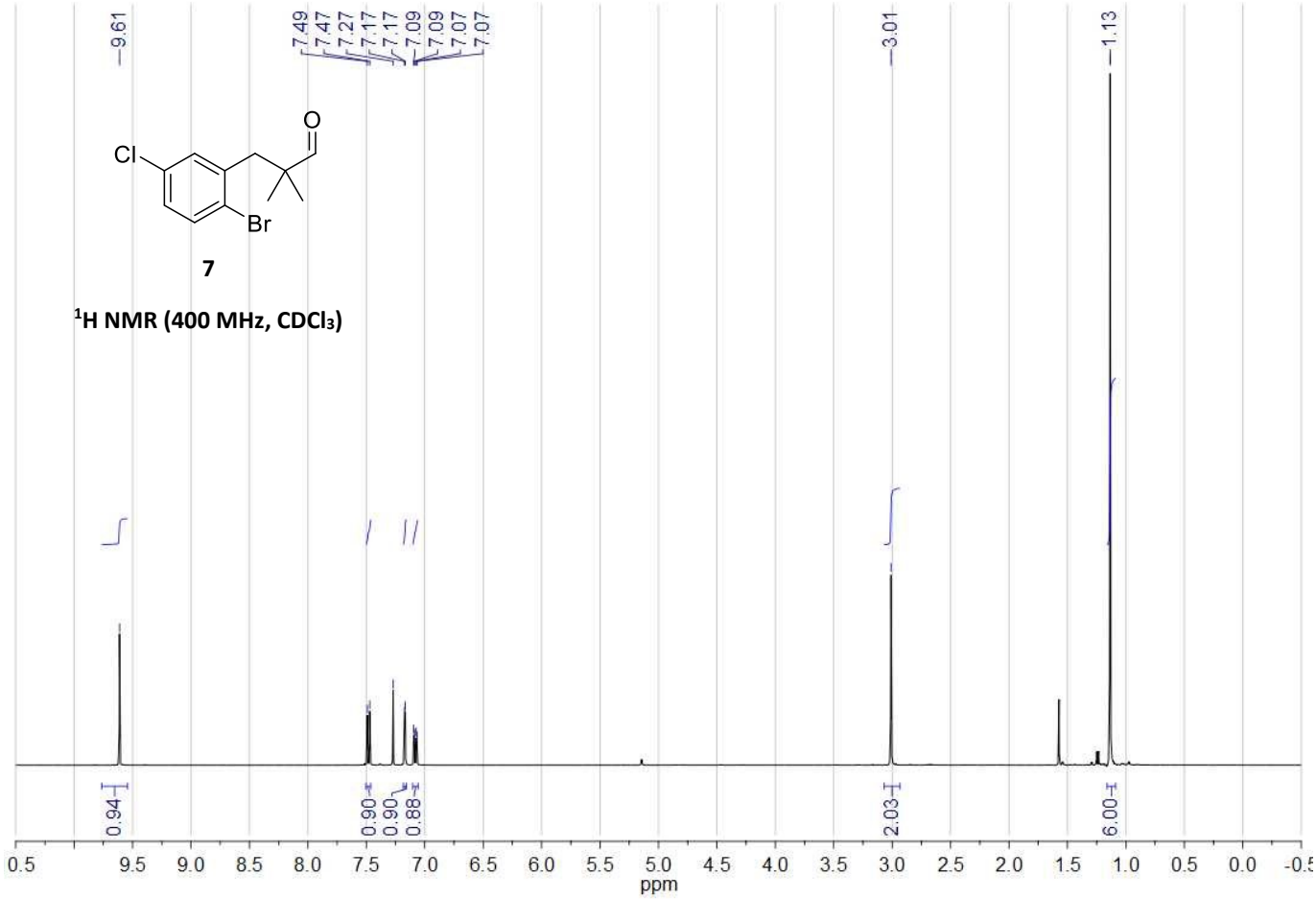
6

^{1}H NMR (400 MHz, $CDCl_3$)



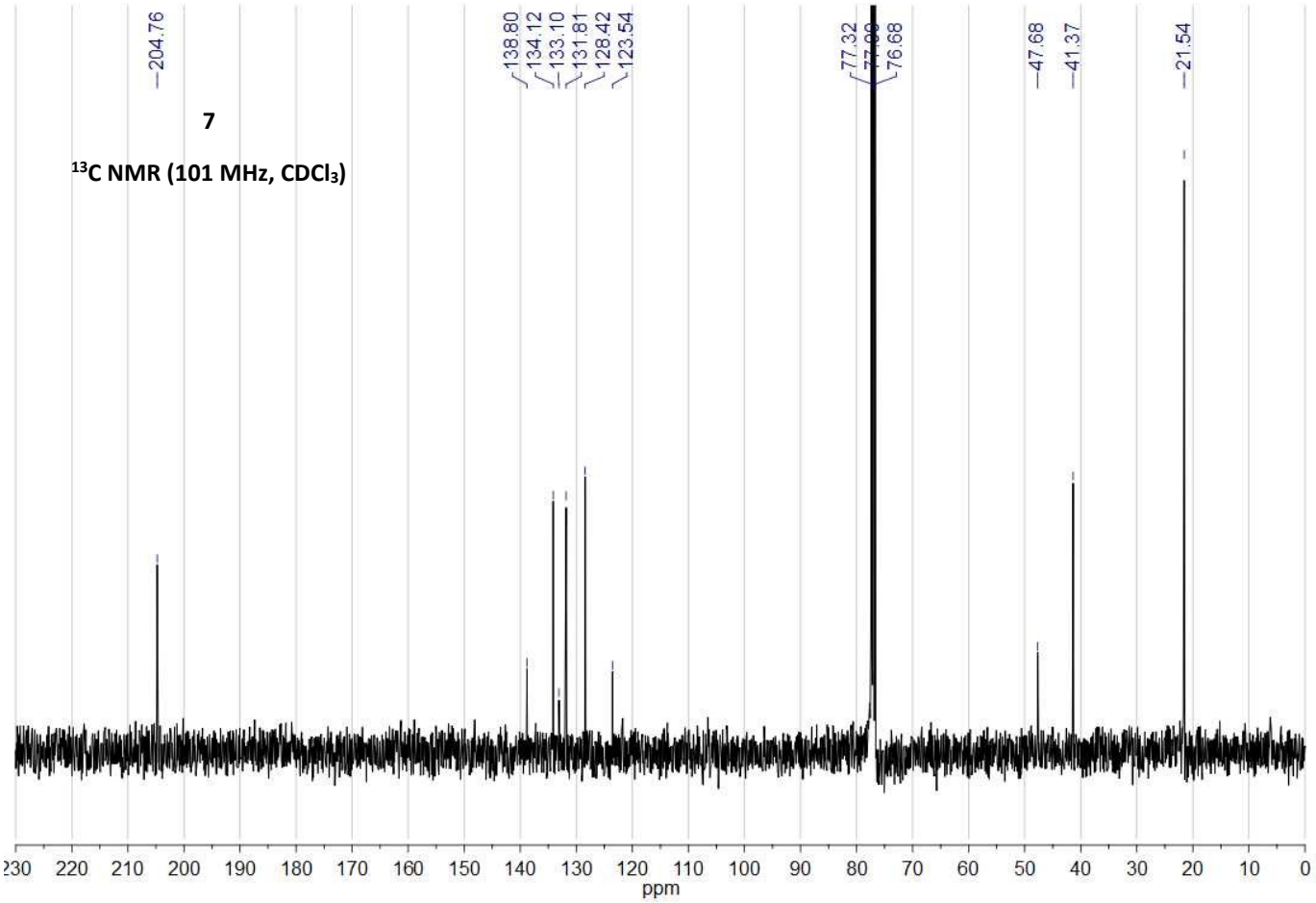
6

^{13}C NMR (101 MHz, $CDCl_3$)



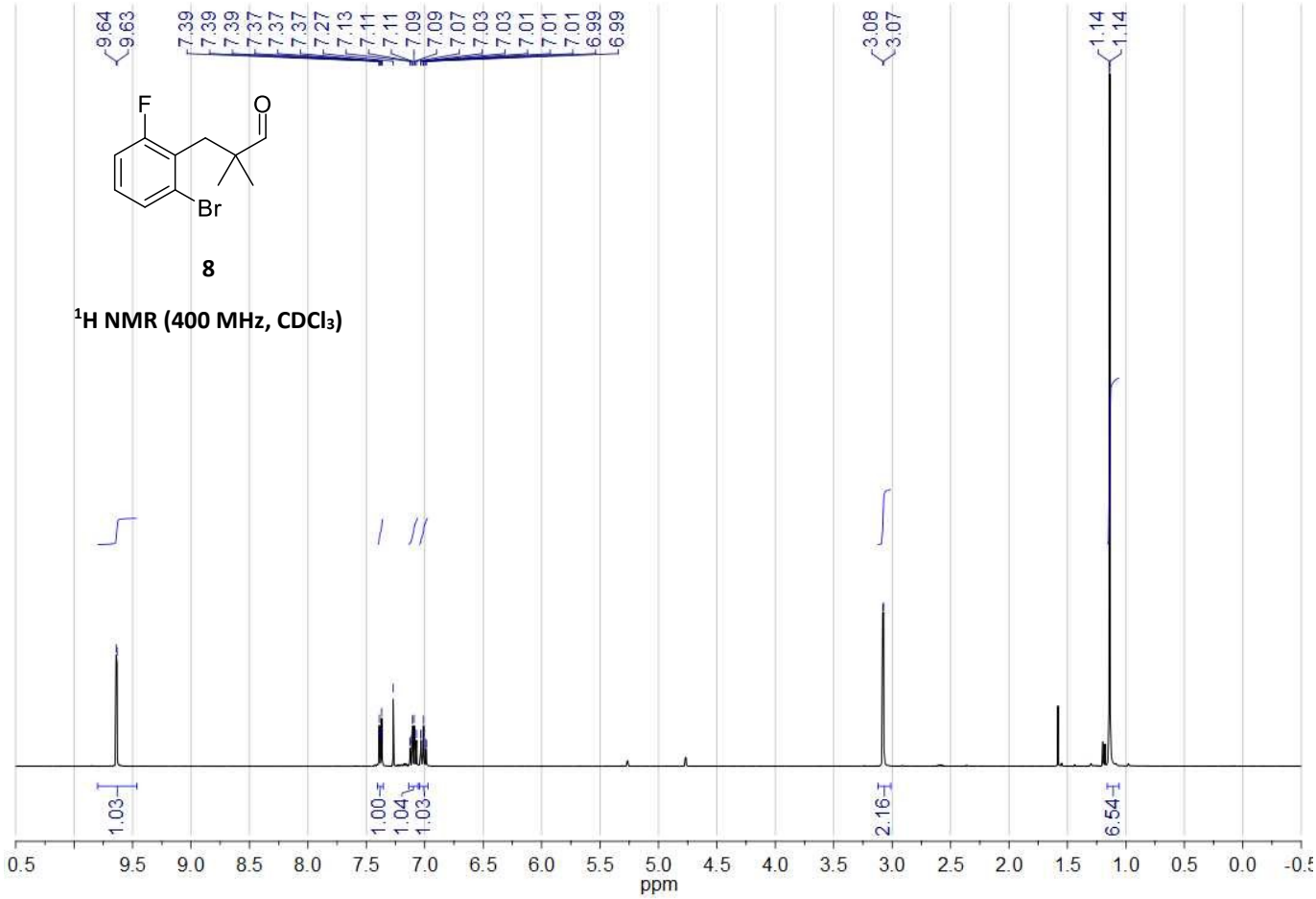
7

^{1}H NMR (400 MHz, $CDCl_3$)



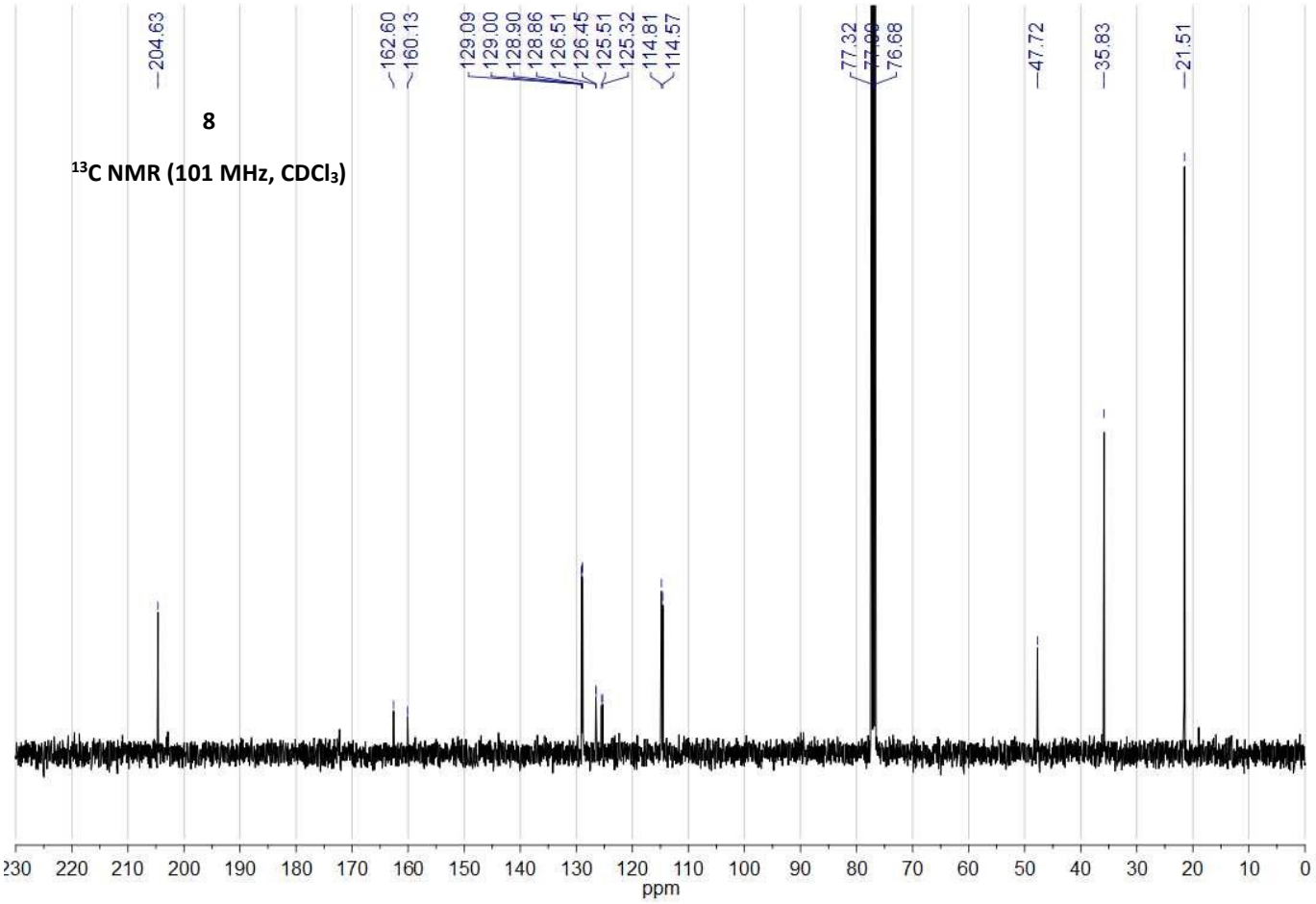
7

^{13}C NMR (101 MHz, $CDCl_3$)



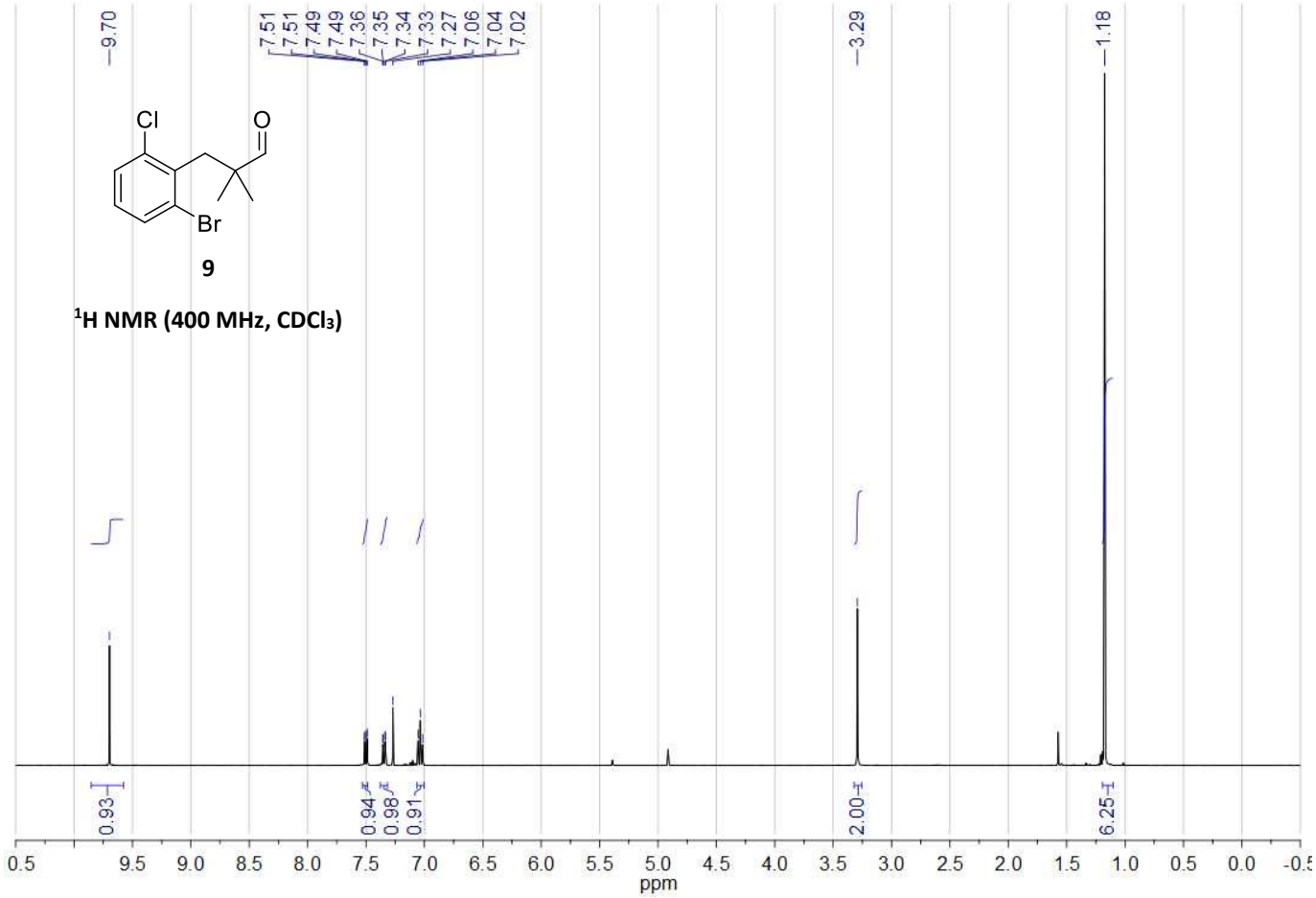
8

^{1}H NMR (400 MHz, $CDCl_3$)



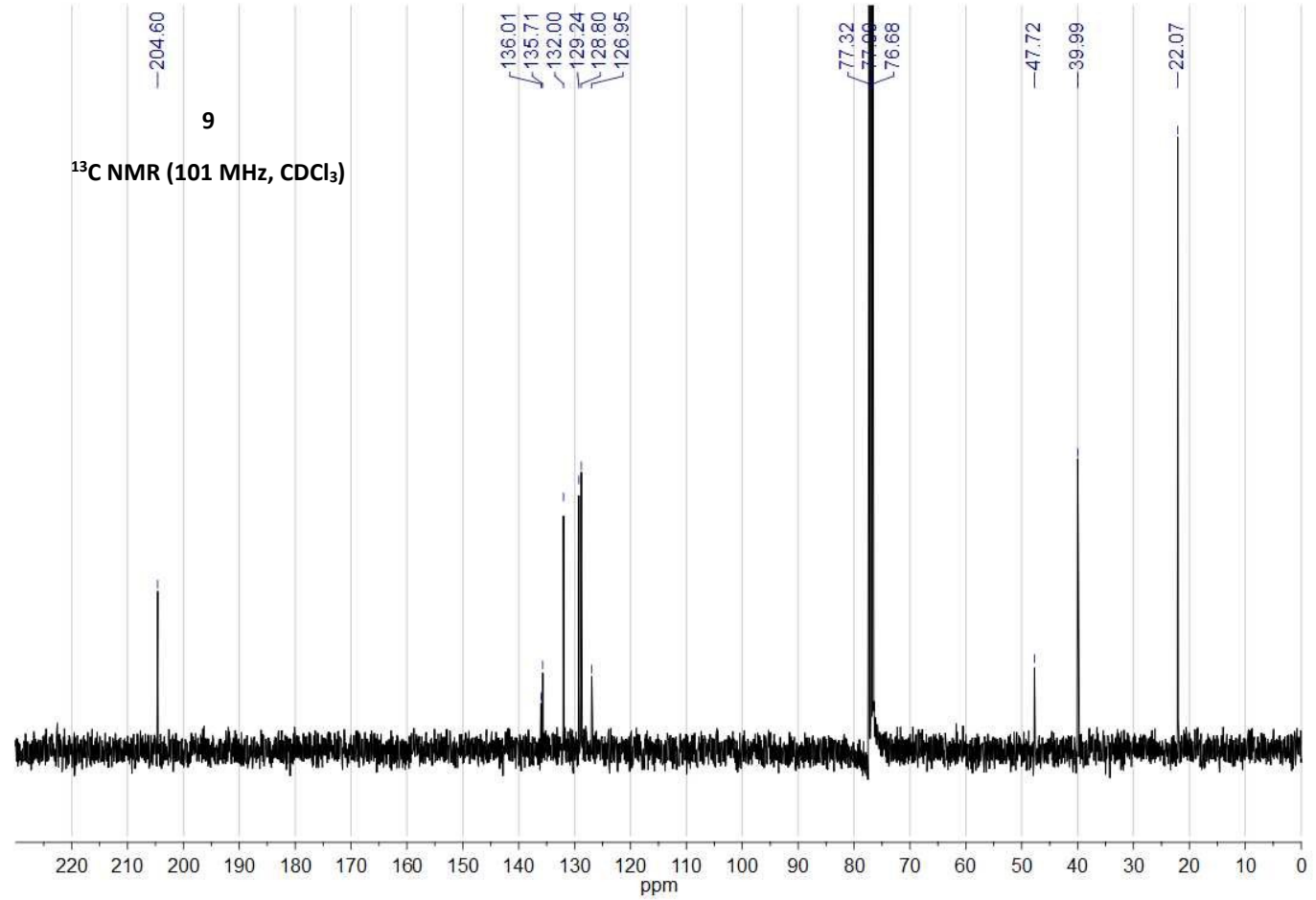
8

^{13}C NMR (101 MHz, $CDCl_3$)



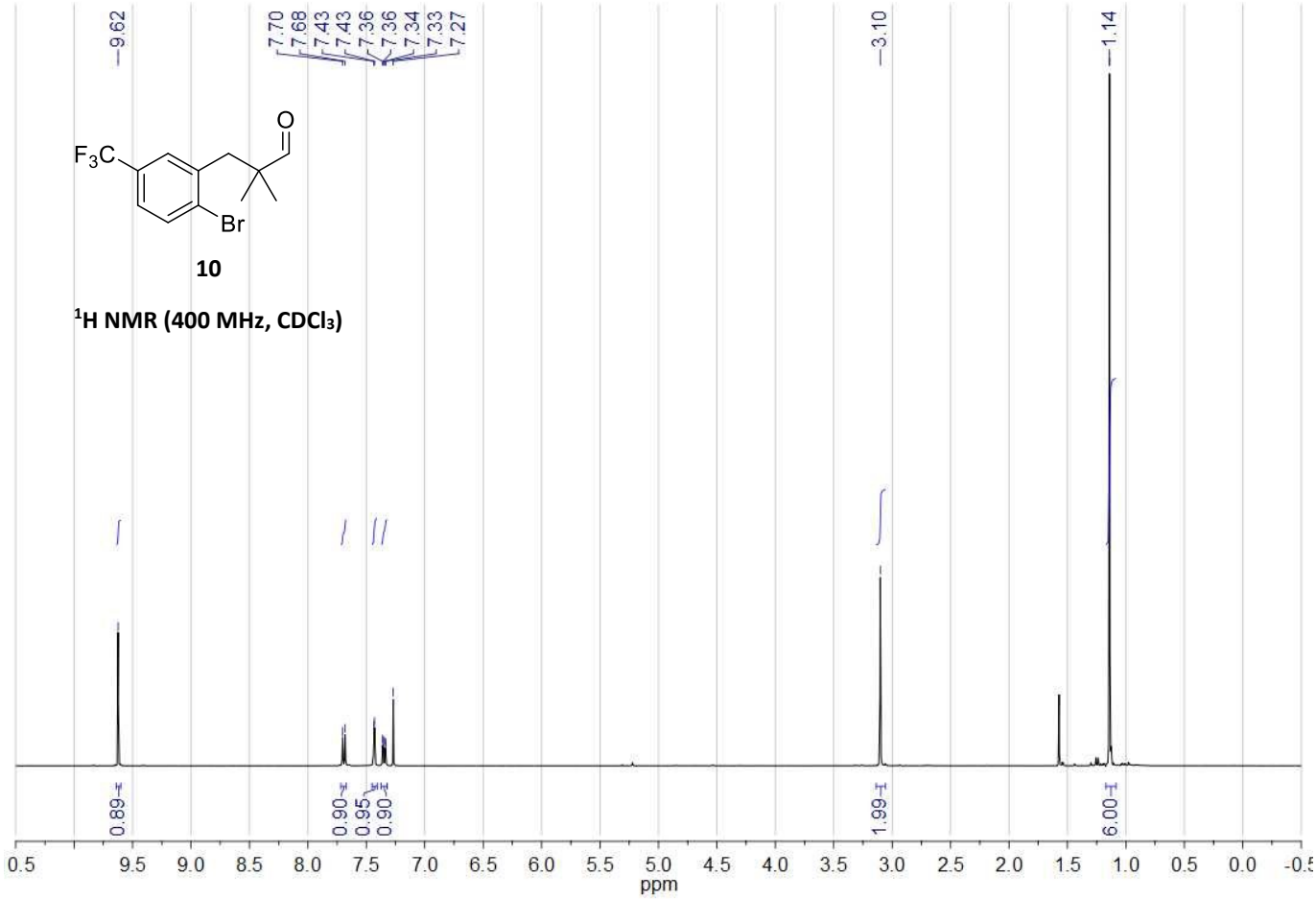
9

^{1}H NMR (400 MHz, $CDCl_3$)



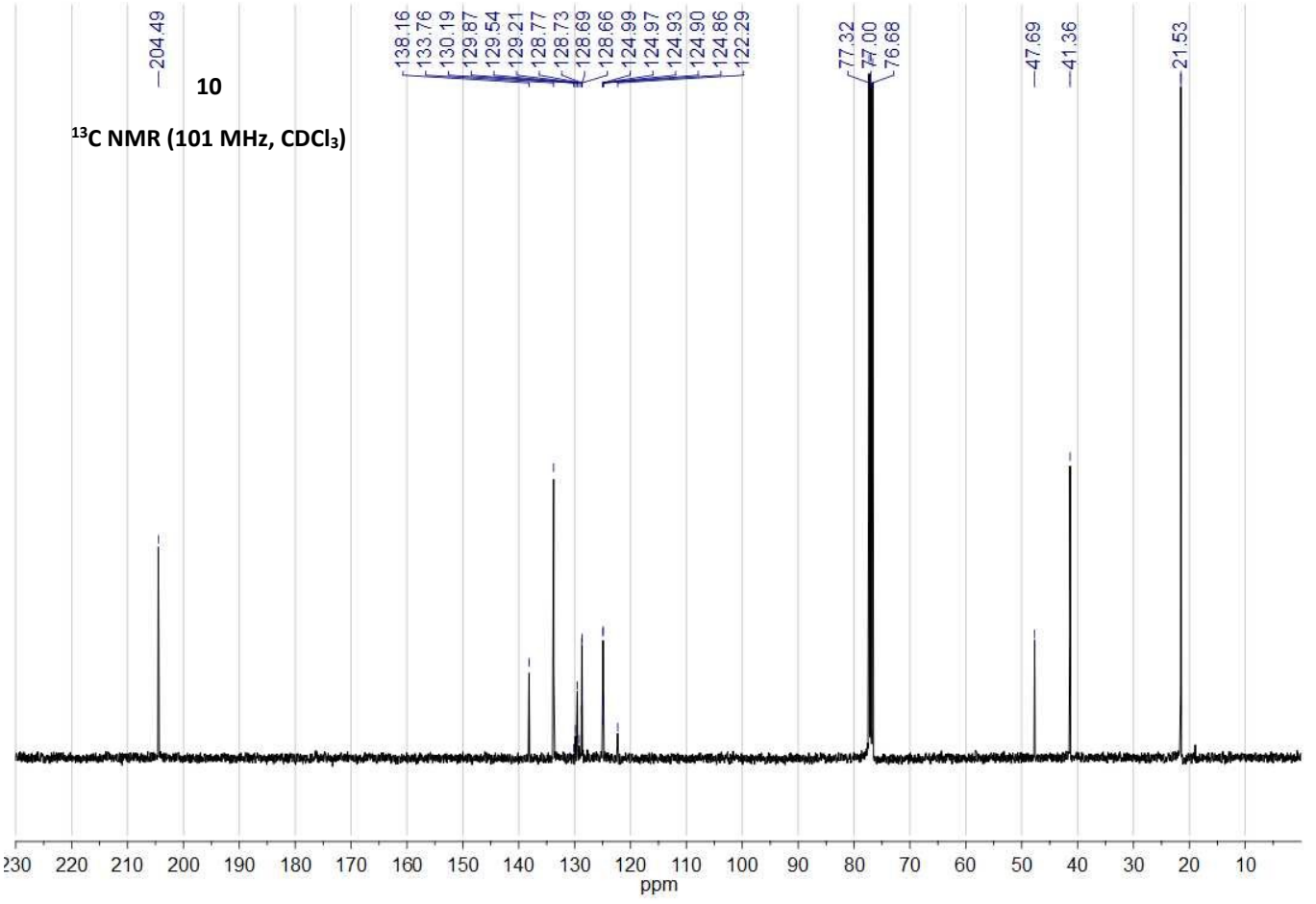
9

^{13}C NMR (101 MHz, $CDCl_3$)



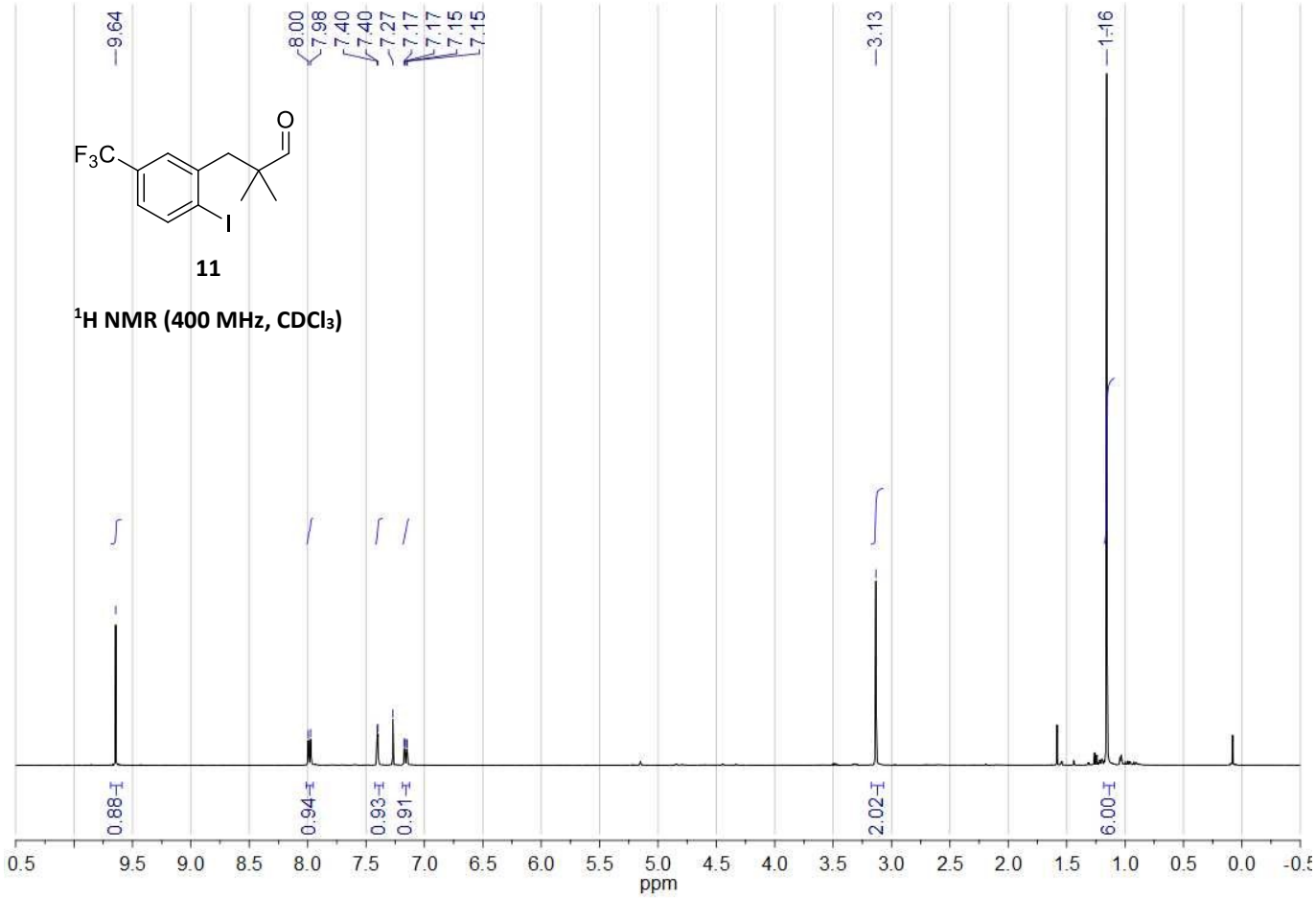
10

^{1}H NMR (400 MHz, $CDCl_3$)



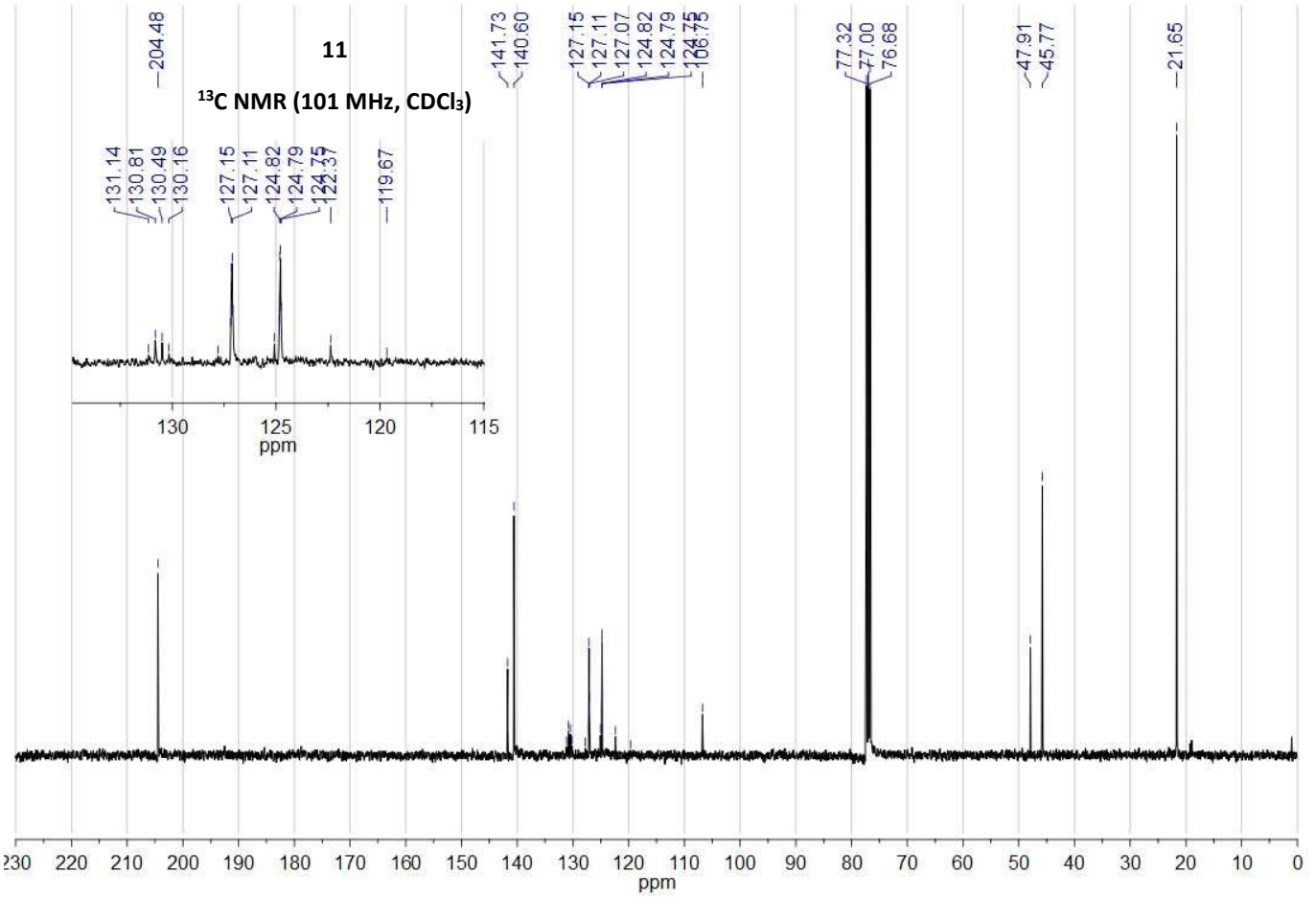
10

^{13}C NMR (101 MHz, $CDCl_3$)



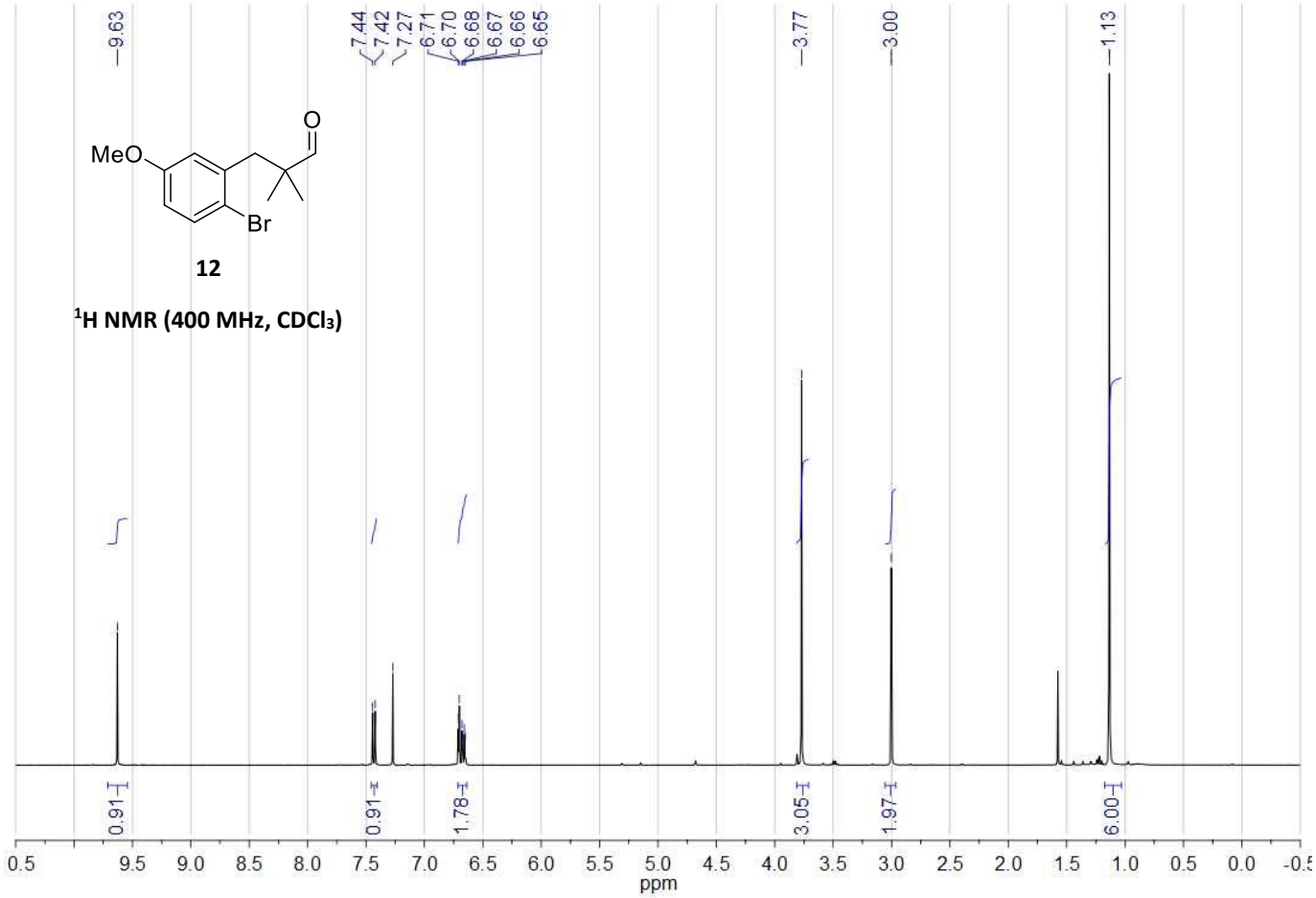
11

^{1}H NMR (400 MHz, $CDCl_3$)



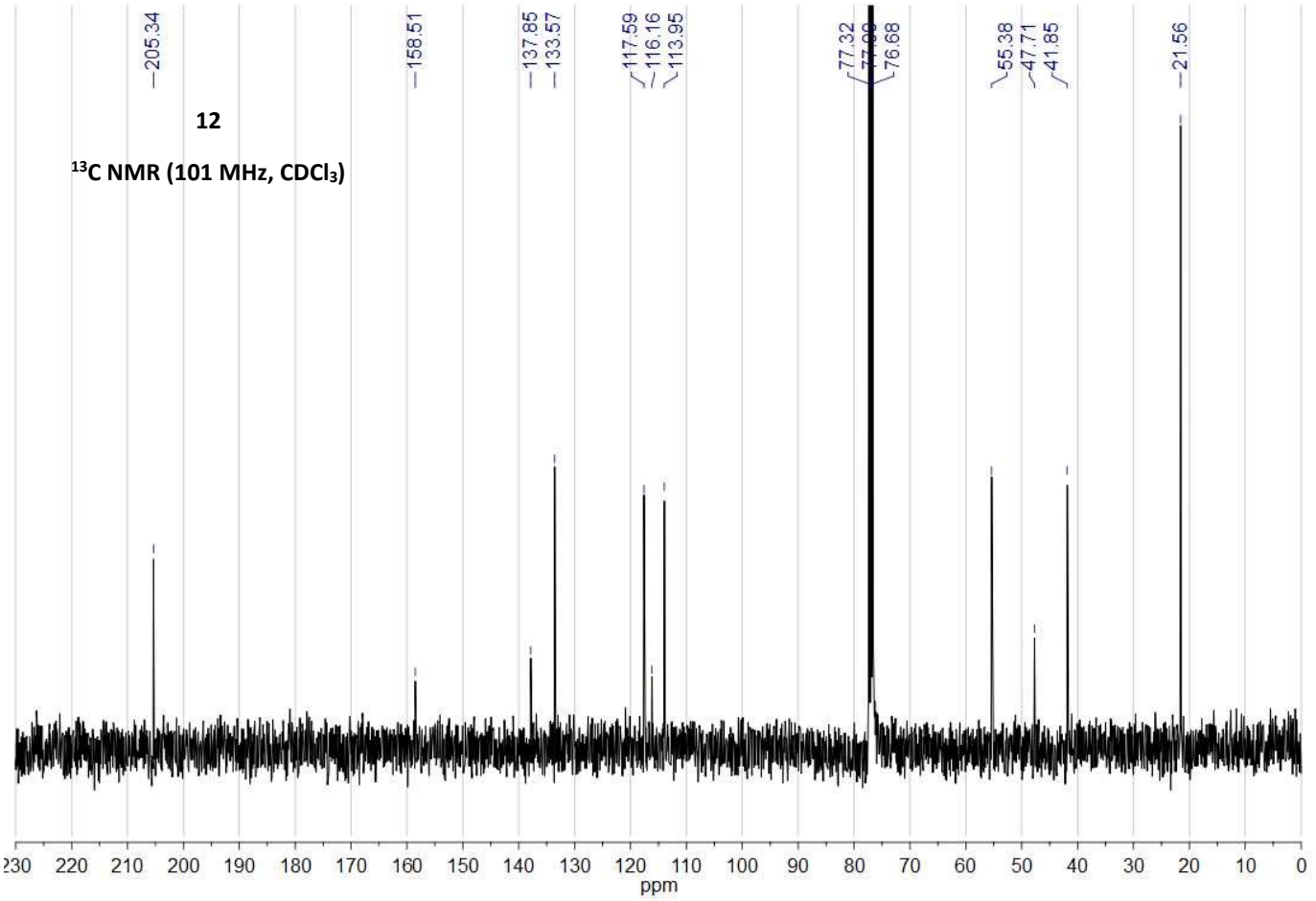
11

^{13}C NMR (101 MHz, $CDCl_3$)



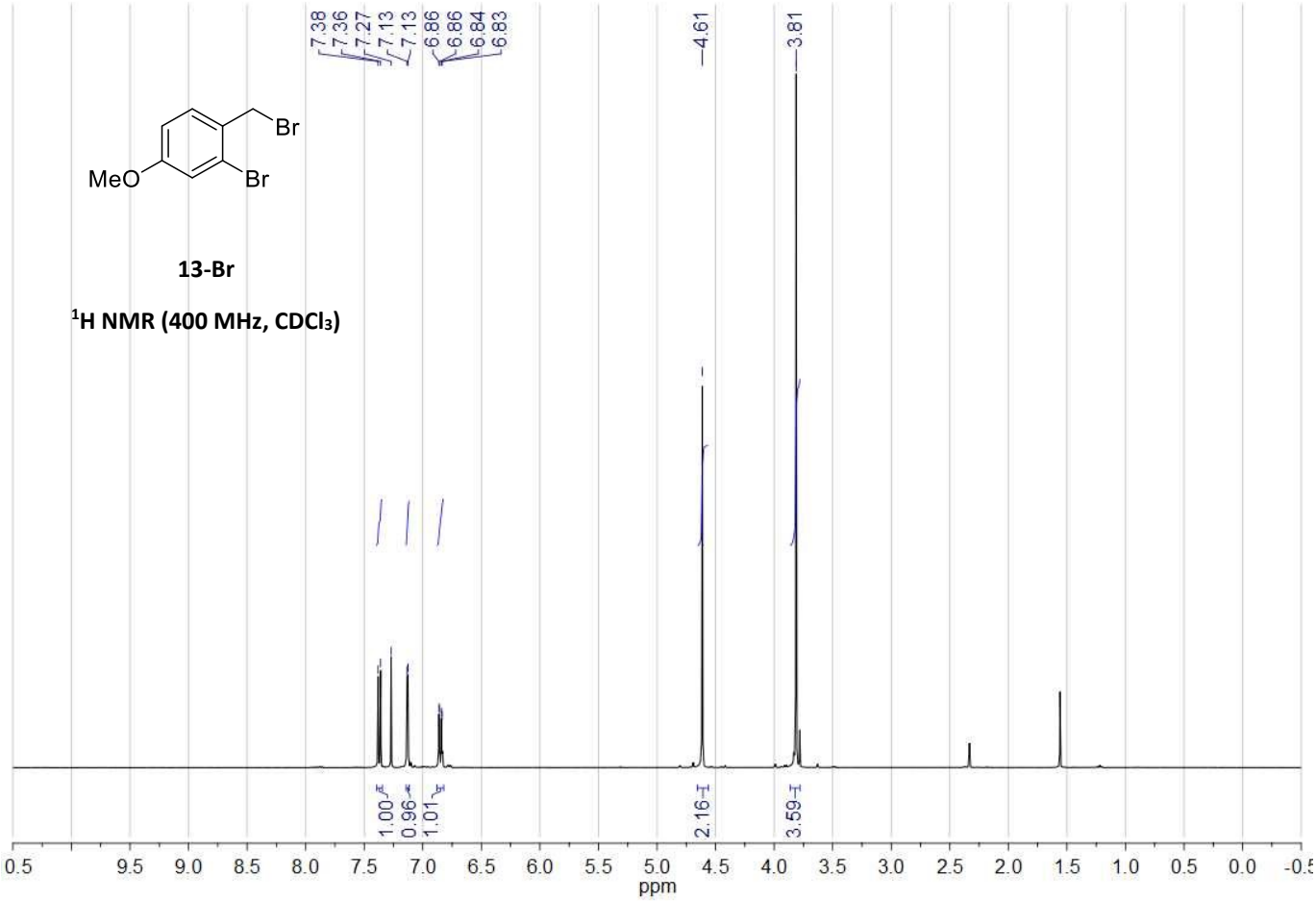
12

^{1}H NMR (400 MHz, $CDCl_3$)



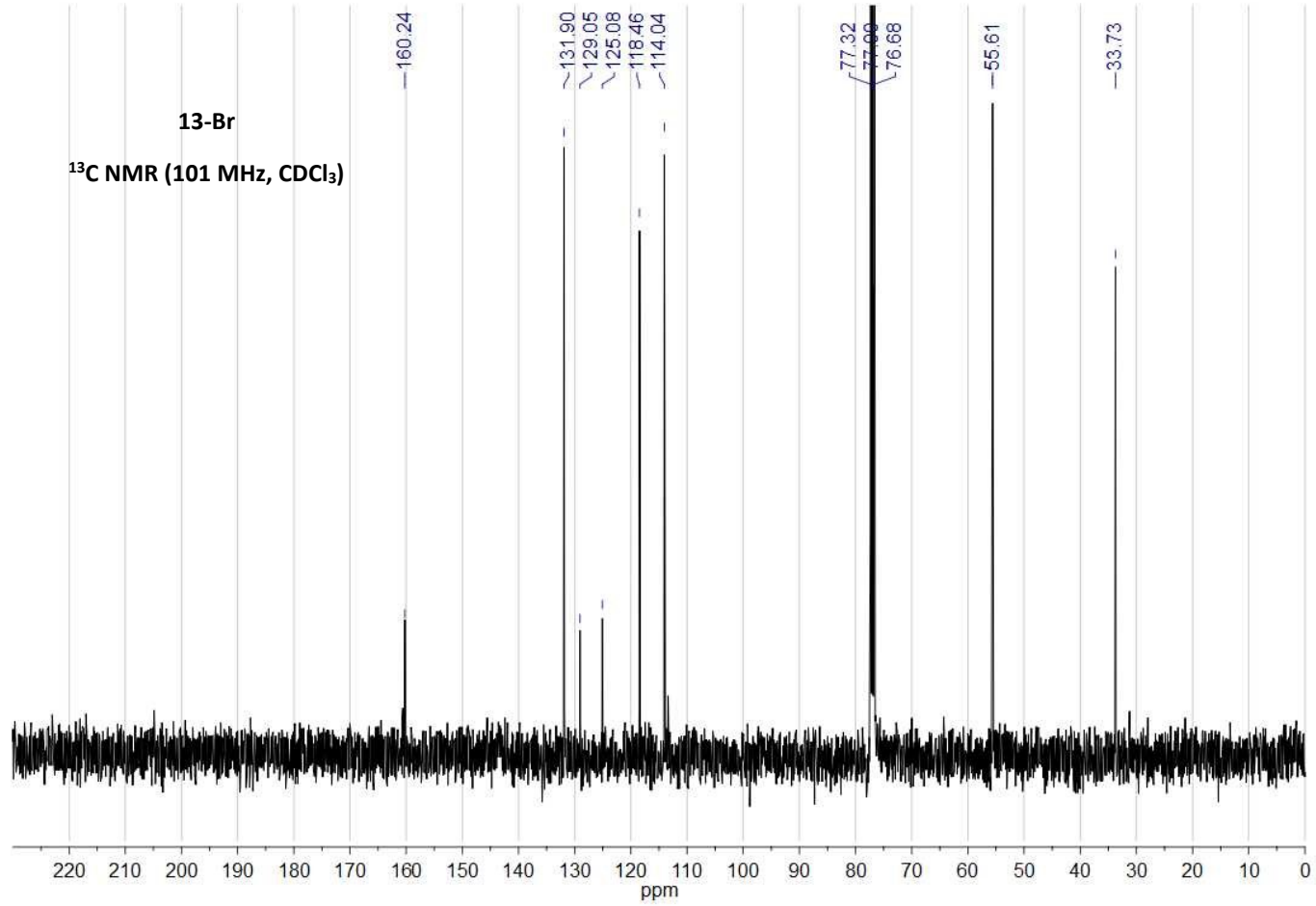
12

^{13}C NMR (101 MHz, $CDCl_3$)



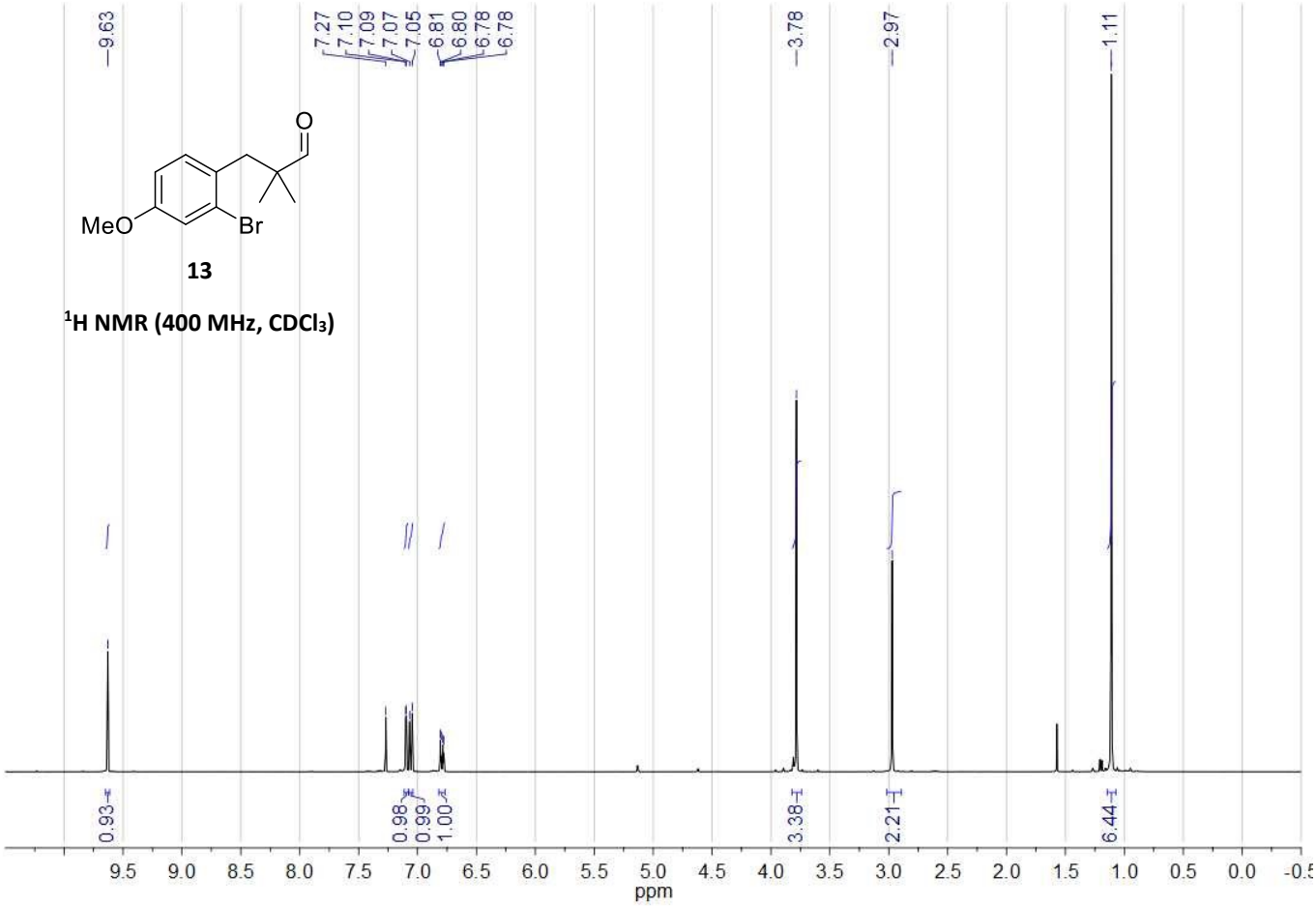
13-Br

^{1}H NMR (400 MHz, $CDCl_3$)



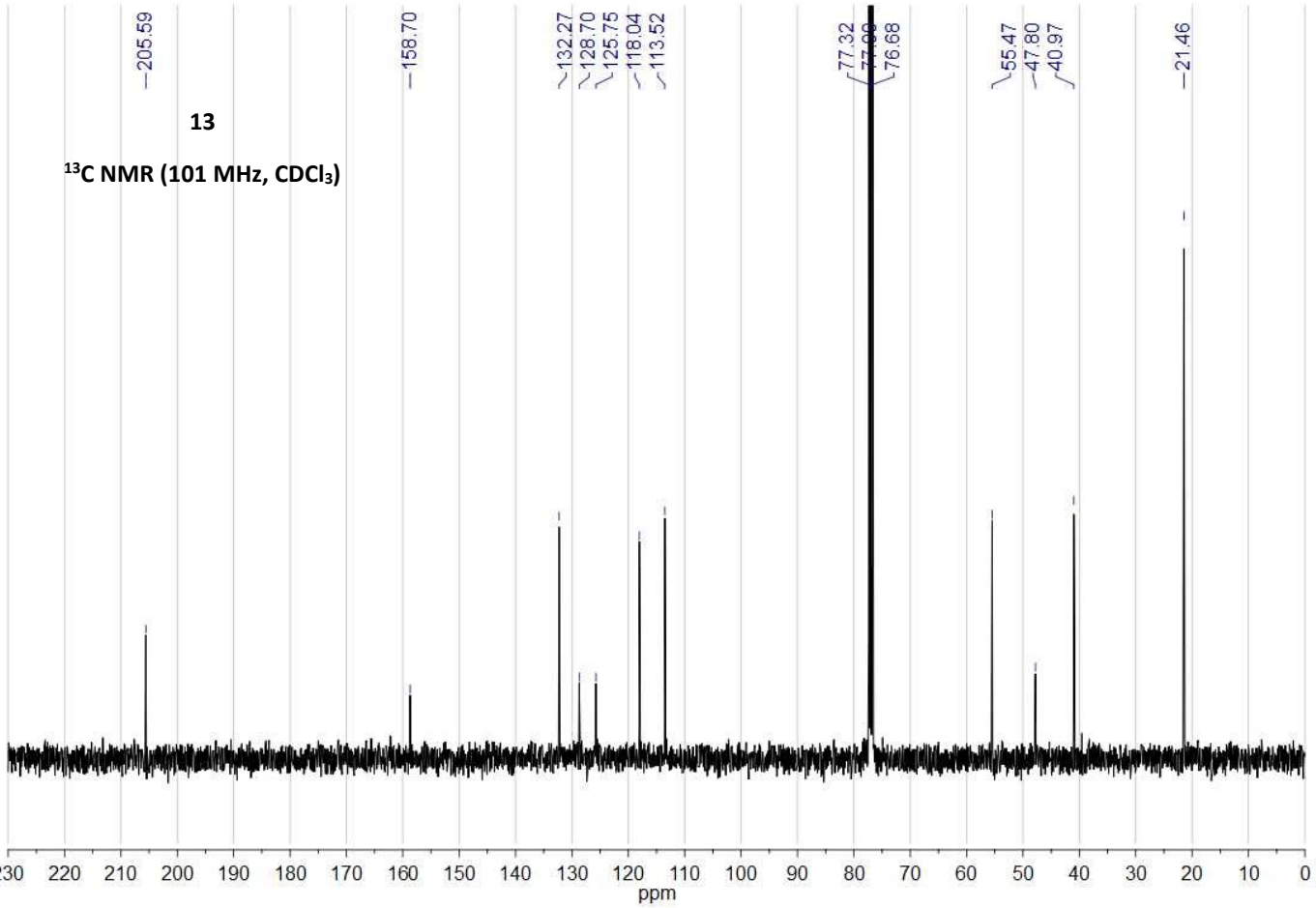
13-Br

^{13}C NMR (101 MHz, $CDCl_3$)



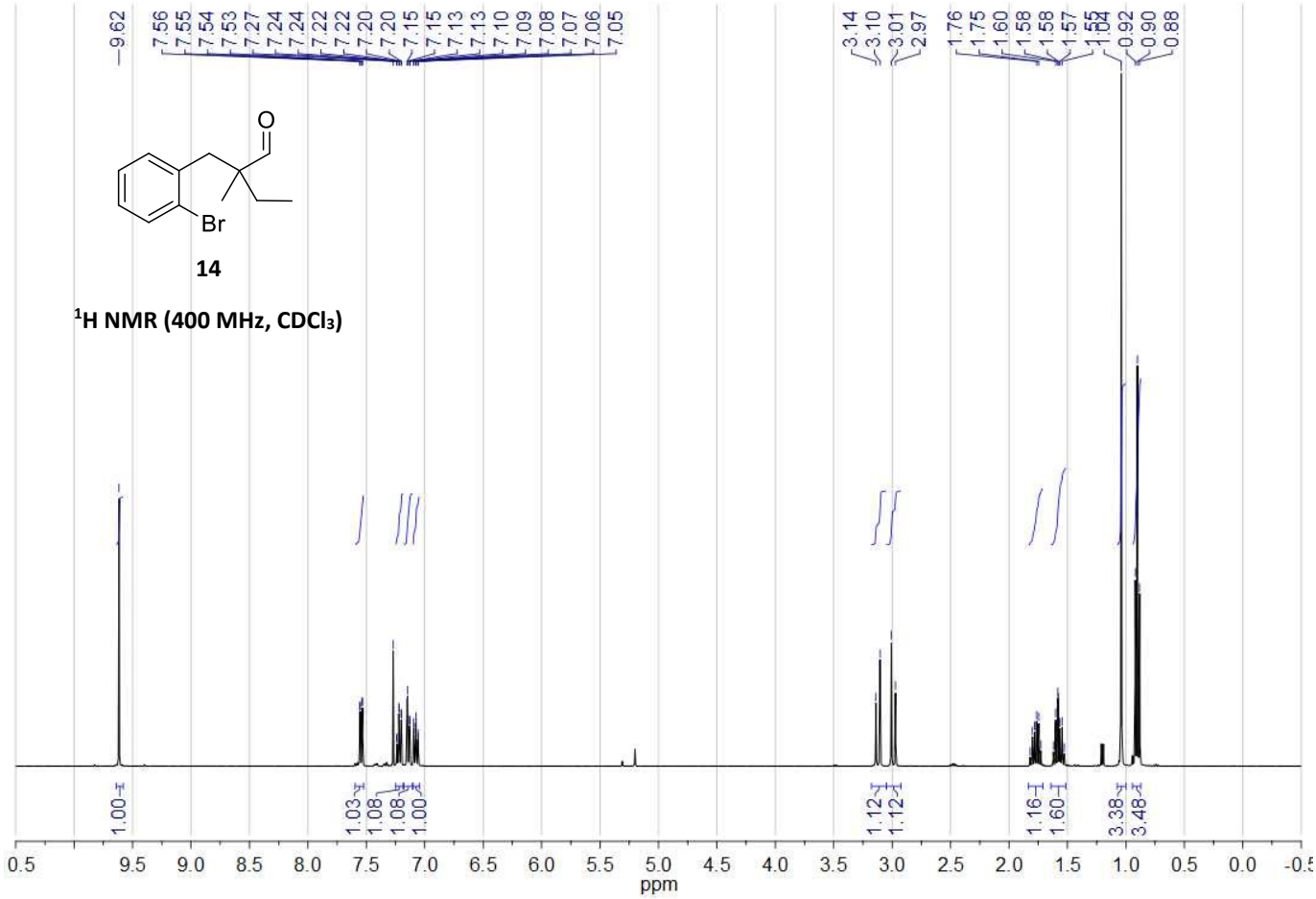
13

^{1}H NMR (400 MHz, $CDCl_3$)



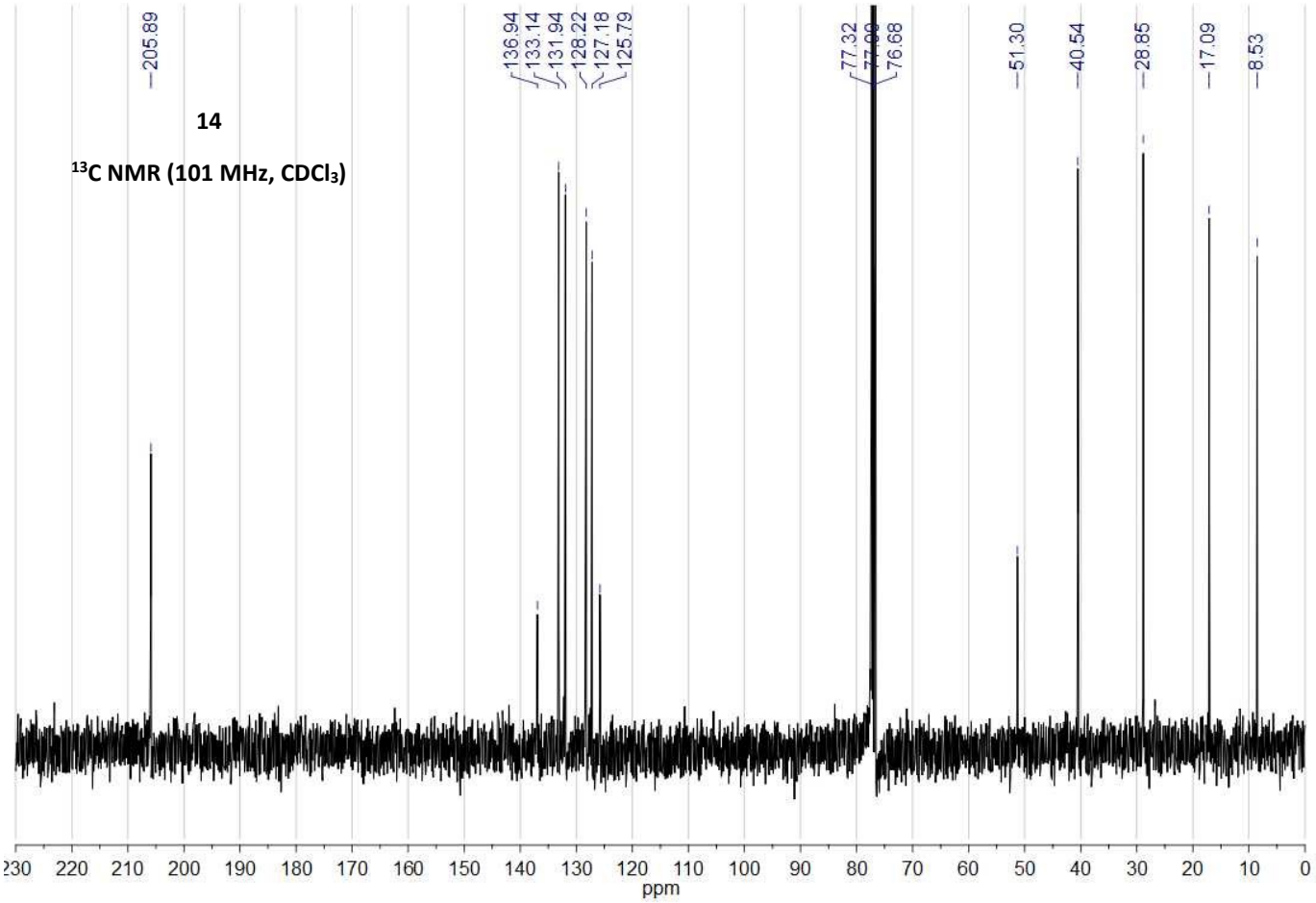
13

^{13}C NMR (101 MHz, $CDCl_3$)



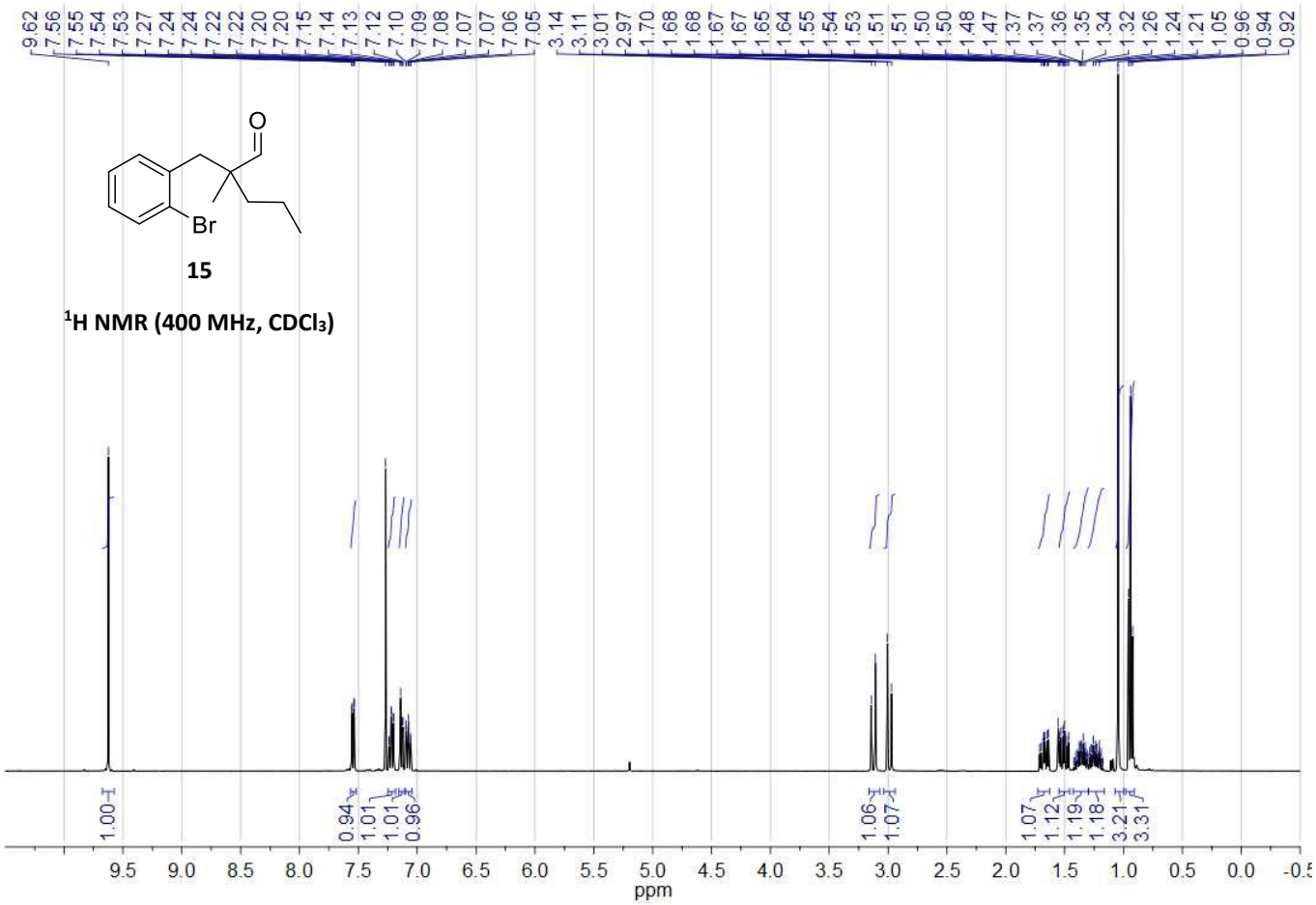
14

^{1}H NMR (400 MHz, $CDCl_3$)



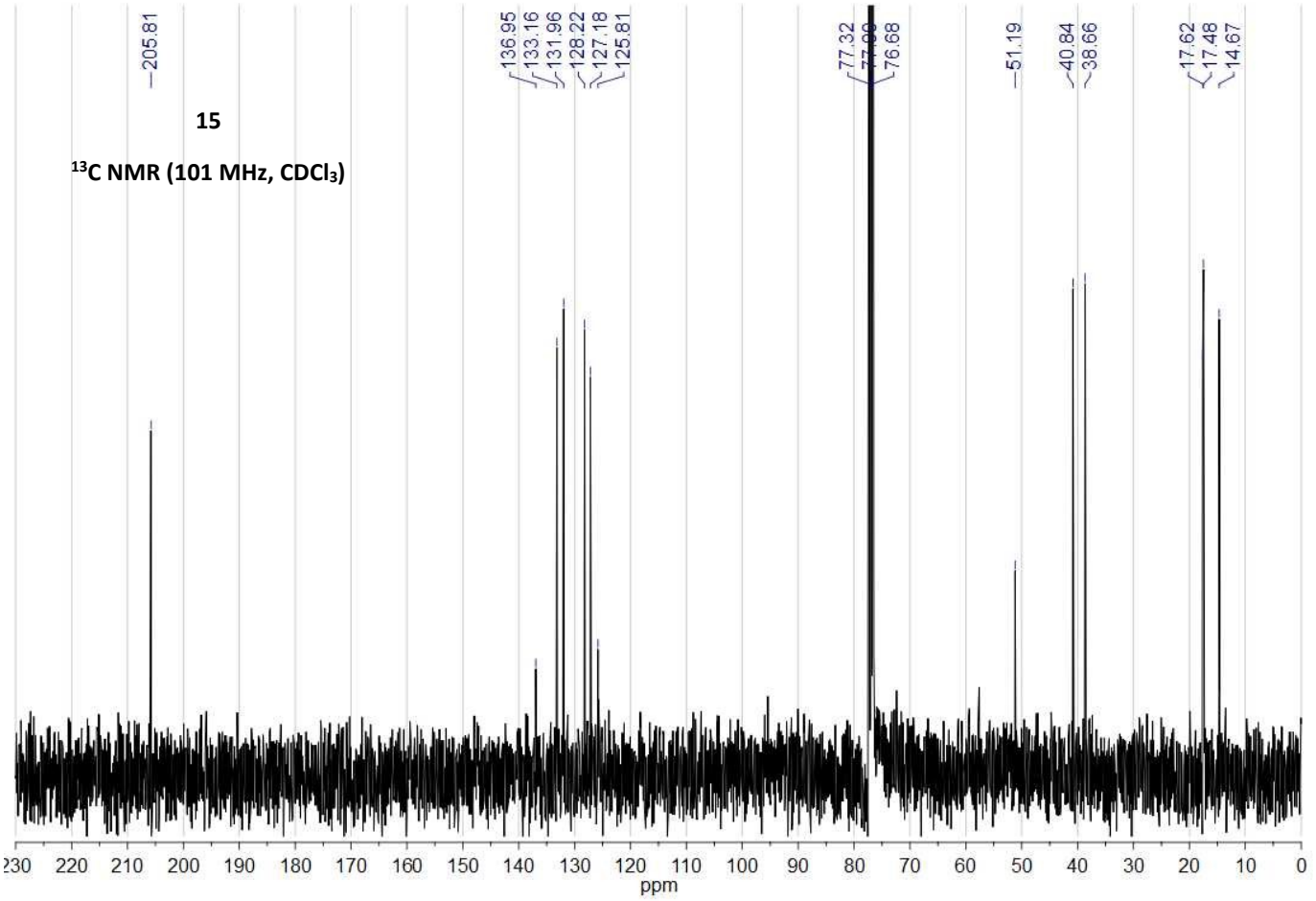
14

^{13}C NMR (101 MHz, $CDCl_3$)



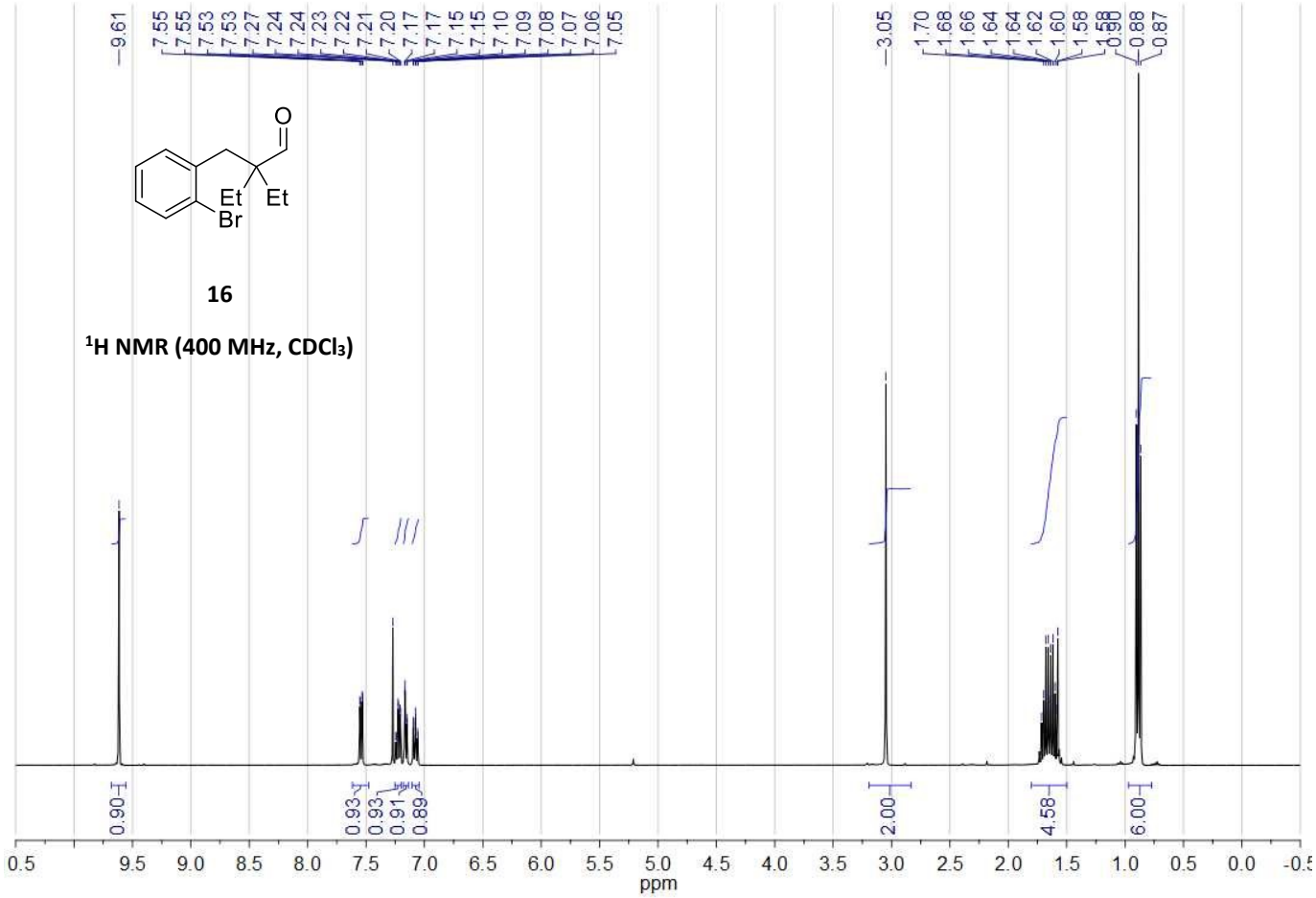
15

^{1}H NMR (400 MHz, $CDCl_3$)



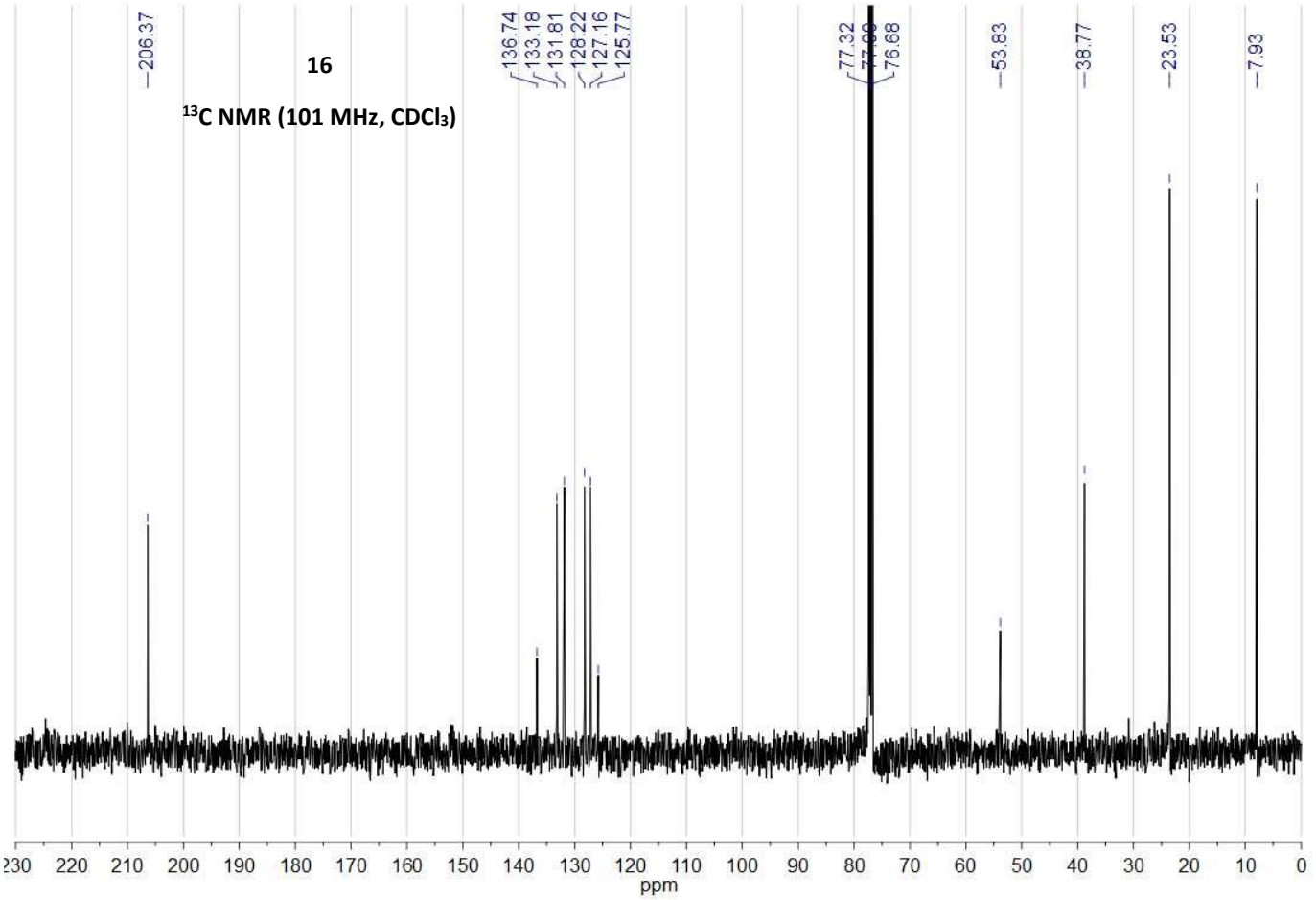
15

^{13}C NMR (101 MHz, $CDCl_3$)



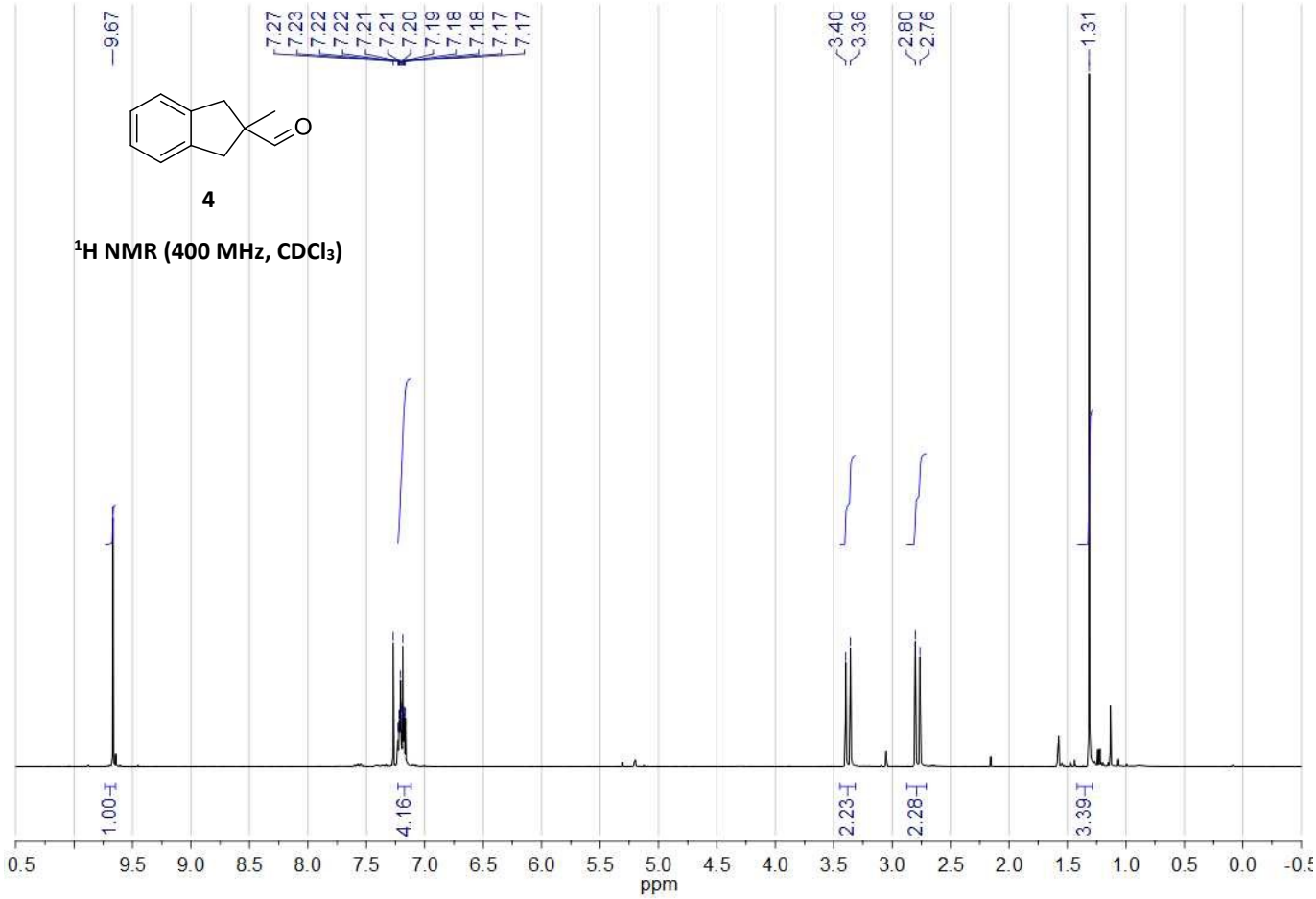
16

^{1}H NMR (400 MHz, $CDCl_3$)



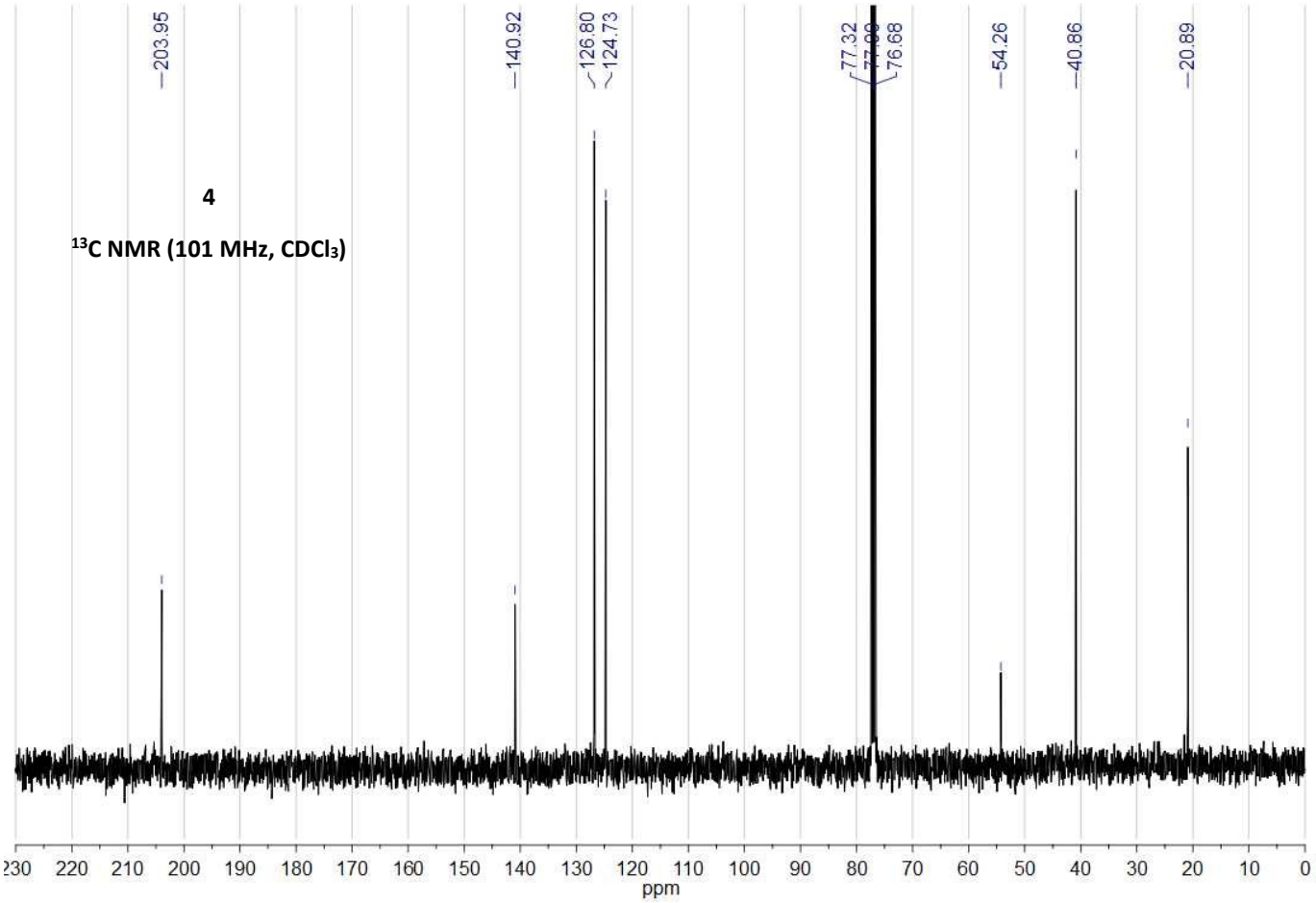
16

^{13}C NMR (101 MHz, $CDCl_3$)



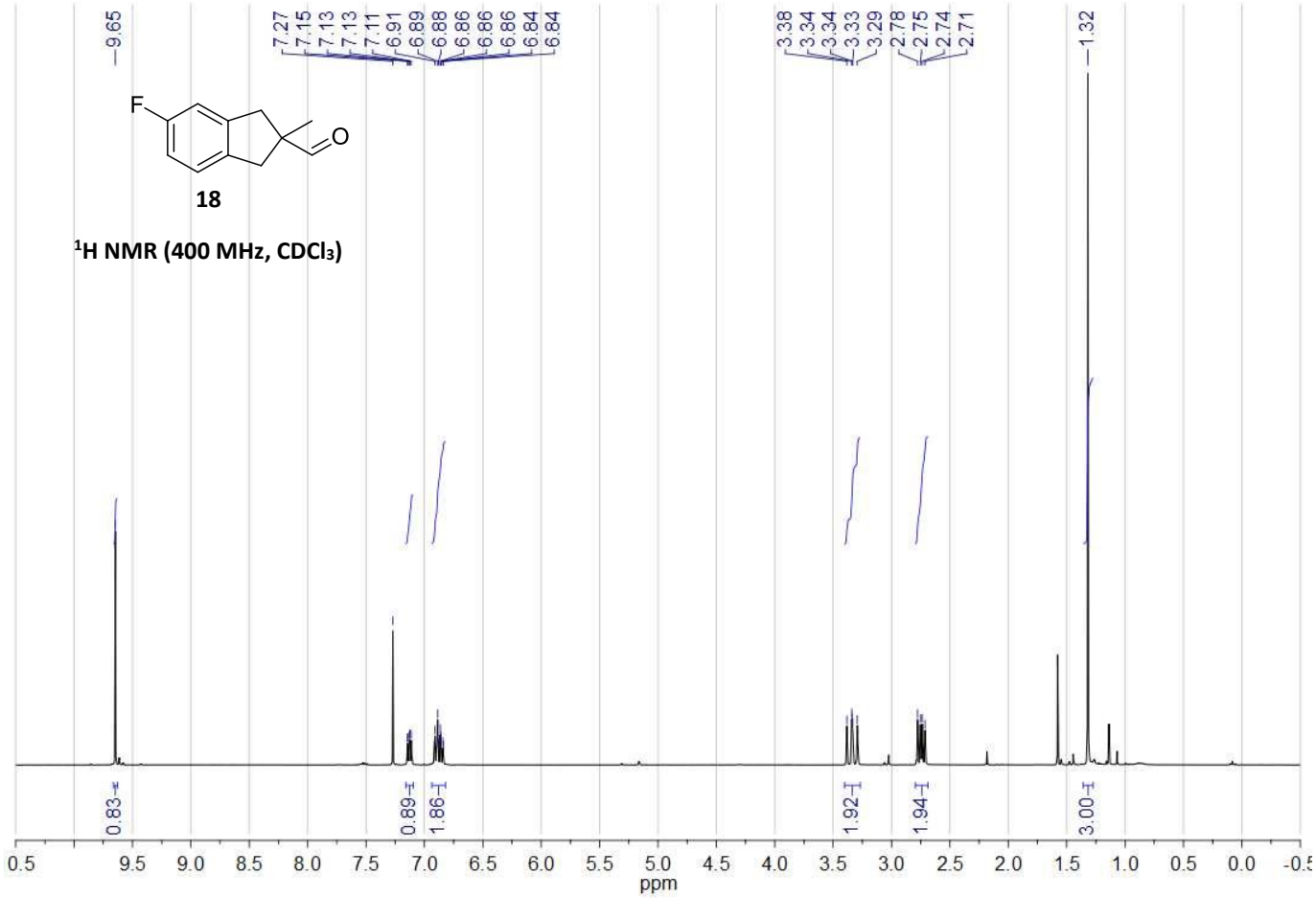
4

^{1}H NMR (400 MHz, $CDCl_3$)



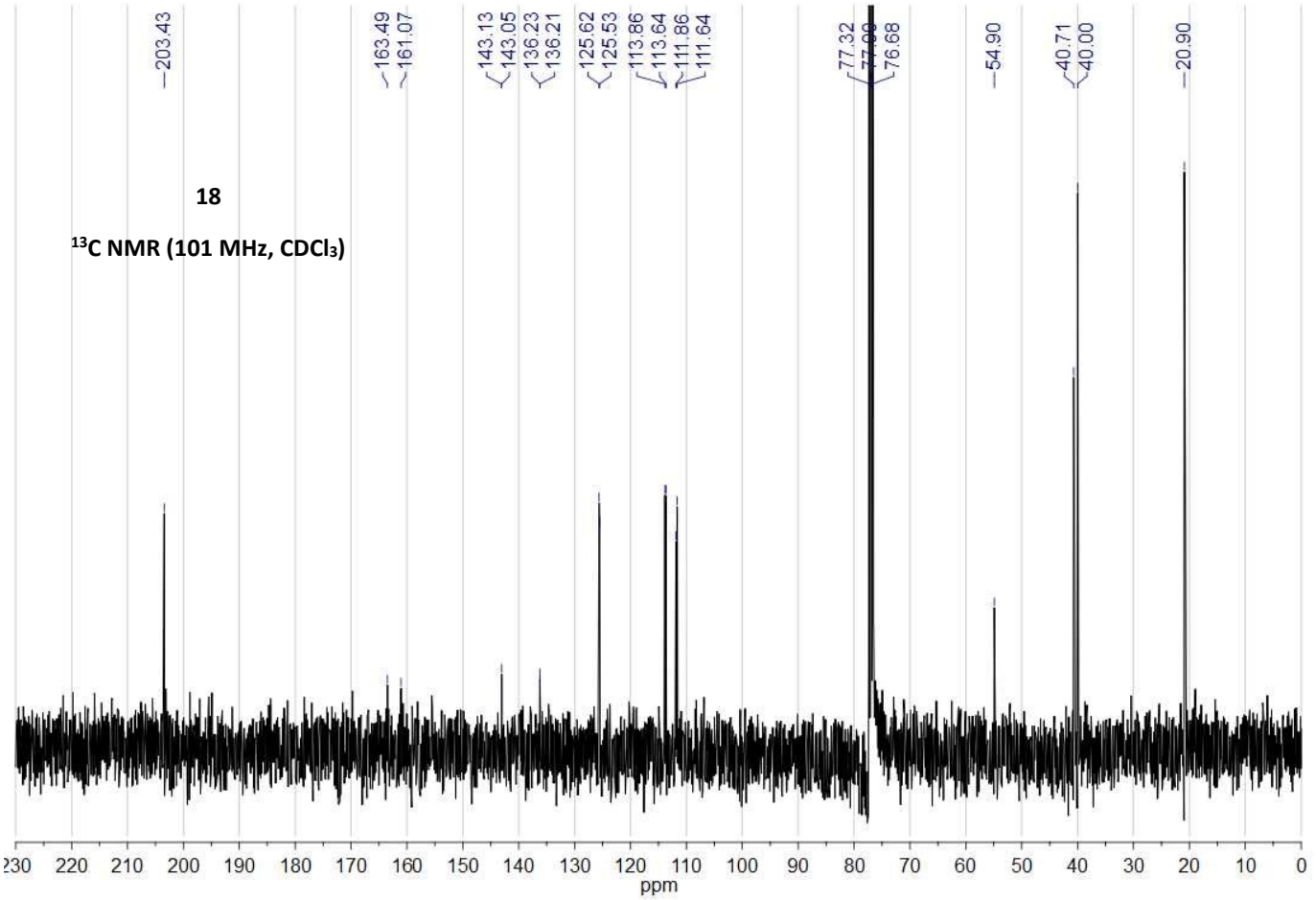
4

^{13}C NMR (101 MHz, $CDCl_3$)



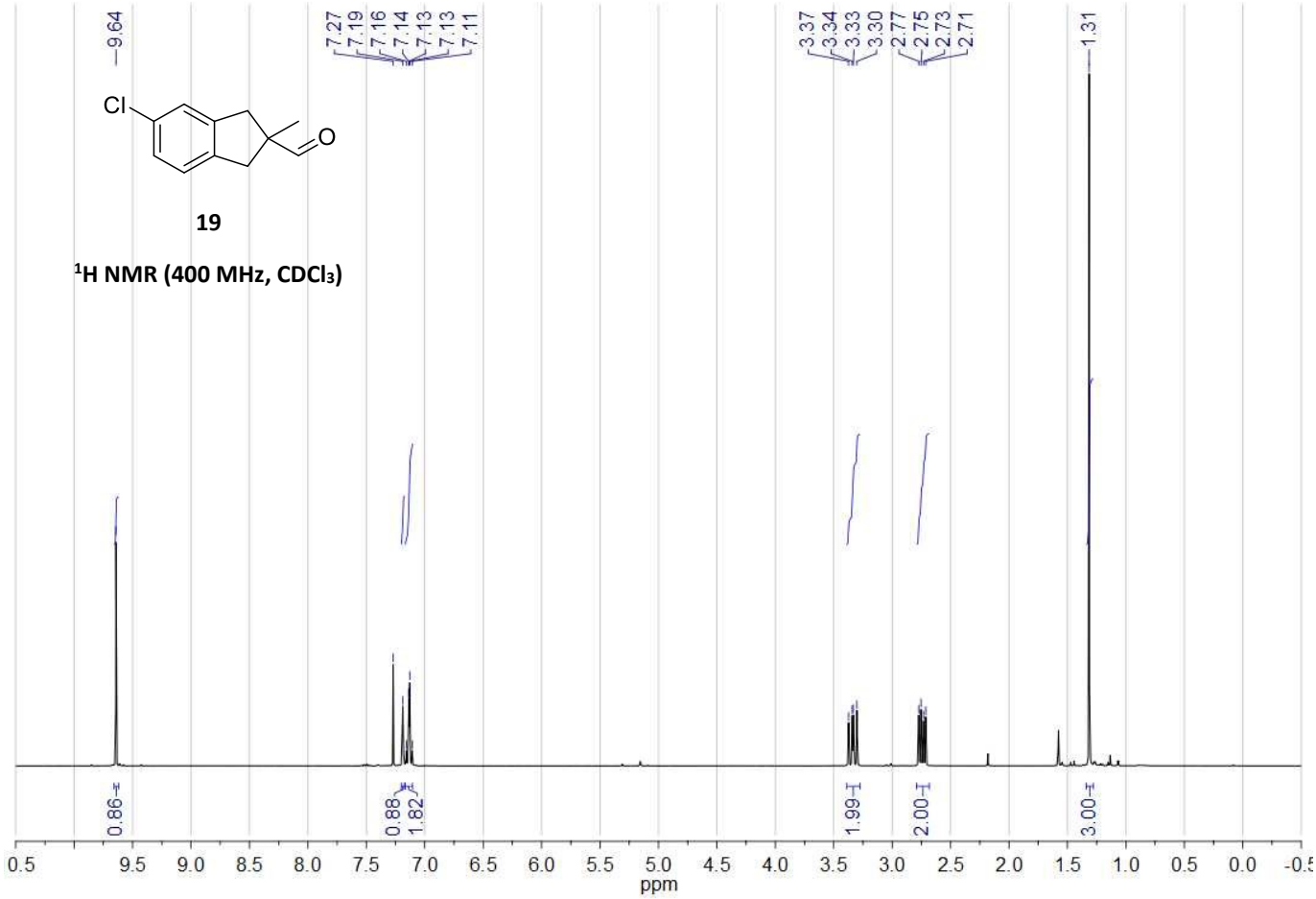
18

^{1}H NMR (400 MHz, $CDCl_3$)



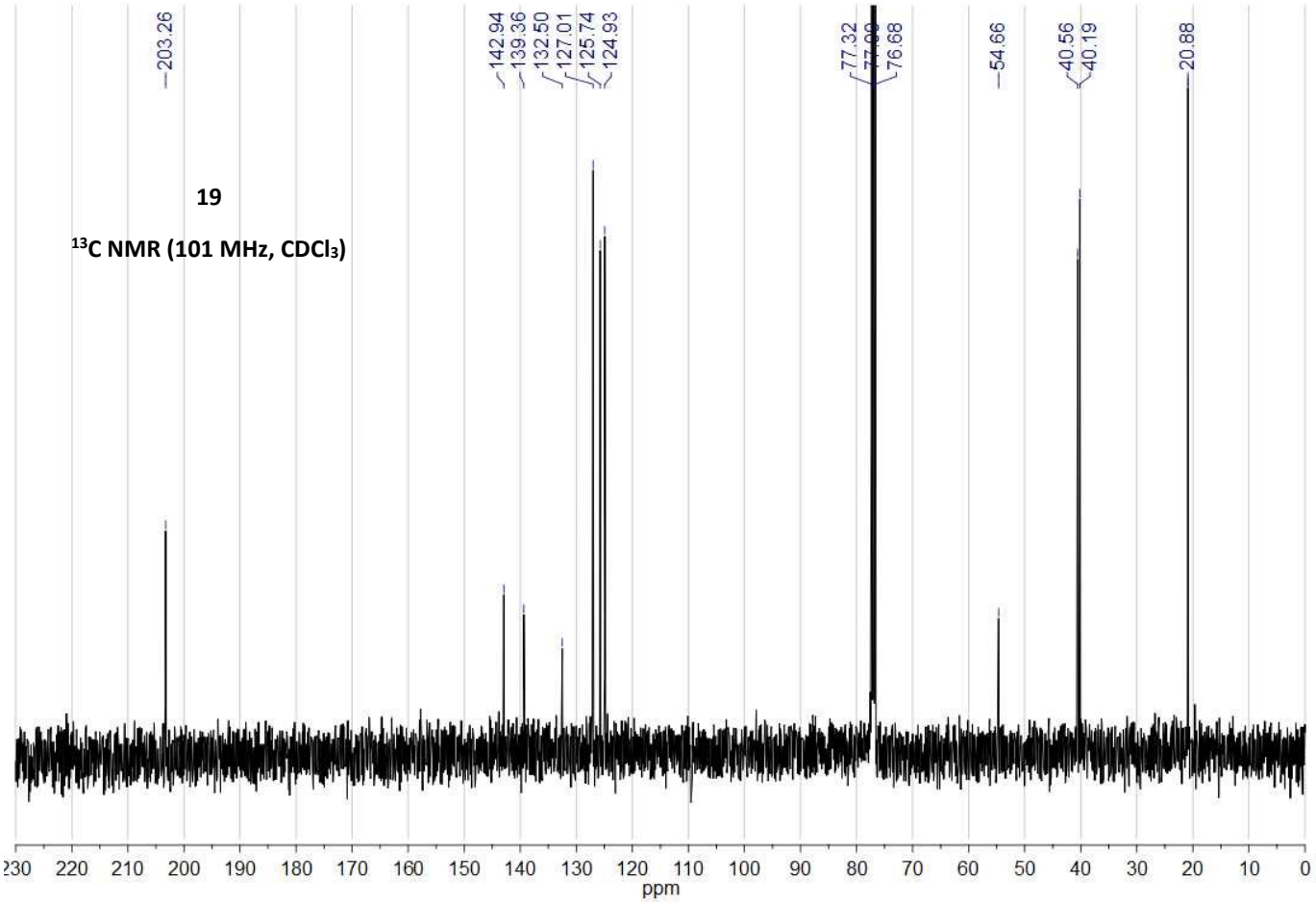
18

^{13}C NMR (101 MHz, $CDCl_3$)



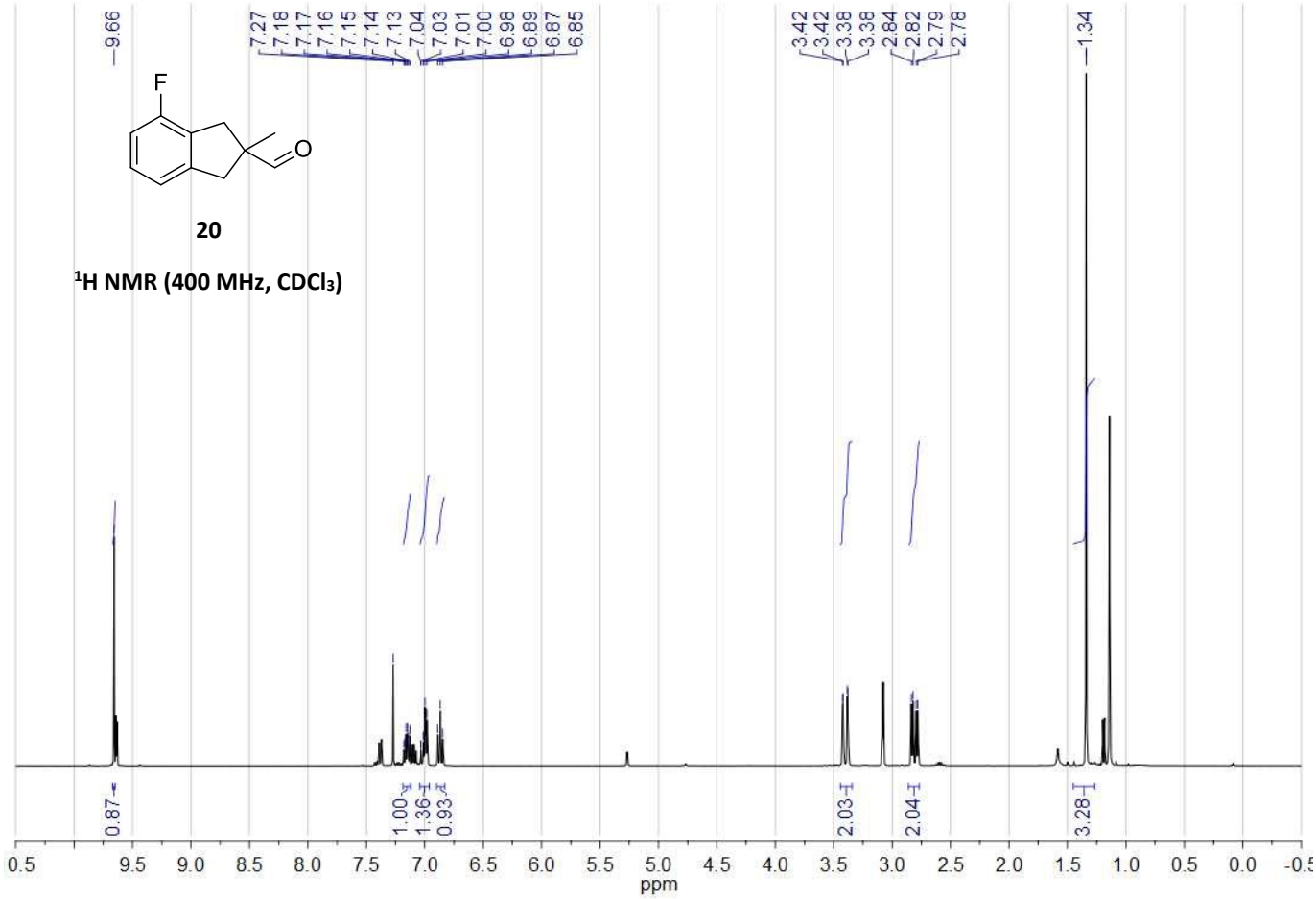
19

^{1}H NMR (400 MHz, $CDCl_3$)



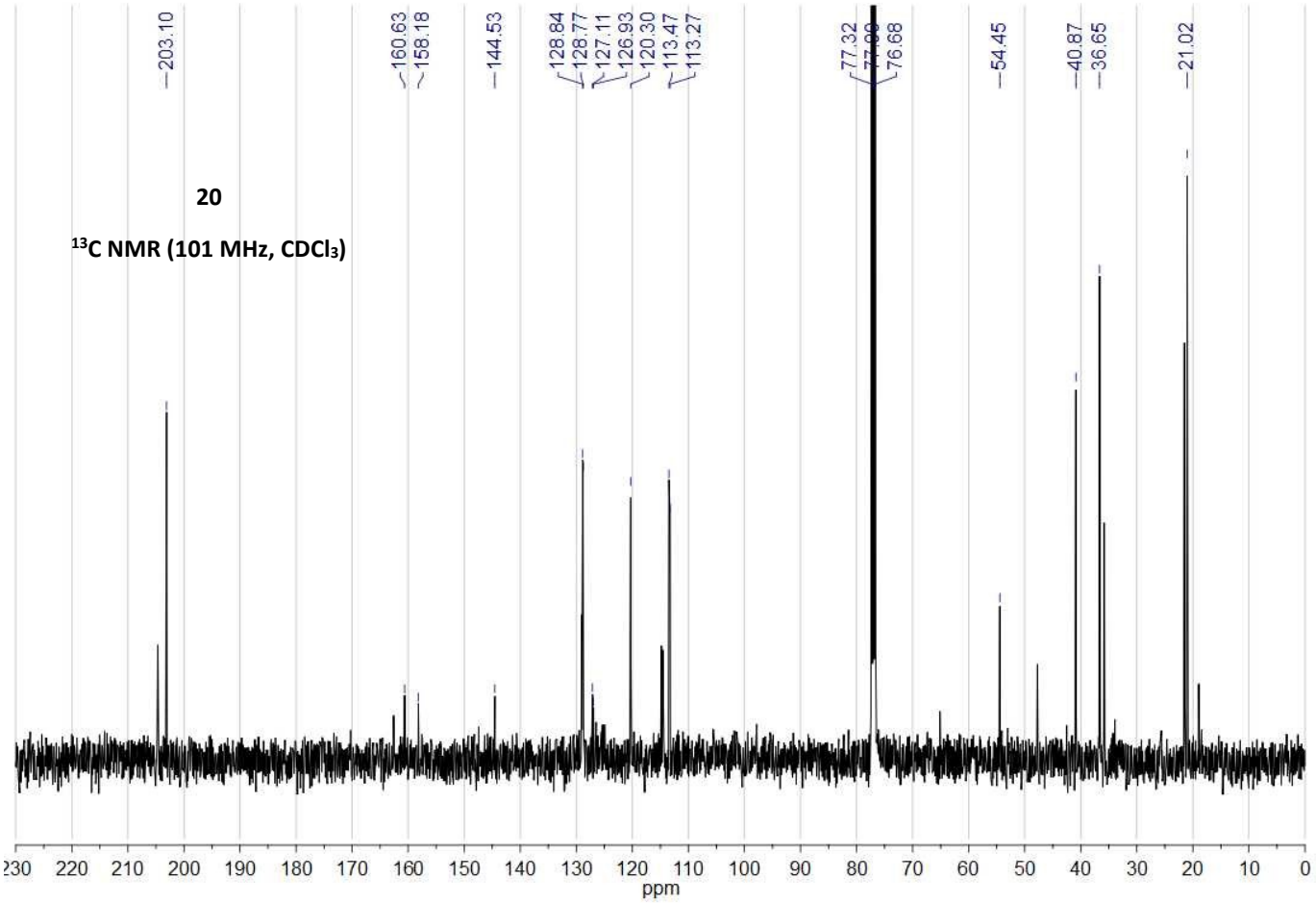
19

^{13}C NMR (101 MHz, $CDCl_3$)



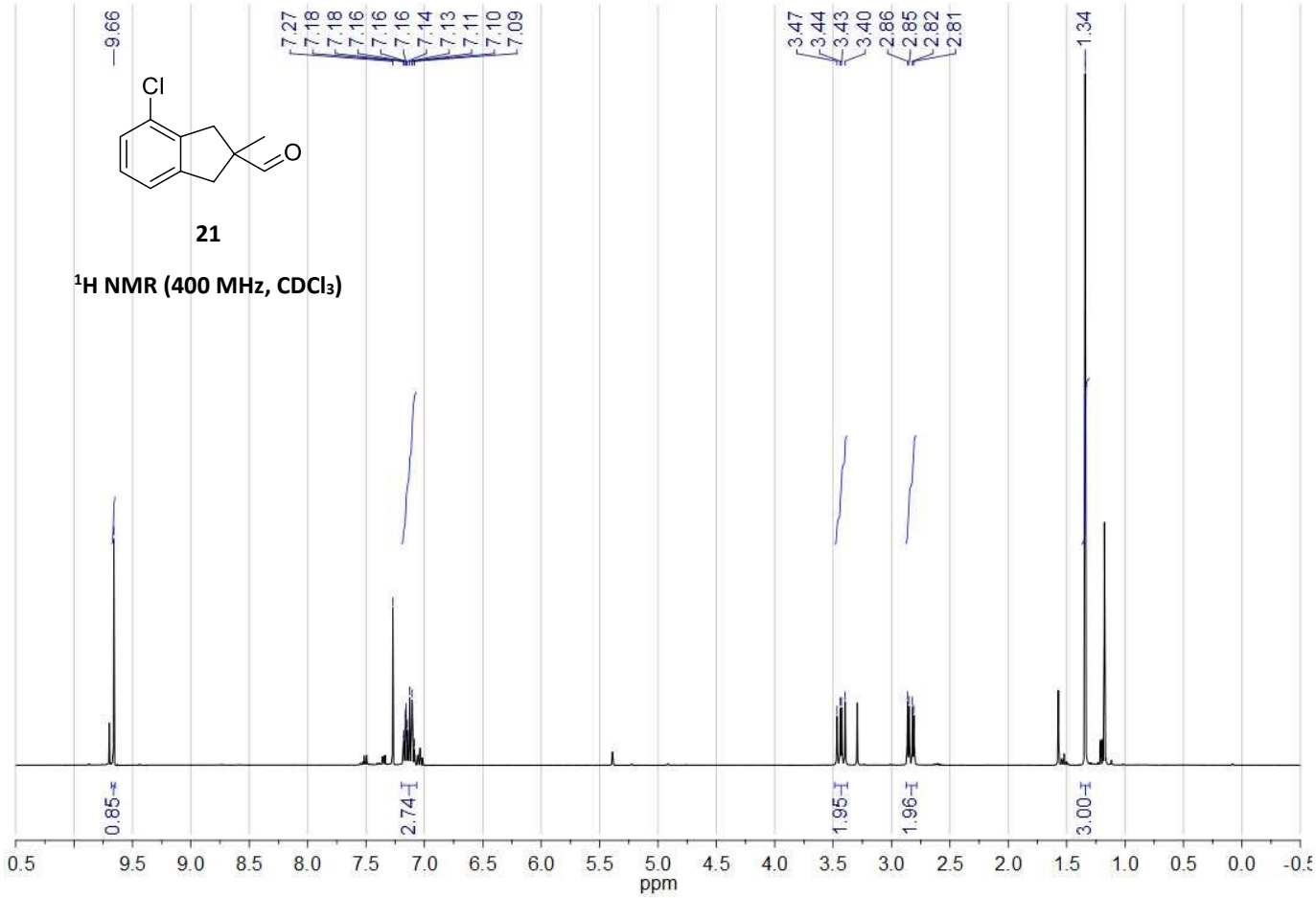
20

^{1}H NMR (400 MHz, $CDCl_3$)



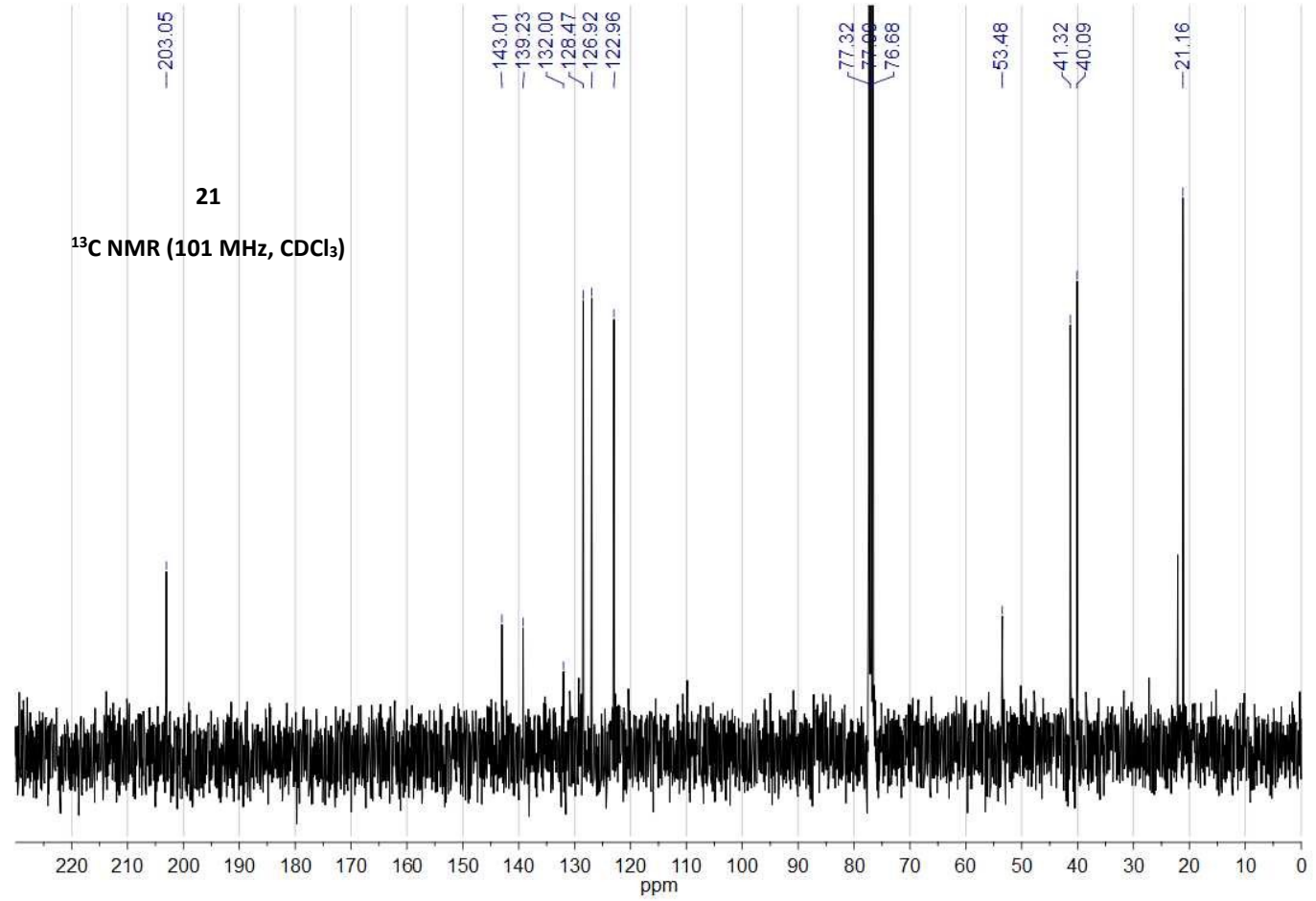
20

^{13}C NMR (101 MHz, $CDCl_3$)



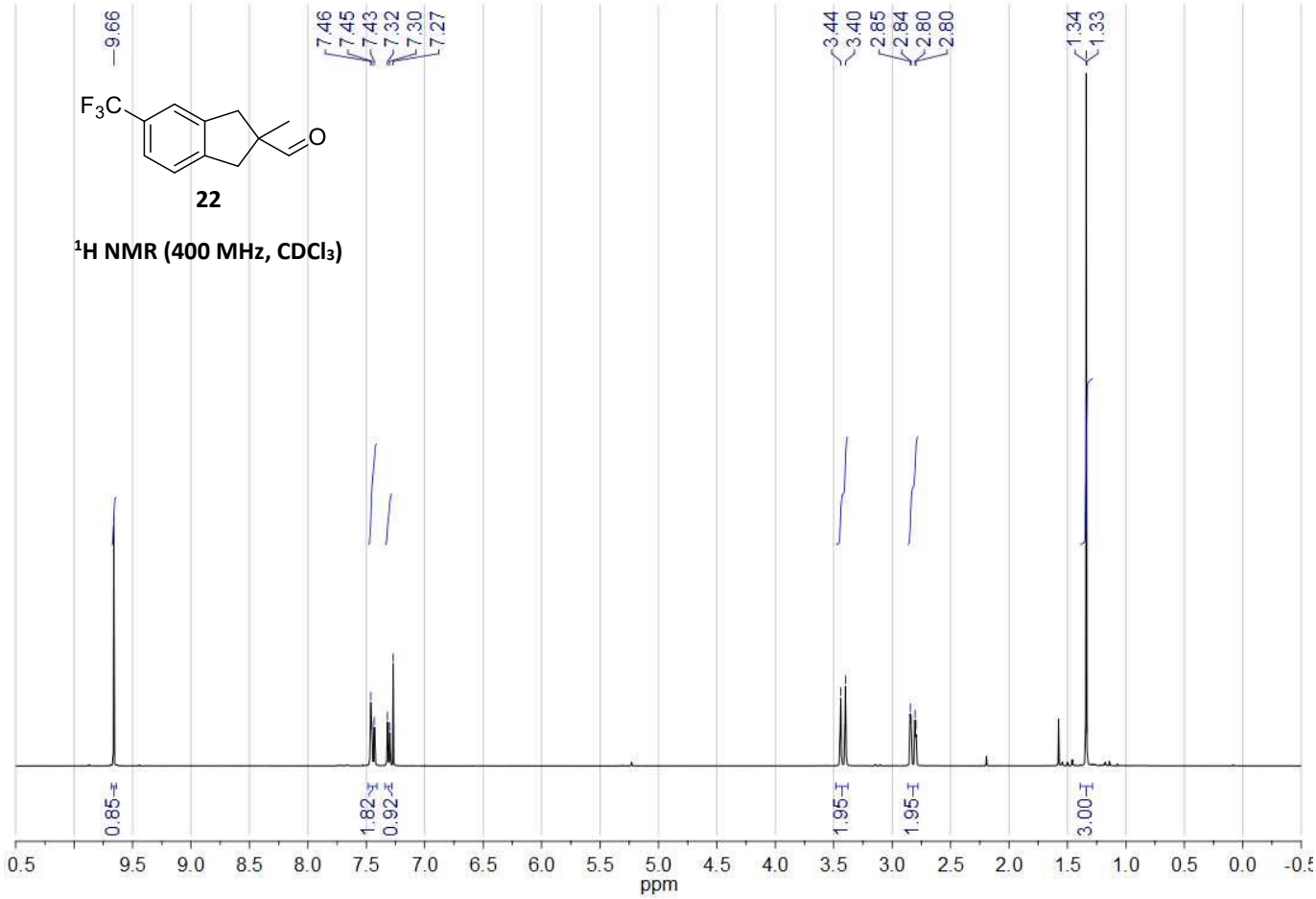
21

^{1}H NMR (400 MHz, $CDCl_3$)



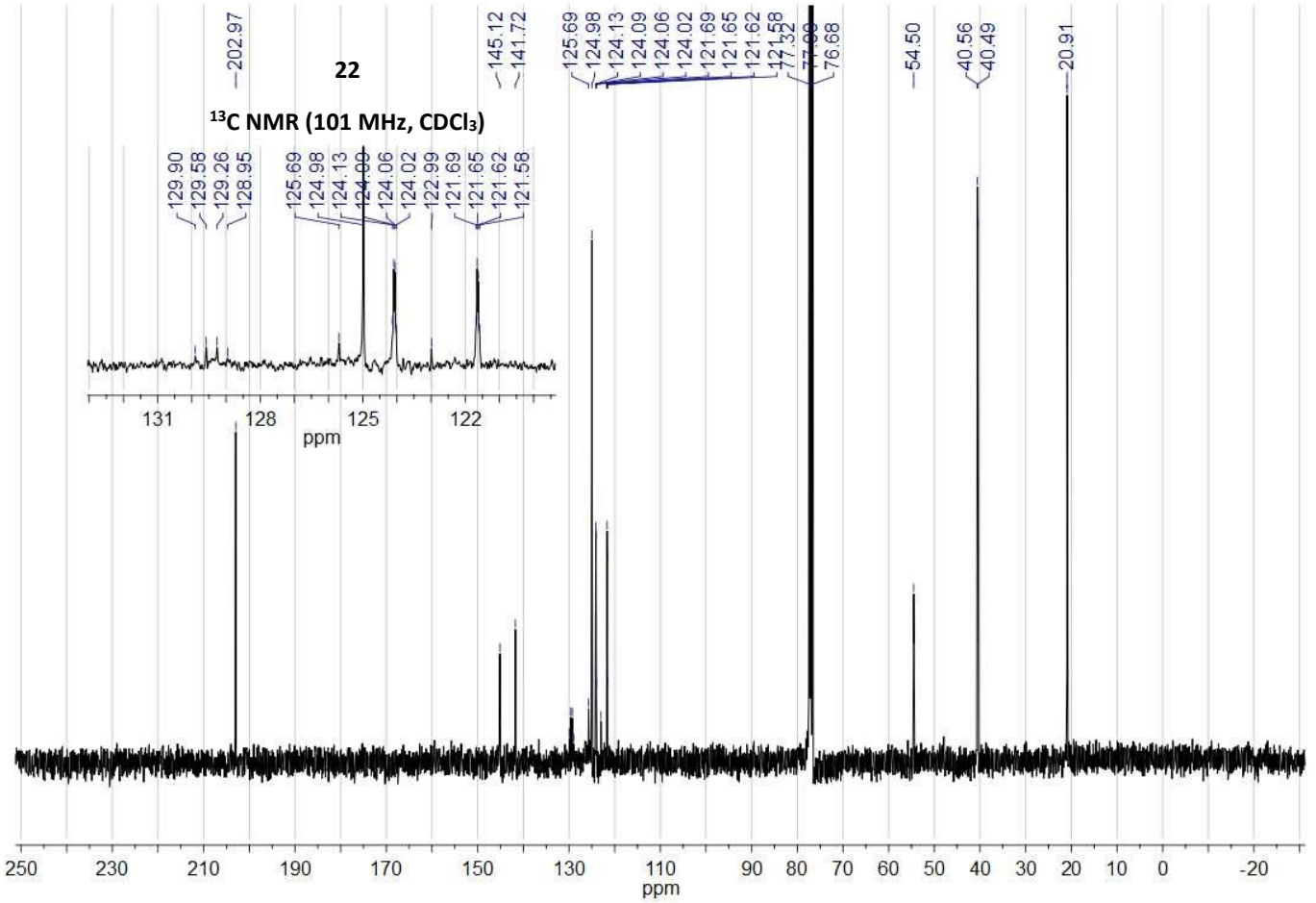
21

^{13}C NMR (101 MHz, $CDCl_3$)



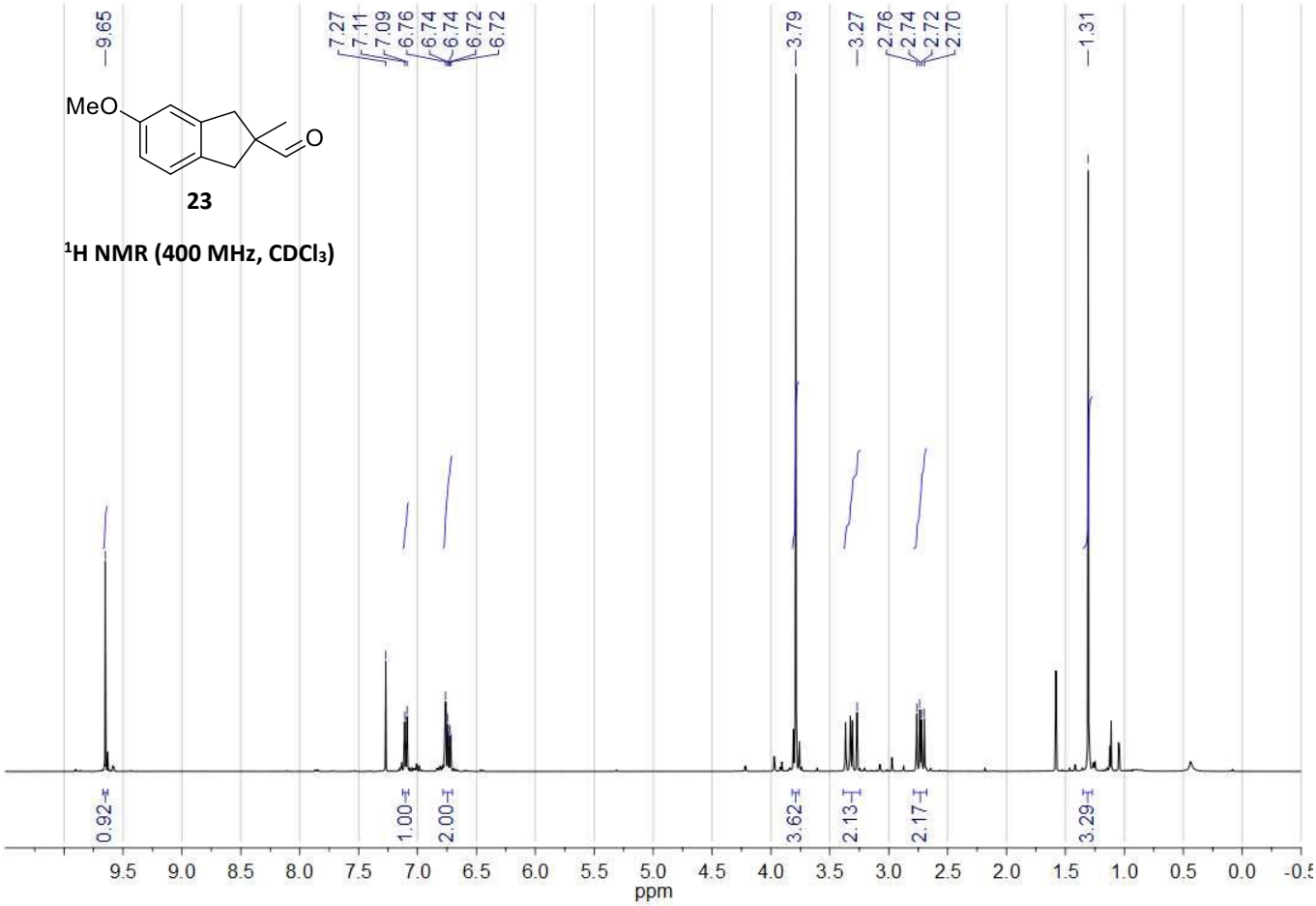
22

^{1}H NMR (400 MHz, $CDCl_3$)



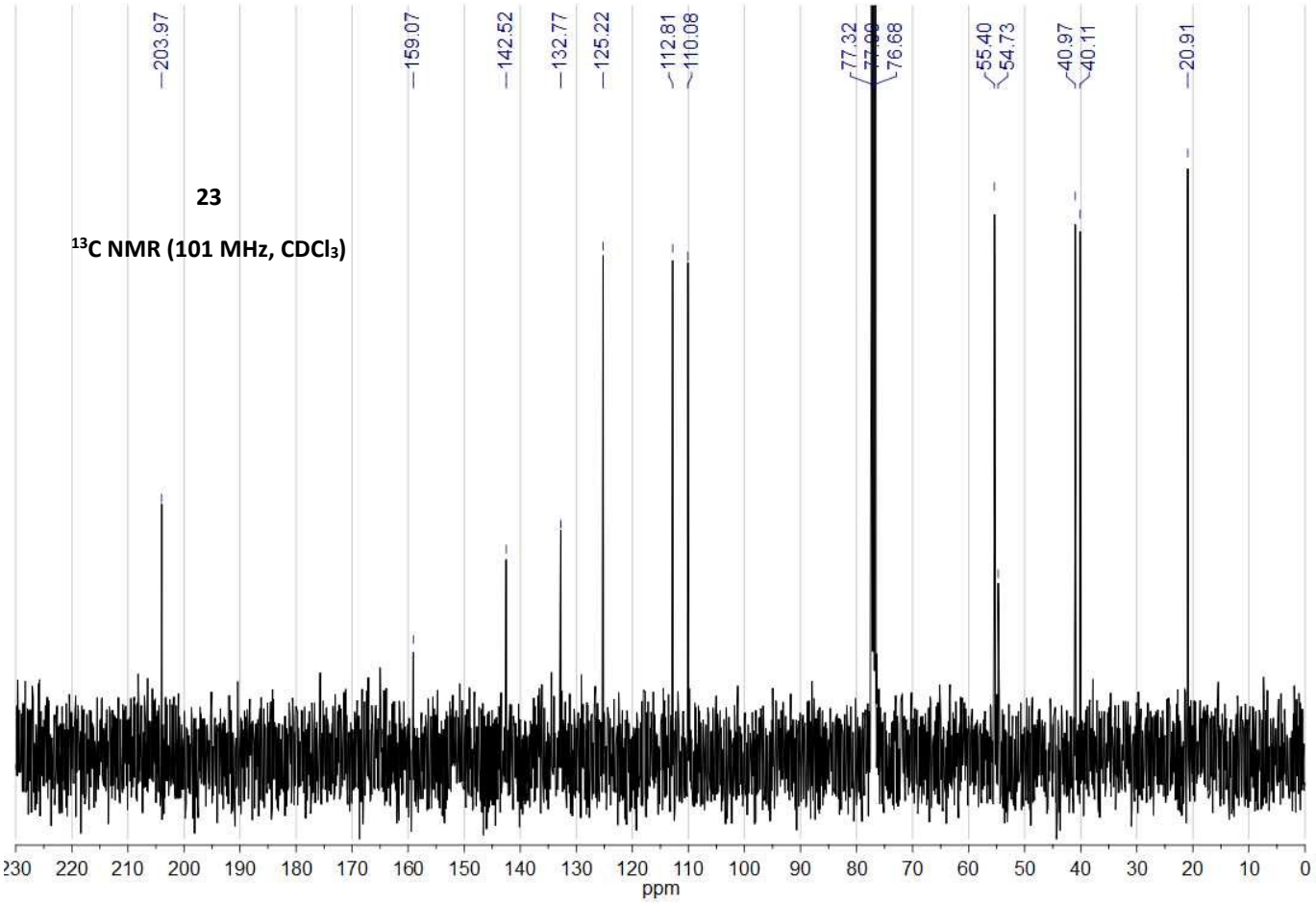
22

^{13}C NMR (101 MHz, $CDCl_3$)



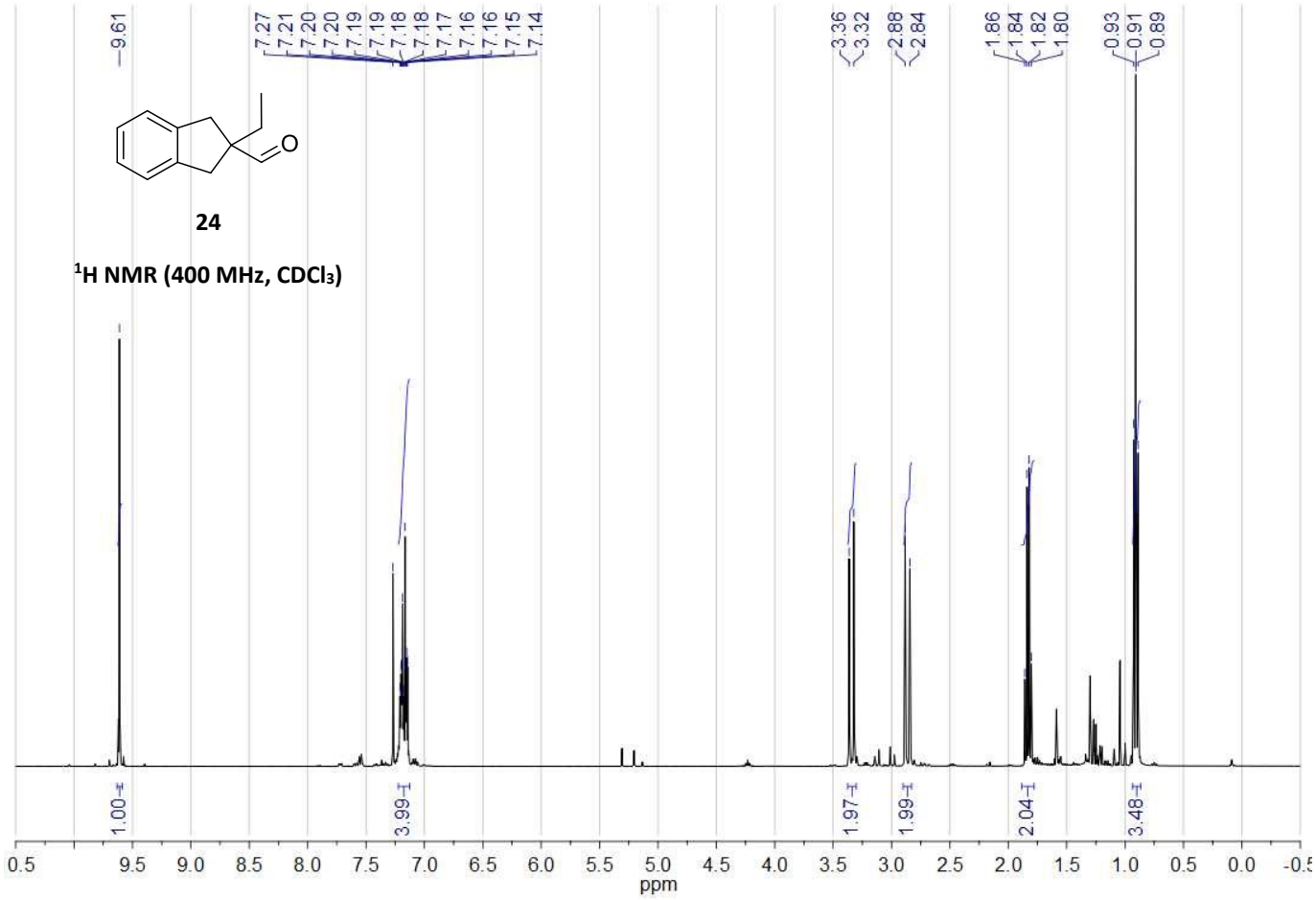
23

^{1}H NMR (400 MHz, $CDCl_3$)



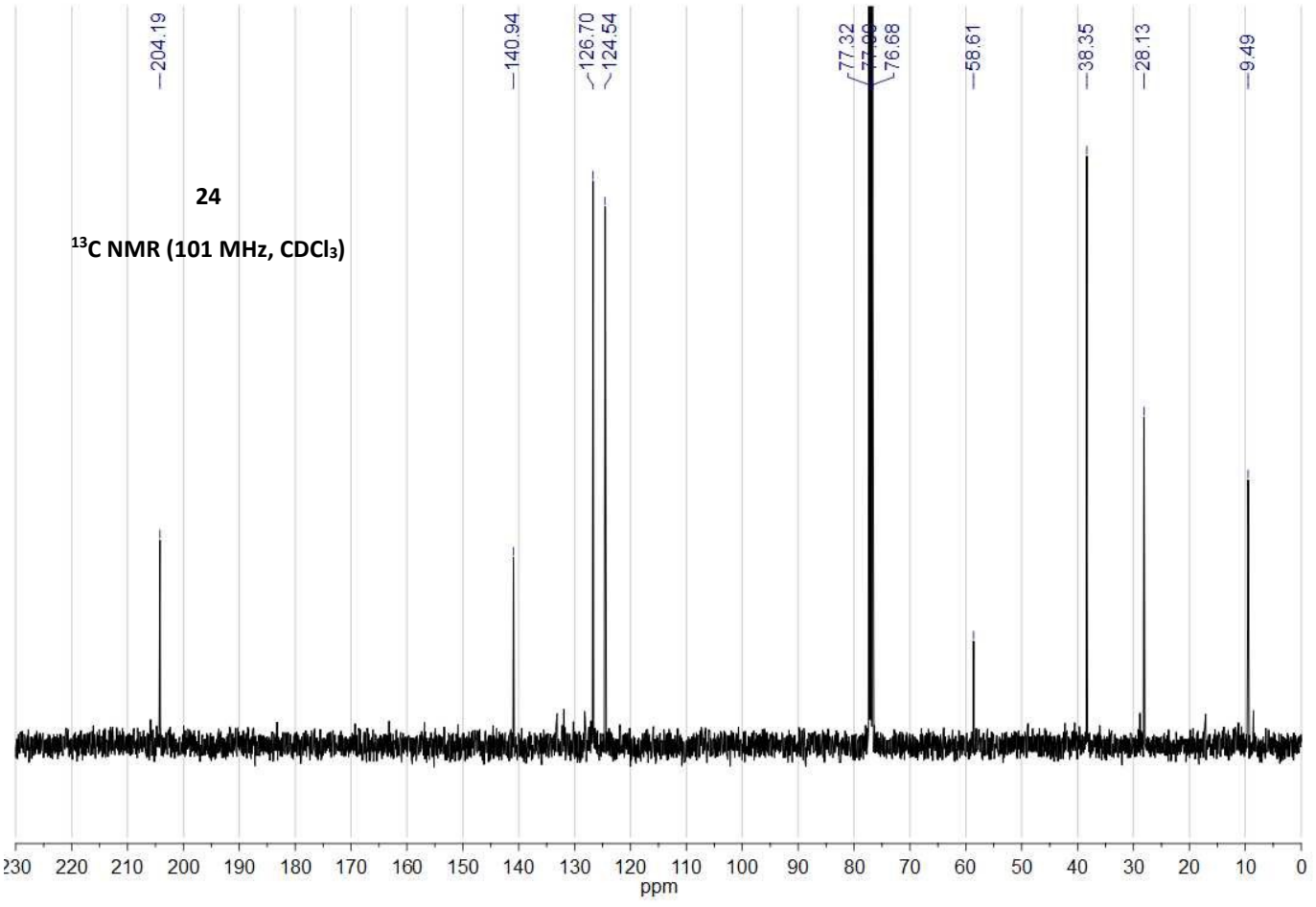
23

^{13}C NMR (101 MHz, $CDCl_3$)



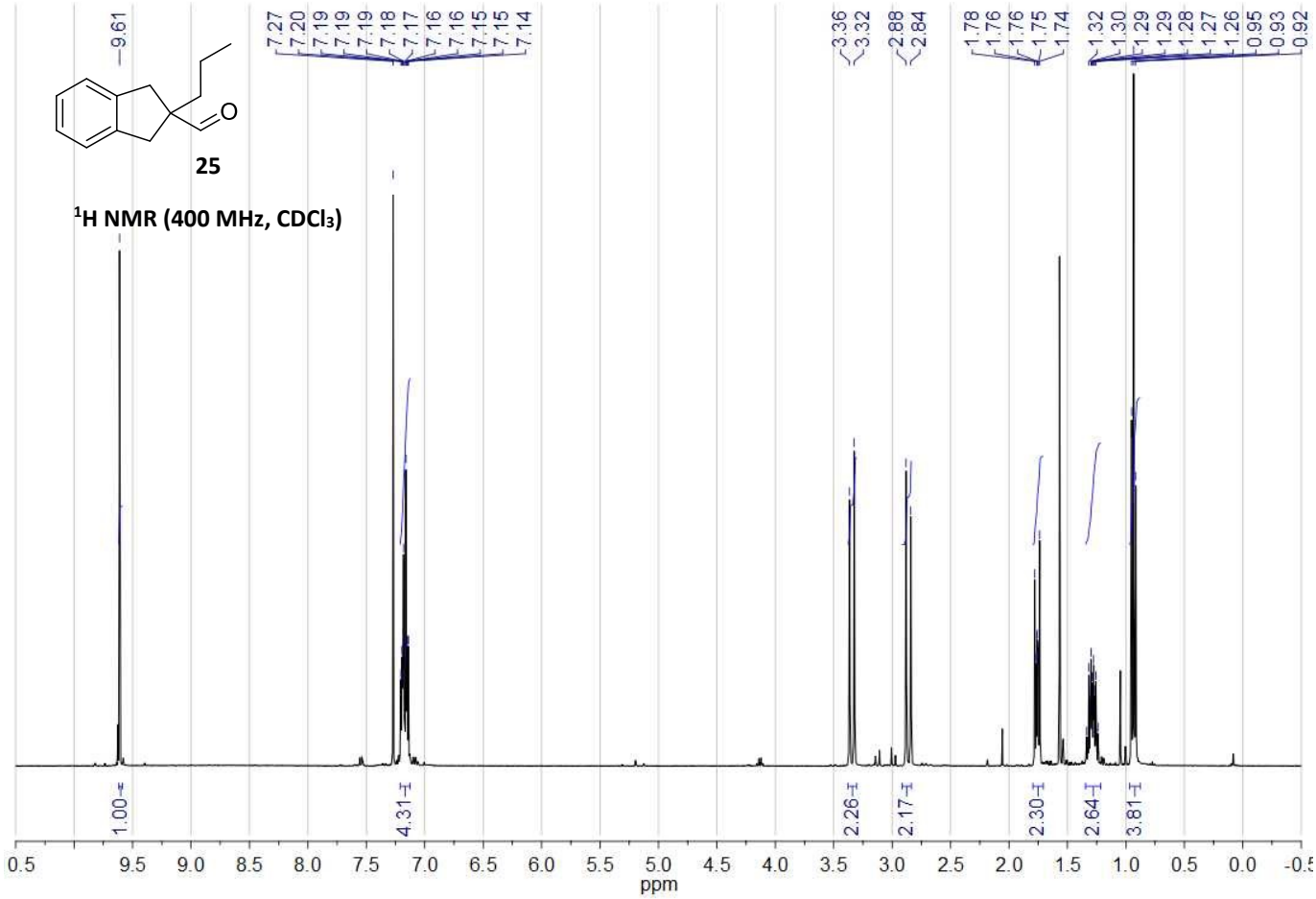
24

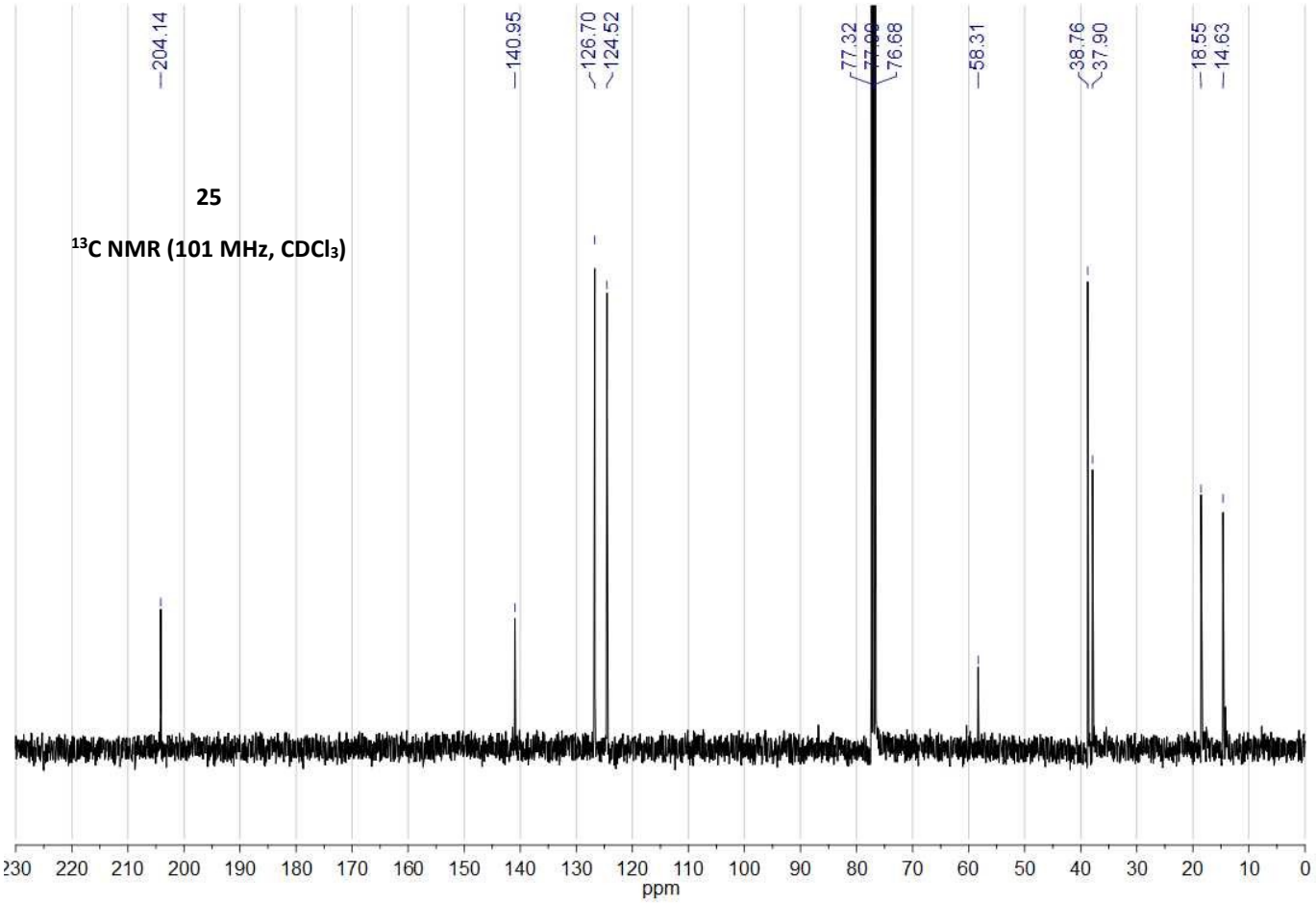
^{1}H NMR (400 MHz, $CDCl_3$)

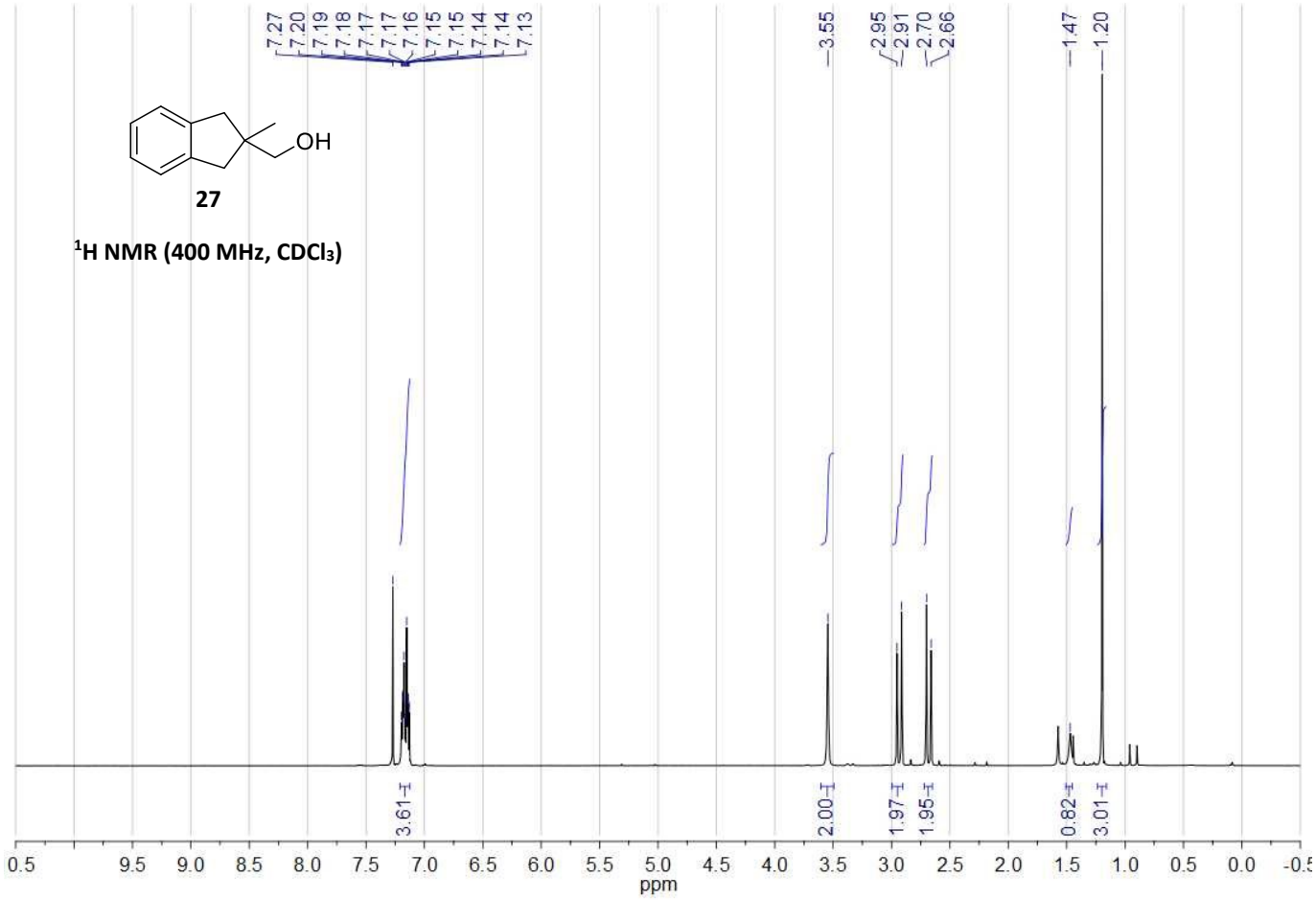


24

^{13}C NMR (101 MHz, $CDCl_3$)

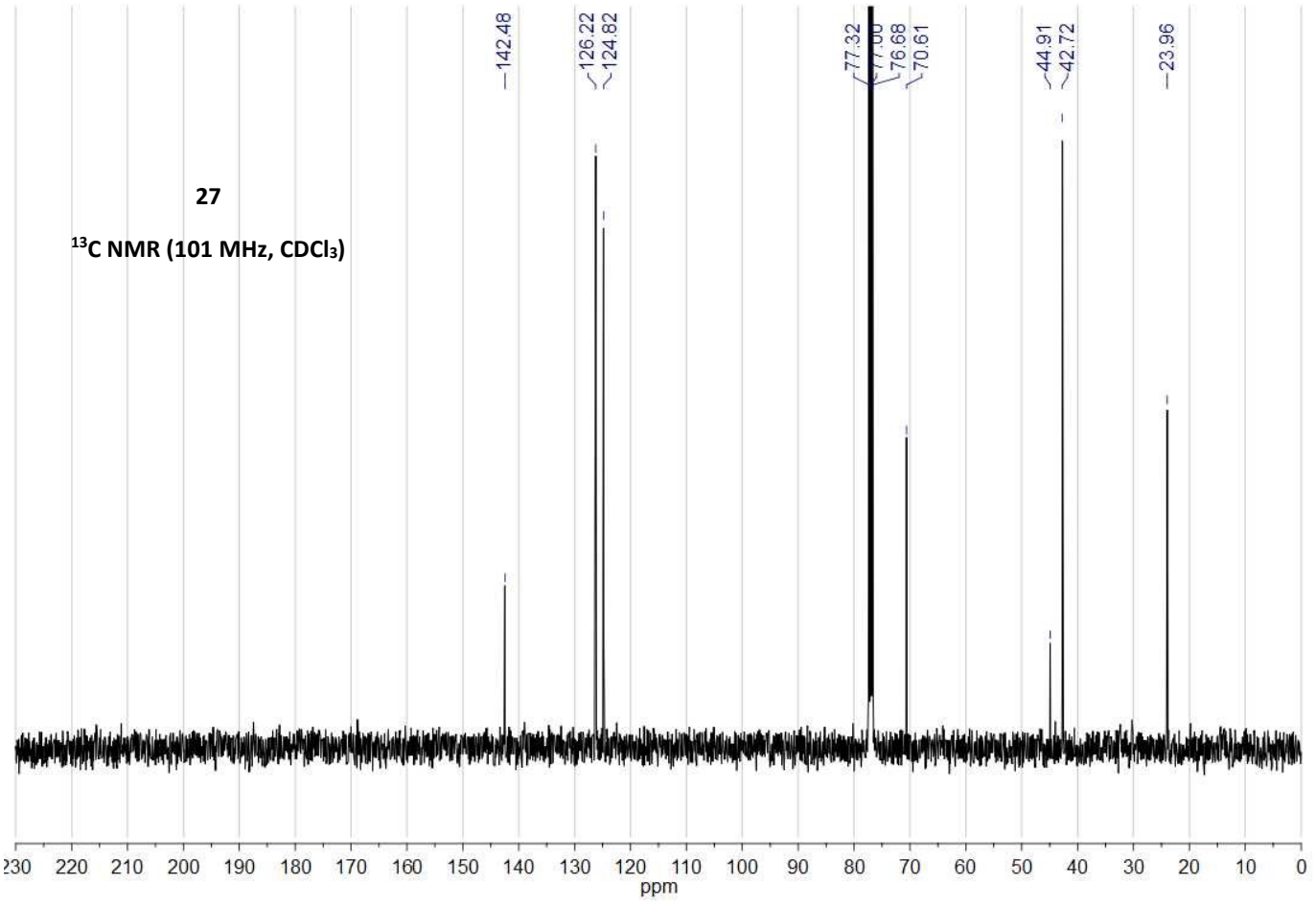

9.61
7.27
7.20
7.19
7.19
7.19
7.18
7.17
7.16
7.16
7.15
7.15
7.14
3.36
3.32
2.88
2.84
1.78
1.76
1.76
1.75
1.74
1.32
1.30
1.29
1.29
1.28
1.27
1.26
0.95
0.93
0.92
O
25
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
4.31
2.26
2.17
2.30
2.64
3.81
0.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


204.14
140.95
126.70
124.52
77.32
77.00
76.68
58.31
38.76
37.90
18.55
14.63
25
^{13}C NMR (101 MHz, CDCl$_3$)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm



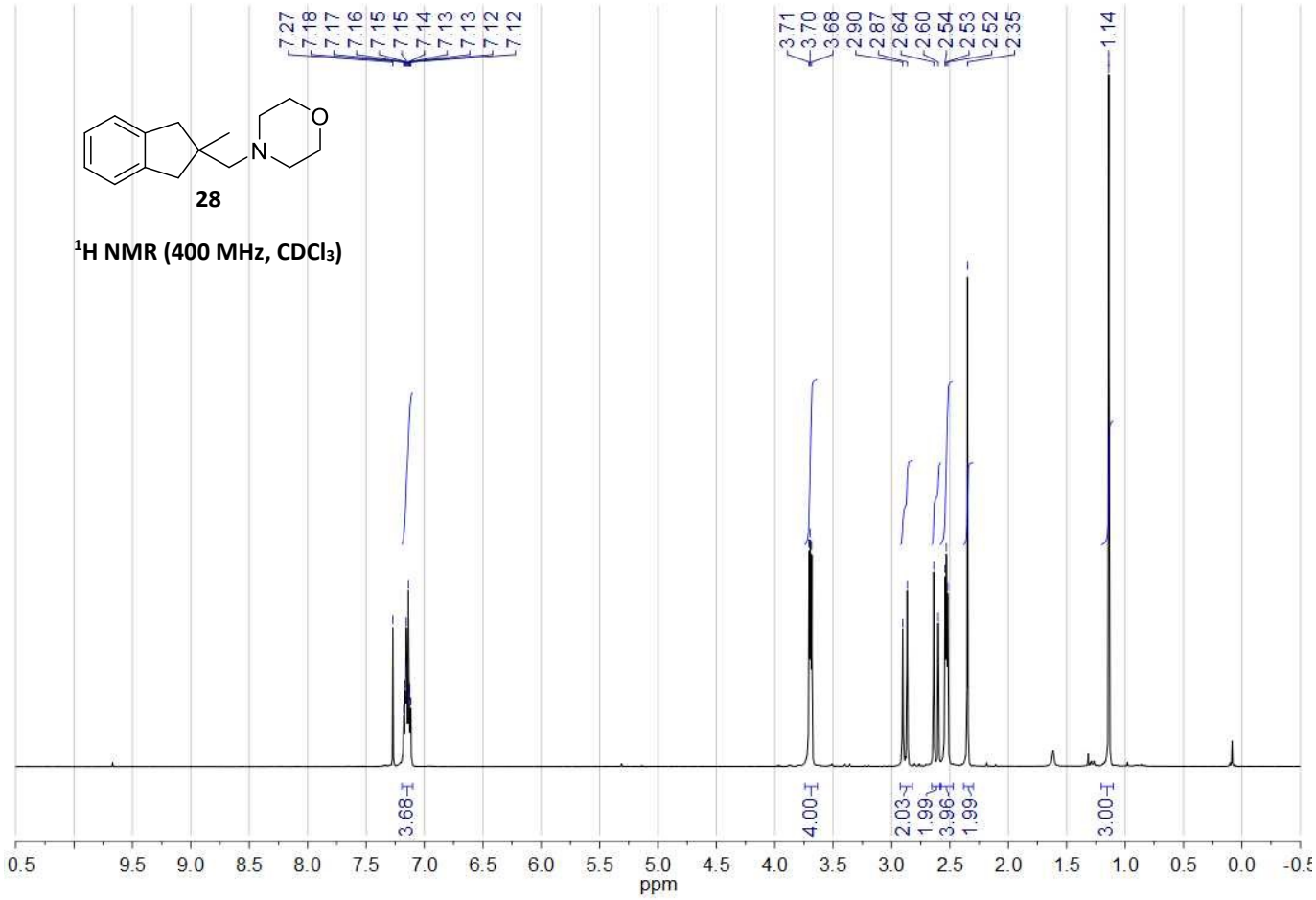
27

^{1}H NMR (400 MHz, $CDCl_3$)



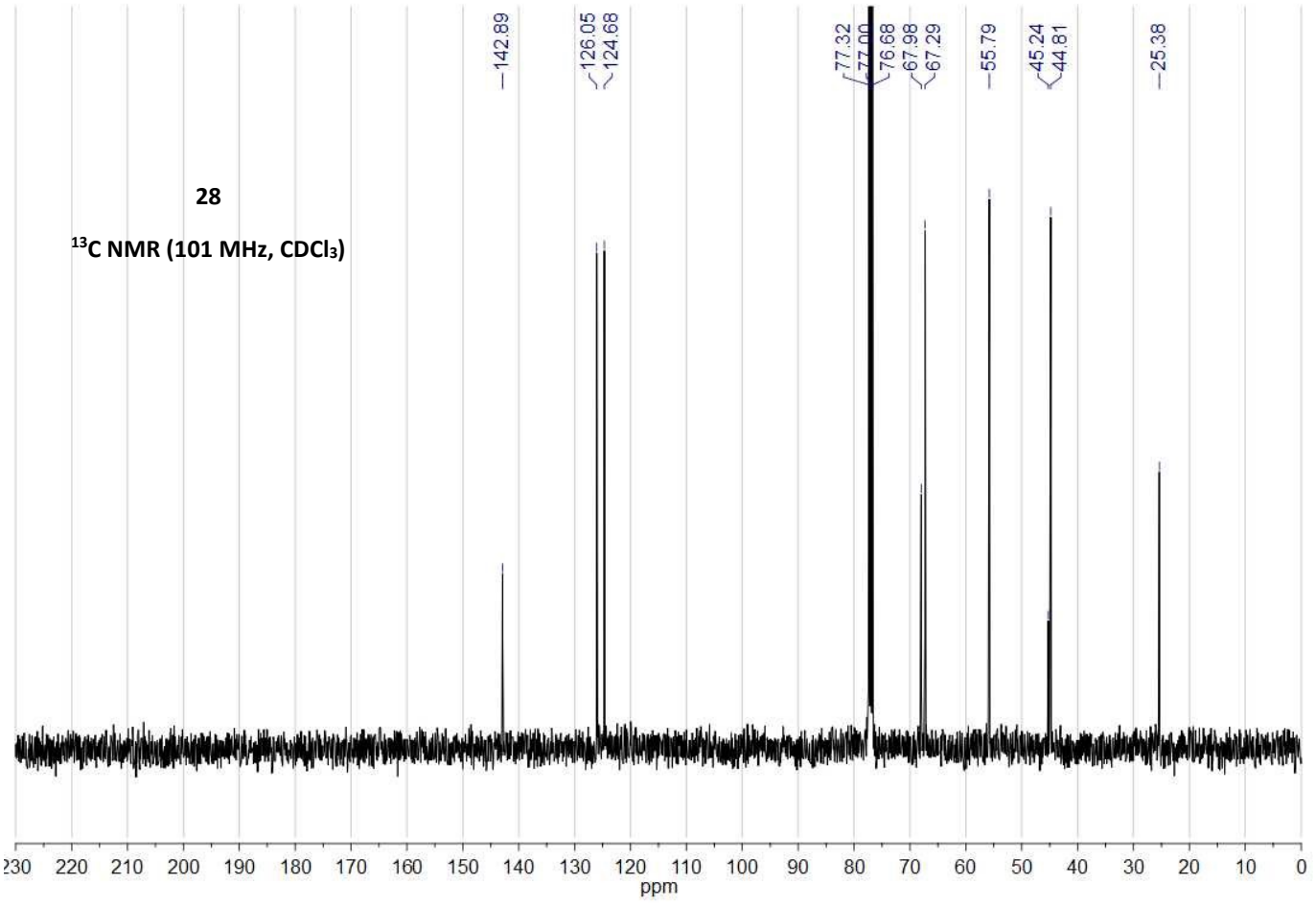
27

^{13}C NMR (101 MHz, $CDCl_3$)



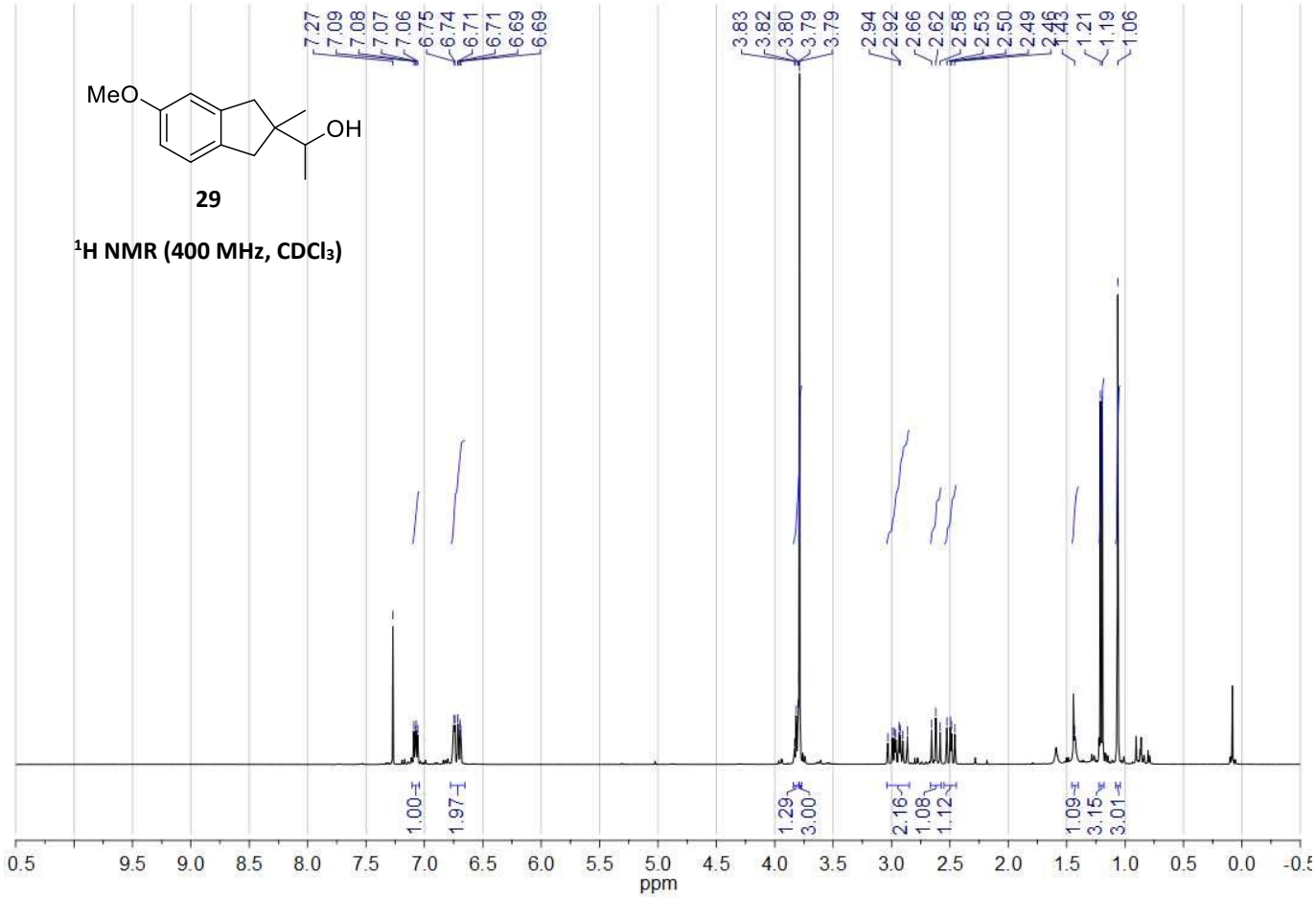
28

^{1}H NMR (400 MHz, $CDCl_3$)



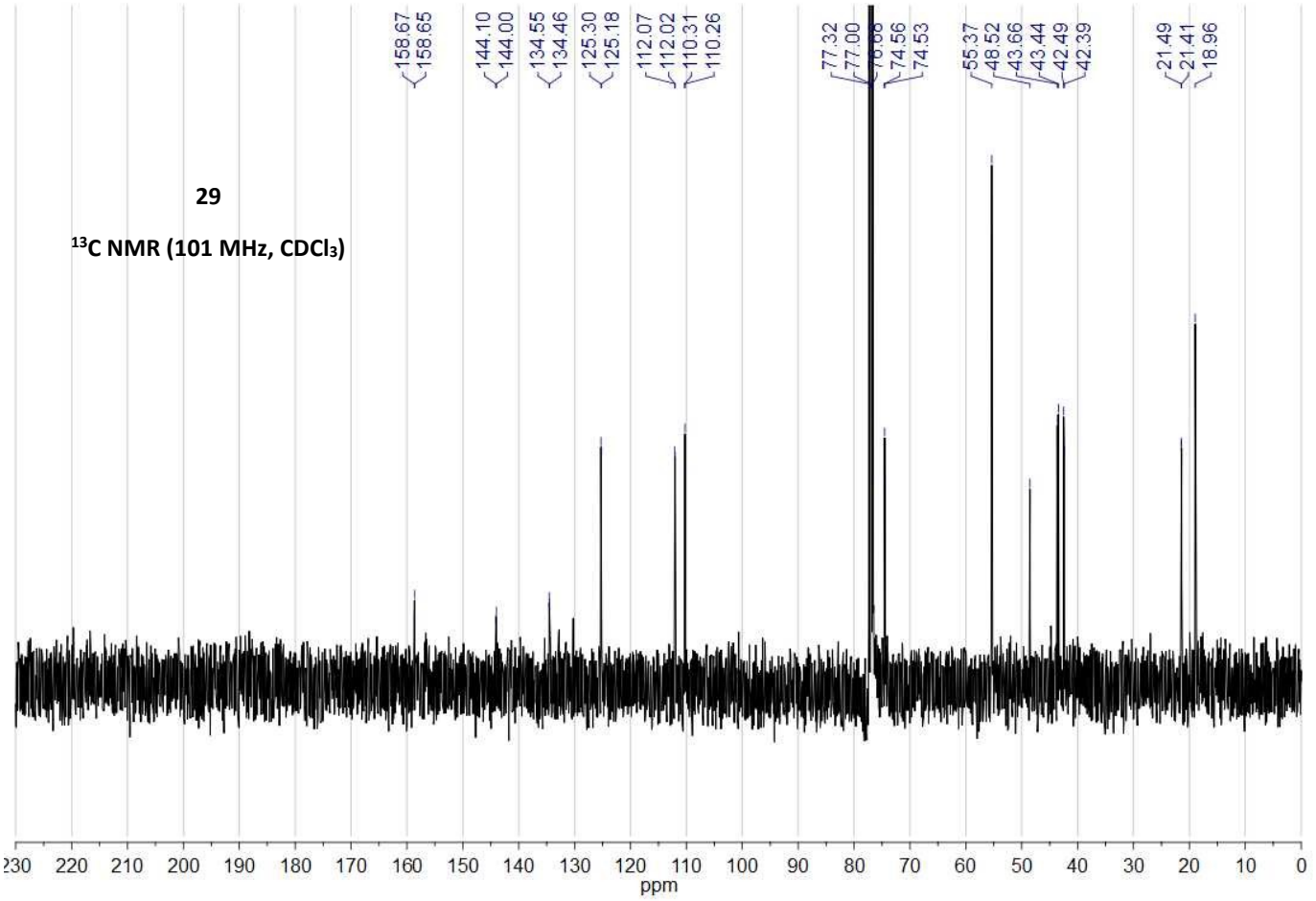
28

^{13}C NMR (101 MHz, $CDCl_3$)



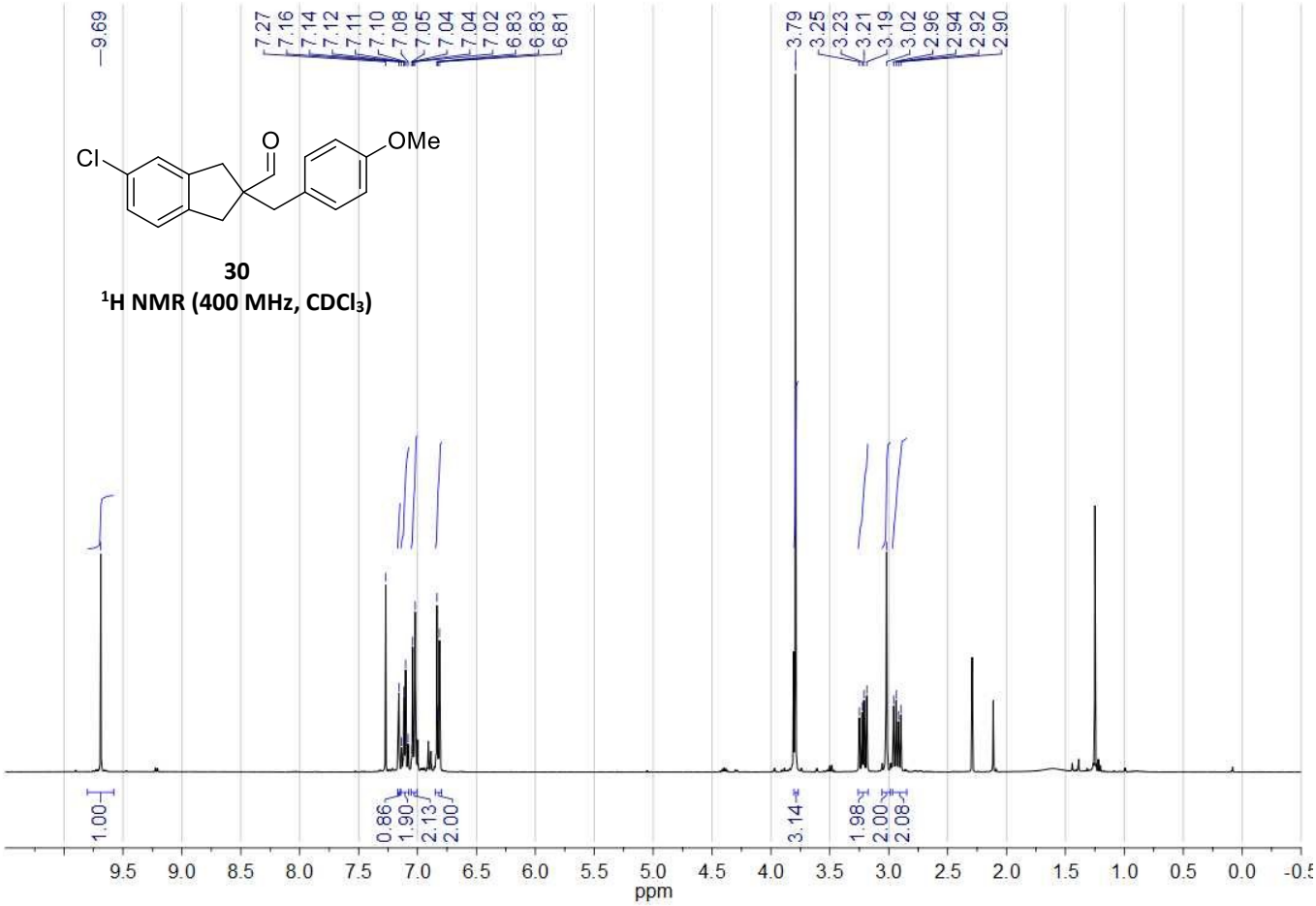
29

^{1}H NMR (400 MHz, $CDCl_3$)



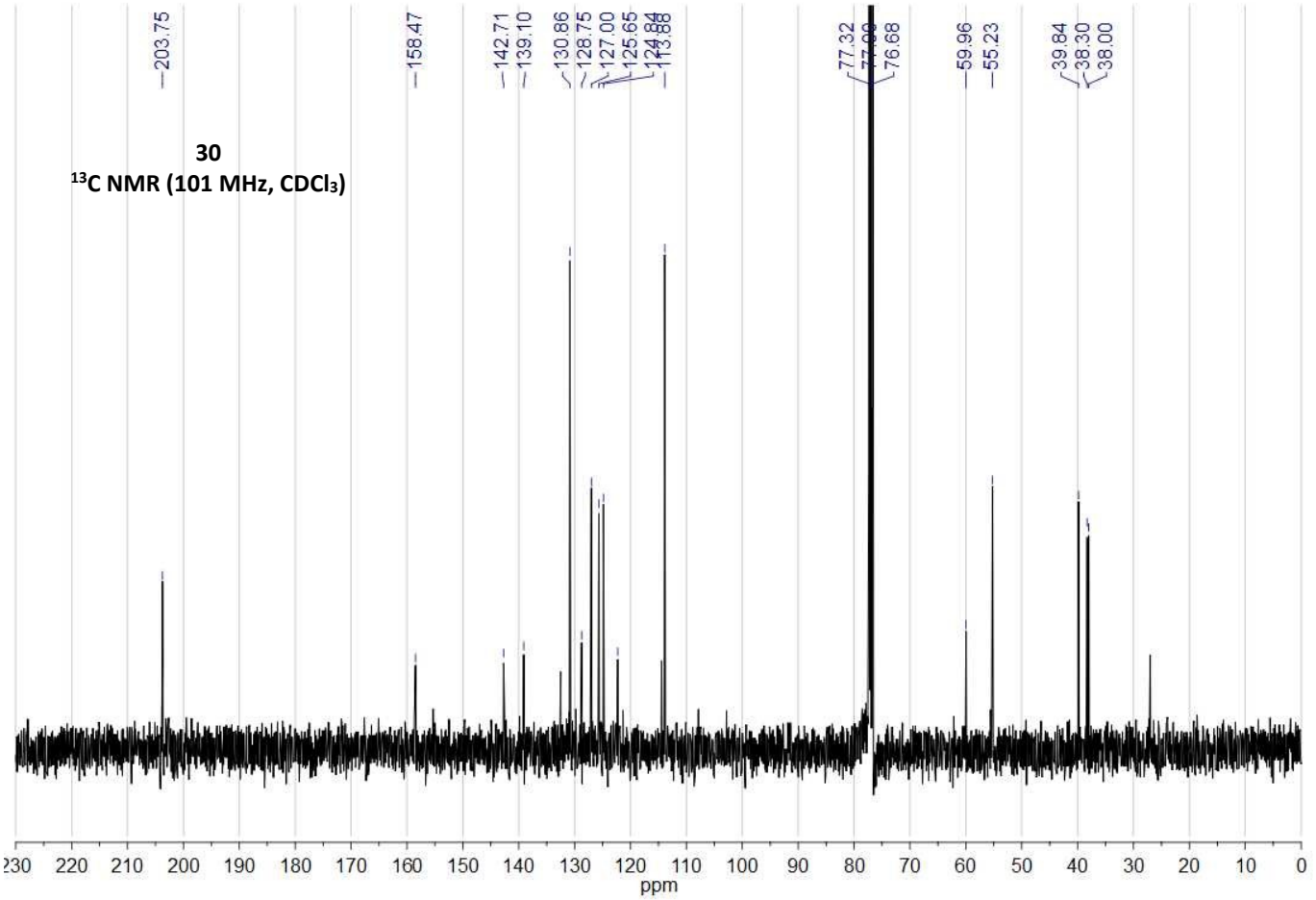
29

^{13}C NMR (101 MHz, $CDCl_3$)



30

^{1}H NMR (400 MHz, $CDCl_3$)



30

^{13}C NMR (101 MHz, $CDCl_3$)