Supplementary Information (SI) for ChemComm.

Controlled Synthesis of CD_2H-ketones

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General Information

Solvents were purchased from standard chemical suppliers (Fisher, Sigma-Aldrich, VWR, Fluorochem) and dried over molecular sieves and degassed by sparging with dry nitrogen. Other reagents were used as purchased. Reactions were performed under an atmosphere of dry nitrogen gas. Thin layer chromatography (TLC) was performed on Merck DFAlufoilien 60F254 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using anisaldehyde or potassium permanganate staining solutions as appropriate. Flash column chromatography was carried out using a CombiFlash Nextgen 300+. Melting points are uncorrected. NMR spectra were recorded on a Bruker Avance III HD 500 MHz instrument. For ^{1}H NMR spectra, chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.26 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), br (broad), m (multiplet), app (apparent), quintq (quintet of quartets). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. For proton decoupled ^{13}C NMR spectra, chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.16 ppm). For proton-decoupled ^{19}F NMR spectra, chemical shifts (δ) are quoted in parts per million (ppm) downfield of $CFCl_3$, using residual protonated solvent as internal standard ($CFCl_3$ at 376.38 MHz with respect to tetramethylsilane at 400.00 MHz). High resolution mass spectra were recorded using electrospray ionization (ESI) techniques on a Thermo Scientific Exactive Orbitrap instrument.

Calculation of percentage di-deuteration and overall deuteration (mono +di).

We have particularly used ^{1}H NMR to determine the percentage of di-deuteration as well as overall deuteration in the synthesized molecules. ^{1}H NMR of the one proton ($-C(O)CD_2H$) in the proposed di-deuterated methyl ketone was expected to show a quintet around 1.5 - 2.5 ppm through coupling with the two geminal deuterium atoms. If the reaction would yield a mono-deuterated methyl ketone, the ^{1}H NMR of the two protons on $-C(O)CDH_2$ would show a triplet around 1.5 - 2.5 ppm through coupling with the one geminal deuterium atom. In case of no deuteration and only proton capture, $-C(O)CH_3$ of the methyl ketone would show as a singlet on its ^{1}H NMR spectrum. A similar splitting pattern was also observed in the ^{13}C NMR of the synthesized molecules which has elaboratively been assigned for **3c** on page 24. However, in the ^{13}C NMR, the triplet corresponding to $-C(O)CDH_2$ and the singlet corresponding to $-C(O)CH_3$ were not very clearly defined for many of the examples as expected for very small amounts of these isotopologues.

As expected, we mostly observed a combination of a singlet (integration = x), a triplet (integration = y) and a quintet (integration = z) corresponding to the non-deuterated, mono-deuterated and di-deuterated methyl ketones. To calculate their molar ratios, the relative integrations were corrected for the number of protons in their corresponding signals, e.g., $-C(O)CH_3 : -C(O)CDH_2 : -C(O)CD_2H = x/3 : y/2 : z/1$. These ratios were then used to calculate the relevant percentages as follows;

% di-deuteration = $(z/1)/(x/3 + y/2 + z/1)*100$

% overall deuteration (mono + di) = $(y/2 + z/1)/(x/3 + y/2 + z/1)$

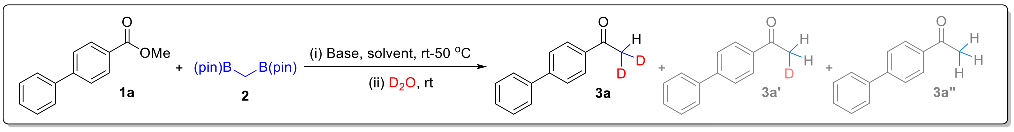
We also confirmed using HRMS and ^{13}C NMR that the amount of CD_3 compound present was minimal. In each case this was shown to be < 5%

Di-deuterative coupling of non-enolizable esters with geminal bis(boron) compounds

Optimization of dideuteration for non-enolizable esters.

Methyl 4'-phenylbenzoate (**1a**, 0.085 g, 0.40 mmol) was initially used to optimize conditions for di-deuteration. Bis[(pinacolato)boryl]methane (**2**, 2 equiv.) as bis(boron) derivative and sodium bis(trimethylsilyl)amide (NaHMDS, 2 equiv.) as base were used in anhydrous THF to generate the bis(boron) enolate which was then trapped with deuterium oxide (D_2O, 3 equiv.). The reaction worked as expected to yield the ketone **3a** in 47% isolated yield with 66% dideuteration (CD_2H) and more than 95% overall deuteration (D) (Table 1, entry 1). To improve on di-deuteration percentage, a number of trials were performed with the same set of reagents. Decreasing the relative amounts of both the boron reagent **2**, and NaHMDS to 1 equivalent reduced the conversion along with the deuteration ratios (Table 1, entry 2). The deuterium installed on α-position to the carbonyl might potentially be exchangeable in the presence of excess base and trace moisture which might be present in the solvent used, leading to lower deuteration ratios. Clearly, the way to improved di-deuteration was through minimizing the amount of solvent as well as the base used. As expected, we observed better deuteration with 1 mL THF and reduced base equivalents (Table 1, entry 4). Further decrease in the amount of THF (0.5 mL), and an increase in deuterium oxide equivalents (10 equivalents) intensified the overall deuteration to as high as 99% (Table 1, entry 5). Continuous increase in the amount of D_2O up till 10 equivalents confirmed an increase in di-deuteration (Table 1, entry 6-8), however, there wasn't any significant change on di-deuteration with further increase in the amount of D_2O. Reaction in toluene resulted in similar isolated yields, whereas a reaction with LiHMDS as base led to better isolated yields but reduced di-deuteration (Table 1, entry 9-10). In an attempt to trap the trace amount of moisture which might be present in the solvent used, powdered molecular sieves (4Å) were used as additives. This almost completely stopped the reaction potentially because the base was not able to function in the presence of molecular sieves, leading to no deuteration at all with 12% overall yield of the non-deuterated ketone (Table 1, entry 11). Replacing D_2O with deuterated methanol (CD_3OD) also resulted in the synthesis of the expected di-deuterated methyl ketone (**3a**), however with marginally lower ratios of deuteration (Table 1, entry 12). For further experimentations, we standardized the reaction conditions to the one with the best di-deuteration percentage and moderate conversions, i.e., 1.5 equivalent NaHMDS, 2.0 equivalent bis[(pinacolato)boryl]methane in 0.3 mL anhydrous THF and using 10 equivalent of D_2O as deuterium source (Table 1, entry 8).

Table 1: Standardization for dideuteration of non-enolizable esters.



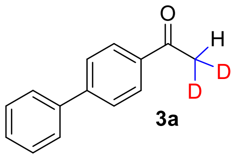
Entry No.	NaHMDS (equiv.)	2 (equiv.)	THF (mL)	D_2O (equiv.)	% Yield	Deuteration (%CD_2H, %D)
1	2.5	2.0	2.0	3	47	66%, >95%
2	1.0	1.0	2.0	3	24	60%, 84%
3	1.5	1.5	2.0	3	41	89%, 97%
4	1.5	2.0	1.0	3	53	>83%, >97%
5	1.5	1.5	0.5	10	58	>86%, 99%
6	1.5	2.0	0.3	3	57	>77%, 97%
7	1.5	2.0	0.3	5	55	>87%, 99%
8	1.5	2.0	0.3	10	62	94%, >99%
9[a]	1.5	2.0	0.3	10	61	87%, >98%
10[b]	1.5	2.0	0.3	10	77	80%, 98%
11[c]	1.5	2.0	0.3	10	12	No deuteration
12[d]	1.5	2.0	0.3	10	65	89%, >96%

Unless otherwise stated, reactions were performed with bis[(pinacolato)boryl]methane in the presence of NaHMDS in anhydrous THF and D_2O as deuterium source. [a]Performed in 0.3 mL toluene instead of THF; [b]1.5 equiv. LiHMDS was used as base instead of NaHMDS; [c]4Å molecular sieves were used as additives; [d]10 equiv. CD_3OD was used as deuterium source instead of D_2O.

General Procedure A: Di-deuterative coupling of non-enolizable esters.

Ester (0.40 mmol) and geminal bis(boron) compound (0.80 mmol) were mixed under nitrogen and dissolved in THF (0.3 mL). Sodium bis(trimethylsilyl)amide (0.60 mmol, 2M in THF) was added and the mixture heated to 50 °C for 15 minutes. After this period the mixture was cooled to room temperature and deuterium oxide (4.0 mmol) was added dropwise. After stirring for 15 minutes at room temperature the mixture was eluted through a short pad of silica gel with sodium sulfate over it (Et_2O) and concentrated. The crude mixture was then purified by flash column chromatography.

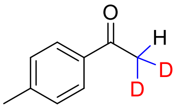
1-([1,1'-biphenyl]-4-yl)ethan-1-one-2,2-d_2 (3a)



3a

This compound was prepared using General Procedure A using Methyl 4-phenylbenzoate (0.085 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as a white solid, Melting point = 118-121 °C; (0.049 g, 62%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:9:148, >99% deuteration, 94% di-deuteration); R_f = 0.51 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.65 – 7.61 (m, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.43 – 7.38 (m, 1H), 2.61 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.9, 145.9, 140.0, 135.9, 129.1, 129.0, 128.4, 127.4, 127.3, 26.3 (quint, *J* = 19.4 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_{14}H_{11}D_2O$ $[M+H]^+$: 199.1092, found: 199.1089.

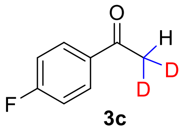
1-(*p*-tolyl)ethan-1-one-2,2-d_2 (3b)



3b

This compound was prepared using General Procedure A using Methyl 4-phenylbenzoate (0.060 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (2%) as eluent to yield the title compound as a colourless liquid (0.041 g, 75%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:6:106, >99% deuteration, >94% di-deuteration); R_f = 0.59 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 2.54 (quint, *J* = 2.2 Hz, 1H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.1, 144.0, 134.8, 129.4, 128.6, 26.2 (quint, *J* = 19.6 Hz), , 21.8; HRMS (ESI$^+$): Exact mass calculated for $C_9H_9D_2O$ $[M+H]^+$: 137.0935, found: 137.0934.

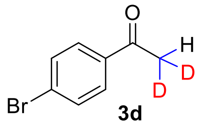
1-(4-fluorophenyl)ethan-1-one-2,2-d_2 (3c)



3c

This compound was prepared using General Procedure A using Ethyl 4-fluorobenzoate (0.067 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as a colourless liquid (0.025 g, 44%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:6:47, >98% deuteration, 87% di-deuteration); R_f = 0.54 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.12 (t, *J* = 8.9 Hz, 2H), 2.55 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 196.7, 165.9 (d, *J* = 254.6 Hz), 133.7 (d, *J* = 3.0 Hz), 131.1 (d, *J* = 9.3 Hz), 115.8 (d, *J* = 21.9 Hz), 26.2 (quint, *J* = 19.6 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ -105.33 (tt, *J* = 8.5, 5.4 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_8H_6D_2FO$ $[M+H]^+$: 141.0685, found: 141.0683.

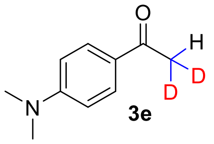
1-(4-bromophenyl)ethan-1-one-2,2-d$_2$ (3d)



3d

This compound was prepared using General Procedure A using Methyl 4-bromobenzoate (0.086 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (2%) as eluent to yield the title compound as an off-white solid, Melting point = 49-52 °C; (0.045 g, 56%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:8:52, >98% deuteration, 85% di-deuteration); R_f = 0.59 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 2.54 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.2, 135.9, 132.0, 129.9, 128.4, 26.2 (quint, *J* = 19.6 Hz),; HRMS (ESI$^+$): Exact mass calculated for $C_8H_6D_2{}^{79}BrO$ $[M+H]^+$: 200.9884, found: 200.9884.

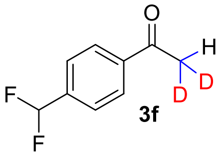
1-(4-(dimethylamino)phenyl)ethan-1-one-2,2-d$_2$ (3e)



3e

This compound was prepared using General Procedure A using Methyl 4-(dimethylamino)benzoate (0.072 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (6%) as eluent to yield the title compound as a white solid, Melting point = 100-103 °C; (0.046 g, 70%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:6:63, >98% deuteration, 90% di-deuteration); R_f = 0.26 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.1 Hz, 2H), 6.65 (d, *J* = 9.1 Hz, 2H), 3.06 (s, 6H), 2.48 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 196.6, 153.5, 130.6, 125.5, 110.7, 40.2, 25.6 (quint, *J* = 19.4 Hz),; HRMS (ESI$^+$): Exact mass calculated for $C_{10}H_{12}D_2NO$ $[M+H]^+$: 166.1201, found: 166.1200.

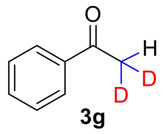
1-(4-(difluoromethyl)phenyl)ethan-1-one-2,2-d$_2$ (3f)



3f

This compound was prepared using General Procedure A using Methyl 4-(difluoromethyl)benzoate (0.074 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3.5%) as eluent to yield the title compound as a colourless liquid (0.050 g, 72%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:6:109, >99% deuteration, 94% di-deuteration); R_f = 0.46 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 6.69 (t, *J* = 56.1 Hz, 1H), 2.60 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.6, 139.0 (t, *J* = 1.7 Hz), 138.6 (t, *J* = 22.4 Hz), 128.7, 126.0 (t, *J* = 6.0 Hz), 114.1 (t, *J* = 239.8 Hz), 26.4 (quint, *J* = 19.6 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ -112.30 (d, *J* = 56.2 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_9H_7D_2F_2O$ $[M+H]^+$: 173.0747, found: 173.0747.

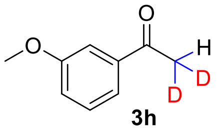
1-phenylethan-1-one-2,2-d$_2$ (3g)



3g

This compound was prepared using General Procedure A using Ethyl benzoate (0.060 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as a viscous pale liquid (0.027 g, 55%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:12:107, >99% deuteration, 89% di-deuteration); R_f = 0.54 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 2.56 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.4, 137.2, 133.2, 128.7, 128.4, 26.2 (quint, J = 19.5 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_8H_7D_2O$ [M+H]$^+$: 123.0779, found: 123.0779. Data is in agreement with that reported in the literature[1]

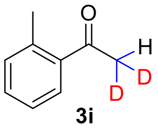
1-(3-methoxyphenyl)ethan-1-one-2,2-d$_2$ (3h)



3h

This compound was prepared using General Procedure A using Methyl 3-methoxybenzoate (0.066 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as a pale liquid (0.049 g, 80%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:5:87, 99% deuteration, 94% di-deuteration); R_f = 0.54 (Et_2O/ hexane (20%)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 7.49 (dd, J = 2.6, 1.6 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.11 (ddd, J = 8.2, 2.7, 1.0 Hz, 1H), 3.86 (s, 3H), 2.57 (quint, J = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.2, 159.9, 138.7, 129.7, 121.3, 119.8, 112.5, 55.6, 26.4 (quint, J = 19.5 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_9H_9D_2O_2$ [M+H]$^+$: 153.0885, found: 153.0884.

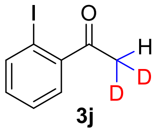
1-(*o*-tolyl)ethan-1-one-2,2-d$_2$ (3i)



3i

This compound was prepared using General Procedure A using Methyl 2-methylbenzoate (0.060 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (1.5%) as eluent to yield the title compound as a colourless oil (0.041 g, 76%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:12:130, >99% deuteration, 91% di-deuteration); R_f = 0.69 (Et_2O/ hexane (20%)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.7, 1.2 Hz, 1H), 7.38 (td, J = 7.5, 1.4 Hz, 1H), 7.28-7.23 (m, , 2H), 2.55 (quint, J = 2.2 Hz, 1H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 201.9, 138.6, 137.8, 132.2, 131.6, 129.5, 125.8, 29.2 (quint, J = 19.5 Hz), 21.7; HRMS (ESI$^+$): Exact mass calculated for $C_9H_9D_2O$ [M+H]$^+$: 137.0935, found: 137.0933.

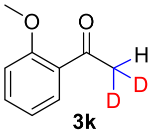
1-(2-iodophenyl)ethan-1-one-2,2-d$_2$ (3j)



3j

This compound was prepared using General Procedure A using Methyl 2-iodobenzoate (0.105 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (2%) as eluent to yield the title compound as a pale liquid (0.067 g, 68%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:13:204, >99% deuteration, 94% di-deuteration); R_f = 0.62 (Et_2O/ hexane (20%)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 7.9 Hz, 1H), 7.45 (dd, J = 7.7, 1.7 Hz, 1H), 7.39 (td, J = 7.6, 1.0 Hz, 1H), 7.10 (td, J = 7.6, 1.7 Hz, 1H), 2.56 (quint, J = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 201.9, 143.9, 140.9, 131.9, 128.4, 128.1, 91.0, 29.1 (quint, J = 19.6 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_8H_6D_2IO$ [M+H]$^+$: 248.9745, found: 248.9746.

1-(2-methoxyphenyl)ethan-1-one-2,2-d$_2$ (3k)

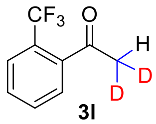


3k

This compound was prepared using General Procedure A using Methyl 2-methoxybenzoate (0.066 g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as a pale liquid (0.043 g, 71%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:12:73, 99% deuteration, 85% di-deuteration); R_f =

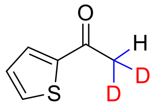
0.54 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.45 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.01 - 6.93 (m, 2H), 3.90 (s, 3H), 2.57 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 200.1, 159.0, 133.8, 130.4, 128.3, 120.6, 111.7, 55.6, 31.4 (quint, *J* = 19.6 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_9H_9D_2O_2$ [M+H]$^+$: 153.0885, found: 153.0883.

1-(2-(trifluoromethyl)phenyl)ethan-1-one-2,2-d$_2$ (3l)


3l

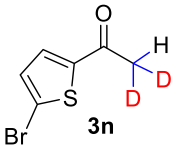
This compound was prepared using General Procedure A using Methyl 2-(trifluoromethyl)benzoate (0.081g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as a colourless liquid (0.053 g, 70%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:16:168, >99% deuteration, 91% di-deuteration); R_f = 0.54 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 2.55 (quint, *J* = 2.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 202.1, 140.6 (q, *J* = 1.9 Hz), 132.0 (q, *J* = 0.9 Hz), 130.3, 127.2, 126.9 (q, *J* = 32.4 Hz), 126.8 (q, *J* = 5.0 Hz), 123.7 (q, *J* = 273.5 Hz), 30.3 (quintq, *J* = 19.6, 1.9 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ -58.17 (s); HRMS (ESI$^+$): Exact mass calculated for $C_9H_6D_2F_3O$ [M+H]$^+$: 191.0653, found: 191.0651.

1-(thiophen-2-yl)ethan-1-one-2,2-d$_2$ (3m)


3m

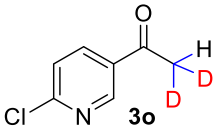
This compound was prepared using General Procedure A using Methyl 2-thiophene carboxylate (0.057g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as an orange liquid (0.030 g, 59%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:15:224, >99% deuteration, >93% di-deuteration); R_f = 0.51 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.63 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.12 (dd, *J* = 5.0, 3.8 Hz, 1H), 2.53 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 190.9, 144.7, 133.9, 132.6, 128.2, 26.6 (quint, *J* = 19.6 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_6H_5D_2OS$ [M+H]$^+$: 129.0343, found: 129.0343.

1-(5-bromothiophen-2-yl)ethan-1-one-2,2-d$_2$ (3n)


3n

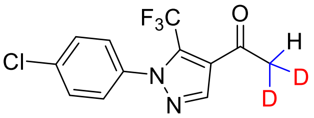
This compound was prepared using General Procedure A using Ethyl 5-bromothiophene-2-carboxylate (0.094g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3.5%) as eluent to yield the title compound as a off-white solid, Melting point = 90-93 °C; (0.052 g, 63%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:2:15, >94% deuteration, >83% di-deuteration); R_f = 0.49 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 4.0 Hz, 1H), 7.10 (d, *J* = 4.0 Hz, 1H), 2.47 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 189.8, 146.1, 132.6, 131.4, 122.9, 25.9 (quint, *J* = 19.7 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_6H_4D_2BrOS$ [M+H]$^+$: 206.9448, found: 206.9449.

1-(6-chloropyridin-3-yl)ethan-1-one-2,2-d$_2$ (3o)


3o

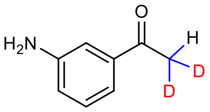
This compound was prepared using General Procedure A using Ethyl 6-chloronicotinate (0.074g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (5%) as eluent to yield the title compound as a white solid, Melting point = 99-102 °C; (0.040 g, 64%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:3:18, >95% deuteration, 82% di-deuteration); R_f = 0.32 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, J = 2.4 Hz, 1H), 8.19 (dd, J = 8.3, 2.4 Hz, 1H), 7.44 (dd, J = 8.3, 0.7 Hz, 1H), 2.59 (quint, J = 2.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 195.6, 155.9, 150.3, 138.2, 131.3, 124.7, 26.4 (quint, J = 19.6 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_7H_5D_2ClNO$ $[M+H]^+$: 158.0342, found: 158.0341.

1-(1-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethan-1-one-2,2-d$_2$ (3p)


3p

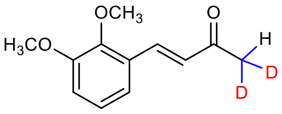
This compound was prepared using General Procedure A using Ethyl 1-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (0.127g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (10%) as eluent to yield the title compound as a off-white solid, Melting point = 79-82 °C; (0.056 g, 48%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:8:97, >99% deuteration, >91% di-deuteration); R_f = 0.26 (Et_2O/ hexane (30%)); ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 0.4 Hz, 1H), 7.49 (d, J = 8.9 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 2.54 (quint, J = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 191.2, 141.9, 137.8, 136.2, 131.4 (q, J = 40.5 Hz), 129.6, 127.2, 127.2, 124.9, 119.2 (q, J = 271.5 Hz), 29.3 (quint, J = 19.6 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ -55.31 (s); HRMS (ESI$^+$): Exact mass calculated for $C_{12}H_7D_2ClF_3N_2O$ $[M+H]^+$: 291.0481, found: 291.0479.

1-(3-aminophenyl)ethan-1-one-2,2-d$_2$ (3q)


3q

This compound was prepared using General Procedure A using Methyl 3-aminobenzoate (0.060g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using EtOAc/hexane (18%) as eluent to yield the title compound as a off-white solid, Melting point = 90-93 °C; (0.017 g, 31%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:8:40, 98% deuteration, 82% di-deuteration); R_f = 0.42 (EtOAc/hexane (50%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (ddd, J = 7.7, 1.5, 1.0 Hz, 1H), 7.27-7.21 (m, 2H), 6.87 (ddd, J = 7.9, 2.5, 1.0 Hz, 1H), 3.80 (s, 2H), 2.53 (quint, J = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.7, 146.8, 138.4, 129.6, 119.8, 119.1, 114.1, 26.4 (quint, J = 19.5 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_8H_8D_2NO$ $[M+H]^+$: 138.0888, found: 138.0888.

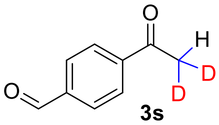
(*E*)-4-(2,3-dimethoxyphenyl)but-3-en-2-one-1,1-d$_2$ (3r)


3r

This compound was prepared using General Procedure A using Methyl (*E*)-3-(2,3-dimethoxyphenyl)acrylate (0.089g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (4%) as eluent to yield the title compound as a wine red liquid (0.053 g, 64%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:9:134, >99% deuteration, 93% di-deuteration);

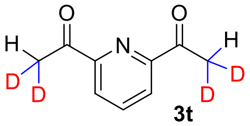
R_f = 0.42 (Et_2O/hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 16.5 Hz, 1H), 7.16 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.94 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.71 (d, *J* = 16.5 Hz, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 2.35 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 199.1, 153.2, 148.6, 138.2, 128.7, 128.7, 124.4, 119.0, 114.3, 61.5, 55.9, 26.8 (quint, *J* = 19.5 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_{12}H_{13}D_2O_3$ [M+H]$^+$: 209.1147, found: 209.1146.

4-(acetyl-2,2-d$_2$)benzaldehyde (3s)


3s

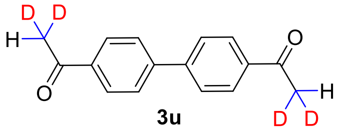
This compound was prepared using General Procedure A using Methyl 4-formylbenzoate (0.066g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in THF (0.3 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (6.5%) as eluent to yield the title compound as a white solid, Melting point = 199-202 °C; (0.020 g, 33%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:3:17, >95% deuteration, 81% di-deuteration); R_f = 0.39 (Et_2O/ hexane (40%)); ^1H NMR (500 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 2.63 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.6, 191.7, 141.4, 139.2, 129.9, 128.9, 26.6 (quint, *J* = 19.5 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_9H_7D_2O_2$ [M+H]$^+$: 151.0728, found: 151.0729.

1,1'-(pyridine-2,6-diyl)bis(ethan-1-one-2,2-d$_2$) (3t)


3t

This compound was prepared using General Procedure A using Dimethyl 2,6-pyridinedicarboxylate (0.078g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.428 g, 1.60 mmol), Sodium bis(trimethylsilyl)amide (0.6 mL, 2M in THF, 1.20 mmol) and Deuterium oxide (0.144 mL, 8.0 mmol) in THF (0.6 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as an off-white solid, Melting point = 78-81 °C; (0.065 g, 49%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:6:28, >97% deuteration, 80% di-deuteration); R_f = 0.51 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.8 Hz, 2H), 7.99 (t, *J* = 7.8 Hz, 1H), 2.76 (quint, *J* = 2.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 199.7, 152.9, 138.1, 124.9, 25.2 (quint, *J* = 19.6 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_9H_6D_4NO_2$ [M+H]$^+$: 168.0963, found: 168.0960.

1,1'-([1,1'-biphenyl]-4,4'-diyl)bis(ethan-1-one-2,2-d$_2$) (3u)


3u

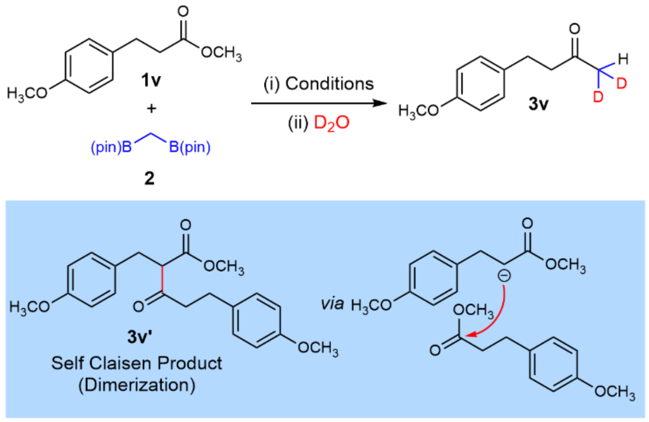
This compound was prepared using General Procedure A using Dimethyl biphenyl-4,4'-dicarboxylate (0.108g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.428 g, 1.60 mmol), Sodium bis(trimethylsilyl)amide (0.6 mL, 2M in THF, 1.20 mmol) and Deuterium oxide (0.144 mL, 8.0 mmol) in THF (0.6 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (5%) as eluent to yield the title compound as a pale solid, Melting point = 193-196 °C; (0.055 g, 57%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:11:130, >99% deuteration, >91% di-deuteration); R_f = 0.34 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.6 Hz, 4H), 7.72 (d, *J* = 8.6 Hz, 4H), 2.61 (quint, *J* = 2.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.8, 144.5, 136.7, 129.1, 127.6, 26.3 (quint, *J* = 19.6 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_{16}H_{11}D_4O_2$ [M+H]$^+$: 243.1323, found: 243.1325.

Di-deuterative coupling of enolizable esters with geminal bis(boron) compounds

Standardization for di-deuteration of enolizable esters.

The challenge that we anticipated with enolizable esters in the presence of a base like NaHMDS was the formation of a self-Claisen type side product **3v'** that might hamper the overall yield of the expected ketone. At the outset, methyl 3-(4-methoxyphenyl) propanoate (**1v**) was subjected to the standard reaction conditions which failed to generate results similar to those with the non-enolizable esters leading to only 15% yield of the dideuterated ketone **3v** with 84% dideuteration (Table 2, entry 1). Formation of self-Claisen product in the presence of excess base was expected to account for lower yields of the expected product, however, reducing NaHMDS loading to 1 equivalent completely put out any synthesis of the dideuterated ketone (Table 2, entry 2). Clearly, the reaction conditions prefered self-Claisen product with lower base concentrations. Next, we kept NaHMDS loading at 1.5 equivalent but doubled the amount of bis(boron) reagent (**2**) which led to 27% isolated yield of the ketone having 83% dideuteration, while 2 equivalent NAHMDS in 0.6 mL THF furnished 18% of the expected product with similar dideuteration (Table 2, entry 3,4). In order to avoid the formation of self-Claisen product, the base was changed to LiTMP (2 equiv.) to deprotonate **2** only and not the enolizable ester which surprisingly increased the isolated yield of the expected ketone to 73% but the dideuteration was significantly diminished to just 37% (Table 2, entry 5). To enhance the percentage of dideuteration, a number of changes in the amounts of LiTMP, THF and D_2O were made including addition of anhydrous $MgSO_4$ to soak up traces of H_2O if present, but nothing could bring about any significant improvements (Table 2, entry 6-8). These continuous failures on improving the dideuteration with LiTMP prompted an inspection on the effects of LiTMP on dideuteration of non-enolizable esters. Methyl 2-methylbenzoate (**1i**) was subjected to di-deuterative coupling in the presence of 2 equivalent LiTMP, which resulted in the synthesis of **3i** (65%) with 38% dideuteration and 75% overall deuteration (91% (CD_2H) and 99% (D) when performed with NaHMDS). Evidently, LiTMP was a great option to avoid self-Claisen reaction, but definitely not very good for deuteration/di-deuteration. In hope to react most of the base for deprotonation of the boron reagent before addition of ester, we tried delayed addition of the ester solution to an already stirred solution of **2** and NaHMDS in THF, but still the results were not very encouraging (Table 2, entry 9). Finally, a change of solvent to anhydrous toluene combined with delayed addition of ester assisted the synthesis of the target ketone in 45% isolated yield with 86% di-deuteration (Table 2, entry 10). These reaction conditions were locked in for further substrate scope of enolizable esters.

Table 2: Standardization for di-deuteration of enolizable esters.

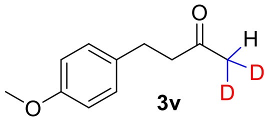


Entry No.	Deviation from Standard Conditions	% Yield	Deuteration (%CD_2H, %D)
1	Standard Conditions	15	84%, >93%
2	1 equiv. NaHMDS	-	-
3	4 equiv. **2**	27	83%, >96%
4	4 equiv. **2**, 2 equiv. NaHMDS, 0.6 mL THF	18	83%, >93%
5	2 equiv. LiTMP, 2mL THF	73	37%, 80%
6	1.5 equiv. LiTMP, 0.9mL THF	44	35%, >68%
7	2 equiv. LiTMP, 0.9mL THF, 100 equiv. D_2O	78	31%, >74%
8	2 equiv. LiTMP, 2 equiv. $MgSO_4$, 0.9 mL THF, 60 equiv. D_2O	67	35%, 77%
9	0.4 mL THF, delayed addition of ester	8	69%, >82%
10	0.6 mL Toluene, delayed addition of ester	45	>86%, >99%

General Procedure B: Di-deuterative coupling of enolizable esters.

Geminal bis(boron) compound (0.80 mmol) was dissolved in Toluene (0.3 mL) under nitrogen. Sodium bis(trimethylsilyl)amide (0.60 mmol, 2M in THF) was added and the mixture was heated to 50 °C for 10 minutes. After this period, a solution of ester (0.40 mmol) in Toluene (0.3 ml) was added and stirred at 50 °C for 15 minutes. On cooling the mixture to room temperature, deuterium oxide (4.0 mmol) was added dropwise and stirred for another 15 minutes. The reaction mixture was then eluted through a short pad of silica gel with sodium sulfate over it (Et_2O) and concentrated. The crude mixture was then purified by flash column chromatography.

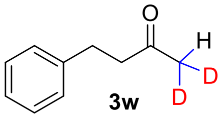
4-(4-methoxyphenyl)butan-2-one-1,1-d$_2$ (3v)



3v

This compound was prepared using General Procedure B using Methyl 3-(4-methoxyphenyl) propanoate (0.078g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in Toluene (0.6 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as a colourless liquid (0.032 g, 45%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:15:100, >99% deuteration, >86% di-deuteration); R_f = 0.49 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.72 (t, *J* = 7.4 Hz, 2H), 2.09 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 208.3, 158.1, 133.1, 129.3, 114.0, 55.3, 45.5, 29.7 (quint, *J* = 19.5 Hz), 28.9; HRMS (ESI$^+$): Exact mass calculated for $C_{11}H_{12}D_2NaO_2$ [M+Na]$^+$: 203.1017, found: 203.1018.

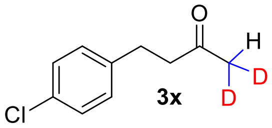
4-phenylbutan-2-one-1,1-d$_2$ (3w)



3w

This compound was prepared using General Procedure B using Methyl 3-phenylpropionate (0.066g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in Toluene (0.6 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (2%) as eluent to yield the title compound as a colourless liquid (0.017 g, 28%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:8:61, 99% deuteration, >87% di-deuteration); R_f = 0.60 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 - 7.23 (m, 1H), 7.19 - 7.14 (m, 1H), 2.88 (t, *J* = 7.6 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.08 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 208.1, 141.1, 128.6, 128.4, 126.2, 45.2, 29.8, 29.6 (quint, *J* = 19.4 Hz); HRMS (ESI$^+$): Exact mass calculated for $C_{10}H_{11}D_2O$ [M+H]$^+$: 151.1092, found: 151.1091.

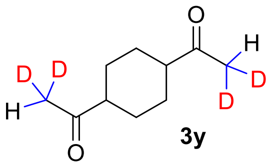
4-(4-chlorophenyl)butan-2-one-1,1-d$_2$ (3x)



3x

This compound was prepared using General Procedure B using Methyl 3-(4-chlorophenyl) propanoate (0.079g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.214 g, 0.80 mmol), Sodium bis(trimethylsilyl)amide (0.3 mL, 2M in THF, 0.60 mmol) and Deuterium oxide (0.072 mL, 4.0 mmol) in Toluene (0.6 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as a colourless liquid (0.027 g, 37%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:14:76, 99% deuteration, >83% di-deuteration); R_f = 0.50 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.73 (t, *J* = 7.4 Hz, 2H), 2.10 (quint, *J* = 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 207.7, 139.6, 131.9, 129.8, 128.7, 45.0, 29.7 (quint, *J* = 19.5 Hz), 29.1; HRMS (ESI$^+$): Exact mass calculated for $C_{10}H_{10}D_2ClO$ [M+H]$^+$: 185.0702, found: 185.0702.

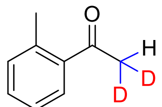
1,1'-(cyclohexane-1,4-diyl)bis(ethan-1-one-2,2-d$_2$) (3y)



3y

This compound was prepared using General Procedure B using Dimethyl cyclohexane-1,4-dicarboxylate (0.080g, 0.40 mmol), Bis[(pinacolato)boryl]methane (0.428 g, 1.60 mmol), Sodium bis(trimethylsilyl)amide (0.6 mL, 2M in THF, 1.20 mmol) and Deuterium oxide (0.144 mL, 8.0 mmol) in Toluene (1.2 mL total). The compound was purified by flash column chromatography using EtOAc/hexane (14%) as eluent to yield the title compound as a white solid, Melting point = 54-57 °C; (0.033 g, 48%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:19:227, >99% deuteration, 92% di-deuteration); R_f = 0.36 (EtOAc/hexane (20%)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 – 2.26 (m, 2H), 2.11 (quint, *J* = 2.2 Hz, 1H), 2.01 (app d, *J* = 7.2 Hz, 4H), 1.40 – 1.29 (m, 4H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 211.6, 50.6, 27.8 (quint, *J* = 19.5 Hz), 27.6; HRMS (ESI$^+$): Exact mass calculated for $C_{10}H_{13}D_4O_2$ [M+H]$^+$: 173.1480, found: 173.1478.

Gram Scale Synthesis of 1-(*o*-tolyl)ethan-1-one-2,2-d$_2$ (3i).



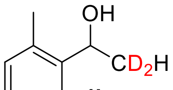
3i

This compound was prepared using General Procedure A using Methyl 2-methylbenzoate (1.20 g, 8.0 mmol), Bis[(pinacolato)boryl]methane (4.28 g, 16.0 mmol), Sodium bis(trimethylsilyl)amide (6.0 mL, 2M in THF, 12.0 mmol) and Deuterium oxide (1.44 mL, 80.0 mmol) in THF (6.0 mL total). The compound was purified by flash column chromatography using Et_2O/hexane (1.5%) as eluent to yield the title compound as a colourless oil (0.708 g, 65 %, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:18:267, >99% deuteration, 93.4% di-deuteration); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.40 (td, *J* = 7.6, 1.4 Hz, 1H), 7.31-7.25 (m, , 2H), 2.57 (quint, *J* = 2.2 Hz, 1H), 2.56 (s, 3H).

Sodium borohydride mediated reduction of di-deuterated methyl ketone.[2]

To an oven dried round bottom flask equipped with a magnetic stir bar was added di-deuterated 2'-methylacetophenone followed by methanol. The mixture was cooled to 0 °C in an ice bath followed by addition of $NaBH_4$. The reaction was monitored by TLC until complete consumption of the starting material was observed. Aqueous NH_4Cl was added and the reaction mixture was then extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ followed by solvent removal under reduced pressure to afford the desired alcohol. Crude mixture was then purified by flash column chromatography.

1-(*o*-tolyl)ethan-2,2-d$_2$-1-ol (4i)



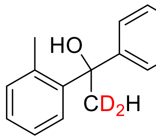
4i

This compound was prepared using Di-deuterated 2'-methylacetophenone (0.030g, 0.22 mmol, 93.4% di-deuterated), Sodium borohydride (0.007 g, 0.18 mmol) in Methanol (0.5 mL). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as a colourless liquid (0.019g, 63%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:39:394, >99% deuteration, 90.8% di-deuteration); R_f = 0.48 (Et_2O/ hexane (20%)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.7 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.18 (td, *J* = 7.4, 1.2 Hz, 1H), 7.15 – 7.12 (m, 1H), 5.13 (d, *J* = 6.2 Hz, 1H), 2.35 (s, 3H), 1.77 (s, 1H), 1.44 (dquint, *J* = 6.42, 1.99 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 143.9, 134.4, 130.5, 127.3, 126.5, 124.6, 66.9, 23.5 (quint, *J* = 19.4 Hz), 19.0; HRMS (ESI$^+$): Exact mass calculated for $C_9H_{10}D_2NaO$ [M+Na]$^+$: 161.0911, found: 161.0909.

Grignard addition to di-deuterated methyl ketone.[3]

To a solution of di-deuterated 2'-methylacetophenone in THF was added aryl magnesium bromide dropwise over 15 min at 0 °C. This reaction mixture was stirred at 0 °C for 2 h and then quenched by saturated aqueous ammonium chloride. The reaction mixture was then extracted with ethyl acetate and the organic layer was dried over $MgSO_4$ followed by solvent removal under reduced pressure. The product was purified by flash chromatography over silica gel.

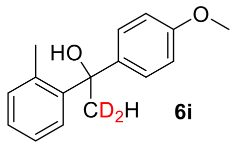
1-phenyl-1-(*o*-tolyl)ethan-2,2-d_2-1-ol (5i)



5i

This compound was prepared using Di-deuterated 2'-methylacetophenone (0.030g, 0.22 mmol, 93.4% di-deuterated) and Phenyl magnesium bromide (3.0 M in diethyl ether, 0.09 mL, 0.264 mmol) in THF (0.3 mL). The compound was purified by flash column chromatography using Et_2O/hexane (1.5%) as eluent to yield the title compound as a colourless liquid (0.035g, 74%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:21:267, >99% deuteration, 92.4% di-deuteration); R_f = 0.68 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.35 – 7.23 (m, 7H), 7.16 – 7.12 (m, 1H), 2.16 (s, 1H), 2.02 (s, 3H), 1.93 (s(broad quintet), 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 148.1, 144.7, 137.3, 132.6, 128.3, 127.8, 126.7, 126.1, 125.5, 125.4, 76.8, 31.7 (quint, *J* = 19.3 Hz), 21.5; HRMS (ESI$^+$): Exact mass calculated for $C_{15}H_{14}D_2NaO$ $[M+Na]^+$: 237.1224, found: 237.1228.

1-(4-methoxyphenyl)-1-(*o*-tolyl)ethan-2,2-d_2-1-ol (6i)



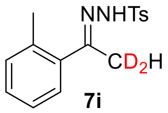
6i

This compound was prepared using Di-deuterated 2'-methylacetophenone (0.030g, 0.22 mmol, 93.4% di-deuterated) and 4-methoxyphenyl magnesium bromide (1.0 M in THF, 0.264 mL, 0.264 mmol) in THF (0.3 mL). The compound was purified by flash column chromatography using Et_2O/hexane (3%) as eluent to yield the title compound as a white solid, Melting point = 92-95 °C; (0.042g, 78%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:20:286, >99% deuteration, 93.2% di-deuteration); R_f = 0.53 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.27 – 7.20 (m, 4H), 7.12 – 7.09 (m, 1H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 2.10 (s, 1H), 2.00 (s, 3H), 1.89 (s (broad quintet), 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.4, 145.0, 140.3, 137.0, 132.5, 127.6, 126.7, 126.0, 125.5, 113.6, 76.5, 55.3, 31.3 (quint, *J* = 19.4 Hz), 21.5; HRMS (ESI$^+$): Exact mass calculated for $C_{16}H_{16}D_2NaO_2$ $[M+Na]^+$: 267.1330, found: 267.1333.

Hydrazone synthesis from di-deuterated methyl ketone.[4]

4-Toluenesulfonohydrazide was added to a hexane solution containing the carbonyl compound. The mixture was stirred at room temperature for 48 h. During this time the resulting tosylhydrazone may precipitate. The crude solid was filtered and washed with hexane (3 times) before purification by flash chromatography.

4-methyl-*N'*-(1-(*o*-tolyl)ethylidene-2,2-d_2)benzenesulfonohydrazide (7i)



7i

This compound was prepared using Di-deuterated 2'-methylacetophenone (0.050g, 0.37 mmol, 93.4% di-deuterated) and *p*-Toluenesulfonyl hydrazide (0.065 g, 0.35 mmol) in Hexane (1.5 mL). The compound was purified by flash column chromatography using Et_2O/hexane (7%) as eluent to yield the title compound as a off-white solid, Melting point = 139-142 °C; (0.084g, 75%, $-CH_3$:$-CH_2D$:$-CD_2H$ = 1:14:127, >99% deuteration, 89.4% di-deuteration); Diastereomeric Ratio = 94 : 6; R_f = 0.22 (Et_2O/ hexane (20%)); ^1H NMR (500 MHz, Acetone D_6) δ 9.30 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.13 (m, 4H), 2.39 (s, 3H), 2.18 (quint, *J* = 2.3 Hz, 1H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, Acetone D_6) δ

156.9, 144.9, 140.4, 138.2, 136.9, 132.0, 130.6, 129.6, 129.3, 129.2, 126.9, 21.9, 21.0, 17.9 (quint, *J* = 19.6 Hz),; HRMS (ESI$^+$): Exact mass calculated for $C_{16}H_{17}D_2N_2O_2S$ [M+H]$^+$: 305.1293, found: 305.1291.

Stability studies of di-deuterated methyl ketones with varying pH.

Buffer solutions for pH 1, 5, 7, 10 and 12 were prepared using the following general methods:

pH 1 Buffer: Mixed 50 mL of 0.2 M potassium chloride (KCl) with 134 mL of 0.2 M hydrochloric acid (HCl)and made up the solution up to 200 mL using deionized water.

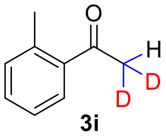
pH 5 Buffer: Mixed 357 mL of 0.1 M acetic acid (CH_3CO_2H) with 643 mL of 0.1 M sodium acetate (CH_3CO_2Na).

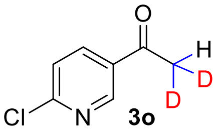
pH 7 Buffer: Dissolved 6.81 g of potassium dihydrogen phosphate (KH_2PO_4) in 291 mL of 0.1 M sodium hydroxide (NaOH) and made up the solution to 1 L using deionized water.

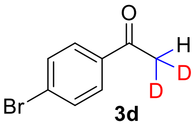
pH 10 Buffer: Mixed 100 mL of 0.05 M sodium hydrogen carbonate ($NaHCO_3$) in 21.4 mL of 0.1 M sodium hydroxide (NaOH) and made up the solution to 200 mL using deionized water.

pH 12 Buffer: Mixed 50 mL of 0.2 M potassium chloride (KCl) in 12 mL of 0.2 M sodium hydroxide (NaOH) and made up the solution to 200 mL using deionized water.

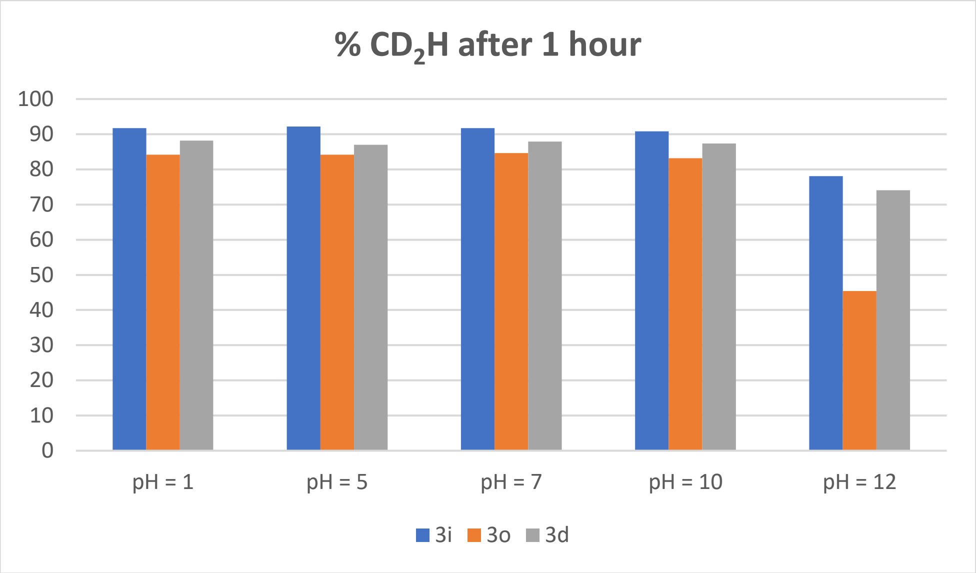
Gram scale reactions were performed to prepare **3i**, **3o** and **3d** in bulk. 25 mg of the di-deuterated ketone was dissolved in 0.2 mL of THF. Added 1 mL buffer solution and stirred at room temperature for 1 hour, 5 hours and 24 hours respectively. The solutions were then topped up with 3.5 mL Ethyl Acetate and stirred for 5 minutes. The top organic layer was then dried on rotary evaporator to get the organic compound which was then analysed via NMR. The results of these studies are reported as follows.

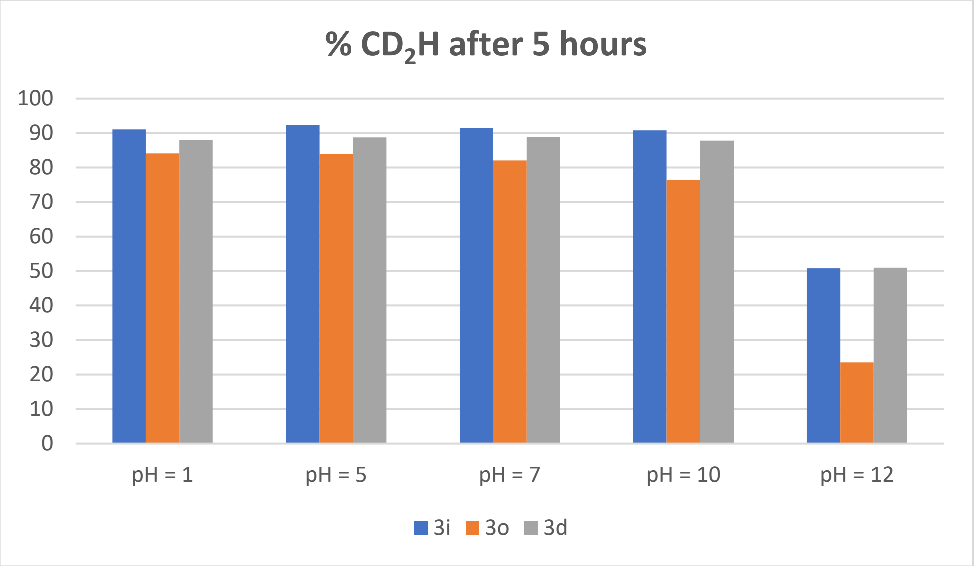
 **3i** CD_2H = 92.4%, $D+D_2$ = 99.3%	**1 hour** **(% CD_2H, % $D+D_2$)**	**5 hours** **(% CD_2H, % $D+D_2$)**	**24 hours** **(% CD_2H, % $D+D_2$)**
pH = 1	91.7, 99.1	91.1, 98.8	91.2, 99.0
pH = 5	92.2, 99.2	92.4, 99.3	91.0, 98.9
pH = 7	91.7, 99.2	91.5, 99.0	91.3, 99.1
pH = 10	90.8, 98.8	90.8, 99.1	88.0, 98.8
pH = 12	78.1, 97.9	50.8, 88.7	9.0, 39.8

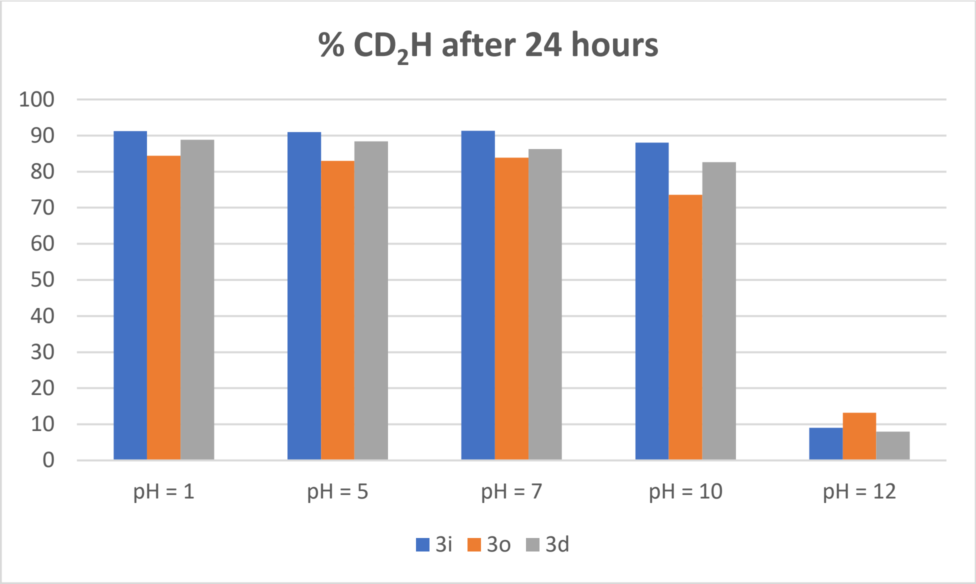
 **3o** CD_2H = 85.2%, $D+D_2$ = 98.6%	**1 hour** **(% CD_2H, % $D+D_2$)**	**5 hours** **(% CD_2H, % $D+D_2$)**	**24 hours** **(% CD_2H, % $D+D_2$)**
pH = 1	84.2, 97.8	84.1, 98.4	84.4, 98.2
pH = 5	84.2, 98.5	83.9, 98.2	83.0, 98.2
pH = 7	84.6, 98.6	82.1, 98.2	83.9, 98.4
pH = 10	83.2, 98.3	76.4, 97.2	73.6, 96.2
pH = 12	45.4, 71.9	23.5, 39.8	13.2, 26.5

 **3d** CD_2H = 88.9%, $D+D_2$ = 98.9%	**1 hour** **(% CD_2H, % $D+D_2$)**	**5 hours** **(% CD_2H, % $D+D_2$)**	**24 hours** **(% CD_2H, % $D+D_2$)**
pH = 1	88.2, 98.7	88.0, 98.7	88.8, 98.8
pH = 5	87.0, 98.5	88.8, 98.8	88.4, 98.7
pH = 7	87.9, 98.8	88.9, 98.8	86.3, 98.7
pH = 10	87.4, 98.6	87.8, 98.8	82.6, 98.2
pH = 12	74.1, 96.8	51.0, 88.8	8.0, 33.1

The data has been plotted to compare the change in di-deuteration for **3i**, **3o** and **3d** with change in pH after 1, 5 and 24 hours respectively.

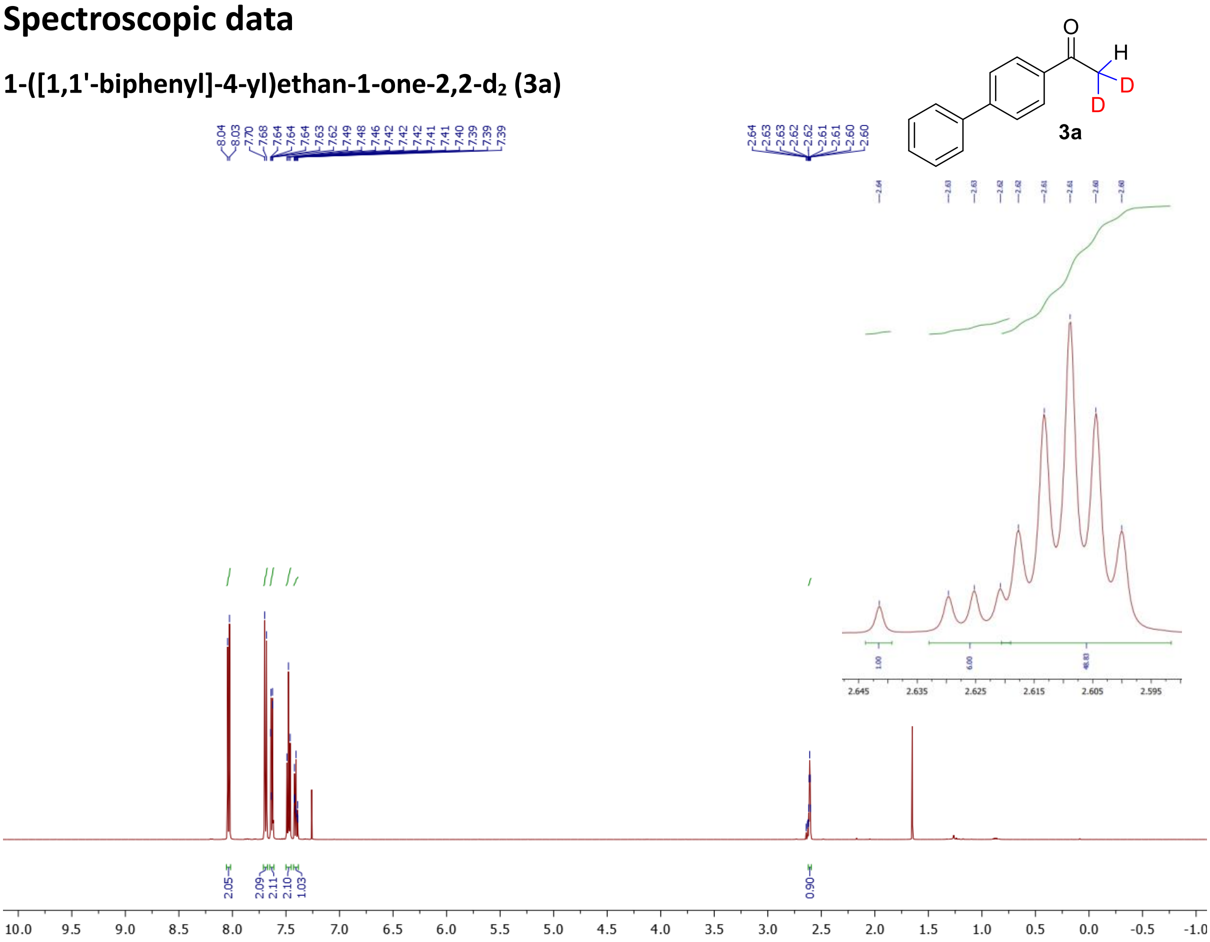


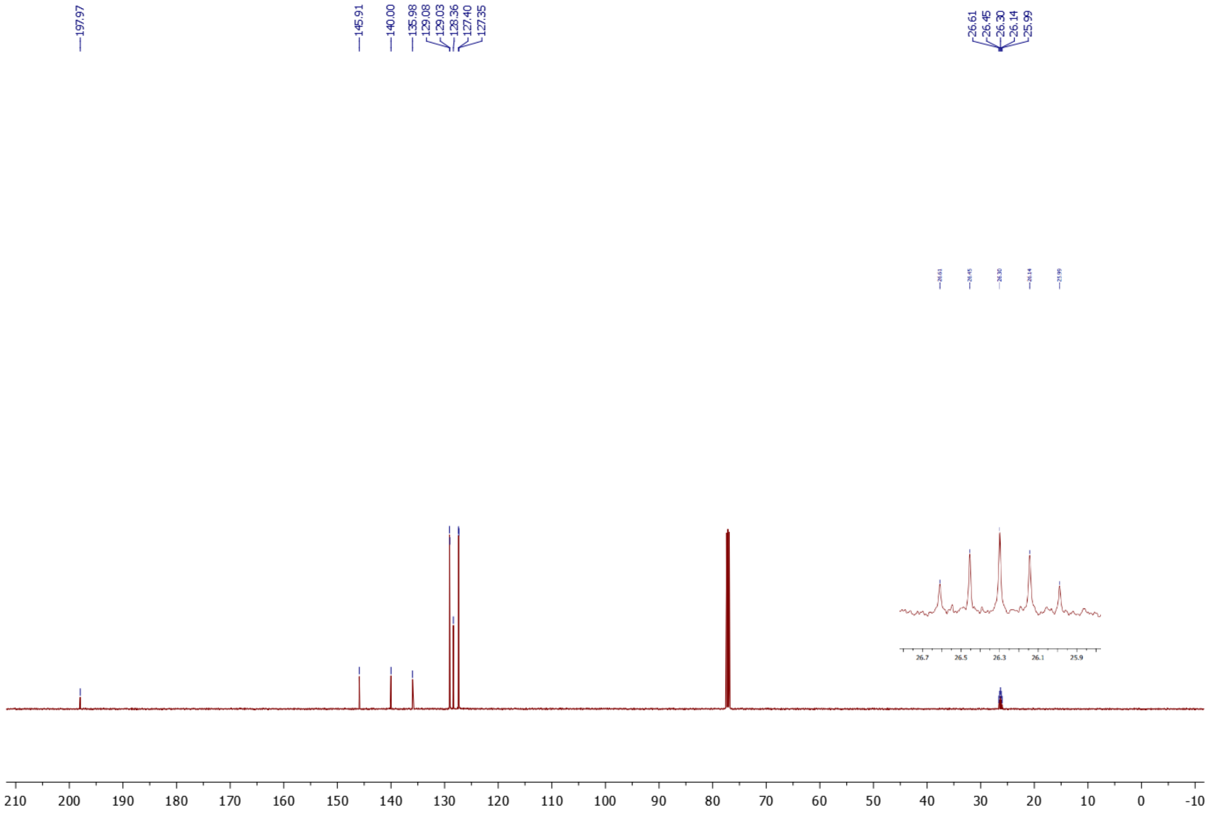



% CD$_2$H after 24 hours
100
90
80
70
60
50
40
30
20
10
0
pH = 1
pH = 5
pH = 7
pH = 10
pH = 12
3i
3o
3d

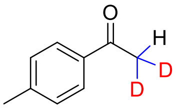
Spectroscopic data

1-([1,1'-biphenyl]-4-yl)ethan-1-one-2,2-d$_2$ (3a)

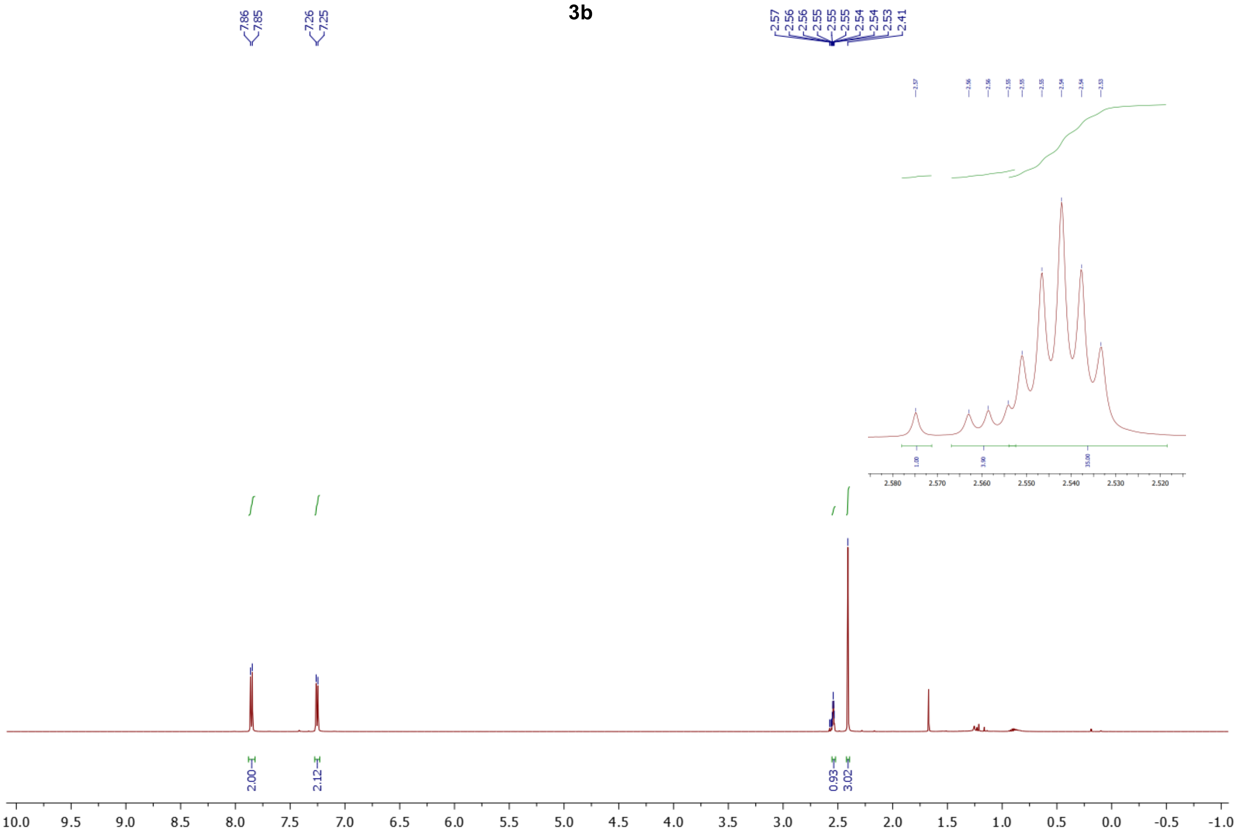

3a

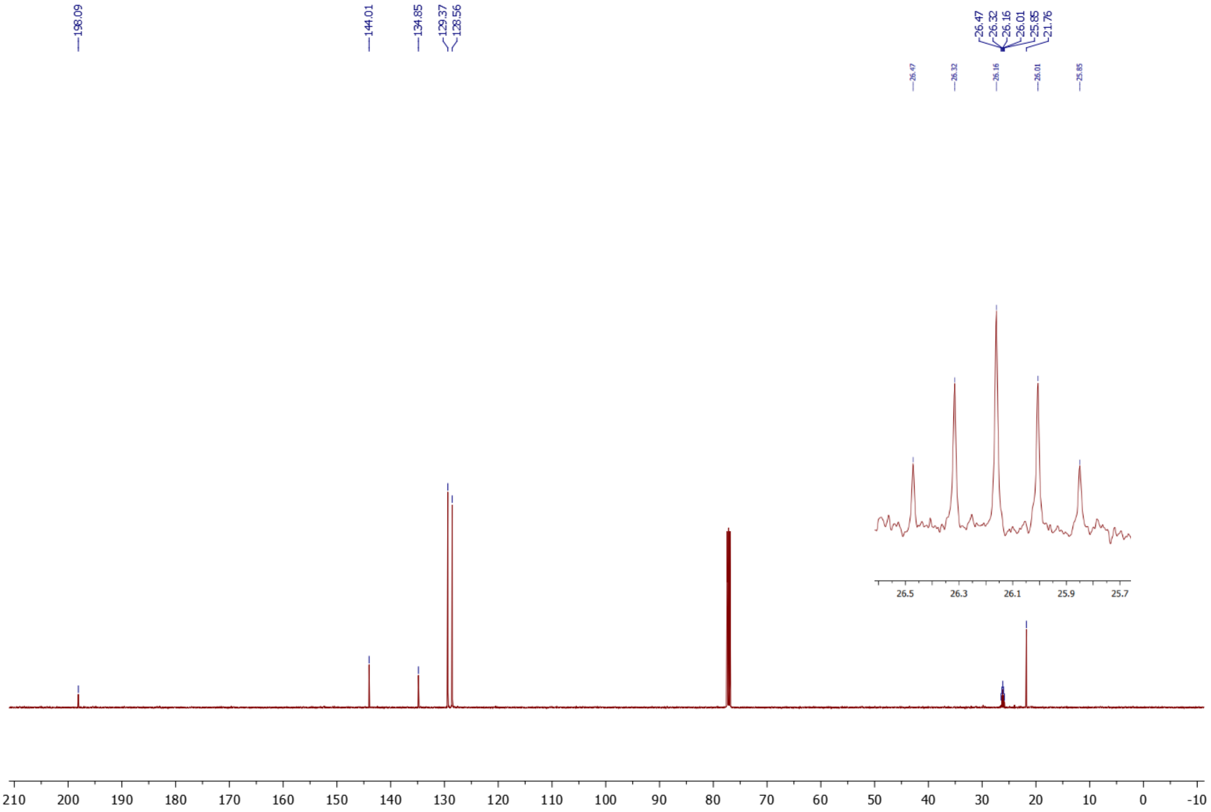


1-(*p*-tolyl)ethan-1-one-2,2-d$_2$ (3b)

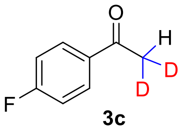


3b

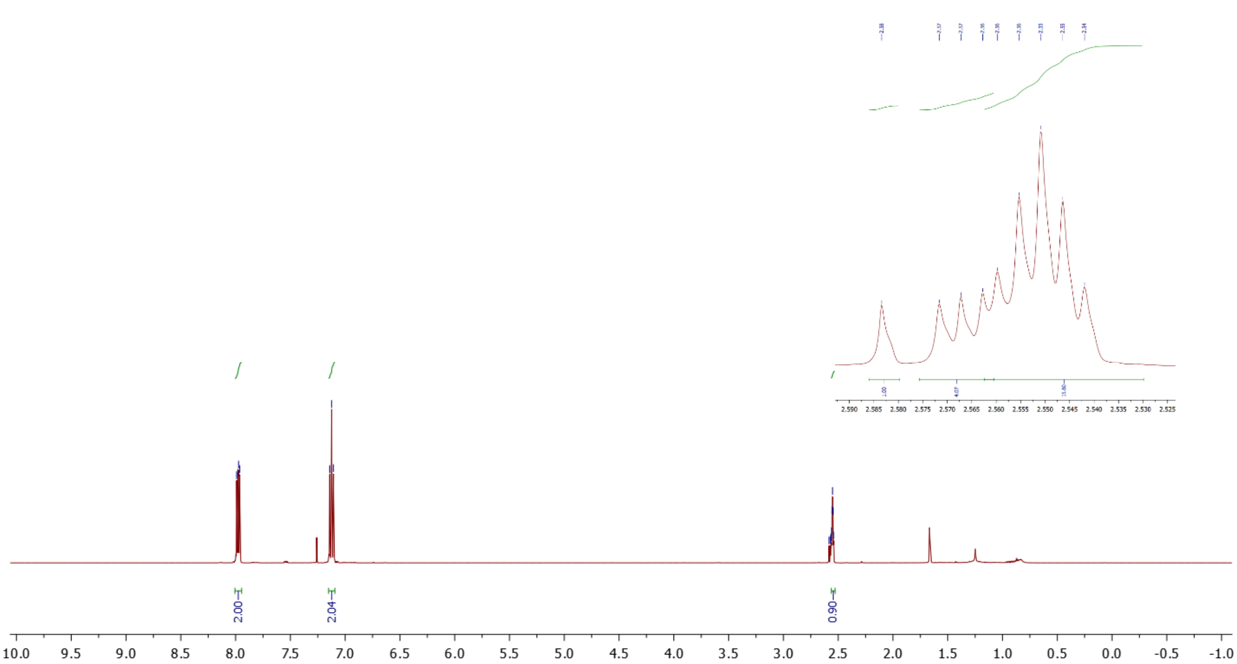


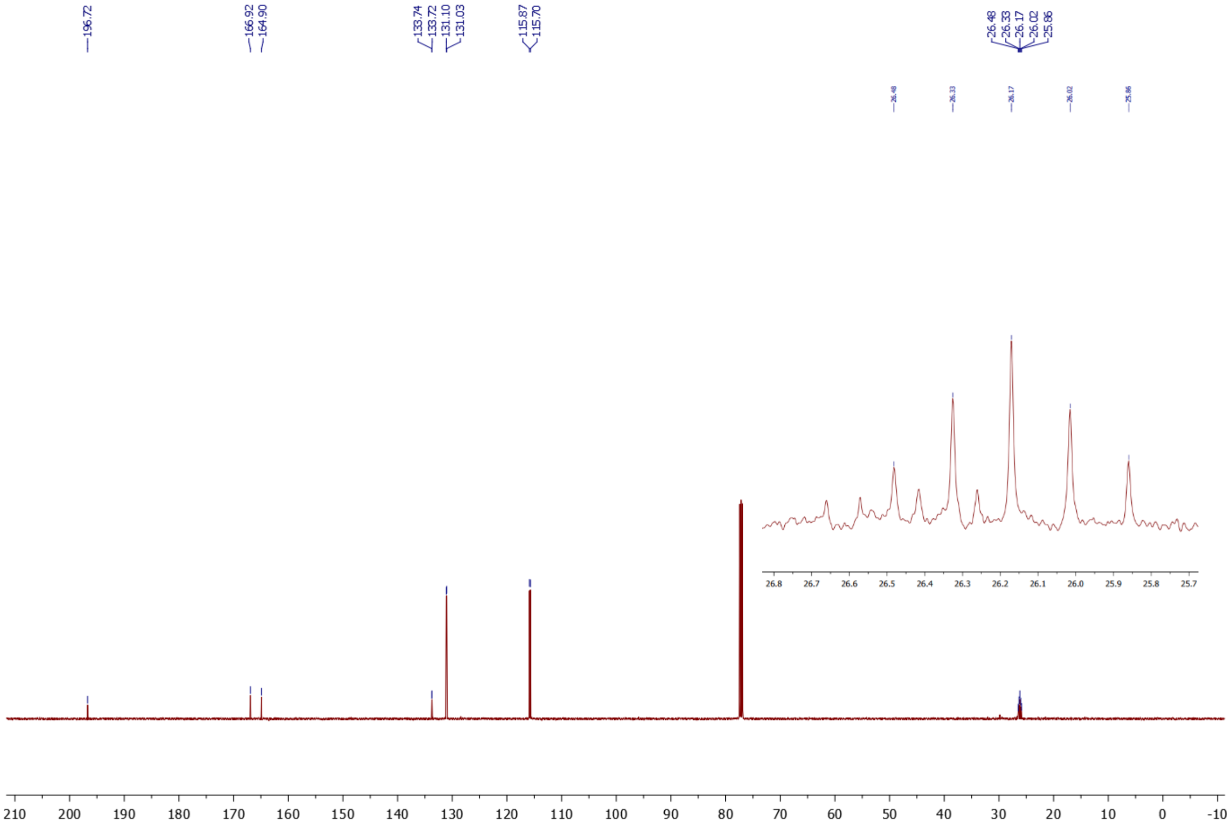


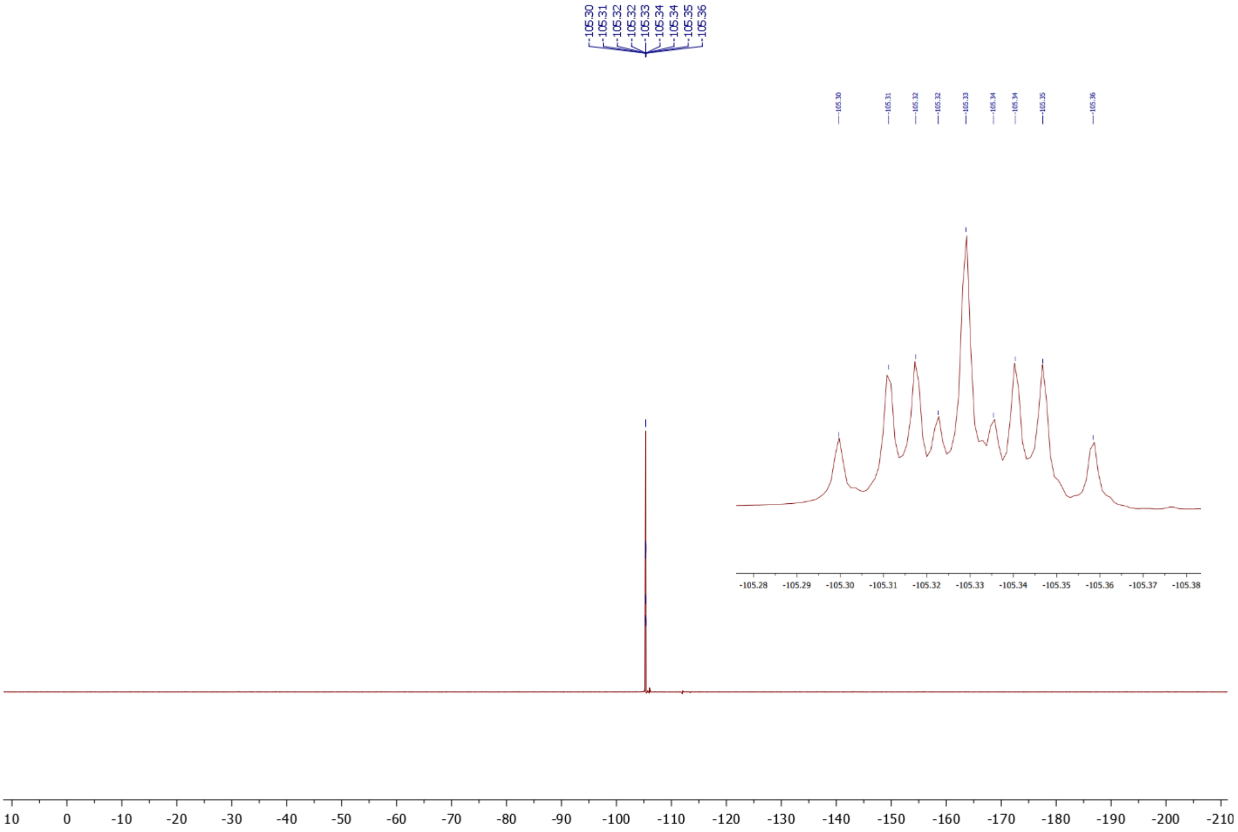
1-(4-fluorophenyl)ethan-1-one-2,2-d$_2$ (3c)



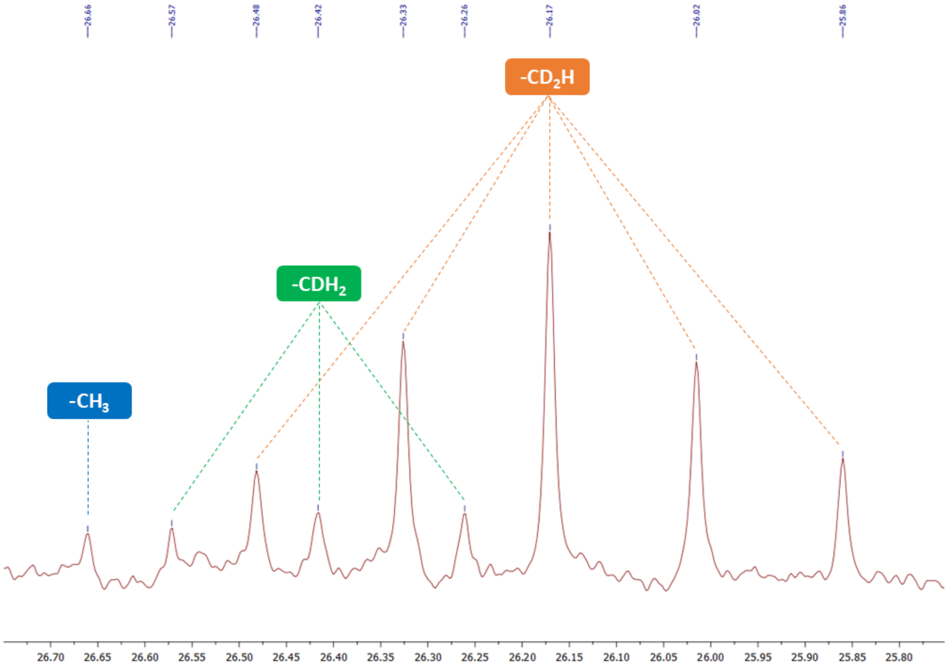
3c



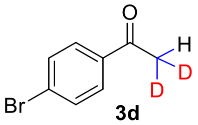




Assignments for -CD_2H, -CDH_2 and -CH_3 on the 13C NMR spectrum of 3c;



1-(4-bromophenyl)ethan-1-one-2,2-d$_2$ (3d)



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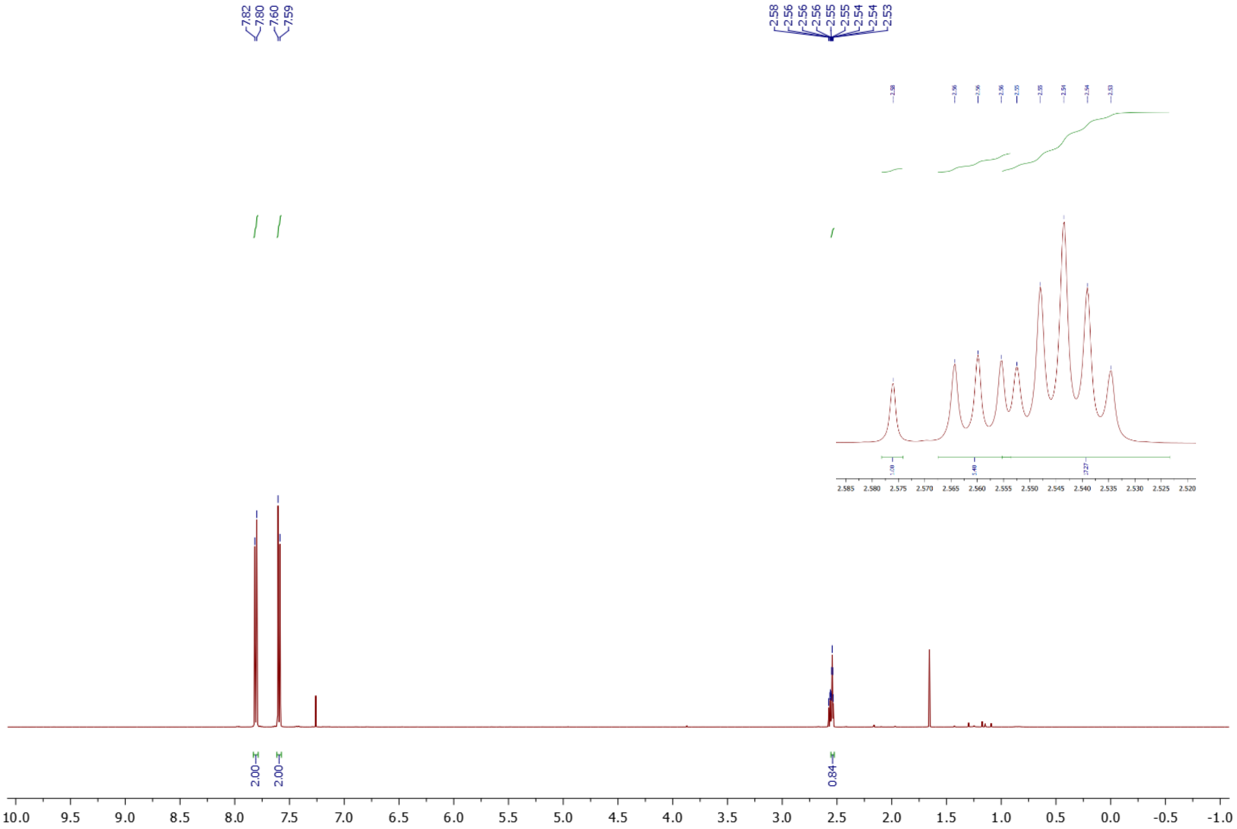
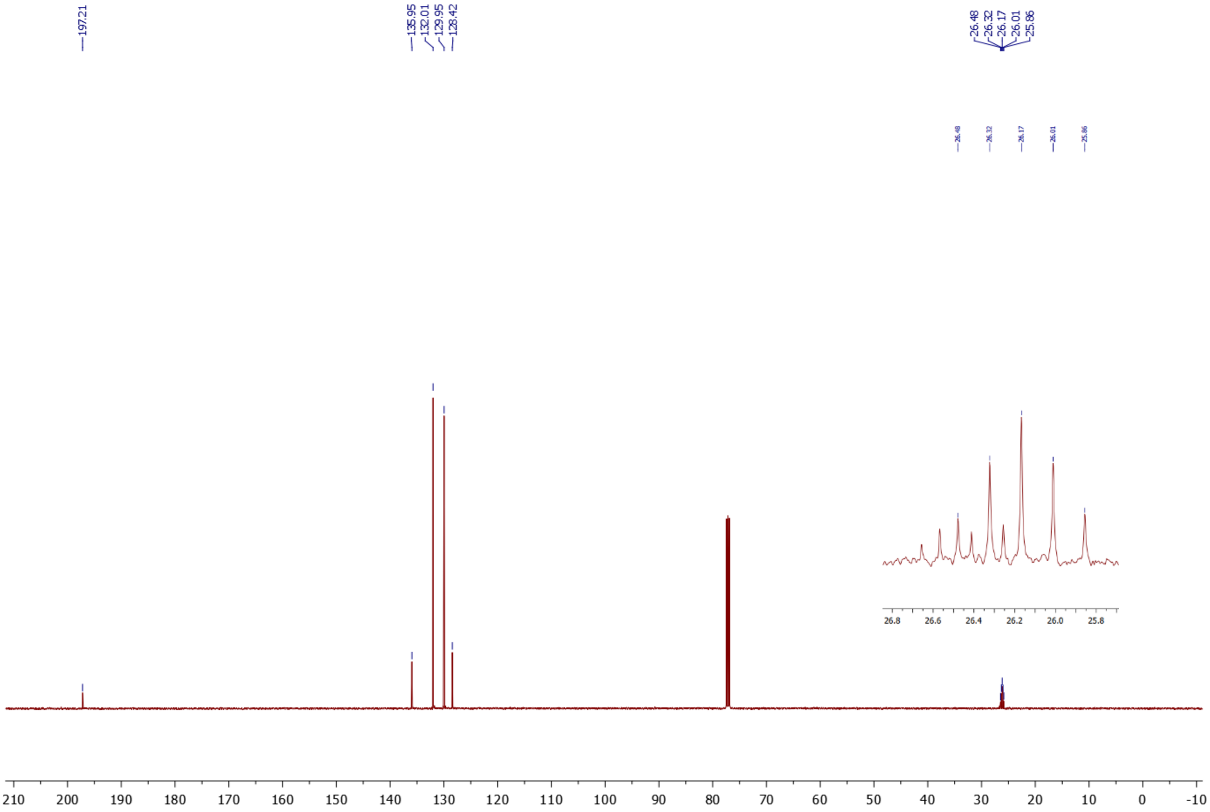
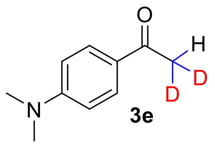




1-(4-(dimethylamino)phenyl)ethan-1-one-2,2-d$_2$ (3e)



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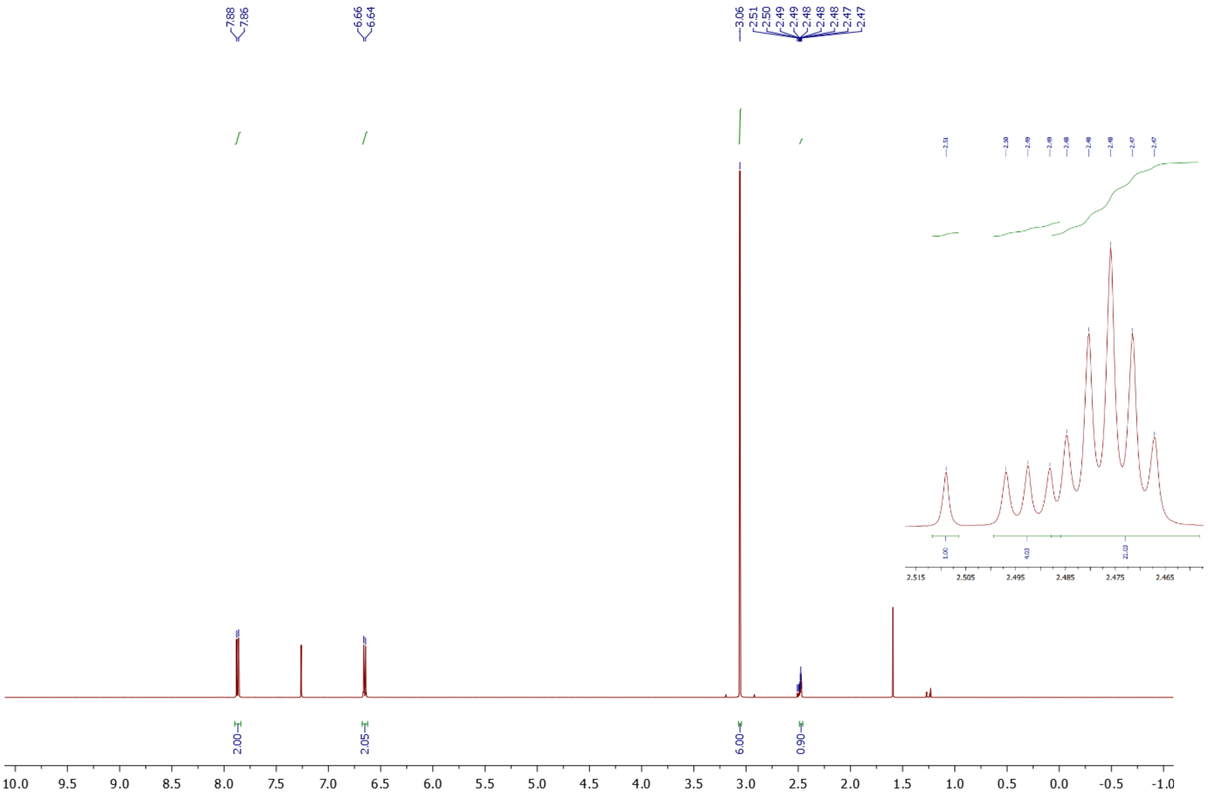
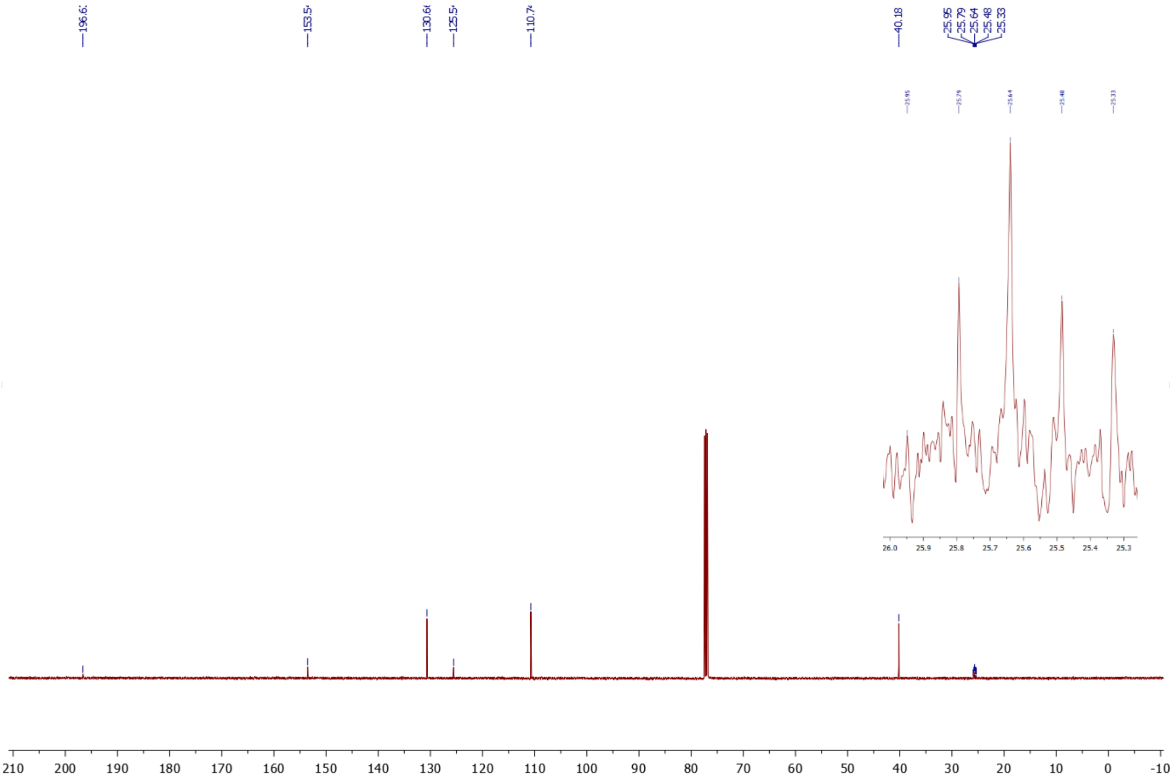
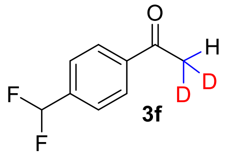




1-(4-(difluoromethyl)phenyl)ethan-1-one-2,2-d$_2$ (3f)



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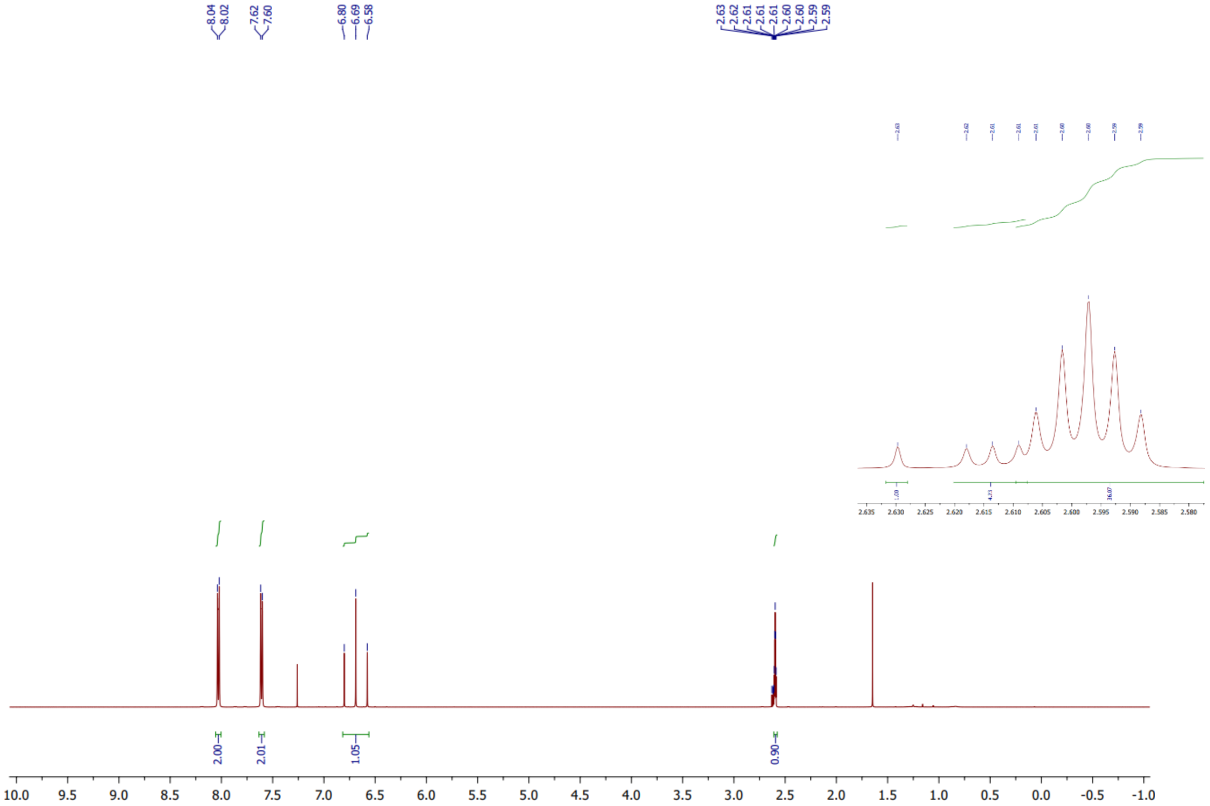

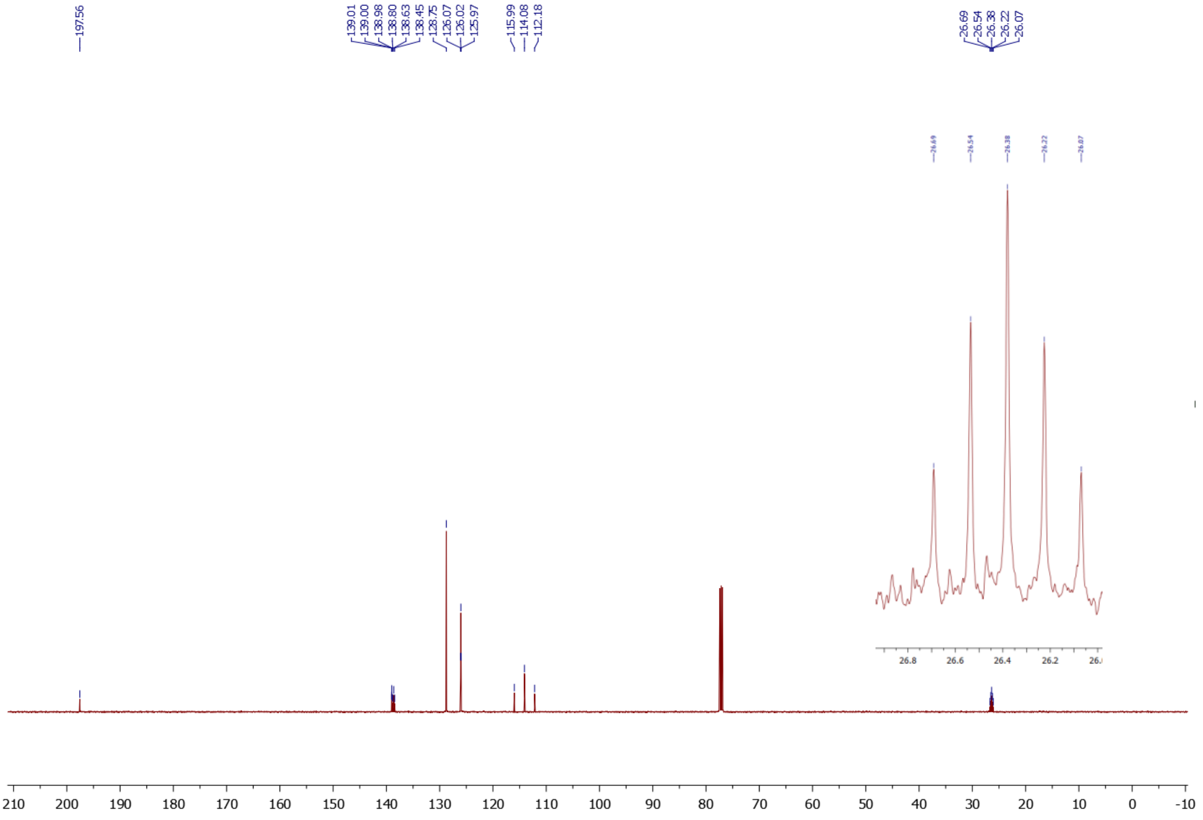

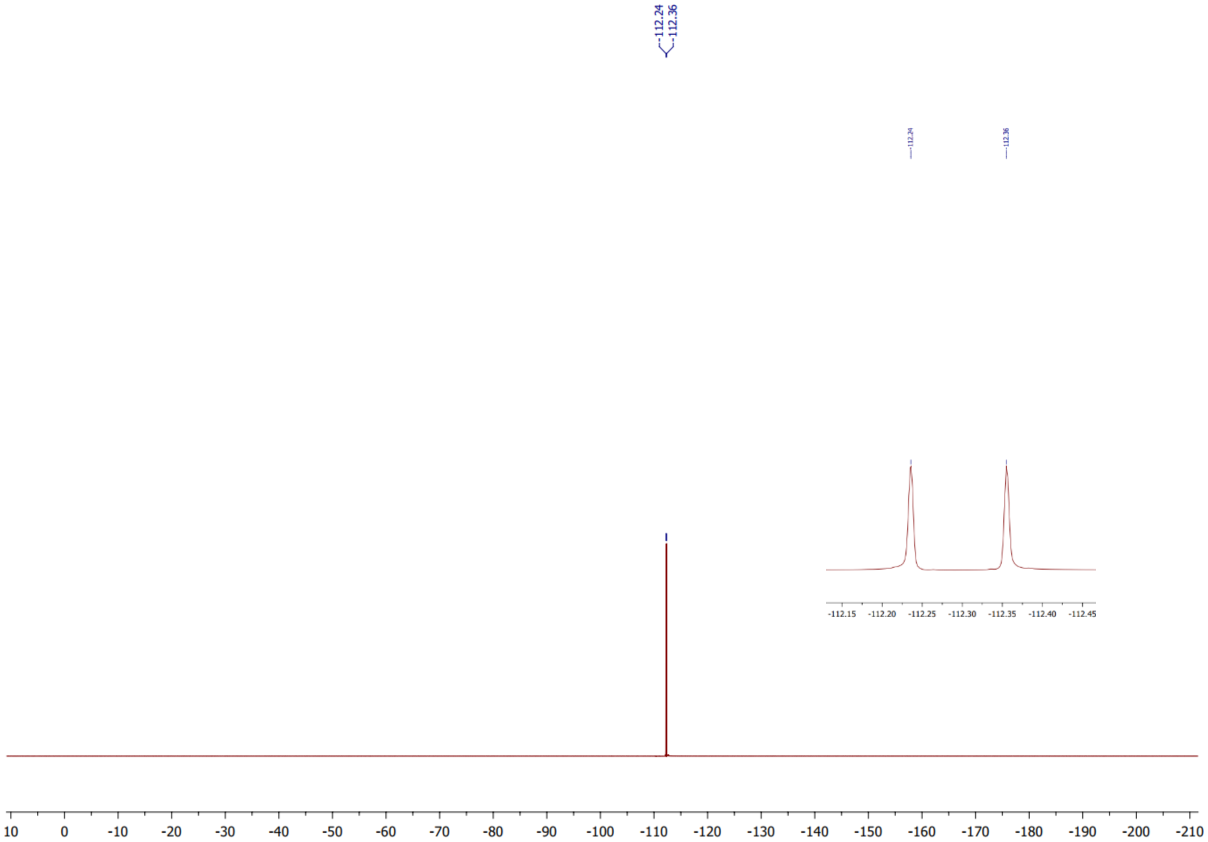
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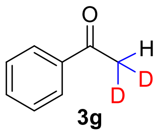
1-phenylethan-1-one-2,2-d$_2$ (3g)



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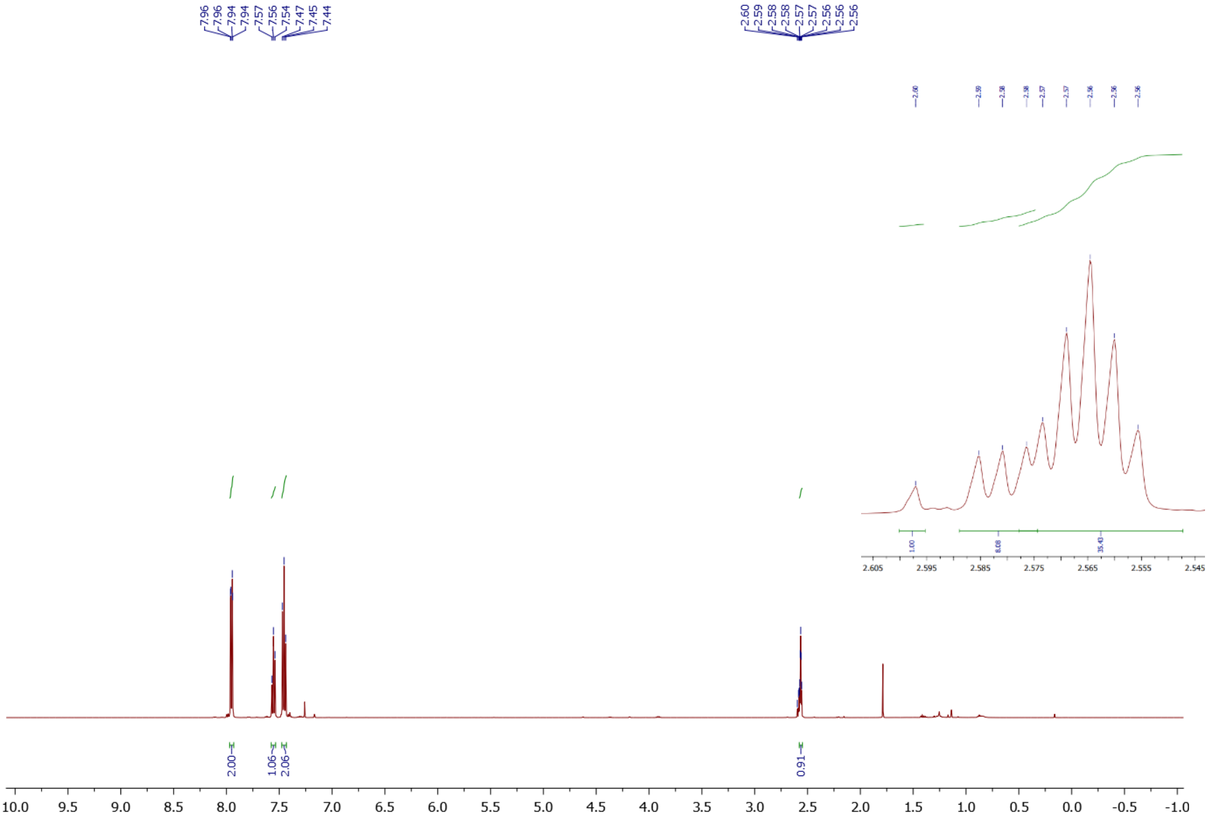
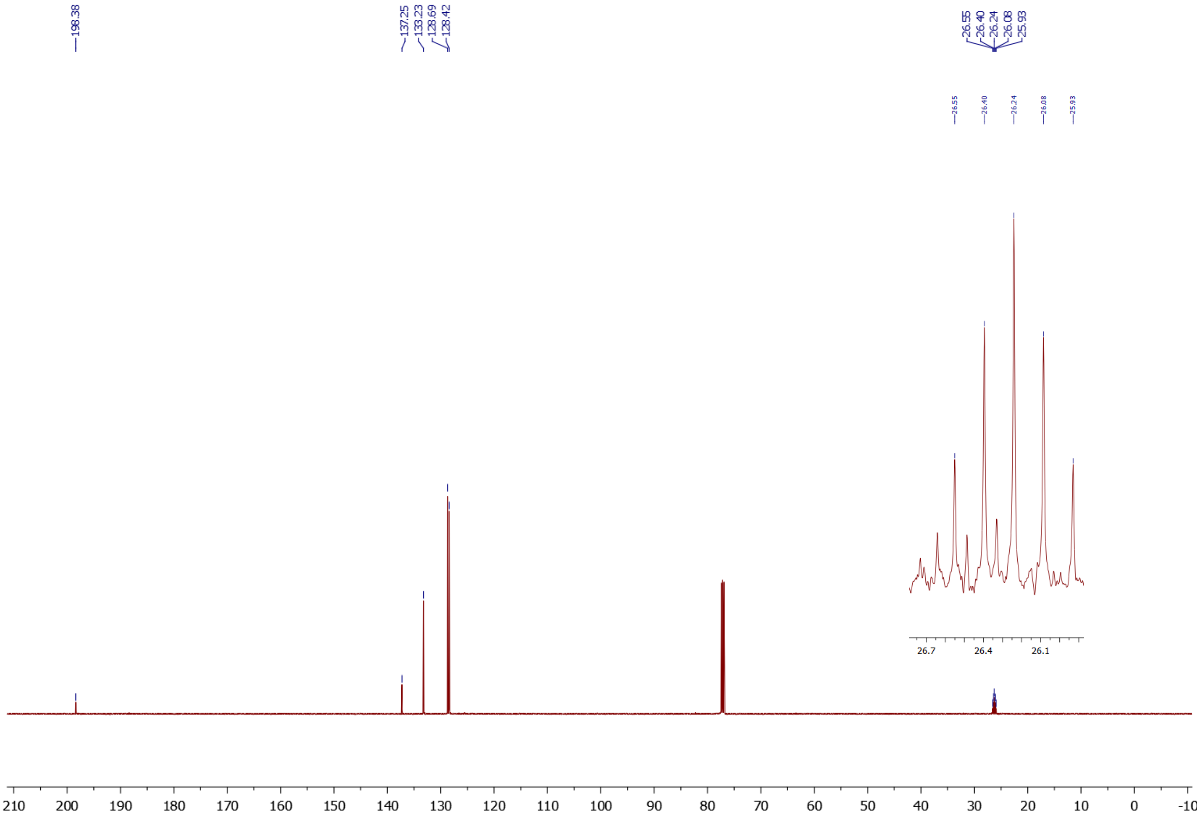
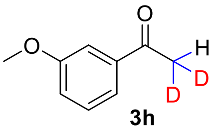




1-(3-methoxyphenyl)ethan-1-one-2,2-d_2 (3h)



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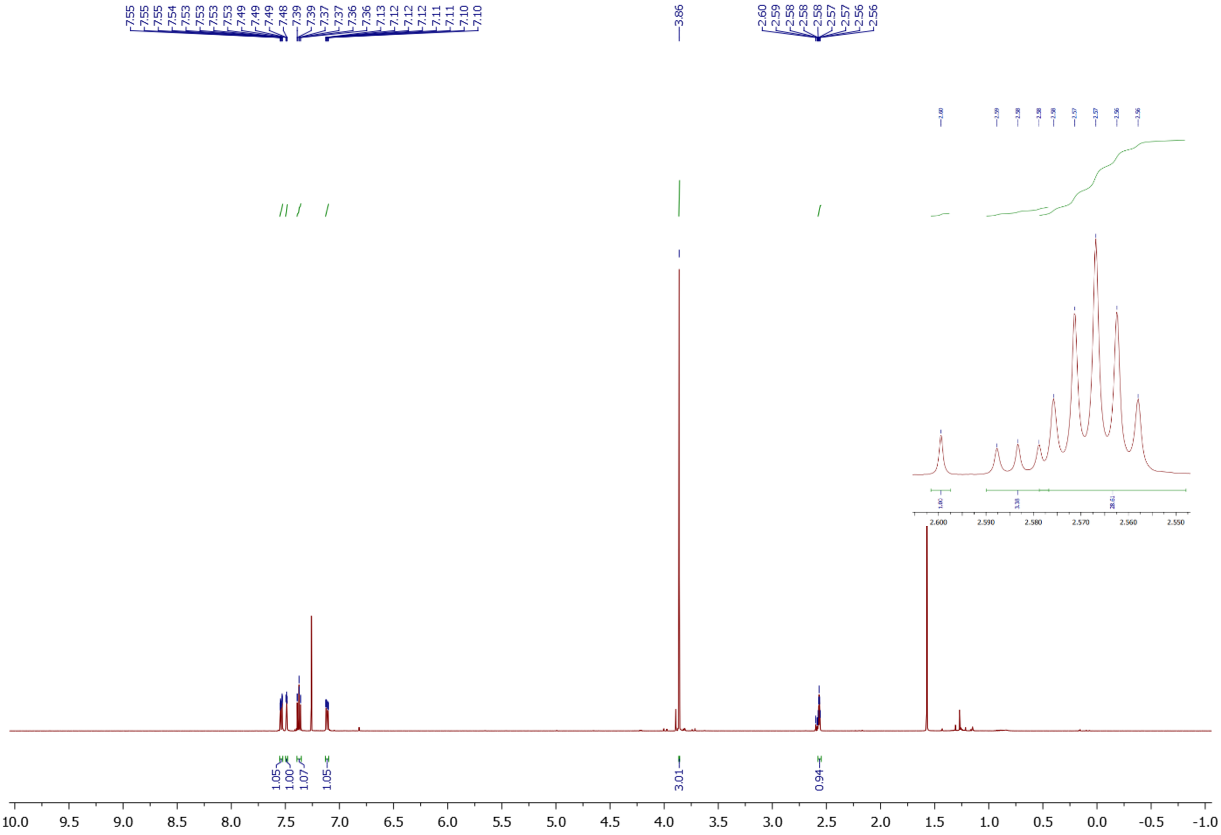
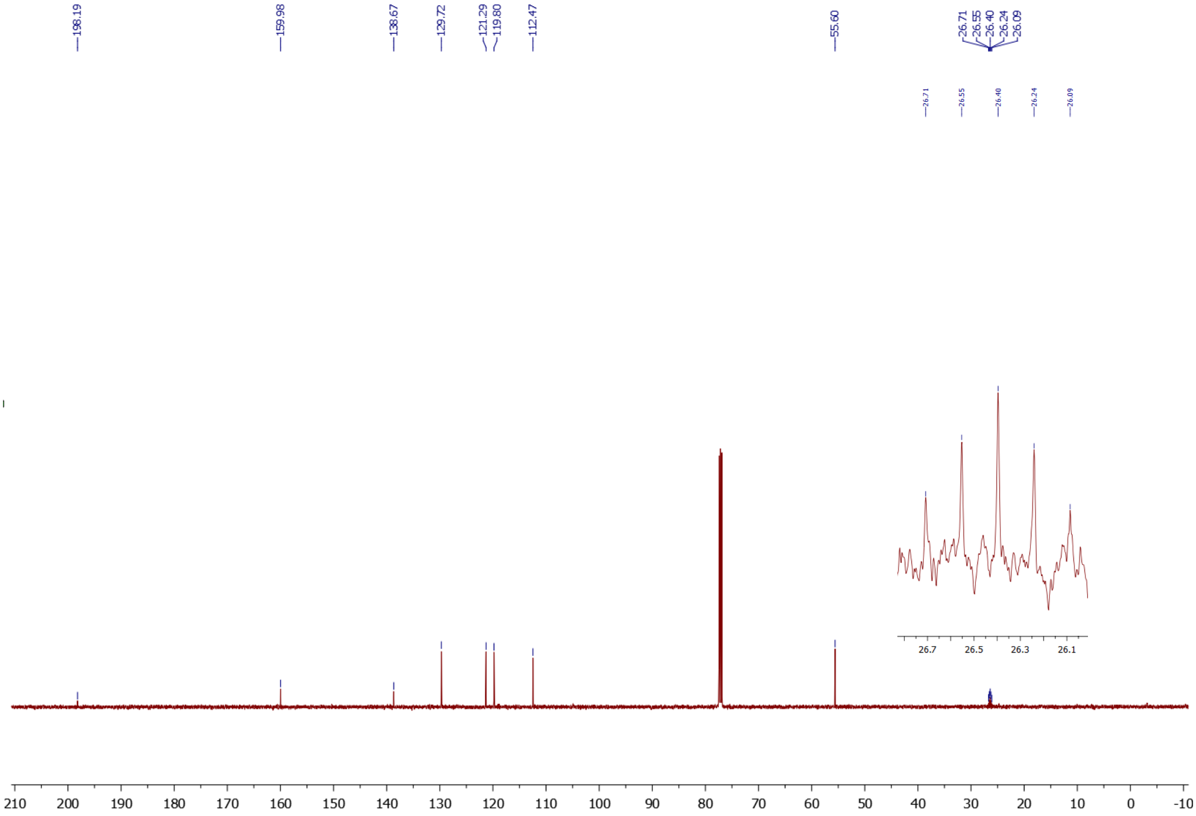
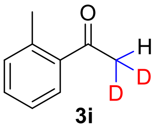




1-(*o*-tolyl)ethan-1-one-2,2-d_2 (3i)



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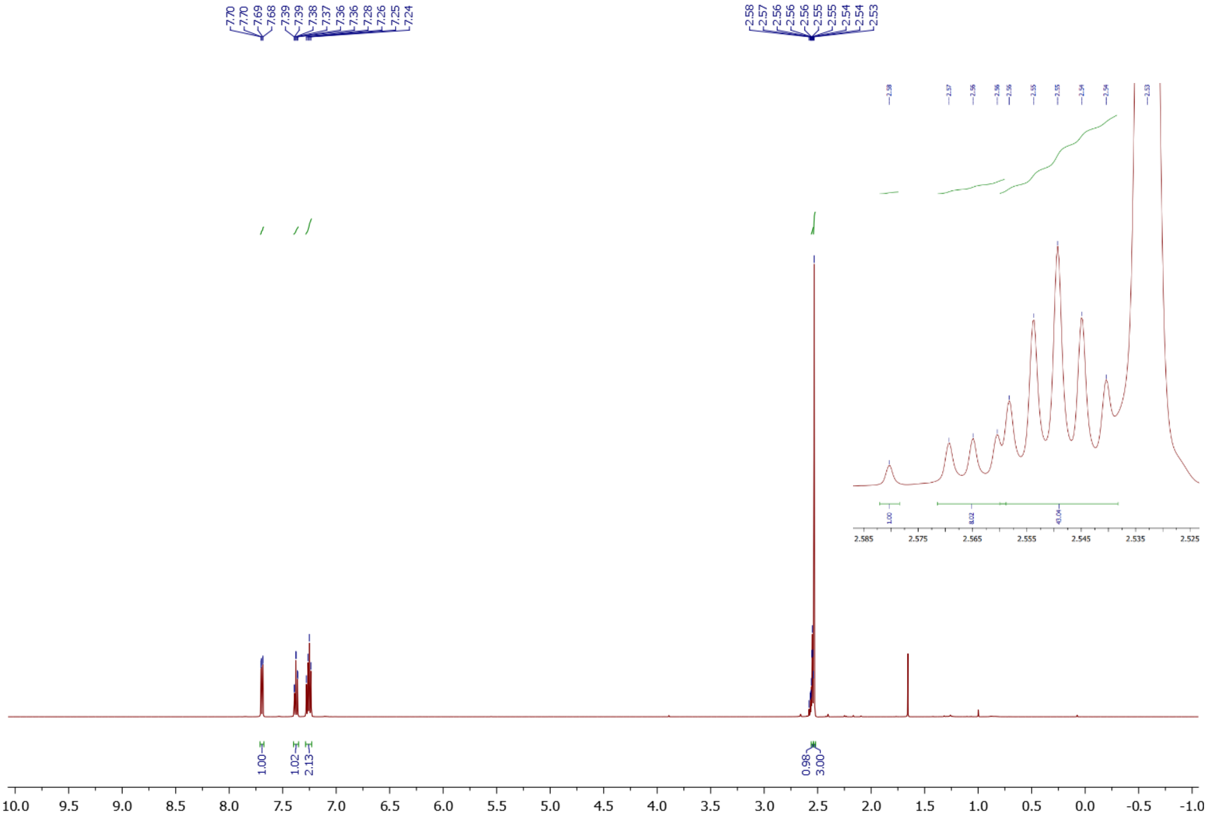
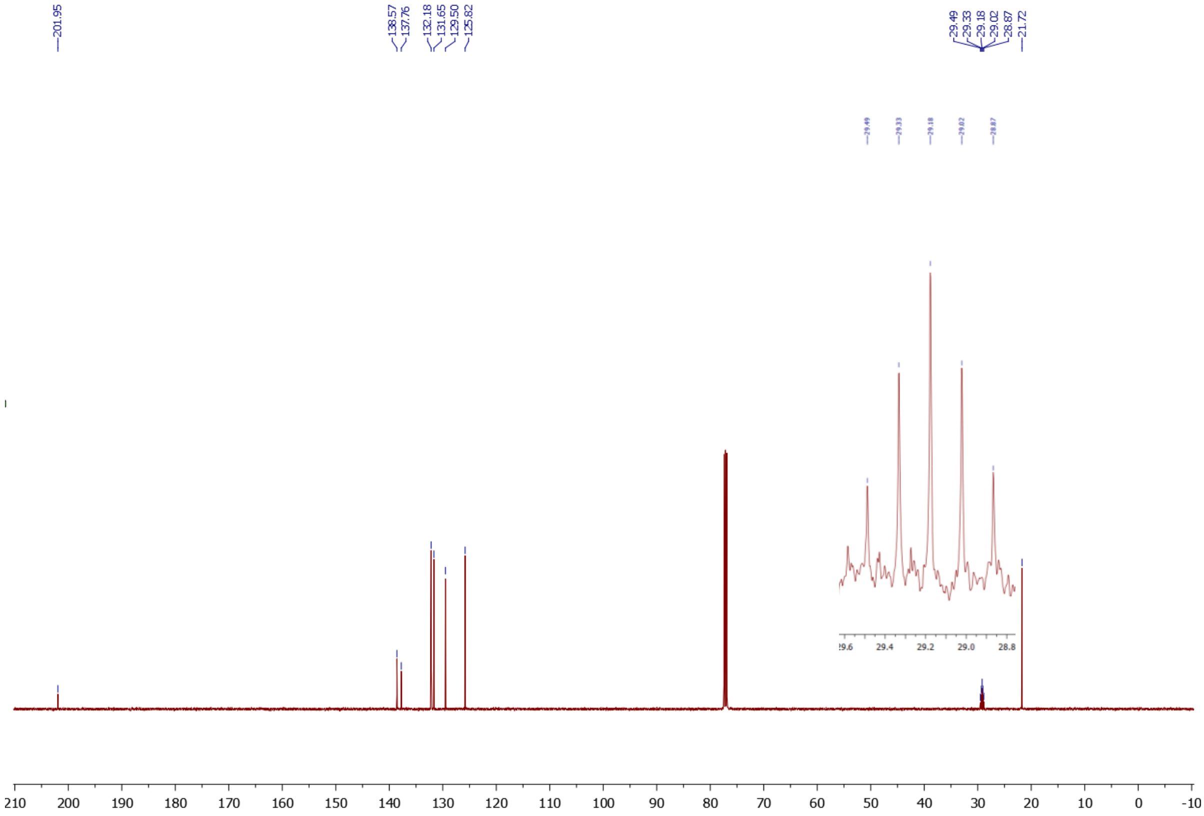
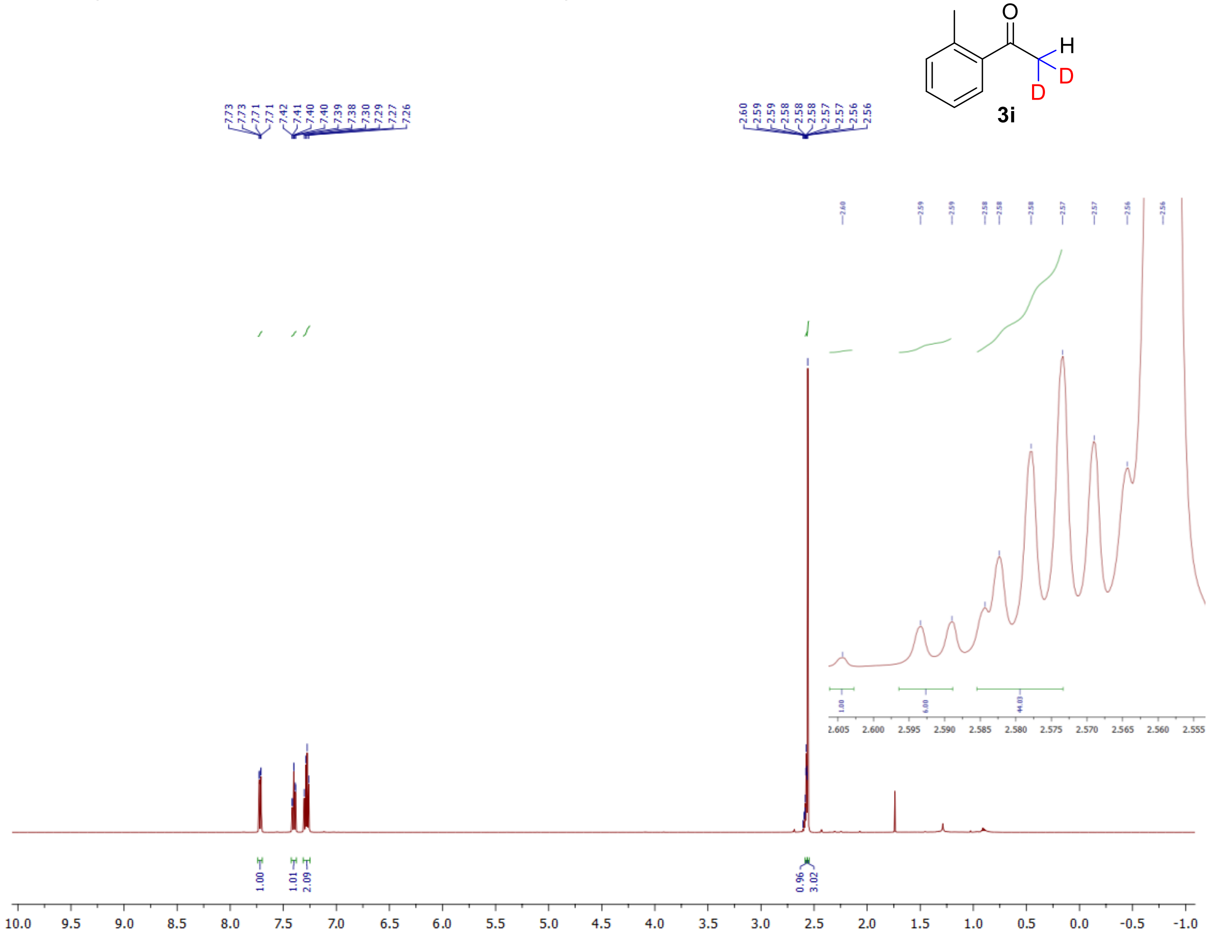
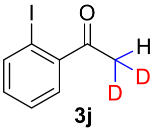




1-(*o*-tolyl)ethan-1-one-2,2-d$_2$ (3i, Gram Scale Synthesis).



1-(2-iodophenyl)ethan-1-one-2,2-d$_2$ (3j)



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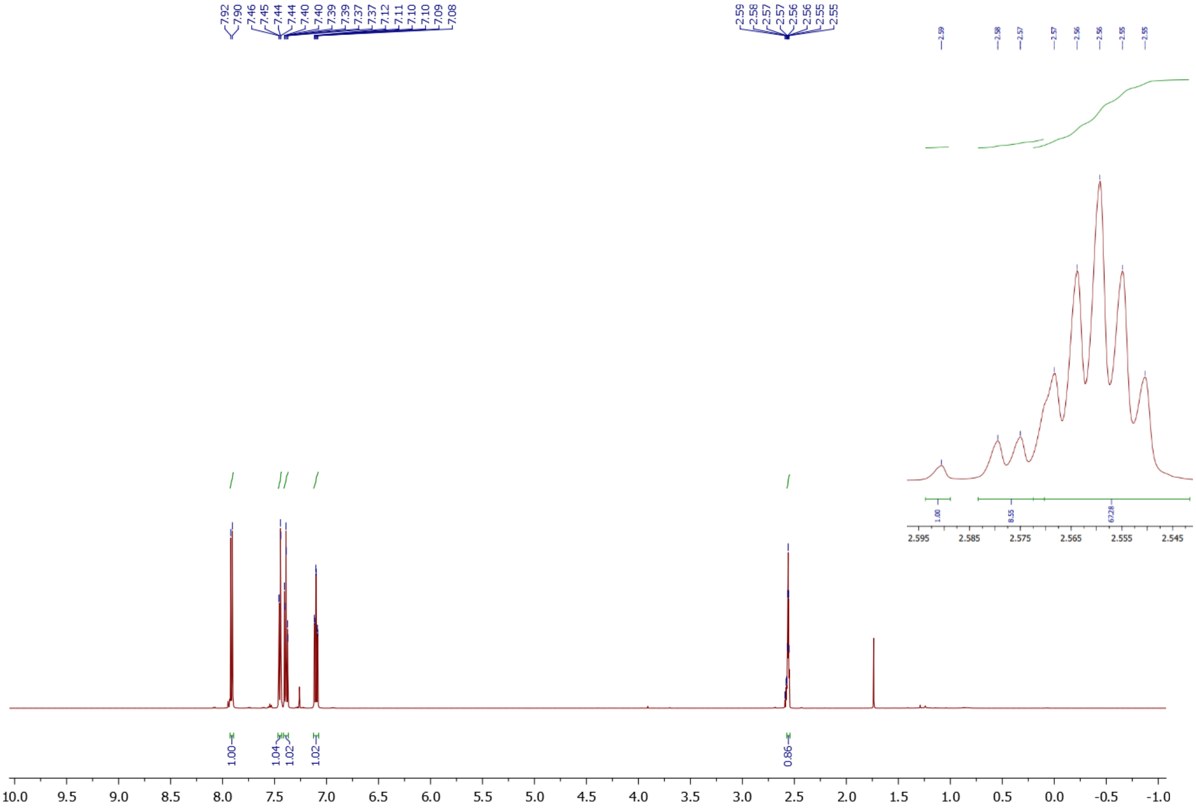
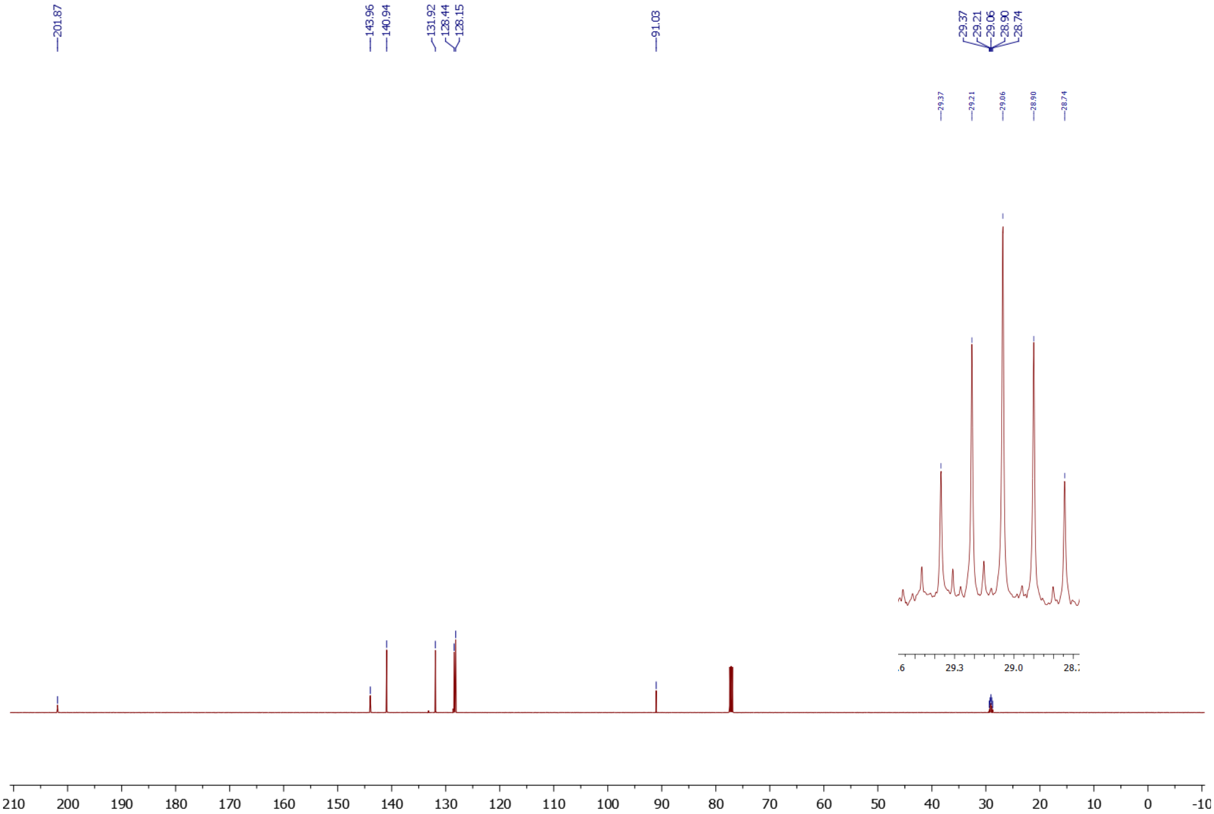
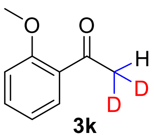




1-(2-methoxyphenyl)ethan-1-one-2,2-d$_2$ (3k)



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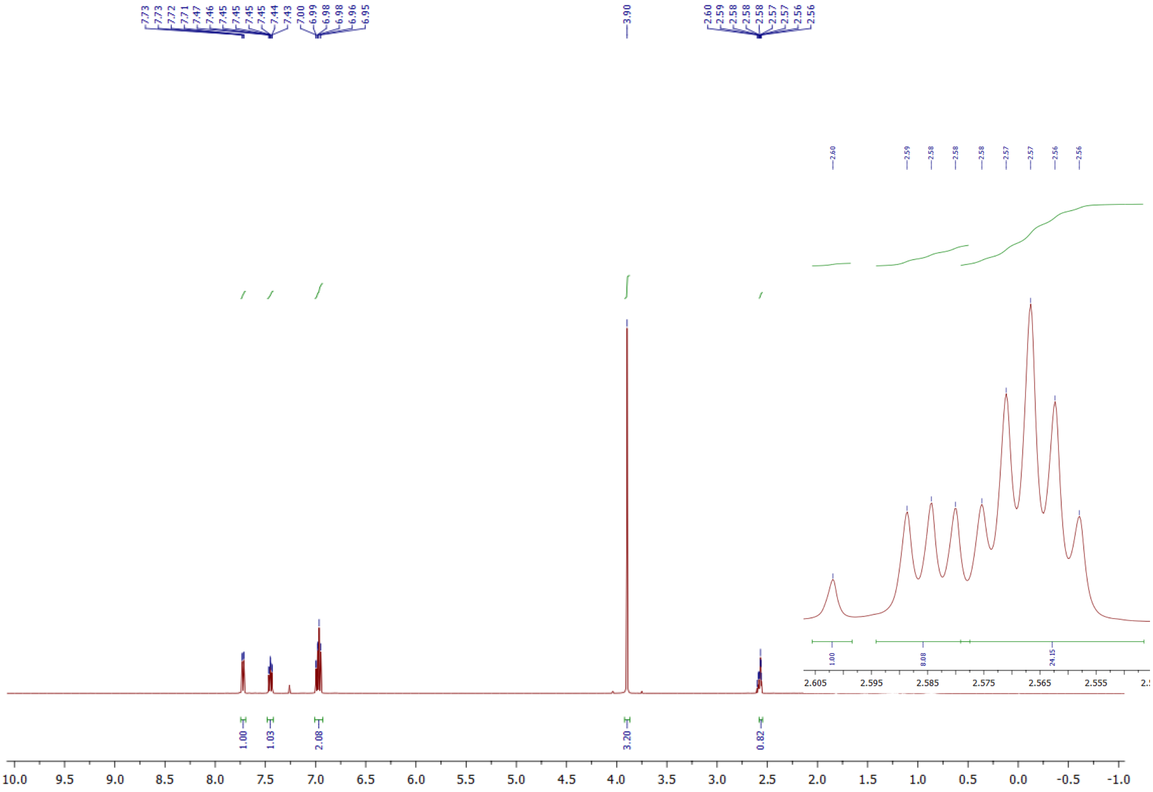
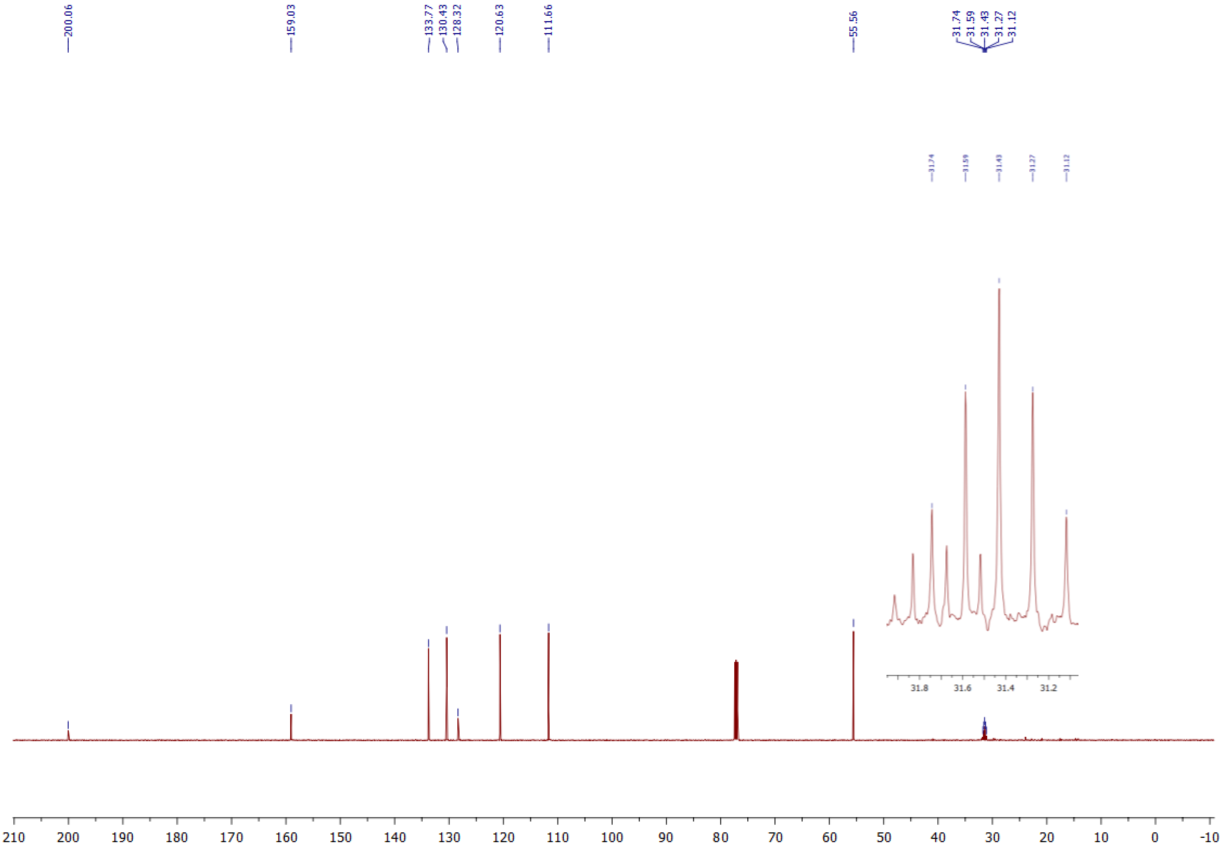
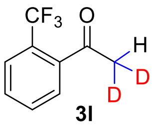




1-(2-(trifluoromethyl)phenyl)ethan-1-one-2,2-d_2 (3l)



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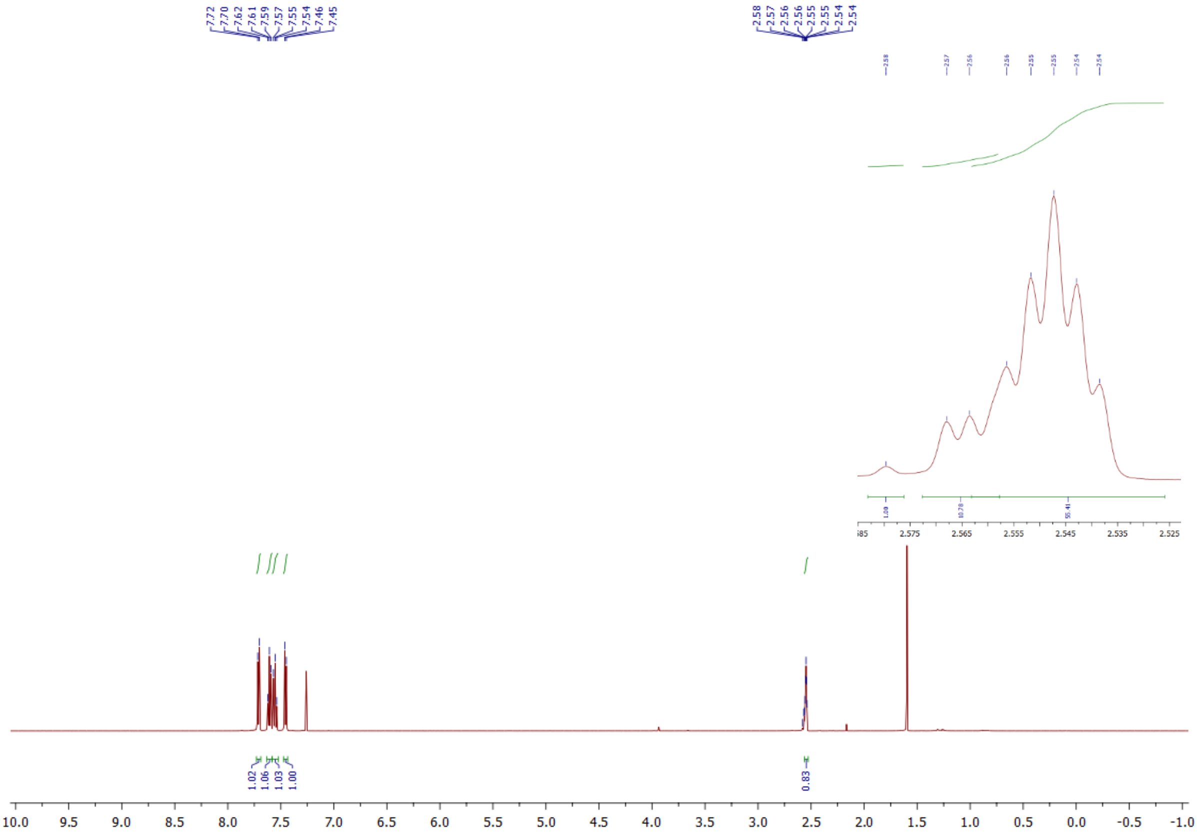

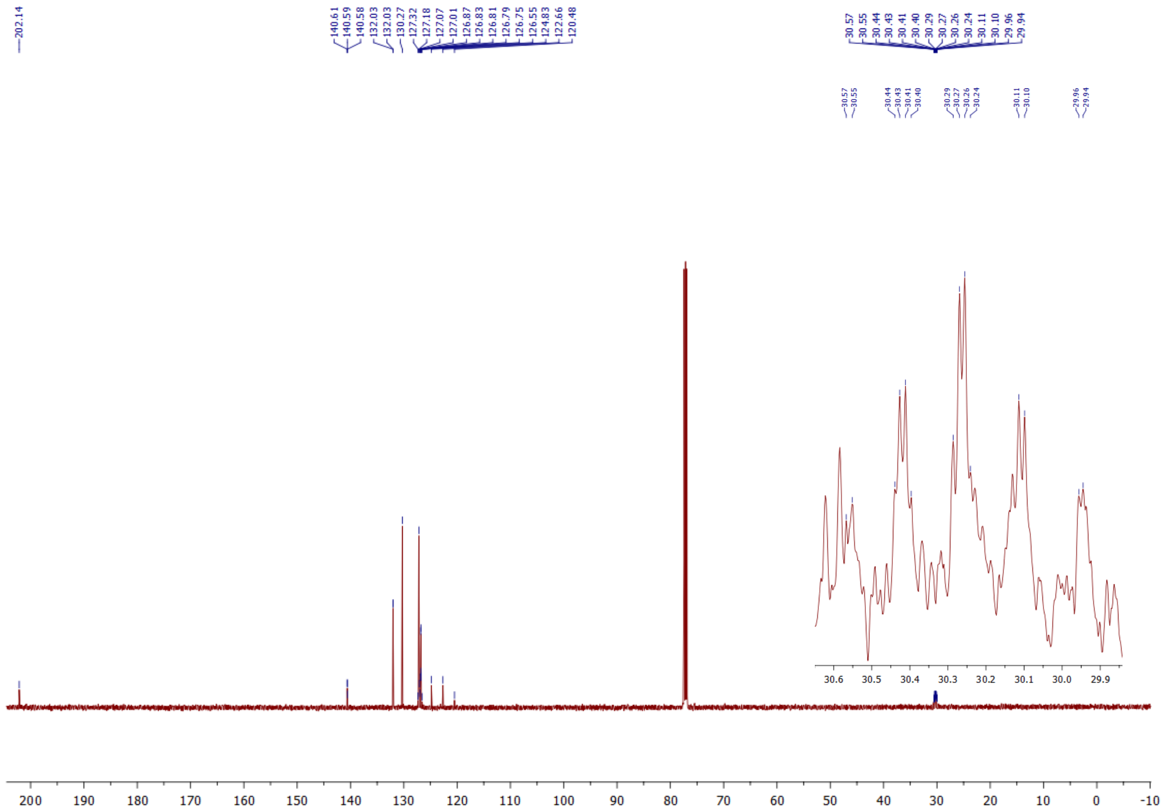

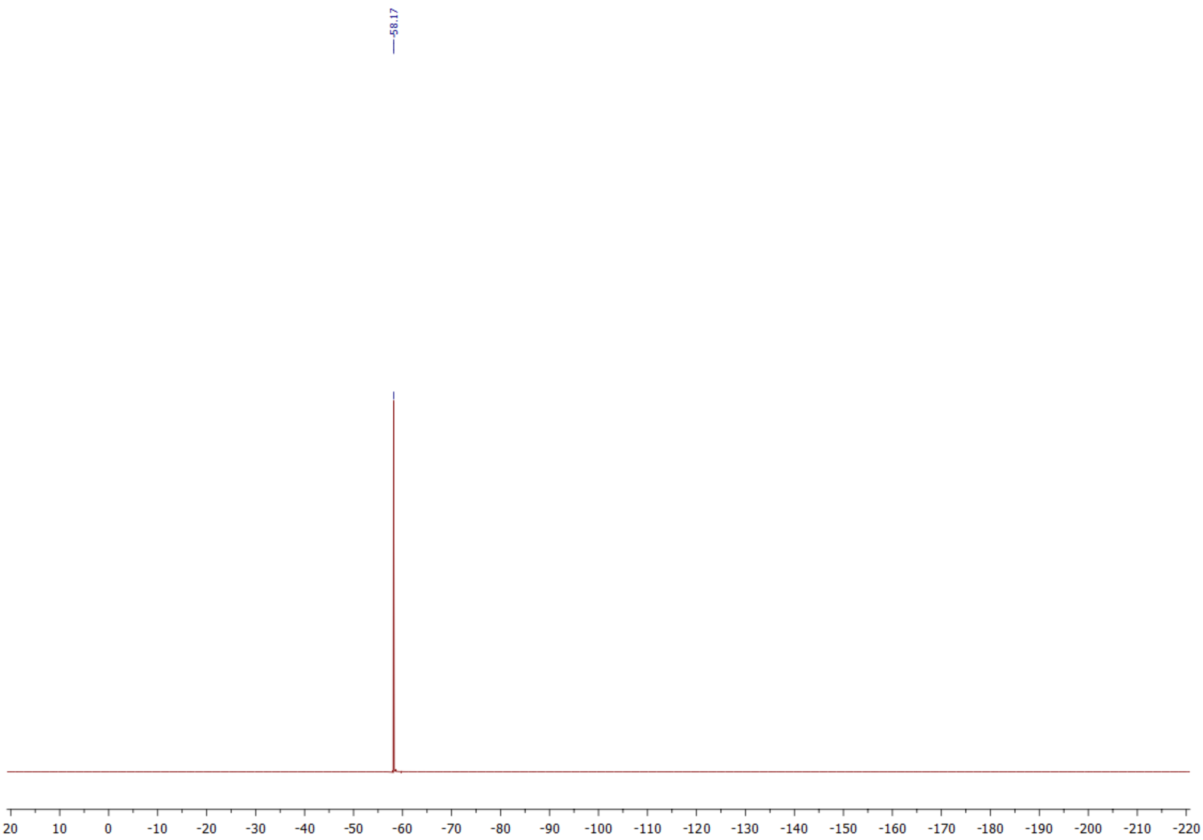

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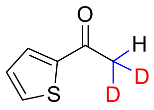
1-(thiophen-2-yl)ethan-1-one-2,2-d$_2$ (3m)



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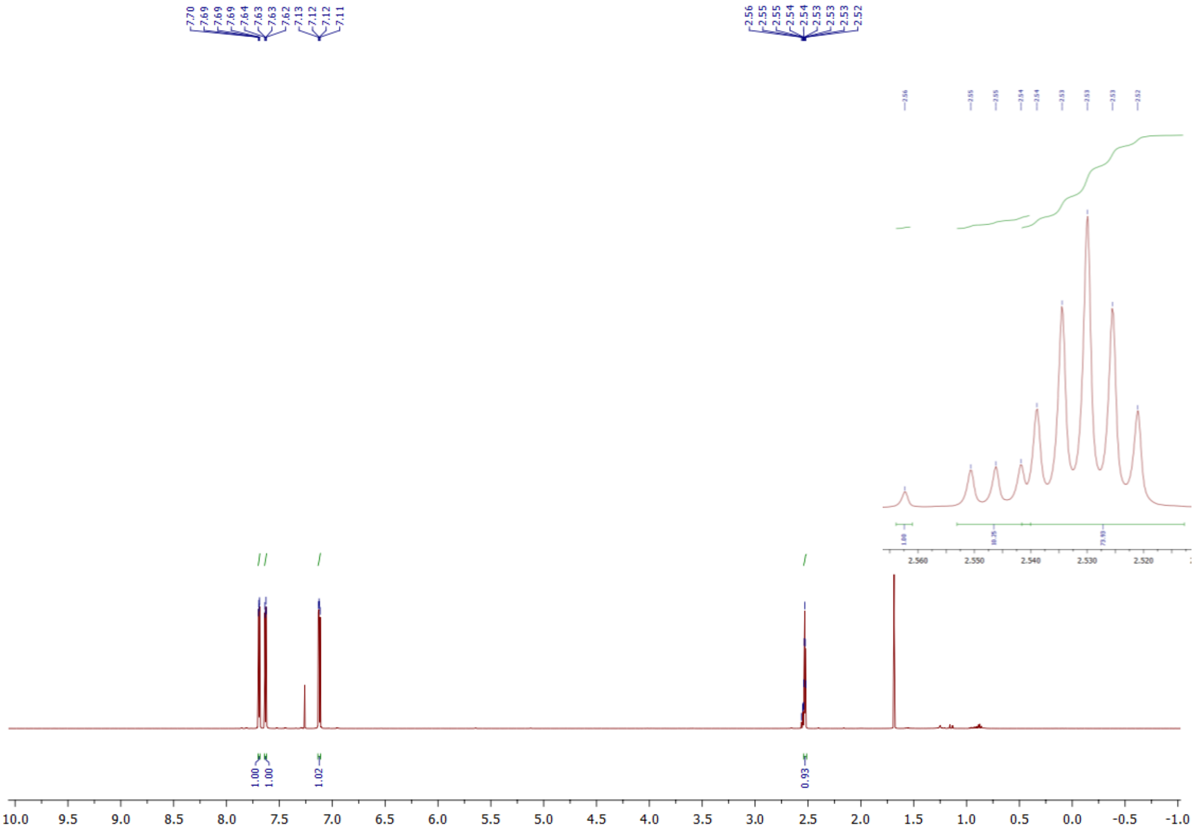
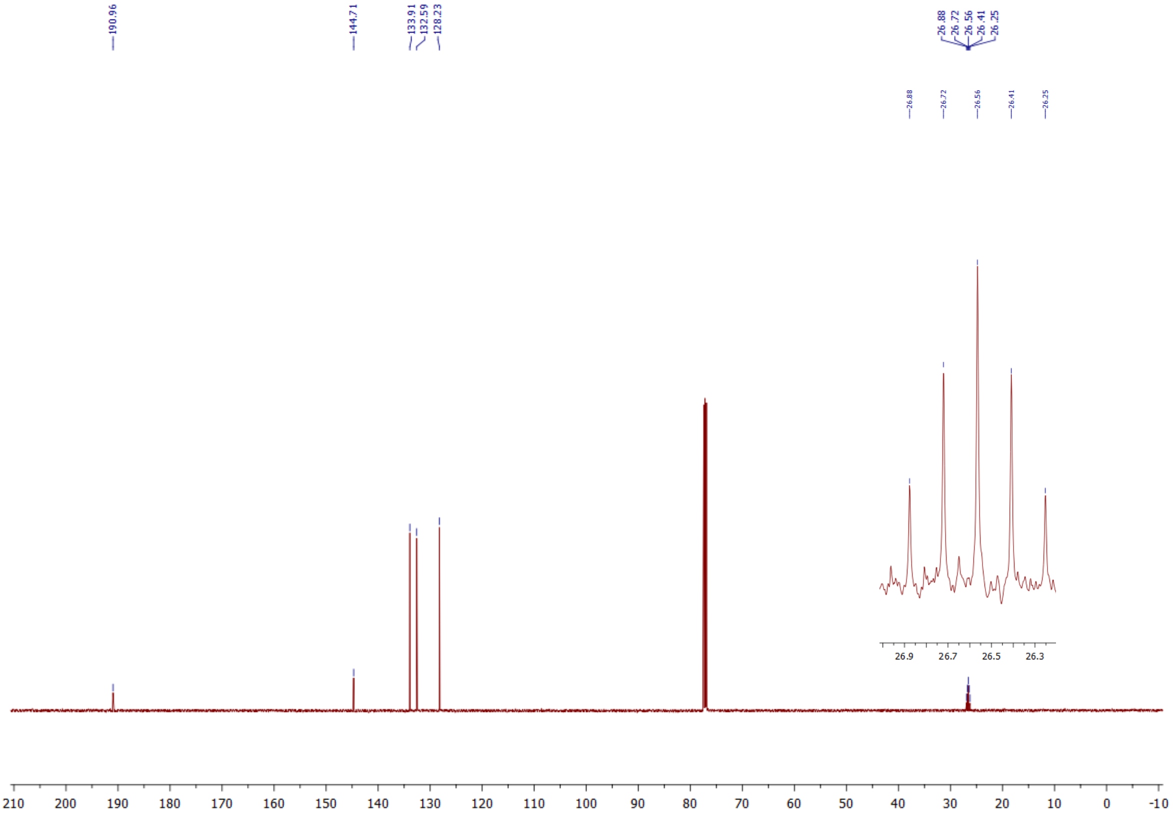
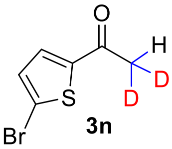




1-(5-bromothiophen-2-yl)ethan-1-one-2,2-d$_2$ (3n)



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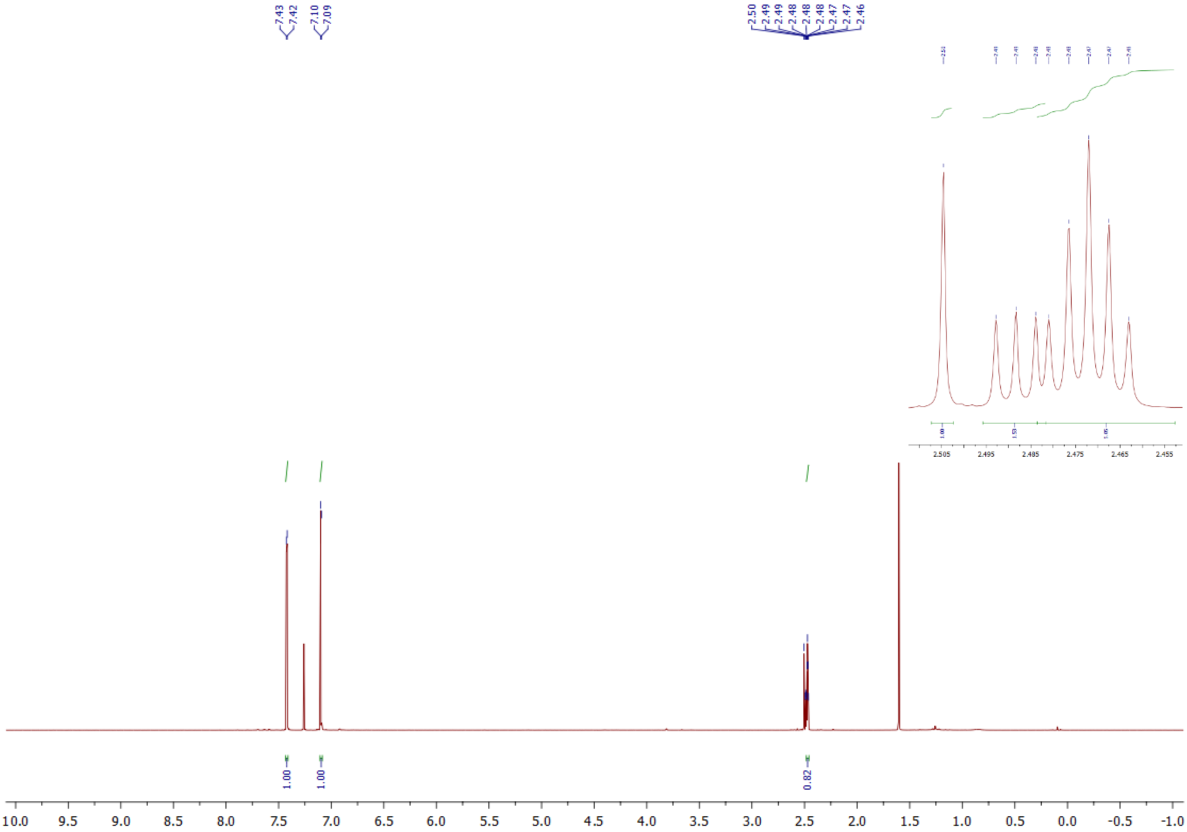
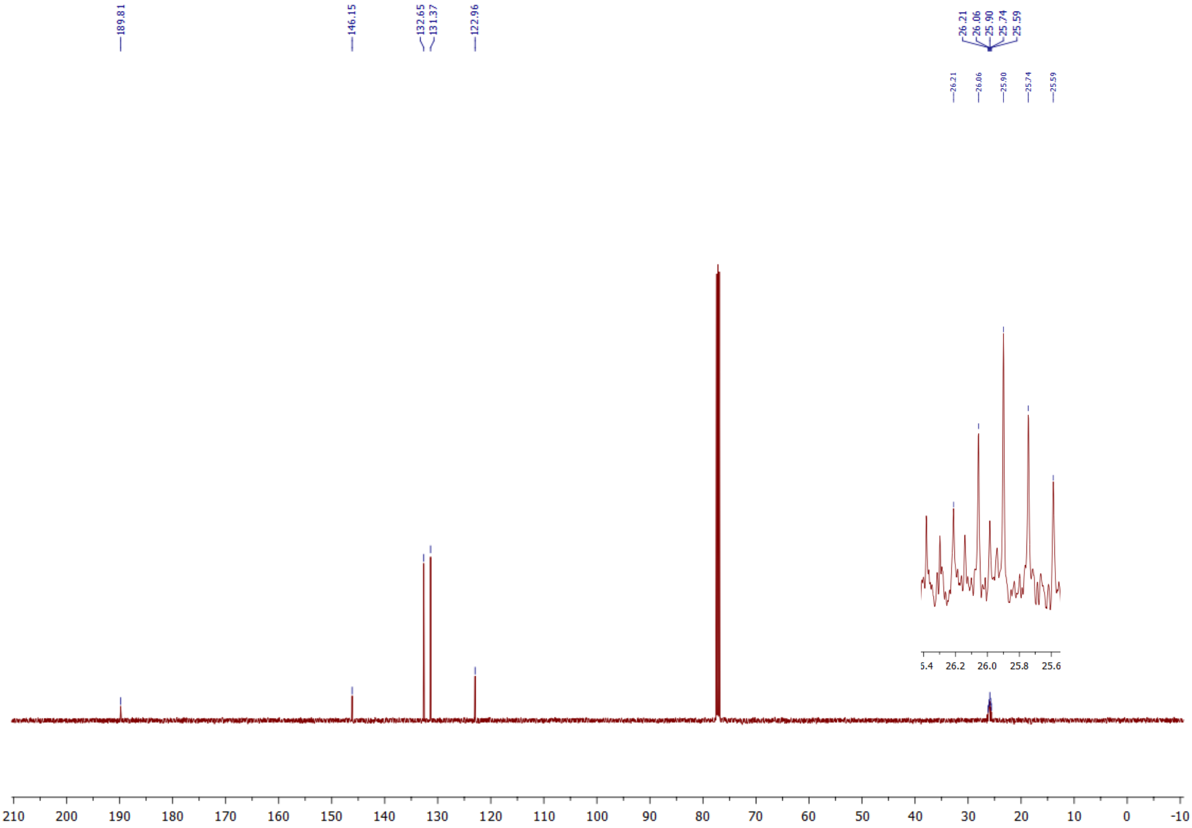
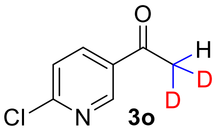




1-(6-chloropyridin-3-yl)ethan-1-one-2,2-d_2 (3o)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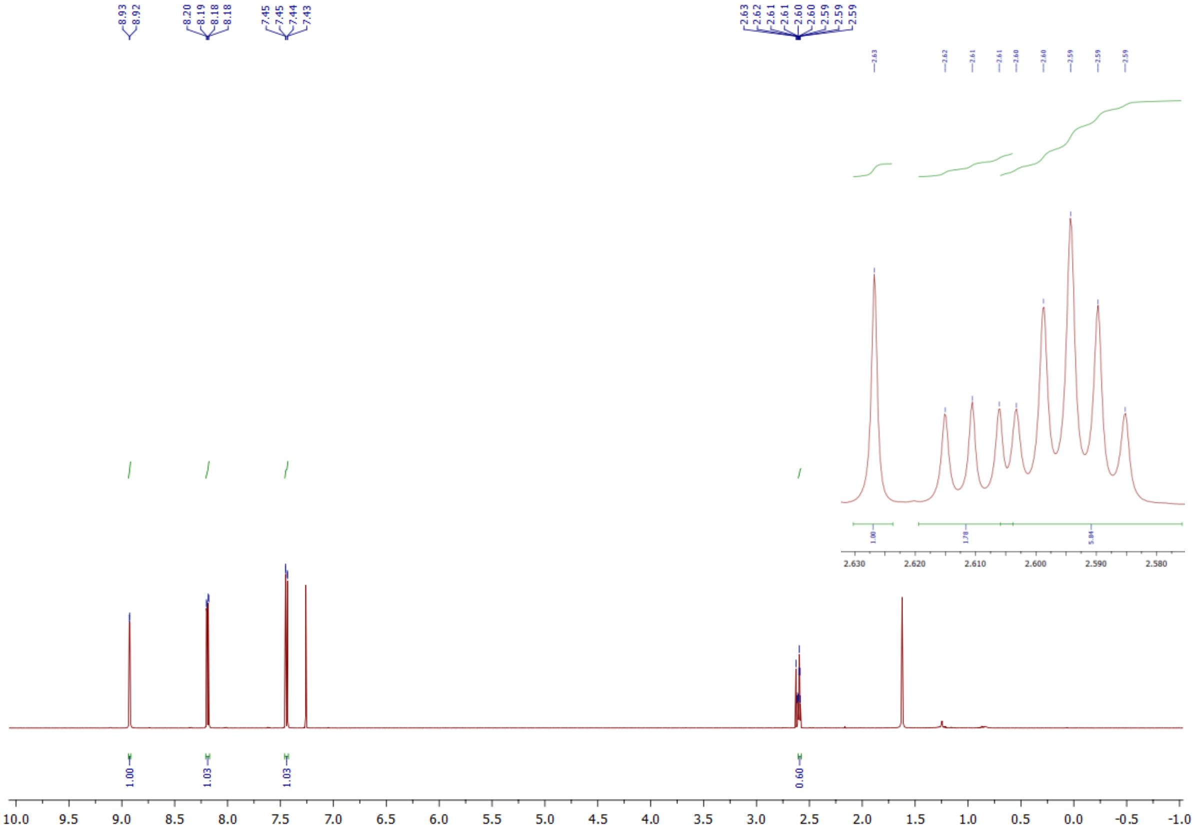
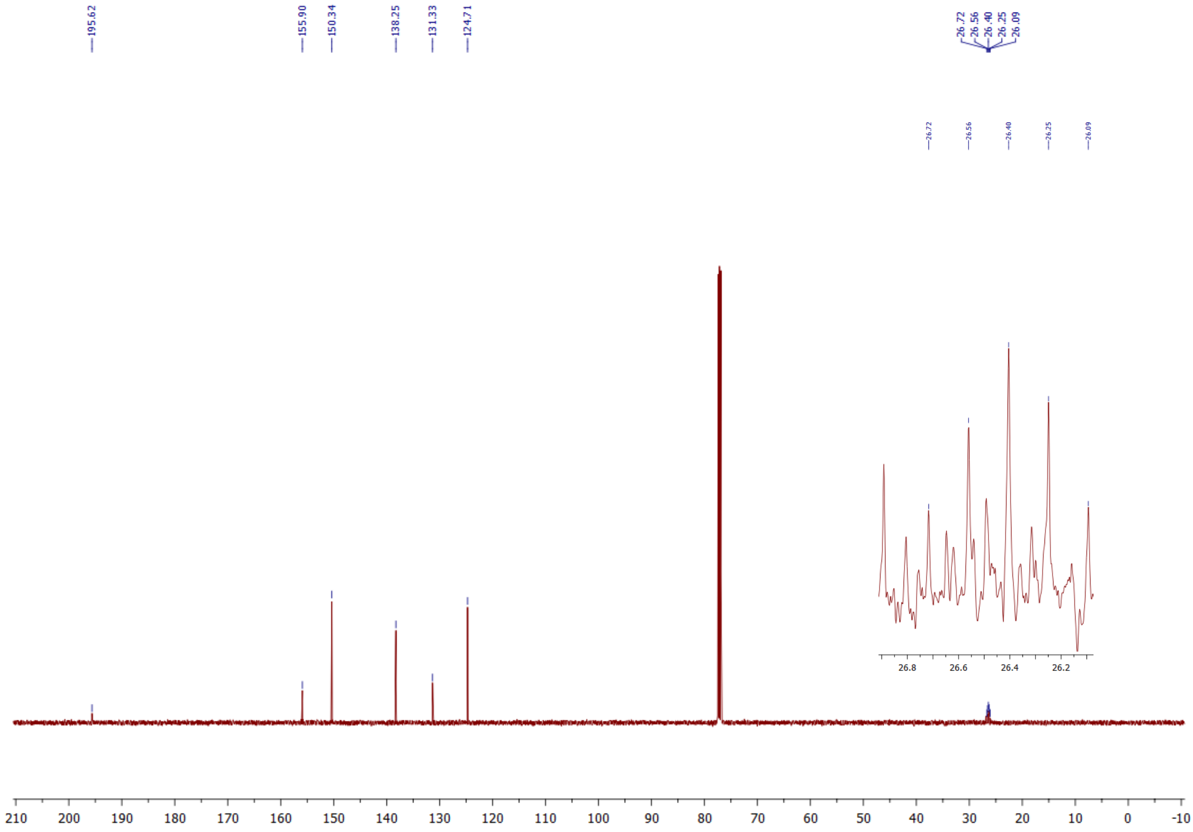
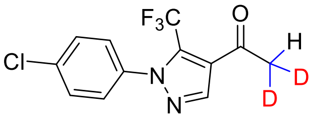




1-(1-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethan-1-one-2,2-d$_2$ (3p)



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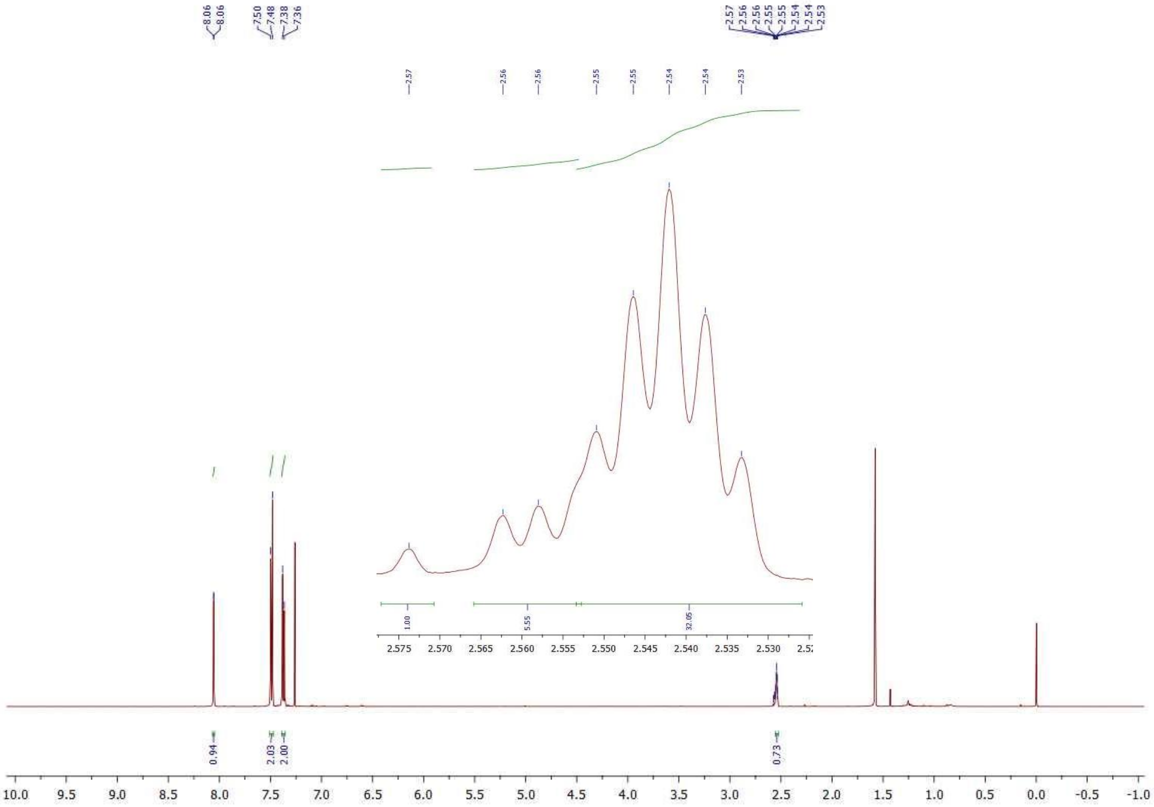

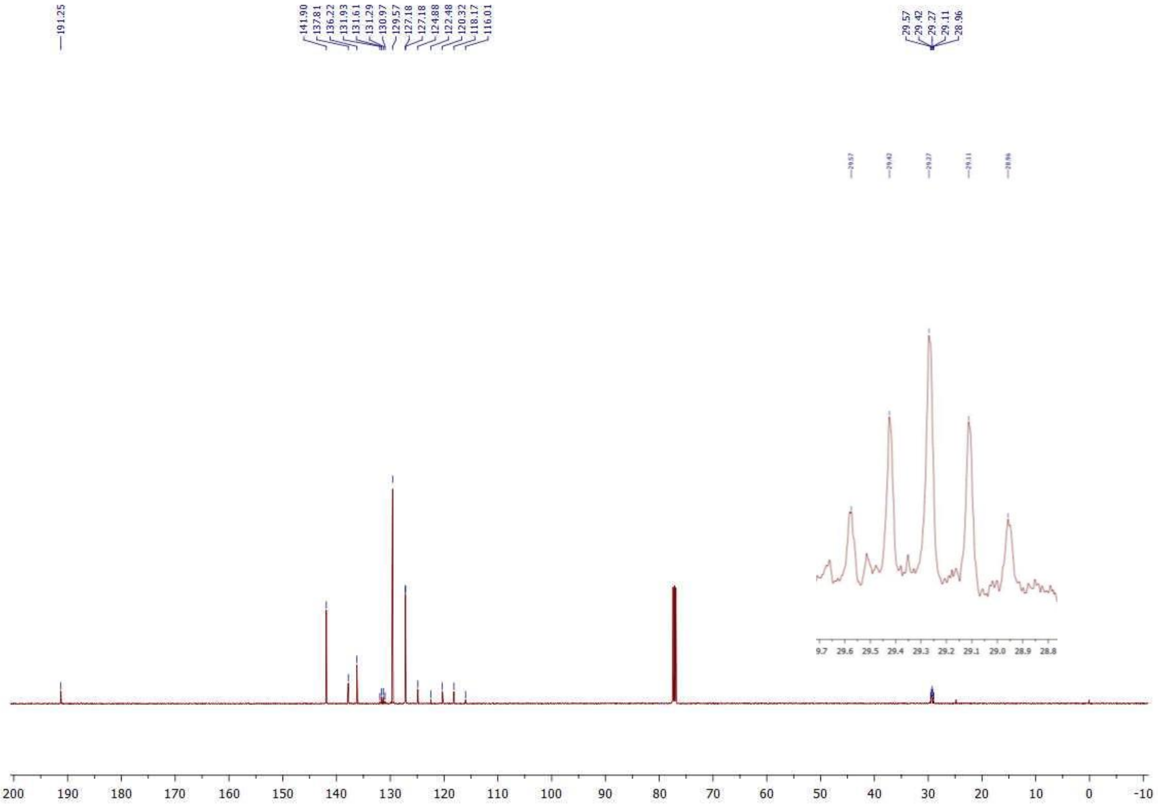

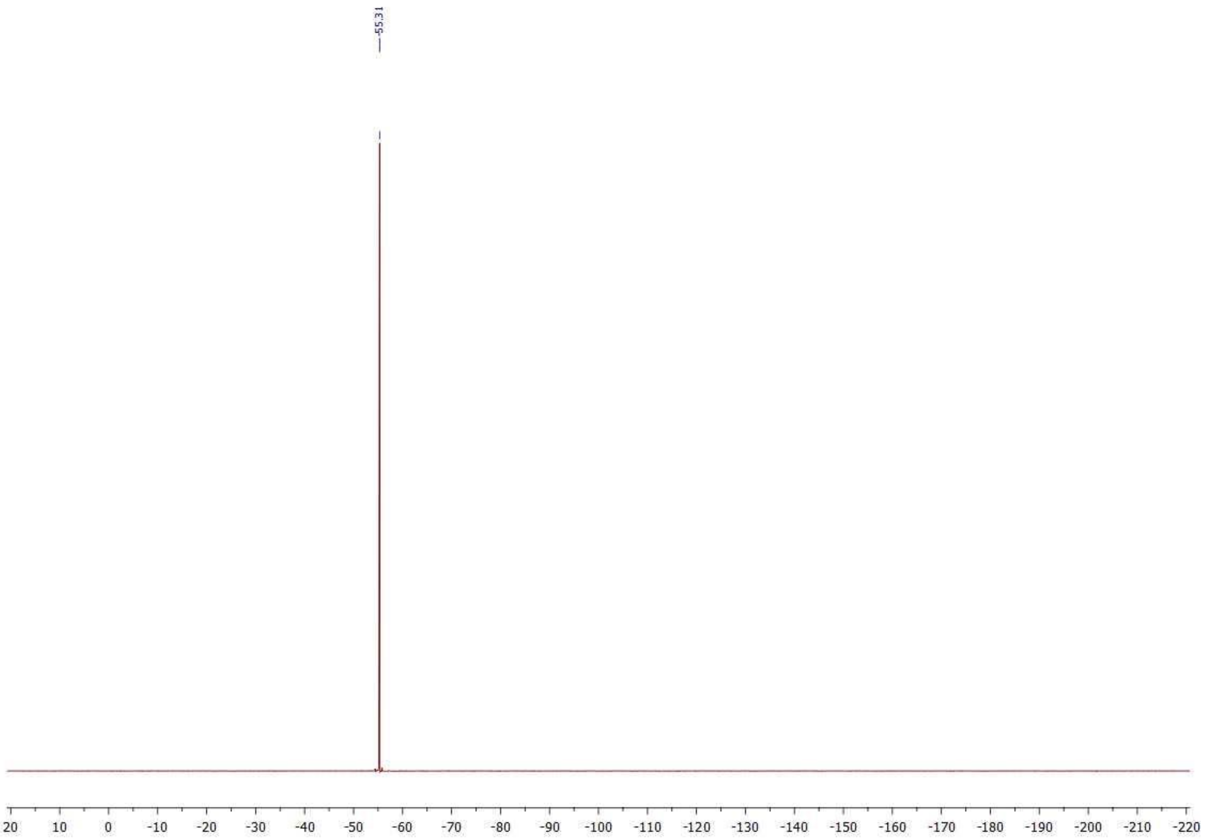
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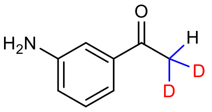
1-(3-aminophenyl)ethan-1-one-2,2-d_2 (3q)



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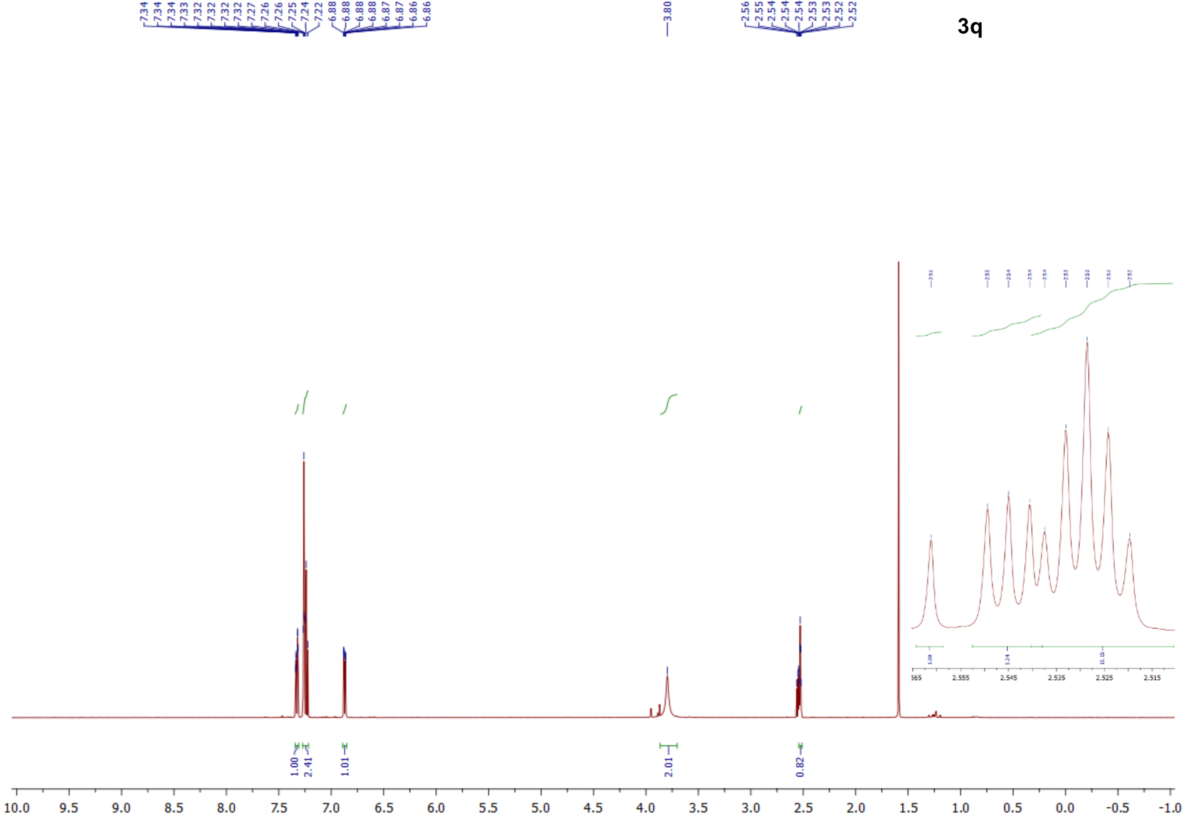
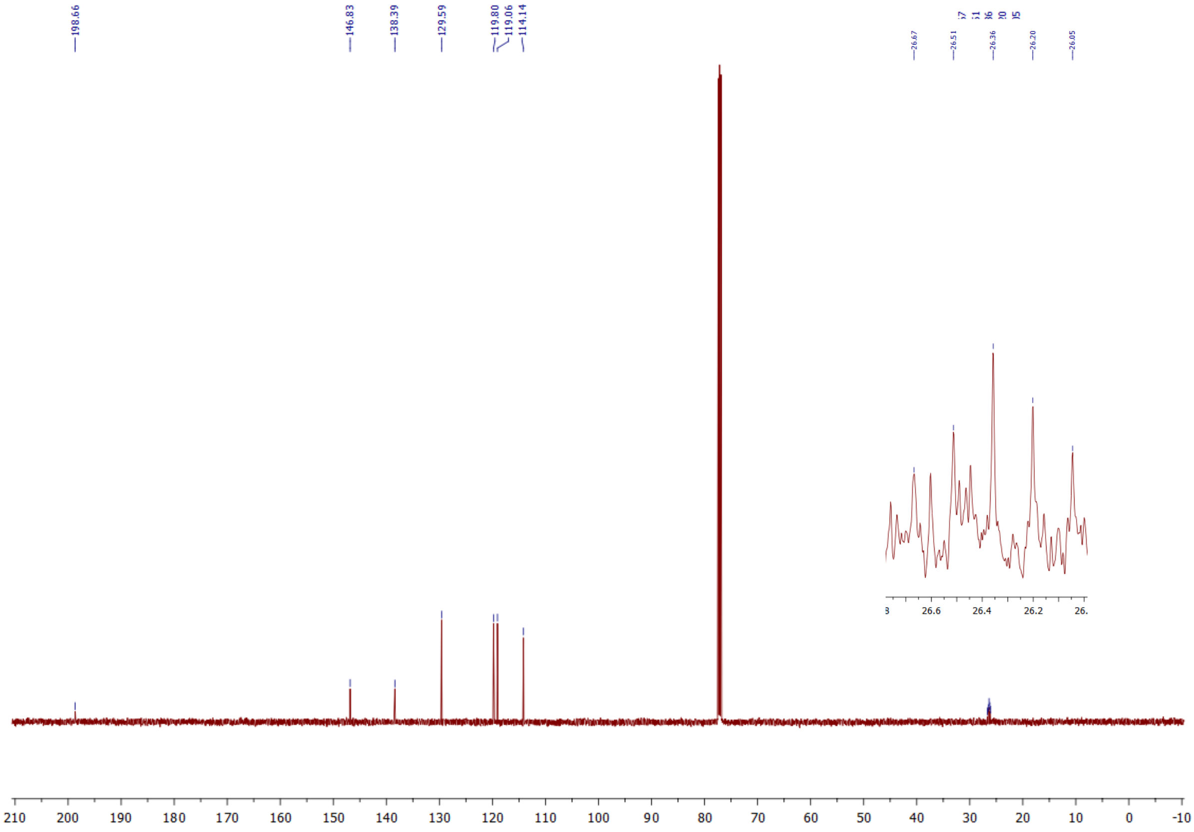
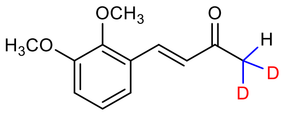




(*E*)-4-(2,3-dimethoxyphenyl)but-3-en-2-one-1,1-d$_2$ (3r)



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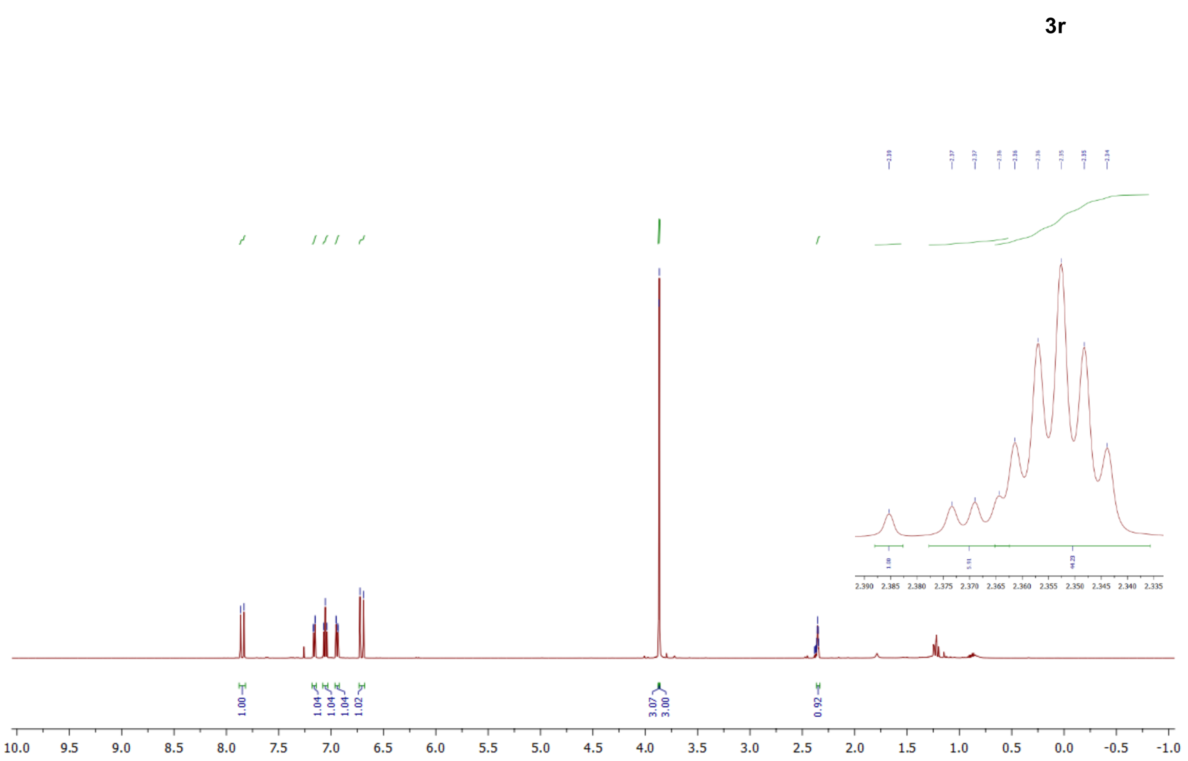
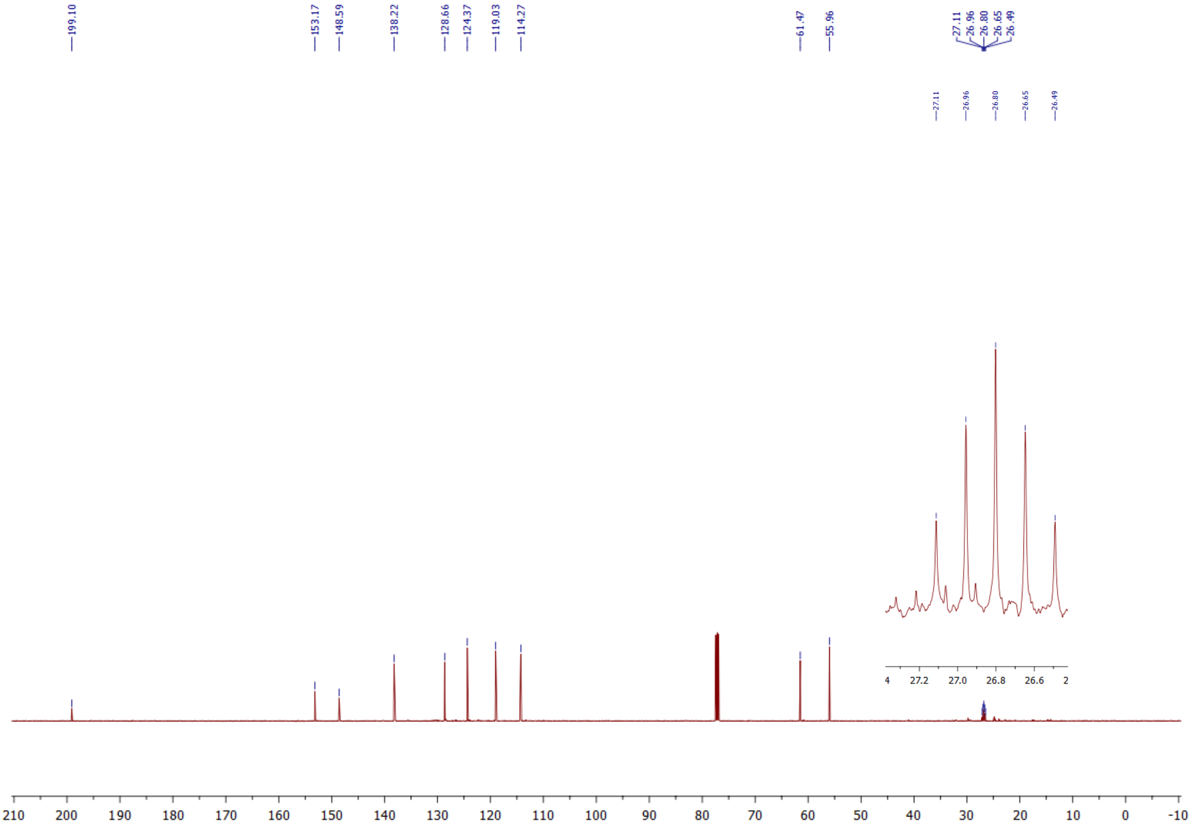
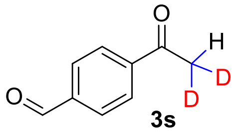




4-(acetyl-2,2-d$_2$)benzaldehyde (3s)



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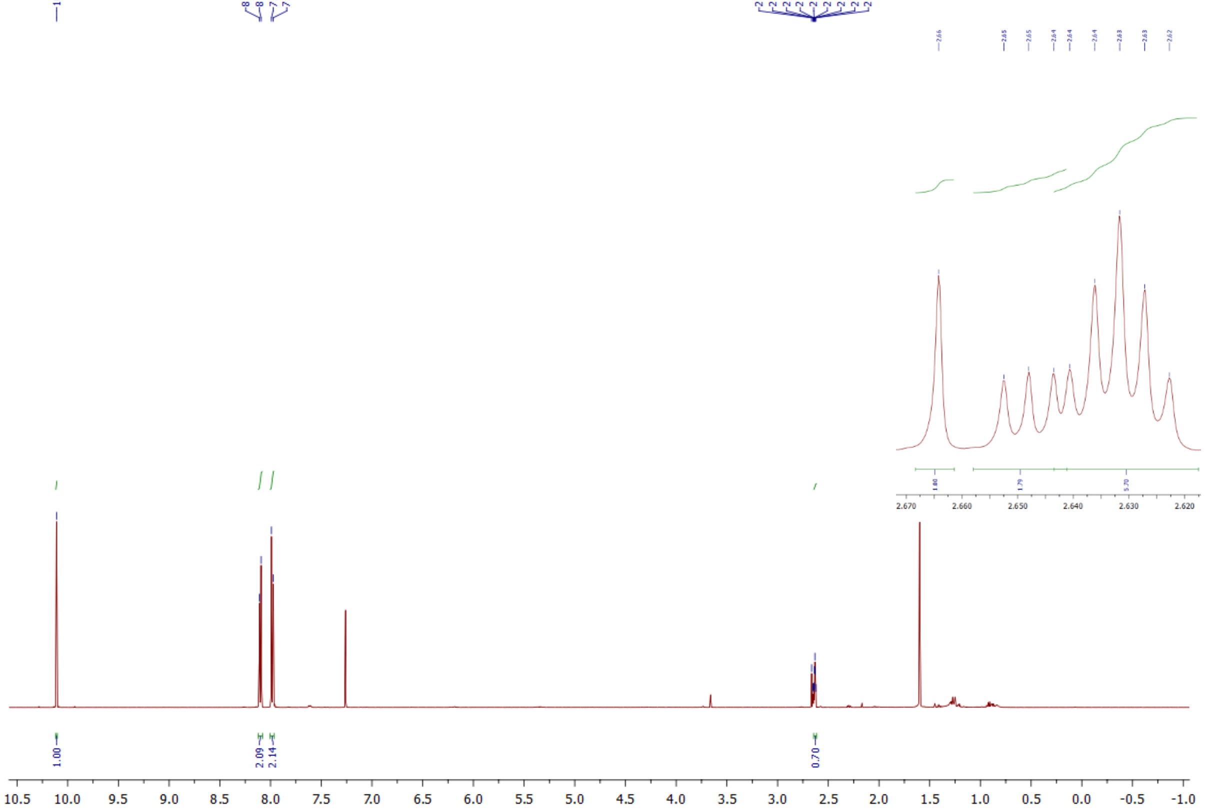
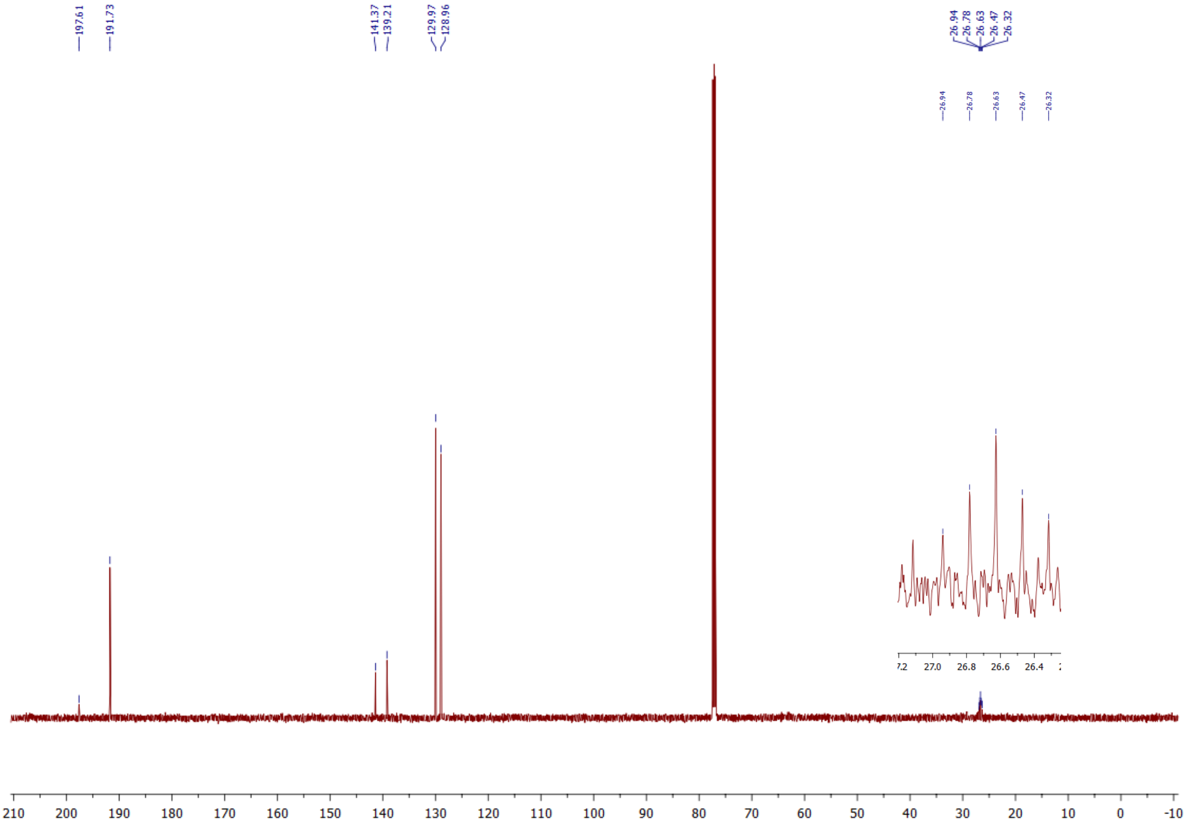
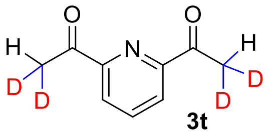




1,1'-(pyridine-2,6-diyl)bis(ethan-1-one-2,2-d$_2$) (3t)



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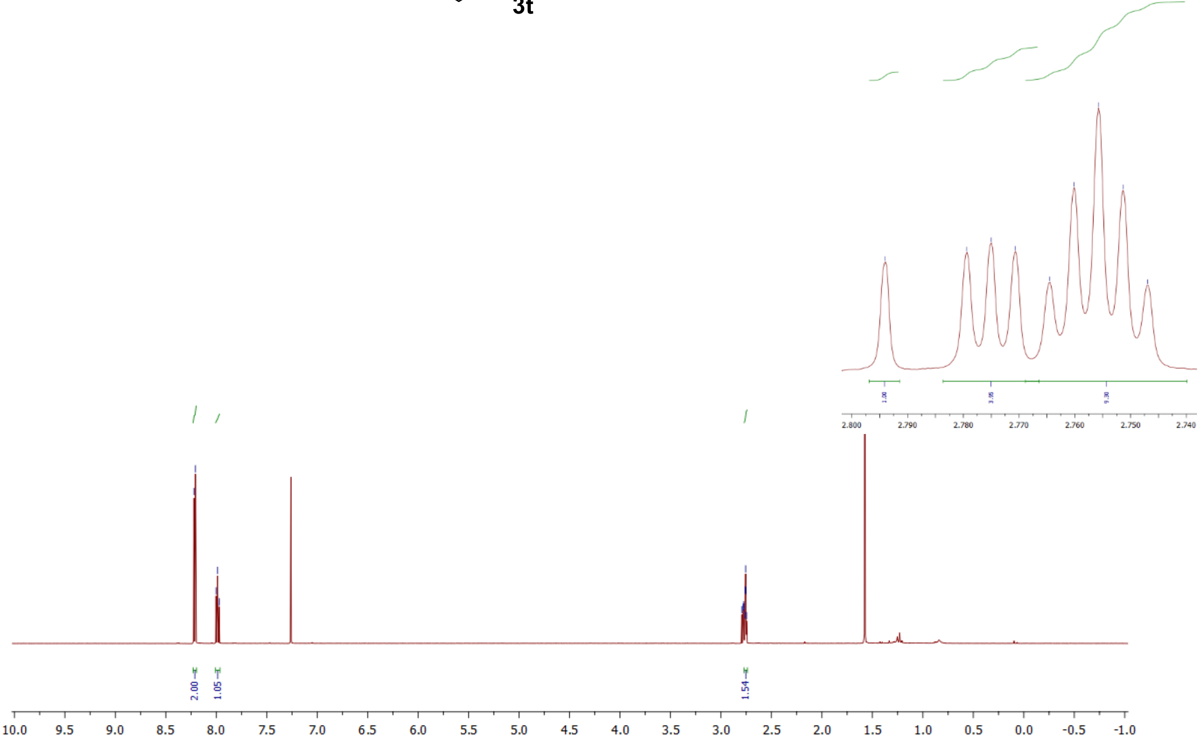
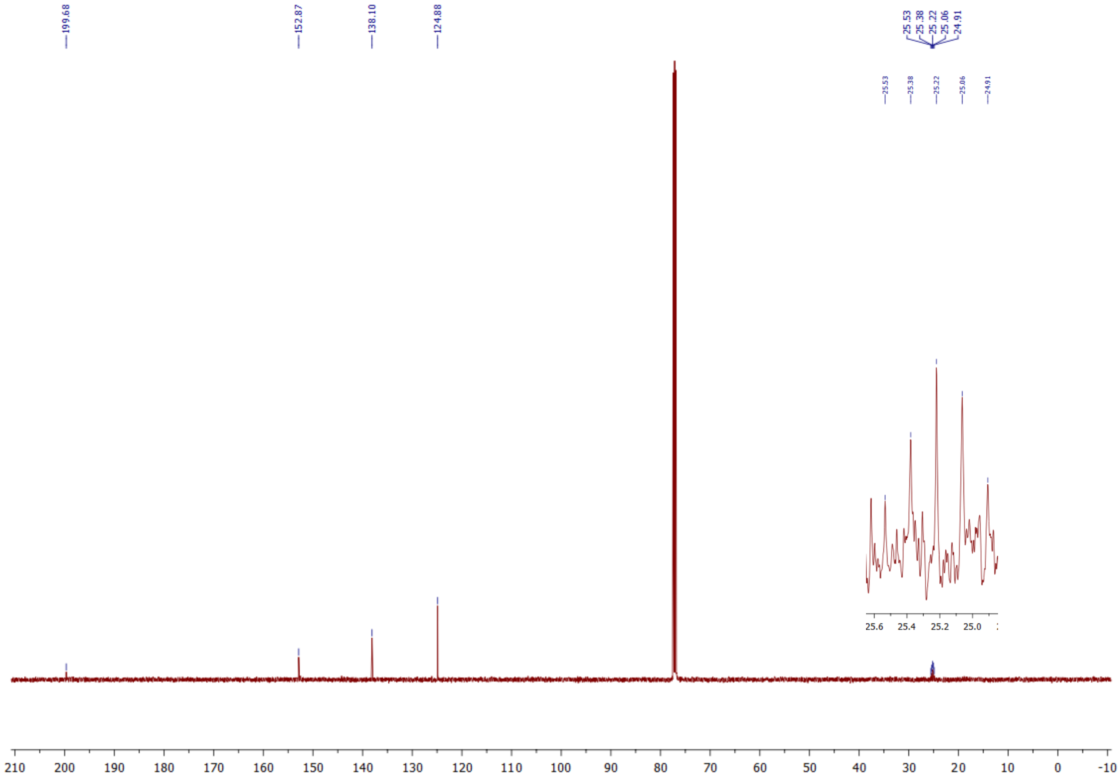
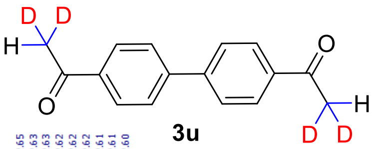




1,1'-([1,1'-biphenyl]-4,4'-diyl)bis(ethan-1-one-2,2-d_2) (3u)



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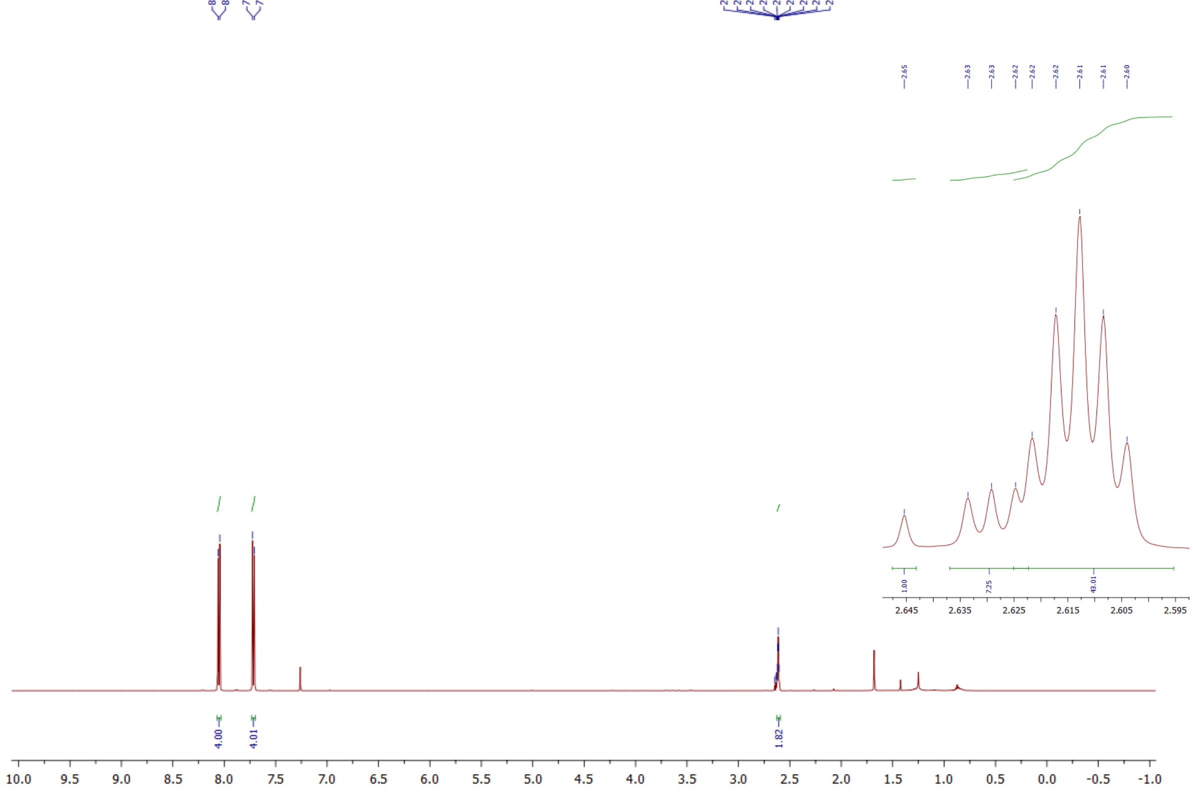
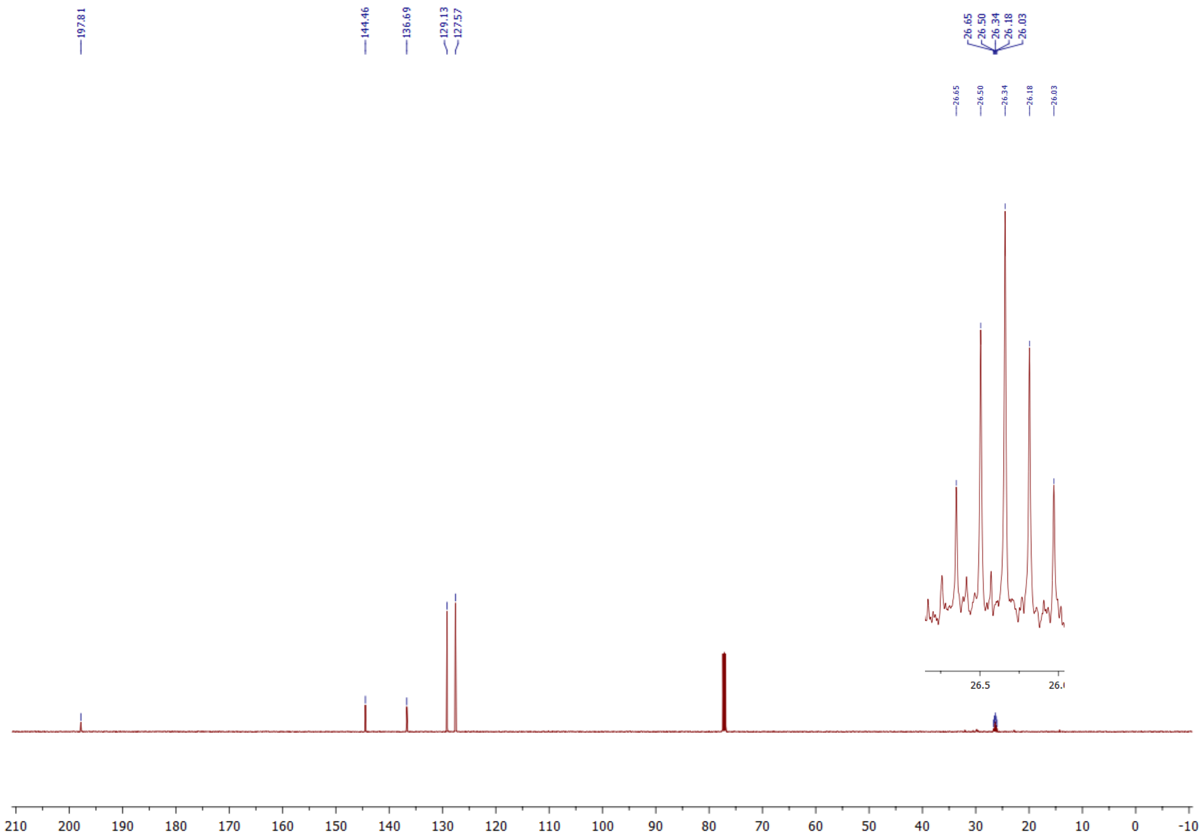
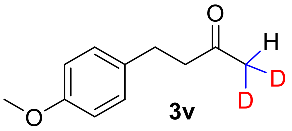




4-(4-methoxyphenyl)butan-2-one-1,1-d$_2$ (3v)



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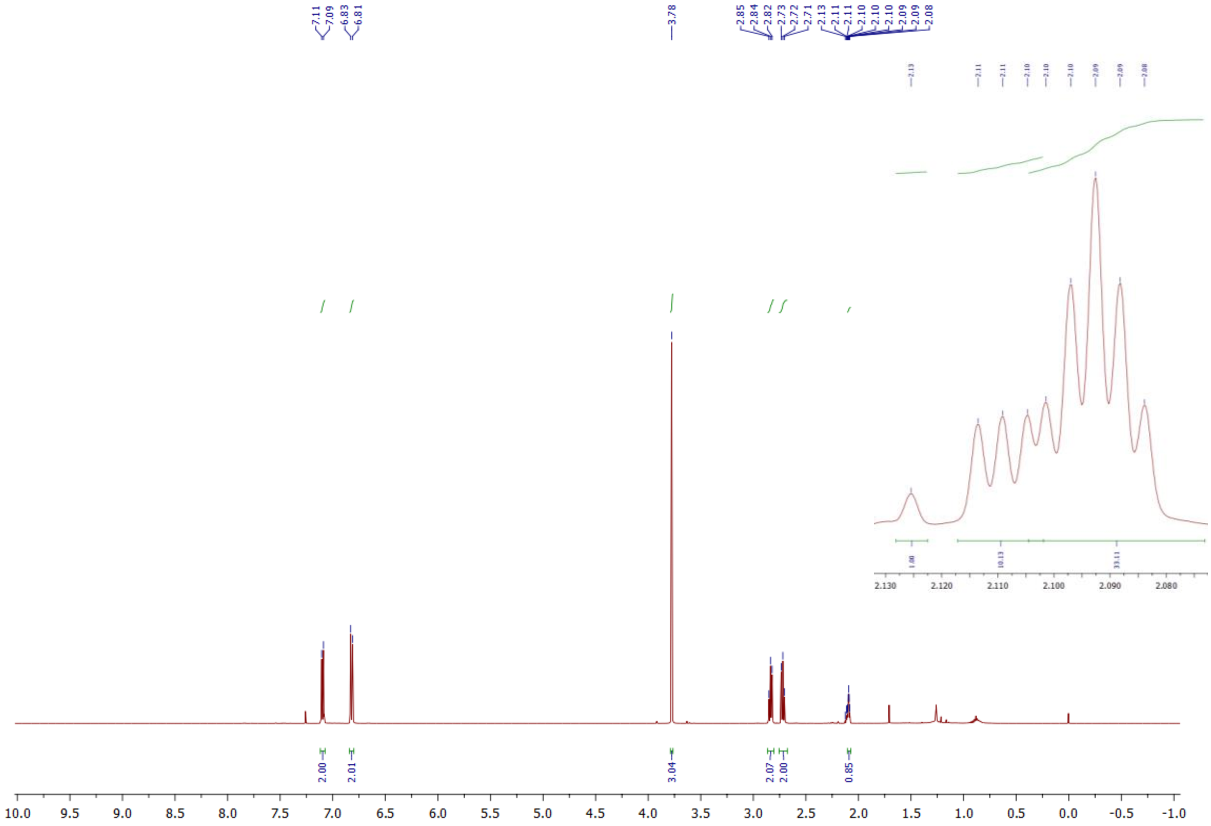
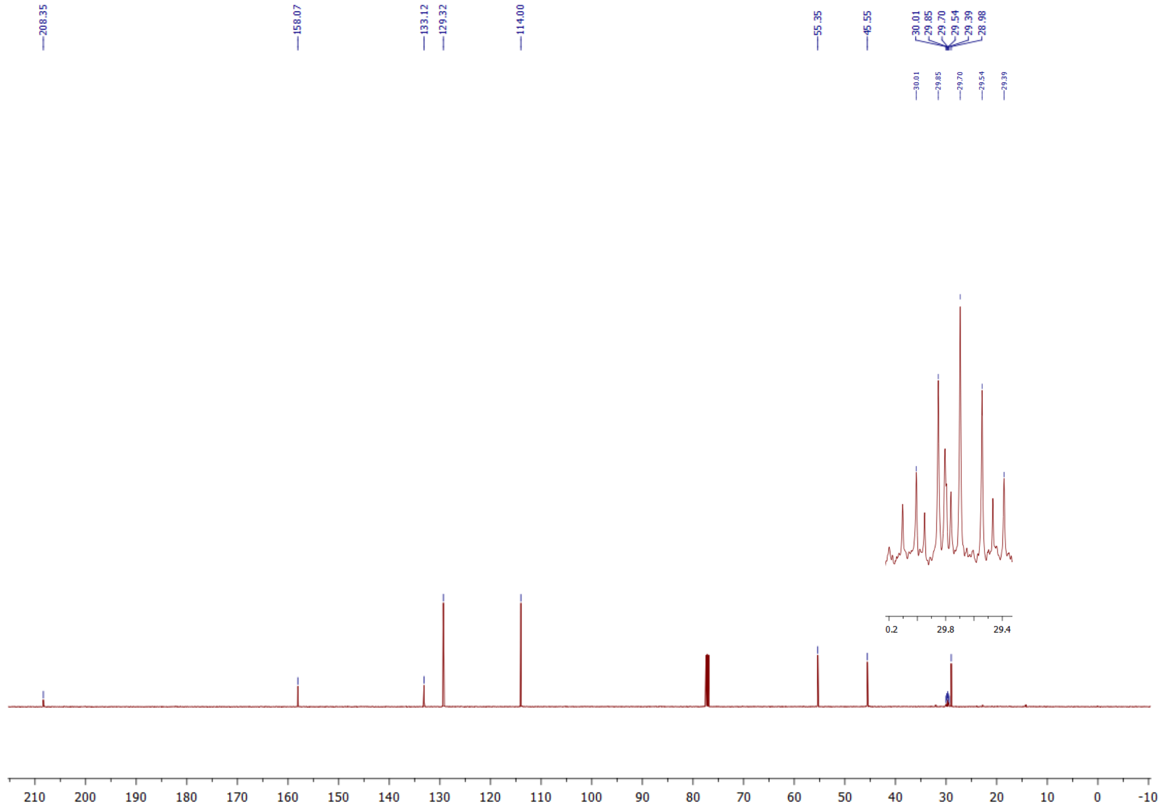
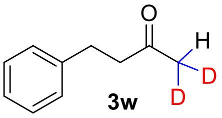
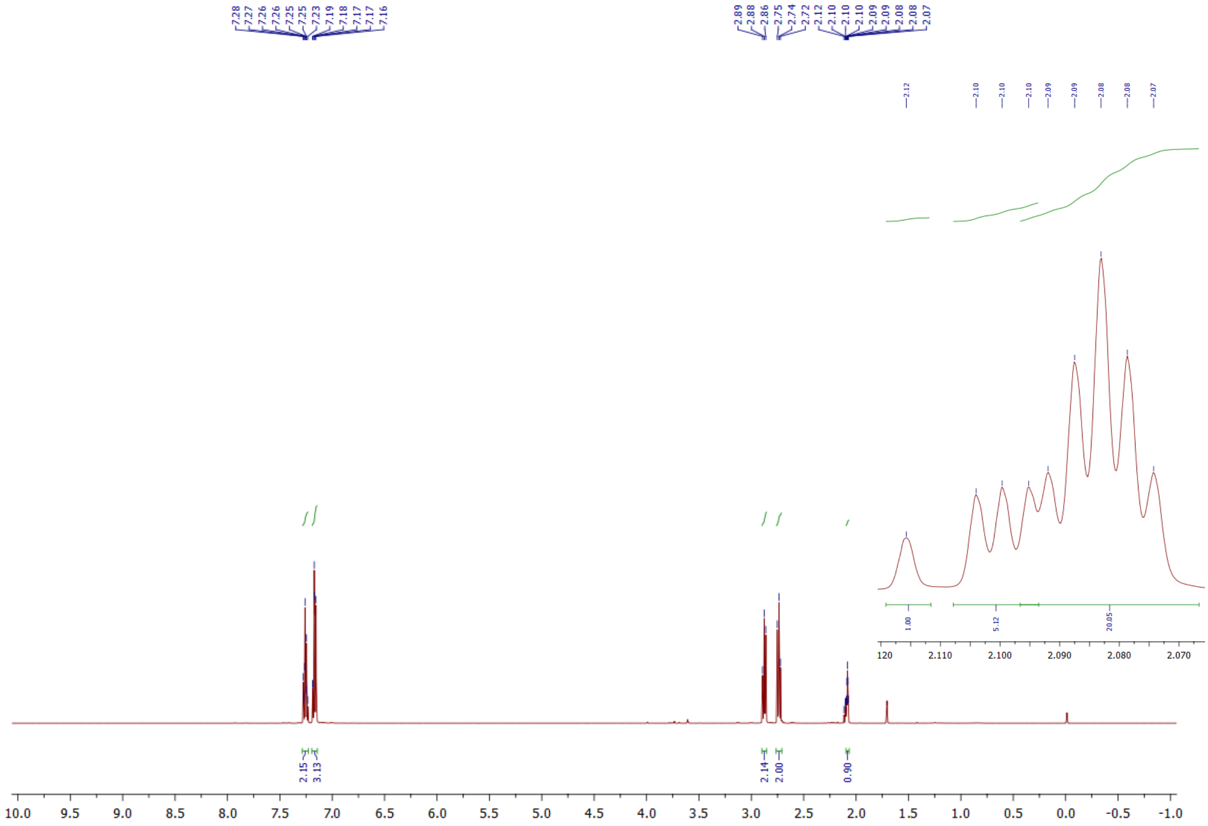
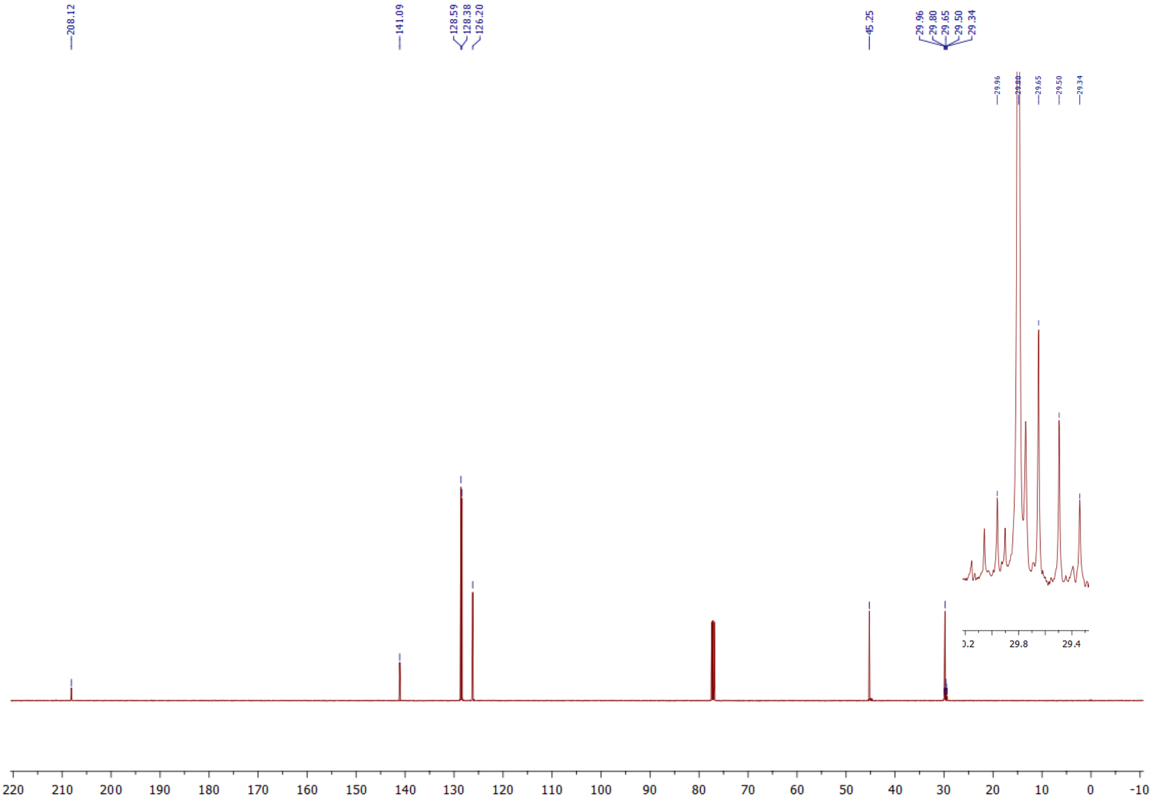




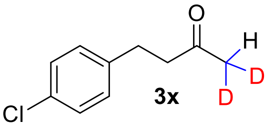
4-phenylbutan-2-one-1,1-d_2 (3w)

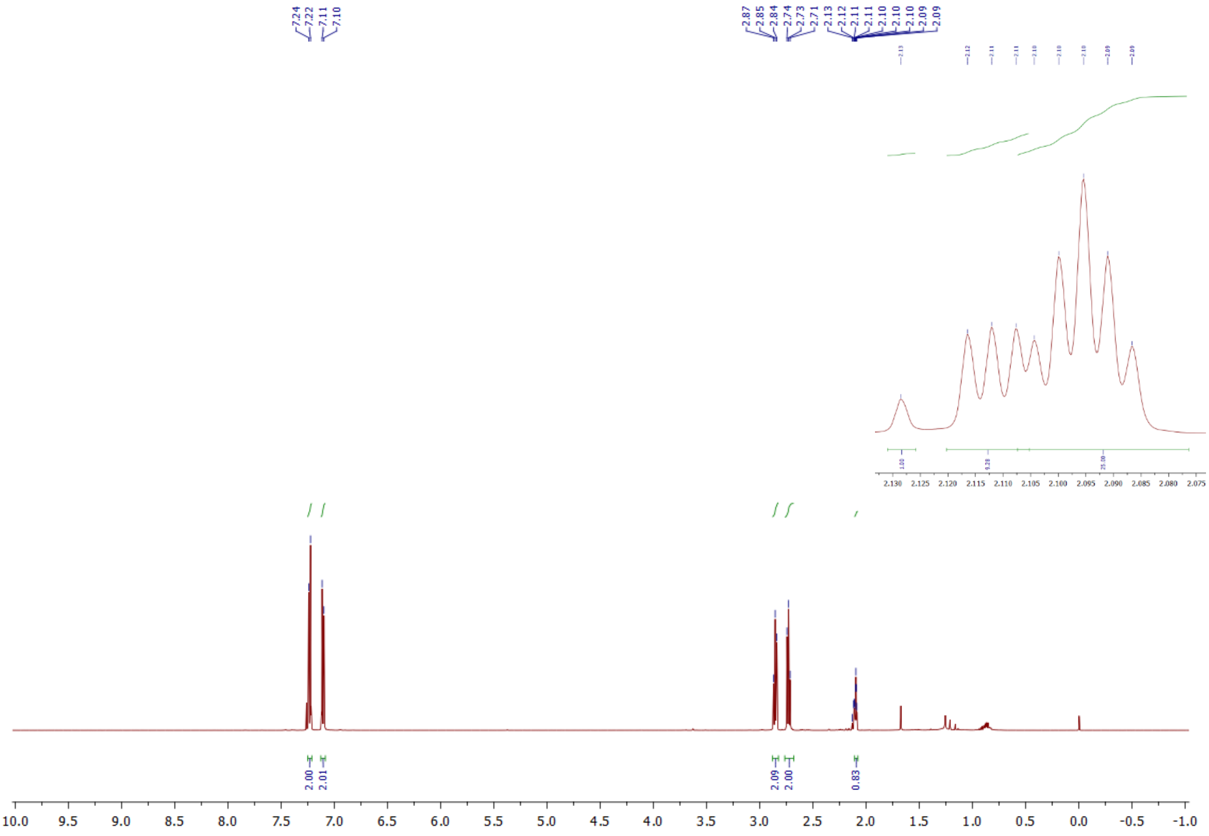


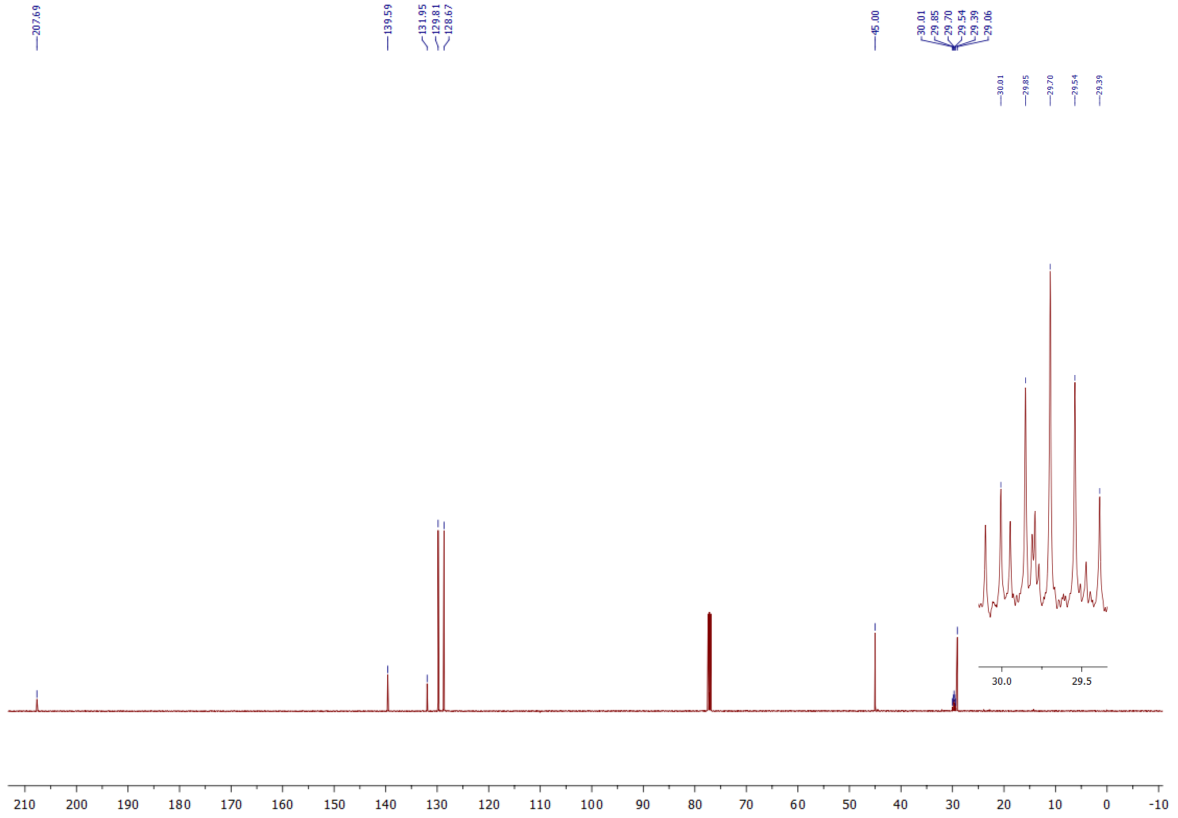




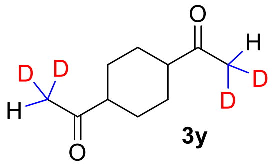
4-(4-chlorophenyl)butan-2-one-1,1-d$_2$ (3x)



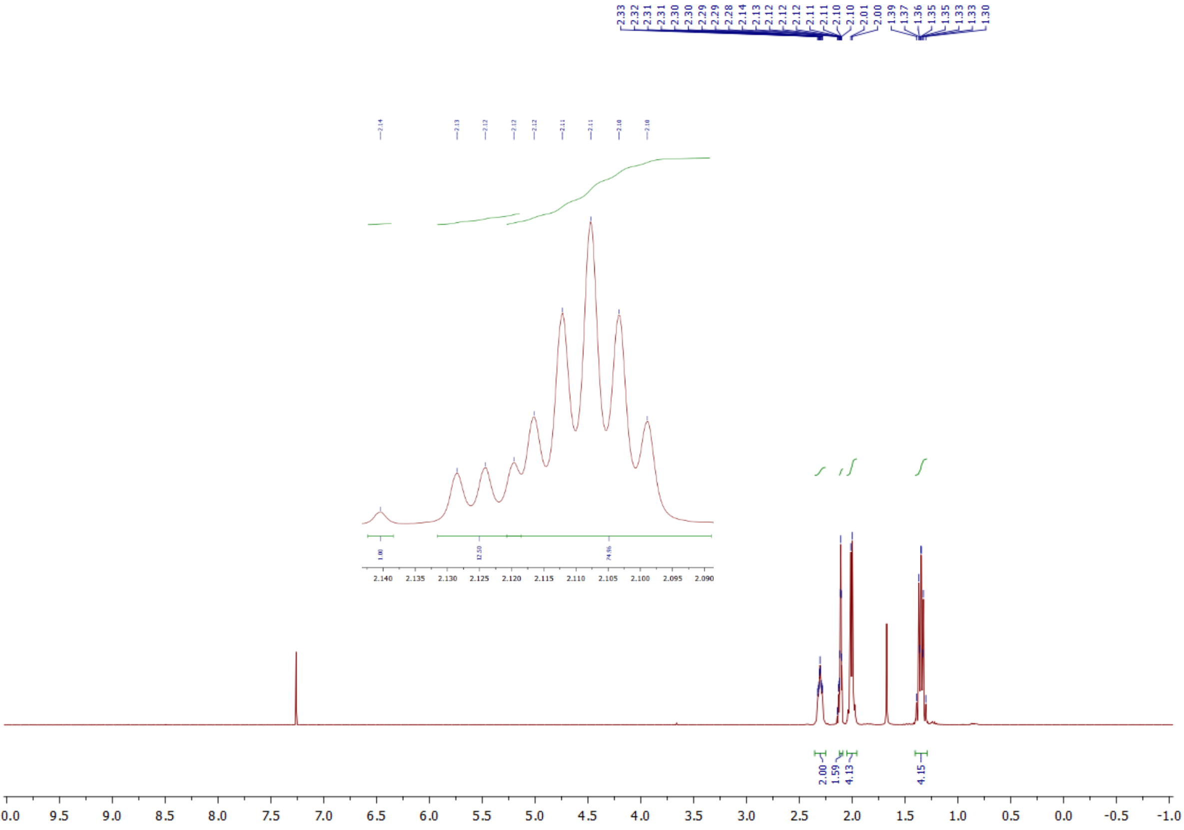


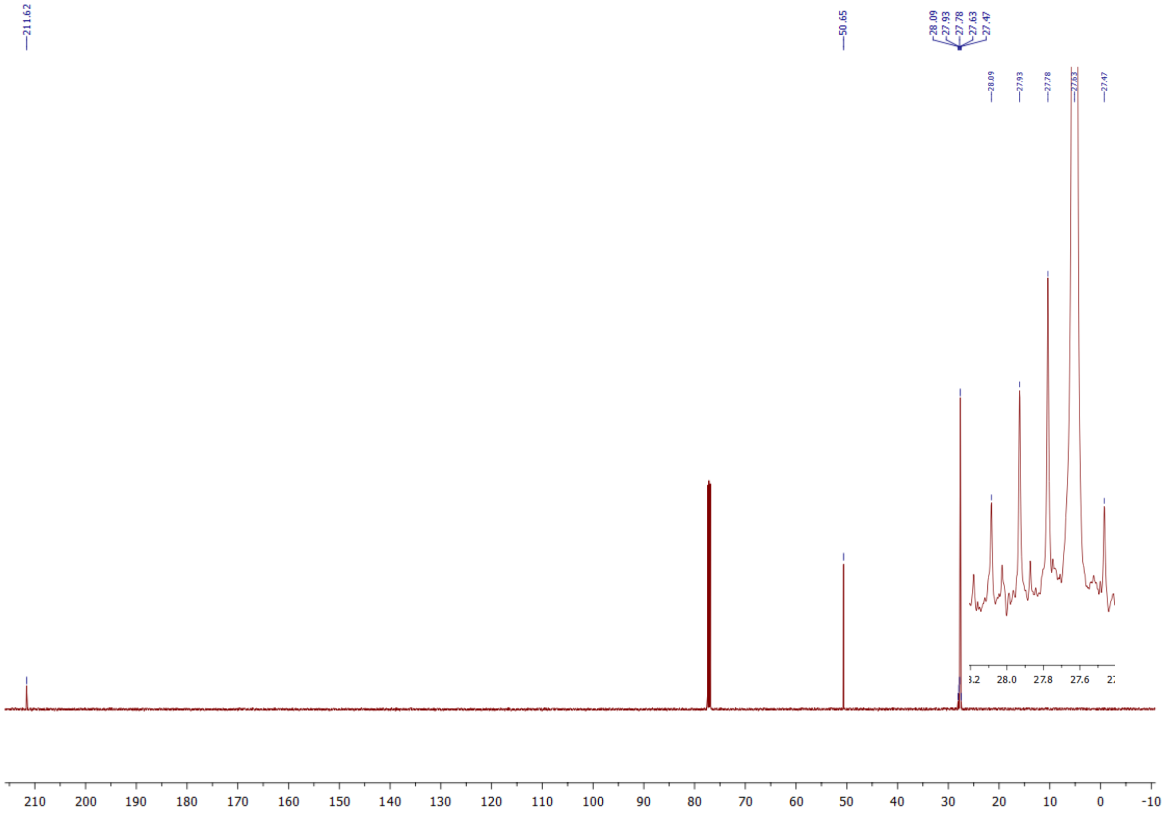


1,1'-(cyclohexane-1,4-diyl)bis(ethan-1-one-2,2-d$_2$) (3y)

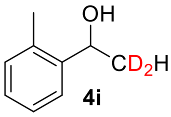


3y

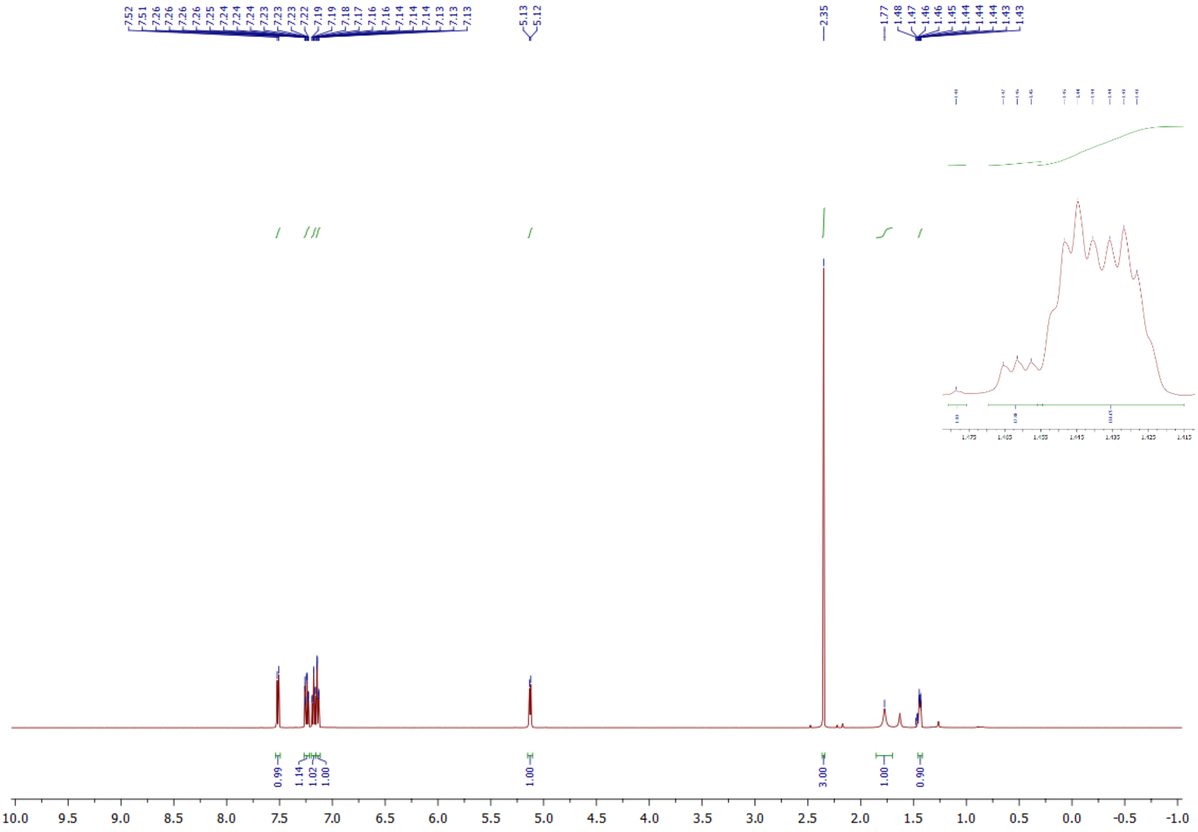


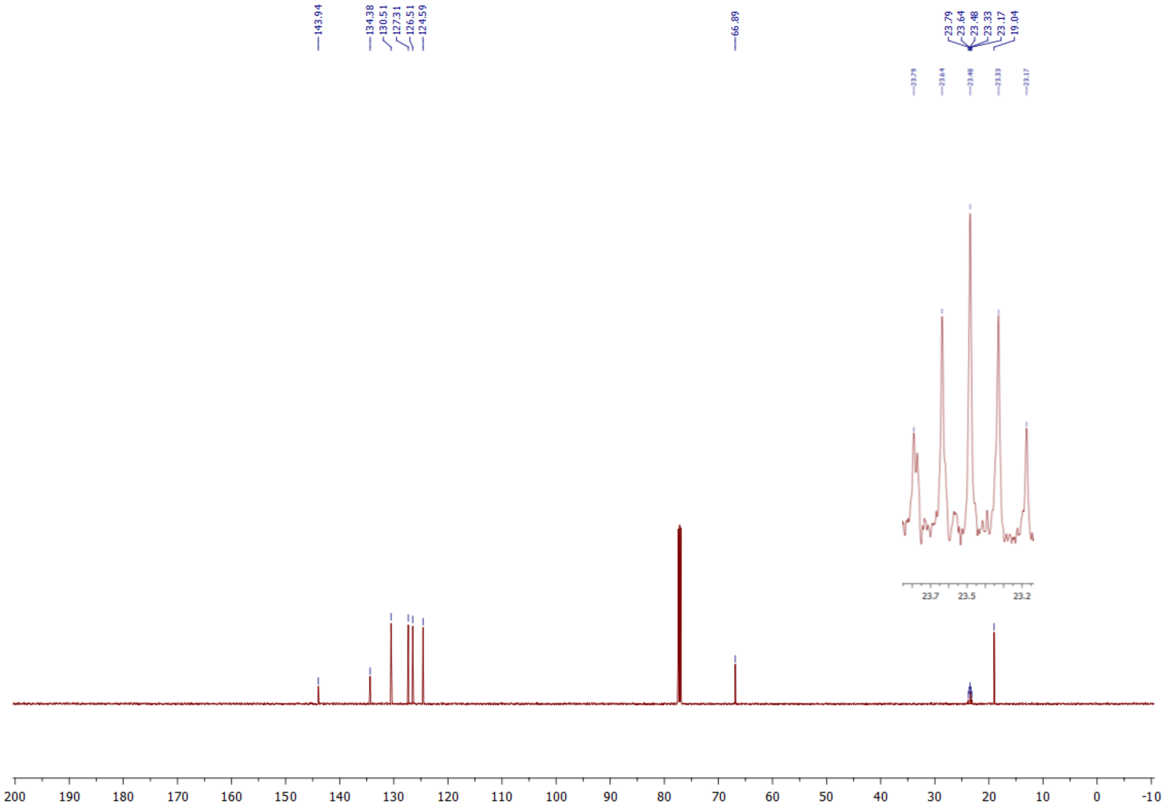


1-(*o*-tolyl)ethan-2,2-d$_2$-1-ol (4i)

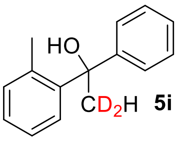


4i

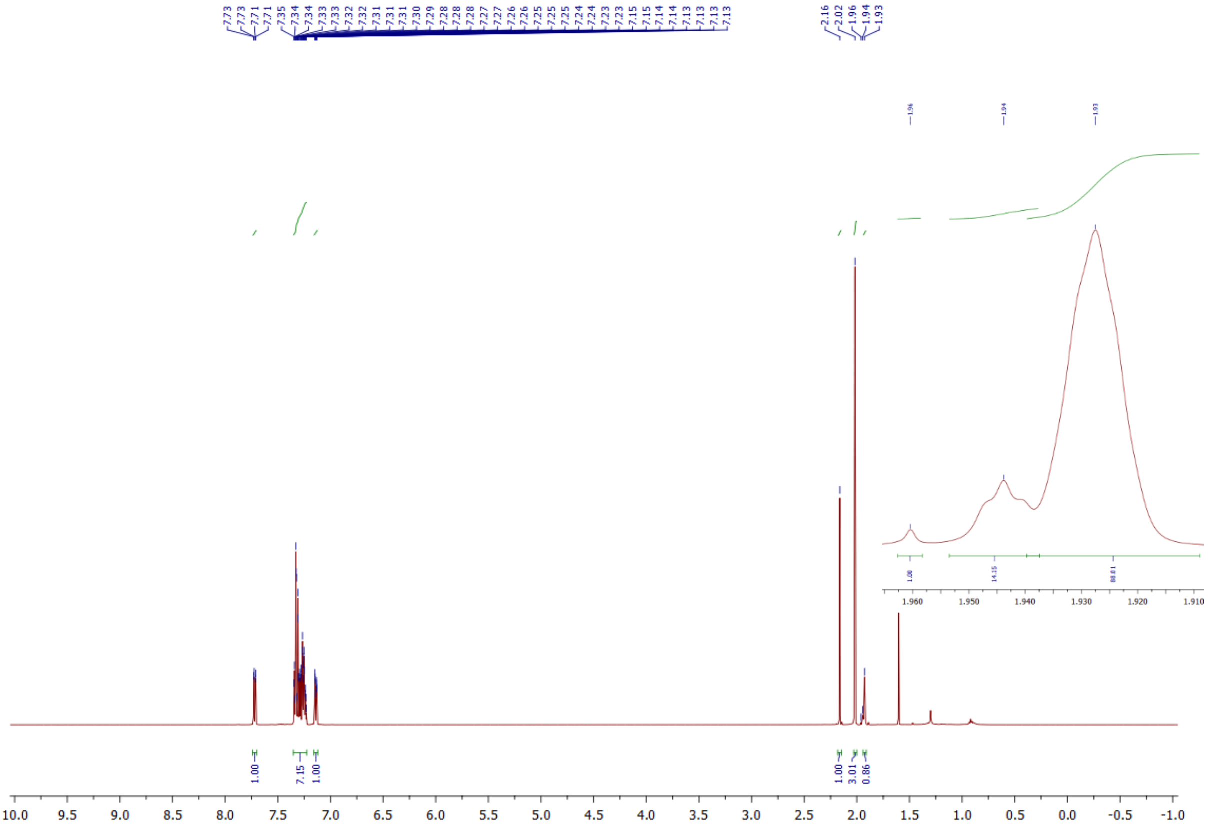


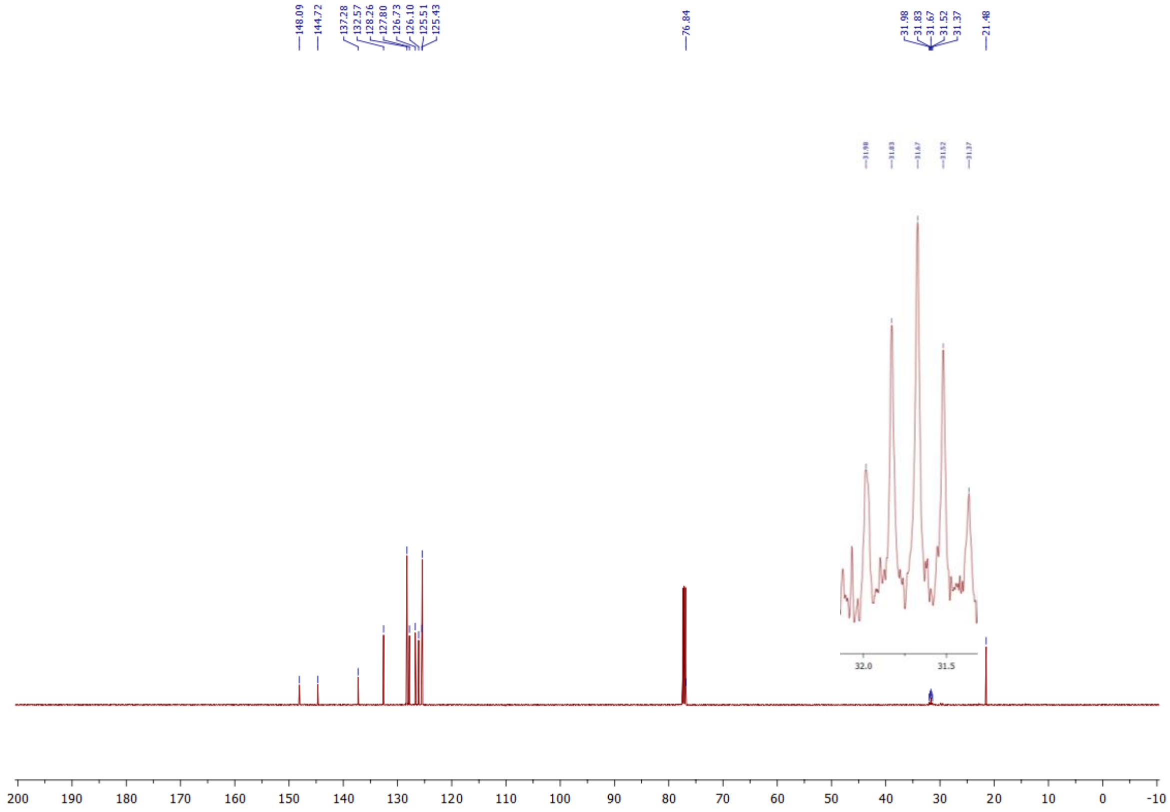


1-phenyl-1-(*o*-tolyl)ethan-2,2-d$_2$-1-ol (5i)

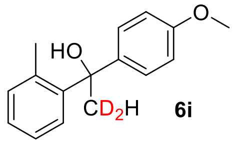


5i

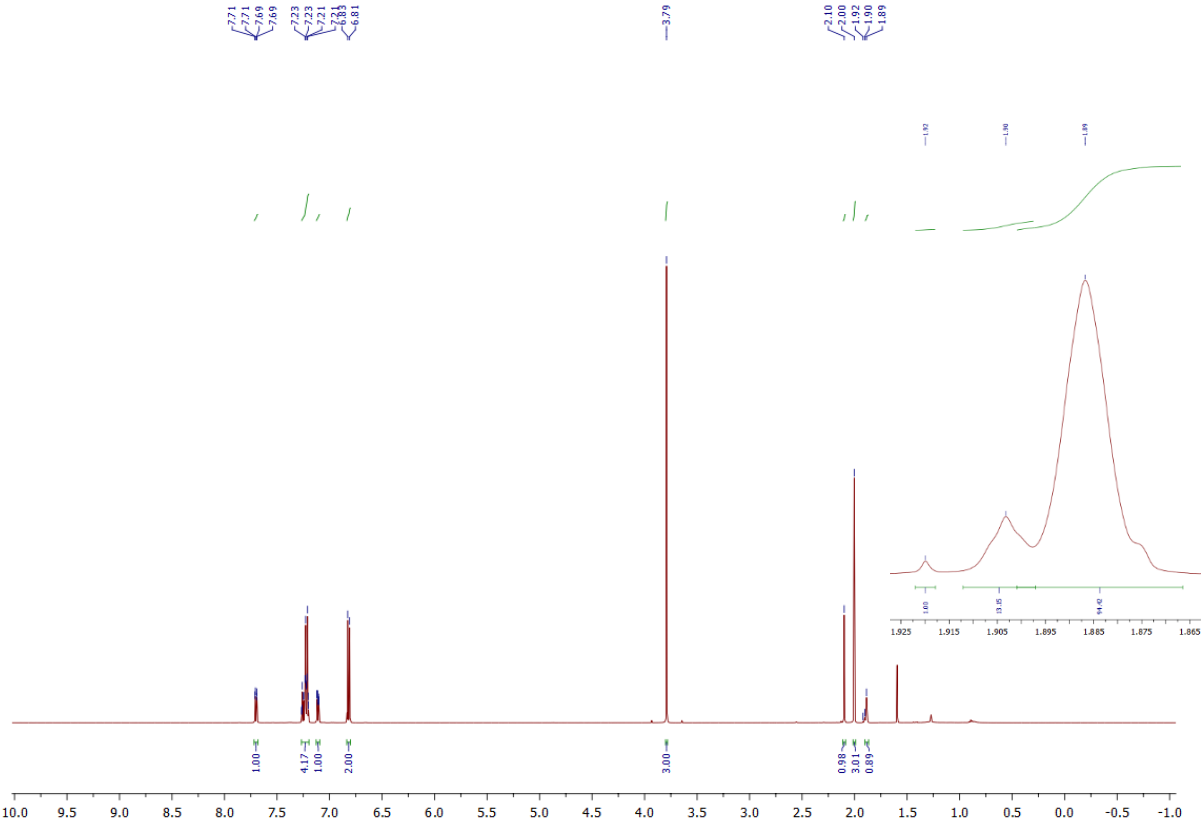


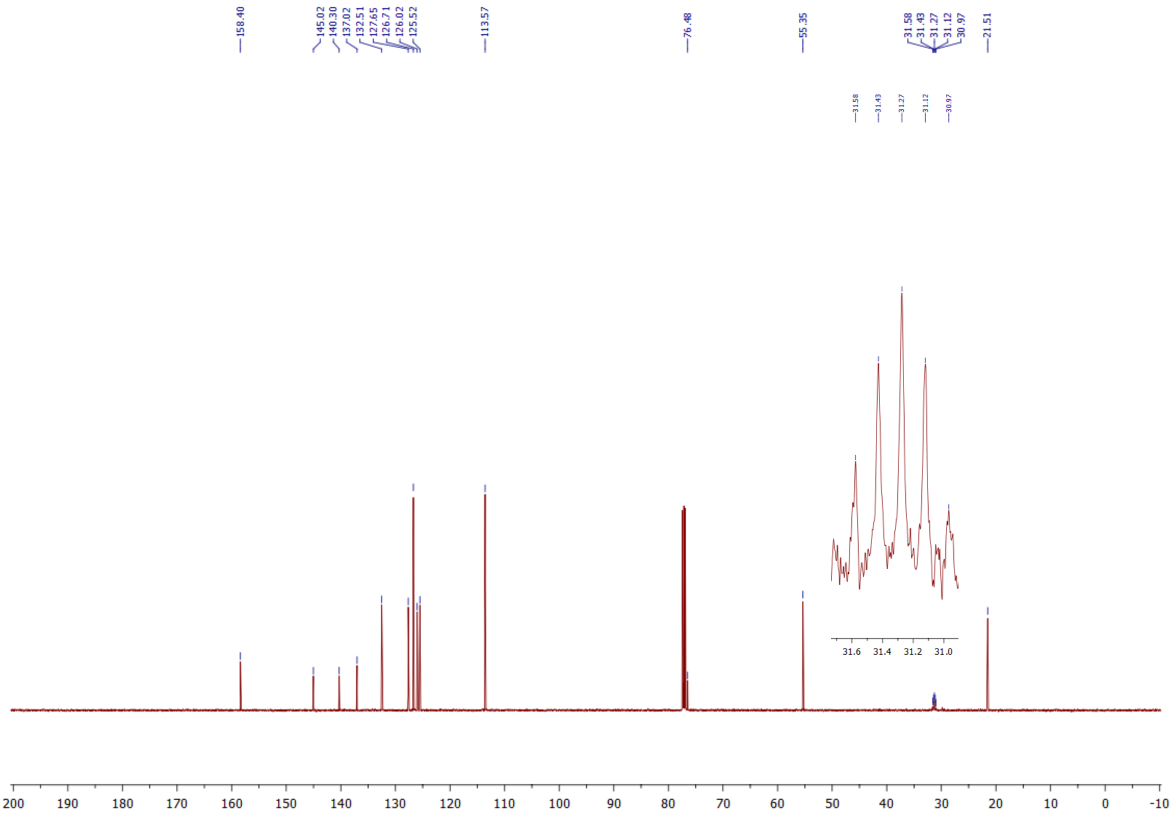


1-(4-methoxyphenyl)-1-(*o*-tolyl)ethan-2,2-d$_2$-1-ol (6i)

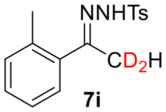


6i

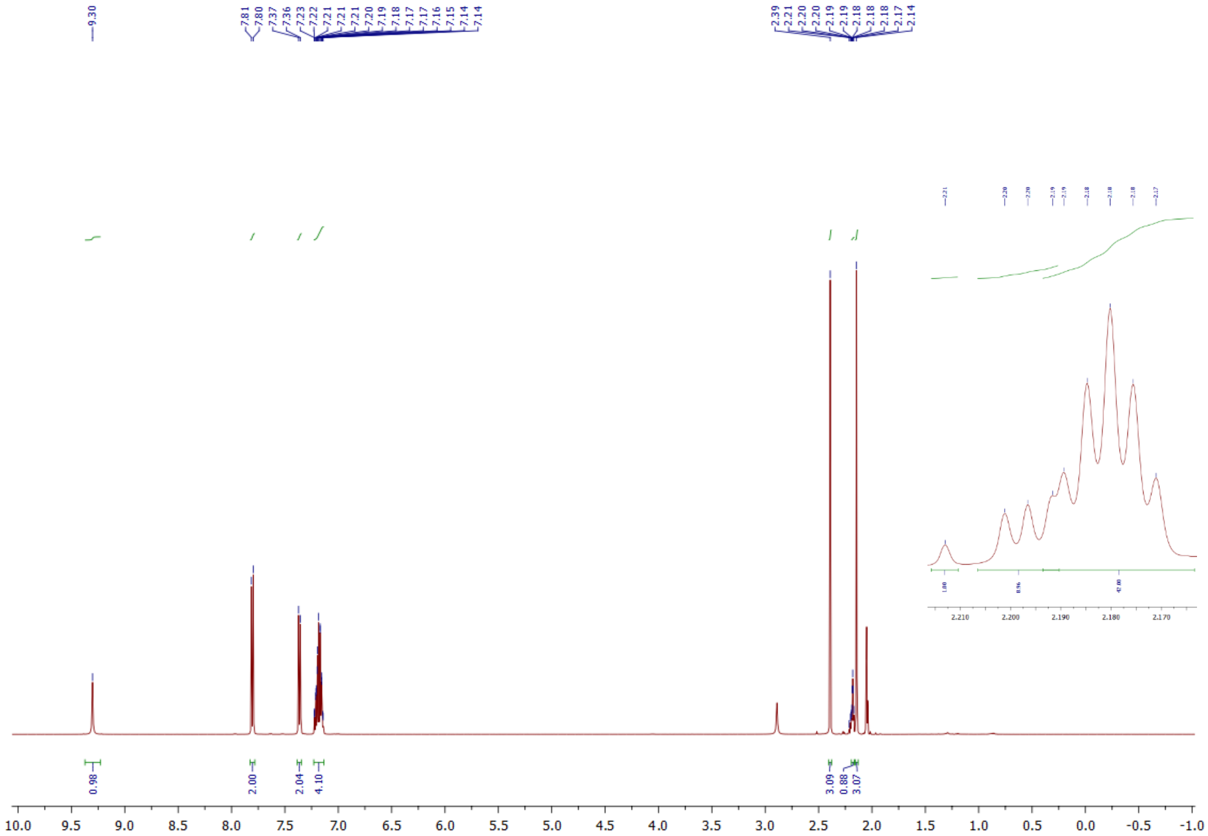


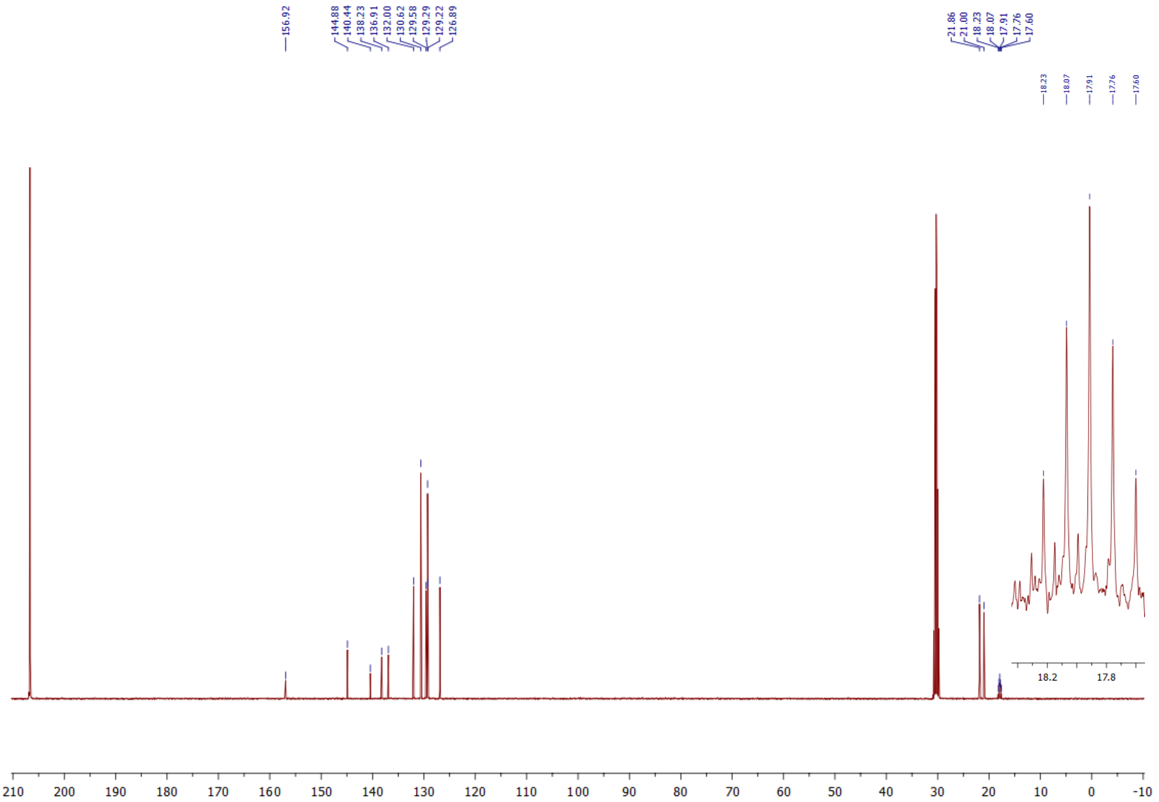


4-methyl-*N'*-(1-(*o*-tolyl)ethylidene-2,2-d₂)benzenesulfonohydrazide (7i)



7i





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[2] (a) D. R. Jensen, M. J. Schultz, J. A. Mueller, M. S. Sigman, *Angew. Chem. Int. Ed.* **2003**, *42*, 3810-3813. (b) A. L. Watkins, C. R. Landis, *J. Am. Chem. Soc.* **2010**, *132*, 10306-10317.

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