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Supporting Information

Organocatalytic *α*-Deuteration of Carbonyl Compounds: *p*TSA/D_2O Strategy for Bioactive and Natural Products

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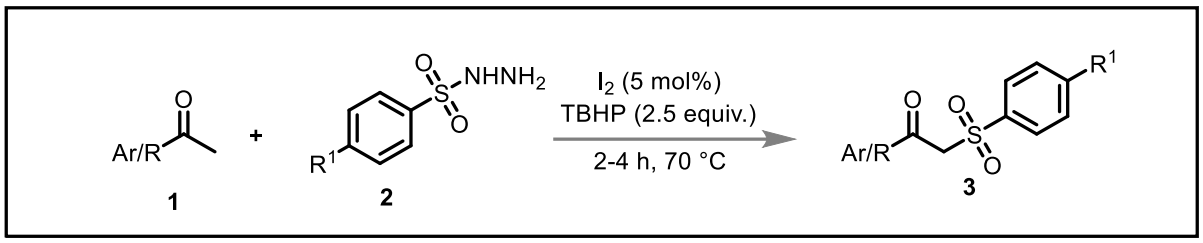
1. General Information:

All reagents and solvents were of pure analytical grade. All experiments were carried out in a dry Schlenk tube equipped with a stirring bar. Chemicals were purchased from Sigma-Aldrich, TCI, Alfa, Aesar, and Sisco Research Laboratories (SRL) and used without further purification. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD Chemical). Visualization of the developed TLC plate was performed by irradiation with UV light. High-resolution mass spectra (HRMS) were recorded on a mass spectrometer using electrospray ionization-time of-flight (ESITOF) reflectron experiments. ^{1}H-NMR and ^{13}C-NMR were recorded on 400 MHz and 500 MHz spectrometers, using $CDCl_3$ as a solvent; the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; $CDCl_3$ δ H (7.26 ppm). Coupling constants are reported in Hertz (Hz). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm, referenced to protium; s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration.

2. Synthetic Procedure for the Preparation of Starting Materials:

All the aromatic, heteroaromatic ketone derivatives and bioactive drug molecules were commercially available. Some bioactive sulfones (**3aa′, 3ab′, 3ac′**) were prepared as per the literature procedures. [1]

2.1 General Procedure for the Synthesis of *β*-Keto Sulfones:



Experimental procedure: In a dry reaction vial (10 mL), sulfonyl hydrazides (**2**, 0.45 mmol, 1.5 equiv.), ketones (**1**, 0.3 mmol, 1.0 equiv.) were taken, followed by the addition of TBHP (0.75 mmol, 2.5 equiv.) and 5.0 mol% iodine. The reaction was stirred at 70 ºC for 2 - 4 h. The completion of the reaction was monitored by a TLC plate in 20% EtOAc in hexane. The crude was purified by column chromatography, eluting with hexane/EtOAc to afford the desired *β*-Keto Sulfones (**3**). The product was characterized and identified by analyzing spectral data (^{1}H and ^{13}C NMR).

3. General Procedure:

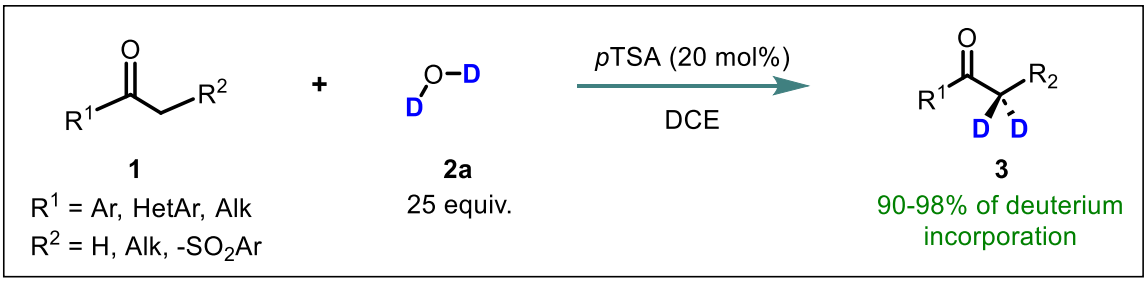
3.1 General procedure for drying *p*TSA (GP1):

To prepare anhydrous *p*-toluenesulfonic acid, begin by dissolving 100.0 g of *p*-toluenesulfonic acid monohydrate in 150 mL of anhydrous toluene within a 250 mL round-bottom flask, ensuring it is

equipped with a magnetic stir bar. Connect the flask to a Dean-Stark apparatus, a condenser, and a nitrogen inlet to maintain an inert atmosphere. Next, reflux the mixture at 150 °C for 2 to 3 h. During this time, water will be continuously removed from the system as an azeotrope. Monitor the progress of the dehydration process by watching for a cessation of water collection in the Dean-Stark trap. To collect the water, open the trap and allow it to flow into a 100 mL beaker. Once the reaction is complete, cool the mixture from 150 °C to room temperature. Subsequently, remove the toluene under reduced pressure. This process will yield anhydrous *p*-toluenesulfonic acid, which should appear as a white crystalline solid.

Figure 1: Dean-Stark apparatus

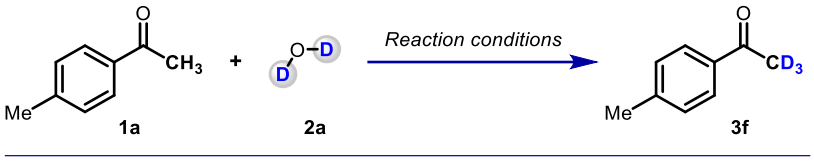
3.2 General procedure for the deuteration (3a-3ap), (GP2):



In a dry sealed tube (10 mL) equipped with a magnetic stir bar, 20 mol% of dry *p*TSA and 0.2 mmol (1.0 equiv.) of substrates were added. The tube was then evacuated and backfilled with nitrogen three times. Following this, 0.1 mL (25 equiv.) of D_2O and 0.2 mL of 1,2-dichloroethane (as a co-solvent) were introduced. The reaction mixture was stirred at 100 °C for 24 hours. After the reaction, pure deuterated products were obtained by diluting the reaction

mixture with chloroform, filtering it through a pad of Na_2SO_4, and concentrating it under reduced pressure, resulting in the desired deuterated product (without the need for column chromatography). The product was characterized and identified by analyzing spectral data (^1H, ^{13}C, and HRMS). The percentage of deuterium [D] incorporation was calculated using the internal alkyl group or internal C-H as the internal standard.

4. Table S1 Optimization Studies:



Entry No.	Catalyst (X mol%)	Time (h)	% of [D]	Yield (%)[b]
1	*p*TSA•H_2O (10)	12	66	93
2	TfOH (10)	12	74	90
3	C_6F_5OH (10)	12	66	90
4	TFA (10)	12	70	93
5	Brookhart's acid (10)	12	70	86
6	TMSCl (10)	12	66	87
7	$B(C_6F_5)_3$ (10)	12	75	89
8	Dry *p*TSA (10)	12	84	90
9[c]	Dry *p*TSA (10)	12	90	92
10[c]	Dry *p*TSA (10)	24	92	90
11[c]	Dry *p*TSA (20)	24	94	90
12	*p*TSA•H_2O (20)	24	82	91
13[d]	Dry *p*TSA (20)	24	76	90
14[e]	Dry *p*TSA (20)	24	70	92

[a]Reaction conditions: 1a = 0.2 mmol (1.0 equiv.); 2a = 5 mmol, (25.0 equiv.); HFIP = 0.2 mL, Temperature 100 ^{0}C, [b]Isolated yields, [c]DCE = 0.2 mL (instead of HFIP as a solvent); [d]2a = 1.8 mmol, (9.0 equiv.), [e]2a = 1.2 mmol, (6.0 equiv.) Brookhart's acid = $[(3,5\text{-}(CF_3)_2C_6H_3)_4B]^-$ $[H(OEt_2)_2]^+$, TMSCl = Trimethylchlorosilane, TFA = Trifloroacetic acid, HFIP = 1,1,1,3,3,3-Hexafluoro-2-propanol.

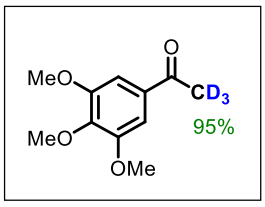
Based on our previous work on Brønsted acid-catalyzed organic transformation,[21-22] and [D] scrambling experiment,[23–24] we present a metal-free catalytic deuteration process utilizing cost-effective D_2O, facilitated by *p*TSA. We report a clean, by-product-free, and site-selective deuteration protocol that yields deuterated products without the need for chromatographic purification. Building on recent advances in deuteration,[25-27] we began our optimization study with 4-methyl acetophenone (**1a**) as a model substrate, utilizing *p*TSA•H_2O as the catalyst. We aimed to optimize the metal-free hydrogen/deuterium (H/D) exchange using D_2O in a co-solvent of HFIP. Through a comprehensive investigation, we achieved notable results, obtaining deuterated 4-methyl acetophenone with a 93% yield and a deuterium uptake of up to 66% at the α-position. This successful outcome was accomplished by conducting the reaction with 10.0 mol% *p*TSA•H_2O in 0.3 mL of solvent (2:1, HFIP: D_2O) over a

period of 12 h at 100 °C under N_2 (Table 1, Entry 1). To enhance deuterium incorporation, we explored a range of Brønsted acid catalysts. In triflic acid, we observed a slight increase in deuterium incorporation (Table 1, Entry 2). We also attempted reactions with pentafluorophenol, trifluoroacetic acid, and Brookhart's acid, although the initial results were not as promising as we had hoped (Table 1, Entries 3-5). A decrease in deuterium incorporation was observed when TMSCl is used (Table 1, Entry 6). However, the deuterium incorporation increased to 75% with $B(C_6F_5)_3$. We achieved a promising deuterium incorporation of up to 84% when using dry *p*TSA (Table 1, Entry 8). This successful outcome was achieved by performing the reaction with 10 mol% of the dry *p*TSA in 0.3 mL of solvent (2:1, HFIP: D_2O) for 12 h at 100 °C. Interestingly, substituting HFIP with anhydrous DCE further improved deuterium incorporation (Table 1, entry 9[c]). After this, we subjected the same reaction to 24 h, resulting in 92% deuterium incorporation (Table 1, entry 10[c]). Finally, we achieved 94% deuterium incorporation with 20.0 mol% catalyst loading for 24 h (Table 1, entry 11[c]). To explore the role of monohydrated *p*TSA, we executed an additional reaction under the same conditions. As a result, we achieved a commendable 91% yield along with 82% deuterium incorporation (Table 1, entry 12). This observation suggests that the presence of monohydrated *p*TSA leads to a reduced level of deuterium incorporation. After achieving optimal conditions, we attempted to reduce the equivalent of D_2O, but the deuterium incorporation also decreased (Table 1, entries 13[d] and 14[e]). The methyl substituents in **1a** serve as an internal standard for calculating the percentage of D incorporation.[5] With optimized conditions (Table 1, entry 11[c]), we explored the substrate scope of this H–D exchange method.

4. Analytical Data of Synthesized Compounds (3a-3ap)

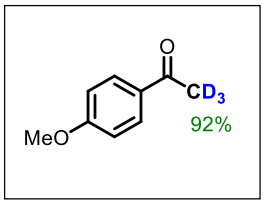
4.1 Analytical Data of Synthesized Compounds (3a-3ah)

1-(3,4,5-Trimethoxyphenyl)-ethan-1-one-2,2,2-*d*$_3$ (3a): Prepared according to **GP2**, 3,4,5-methoxy acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (38.8 mg) in 91% yield with 95% incorporation of deuterium.



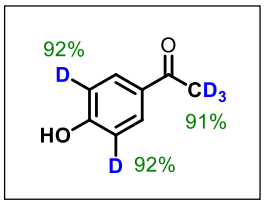
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 2H), 3.92 (s, 9H), 2.56 (s, 0.15H, 95% D) ppm. **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 196.9, 153.0, 142.6, 132.5, 105.8, 60.9, 56.3, 26.1 – 25.4 (m, *J* =11.9 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{11}H_{11}D_3O_4$ 214.1159; Found 214.1167.

1-(4-Methoxyphenyl)-ethan-1-one-2,2,2-*d*$_3$ (3b): Prepared according to **GP2**, 4-methoxy acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 hours using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under



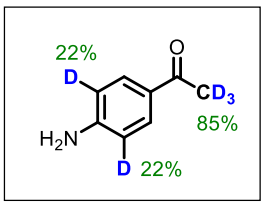
reduced pressure, yielding the pure deuterated compound, a white solid (28.5 mg) in 93% yield with 92% incorporation of deuterium.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 2H), 7.10 – 6.78 (m, 2H), 3.86 (s, 3H), 2.53 – 2.49 (m, *J* = 5 Hz, 0.24H, 92% D) ppm. **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 196.9, 163.5, 130.6, 130.3, 113.7, 55.5, 25.8 – 25.4 (m, *J* =18.9 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_9H_8D_3O_2$ 154.0947; Found 154.0945.

1-(4-Hydroxyphenyl-3,5-*d*$_2$)-ethan-1-one-2,2,2-*d*$_3$ (3c): Prepared according to **GP2**, 4-hydroxy



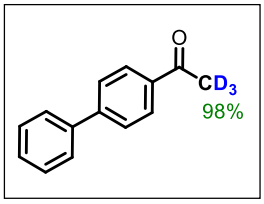
acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (25.9 mg) in 91% yield with [91], [92]% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 2H), 6.94 – 6.92(m, *J* = 8 Hz, 0.16H, 92% D), 2.58 – 2.54 (m, *J* = 4 Hz, 0.27H, 91% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 198.4, 161.1, 131.1, 129.3, 115.5 – 115.1 (m, *J* =17.0 Hz), 25.9 – 25.6 (m, *J* =20.0 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_8H_4D_5O_2$ 142.0916; Found 142.0909.

1-(4-Aminophenyl)-ethan-1-one-2,2,2-*d*$_3$) (3d): Prepared according to **GP2**, 4-amino acetophenone



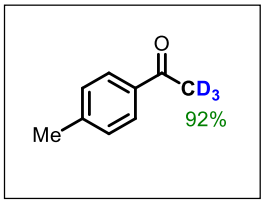
(0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (25.5 mg) in 91% yield with [22],[85]% incorporation of deuterium.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 6.68 – 6.62 (m, 1.56H, 22% D), 4.11 (s, 2H), 2.50 – 2.47 (m, *J* = 4 Hz, 0.45H, 85% D) ppm. **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 196.6, 151.1, 130.8, 127.9, 113.7, 25.3 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_8H_5D_5NO$ 141.1076; Found 141.1071.

1-([1,1'-Biphenyl]-4-yl)-ethan-1-one-2,2,2-*d*$_3$ (3e): Prepared according to **GP2**, 1-([1,1'-biphenyl]-4-

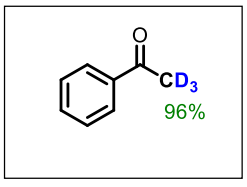


yl) ethan-1-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (37.0 mg) in 93% yield with 98% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 8.01 (m, 2H), 7.73 – 7.67 (m, 2H), 7.66 – 7.61 (m, 2H), 7.51 – 7.44 (m, 2H), 7.44 – 7.37 (m, 1H), 2.62 – 2.60 (m, *J* = 4 Hz, 0.06H, 98% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 198.0, 145.9, 139.9, 135.9, 129.1, 129.0, 128.3, 127.4, 127.3, 26.2 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{14}H_{10}D_3O$ 200.1155; Found 200.1158.

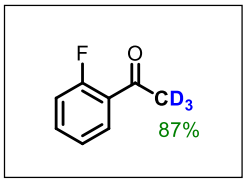
1-(*p*-Tolyl)-ethan-1-one-2,2,2-d_3 (3f): Prepared according to **GP2**, 4-methyl-acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish oil (26.0 mg) in 90% yield with 92% incorporation of deuterium. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.27 – 7.22 (d, 2H), 2.56 – 2.52 (m, *J* = 4 Hz, 0.24H, 92% D), 2.40 (s, 3H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 198.0, 143.9, 134.7, 129.3, 128.4, 26.2 – 25.6 (m, *J* =15.0 Hz), 21.6 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_9H_8D_3O$ 138.0998; Found 138.0994.



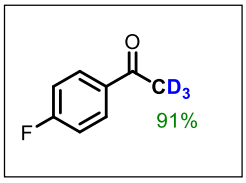
1-Phenyl-ethan-1-one-2,2,2-d_3 (3g):[3] Prepared according to **GP2**, acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish oil (23.3 mg) in 92% yield with 96% incorporation of deuterium. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.92 (m, 2H), 7.58 – 7.52 (m, 1H), 7.49 – 7.42 (m, 2H), 2.57 – 2.53 (m, *J* = 4 Hz, 0.12H, 96% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 198.3, 137.1, 133.1, 128.6, 128.3, 26.2 – 25.6 (m, *J* =19.2 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_8H_6D_3O$ 124.0842; Found 124.0849.



1-(2-Fluorophenyl)-ethan-1-one-2,2,2-d_3 (3h): Prepared according to **GP2**, 2-fluoro acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish liquid (25.4 mg) in 90% yield with 87% incorporation of deuterium.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (t, *J* = 7.8 Hz, 1H), 7.56 – 7.48 (m, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.14 (dd, *J* = 11.1, 8.0 Hz, 1H), 2.64 – 2.60 (m, *J* =5 Hz, 0.34H, 87% D) ppm. **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 196.1, 162.3 (d, *J* = 254.8 Hz), 134.7 (d, *J* = 9.0 Hz), 130.6 (d, *J* = 2.4 Hz), 125.7 (d, *J* = 12.8 Hz), 124.4 (d, *J* = 3.5 Hz), 116.7 (d, *J* = 23.9 Hz), 30.9 – 30.8 (m, *J* = 12.0 Hz) ppm. **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$) δ -109.39 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_8H_5D_3FO$ 142.0747; Found 142.0749.

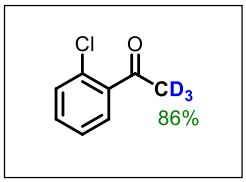


1-(4-Fluorophenyl)-ethan-1-one-2,2,2-*d*$_3$ (3i): Prepared according to **GP2**, 4-fluoro acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish liquid (25.9 mg) in 91% yield with 91% incorporation of deuterium.



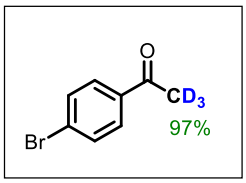
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.11 (dd, *J* = 8.9, 8.4 Hz, 2H), 2.57 – 2.52 (m, *J* =4 Hz, 0.28H, 91% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 196.7, 165.8 (d, *J* = 254.7 Hz), 133.7 (d, *J* = 3.2 Hz), 131.0 (d, *J* = 9.5 Hz), 115.7 (d, *J* = 21.8 Hz), 26.3 – 25.5 (m, *J* = 14.0 Hz). ppm. **^{19}F {^{1}H} NMR** (376 MHz, CDCl3) δ -105.3 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_8H_5D_3FO$ 142.0747; Found 142.0749.

1-(2-Chlorophenyl)-ethan-1-one-2,2,2-*d*$_3$ (3j):[6] Prepared according to **GP2**, 2-chloro acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a clear liquid (28.9 mg) in 92% yield with 86% incorporation of deuterium.



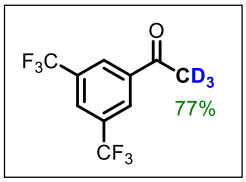
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.51 (m, 1H), 7.39 (q, *J* = 8.7 Hz, 2H), 7.35 – 7.28 (m, 1H), 2.64 – 2.60 (m, *J* = 4 Hz, 0.42H, 86% D) ppm. **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 200.5, 139.1, 132.0, 131.3, 130.6, 129.4, 126.9, 30.5 – 30.1 (m, *J* =10.1 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_8H_5D_3ClO$ 158.0452; Found 158.0461.

1-(4-Bromophenyl)-ethan-1-one-2,2,2-*d*$_3$ (3k):[3] Prepared according to **GP2**, 4-bromophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (38.6 mg) in 96% yield with 97% incorporation of deuterium.



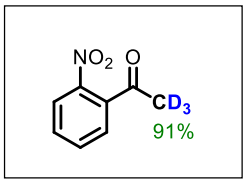
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 2.56 – 2.53 (m, *J* =5 Hz, 0.10H, 97% D) ppm. **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 197.1, 135.8, 131.9, 129.8, 128.3, 26.1 – 25.5 (m, *J* = 18.9 Hz) ppm. **HRMS** (ESI) m/z: $[M + K]^+$ Calculated for $C_8H_4D_3BrKO$ 241.1636; Found 241.1602.

1-(3,5-Bis(trifluoromethyl)-phenyl)-ethan-1-one-2,2,2-*d*$_3$ (3l): Prepared according to **GP2**, 3,5-bis(trifluoromethyl acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish liquid (46.6 mg) in 90% yield with 77% incorporation of deuterium.



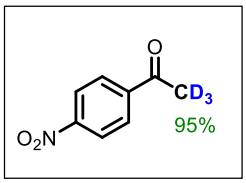
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 2H), 8.06 (s, 1H), 2.67 (m, *J* = 6.9, 2.3 Hz, 0.70H, 77% D) ppm. **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 195.0 (t, *J* = 5.0 Hz), 138.4, 132.8 – 131.9 (q, *J* = 34.0 Hz), 128.3 – 128.2 (q, *J* = 3.7 Hz), 126.3 – 119.6 (q, *J* = 273.42 Hz), 26.7 – 25.5 (m) ppm. **GC-MS** data, m/z: Calculated for $C_{10}H_3D_3F_6O$ 259.0; Found 259.0.

1-(2-Nitrophenyl)-ethan-1-one-2,2,2-*d*$_3$ (3m): Prepared according to **GP2**, 2-nitro acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish liquid (30.9 mg) in 92% yield with 91% incorporation of deuterium.



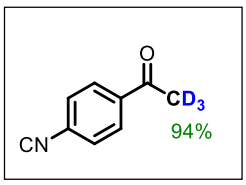
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.98 (m, 1H), 7.74 – 7.64 (m, 1H), 7.63 – 7.53 (m, 1H), 7.46 – 7.38 (m, 1H), 2.51 – 2.47(m, *J* = 4 Hz, 0.26H, 91% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 200.0, 145.9, 137.9, 134.3, 130.8, 127.5, 124.4, 30.0 – 29.2 (m, *J* =19.0 Hz) ppm.
HRMS (ESI) m/z: $[M + H]^+$ Calculated for $C_8H_5D_3NO_3$ 169.0692; Found 169.0699.

1-(4-Nitrophenyl)-ethan-1-one-2,2,2-*d*$_3$ (3n):[3] Prepared according to **GP2**, 4-nitro acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (30.2 mg) in 90% yield with 95% incorporation of deuterium.

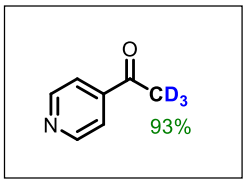


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.0 Hz, 2H), 8.12 (d, *J* = 9.0 Hz, 2H), 2.65 – 2.63 (m, *J* = 5 Hz, 0.15H, 95% D) ppm. **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 196.4, 150.4, 141.4, 129.3, 123.9, 26.5 – 26.1 (m, *J* =18.9 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_8H_5D_3NO_3$ 169.0692; Found 169.0699.

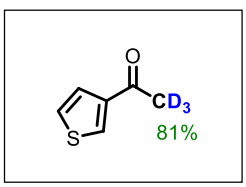
4-(Acetyl-*d*$_3$)-benzonitrile (3o): Prepared according to **GP2**, 4-acetyl-benzonitrile (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 hours using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (27.5 mg) in 93% yield with 94% incorporation of deuterium.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09 – 7.98 (m, 2H), 7.82 – 7.72 (m, 2H), 2.63 – 2.60 (m, *J* = 5 Hz, 0.18H, 96% D) ppm. **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 196.7, 139.9, 132.5, 128.7, 117.9, 116.4, 26.20 – 26.04 (m, *J* =20.2 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_9H_5D_3NO$ 150.0828; Found 150.0818.,



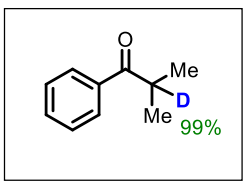
1-(Pyridin-4-yl)-ethan-1-one-2,2,2-*d*$_3$ (3p): Prepared according to **GP2**, 4-acetyl-pyridine (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 hours using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish liquid (21.6 mg) in 87% yield with 93% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 6.1 Hz, 2H), 7.76 – 7.55 (m, 2H), 2.55 – 2.51 (m, *J* = 4 Hz, 0.20H, 93% D) ppm.**^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 197.5, 150.9, 142.3, 121.2, 26.4 – 25.5 (m, *J* =20.2 Hz) ppm. **HRMS** (ESI) m/z: [M - H] Calculated for $C_7H_3D_3NO$ 123.0638; Found 123.0667.



1-(Thiophen-3-yl)-ethan-1-one-2,2,2-*d*$_3$ (3q): Prepared according to **GP2**, 3-acetyl thiophene (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a pale yellow liquid (22.9 mg) in 84% yield with 81% incorporation of deuterium.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 3.3 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.16 – 7.09 (m, 1H), 2.54 (m, *J* = 7.8, 2.4 Hz, 0.56H, 81% D) ppm.**^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ 190.9, 144.6, 133.8, 132.5, 128.1, 26.6 – 26.2 (m, *J* =18.9 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_6H_4D_3OS$ 130.0406; Found 130.0406.

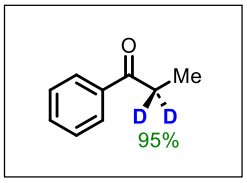


2-Methyl-1-phenylpropan-1-one-2-*d* (3r): Prepared according to **GP2**, 2-methyl-1-phenylpropan-1-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through

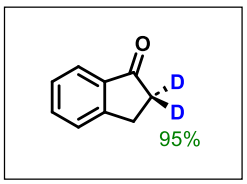


a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish liquid (27.4 mg) in 92% yield with 99% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 – 7.84 (m, 2H), 7.67 – 7.50 (m, 1H), 7.45 (m, *J* = 8.4, 6.6, 1.5 Hz, 2H), 3.61 – 3.51 (m, *J* = 4 Hz, 0.01H, 99% D), 1.19 (s, 6H), ppm.**^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 204.7, 136.3, 132.9, 128.7, 128.4, 34.8, 19.1 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{10}H_{12}DO$ 150.1029; Found 150.1023.

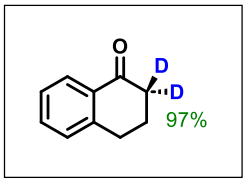
1-Phenyl propan-1-one-2,2-*d*$_2$ (3s):[5] Prepared according to **GP2**, 1-phenyl propan-1-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish liquid (22.6 mg) in 83% yield with 95% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.47 – 7.39 (m, 2H), 3.01 – 2.92 (m, 0.10H, 95% D), 1.23 – 1.18 (m, 3H). **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 200.9, 137.0, 132.9, 128.6, 128.1, 31.8 – 31.3 (m, *J* =18.9 Hz), 8.3 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_9H_9D_2O$ 137.0935; Found 137.0939.



3-Dihydro-1*H*-inden-1-one-2,2-*d*$_2$ (3t): Prepared according to **GP2**, 2,3-dihydro-1*H*-inden-1-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 hours using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish solid (25.2 mg) in 94% yield with 95% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.54 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.45 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.37 – 7.30 (m, 1H), 3.10 (s, 2H), 2.67 – 2.62 (m, *J* = 4 Hz, 0.10H, 95% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 207.3, 155.3, 137.2, 134.7, 127.4, 126.8, 123.8, 35.9 (m), 25.7 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_9H_7D_2O$ 135.0779; Found 135.0780.

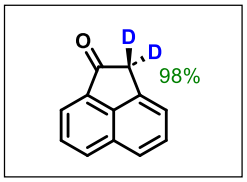


3,4-Dihydronaphthalen-1(2*H*)-one-2,2-*d*$_2$ (3u): Prepared according to **GP2**, 3,4-dihydronaphthalen-1(2H)-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a brown liquid (28.1 mg) in 95% yield with 97% incorporation of deuterium. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.42 (dd, *J* =



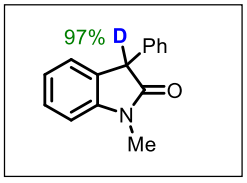
7.5, 1.5 Hz, 1H), 7.30 – 7.18 (m, 2H), 2.93 (t, J = 6.1 Hz, 2H), 2.09 (t, J = 6.1 Hz, 2H), 2.60 (m, J = 4 Hz, 0.06H, 97% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 198.6, 144.6, 133.5, 132.7, 128.9, 127.2, 126.7, 38.7 – 38.3 (m, J = 20 Hz), 29.7, 23.2 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{10}H_9D_2O$ 149.0935; Found 149.0931.

Acenaphthylen-1(2*H*)-one-2,2-*d*$_2$ (3v):[4] Prepared according to **GP2**, Acenaphthylen-1(2*H*)-one (0.2



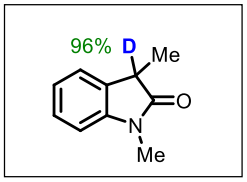
mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish solid (32.6 mg) in 96% yield with 98% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.1, 0.8 Hz, 1H), 7.94 (dd, J = 7.1, 0.7 Hz, 1H), 7.80 (dd, J = 8.4, 0.8 Hz, 1H), 7.69 (dd, J = 8.1, 7.1 Hz, 1H), 7.58 (dd, J = 8.4, 6.8 Hz, 1H), 7.44 (dd, J = 6.9, 0.8 Hz, 1H), 3.78 – 3.76 (m, J = 4 Hz, 0.04H, 98% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 203.2, 143.1, 135.0, 134.8, 131.6, 131.0, 128.5, 128.1, 124.1, 121.5, 121.2, 44.9 – 39.9 (m, J =19.9 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{12}H_7D_2O$ 171.0779; Found 171.0784.

1-Methyl-3-phenylindolin-2-one-3-*d* (3w): Prepared according to **GP2**, 1-methyl-3-phenylindolin-2-



one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish solid (41.7 mg) in 93% yield with 97% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 4H), 7.22 – 7.13 (m, 3H), 7.06 (td, J = 7.5, 1.0 Hz, 1H), 6.89 (dt, J = 7.8, 0.8 Hz, 1H), 4.60 (s, 0.03H, 97% D), 3.25 (s, 3H). ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 185.4, 169.0, 167.4, 144.6, 128.9, 128.5, 128.5, 127.6, 125.2, 122.8, 108.3, 52.1, 26.5 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{15}H_{13}DNO$ 225.1138; Found 225.1132.

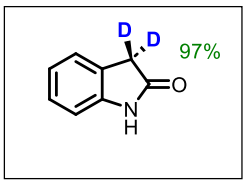
1,3-Dimethylindolin-2-one-3-*d* (3x): Prepared according to **GP2**, 1,3-dimethylindolin-2-one (0.2



mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 hours using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish solid (29.8 mg) in 92% yield with 96% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 7.7, 1.3 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.04 (td, J = 7.5, 1.0 Hz, 1H), 6.81 (dt, J = 7.7, 0.8 Hz, 1H), 3.37 (m, J = 4 Hz, 0.04H, 96%

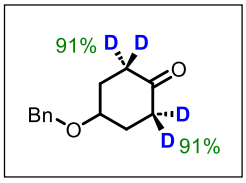
D), 3.20 (s, 3H), 1.46 (s, 3H) ppm.**^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 178.8, 144.1, 130.7, 127.9, 123.6, 122.5, 108.0, 40.6, 26.2, 15.4 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{10}H_{11}DNO$ 163.0982; Found 163.0976.

Indolin-2-one-3,3-*d*$_2$ (3y): Prepared according to **GP2**, Indolin-2-one (0.2 mmol, 1.0 equiv.), D_2O (5



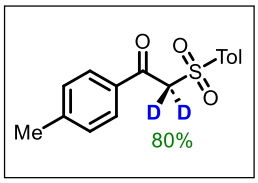
mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (24.8 mg) in 92% yield with 97% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.59 (s, 0.38H), 7.25 – 7.16 (m, 2H), 7.00 (td, J = 7.6, 1.0 Hz, 1H), 6.91 (d, J = 7.9 Hz, 1H), 3.53 – 3.50 (m, 0.07H, 97% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 178.5, 142.8, 128.0, 125.3, 124.6, 122.4, 110.0, 35.9 – 35.7 (m, J =19.9 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_8H_6D_2NO$ 136.0731; Found 136.0760.

4-(Benzyloxy)cyclohexan-1-one-2,2,6,6-*d*$_4$ (3z): Prepared according to **GP2**, 4-



(benzyloxy)cyclohexan-1-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish liquid (37.5 mg) in 90% yield with 91% incorporation of deuterium. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 5H), 4.61 (s, 2H), 3.83 (tt, J = 5.7, 3.0 Hz, 1H), 2.68 – 2.57 (m, 0.18H, 91% D), 2.28 (m, 0.18H, 91% D), 2.20 – 2.10 (m, 2H), 2.02 – 1.92 (m, 2H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 211.6, 138.6, 128.6, 127.7, 127.5, 72.3, 70.4, 36.9 – 36.7 (m), 30.5 ppm. **HRMS** (ESI) m/z: $[M + Na]^+$ Calculated for $C_{13}H_{12}D_4NaO_2$ 231.1299; Found 231.1290.

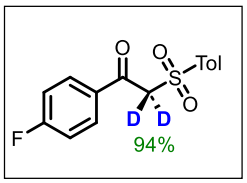
1-(*p*-Tolyl)-2-tosylethan-1-one-2,2-*d*$_2$ (3aa): Prepared according to **GP2**, 1-(*p*-tolyl)-2-tosylethan-1-



one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (48.7 mg) in 84% yield with 80% incorporation of deuterium. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.31 (dt, J = 7.9, 0.7 Hz, 2H), 7.28 – 7.23 (m, 2H), 4.68 – 4.66 (m, J = 4 Hz, 0.43H, 80% D), 2.41 (d, J = 6.8 Hz, 6H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 187.8, 145.6, 145.4, 135.9, 133.5, 129.9,

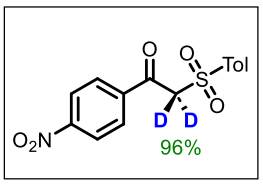
129.6, 129.6, 128.7, 64.1 – 63.6 (m, J = 44.0 Hz), 21.9, 21.8 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{16}H_{15}D_2O_3S$ 291.1024; Found 291.1025.

1-(4-Fluorophenyl)-2-tosylethan-1-one-2,2-d_2 (3ab): Prepared according to **GP2**, 1-(4-fluorophenyl)-2-tosylethan-1-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish solid (49.9 mg) in 85% yield with 94% incorporation of deuterium.



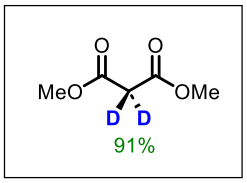
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (ddd, J = 8.3, 5.4, 2.4 Hz, 2H), 7.79 – 7.71 (m, 2H), 7.34 (d, J = 7.8 Hz, 2H), 7.22 – 7.11 (m, 2H), 4.65 (s, 0.12H, 94% D), 2.45 (s, 3H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 186.7, 167.6, 165.5, 145.6, 135.7, 132.4, 132.3, 130.0, 128.6, 116.3, 116.1, 63.8, 21.8 ppm. **HRMS** (ESI) m/z: [M - H] Calculated for $C_{15}H_{10}D_2FO_3S$ 293.0617; Found 293.0643.

1-(4-Nitrophenyl)-2-tosylethan-1-one-2,2-d_2 (3ac): Prepared according to **GP2**, 1-(4-nitrophenyl)-2-tosylethan-1-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish solid (56.5 mg) in 88% yield with 96% incorporation of deuterium.



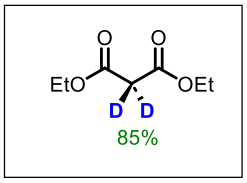
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.90 (m, 2H), 7.81 – 7.66 (m, 2H), 7.37 – 7.30 (m, 2H), 7.20 – 7.09 (m, 2H), 4.65 (s,0.08H, 96% D), 2.44 (s, 3H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 187.4, 145.7, 135.6, 134.6, 132.3, 130.9, 130.1, 130.0, 128.6, 63.8, 21.8 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{15}H_{12}D_2NO_5S$ 322.0718; Found 322.0716.

Dimethyl-malonate-d_2 (3ad): Prepared according to **GP2**, dimethyl malonate (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a clear liquid (21.4 mg) in 80% yield with 91% incorporation of deuterium.



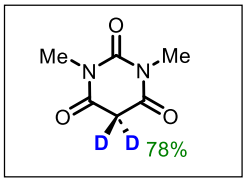
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 6H), 3.43 – 3.37 (m, 0.18H, 91% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 167.1, 52.6, 41.2 – 40.7 (m, J = 20.0 Hz), ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_5H_7D_2O_4$ 135.0626; Found. 135.0615.

Diethyl-malonate-d_2 (3ae):[8] Prepared according to **GP2**, diethyl malonate (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a clear liquid (24.3 mg) in 75% yield with 85% incorporation of deuterium.



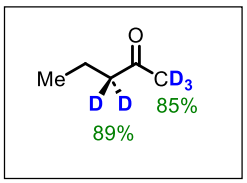
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (dd, *J* = 14.1, 7.1 Hz, 4H), 3.36 – 3.34 (m, 0.29H, 85% D), 1.29 (dt, *J* = 7.9, 7.1 Hz, 6H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 167.4, 166.8, 62.1, 40.6, 14.1 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_7H_{11}D_2O_4$ 163.0939; Found 163.0930.

1,3-Dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione-5,5-d_2 (3af): Prepared according to **GP2**, 1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (28.7 mg) in 91% yield with 78% incorporation of deuterium.



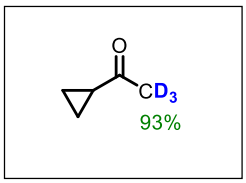
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 – 3.63 (m, 0.44H, 78% D) 3.29 (s, 6H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.8, 151.9, 39.4 – 39.0 (m, *J* = 20.0 Hz), 28.5 ppm. **HRMS** (ESI) m/z: [M - H] Calculated for $C_6H_7D_2O_3$ 138.0998; Found 138.0994.

Pentan-2-one-1,1,1,3,3-d_5 (3ag): Prepared according to **GP2**, pentan-2-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a clean liquid (16.9 mg) in 93% yield with 89% incorporation of deuterium.

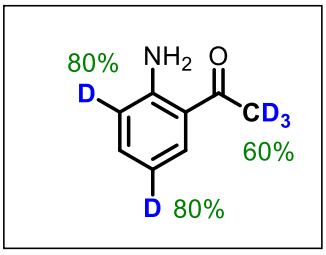


^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 – 2.33 (m, 0.22H, 89% D), 2.10 – 2.06 (m, 0.46H, 85% D), 1.57 (m, 2H), 0.89 (td, *J* = 7.4, 0.8 Hz, 3H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 209.6, 45.6 – 43.5 (m, *J* = 20.0 Hz), 29.7 – 28.9 (m, *J* = 5.0 Hz), 17.2, 13.7 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_5H_6D_5O$ 92.1124; Found 92.1115.

1-Cyclopropylethan-1-one-2,2,2-d_3 (3ah): Prepared according to **GP2,** 1-cyclopropylethan-1-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a clean liquid (14.8 mg) in 85% yield with 93% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.18 – 2.16 (m, 0.21H, 93% D), 1.91 (tt, *J* = 7.8, 4.6 Hz, 1H), 1.03 – 0.95 (m, 2H), 0.89 – 0.81 (m, 2H). **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 209.1, 29.9 – 28.9 (m, *J* = 20.0 Hz), 21.2, 10.7 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_5H_6D_3O$ 88.0842; Found 88.0832.

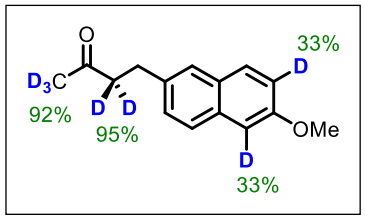


1-(2-Aminophenyl)-ethan-1-one-2,2,2-d_3) (3ah'): Prepared according to **GP2**, 2-amino acetophenone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (25.2 mg) in 90% yield with [80], [60]% incorporation of deuterium. **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.69 (s, 1H), 7.25 (s, 1H), 6.66 – 6.62 (m,0.40H, 80% D), 6.22 (s, 2H), 2.56 – 2.52 (m, 1H, 60% D). ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 200.99, 149.91, 134.29, 132.01, 118.51, 117.46, 116.08, 115.81, 115.56, 27.93, 27.74, 27.49. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_8H_5D_5NO$ 141.1076; Found 141.1081.

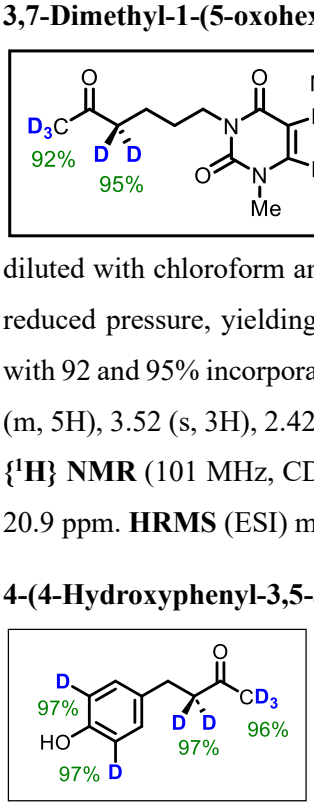


4.2 Analytical Data of Synthesized Compounds (3ah-3ap)

4-(6-methoxynaphthalen-2-yl-5,7-d_2)butan-2-one-1,1,1,3,3-d_5 (3ai):[9] Prepared according to **GP2**, 4-(6-methoxynaphthalen-2-yl) butan-2-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (43.3 mg) in 93% yield with 95% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 1.8 Hz, 1H), 7.32 – 7.24 (m, 1H), 7.16 – 7.09 (m, 2H), 3.90 (s, 3H), 3.00 (s, 2H), 2.84 – 2.80 (m, 0.10H, 95% D), 2.14 (m, 0.24H, 92% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 208 3, 157.4, 136.2, 133.2, 129.2, 129.0, 127.6, 127.0, 126.3, 118.9, 105.7, 55.4, 45.3 (m), 30.2 (m), 29.7 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{15}H_{12}D_5O_2$ 234.1542; Found 234.1543.



3,7-Dimethyl-1-(5-oxohexyl-4,4,6,6,6-d_5)-3,7-dihydro-1*H*-purine-2,6-dione (3aj):[9] Prepared according to **GP2**, 3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish solid (52.1 mg) in 92% yield with 92 and 95% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (s, 0.78H), 4.02 – 3.90 (m, 5H), 3.52 (s, 3H), 2.42 (m, 0.10H, 95% D), 2.06 (m, 0.24H, 92% D), 1.68 – 1.53 (m, 4H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 208 3,155.3, 151.5, 148.8, 141.5, 107.7, 43.5, 40.8, 33.6, 29.7, 27.5, 20.9 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{13}H_{14}D_5N_4O_3$ 284.1771; Found 284.1772.



4-(4-Hydroxyphenyl-3,5-d_2)butan-2-one-1,1,1,3,3-d_5 (3ak): [10] Prepared according to **GP2**, 4-(4-hydroxyphenyl) butan-2-one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish liquid (30.8 mg) in 90% yield with 97% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.01 (s, 2H), 6.76 – 6.74 (t, J = 4 Hz, 0.07H, 97% D), 6.32 (s, 1H), 2.80 (s, 2H), 2.73 – 2.70 (m, J = 5 Hz, 0.06H, 97% D), 2.12 – 2.09 (m, J = 5 Hz, 0.13H, 96% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 210.2, 154.3, 132.6, 129.3, 115.5, 115.5, 115.3, 115.0, 44.8, 29.9 – 29.7 (m), 28.9 ppm. **HRMS** (ESI) m/z: [M - H] Calculated for $C_{10}H_4D_7O_2^-$ 170.1204; Found 170.1200.

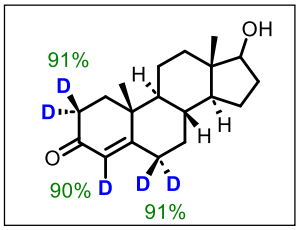
4-(4-Methoxyphenyl)butane-2-one-1,1,1,3,3-d_5 (3al):[10] Prepared according to **GP2**, 4-(4-methoxyphenyl) butane-2 one (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish liquid (32.9 mg) in 90% yield with 97% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 2.82 (s, 2H), 2.70 (m, 0.06H, 97% D), 2.10 – 2.08 (m, 0.08H, 96% D) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 208.6, 158.1, 133.1, 129.3, 113.9, 55.3, 45.1 – 44.5 (m), 29.8 – 29.2 (m), 28.7 (d, *J* = 19.4 Hz) ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{11}H_{10}D_5O_2$ 184.1386; Found 184.1380.

2-(4-((2-Oxocyclopentyl-1,3,3-d_3)-methyl)-phenyl)-propanoic acid (3am): Prepared according to **GP2**, 2-(4-((2-oxocyclopentyl) methyl) phenyl) propanoic acid (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (45.3 mg) in 91% yield with 96 and 98% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 7.15 – 7.09 (m, 2H), 3.70 (q, *J* = 7.1 Hz, 1H), 3.11 (d, *J* = 14.0 Hz, 1H), 2.50 (d, *J* = 14.0 Hz, 1H), 2.51 – 2.31 (m, 0.08H, 96% D), 2.10 – 2.07 (m, 0.02H, 98% D), 2.06 (ddd, *J* = 12.5, 6.3, 2.7 Hz, 1H), 1.94 (ddd, *J* = 12.8, 6.7, 2.6 Hz, 1H), 1.71 (td, *J* = 11.9, 6.3 Hz, 1H), 1.58 – 1.51 (m, 1H), 1.49 (d, *J* = 7.2 Hz, 3H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 220.8, 180.6, 139.2, 137.7, 129.3, 127.7, 51.1 – 50.4 (m), 45.0, 38.2 – 37.4 (m), 35.2, 29.1, 20.4, 18.2 ppm. **HRMS** (ESI) m/z: $[M + Na]^+$ Calculated for $C_{15}H_{15}D_3NaO_3$ 272.1342; Found 272.1347.

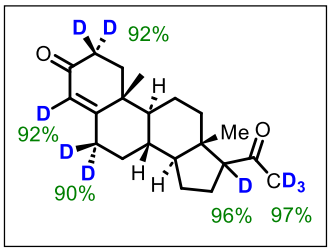
Estrone-d_4 (3an):[11] Prepared according to **GP2**, Estrone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (45.5 mg) in 83% yield with 94% incorporation of deuterium.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.65 – 6.58 (t, *J* = 4 Hz, 0.08H, 94% D), 4.73 (s, 1H), 2.87 (dd, *J* = 7.7, 3.2 Hz, 2H), 2.38 (d, *J* = 9.7 Hz, 1H), 2.24 (t, *J* = 11.2 Hz, 1H), 2.16 – 2.11 (m, 0.15H, 92% D), 1.60 (d, *J* = 7.7 Hz, 3H), 1.52 – 1.39 (m, 3H), 0.91 (s, 3H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 221.3, 153.5, 138.0, 132.2, 126.5, 115.7, 112.9, 50.5, 48.1, 44.0, 38.4,

34.7, 31.6, 29.5, 26.6, 26.0, 21.5, 13.9 ppm. **HRMS** (ESI) m/z: [M - H] Calculated for $C_{18}H_{17}D_4O_2^-$ 273.1798; Found 273.1701.

Testosterone *d_5*-(3ao):[10] Prepared according to **GP2**, Testosterone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a white solid (53.9 mg) in 92% yield with 91% incorporation of deuterium. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.70 (s, 0.10H, 90% D), 3.62 (t, *J* = 8.6 Hz, 1H), 2.46 – 2.20 (m, 0.34H, 91% D), 2.12 – 1.96 (m, 2H), 1.83 (dtt, *J* = 13.0, 5.6, 2.8 Hz, 2H), 1.75 (t, *J* = 4.4 Hz, 1H), 1.68 – 1.41 (m, 6H), 1.38 – 1.22 (m, 1H), 1.16 (s, 3H), 1.11 – 0.85 (m, 4H), 0.76 (s, 3H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 199.8, 171.3, 81.6, 77.3, 54.0, 50.6, 42.9, 38.7, 36.5, 35.7, 35.6, 31.5, 30.5, 23.4, 20.7, 17.5, 11.1 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{19}H_{24}D_5O_2$ 294.2481; Found 294.2471.



Progesterone-*d_9* (3ap):[9] Prepared according to **GP2**, progesterone (0.2 mmol, 1.0 equiv.), D_2O (5 mmol, 25 equiv.) at 100 °C for 24 h using dry *p*TSA (20 mol%) and DCE as a co-solvent (0.2 mL). After completion of the reaction, the reaction mixture was diluted with chloroform and filtered through a pad of Na_2SO_4, and the filtrate was concentrated under reduced pressure, yielding the pure deuterated compound, a yellowish solid (55.6 mg) in 86% yield with 97% incorporation of deuterium. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.71 (s, 0.08H, 92% D), 2.65 (t, *J* = 9.0 Hz, 0.04H, 96% D), 2.52 – 2.41 (m, 0.30H, 92% D), 2.37 – 2.25 (m, 0.12H, 96% D), 2.08 – 1.95 (m, 2H), 1.74 – 1.55 (m, 5H), 1.56 – 1.36 (m, 3H), 1.31 – 1.18 (m, 2H), 1.18 – 1.12 (m, 4H), 1.06 – 0.90 (m, 2H), 0.63 (s, 3H) ppm. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 209.6, 199.7, 170.9, 124.0, 63.1, 56.1, 53.8, 43.9, 43.5, 38.8, 38.7, 38.6, 35.6, 35.6, 31.8, 31.0, 29.8, 24.5, 22.8, 21.1, 17.4, 13.4 ppm. **HRMS** (ESI) m/z: $[M + H]^+$ Calculated for $C_{21}H_{21}D_9O_2$ 324.2889; Found 324.2880.



5. Gram-scale synthesis of product 3f (*see Scheme 3F in manuscript*)

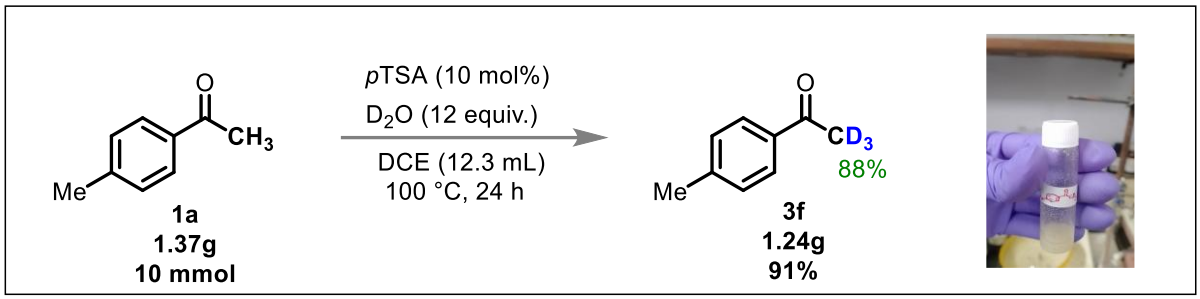
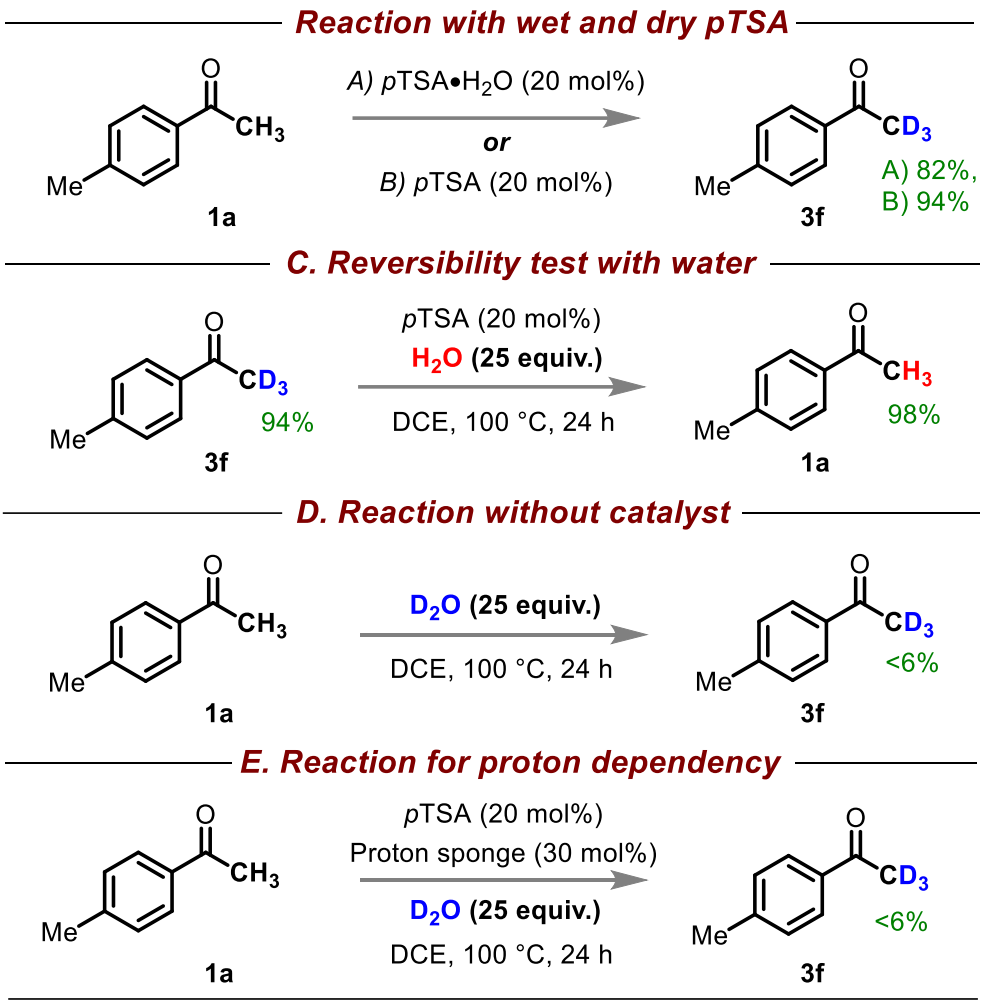


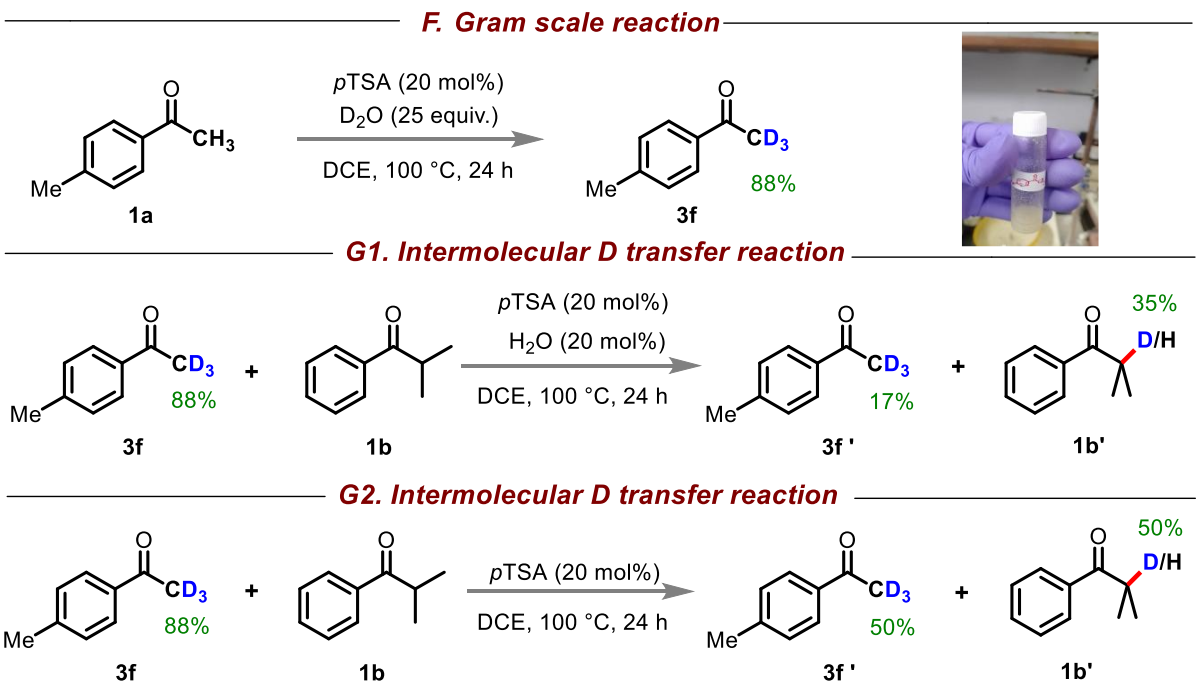
Figure 2: Gram-scale synthesis of **4-methyl-acetophenone**

Experimental procedure: In a dry sealed tube (50 mL) equipped with a magnetic stir bar, 10 mol% of dry *p*TSA was added. The tube was then evacuated and backfilled with nitrogen three times. Following this, 4-methyl acetophenone (**1a**, 1.37 g, 10.0 mmol, 1 equiv.), 2.5 mL (12.5 equiv) of D_2O and 12.3 mL of 1,2-dichloroethane (as a co-solvent) were introduced. The reaction mixture was stirred at 100 °C for 24 h. After the reaction, pure deuterated products were obtained by diluting the reaction mixture with chloroform, filtering it through a Celite pad, and concentrating it under reduced pressure, resulting in the desired deuterated product (without the need for column chromatography). The percentage of deuterium [D] incorporation was calculated using the internal alkyl group as the internal standard.

6. Control Experiments

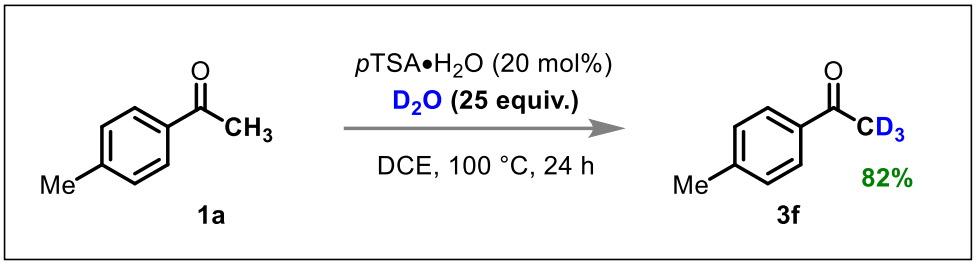


Scheme S1. Control Experiments.



Scheme S2. Control Experiments.

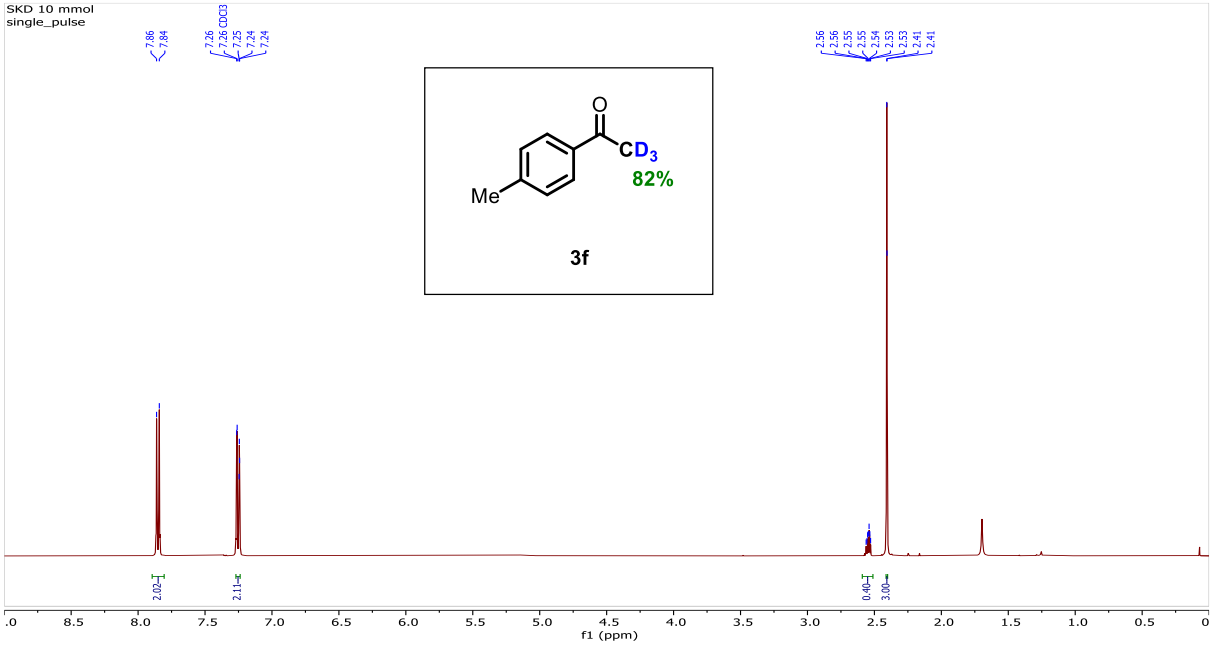
A. Reaction with *p*TSA•H_2O (*see Scheme 2A in manuscript*):



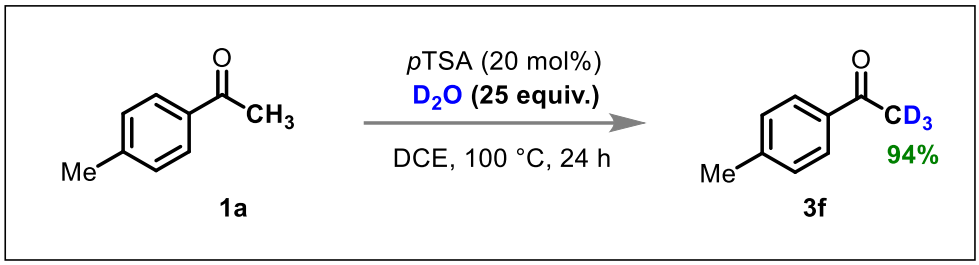
Experimental procedure: In a dry sealed tube (10 mL) equipped with a magnetic stir bar, 20 mol% of *p*TSA•H_2O was added, the tube was then evacuated and backfilled with nitrogen three times. Following this, 4-methyl acetophenone (**1a**, 26.7 mg, 0.2 mmol, 1 equiv.), 0.1 mL (25 equiv) of D_2O and 0.2 mL of 1,2-dichloroethane (as a co-solvent) were introduced. The reaction mixture was stirred at 100 °C for 24 h. After the reaction, pure deuterated products were obtained by diluting the reaction mixture with chloroform, filtering it through a pad of Na_2SO_4, and concentrating it under reduced pressure, resulting in the desired deuterated product (without the need for column chromatography). The percentage of deuterium [D] incorporation was calculated using the internal alkyl group as the internal standard.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.27 – 7.22 (d, 2H), 2.56 – 2.52 (m, J = 4 Hz, 0.48H), 2.40 (s, 3H) ppm.

^{1}H NMR (400 MHz, $CDCl_3$) of **1-(*p*-Tolyl)-ethan-1-one-2,2,2-d_3 (3f)**



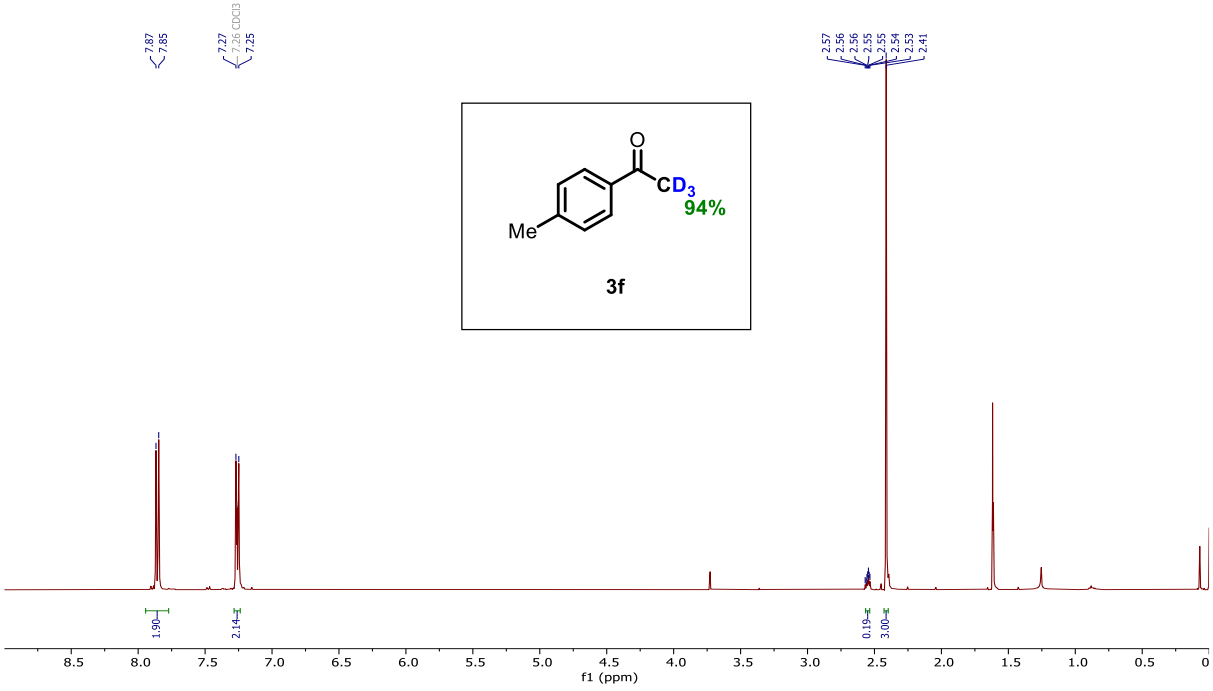
B. Reaction with dry *p*TSA (*see Scheme 2B in manuscript*):



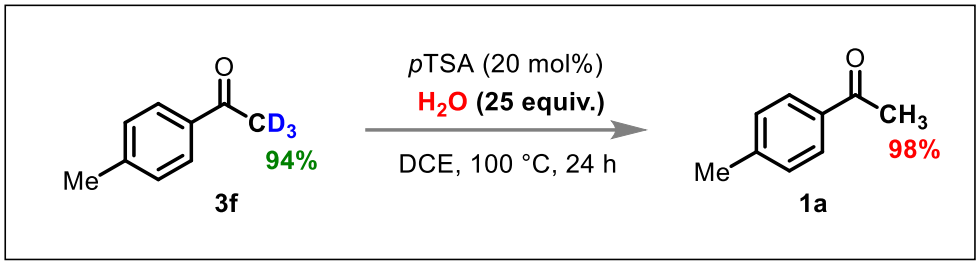
Experimental procedure: In a dry sealed tube (10 mL) equipped with a magnetic stir bar, 20 mol% of dry *p*TSA was added. The tube was then evacuated and backfilled with nitrogen three times. Following this, 4-methyl acetophenone (**1a**, 26.7 mg, 0.2 mmol, 1 equiv.), 0.1 mL (25 equiv) of D_2O and 0.2 mL of 1,2-dichloroethane (as a cosolvent) were introduced. The reaction mixture was stirred at 100 °C for 24 h. After the reaction, pure deuterated products were obtained by diluting the reaction mixture with chloroform, filtering it through a pad of Na_2SO_4, and concentrating it under reduced pressure, resulting in the desired deuterated product (without the need for column chromatography). The percentage of deuterium [D] incorporation was calculated using the internal alkyl group as the internal standard.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.27 – 7.22 (d, 2H), 2.56 – 2.52 (m, J = 4 Hz, 0.19H), 2.40 (s, 3H) ppm.

^{1}H NMR (400 MHz, $CDCl_3$) of **1-(*p*-Tolyl)-ethan-1-one-2,2,2-d_3 (3f)**



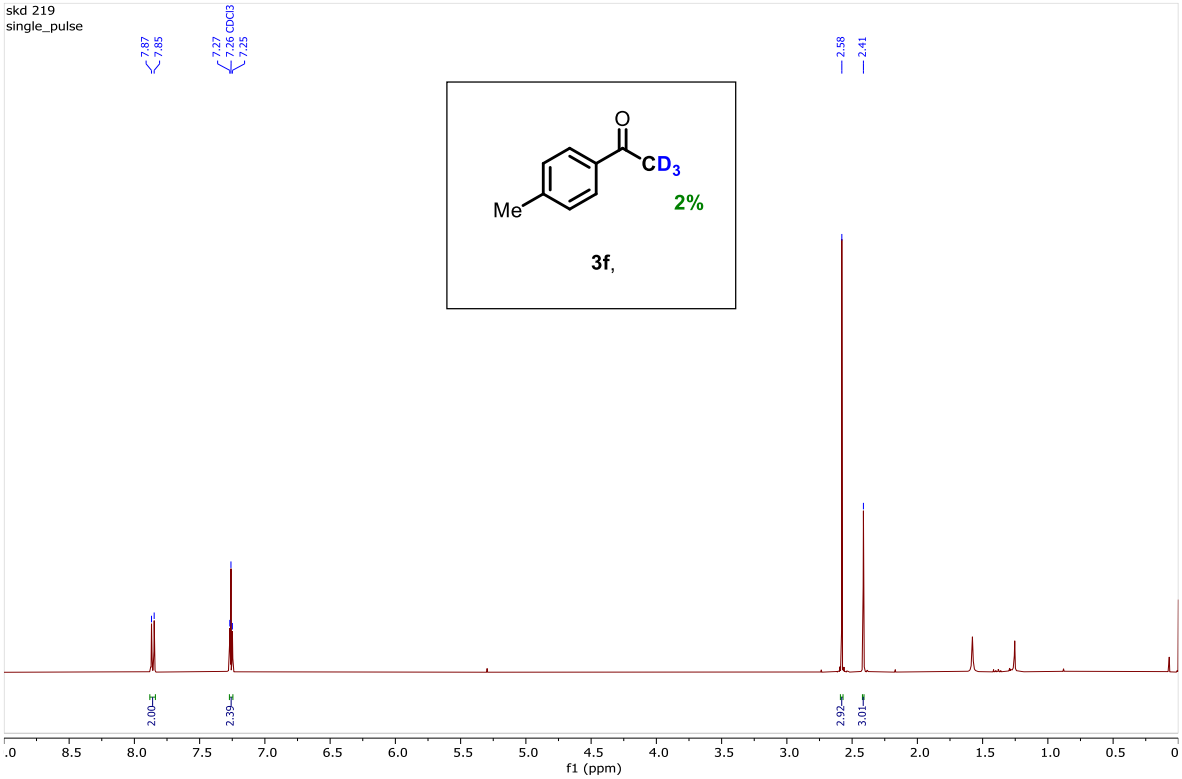
C. Reversibility test with water (*see Scheme 2C in manuscript*):



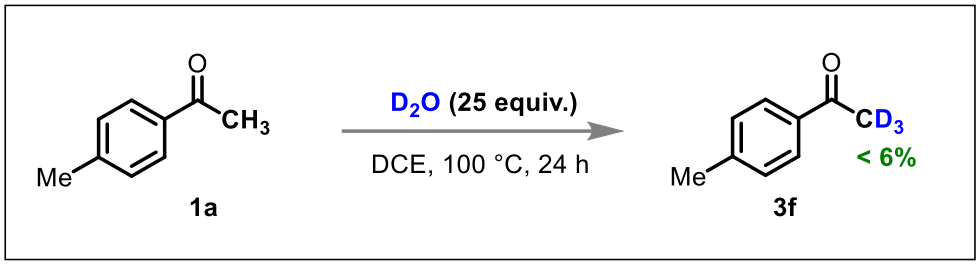
Experimental procedure: In a dry sealed tube (10 mL) equipped with a magnetic stir bar, 20 mol% of dry *p*TSA was added. The tube was then evacuated and backfilled with nitrogen three times. Following this, (**3f**, 27.4 mg, 0.2 mmol, 1 equiv.), 0.1 mL (25 equiv.) of H_2O and 0.2 mL of 1,2-dichloroethane (as a co-solvent) were introduced. The reaction mixture was stirred at 100 °C for 24 h. After the reaction, pure deuterated products were obtained by diluting the reaction mixture with chloroform, filtering it through a pad of Na_2SO_4, and concentrating it under reduced pressure, resulting in the desired deuterated product (without the need for column chromatography). The percentage of deuterium [D] incorporation was calculated using the internal alkyl group as the internal standard.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.27 – 7.22 (d, 2H), 2.58 (s, 2.92H), 2.40 (s, 3H) ppm.

^{1}H NMR (400 MHz, $CDCl_3$) of **1-(*p*-Tolyl)ethan-1-one-2,2,2-d_3 (3f)**



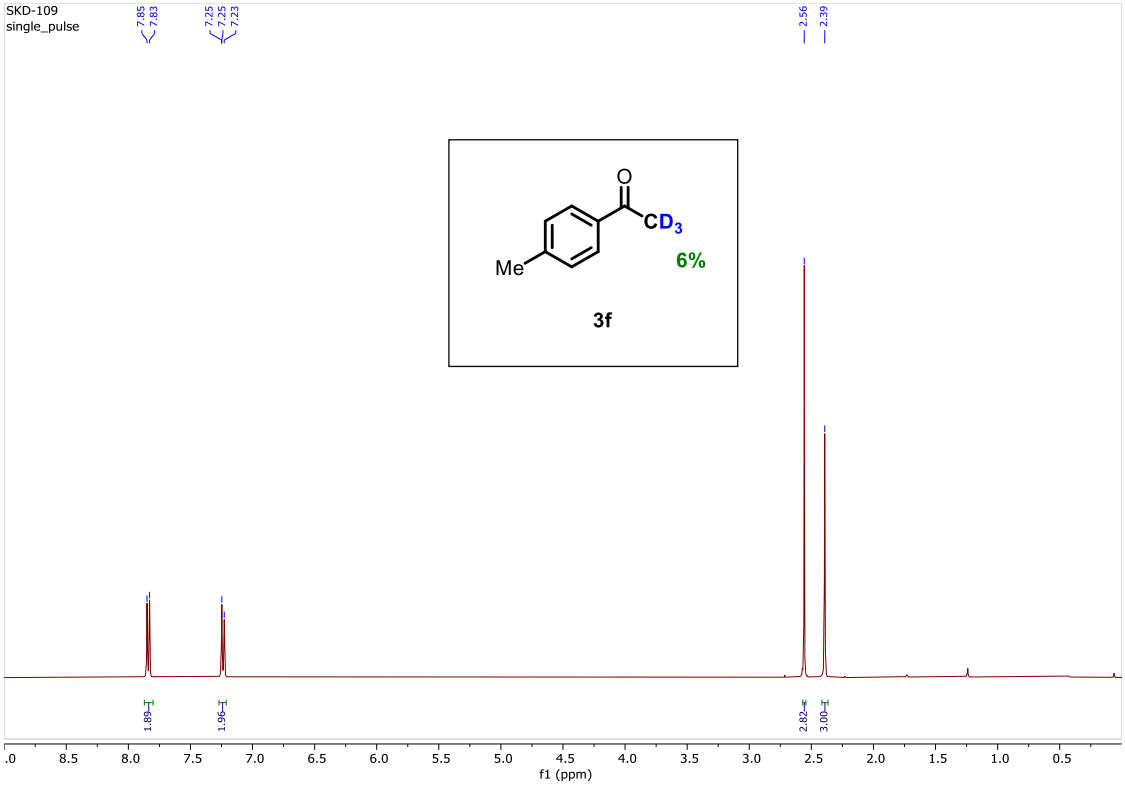
D. Reaction without a catalyst (*see Scheme 2D in manuscript*):



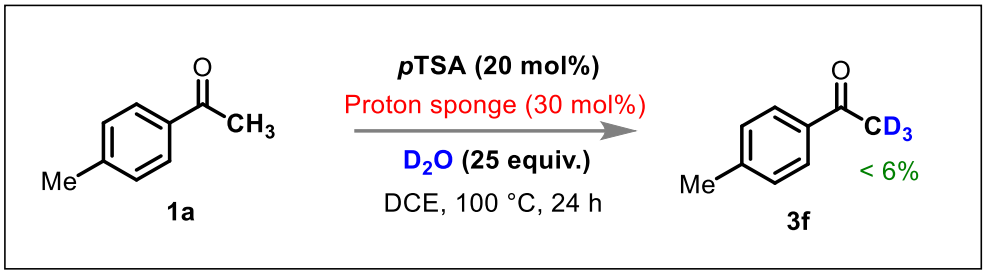
Experimental procedure: In a dry sealed tube (10 mL) equipped with a magnetic stir bar, the tube was then evacuated and backfilled with nitrogen three times. Following this, 4-methyl acetophenone (**1a**, 26.7 mg, 0.2 mmol, 1 equiv.), 0.1 mL (25 equiv.) of H_2O and 0.2 mL of 1,2-dichloroethane (as a co-solvent) were introduced. The reaction mixture was stirred at 100 °C for 24 h. After the reaction, pure deuterated products were obtained by diluting the reaction mixture with chloroform, filtering it through a pad of Na_2SO_4, and concentrating it under reduced pressure, resulting in the desired deuterated product (without the need for column chromatography). The percentage of deuterium [D] incorporation was calculated using the internal alkyl group as the internal standard.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.27 – 7.22 (d, 2H), 2.58 (s, 2.82H), 2.40 (s, 3H) ppm.

.**^{1}H NMR** (400 MHz, $CDCl_3$) of **1-(*p*-Tolyl)ethan-1-one-2,2,2-d_3 (3f)**

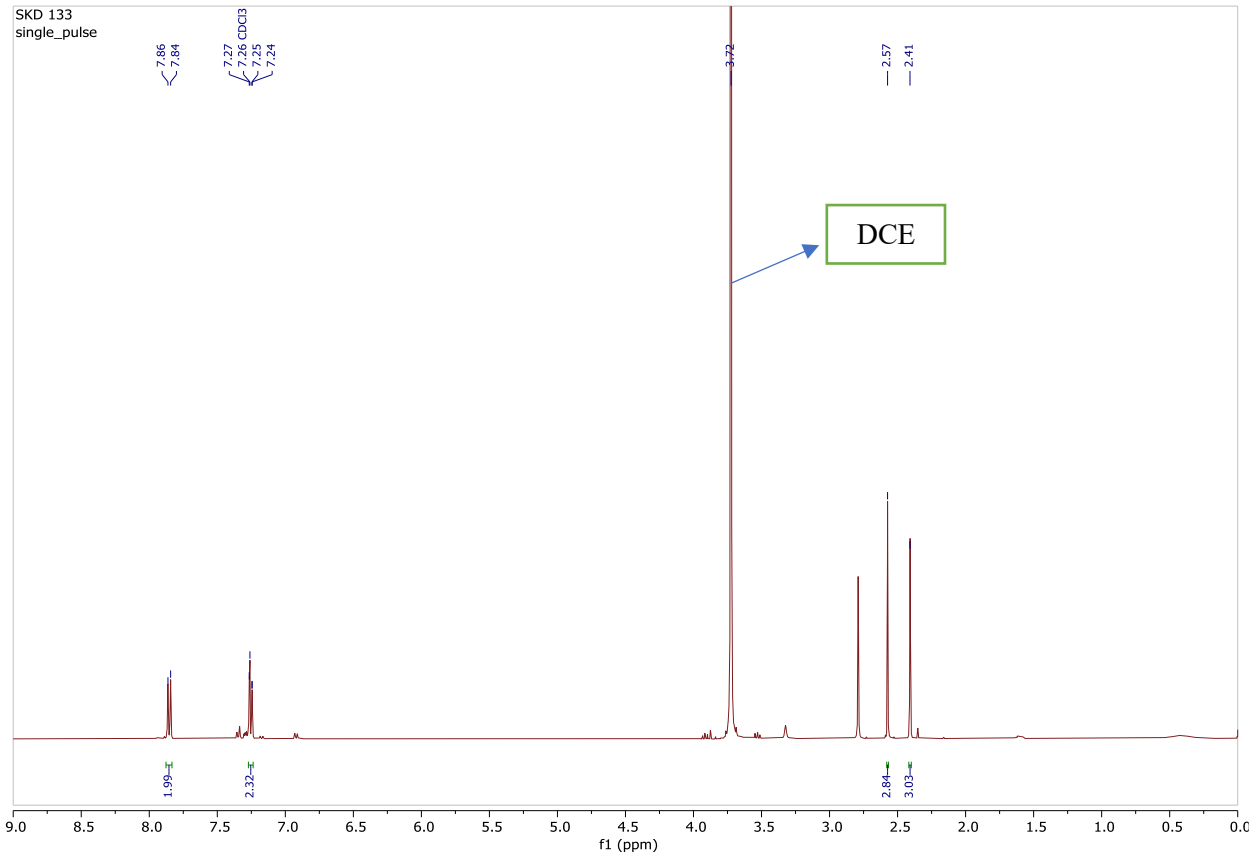


E. Reaction for proton dependency (*see Scheme 2E in manuscript*):

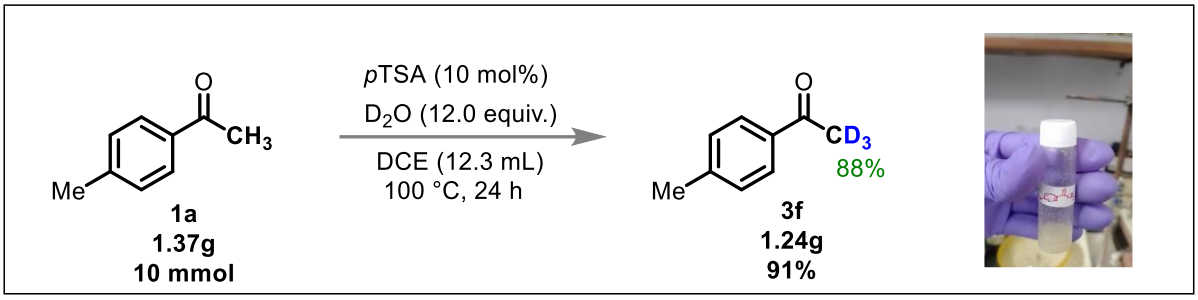


Experimental procedure: In a dry sealed tube (10 mL) equipped with a magnetic stir bar, 20 mol% of dry *p*TSA was added. Then, proton scavenger *N, N, N′, N′*-tetramethyl-1,8-naphthalenediamine (30.0 mol%) was added to the reaction tube. The tube was then evacuated and backfilled with nitrogen three times. Following this, 4-methyl acetophenone (1a, 26.7 mg, 0.2 mmol, 1 equiv.), 0.1 mL (25 equiv.) of D_2O and 0.2 mL of 1,2-dichloroethane (as a co-solvent) were introduced. The reaction mixture was stirred at 100 °C for 24 h. After the reaction, we took crude **^{1}H NMR** and we got <6% [D] incorporation. (The percentage of deuterium [D] incorporation was calculated using the internal alkyl group as the internal standard.)

^{1}H NMR (400 MHz, $CDCl_3$) of crude (Reaction for proton dependency)



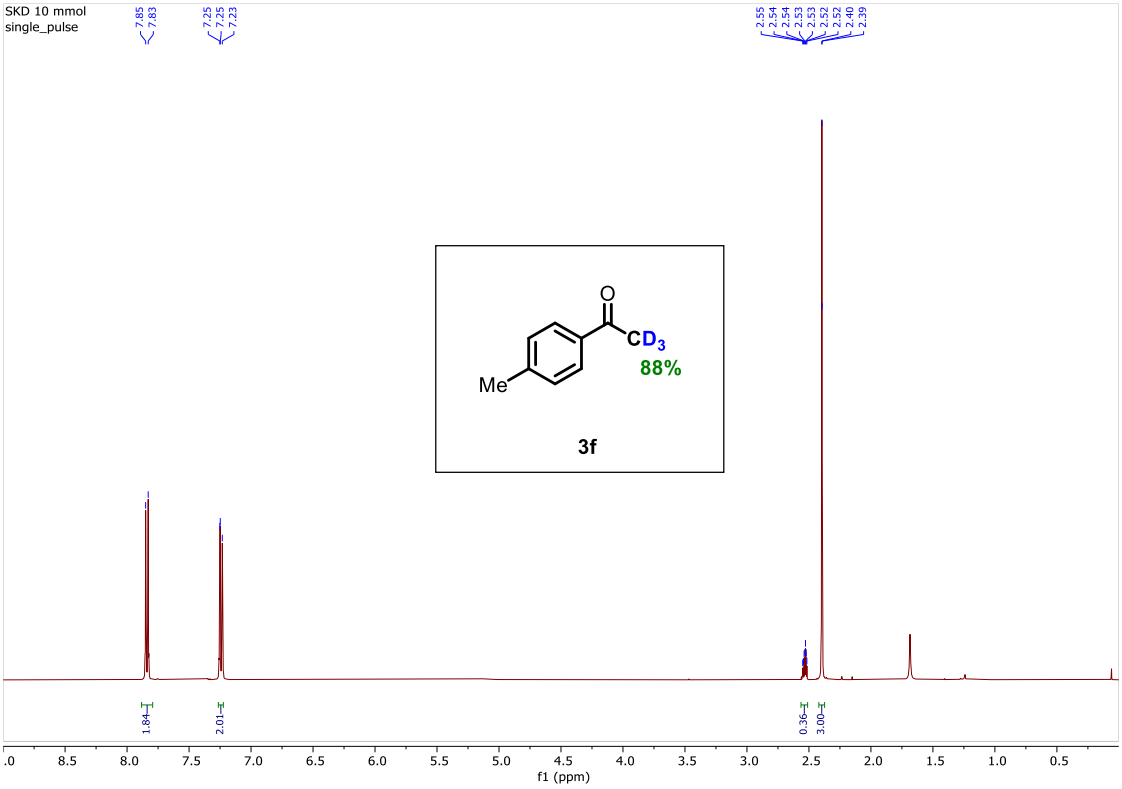
F. Gram-scale reaction :



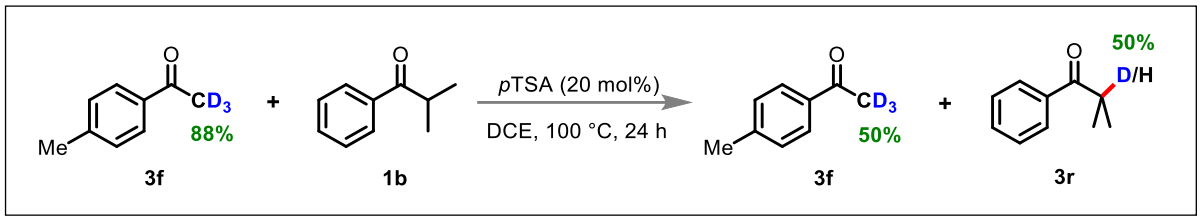
Experimental procedure: In a dry sealed tube (50 mL) equipped with a magnetic stir bar, 10 mol% of dry *p*TSA was added. The tube was then evacuated and backfilled with nitrogen three times. Following this, 4-methyl acetophenone (1a, 1.37 g, 10.0 mmol, 1 equiv.), 2.5 mL (12.0 equiv.) of D_2O and 12.3 mL of 1,2-dichloroethane (as a co-solvent) were introduced. The reaction mixture was stirred at 100 °C for 24 h. After the reaction, pure deuterated products were obtained by diluting the reaction mixture with chloroform, filtering it through a pad of Na_2SO_4, and concentrating it under reduced pressure, resulting in the desired deuterated product (without the need for column chromatography). The percentage of deuterium [D] incorporation was calculated using the internal alkyl group as the internal standard.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.27 – 7.22 (d, 2H), 2.58 (m, 0.36H), 2.40 (s, 3H) ppm.

^{1}H NMR (400 MHz, $CDCl_3$) of **1-(*p*-Tolyl)ethan-1-one-2,2,2-d_3 (3f)**

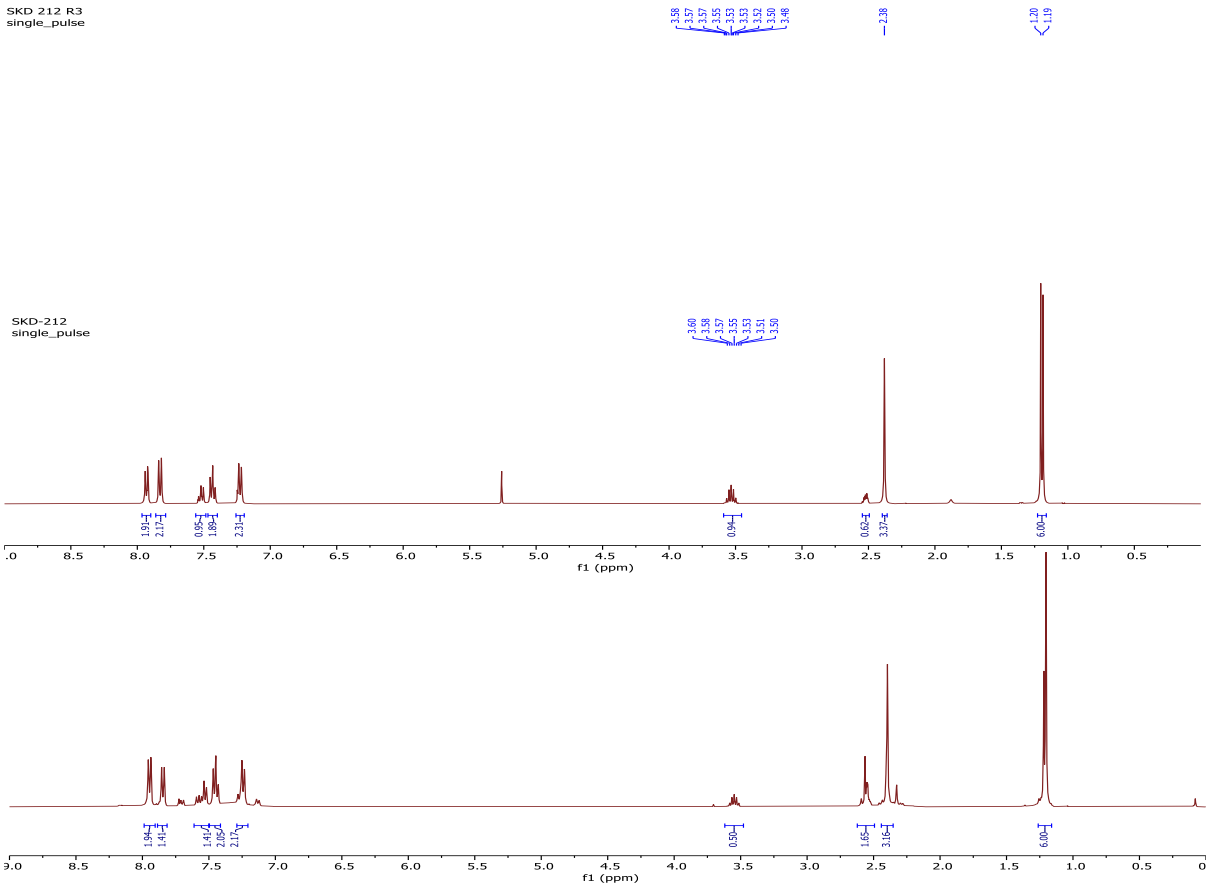


G2. Intermolecular D transfer reaction :

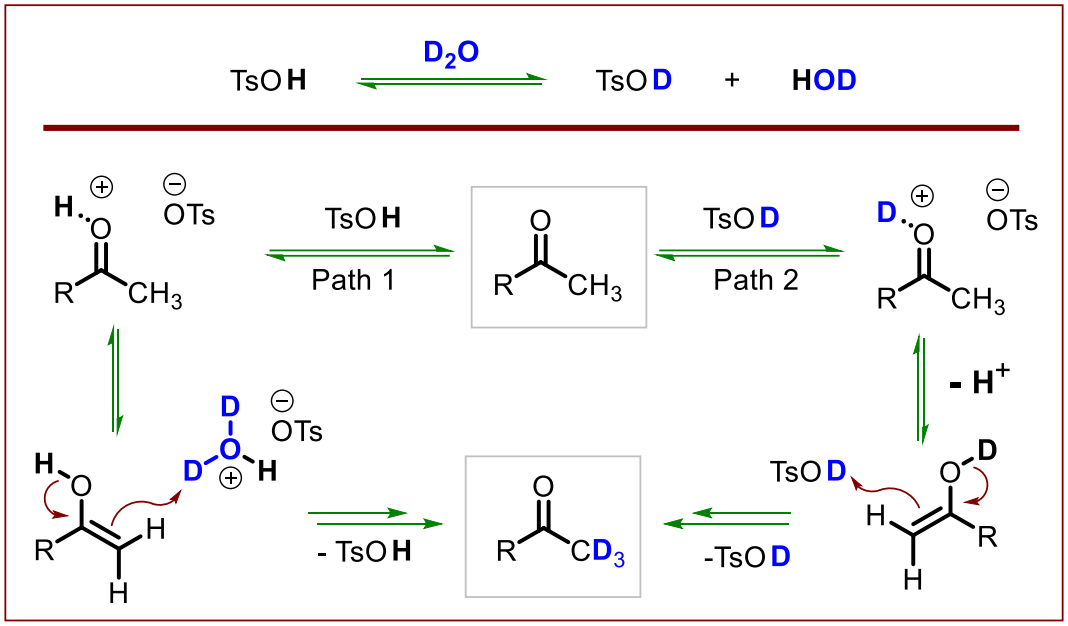


Experimental procedure: In a dry sealed tube (10 mL) equipped with a magnetic stir bar, 20 mol% of dry *p*TSA was added. The tube was then evacuated and backfilled with nitrogen three times. Following this, 88% deuterated 4-methyl acetophenone (**1a**, 0.2 mmol, 1.0 equiv.), isobutyrophenone (**1b**, 30 µL, 0.2 mmol, 1 equiv.), and 0.3 mL of 1,2-dichloroethane (as a co-solvent) were introduced. The reaction mixture was stirred at 100 °C for 24 h. After the reaction, we took crude **^{1}H NMR** and we got 50% [D] incorporation in the isobutyarophenone system. (The percentage of deuterium [D] incorporation was calculated using the internal alkyl group as the internal standard.)

^{1}H NMR (400 MHz, $CDCl_3$) of crude (Intermolecular D transfer reaction)



7. Proposed reaction mechanism:



Scheme S3. Proposed reaction mechanism:

Based on the control experiments, we proposed a catalytic cycle for the deuteration at the alpha position of a carbonyl compound. The process begins with the H/D exchange between D_2O and *p*TSA, which leads to the formation of TsOD and HOD, which are in equilibrium with each other. On the basis of the control experiment (Scheme 2A-2E, Scheme 3G1 and 3G2), we have two pathways. In the presence of TsOH and TsOD simultaneously, the alpha-hydrogen of the carbonyl compound undergoes keto-enol tautomerism, followed by deprotonation.[5] This well-coordinated sequence facilitates the H/D exchange, resulting in the formation of the deuterated carbonyl compound. Finally, the regeneration of the H^+ ion from the deuterated oxonium ion occurs through deprotonolysis, as illustrated in Scheme S4.

8. References:

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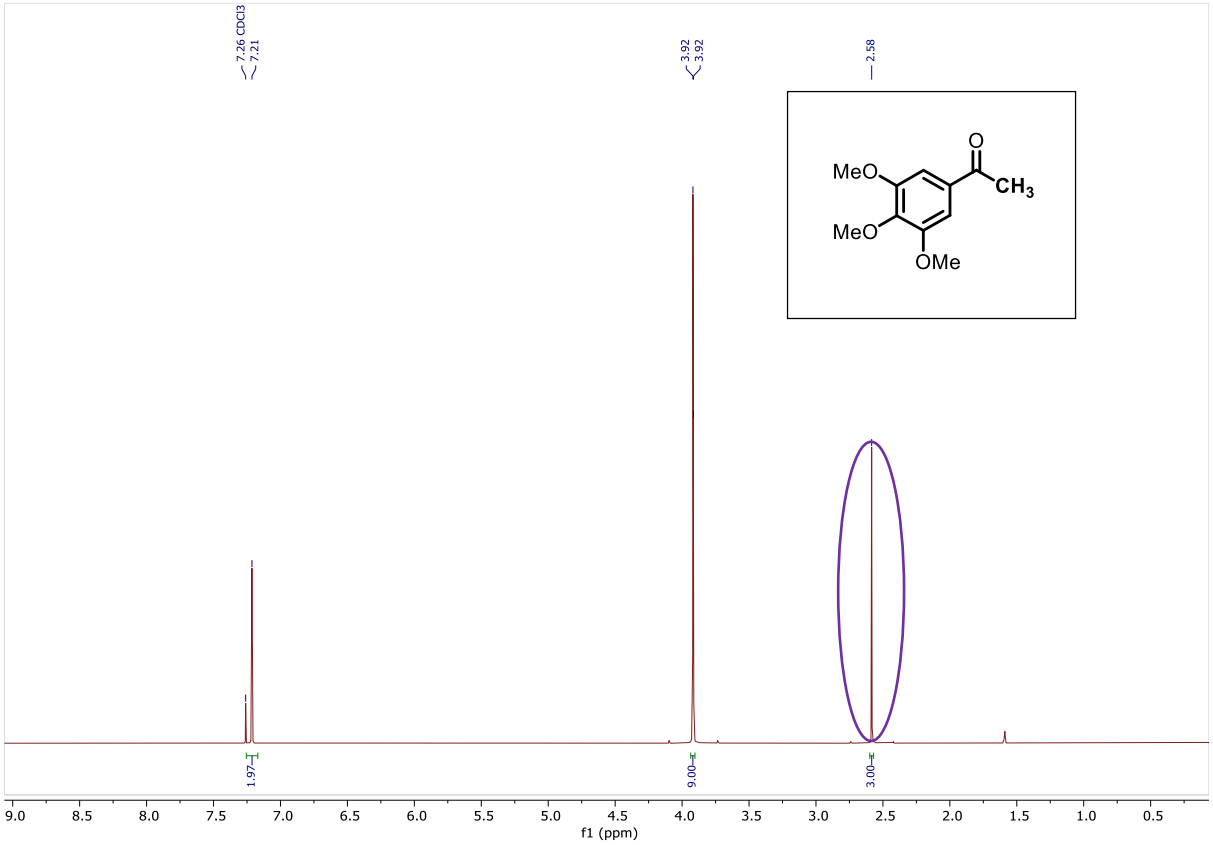
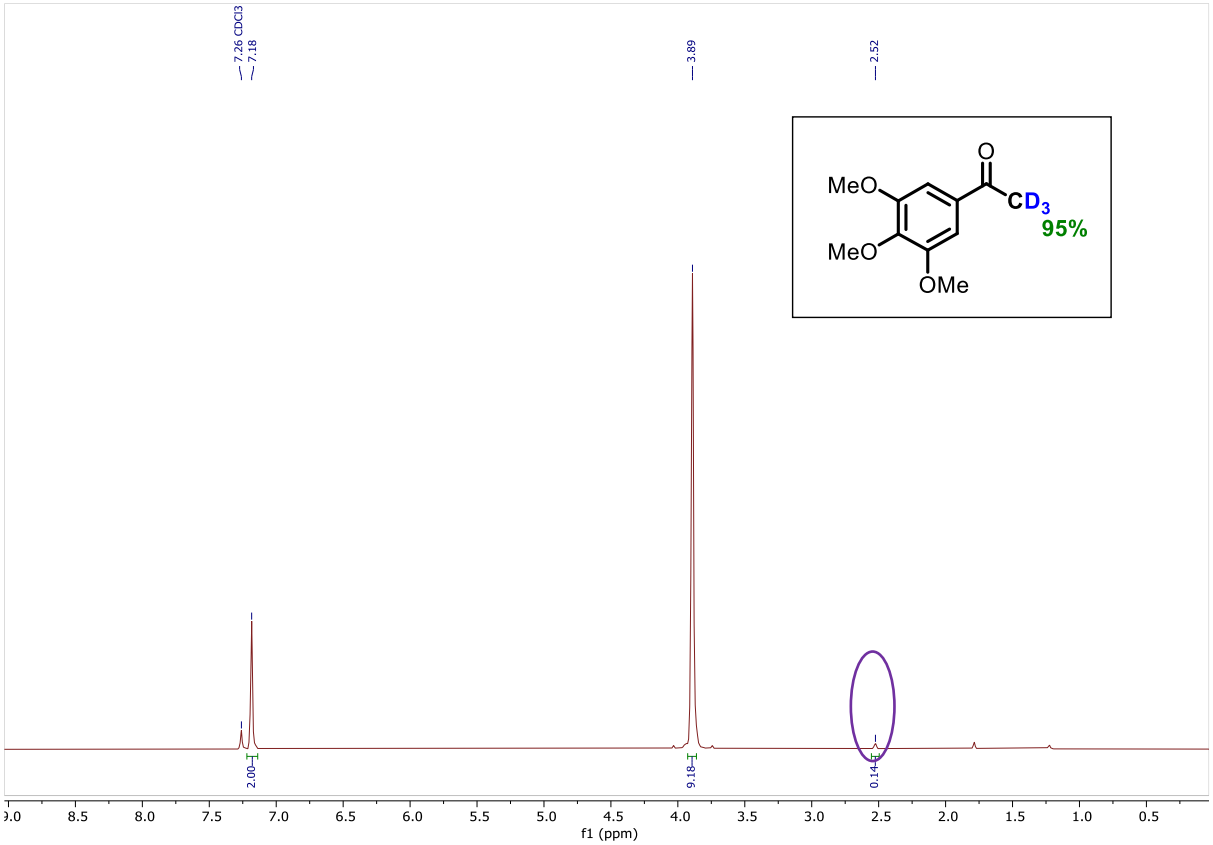
9. Copies of ^{1}H, ^{13}C and ^{19}F NMR

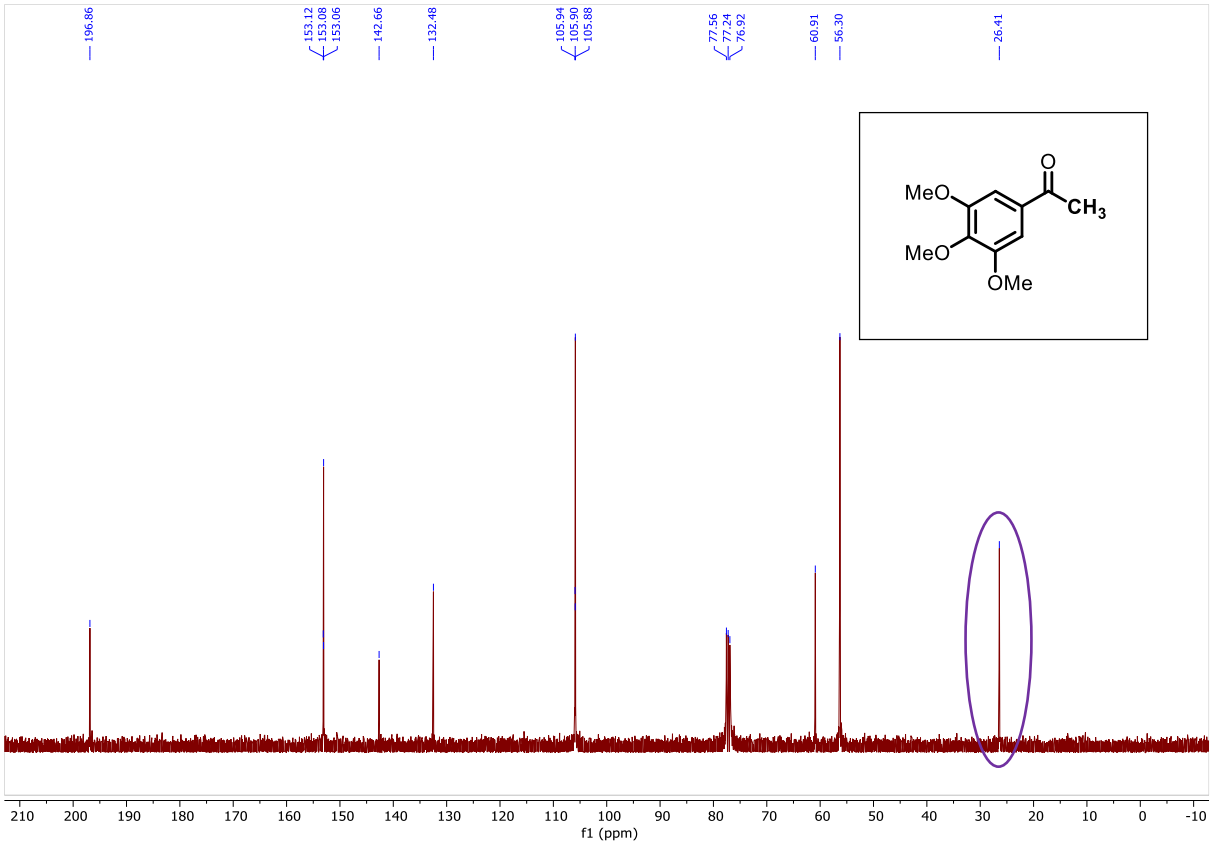
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(3,4,5-Trimethoxyphenyl)-ethan-1-one** (starting material of **3a**)



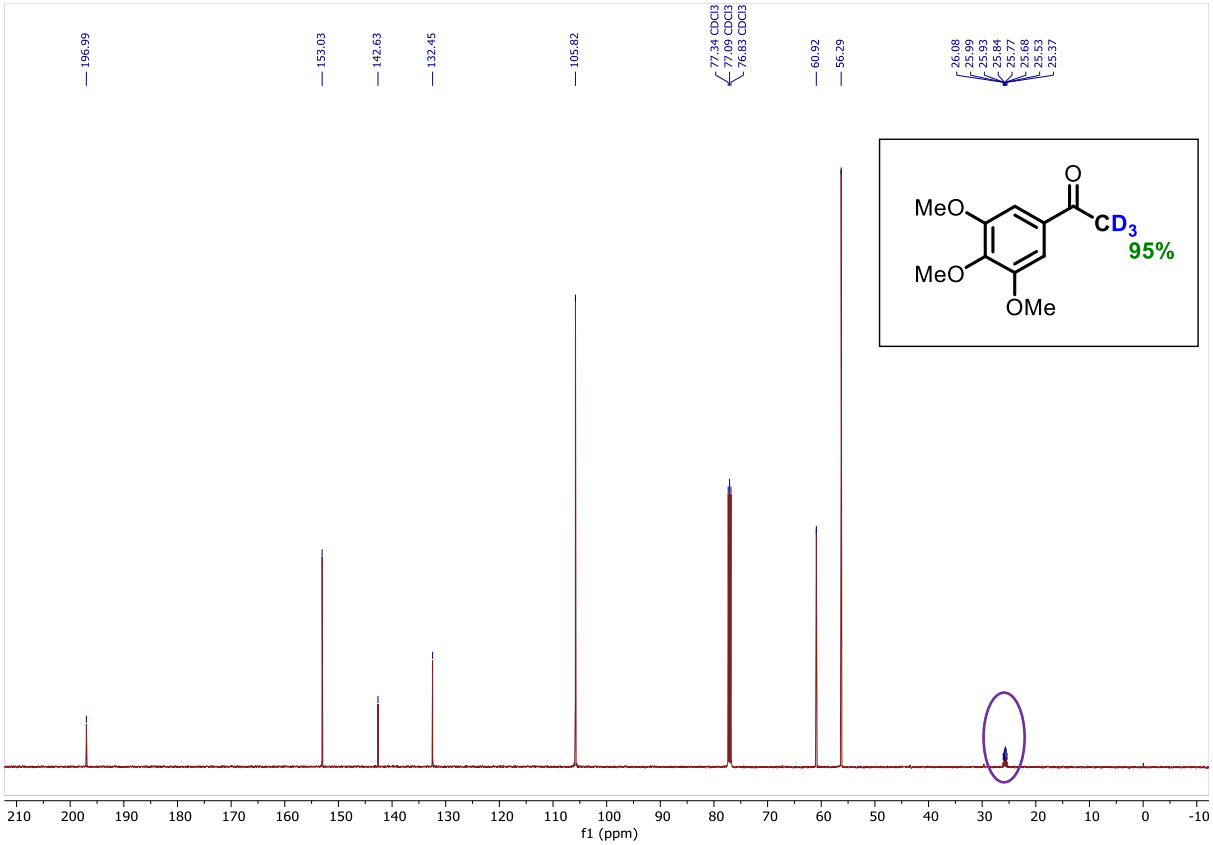
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(3,4,5-Trimethoxyphenyl)-ethan-1-one-2,2,2-d_3 (3a)**



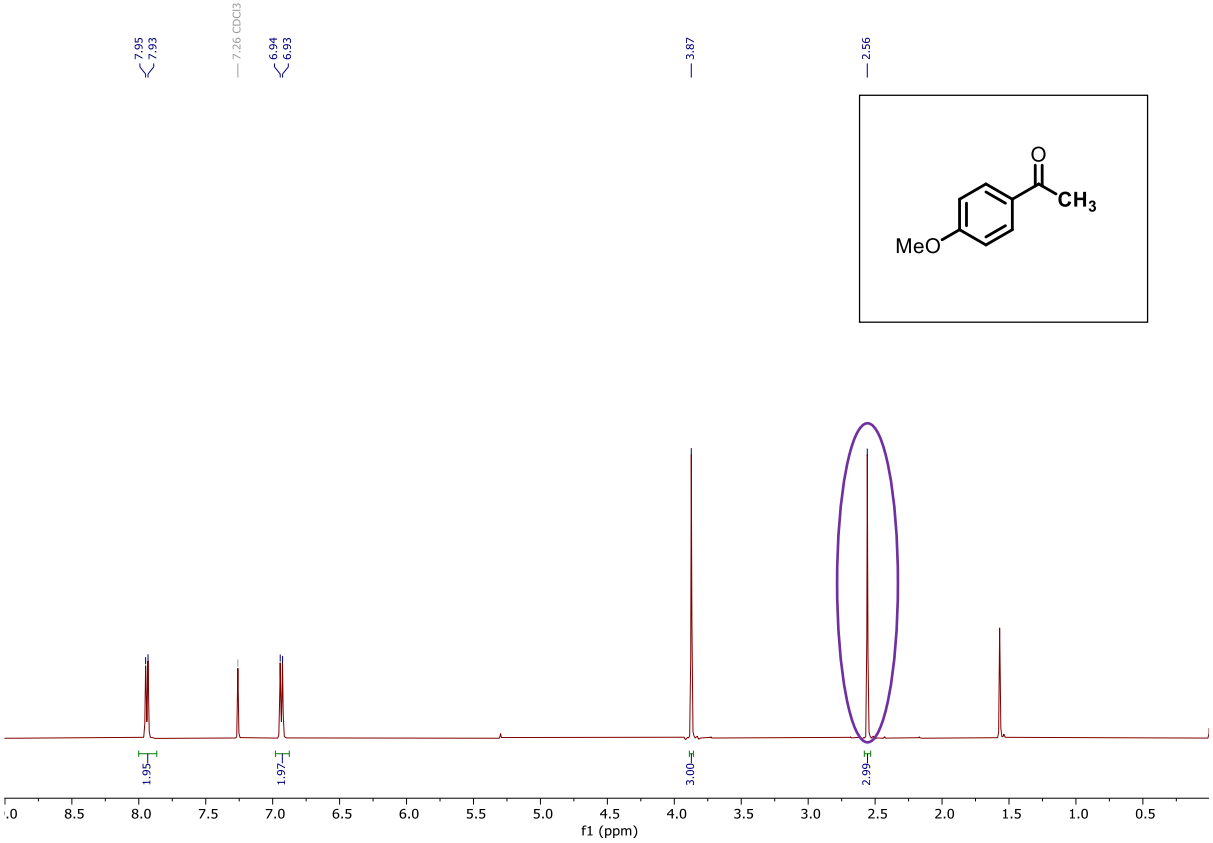
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(3,4,5-Trimethoxyphenyl)-ethan-1-one** (starting material of **3a**)



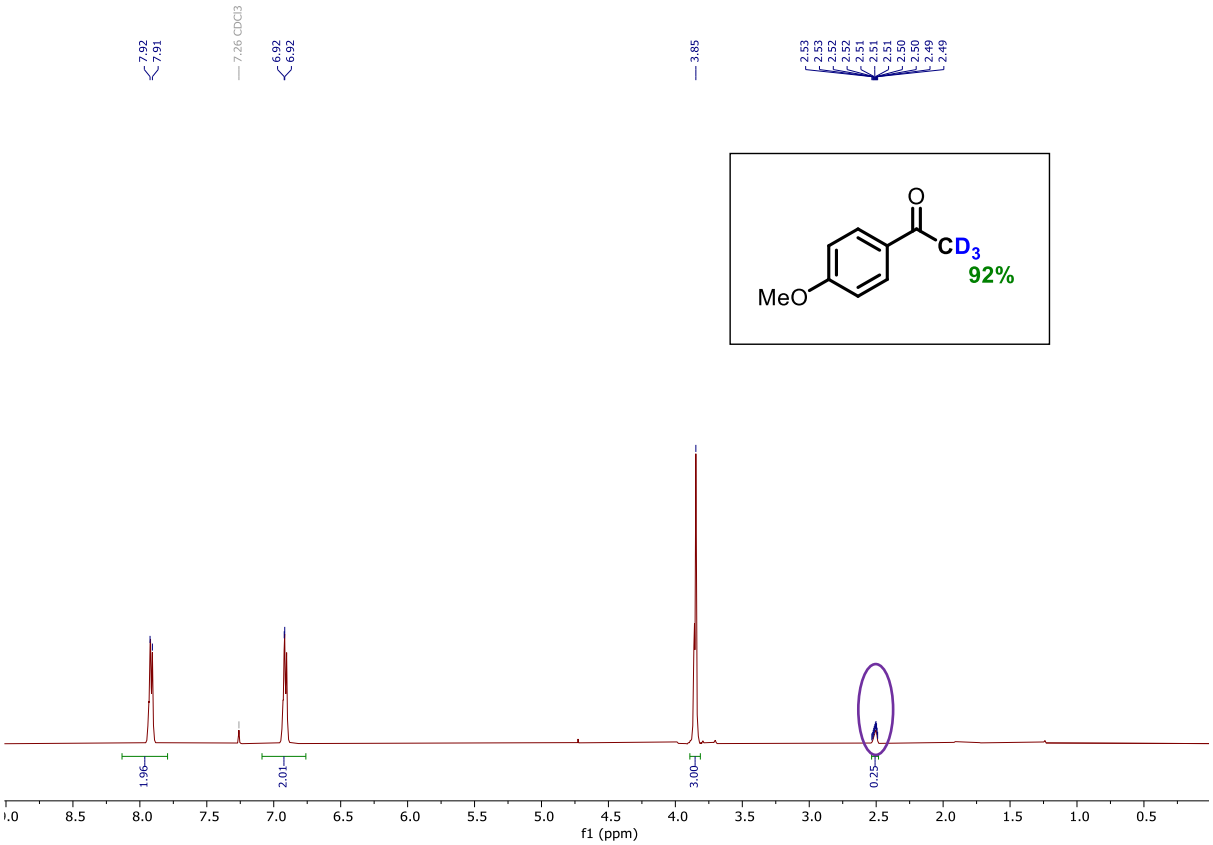
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(3,4,5-Trimethoxyphenyl)-ethan-1-one-2,2,2-*d*$_3$ (3a)**



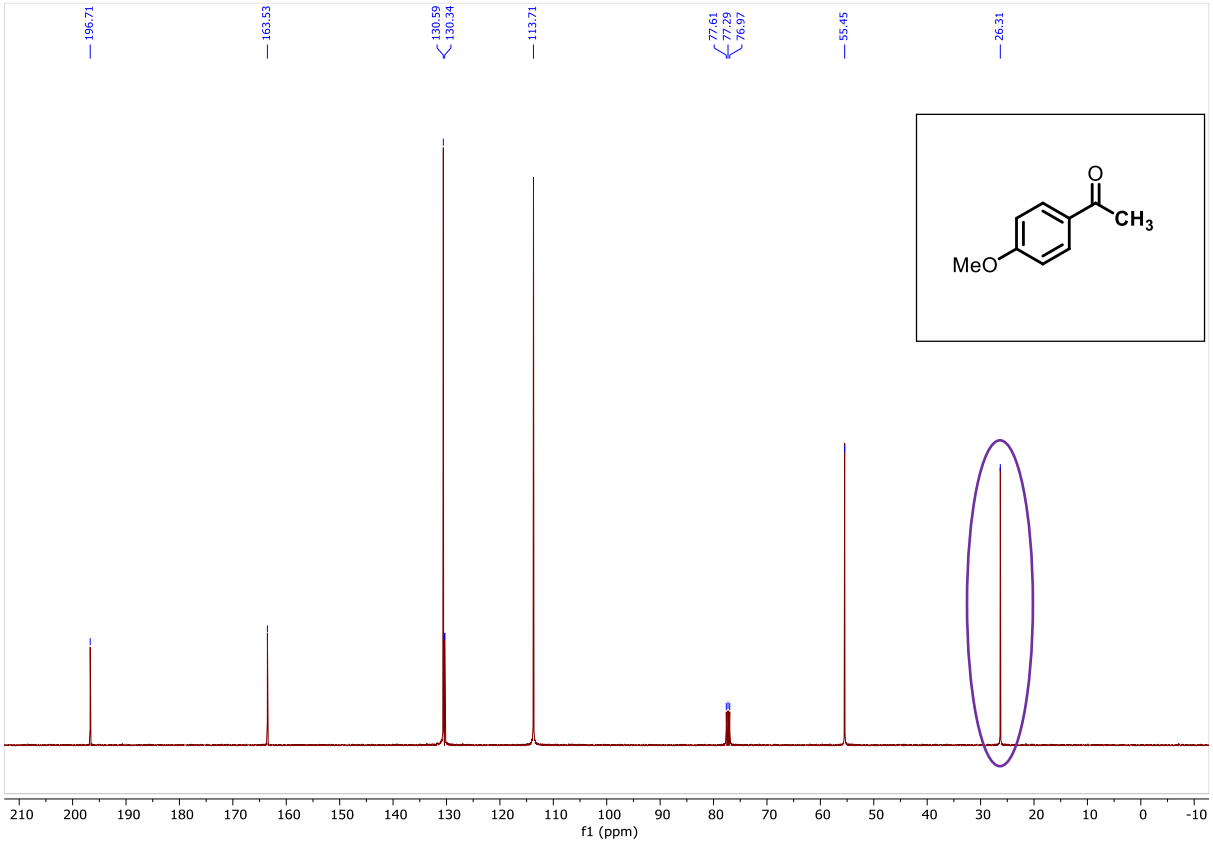
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(4-Methoxyphenyl)-ethan-1-one** (starting material of **3b**)



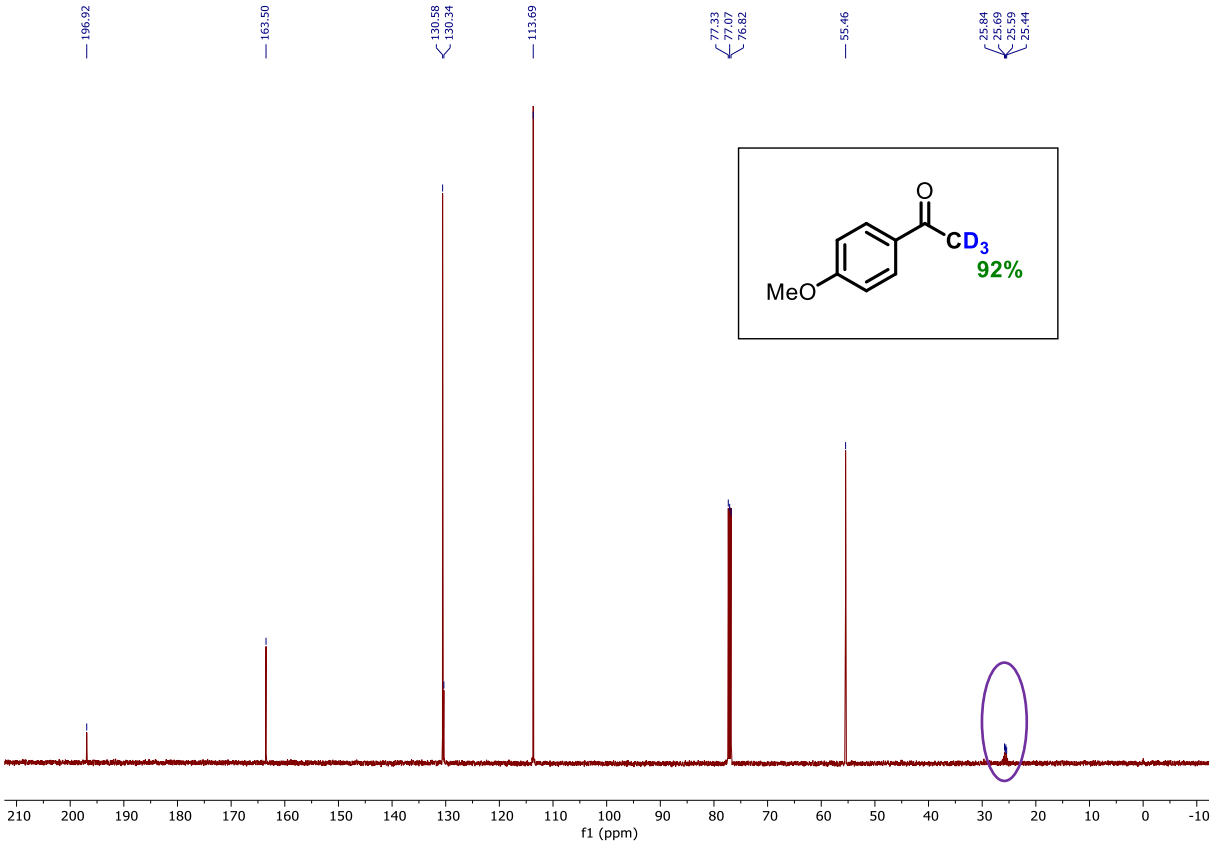
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(4-Methoxyphenyl)-ethan-1-one-2,2,2-*d*$_3$ (3b)**



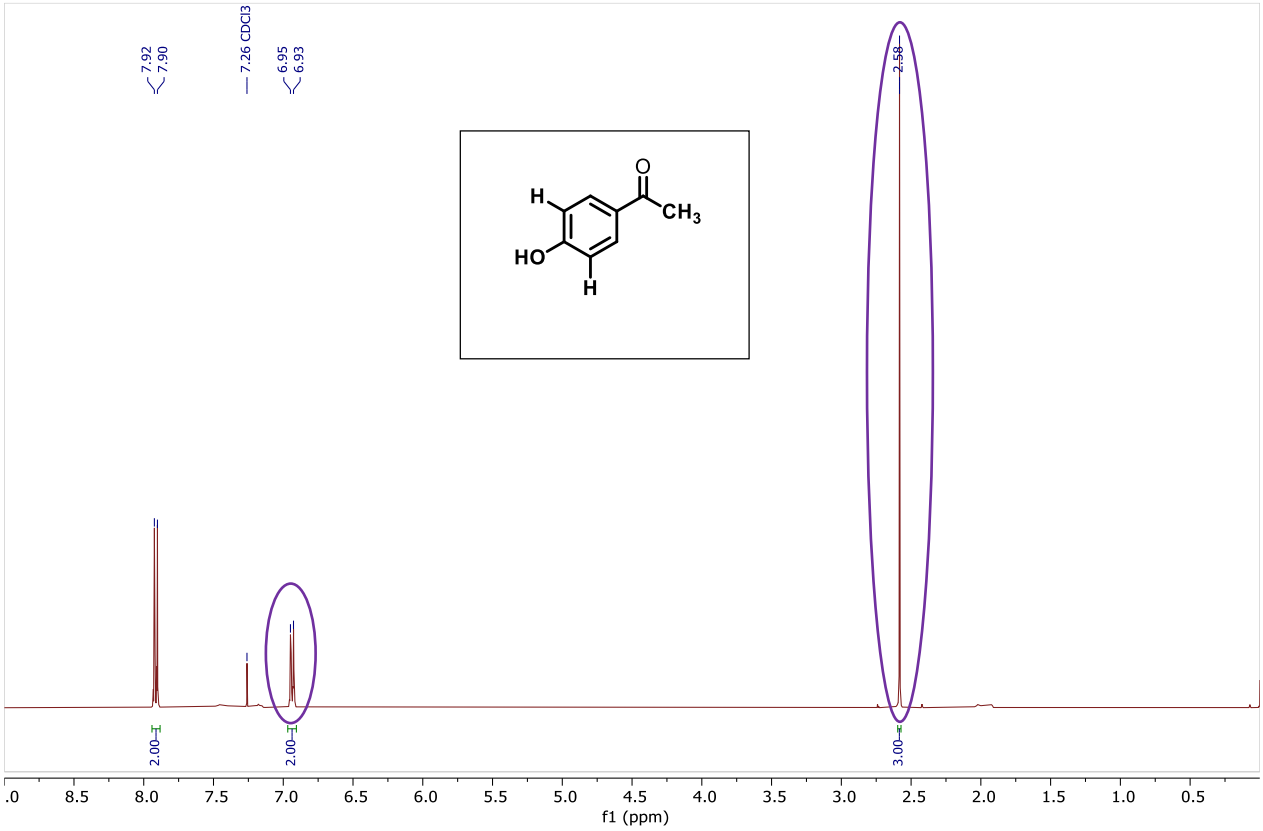
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(4-Methoxyphenyl)-ethan-1-one** (starting material of **3b**)



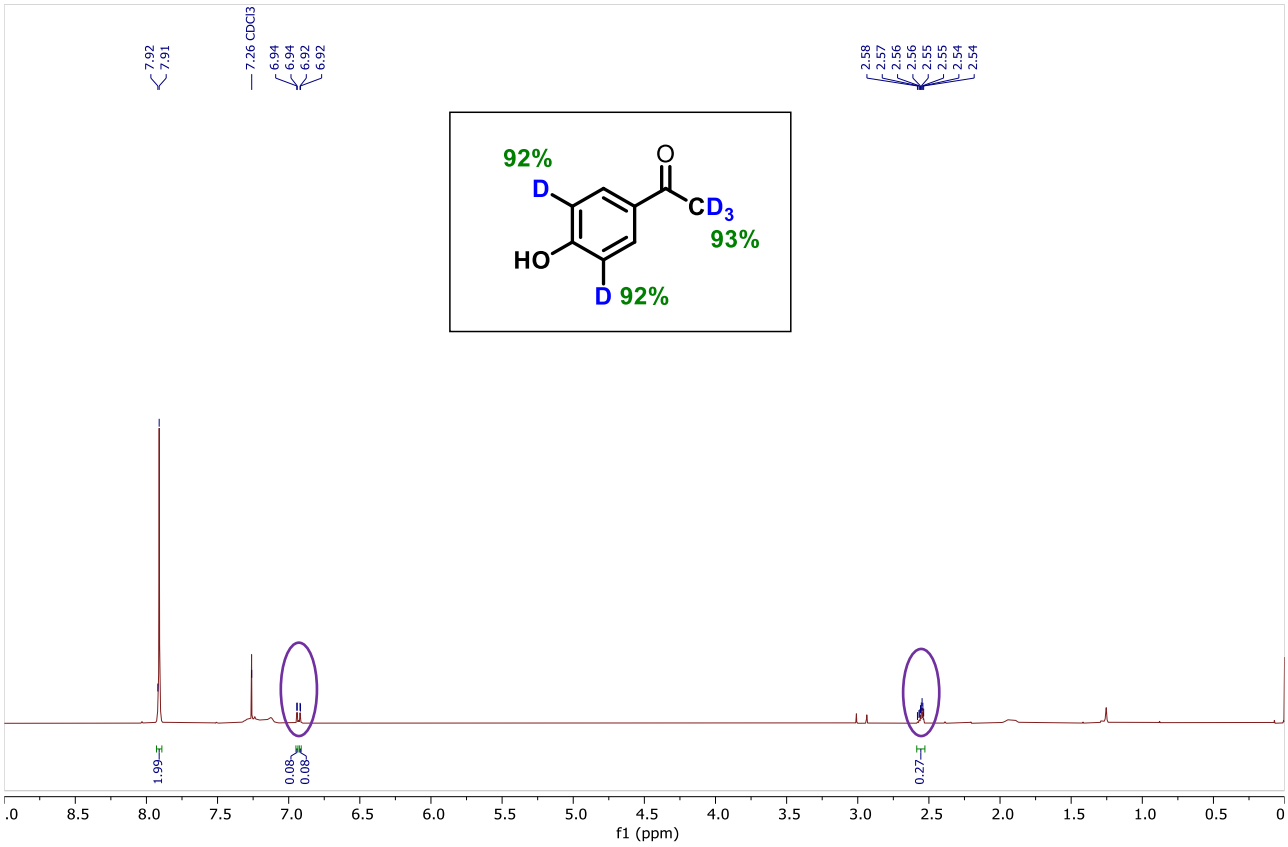
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(4-Methoxyphenyl)-ethan-1-one-2,2,2-*d*$_3$ (3b)**



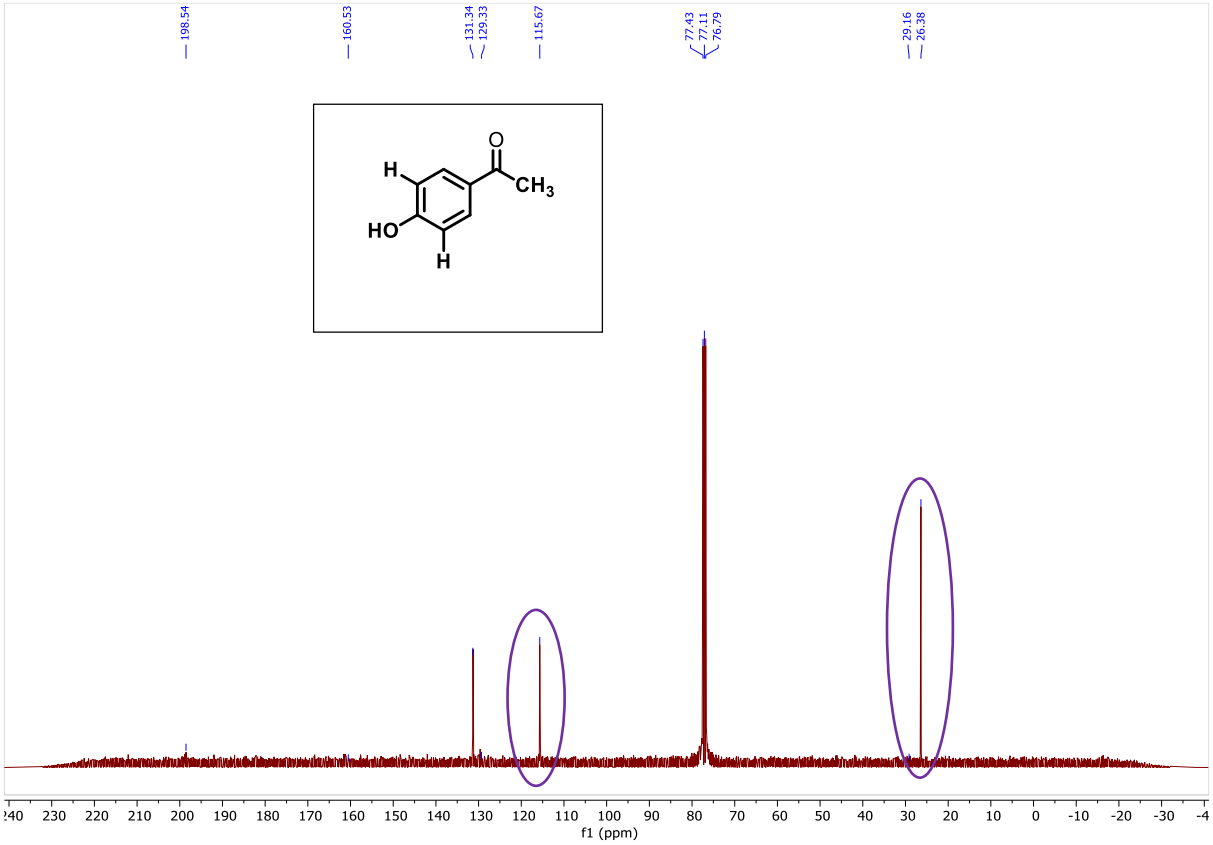
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(4-Hydroxyphenyl)-ethan-1-one** (starting material of **3c**)



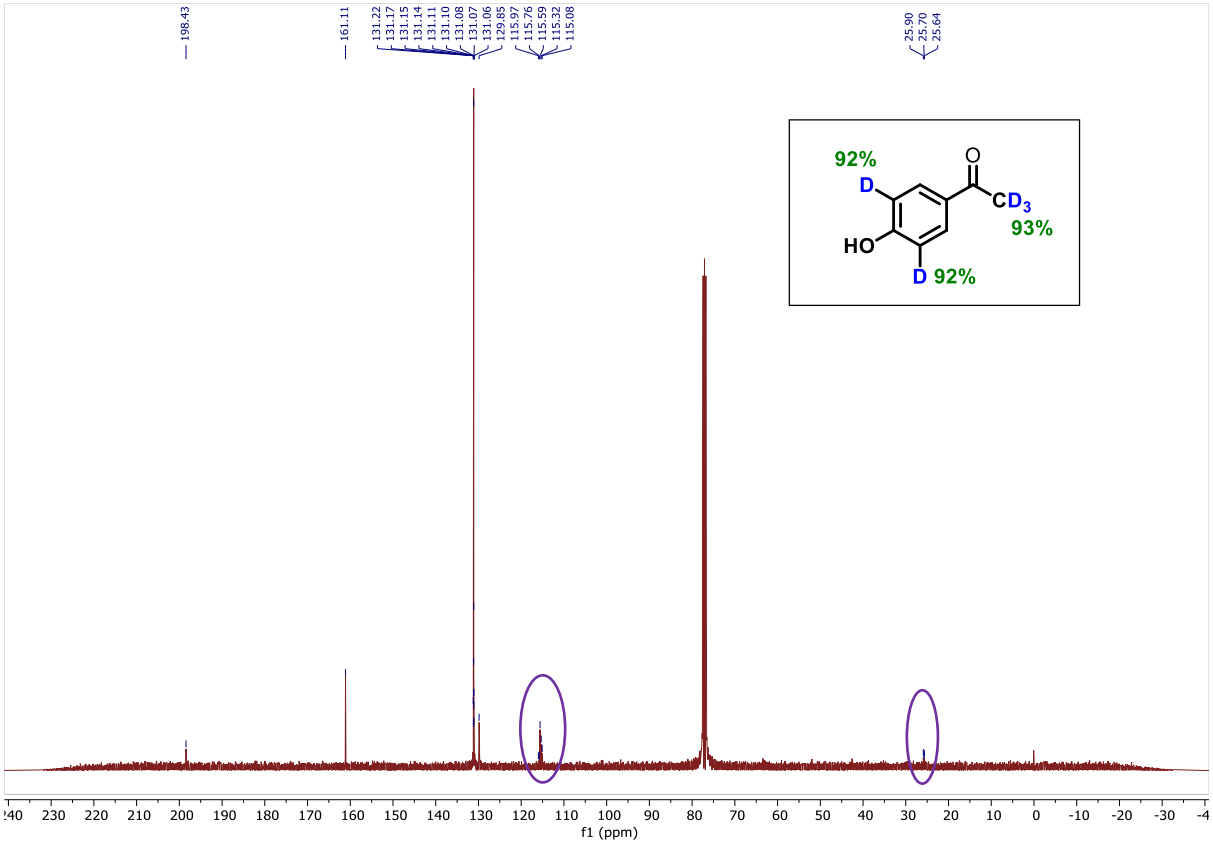
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(4-Hydroxyphenyl-3,5-d_2)-ethan-1-one-2,2,2-d_3 (3c)**



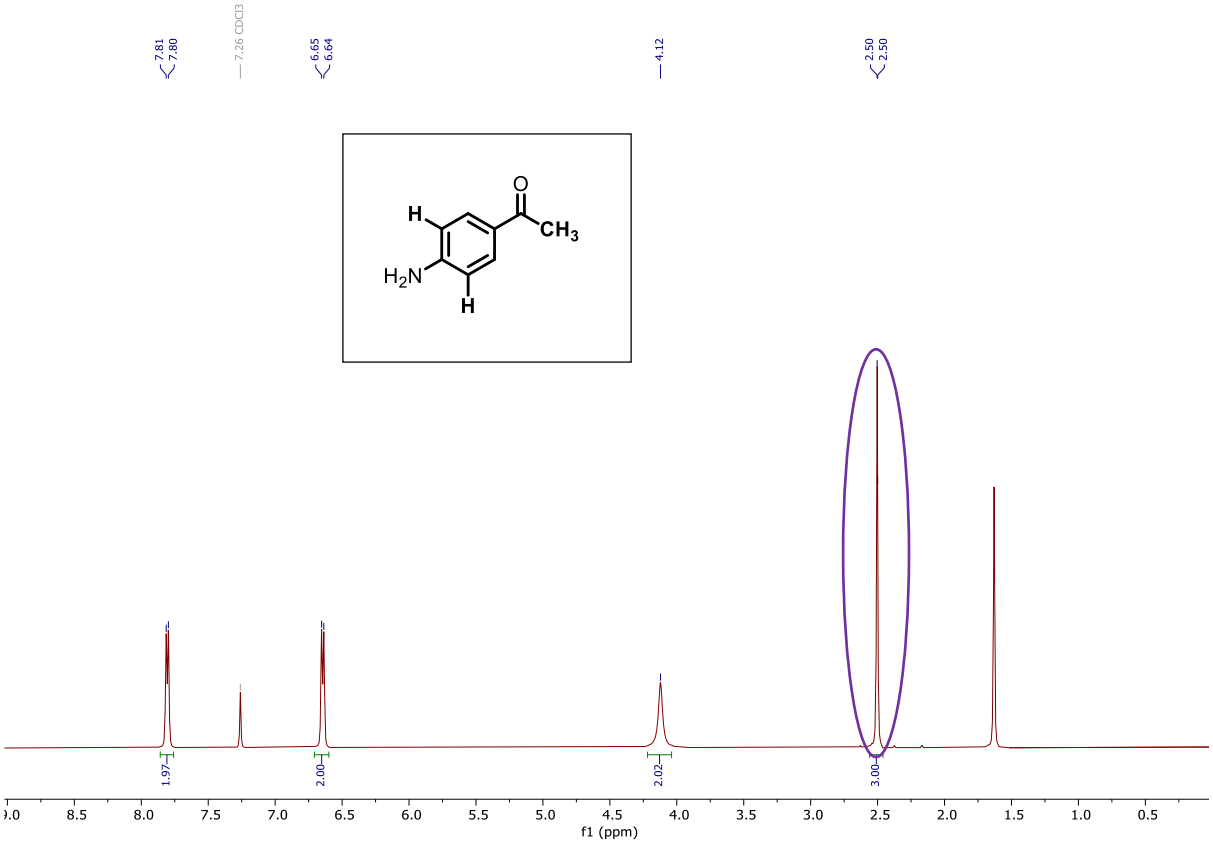
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(4-Hydroxyphenyl)-ethan-1-one** (starting material of **3c**)



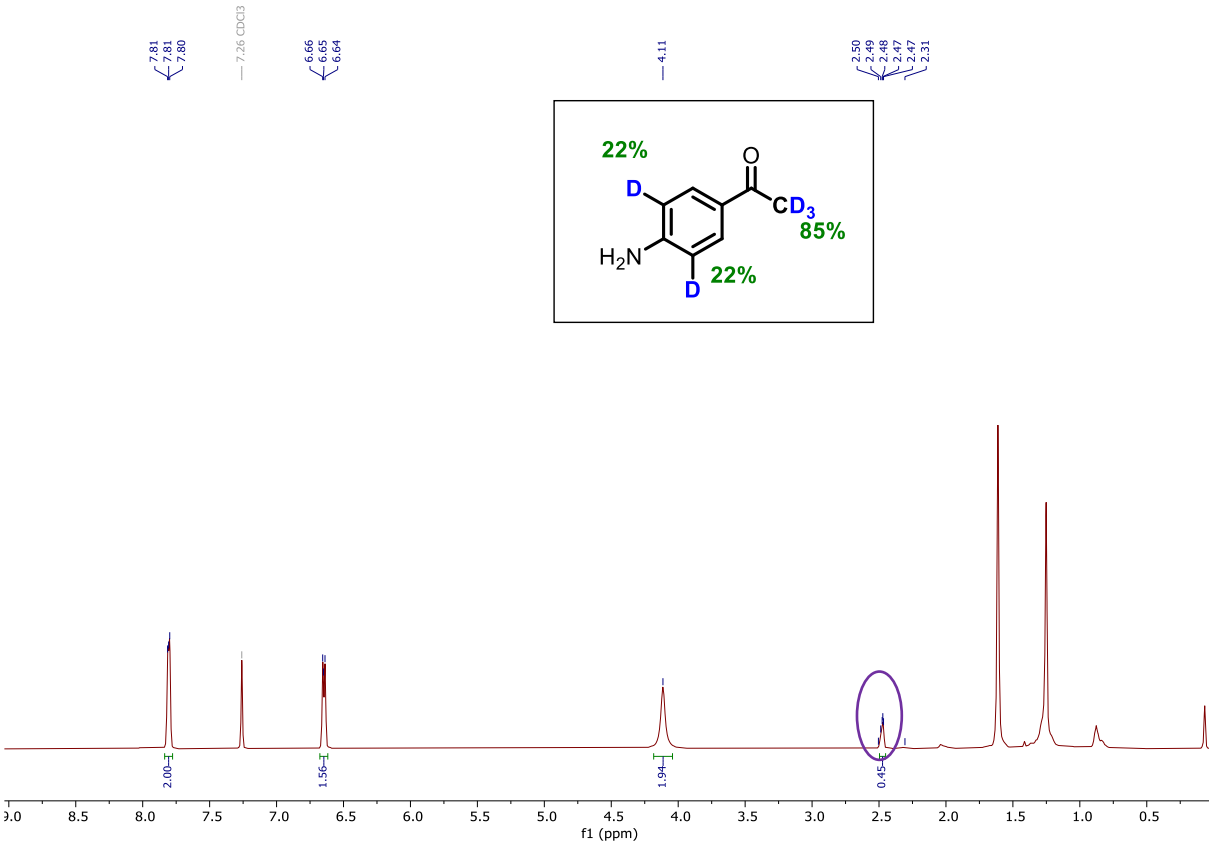
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(4-Hydroxyphenyl-3,5-d_2)-ethan-1-one-2,2,2-d_3 (3c)**



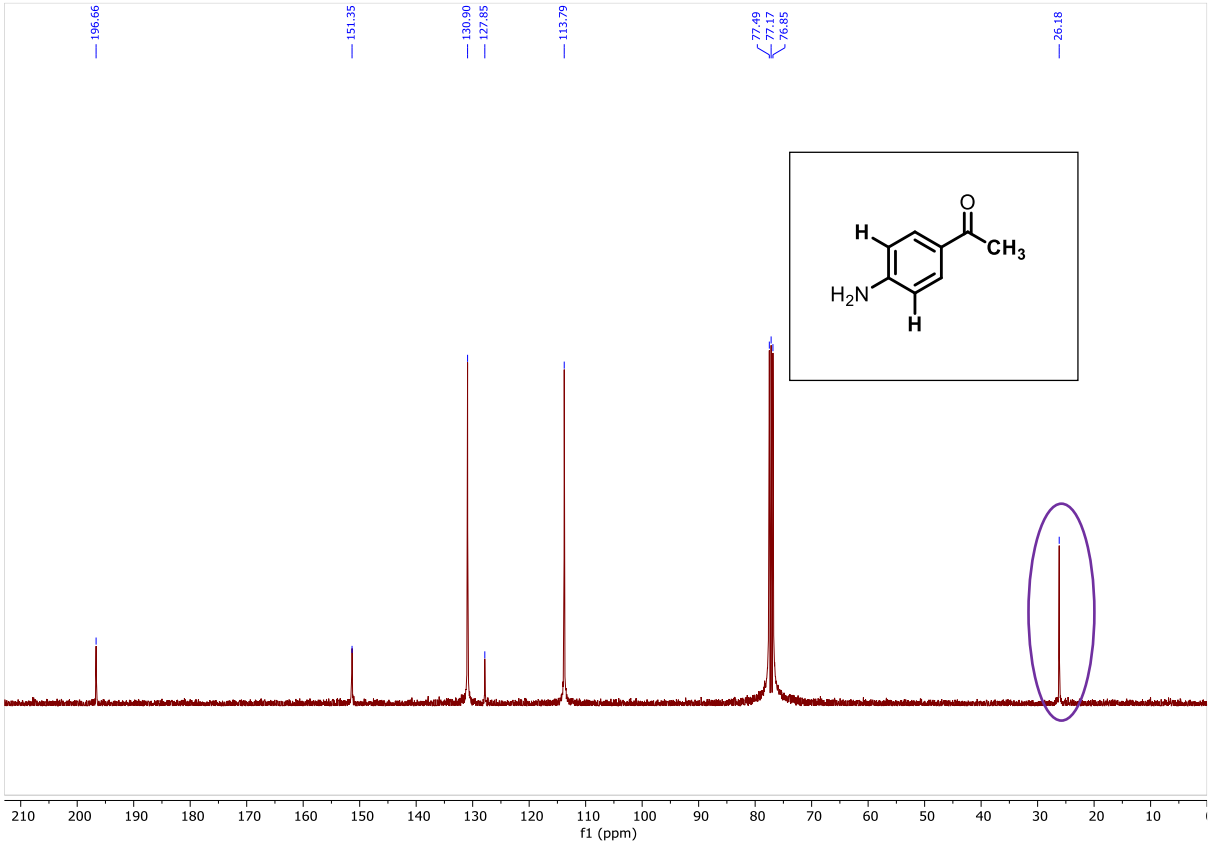
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(4-Aminophenyl)-ethan** (starting material of **3d**)



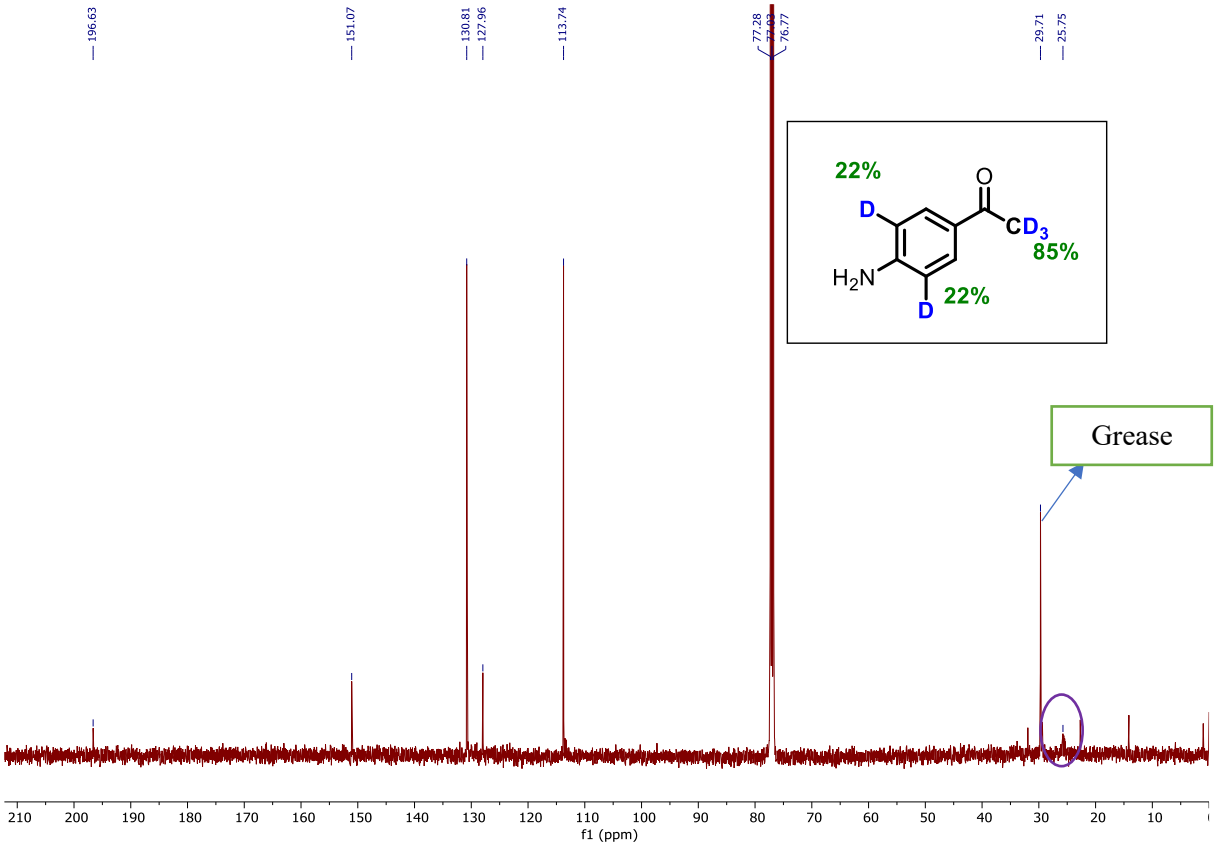
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(4-Aminophenyl)-ethan-1-one-2,2,2-d_3) (3d)**



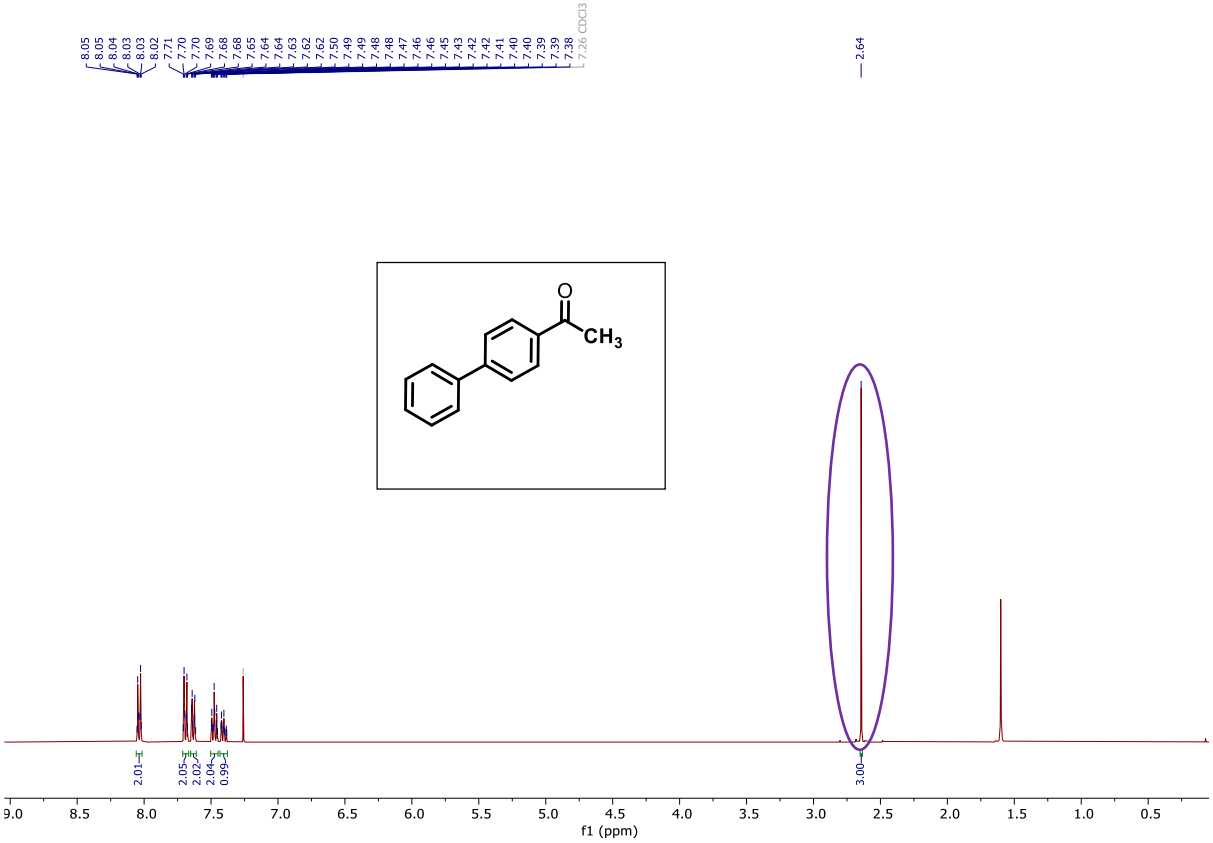
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(4-Aminophenyl)-ethan-1-one** (starting material of **3d**)



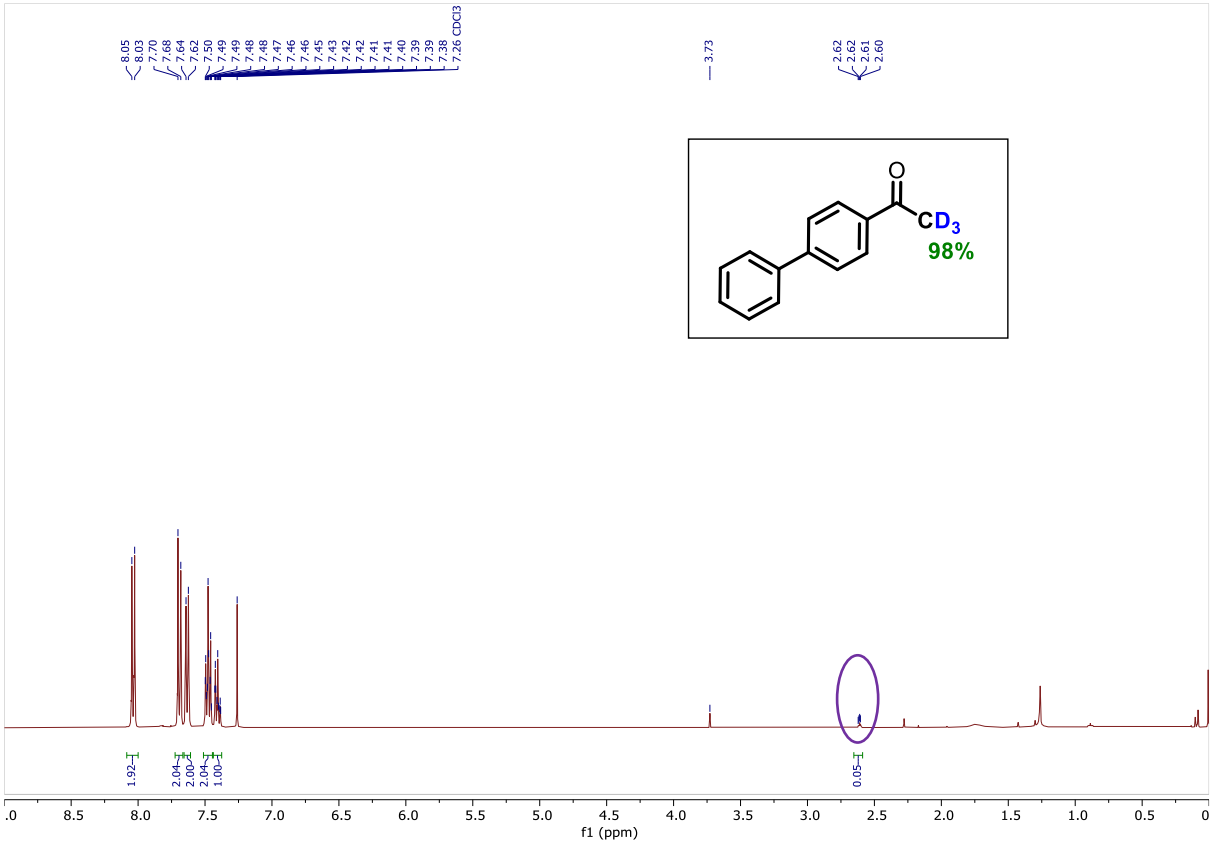
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(4-Aminophenyl)-ethan-1-one-2,2,2-*d*$_3$) (3d)**



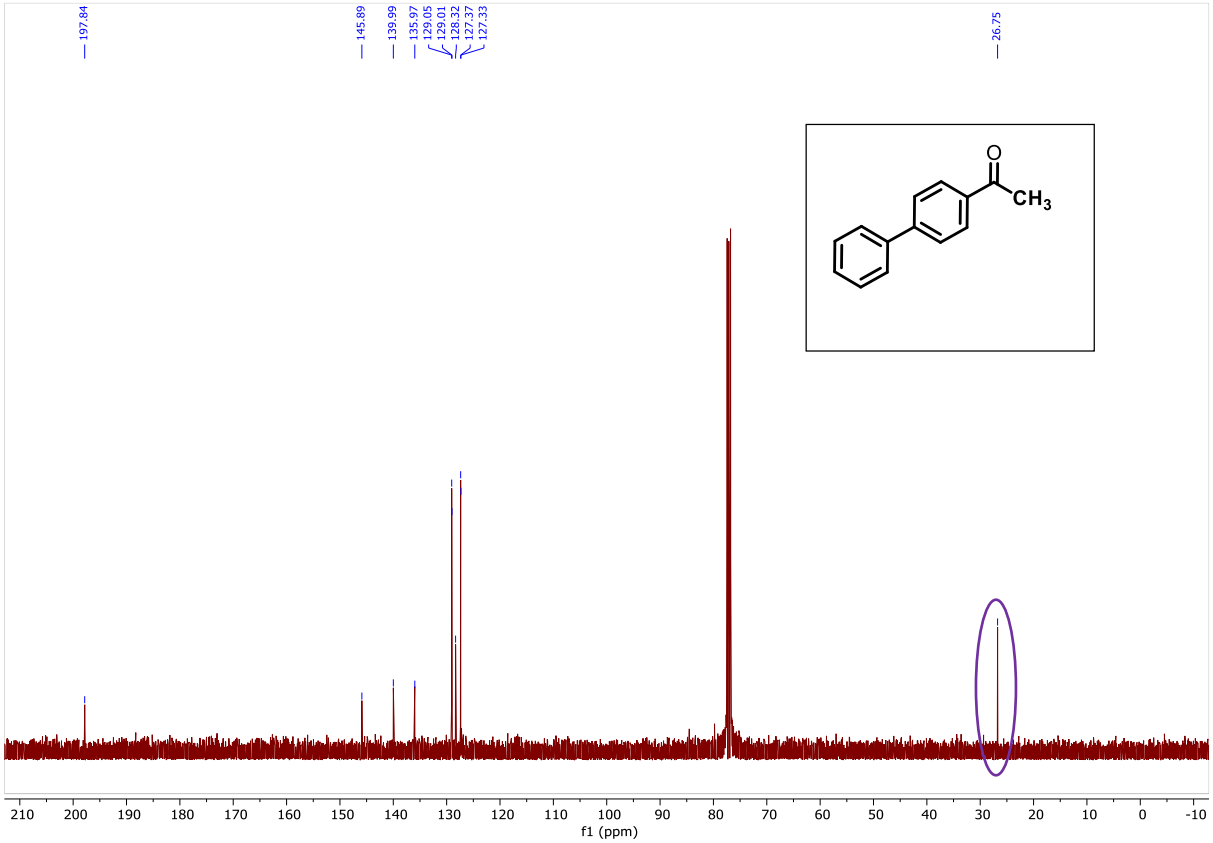
^{1}H NMR (400 MHz, $CDCl_3$) of **1-([1,1'-Biphenyl]-4-yl)-ethan-1-one** (starting material of **3e**)



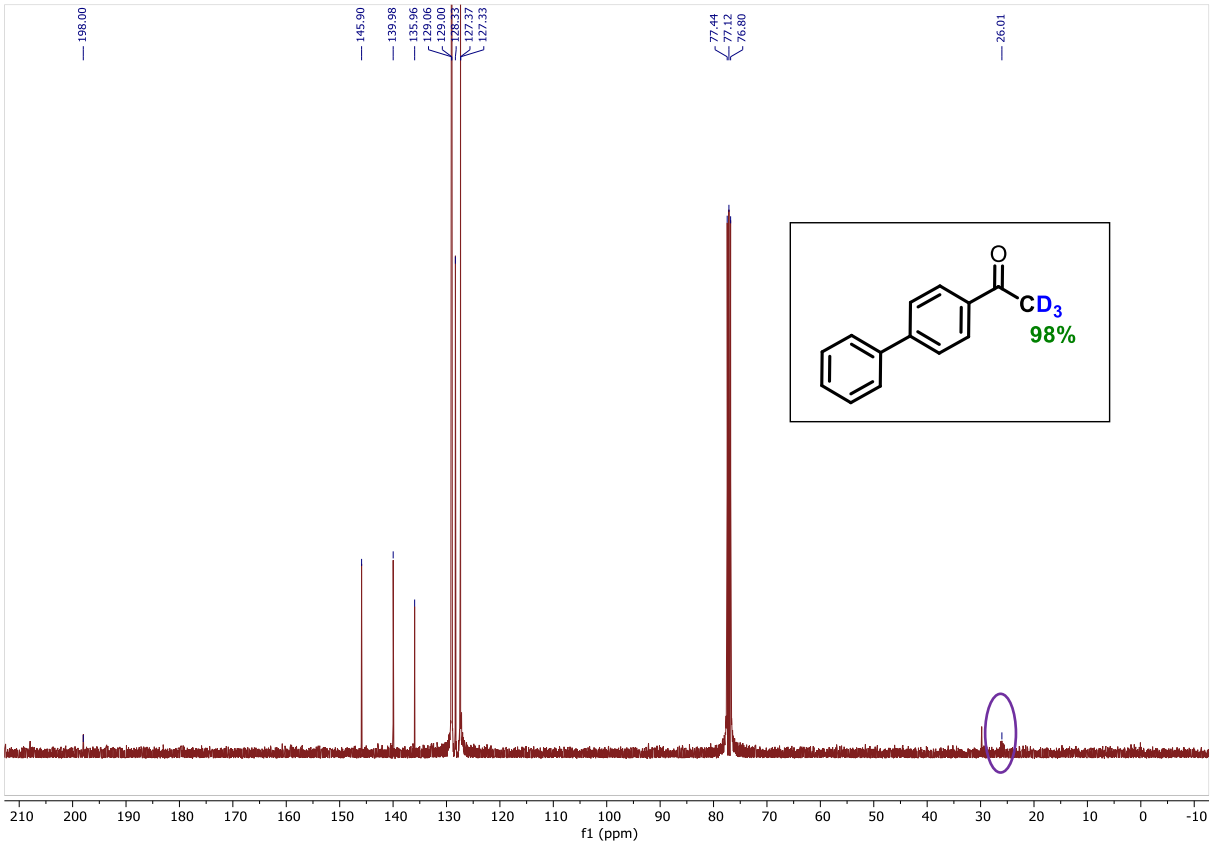
^{1}H NMR (400 MHz, $CDCl_3$) of **1-([1,1'-Biphenyl]-4-yl)-ethan-1-one-2,2,2-d_3 (3e)**



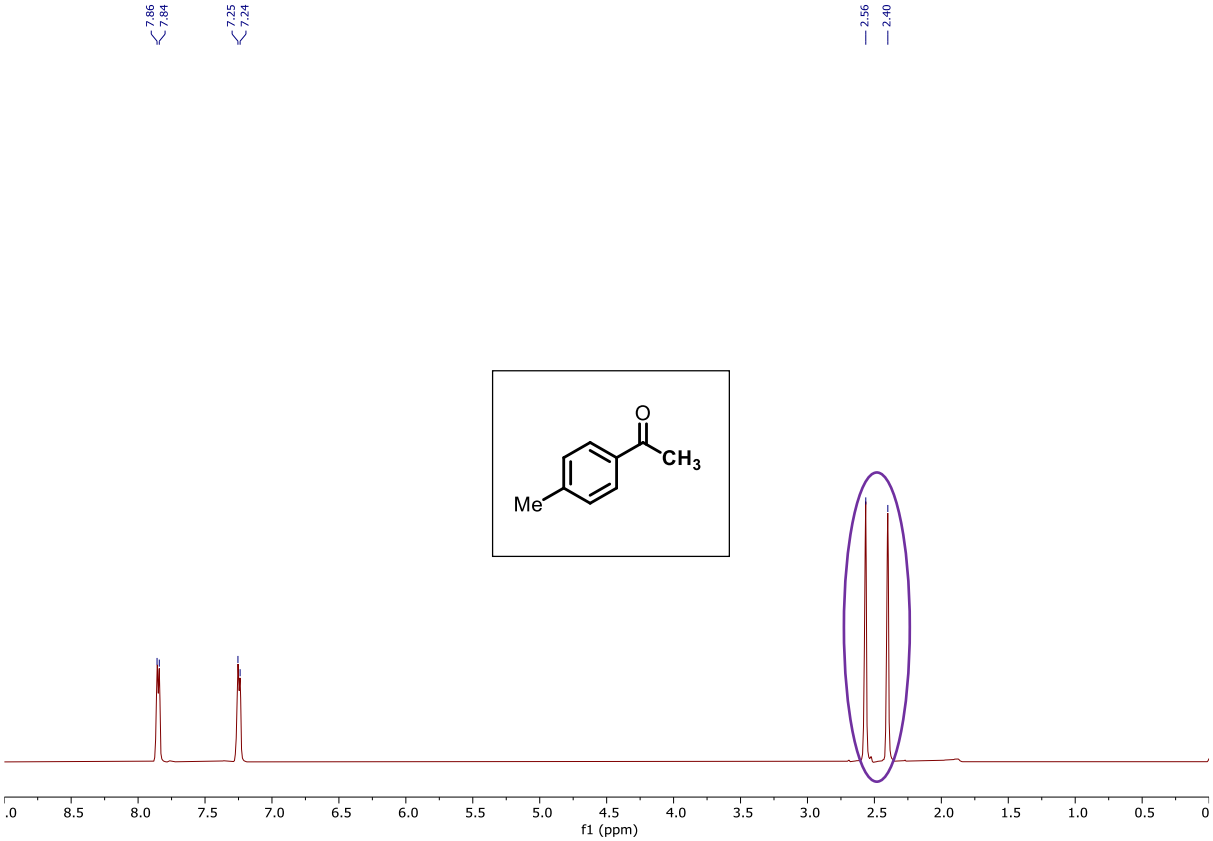
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-([1,1'-Biphenyl]-4-yl)-ethann-1 one** (starting material of **3e**)



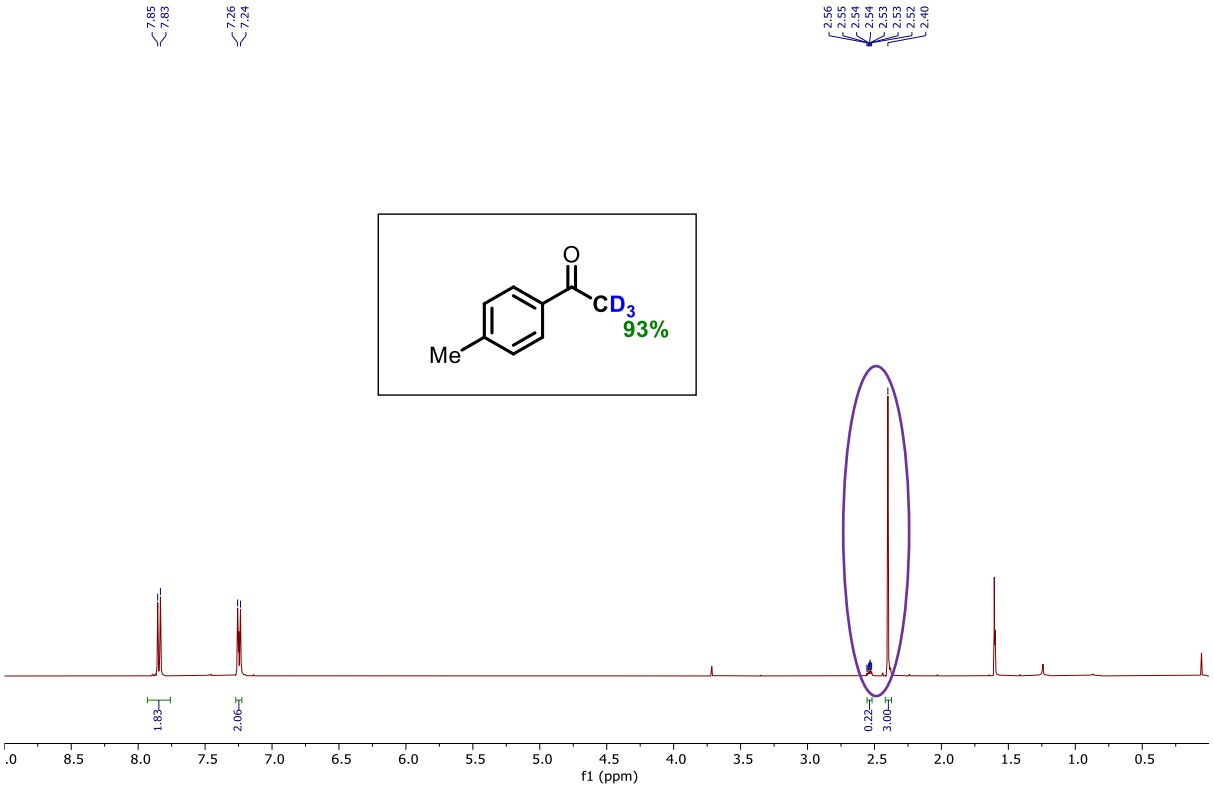
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-([1,1'-Biphenyl]-4-yl)-ethan-1-one-2,2,2-d_3 (3e)**



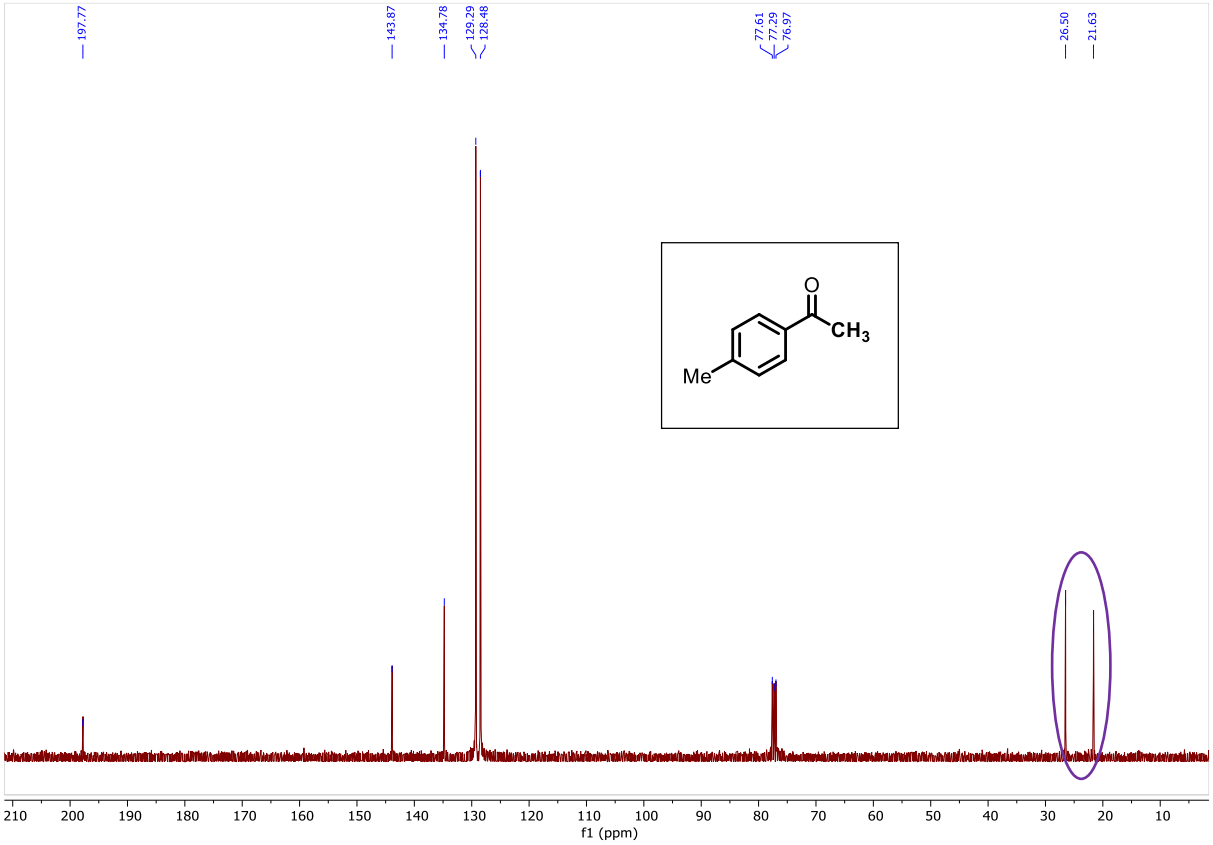
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(*p*-Tolyl)ethan-1-one** (starting material of **3f**)



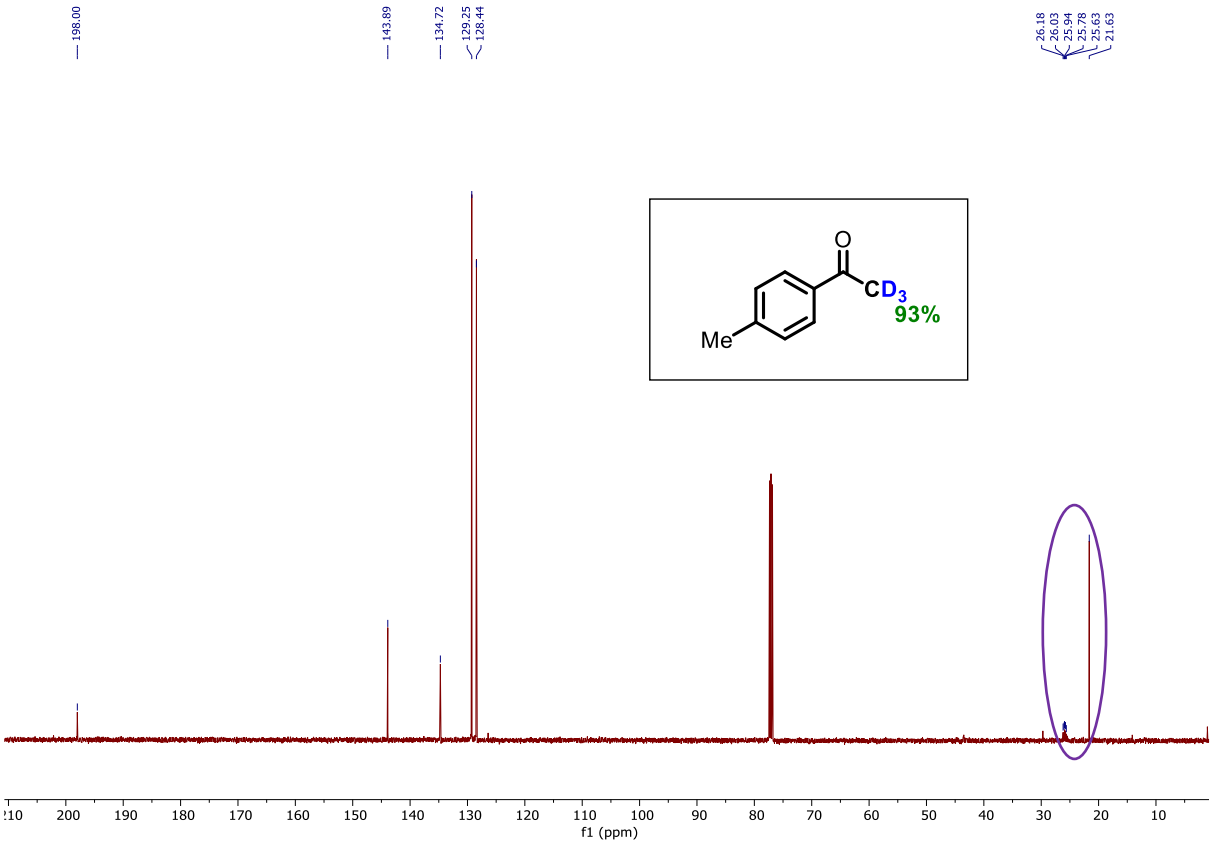
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(*p*-Tolyl)ethan-1-one-2,2,2-d_3 (3f)**



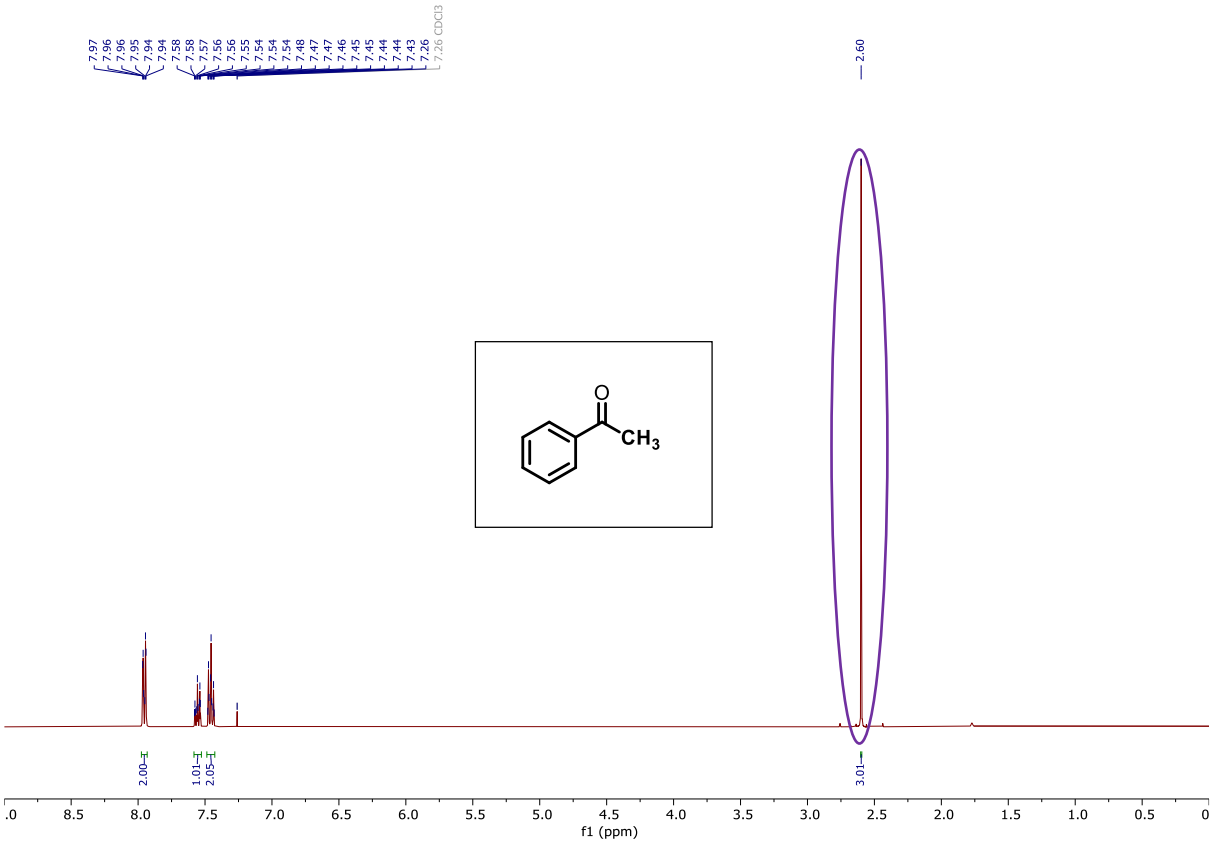
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(*p*-Tolyl)ethan-1-one** (starting material of **3f**)



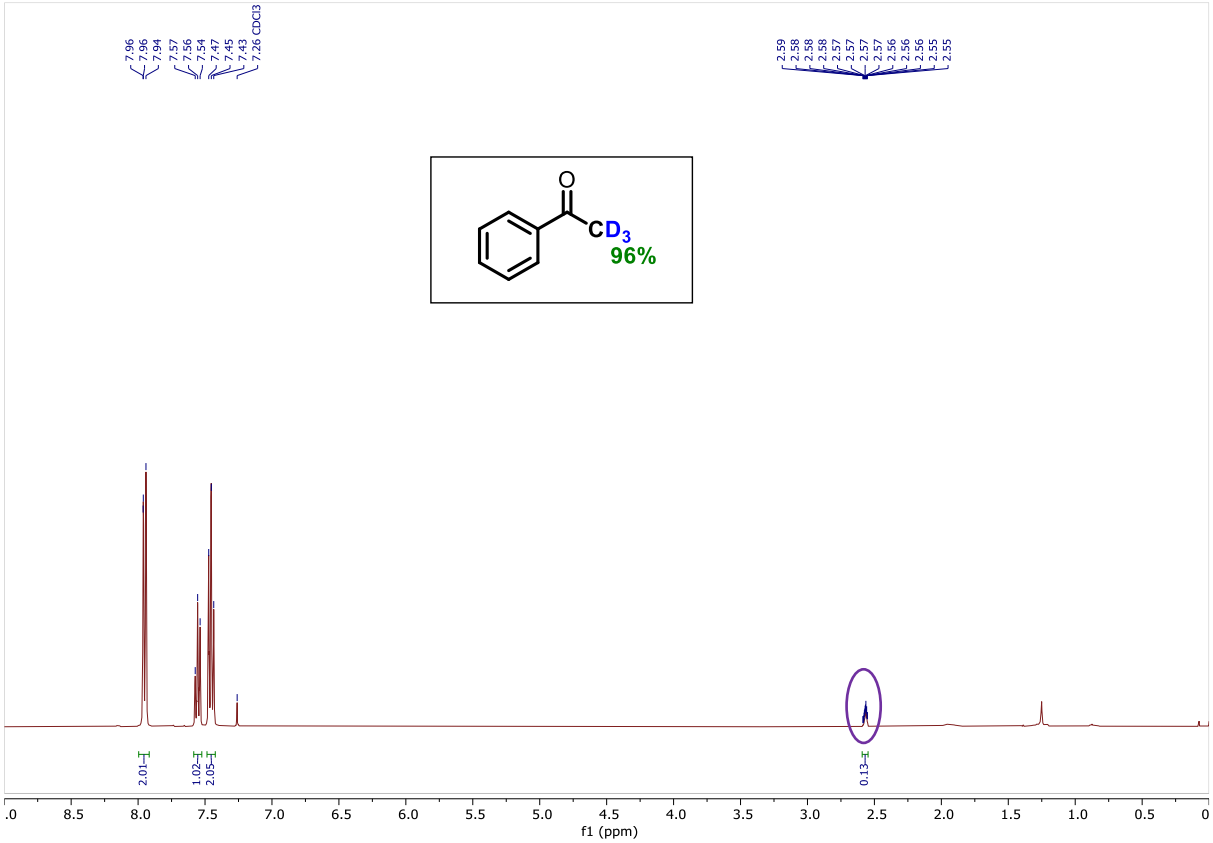
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(*p*-Tolyl)ethan-1-one-2,2,2-d_3 (3f)**



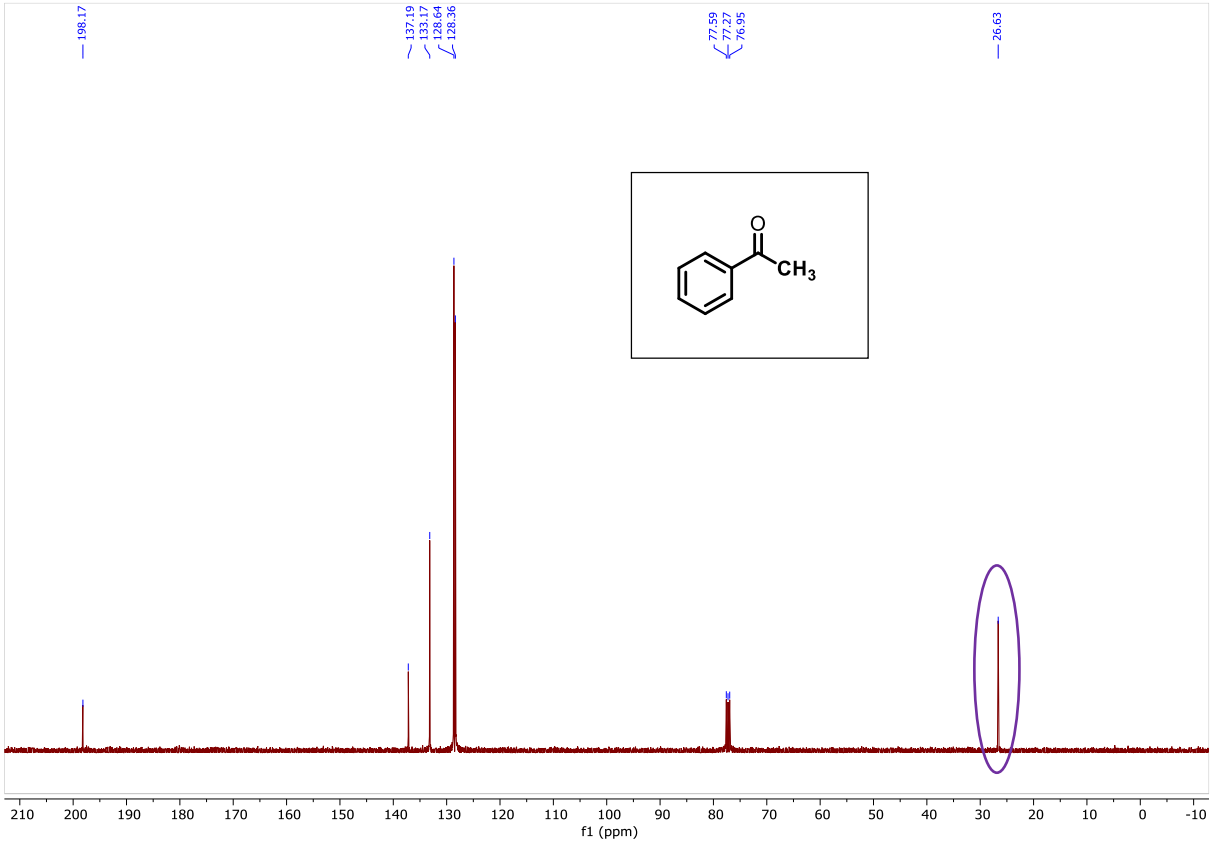
^{1}H NMR (400 MHz, $CDCl_3$) of **1-Phenyl ethan-1-one** (starting material of **3g**)



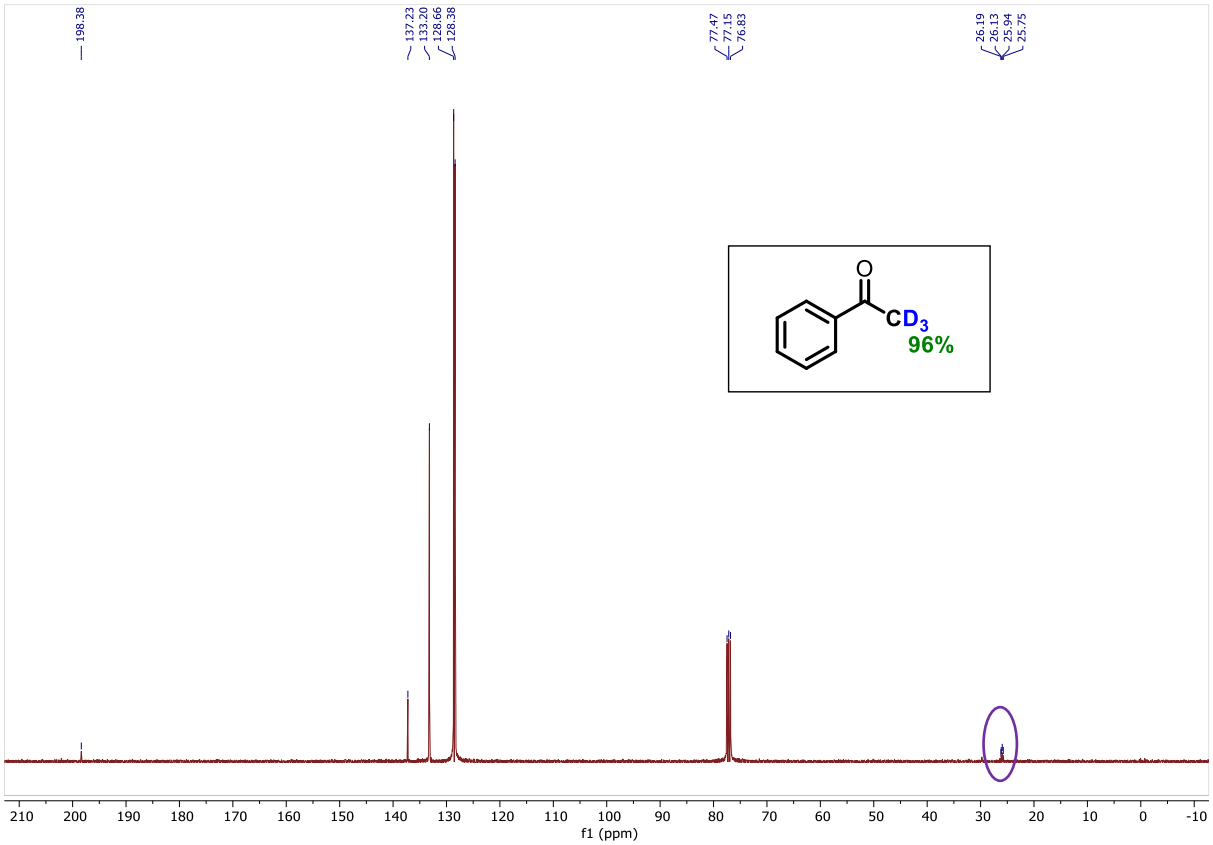
^{1}H NMR (400 MHz, $CDCl_3$) of **1-Phenyl ethan-1-one-2,2,2-d_3 (3g)**



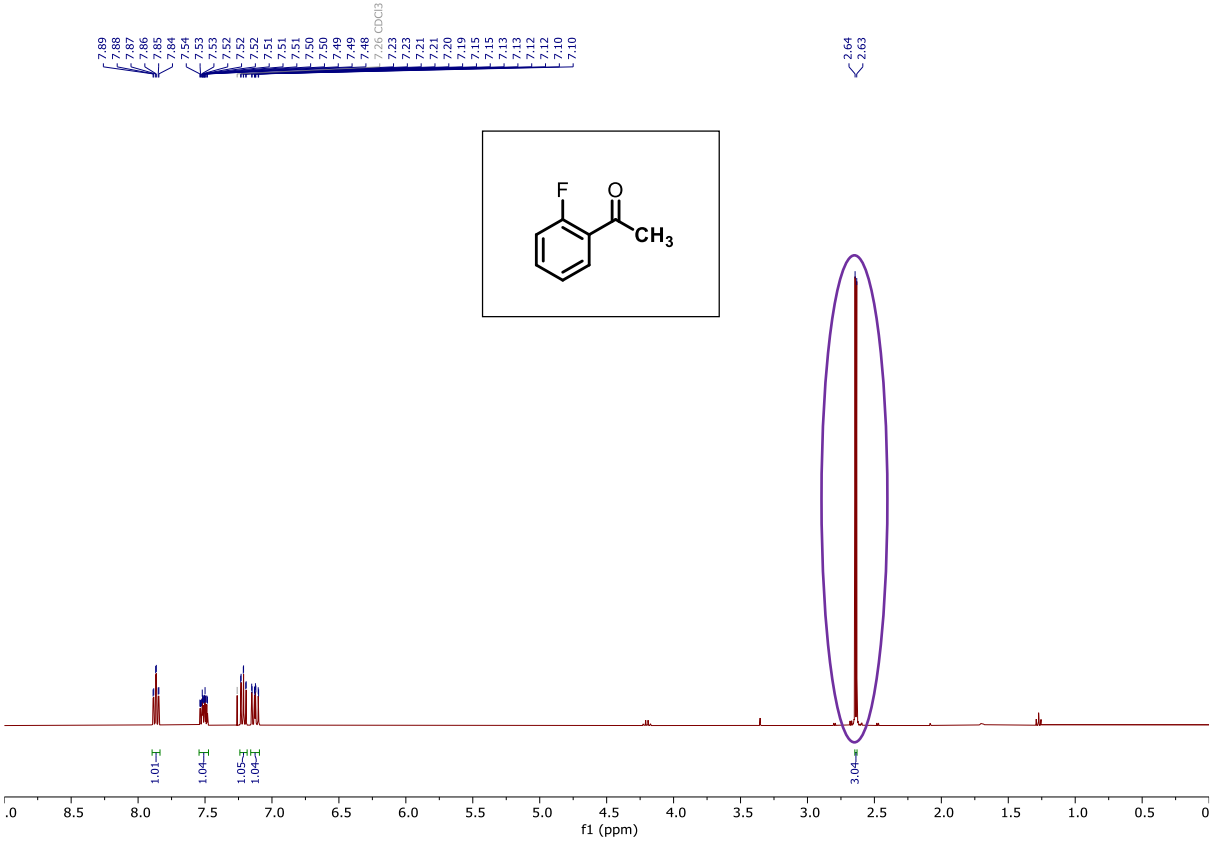
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-Phenyl ethan-1-one** (starting material of **3g**)



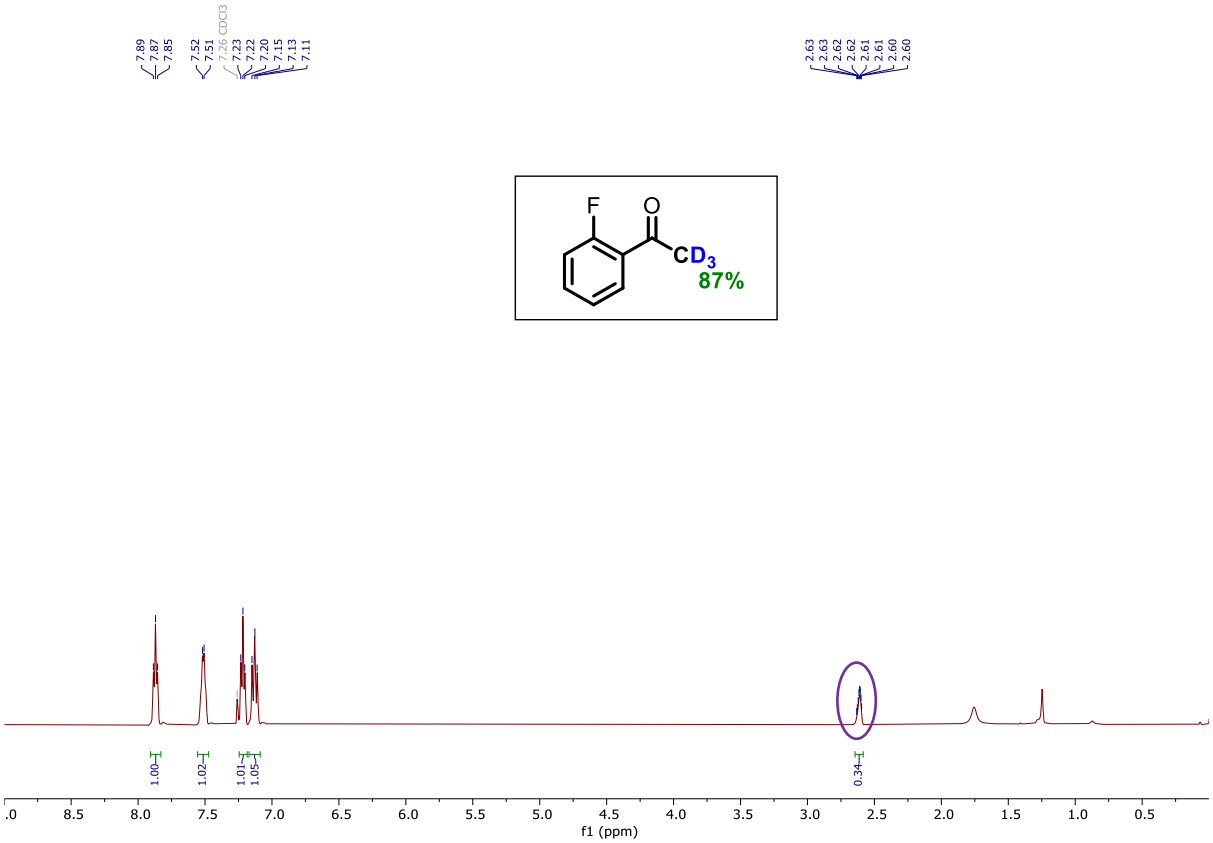
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-Phenyl ethan-1-one-2,2,2-*d*$_3$ (3g)**



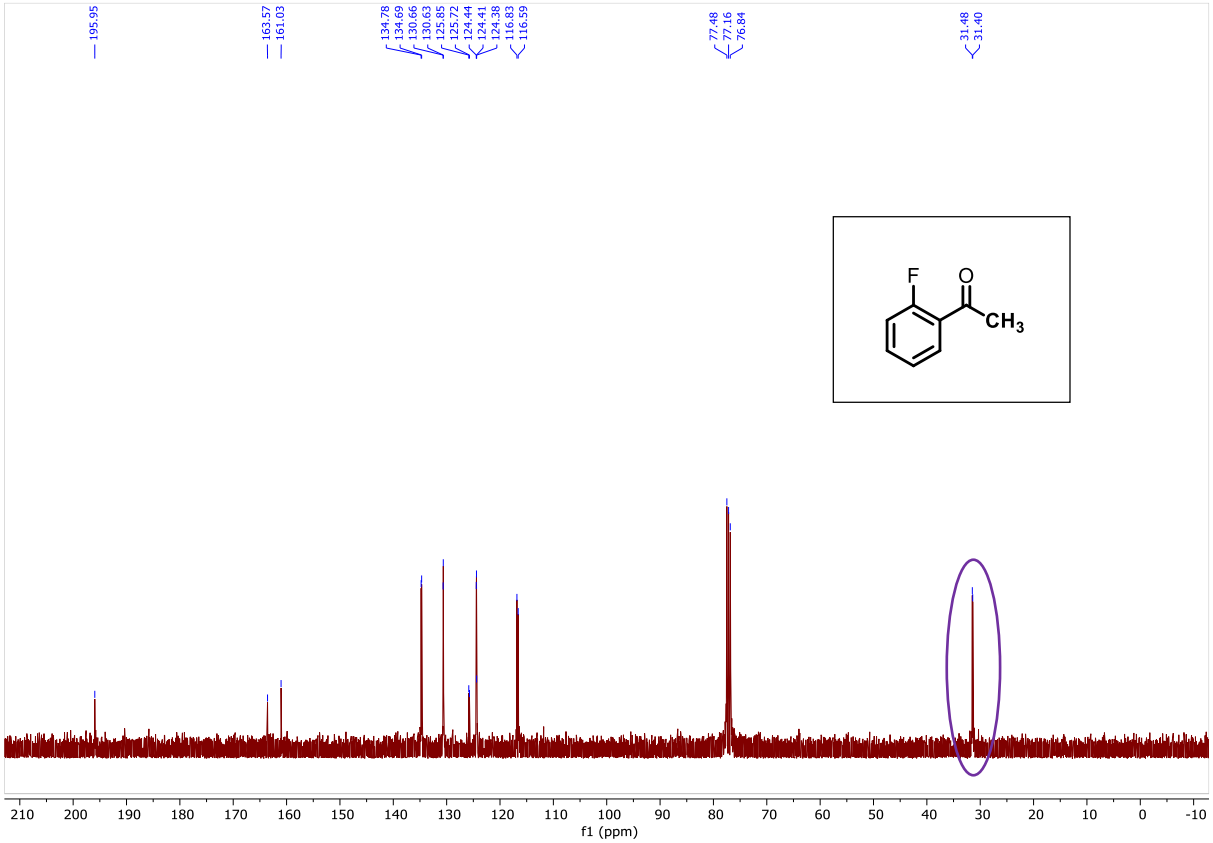
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(2-Fluorophenyl)-ethan-1-one** (starting material of **3h**)



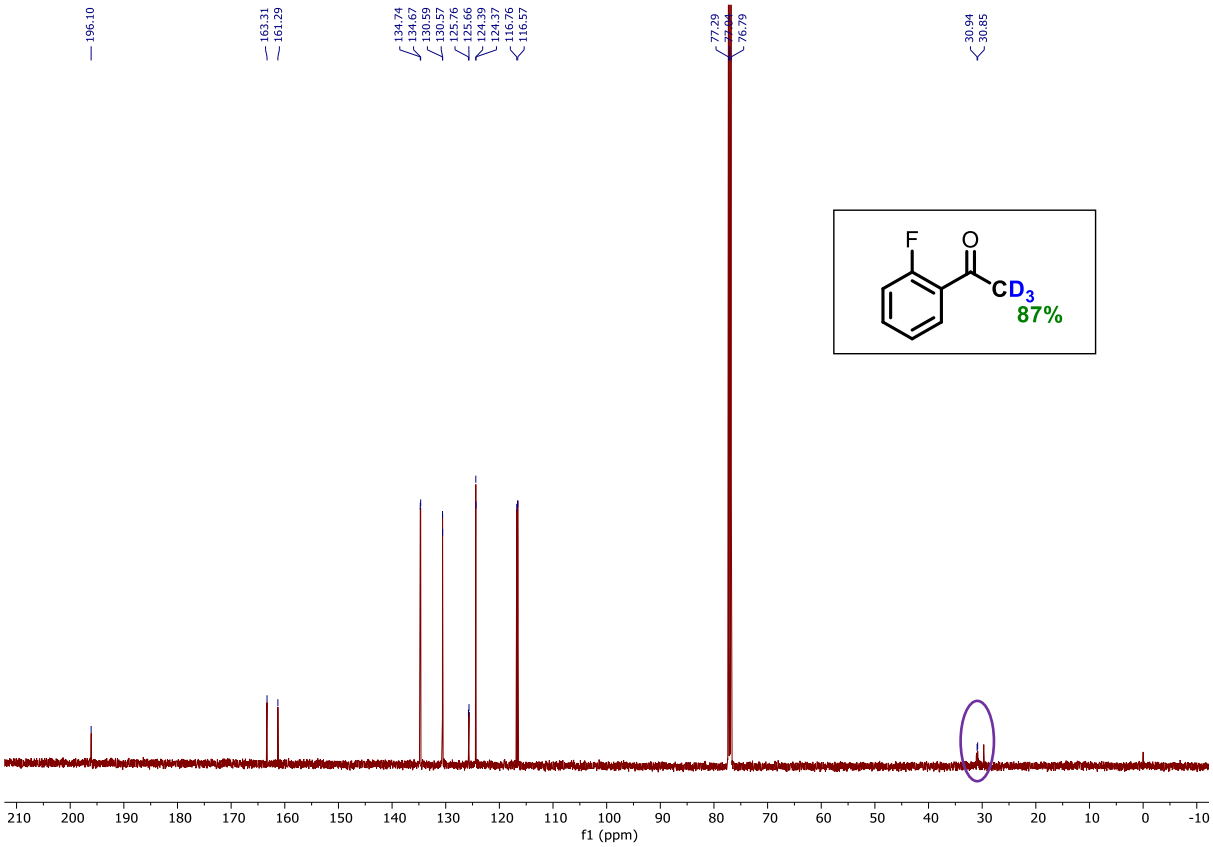
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(2-Fluorophenyl)-ethan-1-one-2,2,2-*d_3*** **(3h)**



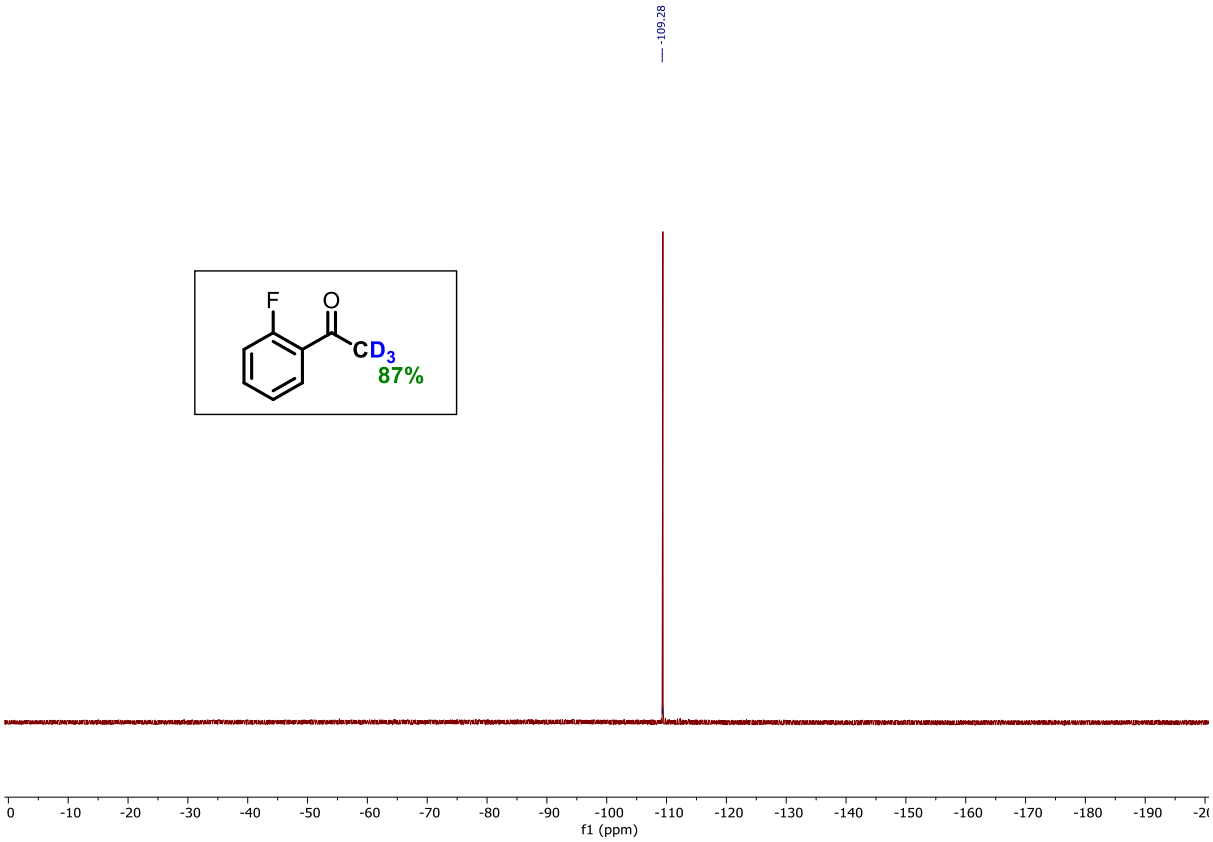
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(2-Fluorophenyl)-ethan-1-one** (starting material of **3h**)



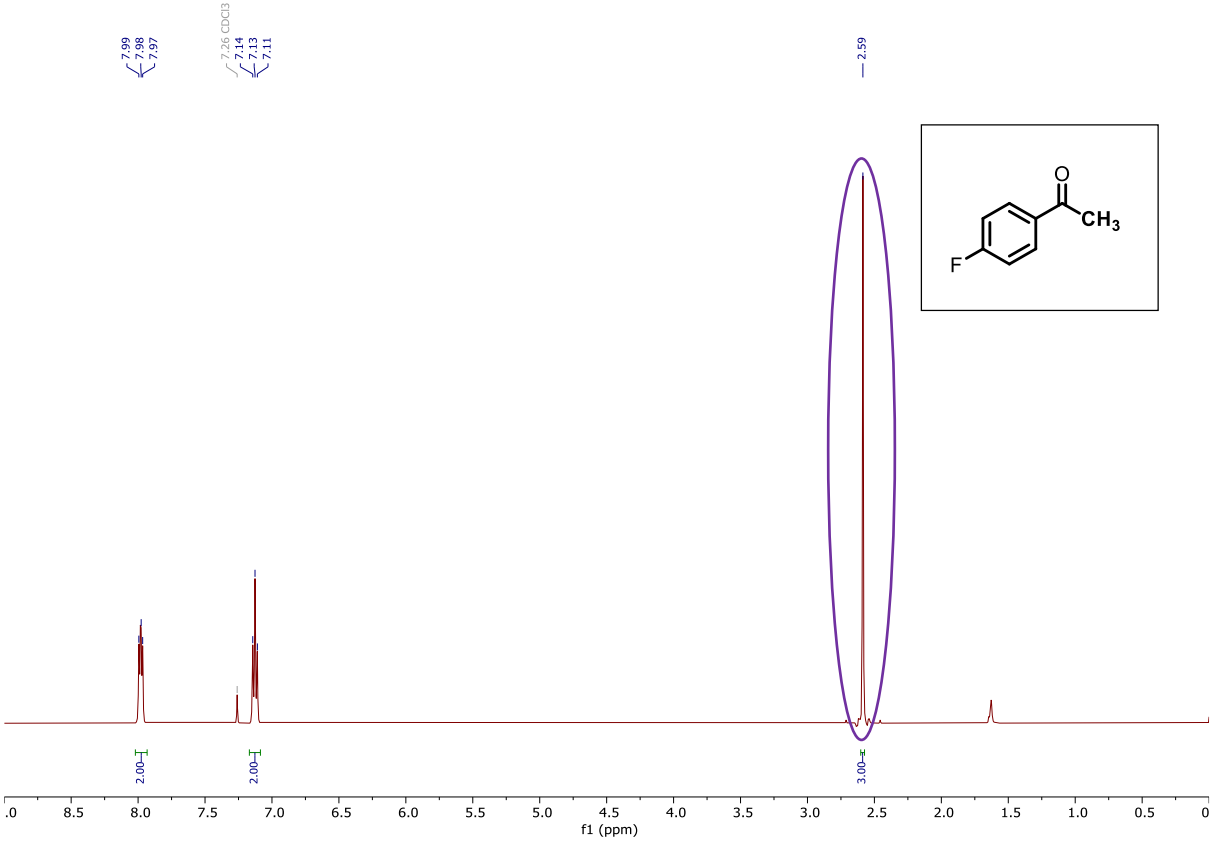
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(2-Fluorophenyl) ethan-1-one-2,2,2-*d_3* (3h)**



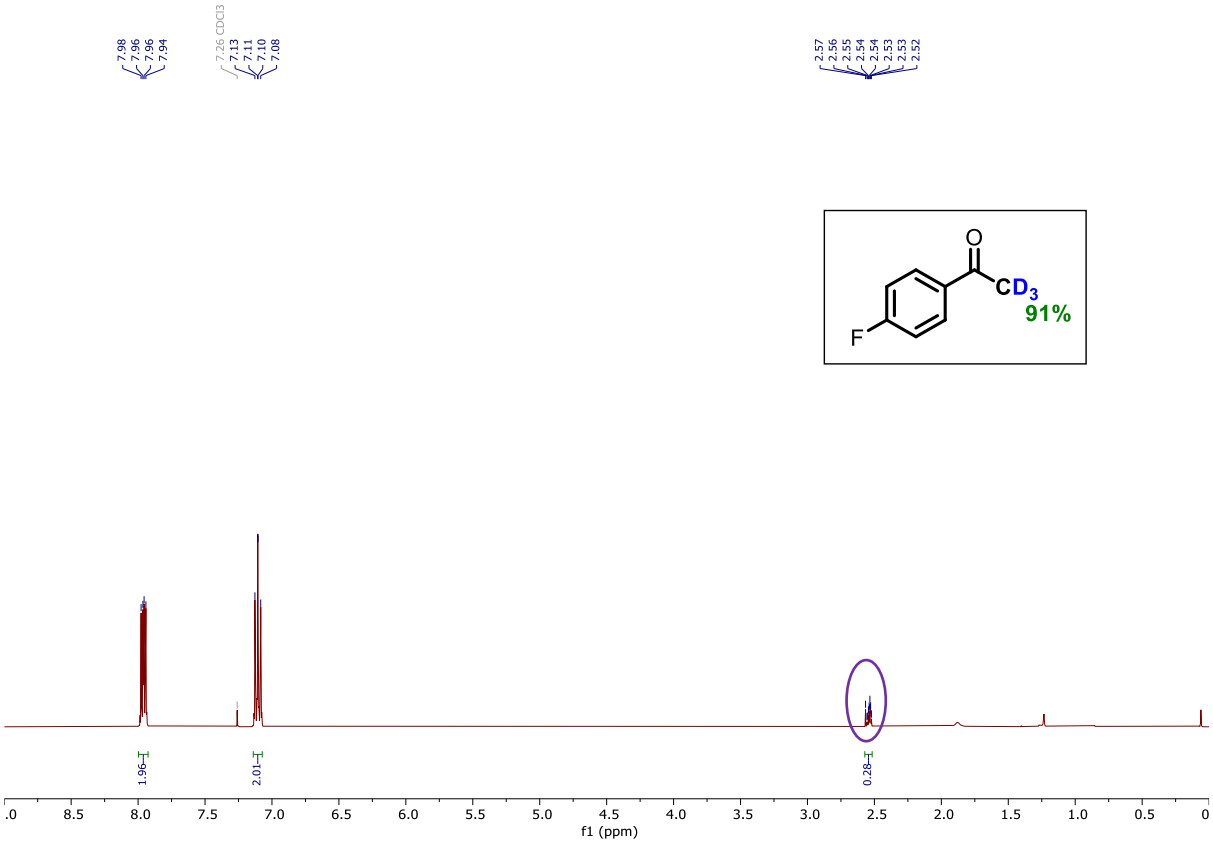
^{19}F NMR (500 MHz, $CDCl_3$) of **1-(2-Fluorophenyl) ethan-1-one-2,2,2-d_3 (3h)**



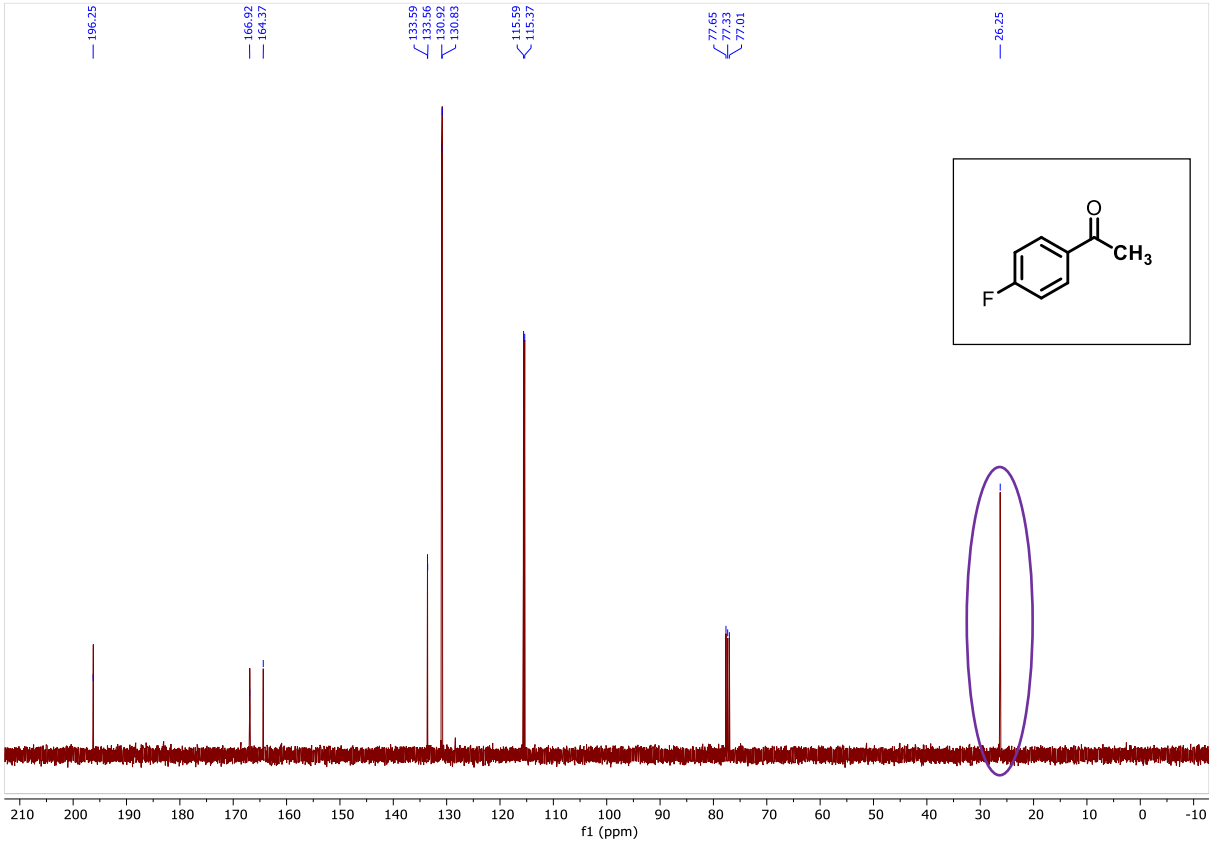
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(4-Fluorophenyl)-ethan-1-one** (starting material of **3i**)



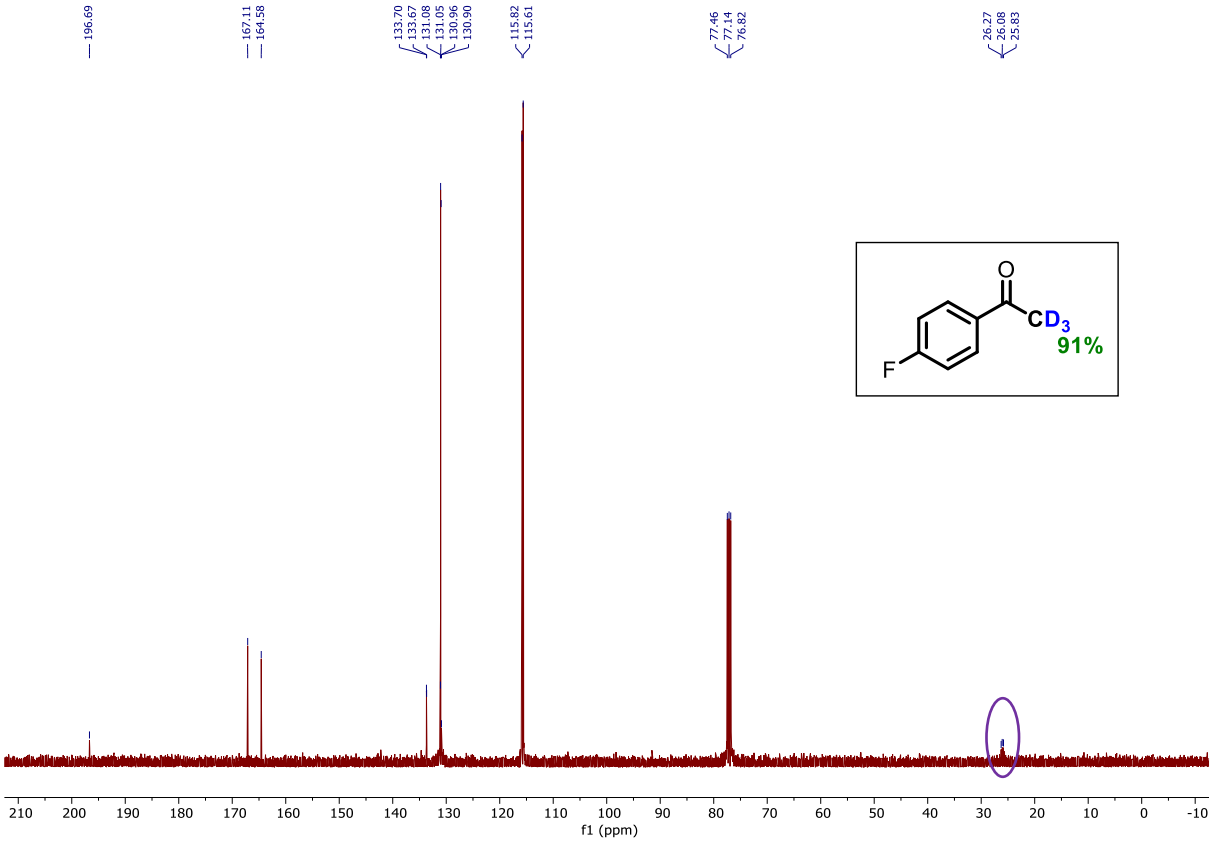
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(4-Fluorophenyl)-ethan-1-one-2,2,2-*d*$_3$ (3i)**



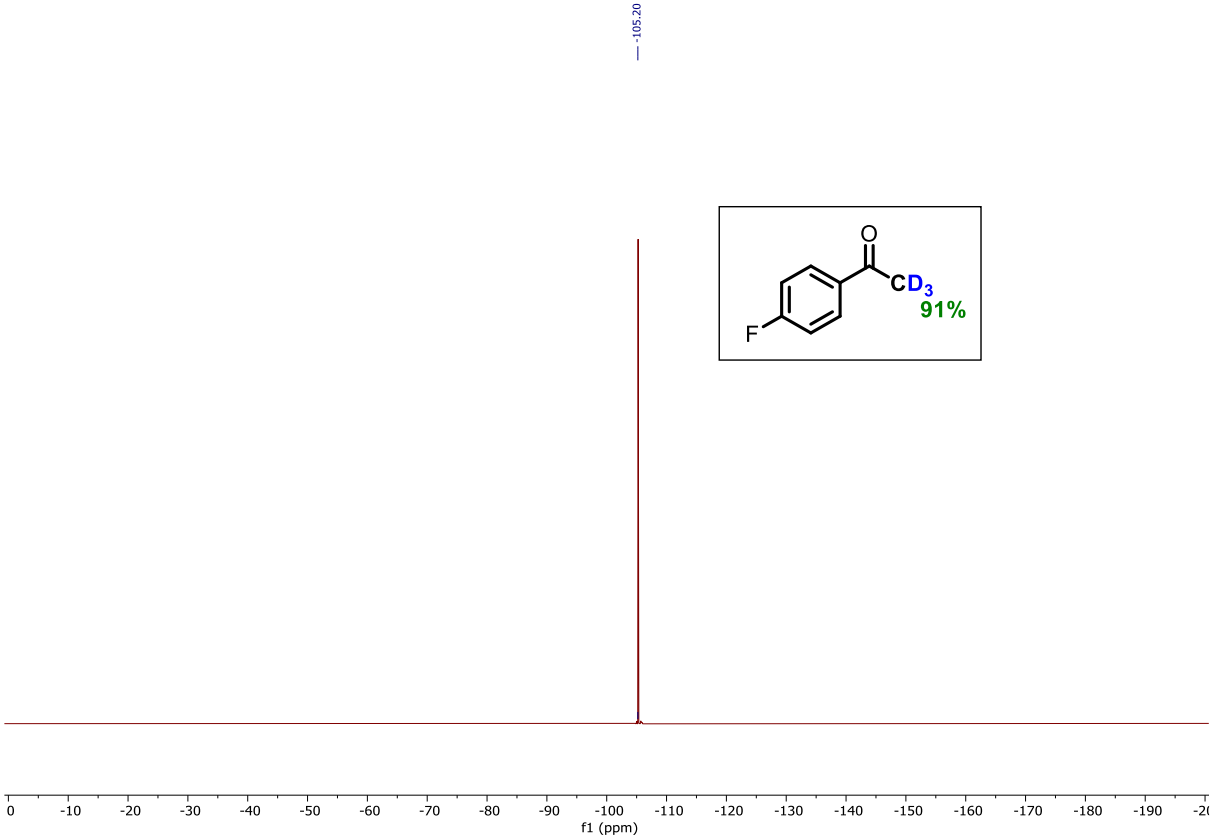
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(4-Fluorophenyl)-ethan-1-one** (starting material of **3i**)



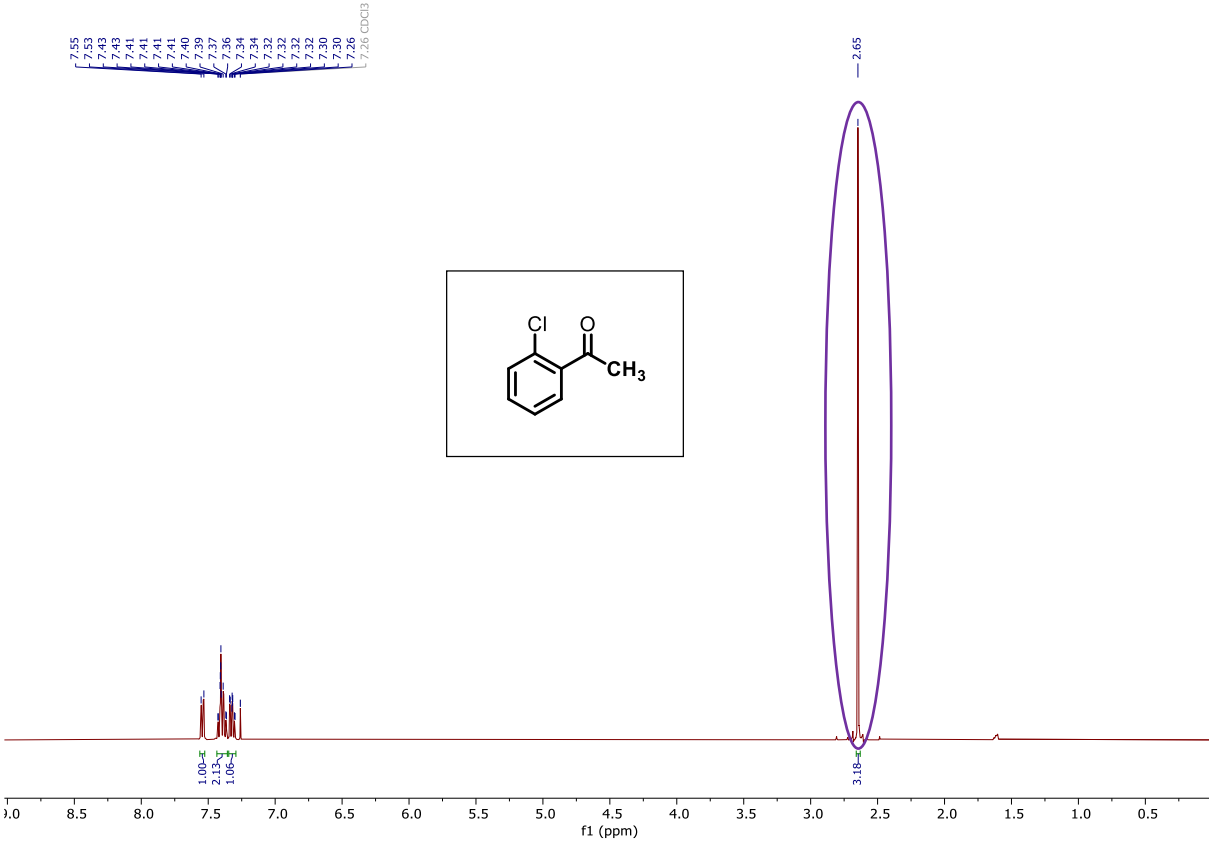
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(4-Fluorophenyl)-ethan-1-one-2,2,2-d_3 (3i)**



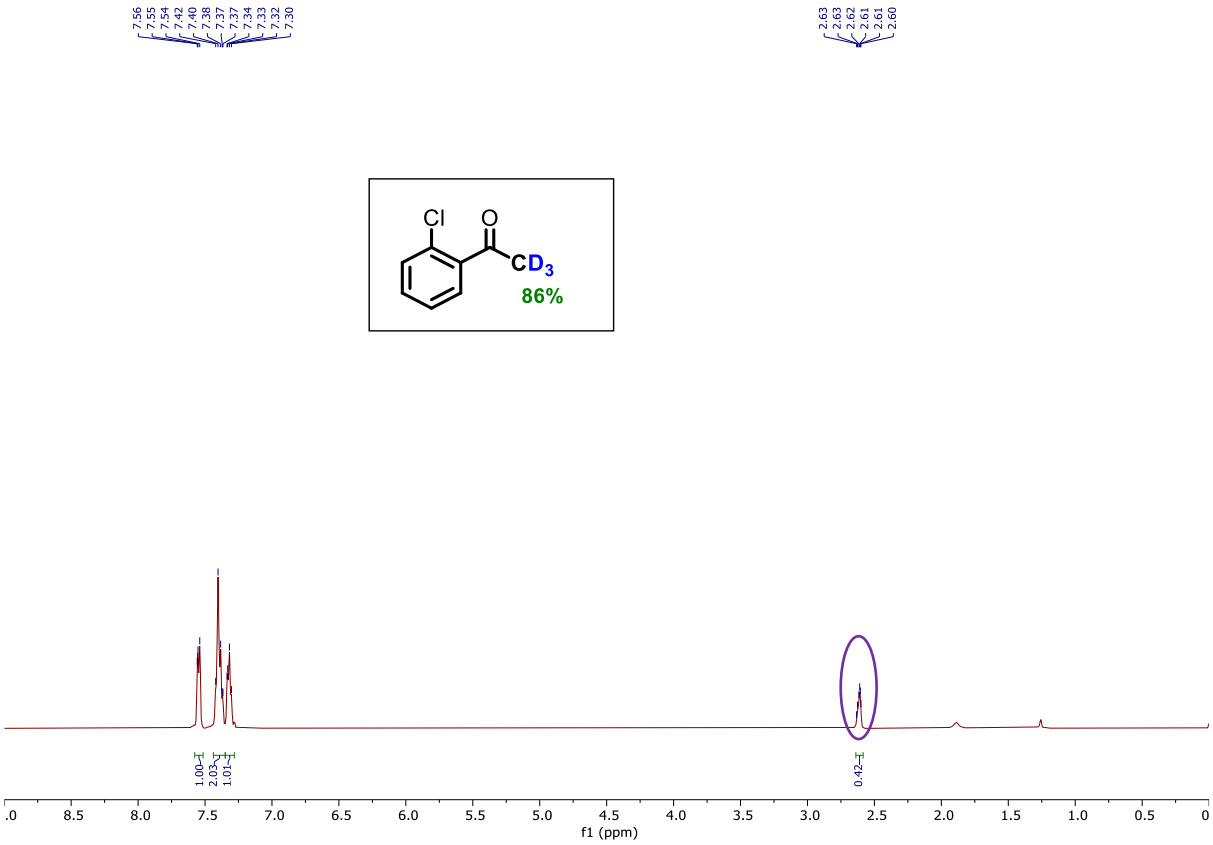
^{19}F NMR (376 MHz, $CDCl_3$) of **1-(4-Fluorophenyl)-ethan-1-one-2,2,2-d_3 (3i)**



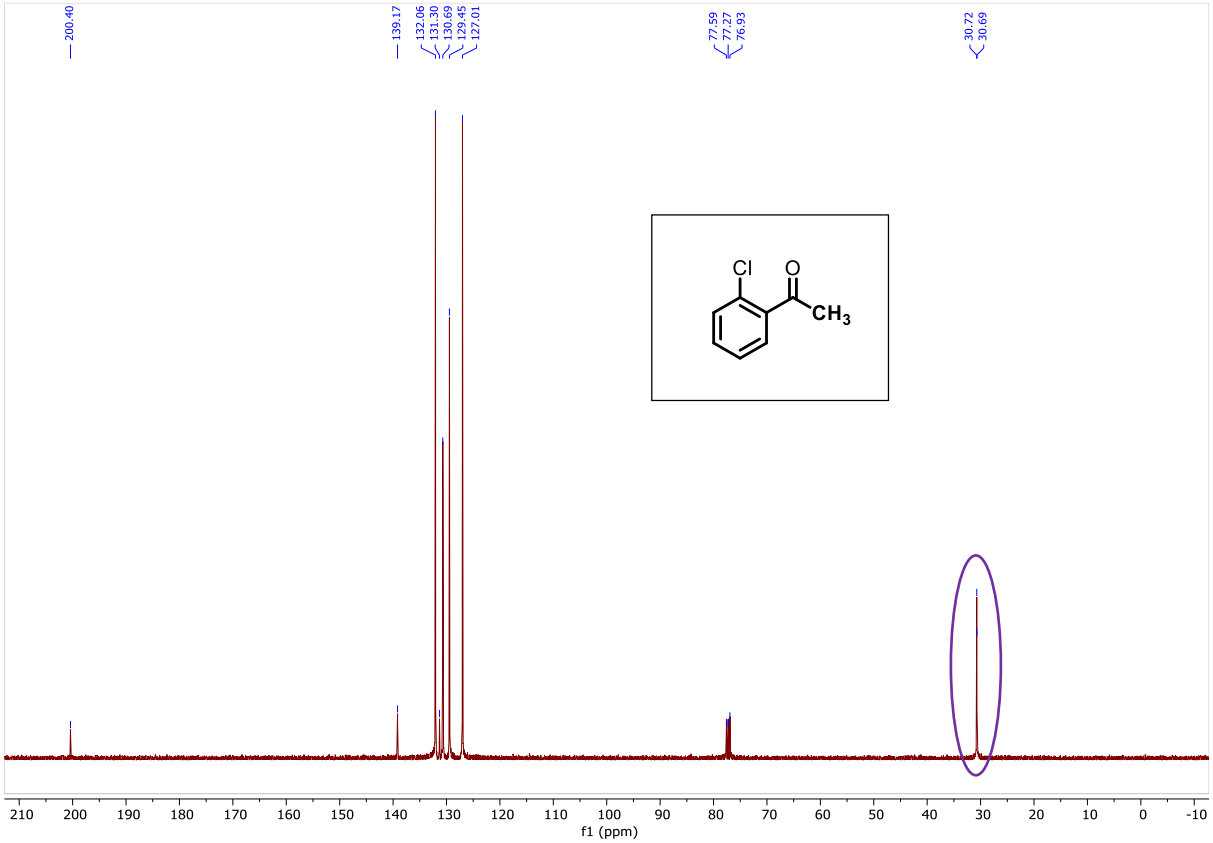
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(2-Chlorophenyl)-ethan-1-one** (starting material of **3j**)



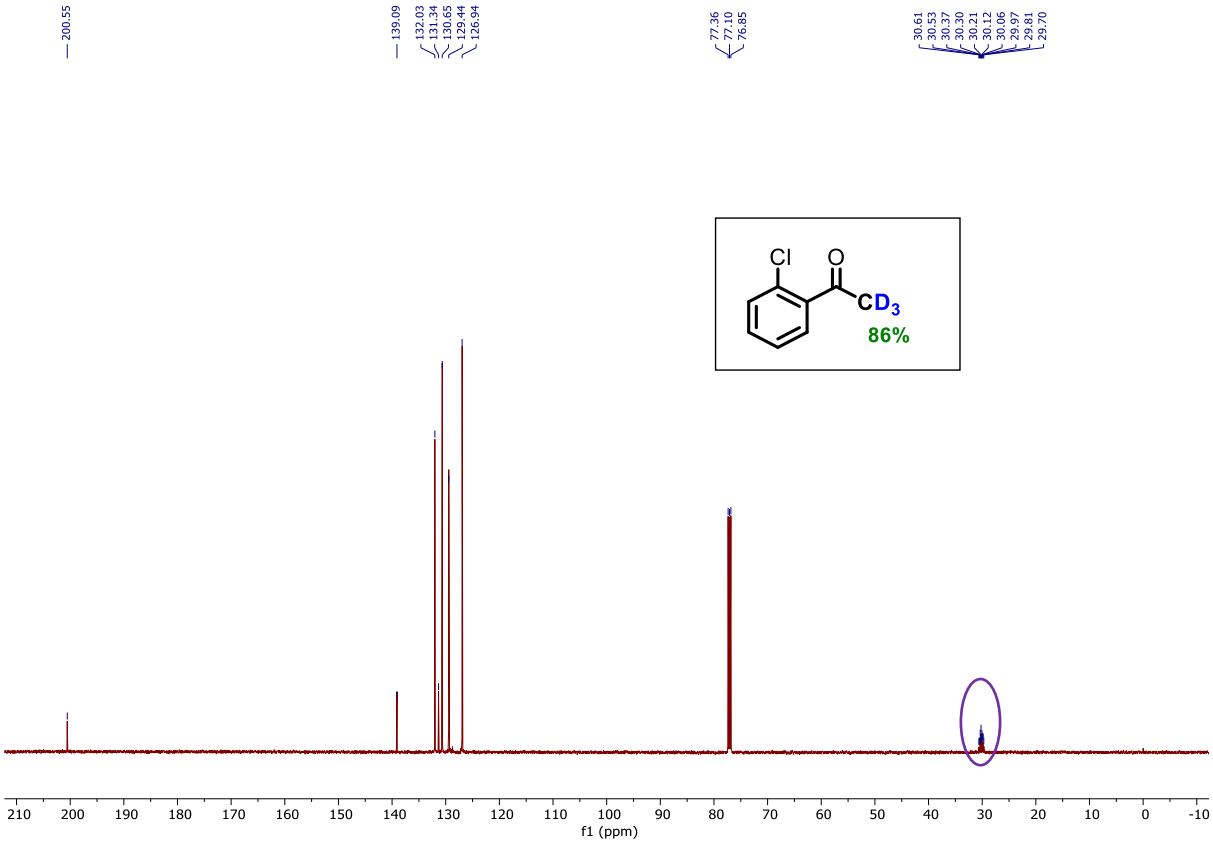
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(2-Chlorophenyl) ethan-1-one-2,2,2-*d_3* (3j)**



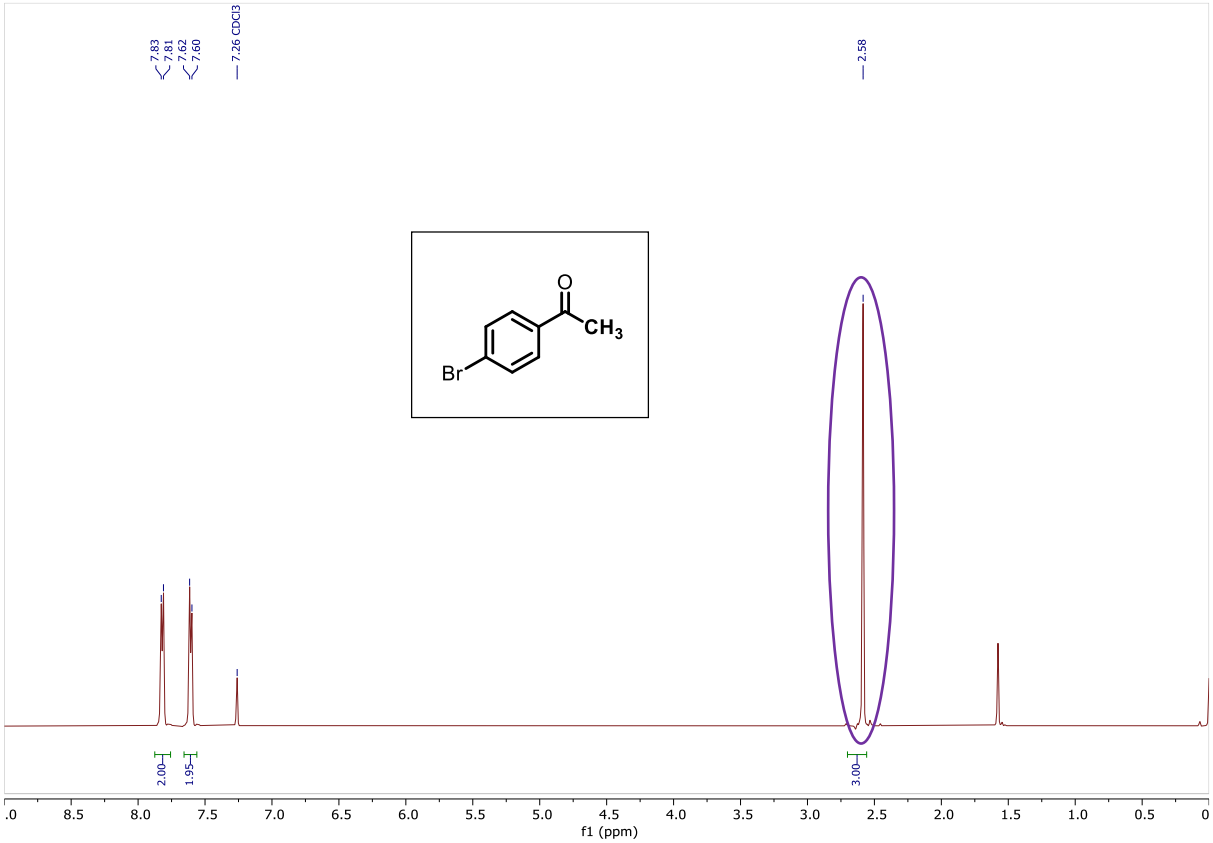
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)of **1-(2-Chlorophenyl) ethan-1-one** (starting material of **3j**)



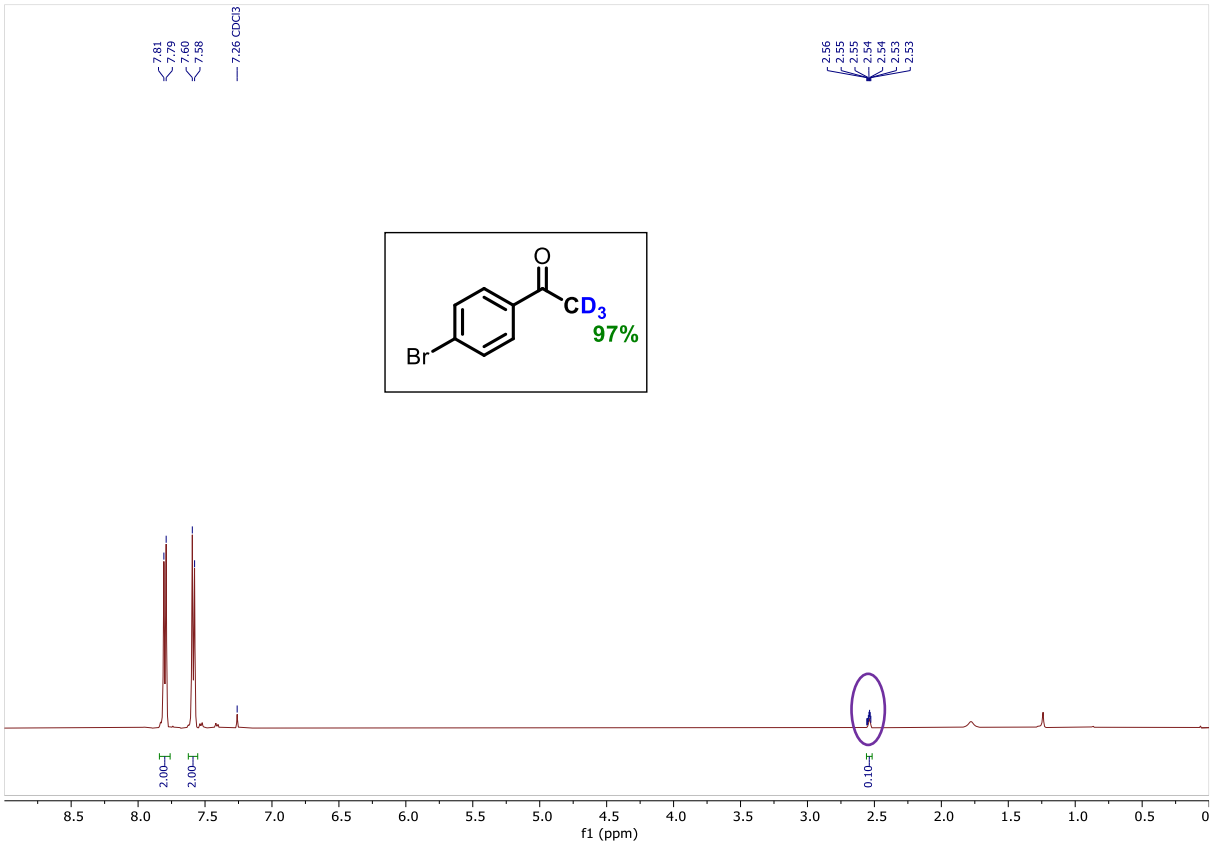
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(2-Chlorophenyl)-ethan-1-one-2,2,2-*d_3* (3j)**



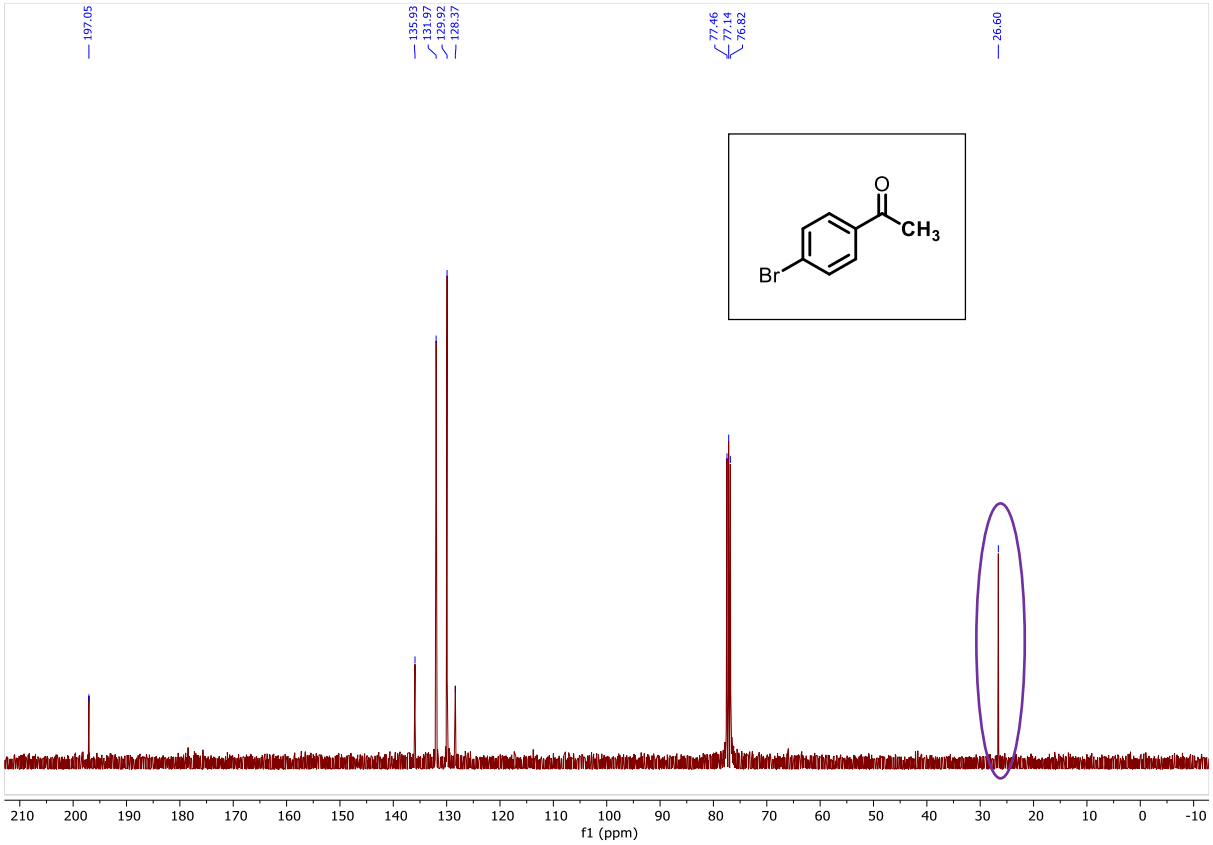
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(4-Bromophenyl)-ethan-1-one** (starting material of **3k**)



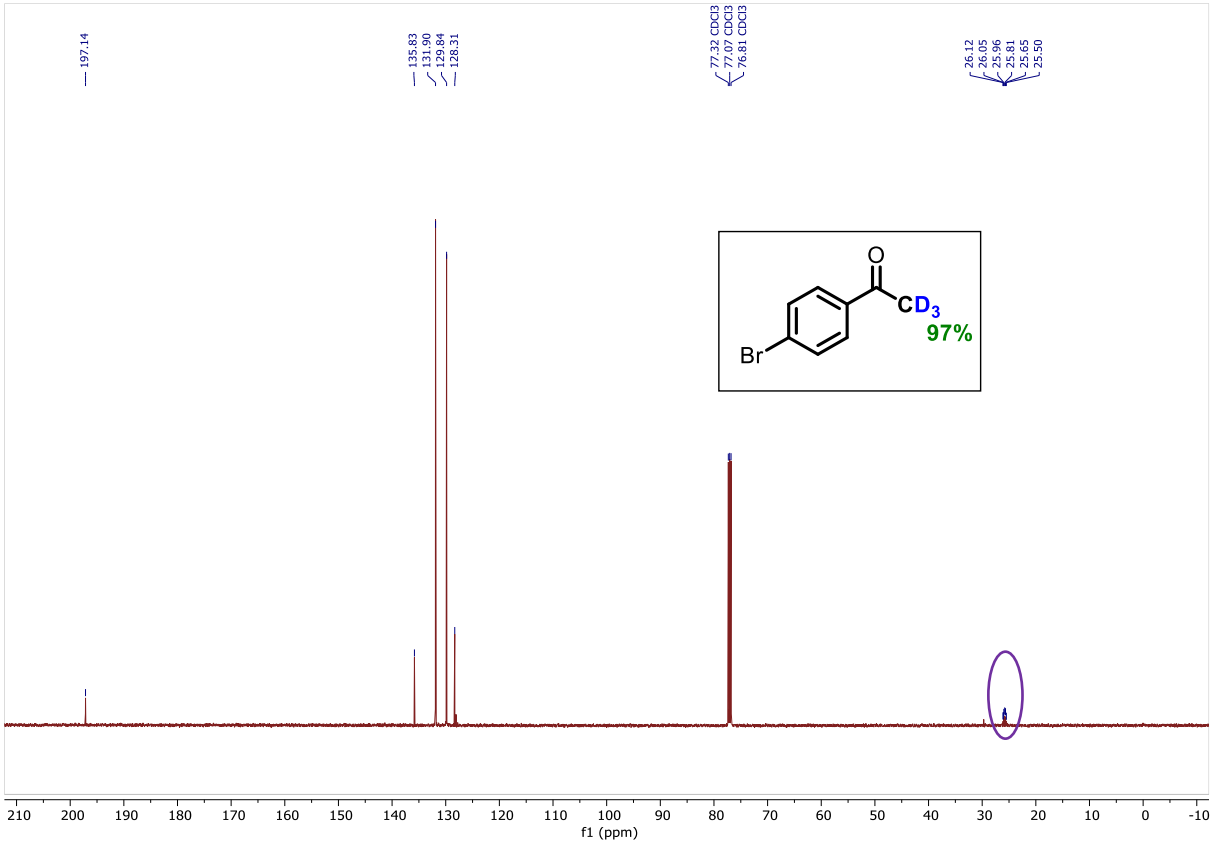
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(4-Bromophenyl)-ethan-1-one-2,2,2-d_3 (3k)**



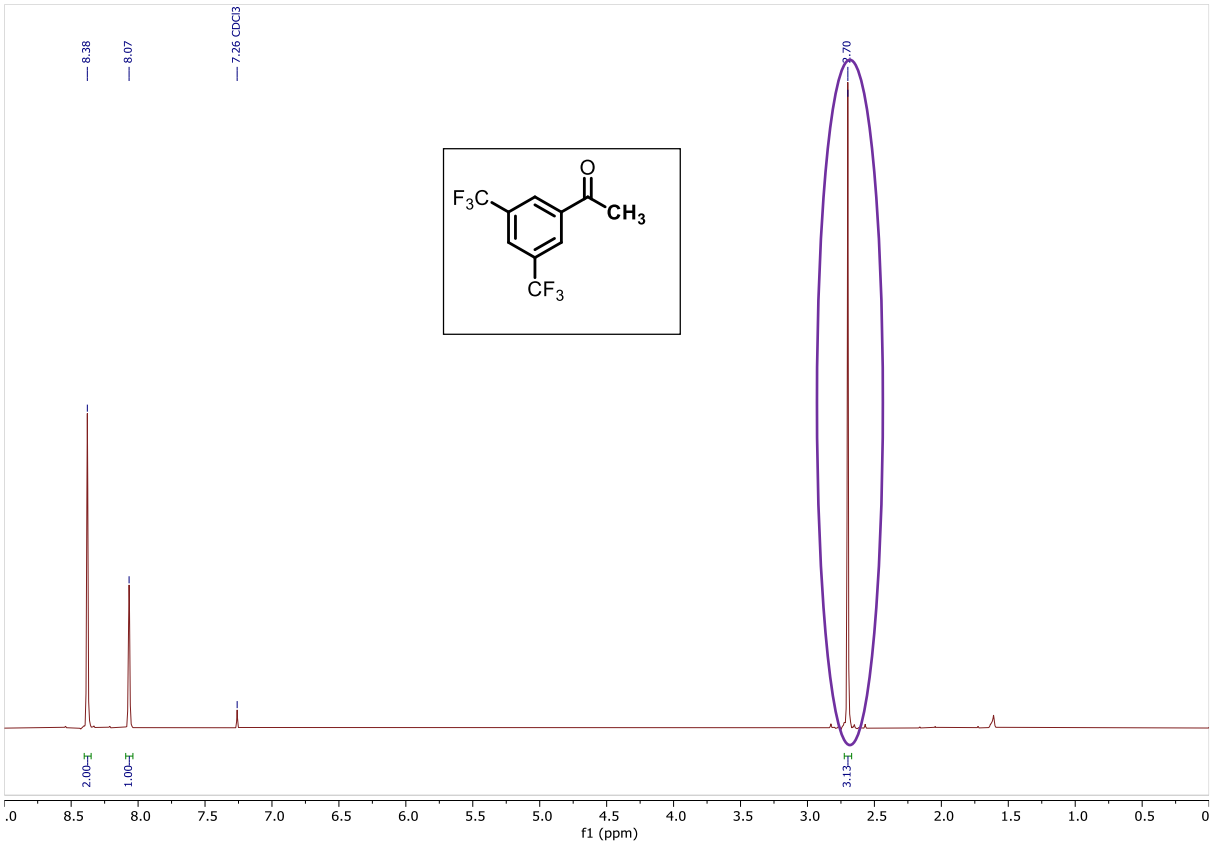
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(4-Bromophenyl) ethan-1-one** (starting material of **3k**)



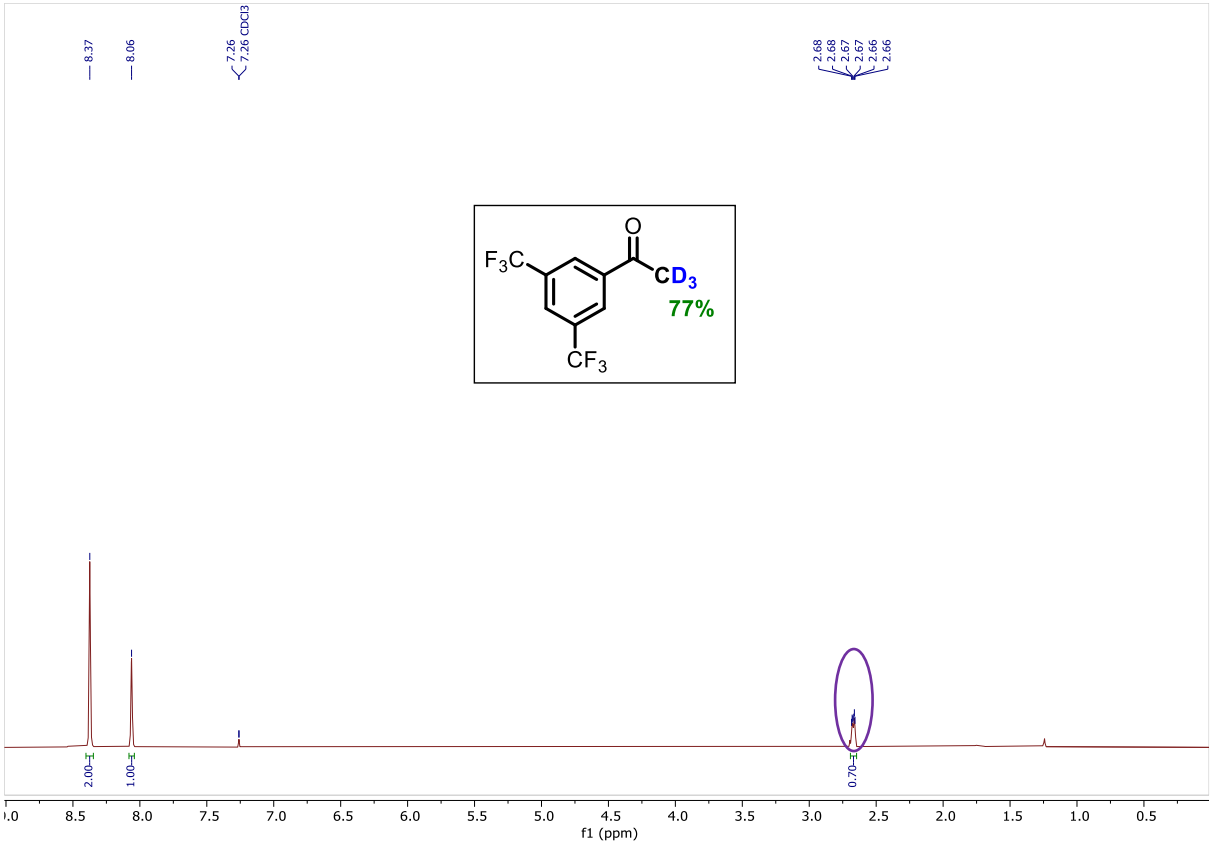
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(4-Bromophenyl)-ethan-1-one-2,2,2-d_3 (3k)**



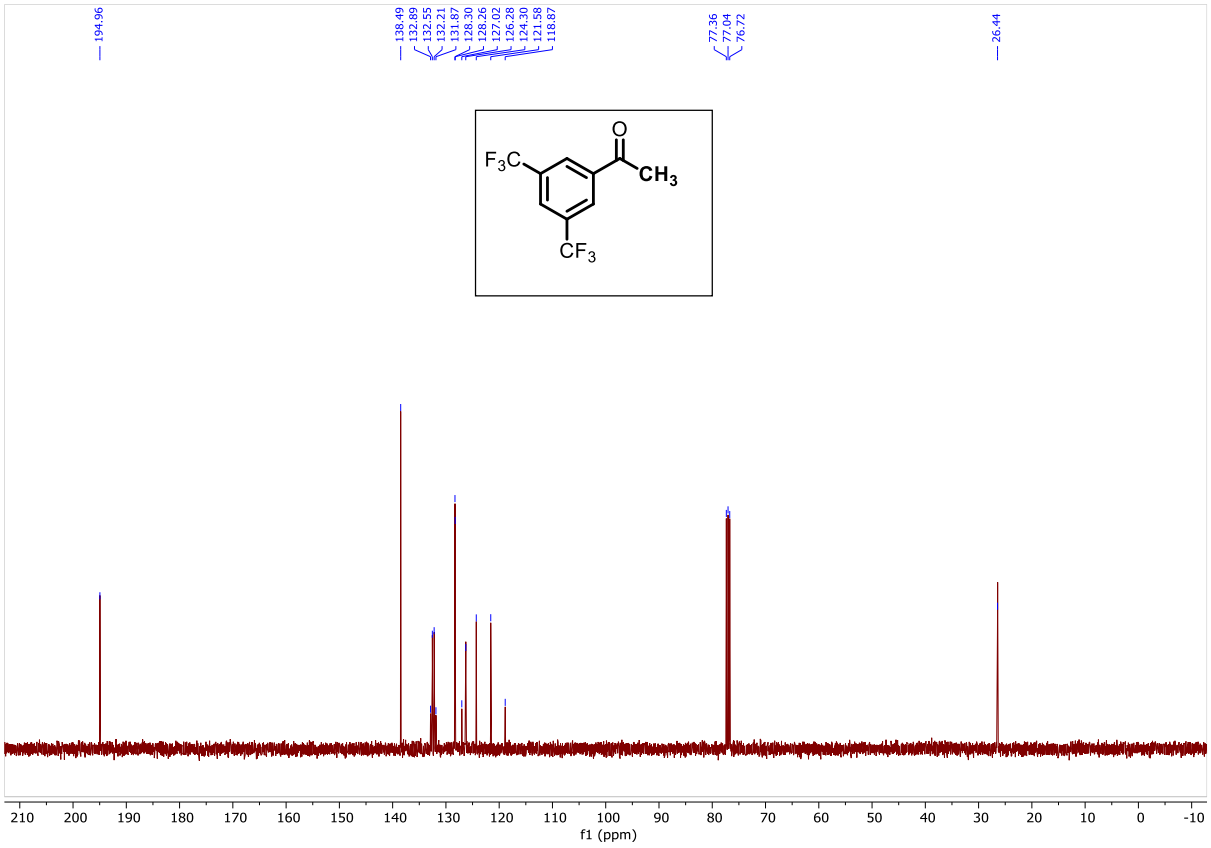
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(3,5-Bis(trifluoromethyl)-phenyl)-ethan-1-one** (starting material of **3l**)



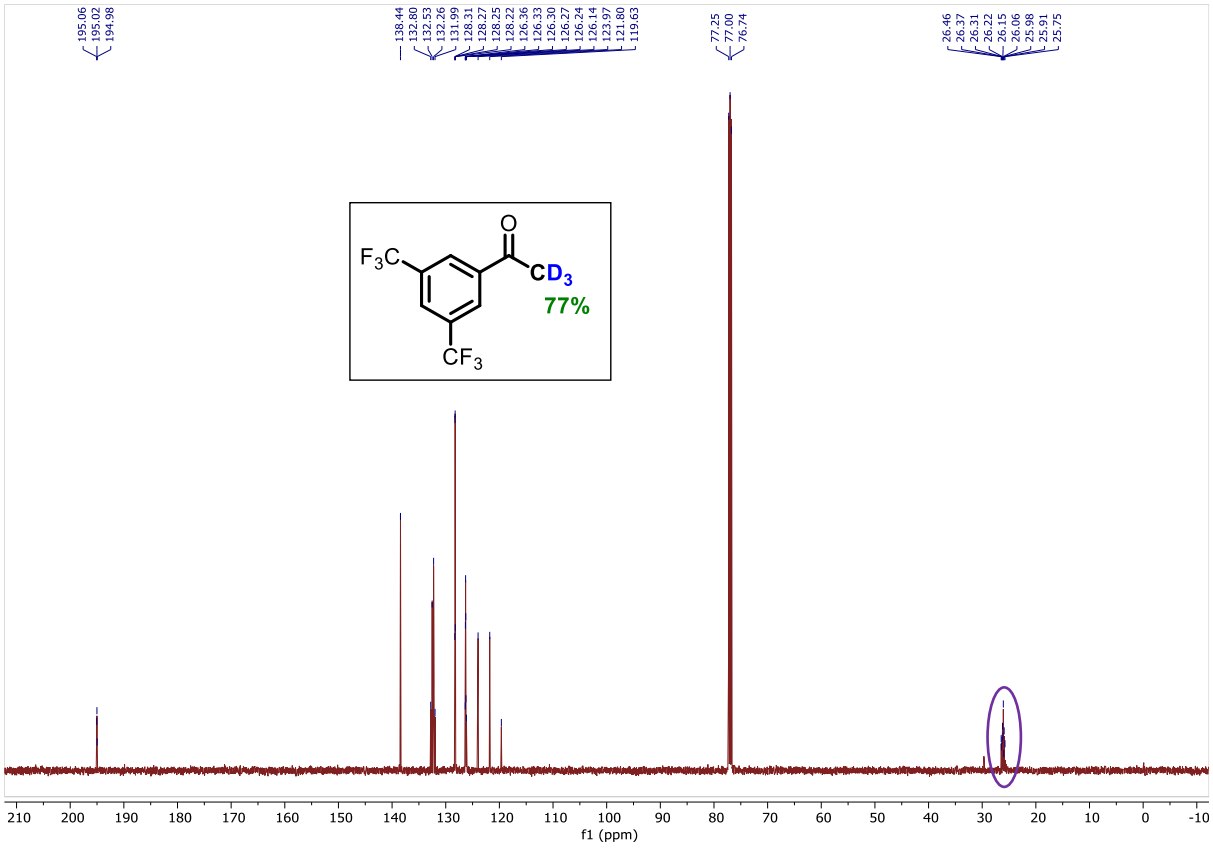
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(3,5-Bis(trifluoromethyl)-phenyl)-ethan-1-one-2,2,2-*d*$_3$ (3l)**



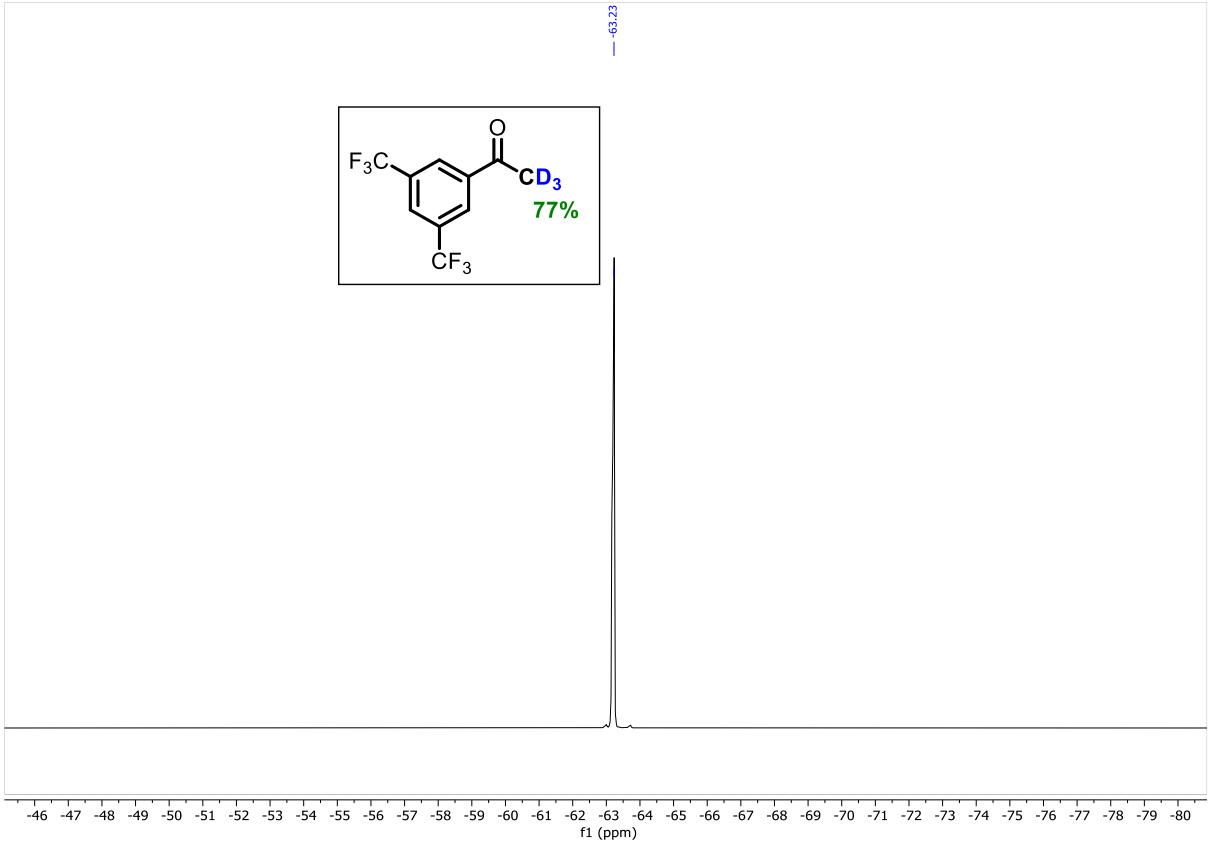
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(3,5-Bis(trifluoromethyl)-phenyl)-ethan-1-one** (starting material of **3l**)



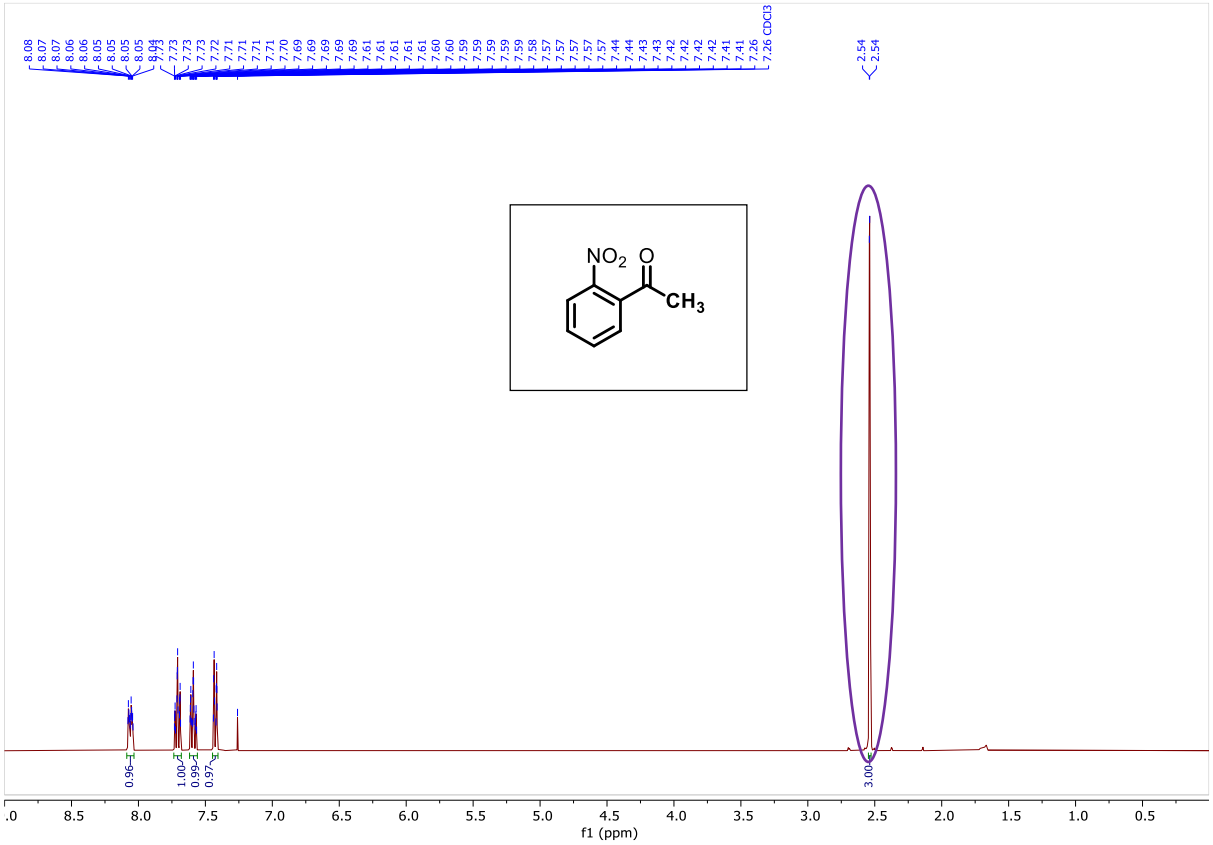
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(3,5-Bis(trifluoromethyl) phenyl) ethan-1-one-2,2,2-*d*$_3$ (3l)**



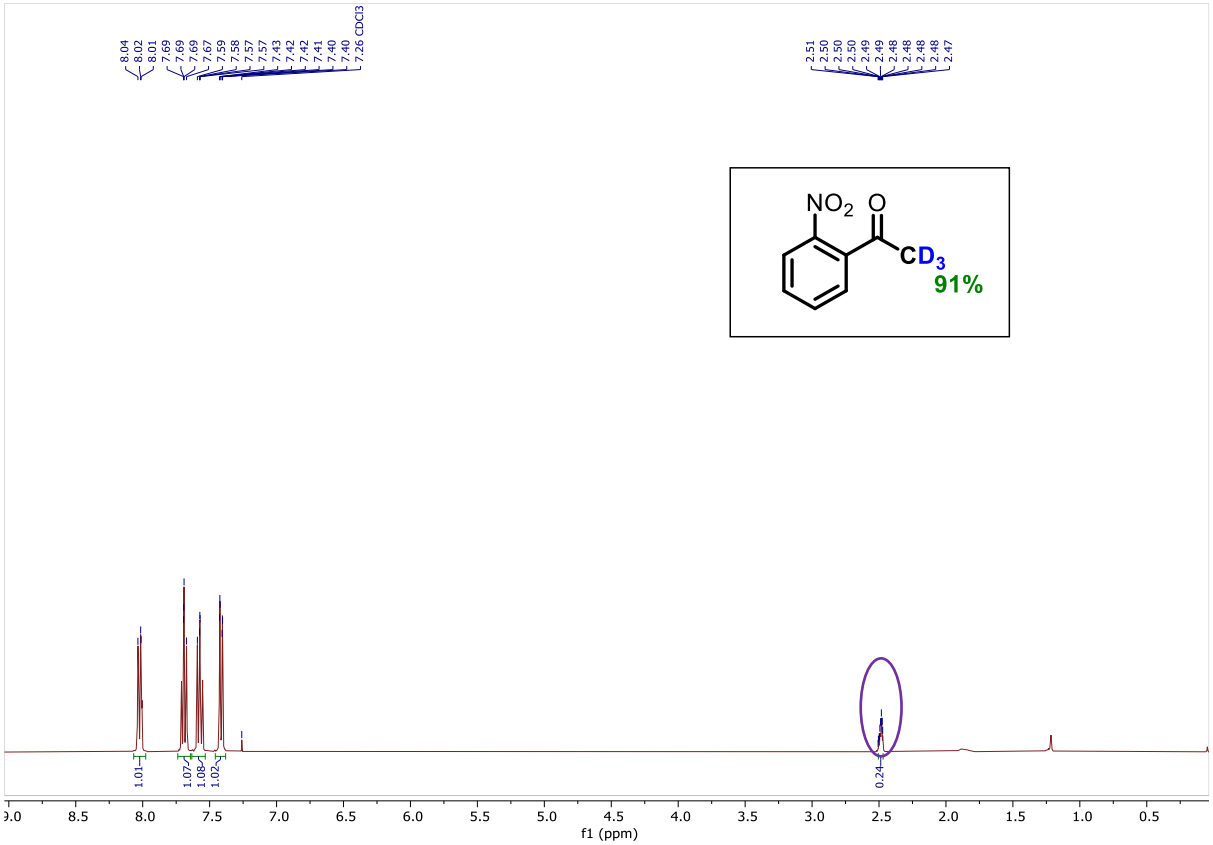
^{19}F NMR (376 MHz, $CDCl_3$) of **1-(3,5-Bis(trifluoromethyl) phenyl) ethan-1-one-2,2,2-*d_3* (3l)**



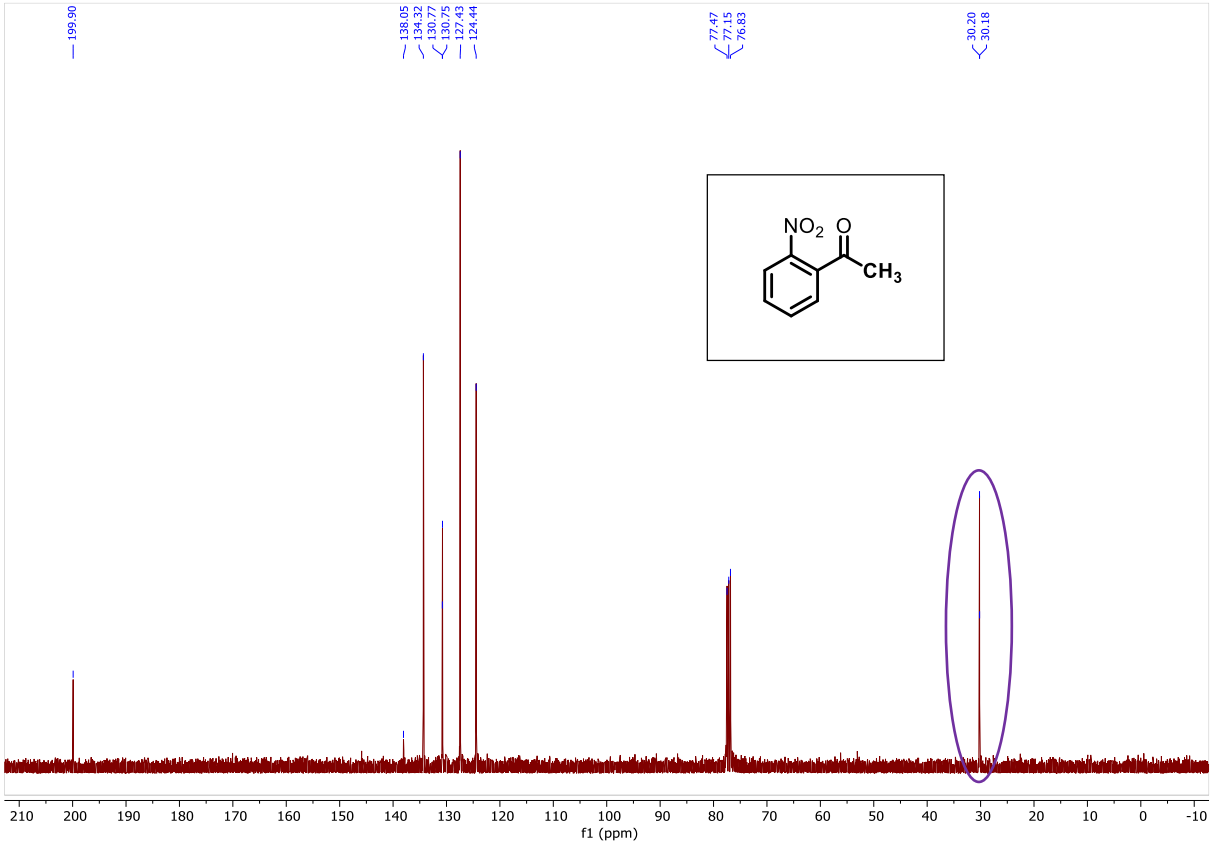
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(2-Nitrophenyl) ethan-1-one** (starting material of **3m**)



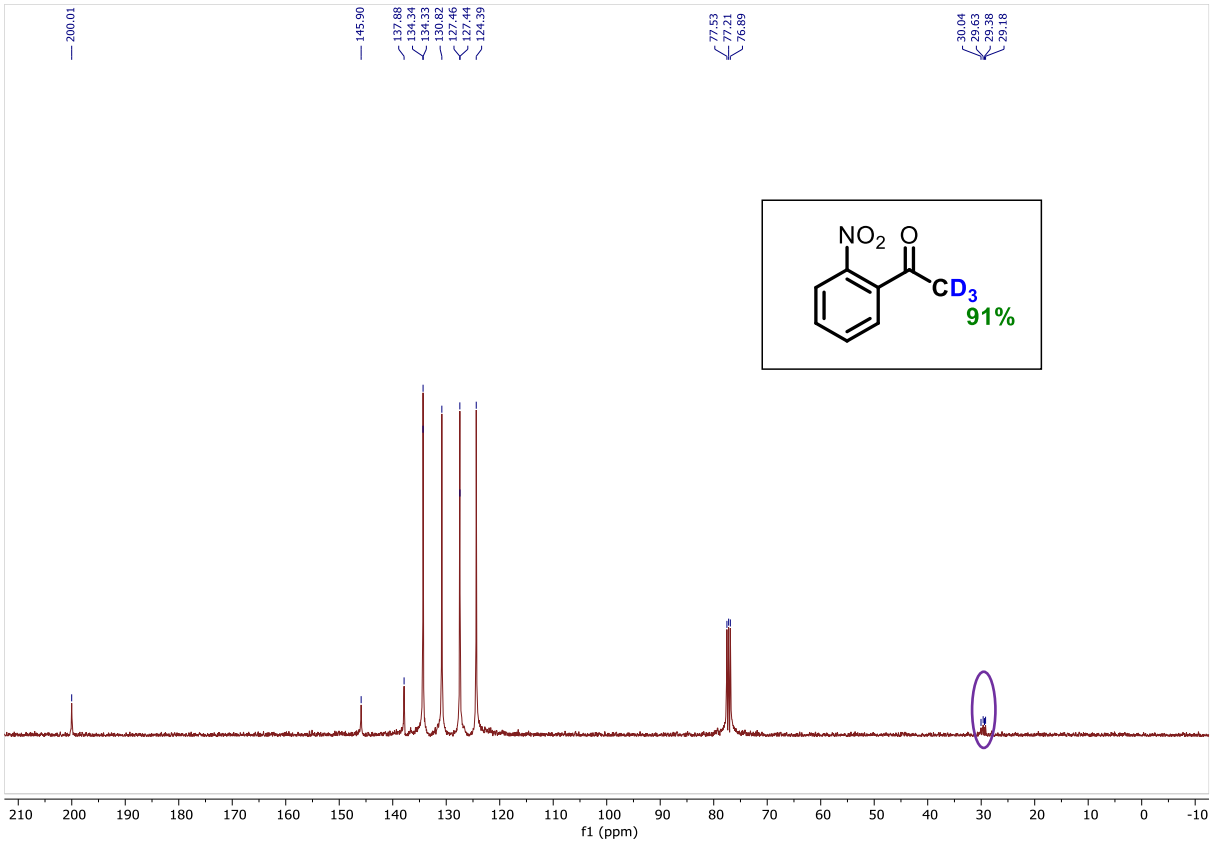
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(2-Nitrophenyl) ethan-1-one-2,2,2-d_3 (3m)**



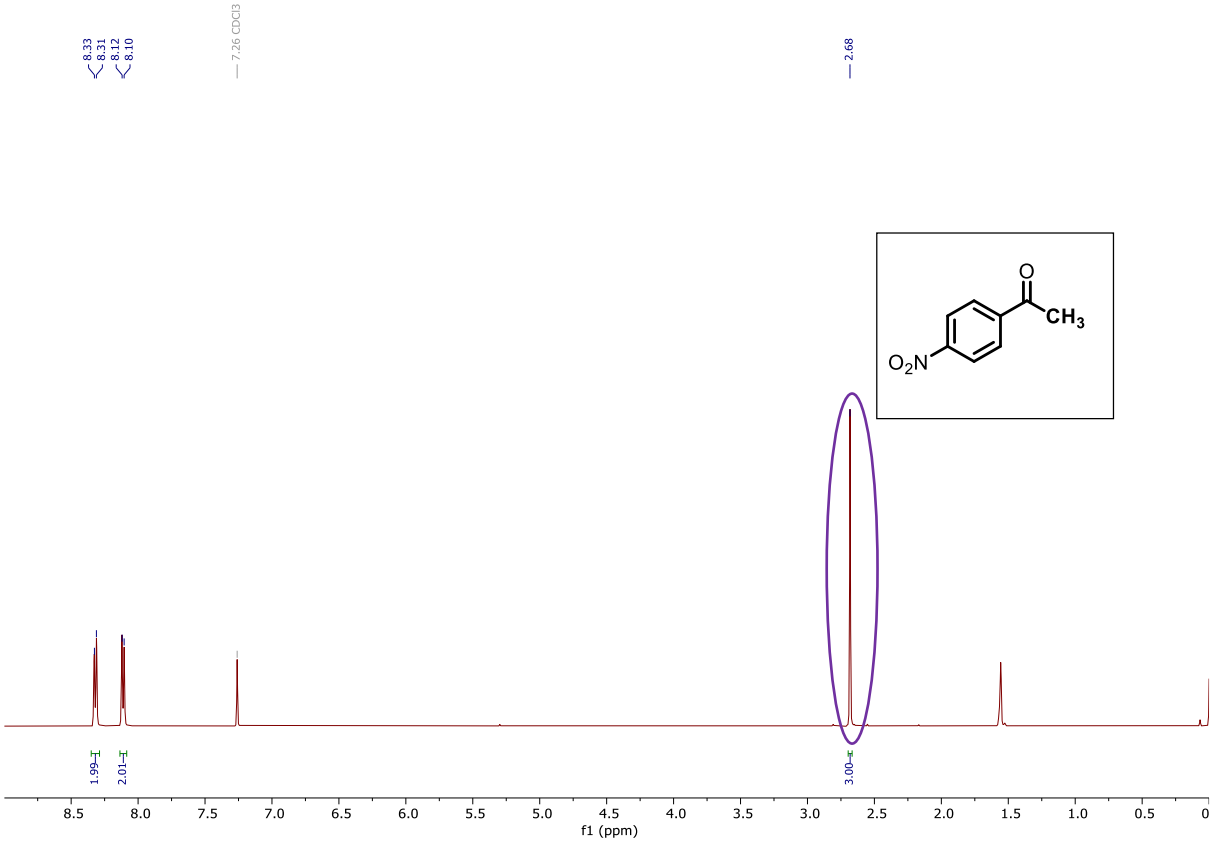
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(2-Nitrophenyl) ethan-1-one** (starting material of **3m**)



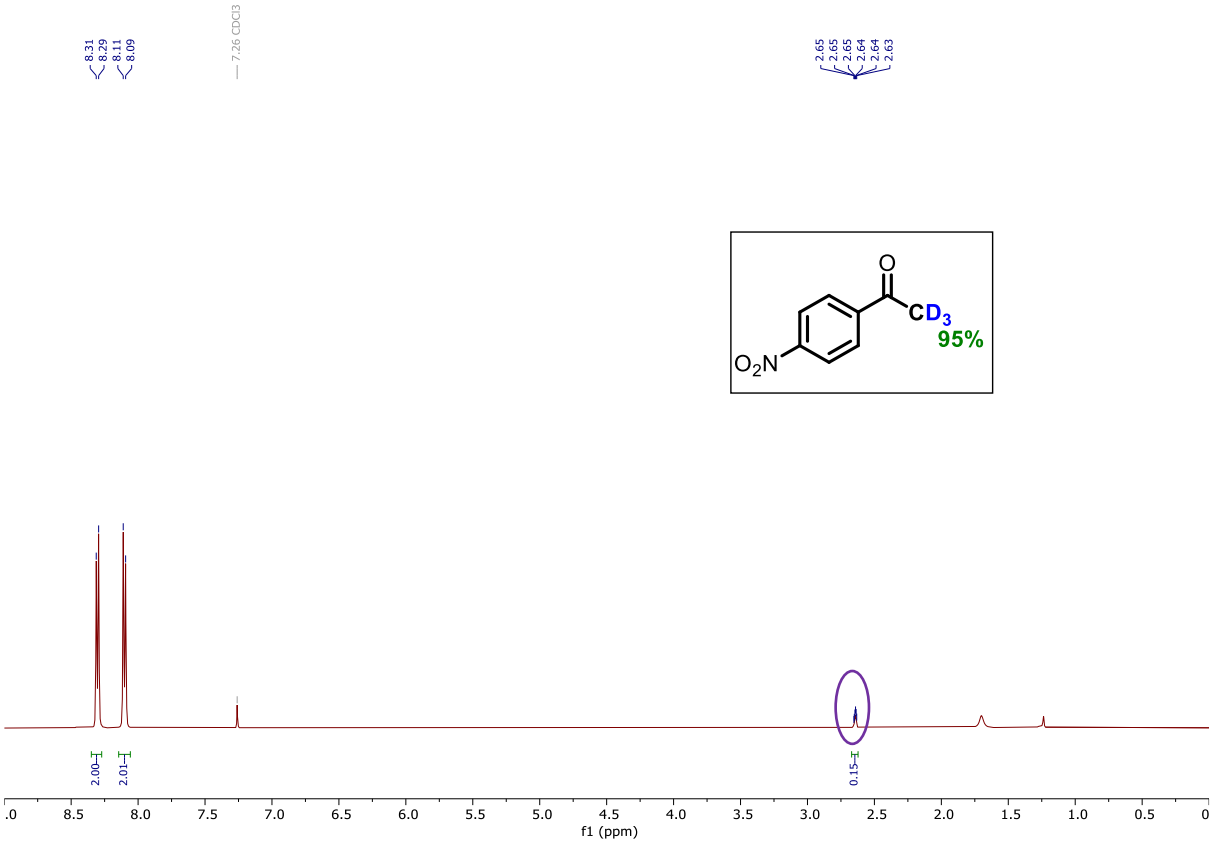
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(2-Nitrophenyl) ethan-1-one-2,2,2-*d*$_3$ (3m)**



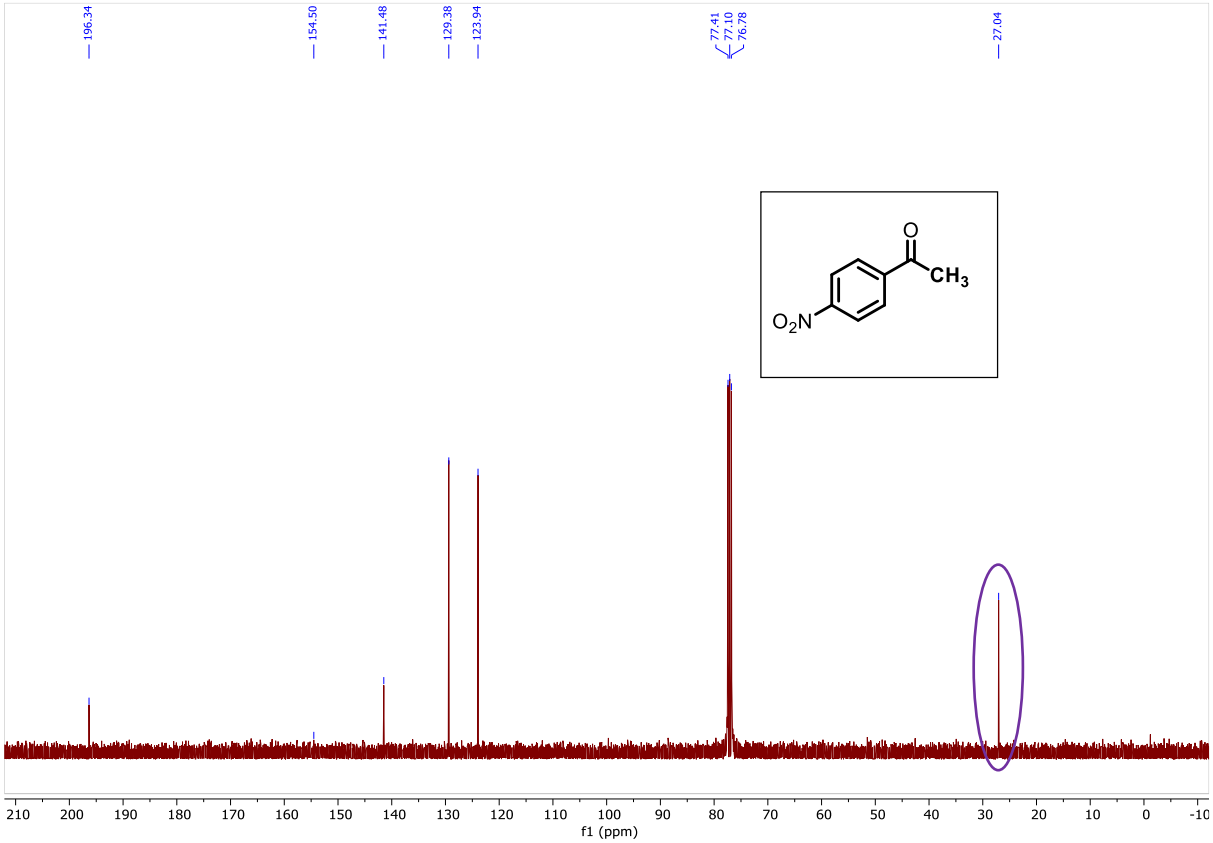
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(4-Nitrophenyl) ethan-1-one** (starting material of **3n**)



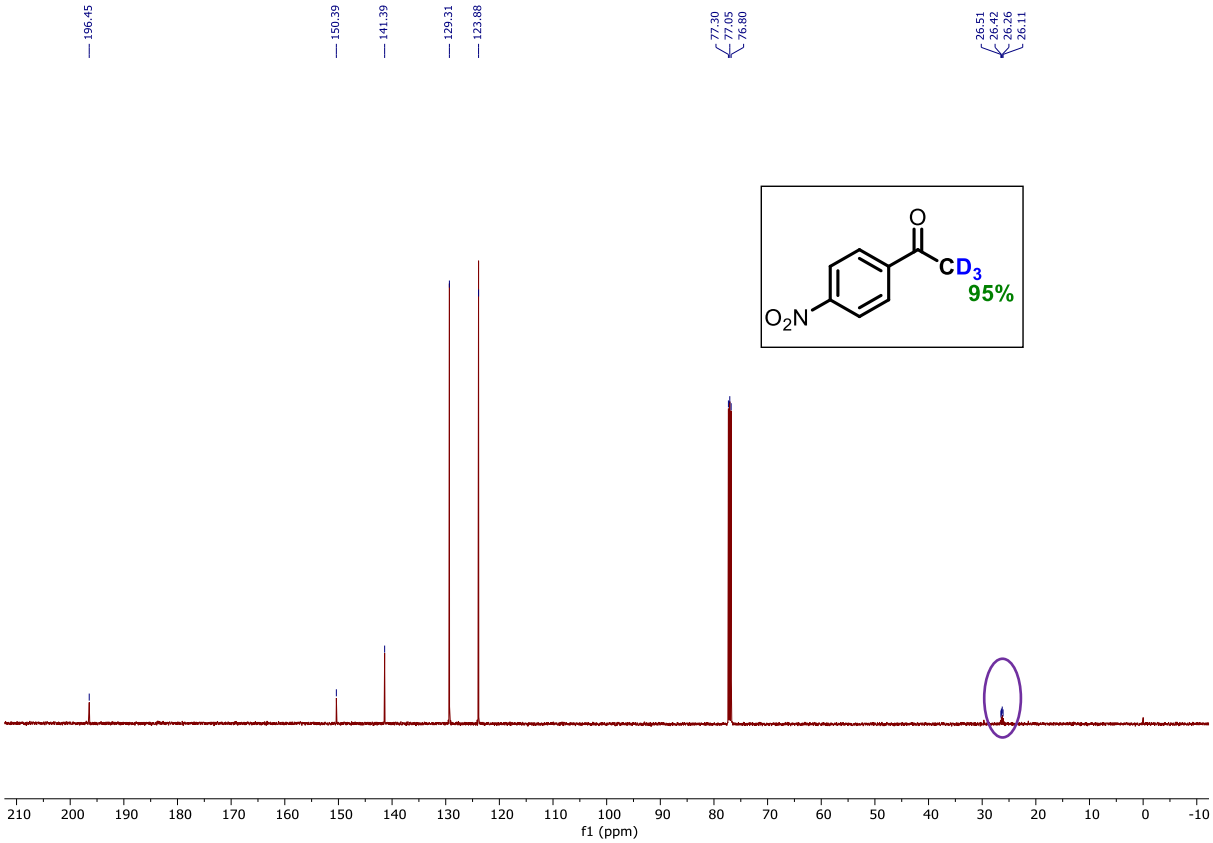
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(4-Nitrophenyl) ethan-1-one-2,2,2-d_3 (3n)**



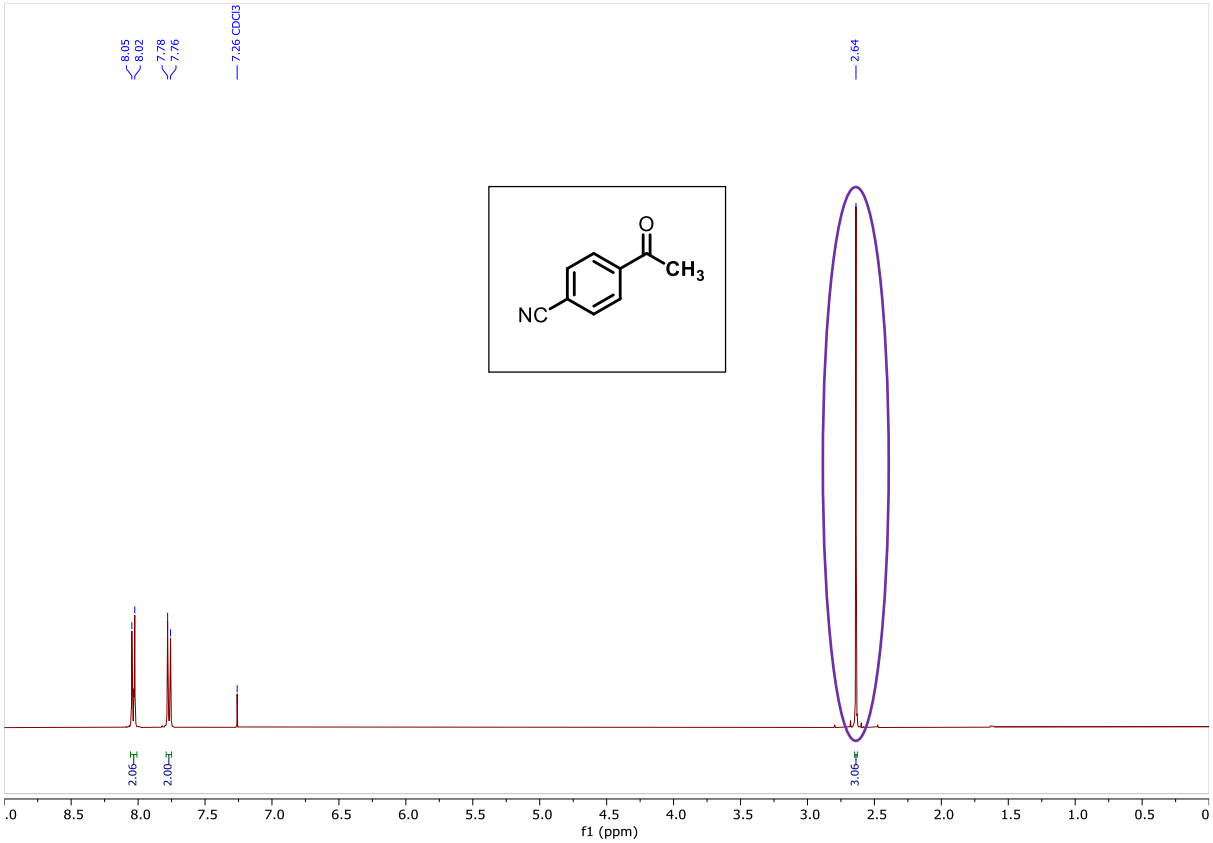
^{13}C {^{1}H} NMR (126 MHz, CDCl3) of **1-(4-Nitrophenyl) ethan-1-one** (starting material of **3n**)



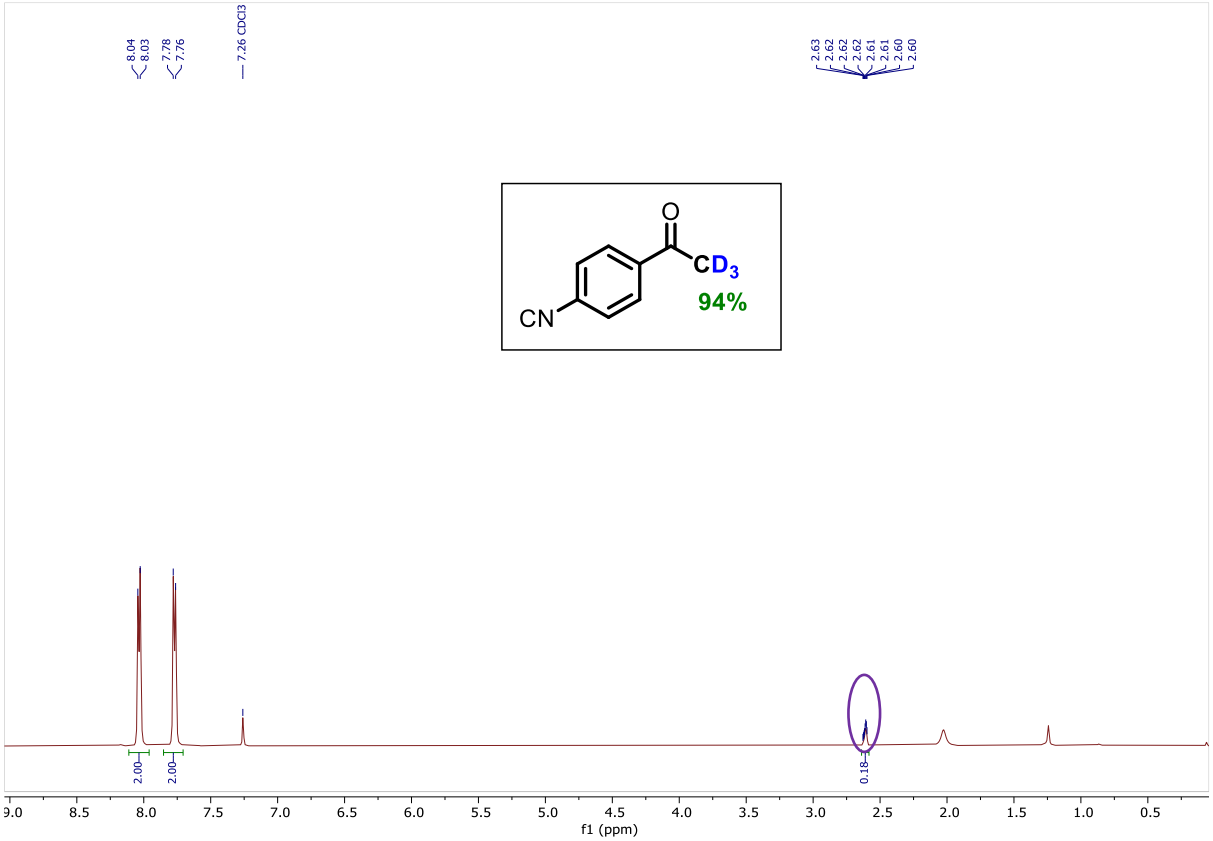
^{13}C {^{1}H} NMR (126 MHz, CDCl3) of **1-(4-Nitrophenyl) ethan-1-one-2,2,2-d_3 (3n)**



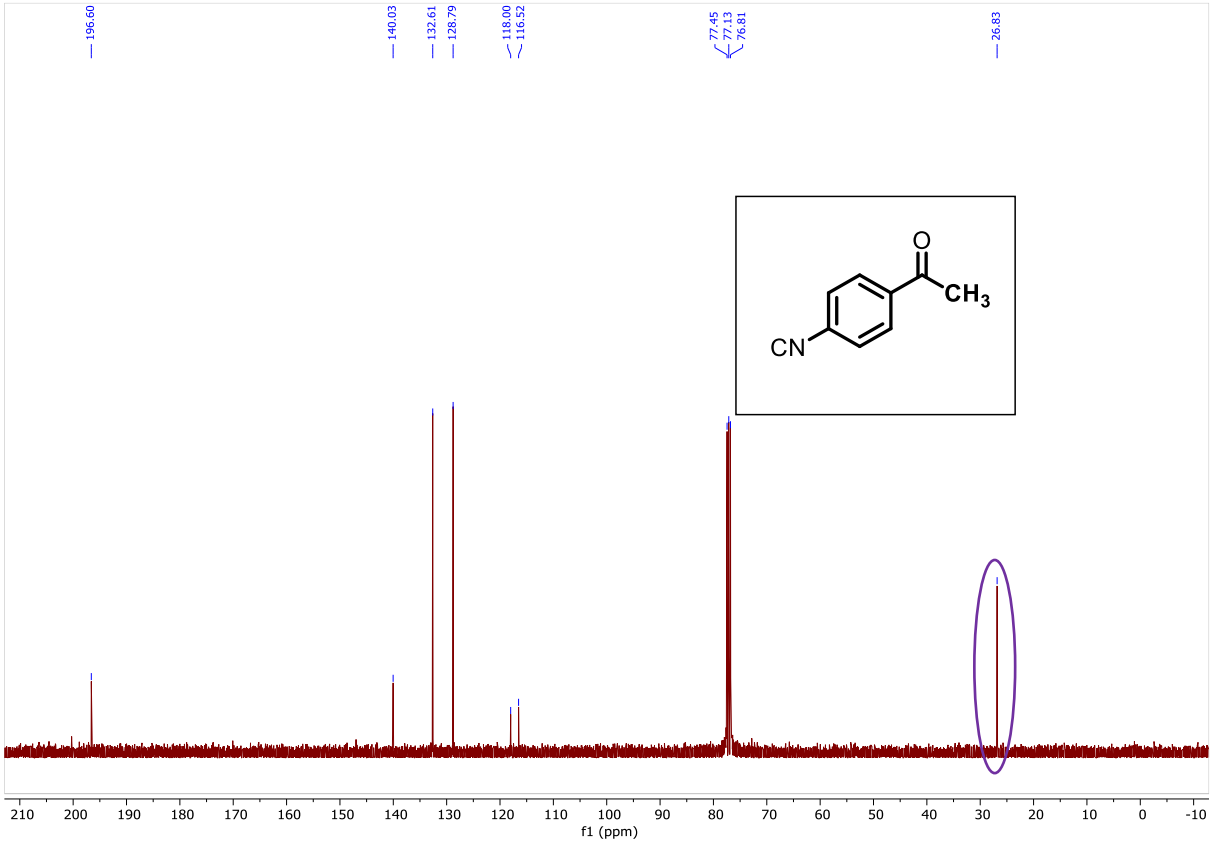
^{1}H NMR (500 MHz, $CDCl_3$) of **4-(Acetyl) benzonitrile** (starting material of **3o**)



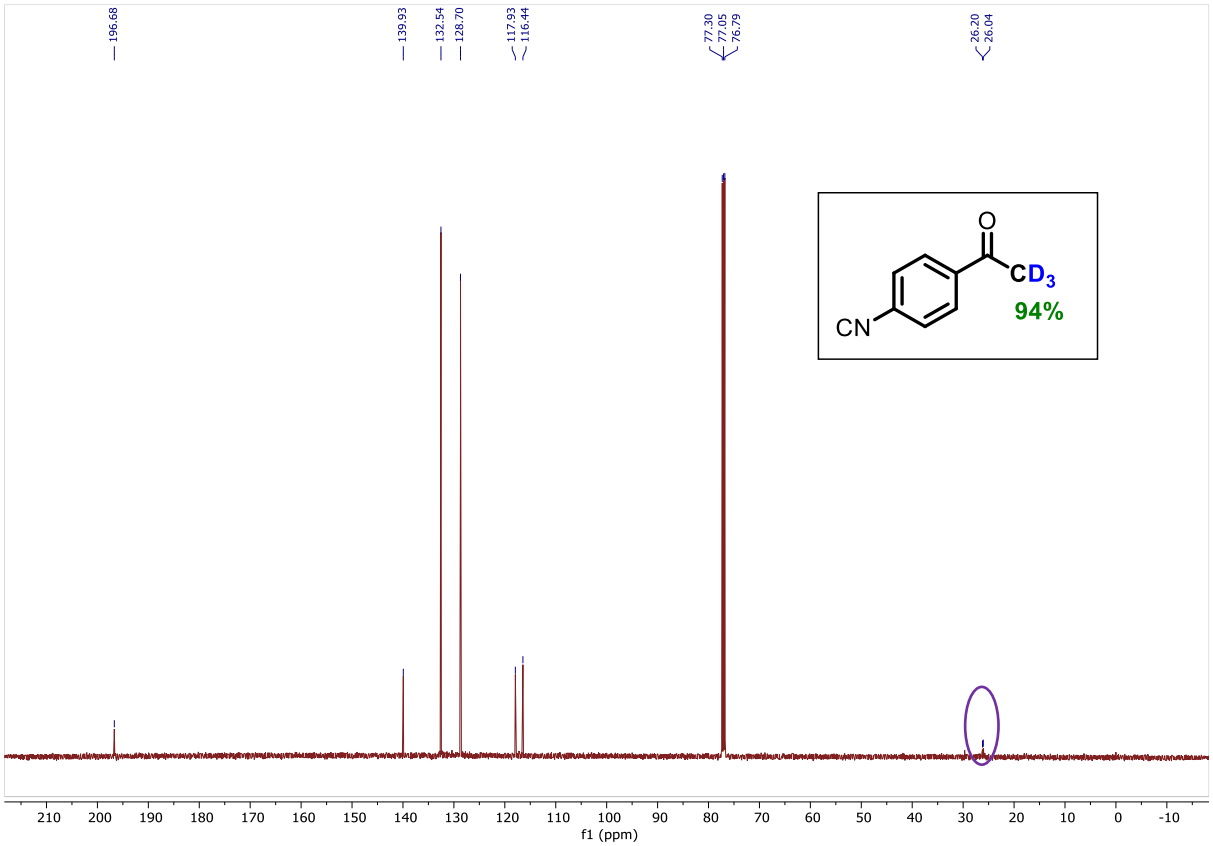
^{1}H NMR (500 MHz, $CDCl_3$) of **4-(Acetyl-d_3)-benzonitrile (3o)**



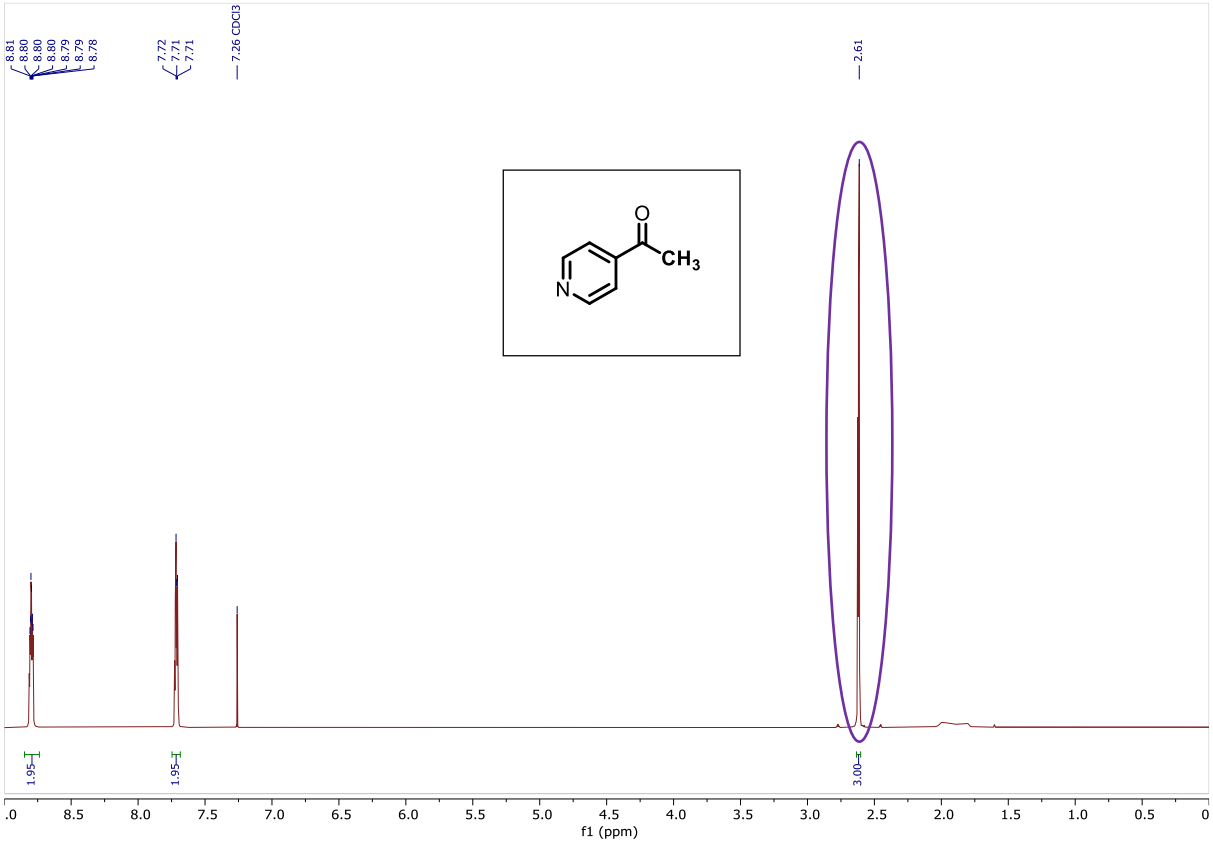
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **4-(Acetyl)-benzonitrile** (starting material of **3o**)



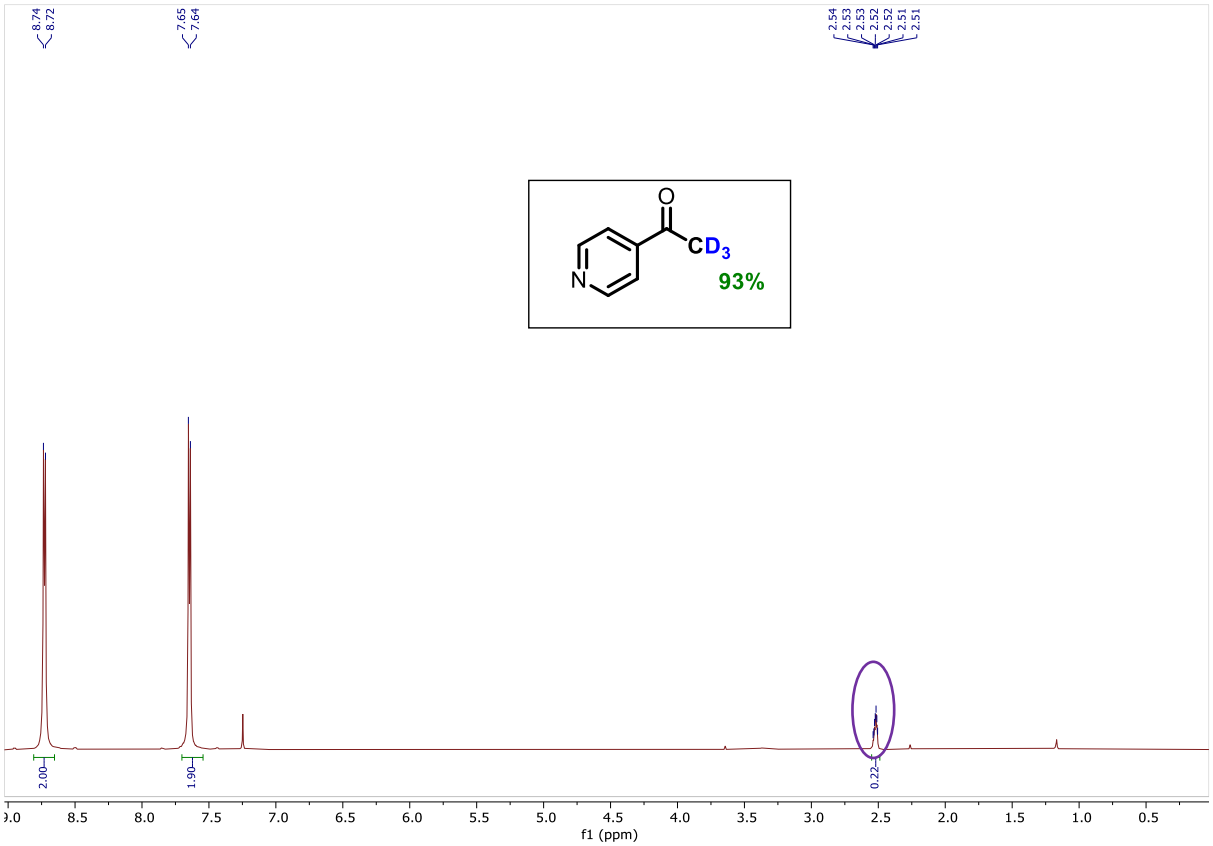
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **4-(Acetyl-*d*$_3$)-benzonitrile (3o)**



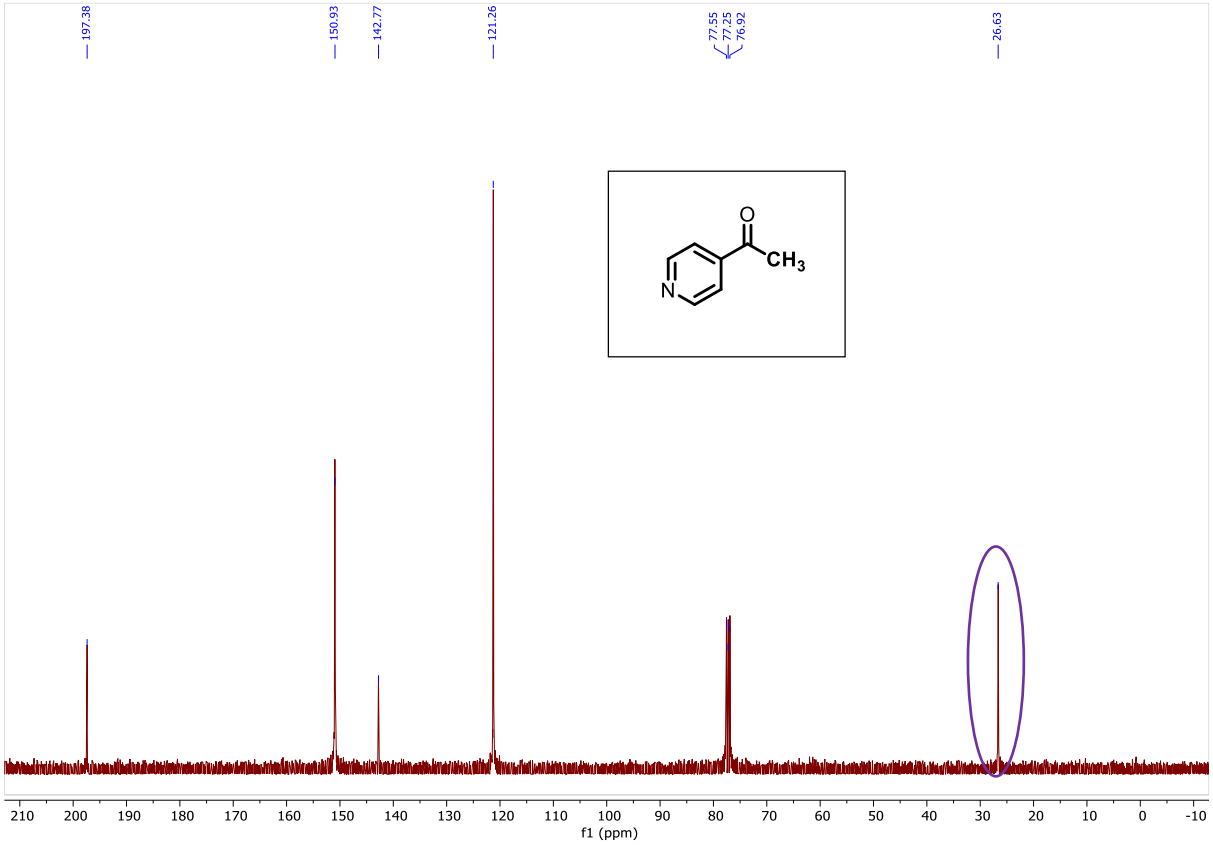
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(Pyridin-4-yl)-ethan-1-one-2,2,2** (starting material of **3p**)



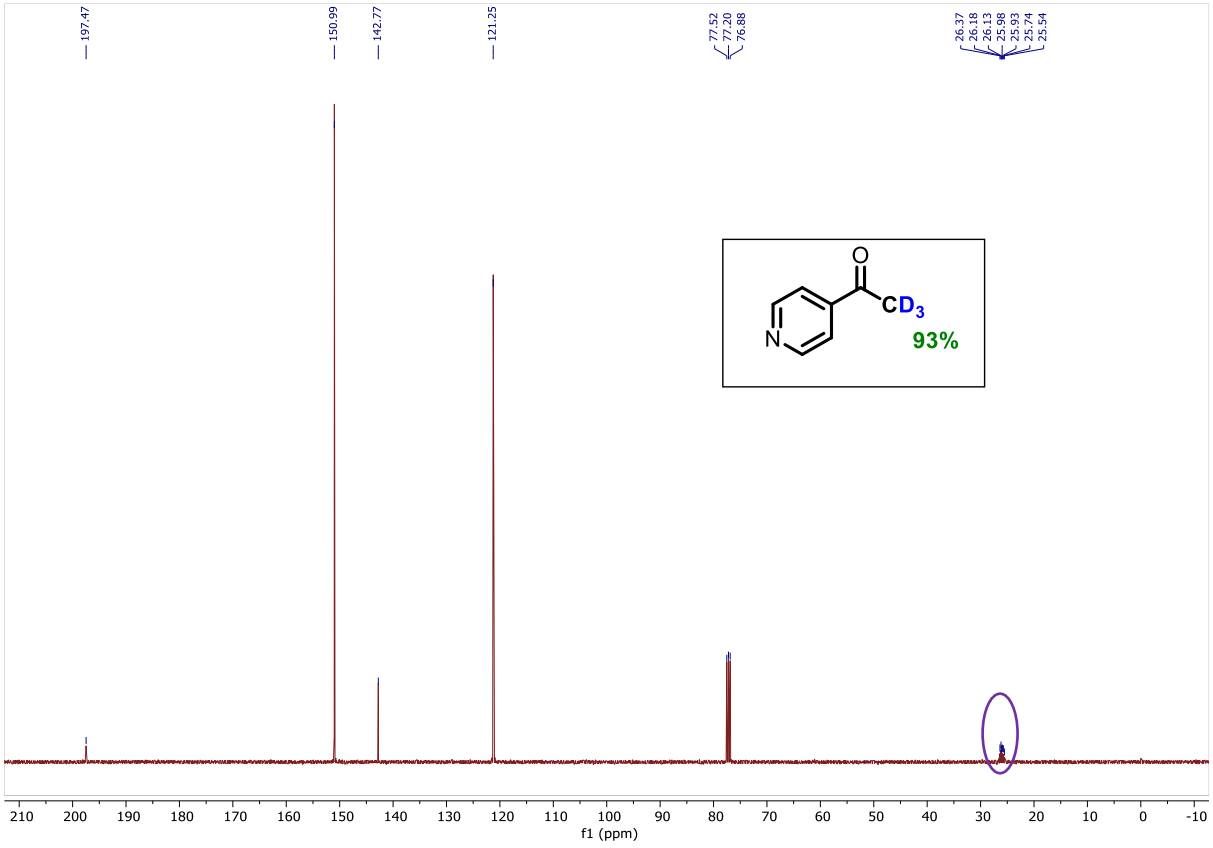
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(Pyridin-4-yl)-ethan-1-one-2,2,2-d_3 (3p)**



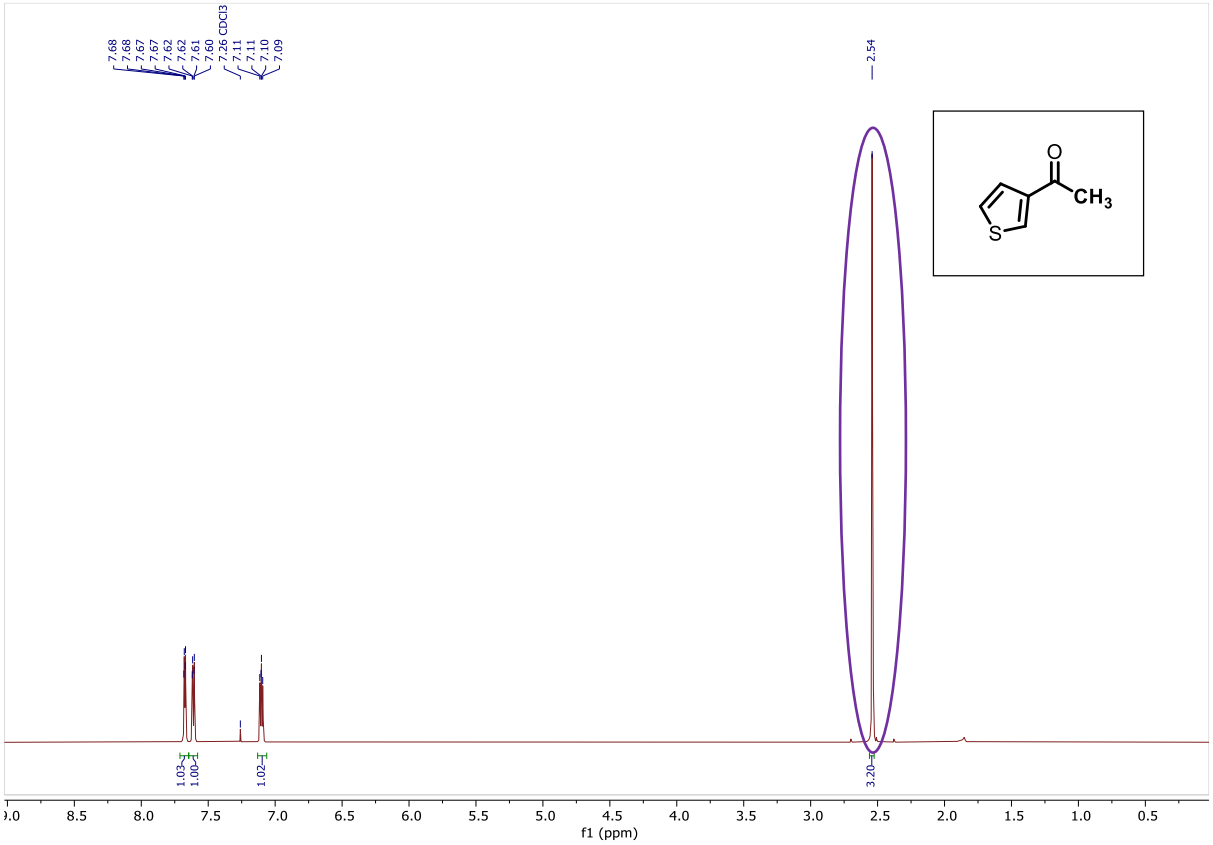
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(Pyridin-4-yl)-ethan-1-one** (starting material of **3p**)



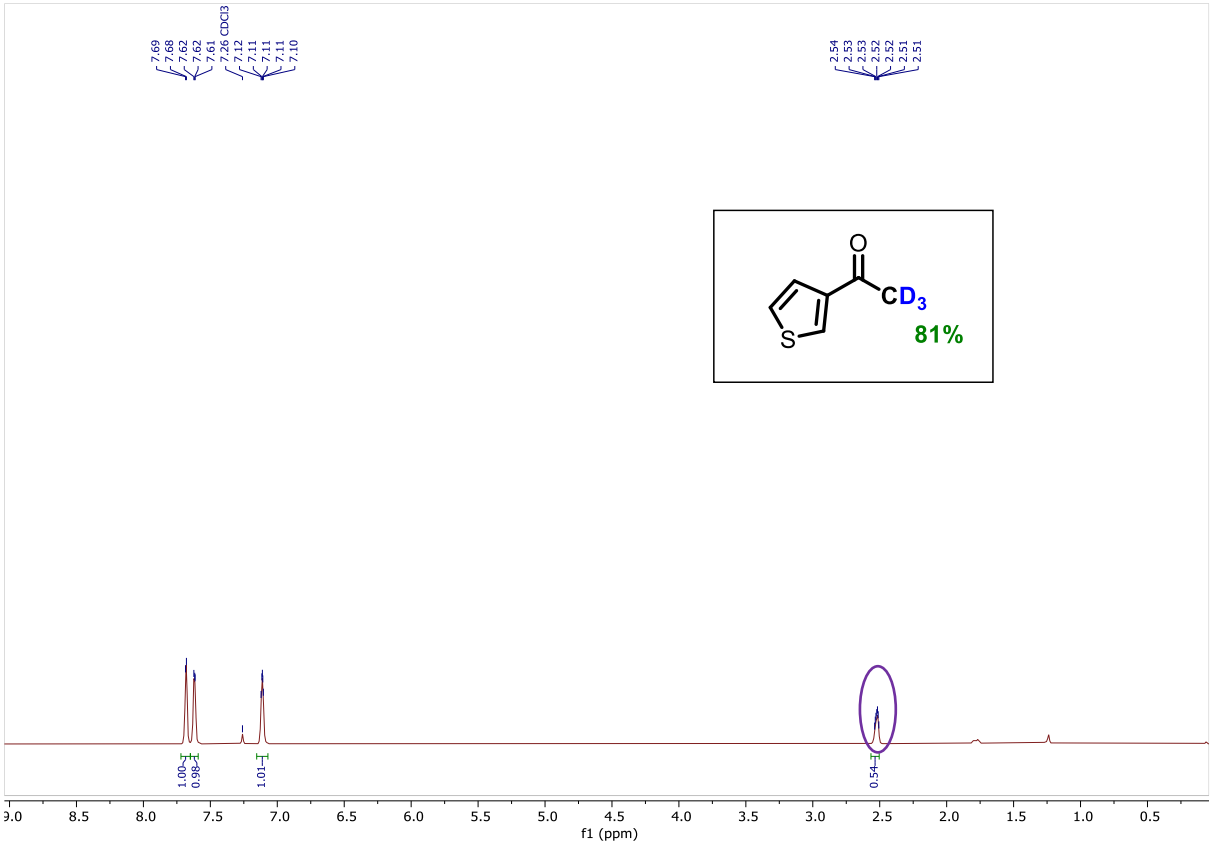
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(Pyridin-4-yl)-ethan-1-one-2,2,2-*d*$_3$ (3p)**



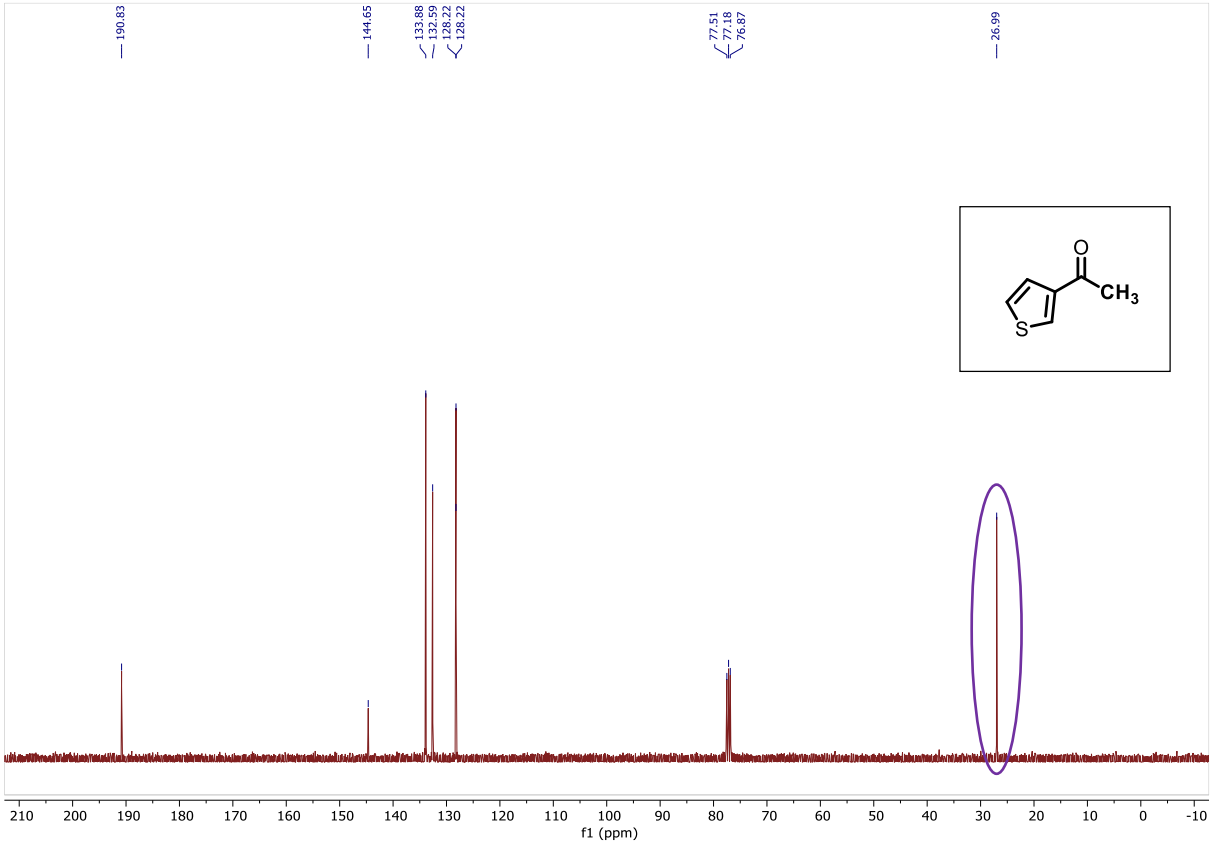
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(Thiophen-3-yl) ethan-1-one** (starting material of **3q**)



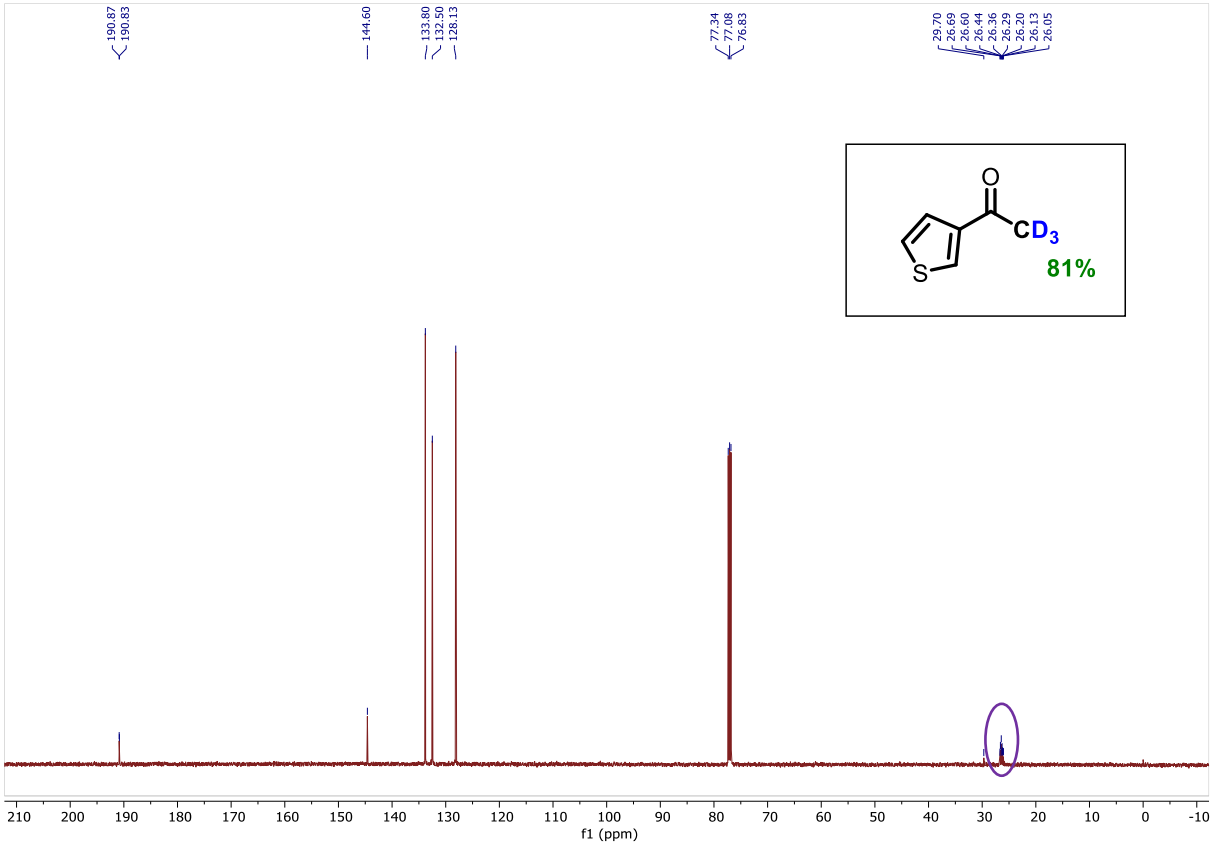
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(Thiophen-3-yl) ethan-1-one-2,2,2-*d_3* (3q)**



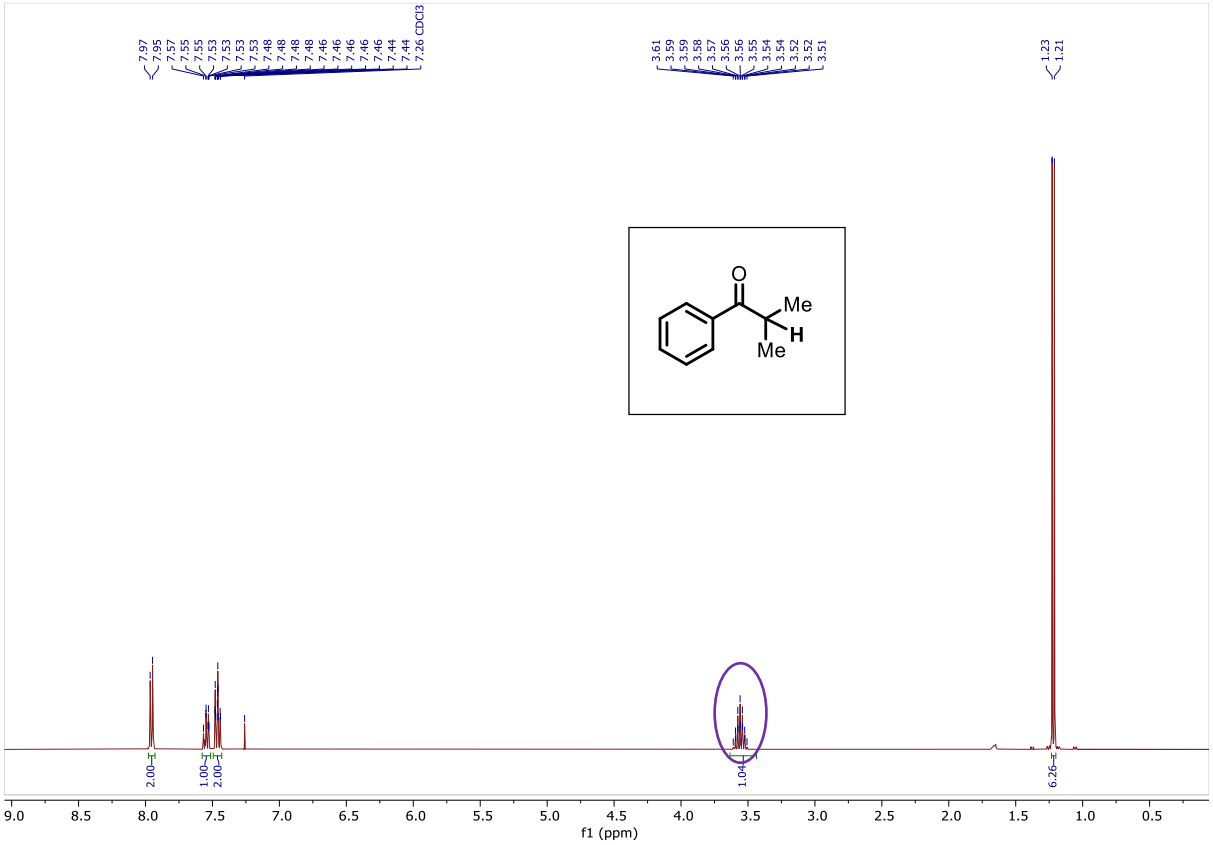
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(Thiophen-3-yl) ethan-1-one** (starting material of **3q**)



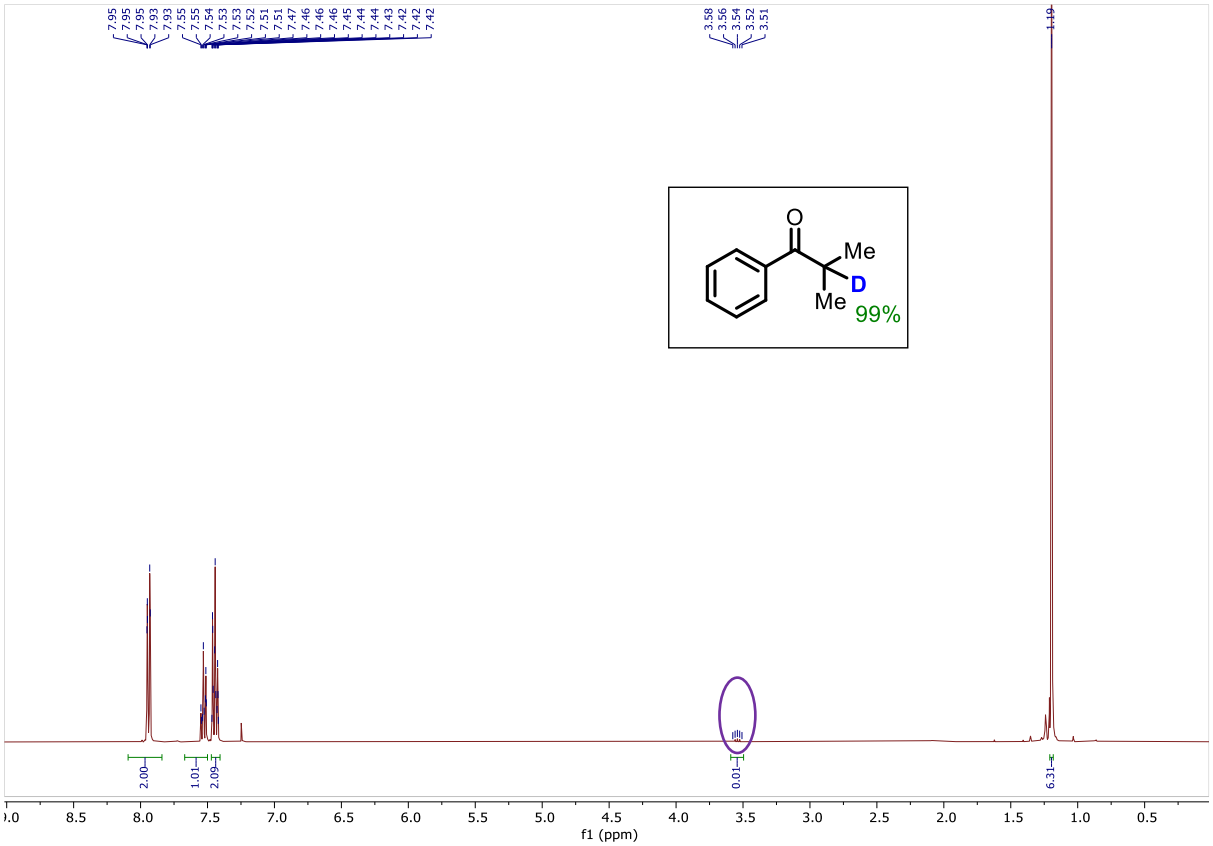
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(Thiophen-3-yl) ethan-1-one-2,2,2-*d*$_3$ (3q)**



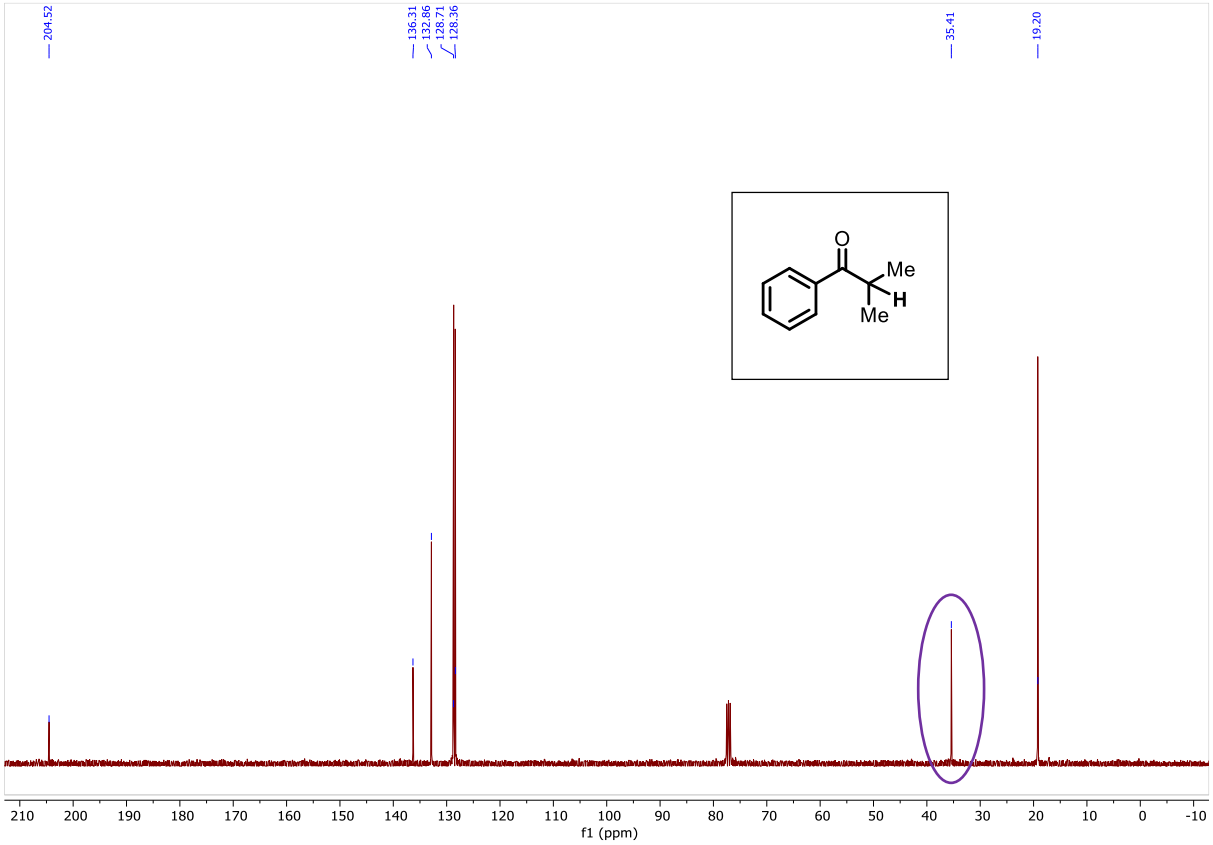
^{1}H NMR (400 MHz, $CDCl_3$) of **2-Methyl-1-phenylpropan-1-one** (starting material of **3r**)



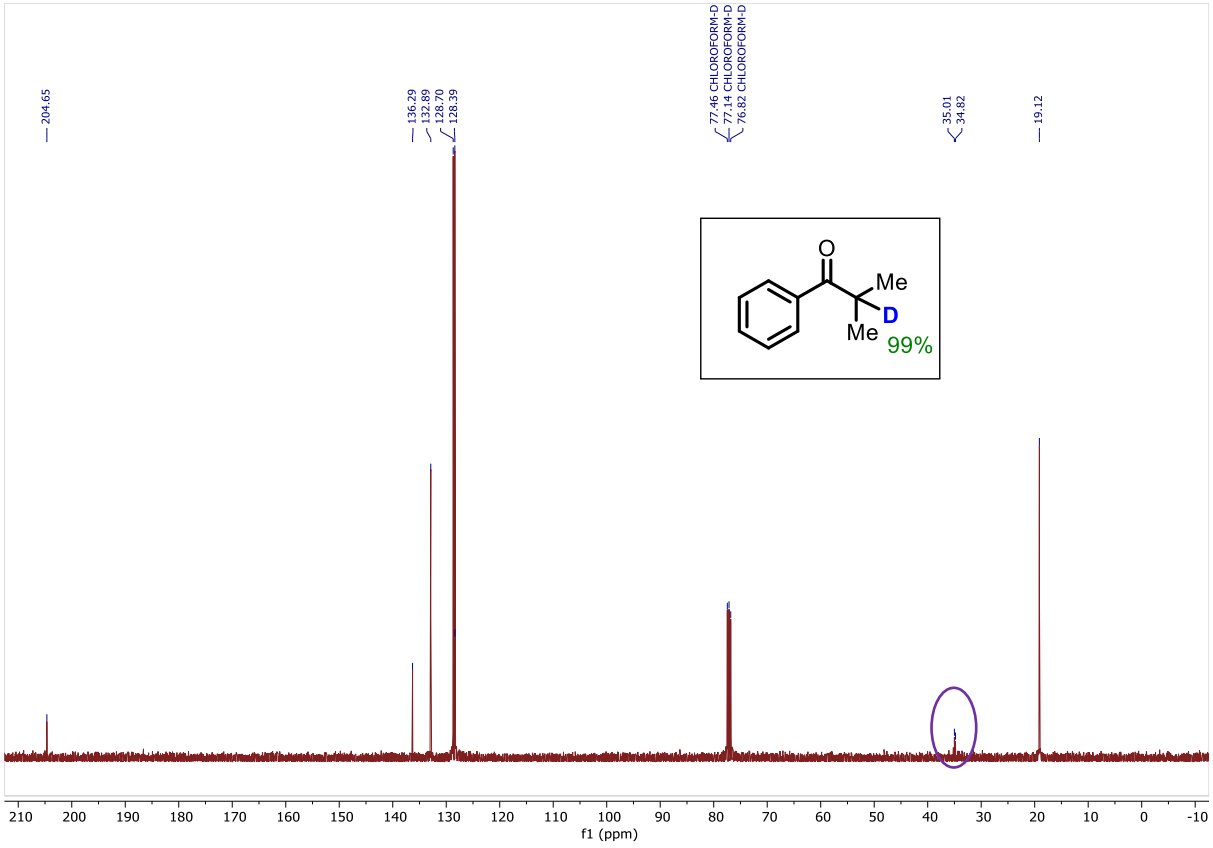
^{1}H NMR (400 MHz, $CDCl_3$) of **2-Methyl-1-phenylpropan-1-one-2-*d* (3r)**



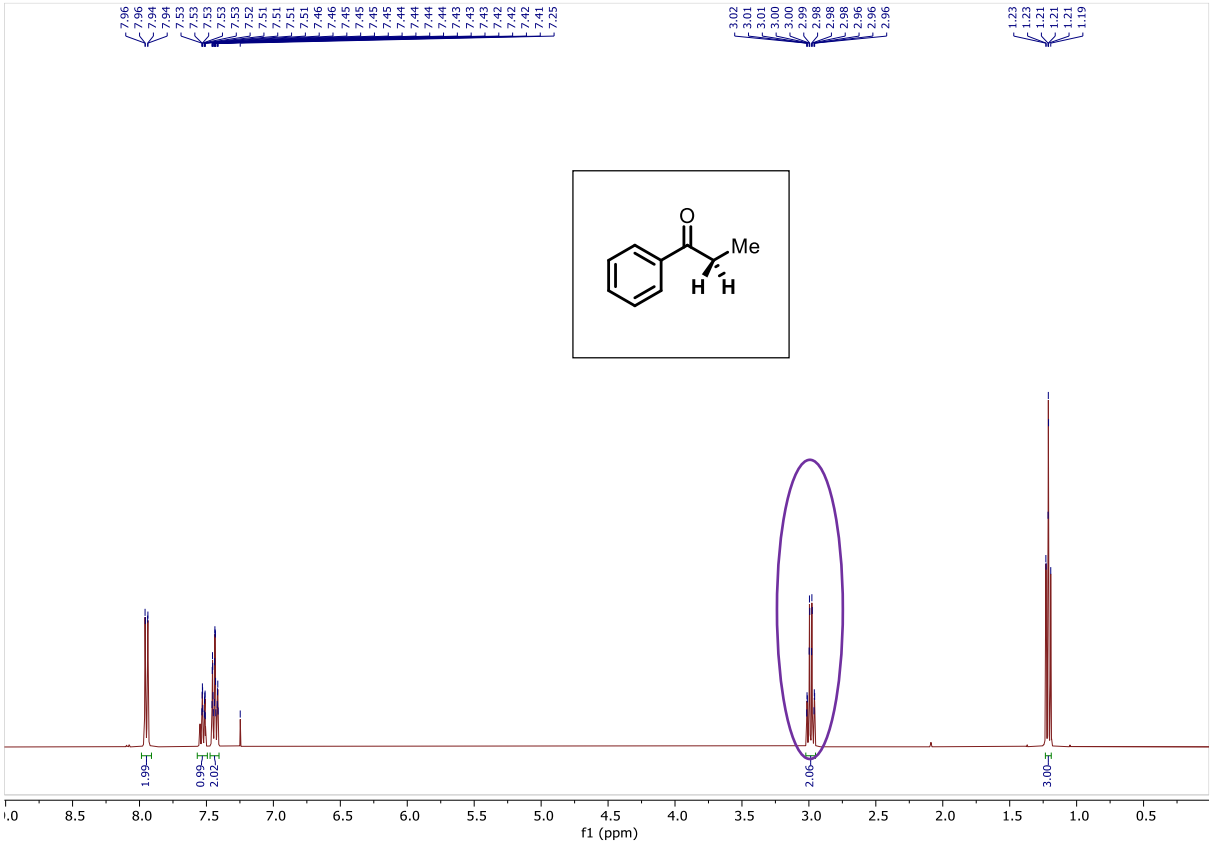
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **2-Methyl-1-phenylpropan-1-one** (starting material of **3r**)



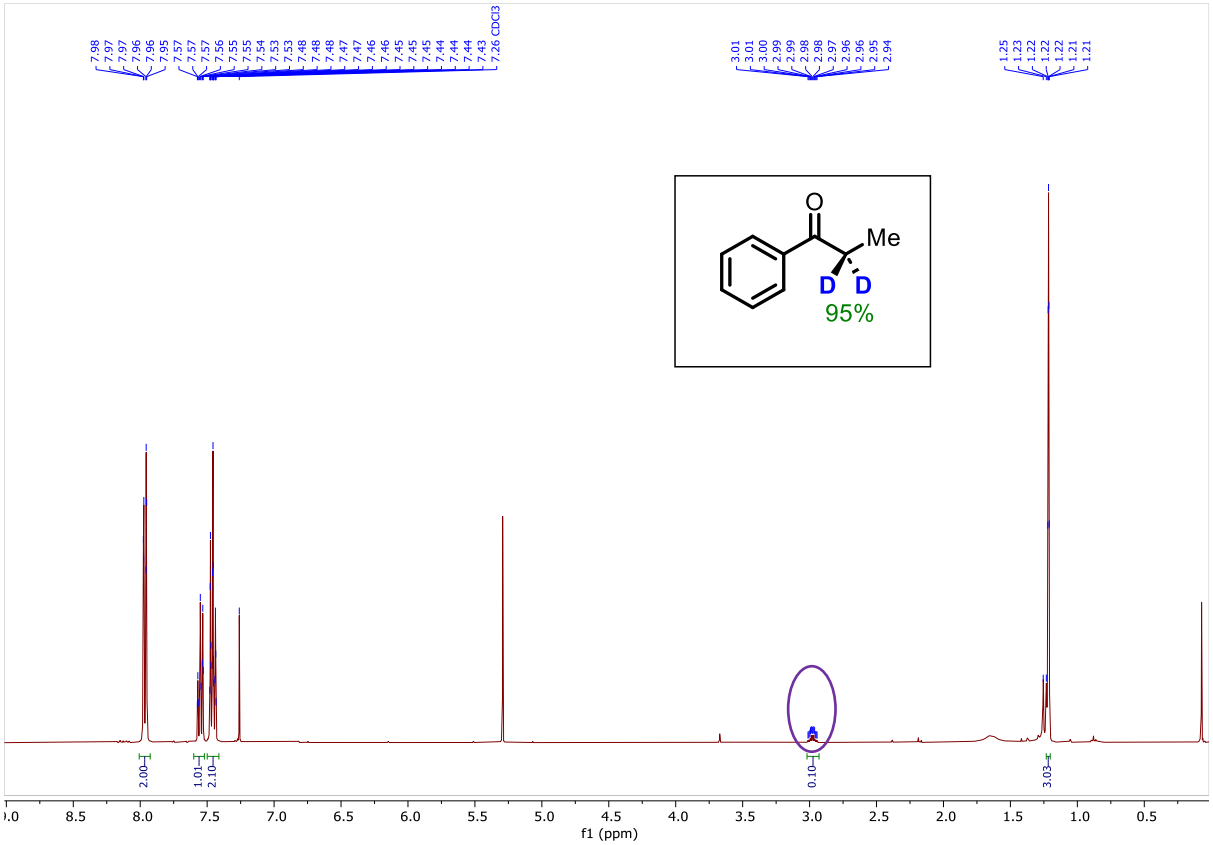
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **2-Methyl-1-phenylpropan-1-one-2-*d* (3r)**



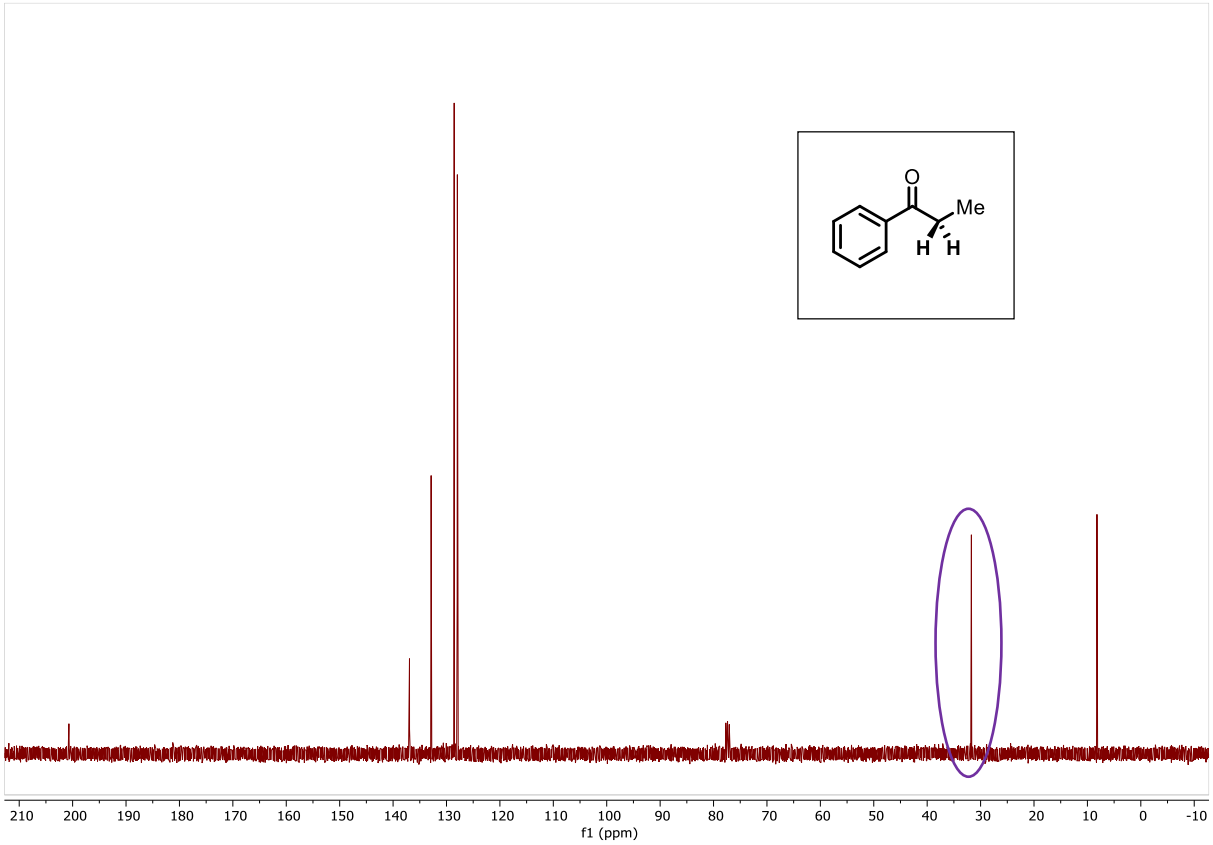
^{1}H NMR (400 MHz, $CDCl_3$) of **1-Phenyl propan-1-one** (starting material of **3s**)



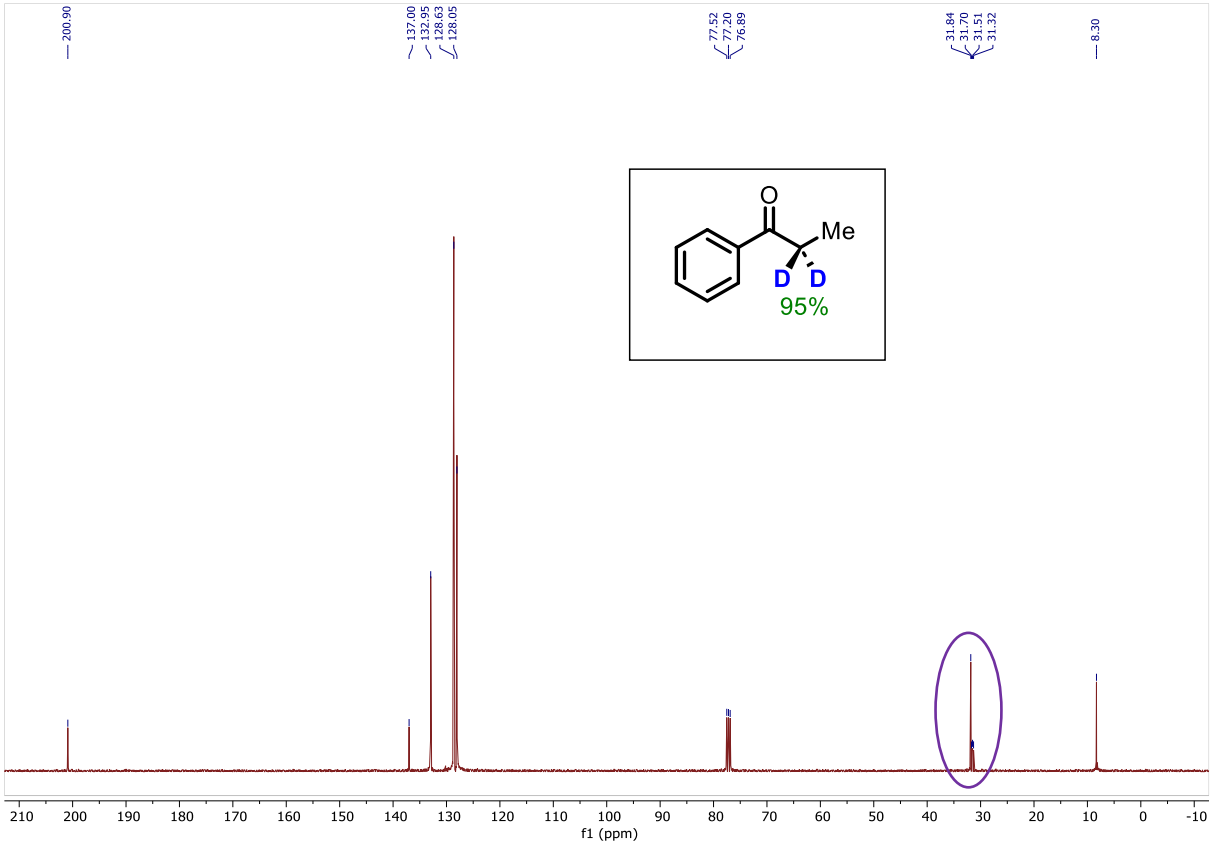
^{1}H NMR (400 MHz, $CDCl_3$) of **1-Phenyl propan-1-one-2,2-d_2 (3s)**



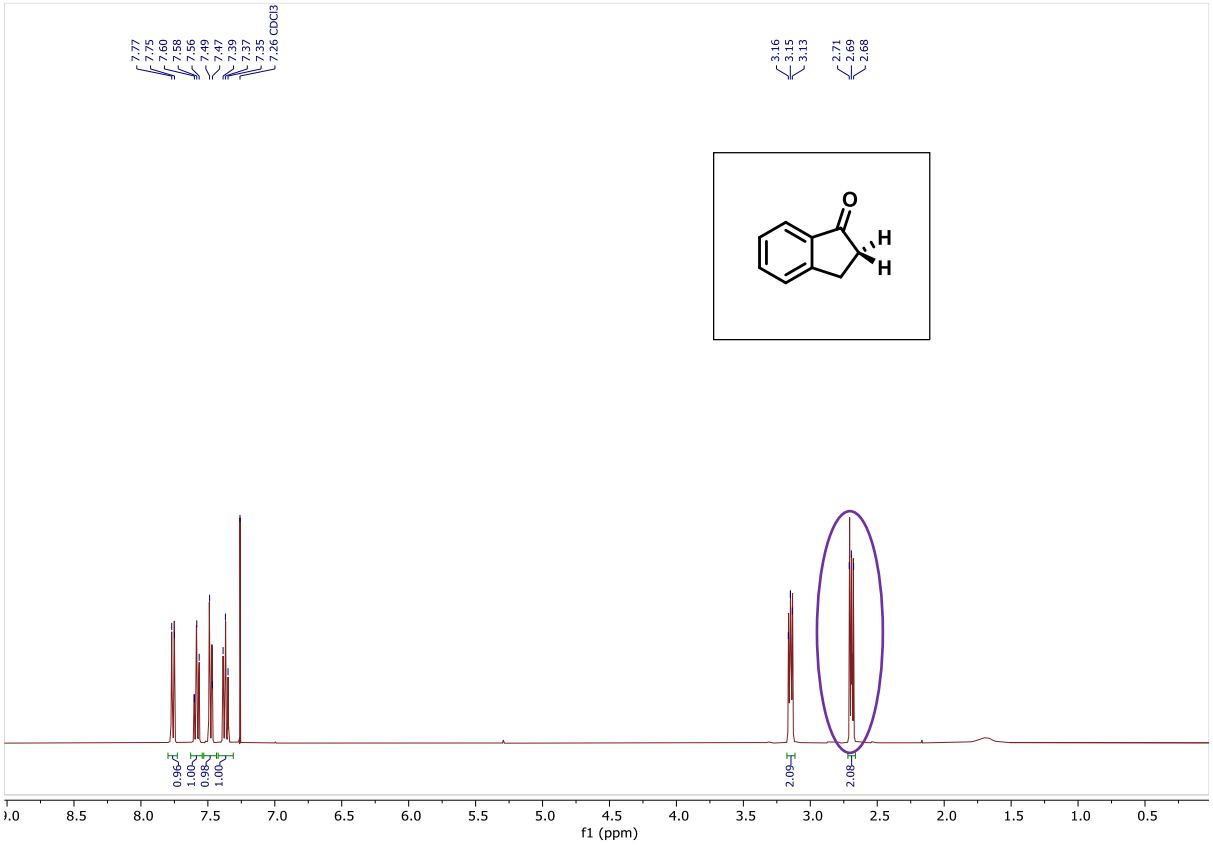
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-Phenyl propan-1-one** (starting material of **3s**)



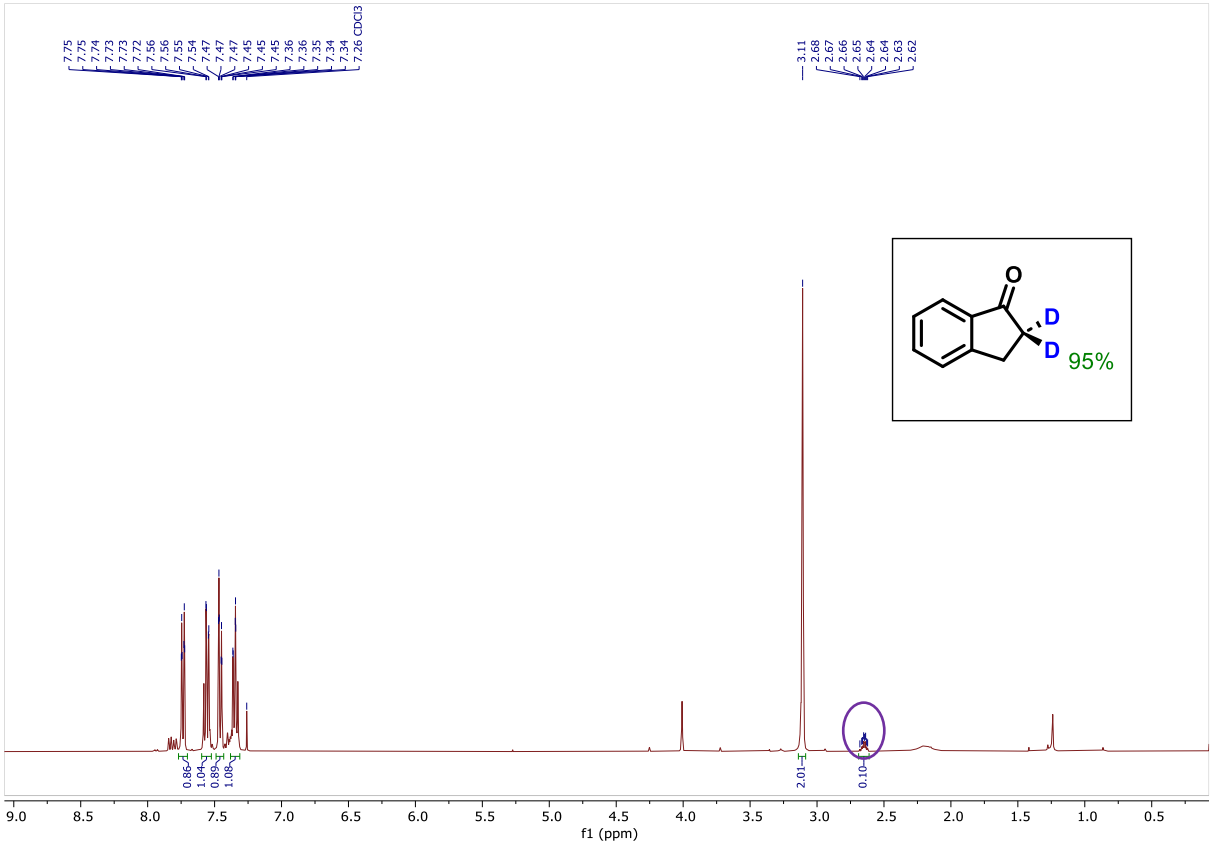
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-Phenyl propan-1-one-2,2-d_2 (3s)**



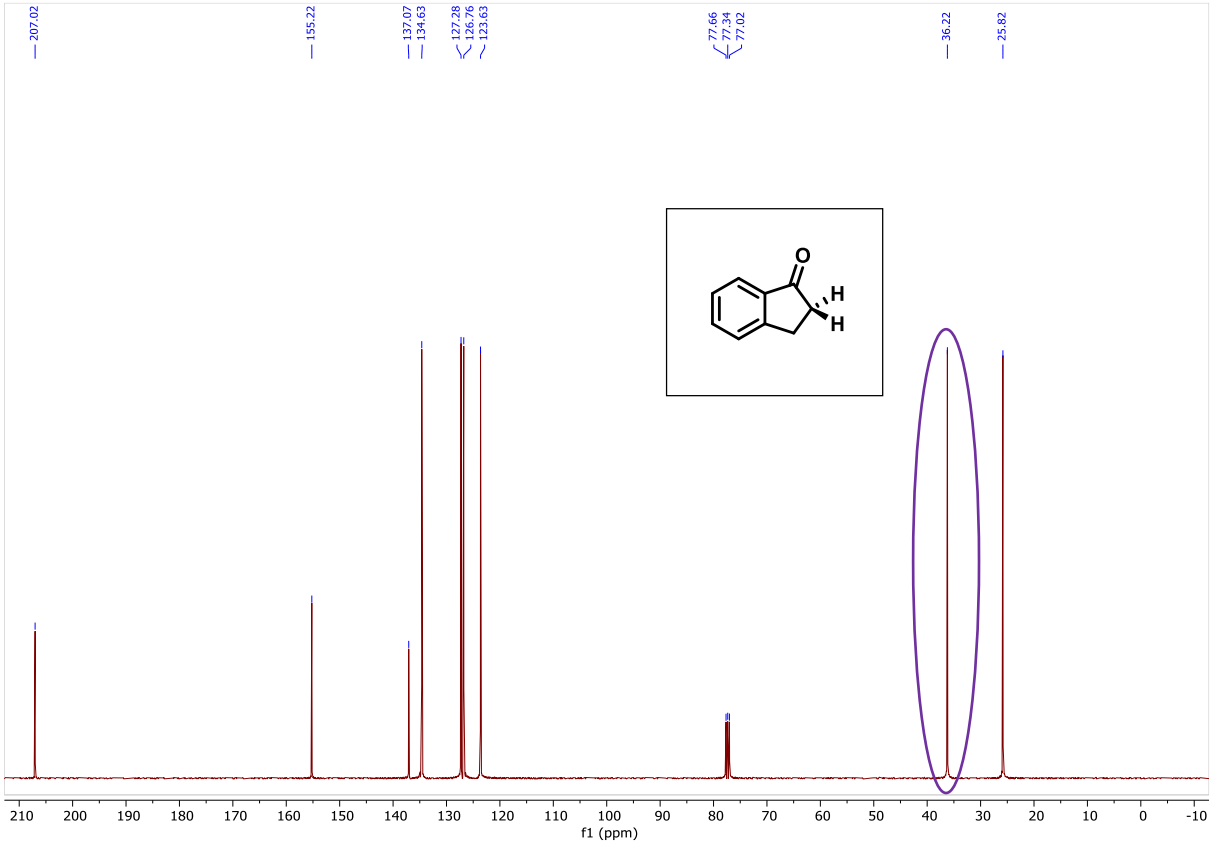
^{1}H NMR (400 MHz, $CDCl_3$) of **2,3-dihydro-1*H*-inden-1-one** (starting material of **3t**)



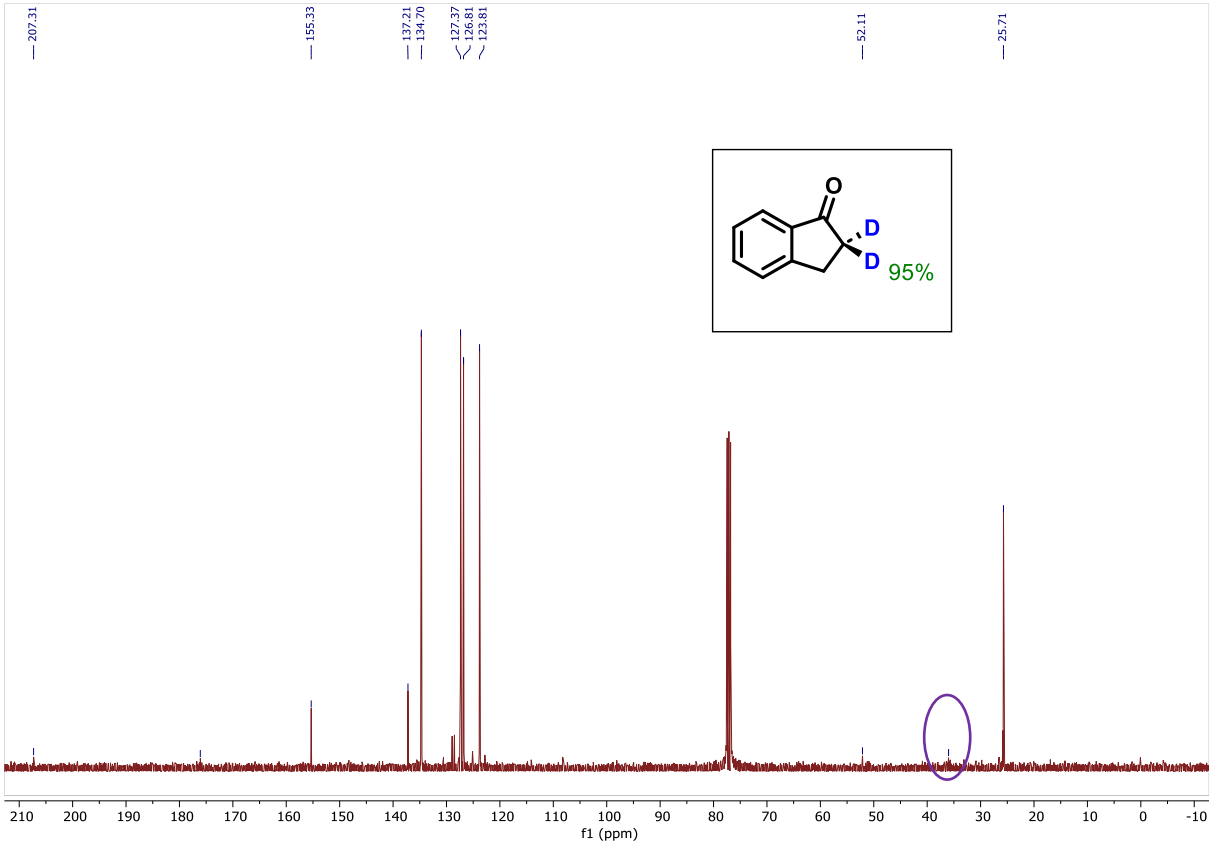
^{1}H NMR (400 MHz, $CDCl_3$) of **3-Dihydro-1*H*-inden-1-one-2,2-d_2 (3t)**



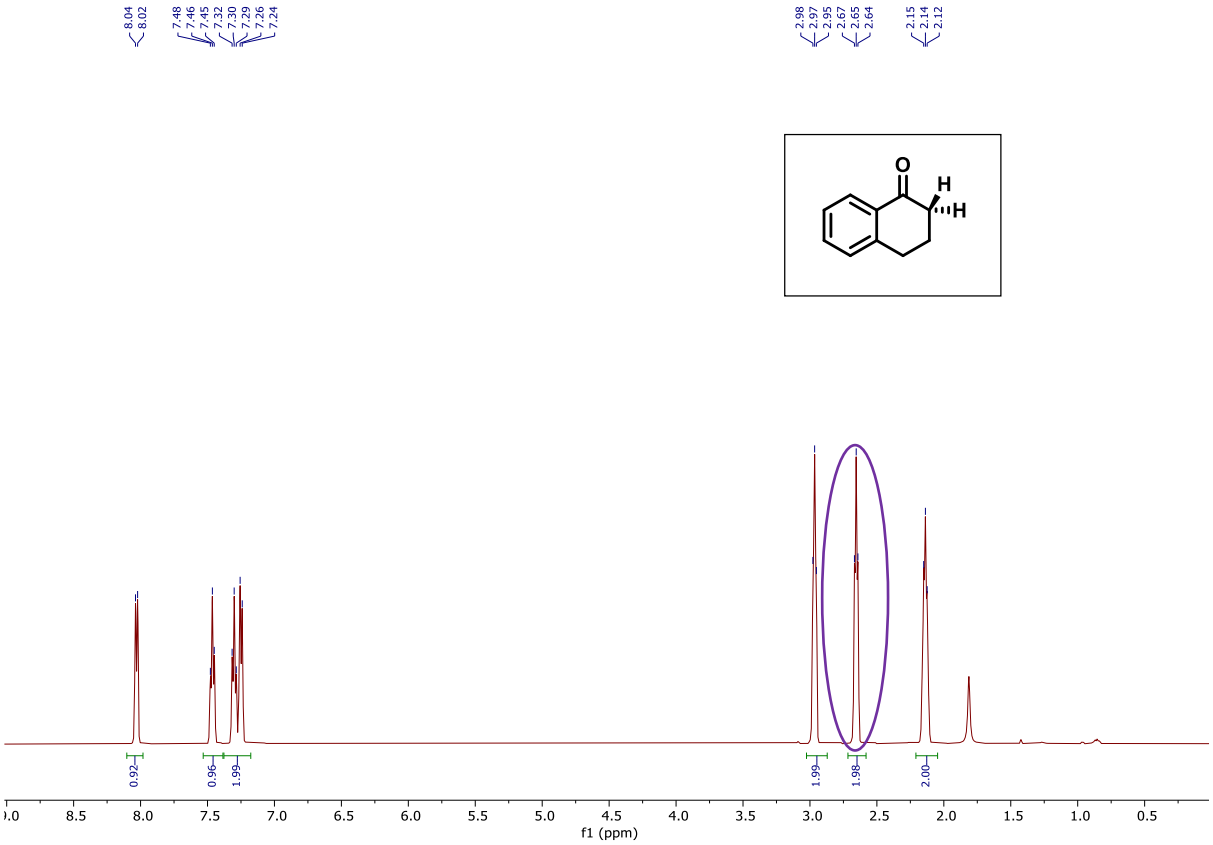
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **2,3-Dihydro-1*H*-inden-1-one** (starting material of **3t**)



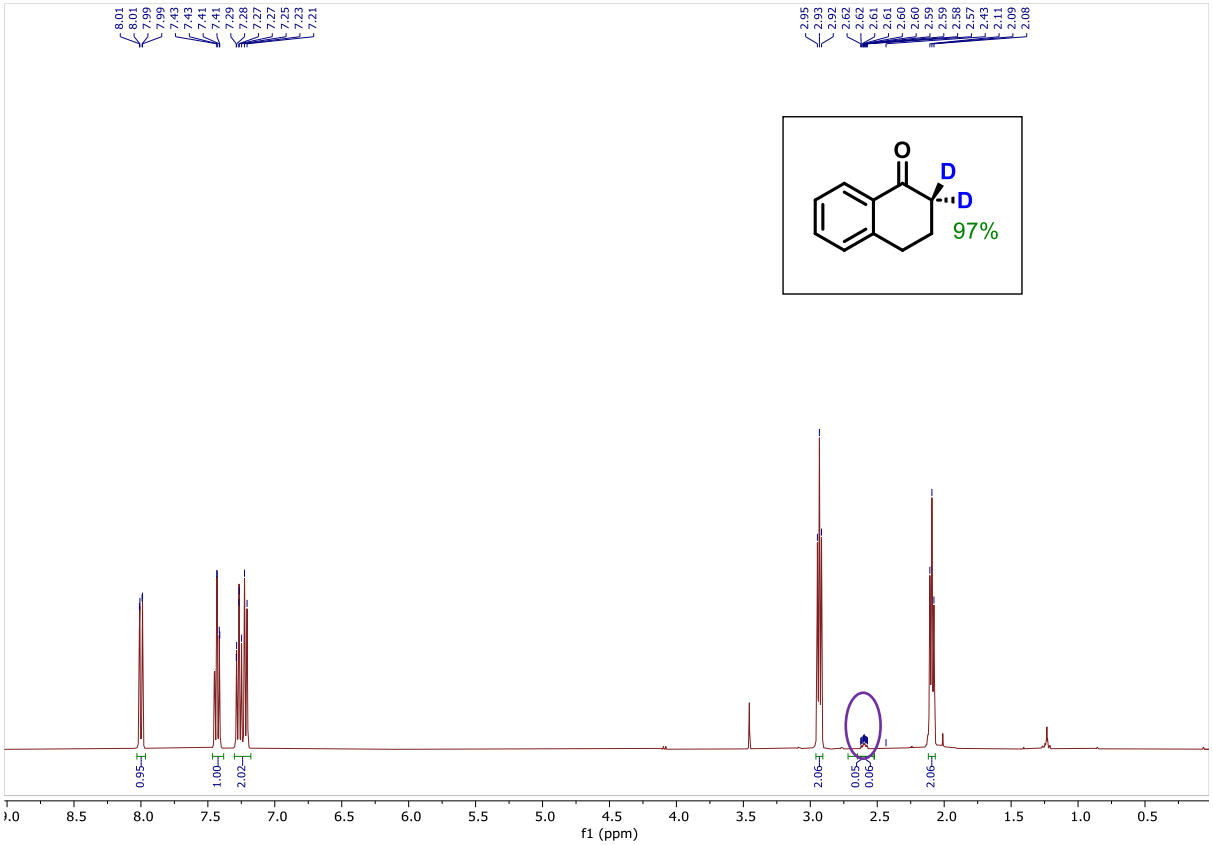
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **3-Dihydro-1*H*-inden-1-one-2,2-d_2 (3t)**



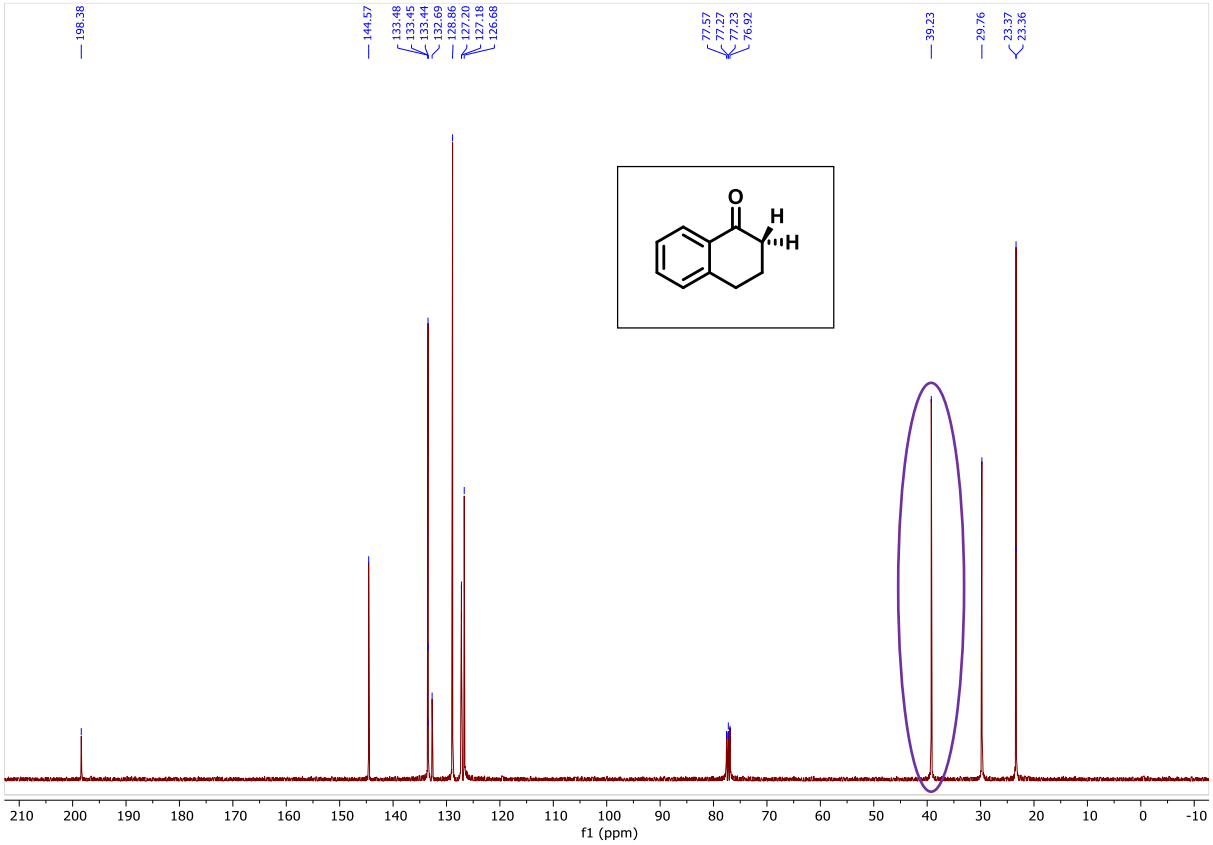
NMR (400 MHz, $CDCl_3$) of **3,4-Dihydronaphthalen-1(2*H*)-one** (starting material of **3u**)



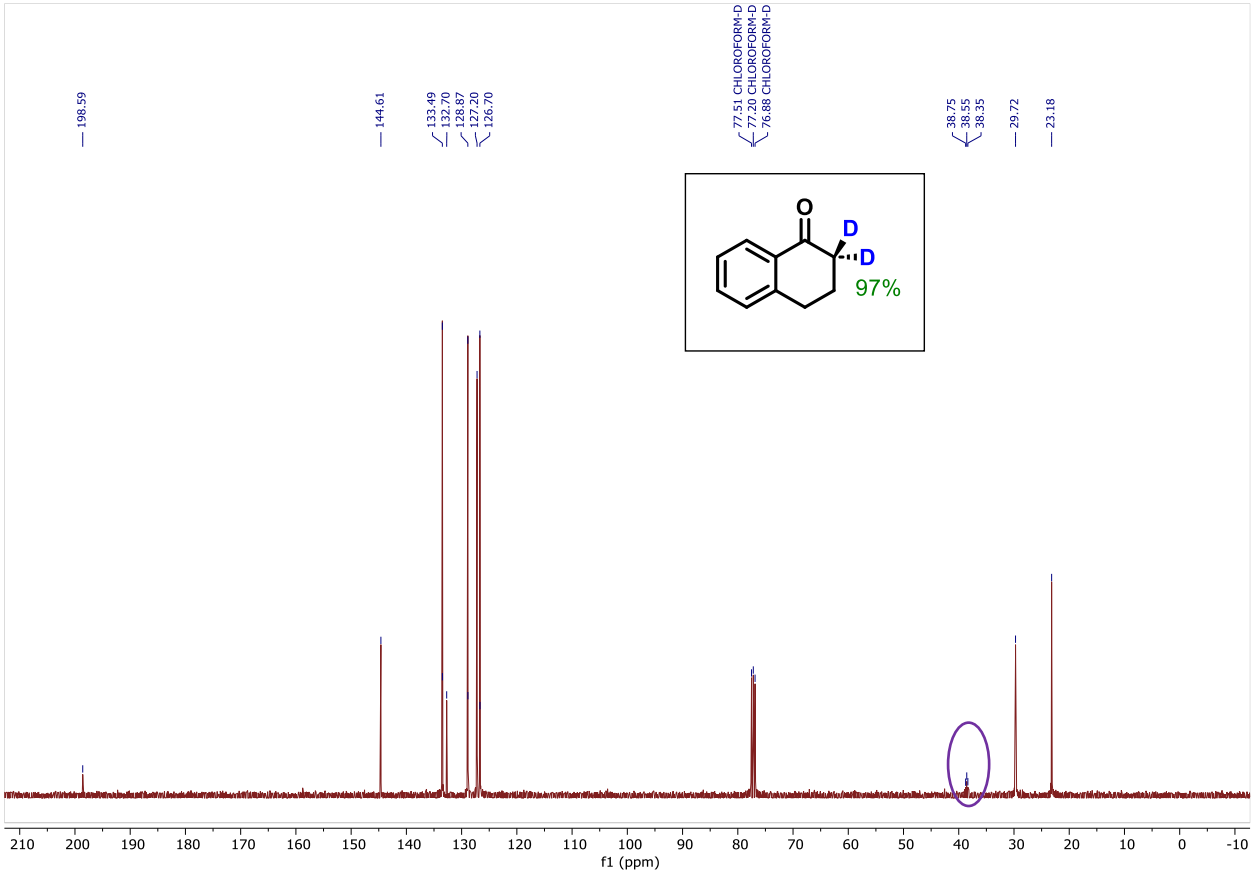
^{1}H NMR (400 MHz, $CDCl_3$) of **3,4-Dihydronaphthalen-1(2*H*)-one-2,2-d_2 (3u)**



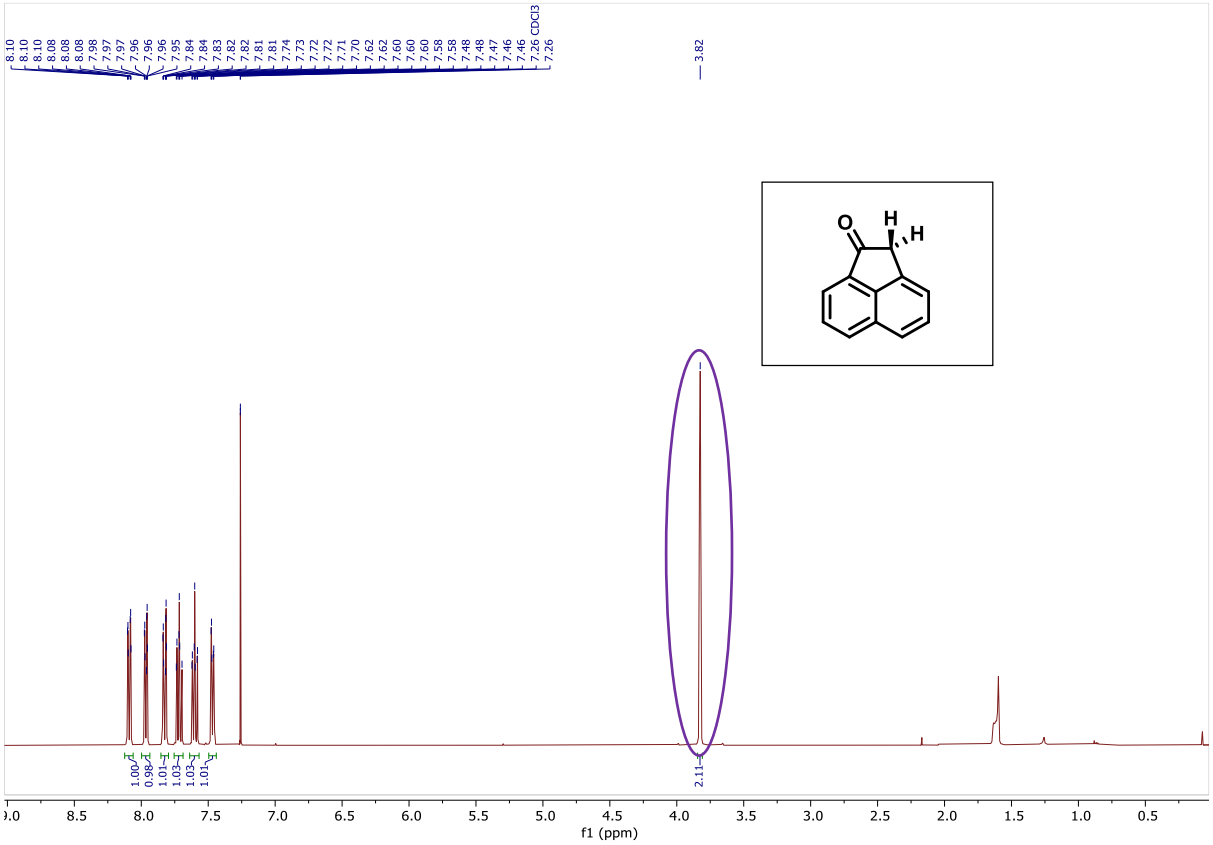
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **3,4-Dihydronaphthalen-1(2*H*)-one** (starting material of **3u**)



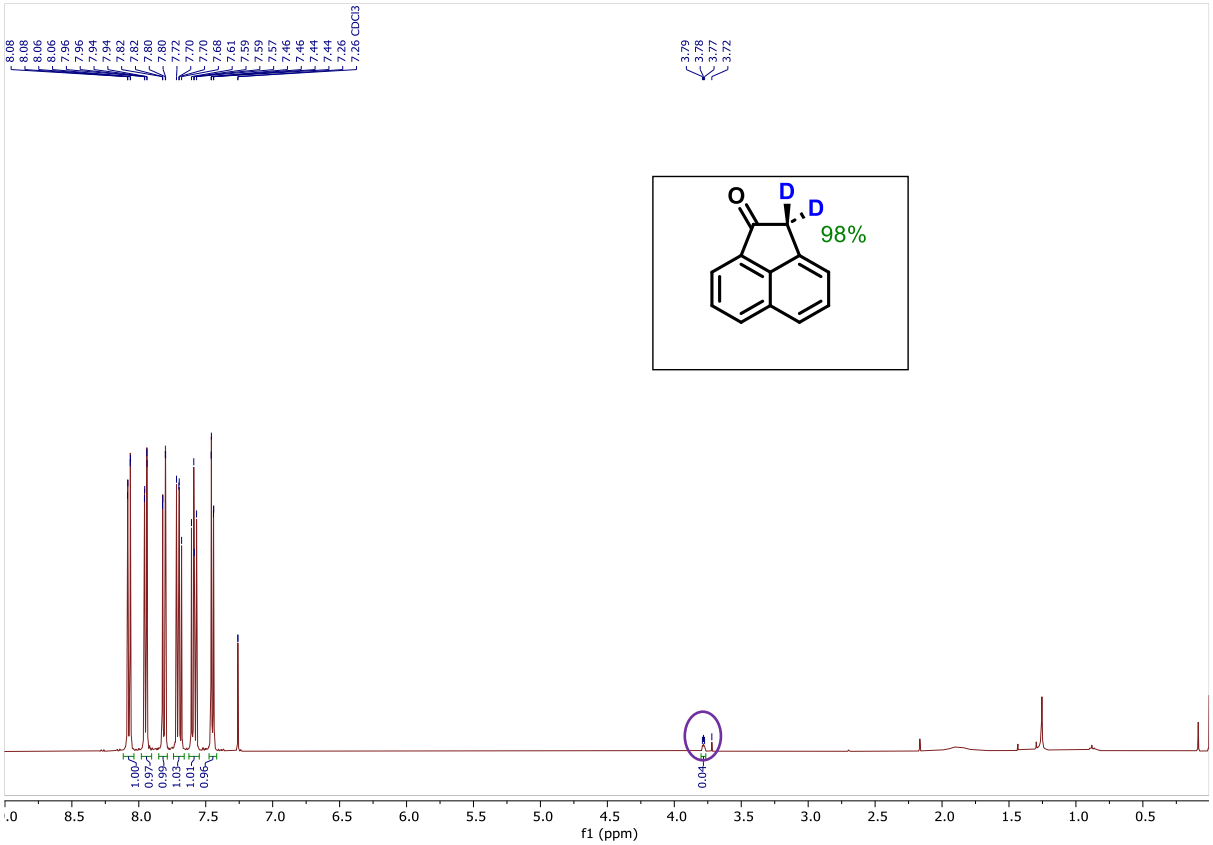
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **3,4-Dihydronaphthalen-1(2*H*)-one-2,2-d_2 (3u)**



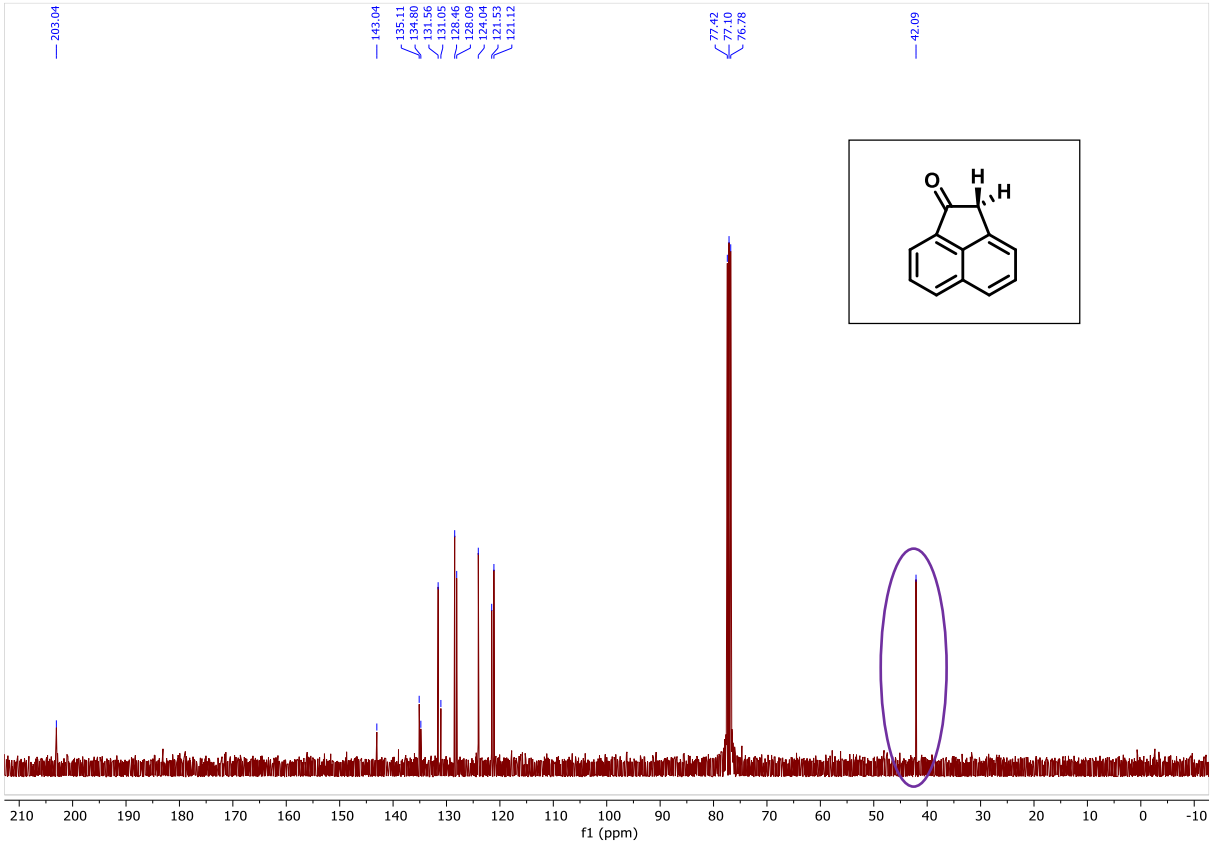
^{1}H NMR (400 MHz, $CDCl_3$) of **Acenaphthylen-1(2*H*)-one** (starting material of **3v**)



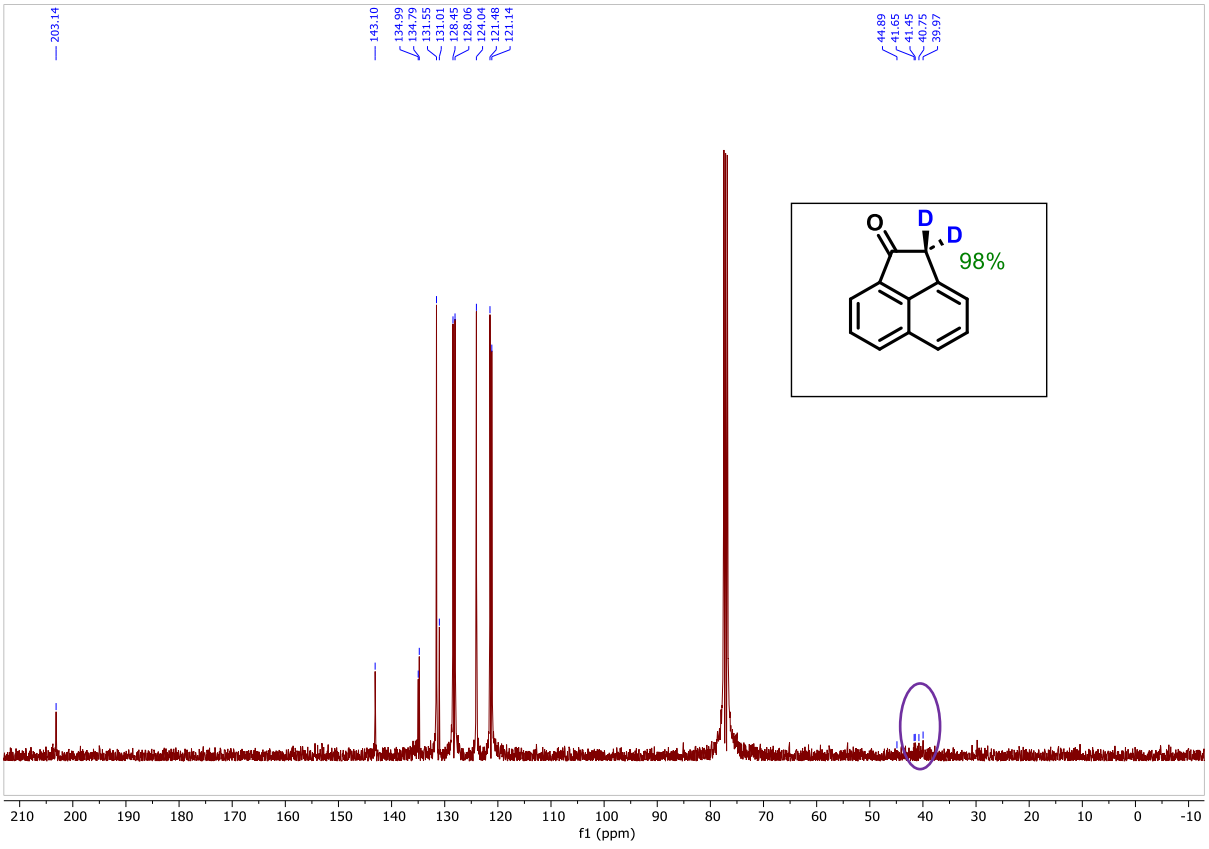
^{1}H NMR (400 MHz, $CDCl_3$) of **Acenaphthylen-1(2*H*)-one-2,2-d_2 (3v)**



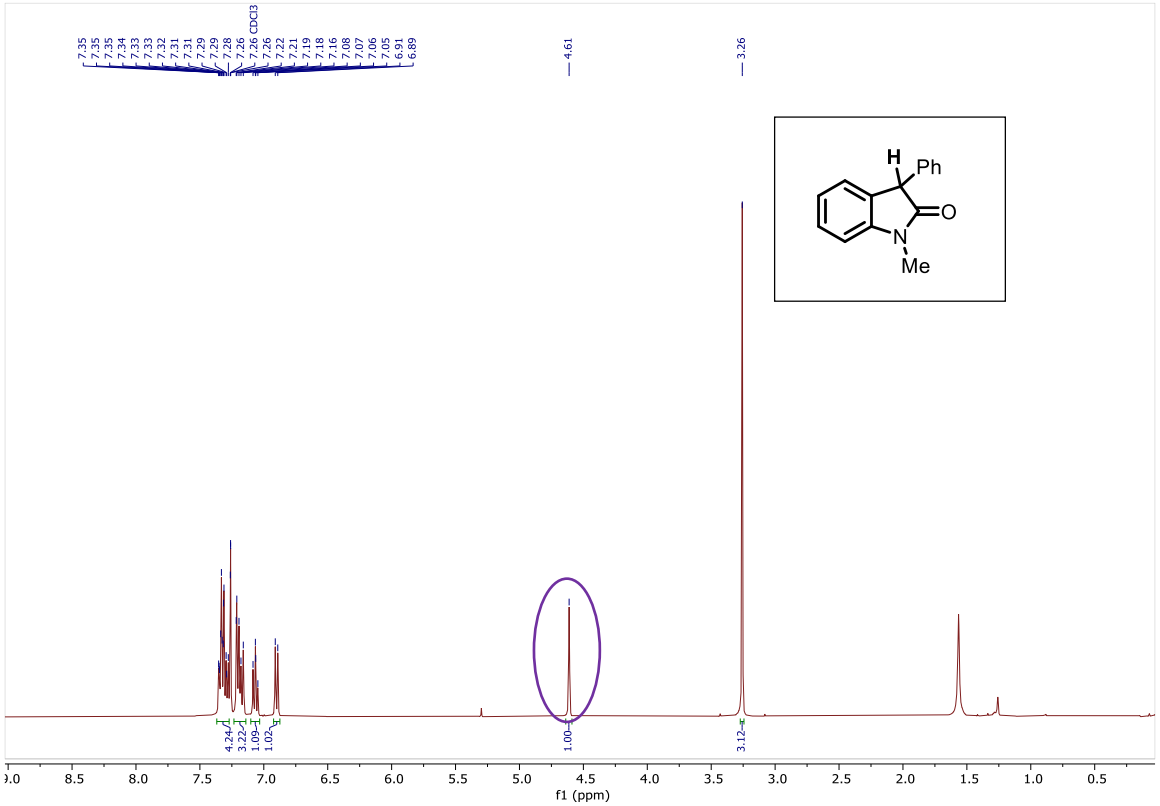
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Acenaphthylen-1(2*H*)-one** (starting material of **3v**)



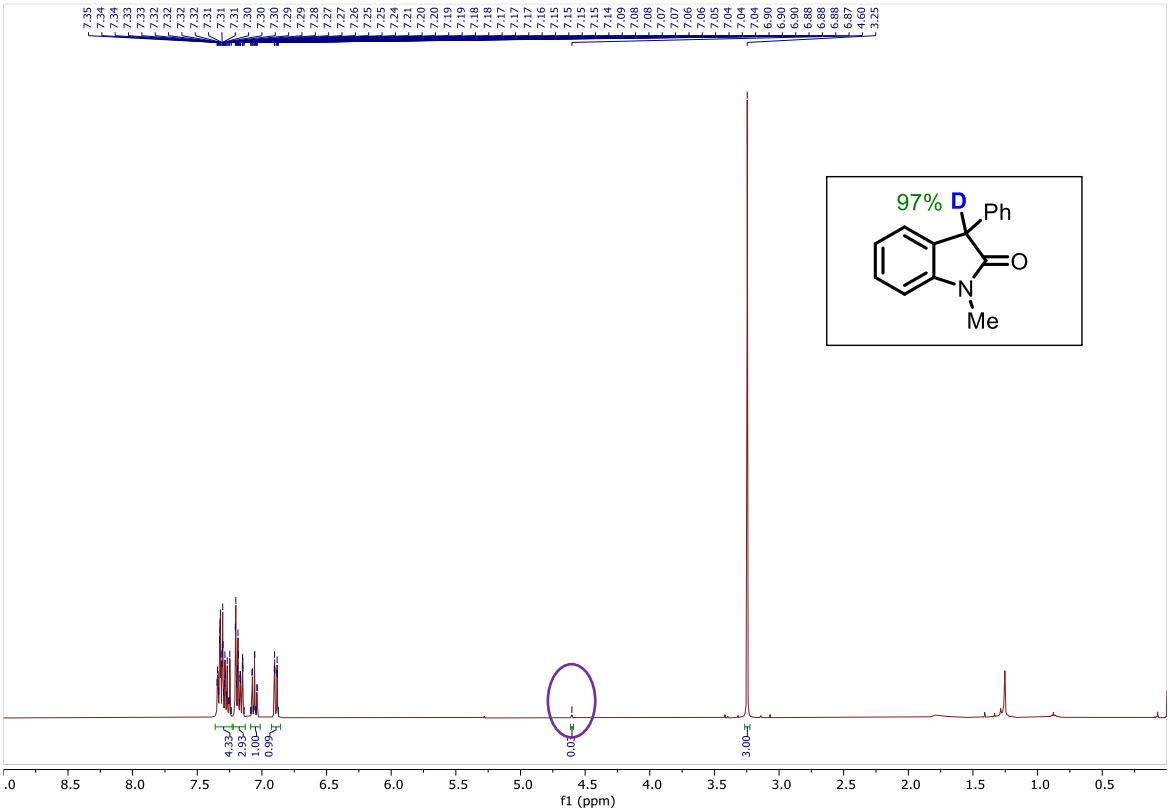
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Acenaphthylen-1(2*H*)-one-2,2-d_2 (3v)**



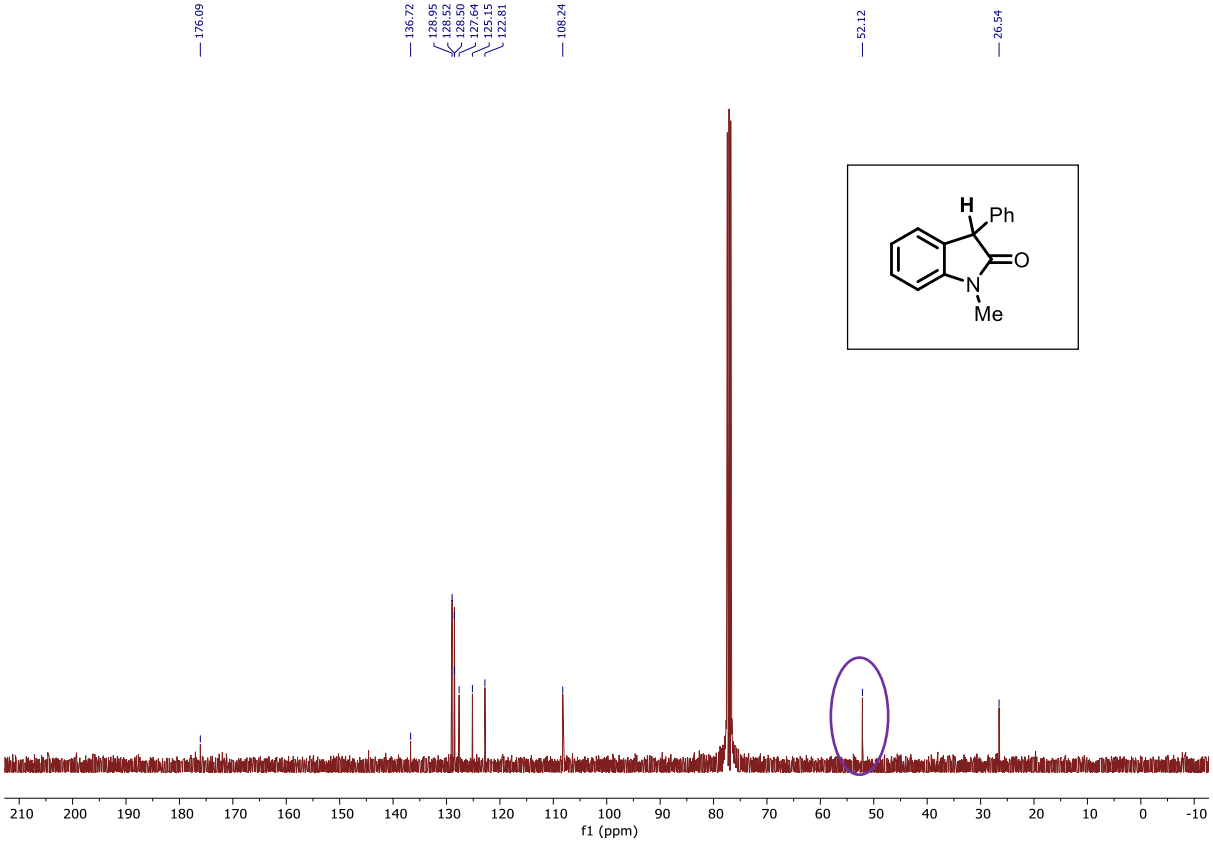
^{1}H NMR (400 MHz, $CDCl_3$) of **1-Methyl-3-phenylindolin-2-one** (starting material of **3w**)



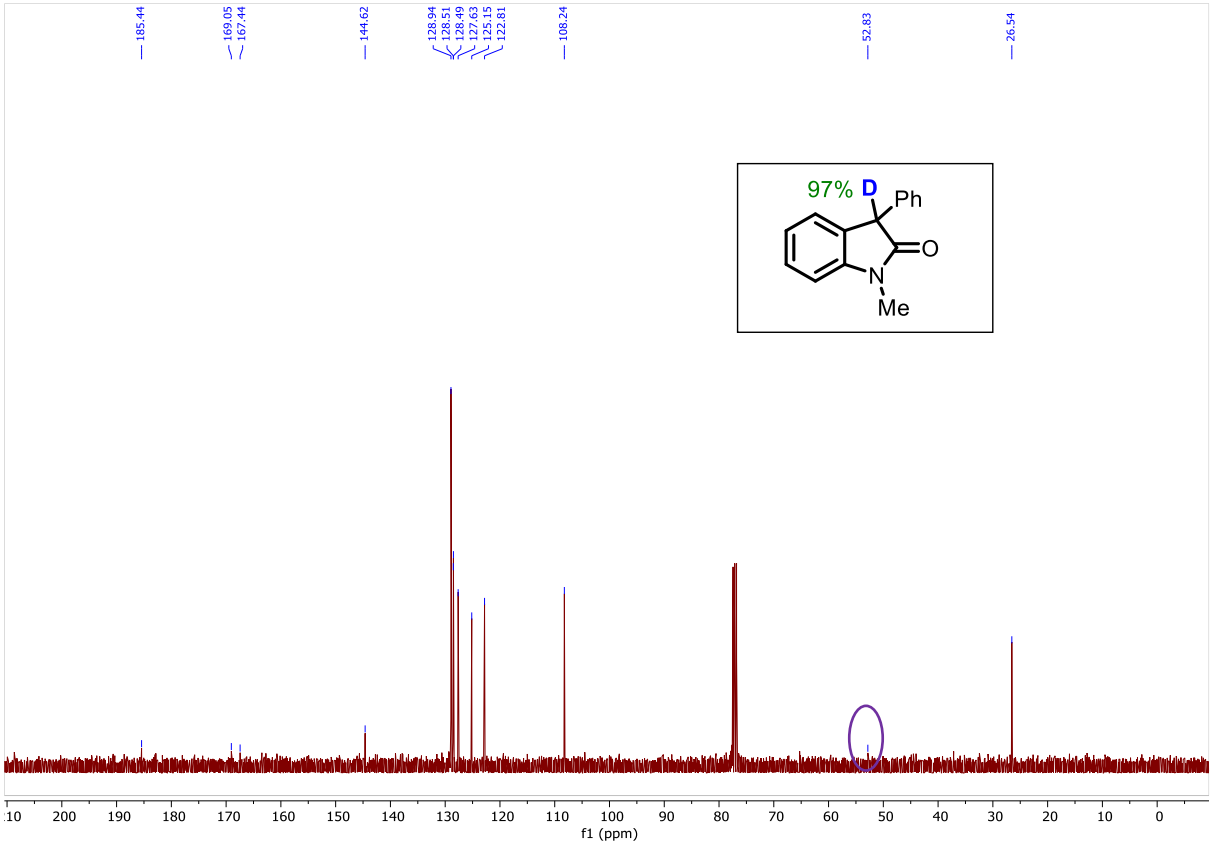
^{1}H NMR (400 MHz, $CDCl_3$) of **1-Methyl-3-phenylindolin-2-one-3-*d* (3w)**



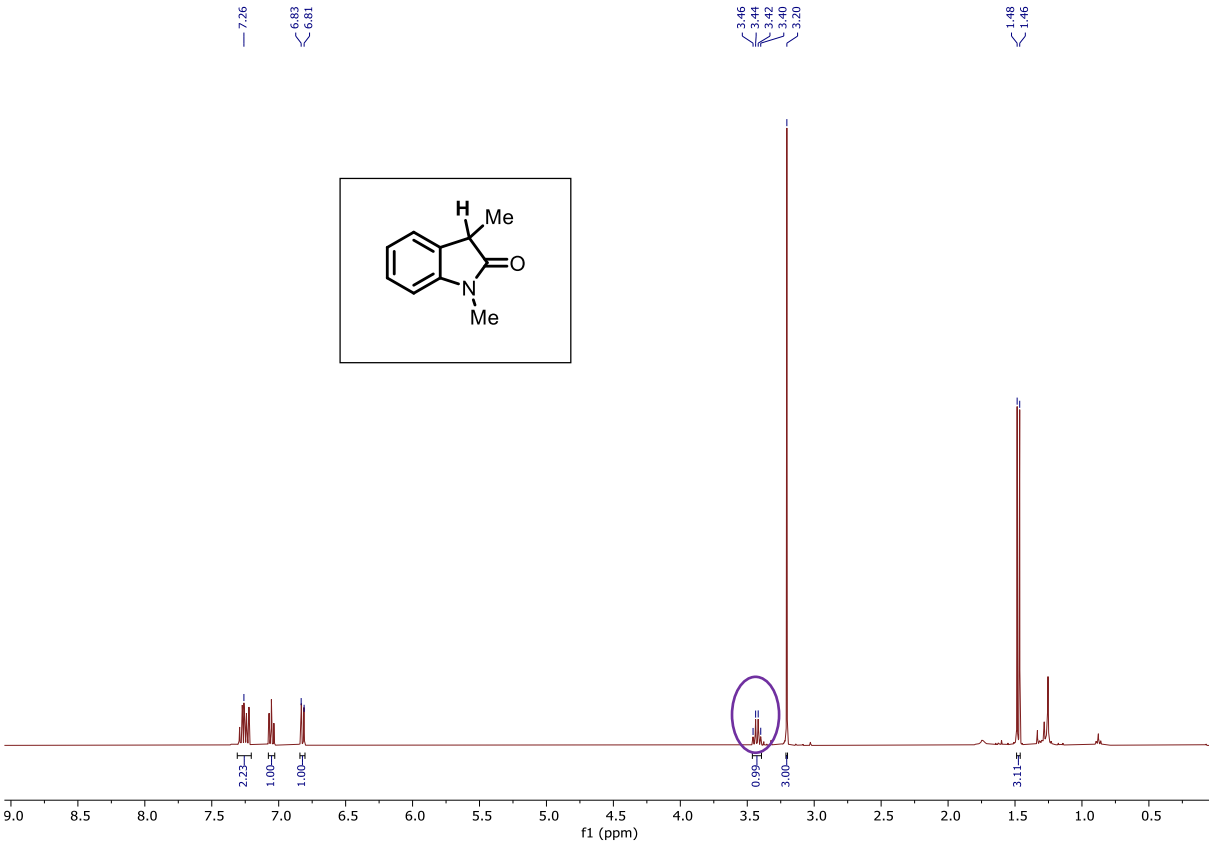
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-Methyl-3-phenylindolin-2-one** (starting material of **3w**)



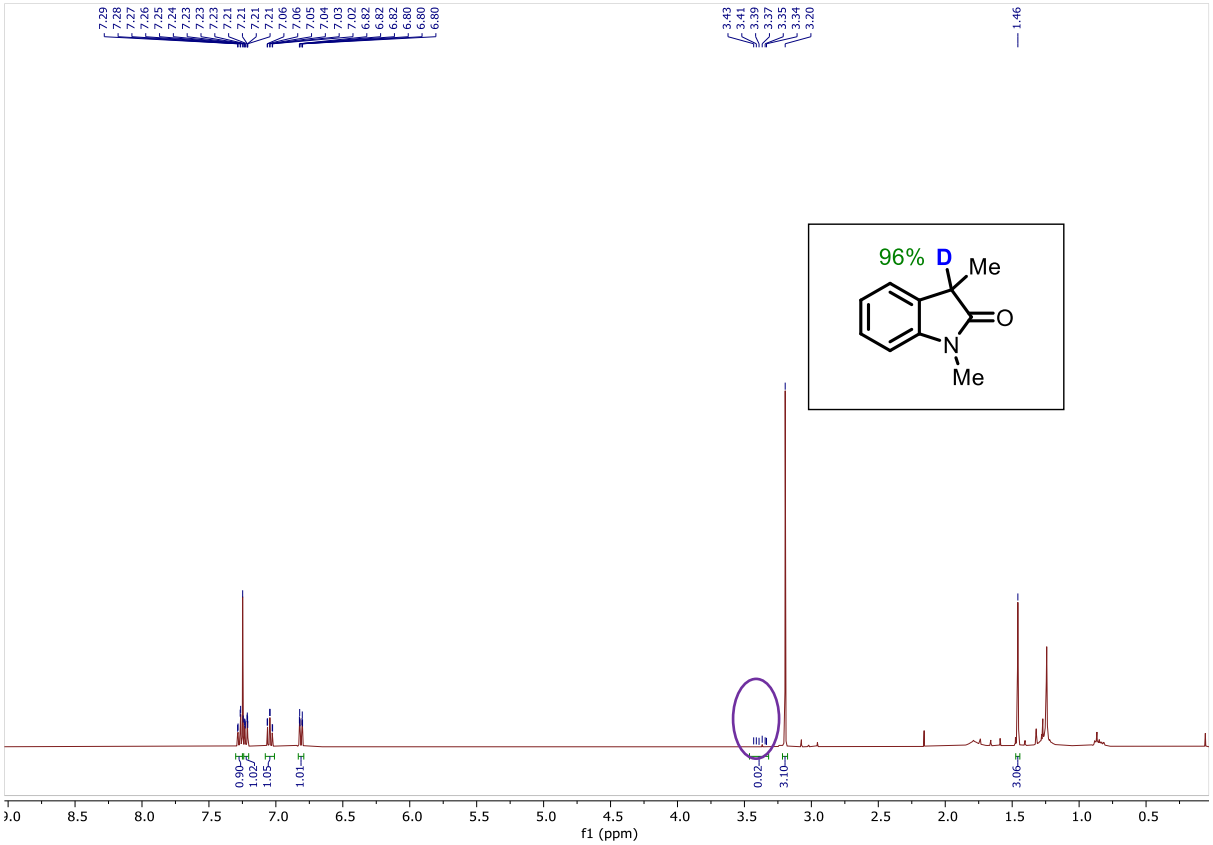
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-Methyl-3-phenylindolin-2-one-3-*d* (3w)**



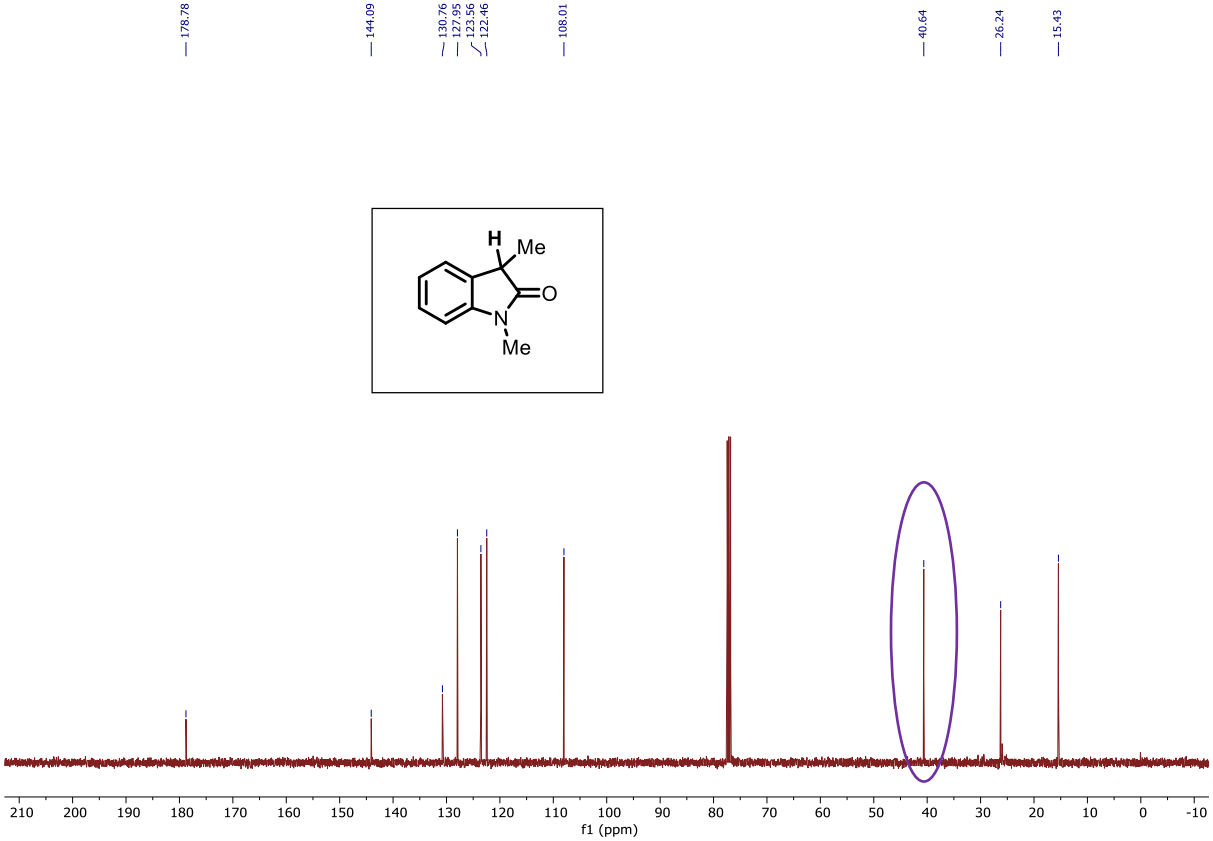
^{1}H NMR (400 MHz, $CDCl_3$) of **1,3-Dimethylindolin-2-one** (starting material of **3x**)



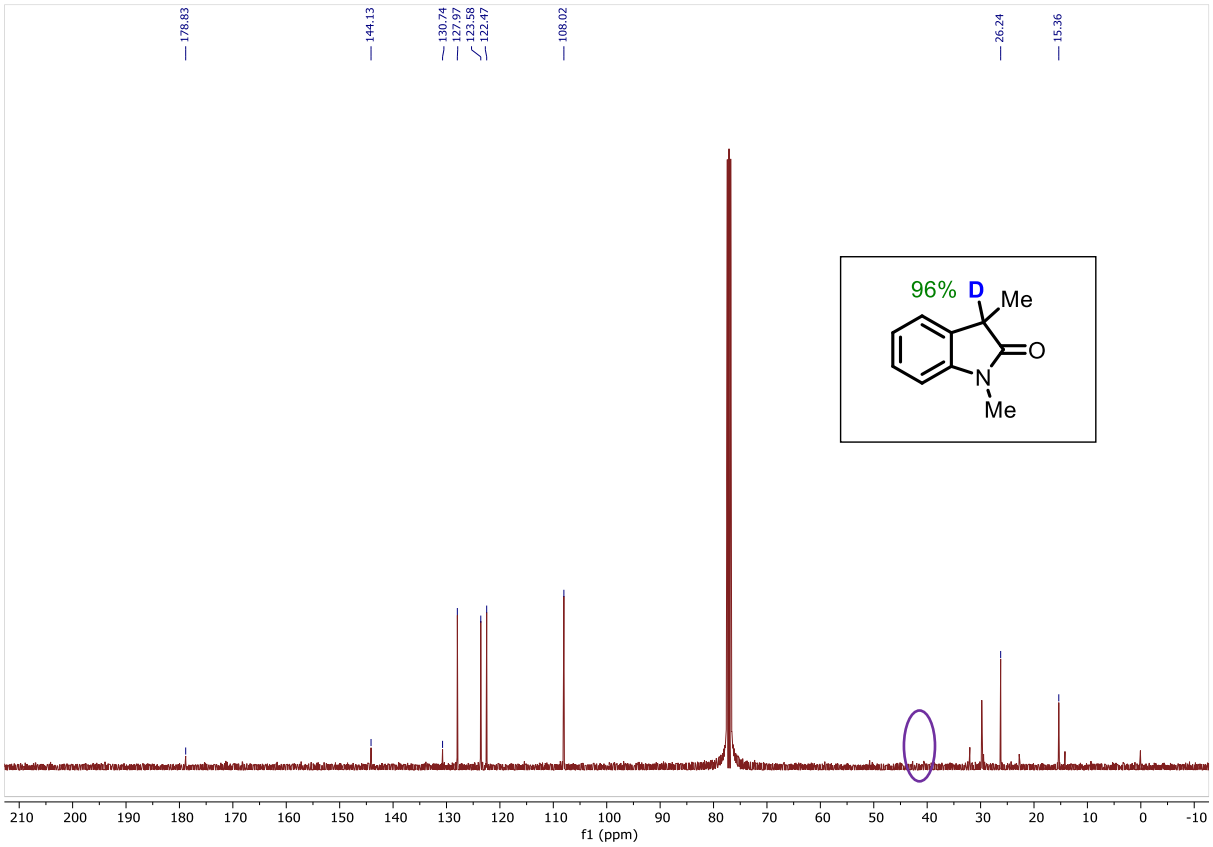
^{1}H NMR (400 MHz, $CDCl_3$) of **1,3-Dimethylindolin-2-one-3-*d* (3x)**



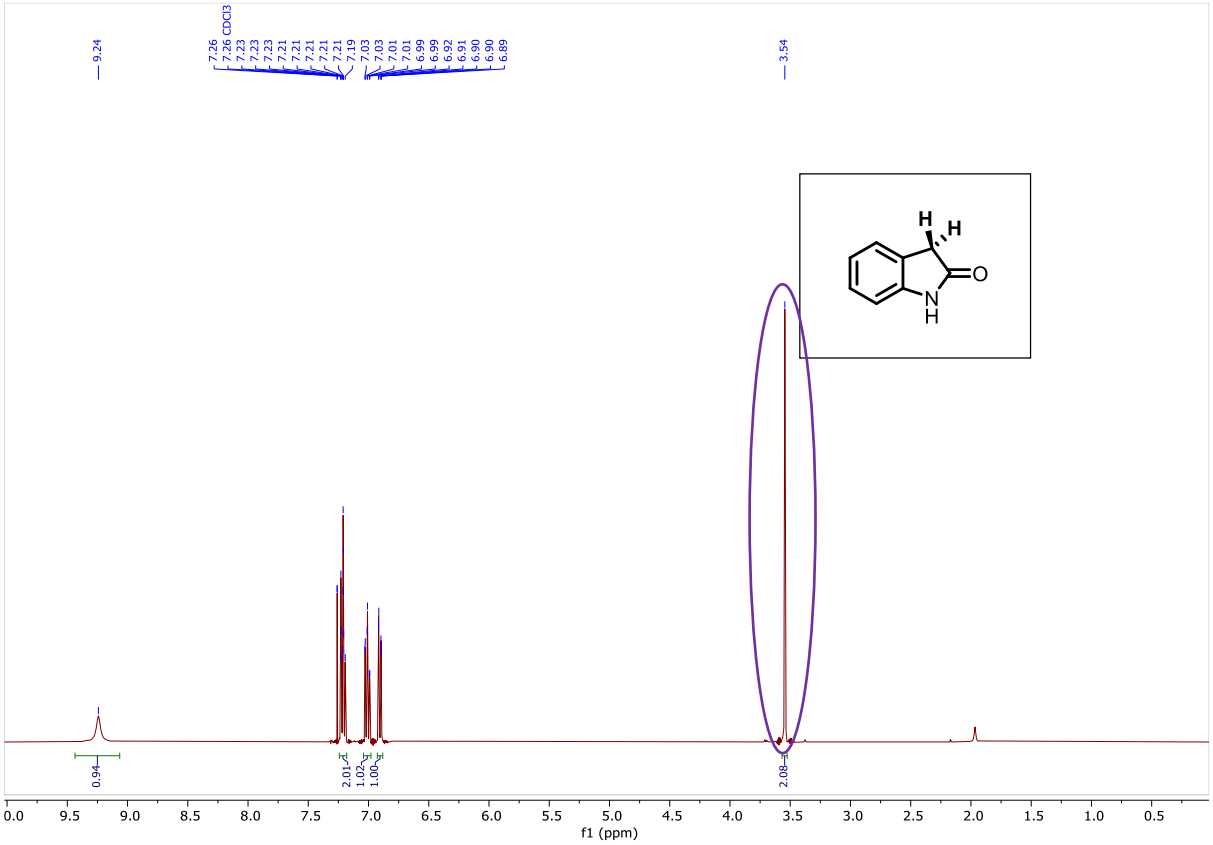
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1,3-Dimethylindolin-2-one** (starting material of **3x**)



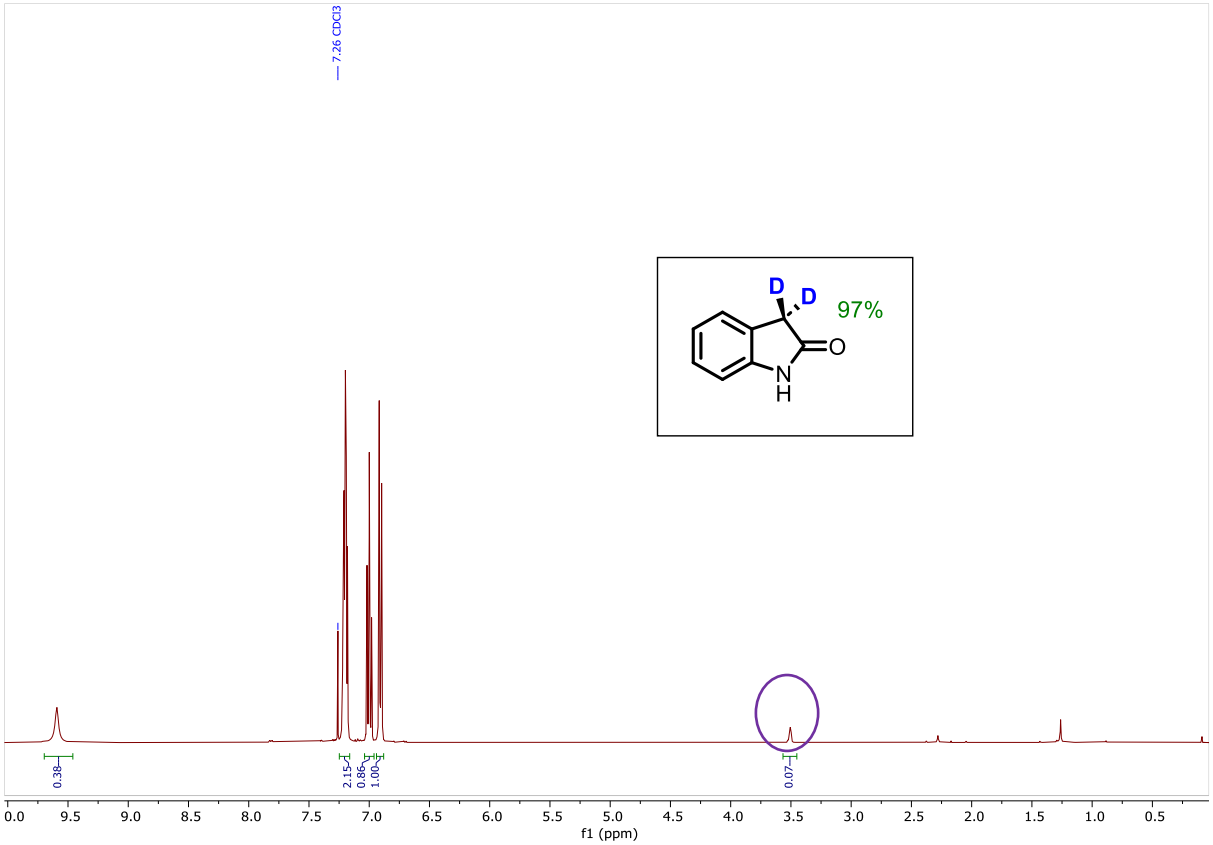
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1,3-Dimethylindolin-2-one-3-*d* (3x)**



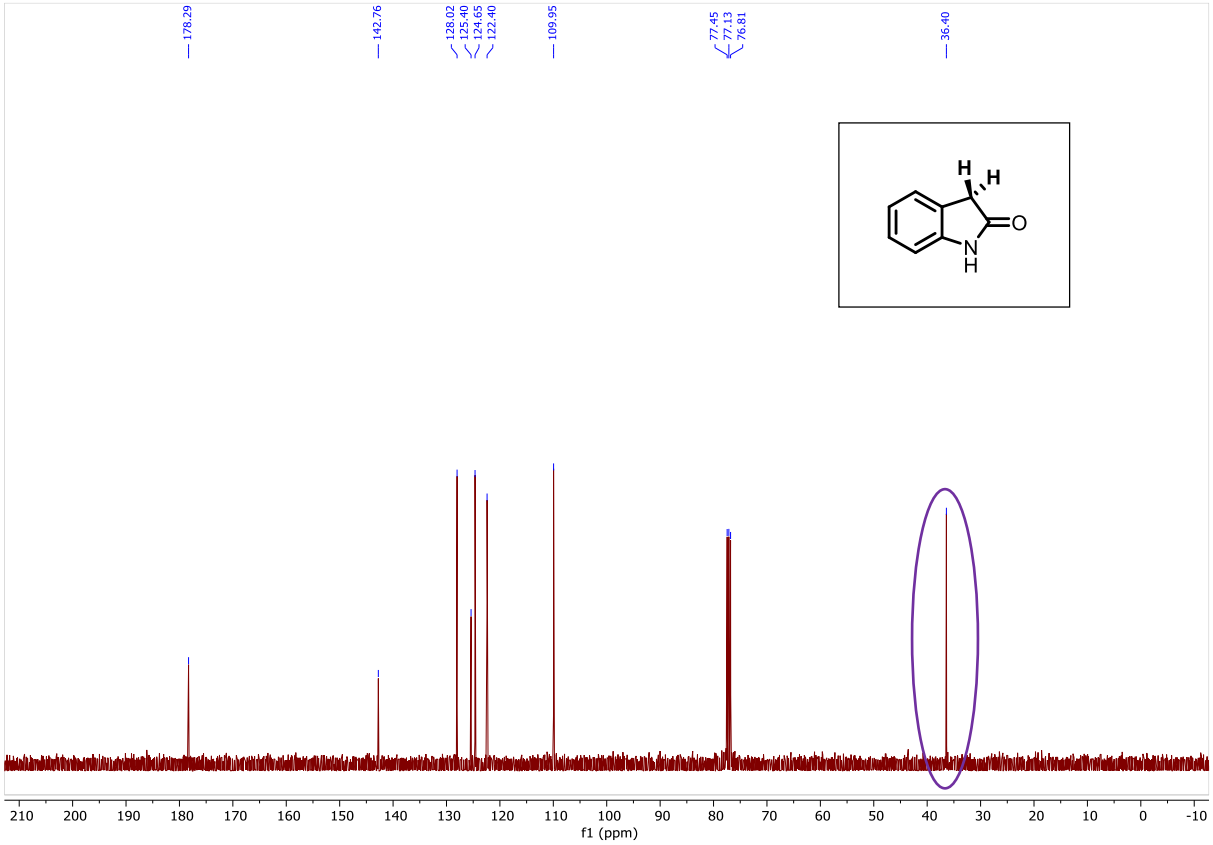
^{1}H NMR (400 MHz, $CDCl_3$) of **Indolin-2-one** (starting material of **3y**)



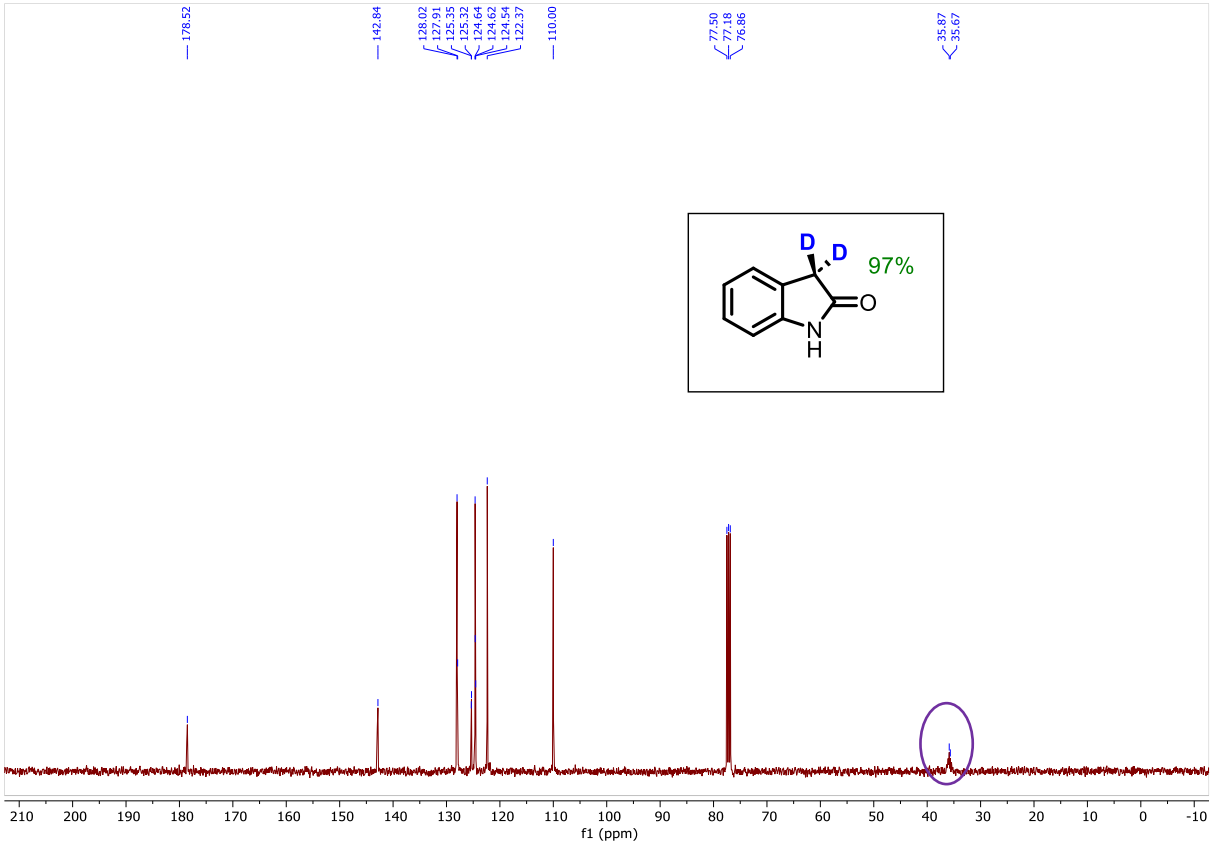
^{1}H NMR (400 MHz, $CDCl_3$) of **Indolin-2-one-3,3-d_2 (3y)**



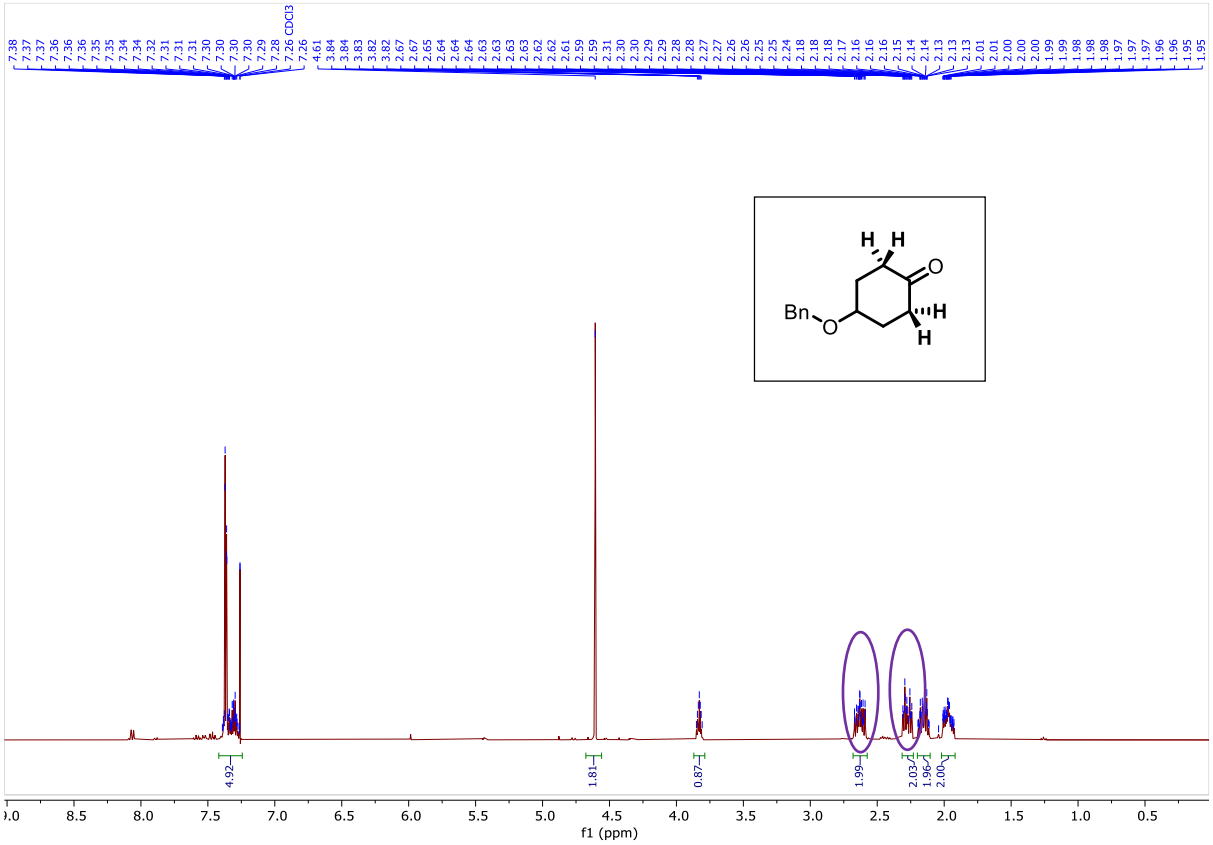
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Indolin-2-one** (starting material of **3y**)



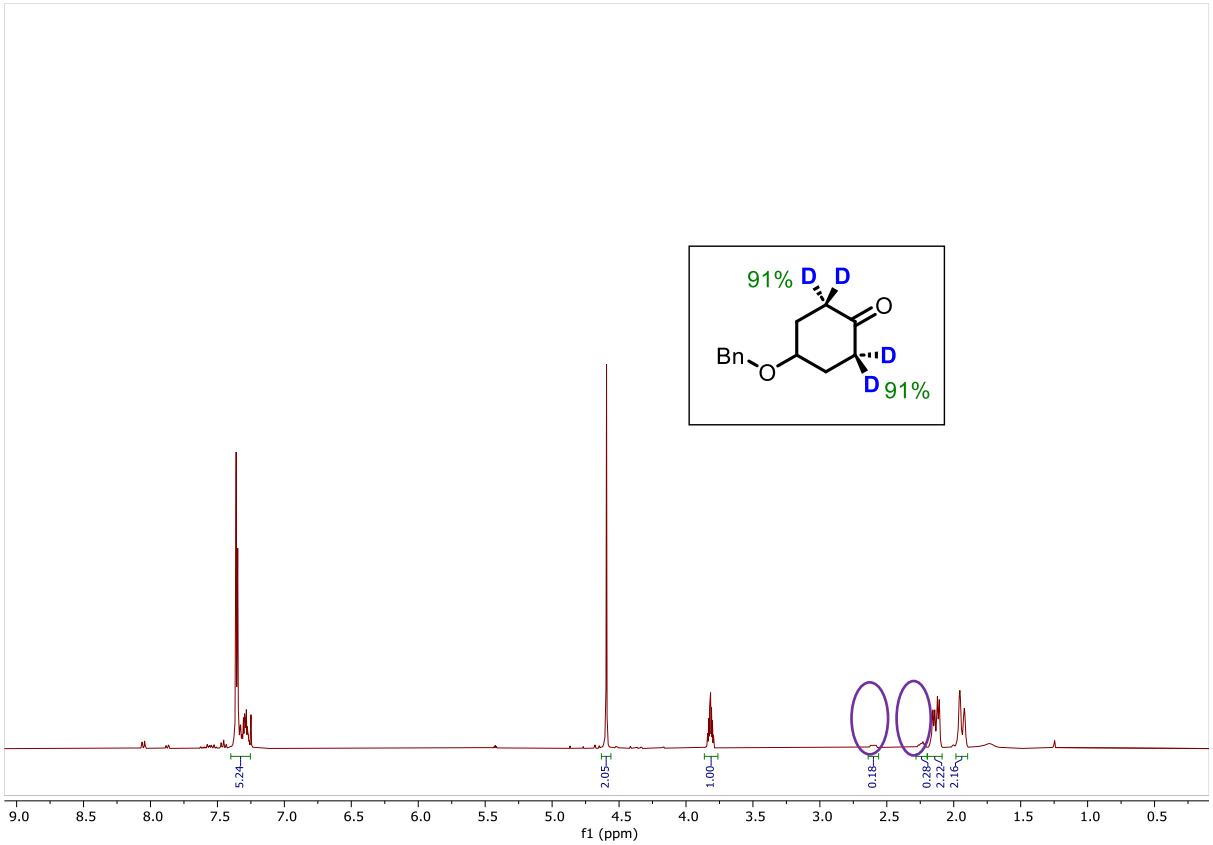
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Indolin-2-one-3,3-d_2 (3y)**



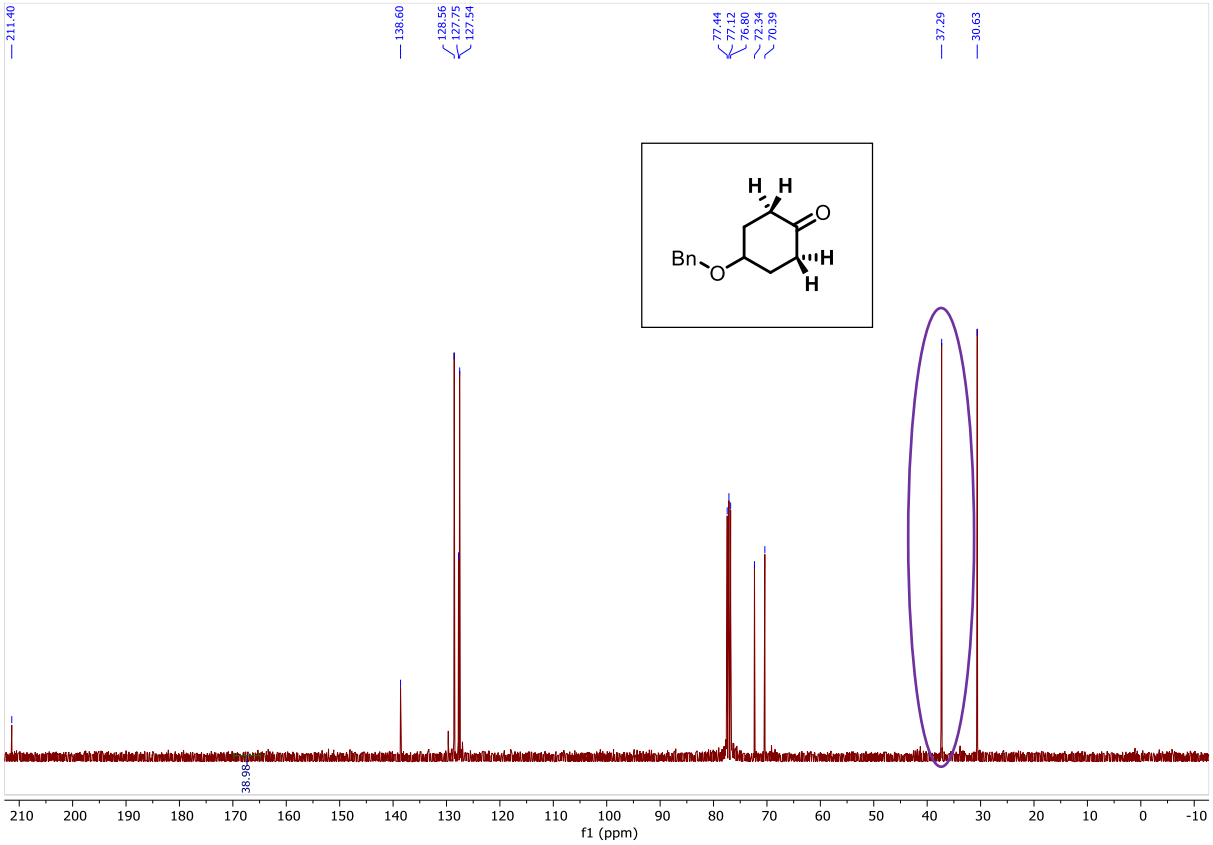
^{1}H NMR (400 MHz, $CDCl_3$) of **4-(Benzyloxy)cyclohexan-1-one** (starting material of **3z**)



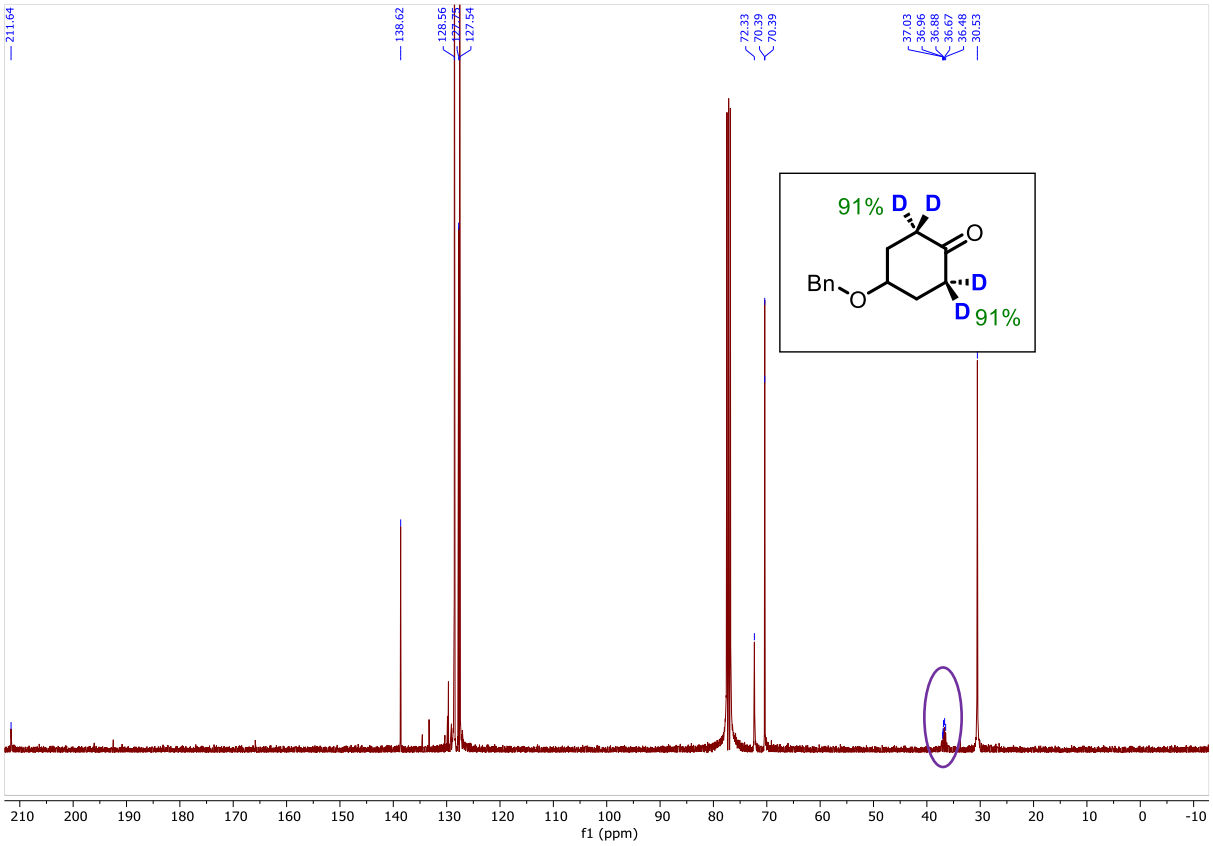
^{1}H NMR (400 MHz, $CDCl_3$) of **4-(Benzyloxy)cyclohexan-1-one-2,2,6,6-*d*$_4$ (3z)**



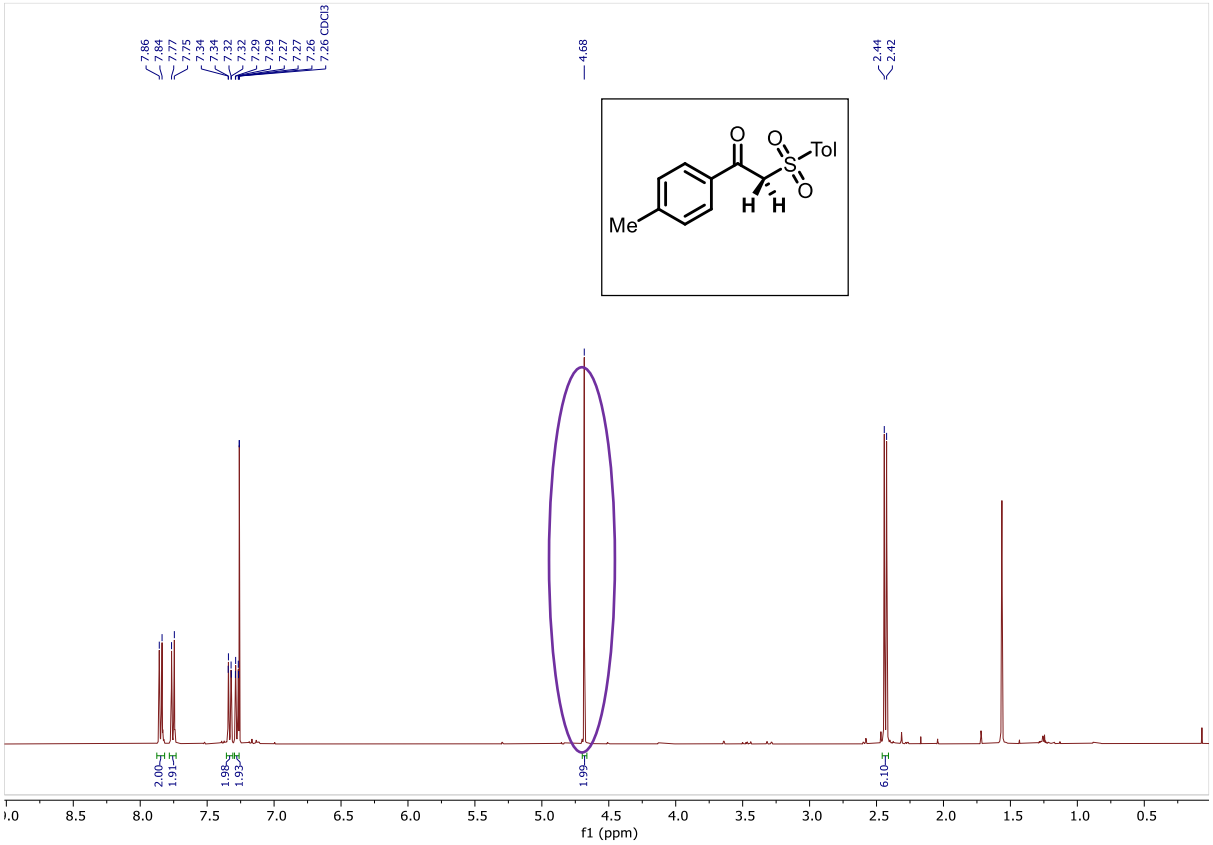
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **4-(Benzyloxy)cyclohexan-1-one** (starting material of **3z**)



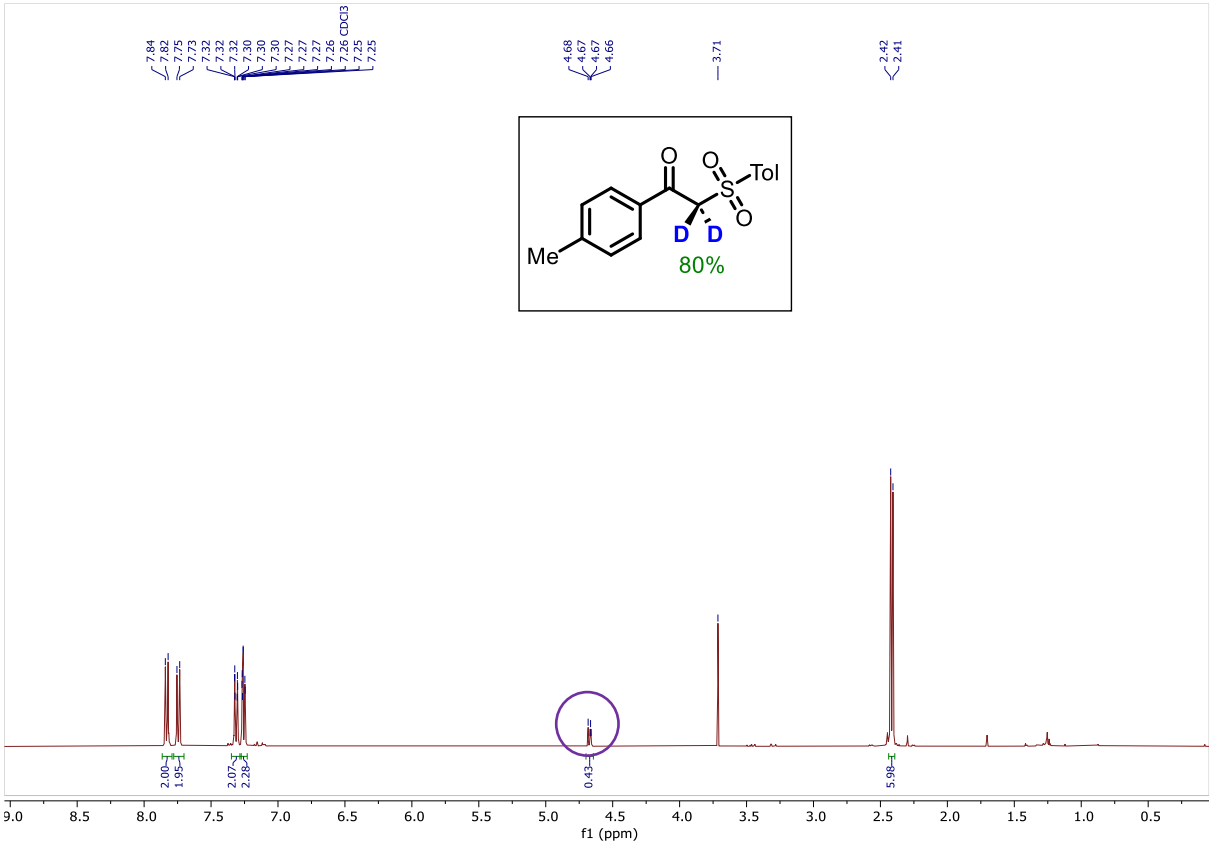
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **4-(Benzyloxy)cyclohexan-1-one-2,2,6,6-*d*$_4$ (3z)**



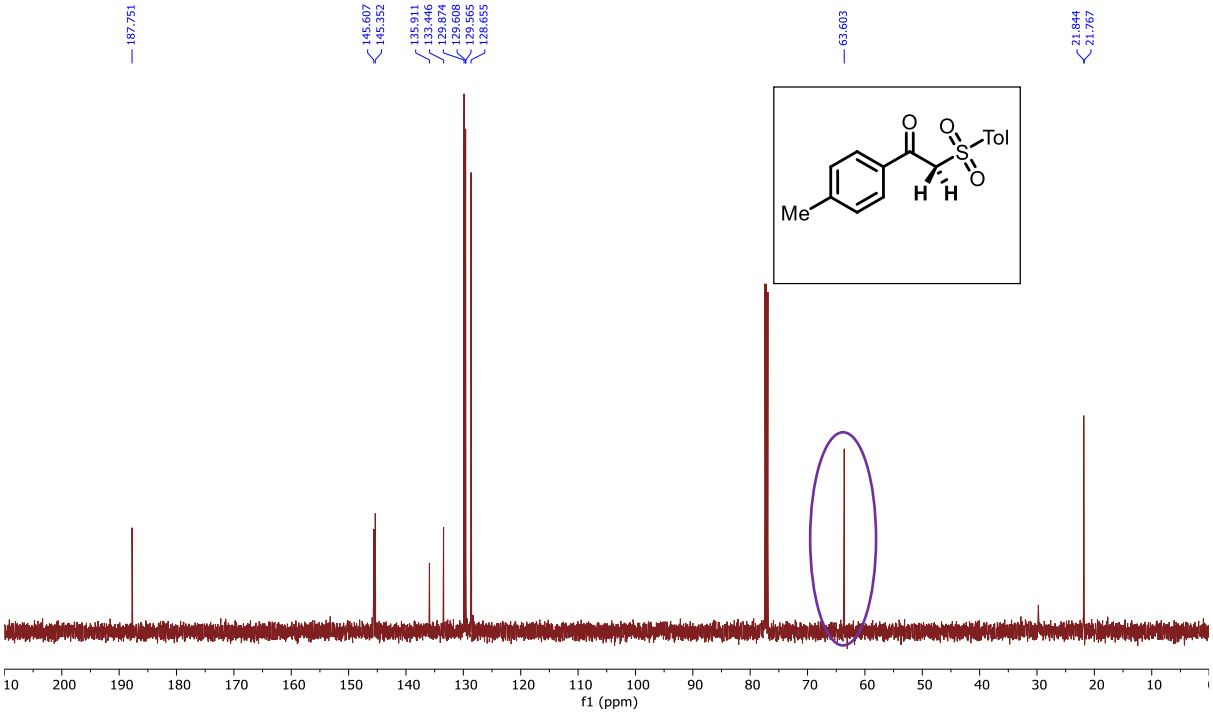
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(*p*-Tolyl)-2-tosylethan-1-one** (starting material of **3aa**)



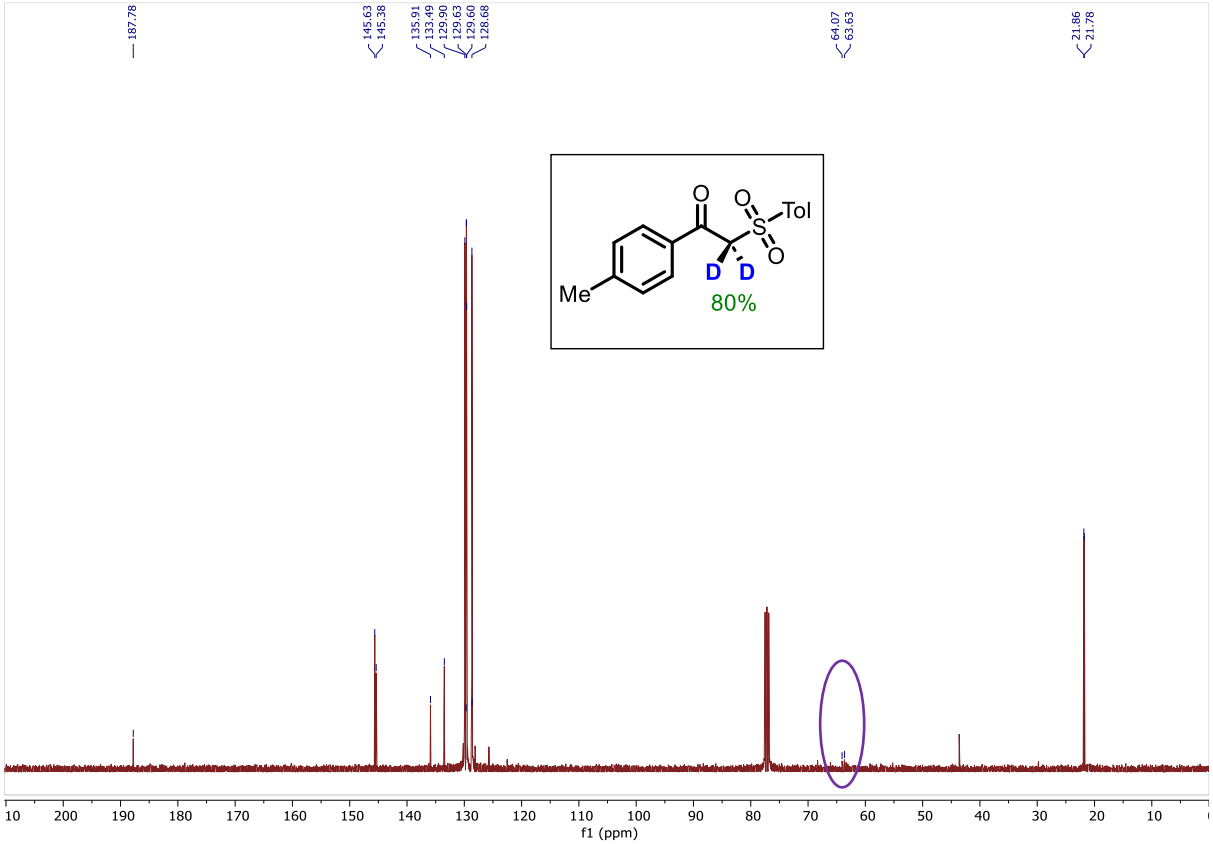
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(*p*-Tolyl)-2-tosylethan-1-one-2,2-d_2 (3aa)**



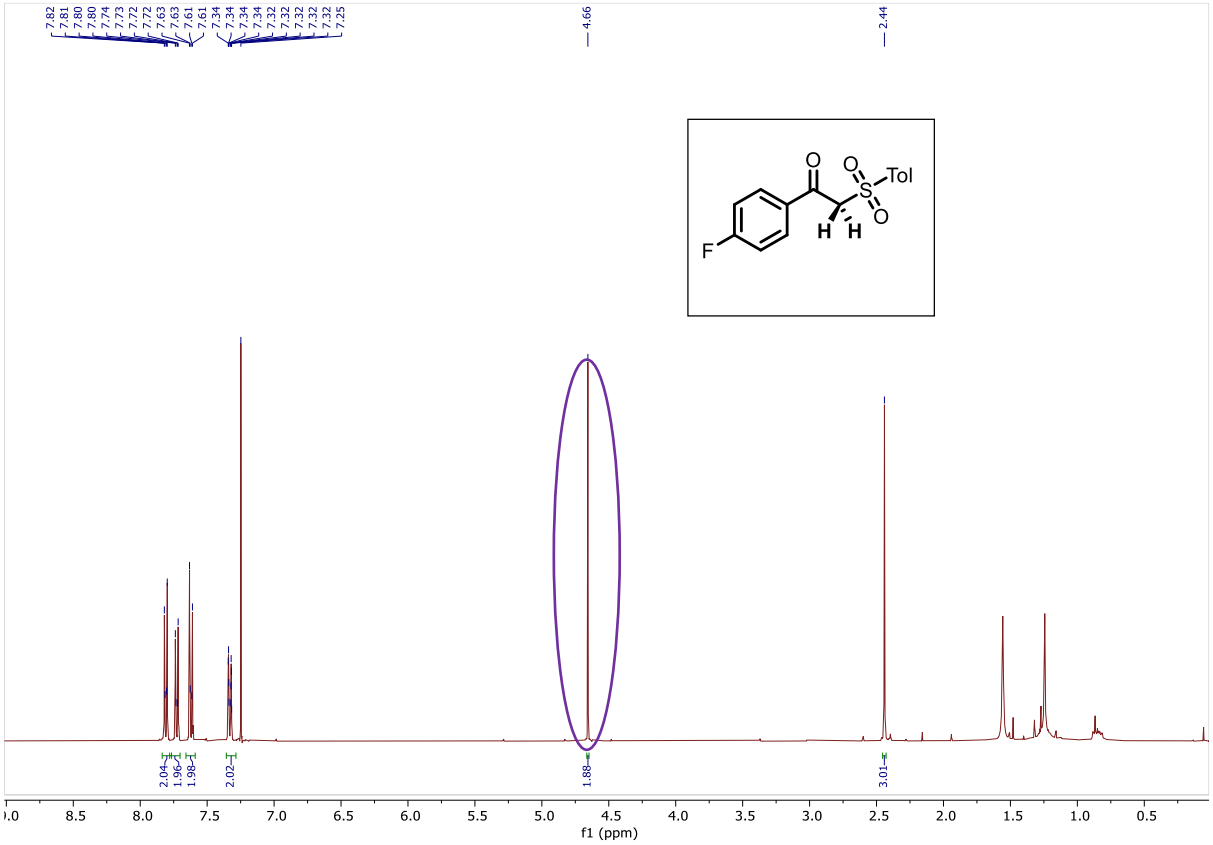
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(*p*-Tolyl)-2-tosylethan-1-one** (starting material of **3aa**)



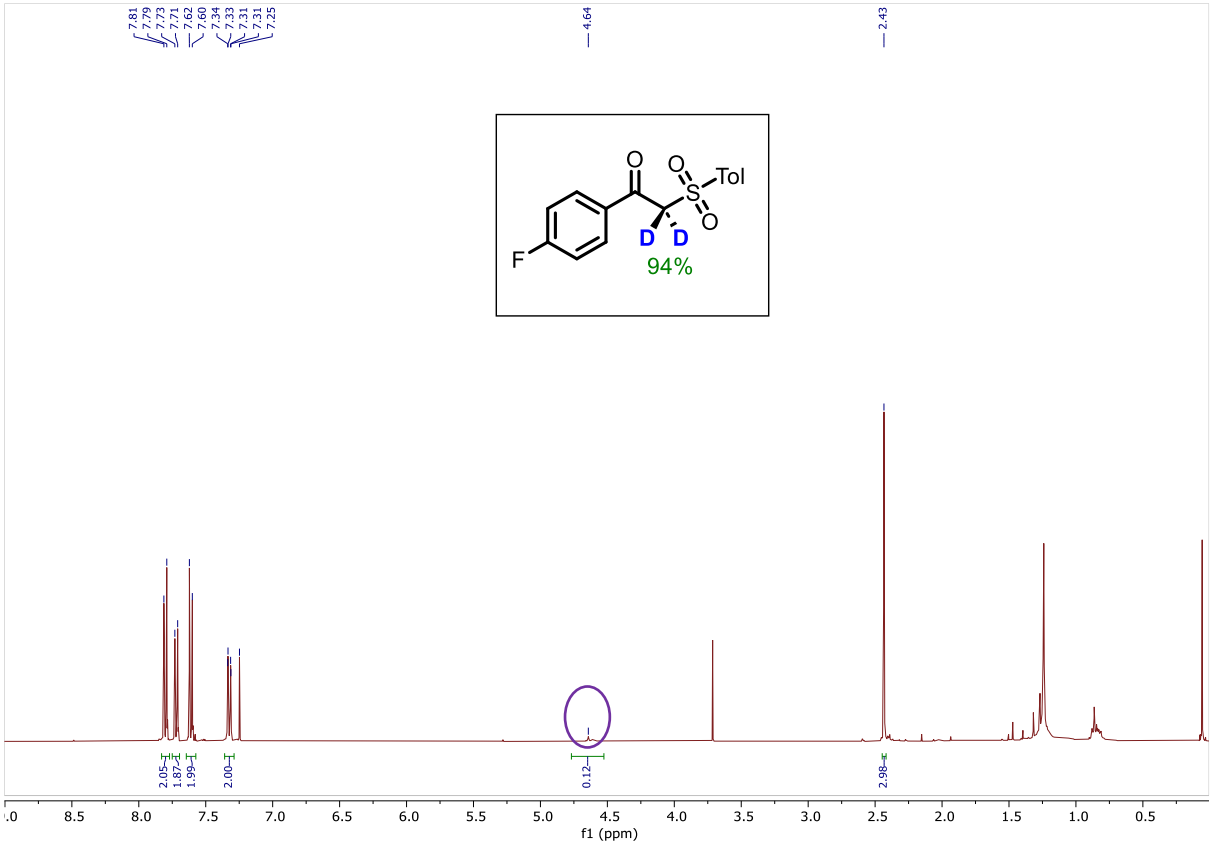
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(*p*-Tolyl)-2-tosylethan-1-one-2,2-d_2 (3aa)**



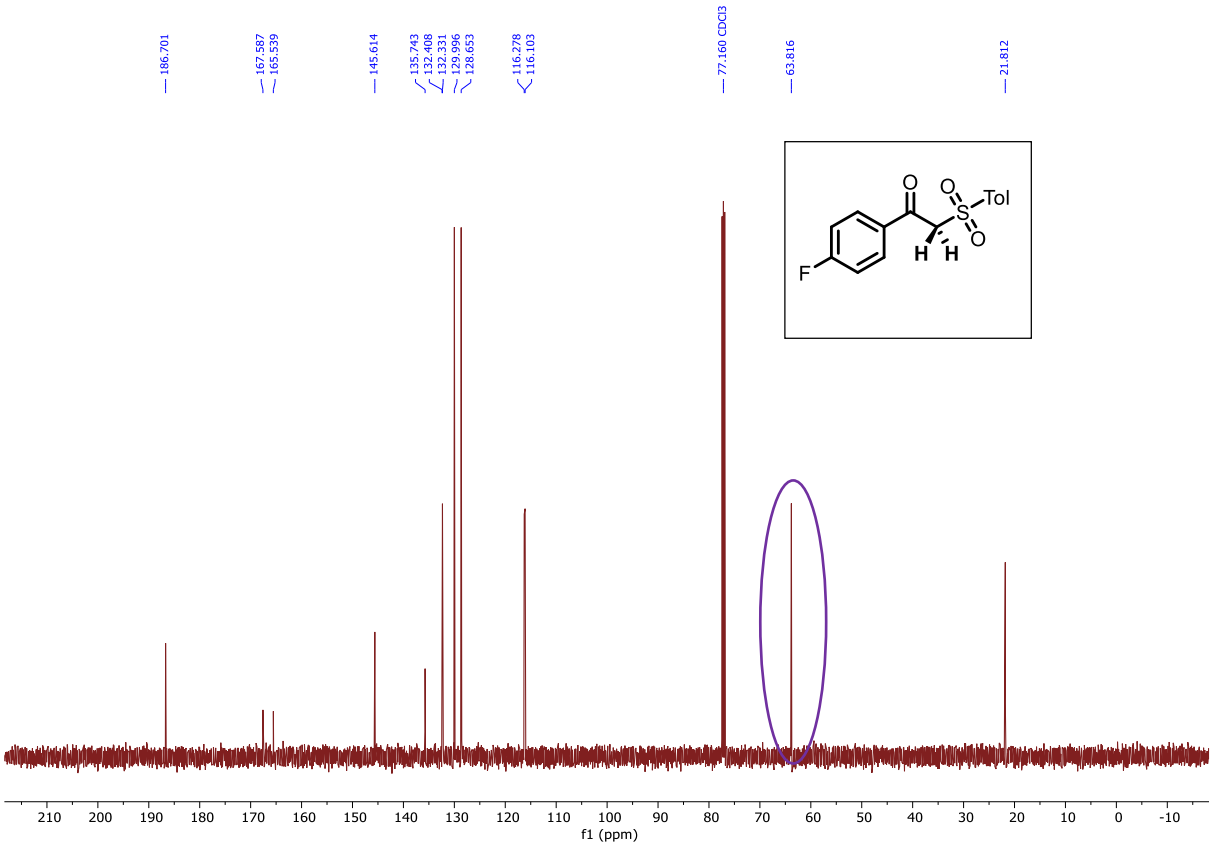
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(4-Fluorophenyl)-2-tosylethan-1-one** (starting material of **3ab**)



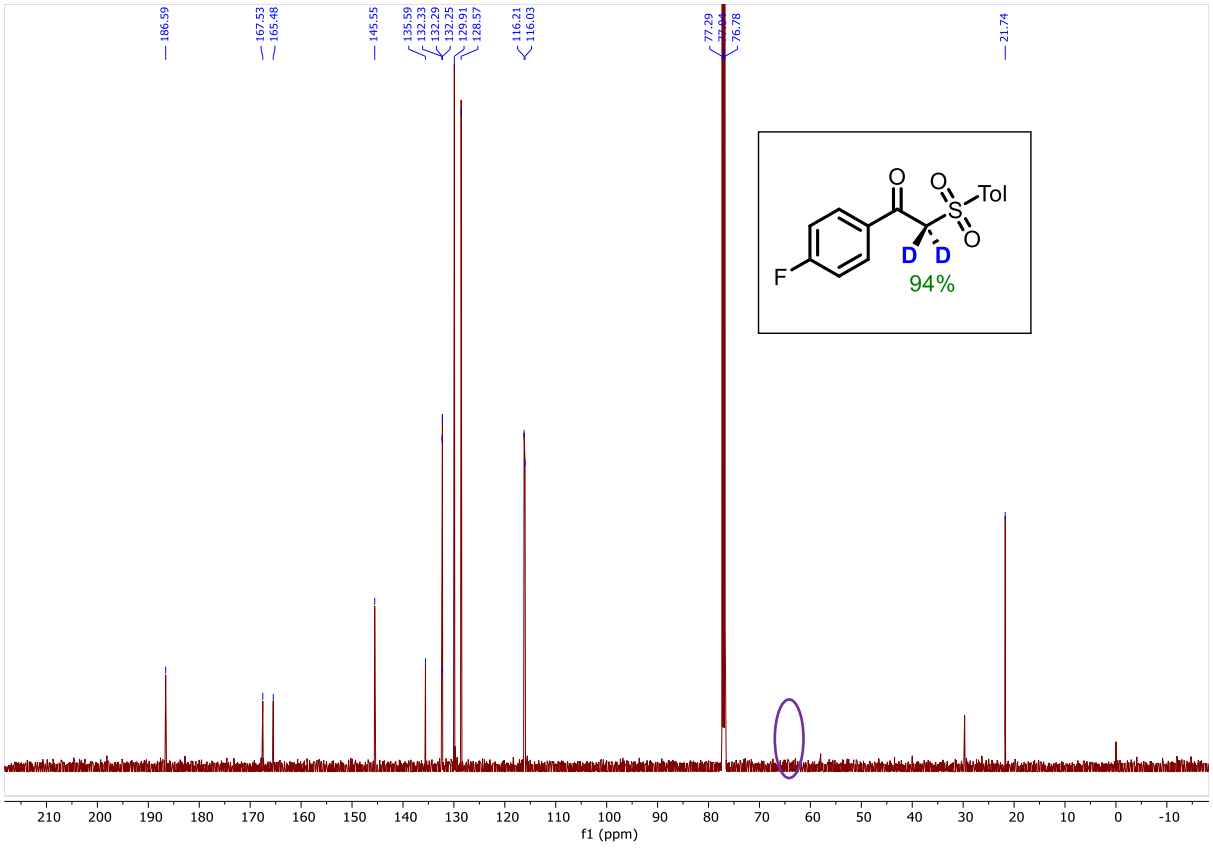
^{1}H NMR (500 MHz, $CDCl_3$) of **1-(4-Fluorophenyl)-2-tosylethan-1-one-2,2-d_2 (3ab)**



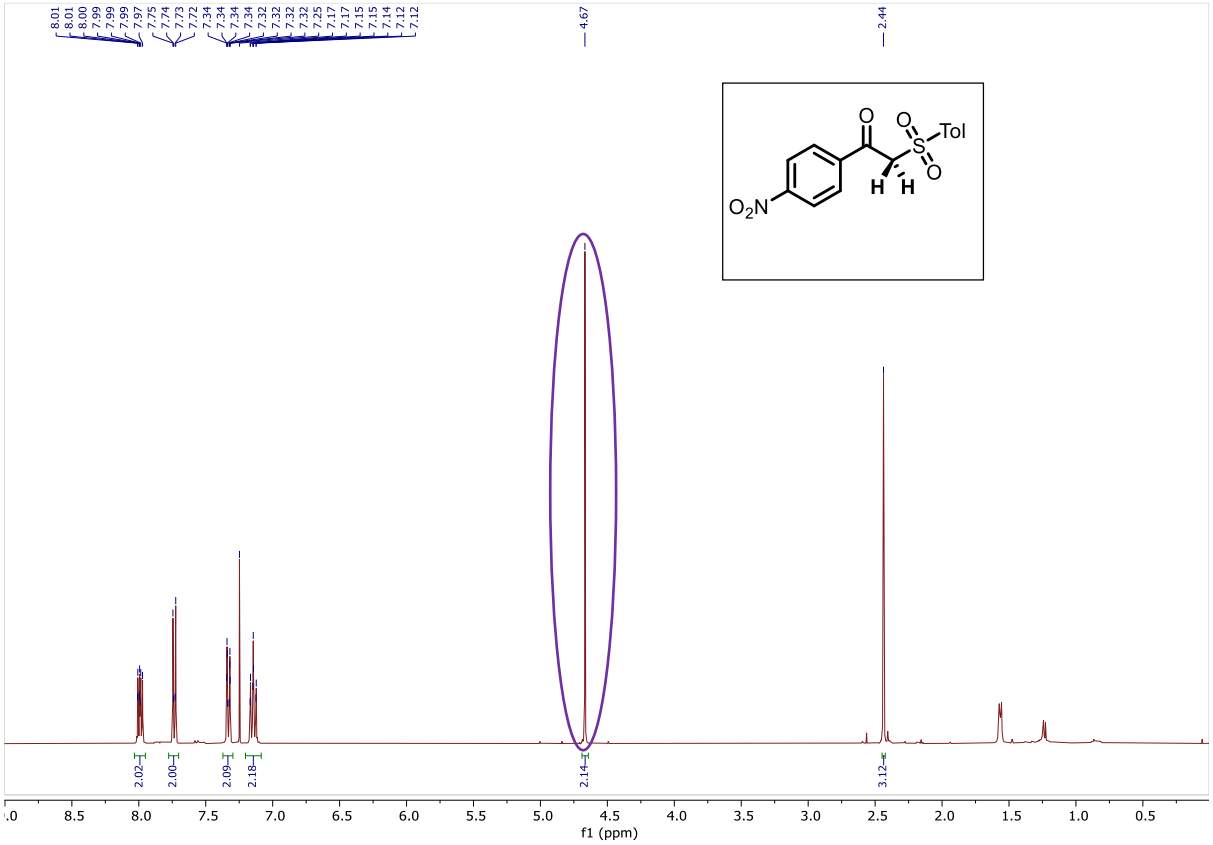
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(4-Fluorophenyl)-2-tosylethan-1-one** (starting material of **3ab**)



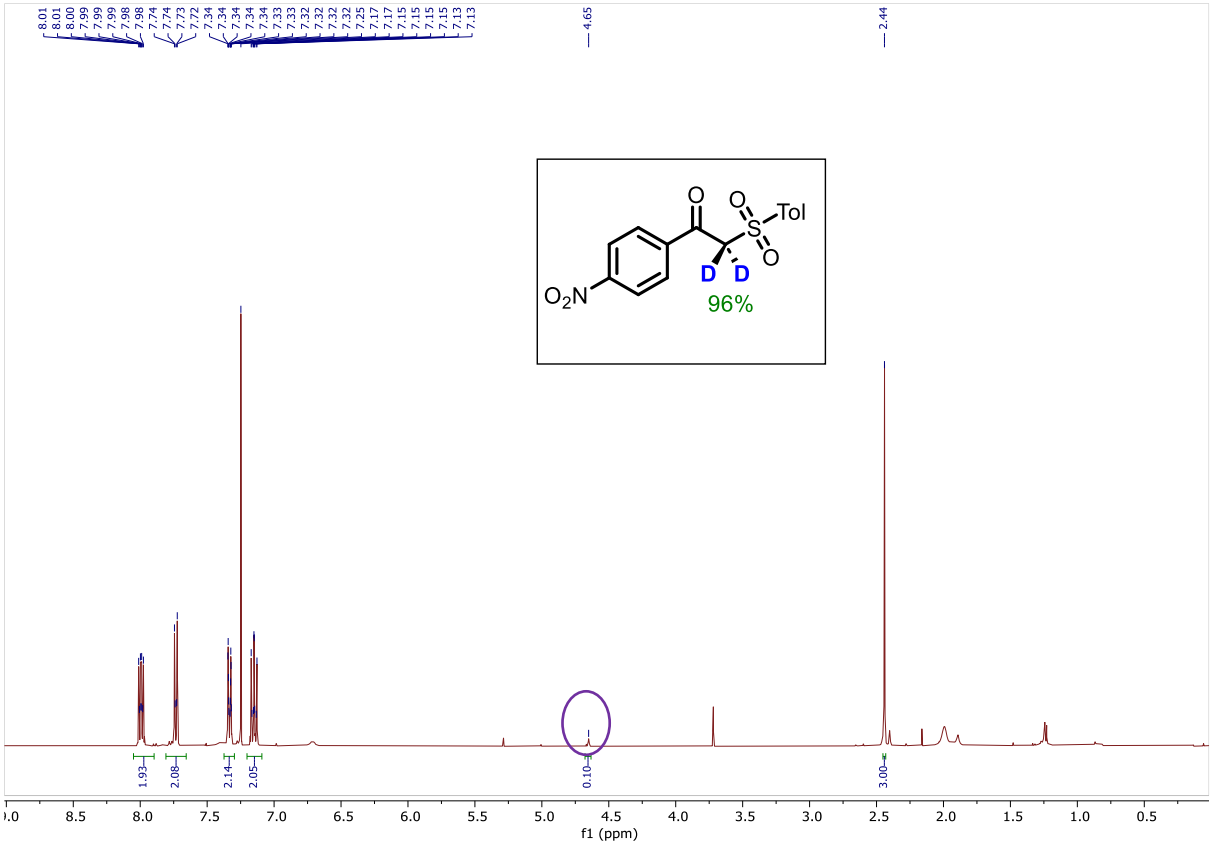
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) of **1-(4-Fluorophenyl)-2-tosylethan-1-one-2,2-d_2 (3ab)**



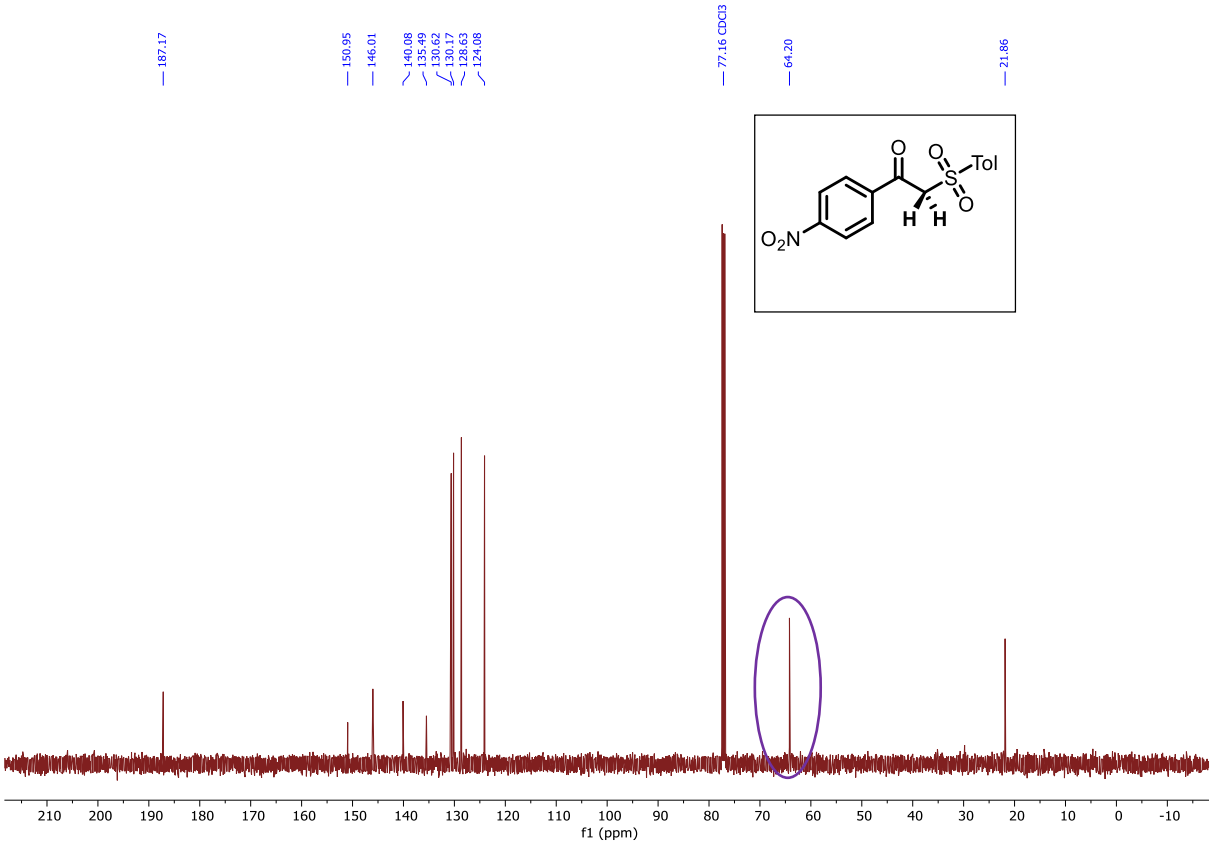
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(4-Nitrophenyl)-2-tosylethan-1-one** (starting material of **3ac**)



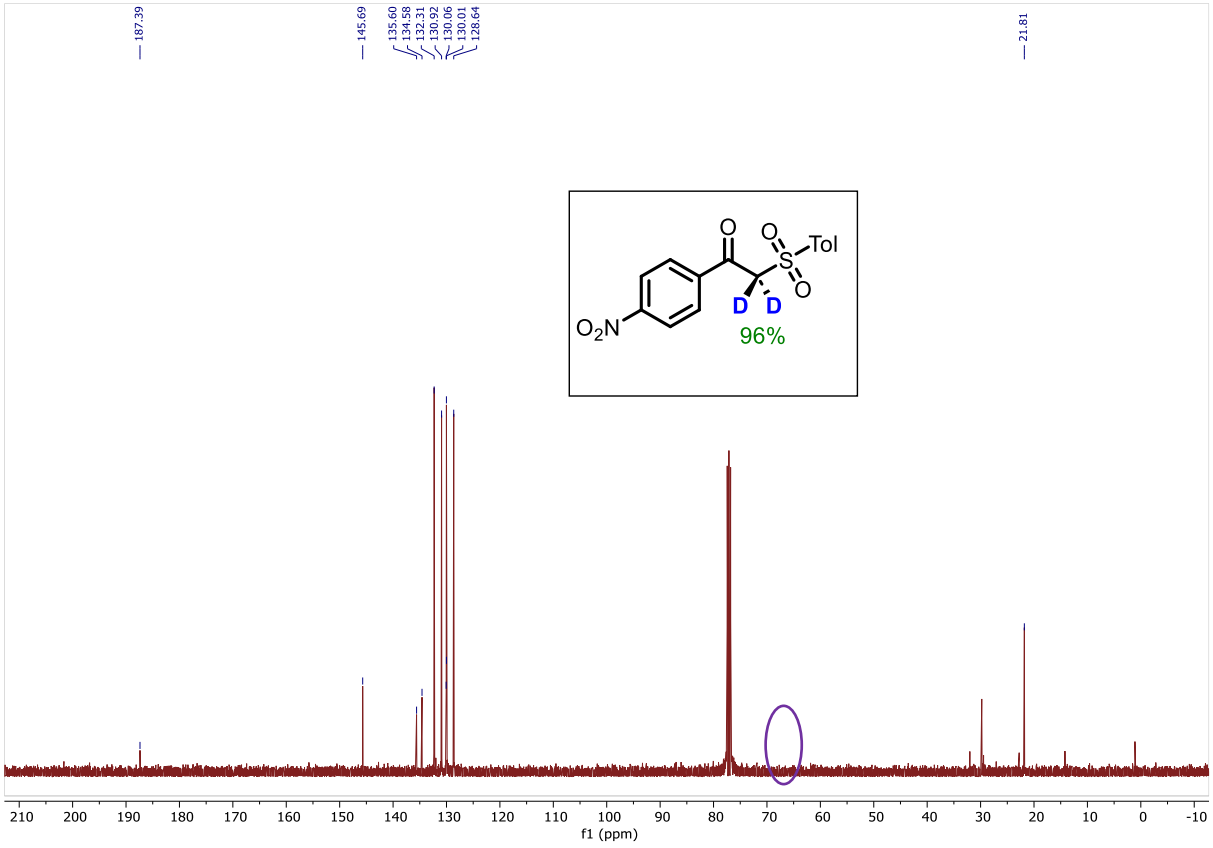
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(4-Nitrophenyl)-2-tosylethan-1-one-2,2-d_2 (3ac)**



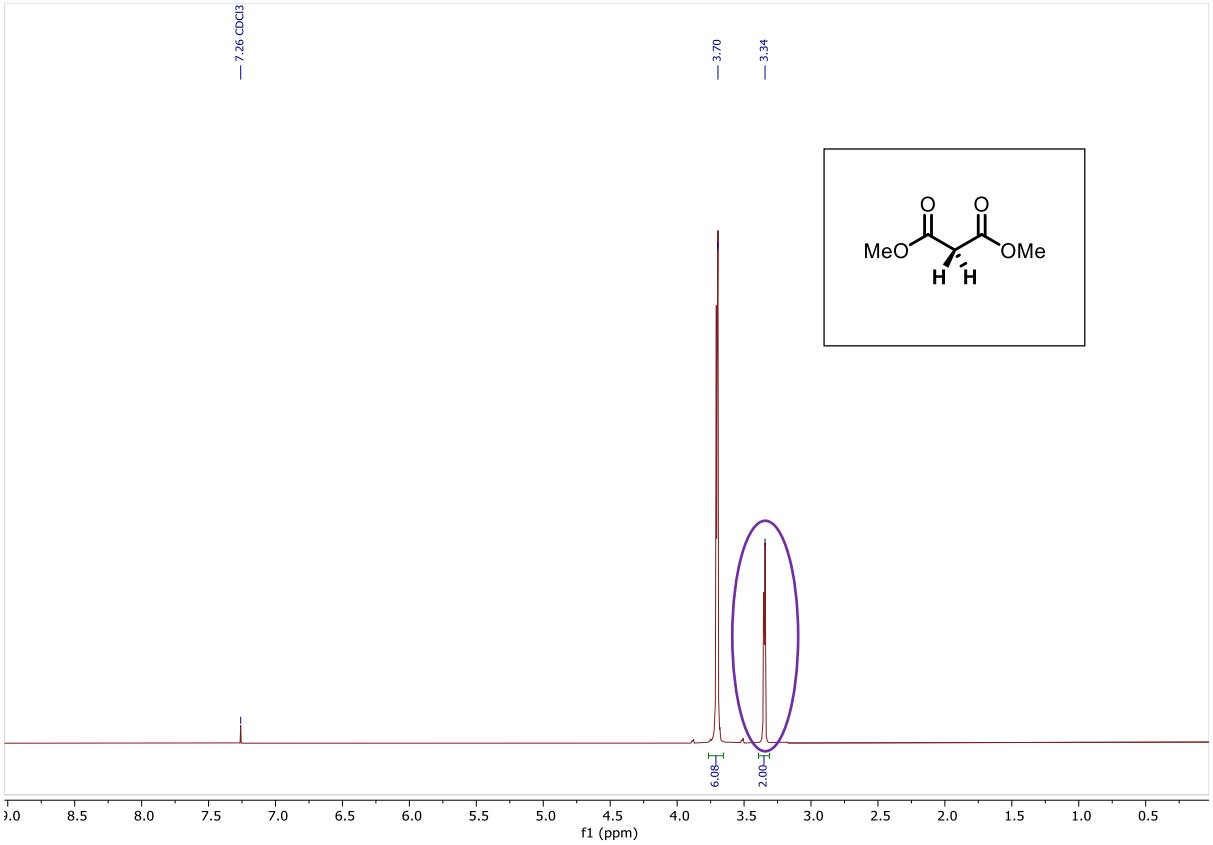
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(4-Nitrophenyl)-2-tosylethan-1-one** (starting material of **3ac**)



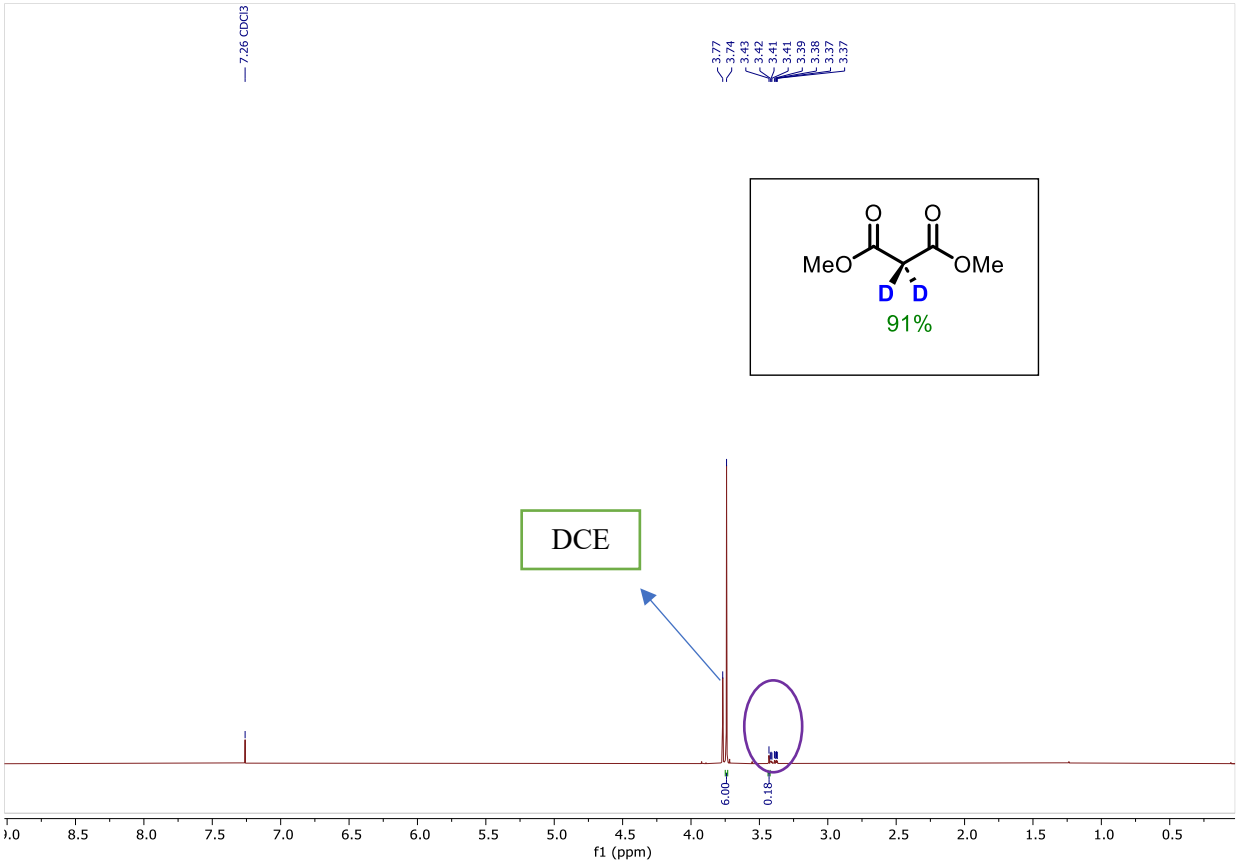
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(4-Nitrophenyl)-2-tosylethan-1-one-2,2-d_2 (3ac)**



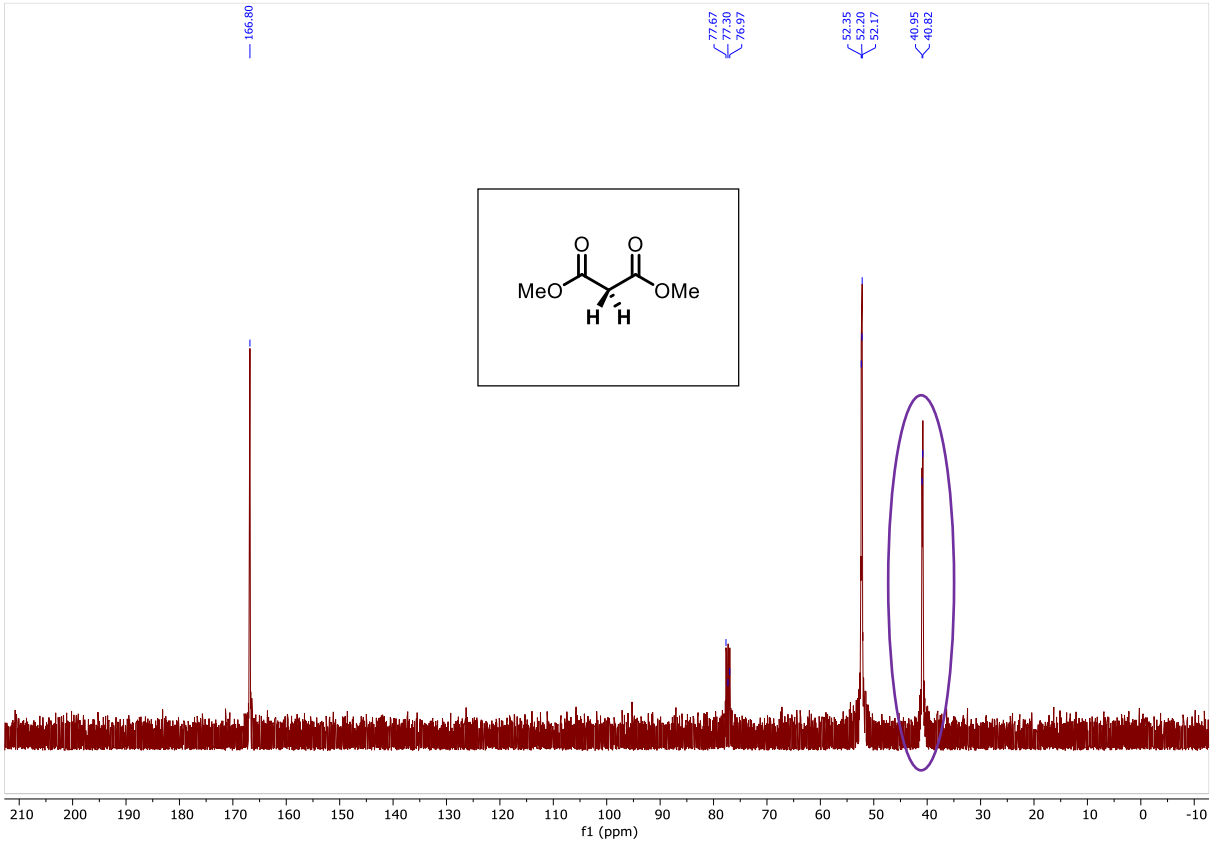
^{1}H NMR (400 MHz, $CDCl_3$) of **Dimethyl malonate** (starting material of **3ad**)



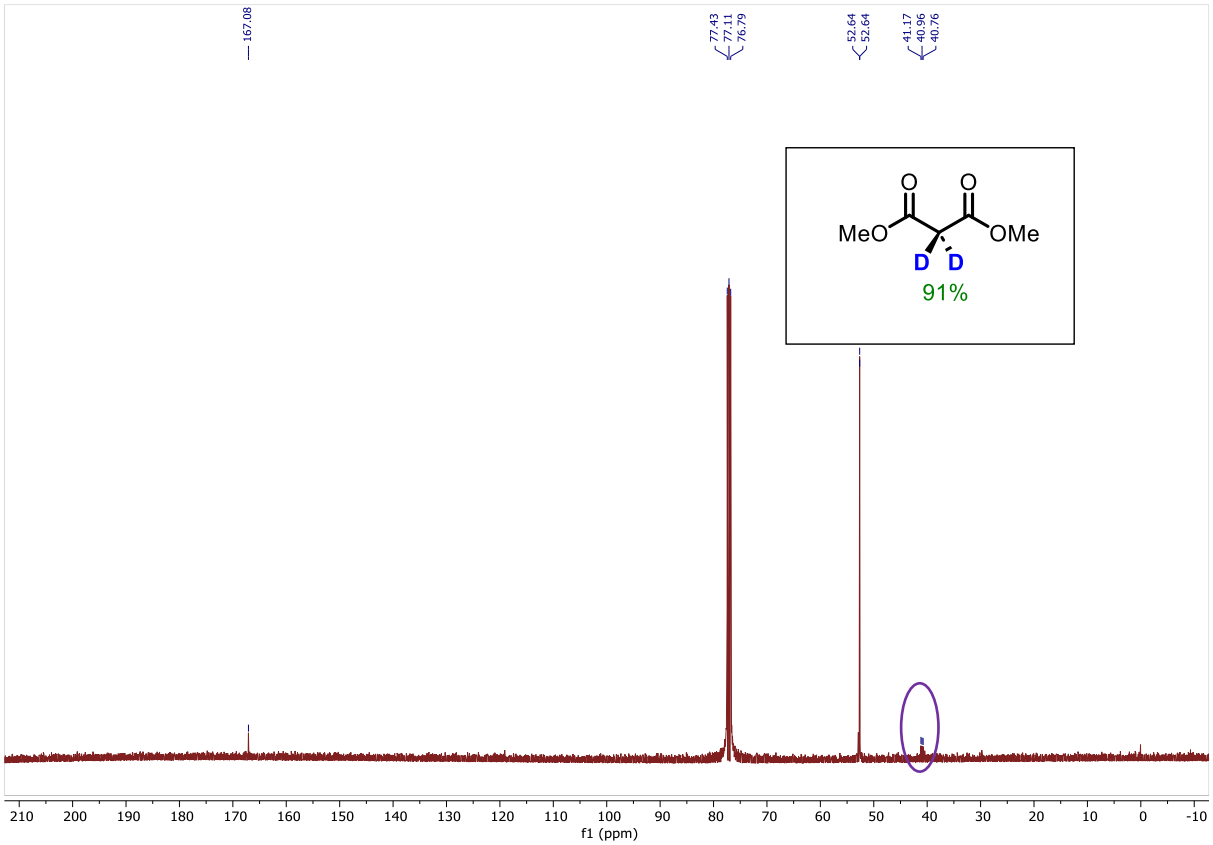
^{1}H NMR (400 MHz, $CDCl_3$) of **Dimethyl-malonate-d_2 (3ad)**



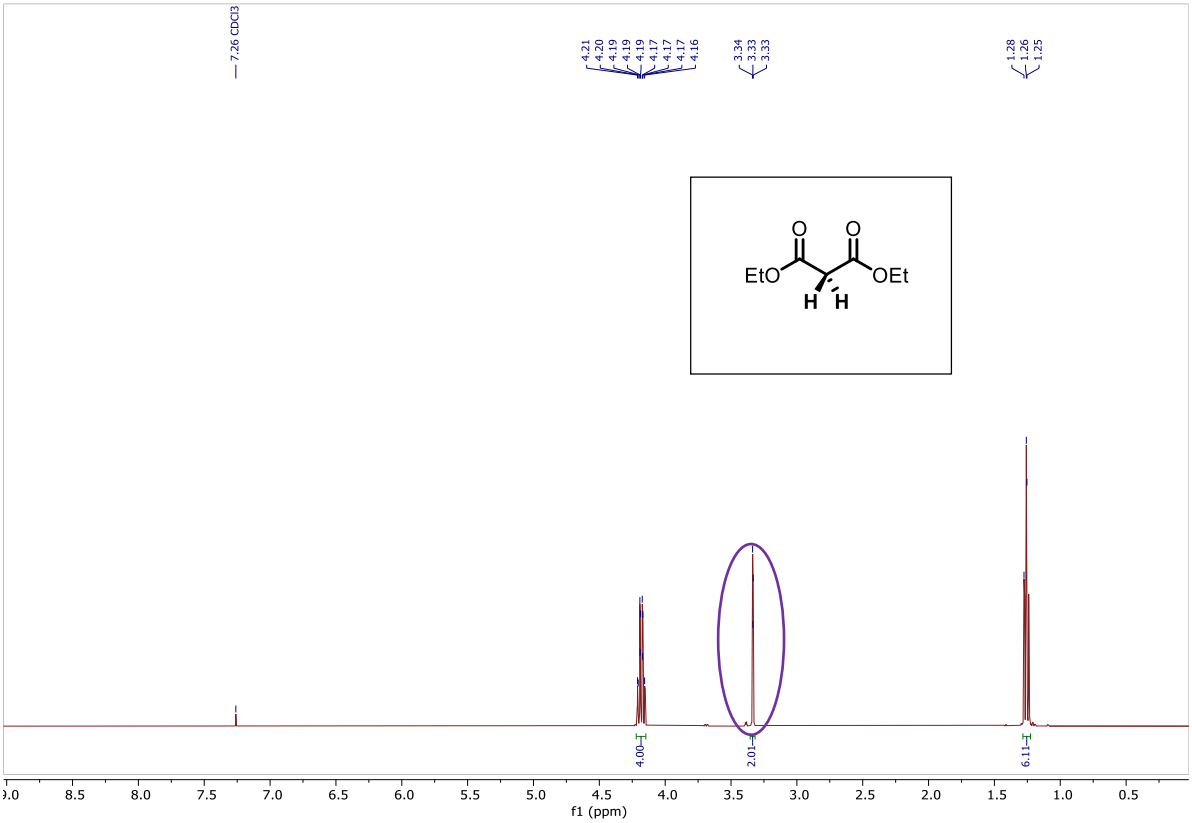
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Dimethyl malonate** (starting material of **3ad**)



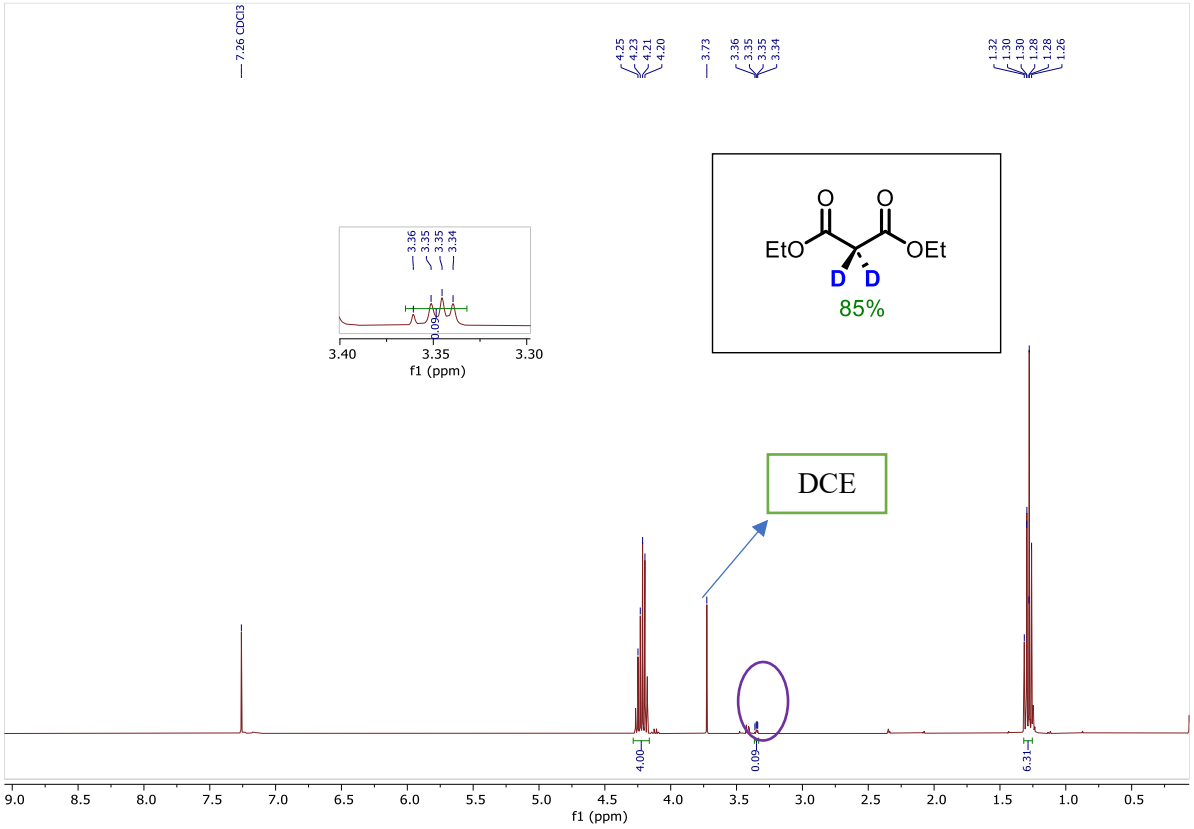
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Dimethyl malonate-d_2 (3ad)**



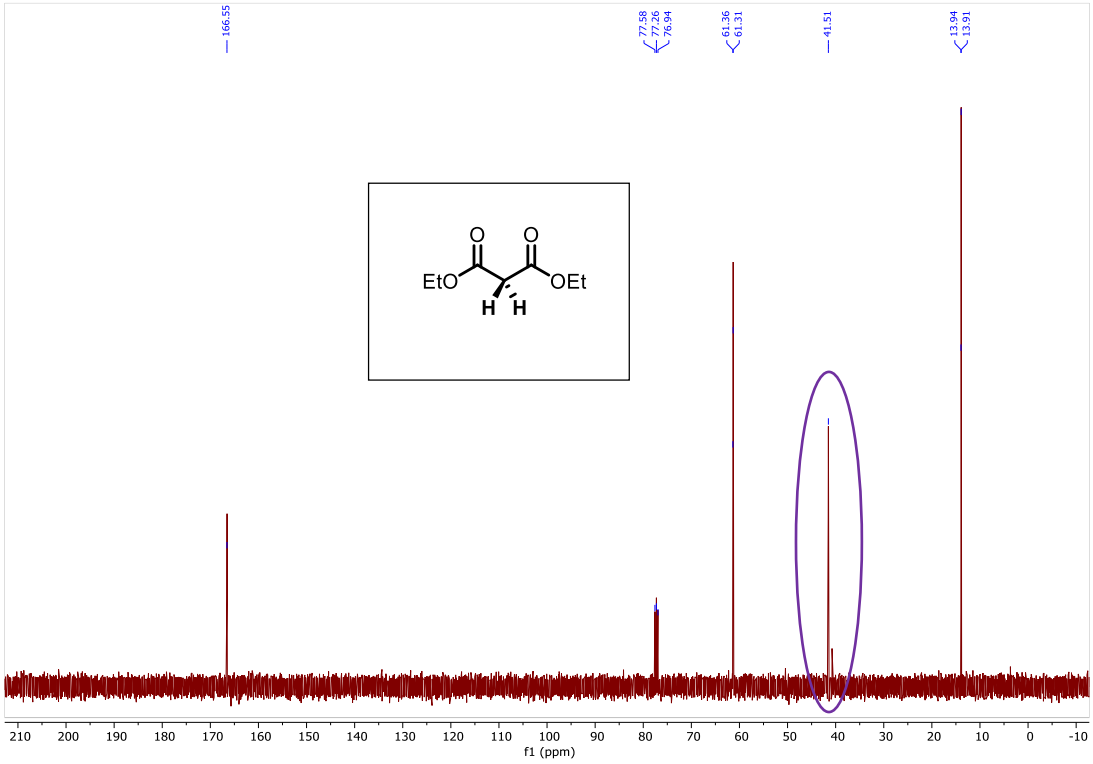
^{1}H NMR (400 MHz, $CDCl_3$) of **Diethyl malonate** (starting material of **3ae**)



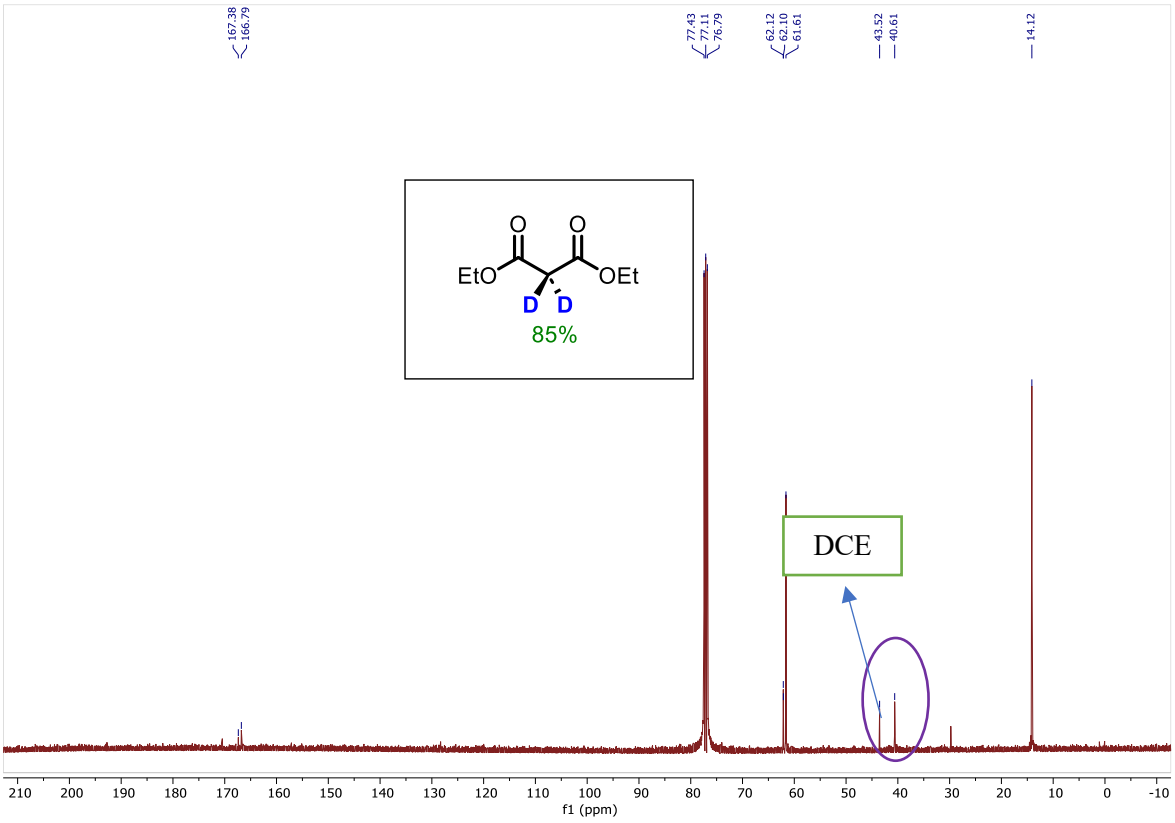
^{1}H NMR (400 MHz, $CDCl_3$) of **Diethyl malonate-d_2 (3ae)**



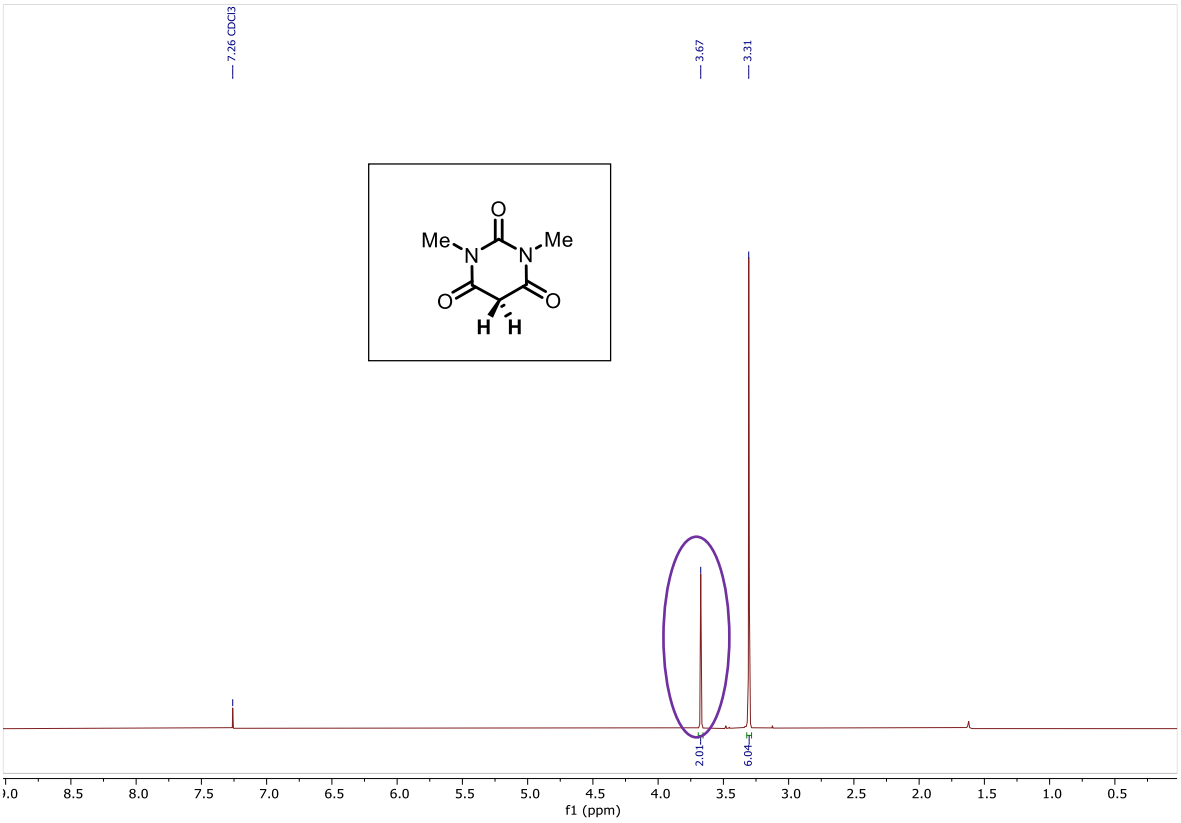
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Diethyl malonate** (starting material of **3ae**)



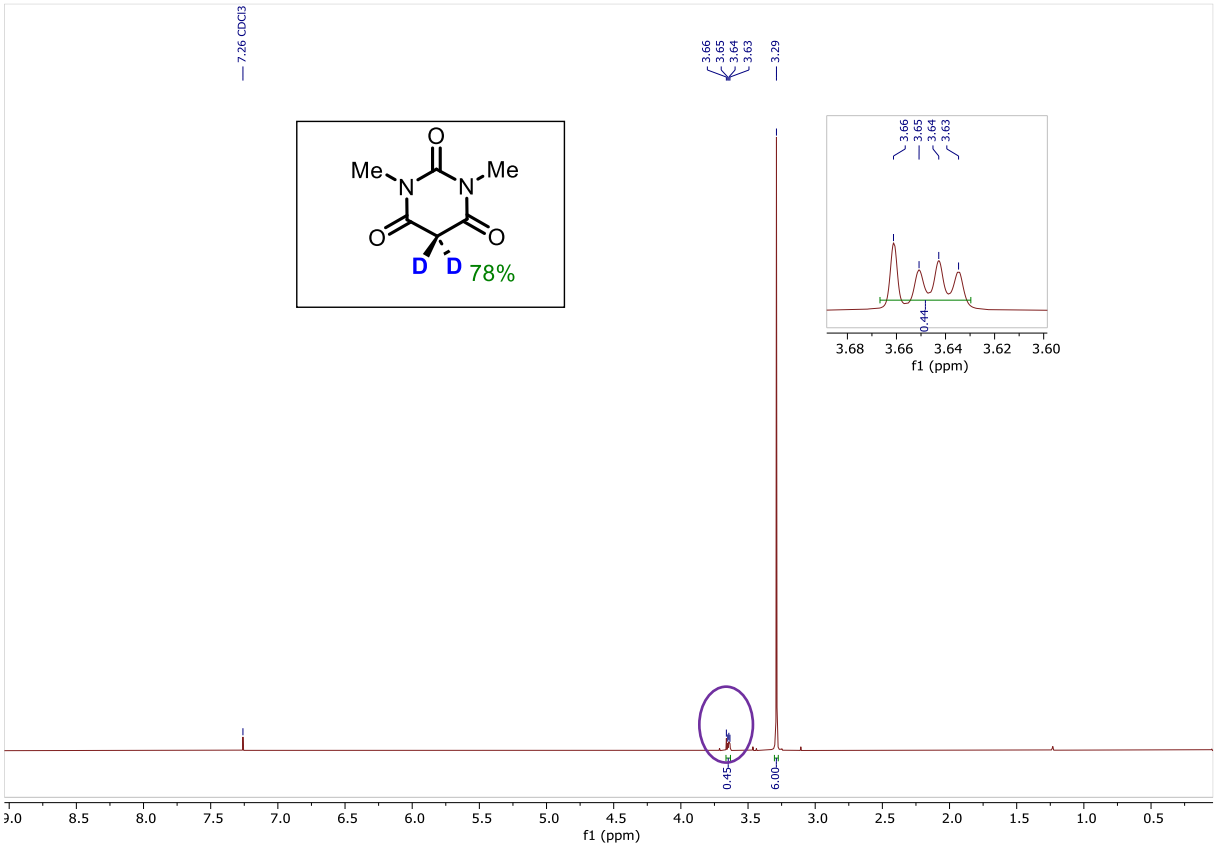
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Diethyl malonate-d_2 (3ae)**



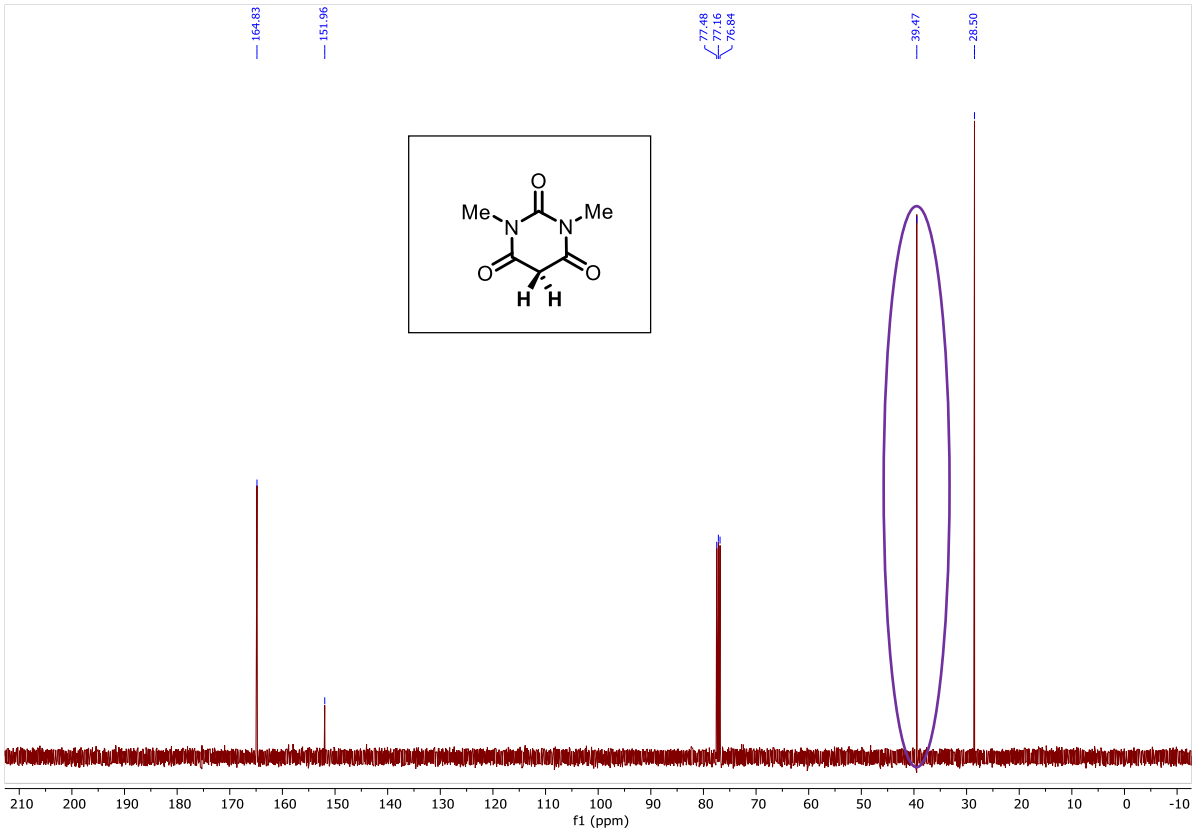
^{1}H NMR (400 MHz, $CDCl_3$) of **1,3-Dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione** (starting material of **3af**)



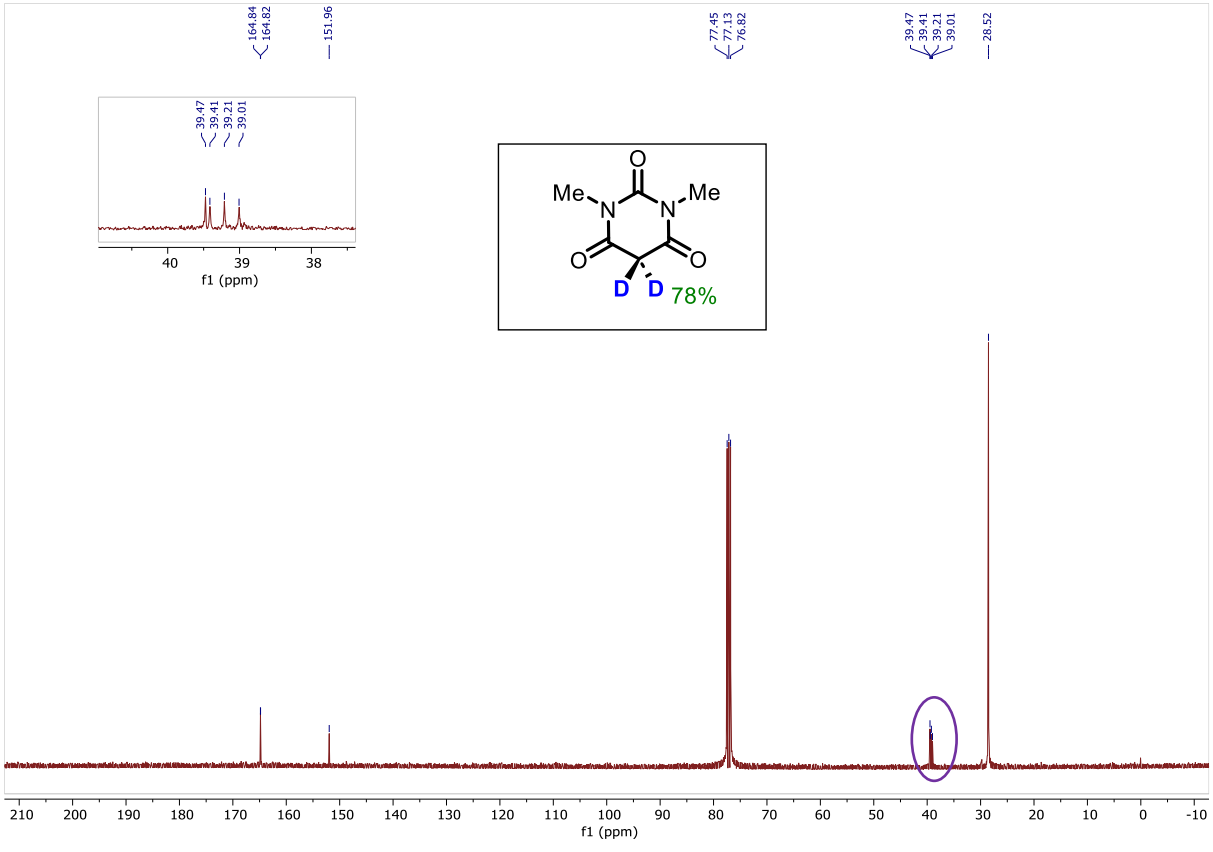
^{1}H NMR (400 MHz, $CDCl_3$) of **1,3-Dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione-5,5-d_2 (3af)**



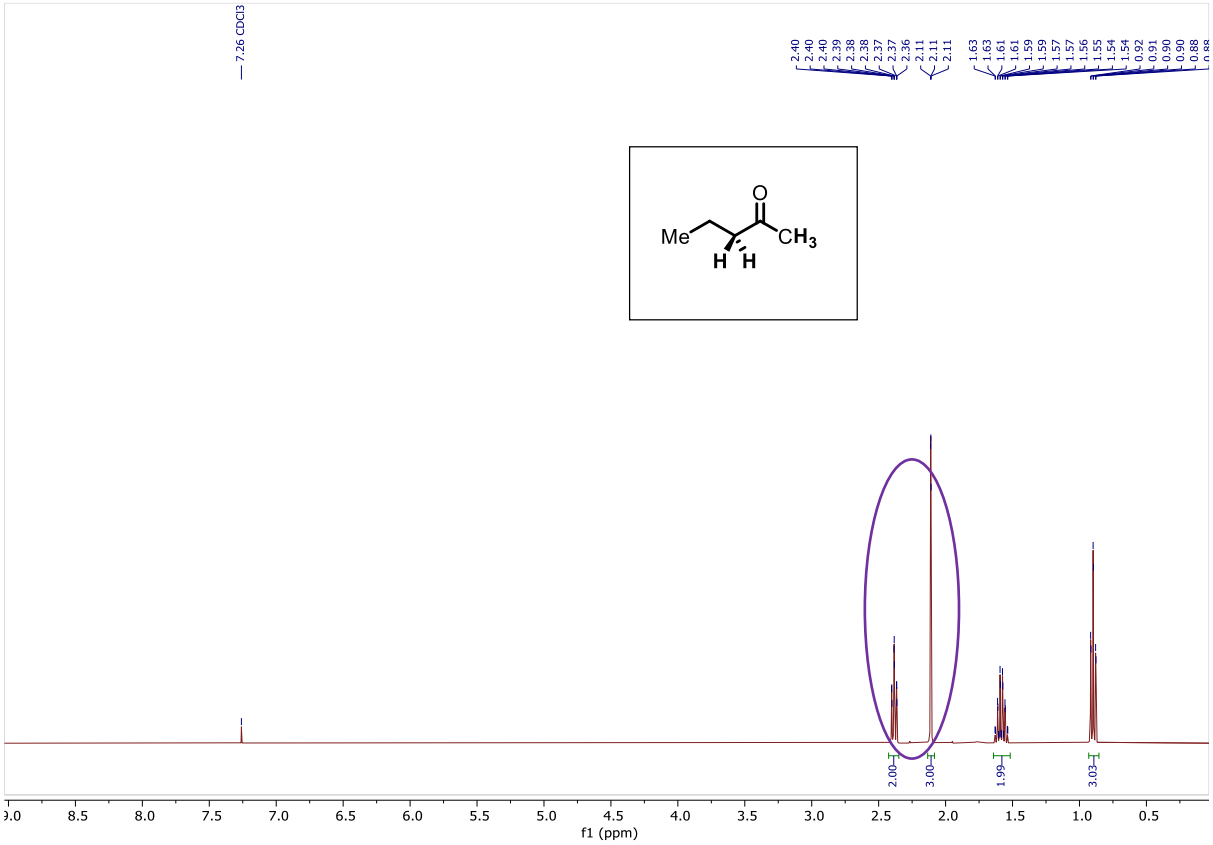
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1,3-Dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione** (starting material of **3af**)



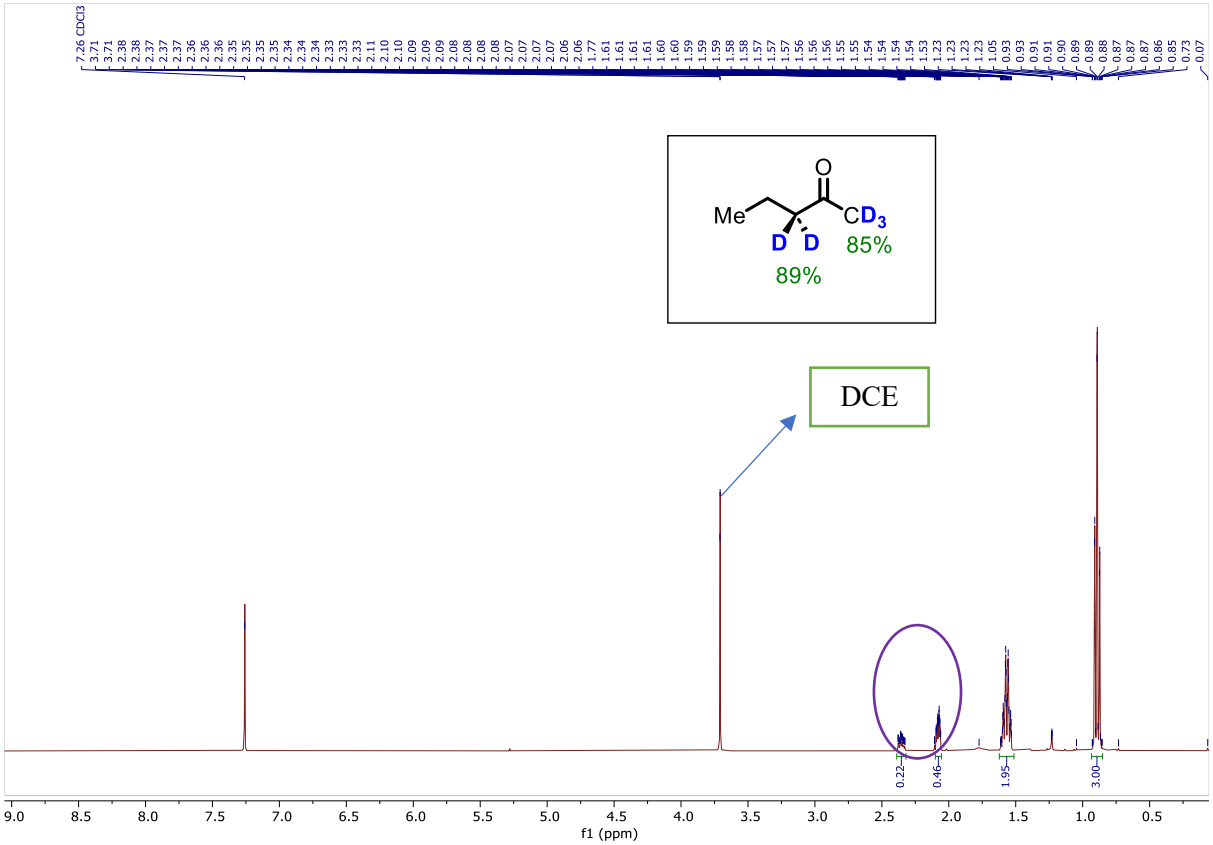
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1,3-Dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione-5,5-d_2 (3af)**



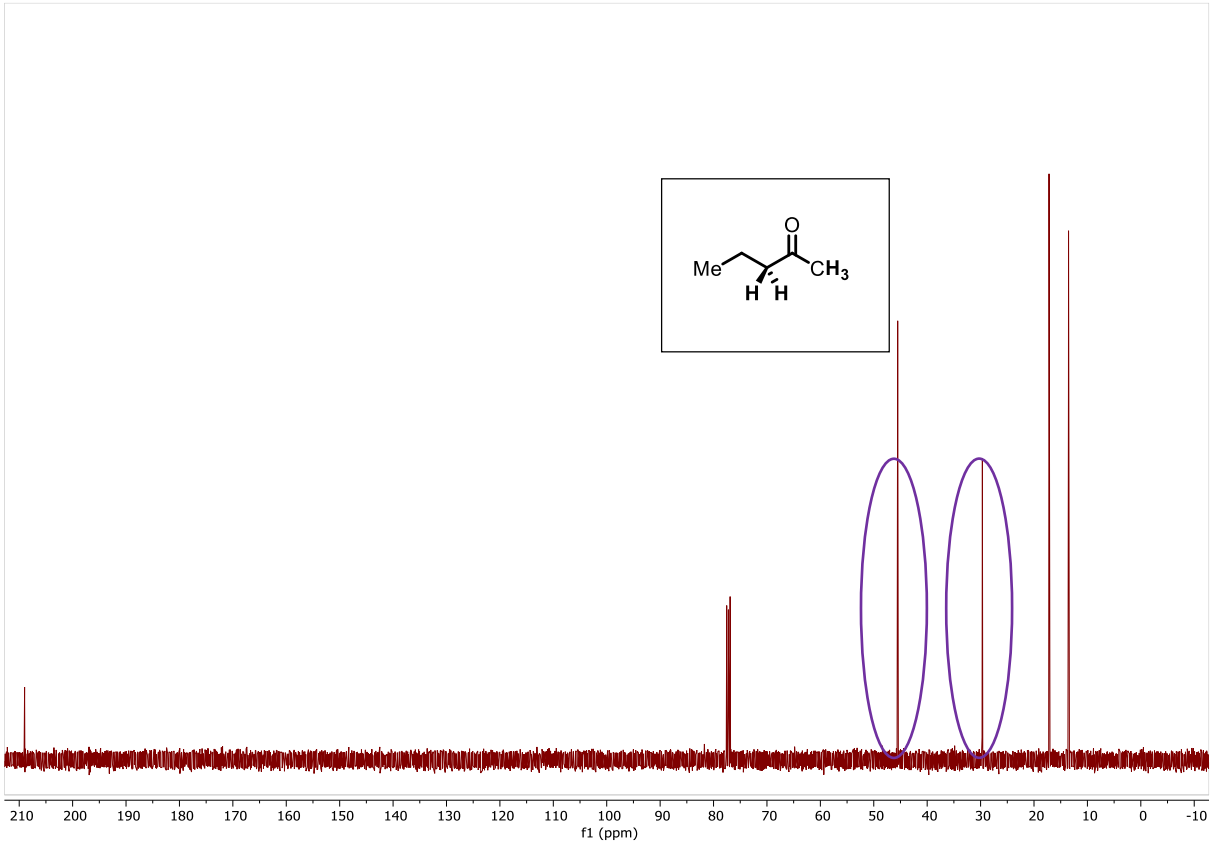
^{1}H NMR (400 MHz, $CDCl_3$) of **Pentan-2-one** (starting material of **3ag**)



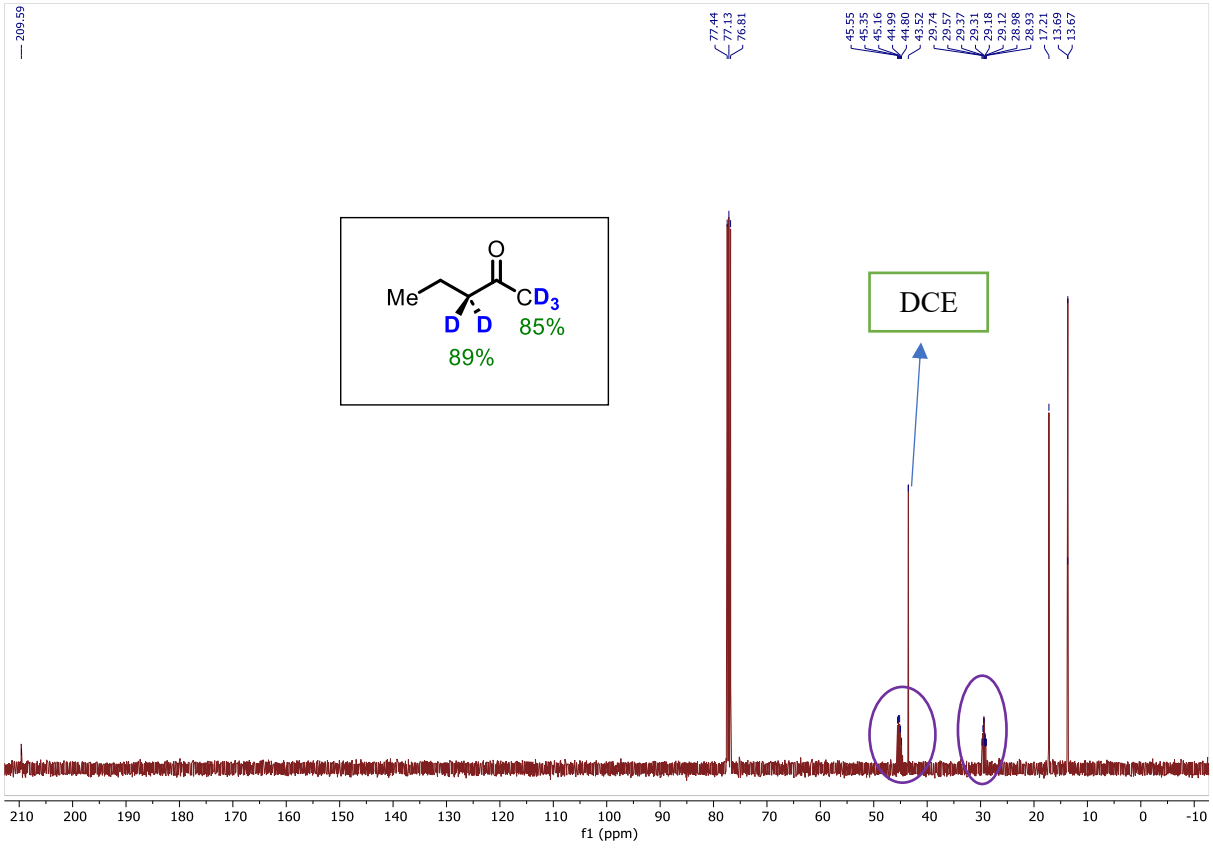
^{1}H NMR (400 MHz, $CDCl_3$) of **Pentan-2-one-1,1,1,3,3-d_5 (3ag)**



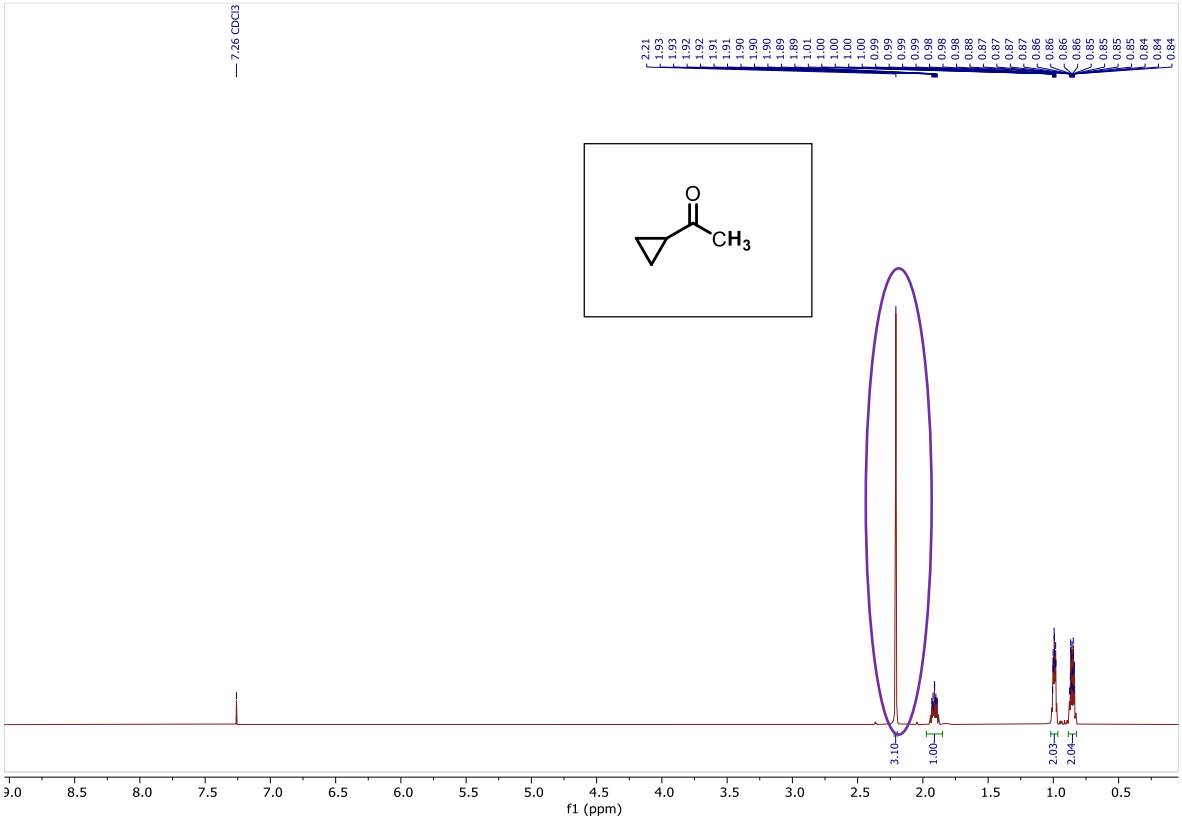
. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) of **Pentan-2-one** (starting material of **3ag**)



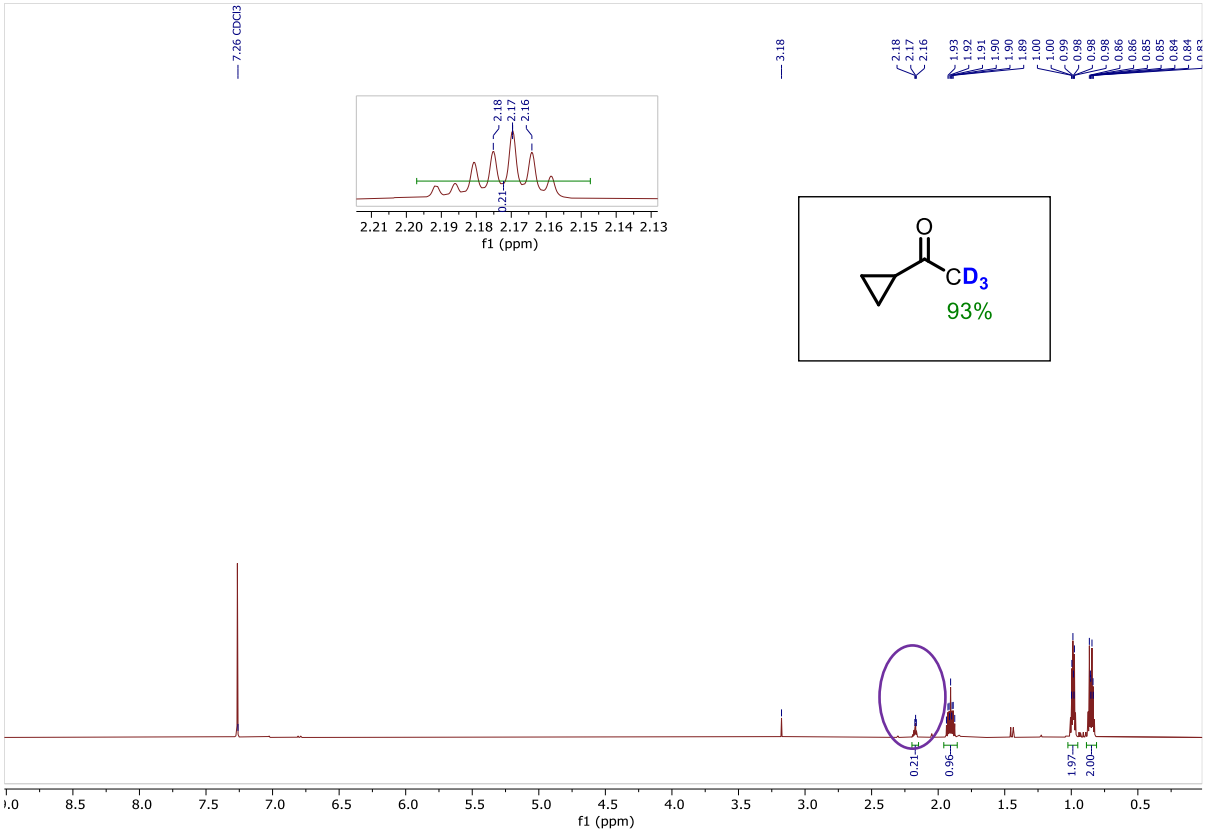
. **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) of **Pentan-2-one-1,1,1,3,3-d_5 (3ag)**



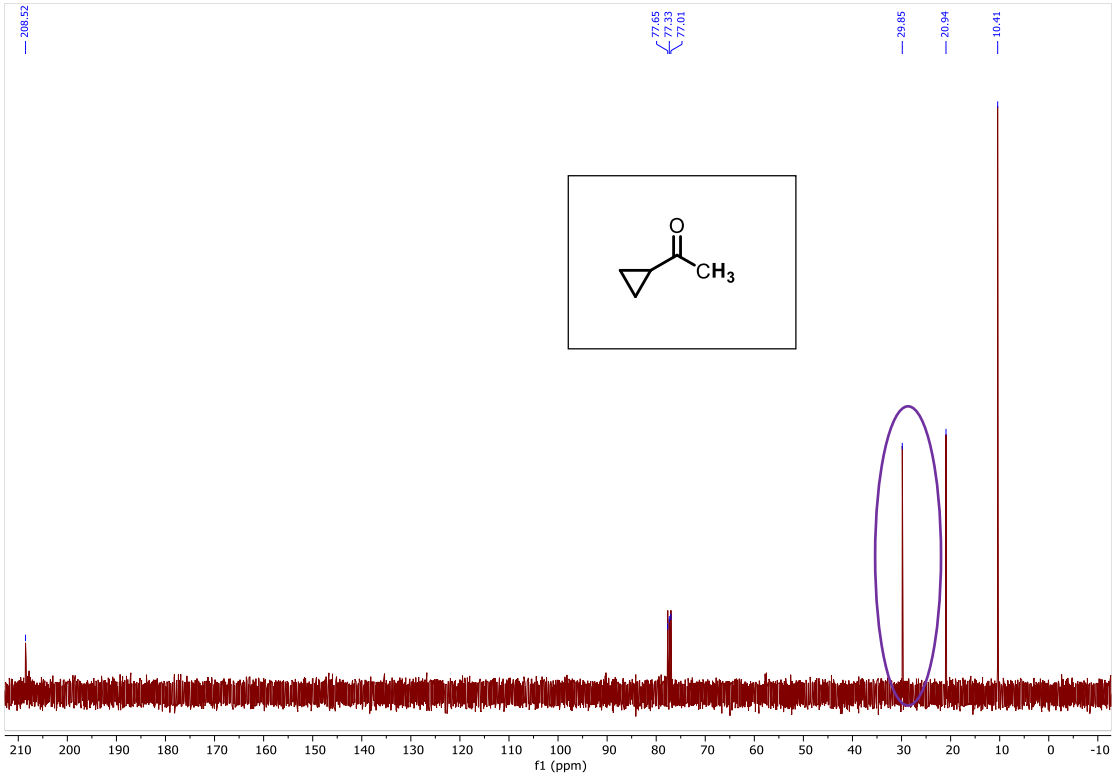
^{1}H NMR (400 MHz, $CDCl_3$) of **1-Cyclopropylethan-1-one** (starting material of **3ah**)



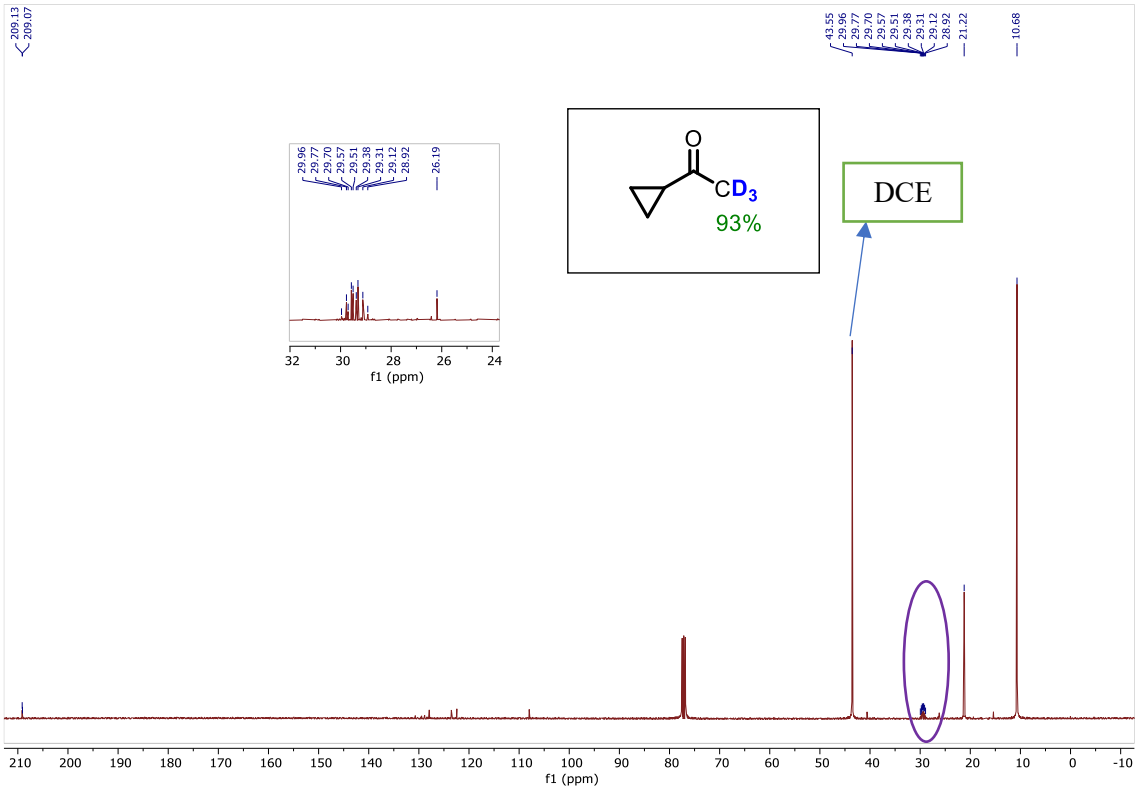
^{1}H NMR (400 MHz, $CDCl_3$) of **1-Cyclopropylethan-1-one-2,2,2-d_3 (3ah)**



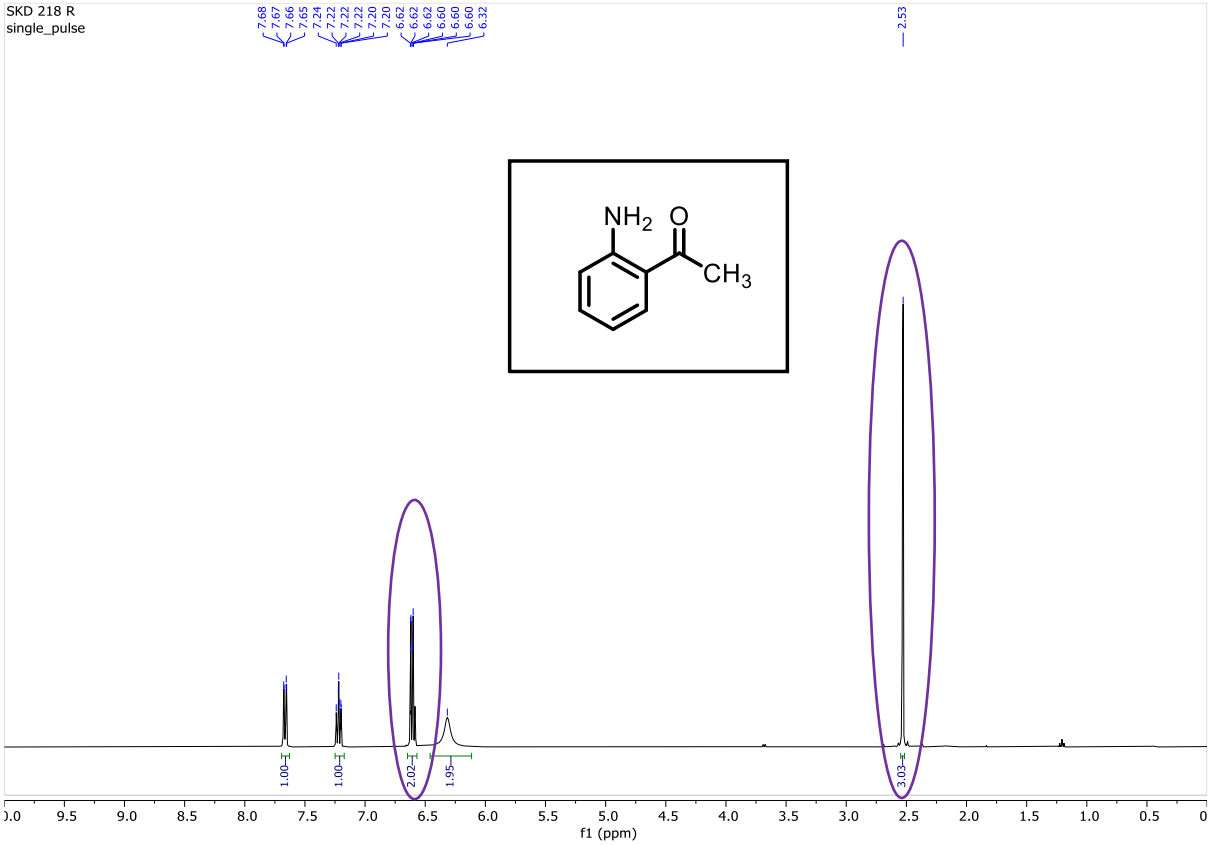
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-Cyclopropylethan-1-one** (starting material of **3ah**)



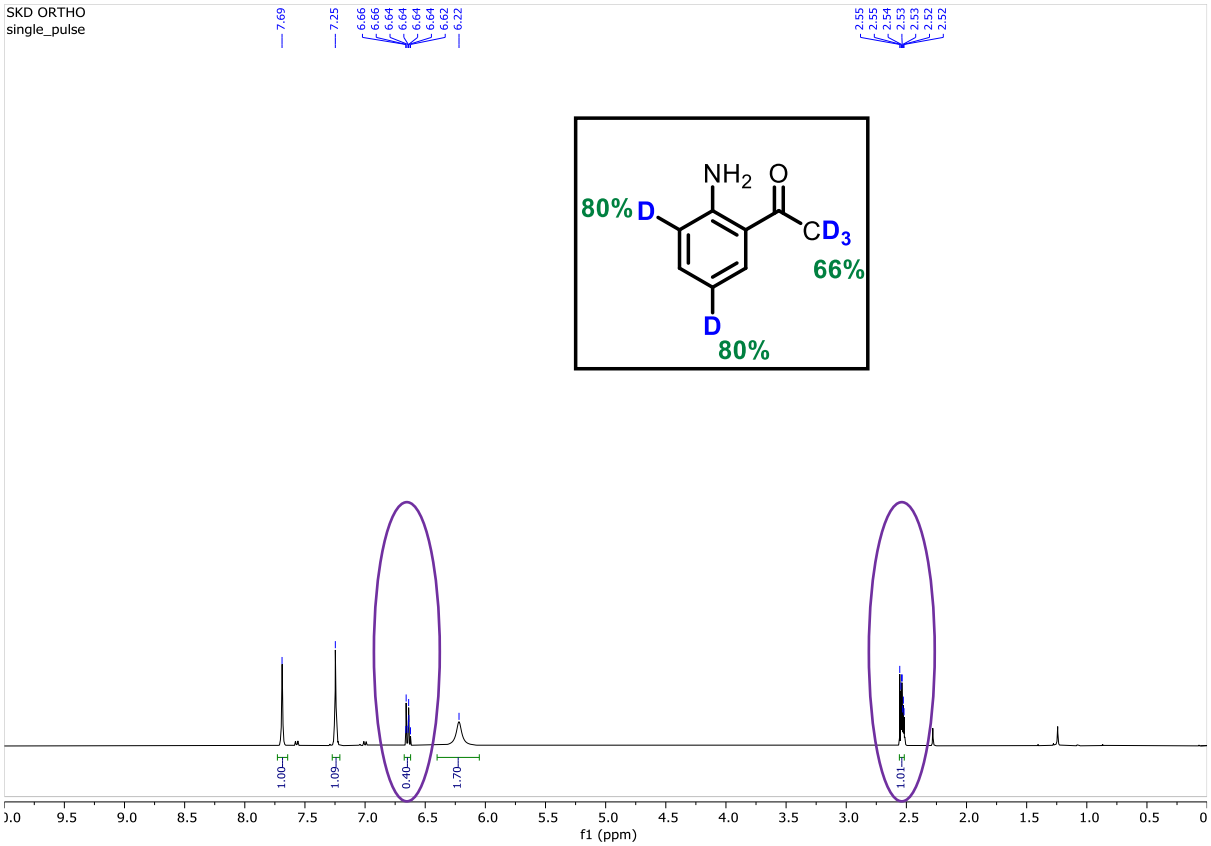
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-Cyclopropylethan-1-one-2,2,2-d_3 (3ah)**



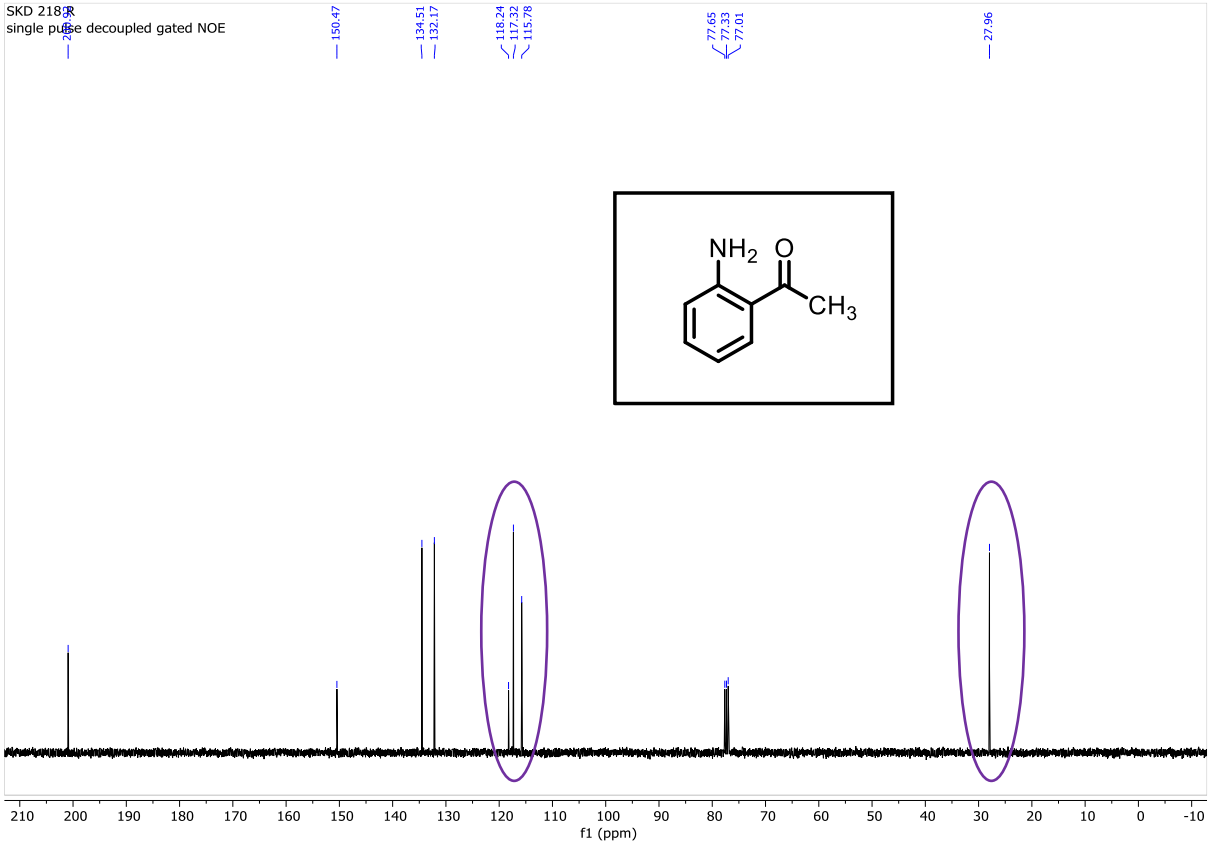
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(2-aminophenyl)ethan-1-one** (starting material of **3ah'**)



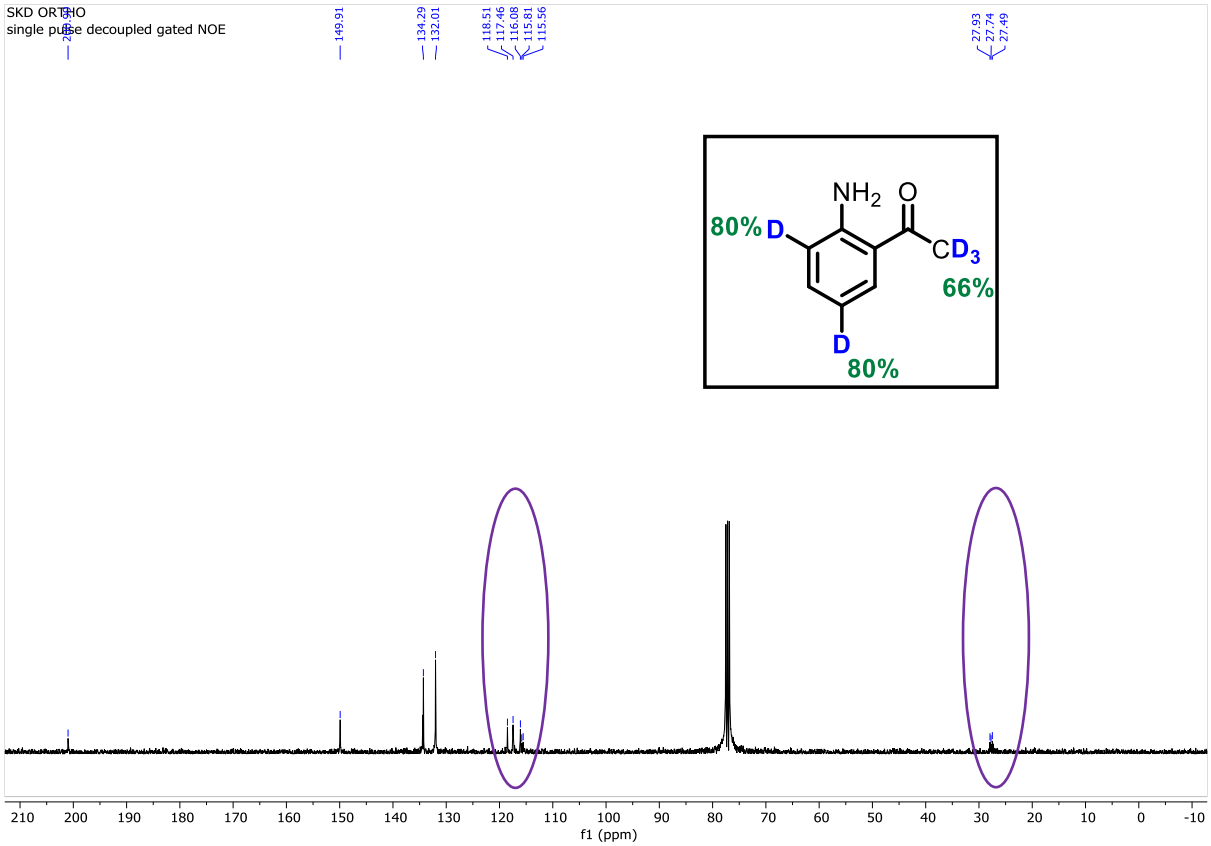
^{1}H NMR (400 MHz, $CDCl_3$) of **1-(2-aminophenyl-3,5-d_2)ethan-1-one-2,2,2-d_3 (3ah')**



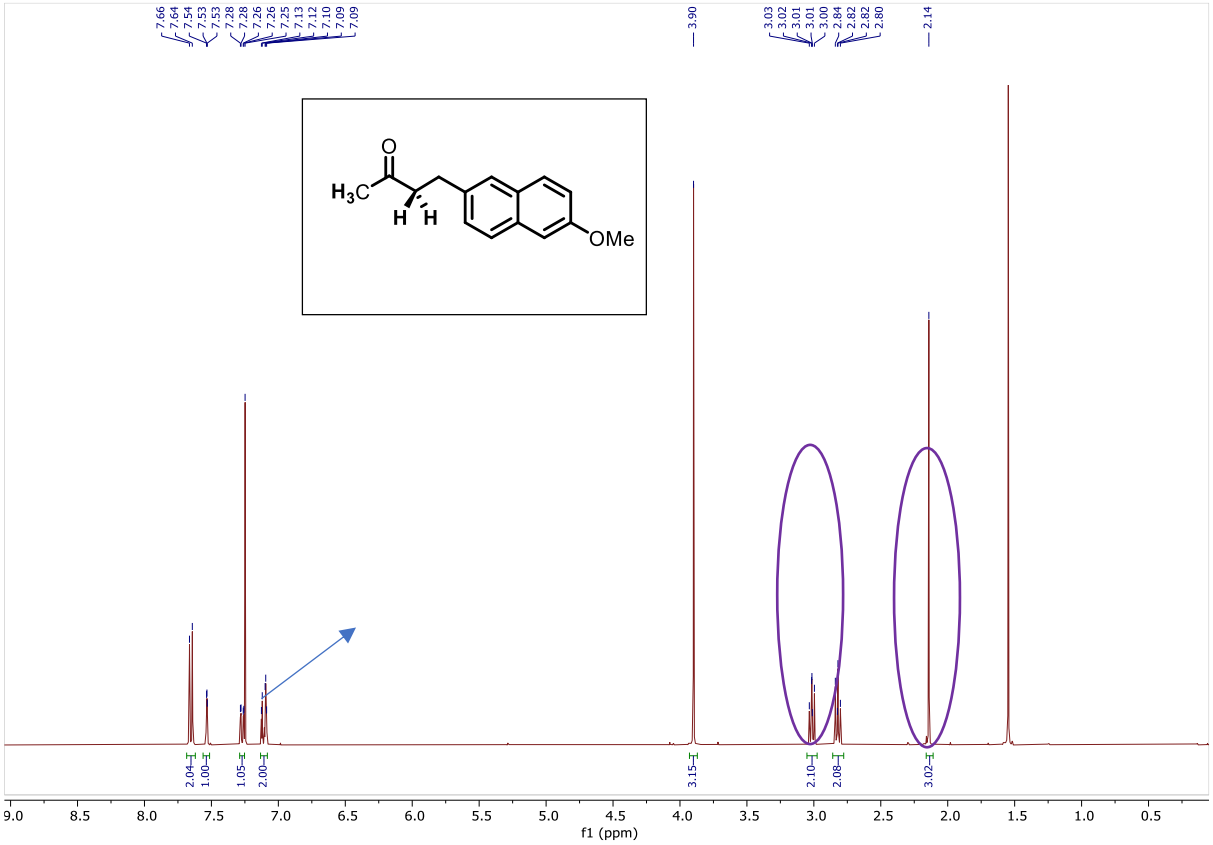
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(2-aminophenyl)ethan-1-one** (starting material of **3ah'**)



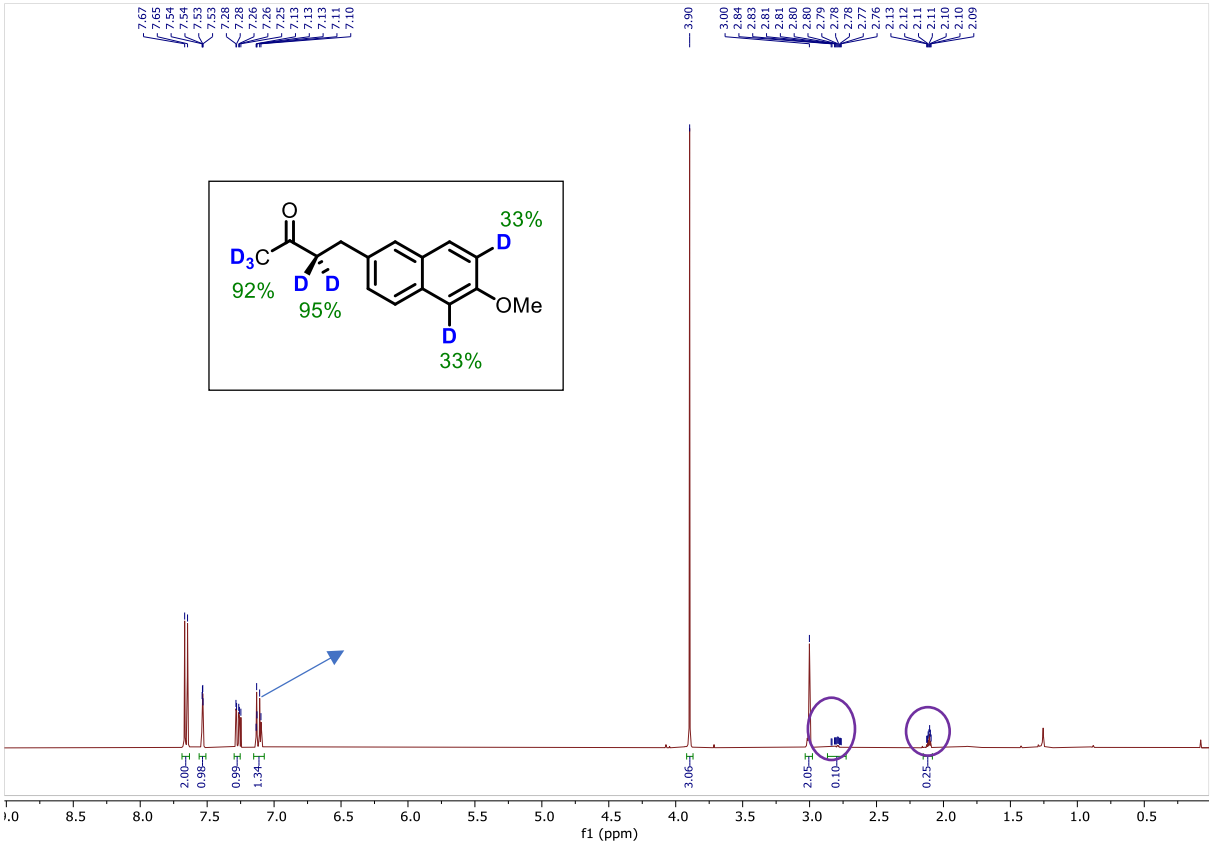
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **1-(2-aminophenyl-3,5-*d*$_2$)ethan-1-one-2,2,2-*d*$_3$ (3ah')**



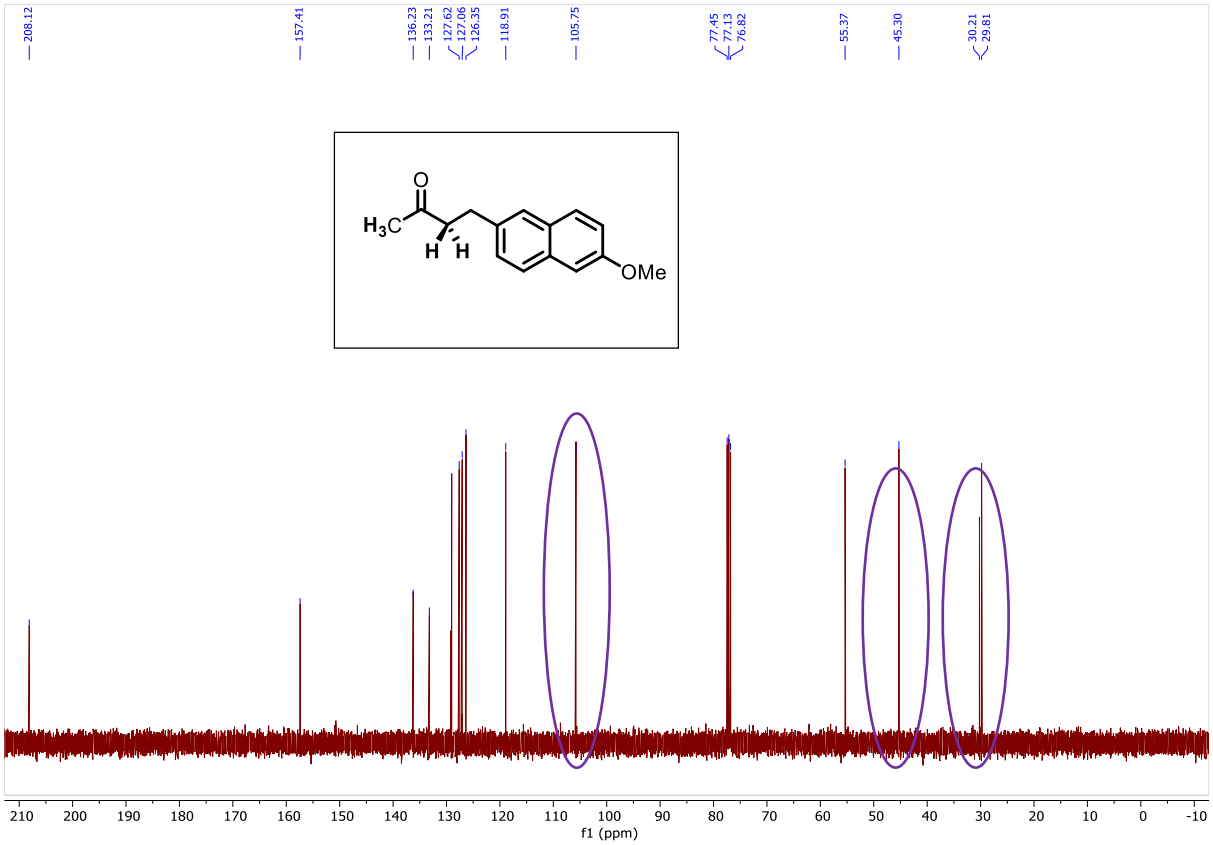
^{1}H NMR (400 MHz, $CDCl_3$) of **4-(6-Methoxynaphthalen-2-yl) butan-2-one** (starting material of **3ai**)



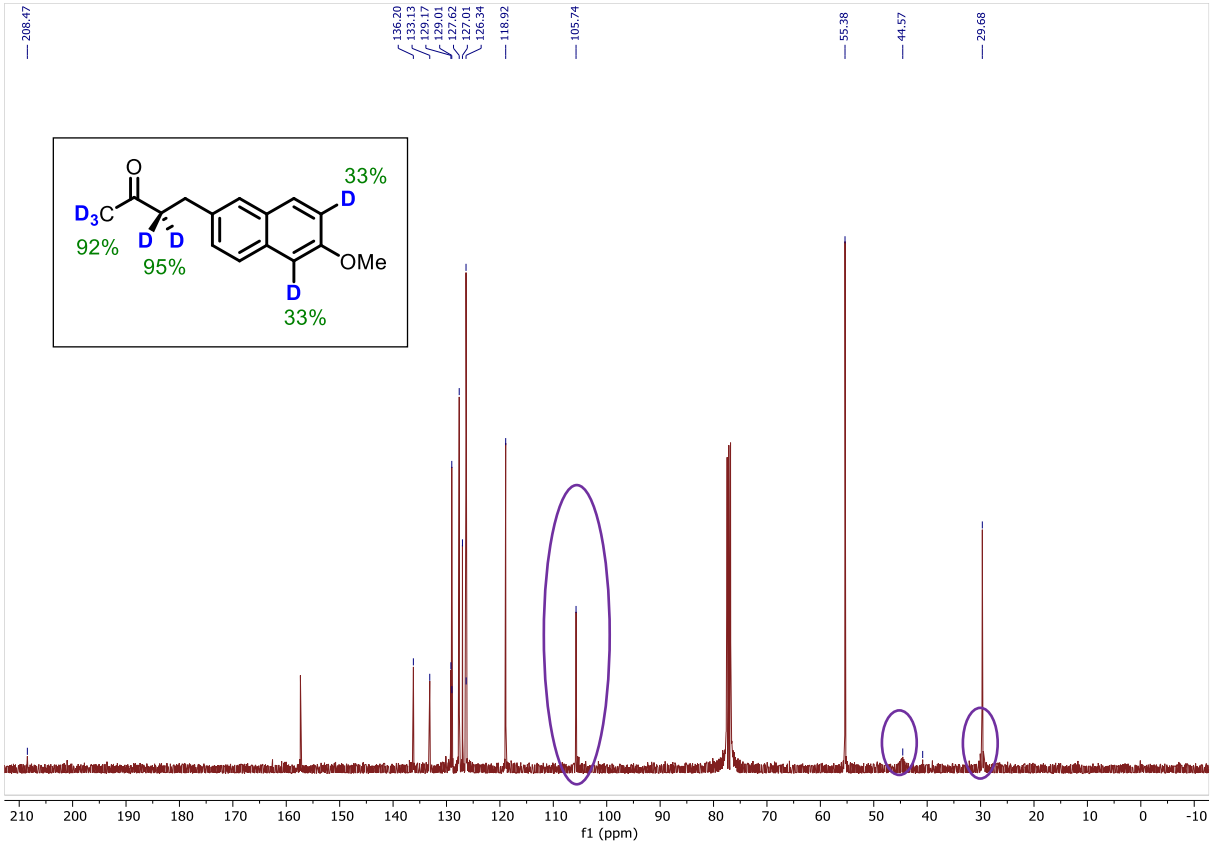
^{1}H NMR (400 MHz, $CDCl_3$) of **4-(6-Methoxynaphthalen-2-yl) butan-2-one-1,1,1,3,3-d_5 (3ai)**



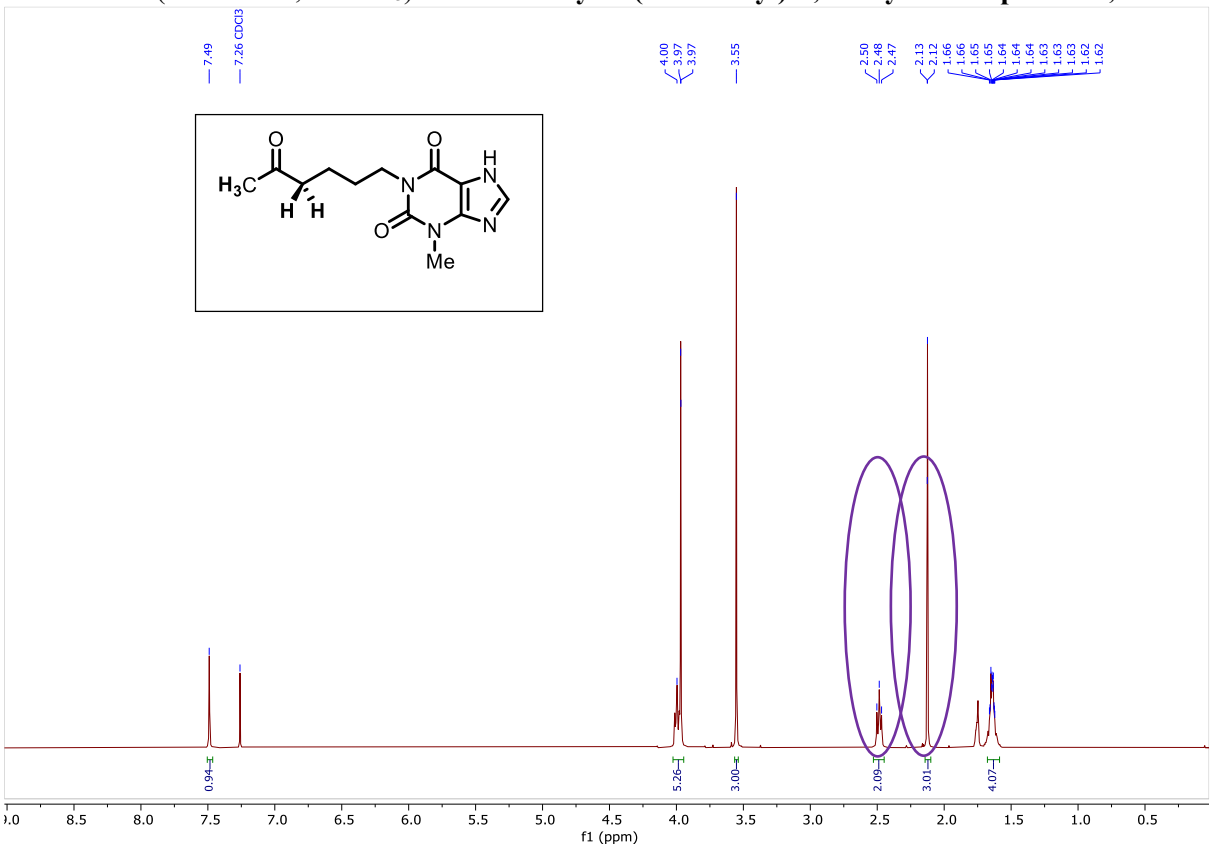
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **4-(6-Methoxynaphthalen-2-yl) butan-2-one** (starting material of **3ai**)



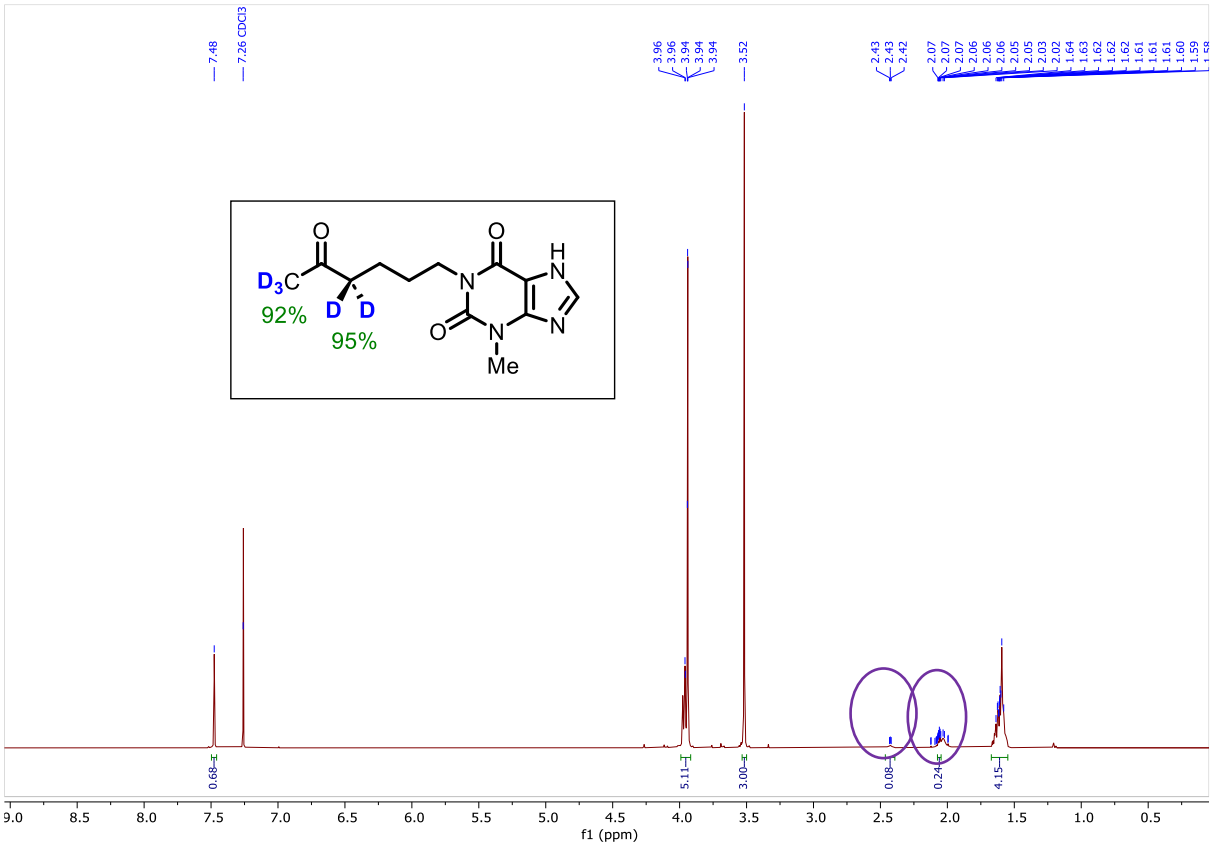
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **4-(6-Methoxynaphthalen-2-yl) butan-2-one-1,1,1,3,3-d_5 (3ai)**



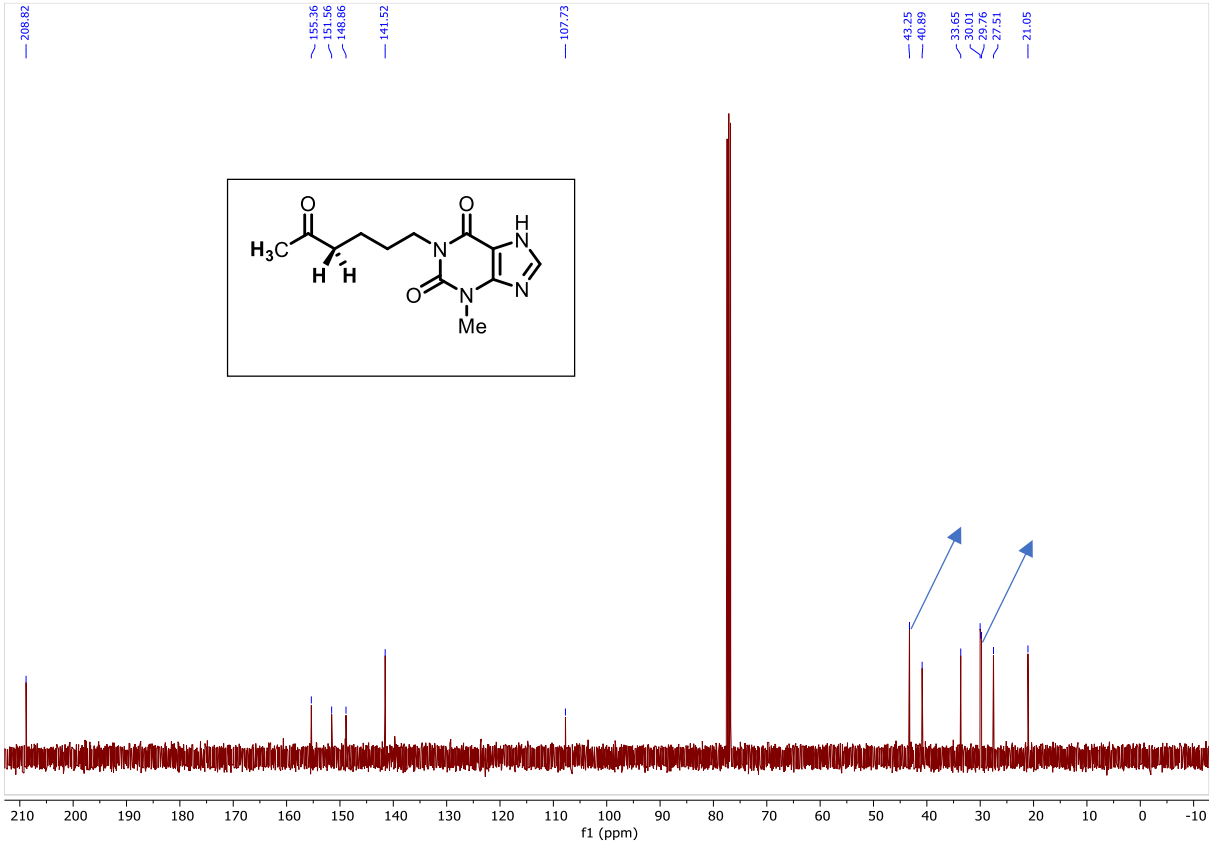
^{1}H NMR (400 MHz, $CDCl_3$) of **3-methyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione**



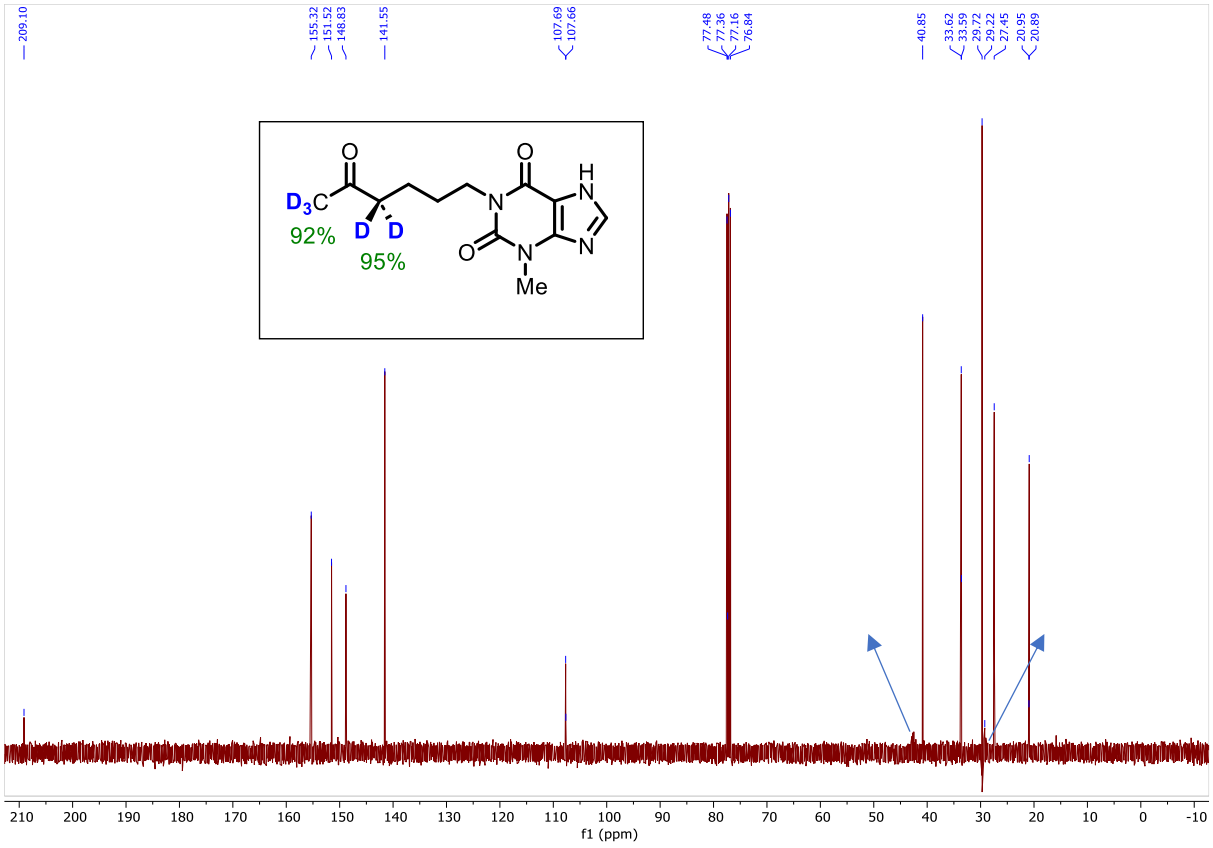
^{1}H NMR (400 MHz, $CDCl_3$) of **3-methyl-1-(5-oxohexyl-4,4,6,6,6-d_5)-3,7-dihydro-*1H*-purine-2,6-dione (3aj)**



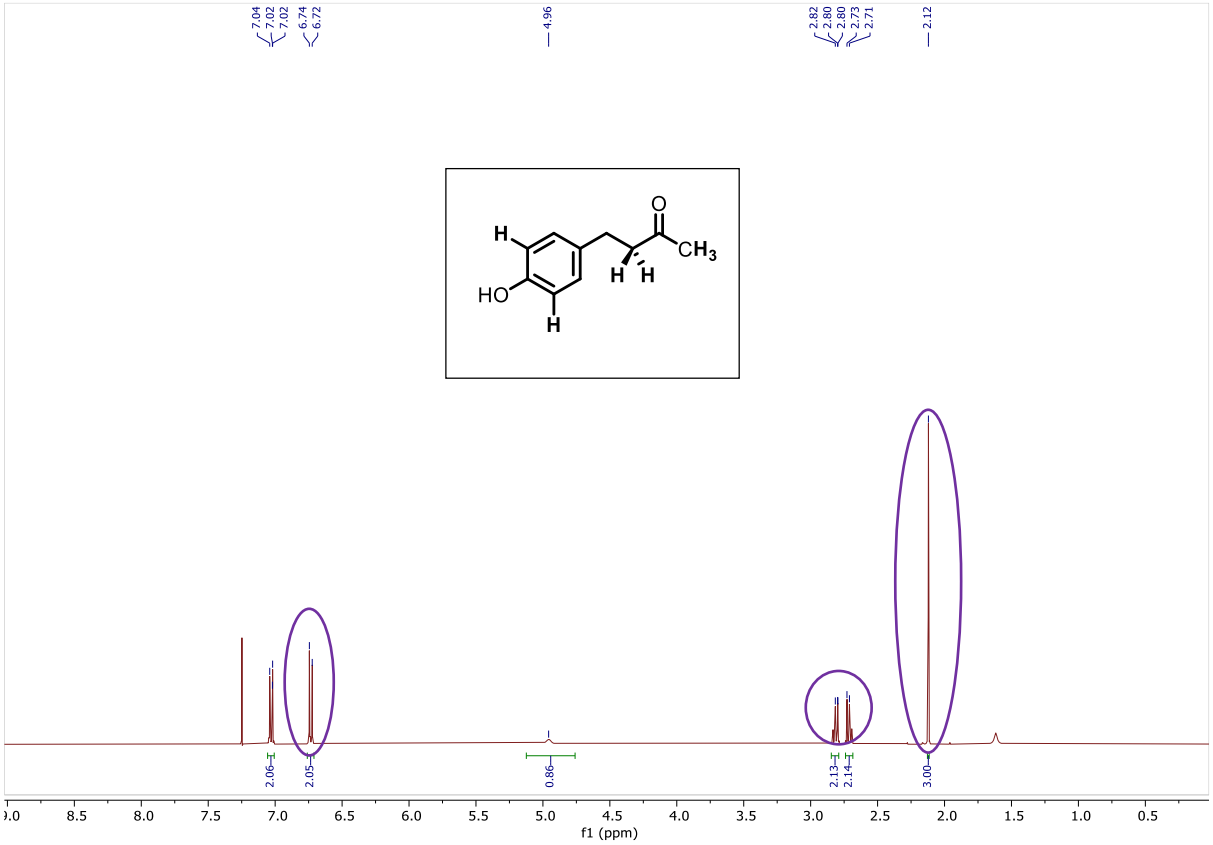
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **3-methyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione**



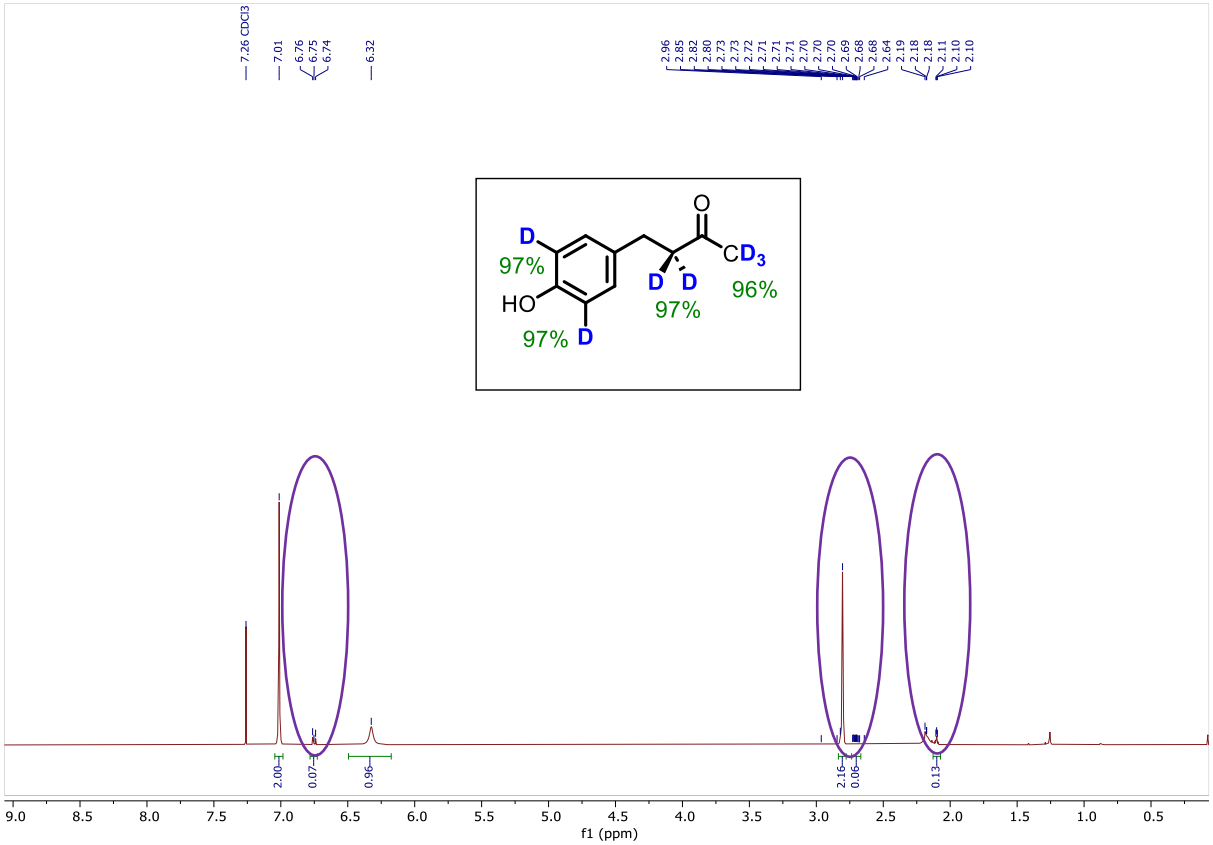
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **3-methyl-1-(5-oxohexyl-4,4,6,6,6-*d*$_5$)-3,7-dihydro-*1H*-purine-2,6-dione (3aj)**



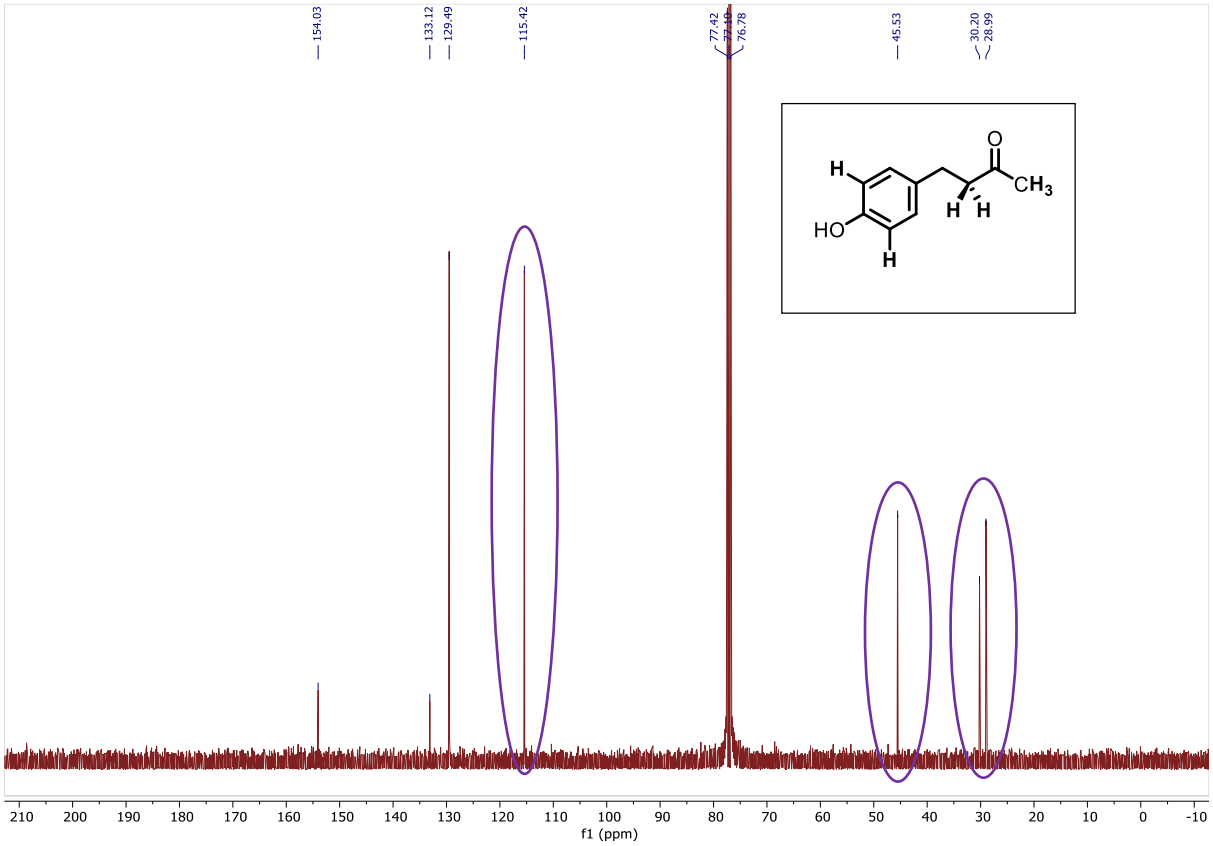
^{1}H NMR (400 MHz, $CDCl_3$) of **4-(4-Hydroxyphenyl) butan-2-one** (starting material of **3ak**)



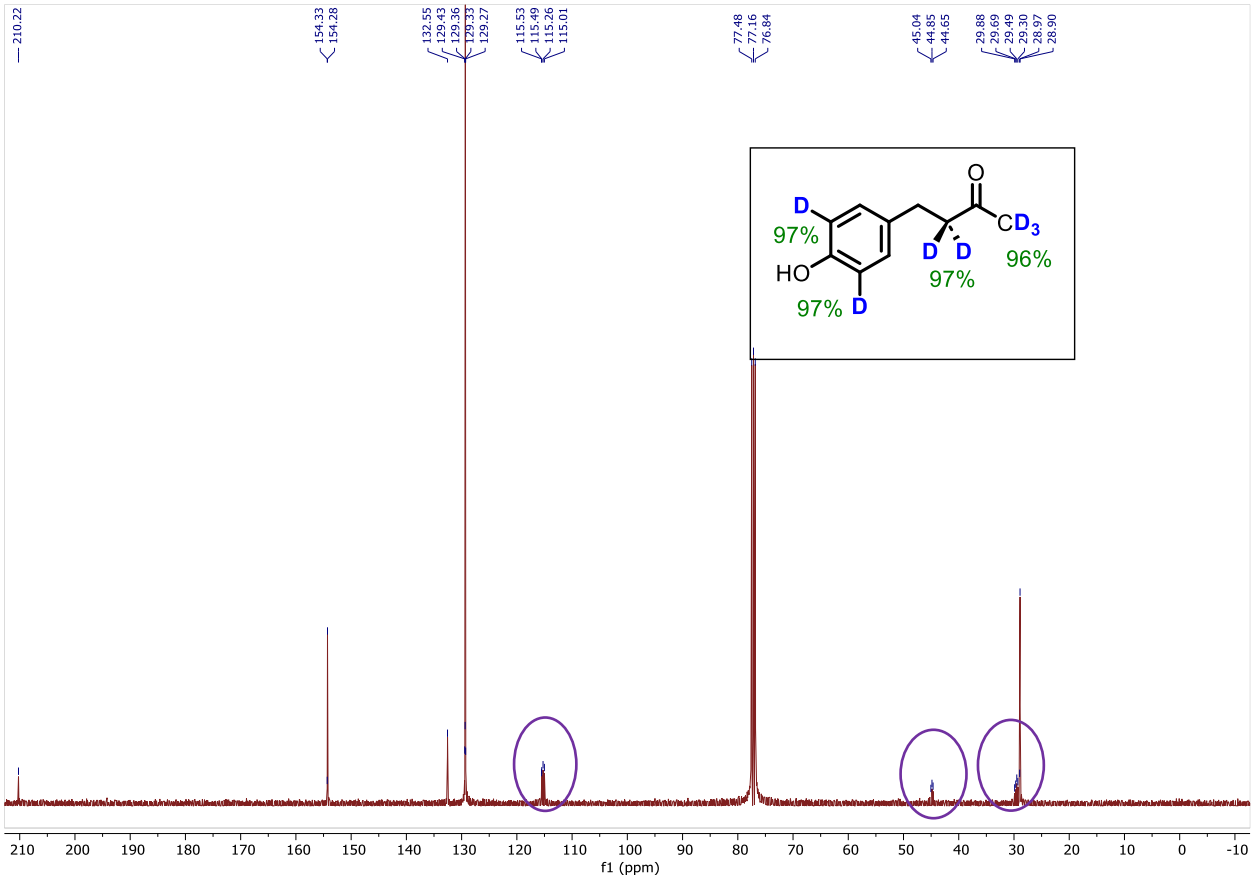
^{1}H NMR (400 MHz, $CDCl_3$) of **4-(4-Hydroxyphenyl-3,5-d_2) butan-2-one-1,1,1,3,3-d_5 (3ak)**



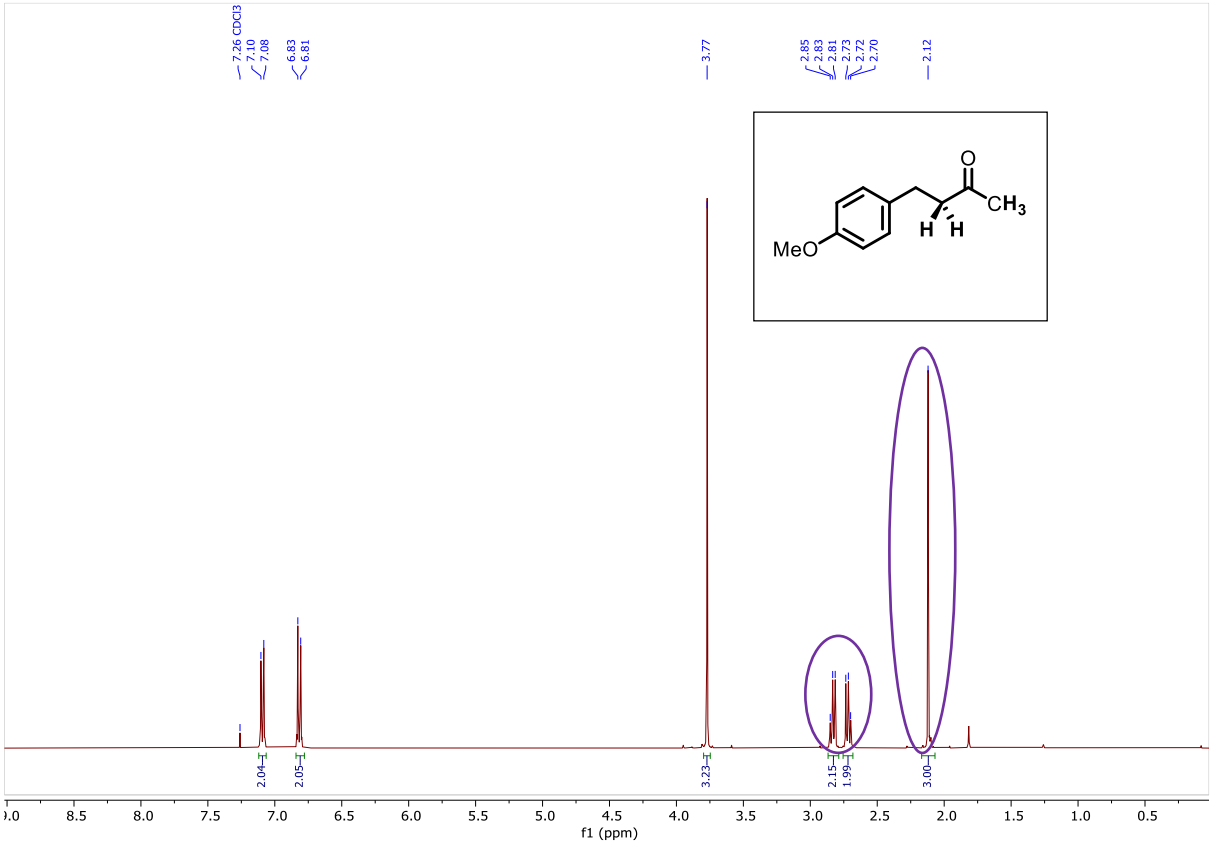
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **4-(4-Hydroxyphenyl) butan-2-one** (starting material of **3ak**)



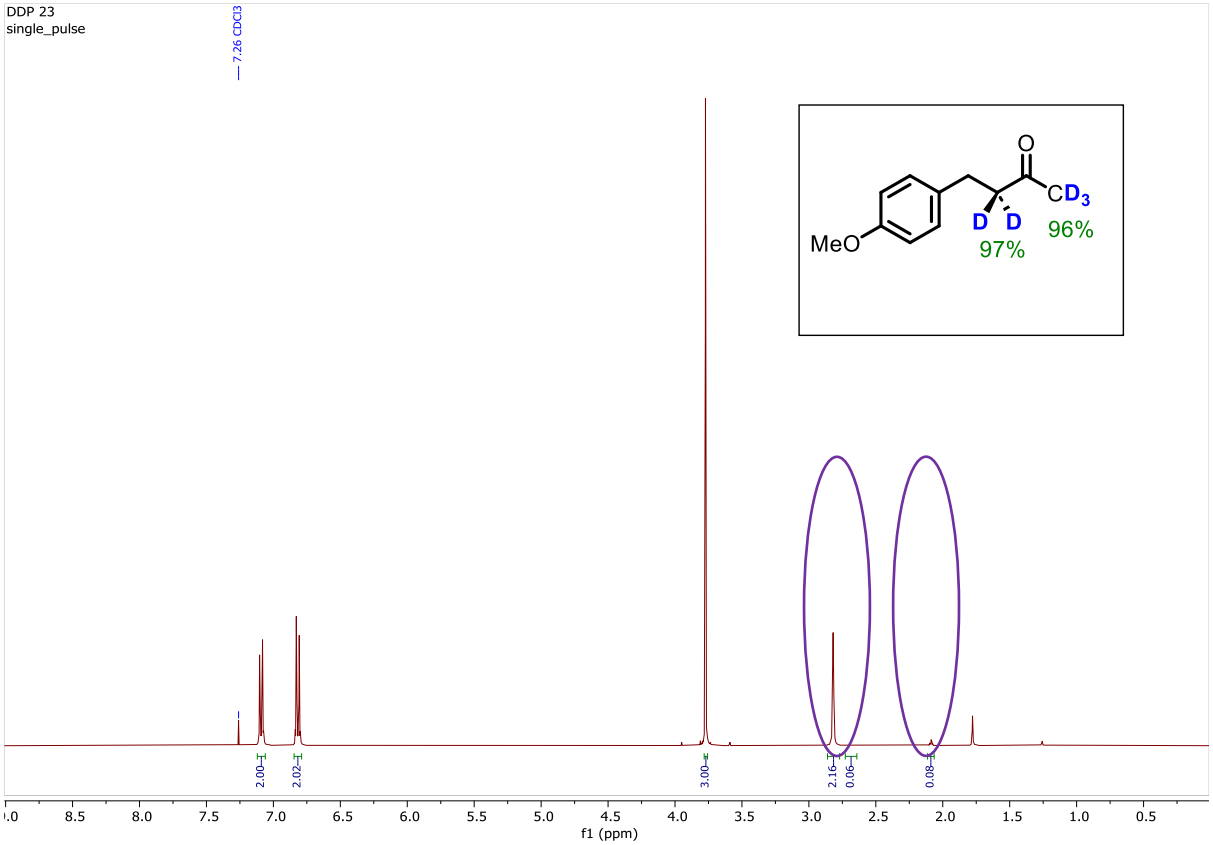
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **4-(4-Hydroxyphenyl-3,5-d_2) butan-2-one-1,1,1,3,3-d_5 (3ak)**



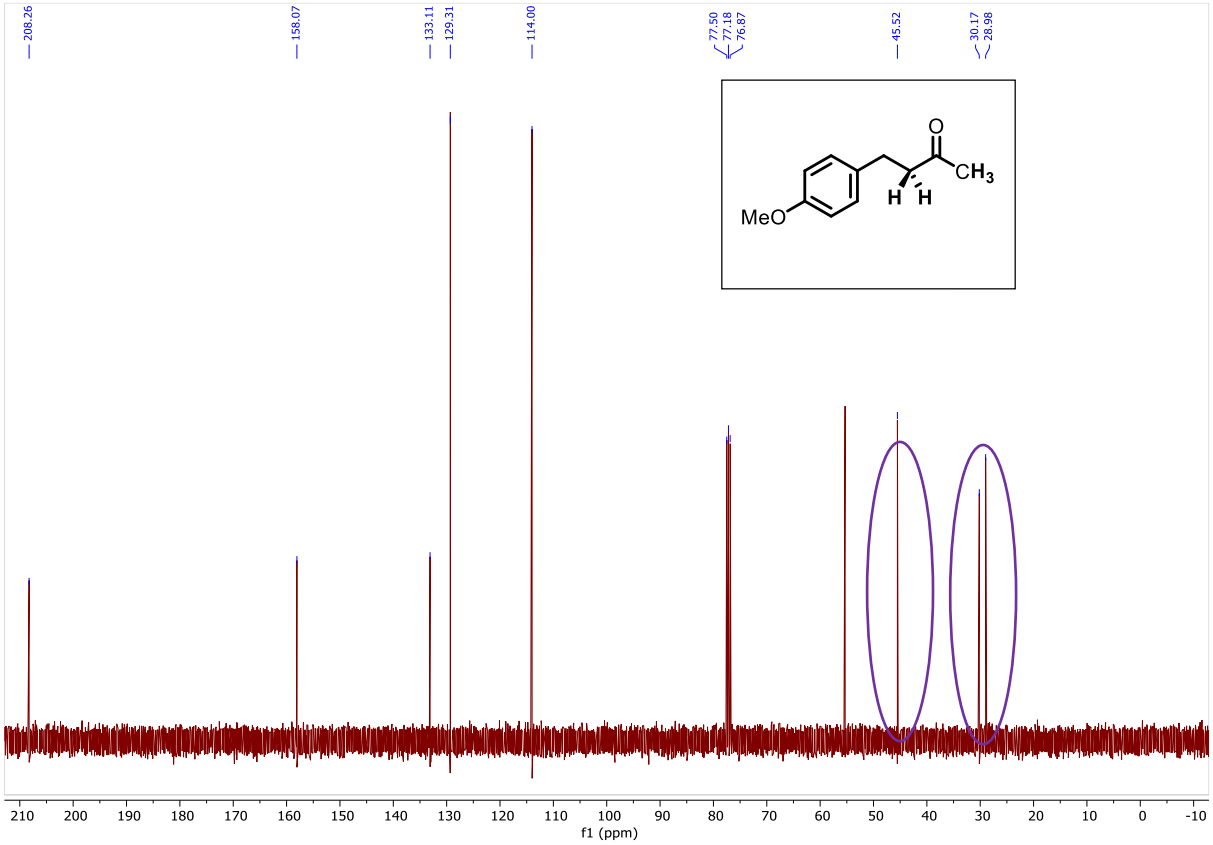
^{1}H NMR (400 MHz, $CDCl_3$) of **4-(4-Methoxyphenyl) butan-2-one** (starting material of **3al**)



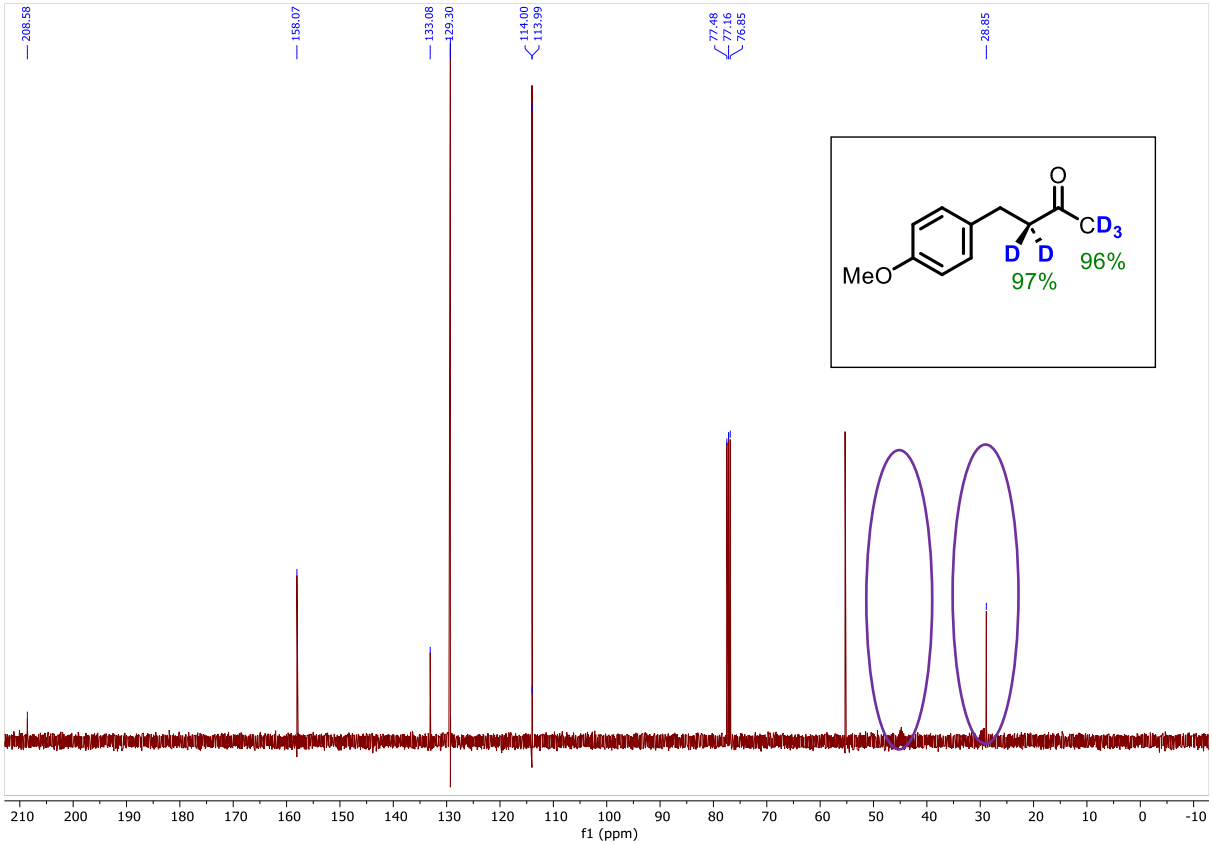
^{1}H NMR (400 MHz, $CDCl_3$) of **4-(4-Methoxyphenyl) butan-2-one-1,1,1,3,3-*d*$_5$ (3al)**



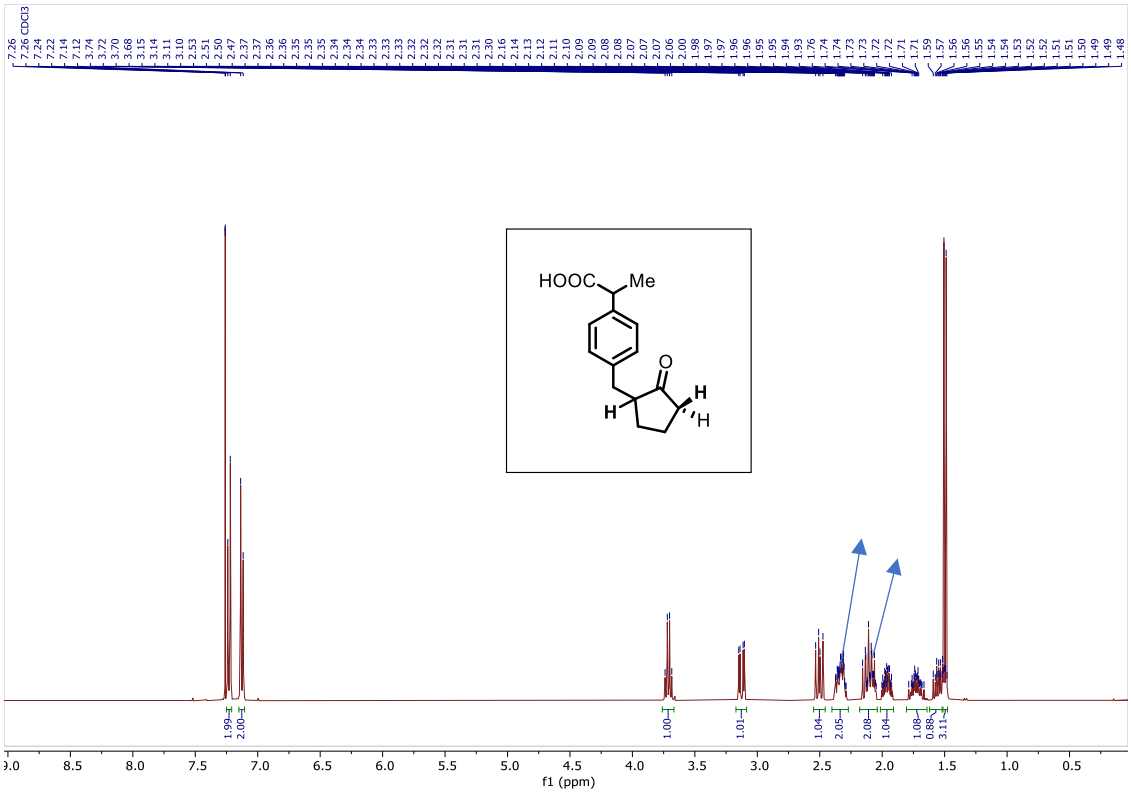
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **4-(4-Methoxyphenyl) butan-2-one** (starting material of **3al**)



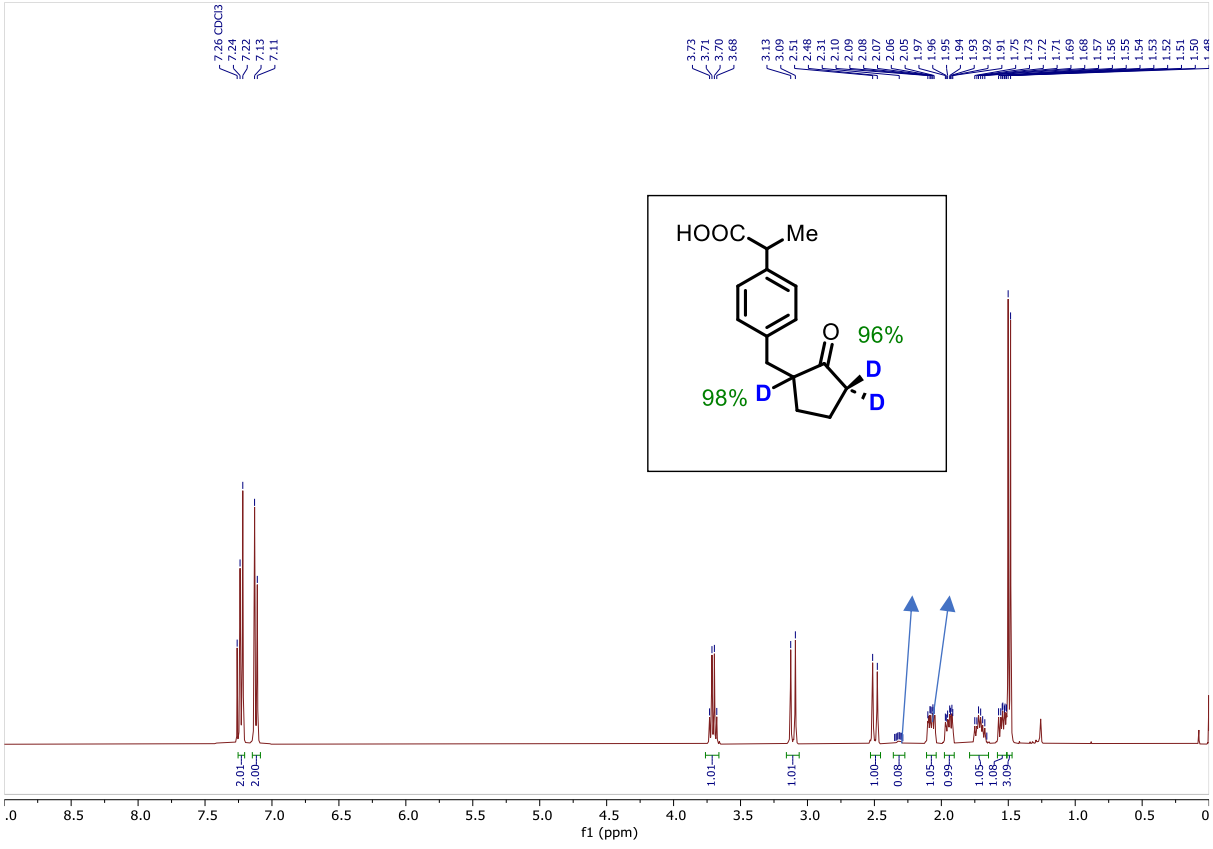
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **4-(4-Methoxyphenyl) butan-2-one-1,1,1,3,3-d_5 (3al)**



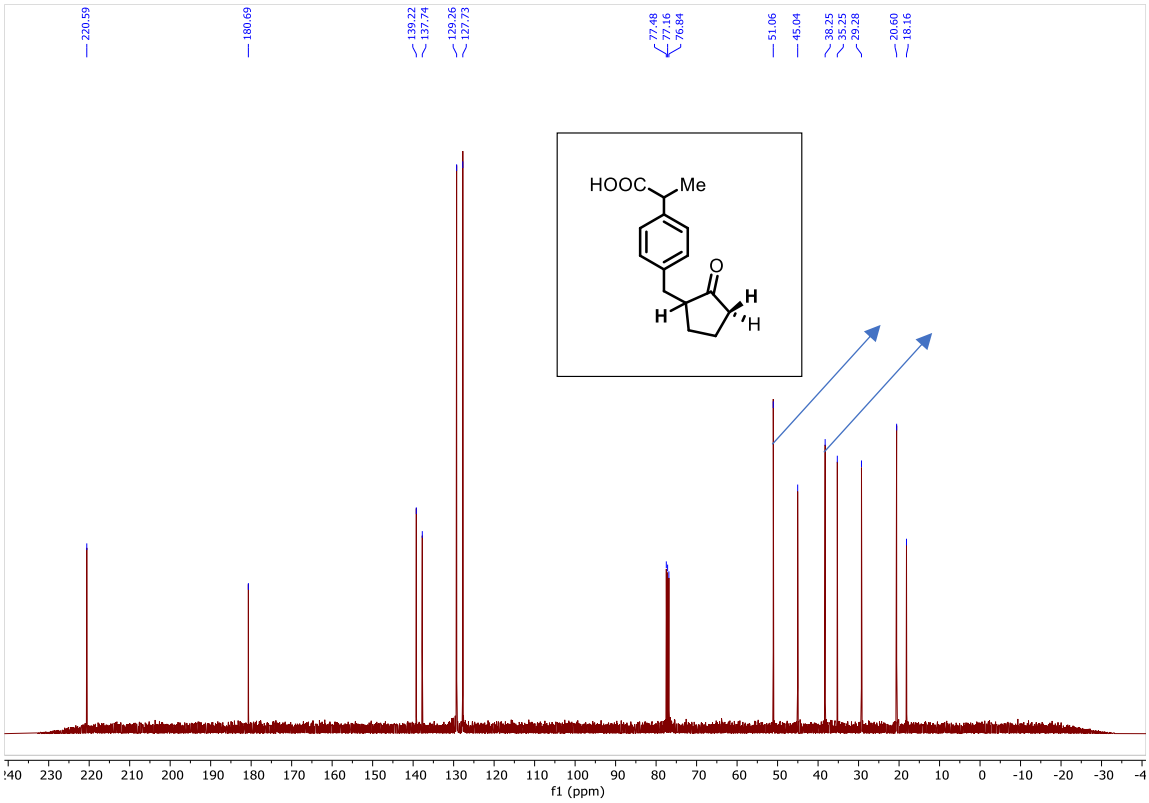
^{1}H NMR (400 MHz, $CDCl_3$) of **2-(4-((2-Oxocyclopentyl) methyl) phenyl) propanoic acid** (starting material of **3am**)



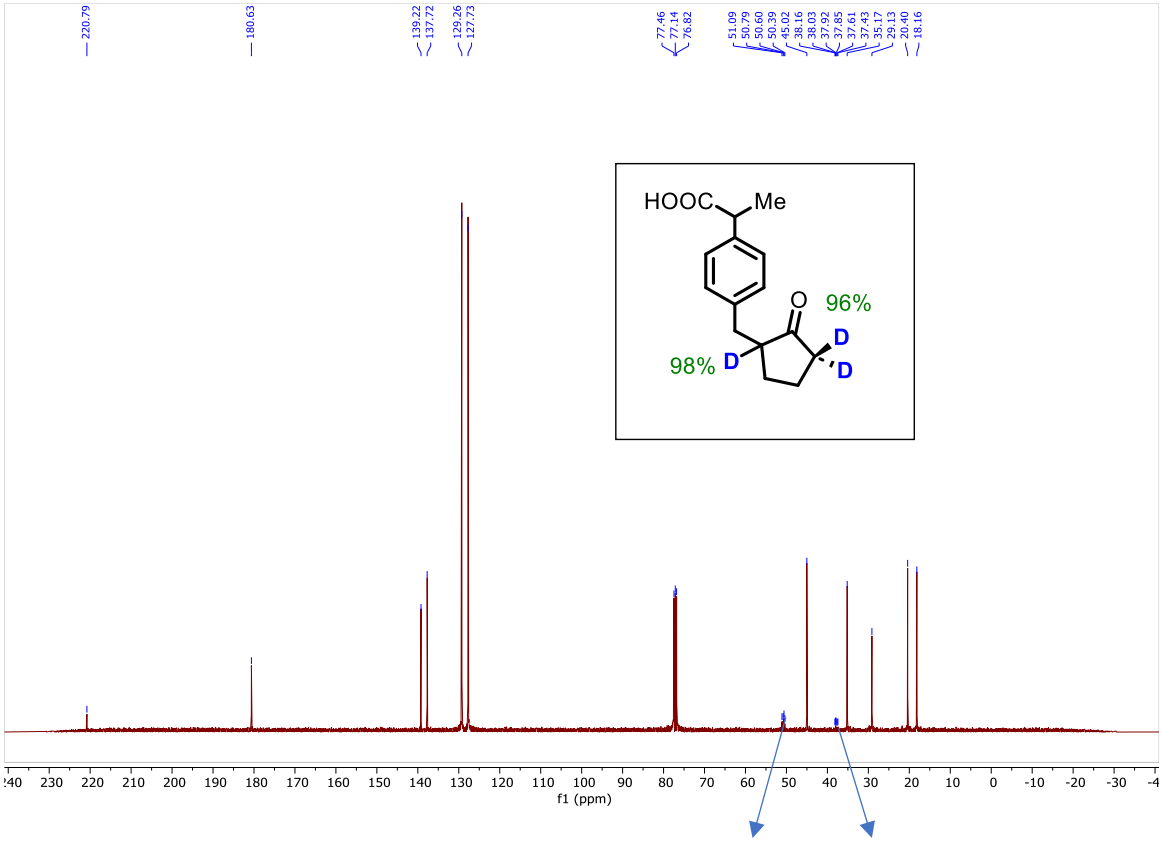
^{1}H NMR (400 MHz, $CDCl_3$) of **2-(4-((2-Oxocyclopentyl-1,3,3-d_3) methyl) phenyl) propanoic acid (3am)**



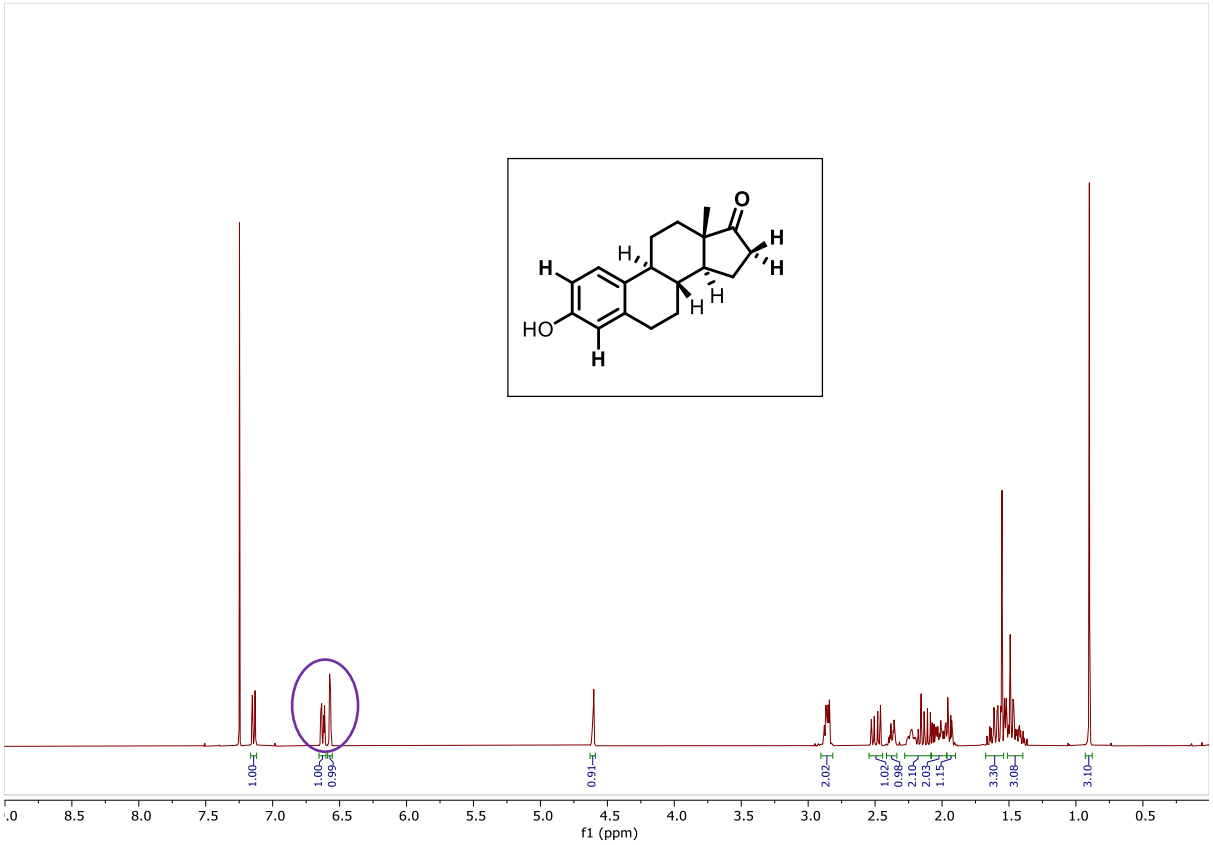
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **2-(4-((2-Oxocyclopentyl) methyl) phenyl) propanoic acid** (starting material of **3am**)



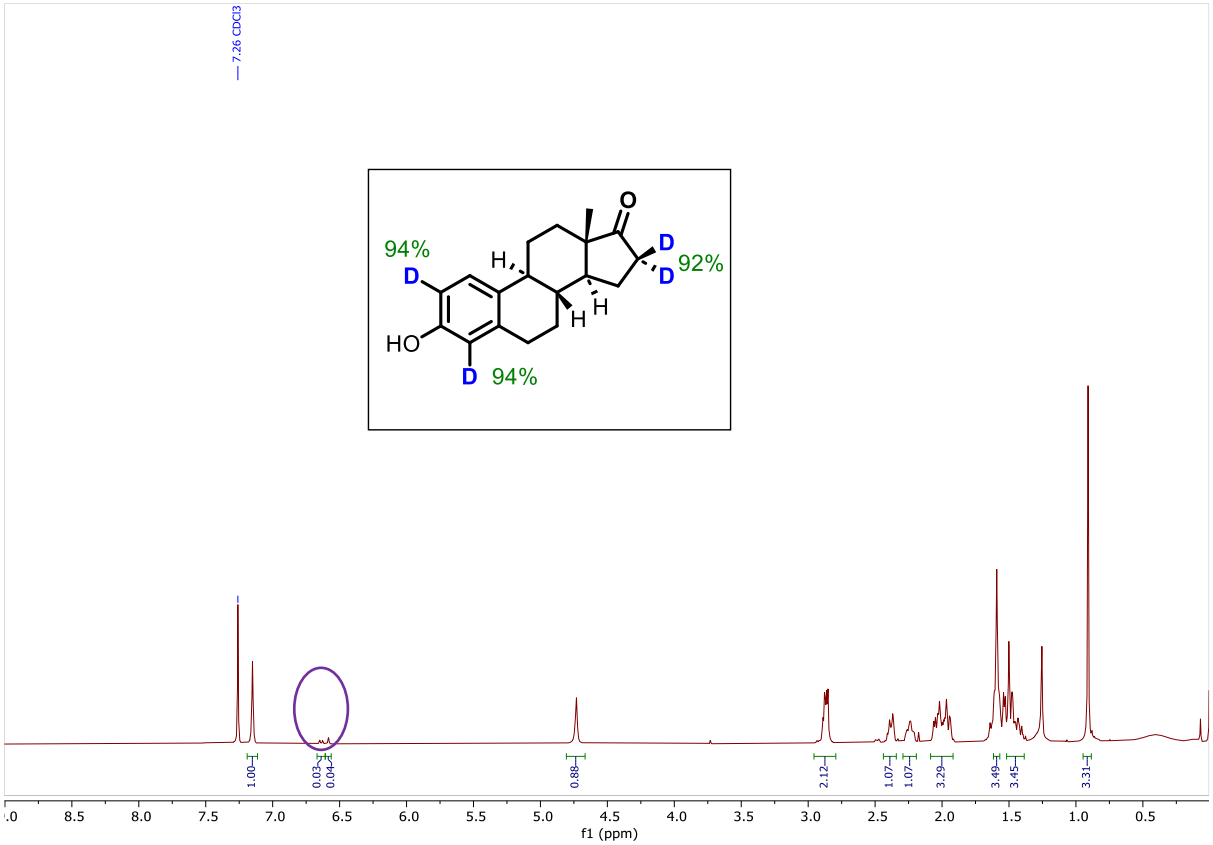
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **2-(4-((2-Oxocyclopentyl-1,3,3-d_3) methyl) phenyl) propanoic acid (3am)**



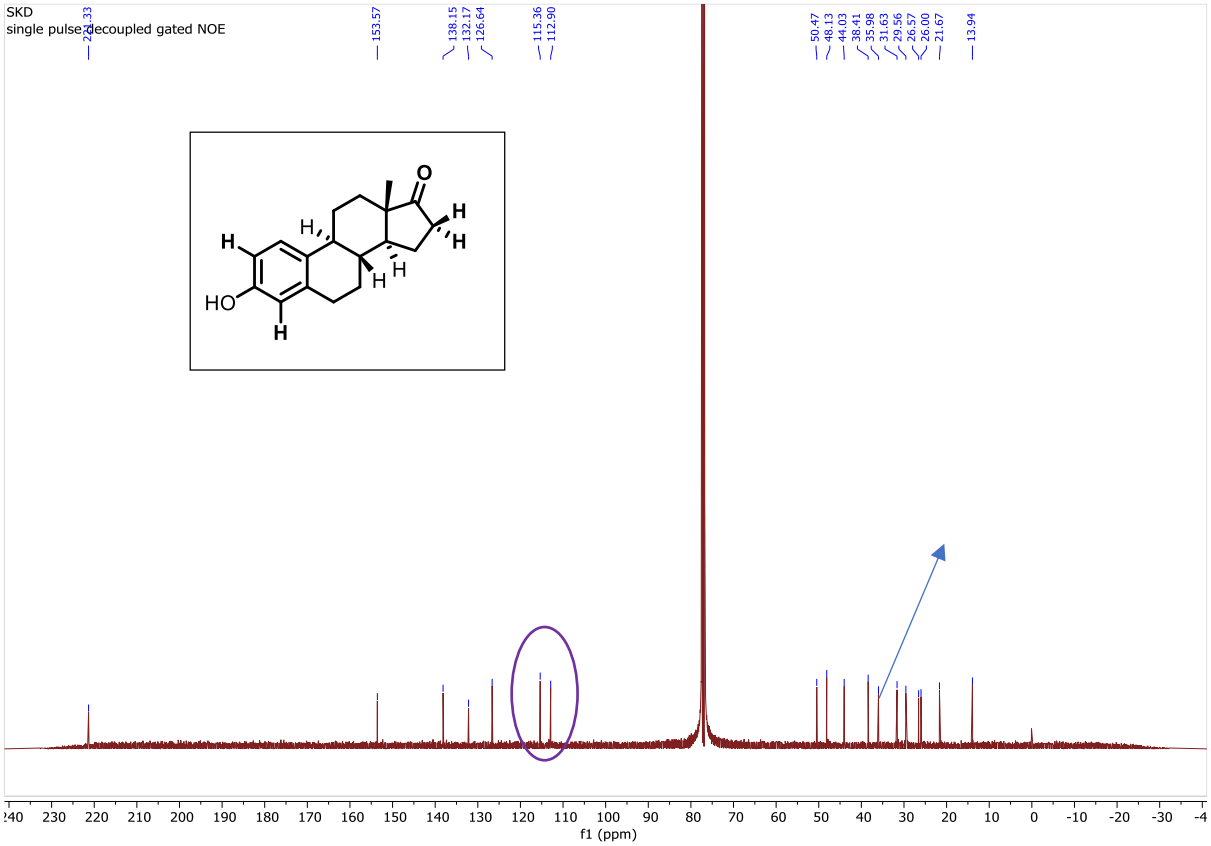
^{1}H NMR (400 MHz, $CDCl_3$) of **Estrone** (starting material of **3an**)



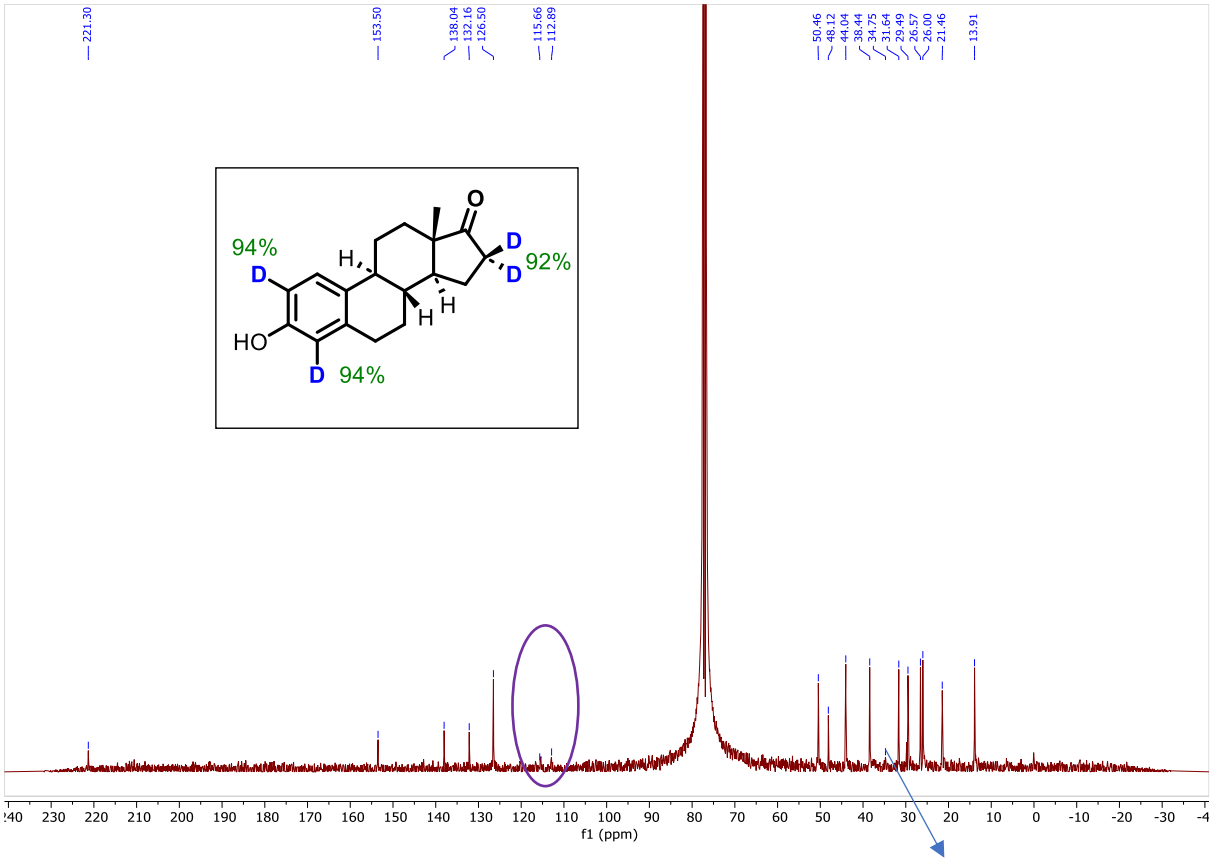
^{1}H NMR (400 MHz, $CDCl_3$) of **Estrone d_4 (3an)**



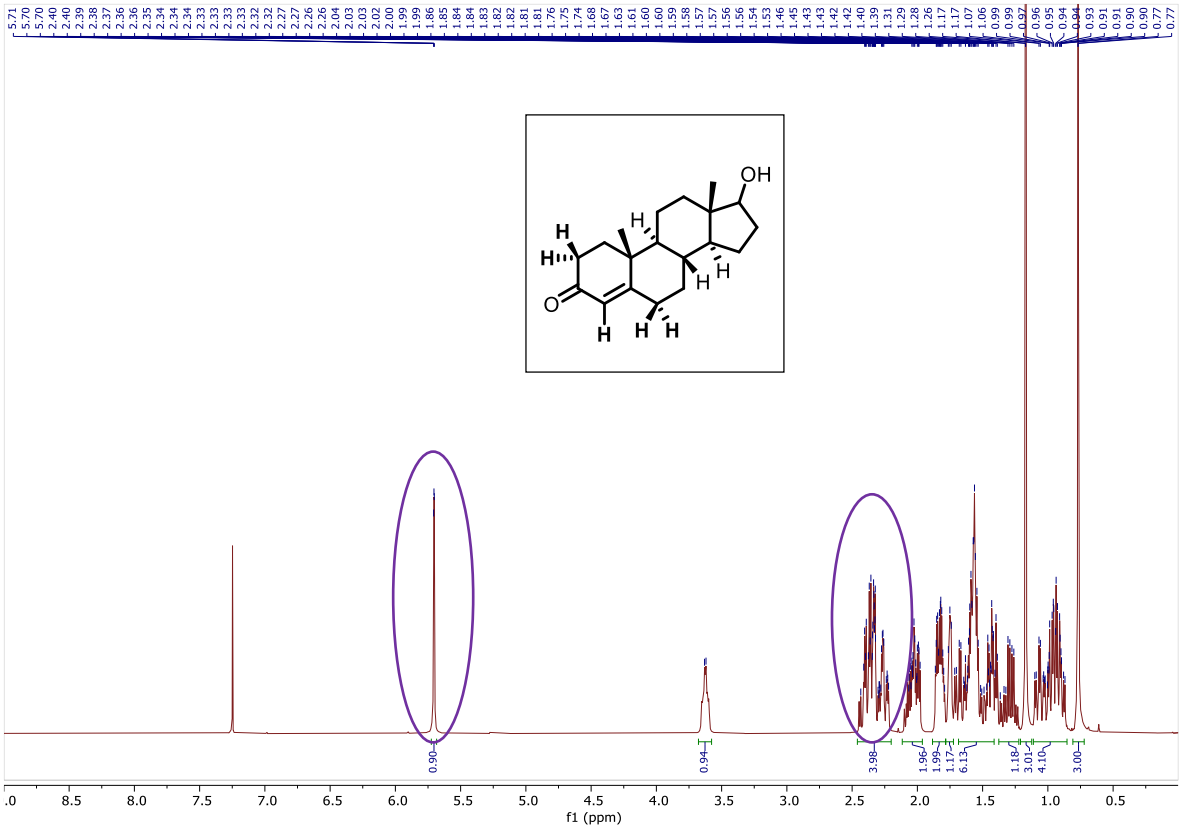
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Estrone** (starting material of **3an**)



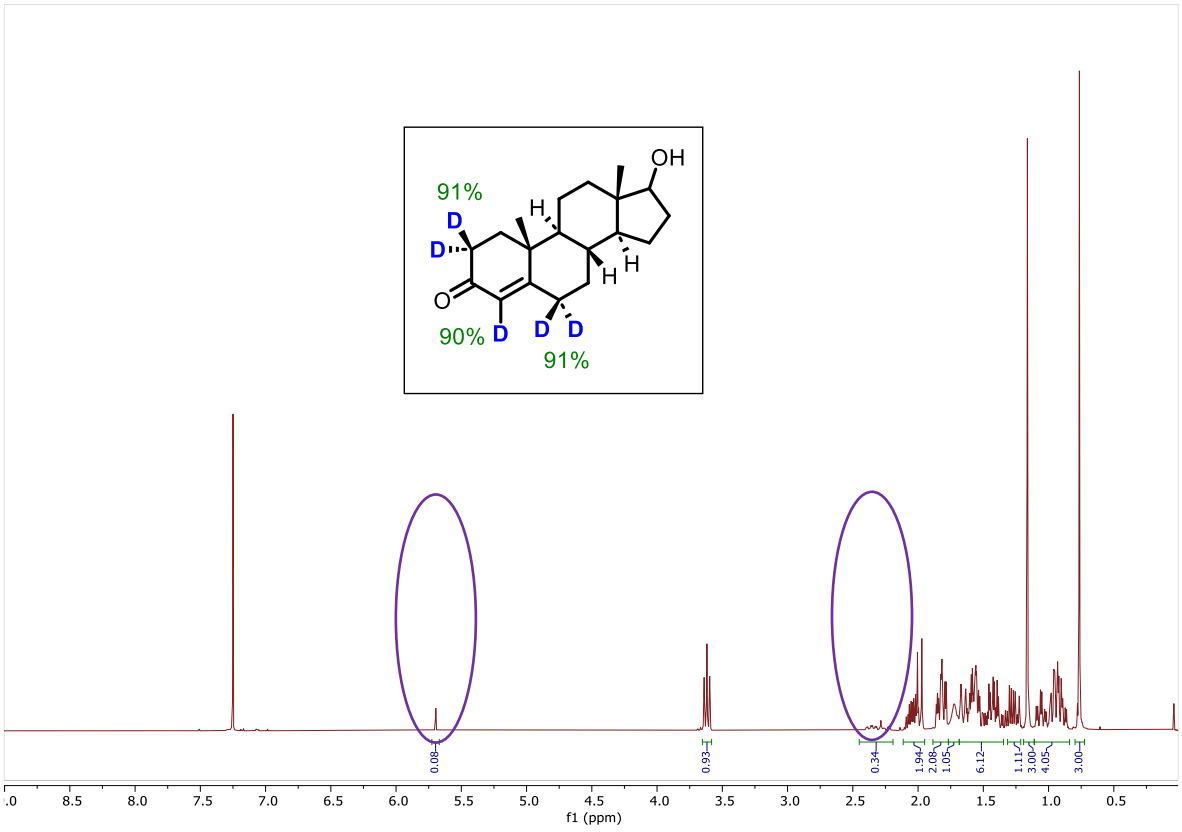
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Estrone d_4 (3an)**



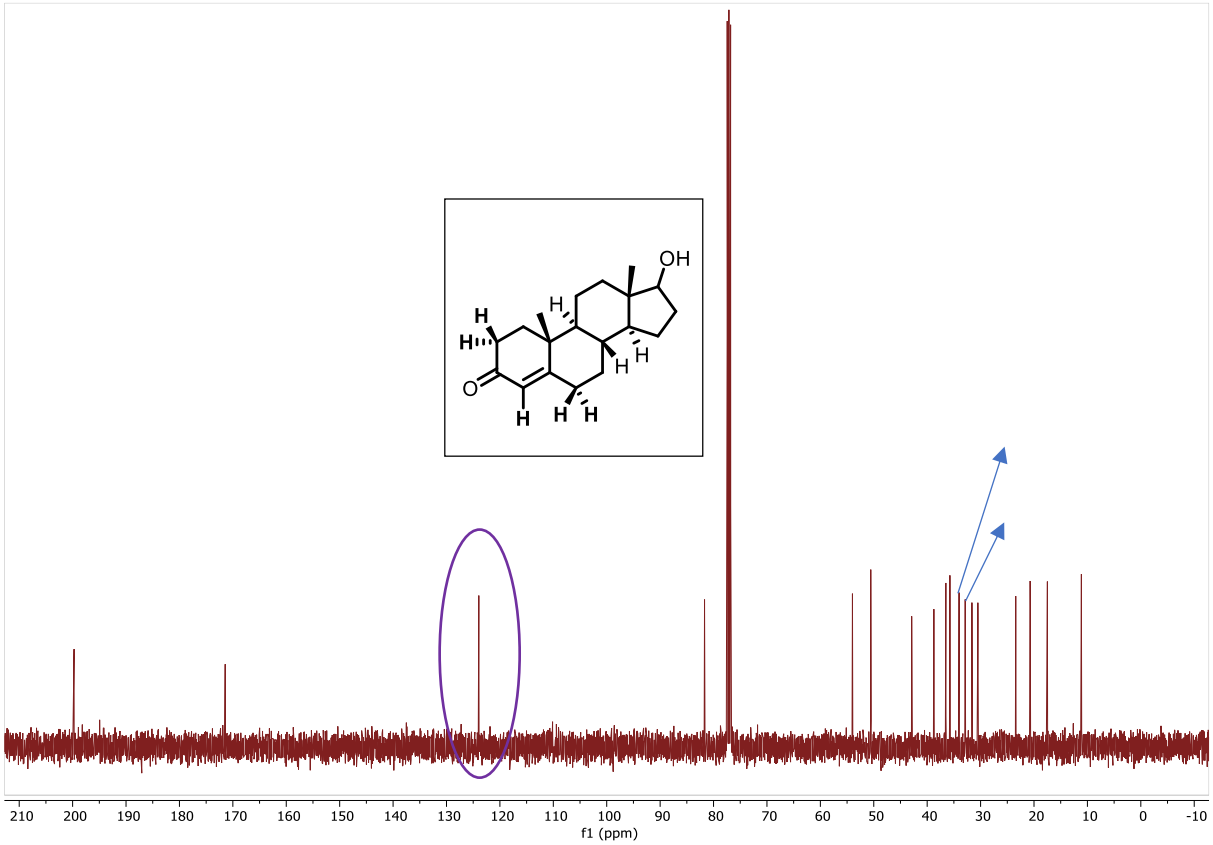
^{1}H NMR (400 MHz, $CDCl_3$) of **Testosterone** (starting material of **3ao**)



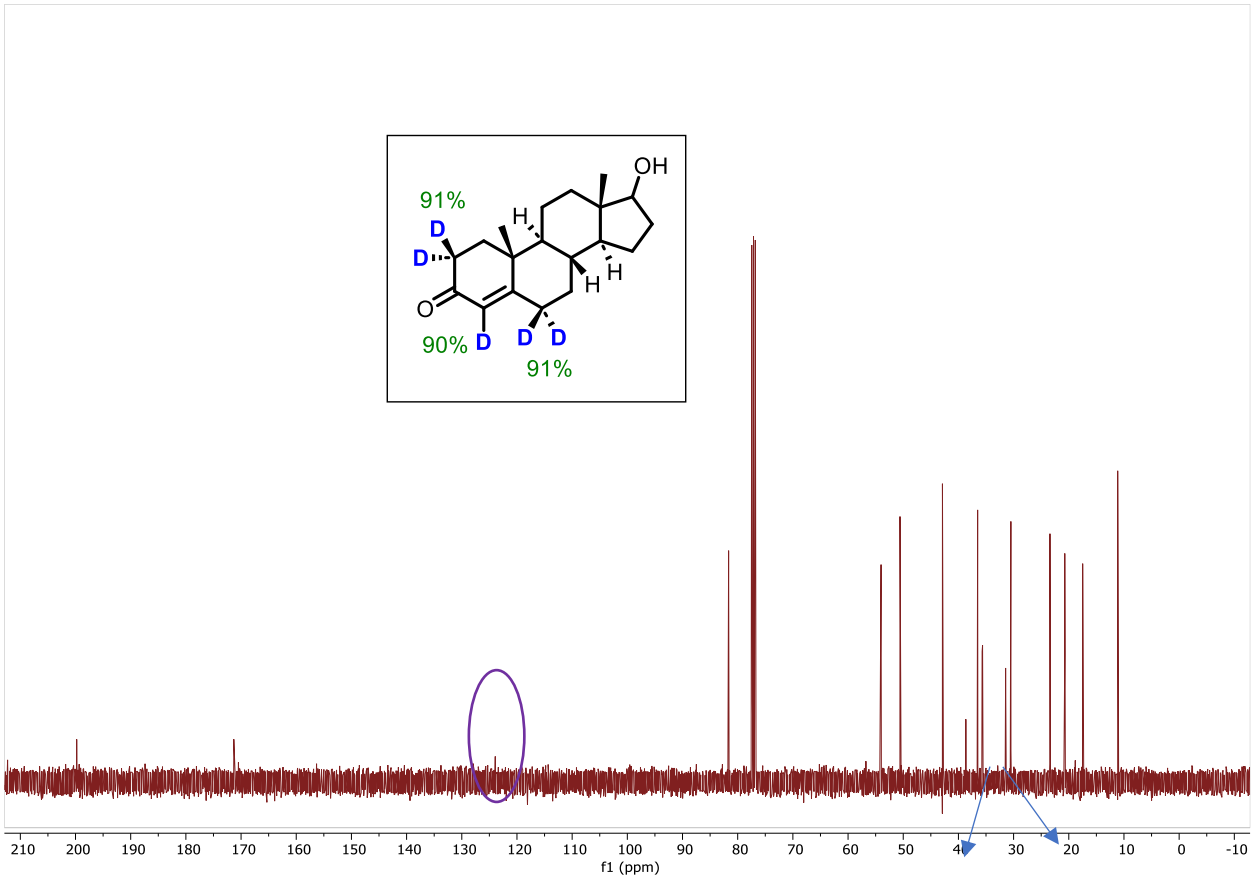
^{1}H NMR (400 MHz, $CDCl_3$) of **Testosterone d_5 (3ao):**



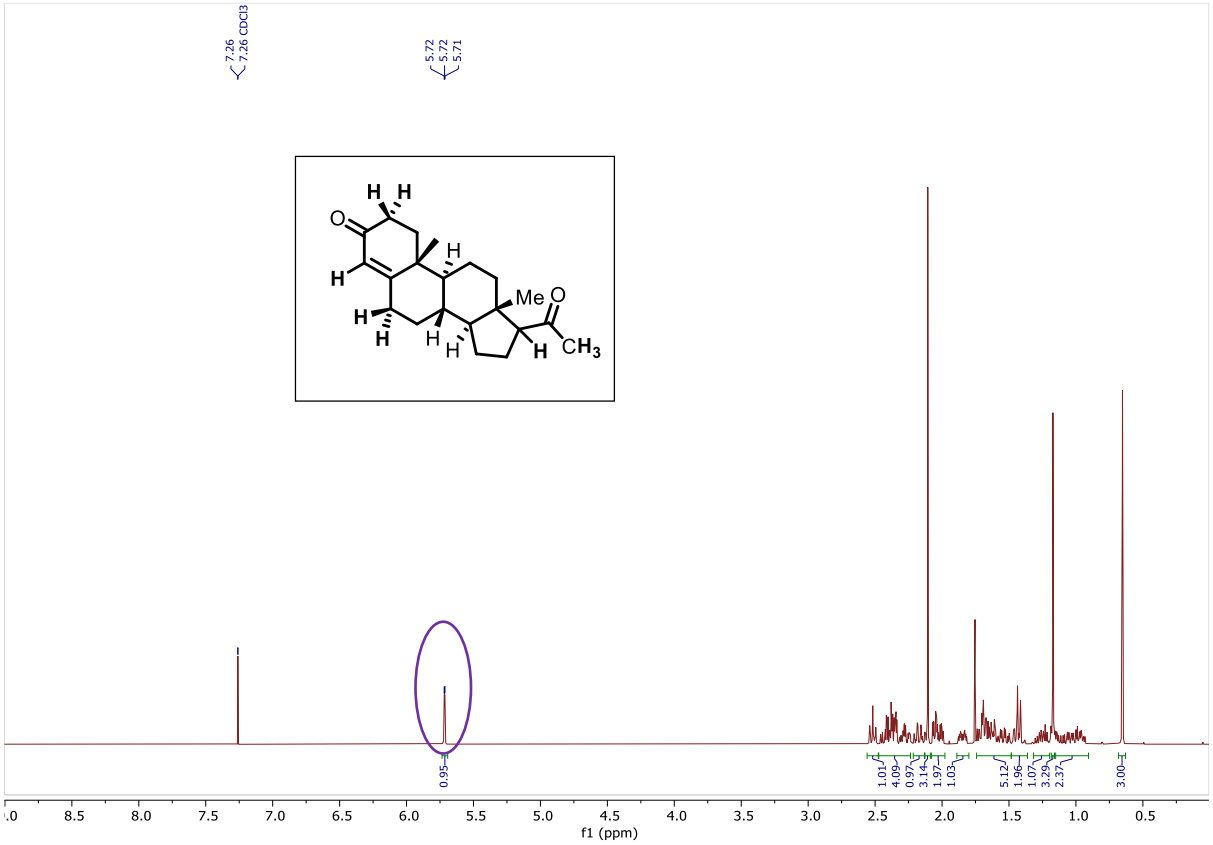
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Testosterone** (starting material of **3ao**)



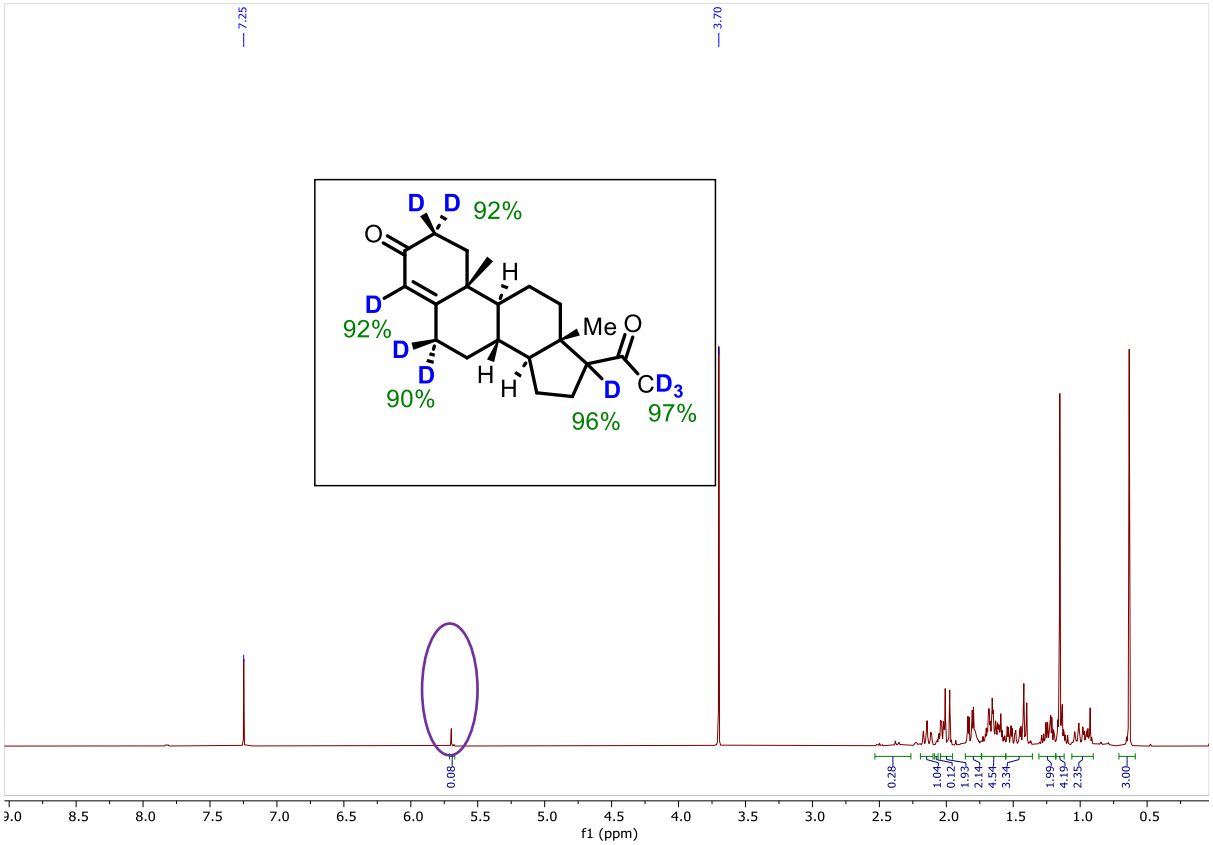
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Testosterone *d_5* (3ao):**



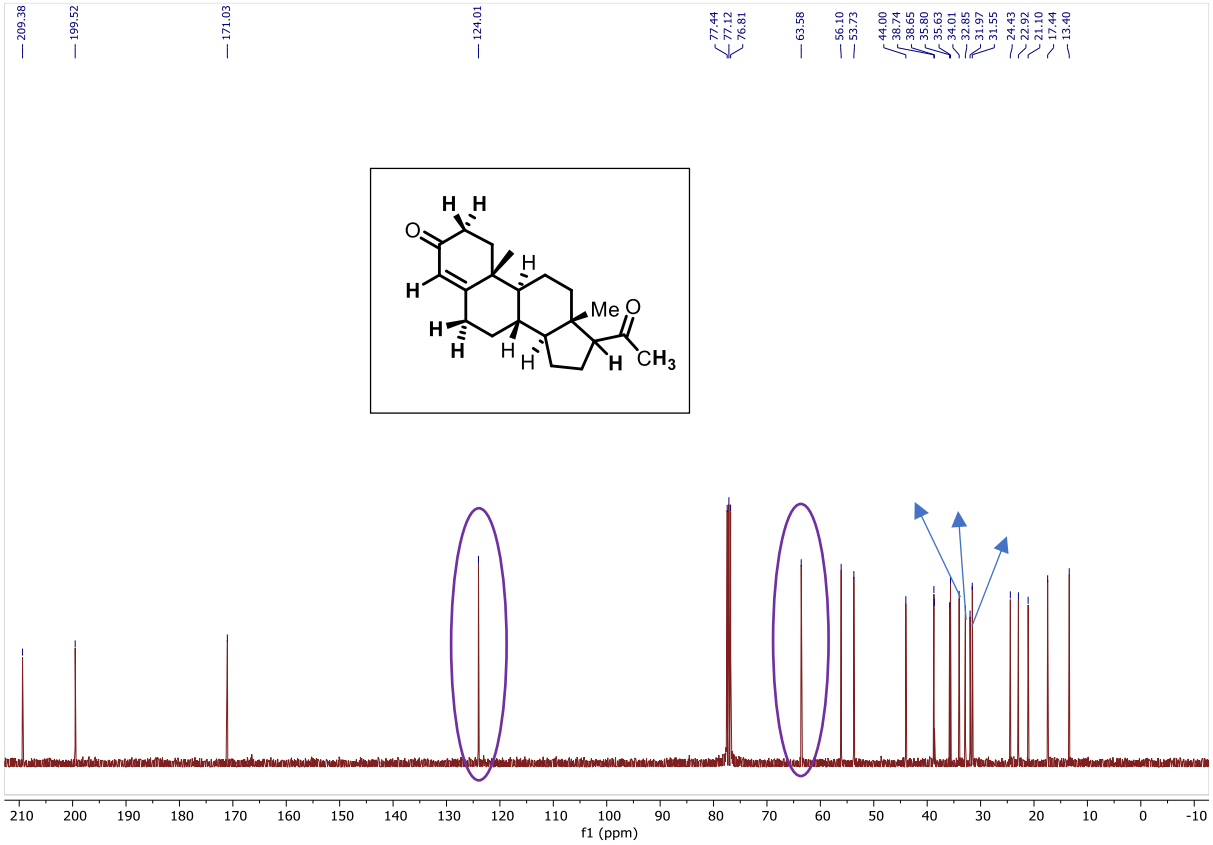
^{1}H NMR (400 MHz, $CDCl_3$) of **Progesterone** (starting material of **3ap**)



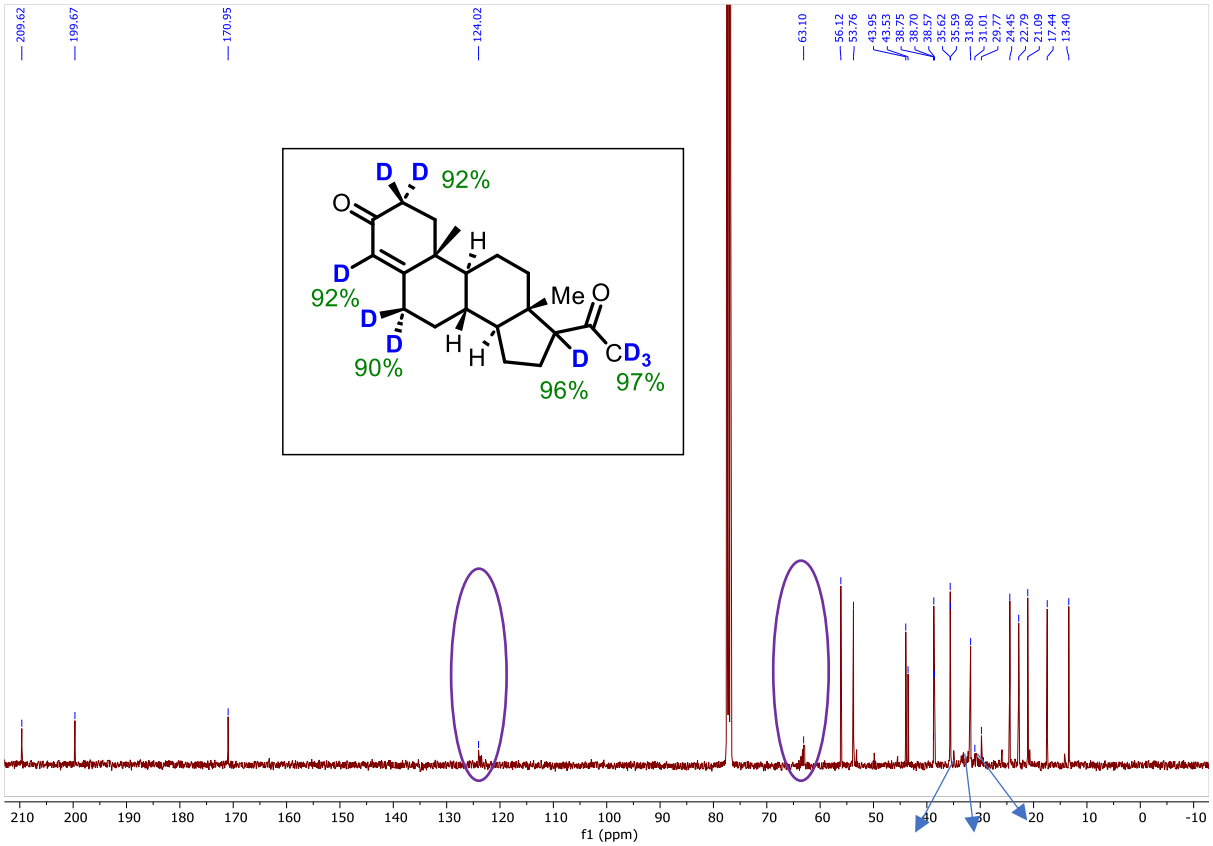
^{1}H NMR (400 MHz, $CDCl_3$) of **Progesterone d_9 (3ap)**



^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Progesterone** (starting material of **3ap**)



^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) of **Progesterone d_9 (3ap)**



The GC-MS spectra of the crude reaction mixture after 24 h of **3l**