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Supplementary Information for

Synthesis of ^{18}O-Alcohols from Unlabelled Alcohols

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General Information

Reagents and Solvents

Unless otherwise noted, reagents were purchased from commercial suppliers and used directly without further purification. 4 M HCl in dioxane was purchased from Acros (product code: MFCD00011324). 4-nitrobenzonitrile was purchased from Acros (product code: MFCD00007279) and dried in an Abderhalden drying pistol using $CaCl_2$ as the dessicant at 50 °C for 24 hours before use. H_2O-[^{18}O] (98% isotopic purity) was purchased from Sercon Ltd. (product code: F03-0027). Unless indicated, technical grade solvents were purchased from commercial suppliers and used without further purification. Petrol refers to 40-60 petroleum ether. Unless otherwise stated, all toluene was dried by passing over two columns of activated alumina and kept over sodium wire. All water was deionised before use. Unless stated, all reactions were carried out in conventional glassware. 'Room temperature' can vary between 18 °C and 25 °C.

Analysis and Characterization

Analytical Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed silica gel 60 F_{254} plates (product code: 105554.) Developed TLC plates were visualized by ultraviolet (UV) irradiation (254 nm) or by staining with a solution of potassium permanganate. Column chromatography was carried out according to Still's method,[1] using Fluorochem silica gel 60 Å, 40–63 mesh (product code = LC401). Melting points were measured using a Stuart SMP3 (Sigma Aldrich product Z645729.) Fourier Transform Infrared Spectrometry (FTIR) was carried out using a Bruker Tensor 27 using an Attenuated Total Reflection (ATR) attachment and peaks are reported in terms of frequency of absorption (cm^{-1}). High Resolution Mass Spectrometry HRMS were acquired using a Bruker microTOF II with Electron Spray Ionization (ESI-TOF). HRMS data were quoted to four decimal places (0.1 mDa). All NMR spectra were recorded at 298 K on either a Bruker AV 400, Bruker AV 3400 or Bruker Ascent 500 and are internally referenced to residual solvent signals ($CDCl_3$ is referenced at δ 7.26 and 77.16 for ^{1}H and ^{13}C NMR respectively, DMSO-d_6 is referenced at δ 2.50 and 39.52 for ^{1}H and ^{13}C NMR respectively, CD_3OD is referenced at δ 3.31 and 49.00 for ^{1}H and ^{13}C NMR respectively). All NMR chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: δ (multiplicity, coupling constant *J*, number of protons.)

Optimization for the Hydrolysis of 4-Nitrobenzonitrile

General Procedure for the Acid-Mediated Hydrolysis of 4-Nitrobenzonitrile

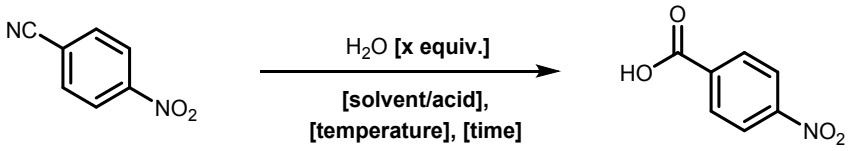
Reactions were run at scales varying from 0.50 mmol to 10.0 mmol.

To a Biotage® microwave vial was added 4-nitrobenzonitrile (1 equiv.), the designated solvent and anhydrous acid source then H_2O (2.20–2.50 equiv.) The microwave vial was capped, heated to the indicated temperature and stirred for the indicated amount of time.

Entries 1–5: Yields were determined by ^1H NMR spectroscopy, using 1,1,2,2-tetrachloroethane as an internal standard.

Entries 6–8: Yields are quoted as isolated yields. The reaction mixture was diluted with $CHCl_3$ (2 × volume of reaction solvent) and the precipitate was collected by filtration. The filter cake was washed with $CHCl_3$ and the solid was dried under vacuum, to afford the pure 4-nitrobenzoic acid.

Table S1. The results of optimization of the hydrolysis of 4-nitrobenzonitrile. *Isolated product was impure, therefore an accurate isolated yield could not be obtained.



Entry	H_2O equiv.	Solvent/Acid	Temperature / (°C)	Time / (h)	Concentration / (M)	Yield / (%)
1	2.50	20% v/v 1 M HCl in diethyl ether in DMF	25 °C	24 h	0.5 M	0%
2	2.50	20% v/v 1 M HCl in diethyl ether in toluene	25 °C	24 h	0.5 M	0%
3	2.50	20% v/v 1 M HCl in diethyl ether in DMSO	25 °C	24 h	0.5 M	0%
4	2.50	5% w/v Amberlyst® 15 in 1,2-DCE	85 °C	24 h	0.5 M	<5%
5	2.20	35% v/v TfOH in dioxane	90 °C	24 h	2.0 M	85%
6	2.50	4 M HCl in dioxane	90 °C	16 h	0.5 M	83%
7	2.50	4 M HCl in dioxane	90 °C	16 h	1.8 M	91%
8	2.50	4 M HCl in dioxane	90 °C	16 h	2.8 M	n/a*

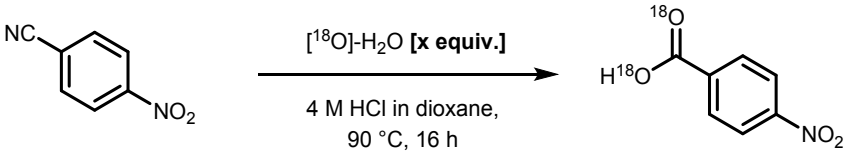
General Procedure for the Acid-Mediated Hydrolysis of 4-Nitrobenzonitrile

A 0.5–2 mL Biotage® microwave vial (Biotage® product code: 352016) containing a magnetic stirrer bar was dried in an oven at 130 °C for 24 hours. 4-Nitrobenzonitrile (148 mg, 1.00 mmol) was then added and the vial was capped with a Biotage® cap with septum (Biotage® product code: 352298). The vial was purged with argon and allowed to cool to room temperature under an argon atmosphere. 4 M HCl in dioxane (0.4 mL) was added followed by [^{18}O]-H_2O (2.00–2.50 equiv.). The reaction mixture was heated to 90 °C and stirred for 16 hours. The reaction mixture was then cooled to room temperature, diluted with $CHCl_3$ (0.8 mL) and the precipitate was collected by filtration. The

filter cake was washed with $CHCl_3$ and the solid was dried under vacuum, to afford pure ^{18}O-enriched 4-nitrobenzoic acid.

Yields are quoted as isolated yields.

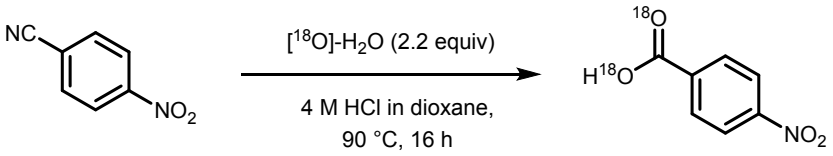
Table S2. The results of optimization of the hydrolysis of 4-nitrobenzonitrile using H_2O-[^{18}O]. ^{18}O-enrichment is quoted as the mol% of sample enriched with two ^{18}O labels.



Entry	H_2O equivalents	Yield / (%)	^{18}O-enrichment / (%)
1	2.50	91	92*
2	2.20	92	93*
3	2.00	84	89*

Synthesis Procedures and Characterization Data

Preparation of ^{18}O-Enriched 4-Nitrobenzoic acid-[^{18}O]$_2$ (2)



A 10–20 mL Biotage® microwave vial (Biotage® product code: 354833) containing a magnetic stirrer bar was dried in an oven at 130 °C for 24 hours. 4-Nitrobenzonitrile (3.36 g, 22.7 mmol) was then added and the vial was capped with a Biotage® cap with septum (Biotage® product code: 352298). The vial was purged with argon then allowed to cool to room temperature under an argon atmosphere. 4 M HCl in dioxane (9 mL) was added *via* the septum followed by H_2O-[^{18}O] (900 µL, 50.0 mmol). The reaction mixture was heated to 90 °C and stirred for 16 hours. The reaction mixture was cooled to room temperature, $CHCl_3$ (18 mL) was then added and the precipitate was collected by filtration. The filter cake was washed with $CHCl_3$ and the solid was dried under vacuum, to afford the title compound as an off-white solid (3.46 g, 89%). **^{1}H NMR** (400 MHz, CD_3OD) δ 8.33 (d, *J* = 8.9 Hz, 2H), 8.24 (d, *J* = 8.9 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, CD_3OD) δ 167.5, 152.0, 137.6, 131.9, 124.5; **HRMS** (ESI-TOF) *m/z* calc'd for $C_7H_4N^{16}O_2{}^{18}O_2$ $[M - H]^-$: 170.0231; found 170.0233. also *m/z* calc'd for $C_7H_4N^{16}O_3{}^{18}O$ $[M - H]^-$: 168.0188; found 168.0188. The ratio of relative peak intensities for the relevant isotopologues was 93:7 ($C_7H_4N^{16}O_2{}^{18}O_2$:$C_7H_4N^{16}O_3{}^{18}O$). No *m/z* corresponding to the unlabeled substrate was detected; **m.p.:** 236–239 °C (lit. m.p. = 237–239 °C).[2] Data are consistent with those reported in the literature.[3]

Additional Notes

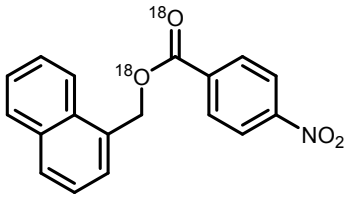
It is very important that anhydrous HCl in dioxane is used. Once the commercial reagent is opened the ingress of $^{16}OH_2$ will result in lower ^{18}O incorporation. The following points should be noted:

- 4 M HCl in dioxane was purchased from Acros (product code: MFCD00011324) since it was found to give the highest ^{18}O enrichment. Please ensure that the reagent is contained and stored in a bottle equipped with an AcroSeal®.
- Once opened and used for the first time, the longer the 4 M HCl in dioxane is kept in storage, the lower the ^{18}O enrichment will be (as the reagent is hygroscopic.) *Ideally, the reagent should be new and unopened when used in this reaction.*
- Attempts to dry the 4 M HCl in dioxane with common desiccants ($MgSO_4$, 3 Å, 4 Å and 5 Å molecular sieves) were unsuccessful.
- The glassware **must** be allowed to cool to room temperature before the 4 M HCl in dioxane is added.

General Procedure for the Synthesis of ^{18}O-enriched Esters

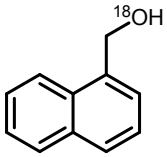
To a solution of alcohol (0.50 mmol), ^{18}O-enriched 4-nitrobenzoic acid (0.50 mmol) and triphenylphosphine (0.60 mmol) in THF (2 mL) was added DIAD (0.60 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2–48 hours. The reaction mixture was then diluted with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL) dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography to afford the ^{18}O-enriched ester.

Naphthalen-1-ylmethyl 4-nitrobenzoate-[^{18}O]$_2$ (S1)



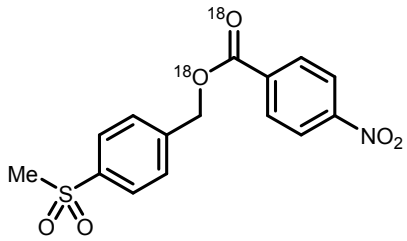
Synthesised according to the general procedure using 1-naphthalenemethanol (79 mg, 0.50 mmol), 4-nitrobenzoic acid-[^{18}O]$_2$ **(2)** (86 mg, 0.50 mmol), PPh_3 (157 mg, 0.600 mmol) and DIAD (120 µL, 0.600 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 4 hours. Purification by flash column chromatography (SiO_2, 3:17 Et_2O:petrol) afforded the title compound as a colourless solid (121 mg, 78%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.1 Hz, 2H), 8.21 (d, *J* = 9.1 Hz, 2H), 8.13 – 8.07 (m, 1H), 7.95 – 7.88 (m, 2H), 7.64 (dd, *J* = 7.0, 1.3 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.50 (dd, *J* = 8.3, 7.0 Hz, 1H), 5.87 (s, 2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 164.7, 150.7, 135.6, 134.0, 131.9, 131.0, 130.9, 130.0, 129.1, 128.2, 127.0, 126.3, 125.5, 123.7, 123.5, 66.2; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{18}H_{13}NaN^{16}O_2{}^{18}O_2$ [M + Na]$^+$: 334.0822; found 334.0819. also *m/z* calc'd for $C_{18}H_{13}NaN^{16}O_3{}^{18}O_1$ [M + Na]$^+$: 332.0779; found 332.0788. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{18}H_{13}NaN^{16}O_2{}^{18}O_2$:$C_{18}H_{13}NaN^{16}O_3{}^{18}O_1$); **m.p.:** 120–122 °C (lit. m,p, = 121 °C)[4]; **TLC:** R_f = 0.80 (4:1 Et_2O/petrol). Data are consistent with those reported in the literature.[4]

1-Naphthalenemethanol-[^{18}O] (3a)



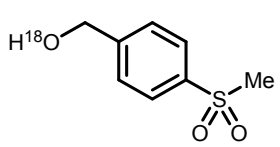
To a solution of **S1** (40 mg, 0.13 mmol) in 1:1 THF/MeOH (2 mL) was added LiOH (190 µL of a 2 M aqueous solution, 0.380 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated, to afford the title compound as a colourless solid (19 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.2 Hz, 1H), 7.91 – 7.86 (m, 1H), 7.84 – 7.80 (m, 1H), 7.58 – 7.49 (m, 3H), 7.46 (dd, *J* = 8.2, 7.0 Hz, 1H), 5.16 (s, 2H), 1.86 (s, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 136.4, 133.9, 131.4, 128.8, 128.7, 126.5, 126.0, 125.5, 125.5, 123.8, 63.8; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{10}Na^{18}O$ [M + Na]$^+$: 183.0666; found 183.0672. also *m/z* calc'd for $C_{11}H_{10}Na^{16}O$ [M + Na]$^+$: 181.0624; found 181.0641. The ratio of relative peak intensities for the relevant isotopologues was 94:6 ($C_{11}H_{10}Na^{18}O$: $C_{11}H_{10}Na^{16}O$); **m.p.:** 62–64 °C (lit. m.p. = 61–63 °C)[5]; **TLC:** R_f = 0.50 (4:1 Et_2O/petrol). Data are consistent with those reported in the literature.[6]

(4-(Methylsulfonyl)phenyl)methanyl 4-nitrobenzoate-[$^{18}O]_2$ (S2)



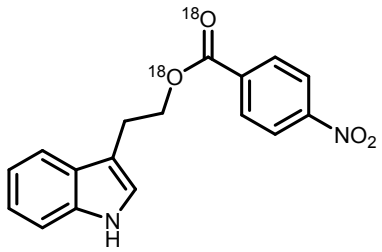
Synthesised according to the general procedure using 4-(methylsulfonyl)benzyl alcohol (93 mg, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O]_2$ **(2)** (86 mg, 0.50 mmol), PPh_3 (157 mg, 0.600 mmol) and DIAD (120 µL, 0.600 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 4 hours. Purification by flash column chromatography (SiO_2, 9:11 EtOAc:petrol) afforded the title compound as a colourless solid (68 mg, 40%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.1 Hz, 2H), 8.25 (d, *J* = 9.1 Hz, 2H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 5.49 (s, 2H), 3.07 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.4, 151.0, 141.6, 140.9, 135.0, 131.0, 129.0, 128.1, 123.9, 66.4, 44.7; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{15}H_{17}N_2{}^{16}O_4{}^{18}O_2S$ $[M + NH_4]^+$: 357.0887; found 357.0883. also *m/z* calc'd for $C_{15}H_{17}N_2{}^{16}O_5{}^{18}OS$ $[M + NH_4]^+$: 355.0844; found 355.0846. The ratio of relative peak intensities for the relevant isotopologues was 91:9 ($C_{15}H_{17}N_2{}^{16}O_4{}^{18}O_2S$:$C_{15}H_{17}N_2{}^{16}O_5{}^{18}OS$); **FTIR** (neat) ν_{max}/cm^{-1} 3112, 3022, 2920, 1691, 1603, 1524, 1322, 1247, 1145, 1089, 1010; **m.p.:** 156–158 °C; **TLC:** R_f = 0.24 (7:3 EtOAc/petrol).

(4-(Methylsulfonyl)phenyl)methanol-^{18}O (3b)



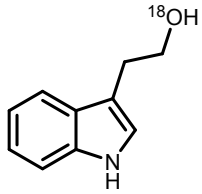
To a solution of **S2** (62 mg, 0.18 mmol) in 1:1 THF/MeOH (2 mL) was added LiOH (270 µL of a 2 M aqueous solution, 0.540 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated, to afford the title compound as a colourless solid (30 mg, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 4.82 (s, 2H), 3.04 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 147.4, 139.6, 127.7, 127.4, 64.3, 44.7; **HRMS** (ESI-TOF) *m/z* calc'd for $C_8H_{10}Na^{16}O_2{}^{18}OS$ $[M + Na]^+$: 211.0285; found 211.0285. also *m/z* calc'd for $C_8H_{10}Na^{16}O_3S$ $[M + Na]^+$: 209.0243; found 209.0247. The ratio of relative peak intensities for the relevant isotopologues was 95:5 ($C_8H_{10}Na^{16}O_2{}^{18}OS$:$C_8H_{10}Na^{16}O_3S$); **m.p.:** 82–86 °C (lit. m.p.: 82–84 °C)[7]; **TLC:** R_f = 0.62 (7:3 EtOAc/petrol). Data are consistent with those reported in the literature.[7]

2-(1*H*-Indol-3-yl)ethyl 4-nitrobenzoate-[^{18}O]$_2$ (S3)



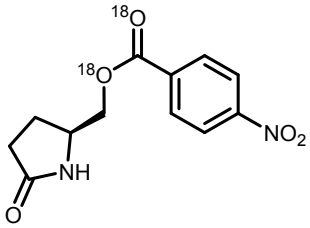
Synthesised according to the general procedure using 3-(2-hydroxyethyl)indole (81 mg, 0.50 mmol), 4-nitrobenzoic acid-[^{18}O]$_2$ **(2)** (86 mg, 0.50 mmol), PPh_3 (157 mg, 0.600 mmol) and DIAD (120 µL, 0.600 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 4 hours. Purification by flash column chromatography (SiO_2, 11:9 CH_2Cl_2:petrol) afforded the title compound as a bright orange solid (82 mg, 51%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 8.18 (d, *J* = 9.0 Hz, 2H), 8.04 (s, 1H), 7.67 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.39 (apparent dt, *J* = 8.2, 1.0 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.18 – 7.09 (m, 2H), 4.66 (t, *J* = 7.1 Hz, 3H), 3.27 (td, *J* = 7.1, 1.0 Hz, 2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 164.9, 150.7, 136.4, 135.9, 130.9, 127.5, 123.7, 122.5, 122.2, 119.8, 118.9, 111.9, 111.4, 66.1, 24.9; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{14}N_2Na^{16}O_2{}^{18}O_2$ $[M + Na]^+$: 337.0931; found 337.0935. also *m/z* calc'd for $C_{17}H_{14}N_2Na^{16}O_3{}^{18}O$ $[M + Na]^+$: 335.0888; found 335.0885. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{17}H_{14}N_2Na^{16}O_2{}^{18}O_2$:$C_{17}H_{14}N_2Na^{16}O_3{}^{18}O$); **FTIR** (neat) ν_{max}/cm^{-1} 3373, 1679, 1599, 1362, 1311, 1222, 1099, 1011; **m.p.:** 151–152 °C; **TLC:** R_f = 0.56 (4:1 Et_2O/petrol).

2-(1*H*-Indol-3-yl)ethanol-[^{18}O] (3c)



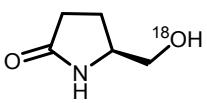
To a solution of **S3** (50 mg, 0.16 mmol) in 1:1 THF/MeOH (2 mL) was added LiOH (240 µL of a 2 M aqueous solution, 0.480 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated, to afford the title compound as a colourless solid (24 mg, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.63 (apparent dt, *J* = 7.9, 1.0 Hz, 1H), 7.38 (apparent dt, *J* = 8.2, 1.0 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.17 – 7.07 (m, 2H), 3.92 (t, *J* = 6.3 Hz, 2H), 3.05 (td, *J* = 6.3, 0.8 Hz, 2H), 1.60 (s, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 136.6, 127.6, 122.6, 122.4, 119.6, 119.0, 112.5, 111.4, 62.8, 28.9; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{10}H_{12}N^{18}O$ $[M + H]^+$: 164.0956; found 164.0960. also *m/z* calc'd for $C_{10}H_{12}N^{16}O$ $[M + H]^+$: 162.0913; found 162.0920. The ratio of relative peak intensities for the relevant isotopologues was 96:4 ($C_{10}H_{12}N^{18}O$:$C_{10}H_{12}N^{16}O$); **m.p.:** 58–60 °C (lit. m.p.: 56–59 °C)[8]; **TLC:** R_f = 0.24 (4:1 Et_2O/petrol). Data are consistent with those reported in the literature.[9]

(*S*)-(5-Oxopyrrolidin-2-yl)methyl 4-nitrobenzoate-[^{18}O]$_2$ (S4)



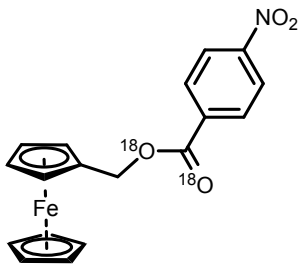
Synthesised according to the general procedure using (*S*)-(+)-5-hydroxymethyl-2-pyrrolidinone (115 mg, 1.00 mmol), 4-nitrobenzoic acid-[^{18}O]$_2$ **(2)** (216 mg, 1.20 mmol), PPh_3 (315 mg, 1.20 mmol) and DIAD (236 µL, 1.200 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 48 hours. Purification by flash column chromatography (SiO_2, 4:96 MeOH:EtOAc) afforded the title compound as a colourless solid (203 mg, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 9.1 Hz, 2H), 8.24 (d, *J* = 9.1 Hz, 2H), 7.01 (s, 1H), 4.51 (dd, *J* = 11.2, 3.8 Hz, 1H), 4.19 (dd, *J* = 11.2, 7.5 Hz, 1H), 4.12 – 4.04 (m, 1H), 2.44 – 2.32 (m, 3H), 1.99 – 1.86 (m, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 178.5, 164.5, 150.9, 135.0, 131.1, 123.8, 68.4, 53.0, 29.8, 23.3; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{12}H_{13}N_2{}^{16}O_3{}^{18}O_2$ $[M + H]^+$: 269.0904; found 269.0897. also *m/z* calc'd for $C_{12}H_{13}N_2{}^{16}O_4{}^{18}O_1$ $[M + H]^+$: 267.0861; found 267.0856. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{12}H_{13}N_2{}^{16}O_3{}^{18}O_2$: $C_{12}H_{13}N_2{}^{16}O_4{}^{18}O_1$); **FTIR** (neat) ν_{max}/cm^{-1} 3205, 3075, 2984, 1703, 1679, 1606, 1520; **m.p.:** 164–166 °C; **TLC:** R_f = 0.18 (3:97 MeOH/CH_2Cl_2).

(*S*)-(5-Oxopyrrolidin-2-yl)methanol (3d)



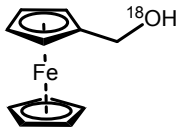
To a solution of **S4** (81 mg, 0.28 mmol) in 1:1 MeOH/H_2O (2 mL) was added K_2CO_3 (104 mg, 0.75 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 1:5 MeOH/EtOAc) to afford the title compound as a colourless oil (38 mg, 96%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 4.66 (s, 1H), 3.79 – 3.71 (m, 1H), 3.62 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.41 (dd, *J* = 11.4, 6.9 Hz, 1H), 2.39 – 2.23 (m, 2H), 2.17 – 2.06 (m, 1H), 1.75 (dddd, *J* = 12.9, 9.6, 7.2, 5.4 Hz, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 179.6, 65.7, 56.6, 30.4, 22.7; **HRMS** (ESI-TOF) *m/z* calc'd for $C_5H_9NNa^{16}O^{18}O$ $[M + Na]^+$: 140.0568; found 140.0596. also *m/z* calc'd for $C_5H_9NNa^{16}O_2$ $[M + Na]^+$: 138.0525; found 138.0524. The ratio of relative peak intensities for the relevant isotopologues was 96:4 ($C_5H_9NNa^{16}O^{18}O$:$C_5H_9NNa^{16}O_2$); **TLC:** R_f = 0.25 (1:5 MeOH/EtOAc). Data are consistent with those reported in the literature.[10]

Ferrocenemethanyl 4-nitrobenzoate-[$^{18}O]_2$ (S5)



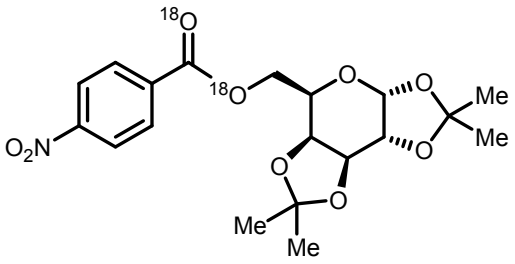
To a solution of ferrocenemethanol (108 mg, 0.500 mmol), 4-nitrobenzoic acid-[$^{18}O]_2$ **(2)** (128 mg, 0.750 mmol) and PPh_3 (197 mg, 0.750 mmol) in THF (2.5 mL) was added DIAD (148 µL, 0.750 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 8 hours. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 ×10 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL) dried over $MgSO_4$ and concentrated. As the product was unstable to normal phase silica gel, the crude material was used without further purification. Characteristic NMR signals: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.0 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 5.20 (s, 2H), 4.36 (t, *J* = 1.8 Hz, 2H), 4.23 (t, *J* = 1.8 Hz, 2H), 4.20 (s, 5H); **TLC:** R_f = 0.16 (1:9 Et_2O/petrol).

Ferrocenemethanol-[^{18}O] (3e)



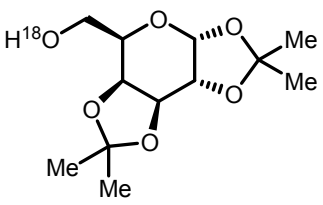
The crude mixture of **S5** was dissolved in 1:1 THF/MeOH (5 mL) and LiOH (750 µL of a 2 M aqueous solution, 1.50 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified twice by flash column chromatography (SiO_2, 1:3 EtOAc/petrol then 1:99 MeOH/CH_2Cl_2 to afford the title compound as an orange solid (87 mg, 80%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.33 (d, *J* = 5.8 Hz, 2H), 4.24 (t, *J* = 1.8 Hz, 2H), 4.20 – 4.15 (m, 7H), 1.53 (t, *J* = 5.8 Hz, 1H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 88.6, 68.5, 68.4, 68.0, 60.9. **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{12}FeNa^{18}O$ $[M + Na]^+$: 241.0172; found 241.0163. also *m/z* calc'd for $C_{11}H_{12}FeNa^{16}O$ $[M + Na]^+$: 239.0130; found 239.0157. The ratio of relative peak intensities for the relevant isotopologues was 87:13 ($C_{11}H_{12}FeNa^{18}O$:$C_{11}H_{12}FeNa^{16}O$); **m.p.:** 75–80 °C (lit. m.p.: 78–81 °C)[11]; **TLC:** R_f = 0.33 (4:6 EOAc/petrol). Data are consistent with those reported in the literature.[12]

1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose 4-nitrobenzoate-[$^{18}O]_2$ (S6)



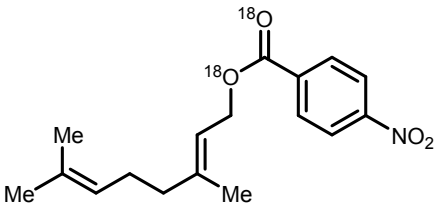
Synthesised according to the general procedure using 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (130 mg, 0.500 mmol), 4-nitrobenzoic acid-[$^{18}O]_2$ **(2)** (256 mg, 1.50 mmol), PPh_3 (524 mg, 2.00 mmol) and DIAD (394 µL, 2.00 mmol) in THF (3 mL). The reaction mixture was stirred at room temperature for 7 hours. Purification by flash column chromatography (SiO_2, 3:7 Et_2O:petrol) afforded the title compound as a colourless oil (142 mg, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.9 Hz, 2H), 8.22 (d, *J* = 8.9 Hz, 2H), 5.57 (d, *J* = 5.0 Hz, 1H), 4.66 (dd, *J* = 7.8, 2.5 Hz, 1H), 4.57 (dd, *J* = 11.6, 4.4 Hz, 1H), 4.49 (dd, *J* = 11.6, 7.8 Hz, 1H), 4.36 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.32 (dd, *J* = 7.8, 1.9 Hz, 1H), 4.22 – 4.16 (m, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.7, 150.7, 135.6, 131.0, 123.7, 110.0, 109.0, 96.5, 71.3, 70.9, 70.6, 66.2, 65.0, 26.2, 26.1, 25.1, 24.6; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{19}H_{23}NNa^{16}O_7{}^{18}O_2$ $[M + Na]^+$: 436.1350; found 436.1347. also *m/z* calc'd for $C_{19}H_{23}NNa^{16}O_8{}^{18}O$ $[M + Na]^+$: 434.1307; found 434.1318. The ratio of relative peak intensities for the relevant isotopologues was 91:9 ($C_{19}H_{23}NNa^{16}O_7{}^{18}O_2$:$C_{19}H_{23}NNa^{16}O_8{}^{18}O$); **FTIR** (neat) ν_{max}/cm^{-1} 2987, 2937, 1696, 1608, 1528, 1382, 1373, 1347, 1265, 1211, 1166, 1092, 1066, 1004; **TLC:** R_f = 0.22 (3:7 Et_2O/petrol)

1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose-[^{18}O] (3f)



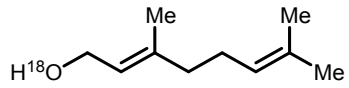
To a solution of **S6** (82 mg, 0.20 mmol) in 1:1 THF/MeOH (5 mL) was added LiOH (300 µL of a 2 M aqueous solution, 0.600 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 4:6 EtOAc/petrol) to afford the title compound as a colourless oil (51 mg, 97%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.57 (d, *J* = 5.0 Hz, 1H), 4.61 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.34 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.27 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.90 – 3.83 (m, 2H), 3.78 – 3.70 (m, 1H), 2.11 (d, *J* = 8.0 Hz, 1H), 1.53 (s, 3H), 1.46 (s, 3H), 1.34 (apparent s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 109.6, 108.8, 96.5, 71.8, 70.9, 70.7, 68.2, 62.6, 26.2, 26.1, 25.1, 24.5; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{12}H_{20}Na^{16}O_5{}^{18}O$ $[M + Na]^+$: 285.1195; found 285.1199. also *m/z* calc'd for $C_{12}H_{20}Na^{16}O_6$ $[M + Na]^+$: 283.1152; found 283.1162. The ratio of relative peak intensities for the relevant isotopologues was 95:5 ($C_{12}H_{20}Na^{16}O_5{}^{18}O$:$C_{12}H_{20}Na^{16}O_6$); **TLC:** R_f = 0.24 (1:1 EtOAc/petrol). Data are consistent with those reported in the literature.[13]

Geranyl 4-nitrobenzoate-[$^{18}O]_2$ (S7)



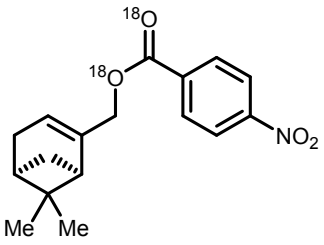
Synthesised according to the general procedure using geraniol (154 mg, 1.00 mmol), 4-nitrobenzoic acid-[$^{18}O]_2$ **(2)** (171 mg, 1.00 mmol), PPh_3 (315 mg, 1.20 mmol) and DIAD (236 µL, 1.200 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 18 hours. Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a colourless oil (231 mg, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.0 Hz, 2H), 8.21 (d, *J* = 9.0 Hz, 2H), 5.47 (apparent tp, *J* = 7.1, 1.3 Hz, 1H), 5.09 (apparent ddq, *J* = 6.8, 5.3, 1.5 Hz, 1H), 4.89 (d, *J* = 7.1 Hz, 2H), 2.15 – 2.05 (m, 4H), 1.78 (d, *J* = 1.3 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.61 (d, *J* = 1.3 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.8, 150.6, 143.6, 136.1, 132.1, 130.9, 123.6, 123.6, 117.8, 62.9, 39.7, 26.4, 25.8, 17.9, 16.7; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{21}NNa^{16}O_2{}^{18}O_2$ $[M + Na]^+$: 330.1448; found 330.1453. also *m/z* calc'd for $C_{17}H_{21}NNa^{16}O_3{}^{18}O$ $[M + Na]^+$: 328.1405; found 328.1426. The ratio of relative peak intensities for the relevant isotopologues was 90:10 ($C_{17}H_{21}NNa^{16}O_2{}^{18}O_2$:$C_{17}H_{21}NNa^{16}O_3{}^{18}O$); **m.p.:** 37–41 °C (lit. m.p.: 37.8–38.2 °C[14]); **TLC:** R_f = 0.18 (3:97 MeOH/CH_2Cl_2). Data are consistent with those reported in the literature.[15]

Geraniol-[^{18}O] (3g)



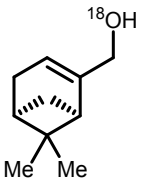
To a solution of **S7** (154 mg, 0.50 mmol) in 1:1 THF/MeOH (2 mL) was added LiOH (500 µL of a 2 M aqueous solution, 1.00 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 hours. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated, to afford the title compound as a colourless oil (61 mg, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.45 – 5.39 (m, 1H), 5.12 – 5.06 (m, 1H), 4.15 (d, *J* = 6.9 Hz, 2H), 2.15 – 2.06 (m, 2H), 2.06 – 1.98 (m, 2H), 1.69 – 1.65 (m, 6H), 1.60 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 140.0, 131.9, 124.0, 123.5, 59.6, 39.7, 26.5, 25.8, 17.8, 16.4; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{10}H_{18}Na^{18}O$ $[M + Na]^+$: 179.1292; found 179.1291. also *m/z* calc'd for $C_{10}H_{18}Na^{18}O$ $[M + Na]^+$: 177.1250; found 177.1243. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{10}H_{18}Na^{18}O$:$C_{10}H_{18}Na^{18}O$); **TLC:** R_f = 0.33 (1:4 EtOAc/petrol). Data are consistent with those reported in the literature.[16]

(1*R*)-(−)-Myrtenyl 4-nitrobenzoate-[^{18}O]$_2$ (S8)



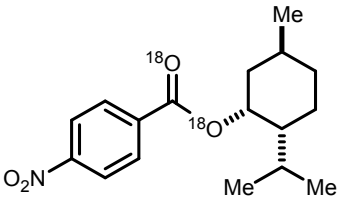
Synthesised according to the general procedure using (1*R*)-(−)-myrtenol (80 µL, 0.50 mmol), 4-nitrobenzoic acid-[^{18}O]$_2$ **(2)** (86 mg, 0.50 mmol), PPh_3 (157 mg, 0.600 mmol) and DIAD (120 µL, 0.600 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 4 hours. Purification by flash column chromatography (SiO_2, 1:39 Et_2O:petrol) afforded the title compound as a colourless solid (91 mg, 60%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.9 Hz, 2H), 8.19 (d, *J* = 8.9 Hz, 2H), 5.71 – 5.67 (m, 1H), 4.75 – 4.73 (m, 2H), 2.45 (apparent dt, *J* = 8.7, 5.6 Hz, 1H), 2.37 (d, *J* = 18.1 Hz, 1H), 2.29 (d, *J* = 18.1 Hz, 1H), 2.22 (apparent td, *J* = 5.6, 1.5 Hz, 1H), 2.17 – 2.11 (m, 1H), 1.31 (s, 3H), 1.23 (d, *J* = 8.7 Hz, 1H), 0.86 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.7, 150.7, 142.5, 136.0, 130.8, 123.7, 122.9, 68.6, 43.9, 40.8, 38.3, 31.7, 31.5, 26.3, 21.3; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{19}NNa^{16}O_2{}^{18}O_2$ [M + Na]$^+$: 328.1291; found 328.1289. also *m/z* calc'd for $C_{17}H_{19}NNa^{16}O_3{}^{18}O$ [M + Na]$^+$: 326.1249; found 326.1255. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{17}H_{19}NNa^{16}O_2{}^{18}O_2$:$C_{17}H_{19}NNa^{16}O_3{}^{18}O$); **FTIR** (neat) ν_{max}/cm^{-1} 3117, 2982, 2937, 2912, 2885, 2831, 1680, 1597, 1520, 1456, 1344, 1262, 1083, 1010; **m.p.:** 76–78 °C; **TLC:** R_f = 0.34 (1:9 Et_2O/petrol)

(1*R*)-(−)-Myrtenol-[^{18}O] (3h)



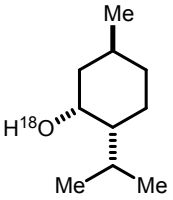
To a solution of **S8** (80 mg, 0.26 mmol) in 1:1 THF/MeOH (2 mL) was added LiOH (390 µL of a 2 M aqueous solution, 0.780 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 hours. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 3:7 Et_2O/petrol) to afford the title compound as a colourless oil (38 mg, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.50 – 5.44 (m, 1H), 4.01 – 3.95 (m, 2H), 2.41 (apparent dt, *J* = 8.6, 5.6 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.28 – 2.19 (m, 1H), 2.17 – 2.08 (m, 2H), 1.29 (s, 3H), 1.18 (d, *J* = 8.6 Hz, 1H), 0.84 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.8, 117.9, 66.0, 43.4, 40.9, 38.0, 31.6, 31.1, 26.1, 21.1; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{10}H_{16}Na^{18}O$ [M + Na]$^+$: 177.1136; found 177.1126. also *m/z* calc'd for $C_{10}H_{16}Na^{16}O$ [M + Na]$^+$: 175.1083; found 175.1074. The ratio of relative peak intensities for the relevant isotopologues was 95:5 ($C_{10}H_{16}Na^{18}O$:$C_{10}H_{16}Na^{16}O$); **TLC:** Rf = 0.11 (3:7 Et_2O/petrol). Data are consistent with those reported in the literature.[17]

(±)-Neomenthyl 4-nitrobenzoate-[$^{18}O]_2$ (S9)



Synthesised according to the general procedure using (±)-menthol (78 mg, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O]_2$ **(2)** (342 mg, 2.00 mmol), PPh_3 (524 mg, 2.00 mmol) and DIAD (392 µL, 2.00 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 24 hours. Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as pale yellow oil (122 mg, 79%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.8 Hz, 2H), 8.20 (d, *J* = 8.8 Hz, 2H), 5.51 – 5.48 (m, 1H), 2.09 (apparent dq, *J* = 14.5, 3.3 Hz, 1H), 1.91 – 1.80 (m, 2H), 1.75 – 1.63 (m, 1H), 1.58 – 1.45 (m, 2H), 1.23 – 1.11 (m, 2H), 1.06 – 0.96 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.86 (m, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 164.1, 150.6, 136.5, 130.8, 123.7, 73.3, 47.1, 39.3, 34.9, 29.6, 27.0, 25.5, 22.3, 21.1, 20.9.; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{23}NNa^{16}O_2{}^{18}O_2$ $[M + Na]^+$: 332.1604; found 332.1602. also *m/z* calc'd for $C_{17}H_{23}NNa^{16}O_3{}^{18}O$ $[M + Na]^+$: 330.1562; found 330.1559. The ratio of relative peak intensities for the relevant isotopologues was 86:14 ($C_{17}H_{23}NNa^{16}O_2{}^{18}O_2$:$C_{17}H_{23}NNa^{16}O_3{}^{18}O$); **TLC:** R_f = 0.31 (1:19 EtOAc/petrol). Data are consistent with those reported in the literature.[18]

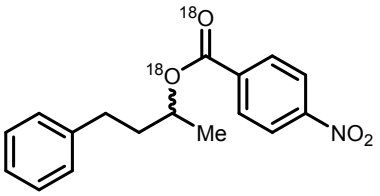
(±)-Neomenthol-[^{18}O] (3i)



To a solution of **S9** (74 mg, 0.24 mmol) in 1:1 THF/MeOH (1 mL) was added LiOH (500 µL of a 2 M aqueous solution, 1.00 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 hours. The reaction mixture was then heated to 50 °C and stirred for 3 hours. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 1:9 EtOAc/petrol) to afford the title compound as a colourless oil (36 mg, 95%).* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.10 (apparent q, *J* = 2.9 Hz, 1H), 1.83 (apparent dq, *J* = 13.7, 3.4 Hz, 1H), 1.78 – 1.61 (m, 3H), 1.52 (apparent dp, *J* = 9.3, 6.7 Hz, 1H), 1.33 – 1.18 (m, 2H), 1.08 (ddd, *J* = 13.8, 12.1, 2.6 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88 – 0.83 (m, 4H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 67.9, 48.1, 42.7, 35.2, 29.3, 26.0, 24.3, 22.5, 21.3, 20.9; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{10}H_{20}Na^{18}O$ $[M + Na]^+$: 181.1449; found 181.1449. also *m/z* calc'd for $C_{10}H_{20}Na^{16}O$ $[M + Na]^+$: 179.1406; found 179.1406. The ratio of relative peak intensities for the relevant isotopologues was 93:7 ($C_{10}H_{20}Na^{18}O$:$C_{10}H_{20}Na^{16}O$); **TLC:** R_f = 0.25 (1:9 EtOAc/petrol). Data are consistent with those reported in the literature.[19] ^{13}C NMR data does not match the retention product (menthol).[20]

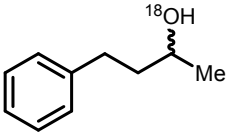
*Sample contained 7 mol% CH_2Cl_2 95% yield accounts for this.

4-Phenylbutan-2-yl 4-nitrobenzoate-[^{18}O]$_2$ (S10)



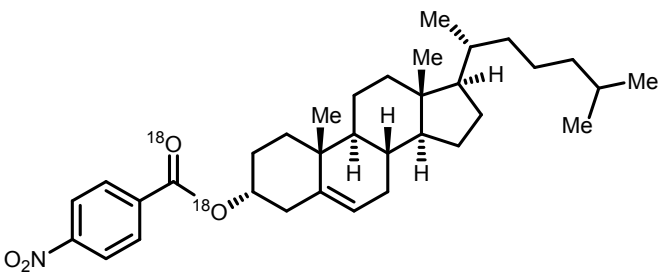
Synthesised according to the general procedure using 4-phenyl-2-butanol (451 mg, 3.00 mmol), 4-nitrobenzoic acid-[^{18}O]$_2$ **(2)** (514 mg, 3,00 mmol), PPh_3 (944 mg, 3.60 mmol) and DIAD (709 µL, 3.60 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 8 hours. Purification by flash column chromatography (SiO_2, 3:97 Et_2O:petrol) afforded the title compound as a colourless oil (719 mg, 80%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9 Hz, 2H), 8.16 (d, *J* = 8.9 Hz, 2H), 7.27 (dd, *J* = 8.2, 6.9 Hz, 2H7.22 – 7.17 (m, 3H), 5.23 (dqd, *J* = 7.8, 6.2, 4.8 Hz, 1H), 2.82 – 2.67 (m, 2H), 2.14 (dddd, *J* = 14.0, 9.1, 7.7, 6.7 Hz, 1H), 2.00 (dddd, *J* = 14.0, 9.1, 6.7, 4.9 Hz, 1H), 1.42 (d, *J* = 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 164.3, 150.6, 141.3, 136.2, 130.8, 128.6, 128.4, 126.2, 123.6, 72.7, 37.6, 32.0, 20.2; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{17}NNa^{16}O_2{}^{18}O_2$ [M + Na]$^+$: 326.1135; found 326.1134. also *m/z* calc'd for $C_{17}H_{17}NNa^{16}O_3{}^{18}O$ [M + Na]$^+$: 324.1092; found 324.1089. The ratio of relative peak intensities for the relevant isotopologues was 91:9 ($C_{17}H_{17}NNa^{16}O_2{}^{18}O_2$:$C_{17}H_{17}NNa^{16}O_3{}^{18}O$); **TLC:** R_f = 0.28 (1:19 Et_2O/petrol). Data are consistent with those reported in the literature.[21]

4-Phenyl-2-butanol-[^{18}O] (3j)



To a solution of **S10** (680 mg, 2.25 mmol) in 1:1 THF/MeOH (8 mL) was added LiOH (3.38 mL of a 2 M aqueous solution, 6.75 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction mixture was then diluted with 1 M NaOH (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (1:9 EtOAc/petrol) to afford the title compound as a colourless oil (310 mg, 91%). **^{1}H NMR** (500 MHz, $CDCl_3$) 7.31 – 7.27 (m, 2H), 7.22 – 7.17 (m, 3H), 3.83 (apparent sextet, *J* = 6.2 Hz, 1H), 2.76 (ddd, *J* = 13.7, 9.2, 6.3 Hz, 1H), 2.68 (ddd, *J* = 13.7, 9.2, 7.1 Hz, 1H), 1.85 – 1.71 (m, 2H), 1.33 (s, 1H), 1.23 (d, *J* = 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 142.2, 128.5 (4 × Ar<u>C</u>), 126.0, 67.7, 41.0, 32.3, 23.8; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{10}H_{14}Na^{18}O$ [M + Na]$^+$: 175.0979; found 175.0982. also *m/z* calc'd for $C_{10}H_{14}Na^{16}O$ [M + Na]$^+$: 173.0937; found 173.0939. The ratio of relative peak intensities for the relevant isotopologues was 94:6 ($C_{10}H_{14}Na^{18}O$:$C_{10}H_{14}Na^{16}O$); **TLC:** R_f = 0.18 (1:4 EtOAc/petrol). Data are consistent with those reported in the literature.[22]

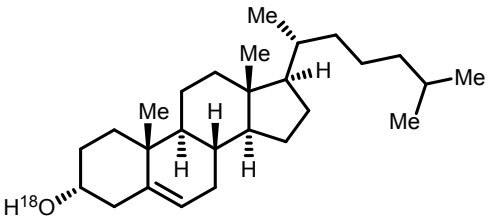
***epi*-Cholesteryl 4-nitrobenzoate-[$^{18}O]_2$ (S11)**



Synthesised according to the general procedure using cholesterol (194 mg, 0.500 mmol), 4-nitrobenzoic acid-[$^{18}O]_2$ **(2)** (128 mg, 0.750 mmol), PPh_3 (196 mg, 0.750 mmol) and DIAD (148 µL, 0.750 mmol) in THF (2 mL). The reaction was mixtutre was stirred at room temperature for 18 hours prior to workup. Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as an off-white solid (110 mg, 37%).* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9 Hz, 2H), 8.15 (d, *J* = 8.9 Hz, 2H), 5.35 – 5.31 (m, 1H), 5.31 – 5.26 (m, 1H), 2.66 – 2.58 (m, 1H), 2.36 (apparent dt, *J* = 15.4, 2.6 Hz, 1H), 2.08 – 1.67 (m, 6H), 1.64 – 0.96 (m, 23H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.86 (dd, *J* = 6.6, 1.8 Hz, 6H), 0.70 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.1, 160.1, 150.5, 138.3, 136.7, 130.7, 123.7, 122.8, 72.6, 56.9, 56.3, 50.6, 42.5, 39.9, 39.7, 37.3, 36.6, 36.3, 36.0, 34.1, 32.1, 32.0, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 21.0, 19.1, 18.9, 12.0; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{34}H_{53}N^{16}O_2{}^{18}O_2$ $[M + NH_4]^+$: 557.4085; found 557.4085; **TLC:** R_f = 0.27 (1:19 EtOAc/petrol).

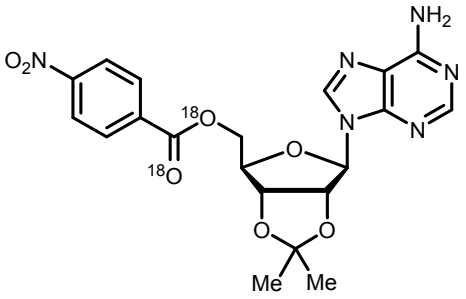
*sample contained 25 mol% DIAD•H_2. The 37% yield accounts for this.

***epi*-Cholesterol-[^{18}O] (3k)**



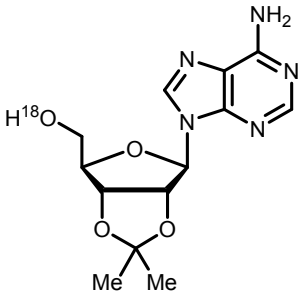
To a solution of **S11** (55 mg, 93 µmol) in 1:1 THF/MeOH (2 mL) was added LiOH (500 µL of a 2 M aqueous solution, 1.00 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (1:9 EtOAc/petrol) to afford the title compound as a colourless oil (33 mg, 92%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.43 – 5.38 (m, 1H), 4.01 (apparent t, *J* = 2.9 Hz, 1H), 2.60 – 2.53 (m, 1H), 2.07 (apparent dt, *J* = 14.7, 2.7 Hz, 1H), 2.05 – 1.94 (m, 2H), 1.83 (apparent dtd, *J* = 13.3, 9.5, 5.8 Hz, 1H), 1.77 – 0.95 (m, 27H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (apparent dd, *J* = 6.6, 2.3 Hz, 6H), 0.68 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 138.7, 124.2, 67.3, 56.9, 56.3, 50.5, 42.5, 40.0, 39.9, 39.7, 37.5, 36.3, 35.9, 33.4, 32.1, 32.0, 29.1, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 20.9, 18.9, 18.8, 12.0; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{27}H_{46}Na^{18}O$ $[M + Na]^+$: 411.3483; found 411.3475. also *m/z* calc'd for $C_{27}H_{46}Na^{16}O$ $[M + Na]^+$: 409.3441; found 409.3423. The ratio of relative peak intensities for the relevant isotopologues was 90:10 ($C_{27}H_{46}Na^{18}O$:$C_{27}H_{46}Na^{16}O$); **TLC:** R_f = 0.30 (1:4 EtOAc/petrol); Data are consistent with those reported in the literature.[23] ^{13}C NMR data does not match the retention product (cholesterol).[24]

2',3'-*O*-isopropylideneadenosyl 4-nitrobenzoate-[$^{18}O]_2$ (S12)



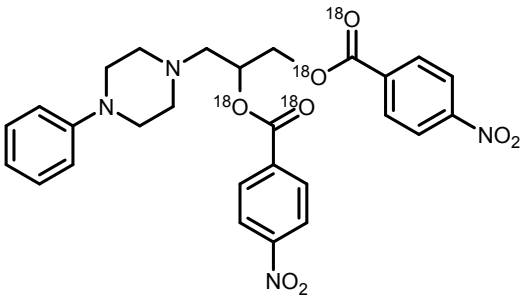
Synthesised according to the general procedure using 2',3'-*O*-isopropylideneadenosine (154 mg, 0.500 mmol), 4-nitrobenzoic acid-[$^{18}O]_2$ **(2)** (171 mg, 1.00 mmol), PPh_3 (262 mg, 1.00 mmol) and DIAD (197 µL, 1.00 mmol) in THF (2 mL). Purification by flash column chromatography (SiO_2, 1:19 MeOH:EtOAc) afforded a 1:2.0 mixture of the title compound and triphenylphosphine oxide respectively (324 mg of mixture, 147 mg, 64% effective yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.23 (d, *J* = 8.9 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 2H), 7.87 (s, 1H), 6.10 (d, *J* = 1.9 Hz, 1H), 5.69 (s, 2H), 5.60 (dd, *J* = 6.3, 1.9 Hz, 1H), 5.23 (dd, *J* = 6.3, 3.6 Hz, 1H), 4.68 (dd, *J* = 11.3, 4.0 Hz, 1H), 4.60 (apparent dt, *J* = 6.1, 3.8 Hz, 1H), 4.53 (dd, *J* = 11.3, 6.1 Hz, 1H), 1.64 (s, 3H), 1.42 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.3, 155.6, 153.3, 150.8, 149.3, 140.2, 135.0, 130.9, 123.6, 120.6, 114.9, 65.2, 27.4, 25.6; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{20}H_{21}N_6{}^{16}O_5{}^{18}O_2$ $[M + H]^+$: 461.1551; found 461.1540. also *m/z* calc'd for $C_{20}H_{21}N_6{}^{16}O_6{}^{18}O$ $[M + H]^+$: 459.1509; found 459.1500. The ratio of relative peak intensities for the relevant isotopologues was 80:20 ($C_{20}H_{21}N_6{}^{16}O_5{}^{18}O_2$: $C_{20}H_{21}N_6{}^{16}O_6{}^{18}O$); **FTIR** (neat) ν_{max}/cm^{-1} 3325, 3167, 3055, 2987, 1697, 1639, 1596, 1526; **TLC:** R_f = 0.72 (1:9 MeOH/CH_2Cl_2).

2',3'-*O*-isopropylideneaenosine-[^{18}O] (3l)



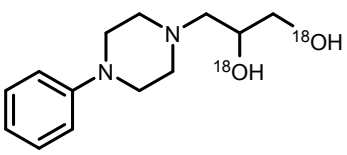
To a solution of **S12** (100 mg of a 1:2 mixture with triphenylphosphine oxide, 99 µmol) in 1:1 THF/MeOH (1 mL) was added LiOH (500 µL of a 2 M aqueous solution, 1.00 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 hours. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 1:19 MeOH/EtOAc) to afford the title compound as a colourless solid (23 mg, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.84 (s, 1H), 6.54 (d, *J* = 11.6 Hz, 1H), 5.85 (d, *J* = 5.0 Hz, 1H), 5.80 (s, 2H), 5.21 (apparent t, *J* = 5.4 Hz, 1H), 5.12 (d, *J* = 5.9 Hz, 1H), 4.54 (s, 1H), 4.04 – 3.94 (m, 1H), 3.86 – 3.71 (m, 1H), 1.65 (s, 3H), 1.38 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 156.1, 152.8, 148.6, 140.5, 121.4, 114.2, 94.6, 86.2, 83.1, 81.9, 63.6, 27.8, 25.4; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{13}H_{17}N_5Na^{16}O_3{}^{18}O$ $[M + Na]^+$: 332.1215; found 332.1214. also *m/z* calc'd for $C_{13}H_{17}N_5Na^{16}O_4$ $[M + Na]^+$: 330.1173; found 330.1170. The ratio of relative peak intensities for the relevant isotopologues was 90:10 ($C_{13}H_{17}N_5Na^{16}O_3{}^{18}O$:$C_{13}H_{17}N_5Na^{16}O_4$); **m.p.:** 219–221 °C (lit. m.p.: 218–220 °C)[25]; **TLC:** R_f = 0.14 (1:19 MeOH/EtOAc). Data are consistent with those reported in the literature.[25,26]

Dropropizine bis(4-nitrobenzoate)-[$^{18}O]_4$ (S13)



Synthesised according to the general procedure using dropropizine (118 mg, 0.500 mmol), 4-nitrobenzoic acid-[$^{18}O]_2$ **(2)** (257 mg, 1.50 mmol), PPh_3 (393 mg, 1.50 mmol) and DIAD (295 µL, 1.50 mmol) in THF (6 mL). Purification by flash column chromatography (SiO_2, 3:97 (10% *v*/*v* NH_4OH in methanol):petrol) afforded the title compound as a pale yellow solid (180 mg, 57%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.31 – 8.26 (m, 4H), 8.22 – 8.15 (m, 4H), 7.29 – 7.23 (m, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.86 (t, *J* = 7.3 Hz, 1H), 5.71 (apparent qd, *J* = 6.6, 2.8 Hz, 1H), 4.82 (dd, *J* = 12.1, 2.9 Hz, 1H), 4.65 (dd, *J* = 12.2, 7.0 Hz, 1H), 3.21 – 3.14 (m, 4H), 2.87 – 2.79 (m, 2H), 2.78 – 2.73 (m, 4H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 164.5, 164.2, 151.2, 150.9, 135.3, 135.1, 130.9, 130.9, 129.3, 123.8, 120.1, 116.2, 70.8, 65.6, 58.3, 53.9, 49.4; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{27}H_{27}N_4{}^{16}O_4{}^{18}O_4$ $[M + H]^+$: 543.1993; found 543.1990; also *m/z* calc'd for $C_{27}H_{27}N_4{}^{16}O_5{}^{18}O_3$ $[M + H]^+$: 541.1951; found 541.1943. The ratio of relative peak intensities for the relevant isotopologues was 82:18 ($C_{27}H_{27}N_4{}^{16}O_4{}^{18}O_4$:$C_{27}H_{27}N_4{}^{16}O_5{}^{18}O_3$); **TLC:** R_f = 0.68 (1:49 $MeOH/CH_2Cl_2$).

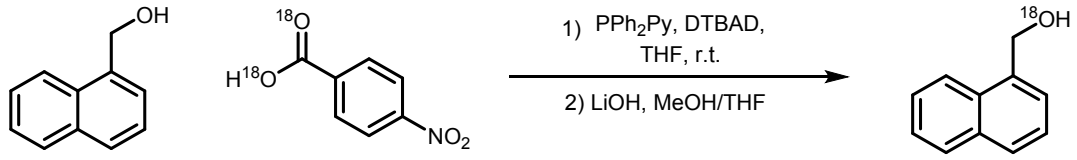
Dropropizine-[$^{18}O]_2$



To a solution of **S13** (74 mg, 0.24 mmol) in 1:1 MeOH/THF (1 mL) was added LiOH (500 µL of a 2 M aqueous solution, 1.00 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with EtOAc (1 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (7:93 (10% *v*/*v* NH_4OH in MeOH)/petrol) to afford the title compound as a colourless solid (35 mg, 98%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 6.87 (t, *J* = 7.3 Hz, 1H), 3.87 (apparent dd, *J* = 9.3, 4.5 Hz, 1H), 3.76 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.53 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.26 – 3.16 (m, 4H), 2.88 – 2.56 (m, 5H), 2.42 (dd, *J* = 12.4, 3.9 Hz, 1H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.2, 129.2, 120.1, 116.3, 67.1, 65.0, 60.4, 53.5, 49.4; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{13}H_{21}N_2{}^{18}O_2$ $[M + H]^+$: 241.1682; found 241.1680. also *m/z* calc'd for $C_{13}H_{21}N_2{}^{16}O^{18}O$ $[M + H]^+$: 239.1640; found 239.1634; also *m/z* calc'd for $C_{13}H_{21}N_2{}^{16}O_2$ $[M + H]^+$: 237.1598; found 237.1534. The ratio of relative peak intensities for the relevant isotopologues was 90.3:9.4:0.3 ($C_{13}H_{21}N_2{}^{18}O_2$:$C_{13}H_{21}N_2{}^{16}O^{18}O$:$C_{13}H_{21}N_2{}^{16}O_2$); **m.p.:** 98–102 °C; **TLC:** R_f = 0.26 (7:93 (10% *v*/*v* NH_4OH in MeOH)/petrol). Data are consistent with those reported in the literature.[27]

Investigating Alternative Mitsunobu Conditions

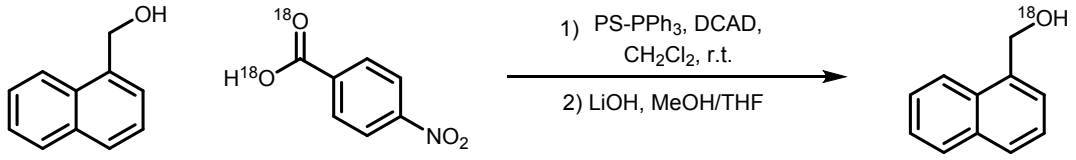
1-Naphthalenemethanol-[^{18}O]$_2$ (S14)



Synthesised according to an adapted literature procedure.[28] To a solution of 1-napthalenemethanol (79 mg, 0.50 mmol), 4-nitrobenzoic acid-[^{18}O]$_2$ **(2)** (128 mg, 0.75 mmol) and diphenyl-2-pyridylphosphine (197 mg, 0.75 mmol) in THF (2 mL) was added di-*tert*-butyl azodicarboxylate (173 mg, 0.75 mmol) and the reaction mixture was stirred at room temperature for 16 hours. 4M hydrogen chloride in dioxane (2 mL) was subsequently added and the reaction was stirred for a further 1 hour. The reaction was diluted with HCl (10 mL of a 2M aqueous solution) was added and the organics were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (1:9 Et_2O/cyclohexane) afforded the title compound as a colourless solid (124 mg, 80%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **S1**.

To the ^{18}O-enriched ester product (78 mg, 0.25 mmol) in 1:1 MeOH/THF (2 mL) was added LiOH (375 µL of a 2 M aqueous solution, 0.750 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated to afford the title compound as a colourless solid (38 mg, 96%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **3a**; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{10}Na^{18}O$ $[M + Na]^+$: 183.0666; found 183.0663. also *m/z* calc'd for $C_{11}H_{10}Na^{16}O$ $[M + Na]^+$: 181.0624; found 181.0631. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{11}H_{10}Na^{18}O$: $C_{11}H_{10}Na^{16}O$).

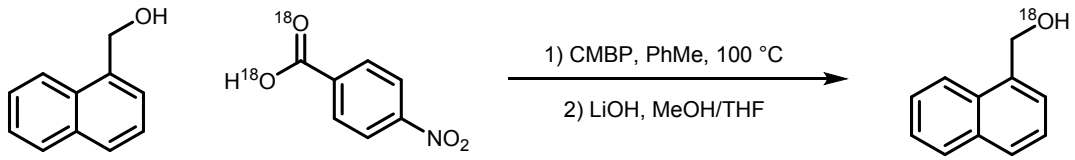
1-Naphthalenemethanol-[^{18}O]$_2$ (S15)



Synthesised according to an adapted literature procedure.[29] To a solution of 1-napthalenemethanol (79 mg, 0.50 mmol), 4-nitrobenzoic acid-[^{18}O]$_2$ **(2)** (103 mg, 0.600 mmol) and polymer-bound triphenylphosphine (200 mg, 3 mmol/g PPh_3 loading, 0.600 mmol) in CH_2Cl_2 (2 mL) was added di-(4-chlorobenzyl)azodicarboxylate (220 mg, 0.600 mmol) in CH_2Cl_2 (2 mL) and the reaction mixture was stirred at room temperature for 4 hours, after which, a further 2 mL CH_2Cl_2 was added and the suspension was filtered through a pad of celite. The filtrate was concentrated and purified by flash column chromatography (1:9 Et_2O/cyclohexane) to afford the title compound as a colourless solid (80 mg, 51%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **S1**.

To the ^{18}O-enriched ester product (62 mg, 0.20 mmol) in 1:1 MeOH/THF (2 mL) was added LiOH (300 µL of a 2 M aqueous solution, 0.600 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated to afford the title compound as a colourless solid (31 mg, 97%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **3a**; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{10}Na^{18}O$ $[M + Na]^+$: 183.0666; found 183.0666. also *m/z* calc'd for $C_{11}H_{10}Na^{16}O$ $[M + Na]^+$: 181.0624; found 181.0637. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{11}H_{10}Na^{18}O$: $C_{11}H_{10}Na^{16}O$).

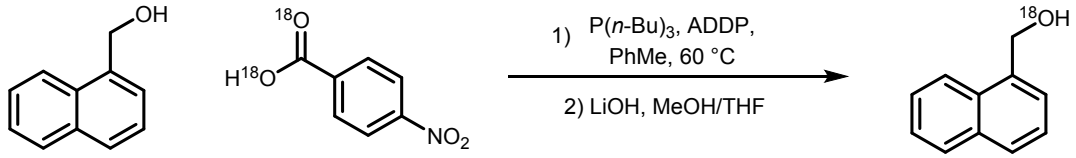
1-Naphthalenemethanol-[$^{18}O]_2$ (S16)



Synthesised according to an adapted literature procedure.[30] Under an atmosphere of argon, to a solution of 1-napthalenemethanol (79 mg, 0.50 mmol) and 4-nitrobenzoic acid-[$^{18}O]_2$ **(2)** (128 mg, 0.750 mmol) in anhydrous toluene (2 mL) was added 1 M cyanomethylenetributylphosphorane in toluene (750 µL, 0.750 mmol) The reaction mixture was heated to 100 °C and stirred for 16 hours. The reaction mixture was then concentrated and purified by flash column chromatography (1:9 Et_2O/cyclohexane) to afford the title compound as a colourless solid (102 mg, 65%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **S1**.

To the ^{18}O-enriched ester product (62 mg, 0.20 mmol) in 1:1 MeOH/THF (2 mL) was added LiOH (300 µL of a 2 M aqueous solution, 0.600 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated to afford the title compound as a colourless solid (30 mg, 94%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **3a**; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{10}Na^{18}O$ $[M + Na]^+$: 183.0666; found 183.0670. also *m/z* calc'd for $C_{11}H_{10}Na^{16}O$ $[M + Na]^+$: 181.0624; found 181.0644. The ratio of relative peak intensities for the relevant isotopologues was 93:7 ($C_{11}H_{10}Na^{18}O$: $C_{11}H_{10}Na^{16}O$).

1-Naphthalenemethanol-[$^{18}O]_2$ (S17)

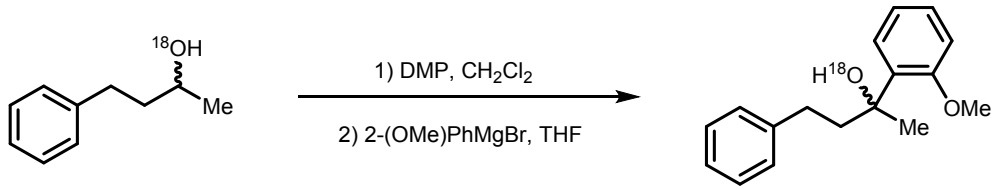


Synthesised according to an adapted literature procedure.[31] Under an atmosphere of argon, to a solution of naphthalenemethanol (79 mg, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O]_2$ **(2)** (128 mg, 0.75 mmol) and tri-*n*-butylphosphine (187 µL, 0.75 mmol) in toluene (1 mL) was added 1,1'-(azodicarbonyl)dipiperidine (173 mg, 0.75 mmol) in toluene (1 mL). The reaction mixture was heated to 60 °C and stirred for 16 hours. The reaction mixture was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (1:9 Et_2O/cyclohexane) afforded the title compound as a colourless solid (83 mg, 53%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **S1**.

To the ^{18}O-enriched ester product (62 mg, 0.20 mmol) in 1:1 MeOH/THF (2 mL) was added LiOH (300 µL of a 2 M aqueous solution, 0.600 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was then diluted with 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated to afford the title compound as a colourless solid (30 mg, 94%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **3a**; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{10}Na^{18}O$ $[M + Na]^+$: 183.0666; found 183.0669. also *m/z* calc'd for $C_{11}H_{10}Na^{16}O$ $[M + Na]^+$: 181.0624; found 181.0698. The ratio of relative peak intensities for the relevant isotopologues was 88:12 ($C_{11}H_{10}Na^{18}O$: $C_{11}H_{10}Na^{16}O$).

Synthesis of ^{18}O-enriched Tertiary Alcohol

2-(2-methoxyphenyl)-4-phenylbutan-2-ol-[^{18}O] (5)

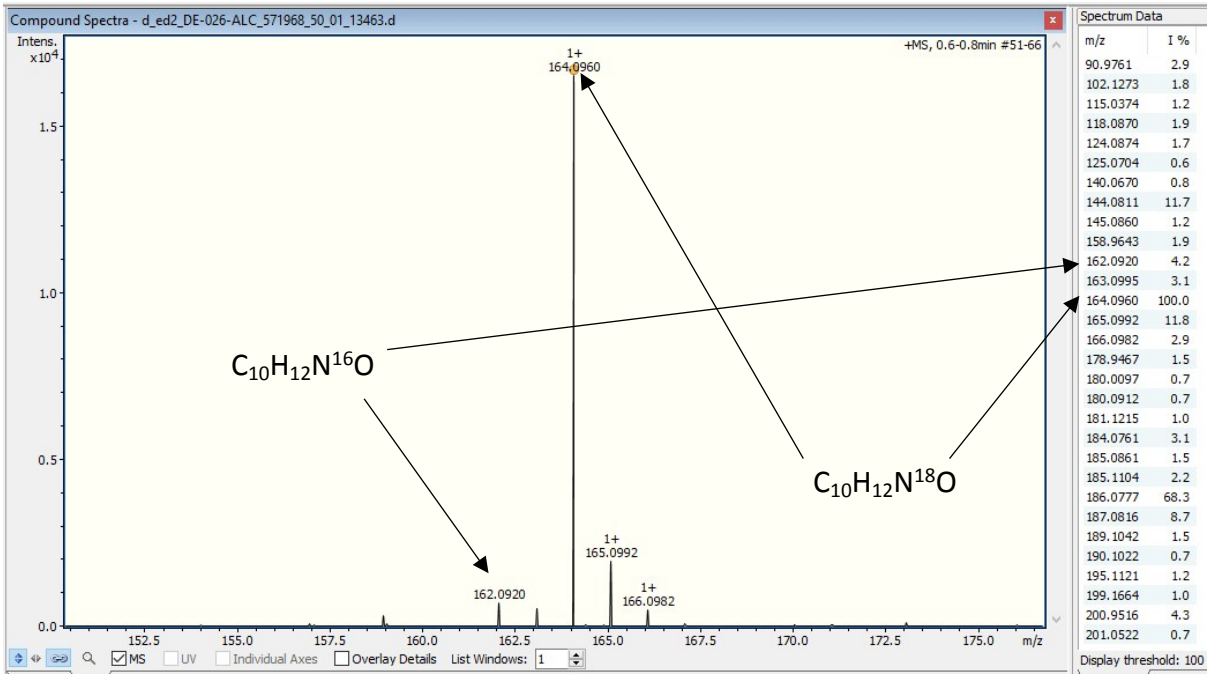


Synthesised according to an adapted literature procedure.[32] To a solution of alcohol **3j** (76 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (8 mL) was added Dess-Martin periodinane (254 mg, 0.60 mmol) at room temperature and the reaction mixture was stirred for 90 minutes. The reaction mixture was then concentrated, 1:9 EtOAc/cyclohexane (5 mL) was added and the suspension was filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography (8:92 EtOAc/cyclohexane) afforded the ketone as a colourless oil.

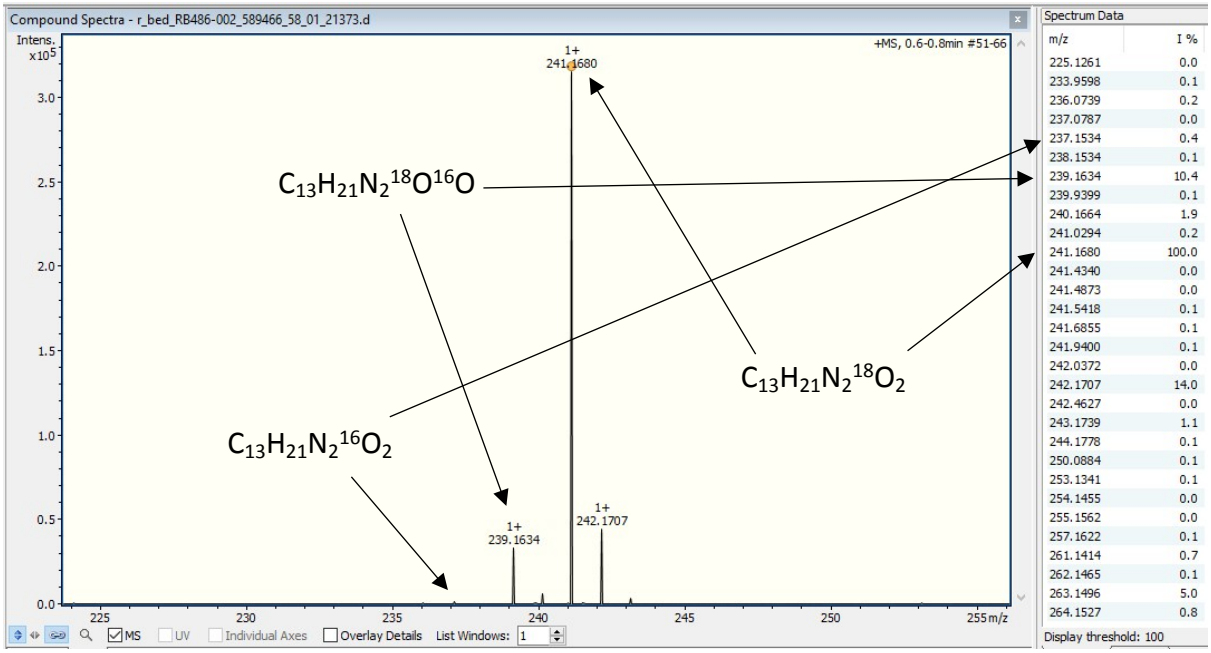
The ketone was dissolved in anhydrous THF (3 mL) and 2-methoxyphenylmagnesium bromide (1.11 mL of a 0.9 M solution in 2-MeTHF) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2.5 hours. The reaction mixture was quenched with NH_4Cl (5mL of a 1 M aqueous solution), diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10mL). The combined organic extracts were washed with a saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (5:95 to 8:92 gradient of acetone/cyclohexane) afforded the title compound as a colourless oil (87 mg, 67% over 2 steps). **^{1}H NMR** (500 MHz, $CDCl_3$) δ7.35 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.28 – 7.22 (m, 3H), 7.17 – 7.11 (m, 3H), 6.98 (apparent td, *J* = 7.5, 1.2 Hz, 1H), 6.93 (dd, *J* = 8.3, 1.2 Hz, 1H), 3.90 (s, 3H), 2.65 – 2.50 (m, 2H), 2.30 (ddd, *J* = 13.5, 11.7, 5.3 Hz, 1H), 2.16 (ddd, *J* = 13.5, 11.7, 5.5 Hz, 1H), 1.64 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 157.0, 142.9, 134.7, 128.46, 128.42, 128.36, 126.9, 125.7, 121.1, 111.5, 75.2, 55.5, 44.1, 31.1, 27.7; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{20}Na^{16}O^{18}O$ $[M + Na]^+$: 281.1398; found 281.1379. also *m/z* calc'd for $C_{17}H_{20}Na^{16}O_2$ $[M + H]^+$: 279.1356; found 279.1352. The ratio of relative peak intensities for the relevant isotopologues was 93:7 ($C_{17}H_{20}Na^{16}O^{18}O$:$C_{17}H_{20}Na^{16}O_2$); **FTIR** (neat) ν_{max}/cm^{-1} 3444, 2975, 2933, 1496, 1420, 1120, 1048; **TLC:** R_f = 0.18 (1:9 acetone/petrol).

Representative Examples of a High-Resolution Mass Spectra

Compound 3c

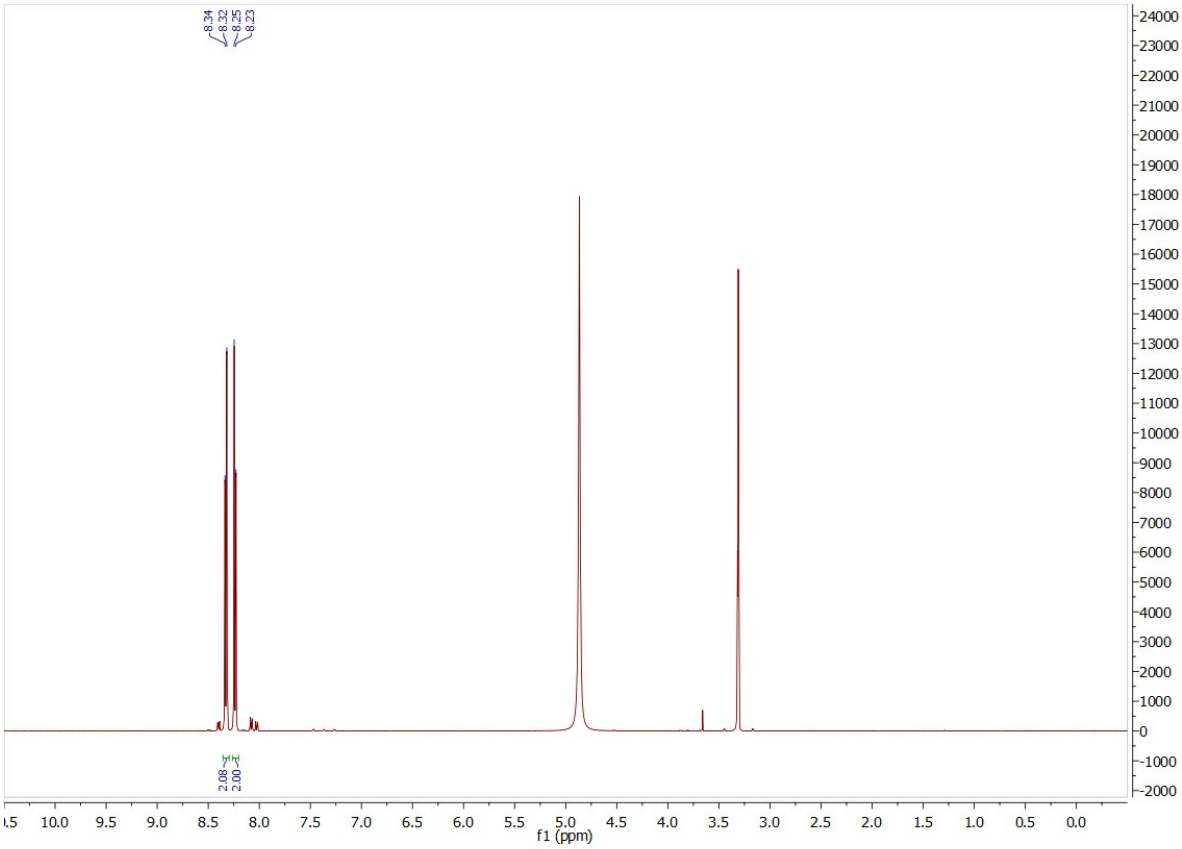


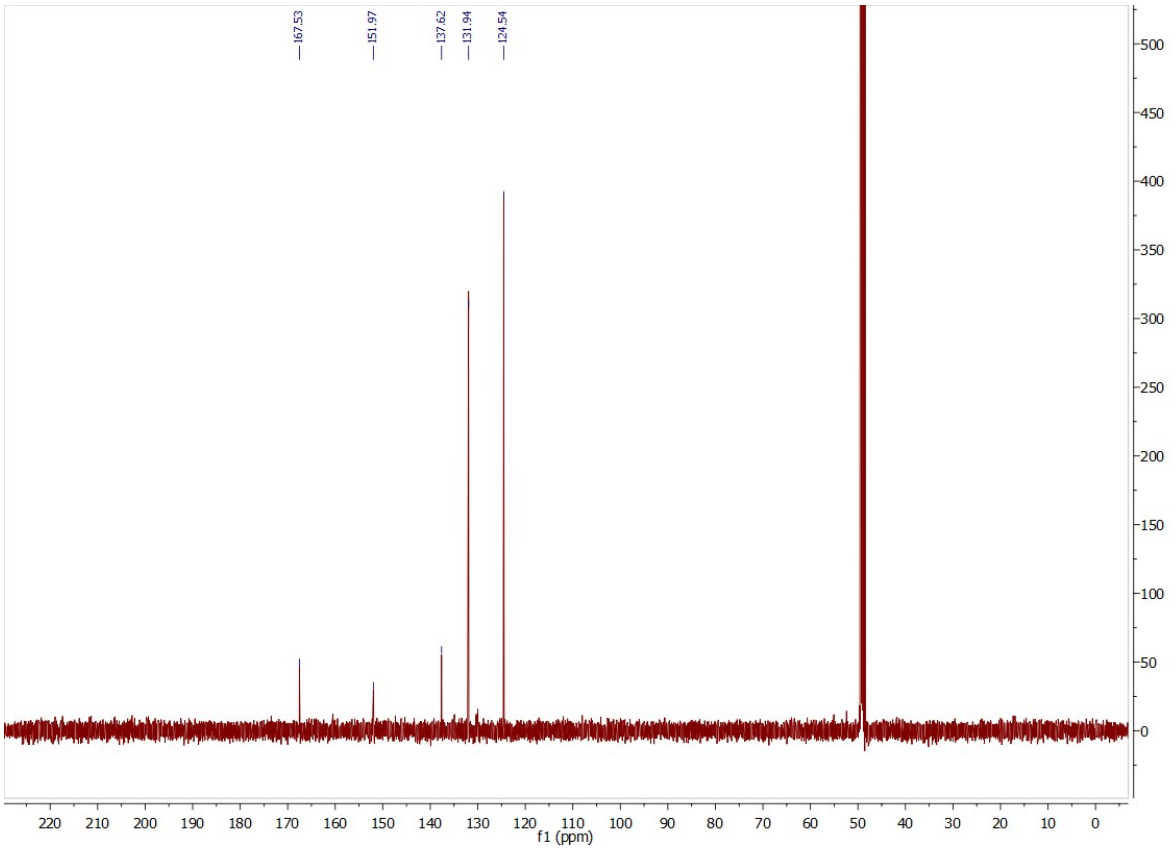
Dropropizine-[^{18}O]$_2$

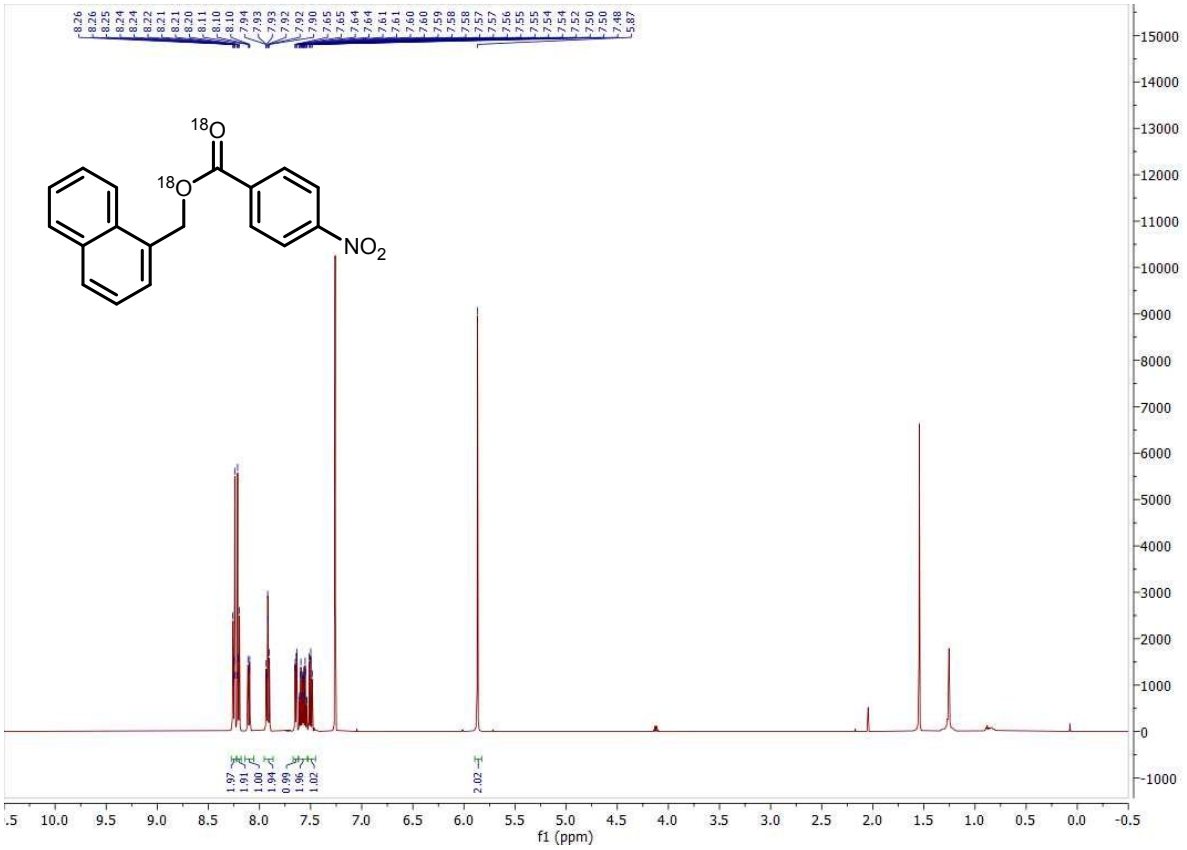


NMR Spectra

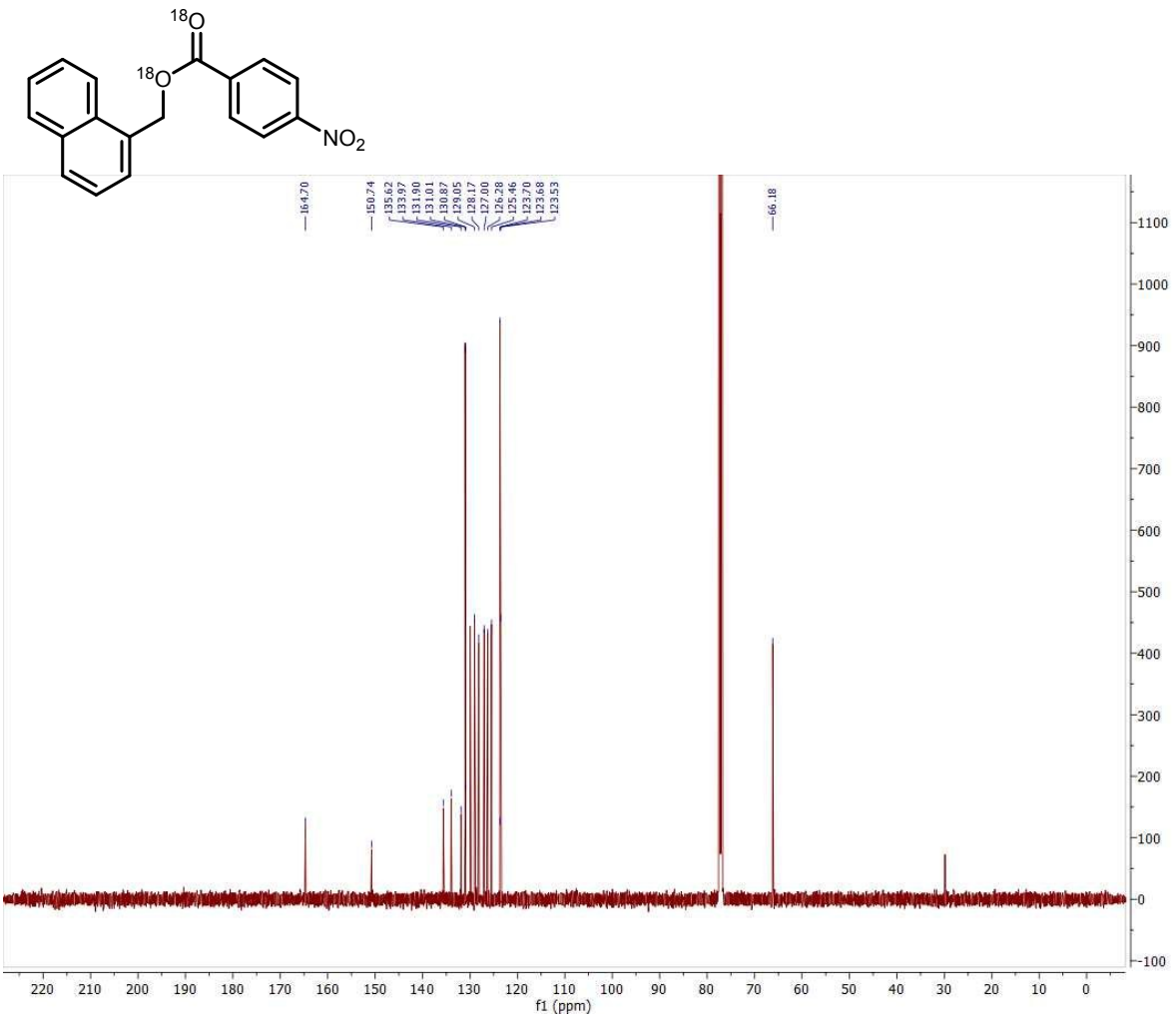
^{1}H and ^{13}C NMR Spectra for Compound 2

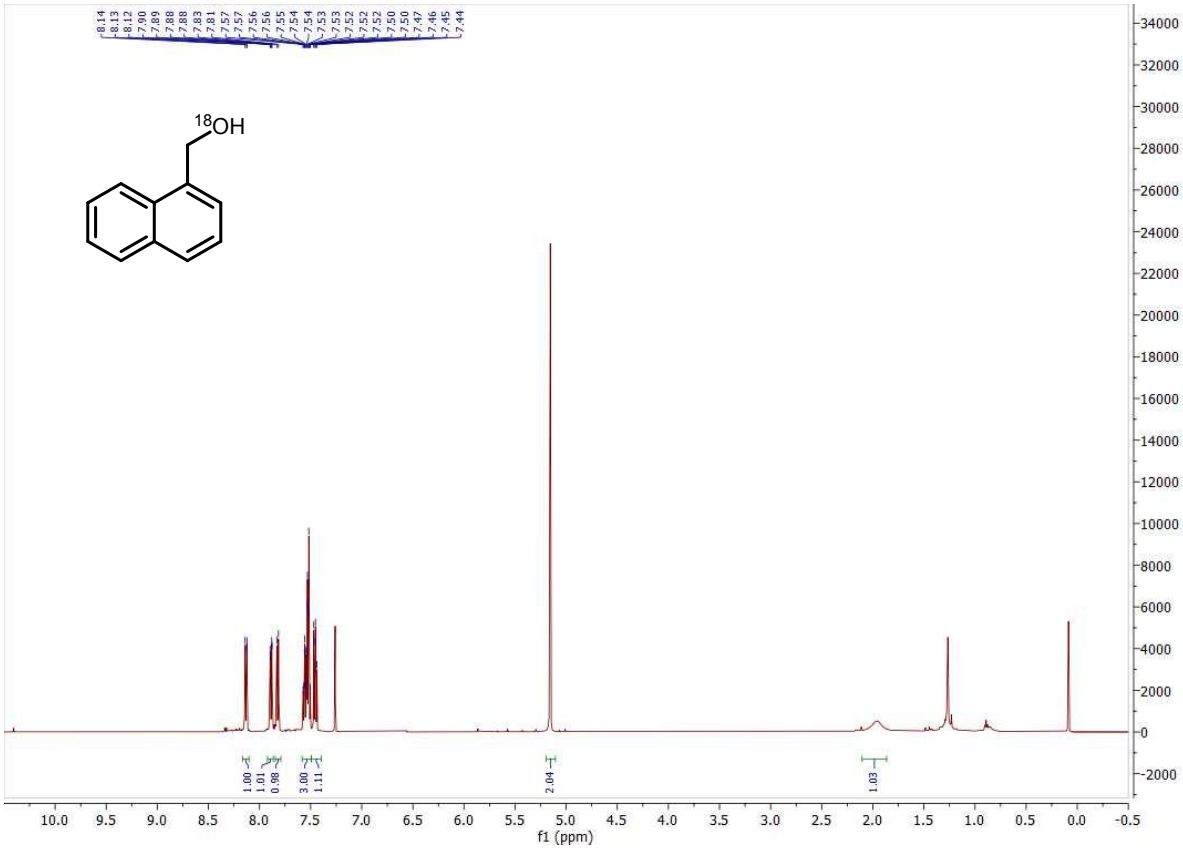


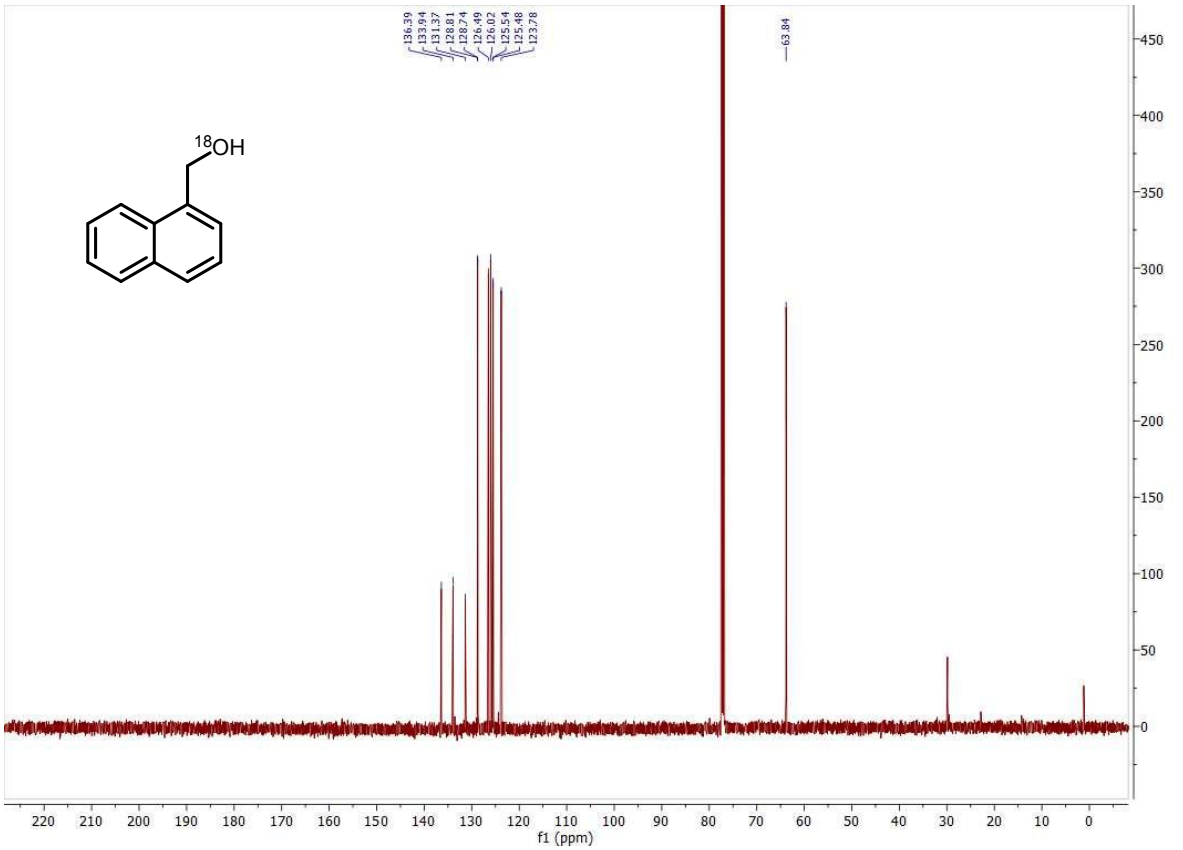




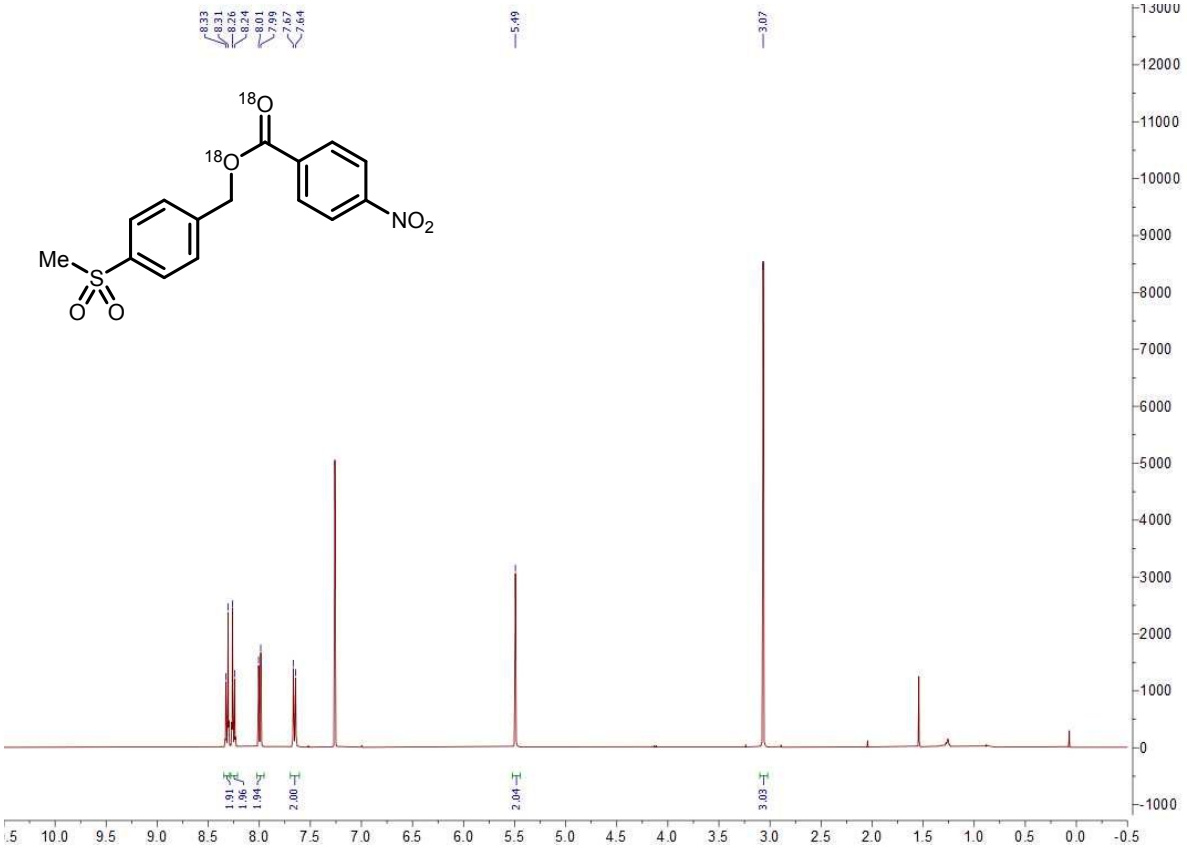
^{1}H and ^{13}C NMR Spectra for Compound S1

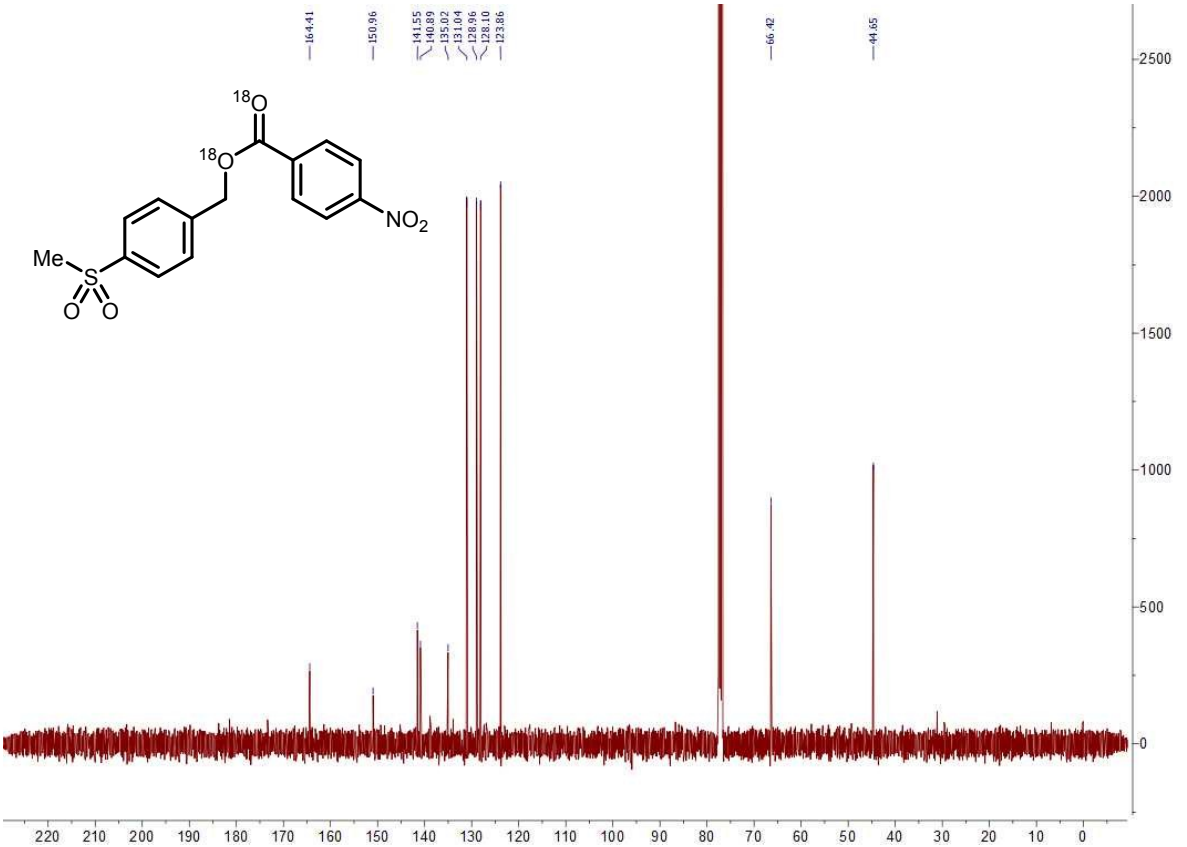




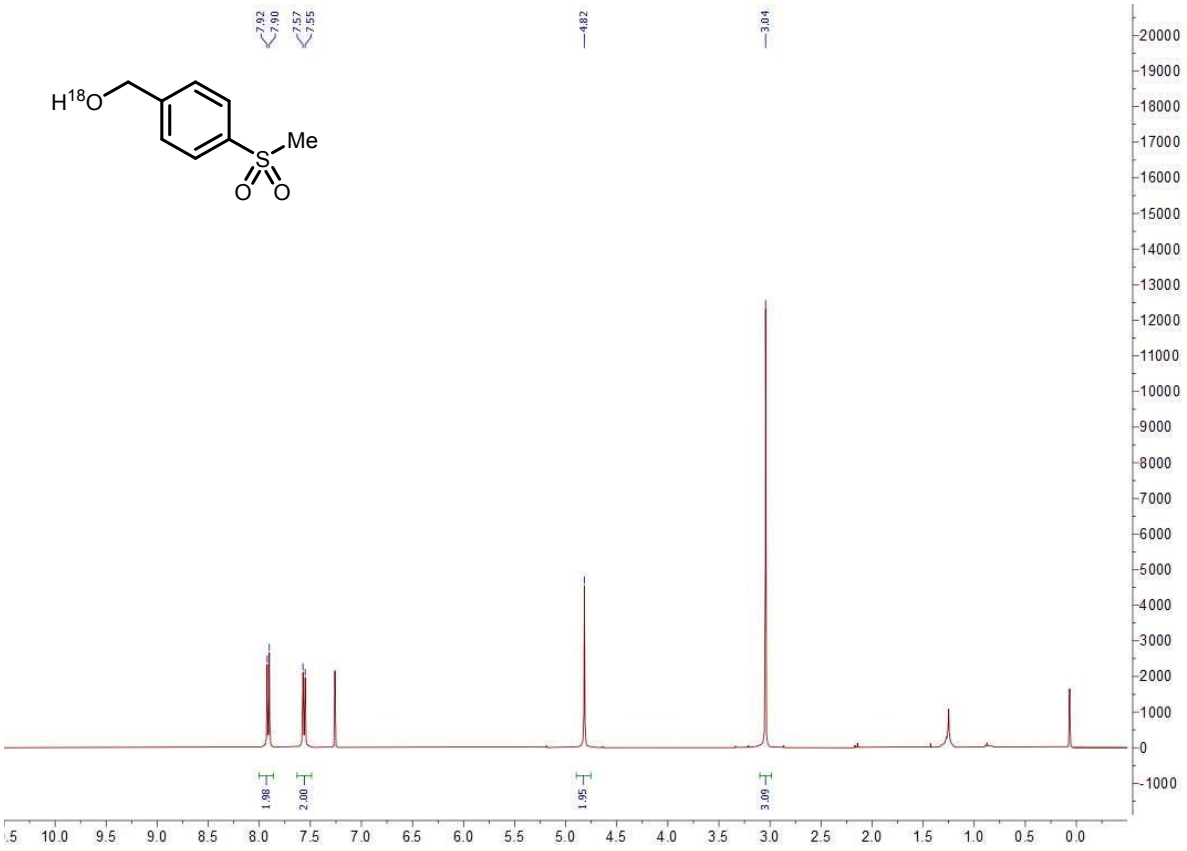


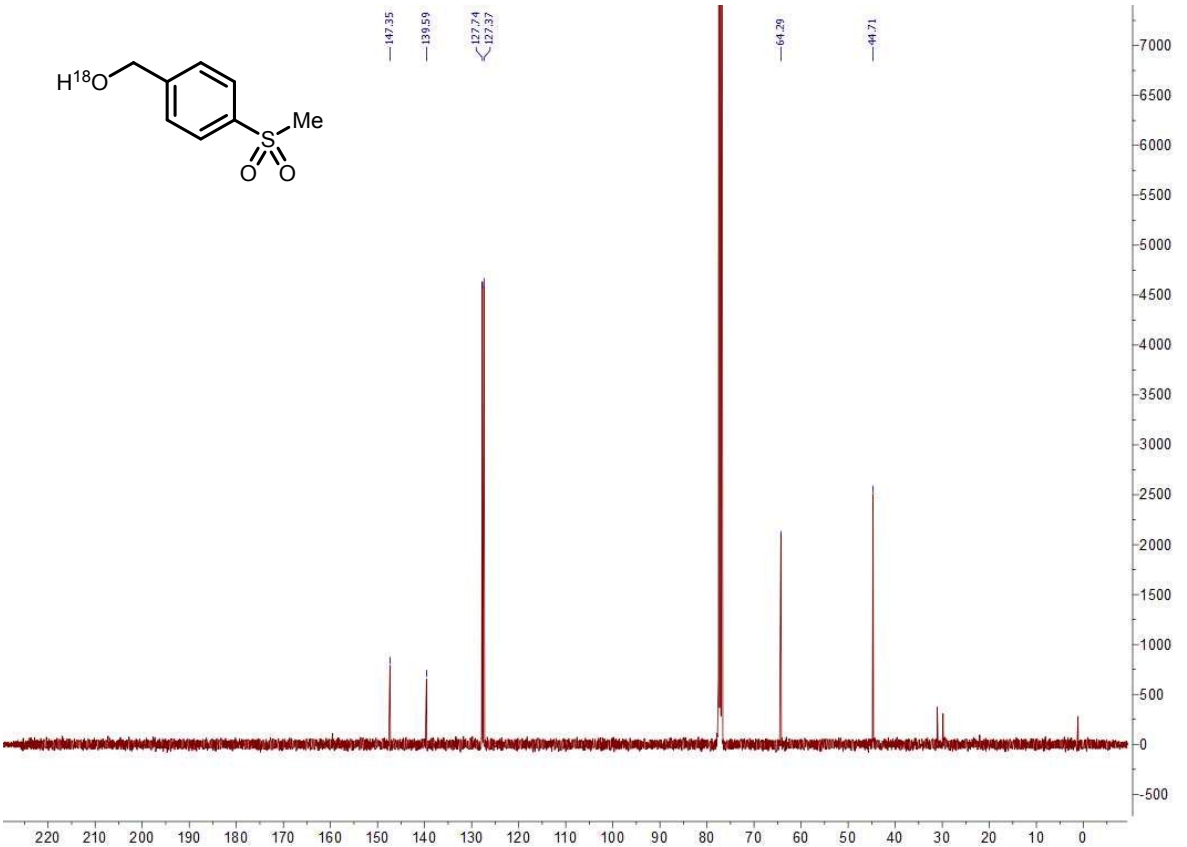
^{1}H and ^{13}C NMR Spectra for Compound 3a



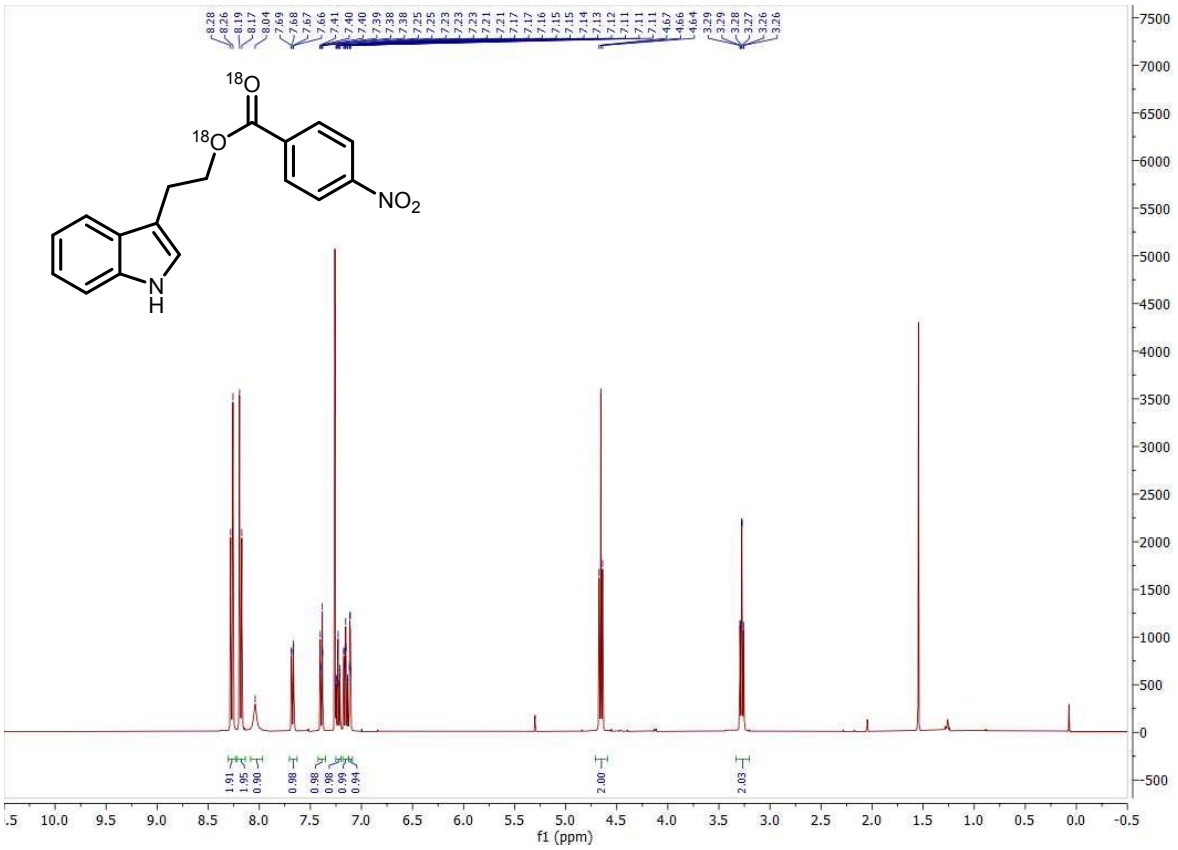


^{1}H and ^{13}C NMR Spectra for Compound S2

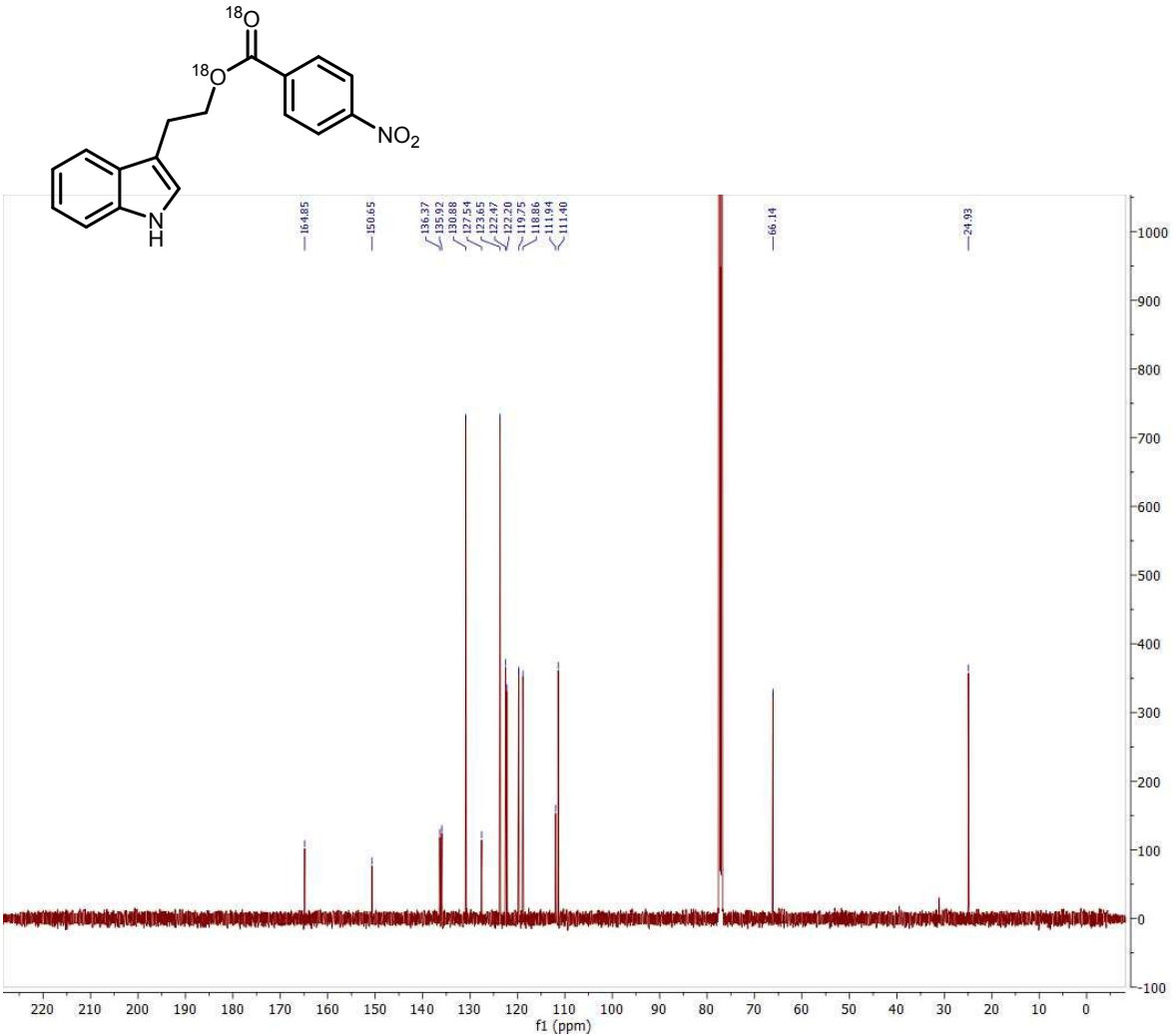


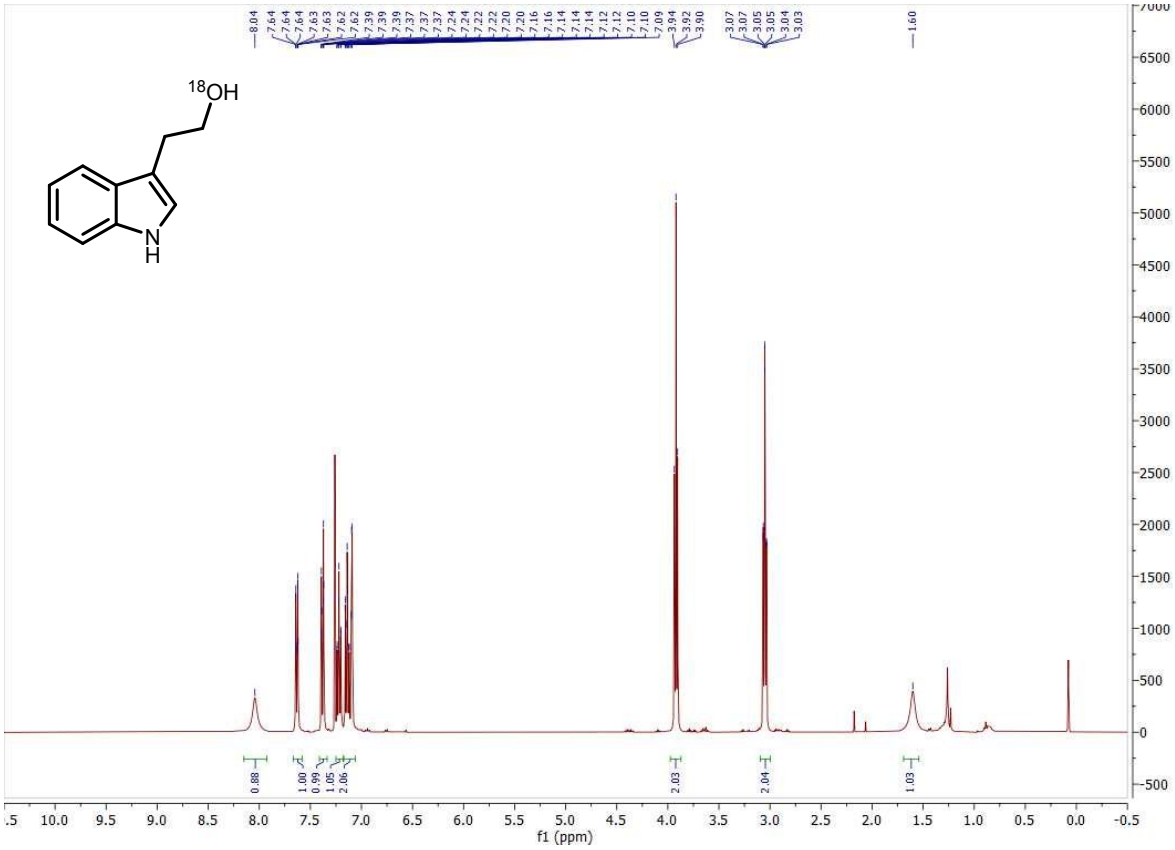


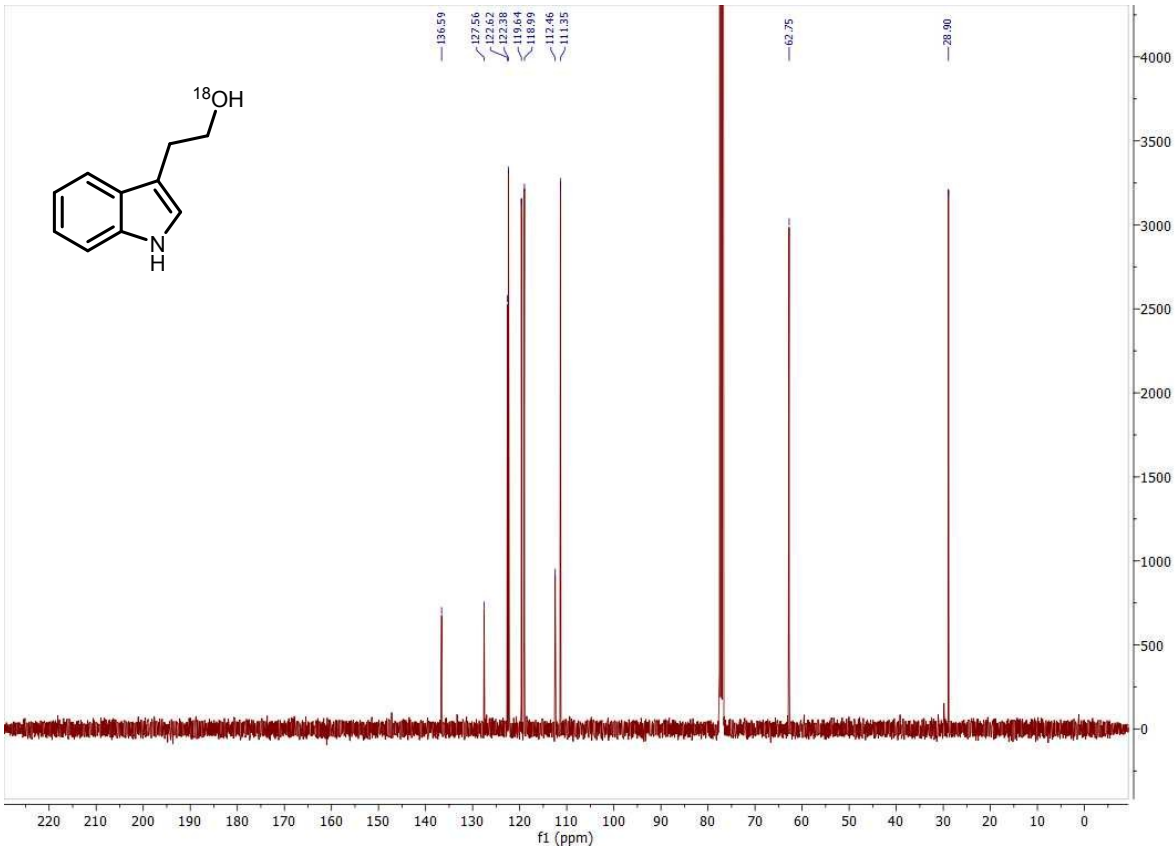
^{1}H and ^{13}C NMR Spectra for Compound 3b



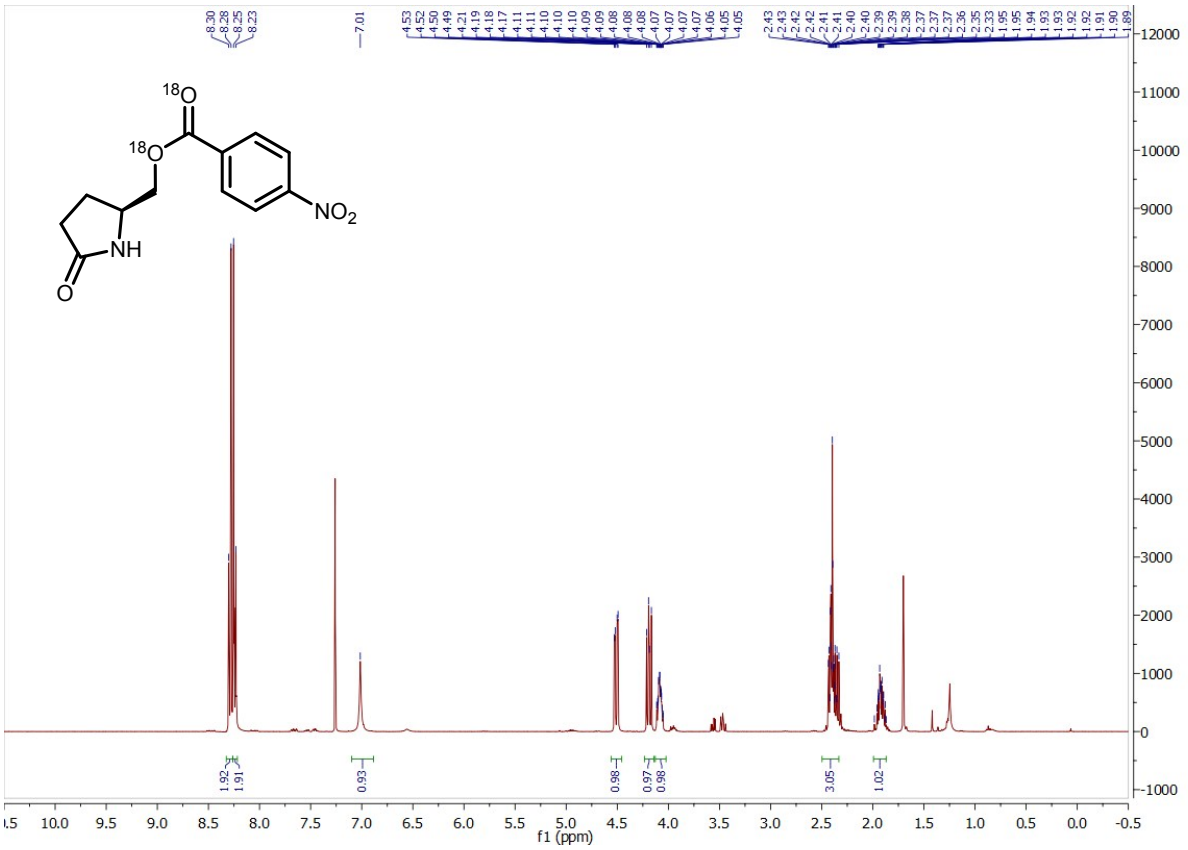
^{1}H and ^{13}C NMR Spectra for Compound S3

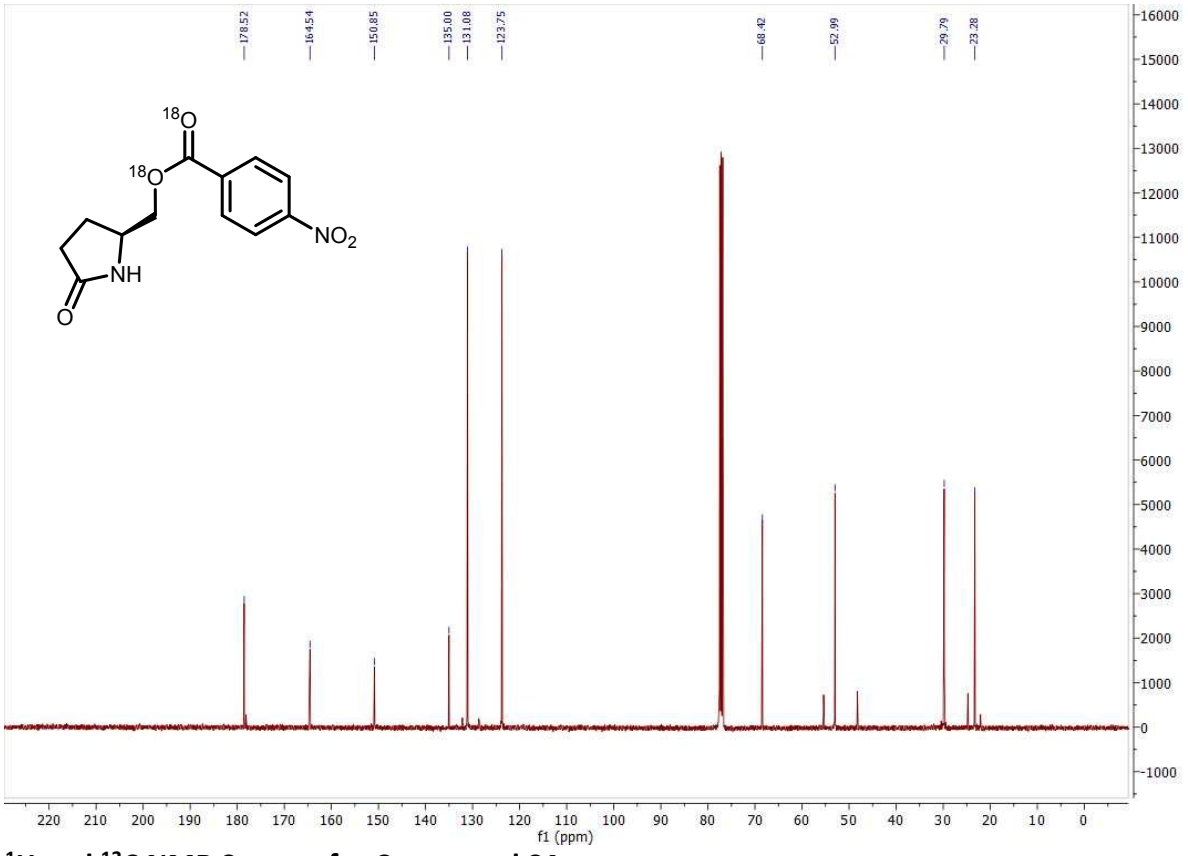




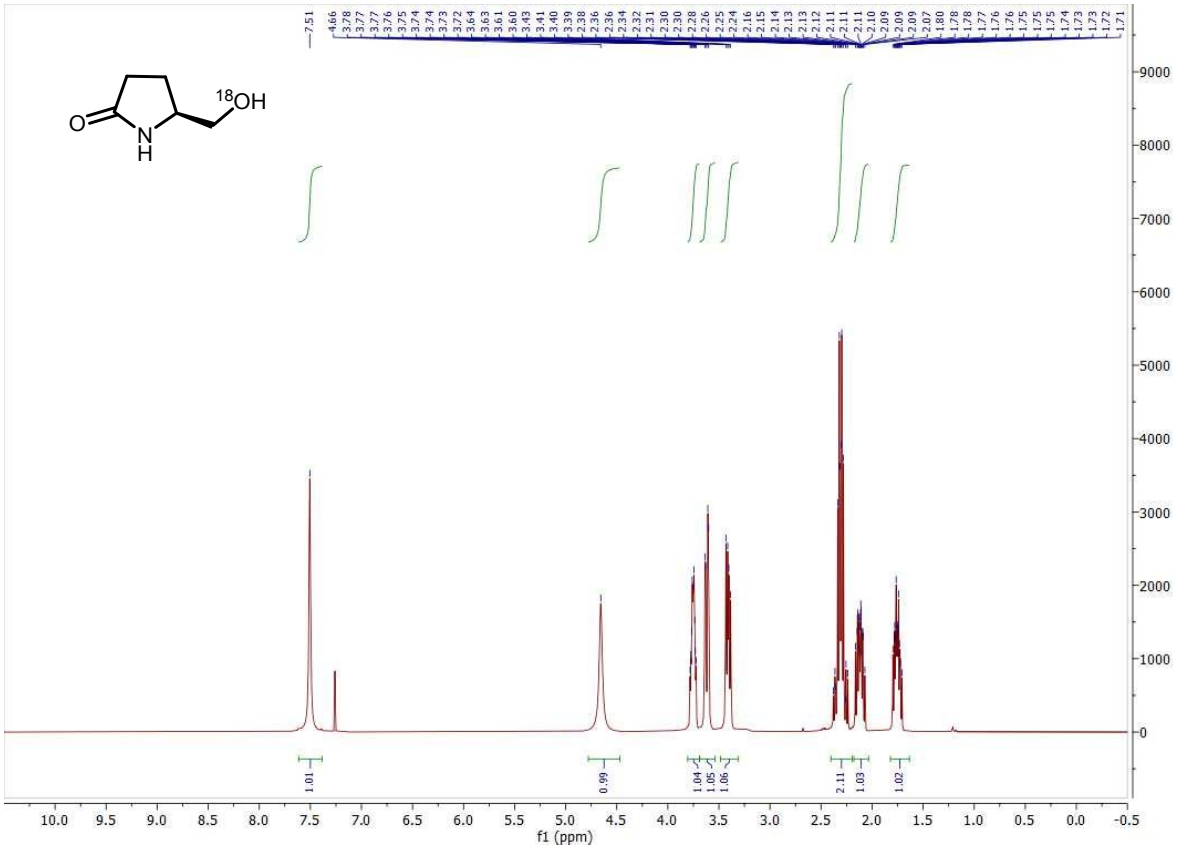


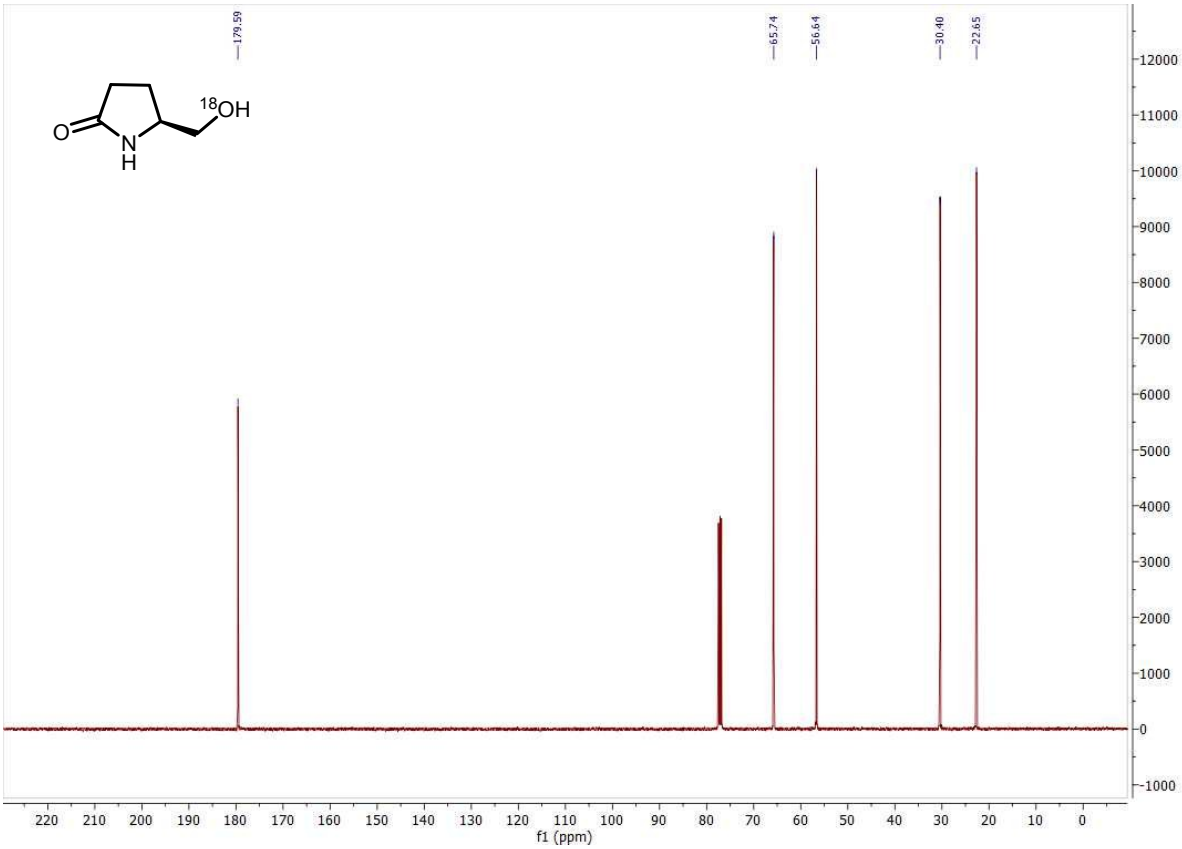
^{1}H and ^{13}C NMR Spectra for Compound 3c





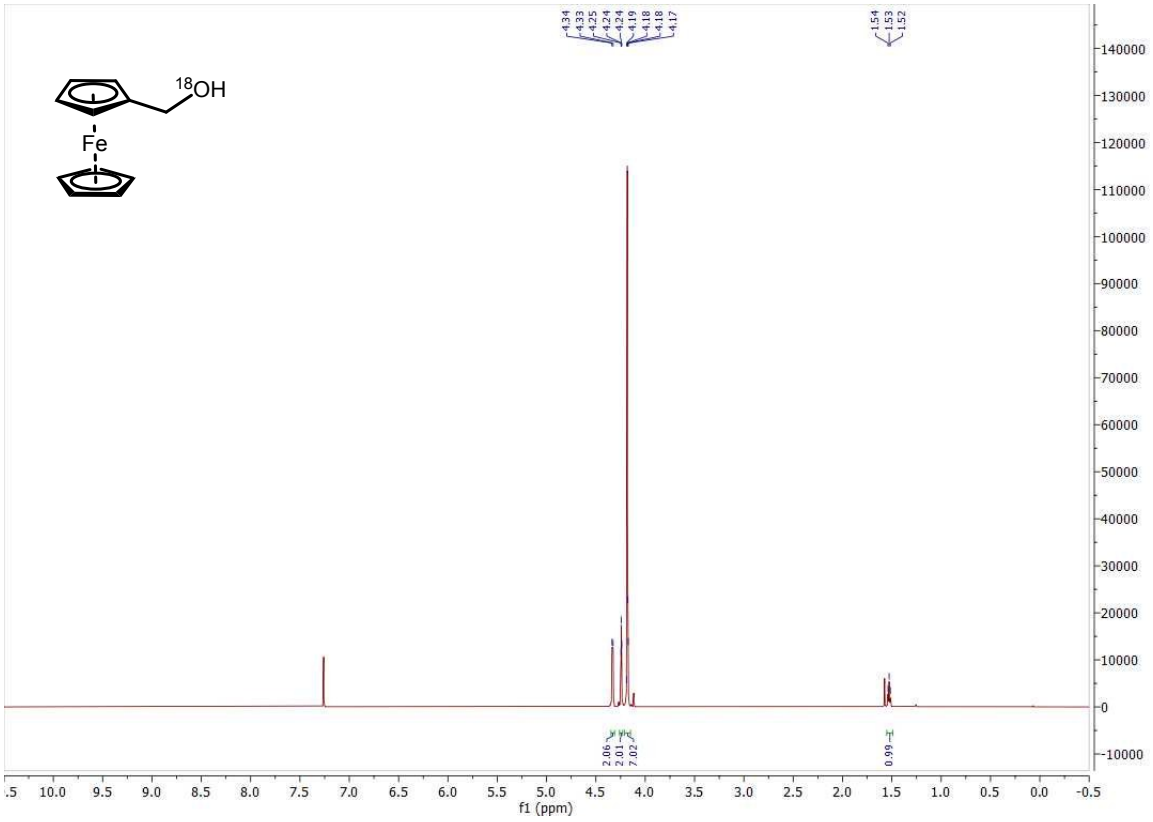
^{1}H and ^{13}C NMR Spectra for Compound S4

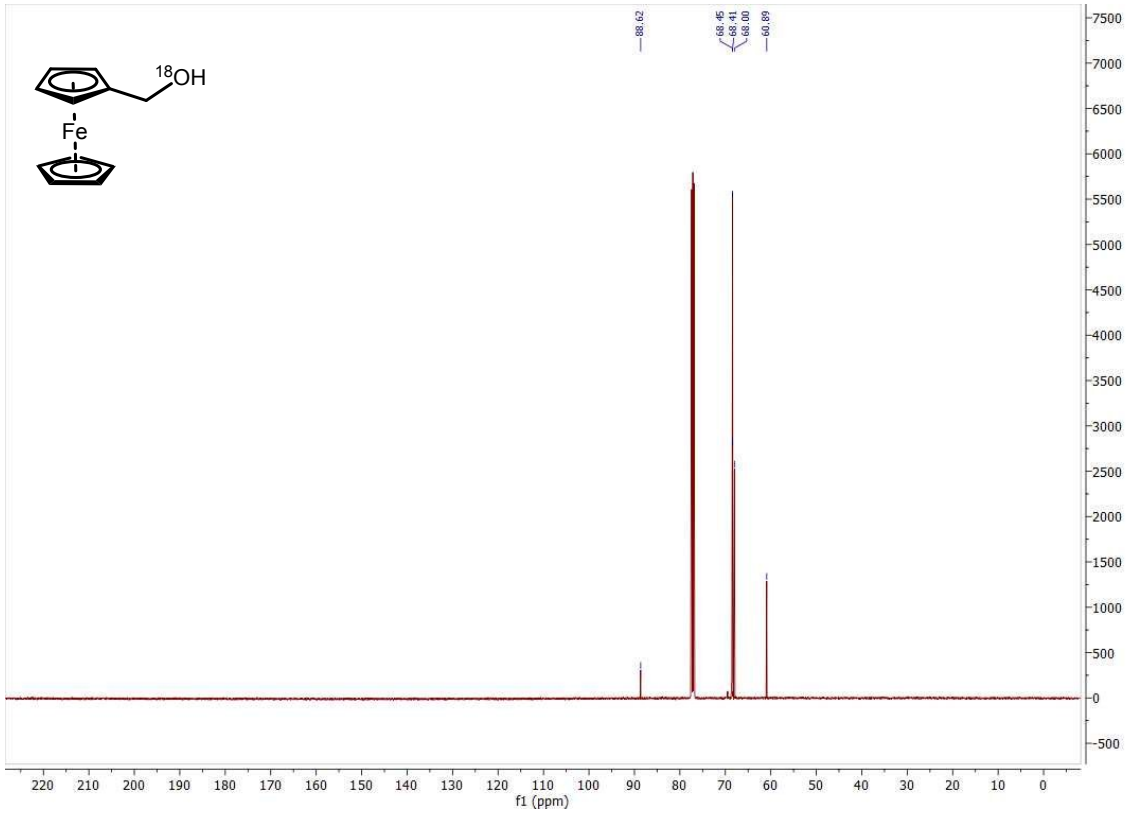


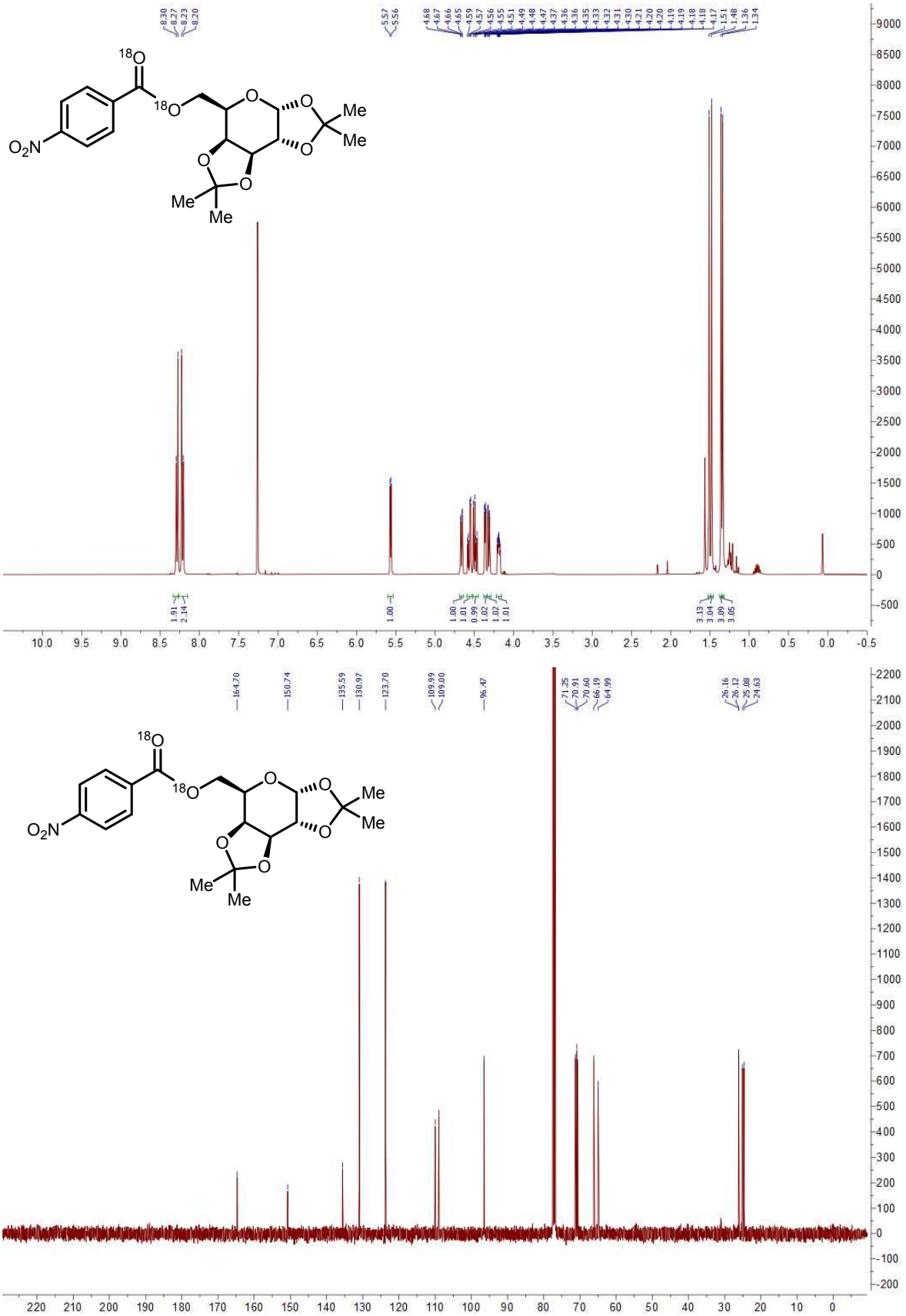


^{1}H and ^{13}C NMR Spectra for Compound 3d

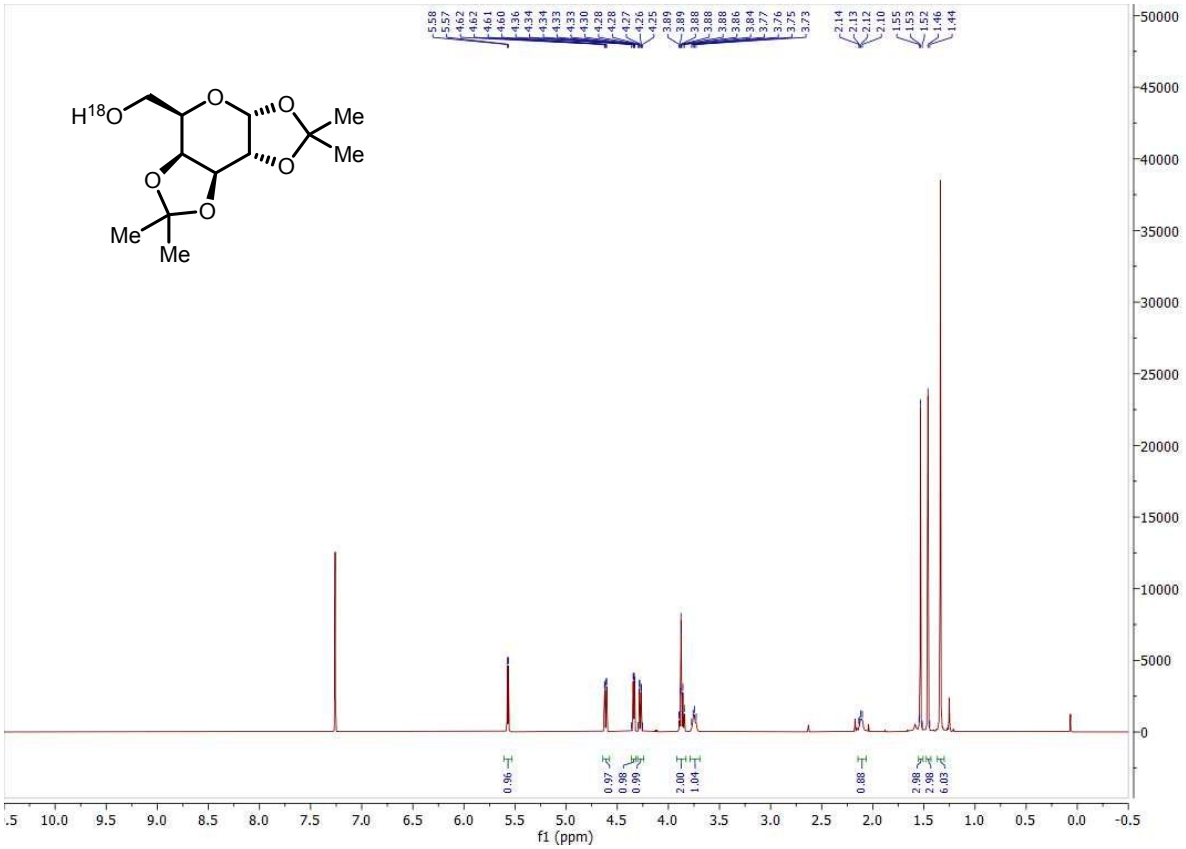
^{1}H and ^{13}C NMR Spectra for Compound 3e



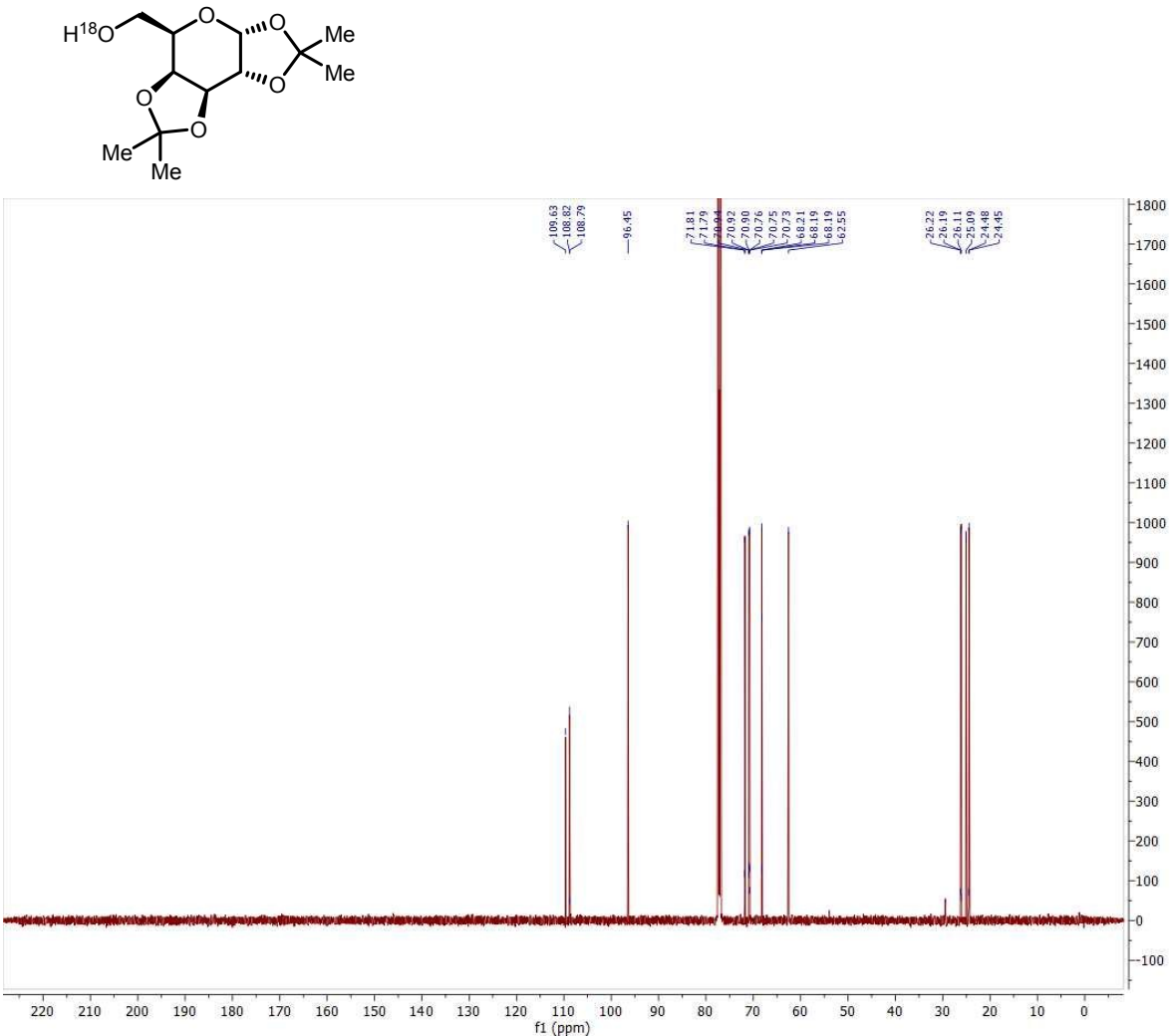


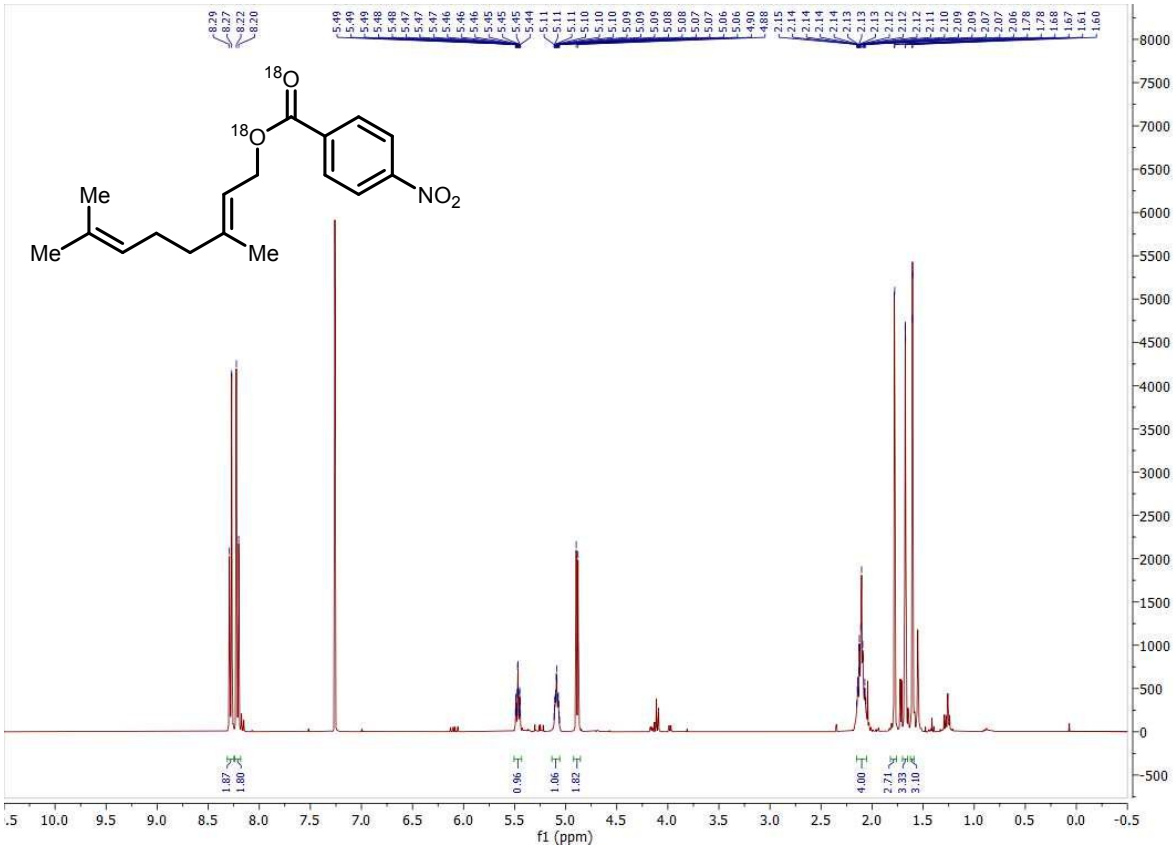


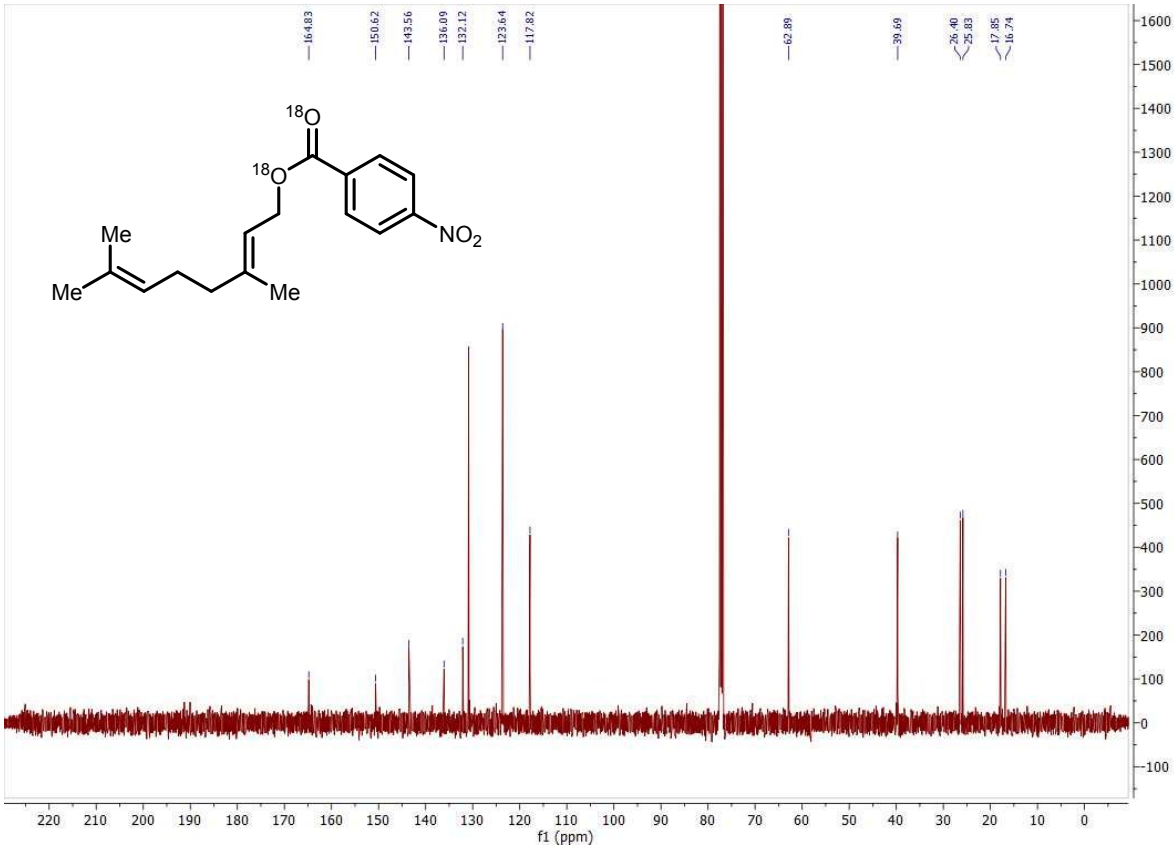
^{1}H and ^{13}C NMR Spectra for Compound S6



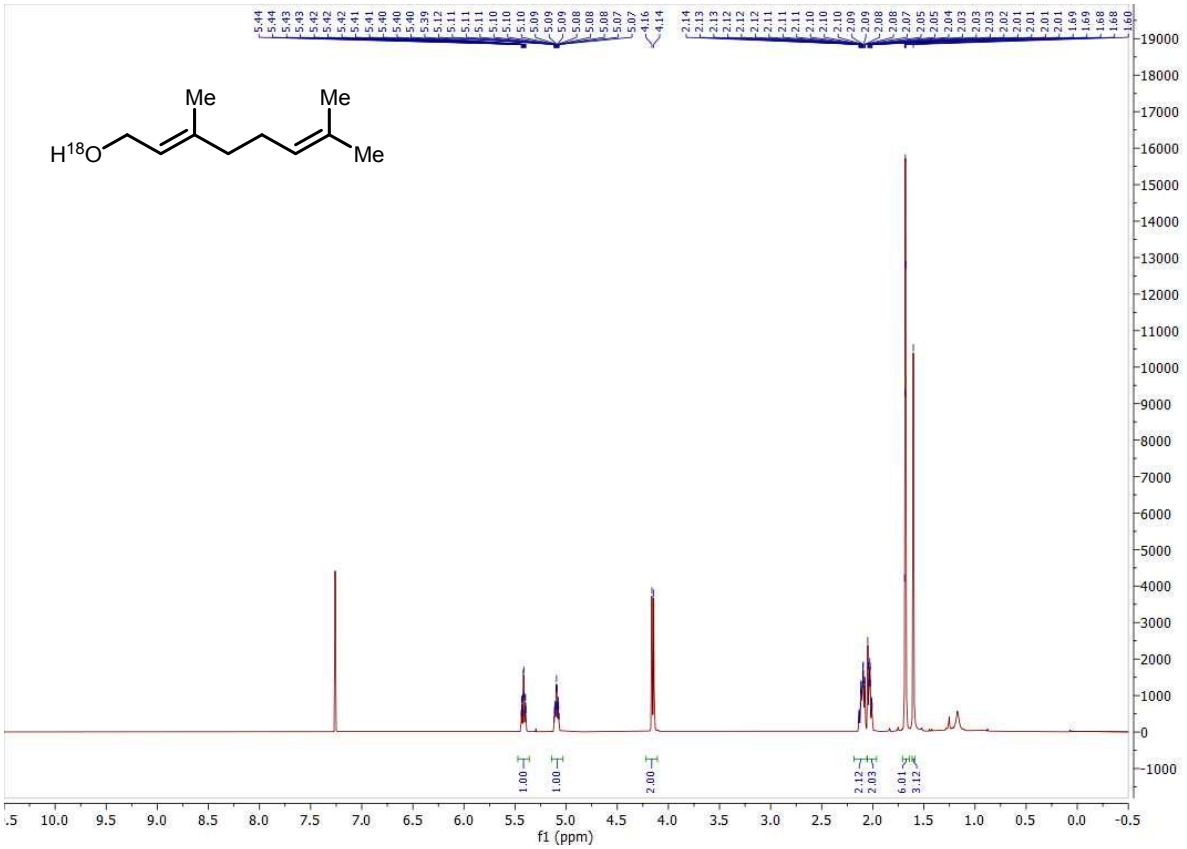
^{1}H and ^{13}C NMR Spectra for Compound 3f

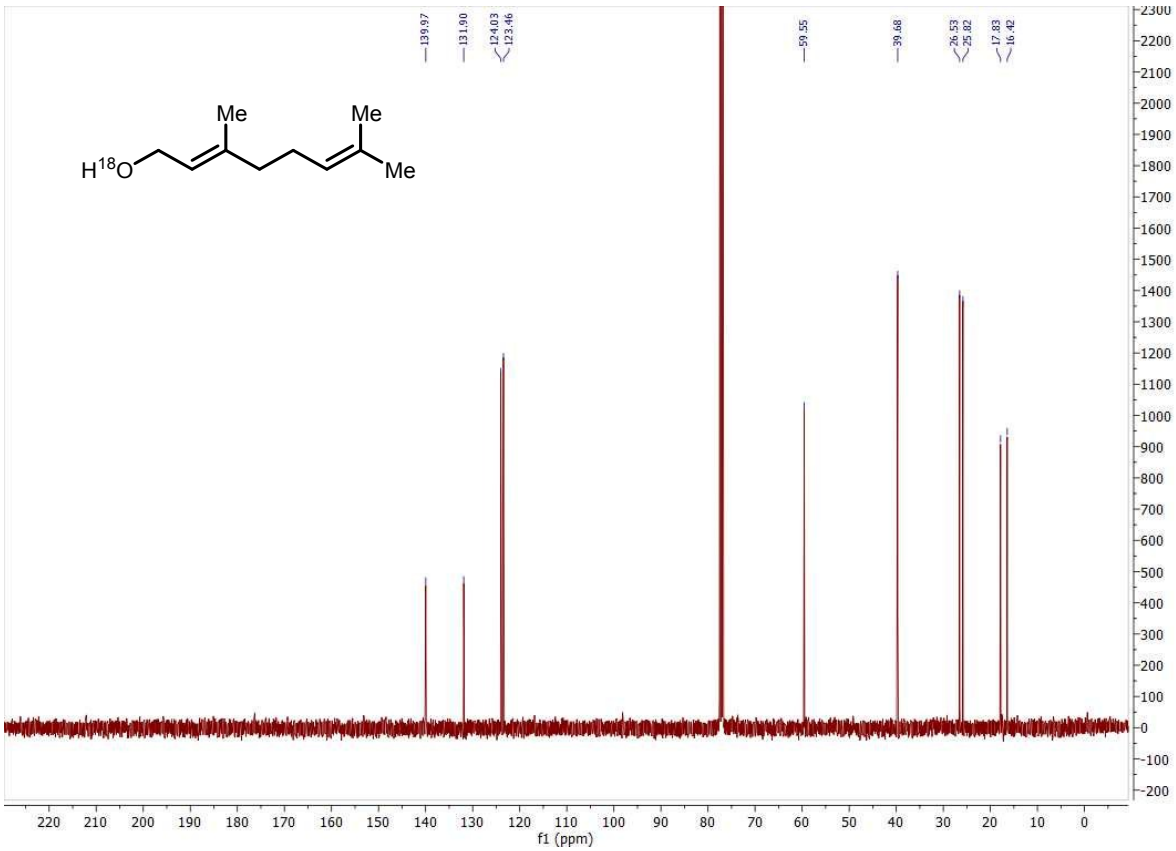




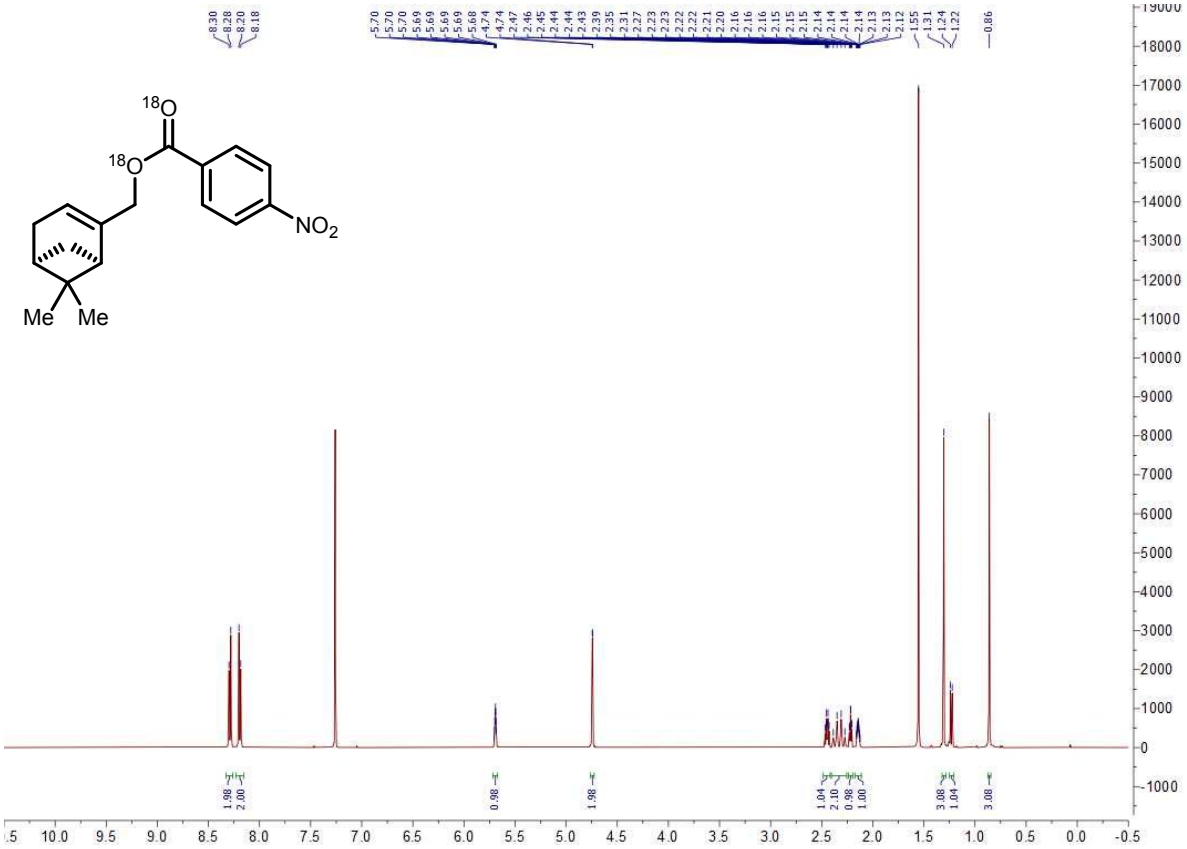


^{1}H and ^{13}C NMR Spectra for Compound S7

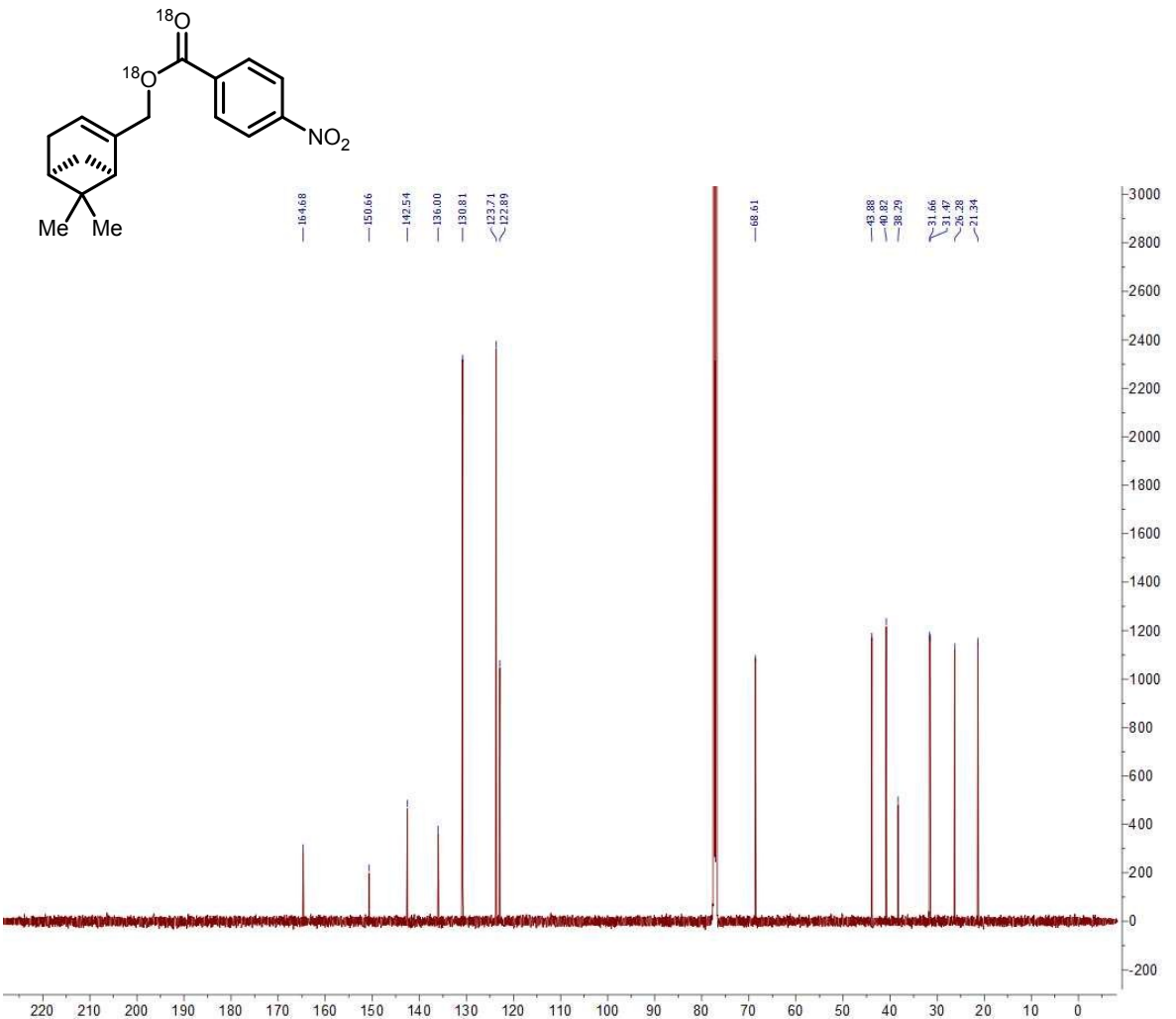


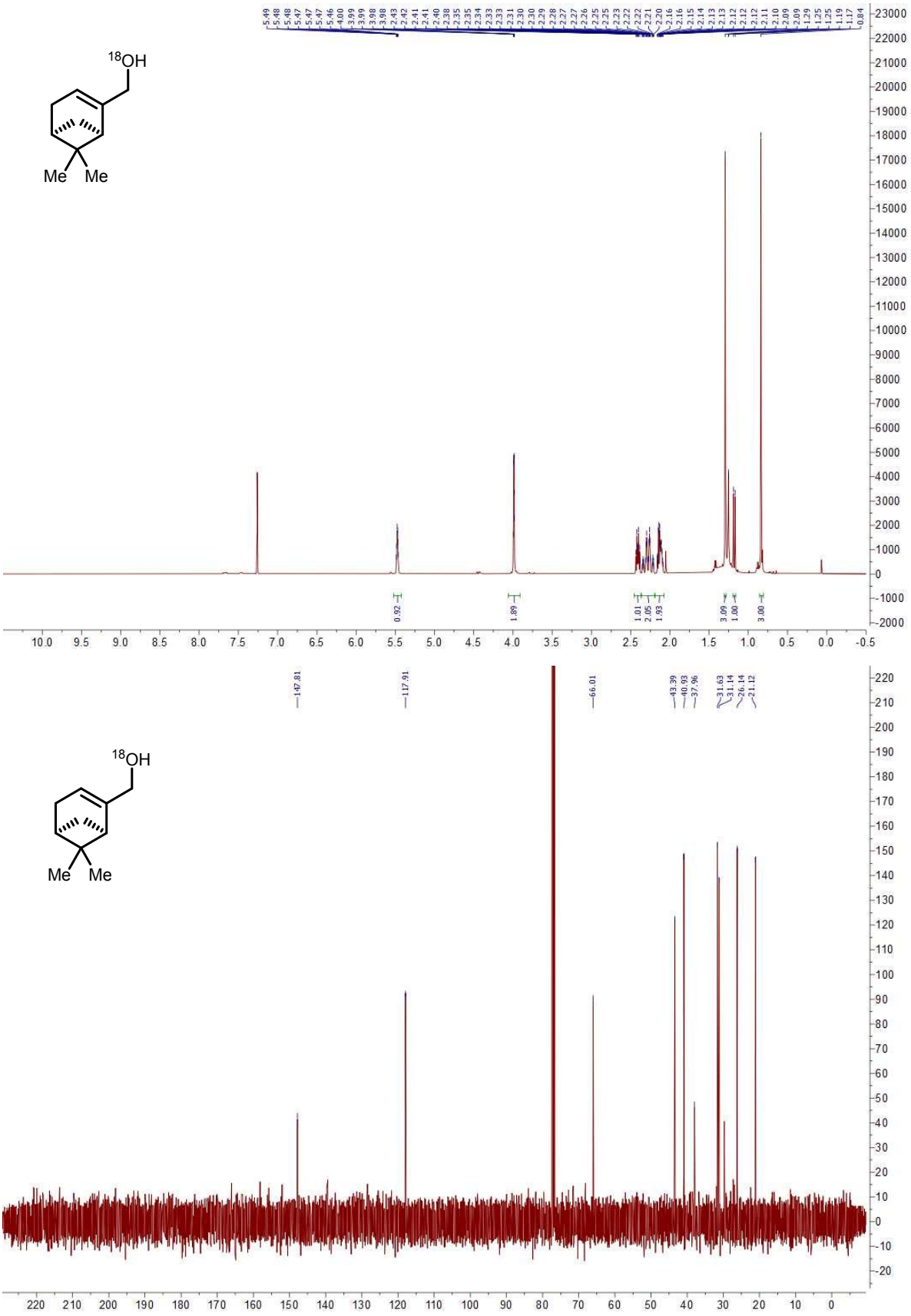


^{1}H and ^{13}C NMR Spectra for Compound 3g

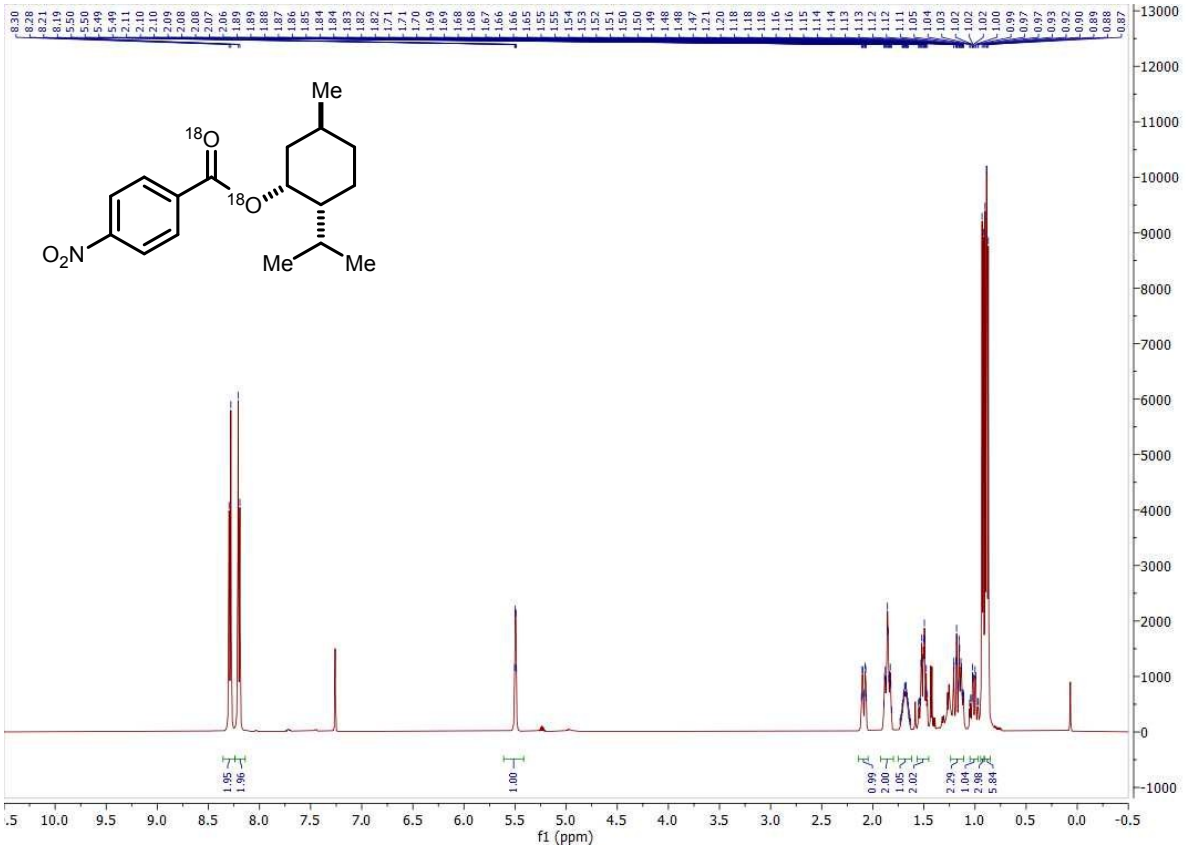


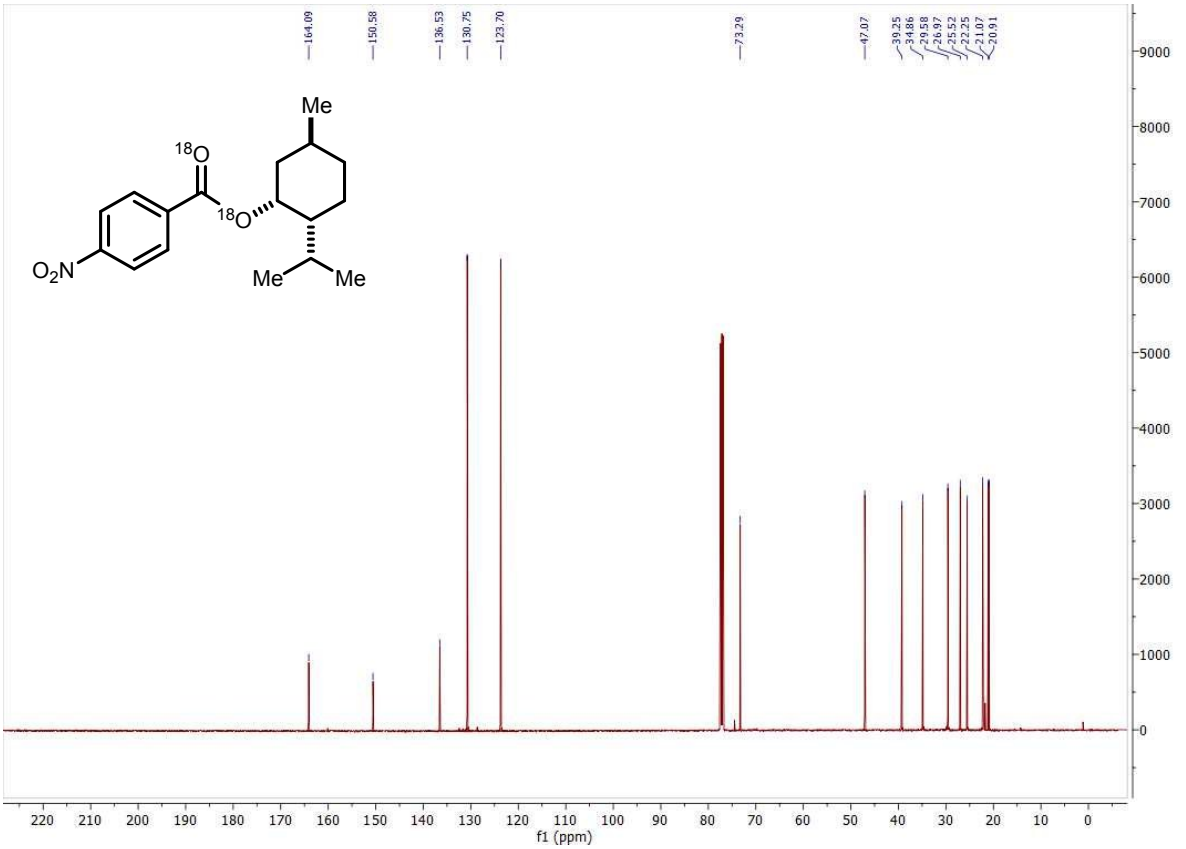
^{1}H and ^{13}C NMR Spectra for Compound S8



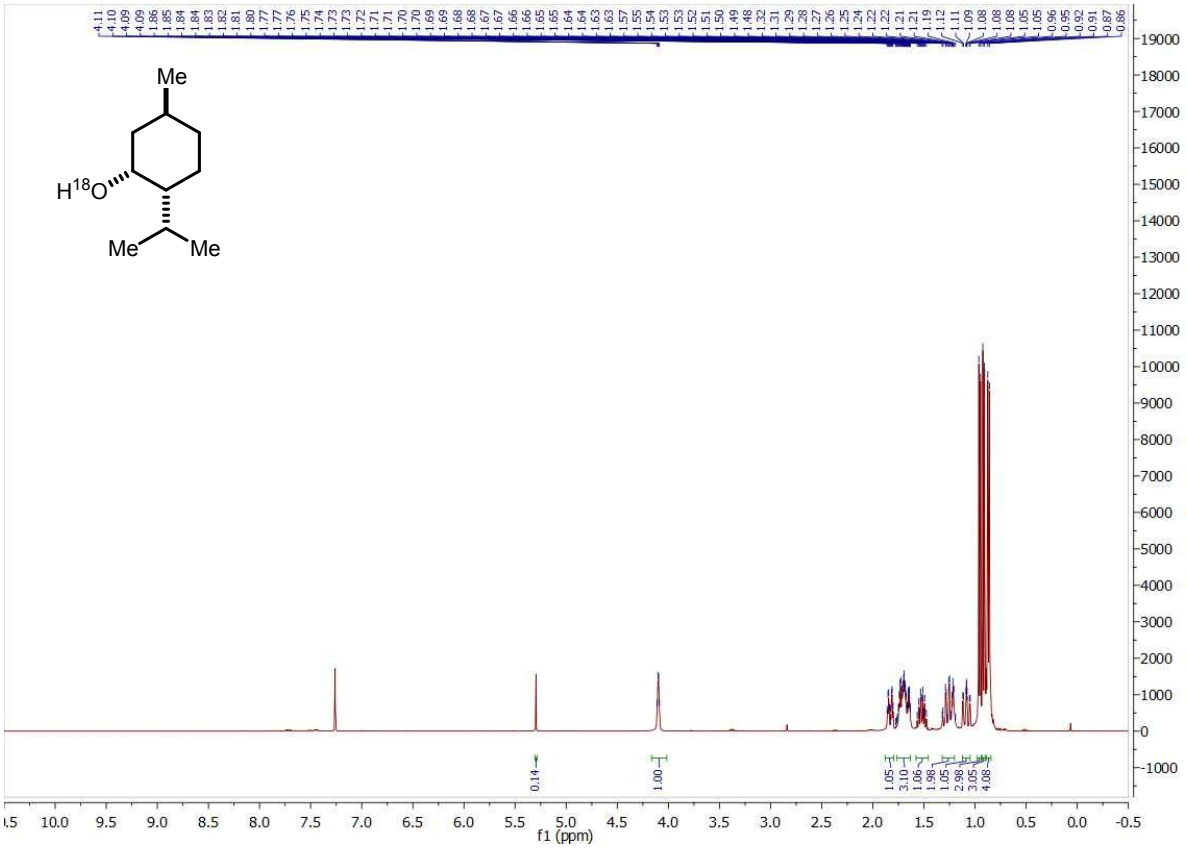


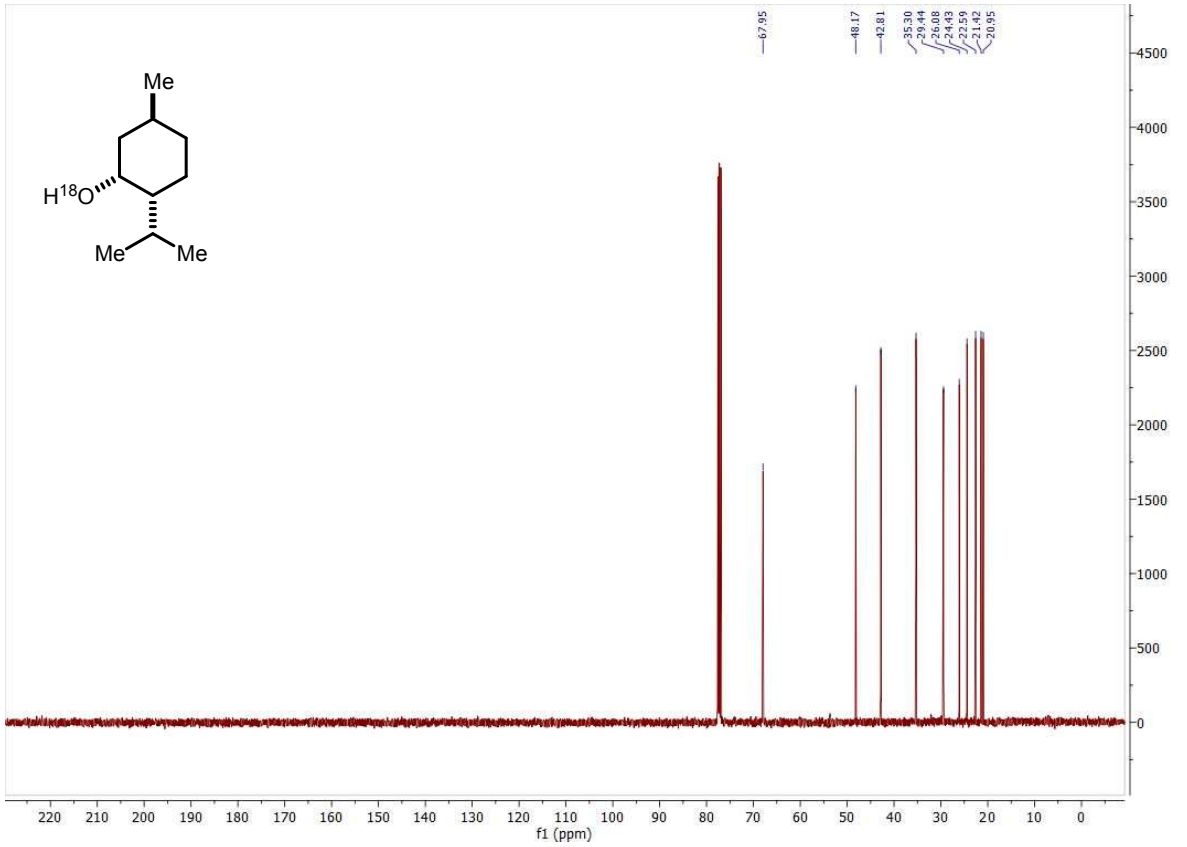
^{1}H and ^{13}C NMR Spectra for Compound 3h



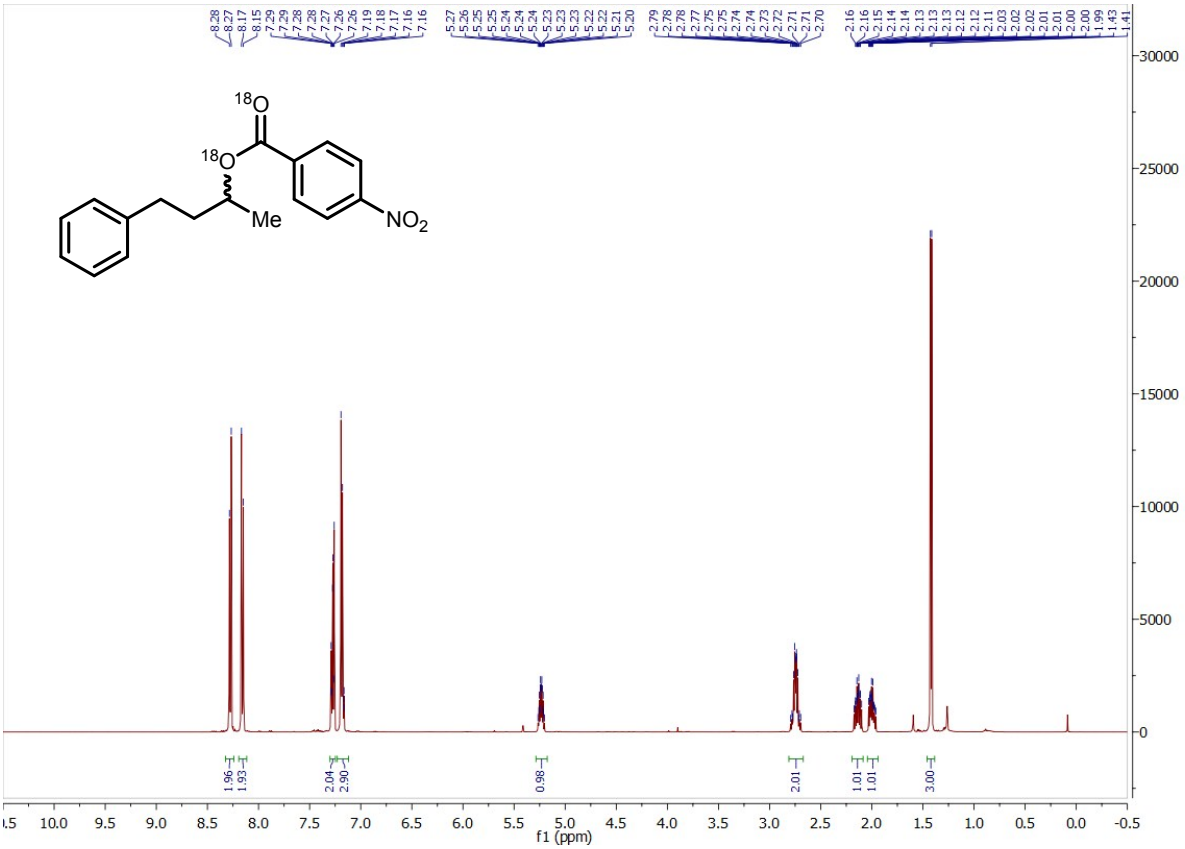


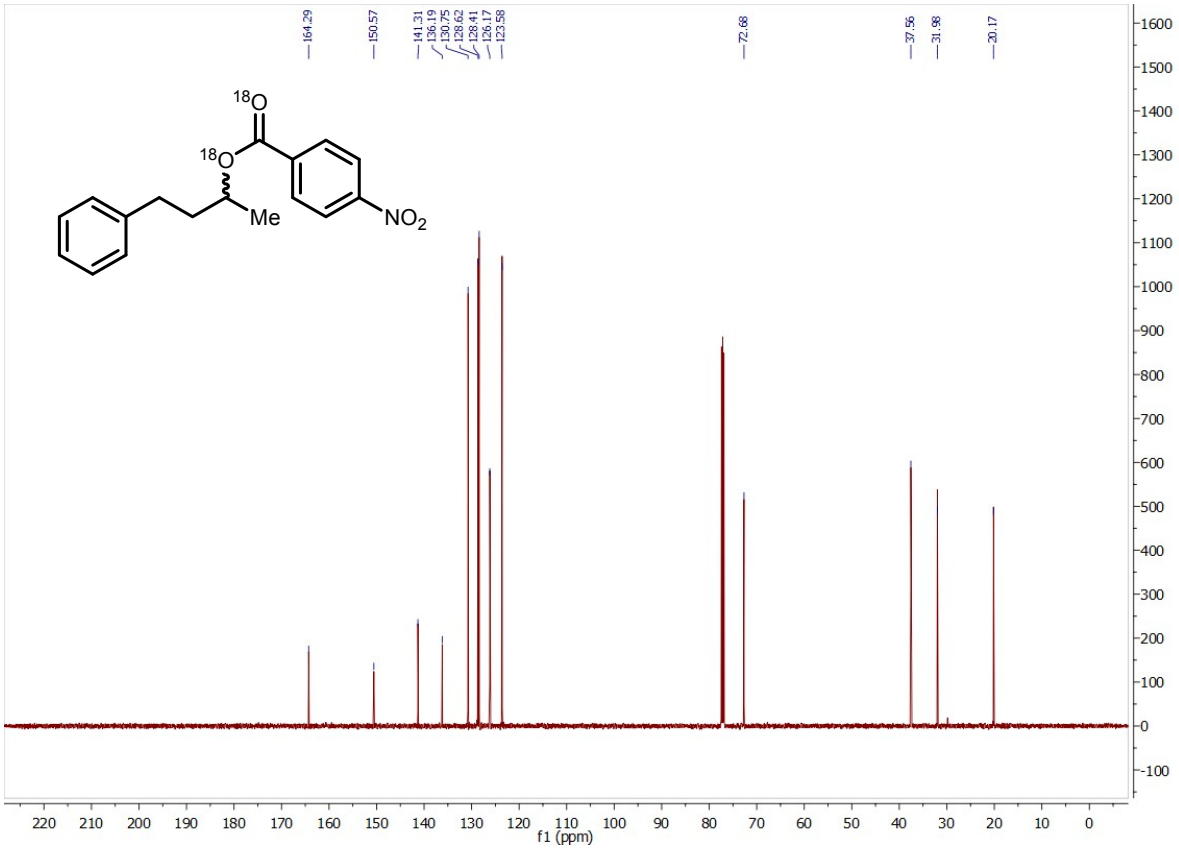
^{1}H and ^{13}C NMR Spectra for Compound S9



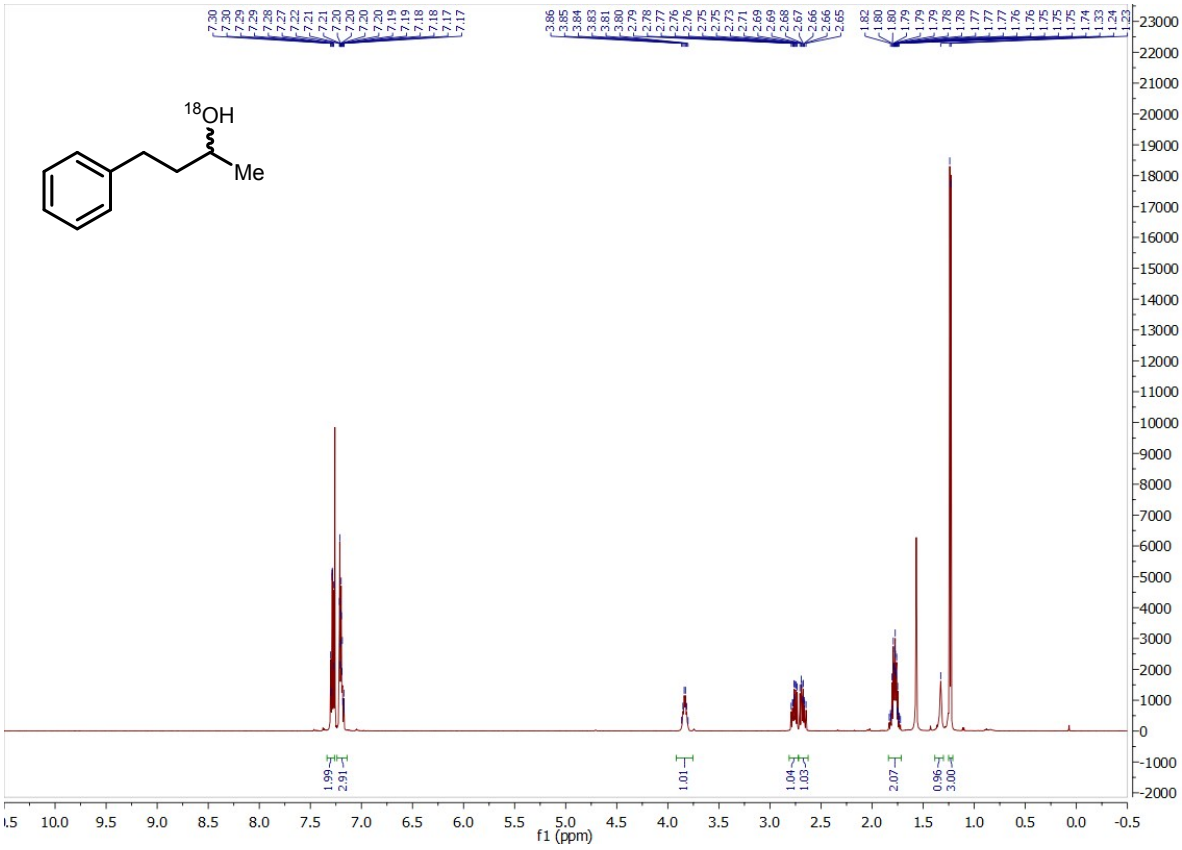


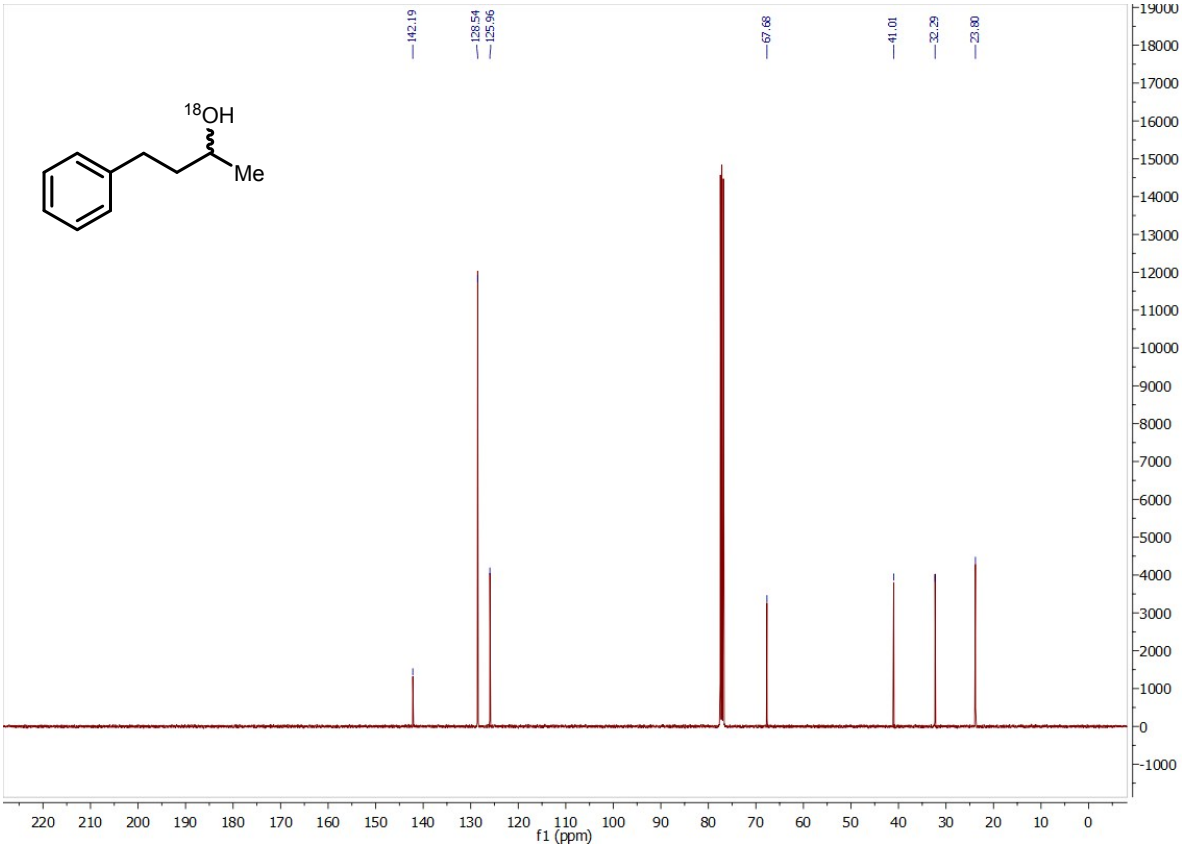
^{1}H and ^{13}C NMR Spectra for Compound 3i



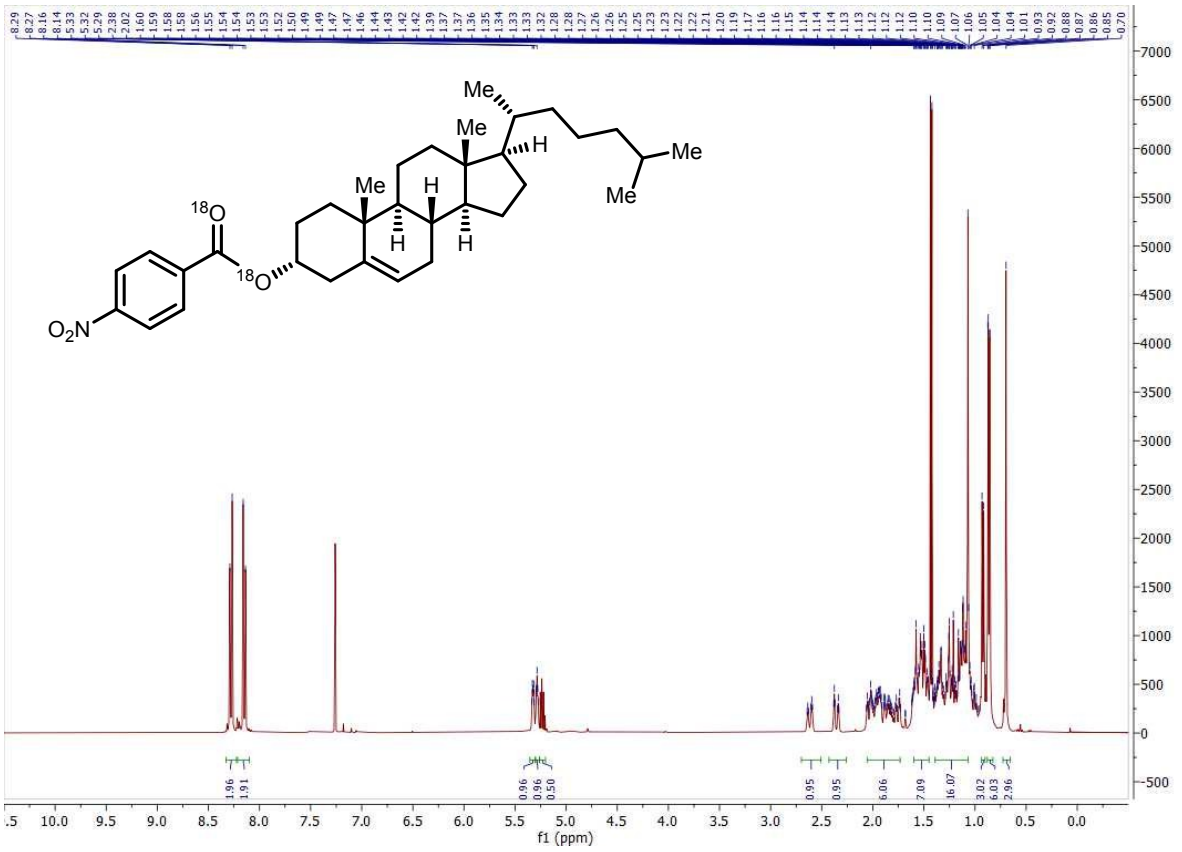


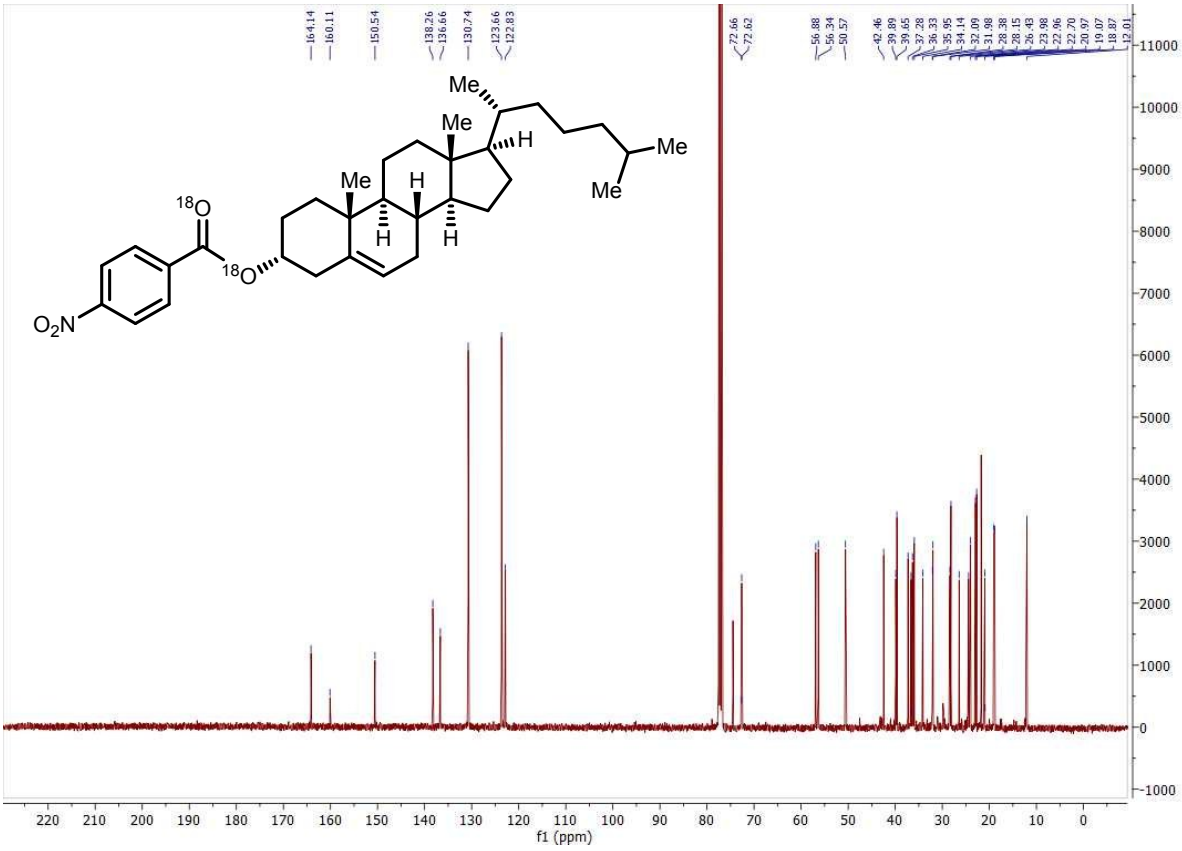
^{1}H and ^{13}C NMR Spectra for Compound S10



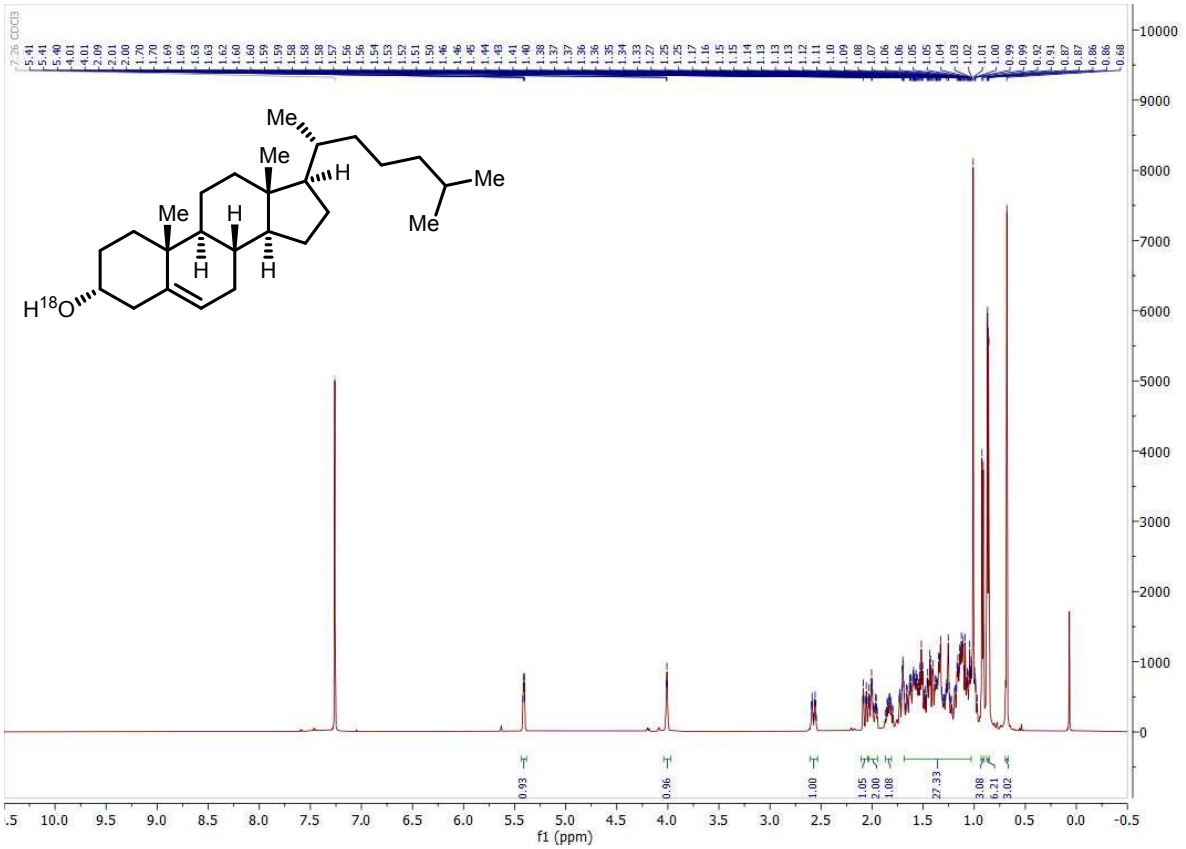


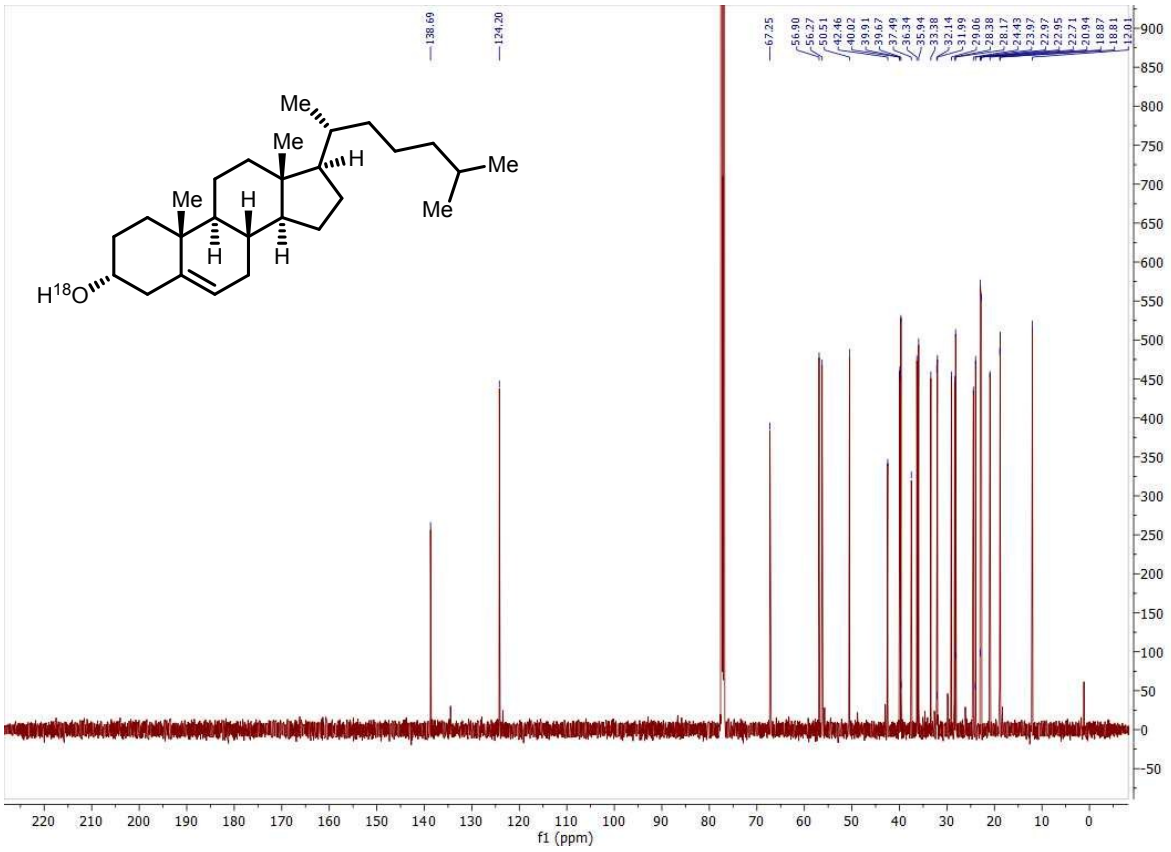
^{1}H and ^{13}C NMR Spectra for Compound 3j



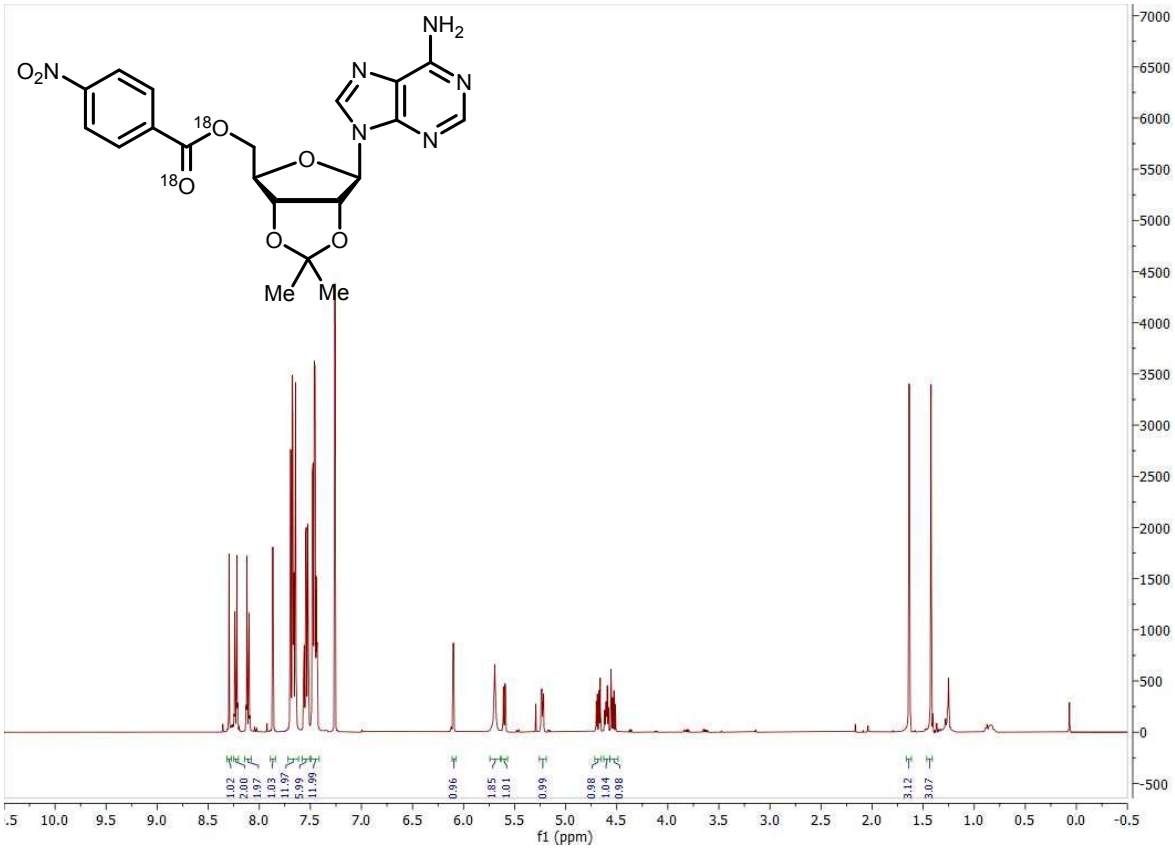


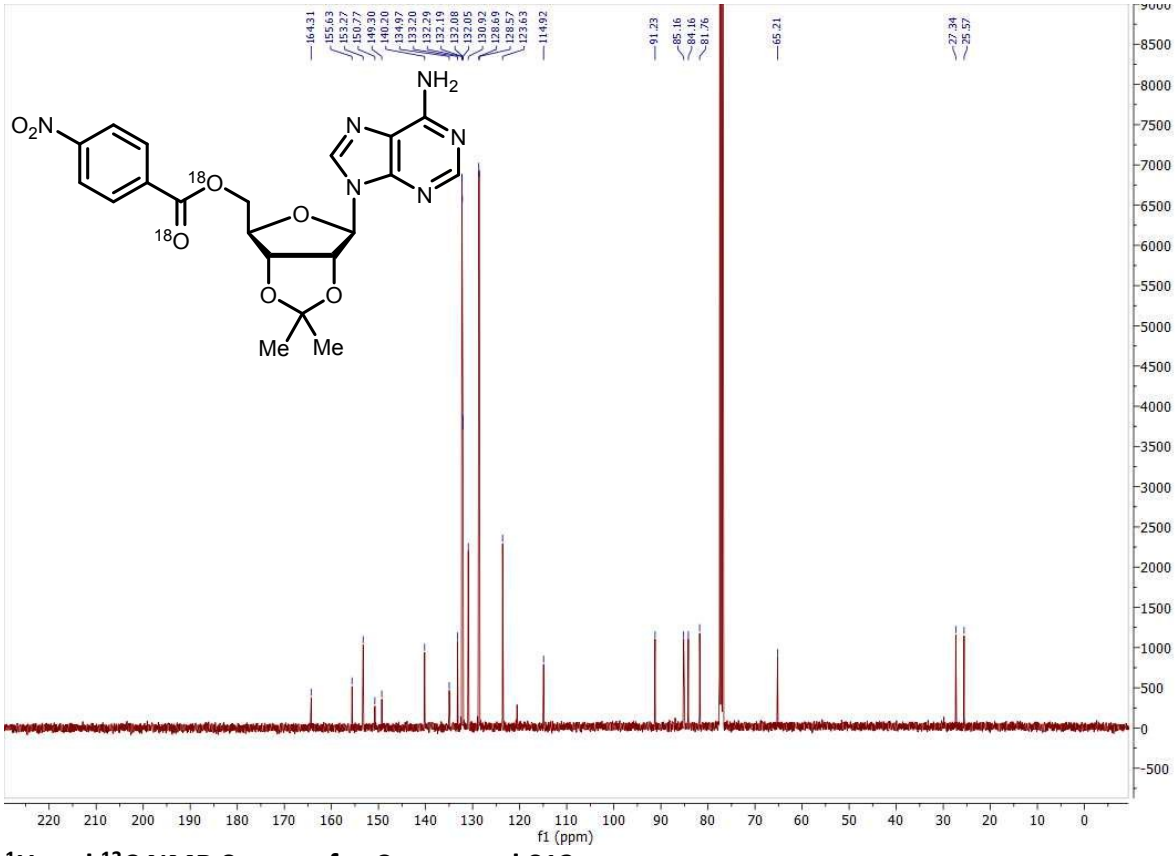
^{1}H and ^{13}C NMR Spectra for Compound S11



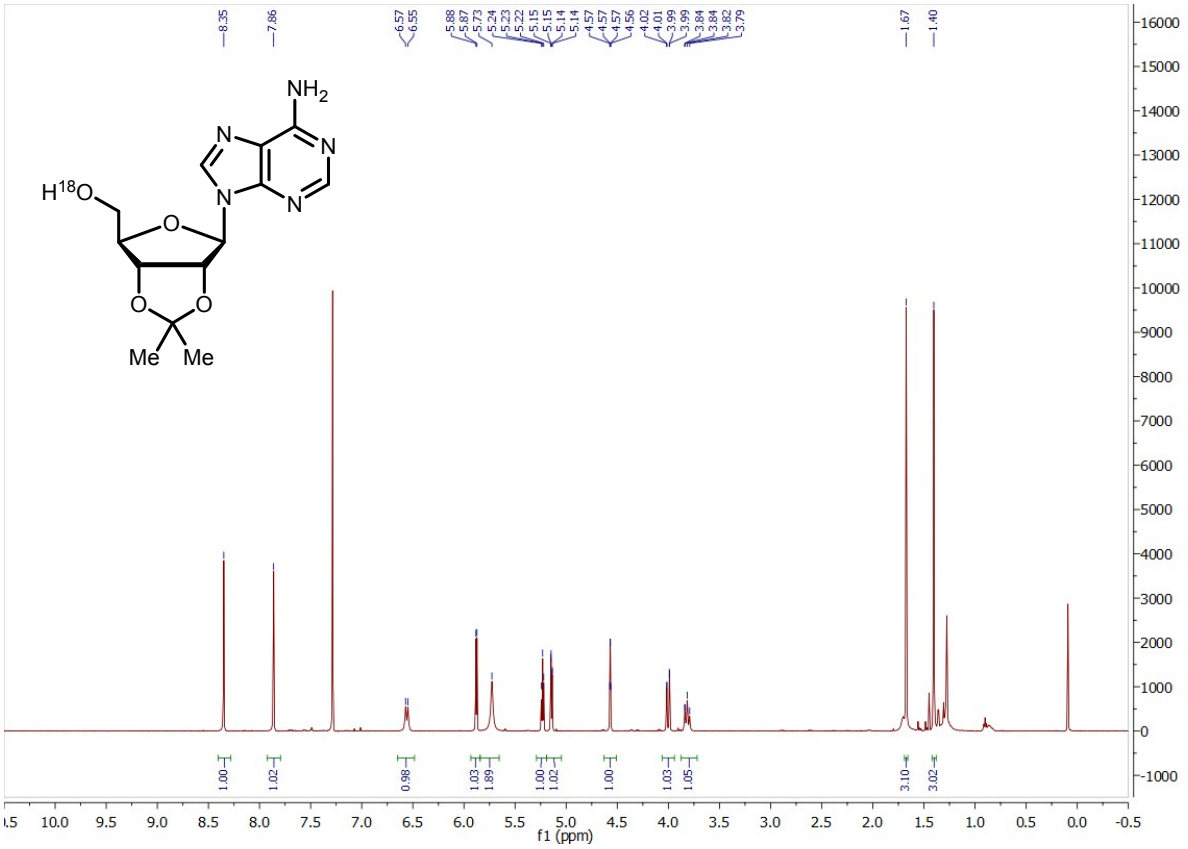


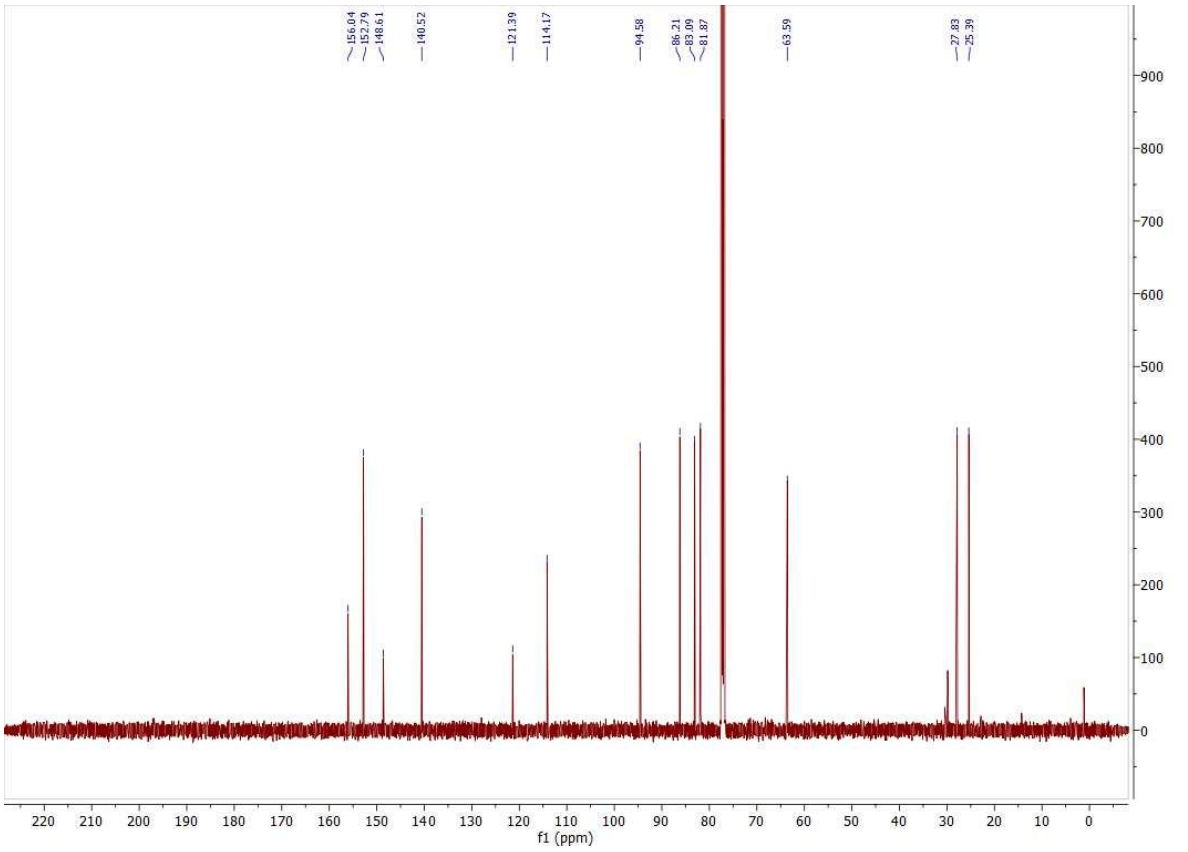
^{1}H and ^{13}C NMR Spectra for Compound 3k



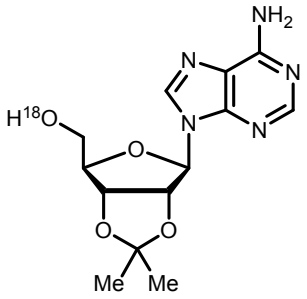


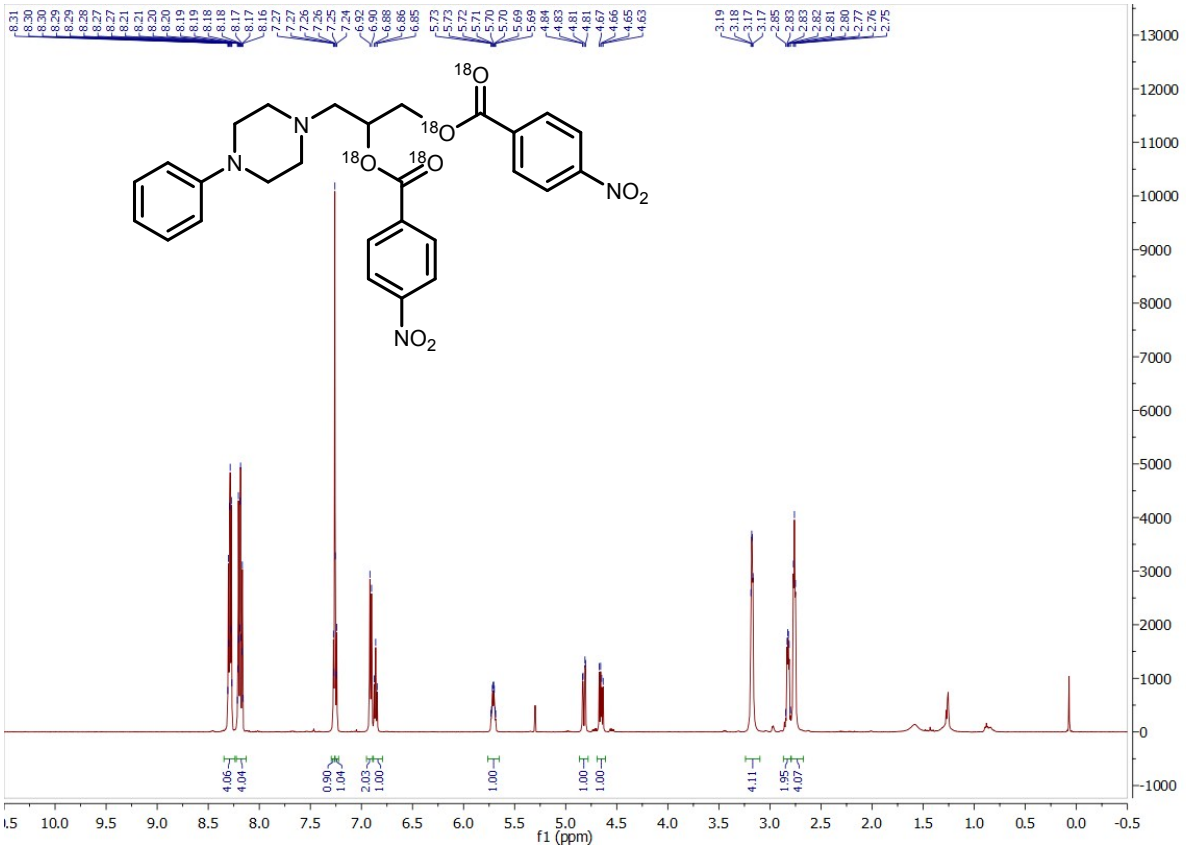
^{1}H and ^{13}C NMR Spectra for Compound S12

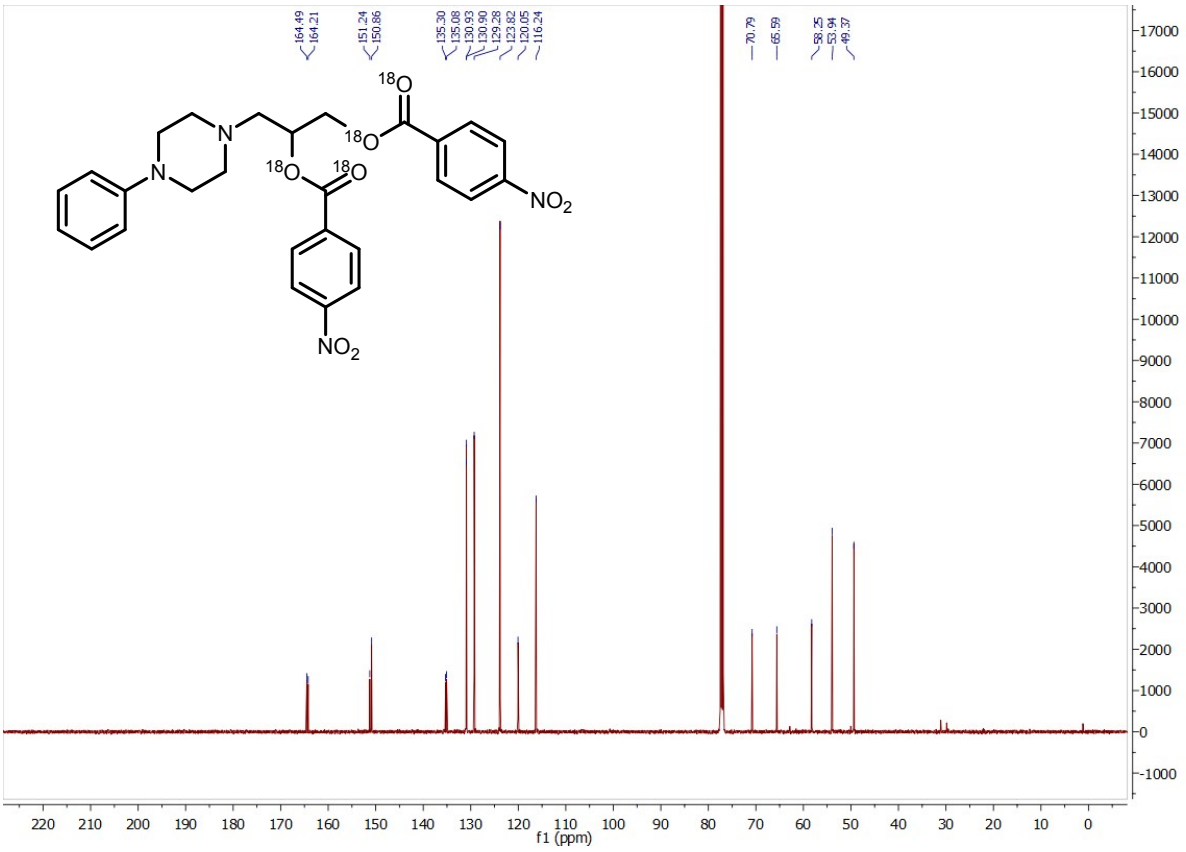




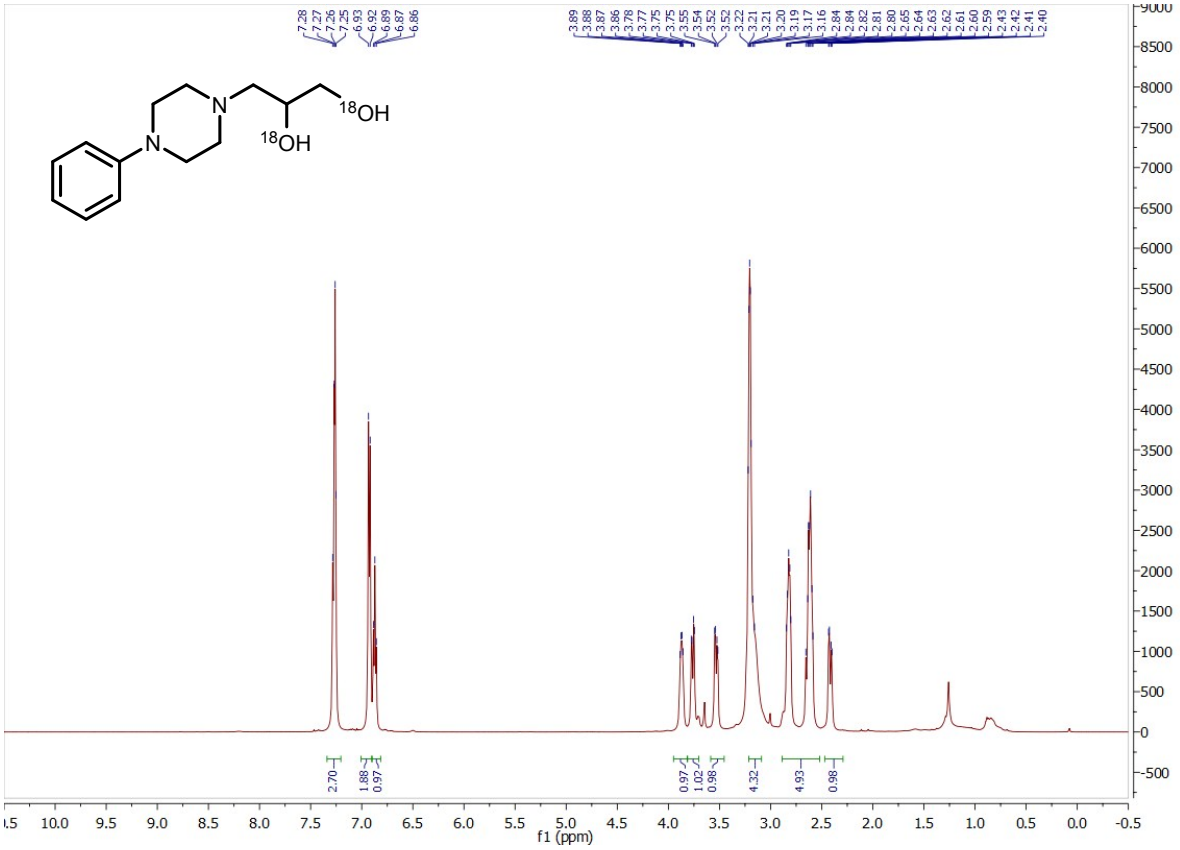
^{1}H and ^{13}C NMR Spectra for Compound 3l

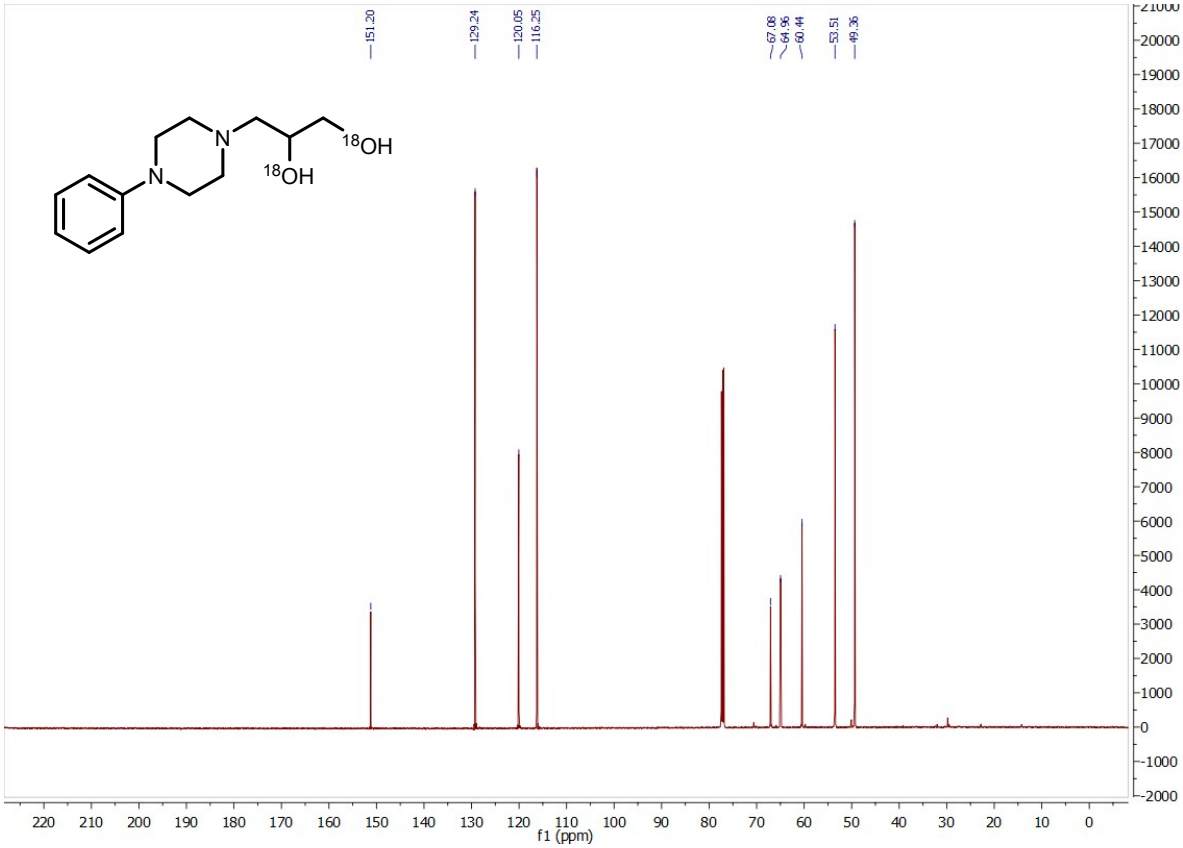

NH2
N
N
N
N
H18O
O
O
O
Me
Me



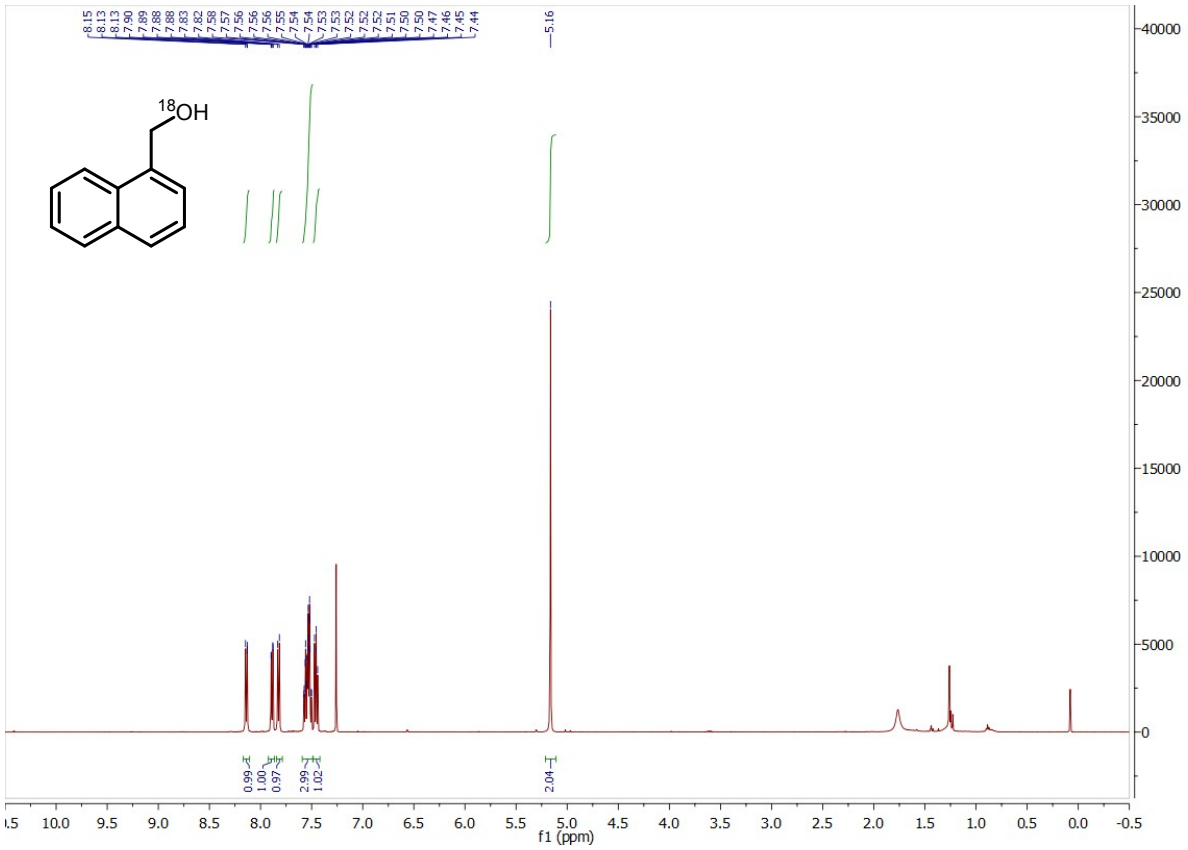


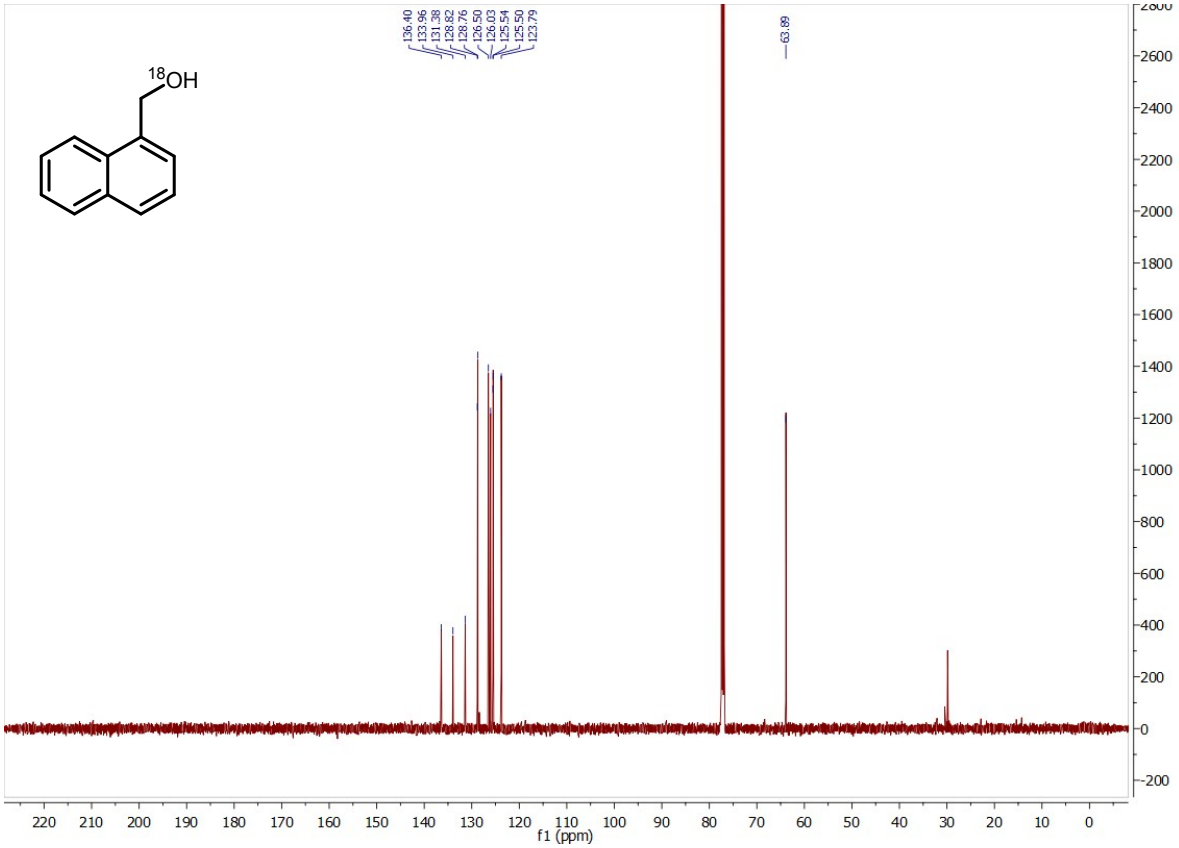
^{1}H and ^{13}C NMR Spectra for Compound S13



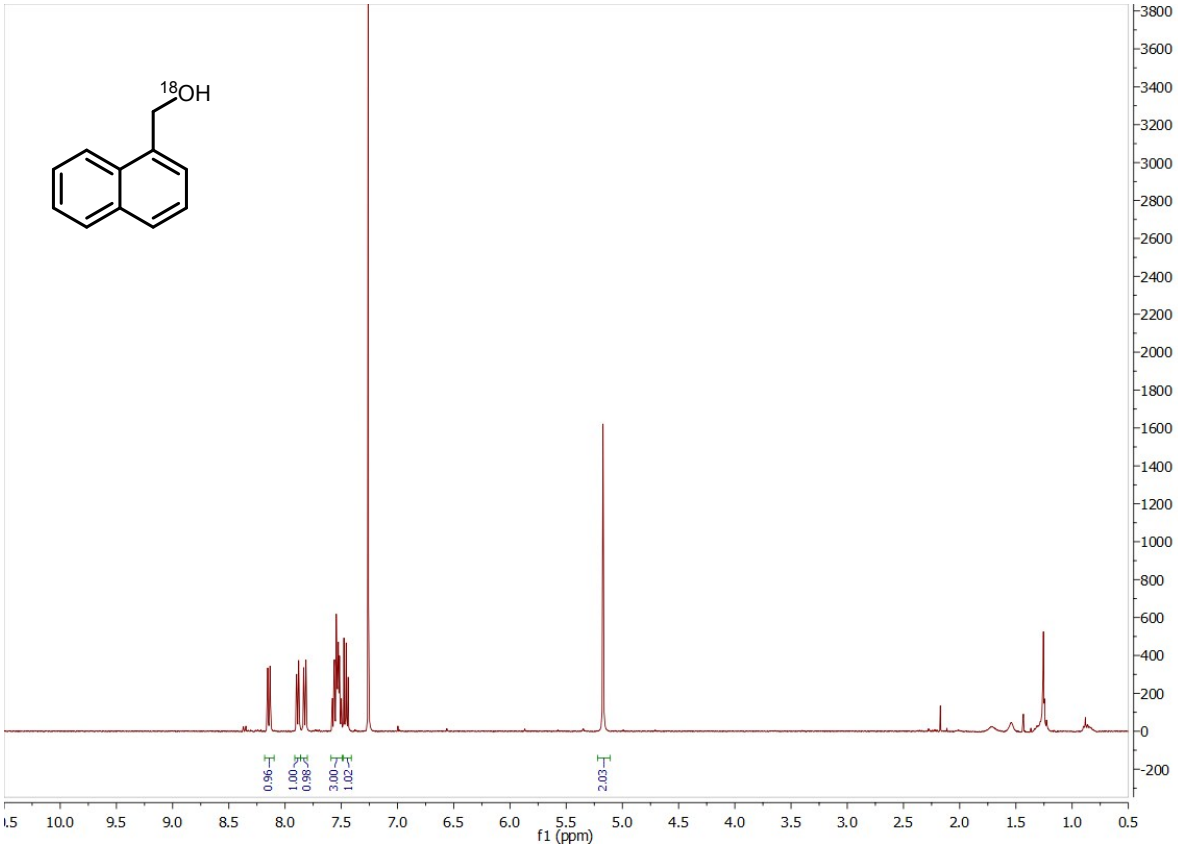


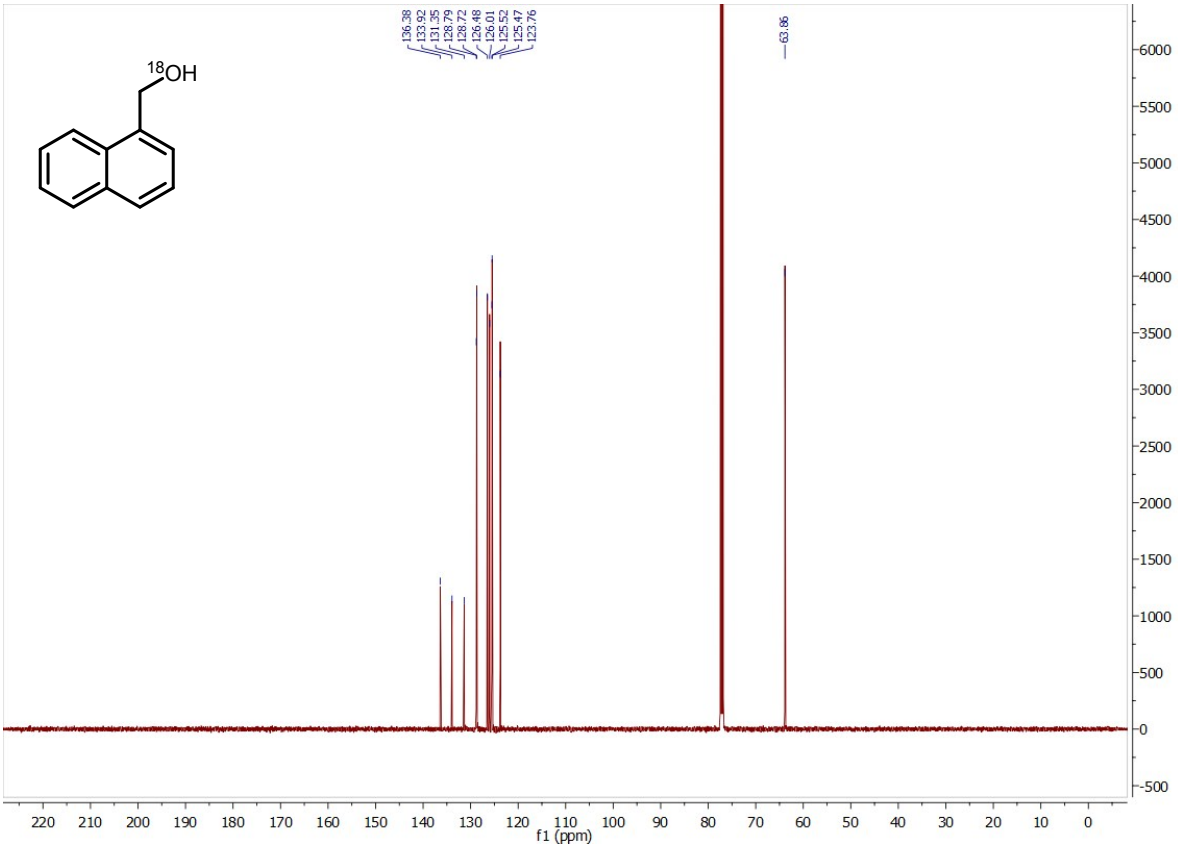
^{1}H and ^{13}C NMR Spectra for Dropropizine-[^{18}O]$_2$



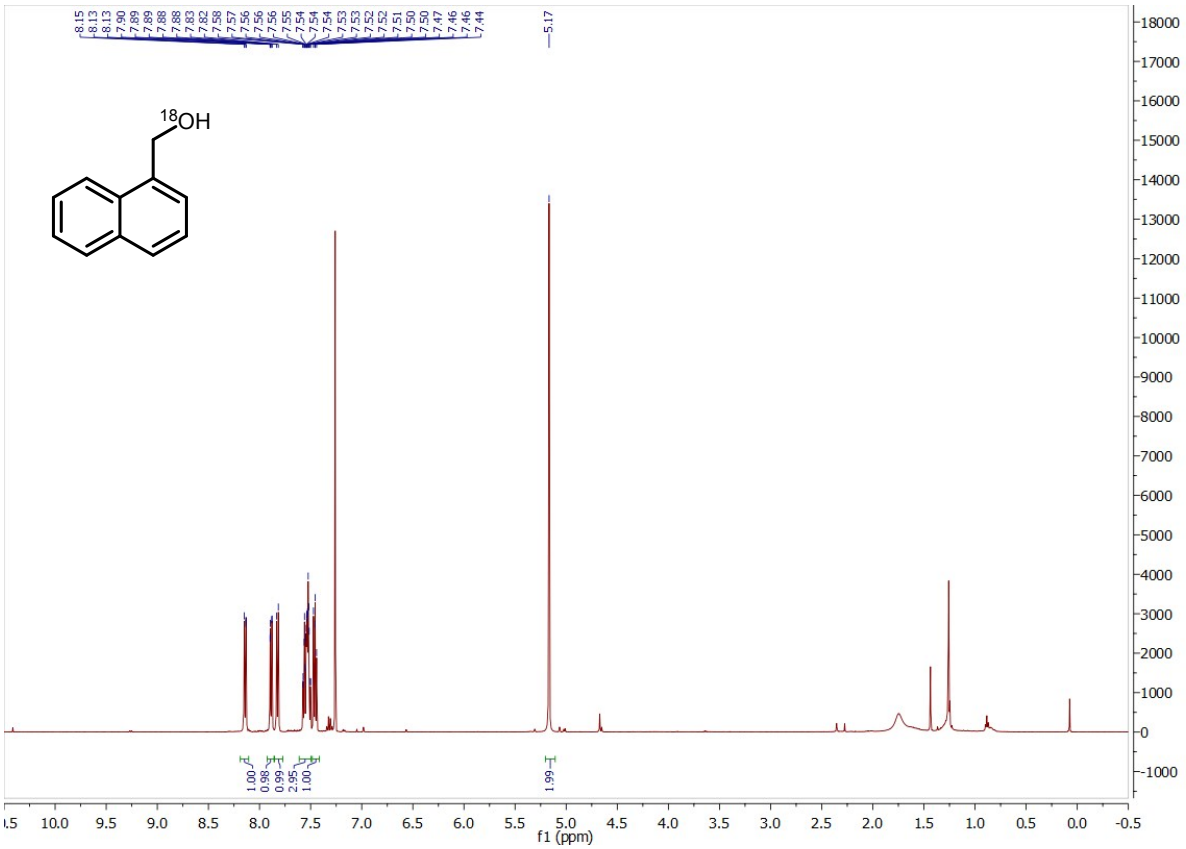


^{1}H and ^{13}C NMR Spectra for Compound S14

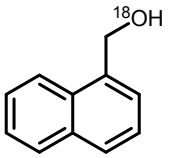


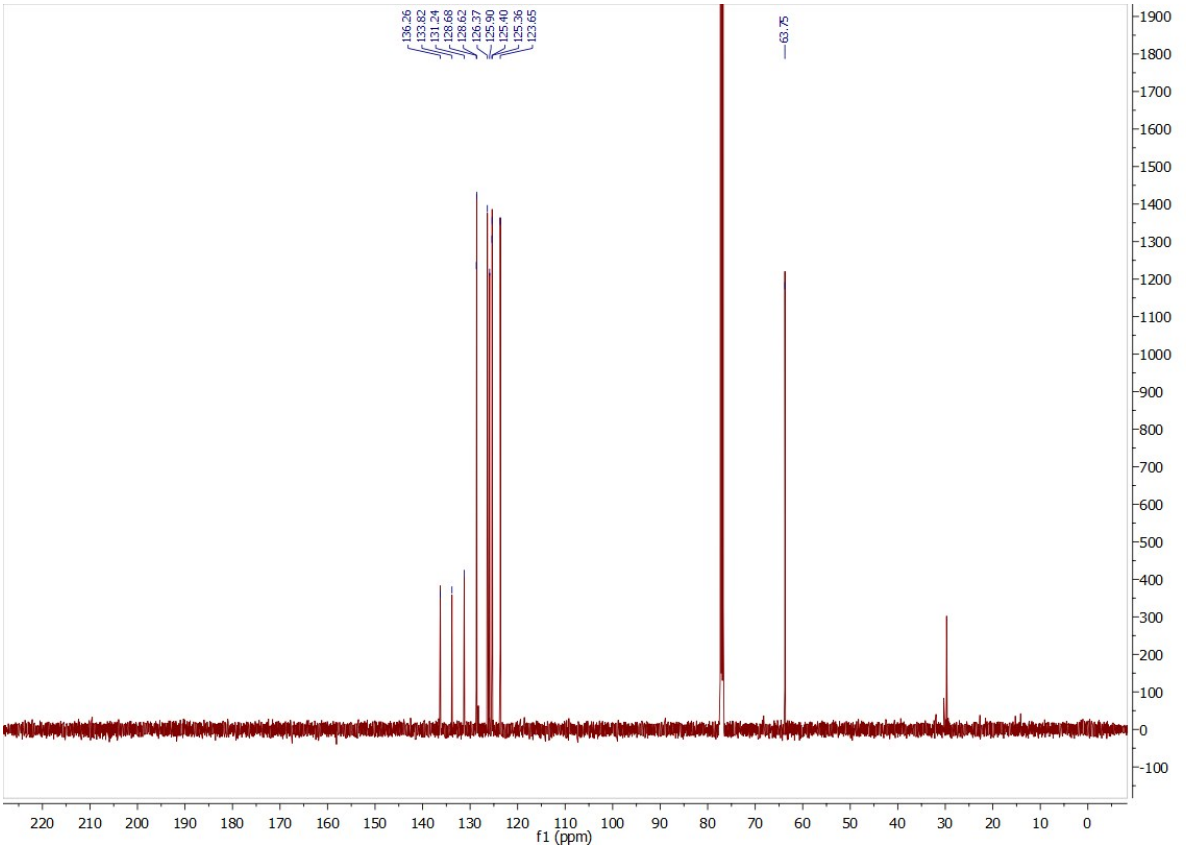


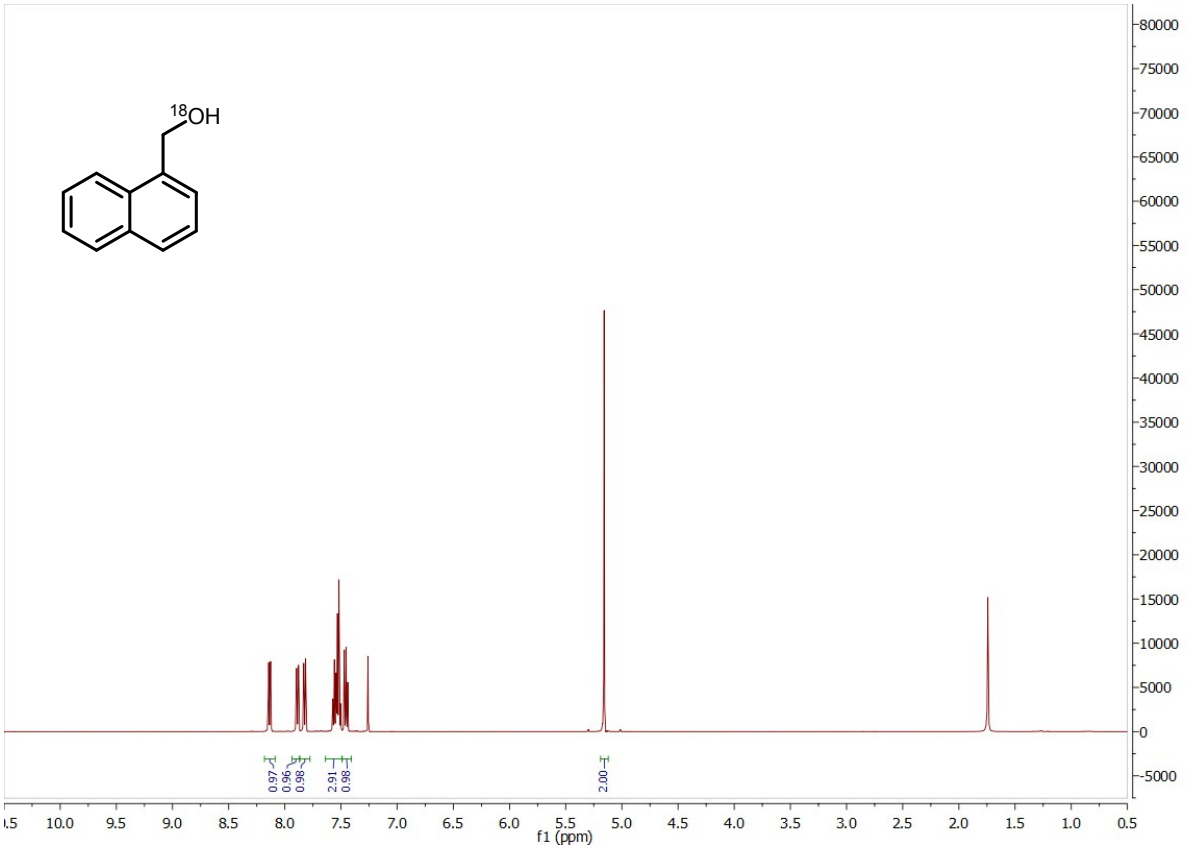
^{1}H and ^{13}C NMR Spectra for Compound S15

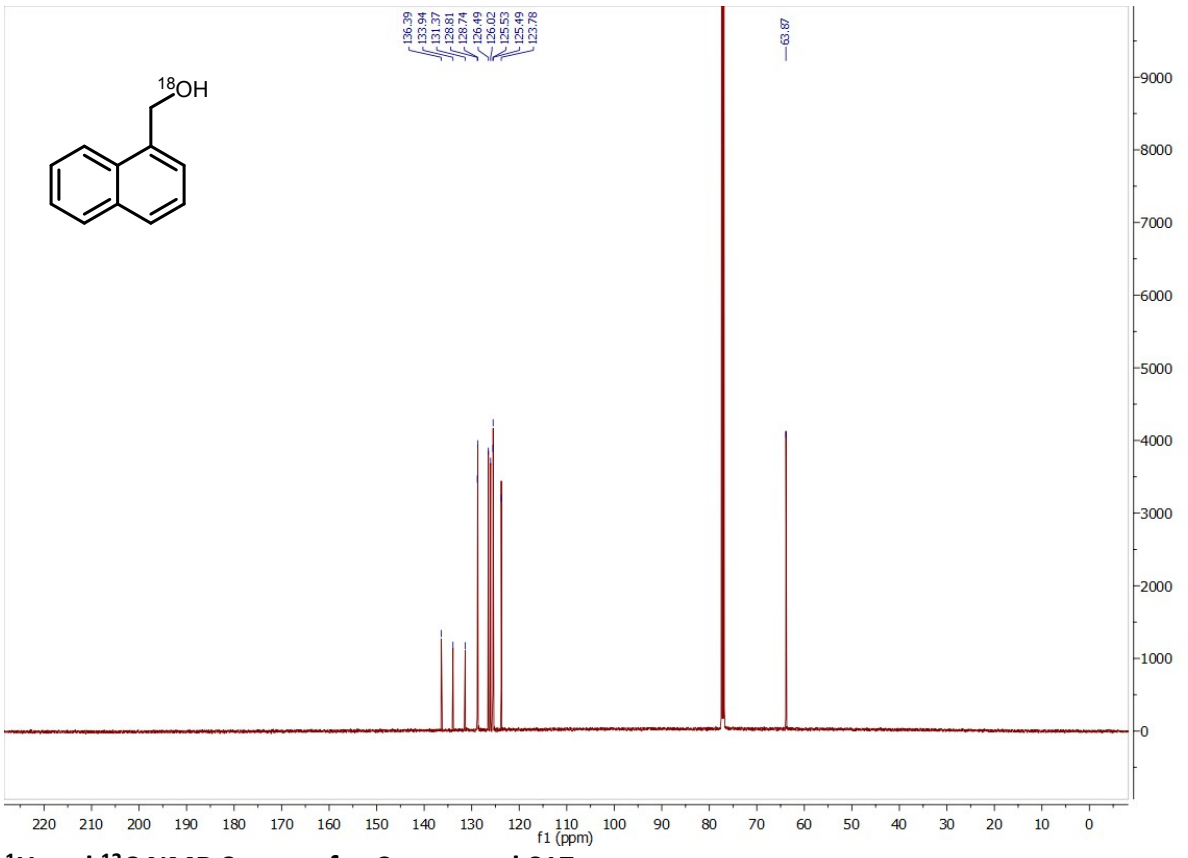


^{1}H and ^{13}C NMR Spectra for Compound S16

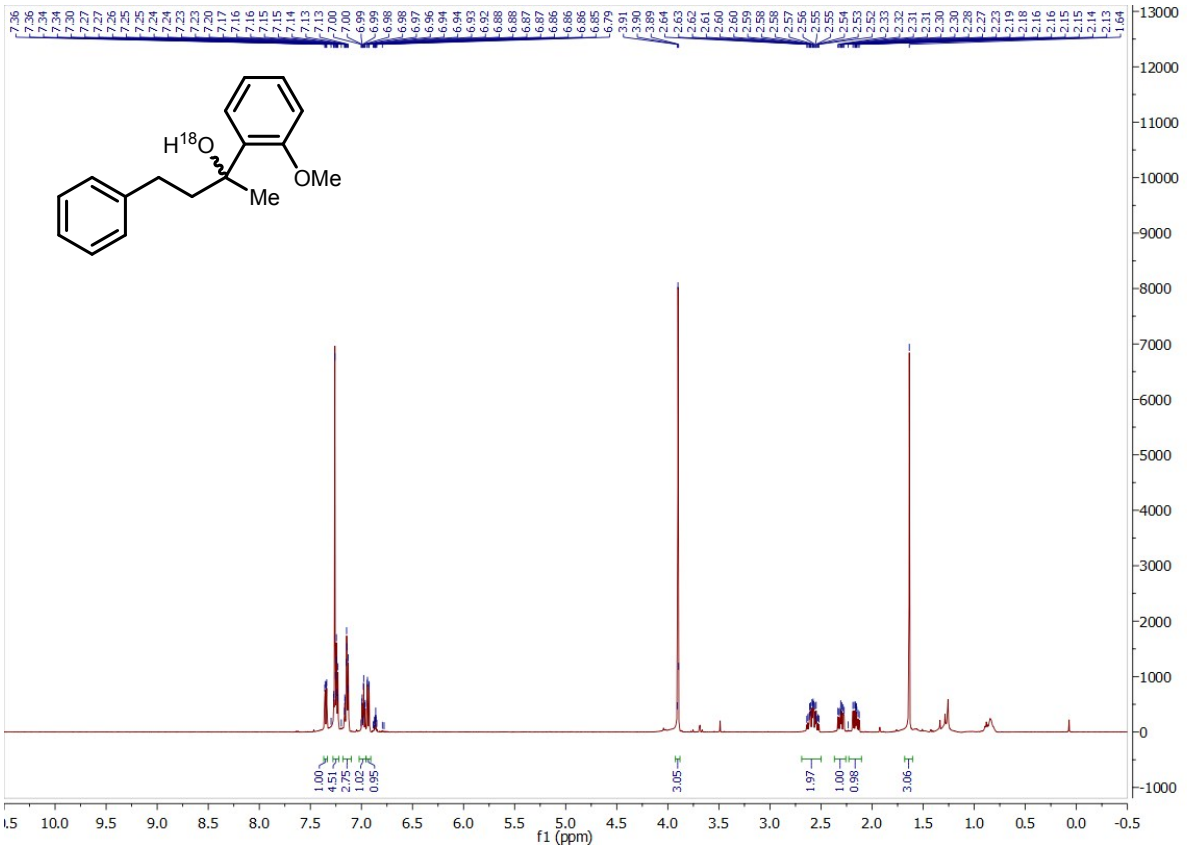




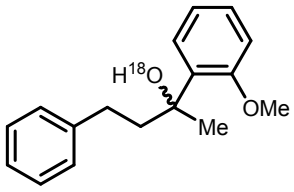


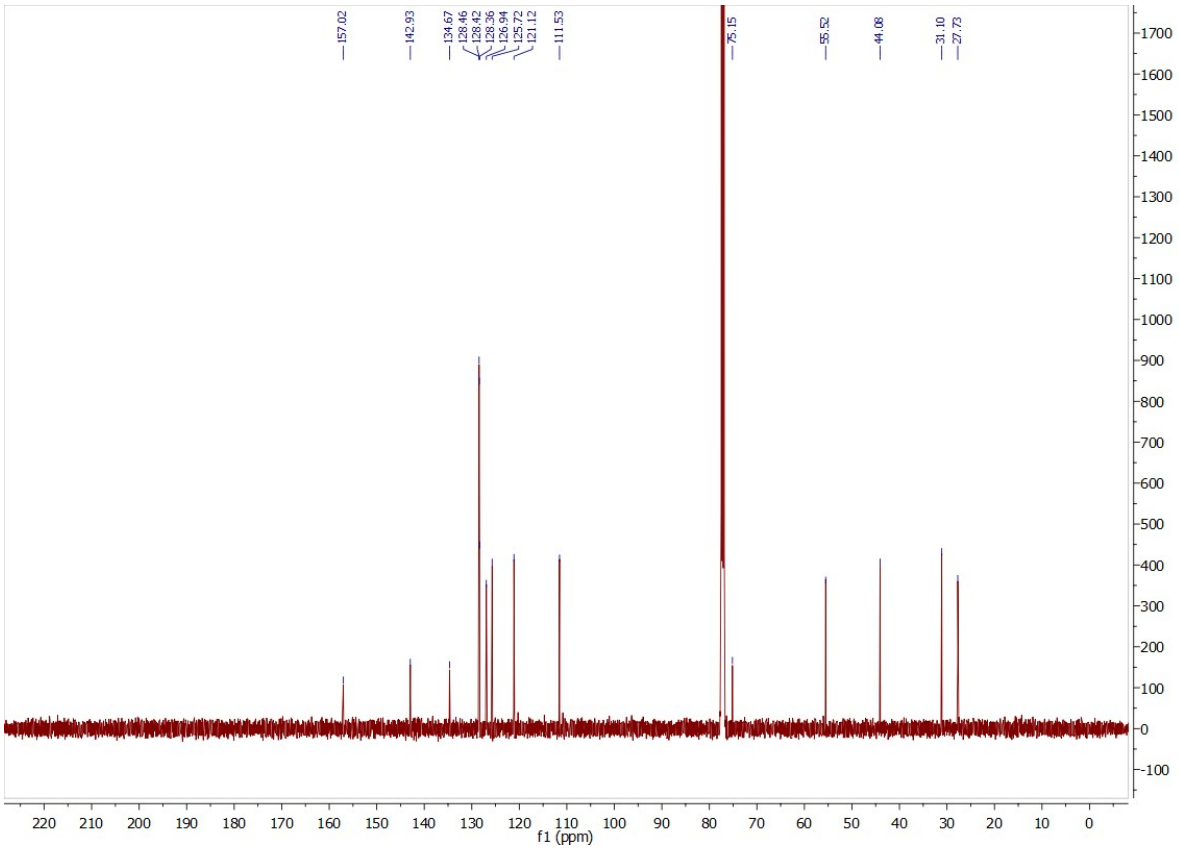


^{1}H and ^{13}C NMR Spectra for Compound S17



^{1}H and ^{13}C NMR Spectra for Compound 5




157.02
142.93
134.67
128.46
128.42
128.36
126.94
125.72
121.12
111.53
76.15
55.52
44.08
31.10
27.73
f1 (ppm)

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